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Spandan Chennamadhavuni Date

SYNTHESIS OF SMALL MOLECULE THERAPEUTICS UTILIZING RHODIUM CARBENOID CHEMISTRY

By

Spandan Chennamadhavuni

Doctor of Philosophy

Chemistry

SYNTHESIS OF SMALL MOLECULE THERAPEUTICS UTILIZING RHODIUM CARBENOID CHEMISTRY

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SYNTHESIS OF SMALL MOLECULE THERAPEUTICS UTILIZING RHODIUM CARBENOID CHEMISTRY

By

Spandan Chennamadhavuni

Advisor: Huw M. L. Davies, Ph.D.

An abstract of

A dissertation submitted to the Faculty of the

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ABSTRACT: SYNTHESIS OF SMALL MOLECULE THERAPEUTICS UTILIZING RHODIUM CARBENOID CHEMISTRY
BY SPANDAN CHENNAMADHAVUNI

The primary objective of this thesis was to utilize the reactions of donor/acceptor substituted rhodium carbenoids for the synthesis of small molecule therapeutics. The first major section of this thesis was devoted to explore a novel class of diarylcyclopropyl amines (CP-amines) (generated *via* an intermolecular asymmetric cyclopropanation reaction) as potential therapeutic agents for the treatment of cocaine addiction. A series of novel analogues were synthesized and a compound with 6 nM binding affinity towards $5HT_{2A}$ receptor and 89 fold selectivity for $5HT_{2A}$ receptor over $5HT_{2C}$ receptor was identified. Extensive molecular modeling studies have been performed to rationalize the existing activity trend among this novel class of CP-amines. Analogues of CP-amines were docked into a homology structure of the human 5-HT_{2A} receptor-using the Glide docking method. The effects of selected CP-amines on cocaine self-administration in primates were also studied and preliminary *in vivo* data suggests that there is a considerable dose-dependent decrease in cocaine self-administration. Most importantly, these compounds showed pharmacological effect even after 48 hours after administration.

The second major section of this thesis began with discovery of novel class of cyclopropane based selective serotonin-norepinephrine reuptake inhibitors (SNRI's) as potential therapeutic agents for the treatment of neuropathic pain. Over all, ~ fifty novel compounds and twenty aryl CP-amines compounds were synthesized. *In vitro* data for these novel compounds showed a wide diversity of potencies and specificities at monoamine transporter sites. One of the lead compounds was found to be efficacious in reversing a symptom of neuropathic pain (mechanical allodynia) in nerve-injured rats and is quite potent compared to medications approved for clinical treatment of chronic pain. Extensive molecular docking studies in SERT, NET and DAT allowed us to rationalize the molecular basis for the activity of novel CP-amines.

The third section of this thesis began with a convergent approach to the total synthesis of 5-Z-7-oxozeaenol, a potent and selective TAK1 inhibitor. A library of over 45 novel acyclic resorcyclic acid lactones (RALs) analogues was synthesized using carbenoid-induced ring-fragmentation of furans strategy. Many lead compounds were identified that showed sub μM inhibition of TAK1. Importantly, these synthetic analogs were found to be less toxic to normal cells and have higher tolerable dose of 200 mg/kg. Few analogues showed decreased growth of human breast carcinoma xenograft in a mouse preclinical model without noticeable side effects such as distress or weight loss. Several compounds were identified as promising leads for further optimization as drug candidates.

In summary, we were able to initiate, execute and complete three different medicinal chemistry projects using enabling technology unique to Davies' group. Our multidimensional, multidisciplinary rational approach and collaborative efforts led to the discovery of three novel scaffolds for various targets, which might have a greater potential and broader impact in medication development for cocaine addiction, neuropathic pain and cancer.

SYNTHESIS OF SMALL MOLECULE THERAPEUTICS UTILIZING RHODIUM CARBENOID CHEMISTRY

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For my parents

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During my exciting PhD journey, I met and worked closely with quite a few remarkable people. I also took lot of help from many people. I would like to thank each and every one of those people who have helped me achieve this goal.

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p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
APCI	Atomspheric pressure chemical ionization
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
$(Boc)_2O$	di-*tert*-butyldicarbonate
bp	boiling point
Bu	*n*-butyl
Bz	benzoyl
CAN	cerium (IV) ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DMP	Dess Martin Periodinane
DMB	2,2-dimethylbutane
DMSO	dimethyl sulfoxide
DOSP	*N*-(4-dodecylbenzenesulfonyl)prolinate
dr	diastereomeric ratio

EDA	ethyl diazoacetate
EDG	electron-donating group
eq	equivalent
Et	ethyl
Et_2O	diethyl ether
EWG	electron-withdrawing group
ESI	Electrospray ionization
FTIR	Fourier-transform Infrared
HMDS	hexamethyldisilazane
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
Moc	methoxycarbonyl
mp	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
PCC	pyridinium chlorochromate
Ph	phenyl

$Rh_2(OAc)_4$	rhodium acetate dimer
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TON	Turnover number
TOF	Turnover frequency
Ts	tosyl (*para*-toluenesulfonyl)
TsOH	toluenesulfonic acid
μW	microwave
MMGBSA	**M**olecular **m**echanics, the **g**eneralized **B**orn model and **S**olvent **a**ccessibility method
XP dock	E**x**tra **P**recision dock
FDA	Federal Drug Administration
5-HT /SE	Serotonin
NE	Norepinephrine
DE	Dopamine
SERT	Serotonin transporter protein
NET	Norepinephrine transporter protein

DAT	Dopamine transporter protein
IC_{50}	Half maximal inhibitory concentration
ED_{50}	Half maximal effective dose
K_i	binding affinity of the inhibitor
MTD	Maximum tolerated dose
AMDA	9-(aminomethyl)-9,10-dihydroantharacene
ADME	Absorption Distribution Metabolism Excretion
MDD	major depression disorder
TAK1	**T**ransforming growth factor-β-**A**ctivated protein **K**inase **1**
MMP9	Matrix metalloproteinase 9
RAL	resorcylic acid lactones
CNS	Central nervous system
GPCR	G-protein coupled receptors
TMH	Trans-membrane helices
SSRI	Selective serotonin reuptake inhibitors
SNRI	Serotonin and norepinephrine reuptake inhibitors
NARI	Selective noradrenalin reuptake inhibitors
TCA	Tricyclic antidepressants
i.t	Intrathecal
i.v	Intravenous
i.m	Intramuscular
SNL	Spinal nerve ligated
GUI	Graphical User Interface
BLAST	Basic Local Alignment Search Tool

Chapter 1: Introduction to Rhodium Carbenoid Chemistry

Introducing new C–C bonds into organic substrates in both a regio- and stereoselective fashion, and, thereby, developing novel methodologies to access highly functionalized molecules including potential therapeutic agents, has always been a primary focus of organic chemists.[1-3] Even though functional group modifications can be carried out on polarized bonds, functionalization of unactivated C–H bonds has always been a challenge, which has begun to be addressed utilizing transition metal induced C–H insertion reactions.[4-8]

There are two C–H activation strategies. A traditional approach of C–H activation involves insertion of highly reactive metal complex into a C–H bond. C–H functionalization also could be achieved by inserting divalent carbene into C–H bond (Fig. 1.1). This latter approach of C–H activation can be affected both asymmetrically and catalytically by decomposing diazo compounds in the presence of chiral dirhodium complexes to access structurally complex and synthetically diverse molecules relatively quickly.[5] The diazo compounds will decompose in the presence of a metal giving rise to highly reactive carbenoid species, which then undergo a variety of transformations such as cyclopropanation, C–H insertion, and ylide formation (Fig. 1.1). The driving force for this reaction is the liberation of nitrogen.

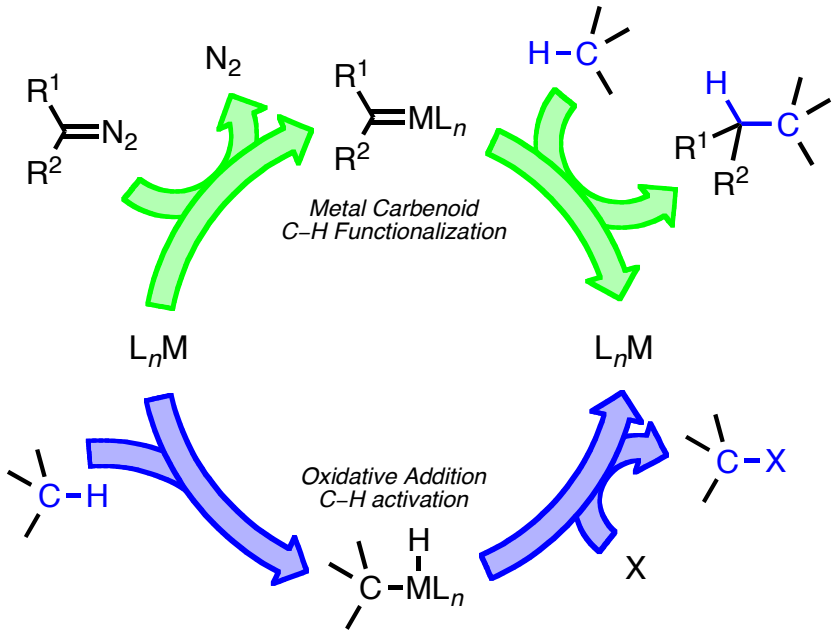
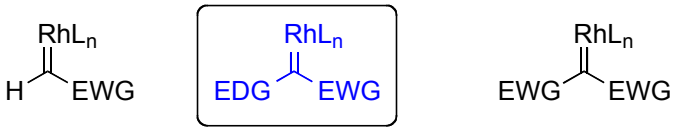


Figure 1.1: Catalytic cycle for C–H activation

Metal carbenoids can be classified into acceptor, acceptor-acceptor, and donor-acceptor carbenoids based on the electron withdrawing (EWG) and donating (EDG) capacity of the groups present on the carbenoid center. The unique class of donor-acceptor carbenoids are less reactive than acceptor and acceptor-acceptor carbenoids, but have been found to display very high levels of selectivity in a variety of transformations, such as cyclopropanation and C–H insertion reactions (Fig. 1.2).[5]



Electron Withdrawing Groups (EWG) = CO_2R, COR, NO_2, $PO(OR)_2$, SO_2R, CN, CF_3
Electron Donating Groups (EDG) = Vinyl, alkynyl, aryl, heteroaryl

Figure 1.2: Classification of carbenoid intermediates

Apart from developing a novel class of carbenoids, the Davies' group has also been involved in developing new chiral dirhodium catalysts. The prolinate catalysts Rh_2(*S*-DOSP)$_4$ (**1-1**) and Rh_2(*S*-biDOSP)$_4$ (**1-2**) have been proposed to exist in a D_2 symmetric conformation (*N*-sulfonyl groups were thought to be adapting up-down-up-down arrangement in non polar solvents) and can induce asymmetric induction in many transformations (Fig. 1.3). Recently phthalimide based Rh_2(*S*-PTAD)$_4$ (**1-3**) with a bulky adamantyl group was developed, which is thought to have C_2 symmetry. This catalyst can induce very high levels of asymmetric induction in cyclopropanation of donor-acceptor diazo compounds with trifluoromethyl and nitrile groups as EWG[9,10] (Fig. 1.3).

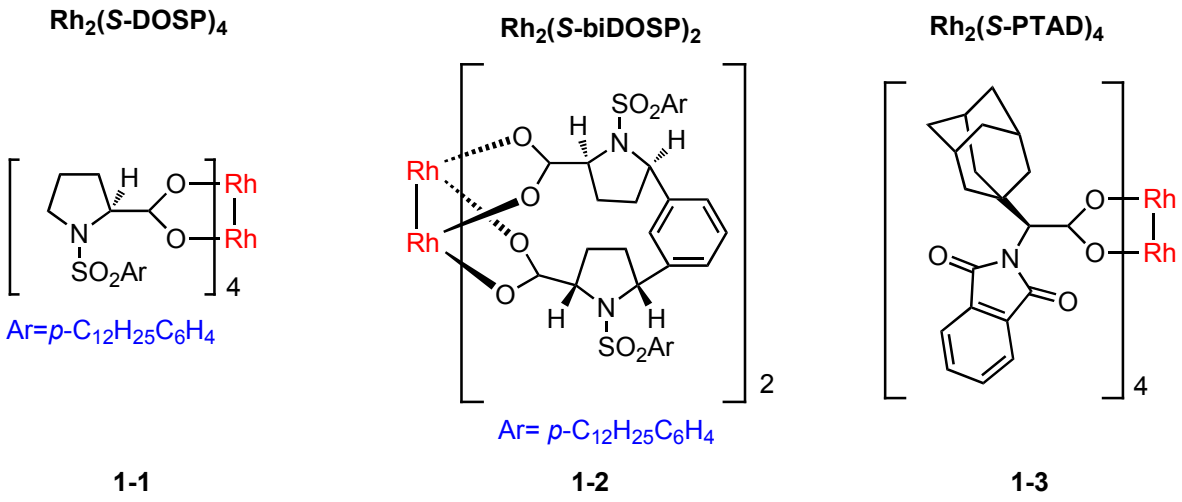


Figure 1.3: Various chiral dirhodium catalysts developed and designed in the Davies group

In the presence of suitable chiral catalysts, high enantiomeric excesses have been achieved in a variety of transformations, such as cyclopropanation (**1-4**), Si-H insertion

(**1-5**), the combined C–H activation/Cope rearrangement (**1-6**), C–H insertion (**1-7**), [3+2] cycloaddition (**1-8**) and [4+3] cycloaddition (**1-9**) (Fig. 1.4).

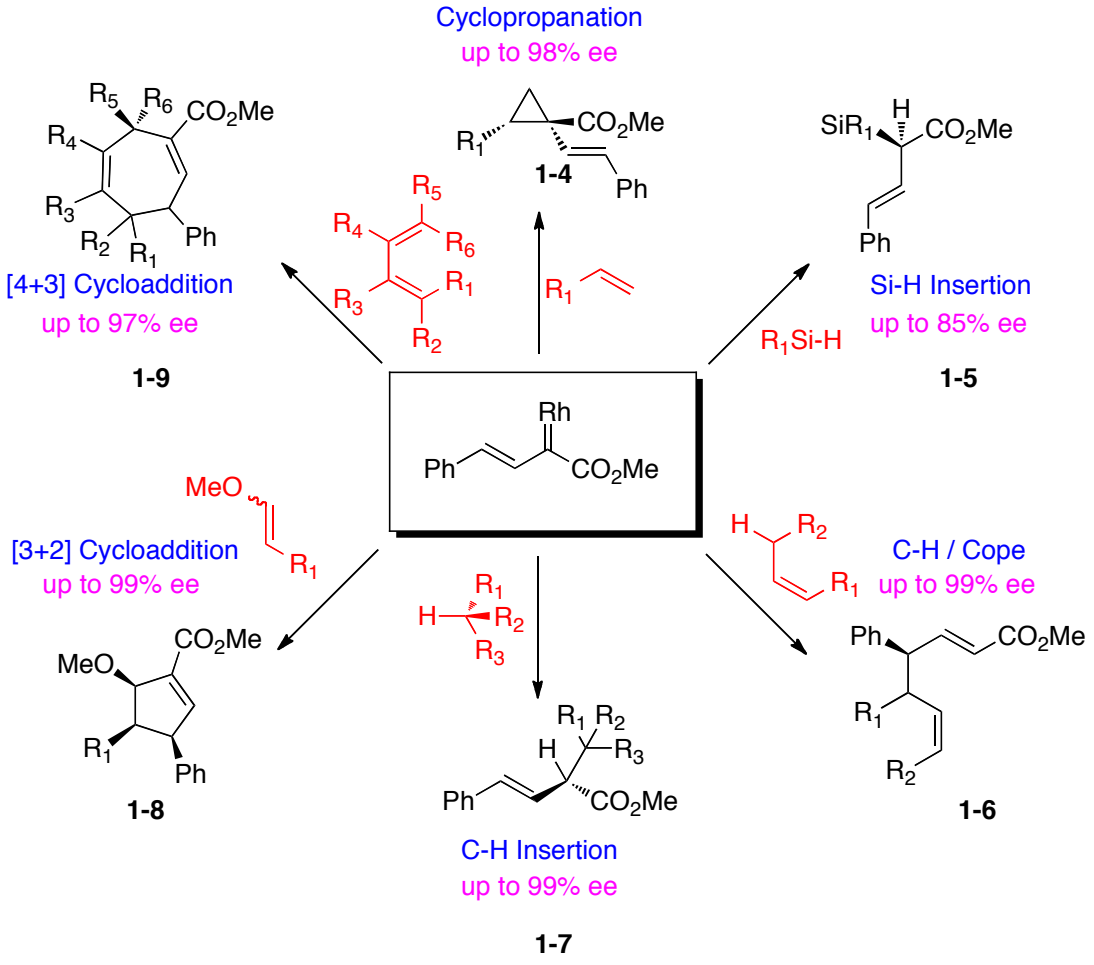


Figure 1.4: Various methodologies developed in the Davies' group

The combined C–H activation/Cope rearrangement is a powerful methodology developed in the Davies group, which has been applied to the total syntheses of several marine natural products (**1-10**) to (**1-17**). This reaction can generate upto three stereocenters in a single step with excellent diastereo- and enantiocontrol (Fig. 1.5).[11-13] It

was shown recently, that this reaction proceeds through a concerted, but highly asynchronous, hydride-transfer followed by C-C bond-forming event.[14]

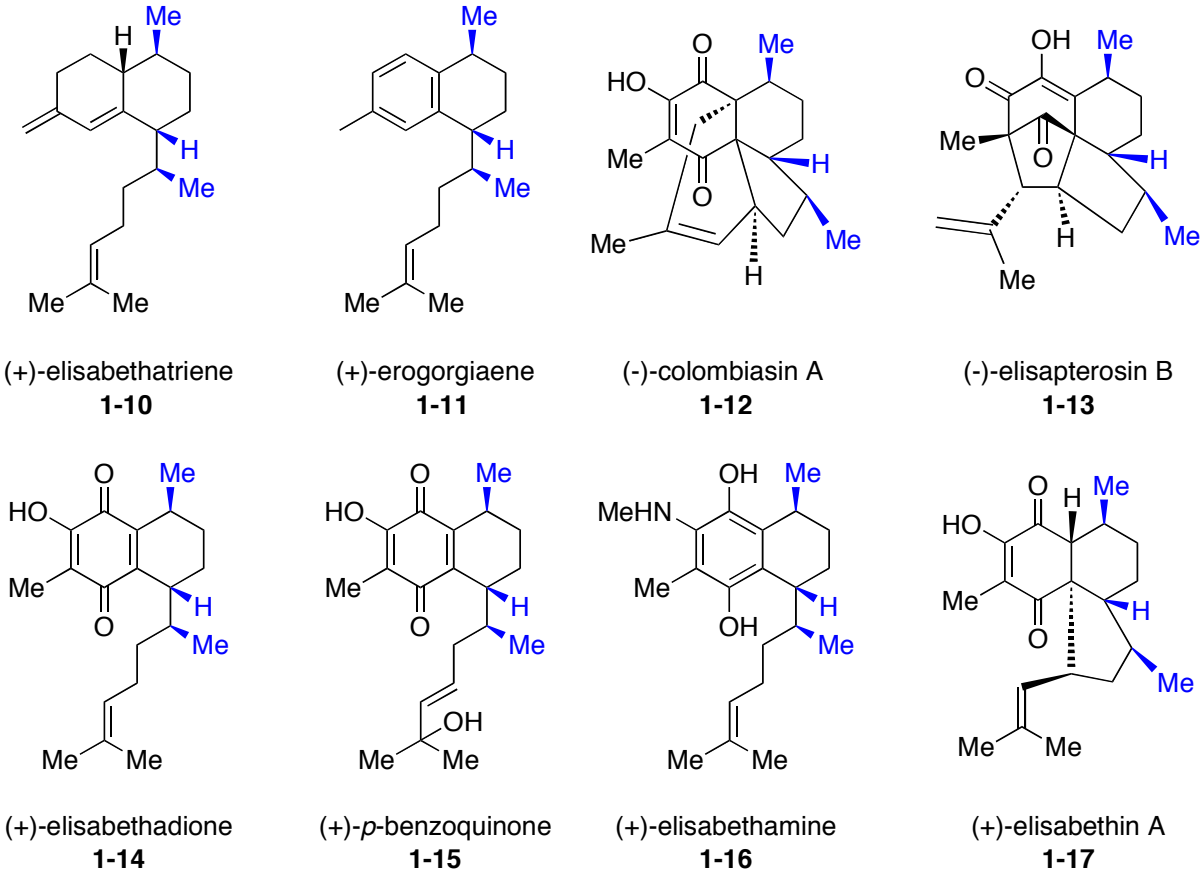


Figure 1.5: Total syntheses of complex natural products completed in the Davies' group

The novel methods developed in the Davies' group were also applied in the syntheses of biologically relevant compounds. A few highlights of the applications of rhodium carbenoid induced C–H activation in the synthesis of therapeutic agents include:

- Rh_2(*S*-PTAD)$_4$ catalyzed enantioselective synthesis of tropane analogs (**1-18**) by [4+3] cycloaddition between vinyl carbenoids and *N*-Boc pyrrole.[15]
- Rh_2(*S*-biDOSP)$_2$ catalyzed enantioselective synthesis of Ritalin (**1-19**) by direct insertion of methyl phenyldiazoacetate α to nitrogen in *N*-Boc piperidine.[16,17]

- Rh_2(*S*-DOSP)$_4$ catalyzed enantioselective synthesis of (+)-indatraline (**1-24**) or (+)-cetiedil (**1-23**) and (+)-sertraline (Zoloft) (**1-22**) by C–H insertion of phenyl diazoacetate, phenyl vinyldiazoacetate into 1,4-cyclohexadiene and 1,3-cyclohexadiene, respectively.[18,19]
- Rh_2(*S*-DOSP)$_4$ catalyzed enantioselective synthesis of (*S*)-venlafaxine **1-25** by C–H insertion α to nitrogen in STABASE.[20]

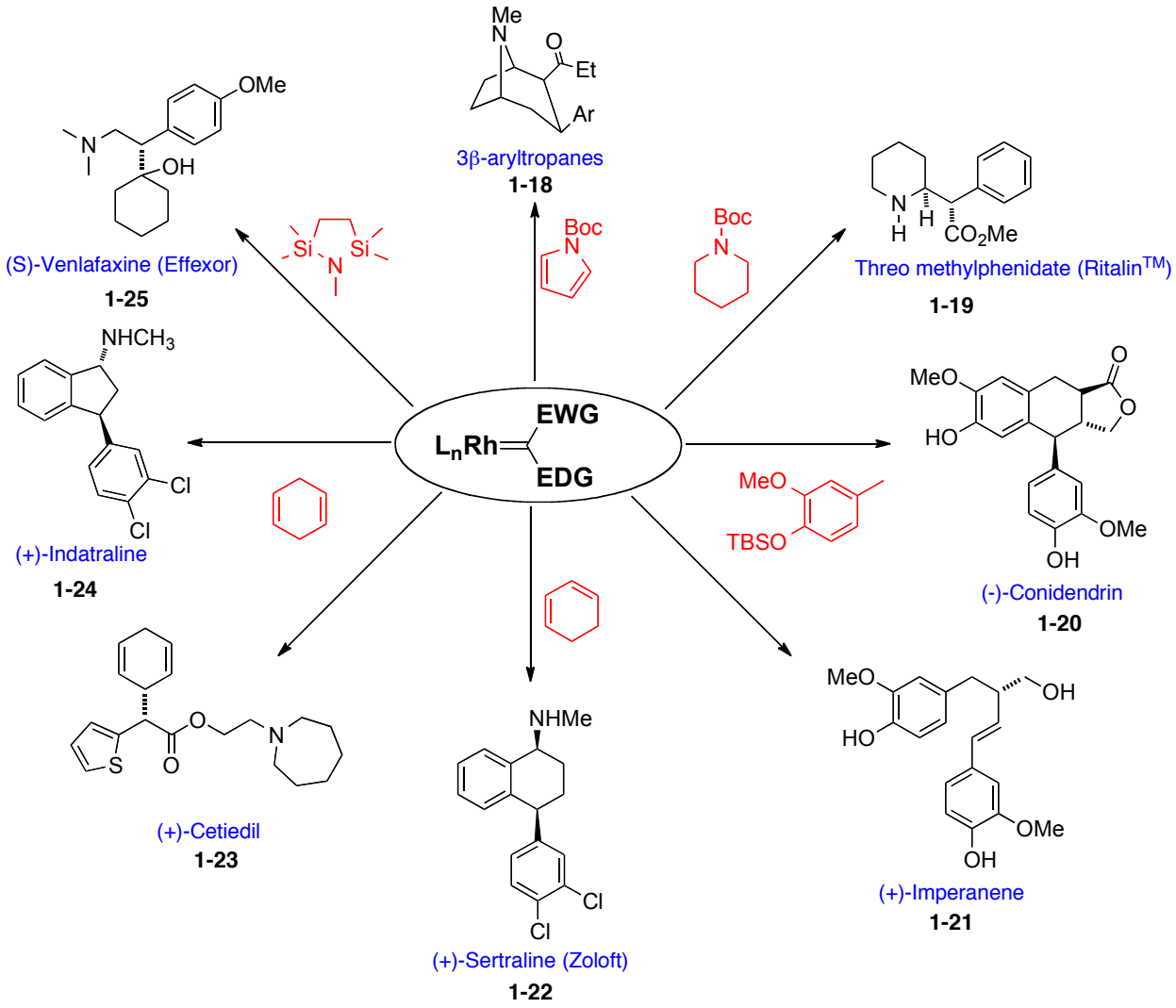


Figure 1.6: Various pharmaceutical targets synthesized in the Davies group.

Apart from developing novel methodologies, the Davies group is also involved in utilizing strategies such as enantiodifferentiation, kinetic resolution and desymmetrization to generate chiral building blocks with multiple stereocenters. Recently, Davies' group also started utilizing theoretical calculations to understand and expand novel methodologies.

In summary, Davies' group pioneered in the chemistry of donor/acceptor carbenes. Research in the Davies' group is directed towards design and development of chiral dirhodium catalysts,[21-24] the development of novel methodologies involving C–H activation,[25-35] application of new methods in the synthesis of complex natural products [11-13,36-38] and pharmaceutical targets.[20,39-43]

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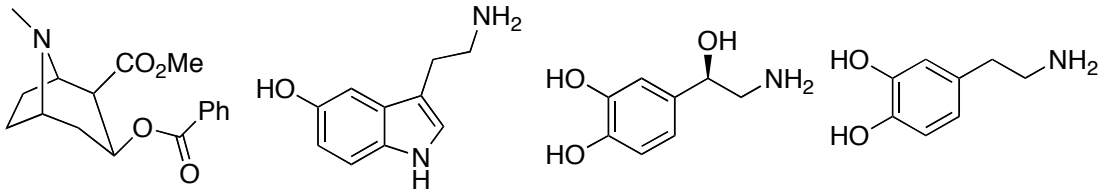
CHAPTER 2: Synthesis, molecular docking and binding studies of novel 5-HT_{2A} receptor antagonists - Potential therapeutic agents for cocaine addiction

2.1 Introduction

2.1.1 Cocaine addiction

Cocaine **(2-1)** (Fig. 2.1) is a crystalline tropane alkaloid that is obtained from the leaves of the 'coca' plant. It is a powerful CNS stimulant. According to the 2008 National Survey on Drug Use and Health, approximately 36.8 million Americans aged 12 and older had tried cocaine at least once in their lifetimes. Cocaine addiction not only has severe negative consequences for individuals with addictive behavior but also for society. It was estimated that the total costs of substance abuse in the United States, including lost productivity and health- & crime-related costs, totals over 600 billion dollars annually.[1]



2-1 **cocaine** | **2-2** **serotonin (5HT or SE)** | **2-3** **norepinephrine (NE)** | **2-4** **dopamine(DA)**

Figure 2.1: Cocaine and monoamine neurotransmitters.

Cocaine addiction is a prevalent drug abuse problem and pressing issue in today's world. This chronic relapsing disorder is associated with severe medical and

psychological complications and can be incredibly difficult to overcome with few effective pharmaceutical treatment options currently available. Approximately 60% of cocaine dependent patients who receive treatment medication relapse into drug use with in one year.[2] Currently, there is no Federal Drug Administration (FDA) approved medication for the treatment of cocaine addiction.[3] Thus, developing novel pharmacotherapeutic approaches for the treatment of cocaine addiction is of great importance and has gained much attention in recent years.

2.2 Background

2.2.1 Neurotransmission and mechanism of action of cocaine

The development of medication of cocaine addiction is challenging mainly because of complexity in the mechanism of action of cocaine in the body. In the human brain, neurons transmit impulses from presynaptic neuron to postsynaptic neuron via a synaptic cleft, a 20 nm wide gap between transmitting neurons (Fig. 2.2).[4] There are three different kinds of monoamine neurotransmitters: serotonin (SE or 5-HT), norepinephrine (NE) and dopamine (DA) (structures in Fig. 2.1). These biogenic amines, once released into the synaptic cleft, will bind to the receptor on the postsynaptic neuron, which in turn cause impulse transmission. This signaling cascade is terminated by reuptake of these neurotramitters by their corresponding transporter proteins namely serotonin transporter (SERT), norepinephrine transporter (NET) and dopamine transporter (DAT) present in presynaptic neuron.

Cocaine, being a nonselective drug with very high affinity towards SERT, NET and DAT, inhibits reuptake channels for dopamine (DA), serotonin (SE or 5-HT), and

norepinephrine (NE). This causes an increase in the amount of neurotransmitters in the synaptic cleft, allowing for continual stimulation of neurons leading to the state of "high" (euphoria) in cocaine users.[5] Cocaine is also a short acting dopamine agonist that causes this euphoria effect that lasts only for a few hours leading to the strong craving or addictive behavior. Acute use of cocaine can cause itching, hallucinations and paranoic delusions, whereas chronic use can cause hemoptysis, bronchospasm, dyspnea, lupus, glomerulonephritis, series of kidney diseases and renal failure. Psychological dependency on cocaine may lead to physiological damage to all parts of the body, psychosis, depression and can be fatal in many cases.[6]

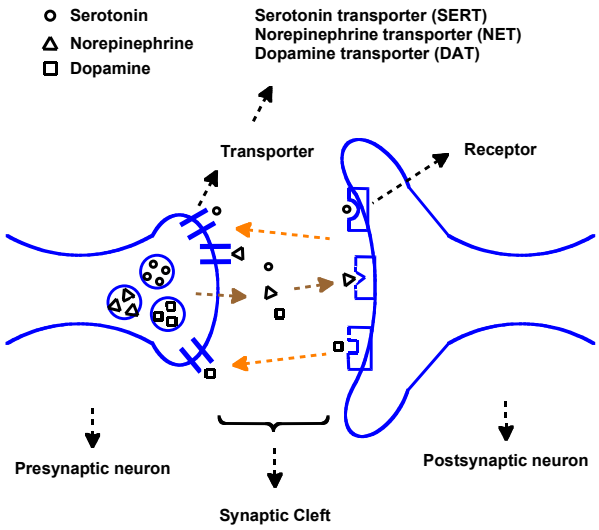


Figure 2.2: Graphical representation of neurotransmission in the synaptic cleft

2.2.2 Animal model of cocaine addiction

A number of animal models were used to understand the effect of cocaine on the neurobiological mechanism (Fig 2.3).[7] The cycle of addiction starts with the initial cocaine use leading to intoxication and euphoric effects. This stage of addiction can be

examined in animals by measuring hyperactivity and drug discrimination behavior. The subject then becomes addicted mainly because of positive reinforcing effects of cocaine eventually leading to 'rewarding effects'. This stage in animals is measured via cocaine self-administration model or conditional place preference (CPP) model. In the third stage, the subject loses control over cocaine usage and continues to use cocaine despite negative consequences. If the subject was stopped from using cocaine, the user would go through a period of withdrawal. This stage can be tested in animals by examining the anxiety or depression-like states. However, this period of abstinence is typically followed by a relapse stage. This stage can be measured in animals using reinstatement models of self-administration.[8]

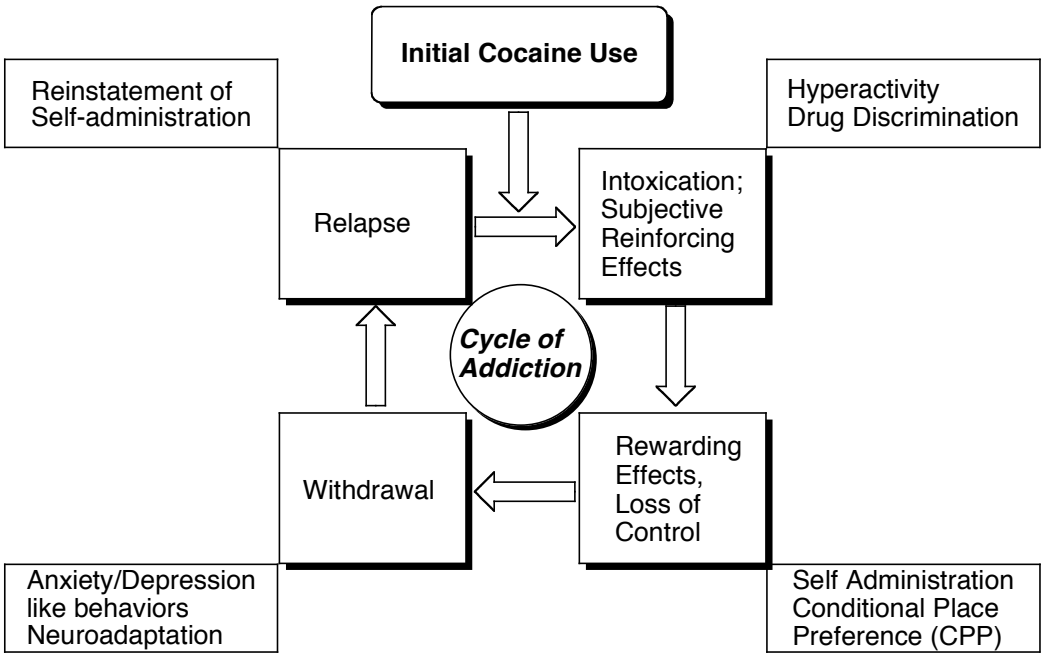


Figure 2.3: A schematic diagram showing the stages in cycle of addiction.[8]

2.2.3 Pharmacology of cocaine addiction

Initially, the dopamine (DA) neurotransmitter system has been the target for developing therapeutic agents mainly because of its role in the "rewarding" aspects of abused drugs.[9,10,11] Consequent efforts towards the development of long acting agonists in the form of dopamine reuptake (DAT) inhibitors[12] for the treatment of cocaine addiction proved to be ineffective in the clinic.[8] Many other classes of compounds including cocaine analogues were also evaluated as therapeutics for cocaine addiction.[13]

During these studies, it was found that the serotonin (5-hydroxytryptamine, 5-HT) neurotransmitter system can also modulate the concentration of dopamine in the synaptic cleft, which led to the idea that it may be a favorable target for development of pharmacotherapeutics for drug addiction. Some of the other targets explored for the same purpose include 1) neurotransmitter storage vesicles 2) M_5 muscarinic acetyl cholinergic,[14] 3) glutamergic,[15] 4) GABA,[16] and 5) kappa opioid systems.[17]

In the serotonin system, the action of 5-HT is mediated through at least sixteen receptor subtypes, which have been grouped into seven families (5-HT_1 – 5-HT_7) according to their structural and functional characteristics. Within the central nervous system (CNS), the 5-HT_2-receptor family is made up of three subtypes (5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}).

Cunningham *et al. has* summarized the large volume of pre-clinical data, that has been reported thus far to get a complete understanding of the subtle effects of various kinds of 5-HT ligands on the addictive behavior in rodents in response to cocaine (Table 2.1).[8]

Behavior	**5-HT_{2A} Agonist**	**5-HT_{2A} Antagonist**	**5-HT_{2C} Agonist**	**5-HT_{2C} Antagonist**
Hyperactivity	Increase	Decrease	Decrease	Increase
Drug discrimination	Increase	Decrease	Decrease	Increase
Self-administration		No effect	Decrease	Increase
Cocaine reinstatement		Decrease	Decrease	Increase
Cue reinstatement		Decrease	Decrease	
Conditioned Place Preference		Decrease	Decrease	
Conditioned hyperactivity			Decrease	Increase

Table 2.1: Cunningham's summary of rodent behavioral response to cocaine in the presence of 5-HT ligands.

The behavioral data in Table 2.1 clearly shows that 5-HT_{2A} *antagonists* and/or 5-HT_{2C} *agonists* may effectively modulate the behavior effects of cocaine. 5-HT_{2A} *antagonists* have displayed potential to act as "abstinence enhancing" drugs that attenuate addictive behavior in rat models.[8] Some of the recent preclinical studies also suggested that the 5-HT_{2A} receptor (5-HT_{2A}) contributes to the regulation of impulsive behavior and also mediates some of the behavioral effects associated with the use of cocaine.[18]

2.2.4 Serotonin ligands – Potential treatment agents for cocaine addiction

Many synthetic compounds targeting subtypes of serotonin receptor were developed over the last fifty years. Apart from being used for cocaine addiction treatment, 5-HT_{2A} and 5-HT_{2C} ligands have also been used for the treatment of many

other psychotic conditions, including schizophrenia, depression, sleep disorder,[19] obesity as well as obsessive compulsive disorder.

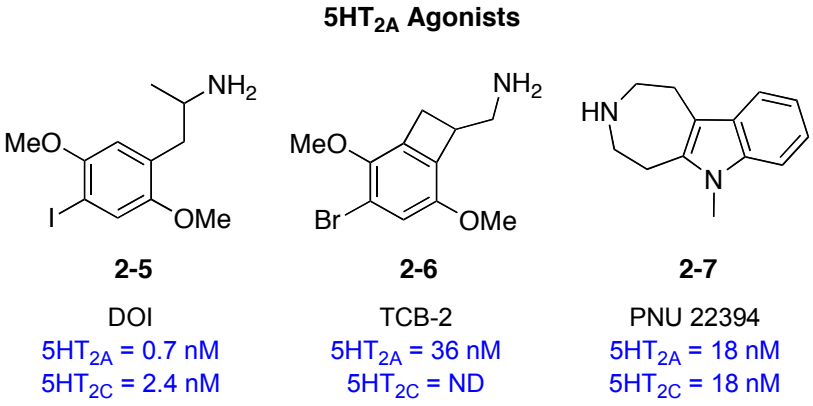
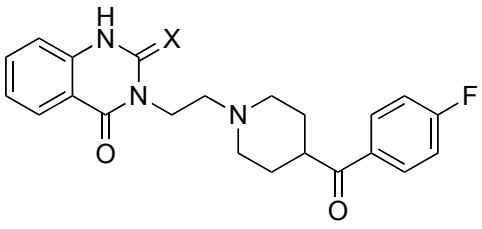


Figure 2.4: List of representative 5-HT_{2A} agonist.

Many of the known 5-HT_{2A} agonists have been shown to be nonselective. The phenylisopropylamine compound, DOI **(2-5)**, was found to be a mixed 5-$HT_{2A/2C}$ agonist;[20] however its conformationally restricted cyclobutane derivative, TCB-2 **(2-6)** was found to be a potent, high affinity 5-HT_{2A} agonist.[21] An Azepino indole derivative, PNU 22394 **(2-7)**, was found to be a 5-HT_{2C} agonist and 5-$HT_{2A/2B}$ partial agonist (Fig. 2.4).[22]

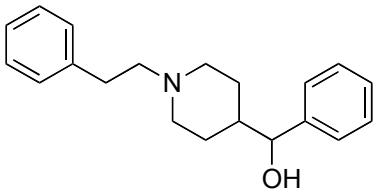
$5HT_{2A}$ Antagonists



2-8 **2-9**

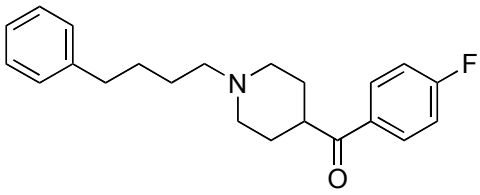
X = O Ketanserin
$5HT_{2A}$ = 3 nM
$5HT_{2C}$ = 11 nM

X = S Altanserin
$5HT_{2A}$ = 0.13 nM
$5HT_{2C}$ = 40 nM



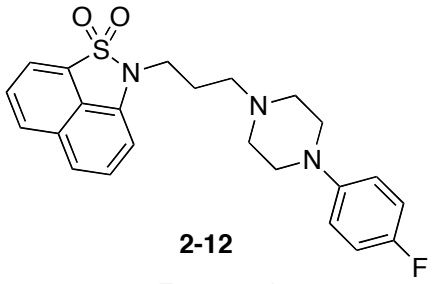
2-10

MDL- 11939
$5HT_{2A}$ = 3.2 nM
$5HT_{2C}$ = 360 nM



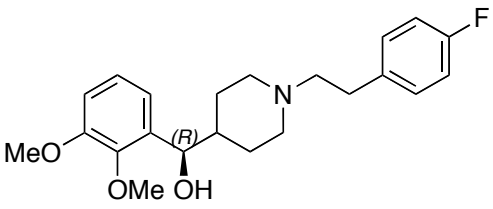
2-11

4F 4PP
$5HT_{2A}$ = 5.3 nM
$5HT_{2C}$ = 620 nM

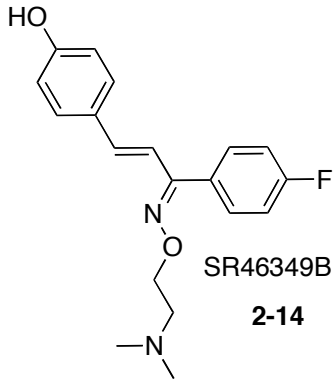


2-12

Fananserin
$5HT_{2A}$ = 0.26 nM
$5HT_{2C}$ = ND

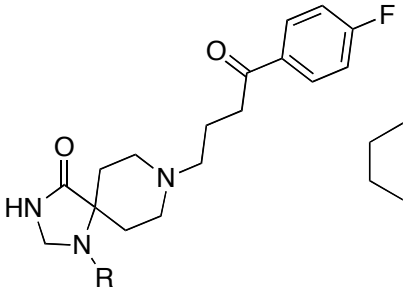


2-13 M100907

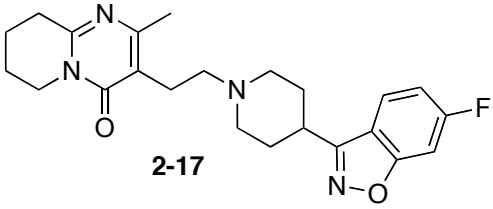


SR46349B

2-14

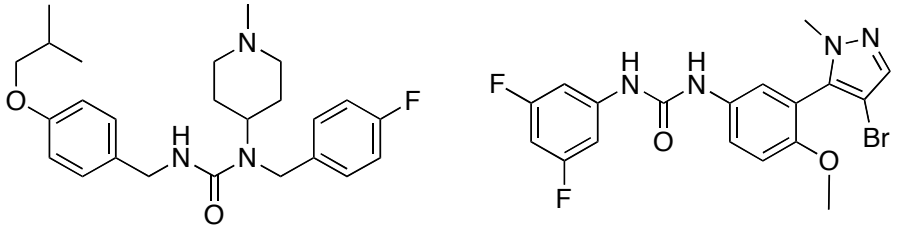


R = Ph: Spiperone **2-15**
R = Me **2-15**



2-17

Risperidone



2-18
Pimavanserin
ACP-103

2-19
Nelotanserin
APD-125

Figure 2.5: List of representative 5-HT_{2A} antagonists.

Among the most studied 5-HT_{2A} antagonists (Fig. 2.5), Ketanserin **(2-8)** is a potent inhibitor of both 5-HT_{2A} and 5-HT_{2C} receptor.[23] It has also been found to antagonize 5-HT_{1D} receptor. MDL-11939 **(2-10)** was developed based on ketanserin and found to be more than 100 fold selective towards 5-HT_{2A} *vs.* 5-$HT_{2C.}$[24] A structurally similar phenylalkylamine, 4F 4PP **(2-11)**, was also found to antagonize with almost as high potency as ketanserin but with lower affinity for 5-HT_{2C} sites.[25]

M100907, [R- (+)-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol] **(2-13)**, a 5-HT_{2A} antagonist, was found to attenuate cocaine-induced increases in locomotor activity and the discriminative stimulus effects of cocaine in rats.[26, 27] This compound was found to be 100-fold more selective for 5-HT_{2A} (K_i = 0.85 nM) than for 5-HT_{2C} (K_i = 88 nM) and at least a 100-fold lower affinity for other receptors. It is currently in late stage clinical trials for the treatment of insomnia.

Another 5-HT_{2A} antagonist, SR46249B **(2-14),** was found to attenuate cocaine reinstatement at doses, but did not induce behavioral effects when administered alone.[28] Clinical studies on Resperidone **(2-17)** in an effort to reduce cocaine addictive behavior were not successful mainly because of its comparable affinity to various other targets

such as dopamine, muscarinic, adrenergic and transporter sites. This lead to some serious side effects and poor retention in the individuals treated with this compound.[29] Another selective 5-HT_{2A} receptor inverse agonist that are based on phenyl pyrazole urea motif, pimavanserin **(2-18)** and nelotanserin **(2-19)**, are currently in Phase II clinical trails for treating insomnia.[19]

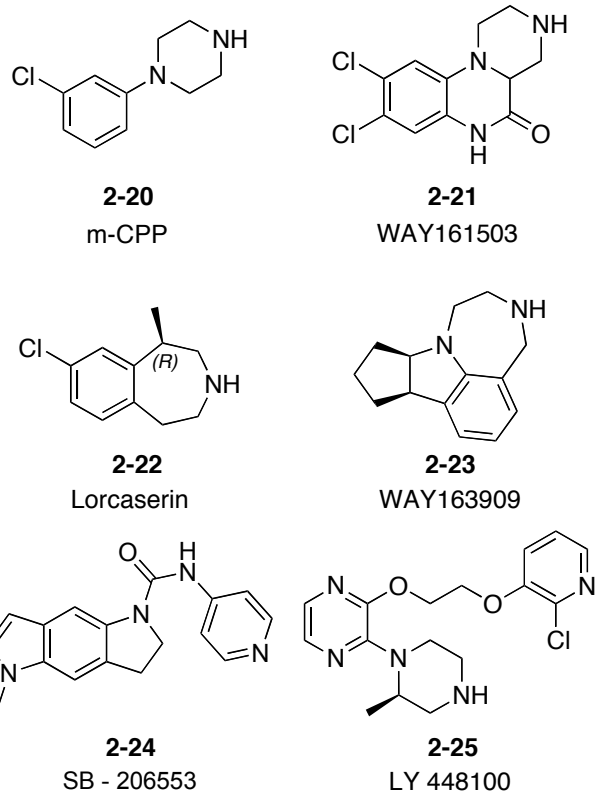


Figure 2.6: List of representative 5-HT_{2C} agonist.

Some of the 5-HT_{2C} agonist ligands were also evaluated for their therapeutic use for treating cocaine addiction and other CNS disorders. They are listed in the Fig. 2.6.

1-(3-Chlorophenyl)piperazine (m-CPP) **(2-20)** has shown modest selectivity towards 5-HT_{2C} (Ki = 20 nM) over 5-HT_{2A} (Ki = 199 nM). *In vivo* study of this

compound showed decrease in craving for cocaine,[30] but also increased the undesirable anxiety in response to m-CPP exposure.

WAY 161503 **(2-21)** is a potent and selective 5-HT_{2C} agonist (Ki = 4 nM). (7b*R*,10a*R*)- -octahydro-1*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole derivative (WAY 163909) **(2-23)** has been shown to be a full 5-HT_{2C} agonist with no efficacy at 5-HT_{2A}. This compound has shown to decrease the dopamine release, a typical characteristic of a drug targeting cocaine abuse.[31]

(*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, Lorcaserin **(2-22)**, was found to be 18 fold more selective towards 5-HT_{2C} over 5-HT_{2A} and is currently in Phase III clinical trails for the treatment of obesity.[32] SB – 206553 **(2-24)** was found to be the most selective 5-HT_{2C} ligand. (5-HT_{2C} = 19 nM *vs* 5-HT_{2A} = 1010 nM).

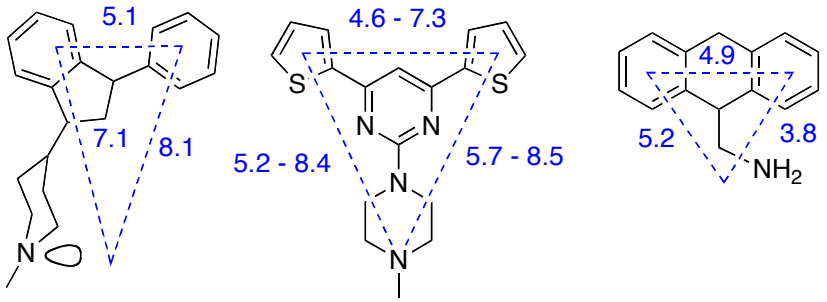
Researchers in GlaxoSmithKline recently reported their extensive medicinal chemistry efforts to find a selective 5-HT_{2C} agonist,[33] that could potentially be used for CNS diseases.

In summary, a large number of 5-HT ligands have failed in early or late stage clinical trials for treatment of various CNS disorders mainly because of lack of pharmacological selectivity between various subtypes of 5-HT receptors. Although many compounds have been developed to affect serotonin transmission, very few show much selectivity between 5-HT_{2A} and 5-HT_{2C} receptor subtypes. When stimulated, each of these receptor subtypes seems to provide an opposite effect on DA neurons from the other. Therefore, it is extremely important that compounds with high selectivity only for 5-HT_{2A} receptors be developed in order to further study the pharmaceutical potential of such drugs.

This suggests that there is a need for exploring novel synthetic scaffolds as therapeutic agents to effectively probe 5-HT_{2A} and 5-HT_{2C} ligands in clinical setting. This also indicates that a molecular level of understanding of 5-HT_{2A} and 5-HT_{2C} receptor proteins might be necessary to get clues about the structural differences between these receptors, which facilitate in designing novel ligands.

2.2.5. 5-HT_{2A} pharmacophore models

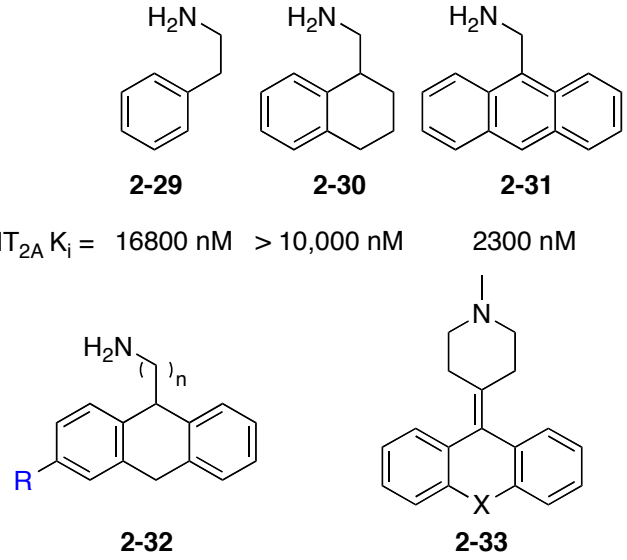
Over twenty years, a number of pharmacophore models have been proposed based on the structure-activity relationship studies on various kinds of 5-HT_{2A} receptor ligands. Recently, Bojarski *et al.* summarized the models proposed for all 5-HT receptor ligands.[34] The first pharmacophore model for 5-HT_{2A} was proposed in 1991.[35] Since then, the models have been revised many times. In 1994, Anderson *et al.* [36] proposed a three point pharmacophore **(2-26)** based on the indole and indane derivatives whereas Mokrosz *et al.* [37] proposed model based on piperazine **(2-27)** derivatives (Fig. 2.7). A large number of chemical compounds can fit the criteria of these models. Westkaemper *et al.* discussed a more defined pharmacophore model **(2-28)** based on the docking studies in rhodopsin crystal structure and through an extensive structure-activity relationship studies on 9-(aminomethyl)-9,10-dihydroantharacene (AMDA) (**2-32 a**).[38]



2-26 **2-27** **2-28**

Figure 2.7: Pharmacophore models of 5-HT_{2A} antagonists (numbers shown are spatial distance in Å).[34]

Westkaemper *et al.* did an extensive SAR study with AMDA and its analogues (Fig.2.8), which provided some clues about the structural features that need to be present in 5-HT_{2A} antagonists. Simple unsubstituted phenylethylamines **(2-29)**, (1,2,3,4-tetrahydronaphthalen-1-yl) methanamine **(2-30)** and anthracen-9-ylmethanamine **(2-31)** showed very low affinity for 5-HT_{2A} receptor, whereas 9-(aminomethyl)-9,10-dihydroantharacene **(2-32 a)** was shown to have an optimal affinity suggesting that the nature of the tricyclic ring system needed to have a substantial symmetrical fold in the central ring that is flanked by the two aryl systems to have higher affinities. It was also found that the spatial distance between both aromatic groups have to be 4.9 Å, whereas amine aromatic center distance have to be 3.8 Å and 5.2 Å respectively (**2-28**). It was also reported that alkyl (**2-32 c**) or alkylaryl (**2-32 d**) or halogen (**2-32 e**) substitution at 6-position of AMDA improved the activity several fold.



entry	R	5-HT$_{2A}$ K_i (nM)	n
a	H	20	1
b	H	13	3
c	C_6H_{13}	7	1
d	$(CH_2)_3Ph$	3.2	1
e	Br	1.3	1

entry	X	5-HT$_{2A}$ K_i (nM)
a	H, H	13
b	$-C_2H_5$	9
c	-O-	4
d	-CH=CH-	1.6
e	$-CH_2$	0.7

Figure 2.8: Summary of Structure-activity relationship study for tricyclic compounds.

2.2.6: Bioactive cyclopropane compounds

Previously, using cyclopropane scaffolds for therapeutic use was hindered mainly because of lack of effective methods for their synthesis. But recently, many number of novel methods for the synthesis of cyclopropanes have been developed, which led to the exploration of these carbocycles for various biological activities. It was found that many number of compounds with cyclopropane moiety have significant CNS activity.

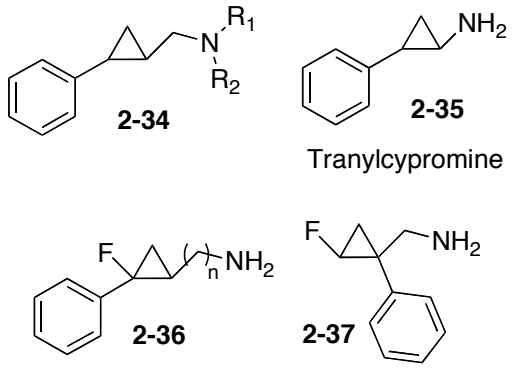
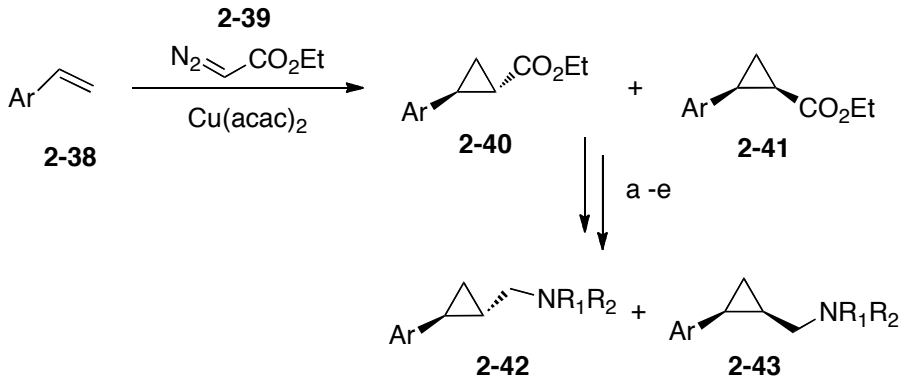


Figure 2.9: List of monoamine oxidase inhibitors.

In 1967, biological properties of aminomethyl-2-phenylcyclopropane derivatives **(2-34)** (Fig. 2.9) were evaluated and compared with tranylcypromine **(2-35)**. These compounds found to have a pharmacological function of inhibiting monoamine oxidase enzyme (MOI)[39]. Based on the structure of **2-34**, extensive SAR studies were performed. Researchers found that the presence of fluorine substitution on cyclopropane **2-36** and **2-37** will enhance their monoamine oxidase inhibition activity.[40]

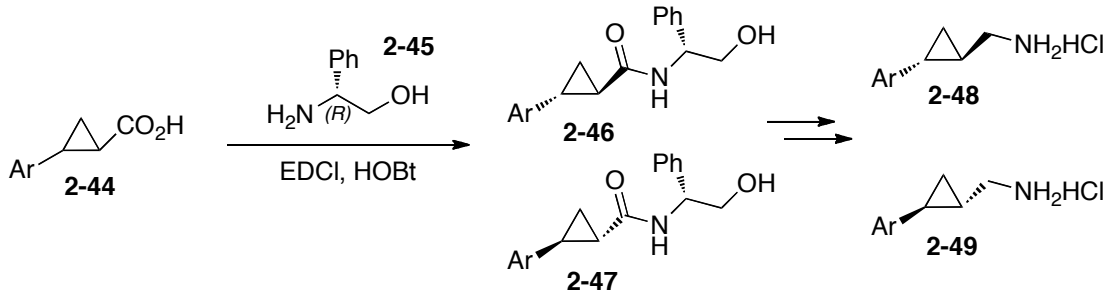
Recently, Kozikowski *et al.* reported the synthesis (Scheme 2.1) and pharmacological properties (Table 2.2) of *trans* aryl cyclopropyl amine compounds.[41,42] A series of 1-aminomethyl-2-phenylcyclopropane **(2-42)** derivatives were synthesized. In their initial experiments, they examined the effects of side chain homologation, stereochemistry, and amine substitution on the inhibition activity towards 5-HT_{2A} and 5-HT_{2C} receptors. Most of the compounds evaluated in this study were racemic mixtures, but some enantiopure compounds were also evaluated for activity.



a) 2N KOH/MeOH; b) $SOCl_2$; c) Liq. NH_3; d) BH_3.THF (1M in THF);
e) RCHO or $R_1R_2C=O$, $NaBH_3CN$)

Scheme 2.1: Kozikowski's racemic cyclopropylamine synthesis.

Kozikowski's synthesis starts with the cyclopropanation of ethyl diazoacetate **(2-39)** with styrene derivatives **(2-38)** in the presence of $Cu(acac)_2$ as a catalyst. The ester was produced as 2:1 mixture of *cis* **(2-41)** and *trans* **(2-40)** isomers. After separating the diastereomers *via* column chromatography, the esters were converted to their corresponding amine derivatives **2-41** and **2-41** by employing a standard sequence of reactions involving converting the ester to acid; acid was converted to acid chloride using $SOCl_2$ and then reacted with ammonia to give the corresponding amide. Borane reduction of the amide gave the desired amine products **2-41, 2-42** and **2-43** (Scheme 2.1).

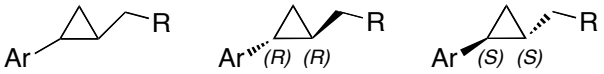


Scheme 2.2: Kozikowski's enantiopure cyclopropylamine synthesis

They were also able to synthesize enantiopure *trans* aryl cyclopropylamines through chiral resolution. Racemic carboxylic acid **2-44** was reacted with (*R*)-phenylglycinol **(2-45)**. The resultant diastereomeric mixture **2-46** and **2-47** were separated via column chromatography and then subjected to the same reaction conditions mentioned in Scheme 2.1 to get to the corresponding enantiopure cyclopropylamines **2-48** and **2-49** (Scheme 2.2).

2.2.6.1: SAR of *trans* aryl cyclopropylmethylamine compounds

A summary of some of Kozikowski's best lead compounds found in his study and their binding affinities to the 5-HT_{2A} and 5-HT_{2C} receptor are tabulated in Table 2.2. Racemic 1-aminomethyl-2-phenylcyclopropane **2-50** (Entry 1, Table 2.2) was found to be potent with 5 fold selectivity towards 5-HT_{2C} compared to 5-HT_{2A}. When enantiopure compounds **2-51** and **2-52** were evaluated, it was found that the activity lies in (1*S*, 2*S*) isomer. Methyl or benzyl substitution on the amine decreased inhibition activity (Entry 4 and 5, Table 2.2). 2-naphthyl substitution (Entry 6, Table 2.2) did not improve potency. As a general trend, halogen substitution at 2- and 4- position on the aryl group (Entry 7 to 13, Table 2.2) enhanced the inhibition activity many fold. The compound with fluoro substitution at the 2- position was found to be the most potent (0.62 nM against 5-HT_{2A}) (entry 13, Table 2.2). It was noted that the selectivity between 5-HT_{2A} and 5-HT_{2C} receptor inhibition was lacking in their most efficacious compounds. Evaluating racemic mixtures for inhibition activity might be the reason for poor selectivity profile.



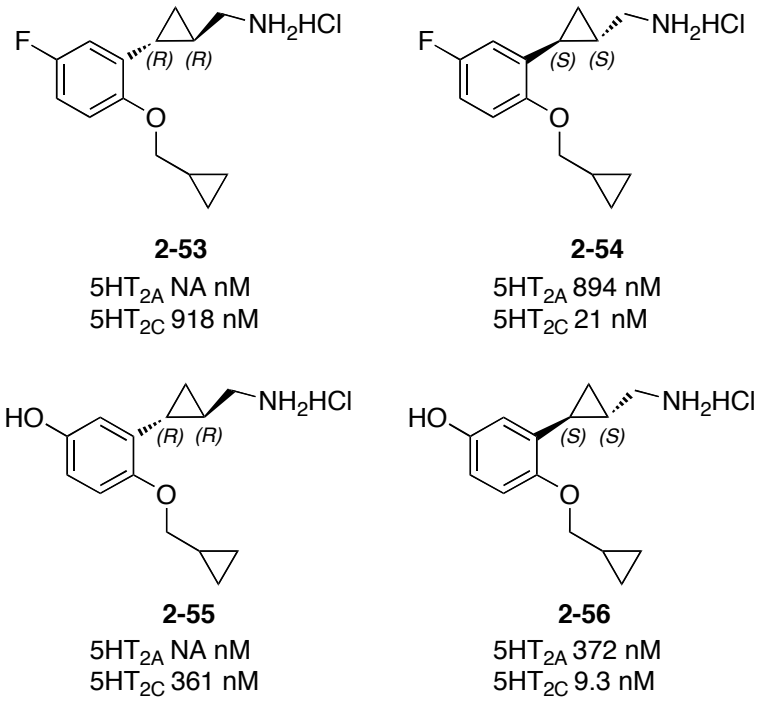
2-50 **2-51** **2-52**

Entry	Isomer	Aryl	R	5-HT_{2A}	5-HT_{2C}	2A/2C
1	±	Ph	NH_2	49.7	9.6	5
2	(1*S*, 2*S*)	Ph	NH_2	44.3	4.5	10
3	(1*R*, 2*R*)	Ph	NH_2	1685	280	6
4	±	Ph	NHMe	3714	717.6	5
5	±	Ph	NHBz	123328	7458	16
6	±	2-naphthyl	NH_2	951.4	6749	0.1
7	±	4-BrPh	NH_2	1061	179.9	6
8	±	3-BrPh	NH_2	29.5	1.8	16
9	(1*S*, 2*S*)	2-BrPh	NH_2	48.7	11.4	4
10	(1*R*, 2*R*)	2-BrPh	NH_2	2271	307	7
11	±	4-FPh	NH_2	7.1	7.4	1
12	±	3-FPh	NH_2	63.4	63.2	1
13	±	2-FPh	NH_2	0.62	0.66	1

Table 2.2: K_i values (nM ± SEM) of *trans* cyclopropylamine analogues in binding to 5-HT_{2A} and 5-HT_{2C} receptors. (Kozikowski *et al.*)

Kozikowski *et al.* found a novel class of compounds **2-53**, **2-54**, **2-55 and 2-56**, through an extensive medicinal chemistry study and high-throughput screening (HTS),

which are efficacious and selective for 5-HT_{2C} receptor (Figure 2.10). These compounds have a potential use in treatment of Schizophrenia.[43]



2-53
$5HT_{2A}$ NA nM
$5HT_{2C}$ 918 nM

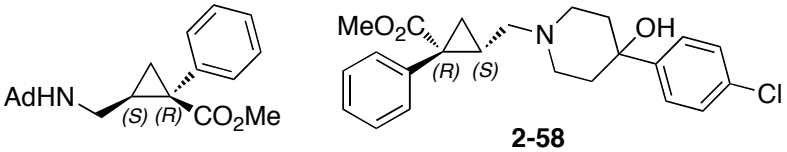
2-54
$5HT_{2A}$ 894 nM
$5HT_{2C}$ 21 nM

2-55
$5HT_{2A}$ NA nM
$5HT_{2C}$ 361 nM

2-56
$5HT_{2A}$ 372 nM
$5HT_{2C}$ 9.3 nM

Figure 2.10: List of 5-HT_{2C} selective ligands for the treatment of Schizophrenia. (NA = Not Available)

Ronsisvalle *et al.* reported potent and selective σ-ligands (Fig. 2.11) which contain the cyclopropane moiety.[44-48] These compounds have shown to possess anti-opiod effects *in vivo*.



2-57

σ_1 4 nM
σ_2 32 nM

2-58
MR200

$5HT_{2A}$ 1025 nM
$5HT_{2C}$ >10K nM
σ_1 1.5 nM
σ_2 21.9 nM

Figure 2.11: Ronsisvalle's selective σ-ligands.

2.2.7: Application of computational modeling in drug discovery and development

Drug discovery is an interdisciplinary, time consuming and expensive process. The costs of pharmaceutical R&D have increased dramatically. The number of drugs approved each year has dropped in the past decade,[49] despite much scientific advancement in the way novel bioactive molecules are being generated. After analyzing 415,284 molecules reported in Journal of Medicinal Chemistry (JMC) from 1959 to 2009, it was found that many compounds synthesized were not 'drug-like' mainly because of relying heavily on 'easy' chemistry. It was suggested that novel structural scaffolds with desirable Absorption Distribution Metabolism Excretion (ADME) properties need to be explored for which new methods of synthesis need to be developed. Greater emphasis on the art of synthesis in medicinal chemistry would dramatically improve the number of novel drugs in the clinic.

Advances in computational techniques enabled many *in silico* methods, which accelerated new target selection and lead optimization in the drug discovery process.[50]

Some drugs such as Captopril, Dorzolamine, Saquinavir, Zanamivir, Oseltamivir, Aliskiren, Boceprevir, Nolatrexed, TM-005, LY-517717, Rupintrivir and NVP-AUY922 were discovered and/or optimized using computer-aided drug design and are now being approved for clinical use or in clinical trails. Thus, application of various computational tools in the process of drug discovery and development has proved to be very effective.[51,52] Modeling approaches provide structural information about the molecular level of interactions between drug compounds and target protein. A wide range of computational tools has been developed in the past couple of decades, and if used systematically, could enhance the drug discovery process.

Computational modeling can enhance the rational drug design in many ways. A few examples are listed below:

1) When the structure of the target protein is not known

a) A 'pharmacophore model' can be constructed using existing activity data generated by SAR-directed organic synthesis and experimental high-throughput screening (HTS) by modifying and repositioning key structural features of the ligands. These models can potentially be used as templates and novel structural scaffolds can be designed.

b) A ligand-based approach can be employed, in which similarity matching can be done against known actives for the target of interest.

c) A homology model of the protein of interest can be built based on a structurally and functionally similar protein and can then be used for design of novel ligands either by high-throughput virtual screening or by performing docking experiments.

2) When the structure of the target protein is known, then

a) Molecular docking studies can be done by docking potential ligands in the binding site and by rationalizing or predicting activities. This method has been used extensively in the lead optimization processes.

b) If any active ligands are not known, then computational virtual screening can be employed.

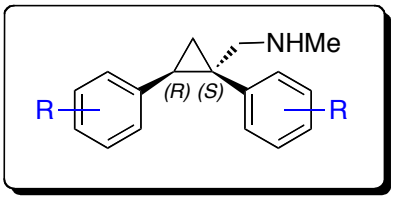
Apart from computational methods, many computational tools are also available to predict the pharmacokinetic properties of ligands, which can guide the lead optimization process in the right direction. Lipinski rule of five[53] and Murcko guiding principles[49] motivated scientists to consider ADME properties early in the process of drug discovery to avoid costly late-stage clinical failures.

2.2.8 Previous synthesis of novel class of 5-HT_{2A} receptor antagonists in the Davies group - Diaryl cyclopropylmethylamines

The primary goal of this project when initiated in 2006 was to find small molecule therapeutic agents that would have high potency and selectivity towards the 5-HT_{2A} receptor over the 5-HT_{2C} receptor. Medicinal chemistry and computational modeling were performed in the Davies' group; *in vitro* evaluation of novel compounds was performed in Steve Childer's laboratory and *in vivo* evaluation in non-human primate model was performed in Mike Nader's laboratory at Wake Forest University.

It was hypothesized that diarylcyclopropylmethylamine (**2-59**) compounds (Fig. 2.12) might have potential to be 5-HT_{2A} receptor inhibitors and could possibly be used as therapeutic agents for treating cocaine addiction. Even though this novel class of compounds are structurally unique and very different from the typical classes of 5-HT_{2A}

receptor antagonists, they still fit well with the three point pharmacophore model of 5-HT_{2A} receptor ligands.[54] Preliminary three-dimensional analysis of the lowest energy conformation for a diaryl cyclopropylamine (both enantiomers) (Fig 2.13) indicated that the cyclopropyl ring orients the two-aryl groups in an angular fashion, a feature that was thought to be responsible for bioactivity in the case of tricyclic compounds (mentioned in Fig. 2.8). Moreover, the spatial distance between the two aryl groups and amine was with in the distances defined in the previous pharmacophore model proposed for 5-HT_{2A} ligands. It was also hypothesized that the bioactivity for both enantiomers would be considerably different mainly because of the difference in their three dimensional orientation in the receptor active site which can be exploited to achieve the selectivity between two subtypes of 5-HT receptors. This structurally unique scaffold can be synthesized by utilizing rhodium (II) carbene-mediated catalytic asymmetric intermolecular cyclopropanation methodology developed previously in the Davies group.



2-59

Fig 2.12: Novel 5-HT_{2A} receptor antagonists designed in the Davies group.

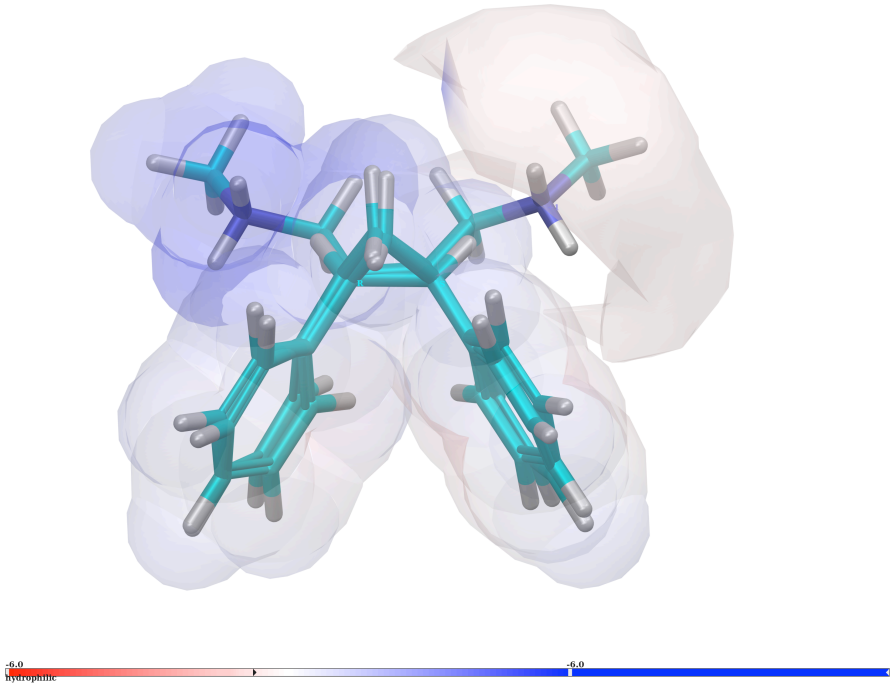


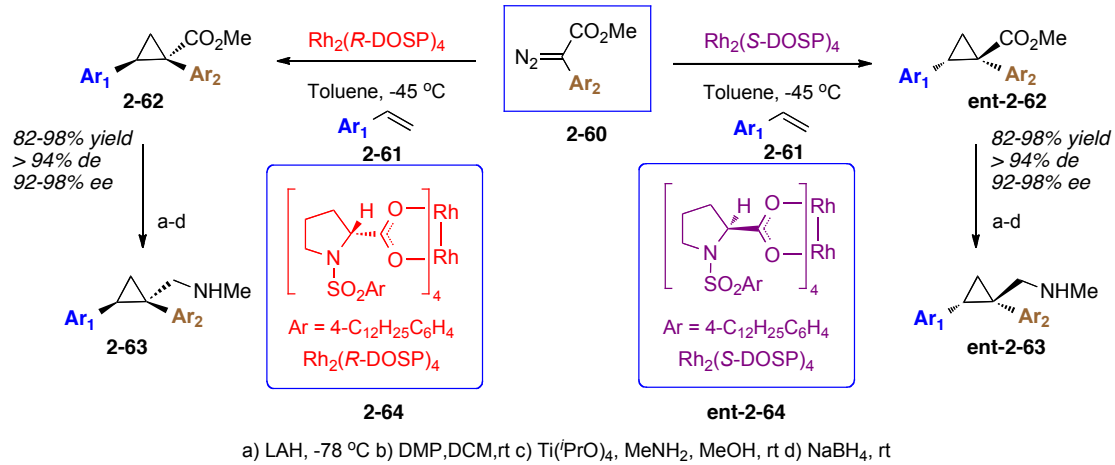
Fig 2.13: Lowest energy conformation of diarylcyclopropylamine (Both enantiomers superimposed).

Previously, an efficient process for the synthesis of a series of 1,2-diarylcyclopropylmethylamines was also developed (Scheme 2.3) in the Davies group.

The reaction of aryl diazoacetate **(2-60)** with styrene derivatives **2-61** in the presence of prolinate based chiral catalysts, Rh_2(*S*-DOSP)$_4$ **ent-2-64** or Rh_2(*R*-DOSP)$_4$ **2-64** generated the diarylcyclopropane ester compound (**ent-2-62** or **2-62**) in yields ranging from 82-98%. This reaction proceeds with a very high levels of diastereo (>95% de) and enantioinduction (>90%) at room temperature. The enantioselectivity was improved further when the reaction was performed at lower temperature (-45 ^{o}C). In all the cases, diaryl cyclopropane ester compounds can be enantioenriched to enantiopurity upon single recrystalization.

In the subsequent steps, the ester functionality is reduced to an alcohol using lithium aluminum hydride and quenched with sodium sulfate decahydrate, and then oxidized to the corresponding aldehyde using the Dess Martin Periodinane (DMP) reagent in a one-pot procedure in moderate yields. The reductive amination of the cyclopropane aldehyde with methylamine in the presence of titanium(IV) isopropoxide and sodium borohydride generated the diarylcyclopropylmethylamines (**2-63** or **ent-2-63)**, in good yields. The diarylcyclopropylmethylamines were then directly converted to the corresponding hydrochloride, fumarate or tartrate salts using a stoichiometric amount of hydrochloric, fumaric, or tartric acid.

The only diastereomer formed in the asymmetric cyclopropanation reaction has both aryl groups oriented in a *cis* configuration to each other. The absolute stereochemistry for the diarylcyclopropylamines (CP-amine) generated using Rh_2(*S*-DOSP)$_4$ **ent-2-63** was found to have (1*R*, 2*S*) configuration, whereas the cyclopropylamine obtained by using Rh_2(*R*-DOSP)$_4$ **2-63** was found to have (1*S*, 2*R*) configuration, assigned based on analogy.

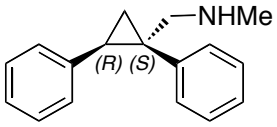


Scheme 2.3: Diarylcyclopropylmethylamine compound synthesis.

There are many advantages of applying this novel cyclopropanation methodology in the synthesis of pharmaceutically relevant compounds. One obvious advantage is selectivity. This reaction is regio, diastereo and enantioselective. Both enantiomers of the diarylcyclopropylmethylamines (**2-63** and **ent-2-63**) can be accessed because of the availability of both enantiomers of the chiral catalyst (Rh_2(*S*-DOSP)$_4$ **ent-2-64** and Rh_2(*R*-DOSP)$_4$ **2-64**, which allows the study of subtle differences in the bioactivity of both enantiomers. This reaction can be conducted routinely with extremely low catalyst loading,[55] thus achieving a million turnover numbers. This high catalyst efficiency makes this route an environmentally benign method. This reaction can be scaled-up to multi-gram quantities, while retaining the same efficiency in selectivity. Over last few years, the scope and limitations of this methodology was studied in the Davies group (described in a separate section in chapter 3). This reaction can tolerate a range of functional groups; thus, a diverse library of compounds with the diaryl cyclopropane core can be synthesized. The aryldiazo compounds, Rh (II) catalysts and cyclopropane products are air and moisture stable. Dirhodium catalysts can be stored at room temperature without diminishing its efficiency. Wider arrays of other chiral catalysts are also available and can be explored in this reaction in the cases where **2-64** did not work. The ability to synthesize these cyclopropylamine compounds in relatively few steps marks their potential as viable pharmaceutical agents in future drug discovery.

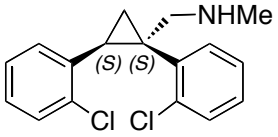
2.2.9 SAR of previously synthesized diaryl cyclopropylamines.

Considering the practicality and efficiency of the Davies cyclopropanation reaction, a library of diarylcyclopropylmethylamine compounds (both enantiomers) was synthesized. In the initial series of compounds, the diversity within structural entities was introduced by modifying the substituents on the aryl group or amine. 5-HT_{2A} receptor-binding affinities were determined in Steve Chider's laboratory.



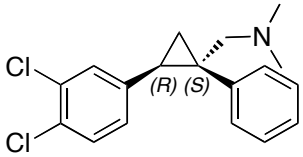
2-64 (1*S*,2*R*) HD-230 (10K,1K)

ent-2-64 (1*R*,2*S*) HD-229 (10K,10K)



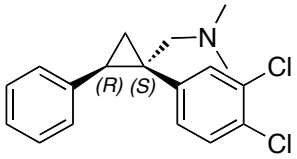
2-65 (1*S*,2*S*) HD-295 (4317,1K)

ent-2-65 (1*R*,2*R*) HD-296 (10K,1K)



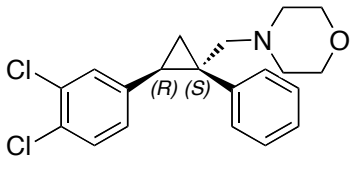
2-66 (1*S*,2*R*) HD-209 (3871,1K)

ent-2-66 (1*R*,2*S*) HD-207 (10K,1K)



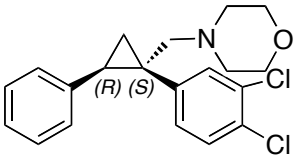
2-67 (1*S*,2*R*) HD-210 (594,1K)

ent-2-67 (1*R*,2*S*) HD-208 (437,500)



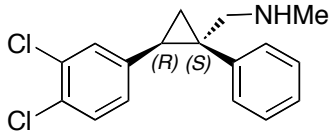
2-68 (1*S*,2*R*) HD-213 (1500,10K)

ent-2-68 (1*R*,2*S*) HD-211 (10K,10K)



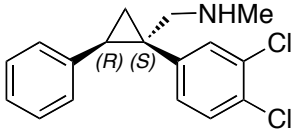
2-69 (1*S*,2*R*) HD-214 (820,10K)

ent-2-69 (1*R*,2*S*) HD-212 (10K,10K)



2-70 (1*S*,2*R*) HD-220 (206,564)

ent-2-70 (1*R*,2*S*) HD-219 (7330,10K)



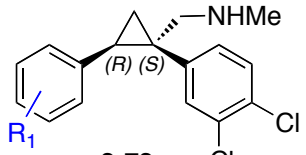
2-71 (1*S*,2*R*) HD-222 (109,904)

ent-2-71 (1*R*,2*S*) HD-221 (2996,10K)

Figure 2.14: SAR of first set of compounds (K_i values in nM for 5-HT_{2A} and 5-HT_{2C}) (Compounds were synthesized by Tim Gregg) *(HD-number = is the reference code given to each sample when sent for in vitro analysis)*

Both enantiomers of the unsubstituted 1,2-diphenylcyclopropyl)-*N*-methylmethanamine (**HD-230** & **HD-229**) were inactive (Fig 2.14). Based on the SAR study on AMDA **2-32**, halogen was introduced into the scaffold. Chloro substitution on both aryl groups at two position **HD-295** and **HD-296** did not led to any increase in activity, whereas chloro substitution at three and four positions of either of the aryl groups, led to 50 fold enhancement in 5-HT_{2A} and 5-HT_{2C} inhibition activity. A quick SAR study on compounds with various substitutions on amine revealed that secondary methylamine functionality **HD-219** to **HD-222** would improve the binding affinities at the 5-HT_{2A} receptor 5-10 fold as compared to tertiary dialkyl amines **HD-207** to **HD-210** and tertiary morpholine **HD-211** to **HD-214** functionality. A consistent general trend in the bioactivity difference between two enantiomers was also observed. The diaryl cyclopropanes with (1*S*, 2*R*) configuration synthesized using Rh_2(*R*-DOSP)$_4$ as catalyst were 20-50 fold more active at the 5-HT receptors than the enantiomer with (1*R*, 2*S*) configuration , which were obtained using Rh_2(*S*-DOSP)$_4$ as catalyst.

Based on these preliminary results, a systematic study of trends in activity was done by introducing various substitution patterns on one of the aryl moiety by keeping 3,4-dichloro substitution on the other aryl group.



2-72

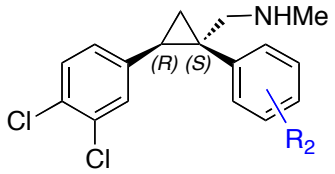
Entry	Analogue	R_1	Isomer	5-HT_{2A}	5-HT_{2C}
1	HD-309	3,4-OCH_2O	(1*S*, 2*R*)	1570 ± 640	>1000
2	HD-310	3,4-OCH_2O	(1*R*, 2*S*)	>1000	>1000
3	HD-250	4-OCH_3	(1*S*, 2*R*)	840 ± 160	>1000
4	HD-251	4-OCH_3	(1*R*, 2*S*)	>10,000	>10,000
5	HD-307	4-CF_3	(1*S*, 2*R*)	549 ± 43	699 ± 78
6	HD-308	4-CF_3	(1*R*, 2*S*)	>1000	>1000
7	HD-291	2-Cl	(1*S*, 2*R*)	498 ± 81	>10,000
8	HD-292	2-Cl	(1*R*, 2*S*)	1070 ± 80	>1000
9	HD-222	H	(1*S*, 2*R*)	109	904
10	HD-221	H	(1*R*, 2*S*)	3000	>10,000
11	HD-255	3,4 -CH=CH-	(1*S*, 2*R*)	98.7 ± 4.2	>1000
12	HD-256	3,4 -CH=CH-	(1*R*, 2*S*)	1640 ± 320	>1000

Table 2.3: SAR of second set of compounds (K_i values in nM for 5-HT_{2A} and 5-HT_{2C}) (Compounds were synthesized by Josh Alford, Tim Gregg and Jeremy Olson).

Cyclopropanation reactions of a series of substituted styrenes with 3,4-dichlorophenyl diazoacetate followed by reduction, oxidation and reductive amination sequence (Scheme 2.3) gave a series of compounds. *In vitro* assay for inhibition of 5-HT_{2A} and 5-HT_{2C} receptor showed some interesting trends (Table 2.3). The isomer with (1*S*, 2*R*) configuration consistently showed better inhibition activity as compared to its' opposite enantiomer. It appears that the bioactivity is very sensitive to the position and kind of substitution present on the aryl group. The compounds, in which aryl group with electron donating substituents such as methoxy **HD-250** or benzo[*d*][1,3]dioxole **HD-309** moiety showed reasonable activity of 1570 nM and 840 nM respectively (entry1 & 3 in Table 2.3). The trifluoromethyl substitution at the 4 position (**HD-307)** and chloro substitution at the 2 position (**HD-291)** on the aryl group improved the inhibition activity one fold (entry 5 & 7 in Table 2.3), whereas the cyclopropylamine compounds derived from unsubstituted styrene **HD-222** & 2-napthyl styrene **HD-255** showed a five fold improvement, with activity of 109 nM and 98 nM, respectively (entry 9 & 11). A 2-naphthyl group was introduced with the idea of improving hydrophobic, pi-pi interactions in the active site of 5-HT receptor. The selectivity between 5-HT_{2A} and 5-HT_{2C} was not comparable as all the compounds in Table 2.3 were not efficacious.

To improve the activity further, a new series of diaryl cyclopropylamine compounds were synthesized. In this case, various aryl substituted diazoacetate

compounds were reacted with 3,4-dichloro styrene to obtain **2-73** (Table 2.4). Again, having 2-naphthyl substitution **HD-253** (Entry 7, Table 2.4) was found to be optimal, which showed inhibition activity of 51 nm towards 5-HT_{2A} receptor.



Entry	Analogue	R_2	Isomer	5-HT_{2A}	5-HT_{2C}
1	HD-258	4-OCH_3	(1*S*, 2*R*)	1050 ± 110	>1000
2	HD-259	4-OCH_3	(1*R*, 2*S*)	155 ± 20	346 ± 79
3	HD-293	2-Cl	(1*S*, 2*R*)	561 ± 74	>1000
4	HD-294	2-Cl	(1*R*, 2*S*)	>1000	>1000
5	HD-220	H	(1*S*, 2*R*)	206	564
6	HD-219	H	(1*R*, 2*S*)	7330	>10,000
7	HD-253	3,4 -CH=CH-	(1*S*, 2*R*)	51.3 ± 5.0	397 ± 69
8	HD-254	3,4 -CH=CH-	(1*R*, 2*S*)	1160 ± 33	730 ± 220

Table 2.4: SAR of third set of compounds (K_i values in nM for 5-HT_{2A} and 5-HT_{2C}) (Compounds were synthesized by Josh Alford, Tim Gregg and Jeremy Olson).

From this series, it was quite evident that adding halogen substitution at the 3- and 4- position of either of the aryl groups, as well as adding hydrophobic functionality

resulted in improved activity. This led to the synthesis of a fourth set of compounds in which chloro or bromo substituents were introduced in both aryl groups (Fig. 2.15).

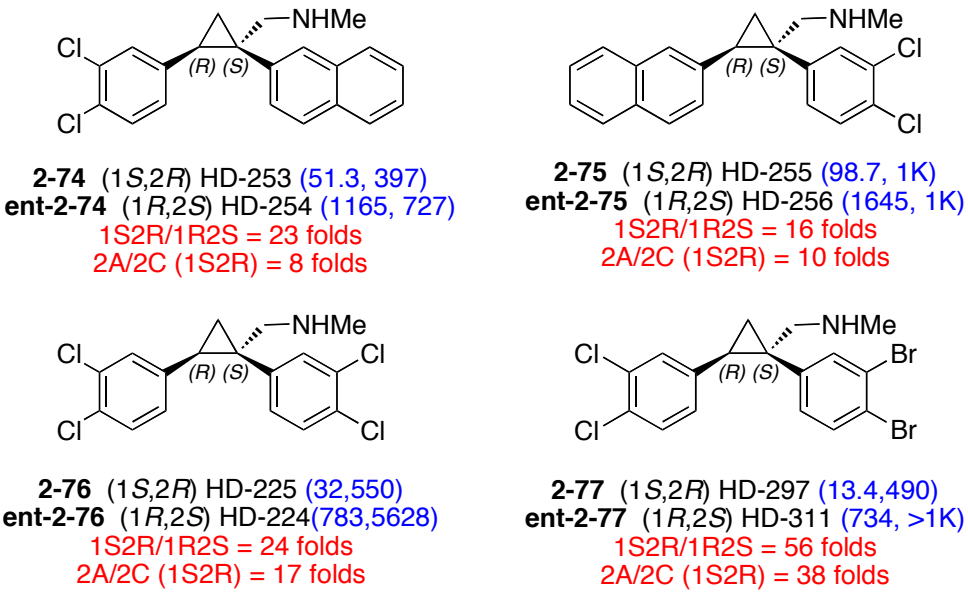
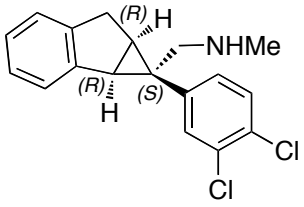


Figure 2.15: SAR of fourth set of compounds (K_i values in nM for 5-HT_{2A} and 5-HT_{2C}) (Compounds were synthesized by Josh Alford, Tim Gregg and Jeremy Olson)

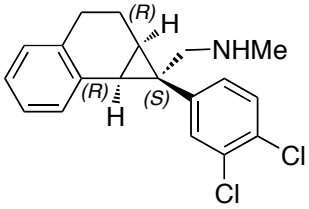
1-((1*S*,2*R*)-1,2-bis(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine **(HD-225)** was found to be potent at 5-HT_{2A} receptors (K_i 32 nM). It also displayed significant selectivity among isomers. (1*S*, 2*R*) isomer was found to be 24 fold more active than (1*R*, 2*S*) isomer. A considerable selectivity between two subtypes of 5-HT receptors (17-fold) was also observed. Recently, a structurally similar compound, 1-((1*S*, 2*R*)-1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine **(HD-297)** was also synthesized and found to have even better potency (k_i 13 nM) and/or selectivity (38 fold) than **HD-225**.

It was also hypothesized that imposing a conformation constraint on the diarylcyclopropane might lead to enhanced receptor specificity. To test this hypothesis, novel diaryl cyclopropylamine compounds (Fig. 2.16) were also synthesized.

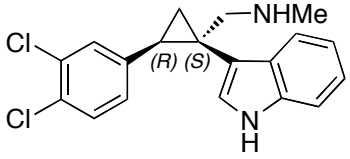
The cyclopropanation reaction of 3,4-dichloro phenyl diazo acetate with indene and 1,2 dihydronapthalene gave products which were then converted to their corresponding amines (**HD-301, HD-302, HD-303** and **HD-304**) using the same synthetic scheme described earlier. An indole cyclopropane derivative (**HD-305** & **HD-306**) was also synthesized. It appears that restricting the carbon-carbon bond rotation between cyclopropane carbon and aryl carbon lead to reduced activity. We were intrigued by the fact that none of these compounds were found to be efficacious, probably because of steric and electrostatic repulsions with the residues in the active pocket of 5-HT_{2A} receptor.



2-78 (1*S*,1a*R*,6a*R*) HD-301 (1666, >1K)
ent-2-78 (1*R*,1a*S*,6a*S*) HD-302 (10K, >1K)



2-79 (1*S*,1a*R*,7b*R*) HD-303 (1674, >1K)
ent-2-79 (1*R*,1a*S*,7b*S*) HD-304 (6833, >1K)



2-80 (1*S*,2*R*) HD-305 (291, >500)
ent-2-80 (1*R*,2*S*) HD-306 (10K, >1K)

Figure 2.16: SAR of fifth set of compounds (K_i values in nM for 5-HT_{2A} and 5-HT_{2C}) (Compounds were synthesized by Josh Alford).

In conclusion, through extensive synthetic efforts and a systematic SAR study, four lead compounds **HD-225, HD-253, HD-255,** and **HD-297** (K_i 5-HT_{2A} = < 100 nM) were identified in the Davies group. Many number of compounds could be synthesized due to the robust nature of the cyclopropanation methodology, which warrants a guided approach that would allow us to make informed decisions about the type of structural modifications to make on lead compounds to enhance the efficacy and selectivity further. This approach would accelerate our drug discovery efforts towards finding a clinical candidate for the treatment of cocaine addiction.

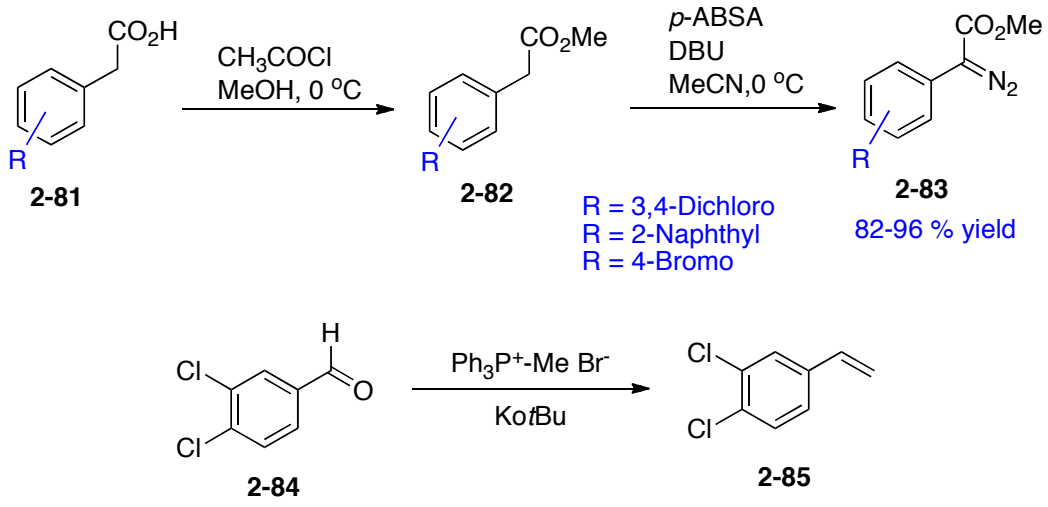
2.3 Results and discussions

2.3.1 Synthesis of new series of diarylcyclopropylmethylamines – Lead optimization and activity trend rationalization

As a part of the ongoing project, a new set of diarylcyclopropylamine compounds were designed and synthesized with the aim of further improving efficacy and selectivity towards 5-HT_{2A} receptor. One of the major driving forces for the synthesis of this new set of compounds comes from the structural information gained through extensive computational modeling studies. This study revealed that the binding pocket of 5-HT_{2A} receptor is sufficiently large enough to fit bulky cyclopropylmethyl amines. It was also

found that the size and three-dimensional shape of the 5-HT_{2A} receptor-binding site differ considerably from that for the 5-HT_{2C} receptor. This led to the hypothesis that greater efficacy and selectivity for ligand could be achieved by increasing bulk around the cyclopropane moiety.

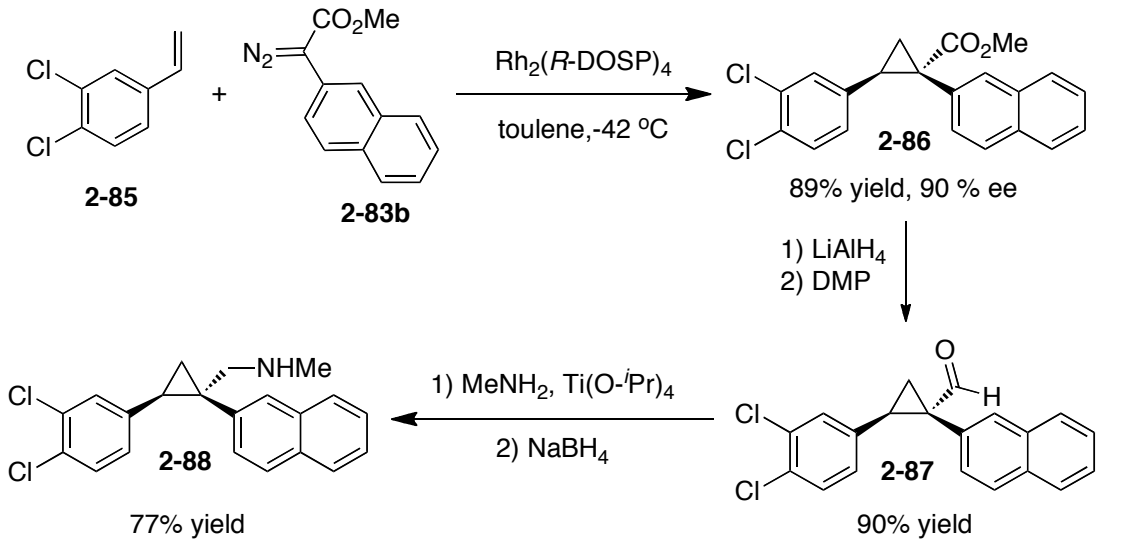
First, a large-scale synthesis of one of the lead compounds (**HD-255**) was done following the synthetic Scheme 2.5. The starting materials for the cyclopropanation reaction were synthesized following the Scheme 2.4. The corresponding 2-phenyl ethanoic acids (**2-81**) were esterified in the presence of acetyl chloride and methanol to produce the esters (**2-82**) in quantitative yields. Diazo transfer in the presence of *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and the base 1,8-diazabicycloundec-7-ene (DBU) in acetonitrile yielded the corresponding diazo compounds (**2-83**) in good to excellent yields. These reactions were repeated several times throughout the project. The diazo compounds used in the project were stable at room temperature. This reaction was performed several times in 80 g scale.



Scheme 2.4: Synthesis of aryldiazo acetates and substituted styrene compounds.

The substituted styrenes (**2-85**) were synthesized from the corresponding commercially available benzaldehydes (**2-84**) through a Wittig reaction with methyl triphenylphosphonium bromide and potassium *tert*-butoxide. Typically, 60-70% yields were obtained in this reaction. 1,2-dichloro-4-vinylbenzene (**2-85**) was synthesized several times in 50 g scale.

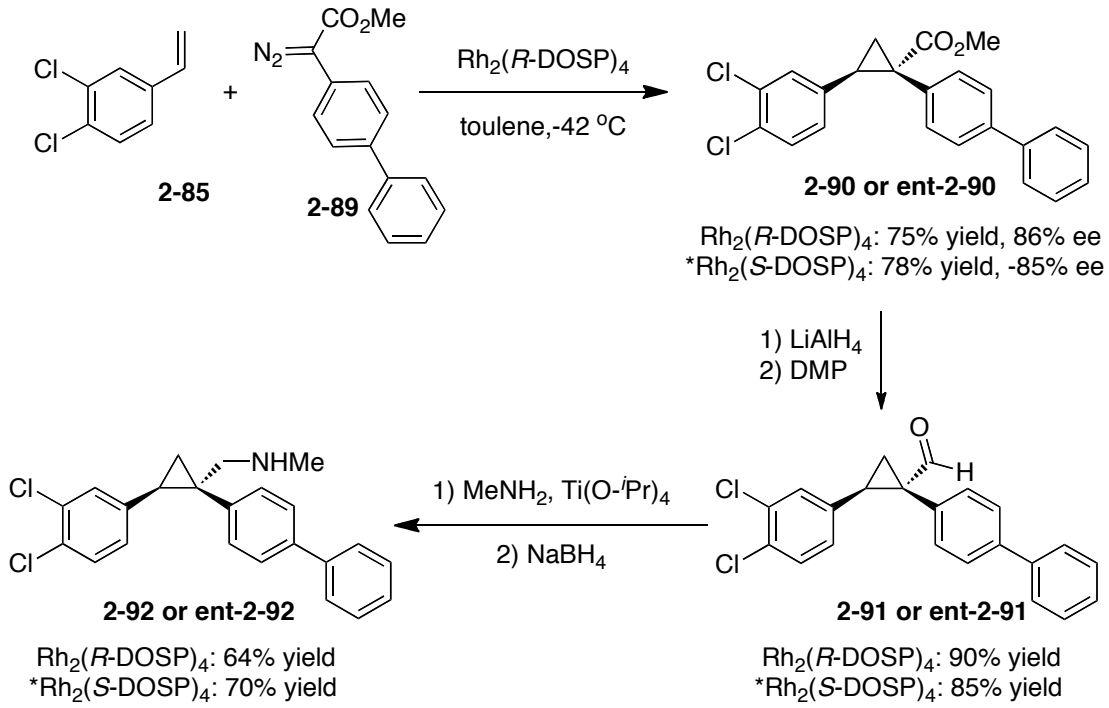
The intermolecular cyclopropanation of 3,4-dichlorostyrene (**2-85**) with methyl 2-diazo-2-(naphthalen-2-yl)acetate **(2-83b)** in the presence of catalytic amount of Rh_2(*R*-DOSP)$_4$ at - 42 ^oC generated the diarylcyclopropane product **(2-86)** in 89% yield and 90% ee as a single diastereomer. The enantioenriched material was then reduced to corresponding alcohol using lithium aluminum hydride and quenched with sodium sulfate decahydrate, and then subsequently oxidized to the corresponding aldehyde **(2-87)** using the Dess Martin Periodinane (DMP) reagent in a one-pot procedure in excellent yield. The reductive amination of the aldehyde with methylamine in the presence of titanium(IV) isopropoxide and sodium borohydride generated the diarylcyclopropylmethylamines **(2-88)** in 77% yield. The diaryl cyclopropylmethylamine was directly converted to the corresponding fumarate salt using a stoichiometric amount of furamic acid. This reaction was performed in 10 mmol scale to obtain ~ 1 g of final amine product, which was sent for *in vivo* evaluation (*in vivo* data will be discussed in the later sections).



Scheme 2.5: Large scale synthesis of 1-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanamine.

Based on the computational modeling results, a new series of enantiopure cyclopropylamines with biphenyl or naphthyl functionality were synthesized.

The first set of enantiomers synthesized was **2-92** and **ent-2-92**. The cyclopropanation reaction of 3,4-dichlorostyrene (**2-85**) with biphenyl diazoacetate (**2-89**) in the presence of 1 mol% Rh_2(*R*-DOSP)$_4$ or Rh_2(*S*-DOSP)$_4$ gave the corresponding cyclopropane esters **2-90** or **ent-2-90** in good yields. This reaction was later scaled-up to 7 mmol scale and enantioselectivity was improved to 92%. Both enantiomers were carried on to synthesize their corresponding amines following Scheme 2.6.



* Opposite enantiomer was formed.

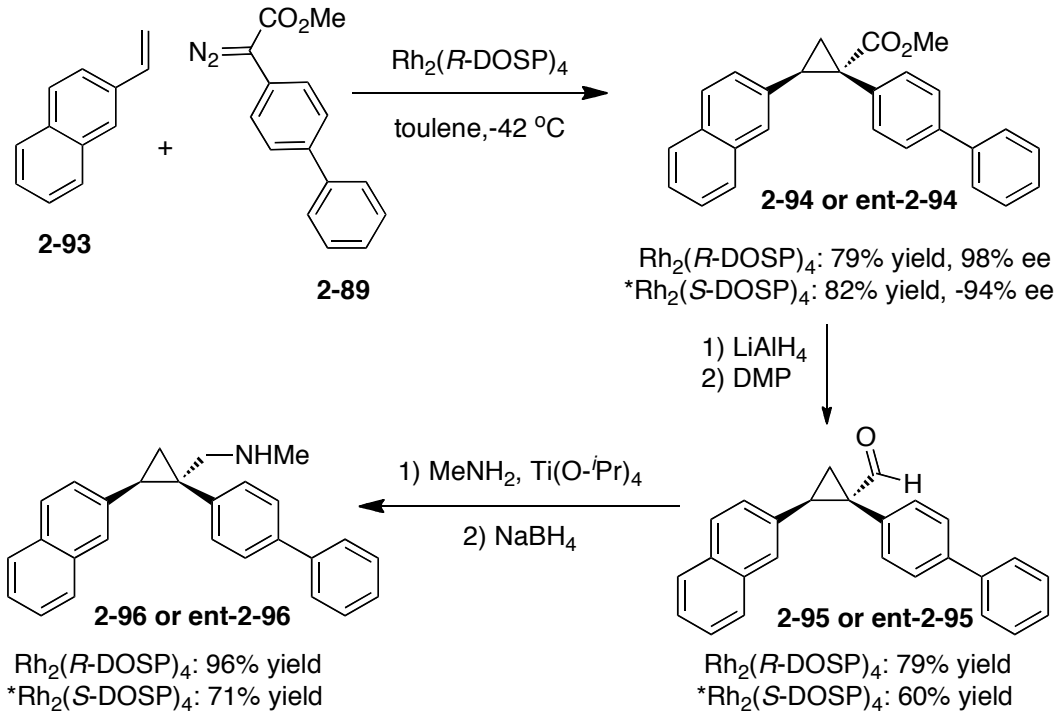
Scheme 2.6: Synthesis of both enantiomers of 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine.

While performing NMR analysis of this set of compounds, it was observed that these novel compounds are very hydrophobic and not quite soluble in MeOH. Based on a series of solubility experiments, it was concluded that the solubility of the diaryl cyclopropylamine compounds could be improved dramatically by formulating them with tartrate salt rather than with fumerate salt. Tartrate salts of **2-92** and **ent-2-92** were made and sent to Steve Childer's lab, to obtain binding affinity data.

As shown in section 2.2.9, the four lead compounds discovered in the Davies' lab have either halogen functionality or naphthyl functionality. In an effort to improve the

efficacy and selectivity, keeping naphthyl and halogen functionality was essential. At the same time, more bulky groups were needed to be introduced into the lead scaffold.

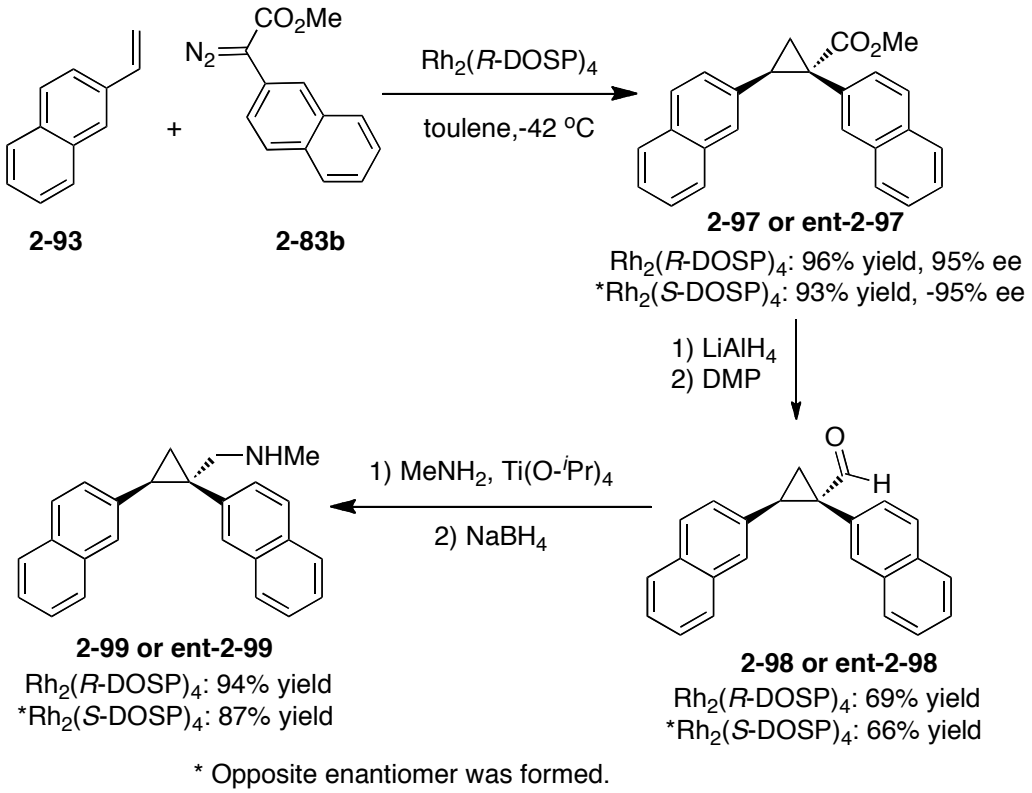
In the next set of compounds, naphthyl functionality was introduced. 2-vinylnaphthalene was commercially available and was used as is. The cyclopropanation reaction of 2-vinylnaphthalene **(2-93)** with biphenyl diazoacetate in the presence of chiral dirhodium catalyst gave corresponding cyclopropane product in good yields and excellent enantioselectivities. The methyl ester was converted to amine by reduction, oxidation followed by reductive amination sequence to get the product in very good yields (Scheme 2.7).



* Opposite enantiomer was formed.

Scheme 2.7: Synthesis of both enantiomers of 1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl) cyclopropyl)-*N*-methylmethanamine.

Last set of compounds synthesized in this series has two naphthyl groups. The intermolecular cyclopropanation reaction of 2-vinylnaphthalene with naphthyl diazocatate gave the corresponding cyclopropane product in quantitative yields and with excellent stereo selectivity. The products formed in the reaction found to have 95% ee and were carried all the way to amine following the same synthetic sequence described before.

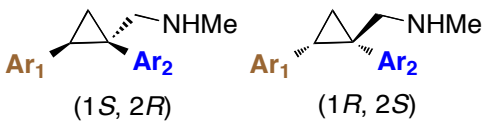


Scheme 2.8: Synthesis of both enantiomers of 1,2-di(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanamine.

2.3.2 *In vitro* data for new series of diarylcyclopropylmethylamines

Binding data obtained for these novel set of compounds was summarized in Table 2.5. **HD-323**, compound with 3,4-dichloro phenyl functionality and biphenyl functionality was found to have 6 nM binding affinity towards 5-HT_{2A} receptor and 518 nM binding affinity towards 5-HT_{2C} receptor (83-fold selectivity between two subtypes of 5-HT receptors). One of the most intriguing aspects of these latest results was that the bioactive enantiomer was found to have (1*S*, 2*R*) absolute configuration, in all diaryl cyclopropylamine compounds synthesized earlier whereas bioactive enantiomer was found to have (1*R*, 2*S*) absolute configuration in the latest set of 1-biphenyl derivative **HD-323**. The observation of a switch in enantiomer specificity would have been missed if the initial evaluation had been carried out on racemic compounds.

In summary, even though only a small set of compounds were synthesized, they were designed based on the structural information gained from the molecular modeling studies, which enabled the discovery of most potent and selective 5-HT_{2A} antagonist **HD-323** to date. Moreover, this discovery opened up a new research direction, in which a diverse range of products could be quickly synthesized and evaluated for activity by utilizing the complimentary reactivity of rhodium (II) and palladium (II) catalyzed reactions.



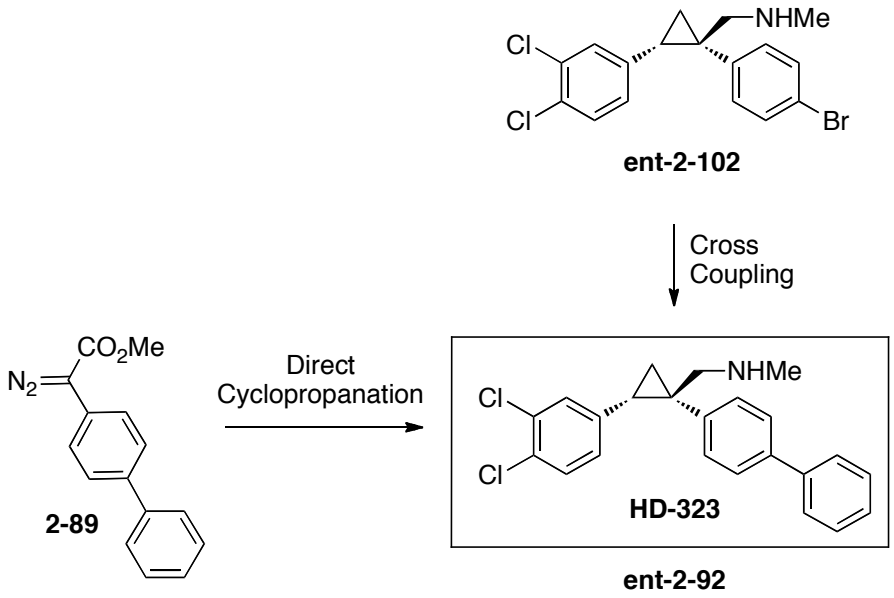
Entry	Analogue	Ar_1	Ar_2	Isomer	5-HT_{2A}	5-HT_{2C}
1	**HD-322**	3,4-diClC_6H_3	4-PhC_6H_4	(1*S*, 2*R*)	117 ± 9.2	2420 ± 460
2	**HD-323**	3,4-diClC_6H_3	4-PhC_6H_4	(1*R*, 2*S*)	6.27 ± 2.7	518 ± 133
3	**HD-318**	2-naphthyl	2-naphthyl	(1*S*, 2*R*)	464 ± 81	>1000
4	**HD-319**	2-naphthyl	2-naphthyl	(1*R*, 2*S*)	>10,000	>1000
5	**HD-320**	2-naphthyl	4-PhC_6H_4	(1*S*, 2*R*)	531 ± 74	>1000
6	**HD-321**	2-naphthyl	4-PhC_6H_4	(1*R*, 2*S*)	251 ± 42	>1000

Table 2.5: K_i values **(nM ± SEM)** in radioligand binding assays at 5-HT_{2A} and 5-HT_{2C} receptors were determined in membranes from transfected cells. (Data was obtained in Steve Childers laboratory)

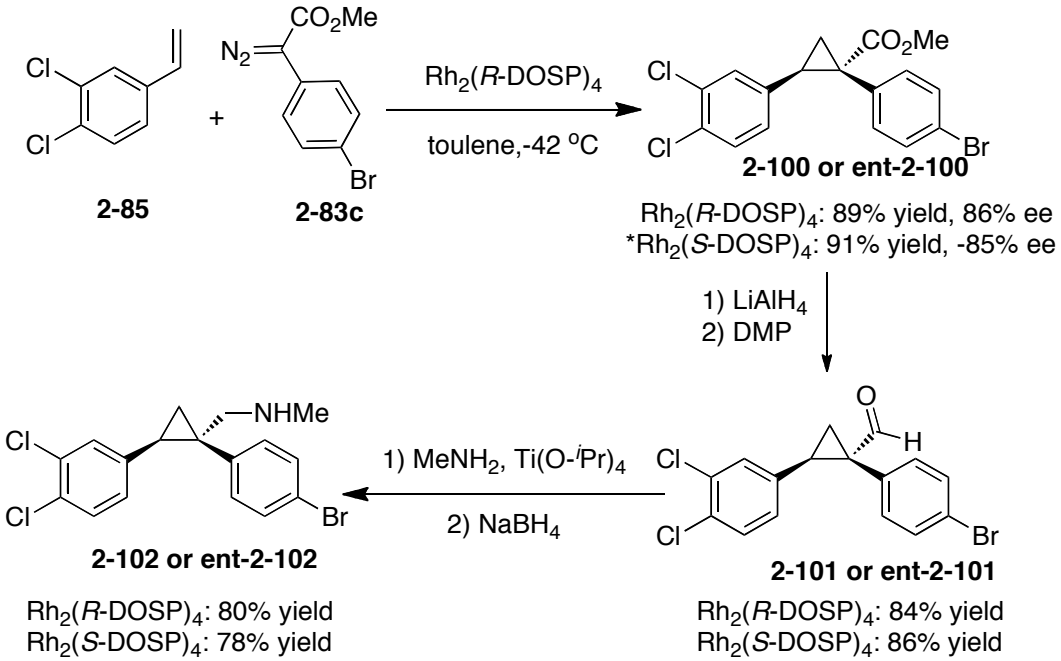
2.3.3 Reverification of the *in vitro* data

As the switch in bioactive enantiomer was not observed earlier. Thus, it would be appropriate to validate the results. HPLC analysis as well as optical rotation data conformed that the cyclopropane products in diaryl derivatives and biphenyl derivatives have same absolute configuration, which prompted us to employ a simple alternate approach in which, the lead biphenyl compound **HD-323** was prepared *via* two separate synthetic routes by two different researchers (Spandan Chennamadhavuni and Josh Alford) to avoid any ambiguity in the out come.

The idea was to synthesize the active enantiomer via intermolecular cyclopropanation to generate the lead compound again. At the same time, it was planned to use **ent-2-102 (**synthesized via a separate synthetic sequence) in a cross coupling reaction to get to the same lead compound **HD-323** (Scheme 2.9).



Scheme 2.9: Newer approach to verify binding assay results.



Scheme 2.10: Synthesis of both enantiomers of 1-1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine.

The required newer set of enantiomers **2-102** and **ent-2-102** were synthesized using 4-bromo phenyl diazoacetate **(2-83c)** as starting material. Two large-scale reactions were performed using both enantiomers of the chiral catalysts. The required 4-bromo diazoacetate **(2-83c)** was synthesized in more than 60 g scale. The intermolecular cyclopropanation of 3,4-dichlorostyrene (**2-85**) with **2-83c** in the presenceof catalytic amount of Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ at -42 °C generated the diarylcyclopropane product in 86% ee and 85% ee respectively. This reaction was performed in 22 mmol scale to obtain both enantiomers of cyclopropane ester products **2-100** or **ent-2-100** (~7 g each). Considering the scale of the reaction, remarkable stereo specificity was observed in this reaction. Both enantiomers were carried to the amine

stage after recrystalizing to enantiopurity. The enantiopure material was then reduced to corresponding alcohol using lithium aluminum hydride and quenched with sodium sulfate decahydrate, and then subsequently oxidized to the corresponding aldehyde using the Dess Martin Periodinane (DMP) reagent in a one-pot procedure in excellent yield. The reductive amination of the aldehyde with methylamine in the presence of titanium(IV) isopropoxide and sodium borohydride generated the diarylcyclopropylmethylamines **(2-102)** or **ent-2-102** in 80% and 78% yield respectively (Scheme 2.10).

A series of coupling reactions were performed using both enantiomers of 4-bromo derivatives synthesized earlier. In one of the reactions, cross coupling reaction was performed using phenyl boronic acid to get the same product obtained *via* cyclopropanation reaction of biphenyl diazocaceate **(2-89)**. Both enantiomers generated in two different routes along with various salt forms were send to Steve Childers laboratory to find the binding results, which are summarized in Table 2.6.

Analogue	**Isomer**	**5-HT$_{2A}$**
HD-322-Tartrate salt using Rh_2(*R*-DOSP)$_4$	(1*S*, 2*R*)	110.1 ± 28.7
HD-322-Fumerate salt using Rh_2(*R*-DOSP)$_4$	(1*S*, 2*R*)	134.6 ± 18.9
HD-322- Fumerate salt from coupling rxn*	(1*S*, 2*R*)	263.8 ± 27.0
HD-323-Tartrate salt using Rh_2(*S*-DOSP)$_4$	(1*R*, 2*S*)	3.1 ± 0.2
HD-323-Fumerate salt using Rh_2(*S*-DOSP)$_4$	(1*R*, 2*S*)	9.0 ± 2.6
HD-323- Fumerate salt from coupling rxn*	(1*R*, 2*S*)	7.6 ± 2.2

Table 2.6: K_i values **(nM ± SEM)** in radioligand binding assays at 5-HT_{2A} receptors were determined in membranes from transfected cells. (Data was obtained in Steve Childers laboratory). (* Compounds synthesized by Josh Alford)

As seen in Table 2.6, The enantiomer obtained from cyclopropanation reaction in the presence of Rh_2(*S*-DOSP)$_4$ with a absolute configuration of (1*R*, 2*S*) was found to have 3 nM binding affinity consistent to the results obtained earlier. All the data reconfirms that in the case of biphenyl substituent, the switch in bioactive enantiomer was real. These results not only added value to our approach of testing both enantiomers for bioactivity but also opened up a new synthetic approach to improve efficacy and selectivity.

Moreover, some of the recent set of compounds (not shown) synthesized *via* cross coupling methodology (starting from **ent-2-102)** was found to have similar potency to **HD-323**. The switch in bioactivity was also observed in this newer set (not shown). **HD-323** derivative with fluoro substituents on the biphenyl group was found to be as efficacious as **HD-323**.

In summary, a focused library of compounds were designed and synthesized based on the SAR of previously synthesized compounds and the computational modeling results. Intermolecular asymmetric catalytic cyclopropanation reaction, an enabling technology was effectively used for generating the enantiopure products which were converted to their corresponding methylamines in three step synthetic sequence. A new

lead compound **HD-323** was found, which is most potent and selective compound to date with 6 nM binding affinity towards 5-HT_{2A} and 89 fold selectivity for 5-HT_{2A} over 5-HT_{2C} receptor. The switch in bioactive enantiomer was observed and reverified. Structural diversity into this new lead compound could be introduced very quickly *via* cross coupling methodology to generate a library of compounds with improved potency and selectivity. Multi-gram quantities of the lead compound **HD-323** was made available, which initiated a thorough *in vivo* evaluation of this new lead in non-human primate model (*in vivo* results will be discussed in the later sections). The preliminary *in vivo* results were promising. More studies are currently underway to further increase potency at 5-HT_{2A} and solubility within this series and to further probe the *in vivo* activity.

2.3.4 Computational modeling

Although we were able to find four lead compounds through iterative structural modifications, this method has some limitations. This process of lead optimization is costly and time consuming. We decided to use modern computational tools to expedite the process of finding an efficacious drug for treatment of cocaine addiction. Complementary to our synthetic efforts, this approach will provide insights about the structural differences between 5-HT_{2A} and 5-HT_{2C} receptor proteins. This molecular level of understanding of the serotonin receptors is quite essential for rationalizing the existing activity data as well as designing more potent and selective compounds targeting either of the receptors.

Two challenging questions to be addressed by a structural analysis of the conformationally constrained cyclopropylamines (CP-amines) are:

1) How does the orientation of the small cyclopropane ring in any given analogue (i.e. (1*S*, 2*R*) *vs* (1*R*, 2*S*)) influence binding to 5-HT_{2A} such that certain substituents (e.g. Ph) can reverse activity of the two enantiomers?

2) How could we examine details of ligand binding geometry and selectivity without having access to experimentally determined 3-D structures of the 5-HT_{2A} and 5-HT_{2C} serotonin receptors?

2.3.4.1 Homology models of the human 5-HT_{2A} receptor

Recently there has been growing interest in evaluating compounds that act on the serotonin (5-HT) system. At present there are 14 distinct serotonin G-protein coupled receptors (GPCR) in humans, which are classified into seven families based on secondary messenger coupling pathways, gene organization and amino acid sequences.[56-58] These families (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7) were further divided into subtypes based on their function and the kind of compounds that can interact with each receptor.[59] Except for the 5-HT_3 receptor, which is a ligand-gated ion channel, all other 5-HT receptors belong to the G-protein-coupled receptor (GPCR) super family.[60]

Within the central nervous system (CNS), the 5-HT_2 subtype family includes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. The 5-HT_{2A} receptor is of significant clinical interest because of its involvement in mental disorders. It is a major target for treating schizophrenia and insomnia. An increasing number of recent reports suggests that the 5-HT_{2A} subtype receptor has been linked to the reversal of negative effects associated with

cocaine withdrawal, whereas, 5-HT_{2C} subtype receptor has been linked to obesity, eating disorder, obsessive-compulsive disorder, epilepsy and erectile dysfunction.

Despite extensive clinical importance for serotonin receptors, the structural studies of these proteins is lacking due to difficulties in determining the crystal structure of membrane-bound proteins. The information about the structure and function of the serotonin receptor is still very limited. Many homology models of 5-HT_{2A} receptor have been proposed and evaluated.[61] The homology models of G-protein-coupled receptors based on X-ray structures are rising in recent years.[62]

Until late 2007, the only high-resolution crystal structure of a GPCR that was available was of bovine rhodopsin (PDB code: 1U19).[63,64] Most of the homology models built prior to 2007 were based on this template. Rhodopsin is a retinal-binding protein, functionally very different from 5-HT_{2A} receptor so the accuracy of the homology models was debatable.

In 2007, a high resolution (2.4 Å) crystal structure of the human β_2 –adrenergic receptor (PDB code: 2RH1) was solved.[65-67] It revealed considerable structural difference in the position and orientation of the trans membrane (TM) helices and structure of the loop region between rhodopsin and other classes of GPCRs. Importantly, the β_2-adrenergic receptor crystal structure has higher homology with 5-HT_{2A} and 5-HT_{2C} receptors (>40%) vs. rhodopsin (< 20%).

Since then, a number of new GPCR homology models based on the β_2-adrenergic template has been reported. Recently McRobb *et al.* reported the homology models of 5-HT_{2A} and 5-HT_{2C}, which were made available to the research community.[68] They refined these homology models using Prime (Schrödinger suite) and evaluated the structural

quality using protein validation tools such as PROCHECK[69] and WHAT_CHECK. It was also reported that the 5-HT_{2A} homology model displayed the high enrichment in virtual screening experiments with enrichment factors of 6.1, 6.9 and 5.9 at 2, 5 and 10%, respectively. They also performed docking studies of the known 5-HT_{2A} active compound, Citalopram, to further validate these models.

As these robust 5-HT_{2A} and 5-HT_{2C} receptor homology models were available, we employed them to perform docking studies of our novel diaryl cyclopropylamine compounds to explain the trends in activity arising from substituent variation on the aromatic rings.

2.3.4.2 Structural information about 5-HT_{2A} and 5-HT_{2C} receptor

The X-ray crystal structure for any of the subtypes of serotonin receptor is currently not solved. The only available method of finding the structural information about 5-HT receptor is to use homology models. It is challenging to find a suitable template to built homology models. Recently, McRobb *et al.* built the homology models of 5-HT_{2A} and 5-HT_{2C} using the β-adrenergic receptor as a template. To understand the structural similarity and homology between these subtypes of serotonin receptors and the β-adrenergic receptor, the sequences of the human β_2-adrenergic receptor, 5-HT_{2A} receptor and 5-HT_{2C} receptor were obtained from the Universal Protein Resource (http://www.uniprot.org) and aligned using ClustalW, a multiple sequence alignment tool (http://www.genome.jp/tools/clustalw/). The sequence alignments and % homologies are listed in Fig 2.17 and Table 2.7.

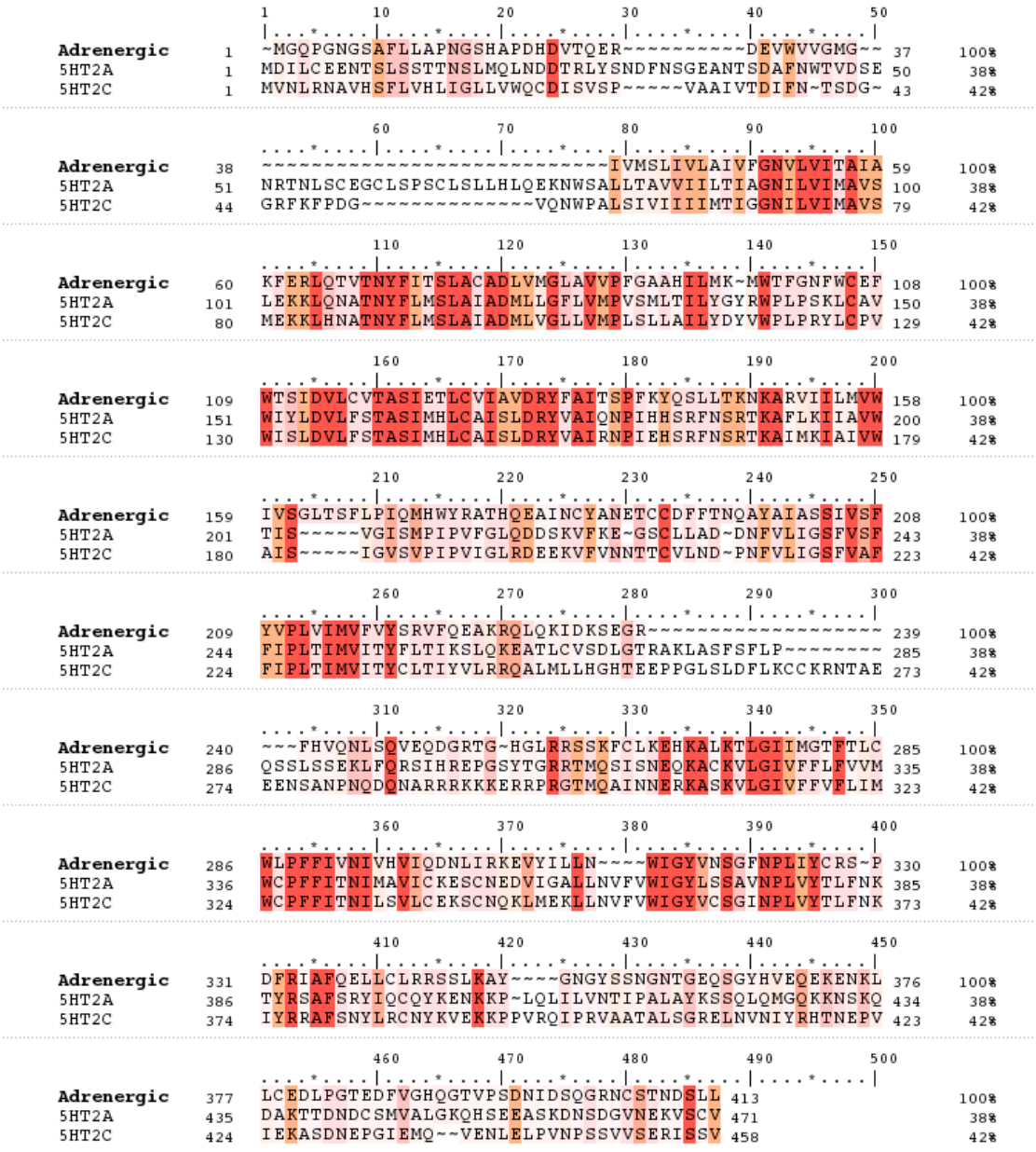


Figure 2.17: sequence alignments of 5-HT_{2A} and 5-HT_{2C} receptors with the β_2-adrenergic receptor (Dark red regions indicate conserved residues).

Alignment of all three receptor sequences (Fig. 2.17) showed that 5-HT_{2A} and 5-HT_{2C} have 38% and 42% similarity with the β_2-adrenergic receptor, respectively. Moreover, % identity (same residue in the sequence, highlighted dark red in Fig. 2.17) is also acceptable at 24% and 26% for 5-HT_{2A} and 5-HT_{2C} respectively. This clearly shows that building homology models for serotonin receptors based on functionally similar adrenergic receptors is a viable option.

No	*Protein*	*% Similarity*	*% Identity*	*% Homology*	*Total no. Of Residues*	*Gaps*
1	Adrenergic	100	100	100	413	74
2	5-HT_{2A}	38	24	41	471	16
3	5-HT_{2C}	42	26	44	458	29

Table 2.7: % homology between 5-HT_{2A} and 5-HT_{2C} receptor with β_2-adrenergic receptor.

Secondary structure alignment (Fig. 2.18) of 2A and 2C homology models shows that they both are structurally very similar with the 7-transmembrane helices aligned properly. They differ slightly in the loop region away from the binding site (Fig. 2.18). The amino acid sequence of all subtypes of serotonin receptors shares a high degree (>70%) of identity within the transmembrane segments (where the active site is) and consequently, it is not surprising that many compounds bind with high affinity to all these three receptor subtypes. The high degree of sequence homology makes identification of selective 5-HT_{2A} ligands difficult.

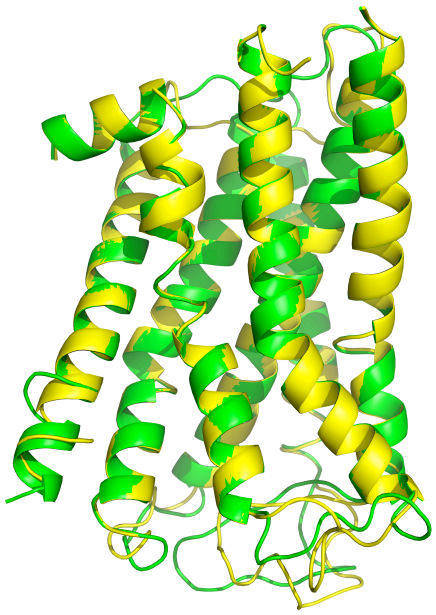


Figure 2.18: Aligned secondary structures of 5-HT_{2A} (green) and 5-HT_{2C} (yellow) homology models.

2.3.4.3 5-HT_{2A} and 5-HT_{2C} receptor active site comparison

The castP (http://sts.bioengr.uic.edu/castp/) server was used to calculate the volume and area of the active site of 5-HT_{2A} and 5-HT_{2C}. It uses the weighted Delaunay triangulation and the alpha complex for shape measurements. It provides identification and measurements of surface accessible pockets as well as interior inaccessible cavities for proteins.[70] It measures analytically the area and volume of each pocket and cavity, both in solvent accessible surface (SA, Richards' surface) and molecular surface (MS, Connolly's surface).

Protein	Volume	Area
5-HT_{2A}	3189	1609
5-HT_{2C}	2026	1400

Table 2.8: Volume and area of 5-HT_{2A} and 5-HT_{2C} active sites in Å³.

CastP calculations showed that the volume and area of the 5-HT_{2A} active site was considerably higher than the 5-HT_{2C} receptor active site (Table 2.8). The volume of the 5-HT_{2A} active site was found to be 3189 Å³, whereas it is 2026 Å³ for 5-HT_{2C}. This size and shape difference can be exploited for the design and synthesis of either 5-HT_{2A} or 5-HT_{2C} selective antagonists.

It was also noted that the 3D structure of the 5-HT_{2A} and 5-HT_{2C} receptor active sites are considerably different mainly because of the way the residues orient themselves in the active site. Based in these observations, a small set of enantiopure compounds were synthesized containing biphenyl functionality (For details refer to section 2.3.1). A complete list of residues that make up the binding pocket in 5-HT_{2A} and 5-HT_{2C} receptor are highlighted in Fig. 2.19.

Figure 2.19: Residues around the active sites in 5-HT_{2A} and 5-HT_{2C}.

2.3.3.4 Ligand based approach

In the early phase of the project, standard commercial antagonists selective for 5-HT_{2A} receptors (vs. 5-HT_{2C}) were identified. They are listed in the Fig. 2.20. MDL-11939 **(2-10)** was identified as a positive control (112-fold selective towards 5-HT_{2A}) whereas SB-206553 **(2-24)** was used as negative control (84-fold selective towards 5-HT_{2C}). Ketanserin **(2-8)** is a non selective but potent antagonist.

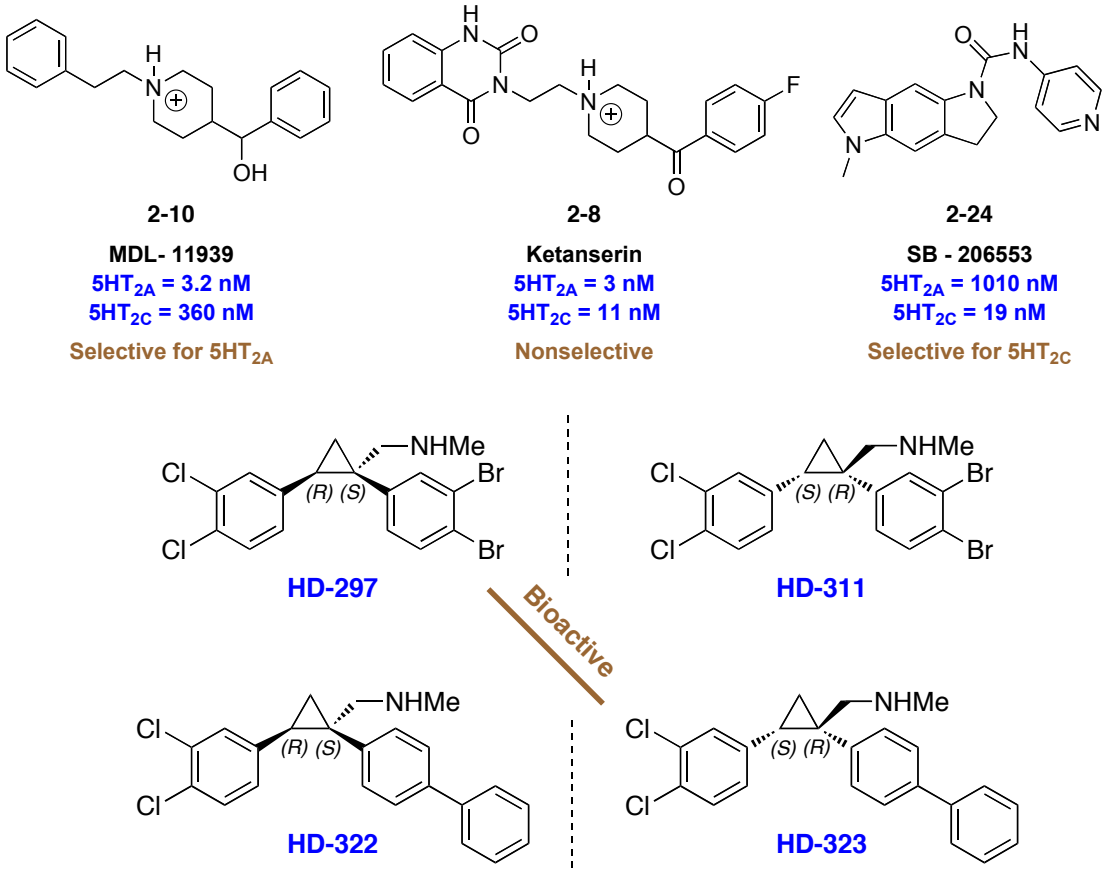


Figure 2.20: Standard 5-HT antagonists and diarylcyclopropylamine compounds used for 3-D mapping and docking studies.

Our initial approach was based on identifying structural similarities between commercial 5-HT_{2A} antagonists (listed in Fig. 2.20) and novel diarylcyclopropylamine lead compounds **HD-225, HD-253, HD-297** and **HD-323** (listed in Fig. 2.15). We employed 'ROCS', a fast shape comparison tool for this purpose. This module is routinely used in lead-hopping, a method for identifying potential compounds that possess similar shape and electrostatic hot-spots by comparison to a known lead

compound. This method works on the basic idea that two ligands with similar shape and surface charges, when overlaid on top of each other, the difference in their volume is a measure of dissimilarity. This is measured using the Tanimoto Combo value. This value can vary between zero to two, where zero represents minimum or no similarity, and two represents maximum similarity. Many recent publications reported the usage of this 3-D mapping tool in virtual screening.[71]

Thus, conformational searches for four active CP-amine leads **(HD-225, HD-253, HD-297** and **HD-323** (IC_{50} 5-HT_{2A} 6 nM - 50 nM) and the control **MDL-11939**, **Ketanserin** and **SB-206553** compound were performed using the OPLS-2005 force field in MacroModel.[72] 3D mapping (ROCS and VIDA, Openeye software[73]) of all low energy CP-amine conformers (within a 7 kcal/mol energy window) onto all low energy conformers of the two 5-HT_{2A} antagonist controls resulted in rather low TanimotoCombo similarity values (< 0.7) (Fig. 2.21 and Table 2.9). This suggests that receptor-ligand interactions are more discriminating than ligand-ligand comparisons, implying the need for a more complex model. The fact that **MDL-11931** and **HD** lead compounds display activities at the 5-HT_{2A} receptor (nanomolar active against 5-HT_{2A} receptor) but still structurally dissimilar to each other imply that there might be at least two different modes of binding.

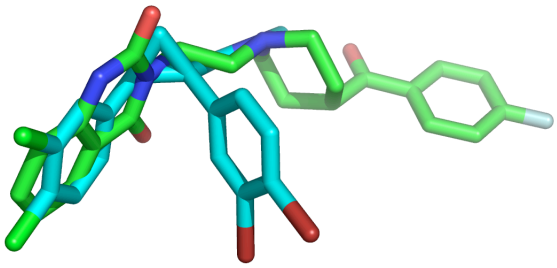
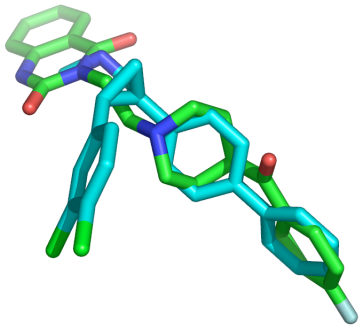
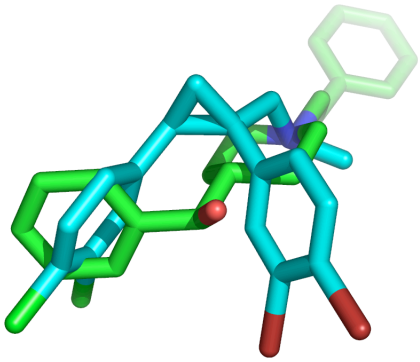
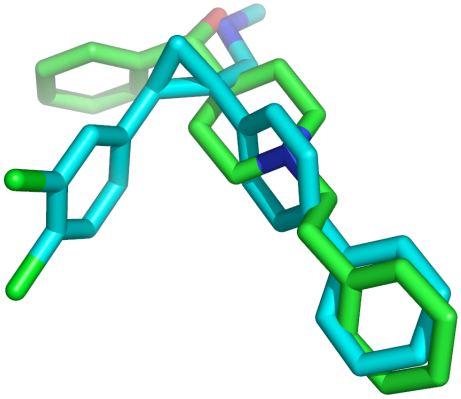
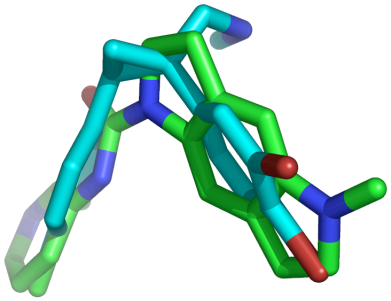
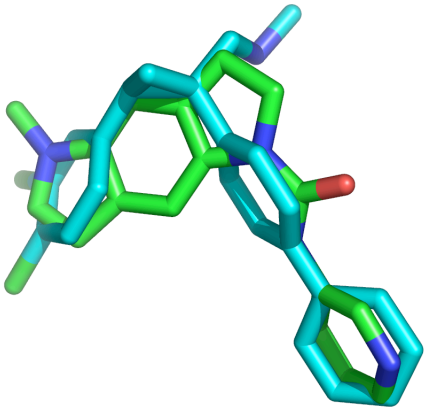
	
Ketanserin – HD 297	**Ketanserin – HD 323**
	
MDL-11931 – HD 297	**MDL-11931 – HD 323**
	
SB-206553 – HD 297	**SB-206553 – HD 323**

Figure 2.21: 3D mapping of standard antagonists with **HD** lead compounds – only representative examples are included. Similar results were obtained when **HD-225, HD-253, HD-230** and their corresponding inactive enantiomers were mapped (see Table 2.9).

Entry	Analogue	Ketanserin	MDL	SB
1	**HD-230**	0.5	0.8	0.8
2	**HD-229**	0.6	0.8	0.8
3	**HD-297**	0.6	0.6	0.7
4	**HD-311**	0.5	0.5	0.7
5	**HD-225**	0.6	0.7	0.8
6	**HD-224**	0.6	0.6	0.7
7	**HD-253**	0.5	0.7	0.9
8	**HD-254**	0.5	0.7	0.8
9	**HD-323**	0.6	0.6	0.9
10	**HD-322**	0.7	0.6	0.8

Table 2.9: TanimotoCombo values of 3D mapping of lead compounds with standard antagonists.

2.3.4.5 Receptor based approach

To extend the preliminary findings in a quantitative fashion, molecular dockings of standard 5-HT_{2A} antagonists and the entire novel CP-amines were performed in the well-validated homology models of 5-HT_{2A} and 5-HT_{2C}, which were built using a β2-adrenergic receptor (2RH1) crystal structure as a template. The binding pocket was localized on the basis of the results of previous single point mutation studies.[74,75]

Each diaryl cyclopropylmethylamine compound was built *in silico* and energy minimized using Macromodel. Conformational searches for each ligand were performed and the top ten lowest energy conformers were used for docking. Coordinates of 5-HT_{2A} and 5-HT_{2C} homology models were obtained from Mcrobb and prepared for docking using the protein preparation wizard tool integrated into Maestro GUI. The docking studies were performed by keeping the receptor rigid and making the ligand flexible. This method not only searches for favorable interactions between ligand and receptor but also generates the low energy conformations for each input ligand. Glide Extra Precision (XP) docking was performed to dock all the CP-amines analogues into the receptor active site using Glide and docking scores were obtained. Prime/MMGBSA was used to calculate the binding energies of the docking results and the top-scoring poses of each analogue were analyzed. Each binding pose was inspected visually to be assured that the ligand was actually docked into the expected binding site and the interactions with the key residues in the binding site were maintained. All the XP docking scores and MMGBSA values for all cyclopropylmethylamines are summarized in Table 2.11.

Ligand	Hydrogen bond residues on side chain	Hydrophobic residues	Pi-Pi stacking residues
MDL – 11939	Asp155 **Ser159**	Ile135, Ile152 Val156, Val366 Phe234, Phe339, Phe340 Trp151, Trp336, Trp367 Tyr370	Trp151 **Phe340**
Ketanserin	Cys227*	Leu228 Ile152 Val156, Val235, Val366 Phe234, Phe339, Phe340 Trp151 Tyr139, Tyr370 Cys227	Trp151
SB – 206553		Ala230, Ala346 Leu228, Leu362 Val156, Val235, Val347 Phe234, Phe243, Phe339, Phe340 Trp336	Phe340
HD-297 (1*S*, 2*R*) Active	Asp155	Ala230 Leu228, Leu229 Ile152 **Val156**, Val235, Val366 Phe234, Phe339, Phe340 **Trp151**, Trp336 Tyr370	Phe340
HD-311 (1*R*, 2*S*) Inactive	Asp155	Ala230 Leu228, Leu362 Ile152 Val235, Val366 Phe234, Phe339, Phe340 Trp336 Tyr370	Phe339 Phe340
HD-323 (1*R*, 2*S*) Active		Ala230 Ile152 Leu228 Val156, Val235 Phe234, Phe339, Phe340 Trp151, Trp336 Tyr370	Phe339 Phe340
HD-322 (1*S*, 2*R*) Inactive	**Asp155**	Ala230 Ile152 Leu228, **Leu362**	Phe339 Phe340

		Val156, Val235, **Val 366** Phe234, Phe339, Phe340 Trp151, Trp336, Tyr 370	

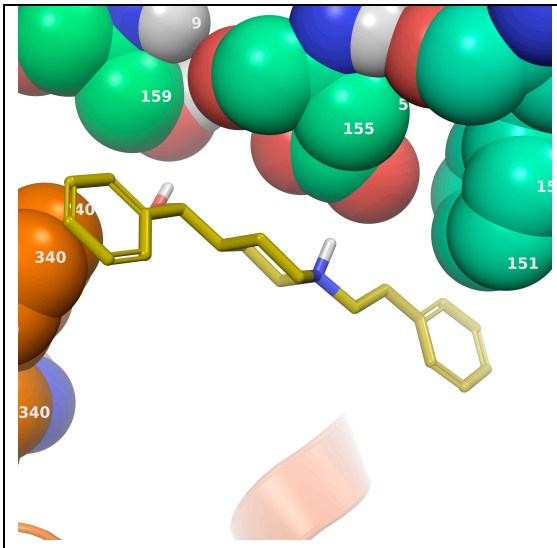
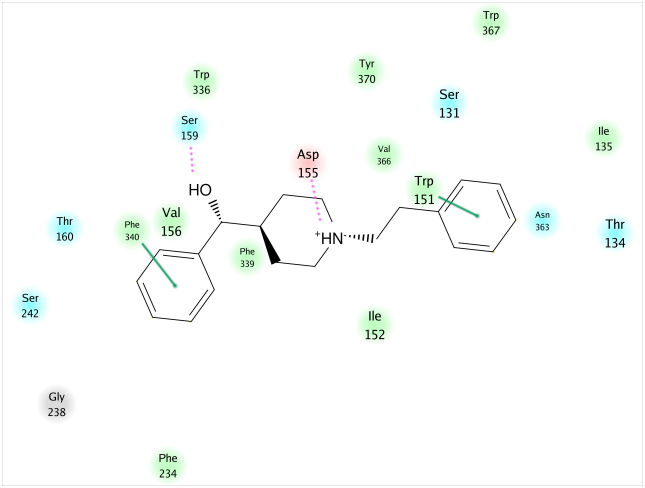
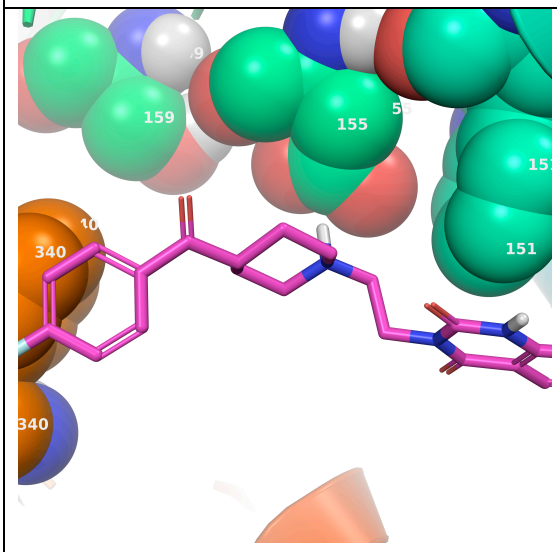
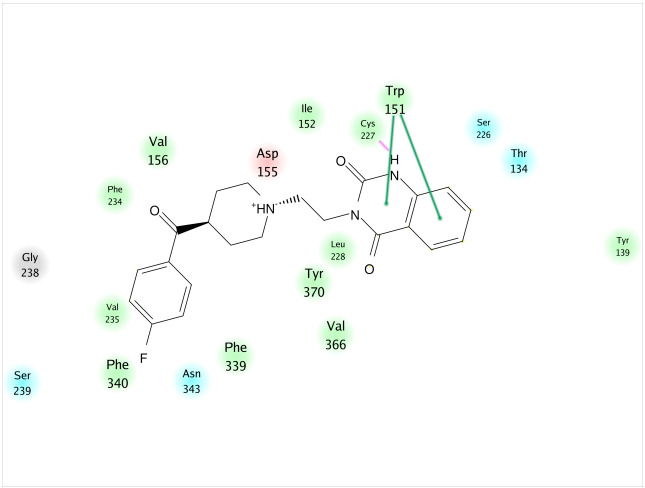
Table 2.10: Analysis of the docked conformations for hydrogen bonds, hydrophobic and pi-pi interactions. (Polar interactions were excluded from the table for clarity, but can be found in the docking pose figures). (* Hydrogen bond residue is on the backbone) (Molecular interactions with the residues (bolded) might be the reason for the difference in the activity in between opposite enantiomers.)

2.3.4.5.1 Docking of standard 5-HT_{2A} and 5-HT_{2C} ligands

At the beginning, standard 5-HT_{2A} ligands MDL-11939, Ketanserin and SB-206553 were docked in order to validate the McRobb 5-HT_{2A} model. The residues potentially involved in ligand binding, the differences in the docking pose and molecular interactions with residues in the active site among these three ligands were identified and listed in Table 2.10.

It was found that both MDL-11939 and Ketanserin docked with a better binding score (-9.2 kcal) than the SB-206553 compound (XP binding score -7.4 kcal), consistent with their *in vitro* data (Fig. 2.22). Further visual analysis of the binding poses of MDL-11939 and Ketanserin revealed that MDL-11939 possesses a two hydrogen bond interactions with amino acid residues Asp155 and Ser159, whereas Ketanserin exhibits only a single hydrogen bond interaction with Cys227 (residue on the backbone). Moreover, MDL-11939 has one extra pi-pi interaction with Phe340, which was lacking in

Ketanserin. The complete list of residues that make hydrophobic contacts with MDL-11939 and Ketanserin are listed in Table 2.10. The lack of activity for SB-206553 compounds towards the 5-HT_{2A} receptor can be attributed to lack of hydrogen bonding capabilities with any of the residues in the active site preventing the anchoring of the molecule tightly against site residues.

	
Binding pose of MDL in the 5-HT_{2A} active site.	Molecular interactions of MDL in the 5-HT_{2A} active site. (XP docking score -9.2 kcal/mol)
	
Binding pose of Ketanserin in the 5-HT_{2A} active	Molecular interactions of Ketanserin in the 5-HT_{2A} active

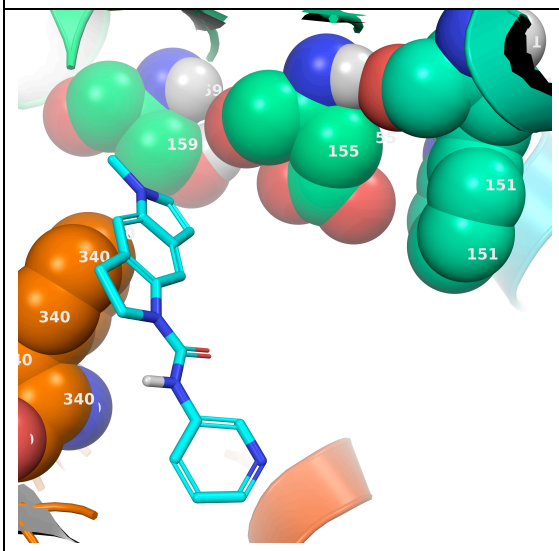
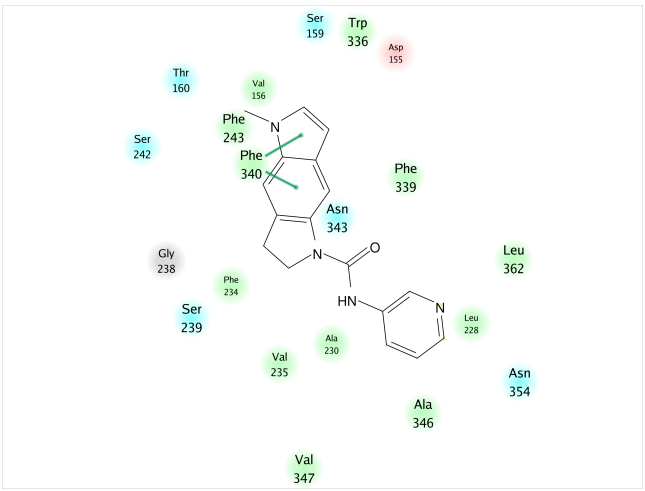
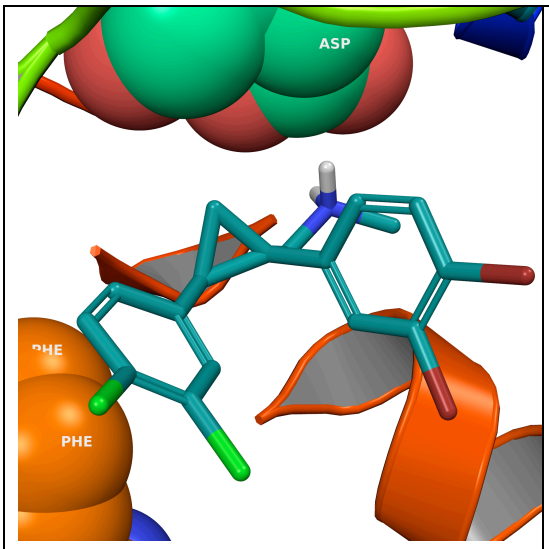
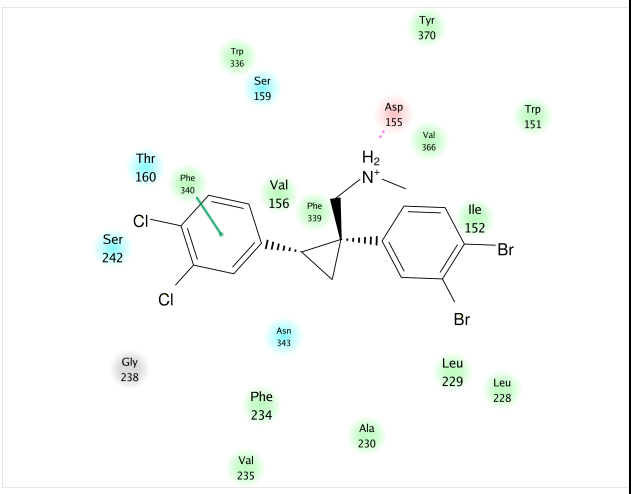
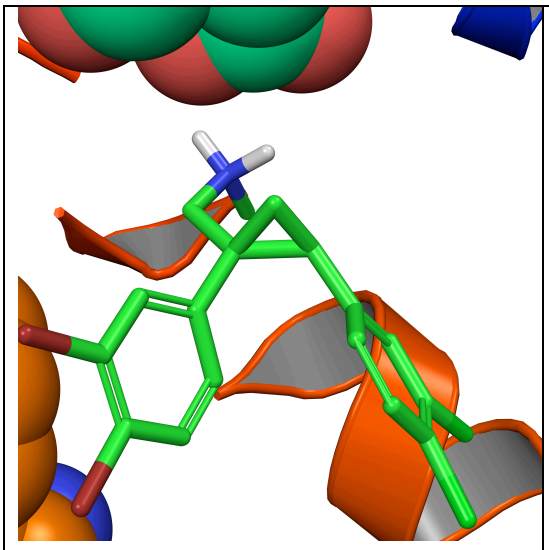
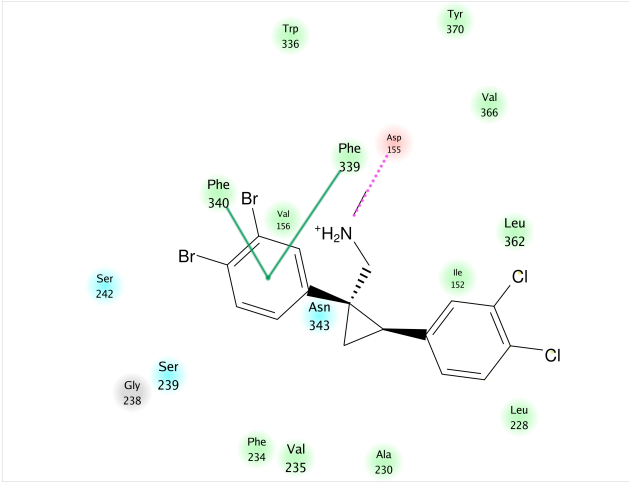
site.	site. (XP docking score -10.2 kcal/mole)
	
Binding pose of SB in the 5-HT$_{2A}$ active site	Molecular interactions of SB in the 5-HT$_{2A}$ active site (XP docking score -7.4 kcal/mol)

Figure 2.22: Binding poses and molecular interactions of **MDL-11939**, **Ketanserin** and **SB-206553** in the 5-HT$_{2A}$ active site. (XP docking scores values in kcal/mol)

	
Binding Pose of bioactive **HD-297** (1*S*, 2*R*) in the 5-HT$_{2A}$ active site.	Molecular interactions for **HD-297** in the 5-HT$_{2A}$ active site. (XP docking score -9.9 kcal/mol)



Binding Pose of bio-inactive **HD-311** (1*R*, 2*S*) in the 5-HT_{2A} active site.



Molecular interactions for **HD-311** in the 5-HT_{2A} active site. (XP docking score -9.8 kcal/mol)

Figure 2.23: Binding poses and molecular interactions of **HD-297** and **HD-323** in the 5-HT_{2A} active site. (XP docking scores values in kcal/mol)

Encouraged by these preliminary docking results, we docked our lead diaryl cyclopropylmethylamine compounds (**HD-297** and **HD-323**) and their inactive enantiomers (**HD-311** and **HD-322**) into the human 5-HT_{2A} receptor site (Fig. 2.23). We found that the binding scores show a trend that accords with experimentally determined binding affinities. We also used another scoring function (MM-GBSA score) that did not support the trends shown in binding scores.

2.3.4.5.2 Docking of HD-297 and HD-311 ligands

The principal ligand-receptor interactions were analyzed for **HD-297** at the 5-HT_{2A} receptor-binding site. A summary of the interactions for the 5-HT_{2A} receptor is shown in Figure 2.23. An ionic interaction between the protonated amine of **HD-297** and the Asp155 residue is evident. Substantial hydrophobic interactions also exist between the ligand aromatic groups and Trp151, Ile152, Leu228, Leu229, Ala230, Val235 and Phe23 residues. A pi-pi stacking interaction is present between the aryl group and the Phe340 residue.

It was also found that active enantiomer **(HD-297)** with (1*S*, 2*R*) configuration has a very distinct binding pose as compared to its inactive enantiomer **(HD-311)** with (1*R*,2*S*) configuration (Fig 2.23). Moreover, it was also observed that **HD-297** binds with slightly better binding score (-9.9 *vs* -9.8) than **HD-311.** In this case, MM-GBSA comparison favors HD-297 by 2 kcal/mol (MM-GBSA energy: -35.2 kcal/mol for **HD-297** *vs* -32.9 kcal/mol for **HD-311**) in agreement with experimentally determined *in vitro* data. Both enantiomers possess hydrogen-bonding interactions with Asp155. Pi-pi stacking interaction with Phe339 and Phe340 was observed. Further analysis of the hydrophobic interactions between receptor and ligands showed a number of common residues (Ala230, Leu228, Leu229, Ile152, Val235, Phe234, Phe339, Phe340, Trp336, Tyr370) that could be important for the efficacy. It appears that the extra hydrophobic interactions of **HD-297** with Val156 and Trp151 residues of the receptor may well be responsible for enhancement in the binding affinity (K_i = 16 nM for **HD-297** and 918 nM

for **HD-311**). This result is consistent with single point mutation studies on these residues.

The comparison of the binding poses of **MDL-11939** and **HD-297** suggests that both provide satisfying poses in the 7-TM binding pocket, but do so by utilizing different sub-pockets and protein side chains, a well-known phenomenon.

Based on this result, all the diarylcyclopropylmethylamine compounds synthesized so far (Table 2.11) were built *in silico* and docked in the active site of the 5-HT_{2A} receptor. This extensive docking study revealed that in 14 out of 17 cases (82%), compounds with the (1*S*, 2*R*) configuration were predicted to have a better binding score than compounds with the (1*R*, 2*S*) configuration with the exception of biphenyl compounds, which do not show a consistent trend.

Entry	Analogue	$Aryl_1$	$Aryl_2$	Isomer	5-HT_{2A} IC_{50} (nM±SEM)	Docking Score (XP) 5-HT_{2A}	Poses
	MDL				3.2 ± 0.4	-9.2	4
	Ketan				5.2 ± 3.8	-10.2	5
	SB				1010	-7.4	2
1	HD-230	C_6H_5	C_6H_5	(1*S*, 2*R*)	>10K	-9.3	1
2	HD-229	C_6H_5	C_6H_5	(1*R*, 2*S*)	>10K	-9.0	3
3	HD-295	2-ClC_6H_4	2-ClC_6H_4	(1*S*, 2*R*)	5957	-9.8	4
4	HD-296	2-ClC_6H_4	2-ClC_6H_4	(1*R*, 2*S*)	>10K	-10.4	3
5	HD-309	3,4-$OCH_2OC_6H_3$	3,4-diClC_6H_3	(1*S*, 2*R*)	2086 ± 857	-10.6	2
6	HD-310	3,4-$OCH_2OC_6H_3$	3,4-diClC_6H_3	(1*R*, 2*S*)	4094	-10.0	2
7	HD-250	4-$OCH_3C_6H_4$	3,4-diClC_6H_3	(1*S*, 2*R*)	840 ± 164	-10.6	2

8	HD-251	4-$OCH_3C_6H_4$	3,4-diClC_6H_3	(1*R*, 2*S*)	>10K	-9.0	5
9	HD-307	4-$CF_3C_6H_4$	3,4-diClC_6H_3	(1*S*, 2*R*)	719 ± 56	-10.5	1
10	HD-308	4-$CF_3C_6H_4$	3,4-diClC_6H_3	(1*R*, 2*S*)	7782	-9.5	4
11	HD-291	2-ClC_6H_4	3,4-diClC_6H_3	(1*S*, 2*R*)	667 ± 109	-10.6	4
12	HD-292	2-ClC_6H_4	3,4-diClC_6H_3	(1*R*, 2*S*)	1432 ± 107	-9.7	4
13	HD-299	2-ClC_6H_4	3,4-diBrC_6H_3	(1*S*, 2*R*)	449 ± 73.2	-10.6	2
14	HD-300	2-ClC_6H_4	3,4-diBrC_6H_3	(1*R*, 2*S*)	1034 ± 252	-9.2	4
15	HD-222	C_6H_5	3,4-diClC_6H_3	(1*S*, 2*R*)	109	-9.7	1
16	HD-221	C_6H_5	3,4-diClC_6H_3	(1*R*, 2*S*)	2996	-8.5	4
17	HD-255	2-naphthyl	3,4-diClC_6H_3	(1*S*, 2*R*)	98.7 ± 4.2	-11.0	1
18	HD-256	2-naphthyl	3,4-diClC_6H_3	(1*R*, 2*S*)	1645 ± 319	-8.8	4
19	HD-258	3,4-diClC_6H_3	4-$OCH_3C_6H_4$	(1*S*, 2*R*)	1046 ± 109	-10.4	1
20	HD-259	3,4-diClC_6H_3	4-$OCH_3C_6H_4$	(1*R*, 2*S*)	155.1 ± 19.9	-8.3	3
21	HD-293	3,4-diClC_6H_3	2-ClC_6H_4	(1S, 2R)	752 ± 98.3	-10.2	1
22	HD-294	3,4-diClC_6H_3	2-ClC_6H_4	(1*R*, 2*S*)	8390	-7.3	1
23	HD-220	3,4-diClC_6H_3	C_6H_5	(1*S*, 2*R*)	206	-10.3	3
24	HD-219	3,4-diClC_6H_3	C_6H_5	(1*R*, 2*S*)	7330	-8.5	4
25	HD-253	3,4-diClC_6H_3	2-naphthyl	(1*S*, 2*R*)	51.3 ± 4.9	-10.6	3
26	HD-254	3,4-diClC_6H_3	2-naphthyl	(1*R*, 2*S*)	1165 ± 33.2	-6.3	4
27	HD-225	3,4-diClC_6H_3	3,4-diClC_6H_3	(1*S*, 2*R*)	38.2 ± 5.4	-10.5	1
28	HD-224	3,4-diClC_6H_3	3,4-diClC_6H_3	(1*R*, 2*S*)	783	-8.2	1
29	HD-297	3,4-diClC_6H_3	3,4-diBrC_6H_3	(1*S*, 2*R*)	16.8 ± 5.99	-9.9	1
30	HD-311	3,4-diClC_6H_3	3,4-diBrC_6H_3	(1*R*, 2*S*)	918 ± 214	-9.8	4
31	HD-322	3,4-diClC_6H_3	4-PhC_6H_4	(1*S*, 2*R*)	117.3 ± 9.2	-7.3	5
32	HD-323	3,4-diClC_6H_3	4-PhC_6H_4	(1*R*, 2*S*)	6.3 ± 2.7	-8.9	1

33	HD-318	2-naphthyl	2-naphthyl	(1*S*, 2*R*)	668 ± 117	-11.2	1
34	HD-319	2-naphthyl	2-naphthyl	(1*R*, 2*S*)	>10K	-8.2	5
35	HD-320	2-naphthyl	4-PhC_6H_4	(1*S*, 2*R*)	750 ± 105	-7.9	3
36	HD-321	2-naphthyl	4-PhC_6H_4	(1*R*, 2*S*)	355 ± 58.8	-8.7	4
37	HD-334	3,4-diClC_6H_3	4-$PhCO_2HC_6H_4$	(1*S*, 2*R*)		-8.5	4
38	HD-335	3,4-diClC_6H_3	4-$PhCO_2HC_6H_4$	(1*R*, 2*S*)		-7.8	2
39	HD-336	3,4-diClC_6H_3	4-$PhOCH_3C_6H_4$	(1*S*, 2*R*)		-7.7	1
40	HD-337	3,4-diClC_6H_3	4-$PhOCH_3C_6H_4$	(1*R*, 2*S*)		-8.7	2
41	HD-338	3,4-diClC_6H_3	4-$PhDiFC_6H_4$	(1*S*, 2*R*)		-8.3	1
42	HD-339	3,4-diClC_6H_3	4-$PhDiFC_6H_4$	(1*R*, 2*S*)		-8.9	1
43	HD-340	3,4-diClC_6H_3	4-$PyFC_6H_4$	(1*S*, 2*R*)		-8.2	1
44	HD-341	3,4-diClC_6H_3	4-$PyFC_6H_4$	(1*R*, 2*S*)		-8.5	3
45	HD-342	3,4-diClC_6H_3	4-$PhSO_2MeC_6H_4$	(1*S*, 2*R*)		-7.9	1
46	HD-343	3,4-diClC_6H_3	4-$PhSO_2MeC_6H_4$	(1*R*, 2*S*)		-8.4	4

Table 2.11: Binding scores and MMGBSA values for all diarylcyclopropylamine compounds (XP docking scores in kcal/mol).

In summary, Glide extra precision (XP) docking scores of the entire set of HD compounds generally predicts that the enantiomer with the (1*S*, 2*R*) configuration would complex the 5-HT_{2A} protein with a better binding score as compared to its opposite enantiomer. While the present homology model does not explain the trends in relative enantiomer activity with quantitative accuracy it does appears to decriminate enatiomers in most instances by comparison with the available in vitro IC_{50}'s. Unfortunately, the

current homology model does not explain the switch in bioactive enantiomer in the case of biphenyl substitution (e.g. HD-323 vs HD-322). As all the analogues were docked in to the binding pocket 1, larger biphenyl analogues are likely to be squeezed with difficulty in to site 1, the basis for current modeling. These larger biphenyl analogues needed to be evaluated in binding site 2 of 5-HT_{2A} to better understand the switch in bioactivity. Further validation of the current homology model as well as efforts to refine the model to explain bioactivity trends are currently being pursued in the Snyder laboratory. In particular, the more expansive site 2 will be examined in the case of the larger biphenyl ligands.

2.3.5 *in vivo* data for novel diaryl cyclopropylamine compounds

Considering the clinical importance of this study, multi-gram quantities of four lead compounds **HD-225** (Jeremy Olson), **HD-255** (Spandan Chennamadhavuni), **HD-297** (Josh Alford) and **HD-323** (Spandan Chennamadhavuni) were synthesized and sent to Dr. Nader's laboratory for behavioral testing in cocaine self-administering monkeys.

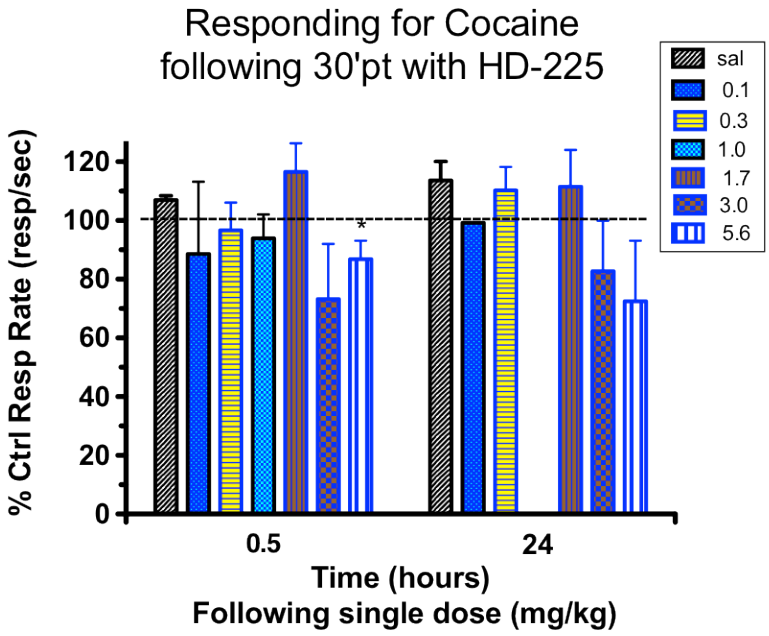


Figure 2.24: Behavioral effect of **HD-225** on cocaine self-administration in monkeys.

All behavioral studies were performed in Mike Nader's laboratory at Wake Forest University Primate Center. Monkeys were trained to respond on a fixed-ratio (FR) 30 schedule of i.v. cocaine reinforcement. Experimental sessions lasted for 1 h or until maximum number of reinforcers were obtained (30 cocaine injections). The dose of cocaine that maintained peak response rates was studied (0.01 or 0.03 mg/kg/injection) and all drugs were administered intramuscularly either 15 or 30 minutes prior to the start of the experimental session.

Administration of **HD-225** at lower doses (up to 3.0 mg/kg) did not show any immediate therapeutic effect. But, significant reduction in response rate (~30%) was observed for self-administration of cocaine when higher dose was tested (5.6 mg/kg).

Moreover, reduction in response rates was observed even after 24 h post injection, when drug was administered at highest doses (3.0 & 5.6) (Fig. 2.24).

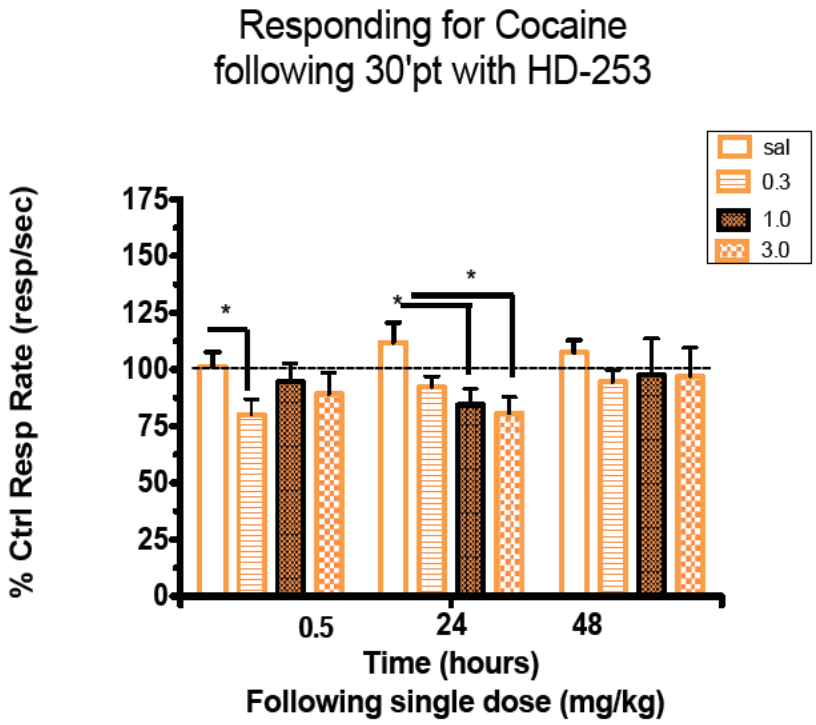


Figure 2.25: Behavioral effect of **HD-253** on cocaine self-administration in monkeys.

Similar results were obtained when **HD-253** was injected. When lowest dose of 0.3 mg/kg was tested, a significant reduction (~20%) in cocaine response rates was observed. Additionally, when two highest doses were tested (1.0 & 3.0 mg/kg) did not show immediate therapeutic effect but did produce significant reductions in rate 24 h post injection when compared to saline (Figure 2.25).

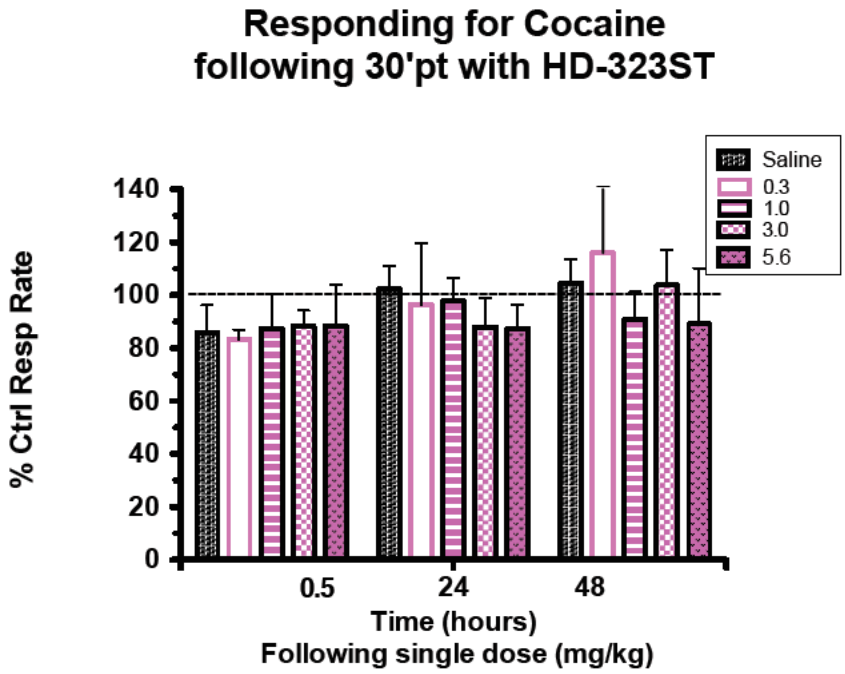


Figure 2.26: Behavioral effect of **HD-323** on cocaine self-administration in monkeys.

Although **HD-323** found to be 6 nM active *in vitro* against 5-HT_{2A} receptor, when this compound was administered in monkeys, no significant reduction in response rate was observed even at higher doses (Fig. 2.26). In summary, all the HD lead compounds appear to be not potent, generating only modest decreases in response rate for self-administration of cocaine.

All the lead compounds found in this project are hydrophobic (logP > 6) and it appears that these compounds might not be able to cross the blood brain barrier making them less bioavailable, thus not showing significant therapeutic effect *in vivo*.

Currently, research in this project is directed towards design of novel compounds containing improved pharmokinetic properties. The preliminary computational studies

have already established a robust predictive model of the binding affinities for the $5HT_{2A}$ and $5HT_{2C}$ receptors and have lead to the identification of a number of promising synthetic leads. Our newer approach utilizes modern computational techniques such as CombiGlide to generate a library of drug-like compounds based on cyclopropane scaffold that will then be refined based on ADME predictions (using Quickprop). Only compounds with desired solubility, cell permeability will be favored for synthesis and activity evaluation. This guided approach not only reduces the number of compounds that needed to be evaluated, but also reduces the time and cost, expediting our drug discovery efforts towards finding a therapeutic agent for treating cocaine addiction.

2.4 Conclusions

Overall, a library of diarylclopropylmethylamines was synthesized by utilizing the enantioselective cyclopropanation of substituted styrene derivatives with carbenoids derived from various donor-acceptor diazo compounds in the presence of catalytic amounts of either Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ followed by oxidation, reduction and a reductive amination synthetic sequence. The cyclopropyl compounds with low nanomolar binding affinities towards 5-HT_{2A} receptor were found through a series of structure-activity relationship (SAR) studies. One of the lead compounds **HD-323** exhibits very high level of selectivity towards 5-HT_{2A} over 5-HT_{2C} receptor. These compounds were also tested on the reinforcing effects of cocaine in non-human primate model and initial results were promising.

Extensive molecular docking studies were also performed on these novel diarylcyclopropylamine compounds in order to rationalize the structure activity

relationships determined to date and to assist in the design of novel structural scaffolds, which would exhibit selectivity towards the 5-HT_{2A} receptor over the 5-HT_{2C} receptor. Various modules of Schrödinger suite were used for performing the computational modeling studies. New ligands were designed with desirable ADME properties with the aim of improving efficacy and selectivity. Analogues of cyclopropylamines were docked into a homology structure of the human 5-HT_{2A} receptor-using the Glide docking method. The Glide docking algorithm show a trend in docking scores that are in agreement with the experimental *in vitro* data in most instances. Further analysis of the docking poses revealed an important interaction between the protonated nitrogen of the cyclopropylamine and residue Asp155 in the 5-HT_{2A} receptor-binding pocket. Once, this homology model validated and evaluated further, could be used as robust predictive model, which could be extensively used in lead optimization. The novel scaffolds designed in computational modeling could then be further developed as potential therapeutic agents for the treatment of cocaine addiction.

2.5 References

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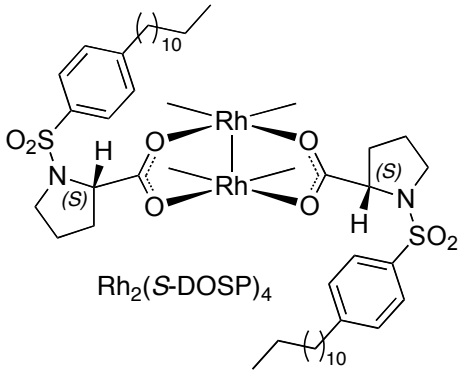
Experimental for 5-HT_{2A} antagonists project

All compounds from commercial sources were used as received except where indicated. Hexanes, toluene, acetonitrile, DCM, diethyl ether, and THF were dried by passage through activated alumina columns in a solvent purification system. DMB was dried by distillation under argon from sodium metal. Degassing of reactions was achieved by bubbling argon through the solvent for 15 min prior to use. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 300, 400 or 500 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ H 7.26 for the residual protons in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant (J/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 75 or 125 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δ C 77.0 for $CDCl_3$. Mass spectral determinations were performed by the Instrument Center of the Department of Chemistry at Emory University. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross GA. Melting points were measured on an Electro thermal melting point apparatus and are uncorrected. Infrared spectral data are reported in units of cm^{-1}. Optical rotations were measured at the sodium D line (589 nm) and reported as follows: $[\alpha]_D^{25}$, concentration (*c* in g/100 mL) and solvent (all rotations were measured at 25.0 °C). Enantiomeric excess was determined by HPLC using a Chiralcel OD, Chiralcel OD-H, Chiralcel OJ, Chiralpak AD-H, Chiralpak AS-H, Chiralpak AD-RH, (*R,R*)-Whelk, or (*S,S*)-Whelk chiral analytical column (UV detection at 254 or 273 nm). Analytical TLC was performed on 0.25 mm E. Merck silica gel plates

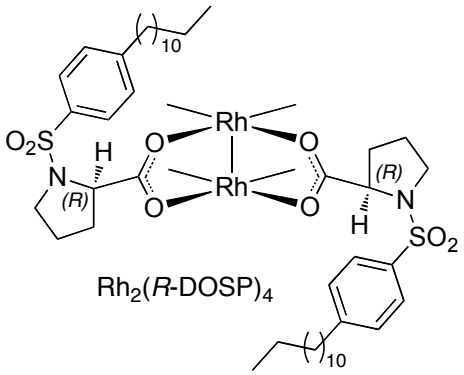
using UV light. Phosphomolybdic acid (PMA) and/or $KMnO_4$ TLC stains were used as visualizing agents if necessary. Flash column chromatography was performed on Merck silica gel 60Å (230-400 mesh). Glassware was flame-dried under vacuum prior to use. Reactions were conducted under an argon atmosphere. Hydrogenations were carried out using a Parr hydrogenation apparatus. μW (microwave) assisted reactions were conducted in an Emrys™ vial (5 mL) in an Emrys™ Creator apparatus (personalchemistry®).

Tetrakis[*N*-[(4-dodecylphenyl)sulfonyl]-(*L*)-prolinato]dirhodium (Rh_2(*S*-DOSP)$_4$



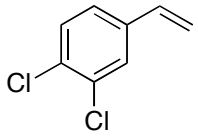
This compound was prepared by Dr. James Manning and Dr. Dominic Ventura and was used as is

Tetrakis[*N*-[(4-dodecylphenyl)sulfonyl]-(*D*)-prolinato]dirhodium (Rh_2(*R*-DOSP)$_4$)



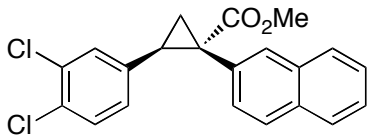
This compound was prepared by Dr. James Manning and Dr. Dominic Ventura was used as is.

1,2-Dichloro-4-vinylbenzene (2-85)



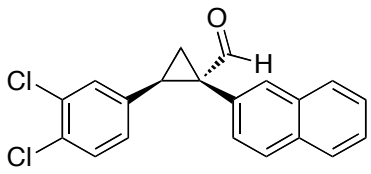
Methyltriphenylphosphine bromide (44.9 g, 125 mmol) in THF (250 mL) was treated with potassium *tert*-butoxide (29.4 g, 262 mmol) and stirred for 30 minutes. 3,4-Dichlorobenzaldehyde (20.0 g, 114 mmol) in THF (50 mL) was added dropwise over 30 minutes, and then stirred for an additional 16 h. The reaction was then concentrated under reduced pressure and diluted with pentane and poured into a solution of DI H_2O. The organic extract was washed with brine and dried with $MgSO_4$. The organic phase was concentrated under reduced pressure and the residue was re-dissolved in hexanes and filtered. The filtrate was then concentrated under reduced pressure to give orange oil. The crude material was distilled using a Kugelrohr distillation apparatus to obtain **2-85** as a colorless liquid in 54% yield (10.7 g). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.47 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.21 (dd, J = 8.4, 1.8 Hz, 1H), 6.61 (dd, J = 17.7, 10.8 Hz, 1H), 5.74 (d, J = 17.7 Hz, 1H), 5.32 (d, J = 10.8 Hz, 1H). The spectroscopic data was in accordance with the literature.

(1*S*, 2*R*)-Methyl 2-(3,4-dichlorophenyl)-1-(naphthalen-2-yl) cyclopropane carboxylate (2-86)



In a 100 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (3.4 g, 20 mmol, 2 eq.) and Rh_2(*R*-DOSP)$_4$ (70 mg, 0.25 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (2.2 g, 10 mmol, 1eq.) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 6 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-86** as a clear liquid in 89% yield (3.3 g), > 94% de (determined by ^{1}H-NMR of the crude reaction mixture). HPLC analysis: 90% ee (SS-Whelk column, 9% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 15.9 (major) and 37.5 (minor) min, UV 254 nm); recrystallized from hexanes to give >92% ee; R_f = 0.31 (4:1 Hexanes: EtOAc); ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.77 (m, 2H), 7.63 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.46 (m, 2H), 7.12 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.67 (s, 3H), 3.20 (m, 2H), 2.27 (m, 1H), 2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 136.7, 132.8, 132.3, 131.5, 130.2, 130.2, 130.0, 129.5, 129.4, 127.5, 127.4, 127.3, 126.5, 125.9, 125.8, 52.5, 37.5, 31.8, 20.6; Spectroscopic data matches with the previously reported data in the Davies group.

(1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(naphthalen-2-yl)cyclopropanecarbaldehyde (2-87)

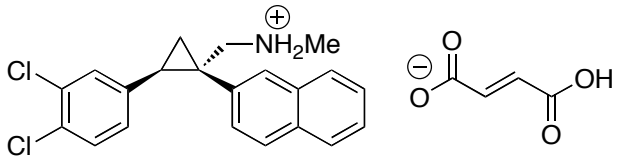


In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-methyl 2-(3,4-dichlorophenyl)-1-(naphthalen-2-yl) cyclopropane carboxylate **(2-86)** (1.4 g, 4 mmol, 1eq.) was dissolved in THF (30 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (189 mg, 5 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (50 mL) and Dess Martin periodinane reagent (2.5 g, 6 mmol) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **2-87** as a clear liquid in 90% yield (1.2 g). R_f = 0.4 (4:1 Hexanes: EtOAc); ^{1}H-NMR (400 MHz; $CDCl_3$): δ 9.68 (s, 1H), 7.77 (m, 2H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.47 (m, 2H), 7.11 (d, *J* = 1 Hz, 1H), 7.08 (m, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.56 (dd, *J* = 8.3, 2 Hz, 1H), 3.02 (dd, *J* = 9.0, 7.4 Hz, 1H), 2.27 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.1-2.0 (m, 1 H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 200.1, 136.0, 133.1, 132.7, 131.9, 130.7, 130.6, 130.4, 130.2, 129.7, 128.5, 128.3, 127.6, 126.7, 126.3, 126.3, 46.2, 34.1, 20.1; Spectroscopic data matches with the previously reported data in the Davies group.

1-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (2-88)

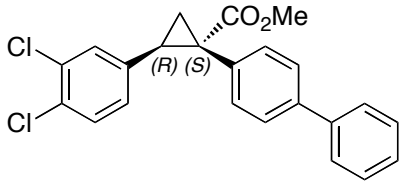


In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-(naphthalen-2-yl)cyclopropanecarbaldehyde **2-87** (1 g, 3 mmol) was dissolved in methanol (50 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 4 mL, 6 mmol) and Ti(O-*i*Pr)$_4$ (2 mL, 6 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (180 mg, 4.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give clear oily liquid in 77 % yield (818 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.65 (m, 3H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.39 (ddd, *J* = 7.0, 4.7, 1.8 Hz, 2H), 7.12 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.38 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.17 (dd, *J* = 12.1, 1.3 Hz, 1H), 2.58 (d, *J* = 12.2 Hz,

1H), 2.36 (s, 3H), 2.25 (dd, *J* = 8.6, 5.9 Hz, 1H), 1.62 (d, *J* = 1.4 Hz, 1H), 1.52 (dd, *J* = 8.6, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9, 136.1, 133.5, 132.6, 131.7, 130.3, 130.2, 129.9, 129.7, 129.6, 129.2, 128.6, 128.3, 127.8, 126.5, 126.4, 126.2, 126.0, 62.79, 36.8, 36.7, 27.7, 18.8; Spectroscopic data matches with the previously reported data in the Davies group.

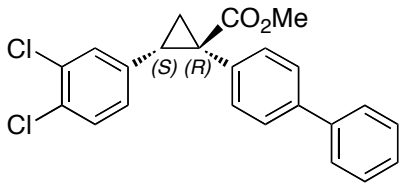
The free amine was dissolved in isopropanol (20 mL) and then treated with fumaric acid (783 mg, 2.2 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.79-7.63 (m, 4H), 7.45-7.35 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.69 (m, 1H), 6.61 (s, 2H), 3.87-3.79 (m, 1H), 3.00 (d, *J* = 13.0 Hz, 1H), 2.57 (s, 3H), 1.96 (d, *J* = 1.5 Hz, 1H), 1.67 (dd, *J* = 9.0, 6.1 Hz, 1H), 1.09 (d, *J* = 6.2 Hz, 1H); Spectroscopic data matches with the previously reported data in the Davies group.

(1*S*,2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl) cyclopropane carboxylate (2-90)



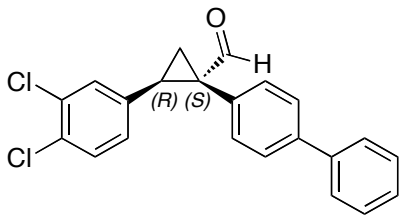
In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (1.8 g, 10.5 mmol) and Rh_2(*R*-DOSP)$_4$ (98 mg, 0.5 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (1.76 g, 7 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-90** as a colorless oil in 89 % yield (2.47 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 75% (301 mg) of product. HPLC analysis: 92% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.8 (minor) and 13.7 (major) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 4H), 7.35-7.28 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 3H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.54 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.69 (s, 3H), 3.06 (dd, *J* = 9.1, 7.3 Hz, 1H), 2.18 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.84 (dd, *J* = 7.0, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 140.2, 139.9, 136.8, 132.8, 131.9, 131.6, 130.1, 130.0, 129.4, 128.5, 127.1, 126.8, 126.8, 126.4, 52.5, 37.1, 31.8, 20.6; FT-IR (neat): 1715, 1486, 1252, 906, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{23}H_{19}O_2Cl_2$: 397.0756; Found: 397.0759; Anal. Calcd. for $C_{23}H_{18}Cl_2O_2$: C, 69.53; H, 4.57; Found: C, 69.77; H, 4.50.

(1*R*,2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl) cyclopropane carboxylate (ent-2-90)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (1.8 g, 10.5 mmol) and Rh_2(*S*-DOSP)$_4$ (98 mg, 0.5 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (1.76 g, 7 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-2-90** as a colorless oil in 86 % yield (2.39 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 78% (312 mg) of product. HPLC analysis: 86 % ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.8 (major) and 13.7 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **2-90**.

(1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (2-91)

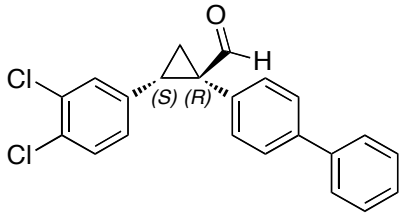


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate **2-90** (2.1 g, 5.5 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (260 mg, 6.8 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure to obtain 81 % (1.6 g) of product.

((1*S*,2*R*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropyl)methanol (738 mg, 2 mmol, 1eq.) was dissolved in methylene chloride (20 mL) and Dess Martin Periodinane (DMP) reagent (1.2 g, 3 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored). The mixture was diluted with ether and washed with aqueous NaOH (2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **2-91** as an oily liquid in 90 % yield (664 mg); R_f = 0.30 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.40 (t, *J*

= 7.5 Hz, 2H), 7.08-7.15 (m, 3H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.1 Hz, 1H), 2.94 (dd, *J* = 9.0, 7.5 Hz, 1H), 2.19 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.06-1.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 140.9, 140.3, 136.2, 132.2, 132.1, 131.7, 130.4, 130.2, 129.9, 128.9, 127.6, 127.5, 127.1, 46.0, 34.3, 20.1; FT-IR (neat): 1701, 1486, 1134, 729 $cm^{-1;}$ HRMS (pos-APCI) calcd for $C_{22}H_{16}Cl_2O$: 367.0651; Found: 367.0653; Anal. Calcd. for $C_{20}H_{14}Cl_2O$: C, 70.40; H, 4.14; Found: C, 70.23; H, 4.21.

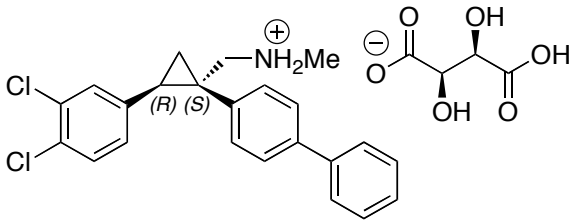
(1*R*, 2S)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-2-91)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate **ent-2-91** (993 mg, 2.5 mmol, 1 eq.) was dissolved in THF (30 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (118 mg, 3.1 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure to obtain crude alcohol, which was taken to the next step without further purification.

((1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropyl)methanol was dissolved in methylene chloride (20 mL) and Dess Martin Periodinane (DMP) reagent (1.6 g, 3.7 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-2-91** as an oily liquid in 85 % yield (780 mg); R_f = 0.30 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **2-91.**

1-((1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (2-92)



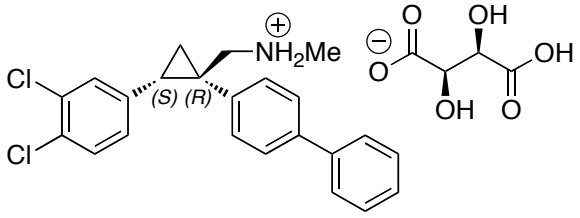
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde **2-91** (664 mg, 2 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 2.4 mL, 4 mmol) and Ti(O-*i*Pr)$_4$ (2 mL, 4 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (114 mg, 3 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was

quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 64 % yield (493 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.9 Hz, 2H), 7.45-7.39 (m, 4H), 7.36-7.28 (m, 1H), 7.25 (s, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 3.11 (d, *J* = 12.2 Hz, 1H), 2.60 (d, *J* = 12.2 Hz, 1H), 2.42 (s, 3H), 2.27 - 2.18 (m, 1H), 1.61 - 1.44 (m, 2H), 1.36 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 139.7, 139.5, 137.1, 131.4, 131.0, 129.6, 129.3, 129.0, 128.6, 127.1, 126.9, 126.9, 126.5, 77.3, 77.0, 76.6, 62.6, 36.5, 35.9, 27.4, 18.5; FTIR (Neat): 3027, 2930, 2790, 1474, 1133, 734, 696 cm^{-1}; HRMS (pos-APCI) calcd for $C_{23}H_{22}Cl_2N_1$: 382.1123; Found: 382.1121; Anal. Calcd. for $C_{27}H_{25}Cl_2NO_4$ (Fumerate salt): C, 65.07; H, 5.06; N, 2.81; Found: C, 64.85; H, 5.00; N, 2.77.

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (130 mg, 1.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.5 (m, 4H), 7.36 (m, 3H), 7.30-7.23 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.39 (s, 2H), 3.90 (d, *J* = 13.0 Hz, 1H), 3.01 (d, *J* = 13.0

Hz, 1H), 2.61 (s, 3H), 2.55 (m, 1H), 1.86 (d, J = 1.5 Hz, 1H), 1.70-1.63 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.9, 142.3, 141.7, 139.7, 135.6, 132.7, 131.3, 130.9, 130.8, 130.0, 128.8, 128.7, 128.6, 128.0, 74.2, 60.3, 34.3, 33.6, 29.4, 17.9; FTIR (Neat): 3029, 1724, 1598, 1133, 1076, 838 cm^{-1}; HRMS (pos-APCI) calcd for $C_{23}H_{22}Cl_2N_1$: 382.1123; Found: 382.1119.

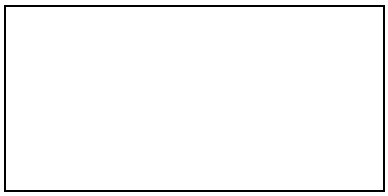
1-((1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (ent-2-92)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde **ent-2-91** (918 mg, 2.5 mmol) was dissolved in methanol (30 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 3 mL, 5 mmol) and Ti(O-*i*Pr)$_4$ (2 mL, 5 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (114 mg, 3 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 70 % yield (671

mg). The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (300 mg, 2 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. Spectroscopic data is same as **2-92**.

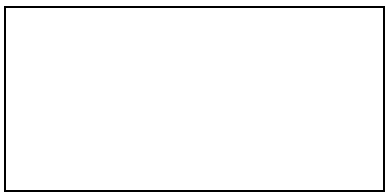
(1*S*, 2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarboxylate (2-94)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 2-vinylnaphthalene (1 g, 6.6 mmol) and Rh_2(*R*-DOSP)$_4$ (54 mg, 0.5 mol %) were dissolved in dry, degassed toluene (50 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (1.51 g, 6 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-94** as a colorless oil in 93 % yield (2.11 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 79 % (301 mg) of product. HPLC analysis: 98 % ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.5 (minor) and 15.3 (major) min, UV

254 nm); R_f = 0.30 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.66 (m, 1H), 7.64-7.59 (m, 1H), 7.55-7.43 (m, 3H), 7.40-7.31 (m, 6 H), 7.30-7.24 (m, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.84 (dd, *J* = 8.5, 1.2 Hz, 1H), 3.71 (s, 3 H), 3.30 (t, *J* = 8.2 Hz, 1H), 2.26 (dd, *J* = 9.4, 4.88 Hz, 1H), 2.07-2.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 140.4, 139.5, 133.9, 133.6, 132.8, 132.1, 131.9, 128.4, 127.3, 127.0, 127.0, 127.0, 126.7, 126.3, 125.9, 125.7, 125.3, 52.5, 37.1, 33.4, 20.7; FTIR (neat): 1713, 1254, 906, 727 cm^{-1}; HRMS (pos-APCI) calcd for $C_{27}H_{23}O_2$: 379.1697; Found: 379.1695.

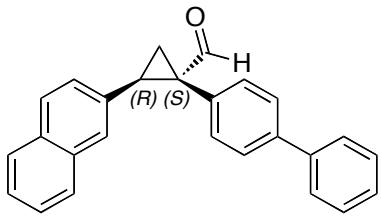
(1*R*, 2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarboxylate (ent-2-94)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 2-vinylnaphthalene (1 g, 6.6 mmol) and Rh_2(*S*-DOSP)$_4$ (54 mg, 0.5 mol %) were dissolved in dry, degassed toluene (50 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (1.51 g, 6 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-2-94** as a colorless oil in 88 % yield (2.02 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 82 % (312 mg) of product. HPLC analysis: 98 % ee

(OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.5 (major) and 15.3 (minor) min, UV 254 nm); R_f = 0.30 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **2-94**.

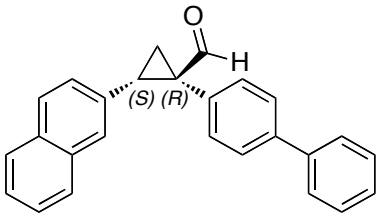
(1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde (2-95)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarboxylate **2-94** (2.1 g, 5.5 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (260 mg, 6.8 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol mixture was dissolved in methylene chloride (50 mL) and Dess Martin Periodinane (DMP) reagent (3.5 g, 8.25 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **2-95**

as an oily liquid in 79 % yield (1.5 g); R_f = 0.40 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.71-7.61 (m, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.44-7.33 (m, 6H), 7.32-7.23 (m, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.90 (dd, *J* = 8.5, 1.22 Hz, 1H), 3.20 (t, *J* = 8.4 Hz, 1H), 2.30 (dd, *J* = 9.1, 5.2 Hz, 1H), 2.22-2.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.3, 140.2, 140.1, 132.9, 132.8, 132.6, 132.1, 131.5, 128.5, 127.4, 127.3, 127.1, 127.09, 126.9, 126.8, 125.9, 125.7, 125.5, 46.1, 35.5, 19.8; FT-IR (neat): 1700, 1487, 906, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{26}H_{20}O$: 348.1508; Found: 348.1510; Anal. Calcd. for $C_{26}H_{20}O$: C, 89.62; H, 5.79; Found: C, 89.36; H, 5.78.

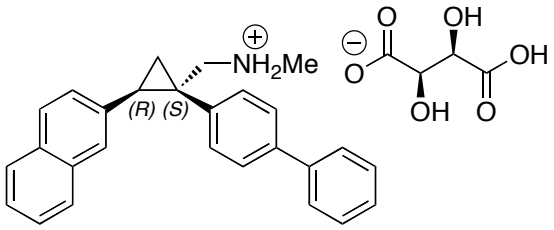
(1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde (ent-2-95)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarboxylate **ent-2-94** (2.1 g, 5.5 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (260 mg, 6.8 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure.

The crude alcohol mixture was dissolved in methylene chloride (50 mL) and Dess Martin Periodinane (DMP) reagent (3.5 g, 8.25 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-2-95** as an oily liquid in 60 % yield (1.13 g); R_f = 0.40 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **2-95**.

1-((1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (2-96)

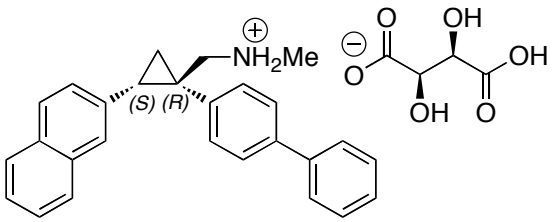


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde **2-95** (348 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1.2 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (57 mg, 1.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water,

then brine, and 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: triethylamine = 9:1) to give a ligh yellow oil in 96 % yield (350 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.0 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.52-7.44 (m, 3H), 7.41-7.24 (m, 8H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.82 (dd, *J* = 8.5, 1.2 Hz, 1H), 3.17 (d, *J* = 11.9 Hz, 1H), 2.69 (d, *J* = 12.2 Hz, 1H), 2.47 (s, 3H), 2.46 (m, 1H), 1.69 (t, *J* = 5.49 Hz, 1H), 1.51 (dd, *J* = 8.5, 5.19 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 139.0, 137.9, 136.6, 133.0, 131.5, 131.0, 127.3, 127.1, 126.9, 126.8, 126.7, 126.6, 126.0, 125.5, 124.7, 63.0, 36.4, 35.5, 28.5, 18.1; FT-IR (neat): 2791, 1486, 767, 727 cm^{-1}; HRMS (pos-APCI) calcd for $C_{27}H_{26}N_1$: 364.2059; Found: 364.2056; Anal. Calcd. for $C_{31}H_{31}NO_6 + H_2O$: C, 72.50; H, 6.08; N, 2.73; Found: C, 69.93; H, 6.14; N, 2.61.

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (150 mg, 1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to get 513 mg of white solid.

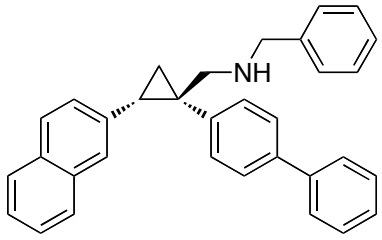
1-((1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (ent-2-96)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde **ent-2-95** (174 mg, 0.5 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1 mmol) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (29 mg, 0.75 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 71 % yield (139 mg).

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (60 mg, 0.4 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to get 63 mg of white solid.); Spectroscopic data is same as **2-96**.

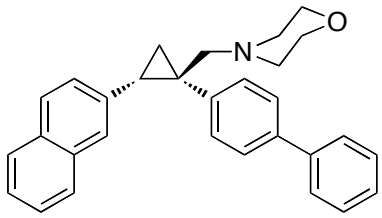
1-((1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-benzylmethanamine (ent-2-96 a)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde **ent-2-95** (174 mg, 0.5 mmol, 1eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with phenylmethanamine (64 mg, 0.6 mmol. 1.1 eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (30 mg, 1 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 76 % yield (171 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.63 (m, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 4H), 7.42-7.16 (m, 14H), 6.83 (dd, *J* = 8.5, 1.8 Hz, 1H), 3.86 (d, *J* = 4.9 Hz, 2H), 3.25–3.15 (m, 1H), 2.75 (d, *J* = 12.3 Hz, 1H), 2.44 (dd, *J* = 8.7, 5.9 Hz, 1H), 1.75-1.66 (m, 1H), 1.50 (dt, *J* = 8.8, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ

141.0, 140.8, 139.4, 138.5, 137.2, 133.5, 132.1, 131.6, 129.0, 128.7, 128.7, 128.3, 127.8, 127.7, 127.4, 127.2, 127.1, 126.6, 126.5, 126.1, 125.3, 60.3, 53.8, 36.1, 29.0, 18.6; FT-IR (neat): 3025, 2813, 1486, 1451, 767, 696 cm^{-1}; HRMS (pos-APCI) calcd for $C_{33}H_{30}N_1$: 440.2372; Found: 440.2369.

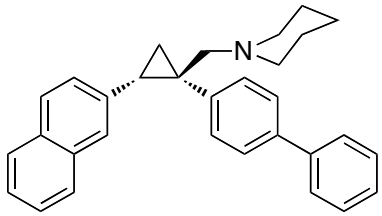
4-(((1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropyl)methyl)morpholine (ent-2-96 b)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde **ent-2-95** (174 mg, 0.5 mmol, 1 eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with morpholine (52 mg, 0.6 mmol, 1.1 eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (30 mg, 1 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 54 % yield (113 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.63 (m, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 3H), 7.40-7.23 (m, 8H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 1H),

3.65 (s, 4H), 2.86 (d, *J* = 12.7 Hz, 1H), 2.60 (d, *J* = 12.7 Hz, 1H), 2.55 (s, 4H), 2.37 (dd, *J* = 8.8, 6.0 Hz, 1H), 1.69 (t, *J* = 5.7 Hz, 1H), 1.45 (dd, *J* = 8.8, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 139.1, 138.9, 136.9, 133.42 132.0, 131.5, 128.9, 127.7, 127.5, 127.2, 127.1, 126.6, 126.4, 126.3, 126.0, 125.2, 70.0, 67.2, 54.5, 33.6, 29.3, 18.4; FT-IR (neat): 2958, 2805, 1735, 1115, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{30}H_{30}N_1O_1$: 420.2321; Found: 420.2317.

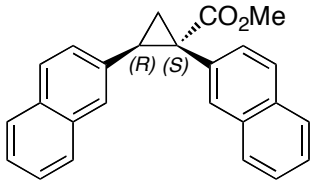
1-(((1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropyl)methyl)piperidine (ent-2-96 c)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(naphthalen-2-yl)cyclopropanecarbaldehyde **ent-2-95** (174 mg, 0.5 mmol, 1 eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with piperidine (51 mg, 0.6 mmol, 1.1 eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (30 mg, 1 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 55 % yield (116

mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.0 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 8.6 Hz, 2H), 7.40–7.22 (m, 9H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.79 (m, 1H), 2.79 (d, *J* = 12.9 Hz, 1H), 2.61 (d, *J* = 13.0 Hz, 1H), 2.5 (br s, 4H), 2.38 (d, *J* = 2.7 Hz, 1H), 1.65 (s, 1H), 1.51 (s, 4H), 1.49 (m, 1H), 1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 139.7, 138.7, 137.4, 133.4, 131.9, 131.5, 128.8, 127.7, 127.5, 127.1, 126.5, 126.3, 125.8, 125.0, 69.9, 55.5, 34.1, 29.3, 26.2, 24.6, 18.3; FT-IR (neat): 2932, 1599, 1112, 782, 730 cm^{-1}; HRMS (pos-APCI) calcd for $C_{31}H_{32}N_1$: 418.2529; Found: 418.2524.

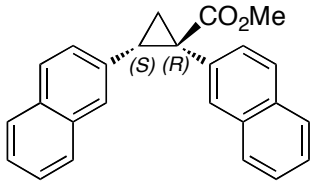
(1*S*,2*R*)-Methyl 1,2-di(naphthalen-2-yl)cyclopropanecarboxylate (2-97)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 2-vinylnaphthalene (925 mg, 6 mmol) and Rh_2(*R*-DOSP)$_4$ (54 mg, 0.5 mol %) were dissolved in dry, degassed toluene (50 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (1.35 g, 6 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-97** as a colorless oil in 95 % yield (2 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 96 % (339 mg) of product. HPLC analysis: 96 % ee (OD-H column, 3% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.9 (minor) and 11.2 (major) min, UV

210 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.54 (m, 4H), 7.49-7.41 (m, 3H), 7.40-7.29 (m, 4H), 7.26 (s, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 3.67 (s, 3H), 3.35 (t, *J* = 8.4 Hz, 1H), 2.30 (dd, *J* = 9.1, 4.88 Hz, 1H), 2.13-2.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 133.6, 132.7, 132.7, 132.3, 132.1, 131.8, 130.2, 129.7, 129.6, 127.4, 127.2, 127.1, 127.0, 126.9, 126.8, 125.5, 125.4, 125.1, 60.0, 52.2, 37.4, 33.2, 20.6, 13.9; FT-IR (neat): 1713, 1434, 1259, 906, 726 cm^{-1}; HRMS (pos-APCI) calcd for $C_{25}H_{21}O_2$: 353.1536; Found:. 353.1541.

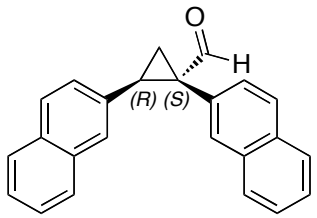
(1*R*,2*S*)-Methyl 1,2-di(naphthalen-2-yl)cyclopropanecarboxylate (ent-2-97)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 2-vinylnaphthalene (925 mg, 6 mmol) and Rh_2(*S*-DOSP)$_4$ (54 mg, 0.5 mol %) were dissolved in dry, degassed toluene (50 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (1.35 g, 6 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-2-97** as a colorless oil in 99 % yield (2.1 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 93 % (329 mg) of product. HPLC analysis: 94 % ee (OD-H column, 3% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.9 (major) and 11.2

(minor) min, UV 210 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **2-97**.

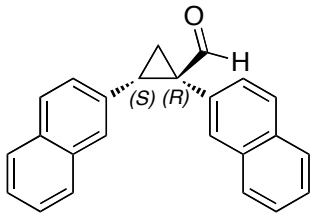
(1*S*,2*R*)-1,2-di(naphthalen-2-yl)cyclopropanecarbaldehyde (2-98)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1,2-di(naphthalen-2-yl)cyclopropanecarboxylate **2-97** (1.92 g, 5.5 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (260 mg, 6.8 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol mixture was dissolved in methylene chloride (50 mL) and Dess Martin Periodinane (DMP) reagent (3.5 g, 8.25 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (x2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **2-98** as an oily liquid in 69 % yield (1.21 g); R_f = 0.45 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 7.69 (br. s, 2H), 7.59 (d, *J* = 8.2 Hz, 3H), 7.49-7.44 (m,

3H), 7.42-7.37 (m, 2H), 7.36-7.29 (m, 2H), 7.13 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 3.26 (t, J = 8.2 Hz, 1H), 2.35 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.3, 132.9, 132.9, 132.8, 132.7, 132.4, 132.0, 131.3, 130.3, 128.6, 127.9, 127.5, 127.4, 127.2, 127.1, 125.8, 125.8, 125.5, 125.4, 46.4, 35.4, 19.9; FT-IR (neat): 1697, 906, 856, 815, 726 cm^{-1}; HRMS (pos-APCI) calcd for $C_{24}H_{18}O$: 322.1352; Found: 322.1353; Anal. Calcd. for $C_{24}H_{18}O$: C, 84.41; H, 5.63; Found: C, 89.19; H, 5.63.

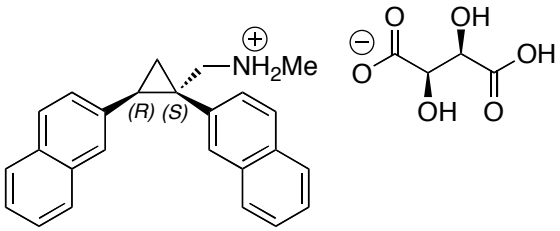
(1*R*,2*S*)-1,2-di(naphthalen-2-yl)cyclopropanecarbaldehyde (ent-2-98)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1,2-di(naphthalen-2-yl)cyclopropanecarboxylate **ent-2-97** (1.92 g, 5.5 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (260 mg, 6.8 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol mixture was dissolved in methylene chloride (50 mL) and Dess Martin Periodinane (DMP) reagent (3.5 g, 8.25 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with

aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-2-98** as an oily liquid in 66 % yield (1.16 g); R_f = 0.45 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **2-98**.

1-((1*S*,2*R*)-1,2-di(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (2-99)

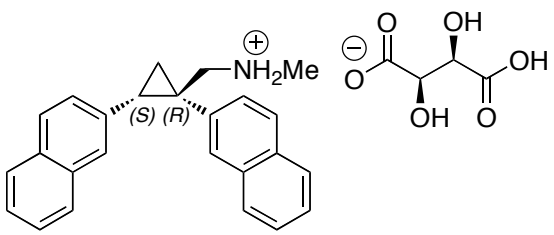


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1,2-di(naphthalen-2-yl)cyclopropanecarbaldehyde **2-98** (322 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1.2 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (57 mg, 1.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 94 % yield (317 mg). ^{1}H NMR (400

MHz, $CDCl_3$): δ 7.76-7.65 (m, 3H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.54 (dd, *J* = 12.2, 8.5 Hz, 2H), 7.44-7.35 (m, 3H), 7.34-7.23 (m, 3H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 3.25 (d, *J* = 12.2 Hz, 1H), 2.68 (d, *J* = 12.2 Hz, 1H), 2.57-2.48 (m, 1H), 2.43 (s, 3H), 1.81 (t, *J* = 5.5 Hz, 1H), 1.58 (dd, *J* = 8.5, 5.2 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 133.1, 133.0, 132.1, 131.5, 129.6, 128.6, 127.7, 127.5, 127.4, 127.3, 127.1, 126.8, 126.1, 125.9, 125.6, 125.5, 125.4, 124.7, 62.9, 36.4, 36.1, 28.6, 18.2; FT-IR (neat): 3052, 2790, 1507, 746, 726 cm^{-1}; HRMS (pos-APCI) calcd for $C_{25}H_{24}N_1$: 338.1903; Found: 338.1899; Anal. Calcd. for $C_{29}H_{29}NO_6 + H_2O$: C, 71.44; H, 6.00; N, 2.87; Found: C, 68.25; H, 6.12; N, 2.81.

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (150 mg, 1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to get 342 mg of white solid.

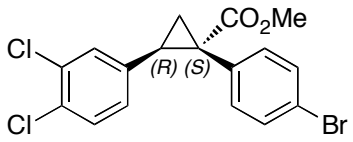
1-((1*R*,2*S*)-1,2-di(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (ent-2-99)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1,2-di(naphthalen-2-yl)cyclopropanecarbaldehyde **ent-2-99** (322 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1.2 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (57 mg, 1.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 87 % yield (342 mg).

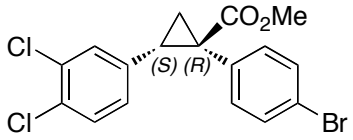
The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (150 mg, 1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to get 342 mg of white solid. Spectroscopic data is same as **2-99**.

(1*S*,2*R*)-Methyl 1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (2-100)



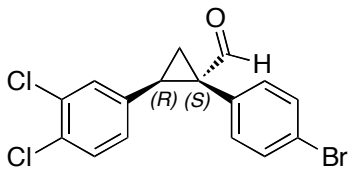
In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-dichloro-4-vinylbenzene (4 g, 22 mmol) and Rh_2(*R*-DOSP)$_4$ (198 mg, 0.5 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(4-bromophenyl)-2-diazoacetate (5 g, 20 mmol) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 6 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-100** as a colorless oil in 89 % yield (7.1 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 89 % (354 mg) of product. HPLC analysis: 92 % ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.7 (minor) and 12.3 (major) min, UV 254 nm); R_f = 0.35 (4:1 Hexanes: EtOAc); The product was recrystalized to get > 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.48 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.64 (s, 3H), 3.04 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.14 (dd, *J* = 9.3, 5.2 Hz, 1H), 1.77 (dd, *J* = 7.2, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 136.5, 133.4, 133.1, 131.9, 131.2, 130.5, 130.2, 129.7, 126.9, 126.9, 121.6, 52.8, 37.0, 31.9, 31.9, 20.5; FT-IR (neat): 1717, 1475, 1253, 1163, 721 cm^{-1}; HRMS (pos-APCI) calcd for $C_{17}H_{14}Br_1Cl_2O_2$: 398.9548; Found: 398.9548.

(1*R*,2*S*)-Methyl 1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (ent-2-100)



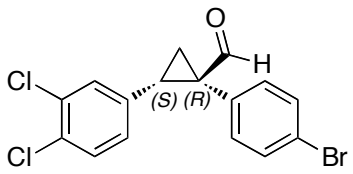
In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-dichloro-4-vinylbenzene (4 g, 22 mmol) and Rh_2(*S*-DOSP)$_4$ (198 mg, 0.5 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(4-bromophenyl)-2-diazoacetate (5 g, 20 mmol) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 6 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-2-100** as a colorless oil in 96 % yield (7.6 g), > 94 de (determined by ^{1}H-NMR of the crude reaction mixture). This reaction was also performed in 1 mmol scale, to obtain 91 % (361 mg) of product. HPLC analysis: 98 % ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.7 (major) and 12.3 (minor) min, UV 254 nm); R_f = 0.35 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **2-100**.

(1*S*,2*R*)-1-(4-Bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (2-101)



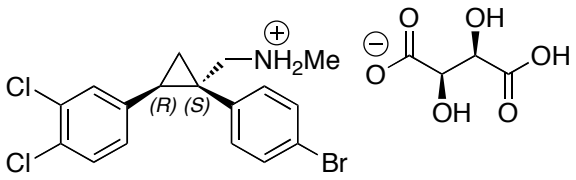
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate **2-100** (6.0 g, 15 mmol, 1 eq.) was dissolved in THF (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (683 mg, 18 mmol, 1.2 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol mixture was dissolved in methylene chloride (100 mL) and Dess Martin Periodinane (DMP) reagent (12.7 g, 30 mmol, 2 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **2-101** as an oily liquid in 98 % yield (5.5 g); $R_f = 0.45$ (4:1 Hexanes: EtOAc);

(1*R*,2*S*)-1-(4-Bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-2-101)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate **ent-2-100** (6.0 g, 15 mmol, 1 eq.) was dissolved in THF (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (683 mg, 18 mmol, 1.2 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol mixture was dissolved in methylene chloride (100 mL) and Dess Martin Periodinane (DMP) reagent (12.7 g, 30 mmol, 2 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (×2). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-2-101** as an oily liquid in 89 % yield (5.5 g); R_f = 0.45 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **2-101.**

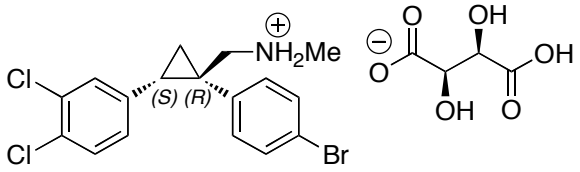
1-((1*S*,2*R*)-1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (2-102)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde **2-101** (5.5 g, 15 mmol, 1 eq.) was dissolved in methanol (100 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 18 mL, 30 mmol) and Ti(O-*i*Pr)$_4$ (15 mL, 30 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (850 mg, 22.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 80 % yield (4.5 g).

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (150 mg, 1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to get 342 mg of white solid.

1-((1*R*,2*S*)-1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate (ent-2-102)

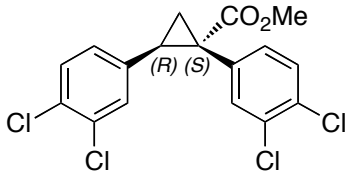


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-(4-bromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde **ent-2-102** (5.5 g, 15 mmol, 1 eq.) was dissolved in methanol (100 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 18 mL, 30 mmol) and Ti(O-*i*Pr)$_4$ (15 mL, 30 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (850 mg, 22.5 mmol) was added and the reaction was stirred for an additional 4 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a light yellow oil in 78 % yield (4.4 g).

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (150 mg, 1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and

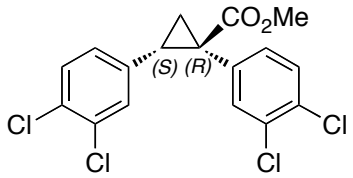
washed with cold acetone to get 342 mg of white solid. Spectroscopic data is same as **2-102**.

(1*S*,2*R*)-methyl 1,2-Bis(3,4-dichlorophenyl)cyclopropanecarboxylate (2-103)



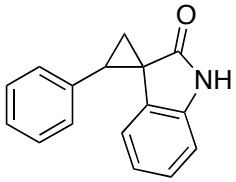
In a 100 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (5.1 g, 30 mmol, 1.5 eq.) and Rh_2(*R*-DOSP)$_4$ (105 mg, 0.25 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (4.9 g, 20 mmol, 1 eq.) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 6 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **2-103** as a clear liquid in 80% yield (6.2 g), > 94% de (determined by ^{1}H-NMR of the crude reaction mixture). HPLC analysis: 80% ee (SS-Whelk column, 7.5 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.5 (major) and 12.8 (minor) min, UV 254 nm); recrystallized from hexanes to give >92% ee; R_f = 0.31 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.3 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 3.68 (s, 3H), 3.06 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.16 (dd, *J* = 9.3, 5.3 Hz, 1H), 1.79 (dd, *J* = 7.3, 5.3 Hz, 1H). Spectroscopic data matches with the previously reported data in the Davies group.

(1*R*,2*S*)-methyl 1,2-bis(3,4-dichlorophenyl)cyclopropanecarboxylate (ent-2-103)



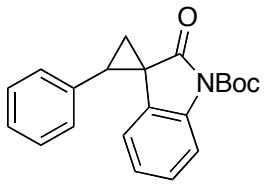
In a 100 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (5.1 g, 30 mmol, 1.5 eq.) and Rh_2(*S*-DOSP)$_4$ (105 mg, 0.25 mol %) were dissolved in dry, degassed toluene (100 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (4.9 g, 20 mmol, 1 eq.) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 6 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-2-103** as a clear liquid in 64 % yield (5 g), > 94% de (determined by ^{1}H-NMR of the crude reaction mixture). HPLC analysis: 82 % ee (SS-Whelk column, 7.5 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.5 (minor) and 12.8 (major) min, UV 254 nm); recrystallized from hexanes to give >92% ee; R_f = 0.31 (4:1 Hexanes: EtOAc). Spectroscopic data matches with the previously reported data in the Davies group.

2-Phenylspiro[cyclopropane-1,3'-indolin]-2'-one (2-104)



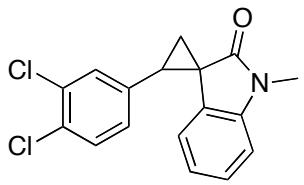
In a 50 mL round bottom flask equipped with a magnetic stir bar, styrene (0.52 mL, 5 mmol, 5 eq.) and Rh_2(*S*-DOSP)$_4$ (10 mg, 0.001 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (10 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. 3-Diazoindolin-2-one (318 mg, 1 mmol, 1 eq.) was dissolved in dry, degassed toluene (10 mL) and added by syringe pump over 1 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) to obtain **2-104** as a colorless oil in 68 % yield (303 mg), 82% de (determined by ^{1}H-NMR of the crude reaction mixture). HPLC analysis: 5 % ee (OD-H column, 2% 2-PrOH in hexanes, 0.8 mL/min, 1mg/mL, t_R = 25.2 (major) and 32.9 (minor) min, UV 254 nm); R_f = 0.1 (1:1 Hexanes: EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.32 (m, 4H), 7.25 (d, *J* = 6.4 Hz, 2H), 7.12 (t, *J* = 8.4 Hz, 1H) 7.01 (d, *J* = 7.6 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 3.43 (t, *J* = 8.4 Hz, 1H) 2.29 (q, *J* = 4.8 Hz, 1H), 2.07 (q, *J* = 4.4 Hz, 1H). Spectroscopic data matches with the data reported previously in the Davies group.

***tert*-Butyl 2'-oxo-2-phenylspiro[cyclopropane-1,3'-indoline]-1'-carboxylate (2-105)**



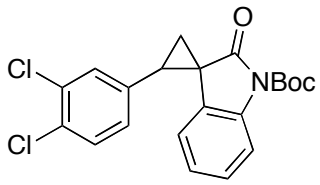
In a 50 mL round bottom flask equipped with a magnetic stir bar, styrene (0.26 mL, 2.5 mmol, 5 eq) and Rh_2(*S*-DOSP)$_4$ (10 mg, 0.001 mmol, 0.02 eq) were dissolved in dry, degassed hexane (10 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. N-Boc 3-diazoindolin-2-one (124 mg, 0.5 mmol, 1 eq) was dissolved in dry, degassed hexane (10 mL) and added by syringe pump over 1 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) to obtain **2-105** as a colorless oil in 62 % yield (101 mg), 85% de (determined by ^{1}H-NMR of the crude reaction mixture). HPLC analysis: 5 % ee (OD-H column, 2% 2-PrOH in hexanes, 0.8 mL/min, 1mg/mL, t_R = 6.28 (major) and 7.66 (minor) min, UV 254 nm); R_f = 0.1 (1:1 Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.24 (m, *J* = 5.2 Hz, 3H), 7.15 (d, *J* = 7.6 Hz, 3H), 6.75 (t, *J* = 7.6 Hz, 1H), 5.90 (d, J = 7.6 Hz, 1H), 3.38 (t, *J* = 8.8 Hz, 1H), 2.26 (q, *J* = 4.4 Hz, 1H), 1.99 (q, *J* = 4.8 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.42, 174.40, 148.99, 139.38, 133.94, 129.67, 128.10, 127.29, 126.50, 125.99, 123.11, 120.07, 120.02, 114.37, 114.34, 83.60, 37.77, 37.73, 33.25, 27.82, 27.79, 27.73, 23.65. HRMS (pos-APCI) calcd for $C_{21}H_{22}O_3N_1$: 336.1594; Found: 336.1596. Spectroscopic data matches with the data reported previously in the Davies group.

2-(3,4-Dichlorophenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (2-106)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-dichloro-4-vinylbenzene (173 mg, 1 mmol, 4 eq) and $Rh_2(OAc)_4$ (1 mg, 1 mol %) were dissolved in dry, degassed methylene chloride (10 mL). 3-diazo-1-methylindolin-2-one (40 mg, 0.25 mmol, 1 eq) was dissolved in dry, degassed methylene chloride (10 mL) and added by syringe pump over 1 h while refluxing. The reaction mixture was stirred for 1 h at reflux temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) to obtain **2-106** as a colorless oil in 43 % yield (34 mg). R_f = 0.1 (1:1 Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.29 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.01 (d, *J* = 7.3 Hz, 1H), 3.32 (s, 3H), 3.26-3.17 (m, 1H), 2.18 (dd, *J* = 8.8, 4.58 Hz, 1H), 1.91 (dd, *J* = 7.4, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 143.7, 135.5, 132.3, 131.5, 131.3, 130.2, 129.2, 126.9, 126.5, 121.6, 120.4, 107.9, 34.2, 33.1, 26.5, 26.5, 22.0; FT-IR (neat): 1701, 1614, 1468, 1375, 1127, 729 cm^{-1}; HRMS (pos-APCI) calcd for $C_{17}H_{14}O_1N_1$: 318.0447; Found: 318.0451.

***tert*-Butyl 2-(3,4-dichlorophenyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-carboxylate (2-107)**



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-dichloro-4-vinylbenzene (173 mg, 1 mmol, 4 eq) and $Rh_2(OAc)_4$ (1 mg, 1 mol %) were dissolved in dry, degassed methylene chloride (10 mL). *tert*-butyl 3-diazo-2-oxoindoline-1-carboxylate (61 mg, 0.25 mmol, 1 eq) was dissolved in dry, degassed methylene chloride (10 mL) and added by syringe pump over 1 h while refluxing. The reaction mixture was stirred for 1 h at reflux temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) to obtain **2-107** as a colorless oil in 10 % yield (39 mg). R_f = 0.1 (1:1 Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.39-7.28 (m, 2H), 7.21 (t, *J* = 7.93 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 5.98 (d, *J* = 7.3 Hz, 1H), 3.28 (t, *J* = 8.7 Hz, 1H), 2.27 (dd, *J* = 9.1, 4.88 Hz, 1H), 1.93 (dd, *J* = 8.0, 4.73 Hz, 1H), 1.68 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 27.6, 28.0, 33.4, 36.4, 84.3, 114.8, 120.2, 123.6, 125.4, 127.2, 129.4, 130.3, 131.7, 131.7, 132.5, 134.7, 139.7, 149.1, 174.4; FT-IR (neat): 1782, 1752, 1728, 1147, 729 cm^{-1}; HRMS (pos-APCI) calcd for $C_{18}H_{19}O_2N_2Cl_2$: 365.0818; Found: 365.0824.

Chapter 3: Synthesis and docking studies of novel class of selective Serotonin Norepinephrine Reuptake Inhibitors (SNRI's) for the treatment of neuropathic pain

3.1 Introduction

Neuropathic pain is defined as " *Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".*[1] This is a serious health care problem and costs billions of dollars annually in treatment expense and lost productivity in the United States.[2] Recent studies and surveys have suggested that up to 30% of adults in the US report suffering from moderate to severe chronic pain.[3] Moreover, this pain condition will have severe impact on quality of life and mood of affected patients due to the long-term nature 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 system, which can lead to spontaneous action-potential firing in the sensory neurons.[4] This abnormality in the sensory system would cause hypersensitivity and spontaneous pain.

The major symptoms of neuropathic pain include hyperalgesia (increased response to a mild painful stimulus) and allodynia (a painful response to a normally innocuous stimulus). The stimuli can be mechanical or thermal in nature.

Many options were available for the treatment of chronic neuropathic pain such as tricyclic antidepressants (TCA's),[5] antiepileptic drugs,[6] analgesics, α_2-adrenergic

agonists,[7] and anticonvulsants;[8] however, opioids remain a mainstay of therapy.[9] Recent clinical studies concluded that these agents do not provide adequate relief for many patients and a significant number of the agents have shown dose limiting side effects such as sedation, confusion and impairment. Even though opioids are somewhat effective in clinic, they have some serious limitations, which include, 1) the development of tolerance; 2) physical dependency; 3) the substantial abuse liability; 4) potential for addiction; 5) potential for diversion of medication to the illicit drug market.[10] There is enormous need for the development of efficacious alternatives to opioids to reduce the burden of prescription abuse on society.

One alternate approach of therapy would be to administer the drug directly in to the intrathecal (i.t) space to avoid side effects associated with systemic administration.[11] However, relatively few drugs were identified to have sufficient potency and efficacy for practical application of this method to patients with neuropathic pain. Opioids, clonidine[12] and ziconotide[13,14] are used most frequently in the clinic; however, each displays dose-limiting side effects. Antidepressants have shown limited efficacy against neuropathic pain when given intrathecally.

Serotonin (SE) and norepinephrine (NE) were recognized as the main neurotransmitters involved in the modulation of endogenous pain mechanism *via* descending pain inhibitory pathway, which extends from the brain-stem to the dorsal horn. A study with knockout mice lacking SE neurons proved the importance of serotonergic neurons in the pain pathway.[15] Recently, a comprehensive review of all current medications available for treating neuropathic pain along with their clinical

studies has been reported.[4] 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-mediated mechanisms. Several dual SERT/NET reuptake inhibitors (SNRI's) such as duloxetine and milnacipran were found to be effective in treating neuropathic pain but they also showed some adverse side effects such as nausea, vomiting, and dry mouth. In some cases, severe life threatening conditions such as hepatotoxicity and cardiac arrhythmias were also observed.[16] A number of models are available to study neuropathic pain in animals. Novel compounds could be tested for their efficacy in animals to get better understanding of pain pathology before administrating in clinic.[12,17]

In summary, there is no proven treatment for neuropathic pain and there is an unmet clinical need to develop drugs that are sufficiently potent to provide adequate pain control without any adverse effects when administered intrathecally.

3.2 Background

3.2.1 Monoamine reuptake inhibitors – classification

There are three different kinds of monoamine neurotransmitter's serotonin (SE), Norepinephrine (NE) and dopamine (DA) in the human brain that transmit nerve impulses from presynaptic neurons to postsynaptic neurons (Fig. 3.1). When an impulse gets transmitted, neurotransmitters will 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 modulate sleep, mood, emotion and appetite.[18]

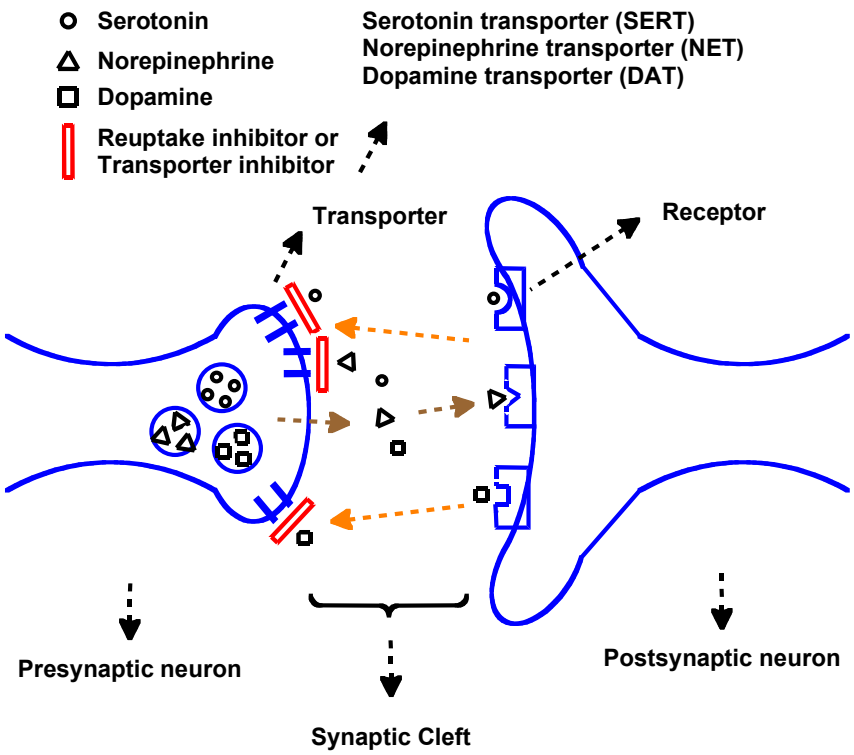


Figure 3.1: Graphical representation of monoamine reuptake inhibition.

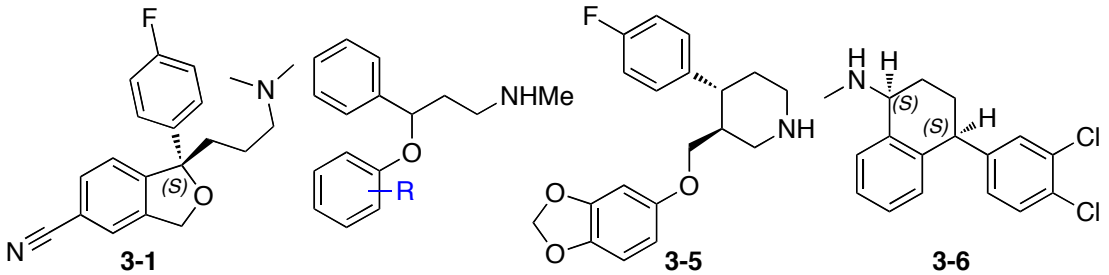
Many classes of clinical drugs target these three transporters and there by have been classified into many groups based on their ability to selectively inhibit serotonin and/or noradrenaline and/or dopamine reuptake into the presynaptic neurons. Monoamine transporter inhibitors are an established drug class that has proven utility for the treatment of a number of CNS disorders, especially major depression disorder (MDD).[19] The structures of some of the clinical drugs are summarized in Fig. 3.1 and their binding affinities towards various transporters are tabulated in Table 3.1.

1. Selective serotonin reuptake inhibitors (SSRI's) – inhibit serotonin reuptake by binding to SERT. The drugs in this class are used for the treatment of major depression, obsessive-compulsive, panic and social anxiety disorders. Some examples of this class include:
    - Escitalopram (Laxapro)(**3-1**) - It is a 2nd most prescribed antidepressant in the United States.[20]
    - Fluoxetine (Prozac) (**3-2**) – marketed by Eli Lily, it is a 5th most prescribed antidepressant in the United States.[21]
    - Peroxetine (Paxel) **(3-5)** – marketed by GlaxoSmithKline.[22]
    - Sertraline (Zoloft) (**3-6**) – marketed by Pfizer, it is a 4th most prescribed antidepressant in the United States.[23]

2. Serotonin and norepinephrine reuptake inhibitors (SNRI's) – inhibit reuptake of serotonin and norepinephrine by binding to both SERT and NET. Some examples of this class include:
    - Duloxetine (Cymbalta) (**3-7)** – marketed by Eli Lilly in its (*S*)-enantiomeric form. It is a 7th most prescribed antidepressant in the United States and appears to alleviate pain associated with diabetic neuropathy[24] and fibromyalgia.
    - Venlafaxin (Effexor) (**3-9**) – marketed by Pfizer. It is a 9th most prescribed antidepressant in the United States[25].

3. Selective noradrenalin reuptake inhibitors (NARI's) – inhibit reuptake of norepinephrine by binding exclusively to NET. These compounds were found to modulate the concentration and motivation in the treated individuals. Some examples of this class include:

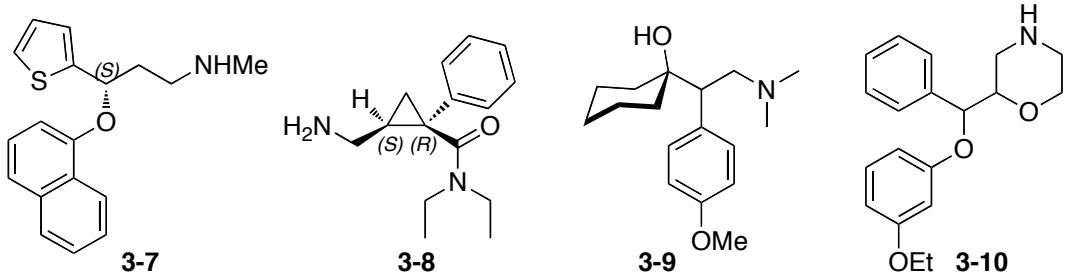
   - Atomoxetine (Strattera) (**3-3**) – marketed by Sun pharmaceuticals for the treatment of attention-deficit hyperactivity disorder (ADHD).[26]
   - Reboxetine (Edronax) (**3-10**) – marketed by Pfizer in European countries, but not in the United States due to lack of proven efficacy.[27]
   - Nisoxetine (**3-4**) – not currently used in humans.



Escitalopram R = 4-CF_3; Fluoxetine **3-2**
R = 2-Me; Atomoxetine **3-3**
R = 2-OMe; Nisoxetine **3-4**

Paroxetine

Sertraline

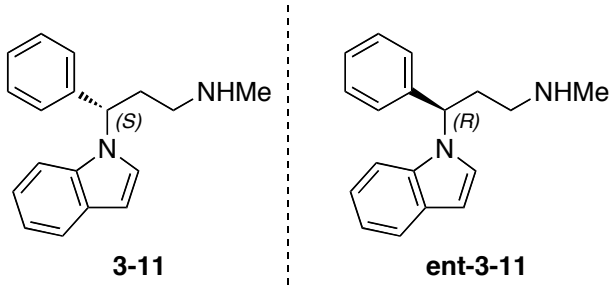


Duloxetine

Milnacipran

Venlafaxine

Reboxetine



3-11 **ent-3-11**

Figure 3.2: Representative examples of clinical monoamine reuptake inhibitors.

Entry	Type	Name	SERT	NET	DAT
3-1	SSRI	Escitalopram	1.16	4070	28100
3-2		Fluoxetine	0.81	240	3600
3-5		Paroxetine	0.13	40	490
3-6		Sertraline	0.29	420	25
3-7	SNRI	(S)-Duloxetine	0.8	7.5	240
3-8		Milnacipran	62	31	10K
3-9		Venlafaxine	82	2480	7647
3-3	NARI	Atomoxetine	8.9	2.03	1080
3-10		Reboxetine	720	11	10K
3-4		Nisoxetine	383	5	477

Table 3.1: Binding affinities of monoamine reuptake inhibitors towards SERT, NET and DAT (K_i values in nM).[28]

Apart from clinical antidepressants, many new classes of compounds have been identified to inhibit reuptake of monoamine neurotransmitters. Indole derivatives **(3-11)** were found to be potent against both SERT and NET.[29] New duloxetine analogues have also been synthesized using asymmetric cyclopropanation of allylic alcohols.[30]

3.2.2 Milnacipran

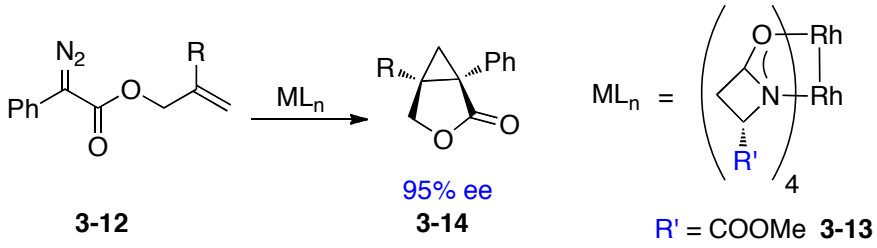
Milnacipran (**3-8**) is a commercially available antidepressant (Ixel®) in France, Japan, and Austria. In 2009, Federal Drug Administration (FDA) approved milnacipran for the treatment of fibramyalgia, a chronic pain condition.[31-34] It acts as a **S**erotonin (decrease depression) **N**orepinephrin (decrease chronic pain) **R**euptake **I**nhibitor (SNRI).[31,35] Extensive studies provided clear-cut evidence of its efficacy for depression treatment in various clinical trails. Even though it inhibits both SERT and NET, there was no significant effect on post synaptic H_1, α-1, D_1, D_2 and muscarinic receptors, as well as on benzodiazepine/opiate binding site.[36-41,42-49] It was shown that the conformationally restricted analogues of milnacipran would act as *N*-methyl-D-aspartic acid (NMDA) receptor antagonists.[4350]

A number of SAR studies of milnacipran have been reported.[51] In 2008, Chen *et al.* reported thiophene derivatives of milnacipran, which were found to inhibit both serotonin and norepinephrine reuptake. They tested their novel analogues for the treatment of neuropathic pain.[52]

In the US, milnacipran is still in Phase I and Phase II clinical trails for the treatment of depression. This drug has been found to have a high bioavailability of 85%. The recommended dosage for the drug is 50 mg × 2 per day for 9 months to have therapeutic effect.

One of the limitations of using this drug was that it is commercially available as a racemate and this might be the reason for few of the side effects which include itching, nausea, vertigo, increased anxiety, sweats, shivering, dysuria and testicle pain. It takes 1 to 3 weeks for the drug to show antidepressive action. 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.

3.2.3 Enantioselective synthesis of milnacipran

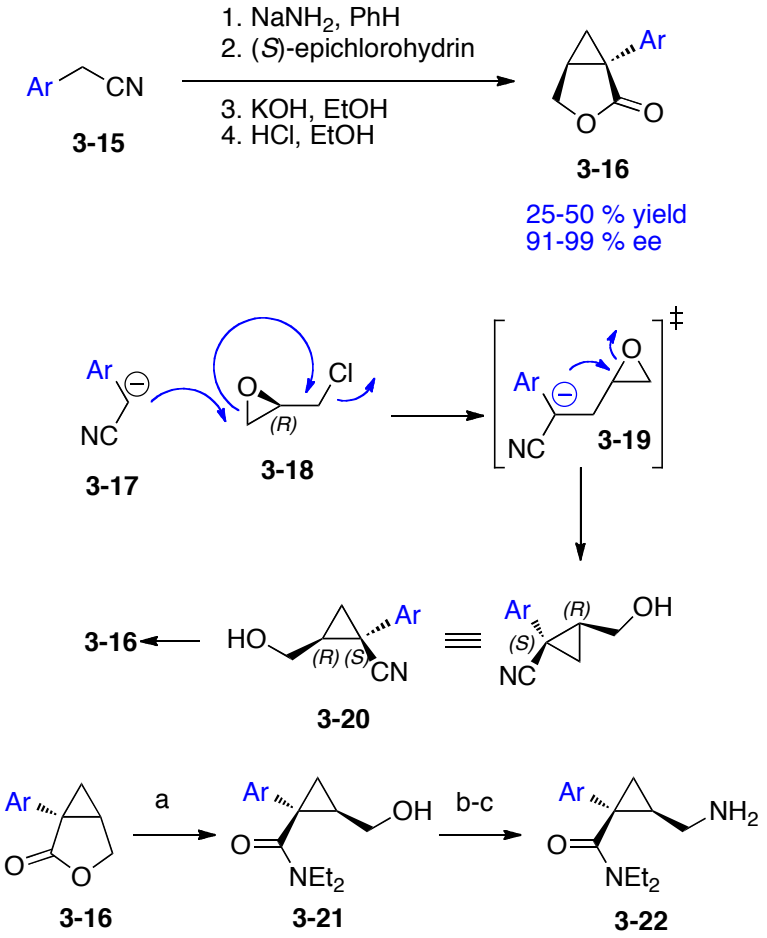


Scheme 3.1: Enantioselective synthesis of Milnacipran.

In 2001, Doyle *et al.* reported an enantioselective synthesis of milnacipran and its' derivatives.[53,54] The intramolecular cyclopropanation reaction of allyl phenyldiazoacetate (**3-12**) in the presence of the carboxamidate catalyst **3-13** led to a cyclopropane fused

lactone (**3-14**) in 85% yield and up to 95% ee, which could be converted to milnacipran in the synthetic sequence mentioned in Scheme 3.2. Even though high enantioinduction was observed in some cases (R=Me), the intramolecular reaction where R = H, moderate ee (68%) was observed.

Later in 2002, a general strategy for the synthesis of enantiopure milnacipran was reported.[55] Since then, it has been used as a standard procedure for the synthesis of various analogues and derivatives of milnacipran, which has facilitated a broad SAR study around this novel scaffold. This strategy involves, a one-pot reaction of various aryl acetonitriles (**3-15**) with sodium amide and (*S*) or (*R*)-epichlorohydrin (**3-18**) resulted in a synthesis of a series of highly enriched bicyclic lactones (**3-16**). The mechanism of this reaction involves a cyclopropane ring-closure reaction between **3-17** and **3-18**. In the presence of a base, **3-15** gets deprotonated to form **3-17** that can attack the terminal epoxide in a complete regioselective fashion leading to the formation of second epoxide intermediate **(3-19)**. This would then be opened-up to form cyclopropane **3-20**. The resultant bicyclic lactone **(3-16)** could be converted to milnacipran by aminolysis with diethylamine to get hydroxyl amide **(3-21)**. Reaction of the hydroxyl amide with sodium azide in the presence of CBr_4 and PPh_3 would give the corresponding azide which could be reduced to get final product **(3-22)**. As both enantiomers of epichlorohydrins are commercially available, both enantiomers of milnacipran derivatives could be synthesized.



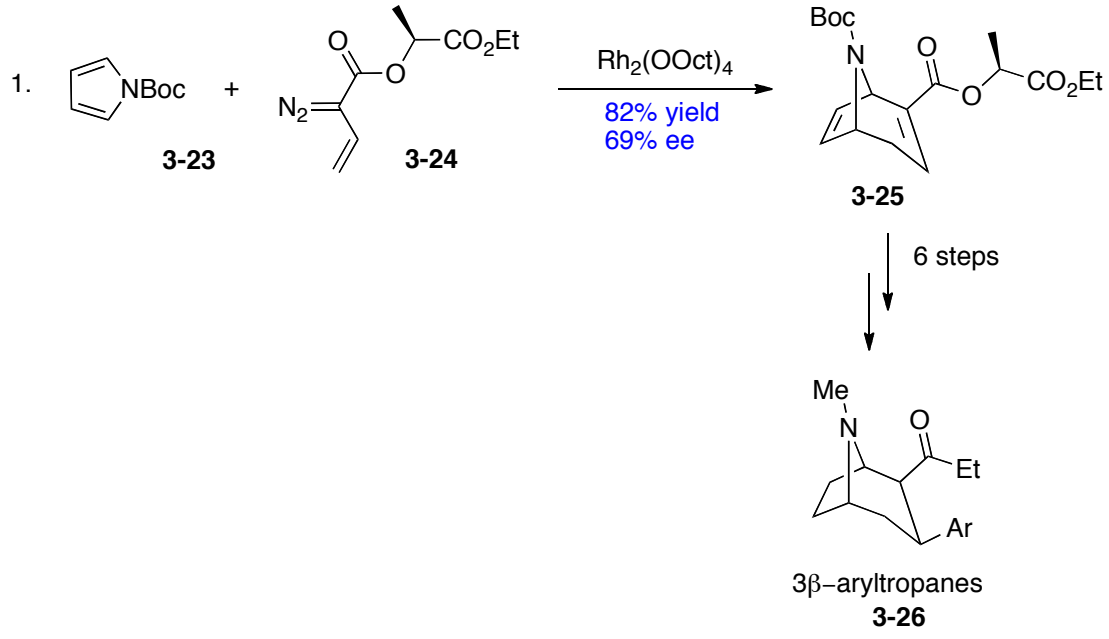
a) Et_2NH, BuLi, THF, -78 °C; b) LiN_3, CBr_4, PPh_3;
c) 10% Pd-C, H_2, MeOH, rt;

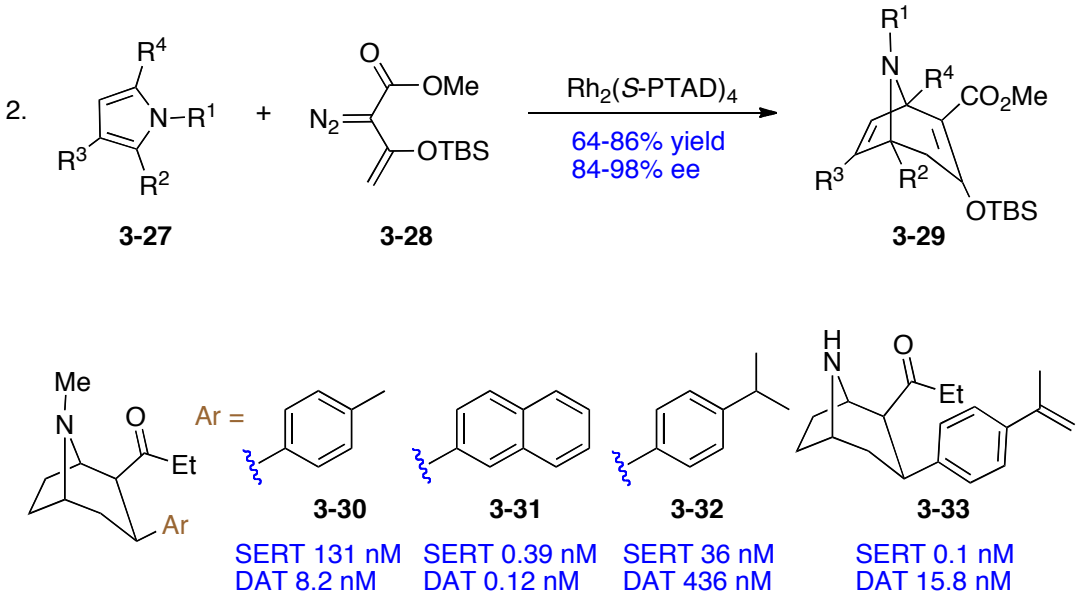
Scheme 3.2: Synthesis of bicyclic lactone derivatives, mechanism of cyclopropane formation, and milnacipran analogues synthesis.

Recently, Tore Hansen *et al.* used the same strategy to synthesize enantiomers milnacipran analogues and found that the analogue with naphthyl substitution was more potent that milnacipran itself.[56]

3.2.4 CNS drug development in the Davies' group

One of the central themes of Davies' research program has been the development of enabling technologies for the rapid construction of potential therapeutic agents for drug abuse and CNS diseases. Many pharmaceutically relevant compounds have been synthesized in the Davies group in the last few years. Much of the earlier work was focused on the synthesis of cocaine-like tropane alkaloids (**3-26**). Davies' group developed a remarkable tandem cyclopropantion/cope rearrangement strategy,[57-59] where rhodium stabilized carbenoid generated from decomposition of vinyl diazo compound **(3-24)** reacted with N-Boc pyrrole **(3-23)** to give easy access to bicyclic system **3-25** (Scheme 3.3; eq. 1). Earlier work relied on a chiral auxillary to achieve enantioinduction (eq. 1), but recently an enantioselective asymmetric reaction was also reported (eq. 2).[60]

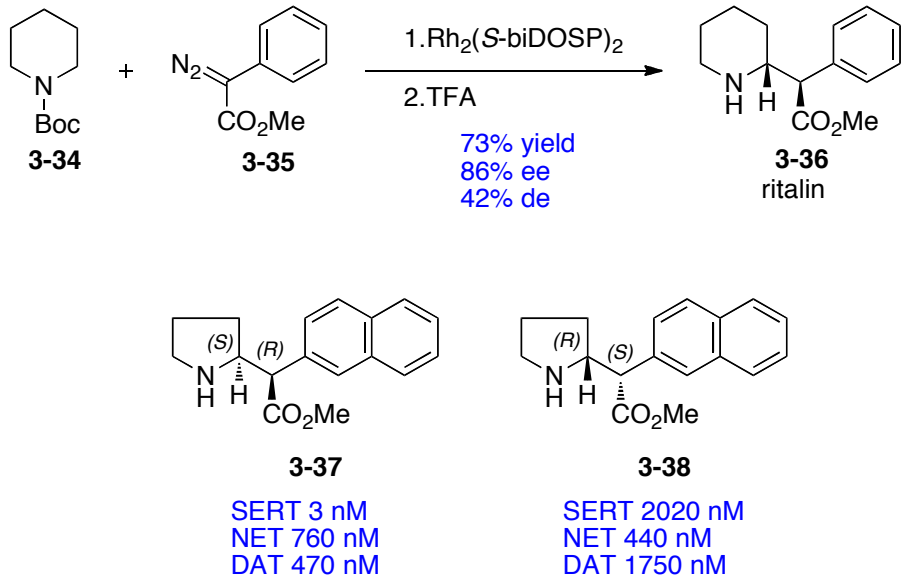




Scheme 3.3: Davies' asymmetric synthesis of tropane analogues.

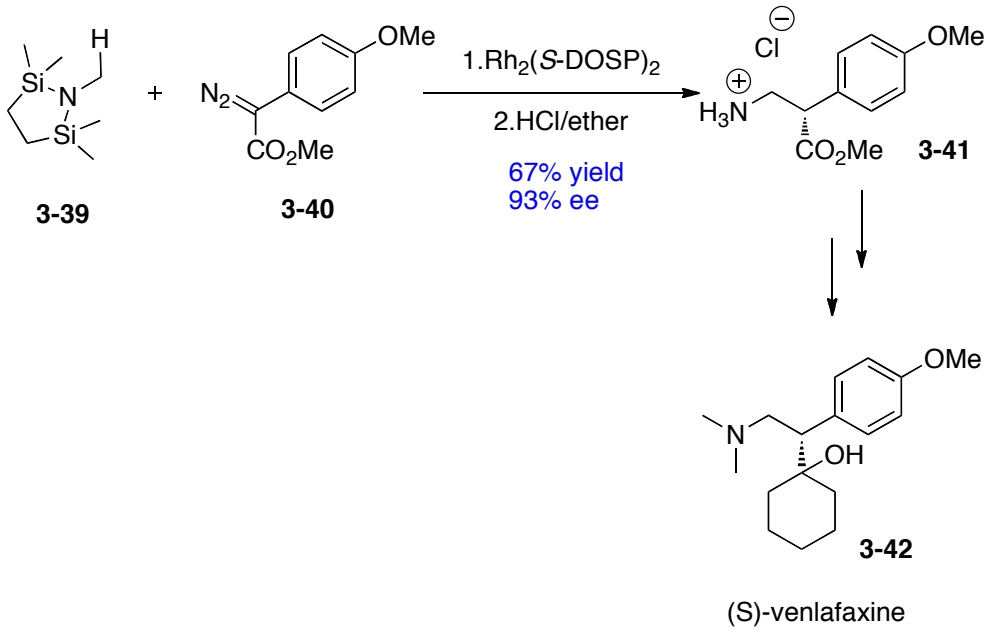
When these novel tropane analogues were tested for their binding affinity to the monoamine transporters it was found that many of these compounds were very potent in binding to DAT. A naphthyl derivative **(3-32)** was found to have 0.12 nM binding to DAT.[61,62]

Threomethylphenidate (ritalin) is a commercially available monoamine reuptake inhibitor for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The Davies' group developed a general method to access this drug; C–H activation adjacent to nitrogen by rhodium carbenoid, to give enantiopure ritalin analogues. [63,64] The bridged catalyst Rh_2(*S*-biDOSP)$_2$ was found to be most effective for this reaction (Scheme 3.4).



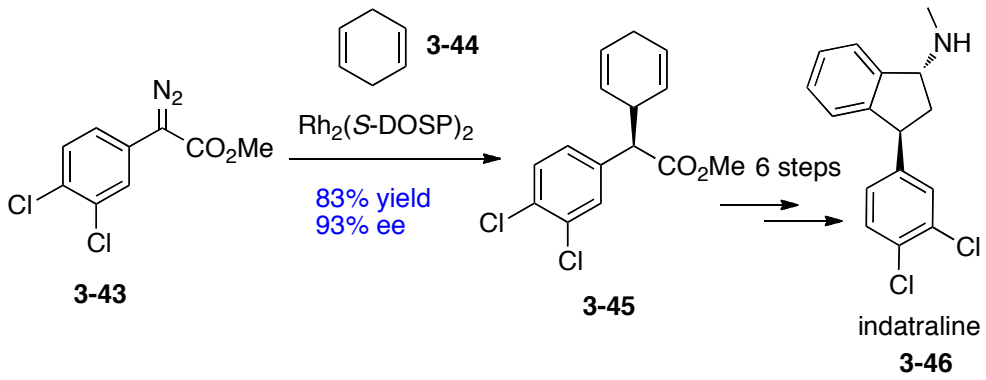
Scheme 3.4: Davies' asymmetric synthesis of ritalin analogues.

When these ritalin analogues were tested for their monoamine inhibition activity, a naphthyl derivative **(3-37)** was found to be SERT selective (3 nM). Moreover, great bioactivity difference in between **3-37** and **3-38** was also observed.



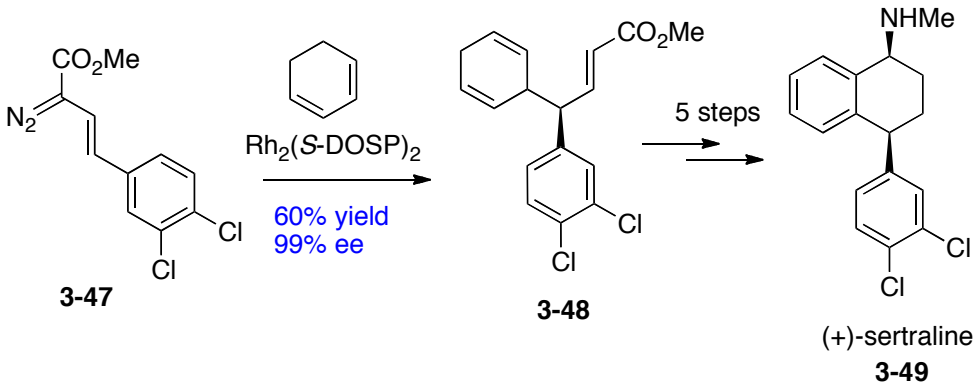
Scheme 3.5: Davies' asymmetric synthesis of venlafaxine.

A three step synthesis of venlafaxine **(3-42)**, a SERT/NET inhibitor was also reported, which utilizes C–H insertion at the α-carbon adjacent to silyl protected nitrogen (Scheme 3.5).[65]



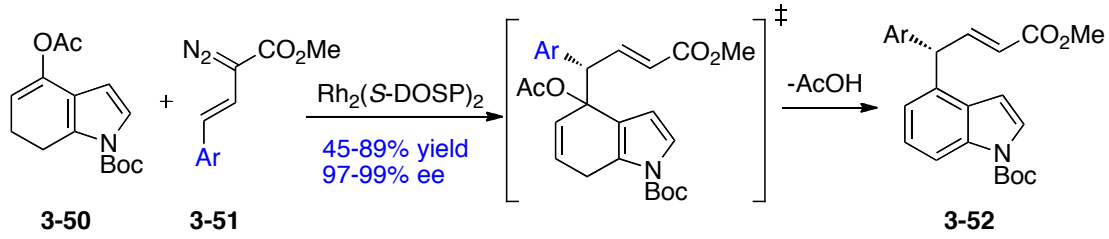
Scheme 3.6: Davies' asymmetric synthesis of Indatraline.

A 7-step synthesis of the very potent but unselective monoamine reuptake inhibitor, Indatraline **(3-46)** was also reported. This method involves C–H insertion of aryl diazoacetate **(3-43)** onto 1,4- cyclohexadiene **(3-44)** to get **3-45**, which was subsequently converted to Indatraline (Scheme 3.6). [66]



Scheme 3.7: Davies' asymmetric synthesis of sertraline.

The combined C–H activation/Cope rearrangement methodology was effectively used for enantioselective synthesis of sertraline **(3-49)**. The reaction of vinyldiazoacetate **3-47** with 1,3-cyclohexadiene in the presence of Rh_2(*S*-DOSP)$_4$ gave a 59% yield of Combined C–H/Cope product **3-48** in 99% ee, which was then converted to sertraline **(3-48)** in 5 steps.



Scheme 3.8: Synthesis of duloxetine analogues.

Recently, a novel method for the synthesis of 4-substituted indoles was reported.[67] Indole sub-units are very common components of many pharmaceutical agents but 4-substituted indoles have never been explored for biological activity due to the difficulty associated with functionalization at the 4-position *via* conventional methods. The key step is a reaction of dihydroindole derivative **(3-50)** with styryl diazoacetates **(3-51)** to get a Combined C–H/Cope product intermediate that provided the desired product **(3-52)** in 64% yield and >98% ee. A series of duloxetine analogues (**3-53** to **3-60**) have been synthesized based on this methodology. The complete list of analogues and their biological activity is summarized in Fig. 3.3.

As a general trend, these novel compounds were found to be very potent and selective for both SERT and DAT. The most potent compound in this series **3-57** has 0.8 nM inhibition for SERT and 3.81 nM inhibition for DAT. It also needs to be noted that there was no effect of carbon chain length (compare **3-57** with **3-58**) on the bioactivity. All the compounds were relatively inactive towards 5-HT_{2A} and 5-HT_{2C} receptors. These compounds have a great potential as therapeutic agents, especially as selective SERT/DAT inhibitors, which are not common in the literature.

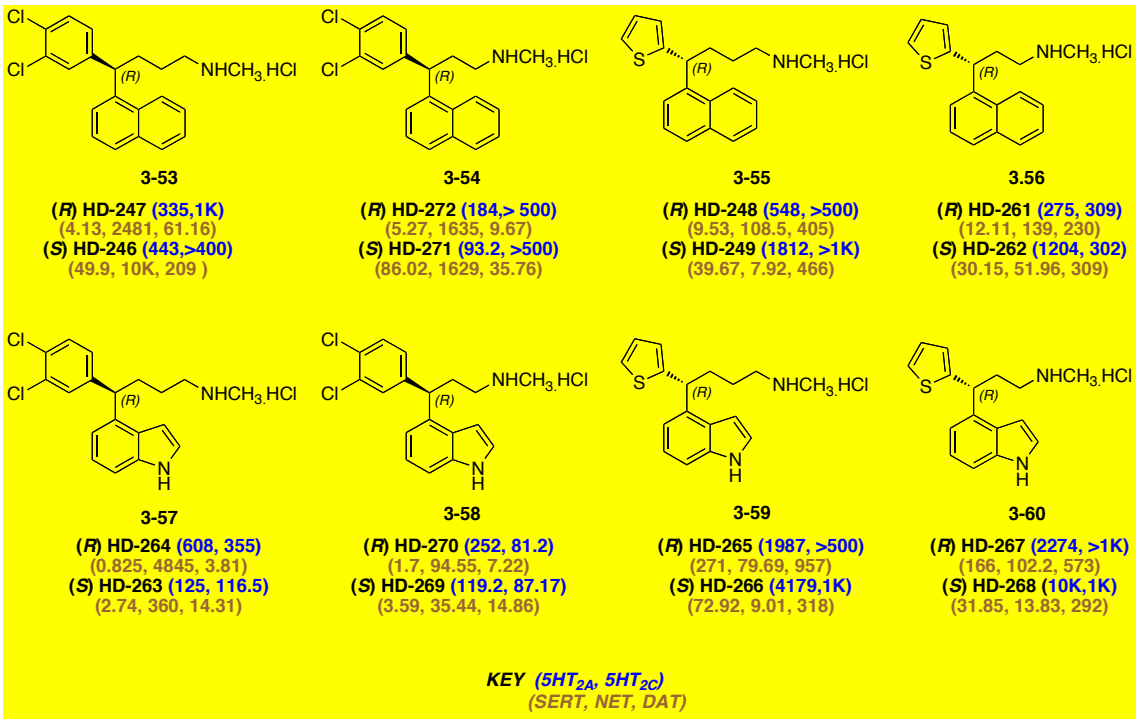


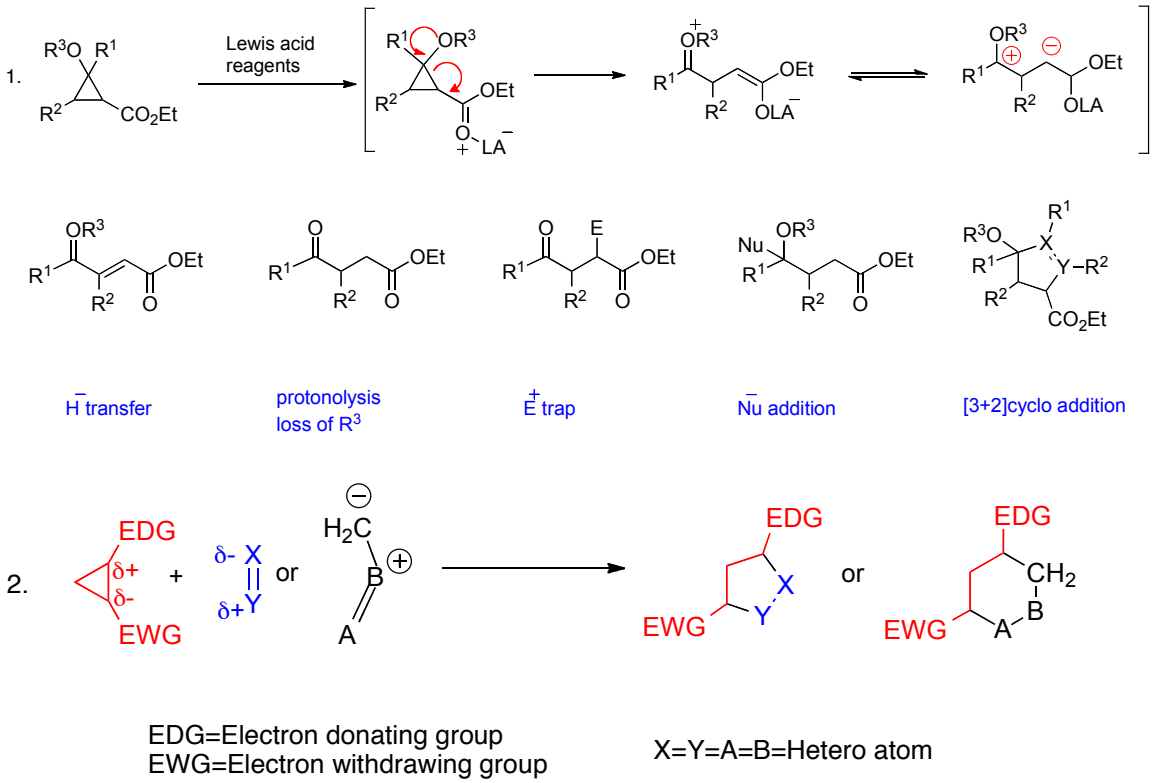
Figure 3.3: Bioactivity of duloxetine analogues (K_i values in nM)*(HD-numbers are reference codes given to compounds, when sent for bio-analysis)*.

In summary, developing powerful novel synthetic methods to give quick and easy access to pharmaceutically relevant compounds and therapeutic agent is an on going research program in the Davies group.

3.2.5 Intermolecular asymmetric catalytic cyclopropanation – An enabling technology for CNS drug development

The cyclopropyl group, a three membered strained carbocycle is different from other cycloalkanes in both its reactivity and properties.[68] This structural moiety can be

found in many natural products[69,70,71] and biologically relevant compounds.[72,73] Cyclopropanes display reactivity analogous to that observed for alkenes, and reactions with nucleophiles, electrophiles and radical species are reported (Scheme 3.9, eq. 1).[74] They also serve as intermediates in complex molecule synthesis[75] and heterocycles synthesis.[76]



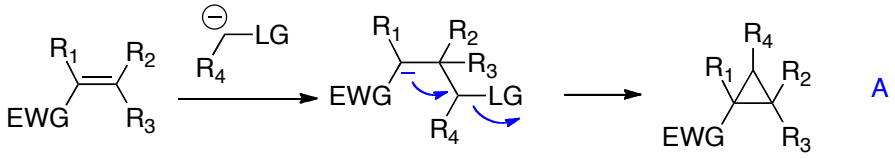
Scheme 3.9: Reactivity of cyclopropanes.

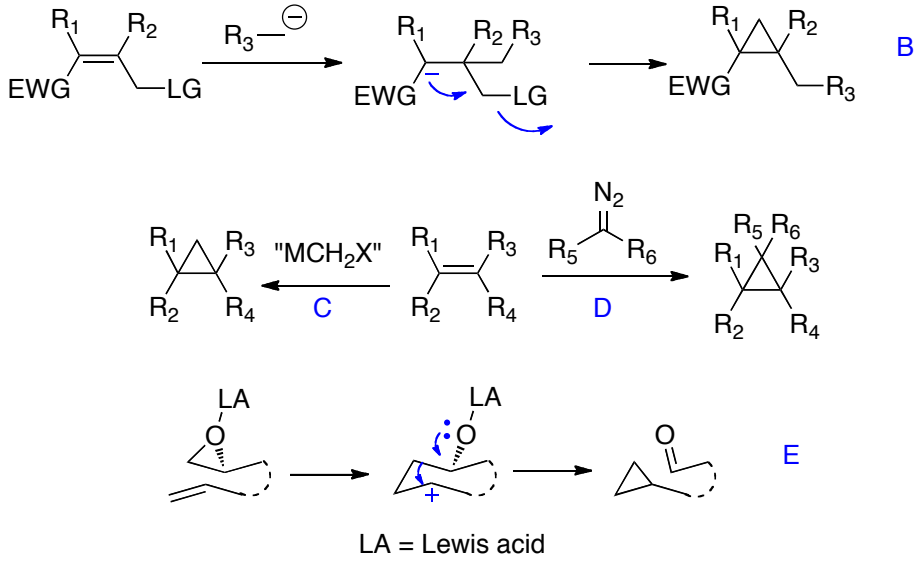
In recent years, ring expansion reactions of cyclopropane compounds have been effectively used for the synthesis of a variety of complex heterocyclic systems (Scheme 3.9, eq. 2). A multitude of dipolar reagents (aldehydes, imines, nitrones, diazenes, nitriles, azomethine imines) readily react with cyclopropane compounds to form five- and

six membered hetercycles.[76] Considering their versatile synthetic utility, many methods for the synthesis of cyclopropanes bearing an array of functional groups have been developed. Several reviews detailing their syntheses have been published.[77,78,79]

In recent years, interest has shifted towards intermolecular stereospecific cyclopropanation reactions. Most common methods include nucleophilic addition-ring closure reactions (Scheme 3.10, method A & B), halomethylmetal-mediated reactions (Simmons-Smith reaction)[80] (Scheme 3.10, method C), and transition metal-catalyzed decomposition of diazo compounds (Scheme 3.10, method D)[81,82,83]. Recently Kulinkovich-de Meijere reaction[84,85] and organocatalytic Michael-initiated ring closure reactions [86,87] were also reported. Methylene transfer reagents such as Simmons-Smith reagents or carbenoids derived from cobalt, rhodium, ruthenium, or copper catalysts are highly reactive and can overcome the ring strain (28 kcal/mol) generated in the newly formed cyclopropane, thus are very effective methods of cyclopropanation.

Chemists later directed their efforts towards development of more stable and environmentally benign methylene sources for cyclopropanation reaction that led to the discovery of the epoxide-methylene transfer cyclopropanation reaction[88,89] (Scheme 3.10, method E). In this intramolecular cyclopropanation reaction, an epoxide was used as a methylene source and was opened by the nucleophilic attack of the alkene followed by a semipinacol-type rearrangement led to the formation of the cyclopropane product.



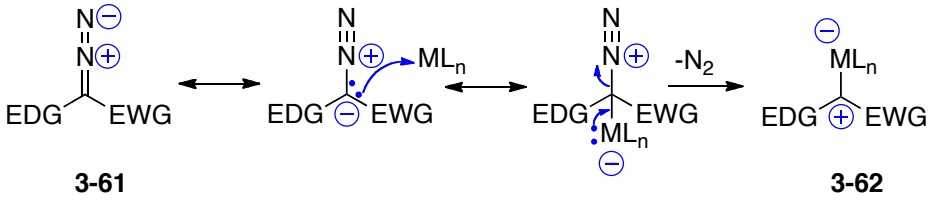


Scheme 3.10: Typical methods for the synthesis of cyclopropanes.

The transition-metal catalysed asymmetric cyclopropanation reaction of alkenes using diazo compound as a carbene precursor is among the best developed and most useful transformations available to the organic chemist. Enormous progress has been made in finding suitable metal catalysts/chiral ligand systems to accomplish this reaction in a stereospecific manner. Both inter- and intramolecular versions of the reactions were developed and very high levels of regio-, chemo-, diastereo- and enantioselectivities were achieved.

The Davies' group employs a special class of carbenoids known as donor/acceptor carbenoids (Scheme 3.11), which has one electron-withdrawing group (EWG) and one electron-donating group (EDG) flanking the carbenoid carbon. The EDG

will stabilize the electrophilic carbenoid carbon modulating it's reactivity thereby leading to higher selectivity in the asymmetric reactions.



Scheme 3.11: Mechanism of metal-stabilized carbenoid formation from diazo compound.

The detailed and systematic studies of the intermolecular cyclopropanation reaction of alkenes with donor/acceptor diazo compounds have been carried out in the Davies' group over past fifteen years. A major advance in this area has been achieved by Davies and coworkers with the development of proline based dirhodium tetracarboxylate catalyst, Rh_2(*S*-DOSP)$_4$ (**3-63**)(Fig. 3.4). The presence of dodecyl chain in the catalyst improved its' solubility in the hydrocarbon solvents that facilitated low catalysts loading. The ligands around this catalyst are believed to exist in an "Up-Down-Up-Down" conformation making the overall dirhodium complex D_2 symmetric. This D_2 symmetry allows the same asymmetric induction to be achieved irrespective of which face of the catalyst is approached by the substrate. Recently, another catalyst Rh_2(*S*-PTAD)$_4$ (**3-64**) was also found to be an effective catalyst for many asymmetric transformations.

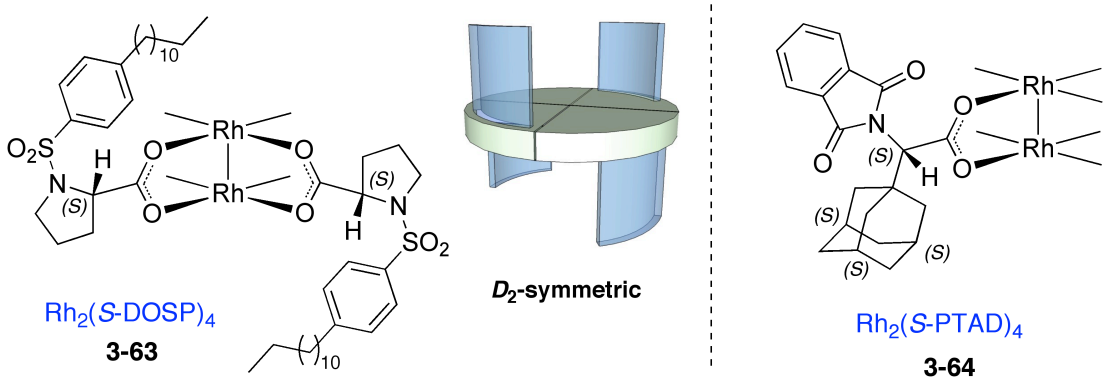
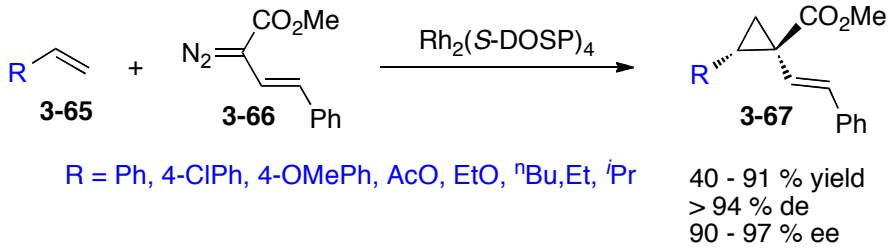


Figure 3.4: Structures of the dirhodium catalysts developed in the Davies' group.

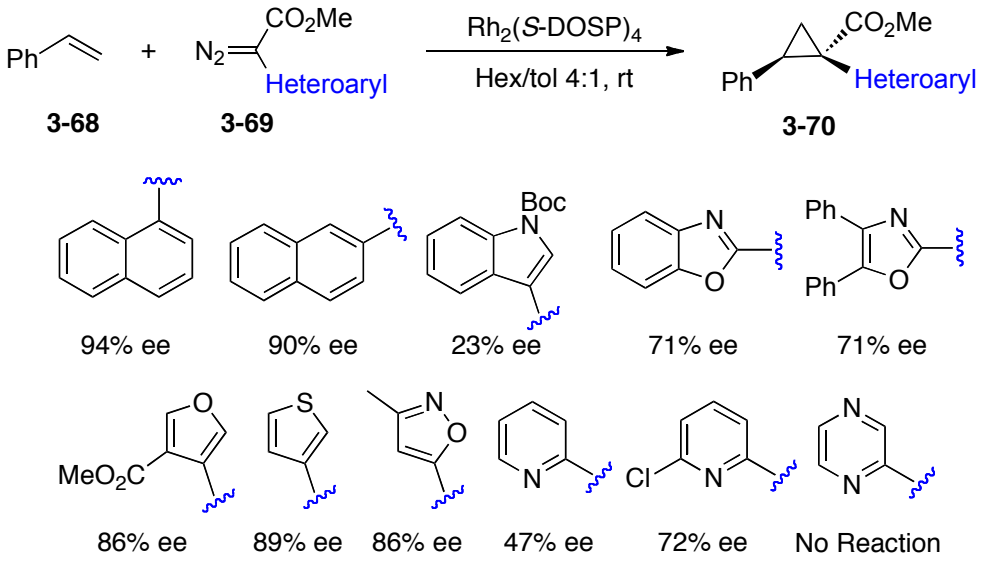
The development of donor/acceptor carbenoids along with very efficient chiral catalysts led to the extensive exploration of scope and limitations of asymmetric intermolecular cyclopropanation reaction.

In 1996, The reaction of (*E*)-methyl 2-diazo-4-phenylbut-3-enoate (**3-66**) with Rh_2(*S*-DOSP)$_4$ in the presence of alkenes was reported, in which, the vinyl cyclopropane **3-67** was generated in moderate to good yields. Only one diastereomer was formed in the reaction. The degree of asymmetric induction observed in this reaction depends on combination of factors. High levels of enantioselectivity was observed 1) when Rh_2(*S*-DOSP)$_4$ was used as catalyst; 2) when the reaction was done in hydrocarbon solvents such as pentane at lower temperature; 3) when small EWG such as methyl ester is present on the carbenoid; 5) when phenyl or vinyl EDG present on the carbenoid; 6) when electron neutral and EDG are present on alkene.[90]



Scheme 3.12: Asymmetric cyclopropanation between vinyldiazoacetates and alkenes

Similarly, various aryl and heteroaryl diazoacetates were also explored in the cyclopropanation reaction (Scheme 3.13). Both electron-rich and electron-deficient heteroaryldiazoacetates (**3-69**) underwent cyclopropanation effectively with high diastereoselectivity. Again, enantioselectivity was substrate based. High ee was observed when 1-naphthyl or 2-naphthyl groups were present on diazo compound, where as furan, thiophene, oxazole, isoxazole, benzoxazole and pyridine groups on diazo led to moderate ee. N-Boc protected indole substitution gave low ee of 23 %. This study broaden the range of diazo compounds that could be used in cyclopropanation reaction.[91]



Scheme 3.13: Cyclopropanation of heteroaryl diazoacetates.

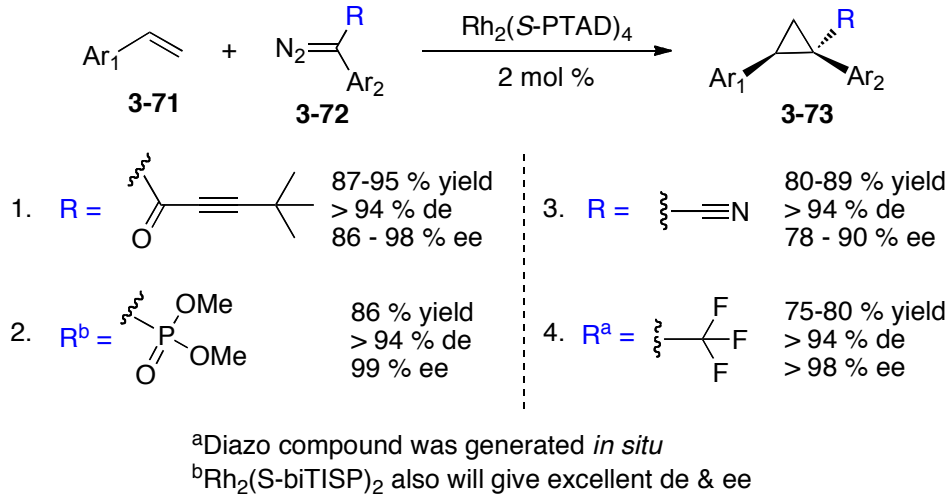
The methyl ester group has been widely used as acceptor group in the donor/acceptor class of carbenoids to achieve high levels of stereospecificity. But recently, it was shown that enantioselective cyclopropanation reaction also could be achieved in the presence of other functional groups expanding the scope of this reaction (Scheme 3.14). It was demonstrated that wide variety of α-aryl-α– diazo ketones could be reacted with activated alkenes, in the presence of adamantane glycine –derived dirhodium catalysts, Rh_2(*S*-PTAD)$_4$ to generate cyclopropyl ketones with high enantio- and diastereoselectivity. Usually alkynyl functional groups on the diazo ketones give excellent ee, alkyl groups give moderate ee, where as aryl substituents show poor (51 % ee) enantioselectivity in this reaction (Scheme 3.14, eq. 1).[92]

It was also shown, that moderate to high levels of enantioselectivity could be achieved in the intermolecular cyclopropanation reaction of 2-diazo-2-phenylacetonitrile

with various styrene derivatives in presence of Rh_2(*S*-PTAD)$_4$ catalyst. It was suggested that high diastereoselectivity in this reaction is due to pi-stacking interactions at the donor group (Scheme 3.14, eq. 3).[93]

The scope of the reaction was further extended when 1-aryl-2,2,2-trifluoromethyldiazomethanes were explored in asymmetric cyclopropanation reaction. One fundamental strategy to improve efficacy and bioavailability of any pharmaceutical drug is to slow down the drug metabolism by incorporating either fluorine, or trifluoromethyl functional groups in to the drug candidate. Thus, having access to fluorinated derivatives of cyclopropane compounds would greatly expand their utility as potential therapeutic agents. Rh_2(*S*-PTAD)$_4$ can effectively decompose 1-phenyl-2,2,2-trifluoromethyldiazomethane and its derivatives (generated *in situ*) in presence of styrene derivatives to give chiral trifluoromethyl-substituted cyclopropanes with high enantioselectivity (Scheme 3.14, eq. 4).[94]

Dimethyl aryldiazomethylphosphonates were shown to react with styrene in presence of Rh_2(*S*-PTAD)$_4$ to obtain cyclopropylphosphonates containing quaternary stereo-centers with high asymmetric induction. Rh_2(*S*-biTISP)$_2$ was found to be effective in this transformation (Scheme 3.14, eq. 2).[95,96]



Scheme 3.14: Expanding the scope of EWG on the donor/acceptor diazo compounds.

The donor/acceptor substituted carbenoids are sensitive to steric influences of olefin used in the cyclopropanation reaction (Fig. 3.5). Cyclopropanation of 1-substituted, 1,1-disubstituted, and *cis* 1,2-disubstituted alkenes are favorable, while *trans*- 1, 2 – disubstituted and 1,1,2-trisubstituted and tetrasubstituted alkenes are typically unreactive.[97] In some selected substrates, it was shown that electron-rich trisubstituted alkenes could also can undergo cyclopropanation reaction.[98]

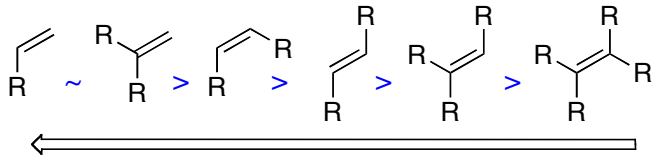
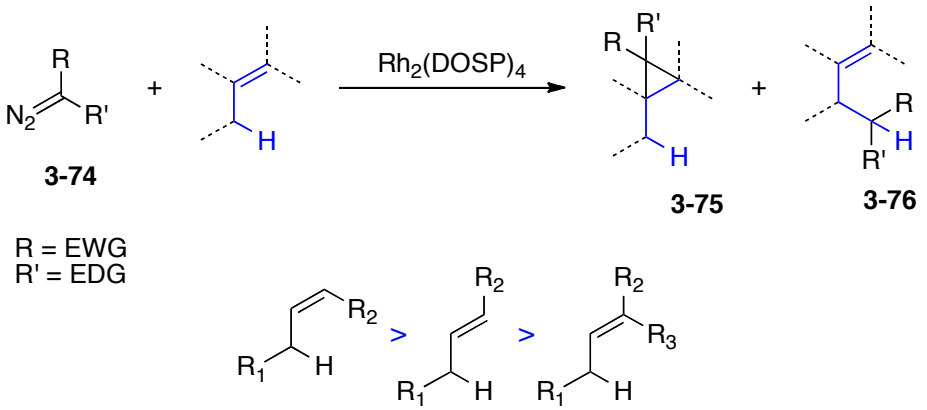


Figure 3.5: General reactivity trend of alkenes for cyclopropanation reaction.

The reactivity of donor/acceptor carbenoids with alkenes possessing hydrogen on the α-carbon; allylic system can be influenced by many factors. These substrates have the potential to undergo both cyclopropanation on alkene **(3-75)** as well as C-H insertion on to the allylic C-H bond **(3-76)**. The product distribution is influenced by many factors including, the nature of donor group on the carbenoid, the structure of the alkene and the rhodium catalyst (Scheme 3.15).[97]

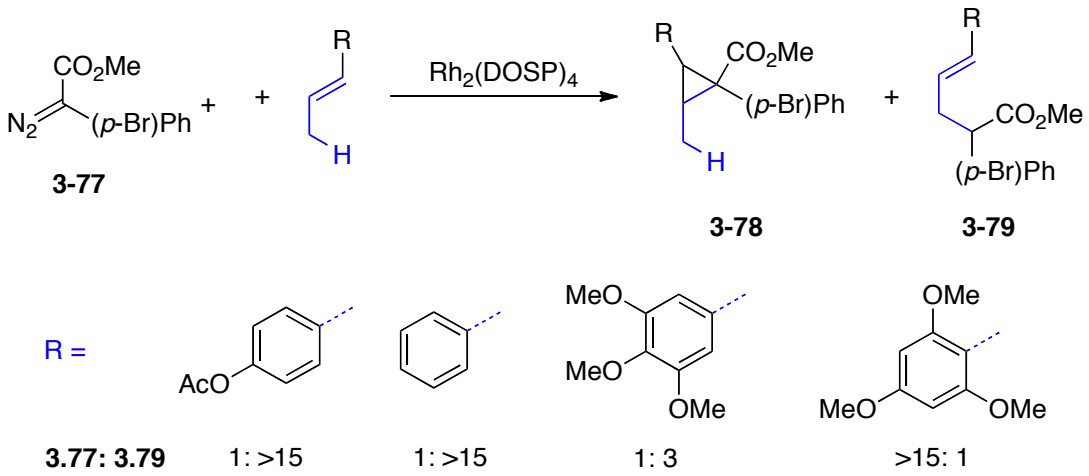


Scheme 3.15: Cyclopropanation in the allylic systems.

Even in the allylic system, If alkene is *cis*-1,2 –disubstituted, cyclopropane product was favored where as *trans*-1,2 disubstituted and trisubstituted allylic systems favor C-H functionalization of the allylic C-H bond.[98]

In case of *trans*-1, 2 alkene with allylic C-H bond, the electronic nature of the substituents present on the olefin would have greater influence on the outcome of the reaction (Scheme 3.16). Presence of electron withdrawing groups such as acetate (4-

$AcOC_6H_4$) led to the formation of C-H insertion product exclusively, where as electron rich alkenes ($(1,3,5\text{-}MeO)_3C_6H_2$) form cyclopropane product exclusively.

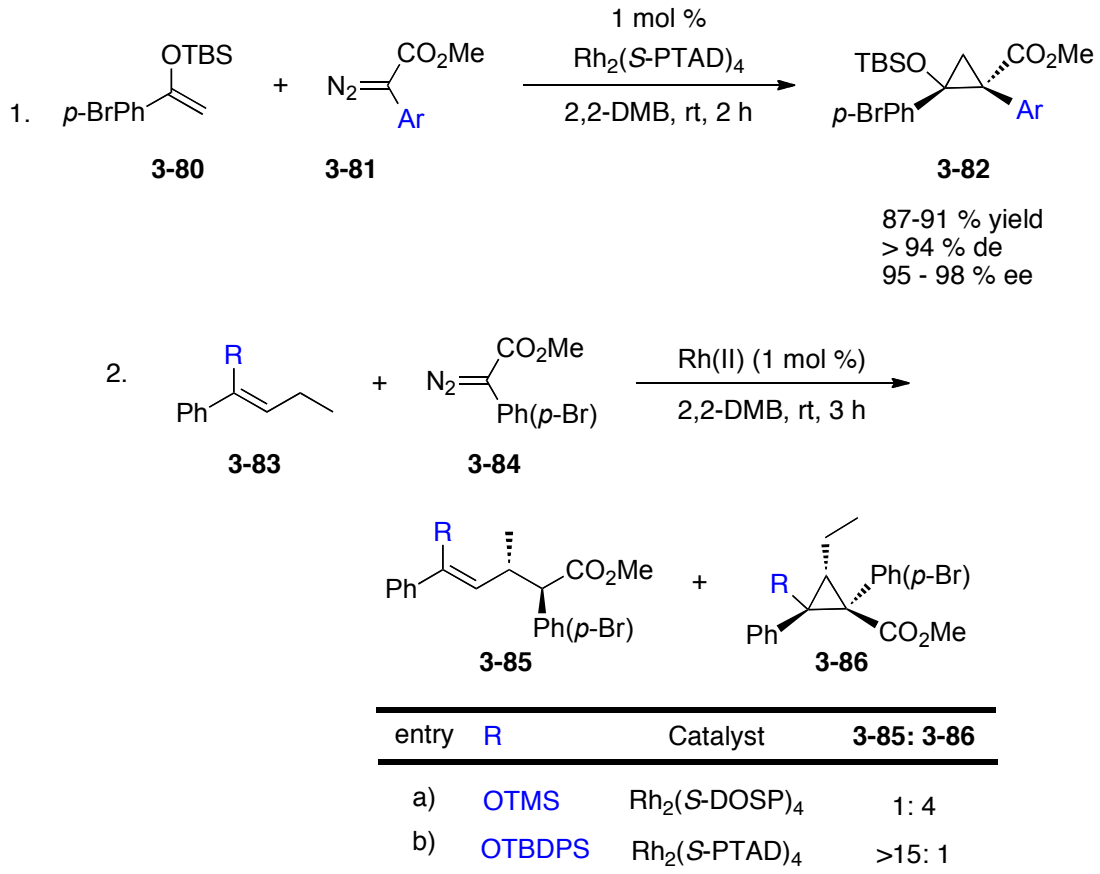


Scheme 3.16: Reaction of trans 1,2 disubstituted alkene bearing α-hydrogen.

In summary, the reaction of donor/acceptor carbenoids with allylic systems can be fine-tuned to get either cyclopropanation product or C-H functionalization product exclusively by controlling the electronics and steric influences on the substrates.[98]

Cyclopropanation reaction of vinyl ethers was also systematically studies in the Davies' group.[99,100] The nature of the substrate and the catalyst was shown to have profound influence on the stereo chemical outcome and the product distribution in these reactions. Highly enantioselective cyclopropantion of 1-aryl vinyl ethers (**3-80**) with aryl diazoaceates (**3-81**) was achieved in the presence of 1 mol % Rh_2(*S*-PTAD)$_4$ catalyst (Scheme 3.17, eq. 1). If vinyl ether was protected with small trimethylsilyl (TMS) protecting group (Scheme 3.17, eq. 2, entry a), cyclopropane product was favored,

whereas bulky TBDPS group have shown to favor C-H insertion on allylic carbon (Scheme 3.17, eq. 2, entry b).

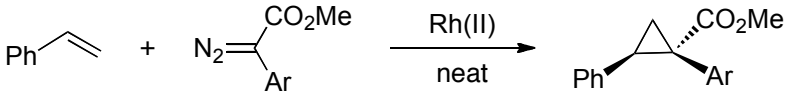


entry	R	Catalyst	3-85: 3-86
a)	OTMS	Rh_2(*S*-DOSP)$_4$	1: 4
b)	OTBDPS	Rh_2(*S*-PTAD)$_4$	>15: 1

Scheme 3.17: Reaction of aryldiazoacetates with vinyl ethers.

Cyclopropanation reactions also could be carried out in the absence of solvent.[101] This reaction was performed by dissolving phenyl diazoacetate **(3-81)** in neat styrene (**3-68**) and adding various mol % of chiral catalyst to the reaction mixture. It was found that the reaction was too exothermic, when 0.01 mol % catalysts was added, even at -20 ^{o}C. When the temperature was lowered to -30 ^{o}C, the reaction went to completion in 3 h and cyclopropane product formed was found to have 75% ee. These studies clearly

demonstrated that very high turn over numbers (TON) and turn over frequencies (TOF) could be achieved in the cyclopropanation reaction (Scheme 3.18), when very reactive trapping agents were used. [101,102]



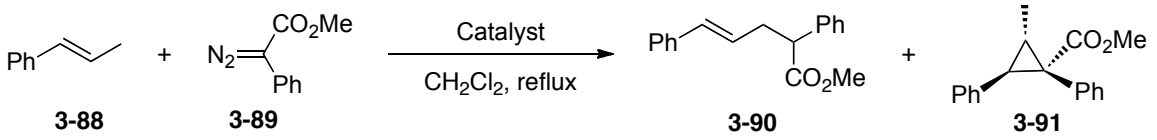
3-68 **3-81** **3-87**

Ar	Catalyst (mol%)	TON	TOF/h^{-1}
Ph[a]	Rh_2(*S*-DOSP)$_4$ (0.00005)	1.5 x 10^6	1.5 x 10^4
p-(OMe)Ph	Rh_2(*S*-PTAD)$_4$ (0.00005)	1.8 x 10^6	2.5 x 10^4

[a]Rh_2(*S*-biTISP)$_2$ also can catalyze this reaction 9.2 x 10^4 TON

Scheme 3.18: Solvent free cyclopropanation reaction.

Cyclopropanation reaction of sterically hindered alkenes **(3-88)** also could be achieved by employing silver catalysts (Scheme 3.19).[103] In general, high levels of diastereoselectivity could be achieved in the cyclopropanation reaction of styrene **(3-68)** with phenyl diazoacetate **(3-89)** in the presence of $Rh_2(OAc)_4$ as well as silver hexafluoroantimonate ($AgSbF_6$) catalyst. It was interesting to find that highly diastereoselective cyclopropane product **(3-91)** could be produced when phenyl diazoacetate **(3-89)** was reacted with *trans*-β-methylstyrene (**3-88)** in the presence of $AgSbF_6$ catalyst. **3-88** was unreactive under rhodium (II) acetate-catalyzed conditions.



3-88 **3-89** **3-90** **3-91**

Catalyst	yield (%)	**3-90** : **3-91** (de, %)
$Rh_2(OAc)_4$	4	>20 : 1
$AgSbF_6$	80	1 : >20 (>94)

Scheme 3.19: Selectivity with different metal catalysts

It was also shown that cyclopropanation reaction could be performed using Rh_2(*S*-DOSP)$_4$ catalyst on solid support.[104,105] Highly cross-linked macroporous polystyrene resin was used to immobilize the catalyst. No noticeable decrease in efficiency of the catalyst was observed, when recycled catalysts was employed in cyclopropanation reaction.

Based on a series of ^{13}C kinetic isotope effect (KIE) results and density functional theory (DFT) calculations, the mechanism of the dirhodium tetracarboxylate catalyzed cyclopropanation of alkenes with aryl diazoacetates was proposed. The reaction proceeds *via* complexation of the diazoester to rhodium followed by loss of nitrogen gas to form a rhodium carbenoid, which reacts with alkene in asynchronous concerted fashion to form the cyclopropane product.[106]

Davies' also proposed a predictive model to explain the reason for exceptional stereocontrol in Rh_2(*S*-DOSP)$_4$ catalyzed cyclopropanation reaction. It was believed that the catalyst exists in D_2 symmetry in the solution, with four aryl sulfone groups pointing in 'up-down-up-down" orientation, which creates a very distinct chiral environment

around the carbenoid center (Fig. 3.5). As seen from the top view of the catalyst (Fig. 3.6), the donor group sits in the plane of the rhodium bound carbene, where as the electron withdrawing ester group sits perpendicular to the plane of the carbene. There are four distinct angles for the substrate to approach the carbene center. when substrate approaches the carbenoid center in 'end-on' fashion, two possible vectors were blocked efficiently by bulky sulfonate groups of the ligands on the catalyst, where as the third vector was blocked due to the steric presence of ester functionality. This leaves only one angle of approach for the substrate; over the donor group. It was also speculated that cyclopropanation of styrene derivatives with donor/acceptor diazo compounds always results in a single diastereomer in which, both aryl group on the diazo compound and aryl group on the olefin orient in *cis* configuration to each other due to the possibility of forming a charge transfer complex between two aryl groups arising from pi-pi stacking interactions.[98]

In summary, intermolecular asymmetric cyclopropanation reaction is a well-established, well-studied reaction in the Davies' group. The substrate scope, and limitations are very well understood. This enabling technology give access to structurally unique chiral cyclopropane scaffolds, which can be explored as potential pharmaceutical agents in drug discovery.

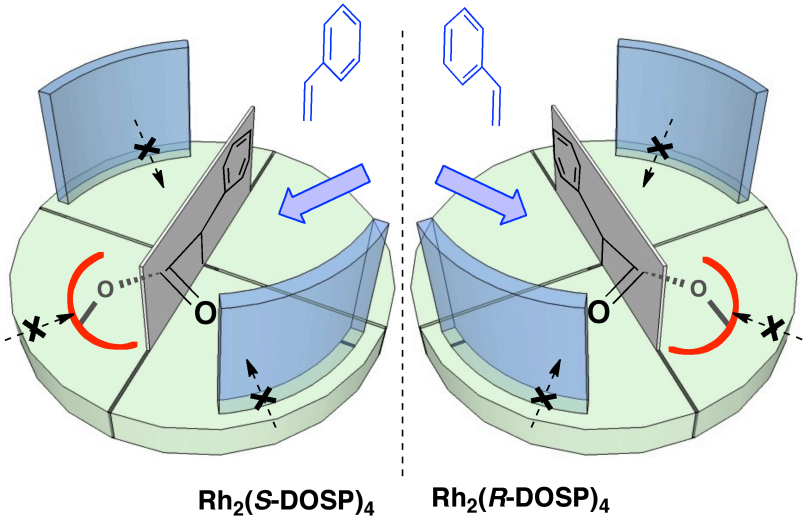


Figure 3.6: Steric factors that influence the facial selectivity.

3.3 Results and Discussions

3.3.1 Synthesis of milnacipran analogues

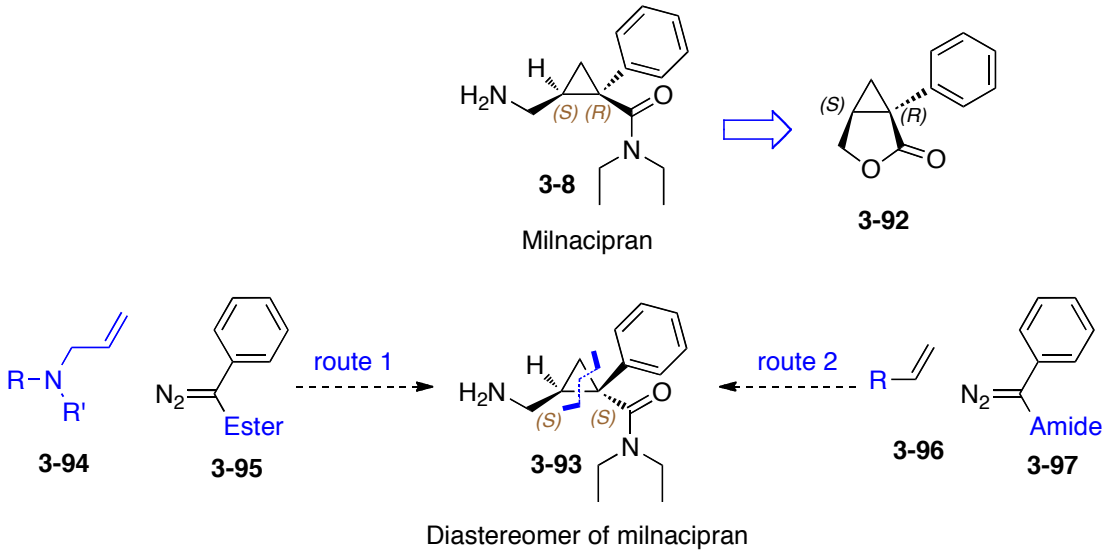
The primary aim of this project was to design and synthesize small molecule therapeutic agents with enhanced selectivity and potency towards the monoamine transporters. The design, synthesis, and molecular modeling of analogues were performed in the Davies' lab and the potencies of novel compounds at CNS monoamine transporter sites (SERT, NET and DAT) were determined in the Steve Childers' lab.

The inspiration for this project came from a commercial antidepressant drug "Milnacipran" **(3-8).** This compound is a dual SERT/NET inhibitor with binding affinities in the 20-30 nM ranges. The structure of Milnacipran is based on cyclopropane scaffold with a *Z* orientation between the amide and the methylamine group. Since its

discovery in 1985, this compound was developed as a drug candidate due to availability of a synthetic method, which gives easy access to this cyclopropane scaffold from the bicyclic precursor **3-92** (Scheme 3.20).

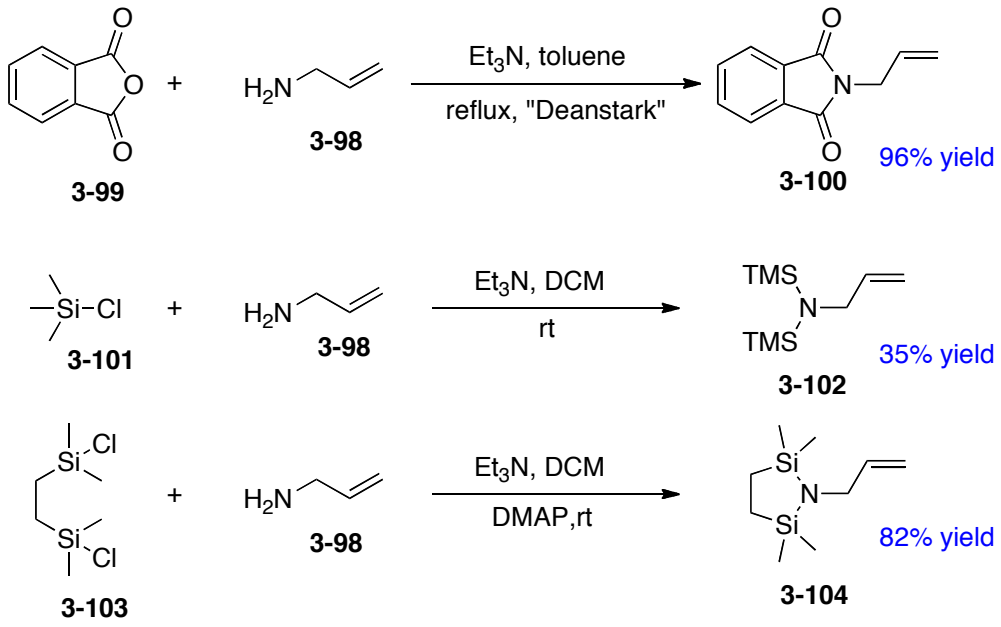
As described in section **3.2.4**, a number of innovative synthetic methods were developed in the Davies' group that has been applied in drug discovery. It was envisioned that a series of *E* isomer analogues (**3-93**) of milnacipran could be readily accessed using an intermolecular asymmetric cyclopropanation reaction. It was also thought that these diastereomers of milnacipran might have completely different biological profile compared to **3-8** itself, as they were not synthesized earlier and have never been explored for any biological activity. This prompted the study for the exploration of novel synthetic approaches towards the *E* isomer analogues of milnacipran **(3-93)**.

In the first synthetic plan (Scheme 3.20), two possible routes can be envisaged to access **3-93**. In the first route, an intermolecular reaction between donor/acceptor diazo compounds (**3-95**) with *N*-protected allylamines (**3-94**) could be explored, which could give direct access to cyclopropane (**3-93**). The second route would be to explore the reactivity profile of unprecedented aryl diazoamides (**3-97**) in an asymmetric cyclopropanation reaction to give the same product.



Scheme 3.20: First synthetic approach to access diastereomers of milnacipran.

The scope and limitations of dirhodium carbene-mediated asymmetric cyclopropanation reactions have been studied thoroughly in the Davies' group. It is well known that any free amine in the carbenoid reaction will coordinate to the metal catalyst and shutdown its' reactivity. Due to this reason, coordinating solvents and reagents are typically avoided. Thus a series of allyl amines were synthesized where the amine group was protected with various protecting groups to avoid this coordination with the metal catalyst.

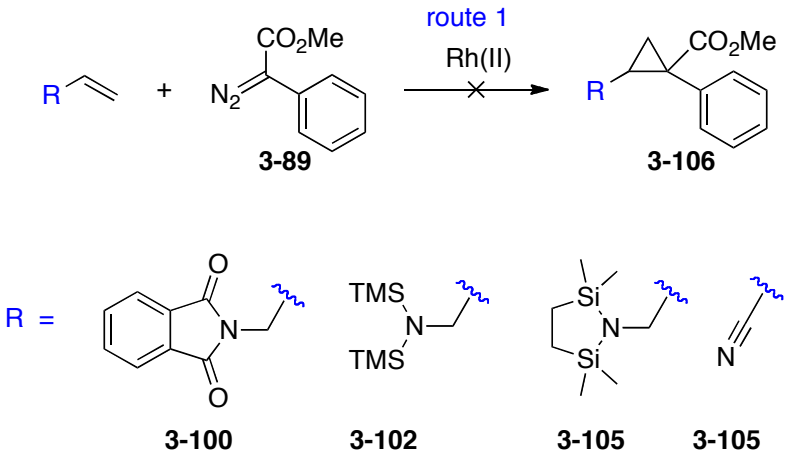


Scheme 3.21: Synthesis of *N*- protected allyl amines.

Three allyl amines were synthesized (Scheme 3.21). First, 2-allylisoindoline-1,3-dione (**3-100**) was synthesized by reacting allyl amine (**3-98**) with phthalic anhydride (**3-99**) in refluxing tolune using a dean-stark apparatus. Second, TMS-protected allyl amine (**3-102**) was synthesized by reacting TMSCl with allyl amine in the presence of Et_3N. Third, corresponding allyl STABASE (**3-104**) was also synthesized in good yield since it is known that STABASE is less labile as compared to TMS or TBS protecting groups.[107]

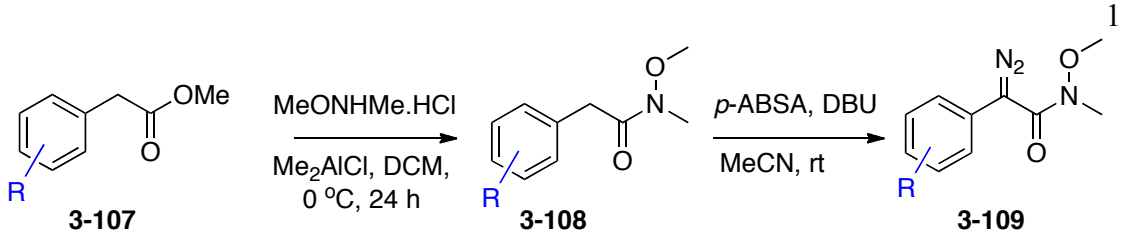
Cyclopropanation reaction of dichlorocarbene with allylamines have been reported.[108] Recently, cyclopropanation of silyl protected allylamines and enamines was effectively used for get GABA-analogous amino acids.[109] Even though the reactions of acrylonitrile **(3-105)** with ethyl diazoacetophenone or ethyl diazoacetate are known,[110] the reaction of **3-105** with aryl diazoacetate (**3-89**) did not give the cyclopropanation product. Cyclopropanation of *N*-silylated allylamines with methyl phenyl diazoacetate (**3-**

89) did not give the desired cyclopropane **(3-106)** product. It appears that allylamines are not activated enough to react with rhodium carbene. The reaction was also performed at a range of temperatures and solvents but with the same outcome.



Scheme 3.22: Reaction of *N*-protected allylamines with phenyl diazoacetate.

Diazo compounds with phenyl or styryl moieties as electron donating groups (EDG) and amides as electron withdrawing groups (EWG) are not common in the literature. However, a series of cyclic and acyclic amides were explored as EWG on diazo compound (not shown). Weinreb amides are a unique class of very useful synthetic intermediates, due to the ease with which they can be converted into their corresponding aldehydes or ketones in the presence of LAH or organometallic reagents, respectively. To expand the synthetic utility of rhodium carbenoid chemistry, aryl diazo weinreb amides (**3-109**) were explored.



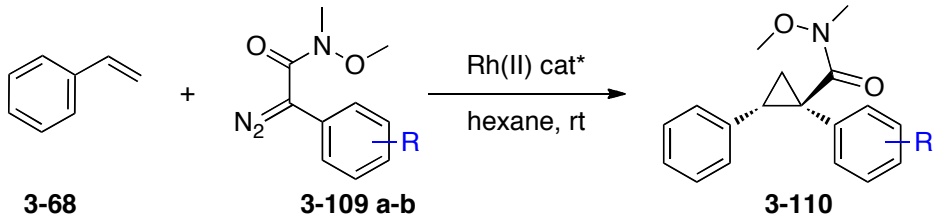
entry	R	yield	yield
a	H	60	97
b	3,4-Cl	94	38
c	4-Cl	62	35
d	4-OMe	66	77

Scheme 3.23: Synthesis of 2-diazo-*N*-methoxy-*N*-methyl-2-arylacetamides.

A small set of diazo weinreb amides (**3-109 a-d**) were synthesized (Scheme 3.23). Yields in this reaction varied with change in stoichiometry of N,O-Dimethylhydroxylamine- hydrochloride used in the reaction. Usually, higher yields were obtained when a large excess (> 5 eq.) of this reagent was used. It is important to note that aryl diazo weinreb amides were not as stable as diazo esters, which make handling of these compounds difficult.

With various aryldiazo amides **3-109 a-d** in hand, cyclopropanation of styrene with **3-109 a-d** was conducted (Scheme 3.24). When Rh_2(*S*-DOSP)$_4$ was employed as the catalyst, the result was very high diastereoselectivity (>94%) but poor enantioselectivity. In an effort to improve the enantioinduction of this reaction, the adamantane based-catalyst Rh_2(*S*-PTAD)$_4$ was tried, which resulted in moderate enantioselectivity (74%). As the cyclopropane product **3-110** cannot be recrystalized to enantiopurity and the ee

achieved in this reaction was not enough to study subtle differences in the bioactivity between opposite enantiomers, a second synthetic strategy was employed.



3-68 **3-109 a-b** **3-110**

> 94% de

entry	R	Cat*	yield	ee
1	H	Rh_2(*S*-DOSP)$_4$	32	18
2	H	Rh_2(*R*-DOSP)$_4$	16	-18
3	3,4-Cl	Rh_2(*S*-DOSP)$_4$	74	13
4	3,4-Cl	Rh_2(*R*-DOSP)$_4$	77	-13
5	3,4-Cl	Rh_2(*S*-PTAD)$_4$	64	-74

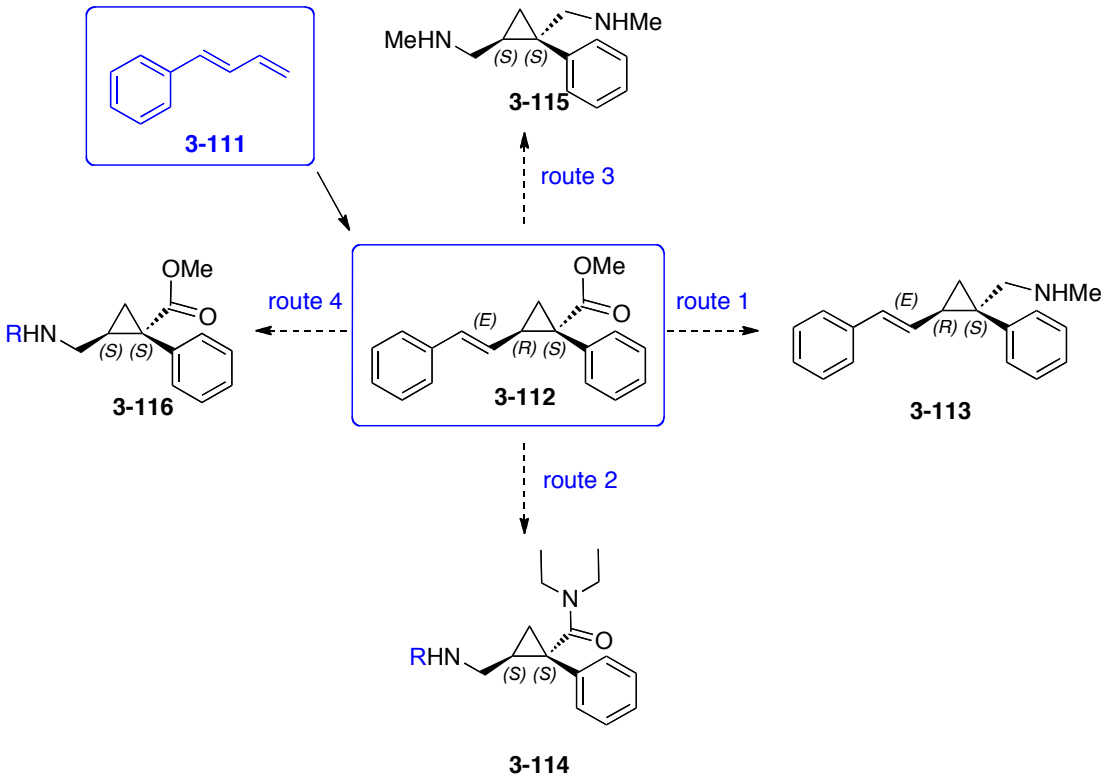
Scheme 3.24: Cyclopropanation reaction of styrene with aryl diazoweinrebamides.

As our first approach towards synthesis of milnacipran analogues was not successful, a second synthetic strategy was employed in which we planned to use phenylbutadiene (**3-111**) to generate the cyclopropane product (**3-112**). This approach does require more synthetic steps to achieve the milnacipran analogues than the first strategy, but using phenylbutadiene as an alkene source has some advantages. It was observed that mono-substituted terminal alkenes are more reactive in cyclopropanation than a 1,2-disubstituted *trans*-alkene. In the case of phenylbutadiene, it was anticipated that cyclopropanation would occur on the terminal alkene leading to high levels of regioselectivity. The terminal olefin is activated due to the electron donating nature of the

aryl group, which was essential for the cyclopropanation reaction to occur. The vinyl cyclopropanation product (**3-112**) formed in the reaction could be used to synthesize a wide range of cyclopropylamines, which did not have prior precedence (Scheme 3.25).

a) Route 1: The ester group on the cyclopropane could be converted to amine to get **3-113** that is structurally similar to diaryl cyclopropylmethylamines. (explored as potential 5-HT_{2A} antagonist in chapter 2).

b) Route 2: The ester group on the cyclopropane could be converted to amide followed by conversion of styryl group to amine would give **3-114**, which would be structurally similar to milnacipran (diastereomers). Moreover, various amine derivatives could be synthesized from the same starting material.

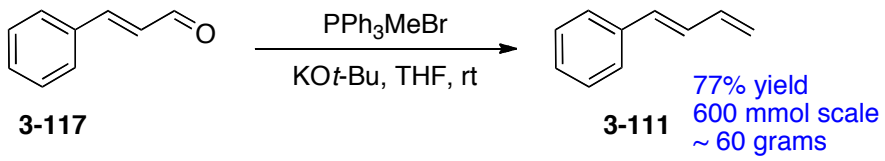


Scheme 3.25: Second synthetic strategy.

c) Route 3: Both ester group and styryl group could be converted to methylamine functionality to give **3-115**. These novel scaffolds could be explored as potential monoamine reuptake inhibitor. To the best of our knowledge, cyclopropyl diamines (**3-115**) were never been synthesized and explored for biological activity.

d) Route 4: Direct conversion of styryl group into amine without modifying ester functionality would give access to a novel scaffold **3-116** that also could be explored as potential monoamine reuptake inhibitors.

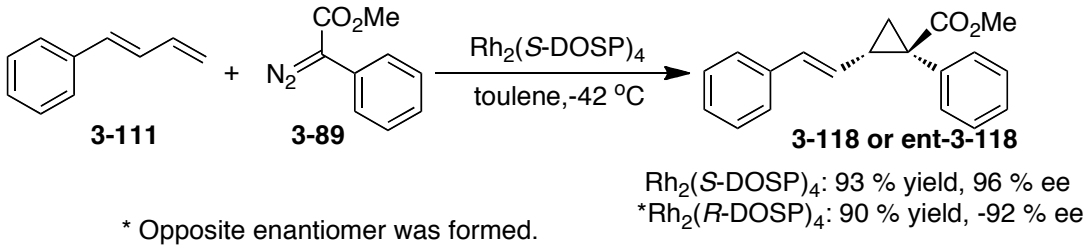
Considering the synthetic utility of this second strategy, phenylbutadiene was used for cyclopropanation reaction throughout this project. Phenylbutadiene (**3-111**) was synthesized *via* a Wittig reaction where cinnamaldehyde (**3-117**) was reacted with triphenyl phosphine methyl bromide and potassium *tert*-butoxide. The resultant crude product was distilled to give a colorless liquid in good yields (Scheme 3.26). This reaction was routinely carried out in 600 mmol scale to obtain 60 g of product each time.



Scheme 3.26: Synthesis of phenylbutadiene.

The optimal reaction conditions for cyclopropanation reaction were found through a quick screening of chiral catalysts, solvents, temperature, rate of diazo addition. Every time, a set of reactions was performed using both enantiomers of the chiral catalysts to

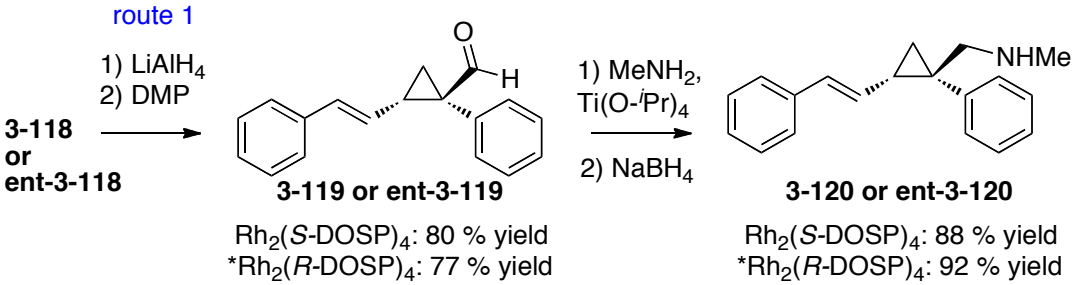
get both enantiomers of the product. The ideal conditions were found to be when phenylbutadiene (**3-111**) was dissolved in toluene and 1 mol % of either Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ catalyst was used at -40 °C. overnight. Only a single diastereomer (*E* orientation between the ester and styryl group) was observed in the crude ^{1}H NMR of the reaction mixture. This diastereomer was found to have. Typically, a very high levels of enantioselectivity (> 92% ee) were observed in this reaction. The product was recrystallized to enantiopurity.



Scheme 3.27: Cyclopropanation reaction of phenylbutadiene with phenyl diazoacetate.

Once both enantiomers of vinyl cyclopropane (**3-118** and **ent-3-118**) were in hand, a three step synthetic sequence was employed to get **3-120** or **ent-3-120** products. The ester group on **3-118** was reduced to primary alcohol using Lithium aluminum hydride (LAH), which was subsequently oxidized to corresponding aldehydes (**3-119** and **ent-3-119**) using Dess Martin Periodinane (DMP) reagent. Reaction of the aldehydes with methylamine in the presence of titanium(IV) isopropoxide generated the imine *in situ*, which was then reduced using sodium borohydride to get the final cyclopropylmethylamines (**3-120** and **ent-3-120**) in good yields. These amines were

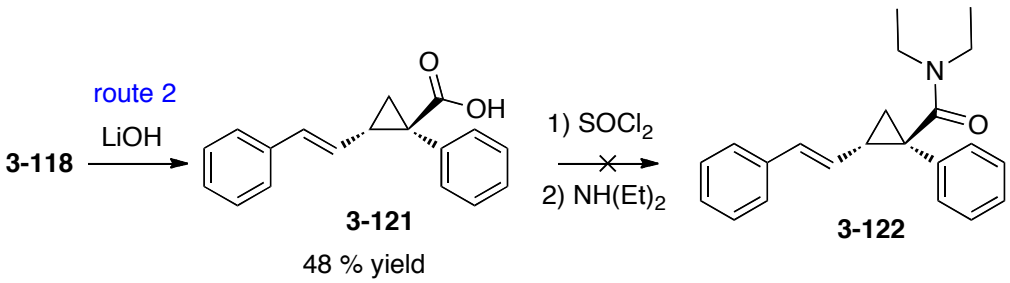
converted to their hydrochlorate salts and sent for biological evaluations (*in vitro* data will be discussed in later section).



* Opposite enantiomer was formed.

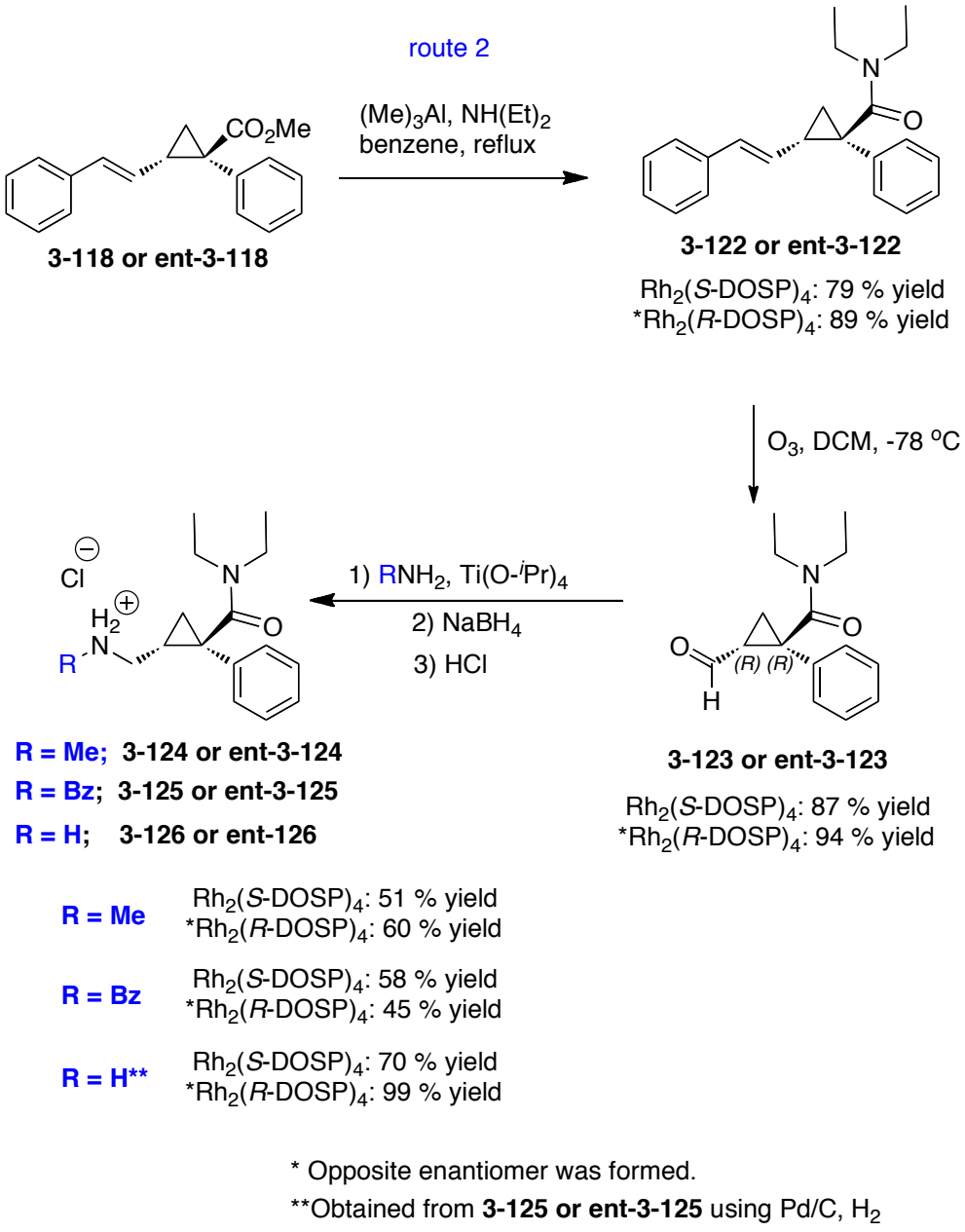
Scheme 3.28: Synthesis of both enantiomers of *N*-methyl-1-1-phenyl-2-((*E*)-styryl)cyclopropyl)methanamine.

Next, focus was shifted towards synthesis of milnacipran analogues (Scheme 3-29). The ester functionality in the cyclopropane (**3-118**) was converted to the acid (**3-121**) in the presence of lithium hydroxide. The idea was to synthesize the amide from the acid chloride, which was generated by reacting with thionyl chloride; however, no amide product was observed. Repeated attempts to carry out this reaction were unsuccessful. *N,N'*-Dicyclohexylcarbodiimide (DCC) coupling reaction was also attempted but no product was observed.



Scheme 3-29: Synthetic attempt to make *N*, *N*-diethyl-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxamide.

An alternate method was employed, where the amide functionality was to be accessed directly from the ester (Scheme **3.30**). The vinyl cyclopropanes (**3-118** or **ent-3-118**) were reacted with diethyl amine in the presence of trimethylaluminium in refluxing benzene for 24 h and gave the desired amide products **3-122** or **ent-3-122** in excellent yields. Ozonolysis of the double bond gave corresponding aldehydes (**3-123** and **ent-123**).



* Opposite enantiomer was formed.

Obtained from **3-125 or ent-3-125 using Pd/C, H_2

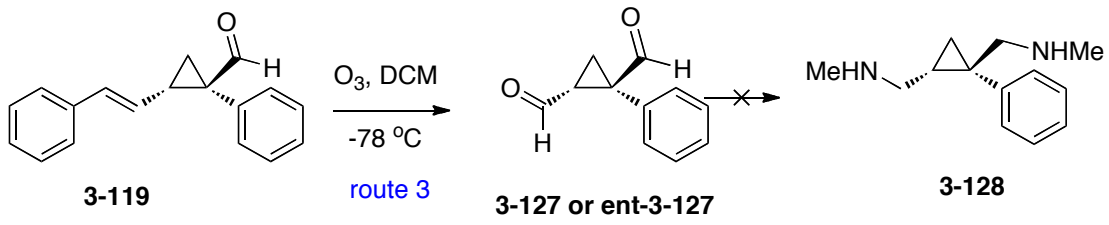
Scheme 3.30: Synthesis of various amine derivatives of 2-(amino)-*N*, *N*-diethyl-1-phenylcyclopropanecarboxamide.

3-123 or **ent-3-123** aldehydes were reacted with either methylamine or benzyl amine in a reductive amination protocol to give amine derivatives **3-124** or **ent-3-124** and

3-125 or **ent-3-125,** respectively. The cyclopropylamines with a benzyl amine group (**3-125** or **ent-3-125)** were converted to primary amine functionality to get **3-126** or **ent-3-126** *via* hydrogenation reaction in the presence of Pd/C.

In summary, six novel milnacipran analogues including exact diastereomer of milnacipran itself were synthesized using the synthetic Scheme 3.30. All the novel compounds were sent to Steve Childers lab to get the binding affinities to all three monoamine reuptake inhibitors (SERT, NET and DAT) as well as 5-HT receptors.

The aldehyde **3-119** or **ent-3-119** were also subjected to ozonolysis conditions to obtain dialdehyde **3-127** or **ent-3-127** in moderate yields. Even though dialdehyde was isolated and characterized, it was pretty evident from the ^{1}H NMR that the product was decomposing. It appears that diamine products **3-128** and **ent-3-128** were not formed in the reductive amination step due to decomposition of aldehyde. This reaction was not repeated. But it is possible to get to the final diamine product, If vinyl aldehyde would have been subjected to three step one pot procedure (described in the later section) without isolating dialdehyde intermediate (Scheme 3.31).

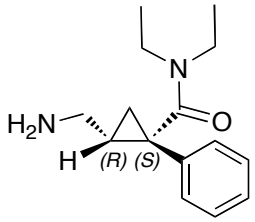
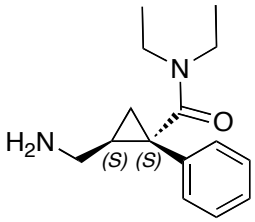
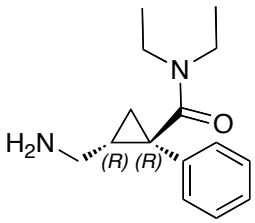
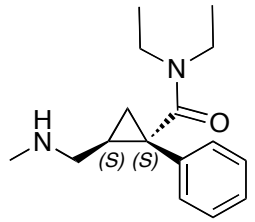


3-119 **3-127 or ent-3-127** **3-128**

Rh_2(*S*-DOSP)$_4$: 64 % yield
*Rh_2(*R*-DOSP)$_4$: 69 % yield

Scheme 3.31: Synthetic attempt to make 1-phenylcyclopropane-1,2-diyl)bis(*N*-methylmethanamine).

3.3.2 *In vitro* data of milnacipran analogues

Entry	Compound	SERT	NET	DAT
3-8		35.1 ± 4.4	23.6 ± 1.7	1970 ± 230
ent-3-126		>10K	>10K	>10K
3-126		>10K	>10K	>10K
ent-3-124		>10K	>10K	>10K

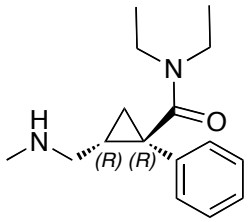
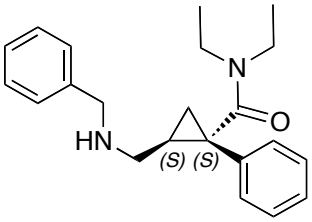
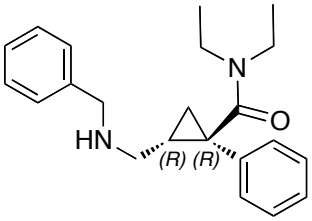
3-124		9370 ± 2500	1510 ± 220	10K
ent-3-125		>10K	>10K	>10K
3-125		>10K	>10K	>10K

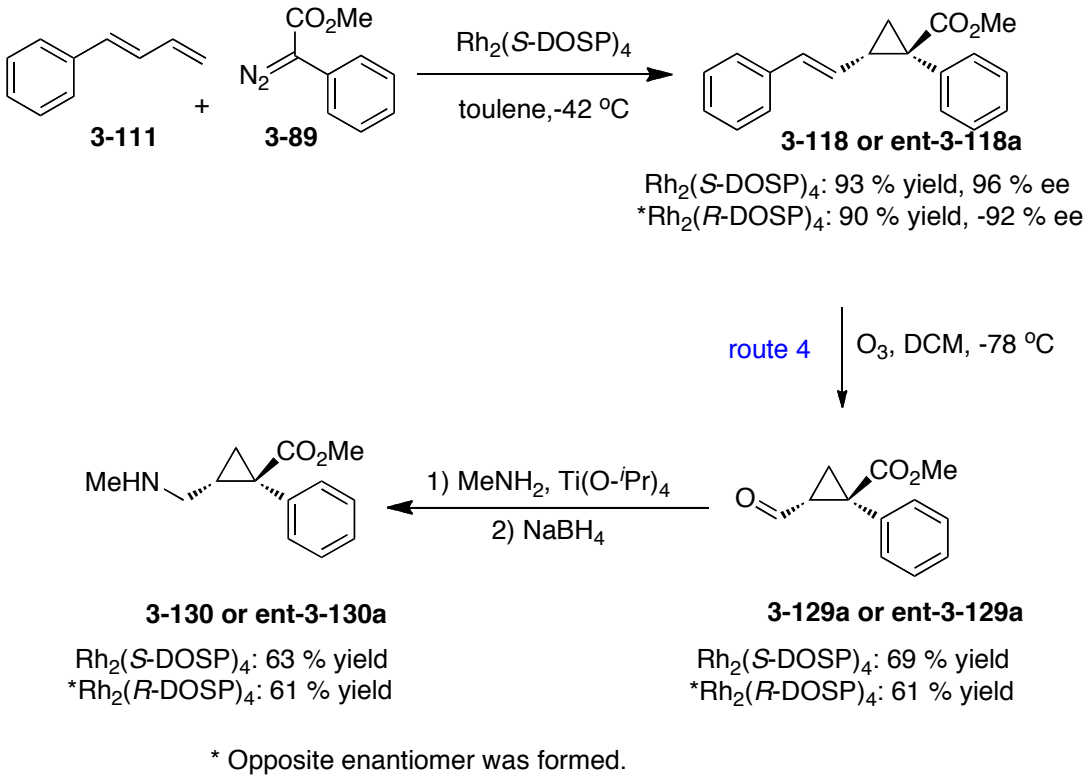
Table 3.2: K_i values (nM ± SEM) for milnacipran analogues in radioligand binding assays at SERT, NET and DAT were determined in rat brain membranes. (Data was obtained in Steve Childers laboratory)

The *in vitro* analysis of various amine derivatives of milnacipran diastereomers (Table 3.2) revealed that none of these compounds were active against any of the monoamine transporters. We later found the reason for lack of activity for these compounds through a computational modeling study (discussed in the later section).

In summary, diastereomers of milnacipran were inactive against all monoamine transporters and the amide functionality was detrimental for activity in the *E* isomeric series.

3.3.3 Synthesis of novel arylcyclopropylamines.

Although many structural modifications were done on milnacipran to improve its efficacy and selectivity, the amide functionality in milnacipran was thought to be essential for activity. For this reason, no other functional groups were evaluated earlier. We were curious to find whether keeping the ester functionality in the original cyclopropane would have any inherent enhanced biological activity. To find answer to this question, route 4 was employed.



Scheme 3.32: Synthesis of both enantiomers of methyl 2-((methylamino)methyl)-1-phenylcyclopropanecarboxylate

The vinyl cyclopropane products formed in the asymmetric cyclopropanation reaction **3-118** or **ent-3-118** were subjected to a two step protocol that includes ozonolysis of the double bond, followed by a reductive amination of the aldehyde to give the corresponding phenyl cyclopropylamine compounds **3-130** or **ent-3-130** in moderate to good yields (Scheme 3.32). These compounds were also sent for bioanalysis.

3.3.4 *In vitro* data of novel aryl cyclopropylamines.

The breakthrough results came when these novel set of compounds were tested for activity. It was found that the aryl cyclopropylamine **(ent-3-130)** with the ester functionality & (1*S*, 2*S*) absolute configuration has 14.8 nM binding affinity to SERT (2 fold more potent than milnacipran), 32 nM binding to NET (comparable to milnacipran) and 950 nM binding to DAT (2 -fold more potent than milnacipran). Moreover, a remarkable selectivity between the two enantiomers was also observed. The bioactive enantiomer **(ent-3-130)** (SERT 14 nM) was found to be 120 -fold more active when compared to its' opposite enantiomer **(3-130)** (SERT 1840 nM). This amazing bioactivity difference would have been missed, if both enantiomers were not synthesized in enantioselective fashion and tested separately. This novel class of compounds falls under the SNRI category as they are relatively potent towards SERT and NET but not for DAT.

Another set of compounds that were found to be very interesting were **3-120** and **ent-3-120**. These compounds were originally designed to target 5-HT_{2A} receptor, but they were found to be inactive against that target. The compound with (1*R*, 2*S*) absolute configuration **3-120** was found to be relatively potent for both SERT (39 nM) and DAT (60 nM) as compared to NET (4390 nM). To the best of our knowledge, the compounds which are selective for both SERT and DAT are not precedented and pharmacological value of these type of compounds is not known.

These *in vitro* results not only added value to our research approach but also opened up a new research direction for us to pursue.

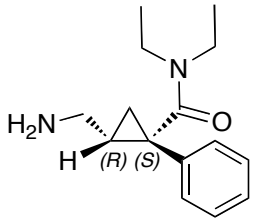
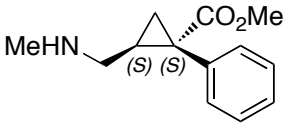
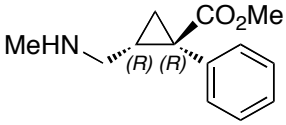
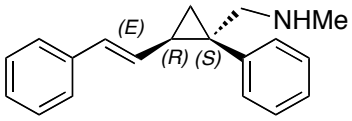
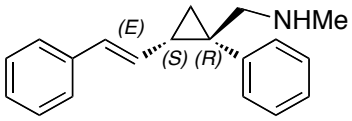
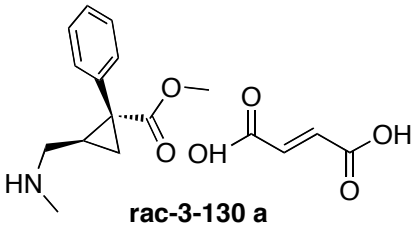
Entry	Compound	SERT K_i(nM ± SEM)	NET K_i(nM ± SEM)	DAT K_i(nM ± SEM)
3-8		35.1 ± 4.4	23.6 ± 1.7	1970 ± 230
Ent-3-130		14.8 ± 3.0	31.9 ± 3.4	950 ± 100
3-130		1840 ± 160	2220 ± 150	10K
Ent-3-120		155 ± 22.0	>10K	290 ± 73.4
3-120		39.5 ± 1.3	4390 ± 720	59.2 ± 10.1

Table 3.3: K_i values (nM ± SEM) for novel aryl cyclopropylamines in radioligand binding assays at SERT, NET and DAT were determined in rat brain membranes. (Data was obtained in Steve Childers laboratory)

The relative geometry was unambiguously determined by X-ray crystallography. It clearly shows E configuration between ester and methyl amine functionality (Fig. 3.7).



rac-3-130 a

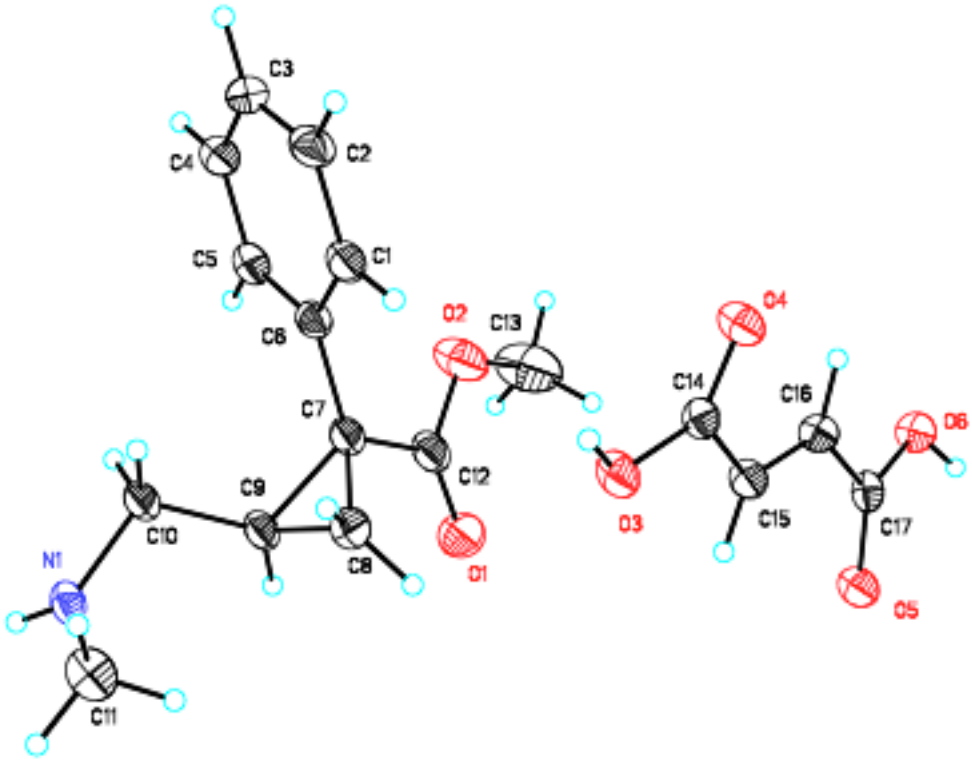
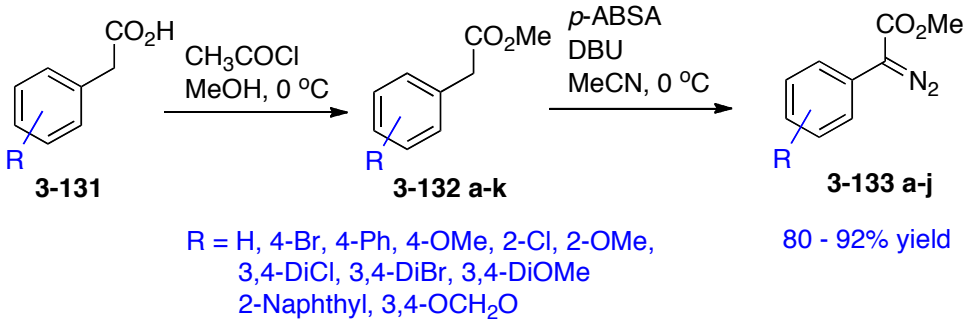


Figure 3.7: X-ray crystal structure of **rac-3-130 a**

3.3.5 Racemic synthesis of novel aryl cyclopropylamines

Based on these promising preliminary results, it was decided that a quick screening of racemic aryl cyclopropylamines was necessary to get better understanding of the activity trend before pursuing enantiomeric synthesis of these novel set of compounds. In the initial series, diversity was introduced by modifying the nature of the aryl group in diazo compound.

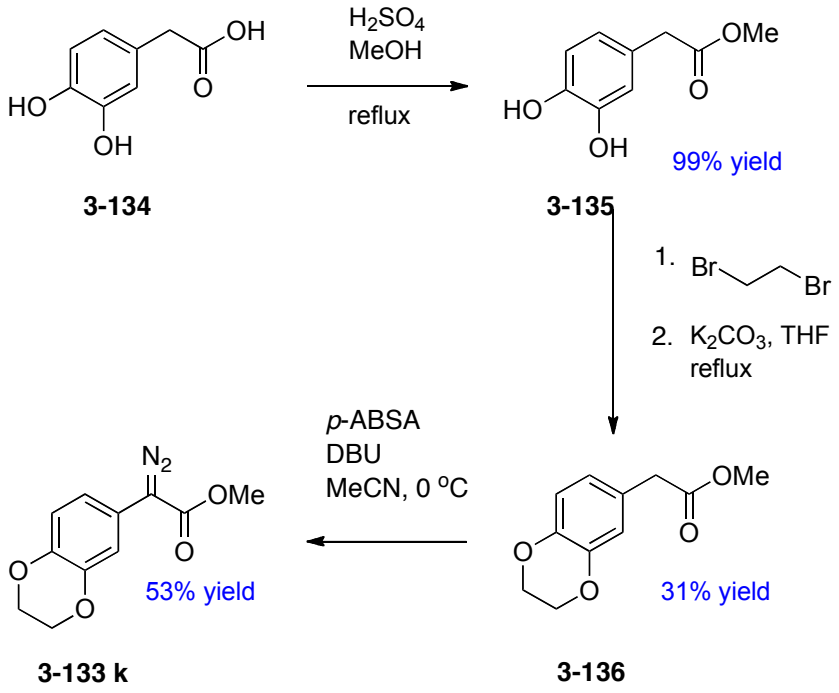


Scheme 3.33: Synthesis of various aryl diazoacetates.

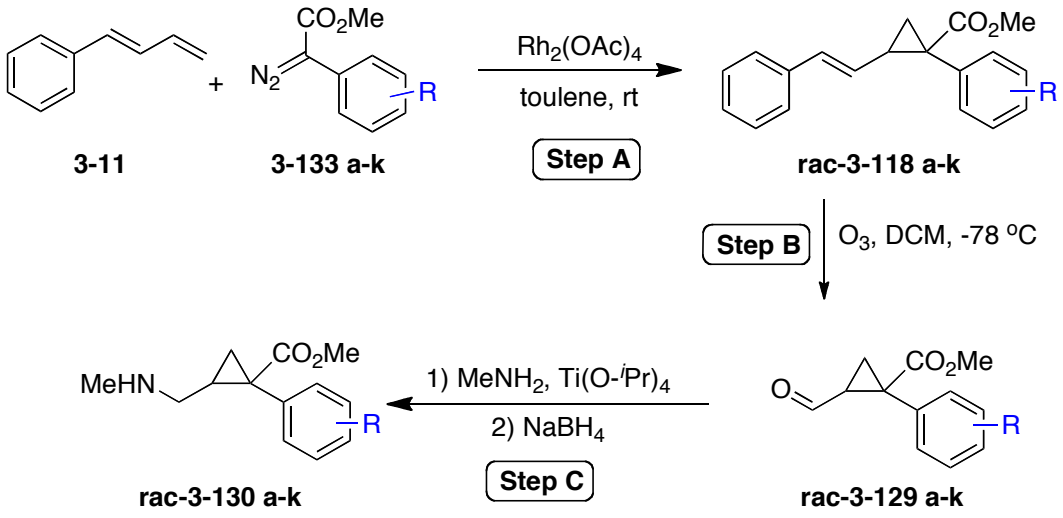
The diazo compounds required for the cyclopropanation reaction were synthesized following the Scheme 3.33. The esterification of 2-phenyl ethanoic acids (**3-131**) in the presence of acetyl chloride in methanol gave the corresponding esters (**3-132**) in quantitative yields. A diazo transfer reaction in the presence of *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and the base 1,8-diazabicycloundec-7-ene (DBU) in acetonitrile yielded the corresponding diazo compounds (**3-133**) in good to

excellent yields. These reactions were performed in large scale to synthesize enough diazo compound, which could be used for both racemic and enantioselective synthesis.

Methyl 2-diazo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acetate **(3-137)** was synthesized starting from 2-(3,4-dihydroxyphenyl)acetic acid **(3-134)**. The acid was esterified in the presence of catalytic amounts of acid in refluxing methanol to get corresponding ester **(3-135)**. The reaction of **3-135** with 1,2-dibromoethane gave **3-136** in low yields. Most of the starting material was recovered and subjected to same reaction conditions to get the product **3-136**. A routine diazo transfer reaction gave the desired product in 53% yield (Scheme 3.34).



Scheme 3.34: Synthesis of methyl 2-diazo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acetate.



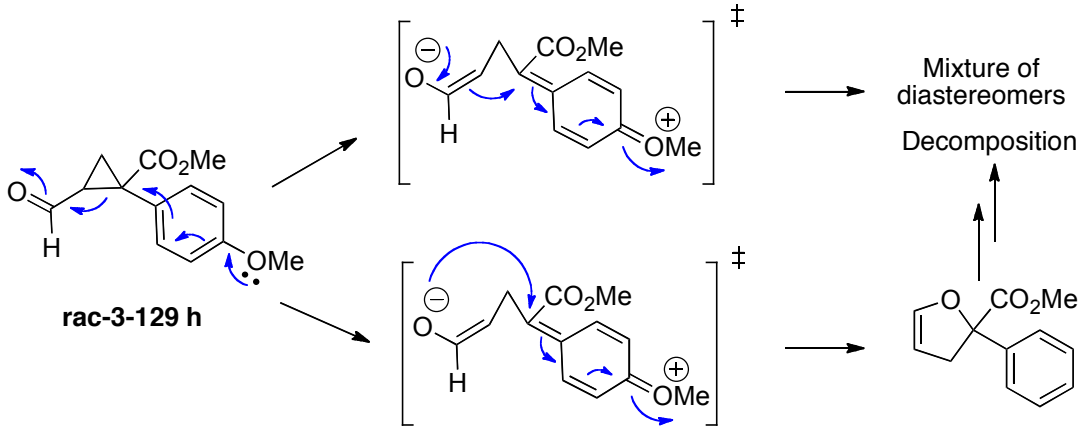
Entry	R	yield **(A)**	yield **(B)**	yield **(C)**
a	H	93	86	63
b	4-Br	94	93	56
c	4-Ph	84	83	78
d	3,4-DiCl	95	88	57
e	2-Naphthyl	90	53	60
f	2-Cl	97	70	60
g	2-OMe	67	DE	NA
h	4-OMe	70	DE	NA
i	3,4-DiOMe	92	NA	56
j	3,4-OCH_2O	98	DE	NA
k	3,4-OCH_2CH_2O	62	49	52

DE = Decomposed; NA = Not available

Scheme 3.35: Synthesis of racemic aryl cyclopropylamines.

As all diazo compounds were available, racemic synthesis of aryl cyclopropylamines **(rac-3-130 a-k)** was pursued. Cyclopropanation reactions were performed in the presence of 1 mol% $Rh_2(OAc)_4$ catalyst at rt. Typically, 62-97% yields were observed in the cyclopropanation reaction. The racemic esters **(rac-3-118 a-k)** were subjected to ozonolysis conditions to get the corresponding aldehydes **(rac-3-129 a-k)** in good yields except in the case of diazo compounds having electron-donating groups. Reductive amination of the aldehydes gave the desired racemic products **(rac-3-130 a-k)** in moderate to good yields. All cyclopropylamine compounds were then converted to their corresponding fumarate salts using a stoichiometric amount of furamic acid.

Cyclopropyl aldehydes with methoxy substitution at 2-position **(rac-3-129 g)** and 4-position **(rac-3-129 h)** decomposed to mixture of products. Two aldehyde peaks were observed in the ^1H NMR of crude reaction mixture, which corresponds to two diastereomers of cyclopropane. It was not completely unanticipated as it was known that electron donation from the methoxy substituent can open up the cyclopropane ring causing both racemization and formation of the rearranged product, which could decompose further (Scheme 3.36).



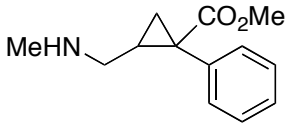
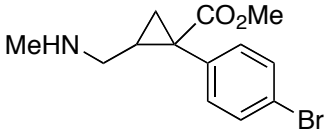
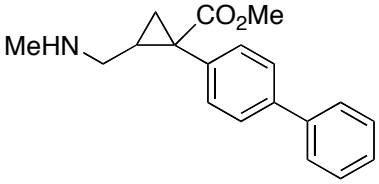
Scheme 3.36: Plausible reason of the decomposition of cyclopropyl aldehyde.

To overcome the decomposition problem, tethered versions of donating groups were introduced **3-133j** and **3-133k**. A one-pot procedure was employed in which the vinylcyclopropane was carried to the amine stage without isolating the aldehyde. The amine product was isolated in moderate yields. All racemic compounds **rac-3-130 a-k** were sent for biological evaluation.

3.3.6 *In vitro* data of racemic aryl cyclopropylamines

In vitro data for the racemic compounds was continued to be promising as most of the compounds found to be active showing low nM binding affinities towards both SERT and NET (Table 3.4). Most of the compounds were relatively weak in binding to DAT, a typical characteristic of most of the neuroleptic drugs.

The selectivity of these compounds towards one transporter over the other is sensitive to the functional group present on the aryl group. A bromo substitution at 4-position (**rac-3-130 b**) (NET 2.66 nM) or a methoxy substitution at both 3 and 4 positions (**rac-3-130 i**) (NET 7.63 nM) made the compounds selective for NET (NARI), where as, a 3,4–dichloro (**rac-3-130 d**) (SERT 3.9 nM; NET 0.57 nM) or 2-naphthyl (**rac-3-130 e**) (SERT 5.8 nM; NET 3.0 nM) substitution made the compounds selective for both SERT and NET (SNRI). A chloro substitution at 2-position (**rac-3-130 f**) and 1,2 diethoxy substitution (**rac-3-130 k**) would lead to decrease in potency. The racemic compound with 3,4-dichloro substitution (**rac-3-130 d**) was found to be 30 fold more potent than milnacipran in binding to NET.

Entry rac-3-130	**Compound**	**Log-P**	**SERT K_i(nM ± SEM)**	**NET K_i(nM ± SEM)**	**DAT K_i(nM ± SEM)**
a		1.65	103 ± 3.8	99.4 ± 42.5	1162 ± 56.8
b		2.51	151 ± 7.37	2.66 ± 0.97	1050 ± 337
c		3.54	4.32 ± 0.9	280.5 ± 91.7	168 ± 70

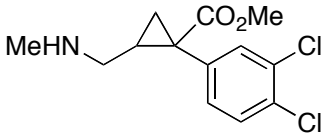
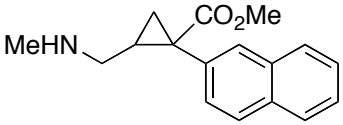
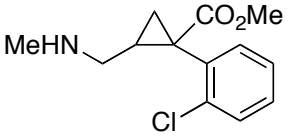
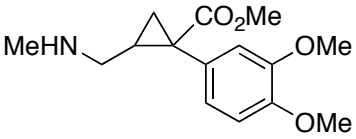
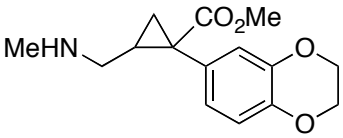
d		2.95	3.9 ± 0.27	0.57 ± 0.01	76.3 ± 15.5
e		2.82	5.8 ± 0.62	3.07 ± 0.56	156 ± 38.5
f		2.36	226 ± 36.7	198.2 ± 16.5	1262 ± 241
i		1.31	93.8 ± 18.1	7.63 ± 0.62	1207 ± 175
k		1.57	>10K	544 ± 69.8	1835 ± 141

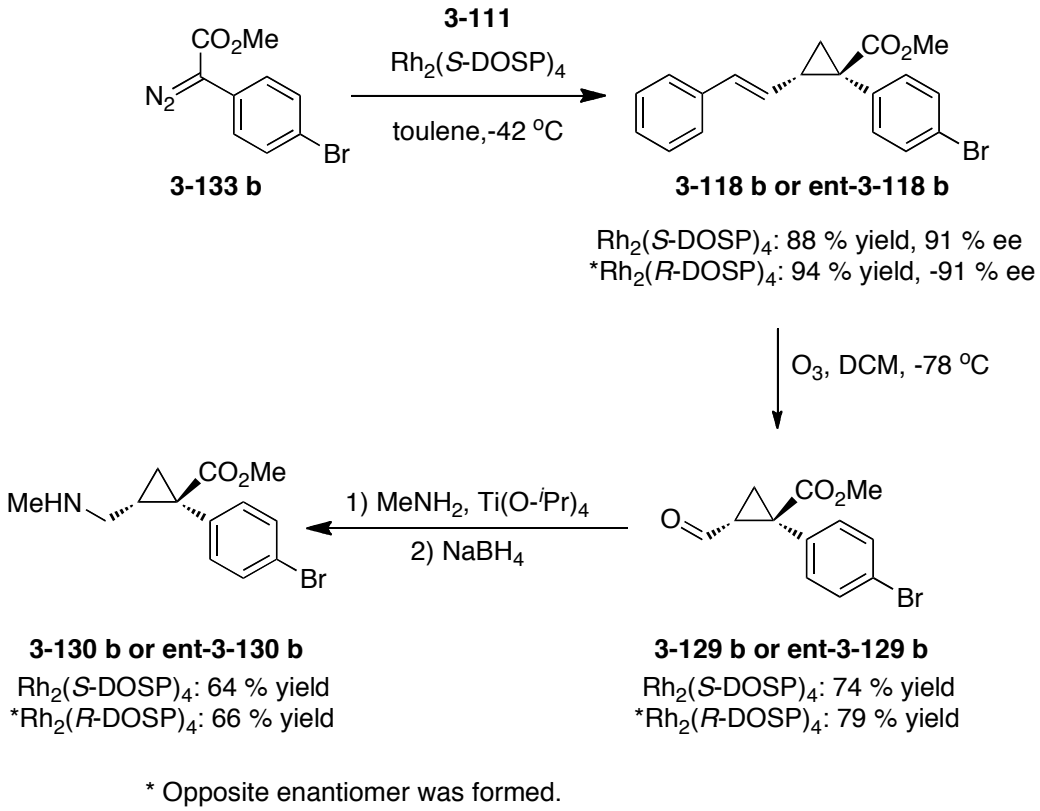
Table 3.4: K_i values (nM ± SEM) of racemic cyclopropylmethylamines in binding to NET, SERT and DAT sites in rat brain membranes. (Data was obtained in Steve Childers laboratory).

In summary, a wide range of diversity of potencies and specificities at monoamine transporters was observed in a small set of racemic aryl cyclopropyl amine compounds.

3.3.7 Enantioselective synthesis of novel aryl cyclopropylamines

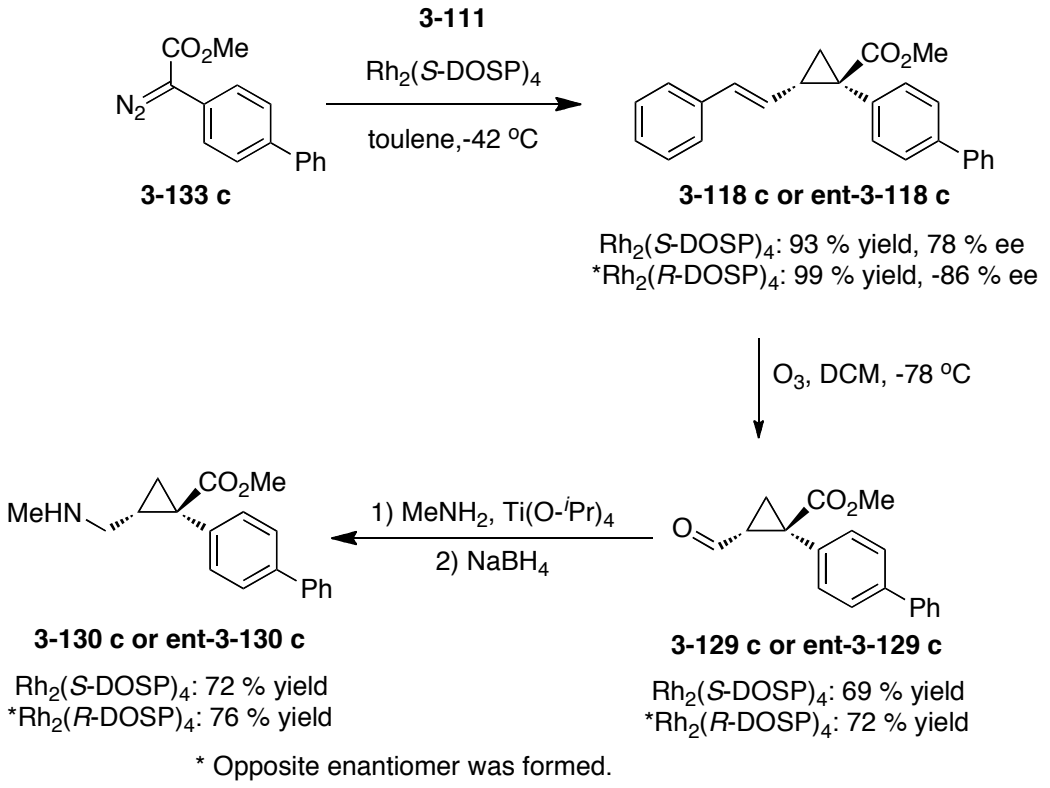
Although *in vitro* results for racemic compounds were very promising, it was anticipated that enantiopure compounds would have even better selectivity and potency profile compared to the racemates, which could be further developed as a potential drug candidate for various kinds of CNS disorders. With this idea, synthesis of enantiopure compounds was pursued.

Every time, a set of reactions was performed using both enantiomers of the catalyst. First set of enantiopure compounds synthesized consists of a bromo substitution at 4-position. Intermolecular asymmetric cyclopropanation reaction of the 4-bromo phenyl diazoacetate (**3-133b**) with phenylbutadiene (**3-111**) in the presence of prolinate based chiral catalyst; Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ gave the desired cyclopropane product in good yield. Typically only one diastereomer was observed in the crude NMR and > 90% enantioselectivity was observed. The corresponding amines were synthesized from cyclopropane ester following the synthetic scheme depicted below (Scheme 3.37).



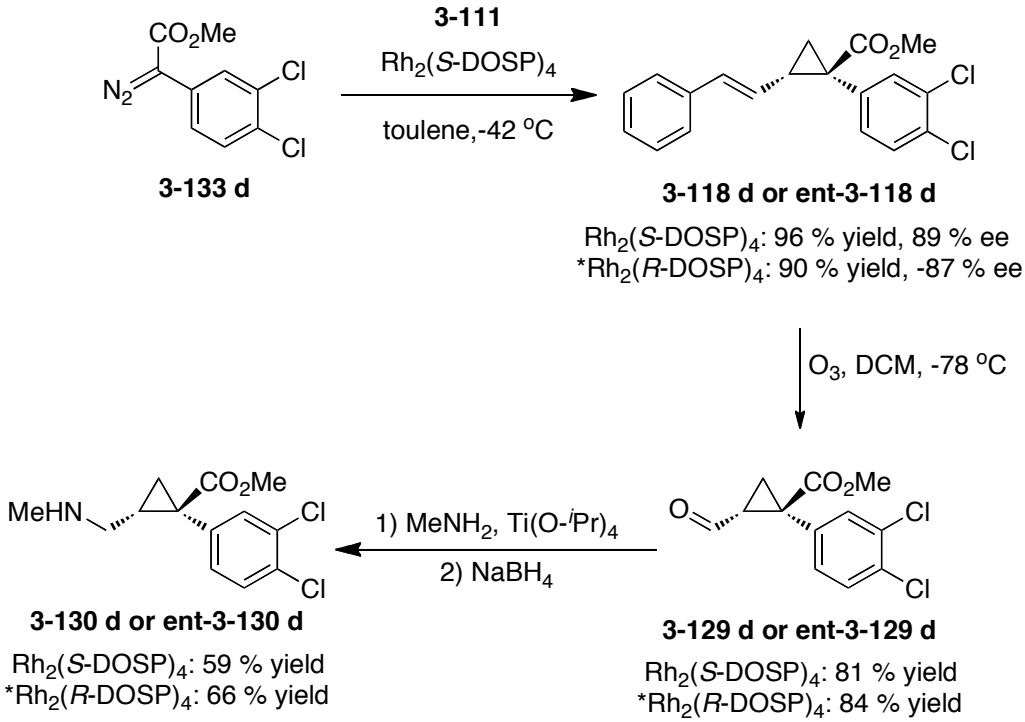
Scheme 3.37: Synthesis of both enantiomers of methyl 1-(4-bromophenyl)-2-((methylamino)methyl)cyclopropanecarboxylate.

Second set of compounds synthesized had a phenyl substitution at 4-position. Reaction of phenylbutadiene **(3-111)** with biphenyl diazoacetate **(3-133 c)** gave the desired cyclopropane product in good yields and moderate ee. These vinyl cyclopropane products were found to be oily liquids and enantio-enrichement was found to be problematic. A wide range of solvent combinations and temperature conditions were screened to find suitable recrystalization method. Only the material, which enantio-enriched was taken to the next step to get final amine in enantiopure form (Scheme 3.38).



Scheme 3.38: Synthesis of both enantiomers of methyl 1-([1,1'-biphenyl]-4-yl)-2-((methylamino)methyl)cyclopropanecarboxylate

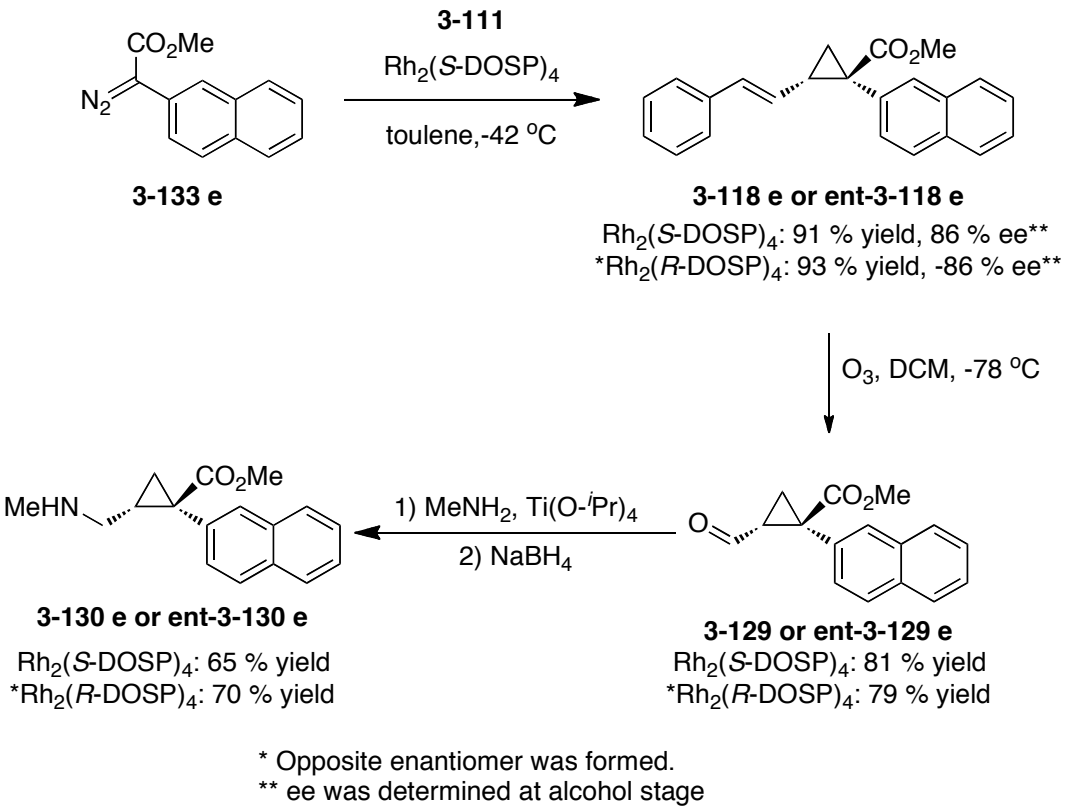
Third set of compounds synthesized had chloro substitution at 3 and 4 position. The cyclopropane products were enantro-enriched to >90% ee before taking them further. The desired amines (**3-130 d** and **ent-3-130 d**) were synthesized following the synthetic Scheme 3.39.



* Opposite enantiomer was formed.

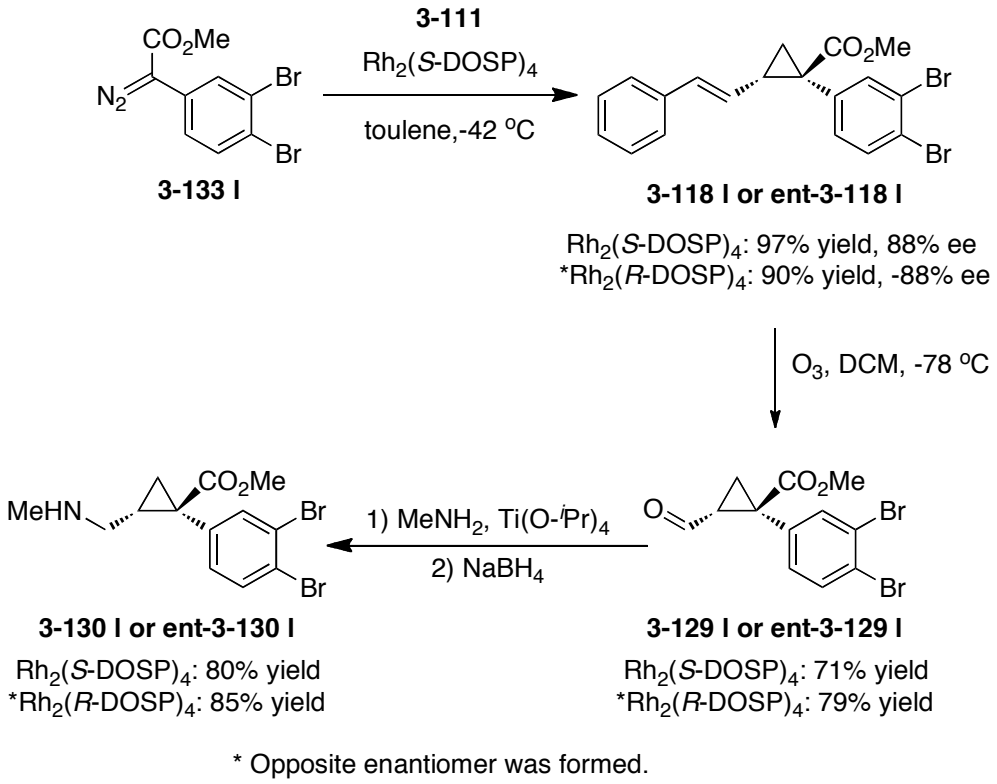
Scheme 3.39: Synthesis of both enantiomers of methyl 1-(3,4-dichlorophenyl)-2-((methylamino)methyl)cyclopropanecarboxylate

Fourth set of compounds synthesized had a 2-naphthyl substitution. The vinyl cyclopropanes **3-118 e** or **ent-3-118 e** did not separate on any of the chiral HPLC columns. The ester group on the cyclopropane was converted to primary alcohol, which was then separated on the HPLC column. Both enantiomers were converted to their corresponding amines **3-130 e** and **ent-3-130 e** (Scheme 3.40).



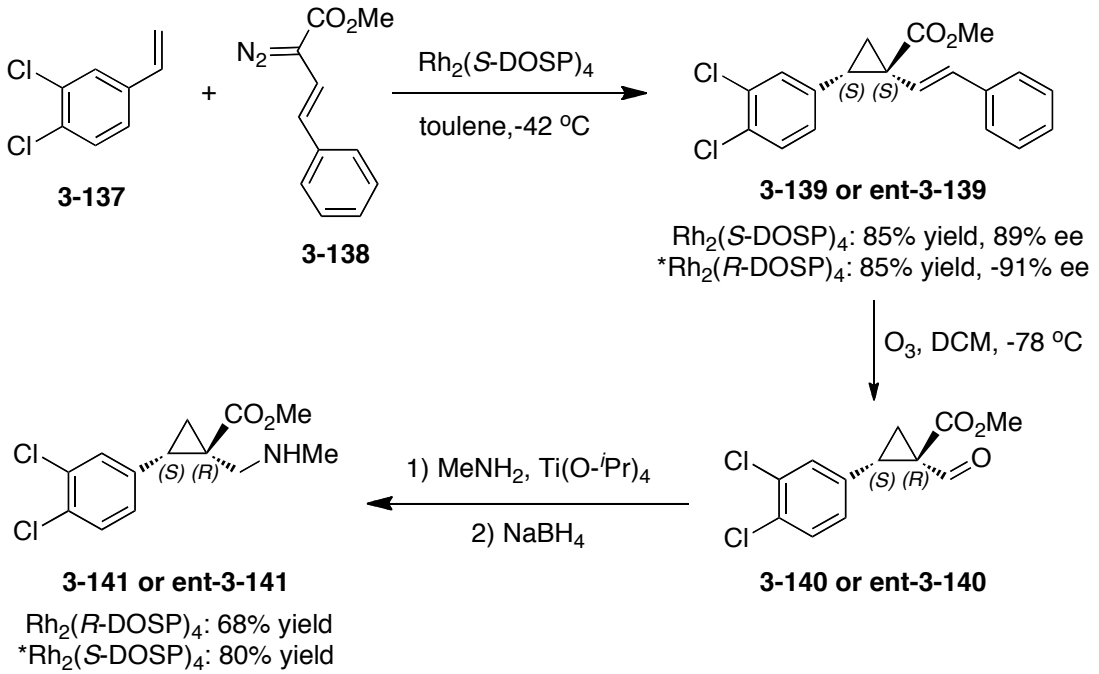
* Opposite enantiomer was formed.
** ee was determined at alcohol stage

Scheme 3.40: Synthesis of both enantiomers of methyl 2-((methylamino)methyl)-1-(naphthalen-2-yl)cyclopropanecarboxylate



Scheme 3.41: Synthesis of both enantiomers of methyl 1-(3,4-dibromophenyl)-2-((methylamino)methyl)cyclopropanecarboxylate

Fifth set of enantiopure compounds synthesized had bromo substitution at 3 and 4 position. Even though racemic amine was not evaluated earlier, it was anticipated that this set of compounds might have same or better biological profile as compared to **3-130 d** and **ent-3-130 d**. The desired amines **3-130 l** or **ent-3-130 l** were synthesized (Scheme 3.41) and all the enantiopure compounds were sent to Steve Childer's laboratory for evaluation.



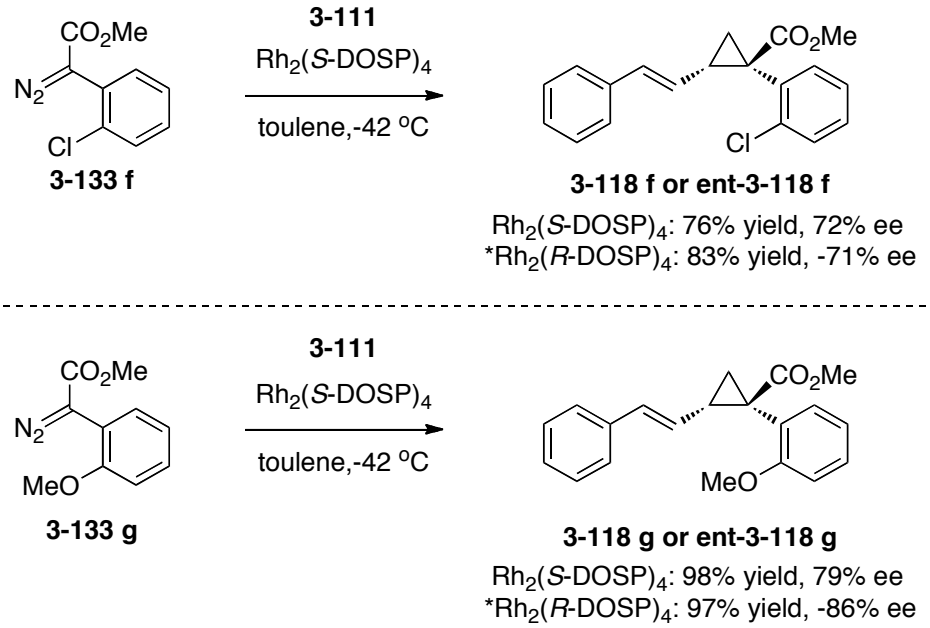
* Opposite enantiomer was formed.

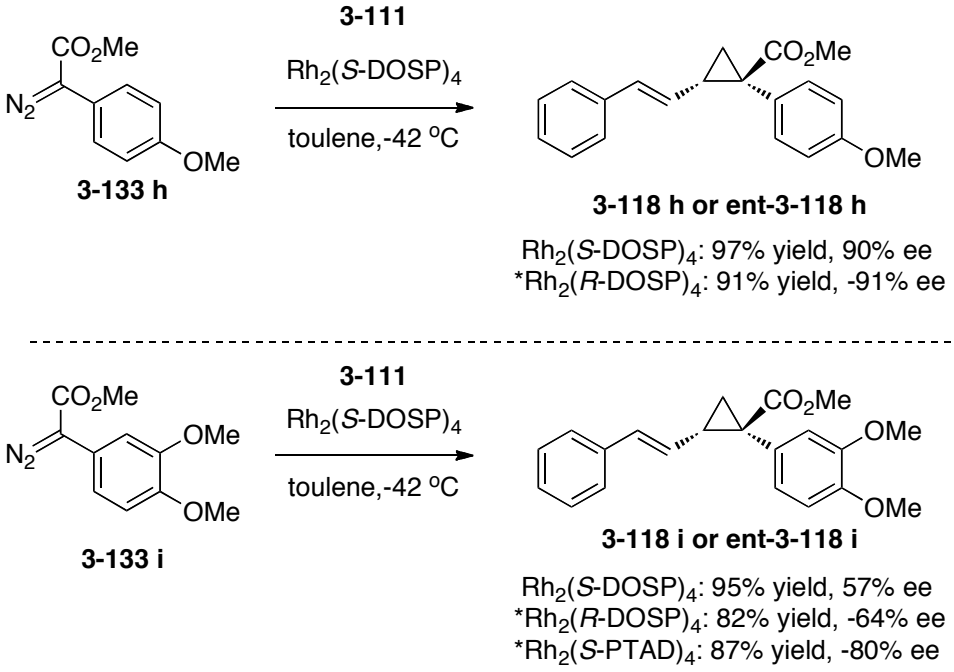
Scheme 3.42: Synthesis of both enantiomers of methyl 2-(3,4-dichlorophenyl)-1-((methylamino)methyl)cyclopropanecarboxylate.

It was evident from previous *in vitro* data that ester functionality on the cyclopropane was necessary in this series of compounds. We were curious to find whether change in the position of the ester group would change the bioactivity of these compounds. To probe this, a new set of compounds were synthesized in which, other regio isomer of lead compound was generated using cyclopropanation reaction of vinyl diazo acetate (Scheme 3.42).

The reaction of 1,2-dichloro-4-vinylbenzene **(3-137)** with (*E*)-methyl 2-diazo-4-phenylbut-3-enoate **(3-238)** in the presence of Rh_2(*S*-DOSP)$_4$ gave the desired

cyclopropane **(3-139** or **ent-3-139)** in 85% yield and excellent ee. This products were subjected to ozonolysis followed by reductive amination conditions in a one pot procedure to get the final cyclopropylamine in good yields (Scheme 3.42). These compounds will be sent for biological evaluation at later stage.





Scheme 3.43: Synthesis of various vinyl cyclopropanes with methoxy and chloro substitution.

Enantioselectivity in cyclopropanation reaction of 2-chloro substituted diazo compound **(3-133 f)** gave poor ee of 71%. The 4-methoxy substituted diazoacetate **(3-133 h)** gave very high enantioinduction of > 90% where as, 2-methoxy substituted diazoacetate **(3-133 g)** gave good ee of 86% in cyclopropanation reaction. Based on the previous *in vitro* data, 3,4-dimethoxy substituted phenyl cyclopropylamine (**rac-3-130 i**) was found to be NET selective. We also thought of exploring the synthetic feasibility of enantiopure aryl cyclopropylamines with methoxy substitution as well. Asymmetric cyclopropanation reaction of 3,4-dimethoxy phenyl diazoacetate **(3-133 i)** in the presence

of Rh_2(*S*-DOSP)$_4$ gave poor ee of 57%. When adamantane based catalyst Rh_2(*S*-PTAD)$_4$ was employed, ee was improved to 80%.

In summary, a series of enantiomerically pure aryl cyclopropylamines were synthesized using intermolecular cyclopropanation reaction as a key step. Overall, more than forty novel compounds have been synthesized in this process. All cyclopropylamine compounds were sent for *in vitro* evaluation.

3.3.8 *In vitro* data of enantiopure aryl cyclopropylamines

In vitro data for newer set of enantiopure compounds showed interesting trends (Table 3.5).

1) As a general trend, enantiomer with (1*R*, 2*R*) configuration was found to be more potent and selective as compared to it's opposite enantiomer with (1*S*, 2*S*) configuration.

2) Milnacipran was modestly potent in binding to both SERT and NET (K_i values of 35 nM and 24 nM). A number of these novel analogues were significantly (5-10 times) more potent at NET than milnacipran, with K_i values in the low nM range.

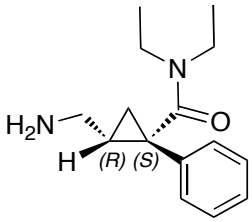
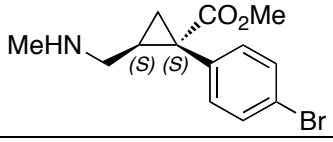
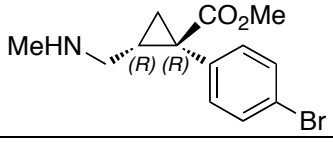
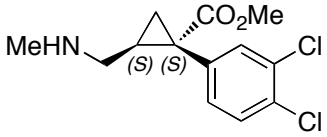
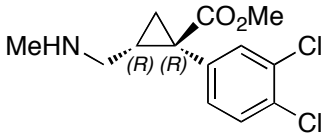
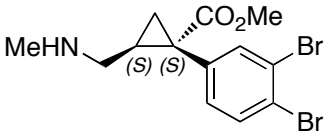
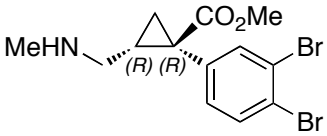
3) In the enantiomeric pair with 4-bromo substitution, (1*R*, 2*R*) isomer **(3-130 b)** was found to be 20 -fold more potent in binding to both SERT and NET than its opposite enantiomer; (1*R*, 2*R*) isomer was found to be very potent at NET (K_i 1.66 nM) and **20** -fold selective over SERT. This compound comes under **NARI** category.

4) In the enantiomeric pair with 3,4 dichloro substitution, (1*R*, 2*R*) isomer **(3-130 d)** was found to be 16 -fold more potent in binding to SERT; 26 -fold more potent in binding to NET than its opposite enantiomer; (1*R*, 2*R*) isomer was found to be extremely potent in binding to both SERT (K_i 1.59 nM) and NET (K_i 0.2 nM) and 8 -fold selective for NET over SERT. This compound also found to be **77** -fold more potent at NET than milnacipran and comes under **SNRI** category.

5) In the enantiomeric pair with 3,4 dibromo substitution, (1*R*, 2*R*) isomer **(3-130 l)** was found to be 10 -fold more potent in binding to SERT; 7 -fold more potent in binding to NET than its opposite enantiomer; (1*R*, 2*R*) isomer was found to be extremely potent in binding to both SERT (K_i 1.22 nM) and NET (K_i 0.45 nM) and only 3 -fold selective for NET over SERT. This compound comes under **SNRI** category. This compounds' and it's potency is comparable to **(3-130 d)**.

6) In the enantiomeric pair with 2-naphthyl substitution, (1*R*, 2*R*) isomer **(3-130 e)** was found to be 2 -fold more potent in binding to both SERT and NET than its opposite enantiomer; (1*R*, 2*R*) isomer was found to be potent at both SERT (K_i 13.2 nM) and NET (K_i 9.1 nM) with equal affinity. This compound comes under **SNRI** category.

7) In the enantiomeric pair with 4-phenyl substitution, (1*R*, 2*R*) isomer **(3-130 c)** was found to be 30 -fold more potent in binding to SERT than its opposite enantiomer; (1*R*, 2*R*) isomer was found to be potent at SERT (K_i 1.78 nM) and **32** -fold selective over NET. This compound comes under **SSRI** category.

Entry	Compound	SERT K_i(nM ± SEM)	NET K_i(nM ± SEM)	DAT K_i(nM ± SEM)
3-8		35.1 ± 4.4	23.6 ± 1.7	1970 ± 230
ent-3-130 b		630.7 ± 47.5	29.9 ± 0.7	>9000
3-130 b		31.34 ± 1.97	1.66 ± 0.05	222 ± 52.8
ent-3-130 d		26.6 ± 2.84	5.34 ± 0.53	197 ± 63.8
3-130 d		1.59 ± 0.2	0.20 ± 0.01	15.7 ± 2.4
ent-3-130 l		13.1 ± 1.8	3.26 ± 0.47	62.8 ± 6.7
3-130 l		1.22 ± 0.04	0.45 ± 0.08	25.1 ± 3.2

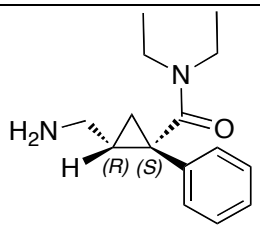
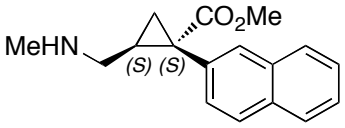
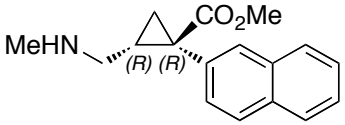
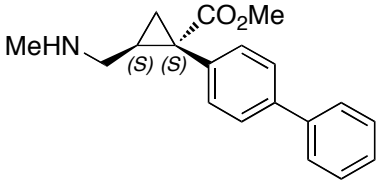
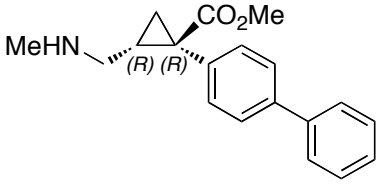
Entry	Compound	SERT K_i(nM ± SEM)	NET K_i(nM ± SEM)	DAT K_i(nM ± SEM)
3-8		35.1 ± 4.4	23.6 ± 1.7	1970 ± 230
ent-3-130 e		23.8 ± 3.0	14.5 ± 0.46	276 ± 48.1
3-130 e		13.2 ± 2.4	9.14 ± 0.78	282 ± 45.3
ent-3-130 c		52.9 ± 14	>10,000	608 ± 41.3
3-130 e		1.78 ± 0.41	57.43 ± 12.86	57.5 ± 24.9

Table 3.5: K_i values (nM ± SEM) of enantiopure cyclopropylmethylamines in binding to NET, SERT and DAT sites in rat brain membranes. (Data was obtained in Steve Childers laboratory)

In summary, high levels of potency and selectivity's was observed in this small set of enantiopure compounds. It was observed that substituent at 4 position made the compound NET selective and bulky substituent at 4 position made the compound SERT

selective and substituent at 3,4 position made the compound very potent and selective for both SERT and NET.

3.3.9 *In vivo* data of aryl cyclopropylamines

In vitro data for both racemic and enantiopure aryl cyclopropylamines was promising, which prompted us to find therapeutic use for these novel set of compounds. All the lead compounds **HD-286** (**rac-3-130 c)** (2 g), **HD-288** (**rac-3-130 d)** (2 g), **HD-327** (**3-130 d)** (3 g) were synthesized in large scale and multi-gram quantities were made available, which facilitated a thorough *in vivo* study. *(NOTE: HD numbers are reference numbers used while sending samples for bio-analysis. These numbers were kept for clarity)*

Typical antidepressants have shown limited efficacy against neuropathic pain, when given directly into the intrathecal (i.t) space due to limited solubility, efficacy, potency. As our novel cyclopropylamines do not have any of the above issues, these compounds were tested in an animal model of neuropathic pain in Jeff Martin laboratory, Wake Forest Medical Center.

Primary aim of this animal study was to determine the optimal ratio of SERT:NET uptake inhibition that produces the maximum efficacy against neuropathic pain while producing little or no motor impairment.

The potency and efficacy of novel SNRI analogues in reversing mechanical hypersensitivity was determined in the L5/L6 spinal nerve ligation (SNL) model of

neuropathic pain in rats. Compounds were administered i.t. and the effect on paw withdrawal threshold was assessed at various time points following treatment.

3.3.9.1 Anti-allodynic effects of racemic cyclopropylamines as compared to clonidine.

Clonidine is a drug approved for treatment of neuropathic pain in humans by spinal administration. Our synthetic compounds were tested against this clinical drug in reversing the mechanical allodynia in SNL rats.

HD-288 (**rac-3-130 d)** (racemic dual SERT/NET inhibitor) was potent following i.t. administration, producing significant anti-allodynic effects with an A50 of 0.6 ± 0.3 μg and increasing the PWT from 2.9 ± 0.4 g to 24.9 ± 2.5 g at 3 μg (Fig. 3.8). **Clonidine** (10 μg, i.t.) and **milnacipran** (30 μg, i.t.) reversed mechanical allodynia in SNL rats similar to literature values (Figure 3.8).[111] The compound **HD-286** (**rac-3-130 c)** (racemic SERT inhibitor) produced an increase in PWT in SNL rats over a similar dose range as **HD-288** (**rac-3-1-130 d)** with significantly lower efficacy, consistent with reports of the limited efficacy of SERT inhibitors against neuropathic pain (Fig. 3.8)[4,111-113]

The maximum effect of **HD-288** (**rac-3-1-130 d)** was found to be significantly greater than **clonidine**, while that of **HD-286** (**rac-3-1-130 c)** was significantly less than **clonidine** (Figure 3.8). Therefore, **HD-288** appears to be efficacious in reversing a symptom of neuropathic pain (mechanical allodynia) in nerve-injured rats and is quite potent compared to medications approved for clinical treatment of chronic pain

(**clonidine, milnacipran**). This also led to the hypothesis that the compounds with higher affinity for both NET and SERT can be effective in treating neuropathic pain.

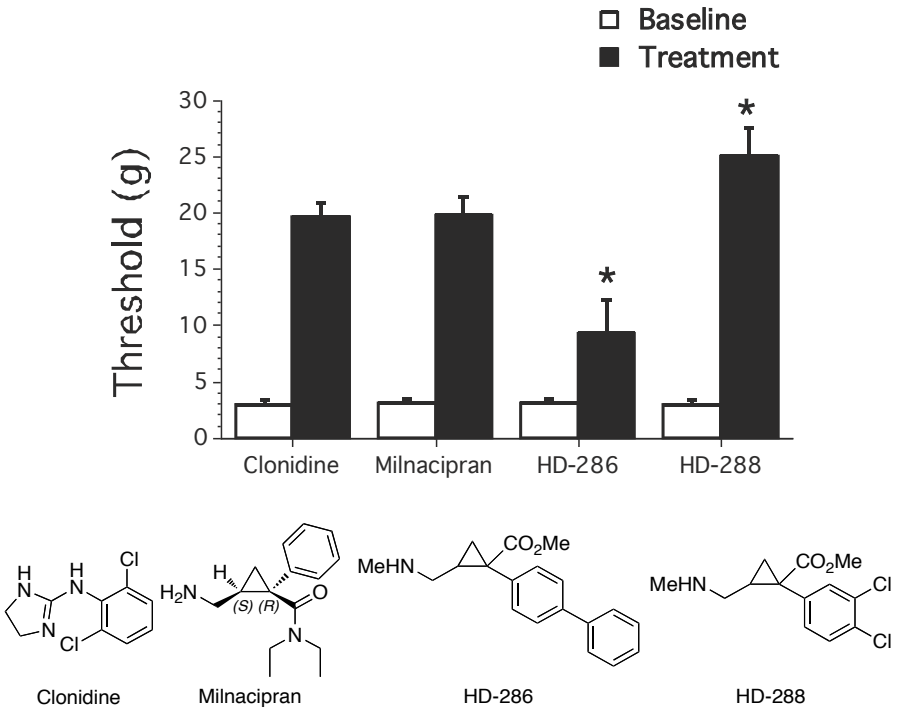


Figure 3.8: Anti-allodynic effects of novel SNRI analogues and clonidine. All compounds were administered as described in Figure 3.8 and paw withdrawal threshold was determined before (Baseline) and following drug treatment (Treatment) in a similar manner. Maximally effective doses were given for clonidine (10 µg), Milnacipran (30 µg), HD-286 (3 µg) and HD-288 (3 µg). N=8-10/group. *, significantly different from clonidine, $p \leq 0.05$. (Results from Jeff Martin Lab at Wake Forest University)

3.3.9.2 Anti-allodynic effects of enantiomers of 3,4-dichlorophenyl cyclopropylamines as compared to milnacipran

It was evident from initial animal studies with racemic compounds that SNRI's are effective in reversing the allodynic effects. So both bioactive and inactive enantiomers were also tested in SNL rats over a wide range of doses.

As can be seen in Table 3.6 & Figure 3.9, only 0.14 μg dosage of **HD-327 (3-130 d)** was enough to show maximum therapeutic effect as compared to milnacipran that require ~40 μg to show the same therapeutic effect. It is remarkable to note that even 60 μg dosage of inactive enantiomer **HD-326** (**ent-3-130 d**) did not show maximum therapeutic effect. Even though, racemate is also as effective as enantiopure material in this study, it would be desirable to study enantiopure compounds further as these compounds expected to have desirable pharmacokinetic properties and less side effects and can be developed as a potential drug candidate for the treatment of neuropathic pain.

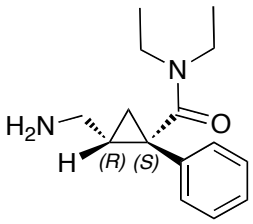
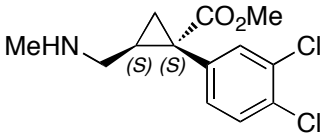
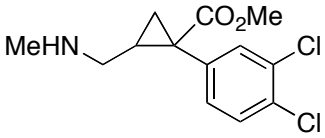
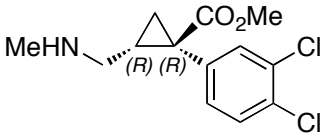
Entry	Compound	ED_{50} (µg)	Dose (µg)	PWT mean ± SEM
Milnacipran 3-8		39.6	3	2.4 ± 0.2
			10	6.5 ± 0.8
			30	19.6 ± 1.7
HD-326 ent-3-130 d		2.8	0.3	6.9 ± 2.4
			1	10.4 ± 2.4
			3	8.4 ± 1.2
			10	11.8 ± 1.8
			30	13.7 ± 2.5
			60	12.7 ± 1.9
HD-288 rac-3-130 d		0.34	0.03	5.0 ± 1.0
			0.1	10.1 ± 0.8
			0.3	9.7 ± 1.2
			1	21.2 ± 2.8
			3	24.9 ± 2.5
HD-327 3-130 d		0.14	0.1	7.9 ± 1.7
			0.3	15.9 ± 2.7
			1	17.6 ± 2.9
			3	19.3 ± 2.3

Table 3.6: ED_{50} values and paw withdrawal thresholds (PWT) (higher numbers = less pain) in spinal nerve ligated (SNL) rats, after injecting drug intrathecally (i.t.) (Determined in Jeff Martin Laboratory at Wake Forest University).

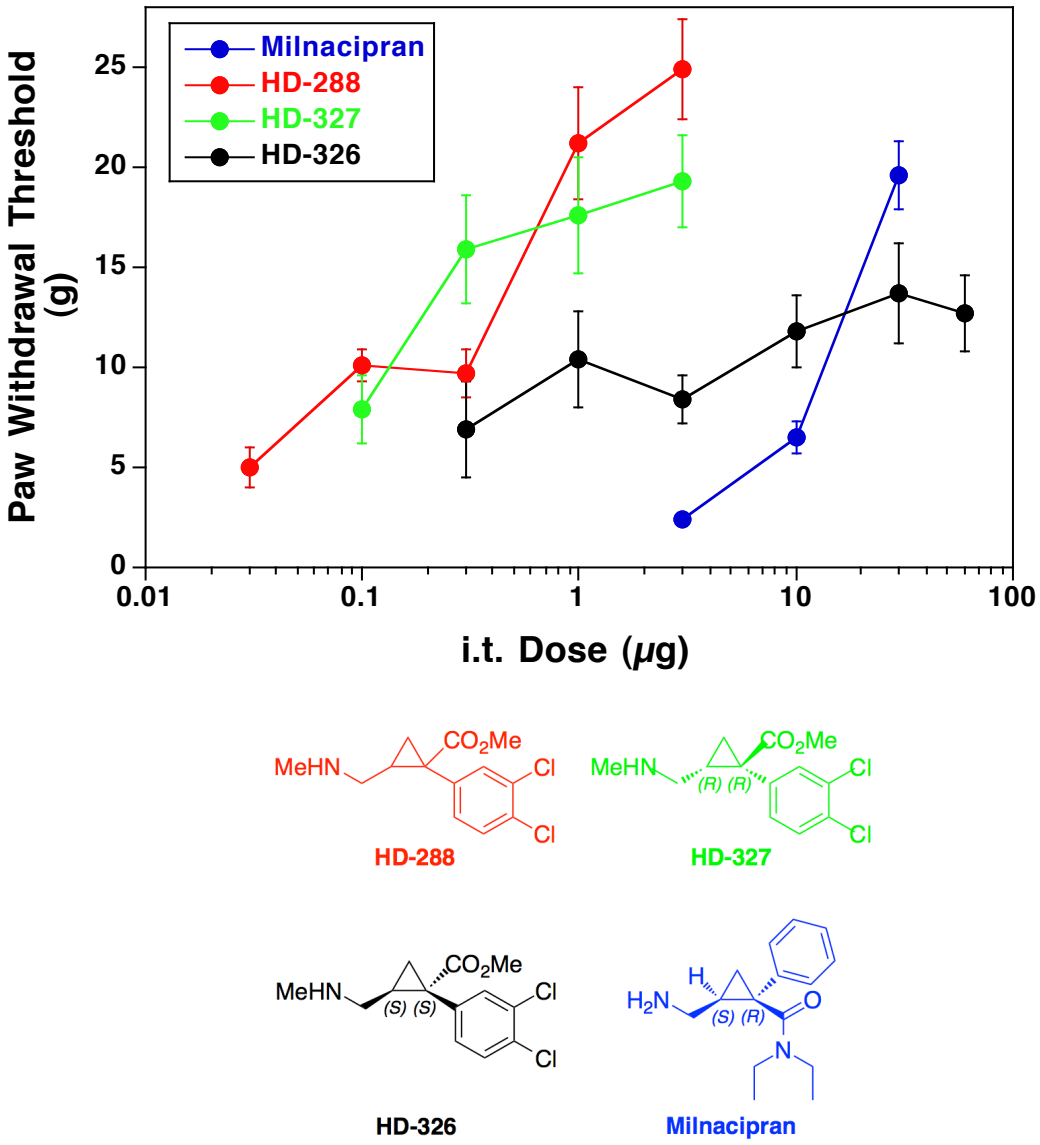


Figure 3.9: **Anti-allodynic effects of novel SNRI analogues in SNL rats.** (The drugs (µg, i.t.) were administered to SNL rats through an i.t. catheter in a volume of 5 µl, followed by 15 µl of saline to flush the catheter. Paw withdrawal threshold (Threshold)

was determined before (baseline, BSL) and 2 h following drug treatment using von Frey filaments and the up-down method with Dixon non-parametric statistics. N=8-10/group. *, significantly different from BSL, $p \leq 0.05$.)

(Determined in Jeff Martin's laboratory)

A large increase in potency of **HD-288** and **HD-327** compared to milnacipran was observed. More importantly, a significant potency (and perhaps efficacy) differences was also observed between the two isomers **HD-327** and **HD-326**, in consistent with the *in vitro* data. In summary, these results clearly showed the importance of studying bioactivity differences between enantiomers and enabling technology developed in the Davies' group gave access to these pharmacologically important compounds in asymmetric fashion.

The pharmacological effects of these novel compounds on wider range of neuropathic pain models are currently being studies in the Jeff Martin's lab.

3.3.9.2 Effects of novel SNRI analogues on sedation and/or motor coordination in the rotarod assay

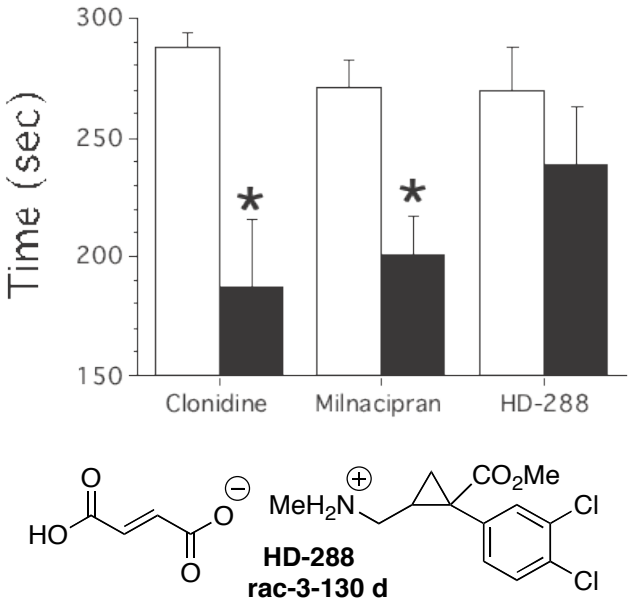


Figure 3.10: Effects of clonidine, milnacipran and **HD-288** on rotarod performance in SNL rats. Rats were trained to walk on a rotarod apparatus during 5 minute trials on two successive days. The rotarod was accelerated from 2 to 5 rpm over a 5 min period and the time until the rat fell from the rotarod was recorded. Each trial was a maximum of 5 min in duration. Shown are the mean ± SEM for time spent on the rotarod before (Baseline) or after (Treatment) drug administration (N=10-13 per group). *, significantly different from Baseline, $p \leq 0.05$. (Results from Jeff Martin Lab)

Rotarod performance was assessed to determine the relative potency of novel SNRI analogues as well as **clonidine** for producing sedation and/or motor impairment, two important dose-limiting side effects of these compounds. **Clonidine** (10 µg, i.t.)

decreased the time rats were able to stay on the rotarod by 35 ± 10% of baseline values [F(1,25)=12.3, p=0.002] (Figure 3.9). Administration of the maximum dose of **HD-288** (3 μg, i.t.) had no significant effect on rotarod performance [F(1,19)=1.02, p=0.3] (Figure 3.9). Sedation is a major dose-limiting side effect of **clonidine**. (Fig. 3.10) Rotarod performance assay is currently being performed using enantiopure compounds.

In summary, **HD-288** appears to produce greater anti-allodynic effects and less sedation than **clonidine** in the rat.

3.3.10 Computational modeling of SERT, NET and DAT

No X-ray crystal structures of human SERT, NET and DAT have been solved. The structural information for these transporter proteins and their interactions with the antipsychotic drugs is limited, but many molecular modeling studies have been reported for them.[114-119]

The primary aims of computational modeling of SERT, NET and DAT have been

1) To get structural understanding of how our novel cyclopropylamines interact with various transporter proteins.

2) To learn how two different enantiomers interact with a particular type of transporter such that one would be bioactive and the other won't.

3) To identify the molecular level differences among these transporter proteins that make our novel compounds selective to one transporter over others.

The information gained from this study can accelerate our future drug discovery efforts as it facilitates designing novel synthetic scaffolds targeting these trans-membrane proteins.

Recently, a number of molecular docking studies reported were based on the homology models built from $LeuT_{Aa}$. Sarkar *et al.* reported that the binding site in which tricyclic antidepressants binds reside in the outer vestibule of SERT.[120] The functional mechanism of DAT was also recently reported.[121]

At the initiation of this project, homology models of SERT, NET and DAT were obtained from Aina W. Ravna, Department of Pharmacology, Institute of Medical biology, Faculty of Medicine, University of Tromsø, Norway. Ravna *et al.* built the homology models of SERT, NET and DAT using the *Aquifex aeolicus* $LeuT_{Aa}$ crystal structure (PDB code: 2a65) as template.[122,123]

3.3.10.1 Structural information of SERT, NET and DAT

SERT, NET, and DAT are very large proteins with 14 trans-membrane (TM) helices. They all come under a large family of Na^+/Cl^- dependent membrane transporters. To understand the structural similarity and homology between SERT, NET, DAT and $LeuT_{Aa}$ receptor, the sequences of the $LeuT_{Aa}$, human SERT, NET, and DAT proteins were obtained from the Universal Protein Resource (http://www.uniprot.org) and aligned using ClustalW, a multiple sequence alignment tool (http://www.genome.jp/tools/clustalw/). The sequence alignments and % homologies are listed in Table 3.7. Considering the size of these trans-membrane proteins, >20%

similarity between $LeuT_{Aa}$ and neurotransmitter transporters is a marginal but acceptable value on which to build homology models. Ravna *et al.* were able to construct models based on this homology.

No	Protein	% Similarity	% Identity	% Homology	Total no. Of Residues	Gaps
1	**$LeuT_{Aa}$**	100	100	100	513	138
2	**SERT**	35	21	38	630	21
3	**NET**	39	25	44	617	34
4	**DAT**	36	22	42	620	31

Table 3.7: Homology between $LeuT_{Aa}$ with the three monoamine reuptake transporters.

Figure 3.11: Aligned secondary structures of SERT, NET and DAT homology models.

(SERT = Cyans; NET = Magentas; DAT = Yellow).

Secondary structure alignment of SERT, NET and DAT (Fig. 3.11) shows that they are structurally very similar with all trans-membrane helices overlapping except at some loop regions away from the possible active site. The ability of different classes of psychotic drugs showing various levels of selectivity for one transporter over the other can be explained if we could understand structural differences at the molecular level among these transporters. To achieve this goal, a detailed structural analysis of the active sites of all three transporters was performed. Ravna *et al.* found two putative binding sites. The castP (http://sts.bioengr.uic.edu/castp/) server was used to calculate the volume and area of these possible active sites of SERT, NET and DAT and the results are summarized in Table 3.8.

As can be seen from Table 3.8, area and volume of all three transporters are very similar indicating that variable residues in the active site most certainly play a significant role in bioactivity and selectivity.

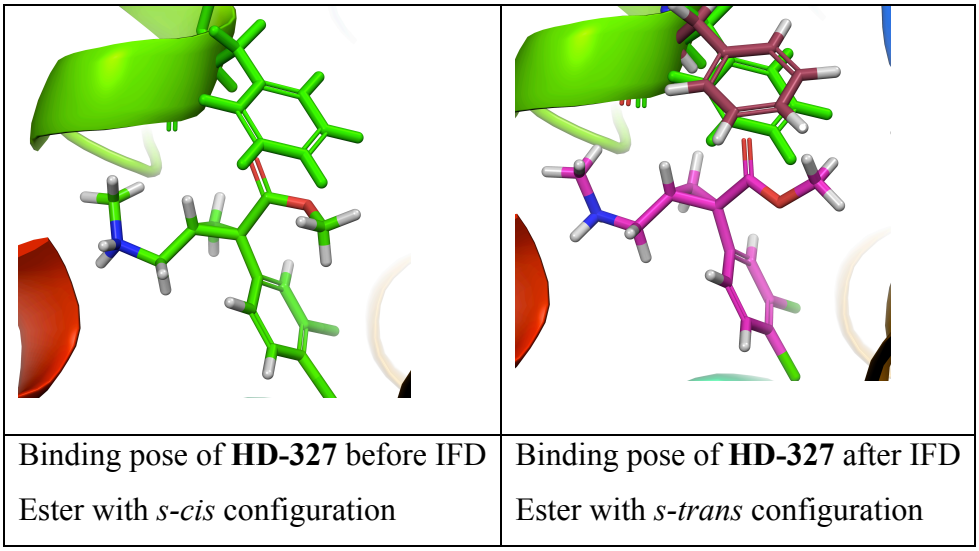
No	Protein	Pocket 1		Pocket 2	
		Area	Volume	Area	Volume
1	**SERT**	330.9	348.9	1325.8	1621.7
2	**NET**	325.4	360.9	1038.6	1631.8
3	**DAT**	324.1	365.7	1209.1	1577.6

Table 3.8: Volume and area of binding pocket 1 and binding pocket 2 in $Å^3$.

3.3.10.2 Initial XP docking of novel cyclopropylamines in pocket 1 of SERT, NET and DAT

All the previous docking studies and single point mutation studies suggest that small molecules such as cocaine bind in pocket 1, corresponding to a leucine binding site in $LeuT_{Aa}$, whereas tricyclic compounds such as clomipramine bind in pocket 2.

Molecular docking studies on milnacipran and all the novel aryl cyclopropylamines discovered in this project were performed with the homology models of SERT, NET and DAT obtained from Ravna *et al.,* which were built using a $LeuT_{Aa}$ crystal structure as a template. The binding pocket was localized on the basis of the docking studies performed on other classes of antipsychotic drugs. For example, molecular docking studies on paroxetine, fluoxetine and novel piperidine oxime derivatives were recently reported, in which docking studies were performed in pocket 1.[124]



Binding pose of **HD-327** before IFD Ester with *s-cis* configuration	Binding pose of **HD-327** after IFD Ester with *s-trans* configuration

Figure 3.12: Initial XP-docking of HD-327 in the SERT binding pocket 1.

Each aryl cyclopropylmethylamine structure was built *in silico* and energy minimized using Maromodel (Schrödinger suite). Conformational searches for each ligand were performed and the ten lowest energy conformers were used for docking. Coordinates of SERT, NET and DAT homology models were obtained from Ravna and prepared for docking using the protein preparation wizard tool integrated into the Maestro GUI. Docking studies were performed by keeping the transporter protein rigid and making the ligand flexible. This method not only searches for favorable interactions between ligand and transporter but also attempts to generate the lowest energy conformations for each input ligand. Glide Extra precision (XP) docking was performed to dock all the aryl cyclopropylamine analogues into the transporter active site using Glide and to provide the corresponding docking scores. Each binding pose was visually inspected to assure that the ligand was actually docked into the expected binding site and that interactions with the key residues in the binding site were maintained.

Initial docking experiments of our novel arylcyclopropylamines led to a conformation of **HD-327** in which the ester group on the cyclopropane was found to have energetically unfavorable *s-cis* configuration. When *s-trans* configured conformer (generated from Macromodel) was docked, the output conformation was found to have the *s-cis* configuration due to steric repulsions from Phe335 in SERT (Fig. 3.12). Similar repulsions were also found with Phe337, when **HD-327** was docked in NET (not shown).

Based on these preliminary results, it was decided that the all the transporter protein structures needed to be refined before performing docking studies. To refine the homology models, Induced Fit Docking (IFD) was employed, in which residues around

the active site were adjusted to accommodate the ligands in a low energy *s-trans* ester conformation. When **HD-327** was docked in the induced fit manner (IFD), it was found that the output conformation possesses an *s-trans* ester group. The spatial distance between hydrogen of the methyl group on ester and Phe335 before IFD was found to be 1.4 Å, where as it was found to be 2.2 Å after IF docking, just enough to allow ester group to attain its more stable *s-trans* configuration. These newly generated refined models of SERT, NET and DAT were used for further docking experiments.

3.3.10.3 XP docking of novel cyclopropylamines in the refined models of SERT, NET and DAT

Initially, our most potent aryl cyclopropylamine compounds **HD-327** and **HD-326** were docked in the induced fit homology models of SERT, NET and DAT. The residues potentially involved in ligand binding, the differences in the docking poses and molecular interactions with residues in the active site for both enantiomers were identified and listed in Table 3.9.

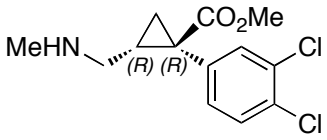
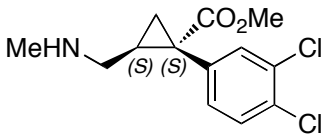
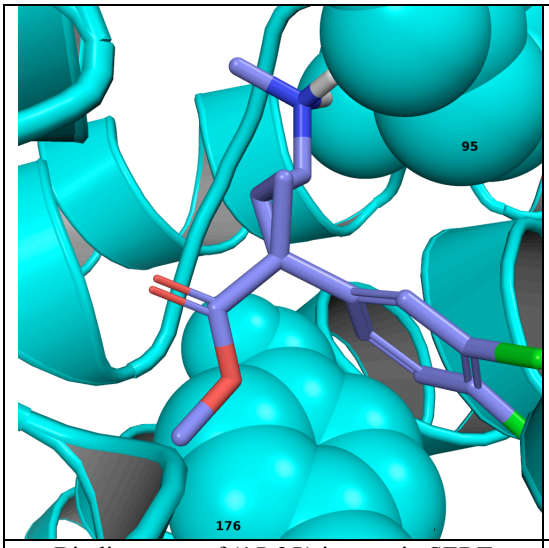
Ligand	SERT	NET	DAT
Bioactive(**HD327**) 	No pi-pi - Tyr176 **H- bond - Tyr95**	**Pi-pi – Phe72** **H- bond – Phe72** **H- bond – Asp75**	**Pi-pi – Phe76** H- bond – Asp79 Pi-pi – Tyr156 H- bond – Phe320
Bioinactive(**HD326**) 	**Pi-pi - Tyr176** No H- bond - Tyr95	No pi-pi – Phe72 No H- bond – Phe72 No H- bond – Asp75	No pi-pi – Phe76 H- bond – Asp79 Pi-pi – Tyr156 H- bond – Phe320

Table 3.9: Molecular interactions of **HD-327** and **HD-326** with residues in the binding pocket 1 of SERT, NET and DAT.

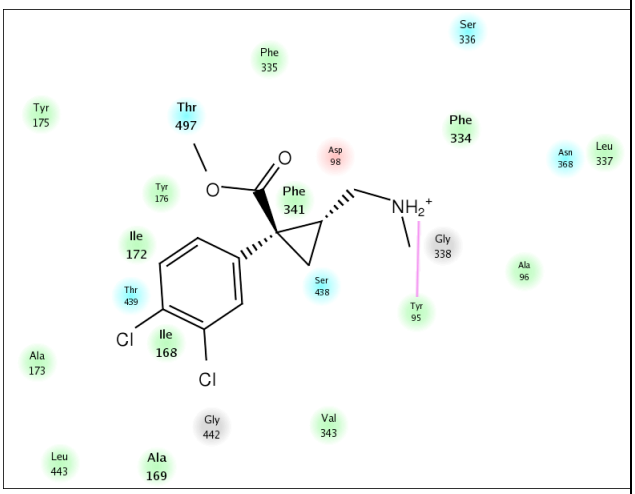
A) XP docking in SERT

When binding poses of active (**HD-327**) and inactive enantiomers (**HD-326**) are compared, it is found that aryl groups orient in the same subsite in both cases. But ester and amine groups are oriented in one direction, whereas they are oriented in a completely opposite direction in the inactive enantiomer. (Fig.3.13)

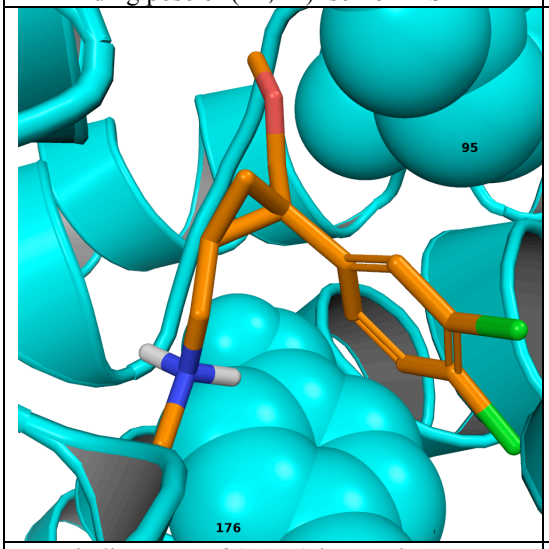
In the case of the active enantiomer with the (1*R*, 2*R*) configuration, the amine group orients itself in such a way that it would be able to make hydrogen bonding with Tyr95 residue. This key interaction was lacking in the inactive enantiomer with the (1*S*, 2*S*) configuration. All other residues around the ligands might be responsible for high binding affinity of these novel cyclopropanes to SERT, but the activity difference between opposite enantiomers likely arises from this key hydrogen bonding (Fig. 3.13).



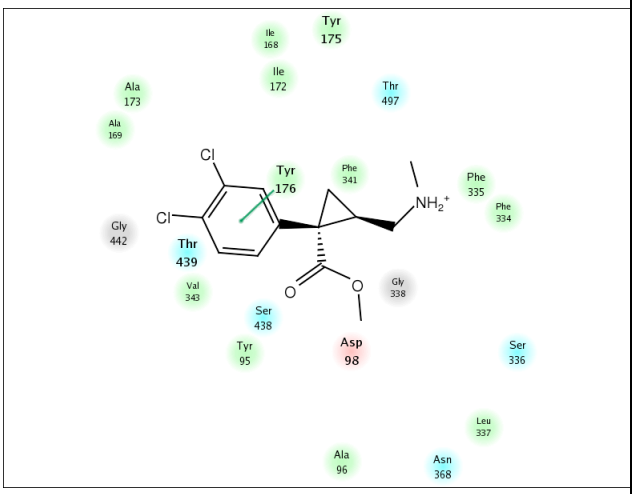
Binding pose of (1*R*,2*R*) isomer in SERT



Bioactive isomer (XP docking score -11.7 kcal)



Binding pose of (1*S*,2*S*) isomer in SERT

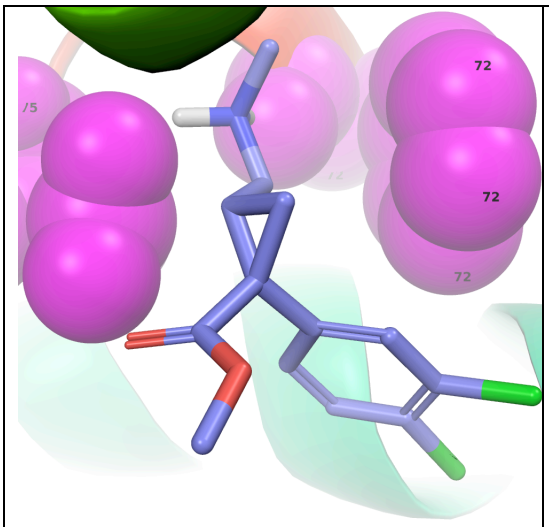


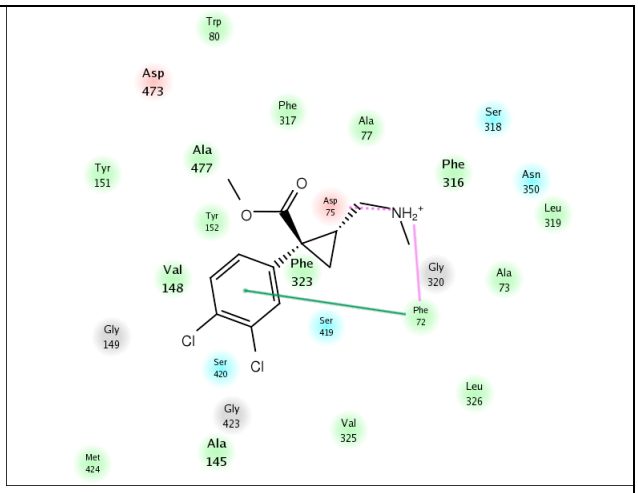
Bioinactive isomer (XP docking score -8.4 kcal)

Figure 3.13: Binding poses and molecular interactions of **HD-327** and **HD-326** in the SERT binding pocket. (XP docking scores in kcal/mol).

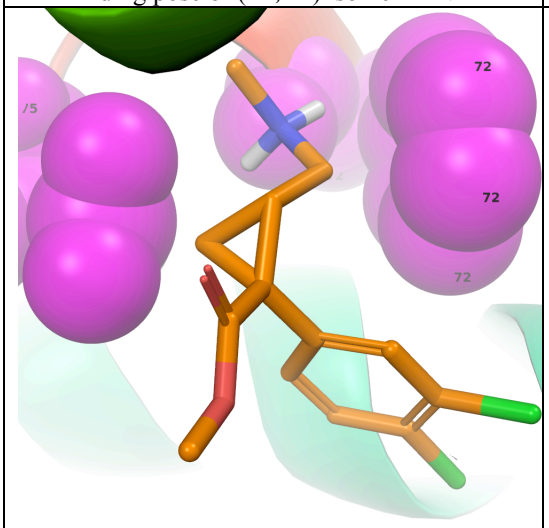
B) XP docking in NET

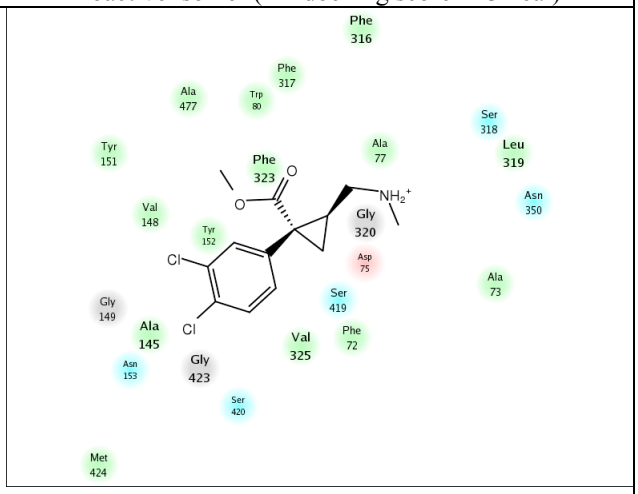
The reason for the activity differences between the bioactive and bio-inactive enantiomers was more evident from the docking poses of **HD-327** and **HD-326** in the active site of NET. When **HD-327** was docked, it appears that it makes two hydrogen-bonding interactions, one with the Phe72 residue and another with the Asp75 residue as well as one pi-pi stacking interaction with the Phe72 residue. All these interactions were lacking in the inactive enantiomer **(HD-326)**. In summary, the binding mode is very sensitive to the chirality of the cyclopropane ring, and this model has the capability of predicting the bioactive enantiomer. (Fig. 3.14)





Binding pose of (1*R*,2*R*) isomer in NET | Bioactive isomer (XP docking score -13 kcal)



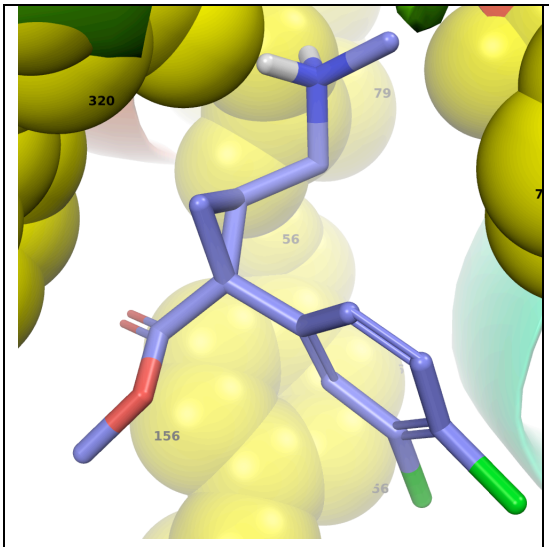


Binding pose of (1*S*,2*S*) isomer in NET | Bioinactive isomer (XP docking score -10.5 kcal)

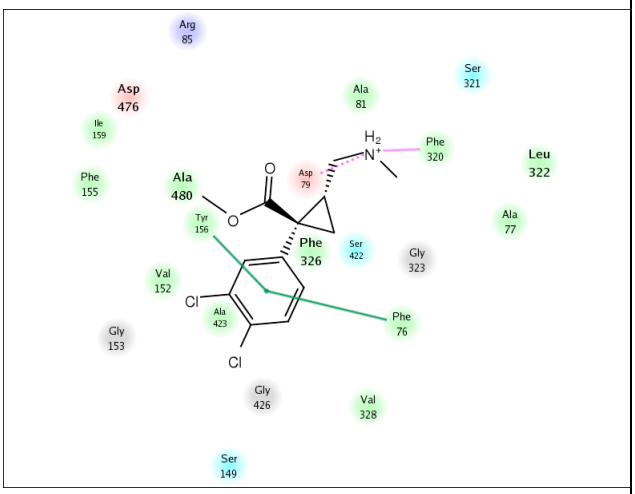
Figure 3.14: Binding poses and molecular interactions of **HD-327** and **HD-326** in the NET binding pocket. (XP docking scores in kcal/mol).

C) XP docking in DAT

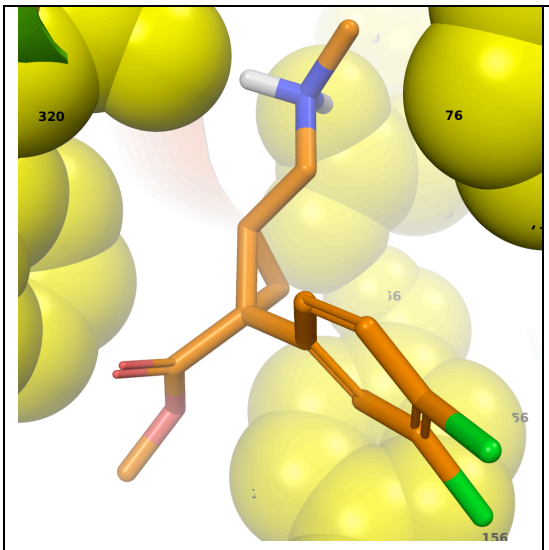
All novel cyclopropylamines are experimentally relatively inactive in binding to DAT. By contrast, in the docking exercises all cyclopropylamines bind tightly in the DAT binding pocket 1, which is inconsistent with the experimental *in vitro* data. Nevertheless, the binding poses of **HD-327** and **HD-326** in DAT show the existence of one pi-pi stacking interaction in the active enantiomer **HD-327** compared to its opposite inactive enantiomer **HD-326**. (Fig. 3.15)

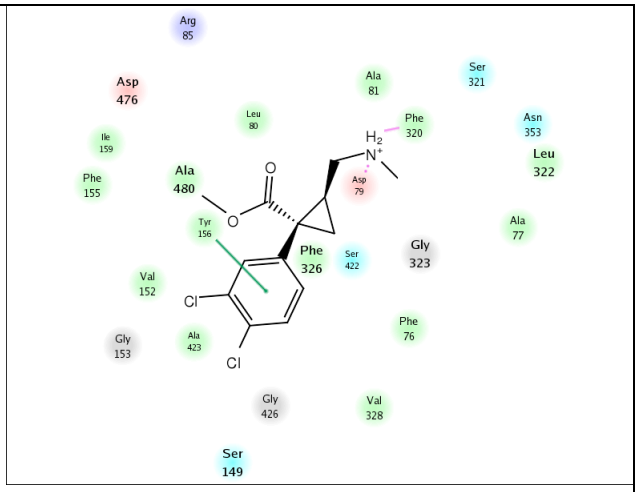


Binding pose of (1*R*,2*R*) isomer in DAT



Bioactive isomer (XP docking score -13.0 kcal)





Binding pose of (1*S*,2*S*) isomer in DAT	Bioinactive isomer (XP docking score -12.7 kcal)

Figure 3.15: Binding poses and molecular interactions of **HD-327** and **HD-326** in the DAT binding pocket. (XP docking score value in kcal/mol).

Inspired by the above finding, all aryl cyclopropylamines were docked in the refined models of SERT, NET and DAT and XP docking scores were determined. All the results are summarized in Table 3.10 (SERT), Table 3.11 (NET), and Table 3.12(DAT).

	Ar	Isomer	SERT K_i(nM ± SEM)	XP Docking Score Kcal/mol	Poses
0	Milnacipran	(*R*,*S*)	35.1 ± 4.4	-9.3	1
1	4-BrC_6H_4	(*S*,*S*)	630.7 ± 47.5	-10.1	3
2	4-BrC_6H_4	(*R*,*R*)	31.3 ± 1.97	-11.9	2
3	3,4-diClC_6H_3	(*S*,*S*)	26.6 ± 2.8	-8.2	2
4	3,4-diClC_6H_3	(*R*,*R*)	1.6 ± 0.2	-11.7	2
5	3,4-diBrC_6H_3	(*S*,*S*)	13.1 ± 1.8	-8.4	2
6	3,4-diBrC_6H_3	(*R*,*R*)	1.2 ± 0.04	-12.6	2
7	2-naphthyl	(*S*,*S*)	23.8 ± 3.0	-9.1	3
8	2-naphthyl	(*R*,*R*)	13.2 ± 2.4	-7.3	1
9	4-PhC_6H_4	(*S*,*S*)	52.9 ± 14	NA	NA
10	4-PhC_6H_4	(*R*,*R*)	1.9 ± 0.41	NA	NA

Table 3.10: XP docking scores for all arylcyclopropylamine compounds in the SERT binding pocket. (in kcal/mol) (NA=Not available).

	Ar	Isomer	NET K_i(nM ± SEM)	XP Docking Score Kcal/mol	Poses
0	Milnacipran	(*R*,*S*)	23.8 ± 1.7	-11.2	4
1	4-BrC_6H_4	(*S*,*S*)	29.9 ± 0.7	-10.0	4
2	4-BrC_6H_4	(*R*,*R*)	1.6 ± 0.05	-12.2	1
3	3,4-diClC_6H_3	(*S*,*S*)	5.3 ± 0.5	-10.5	1
4	3,4-diClC_6H_3	(*R*,*R*)	0.2 ± 0.01	-13.0	1
5	3,4-diBrC_6H_3	(*S*,*S*)	3.2 ± 0.4	-10.5	2
6	3,4-diBrC_6H_3	(*R*,*R*)	0.4 ± 0.08	-12.9	1
7	2-naphthyl	(*S*,*S*)	14.5 ± 0.4	-9.9	2
8	2-naphthyl	(*R*,*R*)	9.1 ± 0.7	-12.3	3
9	4-PhC_6H_4	(*S*,*S*)	>10,000	NA	NA
10	4-PhC_6H_4	(*R*,*R*)	57.4 ± 12.8	NA	NA

Table 3.11: XP docking scores for all arylcyclopropylamine compounds in the NET binding pocket. (in kcal/mol) (NA=Not available).

	Ar	Isomer	DAT K_i(nM ± SEM)	XP Docking Score Kcal/mol	Poses
0	Milnacipran	(*R*,*S*)	1970 ± 230	-11.1	2
1	4-BrC_6H_4	(*S*,*S*)	>9000	-12.3	3
2	4-BrC_6H_4	(*R*,*R*)	222 ± 52.8	-12.5	4
3	3,4-diClC_6H_3	(*S*,*S*)	197 ± 63.8	-12.8	4
4	3,4-diClC_6H_3	(*R*,*R*)	15.7 ± 2.4	-13.0	4
5	3,4-diBrC_6H_3	(*S*,*S*)	62.8 ± 6.7	-12.7	2
6	3,4-diBrC_6H_3	(*R*,*R*)	25.1 ± 3.2	-12.9	3
7	2-naphthyl	(*S*,*S*)	276 ± 48.1	-12.6	3
8	2-naphthyl	(*R*,*R*)	282 ± 45.3	-11.9	2
9	4-PhC_6H_4	(*S*,*S*)	608 ± 41.3	-9.9	2
10	4-PhC_6H_4	(*R*,*R*)	57.5 ± 24.9	-10.6	4

Table 3.12: XP docking scores for all arylcyclopropylamine compounds in the DAT binding pocket. (in kcal/mol)

From all the above data, it is quite evident that the active enantiomer with 1*R* 2*R* configuration in 12 out of 13 cases (92%) binds with a better docking score compared to its opposite inactive enantiomer with (1*S*, 2*S*) configuration in the homology models employed in the work. Even though this Induced fit model discriminates bioactive and bio inactive enatiomers, it does not explain the trends in bioactivity differences between various cyclopropane analogues. Moreover, all ligands show good docking scores in DAT too, which is inconsistent with experimentally determined IC_{50} values. In summary, the current model does not discriminate among the three different transporters very well. Docking studies in pocket 2 of SERT, NET and DAT transporter models as well as MMGBSA calculations for various analogues are currently being pursued in the Snyder laboratory.

In conclusion, these molecular docking studies allowed a rationalization of the molecular basis for the activity of novel enantiomeric pairs of cyclopropylamines in SERT, NET, and DAT, although the binding scores does not correlate quantitatively. More accurate models are required to acquire predictive ability with which novel ligands could be designed.

3.5 Conclusions

In summary, a novel class of cyclopropane based selective serotonin-norepinephrine reuptake inhibitors (SNRI's) was discovered as potential therapeutic agents for the treatment of neuropathic pain. Overall, ~ fifty novel compounds and twenty aryl cyclopropylamine compounds were synthesized. *In vitro* data for these novel compounds showed a wide diversity of potencies and specificities at monoamine

transporter sites. One of the lead compounds was found to be efficacious in reversing a symptom of neuropathic pain (mechanical allodynia) in nerve-injured rats and is quite potent compared to medications approved for clinical treatment of chronic pain. Extensive molecular docking studies in SERT, NET and DAT allowed us to rationalize the molecular basis for the relative activity of enantiomer pairs of novel cyclopropylamines.

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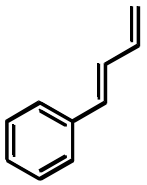
Experimental for SNRI project

^{1}H Nuclear Magnetic Resonance (NMR) spectra were typically recorded on a Varian spectrometer at either 300, 400, 500, or 600 MHz, and ^{13}C NMR at either 75, 100, or 125 MHz with the sample solvent being $CDCl_3$. The following abbreviations are used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. Coupling constants were taken directly from the spectra and are uncorrected. IR spectra were obtained using a Thermo Scientific Nicolet *i*S10 FT-IR and reported in units of cm^{-1}. Melting points were measured on an electrothermal melting point apparatus and are uncorrected. High Resolution Mass spectral (HRMS) determinations (pos-APCI) were performed by the Instrument Center of the Department of Chemistry, Emory University. Elemental analysis was performed at Atlantic Micro labs Inc., Norcross GA. Optical rotations were measured at the sodium D line (589 nm) and reported as follows: $[\alpha]_D^{25}$, concentration (c in g/100 mL) and solvent. All rotations are measured at 25.0 ^{o}C. Enantiomeric excess was determined by Varian Pro Star high performance liquid chromatography (HPLC) using chiral analytical columns (Chiralcel OD, Chiralcel OD-H, Chiralcel OJ, Chiralpak AD-H, Chiralpak AS-H, Chiralpack AD-RH, (*R,R*)-Whelk, or (*S,S*)- Whelk)(UV detection at 254 or 273 nm). Chiral columns and conditions are specified for individual compounds. Analytical TLC was performed on 0.25 mm E. Merck silica gel (60F-254) plates using UV light. Phosphomolybdic acid (PMA), $KMnO_4$, Ninhydrin or dinitrophenylhydrazine (DNP) was used as visualizing agent if necessary.

Glassware was dried in an oven overnight prior to use. Reactions were typically conducted under an atmosphere of argon. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Hexanes, toluene, THF, DCM, diethyl ether and acetonitrile were dried by passage through activated alumina columns in a solvent purification system prior to use. All other reagents were purchased from Aldrich, Alfa Aesar, or Acros chemical companies and used without additional purification unless noted. Rhodium catalysts $Rh_2(OAc)_4$, Rh_2(*S*-DOSP)$_4$, Rh_2(*R*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$, were obtained from lab sources and were used as is.

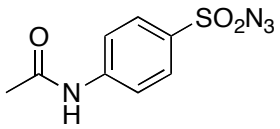
(*E*)-buta-1, 3-dienylbenzene (3-111)



Methyltriphenylphosphine bromide (178 g, 50 mmol) was added to a flame dried 1 L flask and THF (500 mL) was added. The reaction flask was cooled to 0 ^{o}C and potassium *ter*-butoxide (84 g, 75 mmol) was added. Reaction was then stirred for 5 h at 0 ^{o}C. (*E*)-3-Phenylacrylaldehyde (66 g, 50 mmol) in THF (100 mL) was added dropwise over 1 h, then stirred for 16 additional h. The reaction was poured into H_2O (1 L) and extracted into pentane (3 × 200). The combined organic layers were washed with brine, dried over $MgSO_4$. Hexane (100 mL) was added to the reaction flask. Triphenyl phosphine oxide precipitates out. The reaction mixture was filtered through celite/silica gel and the solvent was removed under reduced pressure. The crude material was purified

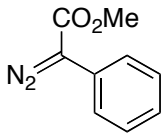
using Kughlerrohr distillation (85 °C) to obtain the titled product as a colorless oil in 87 % yield (56 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 5H), 6.78 (dd, J = 10.4 Hz, 1H), 6.54 (m, 2H), 5.34 (d, J = 16.8 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H). This reaction was performed six times in the same scale to obtain yields ranging from 67 to 87%. The ^{1}H NMR data was consistent with the published values.

***para*-Acetamidobenzenesulfonyl azide (*p*-ABSA) (reagent for the synthesis of 3-133 a)**



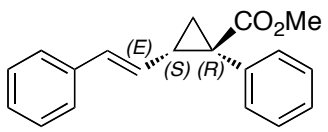
Prepared according to the general procedure of Davies. To a round-bottomed flask charged with a stir bar was added *para*-acetamidobenzenesulfonyl chloride (314 g, 1.34 mol) and acetone (500 mL). A solution of sodium azide (114 g, 1.75 mol) in water (300 mL) was added dropwise over 1 h at ambient temperature. The solution was then stirred overnight and poured into ice water (3 L) to induce precipitation. The solution was stored at 0 ^{o}C for 1 h and the solid collected by vacuum filtration. The solid was washed with several portions of water and then air-dried for several h. The solid was then dried under high vacuum over phosphorus pentoxide for 2 days to give pure *p*-ABSA as a white solid (306 g, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 7.59 (br m, 1H), 2.23 (s, 3H). The ^{1}H NMR data was consistent with the published values.

Methyl 2-diazo-2- phenyl acetate (3-133 a)



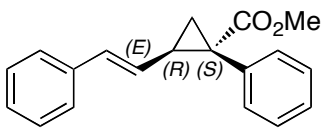
This was prepared according to a modified procedure provided in Baum et al., Synth. Commun. 1987, 17, 1709-16. Methyl phenyl acetate (15 g, 100 mmol) and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (25 g, 110 mmol) were dissolved in acetonitrile (500 mL) and cooled to 0 °C in an ice bath. 1,8-Diazabicycloundec-7-ene (DBU) (27 g, 180 mmol) was added in one portion and the reaction was stirred at 0 °C for 3 h, then 3 additional h at rt. The reaction was poured into a saturated NH_4Cl solution (100 mL) and extracted with diethyl ether (2 × 100). The combined ether layers were dried over $MgSO_4$, filtered and concentrated to obtain the crude product. The crude material was purified by column chromatography (SiO_2, 95:5 petroleum ether/diethyl ether) to obtain 17.9 g (98% yield) of the titled compound as a colored oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (m, 5H), 3.84 (s, 3H). The ^1H NMR data was consistent with the published values.

(1*R*, 2*S*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 a)



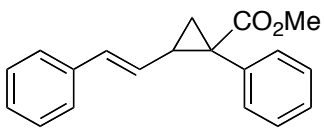
In a 100 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (5.2 g, 40 mmol, 2 eq.) and Rh_2(*S*-DOSP)$_4$ (120 mg, 0.25 % mol) were dissolved in dry, degassed toluene (100 mL) and cooled to -45 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-phenylacetate (3.5 g, 20 mmol, 1 eq.) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 5 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 a** as an oily liquid in 93% yield (5.2 g) > 94% de. HPLC analysis: 96% ee (SS-Whelk column, 1 % 2-PrOH in hexanes, 0.6 mL/min, 1mg/mL, t_R = 24.3 (minor) and 33.5 (major) min, UV 254 nm);) or (OD-H column, 0.7 % 2-PrOH in hexanes, 1 mL/min, 1mg/mL, t_R = 6.4 (major) and 7.6 (minor) min, UV 254 nm);R_f = 0.25 (4:1 Hexanes: EtOAc); $[\alpha]^D_{20}$: -181° (1 mg/mL, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (m, 5H), 7.12 (m, 2H), 7.05 (m, 3H), 6.52 (d, *J* = 15.5 Hz, 1H), 5.18 (dd, *J* = 15.5 Hz, 10.0 Hz, 1H), 3.52 (s, 3H), 2.66 (m, 1H), 2.02 (m, 1H), 1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7(C), 136.8 (C), 135.6 (C), 131.4 (CH), 131.0 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.0 (CH), 126.8 (CH), 125.6 (CH), 52.12 (CH_3), 35.47 (C), 31.65 (CH), 22.26 (CH_2); FTIR (neat): 1717, 1271, 1244, 1193, 1159, 960, 752, 694 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{19}H_{18}O_2Na_1]^+$ 301.1199; Found: 301.1194; Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52; Found: C, 81.51; H, 6.60.

(1*S*,2*R*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 a)



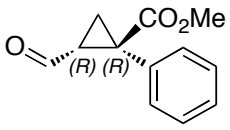
In a 100 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (5.2 g, 40 mmol, 2 eq.) and Rh_2(*R*-DOSP)$_4$ (120 mg, 0.25 % mol) were dissolved in dry, degassed toluene (100 mL) and cooled to -45 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-phenylacetate (3.5 g, 20 mmol, 1 eq.) was dissolved in dry, degassed toluene (100 mL) and added by syringe pump over 5 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 a** as an oily liquid in 90% yield (5.0 g), > 94% de. HPLC analysis: 96% ee (SS-Whelk column, 1 % 2-PrOH in hexanes, 0.6 mL/min, 1mg/mL, t_R = 24.3 (major) and 33.5 (minor) min, UV 254 nm);) or (OD-H column, 0.7 % 2-PrOH in hexanes, 1 mL/min, 1mg/mL, t_R = 6.4 (minor) and 7.6 (major) min, UV 254 nm);R_f = 0.25 (4:1 Hexanes: EtOAc); $[\alpha]^D_{20}$: 181° (1 mg/mL, MeOH); Spectroscopic data is same as **3-118 a**.

Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (rac-3-118 a)



The racemic compound was synthesized (20 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 2.6 g (93 %) of product. Spectroscopic data is same as **3-118 a**.

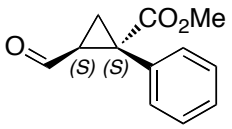
(1*R*, 2*R*)-Methyl 2-formyl-1-phenylcyclopropanecarboxylate (3-129 a)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate **(3-118 a)** (3.6 g, 13 mmol, 1 eq.) was dissolved in dichloromethane (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure and the residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 a** as a colorless oil in 69% yield (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, *J* = 6.4 Hz, 1H), 7.34-7.25 (m, 5H), 3.62 (s, 3H), 2.71 (dd, *J* = 8.5, 6.41 Hz, 1H), 2.10 (dd, *J* = 8.5, 4.88 Hz, 1H), 2.08-2.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 171.8, 133.5, 130.8, 128.4, 128.0, 52.8, 37.2, 36.1,

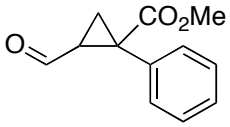
19.1; FT-IR (neat): 1706, 1249, 1155, 699 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{19}O_3$: 247.1328; Found: 247.1328.

(1*S*,2*S*)-Methyl 2-formyl-1-phenylcyclopropanecarboxylate (ent-3-129 a)



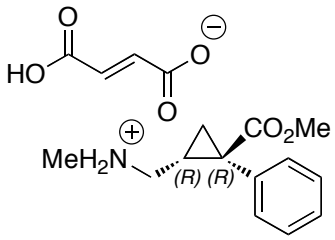
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (**ent-3-118 a)** (3.4 g, 11 mmol, 1 eq.) was dissolved in dichloromethane (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure and the residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 a** as a colorless oil in 61% yield (1.2 g). Spectroscopic data is same as **3-129 a**.

Methyl 2-formyl-1-phenylcyclopropanecarboxylate (rac-3-129 a)



The racemic aldehyde was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 526 mg (86 %) of product. Spectroscopic data is same as **3-129 a**.

1-((1*R*,2*R*)-2-(methoxycarbonyl)-2-phenylcyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (3-130 a)

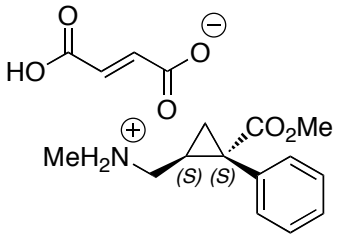


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*R*)-methyl 2-formyl-1-phenylcyclopropanecarboxylate **(3-129 a)** (612 mg, 3 mmol) was dissolved in methanol (50 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 3 mL, 6 mmol) and Ti(O-*i*Pr)$_4$ (2.4 mL, 6 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (170 mg, 4.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 63% yield (413 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.15 (m, 5H), 3.62 (s, 3H), 2.45 (dd, *J* = 12.3, 5.9 Hz, 1H), 2.32 (s, 3H), 2.14-2.02 (m, 1H), 2.00-1.90 (m, 1H), 1.74 (dd, *J* = 9.1, 4.27 Hz, 1H), 1.24 (dd, *J* = 6.4, 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 135.6, 130.8, 127.8, 127.0, 52.1, 36.1, 33.0, 27.7, 20.0; FT-IR (neat): 2949, 2843, 1715, 1434, 1251, 700 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{18}O_2N$: 220.1332; Found: 220.1330.

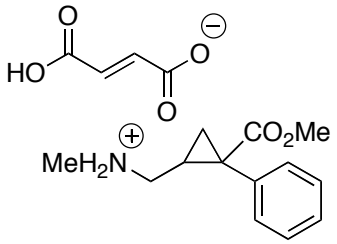
The free amine was dissolved in isopropanol (20 mL) and then treated with fumaric acid (249 mg, 2.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.38-7.26 (m, 5H), 6.67 (s, 2H), 3.58 (s, 3H), 3.23 (dd, *J* = 12.81, 3.97 Hz, 1H), 2.59 (s, 3H), 2.24-2.12 (m, 1H), 1.95 (dd, *J* = 12.51, 10.98 Hz, 1H), 1.78 (dd, *J* = 8.54, 4.88 Hz, 1H), 1.58-1.47 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 175.0, 171.5, 136.3, 135.8, 132.3, 129.7, 129.1, 53.3, 51.1, 34.8, 33.4, 33.4, 23.5, 21.0; FT-IR (neat): 3000, 1713, 1560, 1261, 1171, 702 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{18}O_2N$: 220.1332; Found: 220.1329; Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; Found: C, 60.86; H, 6.34.

1-((1*S*,2*S*)-2-(Methoxycarbonyl)-2-phenylcyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (ent-3-130 a)



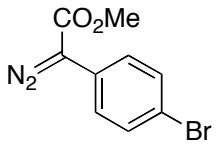
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*S*)-Methyl 2-formyl-1-phenylcyclopropanecarboxylate **(ent-3-129 a)** (612 mg, 3 mmol) was dissolved in methanol (50 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 3 mL, 6 mmol) and Ti(O-*i*Pr)$_4$ (2.4 mL, 6 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (170 mg, 4.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 61% yield (400 mg). The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (230 mg, 2 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. Spectroscopic data is same as **3-130 a**.

1-(2-(Methoxycarbonyl)-2-phenylcyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (rac-3-130 a)



The racemic amine was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 413 mg (63 %) of product. Spectroscopic data is same as **3-130 a**.

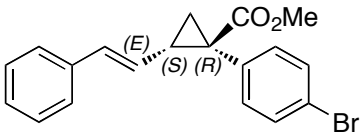
Methyl 2-(4-bromophenyl)-2-diazoacetate (3-133 b)



In a flame dried round bottom flask, 2-(4-bromophenyl) acetic acid (50 mmol, 1 eq.) was dissolved in MeOH (50 mL) and cooled to 0 ^{o}C. Acetyl chloride (60 mmol, 1.2 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(60 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (120 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (29 × 100); The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 11.16 g (93 % yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H). The ^{1}H NMR data was consistent with the published values.

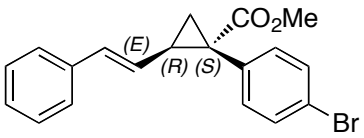
(1*R*, 2*S*)-Methyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate(3-118 b)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(4-bromophenyl)-2-diazoacetate (510 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 b** as an oily liquid in 88% yield (312 mg), > 94% de. The

same reaction was also performed at -40 °C in 2 mmol scale, 619 mg (86%) product was obtained. 94 % ee. HPLC analysis: 91% ee (SS-Whelk column, 1.5 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.2 (minor) and 22.4 (major) min, UV 254 nm); R_f = 0.31 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.27-7.03 (m, 7H), 6.55 (d, *J* = 15.7 Hz, 1H), 5.17 (dd, *J* = 15.8, 9.7 Hz, 1 H), 3.59 (s, 3H), 2.73-2.62 (m, 1H), 2.04 (dd, *J* = 8.8, 4.5 Hz, 1H), 1.40 (dd, *J* = 6.4, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 136.7, 134.8, 133.2, 131.6, 131.1, 128.3, 127.9, 127.1, 125.7, 121.3, 52.4, 34.9, 31.8, 22.4; FTIR (Neat): 1716, 1488, 1270, 1242, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{19}H_{18}O_2{}^{79}Br$: 357.0484. Found 357.0483; HRMS (neg-APCI) calcd for $C_{19}H_{16}O_2{}^{79}Br$: 355.0339; Found 355.0339.

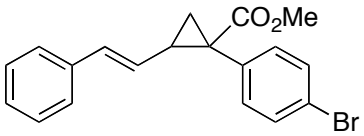
(1*S*, 2*R*)-Methyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate(ent-3-118 b)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(4-bromophenyl)-2-diazoacetate (510 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced

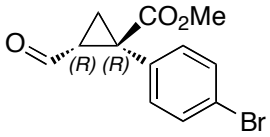
pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 b** as an oily liquid in 94% yield (337 mg)), > 94% de. The same reaction was also performed at -40 °C in 2 mmol scale, 626 mg (89%) product was obtained. 91 % ee. HPLC analysis: 91% ee (SS-Whelk column, 1.5 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.2 (major) and 22.4 (minor) min, UV 254 nm); R_f = 0.31 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **3-118 b**.

Methyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate(rac-3-118 b)



The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain1.0 g (94 %) of product. Spectroscopic data is same as **3-118 b**.

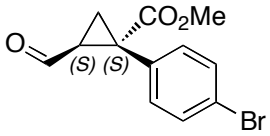
(1*R*,2*R*)-Methyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate (3-129 b)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-methyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (**3-118 b)** (535 mg, 1.5 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the

solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 b** as a colorless oil in 74% yield (314 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 6.1 Hz, 1 H), 7.52 - 7.42 (m, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 3H), 2.77 (dt, *J* = 8.5, 6.25 Hz, 1H), 2.12 (dd, *J* = 8.7, 5.03 Hz, 1H), 2.08-2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 171.1, 133.3, 132.4, 131.4, 129.8, 128.1, 121.9, 52.8, 36.7, 35.9,19.0; FTIR (Neat): 1707, 1450, 1250, 1157,713 cm^{-1}; HRMS (pos-API) calcd for $C_{21}H_{10}O_4Br$: 296.9767; Found 296.9767.

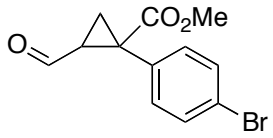
(1*S*,2*S*)-Methyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate (ent-3-129 b)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-methyl 1-(4-bromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (**ent-3-118 b)** (535 mg, 1.5 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column

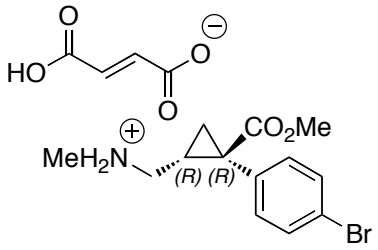
chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 b** as a colorless oil in 79% yield (334 mg). Spectroscopic data is same as **3-129 b**.

Methyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate (rac-3-129 b)



The racemic aldehyde was synthesized (1.5 mmol scale) in the same reaction conditions as described above, to obtain 401 mg (93 %) of product. Spectroscopic data is same as **3-129 b**.

1-((1*R*,2*R*)-2-(4-Bromophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (3-130 b)



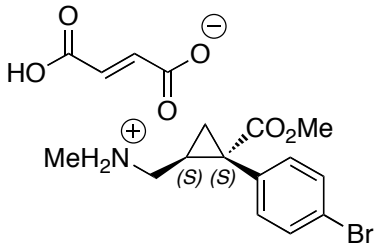
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate (**3-129 b)** (283 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1

mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 64% yield (190 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 2.42 (dd, *J* = 12.2, 5.8 Hz, 1H) 3.60 (s, 3H), 2.32 (s, 3H), 2.12-2.01 (m, 1H), 1.92-2.00 (m, 1H), 1.75 (dd, *J* = 8.8, 4.2 Hz, 1H), 1.24 (br. s., 1H), 1.19 (dd, *J* = 6.5, 4.42 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 134.7, 132.5, 131.0, 121.1, 52.2, 52.0, 36.2, 32.5, 27.7, 20.1; FTIR (Neat): 1707, 1474, 1247, 1159, 726 cm^{-1}; HRMS (Pos-APCI) calcd for $C_{12}H_9O_3Cl_2$: 270.9934; Found 270.9933; Anal. Calcd. for $C_{17}H_{20}BrNO_6$: C, 49.29; H, 4.87; N, 3.38; Found: C, 47.58; H, 4.76; N, 3.35.

The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (70 mg, 0.6 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.68 (s, 2H), 3.63 (s, 3H), 3.27 (dd, *J* = 12.6, 3.81 Hz, 1H), 2.63 (s, 3H), 2.26-2.13 (m, 1H), 1.99 (dd, *J* = 12.5, 10.9 Hz, 1H), 1.82 (dd, *J* = 8.39, 4.73 Hz, 1H), 1.55 - 1.47 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.5, 171.5, 136.3, 135.1, 134.3, 132.8, 123.1, 53.4, 51.1, 34.3, 33.6, 23.6, 21.1; FT-IR

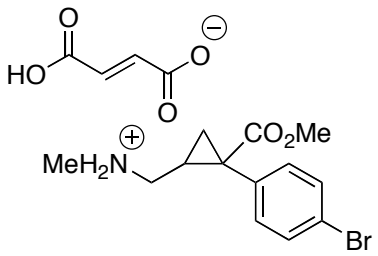
(neat): 3027, 2954, 2768, 1720, 1262 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{17}O_2N$: 298.0437; Found: 298.0436.

1-((1*S*,2*S*)-2-(4-Bromophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (ent-3-130 b)



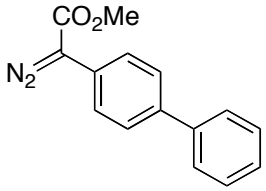
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 1-(4-bromophenyl)-2-formylcyclopropanecarboxylate (**ent-3-129 b)** (283 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 66% yield (195 mg). Spectroscopic data is same as **3-130 b**.

1-(2-(4-Bromophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (rac-3-130 b)



The racemic amine was synthesized (1 mmol scale) using the same reaction conditions as described above, to obtain 166 mg (56 %) of product. Spectroscopic data is same as **3-130 b**.

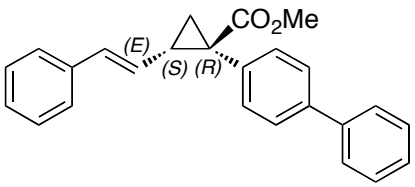
Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (3-133 c)



In a flame dried round bottom flask, 2-([1,1'-biphenyl]-4-yl) acetic acid (50 mmol, 1 eq.) was dissolved in MeOH (50 mL) and cooled to 0 ^{o}C. Acetyl chloride (60 mmol, 1.2 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(60 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (120 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 9.6 g (80 % yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 - 7.66 (m, 6H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.33 - 7.39 (m, 1H), 3.90 (s, 3H). The ^{1}H NMR data was consistent with the published values.

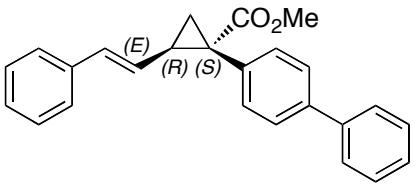
(1*R*, 2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 c)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (390 mg, 3 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (14 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (252 mg, 1 mmol) was dissolved in dry, degassed toluene (10 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced

pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 c** as an oily liquid in 93% yield (329 mg), >94% de. HPLC analysis: 78% ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.8 (major) and 12.4 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 3H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 3H), 6.60 (d, *J* = 15.8 Hz, 1H), 5.26 (dd, *J* = 15.8, 9.76 Hz, 1H), 3.67 (s, 3H), 2.76-2.66 (m, 1H), 2.09 (dd, *J* = 8.8, 4.5 Hz, 1H), 1.51 (dd, *J* = 6.2, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 140.7, 140.0, 137.1, 134.9, 132.0, 131.3, 128.8, 128.7, 128.4, 127.2, 127.1, 127.0, 126.7, 125.9, 52.6, 35.4, 32.1, 22.6; FTIR (Neat): 1716, 1487, 1270, 1243, 753 cm^{-1}; HRMS (pos-APCI) calcd for $C_{25}H_{23}O_2$: 355.1692; Found 355.1690.

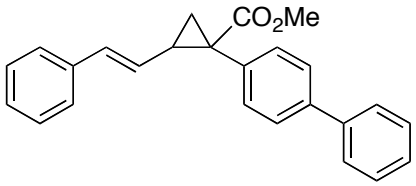
(1*S*,2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-((*E*)-styryl)cyclopropanecarboxylate(ent-3-118 c)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (390 mg, 3 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (14 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (252 mg, 1 mmol) was dissolved in dry, degassed toluene (10 mL) and added by syringe pump over 2 h. The reaction was stirred

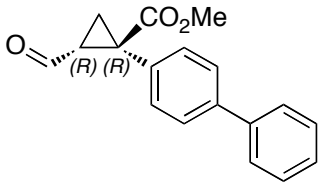
overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 c** as an oily liquid in 99% yield (350 mg) , >94% de. HPLC analysis: 86% ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.8 (minor) and 12.4 (major) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); $[\alpha]^D_{20}$: **XX**° (**XX** mg/mL, MeOH);). Spectroscopic data is same as **3-118 c**.

Methyl 1-([1,1'-biphenyl]-4-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (rac-3-118 c)



The racemic compound was synthesized (25 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 1.96 g (85 %) of product. Spectroscopic data is same as **3-118 c**.

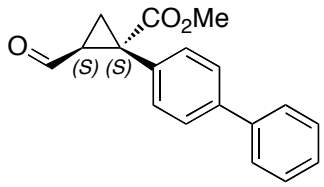
(1*R*,2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-formylcyclopropanecarboxylate (3-129 c)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (**3-118 c)** (531 mg, 1.5

mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 c** as colorless oil in 69% yield (289 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 6.4 Hz, 1H), 7.54 (dd, *J* = 7.3, 6.10 Hz, 4H), 7.45-7.28 (m, 5H), 2.82-2.70 (m, 1H) 3.61 (s, 3H), 2.19-2.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 171.7, 140.7, 140.0, 133.3, 132.4, 131.1, 129.8, 128.5, 128.2, 127.3, 127.0, 126.8, 52.7, 36.9, 36.1, 19.1; FTIR (Neat): 1707, 1487, 1249, 1155, 763 cm^{-1}; HRMS (Pos-API) calcd for $C_{18}H_{15}O_3$: 279.10267; Found 279.1025.

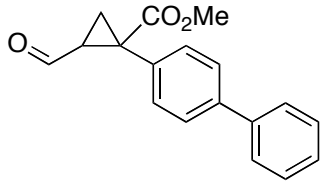
(1*S*,2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-formylcyclopropanecarboxylate (ent-3-129 c)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (**ent-3-118 c)** (531 mg, 1.5 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The

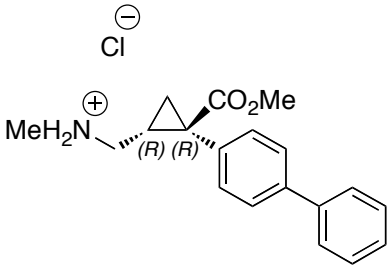
solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 c** as a colorless oil in 72% yield (301 mg). Spectroscopic data is same as **3-129 c**.

Methyl 1-([1,1'-biphenyl]-4-yl)-2-formylcyclopropanecarboxylate (rac-3-129 c)



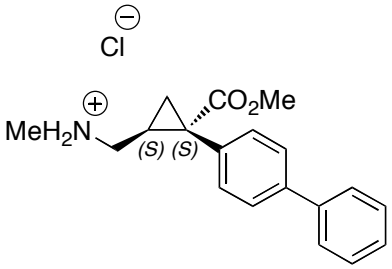
The racemic aldehyde was synthesized (1.5 mmol scale) in the same reaction conditions as described above, to obtain 348 mg (83 %) of product. Spectroscopic data is same as **3-129 c**.

1-((1*R*,2*R*)-2-([1,1'-biphenyl]-4-yl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium chloride (3-130 c)



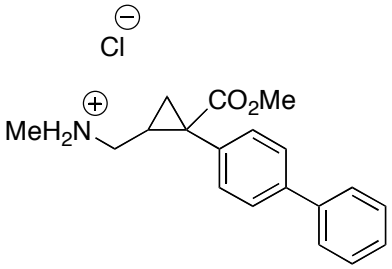
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*R*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-formylcyclopropanecarboxylate (**3-129 c)** (280 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 72% yield (214 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 16.7, 7.63 Hz, 4H), 7.45-7.38 (m, 2H), 7.37-7.29 (m, 3H), 3.60 (s, 3H), 2.48 (dd, *J* = 12.2, 5.80 Hz, 1H), 2.31 (s, 3H), 2.13-2.05 (m, 1H), 2.04-1.95 (m, 1H), 1.76 (dd, *J* = 8.7, 4.4 Hz, 1H), 1.65 (br. s., 1H), 1.27 (dd, *J* = 6.4, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 140.4, 139.8, 134.5, 131.2, 128.5, 127.0, 126.8, 126.6, 52.2, 52.0, 36.1, 32.7, 27.7, 20.1; FT-IR (neat): 1716, 1487, 1434, 1250, 1010, 763 cm^{-1}; HRMS (pos-APCI) calcd for $C_{19}H_{22}O_2N_1$: 296.1645; Found: 296.1642.

1-((1*S*,2*S*)-2-([1,1'-biphenyl]-4-yl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium chloride (ent-3-130 c)



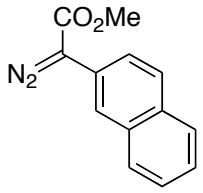
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-formylcyclopropanecarboxylate (**ent-3-129 c)** (280 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 76% yield (226 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. Spectroscopic data is same as **3-130 c**.

1-(2-([1,1'-biphenyl]-4-yl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium chloride (rac-3-130 c)



The racemic amine was synthesized (5.5 mmol scale) in the same reaction conditions as described above, to obtain 1.1 g (68 %) of product. Spectroscopic data is same as **3-130 c**.

Methyl 2-diazo-2- (naphthalene-2-yl) acetate (3-133 e)

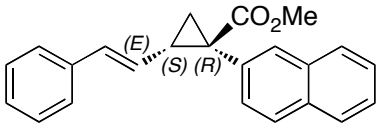


In a flame dried round bottom flask, 2-(naphthalen-2-yl)acetic acid (5.00 g, 24.8 mmol) was dissolved in MeOH (50 mL) and cooled to 0 ^{o}C. Acetyl chloride (3.68 g, 46.8 mmol) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.80 (m, 3H), 7.72 (s, 1H), 7.44 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 1H), 3.75 (m, 2H), 3.70 (s, 3H).

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (7.49 g, 31.2 mmol) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (7.51 mL, 49.9 mmol) was added dropwise at 0 ^oC. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 4.59 g (80% yield) of yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1 H), 7.86 (d, *J* = 8.6 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 7.54 (dd, *J* = 8.8, 1.7 Hz, 1 H), 7.42 - 7.51 (m, 2 H), 3.92 (s, 3 H). The ^1H NMR data was consistent with the published values.

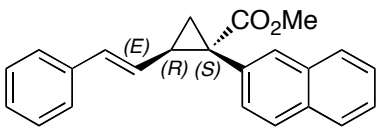
(1*R*,2*S*)-Methyl 1-(naphthalen-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 e)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (452 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred

overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 e** as an oily liquid in 91 % yield (601 mg), >94% de. HPLC analysis: did not separate on any chiral HPLC column at ester stage. Ester was reduced with LAH to get alcohol, which separated on HPLC column 85 % ee (alcohol) (OD-H column, 10 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.3 (minor) and 12.7 (major) min, UV 254 nm); R_f = 0.32 (4:1 Hexanes: EtOAc); The same reaction was also performed at -40 °C in 15 mmol scale, 4.7 g (95%) product was obtained. 86 % ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.81 (m, 4H), 7.42 (dt, *J* = 6.4, 3.2 Hz, 3H), 7.01-7.14 (m, 5H), 6.60 (d, *J* = 15.5 Hz, 1H), 5.20 (dd, *J* = 15.8, 9.7 Hz, 1H), 3.58 (s, 3H), 2.75 (td, *J* = 9.3, 6.7 Hz, 1H), 2.12 (dd, *J* = 9.0, 4.4 Hz, 1H), 1.59 (dd, *J* = 6.4, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 136.9, 133.5, 133.0, 132.5, 131.3, 129.9, 129.9, 128.5, 128.3, 127.7, 127.5, 127.4, 126.9, 125.9, 125.7, 52.4, 35.7, 32.1, 22.6; FT-IR (neat): 1715, 1434, 1270, 1244, 906, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{23}H_{21}O_2$: 329.1536; Found: 329.1534.

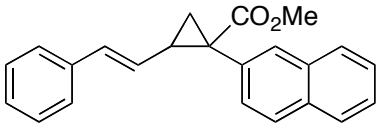
(1*S*,2*R*)-Methyl 1-(naphthalen-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 e)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were

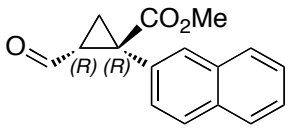
dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(naphthalen-2-yl)acetate (452 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 e** as an oily liquid in 93 % yield (620 mg), > 94% de. HPLC analysis: did not separate on any chiral HPLC column at ester stage. Ester was reduced with LAH to get alcohol, which separated on HPLC column 86 % ee (alcohol) (OD-H column, 10 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.3 (major) and 12.7 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); The same reaction was also performed at -40 °C in 15 mmol scale, 4.79 g (97%) product was obtained. 85 % ee. Spectroscopic data is same as **3-118 e**.

Methyl 1-(naphthalen-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (rac-3-118 e)



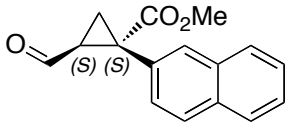
The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 887 mg (90 %) of product. Spectroscopic data is same as **3-118 e**.

(1*R*,2*R*)-Methyl 2-formyl-1-(naphthalen-2-yl)cyclopropanecarboxylate (3-129 e)



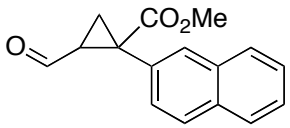
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-Methyl 1-(naphthalen-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylate (**3-118 e)** (328 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{0}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 e** as a colorless oil in 81% yield (205 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 6.7 Hz, 1H), 7.81 (d, *J* = 8.24 Hz, 4H), 7.55-7.45 (m, 2H), 7.40 (dd, *J* = 8.7, 1.07 Hz, 1H), 3.64 (s, 3H), 2.81 (q, *J* = 7.2 Hz, 1H), 2.21 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 170.9, 141.2, 141.0, 139.3, 134.9, 133.8, 132.7, 132.4, 132.3, 130.3, 130.2, 53.0, 36.6, 36.0, 19.2; FT-IR (neat): 1706, 1435, 1252, 1153, 733 cm^{-1}; HRMS (pos-APCI) calcd for $C_{16}H_{13}O_3$: 253.0870; Found: 253.0869.

(1*S*,2*S*)-Methyl 2-formyl-1-(naphthalen-2-yl)cyclopropanecarboxylate (ent-3-129 e)



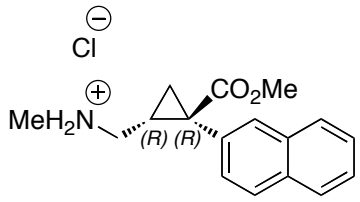
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-(naphthalen-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylate **(ent-3-118 e)** (328 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 e** as a colorless oil in 79% yield (200 mg). Spectroscopic data is same as **3-129 e**.

Methyl 2-formyl-1-(naphthalen-2-yl) cyclopropanecarboxylate (rac-3-129 e)



The racemic aldehyde was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 403 mg (53%) of product. Spectroscopic data is same as **rac-3-129 e**.

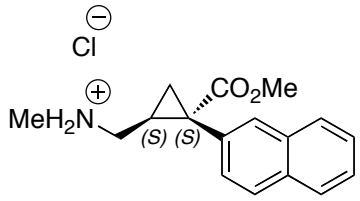
1-((1*R*,2*R*)-2-(Methoxycarbonyl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium chloride(3-130 e)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 2-formyl-1-(naphthalen-2-yl)cyclopropanecarboxylate **(3-129 e)** (254 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 65% yield (176 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in

diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.5 Hz, 3H), 7.72 (s, 1H), 7.49-7.41 (m, 3H), 3.60 (s, 3H), 2.46 (dd, *J* = 12.5, 6.10 Hz, 1H), 2.20-2.08 (m, 1H) 2.27 (s, 3H), 2.05-1.90 (m, 1H), 1.81 (dd, *J* = 8.8, 4.2 Hz, 1H), 1.37 (dd, *J* = 6.5, 4.4 Hz, 1H), 1.28 (br. s., 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 133.3, 133.0, 132.4, 129.3, 129.1, 127.6, 127.4, 127.3, 125.9, 125.8, 52.2, 52.0, 36.2, 33.2, 28.0, 20.2; FT-IR (neat): 1715, 1433, 1255, 1165, 749 cm^{-1}; HRMS (pos-APCI) calcd for $C_{17}H_{20}O_2N$: 270.1488; Found: 270.1488.

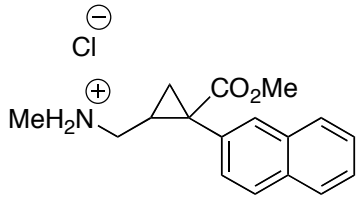
1-((1*S*,2*S*)-2-(methoxycarbonyl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium chloride(ent-3-130 e)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 2-formyl-1-(naphthalen-2-yl)cyclopropanecarboxylate **(ent-3-129 e)** (254 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and

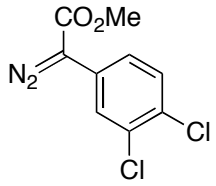
dried over $MgSO_4$. The organic phase was then filtered and concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 70% yield (189 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. Spectroscopic data is same as **3-130 e**.

1-(2-(Methoxycarbonyl)-2-(naphthalen-2-yl)cyclopropyl)-*N*-methylmethanaminium chloride (rac-3-130 e)



The racemic amine was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 549 mg (60 %) of product. Spectroscopic data is same as **3-130 e**.

Methyl 2-diazo-2- (3,4-dichlorophenyl) acetate (3-133 d)

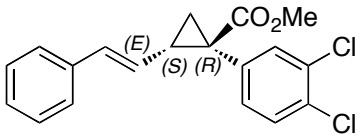


In a flame dried round bottom flask, 3,4-dichlorophenylacetic acid (5.50 g, 26.8 mmol) was dissolved in MeOH (50 mL) and cooled to 0 ^{o}C. Acetyl chloride (4.21 g, 53.7 mmol) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.61 (m, 2H).

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (7.03 g, 30.4 mmol)was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (7.40 mL, 48.7 mmol) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 4.96 g (83% yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 1.9 Hz, 1H),

7.43 (d, *J* = 8.6 Hz, 1H), 7.29 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.88 (s, 3H). The ^{1}H NMR data was consistent with the published values.

(1*R*, 2*S*)-Methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 d)

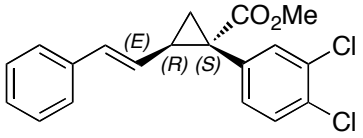


In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (490 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 d** as an oily liquid in 96 % yield (666 mg), >94 % de. The same reaction was also performed at -40 °C in 1 mmol scale, 288 mg (82% yield) (90 % ee) product was obtained. HPLC analysis: 89 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.3 (major) and 10.9 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 1.8 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H) , 7.26-7.20 (m, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.15-7.10 (m, 3H), 6.59 (d, *J* = 15.8 Hz, 1H), 5.18 (dd, *J* = 15.7, 9.6 Hz, 1H), 3.64 (s, 3H), 2.68 (td, *J* = 9.2, 6.8 Hz, 1H), 2.06 (dd, *J* = 9.0, 4.7 Hz, 1H), 1.42 (dd, *J* = 6.5, 4.73 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 136.7, 136.1, 133.3, 132.2, 132.0, 131.5, 131.2, 129.9, 128.4,

127.5, 127.3, 125.9, 52.6, 34.7, 32.0, 22.5; FT-IR (neat): 1717, 1473, 1272, 1241, 956, 753, 727 cm^{-1}; HRMS (pos-APCI) calcd for $C_{19}H_{15}O_2{}^{35}Cl_2$: 345.0454; Found: 345.0454.

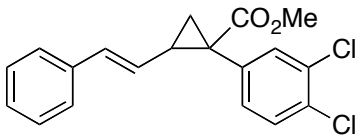
The same reaction was also performed at -40 °C in 100 mmol scale, 32.9 g (95% yield) (90% ee) of product was obtained. (Large scale synthesis of lead compound for *in vitro* analysis)

(1*S*,2*R*)-methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 d)



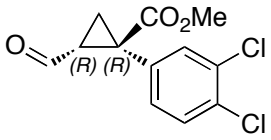
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (490 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 d** as an oily liquid in 90 % yield (623 mg), >94 % de. The same reaction was also performed at -40 °C in 1 mmol scale, 264 mg (76%) (90 % ee) product was obtained. HPLC analysis: 87 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.3 (minor) and 10.9 (major) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-118 d**.

Methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (rac-3-118 d)



The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 988 mg (95 %) of product. Spectroscopic data is same as **3-118 d**.

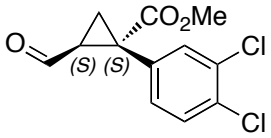
(1*R*,2*R*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (3-129 d)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate **(3-118 d)** (346 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 d** as a colorless oil in 81% yield (221 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 5.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.14 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.67 (s, 3H), 2.80 (dt, *J* = 8.4,

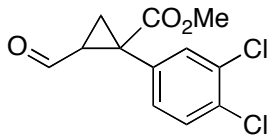
6.14 Hz, 1H), 2.13 (dd, J = 8.7, 5.0 Hz, 1H), 2.08-2.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 170.9, 133.8, 132.7, 132.4, 132.3, 130.3, 130.3, 53.0, 36.6, 36.0, 19.2; FT-IR (neat): 1707, 1474, 1247, 1159, 726 cm^{-1}; HRMS (pos-APCI) calcd for $C_{12}H_9O_3Cl_2$: 270.9934; Found: 270.9933. The same reaction was also performed in 30 mmol scale, 6.9 g (88% yield) of product was obtained. (Large scale synthesis of lead compound for *in vitro* analysis)

(1*S*,2*S*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (ent-3-129 d)



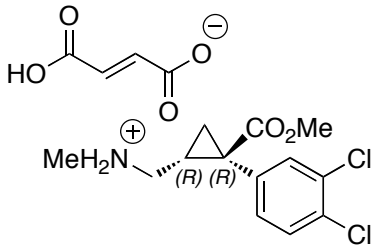
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-methyl 1-(3,4-dichlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate **(ent-3-118 d)** (346 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 °C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 d** as a colorless oil in 84% yield (229 mg). Spectroscopic data is same as **ent-3-129 d**.

(1*S*,2*S*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (rac-3-129 d)



The racemic aldehyde was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 778 mg (95 %) of product. Spectroscopic data is same as **3-129 d**.

1-((1*R*,2*R*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (3-130 d)



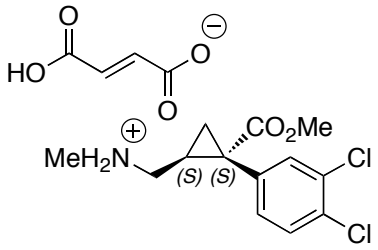
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (**3-129 d)** (273 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and

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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 59% yield (169 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.38 (m, 2H), 7.26 (s, 1H), 7.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.63 (s, 3H), 2.43 (dd, *J* = 11.7, 5.34 Hz, 1H), 2.35 (s, 3H), 2.13-1.94 (m, 2H), 1.77 (dd, *J* = 8.7, 4.4 Hz, 1H), 1.18 (dd, *J* = 6.4, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 136.1, 132.8, 131.9, 131.3, 130.5, 129.9, 52.4, 52.0, 36.3, 32.4, 28.0, 20.3; FT-IR (neat): 2950, 2843, 1718, 1474, 1247 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{16}O_2NCl_2$: 288.0552; Found: 288.0551.

The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (130 mg, 1.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.54-7.48 (m, 2H), 7.25 (dd, *J* = 8.2, 1.83 Hz, 1H), 6.66 (s, 2H), 3.62 (s, 3H), 2.62 (s, 3H), 2.24-2.11 (m, 1H), 2.05-1.94 (m, 1H), 1.81 (dd, *J* = 8.3, 5.0 Hz, 1H), 1.47-1.56 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.1, 171.5, 136.7, 136.3, 134.4, 133.5, 133.2, 132.3, 131.7, 53.5, 50.9, 34.0, 33.5, 33.5, 23.8, 21.2; FT-IR (neat): 3022, 2771, 1719, 1270 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{16}O_2NCl_2$: 288.0552; Found: 288.0552; Anal. Calcd. for $C_{17}H_{19}Cl_2NO_6$: C, 50.51; H, 4.74; N, 3.46; Found: C, 50.26; H, 4.77; N, 3.53.

The same reaction was also performed in 20 mmol scale, 5.1 g (89% yield) of product was obtained. (Large scale synthesis of lead compound for *in vitro* analysis).

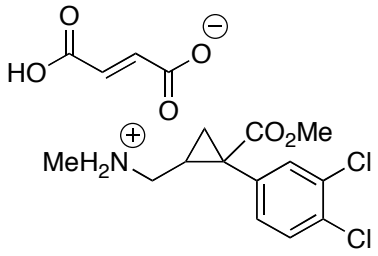
1-((1*S*,2*S*)-2-(3,4-dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (ent-3-129 d)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 1-(3,4-dichlorophenyl)-2-formylcyclopropanecarboxylate (**ent-3-129 d)** (273 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 66% yield (191 mg). The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (130 mg, 1.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under

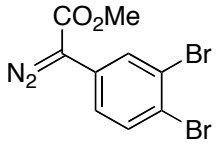
reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. Spectroscopic data is same as **3-130 d**.

1-(2-(3,4-Dichlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (rac-3-130 d)



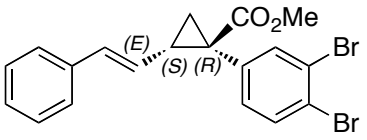
The racemic amine was synthesized (3 mmol scale) in the same reaction conditions as described above, to obtain 492 mg (57 %) of product. Spectroscopic data is same as **3-130 d**.

Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (3-133 l)



This compound was obtained from Josh Alford and used as is.

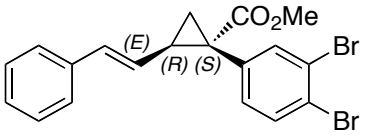
(1*R*,2*S*)-methyl 1-(3,4-dibromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (260 mg, 2 mmol, 2 eq.) and Rh_2(*S*-DOSP)$_4$ (14 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate **(3-133 l)** (333 mg, 1 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 7:1) to obtain **3-118 l** as an oily liquid in 97 % yield (426 mg), >94 % de. HPLC analysis: 88 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 6.9 (major) and 9.7 (minor) min, UV 254 nm); R_f = 0.35 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.50 (m, 2H), 7.29-7.22 (m, 2H), 7.22-7.13 (m, 3H), 7.10 (s, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 5.19 (ddd, *J* = 15.8, 9.7, 1.0 Hz, 1H), 3.65 (s, 3H), 2.68 (td, *J* = 9.3, 6.8 Hz, 1H), 2.07 (dd, *J* = 9.0, 4.7 Hz, 1H), 1.48-1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 136.7, 136.3, 136.1, 132.8, 131.9, 131.8, 128.1, 127.2, 127.0, 125.5, 123.9, 123.4, 52.2, 34.3, 31.6, 22.1; FT-IR (neat):

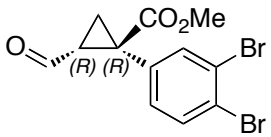
1717, 1462, 1271, 906, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{19}H_{17}O_2{}^{35}Br_2$: 434. 9589; Found; 434.9586.

(1*S*,2*R*)-methyl 1-(3,4-dibromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 l)



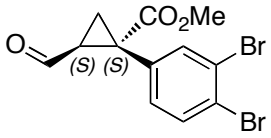
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (520 mg, 4 mmol, 2 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate **(3-133 l)** (667 mg, 2 mmol) was dissolved in dry, degassed toluene (40 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 7:1) to obtain **ent-3-118 l** as an oily liquid in 90 % yield (791 mg), >94 % de. HPLC analysis: 88 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 6.9 (minor) and 9.7 (major) min, UV 254 nm); R_f = 0.35 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-118 l**.

(1*R*,2*R*)-methyl 1-(3,4-dibromophenyl)-2-formylcyclopropanecarboxylate (3-129 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-(3,4-dibromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (436 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-129 l** as a colorless oil in 71% yield (257 mg) and was taken to the next step.

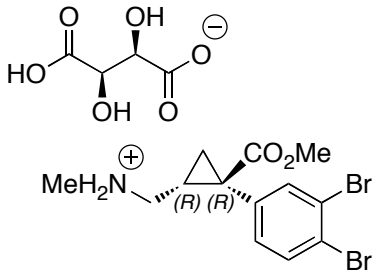
(1*S*,2*S*)-methyl 1-(3,4-dibromophenyl)-2-formylcyclopropanecarboxylate (ent-3-129 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-methyl 1-(3,4-dibromophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (436 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced

pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-129 l** as a colorless oil in 79% yield (285 mg) and was taken to the next step.

1-((1*R*,2*R*)-2-(3,4-dibromophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate(ent-3-129 l)

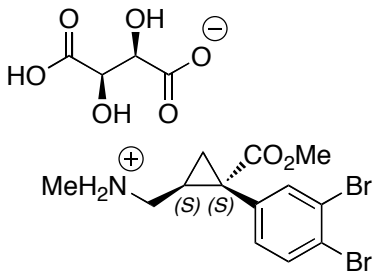


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*R*)-methyl 1-(3,4-dibromophenyl)-2-formylcyclopropanecarboxylate **(3-129 l)** (436 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 80% yield (302 mg). ^{1}H NMR (400 MHz, CD_3OD): δ 7.76-7.72 (m, 2H), 7.25 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.58 (s, 3H), 2.5-2.4 (m, 2H), 2.25 (s, 3H), 2.05-1.94 (m, 1H), 1.81 (dd, *J* = 8.3, 5.0 Hz, 1H), 1.47-1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 136.6, 135.7, 132.8, 131.1, 123.9, 123.2, 52.2, 52.1, 35.9, 32.0, 27.6, 20.1; FT-IR (neat): 1717, 1463, 1268, 1012, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{16}Br_2O_2N_1$: 375.9542; Found: 375.9538; Anal. Calcd. for $C_{17}H_{21}Br_2NO_8 + H_2O$: C, 38.73; H, 4.02; N, 2.66; Found: C, 40.77; H, 3.95; N, 2.89.

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (130 mg, 1.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid.

1-((1*S*,2*S*)-2-(3,4-dibromophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (2*R*,3*R*)-3-carboxy-2,3-dihydroxypropanoate(ent-3-130 l)

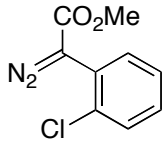


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*S*)-methyl 1-(3,4-dibromophenyl)-2-formylcyclopropanecarboxylate (**ent-3-129 l)** (872 mg, 1 mmol) was dissolved in methanol (40 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 2 mL, 4 mmol) and Ti(O-*i*Pr)$_4$ (2 mL, 4 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (112 mg, 3 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 85% yield (646 mg). Spectroscopic data is same as **3-130 l**.

The product was dissolved in isopropanol (20 mL) and then treated with L-tartaric acid (130 mg, 1.1 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled

to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid.

Methyl 2-(2-chlorophenyl)-2-diazoacetate (3-133 f)

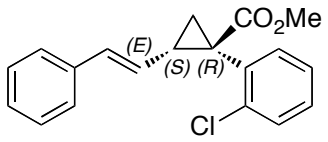


In a flame dried round bottom flask, 2-(2-chlorophenyl) acetic acid (55 mmol, 1 eq.) was dissolved in MeOH (100 mL) and cooled to 0 ^{o}C. Acetyl chloride (66 mmol, 1.2 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(66 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-diazabicycloundec-7-ene (DBU) (110 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 10.16 g (87 % yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.0 Hz, 1

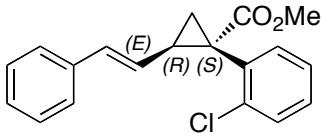
H), 7.43 (d, *J* = 7.4 Hz, 1 H), 7.36 - 7.23 (m, 2 H), 3.85 (s, 3 H). The ^{1}H NMR data was consistent with the published values.

(1*R*, 2*S*)-Methyl 1-(2-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 f)



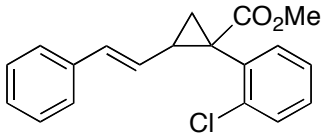
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (421 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 f** as an oily liquid in 62% yield (511 mg). HPLC analysis: 72% ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.1 (major) and 9.6 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H), 7.20-7.03 (m, 7H), 6.52 (d, *J* = 15.5 Hz, 1H), 5.30 (br. s, 1H), 3.57 (s, 3H), 2.89 (br. s, 1H), 1.92 (br. s, 1H), 1.49 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 137.0, 136.9, 129.3, 128.6, 128.2, 126.9, 126.2, 125.7, 52.3, 35.1, 32.2, 22.2; FT-IR (neat): 1718, 1434, 1268, 1241, 953, 748 cm^{-1}; HRMS (pos-APCI) calcd for $C_{19}H_{18}O_2{}^{35}Cl_1$: 313.0989; Found: 313.0989.

(1*S*,2*R*)-Methyl 1-(2-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 f)



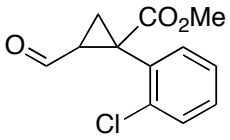
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (421 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 f** as an oily liquid in 63% yield (522 mg). HPLC analysis: 71% ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.1 (minor) and 9.6 (major) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); Spectroscopic data is same as **3-118 f**.

Methyl 1-(2-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (rac-3-118 f)



The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 912 mg (97 %) of product. Spectroscopic data is same as **3-118 f**.

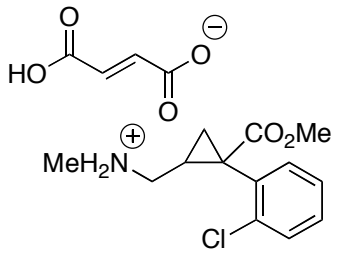
Methyl 1-(2-chlorophenyl)-2-formylcyclopropanecarboxylate (rac-3-129 f)



In a 50 mL round bottom flask equipped with a magnetic stir bar, Methyl 1-(2-chlorophenyl)-2-((*E*)-styryl)cyclopropanecarboxylate **(rac-3-118 f)** (312 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **rac-3-129 f** as a colorless oil in 70 % yield (166 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br. s., 1H), 7.54 - 7.18 (m, 4H), 3.66 (s, 3H), 3.11 (br. s., 1H), 2.29-1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 171.2, 133.6, 131.9, 130.1, 129.6, 129.5, 128.4, 127.0, 53.1, 36.1, 20.4; FT-IR (neat): 1708,

1435, 1250, 1158, 727 cm^{-1}; HRMS (pos-APCI) calcd for $C_{12}H_{10}O_3Cl$: 237.0324; Found: 237.0319.

1-(2-(2-chlorophenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (rac-3-130 f)

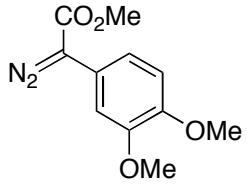


In a 50 mL round bottom flask equipped with a magnetic stir bar, Methyl 1-(2-chlorophenyl)-2-formylcyclopropanecarboxylate (119 mg, 0.5 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 3 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (37 mg, 1 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 60% yield (74 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (m, 1H), 7.31-7.20 (m, 2H), 3.59 (s, 3H), 2.74 (dd, *J* = 12.36, 5.03 Hz, 1H), 2.34 (s, 3H), 1.86-1.59 (m, 2H), 1.41 (br. s, 1H), 1.28 (br. s, 1H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 173.2, 136.4, 134.4, 131.5, 129.1, 128.4, 126.4, 52.1, 50.8, 35.9, 32.2, 27.0, 20.6; FT-IR (neat): 2949, 1719, 1434, 1266, 1249, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{16}ClO_2N$: 254.0942; Found: 254.0941.

The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (60 mg, 0.5 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^1H NMR (400 MHz, CD_3OD): δ 7.47-7.41 (m, 1H), 7.39-7.30 (m, 3H), 6.66 (s, 2H), 3.60 (s, 3H), 3.43 (d, *J* = 10.3 Hz, 1H), 2.61 (s, 3H), 2.43 (br. s, 1H), 1.90 (br. s, 1H); 1.77-1.56 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.0, 171.5, 136.3, 134.6, 133.8, 130.9, 130.8, 128.7, 53.4, 48.6, 33.4, 33.4, 22.3, 20.1. Anal. Calcd. for $C_{17}H_{20}ClNO_6$: C, 55.21; H, 5.45; N, 3.79; Found: C, 55.02; H, 5.43; N, 3.80.

Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (3-133 i)

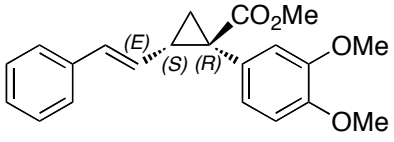


In a flame dried round bottom flask, 2-(3,4-dimethoxyphenyl) acetic acid (50 mmol, 1 eq.) was dissolved in MeOH (100 mL) and cooled to 0 °C. Acetyl chloride (60 mmol, 1.2 eq.) was added dropwise at 0 °C. The resultant reaction mixture was stirred at

rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(60 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (120 mmol, 2 eq.) was added dropwise at 0 ^oC. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 11.12 g (94 % yield) of yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 1 H), 7.19 (d, *J* = 1.1 Hz, 1 H), 6.90 - 6.87 (m, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H) 3.86 (s, 3 H). The ^1H NMR data was consistent with the published values.

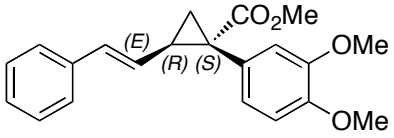
(1*R*,2*S*)-Methyl 1-(3,4-dimethoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 i)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were

dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (472 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 i** as an oily liquid in 87 % yield (591 mg). HPLC analysis: 57 % ee (OD-H column, 6 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.4 (minor) and 18.2 (major) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.07 (m, 5H), 6.88-6.75 (m, 3H), 6.56 (d, *J* = 15.87 Hz, 1H), 5.25 (dd, *J* = 15.87, 9.76 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 3.73 (s, 3H), 2.70-2.60 (m, 1H), 2.03 (dd, *J* = 8.85, 4.27 Hz, 1H), 1.40-1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 147.9, 147.8, 136.7, 130.7, 128.7, 128.1, 127.9, 126.7, 125.4, 123.3, 114.5, 110.2, 55.3, 55.3, 52.0, 34.9, 31.6, 22.6; FT-IR (neat): 1715, 1516, 1246, 1226, 756, 727 cm^{-1}; HRMS (pos-APCI) calcd for $C_{21}H_{23}O_4$: 339.1590; Found: 339.1589.

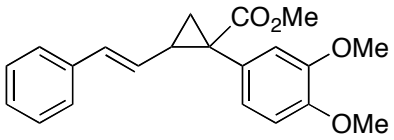
(1*S*,2*R*)-Methyl 1-(3,4-dimethoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 i)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath.

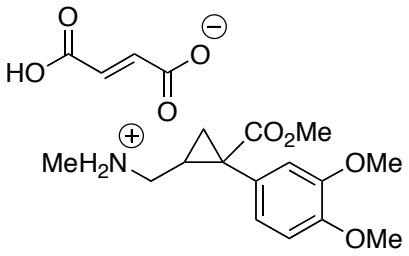
Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (472 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 i** as an oily liquid in 82 % yield (556 mg). HPLC analysis: 64 % ee (OD-H column, 6 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.4 (major) and 18.2 (minor) min, UV 254 nm); When Rh_2(*S*-PTAD)$_4$ was used in the similar conditions 591 mg (87 % yield) (80% ee) of product was obtained. HPLC analysis: 64 % ee (OD-H column, 6 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.4 (major) and 18.2 (minor) min, UV 254 nm); R_f = 0.29 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-118 i**.

(*E*)-Methyl 1-(3,4-dimethoxyphenyl)-2-styrylcyclopropanecarboxylate (rac-3-118 i)



The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 933 mg (92 %) of product. Spectroscopic data is same as **3-118 i**.

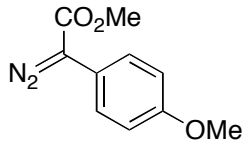
1-(2-(3,4-Dimethoxyphenyl)-2-(methoxycarbonyl)cyclopropyl)-*N*-methylmethanaminium (*E*)-3-carboxyacrylate (rac-3-130 i)



In a 50 mL round bottom flask equipped with a magnetic stir bar, crude mixture of methyl 1-(3,4-dimethoxyphenyl)-2-formylcyclopropanecarboxylate (264 mg, 1 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 2 mmol) and Ti(O-*i*Pr)$_4$ (0.4 mL, 2 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (56 mg, 1.5 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 58 % yield (162 mg) over two steps. The product was dissolved in isopropanol (20 mL) and then treated with fumaric acid (60 mg, 0.5 mmol) and stirred for 30 minutes at rt. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 2:1:1 isopropanol/hexanes/ethyl acetate (10 mL) and refluxed for 2 h. The solution was cooled to rt and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ

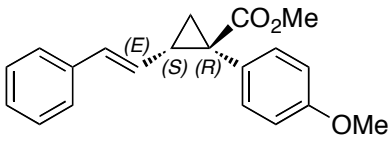
6.75 (d, J = 16.48 Hz, 3H), 3.77 (d, J =1.83 Hz, 6H), 3.51 (s, 3H), 2.40-2.30 (m, 1H), 2.23 (s, 3H), 1.94 (d, J = 7.93 Hz, 2H), 1.61 (dd, J = 7.93, 3.97 Hz, 1H), 1.19 (br. s, 1H), 1.10 (t, J = 5.03 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 148.0, 147.8, 127.9, 122.8, 113.9, 110.2, 55.5, 55.3, 51.9, 51.9, 36.1, 32.6, 27.7, 20.1; FT-IR (neat): 2950, 2837, 1715, 1516, 1249, 1226, 726 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{22}O_4N$: 280.1543; Found: 280.1543.

Methyl 2-diazo-2-(4-methoxyphenyl)acetate (3-133 h)



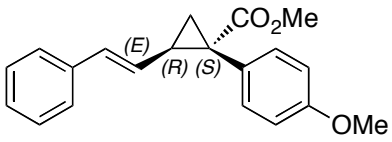
Methyl 2-(4-methoxyphenyl) acetate (9.9 g, 55 mmol, 1 eq.) was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(66 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (110 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 11.1 g (98 % yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 9.2 Hz, 2H), 7.21 (d, J = 9.2 Hz, 2H), 3.85 (s, 3H), 3.68 (s, 3H). The ^{1}H NMR data was consistent with the published values.

(1*R*,2*S*)-Methyl 1-(4-methoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 h)



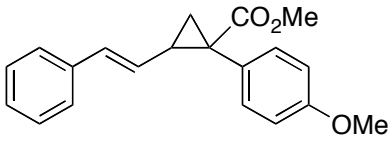
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (412 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 h** as an oily liquid in 97 % yield (601 mg). HPLC analysis: 90 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 12.5 (minor) and 15.3 (major) min, UV 254 nm); R_f = 0.15 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.2 Hz, 2H), 7.13-7.09 (m, 5H), 6.78-6.76 (m, 2H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.23 (dd, *J* = 15.8, 9.7 Hz, 1 H), 3.59 (s, 3H), 2.66-2.60 (m, 1H), 2.0 (dd, *J* = 8.8, 4.5 Hz, 1H), 1.3 (dd, *J* = 6.4, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 158.6, 136.9, 132.5, 130.9, 130.1, 128.8, 128.3, 127.7, 126.9, 125.7, 54.8, 52.1, 34.8, 31.8, 22.5; FTIR (Neat): 1715, 1434, 1293, 1241, 730 cm^{-1}; HRMS (pos-APCI) calcd for $C_{20}H_{21}O_3$: 309.1485; Found 309.1484.

(1*S*,2*R*)-Methyl 1-(4-methoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 h)



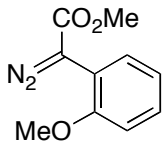
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(4-methoxyphenyl)acetate (412 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 h** as an oily liquid in 91 % yield (561 mg). HPLC analysis: 91 % ee (OD-H column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 12.5 (major) and 15.3 (minor) min, UV 254 nm); R_f = 0.15 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-118 h**.

(*E*)-Methyl 1-(4-methoxyphenyl)-2-styrylcyclopropanecarboxylate (rac-3-118 h)



The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 650 mg (70 %) of product. Spectroscopic data is same as **3-118 h**.

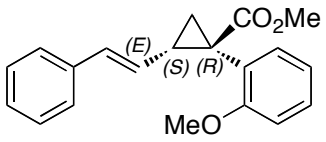
Methyl 2-diazo-2-(2-methoxyphenyl)acetate (3-133 g)



In a flame dried round bottom flask, 2-(2-methoxyphenyl) acetic acid (55 mmol, 1 eq.) was dissolved in MeOH (100 mL) and cooled to 0 ^{o}C. Acetyl chloride (66 mmol, 1.1 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl solution. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

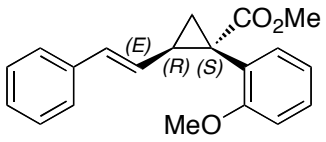
The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(66 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (124 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 10.1 g (89 % yield) of yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 7.8, 1.7 Hz, 1H), 7.30-7.23 (m, 2H), 7.02 (td, J = 7.6, 1.2 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H). The ^{1}H NMR data was consistent with the published values.

(1*R*,2*S*)-Methyl 1-(2-methoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (3-118 g)



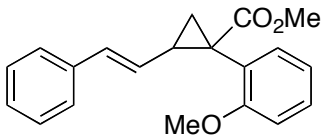
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*S*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(2-methoxyphenyl)acetate (412 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-118 g** as an oily liquid in 96 % yield (591 mg). HPLC analysis: 79 % ee (SS-Whelk column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.8 (major) and 17.3 (minor) min, UV 254 nm); R_f = 0.15 (4:1 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3-7.12 (m, 2H), 7.27-7.22 (m, 2H), 7.21-7.14 (m, 3H), 7.00 (s, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 5.38 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 2.90 (td, *J* = 9.1, 6.7 Hz, 1H), 2.02 (dd, *J* = 8.9, 4.5 Hz, 1H), 1.53 (dd, *J* = 6.7, 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 159.3, 137.3, 130.8, 128.8, 128.5, 128.3, 126.8, 125.6, 124.8, 120.4, 120.0, 110.5, 55.4, 52.2, 32.1, 31.1, 22.5; FT-IR (neat): 1716, 1462, 1269, 1010, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{20}H_{21}O_3$: 309.1485; Found: 309.1484.

(1*S*,2*R*)-Methyl 1-(2-methoxyphenyl)-2-((*E*)-styryl)cyclopropanecarboxylate (ent-3-118 g)



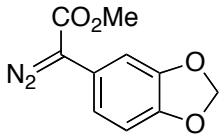
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (781 mg, 6 mmol, 3 eq.) and Rh_2(*R*-DOSP)$_4$ (28 mg, 1 % mol) were dissolved in dry, degassed toluene (5 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(2-methoxyphenyl)acetate (412 mg, 2 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-118 g** as an oily liquid in 97 % yield (599 mg). HPLC analysis: 86 % ee (SS-Whelk column, 1 % 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.8 (minor) and 17.3 (major) min, UV 254 nm); R_f = 0.15 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-118 g**.

(*E*)-Methyl 1-(2-methoxyphenyl)-2-styrylcyclopropanecarboxylate (rac-3-118 g)



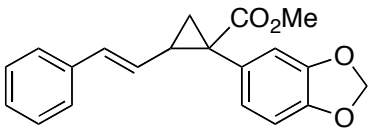
The racemic compound was synthesized (3 mmol scale) using $Rh_2(OAc)_4$ (1 mol%) as catalyst in the same reaction conditions as described above, to obtain 621 mg (67 %) of product. Spectroscopic data is same as **3-118 g**.

Methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-diazoacetate (3-133 j)



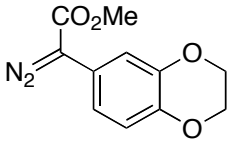
In a flame dried round bottom flask, methyl 2-(benzo[*d*][1,3]dioxol-5-yl)acetate (5.4 g, 28 mmol, 1 eq.) was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(7 g, 30 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (7.6 g, 56 mmol, 2 eq.) was added dropwise at 0 ^oC. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 5.9 g (97 % yield) of yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.1 (s, 1H), 6.9 (m, 2H), 5.9 (s, 2H), 3.83 (s, 3H). ^1H NMR (400 MHz, $CDCl_3$): δ 165.9, 148.4, 146.1, 117.8, 108.8, 105.7, 101.3, 52.0, 40.8.

(*E*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2-styrylcyclopropanecarboxylate (rac-3-118 j)



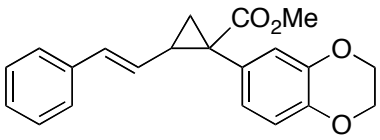
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (2.3 g, 18 mmol, 3 eq.) and $Rh_2(OAc)_4$ (24 mg, 1 % mol) were dissolved in dry, degassed toluene (50 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-diazoacetate (1.3 g, 6 mmol) was dissolved in dry, degassed toluene (50 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **rac-3-118 j** as an oily liquid in 98 % yield (1.5 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2-7.1 (m, 5H), 6.8-6.7 (m, 3H), 6.56 (d, *J* = 15.7 Hz, 1H), 5.93 (s, 2H), 5.27 (dd, *J* = 15.8, 9.5 Hz, 1H), 3.63 (s, 3H), 2.90 (td, *J* = 9.1, 6.7 Hz, 1H), 2.0 (dd, *J* = 8.9, 4.5 Hz, 1H), 1.53 (dd, *J* = 6.7, 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 147.5, 147.0, 137.3, 131.5, 129.7, 128.9, 128.7, 127.3, 126.1, 125.0, 112.2, 108.1, 101.3, 101.2, 52.8, 35.6, 32.4, 23.1; FT-IR (neat): 1714, 1435, 1228, 1036, 747 cm^{-1}; HRMS (pos-APCI) calcd for $C_{20}H_{19}O_4$: 323.1277; Found: 323.1277. Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63; Found: C, 74.46; H, 5.68.

Methyl 2-diazo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acetate (3-133 k)



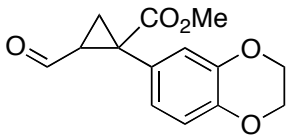
In a flame dried round bottom flask, methyl 2-(3,4-dihydroxyphenyl)acetate (5.4 g, 30 mmol, 1 eq.) was dissolved in THF (100 mL) and 1,2-dibromoethane (6.2 g, 33 mmol, 1.1 eq.) was added. K_2CO_3 was added to the reaction mixture and refluxed for 48 h. The reaction mixture was filtered through celite, washed with THF and concentrated *in vacuo* to get crude methyl 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl) acetate in 31% (1.9 g) yield. The crude mixture was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA)(2 g, 8.8 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (2.1 g, 14.4 mmol, 1.8 eq.) was added dropwise at 0 ^oC. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 996 mg (53 % yield) of yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, J = 1.8 Hz, 1H), 6.77-6.98 (m, 2H), 4.26 (s, 4H), 3.85 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 143.7, 141.7, 117.7, 117.5, 117.3, 113.3, 64.1, 51.7; FT-IR (neat): 2077, 1693, 1507, 1244 cm^{-1}; HRMS (pos-APCI) calcd for $C_{22}H_{21}O_8N_2$: 441.1292; Found: 441.1287.

(*E*)-Methyl 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-styrylcyclopropanecarboxylate (rac-3-118 k)



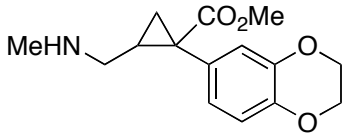
In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (585 mg, 4.5 mmol, 3 eq.) and $Rh_2(OAc)_4$ (4 mg, 1 % mol) were dissolved in dry, degassed toluene (20 mL) and cooled to -78 °C in a dry ice/acetone bath. Methyl 2-diazo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acetate (351 mg, 3 mmol, 1 eq.) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **rac-3-118 k** as an oily liquid in 62 % yield (312 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.28 (m, 2H), 7.13-7.19 (m, 3H), 6.72-6.84 (m, 3H), 6.56 (d, *J* = 15.8 Hz, 1H), 5.27 (dd, *J* = 15.8, 9.7 Hz, 1H), 4.26 (s, 4H), 3.65 (s, 3H), 2.57-2.68 (m, 1H), 1.99 (dd, *J* = 9.00, 4.42 Hz, 1H), 1.42 (dd, *J* = 6.4, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 142.9, 142.8, 137.2, 131.1, 128.9, 128.8, 128.4, 127.0, 125.9, 124.6, 120.3, 116.7, 64.3, 64.2, 52.5,35.1, 32.1, 22.7; FT-IR (neat): 1715, 1507, 1273, 1244 cm^{-1}; HRMS (pos-APCI) calcd for $C_{21}H_{21}O_4$: 337.14344; Found: 337.14326. Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.98; H, 5.99; Found: C, 74.44; H, 5.94.

Methyl 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-formylcyclopropanecarboxylate (rac-3-129 k)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (*E*)-Methyl 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-styrylcyclopropanecarboxylate (**rac-3-118 k)** (168 mg, 0.5 mmol, 1 eq.) was dissolved in dichloromethane (10 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **rac-3-129 k** as a colorless oil in 49 % yield (64 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 6.7 Hz, 1H), 6.93-6.68 (m, 3H), 4.25 (s, 4H), 3.66 (s, 3H), 2.68 (dt, *J* = 8.5, 6.4 Hz, 1H), 2.24-1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.4, 172.0, 143.4, 143.2, 133.4, 130.0, 128.3, 126.6, 123.7, 119.7, 117.3, 64.2, 52.9,36.7, 36.4, 19.4; FT-IR (neat): 1705, 1508, 1247, 1065, 732 cm^{-1}; HRMS (pos-APCI) calcd for $C_{14}H_{15}O_5$: 263.0914; Found: 263.0915.

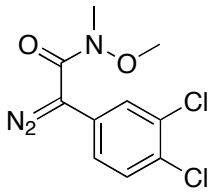
Methyl 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-((methylamino)methyl)cyclopropanecarboxylate (rac-3-130 k)



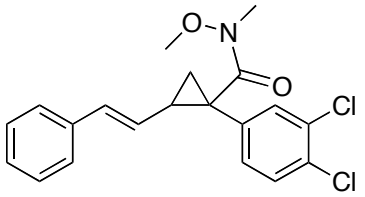
In a 50 mL round bottom flask equipped with a magnetic stir bar, Methyl 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-formylcyclopropanecarboxylate (**rac-3-118 k)** (65 mg, 0.5 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 1 mmol) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (28 mg, 0.75 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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, Isolera, ethyl acetate: triethylamine = 9:1) to give a colorless oil in 70% yield (96 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91-6.63 (m, 3H), 4.26 (s, 4H), 3.62 (s, 3H), 2.53-2.45 (m, 1H), 2.34 (s, 3H), 2.06-1.93 (m, 2H), 1.68 (dd, *J* = 8.5, 4.2 Hz, 1H), 1.54 (br. s., 1 H), 1.20-1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 142.8, 142.6, 128.7, 123.9, 119.6, 116.7, 64.2, 52.3, 52.1, 36.2, 32.5, 27.8, 20.4; FT-IR (neat): 2948, 2876,

1713, 1507, 1246, 1065 729 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{20}O_4N_1$: 278.1386; Found: 278.1388.

2-diazo-2-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methylacetamide (3-109 b)



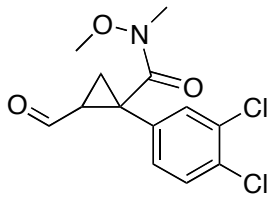
(*E*)-1-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methyl-2-styrylcyclopropanecarboxamide (rac-3-118 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, *(E)*-buta-1, 3-dienylbenzene (520 mg, 4 mmol, 2 eq.) and $Rh_2(OAc)_4$ (8 mg, 1 % mol) were dissolved in dry, degassed toluene (20 mL). 2-Diazo-2-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methylacetamide (548 mg, 2 mmol, 1 eq.) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 2 h at rt. Diazo compound did not decompose completely after 4 h of stirring at rt. The reaction was stirred overnight at rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **rac-3-118 l** as an oily liquid in 56 % yield (418 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 2.1 Hz, 1H), 7.36 (d,

J = 8.3 Hz, 1H), 7.25-7.15 (m, 3H), 7.18-7.07 (m, 3H), 6.58 (d, *J* = 15.8 Hz, 1H), 5.24 (dd, *J* = 15.8, 9.3 Hz, 1H), 3.20 (s, 3H), 3.11 (s, 3H), 2.77 (td, *J* = 9.1, 6.4 Hz, 1H), 1.64 (dd, *J* = 9.0, 5.4 Hz, 1H), 1.53 (dd, *J* = 6.5, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 138.0, 137.2, 132.4, 132.2, 131.8, 131.2, 130.3, 129.5, 128.7, 127.9, 127.4, 126.1, 60.4, 60.4, 36.5, 33.7, 27.9, 19.3; FT-IR (neat): 1647, 1472, 1377, 1134, 907, 728 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{20}H_{20}O_2N_1Cl_2$: 376.0865; Found: 376.0866.

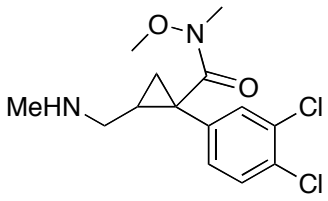
1-(3,4-dichlorophenyl)-2-formyl-*N*-methoxy-*N*-methylcyclopropanecarboxamide (rac-3-129 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (*E*)-1-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methyl-2-styrylcyclopropanecarboxamide (**rac-3-118 l)** (376 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **rac-3-129 l**

as a colorless oil in 54 % yield (126 mg). The product was isolated as a single diastereomer, but decomposed into mixture of diastereomers with in 1 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.0 (d, *J* = 6.0 Hz, 1H), 7.48-7.47 (m, 1H), 7.41-7.40 (m, 1H), 7.22-7.21 (m, 1H), 3.25 (s, 3H), 3.12 (s, 3H), 2.87-2.85 (m, 1H), 2.23-2.21 (m, 1H), 1.71-1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 134.7, 132.3, 131.1, 130.2, 129.7, 128.6, 60.1, 39.5, 33.0, 32.9, 16.5; FT-IR (neat): 1709, 1651, 1379, 1170, 728 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{13}H_{14}O_3N_1Cl_2$: 302.0345; Found: 302.0344.

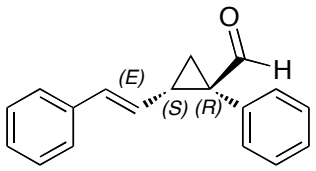
1-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methyl-2-((methylamino)methyl)cyclopropanecarboxamide (rac-3-130 l)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-(3,4-dichlorophenyl)-2-formyl-*N*-methoxy-*N*-methylcyclopropanecarboxamide **(rac-3-130 l)** (116 mg, 0.5 mmol, 1 eq.) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.8 mL, 1.5 mmol, 3eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1.5 mmol, 3 eq.) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (38 mg, 1 mmol, 2 eq.) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 53 % yield (66 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.20 (s, 1H), 7.12 (m, 1H), 3.10 (s, 3H), 3.05 (s, 3H), 2.50 (m, 1H), 2.40 (s, 3H), 2.15 (m, 1H), 1.92 (m, 1H), 1.3 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 132.2, 130.9, 130.9, 130.1, 128.5, 60.1, 51.6, 36.3, 33.7, 33.4, 23.1, 16.3; FT-IR (neat): 2935, 2786, 1649, 1473, 1135, 1029 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{14}H_{19}O_2N_2Cl_2$: 317.0818; Found: 317.0817.

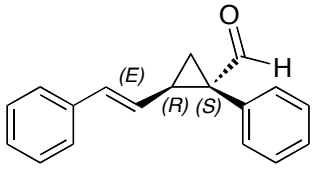
(1*R*,2*S*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde (3-119)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (**3-118 a)** (556 mg, 2 mmol, 1 eq.) was dissolved in THF (50 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (94 mg, 2.5 mmol, 1.5 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol was dissolved in methylene chloride (20 mL) and Dess Martin Periodinane (DMP) reagent

(1.2 g, 3 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (2 × 10). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-119** as an oily liquid in 80 % yield (398 mg); R_f = 0.30 (4:1 Hexanes: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.39-7.22 (m, 5H), 7.19-7.10 (m, 5H), 6.56 (d, *J* = 16.0 Hz, 1H), 5.25 (dd, *J* = 16.0 Hz, 6.0 Hz, 1H), 2.57 (m, 1H), 2.08 (m, 1H), 1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5, 136.8, 134.7, 132.0, 131.0, 128.7, 128.4, 127.8, 127.5, 127.3, 125.9, 44.6, 34.3, 21.7; FT-IR (neat): 1717, 1271, 1244, 1193, 1159, 960, 752, 694 cm^{-1}; Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49; Found: C, 87.30; H, 6.59.

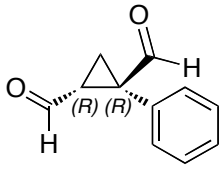
(1*S*,2*R*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde (ent-3-119)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate (**ent-3-118 a)** (139 mg, 0.5 mmol, 1 eq.) was dissolved in THF (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (24 mg, 0.6 mmol, 1.25 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 1.5 h. The reaction was quenched with $NaSO_4$•$10H_2O$

(added until bubbling ceased) and filtered through celite. The solids were rinsed with THF and the combined extracts were concentrated under reduced pressure. The crude alcohol was dissolved in methylene chloride (20 mL) and Dess Martin Periodinane (DMP) reagent (318 mg, 0.75 mmol, 1.5 eq.) was added. The reaction was stirred at rt for 3 h (TLC monitored) until it was diluted with ether and washed with aqueous NaOH (2 × 10). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-119** as an oily liquid in 77 % yield (96 mg); R_f = 0.30 (4:1 Hexanes: EtOAc). Spectroscopic data is same as **3-119**.

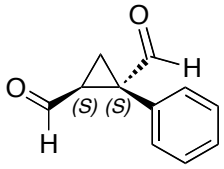
(1*R*,2*R*)-1-phenylcyclopropane-1,2-dicarbaldehyde (3-127)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde (**3-119)** (124 mg, 0.5 mmol, 1 eq.) was dissolved in dichloromethane (10 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced

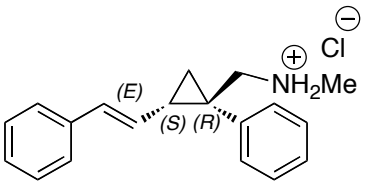
pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-127** as a colorless oil in 64 % yield (56 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.43 (s, 1H), 8.67 (d, *J* = 6.2 Hz, 1H), 7.46-7.26 (m, 5H), 2.66 (dt, *J* = 8.7, 6.2 Hz, 1H), 2.25 (dd, *J* = 6.2, 5.1 Hz, 1H), 2.06 (dd, *J* = 8.7, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 197.1, 132.2, 130.5, 129.1, 128.6, 44.4, 36.7, 18.2; FT-IR (neat): 1701, 1167, 994, 715, 699 cm^{-1}; HRMS (pos-APCI) calcd for $C_{11}H_{11}O_2$: 175.0753; Found: 175.0751.

(1*S*,2*S*)-1-phenylcyclopropane-1,2-dicarbaldehyde (ent-3-127)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde **(ent-3-119)** (124 mg, 0.5 mmol, 1 eq.) was dissolved in dichloromethane (10 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-127** as a colorless oil in 69 % yield (60 mg). Spectroscopic data is same as **3-127**.

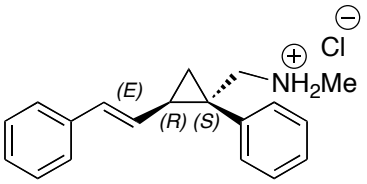
N-Methyl-1-((1*R*,2*S*)-1-phenyl-2-((E)-styryl)cyclopropyl)methanaminium chloride (3-120)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*, 2*S*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde **(3-119)** (496 mg, 2 mmol, 1 eq.) was dissolved in methanol (30 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1.6 mL, 3 mmol) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (75 mg, 2 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 88 % yield (462 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.31 (m, 5H), 7.30-7.07 (m, 5H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.20 (dd, *J* = 16.0 Hz, 6.0 Hz, 1H), 3.50 (s, 1H), 3.00 (s, 1H), 2.47(s, 3H), 2.10 (m, 1H), 1.74 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 137.3, 137.0, 130.5, 129.0, 128.8, 128.3, 127.9, 126.9, 125.7, 67.9, 59.1, 33.6, 30.2, 28.3, 19.3; Anal. Calcd. for $C_{19}H_{22}ClN$: C, 76.11; H, 7.40; N, 4.67; Found: C, 76.07; H, 7.41; N, 4.63.

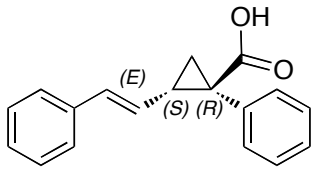
N-Methyl-1-((1*S*,2*R*)-1-phenyl-2-((E)-styryl)cyclopropyl)methanaminium chloride (ent-3-120)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*, 2*R*)-1-Phenyl-2-((E)-styryl)cyclopropanecarbaldehyde **(ent-3-119)** (124 mg, 0.5 mmol, 1 eq.) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.8 mL, 1.5 mmol, 3 eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1.5 mmol, 3 eq.) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (20 mg, 0.5 mmol, 1 eq.) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 92 % yield (121 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white

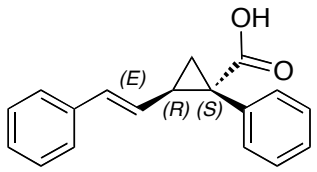
solid was filtered and washed with diethyl ether to obtain white solid. Spectroscopic data is same as **3-120**.

(1*R*,2*S*)-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylic acid (3-121)



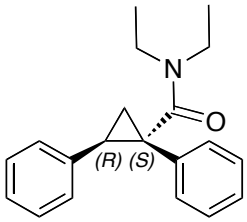
In a 50 mL round bottom flask equipped with a magnetic stir bar, **(**1*R*, 2*S*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate **(3-118)** (278 mg, 1 mmol, 1 eq.) was dissolved in THF (20 mL) and flushed with argon. The solution was then cooled to 0 °C. Lithium hydroxide (84 mg, 3.5 mmol, 3.5 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 6 h. The reaction was quenched with 1N HCl and extracted (3 × 100) to get the entire acid product into the organic layer. The combined extracts were concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 1:1 hexanes: ethyl acetate) to give **3-121** as an oily liquid in 48 % yield (126 mg); R_f = 0.30 (1:1 Hexanes: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.18 (m, 5H), 7.17-7.07 (m, 5H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.20 (dd, *J* = 16 Hz, 6 Hz, 1H), 2.10 (m, 1H), 1.74 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 135.9, 134.0, 130.6, 127.4, 127.3, 127.1, 126.6, 126.2, 124.9, 34.5, 31.7, 21.8; FT-IR (neat): 3026, 2572, 1712, 1301, 961 cm^{-1}; HRMS (pos-APCI) calcd for $C_{18}H_{17}O_2$: 265.1223; Found: 265.1223; Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10; Found: C, 81.53; H, 6.23.

(1*S*,2*R*)-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylic acid (ent-3-121)



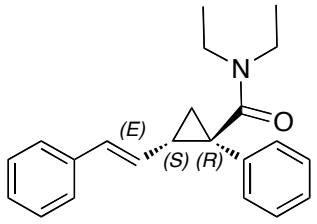
In a 50 mL round bottom flask equipped with a magnetic stir bar, **(**1*S*, 2*R*)-Methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate **(ent-3-118)** (1.11 g, 4 mmol, 1 eq.) was dissolved in THF (20 mL) and flushed with argon. The solution was then cooled to 0 °C. Lithium hydroxide (335 mg, 14 mmol, 3.5 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred for 6 h. The reaction was quenched with 1N HCl and extracted (3 × 100) to get the entire acid product into the organic layer. The combined extracts were concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, 1:1 hexanes: ethyl acetate) to give **ent-3-121** as an oily liquid in 40 % yield (416 mg); R_f = 0.30 (1:4 Hexanes: EtOAc). Spectroscopic data is same as **3-121**.

(1*S*,2*R*)-*N*,*N*-diethyl-1,2-diphenylcyclopropanecarboxamide (Ester to amide test substrate)



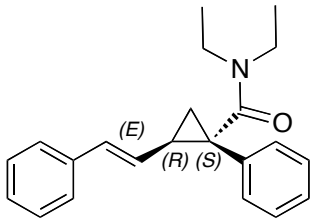
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1,2-diphenylcyclopropanecarboxylate (504 mg, 2 mmol, 1 eq.) was dissolved in benzene (20 mL) and flushed with argon. The solution was then cooled to 0 °C. Trimethylaluminium (25% w/w in Hexane, 1mL, 2.2 mmol, 1.1 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred at refluxing temperature for 24 h. The reaction was quenched with 1N HCl and extracted (3 × 100) to get the entire amide product into the organic layer. The combined extracts were concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 1:1 hexanes: ethyl acetate) to give titled product as an oily liquid in 70 % yield (412 mg); R_f = 0.30 (1:4 Hexanes: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08-6.98 (m, 10H), 3.4 (m, 1H), 3.2 (m, 4H), 2.0 (m, 1H), 1.5 (m, 1H), 1.0 (m, 3H), 0.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 136.9, 136.0, 128.5, 128.3, 127.8,127.4, 126.2, 125.6, 41.3, 39.7, 38.3, 29.6, 29.5, 15.2, 12.7, 12.3; FT-IR (neat): 2978, 2932, 1616, 1458, 730, 696 cm^{-1}; Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77; Found: C, 81.79; H, 7.96; N, 4.76.

(1*R*,2*S*)-*N*,*N*-diethyl-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxamide (3-122)



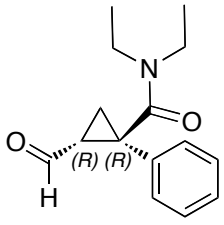
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate **(3-118 a)** (1.11 g, 4 mmol, 1 eq.) was dissolved in benzene (50 mL) and flushed with argon. The solution was then cooled to 0 °C. Trimethylaluminium (25% w/w in Hexane, 2 mL, 4.4 mmol, 1.1 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred at refluxing temperature for 24 h. The reaction was quenched with 1N HCl and extracted (3 × 100) to get the entire amide product into the organic layer. The combined extracts were concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 1:1 hexanes: ethyl acetate) to give **3-122** as an oily liquid in 79 % yield (1.0 g); R_f = 0.30 (1:4 Hexanes: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 4H), 7.17-7.11 (m, 3H), 7.10-7.02 (m, 3H), 6.54 (d, *J* = 15.5 Hz, 1H), 5.18 (dd, *J* = 15.5, 10.0 Hz, 1H), 3.48-3.42 (m, 1H), 3.29-3.16 (m, 3H), 2.79-2.73 (m 1H), 1.67 (t, *J* = 11.6 Hz, 1H), 1.47-1.43 (m, 1H), 1.05-1.02 (m, 3H), 0.59-0.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 137.0, 136.7, 130.7, 128.3, 128.1, 128.0, 127.9, 126.4, 126.3, 125.3, 40.9, 39.4, 37.1, 27.9, 17.3, 12.3, 12.0; FT-IR (neat): 2973, 1627, 1470, 1425, 1274, 957 cm^{-1}; Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38; Found: C, 82.57; H, 8.03; N, 4.38.

(1*S*,2*R*)-*N*,*N*-diethyl-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxamide (ent-3-122)



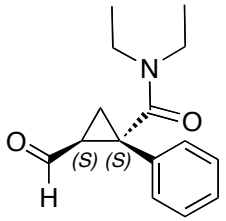
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-phenyl-2-((*E*)-styryl)cyclopropanecarboxylate **(ent-3-118 a)** (1.11 g, 4 mmol, 1 eq.) was dissolved in benzene (50 mL) and flushed with argon. The solution was then cooled to 0 °C. Trimethylaluminium (25% w/w in Hexane, 2 mL, 4.4 mmol, 1.1 eq.) was then added to the stirring solution. Following the addition, the reaction was warmed to rt and stirred at refluxing temperature for 24 h. The reaction was quenched with 1N HCl and extracted (3 × 100) to get the entire amide product into the organic layer. The combined extracts were concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 1:1 hexanes: ethyl acetate) to give **ent-3-122** as an oily liquid in 89 % yield (1.1 g); R_f = 0.30 (1:4 Hexanes: EtOAc); Spectroscopic data is same as **3-122**.

(1*R*,2*R*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide (3-123)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-*N*,*N*-diethyl-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxamide **(3-122)** (319 mg, 1 mmol, 1 eq.) was dissolved in dichloromethane (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **3-123** as a colorless oil in 87 % yield (214 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 5.2 Hz, 1H), 7.39-7.23 (m, 5H), 3.48-3.43 (m, 1H), 3.31-3.21 (m, 3H), 3.19-2.97 (m 1H), 2.39 (t, *J* = 11.6 Hz, 1H), 1.63-1.59 (m, 1H), 1.07-1.03 (m, 3H), 0.61-0.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 168.7, 134.1, 128.6, 128.1, 127.5, 41.2, 40.6, 39.8, 34.3, 15.7, 12.4, 12.0; FT-IR (neat): 1705, 1629, 1445, 1428, 1274, 1135, 700 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{20}O_2N$: 246.1488; Found: 246.1488.

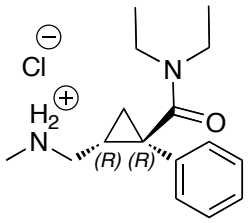
(1*S*,2*S*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide (ent-3-123)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-*N*,*N*-diethyl-1-phenyl-2-((*E*)-styryl)cyclopropanecarboxamide (**ent-3-122)** (958 mg, 3 mmol,

1 eq.) was dissolved in dichloromethane (100 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 °C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give **ent-3-123** as a colorless oil in 94 % yield (694 mg). Spectroscopic data is same as **3-123**.

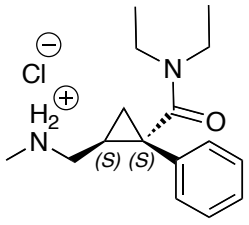
1-((1*R*,2*R*)-2-(Diethylcarbamoyl)-2-phenylcyclopropyl)-*N*-methylmethanaminium chloride (3-124)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide **(3-123)** (669 mg, 2.7 mmol, 1 eq.) was dissolved in methanol (30 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 3 mL, 5.4 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (2 mL, 6 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (114 mg, 3 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and

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: triethylamine = 9:1) to give a colorless oil in 51 % yield (357 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. $[\alpha]^{D}_{20}$: -187.4° (0.98 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.30 (m, 5H), 3.50-3.45 (m, 1H), 3.31-3.17 (m, 4H), 2.31-2.28 (m, 1H), 2.26 (s, 3H), 2.17-2.05 (m, 2H), 1.48-1.45 (m, 1H), 1.19-1.16 (m, 1H), 1.07-1.03 (m, 3H), 0.59-0.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 136.5, 128.1, 127.8, 126.4, 50.9, 40.9, 39.2, 35.7, 34.6, 23.6, 14.5, 12.2, 11.9; FT-IR (neat): 2971, 2934, 1624, 1427, 1274, 701 cm^{-1}; HRMS (pos-APCI) calcd for $C_{16}H_{25}O_1N_2$: 261.19614; Found: 261.19594; Anal. Calcd. for $C_{16}H_{25}O_1N_2$: C, 64.74; H, 8.49; N, 9.44; Found: C, 64.61; H, 8.48; N, 9.26.

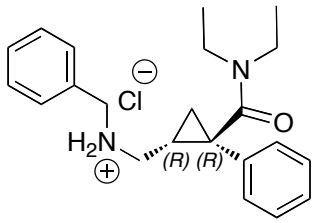
1-((1*S*,2*S*)-2-(Diethylcarbamoyl)-2-phenylcyclopropyl)-*N*-methylmethanaminium chloride (ent-3-124)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide **(ent-3-123)** (318 mg, 1 mmol, 1 eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated

with methylamine (2M in MeOH, 1 mL, 2 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (38 mg, 1 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 60 % yield (203 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. $[\alpha]^{D}_{20}$: 162.1° (0.98 mg/mL, MeOH). Spectroscopic data is same as **3-124**.

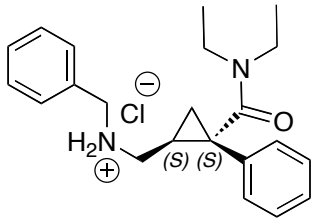
_N_-Benzyl-1-((1_R_,2_R_)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methanaminium chloride (3-125)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide **(3-123)** (686 mg, 2.8 mmol, 1 eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with phenylmethanamine (450 mg, 4.2 mmol, 1.5 eq.) and Ti(O-*i*Pr)$_4$ (2 mL, 6 mmol) and

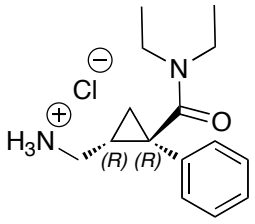
stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (158 mg, 4 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 58 % yield (548 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. $[\alpha]^{D}_{20}$: -130° (1.06 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.27 (m, 4H), 7.24-7.15 (m, 4H), 7.08-7.06 (m, 2H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.45-3.40 (m, 1H), 3.30-3.24 (m, 2H), 3.20-3.13 (m, 1H), 2.32-2.28 (m, 1H), 2.23-2.19 (m, 2H), 1.43-1.40 (m, 1H), 1.16-1.12 (m, 1H), 1.06-1.02 (m, 3H), 0.56-0.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 139.8, 136.4, 128.2, 128.0, 127.9, 127.8, 127.5, 126.4, 126.3, 53.0, 48.2, 40.9, 39.3, 34.8, 23.9, 14.4, 12.2, 12.0; FT-IR (neat): 2971, 2934, 1624, 1427, 1274, 701 cm^{-1}; 2990, 1626, 1453, 1273, 732, 697 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{22}H_{29}O_1N_2$: 337.22744; Found: 337.22744; Anal. Calcd. for $C_{22}H_{29}O_1N_2$: C, 70.85; H, 7.84; N, 7.51; Found: C, 70.61; H, 7.89; N, 7.33.

_N_-Benzyl-1-((1_S_,2_S_)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methanaminium chloride (ent-3-125)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-*N*,*N*-diethyl-2-formyl-1-phenylcyclopropanecarboxamide **(ent-3-123)** (196 mg, 0.8 mmol, 1 eq.) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with phenylmethanamine (160 mg, 1.2 mmol, 1.5 eq.) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (38 mg, 1 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 45 % yield (120 mg). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. $[\alpha]^{D}_{20}$: 122° (1.06 mg/mL, MeOH); Spectroscopic data is same as **3-125**.

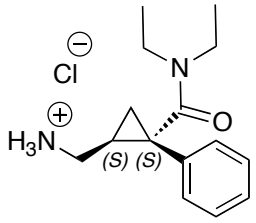
((1*R*,2*R*)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methanaminium chloride (3-126)



To a standard hydrogenation bottle was added (1*R*,2*R*)-2-((benzylamino)methyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide **(3-125)** (84 mg, 0.25 mmol), pd/C (5 %) catalyst (0.025 mmol) and absolute ethanol (10 mL). The bottle was evacuated and filled with H_2 twice and then shaken under 40 psi H_2 for 24 h. The solution was then concentrated *in vacuo*. The residue was then taken up into a 1:1 mixture of pentane: diethyl ether, filtered through another plug of silica gel and concentrated *in vacuo* to yield pure **3-126** as a sticky white solid (43 mg, 70% yield). R_f 0.22 (5:1 pentane: diethyl ether). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid; $[\alpha]^{D}_{20}$: -230° (2.8 mg/mL, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 4.1 Hz, 4H), 7.23-7.16 (m, 1H), 3.39 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.24 (dd, *J* = 7.1, 3.1 Hz, 2H), 3.14 (dt, *J* = 14.4, 7.1 Hz, 1H), 2.40-2.30 (m, 1H), 2.27-2.13 (m, 1H), 2.01 (ddt, *J* = 9.0, 8.0, 6.4 Hz, 1H), 1.37 (dd, *J* = 6.3, 5.2 Hz, 1H), 1.08 (dd, *J* = 9.0, 5.2 Hz, 1H), 1.01 (t, *J* = 7.0 Hz, 3H), 0.52 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 136.9, 128.7, 128.3, 127.0, 42.0, 41.4, 39.9, 35.5, 27.8, 14.6, 12.8, 12.5; FT-IR (neat): 2972, 2934, 2872, 1620, 1427, 701 cm^{-1}; HR-

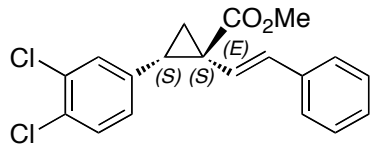
MS (pos-APCI) calcd for $C_{15}H_{23}O_1N_2$: 247.1804; Found: 247.1805; Anal. Calcd. for $C_{15}H_{23}O_1N_2$: C, 63.70; H, 8.20; N, 9.91; Found: C, 60.88; H, 8.29; N, 9.21.

((1*S*,2*S*)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methanaminium chloride (ent-3-126)



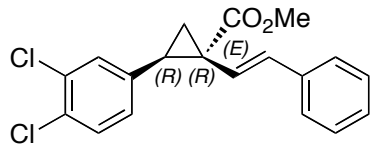
To a standard hydrogenation bottle was added (1*S*,2*S*)-2-((benzylamino)methyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide **(ent-3-125)** (168 mg, 0.5 mmol), pd/C (5 %) catalyst (0.05 mmol) and absolute ethanol (10 mL). The bottle was evacuated and filled with H_2 twice and then shaken under 40 psi H_2 for 24 h. The solution was then concentrated *in vacuo*. The residue was then taken up into a 1:1 mixture of pentane: diethyl ether, filtered through another plug of silica gel and concentrated *in vacuo* to yield pure **ent-3-126** as a sticky white solid (122 mg, 99 % yield). R_f 0.22 (5:1 pentane: diethyl ether). The product was dissolved in diethyl ether (15 mL), then treated with hydrochloric acid in diethyl ether (2M in diethyl ether, 1 mL), and the resulting white solid was filtered and washed with diethyl ether to obtain white solid. $[\alpha]^D_{20}$: 217° (2.8 mg/mL, MeOH); Spectroscopic data is same as **3-126**.

(1*S*,2*S*)-Methyl 2-(3,4-dichlorophenyl)-1-((*E*)-styryl)cyclopropanecarboxylate (3-139)



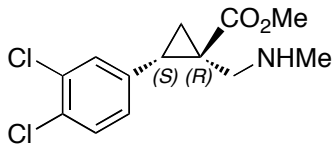
In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (692 mg, 4 mmol) and Rh_2(*S*-DOSP)$_4$ (8 mg, 1 mol %) were dissolved in dry, degassed pentane (20 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. (*E*)-methyl 2-diazo-4-phenylbut-3-enoate (404 mg, 2 mmol) was dissolved in dry, degassed pentane (20 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **3-139** as a colorless oil in 85 % yield (589 mg), > 94 de (determined by ^{1}H-NMR of crude reaction mixture). HPLC analysis: 89 % ee (SS-Whelk column, 1.5 % 2-PrOH in hexanes, 0.7 mL/min, 1mg/mL, t_R = 17.9 (minor) and 25.9 (major) min, UV 254 nm); R_f = 0.31 (4:1 Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.20 (m, 5H), 7.22-7.14 (m, 2H), 6.90 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 3H), 2.90 (dd, *J* = 9.1, 7.2 Hz, 1H), 2.08-1.95 (m, 1H), 1.76 (dd, *J* = 7.2, 5.2 Hz, 1H). Spectroscopic data matches with the data reported previously in the Davies group.

(1*R*,2*R*)-Methyl 2-(3,4-dichlorophenyl)-1-((*E*)-styryl)cyclopropanecarboxylate (ent-3-139)



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (692 mg, 4 mmol) and Rh_2(*R*-DOSP)$_4$ (8 mg, 1 mol %) were dissolved in dry, degassed pentane (20 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. (*E*)-methyl 2-diazo-4-phenylbut-3-enoate (404 mg, 2 mmol) was dissolved in dry, degassed pentane (20 mL) and added by syringe pump over 4 h. The reaction was stirred overnight while slowly warming to rt. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 8:1) to obtain **ent-3-139** as a colorless oil in 85 % yield (589 mg), > 94 de (determined by ^{1}H-NMR of crude reaction mixture). HPLC analysis: 91 % ee (SS-Whelk column, 1.5 % 2-PrOH in hexanes, 0.7 mL/min, 1mg/mL, t_R = 17.9 (major) and 25.9 (minor) min, UV 254 nm); R_f = 0.31 (4:1 Hexanes: EtOAc). Spectroscopic data matches with the data reported previously in the Davies group.

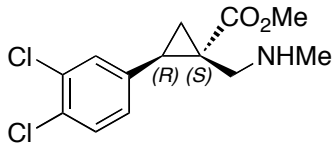
(1*R*,2*S*)-Methyl 2-(3,4-dichlorophenyl)-1-((methylamino)methyl)cyclopropanecarboxylate (3-141)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-Methyl 2-(3,4-dichlorophenyl)-1-((*E*)-styryl)cyclopropanecarboxylate **(3-139)** (555 mg, 1.6 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give crude aldehyde, which was taken to the next step. The aldehyde product was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol, 1.1 eq.) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (80 mg, 2 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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:

triethylamine = 9:1) to give a colorless oil in 68 % yield (314 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.3 Hz, 1H), 7.34-7.28 (s, 1H), 7.05 (ddd, *J* = 8.2, 2.0, 0.8 Hz, 1H), 3.72 (s, 3H), 2.86-2.76 (m, 1H), 2.74 (dd, *J* = 12.8, 1.3 Hz, 1H), 2.23 (s, 3H), 1.96 (d, *J* = 12.9 Hz, 1H), 1.72 (ddd, *J* = 9.0, 5.0, 1.2 Hz, 1H), 1.34 (dd, *J* = 7.2, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 136.8, 132.2, 131.1, 131.0, 130.1, 128.5, 52.2, 51.0, 36.8, 30.5, 30.2, 18.2; FT-IR (neat): 2950, 2846, 2796, 1716, 1246, 736 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{13}H_{16}O_2N_1Cl_2$: 288.0552; Found: 288.0550.

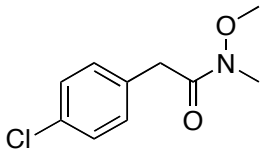
(1*S*,2*R*)-Methyl 2-(3,4-dichlorophenyl)-1-((methylamino)methyl)cyclopropanecarboxylate (ent-3-141)



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-Methyl 2-(3,4-dichlorophenyl)-1-((*E*)-styryl)cyclopropanecarboxylate **(ent-3-139)** (555 mg, 1.6 mmol, 1 eq.) was dissolved in dichloromethane (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Ozone was bubbled through the solution at -78 ^{o}C until the blue color of ozone persists and then oxygen was bubbled through the solution for 5 min. Triphenylphosphine was added to quench the reaction and stirred for 2 h while slowly warming to rt. The reaction mixture was concentrated under reduced pressure. The residue was purified *via* column chromatography (SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give crude aldehyde, which was taken to the next step. The aldehyde product was dissolved in

methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1 mL, 2 mmol, 1.1 eq.) and Ti(O-*i*Pr)$_4$ (1 mL, 3 mmol) and stirred at rt for 16 h. After the allotted time had passed, $NaBH_4$ (80 mg, 2 mmol) was added and the reaction was stirred for an additional 2 h. The reaction was quenched with H_2O (1 mL) and filtered through a short path of celite and rinsed with diethyl ether. The organic filtrate was diluted with diethyl ether and washed with water, then brine, and 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: triethylamine = 9:1) to give a colorless oil in 80 % yield (369 mg). Spectroscopic data is same as **3-141**.

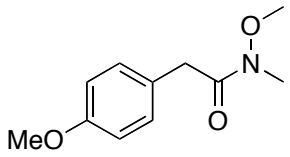
2-(4-chlorophenyl)-*N*-methoxy-*N*-methylethanamide: (3-108 c)



A solution of dimethylaluminium chloride (1.0 M solution in hexane) (18.5 g, 200 mmol, 5 eq.) (50 mL) was added through canula over 1h to a solution of methyl 2-(4-Chlorophenyl) ethanoate (7.38 g, 40 mmol, 1 eq.) and *N, O*-Dimethylhydroxylaminehydrochloride (7.8 g, 80 mmol, 2 eq.) in DCM (100 mL) at 0 ^oC. The reaction mixture was stirred for an additional 1h at 0 ^oC, and then warmed to rt and stirred overnight. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate colorless

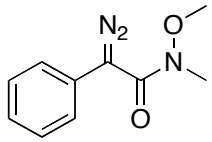
oil, 5.3 g (62%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.68 (s, 2H), 3.57 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (C), 133.1 (C), 132.2 (C), 130.4 (CH), 128.1(CH), 60.9(CH_3), 38.1(CH_2), 31.8 (CH_3). Spectroscopic data matches with the data reported previously in the Davies group.

***N*-Methoxy-2- (4-methoxyphenyl)-*N*-methylethanamide: (3-108 d)**



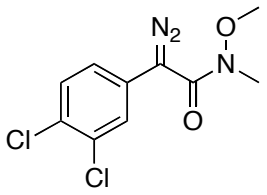
A solution of dimethylaluminium chloride (1.0M solution in hexane) (18.5 g, 200 mmol, 5 eq.) (50 mL) was added through canula over 1h to a solution of methyl 2-(4-methoxyphenyl) ethanoate (7.2 g, 40 mmol, 1 eq.) and *N, O*-Dimethylhydroxylaminehydrochloride (7.8 g, 80 mmol, 2 eq.) in DCM (100 mL) at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred overnight. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate colourless oil, 5.53 g (66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H,), 3.78 (s, 3H), 3.70 (s, 2H), 3.61 (s, 3H), 3.1 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9 (C), 129.8 (CH), 113.3 (CH), 126.5 (C), 60.7 (CH_3), 54.6 (CH_3), 37.8 (CH_2), 31.6 (CH_3). Spectroscopic data matches with the data reported previously in the Davies group.

2-Diazo-*N*-methoxy-*N*-methyl-2-phenylethanamide (3-109 a)



A solution of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) (0.53 mL, 3.6 mmol, 1.8 eq.) dissolved in MeCN (10 mL) was added through syringe pump over 1h to a solution of 2-*N*-methoxy-*N*-methylethanamide (1) (360 mg, 2 mmol, 1 eq.) and *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (502 mgs, 2.2 mmol, 1.1 eq.) in MeCN (10 mL) at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred for additional 1 h. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 3:1 hexane/Et_2O as eluant to isolate colorless oil, 398 mg (97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.19(t, J = 7.0 Hz, 1H), 3.67 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (C), 129.2 (CH), 127.7 (C), 126.5 (CH), 126.0 (CH), 61.6 (CH_3), 34.6 (CH_3). IR ($CHCl_3$): 2972, 2932, 2074, 1635, 755 cm^{-1}. LRMS (EI) *m/z* (relative intensity): 151.1(100), 105.0(92), 77(47). HRMS (EI) *m/z calcd* for $[C_{10}H_{11}N_3O_2]^+$ 205.084; Found: 205.084.

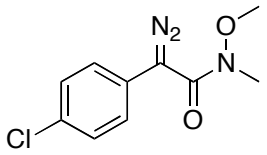
2-Diazo-2- (3,4-dichlorophenyl)-*N*-methoxy-*N*-methylethanamide (3-109 b)



A solution of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) (274 mg, 1.8 mmol, 1.8 eq.) dissolved in MeCN (10 mL) was added through syringe pump over 1h to a solution of 2-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methylethanamide (2) (248 mg, 1 mmol, 1 eq.) and *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (251 mgs, 1.1 mmol, 1.1 eq.) in MeCN (10 mL) at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred at rt overnight. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate colorless oil, 87 mg (32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.34 (d, J = 10.5 Hz, 1H), 7.2 (d, J = 7.5 Hz, 1H), 3.62 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0 (C), 133.5 (C), 131.0 (CH), 130.1 (C), 128.3 (C), 127.3 (C), 124.6 (CH), 61.7(CH_3), 34.5 (CH_3). IR ($CHCl_3$): 2074, 1669, 1632, 1496, 1449, 1407, 1360, 1238 cm^{-1}. LRMS (EI) *m/z* (relative intensity):

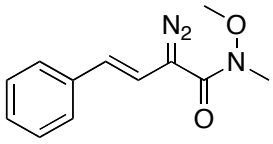
172.9(100), 144.9(54). HRMS (EI) *m/z calcd* for $[C_{10}H_9Cl_2N_3O_2]^+$ 273.006; Found 273.006.

2-(4-Chlorophenyl)-2-diazo-*N*-methoxy-*N*-methylethanamide (3-109 c)



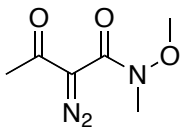
A solution of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) (7.61 g, 50 mmol, 2 eq.) dissolved in MeCN (10 mL) was added through syringe pump over 1h to a solution of 2-(4-chlorophenyl)-*N*-methoxy-*N*-methylethanamide (3) (5.34 g, 25 mmol, 1 eq.) and *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (6.28 g, 27.5 mmol, 1.1 eq.) in MeCN (100 mL) at 0°C. The reaction mixture was stirred for an additional 1h at 0°C, and then warmed to rt and stirred overnight. The reaction mixture quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate colorless oil, 2.13 g (35%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 9.0 Hz, 2H,), 7.34 (d, J = 9.0 Hz, 2H), 3.69 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9 (C), 131.4 (C), 128.7 (CH), 126.4 (CH), 125.7 (C), 61.0 (CH_3), 33.9 (CH_3).

(*E*)-2-Diazo-*N*-methoxy-*N*-methyl-4-phenylbut-3-enamide (3-109 d)



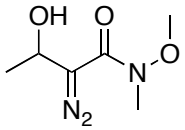
A solution of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) (548 mg, 3.6 mmol, 1.8 eq.) dissolved in MeCN (10 mL) was added through syringe pump over 1h to a solution of (*E*)-*N*-methoxy-*N*-methyl-4-phenylbut-3-enamide (410 mg, 2 mmol, 1 eq.) and *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (433 mg, 2.2 mmol, 1.1 eq.) in MeCN (10 mL) at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred for 1 h. The reaction mixture quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate colored oil, 244 mg (53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.7 (d, *J* = 16.5 Hz, 1H), 5.84 (d, *J* = 16.5 Hz, 1H), 3.50 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 137.2 (C), 128.9 (CH), 127.1 (CH), 126.2 (CH), 121.9 (CH), 113.9 (CH), 61.6 (CH_3), 34.5 (CH_3). IR ($CHCl_3$): 3242, 3057, 3023, 2973, 2937, 2073, 1636, 1408, 1379, 1302, 1203, 948, 748 cm^{-1}.

2-Diazo-*N*-methoxy-*N*-methyl-3-oxobutanamide (3-109 e)



A solution of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) (1.37 g, 9 mmol, 1.8 eq.) dissolved in MeCN (10 mL) was added through syringe pump over 1h to a solution of N-methoxy-*N*-methyl-3-oxobutanamide (725 mgs, 5 mmol, 1 eq.) and *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.25 g, 5.5 mmol, 1.1 eq.) in MeCN (15 mL) at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred overnight. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into diethyl ether, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 3:1 hexane/Et_2O as eluant to isolate colored oil, 211 mg (25%). ^{1}H NMR (500 MHz, $CDCl_3$): 3.53 (s, 3H), 3.04 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.6 (C), 162.2 (C), 61.4 (CH_3), 33.3 (CH_3), 28.7 (CH_3). LRMS (EI) *m/z* (relative intensity): 61 (100%), 111 (98%), 60 (95%). HRMS (EI) *m/z* Calcd for $[C_6H_9N_3O_3]^+$ 171.0643; Found 171.0643.

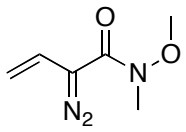
2-Diazo-3-hydroxy-*N*-methoxy-*N*-methylbutanamide (3-109 f)



To a solution of 2-diazo-*N*-methoxy-*N*-methyl-3-oxobutanamide (9) (171 mg, 1mmole, 1 eq.) dissolved in EtOH (20 mL), sodium borohydride ($NaBH_4$) (41 mg, 1.1 mmol, 1.1 eq.) was added in portions at 0 ^{o}C. The reaction mixture was stirred for an additional 1h at 0 ^{o}C, and then warmed to rt and stirred for 1h. The reaction mixture was quenched with water and concentrated *in vacuo*. Extracted twice into DCM, washed with water, dried over $MgSO_4$, Purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as

eluant to isolate colorless oil, 47 mg (27%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.01 (q, *J* = 2.5 Hz, 1H), 3.63 (s, 3H), 3.17 (s, 3H), 1.33 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (C), 123.9 (C), 63.8 (CH), 61.2 (CH_3), 33.9 (CH_3), 18.8 (CH_3).

2-Diazo-*N*-methoxy-*N*-methylbut-3-enamide (3-109 g)



A solution of $POCl_3$ (0.1 mL, 10 mmol, 2 eq.) in DCM (10 mL) was added by syringe pump over 1h to a solution of 2-diazo-3-hydroxy-*N*-methoxy-*N*-methylbutanamide (10) (865 mg, 5 mmol, 1 eq.) and Et_3N (3.48 mL, 25 mmol, 5 eq.) in DCM (20 mL) at -5 ^{o}C. The reaction mixture was stirred at -5 ^{o}C for an additional 1h, allow it to warm up to rt and stirred overnight. The resultant reaction mixture was diluted with DCM, washed with water dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate a colored oil, 770 mg (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.41 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 4.6 (d, *J* = 17.0 Hz, 1H), 3.62 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 122.9 (CH), 106.3 (CH_2), 61.7 (CH_3), 34.6 (CH_3). LRMS (EI) *m/z* (relative intensity): 55 (100%), 67 (33%), 68 (24%), 95 (92%), 155 (22%); HRMS (EI) *m/z Calcd* for $[C_6H_9N_3O_2]^+$ 155.068; Found 155.069.

Chapter 4: Synthesis of TAK1 Kinase Inhibitors as potential anticancer agents.

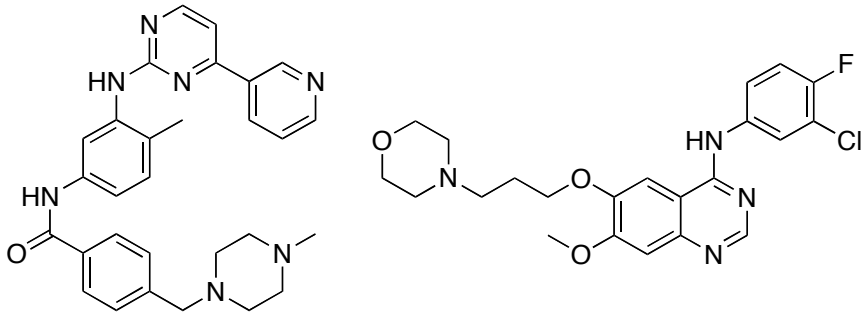
4.1 Introduction

4.1.1 Cancer Therapy

Cancer, uncontrolled growth of cells, is the cause of 13% of all deaths[1]. Breast cancer is the most common cancer among American women. Currently, one in eight women is at risk of contracting breast cancer in her lifetime. It is estimated that over 2 million new cases of invasive breast cancer were diagnosed in 2010 in the United States alone.[2] According to the American Cancer Society latest estimates, around 40,000 women died because of breast cancer in 2010 in the U.S. The cancer related death rate has decreased since 1990, due to advancements in the therapeutics, early detection through screening, and increased awareness.[3,4] However it is still a significant problem that could be solved by identifying novel therapeutic targets and developing chemotherapeutic agents.

There is considerable interest in the development of anticancer and anti-inflammatory drugs that target specific protein kinases. In the human genome, 518 different kinases have been identified to date.[5] Protein kinases are attractive targets for drug discovery due to their diversity and role in cell signaling. The discovery of therapeutic agents that could selectively inhibit the activity of one protein kinase over the other is difficult. In addition, targeting one specific kinase in a biochemical pathway may

not lead to the desired therapeutic effect whereas targeting many kinases may lead to toxicity and undesirable side effects. Only a few selective kinase inhibitors such as **Imatinib** and **Gefitinib** have been identified to be effective in clinical use (Fig. 4.1). **Imatinib**[6] (**4-1**) is a tyrosine kinase inhibitor, which is currently marketed by Novartis as Gleevec in the U.S. In 2010, Federal Drug Administration (FDA) approved it for treating ten different kinds of cancers, including chronic myelogenous leukemia (CML),[7] gastrointestinal stromal tumors (GISTs) and a number of other malignancies. **Gefitinib** (**4-2**)[8] is a epidermal growth factor receptor (EGFR) inhibitor currently marketed by AstraZeneca for treating pulmonary adenocarcinoma and many other types of cancer.



4-1
Imatinib

4-2
Gefitinib

Figure 4.1: Selective kinase inhibitors in clinical use.

These compounds illustrate the value of targeting protein kinases in cancer drug development. There is a considerable need for novel and improved drugs that target one particular kinase over a myriad of other protein kinases. Such drugs would have significant impact on cancer therapy.

The Davies' group has significant experience in the development of new methods for the rapid construction of potential therapeutic agents. In collaboration with Prof. Andrei Bakin at Roswell Park Cancer Institute at Buffalo, we aimed to develop pharmaceutical agents that could be used in cancer therapy.

4.2 Background

4.2.1 Transforming growth factor-beta (TGF-β) and NFkB pathway in breast cancer.

Advanced or metastasis breast cancers are resistant to conventional anti-cancer therapy and are incurable due to the presence of elevated levels of TGF-β and NF-kB in tumor cells. These two biochemical pathways are implicated in cancer progression and metastases (transfer of disease from one part of the body to other parts *via* the blood stream) and are considered as therapeutic targets for treatment of osteolytic tumors.[9] Recently, several studies [101,112] have shown that **T**ransforming growth factor-β-**A**ctivated protein **K**inase **1** (**TAK1**) can mediate oncogenic activities of the TGF-β– NF-kB axis in breast cancer progression. Bakin *et al.* showed that disruption of **TAK1** signaling blocks breast carcinoma invasion, angiogenesis (growth of a new network of blood vessels) and metastasis in preclinical models.[13] It was also reported that blocking **TAK1** could prevent bone destruction by breast carcinoma cells and overcome resistance to chemotherapy in the treatment of pancreatic cancer. Through a series of experiments, it was also found that depleting TAK1 would enhance induced apoptosis (programmed cell death) in tumor cells.[14]

TAK1 is a member of the mitogen activated kinase kinase kinase (MAK3) family. Mitogen-activated protein kinases (MAP) relay, amplify and integrate signals from a variety of extracellular stimuli, thereby regulating a cell's response to its environment. Any chemical substance (Mitogen) can activate the MAP kinase *via* a signaling cascade.[15] It was also found that **TAK1** affects the bone microenvironment and tumor angiogenesis *via* Matrix metalloproteinase (**MMP-9**) production in human carcinoma cells.[13] The therapeutic agents that could suppress the production of MMP-9 or inhibit TAK1 activity have potential to decrease tumor vasculature and metastases. (Fig. 4.2)

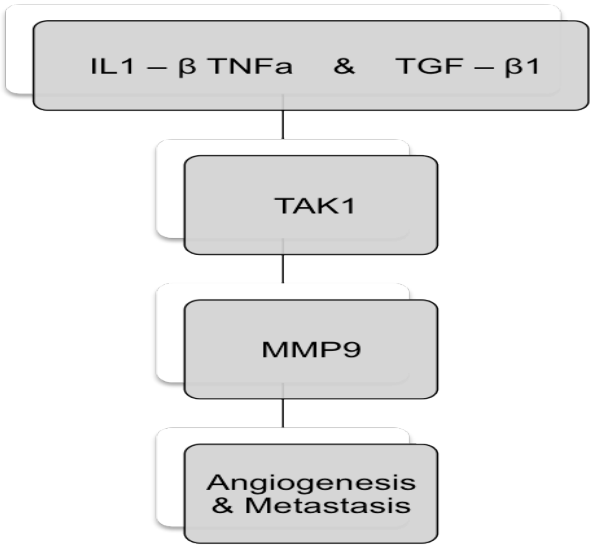


Figure 4.2: Signaling cascade for metastasis cancer.

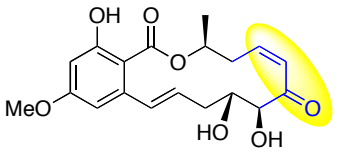
TAK1 is known to rely on an additional binding protein TAB1 for activation. In 2005, a crystal structure of TAK1 bound to TAB1 was solved.[16] It was also found that mutation of a specific cysteine residue (Cys174) present in the active site of TAK1, inactivates TAK1 by altering the ATP binding capacity. Although the exact structural

requirement for TAK1 inhibition activity is not known, it was hypothesized that the therapeutic agent will bind (either reversible or irreversible) to Cys174 covalently to inhibit its' activity.[16]

The primary aim of this project was to develop novel approaches for the synthesis of small molecule therapeutics that can inhibit TAK1 kinase activity.

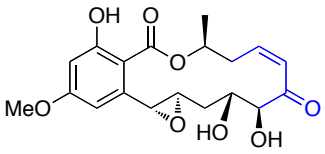
4.2.2. Resorcylic acid lactones (RALs) as TAK1 inhibitors

Recent studies have revealed that a specific class of natural products known as resorcylic acid lactones (Fig. 4.3) was found to display selective kinase inhibition.[17,18,19,20] Resorcylic acid lactones (RALs) are mycotoxins produced by a variety of different fungal strains *via* polyketide biosynthesis.[21] It was identified through high-throughput screening of natural products that some of the natural resorcylic acid lactones (**4-3** to **4-8**) can inhibit protein kinase activity.[17] These RALs were also found to be transcription factor modulators and Heat shock protein (HSP90) inhibitors.[22]



LL-Z1640-2
5-(*Z*)-7-Oxozeaenol
TAK-1 inhibitor (IC_{50}= 8.1 nM)

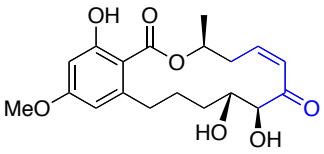
4-3



Hypothemycin

MAP Kinase inhibitor (IC_{50}= 17-90 nM)

4-4



LL-783,277

MEK inhibitor (IC_{50}= 4 nM)

4-5

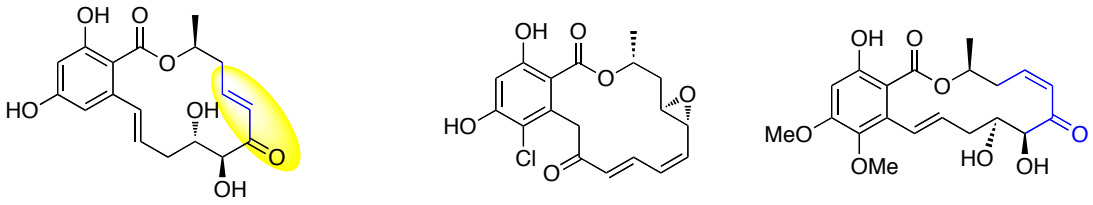


Figure 4.3: Selected members of the resorcylic acid lactone family of natural products and their inhibition activity.

5-(*Z*)-7- Oxozeaenol (**4-3**) is a natural RAL that was isolated from a culture broth of fungal strain f6024 in 1978.[23] Even though this RAL have been known for over 50 years, their selective kinase inhibition was not discovered until recently. 5-(*Z*)-7-Oxozeaenol (**4-3**) was found to be a potent TAK1 inhibitor (IC_{50} 8.1 nM) and more efficacious than its close analogue, hypothemycin (**4-4**) (IC_{50} 101 nM).[17] Moreover, 5-(*Z*)-7- Oxozeaenol (**4-3**) is more potent (IC_{50} 8.1 nM) than its *trans* isomer 5-(*E*)-Oxozeaenol (**4-6**) (IC_{50} 1.2 μM) towards TAK1 inhibition. This indicates that the *cis* geometry of the enone is a required functionality for the inhibition activity. It was also noted that the nature of the benzylic position did not show any affect on their respective selectivities.

Hypothemycin (**4-4**) was isolated in 1980[24,25] and has generated considerable interest because it inhibits Ras-MEK signaling and cytotoxic towards cancer cells.[26,27,28,29] Radicinol (**4-7**) also shows TAK1 inhibition activity at 10 μM concentrations.

Although 5-(*Z*)-7-oxozeaenol (**4-3)** showed nM TAK1 inhibition activity, its metabolic instability preclude its use as a potential anti-inflammatory drug. Recently Shen and co-workers reported an interesting study on the metabolic stability of this compound. It was shown that addition of a methyl group at the C4 position on 5-(*Z*)-7-oxozeaenol (**4-9)** improved its stability while retaining its anti-inflammatory activities.[30] In addition, further modification of lactone ER-803064 (**4-9**) at the C14 position with substituents **4-10** and **4-11** led to the improved *in vivo* potency in anti-inflammatory assays.[31] An extensive medicinal chemistry effort led to the discovery of the analogue **4-12** with *N*-alkyl substitution that was found to be potent *in vitro* and orally active *in vivo* in anti-inflammatory assays. This analogue is currently a clinical candidate.[32]

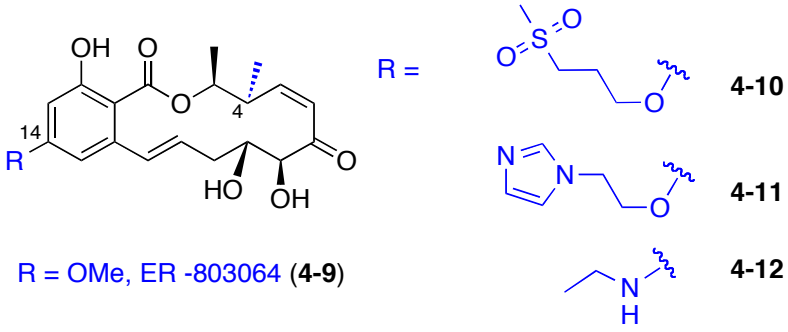
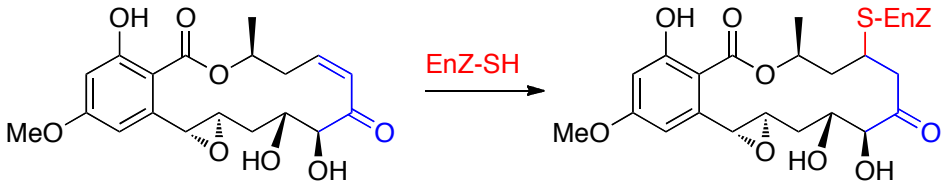


Figure 4.4: Derivatives of 5-(*Z*)-7-oxozeaenol.

The exact mechanism of action of these natural products on TAK1 is not known. But it was speculated that 5-(*Z*)-7-oxozeaenol (**4-3)** might bind to TAK1 there by competitively inhibiting adenosine-5'-triphosphate (ATP) binding leading the blockage of pro-inflammatory signaling. It was also believed that TAK1 inhibition occurs *via* a covalent modification. A number of kinases (46) were found to possess cysteine in their

ATP binding pocket. Hence, it was suggested that the α,β-unsaturated ketone moiety in 5-(*Z*)-7-oxozeaenol (**4-3)** might act as a michael acceptor and binds covalently to protein nucleophiles such as cys-thiolate (**4-13**), thereby deactivating the enzyme irreversibly. Despite the lack of obvious similarities between the RALs and ATP, these natural products were shown to irreversibly bind to the ATP binding pocket.[18,33]

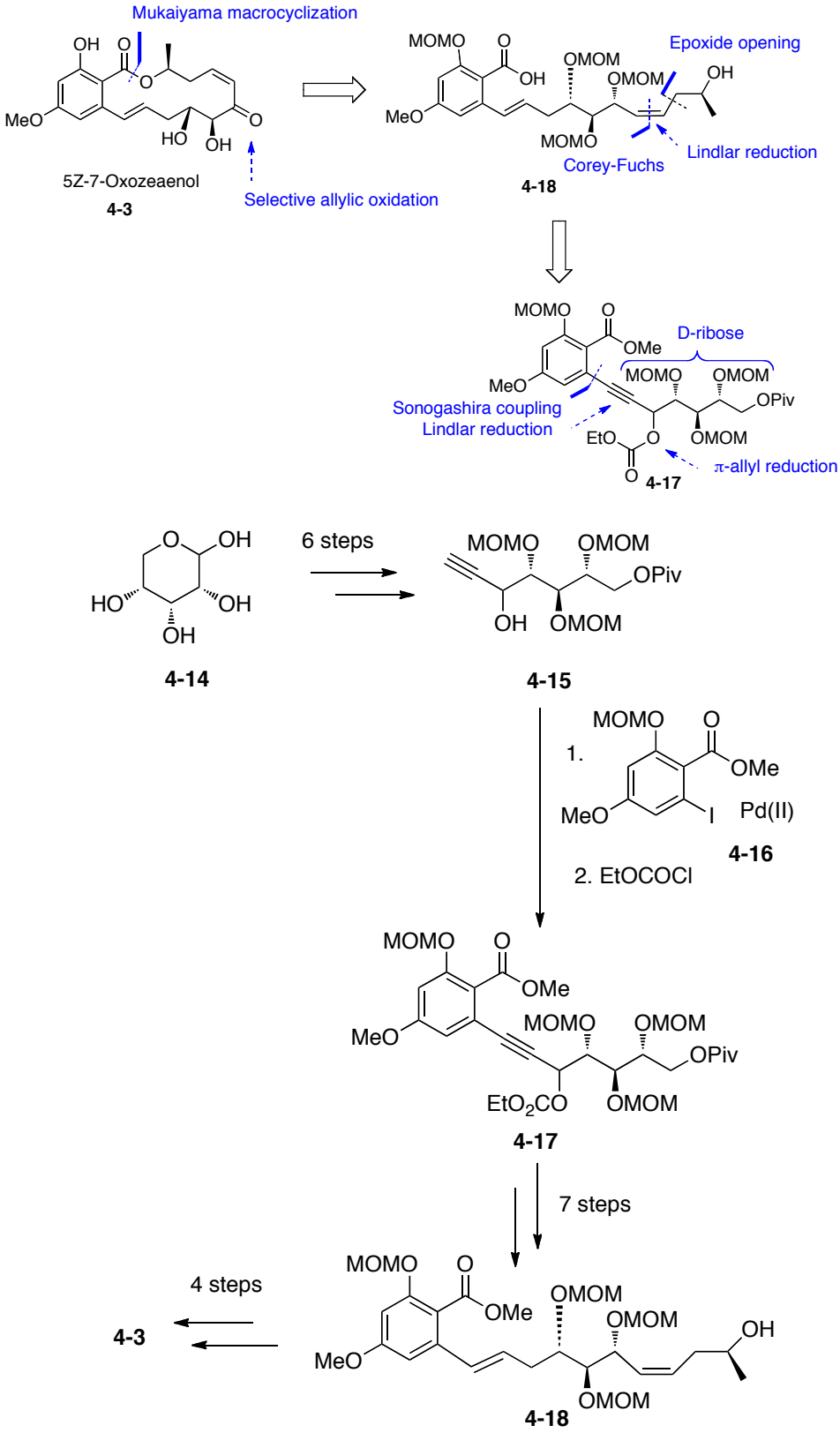


4-3 **4-13**

Figure 4.5: Michael addition of a cys-thiol to a protein kinase.

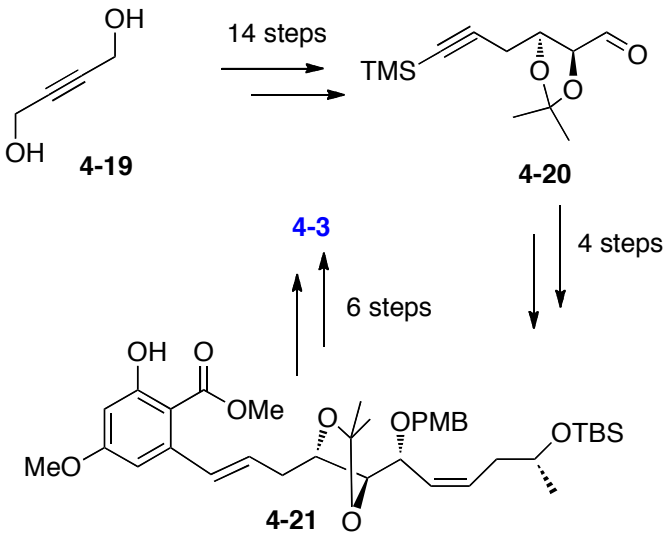
4.2.3 Total synthesis of 5-(*Z*)-7- Oxozeaenol

The total synthesis of 5-(*Z*)-7- Oxozeaenol (**4-3**) and its analogues is challenging because of *cis* enone functionality. Indeed, it has been shown in previous total syntheses that *cis* enones are prone to isomerize to their corresponding thermodynamically stable *trans* isomers. Moreover, cis-enones are susceptible to nucleophilic attack. Several total syntheses of 5-(*Z*)-7- Oxozeaenol (**4-3**) have been reported since its isolation in 1978.


Mukaiyama macrocyclization
Epoxide opening
Lindlar reduction
Corey-Fuchs
Selective allylic oxidation
5Z-7-Oxozeaenol
4-3
4-18
D-ribose
Sonogashira coupling
Lindlar reduction
π-allyl reduction
4-17
6 steps
4-14
4-15
1.
2. EtOCOCl
Pd(II)
4-16
4-17
7 steps
4 steps
4-3
4-18

Scheme 4.1: Retro and forward synthetic approach of Tatsuta *et al*.

Tatsuta *et al.* reported the first total synthesis of 5-(*Z*)-7-Oxozeaenol (**4-3**) in 2001.[34] The total synthesis began with the synthesis of alkyne **4-15** from D-ribose (**4-14**) in 6 steps. Alkyne **4-15** was then coupled with aryl iodide **4-16** to form ester **4-17**. Further functional group modification yielded the corresponding alcohol **4-18**. The required *Z*-olefin was generated by reduction of the alkyne in the presence of the Lindlar catalyst. Macrocyclization of **4-18** followed by deprotection of the diol and oxidation to form the *cis*-enone completed the synthesis in 18 linear steps (Scheme 4.1).



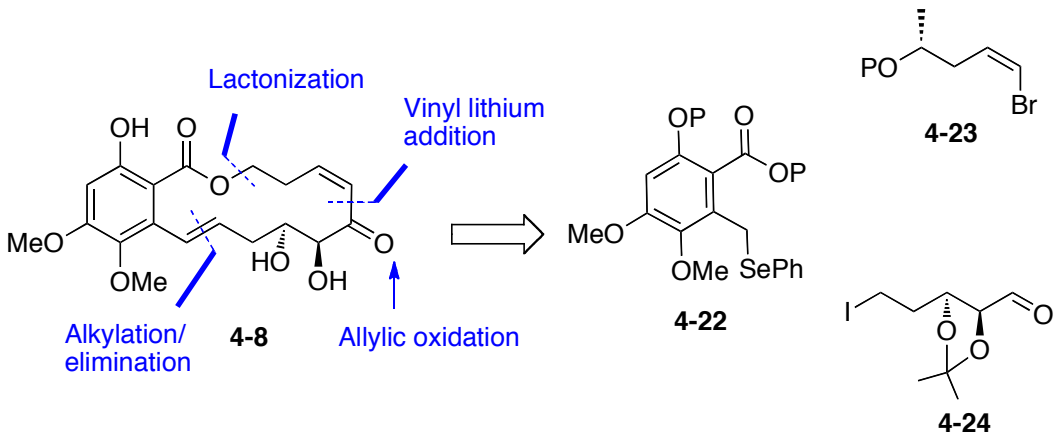
Scheme 4.2: Synthetic approach of Selles and Lett.

Subsequently, Selles and Lett reported the second total synthesis of **4-3** in 2002[35] (scheme 4.2). The overall strategy employed was similar to Tatsuta's synthesis, but the initial chirality was introduced by a Sharpless asymmeric epoxidation/epoxide opening

sequence. As such, the diol **4-19** was converted to the aldehyde **4-20** in 14 steps. The required *cis* alkene was incorporated onto the aldehyde **4-20** and a Stille coupling was used to join this fragment to the aromatic ring to form the intermediate **4-21**. Macrolactonization of intermediate **4-21** followed by a Mitsunobu inversion to set the correct stereo center. A series of functional group interconversions completed the synthesis in 27 linear steps. Again, because of the stepy linear sequence, this approach is not ideal for the rapid synthesis of analogues.

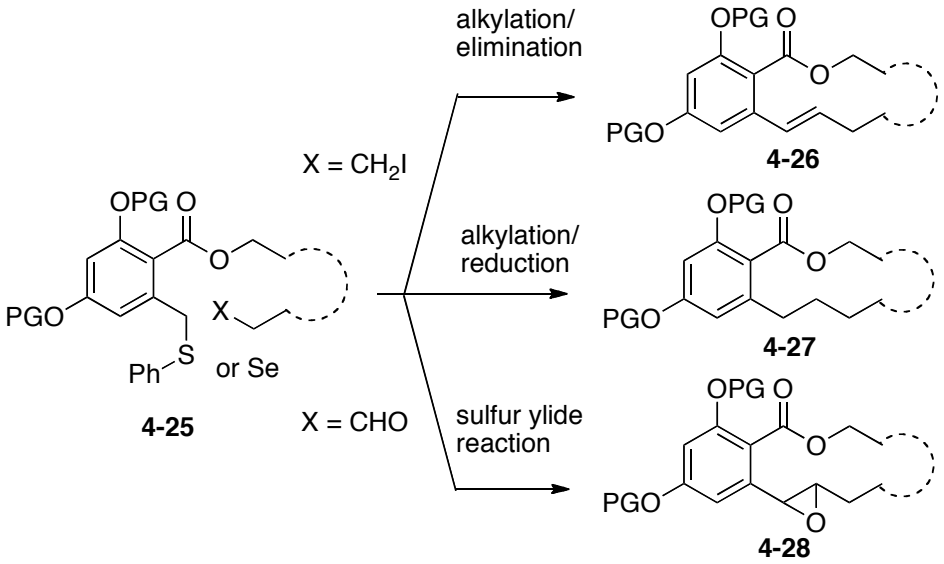
Marquez *et al.* efforts to synthesize 5-(*Z*)-7- Oxozeaenol (**4-3**) by ring closing metathesis as a key step, was unsuccessful due to formation of C-9 epimeric mixtures.[36]

While planning our synthesis of oxozeaenol analogues, Winssinger published a modular synthesis of radicicol A (**4-8**) from fragments **4-22**, **4-23** and **4-24** (Scheme 4.3).[19] In this approach, the aromatic fragment (**4-22**) and iodo aldehyde (**4-24**) were coupled using an alkylation/elimination strategy. Even though this route is also suitable for the synthesis of analogues, this approach is not practical as it involves fluorous isolation technology that is not widely utilized. The required *cis* olefin was obtained by stereospecific isomerization of *trans*-vinylborolane to *cis*-vinyl bromide [37](Scheme 4.3).



Scheme 4.3: Winssinger's initial convergent approach.

Winssinger *et al.* later developed a general approach to access a broad range of RALs containing an entire spectrum of functionalities (Scheme 4.4). Starting from common benzylic sulfide intermediate (**4-25**), macrocycles bearing an alkane **(4-27)** (*via* alkylation/reduction strategy), alkene **(4-26)** (*via* alkylation/elimination strategy)**,** or epoxide **(4-28)** (*via* sulfur ylide strategy) at the benzylic position were synthesized.[38]



Scheme 4.4: Winssinger's divergent approach to the synthesis of various RALs analogues.

Barrett *et al.* published a biomimetic total synthesis of 5-(*Z*)-7-Oxozeaenol (**4-3**) *via* a consecutive macrocyclization and transannular aromatization strategy without using

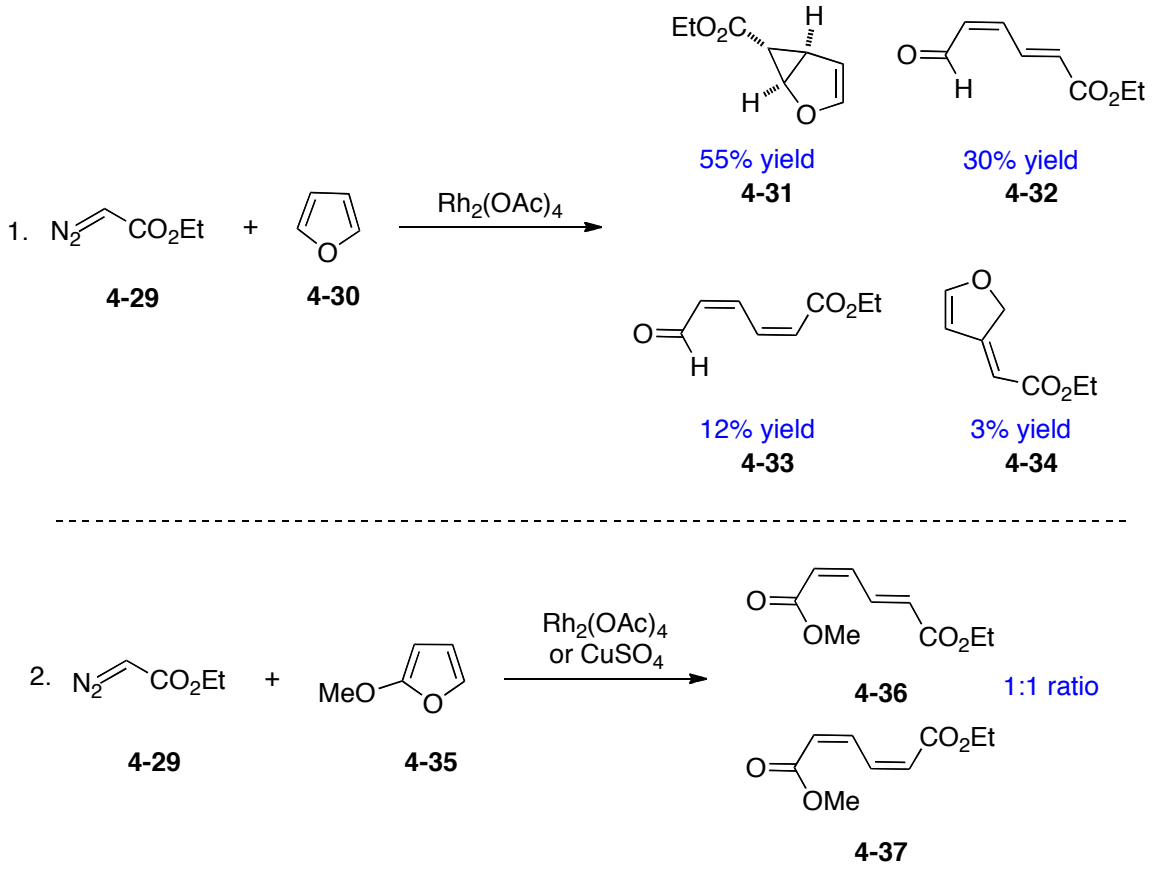
protecting groups.[39] A total synthesis of 5-(*Z*)-7-Oxozeaenol utilizing an intramolecular Nozaki-Hiyama-Kishi reaction was also reported.[40]

It should be noted that in all the previous syntheses, the *cis-enone* functionality was introduced at the latter stage of the synthesis in order to avoid isomerization of *cis-enone*.

4.2.4 Carbenoid-induced ring-fragmentation of furans – A method for synthesis of acyclic RAL analogues.

A diverse range of products can be produced in the reactions between rhodium stabilized carbenoids and heterocyclic compounds. High asymmetric induction can be achieved by controlling the approach of the heterocycle to the rhodium stabilized carbenoid. The type of products formed depends on many factors, such as the structure of the carbenoid and the heterocycle as well as the nature of the catalyst, and reaction conditions.[41]

In 1986, Wenkert *et al.* reported the reaction of ethyl diazoacetate (**4-29**) with furan (**4-30**), in which four products were observed [42,43] (Scheme 4.5, eq. 1). The major product was an *exo*-cyclopropane carboxylate (**4-31**), but two isomeric 1,4-diacyl-1,3-butadienes (**4-32**) and (**4-33**) and alkylation product **4-34** were also formed.

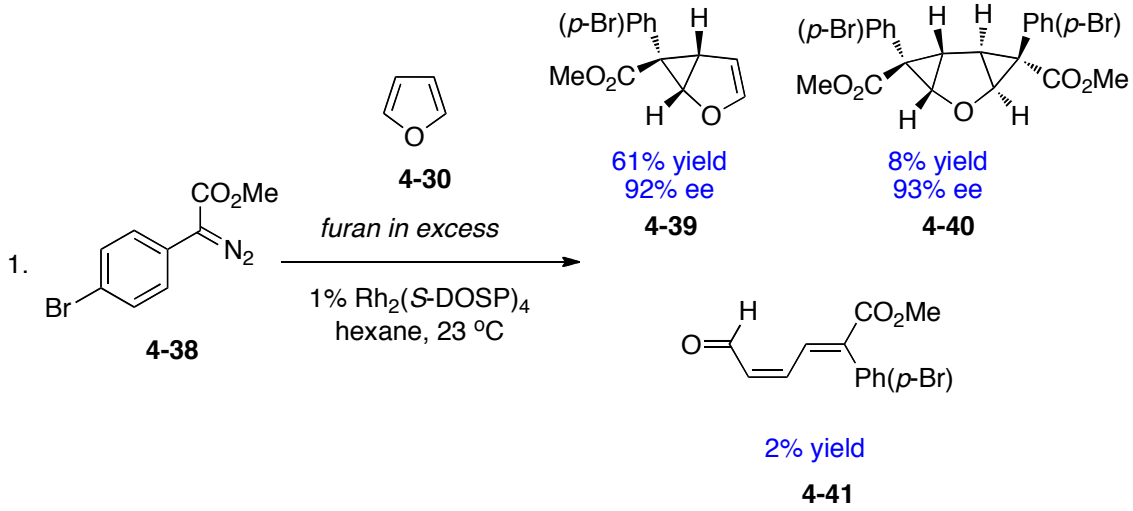


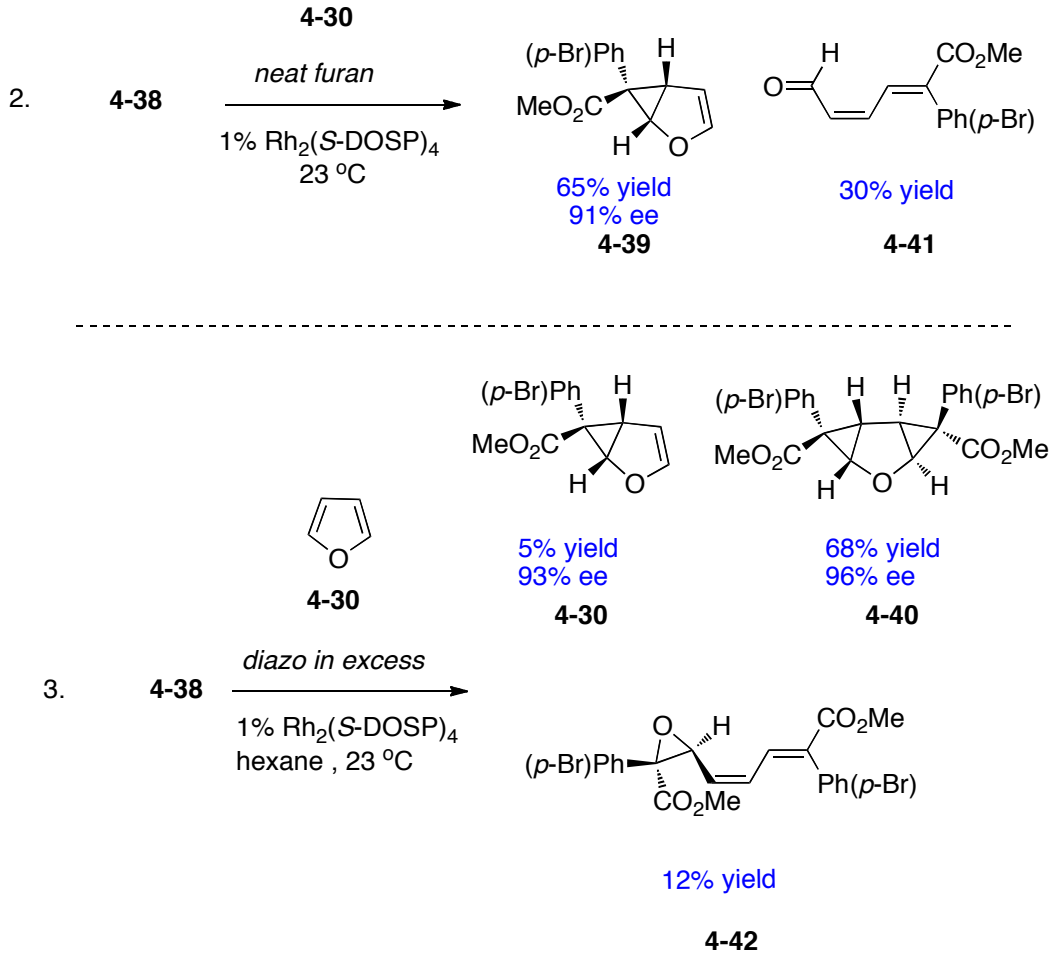
Scheme 4.5: Reaction of acceptor diazo compound with furan and an activated furan.

When the furan ring was activated by introducing an electron-donating group such as methoxy or siloxy at the 2-position, the ring opening products **4-36** and **4-37** were exclusively formed in a 1:1 ratio in the presence of acceptor diazo compound **4-29** (Scheme 4.5, eq. 2).

The product ratio and geometry were highly dependent on the stoichiometry of the reagents, the electron density of the furan, and the type of catalyst used.[44,45] It was observed that the *trans* isomer was favored in the presence of $CuSO_4$.[46]

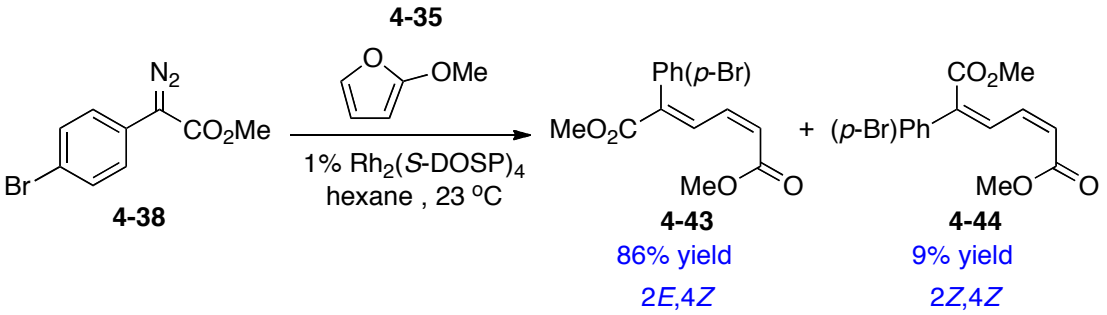
The range of products formed in the reaction of furan (**4-30**) with methyl 2-(4-bromophenyl)-2-diazoacetate (**4-38**) in the presence of Rh_2(*S*-DOSP)$_4$ also depended on the reaction conditions (Scheme 4.6).[47] If furan was used in excess, only a trace amount of the ring opening product **4-41** was observed (Scheme 4.6, eq. 1). In neat furan, the formation of bis-cyclopropanation product **4-40** was not only suppressed but the amount of ring opening product **4-41** increased from 2% to 30% (Scheme 4.6, eq. 2). On the other hand, If the diazo compound (**4-38**) was used in excess, no ring-opening product **4-41** was observed (Scheme 4.6, eq. 3). This indicates that donor-acceptor carbenoids display a different reactivity profile compared to carbenoids derived from acceptor diazo compounds (Scheme 4.6).





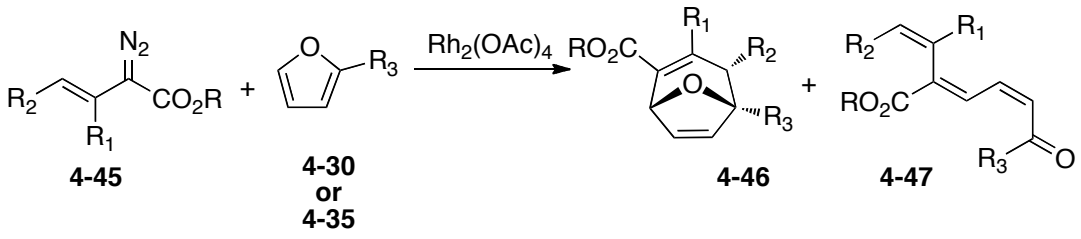
Scheme 4.6: Reaction of donor-acceptor diazo compounds with furan.

Interestingly, the reaction of donor-acceptor diazo compounds **4-38** and **4-45** with the activated furan **4-35** led to unraveling of the heterocycle.[48-50] The reaction of 2-methoxy furan (**4-35**) with diazo **4-38** in the presence of Rh_2(*S*-DOSP)$_4$ provided exclusively the ring opening products with very high selectivity (10:1) in favor of the 2*E*, 4*Z* configuration (**4-43**) over the 2*Z*, 4*Z* configuration (**4-44**) (Scheme 4.7).



Scheme 4.7: Reaction of donor-acceptor diazo compounds with activated furans.

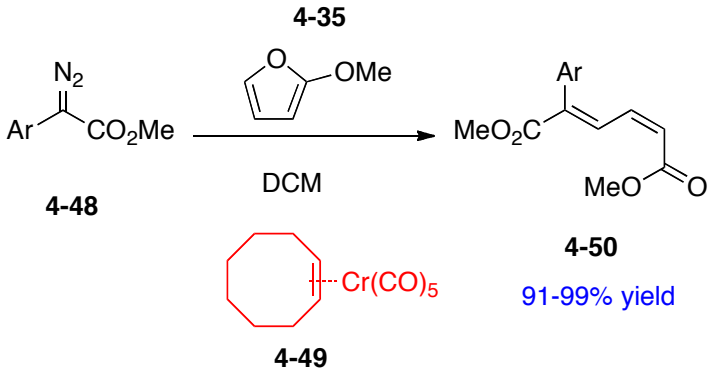
The reaction of vinyl diazoacetate **4-45** with furan (**4-30**) normally generates 8-oxabicyclo- [3.2.1] octane **4-46**, but in the presence of an activated furan such as methoxy furan **4-35**, the triene **4-47** is formed as the exclusive product (Scheme 4.8).[50,51]



R	R_1	R_2	R_3	4-46:4-47
Et	H	CO_2Et	OMe	0:92
Me	OTBS	H	H	90:0

Scheme 4.8: Reaction of vinyl diazo compounds with activated furans.

In 2004, Dotz *et al.* showed that pentacarbonyl (η_2-*cis*-cyclooctene) chromium (0) (**4-49**) could also catalyze the ring-opening reaction of 2-substituted furans. Unsubstituted furans cannot be decomposed in the presence of Cr (0). One drawback of such strategy is the accessibility of the catalyst (Scheme 4.9).[52,53]

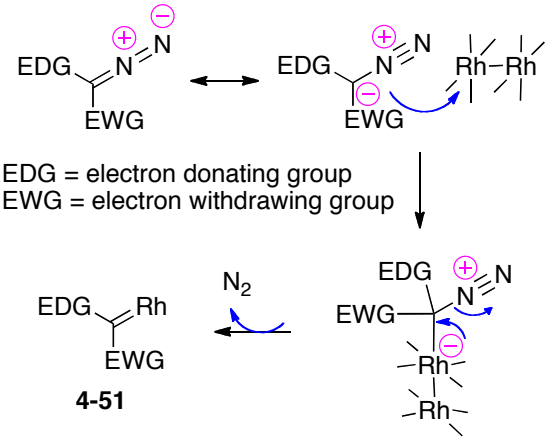


Scheme 4.9: Furan unraveling reaction in the presence of Cr (0).

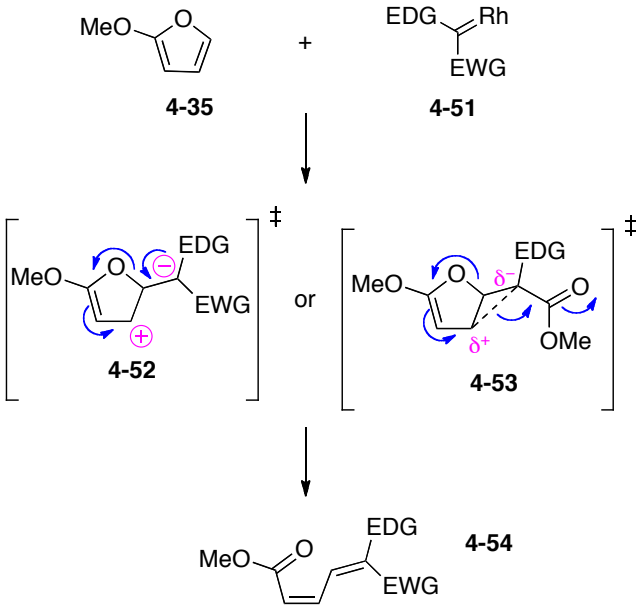
4.2.5 The mechanism of the furan unraveling reaction

Two major pathways are possible in the reaction of a carbenoid generated from aryldiazoacetate compound and 2-methoxy furan. The reaction could proceed either through a concerted non-synchronous cyclopropanation or *via* a zwitterionic intermediate (Scheme 4.10). Once rhodium the carbenoid **4-51** is generated (Scheme 4.10, eq. 1), it can attack the two position of the furan (electrophilic addition) leading to a zwitterionic intermediate **4-52**, which would decompose to dienone **4-54** *via* cycloreversion. Alternatively, cyclopropane **4-53** could also rearrange to the corresponding diene **4-54** *via* a concerted non-synchronous pathway (Scheme 4.10, eq. 2).

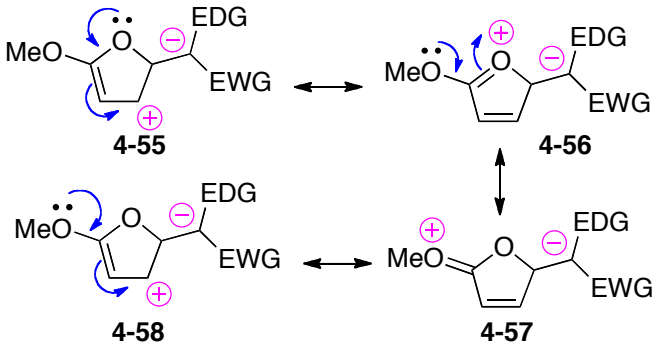
1.


EDG
N
N
EWG
EDG
N
N
Rh–Rh
EWG
EDG = electron donating group
EWG = electron withdrawing group
EDG
Rh
EWG
4-51
N2
EDG
N
N
EWG
Rh
Rh

2.


MeO
O
+
EDG
Rh
EWG
4-35
4-51
MeO
O
EDG
EWG
4-52
or
MeO
O
EDG
δ−
O
δ+
OMe
4-53
MeO
O
EDG
EWG
4-54

3.

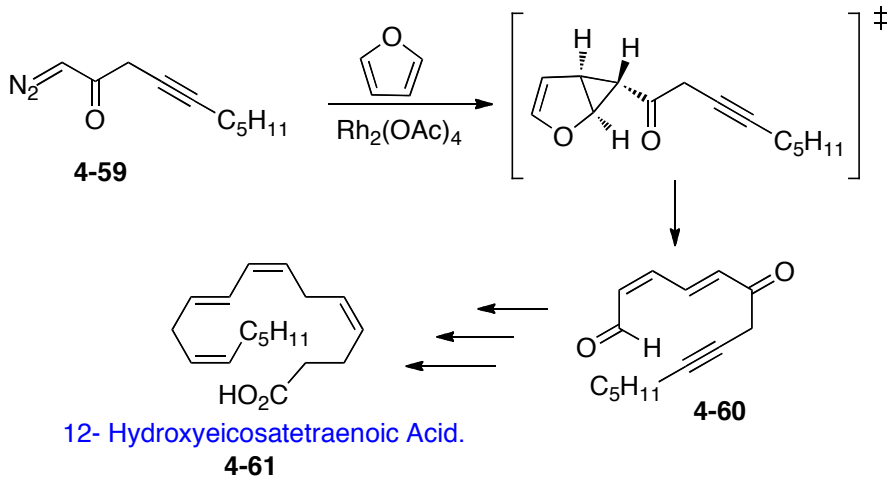

MeO
O
EDG
EWG
4-55
MeO
O
EDG
EWG
4-56
MeO
O
EDG
EWG
4-58
MeO
O
EDG
EWG
4-57

Scheme 4.10: Generation of rhodium carbenoid (eq. 1), possible intermediates in the furan unraveling reaction (eq. 2), resonance stabilization of the zwitterionic intermediate (eq. 3).

It appears that the major driving force for the formation of ring opening products in the furan unraveling reaction is the formation of a new carbonyl bond (C=O), which has an energy of 172 kcal/mol, compared to rearomatization stabilization of furan which only has an energy of 16.2 kcal/mol. Recent DFT calculations showed that the reaction of 2-methoxy furan with aryl diazoacetate derivatives proceeds *via* a zwitter ionic intermediate and the newly formed double bond retains its *cis* configuration. Nevertheless, in the case of reactions of acceptor, acceptor-acceptor diazo compounds with unactivated furans, a concerted non-synchronous cyclopropane intermediate cannot be ruled out.

In conclusion, the reaction of acceptor and acceptor-acceptor diazo compounds with furan proceeds through a concerted non-synchronous cyclopropanation mechanism, whereas the reaction of the donor-acceptor diazo compounds with 2-methoxy furan proceeds through a zwitterionic intermediate due to the possibility of more number of resonance structures **4-55** to **4-58**.

4.2.6 Synthetic utility of the furan unraveling reaction



Scheme 4.11: Application of the furan unraveling reaction in the total synthesis of 12-hydroxyeicosatetraenoic acid.

The furan unraveling reaction was exploited in the synthesis of a leukotriene, 12-hydroxyeicosatetraenoic acid **4-61**.[54] Diazo alkynyl ketone **4-59** was reacted with furan in the presence of rhodium acetate to give the intermediate cyclopropane. Dienone **4-60** was formed after ring opening of cyclopropane, which was then converted to tetraene **4-61** in few synthetic steps. (Scheme 4.11). Although carbenoid induced furan ring opening reaction was utilized as a key step in the complex molecule synthesis, these *cis-enones* were never explored for any therapeutic use earlier.

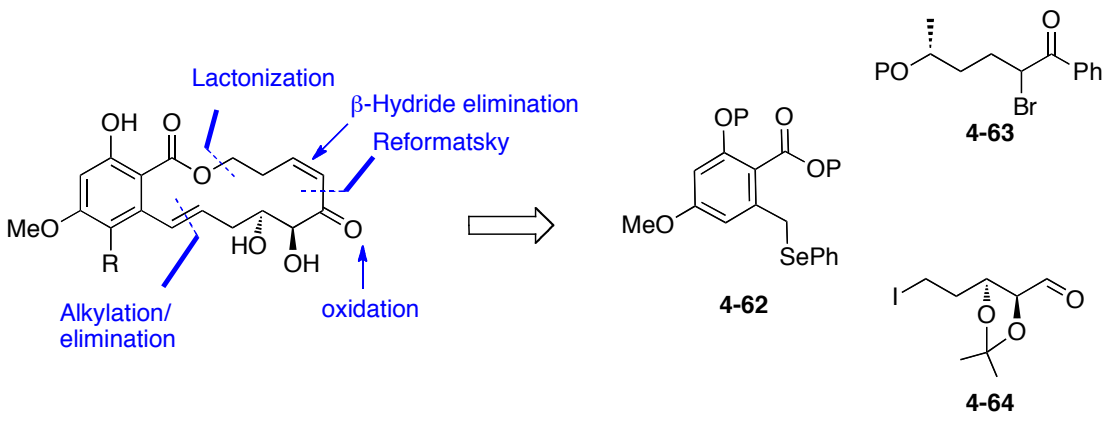
4.3 Results and discussion

The primary aim of this project was to develop new approaches for the inhibition of TAK1 kinase using synthetic compounds. To achieve this goal, two different approaches were employed.

Developing synthetic approaches and synthesis of novel compounds was performed in Prof. Davies laboratory and pharmacological evaluation of novel compounds was performed in Prof. Andrei Bakin laboratory at Roswell Park Cancer Research Institute, Buffalo, NY.

4.3.1 First approach – Proposed convergent synthesis of 5-(*Z*)-7-oxozeaenol (4-3)

5-(Z)-7-Oxazeaenol is a perfect example of a promising natural product whose current accessibility is limiting the broad SAR studies of it and its analogues. There is an enormous need for developing novel enabling synthetic process that could potentially give access to a large number of mimics of RALs to complete the SAR studies. The major problem with the previously published syntheses of 5-(*Z)*-7-oxazeaenol is their long linear sequence that was caused by the challenges associated with the end-game synthesis of the labile *cis-enone*. A novel convergent approach was proposed to solve the *cis-enone* synthesis problem.

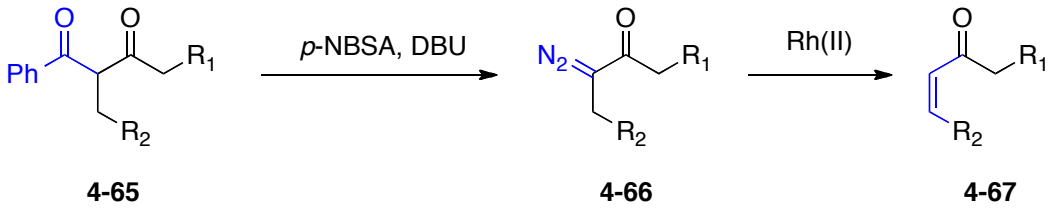


Scheme 4.12: Proposed retrosynthetic analysis for the synthesis of 5-(*Z*)-7-Oxozeaenol analogues – A convergent approach.

A convergent approach was proposed in which the key intermediates **4-62**. **4-63** and **4-64** would be synthesized first. We envisioned that fragments **4-62** and **4-64** can be connected *via* an alkylation/elimination sequence and fragments **4-62** and **4-63** can be combined by lactonization. The key steps would be a macrocycle ring closure by a SmI_2 mediated Reformatsky reaction and Rh(II) catalyzed β–hydride elimination reaction. This proposed modular synthesis could not only improve the synthesis of **4-3** but also would provide access to many analogues that can be used to establish the SAR studies.

In the proposed synthesis, one of the key step to generate a *cis-enone* is a 1,2 hydride shift of the ketocarbenoid using the methodology developed by Taber *et al*. The diazo transfer reaction on diketones **4-65** in the presence of *p*-nitrobenzenesulfonyl azide goes through a selective debenzoylation to provide unsymmetrical α–diazo ketones **4-66** (Scheme 4.13).[55,56] These diazo ketones can then undergo a β–hydride elimination in the

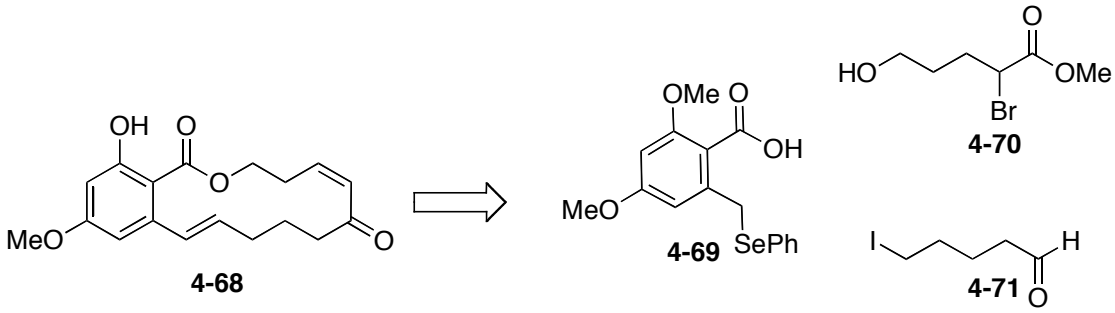
presence of rhodium (II) trifluoroacetate complexes to afford *cis* enone **4-67**. Application of this methodology would simplify the synthesis of 5-(*Z*)-7-oxazeaenol and its' analogues.



4-65 **4-66** **4-67**

Scheme 4.13: Taber's synthesis of *cis* enones.

In order to accomplish the synthesis of oxozeaenol analogues through a late stage β–hydride elimination of diazo compound methodology, a model system was developed in which fragments **4-69, 4-70** and **4-71** could be combined to form the requisite achiral macrocycle (**4-68**) (Scheme 4.14).

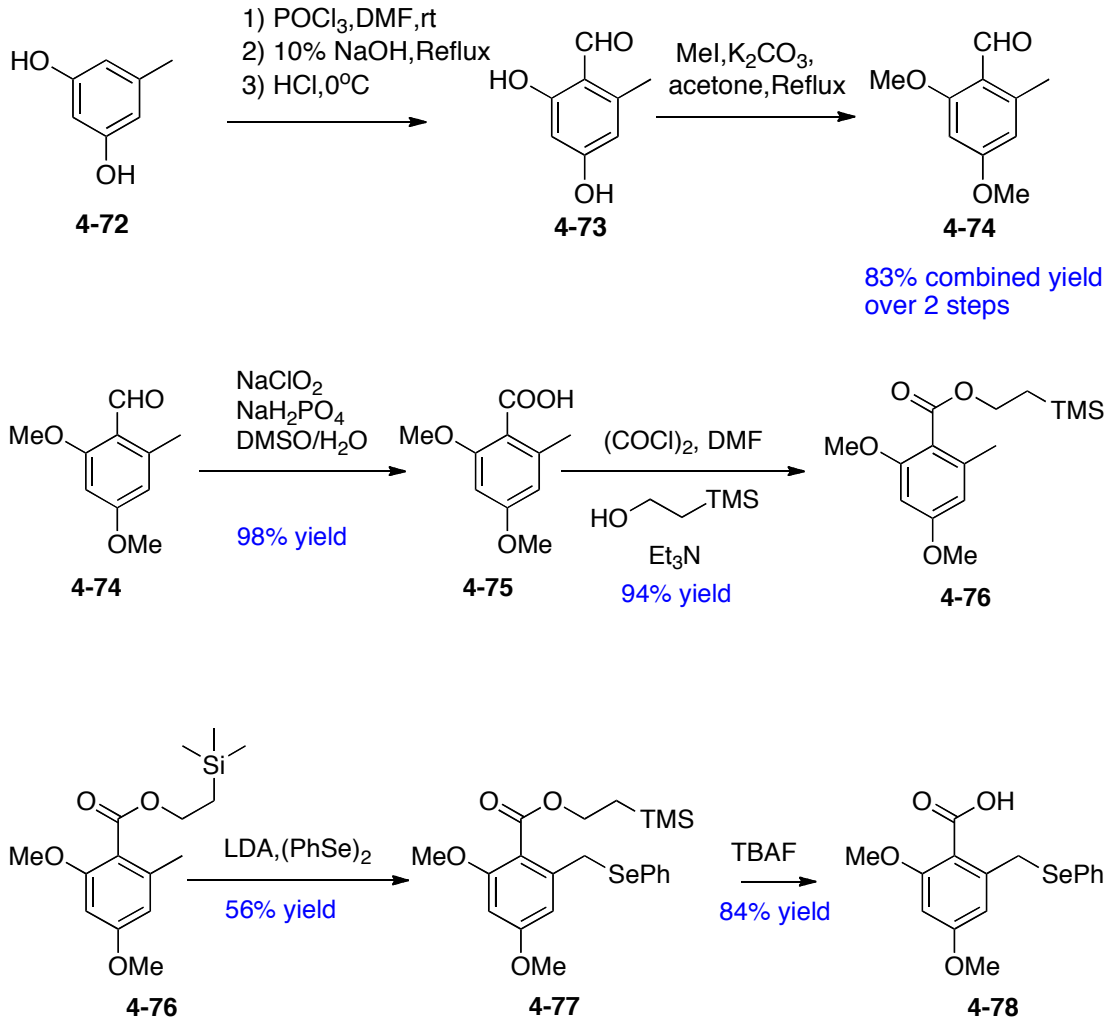


4-68 **4-69** **4-70** **4-71**

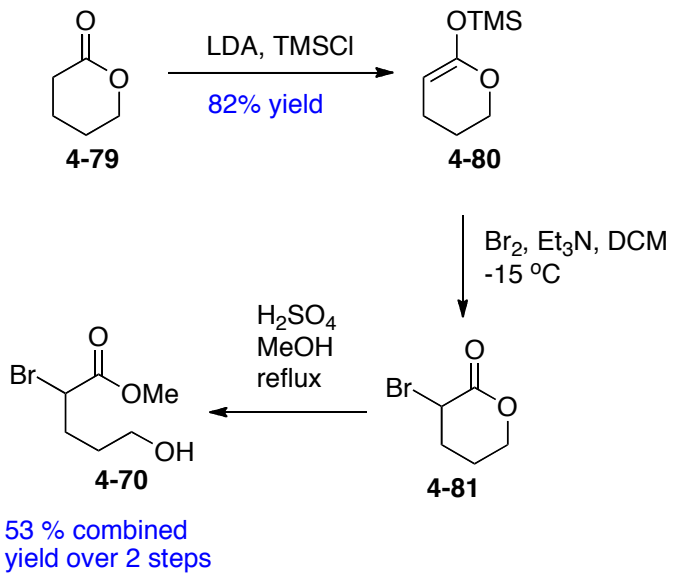
Scheme 4.14: Proof of concept (Model study).

Fragment **4-69** was synthesized starting from orcinol (**4-72**). A vilsmeier Haack formylation of orcinol (**4-72**) followed by methylation of aldehyde **4-73** gave the tri-

substituted benzaldehyde (**4-74**) in 83% overall yield. The latter was then oxidized to the corresponding benzoic acid (**4-75**),[57,58] which was subsequently protected using trimethylsilyl ethanol (**4-76**). Selective selenation onto the methyl group furnished **4-77**, which produced the resultant fragment **4-78** in 84% yield upon deprotection of trimethylsilylethanol moiety (Scheme 4.15).

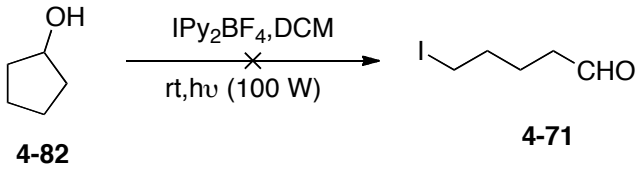


Scheme 4.15: Synthesis of 2,4-dimethoxy-6-(phenylselanylmethyl) benzoic acid



Scheme 4.16: Synthesis of methyl 2-bromo-5-hydroxypentanoate (**4-70**).

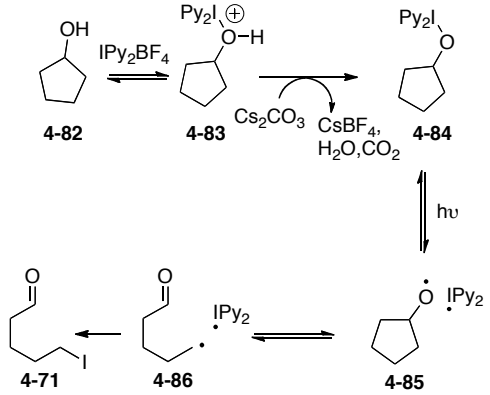
The enolate of δ-valerolactone (**4-79**) was trapped by TMSCl to provide TMS protected enolate (**4-80**) in 82% yield. The resultant enol ether was brominated to yield 2-bromo-δ–valerolactone (**4-81**) and subsequently ring opened under acidic conditions to give fragment **4-70** in 53% yield (Scheme 4.16).[59,60]



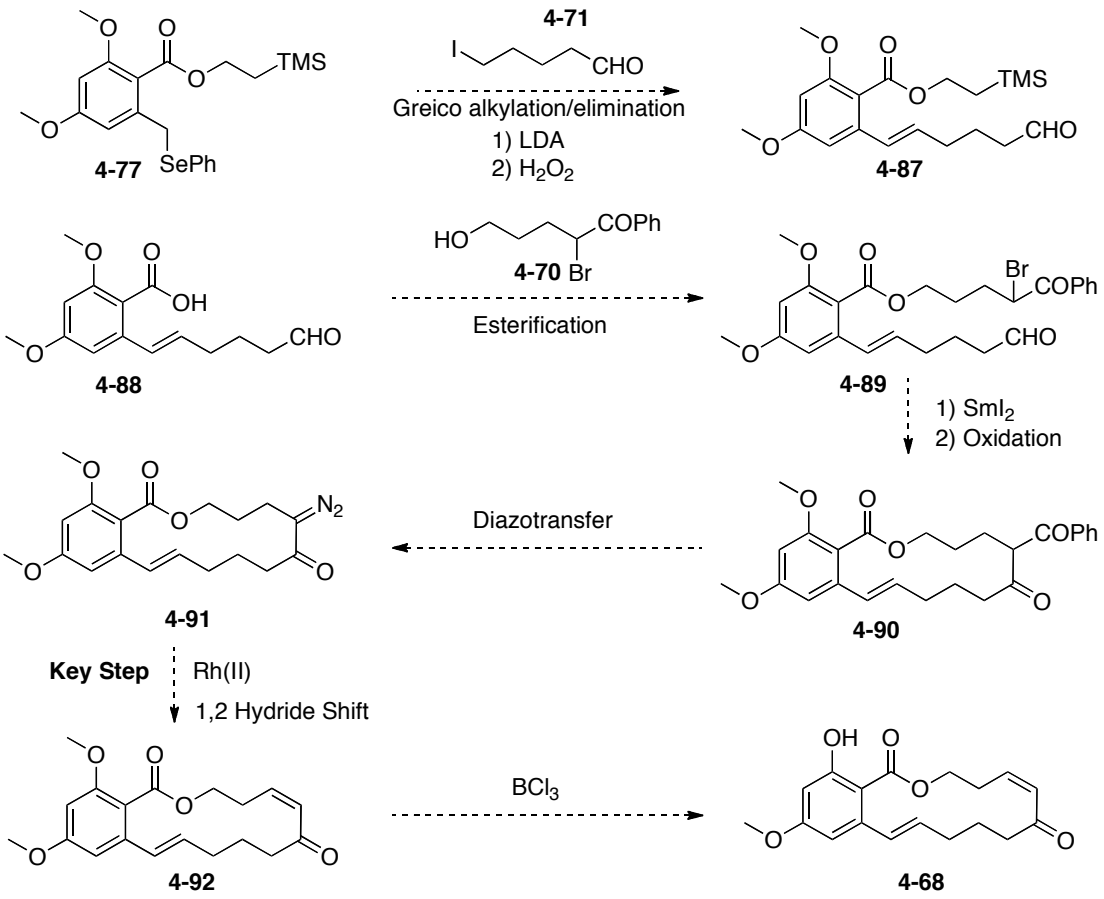
Scheme 4.17: Synthesis of 5-iodopentanal (**4-71**).

The synthesis of fragment **4-71** from cyclopentanol (**4-82**) failed. Repeated attempts to oxidize **4-82** in the presence of bis (pyridine) iodonium tetrafluoroborate were unsuccessful (Scheme 4.17).[61,62] Barluenga *et al.* proposed, that the synthesis of

ω–iodocarbonyl derivatives (**4-71**) from cyclopentanol involves a β–scission reaction.[61] The base abstracts the proton from the oxonium ion. Photolytic homolysis of the resultant iodane (**4-83**) provides the alkoxide radical (**4-84**). Repeated attempts to reproduce this reaction were not successful.



Scheme 4.18: Mechanism involved in the synthesis of 5-iodopentanal (**4-71**).



Scheme 4.19: Proposed model study for the synthesis of oxozeaenol analogues.

A future prospect for this approach includes redesigning the synthetic strategy to synthesize the intermediate **4-71**. Once fragment **4-71** synthesized, all three fragments could be connected in a convergent manner following the synthetic Scheme 4.19. To complete the synthesis of the macrocycle, fragments **4-71** and **4-77** could be coupled *via* a Greico alkylation/elimination sequence to form intermediate **4-87**. Subsequently, the trimethylsilylethanol protecting group could be removed to form **4-88**. Esterification of fragment **4-70** with **4-88** would lead to **4-89**. Macrocyclization of **4-89** by a SmI_2

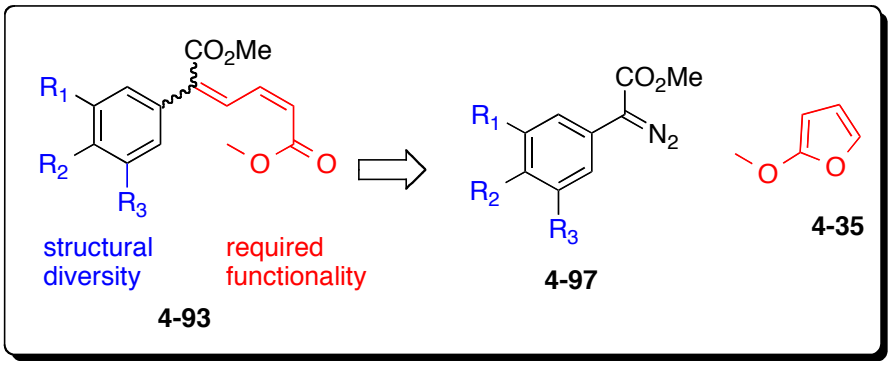
mediated-Reformatsky reaction followed by oxidation would give diketo compound **4-90**. A diazo transfer reaction will afford diazo ketone **4-91**. It is anticipated that in the presence of Rh(II), the β–hydrogen on the diazo ketone will undergo a 1,2-hydride shift to give the required *cis* enone product (**4-92**). Demethylation in the presence of BCl_3 will give the corresponding oxozeaenol analogue **4-68**.

If this convergent synthesis succeeds, then different fragments containing required functionalities could be constructed. This methodology could be used for the synthesis of a diverse range of macrocycles and a SAR could be established around these novel scaffolds.

In conclusion, the modular convergent synthesis of 5-(*Z*)-7-oxozeaenol analogues was proposed. Two of the three fragments required have been synthesized.

4.3.2 Second approach – synthesis of *cis-enones* using furan unraveling reaction.

It was envisioned that the functionality required for the TAK1 inhibition activity could be generated very quickly through the unraveling reaction of activated furans (Scheme 4.20). The initial focused library was generated on the assumption that the cis-enone functionality present in 5Z-7-oxozeaenol was critical element in the pharmacophore. The methodology was sufficiently versatile to generate a wide variety of novel compounds, which were never been explored as TAK1 inhibitors.



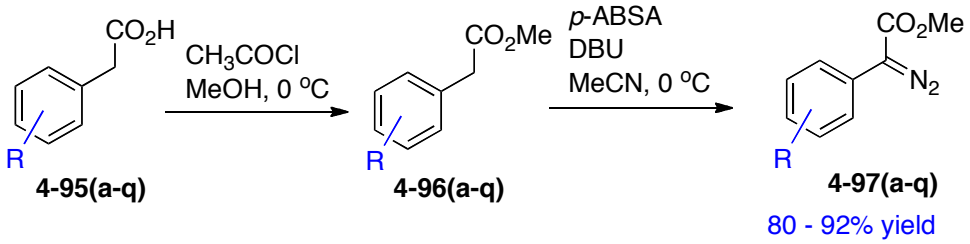
Scheme 4.20: Second synthetic proposal.

The idea was to synthesize various mimics of RAL by reacting donor-acceptor diazo compounds **4-94** with activated furans **4-35** in the presence of a Rh(II) catalyst to obtain ring opening products **4-93**. The structural diversity in the library could be introduced by performing the furan ring opening reaction with various substituted aryl diazo compounds **4-94** (Scheme 4.20).

4.3.2.1 Synthesis of aryl diazoacetates.

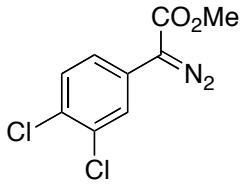
All of the donor-acceptor diazo compounds were obtained either by synthesizing according to the standard procedures[63] or obtained from lab sources and purified *via* column chromatography.

The corresponding 2-phenyl ethanoic acids **4-95(a-q)** were esterified in the presence of acetyl chloride and methanol to produce the corresponding esters **4-96(a-q)** in quantitative yields. A diazo transfer reaction in the presence of *p*-ABSA and DBU in acetonitrile yielded the corresponding diazo compounds **4-97(a-q)** in excellent yields[64] (Scheme 4.21).

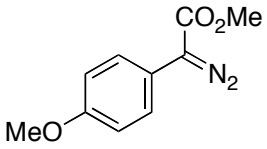


Scheme 4.21: Synthesis of aryl diazo compounds.

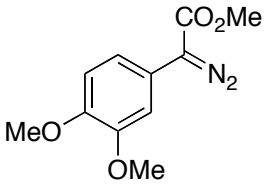
The only diazo compound that was not capable of being synthesized by a regular diazo transfer reaction was the one with the OTBS group at the two position of the phenyl group, methyl 2-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-diazoacetate (**4-97f**). The bulky OTBS group in methyl 2-(2-(*tert*-butyldimethylsilyloxy) phenyl) acetate (precursor of **4-97f**) might be hindering the approach of bulky base (DBU). Either way, repeated attempts to synthesize the OTBS substituted diazo compound utilizing various diazo transfer reagents did not work. OTBS group was introduced at 3-position instead (Table 4.1).



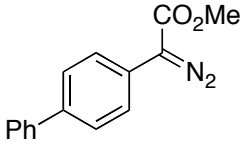
4-97a



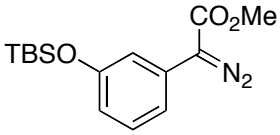
4-97b



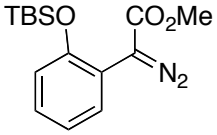
4-97c



4-97d



4-97e



4-97f

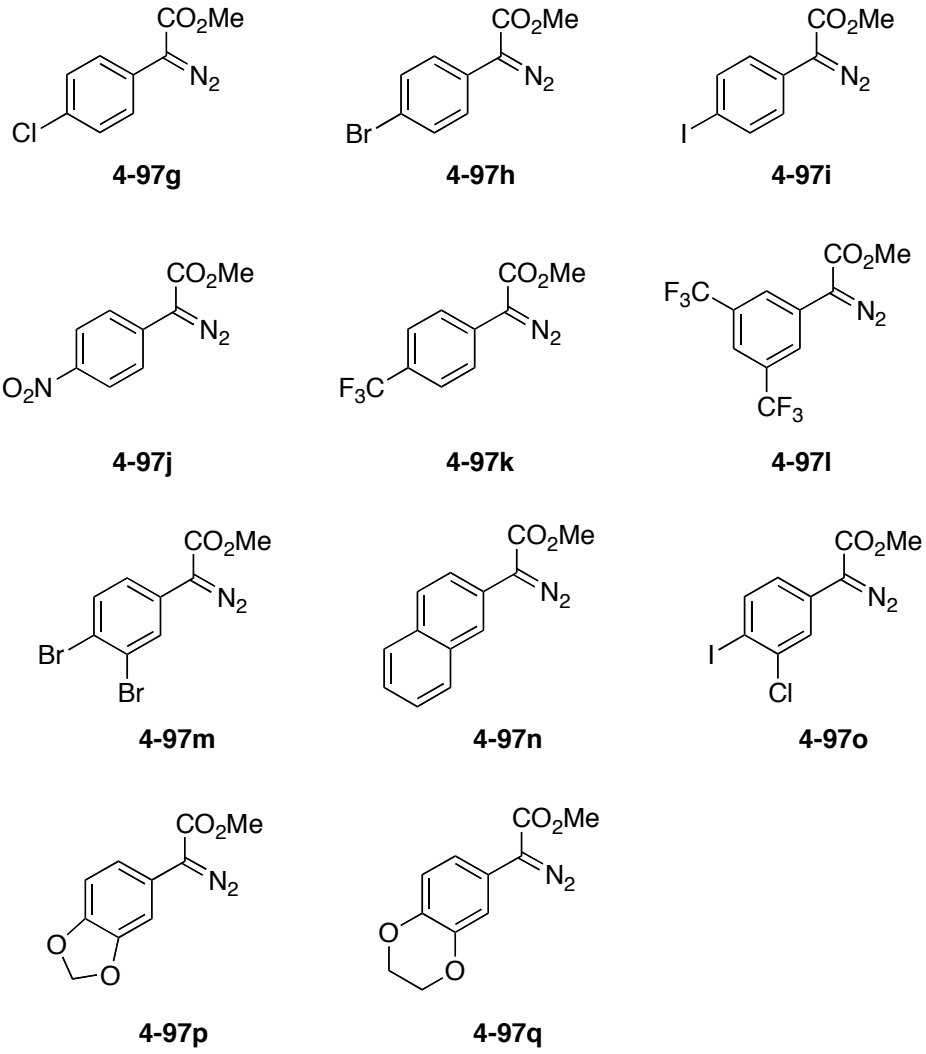


Table 4.1: Structures of diazo compounds used in the furan unraveling reaction.

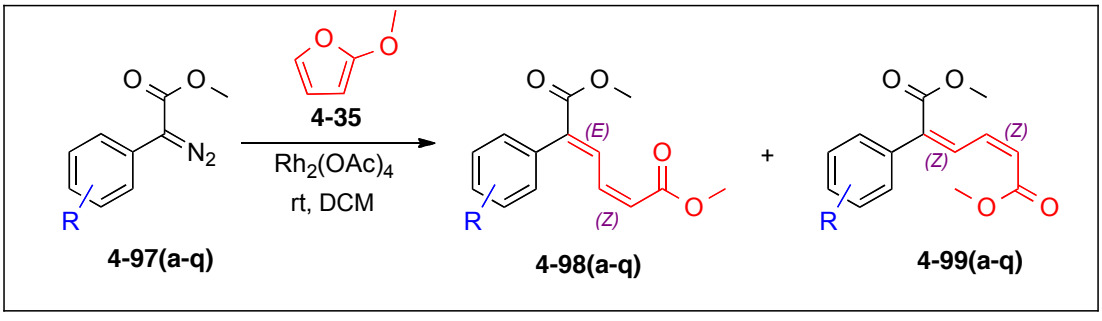
4.3.2.2 Reaction of aryl diazoacetate compounds with 2-methoxy furan

The reaction of the corresponding aryl diazo acetate compounds **4-97(a-q)** with 2-methoxy furan **4-35**, in the presence of catalytic amount of $Rh_2(OAc)_4$ readily formed various functionalized diene compounds **4-98(a-q)** in excellent yields and very high

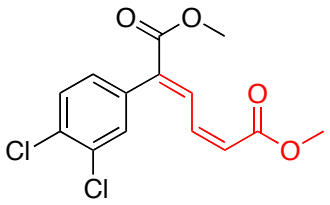
selectivity for (2*E*, 4*Z*) isomer. The minor isomer (2*Z*, 4*Z*) was formed in <5% yield. (Scheme 4.22)

It was anticipated that a considerable diversity in functionalization could be obtained in the synthesis of the first set of RAL mimics. *Cis* enones containing an electron withdrawing group such as 3,4-dichloro **(4-98a)**, 4-chloro **(4-98g)**, 4-bromo **(4-98h)**, 4-iodo **(4-98i)**, 4-nitro **(4-98j)**, 4-trifluoromethyl **(4-98k)**, 3,5-trifluoromethyl **(4-98l)**, 3,4-dibromo, **(4-98m)** 2-naphthyl **(4-98n),** 3-chloro 4-iodo **(4-98o)** were introduced. Electron donating groups such as 4-methoxy (**4-98b)**, 3,4-dimethoxy (**4-98c)**, 3-hydroxy (**4-98f)**, benzo[*d*][1,3]dioxole (**4-98p)** and dihydrobenzo[*b*][1,4]dioxine (**4-98q)** groups were also introduced in order to understand the effect of subtle differences in electronics on TAK1 inhibition activity. In all the reactions, the major isomer was found to have the (2*E*, 4*Z*) configuration. (Scheme 4.22)

All furan ring opening reactions with aryl diazo acetates showed very clean conversion to the expected product. The diazo compound was added drop wise using syringe pump mainly to avoid diazo dimerization.



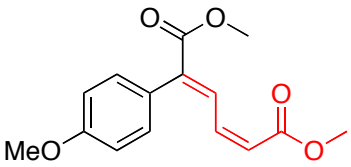
Scheme 4.22: Reaction of aryl diazoacetates with 2-methoxy furan.



HDAB-001

88% yield

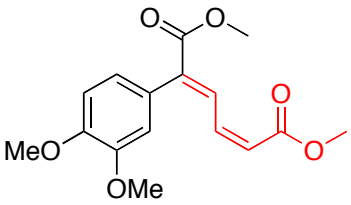
4-98a



HDAB-002

82% yield

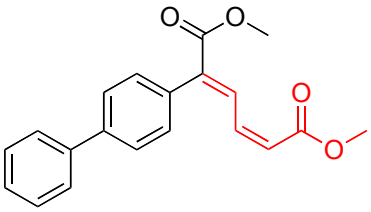
4-98b



HDAB-003

99% yield

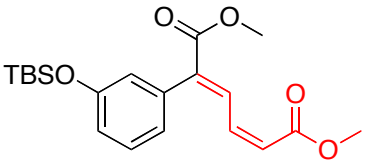
4-98c



HDAB- 18

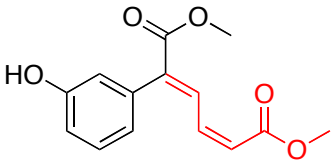
74% yield

4-98d



74% yield

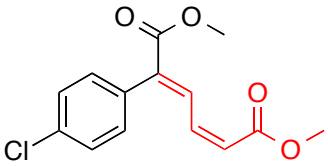
4-98e



HDAB-005

32% yield

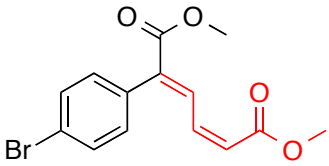
4-98f



HDAB-009

93 % yield

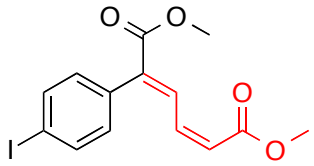
4-98g



HDAB-010

80 % yield

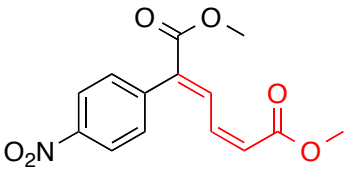
4-98h



HDAB-011

93% yield

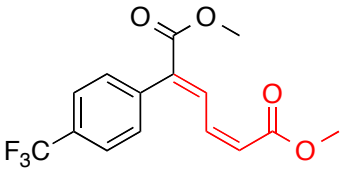
4-98i



HDAB-012

91% yield

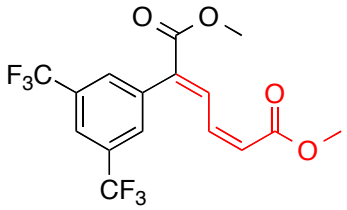
4-98j



HDAB-013

81% yield

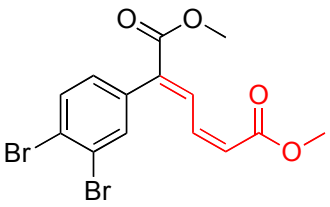
4-98k



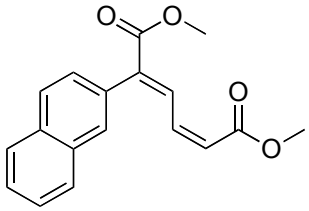
HDAB-014

83% yield

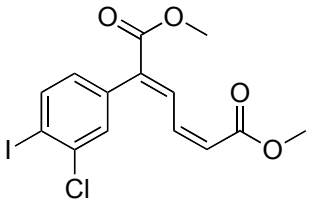
4-98l



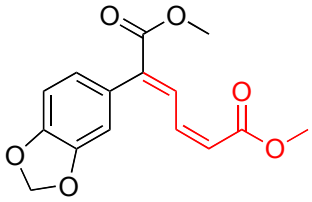
HDAB-022
91% yield
4-98m



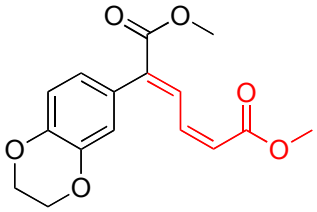
HDAB-028
79% yield
4-98n



HDAB-030
90% yield
4-98o

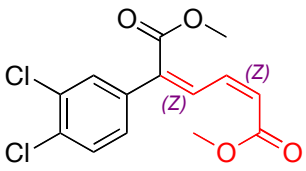


HDAB-036
91% yield
4-98p

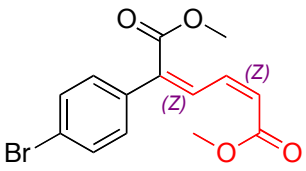


HDAB-037
89% yield
4-98q

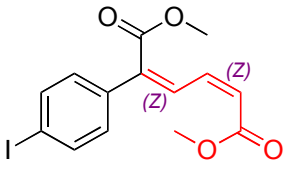
Table 4.2: List of products (*cis enones* with (2*E*, 4*Z*) configuration) formed in the furan unraveling reaction. *(HDAB number is a reference code used when sending the samples for biological evaluation)*



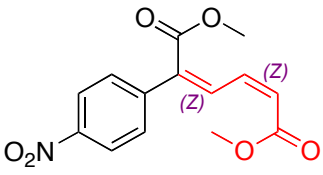
HDAB-007
2% yield
4-99a



HDAB-015
3% yield
4-99h



HDAB-016
3% yield
4-99i

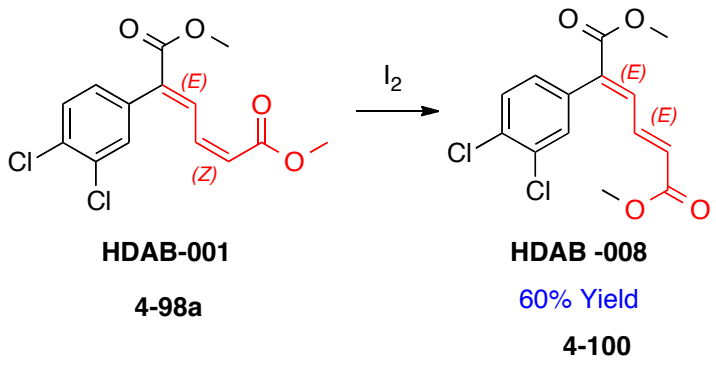


HDAB-017
1% yield
4-99j

Table 4.3: List of isolated minor isomers with (2*Z*, 4*Z*) configuration.

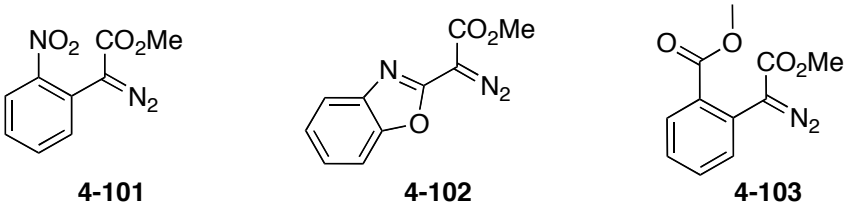
In some cases, the minor products formed in the furan unraveling reaction **4-99 a,h-j** were also isolated and sent for biological evaluation (Table 4.3).

Interestingly, the compound **4-98a** could be isomerized to the compound **4-100** with configuration (2*E*, 4*E*) in the presence of iodine. This technique was used to determine whether the *cis-enone* moiety was essential for TAK1 inhibition activity. As a result, all possible dienes with configurations (2*E*, 4*Z*), (2*Z*, 4*Z*) and (2*E*, 4*E*) were synthesized and sent for biological evaluation.



Scheme 4.23: Isomerization of diene **4-98a**.

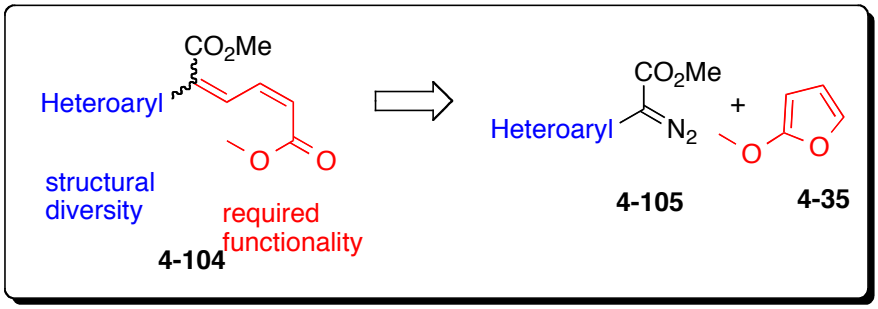
Some of the diazo compounds such as methyl 2-diazo-2-(2-nitrophenyl)acetate **(4-101),** methyl 2-(benzo[*d*]oxazol-2-yl)-2-diazoacetate **(4-102)** and methyl 2-(1-diazo-2-methoxy-2-oxoethyl)benzoate **(4-103)** did not decompose in the presence of Rh(II) at rt. Repeated attempts to perform the reaction at various temperatures and in different solvents were not successful.



4-101 **4-102** **4-103**

Table 4.4: List of diazo compounds that did not form ring-opening products.

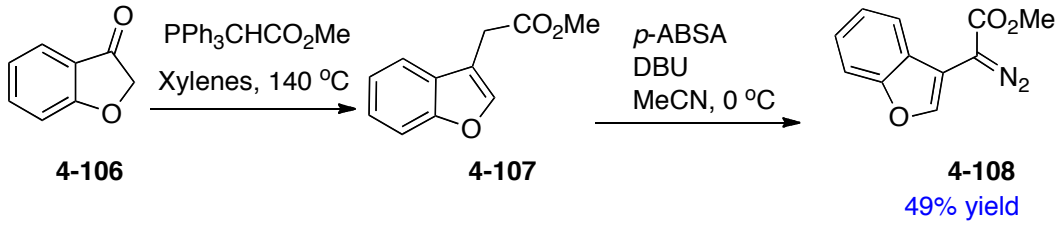
4.3.2.3 Synthesis of heteroaryl diazo compounds and their reaction with 2-methoxy furan



Scheme 4.24: Third synthetic proposal.

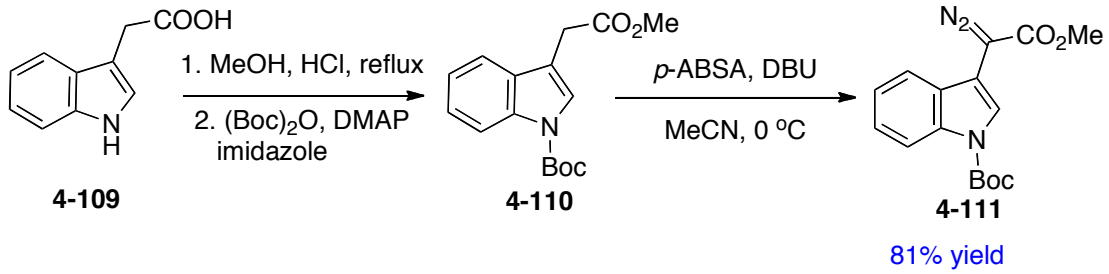
Most of the current pharmaceuticals possess heterocycle moiety.[65,66] It was envisioned that introducing an heteroaryl functionality into the cis-enone moiety might improve the TAK1 inhibition activity. With this idea, selected heteroaryl diazo compounds were synthesized. Diazo derivatives **4-108, 4-111, 4-113a** and **4-113b** were reacted with 2-methoxy furan in order to get the desired ring opening products **4-115a-d** in moderate to good yields (Scheme 4.28).

Methyl 2-(benzofuran-3-yl)-2-diazoacetate (**4-108**) was prepared *via* a Wittig reaction using benzofuran-3- (2*H*)-one **(4-106),** followed by a diazo transfer reaction (Scheme 4.25).[67]



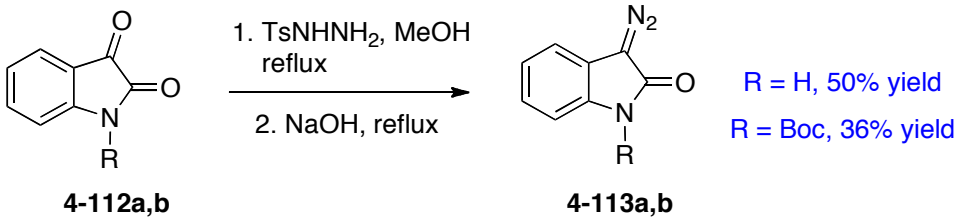
Scheme 4.25: Synthesis of methyl 2-(benzofuran-3-yl)-2-diazoacetate **(4-108).**

Tert-butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (**4-111**) was prepared *via* a 3-step sequence. The methyl indole-3-acetate was synthesized by esterification of indole-3-acetic acid **(4-109)** followed by a N-Boc protection and a diazo transfer reaction (Scheme 4.26).



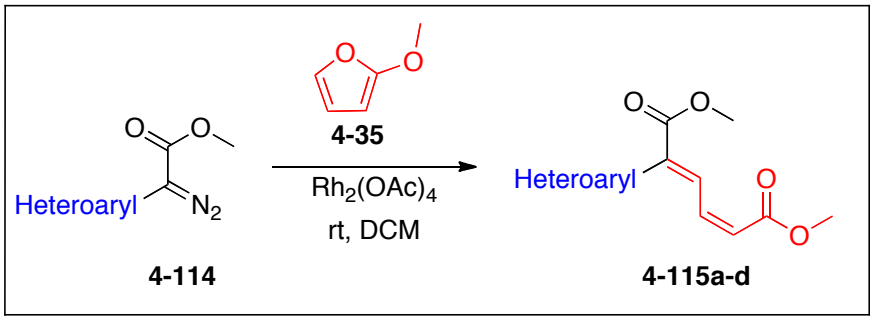
Scheme 4.26: Synthesis of tert-butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate **(4-111)**.

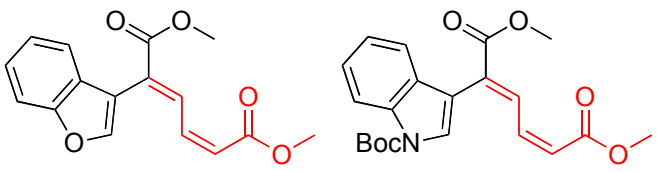
3-diazoindolin-2-one (**4-113a**) and Boc-protected 3-diazoindolin-2-one (**4-113b)** were synthesized from Isatin (**4-112a**). Isatin or Boc-protected isatin were reacted with tosyl hydrazide in methanol to get the corresponding hydrazone, which gave the desired diazo product in moderate yields in the presence of a base (Scheme 4.27).



Scheme 4.27: Synthesis of 3-diazoindolin-2-one **(4-113a,b)**.

With all these heteroaryl diazo compounds in hand, the reaction with 2-methoxy furan was performed. Although the reaction of benzofuran diazo with 2-methoxy furan performed smoothly, reactions with all other heteroaryl diazo compounds were sluggish and did not gave the desired product in good yields. Nevertheless, four diene compounds **4-115(a-d)** were synthesized and sent for biological testing (Scheme 4.28).





HDAB-029

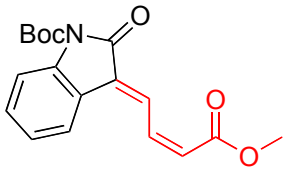
90% yield

4-115a

HDAB-032

48% yield

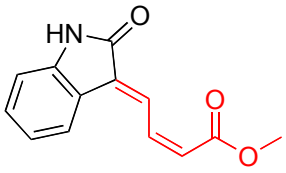
4-115b



HDAB-038

15% yield

4-115c



HDAB-039

33% yield

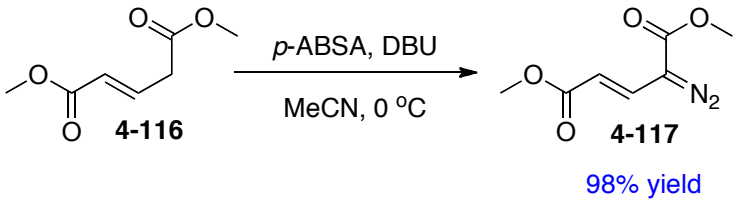
4-115d

Scheme 4.28: Reaction of heteroaryl diazo acetates with 2-methoxy furan and the list of products (*cis enones* with (2*E*, 4*Z*) configuration) formed in the reaction.

4.3.2.4 Synthesis of vinyl diazo compounds and their reaction with 2-methoxy furan

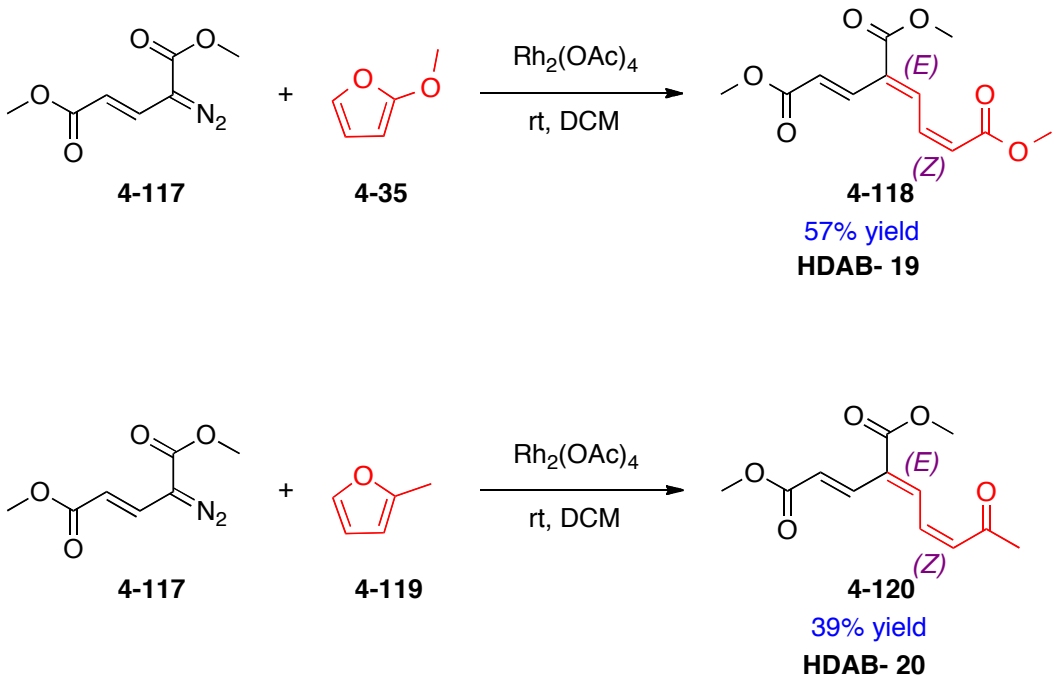
From the limited SAR study on RAL's for TAK1 inhibition activity, it was not clear whether the aryl group was part of the pharmacophore. In order to test whether this activity was arising from *cis* dienoate but not from aryl group, a new set of compounds **4-118** and **4-120** were synthesized.

The vinyl diazo ester (**4-117**) was synthesized from its corresponding vinyl ester (**4-116**) through a standard diazo transfer reaction to get desired product in quantitative yield (Scheme 4.29).



Scheme 4.29: Synthesis of (*E*)-dimethyl 4-diazopent-2-enedioate **(4-117)**.

The reaction of (*E*)-dimethyl 4-diazopent-2-enedioate **(4-117)** with 2-methoxy furan **4-35** and 2-methyl furan in the presence of a catalytic amount of $Rh_2(OAc)_4$ in DCM at rt gave the triene products **4-118** and **4-120** in 57% and 39% yield respectively (Scheme 4.30).

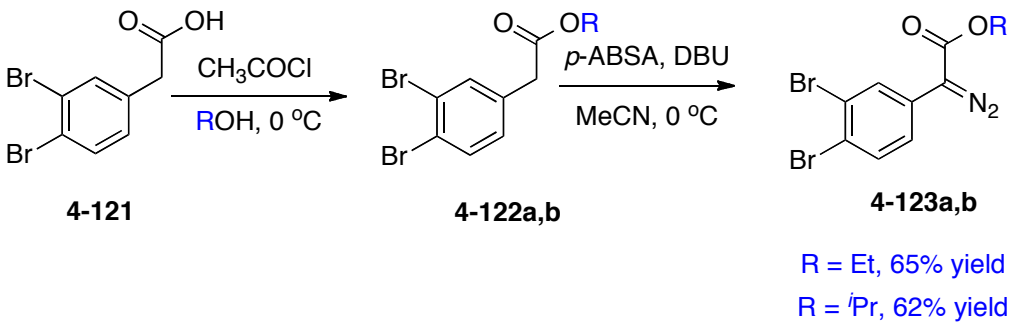


Scheme 4.30: Reaction of (E)-dimethyl 4-diazopent-2-enedioate **(4-117)** with 2-methoxy furan and 2-methyl furan.

4.3.2.5 Synthesis of diazo ester derivatives, phosphonate diazo compound and their reaction with 2-methoxy furan

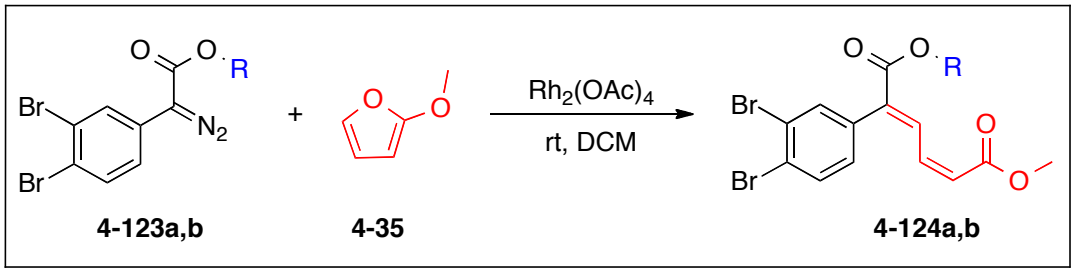
In order to understand whether structural changes in the ester functionality in the dienone would change the activity, ester derivatives **4-123a** and **4-123b** were synthesized.

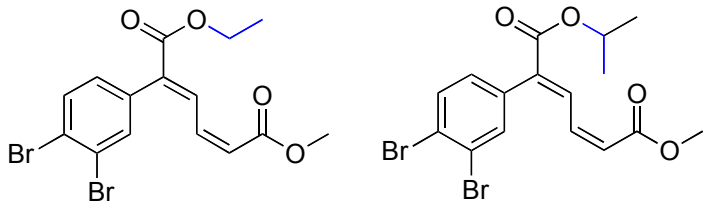
The required diazo compounds were synthesized *via* a 2-step sequence. An esterification followed by a diazo transfer reaction yielded ethyl diazo acetate **4-123a** and isopropyl diazo acetate **4-123b** derivatives in moderate yields (Scheme 4.31).



Scheme 4.31: Synthesis of ethyl and isopropyl diazo esters.

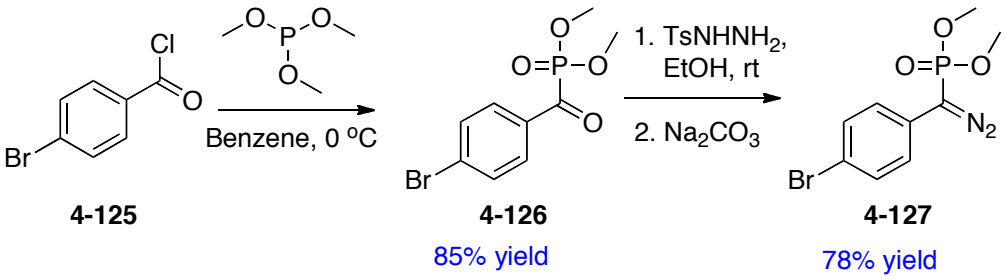
The reaction of ethyl 2-diazo-2-(3,4-dibromophenyl)acetate **(4-123a)** with 2-methoxy furan gave the ring opening product in 84% yield, whereas the reaction of isopropyl 2-diazo-2-(3,4-dibromophenyl)acetate **(4-123b)** with 2-methoxy furan gave the desired product in 92% yield (Scheme 4.32).





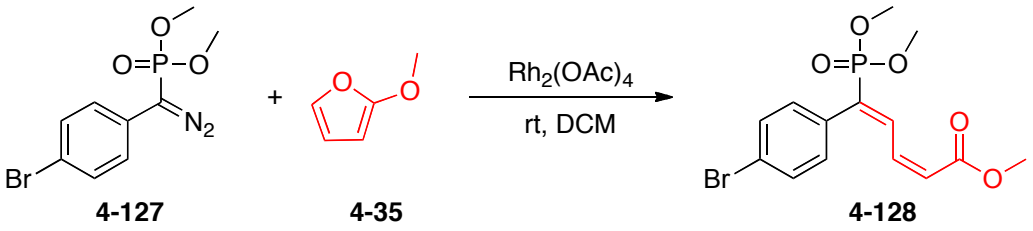
Scheme 4.32: Reaction of ethyl and isopropyl diazo esters with 2-methoxy furan

The phosphonate diazo compound 4-127 was also synthesized and used in furan ring opening reaction. This latter could be accessed from 4-bromobenzoyl chloride (4-125). Benzoyl chloride was reacted with trimethyl phosphite in benzene at 0 °C to get dimethyl (4-bromobenzoyl)phosphonate (4-126), which was then reacted with tosyl hydrazide in ethanol to get corresponding hydrazone in good yields. Finally, the hydrazone was converted to the diazo phosphonate (4-127) in the presence of sodium carbonate (Scheme 4.33).



Scheme 4.33: Synthesis of dimethyl ((4-bromophenyl)(diazo)methyl)phosphonate **(4-127)**

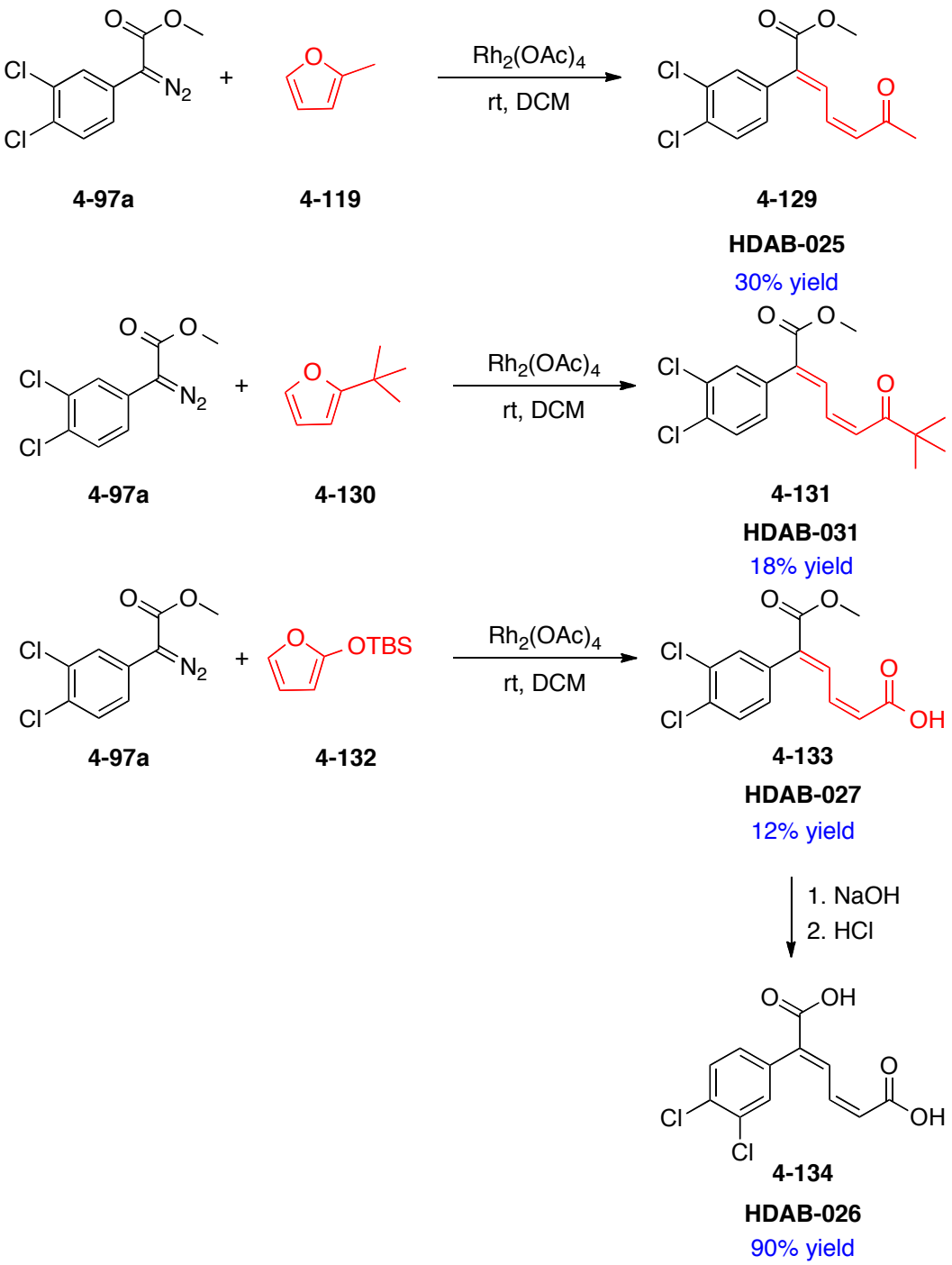
Dimethyl ((4-bromophenyl)(diazo)methyl)phosphonate (**4-127**) was reacted with 2-methoxy furan in the presence of $Rh_2(OAc)_4$ to get (2Z,4E)-methyl 5-(4-bromophenyl)-5-(dimethoxyphosphoryl)penta-2,4-dienoate (**4-128**) (Scheme 4.34).



Scheme 4.34: Reaction of dimethyl ((4-bromophenyl)(diazo)methyl)phosphonate **(4-127)** with 2-methoxy furan

4.3.2.6 Reaction of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate with various 2-substituted furans.

The unraveling reaction of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate **4-97a** with 2-methyl furan was also attempted several times, but the corresponding keto enone compounds seemed to be unstable as compared to their corresponding diester analogues (Scheme 4.35).



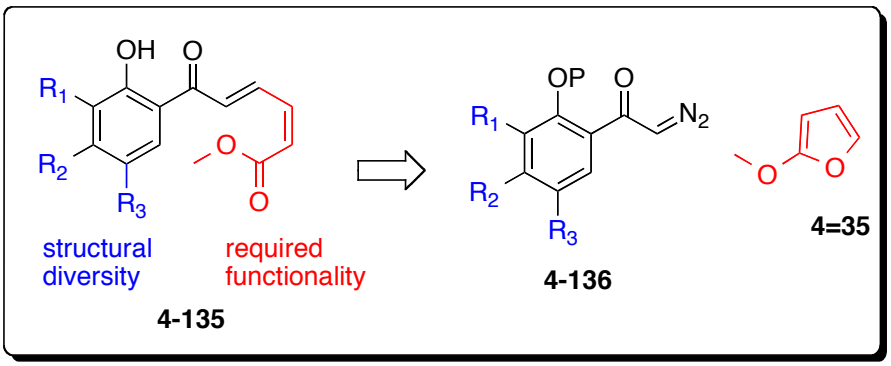
Scheme 4.35: Reaction of 2-diazo-2-(3,4-dichlorophenyl)acetate **(4-97a)** with various furans.

A keto derivative **4-129** was synthesized by reacting methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (**4-97a**) with 2-methyl furan (**4-119**). The desired product was isolated in 30% yield (Scheme 4.35).

The synthesis of *tert*-butyl derivative **(4-131)** was found to be more problematic. The diazo compound **4-97a** did not decompose in the presence of 1 mol % catalyst. It was found that 2-(*tert*-butyl)furan needed to be used in excess and the product only started to form after 4 h of stirring at rt. The desired product was isolated in 18% yield.

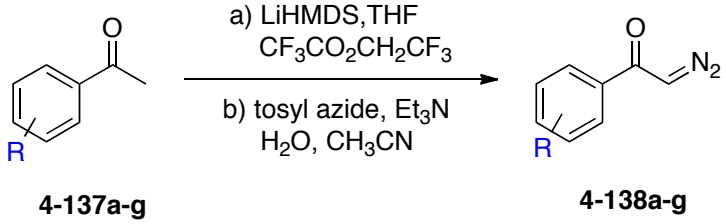
The reaction of 2-diazo-2-(3,4-dichlorophenyl)acetate **(4-133)** with tert-butyl(furan-2-yloxy)dimethylsilane **(4-132)** in the presence of catalytic amounts of $Rh_2(OAc)_4$ did not provide the expected OTBS protected diene. Instead, the corresponding carboxylic acid was isolated, presumably because of the TBS deprotection upon purification on column chromatography. The high polarity of the product might be the reason for the very low isolated yield. In order to overcome this problem, a simple alternate method was employed for purification. The crude product formed in the reaction was washed with 1M NaOH and 1M HCl successively. The diacid product **4-134** was then recrystallized and isolated in good yields.

4.3.2.7 Synthesis of diazoketones



Scheme 4.36: Fourth synthetic proposal.

It was also envisioned that the unique aryl diazo ketones **4-136** could be utilized for the synthesis of a novel set of RAL mimics. This would not only eliminate the ester functionality at the C-2 position in the product but also give quick access to a library of products **4-135** that have higher structural similarity with RALs (Scheme 4.36).



Scheme 4.37: Synthesis of diazo ketones.

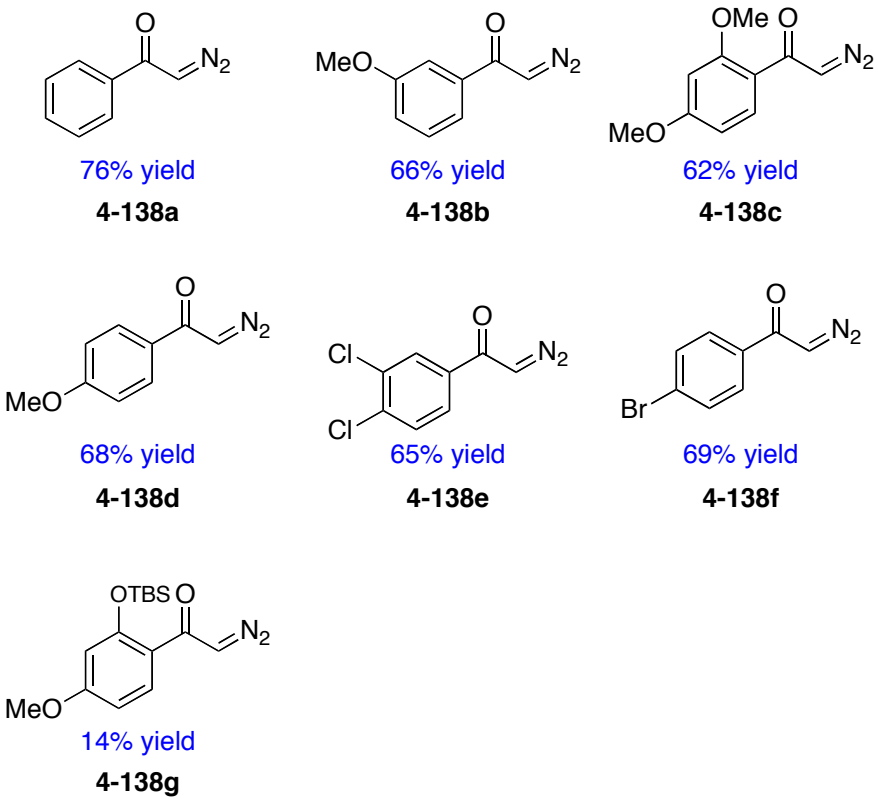
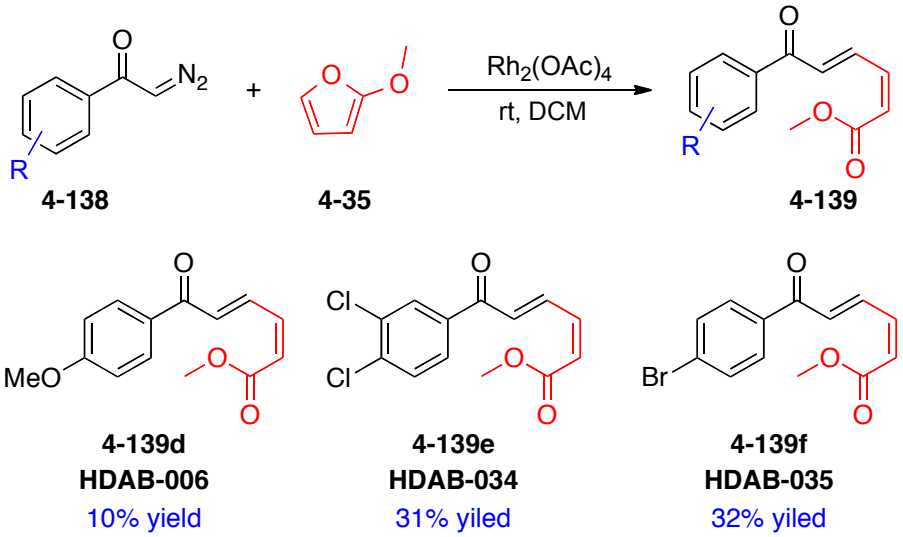


Table 4.3: List of diazo ketones synthesized (acceptor diazo compounds).

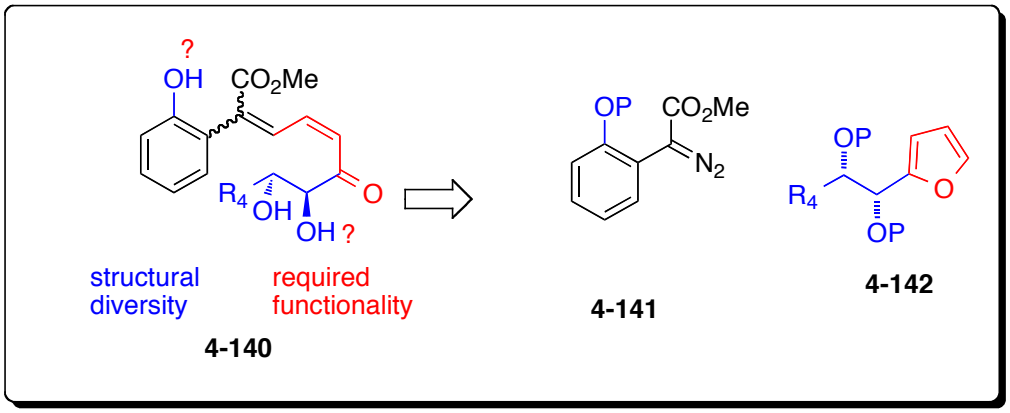
The required diazo ketones **4-138(a-g)** were synthesized according to the slightly modified literature procedure.[68] The enolate of acetophenone was generated in the presence of LiHMDS and then trapped by trifluoroethyl trifluoroacetate (TFEA). The enolate of the corresponding diketone was generated using Et_3N and addition of tosyl azide afforded the desired diazo products in moderate yields (Scheme 4.37)(Table 4.3).



Scheme 4.38: Reactions of diazo ketones with 2-methoxy furan.

The reactions of diazo ketones **4-138** with 2-methyl and 2-methoxy furan led to a complex mixture of products that were not separable even after repeated chromatographic columns. No selectivity was observed even when the reactions were run at lower temperatures. The use of alternative achiral catalysts also did not give the desired product exclusively. Nevertheless, a few *cis* enones **4-139(d-f)** were isolated from the reaction of diazo ketones with 2-methoxy furan were sent for biological evaluation.

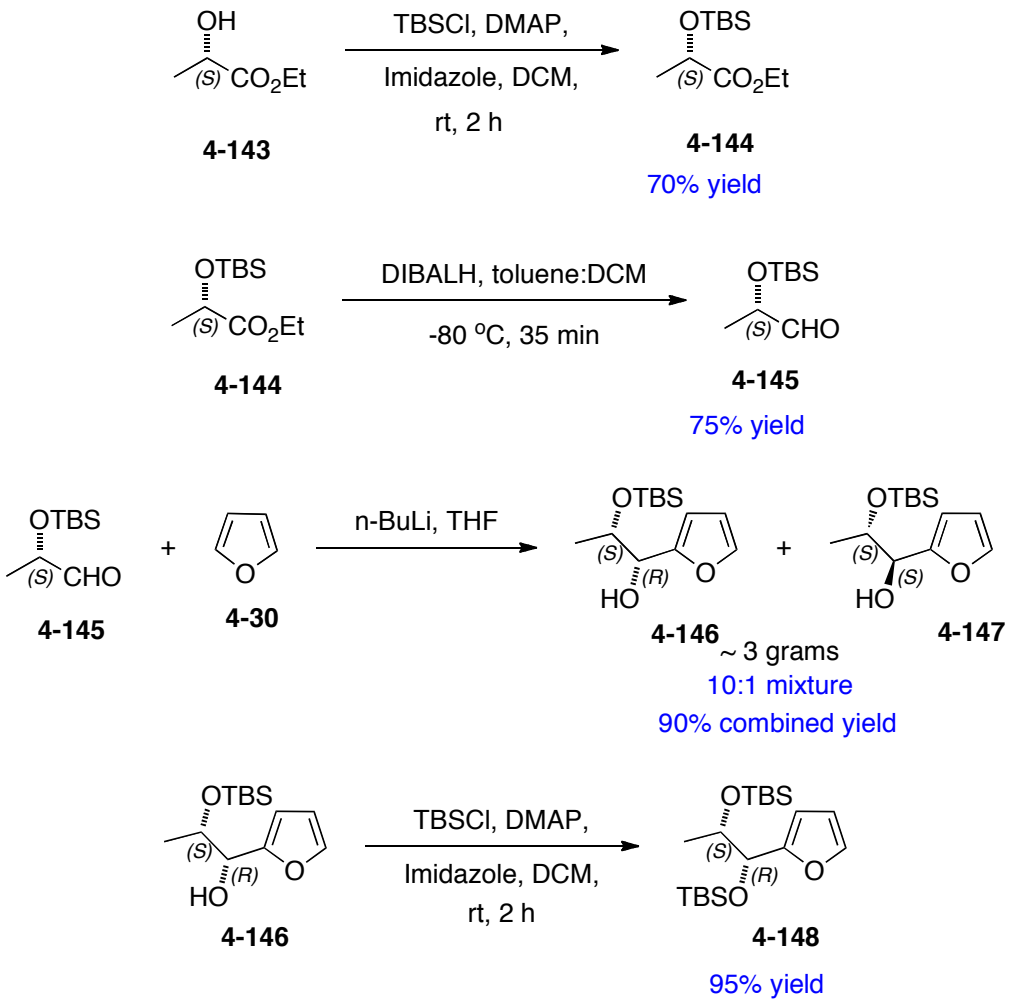
4.3.2.8 Attempts to synthesize more elaborate dienones



Scheme 4.39: Fifth synthetic proposal.

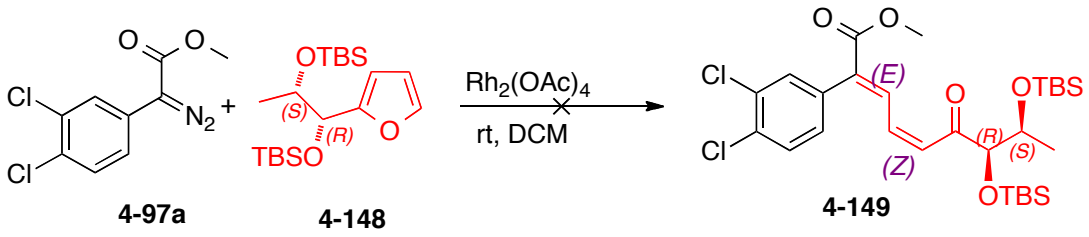
It was not clear from the limited SAR studies on RAL compounds, whether the hydroxy functionality (**4-140**) was essential for TAK1 inhibition activity. It was envisioned, that structurally similar analogues of RALs could be synthesized by introducing hydroxyl functionality into the dienone by utilizing aryl diazo compound with hydroxy substitution at 2-position. Alternatively, furan containing hydroxy substituent also could be employed (Scheme 4.39).

In order to obtain a closer acyclic analogue of **4-3**, TBS protected chiral furan diol **4-148** was synthesized. TBS protection of the secondary alcohol in (S)-ethyl lactate (**4-143**) provided **4-144** followed by DIBAL reduction resulted in the chiral aldehyde **4-145** (Scheme 4.40).



Scheme 4.40: Synthesis of OTBS protected furan diol (**4-147**).

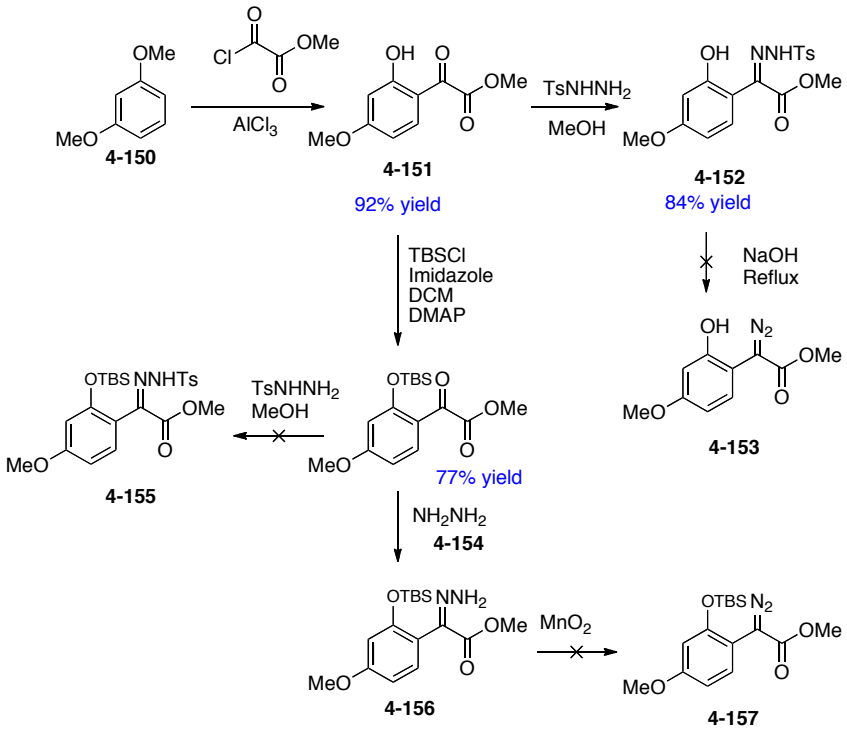
Lithiation of furan occurred exclusively at the 2-position, and subsequent nucleophilic attack on aldehyde **4-145** provided a seperable 10:1 epimeric mixture of propanols **4-146** and **4-147**.[69] The propanol **4-146** was subjected to TBS protection conditions to afford OTBS protected furan diol **4-148** in excellent yield (Scheme 4.40).



Scheme 4.41: Reaction of **4-97a** with **4-148**.

Repeated attempts to react OTBS protected furan diol **4-148** with various donor-acceptor diazo compounds led to mixture of products that decomposed at room temperature. The crude ^{1}H NMR of the reaction mixture showed the ring opening product, but the product decomposed in $CDCl_3$ or upon standing with in hours even at lower temperatures. The chiral diol might not be a good choice for this reaction. Global deprotection of the TBS groups and protection of the diol as the acetonide might be the solution to avoid decomposition.

Synthetic attempts were also made to introduce hydroxyl functional group on to the aryl group of *cis*-enone (Scheme 4.42). The usual method of synthesizing phenyl diazoacetates with 2-hydroxyl substitution **4-97f** failed. As a result, an alternate approach for decomposing hydrazones was employed.



Scheme 4.42: Failed attempts to synthesize **4-157**.

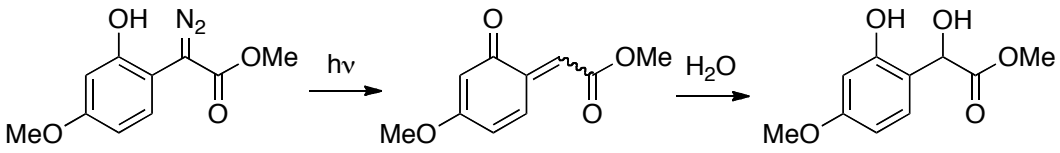
Methyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoethanoate (**4-151**) was synthesized from a modified literature procedure.[70] 1,3 dimethoxybenzene (**4-150**) was acylated with methyl 2-chloro-2-oxoethanoate in the presence of $AlCl_3$ to produce the desired 2-hydroxy product **4-151** in excellent yield (Scheme 4.42).

Ester **4-151** was reacted with tosyl hydrazine in refluxing methanol to afford the corresponding hydrazone **4-152** in 84% yield. However, this intermediate did not yield the desired diazo compound **4-153** under all attempted conditions and an alternate had to be employed.

Ester (**4-151**) was TBS protected to yield **4-154** in good yield. **4-154** was reacted with hydrazine to produce the corresponding hydrazone **4-156**, which did not oxidize to

the diazo compound when treated with an oxidizing agent such as MnO_2. In order to ensure that the diazo formed *in situ* in the reaction mixture was not decomposing over time, styrene and Rh_2(*S*-DOSP)$_4$ were added to the reaction mixture to trap the cyclopropane product. Unfortunately, no cyclopropane product was observed, which indicates that no diazo product was formed in the reaction.

A plausible reason for the decomposition of 2-hydroxy diazo compound could be that methyl 2-hydroxyphenyldiazoacetate (**4-153**) might be forming the o-quinone α-carbomethoxymethide (**4-158**) in the presence of light. The latter would then provide 2-hydroxy mandelate **(4-159)** in the presence of water (Scheme 4.43).[71] Thus, efforts to synthesize analogues with 2-hydroxy substitution were not successful.



4-153 **4-158** **4-159**

Scheme 4.43: Possible rationale for the decomposition of methyl 2-hydroxyphenyldiazoacetate **(4-153).**

4.3.2.9 Structural analysis of the products formed in furan unraveling reaction.

The configuration of the products formed in the furan unraveling reaction was determined by nOe experiments. In the major product, there was an nOe interaction between the hydrogen at the 2-position of the phenyl group and the hydrogen on C-4, indicating the 2*E*, 4*Z* configuration **4-98h**. Similarly, nOe enhancement was observed between hydrogen at the 2-position on the phenyl group and the hydrogen on C-3, indicating 2*Z*, 4*Z* configuration in the minor product. In conclusion, the opened furan ring retains its *cis* configuration at C-4, while the other olefin formed at C-2 appears to isomerizes to the thermodynamically stable *trans* configuration (Fig.4.6).

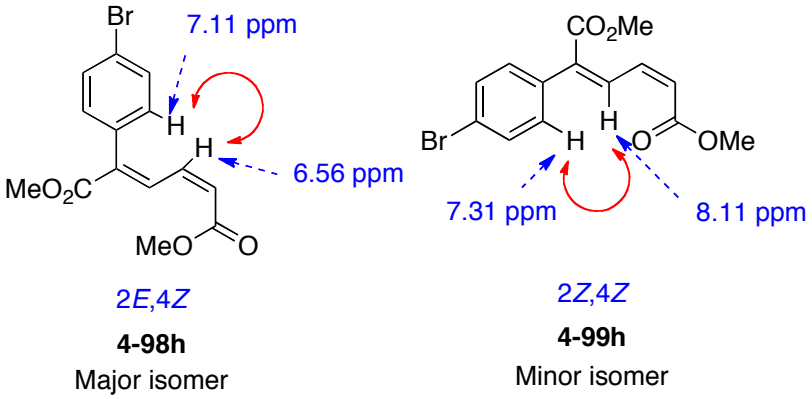
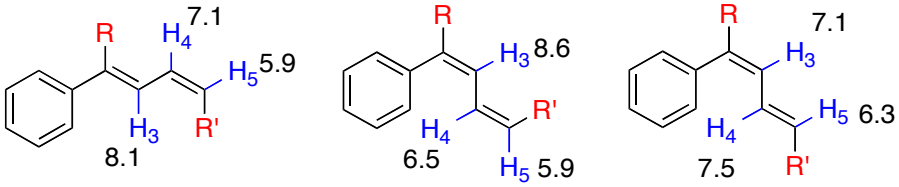


Figure 4.6: nOe conformation of *cis-enone* geometry

The ^{1}H NMR data clearly shows the difference between the geometry of the three isomers. NMR peaks splitting pattern, and coupling constants are summarized in Fig.4.7. Comparison of ^{1}H NMRs of all three isomers was included in Fig 4.8.



(2Z,4Z) **4-99a** *(2E,4Z)* **4-98a** *(2E,4E)* **4-100**

R = R' = CO_2Me

	2*Z*, 4*Z*	2*E*, 4*Z*	2*E*, 4*E*
H_3	8.1 (d, *J* = 11.7 Hz)	8.6 (dd, *J* = 11.8, 1.3 Hz)	7.1 (dd, *J* = 15.3, 11.9 Hz)
H_4	7.1 (t, *J* = 11.6 Hz)	6.5 (t, *J* = 11.6 Hz)	7.5 (t, *J* = 9.9 Hz)
H_5	5.9 (d, *J* = 11.4 Hz)	5.9 (dd, *J* = 11.5, 1.3 Hz)	6.3 (dd, *J* = 15.3, 1.0 Hz)

Figure 4.7: ^{1}H NMR data for various isomers of dimethyl 2-(3,4-dichlorophenyl) hexa-2,4-dienedioate **4-98a**, **4-99a** and **4-100** (Substitution at 3- & 4-position on the aryl group were removed for clarity).

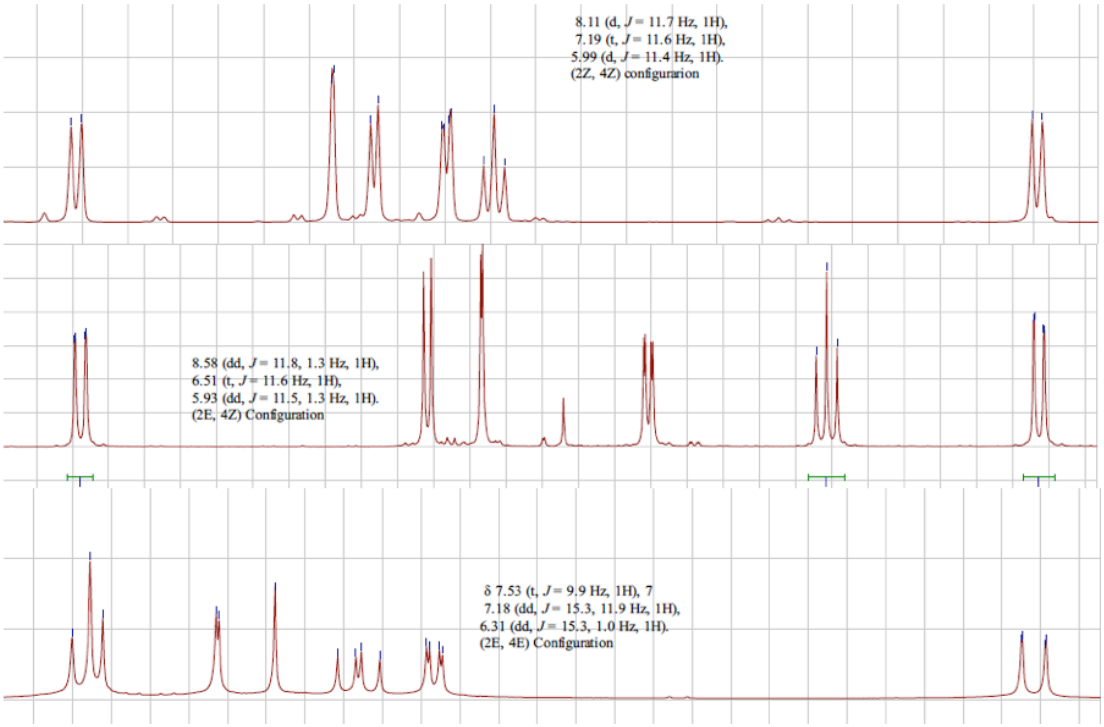


Fig 4.8: ^{1}H NMR comparison of three isomers **4-98a**, **4-99a** and **4-100**

The absolute configuration for the major product formed in the furan unraveling reaction was unambiguously determined by X-ray crystallography.

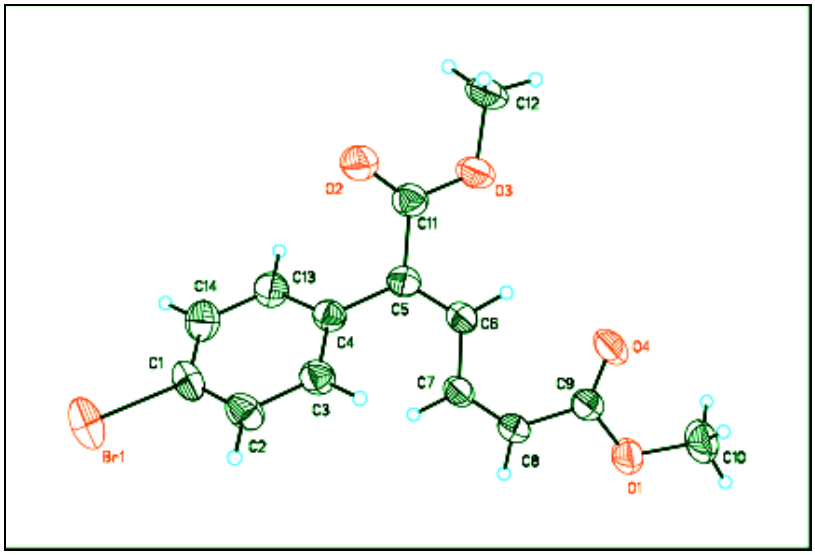


Figure 4.9: X-ray crystal structure of **4-98h**.

The compound was imported into maestro and energy minimized using Macromodel. The lowest energy conformation was generated (Shown in Fig. 4.10) that is more likely the bioactive conformation as well. As described earlier, as X-ray crystal structure of TAK1 is available, molecular docking studies are currently on going in the Davies' laboratory to rationalize the activity trend arising for these novel compounds.

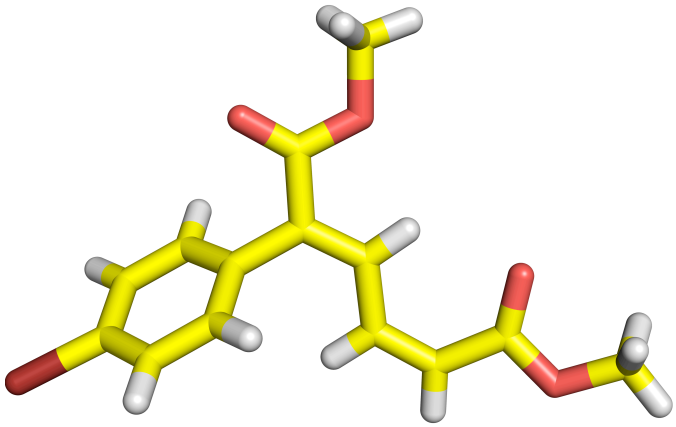


Fig 4.10: Possible bioactive conformer of **4-98h.**

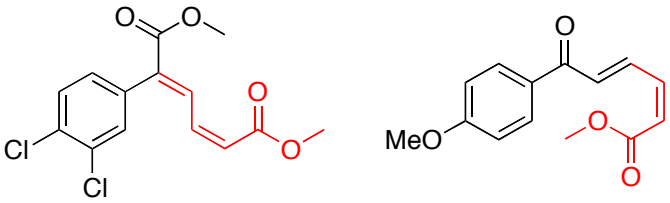
4.3.2.10 Summary of *In vitro* evaluation of acyclic RAL Analogues

The focused library of forty RAL-mimicking compounds (**HDAB-001 to HDAB-040**) generated via furan ring opening reaction along with Hypothemycin **(4-4)** were screened for TAK1 inhibition activity using various tumor and non-tumor cell lines in the laboratory of Prof. Andrei Bakin at Roswell Park Cancer Research Institute at Buffalo, NY. A series of *in vitro* and *in vivo* experiments were performed on acyclic RAL

analogues and two lead compounds were identified (Fig. 4.11). Complete results are summarized below.

1) <u>NFkB-luciferase reporter assay</u>: This assay was performed to test whether the novel synthetic compounds would be able to inhibit the TGF- β -TAK1-NF-kB axis.

It was found that **HDAB-001** and **HDAB-006** compounds at 10 μM reduced the NF-kB-Luc reporter activity by more than 60%, which indicates that these acyclic RAL could be viable therapeutic agents for TAK1 inhibition. These compounds did not show significant inhibition of the SMAD-dependent luciferase reporter.



HDAB-001
4-98a

HDAB-006
4-139d

Figure 4.11: Structures of the lead compounds.

2) <u>Gelatin Zymography assay</u>: This assay was designed to determine inhibition of MMP9 production. An important downstream target of the TGF- β -TAK1-NF-kB axis is MMP9, which contributes to breast cancer invasion, angiogenesis and metastases.

The synthetic compounds were tested in this assay in order to determine whether these novel compounds can inhibit the MMP9 production. It was found that **HDAB-001** and **HDAB-006** at 10 μM inhibited MMP9 production by > 60%. It was also found that

HDAB-001 and **HDAB-006** did not inhibit phosphorylation of ERK, whereas hypothemycin showed inhibition, which indicates selectivity of acyclic analogues.

3) Cytotoxicity studies: Based on these preliminary results, cytotoxicity studies have been performed on lead compounds using various cell lines. The results are summarized in the Table 4.4.

HDAB	Substitution	Isomer	MCF10A IC_{50} (μM)	MDA-231 IC_{50} (μM)	A549 IC_{50} (μM)
	Hypothemycin		2.0 ± 0.2	1.4 ± 0.2	
001	3,4-DiCl	(2*E*,4*Z*)	37.5 ± 5.74	4.6 ± 0.8	2.8 ± 0.2
002	4-OMe	(2*E*,4*Z*)			
003	3,4-DiOMe	(2*E*,4*Z*)			
005	2-OH	(2*E*,4*Z*)			
006	4-OMe-Keto	(2*E*,4*Z*)	1.8 ± 0.4	14.2 ± 2.2	41.27
007	3.4 -DiCl	(2*Z*,4*Z*)	64.2 ± 18.1	6.3 ± 1.0	7.6 ± 0.7
008	3,4- DiCl	(2*E*,4*E*)	13.6 ± 1.2		4.9 ± 0.4
009	4-Cl	(2*E*,4*Z*)			
010	4-Br	(2*E*,4*Z*)	49.9 ± 2.0	4.1 ± 1.1	4.8 ± 0.4
011	4-I	(2*E*,4*Z*)	> 100	4.9 ± 1.0	3.6 ± 0.5
012	4-NO_2	(2*E*,4*Z*)			
013	4-CF_3	(2*E*,4*Z*)			
014	3,5 –DiCF_3	(2*E*,4*Z*)			
015	4-Br	(2*Z*,4*Z*)	32 ± 0.1	1.6 ± 0.58	4.7 ± 1.0
016	4-I	(2*Z*,4*Z*)			
017	4-NO_2	(2*Z*,4*Z*)			
018	4-Ph	(2*E*,4*Z*)			
019	Triene-OMe	(2*E*,4*Z*)			
020	Triene-Me	(2*E*,4*Z*)			
021	Phosphonate	(2*E*,4*Z*)			
022	3,4 -DiBr	(2*E*,4*Z*)		2.1 ± 1.8	
023	3,4-DiBr-Et	(2*E*,4*Z*)		36.5 ± 9.4	
024	3,4-DiBr-^{i}Pr	(2*E*,4*Z*)			
025	3,4-DiCl-Me	(2*E*,4*Z*)		14.7 ± 2.7	
026	Di-acid	(2*E*,4*Z*)		> 100	

027	Mono-acid	(2*E*,4*Z*)		> 100	
028	2-Naphthyl	(2*E*,4*Z*)		4.4 ± 0.5	
029	Benzofuran	(2*E*,4*Z*)		48.2 ± 31.2	
030	3-Cl,4-I	(2*E*,4*Z*)			
031	3,4-DiCl-^{t}Bu	(2*E*,4*Z*)		> 100	
032	Boc-Indole	(2*E*,4*Z*)		> 50	
033	Furan diol	(2*E*,4*Z*)		> 50	
034	3,4DiCl-Keto	(2*E*,4*Z*)		4.9 ± 0.2	
035	4-Br-Keto	(2*E*,4*Z*)		8.4 ± 1.6	
036	3,4-OCH_2O	(2*E*,4*Z*)		18.0 ± 2.5	
037	-$O(CH_2)_2O$	(2*E*,4*Z*)		22.0 ± 3.5	
038	Boc-Isatin	(2*E*,4*Z*)		21.2 ± 2.8	
039	Isatin	(2*E*,4*Z*)		> 45	

Table 4.4: IC_{50} values of RAL analogues in μM. (MCF-10A = Human breast non-tumor cell lines; MDA-231 = Human breast tumor cell lines; A549 = Human lung adenocarcinoma cell lines)

It was found that HDAB compounds were significantly less toxic to normal cells (MCF10A cells) compared to hypothemycin. **HDAB-001** analogue was also tested in many different kinds of cancer cell lines such as MDA-MB-231, MCF7 and Ras-transformed mammary epithelial NMuMG cells. Delightfully, **HDAB-001** analogue was found to reduce the colony formation at 1-2 μM concentration in all tested cell lines. When the cytotoxicity of two isomers of *cis-enone* with bromo substitution at the 4-position was evaluated in cancer cells, the compound with the (1*E*, 2*Z*) configuration **HDAB-010** was found to be less toxic to normal cells as compared to the compound with the (1*Z*, 2*Z*) configuration **HDAB-015**.

In a separate study, it was found that inhibition of TAK1 will sensitize the cancer cells towards drugs such as Taxol. This suggests that selective TAK1 inhibitors (acyclic RAL analogues) could be used in combination with standard chemotherapeutic agents.

In summary, all these studies led to the discovery of two lead compounds **HDAB-001** and **HDAB-006**. In order to test the toxicity of these lead compounds in mice, multi gram quantities of lead compounds was synthesized. **HDAB-001** was synthesized in ~ 20 grams quantity, whereas **HDAB-006** was synthesized in ~ 1 gram quantity.

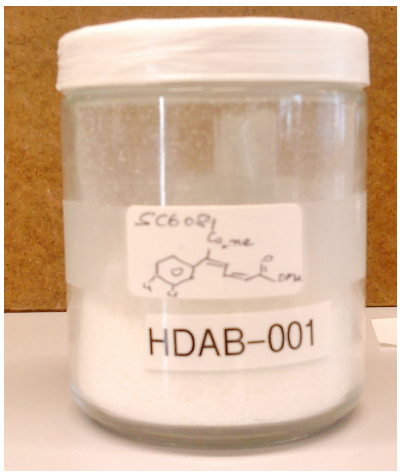


Figure 4.12: Multi gram quantity of one of the lead compounds (**HDAB-001**).

4.3.2.11 Summary of *In vivo* evaluation of lead compounds:

1) **Toxicity studies:** A single-dose Maximum Tolerated Dose (MTD) study was initiated as multi-gram quantities of **HDAB-001** was made available. Mice (SCID/CB17 8-week-old females) tolerated intra-peritoneal injection of 300 mg/kg of **HDAB-001**, which is

three times higher than published MTD for Hypothemycin (100 mg/kg). Moreover, the animal did not show any drug-related weight loss and distress and no animal death was found.

2) Efficacy studies: MDA-MB-231 cell lines (human breast cancer cells) were injected subcutaneously in to mice to induce tumor. A week later, **HDAB-001** compound (100 mg/kg) was injected daily to find the inhibition of tumor growth (TGI). This study clearly showed that **HDAB-001** reduced tumor growth by 56.9% at the end of study, which is statistically significant.

More efforts towards optimizing the efficacy and pharmacological properties of identified lead compounds are currently underway in Dr. Davies laboratory. The studies in the Andrei Bakin lab geared towards testing synthetic compounds against broad spectrum of cancer cell lines and finding out the metabolic stability, solubility, bioavailability, toxicity, cytotoxicity, efficacy of synthetic compounds.

4.4 Conclusions

In the first approach, a convergent synthesis of 5-(*Z*)-7-oxozeaenol was proposed and synthetic attempts were made towards the key fragments in the model substrate. Even with a novel convergent approach, synthesis of 5-(*Z*)-7-oxozeaenol was becoming lengthy and time consuming. In order to expedite the drug discovery process, a second approach was employed in which Rh (II) catalyzed furan unraveling methodology was utilized as a key step to synthesize a novel acyclic RAL library of compounds (~ 40).

These novel analogues are structurally different from RAL natural products but possess the *cis-enone* pharmacophore required for the TAK1 inhibition activity. From the focused library of compounds, lead compounds were identified and attempts were made to further optimize the lead compounds thorough iterative structural modification. Through this collaborative approach, a structure activity relationship for the novel set of compounds was established and a very potent and selective TAK1 inhibitor was identified. A number of analogues were found to show submicromolar inhibition towards TAK1. These analogues were also found to be less toxic to normal cell lines as compared to tumor cell lines. **HDAB001** analogue was found to decrease the growth of human breast carcinoma xenograft in a mouse preclinical model without noticeable side effects such as distress or weight loss. More preclinical, cytotoxic studies on this library of compounds are still on going in Prof. Andrei Bakin laboratory.

4.5 References

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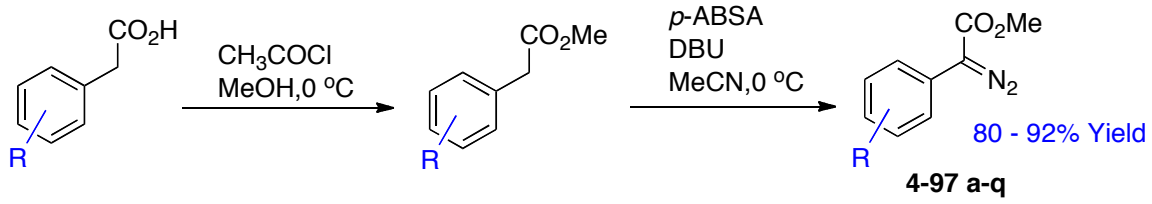
Experimental section for TAK1 project

^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian spectrometer at 300, 400, 500, or 600 MHz, and ^{13}C NMR at either 75, 100, or 125 MHz with the sample solvent being $CDCl_3$ unless stated otherwise. The following abbreviations are used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplet. Coupling constants were taken directly from the spectra and are uncorrected. IR spectra were obtained using a Thermo Scientific Nicolet *i*S10 FT-IR and reported in units of cm^{-1}. Melting points were measured on an electrothermal melting point apparatus and are uncorrected. High Resolution Mass spectral (HRMS) determinations (pos-APCI) were performed by the Instrument Center of the Department of Chemistry, Emory University. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross GA. Optical rotations were measured at the sodium D line (589 nm) and reported as follows: $[\alpha]_D^{25}$, concentration (c in g/100 mL) and solvent all rotations are measured at 25.0 ^{o}C. Enantiomeric excess was determined by Varian Pro Star high performance liquid chromatography (HPLC) using chiral analytical columns (Chiralcel OD, Chiralcel OD-H, Chiralcel OJ, Chiralpak AD-H, Chiralpak AS-H, Chiralpack AD-RH, (*R,R*)-Whelk, or (*S,S*)- Whelk chiral columns and conditions are specified for individual compounds)(UV detection at 254 or 273 nm). Analytical TLC was performed on 0.25 mm E. Merck silica gel (60F-254) plates using UV light. Phosphomolybdic acid (PMA), $KMnO_4$, ninhydrin or dinitrophenylhydrazine (DNP) was used as visualizing agent if necessary.

Glassware was dried in an oven overnight prior to use. Reactions were conducted under an atmosphere of argon unless stated otherwise. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Hexanes, toluene, THF, DCM, Diethyl ether and acetonitrile were dried by passage through activated alumina columns in a solvent purification system prior to use. All other reagents were purchased from Aldrich, Alfa Aesar, or Acros chemical companies and used without additional purification unless noted. Rhodium catalysts like $Rh_2(OAc)_4$, Rh_2(*S*-DOSP)$_4$, Rh_2(*R*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$, were obtained from lab sources and were used as is.

Synthesis of aryl diazoacetates: Representative procedure



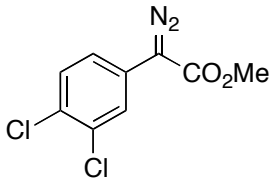
4-97 a-q

In a flame dried round bottom flask, 2-(4-bromophenyl) acetic acid (50 mmol, 1 eq.) was dissolved in MeOH (50 mL) and cooled to 0 °C. Acetyl chloride (60 mmol, 1.2 eq.) was added dropwise at 0 °C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl. Extracted twice; combined organic layers were washed with

brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

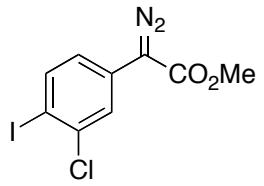
The resultant methyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (60 mmol, 1.2 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (120 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100 mL); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 11.16 g (93 % yield) of ayellow crystalline solid.

Methyl 2-diazo-2- (3,4-dichlorophenyl) acetate (4-97 a)



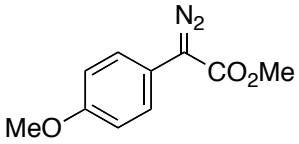
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 3.87 (s, 3H) (94% yield). ^{1}H NMR data was in accordance with the literature.[1]

Methyl 2-(3-chloro-4-iodophenyl)-2-diazoacetate (4-97 o)



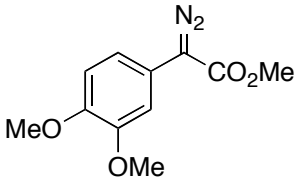
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H) (95% yield). ^{1}H NMR data was in accordance with the literature.[1]

Methyl 2-diazo-2- (4-methoxyphenyl) acetate (4-97 b)



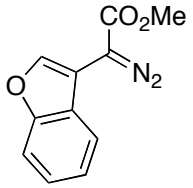
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H) (82% Yield). ^{1}H NMR data was in accordance with the literature.[2,3]

Methyl 2-diazo-2- (3,4-dimethoxyphenyl) acetate (4-97 c)



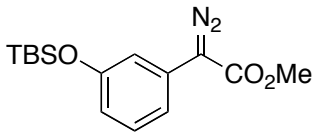
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.03 (d, J = 8.5 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H) (93% Yield). ^{1}H NMR data was in accordance with the literature.[4]

Methyl 2-(benzofuran-3-yl)-2-diazoacetate (4-108)



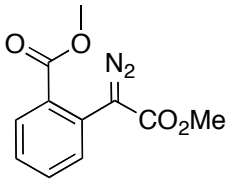
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 3.90 (s, 3H). ^{1}H NMR data was in accordance with the literature.[5]

Methyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl)-2-diazoacetate (4-97 e)



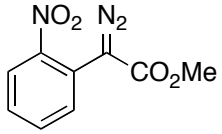
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (t, *J* = 8.0 Hz, 1H), 6.90-6.83 (m, 3H), 3.83 (s, 3H), 0.90 (s, 9H) 0.09 (s, 6H). ^{1}H NMR data was in accordance with the literature.[6]

Methyl 2-(1-diazo-2-methoxy-2-oxoethyl) benzoate (4-103)



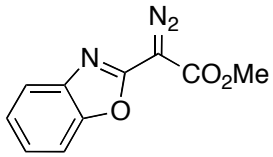
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H). ^{1}H NMR data was in accordance with the literature.[7]

Methyl 2-diazo-2-(2-nitrophenyl)acetate (4-101)



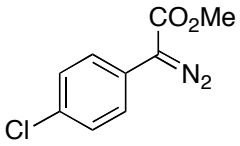
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 3.82 (s, 3H). ^{1}H NMR data was in accordance with the literature.[8,9]

Methyl 2-(benzo[*d*]oxazol-2-yl)-2-diazoacetate (4-102)



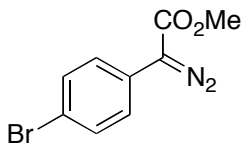
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.32-7.27 (m, 2H), 3.96 (s, 3H). ^{1}H NMR data was in accordance with the literature.[9]

Methyl 2-(4-chlorophenyl)-2-diazoacetate (4-97 g)



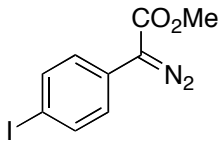
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H). ^{1}H NMR data was in accordance with the literature.[10]

Methyl 2-(4-bromophenyl)-2-diazoacetate (4-97 h)



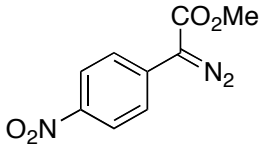
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H). ^{1}H NMR data was in accordance with the literature.[8]

Methyl 2-diazo-2- (4-iodophenyl) acetate (4-97 i)



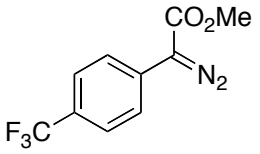
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H). ^{1}H NMR data was in accordance with the literature.[8,11]

Methyl 2-diazo-2- (4-nitrophenyl) acetate (4-97 j)



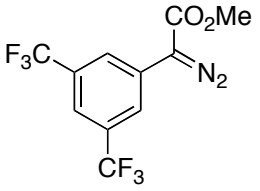
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (t, *J* = 7.5 Hz, 2H), 7.66(t, *J* = 7.5 Hz, 2H), 3.91 (s, 3H). ^{1}H NMR data was in accordance with the literature.[12]

Methyl 2-diazo-2- (4-(trifluoromethyl) phenyl) acetate (4-97 k)



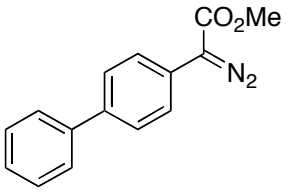
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 4H), 3.88 (s, 3H). ^{1}H NMR data was in accordance with the literature.[13]

Methyl 2-diazo-2- (3,5-(Bis trifluoromethyl) phenyl) acetate (4-97 l)



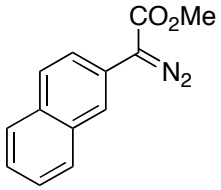
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 2H), 7.65 (s, 1H), 3.91 (s, 3H). ^{1}H NMR data was in accordance with the literature.[14]

Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (4-97 d)



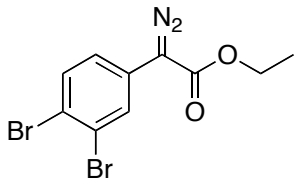
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.33-7.39 (m, 1H), 7.45 (t, J = 7.6 Hz, 2H) 7.54-7.66 (m, 6H). The spectroscopic data matches the previously reported data in the Davies group.

Methyl 2-diazo-2- (naphthalene-2-yl) acetate (4-97 h)



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.42-7.51 (m, 2H), 7.54 (dd, *J* = 8.6, 1.76 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 8.02 (s, 1H). The spectroscopic data matches the previously reported data in the Davies group.

Ethyl 2-diazo-2-(3,4-dibromophenyl)acetate(4-123 a)

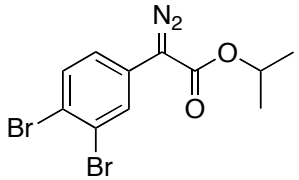


In a flame dried round bottom flask, 2-(3,4-dibromophenyl) acetic acid (293 mg, 1 mmol, 1 eq.) was dissolved in EtOH (10 mL) and cooled to 0 ^{o}C. Acetyl chloride (94 mg, 1.2 mmol, 1.2 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.43 (m, 2H), 7.05 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.50 (s, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 135.2, 134.6,

133.8, 129.8, 124.9, 123.5, 61.4, 40.4, 14.4; FT-IR (neat): 2980, 1731, 1556, 1461, 1157, 1014 cm^{-1}; HRMS (neg-APCI) calcd for $C_{10}H_9O_2Br_2$: 318.8974; Found: 318.8974.

The resultant ethyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (251 mg, 1.1 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^oC and 1,8-Diazabicycloundec-7-ene (DBU) (274 mg, 1.8 mmol, 2 eq.) was added dropwise at 0 ^oC. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2 × 100 mL); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 227 mg (65 % yield) of a yellow crystalline solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 2.3 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.19 (dd, J = 8.5, 2.3 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 133.8, 128.2, 127.0, 125.5, 123.4, 121.2, 61.4, 14.5; FT-IR (neat): 2091, 1694, 1579, 1387, 1232, 1170 cm^{-1}; HRMS (neg-APCI) calcd for $C_9H_5O_1N_3Br_2$: 328.8793; Found: 328.8806.

Isopropyl 2-diazo-2-(3,4-dibromophenyl)acetate (4-123 b)

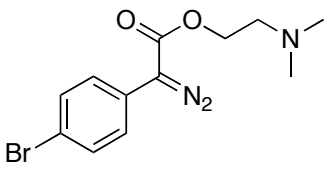


In a flame dried round bottom flask, 2-(3,4-dibromophenyl)acetic acid (293 mg, 1 mmol, 1 eq.) was dissolved in Isopropanol (10 mL) and cooled to 0 ^oC. Acetyl chloride (94 mg, 1.2 mmol, 1.2 eq.) was added dropwise at 0 ^oC. The resultant reaction mixture

was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.44 (m, 2H), 7.05 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.97 (m, *J* = 6.3 Hz, 1H), 3.48 (s, 2H), 1.20 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 135.2, 134.5, 133.6, 129.6, 124.8, 123.3, 68.7, 40.6, 21.8; FT-IR (neat): 1726, 1585, 1102, 1014, 813 cm^{-1}; HRMS (neg-APCI) calcd for $C_{11}H_{11}O_2Br_2$: 328.8793; Found: 332.9129.

The resultant isopropyl acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (251 mg, 1.1 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (274 mg, 1.8 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2X100 mL); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 225 mg (62 % yield) of a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.20 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.25-5.06 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 133.8, 128.3, 127.2, 125.4, 123.4, 121.1, 69.3, 22.1; FT-IR (neat): 2086, 1696, 1581, 1468, 1167, 1102, 807 cm^{-1}; HRMS (neg-APCI) calcd for $C_{10}H_{12}O_1N_1Br_2$: 319.9280; Found: 319.9278.

2-(Dimethylamino)ethyl 2-(4-bromophenyl)-2-diazoacetate (4-123 c)

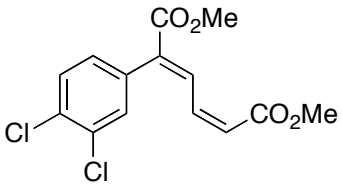


In a flame dried round bottom flask, 2-(4-bromophenyl) acetic acid (530 mg, 1 mmol, 1 eq.) was dissolved in 2-(dimethylamino)ethanol (10 mL) and cooled to 0 ^{o}C. Acetyl chloride (94 mg, 1.2 mmol, 1.2 eq.) was added dropwise at 0 ^{o}C. The resultant reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and saturated NH_4Cl. Extracted twice; combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude methyl acetate mixture was taken to next step without further purification.

The resultant 2-(dimethylamino)ethyl 2-(4-bromophenyl)acetate was dissolved in acetonitrile and *p*-acetamidobenzene sulfonyl azide (*p*-ABSA) (251 mg, 1.1 mmol, 1.1 eq.) was added. The reaction mixture was cooled to 0 ^{o}C and 1,8-Diazabicycloundec-7-ene (DBU) (274 mg, 1.8 mmol, 2 eq.) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at rt overnight. Reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted twice with diethyl ether (2X100 mL); combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate 62 mg (20 % yield) of a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.59 (m, 2H), 7.55-7.44 (m, 2H), 4.51 (d, J = 5.5 Hz, 2H), 2.78 (d, J = 5.3 Hz, 2H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 131.9, 125.2, 124.6, 119.2, 62.9, 57.7,

45.7, 45.7; FT-IR (neat): 2082, 1700, 1490, 1455, 1370, 1033, 810 cm^{-1}; HRMS (neg-APCI) calcd for $C_{12}H_{15}O_2N_3Br_1$: 312.0342; Found: 312.0342.

(2*E*, 4Z)-dimethyl 2-(3,4-dichlorophenyl) hexa-2, 4-dienedioate (4-98 a)



HDAB-001

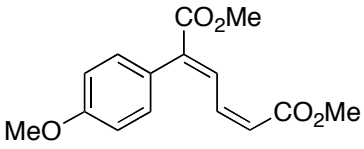
88% Yield

A solution of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (244 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h to a solution of 2-methoxy furan (0.4 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.001 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 276 mg (88%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.6 0(d, J = 11.5 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.06 (dd, J =8.0 Hz, 1H), 6.52 (t, J = 11.5 Hz, 1H), 5.94 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 165.7, 137.9, 136.8, 134.8, 133.8, 132.7, 132.3, 132.0, 130.0, 129.6, 124.8, 52.5, 51.6; FT-IR (neat): 1717, 1437, 1200, 1175, 831 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}Cl_2O_4$: C, 53.36; H, 3.84; Found: C, 53.38; H, 3.92.

This compound was found to be the best lead for TAK1 inhibition. The same reaction was performed in 20 mmol scale to get 3.8 g (80 % yield) of product. This

reaction was later carried out in 100 mmol scale to get 22 g (90 % yield) of product. (sent part of it for *in vivo* analysis)

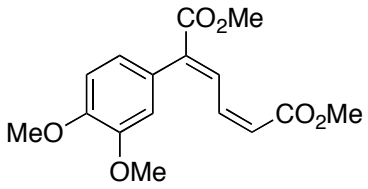
(2*E*, 4*Z*)-dimethyl 2-(4-methoxyphenyl) hexa-2, 4-dienedioate (4-98 b)



HDAB-002
82% Yield

A solution of methyl 2-diazo-2-(4-methoxyphenyl)acetate (412 mg, 2 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h (5 mL/hr rate) to a solution of 2-methoxy furan (0.8 mL, 4 mmol, 2 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 452 mg (82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, J = 11.5 Hz, 1H), 7.15 (dd, J = 8.5 Hz, 2H), 6.89 (dd, J = 8.5 Hz, 2H), 6.63 (t, J = 11.5 Hz, 1H), 5.84 (d, J =11.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.8, 166.3, 159.9, 139.6, 133.3, 131.9, 128.8, 126.2, 123.2, 113.6, 55.4, 52.6, 51.7; FT-IR (neat): 1710, 1605, 1243, 1166, 828; HR-MS (EI) *m/z calcd* for $[C_{15}H_{16}O_5]^+$ 277.1071; Found: 277.1061; Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; Found: C, 65.24; H, 5.95.

(2*E*, 4*Z*)-dimethyl 2-(3,4-dimethoxyphenyl) hexa-2, 4-dienedioate (4-98 c)

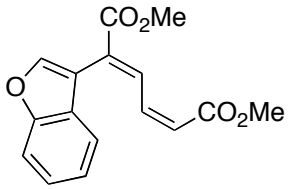


HDAB-003

99% Yield

A solution of methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (472 mg, 2 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h (5 mL/hr rate) to a solution of 2-methoxy furan (0.4 mL, 4 mmol, 2 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 1:1 hexane/Et_2O as eluant to isolate a yellow oily liquid, 605 mg (99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (d, J = 11.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.03 (d, 2H), 6.94 (t, J = 11.5 Hz, 1H), 6.14 (d, J = 11.5 Hz, 1H), 4.16 (s, 3H), 4.12 (s, 3H), 4.08 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4 (C), 166.0 (C), 149.2 (C), 148.3 (C), 139.3 (CH), 139.2 (C), 133.2 (CH), 126.3 (C), 123.2 (CH), 123.0 (CH), 113.4 (CH), 110.5 (CH), 55.8 (CH_3), 55.7 (CH_3), 52.3 (CH_3), 51.4 (CH_3); FT-IR (neat): 1700, 1511, 1242, 1166, 828; HRMS (EI) *m/z calcd* for $[C_{16}H_{18}O_6]^+$ 306.1098; Found: 306.1100.

(2*E*, 4*Z*)-dimethyl 2-(benzofuran-3-yl) hexa-2, 4-dienedioate (4-115 a)

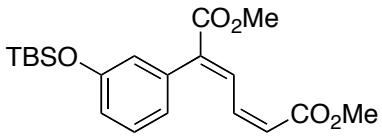


HDAB-004

88% Yield

A solution of methyl 2-(benzofuran-3-yl)-2-diazoethanoate (108 mg, 0.5 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h (5 mL/hr rate) to a solution of 2-methoxy furan (0.1 mL, 1 mmol, 2 eq.) and $Rh_2(OAc)_4$ (3 mg, 0.005 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 126 mg (88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (d, J = 11.8 Hz, 1H), 7.8 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.54-7.43 (m, 2H), 6.96 (t, J = 11.8 Hz, 1H), 6.1 (d, J = 11.8 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (C), 165.9 (C), 154.8 (C), 145.2 (CH), 138.6 (CH), 135.2 (CH), 129.3 (C), 127.1 (C), 124.6 (CH), 123.6 (CH), 122.9 (CH), 120.6 (CH), 114.1 (C), 111.5 (CH), 52.4 (CH_3), 51.5 (CH_3); FT-IR (neat): 1713, 1451, 1239, 1175, 1101, 747; HR-MS (EI) *m/z calcd* for $[C_{16}H_{14}O_5]^+$ 286.0836; Found: 286.0840.

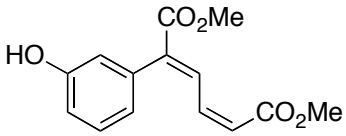
(2*E*, 4*Z*)-dimethyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl) hexa-2, 4-dienedioate (4-98 e)



74% Yield

A solution of methyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl)-2-diazoethanoate (613 mg, 2 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h (5mL/hr rate) to a solution of 2-methoxy furan (0.4 mL, 4 mmol, 2 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate a yellow oily liquid, 560 mg (74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, *J* = 12 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.64 (t, *J* = 11.5 Hz, 1H), 5.90 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 165.8 (C), 155.0 (C), 139.1 (C), 138.9 (CH), 134.9 (C), 133.5 (CH), 128.8 (CH), 123.3 (CH), 123.1 (CH), 121.9 (CH), 120.0 (CH), 52.1 (CH_3), 51.5 (CH_3), 25.4 (CH_3), 17.99 (C), -4.6 (CH_3); FT-IR (neat): 1708, 1432, 1192, 1031, 775; HRMS (EI) *m/z calcd* for $[C_{20}H_{28}O_5Si]^+$ 399.1598; Found: 399.1614.

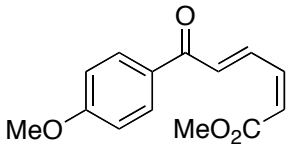
(2*E*, 4*Z*)-dimethyl 2-(3-hydroxyphenyl) hexa-2, 4-dienedioate (4-98 f)



HDAB-005
32% Yield

(2*E*, 4*Z*)-dimethyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl) hexa-2, 4-dienedioate (188 mg, 0.5 mmol, 1 eq.) was dissolved in THF (10 mL) and cooled to 0 ^{o}C. Tetra n-butyl ammonium fluoride (1M solution in THF 0.55 mL, 0.55 mmol, 1.1 eq.) was added slowly over a period of 1 h. The reaction mixture was stirred overnight, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a yellow oily liquid, 43 mg (32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* = 11.7 Hz, 1H), 7.4-7.39 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.93-6.78 (m, 3H), 6.0 (d, *J* = 11.7 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 166.8, 156.2, 139.6, 135.6, 134.5, 129.8, 124.1, 122.9, 117.7, 116.2, 53.1, 52.2; FT-IR (neat): 1710, 1237, 1193, 1170, 776; HRMS (pos-APCI) calcd for $C_{14}H_{15}O_5$: 263.0914; Found: 263.0911.

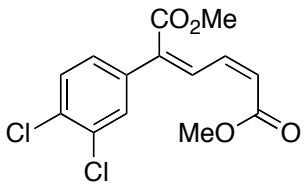
(2*Z*, 4*E*)-methyl 6-(4-methoxyphenyl)-6-oxohexa-2, 4-dienoate (4-139 d)



HDAB-006
10% Yiled

A solution of methyl 2-diazo-1- (4-methoxyphenyl) ethanone (176 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2h (5mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.001 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 25 mg (10%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43-8.34 (dd, *J* = 12 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.1 (d, *J* = 15.3 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.76 (t, *J* = 11.4 Hz, 1H), 6.0 (d, *J* = 11 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5 (C), 166.3 (C), 164.1 (C), 141.8 (CH), 138.0 (CH), 133.6 (CH), 131.5 (CH), 131.0 (C), 125.0 (CH), 114.4 (CH), 56.0 (CH_3), 52.1 (CH_3); FT-IR (neat): 1712, 1602, 1247, 1165, 838; HRMS (pos-APCI) calcd for $C_{14}H_{15}O_4$: 247.0964; Found: 247.0962; Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73; Found: C, 68.11; H, 5.62.

(2*Z*, 4*Z*)-dimethyl 2-(3,4-dichlorophenyl) hexa-2, 4-dienedioate (4-99 a): Minor isomer was also isolated.

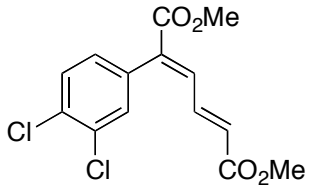


HDAB -007

2% Yield

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, *J* = 12 Hz, 1H), 7.52 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 9 Hz, 1H), 7.17 (t, *J* = 11.5 Hz, 1H), 5.97 (d, *J* = 11.5 Hz, 1H), 3.88 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 166.1 (C), 138.6 (CH), 137.8 (C), 136.4 (C), 133.0 (C), 132.7 (C), 130.5 (CH), 130.4 (CH), 129.3 (CH), 126.8 (CH), 122.6 (CH), 52.45 (CH_3), 51.54 (CH_3); FT-IR (neat): 1717, 1437, 1200, 1175, 831 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{14}H_{13}O_4Cl_2$: 315.0185; Found: 315.0184.

(2*E*, 4*E*)-dimethyl 2-(3,4-dichlorophenyl) hexa-2, 4-dienedioate (4-100)



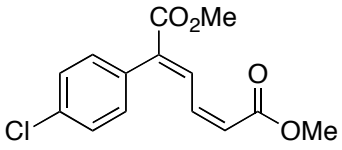
HDAB -008

60% Yield

(2*E*, 4*Z*)-dimethyl 2-(3,4-dichlorophenyl) hexa-2, 4-dienedioate (31 mg, 0.1 mmol, 1 eq.) was dissolved in THF (1mL) and then iodine (3 mg, 0.01 mmol, 0.1 eq.) was added at rt. The reaction mixture was stirred was stirred for an additional 1 h, and

then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate an oily liquid, 6 mg (60%).[15] ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 (t, *J* = 12 Hz, 8.5 Hz, 2H), 7.33 (d, *J* = 2 Hz, 1H), 7.15 (dd, *J* = 12 Hz, 3.5 Hz, 1H), 7.06 (dd, *J* = 8 Hz, 1.5 Hz, 1H), 6.28 (d, *J* = 15.5 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (C), 166.1 (C), 138.3 (CH), 137.7 (CH), 136.8 (C), 133.7 (C), 133.0 (C), 132.5 (C), 131.8 (CH), 130.2 (CH), 129.4 (CH), 129.1 (CH), 52.73 (CH_3), 51.9 (CH_3). FT-IR (neat): 1717, 1437, 1200, 1175, 831 cm^{-1}; HR-MS (pos-APCI) calcd for $C_{14}H_{13}O_4Cl_2$: 315.0185; Found: 315.0184.

(2*E*, 4Z)-dimethyl 2-(4-chlorophenyl) hexa-2, 4-dienedioate (4-98 g)



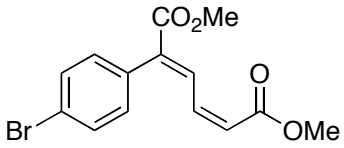
HDAB -009

93 % Yield

A solution of methyl 2-(4-chlorophenyl)-2-diazoacetate (631 mg, 3 mmol, 1 eq.) in hexanes (25 mL) was added by syringe pump over 2.5h (10 mL/hr rate) to a solution of 2-methoxy furan (0.6 mL, 6 mmol, 2 eq.) and $Rh_2(OAc)_4$ (15 mg, 0.003 mmol, 0.01 eq.) in hexane (25 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate an oily liquid, 789 mg (93%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 12.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 11.5 Hz, 1H), 5.91 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 165.9 (C), 138.5 (CH), 138.2 (C), 134.5 (C), 134.1

(CH), 132.3 (C), 131.6 (CH), 128.3 (CH), 124.1 (CH), 52.53 (CH_3), 51.64 (CH_3); FT-IR ($CHCl_3$): 1717, 1437, 1244, 1200, 1175, 1014, 831 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{14}H_{13}O_4Cl_1]^+$ 280.0497; Found: 280.0500; Anal. Calcd. for $C_{14}H_{13}O_4I_1$: C, 59.90; H, 4.67; Found: C, 60.15; H, 4.63.

(2*E*, 4*Z*)-dimethyl 2-(4-bromophenyl) hexa-2, 4-dienedioate (4-98 h)

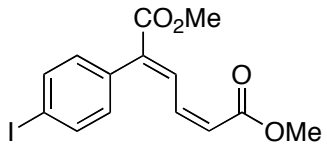


HDAB -010

80 % Yield

A solution of methyl 2-(4-bromophenyl)-2-diazoacetate (765 mg, 3 mmol, 1 eq.) in hexanes (25 mL) was added by syringe pump over 2.5h (10 mL/hr rate) to a solution of 2-methoxy furan (0.6 mL, 6 mmol, 2 eq.) and $Rh_2(OAc)_4$ (15 mg, 0.003 mmol, 0.01 eq.) in hexane (25 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate an oily liquid, 747 mg (80%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, *J* = 12.0 Hz, 1H), 7.53(d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.56 (t, *J* = 11.5 Hz, 1H), 5.91 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8(C), 165.8 (C), 138.4 (CH), 138.2 (C), 134.1 (CH), 132.7 (C), 131.9 (CH), 131.2 (CH), 124.1 (CH), 122.7 (C), 52.48 (CH_3), 51.60 (CH_3); FT-IR ($CHCl_3$): 2951, 1719, 1626, 1578, 1437, 1244, 1011, 830 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{14}H_{13}O_4Br_1]^+$ 323.9992; Found: 323.9996. Anal. Calcd. for $C_{14}H_{13}O_4Br_1$: C, 51.71; H, 4.03; Found: C, 52.02; H, 4.04.

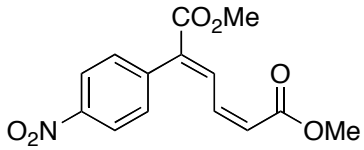
(2*E*, 4*Z*)-dimethyl 2-(4-iodophenyl) hexa-2, 4-dienedioate (4-98 i)



HDAB -011
93% Yield

A solution of methyl 2-diazo-2- (4-iodophenyl) acetate (906 mg, 3 mmol, 1 eq.) in hexanes (25 mL) was added by syringe pump over 2.5h (10 mL/hr rate) to a solution of 2-methoxy furan (0.6 mL, 6 mmol, 2 eq.) and $Rh_2(OAc)_4$ (15 mg, 0.003 mmol, 0.01 eq.) in hexane (25 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate an oily liquid, 1.046 g (93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (d, *J* = 11.5 Hz, 1H), 7.73(d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 11.5 Hz, 1H), 5.91 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9 (C), 165.9 (C), 138.6 (CH), 138.3 (C), 137.2 (CH), 134.2 (CH), 133.4 (C), 132.1 (CH), 124.2 (CH), 52.6 (CH_3), 51.7 (CH_3); FT-IR ($CHCl_3$): 1715, 1434, 1237, 1201, 1166, 1006 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{14}H_{13}O_4I_1]^+$ 371.9853; Found: 371.9854; Anal. Calcd. for $C_{14}H_{13}O_4I_1$: C, 45.18; H, 3.52; Found: C, 45.47; H, 3.54.

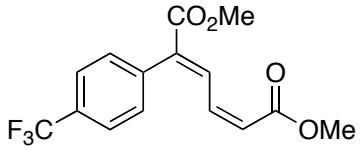
(2*E*, 4*Z*)-dimethyl 2-(4-nitrophenyl) hexa-2, 4-dienedioate (4-98 j)



HDAB -012
91% Yield

A solution of methyl 2-diazo-2- (4-nitrophenyl) acetate (663 mg, 3 mmol, 1 eq.) in hexanes (25 mL) was added by syringe pump over 2.5h (10 mL/hr rate) to a solution of 2-methoxy furan (0.6 mL, 6 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.003 mmol, 0.01 eq.) in hexane (25 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane /Et_2O as eluant to isolate a colorless oily liquid, 796 mg (91%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, J = 12.0 Hz, 1H), 8.26 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H), 6.50 (t, J = 11.5 Hz, 1H), 5.99 (d, J = 11.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (C), 165.6 (C), 147.6 (C), 140.6 (C), 137.4 (CH), 136.9 (C), 135.2 (CH), 131.3 (CH), 125.3 (CH), 123.18 (CH), 52.6 (CH_3), 51.7 (CH_3); FT-IR ($CHCl_3$): 1718, 1519, 1437, 1350, 1246, 1202, 1176 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{14}H_{13}O_6N_1]^+$ 291.0737; Found: 291.0738.

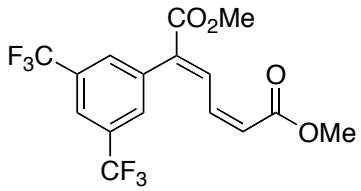
(2*E*, 4*Z*)-dimethyl 2-(4-(trifluoro methyl) phenyl) hexa-2, 4-dienedioate (4-98 k)



HDAB -013
81% Yield

A solution of methyl 2-diazo-2- (4-(trifluoromethyl) phenyl) acetate (244 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 1h (10 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.001 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 254 mg (81%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.65 (d, J = 12.0 Hz, 1H), 7.66 (d, J = 7.5 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H), 6.51 (t, J = 11.5 Hz, 1H), 5.93 (d, J = 11.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (C), 165.8 (C), 138.1 (CH), 137.9 (C), 137.6 (C), 134.7 (CH), 130.6 (CH), 125.0 (CH), 124.7 (CH), 52.6 (CH_3), 51.7 (CH_3). IR ($CHCl_3$): 1720, 1325, 1246, 1201, 1176, 1128, 1111, 1067 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{15}H_{13}O_4F_3]^+$ 314.0760; Found: 314.0755; Anal. Calcd. for $C_{15}H_{13}O_4F_3$: C, 57.33; H, 4.17; Found: C, 57.57; H, 4.19.

(2*E*, 4*Z*)-dimethyl 2-(3,5-(bis trifluoromethyl) phenyl) hexa-2, 4-dienedioate (4-98 l)

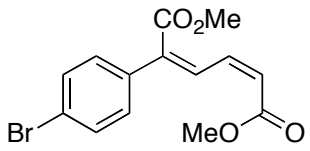


HDAB -014

83% Yield

A solution of methyl 2-diazo-2- (3,5-(Bis trifluoromethyl) phenyl) acetate (312 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 1h (10 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.001 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 8:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 317 mg (83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, J = 11.5 Hz, 1H), 8.56(s, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 6.44 (t, J = 11.5 Hz, 1H), 6.01 (d, J = 11.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.4, 165.9, 137.3, 136.3, 136.2, 136.0, 131.6, 130.7, 126.2, 122.6, 53.0, 52.0; FT-IR (neat): 1721, 1281, 1171, 1137 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{16}H_{12}O_4F_6]^+$ 382.0634; Found: 382.0638.

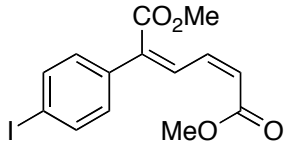
(2*Z*, 4*Z*)-dimethyl 2-(4-bromophenyl) hexa-2, 4-dienedioate (4-98 h): Minor isomer was also isolated.



HDAB -015
3% Yield

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 11.5 Hz, 1H), 7.49(d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 12 Hz, 1H), 5.94 (d, *J* = 11.5 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H). The product was not pure enough to fully characterize.

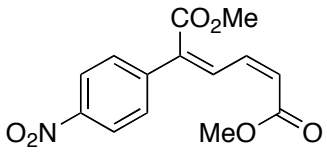
(2*Z*, 4*Z*)-dimethyl 2-(4-iodophenyl) hexa-2, 4-dienedioate (4-99 i): Minor isomer was also isolated.



HDAB -016
3% Yield

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, *J* = 11.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 7 Hz, 2H), 7.13 (t, *J* = 11.5 Hz, 1H), 5.95 (d, *J* = 11.5 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4(C), 166.2 (C), 139.4 (C), 139.0 (CH), 138.2 (C), 137.6 (CH), 135.8 (C), 129.1 (CH), 121.9 (CH), 52.3 (CH_3), 51.4 (CH_3). The product was not pure enough to fully characterize.

(2*Z*, 4*Z*)-dimethyl 2-(4-nitrophenyl) hexa-2, 4-dienedioate (4-98 j): Minor isomer was also isolated.

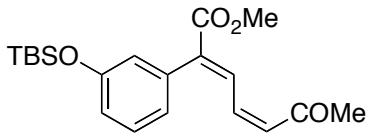


HDAB -017

1% Yield

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.5 Hz, 2H), 8.21(d, *J* = 12 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.26 (t, *J* = 12 Hz, 1H), 6.04 (d, *J* = 11 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H). The product was not pure enough to fully characterize.

(2*E*, 4*Z*)-methyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl)-6-oxohepta-2, 4-dienoate (4-160)

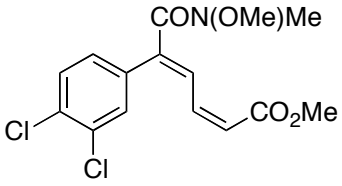


Decomposed

A solution of methyl 2-(3-(*tert*-butyldimethylsilyloxy) phenyl)-2-diazoethanoate (306 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 3h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.001 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 130 mg (36%). The product decomposed at room temperature after isolation. ^{1}H NMR

(500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 11.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.0s Hz, 1H), 6.8 (d, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 6.44(t, *J* = 11.5 Hz, 1H), 6.21 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 2.29 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.5 (C), 167.1 (C), 155.1 (C), 139.7 (C), 136.3 (CH), 135.0 (C), 134.2 (CH), 130.3 (CH), 128.8 (CH), 123.2 (CH), 121.9 (CH), 120.0 (CH), 52.2 (CH_3), 31.46 (CH_3), 25.5 (CH_3), 18.0 (C), 4.5 (CH_3); FT-IR (neat): 1710, 1434, 1190, 1015, 775; HRMS (EI) *m/z calcd* for $[C_{20}H_{28}O_4Si]^+$ 383.1649; Found: 383.1642.

(2*Z*, 4*E*)-methyl 5-(3,4-dichlorophenyl)-6-(methoxy (methyl) amino)-6-oxohexa-2, 4-dienoate (4-161)

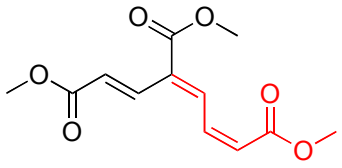


Decomposed

A solution of 2-diazo-2-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methylacetamide (27.41 mg, 0.1 mmol, 1 eq.) in hexanes (5 mL) was added by syringe pump over 1h (5mL/hr rate) to a solution of 2-methoxy furan (0.02 mL, 0.2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (1 mg, 0.001 mmol, 0.01 eq.) in hexane (5 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 30 mg (88%). The product decomposed at room temperature after isolation.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, J = 11.5 Hz, 1H), 7.48 (m, 3H), 6.66 (t, J = 11.5 Hz, 1H), 5.91 (d, J = 11.5 Hz, 1H), 3.76 (s, 3H), 3.48 (s, 3H), 3.23 (s, 3H).

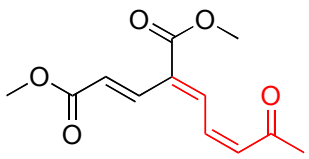
(1*E*,3*E*,5*Z*)-Trimethyl hexa-1,3,5-triene-1,3,6-tricarboxylate (4-118)



HDAB- 19
57% Yield

A solution of (*E*)-dimethyl 4-diazopent-2-enedioate (92 mg, 0.5 mmol, 1 eq.) in hexanes (5 mL) was added by syringe pump over 1 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.1 mL, 0.55 mmol, 1.1 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.02 mmol, 0.05 eq.) in hexane (5 mL). The reaction mixture was stirred for an additional 2 h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 72 mg (57% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, J = 12.0 Hz, 1H), 7.64 (d, J = 16.0 Hz, 1H), 7.11 (t, J = 12.0 Hz, 1H), 6.52 (d, J = 16.0 Hz, 1H), 6.0 (d, J = 12.0 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H). Data matches previously reported results.[16]

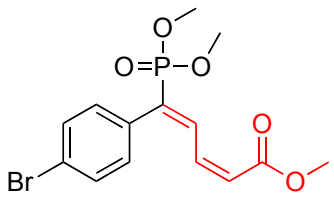
(2*E*,4*E*)-Dimethyl 4-((*Z*)-4-oxopent-2-en-1-ylidene)pent-2-enedioate (4-120)



HDAB- 20
39% Yield

A solution of (*E*)-dimethyl 4-diazopent-2-enedioate (92 mg, 0.5 mmol, 1 eq.) in hexanes (5 mL) was added by syringe pump over 1 h (5 mL/hr rate) to a solution of 2-methyl furan (0.1 mL, 0.55 mmol, 1.1 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.02 mmol, 0.05 eq.) in hexane (5 mL). The reaction mixture was stirred for an additional 2 h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 46 mg (39% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 12.0 Hz, 1H), 7.64 (d, *J* = 16.0 Hz, 1H), 6.92 (t, *J* = 12.0 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.39 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.30 (s, 3H). Data matches previously reported results.[16]

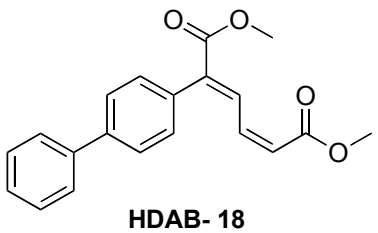
(2*Z*,4*E*)-Methyl 5-(4-bromophenyl)-5-(dimethoxyphosphoryl)penta-2,4-dienoate (4-128)



HDAB- 21
24% Yield

A solution of dimethyl ((4-bromophenyl)(diazo)methyl)phosphonate (150 mg, 0.5 mmol, 1 eq.) in hexanes (5 mL) was added by syringe pump over 1h (5 mL/hr rate) to a solution of 2-methoxy furan (5.5 mL, 55 mmol, 2 eq.) and Rh_2 $(OAc)_4$ (10 mg, 0.02 mmol, 0.05 eq.) in hexane (50 mL). The reaction mixture was stirred for an additional 2 h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 44 mg (24%). ^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 11.8, 1.1 Hz, 1H), 7.99-7.82 (m, 1H), 7.53-7.40 (m, 2H), 7.34-7.25 (m, 2H), 6.00 (dt, J = 11.5, 1.3 Hz, 1H), 3.80-3.61 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.4, 142.2, 142.1, 139.4, 139.3, 131.7, 130.0, 130.0, 123.7, 52.7, 52.7, 51.7; FT-IR ($CHCl_3$): 2951, 1719, 1626, 1578, 1437, 1244, 1011, 830 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{14}H_{17}O_5Br_1P_1]^+$ 374.9990; Found: 374.9991; Anal. Calcd. for $C_{14}H_{17}O_5Br_1P_1$: C, 44.82; H, 4.30; Br, 21.30; Found: C, 45.08; H, 4.25; Br, 21.48.

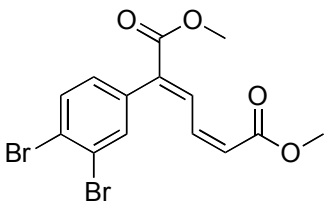
(2*E*,4*Z*)-dimethyl 2-([1,1'-biphenyl]-4-yl)hexa-2,4-dienedioate (4-98 d)



HDAB- 18
74% Yield

A solution of methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (1.2 g, 5 mmol, 1 eq.) in hexanes (50 mL) was added by syringe pump over 4h (25 mL/hr rate) to a solution of 2-methoxy furan (5.5 mL, 55 mmol, 2 eq.) and $Rh_2(OAc)_4$ (10 mg, 0.02 mmol, 0.05 eq.) in hexane (50 mL). The reaction mixture was stirred for an additional 2 h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 5:1 hexane/Et_2O as eluant to isolate an oily liquid, 1.17 g (74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, *J* = 12 Hz, 1H), 7.63-7.60 (m, 4H), 7.48-7.44 (m, 2H), 7.38-7.32 (m, 1H), 7.32-7.26 (m, 2H), 6.69 (t, *J* = 11.5 Hz, 1H), 5.90 (d, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ167.1, 165.8, 141.0, 140.1, 138.9, 138.9, 133.6, 132.6, 130.6, 128.6, 127.3, 126.8, 126.5, 123.4, 52.2, 51.3; FT-IR ($CHCl_3$): 2951, 1719, 1626, 1578, 1437, 1244, 1011, 830 cm^{-1}; HRMS (EI) *m/z calcd* for $[C_{20}H_{19}O_4]^+$ 323.12779; Found: 323.12740. Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.65; H, 5.45.

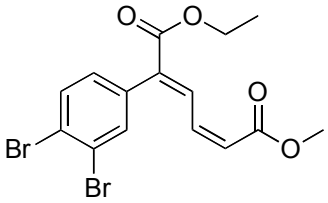
(2*E*,4*Z*)-dimethyl 2-(3,4-dibromophenyl)hexa-2,4-dienedioate (4-98 m)



HDAB-022
91% Yield

Anal. Calcd. for $C_{14}H_{12}Br_2O_4$: C, 41.62; H, 2.99; Found: C, 41.68; H, 2.98.

(2*E*,4*Z*)-1-ethyl 6-methyl 2-(3,4-dibromophenyl)hexa-2,4-dienedioate (4-124 a)

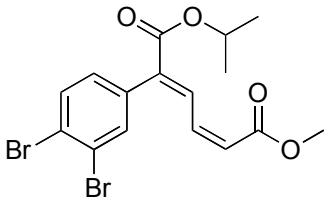


HDAB-023
84% Yield

A solution of ethyl 2-diazo-2-(3,4-dibromophenyl)acetate (345 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 339 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55-8.66 (m, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.0, 1.9 Hz, 1H), 6.55 (t, J = 11.5 Hz, 1H), 5.95 (dd, J =11.5, 0.92 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H), 5.30 (s, 1H), 4.29 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 165.7, 137.9, 137.0, 135.0, 134.5, 134.4, 133.1, 130.3,

124.9, 124.6, 124.4, 61.5, 51.6, 14.1; FT-IR (neat): 1708, 1461, 1195, 1172, 827 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{14}O_4Br_2$: 415.92643 Found: 415.92656; Anal. Calcd. for $C_{14}H_{12}Br_2O_4$: C, 41.62; H, 2.99; Found: C, 41.82; H, 2.88.

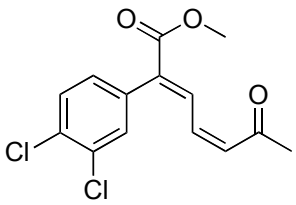
(2*E*,4*Z*)-1-isopropyl 6-methyl 2-(3,4-dibromophenyl)hexa-2,4-dienedioate (4-124 b)



HDAB-024
92% Yield

A solution of isopropyl 2-diazo-2-(3,4-dibromophenyl)acetate (360 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 395 mg (92%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 11.5 Hz, 1H), 7.60-7.69 (m, 1H), 7.50 (s, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.55 (t, J = 11.7 Hz, 1H), 5.94 (d, J =11.2 Hz, 1H), 5.07-5.22 (m, 1H), 3.80 (br. s, 3H), 1.31 (d, J = 5.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 165.4, 138.0, 137.4, 135.1, 134.7, 134.2, 133.1, 130.4, 124.8, 124.5, 124.4, 69.2, 51.6, 21.6; FT-IR (neat): 1705, 1436, 1196, 1172, 1104, 826 cm^{-1}; HRMS (pos-APCI) calcd for $C_{16}H_{16}O_4Br_2$: 429.9420; Found: 429.9420.

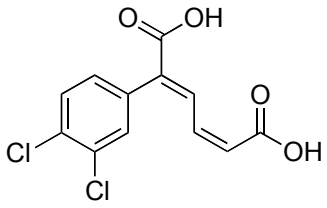
(2*E*,4*Z*)-methyl 2-(3,4-dichlorophenyl)-6-oxohepta-2,4-dienoate (4-129)



HDAB-025
30% Yield

A solution of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (244 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methyl furan (164 mg, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 274 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 11.2 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 1.5 Hz, 1H), 6.41 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.60-5.75 (m, 2H), 3.13 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.2, 166.2, 136.9, 135.4, 134.8, 133.7, 132.4, 131.9, 131.8, 131.4, 129.8, 129.5, 52.3, 31.3; FT-IR (neat): 1712, 1686, 1434, 1236, 1174, 1030, 761 cm^{-1}; HRMS (neg-APCI) calcd for $C_{14}H_{12}O_3Cl_2$: 298.0169; Found: 298.0169.

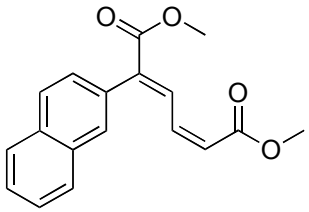
(2*E*,4*Z*)-2-(3,4-dichlorophenyl)hexa-2,4-dienedioic acid (4-134)



HDAB-026
90% Yield

A solution of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (980 mg, 4 mmol, 1 eq.) in hexanes (20 mL) was added by syringe pump over 2 h (10 mL/hr rate) to a solution of *tert*-butyl(furan-2-yloxy)dimethylsilane (1.5 g, 8 mmol, 2 eq.) and $Rh_2(OAc)_4$ (16 mg, 0.001 mmol, 0.01 eq.) in hexane (20 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The product was extracted with ether and 1M NaOH was added. All acid went into aqueous layer. Aqueous layer was washed with ether twice and separated. 1 M HCl solution was added to the aqueous layer until it becomes very acidic. The resultant white solid formed was filtered and dried over P_2O_5 (1 g, 90% yield). ^{1}H NMR (400 MHz, ACETONE-d_6): δ 8.72 (d, J = 12.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1 H), 7.52 (d, J = 1.8 Hz, 1H), 7.27 (dd, J = 8.2, 1.8 Hz, 1H), 6.67 (t, J = 11.7 Hz, 1H), 6.05 (d, J =11.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 166.8, 138.9, 137.8, 136.0, 135.7, 133.1, 132.6, 132.3, 131.4, 131.0, 126.4; FT-IR (neat): cm^{-1}; HRMS (pos-APCI) calcd for $C_{12}H_7O_4Cl_2$: 240.9828; Found: 240.9828.

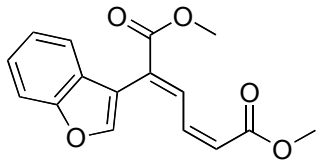
(2*E*,4*Z*)-dimethyl 2-(naphthalen-2-yl)hexa-2,4-dienedioate (4-98 n)



HDAB-028
79% Yield

A solution of methyl 2-diazo-2-(naphthalen-2-yl)acetate (226 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 233 mg (79%). ^{1}H NMR (400 MHz, $CDCl_3$-*d*): δ 8.65 (d, *J* =11.9 Hz, 1H), 7.86 (d, *J* =8.8 Hz, 4H), 7.68 (s, 1H), 7.47-7.59 (m, 2H), 3.81 (s, 3H), 7.35 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.64 (t, *J* = 11.5 Hz, 1H), 5.88 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 165.7, 139.2, 138.8, 133.8, 132.7, 132.5, 131.2, 129.6, 127.8, 127.4, 127.4, 127.4, 126.4, 126.1, 123.5, 52.2, 51.3; FT-IR (neat): 1711, 1434, 1194, 1174, 730 cm^{-1}; HRMS (neg-APCI) calcd for $C_{18}H_{16}O_4$: 296.1054; Found: 296.1054.

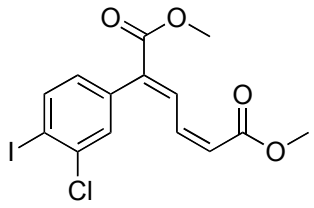
(2*E*,4Z)-dimethyl 2-(benzofuran-3-yl)hexa-2,4-dienedioate (4-115 a)



HDAB-029
90% Yield

A solution of methyl 2-(benzofuran-3-yl)-2-diazoacetate (216 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 257 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 11.9 Hz, 1H), 7.69 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.30-7.43 (m, 2H), 7.21-7.30 (m, 1H), 6.78 (t, J = 11.5 Hz, 1H), 5.92 (d, J = 11.2 Hz, 1H), 5.29 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 165.8, 154.8, 145.2, 145.2, 138.6, 135.2, 129.2, 127.1, 124.5, 123.6, 122.9, 120.6, 114.1, 111.4, 53.3, 52.3, 51.4; FT-IR (neat): 1712, 1451, 1435, 1195, 1173, 744 cm^{-1}; HRMS (neg-APCI) calcd for $C_{16}H_{14}O_5$: 286.0846; Found: 286.0846.

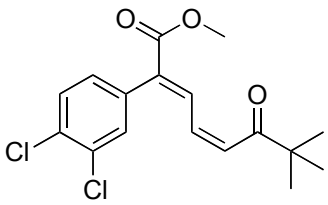
(2*E*,4*Z*)-dimethyl 2-(3-chloro-4-iodophenyl)hexa-2,4-dienedioate (4-97 o)



HDAB-030
90% Yield

A solution of methyl 2-(3-chloro-4-iodophenyl)-2-diazoacetate (335 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and Rh_2 $(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 364 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 11.9 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.16 (dd, J = 8.2, 1.8 Hz, 1H), 6.54 (t, J = 11.5 Hz, 1H), 5.95 (d, J = 11.2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 165.7, 141.4, 138.7, 137.9, 136.5, 134.7, 133.8, 131.3, 128.7, 124.7, 97.7, 52.6, 51.7; FT-IR (neat): 1708, 1231, 1199, 1167, 729 cm^{-1}; HRMS (neg-APCI) calcd for $C_{14}H_{11}O_4Cl_1I_1$: 404.9396; Found: 404.9397; Anal. Calcd. for $C_{14}H_{12}IClO_4$: C, 41.36; H, 2.97; Found: C, 40.96; H, 2.90.

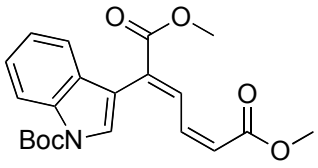
(2*E*,4*Z*)-methyl 2-(3,4-dichlorophenyl)-7,7-dimethyl-6-oxoocta-2,4-dienoate (4-131)



HDAB-031
18% Yield

A solution of methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (244 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-(*tert*-butoxy)furan (280 mg, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 61 mg (18%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 11.5 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.57 (d, J = 11.5 Hz, 1H), 6.37-6.51 (m, 1H), 3.82 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 166.6, 136.7, 135.9, 134.0, 132.6, 132.2, 132.0, 129.9, 129.7, 128.3, 26.1, 52.5, 44.0; FT-IR (neat): 1713, 1681, 1473, 1236, 1067 cm^{-1}; HRMS (neg-APCI) calcd for $C_{17}H_{18}O_3Cl_2$: 340.0638; Found: 340.0639.

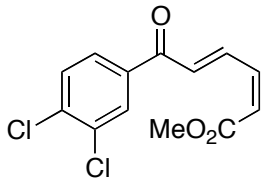
(2*E*,4*Z*)-dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)hexa-2,4-dienedioate(4-115 b)



HDAB-032
48% Yield

A solution of *tert*-butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (315 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 184 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 11.5 Hz, 1H), 8.18 (d, *J* =7.9 Hz, 1H), 7.64 (s, 1H), 7.28-7.40 (m, 2H), 7.16-7.27 (m, 1H), 6.74 (t, *J* = 11.5 Hz, 1H), 5.88 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.59-1.79 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 166.0, 149.2, 139.0, 135.2, 134.9, 131.2, 129.8, 126.7, 124.6, 123.3, 122.8, 120.0, 115.2, 113.7, 84.1, 52.4, 51.5, 28.0; FT-IR (neat): 1719, 1476, 1373, 1247, 1174, 1154 cm^{-1}; HRMS (neg-APCI) calcd for $C_{16}H_{14}O_4N_1$: 384.0928; Found: 384.0928.

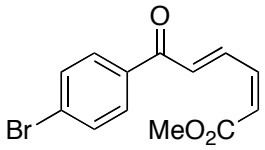
(2*Z*,4*E*)-methyl 6-(3,4-dichlorophenyl)-6-oxohexa-2,4-dienoate(4-139 e)



HDAB-034
31% Yield

A solution of 2-diazo-1-(3,4-dichlorophenyl)ethanone (213 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a pale yellow solid (86 mg, 31% yield). ^1H NMR (400 MHz): δ 8.45 (dd, J = 11.0, 15 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.75 Hz (dd, J = 8.0, 2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 15.0 Hz, 1H), 6.76 (t, J = 11.0 Hz, 1H), 6.07 (d, J = 11.0 Hz, 1H), 3.80 (s, 3H). David Guptil prepared this compound by using the diazo compound provide by me.

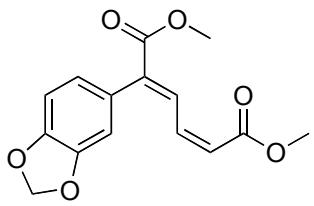
(2*Z*, 4*E*)-methyl 6-(4-bromophenyl)-6-oxohexa-2,4-dienoate(4-139 f)



HDAB-035
32% Yiled

A solution of 1-(4-bromophenyl)-2-diazoethanone (223 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a pale yellow solid (94 mg, 32 %). ^{1}H NMR (400 MHz): δ 8.44 (dd, *J* = 15.5, 11.7 Hz, 1H), 7.82 (d, 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 15.5 Hz, 1H), 6.78 (t, *J* = 11.7 Hz, 1H), 6.08 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H). David Guptil prepared this compound by using the diazo compound provided by me.

(2*E*,4*Z*)-dimethyl 2-(benzo[*d*][1,3]dioxol-5-yl)hexa-2,4-dienedioate(4-97 p)



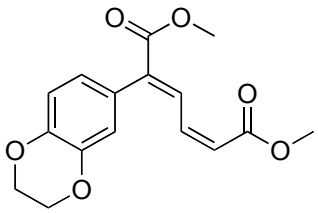
HDAB-036

91% Yield

A solution of methyl 2-(benzo[d][1,3]dioxol-5-yl)-2-diazoacetate (220 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 263 mg (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 11.5 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 1.2 Hz, 1H), 6.62-6.71 (m, 2H), 6.01 (s, 2H), 5.90 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 147.6, 139.3, 139.1, 133.6, 127.6, 124.5, 123.5, 110.7, 108.0, 101.6, 101.5, 101.4, 52.5, 51.6; FT-IR (neat): 1712, 1438, 133, 1195, 1173, 728 cm^{-1}; HRMS (pos-APCI) calcd for $C_{15}H_{15}O_6$: 291.0863; Found: 291.0863.

(2*E*,4*Z*)-dimethyl 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)hexa-2,4-dienedioate(4-97 q)

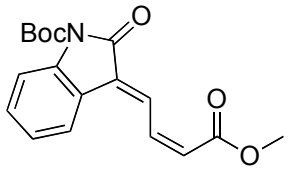


HDAB-037
89% Yield

A solution of methyl 2-diazo-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)acetate (234 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 270 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 11.9 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.62-6.72 (m, 2H), 5.86 (dd, *J* = 11.29, 0.92 Hz, 1H), 4.26 (s, 4H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.8, 143.7, 142.7, 139.0, 138.6, 133.0, 126.6, 123.4, 122.9, 119.0, 116.5, 64.1, 63.9, 51.2, 52.1; FT-IR (neat): 1711, 1506, 1435, 1250, 1173 cm^{-1}; HRMS (neg-APCI) calcd for $C_{16}H_{16}O_6$: 304.0952; Found 304.0956.

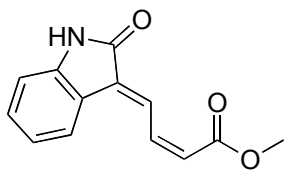
(*E*)-*tert*-butyl 3-((*Z*)-4-methoxy-4-oxobut-2-en-1-ylidene)-2-oxoindoline-1-carboxylate (4-115 c)



HDAB-038
15% Yield

A solution of *tert*-butyl 3-diazo-2-oxoindoline-1-carboxylate (259 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 49 mg (15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 12.2 Hz, 1H), 8.30-8.42 (m, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.12-7.20 (m, 1H), 6.12 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 165.1, 166.4, 165.1, 149.3, 139.7, 137.4, 130.9, 129.8, 129.3, 125.1, 124.4, 123.1, 120.7, 115.4, 28.3, 84.5, 51.7; FT-IR (neat): 1725, 1604, 1466, 1351, 1144, 829 cm^{-1}; HRMS (neg-APCI) calcd for $C_{17}H_{19}O_5N$: 329.1268; Found: 329.1268.

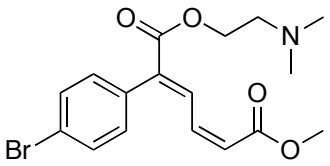
(2*Z*,4*E*)-methyl 4-(2-oxoindolin-3-ylidene)but-2-enoate(4-115 d)



HDAB-039
33% Yield

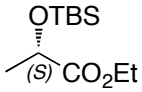
A solution of 3-diazoindolin-2-one (159 mg, 1 mmol, 1 eq.) in hexanes (10 mL) was added by syringe pump over 2 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.2 mL, 2 mmol, 2 eq.) and $Rh_2(OAc)_4$ (5 mg, 0.002 mmol, 0.01 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 75 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 - 8.56 (m, 1H), 8.34-8.45 (m, 1H), 8.15 (br. s., 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.20-7.30 (m, 2H), 6.97-7.07 (m, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.10 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 166.3, 141.0, 137.4, 130.5, 129.3, 124.1, 123.5, 122.2, 121.2, 109.8, 51.5; FT-IR (neat): 3169, 3061, 2921, 1685, 1200, 1179, 742 cm^{-1}; HRMS (pos-APCI) calcd for $C_{13}H_{12}O_3N$: 230.0811; Found: 230.0811.

(2*E*,4*Z*)-1-(2-(Dimethylamino)ethyl) 6-methyl 2-(4-bromophenyl)hexa-2,4-dienedioate(4-162)



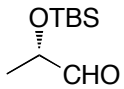
A solution of 2-(dimethylamino)ethyl 2-(4-bromophenyl)-2-diazoacetate (62 mg, 0.2 mmol, 1 eq.) in hexanes (5 mL) was added by syringe pump over 1 h (5 mL/hr rate) to a solution of 2-methoxy furan (0.1 mL, 1 mmol, 5 eq.) and $Rh_2(OAc)_4$ (1 mg, 0.05 mmol, 0.05 eq.) in hexane (10 mL). The reaction mixture was stirred for an additional 1h, and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 33 mg (43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, *J* = 12 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.55 (t, *J* = 11.5 Hz, 1H), 5.88 (d, *J* = 11.5 Hz, 1H), 4.31 (t, *J* = 11.5 Hz, 2H), 3.77 (s, 3H), 2.62 (t, *J* = 11.5 Hz, 2H), 2.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 165.8, 138.4, 138.2, 134.1, 132.7, 132.0, 131.9, 131.2, 124.2, 124.1, 122.7, 63.5, 57.4, 51.6, 45.7, 45.7; FT-IR (neat): 1710, 1623, 1436, 1194, 1171, 1026 cm^{-1}; HRMS (pos-APCI) calcd for $C_{17}H_{21}O_4N_1Br_1$: 382.0648; Found: 382.0650. The product decomposed after one week of standing in the fridge.

(*S*)-ethyl 2-(*tert*-butyldimethylsilyloxy) propionate (4-144)



A solution of *ter*-butyldimethylsilylchloride (8.29 g, 55 mmol, 1.1 eq.) in dichloromethane (20 mL) was added to a solution of (*S*)- ethyl lactate (4.18mL, 50 mmol, 1 eq), imidazole (5.1 g, 75 mmol, 1.5 eq.) and dimethylamino pyridine (183 mg, 1.5 mmol, 0.03 eq.) in dichloromethane (50 mL) at 0 ^{o}C. The reaction mixture was stirred overnight, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 8.12 g (70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.30 (q, *J* =7.0 Hz, 1H), 4.22-4.11 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 14.5 Hz, 6H). ^{1}H NMR data was in accordance with the literature.[17]

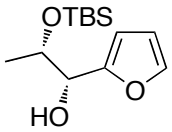
(*S*)-2-(*tert*-butyldimethylsilyloxy) propanal (4-145)



A solution of DIBAL-H (36 mL of 1M solution intoluene) was added to a solution of (*S*)-ethyl 2-(*tert*-butyldimethylsilyloxy) propionate (8.12 g, 35 mmol, 1 eq.) in dichloromethane (50 mL) at -78 ^{o}C slowly dropwise. The reaction mixture was stirred for 1 hr, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 4.9 g (75%).

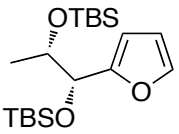
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.61 (s, 1H), 4.11-4.07 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.10 (d, *J* = 6.0 Hz, 6H). ^{1}H NMR data was in accordance with the literature.[18]

(1*R*, 2S)-2-(*tert*-butyldimethylsilyloxy)-1-(furan-2-yl) propan-1-ol (4-146)



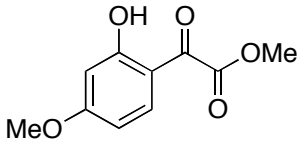
A solution of *n*-BuLi (16 mL of 2.5 M solution in hexane) was added to the freshly distilled furan (2.7 g, 40 mmol, 2 eq.) dissolved in THF (50mL) at 0 ^{o}C. The reaction mixture stirred at 0 ^{o}C for 2 hours and then cooled to -78 ^{o}C. (*S*)-2-(*tert*-butyldimethylsilyloxy) propanal (3.7 g, 20 mmol, 1 eq.) was added dropwise at -78 ^{o}C and stirred at that temperature for 3 hours. The reaction was quenched with $NaHCO_3$, filtered though celite, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified the epimeric mixture by flash chromatography on silica gel using 20:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 2.7 g (52%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (s, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 6.29 (d, *J* = 3.0 Hz, 1H), 4.58 (s, 1H), 4.11(m, 1H), 2.44 (s, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.06 (d, *J* = 22.5 Hz, 6H). ^{1}H NMR data was in accordance with the literature.[18]

(5*R*, 6S)-5-(furan-2-yl)-2,2,3,3,6,8,8,9,9-nonamethyl-4, 7-dioxa-3, 8-disiladecane (4-147)



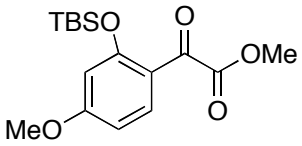
A solution of *ter*-butyldimethylsilylchloride (331 mg, 2.2 mmol, 1.1 eq.) in dichloromethane (10 mL) was added to a solution of **(**1*R*, 2*S*)-2-(*tert*-butyldimethylsilyloxy)-1-(furan-2-yl) propan-1-ol (512 mg, 2 mmol, 1 eq.), imidazole (204 mg, 3 mmol, 1.5 eq.) and dimethylamino pyridine (8 mg, 0.06 mmol, 0.03 eq.) in dichloromethane (10 mL) at 0 ^{o}C. The reaction mixture was stirred overnight, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 704 mg (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.3 (s, 1H), 6.29 (d, *J* = 1.5 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 4.3 (d, *J* = 7.0 Hz, 1H), 4.0-3.9 (m, 1H), 1.22 (d, *J* = 5.5 Hz, 3H), 0.84 (s, 9H), 0.77 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H), -0.15 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 141.0, 110.0, 107.6, 73.9, 71.2, 25.76, 25.74, 20.4, 18.1, 17.9, -4.8, -5.13, -5.15, -5.37; HRMS (EI) *m/z calcd* for $[C_{19}H_{38}O_3Si_2]^+$ 383.1649; Found: 383.1642.

Methyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoethanoate (4-151)



A solution of $AlCl_3$ (6.6 g, 50 mmol, 5 eq.) dissolved in DCE (20 mL) was added through a canula to a solution of 1,3 dimethoxybenzene (1.3 g, 10 mmol, 1eq.) and methyloxalyl chloride (1.2 g, 10 mmol, 1 eq.) was dissolved in DCE (50 mL) at 0 ^oC. The reaction was mixture stirred at rt overnight. The resultant solution was quenched by adding water, extracted twice with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 1.9 g (90%). ^1H NMR (500 MHz, $CDCl_3$): δ 11.6 (s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 6.45 (dd, J = 8.5 Hz, 1H), 6.41 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H). ^1H NMR data was in accordance with the literature.[19,20]

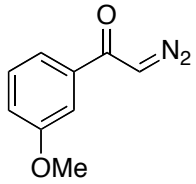
Methyl 2-(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-2-oxoethanoate (4-154)



A solution of *ter*-butyldimethylsilylchloride (165 mg, 1.1 mmol, 1.1 eq.) in dichloromethane (10 mL) was added to a solution of Methyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoethanoate (210 mg, 1 mmol, 1 eq.), imidazole (102 mg, 1.5 mmol, 1.5 eq.) and dimethylamino pyridine (4 mg, 0.03 mmol, 0.03 eq.) in dichloromethane (10 mL) at 0^oC. The reaction mixture was stirred overnight, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was

purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 251 mg (77%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.5 Hz, 1H), 6.59-6.56 (dd, J = 2.0 Hz, 1H), 6.37 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 0.96 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5 (C), 165.6 (C), 165.0 (C), 158.8 (C), 133.0(CH), 118.5 (C), 107.6 (CH), 105.1 (CH), 55.5 (CH_3), 52.3 (CH_3), 25.9 (CH_3), 18.8 (C), -3.87 (CH_3). Anal. Calcd. for $C_{14}H_{12}Cl_2O_4$: C, 59.23; H, 7.46; Found: C, 59.06; H, 7.46.

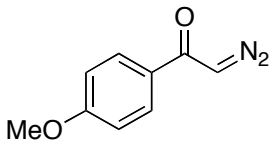
2-Diazo-1- (3-methoxyphenyl) ethanone (4-138 b)



In a flame dried round bottom flask, THF (20mL) was added. 1,1,1,3,3,3 hexamethyldisilazane (1.7 g, 11 mmol, 1.1eq.) was added to the cooled THF solution. n-BuLi (2.5 M solution in hexane) at 0 ^oC. The resultant mixture was cooled to -78 ^oC and 3-methoxy acetophenone (1.5 g, 10 mmol, 1 eq.) dissolved in 10mL of THF was added slowly using syringe pump at -78 ^oC. The reaction mixture was stirred at rt for 3 h and then trifluoroethyltrifluoroacetate (2.1 g, 11 mmol, 1.1 eq.) was added in one portion. The resultant yellow reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and 5% HCl. Extracted twice; combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The crude mixture was taken into next step without further

purification. The resultant yellow solid was dissolved in acetonitrile; water, Et_3N and Tosyl azide were added sequentially. Reaction mixture stirred at rt for few hours. Reaction mixture poured into mixture of ethyl ether and 5% NaOH, extracted twice, combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate yellow crystalline solid, (1.1 g, 66% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.26 (m, 2H), 7.03 (m, 1H), 6.00 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 160.3, 138.4, 130.1, 119.4, 119.2, 112.0, 55.79, 54.85. Data matches previously reported results.[16]

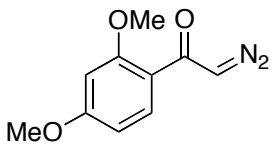
2-Diazo-1- (4-methoxyphenyl) ethanone (4-138 d)



In a flame dried round bottom flask, THF (20mL) was added. 1,1,1,3,3,3 hexamethyldisilazane (4.7 g, 22 mmol, 2.2eq.) was added to the cooled THF solution. n-BuLi (2.5 M solution in hexane) at 0 ^oC. The resultant mixture was cooled to -78 ^oC and 4-methoxy acetophenone (3 g, 20 mmol, 1 eq.) dissolved in 10mL of THF was added slowly using syringe pump at -78 ^oC. The reaction mixture is stirred at rt for 3 h and then trifluoroethyltrifluoroacetate (3 g, 22 mmol, 2.2 eq.) was added at a time. The resultant yellow reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and 5% HCl. Extracted twice; combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in*

vacuo. The crude mixture was taken into next step without further purification. The resultant yellow solid was dissolved in acetonitrile; water, Et_3N and Tosyl azide were added sequentially. Reaction mixture stirred at rt for few hours. Reaction mixture poured into mixture of ethyl ether and 5% NaOH, extracted twice, combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate yellow crystalline solid, (2.3 g, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* =8.8 Hz, 2H), 6.86 (d, *J* =8.8 Hz, 2H), 5.92 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.7(C), 163.7 (C), 129.8 (C), 129.2 (CH), 114.2 (CH), 55.89 (CH_3), 53.97 (CH). Data was in accordance with previously reported data.[16]

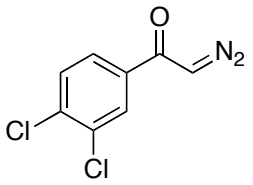
2-Diazo-1- (2,4-dimethoxyphenyl) ethanone (4-138 c)



In a flame dried round bottom flask, THF (20mL) was added. 1,1,1,3,3,3 hexamethyldisilazane (4.7 g, 22 mmol, 2.2eq.) was added to the cooled THF solution. n-BuLi (2.5 M solution in hexane) at 0 ^{o}C. The resultant mixture was cooled to -78 ^{o}C and 1-(2,4-dimethoxyphenyl)ethanone (3.6 g, 20 mmol, 1 eq.) dissolved in 10mL of THF was added slowly using syringe pump at -78 ^{o}C. The reaction mixture is stirred at rt for 3 h and then trifluoroethyltrifluoroacetate (3 g, 22 mmol, 2.2 eq.) was added at a time. The resultant yellow reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and 5% HCl. Extracted twice;

combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The crude mixture was taken into next step without further purification. The resultant yellow solid was dissolved in acetonitrile; water, Et_3N and Tosyl azide were added sequentially. Reaction mixture stirred at rt for few hours. Reaction mixture poured into mixture of ethyl ether and 5% NaOH, extracted twice, combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate yellow crystalline solid, (1.27 g, 62% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.35 (s, 1H), 6.29(s, 1H), 3.78 (s, 3H), 3.75 (s, 3H). Data was in accordance with previously reported data.[16]

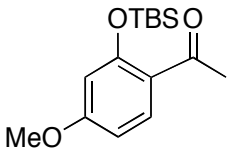
2-Diazo-1-(3,4-dichlorophenyl)ethanone(4-138 e)



In a flame dried round bottom flask, THF (20mL) was added. 1,1,1,3,3,3 hexamethyldisilazane (15.9 g, 75 mmol, 1.1eq.) was added to the cooled THF solution. n-BuLi (2.5 M solution in hexane) at 0 ^oC. The resultant mixture was cooled to -78 ^oC and 1-(3,4-dichlorophenyl)ethanone (12.85 g, 70 mmol, 1 eq.) dissolved in 10mL of THF was added slowly using syringe pump at -78 ^oC. The reaction mixture is stirred at rt for 3 h and then trifluoroethyltrifluoroacetate (10.1 mL, 75 mmol, 1.1 eq.) was added at a time.

The resultant yellow reaction mixture was stirred at rt overnight. The reaction mixture was poured into a separation funnel containing ethyl ether and 5% HCl. Extracted twice; combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The crude mixture was taken into next step without further purification. The resultant yellow solid was dissolved in acetonitrile; water, Et_3N and Tosyl azide were added sequentially. Reaction mixture stirred at rt few hours. Reaction mixture poured into mixture of ethyl ether and 5% NaOH, extracted twice, combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a yellow crystalline solid, (9.5 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.85 (m, 1H), 7.59 (ddd, J = 8.3, 2.1, 0.7 Hz, 1H), 7.54 (dd, J = 8.3, 0.7 Hz, 1H), 7.27 (d, J = 0.8 Hz, 1H). Data was in accordance with previously reported data.[16]

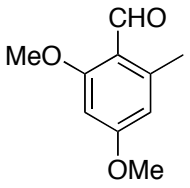
1-(2-(*tert*-Butyldimethylsilyloxy)-4-methoxyphenyl) ethanone (Precursor for 4-138 g)



This compound was synthesized from corresponding *2*-hydroxy, *4*-methoxy acetophenone.[21] A solution of *ter*-butyldimethylsilylchloride (5 g, 33 mmol, 1.1 eq.) in dichloromethane (10 mL) was added to a solution of 4- methoxy 2-hydroxy acetophenone (5 g, 30 mmol, 1 eq.), triethylamine (6.2 mL, 45 mmol, 1.5 eq.) and dimethylamino pyridine (03 g, 3 mmol, 0.1 eq.) in dichloromethane (40 mL) at 0 ^{o}C. The reaction

mixture was stirred overnight, and then added water, extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Et_2O as eluant to isolate a colorless oily liquid, 6.26 g (75% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 9.0 Hz, 1H), 6.46 (d, J = 8.5 Hz, 1H), 6.30 (s, 1H), 3.72(s, 3H), 2.49 (s, 3H), 0.94(s, 9H), 0.23(s, 6H). Data was in accordance with previously reported data.[21]

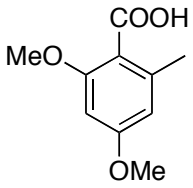
2,4-Dimethoxy-6-methylbenzaldehyde (4-74)



A solution of dimethyl formamide (15.58 mL, 200 mmol, 8.6 eq.) and phosphorus oxychloride (4.77 mL, 51 mmol, 2.2 eq.) was added to a solution of DMF and orcinol (2.9 g, 23 mmol, 1 eq.) at ambient temperature (10 ^oC to 20 ^oC) through canula dropwise. The reaction mixture was stirred at rt for 1 hr. The resultant solution was poured into 300 mL of 1M NaOH and stirred for 1 hr, neutralized with 4M HCl, extracted twice into ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The crude mixture was taken into next step without further purification.The mixture of crude product, methyl iodide (2.5 eq.) and potassium carbonate (2.5 eq.) were dissolved in dry acetone and refluxed at 60 ^oC for 2 hr. After complete conversion to the product, water was added and extracted with ethyl acetate twice, combined organic layers dried over magnesium sulfate and then

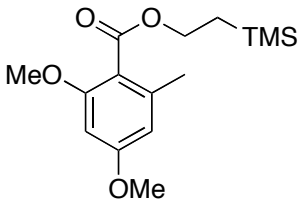
concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Ethyl acetate as eluant to isolate yellow crystalline solid (83% yield). ^{1}H NMR (500 MHz, CD_3OD): δ 10.07 (s, 1H), 6.22 (s, 1H), 6.11 (s, 1H), 4.89 (s, 6H), 2.51 (s, 3H). ^{1}H NMR data was in accordance with the literature.[22,23]

2,4-Dimethoxy-6-methylbenzoic acid (4-75)



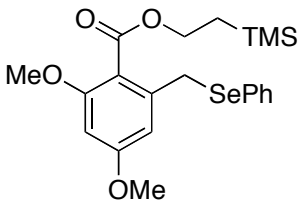
A solution of 2,4-dimethoxy-6-methylbenzaldehyde (90 mg, 0.5 mmol, 1 eq.) dissolved in 1:1 mixture of DMSO/ water (20 mL) was added to a solution of sodium chlorite (108 mg, 1.2 mmol, 2.4 eq.) and $Na_2H_2PO_4$ (172 mg, 1.25 mmol, 2.5 eq.) at 0 ^oC. The reaction mixture was stirred at rt overnight. The resultant solution was extracted with ethyl acetate twice, combined organic layers dried over magnesium sulfate and then concentrated *in vacuo*. The crude reaction mixture was extracted with $NaHCO_3$. The product went into aqueous layer. The aqueous layer was washed with ethyl acetate to get rid of excess DMSO and then neutralized using Concentrated HCl. A white precipitate was formed which was filtered and washed with water, dried *in vacuo* overnight to get pure product (98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.4 (s, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 2.60 (s, 3H). ^{1}H NMR data was in accordance with the literature.[23]

2-(Trimethylsilyl) ethyl 2,4-dimethoxy-6-methylbenzoate (4-76)



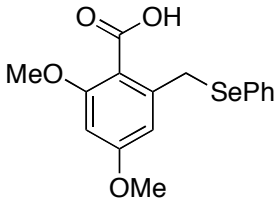
A solution of 2,4-dimethoxy-6-methylbenzoic acid (98 mg, 0.5 mmol, 1 eq.) in DCM (5 mL) was added to a solution of oxalyl chloride (63 mg, 0.5 mmol, 1 eq.) at 0 ^{o}C dropwise. After stirring for 5 minutes, triethyl amine (131 mg, 1.3 mmol, 2.6 eq.) and 2-(trimethylsilyl) ethanol (60 mg, 0.5 mmol, 1 eq.) was added at 0 ^{o}C dropwise. The resultant mixture was stirred for 2 hr. The reaction mixture was washed with water, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Ethyl acetate as eluant to isolate yellow a colorless liquid (94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.30 (s, 2H), 4.38 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.29 (s, 3H), 1.10 (m, 2H), 0.06 (s, 9H). ^{1}H NMR data was in accordance with the literature.[23]

2-(Trimethylsilyl) ethyl 2,4-dimethoxy-6- (phenylselanylmethyl) benzoate (4-77)



A solution of 2-(trimethylsilyl) ethyl 2,4-dimethoxy-6-methylbenzoate (296 mg, 1 mmol, 1 eq.) dissolved in THF was added to a freshly made LDA (*n*-BuLi and isopropyl amine) dropwise at -78 ^{o}C through canula. The resultant dark yellow solution was stirred for 3 hr and then diphenyl diselenide (312 mg, 1 mmol, 1 eq.) dissolved in THF (5 mL) was added at a time. The reaction mixture quenched with NH_4Cl, extracted twice into ethyl acetate, combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 9:1 hexane/Ethyl acetate as eluant to isolate yellow colorless liquid (56% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 5.0 Hz, 2H), 7.26 (s, 3H), 6.34 (s, 1H), 6.14 (s, 1H), 4.4 (t, J = 11.0 Hz, 2H), 4.10 (s, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 1.13 (t, J = 11.0 Hz, 2H), 0.09 (s, 9H). ^{1}H NMR data was in accordance with the literature.[23]

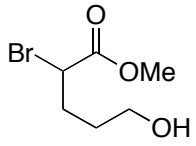
2,4-dimethoxy-6- (phenylselanylmethyl) benzoic acid (4-78)



A solution of 2-(trimethylsilyl) ethyl 2,4-dimethoxy-6- (phenylselanylmethyl) benzoate (90 mg, 0.2 mmol, 1 eq.) was dissolved in THF and then TBAF (1 eq.) was added at 0 ^{o}C. The reaction mixture was stirred at rt for 2 h, washed with water, extracted twice with DCM, dried over magnesium sulfate and then concentrated *in vacuo*. The crude reaction mixture was extracted with $NaHCO_3$. The product went into aqueous

layer. The aqueous layer was washed with ethyl acetate to get rid of excess DMSO and then neutralized using Conc. HCl. A white precipitate was formed which was filtered and washed with water, dried *in vacuo* overnight to get pure product (84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.24 (m, 3H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.13 (d, *J* = 2.0 Hz, 1H), 4.17 (s, 2H), 3.80 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8 (C), 139.4 (C), 133.34 (CH), 133.31 (C), 128.0(CH), 126.6 (CH), 105.8 (CH), 96.46 (CH), 54.45 (CH_3), 53.78 (CH_3); HRMS (EI) *m/z calcd* for $[C_{16}H_{16}O_4Se]^+$ 352.0208; Found: 352.0211.

Methyl 2-bromo-5-hydroxypentanoate (4-70)



A solution of Valerolactone (10 g, 100 mmol, 1 eq.) dissolved in THF was added to a freshly prepared LDA (*n*-BuLi and isopropyl amine) dropwise at -78 ^{o}C through canula. The reaction mixture was stirred at -78 ^{o}C for 2 hr. TMSCl (40 mL. 110 mmol, 1.1 eq.) was added and stirred for 4 hr. The crude mixture was then distilled to get the pure product. The product was dissolved in DCM and bromine was added slowly at -15 ^{o}C. The reaction mixture was quenched with NH_4Cl, extracted twice into DCM, combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The crude mixture was dissolved in MeOH and Conc. H_2SO_4 was added. Refluxed overnight. The reaction mixture quenched with NH_4Cl, extracted twice into DCM, combined organic layers washed with brine, dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by distillation (53% yield)[24]. ^{1}H

NMR (500 MHz, $CDCl_3$): δ 4.44 (m, 1H), 3.98 (m, 1H), 3.90 (m, 1H), 3.72 (s, 3H), 2.23 (m, 1H), 2.14-1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ173.3(C), 76.30(CH), 68.91(CH_2), 51.54 (CH_3), 29.76 (CH_2), 24.88(CH_2). The compound decomposed.

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APPENDIX

1. Crystal Structure of **4-98h (SC3089B)**

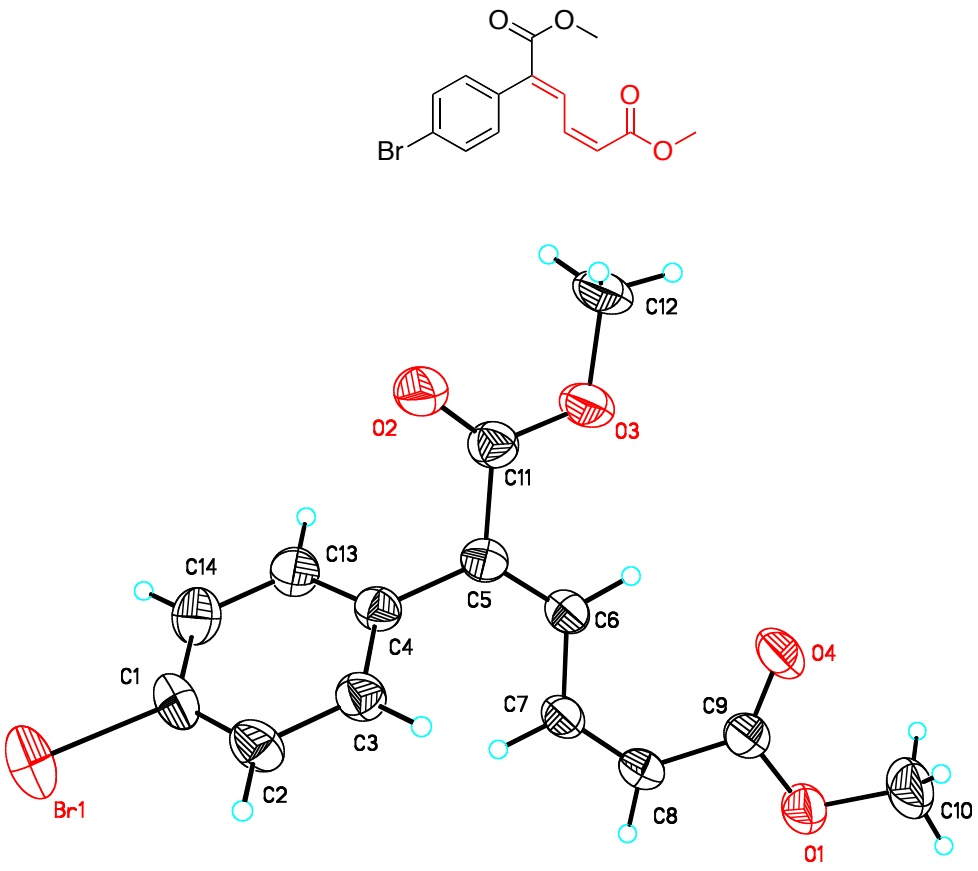


Table 1. Crystal data and structure refinement for **SC3089B**

Identification code	sc3089b_0m

Empirical formula	C14 H13 Br O4	
Formula weight	325.15	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.4664(3) Å	α= 90°.
	b = 8.9406(4) Å	β= 90°.
	c = 24.3966(11) Å	γ = 90°.
Volume	1410.45(11) $Å^3$	
Z	4	
Density (calculated)	1.531 Mg/m^3	
Absorption coefficient	4.051 mm^{-1}	
F(000)	656	
Crystal size	0.30 x 0.15 x 0.06 mm^3	
Theta range for data collection	3.62 to 69.73°.	
Index ranges	-7<=h<=5, -10<=k<=9, -28<=l<=28	
Reflections collected	5493	
Independent reflections	2284 [R(int) = 0.0221]	
Completeness to theta = 69.73°	92.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7931 and 0.3762	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2284 / 0 / 174	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0685	
R indices (all data)	R1 = 0.0273, wR2 = 0.0696	
Absolute structure parameter	0.01(2)	
Largest diff. peak and hole	0.161 and -0.382 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for SC3089B_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	-11499(1)	-2406(1)	-621(1)	64(1)
O(1)	-3561(3)	-4418(2)	-4168(1)	51(1)
O(2)	-13384(3)	-87(2)	-3145(1)	51(1)
O(3)	-11920(3)	-789(2)	-3939(1)	52(1)
O(4)	-6289(3)	-2996(3)	-4366(1)	71(1)
C(1)	-11141(4)	-2261(3)	-1396(1)	42(1)
C(2)	-9367(4)	-1627(3)	-1602(1)	42(1)
C(3)	-9175(4)	-1471(3)	-2167(1)	39(1)
C(4)	-10741(3)	-1942(2)	-2518(1)	34(1)
C(5)	-10516(4)	-1771(3)	-3122(1)	36(1)
C(6)	-9021(3)	-2424(3)	-3420(1)	37(1)
C(7)	-7497(3)	-3448(3)	-3193(1)	36(1)
C(8)	-5902(3)	-4034(3)	-3467(1)	37(1)
C(9)	-5340(4)	-3743(3)	-4041(1)	42(1)
C(10)	-2749(6)	-4094(4)	-4708(1)	66(1)
C(11)	-12095(4)	-794(3)	-3393(1)	40(1)
C(12)	-13382(5)	143(3)	-4231(1)	57(1)
C(13)	-12503(3)	-2580(3)	-2293(1)	40(1)
C(14)	-12717(4)	-2751(3)	-1734(1)	46(1)

Table 3. Bond lengths [Å] and angles [°] for SC3089B_0m.

Br(1)-C(1)	1.909(2)
O(1)-C(9)	1.336(3)
O(1)-C(10)	1.446(3)
O(2)-C(11)	1.209(3)
O(3)-C(11)	1.335(3)
O(3)-C(12)	1.448(3)
O(4)-C(9)	1.204(3)
C(1)-C(2)	1.375(4)
C(1)-C(14)	1.383(4)
C(2)-C(3)	1.391(3)
C(2)-H(2)	0.9500
C(3)-C(4)	1.391(3)
C(3)-H(3)	0.9500
C(4)-C(13)	1.387(3)
C(4)-C(5)	1.489(3)
C(5)-C(6)	1.343(3)
C(5)-C(11)	1.498(3)
C(6)-C(7)	1.455(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.337(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.469(3)
C(8)-H(8)	0.9500
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(14)	1.378(3)
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(9)-O(1)-C(10)	115.7(2)

C(11)-O(3)-C(12)	115.9(2)
C(2)-C(1)-C(14)	121.8(2)
C(2)-C(1)-Br(1)	119.41(19)
C(14)-C(1)-Br(1)	118.72(19)
C(1)-C(2)-C(3)	118.5(2)
C(1)-C(2)-H(2)	120.7
C(3)-C(2)-H(2)	120.7
C(2)-C(3)-C(4)	121.0(2)
C(2)-C(3)-H(3)	119.5
C(4)-C(3)-H(3)	119.5
C(13)-C(4)-C(3)	118.6(2)
C(13)-C(4)-C(5)	120.9(2)
C(3)-C(4)-C(5)	120.5(2)
C(6)-C(5)-C(4)	124.1(2)
C(6)-C(5)-C(11)	120.3(2)
C(4)-C(5)-C(11)	115.6(2)
C(5)-C(6)-C(7)	123.7(2)
C(5)-C(6)-H(6)	118.1
C(7)-C(6)-H(6)	118.1
C(8)-C(7)-C(6)	125.4(2)
C(8)-C(7)-H(7)	117.3
C(6)-C(7)-H(7)	117.3
C(7)-C(8)-C(9)	126.8(2)
C(7)-C(8)-H(8)	116.6
C(9)-C(8)-H(8)	116.6
O(4)-C(9)-O(1)	122.5(2)
O(4)-C(9)-C(8)	126.8(2)
O(1)-C(9)-C(8)	110.8(2)
O(1)-C(10)-H(10A)	109.5
O(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
O(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
O(2)-C(11)-O(3)	123.8(2)
O(2)-C(11)-C(5)	123.6(3)

O(3)-C(11)-C(5)	112.7(2)
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-C(4)	121.2(2)
C(14)-C(13)-H(13)	119.4
C(4)-C(13)-H(13)	119.4
C(13)-C(14)-C(1)	118.8(2)
C(13)-C(14)-H(14)	120.6
C(1)-C(14)-H(14)	120.6

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for SC3089B_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	89(1)	71(1)	33(1)	2(1)	6(1)	-9(1)
O(1)	52(1)	60(1)	40(1)	8(1)	9(1)	16(1)
O(2)	53(1)	60(1)	42(1)	-1(1)	-2(1)	18(1)
O(3)	56(1)	66(1)	35(1)	1(1)	-8(1)	22(1)
O(4)	74(1)	99(2)	39(1)	28(1)	10(1)	40(1)
C(1)	59(2)	39(1)	27(1)	0(1)	1(1)	0(1)
C(2)	48(1)	43(1)	36(1)	0(1)	-9(1)	-9(1)
C(3)	37(1)	43(1)	36(1)	1(1)	-4(1)	-6(1)
C(4)	36(1)	32(1)	33(1)	-2(1)	-3(1)	1(1)
C(5)	34(1)	40(1)	34(1)	-1(1)	-4(1)	-1(1)
C(6)	38(1)	42(1)	31(1)	4(1)	-3(1)	0(1)
C(7)	39(1)	41(1)	29(1)	5(1)	-4(1)	-2(1)
C(8)	40(1)	38(1)	34(1)	7(1)	-5(1)	4(1)
C(9)	43(1)	47(1)	36(1)	3(1)	0(1)	6(1)
C(10)	76(2)	82(2)	41(2)	7(2)	18(2)	22(2)
C(11)	40(1)	42(1)	37(1)	-3(1)	-5(1)	2(1)
C(12)	62(2)	71(2)	39(2)	8(1)	-14(1)	23(2)
C(13)	37(1)	45(1)	39(1)	-6(1)	-4(1)	-8(1)
C(14)	47(1)	44(1)	47(2)	1(1)	7(1)	-8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for SC3089B_0m.

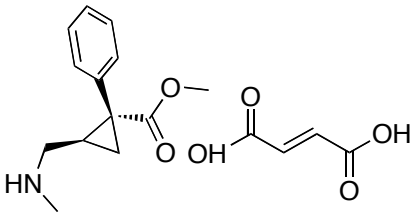
	x	y	z	U(eq)
H(2)	-8295	-1302	-1363	51
H(3)	-7957	-1036	-2315	46
H(6)	-8956	-2205	-3800	44
H(7)	-7648	-3724	-2819	43
H(8)	-5042	-4709	-3271	45
H(10A)	-2525	-3014	-4744	99
H(10B)	-3739	-4427	-4986	99
H(10C)	-1434	-4620	-4759	99
H(12A)	-13214	1186	-4115	86
H(12B)	-14793	-189	-4149	86
H(12C)	-13131	64	-4626	86
H(13)	-13584	-2904	-2528	48
H(14)	-13924	-3198	-1584	55

Table 6. Torsion angles [°] for SC3089B_0m.

C(14)-C(1)-C(2)-C(3)	0.4(4)
Br(1)-C(1)-C(2)-C(3)	-177.20(19)
C(1)-C(2)-C(3)-C(4)	0.1(4)
C(2)-C(3)-C(4)-C(13)	-0.2(4)
C(2)-C(3)-C(4)-C(5)	-179.9(2)
C(13)-C(4)-C(5)-C(6)	-118.5(3)
C(3)-C(4)-C(5)-C(6)	61.2(3)
C(13)-C(4)-C(5)-C(11)	61.7(3)
C(3)-C(4)-C(5)-C(11)	-118.6(2)
C(4)-C(5)-C(6)-C(7)	3.5(4)
C(11)-C(5)-C(6)-C(7)	-176.7(2)
C(5)-C(6)-C(7)-C(8)	-174.9(2)
C(6)-C(7)-C(8)-C(9)	1.5(4)
C(10)-O(1)-C(9)-O(4)	5.1(4)
C(10)-O(1)-C(9)-C(8)	-174.3(2)
C(7)-C(8)-C(9)-O(4)	-4.5(5)
C(7)-C(8)-C(9)-O(1)	174.9(2)
C(12)-O(3)-C(11)-O(2)	0.5(4)
C(12)-O(3)-C(11)-C(5)	-179.4(2)
C(6)-C(5)-C(11)-O(2)	-174.4(2)
C(4)-C(5)-C(11)-O(2)	5.5(3)
C(6)-C(5)-C(11)-O(3)	5.6(3)
C(4)-C(5)-C(11)-O(3)	-174.6(2)
C(3)-C(4)-C(13)-C(14)	-0.1(4)
C(5)-C(4)-C(13)-C(14)	179.6(2)
C(4)-C(13)-C(14)-C(1)	0.6(4)
C(2)-C(1)-C(14)-C(13)	-0.8(4)
Br(1)-C(1)-C(14)-C(13)	176.9(2)

Symmetry transformations used to generate equivalent atoms:

2. Crystal Structure of **rac-3-130 a (SC8083s)**



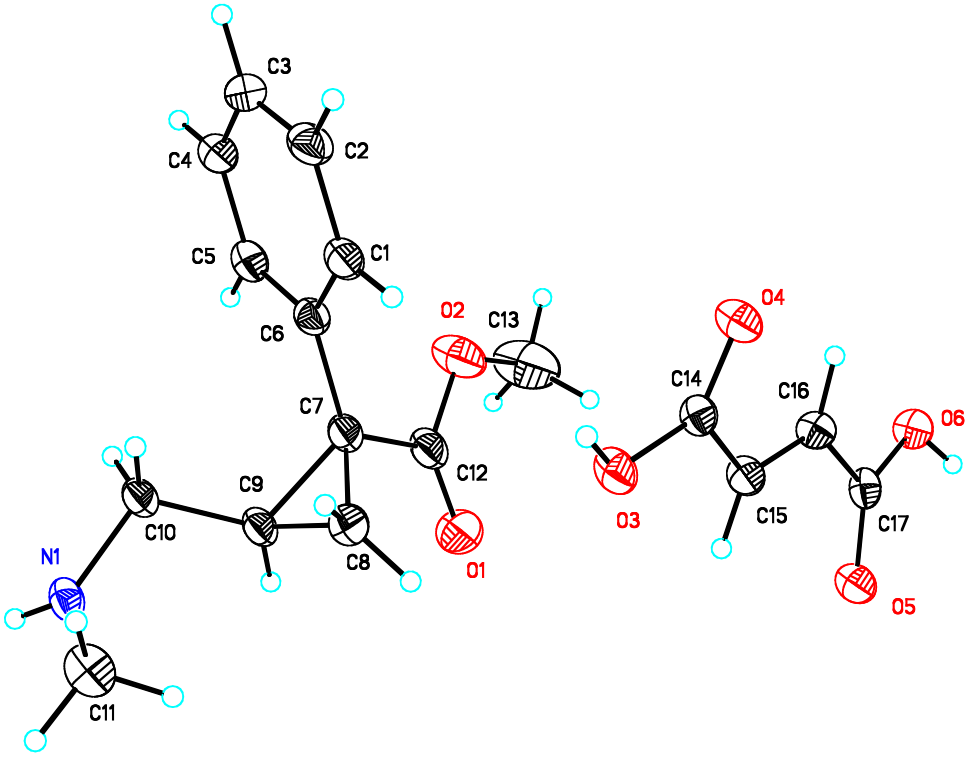


Table 1. Crystal data and structure refinement for **SC8083s**.

Identification code	sc8083s	
Empirical formula	C17 H21 N O6	
Formula weight	335.35	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Fdd2	
Unit cell dimensions	a = 24.3904(12) Å	α= 90°.
	b = 35.2853(17) Å	β= 90°.
	c = 8.0130(3) Å	γ = 90°.
Volume	6896.2(5) $Å^3$	
Z	16	
Density (calculated)	1.292 Mg/m^3	
Absorption coefficient	0.821 mm^{-1}	
F(000)	2848	
Crystal size	0.38 x 0.08 x 0.06 mm^3	
Theta range for data collection	4.41 to 69.61°.	
Index ranges	-21<=h<=29, -31<=k<=42, -9<=l<=7	
Reflections collected	6007	
Independent reflections	2383 [R(int) = 0.0185]	
Completeness to theta = 69.61°	97.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9524 and 0.7455	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2383 / 1 / 217	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.1182	
R indices (all data)	R1 = 0.0541, wR2 = 0.1432	
Absolute structure parameter	0.6(3)	
Largest diff. peak and hole	0.312 and -0.261 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for SC8083s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2006(2)	402(1)	5954(5)	35(1)
C(2)	2359(2)	141(1)	6682(5)	41(1)
C(3)	2919(2)	194(1)	6597(5)	43(1)
C(4)	3128(2)	509(1)	5780(5)	44(1)
C(5)	2773(2)	770(1)	5077(5)	38(1)
C(6)	2207(1)	721(1)	5152(4)	31(1)
C(7)	1833(1)	1005(1)	4374(4)	35(1)
C(8)	1298(1)	1119(1)	5202(5)	39(1)
C(9)	1760(2)	1399(1)	5156(4)	35(1)
C(10)	2081(2)	1482(1)	6707(5)	38(1)
C(11)	1321(2)	1794(1)	8293(5)	48(1)
C(12)	1802(2)	1014(1)	2499(5)	45(1)
C(13)	2162(3)	754(2)	28(6)	91(2)
N(1)	1883(1)	1829(1)	7576(4)	34(1)
O(1)	1530(1)	1232(1)	1703(4)	61(1)
O(2)	2131(2)	753(1)	1831(3)	63(1)
C(14)	610(1)	198(1)	2401(4)	29(1)
C(15)	524(1)	373(1)	720(4)	32(1)
C(16)	607(1)	185(1)	-668(4)	31(1)
C(17)	476(1)	342(1)	-2359(4)	30(1)
O(3)	558(1)	431(1)	3636(3)	39(1)
O(4)	704(1)	-142(1)	2533(3)	37(1)
O(5)	213(1)	638(1)	-2513(3)	40(1)
O(6)	661(1)	140(1)	-3569(3)	36(1)

Table 3. Bond lengths [Å] and angles [°] for SC8083s.

C(1)-C(6)	1.385(5)
C(1)-C(2)	1.387(5)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.381(5)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.386(5)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.384(5)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.393(5)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.493(5)
C(7)-C(12)	1.505(5)
C(7)-C(8)	1.517(5)
C(7)-C(9)	1.534(4)
C(8)-C(9)	1.500(5)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.498(5)
C(9)-H(9A)	1.0000
C(10)-N(1)	1.487(4)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-N(1)	1.490(5)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-O(1)	1.200(4)
C(12)-O(2)	1.335(5)
C(13)-O(2)	1.447(5)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
N(1)-H(1B)	0.8800

C(14)-O(4)	1.225(4)
C(14)-O(3)	1.292(4)
C(14)-C(15)	1.496(4)
C(15)-C(16)	1.309(5)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.498(4)
C(16)-H(16A)	0.9500
C(17)-O(5)	1.231(4)
C(17)-O(6)	1.286(4)
O(3)-H(3)	0.8496
O(6)-H(6)	0.8400

C(6)-C(1)-C(2)	121.1(3)
C(6)-C(1)-H(1A)	119.5
C(2)-C(1)-H(1A)	119.5
C(3)-C(2)-C(1)	120.1(4)
C(3)-C(2)-H(2A)	120.0
C(1)-C(2)-H(2A)	120.0
C(2)-C(3)-C(4)	119.8(4)
C(2)-C(3)-H(3A)	120.1
C(4)-C(3)-H(3A)	120.1
C(5)-C(4)-C(3)	119.7(4)
C(5)-C(4)-H(4A)	120.1
C(3)-C(4)-H(4A)	120.1
C(4)-C(5)-C(6)	121.2(3)
C(4)-C(5)-H(5A)	119.4
C(6)-C(5)-H(5A)	119.4
C(1)-C(6)-C(5)	118.1(3)
C(1)-C(6)-C(7)	121.7(3)
C(5)-C(6)-C(7)	120.2(3)
C(6)-C(7)-C(12)	117.5(3)
C(6)-C(7)-C(8)	121.4(3)
C(12)-C(7)-C(8)	112.8(3)
C(6)-C(7)-C(9)	120.6(3)
C(12)-C(7)-C(9)	112.6(3)
C(8)-C(7)-C(9)	58.9(2)

C(9)-C(8)-C(7)	61.1(2)
C(9)-C(8)-H(8A)	117.7
C(7)-C(8)-H(8A)	117.7
C(9)-C(8)-H(8B)	117.7
C(7)-C(8)-H(8B)	117.7
H(8A)-C(8)-H(8B)	114.8
C(10)-C(9)-C(8)	120.1(3)
C(10)-C(9)-C(7)	117.1(3)
C(8)-C(9)-C(7)	60.0(2)
C(10)-C(9)-H(9A)	116.0
C(8)-C(9)-H(9A)	116.0
C(7)-C(9)-H(9A)	116.0
N(1)-C(10)-C(9)	112.3(3)
N(1)-C(10)-H(10A)	109.1
C(9)-C(10)-H(10A)	109.1
N(1)-C(10)-H(10B)	109.1
C(9)-C(10)-H(10B)	109.1
H(10A)-C(10)-H(10B)	107.9
N(1)-C(11)-H(11A)	109.5
N(1)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
N(1)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(1)-C(12)-O(2)	124.2(4)
O(1)-C(12)-C(7)	124.9(4)
O(2)-C(12)-C(7)	110.9(3)
O(2)-C(13)-H(13A)	109.5
O(2)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(2)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(10)-N(1)-C(11)	114.4(3)
C(10)-N(1)-H(1B)	122.8
C(11)-N(1)-H(1B)	122.8

C(12)-O(2)-C(13)	115.4(3)
O(4)-C(14)-O(3)	125.0(3)
O(4)-C(14)-C(15)	120.4(3)
O(3)-C(14)-C(15)	114.5(3)
C(16)-C(15)-C(14)	122.4(3)
C(16)-C(15)-H(15A)	118.8
C(14)-C(15)-H(15A)	118.8
C(15)-C(16)-C(17)	123.3(3)
C(15)-C(16)-H(16A)	118.4
C(17)-C(16)-H(16A)	118.4
O(5)-C(17)-O(6)	125.3(3)
O(5)-C(17)-C(16)	121.0(3)
O(6)-C(17)-C(16)	113.7(3)
C(14)-O(3)-H(3)	114.8
C(17)-O(6)-H(6)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for SC8083s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	46(2)	28(2)	33(2)	-3(2)	-1(2)	-1(2)
C(2)	58(2)	27(2)	38(2)	3(2)	-2(2)	1(2)
C(3)	46(2)	35(2)	48(2)	-4(2)	-14(2)	9(2)
C(4)	42(2)	34(2)	55(2)	-10(2)	-8(2)	4(2)
C(5)	42(2)	29(2)	43(2)	-5(2)	-2(2)	-5(2)
C(6)	41(2)	27(2)	25(1)	-2(1)	-1(2)	2(1)
C(7)	46(2)	25(2)	34(2)	-3(2)	-9(2)	1(2)
C(8)	40(2)	33(2)	45(2)	-2(2)	-7(2)	-1(2)
C(9)	51(2)	22(2)	31(2)	-3(2)	-7(2)	1(2)
C(10)	51(2)	24(2)	37(2)	-6(2)	-9(2)	3(2)
C(11)	56(2)	43(2)	45(2)	0(2)	8(2)	-4(2)
C(12)	70(3)	27(2)	37(2)	-2(2)	-15(2)	3(2)
C(13)	166(6)	78(4)	30(2)	5(2)	-1(3)	50(4)
N(1)	47(2)	25(1)	30(1)	-2(1)	-4(1)	-6(1)
O(1)	87(2)	54(2)	41(1)	2(2)	-23(2)	19(2)
O(2)	115(3)	46(2)	29(1)	-1(1)	-4(2)	28(2)
C(14)	34(2)	32(2)	22(2)	-1(2)	1(1)	-1(1)
C(15)	45(2)	28(2)	24(2)	4(1)	-4(2)	0(2)
C(16)	37(2)	31(2)	24(2)	6(1)	2(2)	0(1)
C(17)	36(2)	31(2)	23(1)	2(2)	-2(1)	-9(1)
O(3)	62(2)	35(1)	19(1)	-2(1)	-4(1)	3(1)
O(4)	60(2)	30(1)	20(1)	1(1)	2(1)	5(1)
O(5)	60(2)	34(1)	25(1)	1(1)	-7(1)	6(1)
O(6)	47(1)	41(1)	19(1)	2(1)	-1(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for SC8083s.

	x	y	z	U(eq)
H(1A)	1622	361	6006	42
H(2A)	2214	-75	7241	50
H(3A)	3160	16	7097	52
H(4A)	3513	545	5702	53
H(5A)	2918	987	4532	46
H(8A)	978	1167	4471	47
H(8B)	1208	1001	6290	47
H(9A)	1717	1615	4356	42
H(10A)	2054	1263	7475	45
H(10B)	2472	1516	6410	45
H(11A)	1220	2033	8838	72
H(11B)	1315	1589	9114	72
H(11C)	1059	1739	7398	72
H(13A)	2412	554	-344	137
H(13B)	2297	1000	-357	137
H(13C)	1796	708	-438	137
H(1B)	2080	2036	7660	41
H(15A)	404	629	657	39
H(16A)	759	-62	-599	37
H(3)	594	331	4595	58
H(6)	491	194	-4449	53

Table 6. Torsion angles [°] for SC8083s.

C(6)-C(1)-C(2)-C(3)	-0.8(6)
C(1)-C(2)-C(3)-C(4)	-0.1(6)
C(2)-C(3)-C(4)-C(5)	0.9(6)
C(3)-C(4)-C(5)-C(6)	-0.9(6)
C(2)-C(1)-C(6)-C(5)	0.8(5)
C(2)-C(1)-C(6)-C(7)	-179.5(3)
C(4)-C(5)-C(6)-C(1)	0.0(5)
C(4)-C(5)-C(6)-C(7)	-179.6(3)
C(1)-C(6)-C(7)-C(12)	-106.9(4)
C(5)-C(6)-C(7)-C(12)	72.7(4)
C(1)-C(6)-C(7)-C(8)	39.0(5)
C(5)-C(6)-C(7)-C(8)	-141.3(3)
C(1)-C(6)-C(7)-C(9)	109.0(4)
C(5)-C(6)-C(7)-C(9)	-71.4(4)
C(6)-C(7)-C(8)-C(9)	109.2(3)
C(12)-C(7)-C(8)-C(9)	-103.4(3)
C(7)-C(8)-C(9)-C(10)	-105.9(3)
C(6)-C(7)-C(9)-C(10)	0.4(5)
C(12)-C(7)-C(9)-C(10)	-145.3(4)
C(8)-C(7)-C(9)-C(10)	110.8(4)
C(6)-C(7)-C(9)-C(8)	-110.4(4)
C(12)-C(7)-C(9)-C(8)	103.9(4)
C(8)-C(9)-C(10)-N(1)	-96.8(4)
C(7)-C(9)-C(10)-N(1)	-166.2(3)
C(6)-C(7)-C(12)-O(1)	-178.2(4)
C(8)-C(7)-C(12)-O(1)	33.1(6)
C(9)-C(7)-C(12)-O(1)	-31.3(6)
C(6)-C(7)-C(12)-O(2)	-0.1(5)
C(8)-C(7)-C(12)-O(2)	-148.8(3)
C(9)-C(7)-C(12)-O(2)	146.8(3)
C(9)-C(10)-N(1)-C(11)	66.7(4)
O(1)-C(12)-O(2)-C(13)	2.2(7)
C(7)-C(12)-O(2)-C(13)	-175.9(4)
O(4)-C(14)-C(15)-C(16)	-8.2(5)

O(3)-C(14)-C(15)-C(16)	174.0(3)
C(14)-C(15)-C(16)-C(17)	174.2(3)
C(15)-C(16)-C(17)-O(5)	-9.8(5)
C(15)-C(16)-C(17)-O(6)	170.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for SC8083s [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1B)...O(6)#1	0.88	2.43	3.064(4)	128.9
O(3)-H(3)...O(6)#2	0.85	1.63	2.476(3)	179.9
O(6)-H(6)...O(3)#3	0.84	1.75	2.476(3)	142.8

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/4,y+1/4,z+5/4 #2 x,y,z+1 #3 x,y,z-1

3. Methods for monoamine transporter binding studies

Binding affinities for all novel arylcyclopropylamines compounds were determined in Steve Childers' Laboratory.

Affinities of analogs at 5-HT transport sites are determined by displacement of [3*H*]citalopram binding in membranes from rat frontal cortex. Tissue is obtained from frozen rat brains as described above, homogenized in 10 vol of citalopram assay buffer (50 m*M Tris*-HCl, 120 mM NaCl, 5 mM KCl, pH 7.4) with a Polytron, and centrifuged two times at 48,000 x g for 10 min, with fresh buffer resuspension for each centrifugation. Assay tubes contain 50 mg (original wet weight) of membranes, 0.4 n*M* [3*H*]citalopram, and various concentrations of unlabeled drugs dissolved in citalopram assay buffer in a final volume of 2 ml. Tubes are incubated for 60 min at 25°, and the reaction is terminated by rapid filtration with 3 x 4 ml of cold *Tris* buffer through

Whatman GF/B glass fiber filters pre-soaked in *Tris* buffer containing 0.1% BSA for at least 1 h. Non-specific binding is determined in the presence of 10 μ*M* fluoxetine.

Binding of analogs at NE transport sites is determined by displacement of [3*H*]nisoxetine binding. Whole rat brains (minus cerebellum) are homogenized in 30 vol of 120 m*M* NaCl, 5 m*M* KCl, 50 m*M* *Tris*-HCl, pH 7.4, and centrifuged at 48,000 x g for 10 min. The membranes are resuspended in nisoxetine assay buffer (300 m*M* NaCl, 5 m*M* KCl, 50 m*M* *Tris*-HCl, pH 7.4) and centrifuged again before final resuspension in volumes of buffer. Assay tubes contain 750 μL of brain membranes, [3*H*]nisoxetine (0.7 n*M*) together with unlabeled drugs dissolved in nisoxetine assay buffer to a final volume of 1 ml. Tubes are incubated for 40 min at 25°, and the reaction is terminated by rapid filtration with 3 x 4 ml of cold *Tris* buffer through Whatman GF/B glass fiber filters which have been pre-soaked in *Tris* buffer containing 0.1% BSA for at least 1 h. Non-specific binding is determined in the presence of 1 μ*M* desipramine.

Affinities of analogs at dopamine transport sites are determined by displacement of [125I]RTI-55 binding in membranes from rat striatum. Frozen brains from Sprague-Dawley rats are obtained commercially and striata are dissected on ice. Tissue is homogenized in 10 vol of RTI-55 assay buffer (0.32 *M* sucrose, 10 m*M* sodium phosphate buffer, pH 7.4) with a Polytron, and centrifuged three times at 48,000 x g for 10 min, with fresh buffer resuspension for each centrifugation. Assay tubes contain 0.5 mg (original wet weight) of membranes, 0.01 n*M* [125I]RTI-55, and various concentrations of unlabeled drugs dissolved in RTI-55 assay buffer in a final volume of 2

ml. Tubes are incubated for 50 min at 25°, and the reaction is terminated by rapid filtration with 3 x 5 ml of cold Tris buffer through Whatman GF/B glass fiber filters pre-soaked in Tris buffer containing 0.1% BSA for at least 1 hr. Non-specific binding is determined in the presence of 1 μM WF-23.

In [3*H*]citalopram and [3*H*]nisoxetine binding assays, radioactivity is determined by liquid scintillation spectrophotometry (efficiency: 50%) after eluting filters overnight in 5 ml of Ecolite scintillation fluid (ICN). IC_{50} values are calculated from displacement curves using 7-10 concentrations of unlabeled analogs. Because binding of tropanes at dopamine transporter sites is generally regarded as multiphasic, potencies in inhibiting [125I]RTI-55 binding are reported as IC50 values. For [3*H*]paroxetine and [3*H*]nisoxetine binding assays, Ki values are calculated using the Cheng-Prusoff equation. All data are mean values ± S.E.M. of at least three separate experiments, each of which is conducted in triplicate.