Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Date

EXPANDING THE SCOPE OF DONOR/ACCEPTOR CARBENES AND THE SYNTHESIS OF NOVEL THERAPEUTIC AGENTS FOR COCAINE ABUSE

By

Joshua S. Alford
Doctor of Philosophy

Chemistry

_____
Professor Huw M. L. Davies
Advisor

_____
Professor Dennis C. Liotta
Committee Member

_____
Professor Fredric M. Menger
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

EXPANDING THE SCOPE OF DONOR/ACCEPTOR CARBENES AND THE SYNTHESIS OF NOVEL THERAPEUTIC AGENTS FOR COCAINE ABUSE

By

Joshua S. Alford

M.S., Missouri State University, 2008

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

An abstract of

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Chemistry

2014

Abstract

EXPANDING THE SCOPE OF DONOR/ACCEPTOR CARBENES AND THE SYNTHESIS OF NOVEL THERAPEUTIC AGENTS FOR COCAINE ABUSE

By: Joshua S. Alford

Donor/acceptor metallocarbenes are capable of undergoing many synthetically useful transformations primarily catalyzed by dirhodium(II) complexes. It is well established that the donor group plays a crucial role in modulating the reactivity of these donor/acceptor metallocarbenes. Therefore, it is great interest to expand the range of the donor groups to heteroatoms; however, strongly donating groups tend to decrease the thermal stability of the carbene precursor. They represent a highly desirable class of diazo compounds as to allow the introduction of amino and alkoxy functionality.

The second chapter is devoted to exploring whether it is feasible to expand the "donor" group to amino or alkoxy functionality. A major breakthrough in this area was discovered using a different type of carbene precursor, the *N*-sulfonyl triazole. This was a very important advance because these types of diazo compounds were previously too unstable to be isolated. The first part describes the development of 4-amino *N*-sulfonyl triazoles, which participate in the stereoselective cyclopropanation of olefins. A variety of alkenes and dienes undergo a highly diastereoselective cyclopropanation leading to α-amino cyclopropylcarboxaldehydes in good to excellent yields. Furthermore, the reaction can be conducted in a one-pot procedure starting from the *N*-ethynylphthalimide. The second part of this chapter describes the extension of this breakthrough to 4-oxy *N*-sulfonyl triazoles, which also participate in an enantioselective cyclopropanation of styrene derivatives. During these studies, a novel amino acylation reaction that is specific to this class was discovered. This transformation includes a multicomponent one-pot cascade reaction creating four different bonds regioselectively.

The third chapter focuses on extending the *N*-sulfonyl triazole methodology for the synthesis of alkenyl carbene precursors. During these studies, it was discovered that in the absence of a suitable trapping agent, 4-alkenyl *N*-sulfonyl triazoles participate in a rhodium(II)-catalyzed 4π-electrocyclization with the adjacent alkenyl moiety to furnish 2,3-fused pyrroles. The reaction was further extended to the synthesis of substituted indoles.

The fourth chapter focuses selective C–H functionalization of tertiary C–H bonds with *N*-sulfonyl triazoles, which are typically inaccessible to diazoacetates. The change in chemoselectivity towards tertiary C–H bonds is attributed to the lower steric demand of the imino carbene compared to the keto carbene.

The fifth and sixth chapters focus on further development and implementation of cyclopropanation technology. A novel class of diaryl cyclopropylamines with nanomolar binding affinities for the 5-HT_{2A} was discovered. A small, focused library of these diaryl cyclopropylamines were a working SAR model for the receptor site.

EXPANDING THE SCOPE OF DONOR/ACCEPTOR CARBENES AND THE SYNTHESIS OF NOVEL THERAPEUTIC AGENTS FOR COCAINE ABUSE

By

Joshua S. Alford

M.S., Missouri State University, 2008

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

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Chemistry

2014

Table of Contents

Experimental Part

Table of Figures

Table of Schemes

Table of Tables

List of Abbreviations

Ac	acetyl
APCI	atmospheric pressure chemical ionization
Ar	aryl
Bn	benzyl
Bu	butyl
DBU	1,8-diazabicycloundec-7-ene
COD	1,5-cyclooctadiene
Cy	cyclohexyl
dba	bis(dibenzylideneacetone)
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DMAP	*N*,*N*-4-(dimethylamino)pyridine
DMB	2,2-dimethylbutane
DMDO	dimethyldioxirane
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron-donating group

ee	enantiomeric excess
Et	ethyl
equiv.	equivalents
ESI	electrospray ionization
EWG	electron-withdrawing group
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
hv	light
IR	infrared spectroscopy
L	ligand
LDA	lithium diisopropylamide
Me	methyl
mmol	millimoles
Ms	mesyl
NMR	nuclear magnetic resonance
N.R.	no reaction
NSI	nanospray ionization
OMe	methoxy
***p*-ABSA**	*para*-acetamidobenzenesulfonyl azide
Ph	phenyl

Phth	phthalimide
Piv	pivaloyl
Pr	propyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TC	thiophene 2-carboxylate
TEA	triethylamine
temp	temperature
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'N'*-tetramethylethylenediamine
TMS	Trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
Ts	tosyl

Chapter I: Introduction to Donor/Acceptor Carbene Chemistries

The quest for the discovery of new and powerful synthetic methods has been at the forefront of organic chemistry research for more than a century.[1] These synthetic methods can connect readily accessible building blocks and become enabling technologies with broad impact beyond the field of organic chemistry. The central theme in this thesis was the development of a new class of donor/acceptor carbenes in which the donor group is either an alkoxy or amino group. The use of traditional diazo chemistry led to unstable intermediates, therefore an unconventional approach was employed. In this approach, new methodology was developed and implemented to successfully access this novel class. This chemistry was expanded to alkenyl precursors providing synthetically useful pyrroles and indoles. Moreover, recent efforts to push the chemistry into new directions have led to many interesting surprises. This chapter will discuss the fundamental aspects of diazo compounds, the reactions of diazo compounds, and the synthesis of diazo compounds. This brief discussion will serve as the foundation for a majority of the work in this thesis.

1.1 Diazo Compounds

Ethyl diazoacetate was the first diazo compound prepared by Curtius in 1883.[2] Generally, diazo compounds are molecules that bear the general formula R_2N_2 with two main resonance structures contributing to the overall structure. Diazo compounds with a carbonyl group in the α-position to the diazo carbon afford an additional resonance

structure as they can participate in mesomeric delocalization of the electron pair at the diazo carbon atom (Figure 1.1.1).[3] This class of compounds bears very characteristic spectral properties; they vary from yellow to orange to red and have a characteristic diazo band in the IR-spectrum (1950-2300 cm^{-1}).[4] Diazo compounds are inherently reactive molecules as the release of dinitrogen is thermodynamically favorable.

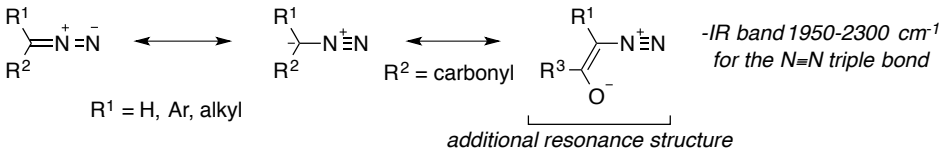
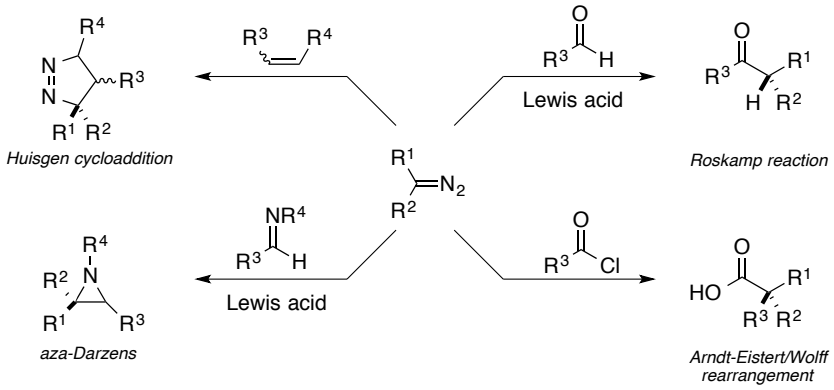


Figure 1.1.1: Resonance structures of diazo compounds.

Diazo compounds have four general reaction modes: 1) reaction without loss of the diazo moiety; 2) reactions with the loss of dinitrogen without carbene or metallocarbene intermediates; 3) reactions with the loss of dinitrogen and generation of free carbenes; 4) reaction with transition-metal catalysts to form the corresponding metallocarbene species (this will be discussed in more detail in a following section). The 1,3-dipolar cycloaddition of diazo compounds with dipolarophiles is a common reaction to prepare pyrazoles and pyrazolines, which in some cases can subsequently lose dinitrogen to form cyclopropane products.[5,6] The homologation of aldehydes with diazoacetates can form a variety of acetate products commonly known as the *Roskamp* reaction.[7,8] A variation of this reaction with cyclic ketones provides ring-expanded products (*Tiffeneau-Demjanow*-type reaction).[9] The use of Lewis acid activation *via* the aza-*Darzens* reaction is a method to prepare aziridines from nucleophilic addition of diazo compounds to imines.[10,11] The *Arndt-Eistert* homologation of carboxylic acids by

the reaction activated carboxylic acids with diazomethane and subsequent *Wolff*-rearrangement of the intermediate diazoketone.[12,13] These reactions are depicted in Scheme 1.1.1.



Scheme 1.1.1: Few select reactions of diazo compounds.

The thermal or photochemical extrusion of dinitrogen from diazo compounds results in the generation of free carbenes, which are inherently a highly reactive species.[14] A carbene is a neutral, divalent carbon atom with 6 electrons in its valence shell and can exist in the singlet or triplet state, depending on whether the *non*-bonding electrons are of the same or opposite spin. In the singlet state, all of the electrons are paired and the carbene can exhibit either electrophilic or nucleophilic behavior depending on the substituents adjourning the carbene carbon.[15] The singlet carbene usually reacts *via* a concerted, stereospecific mechanism.[16] In the triplet state, however, the carbene reacts *via* a stepwise mechanism due to the diradical nature of the carbene.[17] The triplet carbene has its two unpaired electrons located in two different *p* orbitals, which results in non-stereospecific reactions.

1.2 Metallocarbenes

The metal-catalyzed decomposition of diazo compounds to generate transient metallocarbenes, in which the carbene is stabilized by coordination to the metal, has been exploited in a variety of useful synthetic transformations.[18,19] The reactivity profile of metallocarbenes is directly dependent on the metallocarbene structure. In recent years, this has led to the classification of these metallocarbenes according to the substituents adorning the carbene. Thus, transient metallocarbenes can be divided into five major groups: acceptor,[19] acceptor/acceptor,[21] donor,[20] donor/acceptor, [21] and donor/donor[22] as illustrated in Figure 1.2.1. The term "donor" and "acceptor" refer to the ability of the substituent to be electron donating or withdrawing through resonance effects with the exception of the trifluoromethyl group, which is inductively electron-withdrawing. The "acceptor" group affects the metallocarbene's electrophilicity thereby making it more reactive, whereas the "donor" group helps to stabilize the metallocarbene through modulation of its reactivity, thus making it more chemoselective.[21] As a consequence, donor/acceptor-substituted carbenes are generally more chemoselective than carbenes that are substituted with only acceptor groups. This thesis will discuss an alternative entry in the donor/acceptor metallocarbene class.

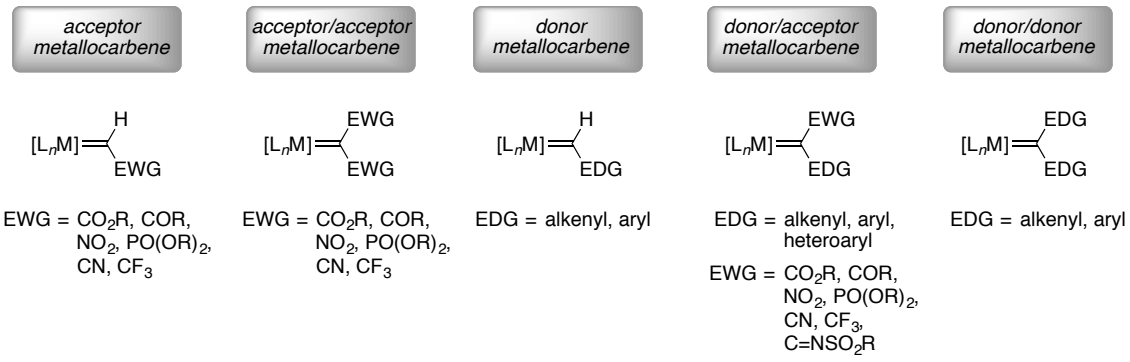
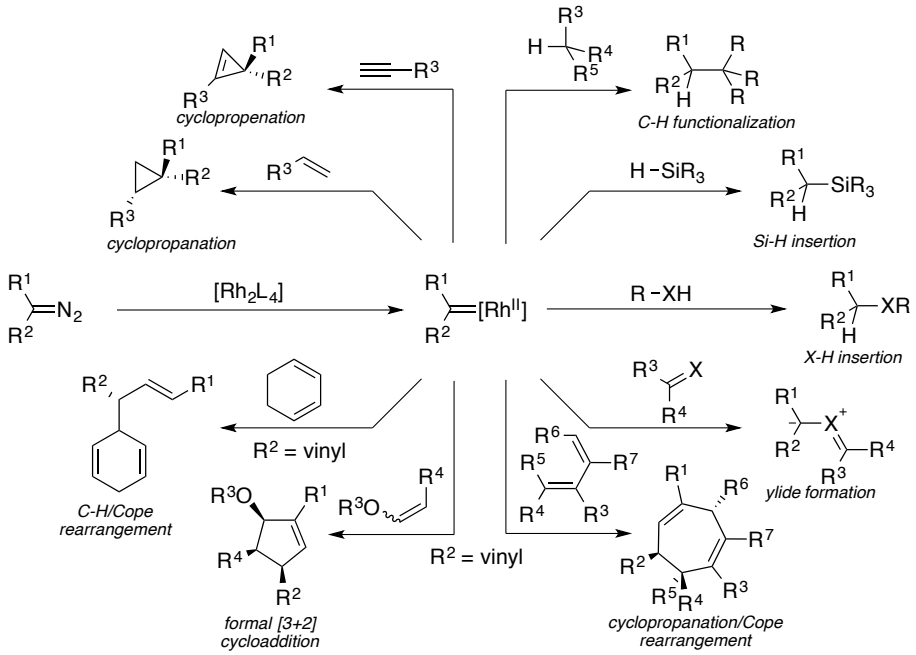


Figure 1.2.1: Types of metallocarbenes.

The decomposition of diazo compounds by rhodium(II) catalysts has been established as a very effective means of generation of a metallocarbene.[23] These Rh^{II}-metallocarbenes have been applied in numerous useful reactions affording high chemo-, regio-, and stereoselectivites, and moderate to high yields. A few selected examples of common reactions involving Rh^{II}-metallocarbenes include cyclopropanation of olefins,[24,25] cyclopropenation of alkynes,[26,27] direct C–H functionalization,[28,29,30] Si–H insertion,[31,32] heteroatom insertion (X–H), and ylide formation. Futhermore, the use of vinyldiazoacetates as the donor/acceptor metallocarbene precursor can lead products derived from a cyclopropanation/Cope rearrangement (CPCR) with dienes, [3+2] cycloaddition with electron rich olefins, and the combined C–H functionalization/Cope rearrangement (CHCR). Selected examples are presented in Scheme 1.2.1.

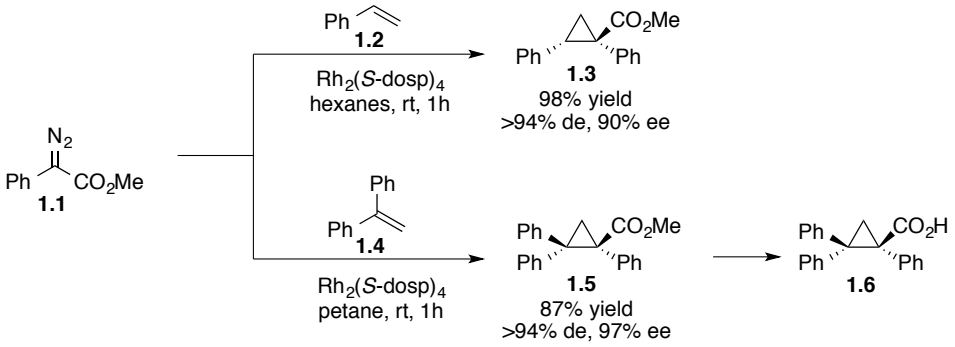


Scheme 1.2.1: Select reactions of Donor/Acceptor metallocarbenes.

The standard cyclopropanation and C–H functionalization of rhodium carbenes will be concisely discussed in this part, with particular discussions on how these transformations relate to the content of this thesis.

1.2.1 Cyclopropanation of olefins

The cyclopropanation of olefins through the metal-catalyzed decomposition of diazo compounds is one the most studied reactions of donor/acceptor metallocarbenes.[33] It has emerged as a "*benchmark reaction*" for the comparison of the efficiency of metallocarbene reactions. The Rh_2(*S*-dosp)$_4$ catalyzed cyclopropanation between donor/acceptor diazo compounds and olefins is highly diastereoselective and enantioselective while remaining very efficient at low catalyst loadings (Scheme 1.2.2).[34] This reaction has high synthetic value since cyclopropanes are important structural entities in organic synthesis,[35,36] natural products,[37] and active pharmaceutical agents.[38,39,40] More recently, enantioenriched cyclopropane carboxylic acids **1.6** derived from the cyclopropanation of 1,1-diphenylethylene **1.4** with phenyldiazoacetates **1.1** have been used for chiral ligand design for novel dirhodium tetracarboxylate catalysts (Scheme 1.2.2).[41] This thesis will discuss the examination of this reaction in new donor/acceptor systems as a key test reaction, and its application to both structural entities of interest in organic synthesis and to potential therapeutic agents (Chapters 2, 5, 6).



Scheme 1.2.2: Highly selective cyclopropantion of olefins.

However, the Rh_2(*S*-dosp)$_4$ catalyzed cyclopropanation reaction is limited to the use of a methyl ester as the acceptor group. Rh^{II}-carboxylate catalysts derived from *N*-phthaloylamino acids have emerged as exceptionally powerful catalysts for cyclopropanation when the acceptor group is expanded to larger esters,[42] phosphonates,[43] trifluoromethyl,[44] keto,[45] and cyano groups (Figure 1.2.2, A).[46] These catalysts have been shown to be C_2-symmetric in which the four phthalimido groups exist in a "chiral crown."[42] In the predictive model, the donor group of the metallocarbene is typically orientated towards the ligand wall with the acceptor group away. It is plausible that a π-stacking interaction between the donor group and the phthalimido crown could assist in this orientation (Figure 1.2.2, B). However, if the donor group is extremely bulky, the smaller acceptor group can inherit the position in close proximity to the phthalimido wall giving the opposite selectivity.[46] Therefore, depending on the relative size of the donor group of the metallocarbene precursor, the *N*-phthaloyl catalysts can furnish products of either the opposite or the same selectivity to that of Rh_2(*S*-dosp)$_4$. This thesis will discuss the use of this class of catalysts for highly asymmetric reactions, and the observation of a switch in selectivity (Chapters 4 and 5).

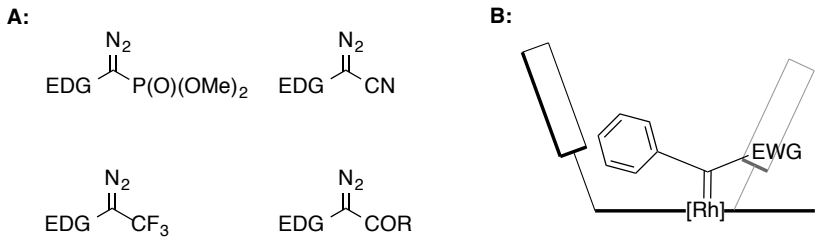
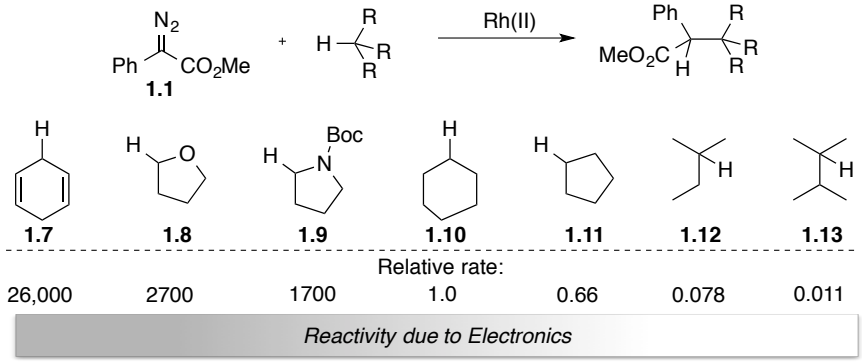


Figure 1.2.2: (A) Compatible Donor/Acceptor diazo compounds with *N*-phthaloyl catalysts; (B) Predictive model for *N*-phthaloyl catalysts.

1.2.2 C–H functionalization

Catalytic C–H functionalization reactions of donor/acceptor metallocarbenes represent a very powerful transformation in organic chemistry, allowing functionalization of an unactivated C–H bond under very mild conditions, rendering this a very valuable synthetic process. The reaction offers alternative strategies to streamline the synthesis of complex organic molecules. However, achieving highly selective C–H functionalization reactions remains a major challenge and focus of ongoing work. The site-selective C–H functionalization of a substrate with a donor/acceptor metallocarbene is governed by the steric and electronic factors. Competitive studies have shown that the relative carbons that can stabilize positive charge are more reactive towards C–H functionalization with metallocarbenes.[47] For example, the activated 1,4-cyclohexadiene **1.7**, which possesses a doubly allylic C–H bond, undergoes C–H functionalization 2.6×10^4 times faster than un-activated cyclohexane **1.10**. Steric effects also play a key role in controlling selectivity; tertiary C–H bonds are electronically more favorable than secondary C–H bonds through inductive effects, but secondary C–H bonds are sterically more accessible towards C–H functionalization reactions. This controlling factor can be seen in the rate difference

between the methylene in cyclohexane **1.10** and the methylene site in 2-methylbutane **1.12**. A general overview of the competing selectivity trends with phenyl diazoacetates is given in Scheme 1.2.3. This thesis will discuss the use of less sterically demanding metallocarbenes for C–H functionalization of tertiary C–H bonds (Chapter 4).



Scheme 1.2.3: Relative rates of reactivity towards C–H functionalization.

1.3 Diazo Synthesis

Diazo compounds have emerged as one of the most versatile and useful class of reagents in organic synthesis as previously illustrated. They are commonly synthesized via one of the following methods:[48] nitrosation of an aliphatic amine, the *Bamford-Stevens* reaction, oxidation of hydrazones, the *Forster* reaction, and the *Regitz* diazo transfer (discussed in more detail in a following section). Caution should be exercised in the preparation and use of any diazo compound. They are thermally unstable and generate free carbenes upon heating.[48] Stability towards thermal decomposition is increased by electron-withdrawing substituents (*i.e. carbonyls*) and decreased upon substitution with electron-donating substituents (*i.e. alkyl, aryl*).[49] Diazo compounds are also acid-labile compounds with diazomethane being the most labile, and unstablized diazoalkanes are

much more acid-labile than the corresponding electron-withdrawing substituted ones (Figure 1.3.1). Simple precautions such as the use of well-ventilated fume hoods and avoidance of high temperatures are sufficient to ensure the safe handling and use of diazo compounds.[49]

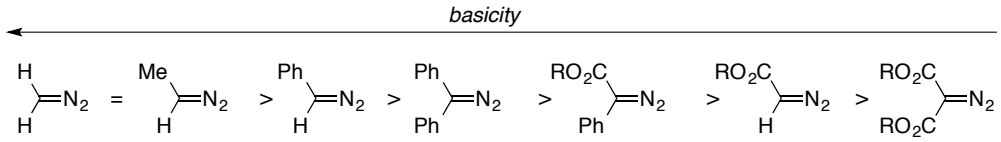
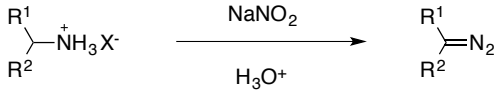


Figure 1.3.1: Relative basicity of diazo compounds.

1.3.1 Nitrosation of an amine

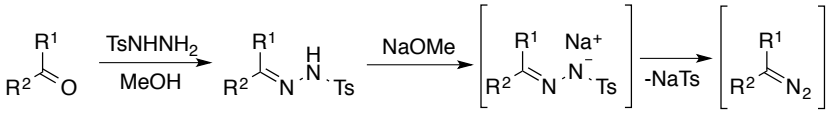
Aliphatic amines can be converted to a diazo compound in the presence of nitrosating agents, with sodium nitrite being the most common (Scheme 1.3.1).[48] In this procedure, an amine salt is dissolved in an acidic media in which the nitrosating agent (sodium nitrite) is added. The method is limited to activated amines bearing an extra electron-withdrawing group on the α-carbon. This method is effective for the preparation of acceptor diazo compounds in which the acceptor group is a phosphonate, trifluoromethyl, keto, or cyano group. An alternative to the aqueous diazotization is the use of alkyl nitrite reagents to perform the diazotization in an organic media.[50] However, the method is not effective in the synthesis of electron-rich diazo compounds.



Scheme 1.3.1: Diazotization of amines.

1.3.2 *Bamford-Stevens* Reaction

The *Bamford-Stevens* reaction is a general method for the preparation of a wide range of electron-rich diazo compounds from the corresponding aldehyde or ketone (Scheme 1.3.2).[51] In this procedure, the carbonyl moiety undergoes a condensation with tosylhydrazine, which can then be deprotonated by a base *in situ* to form the corresponding anion. When the reaction is performed at lower temperatures, the hydrazone salt can sometimes be isolated, but upon warming, the anion will dissociate thus generating the diazo compound. A main requirement for this reaction is that it must be performed in either a polar media, or in a basic aqueous two-phase system. Aggarwal has recently reported a milder protocol ulitizing phase-transfer-catalysts (PTC), in which the hydrazone salts could be cleanly converted to diazo compounds under mild reaction conditions in a wide range of solvents.[20] This method is particularly effective for the preparation of aryldiazomethanes (donor diazo) and diaryldiazomethanes (donor/donor diazo).



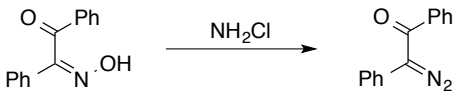
Scheme 1.3.2: *Bamford-Stevens* reaction.

Alternatively, an external oxidant can be employed to convert the hydrazone into the corresponding diazo compound when the corresponding diazo compound has low thermal stability (aliphatic diazo). In 2004, Myers reported the oxidation of *N-tert*-butyldimethylsilylhydrazones with (difluoroiodo)benzene for *in situ* generation of

diazoalkanes.[52] However, the availability and difficult handling of the oxidant limit this method. In 2007, Brewer reported the used of Swern oxidation conditions to efficiently dehydrogenate hydrazones to the respective diazo compounds at -78 °C.[53] This method is effective for the synthesis of aliphatic diazo compounds since no heating is required.

1.3.3 The *Forster* reaction

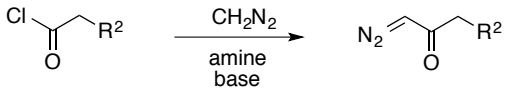
The *Forster* reaction is similar to the *Bamford-Stevens* reaction in that it involves the reaction of an oxime with chloramine (generated from sodium hypochlorite and ammonia) to form aryl diazoketones (Scheme 1.3.3).[54] Chloroamine was reported as the original oxidant, but more recently, hydroxylamine *o*-sulfonic acid as replaced this as a more convenient oxidant.[55] The scope of the reaction is fairly limited.



Scheme 1.3.3: The *Forster* reaction.

1.3.4 Terminal diazo ketone synthesis

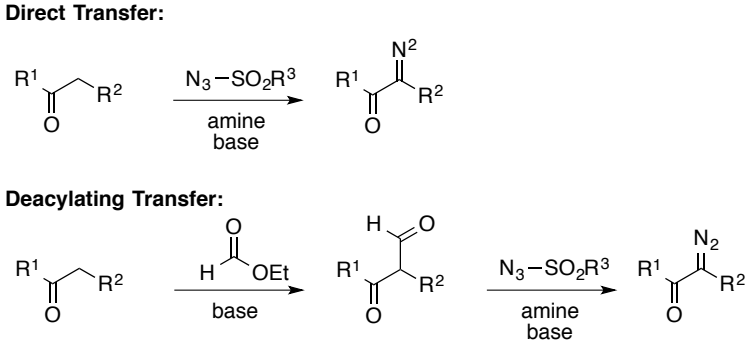
Terminal diazo ketones are synthesized by the addition of an acyl chloride or mixed carbonic anhydride to diazomethane (Scheme 1.3.4).[49] In this reaction, hydrochloric acid is produced during the course of the reaction but is scavenged by an amine base. Usually TMS-diazomethane is used as a safer alternative for diazomethane.



Scheme 1.3.4: Synthesis of terminal diazo ketones.

1.3.5 *Regitz* diazo transfer

Probably the most common method of diazo synthesis is the *Regitz* diazo transfer from sulfonyl azides to activated compounds featuring a carbonyl moiety in the presence of a base (Scheme 1.3.5). This reaction requires the formation of an enolate anion that subsequently reacts with the terminus of the sulfonyl azide. Typical diazo transfer reagents include triflyl azide (TfN_3), mesyl azide (MsN_3), tosyl azide (TsN_3), and 4-acetamidobenzenesulfonyl azide (*p*-ABSA). A variant of this protocol has also found widespread application for diazo transfer to a methylene or methyl group that is not sufficiently acidic to be deprotonated by mild bases. The process begins with a Claisen condensation of the carbonyl compound with trifluoroethyl formate. The resulting 1,3-dicarbonyl compound is then activated towards diazo transfer. Deformylation of the trifluoroformyl group occurs revealing the diazocarbonyl product. This method is effective for the preparation of acceptor, acceptor/acceptor, and donor/acceptor diazo compounds.

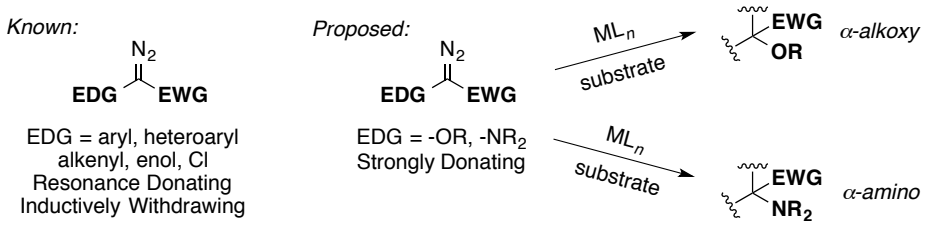


Scheme 1.3.5: Regitz diazo transfer.

Chapter II: Introduction of a Heteroatom Donor Group into the Donor/Acceptor Metallocarbene Scaffold

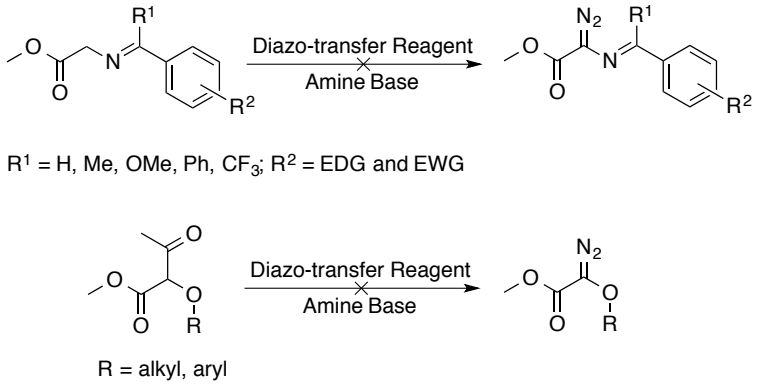
2.1 Introduction

The metal-catalyzed decomposition of diazo compounds to generate transient metal carbenes has broad application in organic synthesis.[19] In recent years, donor/acceptor-substituted metallocarbenes, commonly referred to as a "push-pull" carbene, have been extensively studied because their reactivity is attenuated compared to the more traditional transient metallocarbenes lacking a donor group (Scheme 2.1.1).[21] This singlet carbene possesses a vacant *p* orbital and an unshared electron pair resides in a σ orbital, and when substituted by an electron-donating and an electron-withdrawing group, is further stabilized.[56] However, the donor group is currently limited to a carbon-based scaffold that includes aryl, heteroaryl, vinyl, and alkynyl, and more recently, a chloro group.[29,45,57,58] In order for this chemistry to reach its full potential, however, a broader range of donor groups need to be developed. This would allow the chemistry to shift from the use of phenyl or stryl groups as the donor group to the use of a nitrogen or oxygen functionality, which could be further transformed into either α-amino acid or α-hydroxy acid derivatives respectively. In addition, with this strongly donating group, one might anticipate an enhanced stabilization of the carbene that could be expressed in its selective reactivity.



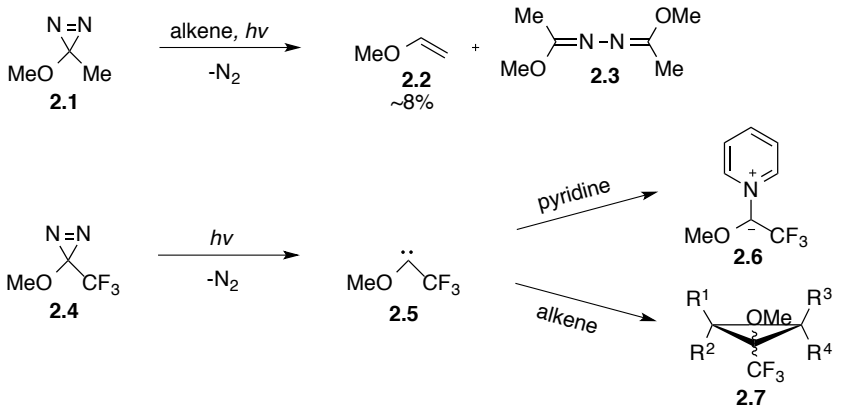
Scheme 2.1.1: Proposed expansion of donor/acceptor metallocarbene chemistries.

Our extensive efforts towards extending the scope of donor/acceptor metallocarbenes to these exciting donor groups, in conjugation with methyl acetate as the acceptor group, have been unsuccessful to date. These groups are too strongly donating, making the corresponding diazo compounds unstable. From these studies, we concluded the most viable way to make metallocarbenes with strong donor groups would be the *in situ* generation of the desired diazo derivative in the presence of the rhodium catalyst. However, all previous attempts at *in-situ* formation of the corresponding donor/acceptor diazo compounds by diazo transfer reactions were also unsuccessful. A few of the representative examples of some of our efforts are illustrated in Scheme 2.1.2. In every case, nitrogen evolution was apparent, suggesting the diazo compound was decomposing as it was being formed. This prompted us to be concerned about the safety of this diazo precursor due to this inherit instability.



Scheme 2.1.2: Failed attempts at accessing heteroatom diazoacetates.

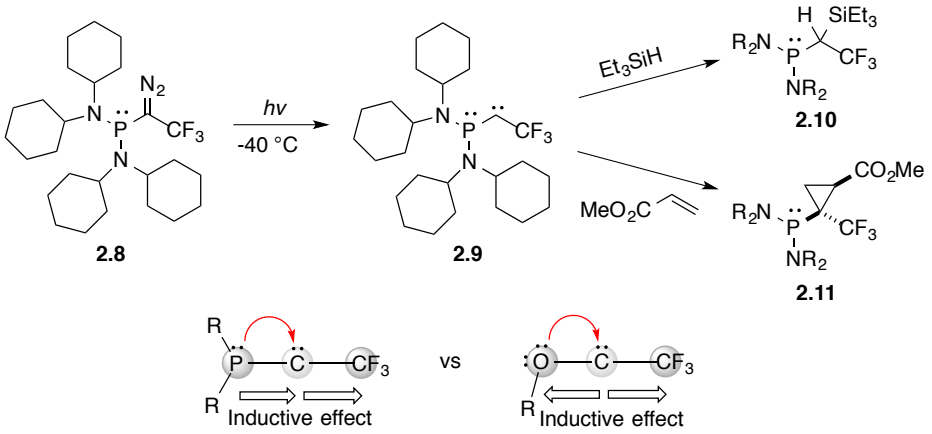
A comprehensive examination of the literature revealed a few early reports of a methoxy-substituted carbene that came from a diazirine. Moss and co-workers reported in 1988 that they were able to isolate a 3-methyl-3-methoxydiazirine (**2.1**) in a nitrogen matrix at 10K.[59] By irradiating the diazirine at 312 nm, they were able to photoisomerize it to produce a small amount of methylmethoxydiazomethane, which was rapidly destroyed in the presence of MeOH (Scheme 2.1.3). They proposed a singlet carbene was generated under these conditions. They were able to follow this up in 1991 and reported the synthesis and reactivity of 3-methoxy-3-trifluoromethyldiazirine (**2.4**).[60] It was found that the corresponding carbene was voraciously reactive and electronically unselective in its reaction with alkenes. They concluded the "pull" effect of the CF_3 dominated the "push" by the methoxy, leading to enhanced reactivity of this carbene over the previous methylmethoxycarbene (**2.1**) rather than the predicted increased stability.



Scheme 2.1.3: Moss's work with methoxy-substituted diazirine.

In 2000, Bertrand and co-workers recognized that the methoxy group in Moss's study has an inductive pull effect, which may have led to the dominating pull effect of the CF_3 group.[61] They chose to introduce a phosphanyl group in its place, which features

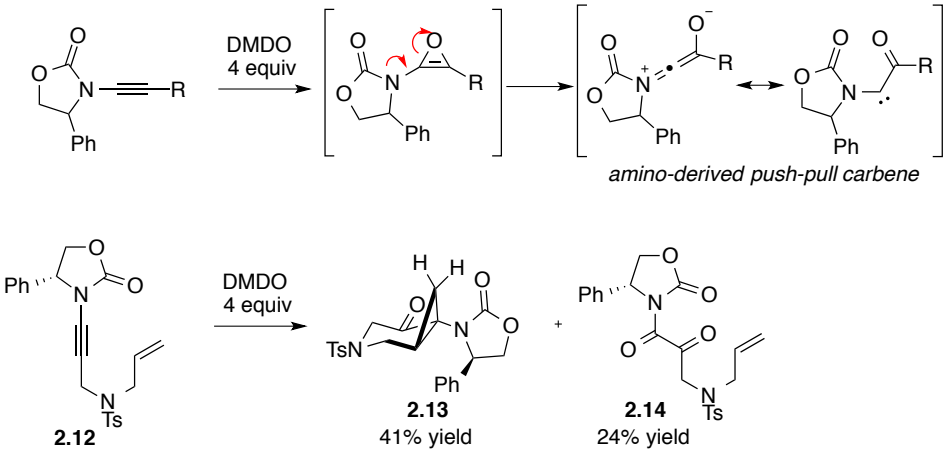
both resonance and inductive push effects, and in addition, considerably greater steric bulk (Scheme 2.1.4). The phosphanyl(trifluoromethyl)carbene (**2.9**) was found to be stable for weeks in a solution at low temperatures. Interestingly, the phosphanyl(trifluoromethyl)carbene (**2.9**) does not react with electron-rich alkenes but cleanly undergoes a diastereoselective cyclopropanation with electron-deficient alkenes, indicating its nucleophilic character. They later followed this up with a donor only amino(aryl)carbene equivalent.[62]



Scheme 2.1.4: Bertrand's extension to a phosphanyl group.

In 2008, Hsung and co-workers reported the first example of a highly diastereoselective intramolecular cyclopropanation of a "push-pull" carbene intermediate in which the donor group was derived from an ynamide.[63] The ynamide first undergoes an epoxidation reaction with DMDO followed by a subsequent rearrangement oxyketene iminium ion/push-pull carbene intermediate (Scheme 2.1.5). This intermediate then participates in an intramolecular cyclopropanation (**2.13**) or is oxidized again by DMDO furnishing the ketoimide product (**2.14**). The reaction was fairly limited, but provides a

detailed and convincing mechanistic profile of the reaction occurring *via* α-amino carbene intermediate.



Scheme 2.1.5: Hsung's intramolecular cyclopropanation involving α-amino carbene intermediate.

In 2010, a potential solution to the *in situ* generation of α-amino and α-alkoxy substituted-diazo precursors emerged from the studies by Fokin in the area of *N*-sulfonyl triazole synthesis. Certain 1,2,3-triazoles bearing a strongly electron-withdrawing group at the *N*-1 position will readily undergo a ring-opening isomerization, thus temporary breaking aromaticity and exposing a diazo functionality. In their report, one example was of particular interest as it contained the ever-allusive alkoxy functionality. When ethoxyacetylene (**2.15**) was treated with tosyl azide (**2.16**) in the presence of the Cu(I) catalyst CuTC, the desired *N*-sulfonyl triazole (**2.17**) was isolated in moderate yield as a bench-top stable solid. Was this a way to get around the instability of strongly donating donor/acceptor metallocarbene precursors? This reaction is discussed in more detail in the upcoming section.

Scheme 2.1.6: Fokin's 4-ethoxy-*N*-tosyltriazole synthesis.

2.2 Synthesis of *N*-Sulfonyl Triazoles

Arthur Michael first reported the synthesis of 1,2,3-triazoles as the product in a thermal reaction between an internal alkyne and an organic azide in 1893.[64] It took over half a century after this initial finding for the thermal reaction to be thoroughly investigated. Huisgen and coworkers studied this 1,3-dipolar cycloaddition, later known as the Huigen 1,3-dipolar cycloaddiiton, in the 1950-70's and found the reaction to be highly exothermic, but its activation barrier was quite high resulting in sluggish reaction rates even at elevated temperatures. He reasoned that since the differences in HOMO-LUMO energy levels for both the organic azide and internal alkynes are of similar magnitude, both dipole-HOMO and dipole-LUMO controlled pathways operate under the reaction conditions.[65] This results in a mixture of regioisomeric 1,2,3-triazole products if the alkyne is unsymmetrically substituted, further limiting the synthetic utility of the reaction (Figure 2.2.1).

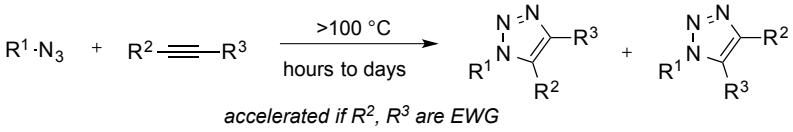


Figure 2.2.1. Huisgen 1,3-dipolar cycloaddition.

2.2.1 The Copper-Catalyzed Azide Alkyne Cycloaddition

The real potential of this 1,3-dipolar cycloaddition was not realized until the discovery of the reliable and broadly useful catalysis by copper(I) now known as the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC). This copper-catalyzed reaction was reported simultaneously and independently by Meldal and coworkers,[66] and by Fokin and Sharpless.[67] The copper catalysis transforms *terminal* alkynes and organic azides into the corresponding 1,4-disubstituted-1,2,3-triazoles at room temperature as a single regioisomer.

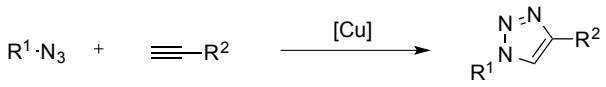
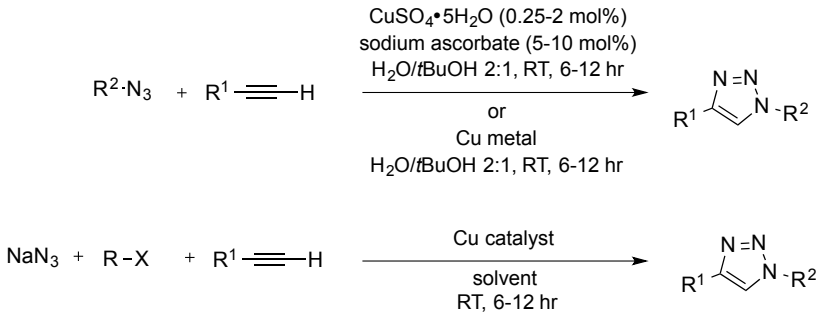


Figure 2.2.2. The CuAAC reaction.

Copper catalysis drastically changes the mechanism of the reaction by converting it to a sequence of discreet steps in contrast to the concerted process of the thermal reaction. The rate of the reaction is further increased by a factor of 10^7 in the presence of copper(I) thereby allowing the reaction to proceed quickly at room temperature.[68] The copper(I)-catalyzed reaction is not significantly affected by the steric and electronic properties of reactive azide and *terminal* alkyne, and the reaction proceeds in many protic and aprotic solvents.

To date, copper is the only metal that has provided useful yields and conversions in the metal-catalysis of the azide-alkyne cycloaddition to provide 1,4-disubstituted-1,2,3-triazoles. A few examples of this reaction can be seen in Scheme 2.2.1. Other

metals that have been explored include Pd(0/II), Pt(II), Au(I/III), and Hg(II).[69] This may be explained by the combination of copper to be able to engage alkynes in both σ- and π-interactions and the rapid exchange of these and other ligands. Different copper sources, CuI, CuBr, CuCl, CuOAc, and CuTC, and copper(II) salts with a reductant, have been shown to catalyze this transformation.



Scheme 2.2.1. CuAAC reaction condition examples.

The reaction mechanism of the CuAAC most likely proceeds in the following manner:

(1) Formation of the copper(I) acetylide which probably occurs through a π-alkyne copper complex intermediate; this coordination greatly increases the acidity of the terminal hydrogen which results in the deprotonation and the formation of a σ-acetylide.

(2) Activation of the organic azide through coordination to copper; this reveals the β-nucleophilic, vinylidene-like properties of the acetylide and causes the azide's terminus to become even more electrophilic.

(3) Formation of the first C-N bond takes place resulting in a strained copper(III) metallacycle intermediate.

(4) Reductive elimination of the Cu(III) results in the formation of the second C-N bond takes place giving way to a Cu(I) triazolyl complex.

(5) Protolysis of the Cu(I) triazolyl complex provides the 1,2,3-triazole and liberates the Cu(I) catalyst.

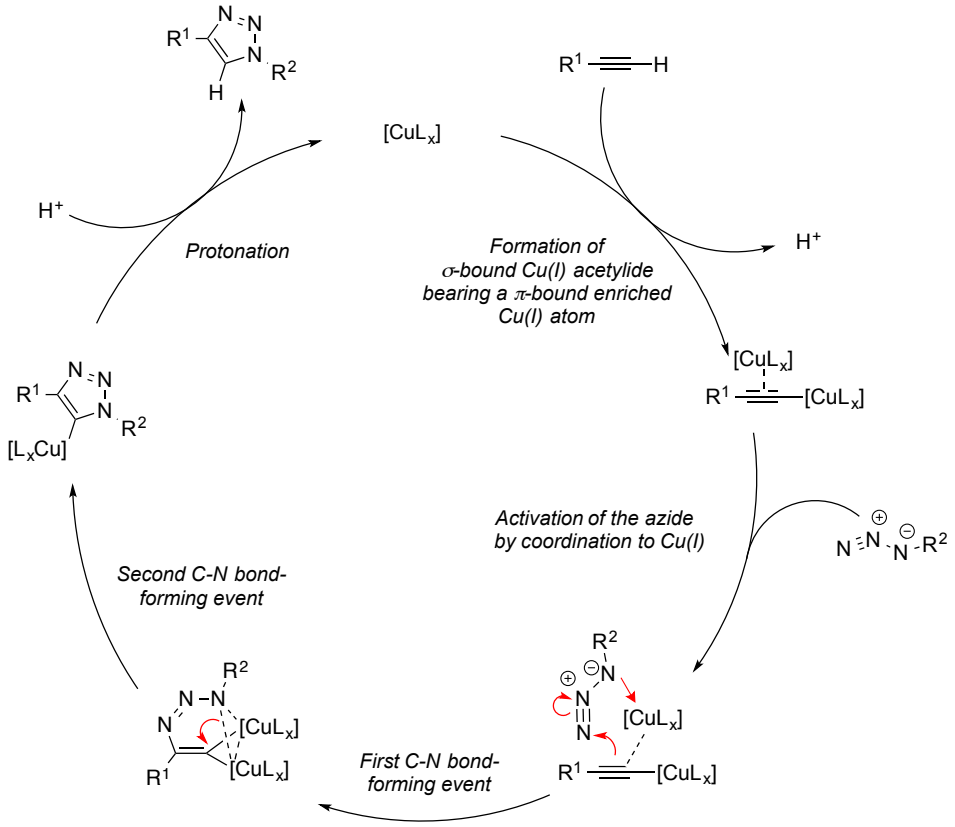
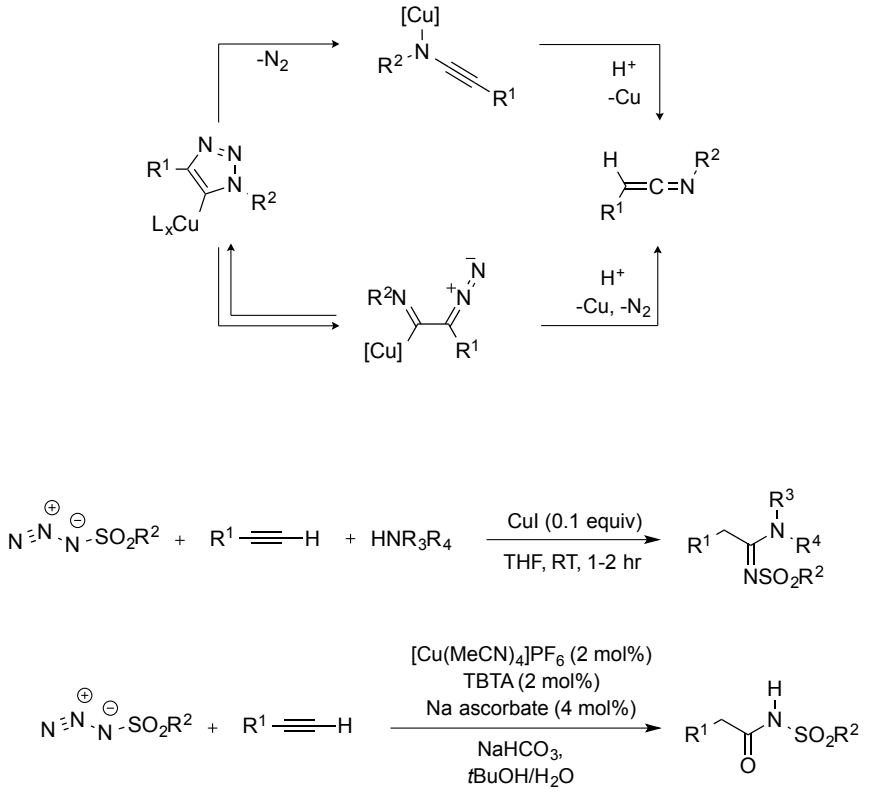


Figure 2.2.3. Reaction mechanism of the CuACC.

Triazoles can be easily synthesized by the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) and many reviews have been published on this topic.[70] This reaction allows for reliable and efficient preparation of 1,4-disubstituted-1,2,3-triazoles from terminal alkynes and organic azides with excellent selectivity. However, the outcome of the CuAAC reaction with sulfonyl azides and terminal alkynes in efforts

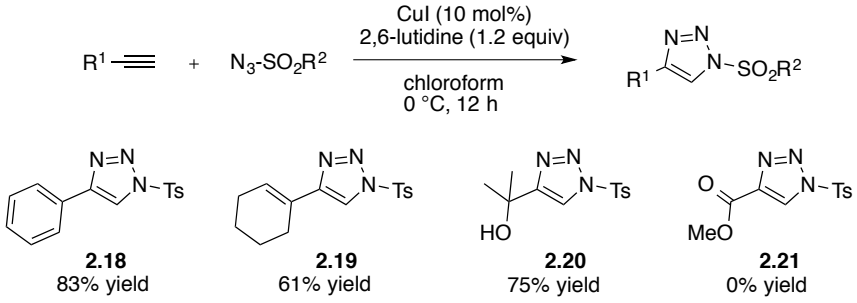
to prepare *N*-sulfonyl triazoles is influenced by a variety of factors and requires a judicious choice of reaction conditions. The electron deficient sulfonyl azides participate in a number of reactions with terminal alkynes under the CuAAC conditions giving rise to products other than the desired *N*-sulfonyl triazole.[69] The strong electron-withdrawing character of the *N*-sulfonyl substituent destabilizes the triazole causing ring-chain isomerization to occur. This forms the cuprated diazoimine, which can lose dinitrogen and give an *N*-sulfonyl ketenimine. When the reaction is conducted in the presence of amines, *N*-sulfonyl amidines are formed; [71] under aqueous conditions, *N*-acyl sulfonamides are formed.[72] With these reactions, a small percentage of the *N*-sulfonyl-1,2,3-triazole was isolated.



Scheme 2.2.2. Reaction of the cuprated diazoimine.

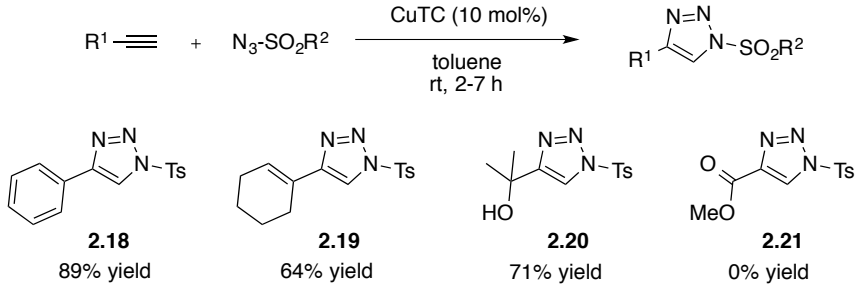
In the mid 2000's, there were a few reports of the synthesis of *N*-sulfonyl triazoles, but none of methods offered a level of generality and simplicity required for general acceptance from the synthetic community. Traditionally, *N*-sulfonyl triazoles were synthesized by treatment of the free N*H*- triazole with a sulfonyl chloride in the presence of an amine base. The sulfonylation of N*H*-triazoles can lead to a mixture of isomeric *N*2- and *N*1-sulfonylated triazoles. This is not an efficient procedure for making precursors to donor/acceptor metallocarbenes because only the *N*1 isomer can undergo ring-chain isomerization to form the desired diazoimine intermediate.

In 2007, Chang conducted a theoretical study of the mechanistic pathways of the CuAAC between sulfonyl azides and copper(I) acetylides in hopes of achieving selective formation of *N*-sulfonyl triazoles. [73] By lowering the reaction temperature and the use of a sterically hindered amine base, Chang was able to discourage the entropically favored loss of dinitrogen from the cuprated open-chain triazole intermediate. They found they could regioselectively prepare *N*-sulfonyl triazoles from a range of terminal alkynes and various sulfonyl azides (Scheme 2.2.3).



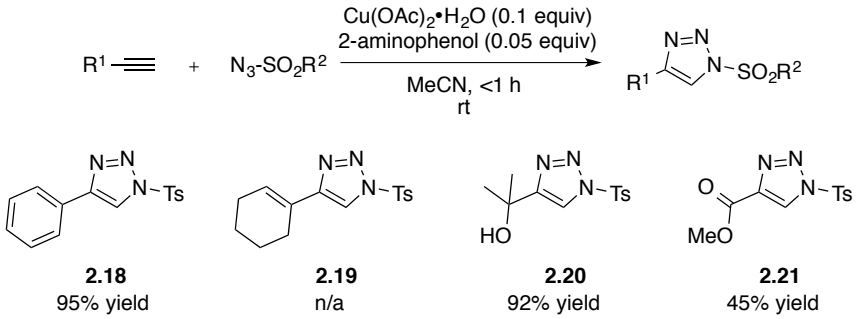
Scheme 2.2.3: Chang's conditions for synthesis of 4-substituted *N*-sulfonyl triazoles.

In 2010, Fokin continued to explore the effect of ligands on the outcome of the reaction. By using a soft sulfur ligand, they were able to report an improved method for the synthesis of sulfonyl triazoles from *in situ* generated Cu^{I}-acetylides and sulfonyl azides,[74] using copper(I) thiophen-2-carboxylate (CuTC) as catalyst (Scheme 2.2.4). An examination of solvents revealed that water and toluene were the optimal solvents furthering demonstrating the broad applicability of the reaction. They found they could regioselectively prepare a wide range of *N*-sulfonyl triazoles from both aryl and aliphatic alkynes, as well as strongly electron-donating and electron-deficient alkynes, with aryl and aliphatic sulfonyl azides. However, strongly electron-deficient alkynes, such as ethyl propiolate, did not provide the desired *N*-sulfonyl triazole as well as strongly electron-deficient sulfonyl azides such as nosyl azide (Scheme 2.2.4).



Scheme 2.2.4: Fokin's conditions for synthesis of 4-substituted *N*-sulfonyl triazoles.

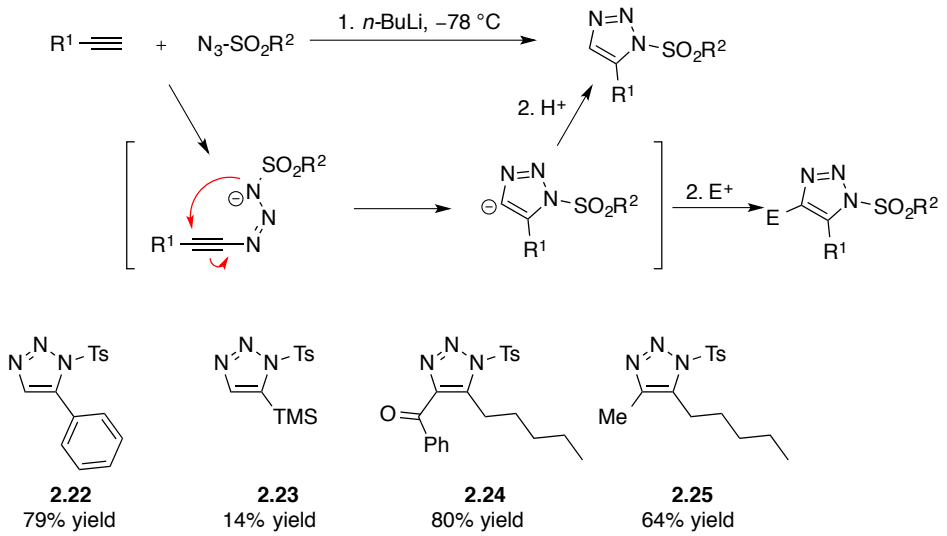
Hu, Wang, and co-workers reported an alternative copper(I)-catalytic system for the synthesis of *N*-sulfonyl triazoles in 2011.[75] The combination of $Cu(OAc)_2 \cdot H_2O$/2-aminophenol in the presence of terminal alkynes and sulfonyl azides effectively afforded the *N*-sulfonyl triazoles within minutes in excellent yields with high selectivity (Scheme 2.2.5). Notably, electron deficient alkynes still participated in the reaction albeit in lower yields providing an *N*-sulfonyl triazole with two strong electron-withdrawing groups.



Scheme 2.2.5: Hu's and Wang's synthesis of 4-substituted *N*-sulfonyl triazoles.

2.2.2 The Anionic Azide Alkyne Cycloaddition

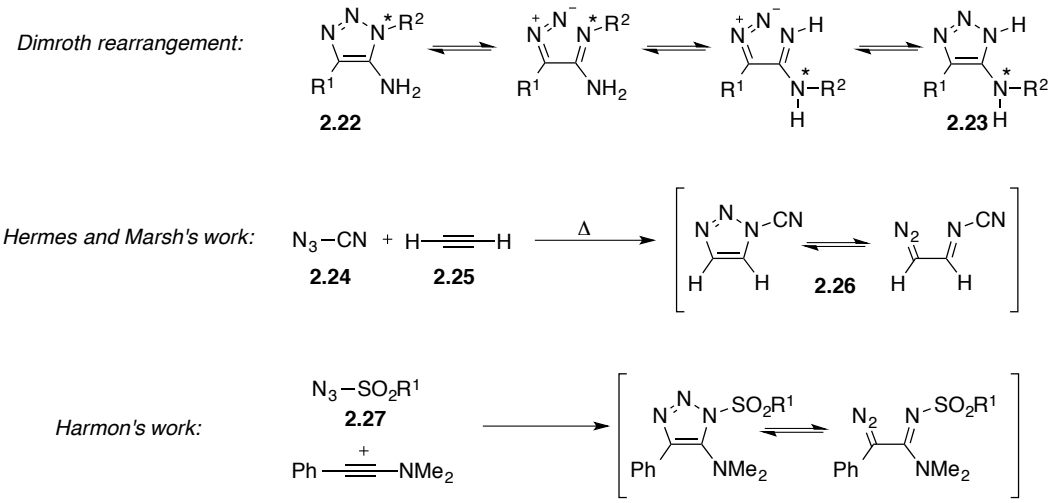
Recently, Croatt reported a selective synthesis of 4,5-disubstituted *N*-sulfonyl triazoles (Scheme 2.2.6).[76] The treatment of terminal alkynes under strongly basic conditions in the presence of sulfonyl azides results in the selective formation of 5-substituted *N*-sulfonyl triazoles in which the triazole anion can be trapped with various electrophiles to form regioselectively 4,5-disubstituted *N*-sulfonyl triazoles. In the proposed mechanism of this reaction, the lithiated acetylide reacts with the terminal nitrogen of the sulfonyl azide followed by subsequent cyclization to form the triazolyl anion. The 5-substituted *N*-sulfonyl triazoles were found to isomerize to 4-substituted *N*-sulfonyl triazoles when being purified by silica gel chromatography; therefore, crystallization was utilized to isolate pure 5-substituted *N*-sulfonyl triazoles. To date, Croatt's method is the only method for the synthesis of 4,5-disubstituted *N*-sulfonyl triazoles.



Scheme 2.2.6: Croatt's synthesis of 4,5-disubstituted *N*-sulfonyl triazoles.

2.3 Ring Opening/Rearrangement of Triazoles

It is well known that 1,2,3-triazoles bearing exocyclic amines (**2.22**) can undergo a rearrangement reaction to isomeric triazoles (**2.23**). The mechanism of the reaction is a ring-opening, ring-closure sequence, known as the Dimroth rearrangement, which proceeds by means of imino diazo intermediates (Scheme 2.3.1).[77] 1,2,3-Triazoles bearing a strongly electron-withdrawing group at the N-1 position tend to drive the equilibrium towards the ring-opened imino diazo structure. In 1967, Hermes and Marsh reported that at slightly above room temperature, 1-cyano-1,2,3-triazole (**2.26**) exists as a 1:1 isomeric mixture of its closed and open-isomer.[78] Shortly after this report, Harmon and co-workers found that *N*-sulfonyl-1,2,3-triazoles with an amino group at the C-5 position also existed as an isomeric mixture of open and closed-chain isomers.[79]

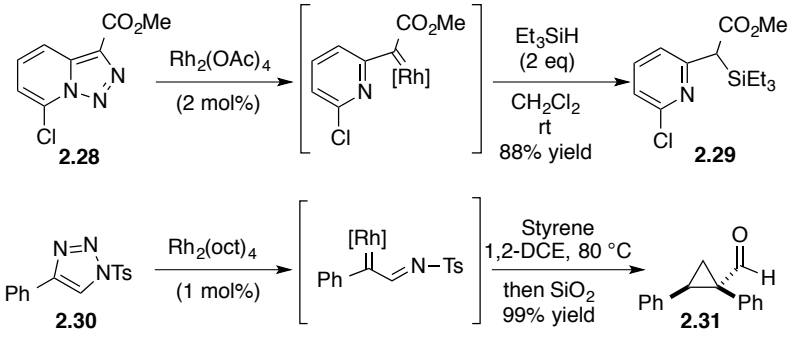


Scheme 2.3.1: Triazole rearrangements/ring-chain isomerization.

Recently it was demonstrated that 4-substituted *N*-sulfonyl-1,2,3-triazoles could undergo a similar ring opening exposing a diazo functionality in the presence of a rhodium(II) catalyst which can then be subsequently decomposed effectively generating metallocarbene intermediates. In 2007, Chuprakov and Gevorgyan reported that the related 7-chloro-substituted pyridotriazole (**2.28**) could be effectively decomposed in the presence of a rhodium(II) catalyst, Rh_2(*S*-dosp)$_4$, to reveal a transient rhodium(II) carbene, thus serving as an alternative entry into rhodium(II)-stabilized carbenes (Scheme 2.3.2).[80] They were able to develop an efficient Rh^{II}-catalyzed transannulation of these pyridotriazoles with alkynes and nitriles for the formation of pyrrolo- and imidazopyridines. The proposed metallocarbene intermediate was confirmed by its insertion into the Si—H bond of triethylsilane.

After reporting that the pyridotriazole could be used as a surrogate of α-imino carbene, continued investigation by Gevorgyan in this area, in collaboration with Fokin, led to the discovery of 4-aryl-*N*-sulfonyl-1,2,3-triazoles (**2.30**) as convenient precursors to rhodium(II)-stabilized α-imino carbenes.[81] They were able to effectively demonstrate

that *N*-sulfonyl triazoles (**2.30**) in the presence of 1 mol% $Rh_2(OAc)_4$ reacted smoothly with styrene providing the *trans*-cyclopropane carboxaldehyde (**2.31**) after hydrolysis of the sulfonyl imine (Scheme 2.3.2). Rhodium(II) tetracarboxylates proved to be superior in this reaction. This reaction is described in more detail in the following section.



Scheme 2.3.2: Triazole rearrangements/ring-chain isomerization.

2.4 Early Reaction Development of *N*-Sulfonyl Triazoles

N-Sulfonyl triazoles can be effectively decomposed in the presence of a suitable metal catalyst. The resulting α-imino metallocarbenes are highly electrophilic and undergo a variety of useful transformations, furnishing unique products that are not accessible *via* conventional donor/acceptor α-oxo metallocarbenes. To date, only $Ni(cod)_2$/ligand, $Ag(CO_2CF_3)$, and $Rh_2(CO_2R)_4$ have been shown to catalyze this reaction, and of these catalysts rhodium(II) tetracarboxylates have proven to be the most versatile.[18] It has been proposed that the Lewis acidic rhodium(II) catalyst plays two roles, facilitating the ring-chain isomerization of the triazole and the subsequent diazo decomposition.[85] Many achiral and chiral rhodium(II) catalysts have been employed. Figure 2 illustrates the most common catalysts used so far. Their specific application is discussed in more detail later in this thesis.

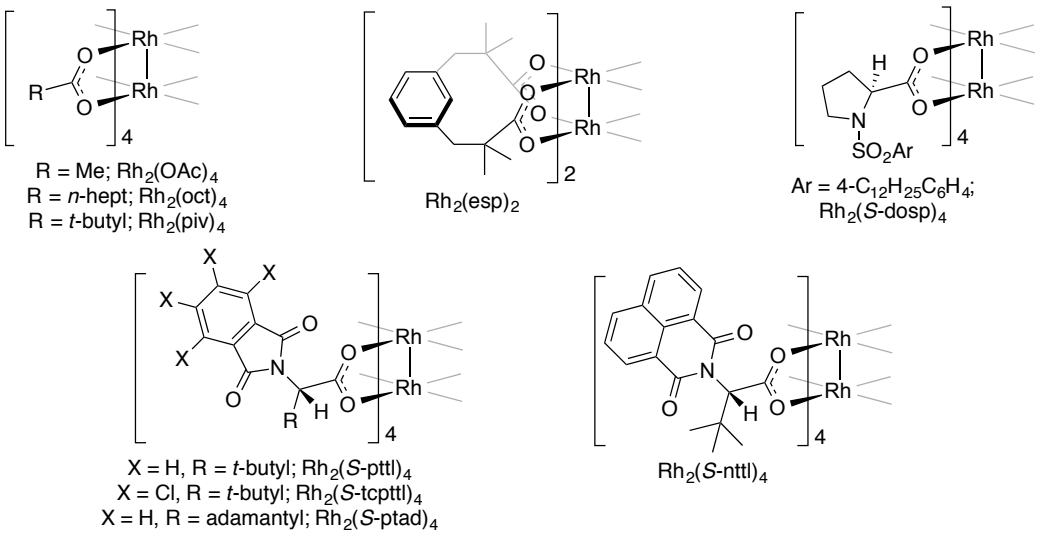
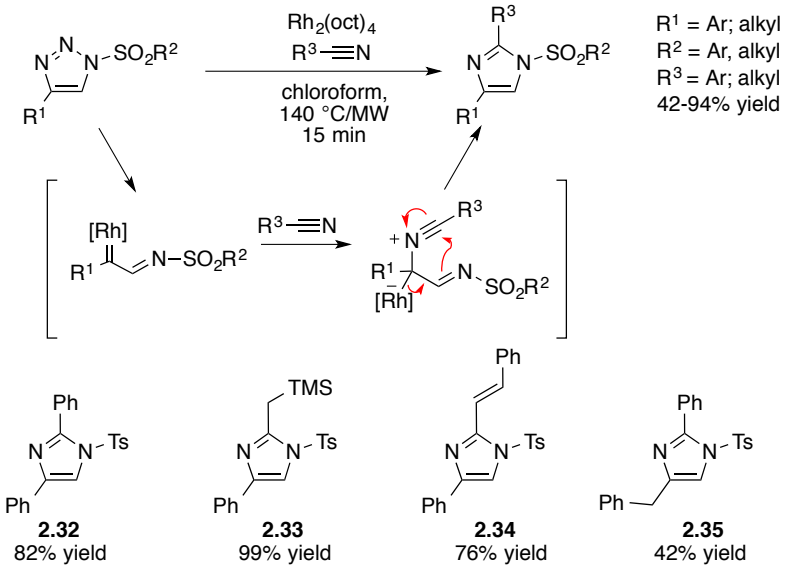


Figure 2.4.1: Rhodium(II) tetracarboxylate catalysts.

2.4.1 Imidazole synthesis from nitriles

A distinctive feature of using *N*-sulfonyl triazoles is the generation of metallocarbenes with a pendant sulfonyl imine group. The nitrogen atom exhibits a higher nucleophilicity than the oxygen atom in the related α-oxo metallocarbene.[82] Due to this increased nucleophilicity, the α-imino group has the ability to participate in reactions involving zwitterionic intermediates, which can then cyclize to new heterocycles. In 2008, Fokin and Gevorgyan exploited this feature and reported that on warming *N*-sulfonyl triazoles in the presence of a rhodium(II) catalyst, they reacted with nitriles in a transannular fashion to furnish imidazoles (**2.32**-**2.35**; Scheme 2.4.1).[81] The reaction scope was broad as various nitriles and *N*-sulfonyl triazoles participated in the reaction. The reaction was found to be effective under both microwave heating and conventional heating conditions. The proposed mechanistic rationale involves a nucleophilic attack of the nitrile on the

metallocarbene leading to the intermediate ylide which subsequently cyclizes with loss of metal catalyst.

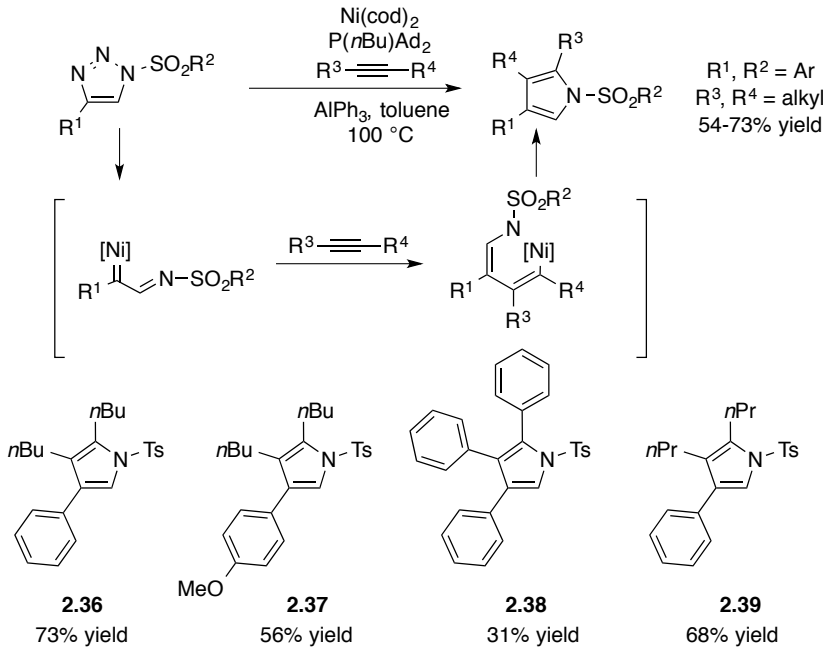


Scheme 2.4.1: Fokin's imidazole synthesis.

2.4.2 Pyrrole synthesis from alkynes

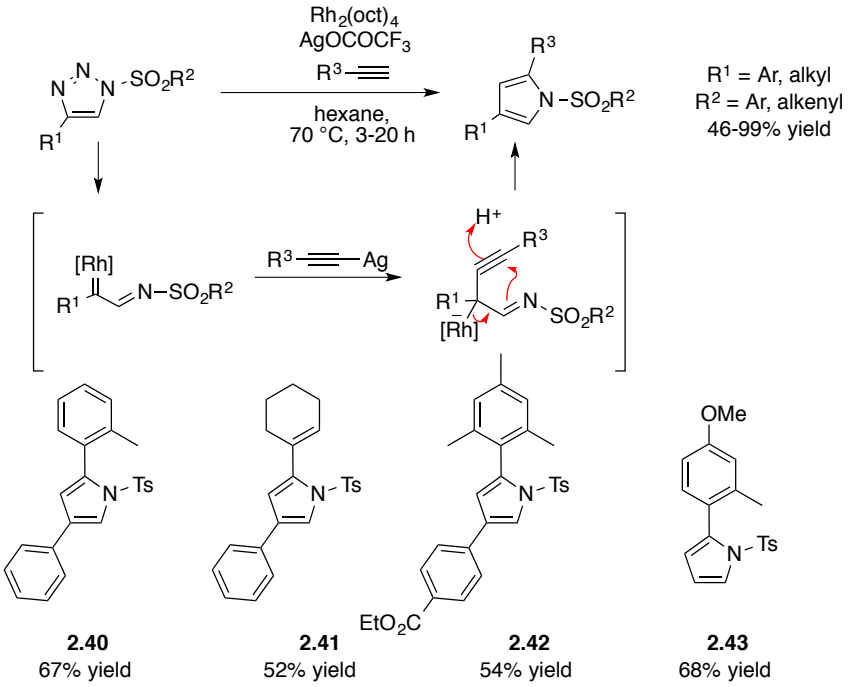
Shortly after this, Murakami reported a nickel/aluminum-catalyzed dinitrogenative transannulation of *N*-sulfonyl triazoles with internal alkynes.[83] The combination of a nickel(0) catalyst, $Ni(cod)_2$, electron-rich and bulky phosphine ligand, $P(n\text{Bu})Ad_2$, and a Lewis acid additive, $AlPh_3$, provided an effective transannulation of symmetrical internal alkynes furnishing the corresponding substituted pyrroles in moderate yields (**2.36-2.39**; Scheme 2.4.2). It is proposed that the *N*-sulfonyl triazole tautomerizes to the α-imino diazo which the nickel catalyst subsequently decomposes. Insertion of the alkyne leads to a six-membered nickelacycle, which then undergoes reductive elimination regenerating the nickel(0) catalyst. The effect of the Lewis acid may be promoting the ring opening of

the *N*-sulfonyl triazole, or accelerating the reductive elimination. The reaction tolerated a variety of *N*-sulfonyl triazoles; however, the use of unsymmetrical alkynes gave a mixture of regioisomers and terminal alkynes failed to participate in the reaction.



Scheme 2.4.2: Murakami's nickel/aluminum-catalyzed pyrrole synthesis.

Gevorgyan then reported the transannulation of *N*-tosyl triazoles with terminal alkynes using a dual rhodium/silver catalyst system.[84] Various C-4 substituted triazoles and electron-rich terminal alkynes participated in the reaction to provide the desired pyrrole products (**2.40**-**2.43**) in good yield; however, electron-poor terminal alkynes did not participate in the reaction (Scheme 2.4.3). The methodology was extended into a three-component, one-pot procedure starting from tosyl azide and two different terminal alkynes, one of which is first added to form the *N*-tosyl triazole. The proposed mechanism involves attack of the rhodium(II) carbene by a silver acetylide followed by a proton-assisted 5-*endo*-*trig* cyclization with concurrent loss of the rhodium catalyst.

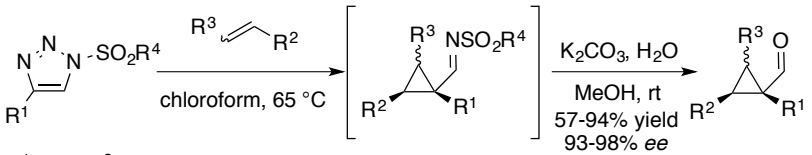


Scheme 2.4.3: Gevorgyan's pyrrole synthesis.

2.4.3 Cyclopropanation of olefins

Rhodium(II)-catalyzed cyclopropanation of alkenes with donor/acceptor carbenes has been shown to be an effective method for the enantioselective synthesis of cyclopropanes generating one or more quaternary stereogenic centers. Fokin and co-workers reported two examples of a highly diastereo- and enantioselective rhodium(II)-catalyzed cyclopropanation of alkenes with the imino metallocarbenes derived from *N*-sulfonyl triazoles (Scheme 2.4.4).[85,86] Subsequent hydrolysis of the resulting sulfonyl imines gave quick and ready access to cyclopropyl carboxaldehydes in good yields and high enantioselectivity. The reduction of the sulfonyl imines provided *N*-sulfonyl homoaminocyclopropanes in excellent yields and high enantioselectivity.[85] However, the reaction proved to be highly dependent on the nature of the sulfonyl group as the use of

tosyl triazole afforded the cyclopropyl carboxaldehydes in good yield, but low to moderate enantioinduction. Switching the sulfonyl group to the less sterically encumbered mesyl resulted in an improved reaction with good yields and very high levels of enantioinduction. The rhodium catalyst, Rh_2(*S*-nttl)$_4$, proved to be the optimum catalyst as seen in Scheme 2.4.4. Not surprisely, Rh_2(*S*-dosp)$_4$ provided the opposite enantiomer when R^4 = isopropyl.



R^1 = Ar, R^2 = aryl, alkyl
R^3 = H, alkyl

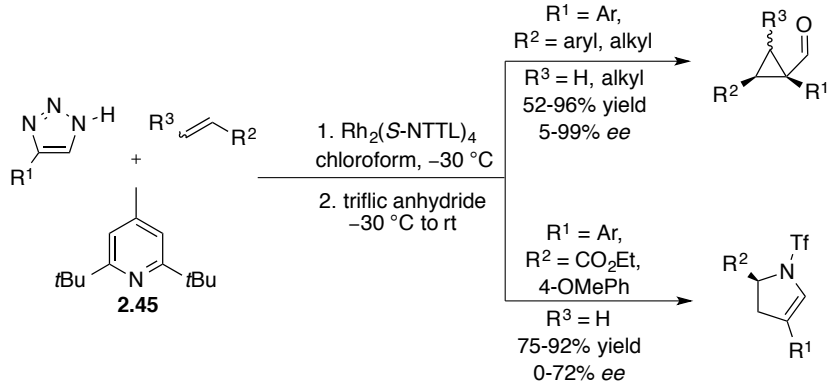
entry	R^1	R^2	R^3	R^4	catalyst	product	% ee[a]	% yield[b]
1	Ph	Ph	H	*p*-Tol	Rh_2(*S*-dosp)$_4$	**2.44**	28	92
2	Ph	Ph	H	*p*-Tol	Rh_2(*S*-ptad)$_4$	**2.44**	74	91
3	Ph	Ph	H	*p*-Tol	Rh_2(*S*-pttl)$_4$	**2.44**	76	87
4	Ph	Ph	H	*p*-Tol	Rh_2(*S*-nttl)$_4$	**2.44**	78	42
5	Ph	Ph	H	Me	Rh_2(*S*-pttl)$_4$	**2.44**	88	91
6	Ph	Ph	H	Me	Rh_2(*S*-nttl)$_4$	**2.44**	96	95
7	Ph	Ph	H	*i*-Pr	Rh_2(*S*-nttl)$_4$	**2.44**	97	83
8	Ph	Ph	H	*i*-Pr	Rh_2(*S*-dosp)$_4$	**2.44**	-16	75

[a]Determined by chiral HPLC; [b]NMR yields.

Scheme 2.4.4: Fokin's enantioselective cyclopropanation.

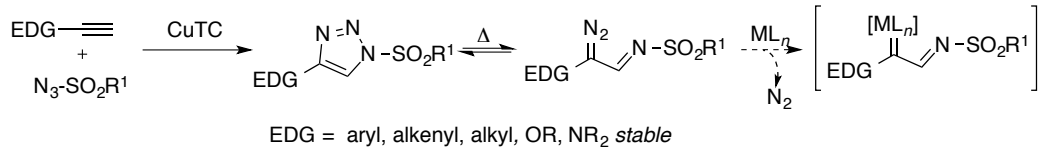
Fokin went on to further illustrate that the reaction could be performed starting from the readily accessible N*H*-triazoles, which could be sulfonylated *in situ* by triflic anhydride in the presence of a hindered pyridine base at low temperatures.[86] Interestingly, the reaction allowed for a visual readout of the reaction progress: a purple solution resulted from the complexation of the N*H*-triazole and the rhodium(II) catalyst, but turned green upon the addition of triflic anhydride indicating all of the N*H*-triazole

had been sulfonylated. Reaction with an electron rich olefin, 4-methoxystyrene, leads to the formation of a 2,3-dihydropyrrole product with moderate enantioinduction.[87] The use of an electron-withdrawing group at the C-4 position of the triazole also resulted in the formation of a 2,3-dihydropyrrole product, but as a racemate. It was concluded that the two products must arise *via* different reaction pathways.



Scheme 2.4.5: Fokin's enantioselective cyclopropanation from N*H*-triazoles.

With encouragement from the early work done with *N*-sulfonyl triazoles that was primarily centered on 4-aryl and 4-alkyl, we envisioned that a suitable precursor to heteroatom functionalized donor/acceptor metallocarbenes would be through *N*-sulfonyl triazole intermediates. We have been intrigued by the possibility of developing new chemistry of *N*-sulfonyl triazoles by incorporation of other types of donor groups, such as amino and alkoxy, into the *N*-sulfonyl triazole scaffold. These donor groups would come from the corresponding heteroatom-substituted alkynes, which represent an extremely versatile class of alkynes due to the electron donating ability of the heteroatom. The stability of the *N*-sulfonyl triazole can be influenced by the nature of the C(4) substituent which will make these type of *N*-sulfonyl triazoles very fascinating.



Scheme 2.4.6: Proposed heteroatom *N*-sulfonyl triazoles.

2.5 Development of a 4-Amino-*N*-Sulfonyl Triazole

Alkynes that contain one nitrogen atom directly attached to the triple bond, ynamines, are especially useful. This alkyne possesses a high level of reactivity due the polarization of the triple bond from the nitrogen in conjugation with a strong differentiation of the two *sp*-hybridized carbon atoms. This increased reactivity has made their preparation and handling difficult, and their synthetic uses rather limited. Unsubstituted ynamines have the propensity to isomerize to the nitrile functionality. However, adding electron-withdrawing groups, carbonyls and sulfonyls, can help to stabilize the alkyne leading to ynamides (1 carbonyl) and ynimides (2 carbonyls). Other ynamide and ynimide analogues include: diaminocetylenes, yne-imines, yne-hydrazides, amidinylynamides, and yne-sulfoximines (Figure 2.5.1).[88]

Ynamides have received an increasing level of interest over the past 20 years.[89] These amino alkynes feature a strong polarization of the triple bond by virtue of the ynamine character, but the electron-withdrawing group attenuates this. Ynamides are more stable compared to ynamines, which has allowed for increased synthetic use and for the development of highly efficient preparations rendering ynamides highly accessible. These preparations include the following: elimination of mono- or dihalogenated

enamides,[90] isomerization of propargyl amides,[91] alkynylation with hypervalent iodonium salts,[92] and copper-catalyzed cross coupling[93] as depicted in Scheme 2.5.1.

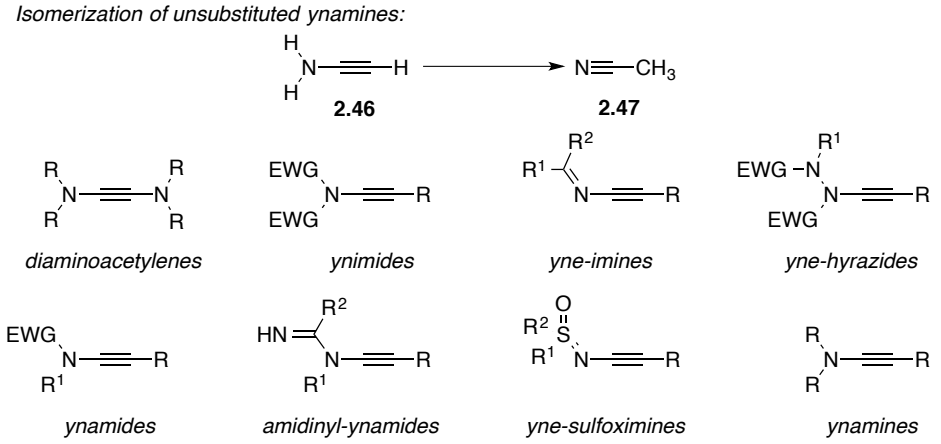
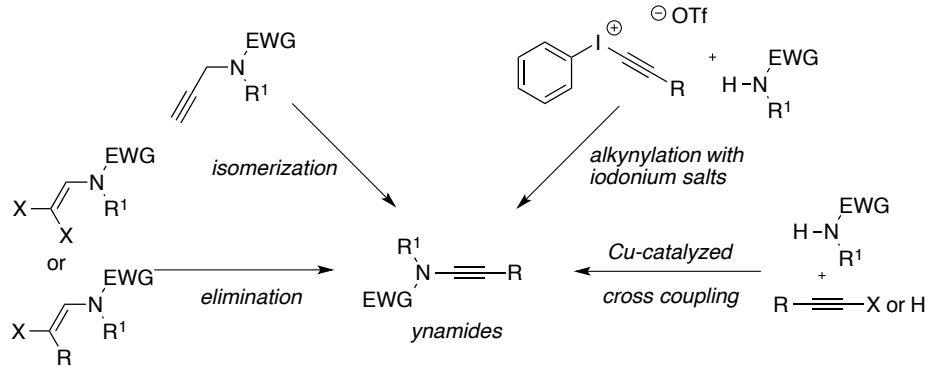


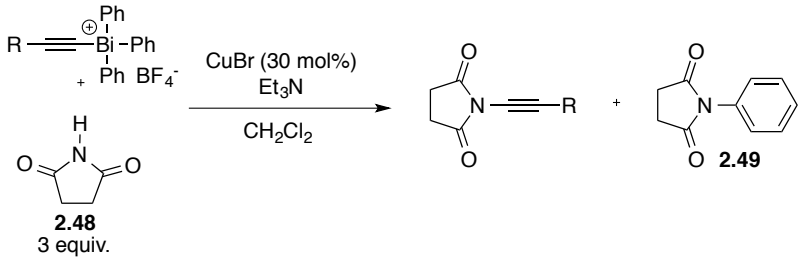
Figure 2.5.1: Ethynyl amines.



Scheme 2.5.1: Synthesis of ynamides.

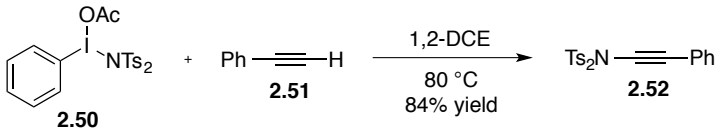
In contrast to ynamides, synthesis of ynimides is very limited. In 2011, Sueda and co-workers reported a copper-catalyzed coupling reaction between alkynyl(triaryl)bismuthonium salts and cyclic imides (**2.48**).[94] The reaction was found to tolerate aliphatic alkynyl groups and some silyl-substituted derivatives, but aryl-substituted bismuthonium salts gave very low yields of the alkynylated product. It was

found that the *N*-aryl imide product (**2.49**) was a major byproduct in all the reactions, thus limiting the applicability of the reaction. Another limiting factor of the reaction was the alkynylbismuth materials took many steps to synthesize and very little is known about their reactivities.



Scheme 2.5.2: Sueda's synthesis of ynimides.

In late 2012, Muñiz and co-workers reported a direct metal-free amination of aryl alkynes with a specialized hypervalent iodine reagent, PhI(OAc)NTs_2 (**2.50**), under mild conditions (Scheme 2.5.3).[95] The reaction tolerated a variety of aryl alkynes, but aliphatic alkynes underwent an intramolecular C–H insertion of an alkylidene carbene intermediate to form cyclopentenes. A variety of bissulfonimides participated in the reaction; however, other nitrogen ynimide sources such as saccharine and phthalimide were not engaged under the reported conditions. This work was published after a majority of the work in this chapter was performed.



Scheme 2.5.3: Muñiz's synthesis of ynimides.

With encouragement from the early work done with *N*-sulfonyl triazoles, we envisioned that a suitable precursor to amino functionalized donor/acceptor metallocarbenes would be a 4-protected-amino-*N*-sulfonyl triazole. A reasonable approach to this triazole would be the copper(I)-catalyzed azide-alkyne cycloaddition of an ethynyl amine with a corresponding sulfonyl azide. Since we were interested in accessing free *N*-H amino acids, the protected-amino group would have to be easily deprotected, so we were particularly interested in a suitable ynimine. *However, there were a few concerns with this proposal that needed to be outlined:*

(1) Synthetic approaches to ynimides were quite limited as previously discussed.

(2) Of the developed coupling methods, unprotected alkynes do not participate or created a bis-coupled product, and silyl-protected alkynes usually were deprotected under the reaction conditions.

(3) There was no example of an ynamide or ynimide participating in a CuAAC reaction with sulfonyl azides.

The initial amino-functionality that was chosen was a phthalimide. This initial choice was made for a few reasons:

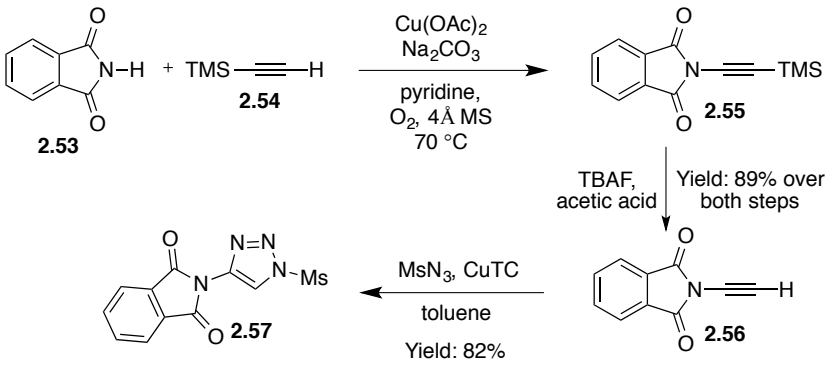
(1) There were multiple methods in the literature depicting various strategies for the unmasking of the primary amine.

(2) Chemistry of phthalimides was quite rich.

(3) It was very cheap starting material.

(4) There were commercially available derivatives with different electronics.

The only published method for the synthesis of *N*-ethynylphthalimide required many steps and resulted in a mixture of products.[94] For this idea to gain wide acceptance, we would need to have a more environmentally friendly and streamlined synthesis of the *N*-ethynylphthalimide (**2.56**). A recent report from the Stahl laboratory of an experimentally simple copper-catalyzed aerobic oxidative amidation of terminal alkynes resulting in the efficient synthesis of ynamides appeared ideal for our needs.[96] Adaptation and slight modification of this procedure to phthalimide (**2.53**) and TMS-acetylene (**2.54**) in the presence of 20 mol% of $Cu(OAc)_2$ under an oxygen atmosphere generated the TMS-protected *N*-ynimide (**2.55**), which was then deprotected using TBAF in the presence of 2 equiv of acetic acid in THF to furnish the *N*-ethynylphthalimide (**2.56**) in 89% yield over both steps. The reaction proved to be both scalable and reliable (ran on 31 g scale). The deprotection step needed to be buffered with a weakly acidic media as the basic nature of TBAF decomposed the *N*-ethynylphthalimide (**2.56**). The *N*-ethynyl ynimide (**2.56**) was then transformed into the benchtop stable 4-phthalimido-*N*-mesyl-1,2,3-triazole (**2.57**) through a copper-catalyzed alkyne-azide cycloaddition by treatment with mesyl azide in the presence of copper(I) thiophene-2-carboxylate (CuTC). This was the first ever report of a 4-amino-substituted-1-sulfonyl triazole.

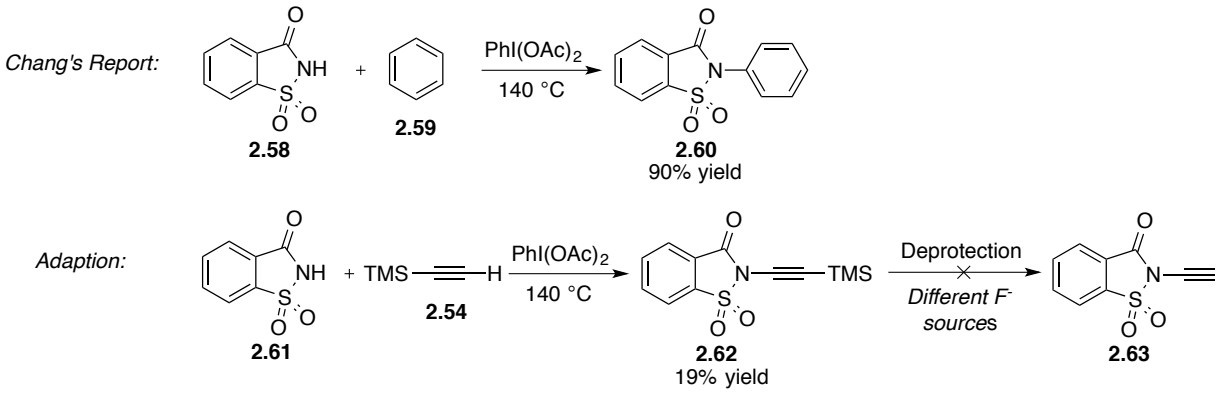


Scheme 2.5.4: Synthesis of 4-phthalimido-*N*-mesyl triazole.

It was envisaged that replacing one of the carbonyls in the phthalimide structure with a sulfonyl group would further de-activate the strong electron donating character of the nitrogen, which lead to the evaluation of saccharin (**2.58**). This idea proved to be very challenging to explore. The addition of the sulfonyl group did indeed de-activate the nitrogen more than the carbonyl based parent derivative, phthalimide. Because of this, the saccharin derivative did not undergo a copper-catalyzed coupling reaction with TMS-protected acetylene. Various nitrogen-alkyne coupling conditions were tried but the desired coupled product was not produced. Intrigued by a report from the Chang laboratory in which intermolecular oxidative C-H imidation of arenes (**2.59**) with sulfimides using $PhI(OAc)_2$ as an oxidant was accomplished.[97] An interesting example in the report involved the use saccharin (**2.58**) in which the desired coupled product (**2.60**) was isolated in good yield.

After analysis of the proposed mechanism which involves an electrophilic *N*-(phenylacetoxyiodo)imido species, a similar reaction may proceed with an alkyne under the forcing conditions. A quick screening of conditions (4 equiv of oxidant, 1 equiv. saccharin, neat, 2 hrs as the optimum) revealed the desired alkyne coupled product could

be formed, albeit in low yields. This was very promising initially, but upon deprotection of the TMS group with a source of either wet or anhydrous fluoride, the *N*-ethynyl saccharin (**2.63**) decomposed. This was mostly likely due to the incompatibly of the sulfonylimido group with the fluoride.

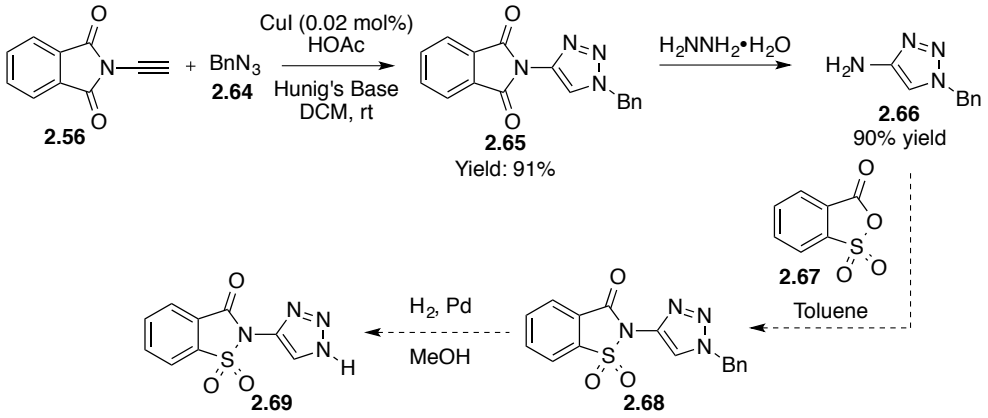


Scheme 2.5.5: Oxidative coupling of saccharin with $PhI(OAc)_2$.

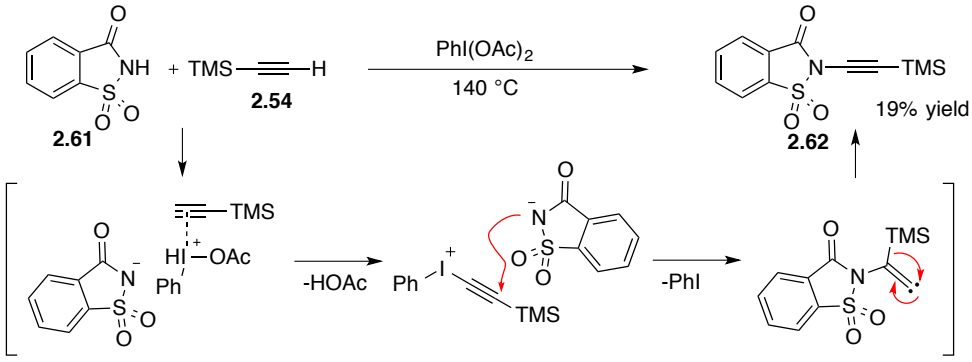
Another synthetic route was envisaged utilizing the previously developed *N*-ethynynl phthalimide (**2.56**) chemistry. The route involved the synthesis of 1-benzyl-1*H*-1,2,3-triazol-4-amine (**2.65**), which could act as a common intermediate to more complex 4-amino triazoles allowing for further derivation and *in situ* sulfonylation. The *N*-ethynyl phthalimide (**2.56**) was treated with benzyl azide (**2.64**) in the presence of a catalytic amount of CuI (0.02 mol%). This gave the desired triazole in excellent yield, which upon treatment with hydrazine hydrate gave the free *N*-H amine (**2.66**) in good yield.[94] This would be followed by a condensation reaction, and subsequent hydrogenation of the benzyl group to give the free *N*-H triazole. However, the condensation reaction proved to be quite difficult. Initial nucleophilic addition of the amine into the electrophilic anhydride was facile, but liberation of water to complete the reaction was never achieved.

The addition of peptide coupling reagents, i.e. DCC, did not provide the desired product. Only the mixed sulfonylimide and acid could be isolated.

With the non-success of the previous method, it was envisaged that using a very electrophilic source of the alkyne under basic conditions with saccharin might result in a coupled product. A re-examination of the earlier reaction result in the hypervalent iodine coupling with saccharin and TMS-acetylene revealed our initial conclusions may have been incorrect. Instead of the reaction progressing through an *N*-iodo(III)-amino complex, it might be an iodo(III)-alkyne complex that is attacked by the soft nucleophile saccharin which proceeds via a carbene intermediate that involves migration of the TMS group (Scheme 2.5.7). This mechanistic rationale was later published by Muñiz and co-workers as described in the previous section.

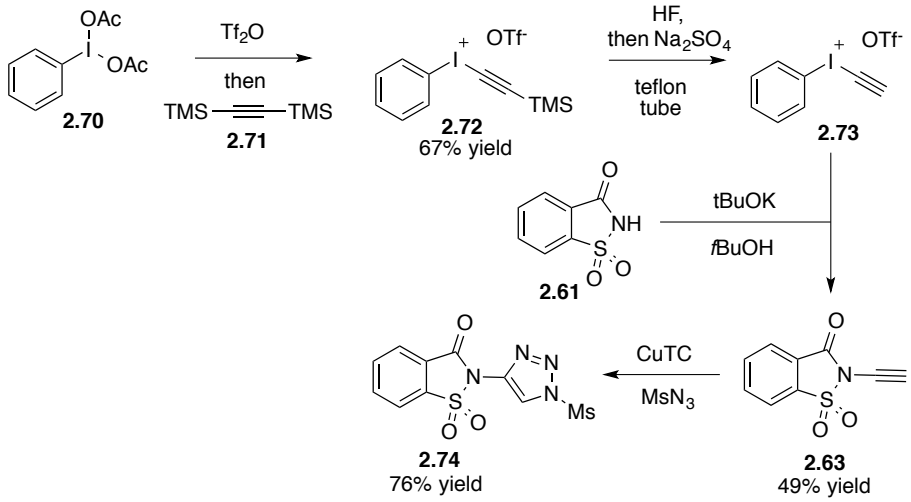


Scheme 2.5.6: Perceived universal route for amino triazoles.



Scheme 2.5.7: Re-examination of the earlier saccharin coupling reaction.

A synthetic plan was then developed to accessing a hypervalent iodo(III) ethynyl (**2.72**) species.[98] This route would allow for the direct access to a deprotected ethynyl moiety. To our delight, 1 equiv of each (iodo species and the potassium salt of saccharin) at RT after a few hours gave the desired product (not optimized). Although that may seem insignificant, it is significant in the realm of nitrogen-alkyne coupling (it proceeds under mild conditions). The ethynyl saccharin derivative was then converted to the *N*-sulfonyl triazole (**2.74**) in the presence of mesyl azide and CuTC.



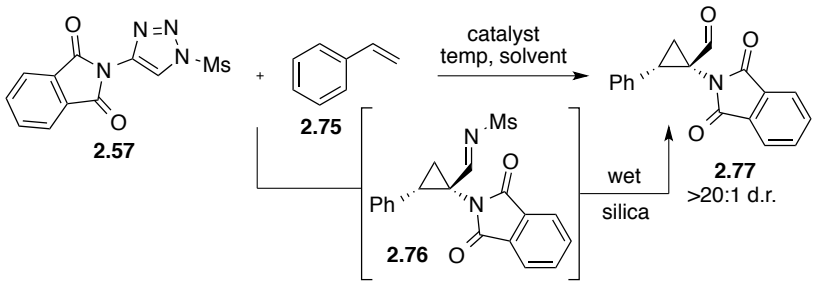
Scheme 2.5.8: Synthesis of *N*-ethynyl saccharin.

The necessary 4-substituted 1,2,3-triazoles were readily prepared by adaptation of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) previously developed. The use of copper(I) thiophene-2-carboxylate (CuTC), Liebeskind's catalyst, in toluene has proved to be an efficient method for the synthesis of 4-amino-*N*-sulfonyl triazoles from ethynylimido derivatives with sulfonyl azides. The procedure is experimentally simple and the 4-amino *N*-sulfonyl triazoles can be readily isolated in high yield.

2.6 Reactions of a 4-Amino-*N*-Sulfonyl Triazole

With the new α-phthalimido *N*-sulfonyl triazole in hand, the first reaction examined was a metal-catalyzed cyclopropanation of styrene. To our delight, the triazole (**2.57**) reacted smoothly at 55 °C in the presence of either rhodium catalyst, Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$, to provide cyclopropane imine (**2.76**) by crude ^{1}H-NMR. Hydrolysis of the sulfonyl imine (**2.76**) was achieved by simply adding wet silica to the reaction flask to furnish the aldehyde (**2.77**) in excellent yield (92-93%) and high diastereoselectivity (>20:1). Even though Rh_2(*S*-DOSP)$_4$ or Rh_2(*S*-PTAD)$_4$ are exceptional chiral catalysts for donor/acceptor carbenoids, the cyclopropanecarboxaldehyde (**2.77**) was formed as a racemate. Further screening of dirhodium(II) catalysts, reaction solvent, and temperature did not provide any enantioinduction. The relative stereochemistry of the major isomer (**2.77**) was determined by nOe experiments to be the *trans* isomer with respect to the aldehyde and phenyl group; further derivation confirmed this assignment.

Table 2.6.1: Initial reaction screening of the 4-phthalimido *N*-mesyltriazole.



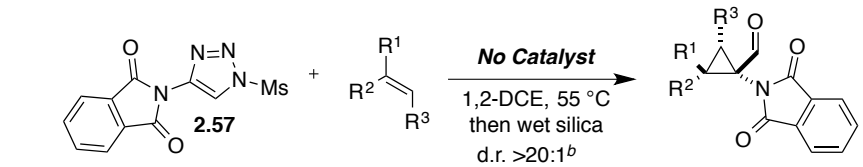
entry	catalyst	solvent	temp (°C)	time (h)	% yield	% ee
1	Rh_2(*S*-ptad)$_4$	1,2-DCE	55	12	93	<2
2	Rh_2(*S*-ptad)$_4$	1,2-DCE	rt	48	71	<2
3	Rh_2(*S*-dosp)$_4$	1,2-DCE	55	12	92	<2
4	Rh_2(*S*-btpcp)$_4$	1,2-DCE	55	12	92	<2
5	Rh_2(*R*-bnp)$_4$	1,2-DCE	55	12	88	<2
6	Rh_2(*S*-bitisp)$_4$	1,2-DCE	45	12	87	<2
7	Rh_2(*S*-ptad)$_4$	EtOAc	55	12	87	<2
8	Rh_2(*S*-ptad)$_4$	CH_3NO_2	55	12	93	<2
9	Rh_2(*S*-ptad)$_4$	Acetone	55	12	32	<2
10	n/a	1,2-DCE	55	12	89	n/a

Triazole (1.0 equiv) and olefin (5 equiv); Isolated yields.

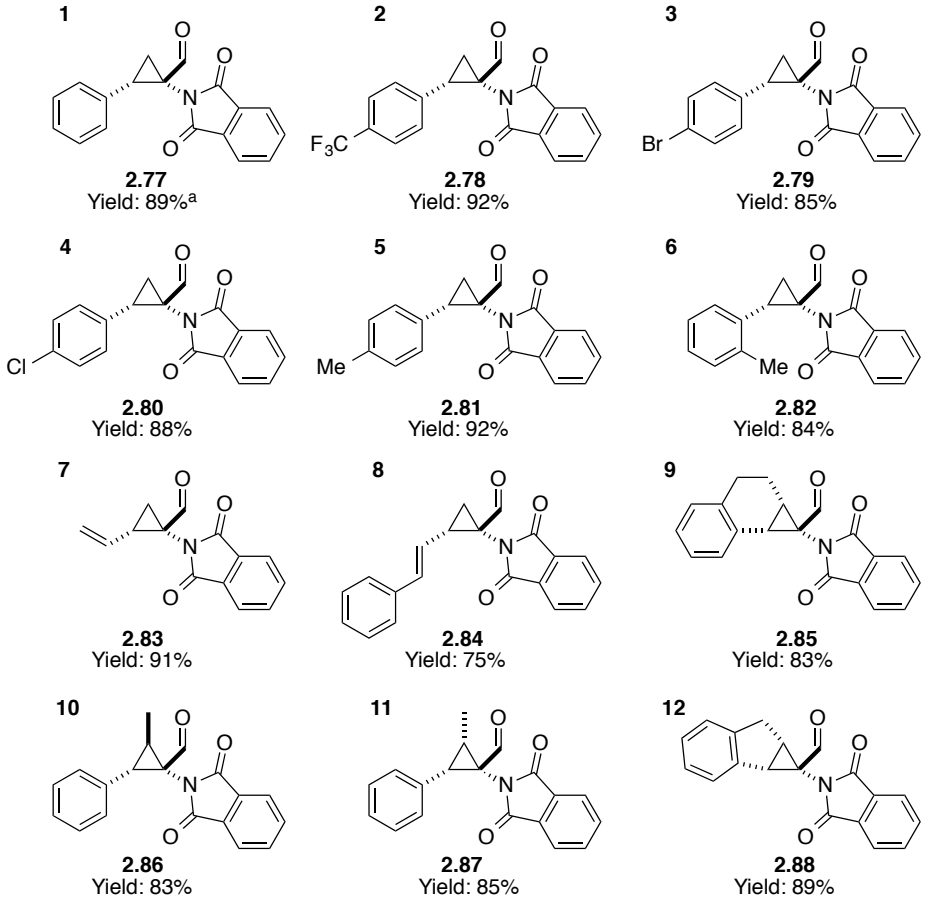
Therefore, the formation of cyclopropanecarboxaldehyde (**2.77**) is unlikely to be a rhodium-catalyzed process even though the reaction is highly diastereoselective. It appears that the 4-phthalimido *N*-sulfonyl triazole (**2.57**) is more labile than their 4-aryl and 4-alkyl triazole counterparts. Earlier studies have shown that the metal-free thermal cyclopropanation with aryldiazoacetates can also be highly diastereoselective.[99] Having discovered that the cyclopropanation was not metal catalyzed, the scope of the catalyst-free, thermal reaction was examined. A broad range of terminal alkenes were transformed into the corresponding cyclopropanecarboxaldehydes in good to excellent yields (**2.77-2.82**; 75-92%) with excellent diastereoselectivity (>20:1). Styrenes possessing either an electron-rich or an electron-deficient aryl group reacted smoothly to produce cyclopropanes. 1,3-Butadiene and 1-phenyl-1,3-butadiene readily gave mono-

cyclopropanecarboxaldehydes **2.83** and **2.84** respectively. The influence of the alkene geometry is not as profound in the thermal reactions as compared to a dirhodium-catalyzed reactions[100] as both *trans*-ß-methylstyrene and *cis*-ß-methylstyrene were readily transformed into the corresponding cyclopropanecarboxyaldehydes **2.86** and **2.87** respectively. Cyclic substrates also furnished cyclopropanes in excellent yield and diastereoselectivity. It is important to note that unlike typical metallocarbene chemistry derived from diazo compounds, there is no need to add the triazole slowly because there it is unlikely to have a build-up of diazo compounds as the ring opened product is of low concentration.

Table 2.6.2: Scope of the thermal reaction.



entries

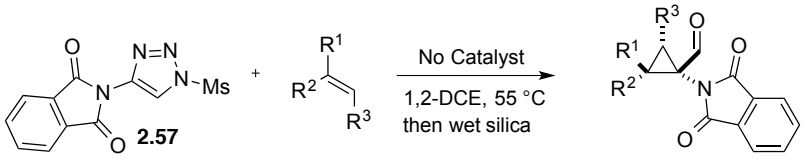


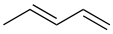
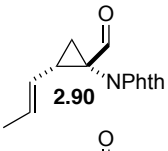
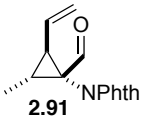
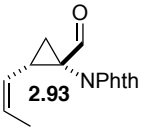
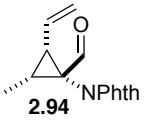
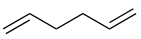
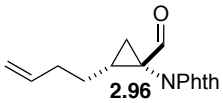
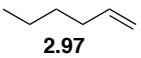
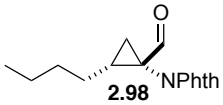
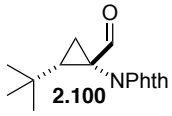
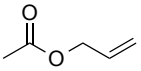
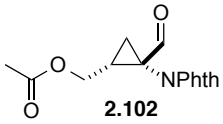
Triazole (1.0 equiv) and olefin (5 equiv); Isolated yields; [a]5.0 mmol scale

Expanding the scope of the cyclopropanation to less sterically demanding 1,3-dialkene olefins lead to small percentage of cyclopropanation of the internal alkene with the *trans* olefin as compared to a much larger percentage with a *cis* olefin; however, the diastereoselectivity still remained high. Moving the second unit of conjugation away from the terminal alkene resulted in an erosion of the diastereoselectivity, giving rise to a

reasonable explanation of the diastereoselectivity of the styrene derivatives involving a π-stacking interaction with the phthalimido group discussed later in this section.

Table 2.6.3: Expanding the scope of the cyclopropanation.



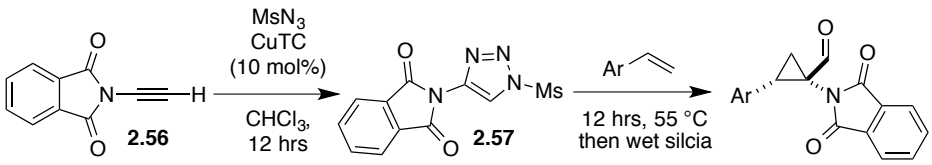
entry	olefin	product A	product B	A:B	% yield
1	 **2.89**	 **2.90**	 **2.91**	9:1	83%
2	 **2.92**	 **2.93**	 **2.94**	3:1	86%
3	 **2.95**	 **2.96**		7:3 d.r.	81%
4	 **2.97**	 **2.98**		7:3 d.r.	84%
5	 **2.99**	 **2.100**		7:3 d.r.	77%
6	 **2.101**	 **2.102**		9:1 d.r.	79%

[a]Triazole (1.0 equiv) and olefin (5 equiv); Isolated yields.

The synthesis of the α-amino cyclopropane-carboxaldehydes starting from the *N*-ethynylphthalimide can be conducted in a one-pot, two-step synthesis as illustrated in Table 3. *N*-Ethynylphthalimide (**2.56**) was treated with mesyl azide (1.1 equiv) in the presence of CuTC (10 mol%) in chloroform to generate the intermediate 4-phthalimido-

N-mesyl-1,2,3-triazole (**2.57**). After 12 h, the styrene derivative (**2.75**; 1.5 equiv) was added to the reaction mixture and the reaction media was warmed to 55 °C for 12 h. Once the allotted time had passed, wet silica gel was added to the reaction to furnish the cyclopropanecarboxaldehydes in good yields (**2.77**-**2.82**; 74-85%) with excellent diastereoselectivity (>20:1). The yields of the one-pot, two-step reaction (Table 2.6.4) are comparable to the yields presented in Table 2.6.2. Key features to this one-pot reaction are the requirement of only a slight excess of the olefin and the formation of only dinitrogen and methanesulfonamide as byproducts. Many other researchers in the field later adopted this strategy.[82,101,111]

Table 2.6.4: Two step, one-pot reaction.



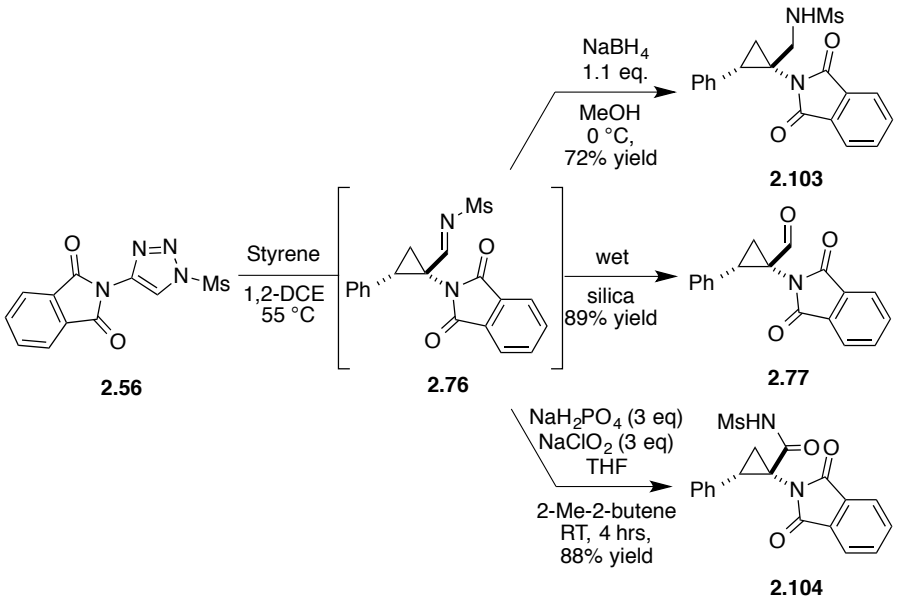
entry	Ar	product	% yield	d.r.
1	Ph	**2.77**	85	>20:1
2	4-CF_3Ph	**2.78**	77	>20:1
3	4-BrPh	**2.79**	74	>20:1
4	4-ClPh	**2.80**	80	>20:1
5	4-MePh	**2.81**	79	>20:1
6	2-MePh	**2.82**	82	>20:1

Ynimide (1.0 equiv), MsN_3 (1.1 equiv) and olefin (5 equiv); Isolated yields.

The initial product of the thermal cyclopropanation, the sulfonyl imine, is a synthetically versatile intermediate. This has been illustrated in Scheme 2.6.1 with examples of *in situ* manipulations of the sulfonyl imine (**2.76**). As already stated, hydrolysis of sulfonyl imine readily forms the aldehyde (**2.77**). Reduction of the sulfonyl imine with sodium borohydride provided easy access to the sulfonated monoamine

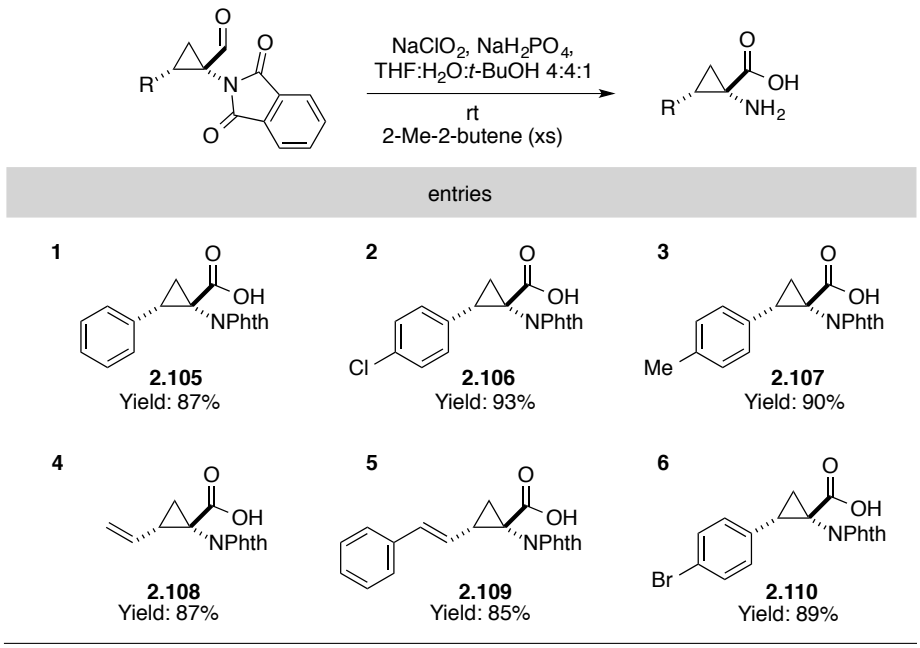
(**2.103**) in good yield.[102] The addition of sodium chlorite under Pinnick oxidation conditions gave the corresponding sulfonyl amide (**2.104**) in high yield.[103] A double reduction of both the phthalimide and sulfonyl imine was attempted but failed to give the desired product.

One of the most attractive features of this thermal cyclopropanation is the opportunity for ready access of cyclopropane α-amino acids. The *N*-cyclopropanecarbaldehyde phthalimide derivatives were converted to the free α-amino acid by first conducting a Pinnick oxidation of the aldehyde to the corresponding acid. The reaction conditions were very mild resulting in a high yield of the desired product.



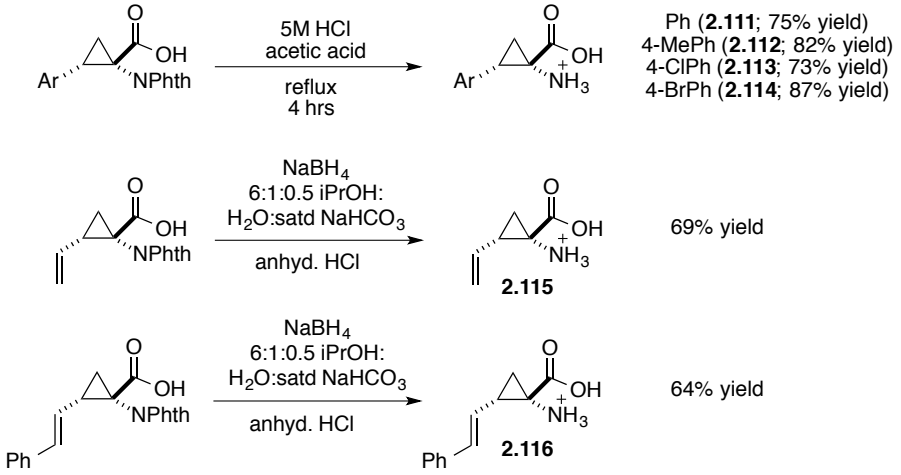
Scheme 2.6.1: Synthetic utility of the sulfonyl imine.

Table 2.6.5: Oxidation of the aldehyde to the carboxylic acid.



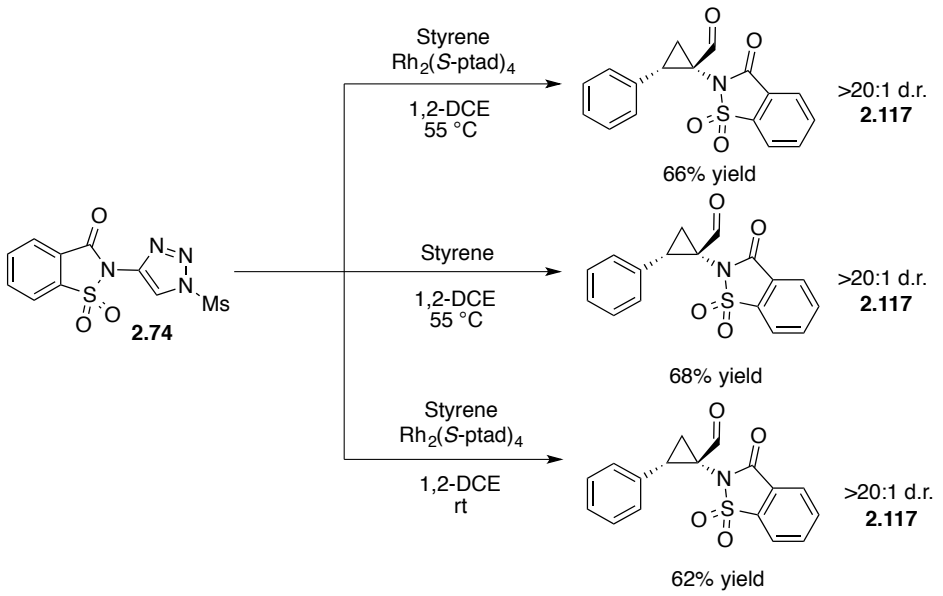
The *N*-phthaloyl acid was then deprotected by either direct acid hydrolysis or a modified sodium borohydride reduction[16] to give the α-amino acid derivatives (**2.111**-**2.114**) 73-87% yields (Scheme 2.6.2). Treatment of the phenyl derivatives with HCl in acetic acid resulted in a clean hydrolysis of the phthalimide to the amine. This proved to be the easiest method for deprotection for this set of *N*-phthaloyl acids. The diene derivatives (**2.108** and **2.109**) proved to be a little more challenging to cleanly deprotect. After screening many methods including: $MeNH_2$ both aqueous and ethanolic, RT and elevated temperatures; H_2NNH_2 in ethanol at RT, reflux, and with scavenger; aqueous NaOH and KOH at RT and elevated temperatures; it was found that the addition of satd $NaHCO_3$ to a modified $NaBH_4$ procedure proved efficient.[104] It is believed that by preventing the coordination of the amide group to the acid will assist the reaction. The

addition of weak base mostly likely plays two roles, the first as indicated and second it may give more hydride character to the $NaBH_4$.



Scheme 2.6.2: Deprotection of the phthalimide.

It was thought by using an even more electron deficient nitrogen source, saccharin, the thermal reaction might not be possible leading to a chance for enantioinduction. Proceeding with the saccharin derived triazole (**2.74**), test reactions were conducted with styrene in the presence of Rh_2(S-PTAD)$_4$ at 55 °C . The reaction worked well and ^{1}H-NMR should a dr >20:1. However, the control reaction with no catalyst also worked. Running the reaction at room temperature also gave the desire cyclopropane product (**2.117**). To our disappointment, though, the products with the rhodium reactions were racemic. Since the control reaction also gave the same cyclopropane product, it is reasonable to conclude that this is still a thermal transformation.



Scheme 2.6.3: Cyclopropanation of the saccharin triazole with styrene.

A plausible mechanism for the thermally-induced cyclopropanation is depicted in Figure 2.6.1 using the phthalimido-based triazole (**2.56**) as an example. Initially, a ring-chain isomerization of the *N*-sulfonyl-1,2,3-triazole generates the α-diazo imine **A** which can then expel dinitrogen to form the free carbene **B**. As the *trans*-cyclopropane is formed predominantly, the alkene must approach the "carbene" with the phenyl *cis* to the phthalimido group. The phenyl group donates electron density into the alkene and the developing positive charge may be stabilized by the polarizable π system of the aromatic ring. There may be some steric interference by the sulfonyl imine group. The evidence of a π-stacking interaction can be seen by the erosion of the d.r. (7:3) in reactions with 3,3-dimethyl-1-butene and 1-hexene (Table 2.6.3).

Alternatively, an inverse demand 1,3-dipolar cycloaddition mechanism for the thermally-induced cyclopropanation reaction as depicted in Figure 2.6.2 using the phthalimido-based triazole (**2.56**) is also plausible. Initially, a ring-chain isomerization of

the *N*-sulfonyl-1,2,3-triazole generates the α-diazo imine which then participates in an inverse 1,3-dipolar cycloaddition with the HOMO of the alkene to give a 1-pyrazole.[105] The favored parallel approach of triazole to the alkene, in which the biggest substituents of both molecules are *anti* to one another, determines the *Z* selectivity of cyclopropane formation. The regioselectivity of this inverse demand 1,3-dipolar cycloaddition reaction is likely to be determined by the interaction of the HOMO of the dipolarphile (styrene) and the LUMO of the 1,3-dipole (phthalimido triazole (**2.56**)), which favors the combination of the large atomic orbital lobes.[106] The 1-pyrazole then undergoes a denitrogenation event leading to the desired cyclopropane. Evidence for this mechanism would be that the cyclopropanation works well with electron-rich dipolarphiles, but when electron-poor dipolarphiles are employed (methyl acrylate), the desired cyclopropane product is not formed. However, attempts to observe the 1-pyrazole product were not successful and this mechanism assumes that intermediate **A** in Figure 2.6.1 is the dominant resonance structure.

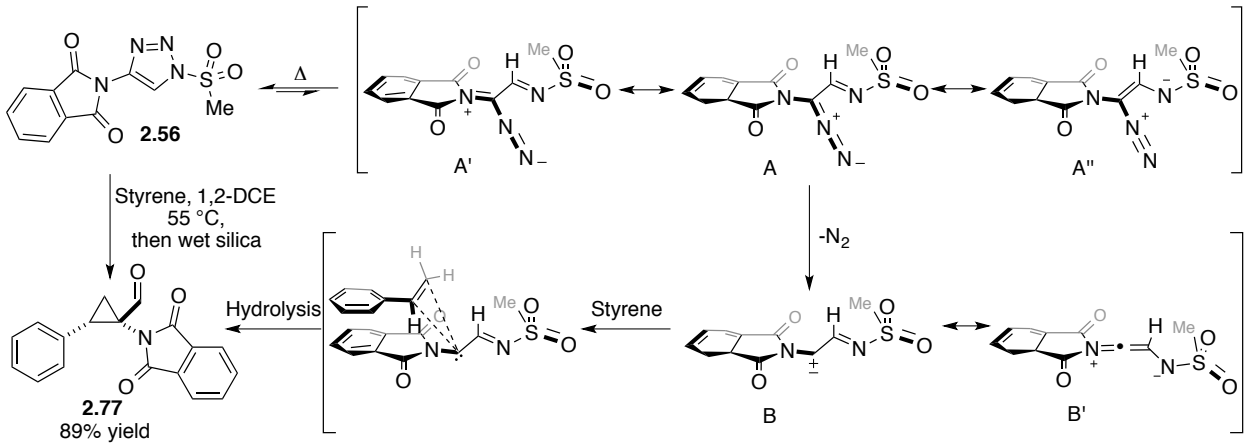


Figure 2.6.1: Proposed mechanism for the thermally-induced cyclopropanation.

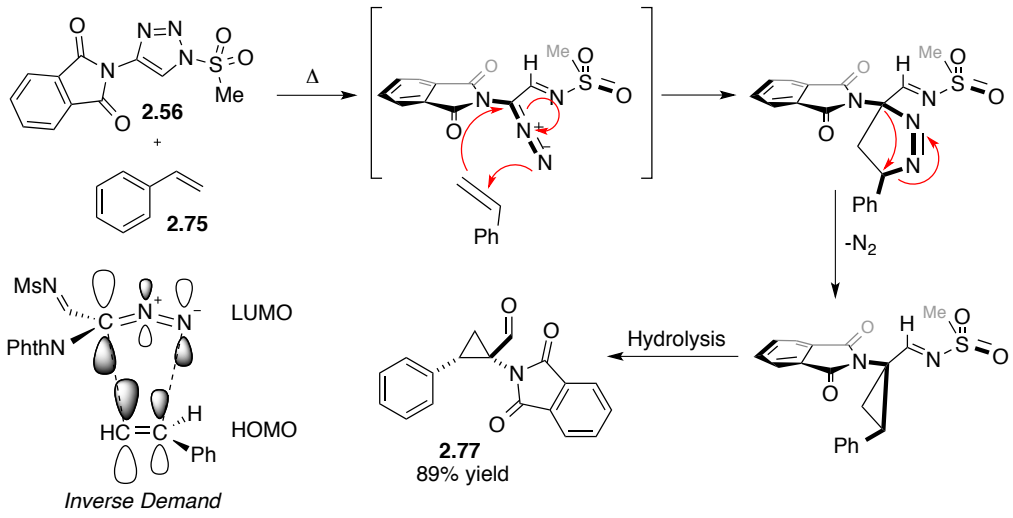
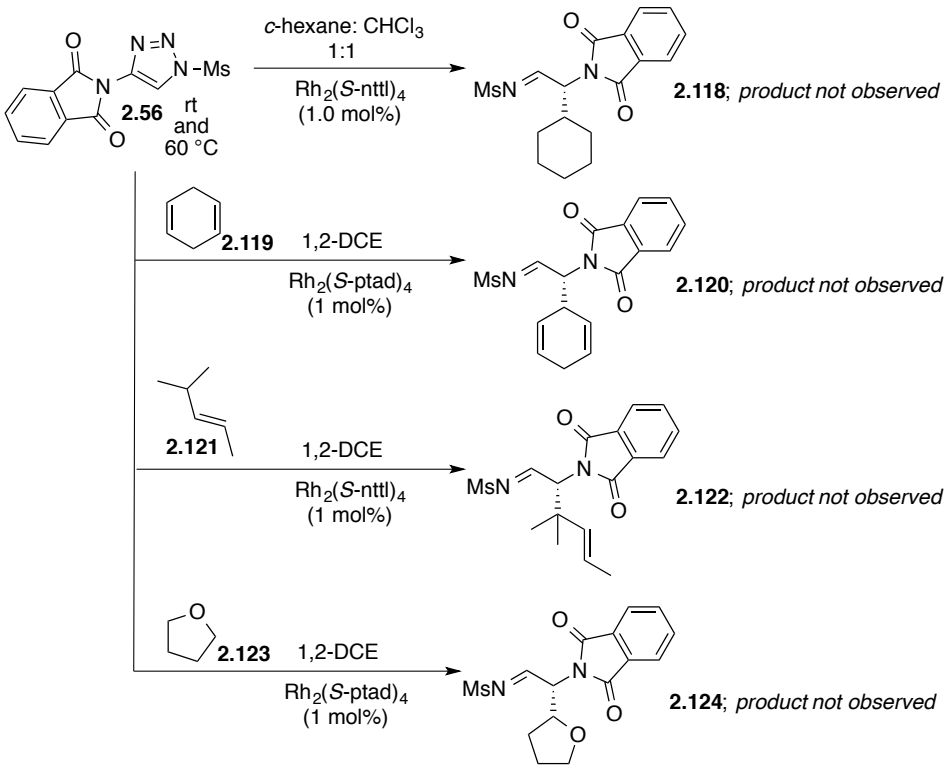


Figure 2.6.2: Proposed alternative mechanism for the thermally-induced cyclopropanation.

We hypothesized the use of the 4-amino-*N*-sulfonyltriazole may allow for C–H functionalization of C–H bonds leading to functionalized α-amino acid derivatives due to success of the cyclopropanation reaction. Initial efforts began with derivatives that are known to perform well in C–H functionalization chemistries with diazo acetates.[163] However, examination of cyclohexane, 1,4-cyclohexadiene (**2.119**), 4-methyl-2-*trans*-pentene (**2.121**), and tetrahydrofuran (**2.123**) did not result in the desired C–H functionalized products both at room temperature and elevated temperatures in the presence of a rhodium catalyst.

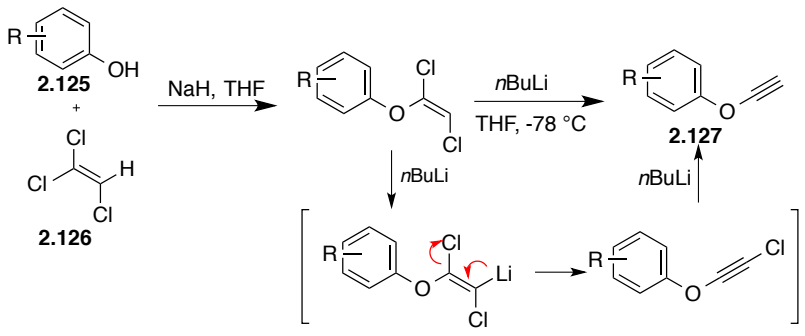


Scheme 2.6.4: Attempted C–H functionalization with 4-phthalimido-*N*-mesyltriazole.

In conclusion, the 4-phthalimido and saccharin-*N*-mesyl-1,2,3-triazoles undergo a facile thermal reaction to generate a donor/acceptor carbene, in which the donor group is the imido group. This carbene undergoes highly diastereoselective cyclopropanation with a range of alkenes and dienes, leading to a ready access to cyclopropane α-amino acids in an experimentally simple way. Future studies are directed towards a better understanding of the thermal dinitrogenation mechanism, developing an enantioselective metal-catalyzed reaction of aminotriazoles and expanding the scope of the chemistry to other classes of substituted triazoles.

2.7 Development of 4-Oxy-*N*-Sulfonyl Triazoles

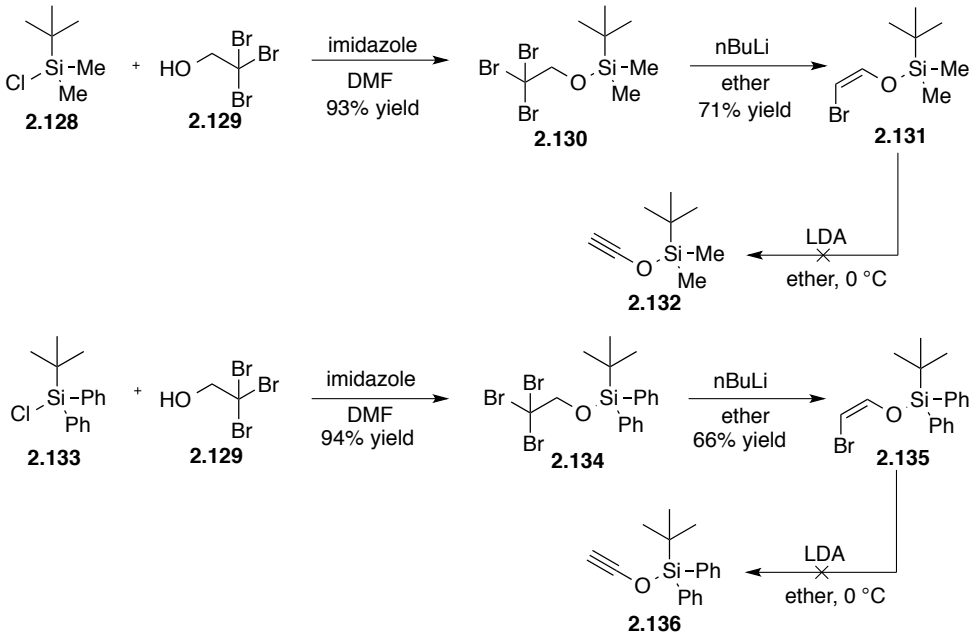
The initial studies of the 4-amino *N*-sulfonyl triazole prompted us to explore the chemistry of 4-oxy *N*-sulfonyltriazoles.[74] We started our study with the synthesis of different ynol ethers. The aryl ynol ethers (**2.127**) were conveniently formed by treatment of the corresponding dichloroenol ether, obtained by treatment of trichloroethylene (**2.126**) with the sodium alkoxides, with three equivalents of *n*-butyllithium.[107] The reaction proceeds via an initial deprotonation forming an intermediate lithiated species, which undergoes a *β*-elimination upon warming.[107] The resulting chloroynol ether participates in a subsequent chlorine-lithium exchange with the excess *n*-butyllithium furnishing the lithiated ethynyl ether, which is protonated upon workup (Scheme 2.7.1). The obtained ynol ethers proved to have some stability issues when neat and could only be stored for a few months in hexanes at -20 °C.



Scheme 2.7.1: Aryl ynol ether synthesis.

We also envisioned the use of a more labile silyloxyalkyne that could be easily deprotected under mild conditions. Danheiser and coworkers reported a three-step synthesis for accessing trialkylsilyloxyalkynes from (*Z*)-2-bromovinyl silyl ethers.[108] The vinyl silyl ethers were prepared from tribromoethanol (**2.129**) in high yield by treatment

with imidazole in DMF. The tribromo analogs (**2.130** and **2.134**) were then exposed to *n*BuLi (1.2 equiv), losing LiBr upon warming, and stereoselectively rearranging through a carbene intermediate to the (*Z*)-2-bromovinyl silyl ethers (**2.131** and **2.135**).[109] However, the treat of the (*Z*)-2-bromovinyl silyl ethers with 2 equivalents of LDA failed to generate the reported lithium trialkylsiloxyacetylides, which would give the parent siloxyethyne derivatives upon quenching with ethanol. It was later reported in a subsequent report the OTBS derivative was unstable under these conditions (Scheme 2.7.2).[108]

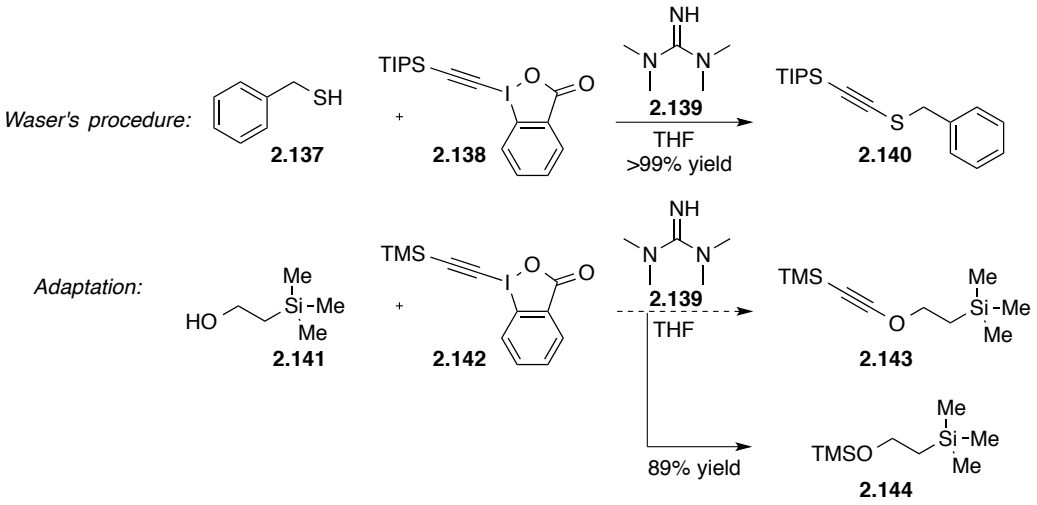


Scheme 2.7.2: Attempted silyloxyalkyne synthesis.

With the previous failed attempt, an alternative strategy was employed using hypervalent iodine alkyne transfer reagents. In this strategy, the reagent is an electrophilic acetylide equivalent that does not require prefunctionalization of the nucleophile and proceeds under mild conditions (Scheme 2.7.3). Waser and co-workers very recent reported a similar thiol-alkynylation procedure utilizing the hypervalent iodine alkyne

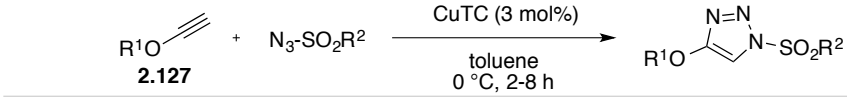
transfer reagent TIPS-ethynyl-benziodoxolone (**2.138**).[110] The reaction proceeds in five minutes at room temperature in an open flask with a broad substrate scope; adopting their procedure seemed very appealing. Initially, the result with trimethylsilylethanol (**2.141**) seemed very promising, but further characterization revealed the actual reaction that took place was a deprotection of the TMS-ethynyl-benziodoxolone (**2.142**) *in situ* by the trimethylsilylethanol (**2.141**). This was further confirmed by the deprotection of the TMS-protected trimethylsilylethanol product (**2.144**) to reveal the parent starting material.

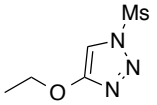
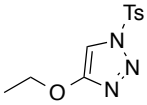
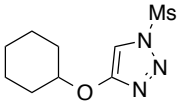
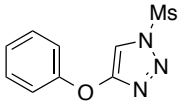
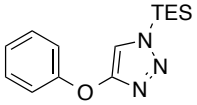
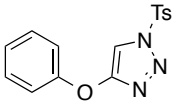
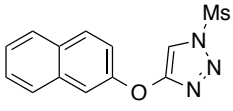
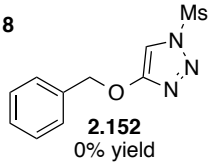
With the unsuccessful attempts at accessing a silyloxyalkyne, attention was redirected back to aryl- and alkyl-substituted ynol ethers. The ynol ethers were then transformed into the benchtop stable 4-alkoxy and 4-aryloxy *N*-sulfonyl-1,2,3-triazoles through a regioselective copper-catalyzed alkyne-azide cycloaddition by treatment with both aryl and aliphatic sulfonyl azides in the presence of copper(I) thiophene-2-carboxylate (CuTC) as seen in Table 2.7.1. Both aliphatic ynol ethers (**2.145**-**2.147**; entries 1-3) afforded the desired 4-alkoxy *N*-sulfonyl triazoles in good yields. The aryl ynol ethers (**2.148**-**2.151**; entries 4-7) were also tolerated, furnishing the desired 4-aryloxy *N*-sulfonyl triazoles in good yields. It is worth noting that entry 5 contains the easily removable SES group. However, benzyl ynol ether (**2.152**; entry 8) was not tolerated, decomposing *in situ* presumably due to the strong electron donating potential of the benzyl group under the copper(I) catalyzed conditions.



Scheme 2.7.3: Another attempted silyloxyalkyne synthesis.

Table 2.7.1: Synthesis of 4-alkoxy and 4-aryloxy *N*-sulfonyl triazoles.



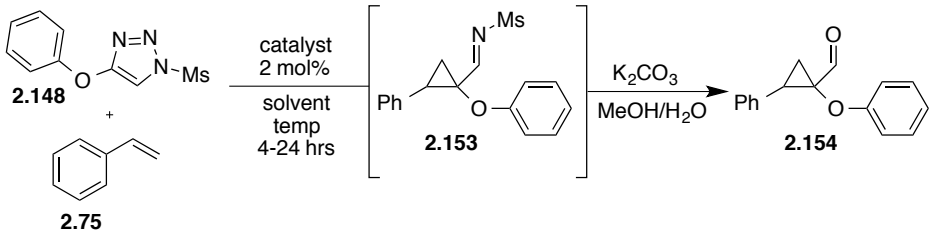
entries		
1  **2.145** 68% yield	2  **2.146** 75% yield	3  **2.147** 76% yield
4  **2.148** 81% yield	5  **2.149** 82% yield	6  **2.150** 84% yield
7  **2.151** 76% yield	8  **2.152** 0% yield	

Sulfonyl azide (1.0 equiv), ynol ether (1.1 equiv), CuTC (3 mol%); [b]Isolated yields after trituration.

With the new 4-aryl and 4-alkoxy *N*-sulfonyl triazoles in hand, the first reaction examined was a metal-catalyzed cyclopropanation of styrene. To our delight, the triazole (**2.148**) reacted smoothly at 80 °C in the presence of either rhodium catalyst, Rh_2(*S*-

DOSP)$_4$ and Rh$_2$(*S*-PTAD)$_4$, to provide cyclopropane imine (**2.153**) by crude ^{1}H-NMR. Hydrolysis of the sulfonyl imine (**2.153**) was achieved by simply adding potassium carbonate with wet methanol to the reaction flask to furnish the aldehyde (**2.154**) in moderate yield (59-62%) with moderate diastereoselectivity (7:3). Even though Rh$_2$(*S*-DOSP)$_4$ or Rh$_2$(*S*-PTAD)$_4$ are exceptional chiral catalysts for donor/acceptor carbenoids, the cyclopropanecarboxaldehyde (**2.154**) was formed as a racemate. Further screening of rhodium(II) catalysts, reaction solvent, and temperature revealed that by lowering the temperature to 45 °C and the use of Rh$_2$(*S*-nttl)$_4$ provided slightly improved diastereoselectivity and some enantioinduction with the major diastereomer in 37% ee (Table 2.7.2). Interestingly, lowering the temperature had a detrimental effect on the Rh$_2$(*S*-dosp)$_4$-catalyzed reaction. Further lowering of the temperature resulted in no reaction. The overall reaction is likely a combination of the free carbene generated thermally with the rhodium-bound carbene; however, the catalyst does not dictate diastereoselectivity. The relative stereochemistry of the major isomer (**2.154**) was determined by nOe experiments to be the *trans* isomer with respect to the aldehyde and phenyl group.

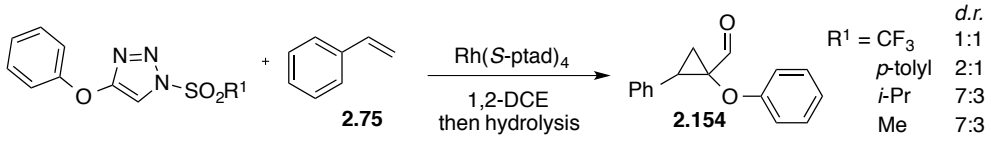
Table 2.7.2: Reaction screen for 4-phenoxy *N*-mesyltriazole with styrene.



entry	temp °C	solvent	catalyst	d.r.	% ee of major	% yield
1	80	1,2-DCE	Rh_2(*S*-dosp)$_4$	7:3	0	59
2	80	1,2-DCE	Rh_2(*S*-ptad)$_4$	7:3	0	62
3	65	toluene	Rh_2(*S*-dosp)$_4$	7:3	26	63
4	65	1,2-DCE	Rh_2(*S*-ptad)$_4$	7:3	17	66
5	45	toluene	Rh_2(*S*-dosp)$_4$	7:3	17	61
6	45	1,2-DCE	Rh_2(*S*-ptad)$_4$	7:3	18	56
7	45	1,2-DCE	Rh_2(*S*-nttl)$_4$	3:1	37	51
8	rt	1,2-DCE	Rh_2(*S*-ptad)$_4$	--	--	no rxn

Triazole (1.0 equiv) and olefin (5 equiv); Isolated yields.

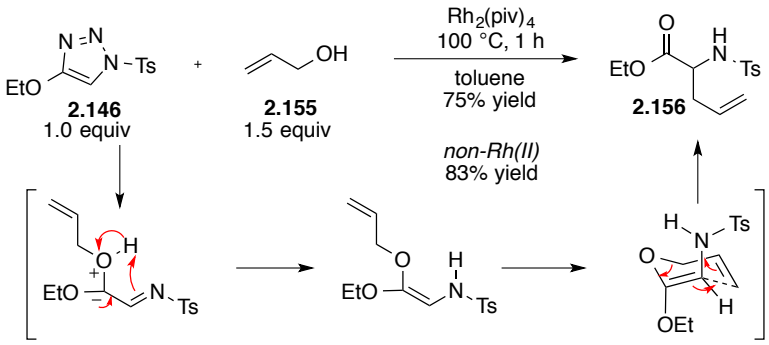
The diastereoselectivity of the reaction could potentially be influenced by the electronic and steric requirements of the sulfonyl group. A brief examination of different sulfonyl groups with varying inductive effects revealed that this is indeed possible. The overall inductive withdrawing-effect of the groups should be: $-SO_2CF_3$ >> $-SO_2$-Tol > $-SO_2i$Pr = $-SO_2$Me. The diastereoselectivity of the reaction is in line with this trend. The use of a sulfonamide group will most likely provide high diastereoselectivity.



Scheme 2.7.4: Examination of the overall inductive effect of the sulfonyl group.

While this work was underway, Murakami and co-workers reported the reaction of 4-ethoxy-1-tosyltriazole with an allylic alcohol under rhodium-catalyzed conditions resulting in a [3,3] sigmatropic rearrangement of the intermediate product.[111] The

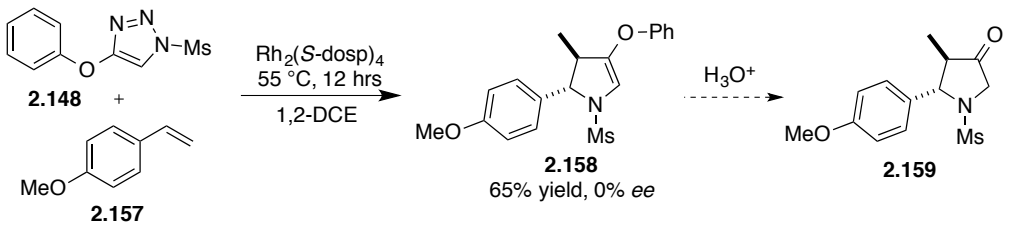
reaction proceeded in moderate yield under a lower catalyst loading (0.5 mol%) compared to the parent reaction. With the previous knowledge and the high temperature of the reaction, it was postulated that the reaction may be proceeding *via* a thermal mechanism. A verification of this reaction was performed and it was found that the reaction actually proceeds in comparable yield under non-rhodium conditions (Scheme 2.7.5). This report helps to validate a potential carbene intermediate.



Scheme 2.7.5: Reaction of 4-ethoxy-1-tosyltriazole with an allylic alcohol.

During our preliminary reaction investigations with the 4-oxy *N*-sulfonyl triazoles, *trans*-anethole (**2.157**) was screened as it is a classic system in aryldiazoacetate chemistry to study competition between cyclopropanation and C–H insertion (Scheme 2.7.6). When the reaction conducted with the 4-phenoxy *N*-mesyltriazole (**2.148**), neither of these types of products was isolated. Instead, the formal [3 + 2] cycloadduct, trans-dihydropyrrole (**2.158**), was produced in 62% yield under the reaction conditions. The reaction presumably proceeds through an initial cyclopropane intermediate that is subsequently ring-expanded due to the electron richness of the methoxy group. The formal [3+2] cycloadduct contains an enol ether functionality that could be readily hydrolyzed in the presence of aqueous acid to an α-amino ketone (**2.159**). This

approached could be applied to the synthesis of 2- or 2,3-disubstituted dihydropyrrolidin-3-ones.

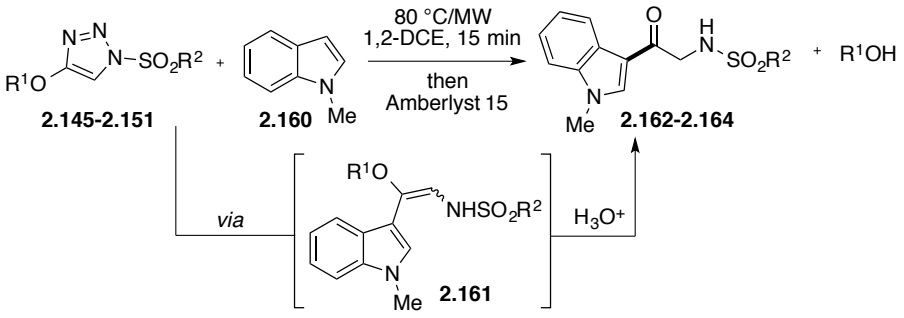


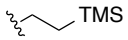
Scheme 2.7.6: Reaction of 4-phenoxy-1-mesyltriazole with *trans*-anethole.

This discovery prompted us to investigate what other electron-rich olefins participate in this reaction. To our delight, electron-rich heterocycles such as indoles and pyrroles result in a similar enol ether that can be readily hydrolyzed to the corresponding α-amino ketones providing a facile method for α-aminoacylation of electron rich heterocycles.[112,113,114,115] We began our investigations with the synthesis of various 4-oxy-1-sulfonyl triazoles from the corresponding sulfonyl azides and commercially available or easily prepared ynol ethers as previously described (**2.145**-**2.151**). These electron rich triazoles were submitted to a metal-free thermal denitrogenative reaction with *N*-methylindole (**2.160**) at 0.2 mmol scale under microwave irradiation in which rapid evolution of gas occurred and the reaction proceeded to completion within 15 min. The intermediate enol ether product (**2.161**) was subsequently hydrolyzed *in situ* to provide the α-amino ketone product (**2.162**-**2.164**; see Table 2.7.3). A range of alkoxy and phenolic substituents were compatible with the reaction as well as many different sulfonyl groups including the easily deprotected SES group (**2.164**; entry 5). The reaction

can also be conducted at larger scale (5.0 mmol) using conventional heating conditions at 70 °C with similar performance (entry 4).

Table 2.7.3: Reaction of 4-oxy *N*-sulfonyl triazoles with *N*-methylindole.

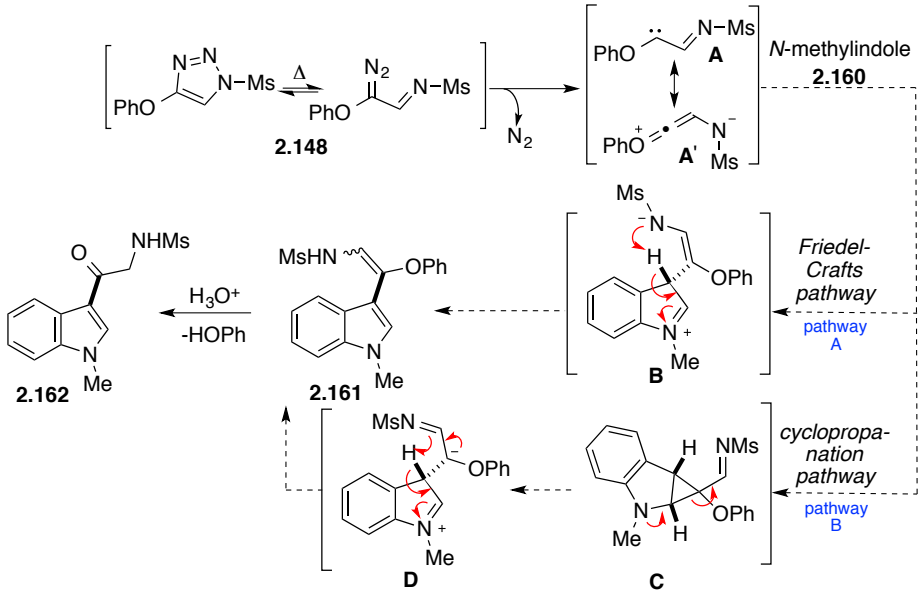


entry	triazole	R^1	$-SO_2R^2$	product	% yield
1	**2.145**	Et	Ms	**2.162**	53
2	**2.146**	Et	Ts	**2.163**	83
3	**2.147**	Cy	Ms	**2.162**	81
4	**2.148**	Ph	Ms	**2.162**	91(87)
5	**2.149**	Ph		**2.164**	84
6	**2.150**	Ph	Ts	**2.163**	90
7	**2.151**	2-Naph	Ms	**2.162**	87

Triazole (1.0 equiv) and indole (1.5 equiv); Isolated yields. (x)Conventional heating on a 5.0 mmol scale.

A proposed mechanism for the formation of the amino acylated product from 4-phenoxy-*N*-mesyltriazole and *N*-methylindole is depicted in Scheme 2.7.7. Microwave irradiation causes the triazole to isomerize to the α-diazo imine which then undergoes a thermal nitrogen extrusion furnishing the resonance-stabilized carbene intermediate **A**.[4,9,15] At this point, there are two possible reaction pathways. In pathway A, the intermediate **A** is engaged by the electron-rich indole derivative at C(3) in a Friedel-Crafts-type substitution to furnish the zwitterionic intermediate **B**, followed by a subsequent re-aromatization of the indole moiety to form enol ether. However, with the

observation of the formal [3+2] product, we propose that intermediate **A** undergoes a thermal cyclopropanation reaction with the electron-rich indole (intermediate **C**, pathway B). An immediate ring opening of the strained cyclopropylindoline intermediate leads to intermediate **D**, which tautomerizes to the enol ether with subsequent re-aromatization of the indole moiety. Hydrolysis of the enol ether leads to the amino acylated product. We have proposed a similar initial cyclopropanation step with C(3)-substituted indoles in our previous studies on [3+2] annulation with 4-aryl *N*-sulfonyltriazoles.[116]

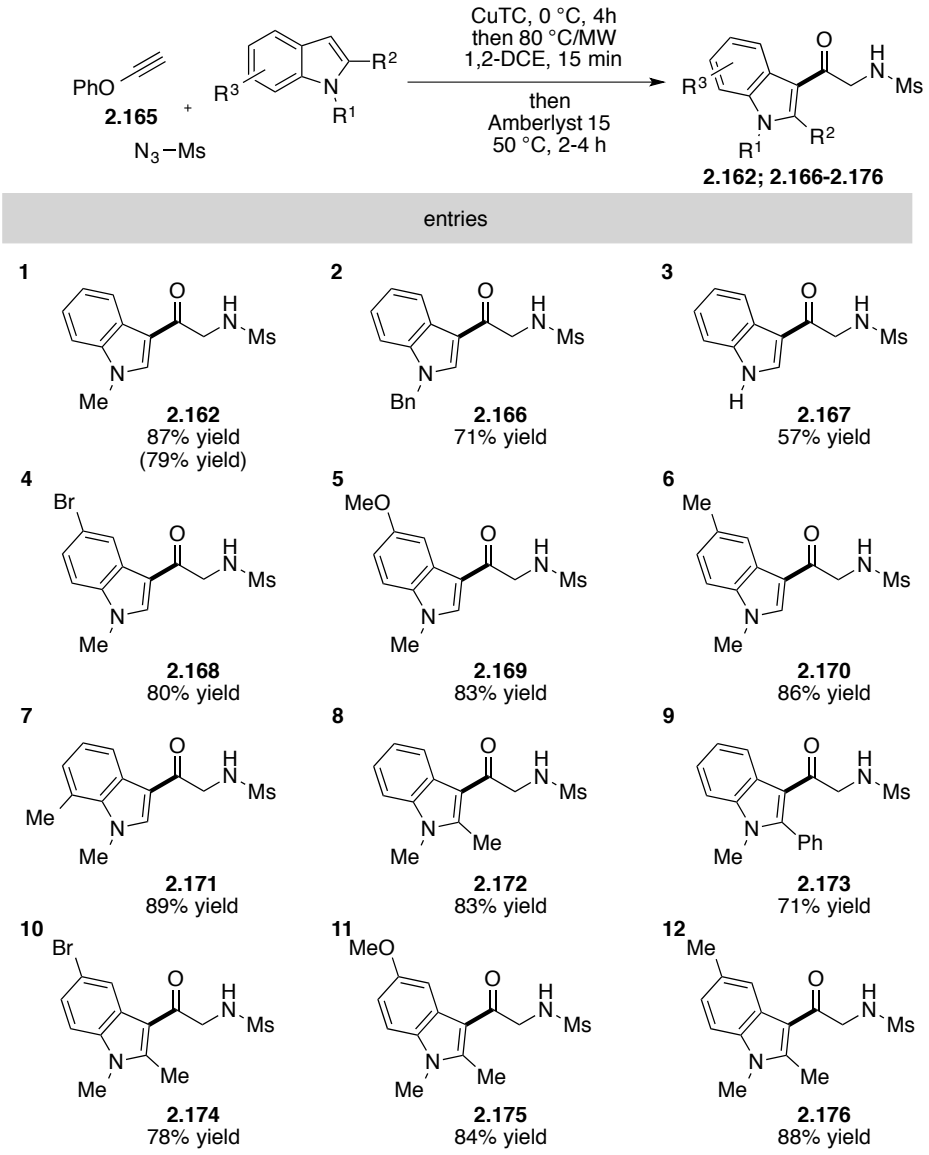


Scheme 2.7.7: Proposed mechanism for reaction with *N*-methylindole.

The next series of experiments were directed towards determining whether a one-pot, three-step procedure was feasible starting with the ynol ether, indole, and sulfonyl azide. A mixture of ynol ether (**2.165**) , indole and mesyl azide was stirred at 0 °C for 4 h in the presence of CuTC (copper(I) thiophene-2-carboxylate; 3 mol%), then warmed to 80 °C for 15 min under microwave irradiation, which was followed by the addition of

Amberlyst 15 to provide the hydrolyzed product. As shown in Table 2.7.3, a broad range of indole derivatives reacted to provide the corresponding aminoacylated products in good to excellent yields (**2.162**; **2.166-2.176**). An evaluation of the substituents on the indolic nitrogen revealed that *N*-H, *N*-alkyl, and *N*-benzyl are compatible with this transformation (entries 1-3); however, electron-withdrawing groups on the indolic nitrogen are not tolerated (e.g. 1-Ts, 1-Boc). An array of electron-rich and electron-deficient indoles substituted at C(5) or C(7) of the indolic core also provided the corresponding aminoacylated products in excellent yields (entries 4-7). The reaction was found to be applicable to a range of C(2)-alkyl and aryl indoles as well (entries 8-12).

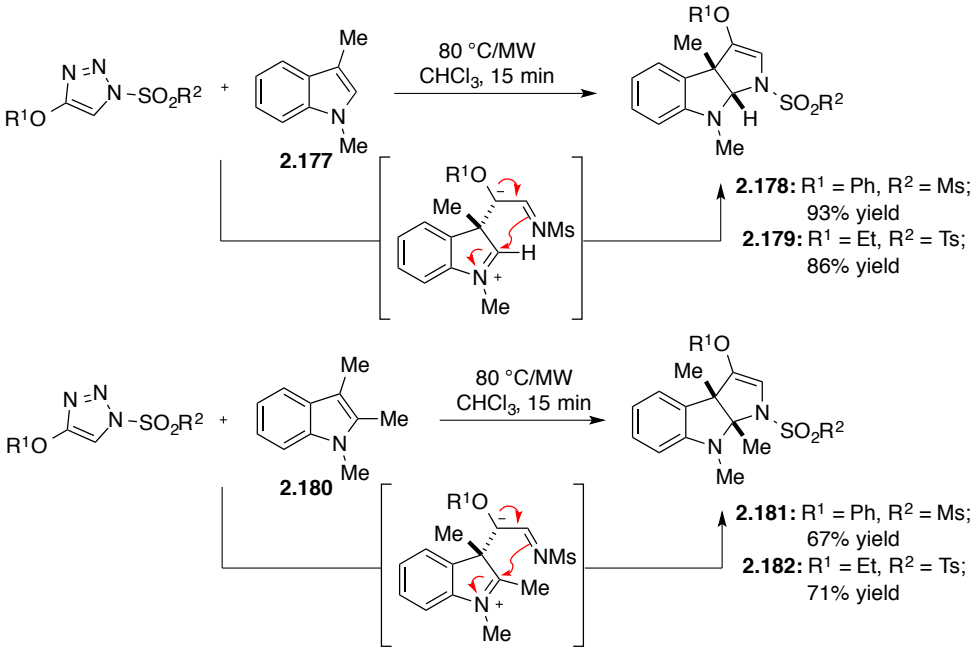
Table 2.7.4: One-pot, three-step procedure with varying indole component.



[a]Ynol ether (1.2 equiv), MsN_3 (1.0 equiv), CuTC (0.03 equiv) and indole (2.0 equiv); Isolated yields. () Conventional heating on a 12.0 mmol scale; TsOH hyrate used for hydrolysis.

Further investigation into substituted indoles with C(3)-substituents revealed that these were also reactive substrates; however, instead of the expected C(2)-acylated product, the dearomatized [3+2] annulation product was observed. This reaction was found to be less sensitive to steric effects as both bulkier sulfonyl groups (e.g. 1-Ts) and

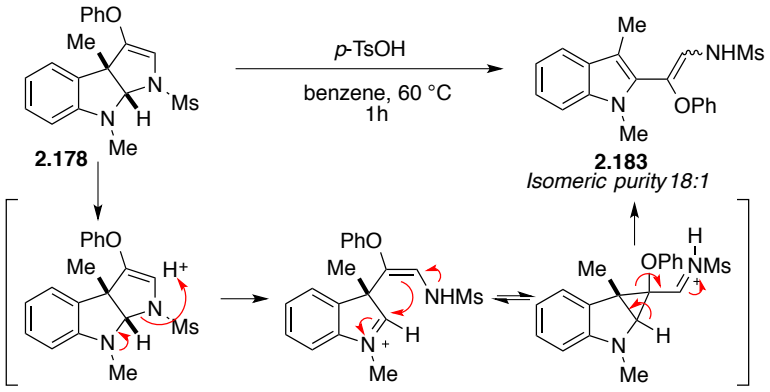
substituents at C(2) were tolerated (Scheme 2.7.8). The relative configuration of the product was confirmed by x-ray analysis.



Scheme 2.7.8: Reaction of 4-oxy *N*-sulfonyl triazoles with C(3)-substituted indoles.

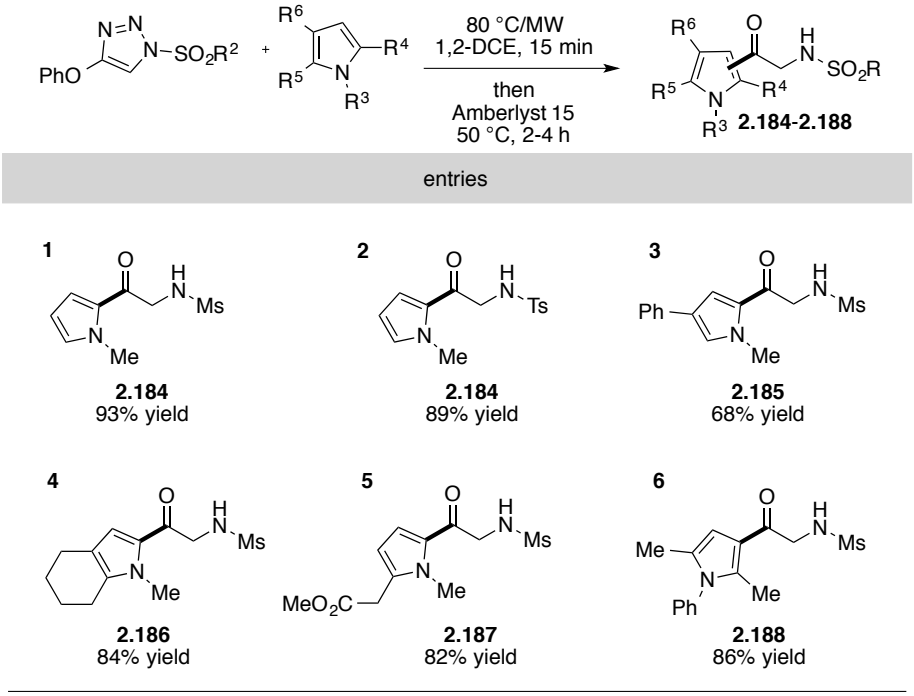
Attempted hydrolysis of the enol ethers with aqueous acid failed to provide the desired pyrroloindolone products (Scheme 2.7.9). The materials that were usually isolated were the starting *N*-methylindole and a glycinate derivative (phenyl (methylsulfonyl)glycinate). Using *p*-TsOH in benzene at elevated temperatures revealed the answer as the C(2) enol ether (**2.183**) was isolated. Re-subjection of this enol ether provided the previously observed products. Presumably, under the acidic conditions, the aminal is protonated triggering a ring opening of the bicyclo[3.3.0] system. Subsequent ring-closure gives a cyclopropyl intermediate which opens upon re-aromatization of the indolyl moiety. It is not fully understood why this is the desired pathway, but it is consistent with our pyrrole synthesis from furans.[117]

The amino acylation reaction was also applicable to electron-rich pyrroles giving either the C(2) or C(3) amino acylated products as shown in Table 2.7.5. Starting from 4-phenoxy-*N*-sulfonyl triazoles a range of pyrrole derivatives reacted under metal-free thermal conditions to provide the corresponding amino acylated products in moderate to excellent yields (**2.184-2.188**). Similar to the results with indole derivatives, *N*-H, alkyl and aryl are well tolerated, but pyrroles with electron withdrawing groups failed to provide the desired products. The use of the bulkier sulfonyl group is also well tolerated (entry 2) as well as various substitutions of the pyrrole (entries 3-5). Interestingly, both the starting pyrrole derivatives in entries 3 and 4 can be derived from *N*-sulfonyl triazoles,[118,119] further showcasing the applicability of the *N*-sulfonyl triazole chemistry. Lastly, the C(3) aminoacylated product (**2.188**) is obtained when both the C(2) and C(5) positions of the pyrrole derivative are substituted (entry 6). [7e] It is presumed that a similar mechanism operates in this system as compared to C(3)-unsubstituted indoles.



Scheme 2.7.9: Attempted hydrolysis of the pyrroloindoline products.

Table 2.7.5: Reaction of 4-oxy *N*-sulfonyl triazoles with *N*-methylpyrroles.

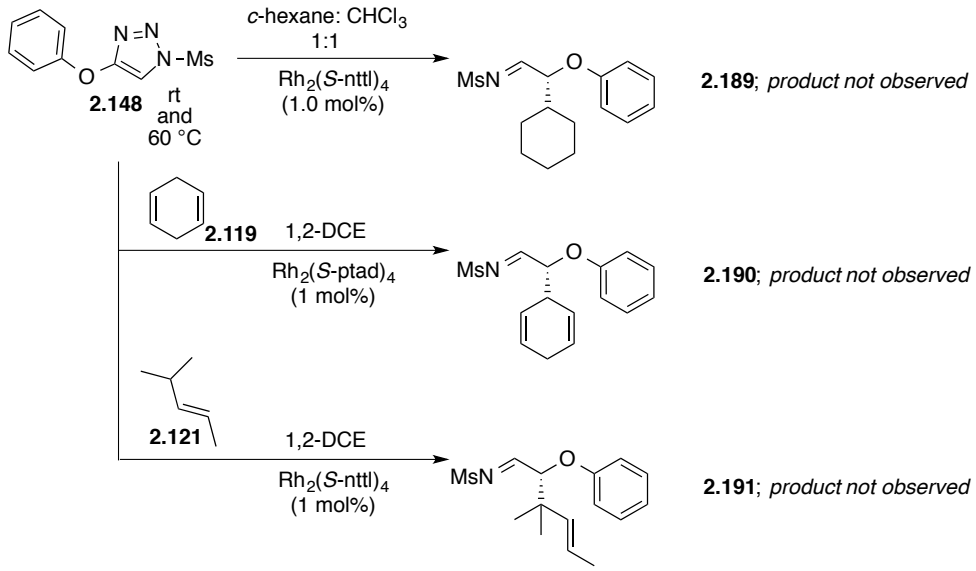


Triazole (1.0 equiv) and indole (1.5 equiv); Isolated yields.

In summary, we have developed an efficient method for aminoacylation of indoles and pyrroles through 4-alkoxy *N*-sulfonyltriazole intermediates from readily available starting materials. The *oxo*-tryptamine and *oxo*-pyrroloethanamine products are synthesized in a multicomponent one-pot cascade reaction. As previously observed with amino-substituted triazoles, the alkoxy-substituted triazoles undergo nitrogen extrusion under relatively mild conditions without requiring the use of a dirhodium catalyst. These studies further demonstrate that metal free donor/acceptor carbenes are capable of selective high-yielding transformations.

We hypothesized the use of the 4-oxy-*N*-sulfonyltriazole may allow for C–H functionalization of C–H bonds leading to functionalized α-oxy acid derivatives due to success of the cyclopropanation and aminoacylation reaction. Initial efforts began with

derivatives that are known to perform well in C–H functionalization chemistries with diazo acetates.[163] However, examination of cyclohexane, 1,4-cyclohexadiene (**2.119**), and 4-methyl-2-*trans*-pentene (**2.121**) did not result in the desired C–H functionalized products both at room temperature and elevated temperatures in the presence of a rhodium catalyst.

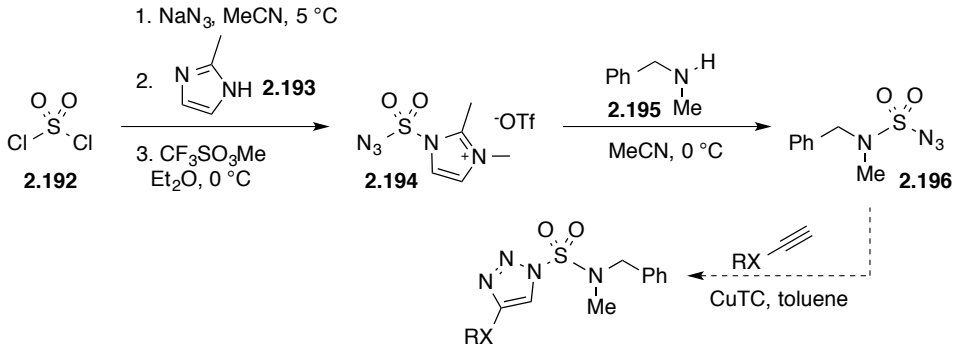


Scheme 2.7.10: Attempted C–H functionalization with 4-phenoxy-*N*-mesyltriazole.

2.8 Conclusion

In this chapter, a family of new donor/acceptor carbene precursors was developed in which the donor group is either an alkoxy or amino functionality. The use of traditional diazo chemistry led to unstable intermediates, therefore new methodology utilizing *N*-sulfonyl triazole technology was developed and implemented to access this novel class. The amino-substituted *N*-sulfonyl triazoles undergo a facile thermal reaction to generate a donor/acceptor carbene, in which the donor group is the imido group. This carbene

undergoes highly diastereoselective cyclopropanation with a range of alkenes and dienes, leading to a ready access to cyclopropane α-amino acids in an experimentally simple way. Further studies are needed to convert this transformation to a metal-catalyzed one. A possible solution can be seen in Scheme 2.8.1 in which a sulfonamide replaces the sulfonyl group. This would make the "acceptor" group less inductively electron-withdrawing. The desired azide (**2.196**) for the CuAAC reaction would come from the reaction of the imidazole-1-sulfonyl azide (**2.192**) with benzyl amine (**2.195**). It has been reported that the *N*-sulfamoyl triazoles are more stable than the corresponding *N*-sulfonyl triazoles and in most cases react in a similar manner, but at elevated temperatures.[120]



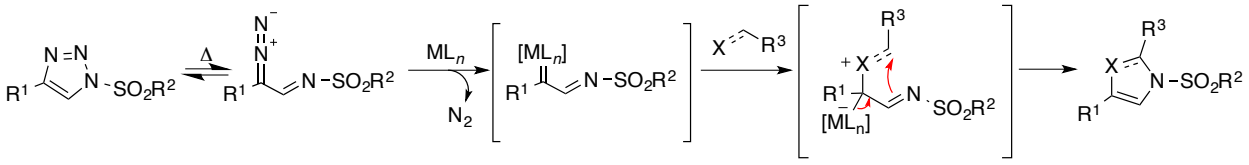
Scheme 2.8.1: Synthesis of a heteroatom *N*-sulfamoyl triazole.

Application of this strategy to the 4-oxy substituted *N*-sulfonyl triazoles will most likely be highly beneficial as well since there was already a trend with the inductively electron-withdrawing sulfonyl group (Scheme 2.7.4). In the future, this technology will offer a general method for the synthesis of a wide range of oxy and amino acids. The ideas discussed in this chapter have the potential to become key strategies in the synthesis of natural products and pharmaceutically relevant targets.

Chapter III: Utilizing *N*-Sulfonyl Triazoles for Heterocycle Synthesis

3.1 Introduction

A distinctive feature of using *N*-sulfonyl triazoles is the generation of metallocarbenes with a pendant sulfonyl imine group. The nitrogen atom exhibits a higher nucleophilicity than the oxygen atom in the related α-oxo metallocarbene.[82] Due to this increased nucleophilicity, the α-imino group has the ability to participate in reactions involving zwitterionic intermediates, which can then cyclize to new heterocycles (Scheme 3.1.1).

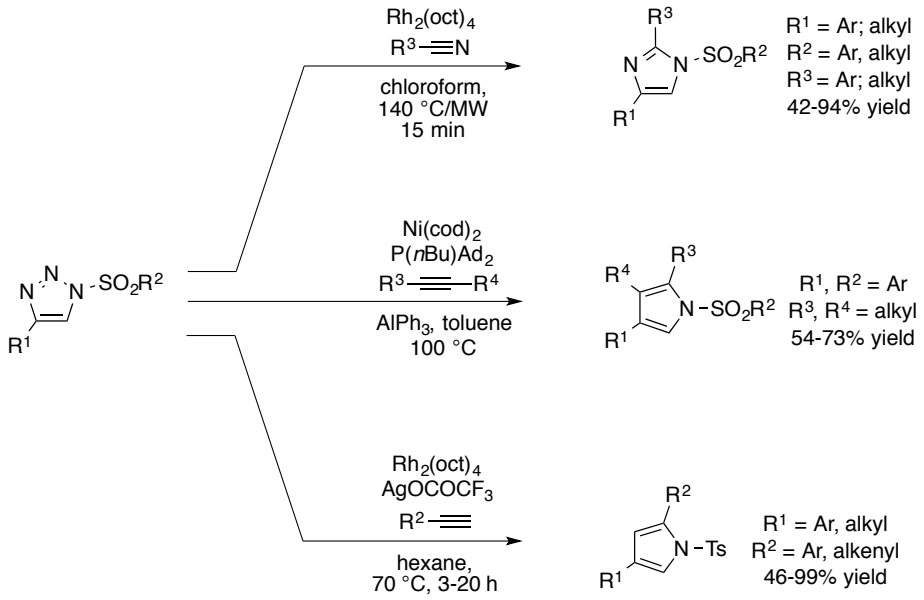


Scheme 3.1.1: Formation of the zwitterionic intermediates.

3.1.1 Early reports with *N*-sulfonyl triazoles

In 2008, Fokin and Gevorgyan reported that on warming *N*-sulfonyl triazoles in the presence of a rhodium(II) catalyst, they reacted with nitriles in a transannular fashion to furnish imidazoles (Scheme 3.1.2, top).[85] The reaction scope was broad as various nitriles and *N*-sulfonyl triazoles participated in the reaction. Shortly after this, Murakami reported a nickel/aluminum-catalyzed dinitrogenative transannulation of *N*-sulfonyl

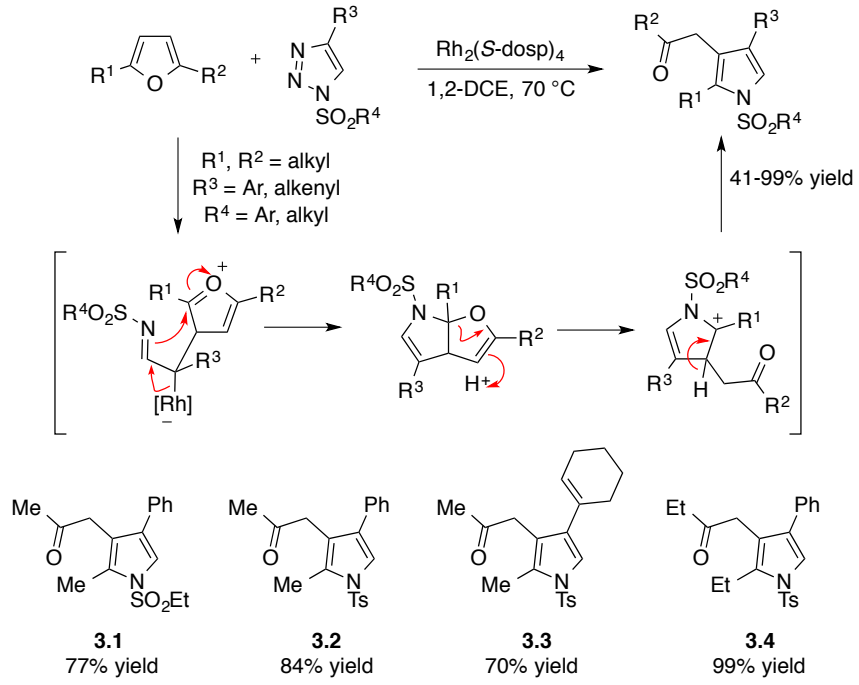
triazoles with internal alkynes.[83] The combination of a nickel(0) catalyst, $Ni(cod)_2$, electron-rich and bulky phosphine ligand, P(*n*Bu)Ad_2, and a Lewis acid additive, $AlPh_3$, provided an effective transannulation of symmetrical internal alkynes furnishing the corresponding substituted pyrroles in moderate yields (Scheme 3.1.2, middle). However, the use of unsymmetrical alkynes gave a mixture of regioisomers and terminal alkynes failed to participate in the reaction. Gevorgyan then reported the transannulation of *N*-tosyl triazoles with terminal alkynes using a dual rhodium/silver catalyst system.[84] Various C-4 substituted triazoles and electron-rich terminal alkynes participated in the reaction to provide the desired pyrrole products x in good yield; however, electron-poor terminal alkynes did not participate in the reaction (Scheme 3.1.2, bottom). The methodology was extended into a three-component, one-pot procedure starting from tosyl azide and two different terminal alkynes, one of which is first added to form the *N*-tosyl triazole. These early reports are thoroughly discussed in the previous chapter and will not be considered in further detail here.



Scheme 3.1.2: Early reports of heterocycle synthesis with *N*-sulfonyl triazoles.

3.1.2 New heterocycle syntheses with *N*-sulfonyl triazoles

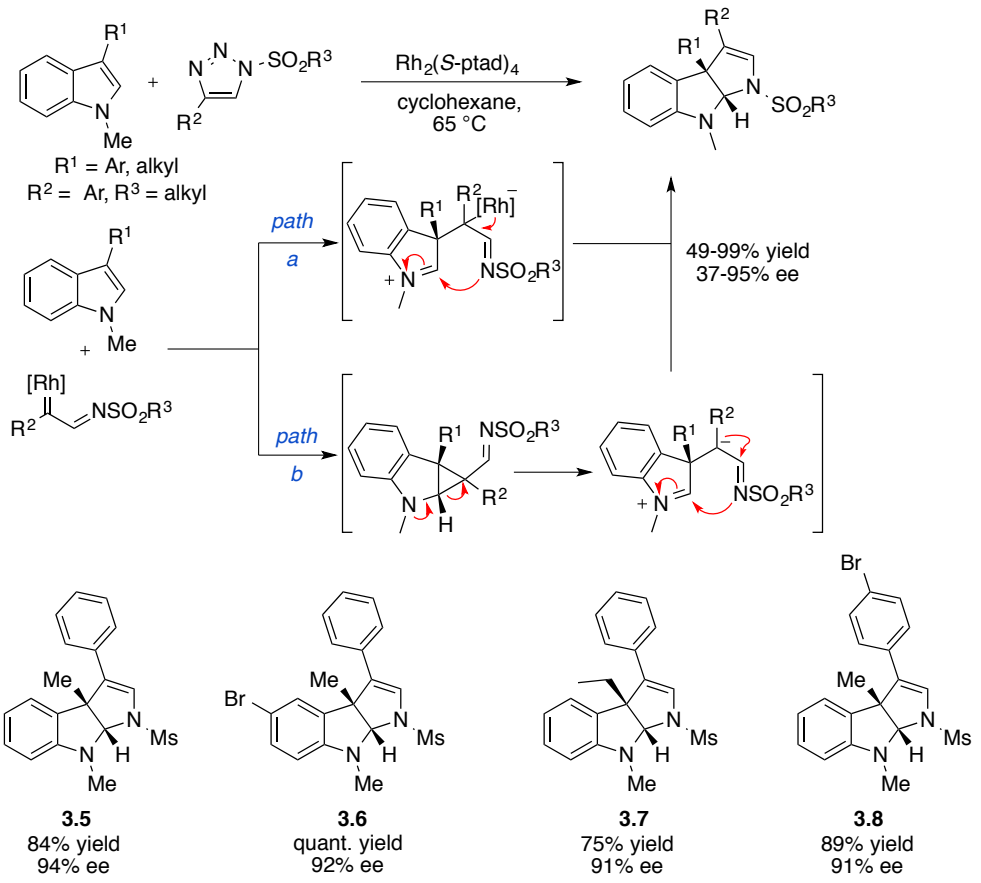
In the last few years, a number of new transannulation reactions have been described. Davies reported a synthesis of trisubstituted pyrroles from a rhodium(II)-catalyzed transannulation of *N*-sulfonyl triazoles with 2,5-disubstituted furans (Scheme 3.1.3).[117] Steric and electronic variations of the triazole had minimal impact on the efficacy of the reaction, but in some cases when the furan was unsymmetrically substituted, mixtures of regioisomers were formed. Although most of the rhodium(II) carboxylate catalysts were effective, Rh_2(*S*-dosp)$_4$ was found to be the optimal catalyst. The proposed mechanism involves the furans reacting with the electrophilic rhodium(II)-stabilized metallocarbenes at the C-3 position to generate zwitterions, which then close to the hemiaminals (formal [3+2]). Under the mildly acidic reaction conditions, the ring then opens to the dihydropyrrole intermediates, which then aromatize to the pyrroles (**3.1-3.4**).



Scheme 3.1.3: Davies' synthesis of trisubstituted pyrroles from furans.

Expanding on this reaction, Davies reported a rhodium(II)-catalyzed synthesis of pyrroloindolines (**3.5-3.8**) *via* an enantioselective formal [3+2] cycloaddition between 4-aryl sulfonyltriazoles and C-3 substituted indoles (Scheme 3.1.4).[116] The reaction proved to be most effective in both conversion and enantioinduction when conducted in nonpolar hydrocarbon solvents with Rh_2(*S*-ptad)$_4$ being the optimal catalyst. Reactions in more polar solvents failed to give any of the pyrroloindoline products. A variety of electron-withdrawing and electron-donating aryl-substituted mesyltriazoles successfully participated in the reaction providing good yields of the pyrroloindoline products with high levels of enantioselectivity. The reaction was found to be susceptible to steric effects as substrates with bulky sulfonyl groups or bulky groups at the indolic nitrogen failed to furnish pyrroloindolines.

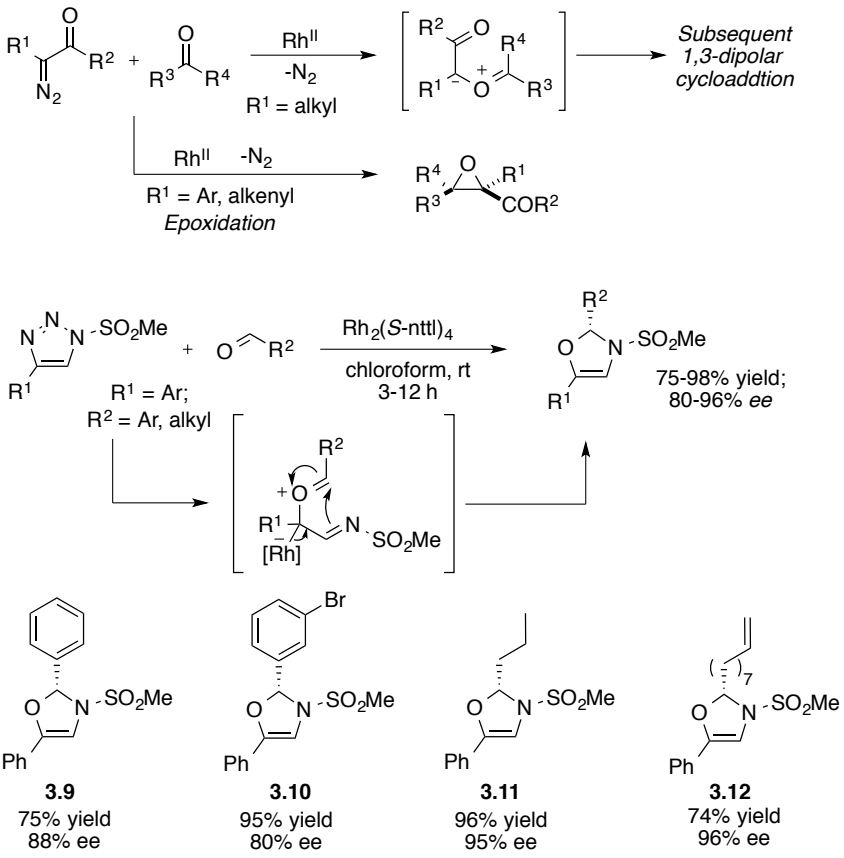
Two possible reaction pathways have been proposed for this transformation. In the first pathway (path a), similar to reaction with furans, the electron-rich indoles react with the electrophilic rhodium(II)-stabilized imino metallocarbenes via a zwitterionic-type pathway followed by cyclization to the pyrroloindolines. In the second pathway (path b), the reaction occurs *via* an initial cyclopropanation of the indoles followed by a subsequent ring opening of the strained cyclopropylindolines and recombination to furnish the pyrroloindolines. The second pathway is more consistent with the observed regioselectivity; with the direct attack of the imino-metallocarbenes by the indoles, zwitterions bound at C(2) would be expected due to sterics at the C(3) position providing the opposite regioselectivity.



Scheme 3.1.4: Davies' enantioselective synthesis of pyrroloindolines.

Diazocarbonyl derivatives react with carbonyl groups to produce either ylides or epoxides, depending on the nature of the R^1 group as depicted in Scheme 3.1.5. The ylides derived from alkyl diazocarbonyl derivatives can further react *via* 1,3-dipolar cycloaddition to provide complex structures. Fokin reported similar ylide formation between Rh(II)-stabilized imino metallocarbenes and aldehydes.[121] The reaction proceeds *via* ylide intermediates, which undergo an intramolecular cyclization with the pendant sulfonyl imine to provide 3-sulfonyl-4-oxazolines (**3.9-3.12**) in excellent yields and high levels of enantioselectivity. A variety of aryl and alkyl aldehydes participate in the reaction with optimal outcomes being obtained with the use of *N*-mesyl-1,2,3-triazoles at

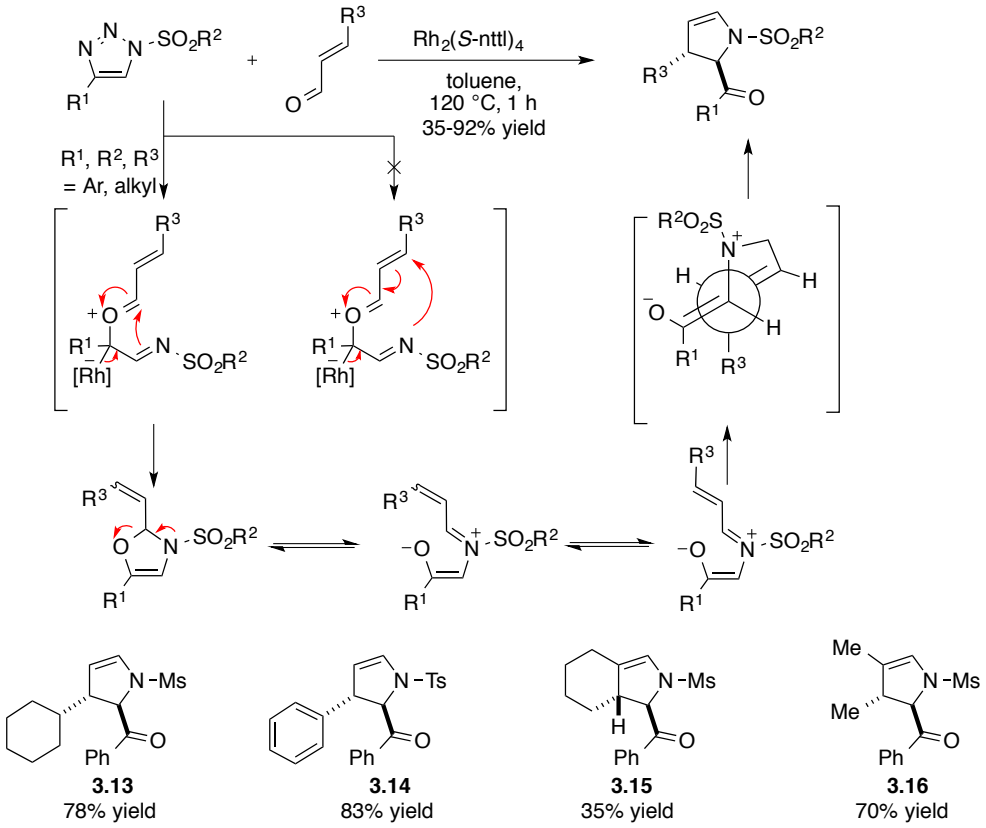
ambient temperature with the rhodium(II) catalyst, Rh_2(*S*-nttl)$_4$, in chloroform. Prolonged reaction times significantly lowered the enantiomeric purity of the products due to the reversible ring opening of the N,O-aminal under the slightly acidic reaction conditions.



Scheme 3.1.5: Fokin's enantioselective synthesis of 4-oxazolines.

Murakami and Miura have reported an extension of this reaction to α,β-unsaturated aldehydes furnishing *trans*-2,3-disubstituted dihydropyrroles (**3.13**-**3.16**; Scheme 3.1.6).[82] The reaction conditions are similar to that reported by Fokin for the synthesis of 4-oxazolines with the exception of heating to 120 °C. This slight change in conditions favours the formation of dihydropyrroles. It is proposed that the reaction first produces 4-oxazolines as seen previously, but under the more vigorous conditions, the

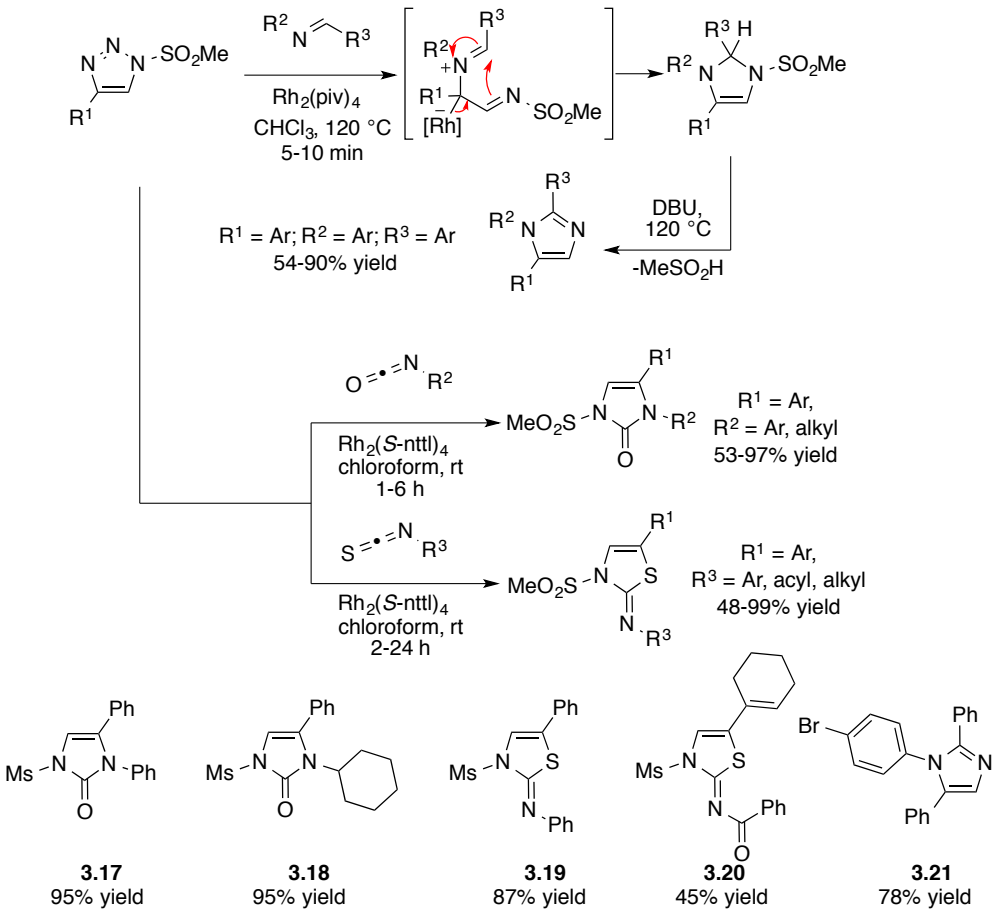
weak aminal bond is cleaved producing zwitterionic intermediates, followed by a double bond isomerization to the more stable (*E*) isomers. The enolate moiety then engages the α,β-unsaturated imine through a conjugate addition to provide the 2,3-dihydropyrroles. Alternatively, a [3,3] sigmatropic rearrangement is also possible. A one-pot procedure for the synthesis of *trans*-2,3-disubstituted dihydropyrroles was carried out to demonstrate the practicality of the method starting from the terminal alkyne, in which the triazoles were produced *in situ*.



Scheme 3.1.6: Murakami and Miura's synthesis of *trans*-2,3-disubstituted dihydropyrroles.

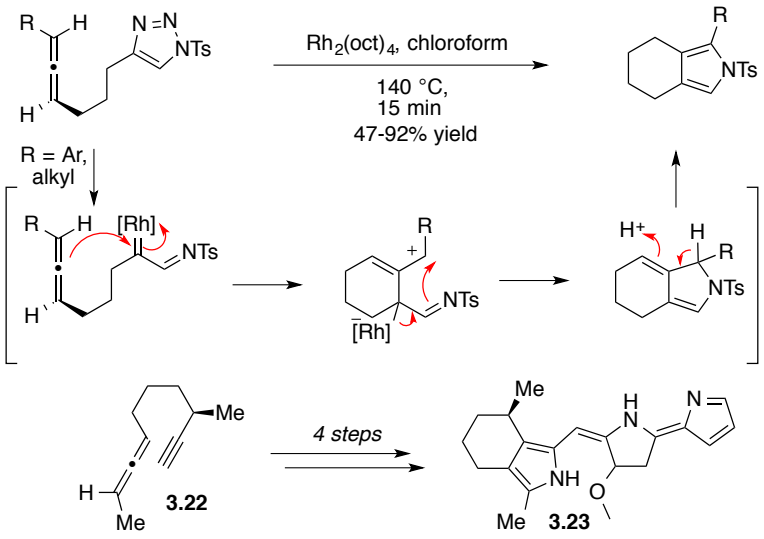
In addition to aldehydes, *N*-sulfonyl triazoles react with aldimines through a cyclization-elimination sequence, providing direct access to 1,2,5-trisubstituted imidazoles (**3.17-3.21**; Scheme 3.1.7).[121] The imidazoles are formed in moderate yield

(54-90%) from the corresponding 4-aryl-substituted triazoles and aldimines. The reaction proceeds through a cyclization of ylide intermediates to provide imidazolines, which then eliminate sulfinic acid to provide imidazoles. Fokin has also disclosed an efficient method for the construction of imidazolones and thiazoles *via* a Rh(II)-catalyzed formal [3+2] cycloaddition of 1-mesyl-1,2,3-triazoles with isocyanates and isothiocyanates, respectively.[122] The nitrogen of the isocyanates react with the imino metallocarbenes forming ylide-type intermediates, followed by cyclization to furnish the imidazolones. In the case of isothiocyanates, the sulfur reacts to form the ylide-type intermediates, which then cyclize to provide the thiazoles with an exocyclic imine group.



Scheme 3.1.7: Fokin's imidazole, imidazolone, and thiazole synthesis.

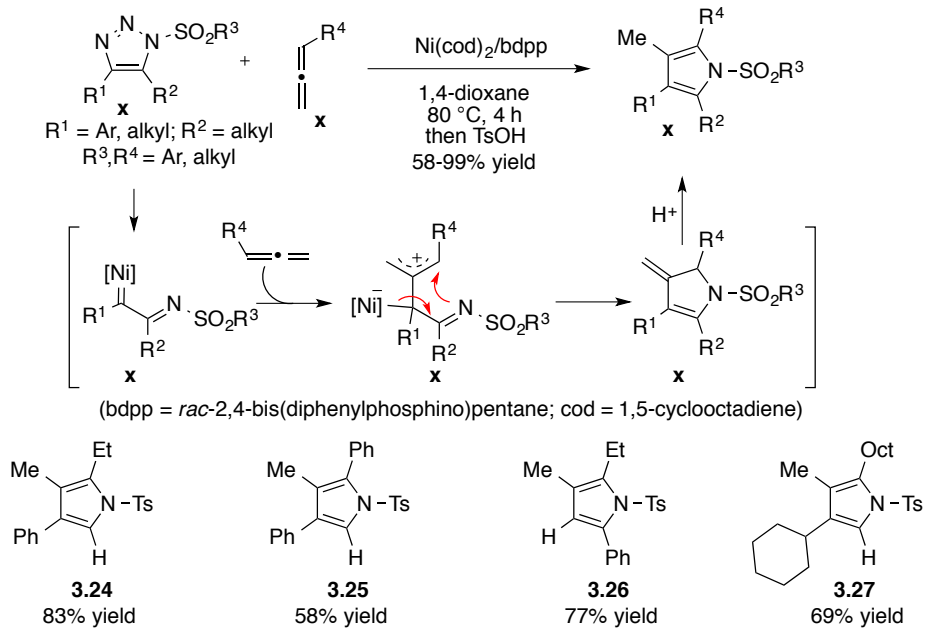
Recently Sarpong demonstrated that α-alkyl imino metallocarbenes generated from the rhodium(II)-catalyzed decomposition of *N*-sulfonyl triazoles could react with pendant allene moieties to form 3,4-fused pyrroles (Scheme 3.1.8).[123] The initially formed ylides, underwent cyclization to dihydropyrroles, which isomerized to the pyrroles. A variety of groups on the allene, including aryl, cycloalkyl, and alkyl, were tolerated. Notably, the α-alkyl group did not undergo the competing 1,2-hydride shift to yield α,β-unsaturated *N*-tosylimines as seen in the reports of Murakami and Fokin.[124] This reaction was further extended to a one-pot sequence starting from allenylalkynes and resulting in the *in situ* formation of the triazoles and their conversion to pyrroles. The utility of this reaction was demonstrated in the enantioselective synthesis of the natural product cycloprodigiosin **3.23** in four steps starting from the enantioenriched allenylalkyne.



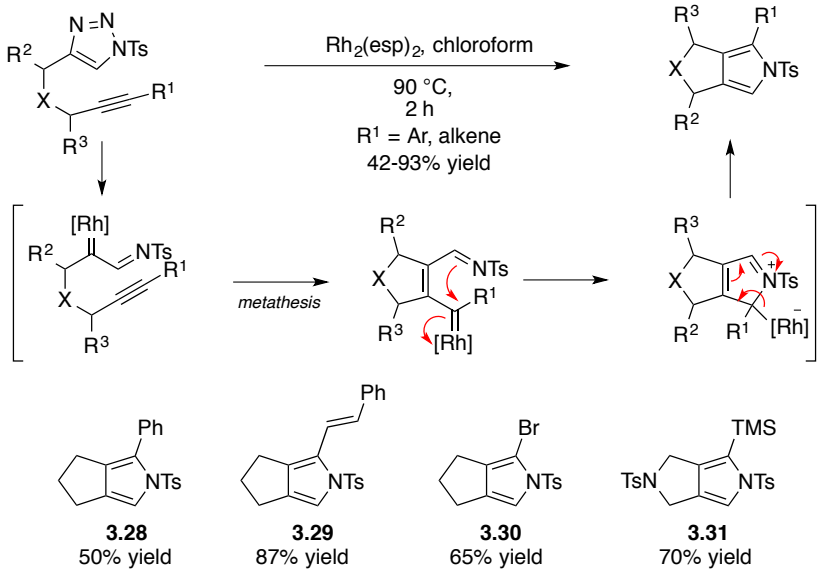
Scheme 3.1.8: Sarpong's synthesis of 3,4-fused pyrroles.

Murakami and Miura have reported a nickel(0)-catalyzed transannulation of *N*-sulfonyl triazoles with allenes to furnish isopyrrole intermediates, which could be further elaborated into polysubstituted pyrroles (**3.24**-**3.27**) or participate in subsequent Alder-ene reactions with suitable enophiles *in situ* (Scheme 3.1.9).[125] A variety of electron-withdrawing and electron-donating aryl- and alkyl-substituted *N*-sulfonyl triazoles successfully participated in the reaction. Interestingly, both 1,5-disubstituted and 1,4,5-trisubstituted *N*-sulfonyl triazoles were also tolerated in the reaction. A plausible mechanism for this transformation begins with the formation of the imino nickel carbenes followed by nucleophilic addition of the allenes to yield zwitterionic intermediates. Subsequent cyclization furnishes isopyrroles with release of the nickel catalyst, which can undergo double bond transposition in the presence of an acid to the pyrroles.

Gevorgyan reported that α-alkyl imino metallocarbenes could engage with pendant alkynes via an alkyne-carbene metathesis step resulting in the synthesis of 3,4-fused pyrroles (**3.28**-**3.31**; Scheme 3.1.10).[126] Similar to the Davies' report,[118] the rhodium(II) catalyst, $Rh_2(esp)_2$, proved to be particularly effective in this transformation. Mechanistically, it is proposed the pendant alkynes interacts with the electrophilic imino metallocarbenes in an alkyne-metathesis step to form the vinyl rhodium(II)-stablized carbenes. Nucleophilic attack by the sulfonyl imine, followed by aromatization of the zwitterionic intermediates provided the fused pyrroles. Only substrates with a C-3 tether furnished the desired pyrrole products but several functional groups were compatible with this chemistry.



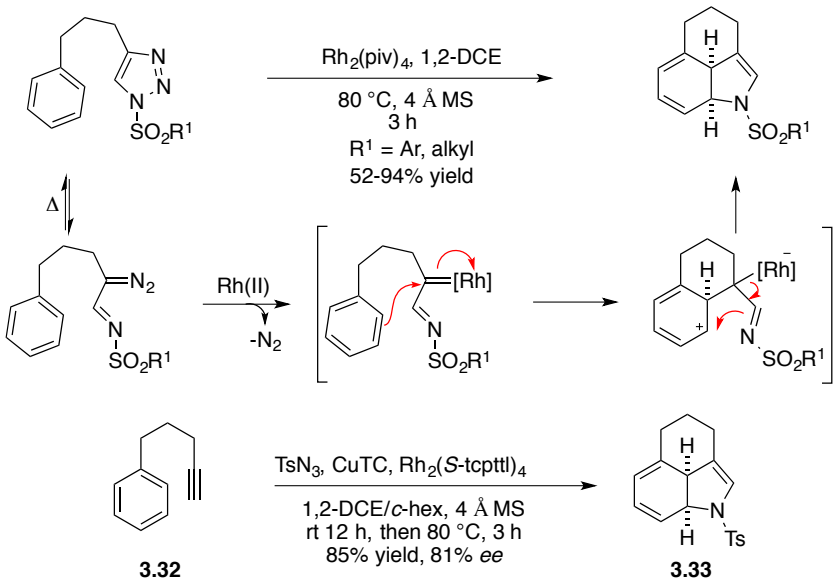
Scheme 3.1.9: Murakami and Miura's synthesis of pyrroles from allenes.



Scheme 3.1.10: Gevorgyan's synthesis of 3,4-fused pyrroles.

Murakami and Miura have reported a rhodium(II)-catalyzed dearomatizing [3+2] annulation of 4-(3-arylpropyl) *N*-sulfonyl triazoles to furnish 3,4-fused indoles (Scheme 3.1.11).[127] The proposed mechanism involves an intramolecular attack of the rhodium(II)

imino-carbenes by the aryl substituent in a 6-exo mode providing intermediates followed by cyclization of the imino group to provide the *cis*-3,4-fused indoles. A variety of substituted aryl groups possessing the three-carbon tether were tolerated, but shorter or longer tethers failed to participate in the reaction. The use of a chiral catalyst, Rh_2(*S*-tcpttl)$_4$, provided 3,4-fused indole (**3.33**) with a good level of asymmetric induction (81% *ee*) in a one-pot sequence starting from the 5-aryl-1-alkyne (**3.32**).

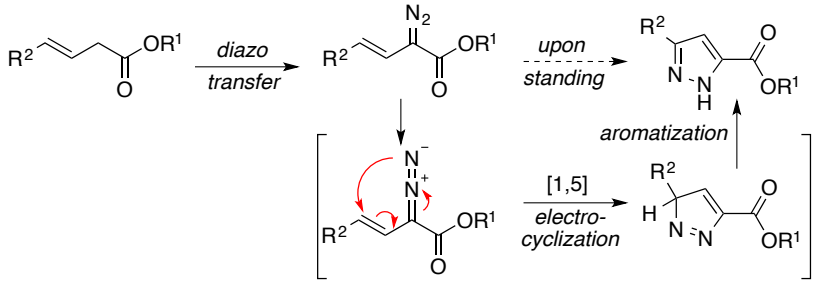


Scheme 3.1.11: Murakami and Muira's 3,4-fused indole synthesis.

3.2 Investigations into Alkenyl *N*-Sulfonyl Triazoles

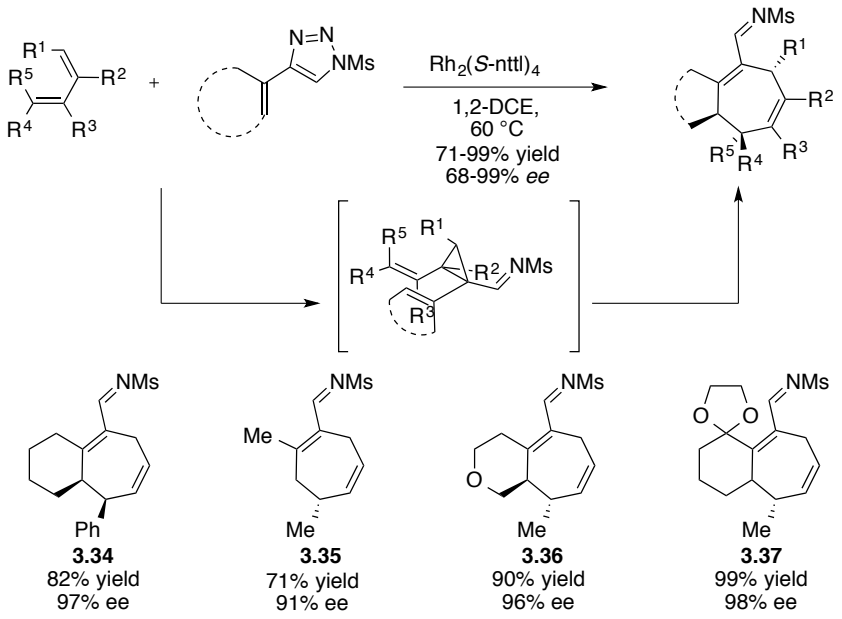
One of the most broadly used subclass of donor/acceptor metallocarbenes is those in which the donor group is an alkenyl substituent. Alkenyl substituted donor/acceptor metallocarbenes participate in a number of synthetically useful reactions, with the foremost being the formal [4+3] cycloaddition reaction resulting in a seven-membered carbocyclic system. However, this subclass has two major drawbacks: their synthesis can be unreliable, and alkenyldiazoacetates, once formed, have a propensity to undergo a

rapid [1,5]-electrocyclization followed by aromatization to form pyrazoles (Scheme 3.2.1).[128] This cyclization is non-reversible, and has the potential to coordinate to the rhodium(II) catalyst thereby impeding the reaction.



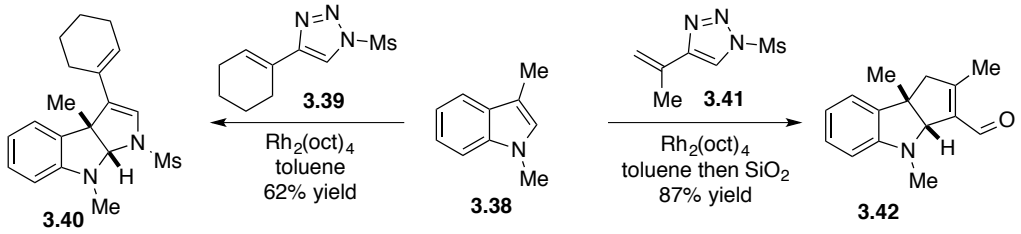
Scheme 3.2.1: Pyrazole formation from an alkenyldiazoacetate.

Recently, the Davies group reported an analogous alkenyldiazo surrogate utilizing *N*-sulfonyl triazoles. Furthermore, the alkenyl *N*-sulfonyl triazole could also participate in a tandem cyclopropanation/Cope rearrangement (Scheme 3.2.2).[129] Similar to earlier cyclopropanation reactions by Fokin, Rh_2(*S*-nttl)$_4$ was the optimal catalyst for inducing high yields and high levels of enantioselectivity. The reaction scope revealed that various cyclic and heterocyclic alkenyl-substituted sulfonyl triazoles were tolerated. This reaction provides an effective method for the enantioselective synthesis of polycyclic imines (**3.34**-**3.37**) generating two stereogenic centers. The sulfonyl imine could be hydrolysed under basic conditions without epimerization of the γ-chiral center affording the α,β-unsaturated aldehyde in high yield with no observable epimerization.



Scheme 3.2.2: Davies' enantioselective formal 4+3 cycloaddition.

In the Davies report of a rhodium(II)-catalyzed synthesis of pyrroloindolines *via* an enantioselective formal [3+2] cycloaddition between 4-aryl sulfonyltriazoles and C-3 substituted indoles (Scheme 3.1.4), 4-alkenyl *N*-sulfonyl triazoles were also explored in this transformation. The acyclic alkenyl *N*-sulfonyl triazole (**3.41**) we found to react with the 1,3-dimethylindole (**3.38**) in a vinylogous manner. However, the cyclic alkenyl *N*-sulfonyl triazole (**3.39**) were found to react with the Rh(II)-bound metallocarbene in a cycloaddition manner as previous described.



Scheme 3.2.3: Reaction of 1,3-dimethylindole with 4-alkenyl *N*-sulfonyl triazoles.

3.3 Cyclization Reactions of Alkenyl *N*-Sulfonyl Triazoles

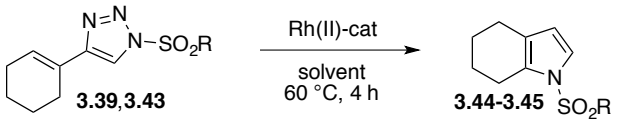
During the course of our investigations with the alkenyl *N*-sulfonyl triazoles, we discovered that the imino alkenylcarbenes, in the absence of a suitable trapping agent, undergo a facile [1,5]-electrocyclization to pyrroles when treated with a rhodium(II) catalyst under thermal conditions. We were excited about this result, as pyrroles are ubiquitous constituents in a wide variety of natural products, therapeutic agents, and high value materials.[130,131,132,133] As a result of this, the development of methods for the synthesis of pyrroles continues to be an active area of research.[134,135] Traditional methods for pyrrole synthesis include the Knorr, Hantzsch, and Paal-Knorr synthesis.[136,137,138] More recently, many metal-catalyzed methods for the synthesis of pyrroles have been reported.[139,140,141,142] However, the synthesis of highly functionalized pyrroles remains challenging, and often requires multiple steps or harsh reaction conditions.

3.3.1 Fused pyrrole synthesis

Our preliminary reaction development was conducted with 4-cyclohexenyl-1-(sulfonyl)-1,2,3-triazole **x** in the presence of 1.0 mol% Rh(II) catalyst (Table 3.3.1). The yield of the desired product was found to be dependent on both the nature of the sulfonyl group and the dirhodium catalyst. After exploring several achiral Rh(II) catalysts, $Rh_2(esp)_2$ was identified as the optimal catalyst for this transformation (entry 4). Increasing the steric bulk of the *N*-sulfonyl substitutent provided improved yields of the desired product (compare entry 4 and 5). The effect of the solvent was less pronounced, which is in contrast to the solvent effect we had observed in our previous reports with *N*-

sulfonyltriazoles. $Rh_2(esp)_2$ is derived from two chelating bis-carboxylate ligands and exhibits superior performance for C–H amination reactions.[143] This rhodium catalyst is less prone to ligand exchange than other simple tetracarboxylate systems and is less susceptible to degradation under given reaction conditions thereby affecting the catalyst turnover and reaction efficiency.[144]

Table 3.3.1: Preliminary reaction development for pyrrole synthesis.



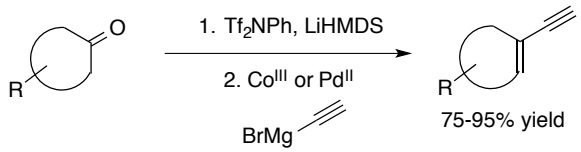
3.39,**3.43** **3.44-3.45**

entry	substrate	-SO_2R	Rh(II)-cat.	solvent	product	yield, %
1	**3.43**	Ts	$Rh_2(OAc)_4$	1,2-DCE	**3.44**	47
2	**3.43**	Ts	$Rh_2(TFA)_4$	1,2-DCE	**3.44**	0
3	**3.43**	Ts	$Rh_2(oct)_4$	1,2-DCE	**3.44**	91
4	**3.43**	Ts	$Rh_2(esp)_2$	1,2-DCE	**3.44**	93 (94)[b]
5	**3.39**	Ms	$Rh_2(esp)_2$	1,2-DCE	**3.45**	81
6	**3.43**	Ts	$Rh_2(esp)_2$	EtOAc	**3.44**	53
7	**3.43**	Ts	$Rh_2(esp)_2$	$PhCH_3$	**3.44**	91
8	**3.43**	Ts	$Rh_2(esp)_2$	$CHCl_3$	**3.44**	92

Triazole (1.0 equiv) and $Rh_2(L)_n$ (0.01 equiv); Isolated yields. [b]5.0 mmol scale (0.1M).

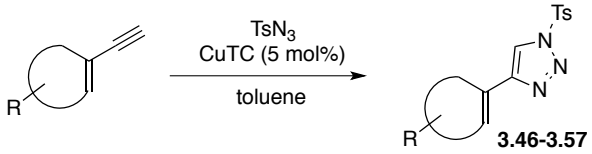
Having established that a 4-alkenyl *N*-sulfonyl triazole could be effectively used for the synthesis of 2,3-fused pyrroles, practical syntheses to generate a variety of alkenyl *N*-tosyltriazoles were developed. The 4-alkenyl-1-tosyl-1,2,3-triazoles (**3.46-3.57**) were prepared in three steps from the cyclic ketones: vinyl triflate formation, a Kumada-type coupling with ethynylmagnesium bromide in the presence of 3 mol% $Co(acac)_3$ (Scheme 3.3.1), [145] and copper(I)-thiophene-2-carboxylate (CuTC) catalyzed azide-alkyne cycloaddition (CuAAC) reaction with TsN_3 (Table 3.3.2).[146] Since the triazole is thermodynamically favored over the diazo imine tautomer, the undesirable rearrangement

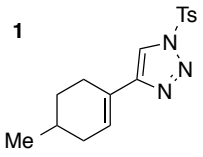
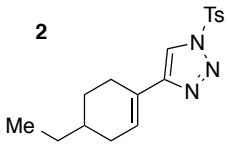
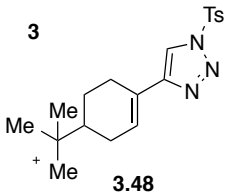
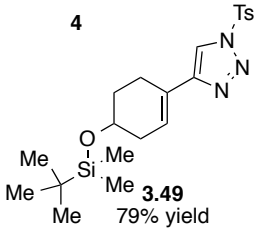
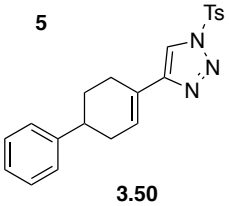
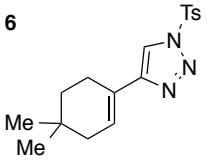
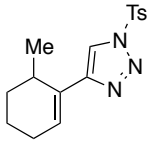
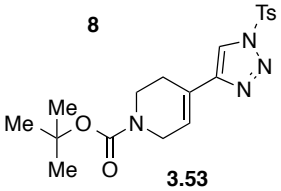
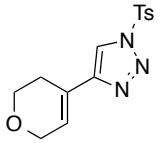
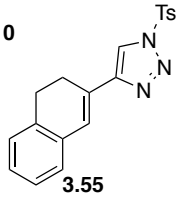
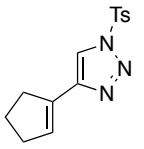
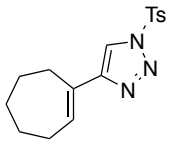
of the triazole to a pyrazole was not observed, providing a benchtop stable alkenyldiazo surrogate.



Scheme 3.3.1: Synthesis of the enynes.

Table 3.3.2: Synthesis of cyclic 4-alkenyl *N*-tosyltriazoles.

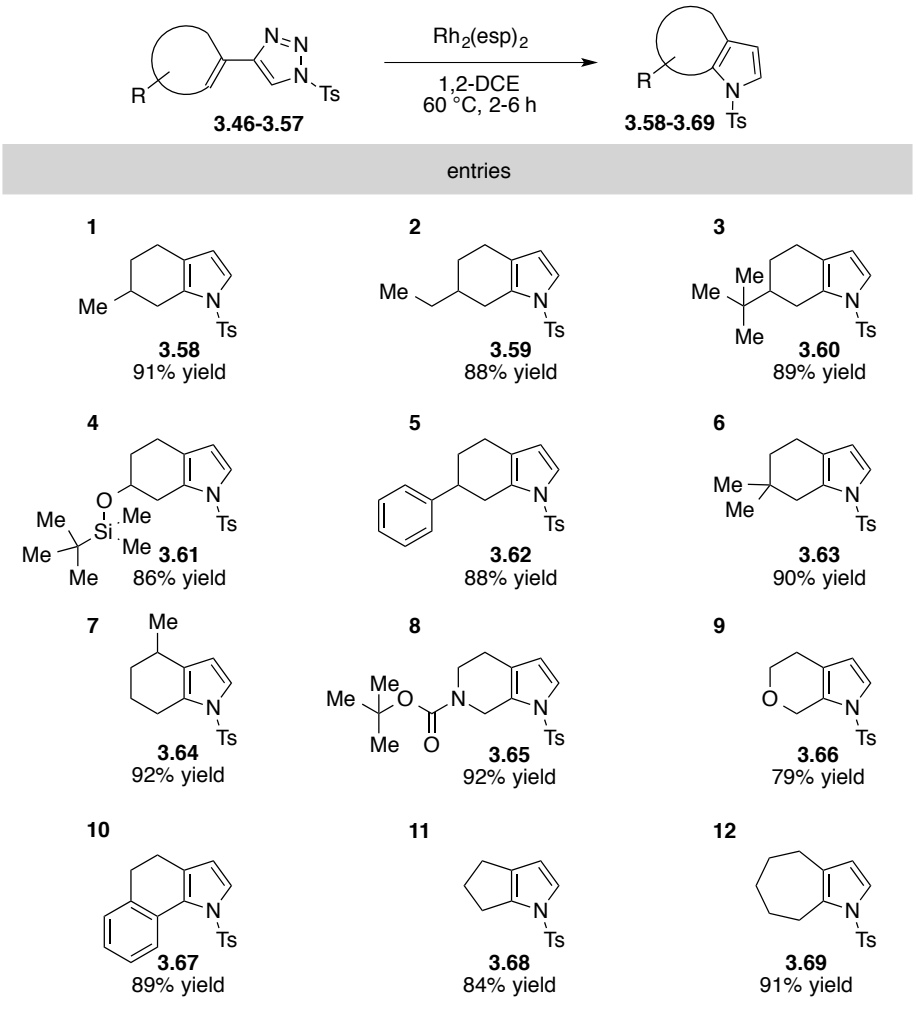


entries			
1  **3.46** 83% yield	2  **3.47** 86% yield	3  **3.48** 85% yield
4  **3.49** 79% yield	5  **3.50** 88% yield	6  **3.51** 84% yield
7  **3.52** 86% yield	8  **3.53** 81% yield	9  **3.54** 77% yield
10  **3.55** 88% yield	11  **3.56** 80% yield	12  **3.57** 83% yield

Enyne (1.0 equiv) and TsN_3 (1 equiv); Isolated yields.

Following the optimization studies for the formation of the tetrahydroindole, we were pleased to find that the reaction of a variety of 2 and 4-substituted cyclohexenyl triazole derivatives provide the desired tetrahydro-1*H*-indoles (**3.58-3.64**) in excellent yields (86-92%; entries 1-7; Table 3.3.3). Heteroatoms in the ring were also tolerated, as both the *N*-Boc piperdinyl and pyranyl alkenyltriazoles (**3.53** and **3.54**) underwent the cyclization to provide pyrroles **3.65** and **3.66** in good yield (entries 8 and 9). The 1,2-dihydronaphthalen-2-yl derivative

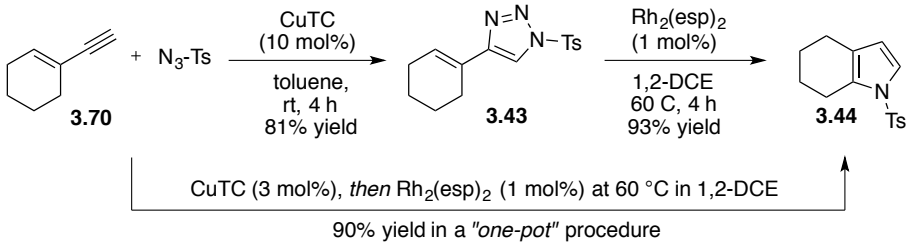
Table 3.3.3: Cyclization of cyclic 4-alkenyl *N*-tosyltriazoles.



Triazole (1.0 equiv) and $Rh_2(esp)_2$ (0.01 equiv); Isolated yields.

3.55 provides the dihydrobenzoindole product (**3.67**) in excellent yield (89%; entry 10). The cyclopentenyl and cycloheptenyl triazole derivatives **3.56** and **3.57** also react to provide the fused pyrroles (**3.68** and **3.69**) in high yield (entries 11 and 12). The reaction appeared to be quite general with the limitation being the selective synthesis of the vinyl triflate from the cyclic ketone.

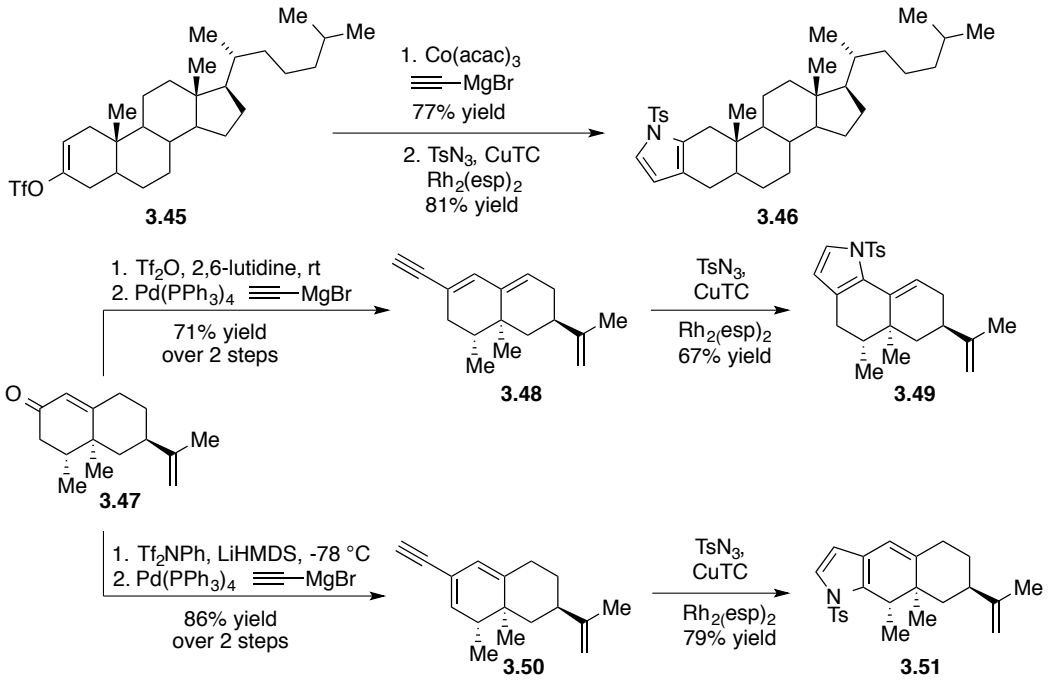
Since the CuAAC reaction can be preformed in halogenated solvents as described in the previous chapter, it was plausible to perform the CuAAC reaction and the rhodium-catalyzed cyclization in the same reaction medium starting from the enyne (**3.70**; Scheme 3.3.2). The one-pot reaction gave the desired 2,3-fused pyrrole product (**3.44**) in higher overall yield (90%) than in the sequence in which the triazole was isolated thus further demonstrating the synthetic robustness of the reaction. The one-pot procedure eliminated the need to isolate the intermediate *N*-sulfonyl triazole (**3.43**) and further simplified the experimental procedure.



Scheme 3.3.2: One-pot 2,3-fused pyrrole synthesis.

The utility of the one-pot 2,3-fused pyrrole synthesis was demonstrated in more complex frameworks, the steroid skeleton of 5-cholestan-3-one and nootkatone (Scheme 3.3.3). For 5-cholestan-3-one, selective formation of the vinyl triflate **3.45** and subsequent Co(III)-catalyzed coupling provided an enyne. The enyne was subsequently

subjected to a one-pot CuAAC and rhodium-catalyzed cyclization furnishing the pyrrole product **3.46** in good yield (81%). With nootkatone, both the kinetic and thermodynamic vinyl triflates could be formed regioselectively and then independently subjected to a palladium catalyzed coupling. The resulting enynes **3.48** and **3.50** were subjected to the one-pot protocol to provide pyrroles **3.49** and **3.51** (67 and 79% yield, respectively). Notably, electrocyclization to form the pyrrole was found to be preferred over a number of potential side reactions.



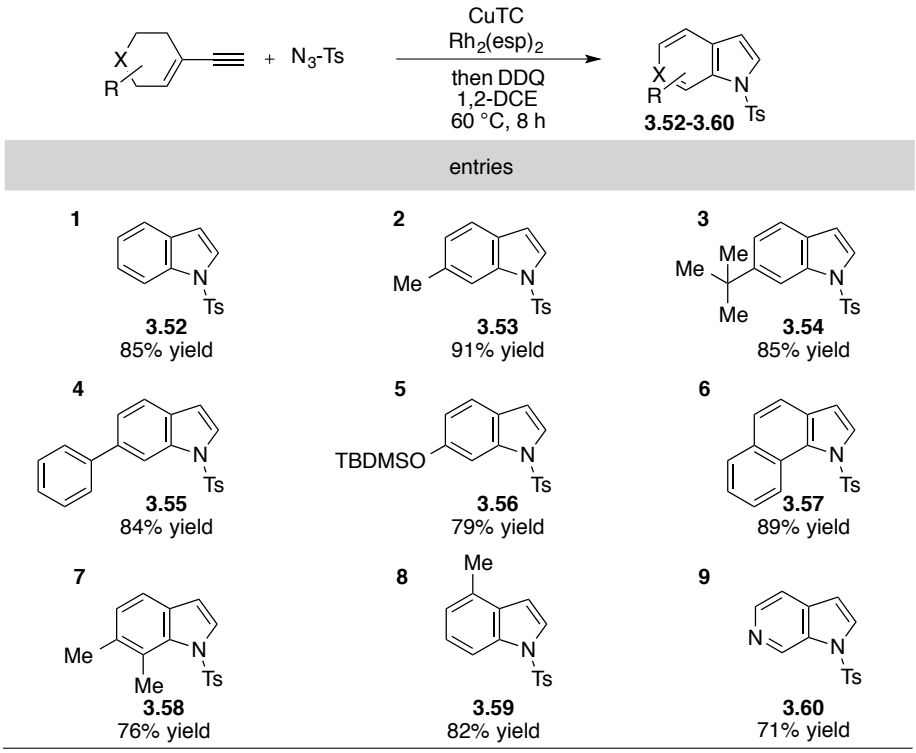
Scheme 3.3.3: Application of the pyrrole synthesis to complex frameworks.

3.3.2 Substituted indole synthesis

Encouraged by the successful syntheses of 2,3-fused pyrroles, our attention turned to the possibility of synthesizing substituted indole derivatives by combining the [1,5]-

electrocyclization with an *in situ* DDQ oxidation of the resulting tetrahydroindole. To our delight, the reaction gave the desired indole products (**3.52**-**3.60**) in good to excellent yield (Table 3.3.4). This one-pot reaction sequence can be extended to a variety of substituted cyclohexenyl derivatives to provide substituted indole products (entries 1-9). Notably, the siloxy-derivative reacts to provide the 6-siloxy indole **3.56** and may serve as a precursor for cross-coupling at the 6-position (entry 5). The 6,7-dimethylindole derivative (**3.57**; entry 7) comes from the parent 6,6-dimethyl-tetrahydroindole **3.63**, but the gem-dimethyl group undergoes a selective Wagner-Meerwein rearrangement under the oxidation conditions. The *N*-Boc-protected piperidine derivative provides ready access to the 6-azaindole (**3.60**; entry 9) through an *in situ* deprotection of the Boc group under the oxidation conditions. The one-pot procedure eliminated the need to isolate the intermediate *N*-sulfonyl triazole and further simplified the experimental procedure. The indole product could be easily isolated by a simple filtration of the reaction through a plug of silica.

Table 3.3.4: One-pot synthesis of substituted indole derivatives.

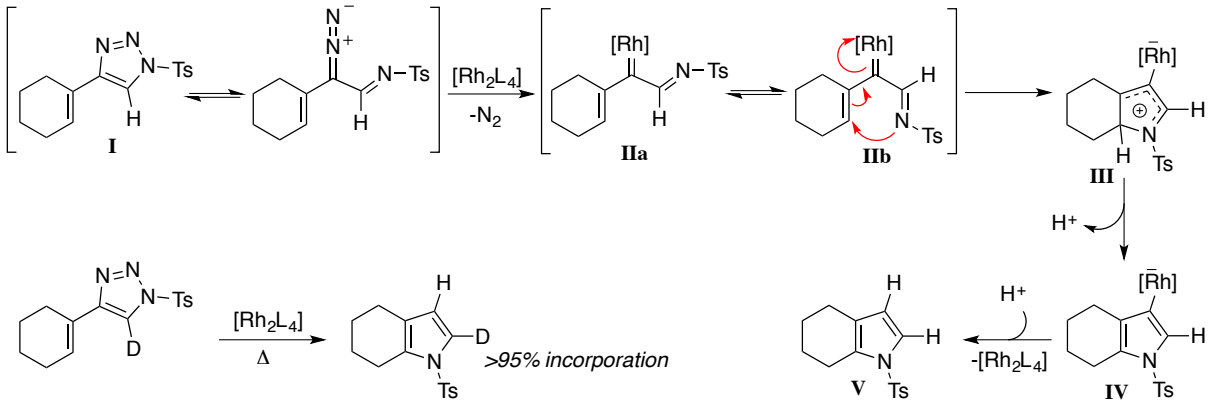


Enyne (1.0 equiv), TsN_3(1.0 equiv), CuTC(0.05 equiv), $Rh_2(esp)_2$ (0.01 equiv), then DDQ (2.0 equiv); Isolated yields.

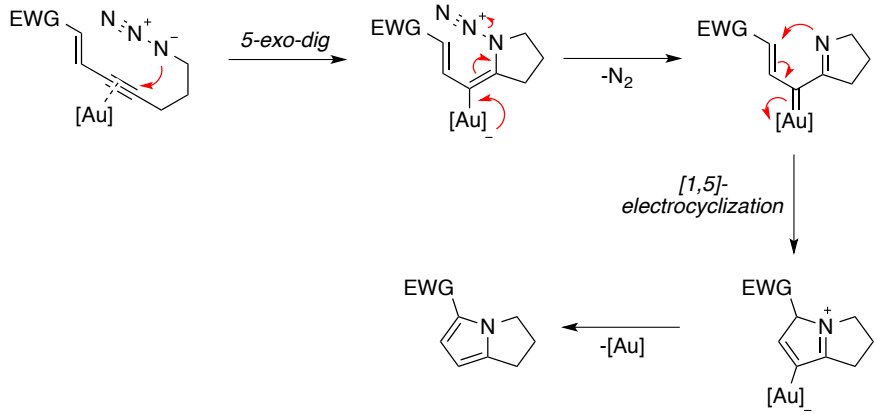
A proposed mechanistic rationale for the formation of the 2,3-fused pyrrole is provided in Scheme 3.3.4. The heating of triazole **I** in the presence of the dirhodium catalyst generates the rhodium-stabilized imino carbene-intermediate **II** *via* ring-chain isomerization and nitrogen extrusion. The imino metallocarbene-intermediate has to adopt an *s-trans* geometry, which then participates in a 4π electrocyclization to form the pyrrolylium cation **III**.[147,148] Proton elimination with aromatization gives pyrrole **IV**. Termination by a unique protonation of the vinyl rhodium species would give the product **V** and complete the catalytic cycle. An alternative possible mechanism for the conversion of **III** to **V** would be two sequential 1,5-*H* shifts followed by Rh release.

Zhang recently proposed a similar mechanism in a gold-catalyzed synthesis of 2,3-dihydro-1*H*-pyrrolizines.[149] In their work, they are able to generate an α-imino gold

carbene that undergoes a 4π electrocyclic ring closure to afford the desired 2,3-dihydro-1*H*-pyrrolizine with an electron-withdrawing group at its 5-position (Scheme 3.3.5). It was noted that the transformation was possible due to the weak back-bonding of gold in which the conjugated cation, the resonance form of the gold carbene, was doubly destablized by the imine moiety and the electron-withdrawing group.



Scheme 3.3.4: Proposed mechanism for pyrrole formation from alkenyl *N*-sulfonyl triazoles.

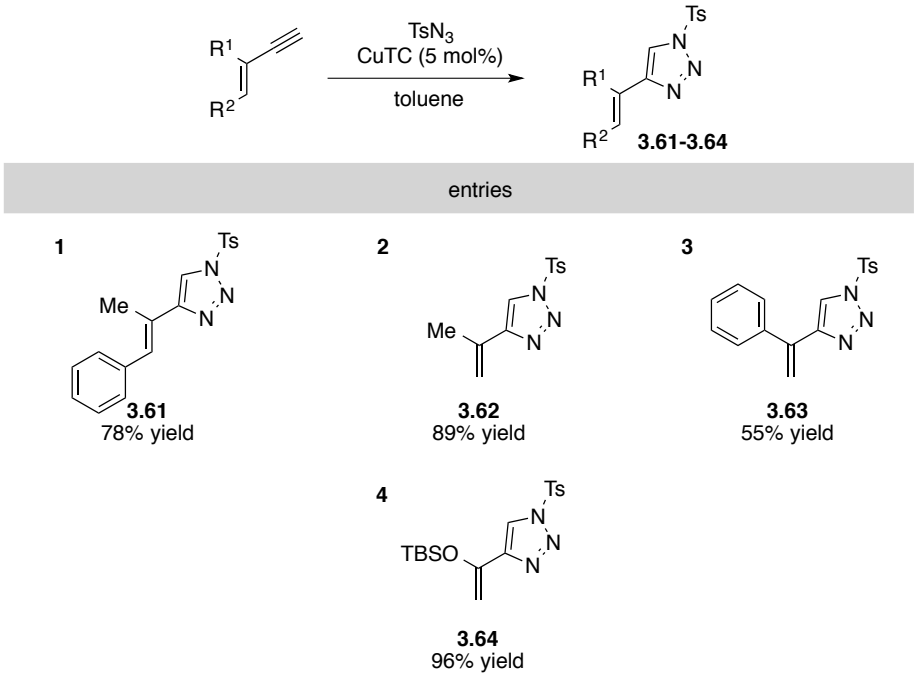


Scheme 3.3.5: Zhang's proposed mechanism for pyrrole formation under gold catalysis.

3.3.3 Acyclic pyrrole synthesis

Following the successful studies for the formation of 2,3-fused pyrroles and substituted indoles from cyclic alkenyl *N*-sulfonyl triazoles, our attention turned towards the feasibility of acyclic alkenyl *N*-sulfonyl triazoles. Similar to the previous cyclic enynes, the vinyl triflates could be obtained from the corresponding ketones that then were subjected to a palladium catalyzed coupling with ethynylmagnesium bromide. The resulting acyclic enyne was then treated with TsN_3 in the presence of CuTC to furnish the desired triazoles in moderate to high yield as depicted in Table 3.3.5.

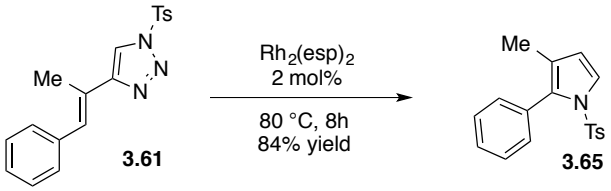
Table 3.3.5: Synthesis of acyclic 4-alkenyl *N*-tosyltriazoles.



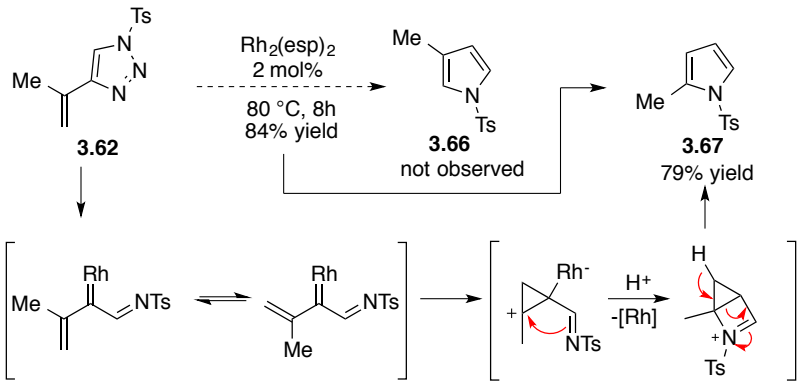
Enyne (1.0 equiv) and TsN_3 (1 equiv); Isolated yields.

A preliminary reaction was conducted with 4-*E*-phenylpropenyl *N*-tosyltriazole **3.61** in the presence of $Rh_2(esp)_2$. The reaction proved to be sluggish with 1 mol% of

$Rh_2(esp)_2$ at 60 °C, so the catalyst loading was increased to 2 mol% and the temperature increased to 80 °C. To our delight, the reaction furnished the desired pyrrole product in good yield. The observed regiochemistry was verified with related characterization data in the literature.[150] However, when the reaction was extended to the isopropenyl derivative **3.62**, a pyrrole product of opposite regiochemistry was observed. The 2-methylpyrrole (**3.67**) must arise *via* a different reaction pathway presumably through a cyclopropyl intermediate x followed by a ring closure/expansion. An azirine intermediate cannot be ruled out at this time.[151] An attempt was made to extend this reaction to *N*-sulfonyl triazole derivatives **3.63** and **3.64**, but both failed to give a pyrrole product.



Scheme 3.3.6: Reaction of 4-*E*-phenylpropenyl *N*-tosyltriazole.



Scheme 3.3.7: Reaction of 4-isopropenyl *N*-tosyltriazole.

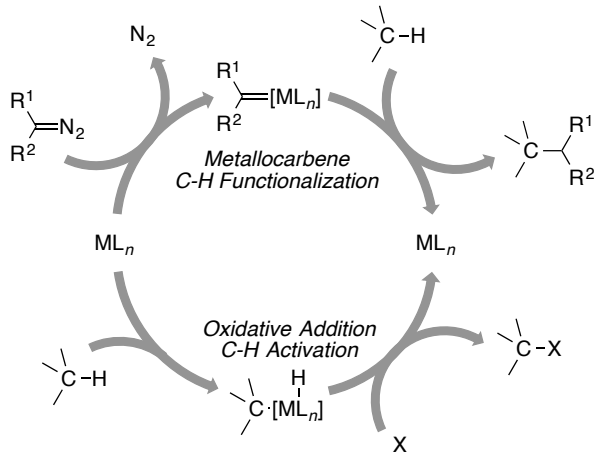
3.4 Summary

In summary, we have developed a highly effective synthesis of 2,3-fused pyrroles from readily available starting materials *via* an intramolecular rhodium-catalyzed cyclization of 4-alkenyl-1-sulfonyl-1,2,3-triazoles. This reaction was further extended to a one-pot synthesis of indoles using a procedure starting from cyclic enynes. The substrate scope of this transformation is broad and the products are formed under mild reaction conditions, which has enabled this methodology to be further extended to more complex frameworks. The full potential of 4-alkenyl *N*-sulfonyl triazoles has not been realized and further studies are currently underway in the Davies laboratory.

Chapter IV: C–H Functionalization of Tertiary C–H Bonds with *N*-Sulfonyl Triazoles

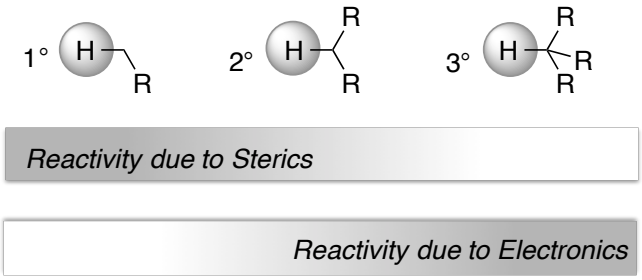
4.1 Introduction

The metal-catalyzed selective functionalization of C–H bonds is an area of intense research. This chemistry greatly allows for a more streamlined synthesis, as other functional groups that serve as reactive partners are no longer needed. Two distinct approaches have been developed to achieve such an outcome. The most widely used has been the insertion of a metal complex into a C–H bond, often considered the more traditional mode of C–H activation, followed by a subsequent transformation to generate synthetically useful products.[152,153,154] An alternative approach has been to insert a metallocarbene or metallonitrene intermediates into the C–H bond, directly leading to the C–H functionalized product.[155,156]



Scheme 4.1.1: Strategies for C–H functionalization.

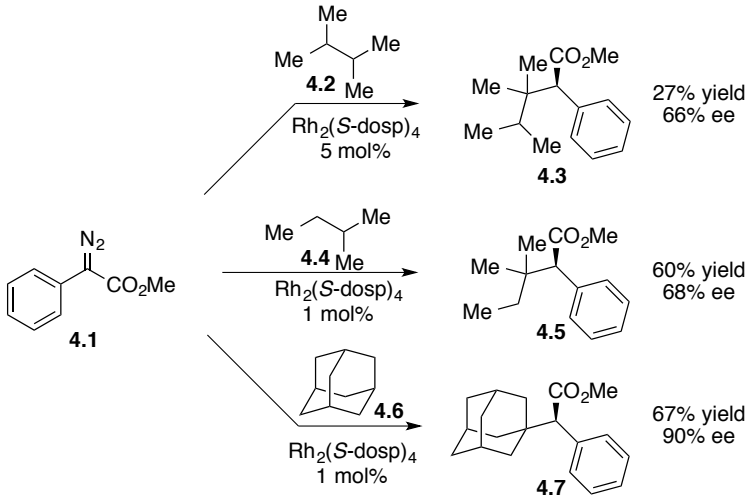
One of the major challenges in C–H functionalization chemistry is achieving site selective reactions.[157] Site selectivity is a delicate balance of steric and electronic effects as seen in Figure 4.1.1. From an electronic perspective, the ability to stabilize the build-up of positive charge during the C–H insertion step is favored, 3° > 2° > 1°, thus favoring a tertiary site; however, depending on the steric requirements of metallocarbene, the reactivity can be reversed favoring a primary site and reversal of the trend 1° > 2° > 3°. Substrates that can stabilize the build-up of positive charge, such as protected heteroatoms and π-systems, are significantly more "activated."[158,159] However, care must be taken to make sure the heteroatoms are non-nucleophilic, as X–H insertion is a much more favorable process, and the π-systems are sterically protected from cyclopropanation.



Scheme 4.1.2: Subtle effects of C–H bonds.

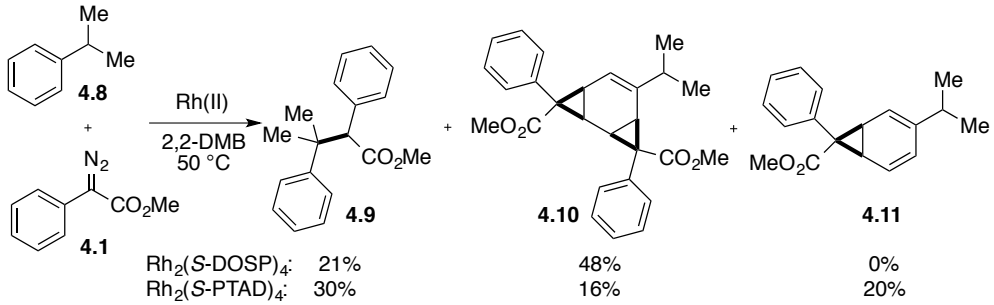
Rhodium(II)-bound metallocarbenes derived from diazoacetates have been found to be significantly more sensitive to steric considerations than the comparable acceptor and acceptor/acceptor metallocarbenes. Although tertiary C–H bonds are electronically activated, the rhodium(II)-ketocarbene is sterically demanding, and functionalization is usually preferred at secondary C–H bonds. Only a few examples of functionalization of

tertiary C–H bonds with diazoacetates are known.[160,161] The three most significant substrates are 2,3-dimethylbutane (**4.2**), 2-methylbutane (**4.4**), and adamantine (**4.6**).



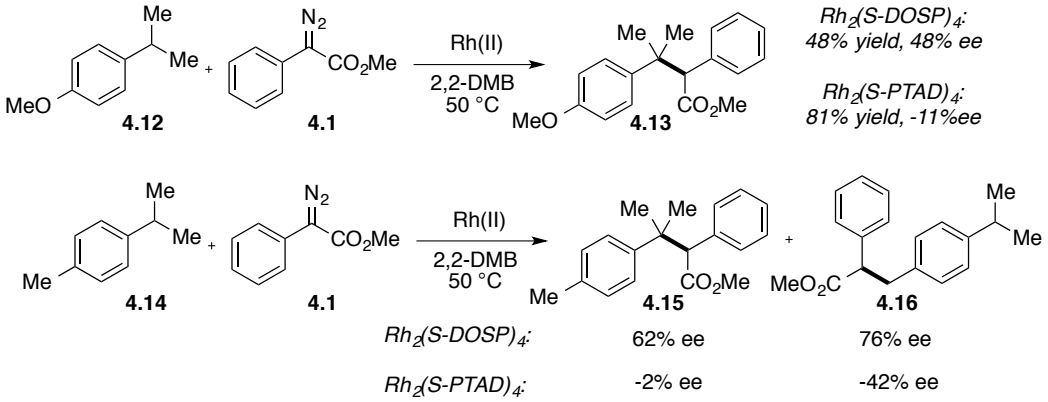
Scheme 4.1.3: Tertiary C–H functionalization with rhodium(II)-bound metallocarbenes.

More recently, Davies and co-workers examined benzylic tertiary C–H bonds for C–H functionalization.[161] In the first system, isopropylbenzene (**4.8**) was examined. Due to the benzene ring not being sterically protected, mono- (**4.11**) and dicyclopropanation (**4.10**) of the benzene ring were formed as the major products with both Rh_2(*S*-dosp)$_4$ and Rh_2(*S*-ptad)$_4$ catalysts. A minor C–H insertion product (**4.9**) was formed, but asymmetric induction was very low in both cases (<10% ee).



Scheme 4.1.4: Examination of isopropylbenzene.

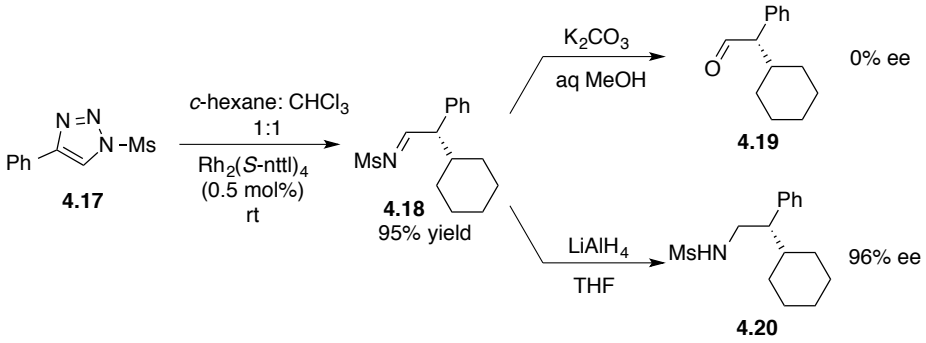
In a second system, they sterically blocked the benzene ring with a 1,4-substitution with *p*-isopropylanisole (**4.12**) and *p*-isopropyltoluene (**4.14**). The reactions with *p*-isopropylanisole gave reasonable yields of the tertiary C–H insertion product (**4.13**) with Rh_2(*S*-dosp)$_4$ having the highest asymmetric induction (48%). The reactions with *p*-isopropyltoluene (**4.14**) gave a mixture of the tertiary and primary C–H insertion products (**4.15** and **4.16**) with both Rh_2(*S*-dosp)$_4$ (2:1; 50% yield) and Rh_2(*S*-ptad)$_4$ (4:1; 57% yield).



Scheme 4.1.5: Examination of 1,4-disubstituted isopropylbenzene derivatives.

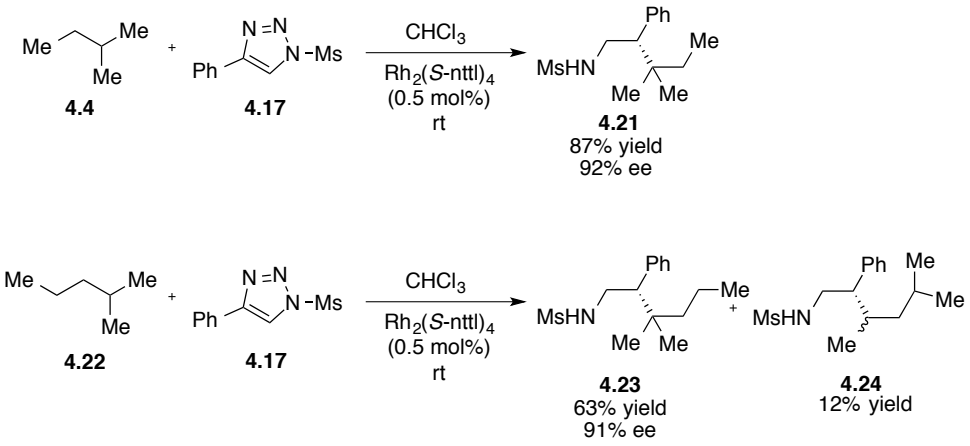
In the summer of 2011, Fokin and co-workers demonstrated that rhodium(II) imino carbenes derived from *N*-sulfonyl triazoles could undergo an enantioselective C–H insertion into unactivated alkanes to furnish a variety of chiral *N*-sulfonylamines in good yield and high enantioselectivity.[162] This C–H insertion reaction tolerated both electron-withdrawing and electron-donating aryl groups on the triazole as well as different sulfonyl groups at the N-1 position. There was an interesting catalyst effect when the size of the sulfonyl group was change. When the sulfonyl group was a mesyl, the optimal catalyst was Rh_2(*S*-nttl)$_4$, and with larger aryl sulfonyl groups, Rh_2(*S*-ptad)$_4$ proved to

optimal. However, when hydrolysis of the enriched sulfonyl imine (**4.18**) was attempted, the corresponding carbaldehyde (**4.19**) was formed as a racemic mixture, presumably through epimerization of the acidic hydrogen at the stereocenter. To solve this issue, the crude sulfonyl imine was treated with lithium aluminum hydride *in situ* to furnish the sulfonyl-protected amine (**4.20**) with high enantioselectivity.

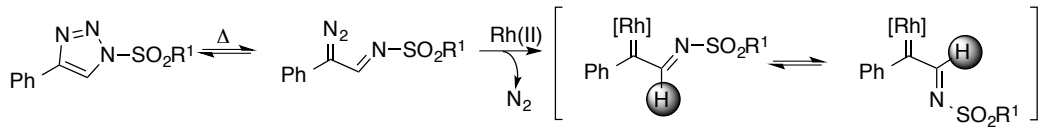


Scheme 4.1.6: C–H insertion with *N*-sulfonyl triazoles.

Intriguingly, the imino metallocarbene has a higher chemoselectivity towards insertion into tertiary C–H bonds over secondary C–H bonds as compared to diazoacetates.[163] When the reaction was conducted with 2-methylbutane (**4.4**), the tertiary C–H insertion went in good yield (**4.21**, 87%) and very high asymmetric induction (92% ee). Furthermore, reaction with the related 2-methylpentane (**4.22**) produced a mixture of products with remarkably high (5:1) selectivity toward insertion into the tertiary C–H bond furnishing the functionalized product in moderate yield (**4.23**, 63%) and very high asymmetric induction (91% ee). The change in chemoselectivity towards tertiary C–H bonds is attributed to the lower steric demand of the sulfonyl imine group compared to the ester group of the diazoacetate.

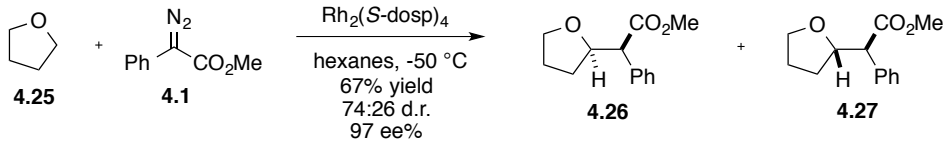


Scheme 4.1.7: Chemoselectivity switch with *N*-sulfonyl triazoles.



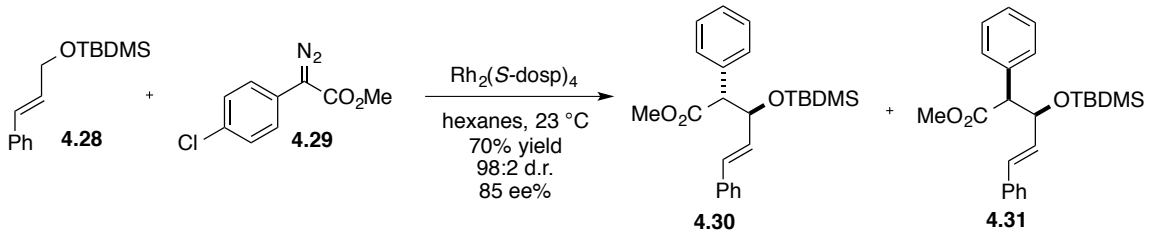
Scheme 4.1.8: Lower steric demand of the sulfonyl imine group.

Traditionally, positions α to oxygen undergo facile C–H functionalization. This system benefits from two factors, the activating nature/charge stabilization of the oxygen atom, and provides access to oxygen-containing products.[160] The intermolecular C–H insertion of aryldiazoacetates adjacent to oxygen in tetrahydrofurans (**4.25**) in the presence of Rh_2(*S*-dosp)$_4$ furnished C–H products (**4.26** and **4.27**) in good yields with excellent levels of enantioselectivity, albeit with modest diastereoselectivies. It is presumed that an oxonium ylide forms as the cyclic ether interacts with the keto-metallocarbene, but the reaction pathway is reversible, and the C–H insertion pathway eventually dominants.



Scheme 4.1.9: C–H insertion into THF with diazoacetates.

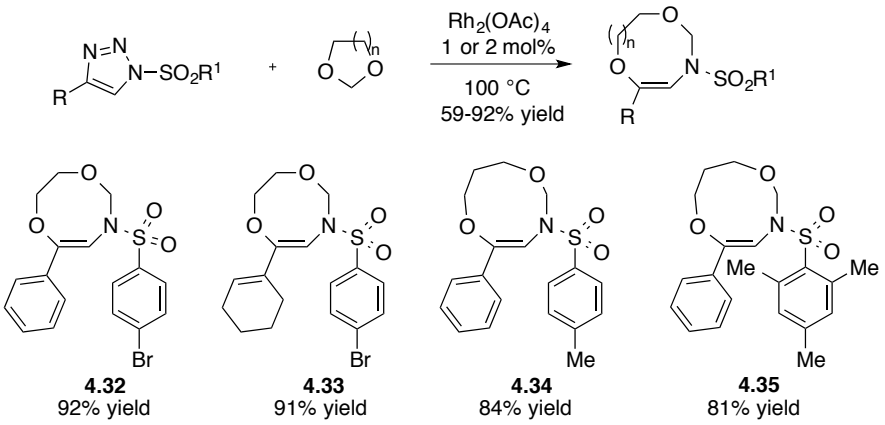
The reaction can be extended to allylic silyl ethers, which benefit from a double activation effect of the allyl and siloxy group, to afford C–H functionalized products in high yields and impressive diastereoselectivities.[164] These substrates demonstrate how subtle electronic effects imparted by the oxygen protecting group and adjacent carbons can influence the reactivity. The use of an electron-withdrawing group such as an acetoxy group deactivates this C–H bond. Furthermore, C–H bonds that are beta to an oxygen heteroatom are deactivated toward C–H functionalization.



Scheme 4.1.10: C–H insertion into allylic ethers with diazoacetates.

In contrast, when *N*-sulfonyl triazoles are reacted with cyclic ethers, medium sized rings containing both oxygen and nitrogen functionality are produced rather than a C–H functionalized products. Lacour and co-workers recently disclosed the reaction of *N*-sulfonyl triazoles with 1,3-dioxolane and 1,3-dioxane to give an 8-member and 9-member dioxazocines (**4.32**-**4.35**), respectively.[165] The reaction involves the formation of an oxonium ylide with one of the oxygen atoms, while the other oxygen atom provokes an opening of the acetal ring leading to a favored 8- or 9-*endo*-*trig* cyclization reaction.

Unlike reactions with diazoacetates, in the presence of the weakly nucleophilic sulfonyl imine, the oxonium ylide does not appear to be a reversible reaction. *This reaction demonstrates a fundamental difference between the keto-carbene and the imino-carbene*.



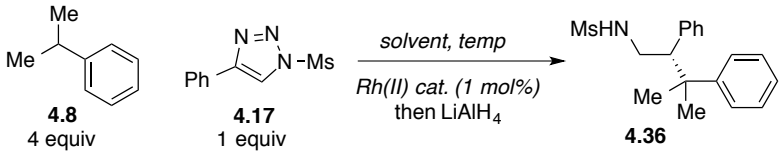
Scheme 4.1.11: Ring expansion of cyclic ethers with *N*-sulfonyl triazoles.

4.2 Preliminary Results

We hypothesized the use of the less sterically demanding imino-metallocarbene could allow for the selective C–H functionalization of tertiary C–H bonds. The reaction of 4-phenyl-*N*-mesyltriazole (**4.17**) with isopropylbenzene (**4.8**) was used for the initial evaluation because this substrate has preformed very poorly in the past (Table 4.2.1). When the established catalyst Rh_2(*S*-nttl)$_4$ was used in chlorinated solvents, the reaction resulted moderate yield of the C–H functionalized product (**4.36**) in moderate enantioselectivity at room temperature. This was a significant advance over of the corresponding keto-metallocarbene reaction.[161] Further examination revealed that the adamantane derivative Rh_2(*S*-ntad)$_4$ gave the highest level of enantioselectivity, generating the product in 76% ee, albeit in slightly lower yield. The use of a non-polar

solvent such as DMB resulted in a poorly performing reaction with less than 10% yield of the C–H functionalized product.

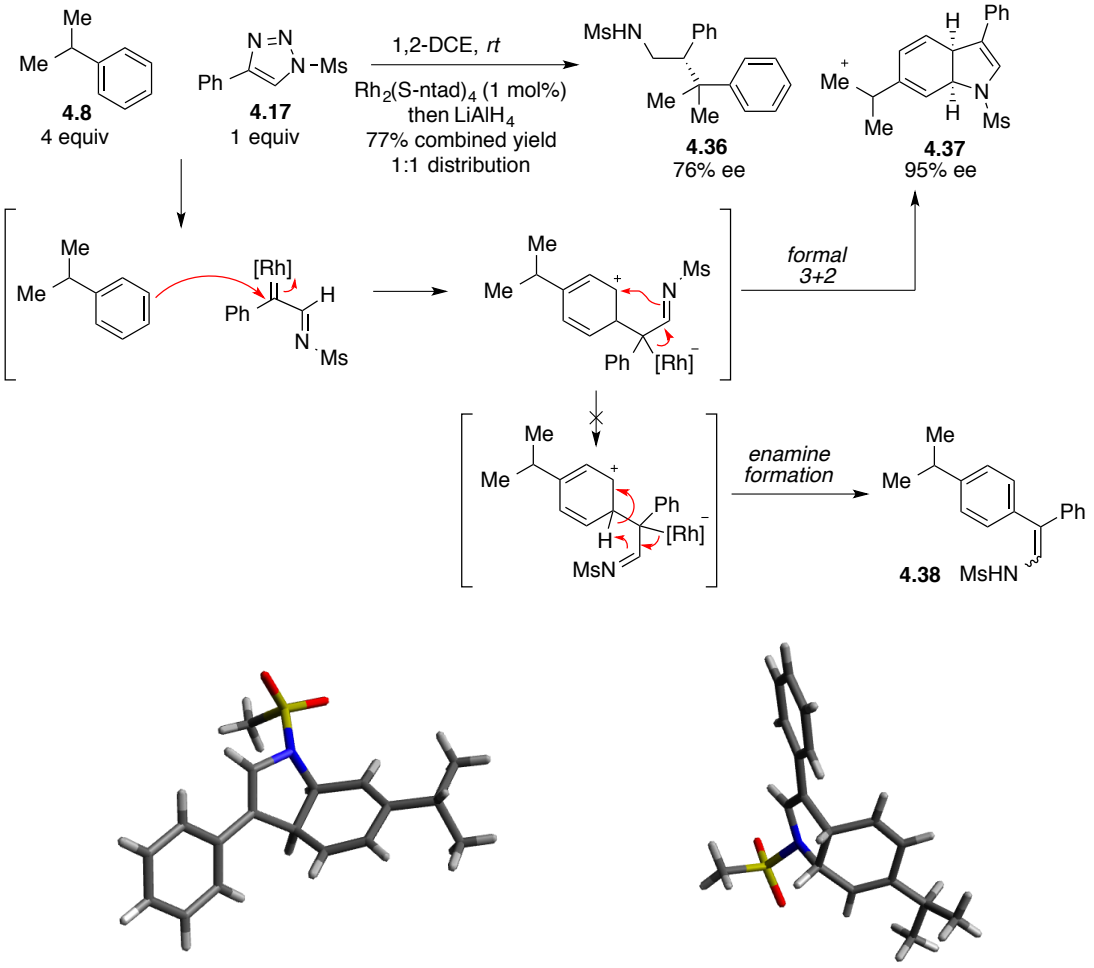
Table 4.2.1: Initial evaluation of isopropylbenzene.



entry	Rh(II) cat.	solvent	temp	time	% yield	% ee
1	Rh_2(*S*-dosp)$_4$	$CHCl_3$	40	72	<10	n/a
2	Rh_2(*S*-ptad)$_4$	$CHCl_3$	rt	24	<10	n/a
3	Rh_2(*S*-nttl)$_4$	$CHCl_3$	rt	12	66	65
4	Rh_2(*S*-nttl)$_4$	1,2-DCE	rt	16	58	69
5	Rh_2(*S*-nttl)$_4$	DMB	rt	16	<10	n/a
6	Rh_2(*S*-ntv)$_4$	1,2-DCE	rt	16	39	34
7	Rh_2(*S*-ntad)$_4$	1,2-DCE	rt	24	41	76

During the evaluation of isopropylbenzene, an unusual by-product (**4.37**) was isolated in varying yields during the course of the reaction, with reactions in 1,2-DCE favoring this product. The characterization data was most consistent with a formal [3+2] product and was later confirmed by x-ray analysis. The product (**4.37**) was derived by an intermolecular annulation of the benzene ring rather than enamine formation as depicted in Scheme 4.2.4. This annulation either occurred *via* (1) a direct attack of the metallocarbene by the isopropylbenzene at the C(4) position followed by subsequent cyclization, or (2) cyclopropanation of the isopropylbenzene followed by a Cloke-Wilson rearrangement; both pathways feature a highly stabilized allylic carbocation. In the reaction with Rh_2(*S*-ntad)$_4$, this product was isolated in 36% yield with a very high level of asymmetric induction (95% ee). The stereochemical rationale for this transformation

can be seen in Figure 4.2.1 in which the isopropylbenzene approaches the metallocarbene from the front.



Scheme 4.2.1: Unusual by-product with isopropylbenzene.

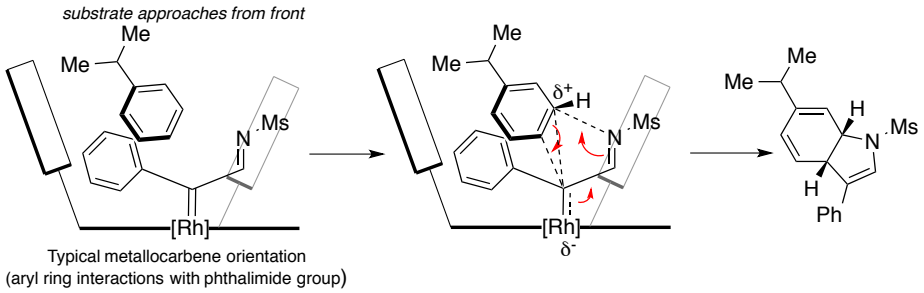
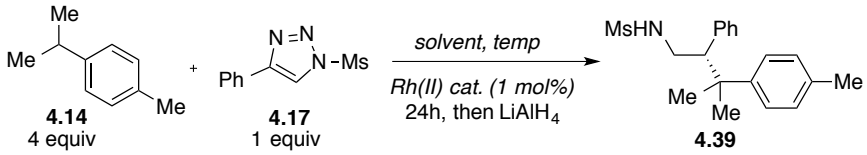


Figure 4.2.1: Stereochemical rationale using the Rh_2(*S*-pttl)$_4$ model.

With the formation of the formal [3+2] product, the sterically blocked *p*-isopropyltoluene (**4.14**) was evaluated with 4-phenyl-*N*-mesyltriazole (**4.17**). When the established catalyst Rh_2(*S*-nttl)$_4$ was used in chlorinated solvents, the reaction resulted moderate yield of both the primary and tertiary C–H functionalized products, favoring the tertiary product (**4.39**) in moderate enantioselectivity at room temperature (Table 4.2.2). 1,2-Dichloromethane gave a higher enantioinduction compared to chloroform. Examination of related catalysts lead to a decreased in enantioinduction, but similar site selectivity. The tertiary product (**4.39**) could be separated from the primary insertion product *via* chromatography.

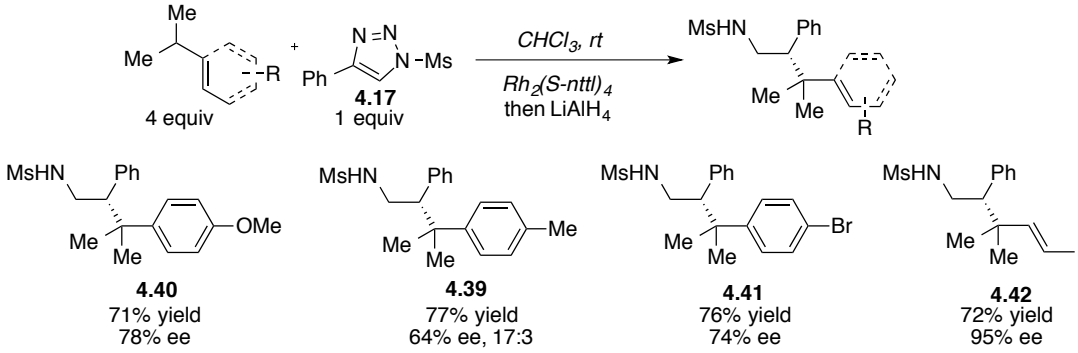
Table 4.2.2: Evaluation of *p*-isopropyltoluene.



entry	Rh(II) cat.	solvent	temp	3°:1°	% yield 3°	% ee
1	Rh_2(*S*-nttl)$_4$	1,2-DCE	rt	85:15	75	70
2	Rh_2(*S*-nttl)$_4$	$CHCl_3$	rt	83:17	77	64
3[a]	Rh_2(*S*-nttl)$_4$	$CHCl_3$	rt	83:17	69	66
4	Rh_2(*S*-nttl)$_4$	DMB	50	n/a	0	n/a
5	Rh_2(*S*-ntv)$_4$	1,2-DCE	rt	83:17	64	62
6	Rh_2(*S*-ntad)$_4$	1,2-DCE	rt	78:22	70	66
7	Rh_2(*S*-4-Cl-nttl)$_4$	1,2-DCE	rt	n/a	0	n/a
8	Rh_2(*S*-ptad)$_4$	1,2-DCE	45	81:19	18	68
9	Rh_2(*S*-pttl)$_4$	1,2-DCE	45	82:18	20	55
10	Rh_2(*S*-tcpttl)$_4$	1,2-DCE	45	80:20	28	43

Further investigation of the reaction revealed a variety of tertiary substrates are compatible with the reaction (Scheme 4.2.2). A 1,4-substitution of the aryl ring was tolerated, providing products with higher levels of asymmetric induction than the parent

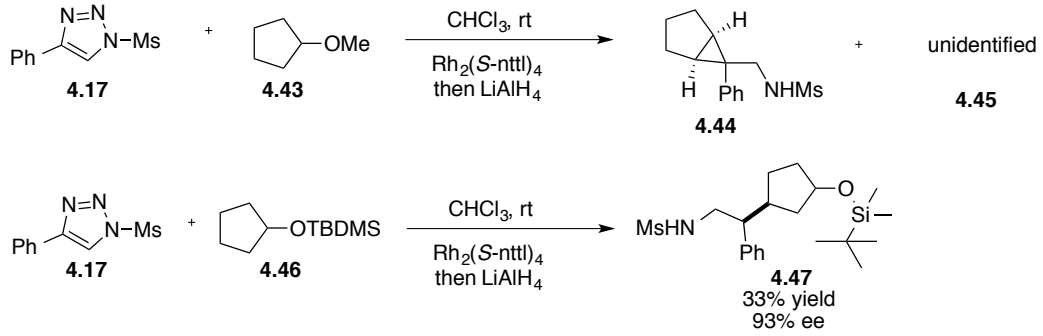
isopropylbenzene reaction. The reaction of *p*-isopropylanisole provided the functionalized product (**4.40**) in 71% yield with 78% ee and *p*-isopropylbromobenzene provided the functionalized product (**4.41**) in 76% yield and 74% ee. *Trans*-4-methyl-2-pentene also afforded a higher performing reaction with higher levels of asymmetric induction. This is most likely due to a better differentiation of the groups on the tertiary carbon; *i.e.* the allyl group is more sterically (larger) demanding compared to the aryl group. Further substrate scoop will reveal a fairly general reaction.



Scheme 4.2.2: Examination of other tertiary sites.

Continued investigation lead to the examination of 1-methoxycyclopentane (**4.43**). The reaction of 4-phenyl-*N*-mesyltriazole with 1-methoxycyclopentane (**4.43**) in the presence of Rh_2(*S*-nttl)$_4$ resulted in the formation of a mixture of products, with a cyclopropanation product (**4.44**; confirmed by x-ray) and an unidentified product (**4.45**) being the major products. The cyclopropane product presumably arises from ylide formation/proton abstraction to provide cyclopentene, which thenis cyclopropanated. Changing the size of the ether group lead to the reaction of 4-phenyl-*N*-mesyltriazole (**4.17**) with TBDMS protected cyclopentanol (**4.46**) in the presence of Rh_2(*S*-nttl)$_4$. This resulted in the formation of a single product (**4.47**) in moderate yield (33%) with a high

level of asymmetric induction (93% ee). 2D-NMR indicated the reaction happened at the C(3) position of the cyclopentanol ring.



Scheme 4.2.3: Examination of tertiary ethers.

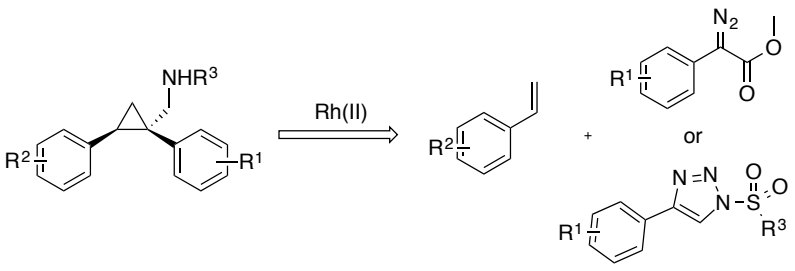
4.3 Conclusion

Preliminary results have demonstrated that the use of *N*-sulfonyl triazoles as a method for reliable tertiary C–H functionalization resulting in functionalized products with moderate to high levels of enantioinduction. The results are very exciting and possibly open the door for new chemistries. It was been shown the imino metallocarbene reactivity profile favors C–H functionalization at lower temperatures and with the appropriate catalyst. There are many considerations for the proposed chemistry that must be further explored; computational and predictive modeling will give more insight into this reaction along with a proper reaction development for predictive reaction conditions based on substrate.

Chapter V: The Study of Rh_2(*S*-ptad)$_4$ with Various Substituted Methyl Phenyldiazoacetates.

5.1 Introduction

The metal-catalyzed decomposition of diazo compounds in the presence of olefins is a general strategy for the stereoselective synthesis of cyclopropanes as outlined in Chapter 1. The Davies group has previously demonstrated highly enantioselective syntheses of cyclopropyl derivatives containing one or more quaternary stereogenic centers *via* a rhodium(II)-catalyzed cyclopropanation of donor/acceptor metallocarbenes. As many cyclopropyl amines are known to have significant CNS activity (Chapter 6), a study was initiated with the goal of a broadly applicable, robust, and highly enantioselective synthetic method for the generation of a wide range of diarylcyclopropyl carboxylates.



Scheme 5.1.1: Route to cyclopropylamines.

The prolinate derived rhodium catalyst, $Rh_2(dosp)_4$, has been the traditional catalyst used with methyl aryldiazoacetates in cyclopropanations providing cyclopropylaceates in good to high yields with excellent diastereo- and enantioselectivity (depicted in Chapter 2; Figure 2.4.1). However, the catalyst has a few limitations: (1) the larger ester groups cause a drop in selectivity; (2) it is very temperature dependent; *i.e.* there is a considerable increase in selectivity when the reaction is cooled to -78 °C as compared to running the reaction at room temperature; (3) significant solvent effect as a *non*-polar hydrocarbon solvent must be used for the best asymmetric induction.

The phthalimido-derived catalyst, $Rh_2(ptad)_4$, has been shown not to suffer from these limitations (depicted in Chapter 2; Figure 2.4.1). When the temperature the temperature is changed from -60 °C to room temperature, there is only a slight drop in selectivity. It has also been shown that altering the acceptor group can have a profound effect in the level of selectivity in asymmetric cyclopropanation with $Rh_2(dosp)_4$, but $Rh_2(ptad)_4$ is unaffected by this alteration.

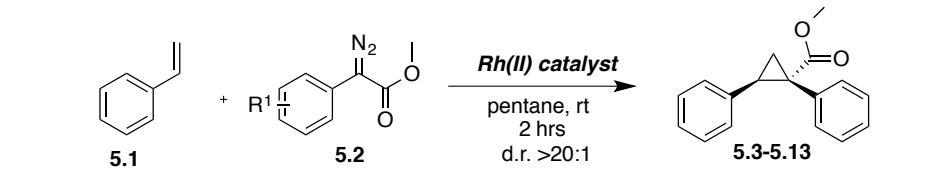
5.2 Results and Discussion

The purpose of the study was to explore the reactivity and selectivity of the adamantyl catalyst Rh_2(*S*-ptad)$_4$ and compare its' reactivity and selective ity to the traditional rhodium catalyst Rh_2(*R*-dosp)$_4$ with substituted methyl aryldiazoacetates in asymmetric cyclopropanation reactions. The study began by exploring the effect of aryl substitution on the enantioselectivity in the cyclopropanation of styrene by methyl aryldiazoacetates. The typical conditions that were employed included: 5 equivalents of styrene (served as the alkene and trapping agent), 1 equivalent of the substituted methyl

aryldiazoacetate, 0.005 equivalent of Rh_2(*S*-ptad)$_4$ or 0.01 equivalent of Rh_2(*R*-DOSP)$_4$, and pentane as the solvent.

The results for a series of methyl aryldiazoacetates using the two chiral rhodium(II) catalysts are summarized in Table 5.2.1. Excellent levels of diastereoselectivity were achieved in all cases (>95:5) and the isolated yields of the diarylcyclopropanes were generally high, ranging from 57-93%. The absolute configuration of the major isomer of the cyclopropanes is tentatively assigned as 1*S*,2*R*. Generally, Rh_2(*R*-dosp)$_4$ provided high levels of enantioinduction when 4-substituted methyl aryldiazoacetates were employed as substrates (**5.3**-**5.8, 5.12, 5.13;** 79-90% ee). For comparison, Rh_2(*S*-ptad)$_4$-catalyzed reactions gave <77% ee for same 4-substituted methyl aryldiazoacetates, with the exception of entry 1, with gave the cyclopropane **5.3** in exceptionally high enantioselectivity (96% ee). The Rh_2(*R*-dosp)$_4$ catalyst also performed well in the reactions of 2-substituted methyl aryldiazoacetates (**5.10** and **5.11**; entries 8-9). Overall, the asymmetric induction with Rh_2(*S*-ptad)$_4$ was variable. Most likely, the aryl group in some of the methyl aryldiazoacetates is too large and an interaction with the ligand wall of the catalyst occurs forcing it to adopt a different orientation causing some of the other enantiomer to form.

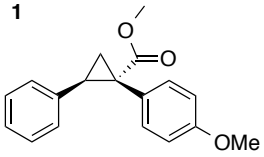
Table 5.2.1: Examination of the influence of substitution of methyl aryldiazoacetates.



5.1 **5.2** **5.3-5.13**

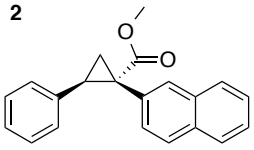
entries

1



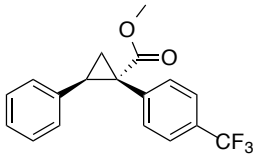
5.3
Rh_2(*S*-ptad)$_4$: 93%, 96% ee
Rh_2(*R*-dosp)$_4$: 66%, 90% ee

2



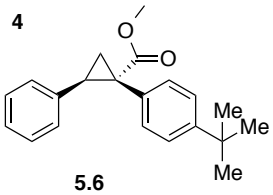
5.4
Rh_2(*S*-ptad)$_4$: 72%, 46% ee
Rh_2(*R*-dosp)$_4$: 68%, 79% ee

3



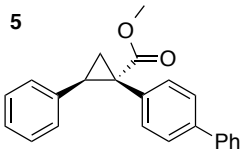
5.5
Rh_2(*S*-ptad)$_4$: 67%, 77% ee
Rh_2(*R*-dosp)$_4$: 93%, 87% ee

4



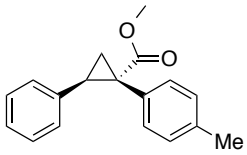
5.6
Rh_2(*S*-ptad)$_4$: 70%, 76% ee
Rh_2(*R*-dosp)$_4$: 77%, 90% ee

5



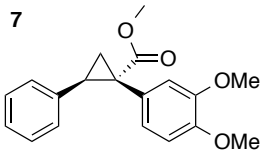
5.7
Rh_2(*S*-ptad)$_4$: 49%, 18% ee
Rh_2(*R*-dosp)$_4$: 57%, 72% ee

6



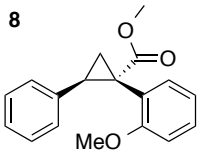
5.8
Rh_2(*S*-ptad)$_4$: 77%, 46% ee
Rh_2(*R*-dosp)$_4$: 84%, 87% ee

7



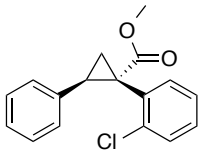
5.9
Rh_2(*S*-ptad)$_4$: 70%, 94% ee
Rh_2(*R*-dosp)$_4$: 74%, 56% ee

8



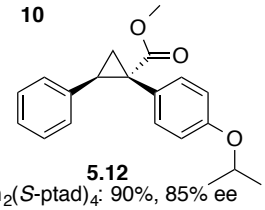
5.10
Rh_2(*S*-ptad)$_4$: 87%, 80% ee
Rh_2(*R*-dosp)$_4$: 92%, 86% ee

9



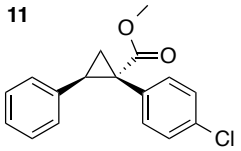
5.11
Rh_2(*S*-ptad)$_4$: 80%, 97% ee
Rh_2(*R*-dosp)$_4$: 89%, 92% ee

10



5.12
Rh_2(*S*-ptad)$_4$: 90%, 85% ee
Rh_2(*R*-dosp)$_4$: 78%, 86% ee

11



5.13
Rh_2(*S*-ptad)$_4$: 71%, 48% ee
Rh_2(*R*-dosp)$_4$: 87%, 88% ee

5.3 Conclusion

These studies reveal the subtle differences in the ability of the chiral rhodium(II) tetracarboxylate catalysts to induce high levels of enantioselectivity in the

cyclopropanation of styrenes. The Rh_2(*R*-dosp)$_4$ catalyst was found to be the most effective catalyst for the broadest range of substituted methyl aryldiazoacetates. In spite of the fact that the Rh_2(*S*-ptad)$_4$ catalyst is the most consistent when the acceptor group of the donor/acceptor metallocarbene is modified, the level of enantioselectivity was found to be highly variable when aryl substitution of the methyl aryldiazoacetate was modified. It is not clear whether it is a steric or electronic factor that dictates the asymmetric induction with the Rh_2(*S*-ptad)$_4$ catalyst.

Chapter VI: Efforts Towards The Design and Synthesis of Therapeutic Agents for Cocaine Addiction

6.1 Introduction

Apart from developing novel methodologies, one of the central themes in the Davies group is the application of these "methodologies" to the biological sciences for the rapid construction of potential therapeutic agents. Many pharmaceutically relevant CNS (central nervous system) active compounds have been developed in the Davies group which include: tropane alkaloids with high binding affinities to the dopamine transporter (DAT);[166] Ritalin analogues that were SERT (serotonin transporter) selective;[167] concise synthesis of Venlafaxine which is a SERT/NET inhibitor;[168] duloxetine analogues that were selective SERT/DAT inhibitors;[169] novel class of cyclopropane analogues that were selective serotonin-norepinephrine reuptake inhibitors for treatment of neuropathic pain.[170]

In recent years, a variety of cyclopropylamines have demonstrated significant CNS activity. Mono-aryl cyclopropylamines have been prepared that have broad biological activity from antidepressant to inhibition of monoamine oxidase, but diarylcyclopropylamines have not been previously prepared and tested. One of the mostly widely known mono-aryl cyclopropylamines is the antidepressant Milnacipran (**6.1**), which inhibits uptake of norepinephrine and serotonin at presynaptic sites.[171] Another series of biologically active mono-aryl cyclopropylamines consisting of a 1-phenyl-2-cyclopropylmethylamine core (**6.3**) were developed by Ronsisvalle that have shown

moderate to high affinity at sigma receptor sites.[172] Mattson created a large series of indole cyclopropylmethylamines (**6.2**) that have a high binding affinity for the serotonin receptor, but exhibit little selectivity for any of the subclass receptors.[173] Recently in the Davies group, aryl cyclopropylamines (**6.4**) were shown to be selective serotonin-norepinephrine reuptake inhibitors.

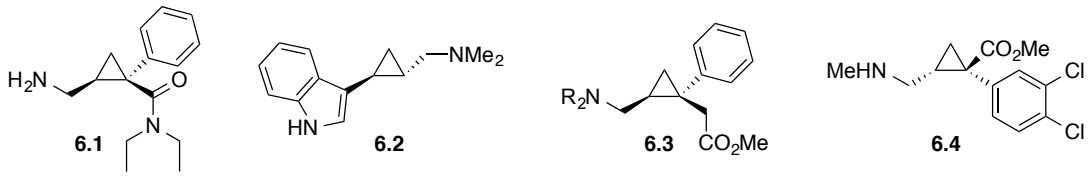


Figure 6.1.1: CNS active cyclopropylamines.

The discovery of a pharmacotherapeutic treatment for cocaine abuse has been a research target that has received much attention in the past decade. Cocaine (**6.5**) is a crystalline tropane alkaloid that is found in nature and can be obtained from the leaves of the coca plant.[174] It is typically found in one of two forms, in its' salt form (hydrochloride or sulfate; water soluble form) or in its' free-base form (otherwise known as crack; insoluble in water). Cocaine is highly addictive, causing one of the major problems in today's society as it carries both a large personal and economic cost. As such, there is a large demand for therapeutic options for cocaine use and addiction. One important therapeutic option is the development of medications that can either decrease the desire for cocaine or block its mode of action. An important step in this direction is the synthesis and study of novel compounds that bind to the same biological sites as cocaine, allowing for a greater understanding of the interactions occurring at the cellular level during after the intake of cocaine, which may lead to effective therapeutic agents.

Cocaine is a nonselective, psychoactive drug that has a high affinity for the dopamine, serotonin, and norepinephrine transporters causing inhibition. The dopamine transporter is prevented from performing its reuptake function, thereby allowing dopamine to accumulate in the synaptic cleft leading to the rewarding effects of cocaine. Most of the work involved with developing therapeutic options for cocaine use and addiction has focused on its interaction with the transporter sites for the three monoamine neurotransmitters: dopamine (**6.6**), norepinephrine (**6.7**), and serotonin (**6.8**) (abbreviated DAT, NET, SERT, respectively).

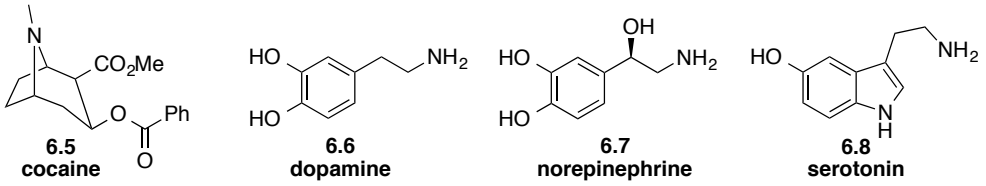
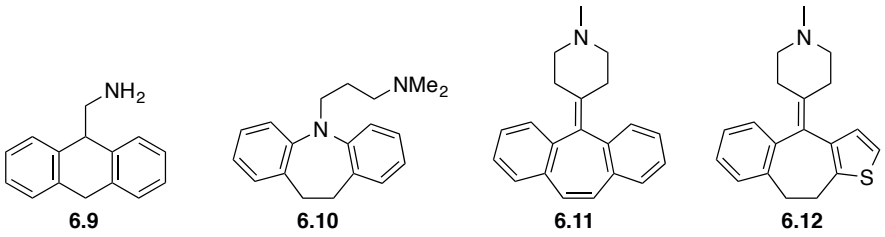


Figure 6.1.2: Cocaine and the monoamine neurotransmitters.

Recently, the 5-hydroxytryptamine (5-HT) class of monoamine neurotransmitters has been a popular target of action for attenuating the cellular and behavioral effects of psychoactive substances.[175] More specifically, there is general agreement that these substances presumably have 5-HT$_{2A}$ receptors as their primary target.[176] McMahon and Cunningham demonstrated that antagonism of the 5-HT$_{2A}$ receptor results in the effective blockade of the hypermotive and discriminative stimulus effects of cocaine.[177] It has also been shown that the blockade of the 5-HT$_{2A}$ receptor with a known antagonist attenuates the cue-evoked reinstatement craving and/or relapse for cocaine.[178] This suggests that the receptor plays an important role in the behavioral effects of cocaine use and the receptor could be a viable target for the therapeutic treatment of cocaine addiction.

Previously designed 5-HT_{2A} receptor ligands have been classified into three main classes: linear, tricyclic, and a general classification that all other compounds with 5-HT_{2A} fall into. We have chosen to focus on the tricyclic class of compounds that feature the general form of two aromatic rings that flank a non-aromatic central ring that has the functionality of an alkyl-amino substituent. A few examples of the tricyclic class would be 9-aminomethyl-9,10-dihydroanthracene (AMDA, **6.9**, K_i = 20 nM), imipramine (**6.10**, K_i = 94 nM), cyproheptadine (**6.11**, K_i = 3 nM), and pizotifen (**6.12**, K_i = 10 nM). This class is remarkably devoid of the pharmacophore features usually associated with high affinity such as multiple heteroatom bonding. Due to the structurally different classes having activity at the 5-HT_{2A}, there is general agreement that there are at least two different modes of antagonist binding at 5-HT_{2A} receptors.



6.9 **6.10** **6.11** **6.12**

Figure 6.1.3: General class of tricyclic analogs.

In recent years, extensive work has been done in determination of a structural activity relationship for the tricyclic class of 5-HT_{2A} antagonists. Westkaemper concluded that the nature of the tricyclic ring system needed to have a substantial symmetrical aromatic fold as compounds with a nearly coplanar or orthogonal orientation have low binding affinities.[179] With this idea, we envisaged the use of arylcyclopropanes to give a similar geometry. The cyclopropyl group orients its' substituents in a very defined

arrangement similar to the tricyclic ring system with the option to have either *cis* or *trans* geometry. This could potentially led to very selective biological activity.

Several pharmacophore models for 5-HT_{2A} receptors have been proposed for the tricyclic class based on the structure-activity relationships of known antagonists. Westkaemper found with AMDA and AMDA-like compounds that the optimal distances between the two aryl rings should be 4.8-4.9 Å, and between the aryl rings and the amine should be 3.8-6.5 Å and 5.2-7.6 Å, respectively, since AMDA is not symmetrical with respect to the two amine-ring distances.[179] Modeling analysis of the lowest energy conformation indicates the overall shape is similar to the previous tricyclic examples and the distance between the two aryl rings is 4.9A.

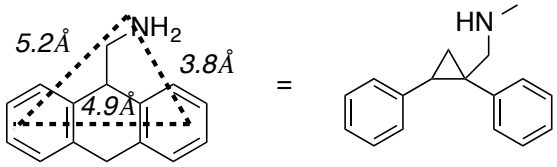


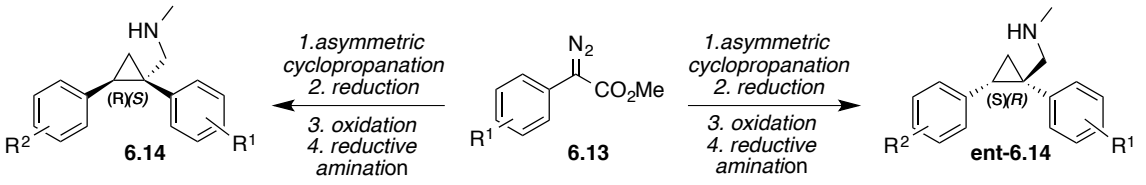
Figure 6.1.4: Pharmacophore model for 5-$HT_{2A.}$

6.2 Results and Discussion

Encouraged by the structural similarity of the diaryl cyclopropylamine to the proposed pharmacophore model, we decided to emark on the design, synthesis, and biological evaluation of novel diaryl cyclopropylamine derivatives with activity at the serotonin 5-HT_{2A} receptor. This would be an excellent showcase of asymmetric cyclopropanation methodology that has been developed in the Davies group. The reaction has excellent regio-, diastereo-, and enatioselective control, and can be routinely performed on a multigram scale. Furthemore, both enantiomers of the commonly employed chiral

rhodium(II) catalysts are available thereby providing access to both enantiomers of the diaryl cyclopropylamine derivatives.

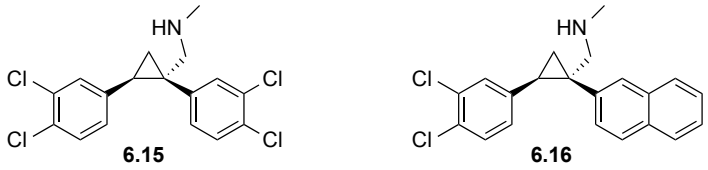
Previously, a small library of diaryl cyclopropylamines was prepared utilizing a four step reaction sequence. The Rh_2(*R*- *or S*-dosp)$_4$ catalyzed reaction of the methyl aryldiazoacetate (**6.13**) with a styrene derivative generated a diaryl cyclopropane in yields ranging from 60-90% and with very high diastereoselectivity (>95%). The typical enantioselectivity of the cyclopropanation conducted at -42 °C is about 90% ee and the cyclopropane can be readily recrystallized to >98% ee. The remaining three steps in the synthesis of a diaryl cyclopropylamine are all standard reactions. Lithium aluminum hydride reduction of the methyl esters generated the primary alcohols, which were subsequently oxidized to the corresponding aldehydes with the use of Dess Martin reagent.[180] Reductive amination of the aldehydes with methylamine in the presence of titanium(IV) isopropoxide with sodium borohydride generated the cyclopropylmethylamines (**6.14** and **ent-6.14**).[181] The amines were then transformed into the corresponding fumarate salt with furamic acid in isopropanol.



Scheme 6.2.1: Diaryl cyclopropylamine synthesis.

These compounds were then tested through the NIDA Addiction Treatment Discovery Program and it was discovered that these compounds were active at the neurotransmitters (SET, NET, and DAT) and at the 5-HT$_{2A}$ receptor. Two compounds in

particular showed very promising results at being very potent at the 5-HT_{2A} receptor as seen in Figure **6.2.1**.



6.15
5-HT_{2A}: 38.2 nM
5-HT_{2C}: 656 nM
HD-225

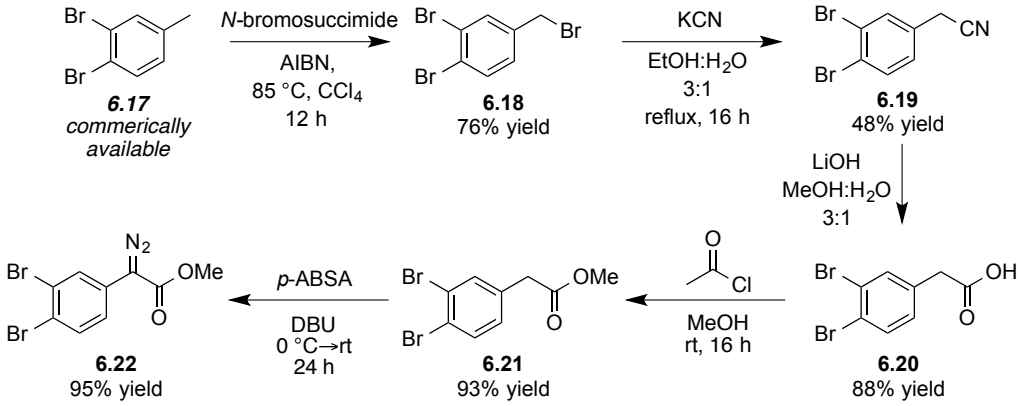
6.16
5-HT_{2A}: 51.3 nM
5-HT_{2C}: 381 nM
HD-253

Figure 6.2.1: Previous *in vitro* pharmacological testing leads.

To probe the stereochemical requirements for 5-HT_{2A} inhibition, enantiomerically pure materials were synthesized from the onset as each enantiomer has the potential to interact differently with the biological environment. It was previously found that the diaryl cyclopropanes with the configuration of (1*S*, 2*R*) were 20-50 fold more active at the serotonin receptors than the opposing (1*R*, 2*S*) enantiomer. Initial screening also found there is a trend based on the substitution of the alkyl amine. A secondary methylamine has higher binding affinities at the 5-HT_{2A} receptor than does tertiary dialkyl amines and tertiary morpholine derivatives. With these preliminary data, our focus then turned to the exploration of the substitution group on the aryl moieties.

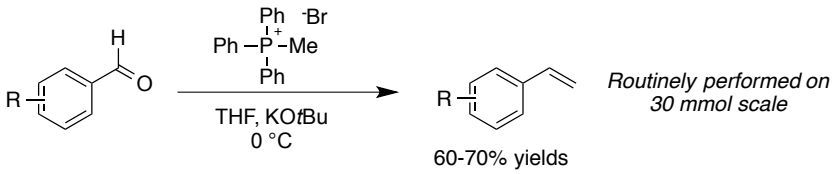
Diversity of the first aryl was introduced by varying the methyl aryldiazoacetate that was being decomposed to produce the electrophilic metallocarbene. Four methyl aryldiazoacetates were chosen to be studied which included 3,4-dibromophenyl, 2-chlorophenyl, 4-biphenyl, and 3-indolyl. The methyl aryldiazoacetates were synthesized by a diazo-transfer reaction with *p*-acetamidobenzenesulfonyl azide[182] (*p*-ABSA) starting from the commercially available methyl arylacetates (Chapter 1) with the exception of

compound (**6.22**). This methyl aryldiazoacetate was previously unknown so a convenient route was employed starting from 3,4-dibromotoluene (**6.17**) as depicted in Scheme 6.2.2. Halogenation of 3,4-dibromotoluene (**6.17**) with NBS and AIBN to gave the halogenoalkane, followed by nucleophilic substitution with cyanide provided the nitrile.[183] Subsequent hydrolysis of the nitrile (**6.19**) under alkaline conditions furnished the phenyl acetic acid (**6.20**) and esterification of the acid with acetyl chloride in methanol provided the ester (**6.21**). A diazo-transfer reaction with *p*-ABSA as previously described furnished the methyl 3,4-dibromophenyldiazoacetate (**6.22**).



Scheme 6.2.2: Synthesis of methyl 3,4-dibromophenyldiazoacetate.

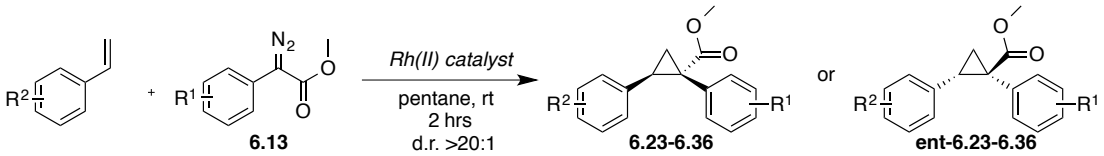
Diversity of the second aryl was introduced by changing the structure of the styrene that was undergoing the cyclopropanation reaction. The substituted styrenes were either obtained directly from commercial sources, or synthesized from the corresponding commercially available benzaldehydes through a Wittig reaction with methyl triphenylphosphonium bromide.



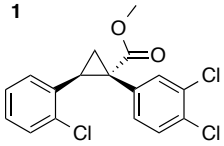
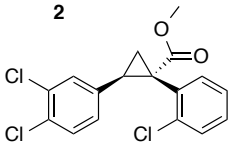
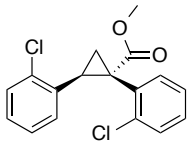
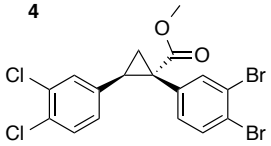
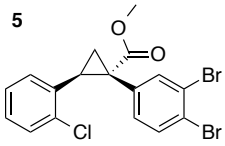
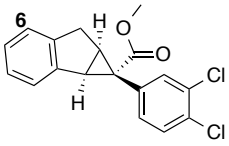
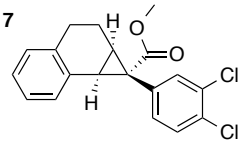
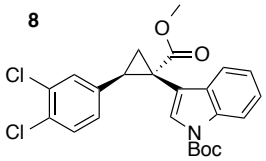
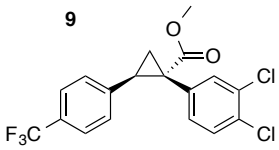
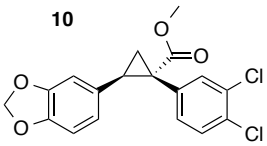
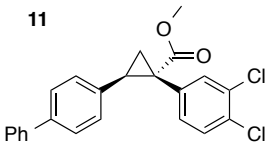
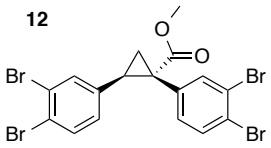
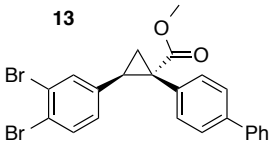
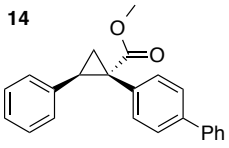
Scheme 6.2.3: Synthesis of substituted styrene derivatives.

The results of the intermolecular cyclopropanation of various styrene derivatives with a methyl aryldiazoacetates catalyzed by Rh_2(*R* and *S*-dosp)$_4$ can be seen in Table 6.2.1. The reaction generated the diarylcyclopropanes in good yields and high enantioselectivities (see Experimental for specific details).

Table 6.2.1: Intermolecular cyclopropanation of styrene derivatives with methyl diazoacetates.



6.13 **6.23-6.36** **ent-6.23-6.36**

entries			
1  Rh_2(*R*-dosp)$_4$: **6.23** 60% yield, 79% ee Rh_2(*S*-dosp)$_4$: **ent-6.23** 59% yield, -67% ee	**2**  Rh_2(*R*-dosp)$_4$: **6.24** 71% yield, 95% ee Rh_2(*S*-dosp)$_4$: **ent-6.24** 73% yield, -96% ee	**3**  Rh_2(*R*-dosp)$_4$: **6.25** 62% yield, 97% ee Rh_2(*S*-dosp)$_4$: **ent-6.25** 64% yield, -97% ee	**4**  Rh_2(*R*-dosp)$_4$: **6.26** 95% yield, 83% ee Rh_2(*S*-dosp)$_4$: **ent-6.26** 86% yield, -86% ee
5  Rh_2(*R*-dosp)$_4$: **6.27** 75% yield, 89% ee Rh_2(*S*-dosp)$_4$: **ent-6.27** 74% yield, -89% ee	**6**  Rh_2(*R*-dosp)$_4$: **6.28** 74% yield, 96% ee Rh_2(*S*-dosp)$_4$: **ent-6.28** 77% yield, -95% ee	**7**  Rh_2(*R*-dosp)$_4$: **6.29** 20% yield, 98% ee Rh_2(*S*-dosp)$_4$: **ent-6.29** 16% yield, >-99% ee	**8**  Rh_2(*R*-ptad)$_4$: **6.30** 60% yield, 65% ee Rh_2(*S*-ptad)$_4$: **ent-6.30** 79% yield, -67% ee
9  Rh_2(*R*-dosp)$_4$: **6.31** 77% yield, 93% ee Rh_2(*S*-dosp)$_4$: **ent-6.31** 66% yield, -94% ee	**10**  Rh_2(*R*-dosp)$_4$: **6.32** 92% yield, 82% ee Rh_2(*S*-dosp)$_4$: **ent-6.32** 90% yield, -83% ee	**11**  Rh_2(*R*-dosp)$_4$: **6.33** 82% yield, 93% ee Rh_2(*S*-dosp)$_4$: **ent-6.33** 74% yield, -94% ee	**12**  Rh_2(*R*-dosp)$_4$: **6.34** 94% yield, 83% ee Rh_2(*S*-dosp)$_4$: **ent-6.34** 95% yield, -84% ee
13  Rh_2(*R*-dosp)$_4$: **6.35** 75% yield, 81% ee Rh_2(*S*-dosp)$_4$: **ent-6.35** 74% yield, -85% ee	**14**  Rh_2(*R*-dosp)$_4$: **6.36** 87% yield, 99% ee Rh_2(*S*-dosp)$_4$: **ent-6.36** 86% yield, -98% ee		

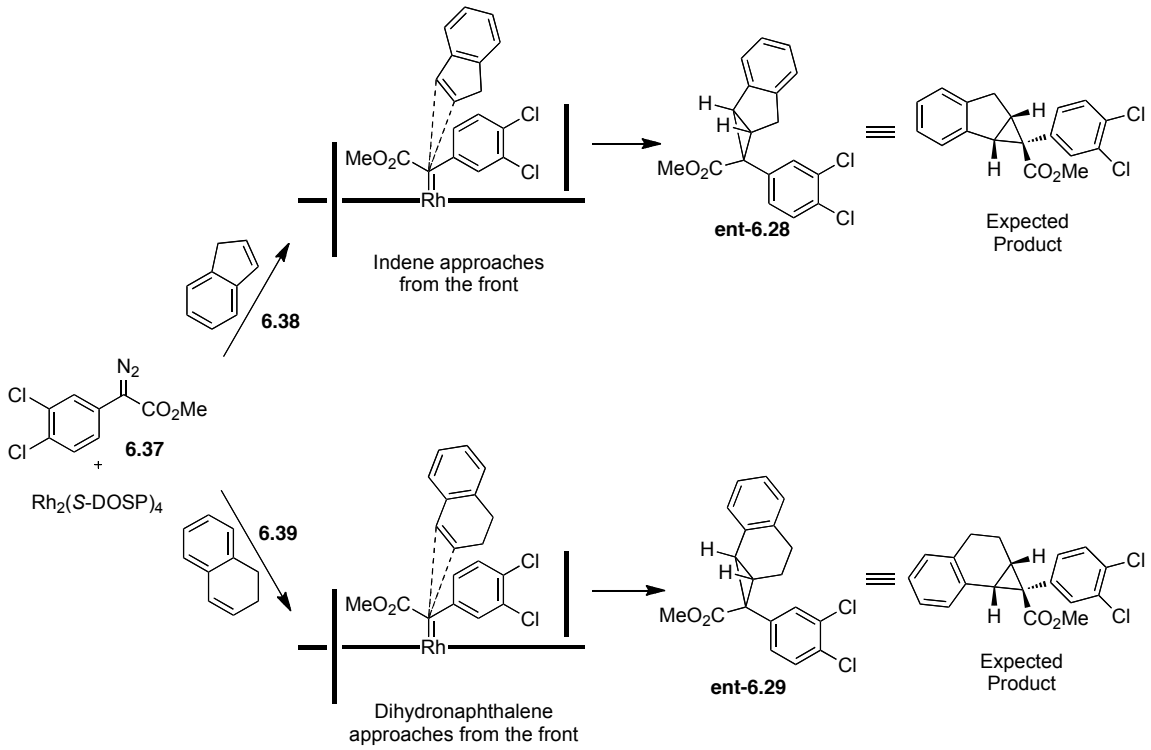
A majority of the reactions were uneventful, but a few entries need further explanation. It was envisaged that the cyclopropylamines might provide higher binding

affinities toward the 5-HT_{2A} receptor if their structures were more rigid. Although the cyclopropylamines that have been synthesized are enantiomerically pure, there is still some flexibility at the C(2) carbon on the cyclopropane. If this flexibility were restricted, then the cyclopropane would become a more rigid structure. This could be accomplished by having the trap be a *cis*-alkene in a five-member or six-member ring system connected to a phenyl ring. The two alkenes that were selected were indene for a five-member ring system and 1,2-dihydronaphthalene for the six-member ring system (entries 6 and 7).

The intermolecular cyclopropanation of indene with 3,4-dichlorophenyldiazoacetate went very smoothly to give the diaryl cyclopropanes (**6.28** and **ent-6.28**) as the sole products in moderate yields and high enantioselectivities (entry 6). However, cyclopropanation of 1,2-dihydronaphthalene with 3,4-dichlorophenyldiazoacetate was not as straight forward (entry 7). The allylic C-H of the hexene ring was activated towards C-H functionalization, which drastically diminished the yield of the cyclopropane products. With Rh_2(*S*-dosp)$_4$, the C-H insertion product at the C(3) position was observed in 1,2-dihydronaphthalene with the ratio of C-H insertion product compared to cyclopropanation product being 1.5:1 at -42 ˚C. With Rh_2(*S*-ptad)$_4$, the C-H insertion product was observed, along with cyclopropanation of the benzene ring. Due to the reaction with Rh_2(*S*-dosp)$_4$ providing more of the desired cyclopropane product, it was then scaled up to gram quantities which allowed for significant quantities of the diaryl cyclopropane (**6.29** and **ent-6.29**) to be synthesized in the presence of the C-H insertion product. The two products were difficult to separate through chromatography, but the diaryl cyclopropane could be isolated from the mother liquor by

recrystallization. This gave the diarylcyclopropane (**6.29** and **ent-6.29**) as enantiomerically pure.

The chiral catalyst is proposed to adopt a D_2 symmetric arrangement and can be imagined as having a blocking group in the front and another one in the back as depicted in Figure 6.2.2. The alkene approaches the stabilized rhodium carbenoid from the front thereby avoiding interactions with the ester group leading to the asymmetric induction due to the interaction of the alkene substituents with the blocking group of the catalyst.[184] Using this predictive "end-on" model for Rh_2(*S*-dosp)$_4$, the expected enantiomers of both reactions with indene and dihydronaphthalene are depicted in Figure 6.2.2.[185] This predictive model was proven correct by obtaining the crystal structure with absolute stereochemistry of the indene reaction with Rh_2(*R*-dosp)$_4$. This can be seen in Figure 6.2.2.



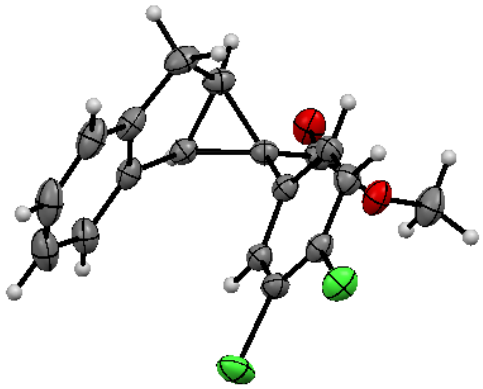


Figure 6.2.2: Predictive model applied to internal alkenes.

A series of indole cyclopropylmethylamines (**x**) that are conformationally restricted homotryptamines have been reported to be potent serotonin reuptake inhibitors as previously described. The *trans* (1*S*, 2*S*) indole cyclopropylmethylamines demonstrated a high affinity for SERT and low selectivity towards DAT, NET, 5-HT_{1A}, and 5-HT_6. Previously, the Davies group has described that various heteroaryldiazoacetates, including indole derived diazoacetates, are capable of highly stereoselective cyclopropanations in the presence of styrene.[186] However, the cyclopropanation of *N*-boc-protected indole-3-diazoacetate with 3,4-dichlorostyrene in the presence of Rh_2(*R*-dosp)$_4$ resulted in low enantioinduction (40% ee). It has recently been shown that this particular diazoacetate undergoes cyclopropanation with styrene in the presence of Rh_2(*S*-ptad)$_4$ in good yield (75%) and excellent enantioselectivity (>98%). An interesting result came out of the rhodium(II)-catalyzed cyclopropanation step of this synthesis when screening the catalysts Rh_2(dosp)$_4$ and Rh_2(ptad)$_4$ (entry 8). Typically, Rh_2(S-DOSP)$_4$ and Rh_2(S-PTAD)$_4$ furnish opposite enantiomers in the cyclopropanation of methyl phenyldiazoacetates, but in the case of the *N*-boc-protected methyl indolyldiazoacetate, both catalysts gave the same enantiomer. The product of the

Rh_2(*S*-ptad)$_4$ reaction was submitted for x-ray analysis as seen in Figure 6.2.3. The absolute configuration was (1*R*, 2*S*) which is consistent with what Rh_2(*S*-dosp)$_4$. This told us that in the case of this particular heteroaryldiazoacetate, Rh_2(*S*-ptad)$_4$ gave the opposite enantiomer than what was predicted presumably due the large nature of the "donor" group (entry 8; Table 6.2.1).

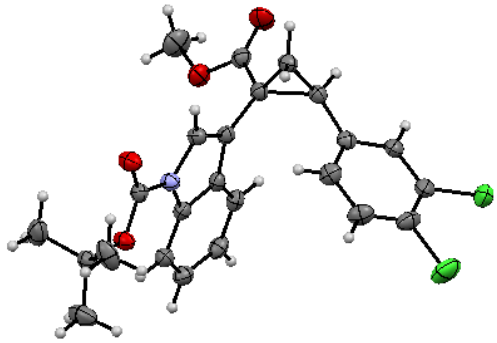
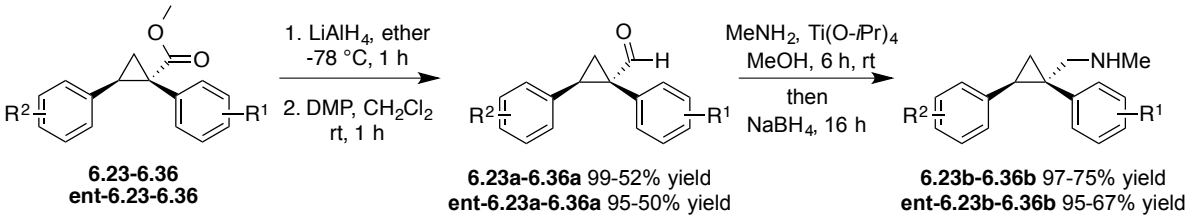


Figure 6.2.3: Crystal structure for *tert*-butyl 3-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-(methoxycarbonyl) cyclopropyl)-1*H*-indole-1-carboxylate (**ent-6.30**).

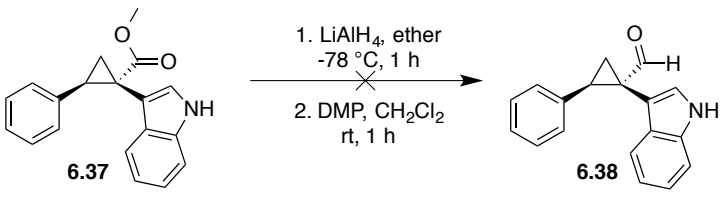
Reactions that furnished cyclopropyl products with <95% ee were recrystallized to enantiomeric purity before continuing further derivation before the remaining three steps in the synthesis of the diaryl cyclopropylamines were then undertaken (Scheme x.x). The reduction of the methyl esters by lithium aluminum hydride generated the primary alcohols, which were subsequently oxidized to the corresponding aldehydes with the use of Dess Martin reagent in a one-pot manner (**6.23a-6.36a**; **ent-6.23a-6.36a**).[180] Reductive amination of the aldehydes with methylamine in the presence of titanium(IV) isopropoxide with sodium borohydride generated the cyclopropylmethylamines (**6.23b-6.36b**; **ent-6.23b-6.36b**).[187] The amines were then transformed into the corresponding fumarate salt with furamic acid in refluxing isopropanol. This resulted in an overall high

yielding sequence that proved to be very reliable and robust (see Experimental for details).



Scheme 6.2.4: Synthetic sequence to cyclopropylmethylamines.

One cyclopropyl derivative (**6.37**) proved to be incompatible with the synthetic sequence. Initially, the plan was to *Boc*-deprotect of the indole moiety, then reduce/oxidize to the aldehyde, next reductive amination of the aldehyde to give the methyl amine, and finally salt formation of the secondary amine with fumaric acid. A few methods of deprotection were tried which include trifluoroacetic acid in methylene chloride, refluxing in *t*-butyl amine,[188] sodium methoxide in methanol,[189] methanol in hydrochloric acid (1:1), and trifluoroethanol under microwave-assisted conditions, with the latter giving the best results. The deprotected indole cyclopropane was then subjected to reduction of the ester moiety with $LiAlH_4$, and then subsequently oxidation with the Dess Martin reagent to the aldehyde. However, the reaction did not proceed as planned due to the unprotected indole readily oxidized by the reagent. The use of PDC also yielded the same results.

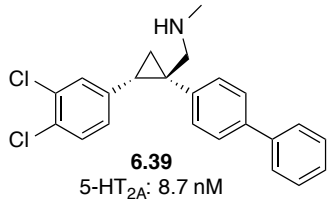


Scheme 6.2.5: Unsuccessful attempt at conversion of the deprotected indole cyclopropane.

The indole needed to be protected until after the reductive amination step, but the carbamate group could be easily reduced into a methyl using $LiAlH_4$, which was not the desired outcome. The use of a slightly milder reducing agent that could selectively reduce the methyl ester over the carbamate group was needed. The use of DIBAL-H in this scenario has been reported to work well as long as the reaction is held and slowly quenched at -78 °C.[190] It was found that the *N*-Boc group could be easily removed under thermal conditions at the amine stage using trifluoroethanol under microwave-assisted conditions (150 °C for 2 minutes).

6.2.3 Cross-coupling derivation

During the course of the previous work, it was discovered that a biphenyl derived triaryl cyclopropylmethylamine (**6.39**; **HD-323**) was very potent at the 5-HT_{2A} receptor (6.2 nM) while still maintaining a19-fold selectivity towards this receptor over the 5-HT_{2C} receptor (117 nM). The intriguing detail of the hit is that it is of the other enantiomeric series (1*R*, 2*S*). It can be proposed that the additional phenyl ring takes away from the overall triangular arrangement and possibly allows the compound to have related behavior at the receptor site to that of the linear class of compounds; we could be, theoretically, accessing a different mode of binding at the receptor site.



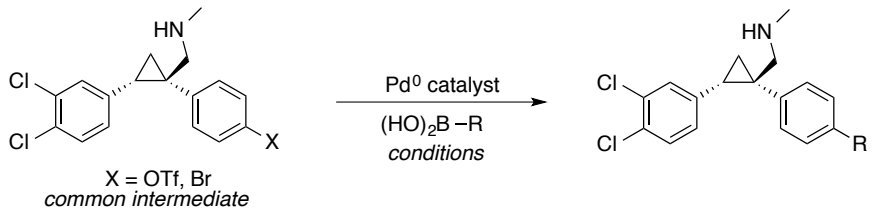
6.39
5-HT$_{2A}$: 8.7 nM
HD-323

Figure 6.2.4: New biphenyl derived triaryl cyclopropylmethylamine lead.

This opened us up into a new direction that could be explored. The biphenyl system is perfectly set up for cross coupling chemistries. The combination of rhodium(II)-catalyzed cyclopropanation followed by palladium(II)-catalyzed cross-coupling would showcase the versatility of the chemistry developed in the Davies group. It has been shown that methyl aryldiazoacetates containing reactive functionality for palladium(II)-catalyzed cross-coupling reactions are capable of highly enantioselective rhodium(II)-catalyzed cyclopropanation without interference from the additional functionality.[191]

A synthetic route can be seen in Scheme 6.2.6. The use of 4-bromo or 4-trifluorosulfonylmethane phenyldiazoacetate in the presence of 3,4-dichlorostyrene and Rh_2(*R* or *S*-dosp)$_4$ would quickly generate the diaryl cyclopropylacetate. This substrate could then be reduced with lithium aluminum hydride, oxidized by Dess Martin reagent, and reduced to the methyl amine with sodium borohydride in the presence of methylamine and Ti(O-^{i}Pr)$_4$ to give intermediate **A**. From here, the subsequent palladium(II)-catalyzed cross coupling reaction with boronic acids would allow us to generate diversity very quickly from intermediate **A** as the multiple reactions could be run in parallel. The cross-coupling chemistry would also allow us to introduce

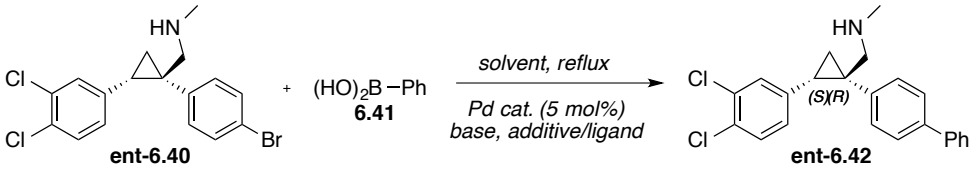
heterocycles, which would increase the water solubility of the diaryl cyclopropylamines (decrease cLogP). This can be seen in Scheme 6.2.6.



Scheme 6.2.6: Proposed cross-coupling strategy.

Initially, the use of Suzuki cross coupling conditions that are typically employed gave unsatisfactory results. The presence of the basic amine functionality, which could potentially coordinate to the palladium catalyst, and the presence of acid functionality in the coupling partner did not allow the reaction to proceed smoothly at first. Low yields or no reaction were observed. Since the starting material and product are quite similar to each other in physical properties, clean isolation of the product was much more difficult if the starting material was not completely consumed leading to any increased yield or degradation of the starting material. A quick screening of several reaction conditions lead to an optimum set of conditions.[192,193] These conditions include the use of the palladium catalyst Pd(dppf)Cl_2, cesium carbonate as the base, and the mixed solvent system of 4:1 THF:H_2O at reflux.[194] One thing to note is these conditions allowed for easy isolation of the desired product.

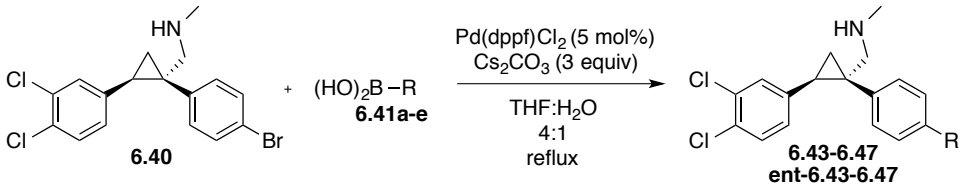
Table 6.2.2: Screening of Suzuki cross-coupling conditions.

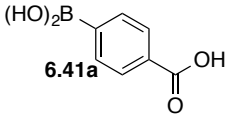
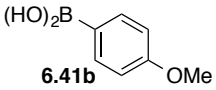
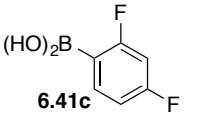
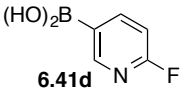
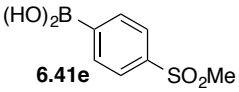


entry	catalyst	base	solvent	additive/ligand	% yield
1	$Pd(Ph_3)_4$	BaOH	H_2O: dioxane (3:1)	none	0
2	$Pd(Ph_3)_4$	K_2CO_3	THF	none	0
3	$Pd(OAc)_2$	K_2CO_3	THF	PPh_3	48
4	$Pd(t\text{BuP})_2$	KF	THF	none	<5
5	$Pd_2(dba)_3$	KF	THF	none	0
6	$Pd(OAc)_2$	Na_2CO_3	H_2O	TBAB	0
7	$Pd(dppf)Cl_2$	Cs_2CO_3	THF:H_2O (4:1)	none	77

These conditions were then applied to variety of arylboronic acids to give moderate to good yields of the desired triaryl cyclopropylamine. The results of this coupling reaction with various boronic acids can be seen in Table 6.2.3.

Table 6.2.3: Cross-coupling results.



entry	boronic acid	configuration	product	% yield
1	 **6.41a**	(1*S*, 2*R*)	**6.43**	61
2		(1*R*, 2*S*)*	**ent-6.43**	64
3	 **6.41b**	(1*S*, 2*R*)	**6.44**	78
4		(1*R*, 2*S*)*	**ent-6.44**	83
5	 **6.41c**	(1*S*, 2*R*)	**6.45**	80
6		(1*R*, 2*S*)*	**ent-6.45**	77
7	 **6.41d**	(1*S*, 2*R*)	**6.46**	76
8		(1*R*, 2*S*)*	**ent-6.46**	77
9	 **6.41e**	(1*S*, 2*R*)	**6.47**	69
10		(1*R*, 2*S*)*	**ent-6.47**	81

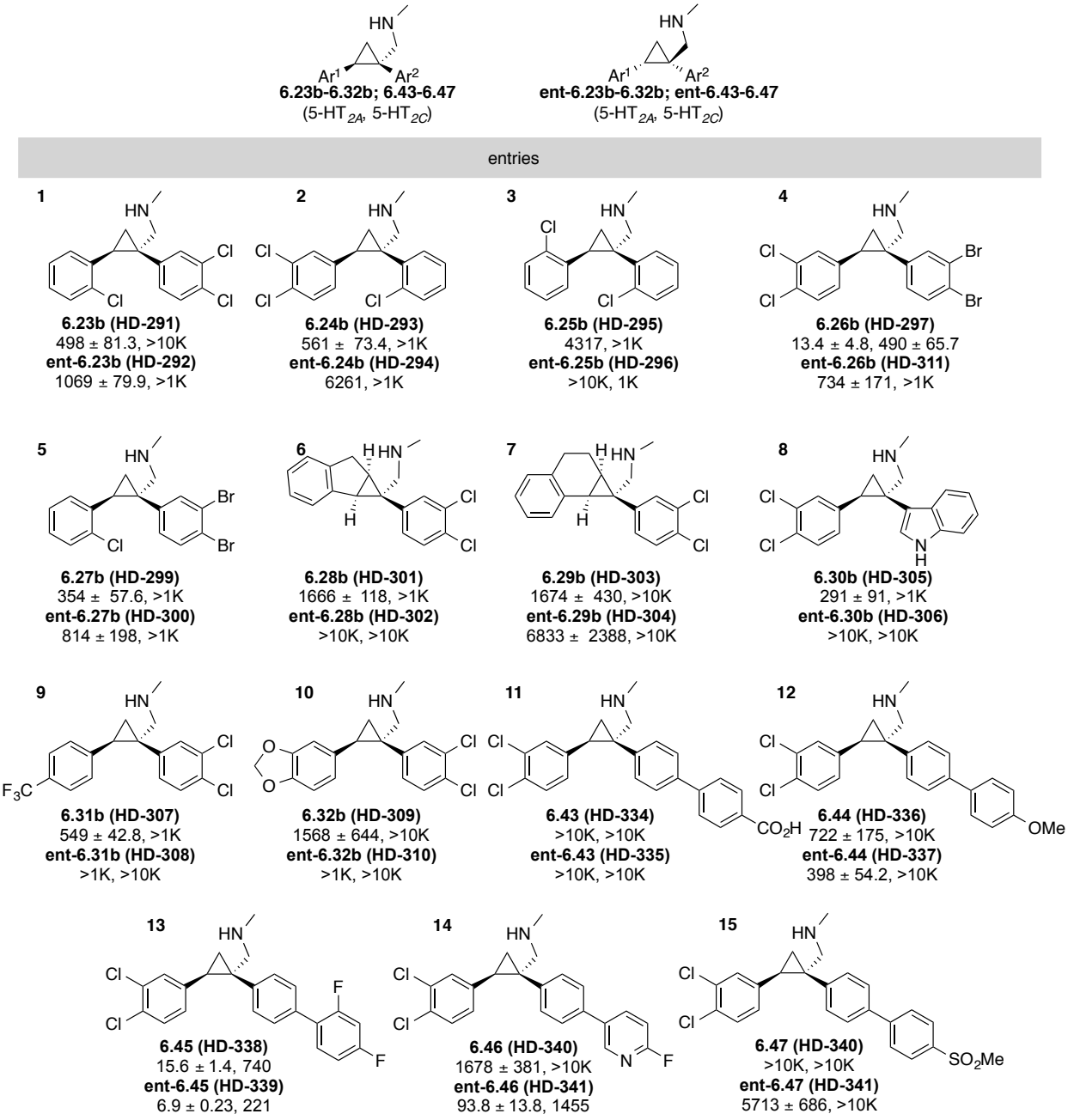
6.3 Biological Data

The previous described library diaryl and triaryl cyclopropylmethylamines were sent to Dr. Steven Childers at Wake Forest University for biological studies of their binding affinities with the 5-HT_{2A} receptor. With such a variety of different diaryl cyclopropylmethylamines, there was the potential to have a better understanding as to the steric and electronic demands of the receptor site. The results of the biological studies for 5-HT_{2A} are summarized in Table **1**. Several trends can be quickly seen with this library. First, the previous observation of the (1*S*, 2*R*) enantiomer being more active than the (1*R*, 2*S*) enantiomer can clearly be seen. This tells us that the binding site of the receptor, one confirmation is preferred over another. This would not have been obvious if the

compounds were racemates. Second, the rotationally constained (**HD-291-295, 299-300**) and fused ring (**HD-301-304**) diaryl cyclopropylmethylamines were not as potent as previously thought, with the latter being only μM at the receptor. This tells us that having some flexibility in the diaryl cyclopropylmethylamine might be beneficial in its' mode of binding with the receptor. The use of a heterocycle, **HD-305**, resulted in a lower binding affinity of 291 nM. Going back to initial lead compound **HD-225**, replacing the 2 chlorine atoms on the first aryl for the slightly larger bromine atom (**HD-297**), gave us a 1-fold increase in potency (13.4 nM) at the 5-HT_{2A} receptor while still maintaining selectivity at the 5-HT_{2C} receptor (734 nM). With the successful result of this compound, it was then synthesized on a multi-gram scale for further development (see *in vivo* study).

The triaryl cyclopropylamine derivatives were not as successful as the diaryl cyclopropylamines. It is interesting to note that the difluoro derivative (entry 13, HD-339) gave a similar result (6.9 nM) as HD-323, but had better selectivity (32-fold as compared to 19-fold with HD-323). The pyridine derivative (entry 8, HD-341) also had moderate potency. This series of compounds helped to confirm the switch in bioactivity with **HD-323**.

Table 6.3.1: K_i values (nM ± SEM) in radioligand binding assays at 5-HT_{2A} and 5-HT_{2C} receptors. Data determined in membranes of tranfected cells.



With the results of the *in vitro* study, compound **HD-297** was then tested in Mike Nader's laboratory at Wake Forest University Primate Center for the reinforcing effects

of cocaine in female cynomolgus monkeys. The primates were trained to respond on a fixed-ratio 30 schedule of *i.v.* cocaine reinforcement. Experimental sessions lasted for one hour or until the maximum number of reinforcers were obtained (30 self injections of cocaine). The dose of cocaine that maintained peak response rates was studied (0.01 or 0.03 mg/kg per injection) and the HD compound was administered intramuscularly 15-30 minutes prior to the start of the experimental session.

When the dose of cocaine that maintained peak response rates was given, **HD-297** (3 mg/kg), decreased cocaine seeking behavior (~20%) and these effects persisted for up to 48 hours after the initial injection of the compound. The long lasting effect of the compound is very intriguing and probably has something to do with its pharmacokinetics.

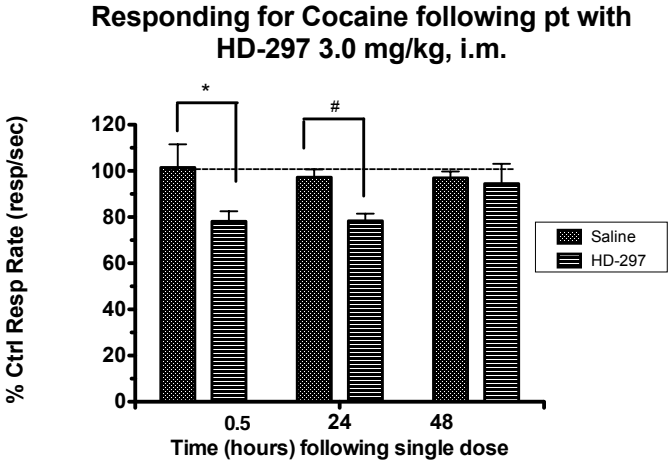


Figure 6.3.1: *In vivo* results with **HD-297**.

The lead compound developed in this study was very hydrophobic (clogP > 6) possibly not permitting the compound to cross the blood brain barrier. Due to this, the bioavailability of the compound is significantly decreased, thereby attenuating the

therapeutic effect *in vivo*. Currently, this research project needs to be directed towards the design and development of novel compounds possessing improved pharmokinetic properties.

6.4 Conclusion

In summary, a focused library of compounds were designed and synthesized based on the SAR of previously synthesized compounds. The rhodium(II)-catalyzed cyclopropanation was employed for the effective synthesis of enantiopure cyclopropane derivatives which were then converted to the corresponding methylamine in a three step synthetic sequence. Two new lead compounds **HD-297** and **HD-339** were identified, with the latter coming about by a late stage cross-coupling strategy. Multi-gram quantities of compound **HD-297** were made available, which initiated a thorough *in vivo* evaluation of this new lead in a non-human primate model.

Experimental Part

General Methods

For flash chromatography, technical grade solvents from Sigma-Aldrich were used. Chromatographic purification was performed as flash chromatography using Merck silica gel 60 (230-400 mesh), using solvents as listed as eluent. Isolera Biotage instruments were used in some cases for chromatographic purification. TLC was performed on Merck silica gel 60 F254 TLC plates and visualized with UV light and potassium permanganate stain.

^{1}H-NMR spectra were run on a Varian nuclear magnetic resonance spectrometer at 600, 400, 300 MHz and ^{13}C-NMR at 151 or 100 MHz with the sample solvent being $CDCl_3$, $(CD_3)SO$, $(CD_3)CO$, or CD_3OD. The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ^{13}C-NMR signals were recorded with ^{1}H-decoupling was running. IR spectra were obtained using a Nicolet Impact series 420 FT-IR. Mass spectral determinations were performed by the Department of Chemistry at Emory University. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, GA. Melting points were measured on an electrothermal melting point apparatus and are uncorrected. The glassware used was dried in an oven prior to use. Screw-cap high pressure vials were purchased from Chemglass. Reactions were conducted under an argon atmosphere. The

solvents were dried in a solvent purifier before use and used without further purification unless noted. Chloroform and 1,2-dichloroethane were purchased from SigmaAldrich, distilled, and stored over molecular sieves prior to use. The degassing of the solvents was performed by bubbling argon gas through the solvent for 15-20 minutes.

7.1 Experimental Part to Chapter 2

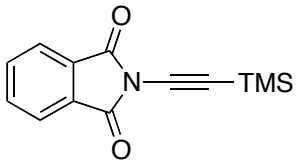
Starting Materials

Commerically available reagents were used without purification unless noted otherwise. Butadiene gas was generated by heating butadiene sulfone neat with stirring. The resulting gas was then bubbled through a concentrated solution of potassium hydroxide, followed by a drying tube before reaching a collection flask cooled to -20 ºC.

The amino triazole can be left at room temperature for 24 h or stored in the freezer (-20 ºC) for two months with no signs of degradation if atmospheric moisture is excluded. Mesyl azide was used as a stock solution (3M in diethyl ether). CuTC was prepared according to the literature procedure and stored in the dark.[195] Catalyst with a light grayish beige color had the best reaction times and yields.

Caution! Sulfonyl azides are potentially explosive materials and must be handled with caution. Failure to do so could result in serious injury!

***N*-(trimethylsilyl)ethynylphthalimide (2.55):**



In a 2-L one neck round-bottom flask equipped with a large magnetic stir bar, $Cu(OAc)_2$ (6.8 mmol, 1.24 g), phthalimide (169.9 mmol, 25.0 g), Na_2CO_3 (68.0 mmol, 7.21 g), and 4Å molecular sieves (20.0 g) were combined together. A solution of pyridine (68.0 mmol, 5.4 g) in 300 mL dry toluene was added to the reaction flask. With vigorous stirring, the reaction flask was flushed with 3 volumes of oxygen gas and stoppered. One large balloon filled with oxygen gas was connected to the reaction flask via a needle. The flask was then placed in a preheated oil-bath at 70 ºC. The flask stirred at this temperature for 2 hours until the reaction media was a milky green. A solution of TMS-acetylene (34.0 mmol, 3.34 g) in 20 mL dry toluene was added to the flask over 4 hours via a syringe pump. After the addition of this solution, the reaction mixture was allowed to stir at 70 ºC for another 12 hours and then the resulting milky teal solution was cooled to room temperature. The crude reaction mixture was filtered warm through a glass frit and the resulting filtrate was concentrated under reduced pressure. The resulting residue was re-suspended in ether and washed with saturated aq NH_4Cl. The layers were separated and the organic was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give an off-white solid (13.4 g). The solid was purified by flash chromatography (hexanes/EtOAc 8:1) to yield the ynimide (7.70 g, 93% yield) as a fluffy white solid.

Note: $Cu(OAc)_2$ came from $Cu(OAc)_2*H_2O$ after being dehydrated at 120 ºC under vacuum (~1 mm of Hg) for 48 hours to yield a dark green solid.

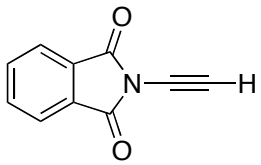
^{1}H-NMR (400 MHz, chloroform-d): δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 0.27 (s, 9H);

^{13}C-NMR (100 MHz, chloroform-d): δ 165.2, 135.4, 131.2, 124.5, 84.7, 83.3, 0.1;

FT-IR: 2960, 2899, 2183, 1739, 1368, 1249, 1204, 987, 841, 706 cm^{-1};

Spectroscopic data was consistent with the literature.[196]

_N_-Ethynylphthalimide (2.56):



In a 250 mL one neck round-bottom flask equipped with a magnetic stir bar, *N*-(trimethylsilyl)ethynylphthalimide (13.0 mmol, 3.16 g) was dissolved in 75 mL of dry THF. The reaction flask was flushed with argon and cooled to 4 ºC using an ice bath. Then acetic acid (2 equiv.) was added and the reaction media stirred for 5 minutes. A solution of TBAF (1M in THF, 1.2 equiv.) was added dropwise to this stirring reaction media over the course of 30 minutes. The reaction continued to stir at 4 ºC for 4 hours until the starting material was completely consumed as judged by TLC analysis. The reaction flask was then warmed to room temperature and transferred to a separatory funnel where it was diluted with ether and saturated aq. $NaHCO_3$. The layers were separated and the organic was dried with Na_2SO_4, filtered, and concentrated under

reduced pressure to give an off-white solid. The solid was purified by flash chromatography (hexanes/EtOAc 4:1) to yield the ynimide (2.07 g, 93%) as an off-white solid. *Note: It is important to have a slightly acidic media otherwise the yield of the deprotected ynimide is low and unreproducible.*

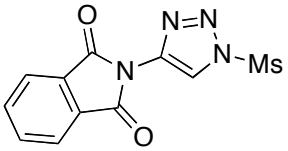
^{1}H-NMR (400 MHz, chloroform-d): δ 7.96 (dd, *J* = 5.5, 2.9 Hz, 2H), 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 3.35 (s, 1H);

^{13}C-NMR (100 MHz, chloroform-d): δ 165.2, 135.6, 131.1, 124.7, 68.2, 66.4;

FT-IR: 3275, 2162, 1742, 1468, 1371, 1062, 882, 712 cm^{-1};

Spectroscopic data was consistent with the literature.[196]

1-(Methylsulfonyl)-4-phthalimido-1*H*-1,2,3-triazole (2.57):



To a stirring solution of *N*-ethynylphthalimide (1 equiv.) in toluene (0.25 M), copper(I) thiophene-2-carboxylate (CuTC, 5 mol%) was added at room temperature. After stirring for 2-4 minutes, a solution of mesyl azide (1.2 equiv) in ether was added dropwise to the resulting mixture. The reaction media was then stirred at room temperature for 12-16 hrs. Once the starting alkyne had been completely consumed as judged by TLC analysis, the mixture was concentrated under reduced pressure, and filtered through a short plug of silica to remove copper catalyst (warm EtOAc as eluent; approx. 500 mL). After removal

of solvent under reduced pressure, an off-white solid was triturated with ether (x3) to afford the desired triazole. Isolated in 78-86% yield as an off-white solid.

m.p. 136-137 °C (dec);

^{1}H-NMR (400 MHz, dmso-d6): δ 8.92 (s, 1H), 8.05 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.97 (dd, *J* = 5.6, 2.8 Hz, 2H), 4.04 (s, 3H);

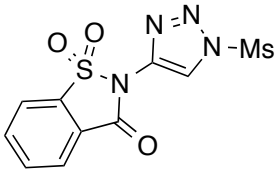
^{13}C-NMR (100 MHz, dmso-d6): δ 171.1, 141.5, 140.8, 136.6, 129.5, 127.5, 127.3, 47.5;

FT-IR: 3144, 3023, 2931, 1789, 1735, 1562, 1374, 1206, 1018, 888, 769, 717 cm^{-1};

HRMS (unstable toward analysis);

Anal. Calcd for $C_{11}H_8N_4O_4S$: C, 45.20; H, 2.76; N, 19.17; S, 10.97; found: C, 45.25; H, 2.77; N, 19.05; S, 10.95.

2-(1-(Methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.74):



To a stirring solution of *N*-ethynylsaccharin (440 mg, 2.12 mmol, 1 equiv.) in toluene (0.25 M), copper(I) thiophene-2-carboxylate (CuTC, 20 mg, 0.106 mmol) was added at room temperature. After stirring for 2-4 minutes, a solution of mesyl azide (2.5 mmol, 1.2 equiv) in ether was added dropwise to the resulting mixture. The reaction media was then stirred at room temperature for 4 hrs. Once the starting alkyne had been completely consumed as judged by TLC analysis, the mixture was concentrated under reduced

pressure, and filtered through a short plug of silica to remove copper catalyst (warm EtOAc as eluent; approx. 100 mL). After removal of solvent under reduced pressure, an off-white solid was triturated with ether (x3) to afford the desired triazole. Title compound was isolated in 76% yield (527 mg) as a light yellow powder.

^{1}H-NMR (400 MHz, dmso-d6): δ 9.23 (s, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.18 (t, *J* = 7.5 Hz, 1H), 8.10 (t, *J* = 7.6 Hz, 1H), 4.07 (s, 3H);

^{13}C-NMR (100 MHz, dmso-d6): δ 157.9, 137.2, 137.1, 136.2, 134.0, 126.4, 125.9, 123.3, 122.7, 42.6;

HRMS (unstable toward analysis).

General Procedure 2.1 for Cyclopropanation of Triazole (GP 2.1):

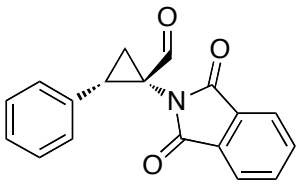
To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, 1-(methylsulfonyl)-4-phthalimido-1*H*-1,2,3-triazole (0.26 mmol) was added under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane and the corresponding olefin (1.28 mmol). The heterogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 55 °C for 12 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and concentrated under reduced pressure for ^{1}H-NMR analysis of crude mixture to determine ratio of diastereomers. The residue was then redissolved in 5 mL of CH_2Cl_2 and 300 mg of wet silica was added. The obtained suspension was stirred for 24 hrs until hydrolysis of the imine was complete. Solvent was removed in vacuum, and the pre-

absorbed silica was then subjected to flash silica chromatography to afford the *trans*-isomer of cyclopropanecarbaldehyde as white solid or colorless oil.

General Procedure 2.2 for One-Pot Cyclopropanation Starting from the Ynimide (GP 2.2):

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, *N*-ethynylphthalimide (0.584 mmol) and CuTC (0.0584 mmol) were added under an argon atmosphere followed by freshly distilled chloroform (3 mL) and freshly prepared mesyl azide (0.642 mmol). The tube was sealed and the reaction mixture was stirred at room temperature for 12 hours. To the resulting greyish suspension, was added the corresponding olefin (0.876 mmol). Then, the reaction mixture was warmed to 55 °C for 12 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and an additional 6 mL of CH_2Cl_2 were added followed by 450 mg of wet silica. The obtained suspension was stirred for 24 hrs until hydrolysis of the imine was complete. Solvent was removed in vacuum, and the pre-absorbed silica was then subjected to flash silica chromatography to afford the *trans*-isomer of the corresponding cyclopropanecarbaldehyde as white solid or colorless oil.

1-(1,3-Dioxoisoindolin-2-yl)-2-phenylcyclopropanecarbaldehyde (2.77):



Title compound was obtained as a white solid from reaction with styrene following **GP 2.1** in 89% yield; **G.P 2.2** provided similar results with a 85% yield.

Rf = 0.38 (3:1 Hexanes:EtOAc);

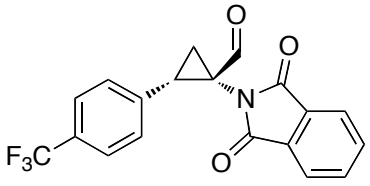
m.p. 138-139 °C;

^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.27 (s, 1H), 8.02-7.52 (m, 4H), 7.17-7.07 (m, 5H), 3.31 (dd, *J* = 9.8, 8.6 Hz, 1H), 2.74 (dd, *J* = 8.6, 7.1 Hz, 1H), 2.30 (dd, *J* = 9.9, 7.1 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.7, 168.1 (br s), 134.5, 133.3, 128.4, 128.2, 127.7, 123.8, 123.7, 47.7, 32.8, 18.0;

HRMS (FTMS+pAPCI): *m/z* 292.0967 $[M+H]^+$ ($C_{18}H_{14}NO_3$ requires 292.0968).

1-(1,3-Dioxoisoindolin-2-yl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarbaldehyde (2.78):



Title compound was obtained as a white solid from the reaction with 4-(trifluoromethyl)styrene (CAS # 402-50-6) following **GP 2.1** gave 92% yield; **G.P 2.2** provided similar results with a 77% yield.

Rf = 0.38 (3:1 Hexanes:EtOAc);

m.p. 156-157 °C;

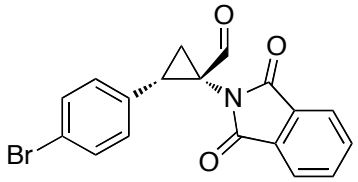
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.28 (s, 1H), 8.08-7.53 (m, 4H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.34 (t, *J* = 9.2 Hz, 1H), 2,75 (dd, *J* = 8.5, 7.2 Hz, 1H), 2.35 (dd, *J* = 9.8, 7.3 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.2, 167.9 (br s), 137.7, 134.8, 134.6, 129.8 (q, *J* = 32.9 Hz), 128.6, 125.4 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 271 Hz), 47.7, 32.0, 18.2;

FT-IR (film): 3065, 2844, 1783, 1720, 1404, 1378, 1326, 1165, 1123, 1069, 719 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 360.0844 $[M+H]^+$ ($C_{19}H_{13}NO_3F_3$ requires 360.0842).

2-(4-Bromophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarbaldehyde (2.79):



Title compound was obtained as a white solid from the reaction with 4-bromostyrene (CAS # 2039-82-9) following **GP 2.1** gave 85% yield; **G.P 2.2** provided similar results with a 74% yield.

Rf = 0.40 (3:1 Hexanes:EtOAc);

m.p. 137-138 °C;

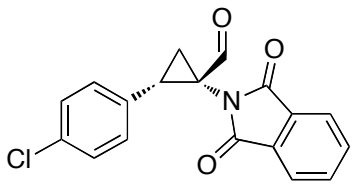
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.26 (s, 1H), 8.07-7.62 (4H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.25 (t, *J* = 8.8 Hz, 1H), 2.68 (dd, *J* = 8.6, 7.2 Hz, 1H), 2.30 (dd, *J* = 9.9, 7.2 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.3, 168.1 (br s), 134.7, 132.5, 131.5, 129.9, 123.9, 121.8, 47.6, 32.0, 18.0;

FT-IR (film): 3065, 2833, 1783, 1715, 1492, 1402, 1376, 1273, 1125, 722 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 370.0076 $[M+H]^+$ ($C_{18}H_{13}NO_3Br$ requires 370.0073).

2-(4-Chlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarbaldehyde (2.80):



Title compound was obtained as a white solid from the reaction with 4-chlorostyrene (CAS # 1073-67-2) following **GP 2.1** gave 88% yield; **G.P 2.2** provided similar results with a 80% yield.

Rf = 0.40 (3:1 Hexanes:EtOAc);

m.p. 143-144 °C;

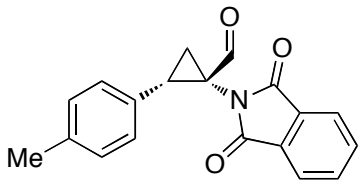
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.26 (s, 1H), 7.98-7.57 (m, 4H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.27 (t, *J* = 8.8 Hz, 1H), 2.69 (dd, *J* = 8.5, 7.2 Hz, 1H), 2.30 (dd, *J* = 9.8, 7.1 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 194.5, 168.4 (br s), 134.7, 134.6, 133.6, 132.0, 129.6, 129.6, 128.6, 128.4, 47.6, 31.9, 18.1;

FT-IR (film): 3101, 2835, 1783, 1718, 1497, 1404, 1377, 1126, 1090, 725 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 326.0580 $[M+H]^+$ ($C_{18}H_{13}O_3NCl$ requires 326.0579).

1-(1,3-Dioxoisoindolin-2-yl)-2-(*p*-tolyl)cyclopropanecarbaldehyde (2.81):



Title compound was obtained as a white solid from the reaction with 4-methylstryene (CAS # 622-97-9) following **G.P 2.1** gave 92% yield; **G.P 2.2** provided similar results with a 79% yield.

Rf = 0.46 (3:1 Hexanes:EtOAc);

m.p. 104-105 °C;

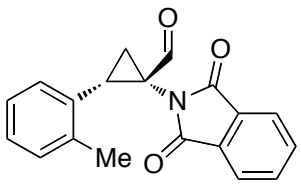
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.25 (s, 1H), 7.97-7.51 (m, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 3.27 (t, *J* = 8.8 Hz, 1H), 2.69 (dd, *J* = 8.6, 7.1 Hz, 1H), 2.29 (dd, *J* = 9.9, 7.1 Hz, 1H), 2.20 (s, 3H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.7, 168.4 (br s), 137.5, 134.5, 130.2, 129.7, 129.1, 128.0, 123.7, 47.7, 32.6, 21.2, 18.1;

FT-IR (film): 3030, 2922, 2852, 1783, 1719, 1519, 1406, 1378, 1275, 1128, 719 cm^{-1};

HRMS (FTMS+pESI): *m/z* 328.0951 $[M+Na]^+$ ($C_{19}H_{15}O_3NNa$ requires 328.0944).

1-(1,3-Dioxoisoindolin-2-yl)-2-(*o*-tolyl)cyclopropanecarbaldehyde (2.82):



Title compound was obtained as a white solid from the reaction with 2-methylstyrene (CAS # 611-15-4) following **G.P. 2.1** gave 84% yield; **G.P 2.2** provided similar results with a 82% yield.

Rf = 0.42 (3:1 Hexanes:EtOAc);

m.p. 135-136 °C;

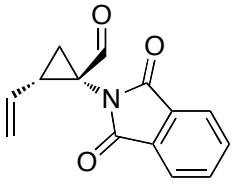
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.38 (s, 1H), 7.95-7.59 (m, 4H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 3.32 (t, *J* = 9.6 Hz, 1H), 2.88 (dd, *J* = 8.8, 7.0 Hz, 1H), 2.54 (s, 3H), 2.28 (dd, *J* = 10.0, 7.0 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 196.1, 168.1 (br s), 139.8, 134.5, 131.1, 130.5, 127.7, 125.5, 124.3, 123.6, 47.8, 30.8, 20.1,17.7;

FT-IR (film): 3029, 2836, 1783, 1718, 1467, 1404,1378, 1274, 719 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 306.1127 $[M+H]^+$ ($C_{19}H_{14}NO$ requires 306.1125).

1-(1,3-Dioxoisoindolin-2-yl)-2-vinylcyclopropanecarbaldehyde (2.83):



The concentration of butadiene in solution was unknown (see Starting material comments). Title compound was obtained from the reaction with 1,3-butadiene in 91% yield as a white solid following **G.P 2.1**.

Rf = 0.46 (3:1 Hexanes:EtOAc);

m.p. 99-100 °C;

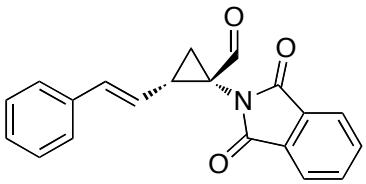
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.05 (s, 1H), 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.62 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.19 (d, *J* = 17.1Hz, 1H), 5.09 (d, *J* = 10.3 Hz, 1H), 2.73 (q, *J* = 8.3 Hz, 1H), 2.22-2.06 (m, 2H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.1, 168.3, 134.6, 131.7, 131.5, 123.9, 118.8, 46.3, 30.1, 18.2;

FT-IR (film): 3088, 2836, 1783, 1715, 1404, 1380, 1273, 1127, 963, 723 cm^{-1};

HRMS (FTMS+pESI): *m/z* 242.0814 $[M+H]^+$ ($C_{14}H_{12}NO_3$ requires 242.0812).

1-(1,3-Dioxoisoindolin-2-yl)-2-((*E*)-styryl)cyclopropanecarbaldehyde (2.84):



Title compound was obtained from the reaction with *trans*-1-phenyl-1,3-butadiene (CAS # 16939-57-4) in 75% yield as a white solid following **G.P 2.1**.

Rf = 0.38 (3:1 Hexanes:EtOAc);

m.p. 76-77 °C;

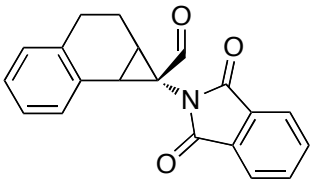
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.10 (s, 1H), 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.22-7.16 (m, 5H), 6.52 (d, *J* = 15.9 Hz, 1H), 5.97 (dd, *J* = 15.8, 6.8 Hz, 1H), 2.89 (q, *J* = 8.8 Hz, 1H), 2.31-2.16 (m, 2H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.2, 168.4, 136.6, 134.7, 133.8, 131.7, 128.7, 128.0, 126.5, 123.9, 123.0, 46.7, 30.4, 18.9;

FT-IR (film): 3027, 2833, 1783, 1716, 1404, 1379, 1275, 1125, 720 cm^{-1};

HRMS (FTMS+pESI): *m/z* 318.1127 $[M+H]^+$ ($C_{20}H_{16}NO_3$ requires 318.1125).

1-(1,3-Dioxoisoindolin-2-yl)-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (2.85):



Title compound was obtained from the reaction of 1,2-dihydronapthalene (CAS # 447-53-0) in 83% yield as a colorless oil following **G.P. 2.1**.

Rf = 0.38 (3:1 Hexanes:EtOAc);

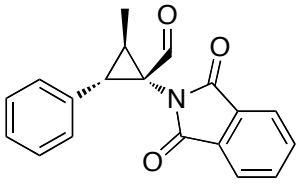
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.03 (s, 1H), 7.87 (d, *J* = 7.3 Hz, 1H), 7.81-7.60 (m, 3H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 3.26 (d, *J* = 9.9 Hz, 1H), 2.78-2.52 (m, 3H), 2.29-2.06 (m, 2H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 194.9, 169.1, 166.6, 134.6, 134.4, 134.1, 132.1, 132.0, 131.8, 129.5, 128.8, 127.5, 126.5, 123.9, 123.7, 51.4, 29.2, 26.5, 26.2, 18.0;

FT-IR (film): 3029, 2925, 2856, 1781, 1717, 1396, 1273, 1119, 721 cm^{-1};

HRMS (FTMS+pESI): *m/z* 318.1127 $[M+H]^+$ ($C_{20}H_{16}NO_3$ requires 318.1125).

***trans*-1-(1,3-Dioxoisoindolin-2-yl)-2-methyl-3-phenylcyclopropanecarbaldehyde (2.86):**



Title compound was obtained from reaction of *trans*-1-phenyl-1-propene (CAS # 873-66-5) in 83% yield as a colorless, sticky oil following **G.P. 2.1**.

Rf = 0.33 (3:1 Hexanes:EtOAc);

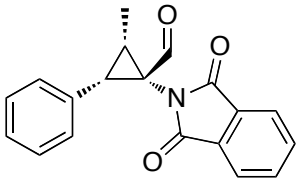
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.43 (s, 1H), 7.94-7.57 (m, 4H), 7.17-7.06 (m, 5H), 3.33 (d, *J* = 8.9 Hz, 1H), 3.00 (dq, *J* = 8.8, 6.4 Hz, 1H), 1.64 (d, *J* = 6.4 Hz, 3H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.6, 168.2 (br s), 134.5, 134.0, 238.0, 237.6, 123.8, 123.7, 123.6, 51.8, 40.3, 28.9, 12.9 ppm;

FT-IR (film): 3063, 3034, 2934, 2874, 1772, 1716, 1396, 1379, 1126, 912, 888, 719 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 304.0969 [M-H] ($C_{19}H_{14}O_3N$ requires 304.0968).

***cis*-1-(1,3-Dioxoisoindolin-2-yl)-2-methyl-3-phenylcyclopropanecarbaldehyde (2.87):**



Title compound was obtained from the reaction of *cis*-1-phenyl-1-propene (CAS # 766-90-5) in 85% yield as a colorless, sticky oil following **G.P. 2.1**.

Rf = 0.33 (3:1 Hexanes:EtOAc);

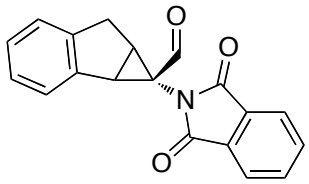
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.02, (s, 1H), 7.94-7.70 (m, 4H), 7.24-7.11 (m, 5H), 3.19 (d, *J* = 10.9 Hz, 1H), 2.52 (dq, *J* = 10.9, 6.8 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.6, 168.1 (br s), 134.6, 133.9, 132.3, 129.4, 128.5, 127.2, 123.9 (br s), 123.8, 50.9, 34.0, 26.0, 10.1;

FT-IR (film): 3063, 3034, 2934, 2874, 1772, 1716, 1396, 1379, 1126, 912, 888, 719 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 304.0969 [M-H] ($C_{19}H_{14}O_3N$ requires 304.0968).

1-(1,3-Dioxoisoindolin-2-yl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carbaldehyde (2.88):



Title compound was obtained from the reaction of indene (CAS # 95-13-6) in 89% yield as a white solid following **G.P. 2.1**.

Rf = 0.40 (3:1 Hexanes:EtOAc);

m.p. 180-181 °C;

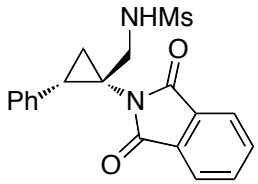
^{1}H-NMR (400 MHz, chloroform-*d*): δ 9.16 (s, 1H), 7.92-7.56 (m, 4H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.03 (t, *J* =7.4 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 3.77 (dd, *J* = 6.6, 1.2 Hz, 1H), 3.39 (dd, *J* = 18.7, 6.6 Hz, 1H), 3.23 (d, *J* = 18.6 Hz, 1H), 3.10 (t, *J* = 6.7 Hz, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 195.4, 168.6, 167.0, 143.4, 137.4, 134.4, 134.3, 131.7, 131.6, 127.5, 126.5, 123.6, 49.4, 38.9, 33.4, 30.4;

FT-IR (film): 3045, 2918, 2844, 1777, 1716, 1467, 1393, 1270, 1125, 881, 721 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 304.0970 $[M+H]^+$ ($C_{19}H_{14}NO_3$ requires 304.0968).

***N*-((1-(1,3-Dioxoisoindolin-2-yl)-2-phenylcyclopropyl)methyl)methanesulfonamide (2.103):**



To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, 1-(methylsulfonyl)-4-phthalimido-1*H*-1,2,3-triazole (0.26 mmol, 75.1 mg) was added under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane and styrene (0.39 mmol, 40.2 mg). The heterogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 55 °C for 12 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to 4 ºC using an ice bath and $NaBH_4$ (0.29 mmol, 11 mg) in 2 mL of MeOH were added. The reaction mixture was allowed to warm to room temperature overnight and then quenched with wet Na_2SO_4. The reaction mixture was then concentrated and redissolved in EtOAc and filtered through a plug of silica followed by concentration under reduced pressure. The resulting residue was purified by column chromatography (1:1hexanes:EtOAc) to give a white solid in 72% yield.

Rf = 0.81 (EtOAc); m.p. 166 °C (dec);

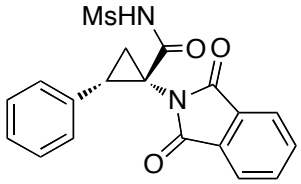
^{1}H-NMR (400 MHz, chloroform-*d*): δ 7.79-7.50 (m, 4H), 7.11-6.96 (m, 5H), 5.14 (dd, *J* = 7.4, 4.2 Hz, 1H), 3.86 (dd, *J* = 14.0, 7.3 Hz, 1h), 3.21 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.92 (s, 3H), 2.65-2.48 (m, 1H), 2.12 (t, *J* = 7.3 Hz, 1H), 1.71-1.61 (m, 1H);

^{13}C-NMR (100 MHz, chloroform-*d*): δ 169.3, 168.2, 135.5, 134.4, 131.7, 130.8, 128.2, 127.6, 126.9, 123.6, 123.4, 50.3, 41.5, 39.4, 27.6, 16.1;

FT-IR (film): 3287, 3029, 2929, 2854, 1776, 1713, 1387, 1321, 1148, 1084, 721 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 371.1060 $[M+H]^+$ ($C_{19}H_{19}N_2O_4S_3$ requires 371.1060).

1-(1,3-Dioxoisoindolin-2-yl)-*N*-(methylsulfonyl)-2-phenylcyclopropanecarboxamide (2.104):



To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, 1-(methylsulfonyl)-4-phthalimido-1*H*-1,2,3-triazole (0.343 mmol, 100.1 mg) was added under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane and styrene (0.514 mmol, 54.0 mg). The heterogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 55 °C for 6 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature, and stirred for 1 hour at which time 4 mL of 1:1 THF:*t*BuOH were added to the screw-cap tube followed by $NaClO_2$ (1.03 mmol, 93.1 mg), $NaH_2PO_4 \bullet H_2O$ (1.03

mmol, 142 mg), and 2-methyl-2-butene (10 equiv.). After the addition, the reaction stirred at room temperature for 4 hours. The reaction was then concentrated under reduced pressure and extracted with EtOAc, washed with NH_4Cl, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then triturated with 1:1 ether: hexanes (5 mL x 2) to give 1-(1,3-dioxoisoindolin-2-yl)-*N*-(methylsulfonyl)-2-phenylcyclo- propane carboxamide as a pure off-white solid in 88% yield.

m.p. 109-110 °C;

^{1}H-NMR (400 MHz, acetone-*d6*): δ 7.97 (dt, *J* = 7.5, 3.2 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.30 (d, *J* = 2.0 Hz, 4H), 6.40 (s, 1H), 3.29 (m, 4H), 1.96 (dd, *J* = 8.1, 5.7 Hz, 1H), 1.87 (dd, *J* = 9.7, 5.7 Hz, 1H);

^{13}C-NMR (100 MHz, acetone-*d6*): δ 171.5, 170.5, 167.6, 139.5, 135.0, 132.9, 130.3, 129.6, 129.5, 128.0, 127.9, 127.1, 41.8, 40.6, 32.8, 20.7;

FT-IR (film): 3551, 3205, 3007, 2631, 1701, 1519, 1439, 1359, 1223, 1126, 882 cm^{-1};

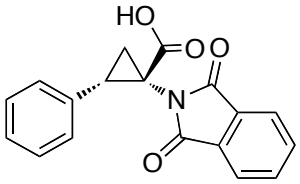
HRMS (FTMS+pAPCI): *m/z* 385.0855 $[M+H]^+$ ($C_{19}H_{17}N_2O_5S$ requires 385.0853).

General Procedure 2.3 for Pinnick Oxidation of Aldehyde to Acid (G.P. 2.3):

To a 100 mL round bottom flask equipped with a magnetic stir bar, the cyclopropanecarbaldehyde (0.154 mmol), sodium hypophosphite (0.464 mmol, 3 equiv.), and 2-methyl-2-butene (20 equiv.) were suspended in 9 mL of 4:4:1 THF:tBuOH:H_2O. Then sodium chlorite (0.464 mmol, 3 equiv.) was added in small portions over 30

minutes to the reaction mixture. After the addition, the reaction stirred at room temperature until the starting material disappeared from TLC (ca. 6 hours). The reaction was then concentrated under reduced pressure. The residue was suspended with ether and extracted with aq $NaHCO_3$ (x2). The aqueous layer was then slowly acidified with conc. HCl until a pH = 2. The aqueous layer was then re-extracted with EtOAc (x2). The organic layer was then dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solid/residue was then triturated with 1:1 ether:hexanes to give pure product.

1-(1,3-Dioxoisoindolin-2-yl)-2-phenylcyclopropanecarboxylic acid (2.105):



Title compound was obtained in 87% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-phenyl cyclopropanecarbaldehyde as a white solid following **G.P. 2.3**.

m.p. 238 °C (dec);

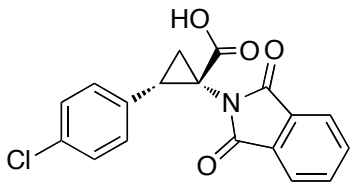
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.87 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.11 (s, 5H), 3.38-3.31 (m, 1H), 2.43 (dd, *J* = 8.4, 6.5 Hz, 1H), 2.19 (dd, *J* = 9.7, 6.5 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 176.0, 172.6, 171.3, 138.7, 138.4, 135.8, 134.8, 131.8, 131.7, 130.8, 127.1, 126.8, 42.9, 35.2, 22.3;

FT-IR (neat): 3061, 1779, 1727, 1703, 1409, 1384, 1271, 1175, 998, 719, 696 cm^{-1};

HRMS (FTMS-pESI): *m/z* 306.0773 [M-H] ($C_{18}H_{12}NO_4$ requires 306.0772).

2-(4-Chlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylic acid (2.106):



Title compound was obtained in 93% yield from 2-(4-chlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarbaldehyde as a white solid following **G.P. 2.3**.

m.p. 194 °C (dec);

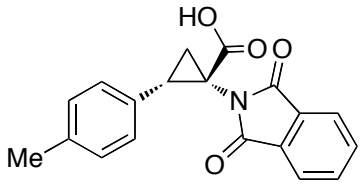
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.85 (d, *J* = 7.4 Hz, 1H), 7.75 (dt, *J* = 21.1, 7.4 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.10 (s, 4H), 3.37 – 3.29 (m, 1H), 2.36 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.19 (dd, *J* = 9.8, 6.6 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 171.8, 168.7, 167.4, 134.6, 133.8, 132.7, 131.9, 130.9, 129.5, 127.8, 123.2, 123.0, 39.0, 30.5, 18.4;

FT-IR (neat): 3329, 2840, 2542, 1778, 1690, 1661, 1514, 1426, 1290, 1266, 1092, 1065, 936, 841, 829, 734 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 342.0528 $[M+H]^+$ ($C_{18}H_{14}NO_4Cl$ requires 342.0528).

1-(1,3-Dioxoisoindolin-2-yl)-2-(*p*-tolyl)cyclopropanecarboxylic acid (2.107):



Title compound was obtained in 90% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-(*p*-tolyl) cyclopropanecarbaldehyde as a white solid following **G.P. 2.3**.

m.p. 209 °C (dec);

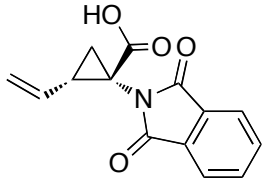
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.83 (d, *J* = 7.4 Hz, 1H), 7.71 (dt, *J* = 24.0, 7.4 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.08 – 6.78 (m, 4H), 3.28 – 3.20 (m, 1H), 2.36 (dd, *J* = 8.4, 6.5 Hz, 1H), 2.19 – 2.06 (m, 4H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 172.1, 168.7, 167.4, 136.7, 134.5, 131.9, 131.7, 130.9, 128.4, 127.8, 123.1, 122.9, 38.9, 31.1, 19.8, 18.4;

FT-IR (neat): 3099, 1781, 1731, 1709, 1414, 1381, 1268, 1161, 1119, 1002, 830, 725 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 322.1074 $[M+H]^+$ ($C_{19}H_{16}NO_4$ requires 322.1074).

1-(1,3-Dioxoisoindolin-2-yl)-2-vinylcyclopropanecarboxylic acid (2.108):



Title compound was obtained in 87% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-vinylcyclopropane carbaldehyde as a white solid following **G.P. 2.3**.

m.p. 192 °C (dec);

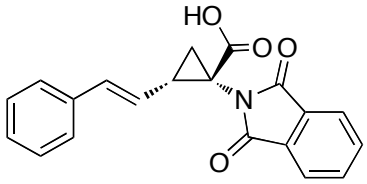
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.47 (m, 3H), 5.67 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.26 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.6 Hz, 1H), 2.45 (q, *J* = 8.5 Hz, 1H), 1.88 (dd, *J* = 9.4, 5.1 Hz, 1H), 1.47 (dd, *J* = 7.6, 5.1 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 174.2, 172.9, 168.1, 138.5, 134.4, 131.9, 130.0, 129.4, 129.3, 127.8, 116.6, 38.5, 31.9, 21.7;

FT-IR (neat): 2820, 2541, 1779, 1718, 1682, 1455, 1395, 1300, 1086, 947, 900, 716 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 258.0760 $[M+H]^+$ ($C_{14}H_{12}NO_4$ requires 258.0761).

1-(1,3-Dioxoisoindolin-2-yl)-2-((*E*)-styryl)cyclopropanecarboxylic acid (2.109):



Title compound was obtained in 85% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-((*E*)-styryl) cyclopropanecarbaldehyde as a white solid following **G.P. 2.3**.

m.p. 186 °C (dec);

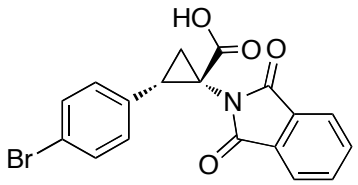
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.54 (m, 1H), 7.54 – 7.45 (m, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 15.9, 8.9 Hz, 1H), 2.60 (q, *J* = 8.9 Hz, 1H), 2.00 (dd, *J* = 9.4, 5.1 Hz, 1H), 1.63 (dd, *J* = 7.6, 5.1 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 174.1, 173.1, 167.9, 138.8, 137.5, 132.4, 132.0, 130.1, 129.3, 129.0, 128.3, 127.8, 127.0, 126.2, 126.0, 39.0, 32.0, 22.3;

FT-IR (neat): 2982, 1773, 1722, 1698, 1385, 1272, 1273, 1121, 1063, 971, 720 cm^{-1};

HRMS (FTMS-pAPCI): *m/z* 332.0933 $[M-H]^-$ ($C_{20}H_{14}NO_4$ requires 332.0928).

2-(4-Bromophenyl)-1-(1,3-dioxoisoindolin-2-yl)cyclopropanecarboxylic acid (2.110):



Title compound was obtained in 89% yield from 2-(4-bromophenyl)-1-(1,3-dioxoisoindolin-2-yl) cyclopropanecarbaldehyde as a white solid following **G.P. 2.3**.

m.p. 189 °C (dec);

^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.90 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.43 (m, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.10 (m, 3H), 3.00 (t, *J* = 8.9 Hz, 1H), 2.10 (dd, *J* = 9.7, 5.7 Hz, 1H), 1.94 (dd, *J* = 8.1, 5.8 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 173.8, 173.1, 168.1, 138.3, 134.3, 131.8, 130.8, 130.0, 129.4, 129.1, 127.5, 120.6, 39.6, 32.0, 20.4;

FT-IR (neat): 3330, 2869, 2541, 1781, 1693, 1662, 1514, 1290, 1092, 1009, 959, 714 cm^{-1};

HRMS (FTMS-pESI): *m/z* 383.9879 $[M-H]^-$ ($C_{18}H_{11}NO_4Br$ requires 383.9877).

General Procedure 2.4 for Phthalimide Deprotection (G.P. 2.4):

To a 25 mL round bottom flask equipped with a magnetic stir bar, the cyclopropanecarboxylic acid (0.150 mmol) was suspended in 2 mL of glacial acetic acid and 4 mL of 5M HCl. The reaction flask was then heated to reflux with stirring for 4 hours, then cooled to room temperature and concentrated to dryness under reduced pressure. The crude solid was washed with 5mL of 3:1 ether:EtOAc (x3) and then dried *in vacou* to afford pure amino acid as a fine white powder.

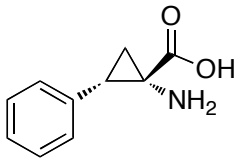
General Procedure 2.5 for Phthalimide Deprotection (G.P. 2.5):

Modified phthalimide $NaBH_4$ reduction procedure. To a stirred solution of cyclopropanecarboxylic acid (0.150 mmol) in 6:1:0.5 *i*PrOH:H_2O:aq. $NaHCO_3$ (satd.) (3 mL) was added sodium borohydride (0.902 mmol, 6 equiv) in one portion at room temperature. After stirring for 3-5 minutes, the flask is stoppered with a balloon of argon and stirred at room temperature for 8 hours. The reaction media was then concentrated under reduced pressure (crude ^{1}H-NMR can be taken in d_4-MeOH to ensure quantitative reduction), re-suspended in THF, filtered, and concentrated again under reduced pressure. The resulting residue was then re-suspended in ether (5 mL) under an argon atmosphere to which anhydrous HCl was added (2M in ether; 1 mL). The reaction mixture was stirred at room temperature until a fine white ppt developed (ca 4 hours), then concentrated under reduced pressure. The solid was washed with 3:1 ether:EtOAc (contains phthalide) and discarded, then 3:1 acetone:MeOH (contains the product) which was then

concentrated under reduced pressure. The off-white solid was then triturated with ether to afford the pure amino acid as a fine white powder.

*Note: Cyclopropanes **2.115** and **2.116** were unstable towards **G.P. 2.4** deprotection conditions and other common phthalimide deprotection procedures (i.e.-$MeNH_2$ both aqueous and ethanolic, RT and elevated temperatures; H_2NNH_2 in ethanol at RT, reflux, and with scavenger; aqueous NaOH and KOH at RT and elevated temperatures).*

1-Amino-2-phenylcyclopropanecarboxylic acid hydrochloric salt (2.111):



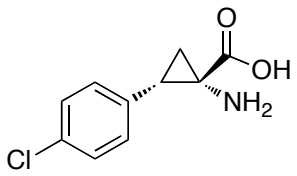
Title compound was obtained in 75% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-phenyl cyclopropanecarboxylic acid as a white solid following **G. P. 2.4**; similar efficiency was obtained with **G.P. 2.5** (72% yield).

m.p. 198 °C (dec);

^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.48-7.29 (m, 5H), 3.18 (t, *J* = 9.1Hz, 1H), 2.02 (dd, *J* = 10.0, 6.5 Hz, 1H), 1.81 (dd, *J* = 8.2, 6.4 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 170.3, 131.8, 129.8, 129.0, 128.4, 38.5, 29.7, 16.5; Spectroscopic data was consistent with the literature.[197]

1-Amino-2-(4-chlorophenyl)cyclopropanecarboxylic acid hydrochloric salt (2.113):



Title compound was obtained in 73% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-(4-chlorophenyl) cyclopropanecarboxylic acid as a white solid following **G. P. 2.4**.

m.p. 198 °C (dec);

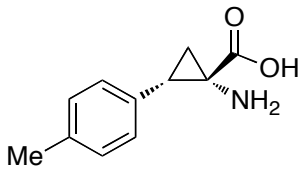
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.39 (q, *J* = 8.6 Hz, 4H), 3.15 (t, *J* = 9.1 Hz, 1H), 2.01 (dd, *J* = 10.0, 6.6 Hz, 1H), 1.82 (t, *J* = 7.4 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 170.2, 134.3, 131.5, 130.7, 129.0, 38.6, 28.9, 16.6;

FT-IR (neat): 3397, 2893, 1724, 1597, 1496, 1425, 1188, 1092, 833 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 212.0473 $[M+H]^+$ ($C_{10}H_{11}NO_2$ requires 212.0473).

1-Amino-2-(*p*-tolyl)cyclopropanecarboxylic acid hydrochloric salt (2.112):



Title compound was obtained in 82% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-(*p*-tolyl) cyclopropanecarboxylic acid as a white solid following **G. P. 2.4**.

m.p. 188 °C (dec);

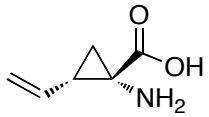
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.32 – 7.13 (m, 4H), 3.09 (t, *J* = 9.0 Hz, 1H), 2.32 (s, 3H), 1.96 (dd, *J* = 9.9, 6.3 Hz, 1H), 1.75 (dd, *J* = 8.2, 6.3 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 170.8, 138.3, 129.6, 129.6, 128.9, 38.7, 29.3, 20.0, 16.5;

FT-IR (neat): 3486, 3089, 2919, 2623, 1732, 1400, 1153, 820, 805 cm^{-1};

HRMS (FTMS+pESI): *m/z* 192.1.018 $[M+H]^+$ ($C_{11}H_{14}NO_2$ requires 192.1019).

1-Amino-2-vinylcyclopropanecarboxylic acid hydrochloric salt (2.115):



Title compound was obtained in 69% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-vinyl cyclopropanecarboxylic acid as a white solid following **G. P. 2.5**.

m.p. 182 °C (dec);

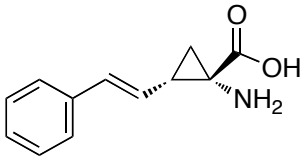
^{1}H-NMR (400 MHz, methanol-*d4*): δ 5.83 – 5.64 (ddd, *J* = 16.9, 10.3, 6.8 Hz, 1H), 5.48 (dd, J = 16.9, 1.6 Hz, 1H), 5.38 (dd, *J* = 10.3, 1.6 Hz, 1H), 2.52 (q, *J* = 8.4 Hz, 1H), 1.82 (dd, *J* = 9.7, 6.2 Hz, 1H), 1.52 (t, *J* = 7.0 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 170.3, 130.4, 121.2, 38.6, 28.5, 17.9;

FT-IR (film): 3373, 2891, 1716, 1636, 1409, 1186, 928 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 128.0707 $[M+H]^+$ ($C_6H_{10}NO_2$ requires 128.0706).

1-Amino-2-((*E*)-styryl)cyclopropanecarboxylic acid hydrochloric salt (2.116):



Title compound was obtained in 64% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-((*E*)-styryl) cyclopropanecarboxylic acid as a white solid following **G. P. 2.5**.

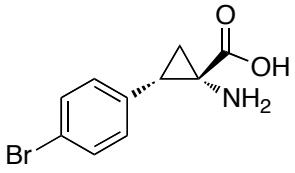
m.p. 182 °C (dec);

^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.45 – 7.21 (m, 5H), 6.82 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.7, 8.5 Hz, 1H), 2.68 (q, *J* = 8.6 Hz, 1H), 1.92 (dd, *J* = 9.8, 6.1 Hz, 1H), 1.64 (t, *J* = 7.1 Hz, 1H); **^{13}C-NMR (100 MHz, methanol-*d4*)**: δ 170.3, 136.6, 136.5, 128.5, 127.9, 126.3, 121.6, 39.1, 28.5, 18.6;

FT-IR (film): 3382, 3025, 2551, 1723, 1633, 1423, 1194, 751, 693 cm^{-1};

HRMS (FTMS-pESI): *m/z* 238.0640 $[M+Cl]^-$ ($C_{12}H_{13}O_2NCl$ requires 238.06480).

1-Amino-2-(4-bromophenyl)cyclopropanecarboxylic acid hydrochloric salt (2.114):



Title compound was obtained in 87% yield from 1-(1,3-dioxoisoindolin-2-yl)-2-(4-bromophenyl) cyclopropanecarboxylic acid as a white solid following **G. P. 2.4**.

m.p. 192 °C (dec);

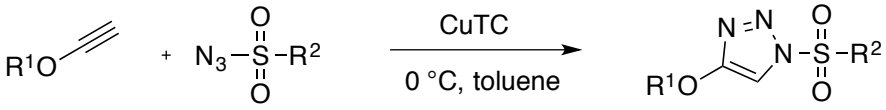
^{1}H-NMR (400 MHz, methanol-*d4*): δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.12 (t, *J* = 9.1 Hz, 1H), 2.00 (dd, *J* = 10.0, 6.5 Hz, 1H), 1.86 – 1.73 (t, *J* = 7.4 Hz, 1H);

^{13}C-NMR (100 MHz, methanol-*d4*): δ 170.4, 132.1, 131.7, 131.3, 122.3, 38.8, 28.9, 16.5;

FT-IR (neat): 3396, 2917, 1723, 1592, 1491, 1426, 1189, 1074, 1011, 830 cm^{-1};

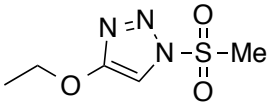
HRMS (FTMS+pAPCI): *m/z* 255.9969 $[M+H]^+$ ($C_{10}H_{11}NO_2Br$ requires 255.9968).

General Prodecure 2.6 for CuTC-catalyzed Azide-Alkyne Cycloaddition (G.P. 2.6):



Copper(I) thiophene-2-carboxylate (CuTC, 3 mol%) was added to a round bottom flask and suspended in toluene at 0 °C. A magnetic stir bar was added and the solution was stirred for 2-4 minutes. Following this, a solution of sulfonyl azide (1.0 equiv) and alkyne (1.1 equiv) in toluene (0.25 M) was added dropwise at 0 °C. The reaction media was then stirred at room temperature for 2-8 hrs. Once the starting alkyne had been completely consumed as judged by TLC analysis, the mixture was concentrated under reduced pressure, and filtered through a short plug of silica to remove copper catalyst eluting with warm 1:1 pentane:EtOAc. After removal of solvent under reduced pressure, an off-white solid was triturated with 2:1 pentane:ether (x2-3 times) to afford the desired triazole in pure form as judged by elemental analysis.

4-Ethoxy-1-(methylsulfonyl)-1*H*-1,2,3-triazole (2.145):



Title compound was obtained in 68% yield from the reaction of ethoxyacetylene (CAS # 927-80-0) and mesyl azide as a white solid after trituration following **G. P. 2.6**.

m.p. 65-66 °C (dec);

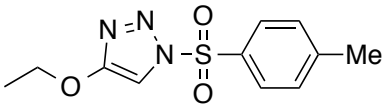
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.50 (s, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 3.48 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 160.2, 105.0, 67.4, 42.5, 14.7;

FT-IR (neat): 3162, 2985, 2932, 1572, 1370, 1312, 1178, 1012, 952, 767 cm^{-1};

Anal. Calcd for $C_5H_9N_3O_3S$: C, 31.41; H, 4.74; N, 21.98; S, 16.77; found: C, 31.55; H, 4.70; N, 22.06; S, 16.64.

4-Ethoxy-1-tosyl-1*H*-1,2,3-triazole (2.146):

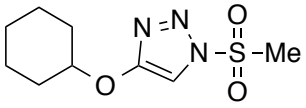


Title compound was obtained in 75% yield from the reaction of ethoxyacetylene (CAS # 927-80-0) and tosyl azide as a white solid after trituration following **G. P. 2.6**.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 4.23 (q, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H);

Characterization data consistent with the literature.[74]

4-(Cyclohexyloxy)-1-(methylsulfonyl)-1*H*-1,2,3-triazole (2.147):



Title compound was obtained in 76% yield from the reaction of (ethynyloxy)cyclohexane and mesyl azide as a white solid after trituration following **G. P. 2.6**.

m.p. 94-95 °C (dec);

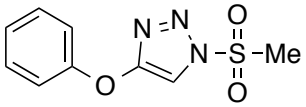
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.49 (s, 1H), 4.50 (td, *J* = 9.0, 4.5 Hz, 1H), 3.47 (s, 3H), 2.13-1.92 (m, 2H), 1.81-1.73 (m, 2H), 1.73-1.46 (m, 3H), 1.46-1.23 (m, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 159.3, 105.9, 79.8, 42.4, 31.6, 25.4, 23.6;

FT-IR (neat): 3160, 3015, 2934, 2859, 1567, 1368, 1312, 1178, 1038, 947, 769 cm^{-1};

Anal. Calcd for $C_9H_{15}N_3O_3S$: C, 44.07; H, 6.16; N, 17.13; S, 13.07; found: C, 44.15; H, 6.12; N, 17.25; S, 13.22.

1-(Methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole (2.148):



Title compound was obtained in 81% yield from the reaction of (ethynyloxy)benzene and mesyl azide as a white solid after trituration following **G. P. 2.6**.

m.p. 84-85 °C (dec);

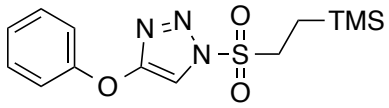
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.67 (s, 1H), 7.42-7.33 (m, 2H), 7.22-7.16 (m, 1H), 7.16-7.09 (m, 2H), 3.52 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 158.1, 156.0, 130.1, 125.0, 118.2, 109.1, 42.5;

FT-IR (neat): 3155, 3015, 2930, 1557, 1491, 1373, 1317, 1181, 1014, 956, 768 cm^{-1};

Anal. Calcd for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56; S, 13.40; found: C, 45.35; H, 3.84; N, 17.55; S, 13.32.

4-Phenoxy-1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-1,2,3-triazole (2.149):



Title compound was obtained in 82% yield from the reaction of (ethynyloxy)benzene and TES azide as a tan solid after trituration and lypophilization from bezene following **G. P. 2.6**.

m.p. 35-36 °C; 70-71 °C (dec);

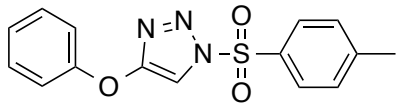
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.67 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.22-7.15 (m, 1H), 7.15-7.10 (m, 2H), 3.71-3.41 (m, 2H), 1.11-0.84 (m, 2H), 0.05 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 157.9, 156.1, 130.1, 124.9, 118.2, 110.1, 52.6, 9.8, -2.0;

FT-IR (neat): 3158, 2952, 1556, 1491, 1372, 1319, 1251, 1184, 1162, 1009, 987, 759 cm^{-1};

Anal. Calcd for $C_{13}H_{19}N_3O_3SSi$: C, 47.98; H, 5.88; N, 12.91; S, 9.85; found: C, 48.26; H, 5.86; N, 12.91; S, 9.82.

4-Phenoxy-1-tosyl-1*H*-1,2,3-triazole (2.150):



Title compound was obtained in 84% yield from the reaction of (ethynyloxy)benzene and tosyl azide as an off-white solid after trituration following **G. P. 2.6**.

m.p. 59-60 °C; 81-82 °C (dec);

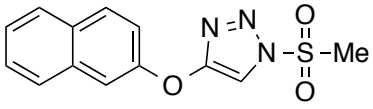
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.68 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.37-7.30 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 158.0, 156.1, 147.7, 132.7, 130.6, 130.0, 128.8, 124.8, 118.1, 109.1, 22.0;

FT-IR (neat): 3154, 3067, 1556, 1490, 1396, 1315, 1193, 1179, 1010, 981, 813, 690 cm^{-1};

Anal. Calcd for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33; S, 10.17; found: C, 57.17; H, 4.22; N, 13.20; S, 10.02.

1-(Methylsulfonyl)-4-(naphthalen-2-yloxy)-1*H*-1,2,3-triazole (2.151):



Title compound was obtained in 76% yield from the reaction of (ethynyloxy)naphthalene and mesyl azide as an off-white solid after trituration following **G. P. 2.6**.

m.p. 97-98 °C (dec);

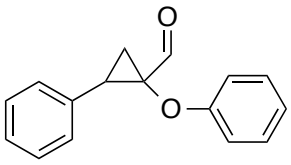
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.90-7.82 (m, 2H), 7.76 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.74 (s, 1H), 7.53-7.43 (m, 3H), 7.33 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.54 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 158.1, 153.7, 134.0, 131.0, 130.5, 127.9, 127.5, 127.1, 125.7, 118.7, 114.1, 109.3, 42.5;

FT-IR (neat): 3155, 3028, 2929, 1559, 1510, 1374, 1316, 1182, 1014, 954, 769 cm^{-1};

Anal. Calcd for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52; S, 11.08; found: C, 54.04; H, 3.93; N, 14.51; S, 11.29.

1-Phenoxy-2-phenylcyclopropane-1-carbaldehyde (2.154):



To a 25 mL flame-dried round bottom flask equipped with a magnetic stir bar, 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole (0.26 mmol) was added under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane and the corresponding styrene (1.28 mmol). The reaction mixture was then placed under an atmosphere of argon. The reaction mixture was stirred at 45 °C for 24 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and concentrated under reduced pressure for ^{1}H-NMR analysis of crude mixture to determine ratio of diastereomers (7:3). The residue was then redissolved in 5 mL of MeOH:CH_2Cl_2 (1:2) and 80 mg of potassium carbonate and 3 drops of water were added. The obtained suspension was stirred for 1 h until hydrolysis of the imine was complete. The reaction was then extracted with CH_2Cl_2, washed with aq. $NaHCO_3$, dried with sodium sulfate, and filtered. Solvent was removed in vacuum, and the crude was then subjected to flash silica chromatography to afford the *trans*-isomer (major) of cyclopropanecarbaldehyde as a colorless oil. Yields can be seen in Table.2.7.2.

^{1}H NMR (600 MHz, Chloroform-*d;* major isomer): δ 9.88 (s, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 3H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.95 (m, 1H), 6.83 (d, *J* = 8.2 Hz, 2H), 2.99 (dd, *J* = 10.2, 8.6 Hz, 1H), 2.19 (dd, *J* = 10.3, 6.1 Hz, 1H), 1.80 (dd, *J* = 8.5, 6.0 Hz, 1H).

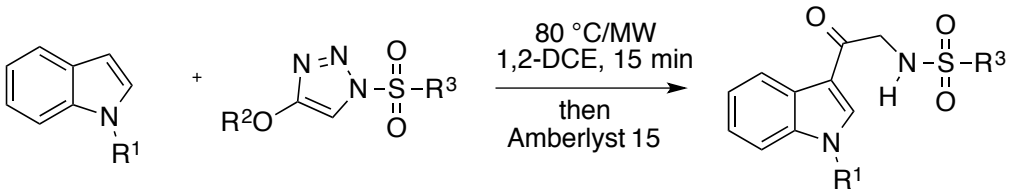
^{1}H NMR (600 MHz, Chloroform-*d*; minor isomer): δ 9.27 (s, 1H), 7.34 (d, *J* = 4.3 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 2.6 Hz, 2H), 7.247.20 (m, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.95 (m, 2H), 3.13 (t, *J* = 9.5 Hz, 1H), 2.37 (dd, *J* = 8.8, 6.4 Hz, 1H), 1.94 (dd, *J* = 10.0, 6.3 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*; major isomer): δ 201.0, 157.3, 133.9, 129.6, 128.4, 128.1, 127.2, 122.0, 115.4, 69.5, 35.7, 21.7;

^{13}C NMR (101 MHz, Chloroform-*d*; minor isomer): δ 197.9, 157.0, 133.6, 129.6, 128.7, 128.6, 127.5, 122.0, 115.5, 69.7, 36.4, 20.3;

HRMS (FTMS+pNSI): *m/z* 239.1070 $[M+H]^+$ ($C_{16}H_{15}O_2$ requires 239.1072).

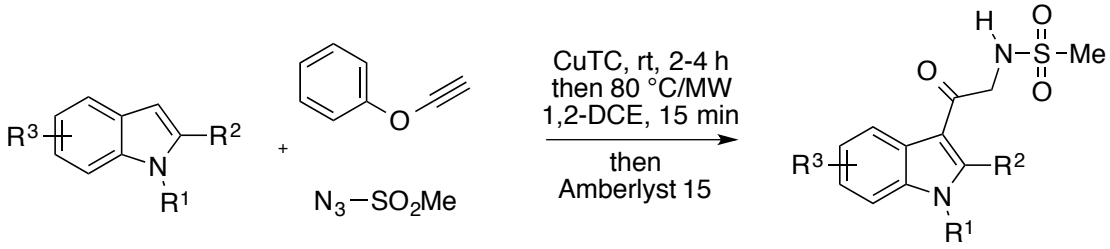
General Procedure 2.7 for Indole Acylation from an Enol *N*-Sulfonyl Triazole (G.P. 2.7):



To a 10 mL high pressure snap-cap tube equipped with a magnetic stir bar, triazole (0.20 mmol) and the appropriate indole (0.30 mmol) were added together under ambient

atmosphere followed by 2.0 mL of dry 1,2-dichloroethane. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was subjected to microwave irradiation at 80 °C for 15 minutes. TLC analysis of the reaction mixture indicated consumption of the triazole. Amberlyst 15 (150 mg) and 2 drops of water were added to the reaction and the resulting mixture was warmed at 50 °C for 2-4 hours until complete hydrolysis as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with ethyl acetate followed by extraction(x3) with a pipette to a separatory funnel containing 0.5M NaOH leaving behind the Amberlyst 15 catalyst. The layers were then separated and the organic was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. It was then subjected to flash silica chromatography (9:1→0:1 pentanes:EtOAc w/ 3%Et_3N; Biotage Isolera) to afford the indole product as tan or off-white solid.

General Procedure 2.8 for Indole Acylation from Ynol Ether (G.P. 2.8):



To a 10 mL high pressure snap-cap tube equipped with a magnetic stir bar, copper(I) thiophene-2-carboxylate (CuTC, 0.006 mmol) and the appropriate indole (0.40 mmol) were added and suspended in dry 1,2-dichloroethane (1mL) at room temperature.

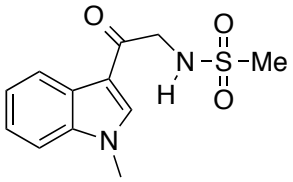
Following this, a solution of mesyl azide (0.20 mmol) and ethynyloxybenzene (0.22 mmol) in dry 1,2-dichloroethane (1mL) was added dropwise under ambient atmosphere. The reaction mixture was flushed with argon and sealed. The reaction media was then stirred at room temperature for 2-4 hrs. Following this, the reaction mixture was subjected to microwave irradiation at 80 °C for 15 minutes. TLC analysis of the reaction mixture indicated consumption of the triazole. Amberlyst 15 (150 mg) and 2 drops of water were added to the reaction and the resulting mixture was warmed at 50 °C for 2-4 hours until complete hydrolysis as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with ethyl acetate followed by extraction(x3) with a pipette to a separatory funnel containing 0.5M NaOH leaving behind the Amberlyst 15 catalyst. The layers were then separated and the organic was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. It was then subjected to flash silica chromatography (9:1→0:1 pentanes:EtOAc w/ 3%Et_3N; Biotage Isolera) to afford the indole product as tan or off-white solid.

General Procedure 2.9 for Indole Acylation from an Ynol Ether (Conventional heating and Scale-Up; G.P. 2.9):

To a 100 mL round bottom flask equipped with a magnetic stir bar, copper(I) thiophene-2-carboxylate (CuTC, 69 mg, 0.36 mmol) and the appropriate indole (24.0 mmol) were added and suspended in dry 1,2-dichloroethane (20 mL) at 0 °C. Following this, a solution of mesyl azide (1.46 g, 12 mmol) and ethynyloxybenzene (1.71 g, 14.5 mmol)

in dry 1,2-dichloroethane (30 mL) was added dropwise under ambient atmosphere at 0 °C. The reaction mixture was flushed with argon and sealed. The reaction media was allowed to warm to room temperature over 4 hrs. Following this, the reaction mixture was heated in an oil bath at 70 °C for 12 hours. TLC analysis of the reaction mixture indicated consumption of the triazole. TsOH hydrate (690 mg, 0.3 equiv) and H_2O (325 mg, 1.5 equiv) were added to the reaction and the resulting mixture was warmed at 50 °C for 2-4 hours until complete hydrolysis as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with ethyl acetate followed by extraction(x3) to a separatory funnel containing 0.5M NaOH. The layers were then separated and the organic was dried with Na_2SO_4, filtered through a pad of celite, 30 g of silica added to the filtrate, and concentrated under reduced pressure. It was then subjected to flash silica chromatography (9:1→0:1 pentanes:EtOAc w/ 3%Et_3N) to afford the indole product.

***N*-(2-(1-Methyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.162):**



Title compound was obtained in 91% yield (48.2 mg) from the reaction of 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole and 1-methylindole as an off-white solid following **G. P. 2.7**; 87% (47.4 mg) yield following **G. P. 2.8**; 79% (2.55 g) yield following **G.P. 2.9**.

m.p. 176-177 °C;

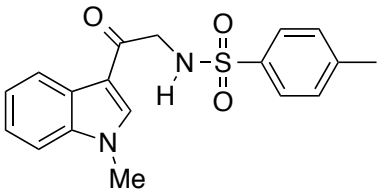
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.19 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 5.8 Hz, 1H), 7.34-7.22 (m, 2H), 4.43 (d, *J* = 5.8 Hz, 2H), 3.87 (s, 3H), 3.00 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.1, 137.6, 137.1, 125.8, 123.1, 122.4, 121.3, 112.5, 110.8, 48.8, 40.5, 33.3;

FT-IR: 3306, 3098, 3017, 2935, 1651, 1528, 1310, 1219, 1147, 1081, 994, 912, 748 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 267.0799 $[M+H]^+$ ($C_{12}H_{15}N_2O_3S$ requires 267.0798).

4-Methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl)benzenesulfonamide (2.163):



Prepared *via* **G.P. 2.7** outlined above using 39 mg (0.3 mmol, 1.5 equiv) of 1-methylindole and 63 mg (0.2 mmol, 1.0 equiv) of 4-phenoxy-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 90% yield (61.1 mg) as an off-white solid.

m.p. 151-152 °C;

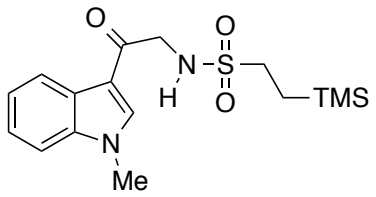
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (s, 1H), 8.10 (d, *J* = 7.4 Hz, 1H), 7.88 (t, *J* = 5.8 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.33-7.19 (m, 2H), 4.20 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H), 2.35 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 187.9, 142.5, 137.8, 137.5, 137.1, 129.5, 126.6, 125.7, 123.0, 122.3, 121.2, 112.4, 110.7, 48.6, 33.3, 21.0;

FT-IR (neat): 3277, 3118, 3053, 2916, 1630, 1526, 1368, 1326, 1219, 1185, 1080, 926, 912, 750 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 365.0930 $[M+Na]^+$ ($C_{18}H_{18}N_2O_3SNa$ requires 365.0930).

***N*-(2-(1-Methyl-1*H*-indol-3-yl)-2-oxoethyl)-2-(trimethylsilyl)ethane-1-sulfonamide (2.164):**



Prepared *via* **G.P. 2.7** outlined above using 61 mg (0.46 mmol, 2.0 equiv) of 1-methylindole and 75.3 mg (0.23 mmol, 1.0 equiv) of 4-phenoxy-1-((2-(trimethylsilyl)ethyl)sulfonyl)-1*H*-1,2,3-triazole. Title compound was isolated in 84% yield (68.2 mg) as an off-white solid.

m.p. 116-117 °C;

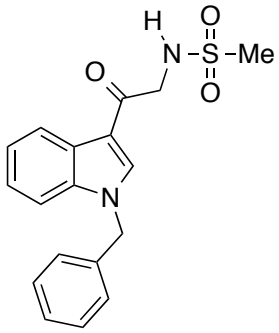
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.17 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.45-7.17 (m, 3H), 4.37 (d, *J* = 5.9 Hz, 2H), 3.85 (s, 3H), 3.09-2.85 (m, 2H), 1.13-0.88 (m, 2H), 0.01 (s, 9H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.8, 137.9, 137.5, 126.2, 123.4, 122.7, 121.7, 112.9, 111.2, 49.1, 48.8, 33.7, 10.4, -1.5;

FT-IR (neat): 3237, 3116, 3049, 2953, 2894, 1634, 1530, 1450, 1376, 1250, 1224, 1166, 1123, 1081, 839, 740 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 353.1355 $[M+H]^+$ ($C_{16}H_{25}N_2O_3SSi$ requires 353.1350).

***N*-(2-(1-Benzyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.166):**



Prepared *via* a modified **G. P. 2.8** outlined above using 62 mg (0.3 mmol, 1.5 equiv) of 1-benzylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Hydrolysis was performed at room temperature over 2 days. Title compound was isolated in 71% yield (48.3 mg) as a tan solid.

m.p. 168-169 °C;

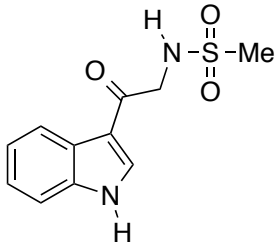
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.36-8.25 (m, 1H), 7.83 (s, 1H), 7.42-7.28 (m, 6H), 7.24-7.14 (m, 2H), 5.46 (br t, *J* = 4.9 Hz, 1H), 5.36 (s, 2H), 4.51 (d, *J* = 4.9 Hz, 2H), 3.00 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 187.7, 137.2, 135.2, 134.6, 129.4, 128.7, 127.4, 126.2, 124.2, 123.5, 122.4, 113.9, 110.7, 51.2, 49.3, 40.7;

FT-IR (neat): 3223, 3112, 3023, 2934, 1648, 1530, 1387, 1307, 1160, 1146, 1057, 968, 920, 743 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 343.1112 $[M+H]^+$ ($C_{18}H_{19}N_2O_3S$ requires 343.1111).

***N*-(2-(1*H*-Indol-3-yl)-2-oxoethyl)methanesulfonamide (2.167):**



Prepared *via* **G.P. 2.8** outlined above using 35.1 mg (0.3 mmol, 1.5 equiv) of 1*H*-indole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 57% yield (28.9 mg) as a light pink solid.

m.p. 194-196 °C (dec);

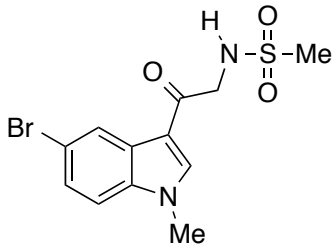
^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (s, 1H), 8.44 (d, *J* = 2.3 Hz, 1H), 8.18 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.49 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.35 (t, *J* = 5.8 Hz, 1H), 7.22 (tt, *J* = 7.2, 5.5 Hz, 2H), 4.45 (d, *J* = 5.7 Hz, 2H), 3.00 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.7, 136.4, 134.0, 125.4, 123.0, 122.0, 121.2, 113.7, 112.3, 48.8, 40.5;

FT-IR (neat): 3350, 3278, 3119, 2983, 1641, 1615, 1525, 1428, 1395, 1301, 1148, 1085, 937, 761 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 275.0460 $[M+Na]^+$ ($C_{11}H_{12}N_2O_3SNa$ requires 275.0461).

***N*-(2-(5-Bromo-1-methyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.168):**



Prepared *via* **G.P. 2.8** outlined above using 63 mg (0.3 mmol, 1.5 equiv) of 5-bromo-1-methylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 80% yield (54.6 mg) as an off-white solid.

m.p. 182-183 °C;

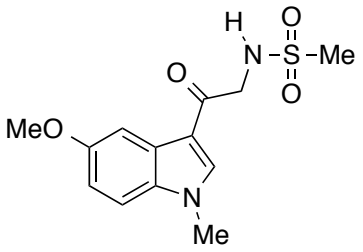
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (s, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.44 (dd, J = 8.7, 2.0 Hz, 1H), 7.41 (t, J = 5.8 Hz, 1H), 4.41 (d, J = 5.7 Hz, 2H), 3.87 (s, 3H), 2.98 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.7, 139.1, 136.3, 127.8, 126.0, 123.7, 115.7, 113.5, 112.3, 49.2, 41.0, 34.0;

FT-IR (neat): 3242, 3130, 2891, 1643, 1531, 1374, 1312, 1228, 1149, 1079, 1046, 932, 788 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 344.9905 $[M+H]^+$ ($C_{12}H_{14}N_2O_3BrS$ requires 344.9903).

***N*-(2-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.169):**



Prepared *via* **G.P. 2.8** outlined above using 48 mg (0.3 mmol, 1.5 equiv) of 5-methoxy-1-methylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 83% yield (48.9 mg) as a white solid.

m.p. 162-163 °C;

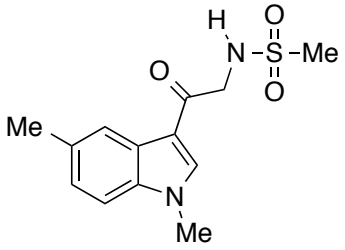
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (s, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.32 (t, *J* = 5.8 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.99 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.3, 156.3, 137.9, 132.5, 127.0, 113.1, 112.6, 112.1, 103.4, 55.7, 49.0, 41.0, 33.9;

FT-IR (neat): 3267, 3113, 2933, 2835, 1645, 1530, 1483, 1370, 1317, 1222, 1150, 1078, 871, 771 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 297.0905 $[M+H]^+$ ($C_{13}H_{17}N_2O_4S$ requires 297.0904).

***N*-(2-(1,5-Dimethyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.170):**



Prepared *via* **G.P. 2.8** outlined above using 44 mg (0.3 mmol, 1.5 equiv) of 1,5-dimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 86% yield (47.4 mg) as an off-white solid.

m.p. 163-164 °C;

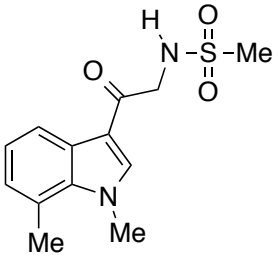
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.99 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 5.8 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.7 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 2.99 (s, 3H), 2.42 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.0, 137.5, 135.6, 131.3, 126.0, 124.5, 121.0, 112.1, 110.4, 48.7, 40.6, 33.3, 21.3;

FT-IR (neat): 3269, 3127, 2930, 1639, 1534, 1374, 1315, 1154, 938, 770 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 303.0777 $[M+Na]^+$ ($C_{13}H_{16}N_2O_3SNa$ requires 303.0774).

***N*-(2-(1,7-Dimethyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.171):**



Prepared *via* **G.P. 2.8** outlined above using 44 mg (0.3 mmol, 1.5 equiv) of 1,7-dimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 89% yield (49.1 mg) as a tan solid.

m.p. 160-161 °C;

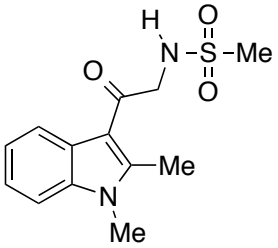
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 5.8 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 4.39 (d, J = 5.7 Hz, 2H), 4.10 (s, 3H), 2.99 (s, 3H), 2.73 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.0, 139.0, 135.7, 126.9, 125.6, 122.5, 122.4, 119.4, 111.9, 48.7, 40.5, 37.3, 19.0;

FT-IR (DMSO): 3581, 3109, 2930, 1651, 1538, 1456, 1316, 1148, 956, 788 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 281.0956 $[M+H]^+$ ($C_{13}H_{17}N_2O_3S$ requires 281.0954).

***N*-(2-(1,2-Dimethyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.172):**



Prepared *via* **G.P. 2.8** outlined above using 44 mg (0.3 mmol, 1.5 equiv) of 1,2-dimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 83% yield (46 mg) as a white solid.

m.p. 159-160 °C;

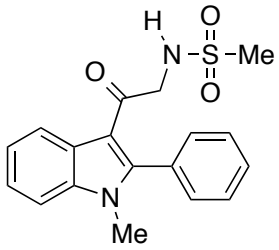
^{1}H NMR (600 MHz, DMSO-d_6): δ 8.06-7.83 (m, 1H), 7.66-7.48 (m, 1H), 7.27-7.23 (m, 3H), 4.47 (d, J = 5.5 Hz, 2H), 3.75 (s, 3H), 3.02 (s, 3H), 2.76 (s, 3H);

^{13}C NMR (151 MHz, DMSO-d_6): δ 189.7, 146.2, 136.5, 125.2, 122.2, 121.9, 120.5, 110.8, 110.5, 51.8, 40.5, 29.7, 12.8;

FT-IR: 3306, 3063, 2932, 1632, 1472, 1379, 1255, 1160, 1143, 1066, 962, 767 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 281.0956 $[M+H]^+$ ($C_{13}H_{17}N_2O_3S$ requires 281.0954).

***N*-(2-(1-Methyl-2-phenyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.173):**



Prepared *via* **G.P. 2.8** outlined above using 62 mg (0.3 mmol, 1.5 equiv) of 2-phenyl-1-methylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 71% yield (48 mg) as a tan solid.

m.p. 130-131 °C;

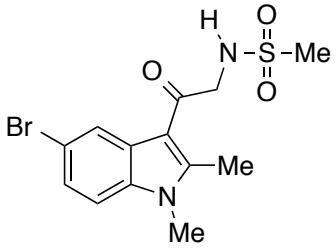
^{1}H NMR (600 MHz, Chloroform-*d*): δ 8.41 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.64-7.60 (m, 3H), 7.54-7.33 (m, 5H), 5.38 (br t, *J* = 4.9 Hz, 1H), 3.77 (d, *J* = 4.9 Hz, 2H), 3.53 (s, 3H), 2.81 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 188.9, 147.2, 136.9, 131.3, 130.6, 129.8, 129.5, 126.4, 124.0, 123.6, 122.4, 112.8, 110.1, 50.9, 40.3, 31.1;

FT-IR (neat): 3278, 3055, 2932, 1639, 1466, 1396, 1322, 1149, 1077, 919, 751 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 343.1112 $[M+H]^+$ ($C_{18}H_{19}N_2O_3S$ requires 343.1111).

***N*-(2-(5-Bromo-1,2-dimethyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.174):**



Prepared *via* **G.P. 2.8** outlined above using 67 mg (0.3 mmol, 1.5 equiv) of 5-bromo-1,2-dimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 78% yield (55.2 mg) as an off-white solid.

m.p. 170-171 °C;

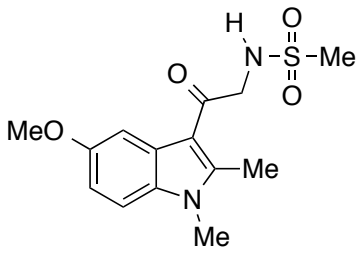
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.28 (t, *J* = 5.5 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 3.75 (s, 3H), 3.01 (s, 3H), 2.74 (s, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 189.8, 147.1, 135.3, 127.2, 124.6, 122.8, 114.9, 112.5, 110.6, 51.6, 40.5, 30.1, 13.0;

FT-IR (neat): 3309, 3266, 1638, 1624, 1436, 1318, 1234, 1161, 1143, 1067, 796, 761 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 359.0062 $[M+H]^+$ ($C_{13}H_{16}N_2O_3BrS$ requires 359.0060).

***N*-(2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3-yl)-2-oxoethyl)methanesulfonamide (2.175):**



Prepared *via* **G.P. 2.8** outlined above using 53 mg (0.3 mmol, 1.5 equiv) of 5-methoxy-1,2-dimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 84% yield (51.1 mg) as an off-white solid.

m.p. 154-155 °C;

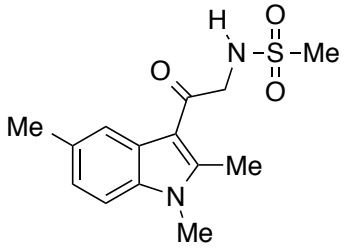
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.59-7.37 (m, 2H), 7.23 (t, *J* = 5.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.01 (s, 3H), 2.72 (s, 3H);

^{13}C NMR (151 MHz, DMSO-d_6): δ 189.5, 155.5, 146.0, 131.6, 126.2, 111.1, 110.9, 110.8, 103.6, 55.4, 51.5, 40.5, 29.9, 13.0;

FT-IR (neat): 3268, 2925, 2853, 1626, 1486, 1318, 1231, 1152, 1073, 772 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 311.1062 $[M+H]^+$ ($C_{14}H_{19}N_4O_4S$ requires 311.1060).

***N*-(2-Oxo-2-(1,2,5-trimethyl-1*H*-indol-3-yl)ethyl)methanesulfonamide (2.176):**



Prepared *via* **G.P. 2.8** outlined above using 48 mg (0.3 mmol, 1.5 equiv) of 1,2,5-trimethylindole, 29 mg (0.24 mmol, 1.2 equiv) of (ethynyloxy)benzene, 24.2 mg (0.2 mmol, 1.0 equiv) of mesyl azide, and 1.1 mg (0.006 mmol, 0.03 equiv) of CuTC. Title compound was isolated in 88% yield (51.4 mg) as an off-white solid.

m.p. 162-163 °C;

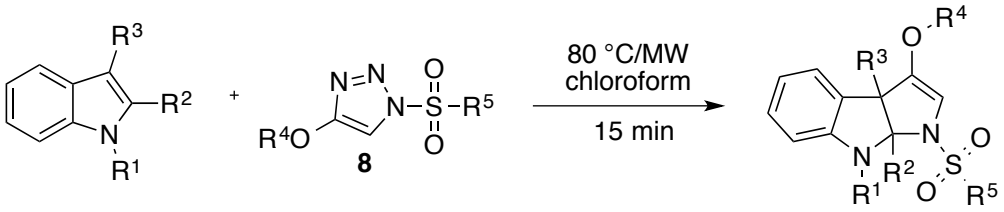
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.74 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 5.5 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H), 3.01 (s, 3H), 2.73 (s, 3H), 2.44 (s, 3H);

^{13}C NMR (151 MHz, DMSO-d_6): δ 190.3, 146.7, 135.6, 131.5, 126.1, 124.0, 121.0, 111.1, 110.8, 52.4, 41.2, 30.4, 22.1, 13.4;

FT-IR (neat): 3240, 2918, 1633, 1418, 1401, 1309, 1150, 1073, 970, 771 cm^{-1};

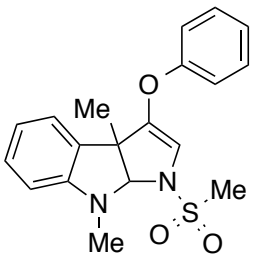
HRMS (FTMS+pNSI): *m/z* 295.1112 $[M+H]^+$ ($C_{14}H_{19}N_2O_3S$ requires 295.1111).

General Procedure 2.10 for Dearomatizing [3+2] Annulation of C(3)-Substituted Indoles with 4-Oxy *N*-Sulfonyl Triazoles (G.P. 2.10):



To a 10 mL high pressure snap-cap tube equipped with a magnetic stir bar, triazole (0.30 mmol) and the appropriate indole (0.60 mmol), were added together under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was subjected to microwave irradiation at 80 °C for 15 minutes. TLC analysis of the reaction mixture indicated consumption of the triazole. It was then subjected to flash silica chromatography (9:1→3:1 pentanes:EtOAc; Biotage Isolera) to afford the indole product as a white solid or colorless oil.

3a,8-Dimethyl-1-(methylsulfonyl)-3-phenoxy-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (2.178):



Prepared *via* **G.P. 2.10** outlined above using 87 mg (0.6 mmol, 2 equiv) of 1,3-dimethylindole and 72 mg (0.30 mmol, 1.0 equiv) of 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 93% yield (99.5 mg) as a white solid.

m.p. 110-111 °C;

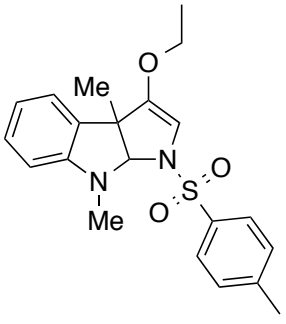
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.32 (t, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.20-7.14 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 5.46 (s, 1H), 5.33 (s, 1H), 3.03 (s, 3H), 2.95 (s, 3H), 1.73 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 156.1, 153.6, 149.4, 130.0, 129.5, 129.0, 125.2, 123.7, 119.8, 117.9, 105.8, 105.0, 91.2, 55.6, 36.4, 31.7, 23.3;

FT-IR (neat): 3114, 3056, 2967, 2927, 2833, 1656, 1607, 1590, 1490, 1344, 1305, 1157, 1094, 1005, 747 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 357.1267 $[M+H]^+$ ($C_{19}H_{21}N_2O_3S$ requires 357.1267).

3-Ethoxy-3a,8-dimethyl-1-tosyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (2.179):



Prepared *via* **G.P. 2.10** outlined above using 88 mg (0.6 mmol, 2 equiv) of 1,3-dimethylindole and 81.2 mg (0.30 mmol, 1.0 equiv) of 4-ethoxy-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 86% yield (101 mg) as a white solid.

m.p. 124-125 °C;

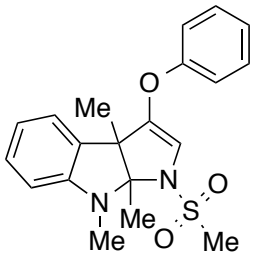
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.09 (td, *J* = 7.7, 1.3 Hz, 1H), 7.00 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 5.55 (s, 1H), 4.98 (s, 1H), 3.72 (q, *J* = 7.0 Hz, 2H), 3.04 (s, 3H), 2.45 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.66 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 154.9, 149.3, 144.1, 133.5, 129.7, 128.6, 128.0, 123.6, 117.2, 105.6, 99.8, 90.5, 66.4, 55.2, 31.3, 22.0, 21.7, 14.5;

FT-IR: 3116, 3053, 2977, 2926, 1651, 1606, 1493, 1347, 1304, 1163, 1088, 1002, 737 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 385.1572 $[M+H]^+$ ($C_{21}H_{25}N_2O_3S$ requires 385.1580).

3a,8,8a-Trimethyl-1-(methylsulfonyl)-3-phenoxy-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (2.181):



Prepared *via* **G.P. 2.10** outlined above using 95 mg (0.6 mmol, 2 equiv) of 1,2,3-trimethylindole and 72 mg (0.30 mmol, 1.0 equiv) of 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 67% yield (88 mg) as a clear oil.

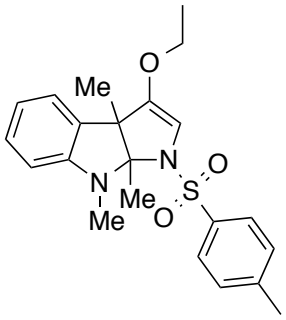
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.35-7.27 (m, 3H), 7.20 (td, *J* = 7.7, 1.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08-7.03 (m, 2H), 6.78 (td, *J* = 7.5, 1.0 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.56 (s, 1H), 3.07 (s, 3H), 2.75 (s, 3H), 1.81 (s, 3H), 1.55 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 156.2, 149.2, 149.1, 131.8, 129.8, 128.9, 124.7, 123.1, 119.6, 118.9, 107.1, 106.6, 96.2, 59.9, 38.8, 31.3, 19.3, 19.2;

FT-IR (neat): 3117, 3031, 2974, 2932, 2824, 1675, 1591, 1488, 1339, 1314, 1256, 1152, 1105, 990, 912, 892, 761, 745 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 371.1415 $[M+H]^+$ ($C_{20}H_{23}N_2O_3S$ requires 371.1420).

3-Ethoxy-3a,8,8a-trimethyl-1-tosyl-1,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole (2.182):



Prepared *via* **G.P. 2.10** outlined above using 95 mg (0.6 mmol, 2 equiv) of 1,2,3-trimethylindole and 81 mg (0.30 mmol, 1.0 equiv) of 4-ethoxy-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 71% yield (85 mg) as a clear oil.

^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.06-6.97 (m, 2H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 5.85 (s, 1H),

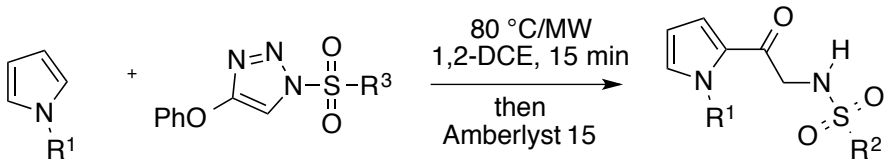
3.89-3.66 (m, 2H), 2.92 (s, 3H), 2.39 (s, 3H), 1.50 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.00 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 151.2, 148.3, 143.0, 138.0, 130.3, 129.3, 128.4, 126.7, 123.3, 117.5, 105.4, 101.9, 95.5, 66.0, 59.0, 28.9, 21.6, 18.4, 16.1, 14.6;

FT-IR (neat): 3114, 3056, 2967, 2927, 2833, 1656, 1607, 1590, 1490, 1344, 1305, 1157, 1094, 1005, 747 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 399.1736 $[M+H]^+$ ($C_{22}H_{27}N_2O_3S$ requires 399.1737).

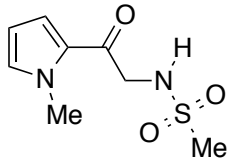
General Procedure 2.11 for Pyrrole Acylation from Enol *N*-Sulfonyl Triazoles (G.P. 2.11):



To a 10 mL high pressure snap-cap tube equipped with a magnetic stir bar, triazole (0.20 mmol) and the appropriate pyrrole (0.30 mmol) were added together under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was subjected to microwave irradiation at 80 °C for 15 minutes. TLC analysis of the reaction mixture indicated consumption of the triazole. Amberlyst 15 (150 mg) and 2 drops of water were added to the reaction and the resulting mixture was warmed at 50 °C for 2-4 hours until complete hydrolysis as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with ethyl acetate followed by extraction(x3) with a pipette to a

separatory funnel containing 0.5M NaOH leaving behind the Amberlyst 15 catalyst. The layers were then separated and the organic was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. It was then subjected to flash silica chromatography (9:1→1:8 pentanes:EtOAc w/ 3%Et_3N; Biotage Isolera) to afford the pyrrole product as tan or off-white solid.

***N*-(2-(1-Methyl-1*H*-pyrrol-2-yl)-2-oxoethyl)methanesulfonamide (2.184):**



Prepared *via* **G.P. 2.11** outlined above using *N*-methylpyrrole and 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 93% yield as an off-white solid.

m.p. 113-115 °C;

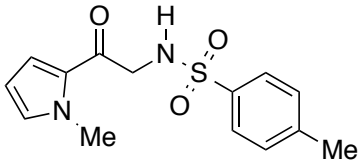
^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.99 (dd, *J* = 4.2, 1.2 Hz, 1H), 6.91-6.89 (m, 1H), 6.17 (dd, *J* = 4.1, 2.5 Hz, 1H), 5.46 (br t, *J* = 5.1 Hz, 1H), 4.43 (d, *J* = 5.0 Hz, 2H), 3.93 (s, 3H), 2.97 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 183.2, 132.4, 127.6, 119.5, 109.1, 48.4, 40.7, 37.6;

FT-IR (neat): 3241, 3113, 2930, 1658, 1530, 1402, 1301, 1134, 1125, 956, 782, 754 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 239.0463 $[M+Na]^+$ ($C_8H_{12}N_2O_3SNa$ requires 239.0461).

4-Methyl-*N*-(2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl)benzenesulfonamide (2.184):



Prepared *via* **G.P. 2.11** outlined above using *N*-methylpyrrole and 1-(tosyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 89% yield as an off-white solid.

m.p. 107-108 °C;

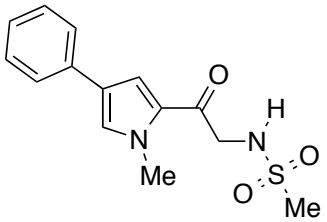
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.88 (dd, *J* = 4.4, 1.5 Hz, 1H), 6.85-6.83 (m, 1H), 6.12 (dd, *J* = 4.3, 2.6 Hz, 1H), 5.65 (br t, *J* = 4.6 Hz, 1H), 4.22 (d, *J* = 4.6 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 182.2, 143.6, 136.2, 132.2, 129.8, 127.6, 127.3, 119.4, 109.0, 47.8, 37.5, 21.6;

FT-IR (neat): 3267, 3114, 2923, 1648, 1528, 1376, 1328, 1121, 1092, 959, 814, 743 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 293.0961 $[M+H]^+$ ($C_{14}H_{17}N_2O_3S$ requires 293.0954).

***N*-(2-(1-Methyl-4-phenyl-1*H*-pyrrol-2-yl)-2-oxoethyl)methanesulfonamide (2.185):**



Prepared *via* **G.P. 2.11** outlined above using 3-phenyl-1-methylpyrrole and 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 68% yield as a white solid.

m.p. 156-159 °C;

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.48 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.31-7.23 (m, 2H), 7.20 (d, *J* = 1.8 Hz, 1H), 5.31 (t, *J* = 5.1 Hz, 1H), 4.51 (d, *J* = 5.0 Hz, 2H), 4.00 (s, 3H), 3.01 (s, 3H);

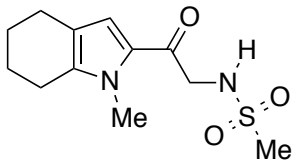
^{13}C NMR (101 MHz, Chloroform-*d*): δ 183.1, 133.5, 129.1, 128.9, 128.1, 126.7, 125.1, 116.0, 48.4, 40.6, 37.8;

FT-IR (neat): 3274, 3112, 3026, 2929, 1662, 1604, 1430, 1382, 1361, 1323, 1148, 972, 761

cm^{-1};

HRMS (FTMS+pNSI): *m/z* 315.0771 $[M+Na]^+$ ($C_{14}H_{16}N_2O_3SNa$ requires 315.0773).

***N*-(2-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-oxoethyl)methanesulfonamide (2.186):**



Prepared *via* **G.P. 2.11** outlined above using 4,5,6,7-tetrahydro-1-methylindole and 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 84% yield as an off-white solid.

m.p. 134-135 °C;

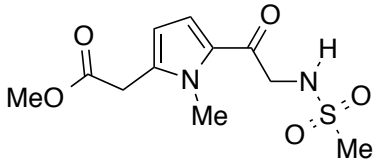
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.77 (s, 1H), 5.38 (t, *J* = 5.0 Hz, 1H), 4.37 (d, *J* = 5.0 Hz, 2H), 3.80 (s, 3H), 2.95 (s, 3H), 2.56 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 6.1 Hz, 2H), 1.88-1.82 (m, 2H), 1.75-1.70 (m, 2H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 181.7, 140.5, 126.2, 120.0, 117.9, 48.1, 40.5, 32.8, 23.2, 22.9, 22.7, 22.3;

FT-IR (neat): 3252, 3024, 2934, 2846, 1651, 1430, 1358, 1315, 1291, 1151, 989, 772 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 271.1113 $[M+H]^+$ ($C_{12}H_{19}N_2O_3S$ requires 271.1111).

Methyl 2-(1-methyl-5-((methylsulfonyl)glycyl)-1*H*-pyrrol-2-yl)acetate (2.187):



Prepared *via* **G.P. 2.11**outlined above using methyl 2-(1-methyl-1H-pyrrol-2-yl)acetate and 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 82% yield as an off-white solid.

m.p. 109-110 °C;

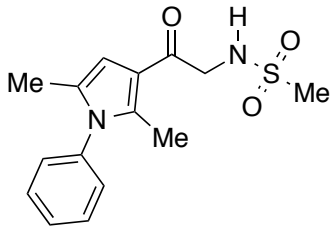
^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.97 (d, *J* = 4.2 Hz, 1H), 6.15 (d, *J* = 4.2 Hz, 1H), 5.30 (br t, *J* = 5.1 Hz, 1H), 4.43 (d, *J* = 5.0 Hz, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.70 (s, 2H), 2.97 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 182.9, 169.6, 135.9, 128.3, 119.3, 110.8, 52.8, 48.5, 40.8, 33.7, 32.7;

FT-IR: 3282, 2958, 2850, 1720, 1648, 1496, 1379, 1249, 1205, 1141, 921, 776, 762 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 289.0855 $[M+H]^+$ ($C_{11}H_{17}N_2O_5S$ requires 289.0853).

***N*-(2-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-2-oxoethyl)methanesulfonamide (2.188):**



Prepared *via* **G.P. 2.11** outlined above using 2,5-dimethyl-1-phenylpyrrole and 1-(methylsulfonyl)-4-phenoxy-1*H*-1,2,3-triazole. Title compound was isolated in 86% yield as an off-white semi-solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.58-7.42 (m, 3H), 7.22-7.08 (m, 2H), 6.29 (s, 1H), 5.48 (br t, *J* = 4.8 Hz, 1H), 4.40 (d, *J* = 4.8 Hz, 2H), 2.97 (s, 3H), 2.31 (s, 3H), 1.98 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 188.8, 137.7, 136.9, 130.1, 129.7, 129.1, 128.0, 116.8, 106.2, 49.8, 40.3, 13.2, 12.8;

FT-IR (neat): 3277, 3022, 2925, 1656, 1522, 1499, 1408, 1325, 1150, 1030, 966, 772 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 307.1114 $[M+H]^+$ ($C_{15}H_{19}N_2O_3S$ requires 307.1111).

7.2 Experimental Part to Chapter 3

Starting Materials

Commerically available reagents were used without purification unless noted otherwise. Vinyl triflates were prepared from a Buchwald protocol using LiHMDS and Tf_2NPh.[198] The selective formation of the thermodynamic vinyl triflate of 5-cholestan-3-one was prepared by KHMDS.[199] The thermodynamic vinyl triflate of nootkatone was prepared with triflic anhydride and 2,6-lutidine.[199] CuTC was prepared according to the literature procedure and stored in the dark.[195] Catalyst with a light grayish beige color had the best reaction times and yields. $Rh_2(esp)_2$ was purchased from Strem and used as received.

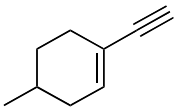
Caution! Sulfonyl azides are potentially explosive materials and must be handled with caution. Failure to do so could result in serious injury!

General Procedure for Enyne Synthesis (G.P. 3.1):

In an oven-dried 250 mL flask, the alkenyl triflate (10 mmol), $Co(acac)_3$ (0.3 mmol), and THF (20 mL) were mixed together and placed under an atmosphere of argon. After

stirring at room temperature for 5 minutes, ethynylmagnesium bromide (0.5M in THF; 20 mmol) was added at a rate of 2mL/min. After the reaction was stirred at room temperature for 12 hours, a 0.1 M HCl aqueous solution was added and the resulting mixture was extracted with either pentanes or diethyl ether (x2). The combined organic layers were washed with brine and dried with $MgSO_4$. The organic layer was then filtered followed by evaporation under reduced pressure. Subjection of the crude material to flash silica gel chromatography (100% pentanes or 19:1 pentanes:ether) afforded the enyne product as a colorless liquid. The use of $Pd(PPh_3)_4$ provided faster reaction times and higher yields contrary to the literature.[200]

1-Ethynyl-4-methylcyclohex-1-ene (3.46a):



Title compound was isolated in 87% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

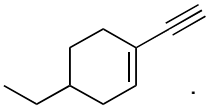
^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.14-6.12 (m, 1H), 2.77 (s, 1H), 2.16-2.13 (m, 3H), 1.78-1.53 (m, 3H), 1.22 (dtd, *J* = 13.0, 10.2, 6.6 Hz, 1H), 0.94 (d, *J* = 6.4 Hz, 3H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 135.9, 119.5, 85.5, 74.6, 34.1, 30.5, 29.1, 27.6, 21.7;

FT-IR (neat): 3311, 3292, 3028, 2950, 2924, 2870, 2825, 2093, 1632, 155, 1434, 1376, 1137, 899, 816 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 121.1011 $[M+H]^+$ (C_9H_{13} requires 121.1012).

4-Ethyl-1-ethynylcyclohex-1-ene (3.47a):



Title compound was isolated in 84% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

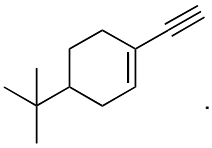
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.19-6.15 (m, 1H), 2.79 (s, 1H), 2.26-2.11 (m, 3H), 1.82-1.62 (m, 2H), 1.47-1.35 (m, 1H), 1.35-1.12 (m, 3H), 0.90 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 136.2, 119.7, 85.6, 74.6, 34.4, 32.1, 29.2, 29.1, 28.3, 11.5;

FT-IR (neat): 3312, 3028, 2960, 2919, 2873, 2825, 2094, 1634, 1460, 1434, 1209, 1143, 911, 832 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 135.1168 $[M+H]^+$ ($C_{10}H_{15}$ requires 135.1168).

4-(*tert*-Butyl)-1-ethynylcyclohex-1-ene (3.48a):



Title compound was isolated in 83% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

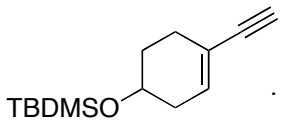
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.19 (dt, *J* = 6.0, 2.7 Hz, 1H), 2.79 (s, 1H), 2.27-2.04 (m, 3H), 1.94-1.72 (m, 2H), 1.34-1.07 (m, 2H), 0.86 (s, 9H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 136.9, 119.7, 85.5, 74.7, 43.2, 32.3, 30.6, 27.5, 27.2, 23.8;

FT-IR (neat): 3313, 3028, 2957, 2868, 2094, 1636, 1477, 1365, 836, 809 cm^{-1};

Data consistent with the literature.[201]

***tert*-Butyl((4-ethynylcyclohex-3-en-1-yl)oxy)dimethylsilane (3.49a):**



Title compound was isolated in 86% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.86 (19:1 Hexanes:EtOAc);

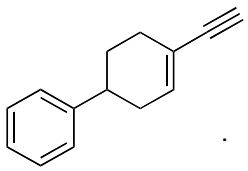
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.05-6.03 (m, 1H), 3.88 (dtd, *J* = 10.2, 4.9, 2.5 Hz, 1H), 2.80 (s, 1H), 2.39-2.25 (m, 2H), 2.25-2.12 (m, 1H), 2.12-2.01 (m, 1H), 1.78 (dd, *J* = 14.6, 6.5 Hz, 1H), 1.69-1.55 (m, 1H), 0.88 (s, 9H), 0.05 (d, *J* = 2.2 Hz, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 133.9, 119.6, 85.0, 75.1, 66.7, 35.5, 31.3, 27.9, 26.0, 18.3, -4.6;

FT-IR (neat): 3314, 2928, 2856, 2097, 1462, 1252, 1094, 867, 831, 772 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 237.1668 $[M+H]^+$ ($C_{14}H_{25}OSi$ requires 237.1669).

4-Ethynyl-1,2,3,6-tetrahydro-1,1'-biphenyl (3.50a):



Title compound was isolated in 81% yield as a colorless solid following **G.P. 3.1**.

Rf = 0.48 (19:1 Hexanes:EtOAc);

m.p. 65-66 °C;

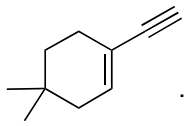
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.36-7.28 (m, 2H), 7.26-7.17 (m, 3H), 6.34-6.25 (m, 1H), 2.88-2.75 (m, 2H), 2.47-2.19 (m, 4H), 2.04-1.93 (m, 1H), 1.79 (ddd, *J* = 23.6, 11.9, 5.8 Hz, 1H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 146.5, 136.1, 128.7, 127.0, 126.5, 120.0, 85.4, 75.3, 39.3, 33.9, 29.9, 29.6;

FT-IR (neat): 3274, 3028, 2917, 2090, 1601, 1494, 1452, 1433, 908, 731 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 183.1168 $[M+H]^+$ ($C_{14}H_{15}$ requires 183.1168).

1-Ethynyl-4,4-dimethylcyclohex-1-ene (3.51a):



Title compound was isolated in 87% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

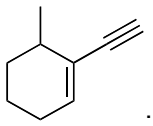
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.10 (dt, *J* = 4.2, 2.2 Hz, 1H), 2.77 (s, 1H), 2.14 (ddt, *J* = 6.5, 4.3, 2.4 Hz, 2H), 1.87-1.84 (m, 2H), 1.36 (t, *J* = 6.5 Hz, 2H), 0.90 (s, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 135.5, 118.7, 85.5, 74.6, 39.5, 35.0, 28.3, 28.2, 27.0;

FT-IR (neat): 3313, 3028, 2951, 2867, 2095, 1450, 1364, 1190, 1014, 815 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 135.1168 $[M+H]^+$ ($C_{10}H_{15}$ requires 135.1168).

1-Ethynyl-6-methylcyclohex-1-ene (3.52a):



Title compound was isolated in 92% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

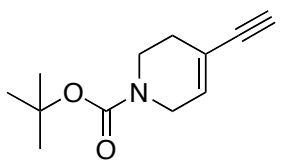
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.17 (td, *J* = 4.1, 1.9 Hz, 1H), 2.80 (s, 1H), 2.32-2.14 (m, 1H), 2.10-1.98 (m, 2H), 1.76 (dtd, *J* = 13.2, 5.4, 2.7 Hz, 1H), 1.71-1.57 (m, 1H), 1.57-1.42 (m, 1H), 1.36-1.22 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 137.0, 125.7, 85.2, 75.7, 32.7, 31.0, 26.3, 20.6, 20.1;

FT-IR (neat): 3296, 3025, 2930, 2870, 2832, 2092, 1677, 1454, 1002, 882, 811 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 121.1011 $[M+H]^+$ (C_9H_{13} requires 121.1012).

***tert*-Butyl 4-ethynyl-5,6-dihydropyridine-1(2*H*)-carboxylate (3.53a):**



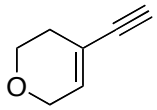
Title compound was isolated in 73% yield as a colorless liquid following **G.P. 3.1**.

^{1}H NMR (600 MHz, $CDCl_3$, 55 °C): δ 6.10 (bs, 1H), 3.97 (s, 2H), 3.50 (s, 2H), 2.90 (s, 1H), 2.26 (bs, 2H), 1.47 (s, 9H);

^{13}C NMR (150 MHz, $CDCl_3$, 55 °C): δ 154.9, 132.4, 119.0, 84.0, 80.1, 76.5, 43.8, 29.4, 28.7;

Data consistent with the literature.[1]

4-Ethynyl-3,6-dihydro-2*H*-pyran (3.54a):



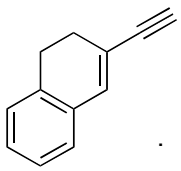
Title compound was isolated in 71% yield as a colorless volatile liquid following **G.P. 3.1**.

^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.17-6.13 (m, 1H), 4.17 (q, J = 3.0 Hz, 2H), 3.76 (t, J = 5.4 Hz, 2H), 2.88 (s, 1H), 2.27-2.20 (m, 2H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 134.1, 117.8, 83.6, 76.4, 65.4, 63.9, 28.9;

Data consistent with the literature.[1]

3-Ethynyl-1,2-dihydronaphthalene (3.55a):



[1] Parr, B. T.; Davies, H. M. L. *Angew. Chem. Int. Ed.* submitted.

Title compound was isolated in 86% yield as a light yellow liquid following **G.P. 3.1**.

Rf = 0.86 (19:1 Hexanes:EtOAc);

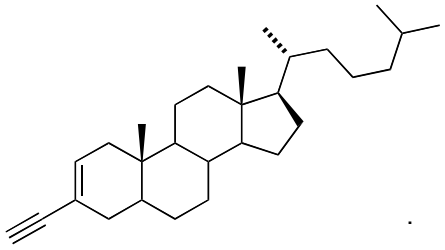
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.22-7.11 (m, 2H), 7.10-7.05 (m, 2H), 6.89 (s, 1H), 3.16 (s, 1H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.49 (td, *J* = 8.2, 1.5 Hz, 2H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 135.0, 134.8, 133.4, 128.1, 127.6, 126.8, 126.6, 120.1, 85.2, 79.1, 30.4, 27.5;

FT-IR (neat): 3285, 3015, 2938, 2833, 2087, 1483, 888, 861, 753 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 155.0855 $[M+H]^+$ ($C_{12}H_{11}$ requires 155.0855).

(10*S*,13*R*,17*R*)-3-ethynyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene (3.45a):



Title compound was isolated in 77% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

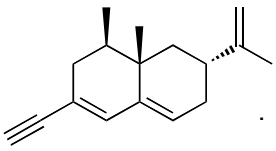
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.17-5.98 (m, 1H), 2.78 (s, 1H), 2.11-0.94 (m, 28H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.74 (s, 3H), 0.73-0.67 (m, 1H), 0.66 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 135.7, 118.7, 85.5, 77.5, 77.2, 76.8, 74.5, 56.5, 56.4, 53.9, 42.6, 41.4, 40.4, 40.1, 39.7, 36.3, 36.0, 35.7, 34.2, 34.0, 31.8, 28.5, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 18.8, 12.1, 12.0;

FT-IR (neat): 3312, 2929, 2866, 2095, 1466, 1443, 1381, 1118, 814 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 395.3676 $[M+H]^+$ ($C_{29}H_{47}$ requires 395.3672).

(2*R*,8*R*,8a*S*)-6-Ethynyl-8,8a-dimethyl-2-(prop-1-en-2-yl)-1,2,3,7,8,8a-hexahydronaphthalene (3.48):



Title compound was isolated in 88% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

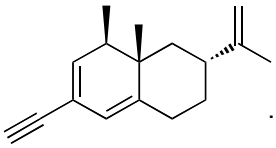
^{1}H NMR (600 MHz, Chloroform-*d*): δ 6.37 (d, *J* = 2.3 Hz, 1H), 5.56 (dd, *J* = 5.3, 2.9 Hz, 1H), 4.75 (s, 2H), 2.95 (s, 1H), 2.43 (br t, *J* = 13.3 Hz, 1H), 2.28 (dt, *J* = 18.9, 5.3 Hz, 1H), 2.15 (dd, *J* = 18.0, 5.1 Hz, 1H), 2.12-1.95 (m, 2H), 1.79-1.68 (m, 4H), 1.55 (dq, *J* = 11.7, 6.0, 5.2 Hz, 1H), 1.17 (t, *J* = 12.7 Hz, 1H), 0.92-0.88 (m, 6H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 150.0, 141.7, 136.5, 126.6, 117.0, 109.0, 85.7, 76.9, 39.9, 38.6, 37.2, 35.7, 35.7, 31.5, 20.8, 17.7, 14.6;

FT-IR (neat): 3308, 3081, 3020, 2967, 2910, 2833, 2090, 1643, 1633, 1457, 1440, 1372, 887 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 227.1793 $[M+H]^+$ ($C_{17}H_{23}$ requires 227.1794).

(3*R*,4a*S*,5*R*)-7-Ethynyl-4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5-hexahydronaphthalene (3.50):



Title compound was isolated in 94% yield as a colorless liquid following **G.P. 3.1**.

Rf = 0.90 (19:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.91-5.75 (m, 1H), 5.59 (s, 1H), 4.71 (s, 2H), 2.79 (s, 1H), 2.44-2.25 (m, 3H), 2.15 (tt, *J* = 12.3, 3.1 Hz, 1H), 1.90 (dt, *J* = 12.9, 2.8 Hz, 1H), 1.85-1.76 (m, 1H), 1.73 (s, 3H), 1.26 (qd, *J* = 12.2, 5.9 Hz, 1H), 1.12 (t, *J* = 12.8 Hz, 1H), 1.02 (d, *J* = 7.5 Hz, 3H), 0.82 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 149.7, 146.2, 138.1, 118.8, 117.2, 108.6, 83.6, 74.6, 45.4, 42.1, 41.0, 40.9, 37.8, 31.1, 31.0, 30.9, 30.1, 20.7, 14.3, 13.0;

FT-IR (neat): 3309, 3081, 2962, 2926, 2875, 2808, 2100, 1642, 1577, 1450, 1431, 1381, 1188, 980, 886, 814, 771 cm^{-1};

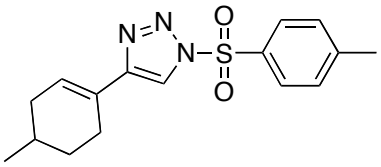
HRMS (FTMS+pAPCI): *m/z* 227.1792 $[M+H]^+$ ($C_{17}H_{23}$ requires 227.1794).

General Procedure 3.2 for CuTC-catalyzed Azide-Alkyne Cycloaddition (G.P. 3.2):

To a stirring solution of alkyne (1 equiv.) in toluene (0.25 M), copper(I) thiophene-2-carboxylate (CuTC, 5 mol%) was added at room temperature. After stirring for 2-4 minutes, a solution of sulfonyl azide (1.0 equiv) in toluene was added dropwise to the

resulting mixture. The reaction media was then stirred at room temperature for 2-8 hrs. Once the starting alkyne had been completely consumed as judged by TLC analysis, the mixture was concentrated under reduced pressure, and filtered through a short plug of silica to remove copper catalyst eluting with 2:1 pentane:EtOAc. After removal of solvent under reduced pressure, an off-white solid was triturated with 2:1 pentane:ether (x3) to afford the desired triazole.

4-(4-Methylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.46):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4-methylcyclohex-1-ene and tosyl azide. Title compound was isolated in 83% yield as an off-white solid.

m.p. 107-108 °C (dec);

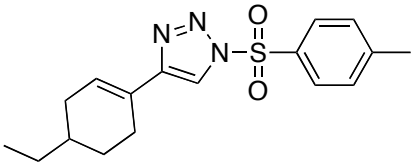
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.89 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.69-6.56 (m, 1H), 2.43 (s, 3H), 2.40-2.21 (m, 3H), 1.89-1.63 (m, 3H), 1.40-1.28 (m, 1H), 0.98 (d, *J* = 6.3 Hz, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 148.9, 147.2, 133.4, 130.5, 128.6, 127.3, 125.5, 117.6, 33.9, 30.5, 28.2, 26.3, 21.9, 21.7;

FT-IR (film): 3145, 2949, 2923, 1594, 1393, 1193, 1176, 1091, 970, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 318.1270 $[M+H]^+$ ($C_{16}H_{20}N_3O_2S$ requires 318.1270).

4-(4-Ethylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.47):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4-ethylcyclohex-1-ene and tosyl azide. Title compound was isolated in 86% yield as an off-white solid.

m.p. 102-103 °C (dec);

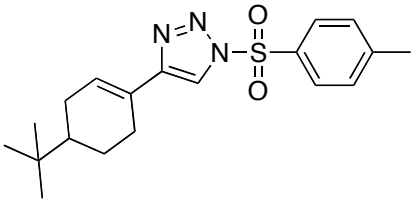
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.62 (dq, *J* = 4.9, 1.8 Hz, 1H), 2.42 (s, 3H), 2.38-2.19 (m, 3H), 1.96-1.69 (m, 2H), 1.51-1.40 (m, 1H), 1.40-1.20 (m, 3H), 0.91 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.9, 147.2, 133.4, 130.5, 128.6, 127.3, 125.8, 117.5, 34.9, 31.8, 29.0, 28.3, 26.4, 21.9, 11.5;

FT-IR (film): 3145, 2958, 2919, 2873, 1594, 1390, 1193, 1176, 973, 670 cm^{-1}:

HRMS (FTMS+pNSI): *m/z* 332.1426 $[M+H]^+$ ($C_{17}H_{22}N_3O_2S$ requires 332.1432).

4-(4-(*tert*-Butyl)cyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.48):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4-*tert*-butylcyclohex-1-ene and tosyl azide. Title compound was isolated in 85% yield as an off-white solid.

m.p. 132-133 °C (dec);

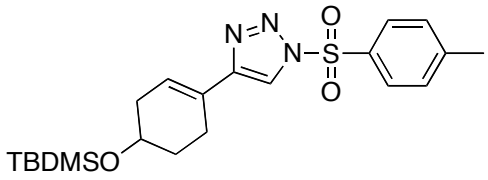
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.87 (s, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.63 (br t, *J* = 5.2 Hz, 1H), 2.41 (s, 4H), 2.35-2.15 (m, 2H), 2.00-1.85 (m, 2H), 1.37-1.15 (m, 2H), 0.87 (s, 9H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.8, 147.2, 133.4, 130.5, 128.6, 128.0, 125.7, 117.5, 43.9, 32.3, 27.8, 27.3, 27.1, 23.8, 21.9;

FT-IR (film): 3132, 3069, 2956, 2126, 1595, 1384, 1195, 1178, 1094, 980, 812 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 360.1738 $[M+H]^+$ ($C_{19}H_{26}N_3O_2S$ requires 360.1740).

4-(4-((*tert*-Butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.49):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4-((tert-butyldimethylsilyl)oxy)cyclohex-1-ene and tosyl azide. Title compound was isolated in 79% yield a light tan solid after being freeze-thawed under vacuum in benzene.

m.p. 88-89 °C (dec);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.90 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.52 (d, *J* = 4.3 Hz, 1H), 3.96 (ddd, *J* = 7.8, 5.0, 3.1 Hz, 1H), 2.54-2.36 (m, 6H), 2.23-2.09 (m, 1H), 1.96-1.81 (m, 1H), 1.81-1.66 (m, 1H), 0.88 (s, 9H), 0.06 (d, *J* = 2.6 Hz, 6H);

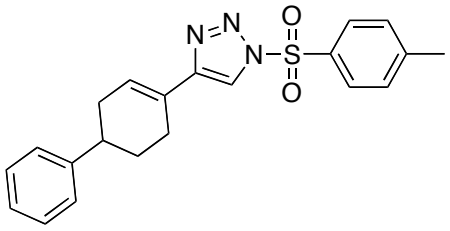
^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.3, 147.2, 133.3, 130.5, 128.6, 125.5, 125.1, 117.8, 67.1, 35.1, 31.2, 26.0, 26.0, 25.0, 21.9, 18.3, -4.6;

FT-IR (film): 3147, 2951, 2927, 2885, 2855, 1594, 1436, 1195, 1176, 1096, 983, 835, 774, 671

cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 434.1927 $[M+H]^+$ ($C_{21}H_{32}O_3N_3SSi$ requires 434.1928).

4-(1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-yl)-1-tosyl-1*H*-1,2,3-triazole (3.50):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4-phenylcyclohex-1-ene and tosyl azide. Title compound was isolated in 88% yield as an off-white solid.

m.p. 133-134 °C (dec);

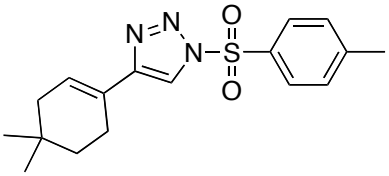
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.95 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.35-7.28 (m, 2H), 7.28-7.18 (m, 3H), 6.80-6.71 (m, 1H), 2.92-2.81 (m, 1H), 2.57-2.41 (m, 6H), 2.42-2.27 (m, 1H), 2.15-2.05 (m, 1H), 1.97-1.82 (m, 1H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.6, 147.3, 146.3, 133.3, 130.5, 128.7, 128.6, 127.1, 126.9, 126.3, 125.8, 117.8, 39.7, 33.4, 29.5, 26.9, 22.0;

FT-IR (film): 3145, 3026, 2919, 1594, 1387, 1194, 1173, 972, 730, 699, 668 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 380.1425 $[M+H]^+$ ($C_{21}H_{22}N_3O_2S$ requires 380.1427).

4-(4,4-Dimethylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.51):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-4,4-dimethylcyclohex-1-ene and tosyl azide. Title compound was isolated in 84% yield as an off-white solid.

m.p. 114-115 °C (dec);

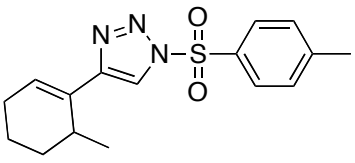
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.58 (tt, *J* = 3.9, 1.8 Hz, 1H), 2.43 (s, 3H), 2.33 (tq, *J* = 6.5, 2.3 Hz, 2H), 1.98 (dt, *J* = 4.6, 2.5 Hz, 2H), 1.49 (t, *J* = 6.4 Hz, 2H), 0.94 (s, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.9, 147.3, 133.5, 130.6, 130.5, 128.8, 126.9, 124.7, 117.6, 39.4, 35.2, 28.8, 28.4, 24.2, 22.0;

FT-IR (film): 3145, 2949, 2916, 2865, 1594, 1432, 1192, 1176, 1092, 970, 812, 669 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 332.1426 $[M+H]^+$ ($C_{17}H_{22}N_3O_2S$ requires 332.1432).

4-(6-Methylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.52):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-2-methylcyclohex-1-ene and tosyl azide. Title compound was isolated in 86% yield as a white solid.

m.p. 93-94 °C (dec);

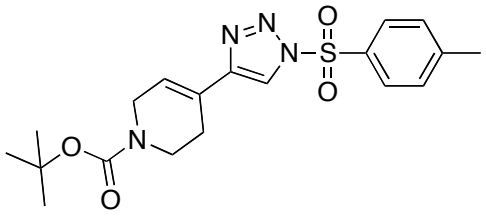
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.50 (t, *J* = 4.0 Hz, 1H), 2.69 (t, *J* = 6.9 Hz, 1H), 2.44 (s, 3H), 2.22-2.10 (m, 2H), 1.82-1.58 (m, 4H), 1.08 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.9, 147.5, 133.7, 131.6, 130.8, 128.9, 128.3, 128.3, 118.3, 118.3, 30.2, 30.0, 26.0, 22.2, 20.3, 18.0;

FT-IR (film): 3144, 2931, 2867, 1593, 1387, 1194, 1175, 975, 811, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 318.1269 $[M+H]^+$ ($C_{16}H_{20}N_3O_2S$ requires 318.1271).

***tert*-Butyl 4-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (3.53):**



Prepared *via* **G.P. 3.2** outlined above using *tert*-butyl 4-ethynyl-5,6-dihydropyridine-1(2*H*)-carboxylate and tosyl azide. Title compound was isolated in 81% yield as a light yellow powder.

m.p. 136-137 °C (dec);

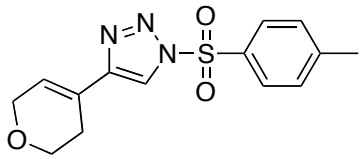
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97-7.95 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.53 (t, *J* = 3.5 Hz, 1H), 4.06 (br d, *J* = 3.2 Hz, 2H), 3.60 (t, *J* = 5.7 Hz, 2H), 2.51-2.38 (m, 5H), 1.46 (s, 9H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 154.8, 147.5, 147.4, 133.1, 130.5, 128.7, 124.8, 123.6 (br s), 118.1, 80.0, 43.7 (br s), 39.3 (br s), 28.5, 26.3, 21.9;

FT-IR (film): 3143, 2975, 2929, 1687, 1594, 1391, 1365, 1239, 1173, 1010, 669 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 405.1589 $[M+H]^+$ ($C_{19}H_{25}N_4O_4S$ requires 405.1591).

4-(3,6-Dihydro-2*H*-pyran-4-yl)-1-tosyl-1*H*-1,2,3-triazole (3.54):



Prepared *via* **G.P. 3.2** outlined above using 4-ethynyl-3,6-dihydro-2*H*-pyran and tosyl azide. Title compound was isolated in 77% yield as an off-white solid.

m.p. 104-107 °C (dec);

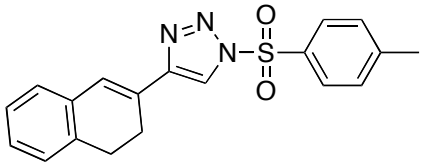
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.00-7.93 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.58 (t, *J* = 2.7 Hz, 1H), 4.29 (m, 2H), 3.89 (t, *J* = 5.5 Hz, 2H), 2.43 (m, 5H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 147.4, 147.4, 133.1, 130.5, 128.7, 125.4, 123.9, 118.1, 65.4, 63.9, 26.2, 21.9;

FT-IR (film): 3143, 2925, 2247, 1593, 1386, 1193, 1175, 974, 667 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 306.0906 $[M+H]^+$ ($C_{14}H_{16}N_3O_3S$ requires 306.0907).

4-(3,4-Dihydronaphthalen-2-yl)-1-tosyl-1*H*-1,2,3-triazole (3.55):



Prepared *via* **G.P. 3.2** outlined above using 3-ethynyl-1,2-dihydronaphthalene and tosyl azide. Title compound was isolated in 88% yield as an off-white solid.

m.p. 111-112 °C (dec);

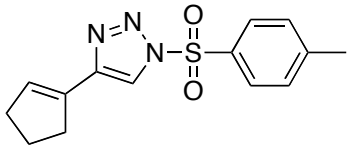
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.10 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.32 (s, 1H), 7.20-7.13 (m, 4H), 2.94 (t, *J* = 8.1 Hz, 2H), 2.68 (t, *J* = 8.1 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.1, 147.5, 135.3, 133.7, 133.3, 130.7, 128.9, 128.0, 127.7, 127.3, 127.0, 126.7, 126.2, 118.8, 27.7, 25.0, 22.1;

FT-IR (film): 3143, 3062, 2933, 2885, 1593, 1389, 1193, 1176, 968, 669 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 352.1110 $[M+H]^+$ ($C_{19}H_{18}N_3O_2S$ requires 352.1114).

4-(Cyclopent-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.56):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-cyclopent-1-ene and tosyl azide. Title compound was isolated in 80% yield as an off-white solid.

m.p. 97-98 °C (dec);

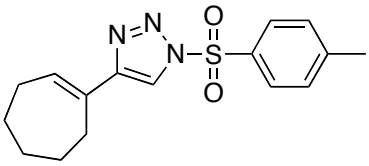
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.1 Hz, 2H), 7.91 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.44 (t, *J* = 2.5 Hz, 1H), 2.70-2.59 (m, 2H), 2.53-2.49 (m, 2H), 2.43 (s, 3H), 2.01 (p, *J* = 15.2, 7.6 Hz, 2H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 147.4, 145.0, 133.4, 131.3, 130.6, 130.6, 128.8, 118.8, 33.5, 33.4, 23.3, 22.1;

FT-IR (film): 3141, 2954, 2847, 1594, 1392, 1334, 1195, 1174, 1092, 981, 813, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 290.0957 $[M+H]^+$ ($C_{14}H_{16}N_3O_2S$ requires 290.0958).

4-(Cyclohept-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole (3.57):



Prepared *via* **G.P. 3.2** outlined above using 1-ethynyl-cyclohept-1-ene and tosyl azide. Title compound was isolated in 83% yield as an off-white solid.

m.p. 79-80 °C (dec);

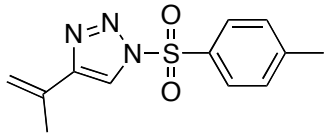
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.91 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.76 (t, *J* = 6.7 Hz, 1H), 2.60-2.52 (m, 2H), 2.43 (s, 3H), 2.31-2.26 (m, 2H), 1.78 (ap q, *J* = 6.2 Hz, 2H), 1.62-1.52 (m, 4H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 150.3, 147.3, 133.5, 132.9, 132.6, 130.6, 128.8, 117.9, 32.3, 31.1, 28.7, 26.7, 26.6, 22.0;

FT-IR (film): 3145, 2921, 2850, 1594, 1391, 1338, 1195, 1176, 1091, 976, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 318.1270 $[M+H]^+$ ($C_{16}H_{20}N_3O_2S$ requires 318.1271).

4-(Prop-1-en-2-yl)-1-tosyl-1*H*-1,2,3-triazole (3.62):



Prepared *via* **G.P. 3.2** outlined above using 2-methylbut-1-en-3-yne and tosyl azide. Title compound was isolated in 89% yield as an off-white solid.

m.p. 81-82 °C (dec);

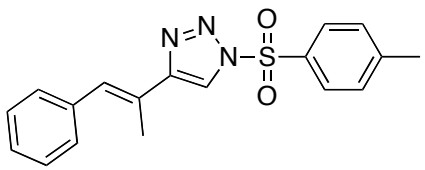
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.16-.81 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 2H), 5.84 (s, 1H), 5.17 (s, 1H), 2.42 (s, 3H), 2.07 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.2, 147.4, 133.1, 132.0, 130.5, 128.7, 119.0, 115.0, 21.9, 20.5;

FT-IR (film): 3144, 2979, 2921, 1594, 1391, 1335, 1193, 1178, 1002, 966, 812, 669 cm^{-1};

HRMS (FTMS+pNSI) *m/z* 264.0800 $[M+H]^+$ ($C_{12}H_{14}N_3O_2S$ requires 264.0801).

(*E*)-4-(1-Phenylprop-1-en-2-yl)-1-tosyl-1*H*-1,2,3-triazole (3.61):



Prepared *via* **G.P. 3.2** outlined above using (*E*)-(2-methylbut-1-en-3-yn-1-yl)benzene and tosyl azide. Title compound was isolated in 78% yield as an off-white solid.

m.p. 106-107 °C (dec);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.07 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.43-7.33 (m, 6H), 7.30-7.25 (m, 1H), 2.45 (s, 3H), 2.24 (d, *J* = 1.6 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 150.4, 147.7, 137.2, 133.6, 130.9, 129.7, 129.5, 129.1, 128.7, 127.6, 125.3, 119.2, 22.3, 16.5;

FT-IR (film): 3134, 3060, 1593, 1393, 1175, 1001, 978, 669 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 340.1112 $[M+H]^+$ ($C_{18}H_{18}N_3O_2S$ requires 340.1114).

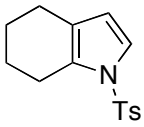
General Procedure 3.3 for Electrocyclization of Triazole (G.P. 3.3):

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, triazole (0.26 mmol) and the appropriate dirhodium catalyst (0.0026 mmol) were added together under ambient atmosphere followed by 2.0 mL of dry 1,2-dichloroethane. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 60 °C for 2-6 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and concentrated under reduced pressure for ^{1}H-NMR analysis of crude mixture. It was then subjected to flash silica chromatography (9:1 pentanes:ether) to afford the pyrrole product as white solid or colorless oil.

General Procedure 3.4 for One-Pot Pyrrole Sythesis Starting from the Enyne (G.P. 3.4):

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, the vinyl alkyne (0.58 mmol) and CuTC (0.029 mmol) were added under an argon atmosphere followed by freshly distilled 1,2-DCE (3 mL) and freshly prepared tosyl azide (0.58 mmol). The tube was sealed and the reaction mixture was stirred at room temperature for 2-4 hours. To the resulting greenish suspension, was added $Rh_2(esp)_2$ (0.0058 mmol). Then, the reaction mixture was warmed to 60 °C for 3-4 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and concentrated under reduced pressure for ^{1}H-NMR analysis of crude mixture. It was then subjected to flash silica chromatography (9:1 pentanes:ether) to afford the pyrrole product as white solid or colorless oil.

1-Tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.44):



Prepared *via* **G.P. 3.3** outlined above using 4-(cyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 93% yield as a colorless solid.

Rf = 0.56 (3:1 Hexanes:EtOAc);

m.p. 98-99 °C;

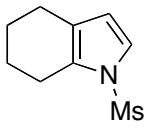
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 3.3 Hz, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.43-2.38 (m, 5H), 1.77-1.66 (m, 2H), 1.66-1.57 (m, 2H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.9, 137.0, 130.4, 129.6, 127.2, 123.9, 120.9, 112.7, 112.6, 23.5, 23.5, 23.3, 23.0, 22.0;

FT-IR (film): 3144, 2926, 2848, 1596, 1486, 1365, 1232, 1166, 1120, 995, 704 cm^{-1};

Spectroscopic data is consistent with the literature.[2]

1-(Methylsulfonyl)-4,5,6,7-tetrahydro-1*H*-indole (3.45):



Prepared *via* **G.P. 3.3** outlined above using 4-(cyclohex-1-en-1-yl)-1-mesyl-1*H*-1,2,3-triazole. Title compound was isolated in 81% yield as a colorless oil.

Rf = 0.61 (3:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.99 (d, *J* = 3.3 Hz, 1H), 6.09 (d, *J* = 3.3 Hz, 1H), 3.07 (s, 3H), 2.76 (t, *J* = 6.1 Hz, 2H), 2.46 (tt, *J* = 6.0, 1.7 Hz, 2H), 1.93-1.76 (m, 2H), 1.74-1.65 (m, 2H);

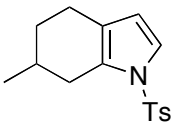
^{13}C NMR (100 MHz, Chloroform-*d*): δ 129.0, 123.8, 120.2, 112.5, 42.5, 23.3, 23.2, 23.1, 22.7;

FT-IR (film): 2930, 2853, 1486, 1445, 1362, 1233, 1181, 1165, 1124, 1003, 772 cm^{-1};

[2] Lubriks, D.; Sokolovs, I.; Suna, E. *Org. Lett.* **2011**, *13*, 4324-4327.

HRMS (FTMS+pAPCI): *m/z* 200.0744 $[M+H]^+$ ($C_9H_{14}NO_2S$ requires 200.0745).

6-Methyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.58):



Prepared *via* **G.P. 3.3** outlined above using 4-(4-methylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 91% yield as a colorless oil.

Rf = 0.56 (3:1 Hexanes:EtOAc);

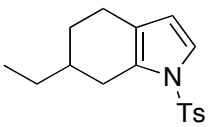
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 3.4 Hz, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 2.88 (dd, *J* = 16.7, 5.3 Hz, 1H), 2.40 (m, 5H), 2.16 (dd, *J* = 16.6, 9.7 Hz, 1H), 1.83-1.69 (m, 2H), 1.30-1.18 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.9, 137.0, 130.4, 129.6, 127.2, 123.6, 121.2, 112.5, 31.6, 31.3, 29.8, 23.1, 22.1, 22.0;

FT-IR (film): 2953, 2925, 2868, 1596, 1358, 1267, 1172, 1115, 1090, 811, 692 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 290.1207 $[M+H]^+$ ($C_{16}H_{20}NO_2S$ requires 290.1209).

6-Ethyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.59):



Prepared *via* **G.P. 3.3** outlined above using 4-(4-ethylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 88% yield as a colorless oil.

Rf = 0.59 (3:1 Hexanes:EtOAc);

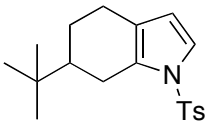
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.32-7.25 (m, 2H), 7.15 (d, *J* = 3.4 Hz, 1H), 6.05 (d, *J* = 3.3 Hz, 1H), 2.89 (dd, *J* = 16.7, 5.3 Hz, 1H), 2.46-2.33 (m, 5H), 2.17 (dd, *J* = 16.7, 9.7 Hz, 1H), 1.83-1.73 (m, 1H), 1.35 (p, *J* = 7.2 Hz, 2H), 1.28-1.18 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.3, 136.4, 129.7, 129.0, 126.6, 123.3, 120.6, 111.9, 36.0, 28.9, 28.5, 28.3, 22.4, 21.5, 11.4;

FT-IR (film): 2958, 2922, 2851, 1596, 1362, 1173, 1118, 813, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 304.1363 $[M+H]^+$ ($C_{17}H_{22}NO_2S$ requires 304.1366).

6-(*tert*-Butyl)-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.60):



Prepared *via* **G.P. 3.3** outlined above using 4-(4-*tert*-butylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 89% yield as a colorless solid.

Rf = 0.58 (3:1 Hexanes:EtOAc);

m.p. 124-125 °C;

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 3.4 Hz, 1H), 6.05 (d, *J* = 3.4 Hz, 1H), 2.83 (dd, *J* = 16.4, 5.0 Hz, 1H),

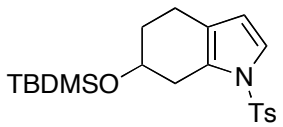
2.53-2.44 (m, 1H), 2.41 (s, 3H), 2.27 (d, *J* = 14.5 Hz, 2H), 1.93-1.81 (m, 1H), 1.39-1.28 (m, 1H), 1.16 (qd, *J* = 12.3, 5.2 Hz, 1H), 0.89 (s, 9H).

^{13}C NMR (150 MHz, Chloroform-*d*): δ 144.7, 136.8, 130.1, 130.0, 127.0, 123.6, 121.0, 112.0, 45.2, 32.7, 27.5, 24.80 24.4, 24.0, 21.8;

FT-IR (film): 2955, 2865, 1596, 1362, 1202, 1130, 668 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 332.1675 $[M+H]^+$ ($C_{19}H_{26}NO_2S$ requires 332.1679).

6-((*tert*-Butyldimethylsilyl)oxy)-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.61):



Prepared *via* **G.P. 3.3** outlined above using 4-(4-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 86% yield as a colorless oil.

Rf = 0.54 (3:1 Hexanes:EtOAc);

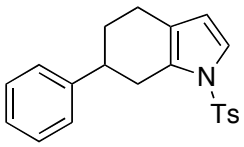
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 3.3 Hz, 1H), 6.05 (d, *J* = 3.3 Hz, 1H), 4.02 (dddd, *J* = 9.5, 6.7, 5.1, 2.8 Hz, 1H), 3.03 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.53 (dd, *J* = 15.2, 5.7 Hz, 1H), 2.44-2.34 (m, 5H), 1.77-1.73 (m, 1H), 1.71-1.61 (m, 1H), 0.84 (s, 9H), 0.03 (d, *J* = 7.6 Hz, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.7, 136.6, 130.1, 127.2, 126.9, 122.9, 121.4, 112.0, 67.9, 33.0, 31.5, 26.0, 25.9, 21.7, 20.4, 18.3, -4.7;

FT-IR (film): 2951, 2927, 2855, 1597, 1367, 1248, 1174, 1092, 835, 673 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 406.1865 $[M+H]^+$ ($C_{21}H_{32}NO_3SSi$ requires 406.1867).

6-Phenyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.62):



Prepared *via* **G.P. 3.3** outlined above using 4-(4-phenylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 88% yield as a colorless oil.

Rf = 0.56 (3:1 Hexanes:EtOAc);

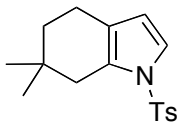
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.40-7.11 (m, 8H), 6.14 (d, *J* = 3.3 Hz, 1H), 3.16 (dd, *J* = 16.7, 5.3 Hz, 1H), 3.00-2.88 (m, 1H), 2.73 (dd, *J* = 16.7, 10.2 Hz, 1H), 2.59-2.50 (m, 2H), 2.43 (s, 3H), 2.06-1.94 (m, 1H), 1.90-1.75 (m, 1H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.8, 144.7, 136.5, 130.1, 128.8, 128.5, 127.0, 126.9, 126.4, 123.3, 121.1, 112.1, 40.7, 30.8, 30.0, 23.1, 21.7;

FT-IR (film): 3028, 2921, 1362, 1210, 1127, 1089, 907, 728;

HRMS (FTMS+pAPCI): *m/z* 352.1364 $[M+H]^+$ ($C_{21}H_{22}NO_2S$ requires 352.1366).

6,6-Dimethyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.63):



Prepared *via* **G.P. 3.3** outlined above using 4-(4,4-dimethylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 90% yield as a colorless oil.

Rf = 0.66 (3:1 Hexanes:EtOAc);

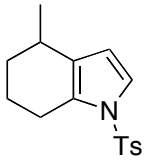
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 3.4 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 2.45 (s, 2H), 2.42-2.36 (m, 5H), 1.39 (t, *J* = 6.4 Hz, 2H), 0.89 (s, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.6, 136.8, 130.0, 129.3, 126.7, 122.3, 121.3, 112.3, 36.9, 35.6, 30.5, 28.1, 21.8, 20.6;

FT-IR (film): 2951, 2915, 2847, 1597, 1365, 1172, 1122, 812, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 304.1363 $[M+H]^+$ ($C_{17}H_{22}NO_2S$ requires 304.1366).

4-Methyl-1-tosyl-4,5,6,7-tetrahydro-1*H*-indole (3.64):



Prepared *via* **G.P. 3.3** outlined above using 4-(2-methylcyclohex-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 92% yield as a colorless oil.

Rf = 0.56 (3:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 3.4 Hz, 1H), 6.14 (d, *J* = 3.4 Hz, 1H), 2.74-2.63 (m, 1H), 2.63- 2.50 (m,

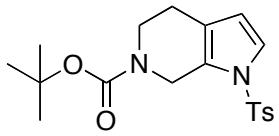
2H), 2.40 (s, 3H), 1.93-1.69 (m, 2H), 1.62-1.55 (m, 1H), 1.25-1.13 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.7, 136.7, 130.1, 129.0, 128.8, 127.0, 120.8, 111.0, 31.6, 28.8, 23.3, 21.9, 21.3;

FT-IR (film): 2927, 2852, 1596, 1367, 1236, 1175, 1124, 706 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 290.1207 $[M+H]^+$ ($C_{16}H_{20}NO_2S$ requires 290.1209).

***tert*-Butyl 1-tosyl-4,5-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-6(7*H*)-carboxylate (3.65):**



Prepared *via* **G.P. 3.3** outlined above using *tert*-butyl 4-(1-tosyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate. Title compound was isolated in 92% yield as a light yellow oil.

Rf = 0.32 (3:1 Hexanes:EtOAc);

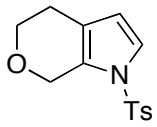
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.78-7.66 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 3.3 Hz, 1H), 6.10 (d, *J* = 3.4 Hz, 1H), 4.58 (br s, 2H), 3.61-3.49 (m, 2H), 2.47 (t, *J* = 5.6 Hz, 2H), 2.41 (s, 3H), 1.45 (s, 9H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 154.8, 145.2, 136.0, 130.3, 127.0, 125.6 (br s), 122.5 (br s), 121.2, 112.4, 80.1, 42.6 (br s), 40.7 (br s), 28.6, 23.1, 21.8;

FT-IR (film): 2976, 2928, 1693, 1596, 1409, 1365, 1169, 1143, 1127, 1089, 907, 729, 669 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 377.1531 $[M+H]^+$ ($C_{19}H_{25}N_2O_4S$ requires 377.1530).

1-Tosyl-1,4,5,7-tetrahydropyrano[3,4-*b*]pyrrole (3.66):



Prepared *via* **G.P. 3.3** outlined above using 4-(3,6-dihydro-2*H*-pyran-4-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 79% yield as a white solid.

Rf = 0.30 (3:1 Hexanes:EtOAc);

m.p. 97-98 °C;

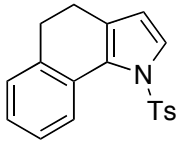
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 3.3 Hz, 1H), 6.13 (d, *J* = 3.3 Hz, 1H), 4.78 (s, 2H), 3.79 (t, *J* = 5.5 Hz, 2H), 2.52 (t, *J* = 5.5 Hz, 2H), 2.40 (s, 3H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 145.2, 136.1, 130.3, 127.0, 126.9, 120.9, 120.8, 112.7, 65.0, 64.4, 24.1, 21.8;

FT-IR (film): 2922, 2848, 1596, 1366, 1173, 1142, 1085, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 278.0844 $[M+H]^+$ ($C_{14}H_{16}NO_3S$ requires 278.0845).

1-Tosyl-4,5-dihydro-1*H*-benzo[*g*]indole (3.67):



Prepared *via* **G.P. 3.3** outlined above using 4-(3,4-dihydronaphthalen-2-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 89% yield as a colorless oil.

Rf = 0.48 (3:1 Hexanes:EtOAc);

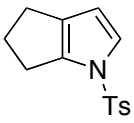
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.32-7.21 (m, 2H), 7.19-7.08 (m, 4H), 6.21 (d, *J* = 3.3 Hz, 1H), 2.62 (dd, *J* = 8.6, 6.0 Hz, 2H), 2.46 (dd, *J* = 8.6, 6.0 Hz, 2H), 2.33 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.6, 136.0, 135.1, 132.0, 131.3, 129.4, 129.4, 128.4, 127.6, 126.9, 126.8, 126.6, 126.3, 125.5, 114.0, 30.3, 22.7, 21.7;

FT-IR (film): 3059, 2937, 2892, 1595, 1478, 1368,1169, 1095, 702 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 324.1049 $[M+H]^+$ ($C_{19}H_{18}NO_2S$ requires 324.1052).

1-Tosyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (3.68):



Prepared *via* **G.P. 3.3** outlined above using 4-(cyclopent-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 84% yield as a colorless oil.

Rf = 0.53 (3:1 Hexanes:EtOAc);

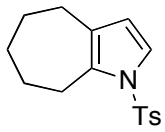
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 3.2 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.1 Hz, 2H), 2.45-2.33 (m, 7H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.8, 137.8, 136.5, 132.3, 130.1, 127.0, 123.9, 109.4, 28.7, 26.5, 25.5, 21.8;

FT-IR (film): 2922, 2860, 1580, 1366, 1172, 1127, 1089, 813, 669 cm^{-1}:

HRMS (FTMS+pAPCI): *m/z* 262.0896 $[M+H]^+$ ($C_{14}H_{16}NO_2S$ requires 262.0896).

1-Tosyl-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrole (3.69):



Prepared *via* **G.P. 3.3** outlined above using 4-(cyclohept-1-en-1-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 91% yield as a colorless oil.

Rf = 0.59 (3:1 Hexanes:EtOAc);

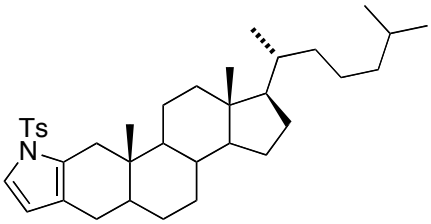
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 3.3 Hz, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 2.91-2.81 (m, 2H), 2.48-2.42 (m, 2H), 2.40 (s, 3H), 1.74-1.65 (m, 2H), 1.58-1.49 (m, 2H), 1.49-1.38 (m, 2H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.6, 136.9, 132.6, 130.0, 128.9, 126.7, 120.0, 113.8, 31.6, 28.1, 27.7, 26.8, 26.2, 21.7;

FT-IR (film): 3145, 2921, 2850, 1594, 1391, 1195, 1176, 1091, 976, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 290.1207 $[M+H]^+$ ($C_{16}H_{20}NO_2S$ requires 290.1209).

(1*R*,10a*S*,12a*R*)-10a,12a-dimethyl-1-((*R*)-6-methylheptan-2-yl)-9-tosyl-1,2,3,3a,3b,4,5,5a,6,9,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[5,6]naphtho[2,1-*f*]indole (3.46):



Prepared *via* **G.P. 3.4** outlined above using (10*S*,13*R*,17*R*)-3-ethynyl-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene and tosyl azide. Title compound was isolated in 81% yield as a colorless oil.

Rf = 0.66 (3:1 Hexanes:EtOAc);

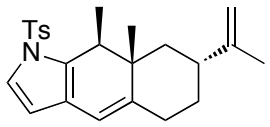
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 3.3 Hz, 1H), 6.03 (d, *J* = 3.3 Hz, 1H), 2.80 (d, *J* = 16.6 Hz, 1H), 2.40 (s, 3H), 2.28 (dd, *J* = 16.4, 4.9 Hz, 1H), 2.12 (d, *J* = 16.8 Hz, 1H), 2.03 (d, *J* = 12.5 Hz, 2H), 1.85-1.77 (m, 1H), 1.63-0.80 (m, 32H), 0.66 (s, 3H), 0.57 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 144.6, 136.9, 130.0, 129.4, 126.8, 122.3, 121.2, 112.1, 56.6, 56.5, 53.9, 42.7, 41.9, 40.1, 39.7, 37.5, 36.4, 36.4, 36.0, 35.8, 34.4, 31.9, 29.0, 28.5, 28.2, 28.1, 24.5, 24.1, 23.1, 22.8, 22.6, 21.9, 21.3, 18.9, 18.9, 14.3, 12.2, 11.9;

FT-IR (film): 2929, 2866, 1597, 1466, 1445, 1370, 1187, 1120, 811, 674 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 564.3869 $[M+H]^+$ ($C_{36}H_{54}NO_2S$ requires 564.3870).

(7*R*,8a*S*,9*S*)-8a,9-Dimethyl-7-(prop-1-en-2-yl)-1-tosyl-5,6,7,8,8a,9-hexahydro-1*H*-benzo[*f*]indole (3.51):



Prepared *via* **G.P. 3.4** outlined above using (3*R*,4a*S*,5*R*)-7-ethynyl-4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5-hexahydronaphthalene and tosyl azide. Title compound was isolated in 79% yield as a colorless oil.

Rf = 0.62 (3:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 3.3 Hz, 1H), 6.08 (d, *J* = 3.3 Hz, 1H), 5.86 (s, 1H), 4.57 (s, 1H), 4.38 (d, *J* = 2.0 Hz, 1H), 2.81 (q, *J* = 6.7 Hz, 1H), 2.43 (tt, *J* = 12.5, 4.2 Hz, 1H), 2.37-2.26 (m, 4H), 2.08 (ddd, *J* = 12.2, 5.0, 2.0 Hz, 1H), 2.02-1.90 (m, 1H), 1.51 (s, 3H), 1.18 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.06-0.95 (m, 2H), 0.82 (ddd, *J* = 12.4, 4.1, 1.6 Hz, 1H);

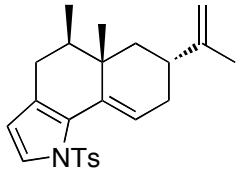
^{13}C NMR (100 MHz, Chloroform-*d*): δ 149.6, 145.3, 144.9, 136.8, 132.9, 130.0, 126.7, 122.2, 122.1, 112.9, 110.3, 108.7, 43.1, 42.6, 40.5, 39.8, 38.0, 31.9, 21.7, 21.0, 19.5, 17.6;

FT-IR (film): 2975, 2920, 2866, 1642, 1596, 1451, 1372, 1362, 1170, 1125, 1095, 884, 671

cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 396.1990 $[M+H]^+$ ($C_{24}H_{30}NO_2S$ requires 396.1992).

(5*R*,5a*S*,7*R*)-5,5a-dimethyl-7-(prop-1-en-2-yl)-1-tosyl-4,5,5a,6,7,8-hexahydro-1*H*-benzo[*g*]indole (3.49):



Prepared *via* **G.P. 3.4** outlined above using (2*R*,8*R*,8a*S*)-6-ethynyl-8,8a-dimethyl-2-(prop-1-en-2-yl)-1,2,3,7,8,8a-hexahydronaphthalene and tosyl azide. Title compound was isolated in 67% yield as a colorless oil.

Rf = 0.62 (3:1 Hexanes:EtOAc);

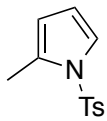
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 3.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.39 (d, *J* = 5.9 Hz, 1H), 6.06 (d, *J* = 3.4 Hz, 1H), 4.75 (d, *J* = 10.4 Hz, 2H), 2.46 (dd, *J* = 16.9, 5.5 Hz, 1H), 2.42-2.25 (m, 4H), 2.02 (q, *J* = 8.8, 7.6 Hz, 2H), 1.77 (s, 3H), 1.64 (dd, *J* = 12.7, 7.4 Hz, 2H), 1.24-1.19 (m, 1H), 1.13 (t, *J* = 11.6 Hz, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.29 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 150.2, 144.7, 135.6, 133.0, 131.8, 129.3, 127.4, 126.3, 125.6, 124.3, 112.9, 108.9, 42.0, 40.7, 38.5, 37.4, 32.1, 29.9, 21.8, 21.2, 16.5, 15.5;

FT-IR (film): 2924, 1644, 1596, 1455, 1367, 1171, 1090, 670 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 396.1990 $[M+H]^+$ ($C_{24}H_{30}NO_2S$ requires 396.1992).

2-Methyl-1-tosyl-1*H*-pyrrole (3.67):



Prepared *via* **G.P. 3.3** outlined above using 4-(prop-1-en-2-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 79% yield as a colorless oil.

Rf = 0.52 (3:1 Hexanes:EtOAc);

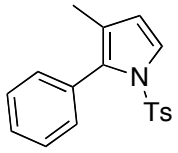
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.37-7.26 (m, 3H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.94 (ddq, *J* = 3.1, 2.2, 1.1 Hz, 1H), 2.41 (s, 3H), 2.29 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.9, 136.4, 130.9, 130.1, 127.1, 127.0, 122.1, 113.2, 111.3, 21.8, 13.7;

FT-IR (film): 3150, 2959, 2925, 1596, 1487, 1360, 1171, 1161, 1090, 1050, 811, 687 cm^{-1};

Data is consistent with the literature.[202]

3-Methyl-2-phenyl-1-tosyl-1*H*-pyrrole (3.65):



Prepared *via* **G.P. 3.3** outlined above using (*E*)-4-(1-phenylprop-1-en-2-yl)-1-tosyl-1*H*-1,2,3-triazole. Title compound was isolated in 84% yield as a colorless solid.

Rf = 0.53 (3:1 Hexanes:EtOAc);

m.p. 90-91 °C;

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.40-7.28 (m, 4H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.14-7.05 (m, 4H), 6.20 (d, *J* = 3.3 Hz, 1H), 2.36 (s, 3H), 1.82 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.5, 136.0, 132.0, 131.3, 130.7, 129.4, 128.2, 127.5, 127.3, 123.9, 122.5, 114.4, 21.7, 11.7;

FT-IR (film): 3146, 3061, 2923, 1596, 1368, 1252, 1170, 1142, 1060, 767, 686 cm^{-1};

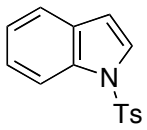
HRMS (FTMS+pAPCI) *m/z* 312.1048 $[M+H]^+$ ($C_{18}H_{18}NO_2S$ requires 312.1053).

General Procedure 3.5 for One-Pot Indole Sythesis Starting from the Enyne (G.P. 3.5):

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, the vinyl alkyne (0.58 mmol) and CuTC (0.029 mmol) were added under an argon atmosphere followed by freshly distilled 1,2-DCE (3 mL) and freshly prepared tosyl azide (0.58 mmol). The tube was sealed and the reaction mixture was stirred at room temperature for 2-4 hours. To the resulting greenish suspension, was added $Rh_2(esp)_2$ (0.0058 mmol). Then, the reaction mixture was warmed to 60 °C for 3-4 hrs until the triazole was completely consumed as judged by TLC analysis. The reaction was then cooled to room temperature and DDQ (1.16 mmol) was added followed by a 2 mL rinse of 1,2-DCE. The reaction mixture was then sealed and warmed again to 60 °C for 1 hr until the pyrrole was completely dehydrogenated as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with CH_2Cl_2 and transferred to a separatory funnel. The organic layer was washed with 0.5M NaOH, dried with $MgSO_4$, and filtered through a short plug of silica. Solvent was removed in vacuum, and the crude material

was then subjected to flash silica chromatography to afford the indole as a white solid or colorless oil.

1-Tosyl-1*H*-indole (3.52):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-cyclohex-1-ene and tosyl azide. Title compound was isolated in 85% yield as a colorless solid.

Rf = 0.50 (3:1 Hexanes:EtOAc);

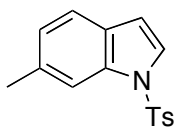
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24-7.19 (m, 3H), 6.66 (d, *J* = 3.4 Hz, 1H), 2.33 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.0, 135.3, 134.9, 130.8, 130.0, 126.9, 126.4, 124.7, 123.4, 121.5, 113.6, 109.1, 21.7;

FT-IR (film): 3143, 2975, 2860, 1596, 1445, 1262, 1173, 1129, 1091, 678 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 272.0739 $[M+H]^+$ ($C_{15}H_{14}NO_2S$ requires 272.0740).

6-Methyl-1-tosyl-1*H*-indole (3.53):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-4-methylcyclohex-1-ene and tosyl azide. Title compound was isolated in 91% yield as a colorless oil.

Rf = 0.50 (3:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.81 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 3.7 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 2.48 (s, 3H), 2.34 (s, 3H);

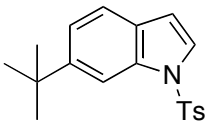
^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.9, 135.5, 135.3, 134.8, 130.0, 128.5, 126.9, 125.8, 124.9, 121.0, 113.7, 109.1, 22.1, 21.7;

FT-IR (film): 3141, 3029, 2920, 1611, 1423, 1367, 1269, 1169, 1115, 1090, 807, 669 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 286.0894 $[M+H]^+$ ($C_{16}H_{16}NO_2S$ requires 286.0896).

Data consistent with the literature.[203]

6-(*tert*-Butyl)-1-tosyl-1*H*-indole (3.54):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-4-*tert*-butylcyclohex-1-ene and tosyl azide. Title compound was isolated in 85% yield as a colorless oil.

Rf = 0.50 (3:1 Hexanes:EtOAc);

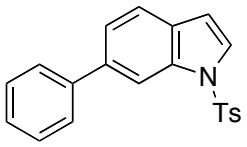
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.09-8.02 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 3.5 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.32 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 3.6 Hz, 1H), 2.32 (s, 3H), 1.42 (s, 9H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 148.2, 144.9, 135.2, 135.1, 129.8, 128.5, 126.9, 126.2, 121.3, 120.7, 110.2, 108.8, 35.1, 31.8, 21.6;

FT-IR (film): 2960, 2904, 2867, 1521, 1424, 1367, 1271, 1171, 1134, 1099, 668 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 328.1364 $[M+H]^+$ ($C_{19}H_{22}NO_2S$ requires 328.1366).

6-Phenyl-1-tosyl-1*H*-indole (3.55):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-4-phneylcyclohex-1-ene and tosyl azide. Title compound was isolated in 84% yield as a colorless oil.

Rf = 0.46 (3:1 Hexanes:EtOAc);

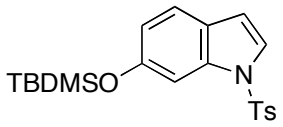
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.62-7.55 (m, 2H), 7.53-7.44 (m, 3H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 3.7 Hz, 1H), 2.33 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.1, 141.5, 138.2, 135.5, 135.4, 130.1, 129.0, 127.6, 127.4, 126.9, 123.1, 121.6, 112.1, 109.0, 21.7;

FT-IR (film): 3140, 1062, 3030, 2922, 1596, 1370, 1275, 1171, 1125, 1091, 673 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 348.1049 $[M+H]^+$ ($C_{21}H_{18}NO_2S$ requires 348.1053).

6-((*tert*-Butyldimethylsilyl)oxy)-1-tosyl-1*H*-indole (3.56):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-4-((tert-butyldimethylsilyl)oxy)cyclohex-1-ene and tosyl azide. Title compound was isolated in 89% yield as a colorless oil.

Rf = 0.48 (3:1 Hexanes:EtOAc);

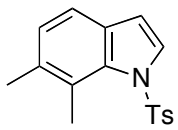
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.45 (dd, *J* = 7.4, 2.9 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.76 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.56 (d, *J* = 3.7 Hz, 1H), 2.34 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 153.6, 145.0, 135.9, 135.4, 129.9, 127.0, 125.5, 125.2, 121.7, 117.4, 109.1, 105.1, 25.9, 21.7, 18.4, -4.3;

FT-IR (film): 2954, 2929, 2857, 1614, 1475, 1371, 1291, 1209, 1171, 1125, 955, 880, 703 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 402.1548 $[M+H]^+$ ($C_{21}H_{28}NO_3SSi$ requires 402.1553).

6,7-dimethyl-1-tosyl-1*H*-indole (3.58):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-4,4-dimethylcyclohex-1-ene and tosyl azide. Title compound was isolated in 76% yield as a colorless oil.

Rf = 0.58 (3:1 Hexanes:EtOAc);

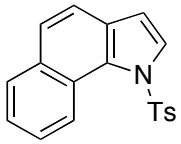
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.65 (d, *J* = 3.8 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 3.8 Hz, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H);

^{13}C NMR (150 MHz, Chloroform-*d*): δ 144.5, 136.6, 136.6, 134.4, 131.6, 130.2, 129.8, 126.8, 126.6, 124.4, 118.5, 109.9, 21.7, 21.1, 17.2;

FT-IR (film): 3156, 2922, 1595, 1449, 1362, 1348, 1171, 163, 1098, 1067, 810, 670 cm^{-1};

HRMS (FTMS+pAPCI) *m/z* 300.1050 $[M+H]^+$ ($C_{17}H_{18}NO_2S$ requires 300.1052).

1-Tosyl-1*H*-benzo[*g*]indole (3.57):



Prepared *via* **G.P. 3.5** outlined above using 3-ethynyl-1,2-dihydronaphthalene and tosyl azide. Title compound was isolated in 89% yield as a colorless oil.

Rf = 0.42 (3:1 Hexanes:EtOAc);

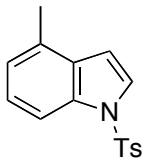
^{1}H NMR (400 MHz, Chloroform-*d*): δ 9.10 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 3.5 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.62-7.47 (m, 4H), 7.48-7.38 (m, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.83 (d, *J* = 3.6 Hz, 1H), 2.24 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.0, 135.5, 132.4, 130.6, 129.9, 129.6, 129.1, 126.9, 126.3, 125.9, 124.7, 123.9, 123.2, 120.2, 109.6, 21.6;

FT-IR (film): 3154, 3059, 2921, 1596, 1359, 1190, 1174, 1103, 812, 668 cm^{-1};

HRMS (FTMS+pAPCI): *m/z* 322.0892 $[M+H]^+$ ($C_{19}H_{16}NO_2S$ requires 322.0896).

4-Methyl-1-tosyl-1*H*-indole (3.59):



Prepared *via* **G.P. 3.5** outlined above using 1-ethynyl-2-methylcyclohex-1-ene and tosyl azide. Title compound was isolated in 89% yield as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 3.7 Hz, 1H), 7.24-7.19 (m, 3H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 3.7 Hz, 1H), 2.47 (s, 3H), 2.32 (s, 3H);

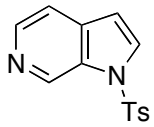
^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.1, 135.5, 134.8, 131.1, 130.6, 130.1, 127.0, 125.9, 124.8, 123.8, 111.2, 107.6, 21.8, 18.7;

FT-IR (film): 3142, 3029, 2919, 2855, 1596, 1484, 1415, 1368, 1359, 1177, 1161, 1123, 757, 662 cm^{-1};

HRMS (FTMS+pNSI): *m/z* 268.0896 $[M+H]^+$ ($C_{16}H_{16}NO_2S$ requires 286.0896).

Data is consistent with the literature.[203]

1-Tosyl-1*H*-pyrrolo[2,3-*c*]pyridine (3.60):



Prepared *via* **G.P. 3.5** outlined above using *tert*-butyl 4-ethynyl-5,6-dihydropyridine-1(2*H*)-carboxylate and tosyl azide with the following modification: The reaction was then cooled to room temperature and DDQ (1.16 mmol) was added followed by a 2 mL rinse of 1,2-DCE. The reaction mixture was then sealed and stirred at rt for 1 hr, then warmed to 40 °C for 4 hrs until the pyrrole was completely dehydrogenated as judged by TLC analysis. The reaction was then cooled to room temperature and diluted with EtOAc and transferred to a separatory funnel. The organic layer was washed with 0.5M NaOH, dried with $MgSO_4$, and filtered through a short plug of silica. Solvent was removed in vacuum, and the crude material was then subjected to flash silica chromatography and the product was isolated as a white solid (71% yield).

Rf = 0.38 (1:1 Hexanes:EtOAc);

^{1}H NMR (400 MHz, Chloroform-*d*): δ 9.30 (s, 1H), 8.39 (d, *J* = 5.3 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 3.6 Hz, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.26-7.18 (m, 2H), 6.65 (d, *J* = 3.6 Hz, 1H), 2.34 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 145.8, 142.6, 136.3, 136.0, 134.8, 131.8, 130.3, 129.7, 127.1, 115.9, 107.9, 21.7;

FT-IR (film): 3138, 3053, 2923, 1595, 1430, 1373, 1188, 1134, 1095, 824, 676 cm^{-1};

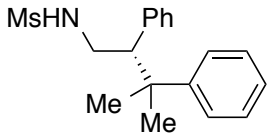
HRMS (FTMS+pNSI): *m/z* 272.0619 $[M+H]^+$ ($C_{14}H_{12}N_2O_2S$ requires 272.0620).

7.3 Experimental Part to Chapter 4

Starting Materials

Commerically available reagents were used when available, but purified by passing through a plug of oven-dried silica eluting with pentane followed by concentration under reduced pressure. Chloroform and 1,2-dichloroethane were freshly distilled over CaH_2 prior to use. The dirhodium tetracarboxylate catalysts were recrystallized from 3:1 Hex:EtOAc, then lypolized in benzene prior to use. The 4-phenyl-*N*-mesyltriazole was recrystallized from ethyl acetate prior to use. All glassware was flame-dried under reduced pressure before use.

(*R*)- *N*-(3-methyl-2,3-diphenylbutyl)methylsulfonamide (4.36):



In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (223 mg, 1.0 mmol) and Rh_2(*S*-nttl)$_4$ (14.5 mg, 0.01 mmol) were added together. The flask was then placed under vacuum and back filled with an argon atmosphere. Then isopropylbenzene (480 mg, 4.0 mmol) and 2 mL of freshly distilled chloroform were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The

resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. The reaction was cooled to 0 °C and diluted with 5 mL of dry THF, followed by 1.2 ml (1.0 M) of lithium aluminum hydride solution (1.2 mmol) was added in one aliquot. The resulting mixture was stirred for 30 minutes at 0 °C, and then carefully quenched with sodium sulfate decahydrate. The mixture was then filtered through a plug of silica eluting with ethyl acetate. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless oil (66% yield; 65% ee).

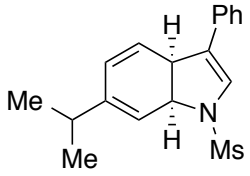
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.36-7.19 (m, 8H), 7.06 (dd, *J* = 7.5, 1.9 Hz, 2H), 3.71 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.37 (td, *J* = 12.2, 3.7 Hz, 1H), 3.27 (ddd, *J* = 12.6, 8.5, 4.0 Hz, 1H), 3.07 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.64 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 147.2, 138.0, 129.9, 128.3, 128.2, 127.4, 126.3, 126.3, 57.3, 43.6, 40.6, 40.0, 28.9, 23.7;

HRMS (FTMS+pNSI): *m/z* 318.1526 ($C_{18}H_{24}NO_2S$ requires 318.1522);

HPLC analysis (see Table 4.2.1)**:** OD-H column, 7% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.55 (major) and 16.36 (minor) min, UV 230 nm).

(3a*S*,7a*S*)-6-Isopropyl-1-(methylsulfonyl)-3-phenyl-3a,7a-dihydro-1*H*-indole (4.37):



Non-optimized conditions; In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (226 mg, 1.01 mmol) and Rh_2(*S*-ntad)$_4$ (17.6 mg, 0.0099 mmol) were added together. The flask was then placed under vacuum and back filled with an argon atmosphere. Then *p*-isopropylbenzene (594 mg, 4.0 mmol) and 2 mL of freshly distilled 1,2-dichloroethane were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless solid (38% yield; 95% ee).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.43-7.15 (m, 5H), 6.85 (s, 1H), 5.98-5.85 (m, 1H), 5.82-5.69 (m, 2H), 4.88 (dd, *J* = 12.8, 5.2 Hz, 1H), 4.37-4.23 (m, 1H), 2.93 (s, 3H), 2.37 (p, *J* = 6.8 Hz, 1H), 1.08 (dd, *J* = 6.9, 2.6 Hz, 6H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 144.2, 132.7, 128.9, 127.1, 125.9, 125.1, 124.8, 124.1, 123.8, 113.0, 59.4, 42.29, 38.8, 33.5, 21.1, 20.9;

HRMS (FTMS+pNSI): *m/z* 316.1371 ($C_{18}H_{22}NO_2S$ requires 316.1366);

HPLC analysis: SS-WHELK column, 7.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 20.48 (major) and 24.43 (minor) min, UV 254 nm);

X-ray analysis: Data were measured using *w* scans scans of 1° per frame for 60 s using MoK_a radiation (fine-focus sealed tube, 45 kV, 30 mA). The total number of runs and images was based on the strategy calculation from the program APEX2 v2014.1-1 (Bruker, 2014). The resolution that was achieved was *Q* = 25.67°.

Unit cell indexing was performed using APEX2 v2014.1-1 (Bruker, V8.34A, 2013) software and refined using APEX2 v2014.1-1 (Bruker, 2014) on 2115 reflections, 28% of the observed reflections.

Data reduction was performed using the SAINT (Bruker, V8.34A, 2013) software which corrects for Lorentz polarisation. The final completeness is 96.80% out to 25.67° in *Q*. The absorption coefficient (μ) of this material is 0.211 mm^{-1} and the minimum and maximum transmissions are 0.7661 and 1.0000.

The structure was solved by Charge Flipping using the Superflip (L. Palatinus & G. Chapuis, 2007) structure solution program and refined by Least Squares using version 2013-4 of ShelXL-97 (Sheldrick, 2008).

The structure was solved in the space group $P2_12_12_1$ (# 19). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

Table 1: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **4.37**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	**x**	**y**	**z**	U_{eq}
S1	-1806(3)	6741.0(9)	5999.7(7)	23.6(4)
O1	-2888(7)	6559(2)	6625.3(18)	28.9(10)

Atom	x	y	z	U_{eq}
O2	-3337(7)	7173(2)	5511.6(18)	27.7(9)
N3	-934(8)	5729(3)	5702(2)	20.1(10)
C1	-5169(11)	3607(4)	7341(3)	29.4(15)
C2	-1845(11)	3630(3)	6439(2)	19.5(12)
C3	7425(10)	4147(3)	4024(3)	25.0(13)
C4	-535(10)	3152(4)	5908(3)	23.3(12)
C5	1266(11)	3549(3)	5557(3)	25.7(14)
C6	-2405(11)	2229(3)	7133(3)	30.3(16)
C7	5874(10)	4332(4)	4549(3)	21.4(12)
C8	2188(11)	4517(3)	5673(3)	23.1(12)
C9	965(10)	7395(3)	6086(3)	26.0(13)
C10	490(10)	5072(3)	6145(2)	19.9(12)
C11	2155(11)	5093(3)	5055(3)	20.2(12)
C12	6928(11)	4537(3)	3430(3)	26.4(13)
C13	-3708(10)	3063(3)	6827(3)	23.2(13)
C14	417(10)	5743(4)	5109(3)	20.5(13)
C15	-1338(10)	4517(3)	6549(2)	21.2(13)
C16	3761(11)	4894(3)	4493(3)	21.3(12)
C17	4796(11)	5098(4)	3363(3)	26.9(14)
C18	3241(11)	5271(3)	3882(3)	21.3(12)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) **4.37**. The anisotropic displacement factor exponent takes the form: $-2p^2[a^{*2} \times U_{11} + ... \ 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	25.1(8)	20.2(6)	25.6(8)	0.3(7)	3.3(8)	5.1(7)
O1	31(2)	27(2)	29(2)	-0.6(17)	7.7(18)	5(2)
O2	29(2)	23.2(18)	31(2)	4.3(17)	0.3(18)	4.1(19)
N3	22(2)	19.6(19)	19(2)	0.2(16)	-0.3(18)	1.6(18)
C1	30(3)	28(3)	30(3)	4(3)	4(3)	1(3)
C2	21(3)	22(2)	16(3)	1.2(19)	-6(2)	2(2)
C3	21(3)	22(2)	32(3)	-2(2)	0(2)	-2(2)
C4	30(3)	17(2)	23(3)	1(2)	-2(2)	3(2)
C5	34(3)	20(2)	23(3)	1(2)	-1(2)	4(2)
C6	38(4)	28(2)	25(3)	8(2)	6(3)	3(3)
C7	21(3)	21(3)	22(3)	-1(2)	-3(2)	-4(2)
C8	26(3)	22(2)	22(3)	-0.6(18)	1(2)	5(2)
C9	29(3)	20(3)	28(3)	-2(3)	3(3)	2(2)
C10	23(3)	19(2)	18(2)	-0.1(19)	-2(2)	5.6(19)
C11	20(3)	18(2)	22(2)	-2.2(19)	-3(2)	-4(2)
C12	26(3)	25(3)	28(3)	-3(2)	3(2)	-2(3)
C13	25(3)	24(2)	21(3)	3(2)	-3(2)	-1(2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C14	24(3)	20(2)	17(3)	1(2)	0(2)	0(2)
C15	27(3)	24(2)	13(3)	-1.0(19)	-3(2)	2(2)
C16	21(3)	16(2)	27(2)	-2(2)	0(2)	-7(2)
C17	28(3)	25(3)	27(3)	0(2)	1(2)	-1(2)
C18	18(3)	19(3)	28(3)	-2(2)	-2(2)	-3(2)

Table 3: Bond Lengths in Å.

Atom	**Atom**	**Length/Å**
S1	O1	1.438(4)
S1	O2	1.437(4)
S1	N3	1.656(4)
S1	C9	1.754(5)
N3	C10	1.520(6)
N3	C14	1.419(6)
C1	C13	1.531(7)
C2	C4	1.471(7)
C2	C13	1.513(7)
C2	C15	1.332(7)
C3	C7	1.387(7)
C3	C12	1.377(7)

Atom	Atom	Length/Å
C4	C5	1.329(7)
C5	C8	1.505(7)
C6	C13	1.529(7)
C7	C16	1.386(7)
C8	C10	1.552(7)
C8	C11	1.527(7)
C10	C15	1.509(7)
C11	C14	1.321(7)
C11	C16	1.466(7)
C12	C17	1.396(8)
C16	C18	1.404(7)
C17	C18	1.374(7)

Table 4: Bond Angles.

Atom	Atom	Atom	Angle/°
O1	S1	N3	106.4(2)
O1	S1	C9	109.8(3)
O2	S1	O1	119.2(2)
O2	S1	N3	106.4(2)
O2	S1	C9	107.8(2)

Atom	Atom	Atom	Angle/°
N3	S1	C9	106.5(2)
C10	N3	S1	118.0(3)
C14	N3	S1	116.6(4)
C14	N3	C10	106.3(4)
C4	C2	C13	116.4(4)
C15	C2	C4	119.1(5)
C15	C2	C13	124.4(5)
C12	C3	C7	120.4(5)
C5	C4	C2	122.7(5)
C4	C5	C8	123.3(5)
C16	C7	C3	121.6(5)
C5	C8	C10	113.4(5)
C5	C8	C11	111.9(4)
C11	C8	C10	103.6(4)
N3	C10	C8	103.5(4)
C15	C10	N3	110.5(4)
C15	C10	C8	116.1(4)
C14	C11	C8	109.1(5)
C14	C11	C16	127.7(5)
C16	C11	C8	123.2(5)

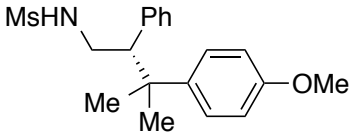
Atom	Atom	Atom	Angle/°
C3	C12	C17	118.7(6)
C1	C13	C6	110.4(4)
C2	C13	C1	114.5(4)
C2	C13	C6	110.9(5)
C11	C14	N3	114.4(5)
C2	C15	C10	123.4(5)
C7	C16	C11	121.1(5)
C7	C16	C18	117.5(5)
C18	C16	C11	121.5(5)
C18	C17	C12	120.8(6)
C17	C18	C16	120.9(5)

Table 5: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$). U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H1A	-3991	3830	7672	44
H1B	-6438	3206	7542	44
H1C	-6014	4134	7137	44

Atom	**x**	**y**	**z**	U_{eq}
H3	8840	3749	4074	30
H4	-996	2533	5813	28
H5	2009	3204	5215	31
H6A	-1056	2440	7423	45
H6B	-1677	1841	6793	45
H6C	-3647	1871	7381	45
H7	6269	4068	4958	26
H8	3953	4494	5847	28
H9A	552	7990	6284	39
H9B	1727	7497	5660	39
H9C	2164	7063	6363	39
H10	1599	5441	6441	24
H12	8015	4426	3072	32
H13	-4986	2818	6515	28
H14	99	6184	4779	25
H15	-2171	4814	6899	25
H17	4417	5363	2954	32
H18	1793	5651	3826	26

(*R*)-*N*-(3-(4-methoxyphenyl)-3-methyl-2-phenylbutyl)methanesulfonamide (4.40):



In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (221 mg, 0.99 mmol) and Rh_2(*S*-nttl)$_4$ (14.4 mg, 0.0099 mmol) were added together. The flask was then placed under vacuum and back filled with an argon atmosphere. Then *p*-isopropylanisole (594 mg, 4.0 mmol) and 2 mL of freshly distilled chloroform were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. The reaction was cooled to 0 °C and diluted with 5 mL of dry THF, followed by 1.2 ml (1.0 M) of lithium aluminum hydride solution (1.2 mmol) was added in one aliquot. The resulting mixture was stirred for 30 minutes at 0 °C, and then carefully quenched with sodium sulfate decahydrate. The mixture was then filtered through a plug of silica eluting with ethyl acetate. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless oil (71% yield; 71% ee).

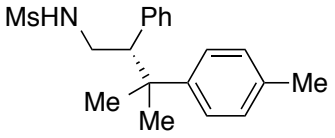
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.30-7.20 (m, 3H), 7.22-7.13 (m, 2H), 7.02 (d, *J* = 7.0 Hz, 2H), 6.91-6.75 (m, 2H), 3.78 (s, 4H), 3.37-3.22 (m, 2H), 3.00 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.59 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H);

^{13}C NMR (151 MHz, Chloroform-*d*): δ 157.8, 139.1, 138.2, 129.9, 128.2, 127.4, 127.3, 113.4, 57.4, 55.2, 43.0, 40.0, 29.1, 24.1;

HRMS (FTMS+pNSI): *m/z* 348.1648 ($C_{19}H_{26}NO_3S$ requires 348.1628);

HPLC analysis: OD-H column, 10% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 17.08 (major) and 15.57 (minor) min, UV 230 nm)

(***R*)- *N*-(3-methyl-2-phenyl-3-(*p*-tolyl)butyl)methylsulfonamide(4.39)**:



In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (223 mg, 1.0 mmol) and Rh_2(*S*-nttl)$_4$ (14.5 mg, 1.0 mmol) were added together. The flask was then placed under vacuum and back filled with an argon atmosphere. Then *p*-isopropyltoluene (538 mg, 4.0 mmol) and 2 mL of freshly distilled 1,2-dichloroethane were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. The reaction was cooled to 0 °C and diluted with 5 mL of dry THF, followed by 1.2 ml (1.0 M) of lithium aluminum hydride solution (1.2 mmol) was added in one aliquot. The resulting mixture was stirred for 30 minutes at 0 °C, and then carefully quenched with sodium sulfate decahydrate. The mixture was then filtered through a plug of silica eluting with ethyl acetate. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless oil (75% yield; 70% ee)

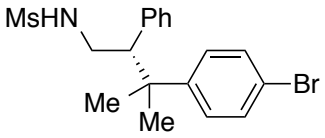
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.34-7.26 (m, 3H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 7.7, 1.8 Hz, 2H), 3.72 (dd, *J* = 8.5, 3.7 Hz, 1H), 3.42-3.23 (m, 2H), 3.06 (dd, *J* = 11.4, 4.1 Hz, 1H), 2.66 (s, 3H), 2.36 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H);

^{13}C NMR (100 MHz, Chloroform-*d*): δ 144.1, 138.1, 135.8, 129.9, 128.9, 128.3, 127.4, 126.2, 57.3, 43.7, 40.2, 40.0, 29.2, 23.7, 20.9;

HRMS (FTMS+pNSI): *m/z* 332.1682 ($C_{19}H_{26}NO_2S$ requires 332.1679);

HPLC analysis: OD-H column, 7% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 12.47 (major) and 14.56 (minor) min, UV 230 nm)

(*R*)- *N*-(3-(4-bromophenyl)-3-methyl-2-phenylbutyl)methylsulfonamide (4.41):



In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (221 mg, 0.99 mmol) and Rh_2(*S*-nttl)$_4$ (14.5 mg, 1.0 mmol) were added together. The flask was then placed under vacuum and back filled with an argon atmosphere. Then *p*-isopropylbromobenzene (786 mg, 4.0 mmol) and 2 mL of freshly distilled 1,2-dichloroethane were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. The reaction was cooled to 0 °C and diluted with 5 mL of dry THF, followed by 1.2 ml (1.0 M) of lithium

aluminum hydride solution (1.2 mmol) was added in one aliquot. The resulting mixture was stirred for 1 h at 0 °C, and then carefully quenched with sodium sulfate decahydrate. The mixture was then filtered through a plug of silica eluting with ethyl acetate. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless oil (76% yield; 74% ee).

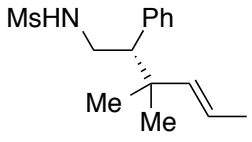
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.51-7.37 (m, 2H), 7.28 (d, *J* = 7.0 Hz, 3H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.04 (dd, *J* = 7.5, 2.0 Hz, 2H), 3.95 (dd, *J* = 8.0, 4.1 Hz, 1H), 3.32 (dtq, *J* = 20.6, 8.0, 4.0 Hz, 2H), 3.05 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.62 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 146.3, 137.7, 131.2, 129.9, 128.3, 128.3, 127.5, 120.2, 57.0, 43.5, 40.5, 40.1, 28.6, 24.1;

HRMS (FTMS+pNSI): *m/z* 396.0628 ($C_{18}H_{23}NO_2SBr$ requires 396.0627);

HPLC analysis: OD-H column, 7% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 27.10 (major) and 17.62 (minor) min, UV 230 nm)

(*S*,*E*)- *N*-(3,3-dimethyl-2-phenylhex-4-en-1-yl)methylsulfonamide (4.42):



In a flame-dried 25-ml equipped with a magnetic stir bar, 4-phenyl-*N*-mesyl triazole (224 mg, 1.0 mmol) and Rh_2(*S*-nttl)$_4$ (14.5 mg, 1.0 mmol) were added together. The flask was

then placed under vacuum and back filled with an argon atmosphere. Then (*E*)-4-methylpent-2-ene (338 mg, 4.0 mmol) and 2 mL of freshly distilled chloroform were added. The reaction mixture was then degassed using vacuum/argon cycles (x3). The resulting green reaction mixture was allowed to stir at ambient temperature for 24 hours until judged complete by TLC analysis. The reaction was cooled to 0 °C and diluted with 4 mL of dry THF, followed by 1.2 ml (1.0 M) of lithium aluminum hydride solution (1.2 mmol) was added in one aliquot. The resulting mixture was stirred for 1 h at 0 °C, and then carefully quenched with sodium sulfate decahydrate. The mixture was then filtered through a plug of silica eluting with ethyl acetate. After removal of solvent, the crude residue was purified by column chromatography on silica gel to furnish the title compound as a colorless oil (71% yield; 95% ee).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.39-7.23 (m, 3H), 7.14 (dd, *J* = 6.9, 1.9 Hz, 2H), 5.52-5.29 (m, 2H), 3.90 (dd, *J* = 8.6, 3.6 Hz, 1H), 3.57 (ddd, *J* = 12.5, 8.5, 4.0 Hz, 1H), 3.35 (td, *J* = 12.2, 3.7 Hz, 1H), 2.73 (s, 3H), 2.64 (dd, *J* = 11.7, 4.0 Hz, 1H), 1.78-1.63 (m, 3H), 0.96 (s, 3H), 0.89 (s, 3H);

^{13}C NMR (101 MHz, Chloroform-*d*): δ 138.7, 138.3, 129.8, 128.4, 127.4, 123.3, 56.4, 44.1, 40.22, 38.6, 27.9, 24.3, 18.3;

HRMS (FTMS+pNSI): *m/z* 282.1520 ($C_{15}H_{24}NO_2S$ requires 282.1522);

HPLC analysis: OD-H column, 4% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 21.61 (major) and 17.98 (minor) min, UV 230 nm)

7.4 Experimental Part to Chapter 5

General Procedure for the Synthesis of Methyl Phenyldiazoacetates[204]

The methyl arylacetate (1 equiv.) and *p*-ABSA (1.3 equiv.) were dissolved in acetonitrile and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (DBU, 1.3 equiv.) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous layer was extracted with diethyl ether (3x). The organic layer was then washed with DI H_2O to remove any residual salts. The combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel (10:1 Hexanes:EtOAc). Characterization data are consistent with the literature.[205]

General Procedure 5.1 for the Synthesis of Methyl Phenylcyclopropanecarboxylates with Rh_2(*S*-PTAD)$_4$ (G.P. 5.1):

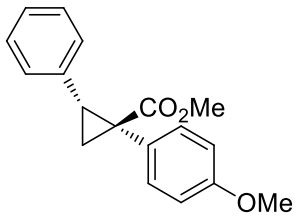
In a 25-mL round bottom flask (Flask A) equipped with a magnetic stir bar, styrene (5 equiv.) and Rh_2(*S*-PTAD)$_4$ (0.005 equiv.) were dissolved in dry, degassed pentane (3 mL). The reaction mixture was then degassed using vacuum/argon cycles

(x3). In a separate 25-mL round bottom flask (Flask B), the methyl phenyldiazoacetate (110 mg, 1 equiv.) was dissolved in dry, degassed pentane (5 mL) and degassed using vacuum/argon cycles (x3). The contents in Flask B were then added to Flask A using a syringe pump for the duration of 1 hour. After the addition, the reaction mixture continued to stir for 1 additional hour. Once the allotted time had passed, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (increasing gradient starting at 10:1 Hexanes:EtOAc).

General Procedure 5.2 for the Synthesis of Methyl Phenylcyclopropanecarboxylates with Rh_2(*R*-DOSP)$_4$ (G.P. 5.2):

In a 25-mL round bottom flask (Flask A) equipped with a magnetic stir bar, styrene (5 equiv.) and Rh_2(*R*-DOSP)$_4$ (0.01 equiv.) were dissolved in dry, degassed pentane (3 mL). The reaction mixture was then degassed using vacuum/argon cycles (x3). In a separate 25-mL round bottom flask (Flask B), the methyl phenyldiazoacetate (110 mg, 1 equiv.) was dissolved in dry, degassed pentane (5 mL) and degassed using vacuum/argon cycles (x3). The contents in Flask B were then added to Flask A using a syringe pump for the duration of 1 hour. After the addition, the reaction mixture continued to stir for 1 additional hour. Once the allotted time had passed, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (increasing gradient starting at 10:1 Hexanes:EtOAc).

(1*S*,2*R*)-Methyl 1-(4-methoxyphenyl)-2-phenylcyclopropanecarboxylate (5.3):



Title compound was obtained as a white solid. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 150 mg, 93% yield, 96% ee (HPLC, OD-H column, 0.7% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.97 (major) and 19.66 (minor) min, UV 254 nm), in DCM (111 mg, 73% yield, 88% ee) ; For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 102 mg, 66% yield, 90% ee (HPLC, OD-H column, 0.7% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.19 (major) and 15.07 (minor) min, UV 254 nm);

Rf = 0.39 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$ = $^{+}$5.1° (c = 1, chloroform);

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.10-7.07 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.80-6.77 (m, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.09 (dd, *J* = 9.2 and 7.6 Hz, 1H), 2.14 (dd, *J* = 9.2 and 4.8 Hz, 1H), 1.84 (dd, *J* = 7.2 and 4.8 Hz, 1H);

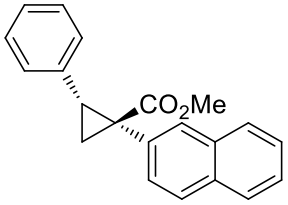
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 158.6, 136.7, 133.1, 128.3, 127.9, 127, 126.5, 113.4, 55.3, 52.8, 36.9, 33.4, 21.0;

FT-IR (film): 3031, 2951, 2836, 1715, 1515, 1245 cm^{-1};

HRMS-ESI: m/z 283.1328 ($C_{18}H_{19}O_3$ requires 283.1329).

Characterization data is consistent with the literature.[206]

(1*S*,2*R*)-Methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate (5.4):



Title compound was obtained in a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 108 mg, 72% yield; For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 102 mg, 68% yield; Characterization data is consistent with the literature.[206]

Rf = 0.42 (4:1 Hexanes:EtOAc);

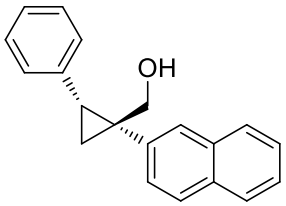
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.71 (dd, *J* = 9.2 and 4.8 Hz, 2H), 7.61 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.42-7.39 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.01-6.98 (m, 3H), 6.82-6.79 (m, 2H), 3.65 (s, 3H), 3.19 (dd, *J* = 9.6 and 7.6 Hz, 1H), 2.22 (dd, *J* = 9.6 and 4.4 Hz, 1H), 2.02 (dd, *J* = 7.2 and 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 136.4, 133.2, 132.8, 132.7, 130.7, 130.3, 128.3, 128, 127.8, 127.3, 126.6, 126, 125.9, 52.9, 37.7, 33.5, 20.9;

FT-IR (film): 3055, 2950, 1716, 1258 cm^{-1};

HRMS-ESI: m/z 303.138 ($C_{21}H_{19}O_2$ requires 303.138).

((1S,2R)-1-(naphthalen-2-yl)-2-phenylcyclopropyl)methanol (5.4a):



(1*S*,2*R*)-Methyl 1-(naphthalen-2-yl)-2-phenylcyclopropanecarboxylate was placed in a 50-mL round bottom flask equipped with a magnetic stir bar and was dissolved in THF. The reaction mixture was placed in an ice bath and cooled to 0 °C. After 10 minutes at 0 °C, the first equivalent of DIBAL-H was added slowly over the course of 1 minute. After 15 minutes had passed, three more equivalents of DIBAL-H were added over the course of 5 minutes. The reaction mixture continued to stir for an additional 3 hours. After the allotted time had passed, the reaction was quenched with diethyl ether. The reaction mixture stirred for 5 minutes and then 10% HCl was added and the mixture continued to stir for 5 minutes. The aqueous layer was then drained away and the organic layer was washed with DI H_2O. The aqueous layer was discarded again and the organic layer was then washed with brine (twice) and DI H_2O. The organic layer was dried with $MgSO_4$ and passed through a short path of silica gel in a glass frit (coarse). The resulting organic layer was then concentrated under reduced pressure and purified by silica gel column chromatography (4:1 Hexanes: EtOAc) provided title compound as a white solid. For Rh_2(*S*-PTAD)$_4$: 46% ee (HPLC, SS-WHELK column, 9% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.05 (major) and 20.61 (minor) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$: 79% ee (HPLC, SS-WHELK column, 9% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 16.74 (major) and 19.5 (minor) min, UV 254 nm);

Rf = 0.17 (4:1 Hexanes:EtOAc);

mp 102-103 °C; $[\alpha]^{20}_D$: ¯181° (c. 1, chloroform);

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.74-7.70 (m, 2H), 7.67 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.42 (m, 2H), 7.12 (dd, *J* = 10.4 and 8.4 Hz, 1H), 6.98 (m, 3H), 6.78 (m, 2H), 3.96

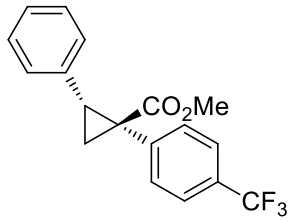
(dd, *J* = 11.2 and 4 Hz, 1H), 3.63 (dd, *J* = 11.2 and 6 Hz, 1H), 2.43 (dd, *J* = 8.8 and 6 Hz, 1H), 1.63 (t, *J* = 6 Hz, 1H), 1.52 (dd, *J* = 8.8 and 5.6 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 135.9, 133.5, 132.6, 130.4, 129.1, 128, 127.9, 127.8, 126.1, 125.9, 125.7, 72.1, 38.2, 27.7, 17.1;

FT-IR (film): 3358, 3055, 2925, 2867, 1601, 1033 cm^{-1};

HRMS-ESI: m/z 257.1324 ($C_{20}H_{17}$ requires 257.1325).

(1S,2R)-methyl 2-phenyl-1-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylate (5.5):



Title compound was obtained in a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 96 mg, 67% yield, 77% ee (HPLC, OD-H column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.44 (minor) and 9.34 (major) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 139 mg, 93% yield, 87% ee (HPLC, OD-H column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.08 (minor) and 10.16 (major) min, UV 254 nm); Characterization data is consistent with the literature.[206]

Rf = 0.44 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$: 19.1 (c. 1, chloroform);

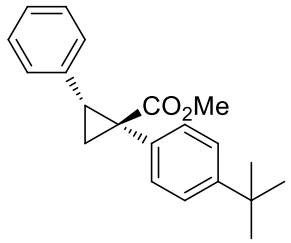
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36 (d, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 2H), 7.06 (m, 3H), 6.74 (m, 2H), 3.66 (s, 3H), 3.14 (dd, *J* = 9.6 and 7.6 Hz, 1H), 2.17 (dd, *J* = 9.2 and 5.2 Hz, 1H), 1.88 (dd, *J* = 7.2 and 5.2 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 139.2, 135.8, 132.4, 128.1, 126.9, 124.8, 53, 37.2, 33.5, 20.4;

IR (film): 3032, 2954, 1719, 1501, 1322, 1257 cm^{-1};

HRMS-ESI: m/z 321.1097 ($C_{18}H_{16}O_2F_3$ requires 321.1097).

(1S,2R)-methyl 1-(4-(tert-butyl)phenyl)-2-phenylcyclopropanecarboxylate (5.6):



Title compound was obtained in a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 104 mg, 70% yield; For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 114 mg, 77% yield;

Rf = 0.49 (4:1 Hexanes:EtOAc);

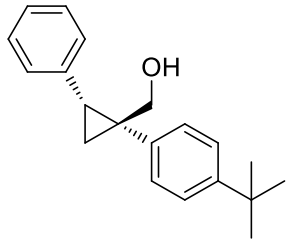
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.12 (d, *J* = 8.8 Hz, 2H), 7.03-7.01 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.73-6.70 (m, 2H), 3.65 (s, 3H), 3.05 (dd, *J* = 9.2 and 7.2 Hz, 1H), 2.12 (dd, *J* = 9.6 and 5.2 Hz, 1H), 1.83 (dd, *J* = 6 and 4.8 Hz, 1H), 1.22 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 150, 136.8, 131.7, 128.2, 127.7, 126.4, 124.8, 52.8, 37.2, 34.6, 33.4, 31.5, 20.9;

FT-IR (film): 3030, 2954, 2904, 1717, 1256 cm^{-1};

HRMS-ESI: m/z 309.185 ($C_{21}H_{25}O_2$ requires 309.1849).

((1S,2R)-1-(4-(tert-butyl)phenyl)-2-phenylcyclopropyl)methanol (5.6a):



Compound (**3d**) was placed in a 50-mL round bottom flask equipped with a magnetic stir bar and was dissolved in THF. The reaction mixture was placed in an ice bath and cooled to 0 °C. After 10 minutes at 0 °C, the first equivalent of DIBAL-H was added slowly over the course of 1 minute. After 15 minutes had passed, three more equivalents of DIBAL-H were added over the course of 5 minutes. The reaction mixture continued to stir for an additional 3 hours. After the allotted time had passed, the reaction was quenched with diethyl ether. The reaction mixture stirred for 5 minutes and then 10% HCl was added and the mixture continued to stir for 5 minutes. The aqueous layer was then drained away and the organic layer was washed with DI H_2O. The aqueous layer was discarded again and the organic layer was then washed with brine (twice) and DI H_2O. The organic layer was dried with $MgSO_4$ and passed through a short path of silica gel in a glass frit (coarse). The resulting organic layer was then concentrated under reduced pressure and purified by silica gel column chromatography (4:1 Hexanes: EtOAc) provided the title compound as a white solid. For Rh_2(*S*-PTAD)$_4$: 76% ee (HPLC, SS-WHELK column, 0% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 24.18

(major) and 31.15 (minor) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$: 90% ee (HPLC, SS-WHELK column, 0% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 16.65 (major) and 21.43 (minor) min, UV 254 nm);

Rf = 0.18 (4:1 Hexanes:EtOAc);

mp 99-100 °C;

[α]$^{20}_D$: ˉ66° (c. 1, chloroform);

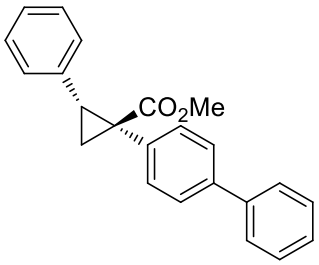
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.17 (d, *J* = 8 Hz, 2H), 7.01 (m, 5H), 6.72 (m, 2H), 3.84 (d, *J* = 11.2 Hz, 1H), 3.58 (d, *J* = 11.2 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 1H), 1.46-1.41 (m, 2H), 1.23 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 139.1, 134.8, 130.9, 127.8, 127.7, 125.5, 125.3, 72.3, 37.7, 34.6, 31.5, 27.6, 17.2;

FT-IR (film): 3301, 3029, 2965, 2905, 2867, 1033 cm^{-1};

HRMS-ESI: m/z 263.1794 ($C_{20}H_{23}$ requires 263.1794).

(1S,2R)-methyl 1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarboxylate (5.7):



Title compound was obtained as a white solid. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 71 mg, 49% yield, 18% ee (HPLC, SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.69 (major) and 31.13 (minor) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$

(G.P. 5.2): 83 mg, 57% yield, 72% ee (HPLC, SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 20.49 (major) and 33.01 (minor) min, UV 254 nm);

Rf = 0.42 (4:1 Hexanes:EtOAc);

mp 157-158 °C;

$[\alpha]^{20}_D$: -26.2° (c. 1, chloroform);

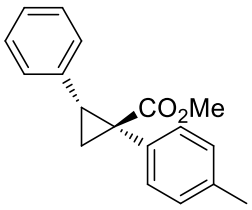
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.44-7.39 (m, 4H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.14-7.07 (m, 5H), 6.86-6.82 (m, 2H), 3.72 (s, 3H), 3.17 (dd, *J* = 9.2 and 7.2 Hz, 1H), 2.21 (dd, *J* = 9.6 and 5.2 Hz, 1H), 1.94 (dd, *J* = 7.2 and 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 140.8, 139.8, 136.5, 134, 132.5, 128.8, 128.3, 128, 127.4, 127.1, 126.54, 126.52, 52.9, 37.3, 33.5, 20.8;

FT-IR (film): 3029, 2950, 1716, 1488, 1254 cm^{-1};

HRMS-ESI: m/z 329.1536 ($C_{23}C_{21}O_2$ requires 329.1536).

(1S,2R)-methyl 2-phenyl-1-(p-tolyl)cyclopropanecarboxylate (5.8):



Title compound was obtained as a white solid. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 120 mg, 77% yield, 46% ee (HPLC, SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.33 (major) and 18.62 (minor) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 133 mg, 84% yield, 87% ee (HPLC, SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.32 (major) and 14.45 (minor) min, UV 254 nm);

Rf = 0.44 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_{D}$: $^{+}$17.2° (c. 1, chloroform);

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.11-7.07 (m, 3H), 6.98-6.92 (m, 4H), 6.82-6.80 (m, 2H), 3.69 (s, 3H), 3.12 (dd, *J* = 9.2 and 7.2 Hz, 1H), 2.27 (s, 3H), 2.16 (dd, *J* = 9.6 and 4.8 Hz, 1H), 1.88 (dd, *J* = 7.2 and 4.8 Hz, 1H);

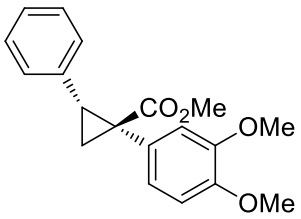
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 136.8, 136.7, 131.9, 131.8, 128.7, 128.3, 127.9, 126.5, 52.9, 37.3, 33.4, 21.4, 20.9;

FT-IR (film): 3028, 2950, 1716, 1255 cm^{-1};

HRMS-ESI: m/z 167.138 ($C_{18}H_{19}O_2$ requires 267.138).

Characterization data is consistent with the literature.[206]

(1S,2R)-methyl 1-(3,4-dimethoxyphenyl)-2-phenylcyclopropanecarboxylate (5.9):



Title compound was obtained as a white solid. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 101 mg, 70% yield, 94% ee (HPLC, OD-H column, 6% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 15.82 (minor) and 18.64 (major) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 109 mg, 74% yield, 56% ee (HPLC, OD-H column, 6% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 15.13 (minor) and 18.31 (major) min, UV 254 nm);

Rf = 0.20 (4:1 Hexanes:EtOAc);

mp 88-89 °C;

$[\alpha]^{20}_{D}$: $^{+}$35.9° (c. 1.1, chloroform);

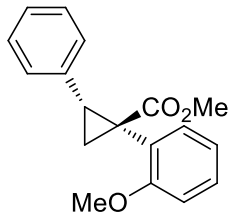
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.09-7.07 (m, 3H), 6.81-6.79 (m, 2H), 6.69-6.68 (m, 2H), 6.37 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.56 (s, 3H), 3.09 (dd, *J* = 9.6 and 7.6 Hz, 1H), 2.14 (dd, *J* = 9.2 and 4.8 Hz, 1H), 1.84 (dd, *J* = 7.2 and 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 148.1, 148, 136.7, 128.3, 128, 127.5, 126.5, 124.3, 115.6, 110.4, 55.8, 52.8, 37.2, 33.4, 21.1;

FT-IR (film): 3001, 2951, 2854, 1715, 1518, 1253 cm^{-1};

HRMS-ESI: m/z 313.1433 ($C_{19}H_{21}O_4$ requires 313.1434).

(1S,2R)-methyl 1-(2-methoxyphenyl)-2-phenylcyclopropanecarboxylate (5.10):



Title compound was obtained as a white solid. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 144 mg, 87% yield, 80% ee (HPLC, SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 12.89 (minor) and 15.03 (major) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 140 mg, 92 % yield, 86% yield (HPLC, SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.53 (minor) and 13.25 (major) min, UV 254 nm);

Rf = 0.45 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$: $^{+}$133.3° (c. 1, chloroform);

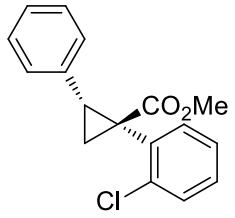
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.19-7.10 (m, 2H), 7.04-6.98 (m, 3H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.81-6.74 (m, 2H), 6.53 (d, *J* = 8 Hz, 1H), 3.65 (s, 3H), 3.36 (s, 3H), 3.24 (dd, *J* = 9.6 and 7.6 Hz, 1H), 1.98 (dd, *J* = 9.2 and 4.8 Hz, 1H), 1.85 (dd, *J* = 7.2 and 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 159.2, 137, 131.8, 128.9, 127.9, 127.3, 126.1, 124.1, 120.1, 110.5, 55.2, 52.7, 34.3, 32.6, 20.8;

FT-IR (film): 3030, 2950, 2835, 1716, 1496, 1242 cm^{-1};

HRMS-ESI: m/z 283.1329 ($C_{18}H_{19}O_3$ requires 283.1329).

(1S,2R)-methyl 1-(2-chlorophenyl)-2-phenylcyclopropanecarboxylate (5.11):



Title compound was obtained as a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 130 mg, 80% yield, 97% ee (HPLC, OJ-H column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.51 (minor) and 18.38 (major) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 134 mg, 89% yield, 92% ee (HPLC, OJ-H column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.47 (major) and 15.27 (major) min, UV 254 nm);

Rf = 0.43 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$: 61.8 (c. 1, chloroform);

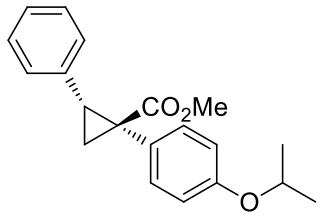
^{1}H NMR (300 MHz; $CDCl_3$): δ 7.18-7.02 (m, 7H), 6.84-6.76 (m, 2H), 3.68 (s, 3H), 3.13 (t, *J* = 8.7 Hz, 1H), 2.10 (m, 1H), 1.91 (dd, *J* = 7.2 and 5.1 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 137.5, 133.5, 129.6, 128.9, 128.2, 127.6, 126.6, 126.4, 52.9, 33.5, 29.9, 21.7;

FT-IR (film): 3031, 2950, 1718, 1251, 694 cm^{-1};

HRMS-ESI: m/z 287.0833 ($C_{17}H_{16}O_2Cl$ requires 287.0833).

(1S,2R)-methyl 1-(4-isopropoxyphenyl)-2-phenylcyclopropanecarboxylate (5.12):



Title compound was obtained as a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 132mg, 90% yield, 85% ee (HPLC, SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 12.72 (major) and 20.65 (minor) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 115 mg, 78% yield, 86% ee (HPLC, SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.15 (major) and 22.02 (minor) min, UV 254 nm);

Rf = 0.47 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$: 0.9 (c. 1, chloroform);

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.07-7.03 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.77-6.74 (m, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.43 (sept, *J* = 6 Hz, 1H), 3.65 (s, 3H), 3.05 (dd, *J* =

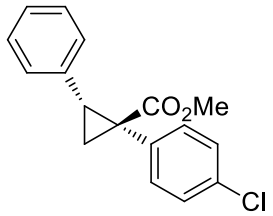
9.6 and 7.6 Hz, 1H), 2.11 (dd, *J* = 9.6 and 4.8 Hz, 1H), 1.81 (dd, *J* = 7.2 and 4.8 Hz, 1H), 1.26 (t, *J* = 6.4 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 157, 136.7, 133.1, 128.3, 127.9, 126.7, 126.4, 115.3, 69.9, 52.8, 36.9, 33.4, 22.3, 22.2, 21;

FT-IR (film): 3032, 2976, 1715, 1512, 1241 cm^{-1};

HRMS-ESI: m/z 311.1643 ($C_{20}H_{23}O_3$ requires 311.1642).

(1S,2R)-methyl 1-(4-chlorophenyl)-2-phenylcyclopropanecarboxylate (5.13):



Title compound was obtained as a transparent oil. For Rh_2(*S*-PTAD)$_4$ (**G.P. 5.1**): 106 mg, 71% yield, 48% ee (HPLC, OJ-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.51 (minor) and 11.95 (major) min, UV 254 nm); For Rh_2(*R*-DOSP)$_4$ **(G.P. 5.2)**: 129 mg, 87% yield, 88% ee (HPLC, OJ-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.64 (minor) and 11.48 (major) min, UV 254 nm);

Rf = 0.56 (4:1 Hexanes:EtOAc);

$[\alpha]^{20}_D$: 4.8 (c. 1, chloroform);

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.12-7.06 (m, 5H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.79-6.76 (m, 2H), 3.67 (s, 3H), 3.12 (dd, *J* = 9.3 and 7.5 Hz, 1H), 2.15 (dd, *J* = 9.3 and 4.8 Hz, 1H), 1.85 (dd, *J* = 7.2 and 4.8 Hz, 1H);

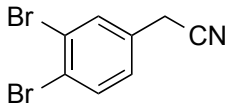
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 136.1, 133.7, 133.4, 133.2, 128.3, 128.2, 128.1, 126.8, 52.9, 36.9, 33.4, 20.6;

FT-IR (film): 3031, 2951, 1717, 1493, 1255 cm^{-1};

HRMS-ESI: m/z 287.0833 ($C_{17}H_{16}O_2Cl$ requires 287.0833).

7.5 Experimental Part to Chapter 6

2-(3,4-Dibromophenyl)acetonitrile (6.19):



In a 500 mL round bottom flask equipped with a magnetic stir bar, NBS (14.95 g, 84 mmol) was added to a solution of 3,4-dibromotoluene (20.0 g, 80 mmol) in carbon tetrachloride (120 mL). The resulting mixture was heated to 85 °C and AIBN (1.31 g, 8 mmol) was added. The reaction mixture continued to stir at 85 °C for 12 hours. The mixture was then cooled to RT and diluted with diethyl ether (200 mL), and washed with 5% HCl (100 mL) and then 5% Na_2CO_3 (100 mL). The organic phase was dried with $MgSO_4$, filtered through a short path of silica, and concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (SiO_2, hexanes) to give 1,2-dibromo-4-(bromomethyl)benzene was a yellow solid in 76% yield (20.2 g).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 4.36 (s, 2H), 7.17 (dd, J = 2 and 8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 2 Hz, 1H).

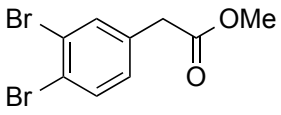
The spectroscopic data matches what was previously reported in the literature.[207]

In a 250 mL round bottom flask equipped with a magnetic stir bar, 1,2-dibromo-4-(bromomethyl)benzene (20.0 g, 60.8 mmol) was suspended in ethanol/water (3:1, 80 mL) and potassium cyanide (5.93 g, 65.1 mmol) was added. The reaction mixture was heated to reflux for 16 hours with stirring. After the allotted time had passed, the reaction mixture was cooled to RT and diluted with ethyl acetate, and washed with brine (x2). The resulting organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (SiO_2, 100% hexanes → 4:1 hexanes: ethyl acetate) to give the title compound as a yellow solid in 48% yield (8.0 g).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.71 (s, 2H), 7.15 (dd, *J* = 1.8 and 8.1 Hz, 1H), 7.61 (m, 2H).

The spectroscopic data matches what was previously reported in the literature.207

Methyl 2-(3,4-dibromophenyl)acetate (6.21):



In a 250 mL round bottom flask equipped with a magnetic stir bar, 2-(3,4-dibromophenyl)acetonitrile (7.0 g, 25.5 mmol) was suspended in methanol/water (3:1, 80 mL) and LiOH (2.44 g, 102 mmol) was added. The resulting mixture was heated to 55 °C for 72 hours. After the allotted time had elapsed, the reaction was cooled to RT and

diluted with chloroform (100 mL) and washed with 25% NaOH (w/v). The aqueous phase was acidified with concentrated HCl to a pH of 1, and extracted with ethyl acetate (x3). The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure to give the title compound as a tan solid in 88% yield (6.6 g).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.59 (s, 2H), 7.09 (dd, *J* = 2.1 and 8.1 Hz, 1H), 7.55 (m, 2H), 11.23 (br s, 1H).

The spectroscopic data matches what was previously reported in the literature.207

In a 250 mL round bottom flask equipped with a magnetic stir bar, 2-(3,4-dibromophenyl)acetic acid (4.6 g, 15.6) was dissolved in methanol (100 mL) and cooled to 0 °C using an ice bath. The reaction mixture was flushed with argon and acetyl chloride (2 mL, 18.8 mmol) was added via a syringe. After 30 minutes, the reaction mixture was allowed to warm to RT and stirred for 12 hours. The reaction was then diluted with ethyl acetate (100 mL) and washed with brine and $NaHCO_3$. The resulting organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to give a yellowish-orange oil. The residue was purified by column chromatography (SiO_2, 9:1 hexanes: ethyl acetate) to give the title compound as a light orange solid in 93% yield (4.51 g).

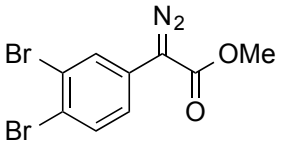
^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.52 (s, 2H), 3.66 (s, 3H), 7.04 (dd, *J* = 2 and 8 Hz, 1H), 7.51 (m, 2H);

^{13}C-NMR (100 MHz; $CDCl_3$): δ 40.3, 52.5, 123.7, 125.0, 129.8, 133.8, 134.7, 135.0, 171.1;

FT-IR (film): 2999, 2951, 1735, 1462, 1435, 1164, 1015, 816 cm^{-1};

HRMS-ESI m/z 306.8964 ($C_9H_9O_2Br_2$ requires 306.8964).

Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (6.22):



In a 250 mL round bottom flask equipped with a magnetic stir bar, methyl 2-(3,4-dibromophenyl)acetate (3.0 g, 9.7 mmol) and *p*-ABSA (3.03 g, 12.6 mmol) were dissolved in acetonitrile (50 mL) and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (1.9 g, 12.6 mmol) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with diethyl ether (3x). The organic phase was then washed with DI H_2O to remove any residual salts. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 9:1 Hexanes:EtOAc) to give the title compound as a yellow solid in 95% yield (3.1 g).

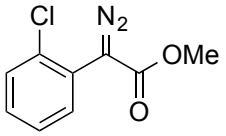
^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.86 (s, 3H), 7.25 (dd, *J* = 2 and 8.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 2.8 Hz, 1H);

^{13}C-NMR (100 MHz; $CDCl_3$): δ 52.5, 121.6, 123.7, 125.7, 127.0, 128.5, 134.0, 164.9;

FT-IR (film): 3091, 2952, 2093, 1702, 1471, 1436, 1238, 737 cm^{-1};

HRMS-ESI m/z 304.8819 ($C_9H_7O_2Br_2$ requires 304.8818).

Methyl 2-(2-chlorophenyl)-2-diazoacetate:



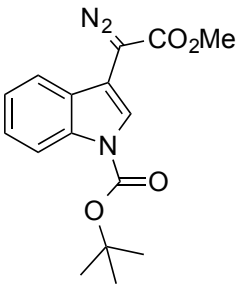
In a 250 mL round bottom flask equipped with a magnetic stir bar, methyl 2-chlorophenylacetate (5.0 g, 27.2 mmol) and *p*-ABSA (7.18 g, 29.9 mmol) were dissolved in acetonitrile (50 mL) and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (4.5 g, 29.9 mmol) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with diethyl ether (3x). The organic phase was then washed with DI H_2O to remove any residual salts. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by

column chromatography (SiO_2, 4:1 Hexanes:EtOAc) to give the title compound as a yellow solid in 97% yield (5.13 g).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.54 (dd, *J* = 2.1 and 7.8 Hz, 1H), 7.42 (dd, *J* = 1.8 and 7.5 Hz, 1H), 7.29 (m, 2H), 3.85 (s, 3H).

Spectroscopic data is consistent with the literature.[208]

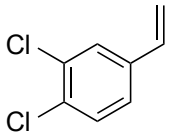
***tert*-Butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate:**



In a 250 mL round bottom flask equipped with a magnetic stir bar, *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (7.025 g, 24.3 mmol) and *p*-ABSA (7.58 g, 31.6 mmol) were dissolved in acetonitrile (50 mL) and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (4.8 g, 31.6 mmol) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 6 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with diethyl ether (2x). The organic phase was then washed with DI H_2O to remove any residual salts. The combined

organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 100% hexanes→4:1 Hexanes:EtOAc) to give the title compound as a pink solid in 64% yield (4.92 g). ^{1}H-NMR (400 MHz; $CDCl_3$) δ 1.68 (s, 9H), 3.90 (s, 3H), 7.27 (m, 1H), 7.37 (m, 1H), 7.49 (dd, *J* = 1.2 and 8 Hz, 1H), 7.88(s, 1H), 8.22 (d, *J* = 8.8 Hz, 1H). Spectroscopic data is consistent with the literature.[209]

1,2-Dichloro-4-vinylbenzene:

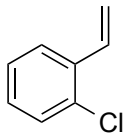


Methyltriphenylphosphine bromide (44.9 g, 125 mmol) in THF (250 mL) was treated with potassium *tert*-butoxide (29.4 g, 262 mmol) and stirred for 30 minutes. 3,4-Dichlorobenzaldehyde (20.0 g, 114 mmol) in THF (50 mL) was added dropwise over 30 minutes, and then stirred for 16 additional hours. The reaction was then concentrated under reduced pressure and diluted with pentane and poured onto 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 an orange oil. The crude material was distilled using Kugelrohr distillation to obtain the title compound as a colorless liquid in 54% yield (10.7 g).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.32 (d, *J* = 10.8 Hz, 1H), 5.74 (d, *J* = 17.7 Hz, 1H), 6.61 (dd, *J* = 10.8 and 17.7 Hz, 1H), 7.21 (dd, *J* = 1.8 and 8.4 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H).

The spectroscopic data matches what was previously reported in the literature.

1-Chloro-2-vinylbenzene:

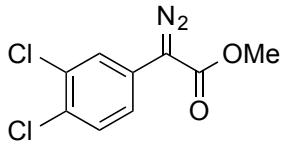


Methyltriphenylphosphine bromide (33.5 g, 93.9 mmol) in THF (200 mL) was treated with sodium hydride (4.0 g, 171 mmol) and stirred for 30 minutes. 2-Chlorobenzaldehyde (12.0 g, 85.3 mmol) in THF (20 mL) was added dropwise over 30 minutes, and then stirred for 16 additional hours. The reaction was then concentrated under reduced pressure and diluted with pentane and poured onto 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 an orange oil. The crude material was distilled using Kugelrohr distillation to obtain **34** as a colorless liquid in 85% yield (10.1 g).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.36 (d, *J* = 10.8 Hz, 1H), 5.72 (dd, *J* = 1.6 and 18 Hz, 1H), 7.09 (dd, *J* = 11.2 and 17.Hz, 1H), 7.19 (m, 2H), 7.33 (dd, *J* = 1.6 and 8 Hz, 1H), 7.55 (dd, *J* = 2 and 7.6 Hz, 1H).

The spectroscopic data matches what was previously reported in the literature.[210]

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

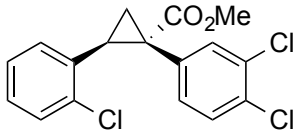


In a 100 mL round bottom flask equipped with a magnetic stir bar, methyl 2-(3,4-dichlorophenyl)acetate (2.0 g, 9.1 mmol) and *p*-ABSA (2.63 g, 10.9 mmol) were dissolved in acetonitrile (25 mL) and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (1.67 g, 10.9 mmol) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed, the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with diethyl ether (3x). The organic phase was then washed with DI H_2O to remove any residual salts. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 4:1 Hexanes:EtOAc) to give **35** as a orange solid in 81% yield (1.8 g).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.62 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 2 and 8.4 Hz, 1H), 3.86 (s, 3H).

The spectroscopic data matches what was previously reported in the literature.

(1*S*,2*S*)-Methyl 2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (6.23):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (854 mg, 6.12 mmol) and Rh_2(*R*-DOSP)$_4$ (23 mg, 0.012 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (300 mg, 1.22) was dissolved in dry, degassed toluene and added by syringe pump over 3 hours. The reaction stirred overnight while slowly warming to room temperature. 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 title compound as white solid in 60% yield (262 mg).

HPLC analysis: 79% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.3 (major) and 12.5 (minor) min, UV 254 nm); recrystallized from hexanes to give 93% ee;

mp 68-69 °C;

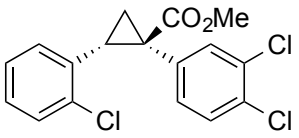
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.96 (dd, *J* = 5.2 and 7.6 Hz, 1Hz), 2.11 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.35 (t, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 6.56 (dd, *J* = 1.2 and 7.6 Hz, 1H), 6.93 (m, 2H), 7.05 (dt, *J* = 1.6 and 7.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 2 Hz, 1H), 7.32 (dd, *J* = 1.6 and 8 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.6, 31.8, 35.7, 53.1, 126.7, 127.7, 128.5, 129.5, 129.9, 130.9, 131.5, 131.8, 133.2, 133.7, 135.5, 136.3, 173.3;

FT-IR (film): 3064, 2952, 1720, 1475, 1434, 1260, 741 cm^{-1};

HRMS-ESI m/z 352.9909 ($C_{17}H_{12}O_2Cl_2$ requires 352.9908).

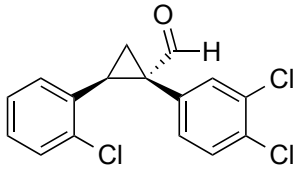
(1*R*,2*R*)-Methyl 2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (ent-6.23):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (854 mg, 6.1 mmol) and Rh_2(*S*-DOSP)$_4$ (23 mg, 0.012 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (300 mg, 1.22 mmol) was dissolved in dry, degassed toluene and added by syringe pump over 3 hours. The reaction stirred overnight while slowly warming to room temperature. 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 title compound as a white solid in 59% yield (259 mg).

HPLC analysis: 67% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.4 (minor) and 13.2 (major) min, UV 254 nm); recrystallized from hexanes to give 94% ee. Spectroscopic data is the same as the other enantiomer.

(1*S*,2*S*)-2-(2-Chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (6.23a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (208 mg, 0.61 mmol)was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (58 mg, 1.53 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (667 mg, 1.57 mmol) was added. The reaction stirred at RT for 1.5 hours (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 title compound as a colorless oil in 88% yield (167 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.17 (m, 2H), 3.22 (t, *J* = 8.8 Hz, 1H), 6.70 (dd, *J* = 1.6 and 7.6 Hz, 1H), 6.94 (dd, *J* = 2 and 8.4 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 7.07 (dt, *J* = 2

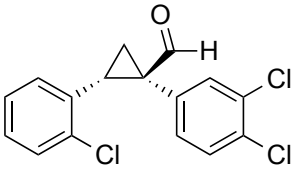
and 7.6 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 2.4, 1H), 7.30 (dd, *J* = 1.2 and 8 Hz, 1H), 9.49 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.5, 33.7, 44.3, 126.9, 127.9, 128.9, 129.6, 130.2, 130.5, 132.1, 132.6, 132.7, 134.2, 136.2, 198.9;

FT-IR (film): 3064, 2828, 2748, 1704, 1477, 1442, 1031, 746 cm^{-1}:

HRMS-ESI m/z 322.9804 ($C_{16}H_{10}OCl_3$ requires 322.9803).

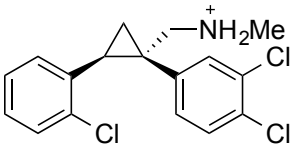
(1*R*,2*R*)-2-(2-Chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-6.23a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (152 mg, 0.45 mmol)was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (43 mg, 1.12 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (517 mg, 1.22 mmol) was added. The reaction stirred at RT for 1.5 hours (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 title compound as a colorless oil in 40% yield (55 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*S*)-2-(2-Chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.23b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (167 mg, 0.50 mmol) was dissolved in ethanol (10 mL) and flushed with argon. This solution was treated with methylamine hydrochloride (68 mg, 1.0 mmol), triethylamine (0.13 mL, 1.0 mmol), and Ti(O-*i*Pr)$_4$ (0.29 mL, 1.0 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (31 mg, 0.8 mmol) was added and the reaction was stirred for an additional 4 hours. 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 88% yield (153 mg). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (50 mg, 0.43 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (122 mg).

mp 203-204 °C;

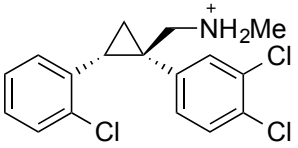
^{1}H-NMR (400 MHz; CD_3OD): δ 1.63 (dd, *J* = 6.4 and 8.8 Hz, 1H), 2.13 (dt, *J* = 1.6 and 6.4 Hz, 1H), 2.64 (s, 3H), 2.73 (dd, *J* = 6.8 and 8.8 Hz, 1H), 3.02 (d, *J* = 13.2 Hz, 1H), 4.09 (dd, *J* = 1.6 and 13.2 Hz, 1H), 6.65 (s, 2H), 6.79 (dd, *J* = 1.6 and 7.6 Hz, 1H), 6.98 (dt, *J* = 1.2 and 7.6 Hz, 1H), 7.06 (dt, *J* = 1.6 and 7.6 Hz, 1H), 7.16 (dd, *J* = 2 and 7.6 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 1.6 and 8 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1H);

^{13}C-NMR (100 MHz, CD_3OD): δ 13.9, 28.4, 30.5, 32.8, 58.0, 126.6, 128.1, 128.2, 128.9, 129.7, 130.4, 131.4, 132.0, 132.2, 134.0, 135.0, 135.6, 136.7, 170.2;

IR (neat): 2971, 2440, 1709, 1640, 1556, 1249, 757 cm^{-1};

Anal. Calcd for $C_{21}H_{20}NO_4Cl_3$: C 55.22, H 4.41, N 3.07; Found C 55.35, H 4.40, N 3.10.

1-((1*R*,2*R*)-2-(2-Chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.23b):

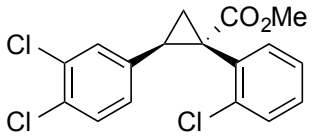


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-2-(2-chlorophenyl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (55 mg, 0.16 mmol) was dissolved in ethanol (10 mL) and flushed with argon. This solution was treated with methylamine hydrochloride (22 mg, 0.32 mmol), triethylamine (0.05 mL, 0.34 mmol), and Ti(O-*i*Pr)$_4$ (0.1 mL, 0.33 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (12 mg, 0.32 mmol) was added and the reaction was stirred for an additional 4 hours. 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 91% yield (52 mg). The product was dissolved in isopropanol (6 mL) and then treated with fumaric acid (17 mg, 0.15 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (6 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed

with cold hexanes to give the title compound as a white solid (39 mg). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{21}H_{20}NO_4Cl_3$: C 55.22, H 4.41, N 3.07; Found C 55.14, H 4.37, N 3.11.

(1*S*,2*R*)-Methyl 1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (6.24):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (1.77 g, 10.2 mmol) and Rh_2(*R*-DOSP)$_4$ (39 mg, 0.02 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (431 mg, 2.05 mmol) was dissolved in dry, degassed toluene (18mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a colorless oil in 71% yield (510 mg).

HPLC analysis: 95% ee (OJ-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 14.5 (minor) and 30.9 (major) min, UV 254 nm);

Rf = 0.47 (4:1 Hexanes: EtOAc);

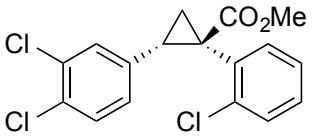
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.83 (dd, *J* = 5.6 and 7.6 Hz, 1H), 2.07 (m, 1H), 3.25 (t, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 6.58 (dd, *J* = 2 and 8.4 Hz, 1H), 6.87 (d, *J* = 2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.15 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.8, 32.1, 37.0, 53.0, 126.7, 127.3, 129.3, 129.5, 129.8, 130.1, 130.5, 131.7, 132.6, 132.8, 136.6, 137.3, 173.1;

FT-IR (film): 2951, 1721, 1476, 1434, 1250, 749, 731 cm^{-1};

HRMS-ESI m/z 352.9909 ($C_{17}H_{12}O_2Cl_3$ requires 352.9908).

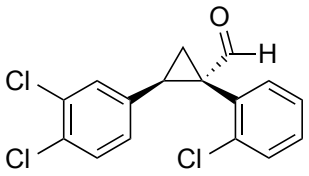
(1*R*,2*S*)-Methyl 1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (ent 6.24):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (1.81 g, 10.4 mmol) and Rh_2(*S*-DOSP)$_4$ (40 mg, 0.021 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (439 mg, 2.09 mmol) was dissolved in dry, degassed toluene (18 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a colorless oil in 73% yield (542 mg).

HPLC analysis: 96% ee (OJ-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 13.6 (major) and 32.5 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1-(2-Chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (6.24a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1*S*,2*R*)-methyl 1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (450 mg, 1.3 mmol)was dissolved in diethyl ether (30 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (120 mg, 3.2 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (25 mL) and Dess Martin reagent (980 mg, 2.32 mmol) was added. The reaction stirred at RT for 1.5 hours (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 the title compound as a colorless oil in 93% yield (383 mg).

mp 79-80 °C;

Rf = 0.46 (4:1 Hexanes: EtOAc);

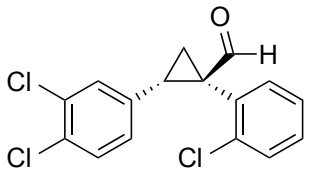
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.96 (dd, *J* = 5.6 and 7.2 Hz, 1H), 2.16 (dd, *J* = 5.2 and 8.8 Hz, 1H), 3.12 (t, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 2 and 8 Hz, 1H), 6.91 (d, *J* = 2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.24 (m, 4H), 9.55 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4, 34.2, 44.9, 127.1, 127.2, 129.7, 129.9, 130.0, 130.2, 130.9, 131.7, 131.9, 133.1, 136.0, 136.9, 199.4;

FT-IR (film): 3062, 2832, 2753, 1704, 1476, 1435, 729 cm^{-1};

HRMS-ESI m/z 322.9803 ($C_{16}H_{10}OCl_3$ requires 322.9802).

(1*R*,2*S*)-1-(2-Chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent 6.24a):

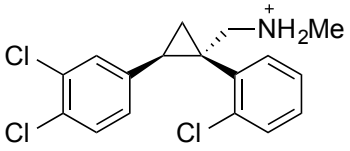


In a 50 mL round bottom flask equipped with a magnetic stir bar, 1*R*,2*S*)-methyl 1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (450 mg, 1.3 mmol)was dissolved in diethyl ether (30 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (121 mg, 3.2 mmol) was

then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (25 mL) and Dess Martin reagent (1.06 g, 2.5 mmol) was added. The reaction stirred at RT for 1.5 hours (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 **27b** as a colorless oil in 94% yield (388 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1-(2-Chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.24b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (130 mg, 0.40 mmol) was dissolved in methanol (12 mL) and flushed with argon. This solution was treated

with methylamine (2M in MeOH, 0.4 mL, 0.8 mmol) and Ti(O-*i*Pr)$_4$ (0.25 mL, 0.8 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (31 mg, 0.8 mmol) was added and the reaction was stirred for an additional 4 hours. 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 (107 mg). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (36 mg, 0.31 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (102 mg).

mp 164-165 °C;

^{1}H-NMR (400 MHz; CD_3OD): δ 1.73 (m, 1H), 1.79 (t, *J* = 6 Hz, 1H), 2.62 (m, 4H), 2.86 (m, 1H), 4.09 (m, 1H), 6.63 (dd, *J* = 2 and 8.4 Hz, 1H), 6.67 (s, 2H), 6.90 (s, 1H), 7.11 (dd, *J* = 8.4 Hz, 1H), 7.27 (m, 3H), 7.60 (s, 1H);

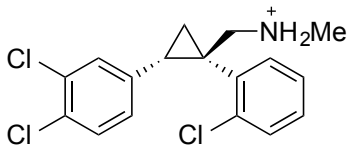
^{13}C-NMR (100 MHz, CD_3OD): δ 17.5, 29.1, 33.1, 56.7, 127.2, 127.4, 129.0, 129.6, 130.0, 130.3, 131.0, 132.6, 134.0, 135.0, 136.3, 138.1, 170.1;

FT-IR (neat): 3449, 3022, 2759, 1691, 1477, 1276, 785 cm^{-1};

HRMS-ESI m/z 340.0420 ($C_{17}H_{17}NCl_3$ requires 340.0421).

Anal. Calcd for $C_{21}H_{20}NO_4Cl_3$: C 55.22, H 4.41, N 3.07; Found C 53.17, H 4.55, N 2.90.

1-((1*R*,2*S*)-1-(2-Chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.24b):

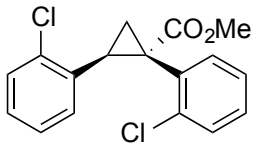


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-(2-chlorophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (131 mg, 0.40 mmol) was dissolved in methanol (12 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.4 mL, 0.8 mmol) and Ti(O-*i*Pr)$_4$ (0.25 mL, 0.8 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (31 mg, 0.8 mmol) was added and the reaction was stirred for an additional 4 hours. 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 95% yield (130 mg). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (46 mg, 0.4 mmol) and stirred for 30 minutes at room

temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (84 mg). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{21}H_{20}NO_4Cl_3$: C 55.22, H 4.41, N 3.07; Found C 55.13, H 4.38, N 3.05.

(1*S*,2*S*)-Methyl 1,2-bis(2-chlorophenyl)cyclopropanecarboxylate (6.25):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (1.07 g, 7.7 mmol) and Rh_2(*R*-DOSP)$_4$ (29 mg, .0154 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (300 mg, 1.54 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a colorless oil in 62% yield (289 mg).

HPLC analysis: 97% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.06 (major) and 8.16 (minor) min, UV 254 nm);

Rf = 0.65 (4:1 Hexanes: EtOAc);

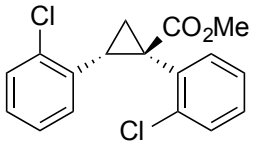
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.91 (dd, *J* = 4.8 and 7.6 Hz, 1H), 2.21 (br s, 1H), 3.68 (m, 4H), 6.24 (br s, 1H), 6.80 (t, *J* = 7.2 Hz, 1H), 7.05 (m, 4H), 7.17 (d, *J* = 8 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 30.5, 32.0, 53.0, 126.0, 126.3, 127.5, 129.9, 129.5, 129.6, 133.1, 133.2, 136.7, 137.5, 173.3;

FT-IR (film): 2950, 1722, 1433, 1252, 754, 735 cm^{-1};

HRMS-ESI m/z 321.0442 ($C_{17}H_{15}O_2Cl_2$ requires 321.0444).

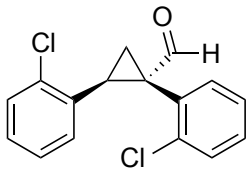
(1*R*,2*R*)-Methyl 1,2-bis(2-chlorophenyl)cyclopropanecarboxylate (ent-6.25):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (1.09 g, 7.7 mmol) and Rh_2(*S*-DOSP)$_4$ (30 mg, 0.016 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-(2-chlorophenyl)-2-diazoacetate (300 mg, 1.54 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as colorless oil in 64% yield (301 mg). HPLC analysis: 97% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.15 (minor) and 7.90 (major) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*S*)-1,2-Bis(2-chlorophenyl)cyclopropanecarbaldehyde (6.25a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 1,2-bis(2-chlorophenyl)cyclopropanecarboxylate (174 mg, 0.57 mmol) was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (54 mg, 1.43 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (474 mg, 1.12 mmol) was added. The reaction stirred at RT for 1.5 hours (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 the title compound as a colorless oil in 95% yield (150 mg).

Rf = 0.49 (4:1 Hexanes: EtOAc);

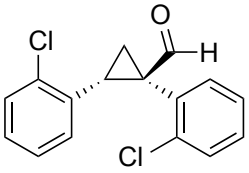
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.08 (dd, *J* = 5.6 and 8 Hz, 1H), 2.26 (dd, *J* = 5.6 and 9.6 Hz, 1H), 3.57 (t, *J* = 9.2 Hz, 1H), 6.33 (dd, *J* = 6.8 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 7.10 (m, 4H), 7.24 (m, 1H), 7.34 (dd, *J* = 1.8 and 7.6 Hz, 1H), 9.45 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.7, 32.2, 44.6, 126.1, 126.6, 126.8, 128.1, 129.5, 129.6, 130.0, 132.0, 133.2, 133.4, 136.5, 199.1;

FT-IR (film): 3063, 2829, 2751, 1706, 1477, 1440, 732 cm^{-1};

HRMS-ESI m/z 289.0193 ($C_{16}H_{11}OCl_2$ requires 289.0192).

(1*R*,2*R*)-1,2-Bis(2-chlorophenyl)cyclopropanecarbaldehyde (ent-6.25a):

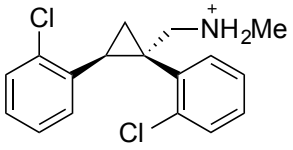


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 1,2-bis(2-chlorophenyl)cyclopropanecarboxylate (168 mg, 0.55 mmol) was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (52 mg, 1.38 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until

bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (492 mg, 1.16 mmol) was added. The reaction stirred at RT for 1.5 hours (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 the title compound as a colorless oil in 98% yield (151 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*S*)-1,2-bis(2-chlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.25b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-1,2-bis(2-chlorophenyl)cyclopropanecarbaldehyde (150 mg, 0.54 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1.1 mmol) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.1 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (42 mg, 1.11 mmol) was added and the reaction was stirred for an additional 4 hours. The reaction was

quenched with H_2O (2 mL) and extracted with diethyl ether. The organic extract was 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 75% yield (118 mg). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (47 mg, 0.40 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (120 mg).

mp 195-196 °C;

$[\alpha]^{D}_{20}$: -95.9° (10.6 mg/mL, MeOH);

^{1}H-NMR (400 MHz; CD_3OD): δ 1.79 (dd, *J* = 6.8 and 9.2 Hz, 1Hz), 1.91 (m, 1H), 2.63 (s, 3H), 3.07 (m, 2H), 4.07 (m, 1H), 6.13 (s, 1H), 6.66 (s, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 7.16-7.40 (m, 5H);

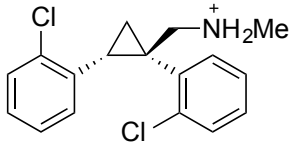
^{13}C-NMR (100 MHz, CD_3OD): δ 17.2, 26.9, 33.2, 57.7, 125.7, 127.2, 129.0, 129.7, 130.1, 132.8, 134.1, 135.0, 135.9, 136.3, 170.2;

FT-IR (neat): 3021, 2760, 2470, 1697, 1479, 1037, 735 cm^{-1};

HRMS-ESI m/z 306.0811 ($C_{17}H_{18}NCl_2$ requires 306.081).

Anal. Calcd for $C_{21}H_{21}NO_4Cl_2$: C 59.73, H 5.01, N 3.32; Found C 58.43, H 5.15, N 3.26.

1-((1*R*,2*R*)-1,2-bis(2-chlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.25b):

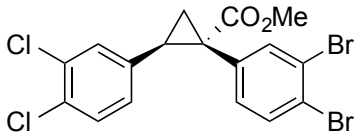


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-1,2-bis(2-chlorophenyl)cyclopropanecarbaldehyde (151 mg, 0.54 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1.1 mmol) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.1 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (42 mg, 1.11 mmol) was added and the reaction was stirred for an additional 4 hours. The reaction was quenched with H_2O (2 mL) and extracted with diethyl ether. The organic extract was 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 95% yield (152 mg). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (47 mg, 0.40 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title

compound as a white solid (102 mg). $[\alpha]^{D}_{20}$: 112.5° (9.9 mg/mL, MeOH); Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{21}H_{21}NO_4Cl_2$: C 59.73, H 5.01, N 3.32; Found C 59.27, H 5.11, N 3.29.

(1*S*,2*R*)-Methyl 1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (6.26):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (788 mg, 4.5 mmol) and Rh_2(*R*-DOSP)$_4$ (18 mg, 0.009 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (301 mg, 0.9 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a white solid in 95% yield (409 mg).

HPLC analysis: 83% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.4 (minor) and 17.7 (major) min, UV 254 nm); recrystallized from hexanes to give 97% ee;

Rf = 0.29 (4:1 Hexanes: EtOAc);

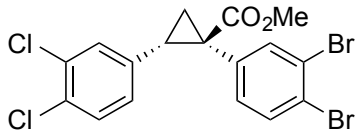
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.79 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.16 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.06 (t, *J* = 8.4 Hz, 1H), 3.68 (s, 3H), 6.52 (dd, *J* = 2.0 and 8.4 Hz, 1H), 6.75 (dd, *J* = 2.4 and 8.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.6, 32.2, 36.7, 53.2, 124.2, 124.5, 127.0, 130.2, 130.6, 131.1, 132.2, 132.4, 133.3, 135.6, 136.2, 136.8, 172.9;

FT-IR (film): 2951, 1719, 1474, 1434, 1256, 730 cm^{-1};

HRMS-ESI m/z 474.8512 ($C_{17}H_{11}O_2Br_2Cl_2$ requires 474.8508).

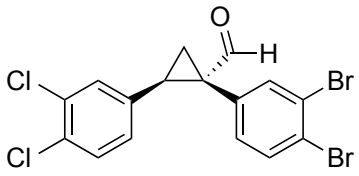
(1*R*,2*S*)-Methyl 1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (ent-6.26):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (780 mg, 4.5 mmol) and Rh_2(*S*-DOSP)$_4$ (17 mg, 0.009 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (300 mg, 0.9 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a white solid in 86% yield (368 mg).

HPLC analysis: 87% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.2 (major) and 18.1 (minor) min, UV 254 nm); recrystallized from hexanes to give 99% ee. Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1-(3,4-Dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (6.26a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (220 mg, 0.46 mmol)was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (44 mg, 1.15 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1.5 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (15 mL) and Dess Martin reagent (487 mg, 1.15 mmol) was added. The reaction stirred at RT for 3 hours (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 the title compound as a white solid in 74% yield (153 mg).

mp 83-84 °C;

Rf = 0.30 (4:1 Hexanes: EtOAc);

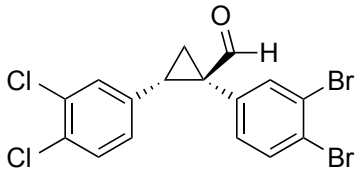
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.98 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.17 (dd, *J* = 5.6 and 9.2 Hz, 1H), 2.95 (t, *J* = 8.4 Hz, 1H), 6.57 (dd, *J* = 2 and 8.8 Hz, 1H), 6.78 (dd, *J* = 2 and 8.4 Hz, 1H), 7.02 (d, *J* = 2 Hz, 1H), 7.17 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 9.43 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.6, 33.9, 45.4, 125.0, 125.3, 130.3, 130.4, 131.5, 132.7, 134.0, 134.4, 135.3, 136.3, 198.6;

IR (film): 3087, 2827, 2748, 1706, 1475, 716 cm^{-1};

HRMS-ESI m/z 444.8404 ($C_{16}H_9OBr_2Cl_2$ requires 444.8403).

(1*R*,2*S*)-1-(3,4-Dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-6.26b):

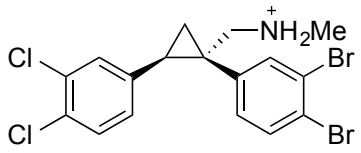


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarboxylate (108 mg, 0.23 mmol)was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (22 mg,

0.56 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1.5 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (15 mL) and Dess Martin reagent (244 mg, 0.58 mmol) was added. The reaction stirred at RT for 3 hours (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 the title compound as a white solid in 69% yield (70 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.26b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (120 mg, 0.27 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.3 mL, 0.53 mmol) and Ti(O-*i*Pr)$_4$ (0.15 mL, 0.53

mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (20 mg, 0.53 mmol) was added and the reaction was stirred for an additional 4 hours. 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 97% yield (129 mg). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (32 mg, 0.28 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (115 mg).

mp 191-192 °C;

$[\alpha]^{D}_{20}$: -62.8° (11.2 mg/mL, MeOH);

^{1}H-NMR (400 MHz; CD_3OD): δ 1.62 (dd, *J* = 6.4 and 9.2 Hz, 1H), 1.89 (t, *J* = 6.4 Hz, 1H), 2.57 (dd, *J* = 6.4 and 9.2 Hz, 1H), 2.62 (s, 3H), 2.96 (d, *J* = 13.2 Hz, 1H), 3.76 (d, *J* = 8.8 Hz, 1H), 6.66 (s, 2H), 6.72 (dd, *J* = 2.4 and 8.8 Hz, 1H), 7.03 (dd, *J* = 2 and 8 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H);

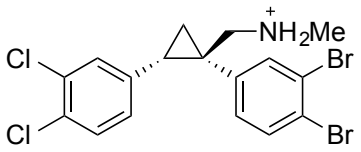
^{13}C-NMR (100 MHz, CD_3OD): δ 16.0, 28.3, 31.6, 32.9, 58.5, 124.1, 124.7, 127.4, 129.7, 130.0, 130.2, 131.4, 131.7, 132.8, 133.9, 135.0, 136.2, 137.0, 137.6, 170.1;

FT-IR (neat): 3007, 2768, 2436, 1710, 1462, 1370, 778 cm^{-1};

HRMS-ESI m/z 461.9029 ($C_{17}H_{16}NBr_2Cl_2$ requires 461.9021).

Anal. Calcd for $C_{21}H_{29}NO_4Br_2Cl_2$: C 43.48, H 3.30, N 2.41; Found C 43.57, H 3.41, N 2.38.

1-((1*R*,2*S*)-1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.26b):

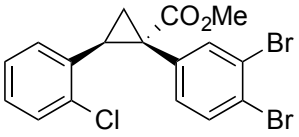


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-(3,4-dibromophenyl)-2-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (70 mg, 0.16 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.15 mL, 0.31 mmol) and Ti(O-*i*Pr)$_4$ (0.10 mL, 0.31 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (12 mg, 0.31 mmol) was added and the reaction was stirred for an additional 4 hours. 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 96% yield (72 mg). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (18 mg, 0.16 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give as a white solid (67 mg). $[\alpha]^{D}_{20}$: 50.1° (9.9 mg/mL, MeOH); Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{21}H_{29}NO_4Br_2Cl_2$: C 43.48, H 3.30, N 2.41; Found C 43.34, H 3.25, N 2.41.

(1*S*,2*S*)-Methyl 2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarboxylate (6.27):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (624 mg, 4.5 mmol) and Rh_2(*R*-DOSP)$_4$ (18 mg, 0.009 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (301 mg, 0.9 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a white solid in 75% yield (222 mg).

HPLC analysis: 89% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.7 (major) and 14.3 (minor) min, UV 254 nm);

mp 84-86 °C;

Rf = 0.34 (4:1 Hexanes: EtOAc);

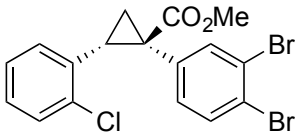
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.98 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.13 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.37 (t, *J* = 8.8 Hz, 1H), 3.72 (s, 3H), 6.59 (dd, *J* = 1.2 and 7.6 Hz, 1H), 6.89 (dd, *J* = 2.4 and 8.4 Hz, 1H), 6.96 (dt, *J* = 0.8 and 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 1.2 and 8 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.6, 31.2, 35.7, 53.1, 100.8, 123.7, 124.1, 126.8, 127.8, 128.6, 129.5, 131.7, 133.0, 133.7, 136.2, 136.3, 136.4, 173.2;

FT-IR (film): 2950, 1720, 1464, 1434, 1256, 739 cm^{-1};

HRMS-ESI m/z 440.8898 ($C_{17}H_{12}0_2Br_2Cl$ requires 440.8898).

(1*R*,2*R*)-Methyl 2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarboxylate (ent-6.27):

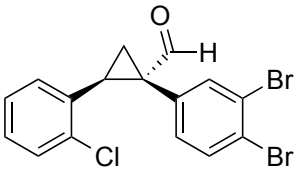


In a 50 mL round bottom flask equipped with a magnetic stir bar, 1-chloro-2-vinylbenzene (622 mg, 4.5 mmol) and Rh_2(*S*-DOSP)$_4$ (17 mg, 0.009 mmol) were

dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (300 mg, 0.9 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as a white solid in 74% yield (219 mg).

HPLC analysis: 89% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 11.9 (minor) and 14.4 (major) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*S*)-2-(2-Chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarbaldehyde (6.27a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-methyl 2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarboxylate (180 mg, 0.41 mmol)was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (38 mg, 1.0 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until

bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (330 mg, 0.78 mmol) was added. The reaction stirred at RT for 1.5 hours (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 the title compound as a colorless oil in 69% yield (117 mg).

Rf = 0.38 (4:1 Hexanes:EtOAc);

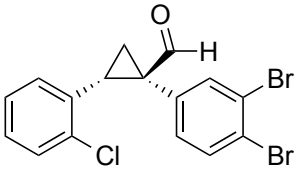
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.16 (m, 2H), 3.22 (t, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 1.6 and 7.6 Hz, 1H), 6.90 (dd, *J* = 2 and 8.4 Hz, 1H), 6.99 (dt, *J* = 1.2 and 7.2 Hz, 1H), 7.08 (dt, *J* = 1.6 and 7.6 Hz, 1H), 7.31 (dd, *J* = 1.6 and 8 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 9.49 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.5, 33.7, 44.2, 124.4, 124.8, 126.9, 127.9, 128.9, 129.6, 131.0, 132.7, 133.7, 135.0, 135.8, 135.9, 198.8;

FT-IR (film): 3063, 2849, 2748, 1704, 1481, 1467, 746 cm^{-1};

HRMS-ESI m/z 410.8796 ($C_{16}H_{10}OBr_2Cl$ requires 410.8792).

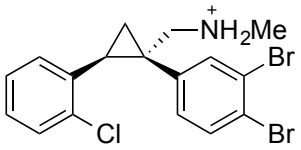
(1*R*,2*R*)-2-(2-Chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarbaldehyde (ent-6.27a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-methyl 2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarboxylate (170 mg, 0.38 mmol)was dissolved in diethyl ether (20 mL) and flushed with argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (36 mg, 0.96 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (324 mg, 0.76 mmol) was added. The reaction stirred at RT for 1.5 hours (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 the title compound as a colorless oil in 64% yield (101 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*S*)-2-(2-Chlorophenyl)-1-(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.27b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*S*)-2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarbaldehyde (80 mg, 0.19 mmol) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.2 mL, 0.38 mmol) and Ti(O-*i*Pr)$_4$ (0.10 mL, 0.38 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (15 mg, 0.38 mmol) was added and the reaction was stirred for an additional 4 hours. 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 96% yield (83 mg). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (27 mg, 0.23 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (77 mg).

mp 193-194 °C;

^{1}H-NMR (400 MHz; CD_3OD): δ 1.62 (dd, *J* = 6.8 and 9.2 Hz, 1H), 2.12 (t, *J* = 7.2 Hz, 1H), 2.63 (s, 3H), 2.72 (dd, *J* = 6.8 and 9.2 Hz, 1H), 3.01 (d, *J* = 13.6 Hz, 1H), 4.07 (dd, *J* = 1.6 and 13.2 Hz, 1H), 6.66 (s, 2H), 6.78 (dd, *J* = 1.6 and 7.6 Hz, 1H), 6.99-7.07 (m, 2H), 7.11 (dd, *J* = 2 and 8.4 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 2 Hz, 1H);

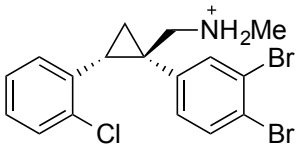
^{13}C-NMR (100 MHz, CD_3OD): δ 13.9, 28.3, 30.5, 32.9, 58.0, 123.6, 124.4, 126.5, 126.6, 128.2, 128.9, 130.5, 131.8, 133.6, 133.9, 135.0, 135.2, 135.6, 137.4, 170.2;

FT-IR (neat): 2971, 2715, 2446, 1708, 1560, 1252, 756 cm^{-1};

HRMS-ESI m/z 427.9416 ($C_{17}H_{17}NBr_2Cl$ requires 427.9411).

Anal. Calcd for $C_{21}H_{20}NO_4Br_2Cl$: C 46.23, H 3.69, N 2.57; Found C 48.85, H 4.00, N 2.73.

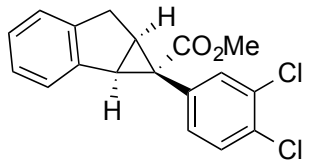
1-((1*R*,2*R*)-2-(2-Chlorophenyl)-1-(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.27b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*R*)-2-(2-chlorophenyl)-1-(3,4-dibromophenyl)cyclopropanecarbaldehyde (80 mg, 0.19 mmol) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.2 mL, 0.38 mmol) and Ti(O-*i*Pr)$_4$ (0.10 mL, 0.38 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$

(15 mg, 0.38 mmol) was added and the reaction was stirred for an additional 4 hours. 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 96% yield (82 mg). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (23 mg, 0.19 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 ethyl acetate/isopropanol (8 mL) and refluxed for 3 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting white solid was filtered and washed with cold hexanes to give the title compound as a white solid (70 mg). Spectroscopic data is the same as the other enantiomer.

(1*S*,1*aR*,6*aR*)-Methyl 1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carboxylate (6.28):



In a 50 mL round bottom flask equipped with a magnetic stir bar, indene (284 mg, 2.45 mmol) and Rh_2(*R*-DOSP)$_4$ (31 mg, 0.016 mmol) were dissolved in dry, degassed toluene

(4 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (400 mg, 1.63 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→40% EtOAc: Hexanes) to obtain the title compound as a white solid in 74% yield (401 mg).

HPLC analysis: 96% ee (SS-WHELK column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 13.5 (minor) and 17.2 (major) min, UV 254 nm);

Rf = 0.52 (4:1 Hexanes: EtOAc);

mp 138-139 °C;

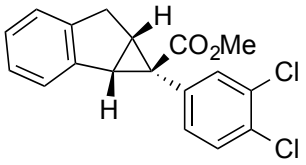
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.70 (d, *J* = 18 Hz, 1H), 2.87 (t, *J* = 6.4 Hz, 1H), 3.27 (dd, *J* = 6.4 and 18 Hz, 1H), 3.48 (d, *J* = 7.2 Hz, 1H), 3.65 (s, 3H), 6.75 (d, *J* = 8 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.98 (td, *J* = 1.2, 7.6, and 7.6 Hz, 1H), 7.05 (s, 1H), 7.12 (m, 2H), 7.41 (d, *J* = 7.2 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.3, 33.3, 37.6, 40.8, 52.9, 124.8, 125.5, 126.8, 127.1, 129.7, 131.0, 131.6, 131.8, 132.9, 134.3, 141.0, 142.7, 173.2;

FT-IR (film): 3024, 2951, 1717, 1474, 1432, 1253, 738 cm^{-1};

HRMS-ESI m/z 333.0451 ($C_{18}H_{15}O_2Cl_2$ requires 333.0444).

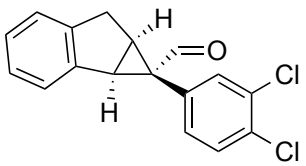
(1*R*,1*aS*,6*aS*)-Methyl 1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carboxylate (ent-6.28):



In a 50 mL round bottom flask equipped with a magnetic stir bar, indene (286 mg, 2.45 mmol) and Rh_2(*S*-DOSP)$_4$ (31 mg, 0.016 mmol) were dissolved in dry, degassed toluene (4 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (401 mg, 1.64 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→40% EtOAc: Hexanes) to obtain the title compound as a white solid in 77% yield (422 mg).

HPLC analysis: 95% ee (SS-WHELK column, 0.5% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 13.3 (major) and 18.1 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,1*aR*,6*aR*)-1-(3,4-Dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carbaldehyde (6.28a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,1*aR*,6*aR*)-methyl 1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carboxylate (300 mg,

0.90 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (75 mg, 1.98 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (838 mg, 1.98 mmol) was added. The reaction stirred at RT for 2 hours (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, Isolera, 5→30% EtOAc: Hexanes) to give the title compound as a colorless oil in 87% yield (238 mg).

Rf = 0.39 (4:1 Hexanes: EtOAc);

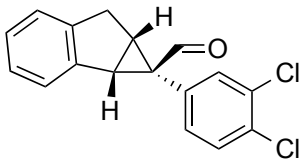
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.75 (d, *J* = 18 Hz, 1H), 2.88 (t, *J* = 6.4 Hz, 1H), 3.32 (dd, *J* = 6.4 and 18.4 Hz, 1H), 3.51 (d, *J* = 6.8 Hz, 1H), 6.77 (dd, *J* = 2 and 8 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.03 (td, *J* = 1.2, 7.6, and 7.6 Hz, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 7.18 (m, 2H), 7.43 (d, *J* = 7.2 Hz, 1H), 9.43 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 33.1, 41.4, 46.8, 124.9, 125.2, 127.0, 127.4, 130.4, 131.5, 131.9, 132.4, 132.5, 134.1, 140.3, 142.7, 199.2;

FT-IR (film): 3025, 2911, 2831, 1698, 1471, 724 cm^{-1};

HRMS-ESI m/z 303.0340 ($C_{17}H_{13}OCl_2$ requires 303.0338).

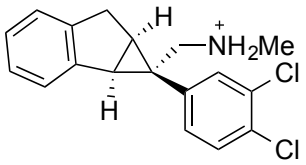
(1*R*,1*aS*,6*aS*)-1-(3,4-Dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carbaldehyde (ent-6.28a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,1*aS*,6*aS*)-methyl 1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carboxylate (301 mg, 0.90 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (76 mg, 2.0 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (836 mg, 1.97 mmol) was added. The reaction stirred at RT for 2 hours (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, Isolera, 5→30% EtOAc: Hexanes) to give the title compound as a colorless oil in 85% yield (233 mg). Spectroscopic data is the same as the other enantiomer.

***N*-Methyl-1-((1*S*,1*aR*,6*aR*)-1-phenyl-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]inden-1-yl)methanamine fumarate (6.28b):**



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,1*aR*,6*aR*)-1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carbaldehyde (180 mg, 0.59 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1.19 mmol) and Ti(O-*i*Pr)$_4$ (0.35 mL, 1.19 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (46 mg, 1.22 mmol) was added and the reaction was stirred for an additional 2 hours. 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 86% yield (163 mg, 0.51 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (60 mg, 0.51 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (8 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an

acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as a white solid (168 mg).

mp 196-197 °C;

$[\alpha]^{D}_{20}$: -4.9° (10.5 mg/mL, MeOH);

^{1}H-NMR (400 MHz; CD_3OD): δ 2.35 (t, *J* = 6.8 Hz, 1H), 2.67 (m, 4H), 3.03 (d, *J* = 12.8 Hz, 1H), 3.11 (d, *J* = 6.8 Hz, 1H), 3.19 (dd, *J* = 7.2 and 18 Hz, 1H), 3.40 (d, *J* = 12.8 Hz, 1H), 6.70 (s, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.24 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H);

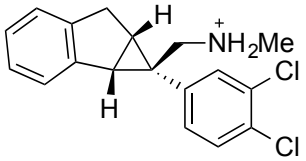
^{13}C-NMR (100 MHz, CD_3OD): δ 28.3, 32.2, 32.6, 33.1, 36.6, 58.3, 124.4, 124.8, 126.3, 126.5, 130.3, 131.2, 131.6, 133.9, 134.4, 135.0, 141.4, 142.6, 170.1;

FT-IR (neat): 3023, 2903, 2784, 1679, 1473, 759 cm^{-1};

HRMS-ESI m/z 318.0812 ($C_{18}H_{18}NCl_2$ requires 318.0811).

Anal. Calcd for $C_{22}H_{21}NO_4Cl_2$: C 60.84, H 4.87, N 3.23; Found C 60.17, H 4.89, N 3.20.

***N*-Methyl-1-((1*R*,1*aS*,6*aS*)-1-phenyl-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]inden-1-yl)methanamine fumarate (ent-6.28b):**

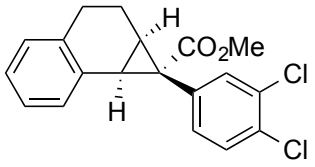


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,1*aS*,6*aS*)-1-(3,4-dichlorophenyl)-1,1*a*,6,6*a*-tetrahydrocyclopropa[*a*]indene-1-carbaldehyde (180 mg, 0.59

mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1.19 mmol) and Ti(O-*i*Pr)$_4$ (0.35 mL, 1.19 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (45 mg, 1.19 mmol) was added and the reaction was stirred for an additional 2 hours. 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 91% yield (172 mg, 0.54 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (62 mg, 0.53 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (8 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as a white solid (144 mg). $\mathbf{[\alpha]^{D}_{20}}$: 5.5° (10.7 mg/mL, MeOH). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{22}H_{21}NO_4Cl_2$: C 60.84, H 4.87, N 3.23; Found C 60.67, H 4.88, N 3.20.

(1*S*,1*aR*,7*bR*)-Methyl 1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*] naphtha-ene-1-carboxylate (6.29):



In a 100 mL round bottom flask equipped with a magnetic stir bar, 1,2-dihydronaphthalene (563 mg, 4.32 mmol) and Rh_2(*R*-DOSP)$_4$ (78 mg, 0.041 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (1.01 g, 4.12 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→30% EtOAc: Hexanes). The residue was then dissolved in 1 mL of hexane to recrystallize and then filtered to obtain the title compound as colorless crystals in 20% yield (286 mg).

HPLC analysis: 98% ee (SS-WHELK column, 0% 2-PrOH in hexanes, 0.5 mL/min, 1mg/mL, t_R = 21.2 (minor) and 25.9 (major) min, UV 254 nm);

Rf = 0.56 (4:1 Hexanes: EtOAc);

mp 86-87 °C;

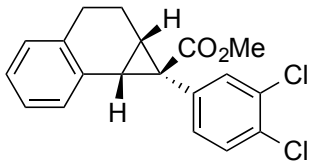
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (ddd, *J* = 7.6, 12, and 16.8 Hz, 1H), 2.03 (m, 1H), 2.15 (m, 1H), 2.28 (dd, *J* = 6.8 and 17.2 Hz, 1H), 2.58 (dd, *J* = 4.4 and 9.6 Hz, 1H), 3.06 (dd, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 6.75-6.81 (m, 2H), 7.08-7.22 (m, 4H), 7.44 (dd, *J* = 1.2 and 7.6 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.0, 25.6, 28.8, 31.2, 38.3, 53.0, 126.5, 127.1, 128.8, 130.1, 130.4, 130.5, 131.5, 132.0, 132.3, 133.1, 135, 135.3, 173.2;

IR (film): 3022, 2927, 2858, 1716, 1473, 1434, 1236 cm^{-1};

HRMS-ESI m/z 347.0607 ($C_{19}H_{17}O_2Cl_2$ requires 347.0600).

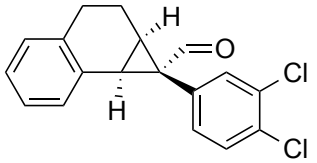
(1*R*,1*aS*,7*bS*)-Methyl 1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*] naphtha-ene-1-carboxylate (ent-6.29):



In a 100 mL round bottom flask equipped with a magnetic stir bar, 1,2-dihydronaphthalene (565 mg, 4.32 mmol) and Rh_2(*S*-DOSP)$_4$ (78 mg, 0.041 mmol) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (1.002 g, 4.09 mmol) was dissolved in dry, degassed toluene (20 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→30% EtOAc: Hexanes). The residue was then dissolved in 1 mL of hexane to recrystallize and then filtered to obtain the title compound as colorless crystals in 16% yield (224 mg).

HPLC analysis: >99% ee (SS-WHELK column, 0% 2-PrOH in hexanes, 0.5 mL/min, 1mg/mL, t_R = 21.0 (major) and 253 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,1*aR*,7*bR*)-1-(3,4-Dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (6.29a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,1*aR*,7*bR*)-methyl 1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (200 mg, 0.60 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (50 mg, 1.32 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (501 mg, 1.18 mmol) was added. The reaction stirred at RT for 16 hours (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, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 93% yield (171 mg). Rf = 0.47 (4:1 Hexanes: EtOAc);

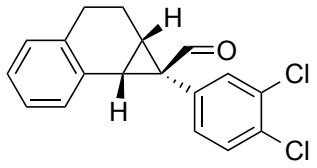
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.32 (ddd, *J* = 8.4, 12.8, and 17.6 Hz, 1H), 2.05 (m, 1H), 2.16 (m, 1H), 2.34 (dd, *J* = 7.2 and 17.2 Hz, 1H), 2.51 (dd, *J* = 2.4 and 8.8 Hz, 1H), 3.04 (d, *J* = 9.2 Hz, 1H), 6.75 (dd, *J* = 2 and 8.4 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 2 Hz, 1H), 7.12 (td, *J* = 1.2, 7.2 and 7.2 Hz, 1H), 7.24 (m, 2H), 7.41 (dd, *J* = 1.2 and 7.6 Hz, 1H), 9.26 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.1, 25.9, 29.7, 31.8, 47.3, 126.7, 127.4, 129, 130.2, 130.8, 131.5, 132.4, 132.8, 134.9, 135.0, 198.7;

FT-IR (film): 3022, 2926, 2856, 1699, 1471, 729 cm^{-1};

HRMS-ESI m/z 317.0495 ($C_{18}H_{15}OCl_2$ requires 317.0495).

(1*R*,1*aS*,7*bS*)-1-(3,4-Dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (ent-6.29a):

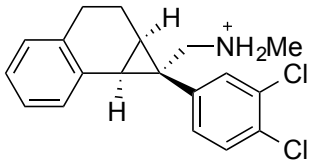


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,1*aS*,7*bS*)-methyl 1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carboxylate (200 mg, 0.60 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum

hydride (50 mg, 1.32 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (508 mg, 1.20 mmol) was added. The reaction stirred at RT for 16 hours (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, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 68% yield (125 mg). Spectroscopic data is the same as the other enantiomer.

_N_-Methyl-1-((1_S_,1_aR_,7_bR_)-1-phenyl-1_a_,2,3,7_b_-tetrahydro-1_H_-cyclopropa[_a_]naphthalen-1-yl)methanamine fumarate (6.29b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,1*aR*,7*bR*)-1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (160 mg, 0.59 mmol) was dissolved in methanol (12 mL) and flushed with argon. This

solution was treated with methylamine (2M in MeOH, 0.5 mL, 1.0 mmol) and Ti(O-*i*Pr)$_4$ (0.30 mL, 1.0 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (38 mg, 1.01 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light yellow oil in 77% yield (129 mg, 0.39 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (45 mg, 0.39 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (8 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as an off-white solid (135 mg).

mp 208-209 °C;

$[\alpha]^{D}_{20}$: -107.9° (10.2 mg/mL, MeOH);

^{1}H-NMR (400 MHz; CD_3OD): δ 1.12 (m, 1H), 1.97-1.84 (m, 2H), 2.18 (dd, *J* = 7.2 and 14 Hz, 1H), 2.27 (dd, *J* = 6.8 and 16.4 Hz, 1H), 2.55 (dd, *J* = 8.8 Hz, 1H), 2.63 (s, 3H), 3.00 (d, *J* = 13.2 Hz, 1H), 3.40 (d, *J* = 13.2 Hz, 1H), 6.67 (s, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 7.06 (td, *J* = 1.2, 7.2 and 7.2 Hz, 1H), 7.17 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 6.4 Hz, 1H);

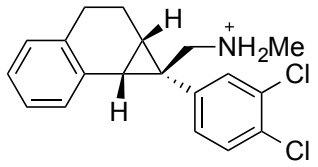
^{13}C-NMR (100 MHz, CD_3OD): δ 17.7, 25.0, 25.6, 26.5, 32.8, 33.1, 60.2, 126, 126.3, 128.4, 129.9, 130.3, 130.8, 131.8, 132.4, 132.6, 133.1, 134.6, 135.1, 136.6, 170.3;

IR (neat): 3438, 2989, 2927, 2859, 1686, 1465 cm^{-1};

HRMS-ESI m/z 332.0967 ($C_{19}H_{20}NCl_2$ requires 332.0967).

Anal. Calcd for $C_{23}H_{23}NO_4Cl_2$: C 61.62, H 5.17, N 3.12; Found C 61.94, H 5.22, N 3.14.

***N*-Methyl-1-((1*R*,1*aS*,7*bS*)-1-phenyl-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalen-1-yl)methanamine fumarate (ent-6.29b):**

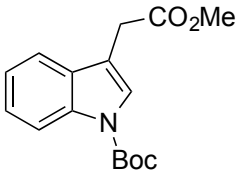


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,1*aS*,7*bS*)-1-(3,4-dichlorophenyl)-1*a*,2,3,7*b*-tetrahydro-1*H*-cyclopropa[*a*]naphthalene-1-carbaldehyde (124 mg, 0.39 mmol) was dissolved in methanol (12 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.4 mL, 0.8 mmol) and Ti(O-*i*Pr)$_4$ (0.25 mL, 0.8 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (31 mg, 0.78 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light yellow oil in 82% yield (107 mg, 0.32 mmol). The product was dissolved in isopropanol (8 mL) and then treated with fumaric acid (37 mg, 0.32 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (8 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as an off-white solid (102 mg). $\mathbf{[\alpha]^{D}_{20}}$: 109.0° (9.8 mg/mL, MeOH). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{23}H_{23}NO_4Cl_2$: C 61.62, H 5.17, N 3.12; Found C 60.34, H 5.31, N 3.08.

***tert*-Butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate:**



In a 250 mL round bottom flask equipped with a magnetic stir bar, 3-indoleacetic acid (10.0g, 57.1 mmol) were dissolved in 50 mL of methanol and a catalytic amount of sulfuric acid was added. The solution was heated to reflux and stirred for 16 hours. The reaction was then cooled to RT and concentrated under reduced pressure. The residue was re-dissolved in ether, washed with aq. $NaHCO_3$, dried with $MgSO_4$, passed through a short plug of silica, and concentrated under reduced pressure to give the acetate in 96%

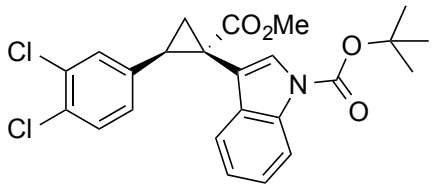
yield (10.47 g) as a brown solid upon standing. The solid (5.2 g, 27.5 mmol) was then dissolved in 40 mL of acetonitrile along with DMAP (1.08 g, 8.8 mmol) and boc anhydride (10.6 g, 48.4 mmol). After the reaction had stirred for 2 hours at RT, imidazole (3.0 g, 44.0 mmol) were added. The reaction stirred for an additional 2 hours and then concentrated under reduced pressure. The residue was diluted with ethyl acetate, washed with aq. NH_4Cl, aq. $NaHCO_3$, and brine, then dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified via column chromatography (SiO_2, 100% hexanes→4:1 hexanes:EtOAc) to give the title compound as a tan solid in 86% yield (7.93 g).

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.67 (s, 9H), 3.72 (s, 3H), 3.73 (s, 2H), 7.27 (td, *J* = 1.2, 7.6, and 7.6 Hz, 1H), 7.32 (t, *J* = 6.9 Hz, 1H), 7.54 (m, 2H), 8.15 (br s, 1 H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.4, 31.1, 52.4, 83.8, 113.3, 115.5, 119.2, 122.8, 124.8, 130.3, 135.3, 149.8, 171.7;

Spectroscopic data is consistent with the literature.[211]

***tert*-Butyl 3-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-(methoxycarbonyl)cyclopropyl)-1*H*-indole-1-carboxylate (6.30):**



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (754 mg, 4.36 mmol) and Rh_2(*S*-PTAD)$_4$ (27 mg, 0.018 mmol) were

dissolved in dry, degassed toluene (3 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. *tert*-Butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (550 mg, 1.75 mmol) was dissolved in dry, degassed toluene (14 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2,100% hexanes→8:1 hexanes:EtOAc) to obtain the title compound as a white foam in 79% yield (634 mg).

HPLC analysis: 67% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.2 (minor) and 10.0 (major) min, UV 254 nm); recrystallized from hexanes/acetone to give >99% ee;

Rf = 0.53 (4:1 Hexanes: EtOAc);

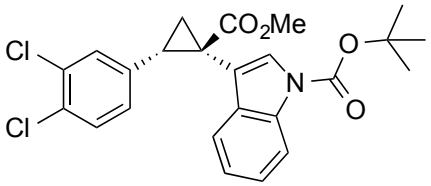
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.62 (s, 9H), 1.83 (dd, *J* = 5.2 and 7.6 Hz, 1H), 2.19 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.19 (dd, *J* = 7.2 and 9.2 Hz, 1H), 3.66 (s, 3H), 6.75 (dd, *J* = 2 and 8.4 Hz, 1H), 7.16-7.08 (m, 4H), 7.25 (m, 1H), 7.33 (d, *J* = 8 Hz, 1H), 8.04 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.6, 28.3, 28.8, 31.8, 53.0, 84.0, 115.4, 119.7, 122.7, 124.6, 126.7, 127.5, 129.7, 130.7, 130.8, 131.9, 137.0, 144.8, 173.8;

FT-IR (film): 2980, 2951, 1720, 1452, 1380, 1246, 747 cm^{-1};

HRMS-ESI m/z 482.0896 ($C_{24}H_{23}O_4NCl_2Na$ requires 482.0896).

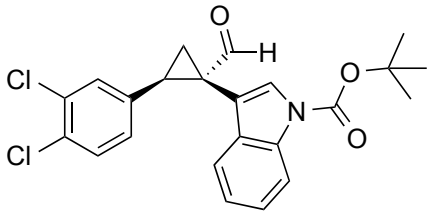
***tert*-Butyl 3-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-(methoxycarbonyl)cyclopropyl)-1*H*-indole-1-carboxylate (ent-6.30):**



In a 50 mL round bottom flask equipped with a magnetic stir bar, 1,2-chloro-4-vinylbenzene (758 mg, 4.38 mmol) and Rh_2(*R*-PTAD)$_4$ (25 mg, 0.016 mmol) were dissolved in dry, degassed toluene (3 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. *tert*-Butyl 3-(1-diazo-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (490 mg, 1.55 mmol) was dissolved in dry, degassed toluene (14 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2,100% hexanes→8:1 hexanes:EtOAc) to obtain the title compound as a white foam in 60% yield (430 mg).

HPLC analysis: 65% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 8.1 (major) and 10.0 (minor) min, UV 254 nm); recrystallized from hexanes/acetone to give >99% ee. Spectroscopic data is the same as the other enantiomer.

***tert*-Butyl 3-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-formylcyclopropyl)-1*H*-indole-1-carboxylate (6.30a):**



In a 250 mL round bottom flask equipped with a magnetic stir bar, *tert*-butyl 3-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-(methoxycarbonyl)cyclopropyl)-1*H*-indole-1-carboxylate (250 mg, 0.54 mmol) was dissolved in methylene chloride (30 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. DIBAL-H (1M in CH_2Cl_2, 0.70 mL, 0.70 mmol) was then added dropwise down the side of the flask to the stirring solution. Following the addition, the reaction stirred for 2 hours at -78 °C. The reaction was quenched with 3 mL of methanol at -78 °C and stirred for 15 minutes. The solution was then slowly warmed to RT and 20 mL of Rochelle's salt was added. The slurry stirred for 1.5 hours under the two layers became transparent. Organic layer was extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 52% yield (120 mg).

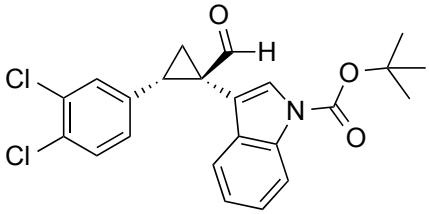
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.64 (s, 9H), 1.99 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.23 (dd, *J* = 4.8 and 9.2 Hz, 1H), 3.13 (dd, *J* = 7.2 and 9.2 Hz, 1H), 6.78 (dd, *J* = 2.4 and 8.4 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.18 (m, 3H), 7.29 (m, 1H), 7.34 (d, J = 8 Hz, 1H), 8.09 (br s, 1H), 9.68 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.6, 28.3, 33.4, 37.5, 84.3, 113.8, 115.7, 119.2, 123.1, 125.1, 127.3, 127.4, 130, 130.4, 130.5, 131.1, 132.1, 136.4, 144.5, 200.3;

FT-IR (film): 2979, 1732, 1706, 1451, 1370, 729 cm^{-1};

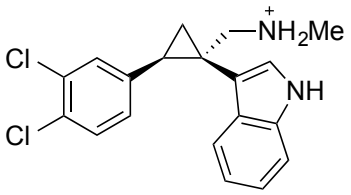
HRMS-ESI m/z 430.0977 ($C_{23}H_{22}O_3NCl_2$ requires 430.0971).

***tert*-Butyl 3-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-formylcyclopropyl)-1*H*-indole-1-carboxylate (ent-6.30a):**



In a 250 mL round bottom flask equipped with a magnetic stir bar, *tert*-butyl 3-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-(methoxycarbonyl)cyclopropyl)-1*H*-indole-1-carboxylate (251 mg, 0.54 mmol) was dissolved in methylene chloride (30 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. DIBAL-H (1M in CH_2Cl_2, 0.70 mL, 0.70 mmol) was then added dropwise down the side of the flask to the stirring solution. Following the addition, the reaction stirred for 2 hours at -78 °C. The reaction was quenched with 3 mL of methanol at -78 °C and stirred for 15 minutes. The solution was then slowly warmed to RT and 20 mL of Rochelle's salt was added. The slurry stirred for 1.5 hours under the two layers became transparent. Organic layer was extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 50% yield (117 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-(1*H*-indol-3-yl)cyclopropyl)-*N*-methylmethanamine fumarate (6.30b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, *tert*-butyl 3-((1*S*,2*R*)-2-(3,4-dichlorophenyl)-1-formylcyclopropyl)-1*H*-indole-1-carboxylate (110 mg, 0.26 mmol) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.3 mL, 0.6 mmol) and Ti(O-*i*Pr)$_4$ (0.15 mL, 0.51 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (19 mg, 0.51 mmol) was added and the reaction was stirred for an additional 3 hours. 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 light yellow oil in 78% yield (89 mg, 0.20 mmol). The product started to immediately darken in color so it was dissolved in trifluoroethanol (3 mL) placed in the microwave at 150 °C for 1.75 minutes. The soln was then concentrated under reduced pressure and the residue was dissolved in isopropanol (10 mL) and then treated with fumaric acid (23 mg, 0.20 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (10 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was

filtered and washed with cold acetone to give the title compound as an off-white solid (52 mg).

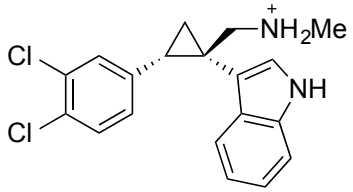
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.65 (dd, *J* = 5.6 and 8.8 Hz, 1H), 1.80 (t, *J* = 5.2 Hz, 1H), 2.59 (m, 4H), 3.02 (d, *J* = 12.8 Hz, 1H), 3.81 (d, *J* = 12.8 Hz, 1H), 6.69 (s, 2H), 6.79 (dd, *J* = 2.4 and 8.8 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 7.06 (m, 4H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.1, 25.2, 27.4, 32.7, 57.9, 108.4, 111.6, 118.4, 119.0, 121.7, 126.8, 127.2, 129.0, 129.2, 129.6, 130.9, 135, 137.2, 138.9, 170.2;

FT-IR (neat): 3416, 2966, 1661, 1636, 1029, 745 cm^{-1};

HRMS-ESI m/z 345.0922 ($C_{19}H_{19}N_2Cl_2$ requires 345.092).

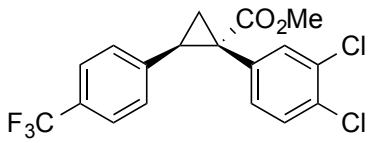
1-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-(1*H*-indol-3-yl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.30b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, *tert*-butyl 3-((1*R*,2*S*)-2-(3,4-dichlorophenyl)-1-formylcyclopropyl)-1*H*-indole-1-carboxylate (72 mg, 0.17 mmol) was dissolved in methanol (10 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.2 mL, 0.4 mmol) and Ti(O-*i*Pr)$_4$ (0.10 mL, 0.34 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (13 mg, 0.34 mmol) was added and the reaction was stirred for an additional 3

hours. 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 light yellow oil in 87% yield (65 mg, 0.15 mmol). The product started to immediately darken in color so it was dissolved in trifluoroethanol (3 mL) placed in the microwave at 150 °C for 1.75 minutes. The soln was then concentrated under reduced pressure and the residue was dissolved in isopropanol (10 mL) and then treated with fumaric acid (17 mg, 0.15 mmol) and stirred for 30 minutes at room temperature. The mixture was then concentrated under reduced pressure and the residue was re-dissolved in 1:1 isopropanol/hexanes (10 mL) and refluxed for 2 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as an off-white solid (25 mg). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-Methyl 1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropane-carboxylate (6.31):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 4-trifluoromethyl styrene (451 mg, 2.62 mmol) and Rh_2(*R*-DOSP)$_4$ (31 mg, 0.016 mmol) were dissolved in dry, degassed toluene (4 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (401 mg, 1.64 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→15% EtOAc: Hexanes) to obtain the title compound as a white solid in 77% yield (490 mg).

HPLC analysis: 93% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.9 (minor) and 13.1 (major) min, UV 254 nm); recrystallized from hexanes to >99% ee (83% recovery);

Rf = 0.49 (4:1 Hexanes: EtOAc);

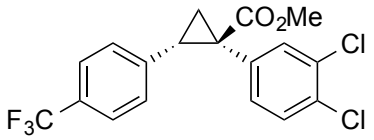
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.88 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.21 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.18 (dd, *J* = 7.2 and 9.2 Hz, 1H), 3.69 (s, 3H), 6.78 (dd, *J* = 2 and 8.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8 Hz, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.8, 32.8, 37.1, 53.1, 125.2, 128.5, 129.5, 129.6, 130.1, 131.4, 131.9, 132.2, 133.7, 134.9, 140.1, 173.1;

IR (film): 2954, 1720, 1474, 1436, 1324, 1115 cm^{-1};

HRMS-ESI m/z 389.0318 ($C_{18}H_{14}O_2Cl_2F_3$ requires 389.0317).

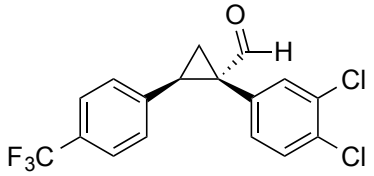
(1*R*,2*S*)-Methyl 1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropane-carboxylate (ent-6.31):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 4-trifluoromethyl styrene (422 mg, 2.45 mmol) and Rh_2(*S*-DOSP)$_4$ (31 mg, 0.016 mmol) were dissolved in dry, degassed toluene (4 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (400 mg, 1.63 mmol) was dissolved in dry, degassed toluene (15 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, Isolera, 5→15% EtOAc: Hexanes) to obtain the title compound as a white solid in 66% yield (419 mg).

HPLC analysis: 94% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 7.9 (major) and 13.7 (minor) min, UV 254 nm); recrystallized from hexanes to >99% ee (82% recovery). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1-(3,4-Dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarbaldehyde (6.31a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylate (307 mg, 0.79 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (60 mg, 1.58 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (502 mg, 1.19 mmol) was added. The reaction stirred at RT for 2 hours (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, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 88% yield (248 mg).

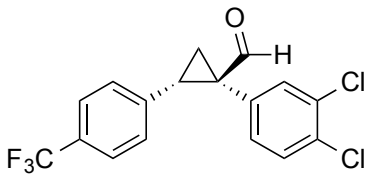
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.09 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.23 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.08 (dd, *J* = 7.2 and 9.2 Hz, 1H), 6.83 (dd, *J* = 2 and 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8 Hz, 2H), 9.45 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.7, 34.3, 45.7, 125.3, 125.4, 128.4, 129.3, 129.7, 130.8, 132.6, 133, 133.3, 133.7, 139.1, 198.7;

FT-IR (film): 2829, 2751, 1708, 1476, 1324, 1121 cm^{-1};

HRMS-ESI m/z 359.0213 ($C_{17}H_{12}OCl_2F_3$ requires 359.0212).

(1*R*,2*S*)-1-(3,4-Dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarbaldehyde (ent-6.31a):

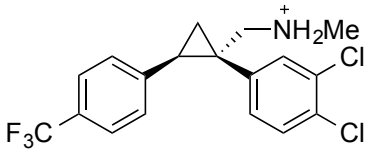


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylate (300 mg, 0.77 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (59 mg, 1.54 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 2 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (499 mg, 1.18 mmol) was added. The reaction stirred at RT for 2 hours (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, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 86% yield (239 mg). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.31b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarbaldehyde (181 mg, 0.50 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 1.0 mmol) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.0 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (38 mg, 1.0 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light

yellow oil in 82% yield (154 mg, 0.41 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (48 mg, 0.41 mmol) and stirred for 30 minutes at room temperature. 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 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as an off-white solid (99 mg).

mp 168-169 °C;

$[\alpha]^{D}_{20}$: -39.3° (10 mg/mL, MeOH);

^{1}H-NMR (400 MHz; CD_3OD): δ 1.7 (dd, *J* = 6.4 and 8.8 Hz, 1H), 1.99 (t, *J* = 6.4 Hz, 1H), 2.65 (s, 3H), 2.70 (dd, *J* = 6.4 and 8.8 Hz, 1H), 3.04 (d, *J* = 13.2 Hz, 1H), 3.80 (dd, *J* = 1.2 and 13.2 Hz, 1H), 6.68 (s, 2H), 7.08 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.40 (m, 3H);

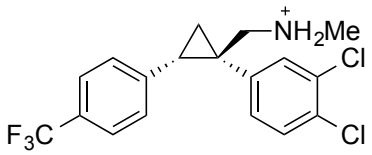
^{13}C-NMR (100 MHz, CD_3OD): δ 16.2, 28.9, 31.9, 33, 58.6, 124.5, 124.6, 128.4, 130.6, 130.8, 131.8, 132.4, 133.1, 135, 136.4, 141.3, 170.2;

FT-IR (neat): 3011, 2771, 1654, 1381, 1325, 1121, 844 cm^{-1};

HRMS-ESI m/z 374.0688 ($C_{18}H_{17}NCl_2F_3$ requires 374.0685).

Anal. Calcd for $C_{22}H_{20}NO_4F_3Cl_2$: C 53.89, H 4.11, N 2.86; Found C 53.86, H 4.24, N 2.78.

1-((1*S*,2*R*)-1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.31b):

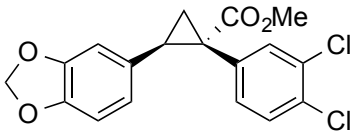


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-(3,4-dichlorophenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropanecarbaldehyde **47b** (180 mg, 0.50 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 1.0 mmol) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.0 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (38 mg, 1.0 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light yellow oil in 91% yield (172 mg, 0.46 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (54 mg, 0.46 mmol) and stirred for 30 minutes at room temperature. 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 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as an off-

white solid (169 mg). **$[\alpha]^{D}_{20}$**: 42.9° (10.1 mg/mL, MeOH). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{22}H_{20}NO_4F_3Cl_2$: C 53.89, H 4.11, N 2.86; Found C 53.60, H 4.20, N 2.84.

(1*S*,2*R*)-Methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (6.32):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 5-vinylbenzo[*d*][1,3]dioxole (768 mg, 5.18 mmol) and Rh_2(*R*-DOSP)$_4$ (39 mg, 0.021 mmol) were dissolved in dry, degassed toluene (7 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (508 mg, 2.07 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 100% hexanes→4:1 hexanes:EtOAc) to obtain the title compound as a white foam in 92% yield (703 mg).

HPLC analysis: 82% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.7 (minor) and 13.9 (major) min, UV 254 nm);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.76 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.11 (dd, *J* = 5.2 and 9.2 Hz, 1H), 3.07 (dd, *J* = 7.2 and 9.2 Hz, 1H), 3.67 (s, 3H), 5.88 (s, 2H), 6.30 (d, *J* = 2

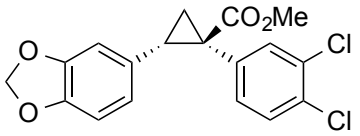
Hz, 1H), 6.35 (dd, *J* = 2 and 8 Hz, 1H), 6.59 (d, *J* = 8 Hz, 1H), 6.84 (dd, *J* = 2 and 8 Hz, 1H), 7.19 (d, *J* = 2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.4, 33.5, 36.3, 53.0, 101.2, 108.2, 108.5, 121.7, 129.3, 129.9, 131.4, 131.5, 131.9, 133.8, 135.6, 146.7, 147.7, 173.5;

FT-IR (film): 3010, 2952, 2892, 1716, 1491, 1435, 1235 cm^{-1};

HRMS-ESI m/z 363.0197 ($C_{18}H_{13}O_4Cl_2$ requires 363.0196).

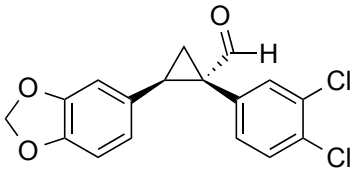
(1*R*,2*S*)-Methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (ent-6.32):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 5-vinylbenzo[*d*][1,3]dioxole (772 mg, 5.18 mmol) and Rh_2(*S*-DOSP)$_4$ (40 mg, 0.021 mmol) were dissolved in dry, degassed toluene (7 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (509 mg, 2.07 mmol) was dissolved in dry, degassed toluene (17 mL) and added by syringe pump over 2 hours. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 100% hexanes→4:1 hexanes:EtOAc) to obtain the title compound as a white foam in 90% yield (681 mg).

HPLC analysis: 83% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.6 (major) and 14.1 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (6.32a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (644 mg, 1.76 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (169 mg, 4.40 mmol) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1.5 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (1.04 g, 2.46 mmol) was added. The reaction stirred at RT for 2 hours (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:EtOAc) to give the title compound as a cream colored solid in 78% yield (461 mg). Unable to enantio-enrich the solid.

Rf = 0.31 (4:1 Hexanes: EtOAc);

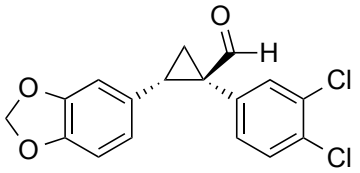
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.99 (dd, *J* = 5.2 and 7.2 Hz, 1H), 2.15 (dd, *J* = 5.2 and 9.2 Hz, 1H), 2.97 (dd, *J* = 7.2 and 9.2 Hz, 1H), 5.87 (s, 2H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.39 (dd, *J* = 2 and 8.4 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.88 (dd, *J* = 2 and 8.4 Hz, 1H), 7.21 (d, *J* = 2 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 9.39 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.3, 35.4, 45.4, 101.3, 108.3, 108.4, 121.9, 128.3, 130.6, 130.8, 132.1, 132.6, 133.2, 134.4, 147, 147.8, 199.1;

FT-IR (film): 3087, 2828, 2749, 1708, 1475, 716 cm^{-1};

HRMS-ESI m/z 335.0239 ($C_{17}H_{13}O_3Cl_2$ requires 335.0236).

(1*R*,2*S*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-6.32a):

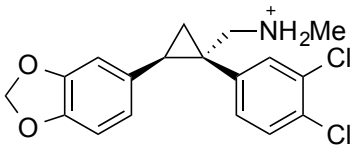


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylate (614 mg, 1.68 mmol) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (160 mg, 4.20 mmol) was then added to the stirring solution. Following the addition, the reaction

was warmed to RT and stirred for 1.5 hours. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased) and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (998 mg, 2.35 mmol) was added. The reaction stirred at RT for 2 hours (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:EtOAc) to give the title compound as a cream colored solid in 74% yield (418 mg). Unable to enantio-enrich the solid. Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (6.32b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (196 mg, 0.58 mmol) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.6 mL, 1.17 mmol) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.17 mmol) and stirred at room temperature for 16 hours. After the allotted time had

passed, $NaBH_4$ (44 mg, 1.0 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light yellow oil in 91% yield (186 mg, 0.53 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (62 mg, 0.53 mmol) and stirred for 30 minutes at room temperature. 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 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as a white solid (198 mg).

mp 171-172 °C;

^{1}H-NMR (400 MHz; CD_3OD): δ 1.55 (dd, *J* = 6.4 and 9.2 Hz, 1H), 1.82 (t, *J* = 6.4 Hz, 1H), 2.53 (dd, *J* = 6.4 and 9.2 Hz, 1H), 2.63 (s, 3H), 2.96 (d, *J* = 12.8 Hz, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 5.82 (s, 2H), 6.41 (m, 2H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 2H), 7.12 (dd, *J* = 2.4 and 8.4 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.40 (d, *J* = 2 Hz, 1H);

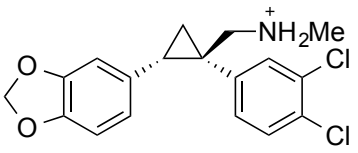
^{13}C-NMR (100 MHz, CD_3OD): δ 15.5, 29.2, 30.8, 32.9, 58.8, 101.4, 107.5, 108.2, 121.3, 130.0, 130.5, 130.7, 131.4, 132.2, 132.9, 135.0, 137.1, 146.4, 147.7, 170.1;

FT-IR (neat): 3008, 2890, 2769, 1659, 1469, 1231, 1039 cm^{-1};

HRMS-ESI m/z 350.0712 ($C_{18}H_{18}O_2NCl_2$ requires 350.0709).

Anal. Calcd for $C_{22}H_{21}NO_6Cl_2$: C 56.67, H 5.54, N 3.00; Found C 56.14, H 4.53, N 2.97.

1-((1*R*,2*S*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine fumarate (ent-6.32b):

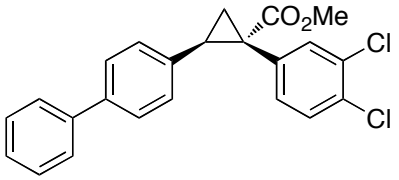


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-2-(benzo[*d*][1,3]dioxol-5-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (370 mg, 1.10 mmol) was dissolved in methanol (20 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 1.1 mL, 2.21 mmol) and Ti(O-*i*Pr)$_4$ (0.6 mL, 2.21 mmol) and stirred at room temperature for 16 hours. After the allotted time had passed, $NaBH_4$ (84 mg, 2.21 mmol) was added and the reaction was stirred for an additional 2 hours. 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 light yellow oil in 67% yield (210 mg, 0.60 mmol). The product was dissolved in isopropanol (10 mL) and then treated with fumaric acid (70 mg, 0.60 mmol)

and stirred for 30 minutes at room temperature. 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 hours. The solution was cooled to room temperature and then to -20 °C using an acetone/ice bath. The resulting solid was filtered and washed with cold acetone to give the title compound as a white solid (195 mg). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{22}H_{21}NO_6Cl_2$: C 56.67, H 5.54, N 3.00; Found C 58.10, H 5.22, N 2.45.

(1*S*,2*R*)-Methyl 2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylate (6.33):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 4-biphenylstyrene (521 mg, 2.89 mmol, 2 eq.) and Rh_2(R-DOSP)$_4$ (27.5 mg, 0.0145 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (355 mg, 1.45 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column

chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain the title compound as white solid in 82% yield (474 mg).

Rf = 0.48 (4:1 Hexanes: EtOAc);

HPLC analysis: 93% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.4 (major) and 25.0 (minor) min, UV 254 nm); recrystallized from hexanes to give >99% ee;

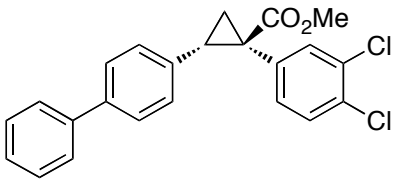
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.90 (dd, *J* = 5.2, 7.2 Hz, 1H), 2.22 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.19 (dd, *J* = 7.6, 9.6 Hz, 1H), 3.71 (s, 3H), 6.85 (dd, *J* = 1.6, 8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 2 Hz, 1H), 7.32-7.44 (m, 5H), 7.53-7.56 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.7, 33.3, 36.7, 53.0, 126.9, 127.1, 127.5, 128.6, 129.0, 130.0, 133.9, 134.8, 135.5, 139.8, 140.6;

IR (film): 3030, 2951, 1720, 1474, 1434, 1259, 741 cm^{-1};

HRMS-ESI m/z 397.0762 ($C_{23}H_{19}O_2Cl_2$ requires 397.0757).

(1*R*,2*S*)-Methyl 2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylate (ent-6.33):



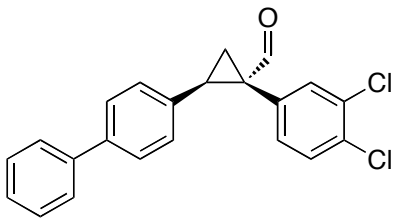
In a 50 mL round bottom flask equipped with a magnetic stir bar, styrene (523 mg, 2.90 mmol, 2 eq.) and Rh_2(S-DOSP)$_4$ (27.7 mg, 0.0145 mmol, 0.01 eq.) were dissolved in

dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (356 mg, 1.45 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain the title compound as white solid in 74% yield (424 mg).

Rf = 0.48 (4:1 Hexanes: EtOAc);

HPLC analysis: 94% ee (SS-WHELK column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.6 (minor) and 24.4 (major) min, UV 254 nm); recrystallized from hexanes to give >99% ee;

(1*S*,2*R*)-2-([1,1'-Biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (6.33a):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylate (274 mg, 0.69 mmol, 1 eq.) was dissolved in diethyl ether (15 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (55 mg,

1.45 mmol, 2.1 eq) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (10 mL) and Dess Martin reagent (614 mg, 1.45 mmol, 2.1 eq.) was added. The reaction was covered in Al foil and stirred at RT for 1 hour (TLC monitored) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the title compound as a white foam in 73% yield (185 mg).

Rf = 0.46 (4:1 Hexanes: EtOAc);

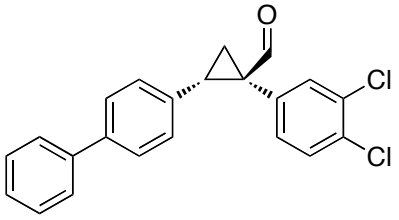
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.12 (dd, *J* = 5.6, 7.2 Hz, 1H), 2.24 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.10 (dd, *J* = 7.6, 9.2 Hz, 1H), 6.90 (dd, *J* = 2, 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.28-7.30 (m, 2H), 7.34-7.46 (m, 5H), 7.55-7.57 (m, 2H), 9.43 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.5, 34.9, 45.8, 127.1, 127.2, 127.7, 128.7, 129.1, 130.7, 131.1, 132.2, 132.7, 133.5, 133.8, 134.4, 140.1, 140.5, 199.1;

IR(film): 3030, 2827, 2749, 1702, 1487, 1378, 1031, 698 cm^{-1};

HRMS-ESI m/z 366.0579 ($C_{22}H_{26}OCl_2$ requires 366.0573).

(1*R*,2*S*)-2-([1,1'-Biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (ent-6.33a):

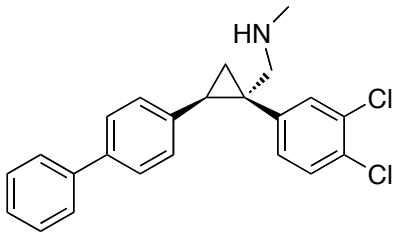


In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylate (229 mg, 0.58 mmol, 1 eq.) was dissolved in diethyl ether (15 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (46 mg, 1.21 mmol, 2.1 eq) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (10 mL) and Dess Martin reagent (513 mg, 1.21 mmol, 2.1 eq.) was added. The reaction was covered in Al foil and stirred at RT for 1 hour (TLC monitored) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the title compound as a white foam in 78%

yield (167 mg). Rf = 0.46 (4:1 Hexanes: EtOAc); Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-2-([1,1'-Biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine (6.33b):



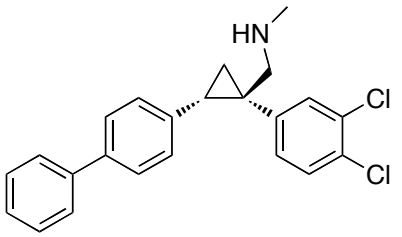
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (185 mg, 0.503 mmol, 1 eq.) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 1.0 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.3 mL, 1.0 mmol, 2 eq.) and stirred at room temperature for 6 hours. After the allotted time had passed, $NaBH_4$ (39 mg, 1.01 mmol, 2 eq.) was added and the reaction was stirred overnight at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 75% yield (148 mg, 0.41 mmol).

Rf = 0.48 (9:1 EtOAc: Et_3N);

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.27 (br s, 1H), 1.46 (dd, *J* = 5.6, 8.8 Hz, 1H), 1.56 (t, *J* = 5.6 Hz, 1H), 2.37 (dd, *J* = 6.4, 8.8 Hz, 1H), 2.46 (s, 3H), 2.65 (d, *J* = 12 Hz, 1H), 3.08 (d, *J* = 12 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.92 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.32-7.45 (m, 6H), 7.54-7.57 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.0, 28.5, 35.4, 36.9, 62.9, 126.7, 127.1, 127.3, 129.0, 130.3, 130.6, 130.8, 132.3, 132.9, 137.5, 138.7, 140.1, 140.9;

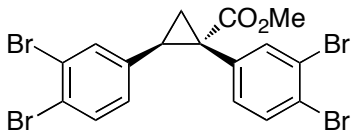
1-((1*R*,2*S*)-2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropyl)-*N*-methylmethanamine (ent-6.33b):



In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-2-([1,1'-biphenyl]-4-yl)-1-(3,4-dichlorophenyl)cyclopropanecarbaldehyde (167 mg, 0.45 mmol, 1 eq.) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.45 mL, 0.90 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.27 mL, 0.90 mmol, 2 eq.) and stirred at room temperature for 6 hours. After the allotted time had passed, $NaBH_4$ (35 mg, 0.91 mmol, 2 eq.) was added and the reaction was stirred overnight at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then

concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 32% yield (58 mg; flask was dropped). Rf = 0.48 (9:1 EtOAc: Et_3N). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-methyl 1,2-bis(3,4-dibromophenyl)cyclopropanecarboxylate (6.34):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 3,4-dibromostyrene (1.07 g, 4.12 mmol, 1.5 eq.) and Rh_2(R-DOSP)$_4$ (52 mg, 0.0275 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (920 mg, 2.75 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain **23a** as white foam in 94% yield (1.49 g).

Rf = 0.43 (4:1 Hexanes: EtOAc);

HPLC analysis: 83% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.5 (minor) and 16.5 (major) min, UV 254 nm);

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.77 (dd, *J* = 5.2, 7.2 Hz, 1H), 2.15 (dd, *J* = 5.2, 9.2 Hz, 1H), 3.03 (dd, *J* = 7.6, 9.2 Hz, 1H), 3.66 (s, 3H), 6.45 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.75 (dd,

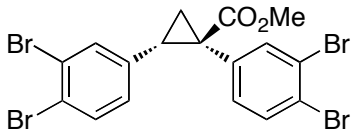
J = 2, 8 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.6, 32.2, 36.8, 53.2, 123.2, 124.2, 124.5, 124.7, 127.8, 132.3, 133.3, 133.4, 133.8, 135.5, 136.8, 137.1, 172.9;

FT-IR(film): 2951, 1717, 1464, 1433, 1254, 1013, 726 cm^{-1};

HRMS-ESI m/z 564.7662 ($C_{17}H_{13}O_2Br_4$ requires 564.7644).

(1*R*,2*S*)-methyl 1,2-bis(3,4-dibromophenyl)cyclopropanecarboxylate (ent-6.34):

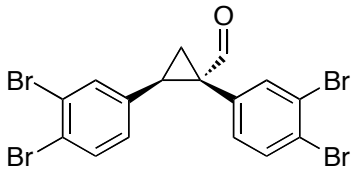


In a 50 mL round bottom flask equipped with a magnetic stir bar, 3,4-dibromostyrene (1.08 g, 4.13 mmol, 1.5 eq.) and Rh_2(R-DOSP)$_4$ (52 mg, 0.0275 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (5 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-diazo-2-(3,4-dibromophenyl)acetate (920 mg, 2.75 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain the title compound as white foam in 95% yield (1.50 g).

Rf = 0.43 (4:1 Hexanes: EtOAc);

HPLC analysis: 84% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.4 (major) and 16.5 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1,2-bis(3,4-dibromophenyl)cyclopropanecarbaldehyde (6.34a):



In a 250 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1,2-bis(3,4-dibromophenyl)cyclopropanecarboxylate (1.49 g, 2.63 mmol, 1 eq.) was dissolved in methylene chloride (100 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. DIBAL-H (1M in toluene, 3.40 mL, 3.4 mmol, 1.3 eq.) was then added dropwise down the side of the flask to the stirring solution. Following the addition, the reaction stirred for 2 hours at -78 °C. The reaction was quenched with 12 mL of methanol at -78 °C and stirred for 15 minutes. The solution was then slowly warmed to RT and 50 mL of Rochelle's salt was added. The slurry stirred for 1.5 hours under the two layers became transparent. Organic layer was extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 82% yield (1.15 g).

Rf = 0.40 (4:1 Hexanes: EtOAc). Product was recrystallized from 2 mL of 1:1 hexanes: acetone;

HPLC analysis: 99% ee (SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 31.7 (minor) and 46.9 (major) min, UV 254 nm);

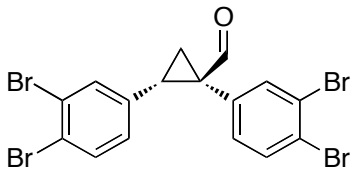
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.00 (dd, *J* = 5.6, 7.6 Hz, 1H), 2.19 (dd, *J* = 5.6, 9.2 Hz, 1H), 2.95 (dd, *J* = 7.6, 9.2 Hz, 1H), 6.55 (dd, *J* = 2, 8.4 Hz, 1H), 6.81 (dd, *J* = 2, 8.4 Hz, 1H), 7.23 (d, *J* = 2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.49 (8.4 Hz), 9.45 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.6, 33.8, 45.4, 123.6, 124.9,125.0,125.3, 127.8, 131.5, 133.5, 133.7, 134.0, 134.4, 136.1, 136.4, 198.5;

FT-IR (film): 3084, 2826, 2748, 1705, 1465, 1013, 714 cm^{-1};

HRMS-ESI m/z 534.7541 ($C_{16}H_{11}OBr_4$ requires 534.7538).

(1*R*,2*S*)-1,2-bis(3,4-dibromophenyl)cyclopropanecarbaldehyde (ent-6.34a):



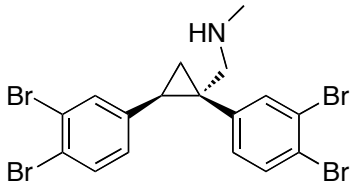
In a 250 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1,2-bis(3,4-dibromophenyl)cyclopropanecarboxylate (1.48 g, 2.62 mmol, 1 eq.) was dissolved in methylene chloride (100 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. DIBAL-H (1M in toluene, 3.40 mL, 3.4 mmol, 1.3 eq.) was then added dropwise down the side of the flask to the stirring solution. Following the addition, the reaction stirred for 2 hours at -78 °C. The reaction was quenched with 12 mL of methanol at -78 °C and stirred for 15 minutes. The solution

was then slowly warmed to RT and 50 mL of Rochelle's salt was added. The slurry stirred for 1.5 hours under the two layers became transparent. Organic layer was extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Isolera, 5→20% EtOAc: Hexanes) to give the title compound as a colorless oil in 79% yield (1.10 g).

Rf = 0.40 (4:1 Hexanes: EtOAc). Product was recrystallized from 2 mL of 1:1 hexanes: acetone;

HPLC analysis: 95% ee (SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 31.3 (major) and 47.8 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1,2-Bis(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine (6.34b):



In a 25 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1,2-bis(3,4-dibromophenyl)cyclopropanecarbaldehyde (247 mg, 0.46 mmol, 1 eq.) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.5 mL, 0.92 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.28 mL, 0.92 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (34 mg, 0.92 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under

reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 57% yield (145 mg, 0.263mmol).

Rf = 0.52 (9:1 EtOAc: Et_3N);

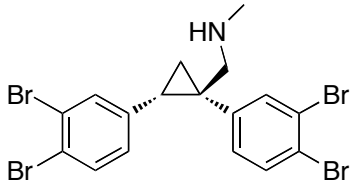
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.42-1.46 (m, 2H), 2.22 (dd, *J* = 6.8, 8.4 Hz, 1H), 2.41 (s, 3H), 2.59 (d, *J* = 12 Hz, 1H), 3.03 (d, *J* = 12 Hz, 1H), 6.40 (dd, *J* = 2, 8 Hz, 1H), 6.80 (dd, *J* = 2, 8 Hz, 1H), 7.18 (d, *J* = 2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.1, 27.7, 35.6, 36.8, 62.4, 121.9, 123.5, 124.4, 124.9, 127.4, 131.1, 133.1, 133.4, 133.7, 135.9, 139.7, 139.9;

FT-IR (neat): 3323, 3062, 2883, 2790, 1463, 1111, 1012, 823 cm^{-1};

HRMS-ESI m/z 549.8014 ($C_{17}H_{16}NBr_4$ requires 549.8011).

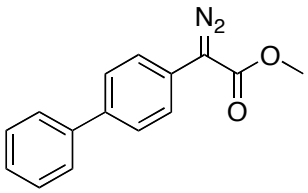
1-((1*R*,2*S*)-1,2-Bis(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine (ent-6.34b):



In a 25 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1,2-bis(3,4-dibromophenyl)cyclopropanecarbaldehyde (424 mg, 0.79 mmol, 1 eq.) was dissolved in

methanol (12 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.8 mL, 1.6 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.5 mL, 1.6 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (59 mg, 0.92 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 63% yield (274 mg, 0.497mmol). **Rf** = 0.52 (9:1 EtOAc: Et_3N). Spectroscopic data is the same as the other enantiomer.

Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate:

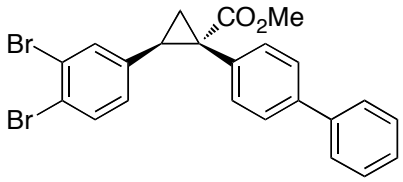


In a 250 mL round bottom flask equipped with a magnetic stir bar, methyl 2-(4-biphenyl)acetate (5.0 g, 22.1 mmol) and *p*-ABSA (6.37 g, 26.5 mmol) were dissolved in acetonitrile (50 mL) and cooled to 0 °C using an ice bath under an argon atmosphere. 1,8-Diazabicycloundec-7-ene (4.19 g, 26.5 mmol) was then added to the stirring mixture over the course of 5 minutes. After the addition of the DBU, the reaction mixture continued to stir at 0 °C for an additional 15 minutes. Once this allotted time had passed,

the ice bath was removed and the reaction mixture was stirred for 24 hours at room temperature. The resulting orange solution was quenched with saturated NH_4Cl and the aqueous phase was extracted with diethyl ether (3x). The organic phase was then washed with DI H_2O to remove any residual salts. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 9:1 Hexanes:EtOAc) to give the title compound as a yellow solid in 92% yield (5.13 g).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.93 (s, 3H), 7.36 (tt, *J* = 1.2, 6.4, 8.8 Hz, H), 7.43-7.48 (m, 2H), 7.55-7.66 (m, 6H). Characterization data is consistent with the literature.[212]

(1*S*,2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl) cyclopropanecarboxylate (6.35):



In a 50 mL round bottom flask equipped with a magnetic stir bar, 3,4-dibromostyrene (0.833 g, 3.18 mmol, 2 eq.) and Rh_2(R-DOSP)$_4$ (30.1 mg, 0.0159 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (4 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (400 mg, 1.59 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column

chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain the title compound as white foam in 75% yield (0.581 g).

Rf = 0.56 (4:1 Hexanes: EtOAc);

HPLC analysis: 81% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.7 (minor) and 14.9 (major) min, UV 254 nm);

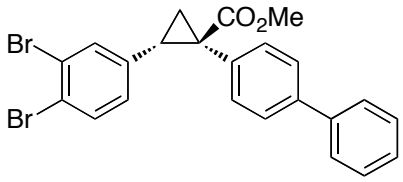
^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.84 (dd, *J* = 5.2, 7.2 Hz, 1H), 2.20 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.05 (dd, *J* = 7.2, 9.6 Hz, 1H), 3.70 (s, 3H), 6.50 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.09-7.12 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.32-7.36 (m, 1H), 7.41-7.46 (m, 4H), 7.55-7.58 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.2, 32.2, 37.6, 53.1, 122.7, 124.3, 127.0, 127.3, 127.6, 128.1, 129.0, 132.4, 133.0,133.2, 133.7, 138.1, 140.4, 140.8, 174.0;

FT-IR (film): 3054, 2950, 1716, 1434, 1253, 1163, 738, 697 cm^{-1};

HRMS-ESI m/z 484.9744 ($C_{23}H_{19}O_2Br_2$ requires 484.9746).

(1*R*,2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl) cyclopropanecarboxylate (ent-6.35):



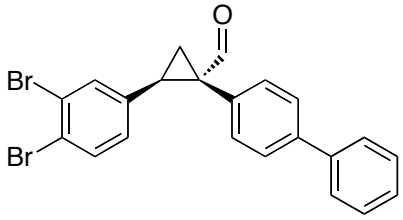
In a 50 mL round bottom flask equipped with a magnetic stir bar, 3,4-dibromostyrene (0.833 g, 3.18 mmol, 2 eq.) and Rh_2(S-DOSP)$_4$ (30.1 mg, 0.0159 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (4 mL) and cooled to -42 °C in a dry ice/acetonitrile

bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (400 mg, 1.59 mmol, 1 eq.) was dissolved in dry, degassed toluene (16 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. The solvent was then removed under reduced pressure and the residue was purified by column chromatography (Isolera; SiO_2, hexanes/ethyl acetate = 19:1 to 17:3) to obtain the title compound as white foam in 74% yield (0.575 g).

Rf = 0.56 (4:1 Hexanes: EtOAc);

HPLC analysis: 85% ee (OD-H column, 1% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 10.4 (major) and 14.9 (minor) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarbaldehyde (6.35a):



In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarboxylate (343 mg, 0.71 mmol, 1 eq.) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (53 mg, 1.41 mmol, 2.0 eq) was then added to the stirring solution. Following the addition, the

reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (598 mg, 1.41 mmol, 2.0 eq.) and 1 mL of pyridine were added. The reaction was covered in Al foil and stirred at RT (TLC monitored; 1hr) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the title compound as a white foam in 57% yield (182 mg).

Rf = 0.53 (4:1 Hexanes: EtOAc);

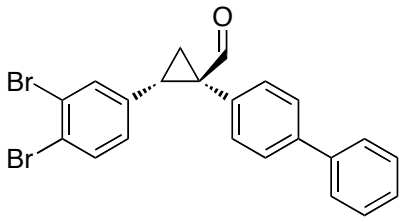
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.05 (dd, *J* = 5.2, 6.8 Hz, 1H), 2.24 (dd, *J* = 5.2, 9.2 Hz, 1H), 2.95 (dd, *J* = 7.2, 9.2 Hz, 1H), 6.58 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.36 (tt, *J* = 1.2, 6.4, 8.8 Hz, 1H), 7.43-7.47 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.56-7.59 (m, 2H), 9.65 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.4, 34.4, 46.2, 123.1, 124.5, 127.3, 127.6, 127.8, 128.0, 129.1, 131.8, 132.3, 133.2, 133.6, 137.2, 140.5, 141.1, 200.2;

FT-IR (film): 3028, 2825, 2751, 2702, 1700, 1487, 1194, 1112, 905, 730 cm^{-1};

HRMS-ESI m/z 454.9640 ($C_{22}H_{17}OBr_2$ requires 454.9640).

(1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarbaldehyde (ent-6.35a):

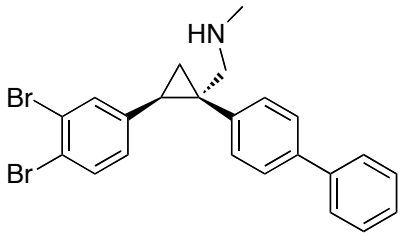


In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarboxylate (424 mg, 0.87 mmol, 1 eq.) was dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (66 mg, 1.74 mmol, 2.0 eq) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (20 mL) and Dess Martin reagent (738 mg, 1.74 mmol, 2.0 eq.) and 1 mL of pyridine were added. The reaction was covered in Al foil and stirred at RT (TLC monitored; 1hr) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the

title compound as a white foam in 53% yield (209 mg). Rf = 0.53 (4:1 Hexanes: EtOAc). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine (6.35b):



In a 25 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarbaldehyde (180 mg, 0.39 mmol, 1 eq.) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.4 mL, 0.79 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.25 mL, 0.79 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (30 mg, 0.79 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 88% yield (164 mg, 0.348 mmol).

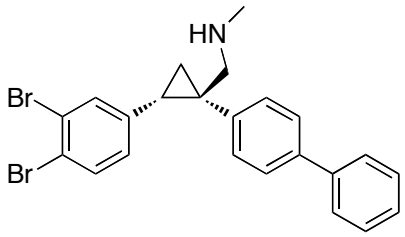
Rf = 0.52 (9:1 EtOAc: Et_3N);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.47-1.52 (m, 2H), 1.85 (br s, 1H), 2.22 (dd, *J* = 6.4, 8.4 Hz, 1H), 2.44 (s, 3H), 2.63 (d, *J* = 12 Hz, 1H), 3.12 (d, *J* = 11.6 Hz, 1H), 6.44 (dd, *J* = 2, 8.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 1H), 7.32 (tt, *J* = 1.2, 6.4, 8.8 Hz, 1H), 7.40-7.46 (m, 4H), 7.54-7.56 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.9, 27.7, 36.2, 36.7, 62.8, 121.4, 124.1, 127.2, 127.3, 127.5, 127.6, 129.0, 131.3, 132.8, 133.3, 137.3, 139.9, 140.8, 140.9;

FT-IR(film): 3026, 2929, 2790, 1464, 1009, 732 cm^{-1};

1-((1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropyl)-*N*-methylmethanamine (ent-6.35b):

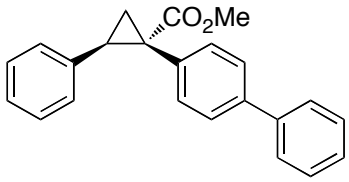


In a 25 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-(3,4-dibromophenyl)cyclopropanecarbaldehyde (201 mg, 0.44 mmol, 1 eq.) was dissolved in methanol (8 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.45 mL, 0.88 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.27 mL, 0.88 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (33 mg, 0.88 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10%

triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 87% yield (181 mg, 0.384 mmol).

Rf = 0.52 (9:1 EtOAc: Et_3N). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarboxylate (6.36):



In a 50 mL round bottom flask equipped with a magnetic stir bar, styrene (332 mg, 3.18 mmol, 2 eq.) and Rh_2(R-DOSP)$_4$ (30 mg, 0.0159 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (3 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (401 mg, 1.59 mmol, 1 eq.) was dissolved in dry, degassed toluene (12 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as white solid in 87% yield (456 mg).

HPLC analysis: 99% ee (SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.2 (major) and 29.0 (minor) min, UV 254 nm).

Rf = 0.49 (4:1 Hexanes:EtOAc);

mp 157-158 °C;

$[\alpha]^{20}_{D}$: -26.2° (c. 1, chloroform);

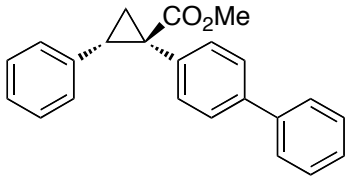
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.44-7.39 (m, 4H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.14-7.07 (m, 5H), 6.86-6.82 (m, 2H), 3.72 (s, 3H), 3.17 (dd, *J* = 9.2 and 7.2 Hz, 1H), 2.21 (dd, *J* = 9.6 and 5.2 Hz, 1H), 1.94 (dd, *J* = 7.2 and 4.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 140.8, 139.8, 136.5, 134, 132.5, 128.8, 128.3, 128, 127.4, 127.1, 126.54, 126.52, 52.9, 37.3, 33.5, 20.8;

FT-IR (film): 3029, 2950, 1716, 1488, 1254 cm^{-1};

HRMS-ESI m/z 329.1536 ($C_{23}C_{21}O_2$ requires 329.1536).

(1*R*,2*S*)-Methyl 1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarboxylate (ent-6.36):



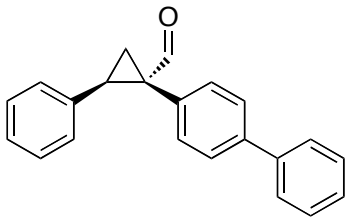
In a 50 mL round bottom flask equipped with a magnetic stir bar, styrene (333 mg, 3.18 mmol, 2 eq.) and Rh_2(R-DOSP)$_4$ (30 mg, 0.0159 mmol, 0.01 eq.) were dissolved in dry, degassed toluene (3 mL) and cooled to -42 °C in a dry ice/acetonitrile bath. Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (400 mg, 1.59 mmol, 1 eq.) was dissolved in dry, degassed toluene (12 mL) and added by syringe pump over 1 hour. The reaction stirred overnight while slowly warming to room temperature. 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 the title compound as white solid in 86% yield (448 mg).

Rf = 0.49 (4:1 Hexanes: EtOAc);

HPLC analysis: 98% ee (SS-WHELK column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 18.3 (minor) and 28.4 (major) min, UV 254 nm). Spectroscopic data is the same as the other enantiomer.

(1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-phenylcyclopropanecarbaldehyde (6.36a):



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-phenylcyclopropanecarboxylate (355 mg, 1.08 mmol, 1 eq.) was dissolved in diethyl ether (15 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (86 mg, 2.27 mmol, 2.1 eq) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4$•$10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (15 mL) and Dess Martin reagent (916 mg, 2.16 mmol, 2.0 eq.) was added. The reaction was covered in Al foil and

stirred at RT (TLC monitored) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the title compound as a white foam in 70% yield (225 mg).

Rf = 0.48 (4:1 Hexanes: EtOAc);

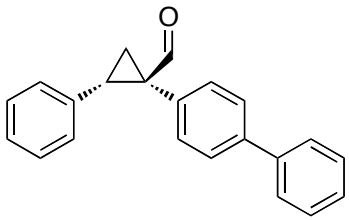
^{1}H-NMR (400 MHz; $CDCl_3$): δ 2.15 (dd, *J* = 5.2, 8.8 Hz, 1H), 2.25 (dd, *J* = 4.8, 9.2 Hz, 1H), 3.08 (dd, *J* = 7.2, 9.2 Hz, 1H), 6.88-6.91 (m, 2H), 7.09-7.18 (m, 5H), 7.36 (tt, *J* = 1.2, 6.4, 8.8 Hz, 1H), 7.41-7.50 (m, 4H), 7.54-7.57 (m, 2H), 9.62 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.0, 35.2, 46.4, 127.0, 127.2, 127.3, 127.6, 128.2, 128.3, 129.0, 132.0, 133.1, 135.6, 140.7, 200.8;

FT-IR (film): 3078, 3036, 2825, 1701, 1489, 695 cm^{-1};

HRMS-ESI m/z 299.1417 ($C_{22}H_{29}O$ requires 299.1430).

(1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-phenylcyclopropanecarbaldehyde (ent-6.36a):



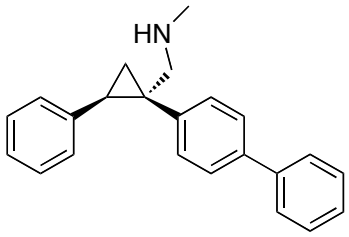
In a 50 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-methyl 1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarboxylate (417 mg, 1.27 mmol, 1 eq.) was

dissolved in diethyl ether (20 mL) and flushed argon. The solution was then cooled to -78 °C using an acetone/dry ice bath. Lithium aluminum hydride (107 mg, 2.67 mmol, 2.1 eq) was then added to the stirring solution. Following the addition, the reaction was warmed to RT and stirred for 1 hour. The reaction was quenched with $NaSO_4 \bullet 10H_2O$ (added until bubbling ceased), dried with $MgSO_4$, and filtered. The solids were rinsed with diethyl ether and the combined extracts were concentrated under reduced pressure.

The residue was re-dissolved in methylene chloride (15 mL) and Dess Martin reagent (1.076 g, 2.54 mmol, 2.0 eq.) was added. The reaction was covered in Al foil and stirred at RT (TLC monitored) until starting material disappeared. It was then diluted with ether and washed with aqueous 1M 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 (Isolera; SiO_2, 100% hexanes → 8:1 hexanes: ethyl acetate) to give the title compound as a white foam in 74% yield (274 mg).

Rf = 0.48 (4:1 Hexanes: EtOAc). Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-1-([1,1'-Biphenyl]-4-yl)-2-phenylcyclopropyl)-*N*-methylmethanamine (6.36b):



In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*S*,2*R*)-1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarbaldehyde (138 mg, 0.46 mmol, 1 eq.) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.45 mL, 0.92 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.28 mL, 0.92 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (34 mg, 0.92 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 85% yield (122 mg).

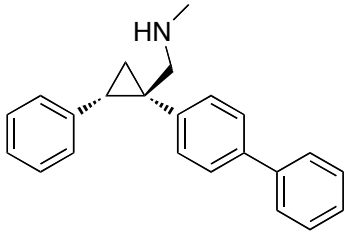
Rf = 0.49 (9:1 EtOAc: Et_3N);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.46 (dd, *J* = 5.2, 8.4 Hz, 1H), 1.59 (t, *J* = 6 Hz, 1H), 1.84 (br s, 1H), 2.32 (dd, *J* = 6, 8.8 Hz, 1H), 2.47 (s, 3H), 2.67 (d, *J* = 12 Hz, 1H), 3.15 (d, *J* = 12.4 Hz, 1H), 6.80-6.82 (m, 2H), 7.01-7.10 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.33 (tt, *J* = 1.2, 6.4, 8.8 Hz, 1H), 7.39-7.45 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.3, 28.7, 35.6, 36.6, 63.2, 125.6, 126.9, 127.1, 127.3, 127.8, 128.9, 131.5, 138.2, 139.2, 139.3, 141.0;

FT-IR (film): 3057, 2929, 2788, 1487, 1032, 837, 695 cm^{-1};

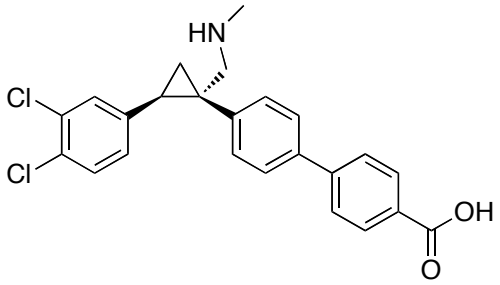
1-((1*R*,2*S*)-1-([1,1'-Biphenyl]-4-yl)-2-phenylcyclopropyl)-*N*-methylmethanamine (ent-6.36b):



In a 100 mL round bottom flask equipped with a magnetic stir bar, (1*R*,2*S*)-1-([1,1'-biphenyl]-4-yl)-2-phenylcyclopropanecarbaldehyde (234 mg, 0.78 mmol, 1 eq.) was dissolved in methanol (15 mL) and flushed with argon. This solution was treated with methylamine (2M in MeOH, 0.75 mL, 1.5 mmol, 2 eq.) and Ti(O-*i*Pr)$_4$ (0.45 mL, 1.5 mmol, 2 eq.) and stirred at room temperature overnight. After the allotted time had passed, $NaBH_4$ (60 mg, 1.57 mmol, 2 eq.) was added and the reaction was stirred for 2 hrs at room temperature. The reaction was quenched with H_2O (1 mL) and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine and filtered through a short plug of silica. The filtrate was then concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, Isolera, ethyl acetate: triethylamine = 9:1) to give the title compound as a colorless oil in 84% yield (207 mg).

Rf = 0.49 (9:1 EtOAc: Et_3N); Spectroscopic data is the same as the other enantiomer.

4'-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-((methylamino)methyl)cyclopropyl)-[1,1'-biphenyl]-4-carboxylic acid (6.43):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (148 mg, 0.38 mmol, 1 eq.), cesium carbonate (374 mg, 1.15 mmol, 3 eq.), 4-carboxyphenylboronic acid (70 mg, 0.42 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (15 mg, 0.019 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed and the bromide had disappeared on TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in methanol, filtered through celite, and concentrated again under reduced pressure. The residue was redissolved in ether and washed with 1M NaOH, The aqueous layer was then acidified with concentrated HCl and extracted with a small amount of ethyl acetate (this removes the residue boronic acid). The aqueous layer was warmed to remove residual organic solvents and then cooled in an ice bath and filtered cold. The solid was then washed with ether to give the title compound as a pure white solid (99 mg) in 61% yield.

Rf = 0.00 (9:1 EtOAc:Et_3N);

^{1}H-NMR (400 MHz; d_4-CD_3OD): δ 1.69 (dd, *J* = 6, 8.8 Hz, 1H), 1.94 (t, *J* = 6.4 Hz, 1H), 2.62 (dd, *J* = 6, 8.4 Hz, 1H), 2.66 (s, 3H), 3.05 (d, *J* = 13.2 Hz, 1H), 3.86 (d, *J* =

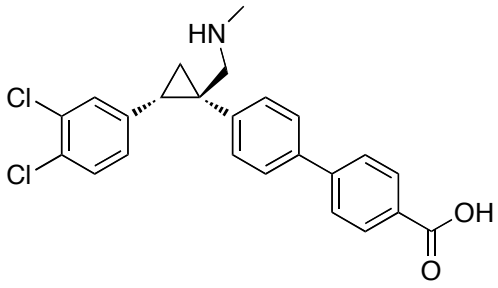
12.8 Hz, 1H), 6.77 (dd, *J* = 2, 8.4 Hz, 1H), 7.09 (d, *J* = 2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H);

^{13}C-NMR (100 MHz, d_4-CD_3OD): δ 16.6, 28.3, 32.3, 33.2, 59.1, 126.7, 127.5, 127.6, 129.5, 129.6, 130.1, 130.2, 131.4, 131.6, 135.4, 138.3, 139.6, 144.8, 168.4;

FT-IR(film): 3405, 3026, 2799, 1694, 1608, 1476, 1396, 1235, 831, 777, 740 cm^{-1};

HRMS-ESI m/z 426.1026 ($C_{24}H_{22}O_2NCl_2$ requires 426.1022).

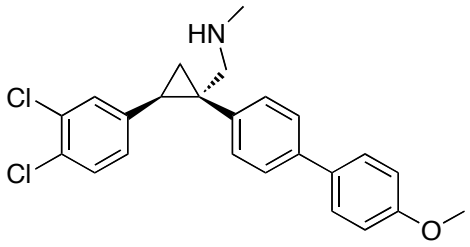
4'-((1*R*,2*S*)-2-(3,4-Dichlorophenyl)-1-((methylamino)methyl)cyclopropyl)-[1,1'-biphenyl]-4-carboxylic acid (ent-6.43):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (149 mg, 0.39 mmol, 1 eq.), cesium carbonate (377 mg, 1.16 mmol, 3 eq.), 4-carboxyphenylboronic acid (71 mg, 0.42 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (15 mg, 0.019 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed and the bromide had disappeared on TLC, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was

redissolved in methanol, filtered through celite, and concentrated again under reduced pressure. The residue was redissolved in ether and washed with 1M NaOH, The aqueous layer was then acidified with concentrated HCl and extracted with a small amount of ethyl acetate (this removes the residue boronic acid). The aqueous layer was warmed to remove residual organic solvents and then cooled in an ice bath and filtered cold. The solid was then washed with ether to give the title compound as a pure white solid (105 mg) in 64% yield. Spectroscopic data is the same as the other enantiomer.

1-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropyl)-*N*-methylmethanamine (6.44):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (109 mg, 0.28 mmol, 1 eq.), cesium carbonate (275 mg, 0.85 mmol, 3 eq.), 4-methoxyphenylboronic acid (48 mg, 0.31 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (12 mg, 0.014 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The

residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a colorless oil (91 mg) in 78% yield.

Rf = 0.37 (9:1 EtOAc:Et_3N);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.46 -1.53 (m, 2H), 2.23 (dd, *J* = 6, 8.4 Hz, 1H), 2.42 (s, 3H), 2.60 (d, *J* = 12.4 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H), 3.84 (s, 3H), 6.48 (dd, *J* = 2, 8.0 Hz, 1H) 6.94-6.97 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 3H), 7.11 (d, *J* = 8.4 Hz, 3H), 7.39 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H);

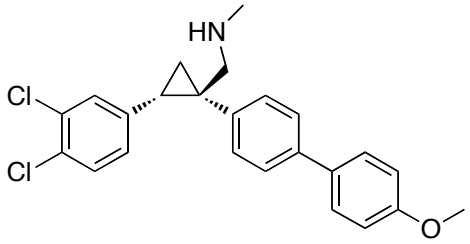
^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.8, 27.7, 36.2, 36.7, 55.5, 63.0, 114.4, 126.8, 128.2, 129.3, 129.6, 130.0, 131.2, 131.7, 133.4, 136.7, 139.4, 140.0, 159.3;

FT-IR (film): 3326, 3026, 2931, 2835, 2790, 1608, 1498, 1246, 822 cm^{-1};

HRMS-ESI m/z 412.1236 ($C_{24}H_{24}ONCl_2$ requires 412.1230).

Anal. Calcd for $C_{28}H_{29}NO_7Cl_2$: C 59.79, H 5.20, N 2.49; Found C 59.53, H 5.18, N 2.42.

1-((1*R*,2*S*)-2-(3,4-Dichlorophenyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-yl)cyclopropyl)-*N*-methylmethanamine (ent-6.44):



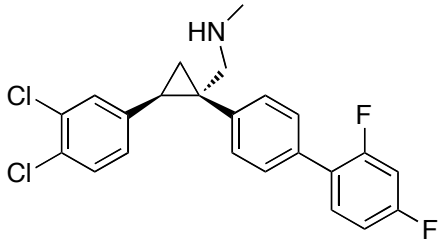
A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (125 mg, 0.32 mmol, 1 eq.), cesium carbonate (315 mg, 0.97 mmol, 3 eq.), 4-

methoxyphenylboronic acid (59 mg, 0.39 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (13 mg, 0.016 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a colorless oil (111 mg) in 83% yield.

Rf = 0.37 (9:1 EtOAc:Et_3N). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{28}H_{29}NO_7Cl_2$: C 59.79, H 5.20, N 2.49; Found C 59.18, H 5.22, N 2.47.

1-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(2',4'-difluoro-[1,1'-biphenyl]-4-yl)cyclopropyl)-*N*-methylmethanamine (6.45):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (114 mg, 0.30 mmol, 1 eq.), cesium carbonate (288 mg, 0.89 mmol, 3 eq.), 2,4-difluorophenylboronic acid (56 mg, 0.35 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (12 mg, 0.014 mmol, 0.05 eq.)

was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a colorless oil (98 mg) in 80% yield.

Rf = 0.40 (9:1 EtOAc:Et_3N);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.47-1.52 (m, 2H), 2.24 (dd, *J* = 2, 8.0 Hz, 1H), 2.45 (s, 3H), 2.63 (d, *J* = 12.4 Hz, 1H), 3.13 (d, *J* = 12.4 Hz, 1H), 6.51 (dd, *J* = 2, 8.0 Hz, 1H), 6.86-6.95 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.31-7.37 (m, 3H);

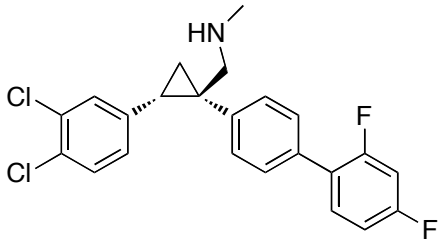
^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.7, 27.7, 36.3, 36.7, 62.8, 104.5 (dd, *J* = 25, 26.9 Hz) 111.7 (dd, *J* = 3.8, 20.9 Hz), 125.0 (dd, *J* = 3.8, 13.3 Hz), 126.9, 129.0 (d, *J* = 2.7 Hz), 129.3, 129.6, 129.9, 131.1, 131.5 (dd, *J* = 5.3, 9.5 Hz), 131.7, 133.7 (d, *J* = 1.5 Hz), 138.0, 139.9, 161.1 (ddd, *J* = 11.7, 249.2, 252.2 Hz)

FT-IR (film): 2932, 2846, 2792, 1593, 1494, 1139, 965, 811 cm^{-1};

HRMS-ESI m/z 418.0941 ($C_{23}H_{20}F_2NCl_2$ requires 418.0935).

Anal. Calcd for $C_{27}H_{25}NO_6Cl_2F_2$: C 57.05, H 4.43, N 2.46; Found C 56.98, H 4.48, N 2.42.

1-((1*R*,2*S*)-2-(3,4-Dichlorophenyl)-1-(2',4'-difluoro-[1,1'-biphenyl]-4-yl)cyclopropyl)-*N*-methylmethanamine (ent-6.45):

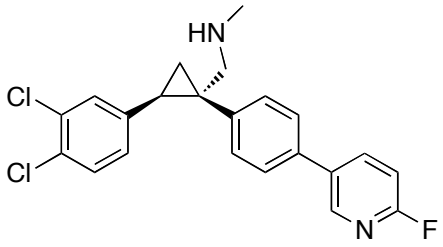


A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (121 mg, 0.31 mmol, 1 eq.), cesium carbonate (303 mg, 0.93 mmol, 3 eq.), 2,4-difluorophenylboronic acid (59 mg, 0.37 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (13 mg, 0.016 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a colorless oil (101 mg) in 77% yield.

Rf = 0.40 (9:1 EtOAc:Et_3N). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{27}H_{25}NO_6Cl_2F_2$: C 57.05, H 4.43, N 2.46; Found C 56.78, H 4.54, N 2.44.

1-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(4-(6-fluoropyridin-3-yl)phenyl)cyclopropyl)-*N*-methylmethanamine (6.46):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (140 mg, 0.36 mmol, 1 eq.), cesium carbonate (352 mg, 1.08 mmol, 3 eq.), 6-fluoro-3-pyridinylboronic acid (61 mg, 0.44 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (15 mg, 0.018 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a light yellow oil (110 mg) in 76% yield.

Rf = 0.24 (9:1 EtOAc:Et_3N);

^{1}H-NMR (300 MHz; $CDCl_3$): δ 1.46-1.55 (m, 2H), 2.25 (dd, *J* = 6, 8.7 Hz, 1H), 2.44 (s, 3H), 2.63 (d, *J* = 12.3 Hz, 1H), 3.13 (d, *J* = 11.4 Hz, 1H), 6.52 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 3.3, 8.7 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.91 (ddd, *J* = 2.7, 7.8, 8.7 Hz, 1H), 8.36 (d, *J* = 2.7 Hz, 1H););

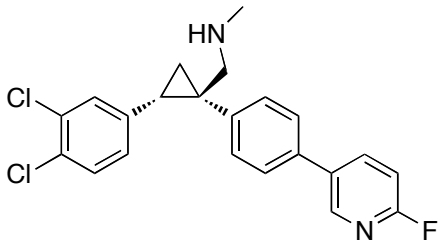
^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.4, 27.7,36.2, 36.8, 62.8, 109.5 (d, *J* = 37.2 Hz), 126.9, 127.1, 129.4, 129.7, 129.9, 131.7, 131.8, 134.5 (d, *J* = 4.5 Hz), 135.3, 138.7, 139.7, 139.8 (d, *J* = 7.6 Hz), 145.9 (d, *J* = 14.8 Hz), 163.2 (d, *J* = 238.2 Hz);

FT-IR (film): 3322, 3028, 2845, 2792, 1591, 1474, 1252, 1133, 824, 730 cm^{-1};

HRMS-ESI m/z 401.0990 ($C_{22}H_{20}N_2Cl_2F$ requires 401.0987).

Anal. Calcd for $C_{26}H_{25}N_2O_6Cl_2F$: C 56.64, H 4.57, N 5.08; Found C 56.74, H 4.52, N 5.05.

1-((1*R*,2*S*)-2-(3,4-Dichlorophenyl)-1-(4-(6-fluoropyridin-3-yl)phenyl)cyclopropyl)-*N*-methylmethanamine (ent-6.46):

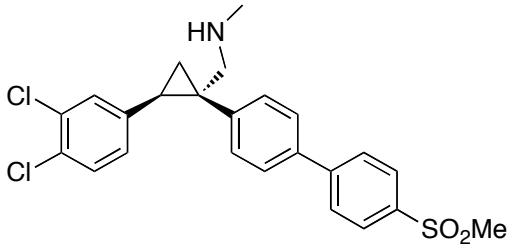


A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (137 mg, 0.35 mmol, 1 eq.), cesium carbonate (345 mg, 1.06 mmol, 3 eq.), 6-fluoro-3-pyridinylboronic acid (60 mg, 0.43 mmol, 1.1 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (14 mg, 0.017 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was

purified via column chromatography (N-H column, Isolera) to give the title compound as a light yellow oil (109 mg) in 77% yield. Rf = 0.21 (9:1 EtOAc:Et_3N). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{26}H_{25}N_2O_6Cl_2F$: C 56.64, H 4.57, N 5.08; Found C 56.53, H 4.61, N 5.11.

1-((1*S*,2*R*)-2-(3,4-Dichlorophenyl)-1-(4-(methylsulfonyl)phenyl)cyclopropyl)-*N*-methylmethanamine (6.47):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (149 mg, 0.39 mmol, 1 eq.), cesium carbonate (377 mg, 1.16 mmol, 3 eq.), 4-(methanesulfonyl)phenylboronic acid (93 mg, 0.46 mmol, 1.2 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and Pd(dppf)Cl_2 (16 mg, 0.019 mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a light yellow foam (119 mg) in 69% yield.

Rf = 0.31 (9:1 EtOAc:Et_3N);

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.47-1.55 (m, 2H), 2.26 (dd, *J* = 2, 8.4 Hz, 1H), 2.43 (s, 3H), 2.62 (d, *J* = 12.0 Hz, 1H), 3.07 (s, 3H), 3.14 (d, *J* = 12.0 Hz, 1H), 6.52 (dd, *J* = 2, 8.0 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.44 (d *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H);

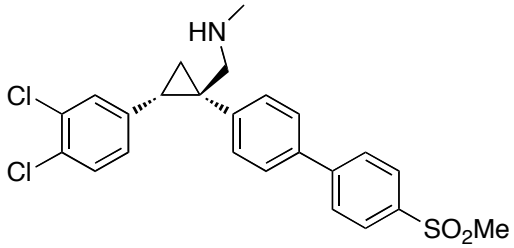
^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.4, 27.7, 36.2, 36.8, 44.8, 62.8, 126.9, 127.5, 128.0, 128.1, 129.4, 129.7, 129.9, 131.6, 131.8, 137.7, 139.2, 139.3, 139.7, 146.4;

FT-IR (film): 2932, 2846, 2792, 1593, 1494, 1139, 965, 811 cm^{-1};

HRMS-ESI m/z 460.0903 ($C_{24}H_{24}O_2NCl_2S$ requires 460.0899).

Anal. Calcd for $C_{28}H_{29}NO_8Cl_2S$: C 55.09, H 4.79, N 2.29; Found C 55.31, H 4.88, N 2.26.

1-((1*R*,2*S*)-2-(3,4-Dichlorophenyl)-1-(4-(methylsulfonyl)phenyl)cyclopropyl)-*N*-methylmethanamine (ent-6.47):



A 25 mL round bottom flask was charged with the bromo-diarylcyclopropylmethylamine (183 mg, 0.47 mmol, 1 eq.), cesium carbonate (463 mg, 1.42 mmol, 3 eq.), 4-(methanesulfonyl)phenylboronic acid (114 mg, 0.57 mmol, 1.2 eq.), and 12 mL of 4:1 THF: H_2O. The flask was then degassed with argon and $Pd(dppf)Cl_2$ (19 mg, 0.020

mmol, 0.05 eq.) was added. The resulting red solution was then heated to reflux for 12 hours. After the allotted time had passed, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in ethyl acetate with 10% triethylamine, filtered through celite, and concentrated again under reduced pressure. The residue was purified via column chromatography (N-H column, Isolera) to give the title compound as a light yellow foam (171 mg) in 81% yield. Rf = 0.31 (9:1 EtOAc:Et_3N). Spectroscopic data is the same as the other enantiomer.

Anal. Calcd for $C_{28}H_{29}NO_8Cl_2S$: C 55.09, H 4.79, N 2.29; Found C 55.62, H 4.68, N 2.33.

References

[1] E. M. Carreira, L. Kvaerno, in *Classics in Stereoselective Synthesis,* Wiley-VCH, Weinheim, 2009, pp. 1-622.

[2] Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.

[3] Hosmane, R.; Liebman, J. *Struct. Chem.* **2002**, *13*, 501.

[4] Regitz, M.; Maas, G. *Diazo Compounds-Properties and Synthesis,* Academic Press, Orlando, **1986**.

[5] Jung, M. E.; Min, S.-J.; Houk, K. N.; Ess, D. *J. Org. Chem.* **2004**, *69*, 9085.

[6] Simovic, D.; Di, M.; Marks, V.; Chatfield, D. C.; Rein, K. S. *J. Org. Chem.* **2007**, *72*, 650.

[7] Holmquist, C. R.; Roskamp, E. J.; *J. Org. Chem.* **1989**, *54*, 3258.

[8] Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W. Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532.

[9] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 14556.

[10] Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358.

[11] Johnston, J.; Muchalski, H.; Troyer, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 2290.

[12] Aoymam, T.; Shioiri, T.; *Tetrahedron Lett.* **1980**, *21*, 4461.

[13] Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

[14] Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed.,* John Wiley & Sons, Ltd., **2000**.

[15] Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15.

[16] Woodworth, R. C.; Skell, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3383.

[17] Richardson, D.; Simmons, M. C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1961**, *83*, 1934.

[18] Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.,* **2009,** *38*, 3061.

[19] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[20] Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

[21] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.,* 2003, **103**, 2861.

[22] Soldi, C.; Lamb, K. N.; Squitieri, R. A.; Gonzalez-Lopez, M.; Di Maso, M. J.; Shaw, J. T. *J. Am. Chem. Soc.* **2014**, *136*, DOI: 10.1021/ja508586t

[23] Kornecki, K. P.; Briones, J. F.; Boyarskikh, V.; Fullilove, F.; Autschback, J.; Schrote, K. E.; Lancaster, K. M.; Davies, H. M. L.; Berry, J. F. *Science* **2013**, *342*, 351.

[24] Davies, H. M. L.; Bruzinski, P.; Hutcheson, D. K.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

[25] Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2006**, *5*, 1403.

[26] Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

[27] Briones, J. F.; Davies, H. M. L. *Tetrahedron* **2011**, *67*, 4313.

[28] Davies, H. M. L.; Dick, A. *Top. Curr. Chem.* **2010**, *292*, 303.

[29] Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

[30] Slattery, C. N.; Ford, A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 6681.

[31] Bagheri, V.; Doyle, M. P.; Taunton, J.; Claxton, E. E. *J. Org. Chem.* **1988**, *53*, 6158.

[32] Buck, R. T.; Doyle, M. P.; Drysdale, M. J.; Ferris, L.; Forbes, D. C.; Haigh, D.; Moody, C. H.; Pearson, N. D.; Zhou, Q. –L. *Tetrahedron Lett.* **1996**, *37*, 7631.

[33] Lebel, H.; Marcoux, J. –F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

[34] Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403.

[35] Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

[36] Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051.

[37] Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

[38] Spencer, C. M.; Wilde, M. I. *Drugs* **1998**, *56*, 405.

[39] Mattson, R. J.; Catt, J. D.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Higgins, M. A.; Marcin, L. R.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Cunningham, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T. Lodge, N. J. *J. Med. Chem.* **2005**, *48*, 6023.

[40] Ronsisvalle, G.; Marrazzo, A.; Prezzavento, O.; Pasquinucci, L.; Falcucci, B.; Di Toro, R.; Spampinato, S. *Bioorg. Med. Chem.* **2000**, *8*, 1503.

[41] Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198.

[42] DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230.

[43] Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437.

[44] Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625.

[45] Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787.

[46] Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238.

[47] Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

[48] Zollinger, H. *Diazo Chemistry I and II,* VCH Weinheim, **1994**.

[49] Doyle, M. P.; Liu, Y.; Ratnikov, M. *Organic Reactions* **2013**, *80*, 1.

[50] Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1975**, *31*, 227.

[51] Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

[52] Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222.

[53] Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789-1792.

[54] Forster, M. O. *J. Chem. Soc.* **1915**, *107*, 260.

[55] MeinWald, J.; Gassman, P. G.; Miller, E. G. *J. Am. Chem. Soc.* **1959**, *81*, 4751.

[56] Panaro, S. A.; Davies, H. M. L. *Tetrahedron* **2000**, 56, 4871.

[57] Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238.

[58] Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, 3, 4176.

[59] Sheridan, R. S.; Moss, R. A.; Wilk, B. K.; Shen, S.; Wlostowski, M.; Kesselmayer, M. A.; Subramanian, R.; Kmiecik-Lawrynowicz, G.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1988**, *110*, 7563.

[60] Moss, R. A.; Zdrojewski, T.; Ho, G. *J. Chem. Soc., Chem. Commun.* **1991**, 946.

[61] Buron, C.; Gornitzka, H.; Romanenko, V.; Bertrand, G. *Science,* **2000,** *288*, 834.

[62] Sole, S.; Gornitzka, H.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Science*, **2001**, 1901.

[63] Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661.

[64] Michael, A. *J. Prakt. Chem./Chem. Ztg.* **1893**, *48*, 94.

[65] Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

[66] Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*, **2002**, *67*, 3057.

[67] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

[68] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

[69] Hein, J. E.; Fokin, V. V.; *Chem. Soc. Rev.* **2010**, *39*, 1302.

[70] M. Meldal, C. W. Tornøe, *Chem. Rev.,* 2008, **108**, 2952.

[71] Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038.

[72] Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3154.

[73] Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1730.

[74] Raushel, J.; Fokin, V. V. *Org. Lett.,* **2010**, *12*, 4952.

[75] Liu, Y.; Wang, X.; Xu, J.; Zhang, Q.; Zhao, Y.; Hu, Y. *Tetrahedron*, **2011**, ***67***, 6294.

[76] Meza-Avina, M. E.; Patel, M. K.; Lee, C. B.; Dietz, T. J.; Croatt, M. P. *Org. Lett.,* **2011**, *13*, 2984.

[77] Dimroth, O. *Justus Liebigs Ann. Chem.* **1909**, *364*, 183.

[78] Hermes, M. E.; Marsh, F. D. *J. Am. Chem. Soc.,* **1967**, *89*, 4760.

[79] Harmon, R. E.; Stanley, F. Jr.; Gupta, S. K.; Johnson, J. *J. Org. Chem.,* **1970**, *35*, 344.

[80] Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 4757.

[81] Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.,* **2008**, *130*, 14972.

[82] Miura, T.; Tanaka, T.; Hiraga, K.; Stewart, S. G.; Murakami, M. *J. Am. Chem. Soc.,* **2013**, *135*, 13652.

[83] Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.,* **2009**, 1470.

[84] Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.,* **2011**, *13*, 3746.

[85] Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.,* **2009**, *131*, 18034.

[86] Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.,* **2010**, *132*, 2510.

[87] Kwok, S. W.; Zhang, L.; Grimster, N. P.; Fokin, V. V. *Angew. Chem. Int. Ed.,* **2014**, *53*, 3452.

[88] Lu, T.; Hsung, R. P. *ARKIVOC,* **2014**, 127.

[89] Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.

[90] Brückner, D. *Synlett*, **2000**, 1402.

[91] Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

[92] Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165-4179.

[93] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

[94] Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996.

[95] Souto, J. A.; Becker, P.; Iglesias, A.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 15505.

[96] Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

[97] Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*. 16382.

[98] Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry: Chemistry, Biology and Material Science;* Wiley-VCH: Weinheim, **2005**.

[99] Ovalles, S. R.; Hansen, J. H.; Davies, H. M. L. *Org. Lett.,* **2011**, *13*, 4284.

[100] Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

[101] Kim, C.-E.; Park, S.; Eom, D.; Seo, B.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1900.

[102] Chuprakov, S.; Malik, J. A.; Zibinsky, M.; Fokin, V. V. *J. Am. Chem. Soc.* **2011**, 133, 10352.

[103] Mohamed, M. A.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 3436.

[104] Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093.

[105] Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433.

[106] Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley & Sons; New York, **1984**; Vol. I.

[107] Verrier, C.; Carret, S.; Poisson, J. *Org. Lett.* **2012**, *14*, 5122.

[108] Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tet. Lett.* **1988**, *29*, 4917.

[109] Shinokubo, H.; Oshima, K.; Utimoto, K. *Tet. Lett.* **1993**, *34*, 4985.

[110] Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.

[111] Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. *Angew. Chem., Int. Ed.,* **2013**, *52*, 3883.

[112] Hedley, S. J.; Davies, H. M. L. *Chem. Soc. Rev*., **2007**, 36, 1109.

[113] Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.,* **2010**, *132*, 440.

[114] DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.,* **2011**, *133*, 1650.

[115] Ma, B.; Qui, H. Q.; Li, M.; Jiang, L.; Lv, F.; Zan, L.; Zhai, C.; Doyle, M. P.; Hu, W. *Nature Chemistry*, **2012**, *4*, 733.

[116] Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.,* **2013**, *135*, 6802.

[117] Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.,* **2013,** *135*, 4716.

[118] Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.,* **2013**, *135*, 11712.

[119] Kim, C.; Park, S.; Eom, D.; Seo, B.; Lee, P. H. *Org. Lett.,* **2014**, *16*, 1900.

[120] Culhane, J. C.; Fokin, V. V. *Org. Lett.* **2011**, *13*, 4578.

[121] Zibinsky, M.; Fokin, V. V.; *Angew. Chem. Int. Ed.,* **2013**, *52*, 1507.

[122] Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.,* **2013**, *135*, 4652.

[123] Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.,* **2013**, *135*, 4696.

[124] Muira, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.,* **2012**, *134,* 194.

[125] Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.*, **2013**, *15*, 3298.

[126] Shi, Y.; Gevorgyan, V. *Org. Lett.,* **2013**, *15*, 5394.

[127] Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc.,* **2014**, *136*, DOI: 10.1021/ja412663a

[128] Supurgibekov, M. B.; Zakharova, V. M.; Sieler, J.; Nikolaev, V. A. *Tetrahedron Lett.,* **2011**, *52*, 341.

[129] Parr, B. T.; Davies, H. M. L. *Angew. Chem. Int. Ed.,* **2013**, *52*, 10044.

[130] Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795-819.

[131] Sundberg, R. J. in *Comphensive Heterocyclic Chemistry II* (Eds. Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V.), Pergamon Press, Oxford **1996**, Vol. 2, pp 119.

[132] Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Chem. Soc. Rev.,* **2012**, *41*, 5626.

[133] Kathirav, M. K.; Salake, A. B.; Chothe, A. S.; Dudhe, P. B.; Watode, R. P.; Mukta, M. S.; Gadhwe, S. *Bioorg. Med. Chem.,* **2012**, *20*, 5678.

[134] Fürstner, A. *Synlett*, **1999**, 1523.

[135] Patil, N. T.; Yamamoto, Y. *ARKIVOC,* **2007**, 121.

[136] Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

[137] Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.,* **2010**, *39*, 4402.

[138] Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.

[139] Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440.

[140] Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312.

[141] Wang, H.; Mueller, D. S.; Sachwani, R. M.; Kapadia, R.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2011**, *76*, 3203.

[142] Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926.

[143] Espino, C. G.; Fiori, K. W.; Kim, M; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

[144] Zalatan, D. N.; Bois, J. D. *J. Am. Chem. Soc.* **2009**, *131*, 7558.

[145] Shirakawa, E.; Sato, T.; Imazaki Y.; Kimura, T.; Hayashi, T. *Chem*. *Commun.,* **2007**, 4513.

[146] Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, 12, 4952.

[147] Alickmann, D.; Fröhlich, R.; Maulitz, A. H.; Würthwein, E. *Eur. J. Org. Chem.* **2002**, 1523.

[148] Narayan, R.; Frohlich, R.; Wurthwein, E. *J. Org. Chem.* **2012**, 1868.

[149] Yan, Z.; Xiao, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8624.

[150] Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

[151] Padwa, A.; Stengel, T. *Tet. Lett.* **2004**, *45*, 5991.

[152] Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

[153] Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem Soc. Rev.* **2009**, *38*, 3242.

[154] Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

[155] Davies, H. M. L.; Manning, J. R. *Nature*, **2008**, *451*, 417.

[156] Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, 704.

[157] Müller, P.; Tohill, S. *Tetrahedron*, **2000**, *56*, 1725.

[158] Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126.

[159] Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. J. *J. Am. Chem. Soc.* **2003,** *125*, 6462.

[160] Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

[161] Nadeau, E.; Li, Z.; Morton, D.; Davies, H. M. L. *SYNLETT*, **2009**, 151.

[162] Chuprakov, S.; Malik, J. A.; Zibinsky, M.; Fokin, V. V. *J. Am. Chem. Soc.,* **2011**, *133*, 10352.

[163] Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.,* **2011**, *40*, 1857.

[164] Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126.

[165] Medina, F.; Besnard, C.; Lacour, J. *Org. Lett.* **2014**, *16*, 3232.

[166] Murthy, V.; Davies, H. M. L.; Hedley, S. J.; Childers, S. R. *Biochem. Pharmacol.* **2007**, *74*, 336.

[167] Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509.

[168] Davies, H. M. L.; Ni, A. *Chem. Commun.* **2006**, 3110.

[169] Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060.

[170] Spandan Chennamadhavuni Thesis **2011**, Emory University, Dr. Huw Davies.

[171] Spencer, C. M.; Wilde. M. I. *Drugs* **1998**, *56*, 405.

[172] Ronsisvalle, G.; Marrazzo, A.; Prezzavento, O.; Pasquinucci, L.; Falcucci, B.; Di Toro, R.; Spampinato, S. *Bioorg. Med. Chem.* **2000**, *8*, 1503-1513.

[173] Mattson, R. J.; Catt, J. D.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Higgins, M. A.; Marcin, L. R.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Cunningham, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T. Lodge, N. J. *J. Med. Chem.* **2005**, *48*, 6023.

[174] Aggrawal, Anil *Narcotic Drugs* **1995**, National Book Trust, 52.

[175] Nichols, D. E., Nichols, C. D. *Chem. Rev.* **2008**, *108*, 1614.

[176] Nichols, D. E. *Pharmacol. Ther.* **2004**, *101*, 131.

[177] McMahon, L. R.; Cunningham, K. A. *Journal of Pharmacology and Experimental Therapeutics* **2001**, *297*, 357.

[178] Dhonnchadha, B. A.; Fox, R. G.; Stutz, S. J.; Rice, K. C.; Cunningham, K. A. *Behavioral Neuroscience* **2009**, *123*, 382.

[179] Westkaemper, R. B.; Glennon, R. A. *Curr. Top. Med. Chem.* **2002**, *2*, 575.

[180] Boeckman Jr, R. J.; George, K. M. **2009**, 1.

[181] Kumpaty, H. J.; Williamson, J. S.; Bhattacharyya, S. *Synth. Commun.* **2003**, *33*, 1411-1416.

[182] Baum, J. S.; Shook, D. A.; Davies, H. M. L. *Synth. Commun.* **1987**, *43*, 4265.

[183] Pour, M.; Špulák, M.; Balšánek, V.; Kuneš, J.; Kubanová, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843.

[184] Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902.

[185] Nadeau, E.; Ventura, D. L.; Brekan, J. A.; Davies, H. M. L. *J. Org. Chem.* **2010**, *75*, 1927.

[186] Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

[187] Kumpaty, H. J.; Williamson, J. S.; Bhattacharyya, S. *Synth. Commun.* **2003**, *33*, 1411.

[188] Suárez-Castillo, O. R.; Montiel-Ortega, L. A.; Meléndez-Rodríguez, M.; Sánchez-Zavala, M. *Tett. Lett.* **2007**, *48*, 17.

[189] Ravinder, K.; Reddy, A. V.; Mahesh, K. C.; Narasimhulu, M.; Venkateswarlu, Y. *Synthetic Communications* **2007**, *37*, 281.

[190] Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

[191] Ni, A.; France, J. E.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5594.

[192] Miyaura, N. Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[193] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[194] Nolt, M. B.; Zhao, Z.; Wolkenberg, S. E. *Tetrahedron Lett.* **2008**, *49*, 3137.

[195] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

[196] Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.*, **2011**, *13*, 3996.

[197] Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

[198] Cho, E. J.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 6552.

[199] Scheiper, B.; Bonnekessel, Krause, H.; Furstner, A. *J. Org. Chem.* **2004**, *69*, 3943.

[200] Shirakawa, E.; Sato, T.; Imazaki Y.; Kimura, T.; Hayashi, T. *Chem. Commun.,* **2007**, 4513.

[201] Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Org. Chem.*, **2010**, *75*, 7573.

[202] Shafi, S.; Kedziorek, M.; Grela, K. *Synlett*, **2011**, 124.

[203] Fan, L.; Liu, W.; Xu, H.; Yang, L.; Lv, M.; Zheng, Y. *Chem. Pharm. Bull.* **2009**, *57*, 797.

[204] Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Organic Syntheses* **1992**, *70*, 93.

[205] Tore Hansen Thesis **2000**, SUNY Buffalo, Dr. Huw Davies.

[206] Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*(9), 1403.

[207] Pour, M.; Špulák, M.; Balšánek, V.; Kuneš, J.; Kubanová, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, *11*, 2843.

[208] Davies, H. M. L.; Hansen, T.; Rowen, M. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

[209] Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

[210] Smith, C. R.; RajanBabu, T. V. *Tetrahedron* **2010**, *66*, 1102.

[211] Knör, S.; Khrenov, A. V.; Laufer, B.; Saenko, E. L.; Hausser, C. A. E.; Kessler, H. *J. Med. Chem.* **2007**, *50*, 4329.

[212] Wang, J.; Burdzinski, G.; Kubicki, J.; Platz, M. *J. Am. Chem. Soc.* **2008**, *130*, 11195.