DEHYDRATIVE CYCLIZATIONS VIA ACID CATALYSIS AS A METHOD FOR MOLECULAR DIVERSITY

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This thesis is dedicated to all those who have walked with me in the many seasons of life.

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A	Acceptor
α	Alpha
Å	Angstrom
ABL	α-alkylidene-γ-butyrolactone
Ac_2O	Acetic anhydride
Ag_2CO_3	Silver carbonate
$Al(OTf)_3$	Aluminum(III) trifluoromethanesulfonate
aq	Aqueous
β	Beta
$BF_3•Et_2O$	Borontrifluoride diethyletherate
Bi	Bismuth
$BiBr_3$	Bismuth (III) tribromide
$Bi(NO_2)_3•5H_2O$	Bismuth(III) nitrate pentahydrate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
$BnEt_3NBr$	Benzyltriethylammonium bromide
br	Broad
Br	Bromo
n-Bu_4NPF_6	Tetrabutylammoniumhexafluorophosphate
n-BuLi	*n*-Butyllithium
t-$BuMe_2SiO$	Tert-Butyldimethylsiloxy
$Ca(NTf_2)_2$	Calcium(II) bis(trifluoromethanesulfonimide)
C	Carbon

°C	Degrees Celsius
^{13}C	Carbon thirteen
$CDCl_3$	Chloroform-d
$CeCl_3$	Cerium(III) chloride
$CeCl_3 \cdot 7H_2O$	Cerium(III) chloride heptahydrate
CF_3	Trifluoromethyl
C_6H_6	Benzene
$CHBr_3$	Bromoform
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
CH_2N_2	Diazomethane
Cl	Chloro
CO_2	Carbon Dioxide
CO_2Et	Ethyl ester
CO_2Me	Methyl ester
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
$Cu(OAc)_2$	Copper(II) acetate
Cu(OTf)•Tol	Copper(I) trifluoromethanesulfonate toluene complex
D	Donor
D	Deuterium (Chapter 4)
d	Doublet
δ	Delta
dd	Doublet of doublets
ddd	Doublet of doublet of doublets

dt	Doublet of triplets
δ	Delta
D-A	Donor-Acceptor
DABCO	1,4-Diazabicyclo[2.2.2]octane
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DIBAL-H	Diisobutylaluminum hydride
DMF	Dimethylformamide
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DOS	Diversity-oriented synthesis
$Dy(OTf)_3$	Dysprosium(III) trifluoromethanesulfonate
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Grams
γ	Gamma
$GaCl_3$	Gallium(III) trichloride
$Ga(OTf)_3$	Gallium(III) trifluoromethanesulfonate
gem	Geminal
h	Hours

H	Hydrogen
^{1}H	Proton
HMPA	Hexamethylphosphoramide
HOAc	Acetic acid
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
$InCl_3$	Indium(III) trichloride
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
$[Ir(cod)Cl]_2$	Bis(1,5-cyclooctadiene)diiridium(I) dichloride
J	Coupling Constant
K_2CO_3	Potassium carbonate
KIE	Kinetic isotope effect
LAH	Lithium aluminum hydride
$La(OTf)_3$	Lanthanum(III) trifluoromethanesulfonate
LHMDS	Lithium bis(trimethylsilyl)amide
Li	Lithium
$LiEt_3BH$	Lithium triethylborohydride
m	Multiplet
M	Molar
Me	Methyl
mg	Milligrams
MHz	Megahertz
MeI	Methyl iodide
mL	Milliliters

mmol	Millimoles
MeOH	Methanol
Me_3SiOTf	Trimethylsilyl trifluoromethanesulfonate
min	Minutes
mol %	Mole percent
MS	Molecular sieves
μm	Micrometers
N	Nitrogen
$NaBH_4$	Sodium borohydride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
ND	Not determined
NDP	No desired product
NEt_3	Triethylamine
NH_4Cl	Ammonium chloride
$Ni(ClO_4)_2 \cdot 6H_2O$	Nickel(II) perchlorate hexahydrate
$Ni(OTf)_2$	Nickel(II) trifluoromethanesulfonate
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Np	Naphthyl
NR	No reaction
O	Oxygen
OMe	Methoxy

p-ABSA	4-Acetamidobenzenesulfonyl azide
Pd	Palladium
Ph	Phenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr	Isopropyl
prep	Preparatory
R_f	Retardation factor
Rh	Rhodium
Rh_2esp_2	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
rr	Regiomeric ratio
rt	Room temperature
s	Singlet
$Sc(OTf)_3$	Scandium(III) trifluoromethanesulfonate
SCXRD	Single crystal X-ray diffraction
SmI_2	Samarium(II) iodide
$SnCl_4$	Tin(IV) chloride
t	Triplet
TBDPS	*tert*-Butyldiphenylsilyl
TLC	Thin layer chromatography
TfOH	Trifluoromethanesulfonic (triflic) acid
Tf_2NH	Trifluoromethanesulfonimide
THF	Tetrahydrofuran
TOS	Target-oriented synthesis
TS	Transition state

TsN_3	*p*-Toluenesulfonyl azide
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
$Yt(OTf)_3$	Yttrium(III) trifluoromethanesulfonate
$Zn(OTf)_2$	Zinc(II) trifluoromethanesulfonate
2°	Secondary
3°	Tertiary

SUMMARY

Development of new synthetic methodologies that allow for efficient access to desirable core structures is a consistently valuable area of research for synthetic chemistry. Good methodologies provide rapid access to systematically varying compounds with desirable properties, enabling functional testing and the discovery of new, useful compounds and materials. Three novel synthetic methodologies that make use of dehydrative cyclizations of carbinols via Lewis acid catalysis have been developed towards this end: (1) A calcium-catalyzed, dehydrative, ring-opening cyclization of cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes; (2) A $Bi(OTf)_3$-catalyzed synthesis of α-alkylidene-γ-butyrolactones from the ring-opening cyclization of cyclopropyl carbinols; (3) A calcium-catalyzed synthesis of cyclopenta[*b*]thiophenes and indenes via dehydrative Nazarov-type electrocyclizations of alkenyl (hetero)aryl carbinols. The mechanistic details of how each of these methods perform have also been investigated. Initial results and proposals for consequent projects, which span the breadth of target synthesis and new methodologies, have also been established.

CHAPTER 1. INTRODUCTION

1.1 Accessing Molecular Diversity

The general goal of any synthetic chemist is to make desirable molecules, or molecules that can be used to solve some sort of problem. Some examples are small molecules with therapeutic functionalities, ligands for catalysis, and polymers with useful structural properties. These desirable molecules come in many shapes and sizes, and new methods for accessing the diversity of these molecules are always in demand, which makes methodology development an attractive focus of synthetic research laboratories worldwide.[1]

1.1.1 Chemical Space

Individual molecular structures can be thought of as single points in multidimensional chemical space, which encompasses all possible unique molecular structures and is effectively infinite. The dimensions in chemical space are physical descriptors of the molecules, such as molecular weight, molecular formula, connectivity, and polarity;[2] molecules that are considered close in molecular space have significant similarity in these dimensions. The concept of chemical space is frequently mentioned within medicinal chemistry, where a subset of all molecular space that have drug-like properties[3] is the primary focus.

It has been calculated that the chemical space of drug-sized molecules is somewhere on the order of 10^{60} compounds, making this subset of chemical space prohibitively large for exhaustive exploration.[4] Currently, the number of known

(characterized) molecules within this defined space is only on the order of 10^8, and of those less than 10^4 have actually become experimental or approved small-molecule drugs.[5] Extrapolating these numbers beyond therapeutics to all useful molecules in all chemical space begets an incredible diversity of molecules, which begs the necessity of a diversity of strategies to identify and synthesize them.

1.1.2 Synthetic Strategies

Numerous approaches to synthesis exist, each with its own specific goals but all preserving the ultimate goal of making useful molecules. The classic approach to synthesis is target-oriented synthesis (TOS), where the chemist has a specific target in mind and goes about developing a strategy to access that particular molecule, or small subset of highly related molecules. A common example of TOS is natural product synthesis, where the target has been identified from being isolated and is either proven or suspected to be biologically active.

Another approach to synthesis, often leveraged by medicinal chemists, is combinatorial chemistry.[6] The approach frequently uses predictive modelling from computational chemists to identify a dense region of chemical space as the target area, followed by the development of large libraries on the order of 10^5 molecules that fit within that region of chemical space.[7] Although an incredible number of molecules can be synthesized and tested this way, limitations in suitable reagents and reactions limit the areas of chemical space that can be accessed through combinatorial chemistry.[8]

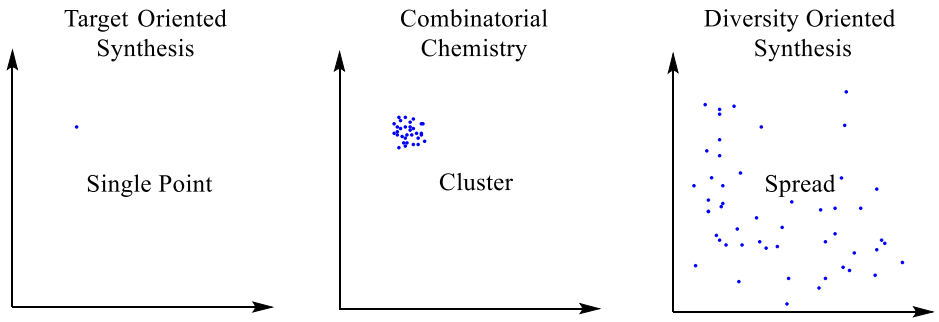


Figure 1 – Visual Representations of Chemical Space Coverage

A third approach to synthesis of small molecules is diversity-oriented synthesis (DOS).[9] This approach to synthesis has the explicit goal of efficiently making a very diverse set of molecules – accessing a broad range of chemical space, as opposed to targeting specific or dense regions of chemical space (Figure 1).[10] The ultimate goal is still to make useful molecules; however, the approach emphasizes creating structural diversity as the strategy towards useful molecules over the incredible library size of combinatorial chemistry or the high-confidence targeted approach of TOS. The four commonly agreed upon principal components of structural diversity are skeletal diversity, functional group diversity, appendage diversity, and stereochemical diversity.[11]

Skeletal diversity describes changes to the core, or molecular scaffold, of the small molecule. Functional group diversity describes variations in functional groups in any part of the molecule. Appendage diversity describes changes to the parts of a molecule around a common core skeleton. Lastly, stereochemical diversity describes variations in connectivity that give rise to differing spatial orientations; this is of particular importance within chiral environments such as the human body. All four of these are crucially

important for DOS; however, changes in skeletal diversity prompt the greatest changes in molecular diversity – and therefore access the broadest ranges of chemical space. It is an emphasis on skeletal diversity that is indicative of DOS strategies, whereas the other three principal components of structural diversity are also observed in TOS and combinatorial chemistry.

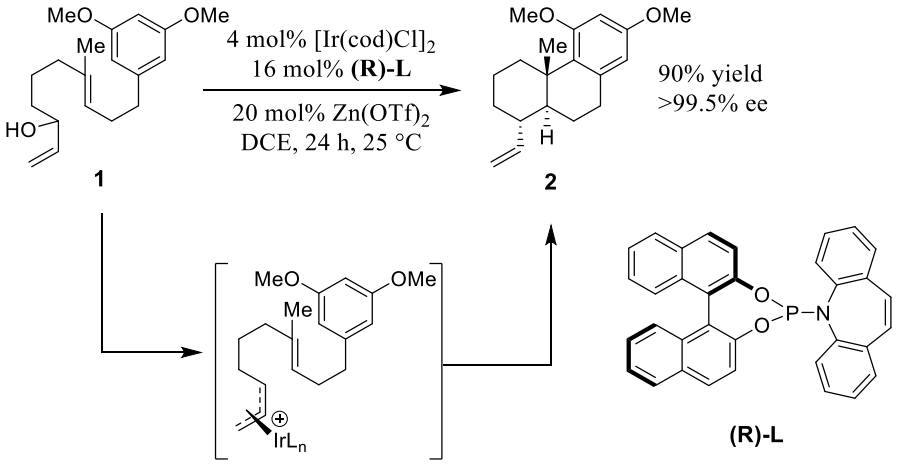
1.2 Cationic Cyclization Reactions

When assembling a small molecule, there are typically a few key transformations that give rise to the core structures, or skeletons, of the desired molecules. These transformations are often the highlighted synthetic steps in syntheses as they are the steps that generate the most complexity. Continued development of reactions that allow for rapid generation of complex core structures is a continued endeavour in synthetic methodology development. These reactions that generate complexity are frequently cyclization reactions, where new rings are formed in a molecule.

Polyene cyclizations, defined as cascade cyclizations of multiple double bonds in an acyclic system which results in the formation of polycyclic compounds, are a prominent example of a key transformation toward complex molecular scaffolds, as they allow for the formation of multiple fused rings in a single synthetic step. These reactions are biosynthetically inspired and particularly powerful in TOS strategies, where the targets are polycyclic triterpenoids and steroidal core scaffolds – common core scaffolds of many natural products.[12] Early foundational work by Bloch,[13] Stork,[14] and Eschenmoser[15] led to continued work by Johnson, resulting in the first asymmetric synthesis of steroids.[16] Corey has since extensively studied the mechanistic nature of such reactions[17] and utilized them

towards the synthesis of numerous natural products.[18] Continued efforts into improving these methods have led to recent advancements in polyene cyclizations with enantioselectivity.[19]

These polyene cyclizations are frequently initiated by the activation of a functional group that generates an electrophilic carbon center. For example, a traditionally used method of generating these electrophilic carbon centers is the activation of an allyl alcohol, though use of a Lewis or Brønsted acid, to generate a carbocation that initiates the polycyclization.[12a] This continues to be a method that has been amiable to the recent enantioselective efforts undertaken by the Carreira group.

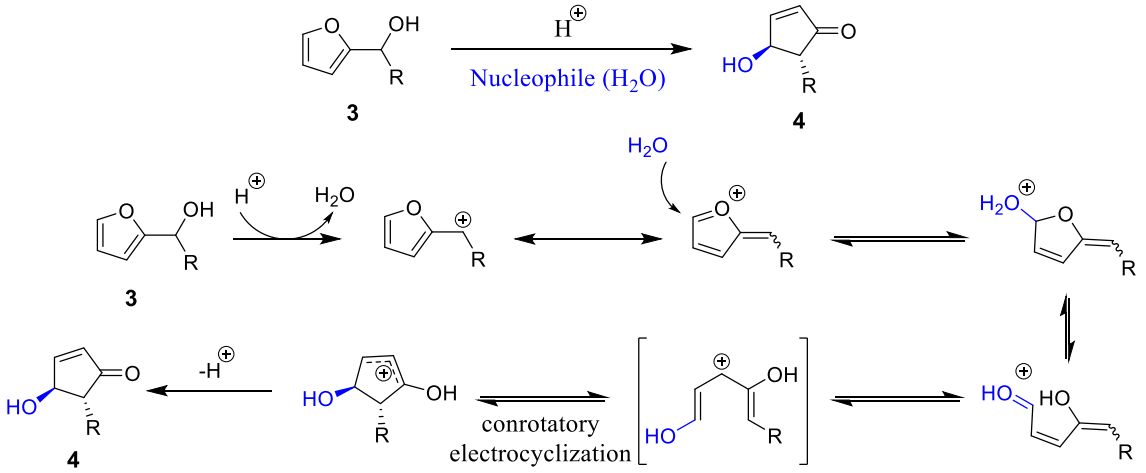


Scheme 1 – Enantioselective Polycyclization Example using Chiral Iridium Catalyst

The Carreira group has used Lewis acid activation of allyl alcohols in the presence of a chiral iridium catalyst to generate an iridium π-allyl species, which initiates the

enantioselective polycyclization (Scheme 1).[20] This newly developed methodology has been leveraged in the synthesis of multiple targets: (+)-asperolide C,[21] (-)-mycoleptokiscin A,[22] and taiwaniadducts B, C, and D. [23] Polyene cyclizations, initiated by the acid promoted loss of an alcohol and consequential generation of a carbocation, represent a robust example of rapid generation of a complex core structure that has been used to great success within the confines of TOS; however, it is also an example of a methodology that does poorly in adhering to the ideals of DOS. This is due to the rigorous constraints on the core structures of the starting materials and products, and the lack of convenient branching points to introduce meaningful skeletal diversity. It does, on the other hand, give strong evidence toward the general utility of cationic cyclization reactions in generating complex core structures. This leads to the prediction that development of other cationic cyclization reactions could be particularly useful when approached with DOS strategies in mind.

Generation of cations within a compound can initiate many changes to the molecular structure, such as making intramolecular bonds, breaking bonds, trapping external nucleophiles, and enabling proper orbital overlaps for electrocyclizations. Taking advantage of these types of reactivity can be particularly useful for DOS strategies incorporating cationic cyclization reactions, as they have the potential to be branching points until the cation is quenched is some way. A good example of many of these cationic reactivities is the Piancatelli reaction.



Scheme 2 – Piancatelli Reaction with Mechanism

The traditional Piancatelli reaction involves the transformation of 2-furyl carbinols (**3**) to 4-substituted 5-hydroxy-3-oxocyclopentenes (**4**) under acidic aqueous conditions (Scheme 2).[24] This reaction has been well studied since then, and the mechanism for the transformation is generally understood, enabling the strategic improvement of the methodology to be one that can accommodate DOS strategies. These improvements include catalytic activation, enantioselective reactivity, trapping by various nucleophiles, aza-Piancatelli development, and branching routes.[25] The Piancatelli reaction continues to be an ongoing focus for methodology development, with the explicit focus and goal of developing divergent syntheses and an appreciable diversity in molecular scaffolds.[26]

The Piancatelli reaction, and its variants, are also another example of using π-activated alcohols in the presence of a Lewis or Brønsted acid to generate a carbocation that initiates a series of cationic transformations resulting in the formation of a new ring. This affirms two things: (1) the prediction that development of cationic cyclization

reactions can be particularly useful when approached with DOS strategies in mind, and (2) the use of π-activated alcohols in the presence of a Lewis or Brønsted acid is an effective route towards initiation of cationic cyclization reactions. Keeping these in mind would be prudent for the continued development of DOS strategies of a similar nature but with different systems.

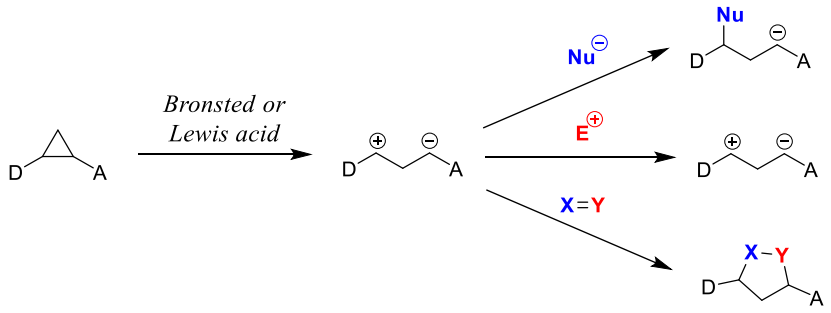
1.3 Strained-Ring Systems

Ring strain, consisting of both torsional and angle strain, is an inherent property of cyclic hydrocarbons.[27] Substituents on the ring can also introduce additional strain associated from being in a ring. Excluding substituent effects, ring size determines the strain energy – a quantitative measure for the combined angle and torsional strains (Table 1).[28] Although ring strain can be a hindrance when it comes to forming rings in cyclization reactions, it can be a boon when it comes to opening rings as it can provide a thermodynamic driving force for subsequent reactivity.[29] An intuitive example is a ring-opening cyclization, where the energy gained from ring-opening is used to propel the generation of a new less-strained ring.

Table 1 – Strain Energy of Cycloalkanes by Ring Size

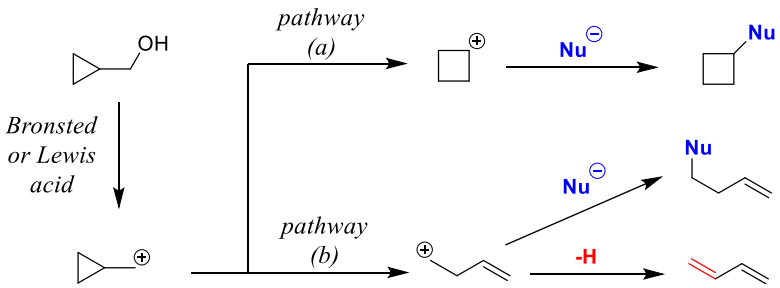
Ring Size	Strain Energy (kcal/mol)		Ring Size	Strain Energy (kcal/mol)
3	27.5		8	9.7
4	26.3		9	12.6
5	6.2		10	12.4
6	0.1		11	11.3
7	6.2		12	4.1

Among simple cyclic hydrocarbons, two ring sizes stand apart from the rest as being highly strained: cyclopropanes and cyclobutanes. They have both shown synthetic utility, but between the two cyclopropanes are both more readily accessed and more frequently used than cyclobutanes.[30] Although they are strained systems, they have the benefit of being chemically inert without some sort of activation. Based on the type of activation, different subsequent reactivities are available. Summarized, these strained ring systems are a stable, directable source of energy – an appealing template for the development of synthetic methodologies.



Scheme 3 – Donor-Acceptor Cyclopropane Reactivity

Two methods of activating cyclopropanes, and by extension cyclobutanes, are through the use of Donor-Acceptor (D-A) cyclopropanes[31] and cyclopropyl carbinols.[32] Vicinal D-A cyclopropanes (Scheme 3) work by placing electron donating and electron accepting groups on adjacent carbons, thereby polarizing the C-C bond between them. An acid activator then can interact with the acceptor, initiating heterolytic cleavage to generate a 1,3-dipole, which can react with electrophiles, nucleophiles, and dipolarophiles.



Scheme 4 – Cyclopropyl Carbinol Reactivity

Cyclopropyl carbinols (Scheme 4) use hydroxymethyl cyclopropanes that are activated by an acid to form a cyclopropyl methylium, which initiates either ring expansion (via bond migration) to a cyclobutyl cation (pathway a) or heterolytic cleavage to form a homoallyl cation (pathway b). These intermediates are then trapped by various nucleophiles or undergo eliminations to generate products.[33] The substituents around the cyclopropyl carbinol determine which pathway will be preferred through relative stabilization or destabilization of the resulting cyclobutyl or homoallyl cation.[34]

Each of these methods of activation provide potentially unique reactivities while sharing acidic means of activation and utilizing the same advantages inherent to strained rings. The diversity of pathways and subsequent steps following activation of the cyclopropanes in each of these cases suggests the viability of strained ring substrates as useful synthetic building blocks in DOS.

1.4 Thesis Outline

The topic of this thesis is the development and use of new and/or improved synthetic methodologies using acid-catalyzed dehydrative cyclization reactions, with a focus toward DOS strategies. This chapter (Chapter 1) has given general background information that will be useful throughout the rest of the thesis, whereas other background information relevant to specific chapters will be discussed within those chapters. The body of the thesis will be comprised of Chapters 2, 3, and 4, which will each discuss a new methodology that has been developed and published. Chapter 5 will discuss some proposed next projects, will show some preliminary results towards them, and will outline what challenges lie ahead for each of them.

Chapter 2 showcases a calcium-catalyzed dehydrative ring-opening cyclization of cyclopropyl carbinols to access functionalized 1-aryl-1,2-dihydronaphthalene core structures (Figure 2A). The cyclopropyl carbinols are prepared directly from D-A cyclopropanes, which are accessed through methodologies previously published from our lab that incorporate DOS values. The development, strengths, weaknesses, and benefits of the new methodology are all discussed.

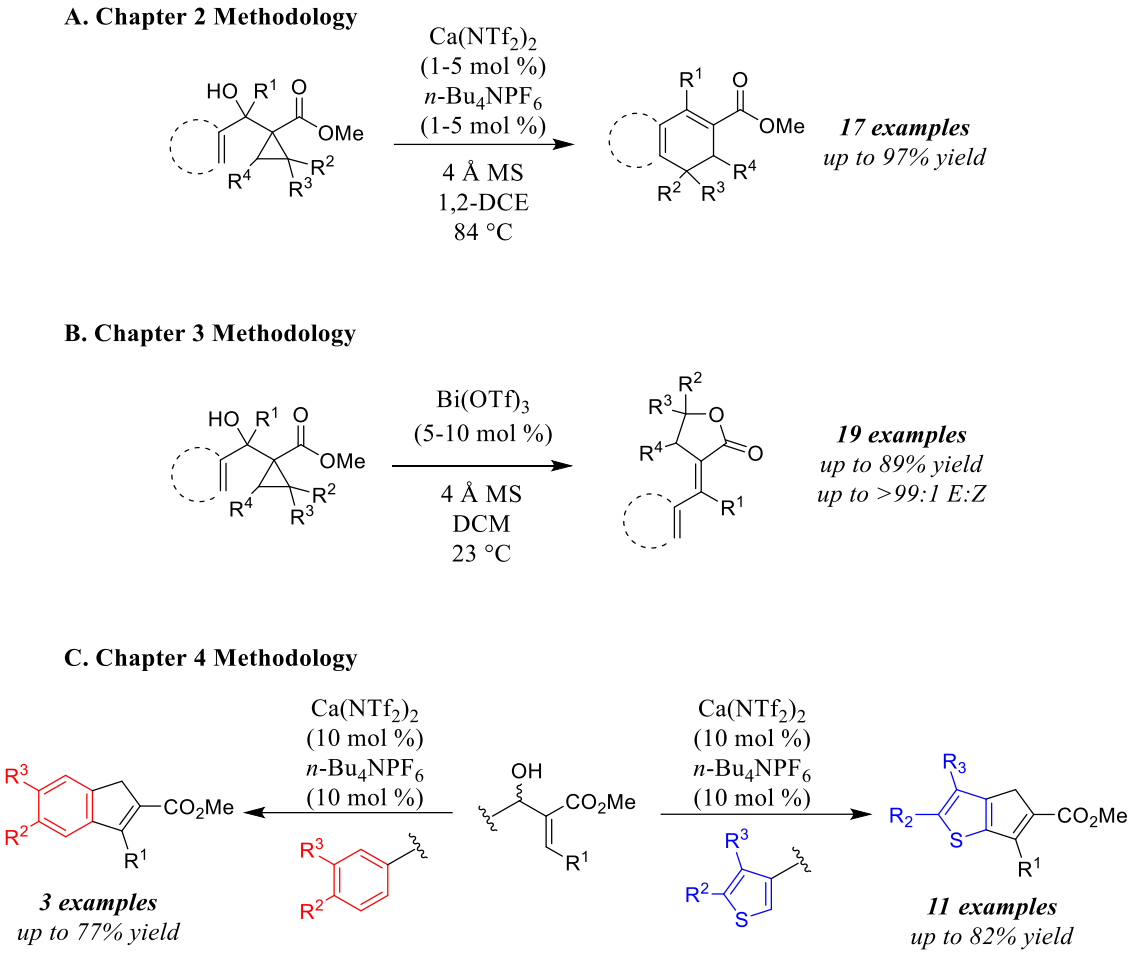


Figure 2 – Developed Methodologies by Chapter

Chapter 3 introduces a new transformation for the cyclopropyl carbinol compounds highlighted in Chapter 2 that enables access to an entirely different yet desirable core structure (Figure 2B). This new methodology uses $Bi(OTf)_3$ to catalyze the dehydrative ring-opening cyclization of cyclopropyl carbinols to selectively access functionalized α‑alkylidene-γ-butyrolactones. Discussion emphasizes the understanding of the mechanism and how substituent effects determine product outcomes.

Chapter 4 presents a dehydrative Nazarov-type electrocyclization of (hetero)aryl carbinols, with a strong focus on synthesizing functionalized cyclopenta[*b*]thiophenes, using the same calcium catalyst system as Chapter 2 (Figure 2C). Although dehydrative Nazarov-type electrocyclizations were already known, expertise we derived from Chapters 2 and 3 allowed for filling a valuable hole present in previous methodologies. Studies into the origins of various product isomers were also done and are discussed.

Chapter 5 provides overall conclusions from Chapters 2, 3, and 4; it then details the proposed next steps to take under the umbrella of acid-catalyzed dehydrative cyclization reactions focused on DOS strategies. Three projects that stem from the research found in this thesis are proposed, outlined, and some initial results are presented. The next steps for each project are then discussed. The three projects are dehydrative cyclization reactions of cyclobutyl carbinols, dehydrative cyclization reactions of alkylidene cyclopropyl carbinols, and natural product synthesis. A summary of the thesis as a whole is also provided.

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CHAPTER 2. DEVELOPING A CATALYTIC DEHYDRATIVE HOMO-NAZAROV TYPE CYCLIZATION OF CYCLOPROPYL CARBINOLS[*,1]

2.1 Rationale of Pursuit

A major focus of study for our lab is the development of new methodologies that meet the expectations set forth by DOS, with a frequent focus on utilizing strained ring systems. Towards that end, we have established he catalytic, formal homo-Nazarov cyclization as a viable template for diversity-oriented synthesis over the past several years.[2] Included in these are the formal homo-Nazarov cyclization, and both arene and allylsilane trapping of formal homo-Nazarov cyclization intermediates (Figure 3). Continued development of new branching-points surrounding our formal homo-Nazarov methodologies is an ongoing endeavor, as each useful branching point provides not only a new method, but concurrently increases the value of the existing methods.

[*] Work on this project performed independently. Adapted with permission from *Org. Lett.* **2016**, *18*, 4218. Copyright 2016 American Chemical Society.

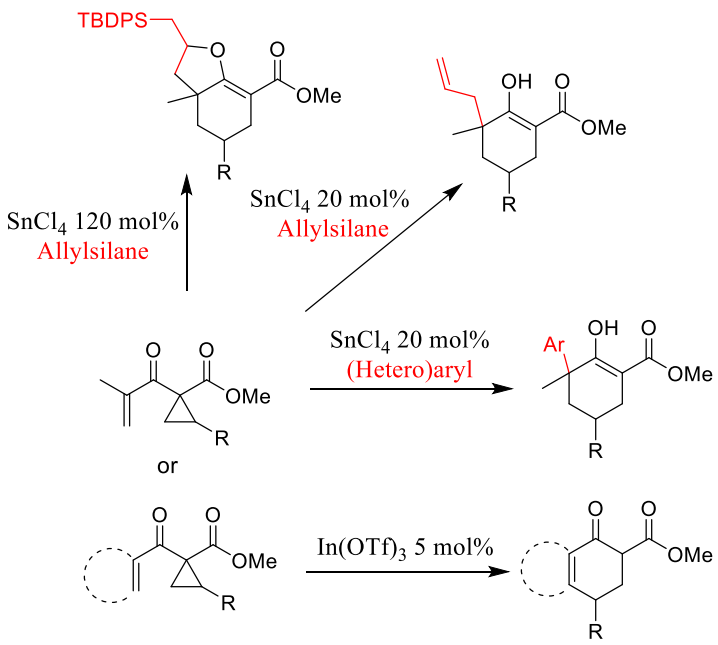


Figure 3 – France Lab Methods Utilizing Formal Homo-Nazarov Cyclizations

In an initial 2010 communication, the Nishii lab showed that aryl cyclopropyl carbinols undergo dehydrative, intramolecular ring-opening cyclizations in the presence of stoichiometric amounts (110 mol %) of $Sc(OTf)_3$ or BF_3•Et_2O to generate functionalized 1-aryl-1,2-dihydronaphthalenes in good to high yields (Figure 4).[3] They first developed a set of optimized conditions for transformations involving secondary alcohols (Figure 4, top) and followed with a second set of optimized conditions for tertiary alcohols containing identical aryl substituents (Figure 4, bottom). Each set of conditions gave moderate to excellent yields, with unsubstituted aryl groups performing best and any substitution decreasing observed yields.

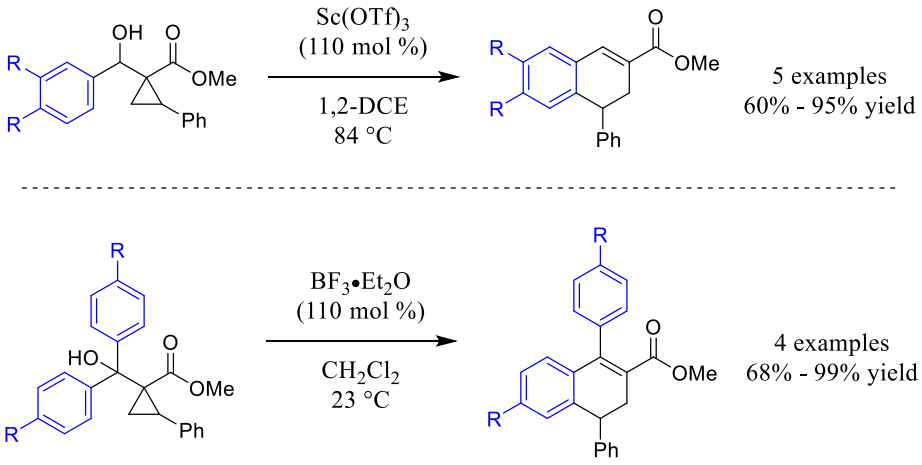
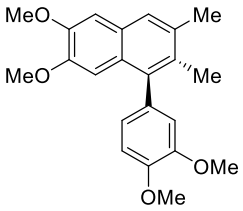
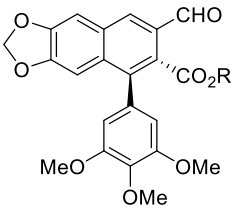


Figure 4 – Nishii's Method to Access 1-Aryl-1,2-dihydronaphthalenes

This method has proven particularly powerful for the target-oriented synthesis of numerous natural products and synthetic analogues within the lignan family – a family of natural products that with a broad range of biological activities.[4] These lignans all have the commonality of being made up of functionalized phenylpropanoids. They are frequently dimers, but can have up to four phenylpropanoid units. Lignans are a frequent focus of the Nishii lab, and they have since highlighted the 2010 method's utility through the efficient total syntheses of (±)-cyclogalgravin[5a] and (+)-podophyllic aldehydes[5b] (Figure 5). Even more recently, the Nishii lab has made efforts to improve the method itself[5c] and the general understanding of its stereochemical outcomes.[5d]



(±)-cyclogalgravin



(+)-podophylic aldehyde A (R = Me)
(+)-podophylic aldehyde B
(R = 3,4,5-trimethoxybenzyl)

Figure 5 – Synthetic Targets Accessed by Nishii Lab

This method caught our eye due to its similarities to the formal homo-Nazarov cyclization, which we are intimately familiar with. Considering the proposed mechanisms for the two, Nishii's reaction (Figure 6A) is mechanistically analogous to the formal homo-Nazarov cyclization of aryl cyclopropyl ketones (Figure 6B). In both, acid-mediated cyclopropane ring opening affords analogous acyclic carbocations (**I** or **III)**. This is followed by intramolecular π-attack and then elimination to provide the resulting six-membered rings products via intermediates **II** and **IV**, which are also very similar in structure.

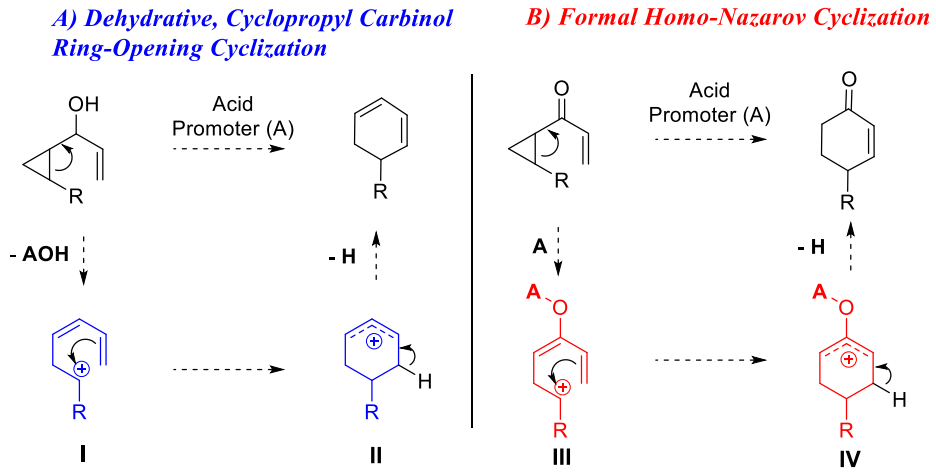


Figure 6 – (A) Dehydrative, Cyclopropyl Carbinol Ring-opening Cyclization vs (B) Formal Homo-Nazarov Cyclization

Despite the demonstrated utility, Nishii's method exhibits several drawbacks that preclude it from being exploited by the greater synthetic community. First, the four-step synthesis of the precursors required the use of several harsh conditions and reagents, including SmI_2 (addressed in a following report),[5c] HMPA, and Jones reagent. Second, stoichiometric amounts of Lewis acid were required to promote the transformations, impeding facile and cheap scale-up. Finally, the substrate scope was limited, with a focus on electron-rich substrates similar to lignan scaffolds. This prevented the ability to extrapolate reactivity patterns for substituent effects apart from substituents being detrimental to the reactivity.

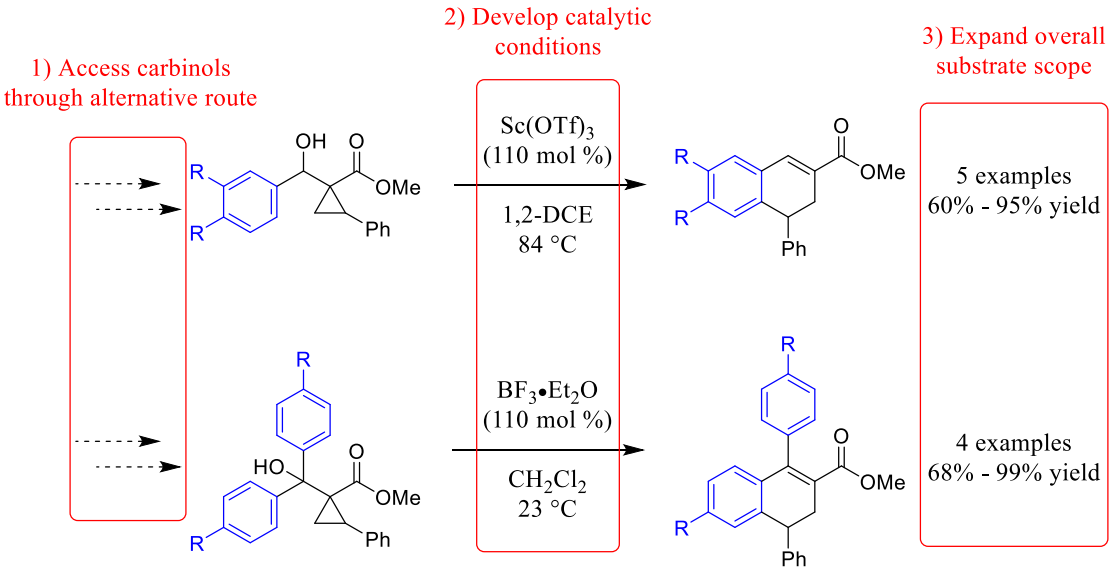


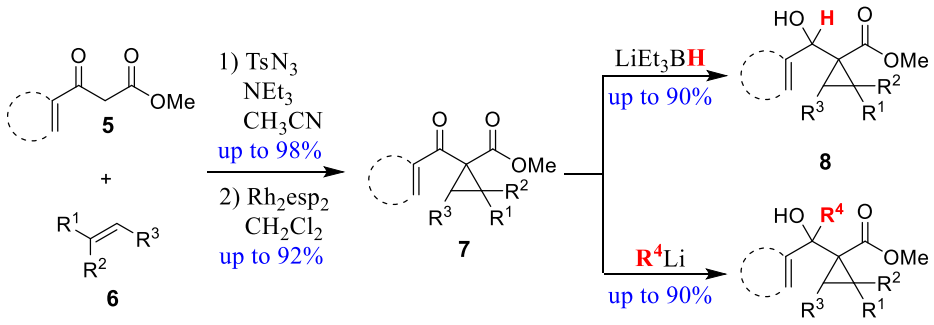
Figure 7 – Areas of Focus for Improvements

Given the analogy between Nishii's method and the formal homo-Nazarov reaction, our interest in the catalytic formation of functionalized six-membered rings, and our desire to introduce new branching points in existing methods to access greater molecular diversity, we decided to push this method to new levels. In function, we sought to directly address the identified drawbacks by (1) accessing the cyclopropyl carbinols by an alternate route, (2) identifying the appropriate conditions to promote catalysis, and (3) expanding the overall substrate scope (Figure 7).

2.2 Synthetic Route to Cyclopropyl Carbinols

The first goal of our endeavor was to overcome the harsh conditions for substrate synthesis. We already had extensive practice in the synthesis of the donor-acceptor (D-A) cyclopropanes **7**, which we envisioned could undergo chemoselective alcohol formation to

form the desired functionalized cyclopropyl carbinols **8** in a single subsequent step (Scheme 5).This approach has a specific advantage over Nishii's synthesis of **8** in that the methods to access the D-A cyclopropanes are well-established, multigram scalable, experimentally facile, and highly functional group tolerant.[2b,6] Starting from the β-ketoester compounds **5**, diazo transfer, Rh(II)-catalyzed cyclopropanation, and subsequent reduction with $LiEt_3BH$ (or treatment with an alkyl or aryl lithiate) afforded the desired cyclopropyl carbinols **8** in modest to high yields for each individual step. This marked the completion of our first goal for this project: accessing the cyclopropyl carbinols by an alternate route. In all cases, the carbinols are prepared and used as mixtures of diastereomers.

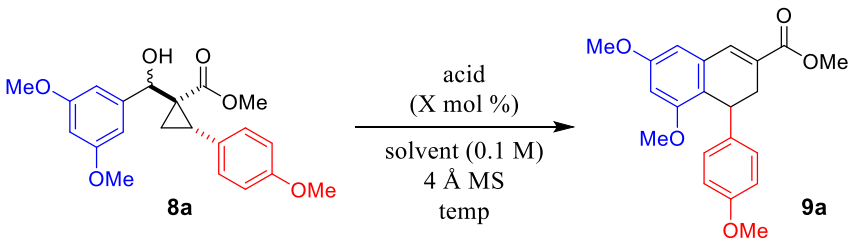


Scheme 5 – Preparation of Cyclopropyl Carbinols 8

2.3 Reaction Optimization

Our next goal was to find viable conditions for catalysis. We chose cyclopropyl carbinol **8a** as our initial model system, with the intention of having a good electron donor on the cyclopropane to help stabilize ring-opening and a symmetric, electron rich aryl ring as the nucleophile in the last mechanistic step. We subjected this substrate to an extensive list of both Lewis and Brønsted acid catalysts (Table 2).

Table 2 – Initial Catalyst Screen



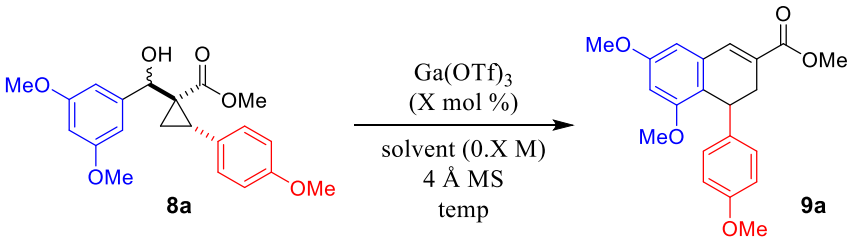
entry[a]	acid (mol %)	solvent (temp °C)	time (h)	yield (%)[b]
1	BF_3•Et_2O (110)	CH_2Cl_2 (23)	1	47[c]
2	$In(OTf)_3$ (15)	CH_2Cl_2 (23)	24	28
3	$Sc(OTf)_3$ (15)	CH_2Cl_2 (23)	24	20
4	$SnCl_4$ (15)	CH_2Cl_2 (23)	24	26
5	TfOH (15)	CH_2Cl_2 (23)	0.33	54
6	TsOH (15)	CH_2Cl_2 (23)	18	8
7	$GaCl_3$ (15)	CH_2Cl_2 (23)	18	48
8	$Ga(OTf)_3$ (15)	CH_2Cl_2 (23)	1	53
9	$Bi(OTf)_3$ (15)	CH_2Cl_2 (23)	0.33	49
10	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	18	58
11	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	18	61

[a]Reaction performed with **8a**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of **9a** after column chromatography. [c]Performed at 0.2 M concentration.

Modest yields were obtained using one set of Nishii's optimized conditions (entry 1), which we used for initial product identification and as a comparison to see the target yield for our optimization substrate. When **8a** was treated with 15 mol % $In(OTf)_3$, $Sc(OTf)_3$, or $SnCl_4$ the desired dihydronaphthalene **9a** was obtained with poor yields (entries 2, 3, and 4). When employing Brønsted acids, modest yields of **9a** were afforded using 15 mol % of TfOH (54%, entry 5), whereas poor yields were afforded using 15 mol % of TsOH (8%, entry 6). $Ga(OTf)_3$ has been successfully shown to catalyze the reactions of aryl carbinols,[7] and Bi(III) complexes have been demonstrated to effectively activate

alcohols for substitution reactions.[8] Modest yields were obtained using both $Ga(OTf)_3$ (53%, entry 8) and $Bi(OTf)_3$ (49%, entry 9). $GaCl_3$ was also used as a comparison to $Ga(OTf)_3$ with similar results (48%, entry 7); however, it is undesirable to work with as it requires dilutions at small scale and fumes when exposed to air, so we quickly determined that the triflate is preferable. We then observed that at 5 mol % both $Ga(OTf)_3$ and $Bi(OTf)_3$ generated higher product yields at 61% and 58%, respectively (entries 10 and 11). Other catalysts that were screened that did not show reactivity were $Yt(OTf)_3$, $Dy(OTf)_3$, $La(OTf)_3$, $Al(OTf)_3$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Cu(OTf)_2$, Cu(OTf)•Tol, $Ni(ClO_4)_2$•$6H_2O$, PPTS, and L-proline.

Table 3 – Condition Optimization with $Ga(OTf)_3$



entry[a]	acid (mol %)	solvent (temp °C)	conc. (M)	time (h)	yield (%)[b]
1	30	CH_2Cl_2 (23)	0.1	1.5	35
2	15	CH_2Cl_2 (23)	0.1	2	48
3	10	CH_2Cl_2 (23)	0.1	4.5	55
4	5	CH_2Cl_2 (23)	0.1	4.5	61
5	1	CH_2Cl_2 (23)	0.1	24	5
6	5	CH_2Cl_2 (23)	0.5	20	24
7	5	CH_2Cl_2 (23)	0.2	4	47
8	5	CH_2Cl_2 (23)	0.05	20	49
9	5	CH_2Cl_2 (0)	0.1	1	23
10	5	CH_2Cl_2 (40)	0.1	1	51
11	5	1,2-DCE (84)	0.1	0.5	ND[c]
12	5	CH_3CN (23)	0.1	18	15
13	5	Toluene (23)	0.1	24	28
14	5	Et_2O (23)	0.1	24	NR
15	5	THF (23)	0.1	24	NR

[a]Reaction performed with **8a**, $Ga(OTf)_3$ at indicated catalyst loading, 4 Å molecular sieves, and solvent at given temperature and concentration. [b]Isolated yield of **9a** after column chromatography. [c]Not determined (ND) due to formation of intractable mixture. NR = No reaction.

At this stage, we intended to move forward with $Ga(OTf)_3$ as the preferred catalyst, as it slightly outperformed $Bi(OTf)_3$. The next step in our study was to optimize the concentration, temperature, catalyst loading, and solvent choice (Table 3). First, we probed catalyst loading ranging from 1 mol % to 30 mol % (entries 1-5), with a 5 mol % loading being preferred, which we held constant for the remainder of the optimization. We next probed changes in reaction concentration (entries 6-8) from 0.5 M to 0.05 M with no improvements over a 0.1 M concentration. Temperatures were also screened from 0 °C to

84 °C, using 1,2-DCE as the solvent to reach the highest temperature (entries 9-11). Reducing temperature below room temperature resulted in less reactivity, whereas increasing beyond room temperature increased side products observed, thereby reducing yield. Lastly, alternative solvents were also screened, with significantly reduced yields observed for acetonitrile and toluene (entries 12 and 13) and no reactivity observed for diethyl ether or tetrahydrofuran (entries 14 and 15). From the screening, we determined that the conditions in Table 3 entry 4 were the optimal conditions for our desired reactivity.

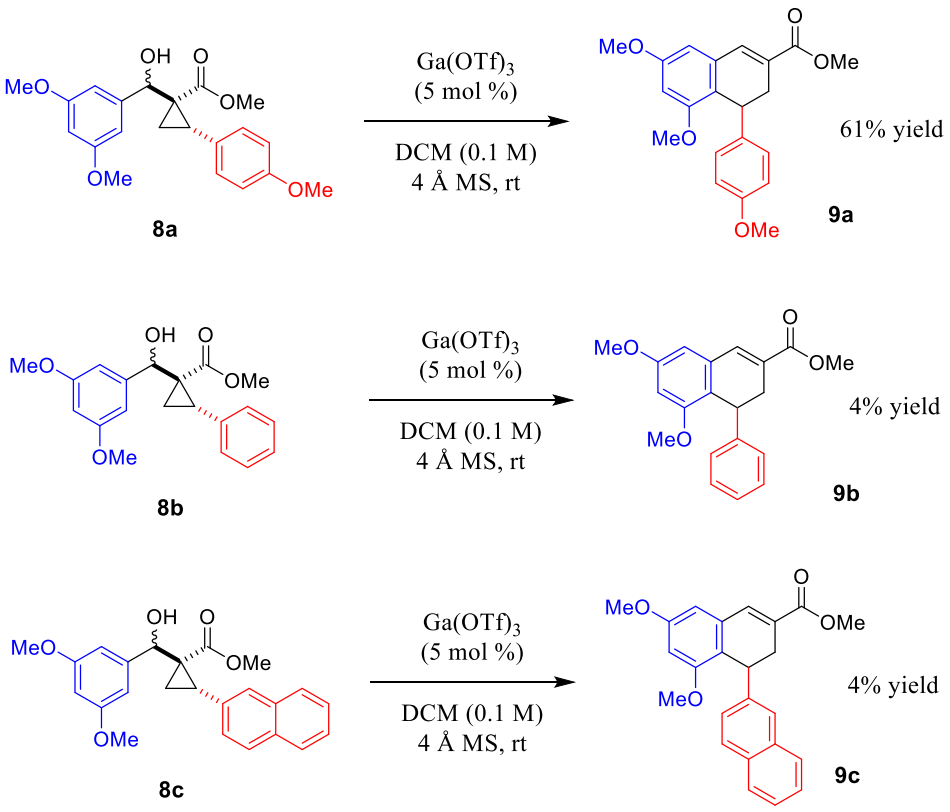


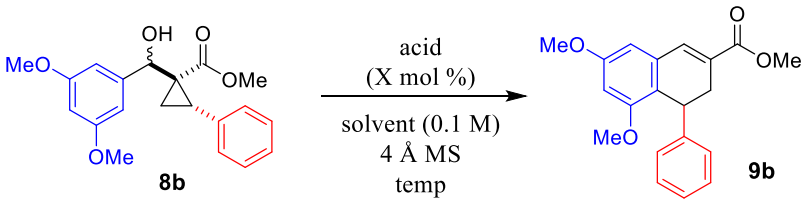
Figure 8 – Substrate Scope Attempt with $Ga(OTf)_3$

With what we thought were optimum conditions, we made a move toward probing substrate scope (Figure 8). Unfortunately, we quickly found that $Ga(OTf)_3$ was not the ideal catalyst, and we halted further scope exploration. The first two substrates we attempted beyond our optimization substrate **8a** were **8b** and **8c**, each with a variation to the donor on the cyclopropane. The shift from a strong donor in **8a** to more moderate donors resulted in both significant side products and reduced overall reactivity. Disappointingly, they both gave yields of 4%, indicating that our optimized conditions were insufficient for the reactivity we sought. Substrate **8c** was not revisited for the remainder of the study due to similarity in performance to **8b,** an overall simpler substrate. We opted to re-optimize the reaction using substrate **8b** as the new optimization substrate with the rationale that if we could get that one to work well, the more favorable substrates should also respond accordingly.

For the new optimization, we analyzed both promising alternative acids from the first catalyst screen as well as a handful of new potential catalysts (Table 4). Drawing conclusions from earlier optimizations, solvents were limited to DCM and 1,2-DCE, concentrations were kept at 0.1 M, and temperatures were kept at or above room temperature. A couple of previously presented $Ga(OTf)_3$ reactions are presented for the sake of easy comparison (entries 1 and 2). The first catalyst we focused on for optimization with substrate **8b** was $Bi(OTf)_3$, which had shown nearly comparable results to $Ga(OTf)_3$ for substrate **8a** and has the benefit of being easily handled. Maintaining the optimized catalyst loading of 5%, first a temperature screen was done from room temp to 84 °C, showing an overall significant improvement over $Ga(OTf)_3$ and incremental increases as the temperature increased (entries 3-5). Attempts to increase yield using a higher loading

of $Bi(OTf)_3$ were unsuccessful (entries 6 and 7). Although $Bi(OTf)_3$ showed considerable improvement over $Ga(OTf)_3$, the best yields we had were still poor, so we decided to next investigate another acid that showed promise in an earlier screening – triflic acid.

Table 4 – Re-optimization on Substrate 8b



entry[a]	acid (mol %)	solvent (temp °C)	time (h)	yield (%)[b]
1	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	18	4
2	$Ga(OTf)_3$ (5)	1,2-DCE (84)	1.5	ND[c]
3	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	18	22
4	$Bi(OTf)_3$ (5)	CH_2Cl_2 (40)	1	25
5	$Bi(OTf)_3$ (5)	1,2-DCE (84)	1	30
6	$Bi(OTf)_3$ (15)	1,2-DCE (84)	0.33	30
7	$Bi(OTf)_3$ (30)	1,2-DCE (84)	0.33	29
8	TfOH (15)	CH_2Cl_2 (23)	1	14
9	TfOH (15)	CH_2Cl_2 (40)	1.5	25
10	TfOH (5)	1,2-DCE (84)	2.5	30
11	TfOH (10)	1,2-DCE (84)	1	33
12	TfOH (15)	1,2-DCE (84)	0.5	37
13	TfOH (30)	1,2-DCE (84)	0.33	38
14	TfOH (100)	1,2-DCE (84)	0.17	43
15	TfOH (15)	1,2-DCE (23)	18	17
16	TFA (30)	1,2-DCE (84)	18	NR
17	H_2O•TsOH (30)	1,2-DCE (84)	18	23
18	MsOH (15)	1,2-DCE (84)	18	21
19	Tf_2NH (20)	1,2-DCE (84)	0.17	29
20	Tf_2NH (10)	1,2-DCE (84)	2	17
21	$Ca(NTf_2)_2$ (5) *n*-Bu_4NPF_6 (5)	CH_2Cl_2 (40)	24	NR
22	$Ca(NTf_2)_2$ (5) *n*-Bu_4NPF_6 (5)	1,2-DCE (84)	0.33	26
23	$Ca(NTf_2)_2$ (1) *n*-Bu_4NPF_6 (1)	1,2-DCE (84)	1	26
24	$Sc(OTf)_3$ (110)	1,2-DCE (84)	1	40
25	BF_3•Et_2O (110)	CH_2Cl_2 (23)	1	17

[a]Reaction performed with **8b**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of **9b** after column chromatography. [c]Not determined (ND) due to formation of an intractable mixture. NR = No reaction.

Triflic acid has some inherent benefits and detriments. Compared to many of the Lewis acid catalysts it is cheaper; however, it is much more difficult to handle from a practicality standpoint. We first screened temperature and solvent with a 15 mol % loading of TfOH (entries 8, 9, and 12). Like $Bi(OTf)_3$, increases in temperature lead to increases in yield – but with a greater effect size than was observed with $Bi(OTf)_3$, leading to overall higher yields. Next, acid loading was explored ranging from 5 mol % to stoichiometric (entries 10-14). Meaningful gains were observed between 5 mol % and 10 mol %, but returns diminished beyond 15 mol %, resulting in entry 12 being the new optimum conditions with a yield of 37%.

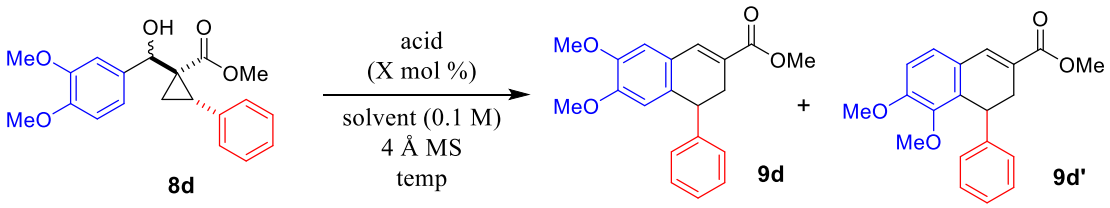
Up to this point most of the catalysts we screened had been Lewis acids. With the new optimum conditions belonging to a Brønsted acid rather than a Lewis acid, we decided that it would be prudent to test some more Brønsted acids next in an attempt to further improve yields. Unfortunately neither weaker acids (entries 16-18) nor a stronger acid (entries 19 and 20) improved yields for the reaction.

During our attempts at improving these generally low yields, we became fascinated by highly Lewis acidic calcium complexes that have been pioneered by Niggemann[9] and others.[10] Abundant in the earth's crust, calcium is inexpensive and considered nontoxic even in large quantities.[9,10] In one series of relevant examples, Ca complexes have been shown to generate carbocations from alcohols (via C−O bond cleavage) that can be used to alkylate arenes.[9a,10c] We decided to do what any curious scientist should do, and we tried it out. The Niggemann combination of $Ca(NTf_2)_2$ and additive *n*-Bu_4NPF_6 in equal molar parts showed no reactivity at reflux in DCM (entry 21). With increased temperature,

however, it did provide a 26% yield of **9b** (entry 22) with no reduction in yield with a surprisingly low 1 mol % loading (entry 23).

After this long series of reactions, we were beginning to realize that substrate **8b** itself is quite resistant to the desired reactivity we were looking for – generating complex mixtures of degradation products in nearly every reaction. We decided to expose **8b** to the optimized conditions laid out by Nishii to see what would happen. Unsurprisingly, the reaction outcomes were not stellar (entries 24 and 25). With this we realized that we should probably test some of our best conditions on an alternate substrate that has already shown good yields by Nishii. We chose one (**8d**) that was similar to **8b**, but with one aryl methoxy shifted from the *meta*-position to the *para*-position.

Table 5 – Final Optimization Substrate



entry[a]	acid (mol %)	solvent (temp ºC)	time (h)	yield **9d** (%)[b]	yield **9d'** (%)[b]
1	$Sc(OTf)_3$ (110)	1,2-DCE (84)	1	61	-
2	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	2.5	ND[c]	-
3	$Ga(OTf)_3$ (5)	1,2-DCE (84)	0.5	62	-
4	$Bi(OTf)_3$ (10)	CH_2Cl_2 (23)	18	28	-
5	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	1	NDP[d]	-
6	$Bi(OTf)_3$ (5)	CH_2Cl_2 (40)	1	49	-
7	$Bi(OTf)_3$ (5)	1,2-DCE (84)	0.5	39	-
8	TfOH (15)	CH_2Cl_2 (23)	0.5	ND[c]	-
9	TfOH (15)	1,2-DCE (84)	18	36	-
10	$Ca(NTf_2)_2$ (10) *n*-Bu_4NPF_6 (10)	1,2-DCE (84)	0.33	62	6
11	$Ca(NTf_2)_2$ (5) *n*-Bu_4NPF_6 (5)	1,2-DCE (84)	0.33	72	7
12	$Ca(NTf_2)_2$ (2.5) *n*-Bu_4NPF_6 (2.5)	1,2-DCE (84)	0.5	75	8
13	$Ca(NTf_2)_2$ (1) *n*-Bu_4NPF_6 (1)	1,2-DCE (84)	0.5	76	9
14	$Ca(NTf_2)_2$ (5) *n*-Bu_4NPF_6 (5)	CH_2Cl_2 (23)	24	NR	NR
15	Tf_2NH (10)	1,2-DCE (84)	0.25	75	8
16	Tf_2NH (1)	1,2-DCE (84)	0.5	41	4
17	$Ca(NTf_2)_2$ (5)	1,2-DCE (84)	24	21	2

[a]Reaction performed with **8d**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of product after column chromatography. [c]Not determined (ND) due to formation of an intractable mixture. [d]No desired product (NDP) formed from reaction. NR = No reaction.

Substrate **8d** was one of the substrates in Nishii's initial report, with a yield of 80% under the stoichiometric $Sc(OTf)_3$ conditions.[3] Confident we should be able to achieve good yields with this substrate, we set out to revisit some of our most promising conditions we previously worked with in hopes of settling on an optimum set of conditions (Table 5).

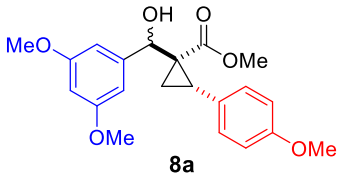
First, we replicated Nishii's conditions, but ended up with a lower yield of 61% for unknown reasons (entry 1). 5 mol % $Ga(OTf)_3$ at low temperatures gave a complicated mixture (entry 2) whereas at high temperatures gave a clean reaction with a 62% yield of **9d** (entry 3). $Bi(OTf)_3$ did not work as well as $Ga(OTf)_3$ for this substrate, as attempts to improve yields to above 50% through temperature and loading optimization all proved fruitless (entries 4-7). Reaction outcomes for TfOH closely resembled those for $Bi(OTf)_3$, (entries 8 and 9).

Switching to the calcium catalyst system of $Ca(NTf_2)_2$ and additive *n*-Bu_4NPF_6 resulted in our most promising results for substrate **8d**. It also was the first occurrance of observing product **9d′** as a minor product. It is the regioisomer resulting from an asymmetric aryl group off the carbinol. It shows the desired reactivity, but at the more sterically hindered site of the aryl ring in **8d**. A brief screening of loadings gratifyingly indicated 1 mol % as the optimum catalyst loading for this substrate, with an overall yield of 85% - outperforming Nishii's reported yield with stoichiometric $Sc(OTf)_3$ conditions. Tf_2NH showed reactivity that was more similar to the calcium system than TfOH (entries 15 and 16). A control was done to ensure the necessity of the additive in the calcium catalyst system (entry 17); results indicate that the additive is crucial for desired catalysis to occur.

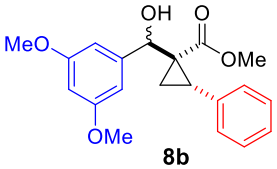
At this point we could definitively say that we had viable methods for catalytic activation of cyclopropyl carbinols that can meet or exceed the previously reported stoichiometric methods. We did not, however, have an obvious catalyst that was overwhelmingly or consistently better than other catalysts. To discern what set of conditions to use for the remainder of the study, we decided to look at identical reactions

across the full set of optimization substrates for direct comparison. To do this we used the following catalyst systems: (i) $Ga(OTf)_3$ (5 mol %), (ii) TfOH (15 mol %), (iii) $Bi(OTf)_3$ (5 mol %) at both elevated and room temperatures and (iv) $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 complex (1 mol %) solely at elevated temperatures as no reactivity is observed at room temperature (Table 6). These catalyst systems represent the pool of best conditions identified from the multiple rounds of optimization.

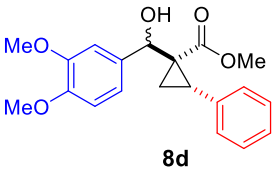
Table 6 – Comparison of Best Conditions



8a



8b



8d

entry[a]	acid (mol %)	solvent (temp ºC)	yield **9a** (%)[b]	yield **9b** (%)[b]	yield **9d** (%)[b,c]
1	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	61	4	ND[d]
2	$Ga(OTf)_3$ (5)	1,2-DCE (84)	ND[d]	ND[d]	62
3	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	58	22	NDP[e]
4	$Bi(OTf)_3$ (5)	1,2-DCE (84)	ND[d]	30	39
5	TfOH (15)	CH_2Cl_2 (23)	57	14	ND[d]
6	TfOH (15)	1,2-DCE (84)	ND[d]	37	36
7	$Ca(NTf_2)_2$ (1) *n*-Bu_4NPF_6 (1)	1,2-DCE (84)	54	26	85

[a]Reaction performed with **8a**, **8b**, or **8d**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of product after column chromatography. [c]Reported yield is combined yields of **9d** and **9d'**. [d]Not determined (ND) due to formation of an intractable mixture. [e]No desired product (NDP) formed from reaction.

Missing data points were filled for any matches of conditions and substrates that were not naturally filled in the optimization process. Looking at the simplified picture

provided by Table 6, we were able to determine our optimized conditions. Although $Ga(OTf)_3$ had a two good data points, it also had the most issues all around (entries 1 and 2). It is also apparent from this table that $Bi(OTf)_3$ and TfOH have remarkably similar reactivity patterns (entries 3-6). The calcium catalyst system stands apart from them on a few different levels. One is that it is the only set of conditions that consistently gave isolable product for all three substrates. The second is that it far outperforms the other conditions for substrate **8d** while maintaining reactivities for **8a** and **8b** that are on par with the others. Lastly, it works at a much lower catalyst loading than any of the other catalysts. With this, we determined our optimum conditions to be the $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 complex at 1 mol % loading in refluxing 1,2-DCE at a 0.1 M concentration with added 4 Å molecular sieves. This marked the completion of our second goal for this project: identifying the appropriate conditions to promote catalysis.

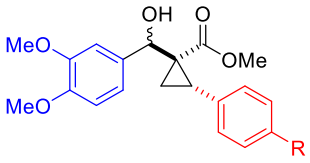
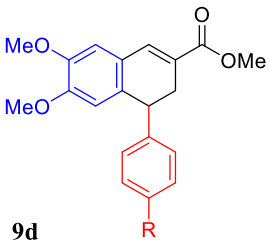
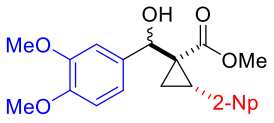
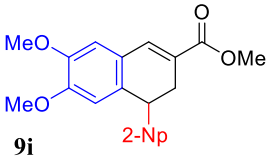
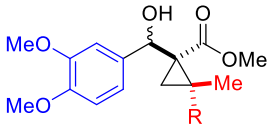
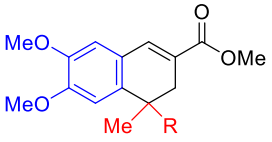
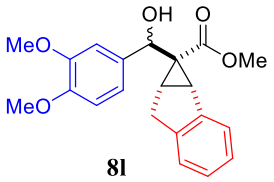
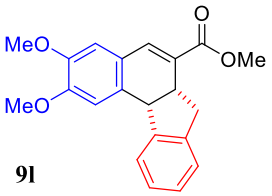
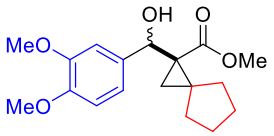
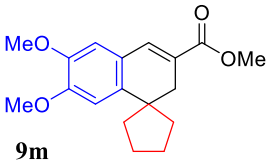
Although our second goal had been met and we started to address our third, a couple of questions remained about the nature of the calcium catalyzed reaction. One was the necessity of molecular sieves, which we tested through omission and observed that they generally assist with the reaction by decreasing side products, resulting in minor improvements to yield and ease of product isolation. The other question we had was if the true catalyst of the reaction was the $Ca(NTf_2)(PF_6)$ active catalyst species or Tf_2NH generated *in-situ*. Table 4 entries 19-23 and Table 5 entries 10-16 indicate that the active calcium catalyst must play some role, as lower loadings of the calcium system more effectively catalyze the reaction than Tf_2NH, which occasionally did not consume all the starting material. It does remain, however, that Tf_2NH does promote the reaction and we were unable to rule out the possibility of a synergistic Lewis and Brønsted acid effect,

especially given the elevated temperatures in the optimum conditions that may facilitate formation of trace amounts of Tf_2NH.

2.4 Substrate Scope

Our final goal was to more fully explore the scope of the reaction in order to observe its strengths and weaknesses. We first explored a scope of substrates that probed changes to the donor group of the cyclopropane while conserving the rest of the molecule, based on the 3,4-dimethoxyphenyl carbinol optimization substrate **8d** (Table 7, entry 1). 4-Methylphenyl cyclopropane **8e** gave **9e** in 93% yield as a 12:1 regioisomeric mixture (entry 2). 4-Methoxyphenyl cyclopropane **8f** cleanly afforded **9f** as the only regioisomer in 90% yield (entry 3). 4-Bromo- and 4-chlorophenyl cyclopropanes **8g** and **8h** each provided their respective dihydronaphthalenes **9g** and **9h** in 75% and 68% yield with a 10:1 rr (entries 4 and 5), although they required a higher catalyst loading of 5 mol % and longer reaction time in order to go to completion. The 2-naphthyl cyclopropane **8i** generated **9i** in 97% yield with a 12:1 rr (entry 6). The pattern we see from these substrates is that a stronger donor on the cyclopropane results in better reactivity. Phenyl rings with donors (entries 2, 3, and 6) outperform an unsubstituted phenyl ring (entry 1), whereas substrates with electron withdrawing substituents on the phenyl ring (entries 4 and 5) underperform an unsubstituted phenyl ring.

Table 7 – Cyclopropane Donor Scope

entry[a]	carbinol 8	product 9	yield of 9 (%)[b]	*rr* (**9**:**9'**)[c]
				
1	**8d** (R = H)	**9d**	76(85)	8:1
2	**8e** (R = Me)	**9e**	86(93)	12:1
3	**8f** (R = OMe)	**9f**	90	>99:1
4[d]	**8g** (R = Br)	**9g**	68(75)	10:1
5[d]	**8h** (R = Cl)	**9h**	62(68)	10:1
6	 **8i**	 **9i**	89(97)	12:1
				
7	**8j** (R = Ph)	**9j**	89(94)	19:1
8[d]	**8k** (R = 3-thienyl)	**9k**	86	>99:1
9[d]	 **8l**	 **9l**	31	>99:1
10[d]	 **8m**	 **9m**	36[e,f]	>99:1

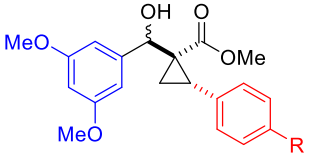
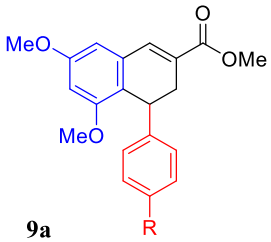
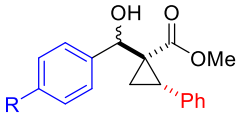
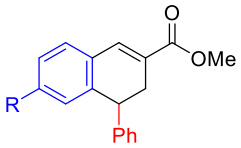
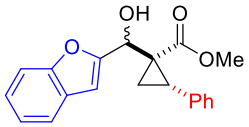
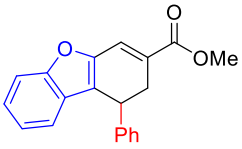
[a]Reactions performed with cyclopropane **8**, $Ca(NTf_2)_2$ (1 mol %), *n*-Bu_4NPF_6 (1 mol %), and 4 Å molecular sieves in 1,2-DCE (0.1 M) at reflux. [b]Isolated yield of **9** after column chromatography. Yields in parentheses represent combined isolated yields of **9** and **9'**. [c]Ratio of isolated yields of **9** to regioisomer **9'** (if applicable). [d]Performed using $Ca(NTf_2)_2$ (5 mol %), and *n*-Bu_4NPF_6 (5 mol %). [e]Yield based on ^1H NMR using dimethyl terephthalate as an internal standard. [f]Inseparable mixture.

Disubstituted cyclopropanes were the next focus of our scope exploration. Gratifyingly, 2-methyl-2-phenyl-substituted cyclopropane **8j** gave **9j** with high yield and regioselectivity (94%, 19:1 rr) (entry 7). Similarly, the 2-methyl-2-(3-thienyl) cyclopropane **8k** provided **9k** in 86% yield with a >99:1 rr (entry 8). In contrast, indanyl-fused cyclopropane **8l** resulted in a more complex reaction mixture, and only a modest 31% yield of **9l** was isolated (entry 9) due to competing elimination following ring-opening. Given that all of the previous examples employed (hetero)-aryl substituents on the cyclopropane, we were particularly interested in the compatibility of alkyl substituents. Unfortunately, when the spiro[2.4]heptane **8m** was subjected to the reaction conditions, an inseparable mixture was obtained that, based on qualitative NMR, contained 36% yield of **9m** (entry 10).

The second set of substrates we explored focused on changes to the carbinol substituent (Table 8). Already presented were the optimization substrates **8a** and **8b** (entries 1 and 2), which sport a 3,5-dimethoxyphenyl substituent off the carbinol. Removing the methoxy groups from the aryl carbinol substituent (as in **8n**) afforded **9n** in 40% NMR yield as an inseparable mixture (entry 3). Placing one methoxy group in the 4-position (as in **8o**) still allows for cyclization to occur in good yield (63%, entry 4). Finally, exchanging the aryl carbinol substituent with a heteroaryl group (as in 2-benzofuran for **8p**) is well tolerated as the anticipated cyclohexenyl-fused benzofuran **9p** is generated in 65% yield (entry 5). From these entries, another clear pattern emerges that sheds light onto our optimization substrate issues. Donating capacity of the aryl groups to the carbinol has a significant effect on the reaction, presumably during the activation step of the carbinol. The dimethoxyphenyl in substrates **8a** and **8b** has a destabilizing effect relative to as simple

phenyl group in **8n**. A properly placed methoxy on the phenyl is stabilizing, as in **8o**, resulting in reactivity where **8o**>**8n**>**8b**. A strong donor on the cyclopropane ring can help to overcome this issue, as seen with **8a**; however, it cannot be entirely resolved.

Table 8 – Secondary Carbinol Substrate Scope

entry[a]	carbinol 8	product 9	yield of **9** (%)[b]
			
1	**8a** (R = OMe)	**9a**	54
2	**8b** (R = H)	**9b**	26
			
3[c]	**8n** (R = H)	**9n**	40[d,e]
4[c]	**8o** (R = OMe)	**9o**	63
			
5	**8p**	**9p**	65

[a]Reactions performed with cyclopropane **8**, $Ca(NTf_2)_2$ (1 mol %), *n*-Bu_4NPF_6 (1 mol %), and 4 Å molecular sieves in 1,2-DCE (0.1 M) at reflux. [b]Isolated yield of **9** after column chromatography. Yields in parentheses represent combined isolated yields of **9** and **9'**. [c]Performed using $Ca(NTf_2)_2$ (5 mol %), and *n*-Bu_4NPF_6 (5 mol %). [d]Yield based on ^{1}H NMR using dimethyl terephthalate as an internal standard. [e]Inseparable mixture.

Lastly, two tertiary carbinols were synthesized and studied for their compatibility under the reaction conditions (Figure 9). Cyclopropane **8q**, containing a methyl carbinol substituent, yields its expected product **9q** in 53% as the only observed regioisomer (Figure

9, top). Cyclopropane **8r**, containing both phenyl and 3,4-dimethoxyphenyl carbinol substituents, afforded two products **9r** and **9r″** in 49% and 28% yield, respectively (Figure 9, bottom). The minor product **9r″** arose from the competing trapping of the allylcarbinyl cation intermediate by the phenyl group.

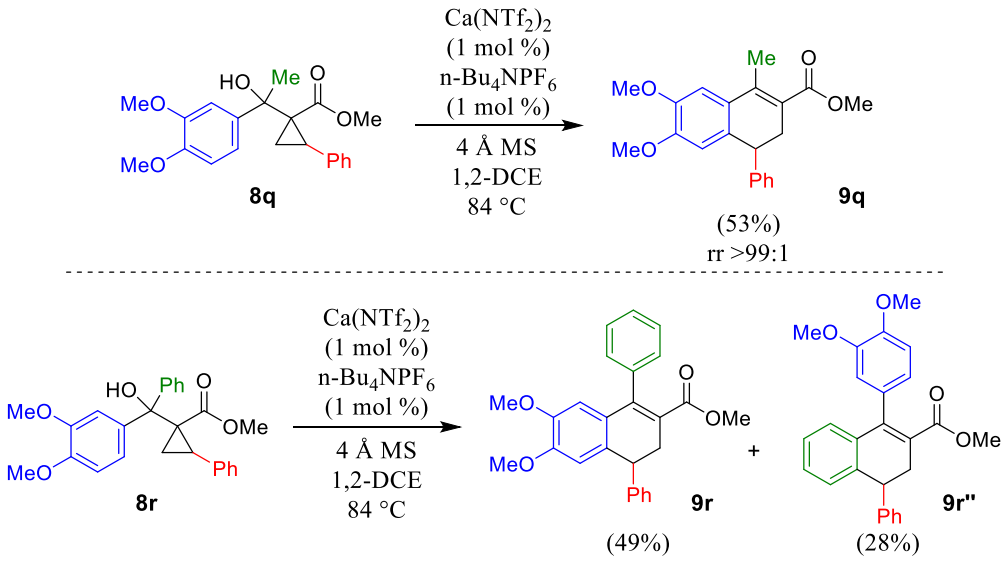


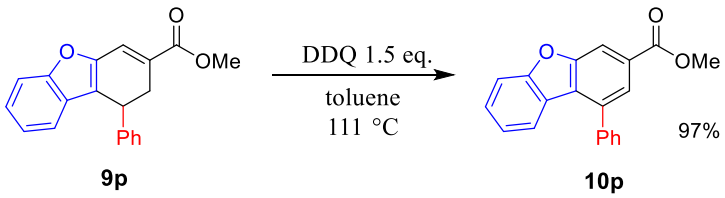
Figure 9 – Tertiary Carbinol Scope

This marked the completion of our third goal for this project: expanding the overall substrate scope. In total, we explored 17 different substrates and were able to identify some reactivity patterns that are useful for any synthetic chemist attempting to apply this method to their own substrates. Most notably are preferences for good donating capacity towards both the carbinol and the cyclopropane.

2.5 Derivatization

Not only does this method excel at accessing lignan core structures, the resulting products can also serve as synthetic building blocks and can be readily derivatized. For example, 2-carboxydihydronaphthalenes **9** have been shown to undergo dihydroxylation,[11] aminohydroxylation,[12] epoxidation,[13] aziridination,[14] conjugate addition,[15] [3 + 2] cycloaddition with CH_2N_2,[16] and oxidation with DDQ.[17]

In keeping with our ongoing interest in accessing benzofused heteroaromatic compounds, we decided to showcase this reaction by exposing **9p** to DDQ oxidation to afford the functionalized dibenzofuran **10p** in 97% yield (Scheme 6). This reaction is noteworthy as functionalized dibenzofurans represent a family of naturally-occurring secondary metabolites from plants, fungi and lichen.[18]



Scheme 6 – DDQ Oxidation of 9p

2.6 Conclusions

In conclusion, we have disclosed a calcium-catalyzed, dehydrative, ring-opening cyclization of cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes in up

to 97% yield. The overall specific merits of our approach include the following: (1) the utilization of earth-abundant calcium as the catalyst system with low loadings (1 mol %); (2) the first examples of catalysis for this type of intramolecular ring-opening cyclization; (3) a straightforward synthetic sequence to access the cyclopropyl carbinols from the corresponding D−A cyclopropanes; and (4) a broader substrate scope.

More broadly, the new method provides an increase in molecular diversity readily available to synthetic chemists utilizing the D-A cyclopropanes we used in our group with the formal homo-Nazarov cyclization. This newly efficient reactivity, accessible from a simple reduction or nucleophilic attack of the D-A cyclopropyl ketone, leads to reactivity that can be described as a dehydrative, formal homo-Nazarov type cyclization – resulting in core structures differing from those that direct use of the formal homo-Nazarov cyclization generates. In addition, observations we made through the course of developing this reaction laid the foundations for the rest of the following research found in this thesis.

2.7 Experimental

The experimental section and characterization for compounds in Chapter 2 can be found in the Supporting Information of the article: Sandridge, M. J.; France, S. *Org. Lett.* **2016**, *18*, 4218.

2.8 References

1) Sandridge, M. J.; France, S. *Org. Lett.* **2016**, *18*, 4218.

2) (a) Martin, M. C.; Shenje, R.; France, S. *Isr. J. Chem*. **2016**, *56*, 499. (b) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev*. **2014**, *43*, 804.

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CHAPTER 3. UNDERSTANDING DEHYDRATIVE CYCLOPROPYL CARBINOL CYCLIZATIONS: NEW CATALYST-DIRECTED CHEMODIVERGENCE TOWARDS A-ALKYLIDENE-Γ-BUTYROLACTONES[*,1]

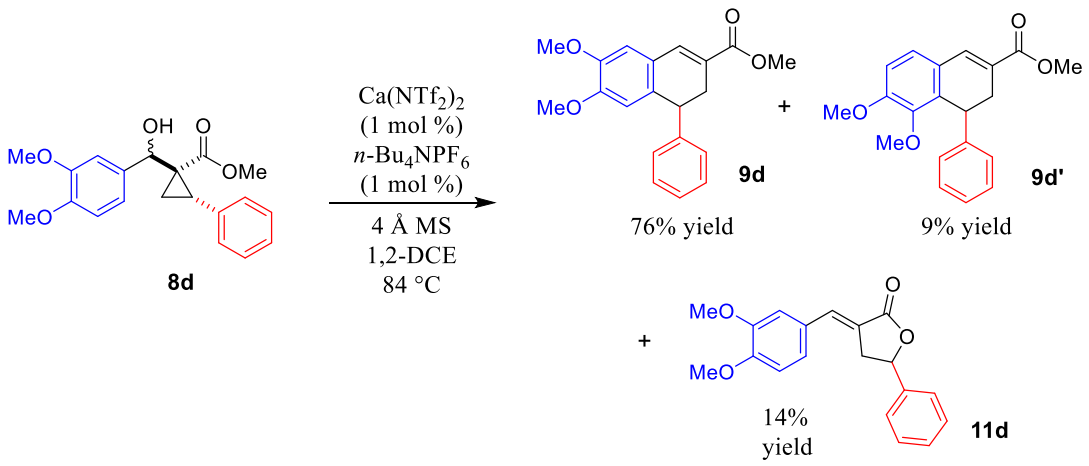
3.1 Avenues Towards α-Alkylidene-γ-butryolactones

It is generally good practice for a synthetic chemist to isolate and identify every product formed from a reaction, especially if it is a new reaction. Identities and yields of all products (whether desired or undesired) can give valuable information about how the reaction proceeds, and in methodology development can also provide insights for how to change the reaction conditions to better access the desired reactivity. On occasion, it can also lead to some serendipitous discoveries of new types of desirable reactivity. This is particularly valuable with DOS in mind, where a new branching point might be found that can be leveraged to quickly access a greater diversity of interesting compounds.

While developing the dehydrative, formal homo-Nazarov type cyclization discussed in Chapter 2,[2] we experienced this sort of serendipitous discovery of a new type of reactivity because we were diligent about isolating and characterizing everything we made. Only the desired dihydronaphthalenes and undesirable side products were formed during our optimization studies for substrates **8a** and **8b**; however, when we switched to our third optimization substrate **8d** we began to observe a new, interesting product. For

[*] Work on this project performed in collaboration with Brett D. McLarney and Corey W. Williams. Adapted with permission from *J. Org. Chem.* **2017**, *82*, 10883. Copyright 2017 American Chemical Society.

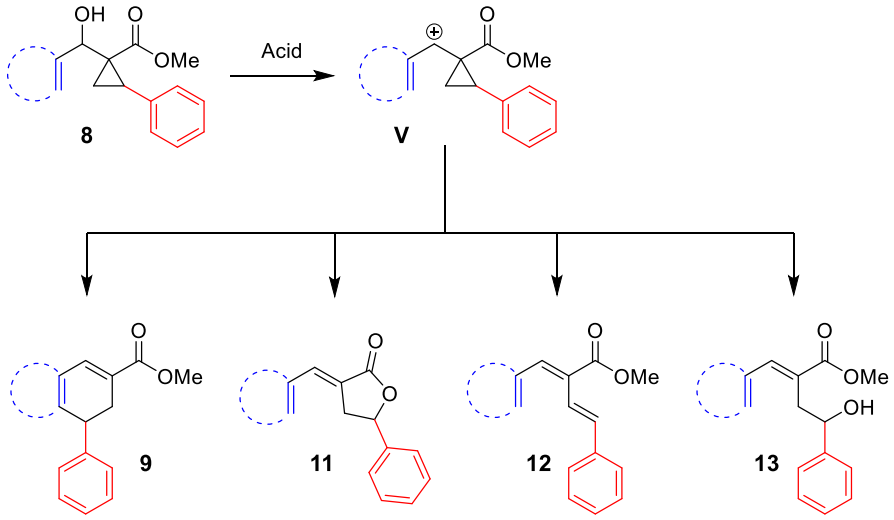
example, we found that when cyclopropyl carbinol **8d** was subjected to the optimized reaction conditions, 14% yield of α-alkylidene-γ-butyrolactone (ABL) **11d** was obtained in addition to the expected dihydronaphthalenes **9d** and **9d′** (Scheme 7). Product **11d** was unexpected, as no mention of α-alkylidene-γ-butyrolactone formation had been reported in the previous literature for the acid-promoted transformations of π-activated cyclopropyl carbinols.[3]



Scheme 7 – ABL Formation from Cyclopropyl Carbinols

During our exploration of ring opening cyclizations of cyclopropyl carbinols, we actually observed four different product types (Scheme 8). We predicted that each product formed after and/or during ring-opening of intermediate **V**, which forms upon acid promoted dehydroxylation of carbinols **8**. The first type of reactivity to form dihydronaphthalene products **9** arises from aryl trapping. ABL products **11** arise from ester trapping followed by hydrolysis, and products **12** and **13** arise from elimination and water

trapping respectively. Unfortunately, products **12** and **13** are not desirable, so we decided they were unproductive pathways that needed to be kept in mind as competing pathways. Fortunately, the instances in which **12** was encountered were few, and formation of **13** could be mostly avoided through the use of molecular sieves.



Scheme 8 – Product Outcomes from Cyclopropyl Carbinol Activation

The α-alkylidene-γ-butyrolactone framework, however, represents an important structural motif to both organic and medicinal chemists (Figure 10). It is found in a vast collection of natural products and potential therapeutics with significant biological activities including anticancer, anti-inflammatory, antibacterial, antifungal, and antiviral.[4] ABLs are also useful building blocks for chemical synthesis due to their facile derivatizations.[5] It was estimated that by 2009 there were more than 5000 identified ABL natural products along with another 9000 synthetic analogues.[6] Synthesis of the ABL

framework is an ongoing endeavor for the synthetic community. As such, several extensive reviews have been published highlighting the diverse approaches that can be taken toward the scaffold.[4,6,7]

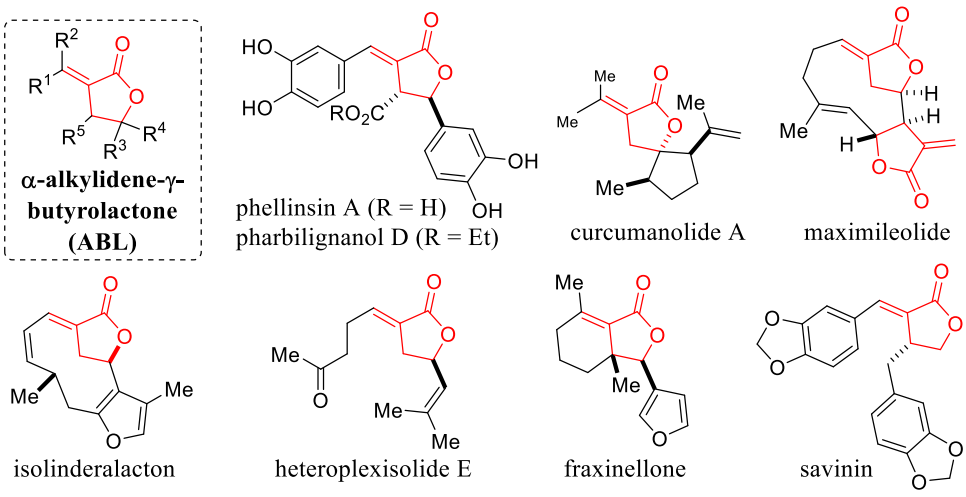
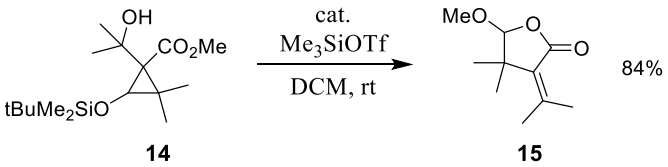


Figure 10 – ABL Core Structures in Natural Products

The general synthetic approaches to the ABL core have been classified into the following types: alkylidenation of γ-butyrolactones,[8] various lactonization approaches,[9] tandem (or sequential) intramolecular C-H insertion/olefination,[10] the Dreiding-Schmidt organometallic approach,[11] cross-methathesis between α-methylene-γ-butyrolactones and olefins,[12] intramolecular enyne metathesis reactions,[13] Pd-catalyzed cross-couplings,[14] Diels-Alder and retro-Diels-Alder reactions,[15] radical cyclizations,[16] and Baeyer-Villiger reactions on cyclobutanones.[17] Despite the abundant literature, the diversity within the

ABLs has made the pursuit of strategic ABL targets and the development of methodologies to access them persistently meaningful endeavors in the synthetic community.[18]



Scheme 9 – ABL from Cyclopropyl Carbinol Literature Precedent

While ABLs have been generated from the reactions of vinyl cyclopropanes with substituted benzaldehydes in the presence of DABCO,[19] only one example of their synthesis from a cyclopropyl carbinol has been reported (Scheme 9).[20] Brückner and Reissig were studying reactivities of methyl 2-siloxycyclopropanecarboxylates and were able to access many different highly substituted furanone derivatives, including the ABL **15**. The authors predict *in situ* generated TfOH from Me_3SiOTf catalyzed the reaction by causing desilylation, ring cleavage, and dehydration, resulting in compound **15**.

Intrigued by the formation of **11d**, we were particularly interested in discerning the factors that govern the chemoselectivity of the reaction (formation of **9** and/or **11**) and how they could be rationalized in terms of substituent effects. We envisioned that this knowledge would contribute to determining the conditions for selective ABL formation, establishing cyclopropyl carbinols **8** as useful common precursors to multiple different, yet desirable, core structures.

This type of approach represents one of the hallmarks of diversity-oriented synthesis.[21] The diversity of core structures is what sets DOS apart from target and combinatorial approaches to synthesis. Developing a new methodology that enables a major branching point towards entirely different, valuable scaffolds is particularly advantageous in the development of diversity-oriented synthetic strategies. With this in mind, we decided to pursue a new set of conditions for the dehydrative, ring opening cyclizations of cyclopropyl carbinols that preferentially formed the ABL core structure.

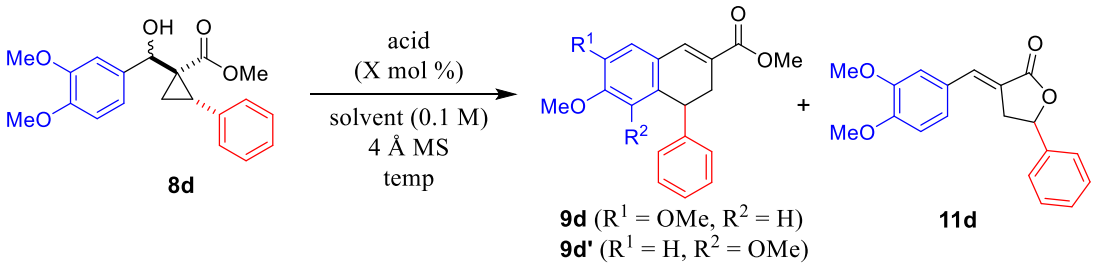
3.2 Optimization

We decided to use cyclopropyl carbinol **8d** as our optimization substrate for the selective synthesis of the ABL scaffold, as it was an optimization substrate for the previous study and it was the first substrate where we encountered ABL formation (Table 9). We already had experience and knowledge about the reactivity of these cyclopropyl carbinols, including a long list of catalysts and solvents that produce no reactivity whatsoever, making this optimization process simpler than the first.

We decided to focus our efforts on catalytic conditions that showed reactivity previously, while generally staying away from using stoichiometric Lewis acids (entry 1) and the calcium catalyst system (entries 2-4) we had previously explored, as they showed strong preference for dihydronaphthalene formation. Instead, we sought to focus on catalysts that had shown high conversion of starting materials with poor conversion to dihydronaphthalenes, as that would likely be a good area to find the competitive formation of ABL products. We decided to keep the best two sets of conditions: DCM at room temperature and 1,2-DCE at reflux, both with 0.1M concentrations and in the presence of

molecular sieves, as the best place to start with catalyst screens. Notably, in every instance where both sets of conditions were used for the same catalyst (entries 7-8, 11-12, and 15-16), the higher temperature reaction pushed the product ratios further in favor of products **9** and away from products **11**.

Table 9 – Catalyst Screening for ABL Formation



entry[a]	acid (mol %)	solvent (temp ºC)	time (h)	yield **9d** (%)[b]	yield **11d** (%)[b]
1	$Sc(OTf)_3$ (110)	1,2-DCE (84)	1	61	0
2	$Ca(NTf_2)_2$ (1) *n*-Bu_4NPF_6 (1)	1,2-DCE (84)	0.5	85	14
3	$Ca(NTf_2)_2$ (10) *n*-Bu_4NPF_6 (10)	1,2-DCE (84)	0.33	68	28
4	$Ca(NTf_2)_2$ (5) *n*-Bu_4NPF_6 (5)	CH_2Cl_2 (23)	24	NR	NR
5	$Sc(OTf)_3$ (15)	CH_2Cl_2 (23)	24	49	35
6	$In(OTf)_3$ (15)	CH_2Cl_2 (23)	24	45	39
7	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	2.5	ND[c]	27
8	$Ga(OTf)_3$ (5)	1,2-DCE (84)	0.5	67	18
9	$InCl_3$ (10)[d]	CH_2Cl_2 (23)	24	52	0
10	$GaCl_3$ (10)	CH_2Cl_2 (23)	2.5	67	ND[c]
11	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	1	ND[c]	62
12	$Bi(OTf)_3$ (5)	1,2-DCE (84)	0.5	39	55
13	$BiBr_3$ (10)[d]	CH_2Cl_2 (23)	24	18	0
14	$Bi(NO_3)_2$•$5H_2O$ (5)[d,e]	CH_2Cl_2 (23)	24	0	0
15	TfOH (15)	CH_2Cl_2 (23)	0.5	ND[c]	61
16	TfOH (15)	1,2-DCE (84)	0.5	26	62
17	TsOH (20)[d]	CH_2Cl_2 (23)	0.5	7	38
18	TFA (20)	CH_2Cl_2 (23)	0.5	NR	NR
19	Tf_2NH (10)	1,2-DCE (84)	0.25	83	0
20	[PyrH][OTf][d]	1,2-DCE (84)	2	18	trace
21	$Bi(OTf)_3$ (10) 2,5-di-*t*-Bu Pyr (30)	1,2-DCE (84)	24	NR	NR

[a]Reaction performed with **8d**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of product after column chromatography. Combined yields of **9d** isomers when appropriate. [c]Not determined (ND) due to formation of an intractable mixture. [d]Reaction did not go to completion, starting material recovered. [e]Water trapping product **13d** was formed in 12% yield. NR = No reaction.

Reactions of **8d** employing $In(OTf)_3$, $Sc(OTf)_3$, or $Ga(OTf)_3$ as catalysts each proceeded to completion at room temperature in DCM. $Sc(OTf)_3$ at 15 mol % loading produced 35% yield of ABL **11d** and 49% of **9d** (entry 5). $In(OTf)_3$ (15 mol %) provided a similar product profile, as **11d** 6a was formed in 39% yield along with 45% of **9d** (entry 6). A modest 27% yield of **11d** was obtained with 5 mol % of $Ga(OTf)_3$ along with **9d** as an intractable mixture (entry 7). $InCl_3$ (10 mol %) never reached completion, and gave a 52% combined yield of **9d** /**9d′** and no ABL product (entry 9). $GaCl_3$ (10 mol %) led to formation of 67% yield of **9d** along with an intractable mixture containing a minor amount of **11d** (entry 10).

In searching for effective catalysts for carbinol activation, we were intrigued by Bi(III) salts. Due to their synthetic utility, low toxicity, and low cost, Bi(III) salts are attractive reagents for the practicing organic chemist.[22] Over the past 15 years, a variety of Bi(III) compounds have been used in organic reactions as organobismuth reagents or as catalysts. They have been shown to be effective catalysts for etherification, allylation, cyanation, cycloaddition, and a host of protection/deprotection reactions.[23] Given this versatilty, we screened three Bi(III) salts in the reaction: $Bi(OTf)_3$, $BiBr_3$, and $Bi(NO_2)_3•5H_2O$.

$Bi(OTf)_3$ provided ABL **11d** in 62% yield as a single diastereomer (entry 11). A small amount of **9d** was also formed as an inseparable, complex mixture. In contrast, the reactions employing $BiBr_3$ and $Bi(NO_2)_3•5H_2O$ did not to go to completion after 24 h and failed to provide any ABL product (entries 13 and 14). In the case of $BiBr_3$, 18% of dihydronaphthalene **9d** was formed, whereas 12% of hydroxylated product **13d** was identified using $Bi(NO_2)_3•5H_2O$.

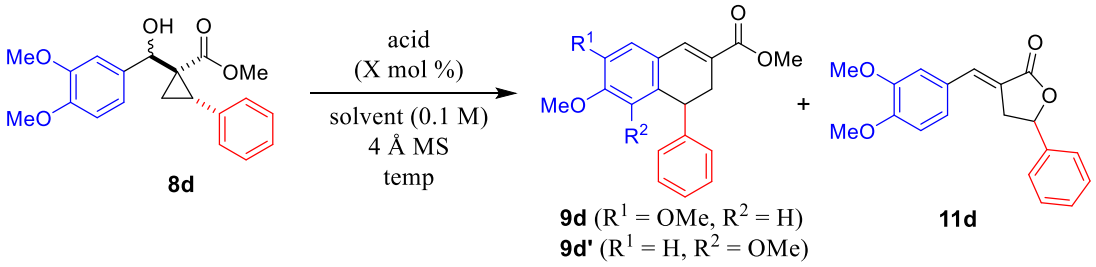
Due to the effectiveness of $Bi(OTf)_3$ in catalyzing the transformation relative to the other Bi(III) salts, we hypothesized that $Bi(OTf)_3$ is serving as a precursor to TfOH, which is generated *in situ* and behaves as the active catalytic species. This behavior of $Bi(OTf)_3$ has precedent and is most commonly observed in esterification reactions.[24] Moreover, the poor performances of all of the non-triflate containing Lewis acids seem to support the importance of TfOH. To probe this hypothesis, **8d** was subjected to TfOH (15 mol %) at room temperature (entry 15). Product **11d** was isolated in 61% yield along with an intractable mixture containing **9d**, which is comparable to the outcome with $Bi(OTf)_3$ (62% yield, entry 11).

TfOH also outperformed other Brønsted acids that were examined. TsOH did not push the reaction to completion after even 24 hours; however, it did show selectivity for the ABL product, with a 38% yield of **11d** as compared to a 7% yield of **9d** (entry 17). TFA proved insufficiently strong to promote reactivity (entry 18). Lastly, Tf_2NH showed excellent reactivity, but with a strong preference for the undesired dihydronaphthalene product, with an 83% yield of **9d** and no observed ABL product (entry 19).

When 15 mol % of pre-formed pyridinium triflate was used as the catalyst, only trace product was generated (entry 20). Finally, when a reaction was run using $Bi(OTf)_3$ (10 mol %) with 30 mol % of added 2,6-di-tert-butylpyridine, no reaction occurred (entry 21). Based on these two controls, and the previously mentioned literature precedent, we are confident that $Bi(OTf)_3$ is serving as a surrogate for TfOH. The $Bi(OTf)_3$ presumably reacts with the carbinol stoichiometrically, as $BiBr_3$ and $Bi(NO_2)_3{\bullet}5H_2O$ did, but is immediately hydrolyzed to generate the TfOH, which proceeds to catalyze the reaction. Moreover, $Bi(OTf)_3$ performed better than the other metal triflates studied due to both its

ability to form TfOH more readily and its unique Lewis acidity.[25] This is important, as the extent of Lewis acid coordination to the ester carbonyl seems to correlate with dihydronaphthalene formation (aryl trapping) versus ABL formation (ester trapping). Ultimately, due its superb ease of handling compared to TfOH, $Bi(OTf)_3$ was chosen as the preferable catalyst moving forward.

Table 10 – Final ABL Product Optimization



entry[a]	acid (mol %)	solvent (temp ºC)	time (h)	yield **9d** (%)[b]	yield **11d** (%)[b]
1	$Bi(OTf)_3$ (5)	CH_2Cl_2 (0)	3	ND[c]	58
2	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	1	ND[c]	62
3	$Bi(OTf)_3$ (5)	CH_2Cl_2 (40)	1	49	36
4	$Bi(OTf)_3$ (5)	1,2-DCE (84)	0.5	39	55
5	$Bi(OTf)_3$ (2)[d]	CH_2Cl_2 (23)	24	20	0
6	$Bi(OTf)_3$ (10)	CH_2Cl_2 (23)	1	28	55
7	$Bi(OTf)_3$ (5)[e]	CH_2Cl_2 (23)	1	ND[c]	60[f]

[a]Reaction performed with **8d**, acid promoter (X mol %), 4 Å molecular sieves, and indicated solvent (0.1M) at indicated temperature. [b]Isolated yield of product after column chromatography. Combined yields of **9d** isomers when appropriate. [c]Not determined (ND) due to formation of an intractable mixture. [d]Reaction did not go to completion, starting material recovered. [e]Reaction performed without 4 Å molecular sieves. [f]Complex, inseparable mixture. Product yield based on ^{1}H NMR using dimethyl terephthalate as an internal standard.

Next we took one last, brief look at optimizing the $Bi(OTf)_3$ reaction conditions (Table 10). Lower temperatures showed favorable reduction in **9d** yield compared to higher

temperatures, which is advantageous considering it competes with **11d** formation (entries 1-4). Lowering temperature below room temperature, however, did not improve yield of **11d**, so we decided to stick with room temperature for the sake of convenience. Reducing the loading of $Bi(OTf)_3$ to 2 mol % resulted in the reaction not going to completion (entry 5). Increasing catalyst loading to 10 mol % resulted in a slight reduction in yield of **11d** and an increase in **9d** yield, with a cleaner overall reaction.

In the previous report, 4 Å molecular sieves were included in the reaction mixture in order to sequester the generated water and prevent unwanted side reactions and Lewis acid deactivation. For ABL formation, the desired reaction pathway requires an equivalent of water in the hydrolysis step of the mechanism, releasing methanol. To determine if the 4 Å molecular sieves were a hindrance or boon for ABL formation, the reaction was performed without the addition of 4 Å molecular sieves for comparison (entry 7). Although the reaction provided 60% NMR yield of ABL **11d**, it resulted in a highly complex mixture, preventing the isolation of pure product. It is likely that the 4 Å molecular sieves help to control the amount of water in the flask, resulting in less side reactions. We decided to continue use of molecular sieves, with the intent to revisit their benefits and detriments with some other substrates. Without any improvements to the reaction in forming **11d**, we settled on using 5 mol % $Bi(OTf)_3$ at room temperature in DCM at a 0.1 M concentration in the presence of 4 Å molecular sieves as our optimum conditions.

3.3 *E/Z* Determination

With ABL **11d** isolated as a single diastereomer, we sought to determine the absolute configuration. We predicted an *E* configuration based on the allylic coupling

constants; however, initial attempts using NOE and 2D NMR techniques failed to conclusively elucidate the configuration. We also lacked the other diastereomer, which would have provided much better evidence by enabling direct comparison of allylic coupling constants. In order to conclusively determine the configuration of **11d**, crystals were grown and the X-ray crystal structure was obtained (Figure 11). This confirmed our initial suspicion that **11d** was indeed the *E*-isomer, and enabled our assignment of later compounds.

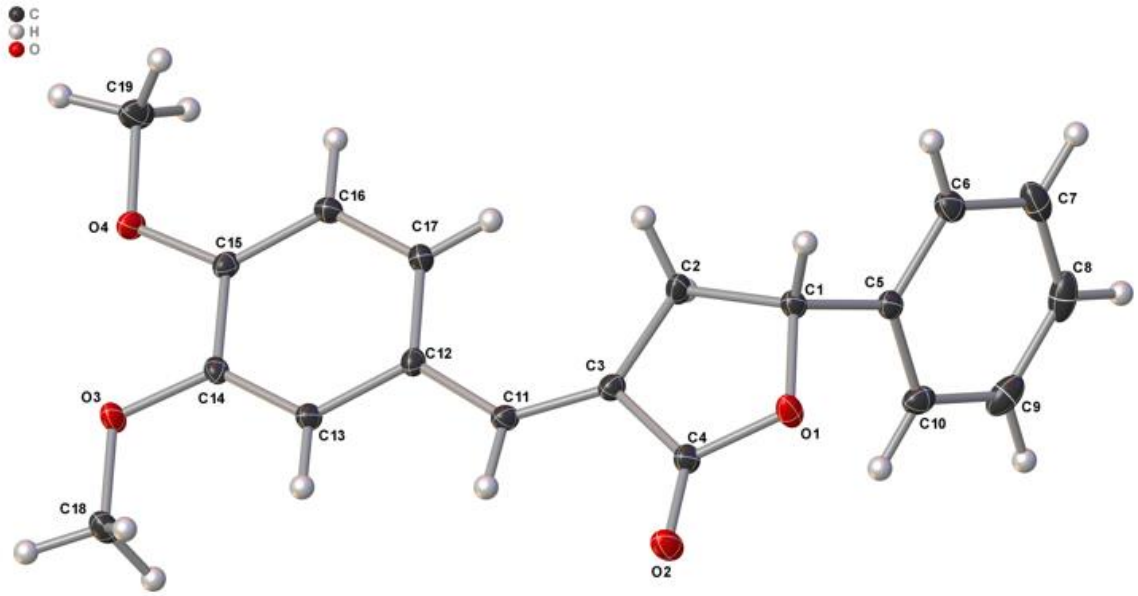
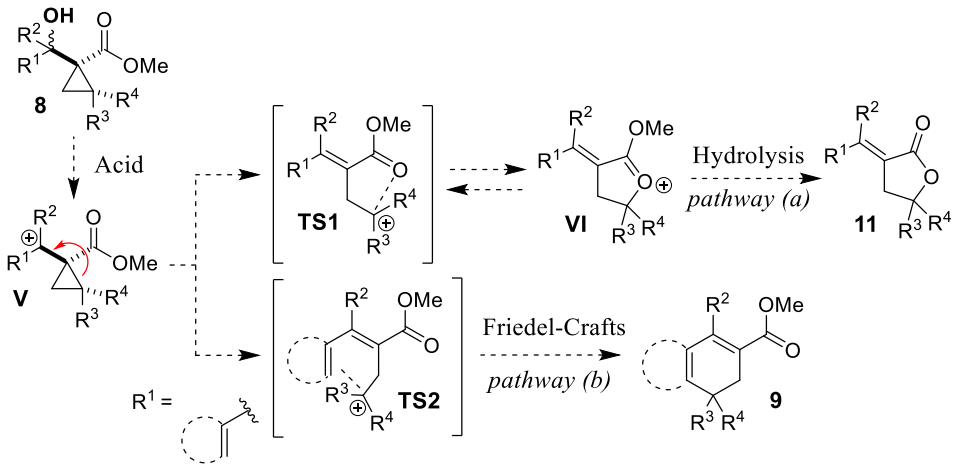


Figure 11 – Crystal Structure of Compound 11d

3.4 Proposed Mechanism



Scheme 10 – Proposed Mechanism

Mechanistically, as discussed in the optimization section, we propose that $Bi(OTf)_3$ first reacts with cyclopropyl carbinol **8** to form cyclopropyl carbinyl carbocation **V** (Scheme 10). In this initial reaction, $Bi(OTf)_3$ is converted to O=Bi(OTf), and TfOH is generated. With $Bi(OTf)_3$ consumed, TfOH catalyzes the transformation of remaining **8** to carbocation **V**. At this stage, the reaction can proceed through two different pathways to afford products **9** and/or **11**. In the path toward product **11**, cyclopropyl carbinyl carbocation **V** undergoes ring opening to form homoallylic carbinyl cation transition state **TS1**. Intramolecular trapping of the cation in **TS1** by the pendant ester would then form oxonium intermediate **VI**.[26] Hydrolysis of **VI** results in the loss of methanol, furnishing ABL **11** (pathway a). If R^1 or R^2 is a π-donating substituent (aryl or alkenyl group), Friedel-Crafts-type π-attack on an alternative ring-opened transition state (**TS2**) would generate

the (hetero)aryl-fused cyclohexa-1,3-diene **9** (pathway b). It is also likely that if hydrolysis is slow, intermediate **VI** could go back toward intermediate **V** and proceed toward product **9**. To fully understand the nature of this chemodivergence, substituent effects on both the cyclopropane and carbinol were studied.

3.5 Substrate Scope*

The next step in our study was to synthesize a large scope of cyclopropyl carbinols to test the new reaction conditions. For all but one cyclopropyl carbinol, the approach taken in the last study was replicated, where they were prepared using a three-step sequence from the corresponding β-ketoesters **5**. Diazo transfer followed by Rh(II)-catalyzed cyclopropanation with various olefins gave donor-acceptor (D-A) cyclopropanes **7**. $LiEt_3BH$ reduction generated secondary (2°) carbinols, whereas tertiary (3°) carbinols were obtained upon addition of methyl- or phenyllithium to the D−A cyclopropane (Figure 12).

* Synthesis of substrates **8ya** and **8yb** performed by co-author Corey W. Williams.

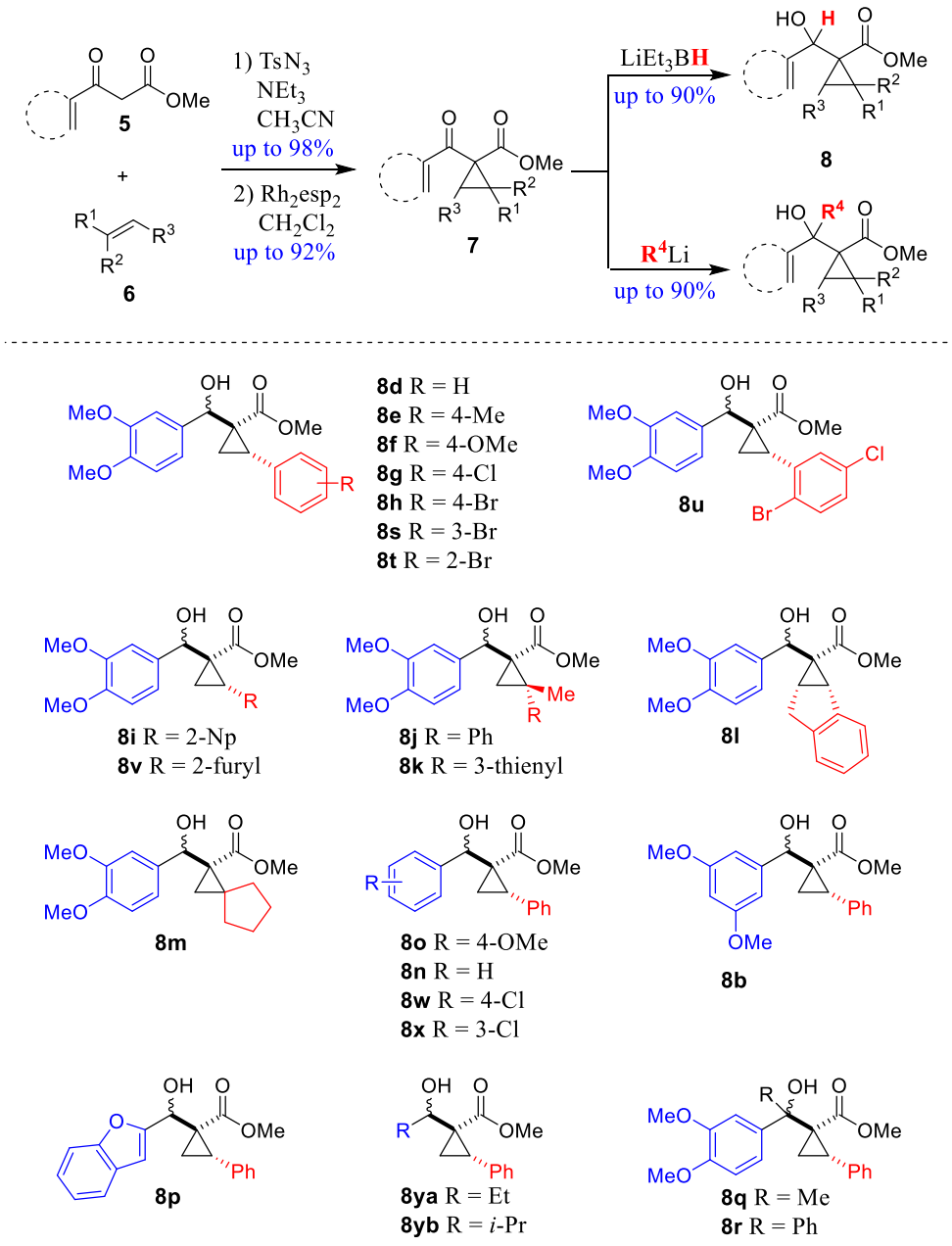
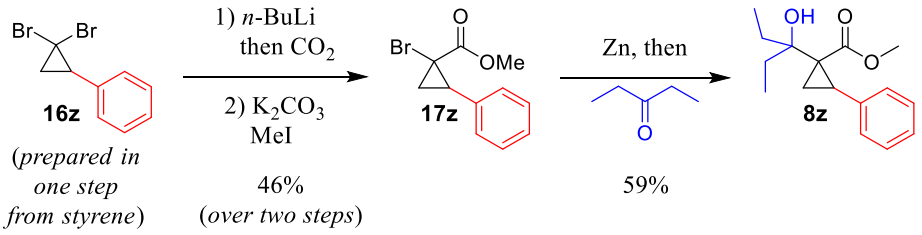


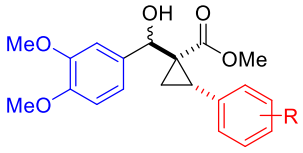
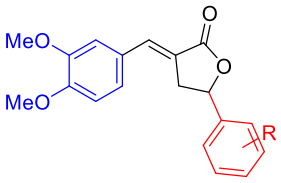
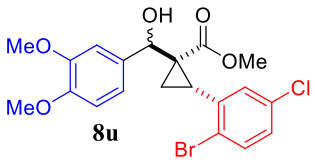
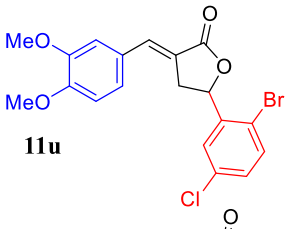
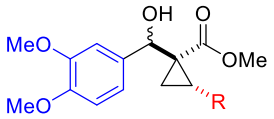
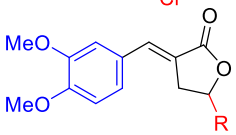
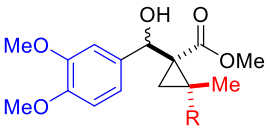
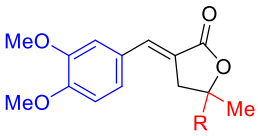
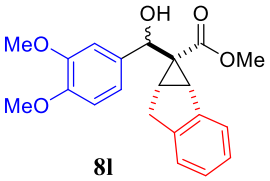
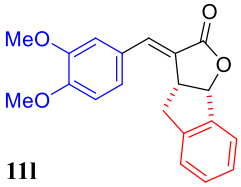
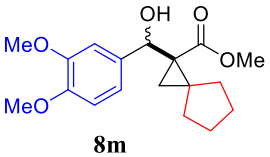
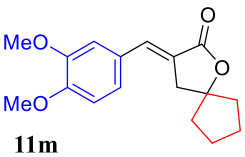
Figure 12 – Synthesis of Cyclopropyl Carbinols 8



Scheme 11 – Synthesis of Substrate 8z

For the preparation of trialkyl 3° carbinol **8z**, the previously discussed sequence failed to provide the desired product. Instead, **8z** was synthesized using Nishii's Reformatsky approach (Scheme 11).[27] 1,1-Dibromocyclopropane **16z** (prepared from the reaction of styrene with $CHBr_3$, aq NaOH, and catalytic $BnEt_3NBr$) was treated with *n*-BuLi and quenched with dry ice (CO_2). Following workup, the crude acid was converted to the ester **17z** using K_2CO_3 and MeI in 46% yield over the two steps. Lastly, formation of the Reformatsky reagent and reaction with 3-pentanone gave carbinol **8z**. In all cases, the carbinols are prepared and used as mixtures of diastereomers.

Table 11 – Cyclopropane Substituent Effects Substrate Scope

entry[a]	Carbinol 8	ABL 11	yield (%)[b]	*E:Z*[c]
				
1[d]	**8d** (R = H)	**11d**	62	>99:1
2[d]	**8e** (R = 4-Me)	**11e**	23	3:1[e]
3	**8f** (R = 4-OMe)	**11f**	0[f]	--
4	**8g** (R = 4-Br)	**11g**	87	>99:1
5	**8h** (R = 4-Cl)	**11h**	81	>99:1
6	**8s** (R = 3-Br)	**11s**	89	>99:1
7	**8t** (R = 2-Br)	**11t**	72	>99:1
8[g]	 **8u**	 **11u**	78	>99:1
				
9	**8i** (R = 2-Np)	**11i**	24	>99:1
10	**8v** (R = 2-furyl)	**11v**	0[h]	--
				
11	**8j** (R = Ph)	**11j**	38	>99:1
12	**8k** (R = 3-thienyl)	**11k**	0[i]	--
13	 **8l**	 **11l**	34	--[j]
14	 **8m**	 **11m**	43[k]	1:1

[a]Reactions performed with cyclopropyl carbinol **8** (1 equiv), $Bi(OTf)_3$ (10 mol %) in CH_2Cl_2 (0.1 M) at room temperature in the presence of 4 Å molecular sieves. [b]Isolated yield of **11** after column chromatography. [c]*E/Z* ratios determined by ^1H NMR on the crude mixture. [d]Reaction performed with 5 mol % $Bi(OTf)_3$. [e]*E/Z* ratio determined by combination of isolated yield of (***E***)-**11e** and ^1H NMR yield of (***Z***)-**11e** using dimethyl terephthalate as an internal standard. [f]Only dihydronaphthalene product **9f** formed. [g]Reaction performed with 5 mol % $Bi(OTf)_3$. [h]Intractable mixture. [i]No desired product formed. [j]Isolated as a 5:1 mixture of unassigned diastereomers. [k]Isolated as a 12:1 mixture of **11m** and elimination product **12m**. Product yield based on ^1H NMR using dimethyl terephthalate as an internal standard.

Toward exploring the scope of the reaction, the effects of changing the cyclopropane substituents were probed (Table 11). First, various aryl substituents were studied to identify any electronic effects. Interestingly, a clear trend emerged. Slightly electron-poor aryl rings favored ABL cyclohexa-1,3-diene products **11**. For instance, changing from the phenyl in **8d** to the more electron-rich tolyl or 4- methoxyphenyl (as in **8e** and **8f**) afforded 23% yield of ABL **11e** (as a 3:1 *E/Z* mixture of diastereomers) in the case of **8e**, whereas no ABL was detected with **8f** (entries 2 and 3). In each case, dihydronaphthalenes **9e** and **9f** were respectively isolated with 49% and 67% yield. In contrast, when the phenyl ring was substituted with a chlorine or bromine, the reaction proceeded efficiently to the ABL product. ABL **11h** was isolated as the *E*-diastereomer in 81% yield from 4-chlorophenylsubstituted cyclopropane **8h** (entry 5). Similarly, the 4-bromophenyl-, 3-bromophenyl-, and 2-bromophenyl-substituted cyclopropanes (**8g**, **8s**, and **8t**) each provided their respective ABL products (**11g**, **11s**, and **11t**) in 87%, 89%, and 72% yield as single *E*-diastereomers, indicating minimal positional electronic effects (entries 4, 6, and 7). To further probe this trend, cyclopropane **8u** (bearing a 2-bromo-4-chlorophenyl substituent) was used. The reaction failed to reach completion under the standard conditions; however, at a higher loading (20 mol %) of $Bi(OTf)_3$, ABL **11u** was obtained in 78% yield as the *E*-diastereomer (entry 8).

Other aryl (and heteroaryl) substituents were also studied. With the electron-rich 2-naphthyl-substituted derivative **8i**, ABL **11i** was obtained in 24% yield as the *E*-diastereomer in addition to 51% of dihydronaphthalene **9i** (entry 9). Next, given its presence in various ABL natural products, a furyl substituent was employed. Unfortunately, an intractable mixture was formed from the 2-furyl substrate **8v** (entry 10).

This outcome is most likely due to acid-mediated furan degradation/polymerization pathways.

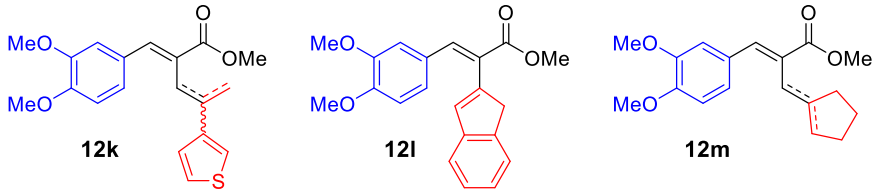
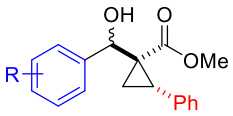
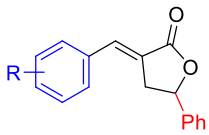
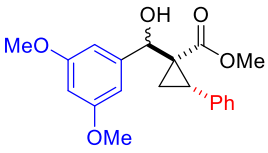
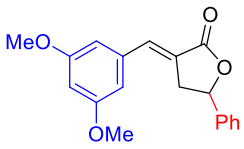
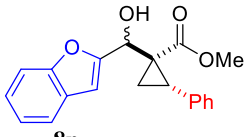
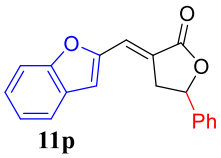
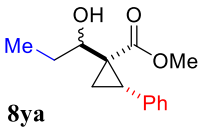
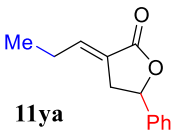
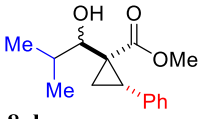
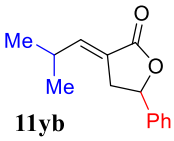
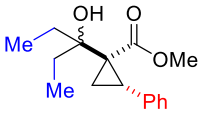
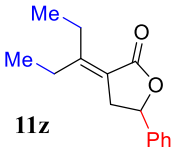
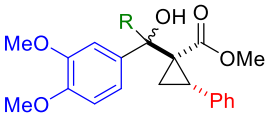
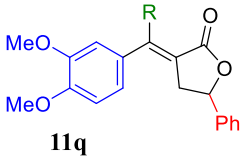


Figure 13 – Elimination Product Structures

The reaction proved amenable to certain geminally substituted cyclopropanes. The gem-methylphenyl cyclopropane **8j** gave its ABL product **11j** in 38% yield as the single *E*-diastereomer with dihydronaphthalene **9j** also present in an inseparable mixture (entry 11). Conversely, no ABL product was formed from the gem-methyl 3-thienyl cyclopropane **8k**, (entry 12); instead, acyclic elimination products **12k** were obtained in 46% yield (Figure 13).[13] These products presumably arise from cyclic oxonium **VI** as undesired E1-type elimination outpaces hydrolysis. Indanyl cyclopropane **8l** gave 34% yield of the desired ABL **11l** along with 43% of similar elimination products **12l** (entry 13). Finally, the gem-dialkyl-substituted, spirocyclic cyclopropane **8m** afforded ABL **11m** in 43% NMR yield as a 12:1 mixture of ABL isomers to elimination product **12m** (entry 14).

Table 12 – Carbinol Substituent Effects Substrate Scope

entry[a]	Carbinol 8	ABL 11	yield (%)[b]	*E:Z*[c]
				
1	**8o** (R = 4-OMe)	**11o**	73	7:1[d]
2	**8n** (R = H)	**11n**	60	1:1
3	**8w** (R = 4-Cl)	**11w**	35[e]	1:1
4	**8x** (R = 3-Cl)	**11x**	0[f]	--
5	 **8b**	 **11b**	78	1:1
6	 **8p**	 **11p**	48	>99:1
7	 **8ya**	 **11ya**	NR	--
8	 **8yb**	 **11yb**	NR	--
9	 **8z**	 **11z**	27	--
				
10[g]	**8q** (R = Me)	**11q**	54	>99:1
11	**8r** (R = Ph)	**11r**	41	--[h]

[a]Reactions performed with cyclopropyl carbinol **8** (1 equiv), $Bi(OTf)_3$ (10 mol %) in CH_2Cl_2 (0.1 M) at room temperature in the presence of 4 Å molecular sieves. [b]Isolated yield of **11** after column chromatography. [c]*E/Z* ratios determined by ^1H NMR on the crude mixture. [d]*E/Z* ratio determined from isolated yields of isolated *E*- and *Z*-isomers. [e]Product yield based on ^1H NMR using dimethyl terephthalate as an internal standard. [f]Intractable mixture. [g]Reaction performed with 5 mol % $Bi(OTf)_3$. [h]Isolated as a 3:1 mixture of unassigned diastereomers.

The carbinol substituent was next changed from the 3,4-dimethoxyphenyl group to other (hetero)aryl and alkyl groups to similarly probe electronic effects (Table 12). The 4-methoxyphenyl carbinol **8o** gave the desired ABL **11o** in 73% yield as a 7:1 *E*/*Z* mixture (entry 1). Phenyl carbinol **8n** afforded ABL product **11n** in 60% yield as a 1:1 *E*/*Z* mixture (entry 2). 4-Chlorophenyl carbinol **8w** generated a complex mixture that contained a 35% NMR yield of ABL **11w** as a 1:1 mixture of diastereomers (entry 3). An intractable mixture was obtained with 3-chlorophenyl carbinol **8x** (entry 4). Using the 3,5-dimethoxyphenyl substrate **8b** also resulted in a complex mixture of products containing ABL product **11b** in 26% yield as a 1:1 mixture of diastereomers by NMR (entry 5). Heteroaromatic ABL **11p** was obtained as the single *E*-diastereomer in 48% yield from benzofuranyl carbinol **8p** (entry 6).

When 2° dialkyl carbinols (as in **8ya** and **8yb**) were employed, no reaction occurred, and starting materials were recovered (entries 7 and 8). In contrast, the trialkyl 3° carbinol **8z** does react to give ABL **11z**, albeit as a complex mixture with a low 27% yield by NMR (entry 9). As expected, tertiary benzylic carbinols similarly undergo the ring-opening cyclization to form ABL products. For instance, in the case of **8q** (bearing methyl and aryl carbinol substituents), ABL **11q** was formed in 54% yield as a single diastereomer (entry 10). For the diaryl-substituted carbinol **8r**, ABL **11r** was obtained in 41% yield as a 3:1 diastereomeric mixture (entry 11). While it is assumed that the *E*-isomer is the major product in both cases, it was impossible to unambiguously assign the major and minor isomers using ^{1}H NMR due to the absence of the allylic coupling. In both cases, dihydronaphthalene products were also observed (5% of **9q**; 36% of **9r**).

The outcomes from the exploration of substrate scope aligned well with the proposed mechanism and also highlighted that substituent effects were critical in determining product outcomes through comparative stabilization of intermediates and/or transition states. For instance, since the carbinol substituents serve to stabilize cyclopropyl carbinyl cation **V**, the carbinols must be sufficiently activated to promote the reaction. While electron-rich aryl substituents are well-tolerated, electron-poor ones give substantially lowered yields, loss of *E*/*Z* selectivity, or increased unwanted side reactions. Similary, secondary (and by extension, primary) carbinols are not amenable to the reaction as the cyclopropyl carbinyl cations do not form. For aryl cyclopropyl carbinols, the ABL formation pathway (ester trapping and hydrolysis) directly competes with the Friedel-Crafts pathway with substituent electronic effects determining product outcomes. Electron-rich aryl substituents on the cyclopropane result in predominantly Friedel-Crafts products while more electron-poor aryl donor substituents give preferential ABL formation. It is plausible that the extent of ester involvement in stabilizing the acyclic carbocationic transition state may facilitate cyclopropane ring opening and, ultimately, determine the chemoselectivity.

3.6 E/Z Modeling[*]

With a handle on trends for ABL vs cyclohexadiene chemodivergence, the origins of *E*/*Z* selectivity were the next subject to be explored. While most substrates were completely *E*-selective, a handful offered either no selectivity or reduced diastereomeric ratios. In hopes of understanding these outliers, we sought the assistance of a group

[*] All computational analysis and modeling performed by co-author Brett D. McLarney

member with expertise in computational work and a familiarity with the project, Brett McLarney. Brett employed DFT calculations to examine the cyclopropane opening transition states between intermediates **V** and **VI**, derived from both the 3,4-dimethoxyphenyl-substituted carbinol **8d** (high selectivity, Figure 14A) and the phenyl carbinol **8n** (low selectivity, Figure 14B). He then used reaction coordinate diagrams to visualize relative energies, given in both Gibbs free energy and enthalpy. The transformation generally agreed with our proposed mechanistic transformation between **V** and **VI**, going through a homoallylic cation partially stabilized through an approaching ester. Consistent with the experimentally observed selectivities, the computations revealed a $\Delta\Delta G^{\ddagger}$ = 3.9 kcal/mol, in favor of *E* isomer formation, for the 3,4-dimethoxyphenyl carbinyl cation **V-d**. Meanwhile, $\Delta\Delta G^{\ddagger}$ = 1.3 kcal/mol for **V-n**, which displayed no *E*/*Z* selectivity under the optimized reaction conditions.

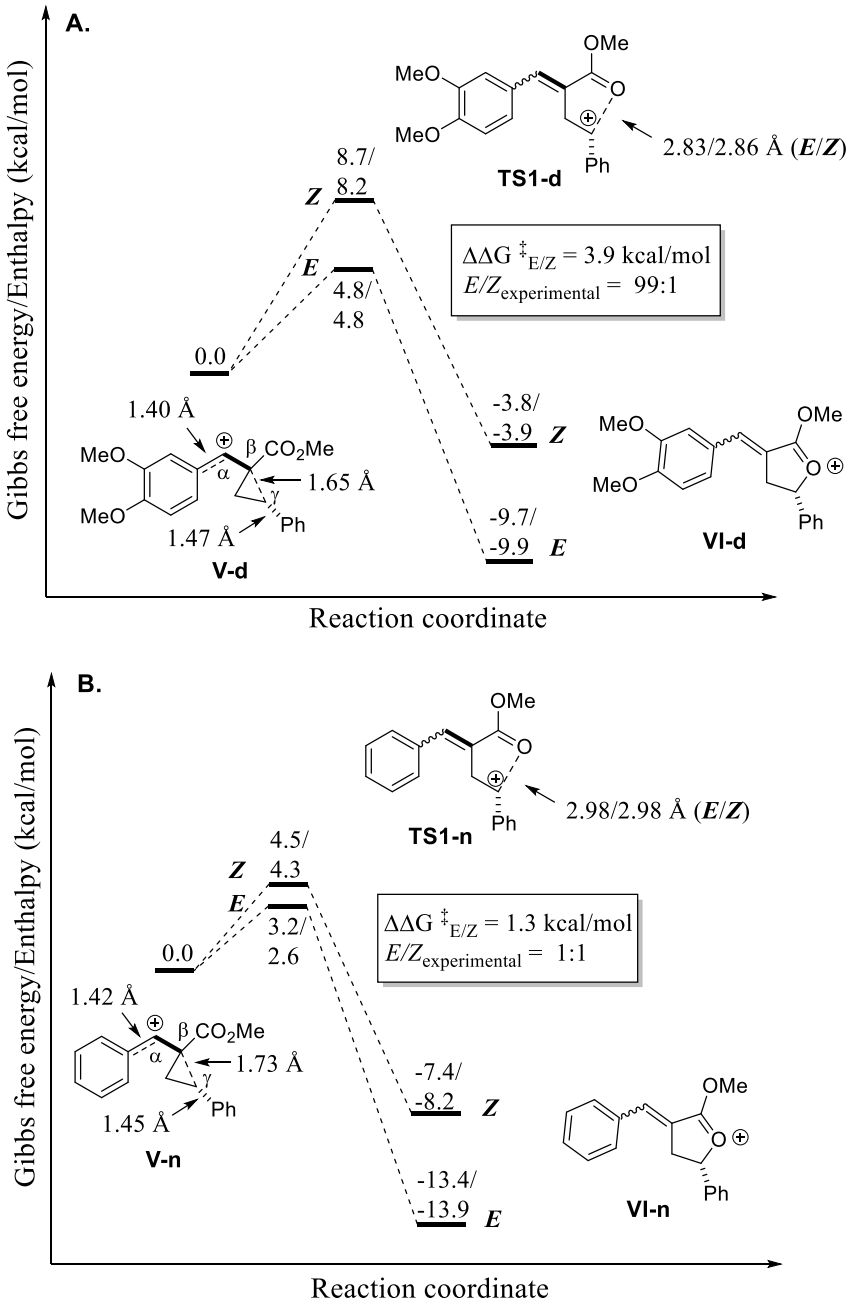


Figure 14 – Ring Opening Reaction Coordinates for V-d (A) and V-n (B)

The more exothermic ring opening for **V-n** suggests an earlier transition state and thus begs the application of Hammond's postulate to rationalize observed selectivities.

Indeed, not only is the transformation more exothermic for **V-n**, but the cyclopropane C_β-C_γ bond in **V-n** is weakened compared to that in **V-d**, 1.73 Å vs 1.65 Å respectively. In this light, the C_β-C_γ bond must undergo more elongation to reach the transition state from **V-d**, prompting a later and more selective transition compared to that from **V-n**.

Here, the difference in cyclopropane lability arises from the different electron donating potentials of the phenyl rings. Methoxy substitutions at the 3 and 4 positions increase stabilization of the benzylic cation at C_α. With less electron-donating potential on the unsubstituted phenyl ring, **V-n** compensates by elongating the C_β-C_γ bond and delocalizing some of the positive charge onto the benzylic C_γ position. This phenomenon is reflected not only in the elongation of C_β-C_γ but also in the shortening of the Ph-C_γ bond (1.47 Å in **V-d** vs 1.45 Å in **V-n**). Atomic partial charges (δ^+) reflect these geometric changes by displaying a shift of positive charge accumulation from C_α to C_γ as the C_β-C_γ length increases.

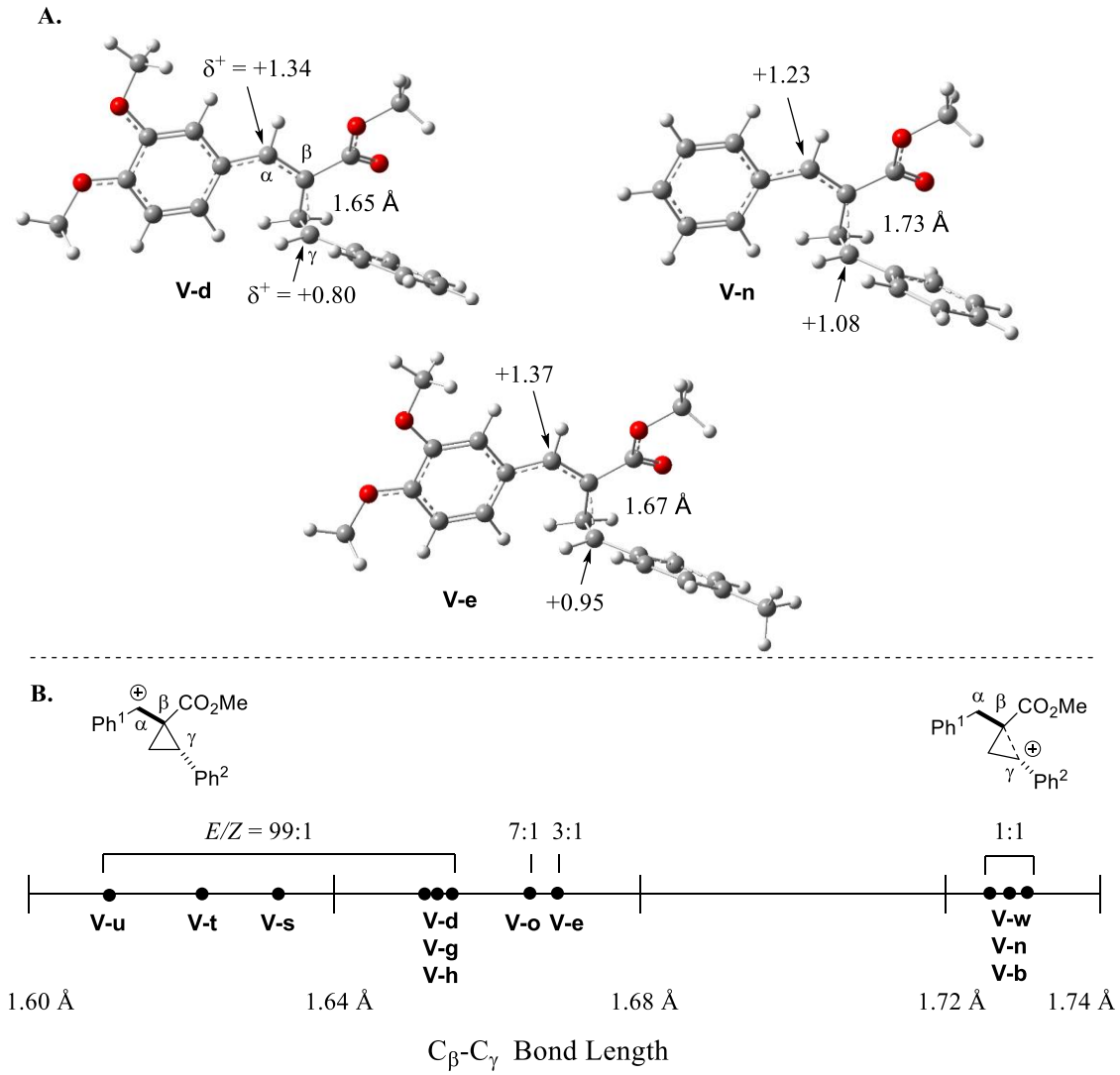


Figure 15 – Substitution Effects on C_β-C_γ Bond Length (A) and their Correlation to *E*/*Z* Selectivities (B)

Hypothetically, the cyclopropane could be polarized via substitution on the second phenyl ring as well. For example, comparing **V-d** and **V-e** we see that 4-methyl substitution is responsible for elongating C_β-C_γ by 0.02 Å in the ground state (Figure 15A); a concomitant drop in *E*/*Z* selectivity from 99:1 to 3:1 is observed in the synthetic experiments. Holding sterics constant and examining this trend across structures **V-b**, **V-**

d, **V-e**, **V-g**, **V-h**, **V-n**, **V-o**, **V-s**, **V-t**, **V-u**, and **V-w** suggests that, as a corollary to Hammond's postulate, electron-donating groups at Ph^1 and electron-withdrawing groups at Ph^2 enhance *E*/*Z* selectivity by strengthening the C_β-C_γ bond in the ground-state carbinylcation **V** (Figure 15B).

Through comparing the experimental results to DFT calculations, the selectivities can be reasonably rationalized by applying Hammond's postulate to the transition from **V** to **VI** through **TS1**. Moreover, the *E*/*Z* selectivity and the polarization (as measured by bond length) of the cyclopropyl C_β-C_γ in the ground-state carbinyl cation **V** can then be correlated. This approach provides an easily accessible calculation (C_β-C_γ bond length in intermediate **V**) as the basis for predicting the *E*/*Z* selectivity in ABL formation.

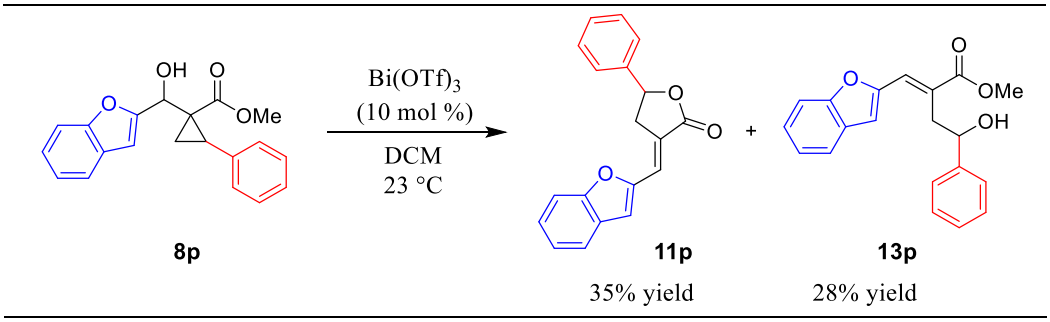
3.7 Understanding Catalysts and Conditions

Newly developed synthetic methods frequently come with uncertainties about how they work, especially if they originate from serendipity rather than rigorous intentional pursuit. It is useful to know how and why a synthetic method works, so rather than just showing what our method does we really sought to showcase a deeper understanding of how it works. A large part of this was the extensive substrate scope we investigated, with each substrate carefully chosen to reveal reactivity patterns and potential limits of the optimized method. Another function of the substrate scope; however, is to provide new potential data points to help resolve ambiguities encountered in the reaction optimization. Our two major ambiguities were whether the use of 4 Å molecular sieves were beneficial to the reaction and what are the differences that exist between using TfOH itself and using $Bi(OTf)_3$ as a source of TfOH. We next sought to revisit these ambiguous decisions we

made during optimization, with an eye towards understanding how the different sets of potentially viable conditions compare to each other on multiple substrates.

3.7.1 Use of Molecular Sieves

The use of 4 Å molecular sieves was an initial part of our system to help control the generated equivalent of water and preserve the catalysts we screened. The desired reaction pathway; however, requires an equivalent of water in the hydrolysis step of the mechanism, releasing methanol. Intuitively, water scavengers would be a hindrance, rather than a boon, to reactivity that necessitates an equivalent of water. During optimization, we decided to observe reactivity without the 4 Å molecular sieves for the purpose of determining whether they were a hindrance or boon for our desired reactivity. We had observed reactivity of optimization substrate **8d** without the molecular sieves. Although the reaction provided 60% NMR yield of ABL **11d**, nearly identical to the optimized 62% yield, it resulted in a highly complex mixture, preventing the isolation of pure product (Table 10, entries 2 and 7). We hypothesized that it is likely that the 4 Å molecular sieves help to control the amount of water in the flask, resulting in fewer side reactions.



Scheme 12 – Reaction without Molecular Sieves

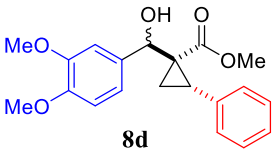
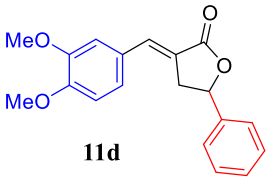
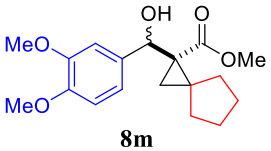
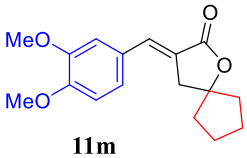
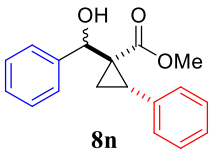
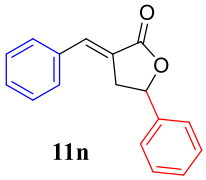
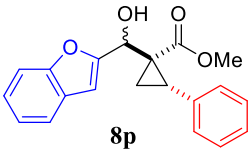
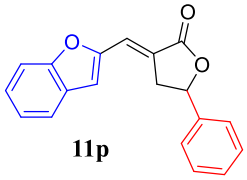
To further test our hypothesis, we decided to also expose benzofuranyl carbinol **8p** to the optimized conditions without the 4 Å molecular sieves for comparison. Benzofuranyl carbinol **8p** was chosen as it represents a unique substrate that shows product yields close to 50%, so it is easy to observe either an increase or a decrease in yield. Upon completion of the reaction, ABL **11p** was isolated in 35% yield (Scheme 12), which is considerably lower than the 48% yield with molecular sieves (Table 12, entry 6). Water-trapping product **13p** was also isolated in a 28% yield. The reaction was also messier and more difficult to purify, much like the reaction of **8d** without molecular sieves. This example is strong evidence that our original prediction of the 4 Å molecular sieves helping to control the amount of water in the flask was correct. In practice, controlling available water occasionally helps with overall yield of products **11** and generally helps with product purification.

3.7.2 Revisiting TfOH as the Catalyst

Despite the fact that $Bi(OTf)_3$ was chosen as the optimum catalyst for the transformation in the optimization studies (due to ease of handling and overall

performance), TfOH also presented itself as a viable option as a catalyst. To probe potential differences between TfOH and $Bi(OTf)_3$ as catalysts, four moderately active substrates with varying *E*/*Z* selectivities were submitted to optimized catalytic TfOH conditions (Table 13).

Table 13 – Catalyst Comparison

entry	**Carbinol 8**	**ABL 11**	$Bi(OTf)_3$[a]	TfOH[b]
1	 **8d**	 **11d**	62% isolated yield[c] >99:1 *E*:*Z*[d]	61% isolated yield[c] >99:1 *E*:*Z*[d]
2	 **8m**	 **11m**	43% NMR yield[e] 1:1 *E*:*Z*[d]	30% NMR yield[e] 1:1 *E*:*Z*[d]
3	 **8n**	 **11n**	60% isolated yield[c] 1:1 *E*:*Z*[d]	73% NMR yield[e] 1:1 *E*:*Z*[d]
4	 **8p**	 **11p**	48% isolated yield[c] >99:1 *E*:*Z*[d]	69% NMR yield[e] 5:1 *E*:*Z*[d]

[a]Reactions performed with cyclopropyl carbinol **8** (1 equiv), $Bi(OTf)_3$ (10 mol %) in CH_2Cl_2 (0.1 M) at room temperature in the presence of 4 Å molecular sieves. [b]Reactions performed with cyclopropyl carbinol **8** (1 equiv), TfOH (15 mol %) in CH_2Cl_2 (0.1 M) at room temperature in the presence of 4 Å molecular sieves. [c]Isolated yield of **11** after column chromatography. [d]*E*/*Z* ratios determined by ^{1}H NMR on the crude mixture. [d]*E*/*Z* ratio determined from isolated yields of isolated *E*- and *Z*-isomers. [e]Product yield based on ^{1}H NMR using dimethyl terephthalate as an internal standard.

As previously mentioned, the reaction outcomes were almost identical for the formation of ABL **11d** (entry 1). For spirocyclic ABL **11m**, $Bi(OTf)_3$ afforded a higher yield than TfOH (43% vs 30%, entry 2), whereas the reverse was observed for ABL **11n** (60% vs 73% yield). In both cases, the same 1:1 *E*/*Z* selectivity was obtained. In contrast, a dramatic selectivity difference occurred with benzofuranyl ABL **11p** (entry 4). While $Bi(OTf)_3$ gave a >99:1 *E*/*Z* ratio with a modest 48% yield, TfOH provided a much higher yield (69%) but with a severely reduced 5:1 *E*/*Z* ratio. From this subset of reactions, it seems that there are some differences between the catalysts, which may arise from the amount of TfOH readily available to catalyze the reaction or the potential for interactions with the Lewis acidic $Bi(OTf)_3$. Neither set of conditions was consistently better than the other in terms of product yields, but $Bi(OTf)_3$ may provide more selectivity based on the outcomes of cyclopropyl carbinol **8p**. This, along with the experimental precautions necessary for TfOH use, suggests $Bi(OTf)_3$ as the catalyst of choice for this transformation; however, TfOH remains a strongly viable catalyst for the transformation should $Bi(OTf)_3$ be unavailable for use.

3.7.3 Origins of Catalyst-Directed Chemodivergence

With optimized condtions for both selective ABL formation and selective (hetero)arylfused cyclohexa-1,3-diene product formation, and plenty of data to pull from, a plausible rationale for the origin of the selectivity can be proposed. Two major changes exist between the two sets of conditions, namely choice of catalyst and temperature of the reaction. The first step in rationalizing the selectivity is to understand how each catalyst works. As discussed earlier, with the information available to us from both our own studies and previous literature evidence, we were able to determine that $Bi(OTf)_3$ likely acts as a

source of TfOH. The TfOH then catalyzes the reaction by protonating the alcohol, making it a good leaving group and thereby activating the reaction (Figure 16B, left).

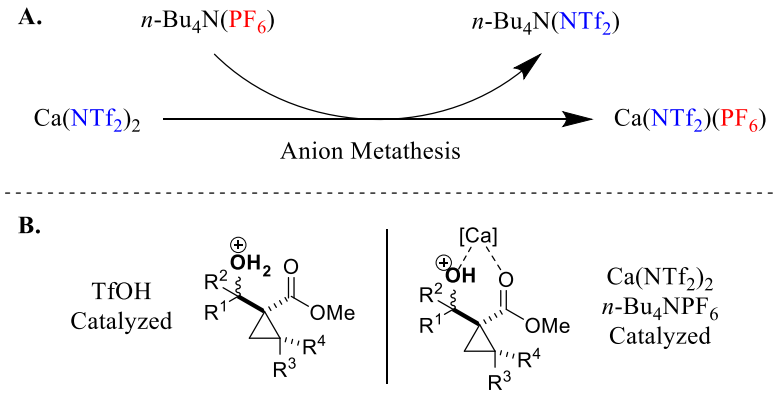


Figure 16 – Active Calcium Complex Formation (A) and Comparative Activated Carbinols (B)

The calcium catalyst system of $Ca(NTf_2)_2$ and additive *n*-Bu_4NPF_6 in equal molar parts works differently. An anion metathesis occurs between the calcium complex and additive, forming the active species $Ca(NTf_2)(PF_6)$ (Figure 16A).[28] This active species is both more Lewis acidic than $Ca(NTf_2)_2$ and a second binding site is open, enabling coordination to two Lewis bases. The active species likely interacts with the cyclopropyl carbinol by coordinating to both the alcohol and the ester (Figure 16B, right).

From our studies, we concluded that the ester plays an important role in stabilizing the transition from intermediate **V** through **TS1** to intermediate **VI** (Scheme 10, pathway a). Furthermore we observed that the more the ester needs to assist in the stabilization of the ring-opening transition state, the higher the percent yield of ABL product. With a

correlation between ester involvement and ABL formation, it follows that having the ester tied up by coordinating to the calcium catalyst may preclude pathway (a) of our proposed mechanism, forcing use of pathway (b) and preventing ABL formation. The catalyst choice has the largest effect size on product outcomes out of any other observed director apart from substrate scaffold.

The other major consideration is temperature. The conditions for selective (hetero)arylfused cyclohexa-1,3-diene product formation utilize refluxing 1,2-DCE, a temperature of 84 °C. This is significantly higher than the room temperature conditions for selective ABL formation. The patterns of ester involvement in the transition state can also be applied to observed product outcomes at varying temperatures. As temperature increases, more energy is readily available to the system, decreasing the need for the ester to be involved in the transition. As a result, observed ABL product decreases. Likewise, at lower temperatures there is less energy readily available, increasing the need for ester involvement and increasing observed ABL formation. Temperature changes show smaller shifts in reaction outcome than changes in catalyst; however, they still provide an important shift in either desired direction. Pulling this all together, our rationale for the origin of the selectivity is the combination of primarily how each catalyst interacts with the carbinols and secondarily how the temperature affects product outcomes.

3.8 Conclusions

In summary, we have disclosed the $Bi(OTf)_3$-catalyzed ring-opening cyclizations of (hetero)aryl cyclopropyl carbinols **8** to form functionalized α-alkylidene-γ-butyrolactones (ABLs) **11**. The overall transformation marks different chemoselectivity

than observed in previous reports for the acid-promoted reactions of (hetero)aryl cyclopropyl carbinols. $Bi(OTf)_3$ likely serves as a stable and user-friendly precursor to TfOH, which proceeds to catalyze the reaction. The resulting ABLs are formed in up to 89% yield, with generally high *E*-diastereoselectivity. Substituent effects play a major role in the determination of reaction chemoselectivity, with cyclopropyl carbinol substituents directly influencing cyclopropane ring-opening. The cyclopropane donor substituents directly influence the overall reaction chemoselectivity, with weakly stabilizing or electron-poor substituents providing better yields of the ABL products. In contrast, highly stabilizing cyclopropane donor substituents give copious amounts of competing products including, most importantly, (hetero)arylfused cyclohexa-1,3-diene products **9**.

Using DFT calculations, a predictive model was developed that correlates *E*/*Z* selectivity with the C_β-C_γ bond length in the ground state cyclopropyl carbinyl cation **V**. The ester plays an important role in stabilizing the transient acyclic homoallylic cation formed upon ring opening or, possibly, in facilitating cyclopropane ring opening by anchimeric assistance. We also were able to probe the benefit of molecular sieves, differences between using $Bi(OTf)_3$ or TfOH, and proposed the origins of chemoselectivity for the reaction. Overall, we now have a better understanding of how different substituents can influence product outcomes through their interactions with intermediate **V** and ring-opening transition states in our proposed mechanism.

This synthetic method in conjunction with the method shown in the previous chapter are a prime example of utilizing acid catalyzed cyclization reactions for DOS. Combined, they show selectivity between two complexity-building synthetic pathways a single substrate can access, with desirable core structures at the end of each path. From a

single branching point, we have developed methods to increase complexity in two very different ways, resulting in molecular diversity in core structures. This was made possible by finding reaction conditions that promoted different parts of the molecule to act as nucleophiles in the cyclization step following ring-opening. This method provides yet another expansion to the molecular diversity readily available through our lab's developed synthetic methods. As with many projects, the completion of this project provides the foundation for more projects that continue to expand the toolbox available to the synthetic chemist. Chapter 4 will continue this theme.

3.9 Experimental

The experimental section, including general methods, computational methods, and synthesis and characterization for compounds in Chapter 3 can be found in the article: Sandridge, M. J.; McLarney, B. D.; Williams, C. W.; France, S. *J. Org. Chem.* **2017**, *82,* 10883. Computational data, X-ray crystallographic data, and NMR spectra are found in the Supporting Information.

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CHAPTER 4. DEHYDRATIVE NAZAROV-TYPE ELECTROCYCLIZATIONS TOWARDS CYCLOPENTA[*B*]THIOPHENES[*,1]

4.1 Dehydrative Nazarov cyclization

In addition to our interests in the homo-Nazarov reaction, our lab is also interested in the Nazarov cyclization itself, a 4π electrocyclization that finds frequent use for the synthesis of functionalized cyclopentenyl rings. In addition to our own methods based on the Nazarov cyclization,[2] there has generally been renewed interest in the Nazarov cyclization, resulting in new methods for activation.[3] Notably, this includes a dehydrative approach that has been explored by several groups where divinyl alcohols and (hetero)aryl-substituted allyl alcohols are employed (Figure 17).[4] This dehydrative, Nazarov-type approach[5] has been shown to be a straightforward route to cyclopentadienes, indenes, and heteroaryl-fused cyclopentadienes.[6] This is another prime example of a dehydrative cyclization reaction that is able to be utilized to rapidly access structural diversity.

[*] Work on this project performed in collaboration with M. Cynthia Martin, Corey W. Williams, and Zola A. Francis.
Published in *Tetrahedron* **2017**, *73*, 4093.

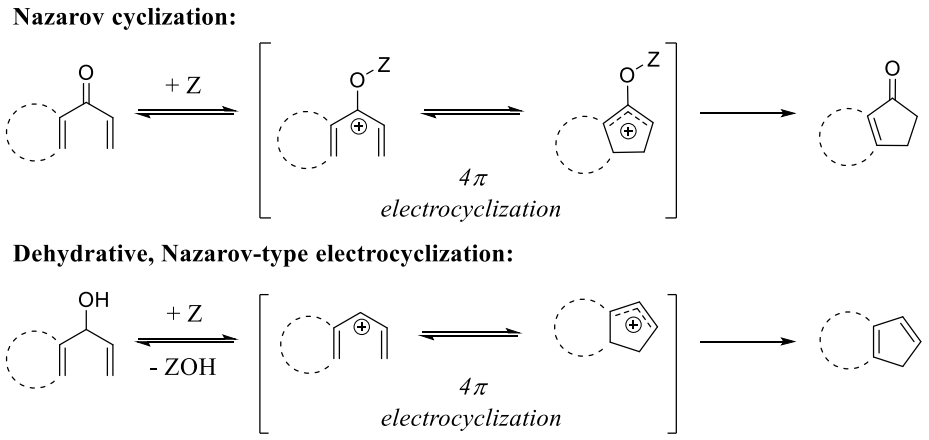


Figure 17 – Nazarov Cyclization vs. Dehydrative, Nazarov-type Electrocyclization

Unfortunately, thiophene-based heteroaromatic compounds have consistently proven problematic for dehydrative, Nazarov-type cyclizations. For instance, in 2011 Singh[7] published a Nazarov-type electrocyclization initiated by a $Sc(OTf)_3$-catalyzed ionization of alkenyl (hetero)aryl carbinols to form [6,6,5,6] and [6,6,5,5] heterocyclic ring systems. While the reaction worked for arenes and indole, the thienyl- and benzothienyl-substituted substrates rapidly decomposed or afforded uncharacterized products. Yamamoto[8] was later able to accomplish cyclization with a benzothienyl substrate, although the corresponding thiophene provided no discernible product. This limitation to dehydrative, Nazarov-type cyclizations is significant, as the potential products of such reactions, such as cyclopenta[*b*]thiophenes, are highly desirable.

4.2 Cyclopenta[*b*]thiophenes

Cyclopenta[*b*]thiophenes represent a unique class of organic molecules that are interesting isosteres of indenes (Figure 18).[9] They exist in equilibrium as mixtures of the

major 4*H*- and 6*H*-isomers and the transient 5*H*-isomer (isosteric with isoindene).[10] The parent compounds have been primarily used as precursors to thiophene-fused cyclopentadienyl metal complexes,[11] whereas, the 5,6-dihydro derivatives have been employed by materials scientists[12] (for use in conjugated polymers, liquid crystalline media, and organic field-effect transistors) and medicinal chemists[13] (as anticancer, anti-bacterial, anti-viral, and anti-fungal agents).

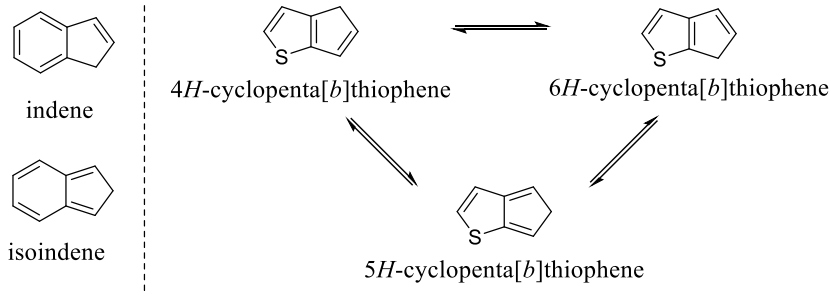
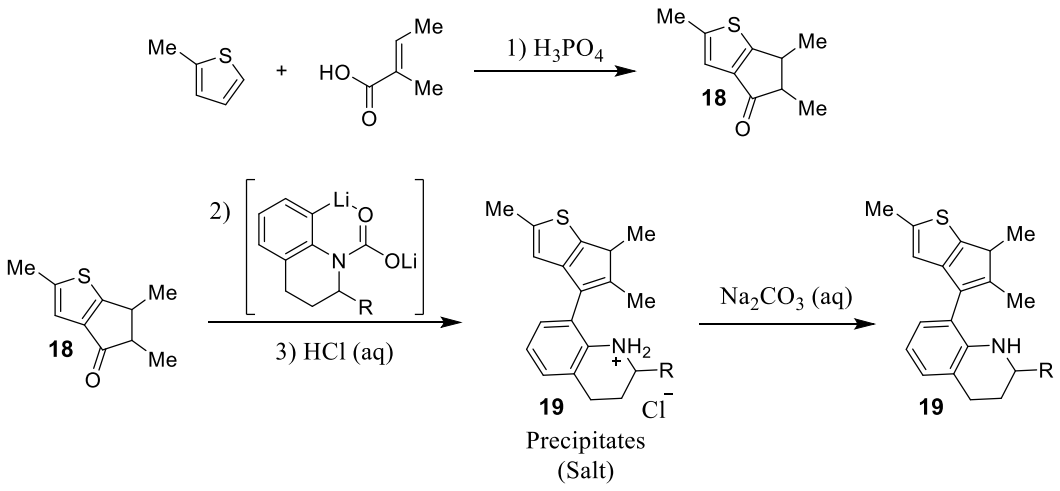


Figure 18 – Isomeric Forms of Cyclopenta[*b*]thiophene

Despite these rich applications, there exists a lack of general and robust methods for the preparation of functionalized cyclopenta[*b*]thiophenes. Only a handful of syntheses have been reported to date, the majority of which start with derivatization of a thiophene-fused cyclopentanone. For example, the most robust method reported by Lee[11b,11c] involves the following three-step sequence (Scheme 13): 1) a one-pot acid-promoted Friedel-Crafts acylation/Nazarov cyclization of thiophene with acrylic acid derivatives to form thiophene-fused cyclopentanones **18**; 2) nucleophilic attack at the carbonyl to form the corresponding alcohols; and 3) acid-promoted dehydration to form the cyclopenta[*b*]thiophenes **19**.

Unfortunately, this approach affords limited scope (only methyl or phenyl substituents on the cyclopenta[*b*]thiophene rings) and low functional group tolerance due to the use of strong acids. Therefore, the design of milder and more generalized approaches to cyclopenta[*b*]thiophenes represents a worthwhile synthetic endeavor, particularly one that circumvents the formation and derivatization of a thiophene-fused cyclopentanone. This could be accomplished if a dehydrative Nazarov-type approach could be taken.



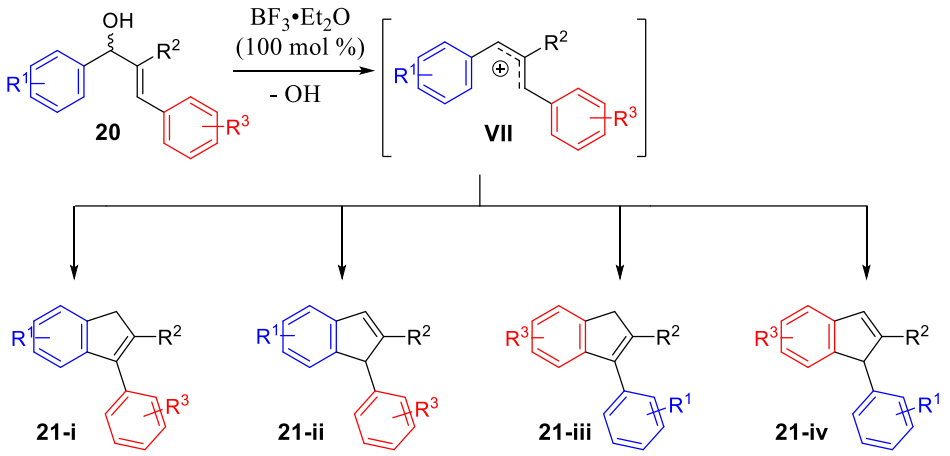
Scheme 13 – Lee's Cyclopenta[*b*]thiophene Synthesis

Aware of both the thiophene-based limitation in the previous examples of the dehydrative Nazarov-type electrocyclizations and the value of cyclopenta[*b*]thiophenes, we have remained attentive to potential solutions. While pursuing the dehydrative homo-Nazarov cyclization,[14] we made sure to probe a thiophene-based substrate, **8k**, among other heteroaromatics. Fortunately, the substrate proved amenable to the reaction conditions, and

the product **9k** was isolated in 86% yield. This outcome was encouraging, as it gives credence to the possibility of using catalytic Lewis acids as the carbinol activator in a thiophene-based dehydrative Nazarov-type electrocyclization. With this in mind, we decided to develop catalytic conditions that were amenable for the general cyclization of alkenyl (hetero)aryl carbinols that specifically allow for the formation of cyclopenta[*b*]thiophenes.

4.3 Mechanism

One major benefit to working with reactions that have been previously studied is that we have a good foundational understanding of how they work, which we can then build upon. In 2010, Batey and co-workers extensively investigated substituent effects on the selectivity of the cyclizations of 1,3-diarylallylic cations **VII**, derived from the diallyl alcohols **20** using stoichiometric BF_3•Et_2O (Scheme 14).[15] The reactions worked when R^2 = Me or CO_2Et, but failed when R^2 = H. Depending on the choice of substituents, mixtures of indenes **21-ii** (from cyclization onto the ring bearing R^1) and **21-iv** (from cyclization onto the ring bearing R^3) were most commonly obtained. Also observed in select cases was indene **21-i**, the product resulting from alkene isomerization. The authors argue that alkene isomerization is most likely due to a base-catalyzed process given the increased acidity of the dibenzylic C-1 proton. A 1,5-hydrogen shift mechanism was ruled out since the reactions were performed at room temperature.



Scheme 14 – Batey's Indene Synthesis using 1,3-Diaryl Allylic Alcohols

Regarding substituent effects, electron-withdrawing aryl substituents disfavored cyclization and only the more electron-rich ring engaged in ring-formation. In the case of electron-donating groups, the selectivity was dependent upon the nature and position of the substituent. The authors then argue that, unlike in electrophilic aromatic substitution, no correlation of selectivity with calculated electron densities was observed, which is consistent with a cationic 4π conrotatory electrocyclization mechanism.

4.4 Synthetic Route to Vinyl Carbinols*

We sought to access the allyl (hetero)aryl-substituted carbinols **20** using a two-step sequence starting from (hetero)aryl β-ketoesters **5** (Figure 19). The β-ketoesters are a commonly used precursor for most methodologies in our lab, a common branching point for the breadth of diversity we access. Knoevenagel condensation of **5** with aldehydes **22**

* Synthesis of substrates performed in collaboration with M. Cynthia Martin, Corey W. Williams, and Zola A. Francis

afforded alkylidene β-ketoesters **23** in up to >99% yield. Subsequent Luche reduction[16] of **23** provided the desired carbinols **20** in up to 66% yield. Unfortunately, the reduction step proved generally low-yielding, as difficult to separate mixtures of competing 1,4-addition of the hydride, incomplete reduction, and the desired product were frequently obtained regardless of attempts to improve the reaction.

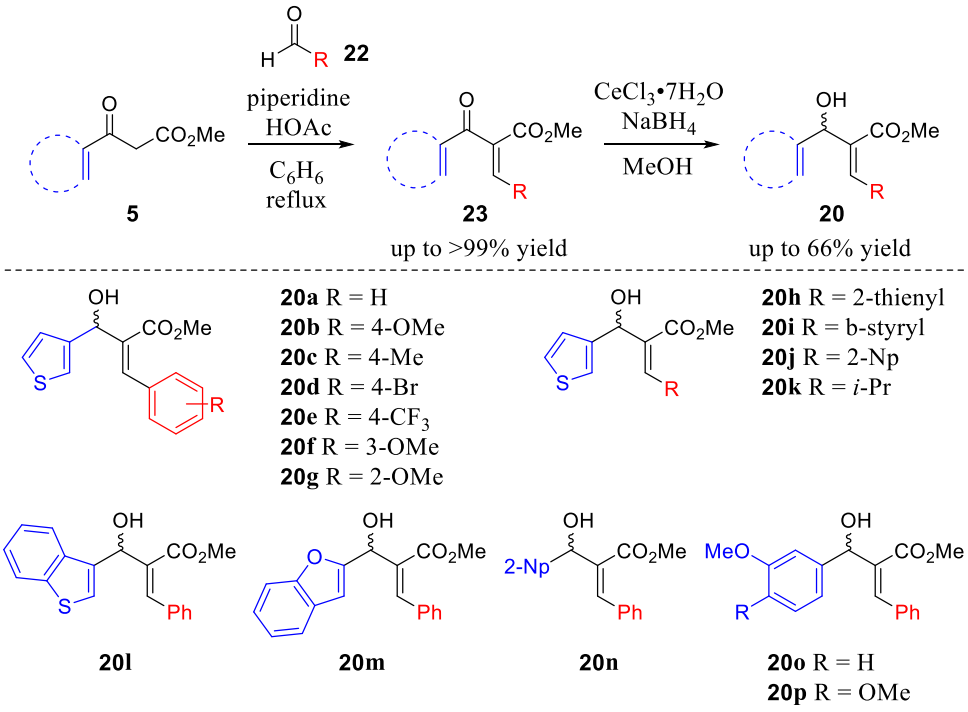


Figure 19 – Synthesis of Carbinols 20

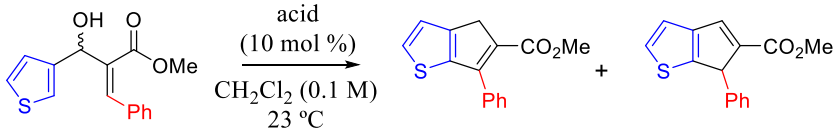
With the emphasis on accessing cyclopenta[*b*]thiophenes, most of the prepared substrates contained the 3-thienyl moiety, using **20a** as the model compound selected for optimization. 3-Benzothienyl, 2-benzofuranyl-, 2-naphthyl-, and aryl-substituted allyl

alcohols were also prepared in order to explore reaction scope once optimized conditions were identified. When **23k** (bearing an *i*-Pr substituent) was subjected to Luche conditions, the desired product **20k** proved inseparable from the fully reduced saturated alcohol.

4.5 Reaction Optimization

Overall, we figured that similar catalysts to what worked for cyclopropyl carbinol activation would also work best for the activation of these thienyl carbinols, as many parts of the substrates are conserved. We decided that we would focus our efforts accordingly, taking advantage of the expertise we built through the other projects in chapters 2 and 3. We began by subjecting 3-thienyl carbinol **20a** to an initial screening of acid catalysts at 10 mol % loading in DCM (Table 14). As a standard to compare to and a bar to hopefully surpass, stoichiometric BF_3•Et_2O (Batey's conditions for indene synthesis) was employed, providing **21a-i** as the only product with 47% yield (entry 1). Interestingly, catalytic loading of BF_3•Et_2O resulted in only slightly reduced yield (43%), but as **21a-i** and **21a-ii** as a 1.5:1 mixture of isomers (entry 2). We were surprised to find that $Sc(OTf)_3$ afforded product, albeit with a poor yield (11%) of **21a-i** and **21a-ii** as a 1.2:1 mixture, as previous conditions using $Sc(OTf)_3$ proved incompatible with thiophenes (entry 3). No desired product was formed with $Yb(OTf)_3$, $La(OTf)_3$, $Dy(OTf)_3$, or $Ni(OTf)_2$ after 24 h (entries 4-7), and trace amounts of product were detected with $Al(OTf)_3$ at 20 h (entry 10). Temporally, these five catalysts were the last we attempted as they were poor performing in our previous studies; however, we did decide to test them as they could work.

Table 14 – Acid Catalyst Screen



20a **21a-i** **21a-ii**

entry[a]	acid	time (h)	yield (%)[b]	**21a-i** : **21a-ii**[c]
1[d]	BF_3•OEt_2	4.0	47	1.0:0
2	BF_3•OEt_2	5.0	43	1.5:1
3	$Sc(OTf)_3$	24.0	11	1.2:1
4	Yb(OTf)	24.0	NR	--
5	$La(OTf)_3$	24.0	NR	--
6	$Dy(OTf)_3$	24.0	NR	--
7	$Ni(OTf)_2$	24.0	NR	--
8	$Al(OTf)_3$	20.0	trace	--[e]
9	$Ga(OTf)_3$	4.0	47	1.0:0
10	$In(OTf)_3$	4.0	51	1.0:0
11	$Bi(OTf)_3$	4.0	57	2.0:1
12	TfOH	0.5	43	1.4:1
13	$Ca(NTf_2)_2$ n-Bu_4NPF_6	4.0	55	1.0:0
14[f]	$Ca(NTf_2)_2$ n-Bu_4NPF_6	0.5	63	1:3
15[f]	$Ca(NTf_2)_2$ n-Bu_4NPF_6	1.0	60	1:2.6
16[f]	$Ca(NTf_2)_2$ n-Bu_4NPF_6	1.75	65	1.0:0
17[f]	$Ca(NTf_2)_2$ n-Bu_4NPF_6	2.5	58	5.5:1

[a]Reaction was performed with carbinol **20a** and acid catalyst (10 mol %) in CH_2Cl_2 (0.1 M) at room temperature. [b]Isolated yield after column chromatography. [c]Ratio determined by ^{1}H NMR of the product mixture. [d]Performed using 100 mol % BF_3•OEt_2 [e]Not determined. [f]Reaction performed at reflux (~40 °C). NR = No Reaction

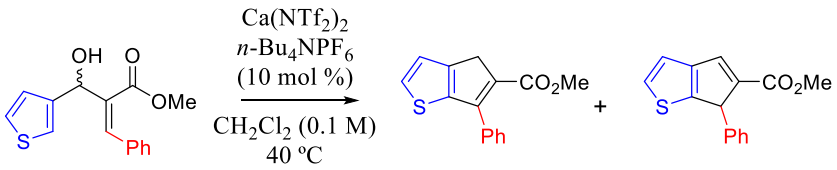
$Ga(OTf)_3$ and $In(OTf)_3$, each gave **21a-i** as the only isomer in 47% and 51% yield, respectively (entries 9 and 10). $Bi(OTf)_3$ gave an increased yield of 57%, appreciably surpassing the 47% yield from Batey's conditons, but with **21a-i** and **21a-ii** as a 2:1 mixture (entry 11). TfOH gave a lower 43% yield as a 1.4:1 ration of isomers favoring **21a-I** (entry

12). The Niggemann combination of $Ca(NTf_2)_2$ and additive *n*-Bu_4NPF_6 (10 mol % each) was next employed. Under these conditions, **21a-i** was obtained as the only product in 55% yield (entry 13). The calcium catalyst system was deemed the preferable catalyst as it was totally selective for one isomer and had a yield on par with $Bi(OTf)_3$.

In an attempt to improve the yields, the reaction was performed at reflux (~40 °C). Unexpectedly, although the yield improved to 63%, a 3:1 ratio was formed with **21a-ii** as the major isomer (entry 14). We were interested in the effects of time at reflux on both the yield and product ratios, so we set reactions with increased reflux times (1 h, 1.75 h, and 2.5 h) to observe results. Like 30 min, 1 h gave approximately a 1:3 mixture with **21a-ii** as the major component in 60% yield (entry 15). Conversely, **21a-i** was obtained in 65% yield as the only observable product at 1.75 h (entry 16). At 2.5 h, some isomerization is observed as the **21a-i** to **21a-ii** ratio erodes to 5.5:1 along with a minor drop in yield (58%). Thus, to optimize for yield and product ratios, 1.75 h was targeted as the ideal reaction time.

In the final phase of optimization, we examined the effects of (1) reducing the catalyst loading, (2) changing the solvent, and (3) changing the reaction concentration (Table 15). The reaction in DCM at 40 °C with 10 mol % catalyst loading was used as the benchmark (65% yield of only **21a-i**, entry 1). First, the catalyst loadings for $Ca(NTf_2)_2$ and *n*-Bu_4NPF_6 were each reduced to 5 and then 2.5 mol %. With each decrease in catalyst loading, a change in isomeric ratio is observed. At 5 mol % loading, a 4.5:1 isomeric mixture is formed, while a 1.4:1 mixture is seen with 2.5 mol % (entries 2 and 3). It is likely that the reduced loading directly effects the rate of the alkene isomerization. Moreover, a longer reaction time was necessary for the 2.5 mol % reaction to reach completion, with a slight drop in yield (57%).

Table 15 – Final Reaction Optimization*



20a **21a-i** **21a-ii**

entry[a]	solvent	time (h)	yield (%)[b]	**21a-i** : **21a-ii**[c]
1	CH_2Cl_2	1.75	65	1.0:0
2	CH_2Cl_2	1.5	63	4.5:1
3	CH_2Cl_2	2.5	57	1.4:1
4	1,2-DCE	1.75	58	1.0:0
5	Toluene	1.75	53	1.0:0
6	CH_3CN	>24.0	--	--
7	THF	3.0	57	6.0:1
8	Benzene	1.75	67 (60)	1.0:0
9	Benzene	1.75	70	1.0:0

[a]Reaction was performed with carbinol **20a** and $Ca(NTf_2)_2$ (10 mol %), *n*-Bu_4NPF_6 (10 mol %) in indicated solvent (0.1 M) at 40 °C. [b]Isolated yield after column chromatography. [c]Ratio determined by ^1H NMR of the product mixture. [d]5 mol % each of $Ca(NTf_2)_2$ and *n*-Bu_4NPF_6 were used. [e]2.5 mol % each of $Ca(NTf_2)_2$ and *n*-Bu_4NPF_6 were used. [f]Yield in parentheses represents the product yield when performed at reflux (~80 °C). [g]Reaction performed at a concentration of 0.05 M. NR = No reaction.

In hopes of replacing DCM, a screening of solvents was then performed to determine the optimum solvent. The reaction temperature was maintained at 40 °C for consistency. Both 1,2-dichloroethane and toluene afforded **21a-i** selectively, albeit with reduced yields (entries 4 and 5). In contrast, CH_3CN proved incompatible, as no desired products were detected (entry 6). This is most likely due to catalyst deactivation through solvent coordination. With THF, **21a-i** was formed in 57% yield as a 6.0:1 isomeric mixture with **21a-ii** (entry 7). Benzene proved to be the best solvent for the reaction as **21a-i** was selectively generated in 67% yield (entry 8). Further increasing temperature in benzene

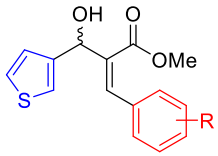
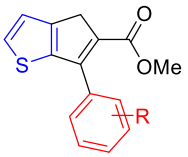
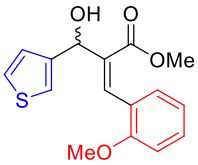
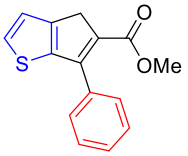
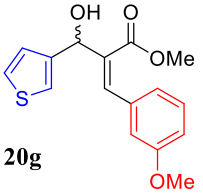
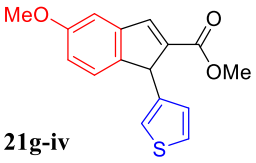
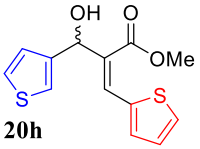
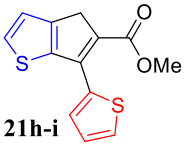
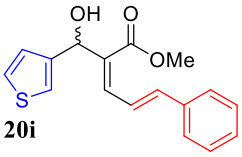
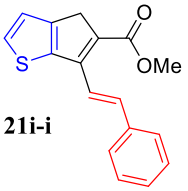
* Final optimization performed by co-author M. Cynthia Martin

proved detrimental to product yields. After further exploration of the reaction concentration, an improved yield (70%) was obtained using a more dilute reaction mixture (0.05 M, entry 9). Ultimately, these conditions (10 mol % $Ca(NTf_2)_2$, 10 mol % *n*-Bu_4NPF_6, benzene, 0.05 M, 40 °C, 1.75 h) were chosen as the optimized conditions for the remainder of the study.

4.6 Substrate Scope

With working conditions, the effect of changing the alkenyl substituent of the carbinol was examined (Table 16). First, the existence of any stereoelectronic effects imparted by substituents on a phenyl ring was probed using carbinols **20a**-**20e**. When the more electron-rich 4-methoxy phenyl group was employed (as in **20b**), **21b-i** was obtained in 82% yield (entry 2). **20c**, bearing a weakly activating 4-tolyl substituent, cyclized to form **21c-i** in 66% yield as a 6.5:1 isomeric mixture (entry 3). Products **21d-i** and **21e-i** were respectively obtained in 69% and 67% yield for substrates bearing a weakly electron-withdrawing 4-bromophenyl group (**20d**) and a strongly withdrawing 4-trifluoromethyl phenyl substituent (**20e**) (entries 4 and 5). These combined outcomes suggest that due to a slight inductive effect, higher yields are anticipated with strong donor groups on the phenyl rings. The range of weak donors to strong withdrawing groups seems to not show any major change in reactivity.

Table 16 – Synthesis of Cyclopenta[*b*]thiophenes

entry[a]	Carbinol 20	Product 21	yield (%)[b]
			
1	**20a** (R = H)	**21a-i**	70%
2	**20b** (R = 4-OMe)	**21b-i**	82%
3	**20c** (R = 4-Me)[c]	**21c-i : 21c-ii** (6.5 : 1)[d]	66%
4	**20d** (R = 4-Br)	**21d-i**	69%
5	**20e** (R = 4-CF_3)	**21e-i**	67%
6	 **20f**	 **21f-ii : 21f-i** (8.0 : 1)[d]	75%
7	 **20g**	 **21g-iv**	79%
8	 **20h**	 **21h-i**	66%
9	 **20i**	 **21i-i**	22%

[a]Reaction was performed with carbinol **20** and $Ca(NTf_2)_2$ (10 mol %), *n*-Bu_4NPF_6 (10 mol %) in benzene (0.05 M) at 40 °C over 1 hour 45 minutes. [b]Isolated yield after column chromatography. [c]7.0:1 ratio of **20c** to unreacted alkylidene **23c**. [d]Ratio determined by ^{1}H NMR of the product mixture.

To further probe substituent effects on the cyclization, the 2-and 3-methoxyphenyl substrates **20f** and **20g** were subjected to the reaction conditions. In the case of **20f**, the cyclization occurred with 75% yield to furnish **21f-ii** as an 8:1 isomeric mixture with **21f-i** (entry 6). This result was unexpected given the outcome of previous substrates and the thermodynamic preference of **21f-i** over **21f-ii**. The most plausible explanation is that steric influences (imparted by the methoxy group) slow the rate of alkene isomerization. By comparison, **20g** did not produce either **21g-i** or **21g-ii**. Instead, **21g-iv**, where cyclization has occurred onto the aryl group, was isolated in 79% yield (entry 7). This result is consistent with Batey's work[15] where in the intermediate prior to cyclization, either of the two aryl groups can act as the nucleophile to form the 5-membered ring, and the more nucleophilic of the two sites determines which of the aryl groups closes the ring.[17] In our case with **20g**, the phenyl ring has a methoxy group para to the nucleophilic site, generating a more nucleophilic position on the phenyl ring than the competing C-2 on the thiophene ring.

In contrast, only **21h-i** was generated (66% yield) with **21h**, as no cyclization onto the 2-thienyl moiety was observed (entry 8). This outcome agrees with the greater nucleophilicity of the thiophene C-2 vs C-3. For **20i** with a β-styryl substituent, only 22% yield of **21i-i** was isolated along with significant degradation and uncharacterized compound mixtures (entry 9). Given the added delocalization, multiple cationic intermediates can be generated that may undergo competing reactions.

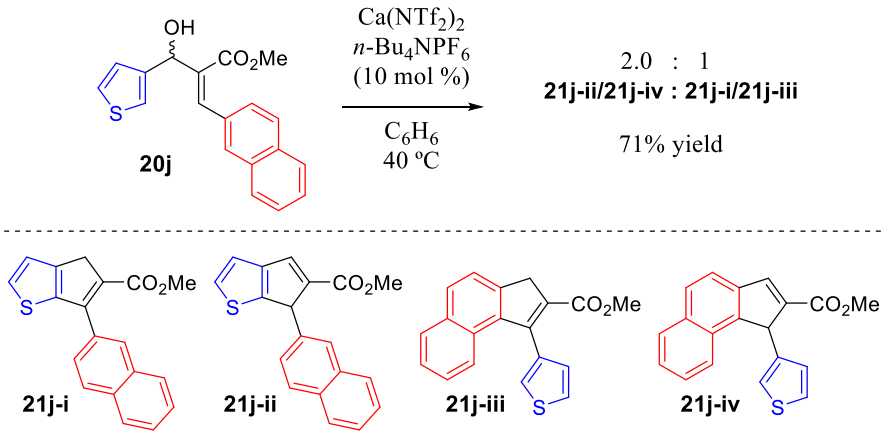
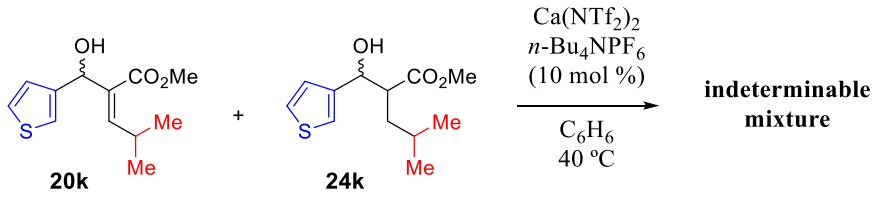


Figure 20 – Complex Product Outcomes of 20j Cyclization

When a 2-naphthyl group was employed as the alkenyl substituent (**20j**), a 20.0:7.0:3.5:1.0 mixture of the four possible isomers was obtained in 71% yield (Figure 20). Given the complexity of the NMR spectra, we were unable to unequivocally correlate each isomer with the observed ratios. Despite that limitation, we were able to determine that a 2.0:1 ratio of trisubstituted alkene isomers (**21j-ii** and **21j-iv**) to tetra-substituted alkene isomers (**21j-i** and **21j-iii**) exists.

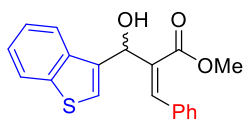
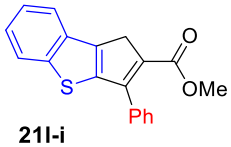
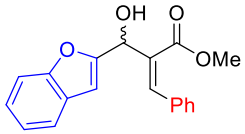
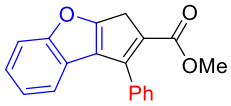
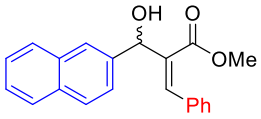
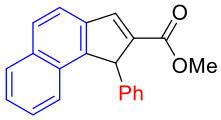
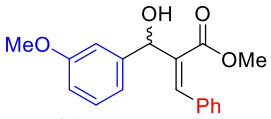
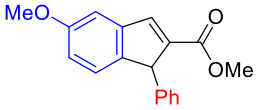
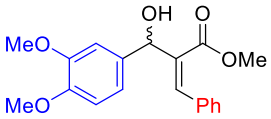
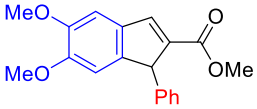
Finally, encouraged by the outcome of **20c** (employed as a mixture with left over starting material **23c**), we subjected the isopropyl-substituted alkenyl substrate **20k** to the cyclization conditions, despite it existing as a 2.0:1 mixture with the fully reduced alcohol **24k** (Scheme 15). Disappointingly, the reaction only gave an indeterminable mixture and neither **20k** nor **24k** was recovered.



Scheme 15 – Attempted Cyclization of 20k Mixture

Next, the effects of replacing the thienyl group with other (hetero)arenes were studied under the optimized conditions (Table 17). 2-Benzothienyl carbinol **20l** cyclized to give benzo[*b*]cyclopenta[*d*]thiophene **21l-i** in 53% yield (entry 1). With 2-benzofuranyl carbinol **20m**, no product **21m** was obtained, as significant decomposition was encountered (entry 2). This outcome is consistent with the low yield (10%) observed by Batey[15] for a similar 3-benzofuranyl derivative.

Table 17 – Changing the (Hetero)aryl Carbinol Substituent

entry[a]	Carbinol 20	Product 21	yield (%)[b]
1	 **20l**	 **21l-i**	53%
2	 **20m**	 **21m-i**	--[c]
3	 **20n**	 **21n-ii**	75%
4	 **20o**	 **21o-ii**	77%
5	 **20p**	 **21p-ii**	68%

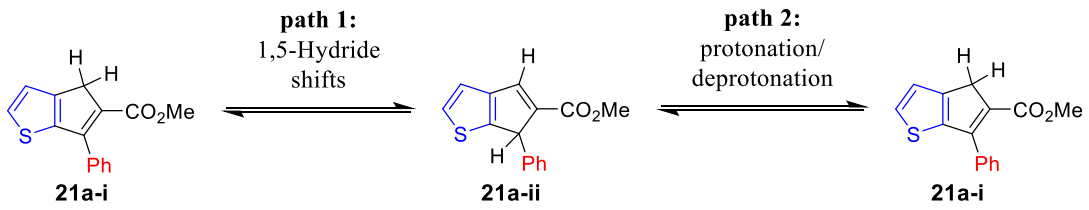
[a]Reaction was performed with carbinol **20** and $Ca(NTf_2)_2$ (10 mol %), *n*-Bu_4NPF_6 (10 mol %) in benzene (0.05 M) at 40 °C over 1 hour 45 minutes. [b]Isolated yield after column chromatography. [c]Decomposition

2-Naphthyl carbinol **20n** proved a competent substrate (75% yield) with alkylation readily occurring at C-1 to form **21n-ii** as the only observable product (entry 3). This result contrasts with what Batey[15] obtained for a 2-naphthyl derivative with a methyl group in place of the ester. In that case, a 3:1 mixture of product from C-1 alkylation and product from cyclization onto the phenyl group was formed. Lastly, in agreement with Batey's observations, 3-methoxysubstituted phenyl carbinols (**20o**) expectedly gave the

corresponding indene **21o-ii** in 77% yield (entry 4). A similar result was obtained with the 3,4-dimethoxy substrate **20p**, yielding the indene **21p-ii** in 68% yield (entry 5).

4.7 Isomerization Studies*

After establishing a good understanding of the effects of changes in substrate, questions about the nature of product ratios persisted. The reaction appeared to be more complicated than a simple kinetic vs thermodynamic product argument due to the fact that the ratios oscillated, changing in both directions. Two plausible mechanisms for the interconversion exist (Scheme 16). In the first case, two 1,5-H shifts occur in tandem (converting from the 4*H*-, 5*H*-, and 6*H*-cyclopenta[*b*]thiophenes and vice versa). The second mechanism involves acid/base-mediated protonation/deprotonation. Another possibility, of course, would be some combination of the two if they occur concurrently. In an attempt to gain a deeper understanding of the interconversion between products **21a-i** and **21a-ii**, a series of control reactions were performed.



Scheme 16 – Plausible Mechanisms for Interconversion

* Work for the isomerization studies performed independently

The control reactions performed during the optimization phase of our study relied on DCM as the solvent, as opposed to benzene. Exposure of **20a** to the $Ca(NTf_2)_2$ and additive *n*-Bu_4NPF_6 for different reaction times (Figure 21, yellow line) resulted in varying ratios of **21a-i** to **21a-ii**, with no apparent pattern other than consistent outcomes at one hour 45 minutes. Exposure of a known ratio of **21a-i** to **21a-ii** to the same conditions (Figure 21, red line) resulted in fluctuations in ratio. These outcomes were sufficient to inform us that something strange was occurring, but did not provide any rationale as to why or how.

To further interrogate the the nature of the interconversion we sought to plot product ratios as a function of exposure time using: (1) the optimized reaction conditions in benzene starting with **20a** (Figure 21, blue line); (2) heating and stirring a known ratio of **21a-i** to **21a-ii** (Figure 21, green line); and (3) heating and stirring a ratio of **21a-i** to **21a-ii** in the presence of a Brønsted acid (Tf_2NH) (Figure 21, purple line). The results of these studies, along with the studies in DCM, are all shown in Figure 21. All reactions were performed at 40 °C. Unfortunately, we were unable to simply do the reaction in an NMR tube due to the low solubility of the $Ca(NTf_2)_2$ in deuterated benzene and poor mixing available in an NMR tube.

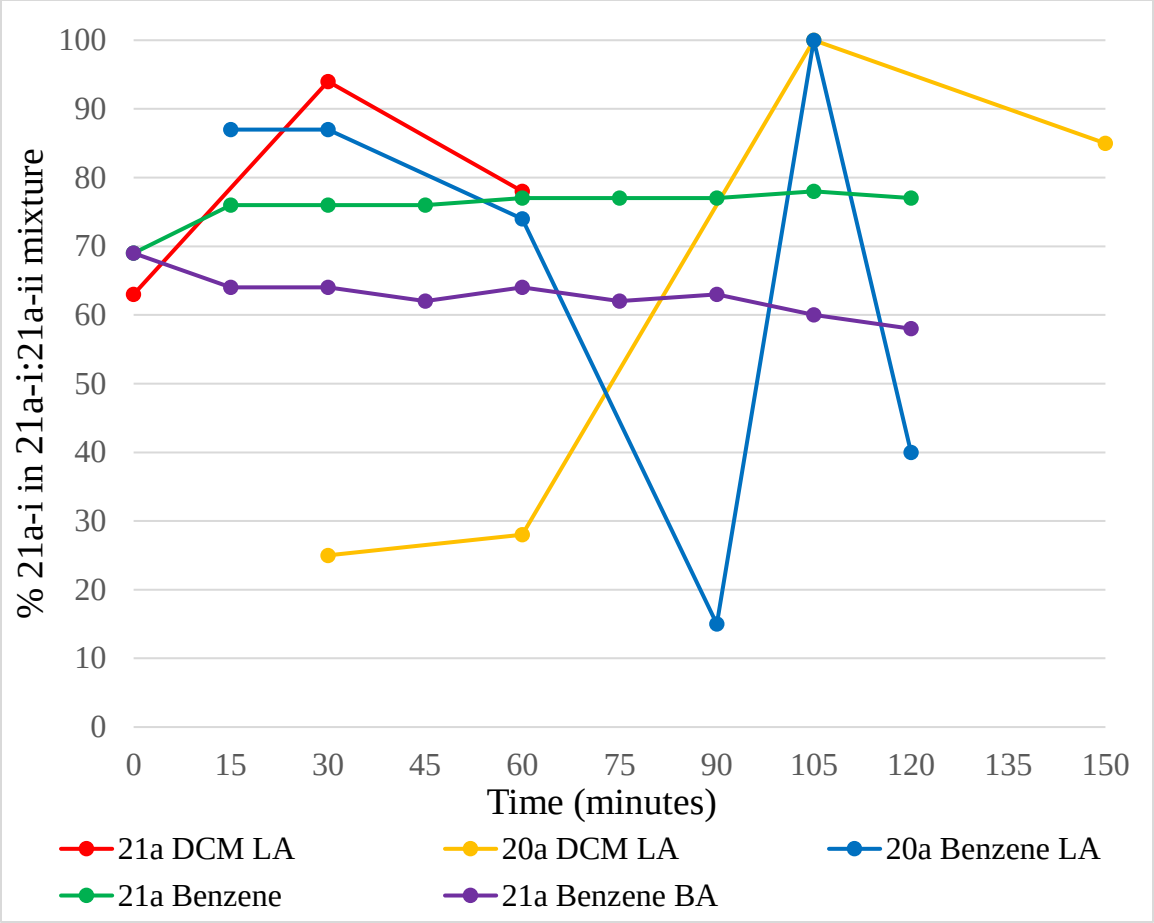


Figure 21 – Control Reactions Probing Product Ratios as a Function of Time

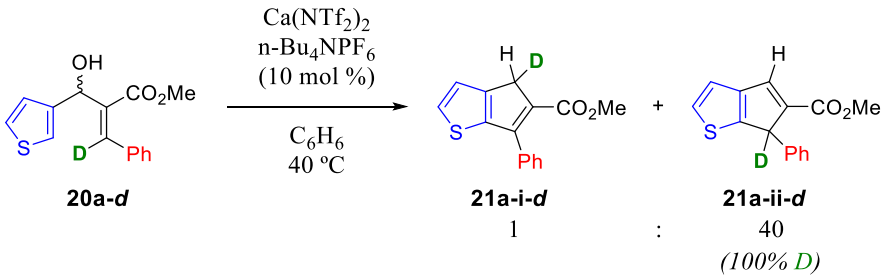
Significant fluctuations in product ratios between 60 and 120 minutes were observed for the optimized reaction starting with **20a** (Figure 21, blue line). Each data point is a unique reaction, set up concurrently with the others but with differing quenching moments. Full conversion of **20a** to **21a** was observed within 15 minutes. Isolated product yields remained consistent for each time point (within 5%) of the optimized 67% yield previously observed. Product degradation does not seem to be an issue, as yields do not seem to worsen over the time span of 15 minutes and 120 minutes. Oscillation of product

ratios was observed under these conditions; however at 105 minutes, only **21a-i** persists in solution (this was replicated between researchers). Although our approach was only able to offer a handful of data points, we were able to definitively conclude that the two isomers exist and interchange within our optimized benzene conditions, not just in DCM.

The next two experiments involved subjecting a 2.2:1 ratio of **21a-i** to **21a-ii** to heating and stirring in benzene either with 10 mol % Tf_2NH (Figure 21, purple line) or without (Figure 21, green line). The reactions were set up using the same solution of **21a** in benzene split into two flasks, both heated to 40 °C in the same oil bath. If the interconversion were the result of purely thermodynamic H-shifts, product oscillation would be observed with simple heating and stirring over time. If it were protonation/deprotonation instead, oscillation should only occur with acid present. The results for both show a minor change (~5%) in ratio within the first 15 min, followed by little change at all (<5%). It seems as though interconversion is very slow or the system had reached equilibrium. This result is distinctly different from the other data sets involving the calcium catalyst, which seems to be responsible for the large oscillations. One can speculate that there may be some sort of complex involving the calcium catalyst and the products that facilitates interconversion. Another plausible explanation for the wide shifts is that with the calcium complex, a heterogeneous mixture is formed whereas the lines that hold steady are homogenous mixtures.

In one final attempt at probing the hydride shift mechanism, the deuterated starting material, **20a-*d***, was synthesized and subjected to the optimized reaction conditions (Scheme 17). **21a-ii-*d*** was obtained as the major product in a 40:1 ratio of **21a-ii-*d*:21a-i-*d***. The major product was fully deuterated. This result was repeated at 30 min and 60 min

reaction times as well, with effectively identical results. Unfortunately, because such small amounts of **21a-i-*d*** formed, the extent of deuterium incorporation was not determined. Similarly, the control reaction of non-deuterated **20a** in deuterated benzene showed no deuterium incorporation, although it did show a change in product ratio, indicating a solvent effect.



20a-*d* **21a-i-*d*** : **21a-ii-*d***

1 : 40

(100% D)

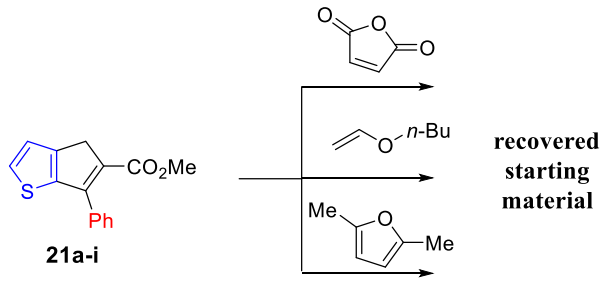
Scheme 17 – Dehydrative Cyclization of 20a-*d*

Some strong mechanistic conclusions can be drawn from these deuterium studies. The consistency over time and overwhelming prevalence of the **21a-ii-*d*** isomer indicates that it forms first in the reaction and the presence of the deuterium prevents isomerization, suggesting a very large kinetic isotope effect. Mechanistically, this means that the **ii** isomer is the first to form in the reaction and it subsequently isomerizes in the instances that we see the **i** isomer. The same is true for the formation of indenes where the aryl off the alkene is the preferential nucleophile, as opposed to the aryl group off the carbinol; the **iv** isomer would form before the **iii** isomer.

Although we cannot make definitive conclusions on how and why the product seems to oscillate between the two isomers **21a-i** and **21a-ii**, we have learned several important details about the reaction from our studies. (1) The reaction initially, and rapidly, generates isomers **ii** (or **iv**) and any variations in isolated product ratios observed are the result of isomerization. (2) There is a large KIE for isomerization. (3) Although the isomerization does not require the calcium catalyst, it is likely the cause for the large oscillations in product ratios. (4) There are observable solvent effects on the isomerization rate.

4.8 Attempted Derivatizations

Inspired by Skramstad's report demonstrating that the transient 5*H*-cyclopenta[*b*]thiophene isomer can undergo Diels-Alder-type cyclizations,[10c] we reacted cyclopenta[*b*]thiophene product **21a** with various dienophiles as well as a diene to explore reactivity (Scheme 18). Unfortunately, no reactivity was observed between **21a** and maleic anhydride (to probe normal electron demand cycloaddition), *n*-butyl vinyl ether (to probe inverse electron demand cycloaddition), or 2,5-dimethylfuran (to probe if **21a** can behave as a dienophile).



Scheme 18 – Attempted Diels-Alder-type Cycloadditions of 21a-i

4.9 Conclusions

In summary, we disclosed a calcium-catalyzed protocol for the dehydrative, Nazarov-type electrocyclization of alkenyl (hetero)aryl carbinols that allows access to functionalized cyclopenta[*b*]thiophenes and indenes. Products are isolated in up to 82% yield. Good tolerance for aryl and heteroaryl substituents on the alkene was demonstrated, whereas a β-styryl substituent gave low yield. Substituent effects play a significant role in determining product outcomes and isomeric ratios. For systems with competing (hetero) aryl substituents, cyclization occurs preferentially on the most nucleophilic ring. When the relative nucleophilicities are close, mixtures are then observed. For the 3-thienyl series (without a competing aryl substituent), the reaction is selective for the thermodynamic alkene isomer in all but one case, whereas the arene series favors the kinetic alkene isomer for the resulting indenes. This transformation represents one of the only examples of catalytic, dehydrative, Nazarov-type electrocyclizations in which thiophenes are compatible. Thus, it allows for the direct formation of cyclopenta[*b*]thiopenes and it circumvents the need for cyclopenta[*b*]thiophenones as precursors. A current lab member is applying this method towards the synthesis of functionalized cyclopenta[*b*]thiophenes,

which they aim to use in the synthesis of new catalysts. This project also set the example of successfully extending the things we learned in our previous dehydrative cyclization methods (Chapters 2 and 3) to similar systems.

4.10 Experimental

The experimental section and characterization for compounds in chapter 4 can be found in the supporting information of the article: Martin, M. C.; Sandridge, M. J.; Williams, C. W.; Francis, Z. A.; France, S. *Tetrahedron* **2017**, *73*, 4093.

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CHAPTER 5. NEXT STEPS AND CONCLUDING REMARKS

5.1 Overview

Towards the goal of developing new methodologies for the synthetic chemist, three novel synthetic methodologies that make use of dehydrative cyclizations of carbinols via Lewis acid catalysis have been developed and outlined in this thesis: (1) A calcium-catalyzed, dehydrative, ring-opening cyclization of cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes; (2) A $Bi(OTf)_3$-catalyzed synthesis of α-alkylidene-γ-butyrolactones from the ring-opening cyclization of cyclopropyl carbinols; (3) A calcium-catalyzed synthesis of cyclopenta[*b*]thiophenes and indenes via dehydrative Nazarov-type electrocyclizations of alkenyl (hetero)aryl carbinols. We placed special emphasis on understanding the mechanistic details of how each of these methods work, allowing readers and potential users the ability to better adapt these methodologies to their own purposes. Each of these methods built upon our understanding of related synthetic methodologies established by our lab, with the first project providing the major foundation for the second two. Just as these projects drew inspiration from other projects, they also provide the inspiration for future projects.

The foundation for these projects, and this thesis, is that the advantages of dehydrative cyclization reactions can be implemented in the cyclization methodologies we previously established that were not originally dehydrative, resulting in new branching points and complimentary reactivity for structural diversity. In keeping to the values of DOS, we established new, meaningful branching points within existing methods that allow for efficient access to a diverse range of molecular structures. These methods used existing

methods to access precursors, followed by a reduction of a ketone to access the useful carbinol substrates in each method.

Many of our synthetic schemes start from (hetero)aryl β-ketoesters, which are then built upon. Each of these methodologies carries a ketone through the synthesis and should allow for a dehydrative variant through use of a reduction step. This begs that the continuation of the pattern of generating dehydrative variants of our previous methodologies could be productive and should be seriously considered. Should uses for the proposed methodologies exist, we should explore them. Two new projects that immediately fit into this scenario are the dehydrative ring-opening cyclizations of cyclobutyl carbinols and alkylidene cyclopropyl carbinols. The other logical next step for continued research beyond a method itself is the application of the method, such as using it to access target molecules. These next steps, the dehydrative ring-opening cyclizations of cyclobutyl carbinols and alkylidene cyclopropyl carbinols as well as progress towards target natural products, are projects we have initiated. The initial results and the projected directions for these projects are outlined in this concluding chapter.

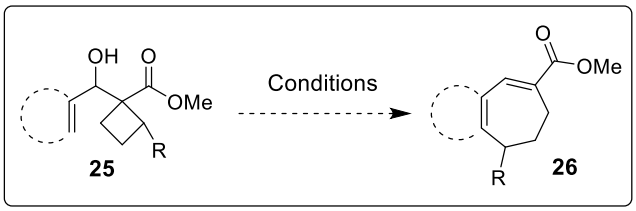
5.2 Dehydrative Ring-opening Cyclizations of Cyclobutyl Carbinols[*]

5.2.1 Background

As mentioned in Chapter 1, cyclobutanes can behave similarly to cyclopropanes in that they are sources of ring strain that can be leveraged in similar ways as cyclopropanes. Applying existing methods for the dehydrative ring opening cyclizations of cyclopropyl

[*] Most synthetic work on this project performed by Akash Doshi, a Georgia Tech undergraduate, under my supervision

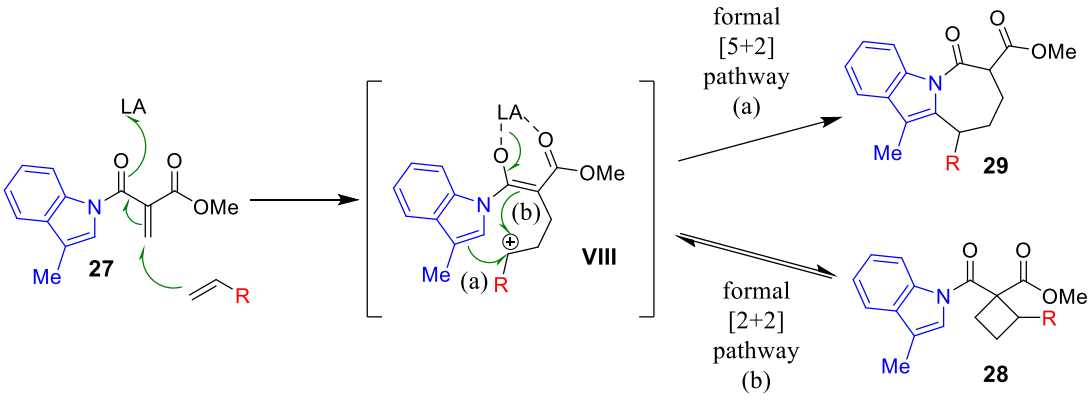
carbinols to cyclobutyl carbinols would potentially allow for similar reactivities but with formed rings that have one more carbon. This would allow for the formation of 7-membered rings **26** when going through the Friedel-Crafts type pathway from cyclobutyl carbinols **25** (Scheme 19). This would be a bit more difficult than the cyclopropyl carbinol projects, however, simply because it is more difficult to form 4- and 7-membered rings than it is to form 3- and 6-membered rings. Our lab does have experience working with these systems, which will help us in this endeavor.



Scheme 19 – Dehydrative Ring-opening Cyclizations of Cyclobutyl Carbinols

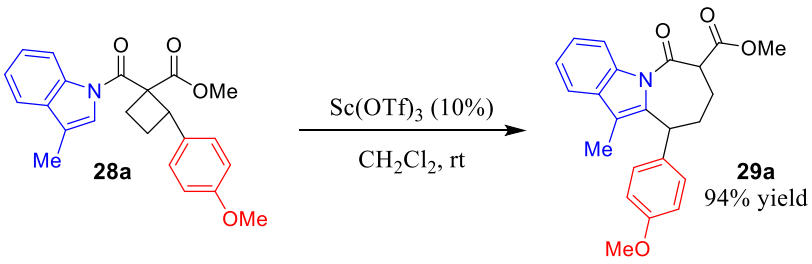
Our lab has previously established a methodology for a formal [5+2] cycloaddition towards azepino[1,2-*a*]indoles **29**.[1] This project originated under the premise of generating the D-A cyclobutanes through a [2+2] cycloaddition, which would then be exposed to a new set of conditions to undergo ring-opening cyclization to form the 7-membered ring. We actually observed that the 7-membered ring could be formed without the isolation of the cyclobutanes, so the method naturally followed that more efficient course. Mechanistically, the intermediate **VIII** serves as branching point towards either the 7- or

4-membered ring formation, where 4-membered ring formation is reversible depending on choice of Lewis acid catalyst that activates alkylidene **27** to Michael addition (Scheme 20).



Scheme 20 – Formal [5+2] Mechanism

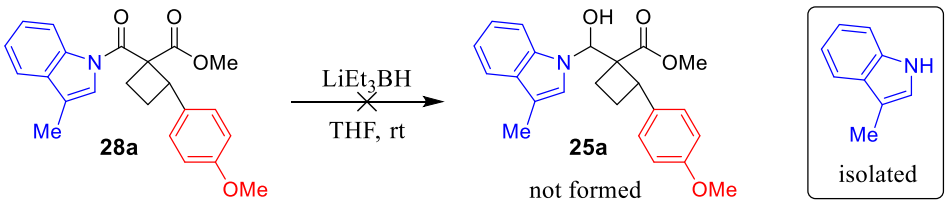
Although we typically sought formation of **29**, we were also able to show that D-A cyclobutanes **28** could be isolated, and exposure of them to catalytic Lewis acid resulting in 7-membered ring formation, presumably through intermediate **VIII**. As an example from the paper, D-A cyclobutane **28a** could be isolated, and upon exposure to catalytic Lewis acid, compound **29a** was isolated in a high yield. This observation provides strong evidence that the transformation of cyclobutyl carbinols **25** to 7-membered rings **26** is viable. We predicted that cyclobutyl carbinols **25** could be accessed from D-A cyclobutanes **28** through reduction conditions similar to those we used to access cyclopropyl carbinols from D-A cyclopropanes.



Scheme 21 – Ring-opening Cyclization of Cyclobutane 28a

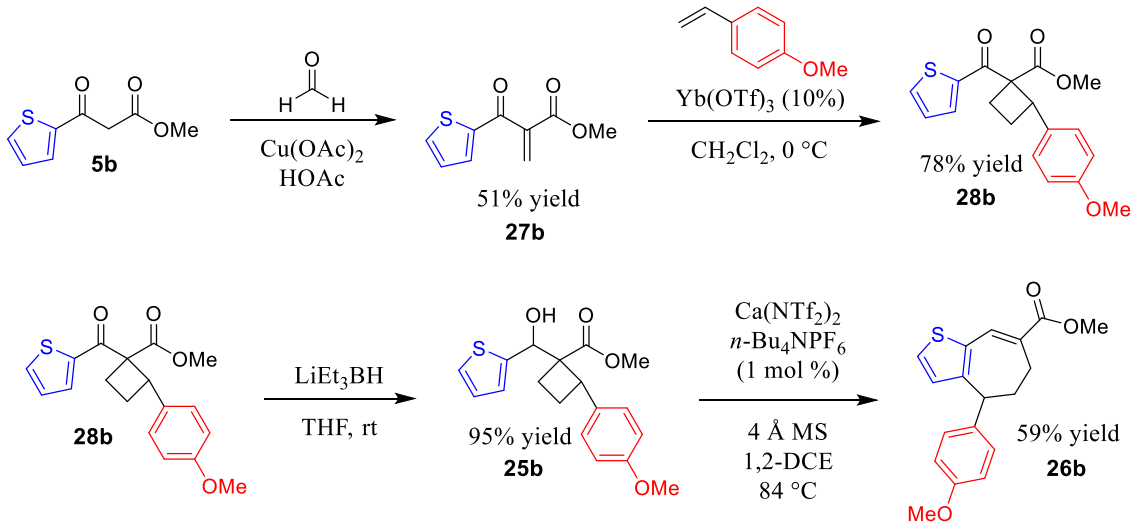
5.2.2 Initial Results

Initially, we took cyclobutane **28a**, which we had previously isolated, and attempted a reduction step to access the cyclobutyl carbinol **25a**, which would be an excellent substrate for a direct comparison to the transformation of **28a** to **29a** (Scheme 22). Unfortunately, 3-methylindole proved to be a good leaving group, and rendered the substrate unamenable to reduction (or nucleophilic attack at the carbonyl). It is highly likely that the presence of a leaving group on the carbonyl would also be an issue for reduction steps in any previous methods discussed in this thesis.



Scheme 22 – Attempted Reduction of 28a

Unfazed by the reduction failure of substrate **28a**, we decided to revisit making some alternative cyclobutanes using the methods we previously employed in the synthesis of **28a**. We synthesized cyclobutane **28b** though a [2+2] cycloaddition of a styrene derivative with alkylidene **26b**, which we access from the β-ketoester **5b** (Scheme 23). We then subjected cyclobutanes **27b** to our previously optimized reduction conditions, which provided the reduced cyclobutyl carbinol **25b** in high yield. We then took the reaction forward and exposed **25b** to the optimized dehydrative homo-Nazarov cyclization conditions. Gratifyingly, the seven membered ring **26b** was formed in a 59% yield, which is highly encouraging for an initial result.



Scheme 23 – Successful Synthesis and Dehydrative Ring-opening Cyclization of Cyclobutyl Carbinol 25b

Unfortunately, the methods for accessing arylketone cyclobutanes **28** are not robust, and many issues prohibited us from obtaining a meaningful substrate scope to test using the synthetic route outlined in Scheme 23. For example, many of the alkylidenes **27** are unstable or the reaction to make them is very low yielding, resulting in a small subset of alkylidenes to use. Those we can make are also not particularly reactive, only providing cyclobutanes in cases where a strong donor is employed in the [2+2] cycloaddition. Alkylidene **27b** was exposed to a total of six more alkenes beyond the one used for **24b** synthesis, including a donating 4-Me styrene. No cyclobutanes formation was observed in any case and the alkylidene degraded (Figure 22A). We attempted a nucleophilic displacement of a known diester cyclobutane **30**, which generated a complex mixture where we could not identify nor disprove the presence of the desired product Figure 22B).

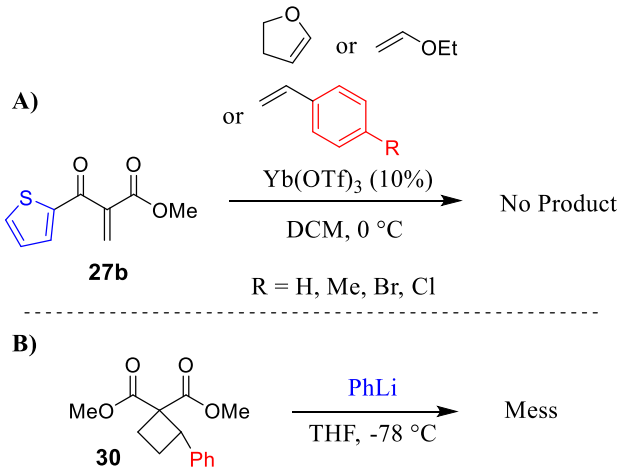
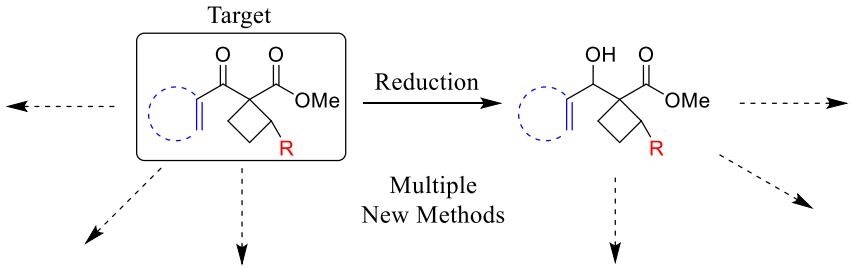


Figure 22 – Unsuccessful Aryl Ketone Cyclobutane Syntheses

5.2.3 New Focus

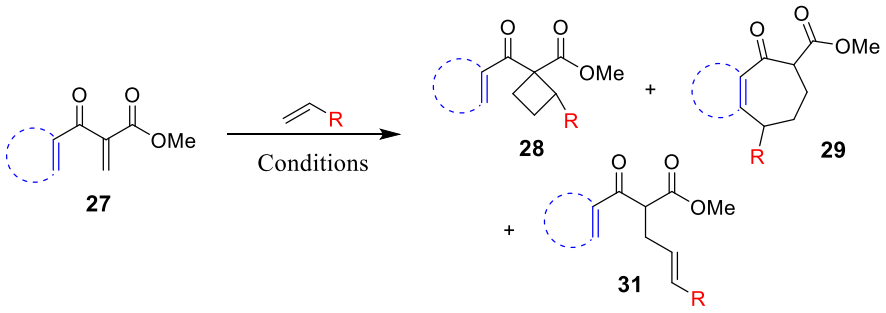
With the limitations of building a suitable scope of cyclobutanes in mind, and numerous attempts to do so using previous methods, we have decided to change the focus of the project. For now we seek to develop a new, robust approach to donor-acceptor cyclobutanes that incorporate geminal acceptors, one being an aryl ketone. Developing this project will not only allow access to the dehydrative methods we have shown, but also access to methods that employ the donor-acceptor cyclobutanes we would be making themselves (Scheme 24).



Scheme 24 – New Focus

Cyclobutanes in general are synthesized frequently both as targets and useful synthetic intermediates; however, the popular method of light-mediated [2+2] cycloaddition frequently employed do not lend themselves well to D-A cyclopropanes containing geminal acceptors, as the excited states generated exhibit Umpolung-type reactivity.[2] This would result in undesired regioselectivity in the [2+2]. We had instead started our investigations with the approach used towards **28b**, outlined in scheme 22,

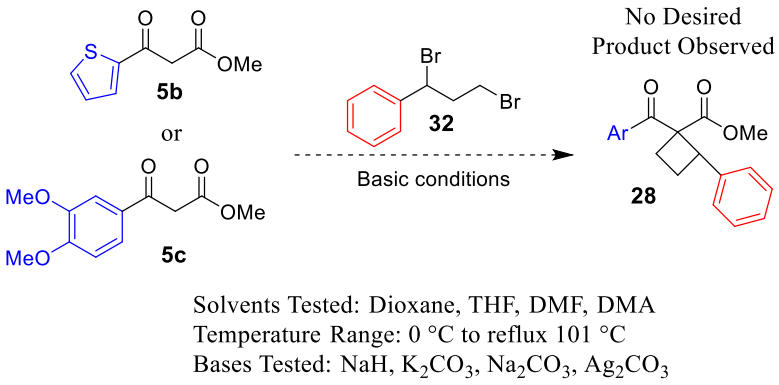
which follows the approach overwhelmingly taken in literature towards D-A cyclobutanes containing geminal acceptor groups. This approach is characterized by the use of a malonate-derived alkylidene, a Lewis acid (Sc, Zn, Fe, In, or Yb based) and an aryl- amino- or alkoxy-substituted alkene.[3] Unfortunately, using similar methods for our system did not provide the diversity of substrates we sought.



Scheme 25 – Reaction Outcomes of [2+2] Reaction Conditions

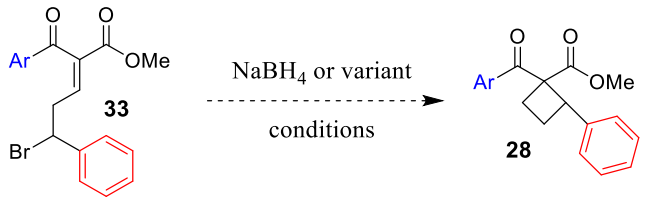
In addition to degradation of the alkylidene **27** without interacting with the partner alkene in a [2+2], competing formal [5+2] to form products **29** and E1 type products **31** exist (Scheme 25). The general difficulty of accessing the alkylidene and the difficulty we have experienced in using them has led us to search for different types of methods. Our initial attempts toward aryl ketone cyclobutanes from the better established malonate cyclobutanes have also not been fruitful. It is still possible; however, that methods used for malonate cyclobutanes may work with β-ketoesters with some tweaking. As such, we have been investigating a dialkylation approach to the cyclobutanes, a rare example of D-A cyclobutane synthesis not employing [2+2] cycloadditions, employed by the Johnson

lab.[3a,4] Unfortunately, we have yet to observe cyclobutane formation with our initial attempts (Scheme 26).



Scheme 26 – Attempted Dialkylation Approach to Cyclobutanes

Even monoalkylation seems to be a major hurdle for our systems, so in our next attempts we might take an alternative approach. One such approach would be to have a hydride-mediated variant of the above reactivity, such that only the second alkylation need occur. We would use substrates of type **33** to test this (Scheme 27). Once we have suitable methods for accessing arylketone cyclobutanes, we will explore the scope of the reaction and concurrently begin to push forward a handful of other projects that make use of the cyclobutanes, including the dehydrative cyclization reactions of cyclobutyl carbinols.

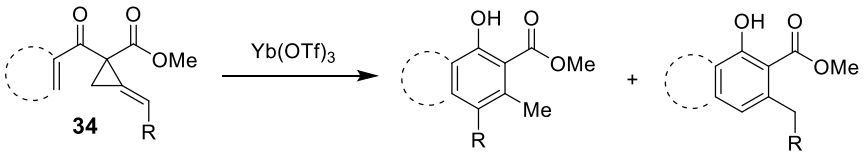


Scheme 27 – Hydride-mediated Alkylation towards Cyclobutanes

5.3 Dehydrative Ring-opening Cyclizations of Alkylidene Cyclopropyl Carbinols*

5.3.1 Background

Another potentially useful methodology to develop would be dehydrative cyclizations of alkylidene cyclopropyl carbinols. This project would be based both on the contents of Chapters 2 and 3 and previous work from the France lab exploring ring-opening cyclizations of alkylidene cyclopropanes **34,** continuing the theme of generating dehydrative variants to our existing methods (Scheme 28).[5]

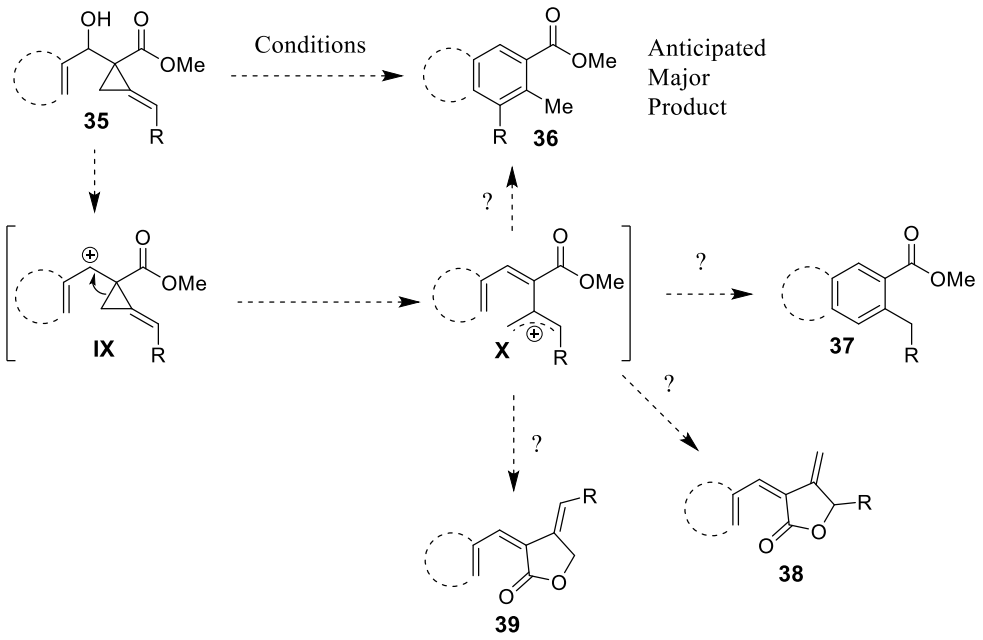


Scheme 28 – Ring-opening Cyclizations of Alkylidene Cyclopropanes

* Work on this project performed independently

5.3.2 Advantages

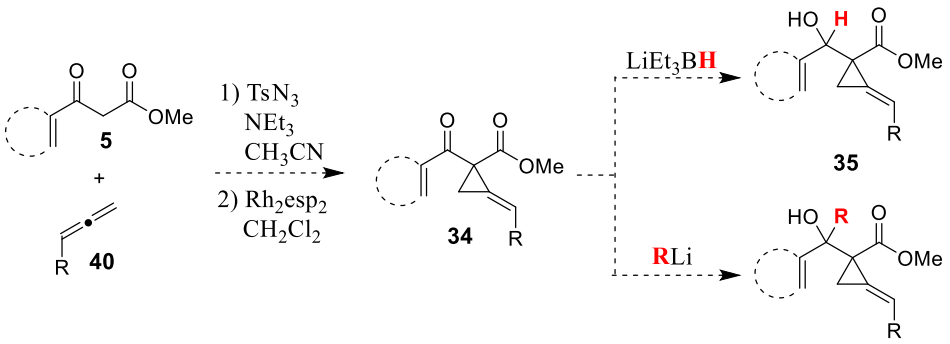
Major advantages to developing this methodology would be the correct carbon count necessary for lignan natural product core structures; our previous methodological examples were missing one carbon. In addition, many different types of desirable core structures could potentially be accessed (Scheme 29). The anticipated major outcome would be products **36**, but products **37**, **38**, and **39** are all plausible outcomes from the ring-opened intermediate **X**. Due to the abundance of potential outcomes, controlling the reactivity will be both meaningful and difficult. We envisioned that the carbinols **33** could be readily accessed from alkylidene cyclopropanes **34** using similar reduction conditions to those employed to access our cyclopropyl carbinols **8**.



Scheme 29 – Potential Interesting Outcomes of Proposed Methodology

5.3.3 Initial Results

Our proposed approach to the alkylidene cyclopropyl carbinols mirrors the typical approach employed in our previous investigations of alkylidene cyclopropanes, where a diazo transfer is performed on β-ketoesters **5**, followed by are reaction with allenes **40** in the presence of a rhodium catalyst to form the alkylidene cyclopropane (Scheme 30). This alkylidene cyclopropane is then reduced or exposed to a suitable nucleophile to afford the desired carbinols **35**.



Scheme 30 – Synthesis of Alkylidene Cyclopropyl Carbinols

We have successfully synthesized one alkylidene cyclopropyl carbinol of type **35**; however, we have yet to make any on a sufficiently large scale for the purposes of testing product outcomes and optimizing observed reaction pathways. We had initially chosen substrate **35a** as our preferred optimization substrate, as it is most similar to optimization substrate **8d** from our previous studies (Figure 23). This potentially provides familiarity in product outcomes.

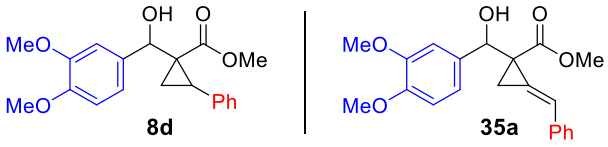


Figure 23 – Optimization Substrates

The second step of our initial proposed approach proved particularly low yielding for the synthesis of unreduced alkylidene cyclopropane **34a** (Figure 24A), so we decided

to use an alternative approach towards **34a** of using an aryl lithiate to displace an ester on a malonate-derived alkylidene cyclopropane **41**, which we could readily access (Figure 24B). Multiple attempts at this reaction were made, frequently resulting in products that were isolated with impurities – only one attempt showed pure cyclopropane **34a**, although it had lower yield than anticipated. Further work on this reaction may be necessary for synthesis of appreciable amounts of **34a**.

Although yields were low for the synthesis of **34a**, we were able to obtain enough material to attempt a reduction reaction (Figure 24C). This was performed on both pure **34a** and impure **34a**, with yields that were moderate and in both cases minor impurities were obtained with the desired product **35a**. This is encouraging in that we were able to achieve formation of products **35** using alkylidene cyclopropanes **34** without further optimizing our reduction conditions.

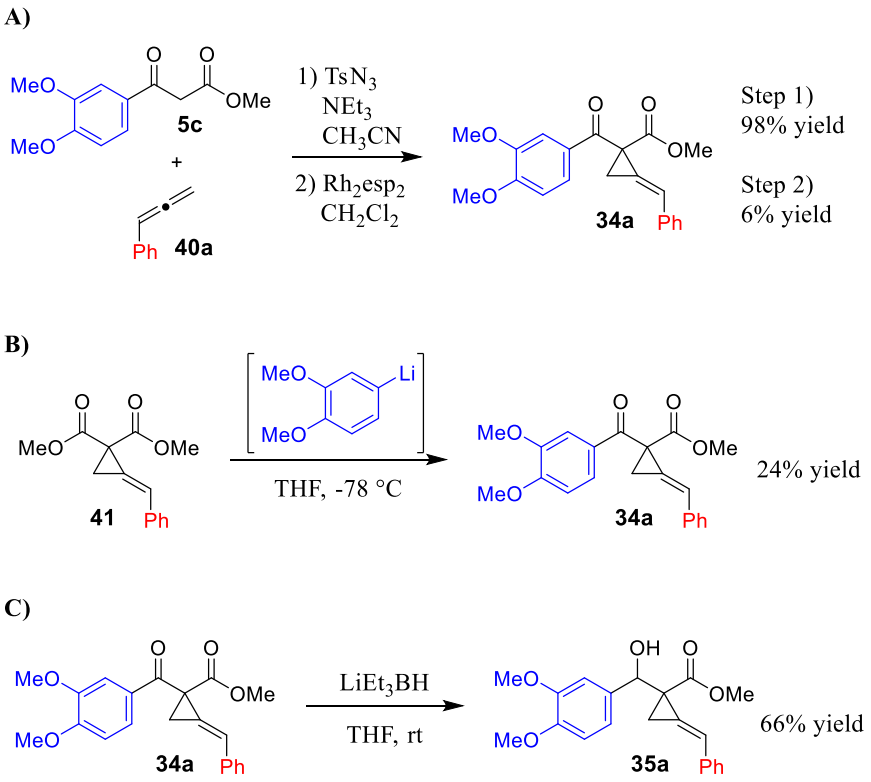
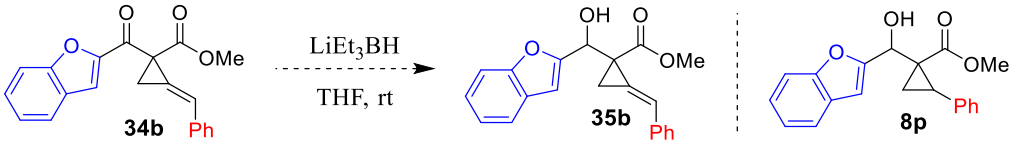


Figure 24 – Synthesis of Alkylidene Cyclopropyl Carbinol 35a

Considering the issues of both low yields and impurities being present independent on the route taken to **35a**, we propose using an alternative substrate for optimization purposes as obtaining grams of **35a** seems difficult at best. We propose benzofuranyl substrate **35b** as the new optimization substrate, considering synthesis of alkylidene cyclopropane **34b**, as shown in our publication,[5] is known and robust (Scheme 31, left). It is also the structurally very similar to substrate **8p** (Scheme 31, right), which performed moderately well in both cyclization reactions in Chapters 2 and 3, indicating it can be controlled. The combination of it being readily accessible as well as our prior evidence for

it being a likely agreeable substrate for manipulating selectivity make substrate **35b** a strong substrate for probing the reactivity of these systems.



Scheme 31 – New Proposed Optimization Substrate

The next steps for this project are to synthesize appreciable amounts of **35b** for probing and optimization of the ring-opening cyclization reaction(s). Following optimization, the project will finish with the exploration of a substrate scope and potentially the synthesis of a target molecule or two.

5.4 Target Synthesis*

5.4.1 Isolation and Syntheses

In 1996, two lignans, (+)-magnoliadiol and (-)-magnofargesin, were both isolated from flower buds of Magnolia fargesii and fully characterized structurally (Figure 25).[6] To date, two syntheses of (-)-magnofargesin exist. In 2006, Wardrop and Fritz published the first total synthesis of racemic (±)-magnofargesin.[7] The final step of their approach yielded a 0.85:1 mixture of (±)-magnofargesin and (±)-7′-epimagnofargesin (Figure 25), which

* Work on this project performed in collaboration with Meghan C. Benda

they separated using semi-preparative HPLC. In 2012 the Roy lab published the first optically active formal synthesis of magnofargesin.[8] The final step resulted in a 1:1 mixture of magnofargesin and 7′-epimagnofargesin, which they were unable to separate. Although they reported an optically active product, neither the identity of the major enantiomer nor a measure of the enantiomeric purity for the synthesis were reported. No synthesis of (+)-magnoliadiol have been reported in the literature to date.

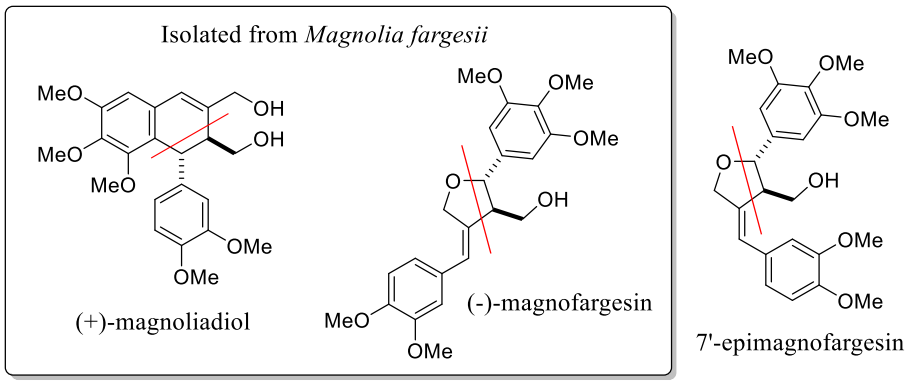
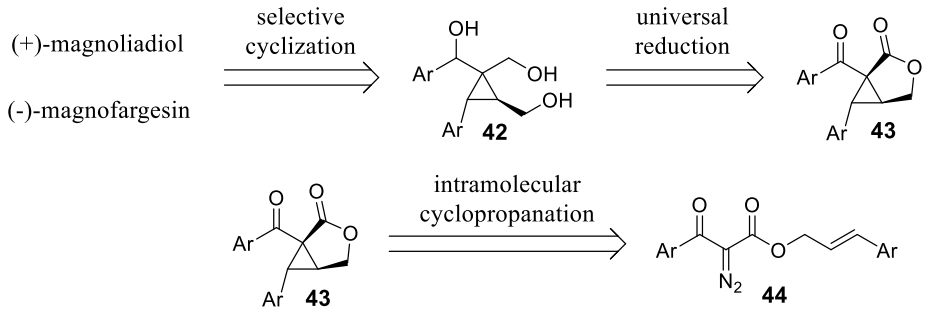


Figure 25 – Lignans (+)-Magnoliadiol and (-)-Magnofargesin with Synthetic Epimer 7′-Epimagnofargesin

Many lignans are dimers of phenyl propanoids, and (+)-magnoliadiol and (-)-magnofargesin seem to be made from the same two building blocks annealed together in different ways – ones with strong similarities to core structures accessible from the first two methodologies presented in Chapters 2 and 3. With this in mind, we view their total synthesis as both a meaningful showcase of the strengths of our established methods as well as an opportunity to take those methods to a new level.

5.4.2 Proposed Approach

Ideally, these two natural products could originate from starting compounds similar to the established cyclopropyl carbinols, with the core structure selectivities also determined by the same set of catalytic conditions. A retrosynthetic analysis shows our approach (Scheme 32). The natural products would come from a cyclopropane **42** containing three alcohols, which would arise from a universal reduction of a fused cyclopropyllactone **43**, which would in turn come from an intramolecular cyclopropanation of diazo **44**, which should be available in 3-6 steps from commercially available starting materials, depending on the aryl groups.



Scheme 32 – Retrosynthetic Analysis for Natural Products

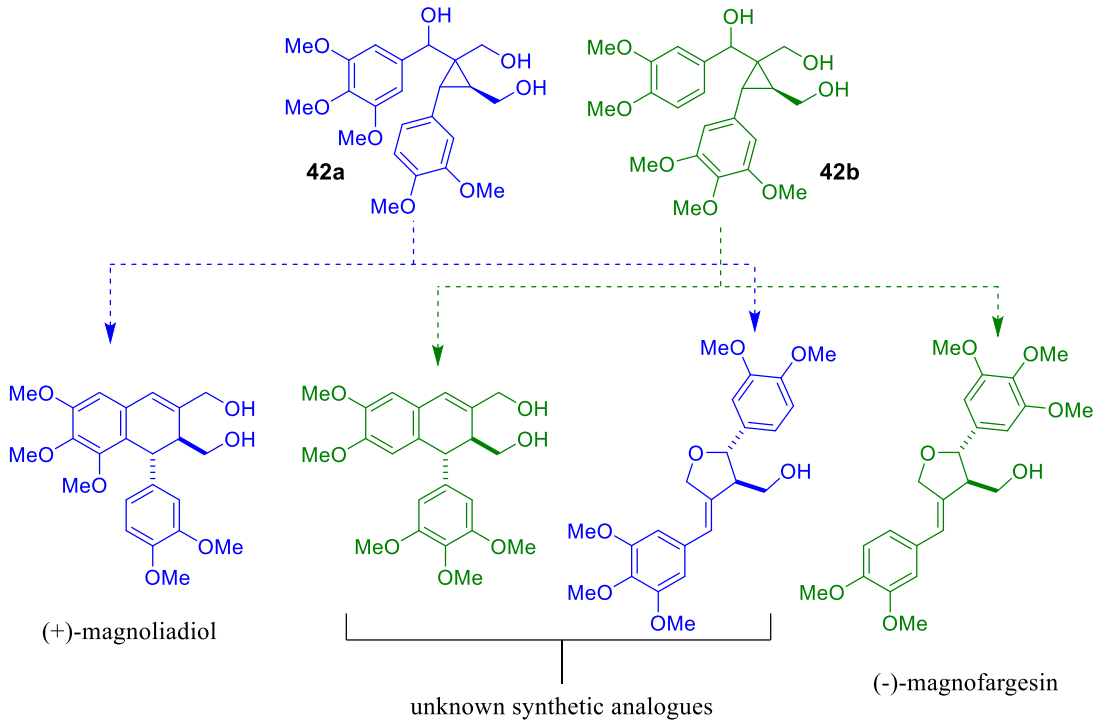


Figure 26 – Natural Product Starting Materials

Although the two natural products seem to be made of the same two parts (and probably are biosynthetically), they require different starting materials to access. Compound **42a** would be used to access (+)-magnoliadiol and substrate **42b** would be used to access (-)-magnofargesin (Figure 26). Although this is a minor inconvenience for the actual synthesis of the two natural products, it is not a hindrance to the method itself. It is likely that the unknown synthetic analogues of the natural products (arising from taking same starting materials, but undergoing the alternative path leading away from the natural product) will have similar biological activities to the natural products themselves, as the only difference is the shift of a methoxy. All four compounds, therefore, would be valuable to obtain and test for various biological activities.

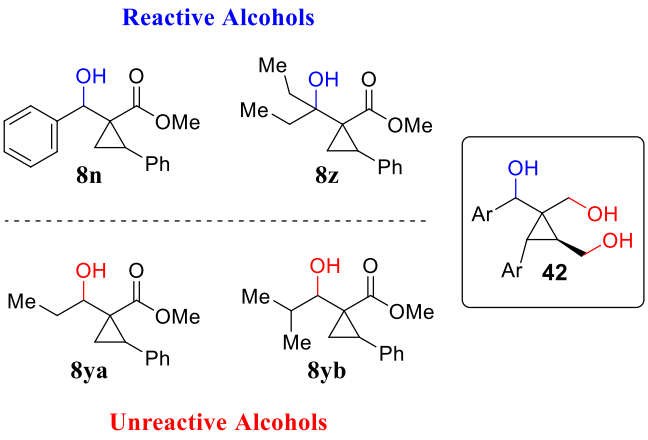


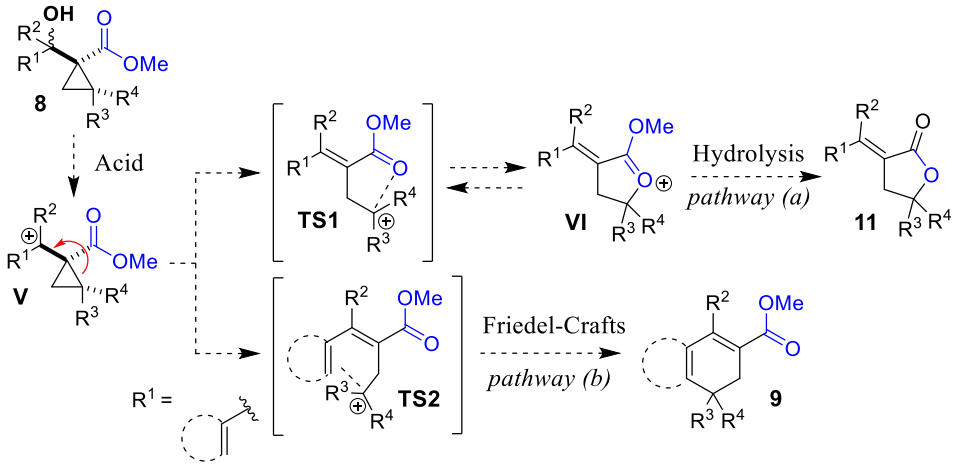
Figure 27 – Reactive and Unreactive Alcohols under Reaction Conditions

The proposed approach to the natural products has multiple obstacles to overcome. The first is that there are multiple free alcohols in the starting material (**42**) of the proposed selective dehydration. Only the π-activated alcohol is expected to be removed, based on our previous substrates (Figure 27). Secondary alcohols **8y** proved unreactive under our reaction conditions whereas tertiary alkyl alcohol **8z** and π-activated alcohols such as **8n** were reactive. Although they are unlikely to undergo dehydrations, the other alcohols may still prove to be a hindrance to the reaction.

In addition to the potential for complications from multiple free alcohols, the reactivity of the cyclopropane ring may also be altered. This is because the starting cyclopropanes **42** also have reduced polarization compared to our previous system, as the ester (previously acting as an acceptor) is gone. This means their reactivity is entirely

dependent on cyclopropyl carbinol chemistry and has little assistance from the D-A aspects previously present.

Setting stereochemistry is also expected to be an obstacle, although only one stereocenter must be set; we intend to set it during the cyclopropanation from **44** to **43** using a chiral rhodium catalyst. Chiral information at other parts of compound **42** will be lost upon ring-opening, and the information at the one stereocenter we set will determine the outcome at the adjacent carbon upon cyclization in at least (+)-magnoliadiol, and hopefully by extension (-)-magnofargesin, as seen in Nishii's work on similar systems.[9]



Scheme 33 – Previously Determined Mechanism

Even more obstacles exist for the formation of (-)-magnofargesin than (+)-magnoliadiol. The most readily obvious is that we will now be employing an alcohol as our trapping agent rather than an ester (Scheme 33, pathway a), which presents a major

change in properties yet remains plausible. Another obstacle is that in our previous reports, highly activated systems, which both of these natural products represent, strongly prefer the Friedel-Crafts type pathway over ester trapping towards ABL formation. This would translate into ease of formation of (+)-magnoliadiol and an increased difficulty in accessing (-)-magnofargesin. In addition, we would be seeking the *Z* isomer for (-)-magnofargesin. 7′-epimagnofargesin is the *E* isomer. Our previously observed selectivities ranged from entirely the *E* isomer to a 1:1 ratio of *E*:*Z*, never a majority *Z*. A 1:1 ratio of magnofargesin to 7′-epimagnofargesin is the current highest ratio of magnofargesin for the two existing total syntheses of magnofargesin. Improvements in this area would be desirable, but difficult.

5.4.3 Initial Results

To test the plausibility of this proposal with readily accessible materials, some test reactions were performed (Figure 28). First, diol **45** was exposed to the optimized ABL forming conditions (Figure 28A). Encouragingly, we were able to confirm trapping by the alcohol in place of an ester, at least in the absence of a competitive intramolecular arene trapping. Next, we worked out universal reduction conditions; excess LAH was able to reduce the ester and ketone of D-A cyclopropane **47** in one step with high yield to afford diol **48** (Figure 28B).

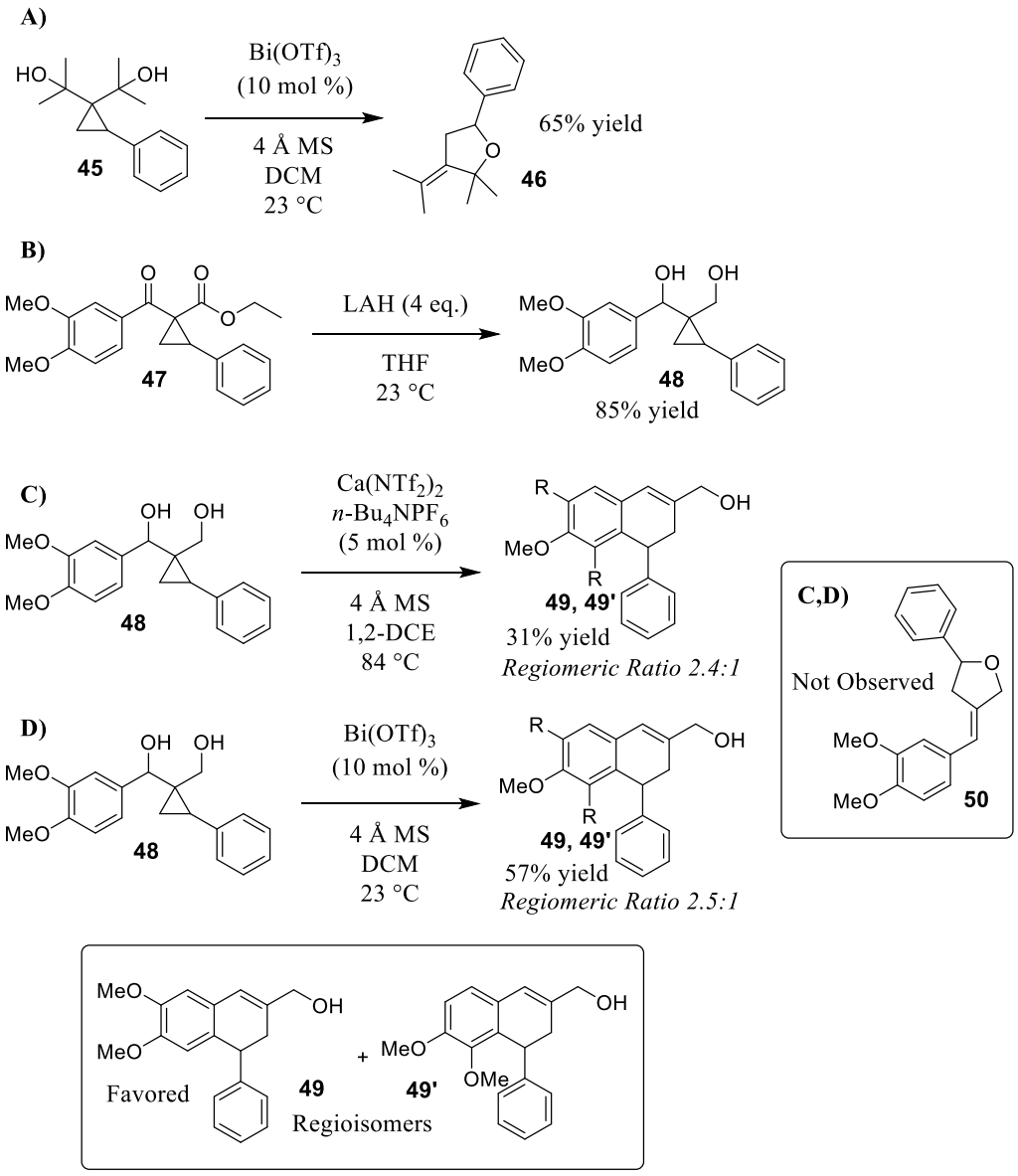
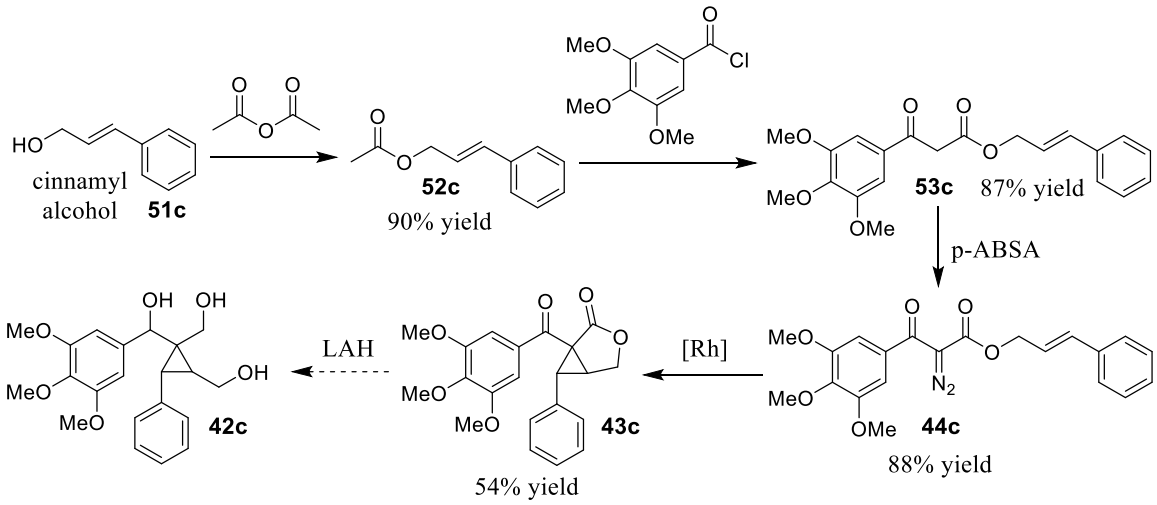


Figure 28 – Test Reactions

We then exposed **48** to each set of optimized conditions from the methodologies in Chapters 2 and 3 in an attempt to observe products **49** and **50** respectively. Results show no formation of **50**, but products **49** and **49′** formed in both cases, with regiomeric ratios close to 2.5:1 – much less selective than we previously observed (Figure 28C and 28D).

Not only that, but the methods used with the intent of selective **50** formation resulted in a significantly higher yield of **49** and **49′** (Figure 28D). This indicates that our systems are similar yet fundamentally different than what we were working with previously; we will likely need to re-optimize the reaction conditions in order to achieve chemodivergence.

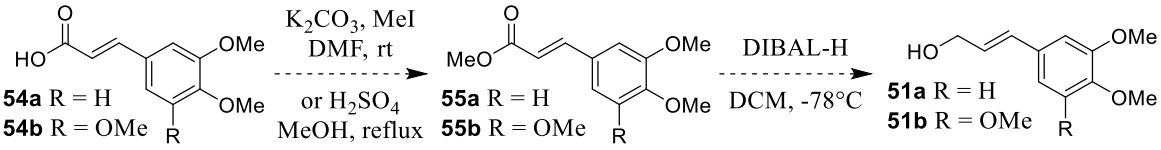


Scheme 34 – Synthesis of Optimization Substrate 42c

We chose compound **42c** as our optimization substrate due to both similarities to the natural product precursors as well as commercial availability of our starting alcohol, cinnamyl alcohol (Scheme 34). The first three synthetic steps have been worked out, optimized, and scaled with high yields. Acylation of cinnamyl alcohol **51c** provides **52c** in high yields. This is then deprotonated and reacted with the aryl acid chloride (generated from the aryl acid) to make the β-ketoester **53c**. A diazo transfer is then performed using p-ABSA as the diazo transfer reagent to form **44c**. Our typical diazo transfer reagent, tosyl azide, was not ideal as it is difficult to separate **44c** from tolyl amine, the by-product of the

diazo transfer that would prevent reactivity in the next step. Intramolecular cyclopropanation of **44c** to form **43c** using a rhodium catalyst has been achieved in 54% yield. Optimization of this step is ongoing.

Universal reduction of **43c** using excess LAH should afford our optimization substrate **42c**. While optimization studies are being performed on the dehydrative cyclization reactions of **42c**, we will work on the synthesis of chiral **43c**. Once we have optimized conditions for both chiral cyclopropanation and selective ring-opening cyclizations for the model substrate, we will move on to the synthesis of the natural products.



Scheme 35 – Synthesis of Alcohols 51a and 51b

The alcohols **51a** and **51b** for the synthesis of the actual natural products are not feasibly purchasable; however their corresponding carboxylic acids **54** are readily available. A known high-yielding two-step process of esterification followed by reduction would provide rapid access to the desired alcohols **51** (Scheme 35).[10] The esterification step can be performed either under basic or acidic conditions; both provide high yields of the esters **55**. Following synthesis of the natural products, a greater scope of synthetic derivatives of the natural products can be pursued as well. Biological testing can, and

should, be performed on all final products. This would make good grounds for collaboration with other labs.

5.5 Summary

In this thesis, three methodology development projects were presented from their initiation through to their completion. These three methods were generated by applying the reactivity of dehydrative cyclization reactions to related methods explored previously in our lab. Utilization of our previous methodology is particularly advantageous towards rapid development of molecular diversity. Three new, related projects to further establish this body of work were presented in this chapter, along with preliminary data and future outlooks for each project, laying a foundation for some of the future work our lab can pursue. These new projects will further increase the diversity of molecular structures accessible from our lab's methods (adding retroactive value to our previous methods) and they begin to apply this body of work towards natural products we seek to synthesize. They may also provide a strong starting point for future generations of scientists within our lab, as the concepts of the projects have been established with clear direction but the bulk of the work and discovery has yet to be accomplished.

5.6 Experimental

5.6.1 General Information

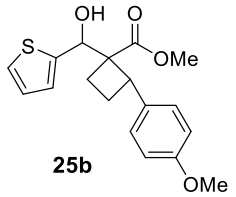
Chromatographic purification was performed as flash chromatography with Silicycle SiliaFlash P60 silica gel (40−63 μm) or preparative thin-layer chromatography (prep-TLC) using silica gel F254 (1000 μm) plates and solvents indicated as eluent with

0.1−0.5 bar pressure. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle SiliaPlate TLC silica gel F254 (250 μm) TLC glass plates. Visualization was accomplished with UV light or iodine chamber.

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer or a Bruker 500 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration.

5.6.2 Experimental Procedures

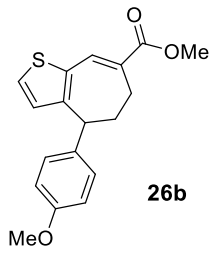
Compounds **28a**,[1] **28b**,[11] **30**,[3a] **5c**,[12] **32**,[13] **40a**,[14] **34b**,[5] and **41**[5] were synthesized according to the literature. The synthesis of all other compounds we made that were discussed in this chapter are presented below in order of appearance in the chapter.



25b

Diastereomeric Ratio: (7:1)

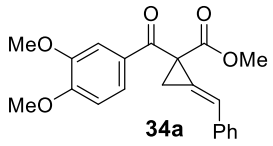
Methyl 1-(hydroxy(thiophen-2-yl)methyl)-2-(4-methoxyphenyl)cyclobutane-1-carboxylate (25b): Cyclobutane **28b** (101 mg, 0.31 mmol) was dissolved in THF to make a 0.1 M solution, and was added to a clean, dry round bottom flask charged with a stir bar under nitrogen. $LiEt_3BH$ (1 M in THF, 0.37 mL, 0.37 mmol) was added in one shot, and the reaction stirred for 18 hours. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (30% EtOAc/Hexanes, R_f = 0.51). Compound **25b** was afforded as a yellow oil (96.8 mg, 95% yield). *Diastereomeric Ratio:* (7:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.30 - 7.18 (m, 3 H), 6.96 - 6.80 (m, 4 H), 5.17 (d, *J* = 10.8 Hz, 1 H), 4.07 (d, *J* = 10.7 Hz, 1 H), 4.02 - 3.94 (m, 1 H), 3.79 (s, 3 H), 3.35 (s, 3 H), 2.68 - 2.51 (m, 2 H), 2.30 - 2.21 (m, 1 H), 2.13 - 2.04 (m, 1 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 173.7, 158.5, 145.4, 131.8, 128.9, 126.6, 124.7, 123.8, 113.4, 113.4, 77.3, 59.5, 55.2, 51.6, 47.5, 24.5, 21.1 **HRMS (EI)** *m/z* $[M]^+$ Calcd. for $C_{18}H_{20}O_4S$ 332.1082, found 332.1074.



26b

Methyl 4-(4-methoxyphenyl)-5,6-dihydro-4H-cyclohepta[*b*]thiophene-7-carboxylate (26b): $Ca(NTf_2)_2$ (2.6 mg, 0.0045 mmol) and *n*-Bu_4NPF_6 (1.8 mg, 0.0045 mmol) were added to a clean, dry round bottom flask charged with a stir bar under nitrogen. Cyclobutyl carbinol **25b** (151 mg, 0.45 mmol) was added as a 0.1 M solution in DCE and heated to

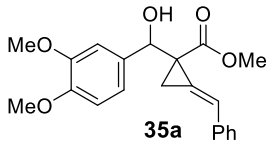
reflux. The reaction refluxed for 30 minutes. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (20% EtOAc/Hexanes, R_f = 0.57). Compound **26b** was afforded as a yellow oil (83.7 mg, 59% yield with minor impurities). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 1.5 Hz, 1 H), 7.28 - 7.24 (m, 1 H), 6.93 - 6.88 (m, 2 H), 6.84 - 6.79 (m, 2 H), 6.75 - 6.68 (m, 1 H), 4.43 (dd, *J* = 3.2, 5.9 Hz, 1 H), 3.79 - 3.73 (m, 6 H), 2.77 (dd, *J* = 5.8, 18.1 Hz, 1 H), 2.49 - 2.30 (m, 1 H), 2.29 - 2.02 (m, 2 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.5, 158.0, 146.0, 137.3, 134.1, 132.3, 130.3, 129.7, 129.0, 127.2, 127.1, 113.7, 55.1, 52.0, 46.2, 30.6, 25.5 . **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{18}H_{19}O_3S$ 315.1049, found 315.1040.



34a

Methyl (*E*)-2-benzylidene-1-(3,4-dimethoxybenzoyl)cyclopropane-1-carboxylate (34a): 4-Bromo-1,2-dimethoxybenzene (260 mg, 1.2 mmol) was dissolved in 8 mL dry THF and added to a clean, dry round bottom flask charged with a stir bar under nitrogen. The reaction was cooled to -78 °C with stirring and *n*-BuLi (2.5 M in hexanes, 0.64 mL, 1.6 mmol) was added dropwise. The reaction continued stirring at -78 °C for 1 hour. Cyclopropane **41** (196 mg, 0.8 mmol) dissolved in 3 mL THF was added dropwise, and the reaction continued stirring at -78 °C for 30 minutes. Upon completion, the reaction was quenched with NH_4Cl (aq) at -78 °C, extracted with EtOAc three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes

as the mobile phase (30% EtOAc/Hexanes, R_f = 0.35). Compound **34a** was afforded as a yellow oil (67.2 mg, 24% yield). *Diastereomeric Ratio:* (>99:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.64 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.57 (d, *J* = 2.1 Hz, 1 H), 7.54 - 7.47 (m, 2 H), 7.40 - 7.27 (m, 3 H), 6.97 (d, *J* = 8.5 Hz, 1 H), 6.91 (t, *J* = 2.6 Hz, 1 H), 3.98 (s, 2 H), 3.95 (s, 3 H), 3.67 (s, 3 H), 2.62 (dd, *J* = 2.6, 9.5 Hz, 1 H), 2.49 (dd, *J* = 2.6, 9.7 Hz, 1 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 189.4, 170.7, 153.5, 149.2, 135.7, 128.9, 128.6, 128.1, 127.4, 124.1, 122.4, 120.7, 110.8, 110.1, 56.1, 56.0, 52.8, 34.6, 18.2 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{21}H_{21}O_5$ 353.1384, found 353.1384.

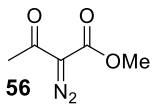


35a

Diastereomeric Ratio: (1.6:1)

Methyl (*E*)-2-benzylidene-1-((3,4-dimethoxyphenyl)(hydroxy)methyl)cyclopropane-1-carboxylate (35a): Alkylidene cyclopropane **34a** (160 mg, 0.46 mmol) was dissolved in THF to make a 0.1 M solution, and was added to a clean, dry round bottom flask charged with a stir bar under nitrogen. $LiEt_3BH$ (1 M in THF, 0.55 mL, 0.55 mmol) was added in one shot, and the reaction stirred for 18 hours. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (30% EtOAc/Hexanes, R_f = 0.20). Compound **35a** was afforded as a colorless oil (106.9 mg, 66% yield with minor impurities). *Diastereomeric Ratio:* (1.6:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.50 - 7.44 (m, 5.78 H), 7.38 - 7.32 (m, 6.43 H), 7.28 - 7.24 (m, 2.09 H), 7.03 (d, *J* = 1.8 Hz, 1.58 H), 7.00 - 6.96 (m, 3.76 H), 6.93 (t, *J* = 2.4 Hz, 2.03 H),

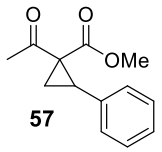
6.90 (dd, *J* = 2.0, 8.4 Hz, 1.08 H), 6.83 - 6.79 (m, 2.68 H), 5.16 (d, *J* = 5.2 Hz, 1.00 H), 4.98 (d, *J* = 7.3 Hz, 1.61 H), 3.89 - 3.85 (m, 13.56 H), 3.84 (d, *J* = 5.2 Hz, 0.92 H), 3.76 (s, 2.95 H), 3.68 - 3.66 (m, 6.05 H), 3.64 (d, *J* = 7.3 Hz, 1.63 H), 2.41 (dd, *J* = 2.6, 9.6 Hz, 1.63 H), 2.26 (dd, *J* = 2.6, 9.6 Hz, 1.18 H), 1.92 (dd, *J* = 2.6, 9.6 Hz, 1.88 H), 1.58 (dd, *J* = 2.7, 9.5 Hz, 1,24 H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 173.7, 173.1, 148.5, 148.5, 148.4, 148.3, 136.3, 136.2, 133.3, 132.6, 128.6, 128.5, 128.5, 127.8, 127.7, 127.1, 127.1, 127.0, 125.6, 124.4, 120.7, 119.8, 119.2, 118.5, 110.5, 110.3, 110.0, 109.9, 77.2, 74.5, 74.1, 55.8, 55.8, 55.6, 52.3, 52.3, 30.8, 30.8, 18.3, 15.9 **HRMS (ESI)** *m/z* $[M+Na]^+$ Calcd. for $C_{21}H_{22}O_5Na$ 377.1359, found 377.1356.



56

Methyl 2-diazo-3-oxobutanoate (56): Methyl 3-oxobutanoate (2.03 g, 17.2 mmol) was dissolved in sufficient CH_3CN to make a 1 M solution and was added to a clean, dry round bottom flask under nitrogen charged with a stir bar. The reaction was cooled to 0 °C with stirring, and triethylamine (2.0 g, 19.8 mmol) was added. TsN_3 (3.77 g, 19.1 mmol) was added and the reaction was allowed to warm to room temperature with stirring. After stirring for 18 hours, the amine byproduct was removed through recrystallization in DCM and filtration through celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase. (20% EtOAc/Hexanes, R_f = 0.50). Compound **56** was afforded as a yellow oil (1.98 g, 81%

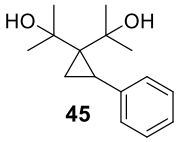
yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.82 (s, 3 H), 2.46 (s, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.1, 161.8, 52.2, 28.2



57

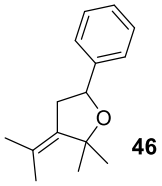
Diastereomeric Ratio: (4.5:1)

Methyl 1-acetyl-2-phenylcyclopropane-1-carboxylate (57): To a clean, dry round bottom flask under nitrogen charged with a stir bar and Rh_2esp_2 (11.2 mg, 0.015 mmol) was added dry CH_2Cl_2 (20 mL) and cooled to 0 °C with stirring. Styrene (1.42 g, 13.6 mmol) was added in one shot. Diazo **56** (1.0 g, 7.04 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and added over 1 minute. The reaction stirred at 0 °C for 15 minutes and was allowed to warm to room temperature. After stirring 18 hours, the reaction was quenched with thiourea (aq), extracted with CH_2Cl_2 three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (20% EtOAc/Hexanes, R_f = 0.55). Compound **57** was afforded as a white solid (1.23 g, 80% yield). *Diastereomeric Ratio:* (4.5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.35 - 7.08 (m, 7.06 H), 3.80 (s, 0.66 H), 3.34 (s, 3.00 H), 3.32 - 3.22 (m, *J* = 8.6, 8.6 Hz, 1.48 H), 2.45 (s, 3.11 H), 2.30 (dd, *J* = 5.0, 8.1 Hz, 0.33 H), 2.24 (dd, *J* = 4.6, 8.1 Hz, 1.13 H), 1.93 (s, 0.69 H), 1.77 - 1.66 (m, 1.36 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 202.2, 168.7, 134.8, 133.7, 128.7, 128.3, 128.3, 128.1, 127.5, 127.4, 52.6, 51.9, 44.6, 35.5, 34.5, 30.2, 29.6, 21.6, 17.8



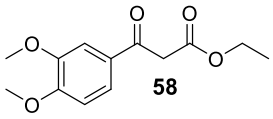
45

2,2'-(2-Phenylcyclopropane-1,1-diyl)bis(propan-2-ol) (45): To a clean, dry round bottom flask under nitrogen charged with a stir bar and dried anhydrous $CeCl_3$ (466 mg, 1.88 mmol) was added THF (4 mL) and stirred at -78 °C to generate a suspension. MeLi (1.6 M in Et_2O, 1.14 mL, 1.83 mmol) was added dropwise and allowed to stir at -78 °C for 1 hour. Compound **57** (197 mg, 0.92 mmol) as a solution in THF (1.6 mL) was added slowly, and after 15 minutes stirring at -78 °C, the reaction was allowed to warm to 0 °C over 30 minutes. The reaction was quenched with NH_4Cl (aq) at -78 °C, extracted with Et_2O three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (30% EtOAc/Hexanes, R_f = 0.36), compound **45** was afforded as a white solid (73.2 mg, 50% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.33 - 7.14 (m, 5 H), 3.65 (br. s., 1 H), 3.13 (br. s., 1 H), 2.20 (dd, *J* = 7.8, 9.4 Hz, 1 H), 1.60 (s, 3 H), 1.39 (dd, *J* = 5.7, 7.5 Hz, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.15 (dd, *J* = 5.7, 9.5 Hz, 1 H), 0.84 (s, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 138.6, 129.8, 128.1, 126.2, 75.2, 74.9, 40.6, 31.2, 31.1, 30.3, 30.3, 27.3, 11.4 **HRMS (ESI)** *m/z* $[M+Na]^+$ Calcd. for $C_{15}H_{22}O_2Na$ 257.1512, found 257.1510.



46

2,2-Dimethyl-5-phenyl-3-(propan-2-ylidene)tetrahydrofuran (46): $Bi(OTf)_3$ (13.6 mg, 0.021 mmol) was added to a clean, dry round bottom flask charged with a stir bar under nitrogen. Diol **45** (51 mg, 0.22 mmol) was added as a 0.1 M solution in CH_2Cl_2 at room temperature and the reaction was stirred for 30 minutes. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (10% EtOAc/Hexanes, R_f = 0.58). Compound **46** was afforded as a yellow oil (30.9 mg, 65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.47 - 7.18 (m, 5 H), 4.89 (dd, *J* = 5.8, 10.5 Hz, 1 H), 2.92 (dd, *J* = 5.7, 15.5 Hz, 1 H), 2.48 (tdd, *J* = 2.2, 10.8, 15.2 Hz, 1 H), 1.74 (s, 3 H), 1.66 (s, 3 H), 1.55 (s, 3 H), 1.47 (s, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 142.3, 139.4, 128.3, 127.4, 126.1, 121.0, 82.0, 76.8, 42.2, 27.9, 25.8, 23.2, 19.9 **HRMS (EI)** *m/z* $[M]^+$ Calcd. for $C_{15}H_{20}O$ 216.1514, found 216.1519.

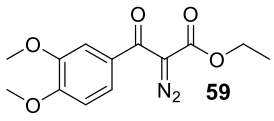


58

30:1 keto:enol ratio

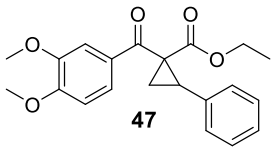
Ethyl 3-(3,4-dimethoxyphenyl)-3-oxopropanoate (58): To a dry flask charged with a stir bar and 3,4-dimethoxybenzoic acid (5.10 g, 28.0 mmol) under nitrogen was added dry CH_2Cl_2 to make a 0.5 M solution. The solution was then cooled to 0 °C. Catalytic DMF (3 drops) was then added. Oxalyl chloride (4.38 g, 34.5 mmol) was added over 1 minute with

stirring at 0 °C with a needle used to vent into a balloon. After 15 minutes, the reaction was allowed to warm to room temperature with continued stirring. The reaction was monitored by TLC until complete conversion of the carboxylic acid was observed (3 hours). Upon completion, the reaction was concentrated under reduced pressure, the generated acid chloride was re-dissolved in dry THF to make a 1 M solution, and the solution was added slowly to the prepared enolate at -78 °C. The enolate was prepared by first adding LHMDS (1 M in THF, 60 mmol, 60 mL) to a dry flask charged with a stir bar under nitrogen and cooling to -78 °C. EtOAc (2.63 g, 29.9 mmol) was added to the solution of LHMDS in one shot and stirred for 45 min at -78 °C. The reaction was monitored by TLC until complete conversion of the acid chloride was observed (30 min). Upon completion, the reaction was quenched with NH_4Cl (aq) at -78 °C, extracted with EtOAc three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (20% EtOAc/Hexanes, R_f = 0.14). Compound **58** was afforded as a yellow oil (6.63 g, 94% yield). *Keto:Enol Ratio:* (30:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.61 - 7.49 (m, 12 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.96 - 3.90 (m, 8 H), 1.25 (t, *J* = 7.2 Hz, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 191.0, 167.7, 153.8, 149.1, 129.2, 123.5, 110.2, 110.0, 61.4, 56.1, 56.0, 45.7, 14.1 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{13}H_{17}O_5$ 253.1071, found 253.1075.



59

Ethyl 2-diazo-3-(3,4-dimethoxyphenyl)-3-oxopropanoate (59): Compound **58** (3.59 g, 14.3 mmol) was dissolved in sufficient CH_3CN to make a 0.5 M solution and was added to a clean, dry round bottom flask under nitrogen charged with a stir bar. The reaction was cooled to 0 °C with stirring, and triethylamine (1.78 g, 17.6 mmol) was added. TsN_3 (3.94 g, 19.9 mmol) was added and the reaction was allowed to warm to room temperature with stirring. After stirring for 18 hours, the amine byproduct was removed through recrystallization in DCM and filtration through celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase. (20% EtOAc/Hexanes, R_f = 0.18). Compound **59** was afforded as a yellow solid (4.0 g, quantitative yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.42 - 7.17 (m, 2 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$ δ = 185.1, 161.3, 152.7, 148.4, 129.2, 123.3, 111.4, 109.5, 61.5, 55.9, 55.9, 14.2 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{13}H_{15}O_5N_2$ 279.0975, found 279.0982.

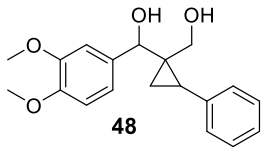


47

Diastereomeric Ratio: (17:1)

Ethyl 1-(3,4-dimethoxybenzoyl)-2-phenylcyclopropane-1-carboxylate (47): To a clean, dry round bottom flask under nitrogen charged with a stir bar and Rh_2esp_2 (9.4 mg, 0.012 mmol) was added dry CH_2Cl_2 (33 mL) and cooled to 0 °C with stirring. Styrene (1.43 g, 13.6 mmol) was added in one shot. Diazo **59** (3.82 g, 13.7 mmol) in CH_2Cl_2 (15 mL) was

cooled to 0 °C and added over 1 minute. The reaction stirred at 0 °C for 15 minutes and was allowed to warm to room temperature. After stirring 45 minutes at room temperature, the reaction was quenched with thiourea (aq), extracted with CH_2Cl_2 three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (20% EtOAc/Hexanes, R_f = 0.26). Compound **47** was afforded as a white solid (1.46 g, 30% yield). *Diastereomeric Ratio:* (17:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.51 (d, *J* = 2.1 Hz, 1 H), 7.37 - 7.19 (m, 5 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 3.99 - 3.89 (m, 6 H), 3.82 - 3.63 (m, 2 H), 3.53 (t, *J* = 8.6 Hz, 1 H), 2.42 (dd, *J* = 4.9, 8.0 Hz, 1 H), 1.62 (dd, *J* = 4.9, 9.0 Hz, 1 H), 0.72 (t, *J* = 7.1 Hz, 3 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 192.9, 168.6, 153.1, 149.0, 134.9, 129.9, 129.1, 128.0, 127.1, 122.9, 110.6, 110.0, 61.1, 56.0, 55.9, 42.1, 30.0, 19.3, 13.6 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{21}H_{23}O_5$ 355.1540, found 355.1537.

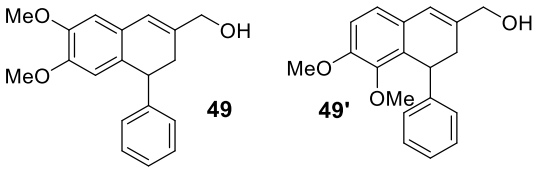


48

Diastereomeric Ratio: (1.35:1)

(3,4-Dimethoxyphenyl)(1-(hydroxymethyl)-2-phenylcyclopropyl)methanol (48): LAH (94 mg, 2.35 mmol) was added to a clean, dry round bottom flask charged with a stir bar under nitrogen. Cyclopropane **47** (192 mg, 0.54 mmol) was added as a 0.1 M solution in THF at room temperature and the reaction was stirred for 18 hours. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel

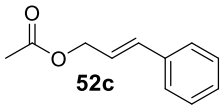
using EtOAc/Hexanes as the mobile phase (50% EtOAc/Hexanes, R_f = 0.22). Compound **48** was afforded as a colorless oil (145 mg, 85% yield). *Diastereomeric Ratio:* (1.35:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.34 - 7.31 (m, 2.70 H), 7.30 - 7.13 (m, 6.98 H), 7.09 - 6.99 (m, 3.41 H), 6.94 - 6.88 (m, 1.72 H), 4.74 (d, *J* = 2.1 Hz, 1.00 H), 4.56 (d, *J* = 5.5 Hz, 0.71 H), 3.98 - 3.88 (m, 10.33 H), 3.73 (d, *J* = 6.1 Hz, 0.71 H), 3.67 (dd, *J* = 6.4, 11.9 Hz, 0.77 H), 3.58 (d, *J* = 11.3 Hz, 1.06 H), 3.46 (d, *J* = 3.1 Hz, 0.98 H), 3.20 - 3.12 (m, 1.78 H), 2.48 (ddd, *J* = 6.4, 8.7, 15.4 Hz, 1.78 H), 2.00 (br. s., 0.99 H), 1.71 - 1.65 (m, 0.76 H), 1.23 - 1.18 (m, 1.75 H), 1.15 - 1.08 (m, 1.76 H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 148.8, 148.7, 148.4, 148.3, 137.8, 137.6, 135.0, 134.4, 128.8, 128.8, 128.4, 128.3, 126.5, 126.4, 118.6, 118.3, 110.8, 110.8, 109.5, 109.4, 80.2, 79.7, 65.3, 64.0, 55.9, 55.9, 34.2, 33.5, 27.6, 25.6, 13.8, 12.7 **HRMS (ESI)** *m/z* $[M+Na]^+$ Calcd. for $C_{19}H_{22}O_4Na$ 337.1410, found 337.1410.



Regiomeric Ratio 2.5:1

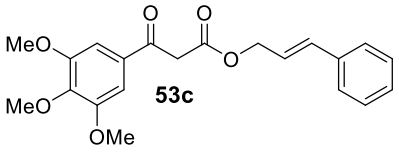
(6,7-Dimethoxy-4-phenyl-3,4-dihydronaphthalen-2-yl)methanol (49): $Bi(OTf)_3$ (12.4 mg, 0.019 mmol) was added to a clean, dry round bottom flask charged with a stir bar under nitrogen. Diol **48** (60 mg, 0.20 mmol) was added as a 0.1 M solution in CH_2Cl_2 at room temperature and the reaction was stirred for 20 minutes. The reaction was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (30% EtOAc/Hexanes, R_f = 0.50). Compounds

49 and **49′** were afforded as a yellow oil (32.2 mg, 57% yield). *Regiomeric Ratio:* (2.5:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.44 - 7.33 (m, 5.74 H), 7.33 - 7.27 (m, 1.49 H), 6.91 - 6.82 (m, 2.30 H), 6.75 - 6.65 (m, 2.13 H), 6.42 - 6.37 (m, 1.00 H), 6.33 (br. s., 0.38 H), 5.05 - 4.96 (m, *J* = 6.4, 8.5 Hz, 1.40 H), 4.91 (d, *J* = 13.4 Hz, 1.05 H), 4.81 - 4.67 (m, *J* = 13.7 Hz, 1.46 H), 4.60 (d, *J* = 13.1 Hz, 0.41 H), 3.93 - 3.83 (m, 9.07 H), 3.25 (dd, *J* = 5.5, 15.6 Hz, 0.43 H), 3.13 (dd, *J* = 6.4, 15.6 Hz, 1.06 H), 2.85 - 2.72 (m, *J* = 9.0, 16.3 Hz, 1.47 H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 148.8, 148.7, 147.8, 147.8, 141.7, 141.6, 139.3, 138.8, 130.6, 130.4, 128.5, 128.4, 127.7, 127.6, 126.0, 125.9, 120.7, 120.6, 120.4, 119.4, 111.3, 111.2, 111.2, 111.1, 81.8, 79.7, 73.1, 69.9, 55.9, 55.8, 55.8, 42.9, 39.7 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{19}H_{21}O_3$ 297.1485, found 297.1485.



52c

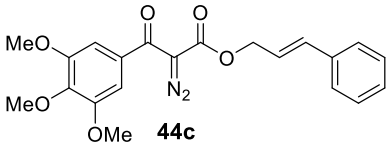
Cinnamyl acetate (52c): Cinnamyl alcohol (1.38 g, 10.3 mmol) was dissolved in 5 mL acetic anhydride and added to a clean, dry round bottom flask charged with a stir bar and 30mg DMAP under nitrogen. The reaction stirred for 24 hours at room temperature. The reaction mixture was diluted with EtOAc, washed 3 times with $NaHCO_3$, and columned on silica gel using EtOAc/Hexanes as the mobile phase and compound **52c** was isolated (1.64 g, 90% yield). Characterization is in agreement with previously reported literature.[15]



7:1 keto:enol ratio

Cinnamyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (53c): To a dry flask charged with a stir bar and 3,4,5-trimethoxybenzoic acid (212 mg, 1.0 mmol) under nitrogen was added dry CH_2Cl_2 to make a 0.5 M solution. The solution was then cooled to 0 °C. Catalytic DMF (2 drops) was then added. Oxalyl chloride (153 mg, 1.2 mmol) was added over 1 minute with stirring at 0 °C with a needle used to vent into a balloon. After 15 minutes, the reaction was allowed to warm to room temperature with continued stirring. The reaction was monitored by TLC until complete conversion of the carboxylic acid was observed (2 hours). Upon completion, the reaction was concentrated under reduced pressure, the generated acid chloride was re-dissolved in dry THF to make a 1 M solution, and the solution was added slowly to the prepared enolate at -78 °C. The enolate was prepared by first adding LHMDS (1 M in THF, 2.1 mmol, 2.1 mL) to a dry flask charged with a stir bar under nitrogen and cooling to -78 °C. **52c** (185 mg, 1.05 mmol, dissolved in minimal THF) was added to the solution of LHMDS in one shot and stirred for 45 min at -78 °C. The reaction was monitored by TLC until complete conversion of the acid chloride was observed (30 min). Upon completion, the reaction was quenched with NH_4Cl (aq) at -78 °C, extracted with EtOAc three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (20% EtOAc/Hexanes, R_f = 0.19). Compound **53c** was afforded as a yellow oil (323.1 mg, 87% yield). *Keto:Enol Ratio:* (7:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.38 - 7.27 (m, 5 H), 7.22

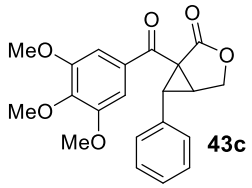
(s, 2 H), 6.63 (d, *J* = 16.0 Hz, 1 H), 6.24 (td, *J* = 6.4, 15.9 Hz, 1 H), 4.81 (dd, *J* = 1.3, 6.4 Hz, 2 H), 4.01 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 6 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 190.9, 167.2, 153.1, 143.1, 135.9, 134.7, 131.0, 128.6, 128.1, 126.5, 122.4, 106.0, 66.0, 60.9, 56.2, 46.0 **HRMS (ESI)** *m/z* $[M+Na]^+$ Calcd. for $C_{21}H_{22}O_6Na$ 393.1309, found 393.1304.



44c

Cinnamyl 2-diazo-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (44c): Compound **53c** (260 mg, 0.70 mmol) was dissolved in sufficient CH_3CN to make a 0.2 M solution and was added to a clean, dry round bottom flask under nitrogen charged with a stir bar. The reaction was cooled to 0 °C with stirring, and triethylamine (100 mg, 1.0 mmol) was added. p-ABSA (185 mg, 0.76 mmol) was added and the reaction was allowed to warm to room temperature with stirring. After stirring for 18 hours, the amine byproduct was removed through recrystallization in DCM and filtration through celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase. (30% EtOAc/Hexanes, R_f = 0.34). Compound **44c** was afforded as a yellow solid (251 mg, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.39 - 7.36 (m, 2 H), 7.35 - 7.31 (m, 2 H), 7.28 (d, *J* = 7.3 Hz, 1 H), 6.95 (s, 2 H), 6.65 (d, *J* = 15.9 Hz, 1 H), 6.31 - 6.22 (m, 1 H), 4.87 (dd, *J* = 1.2, 6.7 Hz, 2 H), 3.89 (s, 3 H), 3.85 (s, 6 H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 185.3, 160.9, 152.6, 141.9, 135.8, 135.3, 131.7,

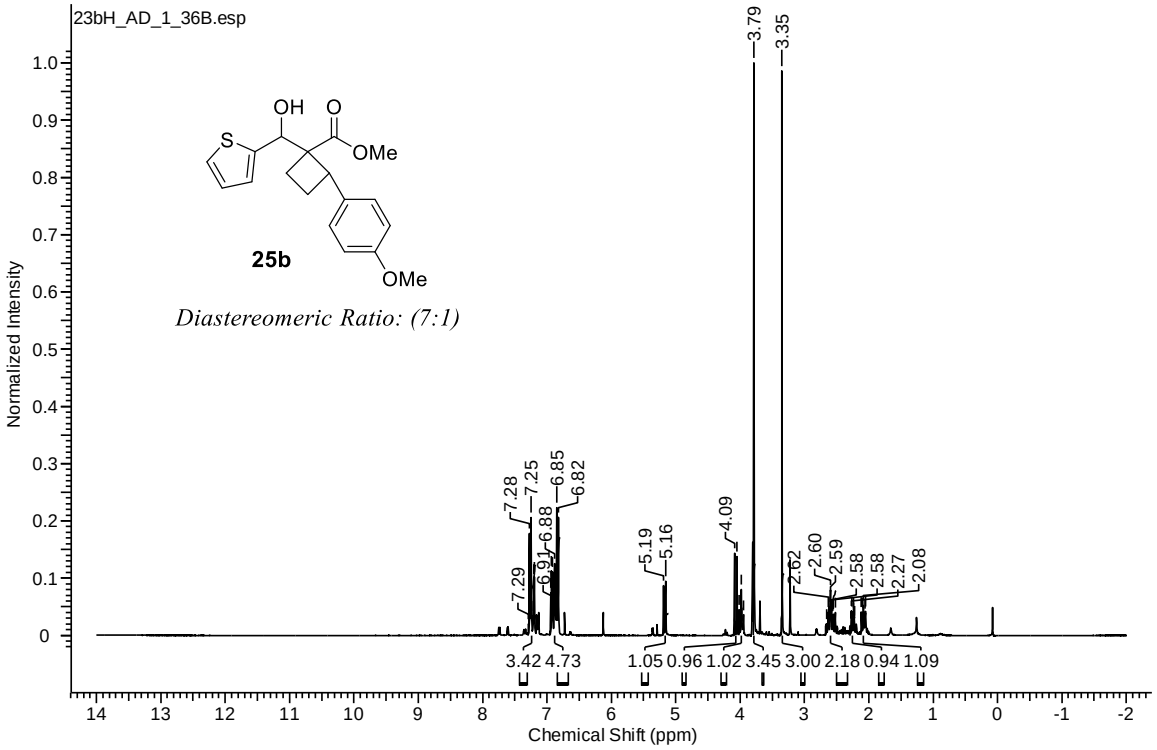
128.6, 128.4, 126.6, 122.1, 106.3, 77.2, 66.0, 60.9, 56.2 **HRMS (ESI)** *m/z* $[M+Na]^+$ Calcd. for $C_{21}H_{20}O_6N_2Na$ 419.1214, found 419.1211.

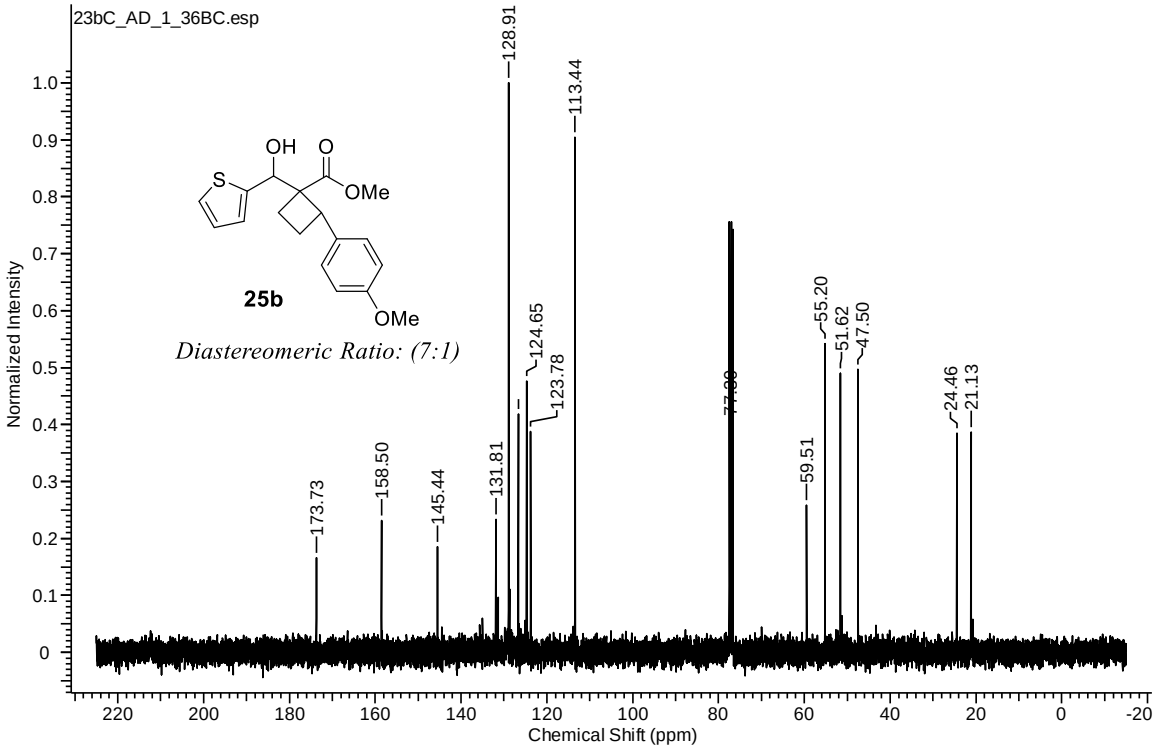


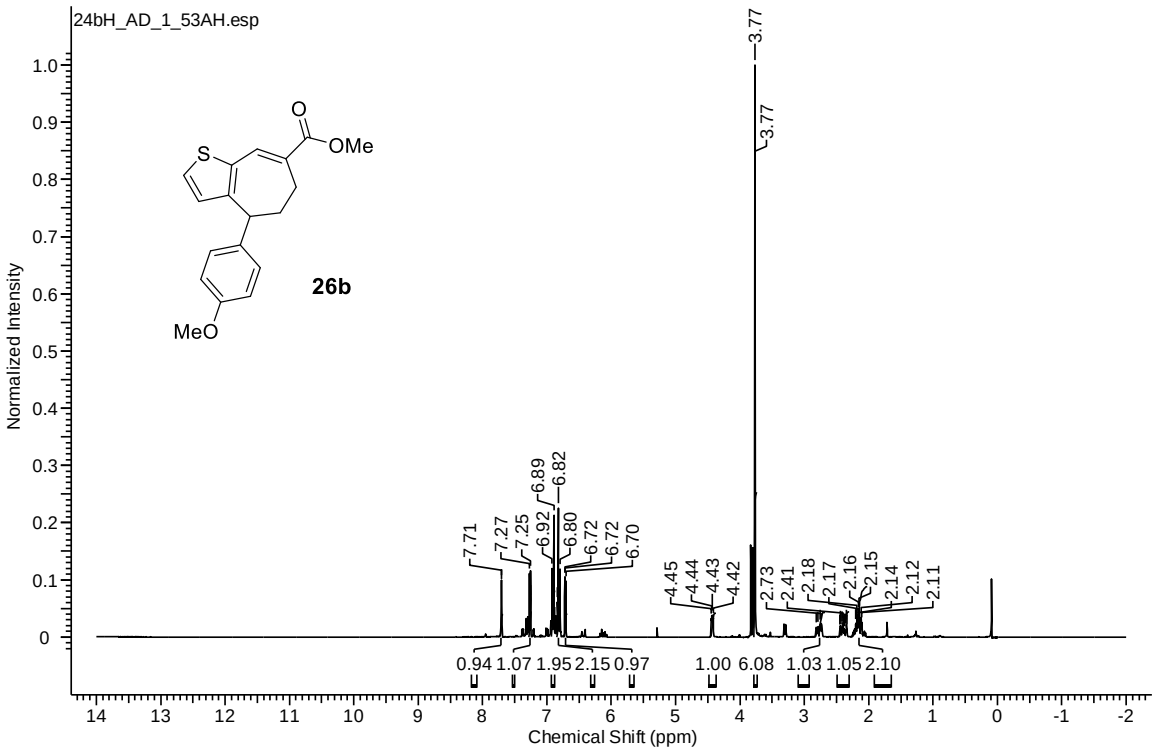
43c

6-Phenyl-1-(3,4,5-trimethoxybenzoyl)-3-oxabicyclo[3.1.0]hexan-2-one (43c): To a clean, dry round bottom flask under nitrogen charged with a stir bar and Rh_2esp_2 (1 mg, 0.00125 mmol) was added dry CH_2Cl_2 (7.5 mL). Diazo **44c** (100 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added over 5 minutes at room temperature with stirring. After stirring 18 hours, the reaction was quenched with thiourea (aq), extracted with CH_2Cl_2 three times, dried using Na_2SO_4, and filtered through celite. The combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel using EtOAc/Hexanes as the mobile phase (30% EtOAc/Hexanes, R_f = 0.18). Compound **43c** was afforded as a yellow solid (50 mg, 54% yield). *Diastereomeric Ratio:* (>99:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.21 - 7.11 (m, 20 H), 7.07 - 7.00 (m, 2 H), 4.59 (dd, *J* = 4.9, 9.5 Hz, 1 H), 4.45 (dd, *J* = 0.5, 9.5 Hz, 1 H), 3.86 (s, 3 H), 3.83 (s, 6 H), 3.41 (t, *J* = 4.8 Hz, 1 H), 2.99 (d, *J* = 5.3 Hz, 1 H) **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 188.2, 171.1, 152.5, 143.1, 132.1, 130.5, 128.6, 128.0, 127.3, 107.7, 77.2, 68.0, 60.8, 56.1, 44.4 **HRMS (ESI)** *m/z* $[M+H]^+$ Calcd. for $C_{21}H_{21}O_6$ 369.1333, found 369.1328.

5.6.3 NMR Spectra



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Chemical Shift (ppm)
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OMe
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4.44
4.43
4.42
2.73
2.41
2.18
2.17
2.16
2.15
2.14
2.12
2.11
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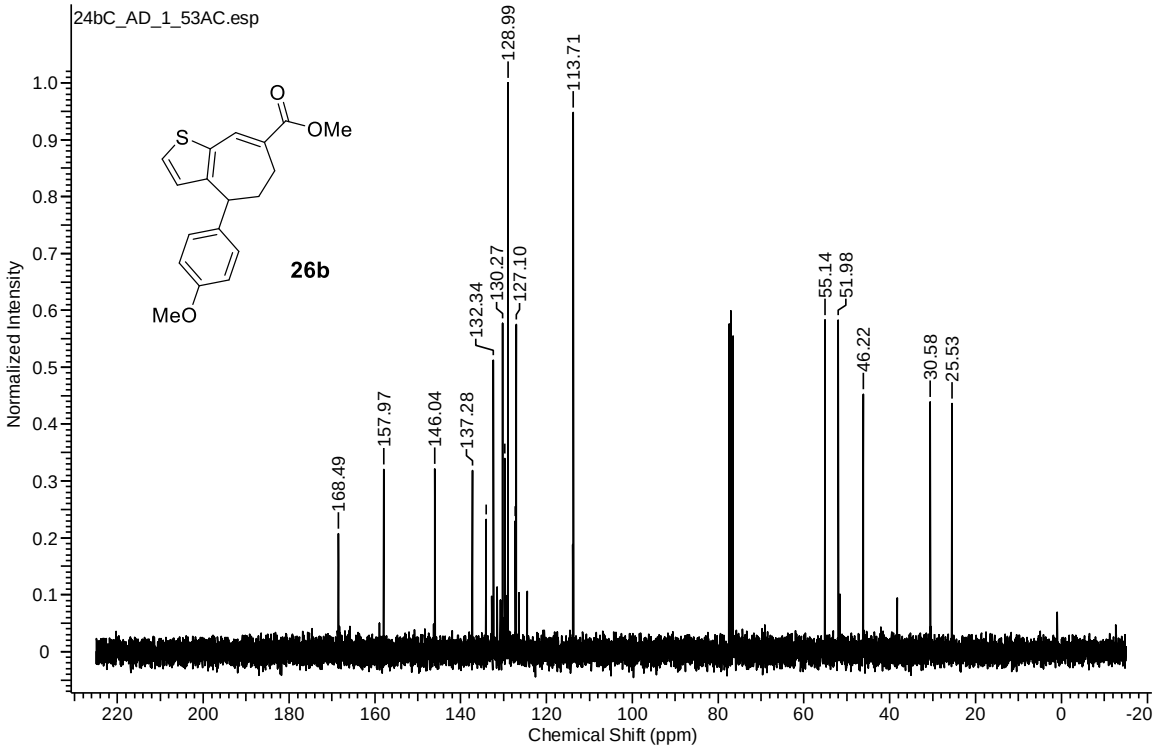
1.00 6.08 1.03 1.05 2.10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55.14
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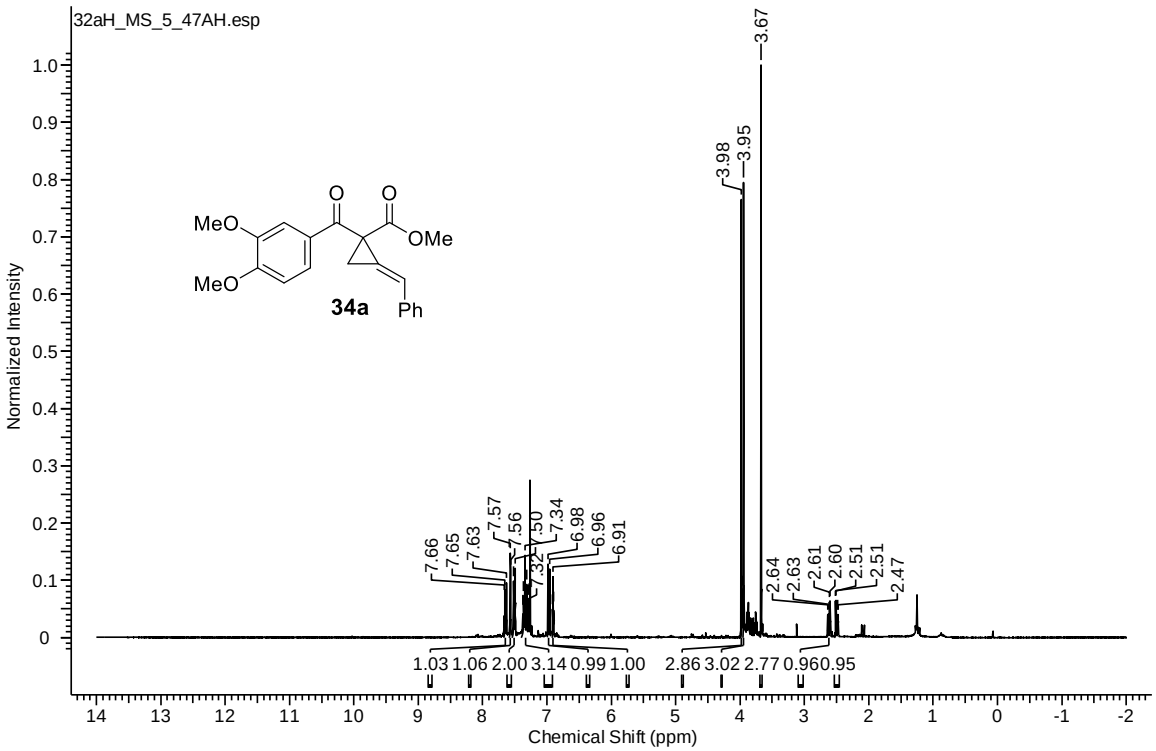
46.22
30.58
25.53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Normalized Intensity
Chemical Shift (ppm)
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MeO
OMe
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6.98
6.96
6.91
2.64
2.63
2.61
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2.47
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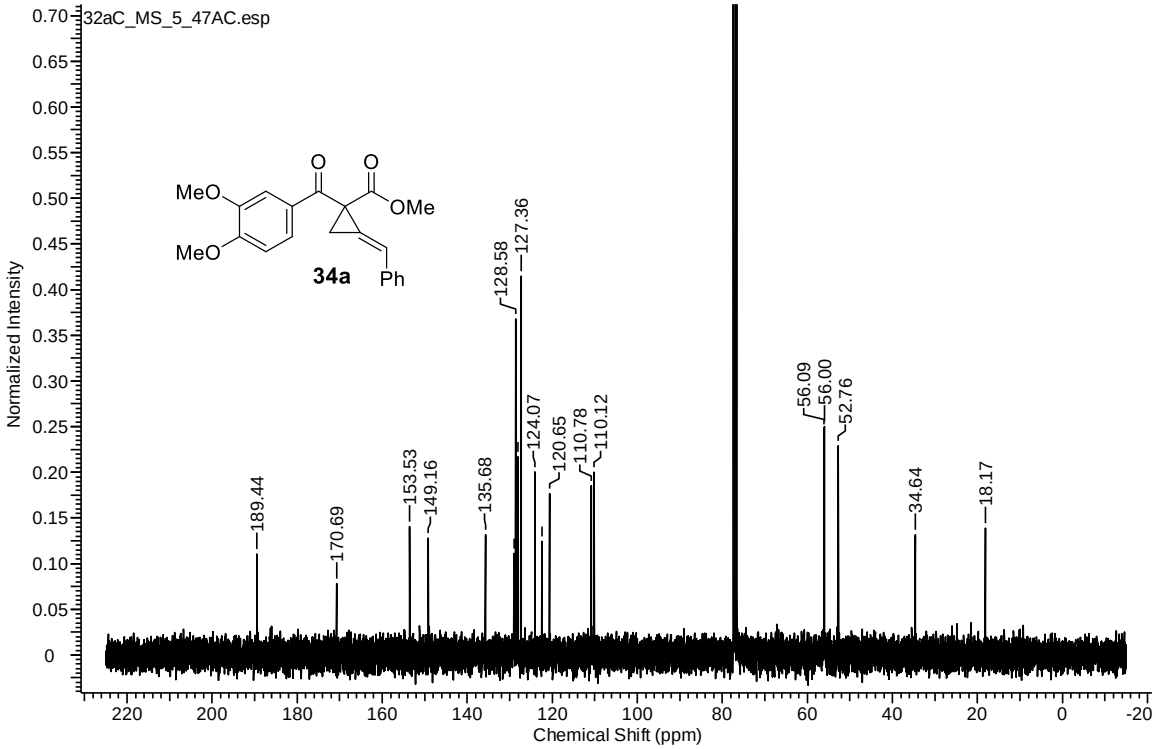
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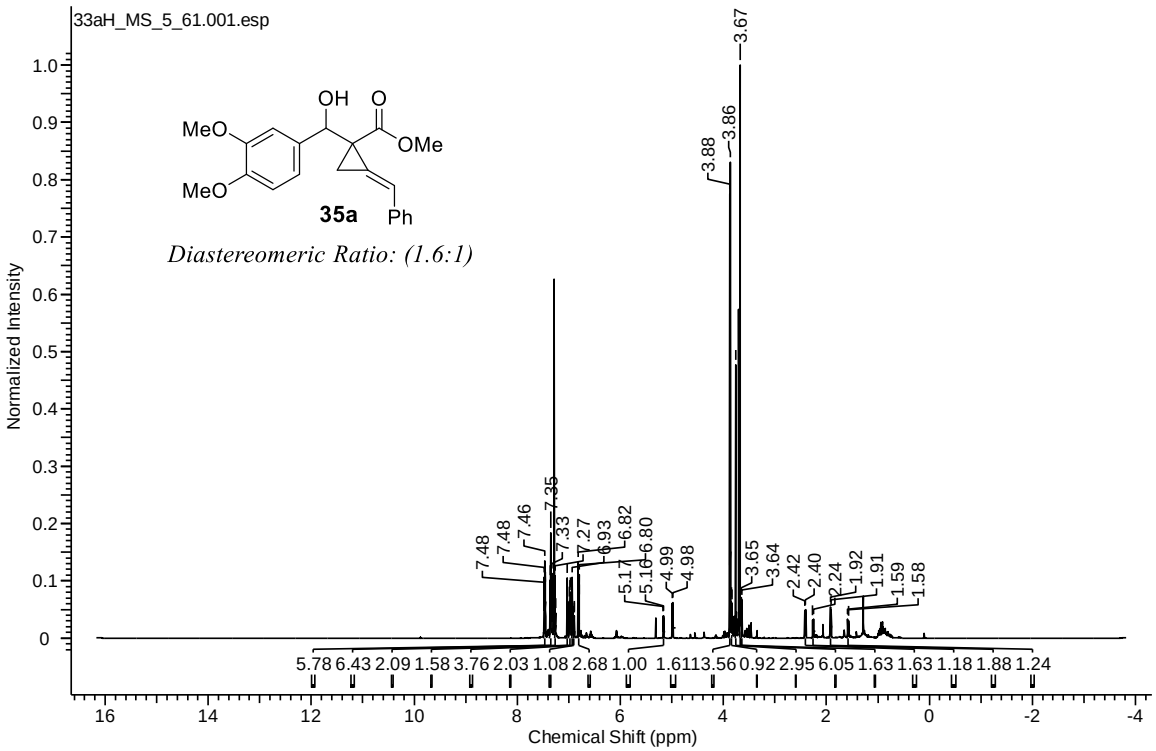
56.09
56.00
52.76
34.64
18.17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Ph
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3.86
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7.35
7.33
7.27
6.93
6.82
6.80
4.99
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3.65
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2.42
2.40
2.24
1.92
1.91
1.59
1.58
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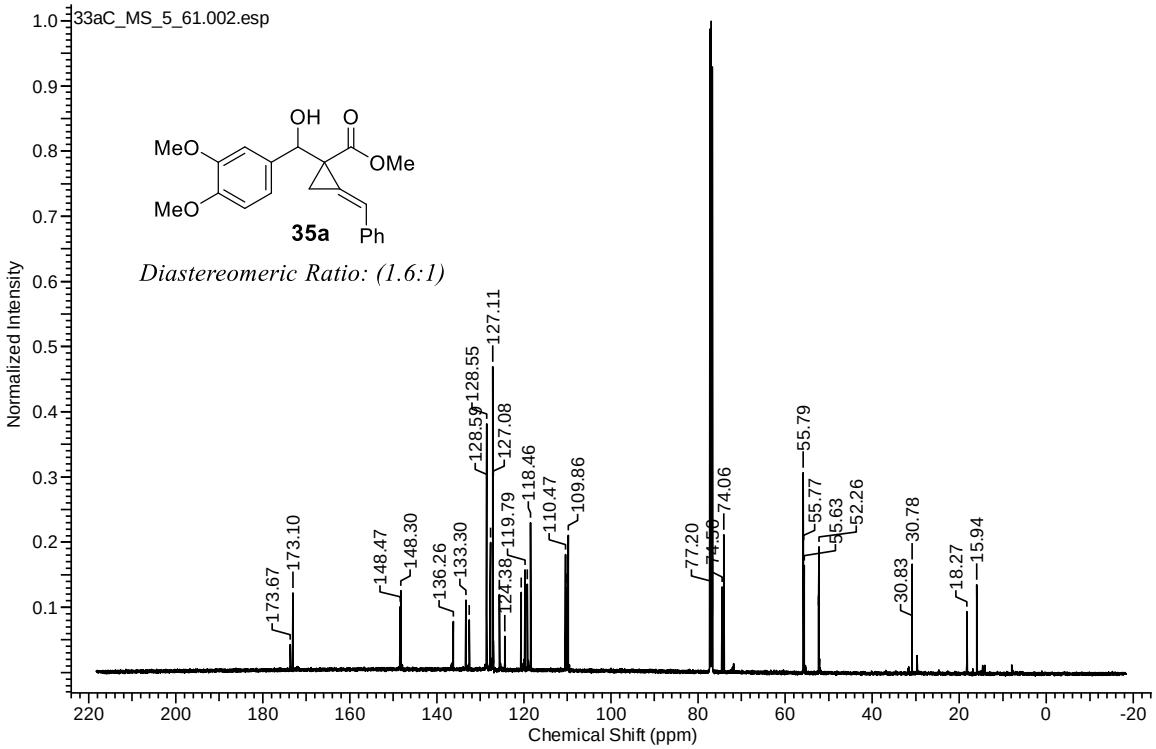
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Chemical Shift (ppm)
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128.52
127.11
127.08
124.38
119.79
118.46
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55.63
52.26
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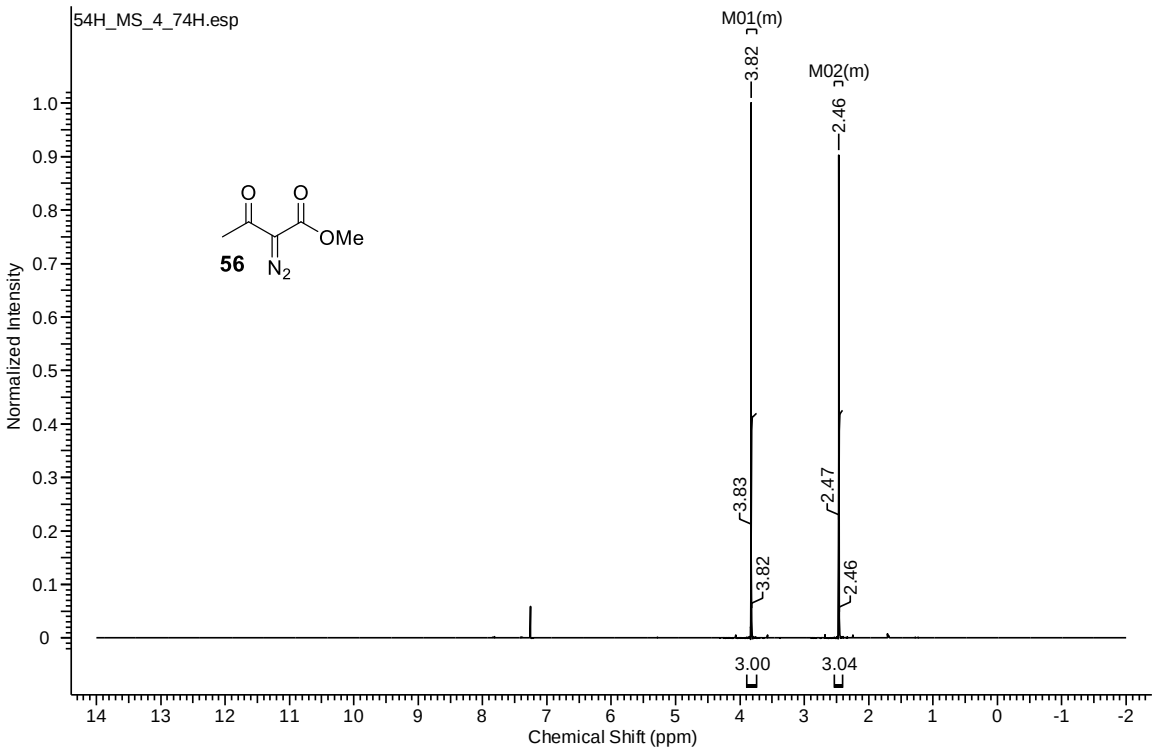
15.94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56
OMe
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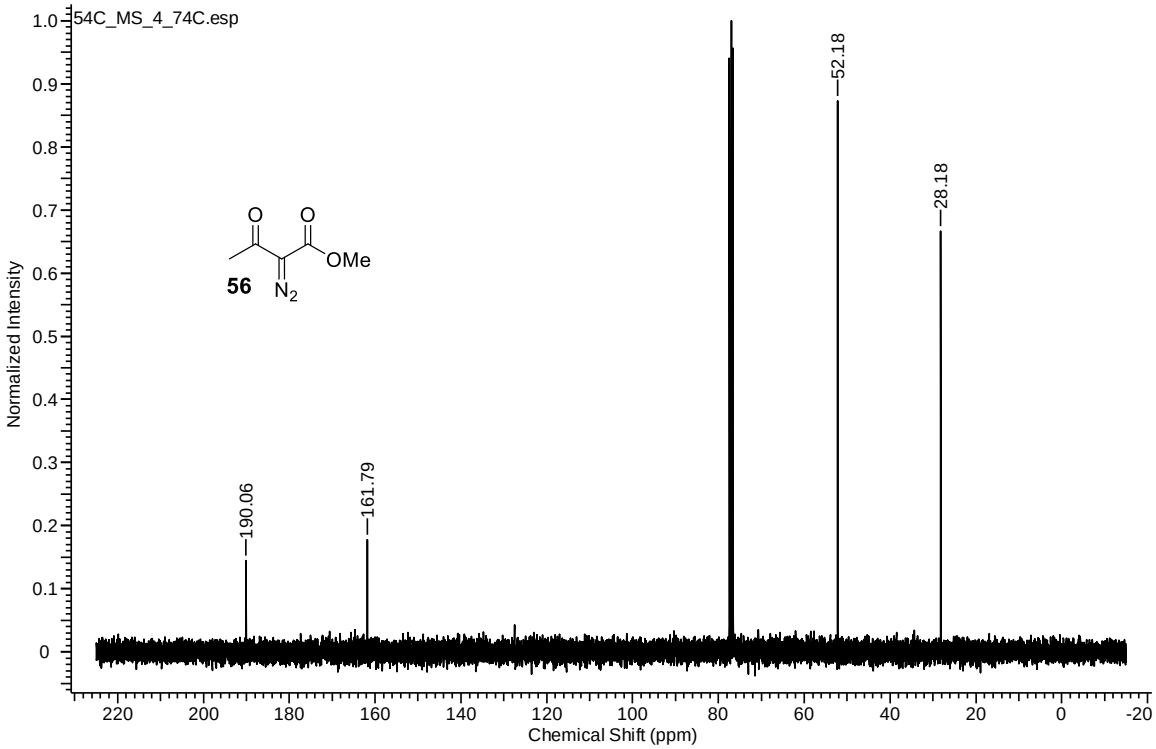
Normalized Intensity
Chemical Shift (ppm)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OMe
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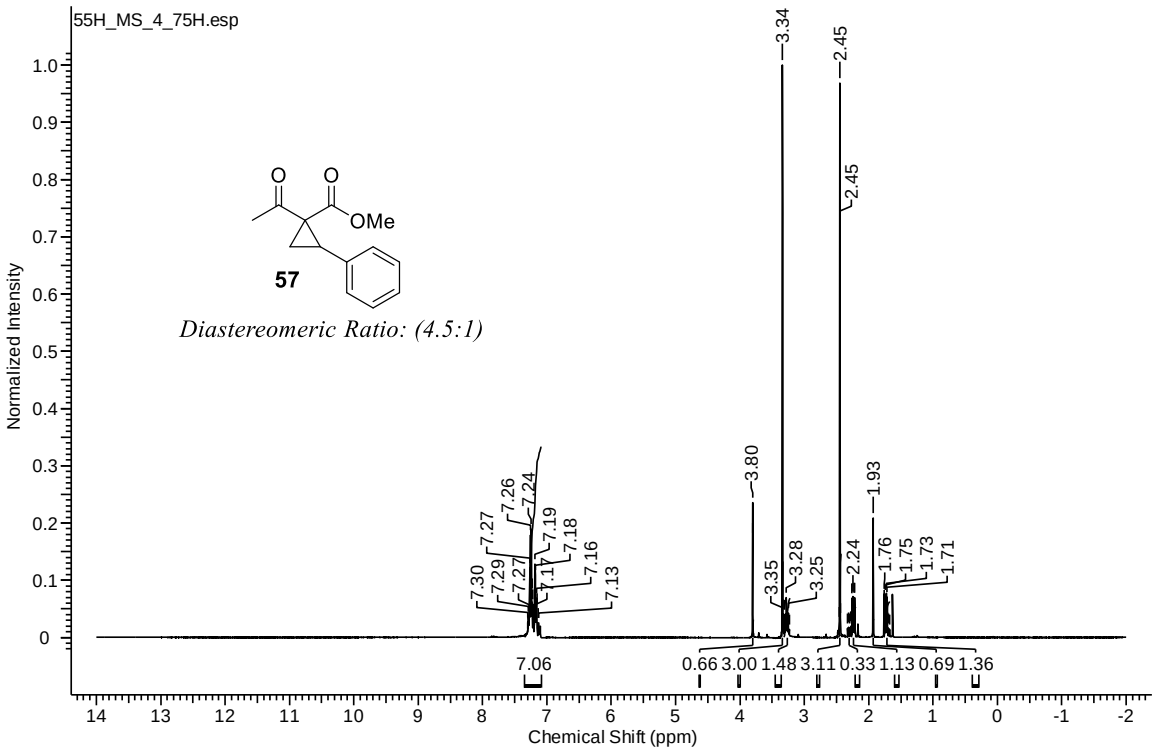
Normalized Intensity
Chemical Shift (ppm)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3.25
2.24
1.76
1.75
1.73
1.71
7.06
0.66
3.00
1.48
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1.13
0.69
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O
OMe
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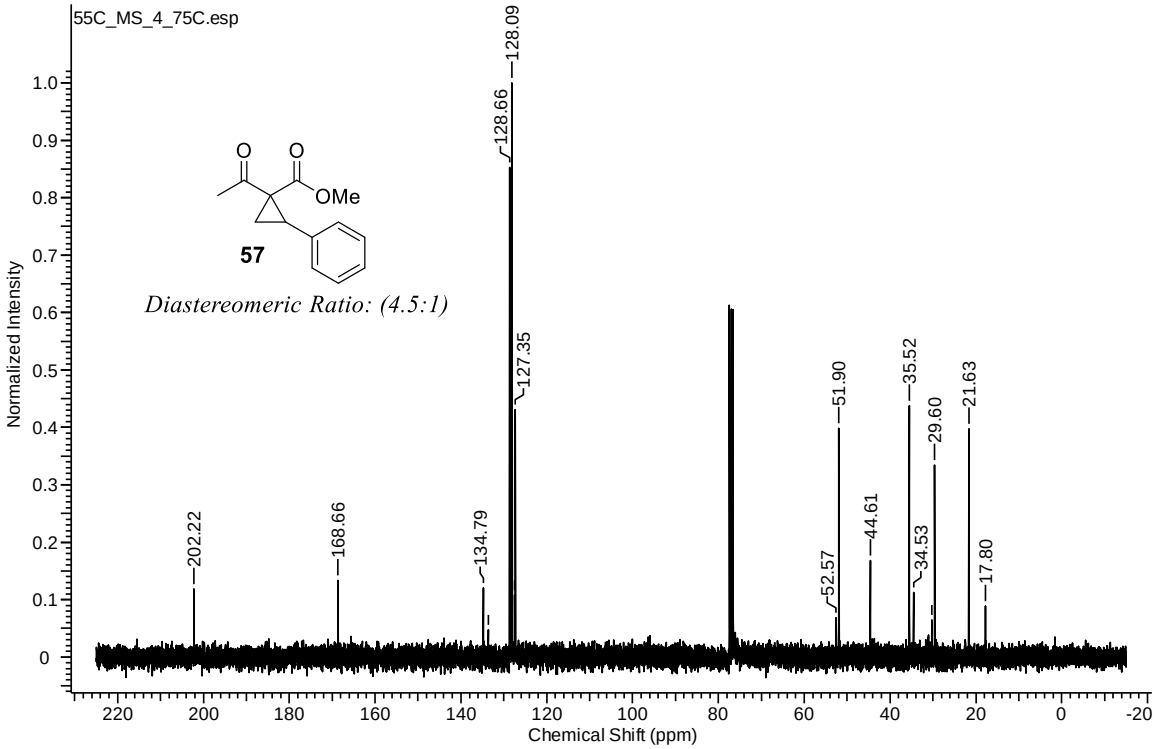
Diastereomeric Ratio: (4.5:1)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Chemical Shift (ppm)
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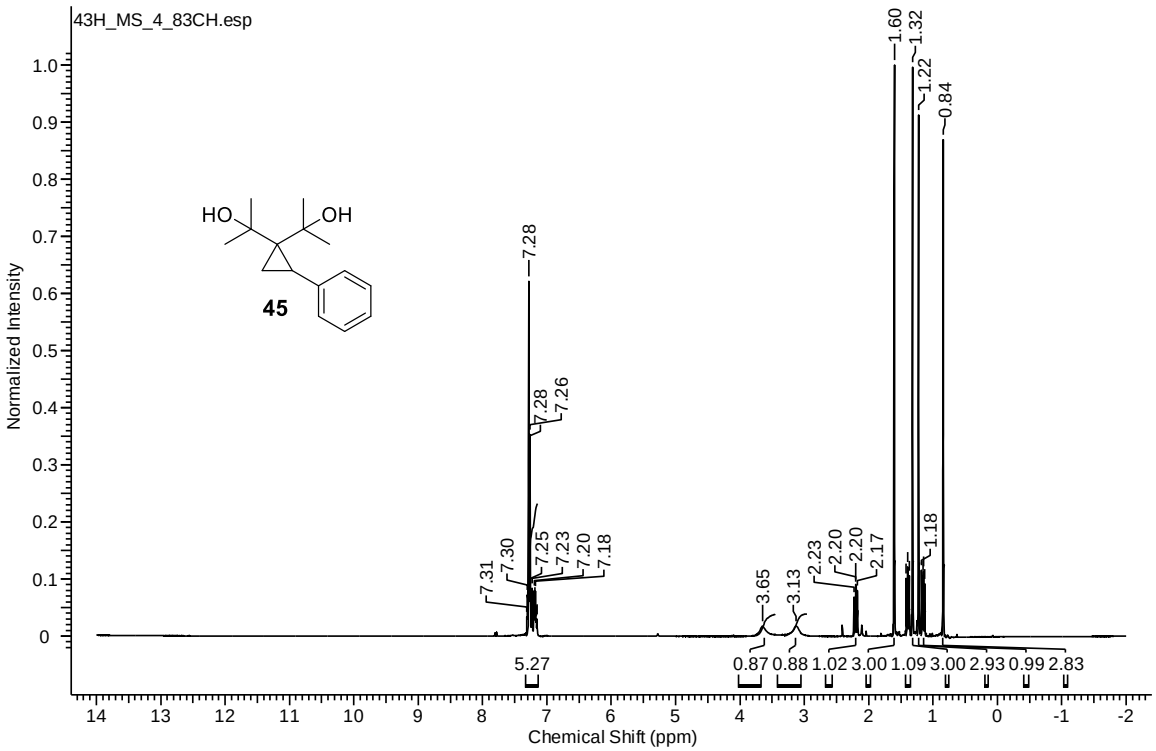
29.60
21.63
44.61
52.57
34.53
17.80
O
O
OMe
57
Diastereomeric Ratio: (4.5:1)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Chemical Shift (ppm)
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7.20
7.18
3.65
3.13
2.23
2.20
2.20
2.17
1.60
1.32
1.22
1.18
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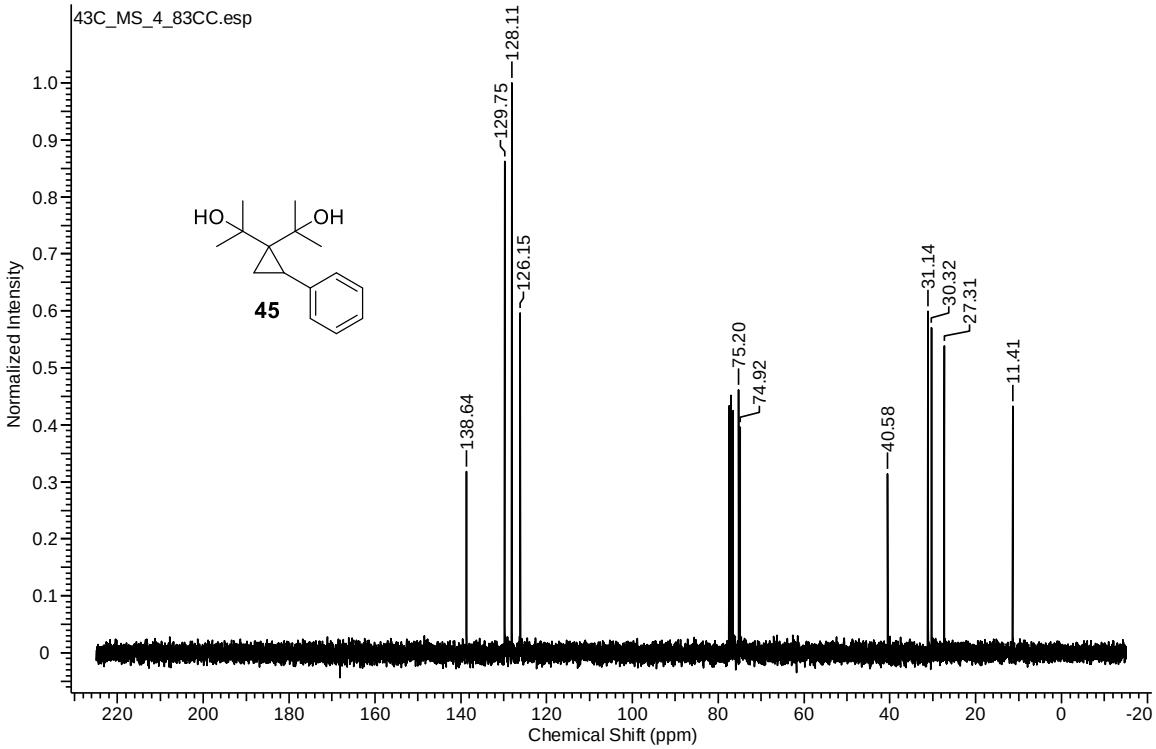
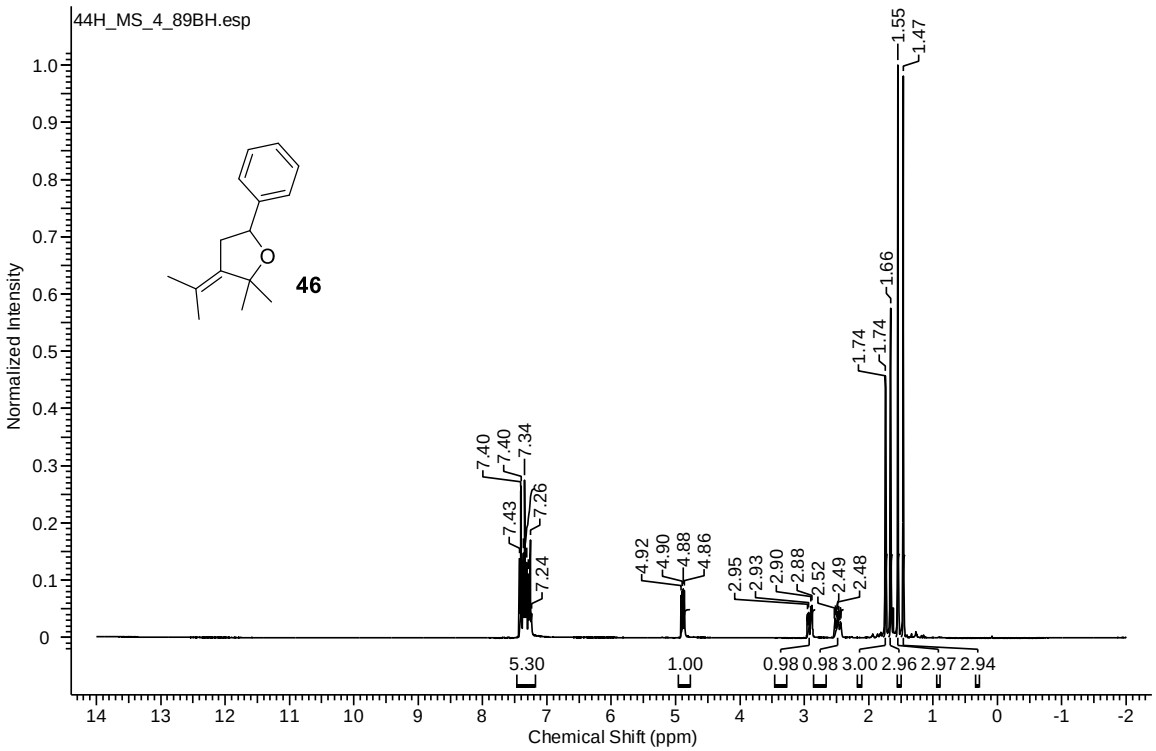
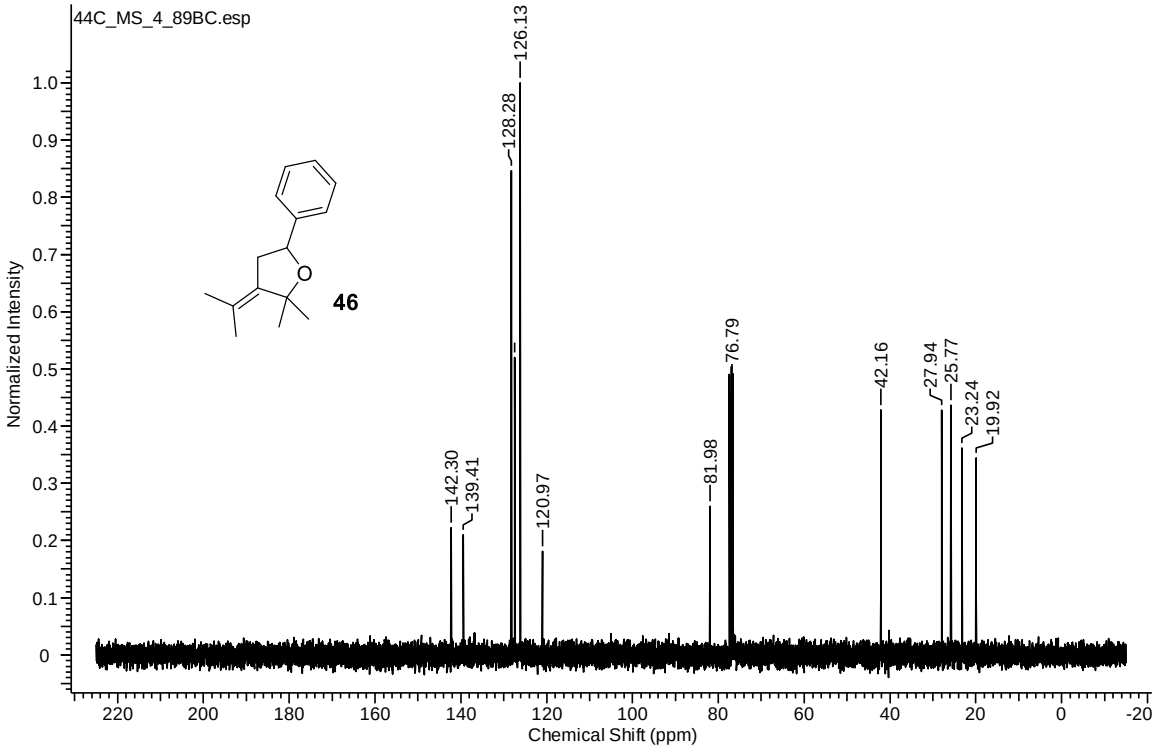
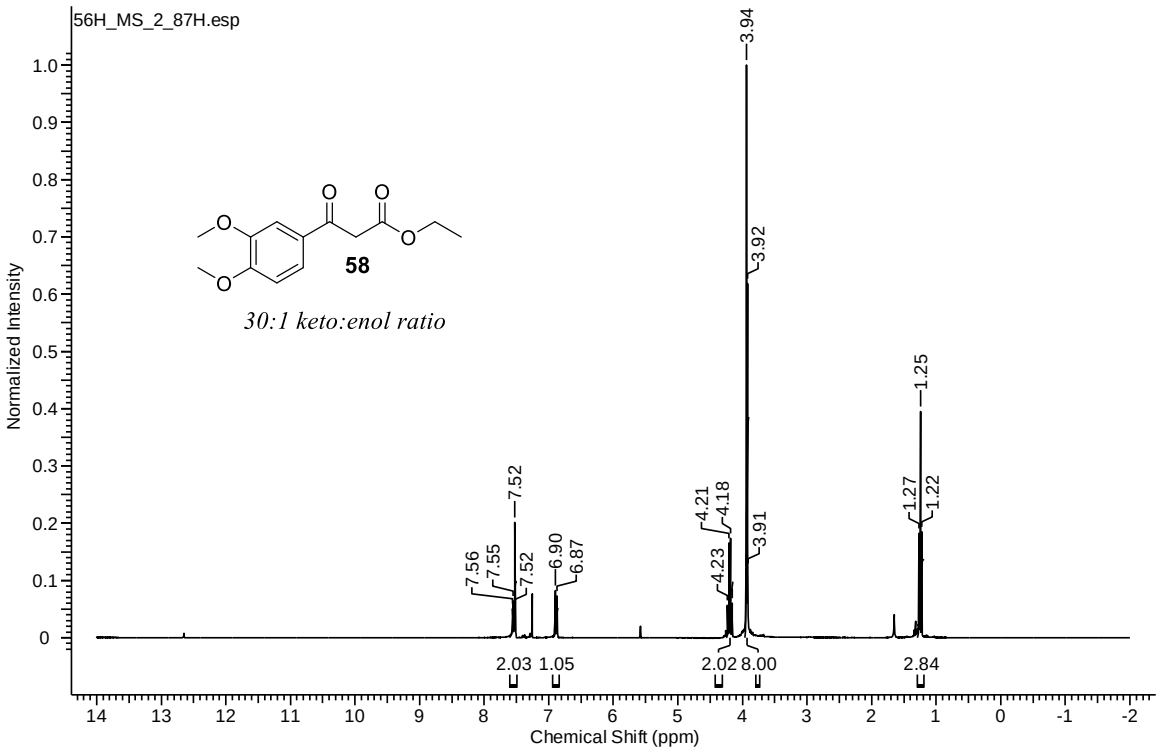
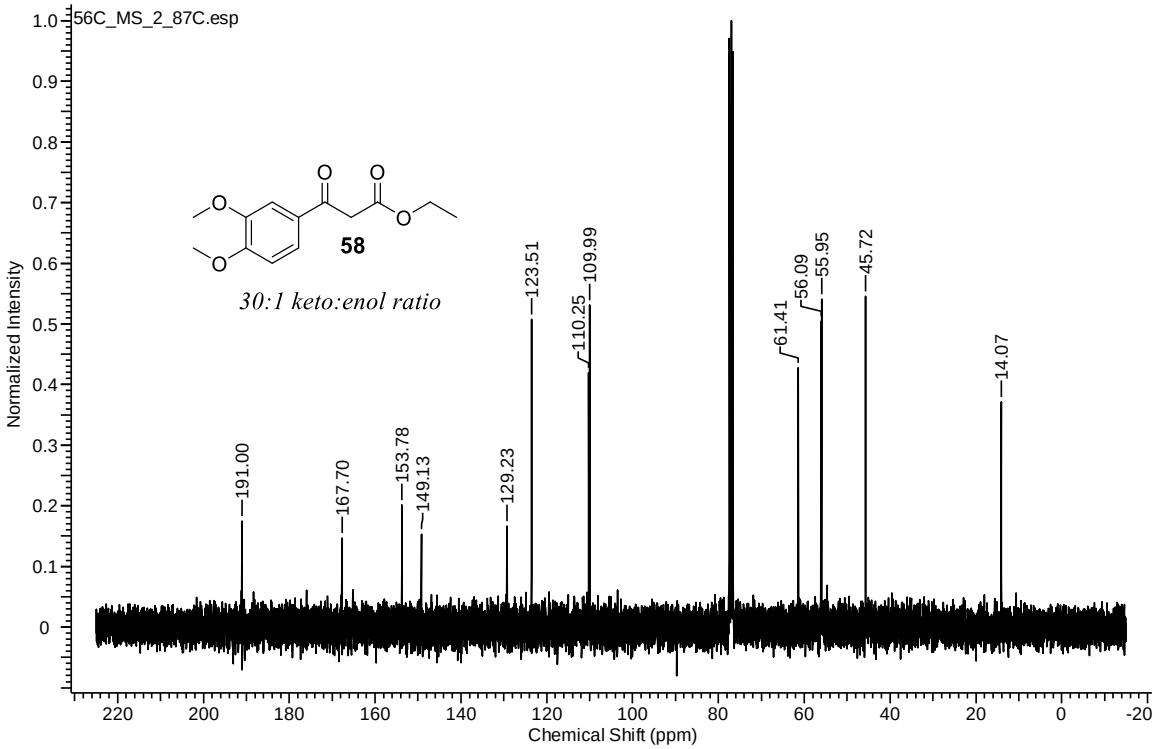
5.27
0.87 0.88 1.02 3.00 1.09 3.00 2.93 0.99 2.83

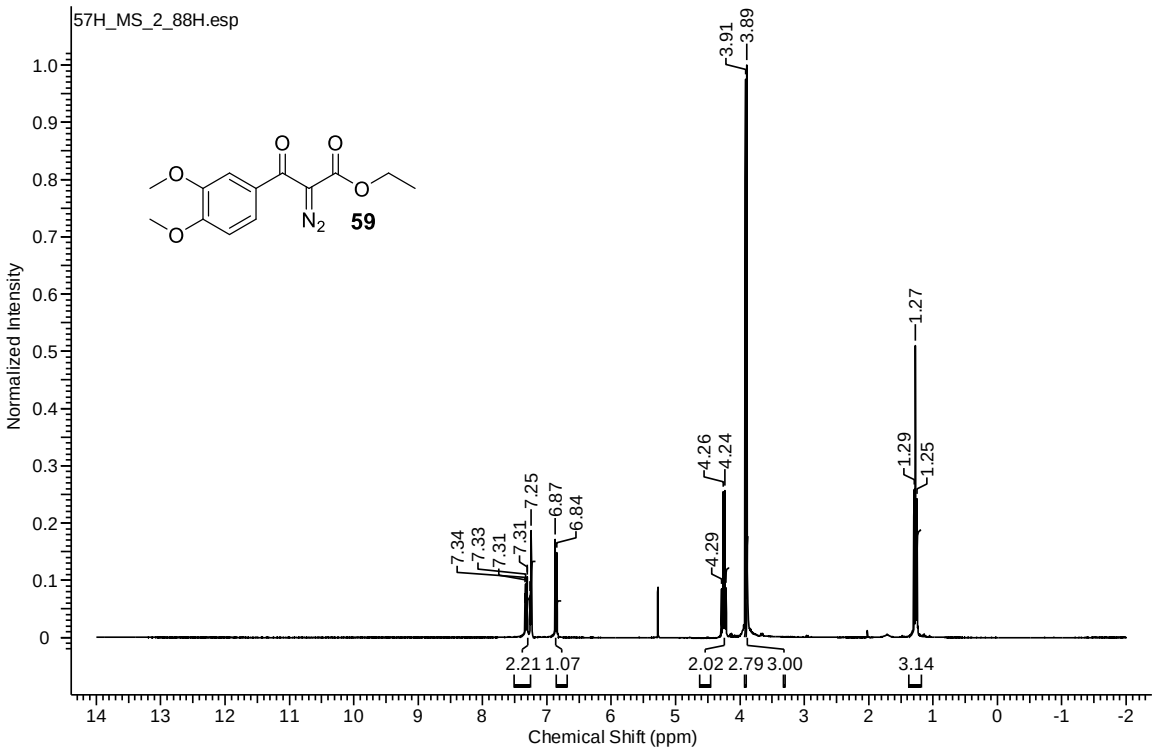

43C_MS_4_83CC.esp
HO
OH
45
Normalized Intensity
Chemical Shift (ppm)
138.64
129.75
128.11
126.15
75.20
74.92
40.58
31.14
30.32
27.31
11.41

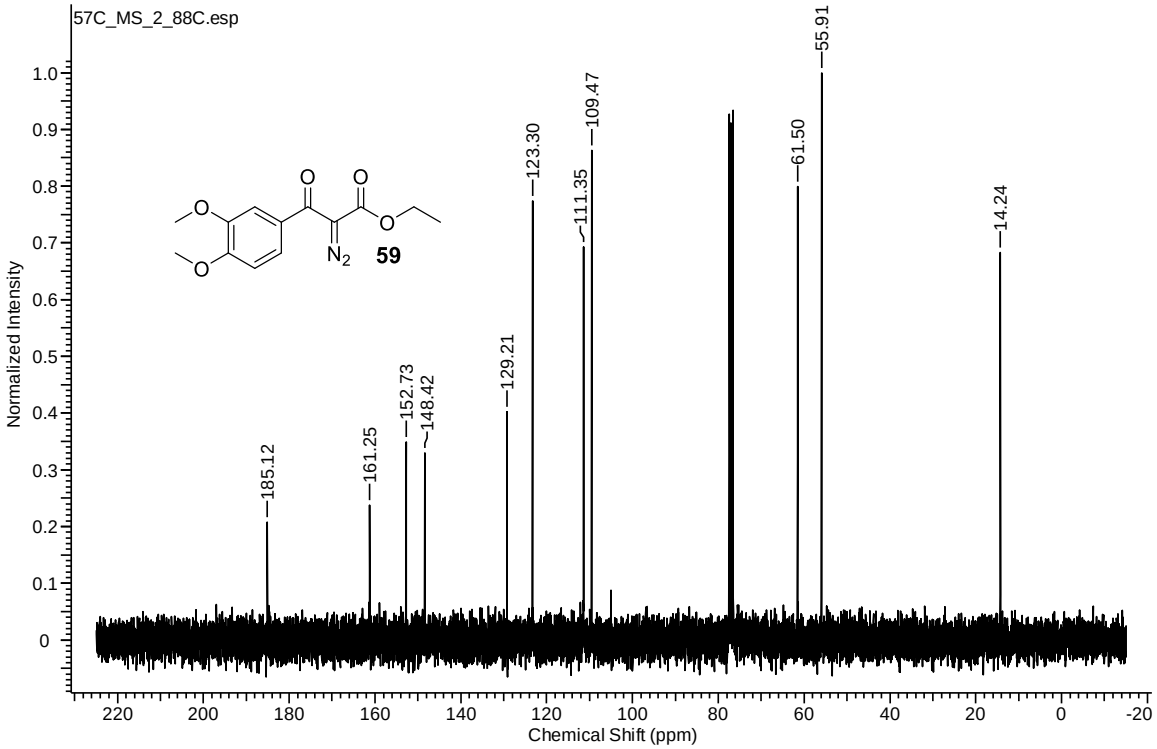

44H_MS_4_89BH.esp
46
Normalized Intensity
Chemical Shift (ppm)
1.55
1.47
1.66
1.74
1.74
7.40
7.40
7.34
7.43
7.26
7.24
4.92
4.90
4.88
4.86
2.95
2.93
2.90
2.88
2.52
2.49
2.48
5.30
1.00
0.98
0.98
3.00
2.96
2.97
2.94

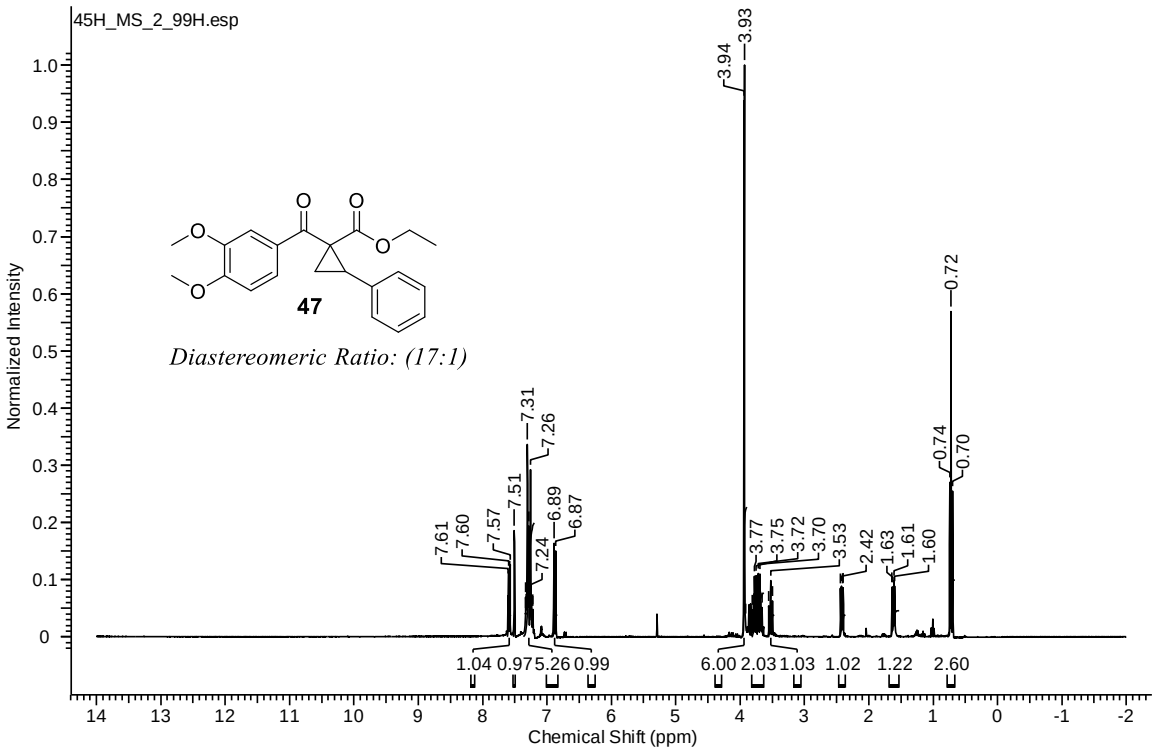

44C_MS_4_89BC.esp
46
Normalized Intensity
Chemical Shift (ppm)
126.13
128.28
142.30
139.41
120.97
81.98
76.79
42.16
27.94
25.77
23.24
19.92

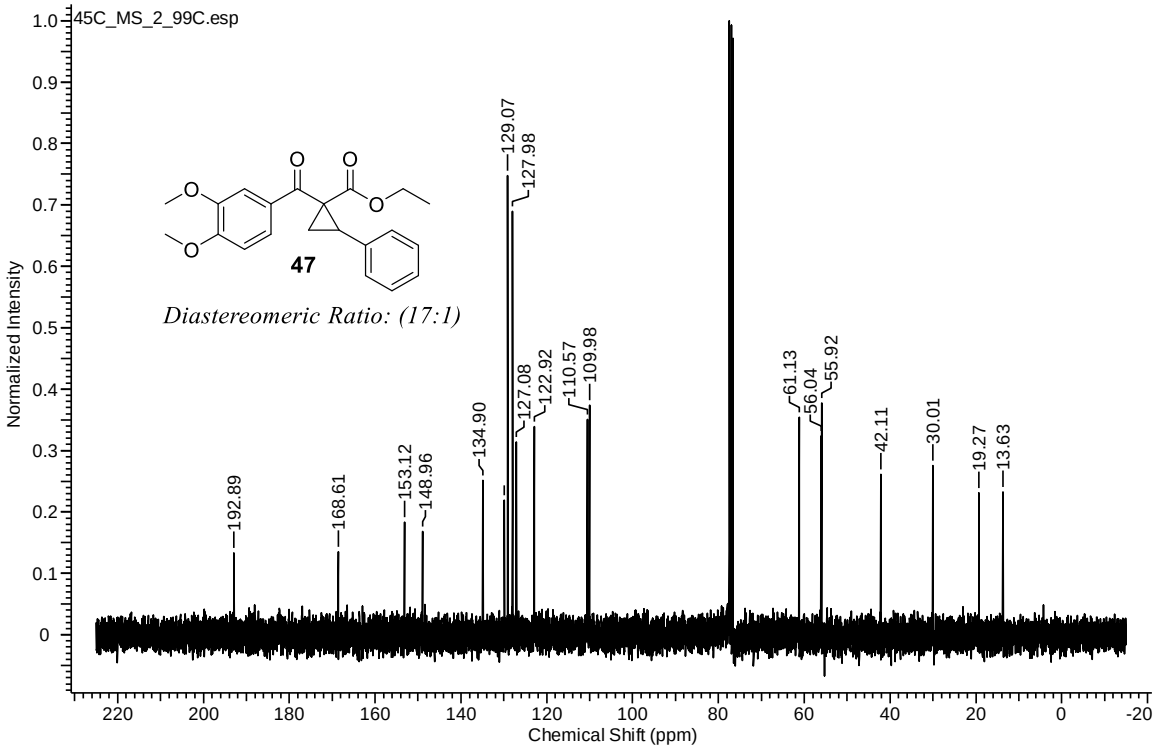

56H_MS_2_87H.esp
Normalized Intensity
Chemical Shift (ppm)
58
30:1 keto:enol ratio
3.94
3.92
1.25
7.52
7.56
7.55
7.52
6.90
6.87
4.21
4.18
4.23
3.91
1.27
1.22
2.03
1.05
2.02
8.00
2.84

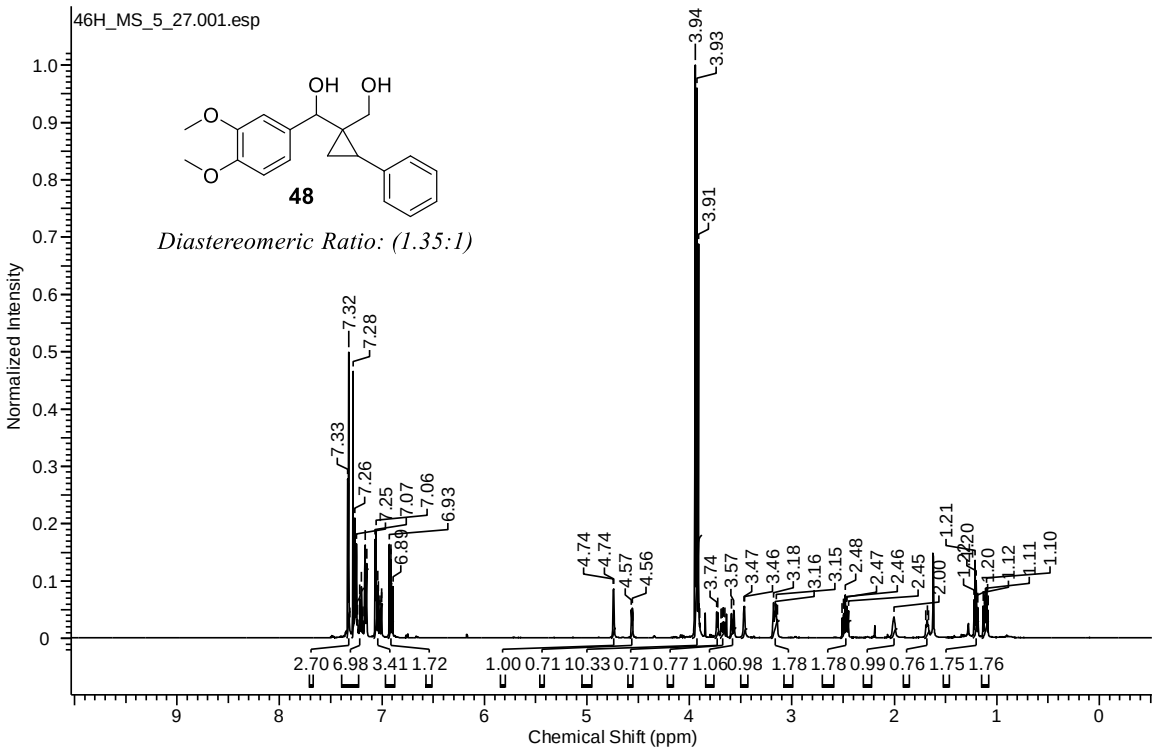

56C_MS_2_87C.esp
Normalized Intensity
Chemical Shift (ppm)
58
30:1 keto:enol ratio
191.00
167.70
153.78
149.13
129.23
123.51
110.25
109.99
61.41
56.09
55.95
45.72
14.07

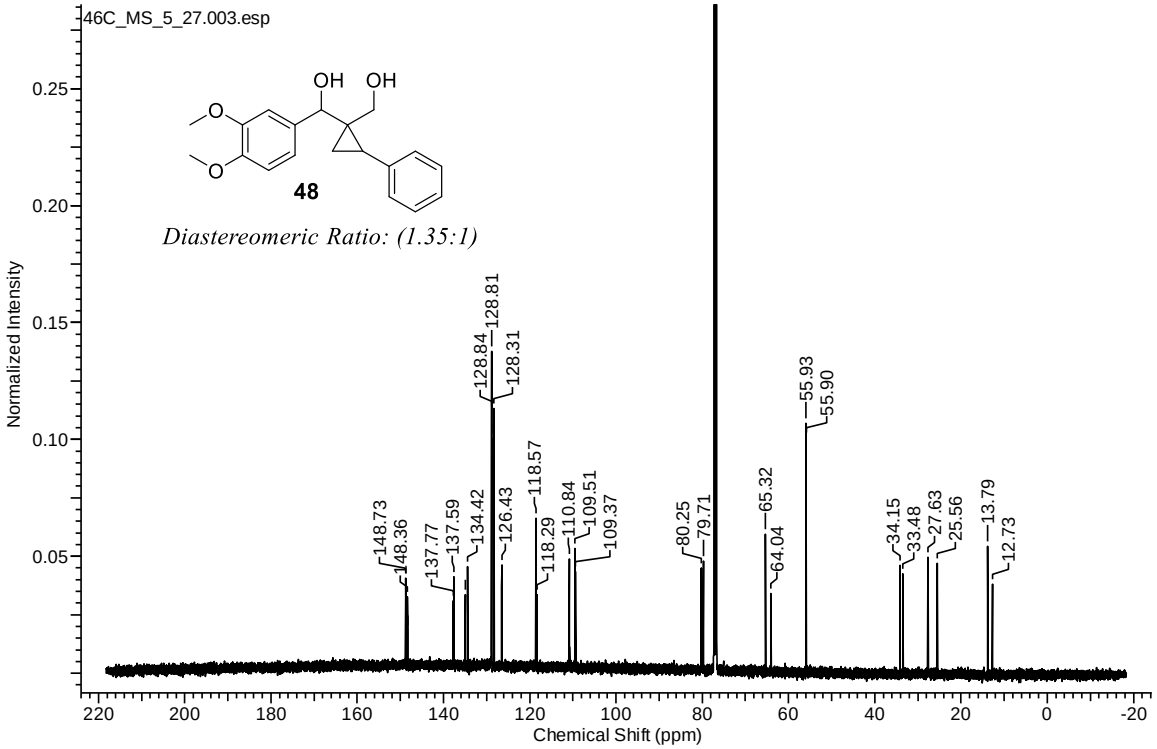

57H_MS_2_88H.esp
59
Normalized Intensity
Chemical Shift (ppm)
3.91
3.89
1.27
4.26
4.24
1.29
1.25
7.34
7.33
7.31
7.25
6.87
6.84
4.29
2.21
1.07
2.02
2.79
3.00
3.14

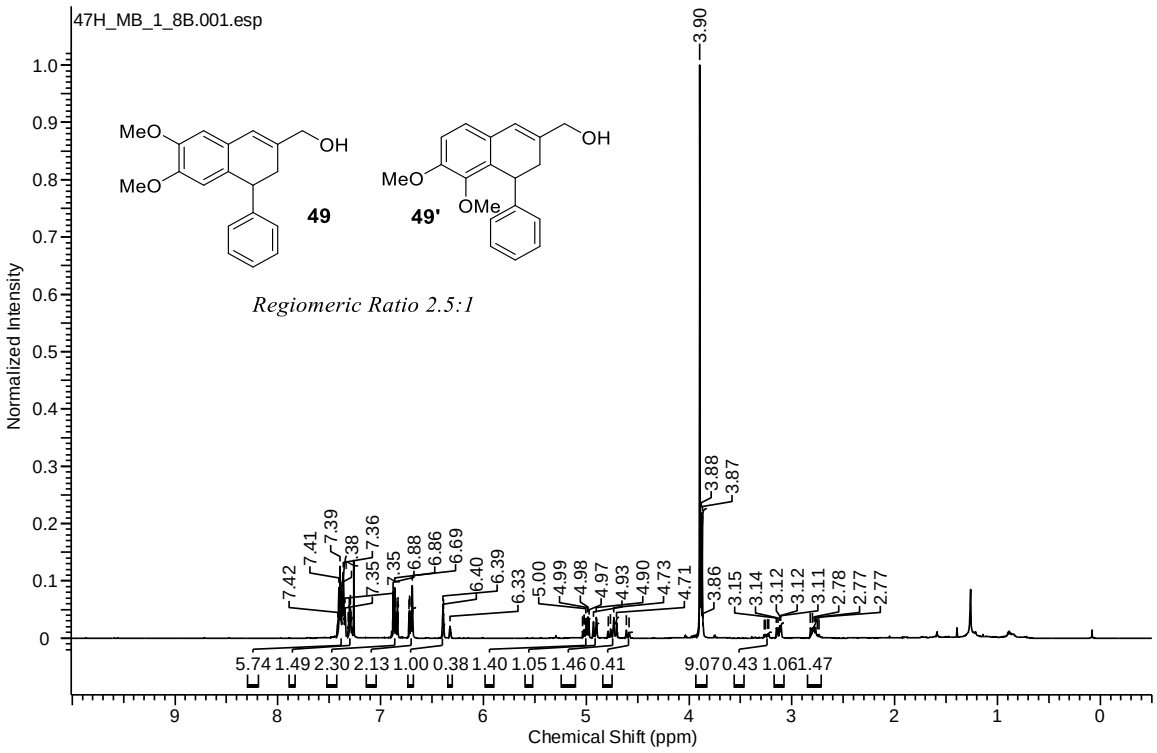

57C_MS_2_88C.esp
59
Normalized Intensity
Chemical Shift (ppm)
55.91
109.47
123.30
111.35
61.50
14.24
129.21
152.73
148.42
161.25
185.12

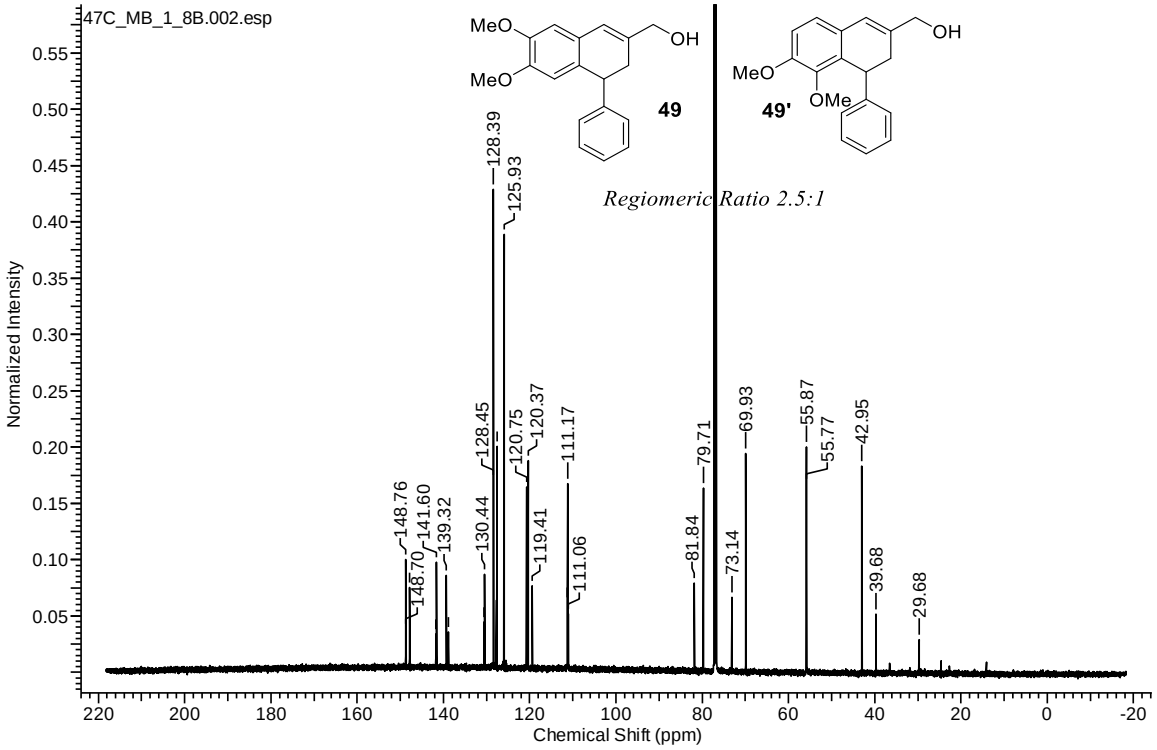

45H_MS_2_99H.esp
47
Diastereomeric Ratio: (17:1)
Normalized Intensity
Chemical Shift (ppm)
3.94
3.93
0.72
7.31
7.26
7.61
7.60
7.57
7.51
6.89
6.87
7.24
0.74
0.70
3.77
3.75
3.72
3.70
3.53
2.42
1.63
1.61
1.60
1.04 0.97 5.26 0.99
6.00 2.03 1.03 1.02 1.22 2.60

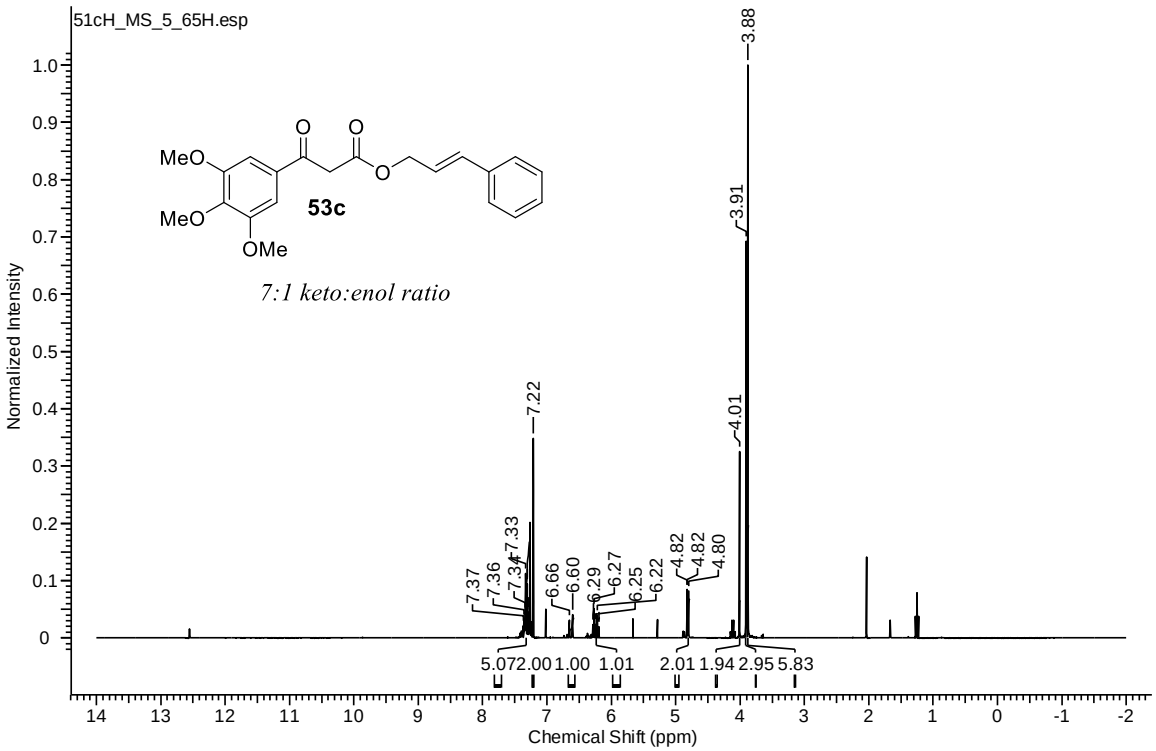

45C_MS_2_99C.esp
47
Diastereomeric Ratio: (17:1)
Normalized Intensity
Chemical Shift (ppm)
129.07
127.98
192.89
168.61
153.12
148.96
134.90
127.08
122.92
110.57
109.98
61.13
56.04
55.92
42.11
30.01
19.27
13.63

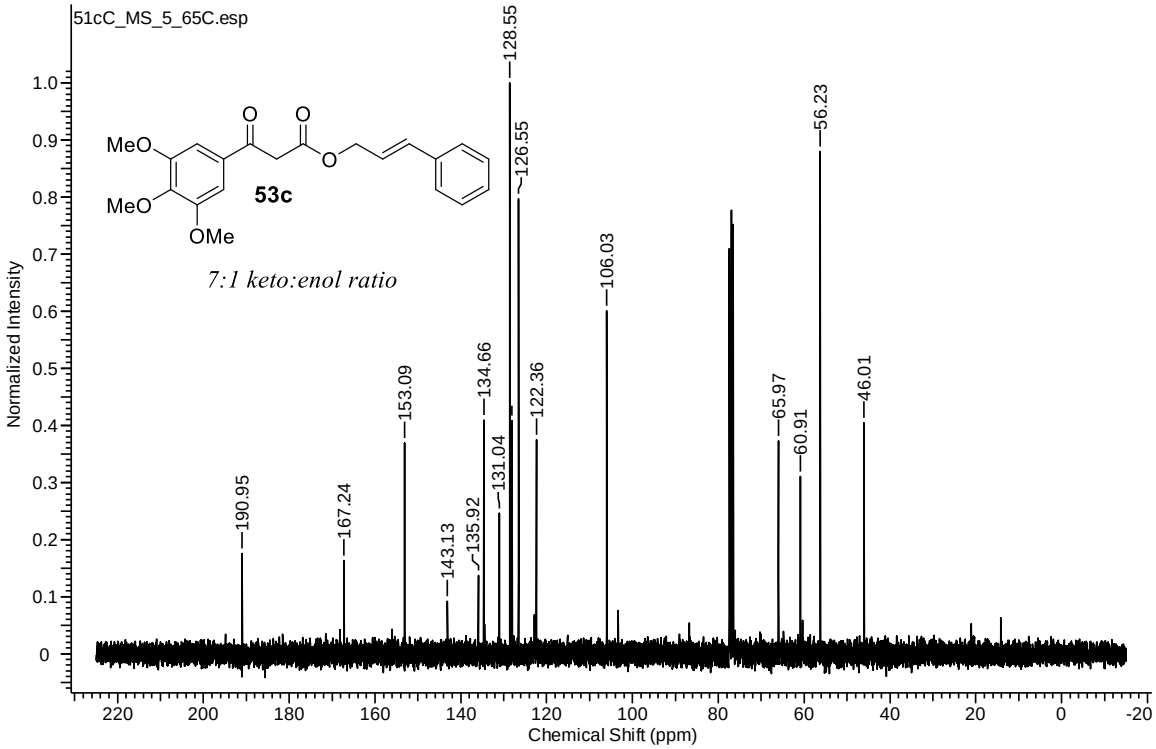

46H_MS_5_27.001.esp
OH OH
O
O
48
Diastereomeric Ratio: (1.35:1)
Normalized Intensity
Chemical Shift (ppm)
3.94
3.93
3.91
7.32
7.28
7.33
7.26
7.25
7.07
7.06
6.93
6.89
4.74
4.74
4.57
4.56
3.74
3.57
3.47
3.46
3.18
3.16
3.15
2.48
2.47
2.46
2.45
2.00
1.21
1.20
1.12
1.11
1.10
2.70 6.98 3.41 1.72
1.00 0.71 10.33 0.71 0.77 1.06 0.98 1.78 1.78 0.99 0.76 1.75 1.76

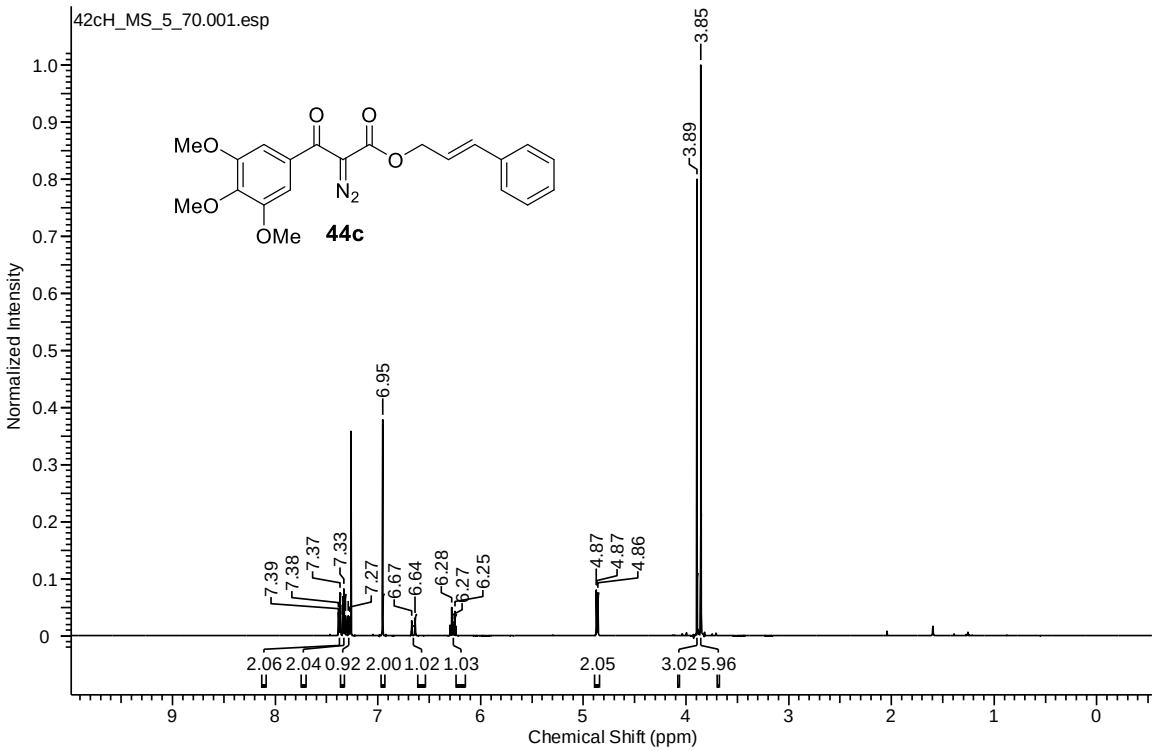

46C_MS_5_27.003.esp
OH OH
O
O
48
Diastereomeric Ratio: (1.35:1)
Normalized Intensity
Chemical Shift (ppm)
128.81
128.84
128.31
148.73
148.36
137.77
137.59
134.42
126.43
118.57
118.29
110.84
109.51
109.37
80.25
79.71
65.32
64.04
55.93
55.90
34.15
33.48
27.63
25.56
13.79
12.73

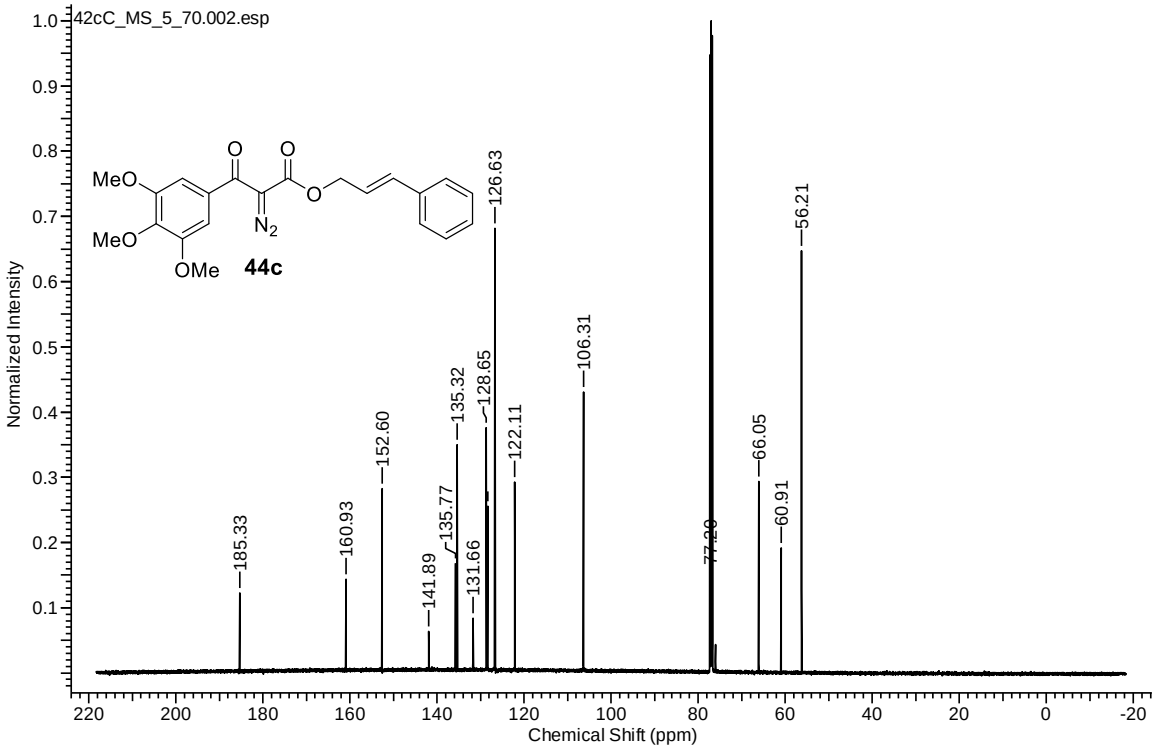

47H_MB_1_8B.001.esp
MeO
MeO
OH
49
MeO
OMe
OH
49'
Regiomeric Ratio 2.5:1
Normalized Intensity
Chemical Shift (ppm)
3.90
3.88
3.87
7.42
7.41
7.39
7.38
7.36
7.35
7.35
6.88
6.86
6.69
6.40
6.39
6.33
5.00
4.99
4.98
4.97
4.93
4.90
4.73
4.71
3.86
3.15
3.14
3.12
3.12
3.11
2.78
2.77
2.77
5.74 1.49 2.30 2.13 1.00 0.38 1.40 1.05 1.46 0.41
9.07 0.43 1.06 1.47

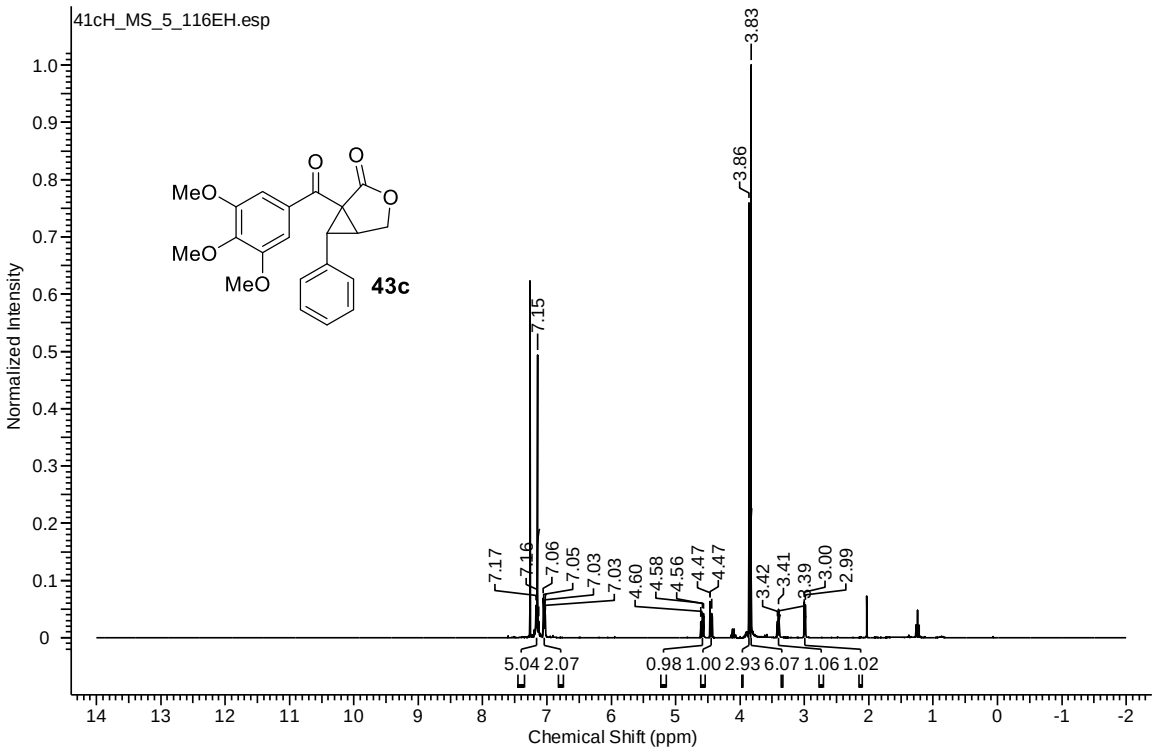

47C_MB_1_8B.002.esp
MeO
MeO
OH
49
MeO
OMe
OH
49'
Regiomeric Ratio 2.5:1
Normalized Intensity
Chemical Shift (ppm)
128.39
125.93
128.45
120.75
120.37
111.17
148.76
141.60
139.32
130.44
119.41
148.70
111.06
81.84
79.71
73.14
69.93
55.87
55.77
42.95
39.68
29.68

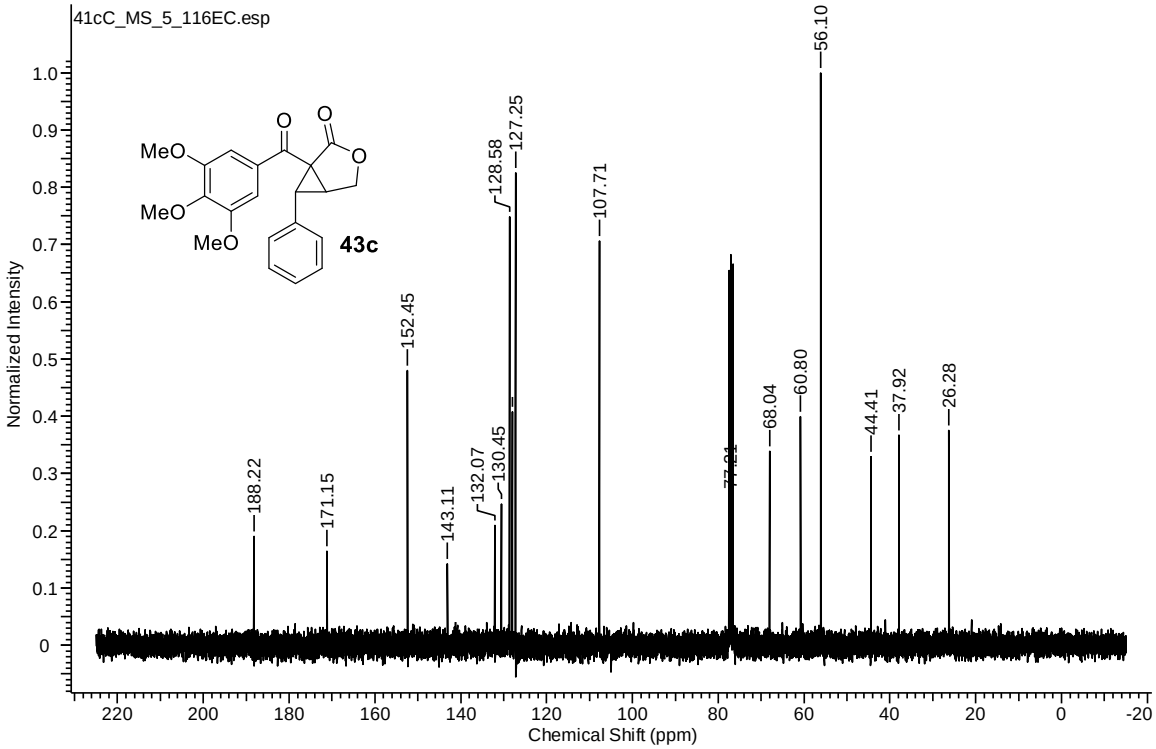

51cH_MS_5_65H.esp
MeO
MeO
OMe
53c
7:1 keto:enol ratio
Normalized Intensity
Chemical Shift (ppm)
3.88
3.91
4.01
7.22
7.37
7.36
7.34
7.33
6.66
6.60
6.29
6.27
6.25
6.22
4.82
4.82
4.80
5.07 2.00 1.00 1.01 2.01 1.94 2.95 5.83


51cC_MS_5_65C.esp
MeO
MeO
OMe
53c
7:1 keto:enol ratio
Normalized Intensity
Chemical Shift (ppm)
128.55
126.55
106.03
56.23
46.01
65.97
60.91
153.09
134.66
131.04
122.36
190.95
167.24
143.13
135.92


42cH_MS_5_70.001.esp
MeO
MeO
OMe
O
O
O
N2
44c
3.85
3.89
6.95
7.39
7.38
7.37
7.33
7.27
6.67
6.64
6.28
6.27
6.25
4.87
4.87
4.86
2.06 2.04 0.92 2.00 1.02 1.03 2.05 3.02 5.96
Normalized Intensity
Chemical Shift (ppm)


42cC_MS_5_70.002.esp
MeO
MeO
OMe
O
O
O
N2
44c
126.63
56.21
106.31
135.32
128.65
152.60
122.11
66.05
60.91
185.33
160.93
135.77
141.89
131.66
77.00
Normalized Intensity
Chemical Shift (ppm)


41cH_MS_5_116EH.esp
MeO
MeO
MeO
43c
Normalized Intensity
Chemical Shift (ppm)
3.83
3.86
7.15
7.17
7.16
7.06
7.05
7.03
7.03
4.60
4.58
4.56
4.47
4.47
3.42
3.41
3.39
3.00
2.99
5.04 2.07 0.98 1.00 2.93 6.07 1.06 1.02


41cC_MS_5_116EC.esp
MeO
MeO
MeO
43c
Normalized Intensity
Chemical Shift (ppm)
188.22
171.15
152.45
143.11
132.07
130.45
128.58
127.25
107.71
77.01
68.04
60.80
56.10
44.41
37.92
26.28

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APPENDIX – COPYRIGHT PERMISSIONS

Title: Calcium-Catalyzed, Dehydrative, Ring-Opening Cyclizations of Cyclopropyl Carbinols Derived from Donor–Acceptor Cyclopropanes

Author: Matthew J. Sandridge, Stefan France

Publication: Organic Letters

Publisher: American Chemical Society

Date: Sep 1, 2016

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