DIVERSITY-ORIENTED SYNTHETIC STRATEGIES TOWARD *N*-HETEROCYCLIC AND CARBOCYCLIC FRAMEWORKS

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Maria Cynthia Martin

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DIVERSITY-ORIENTED SYNTHETIC STRATEGIES TOWARD *N*-HETEROCYCLIC AND CARBOCYCLIC FRAMEWORKS

Approved by:

Dr. Stefan France, Advisor
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. M.G. Finn
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. David Collard
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Wendy L. Kelly
School of Chemistry and Biochemistry
Georgia Institute of Technology

Dr. Andy Bommarius
School of Chemical and Biomolecular Engineering
Georgia Institute of Technology

Date Approved: June 19, 2017

This thesis is dedicated to my loving parents, my mother, Monique Martin and my father, the late Maurice Martin. Without their guidance, wisdom and sacrifices I would not have realized my dreams and become the scientist I am today.

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LIST OF SYMBOLS AND ABBREVIATIONS

A	Acceptor
AcOH	Acetic acid
$Al(OTf)_3$	Aluminium(III) trifluoromethanesulfonate
β	Beta
$BF_3•Et_2O$	Boron trifluoride diethyl etherate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
n-Bu	*n*-Butyl
$Bu_4N(PF)_6$	Tetrabutylammoniumhexafluorophosphate
CaH_2	Calcium hydride
Calc.	Calculated
cat.	Catalytic
$Ca(NTf_2)_2$	Calcium triflimide
^{13}C	Carbon-13
CCl_4	Carbon tetrachloride
$CDCl_3$	Chloroform-*d*
CH_2Cl_2	Dichloromethane
CO	Carbon monoxide
$Cu(ClO_4)_2•6H_2O$	Copper perchlorate hexahydrate
$Cu(OTf)_2$	Copper(II) triflate
$CuSO_4$	Copper(II) sulfate
δ	Delta or chemical shift
D	Donor

D-A	Donor-acceptor
D-A-A	Donor-acceptor-acceptor
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
d	Doublet
dd	Doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
EtOAC	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
EWG	Electron-withdrawing group
FMO	Frontier molecular orbital
γ	Gamma
g	Grams
$Ga(OTf)_3$	Gallium(III) trifluoromethanesulfonate
h	Hour
^1H	Proton NMR
H_2	Hydrogen
H_2O_2	Hydrogen peroxide

$Hf(OTf)_4$	Hafnium(IV) trifluoromethanesulfonate
HRMS	High resolution mass spectrometry
Hz	Hertz
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
i-Pr	Isopropyl
K_2CO_3	Potassium carbonate
$La(OTf)_3$	Lanthanum(III) trifluoromethanesulfonate
$Li(ClO_4)•3H_2O$	Lithium perchlorate trihydrate
LiHMDS	Lithium bis(trimethylsilyl)amide
m	*Meta*
m	Medium or multiplet
M	Molarity
MeOH	Methanol
$Mg(OTf)_2$	Magnesium(II) trifluoromethanesulfonate
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
mL	Milliliter
mmol	Millimole
MO	Molecular orbital
N_2	Nitrogen
$NaBH_4$	Sodium Borohydride
NaH	Sodium Hydride
$NaHCO_3$	Sodium bicarbonate
$NaSO_4$	Sodium sulfate
NEt_3	Triethylamine

$Ni(ClO_4)_2 \bullet 6H_2O$	Nickel perchlorate hexahydrate
$Ni(OTf)_2$	Nickel(II) trifluoromethanesulfonate
NMR	Nuclear magnetic resonance
o	*Ortho*
O_2	Oxygen
p	*Para*
Ph	Phenyl
ppm	Parts-per-million
q	Quartet
R_f	Retention factor
Rh_2esp_2	Bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]
rt	Room temperature
s	Singlet or strong
$Sc(OTf)_3$	Scandium(III) trifluoromethanesulfonate
t	Triplet
t-Butyl	*Tert*-butyl
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
μW	Microwave
UV	Ultraviolet
w	weak
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
$Zn(OTF)_3$	Zinc(II) trifluoromethanesulfonate

SUMMARY

N-Heterocyclic and polycyclic molecular scaffolds are valuable structural motifs present in many biologically active and pharmaceutically-relevant compounds, and also in the field of material science. Much effort has been focused on the development of efficient methods for the formation of these significant scaffolds for the synthesis of natural product targets. In the following thesis, diverse protocols have been designed to access these heterocyclic and carbocyclic targets: (1) the use of strained polarized ring systems in the presence of amine nucleophiles to access small *N*-heterocyclic molecules, (2) the design of a formal [5+2] cycloaddition approach towards seven-membered ring fused indoles, and (3) the dehydrative, Nazarov-type cyclization via calcium catalysis to access directly a wide array of cyclopenta[*b*]thiophenes and indenes. All these catalytic transformations are amenable to various functional groups, thus demonstrating their versatility and scope.

CHAPTER 1. INTRODUCTION

1.1 Diversity-Oriented Synthesis: Producing Chemical Tools

The search for new biological probes capable of regulating biological pathways has led to the rapid development of diversity-oriented synthesis (DOS), a strategy used to access large numbers of structurally unique small molecules.[1-3] A more comprehensive definition for DOS has been suggested by Spring[3b] as "diversity-oriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem." The "complex problem" mentioned in this definition usually refers to the discovery of novel biologically relevant compounds. However, this does not have to be the case, as the DOS approach could potentially be applied to other problems, such as the discovery of a novel ligand or catalyst for a reaction.[3b]

These small molecules are usually potential orally bioavailable compounds that have a molecular weight of less than 1500 Da[4] and that are distinct from naturally occurring biological macromolecules: DNA, RNA and proteins.[5] Moreover, not only do they occupy new chemical space, these molecules need to bind to proteins, be of defined molecular complexity,[6] be structurally rigid, and possess three-dimensionality.[7] Production of these libraries of molecules are not solely based on natural products, due predominantly to difficulties in sourcing, isolating, and identifying the bioactive components, as well as in purifying and chemically modifying these extremely complex structures.[8] Therefore, in terms of making large numbers of compounds for screening, chemical synthesis if generally considered to be the most efficient approach.[9]

1.1.1 Molecular Diversity and Chemical Space

The aim of DOS is to incorporate, as efficiently as possible the maximum degree of structural diversity for a given synthetic sequence.[3e, 9a] Ideally, this should involve four diversity elements:[10]

1. Building block diversity: variation resulting from the choice of starting materials used, usually resulting in the variation of R-groups around a single scaffold.
2. Functional group diversity: a myriad of functional groups present in a molecule, and also at specific sites within the whole structure. This gives the potential for interactions with different polar, apolar, or charged groups present in biological macromolecules.
3. Stereochemical diversity: variation in the orientation of functional groups and potential macromolecule-interacting elements. This is crucial as nature and biological macromolecules are three-dimensional environments.
4. Skeletal diversity: variation in the overall molecular framework such as ring structures and other rigidifying elements, resulting in molecules with distinct scaffolds.

Chemical space, also properly defined as the multidimensional descriptor space, embodies all theoretically possible compounds and is therefore essentially infinite, limited only by the imagination of chemists and current synthetic methodologies.[11] Molecules occupy discrete points within chemical space with "similar" molecules grouped together and "dissimilar" molecules further apart. Molecules' positions in

chemical space are determined by their comparable physical properties, such as molecular weight, log P, and polarizability as well as their topological features.[11, 12]

1.1.2 Synthetic Strategies for Creating Molecular Diversity

There exists a considerable challenge of creating molecular diversity efficiently, which requires strategies that differ from the majority of traditional chemical syntheses. Since the beginnings of DOS almost 20 years ago, two distinct strategies towards generating structural diversity have been established in the literature: (1) the reagent-based approach, where subjecting a given molecule to a range of reaction conditions allows the synthesis of a number of distinct compounds, and (2) the substrate-based approach, where a number of starting materials containing pre-encoded skeletal information are transformed under conditions into a range of molecular structures (Figure 1.1). [3c]

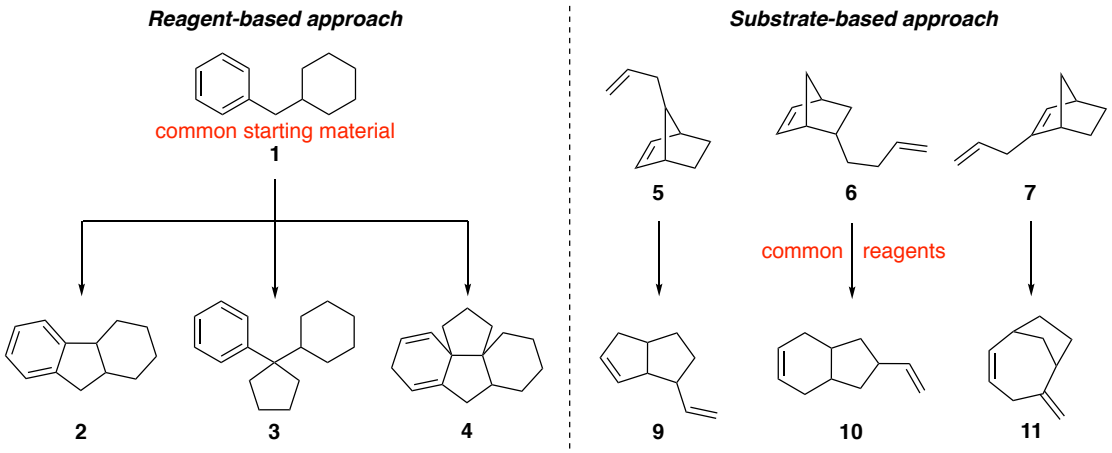


Figure 1.1. Representation of the Two Strategies for Molecular Diversity

1.2 Strained Carbocycles and 1,3-Dicarbonyl Alkylidene Systems as Building Blocks

There are many useful building blocks in the field of synthetic organic chemistry. Strained carbocycles such as cyclopropanes and cyclobutanes, and the 1,3-dicarbonyl alkylidene systems peaked major interest due to their availability of providing unparalleled versatility for access to diverse chemical scaffolds. The unique structure and bonding characteristics of these small rings provide the basis for their incomparable reactivity. Similarly, these alkylidene substrates can undergo a diverse array of transformations to achieve molecular diversity due to its analogy to D-A cyclopropanes. Therefore, efforts to understand the reactivity profiles of these building blocks enable their manipulation for strategic effectuation of novel protocols, an accomplishment beneficial to synthetic chemistry.

1.3 Cyclopropanes: Background

Since its discovery by William Henry Perkin in 1884, cyclopropane has garnered much attention in the organic synthetic community.[13] The reactivity of this three-membered ring can be explained by comparing it with its acyclic counterpart.[14] Contrary to acyclic hydrocarbons, cyclic hydrocarbons have inherent ring strain energy. This strain energy consists of torsional and angle strain. Cyclopropanes suffer from torsional strain due to the rigid, coplanar arrangement of the three carbon atoms, thereby causing eclipsing of ring substituents.[15] The release of the ring strain (27.5 kcal/mol) associated with ring-opening provides the rationalization for high reactivity and the thermodynamic driving force for these reactions.[16]

The unusual properties and reactivity of cyclopropane can be explained following the three main models: (1) valence bond (VB) theory, (2) molecular orbital (MO) theory, and (3) σ-aromaticity. The cyclopropanes have higher percentage of *s* character of the C-C bond forming orbitals, shortened interatomic bond distances, and weaker C-C bonds. In addition, they are able to interact with neighboring π-electron systems and *p*-electron centers, form metal complexes, add reagents (strong acids, halogens, ozone), and undergo catalytic hydrogenation and cycloaddition reactions. To accommodate all of these, two alternative models have been presented: the Coulson-Moffit[17] and Walsh models[18] (Figure 1.2).

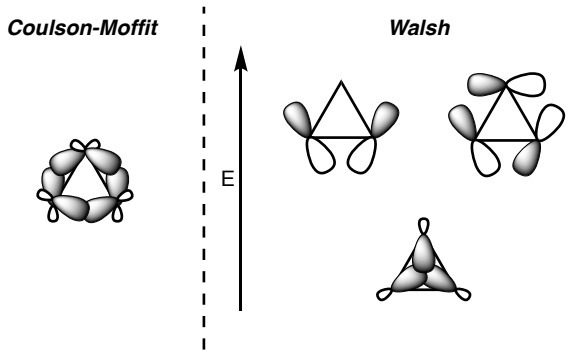


Figure 1.2. The Coulson-Moffit and Walsh Models for Cyclopropane Bonding

1.3.1 Modes of Activation: Vicinal D-A Cyclopropanes

Despite the ring strain, cyclopropanes are often chemically inert and resistant to bond cleavage unless activated. Strategic implementation of substitutents on the cyclopropane allows for facile ring opening. As such, ring activation is accomplished by polarizing one of the C-C bonds through the attachment of electron-donating (donor, D) and electron-accepting (acceptor, A) groups as substituents (Figure 1.3).[19] The primary modes of cyclopropane activation include geminal donor-acceptor (D-A), vicinal donor-

acceptor (D-A), vicinal donor-donor-acceptor (D-D-A), and donor-acceptor-acceptor (D-A-A).

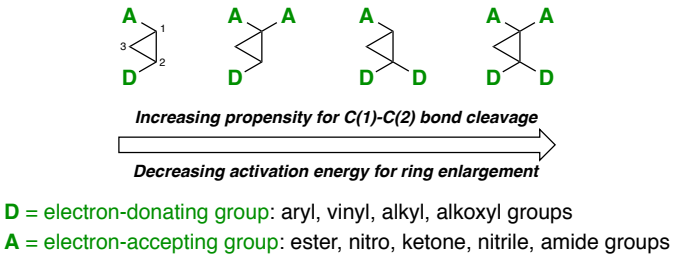
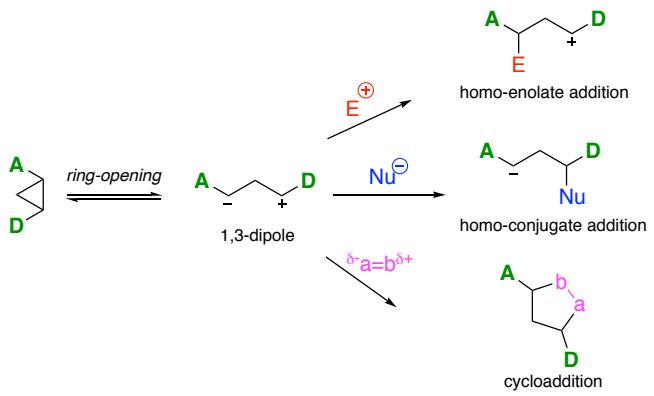


Figure 1.3. Primary Modes of Activation of Cyclopropanes

Incremental C-C bond polarization is possible through additional substitutions with donor and acceptor groups on the cyclopropane. Upon ring opening, a 1,3-dipole is formed with both cationic and anionic centers.[20,21] This intermediate undergoes cyclizations,[22] and is reactive towards electrophiles/nucleophiles[23] in addition to reactions and dipolarophiles in cycloaddition reactions[24] (Scheme 1.1). Thus, D-A cyclopropanes have been used as a means to access cyclohexanones, tetrahydropyrans, and fused heteroaromatics, among many other molecular scaffolds.[20, 25] Lastly, D-A cyclopropanes are also often viewed as analogs of olefin double bonds due to the deviation from the ideal tetrahedral sp^3 hybrid orbitals to bent bonds with more *p* character. Therefore, D-A cyclopropanes are able to react with nucleophiles and electrophiles and can participate in reactions similar to olefins.[26]



Scheme 1.1. Reactivity of D-A Cyclopropanes

1.4 Cyclobutanes: Background

The cyclobutane, the smallest cycloalkane with typical regular, linear alkane characteristics, is progressively catching interest in the field of organic synthesis[27] compared to the cyclopropane, which has been extensively studied and utilized by chemists for decades now. Cyclobutane adopts a puckered conformation with a C-C-C bond angle of 88° (Figure 1.5).[28] While this puckered conformation leads to a decrease in torsional strain, it also results in a smaller C-C-C bond angle, hence increasing angle strain. The balance between angle and torsional strain (total E = 26.3 kcal/mol) dictates the equilibrium geometry.

Moreover, interestingly the methylene units of a cyclobutane are rotated and point inwards in the puckered conformation.[29] This enables these CH_2-units to have local C_{2v} symmetry, which is responsible for the decrease in stability over the puckered one. Another way of visualizing bonding in cyclobutane is by considering it being constructed from CH_2-units, interacting with each other (Figure 1.4).[30] The σ-type and p-type orbitals interact with themselves to form bonding and anti-bonding orbitals. Similar to

cyclopropane, cyclobutane C-C bonds have a high degree of *p*-character, a property that leads to the C-H bonds being oddly strong due to their enhanced *s*-character.[31] The bond dissociation energy of C-H bonds in cyclobutane is 99.8 kcal/mol in comparison with 108.4 kcal/mol for cyclopropane.

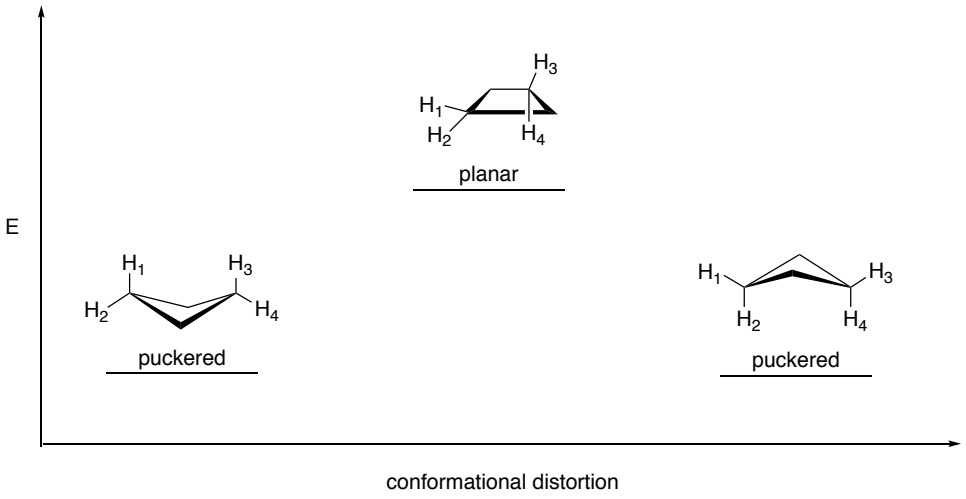


Figure 1.4. Conformations of Cyclobutane

1.4.1 D-A Cyclobutanes

Activation of the cyclobutanes can be done by adding donor (D) and acceptor (A) groups on the ring, known as the D-A cyclobutane (Figure 1.5A).[32] The vicinal substitution allows ring-opening to occur, generating a 1,4-zwitterionic synthon similar to the 1,3-zwitterionic intermediate with D-A cyclopropane. Analogously, this 1,4-zwitterionic intermediate can undergo diverse reactions: (1) rearrangements, (2) addition reactions with electrophiles/nucleophiles, and (3) cycloadditions (Figure 1.5B) in an attempt to achieve molecular diversity and chemical space. It has not been until the past decade that chemists have shown more interest in the reactivity of D-A cyclobutanes and

so far major examples of cycloaddition reactions have been reported with this strained carbocycle.[33]

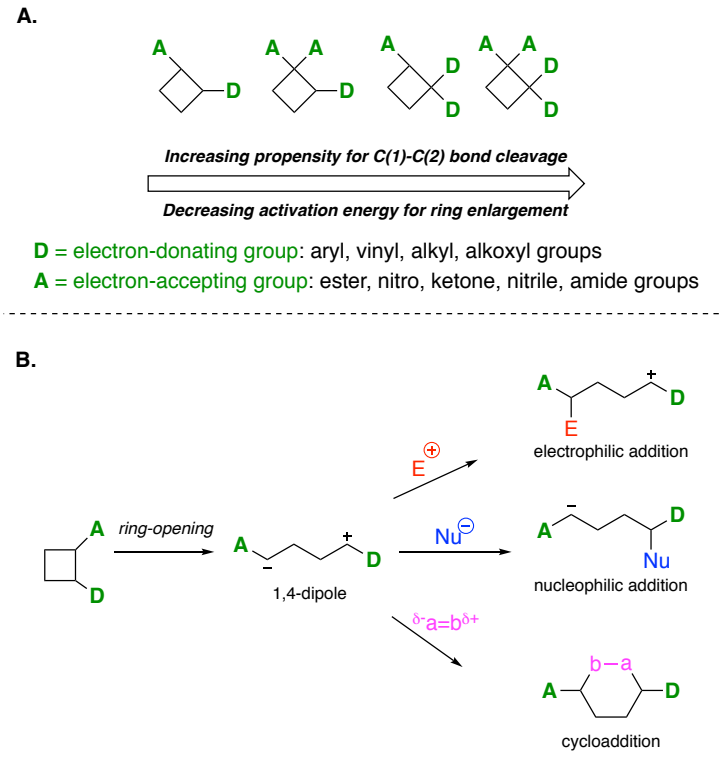


Figure 1.5. Reactivity of D-A Cyclobutanes

1.5 Outline of Thesis

This thesis consists of diversity-oriented synthetic strategies to access a library of small nitrogen-containing molecules and more complex polycyclic scaffolds, commonly found in natural products, pharmaceutically-relevant compounds, and even in the field of material science (Figure 1.6). It can be divided into 2 major categories where the first category (Chapter 2) is about using strained carbocycles as a gateway for *N*-heterocyclic molecule synthesis. The second category (chapter 3 and 4) comprises of using these 1,3-

dicarbonyl-type systems under different conditions to access these 7-membered ring fused indoles and cyclopenta[*b*]heteroaromatics.

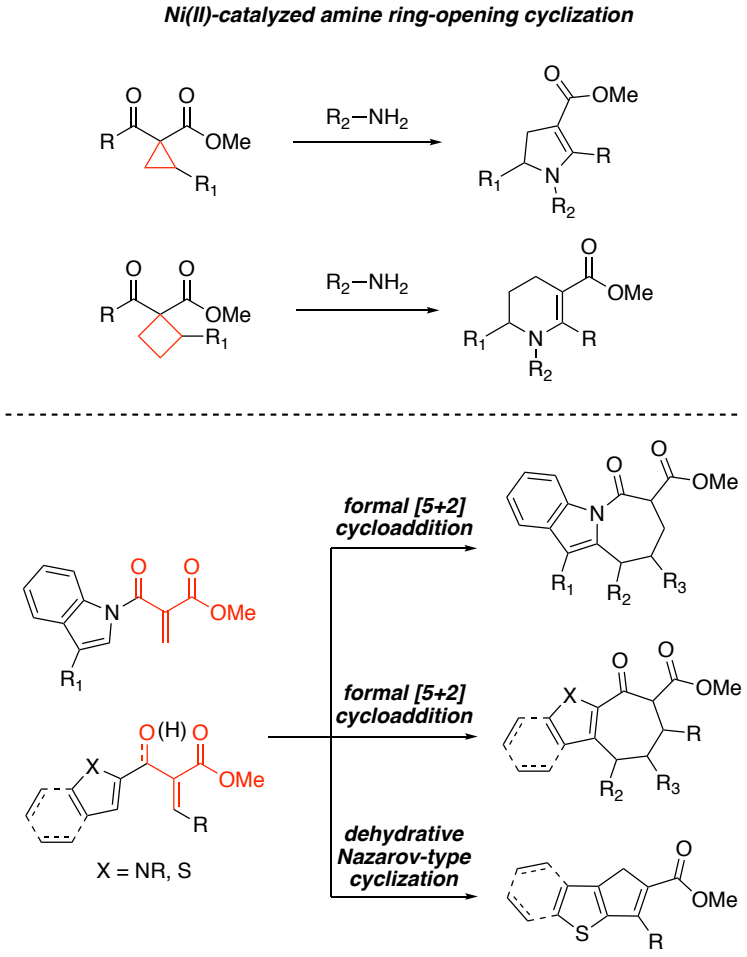


Figure 1.6. Scope of the Dissertation

Chapter 2 entails a milder approach accessing functionalized 2,3-dihydropyrroles and tetrahydropyridines via a Lewis acid-catalyzed amine ring-opening cyclizations of D-A cyclopropanes and D-A cyclobutanes. There is a discussion addressing the limitations from previous approaches in the literature and the attempt of accessing molecular diversity via modifications on the building blocks used. This chapter also demonstrates an efficient tandem process without isolating the *in situ*-generated D-A cyclopropane. In

addition, examples of affording functionalized pyrroles via oxidation of the corresponding dihydropyrroles, is shown. Lastly the application to D-A cyclobutane expands the importance of the potential reactivity of these strained carbocycles, which has been understudied by the organic synthetic community until now.

In chapter 3, the focus is on the importance of natural product scaffolds such as the azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles. A literature survey shows there is a lack of general methods to access these scaffolds in an effective and efficient manner. In addition, previous reports have shown limitations in achieving molecular diversity and chemical space for these particular skeletons. Initially, we addressed these issues by investigating the D-A cyclobutanes as potential building blocks, which would undergo intramolecular ring-opening cyclization to access these scaffolds. Surprisingly, our study provides direct access to azepino[1,2-*a*]indoles via a formal [5+2] cycloaddition between alkylidenes and alkenes under mild Lewis acid catalytic conditions. This similar approach is applied to the synthesis of cyclohepta[*b*]indole framework.

Chapter 4 reports a comprehensive discussion about the Nazarov-type cyclizations, specially the dehydrative, Nazarov-type electrocyclization leading to the synthesis of functionalized cyclopenta[*b*]thiophenes. These molecules commonly used in the field of material science are usually functionalized via cyclopenta[*b*]thiophenone precursor. The direct access to functionalized cyclopenta[*b*]thiophenes via a Lewis acid-catalyzed dehydrative, Nazarov-type electrocyclization is achieved.

Finally chapter 5 summarizes all the findings from the previous chapters, focusing on the value of implementing strained carbocycles for diversity-oriented synthetic

strategies as a way to achieve molecular diversity. Also, some future directions are suggested based on the results obtained from this thesis.

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CHAPTER 2. STRAINED POLARIZED CARBOCYCLES AS A MEANS TO SMALL *N*-HETEROCYCLIC MOLECULES[*, 1]

2.1 Importance of 2,3-Dihydropyrroles

Among nitrogen-containing five membered heterocycles, the 2,3-dihydropyrrole ring system **1** has become a valuable structural motif present in many biologically active compounds.[2,3] In addition, they have been widely employed as important intermediates in the synthesis of natural products **4** and **5**, and preparation of functionalized pyrrolidines[4] **2** and pyrroles[5] **3** (Figure 2.1).

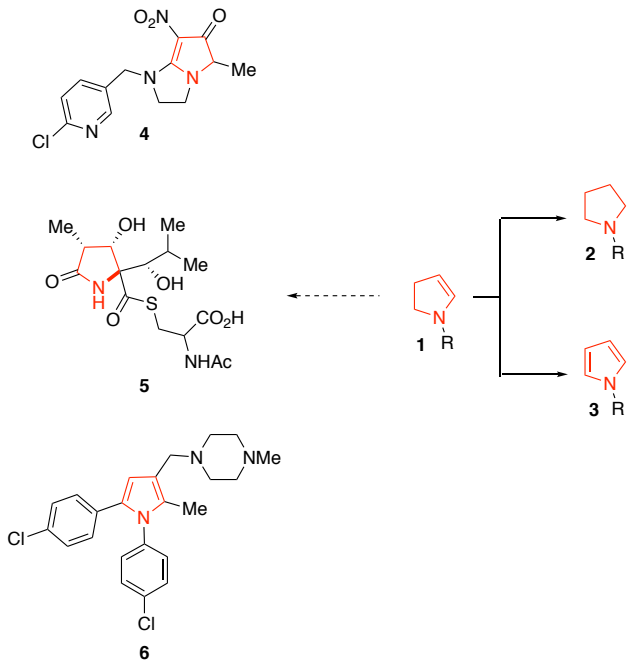


Figure 2.1. Reactivity of Dihydropyrroles and Presence in Natural Products

[*] Work on Lewis acid-catalyzed amine ring-opening cyclizations of D-A cyclopropanes performed in collaboration with Dadasaheb Patil.
Published in *J. Org. Chem.* **2014**, *79*, 3030.

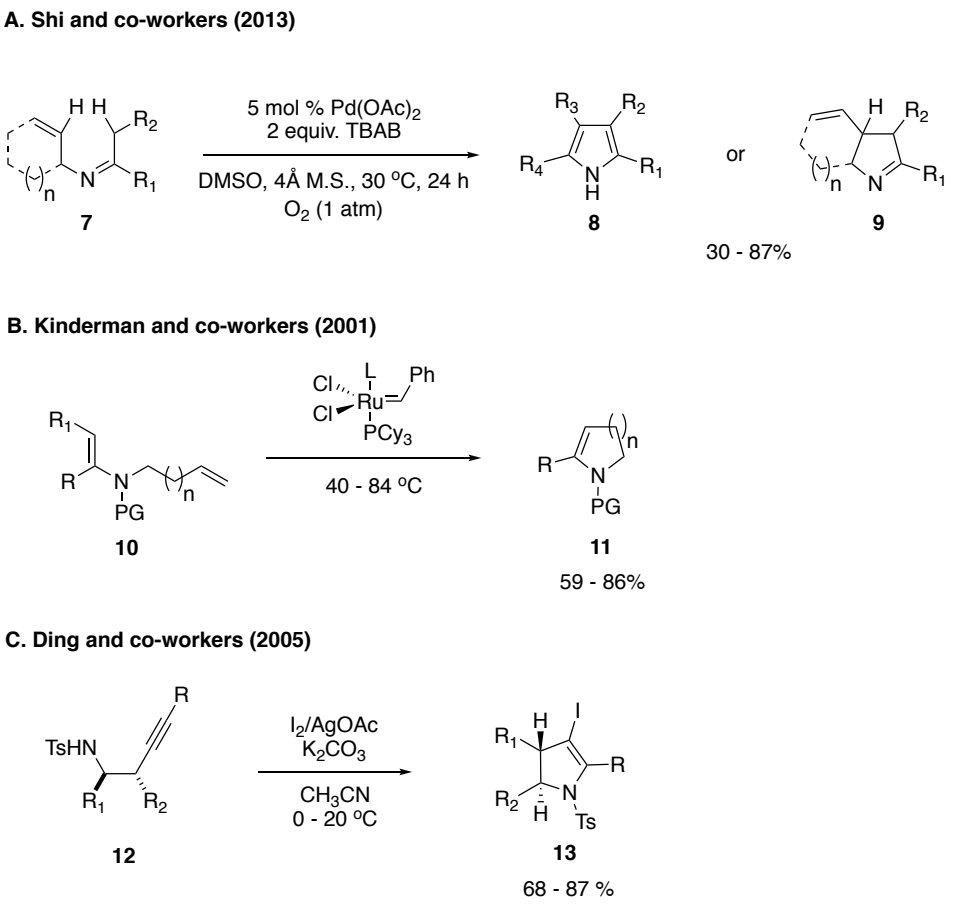
2,3-Dihydropyrroles can be readily exploited for further functionalization because of the presence of the enamine moiety, which can be useful in the synthesis of more complex molecules. When an electron-withdrawing group (EWG) is substituted at the 3-position on the dihydropyrrole, extended conjugation with the enamine is observed, and vinylogous reactivity is possible (Figure 2.2).

Figure 2.2. Importance of Enamine Moiety for further Functionalization

2.2 Selected Methods for the Synthesis of 2,3-Dihydropyrroles

Much effort has been focused on the development of efficient methods[6-11] for the synthesis of 2,3-dihydropyrrole structural motifs. The commonly used synthetic routes involve cycloaddition or cyclization strategies (Scheme 2.1A)[6h] in a one-pot-sequential manner to give the dihydropyrrole skeleton. Other methods include ring-closure metathesis of enamides (Scheme 2.1B),[7] and cyclization of sulfonamide anions with acetylenes in the presence of iodine[10c] (Scheme 2.1C) among many others.

However there are a limited number of published protocols[9b, 12] accessing the vinylogous dihydropyrroles despite the numerous reports of synthetic efforts toward the common 2,3-dihydropyrroles in the literature. The most general approach to 2,3-dihydropyrroles bearing EWGs at the 3-position involves ring-opening cyclizations of cyclopropyl ketones in the presence of primary amines.

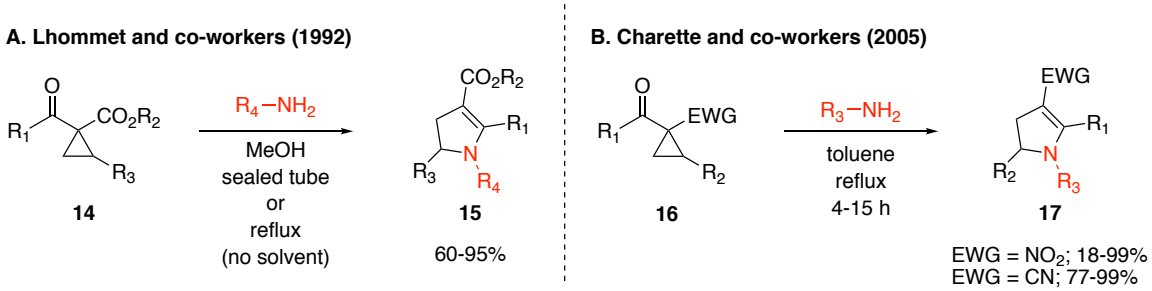


Scheme 2.1. Previous Approaches to 2,3-Dihydropyrroles

2.3 Amine-Ring Opening Cyclizations of D-A Cyclopropanes

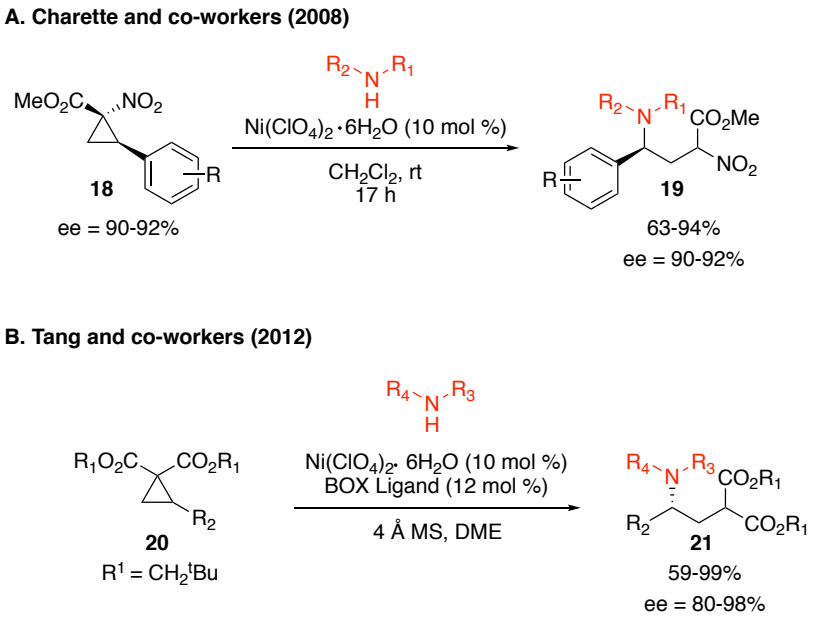
Lhommet[12a] first reported this approach for donor-acceptor (D-A) cyclopropanes **14** derived from β-ketoesters where the EWG = CO_2Me. The reactions gave 4-carboxy-dihydropyrroles **15** in modest to good yields but were performed in refluxing methanol in sealed tubes for up to 24 h or using the amine as solvent under reflux (>140 °C) for up to 8 h. Charette[12c] reported the use of D-A cyclopropanes **16** derived from α-nitro ketones and α-cyano ketones for the formation of 4-nitro- and 4-cyano-dihydropyrroles respectively (Scheme 2.2). Unfortunately, these methods have two major limitations,

which include high reaction temperatures and long reaction times, which render them inefficient and have low functional group tolerance.



Scheme 2.2. Amine Ring-Opening Cyclization of Cyclopropyl Ketones

Lewis acids have recently been shown to promote ring-opening reactions of D-A cyclopropanes in the presence of amines under milder conditions. In representative examples by Charette[13] and Tang,[14] $Ni(ClO_4)_2 \bullet 6H_2O$ effectively promotes the ring-opening reactions of secondary amines with malonate-derived D-A cyclopropanes **18** and **20** to give homoconjugate addition products **19** and **21** (Scheme 2.3).



Scheme 2.3. Lewis Acid-Catalyzed Amine Ring-Opening of D-A Cyclopropanes

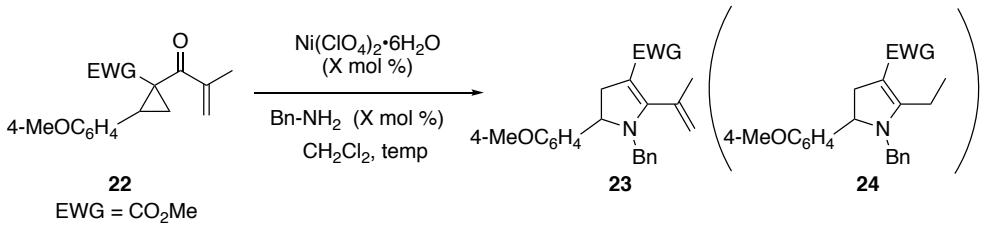
2.4 Lewis Acid-Catalyzed Amine Ring-Opening Cyclizations of D-A Cyclopropanes

2.4.1 Reaction Design and Proof of Principle

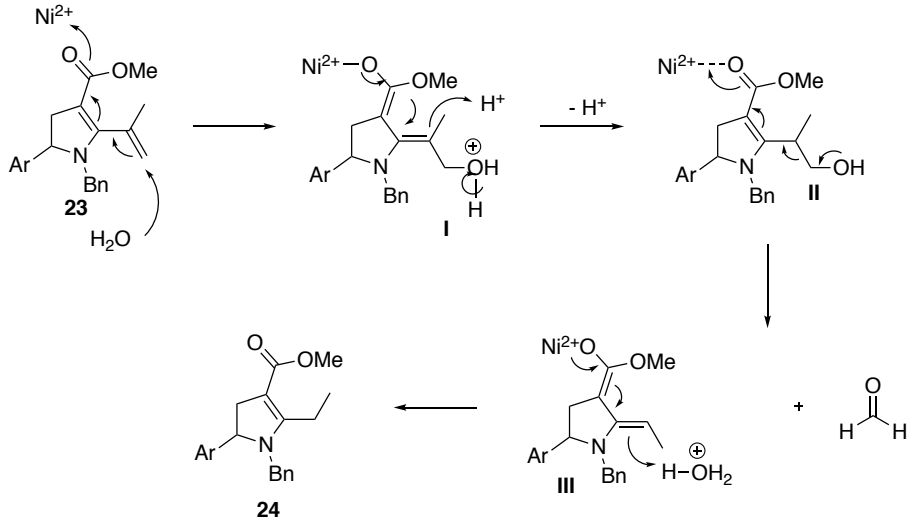
Our lab has reported several examples of Lewis acid-catalyzed intramolecular ring-opening cyclizations of doubly activated D-A cyclopropanes derived from 1,3-dicarbonyl compounds.[15] As a starting point, we began our studies with alkenyl cyclopropyl ketone as the model substrate and $Ni(ClO_4)_2 \bullet 6H_2O$ as the Lewis acid due to its demonstrated success in amine-mediated cyclopropane ring openings (Scheme 2.3).

However, upon treatment of cyclopropane **22** with benzyl amine in CH_2Cl_2 with variable loadings of $Ni(ClO_4)_2 \bullet 6H_2O$ and different reaction temperatures, we observed formation of unexpected side product **24** (Scheme 2.4). As dihydropyrrole **23** is an

extended Michael acceptor, it was possible that a molecule of water could undergo 1,6-addition into the extended π-system (Scheme 2.5). Proton transfer and isomerization produced alcohol **II**, which underwent loss of formaldehyde and protonation to give side product **24**.[16]



Scheme 2.4. Initial Model Substrate for Reaction Conditions Screening

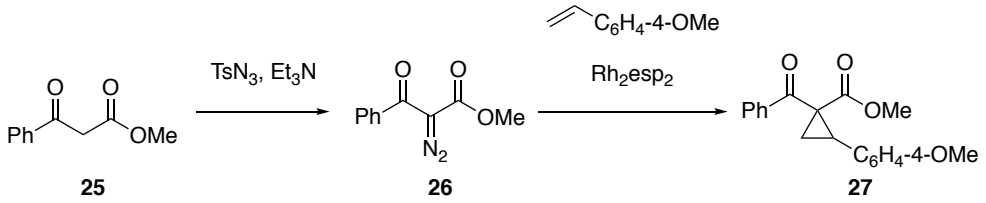


Scheme 2.5. Proposed Mechanism for the Formation of Dihydropyrrole **24**

2.4.2 Model Substrate Synthesis

The above model substrate was changed to cyclopropyl phenyl ketone **25** in order to reduce the side product issue. Cyclopropane **27** was synthesized following our lab's previously reported protocol.[15b] This procedure involved an initial diazo transfer reaction

on β-ketoester **25**. The resulting diazo **26** was subjected to Rh-catalyzed cyclopropanation to afford cyclopropane **27** (Scheme 2.6).



Scheme 2.6. Synthesis of Model Cyclopropane **27**

2.4.3 Reaction Optimization

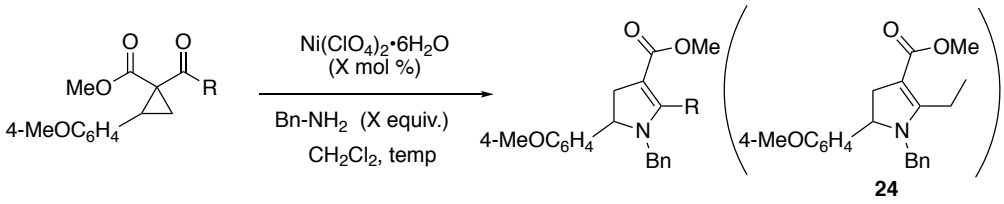
The initial screening conditions were carried out with cyclopropane **22** followed by cyclopropane **27** to avoid formation of undesired side product **24** (Table 2.1). We first treated cyclopropane **22** with benzyl amine (2.5 equiv.) in CH_2Cl_2 with $Ni(ClO_4)_2 \bullet 6H_2O$ (30 mol%) at room temperature and successfully desired dihydropyrrole **23** was obtained in 89% yield after 3 h (entry 1). Then the amount of amine was reduced to improve atom economy and overall reaction efficiency. At both 2.0 and 1.2 equiv. of benzylamine, a decrease in yields was observed (entries 2 and 3).

Next, we investigated the catalyst loadings to obtain the minimum loading required for the transformation to remain effective and efficient. Upon lowering the catalyst loading to 20 mol% and 15 mol%, dihydropyrrole **23** was obtained in 67% yield and 50% yield respectively (entries 4 and 5). At 15 mol%, the reaction failed to go to completion even after more than 16 h. Thus, in order to push the reaction to completion, we heated the reaction with 15 mol% $Ni(ClO_4)_2 \bullet 6H_2O$ at reflux from the beginning and the reaction was complete within 1 h, giving an improved yield of 65% yield (entry 6). Any attempts

to reduce the catalyst loading below 15 mol% resulted in poor product yields (entries 9 and 10). The study of the effect of different solvents has shown to be detrimental to the overall reaction efficiency and products yields except for 1,2-dichloroethane where comparable results were obtained.

To alleviate the formation of side product **24**, we continued our investigation with a new model substrate, cyclopropane **27**. Upon treatment of **27** with 15 mol% $Ni(ClO_4)_2 \bullet 6H_2O$ and benzylamine (2.0 and 1.2 equiv.) in CH_2Cl_2 at reflux, desired dihydropyrrole **28** was obtained in 70% yield and 83% yield respectively (entries 13 and 14). Therefore for this stage of the investigation, the optimal conditions were 15 mol% of $Ni(ClO_4)_2 \bullet 6H_2O$ with 1.2 equiv. of benzylamine in refluxing CH_2Cl_2.

Table 2.1. Initial Reaction Optimization



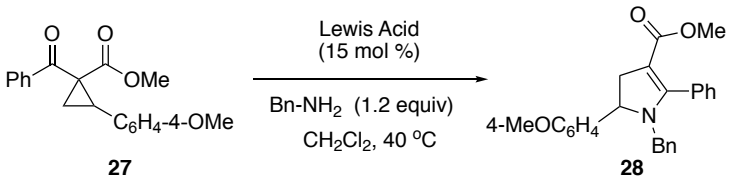
Entry	R	Loading (mol %)	Amine (equiv.)	Temp	Time (h)	Yield (%)
1	2-propenyl (**22**)	30	2.5	rt	3	89
2	2-propenyl (**22**)	30	2.0	rt	3	60
3	2-propenyl (**22**)	30	1.2	rt	3	50
4	2-propenyl (**22**)	20	2.5	rt	6	67
5	2-propenyl (**22**)	15	2.5	rt	>16	50
6	2-propenyl (**22**)	15	2.5	40 °C	1	65
7	2-propenyl (**22**)	15	2.0	40 °C	1	67
8	2-propenyl (**22**)	15	1.2	40 °C	2	80
9	2-propenyl (**22**)	5	2.5	40 °C	2	47
10	2-propenyl (**22**)	5	2.0	40 °C	2	56
11	phenyl (**27**)	30	2.5	rt	2	77
12	phenyl (**27**)	15	2.0	rt	>16	52
13	phenyl (**27**)	15	2.0	40 °C	11	70
14	phenyl (**27**)	15	1.2	40 °C	2	83

rt = reaction performed at room temperature

The experimentation proceeded with the study of a variety of Lewis acids to find the optimal Lewis acid catalyst (Table 2.2). Anhydrous $Ni(OTf)_2$ was employed to analyze the importance of the water ligands. A reduced yield of 58% was obtained (entry 2). This result supported the catalytic role of the nickel but also suggested the significance of the water ligand for amine exchange. As with Ni(II) hydrates, copper(II) hydrates are known to complex with amines by displacing water molecules.[17] However,

when $Cu(ClO_4)_2 \bullet 6H_2O$ was used as the catalyst, a poor 31% yield was obtained (entry 3). To rule out the possibility that the ligand is responsible for the observed catalysis, $Li(ClO_4) \bullet 3H_2O$ was employed but only gave 14% yield of dihydropyrrole **28**. The remaining Lewis acids tested proved to be highly ineffective, most likely due to catalyst deactivation upon amine complexation (entries 5-9). Therefore $Ni(ClO_4)_2 \bullet 6H_2O$ remained the most effective Lewis acid catalyst for this transformation.[18]

Table 2.2. Lewis Acid Screening



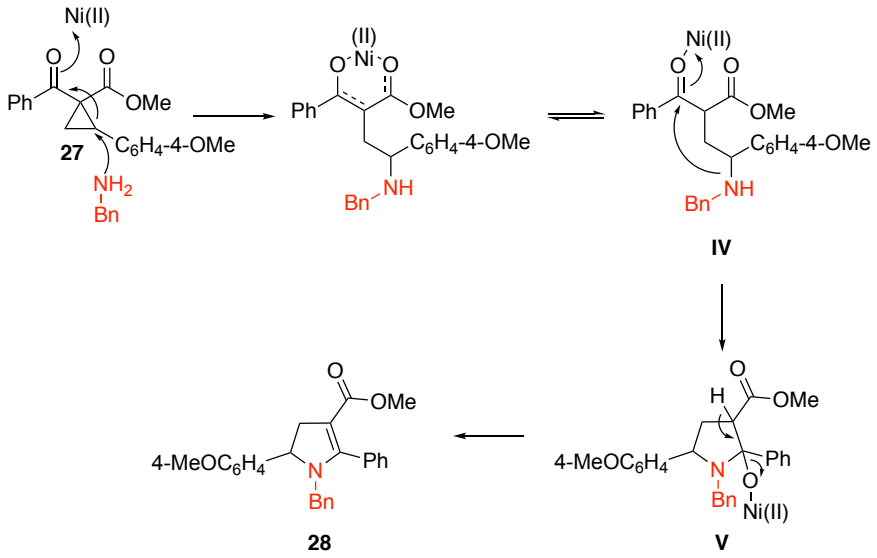
27 **28**

Entry	Lewis acid	Time (h)	Yield (%)
1	$Ni(ClO_4)_2 \bullet 6H_2O$	2	83
2	$Ni(OTf)_2$	3	58
3	$Cu(ClO_4)_2 \bullet 6H_2O$	3	31
4	$Li(ClO_4) \bullet 3H_2O$	>16	14
5	$Sc(OTf)_3$	>16	27
6	$In(OTf)_3$	>16	17
7	$Al(OTf)_3$	>16	8
8	$Mg(OTf)_2$	>16	6
9	$Zn(OTf)_2$	>16	5

2.4.4 Reaction Mechanism

The proposed mechanism for this transformation involves an initial attack of the benzyl amine on cyclopropane **27** to form the secondary amine homo-conjugate **IV**. The

secondary amine nucleophile attacks the phenyl ketone producing the alkoxy pyrrolidine **V**, followed by dehydration to afford the dihyropyrrole **28** (Scheme 2.7).



Scheme 2.7. Proposed Mechanism for the Synthesis of Dihydropyrrole **28**

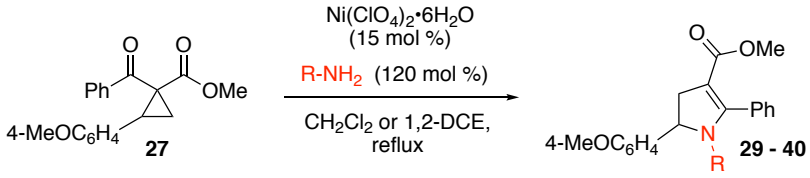
2.4.5 Examination of Substrate Scope

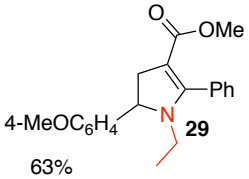
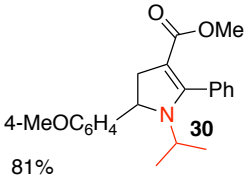
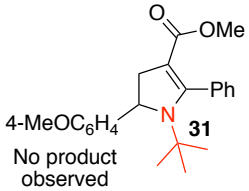
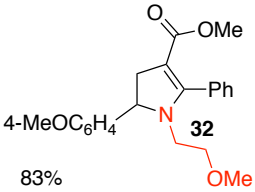
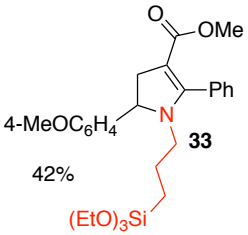
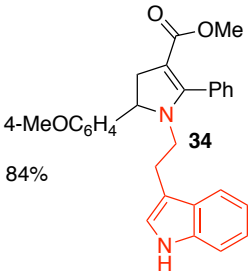
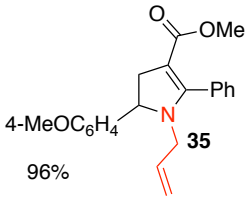
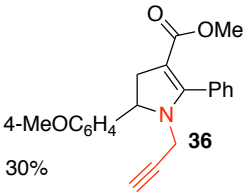
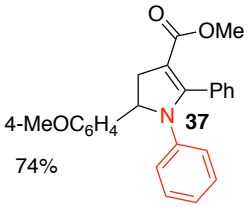
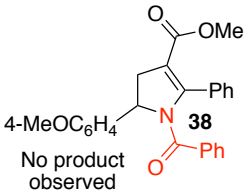
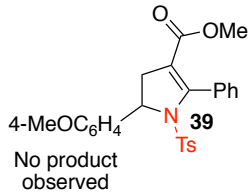
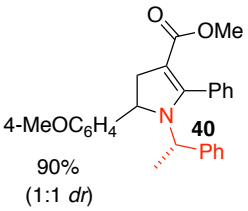
The protocol was amenable to a wide range of primary amines under the optimized conditions (Table 2.3). Alkyl amines such as ethylamine and isopropylamine readily reacted with cyclopropane **27** to give dihydropyrroles **29** and **30** in 63 and 81% yield respectively. Unfortunately, no reactivity was observed with *tert*-butyl amine, which is presumably the result of unfavorable steric interactions that preclude nucleophilic attack. Other functionalized aliphatic amines such as 2-methoxyethan-1-amine and 3-(triethoxysilyl)propan-1-amine also provided their respective dihydropyrroles **32** and **33**, in 83 and 42% yield. We also showed that an unsaturated alkyl amine such as allylamine provided high yields of the desired dihydropyrrole **35** in 96% yield. However, propargylamine afforded only 30% of **36** along with a number of by-products. The poor

reaction efficiency is most likely because of competing reactions resulting from coordination of the alkyne π-system with the Ni catalyst.[19]

More electron-deficient amines, such as aniline, proved to be amenable to the transformation, although the reaction had to be performed at higher temperatures for full conversion to give *N*-aryl dihydropyrrole **37** in 74% yield. Amines bearing stronger electron-withdrawing groups, such as acetamide and tosamide, failed to produce any dihydropyrrole products, even at elevated temperatures because of reduced nucleophilicity. Finally, a chiral amine was also employed in hopes of imparting some diastereocontrol. Unfortunately, when cyclopropane **27** was treated with (*S*)-1-phenylethan-1-amine, dihydropyrrole **40** was obtained in a 1:1 diastereomeric mixture in 90% yield. The poor observed stereo- or diasteroselectivity could be likely due to an S_N1-like ring-opening that generates a transient carbocation prior to unbiased nucleophilic attack.

Table 2.3. Primary Amine Screening



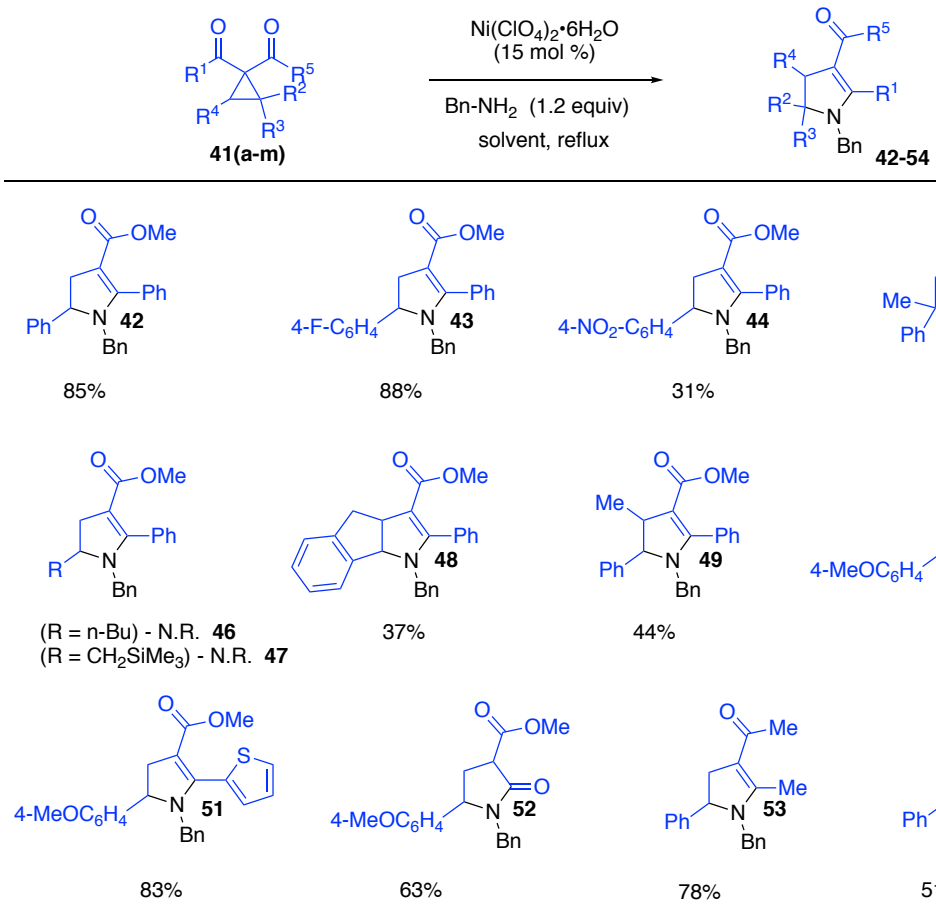
 **29** 63%	 **30** 81%	 **31** No product observed	 **32** 83%
 **33** 42%	 **34** 84%	 **35** 96%	 **36** 30%
 **37** 74%	 **38** No product observed	 **39** No product observed	 **40** 90% (1:1 *dr*)

The scope of the methodology was further studied by applying the reactions to different D-A cyclopropanes with benzylamine (Table 2.4). The investigation of the electronics on the phenyl ring (D group) was coherent with what has been established in the literature. When a phenyl substituent was employed, successful formation of dihydropyrrole **42** in 85% yield was obtained. Similar results were observed for **43**, where 4-fluorophenyl was the donor group. However when the aromatic substituent bears a strong electron-withdrawing group, poor reactivity was observed with only 31% yield of **44** was attained.

When geminal methyl and phenyl groups are the donor groups, the 2,2-disubstituted dihydropyrrole **45** was obtained in 79% yield. However a D-A cyclopropane **41e** bearing a singly alkyl donor group turned out to be unsuccessful and no desired dihydropyrrole product was observed. A more complex polycyclic dihydropyrrole **48** was obtained in 37% yield when an indene derived cyclopropane **41g** was reacted under reflux in toluene. No reaction was observed at reduced temperatures. Similarly, **49** containing substituents in both 2- and 3-positions was obtained in 44% yield. Both outcomes appeared to be the result of steric effects associated with the amine approaching the sterically congested cyclopropanes.

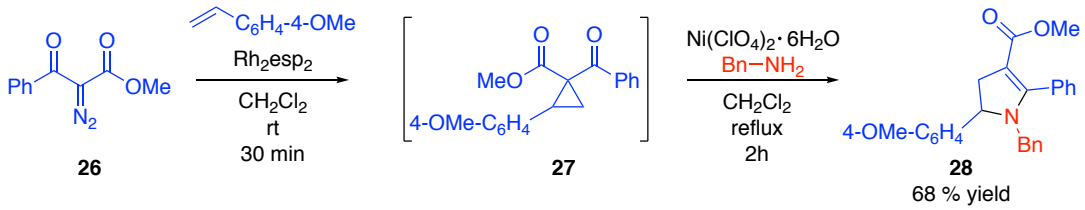
Cyclopropanes derived from other β-ketoesters, where the phenyl group has been replaced with an ethyl, thiophene or methoxy substituent were also successful when subjected to the reaction conditions. Interestingly, dimethyl malonate-derived cyclopropane gave pyrrolidin-2-one **48** in 63% yield upon workup/purification. This result was consistent with observations made by Yamagata.[12b] Finally 1,3-diketones were also studied under our reaction conditions. Cyclopropanes from a symmetric 1,3-diketone and from an unsymmetric 1,3-diketone provided products **53** in 78% yield and **54** in 51% yield respectively. In the case of unsymmetric 1,3-diketone, regioisomers were possible, but only one product was observed with the phenyl ring being in conjugation with the enone π-system.

Table 2.4. Different Substituted D-A Cyclopropanes



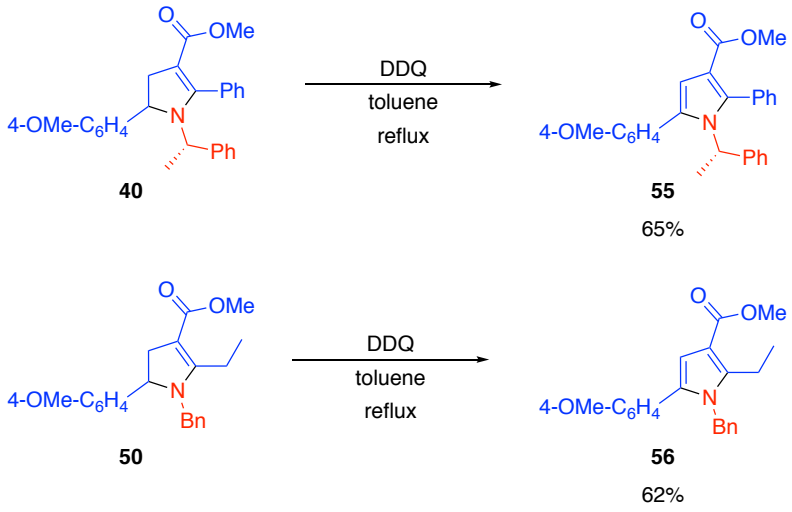
2.5 Applications of the Methodology

Given that both the syntheses of the D-A cyclopropanes (via Rh-catalyzed cyclopropanation of alkenes with α-diazo carbonyls) and the dihydropyrroles take place in CH_2Cl_2, a tandem one-pot cyclopropanation/amine ring-opening cyclization was conducted (Scheme 2.8). Dihydropyrrole **28** was obtained in 68% yield, which corresponds to an average of ~82% yield per step. Hence, the tandem one-pot process has proven to be as effective in forming the 2,3-dihydropyrroles.



Scheme 2.8. One-Pot Tandem Cyclopropanation/Amine Ring-Opening Cyclization

In an attempt to demonstrate that the 2,3-dihydropyrrole products could be used as a building block to access the pyrrole motifs, we treated dihydropyrroles **40** and **50** with 1,2-dichloro-5,6-dicyanobenzoquinone (DDQ)[12c,20] in toluene at reflux. As a result pyrroles **55** and **56** were formed in good yields 65 and 62% yields, respectively (Scheme 2.9). Therefore our methodology could provide access to highly substituted pyrroles, also found in many natural products and pharmaceutically-relevant compounds.



Scheme 2.9. DDQ-Mediated Oxidation of Dihydropyrroles to Pyrroles

2.6 Lewis Acid-Catalyzed Amine Ring-Opening Cyclizations of D-A Cyclobutanes

2.6.1 Project Rationale and Justification

In our lab, we have been heavily focused on small, strained carbocycles as building blocks for molecular diversity and complexity. As highlighted in Chapter 1, D-A cyclopropanes and cyclobutanes share similar reactivity profiles in many ways. However, D-A cyclobutane has not received much attention in the synthetic organic chemistry community until recently.[21] Most of the work reported on D-A cyclobutanes, involved intermolecular reactivity with carbonyls,[22] imines,[23] nitrosoarenes,[24] nitrones[25] and alkynes.[26] However, no example of amine ring-opening cyclization has been reported to date with the D-A cyclobutane synthetic precursors. Our intended strategy here would be to access other classes of *N*-heterocycles such as tetrahydropyridines and pyridines (oxidized counterpart) (Figure 2.3) via a Lewis acid-catalyzed amine ring-opening cyclization of D-A cyclobutanes.

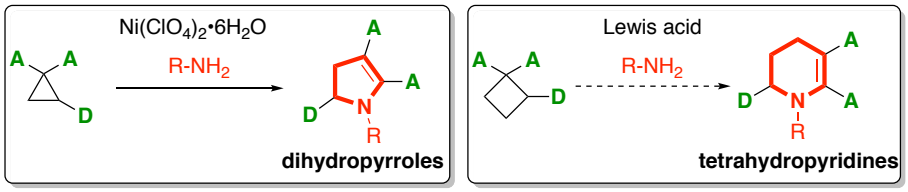
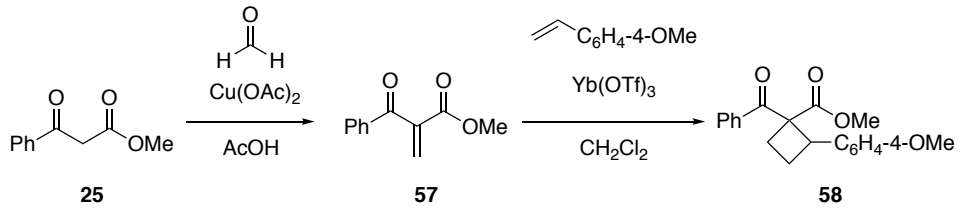


Figure 2.3. Amine Ring Opening Cyclization Strategy with D-A Cyclobutanes

2.6.2 Model Substrate Synthesis

The alkylidene precursor, methyl 2-benzoylacrylate **57** was synthesized via a modified version of the conditions established by Yiotakis.[27] This involved a $Cu(OAc)_2$ catalyzed condensation of β-ketoester **25** with formaldehyde to afford alkylidene **57**. The

latter was then treated with $Yb(OTf)_3$ catalyst and 4-methoxy styrene to afford the resulting D-A cyclobutane **58** (Scheme 2.10).[23]

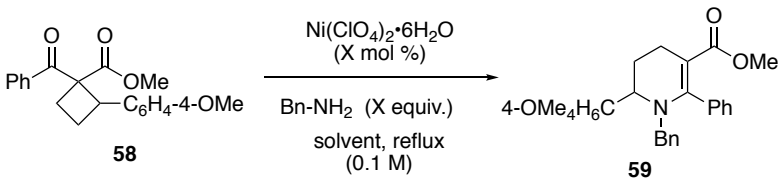


Scheme 2.10. Synthesis of Model Cyclobutane **58**

2.6.3 Reaction Optimization

The optimized conditions used with the D-A cyclopropane system were applied to the D-A cyclobutane **58** (Table 2.5, entry 1), which resulted in poor reactivity and hence the poor yield (8%) of tetrahydropyridine **59** and recovery of the cyclobutane. In an attempt to improve the effectiveness of this transformation, we increased the equivalents of amine used and switched solvent to elevate the temperature of the reaction (entry 4). The improvement in yield (from 8% to 50%) was promising result but the reaction time was long (about 24 h). The next step was to increase the loading of the catalyst in order to reduce the reaction time and hopefully bypass any side reactivity to improve the yield as well. Entry 8 shows that when the catalyst loading was doubled, the reaction time was reduced to 6 h but the yield did not increase much. A study of the reaction concentration with a catalyst loading of 20 mol%, 2.5 equiv. led to a reduction in time, from 20 h to 5 h when increasing the reaction concentration from 0.1 M to 0.2 M with similar yield, 52%.

Table 2.5. Reaction Optimization with D-A Cyclobutanes



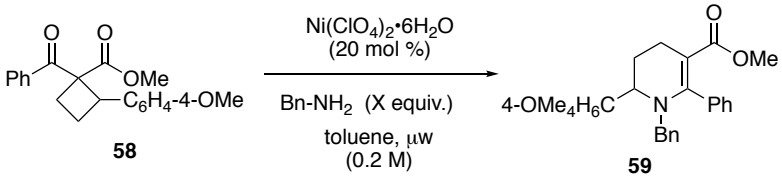
58 **59**

Entry	Loading (mol %)	Solvent	Amine (equiv.)	Time (h)	Yield (%)
1	15	CH_2Cl_2	1.2	>48	8
2	10	Toluene	1.2	24	19
3	15	Toluene	2.5	24	45
4	15	Toluene	5.0	24	50
5	20	Toluene	1.3	24	39
6	20	Toluene	2.5	20	52
7	20	Toluene	5.0	6	53
8	30	Toluene	2.5	6	55
9	-	Toluene	2.5	>24	-

In an attempt to reduce the reaction time even further and to take advantage of the microwave technology, we ran the reaction using 20 mol % $Ni(ClO_4)_2•6H_2O$ in 0.2 M of toluene with varying amount of benzyl amine equivalence, temperature, and time in the microwave (Table 2.6). We first tested the reaction at temp = 110 °C for 10 and 30 min, which led to no reactivity as we observed complete recovery of the starting material (entries 1 and 2). Increasing the temperature to 200 °C for 15 min gave 44% yield of the desired product (entry 4). From this outcome, we tried a higher temperature (250 °C) for the same amount of time (15 min) while maintaining similar pressure inside the vessel. However this afforded 2,3-tetrahydropyridine **59** in poor yield, 23% only along with major decomposition (entry 5). Changing the amount of amine equivalence while keeping the temperature at 200 °C did not result in any improvement in yields (entries 7 and 8).

Therefore, there are several other factors that need to be considered as we further investigate the optimization of the conditions: (1) find a more suitable Lewis acid that coordinates better to the D-A cyclobutane dicarbonyl system to initiate the ring-opening (2) the orbitals of a cyclobutane is different from the orbitals of a cyclopropane (see Chapter 1) and therefore the nucleophilic attack nature of the primary amine is hypothetically different with D-A cyclobutanes (3) examine the potential effect of solvent in this transformation which can render the effective amine ring-opening cyclization transformation with D-A cyclobutane.

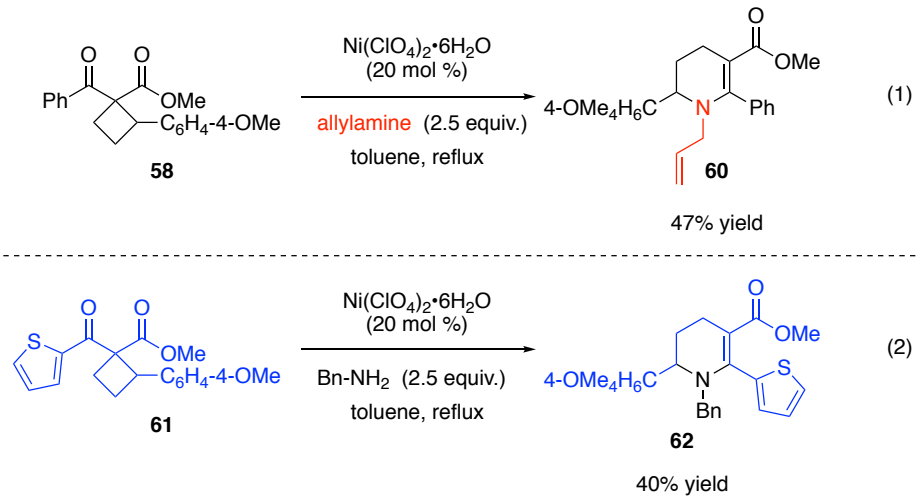
Table 2.6. Microwave Study for Synthesis of 2,3-Tetrahydropyridines



Entry	Amine (equiv.)	Temp (°C)	Time (min)	Yield (%)
1	2.5	110	10	-
2	2.5	110	30	-
3	2.5	200	10	21
4	2.5	200	15	44
5	2.5	250	15	23
6	2.5	200	30	39
7	1.2	200	30	28
8	5.0	200	30	35

2.6.4 Examination of Substrate Scope

In an attempt to prove that our protocol was amenable to other amines and D-A cyclobutanes, we first tested allylamine with cyclobutane **58** since it was our best substrate with D-A cyclopropane (see Table 2.3). The reaction worked modestly to afford tetrahydropyridine **60** in 47% yield (Scheme 2.11 – (1)). Next, we investigated a different D-A cyclobutane **61** with benzylamine (2.5 equiv.), which similarly gave the desired tetrahydropyridine **62** in 40% yield (Scheme 2.11 – (2)). These two reactions proved that the amine chemistry does work with D-A cyclobutane, but more optimization studies are necessary to render this approach more effective and efficient.

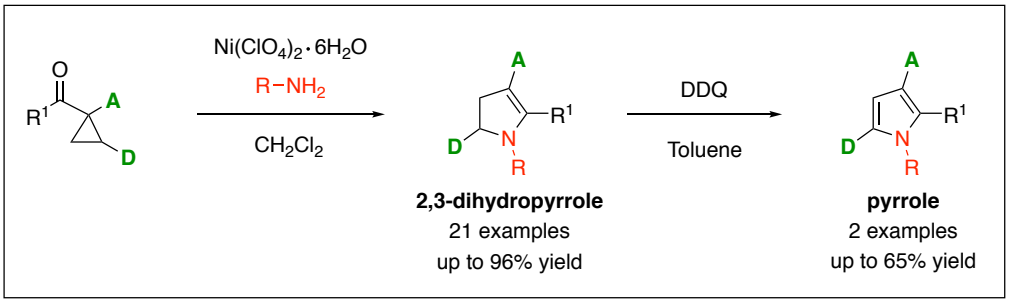


Scheme 2.11. Study of Scope of the Protocol

2.7 Summary

2,3-Dihydropyrroles are found in several bioactive products but they are also significant versatile building blocks used in the synthesis of natural product targets. This chapter describes an efficient and general Ni(II)-catalyzed approach to 4-keto- and 4-

carboxy-2,3-dihydropyrroles using activated D-A cyclopropanes under milder conditions than previously reported (Scheme 2.12). The method is amenable to a variety of primary amine nucleophiles as well as substituted D-A cyclopropanes to provide highly substituted dihydropyrroles. Furthermore, the one-pot tandem process has proven effective and efficient with an average of ~82% yield per step. Also, the dihydropyrrole products can readily be converted to highly functionalized pyrroles, another 5-membered *N*-heterocyclic scaffold found in several natural product targets and pharmaceutically-relevant compounds. Preliminary results obtained with other polarized strained rings, D-A cyclobutanes show a potential for representative first examples of amine ring-opening cyclizations of these strained carbocycles.



Scheme 2.12. General Ni(II)-catalyzed Approach to 2,3-dihydropyrroles

2.8 Experimental Section

2.8.1 2,3-Dihydropyrroles:

For Lewis acid-catalyzed amine ring opening cyclization of D-A cyclopropanes, the experimental section and characterization can be found in the supporting information of article: Martin, M. C.; Patil, D.; France, S. *J. Org. Chem.* **2014**, 79, 3030.

2.8.2 2,3-Tetrahydropyridines:

2.8.2.1 General Methods

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished when exposed to 254nm UV light.

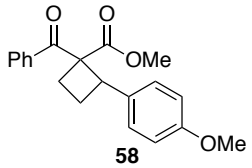
Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbitThermoelectronic Corp and by attenuated total reflection (ATR) through a diamond plate on a Bruker Optics Alpha-P FTIR spectrometer. The IR bands are characterized as weak (w), medium (m), and strong (s). 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. Mass spectra were obtained MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

Yields refer to isolated yields of analytically pure material unless otherwise noted. All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-dichloroethane and dichloromethane was purified by distillation from calcium hydride under N_2 prior to use. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted.

2.8.2.2 Experimental Procedures:

General procedure for the synthesis of D-A cyclobutanes **58** and **61**: To a flask charged with $Yb(OTf)_3$ (10 mol %) and a stir bar was added a solution of methyl 2-benzoylacrylate **57** (1.0 equiv.) in DCM (0.1 M) at 0 °C. 4-Methoxystyrene (1.3 equiv.) was added to the reaction mixture and allowed to stir for 1 h. Once reached completion, the reaction mixture was concentrated under reduced pressure and purified using silica gel flash chromatography to afford the desired cyclobutanes.

Synthesis of cyclobutane 58:

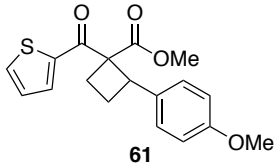


58

The general procedure was followed using methyl 2-benzoylacrylate **57** (333 mg, 1.75 mmol), *para*methoxy styrene (0.30 mL, 2.28 mmol), $Yb(OTf)_3$ (109 mg, 0.175 mmol) and CH_2Cl_2 (8.75 mL) at room temperature. After 30 min, the reaction was concentrated

under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.420) afforded **58** as a white solid (348 mg, 61 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.83 - 7.76 (m, 2 H), 7.58 - 7.50 (m, 1 H), 7.47 - 7.39 (m, 2 H), 7.36 - 7.28 (m, 2 H), 6.88 - 6.80 (m, 2 H), 4.64 (t, J = 10.3 Hz, 1 H), 3.78 (s, 3 H), 3.10 (s, 3 H), 2.99 - 2.90 (m, 1 H), 2.79 - 2.65 (m, 1 H), 2.33 - 2.12 (m, 2 H).

Synthesis of cyclobutane 61:



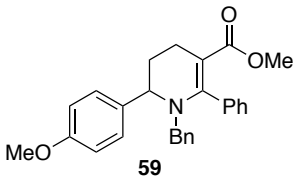
61

The general procedure was followed using methyl 2-(thiophene-2-carbonyl)acrylate (75 mg, 0.382 mmol), *para*methoxy styrene (0.07 mL, 0.543 mmol), $Yb(OTf)_3$ (23.7 mg, 0.038 mmol) and CH_2Cl_2 (2.25 mL) at room temperature. After 1 h, the reaction was concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.462) afforded **61** as a white solid (80 mg, 63 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.61 (dd, J = 1.2, 5.0 Hz, 1 H), 7.40 (dd, J = 1.1, 3.9 Hz, 1 H), 7.31 - 7.25 (m, 2 H), 7.06 (dd, J = 3.8, 5.0 Hz, 1 H), 6.85 - 6.79 (m, 2 H), 4.57 (t, J = 9.8 Hz, 1 H), 3.76 (s, 3 H), 3.12 (s, 3 H), 2.96 - 2.87 (m, 1 H), 2.74 - 2.60 (m, 1 H), 2.36 - 2.25 (m, 1 H), 2.22 - 2.10 (m, 1 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 188.8, 170.6, 158.4, 141.5, 133.8, 131.8, 131.1, 128.9, 128.1, 113.2, 64.8, 55.1, 51.9, 43.1, 27.1, 20.9.

General procedure for the synthesis of tetrahydropyridines **59**, **60** and **62**: To a round bottom flask charged with $Ni(ClO_4)_2$•$6H_2O$ (20 mol%) and amine (2.5 or 5.0 equiv.) in CH_2Cl_2 heated under reflux was added a solution of cyclobutane **58** (1.0 equiv.) in

CH_2Cl_2 or toluene. Once the reaction reached completion, the reaction mixture was concentrated under reduced pressure and purified using silica gel flash chromatography to afford the desired tetrahydropyridines.

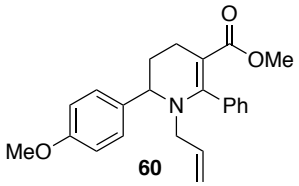
Synthesis of tetrahydropyridine 59:



59

The general procedure was followed using cyclobutane **58** (60 mg, 0.185 mmol), benzylamine (0.10 mL, 0.925 mmol), $Ni(ClO_4)_2 \bullet 6H_2O$ (13.5 mg, 0.037 mmol) and toluene (1.80 mL) at reflux. After 6 h, the reaction was allowed to cool down to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.400) afforded **59** as a yellow oil (40.6 mg, 53 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.49 - 7.22 (m, 10 H), 7.14 - 7.09 (m, 2 H), 6.98 - 6.93 (m, 2 H), 4.43 (t, J = 4.4 Hz, 1 H), 4.36 (d, J = 16.5 Hz, 1 H), 3.89 - 3.82 (m, 4 H), 3.44 (s, 3 H), 2.72 - 2.65 (m, 1 H), 2.27 - 2.19 (m, 1 H), 2.14 - 2.06 (m, 1 H), 2.03 - 1.96 (m, 1 H).

Synthesis of tetrahydropyridine 60:

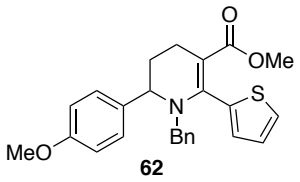


60

The general procedure was followed using cyclobutane **58** (60 mg, 0.185 mmol), benzylamine (0.04 mL, 0.463 mmol), $Ni(ClO_4)_2 \bullet 6H_2O$ (13.5 mg, 0.037 mmol) and

toluene (0.92 mL) at room temperature. After 6 h, the reaction was allowed to cool down to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.385) afforded **59** as a yellow oil (31.8 mg, 47 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.43 - 7.34 (m, 3 H), 7.34 - 7.27 (m, 2 H), 7.25 - 7.18 (m, 2 H), 6.95 - 6.88 (m, 2 H), 5.64 - 5.49 (m, 1 H), 5.11 - 4.96 (m, 2 H), 4.53 - 4.48 (m, 1 H), 3.82 (s, 3 H), 3.64 - 3.54 (m, 1 H), 3.36 (s, 3 H), 3.30 - 3.20 (m, 1 H), 2.69 - 2.59 (m, 1 H), 2.23 - 2.01 (m, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 181.9, 168.4, 158.6, 156.5, 138.1, 134.4, 134.2, 128.1, 127.8, 127.3, 116.6, 113.9, 96.0, 58.3, 55.3, 52.5, 50.4, 28.4, 19.1.

Synthesis of tetrahydropyridine 62:



62

The general procedure was followed using cyclobutane **61** (60 mg, 0.182 mmol), benzylamine (0.05 mL, 0.454 mmol), $Ni(ClO_4)_2$•$6H_2O$ (13.5 mg, 0.036 mmol) and toluene (0.92 mL) at room temperature. After 23 h, the reaction was allowed to cool down to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.385) afforded **59** as a yellow oil (30.2 mg, 40 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.41 - 7.37 (m, 1 H), 7.35 - 7.24 (m, 3 H), 7.18 - 7.12 (m, 4 H), 7.04 - 7.00 (m, 2 H), 6.94 - 6.88 (m, 2 H), 4.49 (d, J = 16.0 Hz, 1 H), 4.43 - 4.38 (m, 1 H), 3.91 - 3.80 (m, 4 H), 3.48 (s, 3 H), 2.68 - 2.58 (m, 1 H), 2.21 - 1.93 (m, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.2, 158.7, 148.5, 138.4, 138.1, 133.6,

128.5, 127.3, 127.2, 127.1, 126.9, 126.8, 126.3, 113.9, 99.9, 58.2, 55.3, 53.2, 50.7, 28.1, 19.8.

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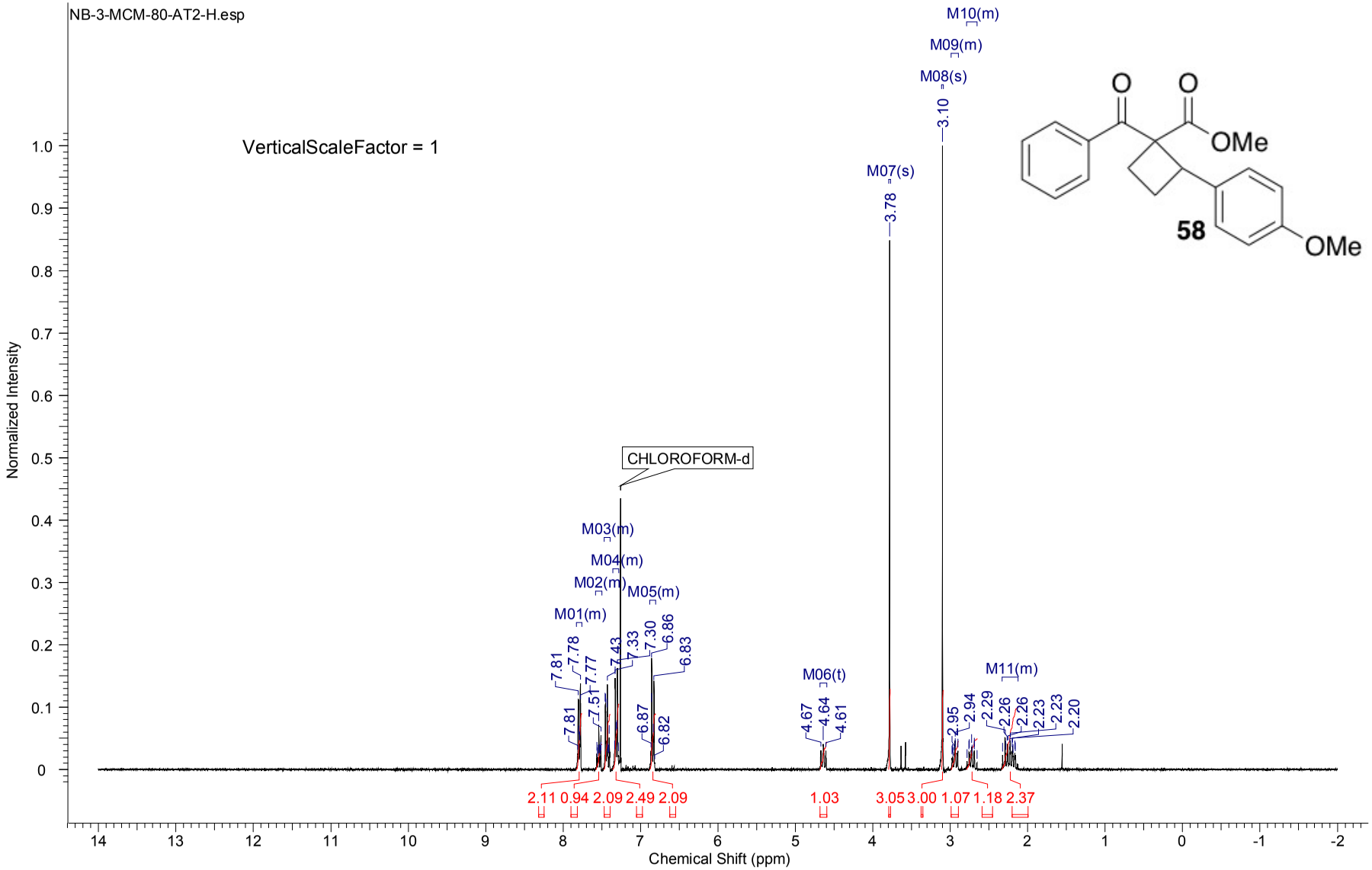

Acquisition Time (sec)	3.5504	***Comment***	Red cap	***Date***	Apr 9 2014	***Date Stamp***	Apr 9 2014
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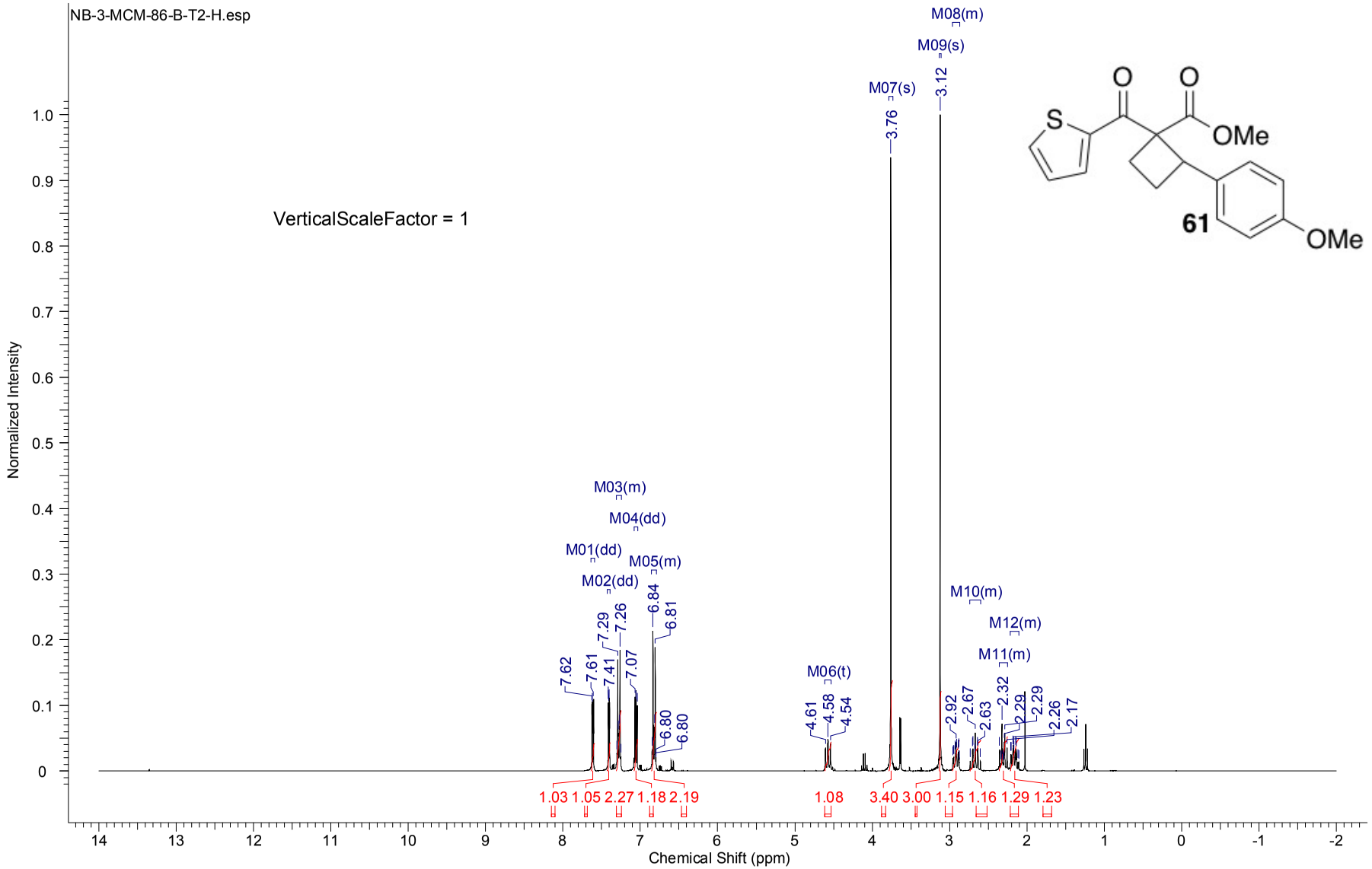

Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Apr 9 2014
Date Stamp	Apr 9 2014	***File Name***	D:\Experimental section\Amine project\NB-3-MCM-86-B-T2-C.fid\fid				
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Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d
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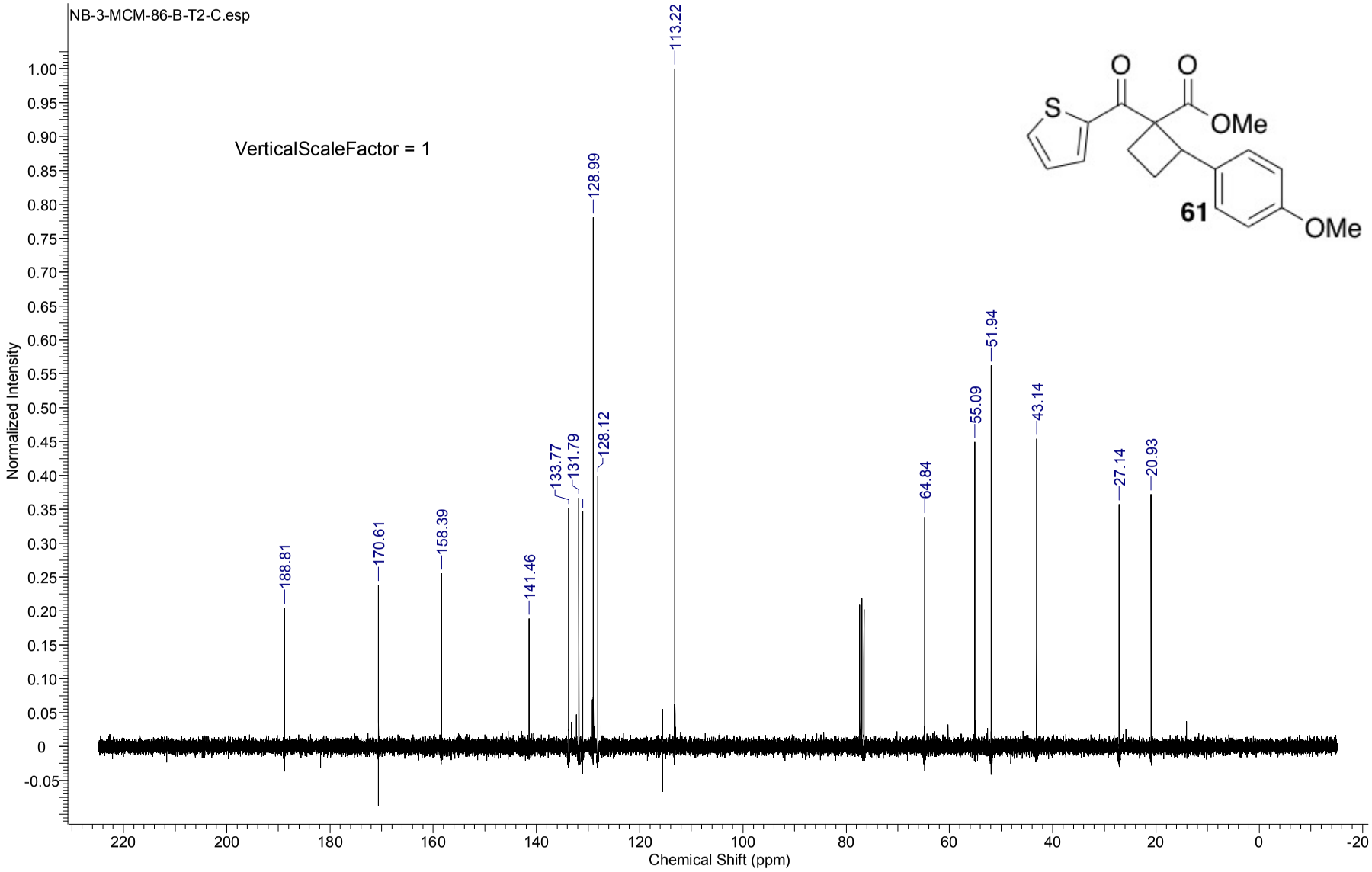

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Receiver Gain	46.70	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
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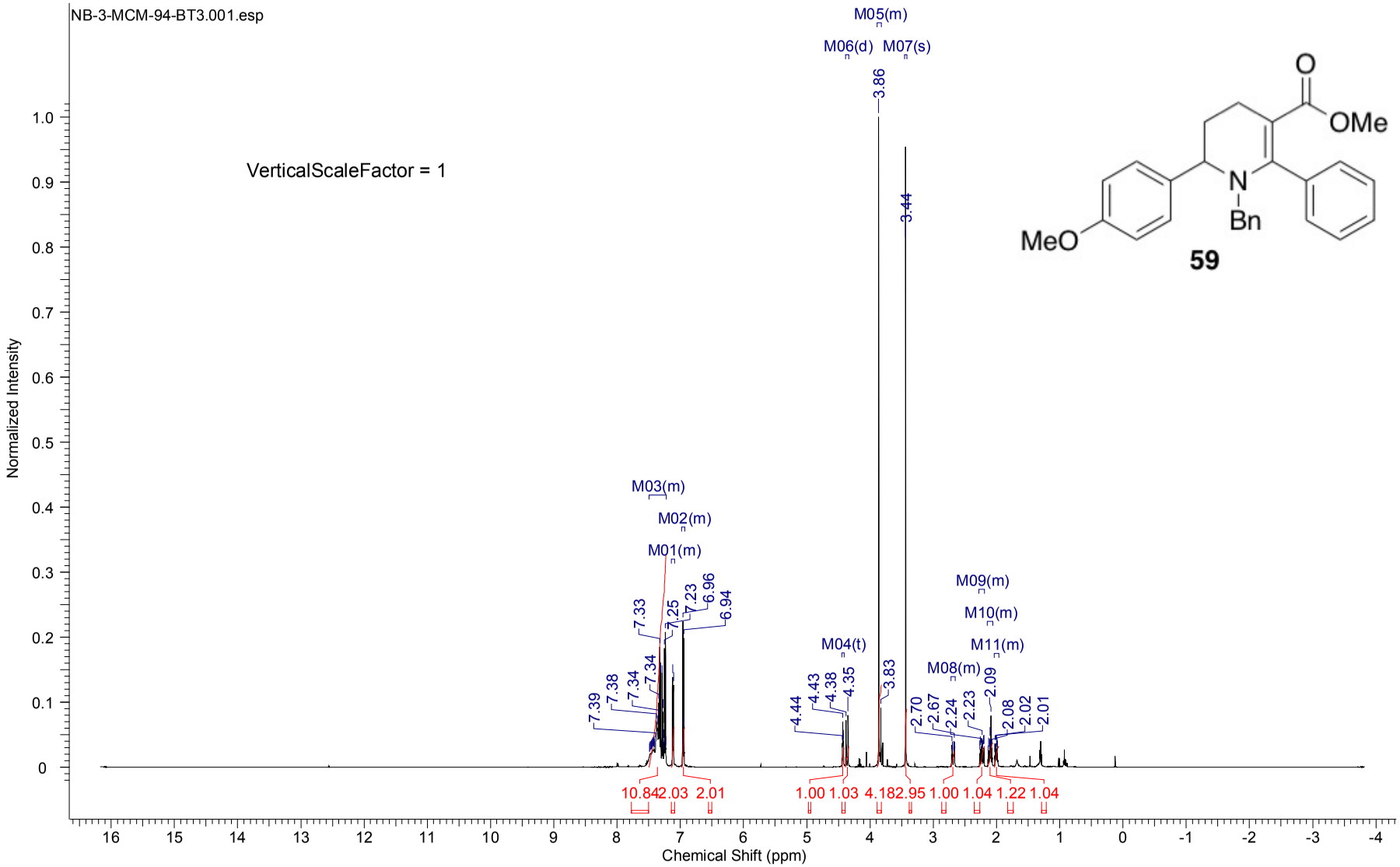

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Frequency (MHz)	300.22	***Nucleus***	1H	***Number of Transients***	12	***Original Points Count***	17053
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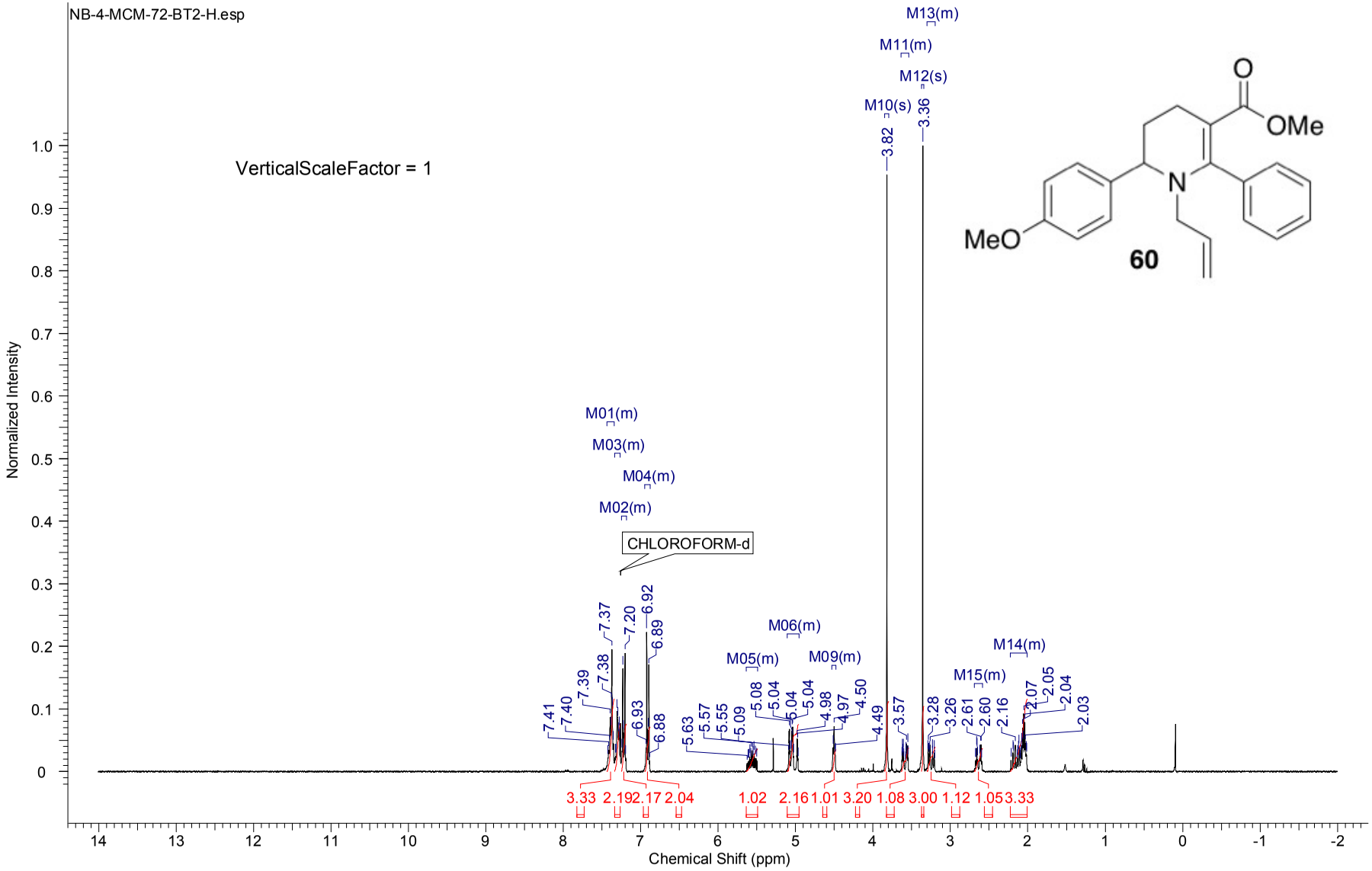

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Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d
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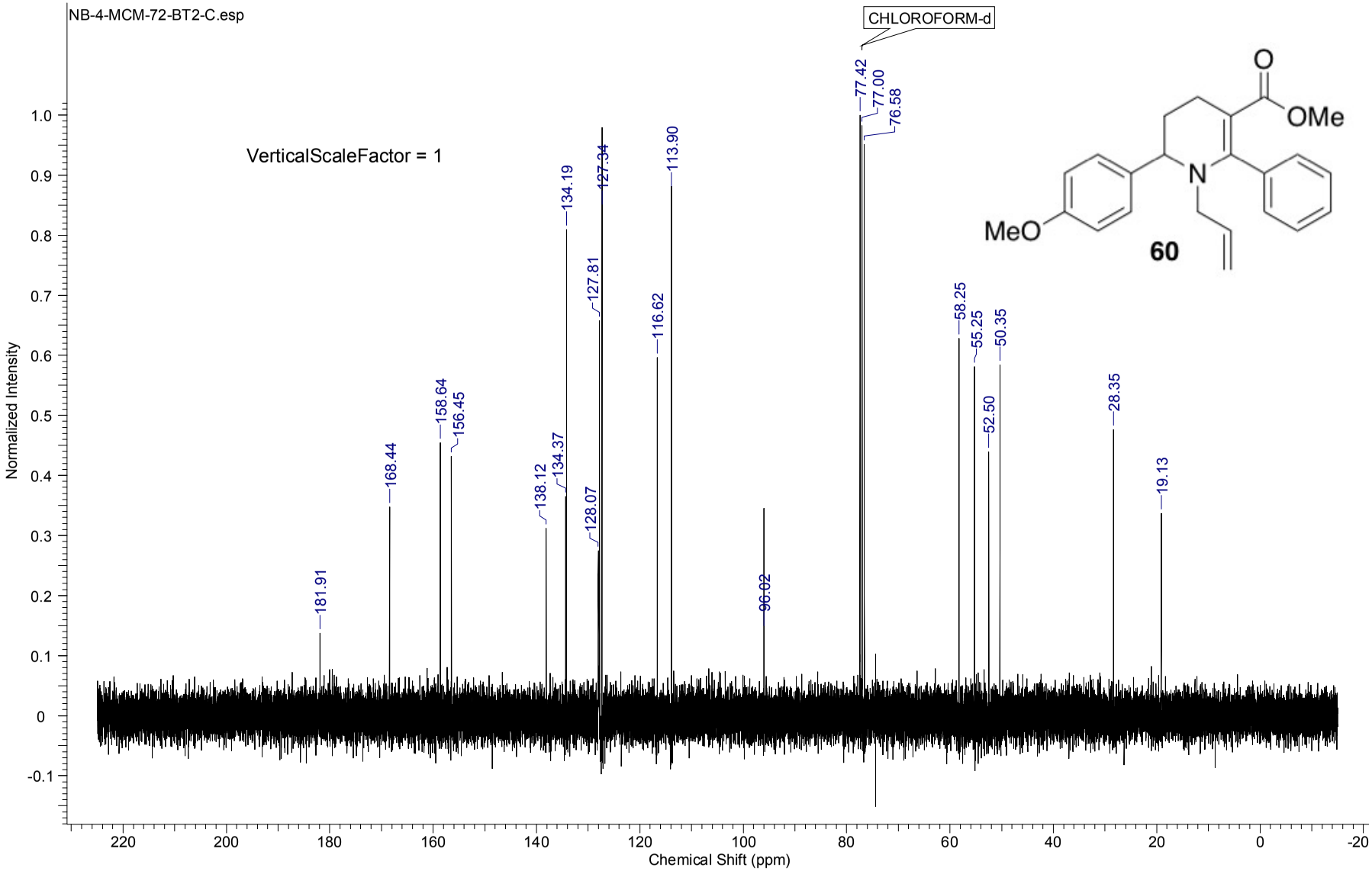

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Nucleus	1H	***Number of Transients***	16	***Original Points Count***	17053	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d		
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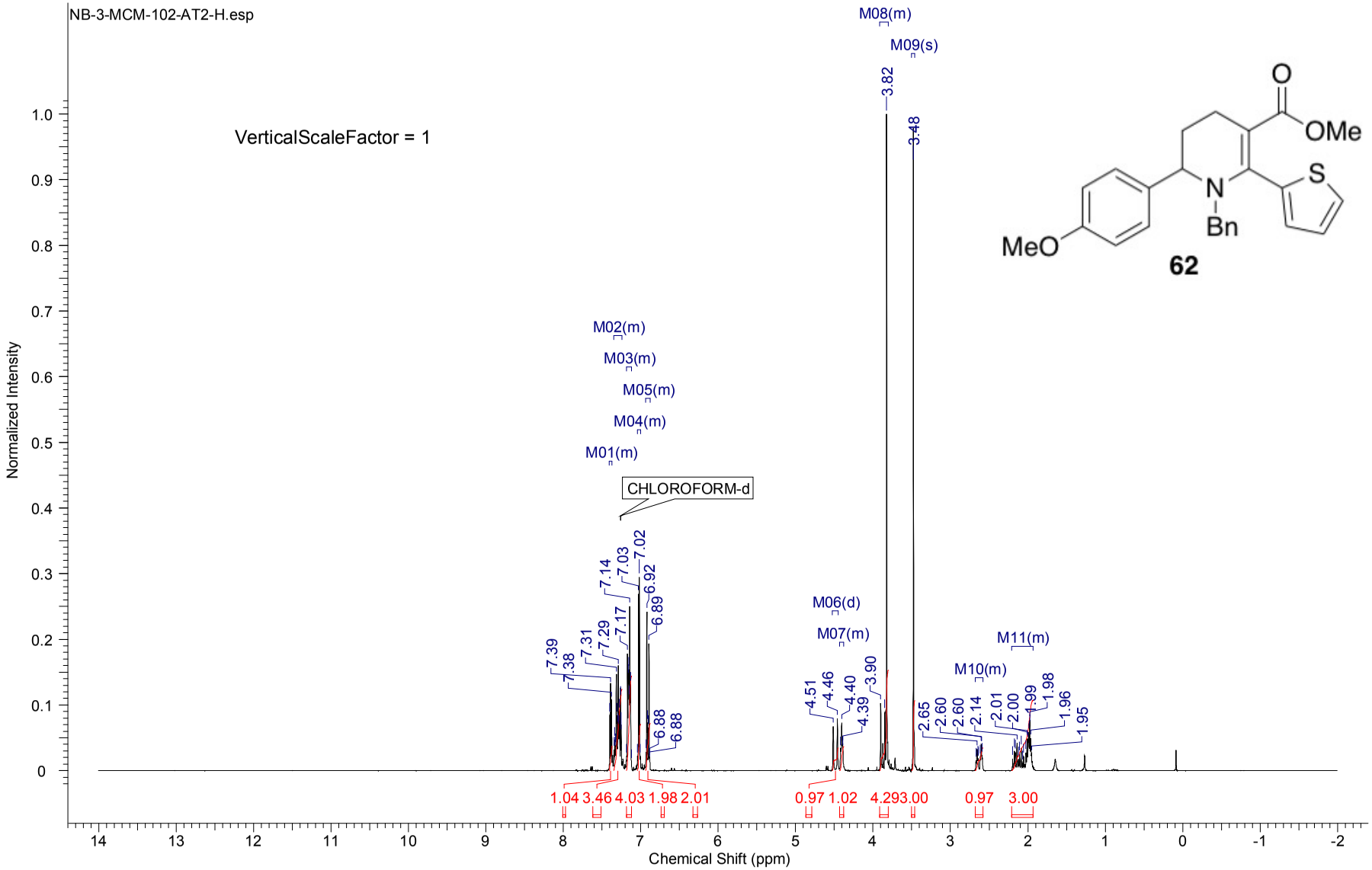

Acquisition Time (sec)	1.3005	***Comment***	Green cap	***Date***	May 5 2014	***Date Stamp***	May 5 2014
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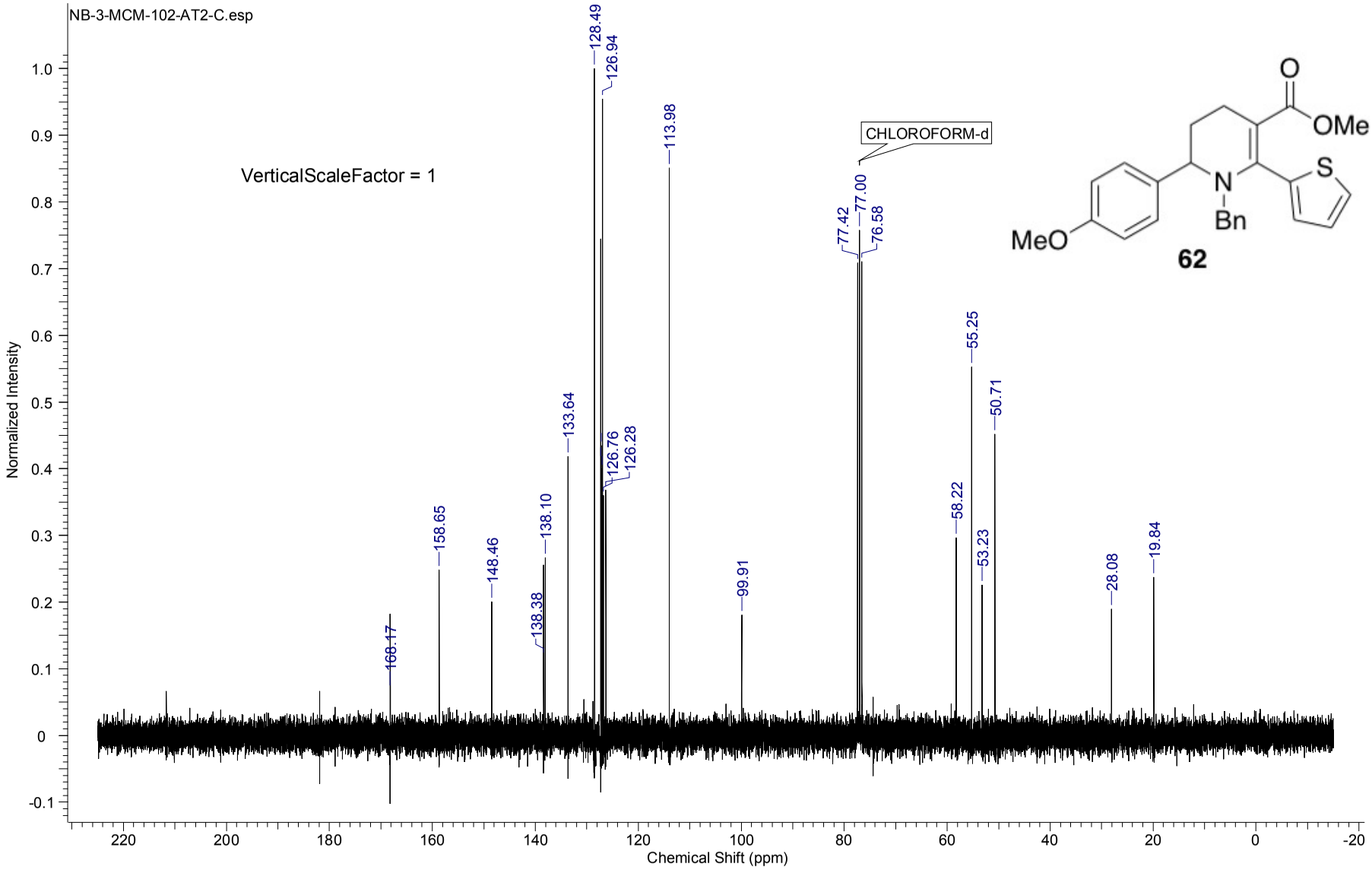

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CHAPTER 3. FORMAL [5+2] CYCLOADDITIONS TOWARDS 7-MEMBERED RING FUSED INDOLES: SYNTHESIS OF AZEPINO[1,2-*A*]INDOLES AND CYCLOHEPTA[*B*]INDOLES[*†]

3.1 Significance of Azepino[1,2-*a*]indole and Cyclohepta[*b*]indole frameworks

The indole moiety has been found to be a popular scaffold used in both the chemical and pharmaceutical industries.[2] The indole framework is found in a large number of important compounds that occur in nature such as indole alkaloids.[3] Azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles are interesting subclasses of the indole alkaloid family of natural products (Figure 3.1). For instance the azepino[1,2-*a*]indole **1**, correantine B,[4] represents a set of exciting compounds isolated from *Psychotria Correae*, which is structurally similar to the dihydro-cycloakagerine **2**,[5] which possesses antiprotozoal activity. In addition, the cyclopropyl azepine **3** belongs to a small molecule library (>1000) developed by Bristol-Myers Squibb as Hepatitis C NS5B inhibitors.[6] Likewise, the cyclohepta[*b*]indoles **4** – **6** are found to exhibit significant biological activities such as anticancer, antidepressant, anti-HIV, antimicrobial, antileishmanial and potential therapeutic agents for the treatment of cardiovascular disease.[7]

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[*] Work on catalytic formal [5+2] cycloaddition approach for the synthesis of azepino[1,2-*a*]indoles was performed in collaboration with Raynold Shenje.
Published in *Angew. Chem. Int. Ed.* **2014**, *53*, 13907.

[†] Work on catalytic formal [5+2] cycloaddition approach for the synthesis of cyclohepta[*b*]indoles was performed in collaboration with Raynold Shenje.
Manuscript in preparation.

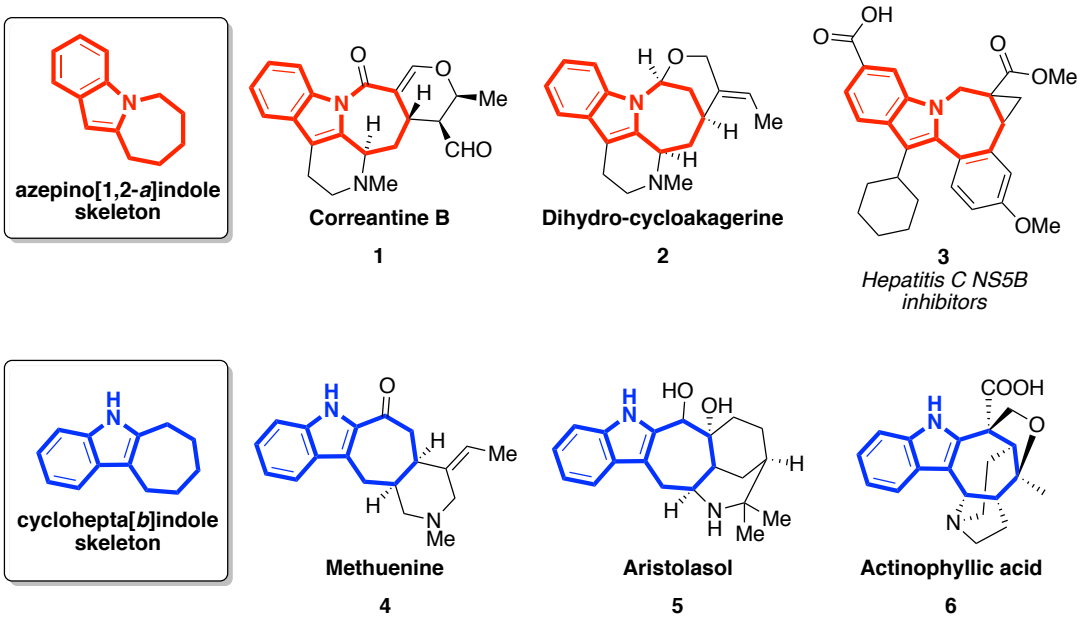
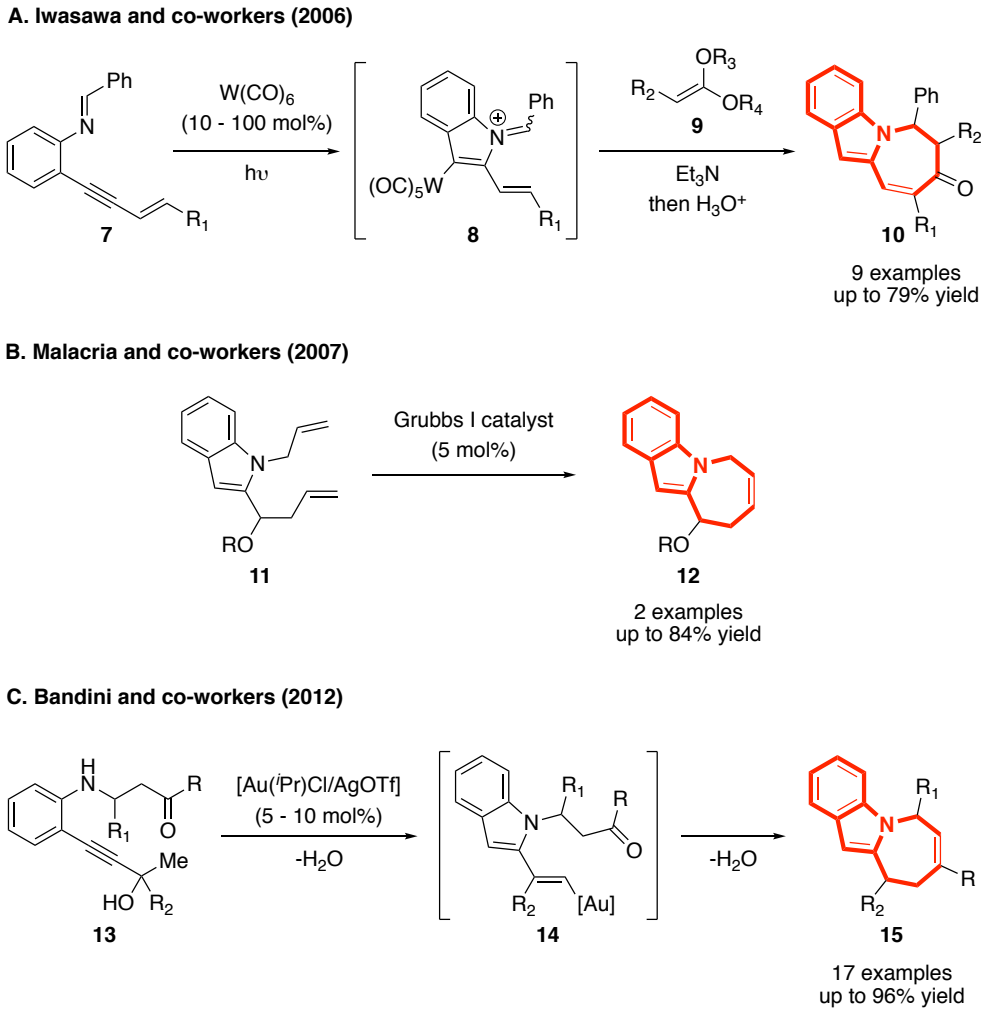


Figure 3.1. Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles in Natural Products

3.2 Past Synthetic Methods Accessing these 7-Membered Ring Structural Motifs

These two subclasses of the indole alkaloid natural products featuring 6-5-7 ring scaffolds have garnered much attention from the synthetic community.[1,8] Much effort has been dedicated in developing general protocols to access these interesting frameworks. Some of these approaches are hetero[5+2] cycloadditions,[8f] olefin metatheses,[9] radical cyclizations[10] or transition-metal-catalyzed intramolecular cyclization cascades.[11] As such, Scheme 3.1 shows 3 examples of prior syntheses of azepino[1,2-*a*]indoles. Iwasawa and co-workers[8f] reported a W-mediated cyclization of imino alkyne **7** to afford azomethine ylides **8**, which underwent subsequent hetero-[5+2] cycloadditions with ketene acetals **9** to form the desired azepino[1,2-*a*]indoles **10** (Scheme 3.1A). Moreover, Malacria and co-workers[8b] pioneered a simple ring-closing metathesis approach to azepino[1,2-*a*]indoles **12** using indole-based dienes **11** (Scheme 3.1B). Lastly, Bandini

and co-workers[8c] designed an effective synthesis to the azepinoindole scaffold via Au-catalyzed tandem hydroamination/dehydrative cyclizations to obtain azepino[1,2-*a*]indoles **15** in good chemoselectivities and yields (Scheme 3.1C).

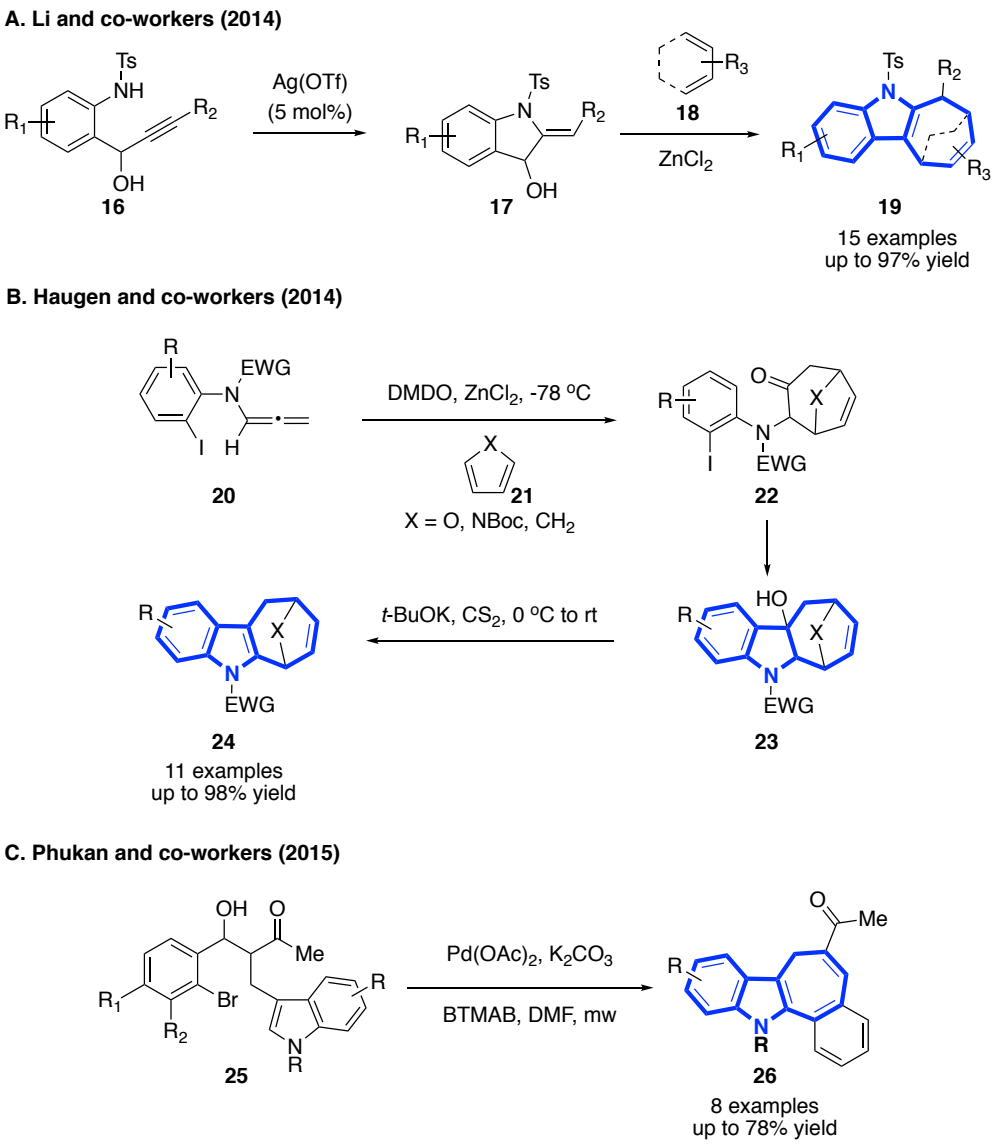


Scheme 3.1. Prior Selected Syntheses of Azepino[1,2-*a*]indoles

Unfortunately, these pioneering routes to the azepino[1,2-*a*]indole framework suffer from one of these limitations: (1) high catalyst loadings, (2) low functional tolerance (3) limitations in substrate scope, and (4) multiple steps to generate the necessary starting precursors. With these limitations in mind, we sought to design a novel

protocol for the synthesis of the azepino[1,2-*a*]indole focusing on achieving efficiency, selectivity and modularity.

Otherwise, recent examples of prior syntheses accessing the cyclohepta[*b*]indole core are shown in Scheme 3.2. Li and co-workers[12] reported this novel approach to cyclohepta[*b*]indoles via one-pot hydroamination/[4+3] cycloaddition. This 2-step process involved hydroamination of alkyne **16** to generate intermediate **17**, followed by [4+3] cycloaddition of **17** with dienes **18** (Scheme 3.2A). In the same year, Haugen and co-workers[8e] developed this protocol for the synthesis of highly functionalized cyclohepta[*b*]indoles from precursor allenamides **20** through an efficient sequence of a [4+3] cycloaddition – cyclization – elimination (Scheme 3.2B). Finally, Phukan and co-workers[13] developed this new approach for the synthesis of molecular scaffolds of indole rings fused with seven-membered carbocyclic skeletons such as the cyclohepta[*b*]indole (Scheme 3.2C). This involved an intramolecular Heck cross-coupling reaction of aryl bromide **25** using $Pd(OAc)_2$ as catalyst in the presence of benzyltrimethylammonium bromide (BTMAB) under microwave conditions. While these effective methods afforded highly functionalized cyclohepta[*b*]indoles, there is a need to design more concise protocols to access this particular scaffold in a streamlined and modular fashion.



Scheme 3.2. Prior Selected Syntheses of Cyclohepta[*b*]indoles

3.3 Design of a Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles via Putative D-A Cyclobutane Intermediates

3.3.1 Project Rationale and Justification

Our lab's background involved the use of strained carbocycles as building blocks for molecular diversity and complexity. We have developed a variety of intramolecular

ring-opening cyclizations of D-A cyclopropanes[14] and activated cyclopropenes[15] as a means to access a range of diverse polycyclic molecules. As highlighted in Chapter 1, D-A cyclopropanes and cyclobutanes share similar reactivity profiles in many ways. D-A cyclopropanes have been a popular topic and extensively studied in organic synthesis[16]. On the other hand, D-A cyclobutane has not received much attention until more recently.[17] Most of the work reported involved intermolecular reactivity of D-A cyclobutanes with carbonyls,[18] imines,[19] nitrosoarenes,[20] nitrones[21] and alkynes.[22] Despite these important examples, there were no examples of any reports of D-A cyclobutanes undergoing intramolecular ring-opening cyclization reactions to our knowledge. Therefore, from the success with D-A cyclopropanes, we envisioned homologous intramolecular ring-opening reactivity with D-A cyclobutanes. If this strategy is successfully implemented, it will not only allow an effective and new approach for the synthesis of azepino[1,2-*a*]indoles (Figure 3.2) but also provide the first example of intramolecular ring-opening cyclization reactivity with D-A cyclobutanes.

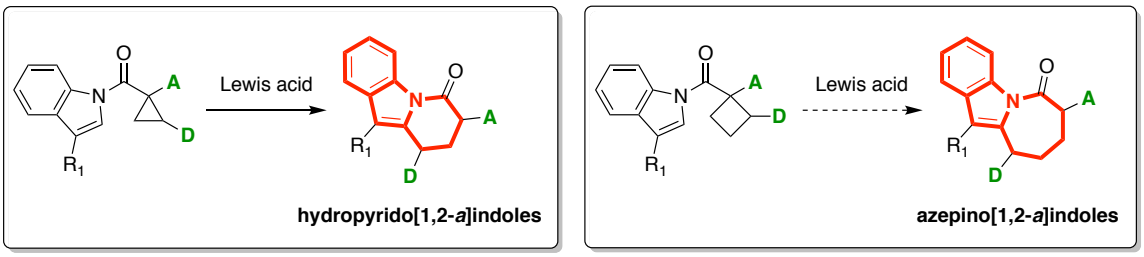
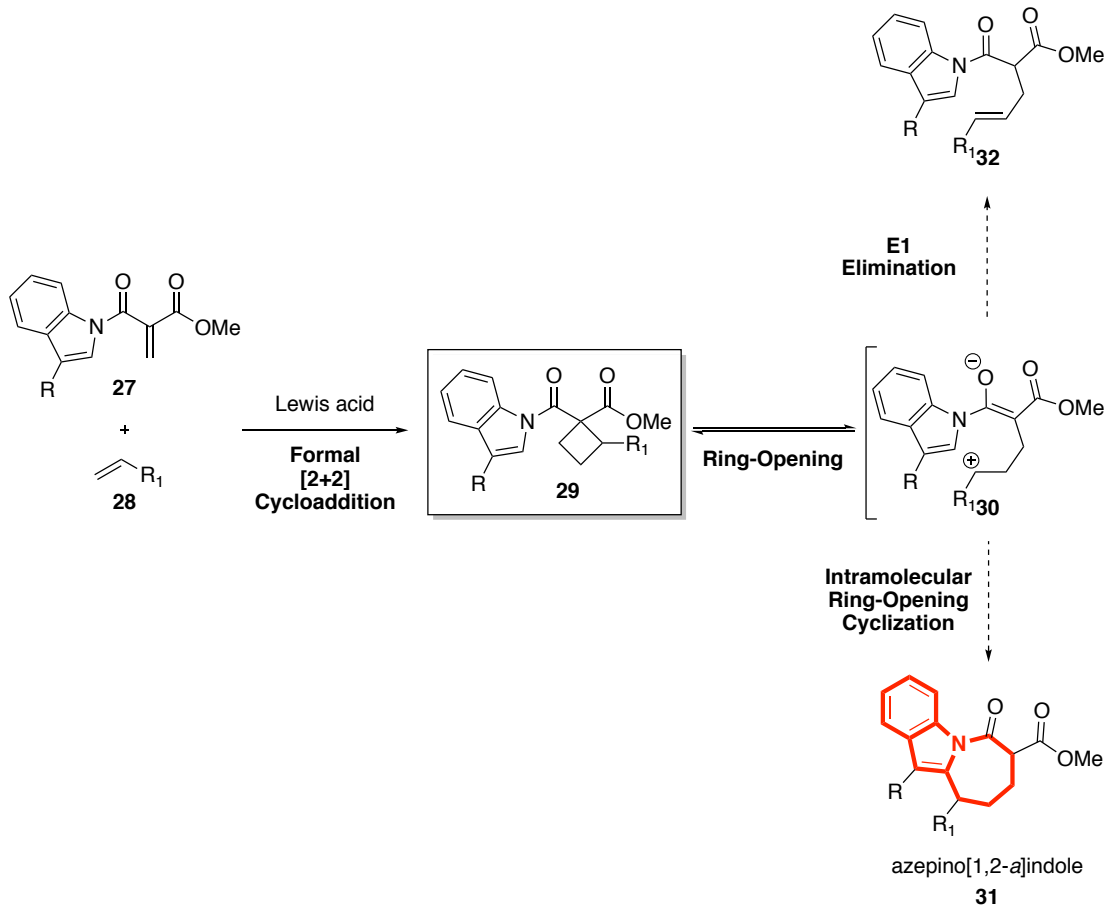


Figure 3.2. Intramolecular Ring-Opening Cyclization Strategy with D-A Cylobutanes

3.3.2 Reaction Design

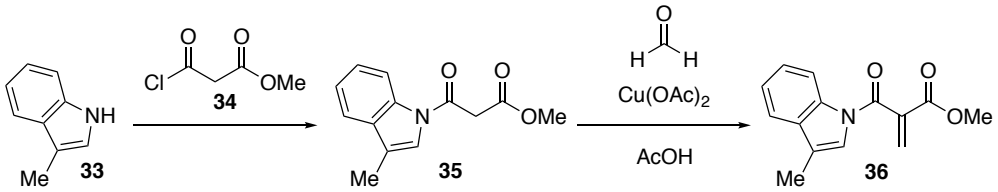
To explore such strategy, we sought to prepare the desired D-A cyclobutanes using Lewis acid promoted formal [2+2] cycloadditions of alkylidene **27** with alkenes **28** (Scheme 3.3). While the anticipated cycloisomerization works well with D-A cyclopropanes, its application to D-A cyclobutanes has not been previously explored and could pose certain difficulties. Firstly, the formation of larger 7-membered rings (with D-A cyclobutane reactions) is entropically less favored compared to 6-membered rings (with D-A cyclopropane reactions).[23] Secondly, once ring-opening occurs to form the 1,4-dipole intermediate **30**, it is necessary that the π-attack in a Friedel-Crafts-type manner, occurs immediately to prevent side reactions such as E1-elimination to form alkene **32** or any potential degradation pathways (Scheme 3.3). However the selected indole π-nucleophile is suitable for this transformation since it has been shown to undergo rapid and smooth reactivity in Friedel-Crafts-type transformations.[24]



Scheme 3.3. D-A Cyclobutane Strategy for the Synthesis of Azepino[1,2-*a*]indole

3.3.3 Model Substrate Synthesis

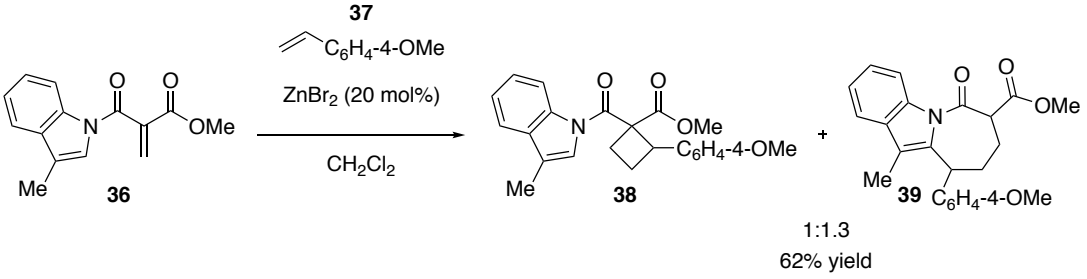
The alkylidene precursor, *N*-indolyl malonamide **36** was synthesized via a two-step sequence in which commercially available 3-methylindole **33** was reacted with methyl malonyl chloride **34** to form *N*-acylated indole **35** (Scheme 3.4). Then indole **35** underwent $Cu(OAc)_2$-catalyzed condensation with formaldehyde to afford alkylidene **36**.



Scheme 3.4. Synthesis of Model *N*-Indolyl Malonamide **36**

3.3.4 Proof of Principle

We started our study by synthesizing the required cyclobutane via a Lewis acid-catalyzed formal [2+2] cycloaddition approach established by Roberts and co-workers (Scheme 3.5).[8a] *N*-Indolyl malonamide **36** was treated with 4-methoxy styrene **37** and 20 mol% $ZnBr_2$ as the catalyst, which gave a 1:1.3 ratio mixture of D-A cyclobutane **38** and azepino[1,2-*a*]indole **39** in 62% yield after 24 h. This exciting result suggested the possibility of accessing the azepino[1,2-*a*]indole directly in a one-pot fashion from the alkene and alkylidene precursors via a formal [5+2] cycloadditon approach.



Scheme 3.5. Initial Test Reaction for the Synthesis of Azepino[1,2-*a*]indole

3.3.5 Reaction Optimization

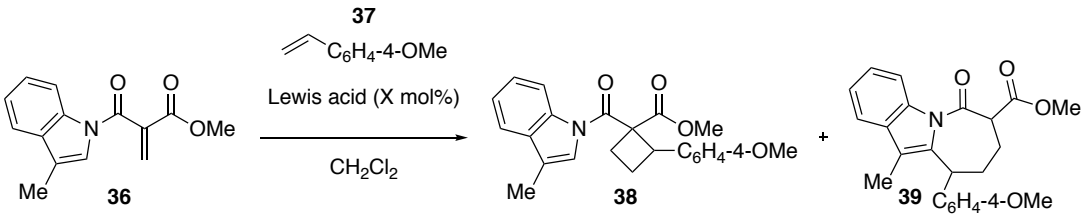
With the initial conditions (20 mol% $ZnBr_2$ in CH_2Cl_2), we observed formation of both cyclobutane **38** and azepino[1,2-*a*]indole **39**. So, an extensive study of Lewis acid

screening was performed in an attempt to identify a catalytic approach for the formation of exclusively azepino[1,2-*a*]indole **39** (Table 3.1). We first investigated the effect of the loading of $ZnBr_2$ on the reaction outcome. Using 30 and 100 mol% loading led solely to the production of azepino[1,2-*a*]indole **39** in 49% and 52% yield respectively (entries 1 and 2). Surprisingly, no change in reaction time (24 h) was observed irrespective of the amount of $ZnBr_2$ used.

Other oxophilic Lewis acids with the ability to bind to the dicarbonyl moiety of alkylidene **36** were probed. Using $Sc(OTf)_3$ at loadings of 20 and 10 mol% led to the formation of azepine **39** in 72% and 78% yield respectively (entries 3 and 4). Other Lewis acids, such as $Yb(OTf)_3$, $Mg(OTf)_2$ and $La(OTf)_3$ gave either low yields of azepino[1,2-*a*]indole **39** or a mixture of cyclobutane **38** and azepine **39** (entries 5, 8 and 12).

During the optimization study, we also observed that whenever exclusive formation of azepinoindole **39** was obtained, the *cis/trans* diastereomeric ration (*dr*) was >8:1. The $ZnBr_2$ catalyzed reactions gave *dr*'s in the range of 11:1 to 16:1 while $Yb(OTf)_3$, $Mg(OTf)_2$ and $La(OTf)_3$ gave *dr*'s of 12:1, 19:1 and 8:1 respectively. Fortunately, the optimum Lewis acid, $Sc(OTf)_3$ not only afforded azepinoindole **39** in the highest yield (78%) but also gave the best diastereoselectivity (33:1) (entry 4).

Table 3.1. Lewis Acid Screening for Azepino[1,2-*a*]indole Synthesis



Entry	Lewis acid	Loading (mol %)	Time (h)	Yield (%)	**38:39**	*dr*
1	$ZnBr_2$	30	24	49	0:1	16:1
2	$ZnBr_2$	100	24	52	0:1	14:1
3	$Sc(OTf)_3$	20	1	72	0:1	11:1
4	$Sc(OTf)_3$	10	2	78	0:1	33:1
5	$Yb(OTf)_3$	10	7	44	1:1.3	12:1
6	$In(OTf)_3$	10	0.5	-	-	-
7	$Al(OTf)_3$	10	0.5	-	-	-
8	$Mg(OTf)_2$	10	48	25	0:1	19:1
9	$Zn(OTf)_2$	10	24	-	-	-
10	$Cu(OTf)_2$	10	24	-	-	-
11	$Ga(OTf)_2$	10	0.5	-	-	-
12	$La(OTf)_3$	10	7	25	1.6:1	8:1
13	$Ni(OTf)_2$	10	24	-	-	-

Finally, a solvent screening was performed to investigate the effects of different solvents on the reaction outcome (Table 3.2). Weakly coordinating, non-polar solvents such as dichloromethane (CH_2Cl_2), benzene and toluene worked well and led to the desired product in 78%, 64%, and 57% yield respectively (entries 1, 2 and 3). On the other hand, polar coordinating solvents gave low reaction yields (32% yield with EtOAc) (entry 6) or no product formation (with MeCN and THF) (entries 4 and 5). It is likely that the coordinating solvents bind to the metal center of the catalyst, hence altering the Lewis

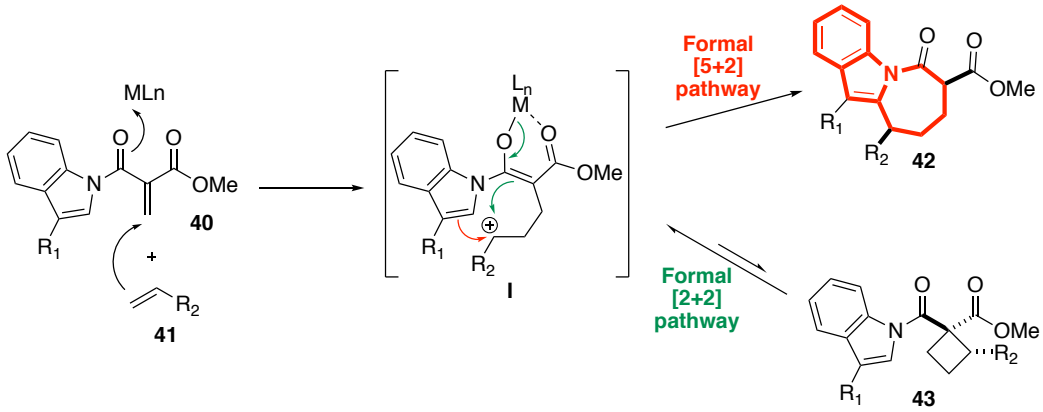
acidity of the catalyst or complete sequestration leading to no desired reactivity. The last stage of our optimization studies involved modifying the reaction concentration and temperature. However these condition factors were unproductive and did not contribute to any improvement in either yield or diastereoselectivity for the transformation.

Table 3.2. Solvent Screening for Azepino[1,2-*a*]indole Synthesis

Entry	Solvent	Time (h)	Yield (%)
1	CH_2Cl_2	2	78
2	benzene	4.5	64
3	toluene	4.5	57
4	MeCN	2	-
5	THF	7	-
6	EtOAc	24	32

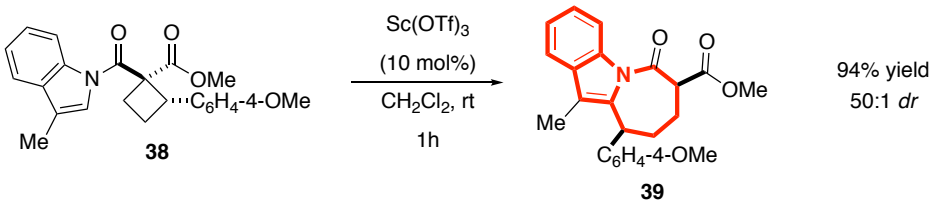
3.3.6 Reaction Mechanism

Mechanistically, the transformation proceeds initially by an intermolecular π-attack by the alkene **41** to form 1,4-dipolar intermediate **I** (Scheme 3.6). Intermediate **I** can undergo two parallel pathways: (a) a direct intramolecular Friedel-Crafts-type alkylation (formal [5+2] route) to afford azepino[1,2-*a*]indole **42**, or (b) a 4-(enol-*exo*)-*exo-trig* cyclization (formal [2+2] cycloaddition route) to form cyclobutane **43**.



Scheme 3.6. Proposed Mechanism for Azepino[1,2-*a*]indole Synthesis

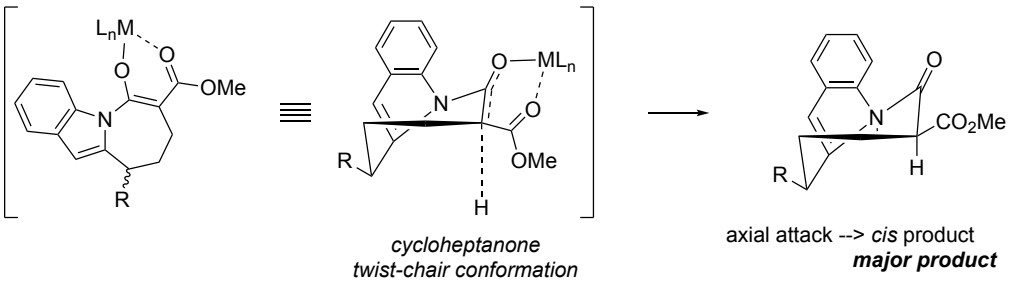
The transformation likely proceeds via the cyclobutane **43** first, followed by a cycloisomerization to give azepino[1,2-*a*]indole **42**, given entropic considerations for ring-forming reactions.[25] Cyclobutane **38** was isolated and subjected to the optimized conditions to show its potential as an intermediate in the reaction (Scheme 3.7). The formation of azepino[1,2-*a*]indole **39** in 94% yield with a 50:1 *dr* in less than 1 h, supported our hypothesis. In addition this reaction represents the first example of intramolecular ring-opening/cyclization of a D-A cyclobutane in literature.



Scheme 3.7. Intramolecular Ring-Opening Cyclization of D-A Cyclobutane

The formation of azepinoindole occurred with high diastereoselectivity, with the *cis*-product as the major diastereomer. Presumably, the stereochemistry is set during the protonation step after the formation of the 7-membered ring. The Lewis acid-azepino[1,2-

a]indole enolate complex is anticipated to adopt a twist-chair conformation similar to that of cycloheptenone systems (Scheme 3.8). Finally, a preferred pseudoaxial protonation leads to the *cis* product as the major diastereomer (kinetic product).



Scheme 3.8. Rationale for Diastereoselectivity

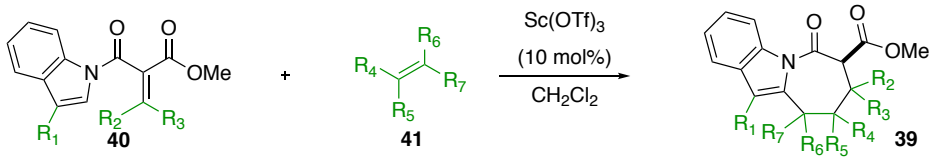
3.3.7 Examination of Substrate Scope

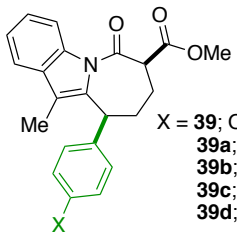
After finalizing the optimized conditions for the synthesis of azepino[1,2-*a*]indole scaffold, we examined the scope and limitation of this formal [5+2] cycloaddition reaction by employing different substituted alkenes **41** and *N*-indolyl alkylidene *β*-amide esters **40** (Table 3.3). First, we explored the reactivity of alkylidene **40** with different mono-substituted alkenes **41**. Styrenes with strong electron-donating groups in the *para*-position led to azepinoindoles **39** and **39a** in high yields. In contrast, when a strong electron-withdrawing group substituent is used such as a nitro group (**39d**), no desired product was obtained at all. This trend pointed towards a carbocation-type mechanism in which a build-up of positive charge on the benzylic position is experienced during the reaction.

Ortho-Substituted styrenes reacted not at all or very poorly to give azepino[1,2-*a*]indoles **39f-39h** in reduced yields and/or diastereoselectivities. When *ortho*-methoxy

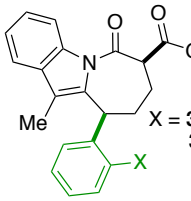
styrene was used, no product was formed whereas *ortho*-bromo styrene gave azepine **39f** in 15% yield. Other *ortho*-substituted styrene such as, 2,4-dimethoxy styrene and 2-bromo-4-methoxy styrene worked moderately and afforded azepinoindoles **39g** and **39h** in 25% and 66% yield respectively. This poor reactivity is likely due to the undesired steric repulsion between the *ortho*-substituent and the indole methyl group, which prevents ring closure to form the azepine ring.

Table 3.3. Scope for Azepino[1,2-*a*]indole Synthesis

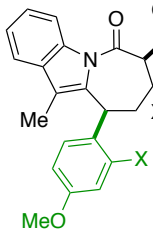




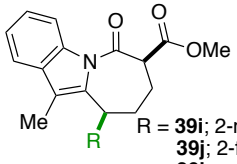
X = **39**; OMe, 78%, 33:1 *dr*
39a; Me, 62%, 20:1 *dr*
39b; Cl, 33%, 34:1 *dr*
39c; H, 24%, 10:1 *dr*
39d; NO_2, no product



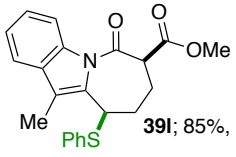
X = **39e**; OMe, no product
39f; Br, 15%, 2.3:1 *dr*



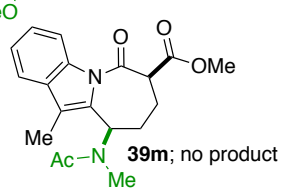
X = **39g**; OMe, 25%, 1.6:1 *dr*
39h; Br, 66%, 3:1 *dr*



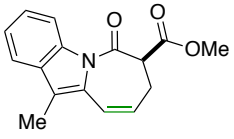
R = **39i**; 2-naphthyl; 45%, 16:1 *dr*
39j; 2-furyl; 62%, 8:1 *dr*
39k; *n*-Bu; no product



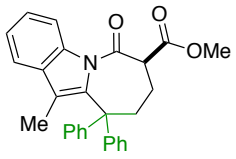
39l; 85%, 11:1 *dr*



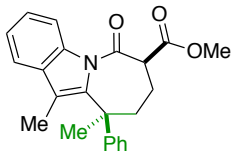
39m; no product



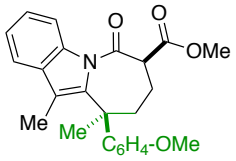
39n; 81%



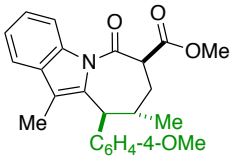
39o; 78%



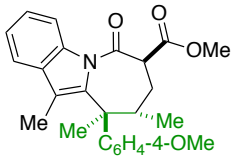
39p; 92%, 2:1 *dr*



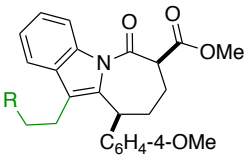
39q; 64%, 2:1 *dr*



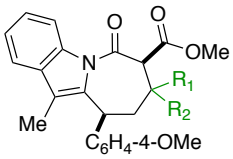
39r; 82%, 10:1:0:0 *dr*



39s; 84%, 7:1.3:1:0 *dr*

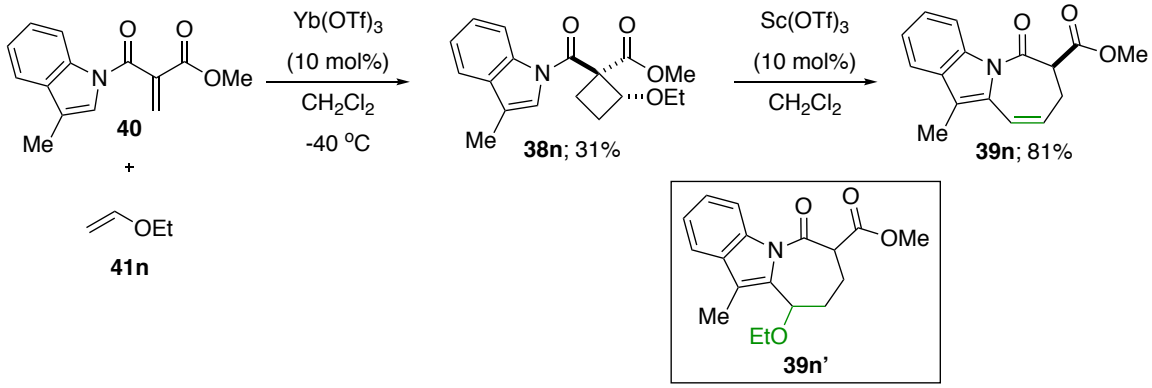


39t; R = Br, 78%, 12:1 *dr*
39u; R = CO_2Me, 54%, 29:1 *dr*



39v; R_1=R_2=Me, no product
39w; R_1=H, R_2= C_6H_4-4-OMe, no product

Other alkenes, such as 2-vinyl naphthalene, 2-vinyl furan and phenyl vinyl sulfide were tolerated and azepinoindoles **39i**, **39j** and **39l** were obtained in 45%, 62% and 85% yield respectively. However, no desired azepinoindole **39m** was obtained when *N*-methyl-*N*-vinylacetamide was employed. We observed Michael addition of the enamide **41m** to the alkylidene **36** occurring, but no subsequent intramolecular Mannich reaction happened. Instead, we obtained about 15-20% yield of the aldehyde resulting from hydrolysis of the Mannich intermediate along with indiscernible side products, presumably resulting from the carbocation degradation pathways. On the other hand, using ethyl vinyl ether in the reaction did not lead to the desired product since it easily degraded or polymerized in the presence of strong Lewis acids.[26] Instead, we subjected ethyl vinyl ether to 10 mol% $Yb(OTf)_3$ where only cyclobutane **38n** was obtained (Scheme 3.9). Then, treating cyclobutane **38n** to the optimized $Sc(OTf)_3$-catalyzed conditions afforded the formation of unsaturated azepino[1,2-*a*]indole **39n** in 81% yield. The unsaturation presumably arises from the Lewis acid mediated elimination of EtOH after formation of the seven-membered ring **39n'**.



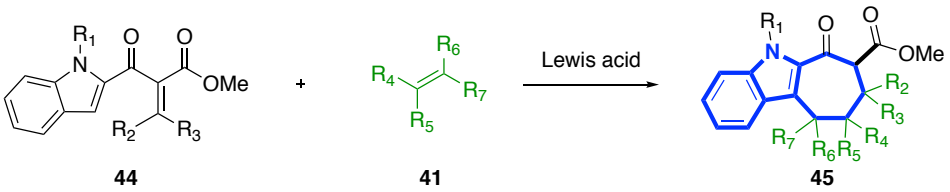
Scheme 3.9. Synthesis of Unsaturated Azepino[1,2-*a*]indole **39n**

Multi-substituted alkenes gave desired products, providing one of the substituents was aromatic. For instance, 1,1-diphenylethylene and α-methyl styrene gave azepines **39o** and **39p** in 78% and 92% yield, respectively. A tri-substituted alkene **41s** led to azepinoindole **39s** in 84% yield. Finally, changes to the substituent at the 3-position of the indole moiety such as alkylidenes derived from 3-(2-bromoethyl)indole and indole acetic acid methyl ester readily reacted with *para*-methoxy styrene to give the azepines **39t** and **39u** in 78% and 54% yield, respectively. However, when alkyl or aryl substituents were placed on alkylidene **40**, no reactivity was observed (**39v** and **39w**). The lack of reactivity presumably originates from the undesired steric interactions between the ester group and the alkylidene substituent that force the enone into the unreactive s-*cis* conformation.[27]

3.4 Design of a Formal [5+2] Cycloaddition Approach to Cyclohepta[*b*]indoles

3.4.1 Reaction Design

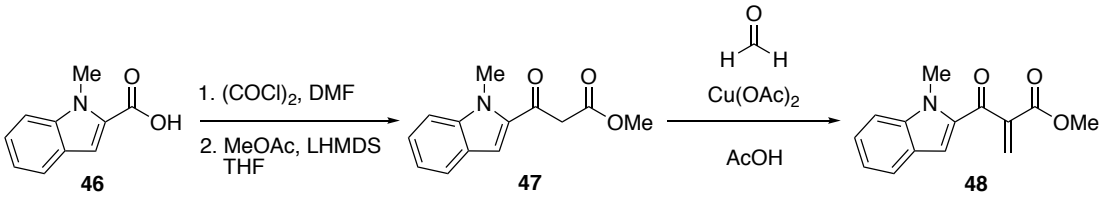
Given the importance of the indole moiety, we attempted to extend the formal [5+2] cycloaddition chemistry to the synthesis of similar scaffolds such as the cyclohepta[*b*]indoles. This approach could potentially be applied to *C*-acylated indolyl alkylidene *β*-ketoester **44** with various substituted alkenes **41** to afford the synthesis of highly functionalized cyclohepta[*b*]indoles **45** (Scheme 3.10).



Scheme 3.10. Formal [5+2] Cycloaddition Approach to Cyclohepta[*b*]indole Synthesis

3.4.2 Model Substrate Synthesis

The alkylidene precursor, *C*-acylated indolyl alkylidene *β*-ketoester **48** was synthesized via a three-step sequence in which commercially available 1-methyl-1*H*-indole-2-carboxylic acid **46** was reacted with oxalyl chloride and catalytic DMF to form *N*-methyl indole-2-carbonyl chloride *in situ* (Scheme 3.11). A solution of enolate of methyl acetate was added to the acid chloride, forming *β*-ketoester **47**. Finally, this indole *β*-ketoester **47** underwent $Cu(OAc)_2$-catalyzed condensation with formaldehyde to afford alkylidene **48**.

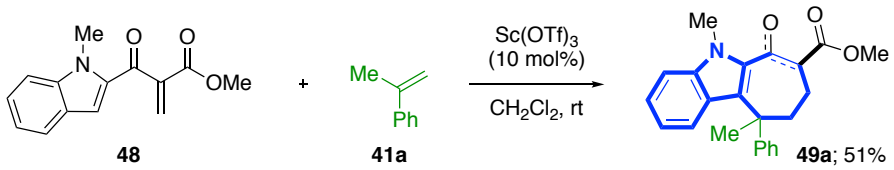


Scheme 3.11. Synthesis of Model *C*-acylated indolyl alkylidene *β*-ketoester **48**

3.4.3 Proof of Principle

Initially, we subjected alkylidene **48** and α-methyl styrene (5.0 equiv.) to the optimized Lewis acid (10 mol% of $Sc(OTf)_3$) used for the synthesis of azepino[1,2-*a*]indoles. This reaction led to the formation of a keto-enol mixture of

cyclohepta[*b*]indole **49** in 51% yield within 1 h (Scheme 3.12). This result proved that the formal [5+2] cycloaddition strategy can be applied to chemotypes other than the azepino[1,2-*a*]indole framework.



Scheme 3.12. Initial Test Reaction for the Synthesis of Cyclohepta[*b*]indoles

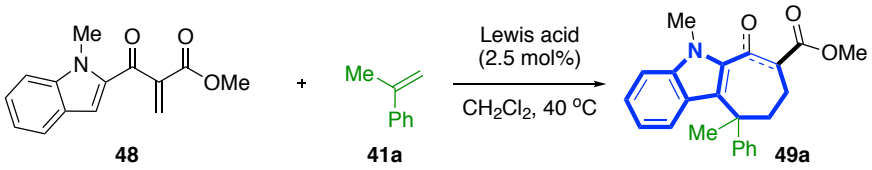
3.4.4 Reaction Optimization

The amount of the catalyst loading was decreased to 2.5 mol% and heated at reflux in CH_2Cl_2, giving to improved yield of 65% (Table 3.4, entry 1). This led to a screening of various oxophilic Lewis acids which would promote this formal [5+2] cycloaddition approach. Lewis acids such as $Al(OTf)_3$, $Hf(OTf)_4$ and $Yb(OTf)_3$ afforded keto-enol mixture of cyclohepta[*b*]indole **49a** in yields above 50% (entries 2-4). Interestingly, a 1:1 mole ratio of $Ca(NTf_2)_2$:(n-Bu_4N)(PF_6) provided the highest yield, 78% (entry 11). This catalytic system was developed by Leonori and co-workers[28], which presumably undergoes anion metathesis that results in the formation of $Ca(NTf_2)(PF_6)$, a complex with increased Lewis acidity and the availability of two binding sites, suitable for a 1,3-dicarbonyl system (similar to **48**) to chelate to the metal center and be activated.[29]

The importance of the combination of both $Ca(NTf_2)_2$ and (n-Bu_4N)(PF_6) was justified after subjected them separately to alkylidene **48** and alkene **41a** where no reactivity was observed (entries 12 and 13). Efforts to optimize temperature and reaction

concentration did not lead to any improvement in yield. Therefore, the optimized conditions for this transformation was 2.5 mol% of $Ca(NTf_2)_2$ and 2.5 mol% of additive, (n-Bu_4N)(PF_6) in CH_2Cl_2 with 5.0 equiv. of alkenes. The success of developing a Ca^{2+}-catalyzed transformation has many advantages: (1) low cost, (2) low toxicity, and (3) ease of disposal, rendering a sustainable and non-expensive catalytic protocol.[28]

Table 3.4. Lewis Acid Screening for Cyclohepta[*b*]indole Synthesis

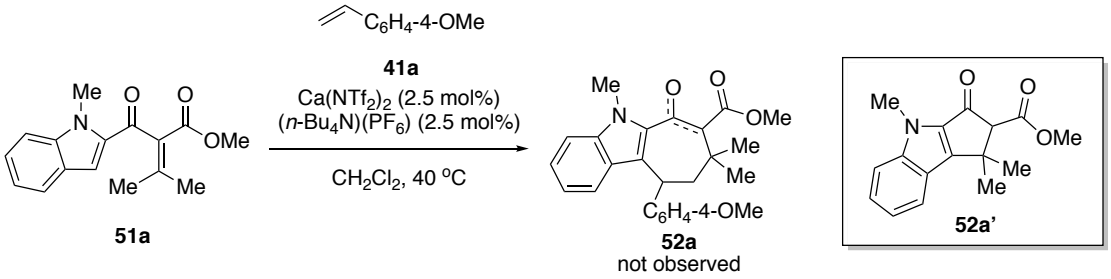


Entry	Lewis acid	Time (h)	Yield (%)
1	$Sc(OTf)_3$	1	65
2	$Al(OTf)_3$	1	73
3	$Hf(OTf)_4$	0.5	73
4	$Yb(OTf)_3$	1	51
5	$Cu(OTf)_2$	0.5	44
6	$In(OTf)_3$	1	43
7	$La(OTf)_3$	1	33
8	$Zn(OTf)_2$	1.5	31
9	$ZnBr_2$	1	42
10	$Mg(OTf)_2$	1	-
11	$Ca(NTf_2)_2$ (n-Bu_4N)(PF_6)	0.5	78
12	$Ca(NTf_2)_2$	24	-
13	(n-Bu_4N)(PF_6)	24	-

3.4.5 Examination of Substrate Scope

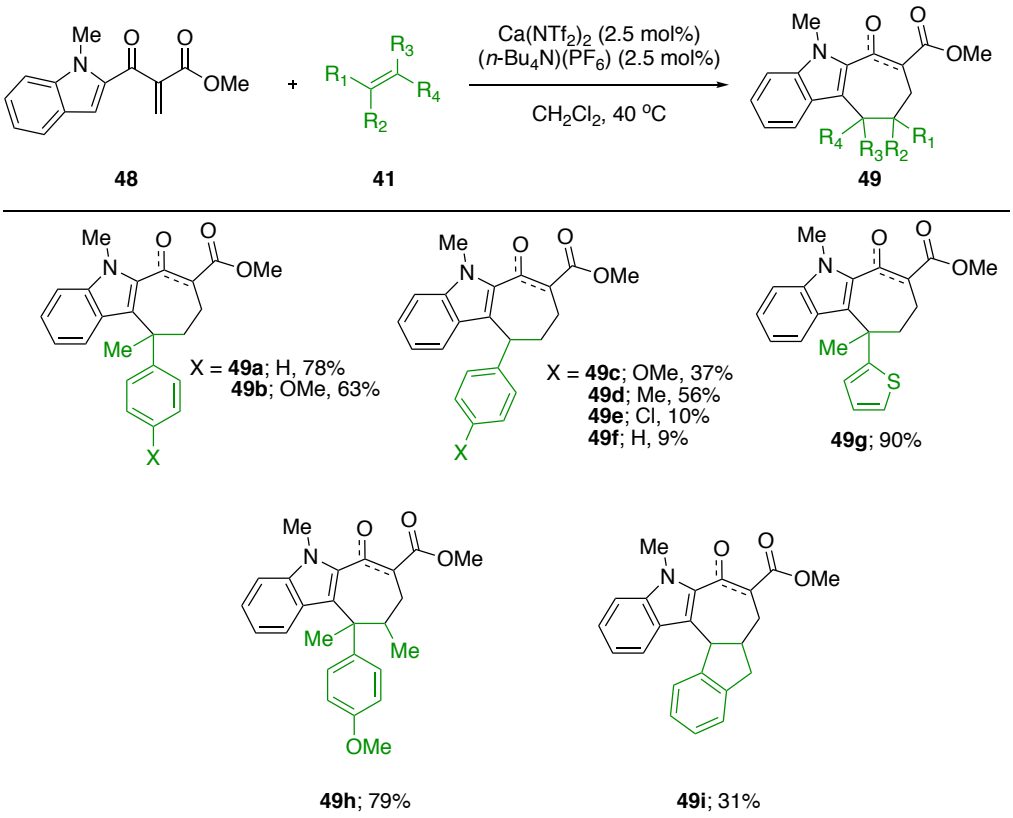
The scope of this transformation was investigated by first studying different substituted alkenes **41** (Table 3.5). *Para*-Substituted styrenes gave cyclohepta[*b*]indoles **49c** to **49f** in poor yields due to significant degradation and polymerization of the styrenes under the optimized conditions. 1,1-substituted alkenes were revealed to work better for this transformation leading to the desired cyclohepta[*b*]indoles **49a**, **49b**, and **49g** in 78%, 63% and 90% yield. Possibly the 1,1-disubstitution provides better stabilization for the initial carbocation generated during the transformation. In addition, the tri-substituted alkene **41h** led to the formation of the cyclohepta[*b*]indole **49h** in 79% yield. Finally, indene provided with an interesting polycyclic cyclohepta[*b*]indole **49i** in 31% yield, which underwent decarboxylation (**50i**) for structural confirmation. Further investigation of the scope is under progress involving other alkenes bearing heteroatoms and finding an alternative Lewis acid for mono-substituted styrenes in an attempt to reduce degradation, hence improving the yields.

However, when alkyl substituents were placed on the alkylidene, no desired cyclohepta[*b*]indole product was obtained. **51a** was subjected to the optimized Ca^{2+} optimized conditions, no desired reactivity was observed. Instead the Nazarov cyclization occurred leading to the five-membered ring fused indole **52a'** in high yield (Scheme 3.13).



Scheme 3.13. Effect of alkyl substituent on alkylidene **51a**

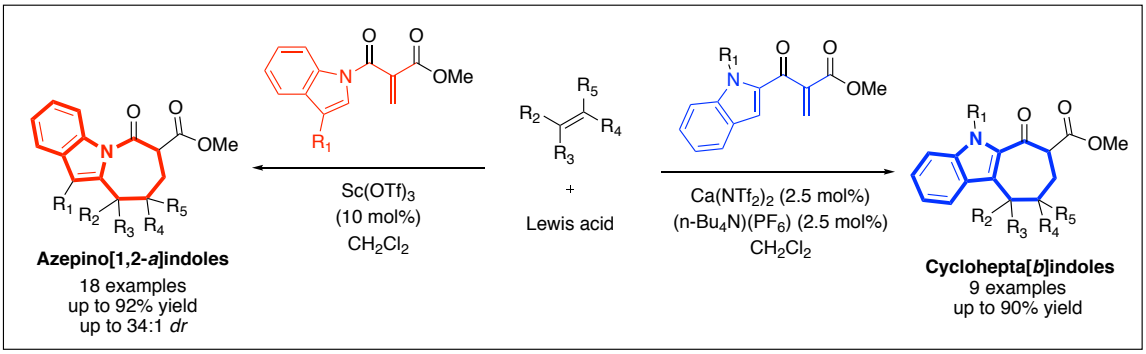
Table 3.5. Scope for Cyclohepta[*b*]indole Synthesis



3.5 Summary

We described in this chapter a formal [5+2] cycloaddition strategy (Scheme 3.13), accessing the azepino[1,2-*a*]indole and cyclohepta[*b*]indole scaffold found in many natural product targets with prominent bioactive properties. Indole-based alkylidenes **40**

or **48** react with alkenes in the presence of appropriate catalytic amount of Lewis acid affording the desired indole-fused 7-membered rings. Variations in the alkylidenes and alkenes have shown to provide a wide breadth of scope under mild conditions, thus offering highly functionalized azepino[1,2-*a*]indole and cyclohepta[*b*]indole scaffolds. Interestingly, we have also demonstrated the first examples of Lewis acid catalyzed intramolecular ring-opening cyclizations of D-A cyclobutanes **38** and **38n**. To date, these approaches represent the most efficient routes to functionalized azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles.



Scheme 3.13. Formal [5+2] Cycloaddition Approach

3.6 Experimental Section

3.6.1 Azepino[1,2-*a*]indoles:

For the formal [5+2] cycloaddition approach towards Azepino[1,2-*a*]indoles, the experimental section and characterization can be found in the supporting information of article: Shenje, R.; Martin, M. C.; France, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13907.

3.6.2 Cyclohepta[*b*]indoles:

3.6.2.1 General Methods

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished when exposed to 254nm UV light.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbitThermoelectronic Corp and by attenuated total reflection (ATR) through a diamond plate on a Bruker Optics Alpha-P FTIR spectrometer. The IR bands are characterized as weak (w), medium (m), and strong (s). 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 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. Mass spectra were obtained MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

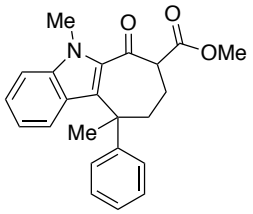
Yields refer to isolated yields of analytically pure material unless otherwise noted.

All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and Diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-dichloroethane and dichloromethane was purified by distillation from calcium hydride under N_2 prior to use. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted. Description of the experimental section and characterization of alkylidene **48** and cyclohepta[*b*]indole **49c** can be found in the supporting information of article: Shenje, R.; Martin, M. C.; France, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13907.

3.6.2.2 Experimental Procedures:

General procedure for the synthesis of cyclohepta[b]indoles **49**: To a round bottom flask charged with $Ca(NTf_2)_2$ (2.5 mol%) and (n-Bu_4N)(PF_6) (2.5 mol%) in CH_2Cl_2 at 40 °C and a magnetic stir bar was added a solution of alkylidene **48** (1.0 equiv.) and alkene **41** (5.0 equiv.) in CH_2Cl_2 (0.10 M). After complete consumption of the alkylidene, the reaction mixture was concentrated under reduced pressure and purified by silica gel flash chromatography eluting with EtOAc:Hexanes.

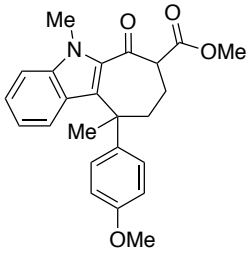
Synthesis of cyclohepta[*b*]indole 49a:



49a

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), *α*-methylstyrene **41a** (0.23 mL, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 30 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.386) afforded **49a** as a colorless oil keto-enol mixture (98.7 mg, 78 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.45 (s, 0.22), 7.41 - 7.15 (m, 18.67), 7.00 - 6.83 (m, 3.36), 4.02 (s, 0.73), 3.98 - 3.91 (m, 1.83), 3.90 (d, J = 3.7 Hz, 5.82), 3.87 - 3.85 (m, 1.05), 3.79 (s, 2.69), 3.74 (s, 3.00), 2.41 - 2.02 (m, 11.41), 1.89 (s, 2.88). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 193.8, 193.5, 170.9, 147.8, 139.8, 134.2, 128.9, 128.3, 128.2, 128.1, 127.9, 127.3, 126.5, 126.3, 126.1, 126.0, 125.6, 125.4, 125.2, 125.1, 124.3, 124.1, 123.9, 123.9, 123.5, 119.7, 119.5, 118.9, 110.3, 109.9, 60.3, 59.9, 52.3, 51.9, 47.4, 45.1, 43.8, 42.7, 33.8, 31.8, 31.7, 29.5, 28.4, 22.2, 21.3, 19.1.

Synthesis of cyclohepta[*b*]indole 49b:



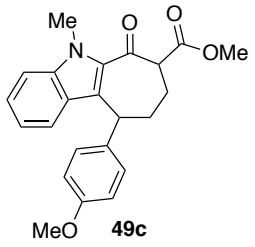
49b

The general procedure was followed using alkylidene **48** (84 mg, 0.345 mmol), *α*-methyl-*para*methoxy styrene **41b** (256 mg, 1.73 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 15 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.386) afforded **49b** as a colorless oil

keto-enol mixture (84.7 mg, 63 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.44 (s, 0.17), 7.38 - 7.34 (m, 2.14), 7.32 - 7.27 (m, 2.10), 7.25 - 7.21 (m, 2.51), 7.20 - 7.17 (m, 1.28), 7.16 - 7.12 (m, 1.98), 7.00 - 6.87 (m, 3.47), 6.84 - 6.80 (m, 2.18), 6.80 - 6.75 (m, 2.35), 3.99 (s, 0.55), 3.93 (dd, J = 7.0, 10.4 Hz, 1.14), 3.90 - 3.86 (m, 7.18), 3.83 (s, 0.55), 3.79 (s, 3.07), 3.76 (d, J = 3.4 Hz, 6.20), 3.71 (s, 3.00), 2.36 - 2.26 (m, 1.26), 2.25 - 2.07 (m, 5.05), 2.06 - 1.99 (m, 2.27), 1.97 (s, 3.08), 1.92 (s, 0.59), 1.84 - 1.82 (m, 3.10).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.9, 193.5, 170.9, 170.8, 157.7, 157.6, 140.5, 139.8, 139.6, 134.0, 134.0, 129.2, 128.9, 128.4, 127.8, 127.6, 125.3, 125.2, 125.2, 125.1, 124.2, 123.9, 123.6, 119.7, 119.5, 118.9, 113.5, 113.3, 113.2, 110.3, 60.3, 59.9, 55.1, 55.0, 52.3, 51.9, 44.5, 44.4, 43.9, 42.7, 31.8, 31.7, 29.8, 29.6, 28.6, 22.2, 21.2.

Synthesis of cyclohepta[*b*]indole 49c:

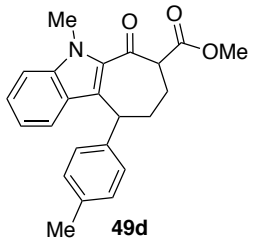


49c

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), *para*methoxy styrene **41c** (0.25 mL, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-$Bu_4N)(PF_6)$ (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 15 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, Rf = 0.407) afforded **49c** as a yellow oil keto-enol mixture (48.3 mg, 37 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.34 (s, 0.15), 7.41 - 7.29 (m, 4.33), 7.14 (d, J = 8.2 Hz, 0.51), 7.11 - 7.07 (m, 0.54), 7.07 - 6.99

(m, 4.09), 6.98 - 6.90 (m, 0.78), 6.83 - 6.75 (m, 3.56), 4.81 (dd, J = 3.7, 6.4 Hz, 0.97), 4.78 - 4.74 (m, 0.49), 4.63 (t, J = 8.7 Hz, 0.17), 3.99 (s, 0.51), 3.98 - 3.96 (m, 3.03), 3.94 (s, 1.76), 3.88 - 3.83 (m, 1.58), 3.79 (s, 1.52), 3.77 - 3.74 (m, 5.13), 3.71 (d, J = 6.7 Hz, 3.00), 2.42 - 2.22 (m, 4.81), 2.14 - 2.07 (m, 0.91), 2.05 - 1.95 (m, 0.73).

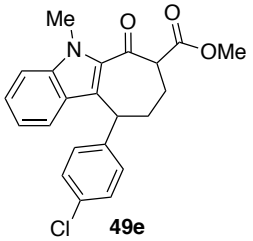
Synthesis of cyclohepta[*b*]indole 49d:



49d

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), *para*methyl styrene **41d** (0.23 mL, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-$Bu_4N)(PF_6)$ (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 30 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.425) afforded **49d** as a colorless oil keto-enol mixture (70.3 mg, 56 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.35 (s, 0.30), 7.41 - 7.29 (m, 8.53), 7.09 - 6.90 (m, 18.12), 4.83 (dd, J = 3.8, 6.6 Hz, 2.03), 4.79 - 4.76 (m, 0.89), 4.65 (t, J = 8.7 Hz, 0.35), 3.97 (s, 5.54), 3.94 (s, 2.65), 3.86 (dd, J = 6.1, 9.5 Hz, 2.21), 3.79 (s, 2.76), 3.71 (s, 6.00), 2.43 - 2.22 (m, 22.18), 2.13 - 2.07 (m, 2.05), 2.07 - 2.05 (m, 3.70).

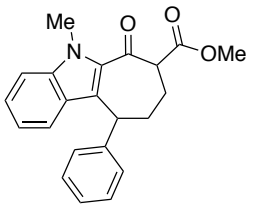
Synthesis of cyclohepta[*b*]indole 49e:



49e

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), *para*chloro styrene **41e** (0.25 mL, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 30 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, Rf = 0.400) afforded **49e** as a colorless oil keto-enol mixture (20 mg, 10 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.33 (s, 0.18), 7.43 - 7.29 (m, 7.67), 7.25 - 7.18 (m, 4.91), 7.11 - 7.01 (m, 6.51), 7.01 - 6.92 (m, 1.68), 4.83 - 4.75 (m, 2.00), 4.69 - 4.62 (m, 0.36), 4.00 - 3.97 (m, 1.27), 3.97 - 3.94 (m, 4.40), 3.93 (s, 2.62), 3.79 - 3.77 (m, 2.45), 3.71 (s, 4.12), 2.39 - 2.29 (m, 4.53), 2.29 - 2.21 (m, 1.58), 2.12 - 1.99 (m, 2.23).

Synthesis of cyclohepta[*b*]indole 49f:

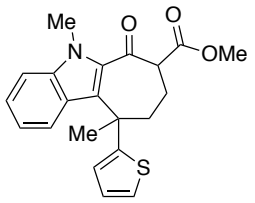


49f

The general procedure was followed using alkylidene **48** (100 mg, 0.411 mmol), styrene **41f** (0.24 mL, 2.06 mmol), $Ca(NTf_2)_2$ (6.2 mg, 0.010 mmol), (n-Bu_4N)(PF_6) (4.0 mg, 0.010) and CH_2Cl_2 (4.11 mL) at 40 °C. After 1.5 h, the reaction was allowed to cool to

room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.480) afforded **49f** as a colorless oil keto-enol mixture (13.1 mg, 9 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.33 (s, 0.13), 7.39 - 7.37 (m, 1.91), 7.36 (q, J = 1.4 Hz, 1.17), 7.34 - 7.30 (m, 1.36), 7.24 - 7.22 (m, 1.53), 7.22 - 7.15 (m, 2.53), 7.14 - 7.09 (m, 3.36), 7.08 - 7.00 (m, 1.60), 6.97 - 6.90 (m, 0.70), 4.88 - 4.83 (m, 1.00), 4.80 (t, J = 4.9 Hz, 0.50), 4.68 (t, J = 8.9 Hz, 0.24), 4.00 - 3.95 (m, 4.03), 3.94 (s, 1.58), 3.83 (s, 1.00), 3.79 - 3.76 (m, 1.54), 3.71 (s, 3.20), 2.45 - 2.19 (m, 5.13), 2.15 - 1.97 (m, 2.01).

Synthesis of cyclohepta[*b*]indole 49g:

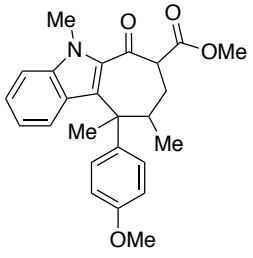


49g

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), styrene **41g** (0.19 mg, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.3 mg, 0.009) and CH_2Cl_2 (3.49 mL) at 40 °C. After 3 h, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.480) afforded **49g** as a colorless oil keto-enol mixture (115.9 mg, 90 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.95 - 7.85 (m, 12.71), 7.75 - 7.70 (m, 3.52), 7.59 - 7.50 (m, 9.35), 7.41 (dd, J = 0.8, 8.3 Hz, 3.73), 7.31 (dt, J = 1.4, 7.6 Hz, 3.37), 7.21 - 7.15 (m, 3.84), 6.78 (d, J = 0.8 Hz, 2.92), 3.75 (s, 9.16), 3.47 (s, 9.23), 2.69 - 2.59 (m, 3.18), 2.52 (td, J = 5.6, 13.6 Hz, 3.16), 2.45 - 2.35 (m, 3.35), 2.21 (ddd, J = 5.8,

8.5, 13.9 Hz, 3.25), 1.78 (s, 9.00). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 167.5, 153.4, 141.8, 137.2, 135.4, 133.1, 132.4, 128.4, 128.1, 127.4, 127.2, 126.7, 126.2, 126.0, 123.3, 122.7, 122.1, 121.2, 119.6, 109.5, 107.6, 102.4, 80.5, 52.5, 51.3, 31.9, 30.5, 29.65, 28.7, 20.4.

Synthesis of cyclohepta[*b*]indole 49h:

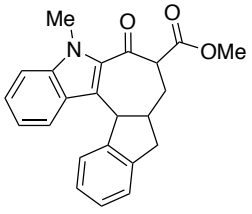


49h

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), alkene **41h** (283 mg, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.4 mg, 0.009) and CH_2Cl_2 (3.5 mL) at 40 °C. After 30 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, Rf = 0.325) afforded **49h** as a colorless oil keto-enol mixture (111.6 mg, 79 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 13.36 (s, 0.20), 7.32 - 7.27 (m, 1.84), 7.27 - 7.16 (m, 2.76), 7.14 - 7.08 (m, 2.88), 6.87 - 6.78 (m, 2.68), 6.77 - 6.71 (m, 3.49), 3.99 - 3.94 (m, 1.76), 3.85 (s, 2.40), 3.83 (s, 2.84), 3.81 (s, 1.79), 3.75 (s, 1.73), 3.73 (d, J = 6.4 Hz, 6.72), 2.66 - 2.52 (m, 1.27), 2.52 - 2.46 (m, 0.78), 2.35 - 2.28 (m, 0.57), 2.25 - 2.19 (m, 0.56), 2.17 - 2.10 (m, 1.18), 1.99 - 1.93 (m, 1.08), 1.92 (s, 3.00), 1.87 (s, 0.70), 1.83 (s, 1.72), 0.92 - 0.86 (m, 3.81), 0.79 (d, J = 6.7 Hz, 1.71). **^{13}C NMR** (126 MHz,

$CDCl_3$) δ = 193.8, 193.1, 173.2, 170.9, 170.8, 163.3, 157.4, 157.3, 141.2, 140.3, 139.9, 139.8, 139.0, 133.6, 133.5, 131.1, 130.8, 129.0, 127.9, 125.5, 125.0, 124.9,123.7, 123.6, 123.2, 119.6, 118.9, 113.1, 112.9, 110.1, 110.0, 109.8, 104.0, 59.8, 58.5, 54.9. 54.9, 52.3, 52.2, 51.9, 48.3, 47.6, 46.7, 46.3, 44.1, 42.8, 33.7, 31.6, 31.5, 30.0, 29.9, 26.8, 21.6, 19.3, 19.0, 17.8, 17.7, 16.9.

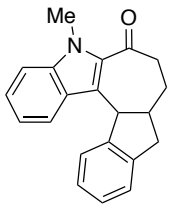
Synthesis of cyclohepta[*b*]indole 49i:



49i

The general procedure was followed using alkylidene **48** (85 mg, 0.349 mmol), indene **41i** (0.20 mL, 1.75 mmol), $Ca(NTf_2)_2$ (5.2 mg, 0.009 mmol), (n-Bu_4N)(PF_6) (3.4 mg, 0.009) and CH_2Cl_2 (3.5 mL) at 40 °C. After 1 h 15 min, the reaction was allowed to cool to room temperature, then concentrated under reduced pressure and column chromatography (25% EtOAc/hexane, *Rf* = 0.375) afforded **49i** as a yellow oil keto-enol mixture (38.8 mg, 31 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 13.33 (s, 0.27), 7.44 - 7.30 (m, 11.82), 7.25 - 7.19 (m, 7.00), 7.10 (d, J = 0.9 Hz, 1.46), 7.08 - 7.02 (m, 8.36), 7.01 - 6.93 (m, 2.56), 4.83 - 4.75 (m, 3.09), 4.69 - 4.62 (m, 0.53), 3.99 - 3.97 (m, 1.87), 3.95 (s, 6.30), 3.93 (s, 3.92), 3.84 - 3.83 (m, 2.10), 3.79 - 3.77 (m, 3.39), 3.71 (s, 6.00), 2.41 - 2.29 (m, 7.27), 2.28 - 2.21 (m, 2.42), 2.12 - 2.01 (m, 3.03).

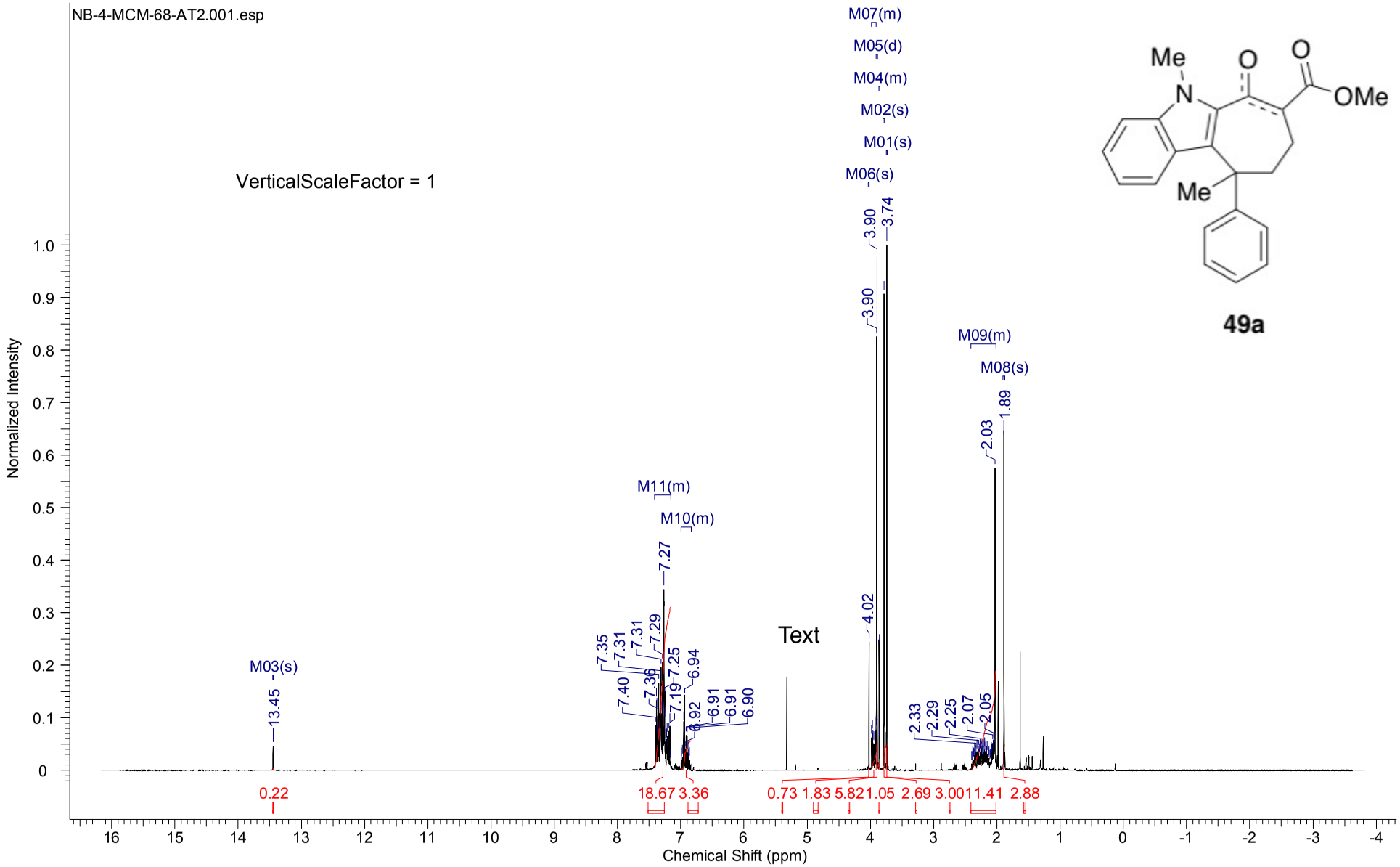
Synthesis of cyclohepta[*b*]indole 50i:



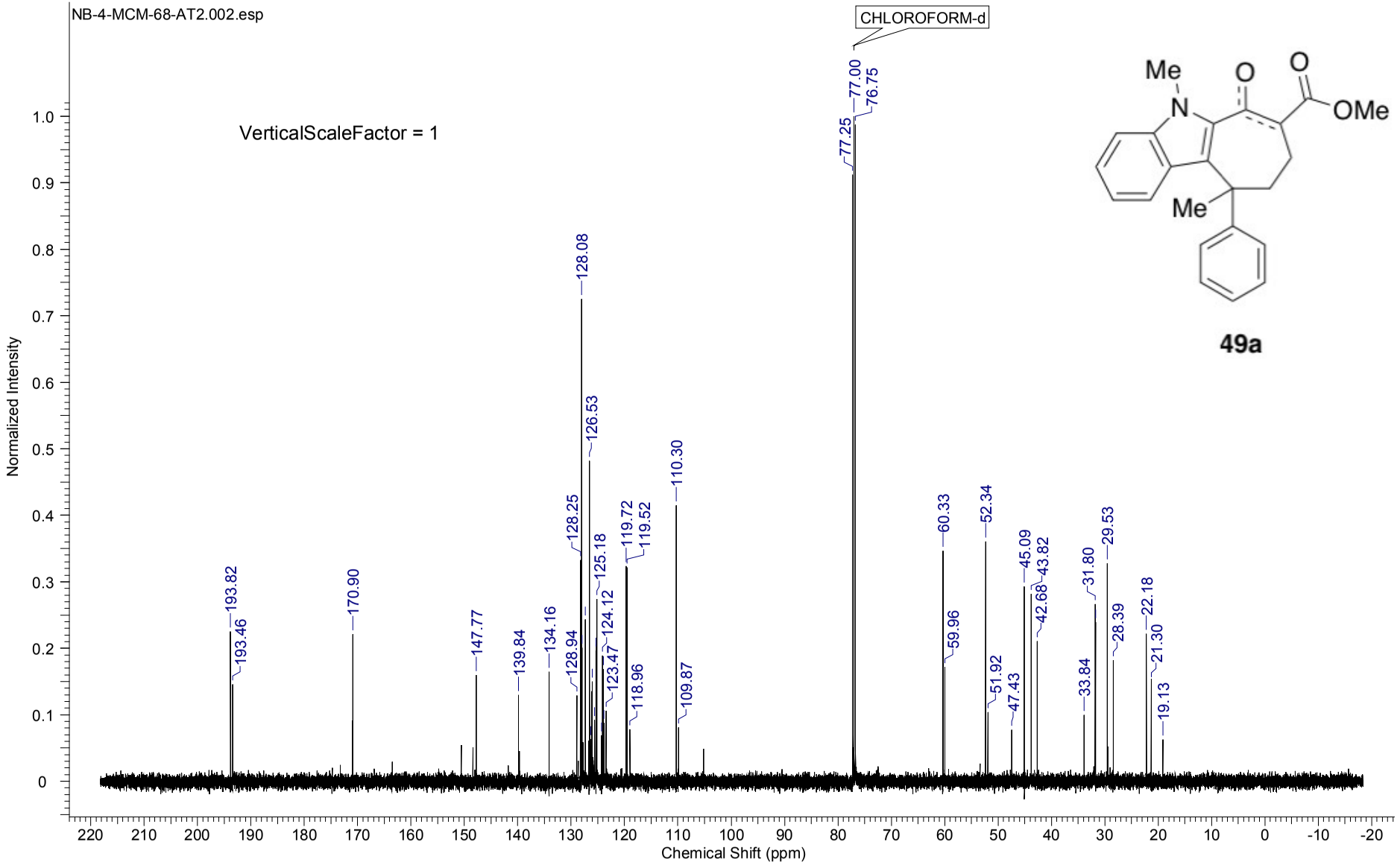
50i

To a round bottom flask charged with cyclohepta[*b*]indole **49i** (38.8 mg, 0.108 mmol) in DMSO (0.43 mL) and a magnetic stir bar was added sodium chloride (18.9 mg, 0.3237 mmol) in water (1.9 mL). After 2 h, the reaction mixture was concentrated under reduced pressure and purified by prep-TLC afforded **50i** as a colorless oil (11.3 mg, 35%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.2 Hz, 1 H), 7.47 - 7.43 (m, 2 H), 7.25 - 7.19 (m, 2 H), 7.14 - 7.09 (m, 1 H), 7.00 - 6.95 (m, 1 H), 6.53 (d, J = 7.3 Hz, 1 H), 5.25 (d, J = 8.2 Hz, 1 H), 4.03 (s, 3 H), 3.55 (dd, J = 8.4, 16.6 Hz, 1 H), 3.19 - 3.11 (m, 1 H), 2.90 (td, J = 1.0, 16.3 Hz, 1 H), 2.53 (dd, J = 7.9, 17.4 Hz, 1 H), 2.35 - 2.27 (m, 1 H), 2.12 - 2.04 (m, 1 H), 1.97 - 1.90 (m, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.4, 146.5, 142.5, 139.2, 131.9, 127.3, 126.8, 126.7, 123.9, 123.5, 120.6, 120.4, 110.3, 44.4, 39.8, 39.7, 39.3, 32.2, 29.8.

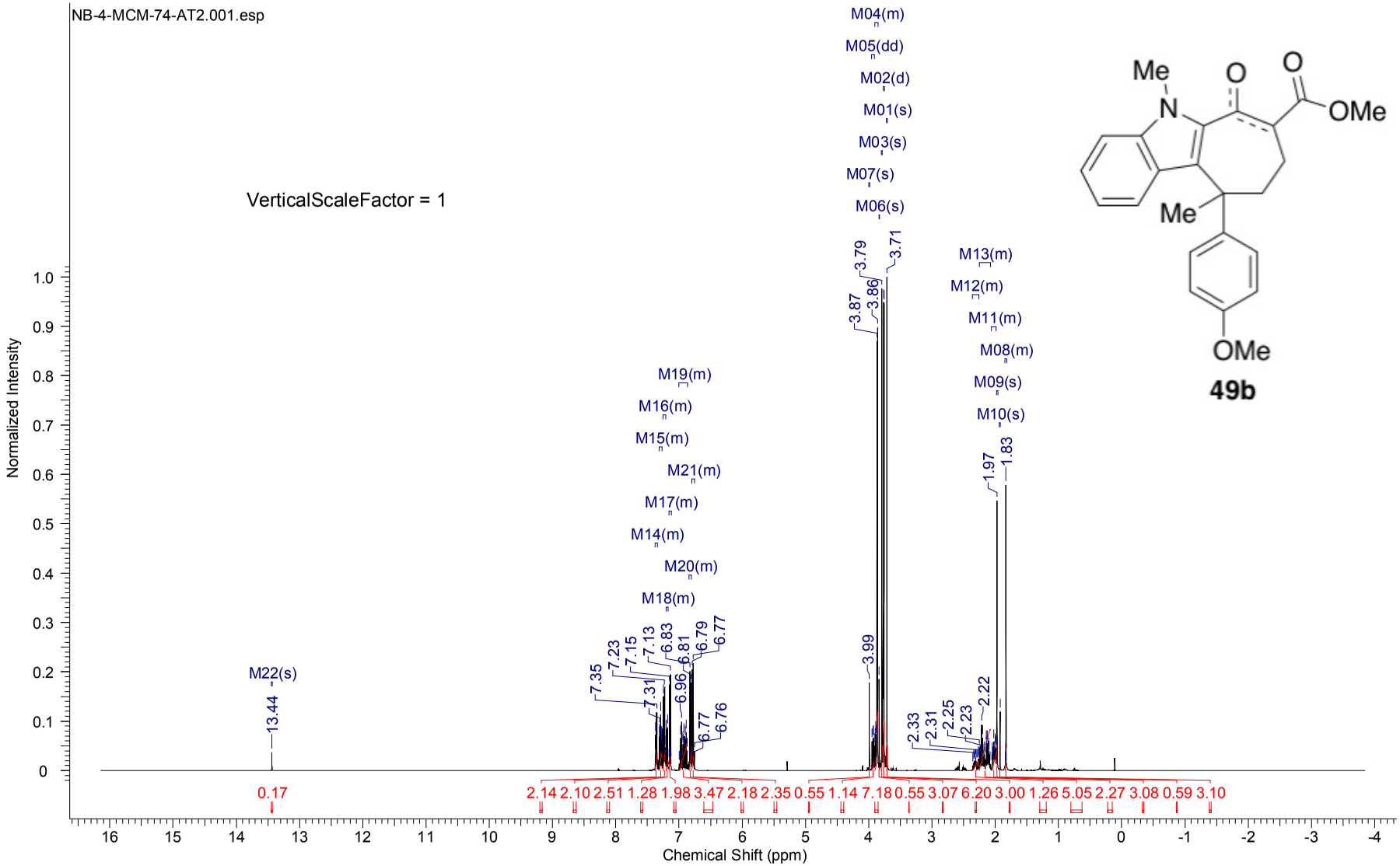
Acquisition Time (sec)	3.2768	***Comment***	NB-4-MCM-68-AT2			***Date***	11 Dec 2014 14:20:32
Date Stamp	11 Dec 2014 14:20:32			***File Name***	D:\Experimental section\C-acyl project\NB-4-MCM-68-AT2\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	46.70	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3089.3706	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.170



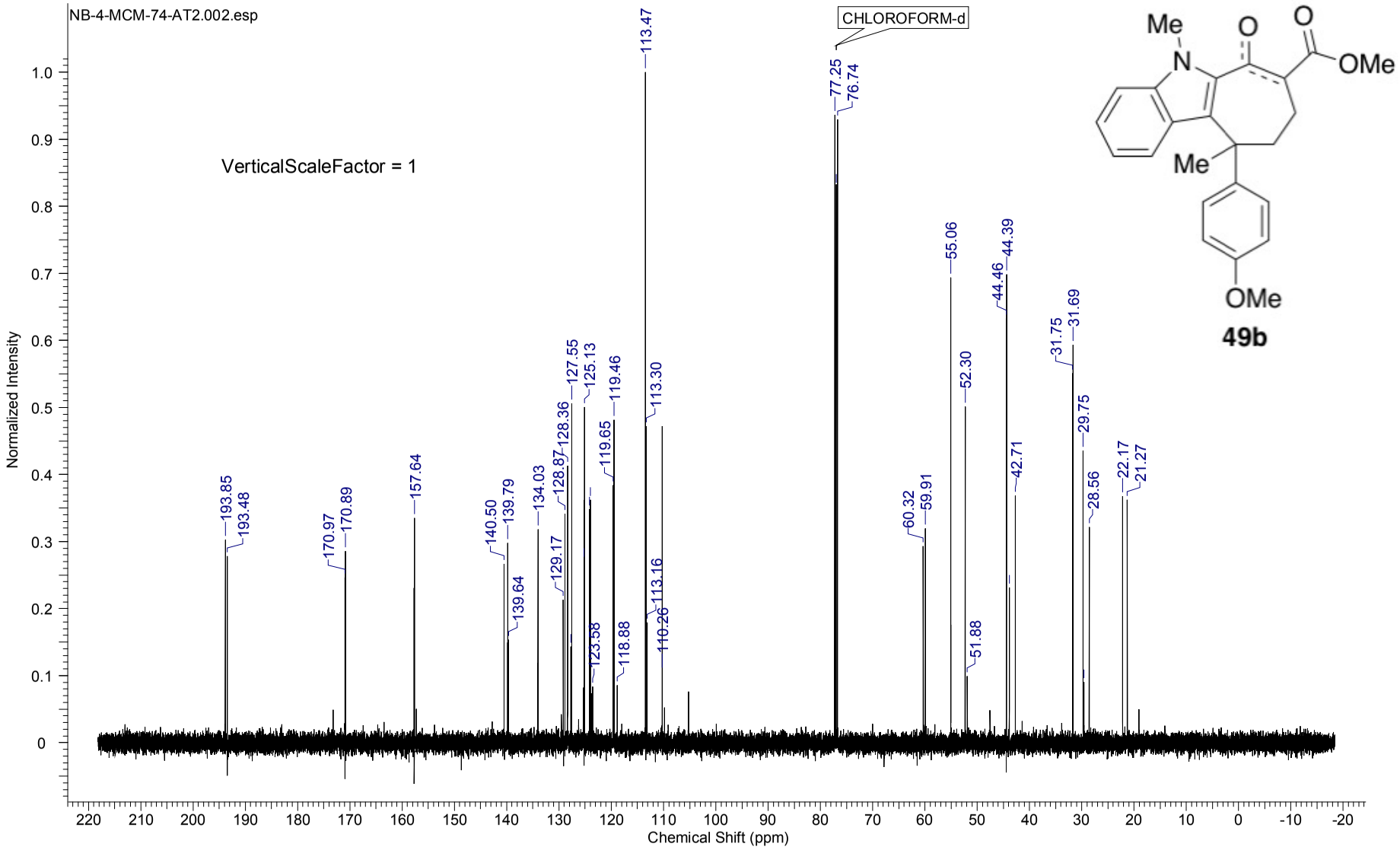
Acquisition Time (sec)	1.1010	***Comment***	NB-4-MCM-68-AT2			***Date***	11 Dec 2014 14:29:04
Date Stamp	11 Dec 2014 14:29:04			***File Name***	D:\Experimental section\C-acyl project\NB-4-MCM-68-AT2\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	208	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12568.4287	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	25.734



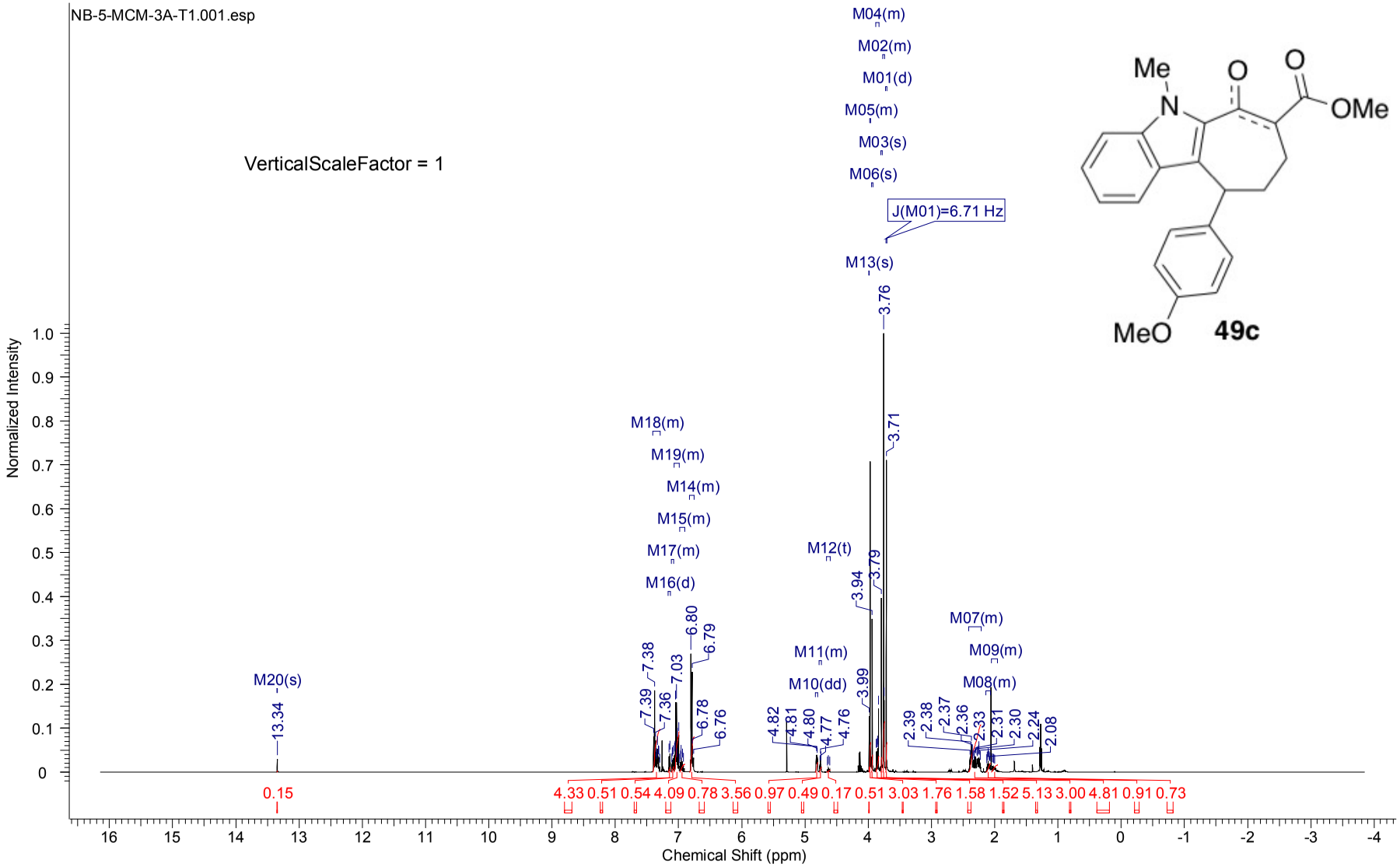
Acquisition Time (sec)	3.2768	***Comment***	NB-4-MCM-74-AT2			***Date***	07 Jan 2015 15:16:00
Date Stamp	07 Jan 2015 15:16:00			***File Name***	D:\Experimental_section\C-acyl project\NB-4-MCM-74-AT2\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	11	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3075.5791	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.029



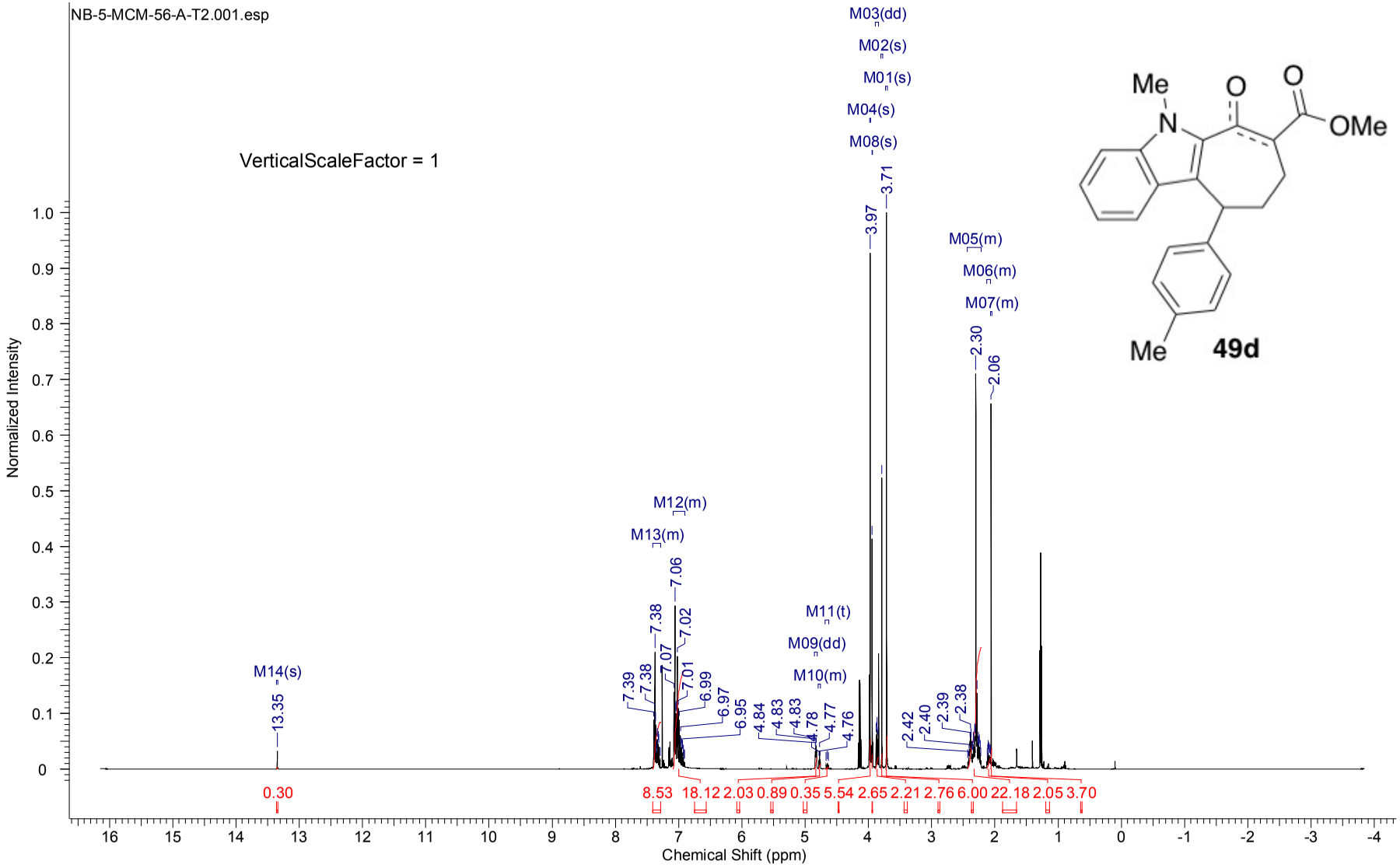
Acquisition Time (sec)	1.1010	***Comment***	NB-4-MCM-74-AT2			***Date***	07 Jan 2015 15:20:16
Date Stamp	07 Jan 2015 15:20:16			***File Name***	D:\Experimental section\C-acyl project\NB-4-MCM-74-AT2\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	81	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12562.9795	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	24.610



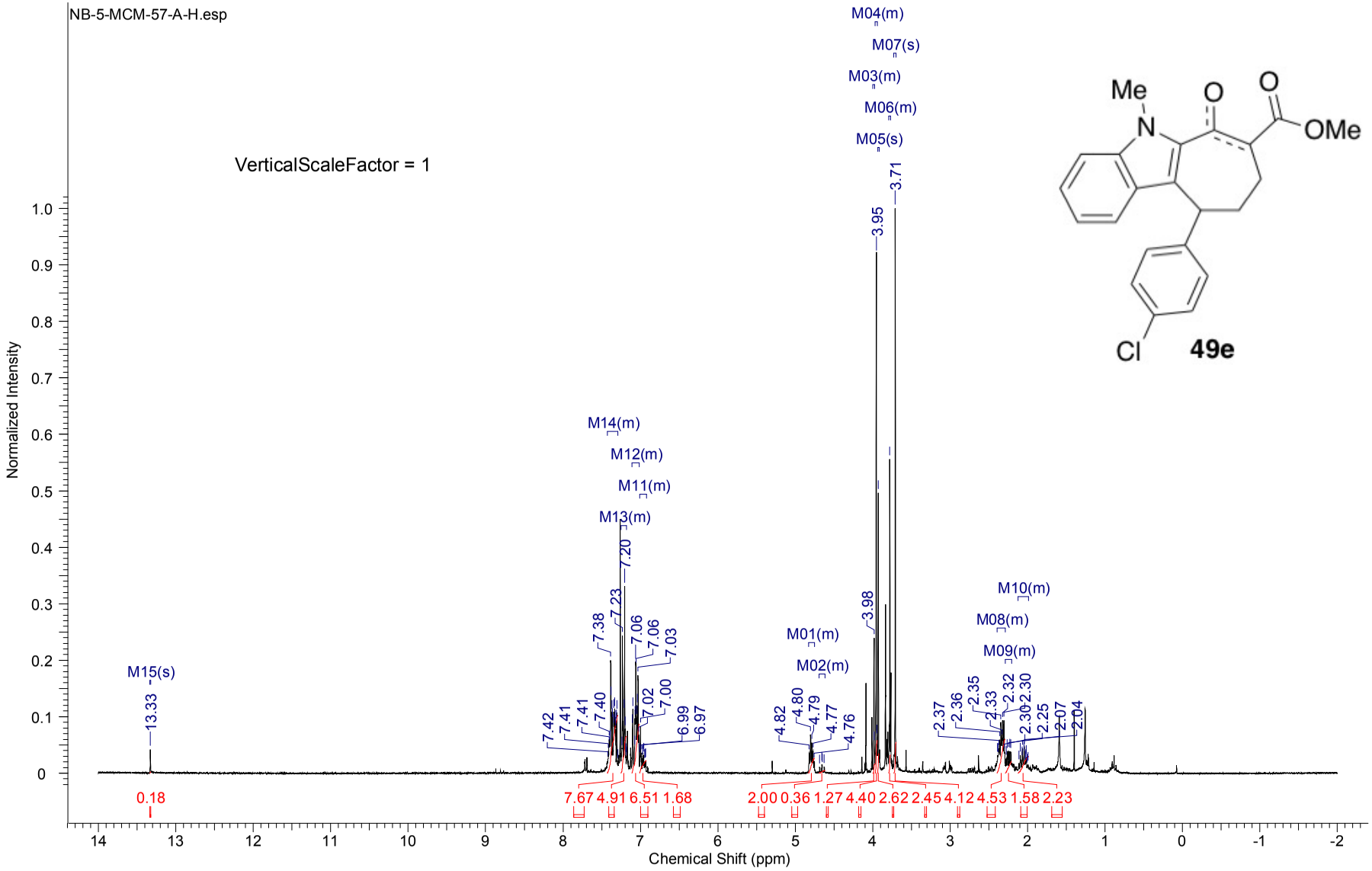
Acquisition Time (sec)	3.2768	***Comment***	NB-5-MCM-3A-T1			***Date***	09 Apr 2015 08:22:24
Date Stamp	09 Apr 2015 08:22:24			***File Name***	D:\Experimental section\C-acyl project\NB-5-MCM-3A-T1\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	105.59	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3075.2031	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	23.987



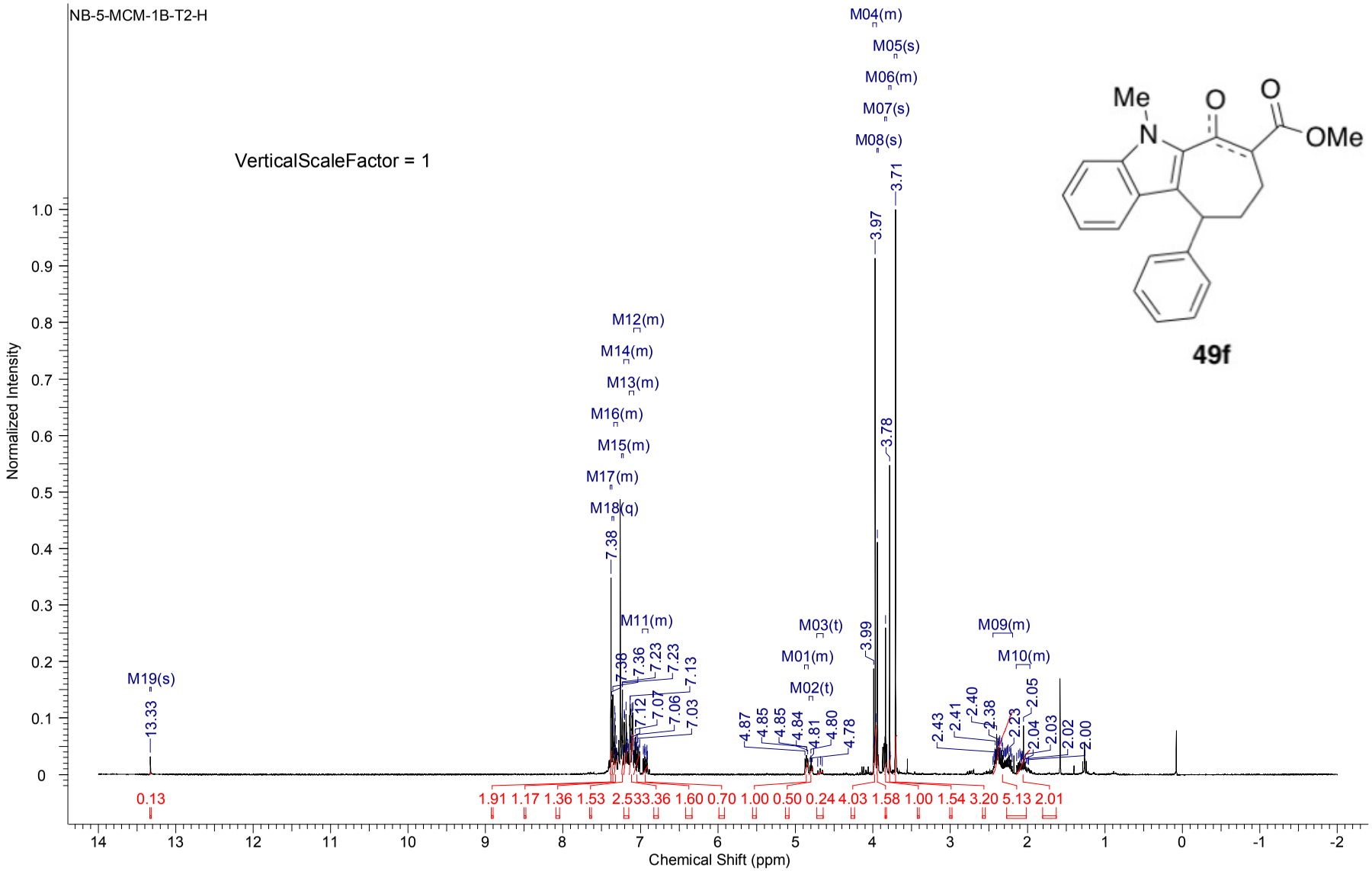
Acquisition Time (sec)	3.2768	***Comment***	NB-5-MCM-56-A-T2			***Date***	30 Oct 2015 08:30:56
Date Stamp	30 Oct 2015 08:30:56			***File Name***	D:\Experimental section\C-acyl project\NB-5-MCM-56-A-T2\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	29.88	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.5496	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	23.738



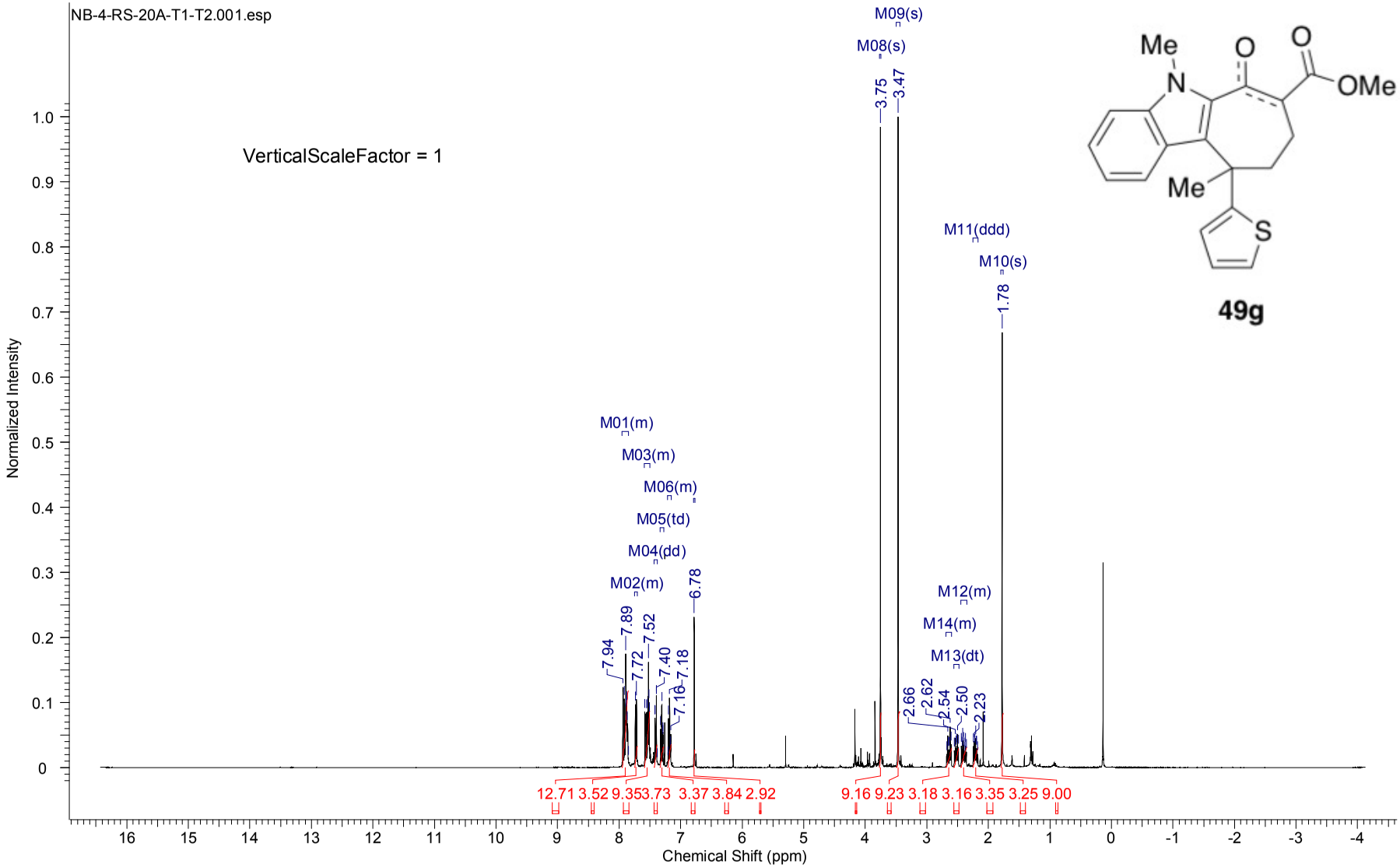
Acquisition Time (sec)	3.5504	***Comment***	WHite cap	***Date***	Nov 9 2015	***Date Stamp***	Nov 9 2015
File Name	D:\Experimental section\C-acyl project\NB-5-MCM-57-A-H.fid\fid					***Frequency (MHz)***	300.22
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	17053	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	1801.6582	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4803.07	***Temperature (degree C)***	AMBIENT TEMPERATURE



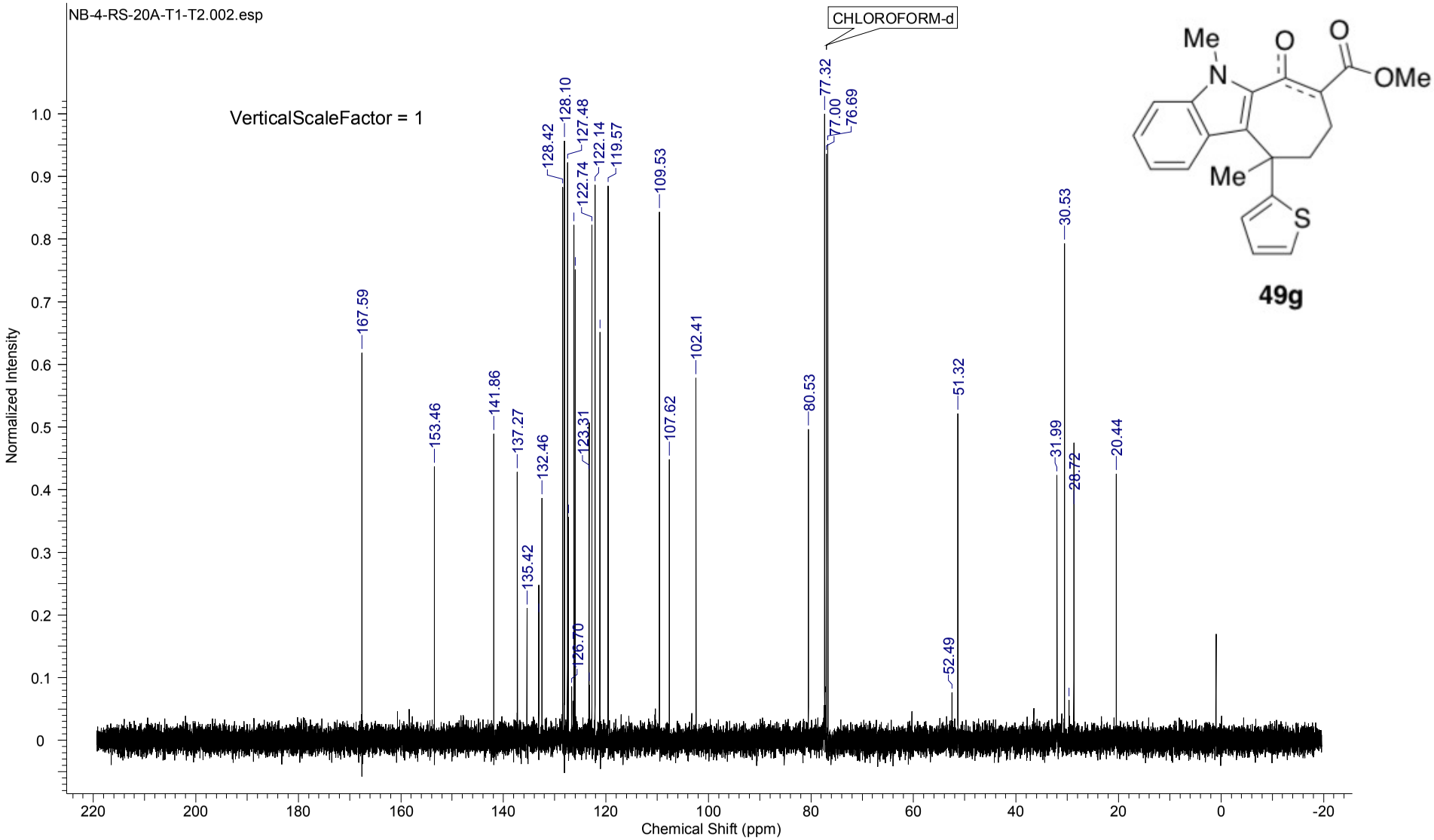
Acquisition Time (sec)	3.5504	***Comment***	white cap	***Date***	Apr 4 2015	***Date Stamp***	Apr 4 2015
File Name	D:\Experimental section\C-acyl project\NB-5-MCM-1B-T2-H.fid\fid					***Frequency (MHz)***	300.22
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	17053	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	1801.4688	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4803.07	***Temperature (degree C)***	AMBIENT TEMPERATURE



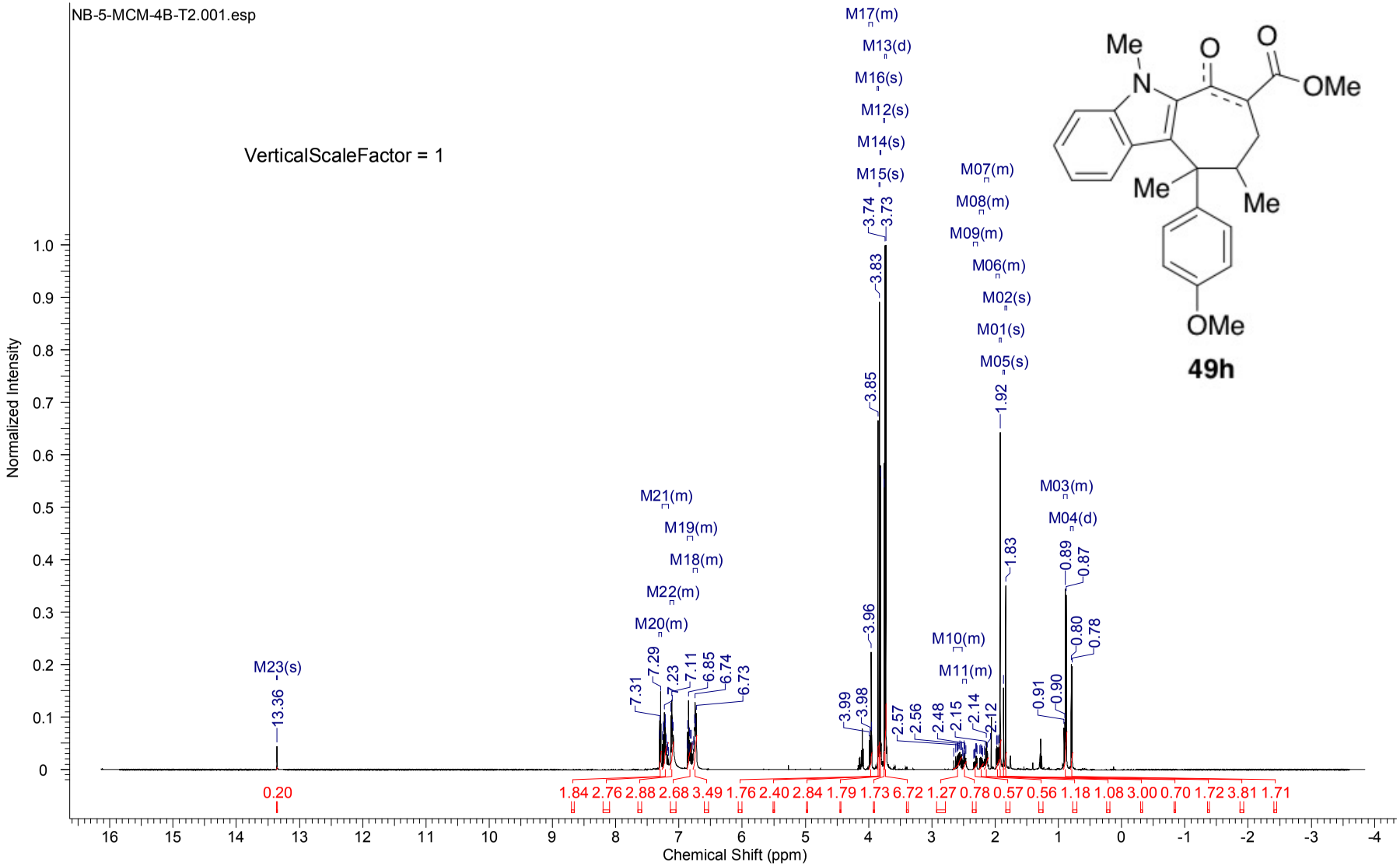
Acquisition Time (sec)	3.9846	***Comment***	NB-4-RS-20A-T1-T2-H			***Date***	01 Jun 2015 14:33:36
Date Stamp	01 Jun 2015 14:33:36			***File Name***	C:\Users\Cynthia\Desktop\NB-4-RS-20A-T1-T2\1\fid		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	shenje	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	60.80	***SW(cyclical) (Hz)***	8223.68	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2461.3599	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8223.43	***Temperature (degree C)***	21.305



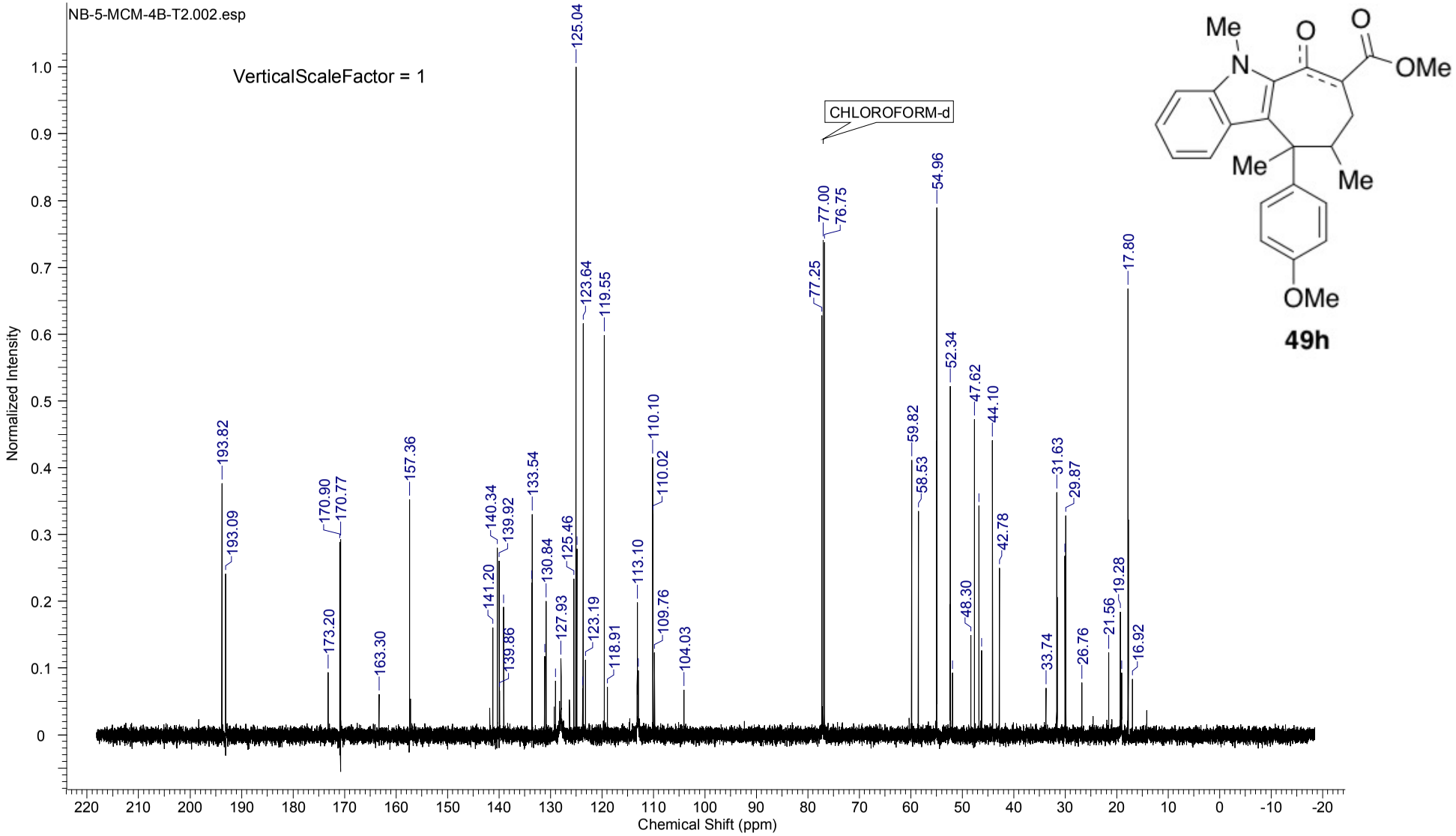
Acquisition Time (sec)	1.3631	***Comment***	NB-4-RS-20A-T1-T2-C			***Date***	01 Jun 2015 14:42:08
Date Stamp	01 Jun 2015 14:42:08			***File Name***	C:\Users\Cynthia\Desktop\NB-4-RS-20A-T1-T2\2\fid		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	159	***Origin***	spect
Original Points Count	32768	***Owner***	shenje	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	198.57	***SW(cyclical) (Hz)***	24038.46	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10047.3730	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24037.73	***Temperature (degree C)***	22.205



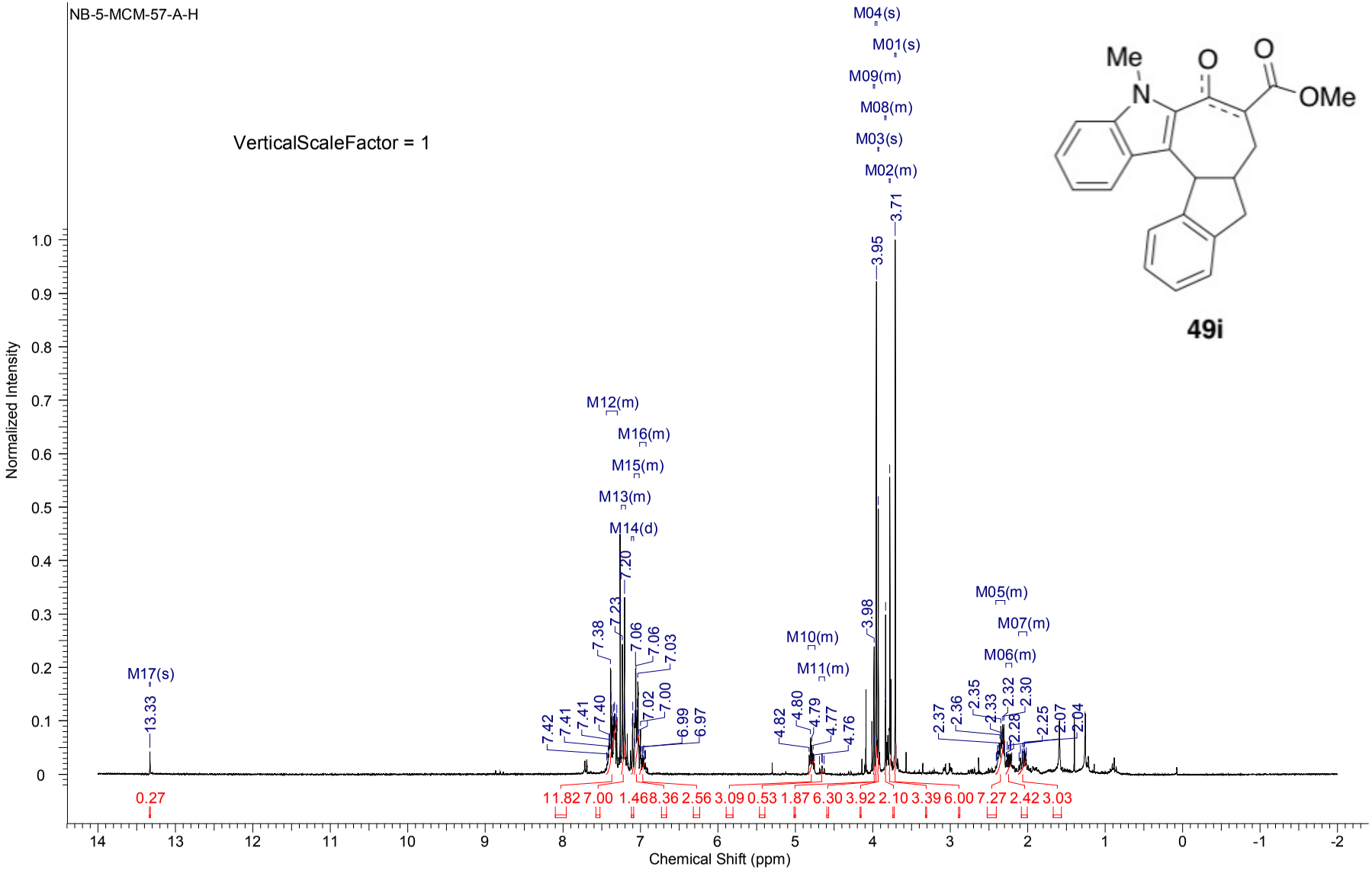
Acquisition Time (sec)	3.2768	***Comment***	NB-5-MCM-4B-T2			***Date***	09 Apr 2015 08:48:00
Date Stamp	09 Apr 2015 08:48:00			***File Name***	D:\Experimental section\C-acyl project\NB-5-MCM-4B-T2\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	54.49	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3074.9485	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	23.672



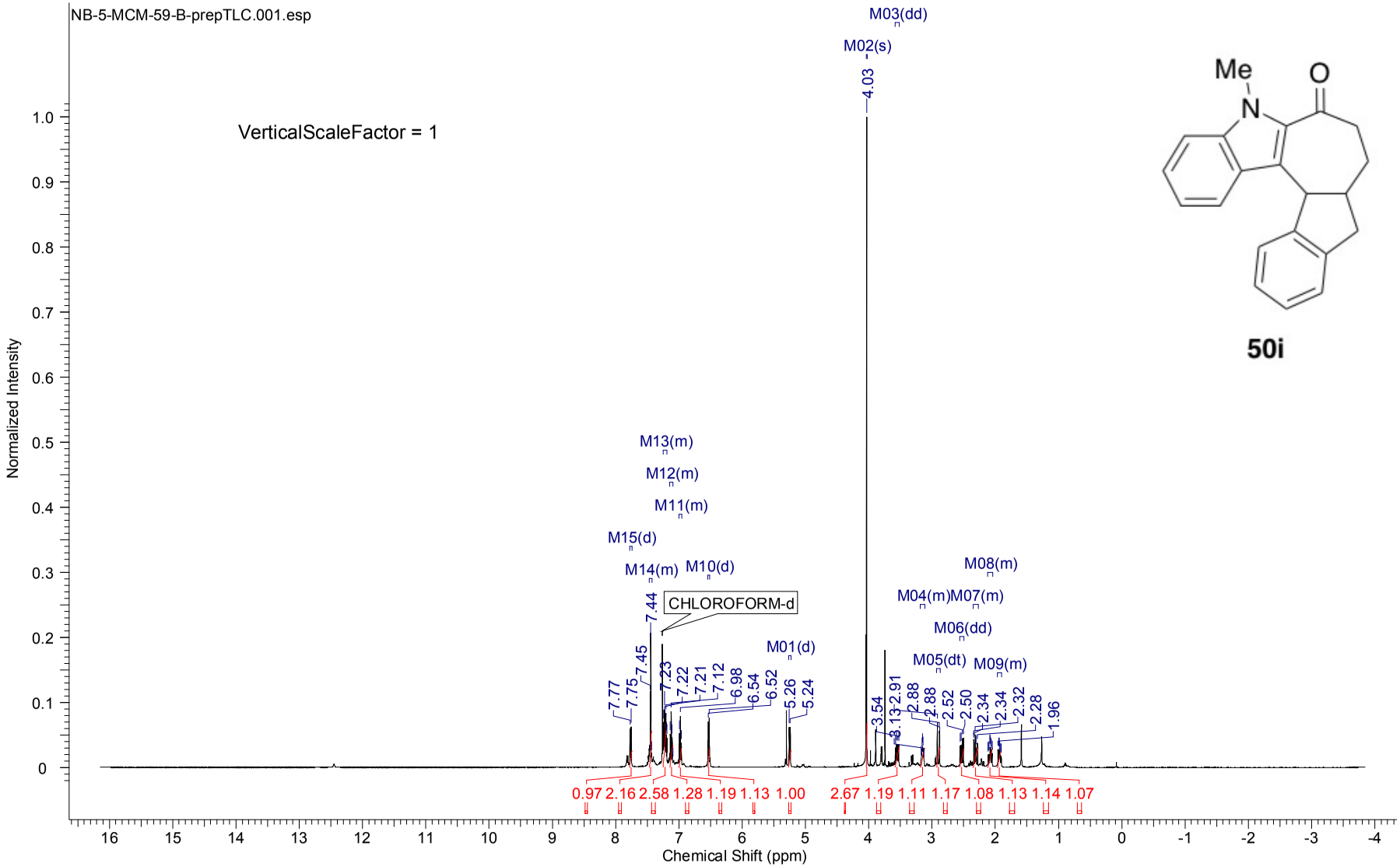
Acquisition Time (sec)	1.1010	***Comment***	NB-5-MCM-4B-T2			***Date***	09 Apr 2015 08:54:24
Date Stamp	09 Apr 2015 08:54:24			***File Name***	D:\Experimental	section\C-acyl project\NB-5-MCM-4B-T2\2\fid	
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	99	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12558.4375	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	23.883



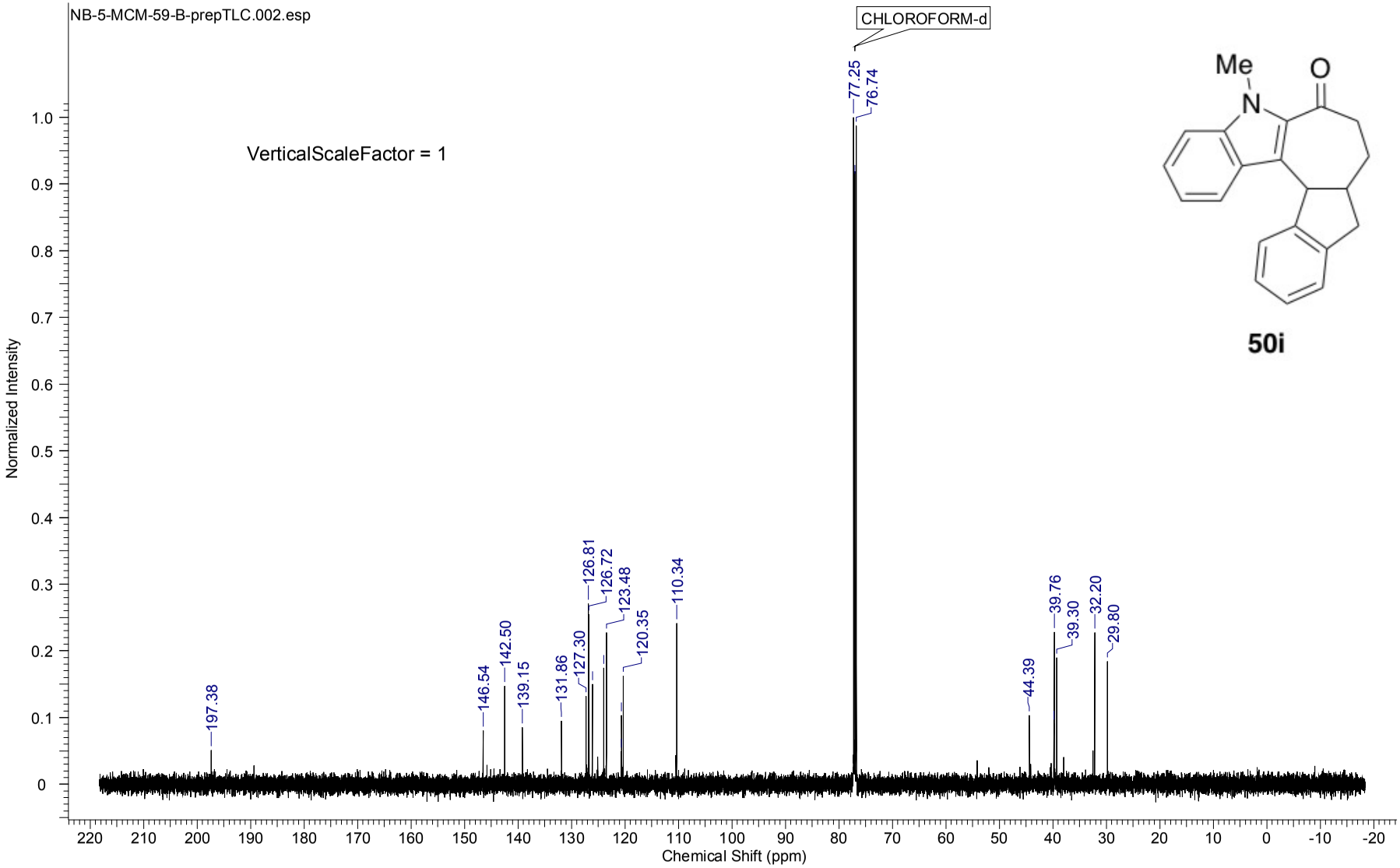
Acquisition Time (sec)	3.5504	***Comment***	WHite cap	***Date***	Nov 9 2015	***Date Stamp***	Nov 9 2015
File Name	D:\Experimental section\C-acyl project\NB-5-MCM-57-A-H.fid\fid					***Frequency (MHz)***	300.22
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	17053	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	1801.6582	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4803.07	***Temperature (degree C)***	AMBIENT TEMPERATURE



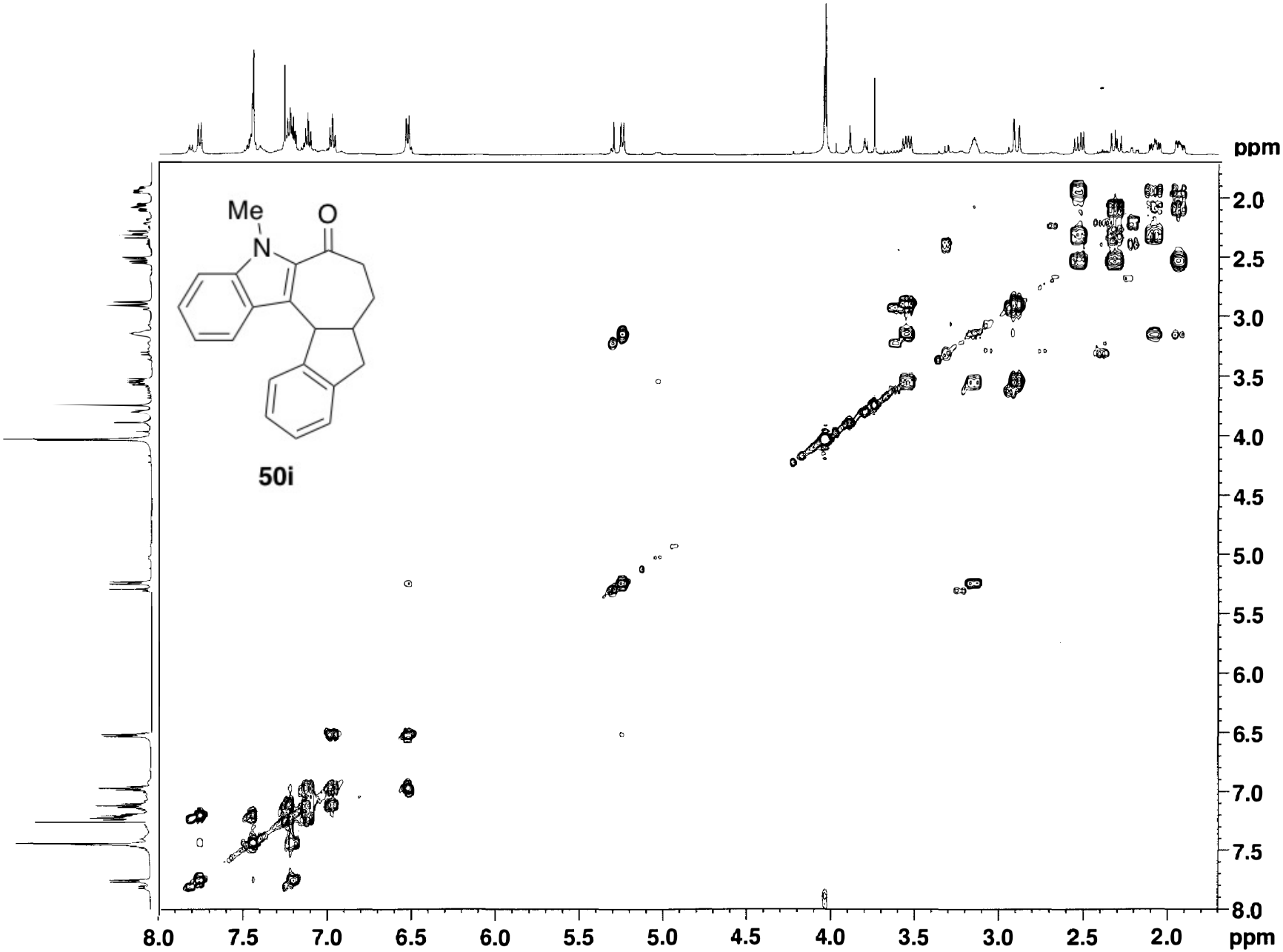
Acquisition Time (sec)	3.2768	***Comment***	NB-5-MCM-59-B-prepTLC			***Date***	19 Nov 2015 08:32:48
Date Stamp	19 Nov 2015 08:32:48			***File Name***	D:\Experimental section\C-acyl project\NB-5-MCM-59-B-prepTLC\1\fid		
Frequency (MHz)	500.27	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	92.31	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3076.6931	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	23.155



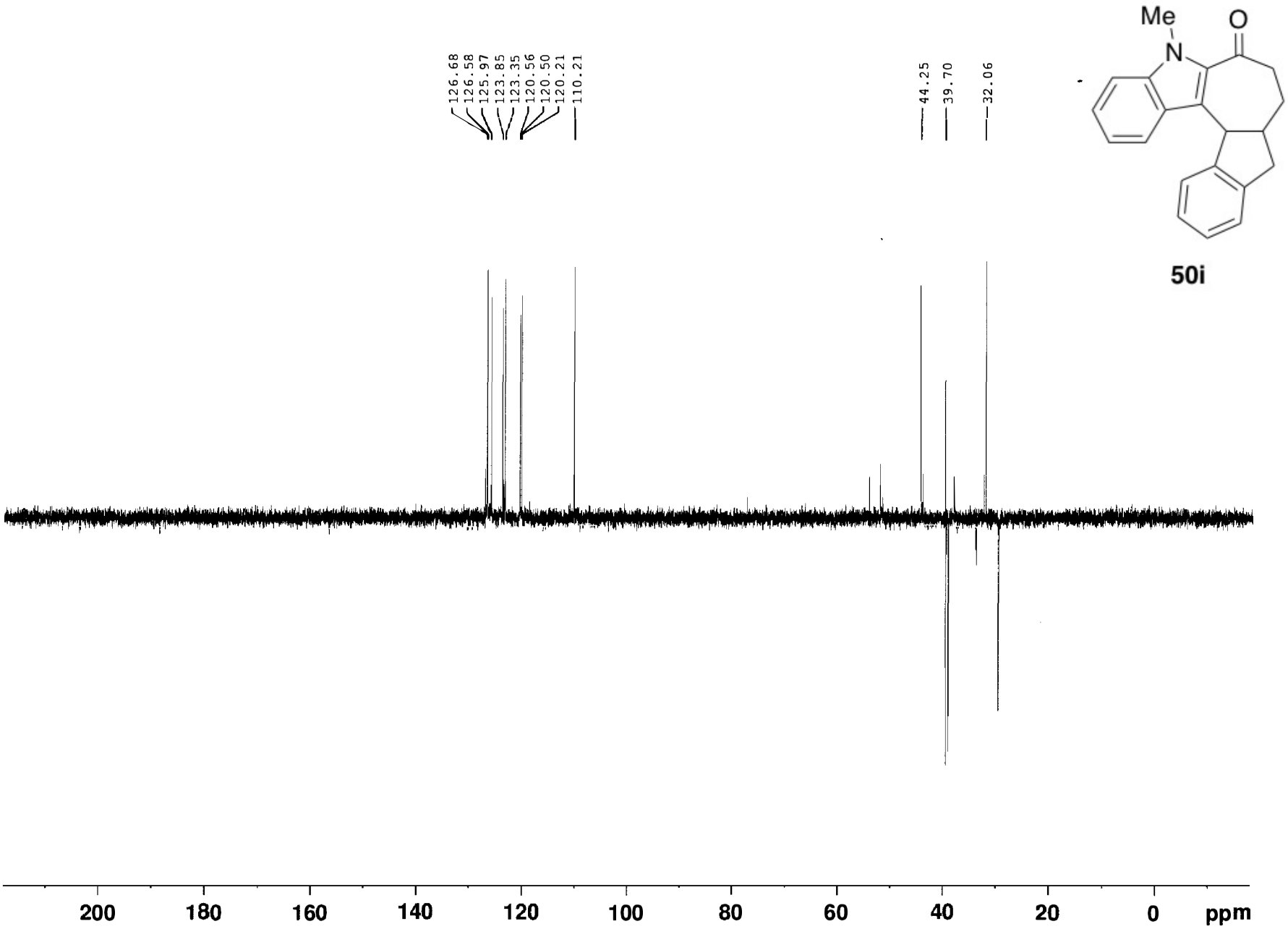
Acquisition Time (sec)	1.1010	***Comment***	NB-5-MCM-59-B-prepTLC			***Date***	19 Nov 2015 08:39:12
Date Stamp	19 Nov 2015 08:39:12			***File Name***	D:\Experimental section\C-acyl project\NB-5-MCM-59-B-prepTLC\2\fid		
Frequency (MHz)	125.79	***Nucleus***	13C	***Number of Transients***	203	***Origin***	spect
Original Points Count	32768	***Owner***	cmartin	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	186.56	***SW(cyclical) (Hz)***	29761.90	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12571.1533	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	29761.00	***Temperature (degree C)***	23.786



NB-5-MCM-59-B-prepTLC-COSY



NB-5-MCM-59-B-prepTLC-DEPT135



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CHAPTER 4. CA(II)-CATALYZED DEHYDRATIVE, NAZAROV-TYPE ELECTROCYCLIZATIONS: ACCESS TO CYCLOPENTA[B]THIOPHENES AND INDENE DERIVATIVES[*,1]

4.1 Importance of Cyclopenta[*b*]thiophenes and Indenes

Cyclopenta[*b*]thiophenes exemplify a unique class of organic molecules which have shown to be isosteres of indenes (Figure 4.1)[2] and therefore are useful in broad range of applications. For example, the parent compounds have been primarily used as precursors to thiophene-fused cyclopentadienyl metal complexes, zirconium complexes effectively catalyze the regiospecific polymerization of 1-alkenes.[3] On the other hand, the 5,6-dihydro derivatives are used in the field of material science for conjugated polymers, liquid crystalline media and organic field-effect transistors.[4]

[*] Work on Ca-catalyzed dehydrative Nazarov-type electrocyclization was performed in collaboration with Matthew Sandridge, Corey Williams and Zola Francis.
Published in *Tetrahedron.* **2017**, *73*, 4093.

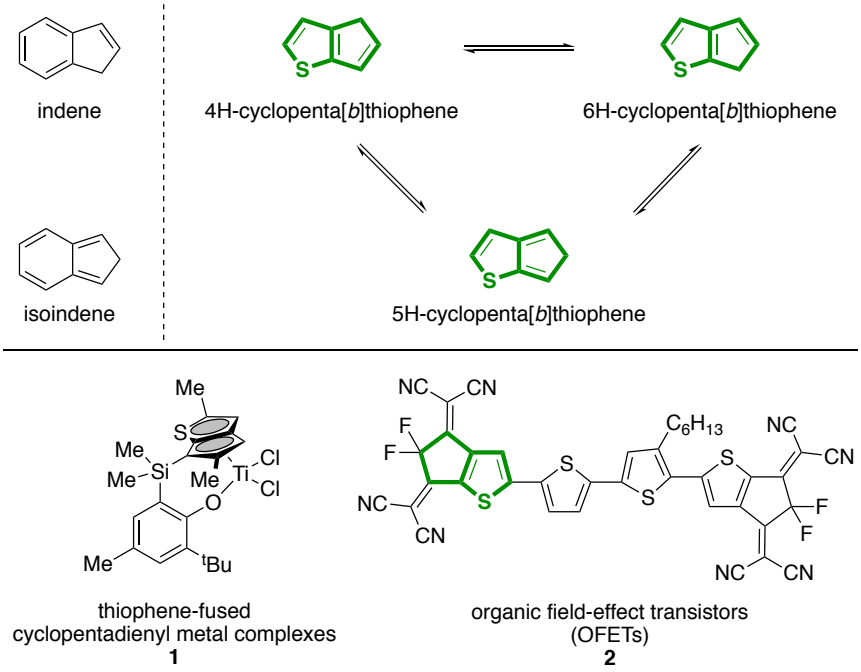


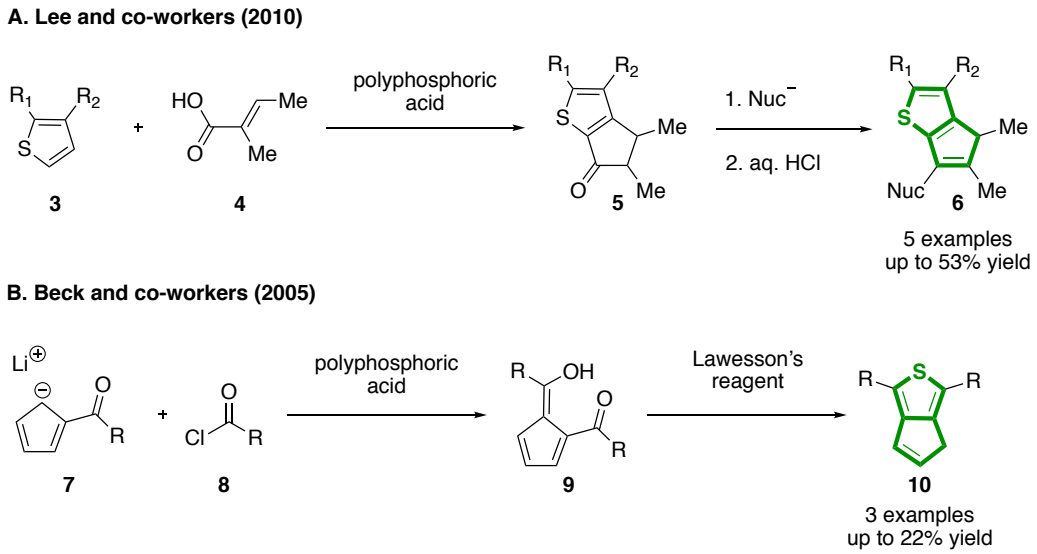
Figure 4.1. Isomeric Forms of Cyclopenta[*b*]thiophene

4.2 Previous Approaches towards Cyclopenta[*b*]thiophenes

There is a lack of general and robust methods for the preparation of functionalized cyclopenta[*b*]thiophenes and only a handful of syntheses have been reported to date, mostly involving the derivatization of a thiophene-fused cyclopentanone. For example, the most robust method reported by Lee and co-workers (Scheme 4.1A),[3k, 3l] involved a three-step sequence: 1) a one-pot acid-promoted Friedel-Crafts acylation/Nazarov cyclization of thiophene with acrylic acid derivatives to form thiophene-fused cyclopentanones **5**, 2) nucleophilic attack at the carbonyl to form the corresponding alcohols 3) acid-promoted dehydration to form the cyclopenta[*b*]thiophenes **6**. An alternative approach reported by Berck and co-workers[5] involved a two-step sequence. Firstly, 1,2-diacylcyclopentadienes **9** were prepared by reactions of acyl chloride **8** with

cyclopentadienyllithium **7**.[6] Then cyclopentadienes **9** were treated with Lawesson's reagent to afford cyclopenta[*b*]thiophenes **10**.

Alas, these approaches had shown several limitations: 1) limited scope (only methyl or phenyl substituents) 2) low functional group tolerance as a result of using strong acids, 3) low yielding transformations. With these limitations in mind, we sought to design a milder and more generalized protocol for the synthesis of cyclopenta[*b*]thiophenes focusing on achieving catalysis, efficiency, and modularity.

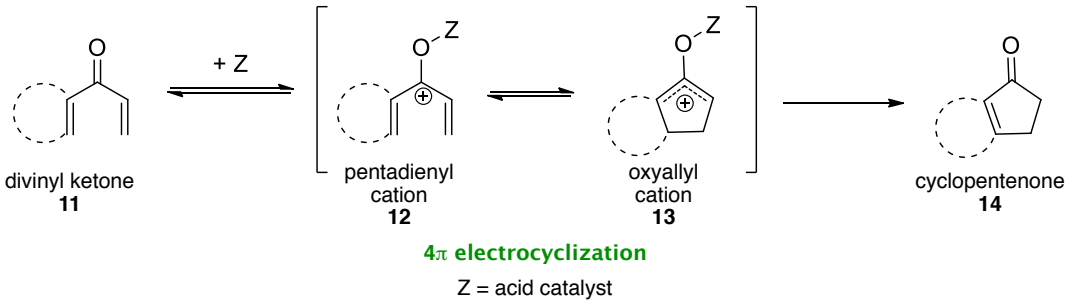


Scheme 4.1. Previous Approaches to Cyclopenta[*b*]thiophenes

4.3 The Nazarov Cyclization: Initiation of the 4π-Electrocyclization

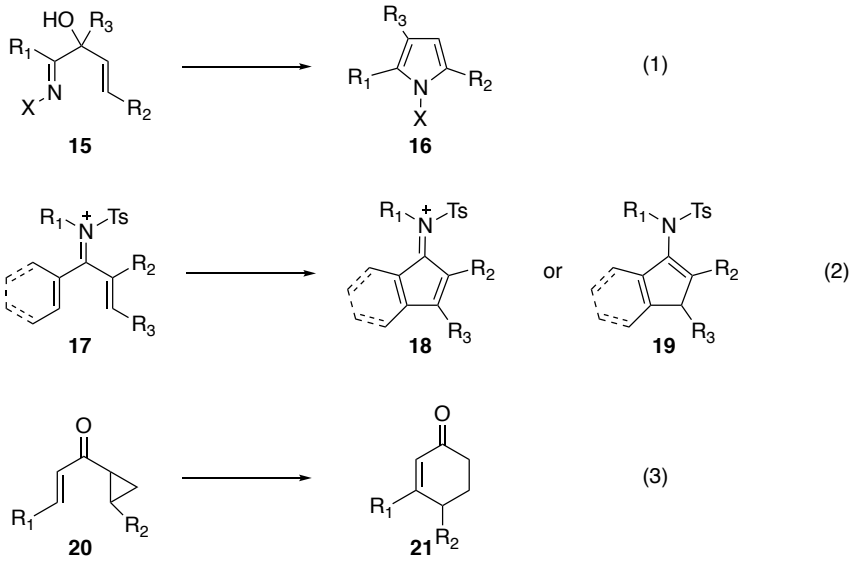
The Nazarov cyclization[7] has become a useful strategy for carbon-carbon σ-bond-forming reactions that produce quaternary centers, specifically all-carbon-atom centers. For example, it has become an interesting tool for the assembly of five membered carbocycles such as cyclopentenones. Mechanistically, the Nazarov cyclization involves

a 4π-electrocyclization of the 1,4-pentadienyl cation **12**, generated from the cross-conjugated divinyl ketones **11** (Scheme 4.2). Due in large part to initially harsh reaction conditions, this cyclization was of limited utility until most recently.



Scheme 4.2. Nazarov Cyclization Mechanism

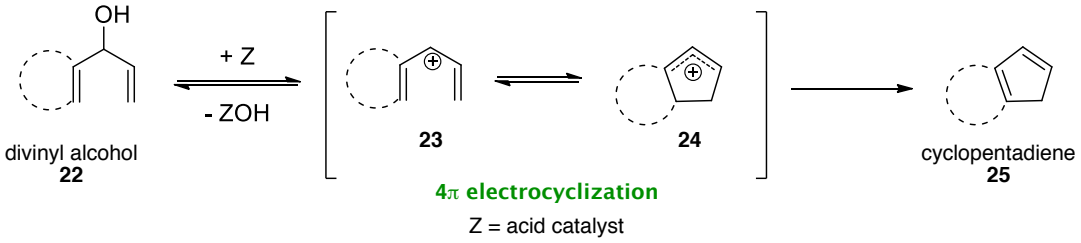
Renewed interest in the Nazarov cyclization led to the breakthrough of a more diverse set of starting materials used for "Nazarov-like" reactions (Scheme 4.3).[8] Hetero-Nazarov cyclizations, in which nitrogen or oxygen has been incorporated into the divinyl ketone framework, allow for the synthesis of various heterocycles (Scheme 4.3-(1)(2)). Moreover, the replacement of one of the alkene moieties with an alternative group such as a cyclopropyl afforded the synthesis of cyclohexenones via a formal homo-Nazarov cyclization (Scheme 4.3-(3)).



Scheme 4.3. General Examples of Nazarov-like Reactions

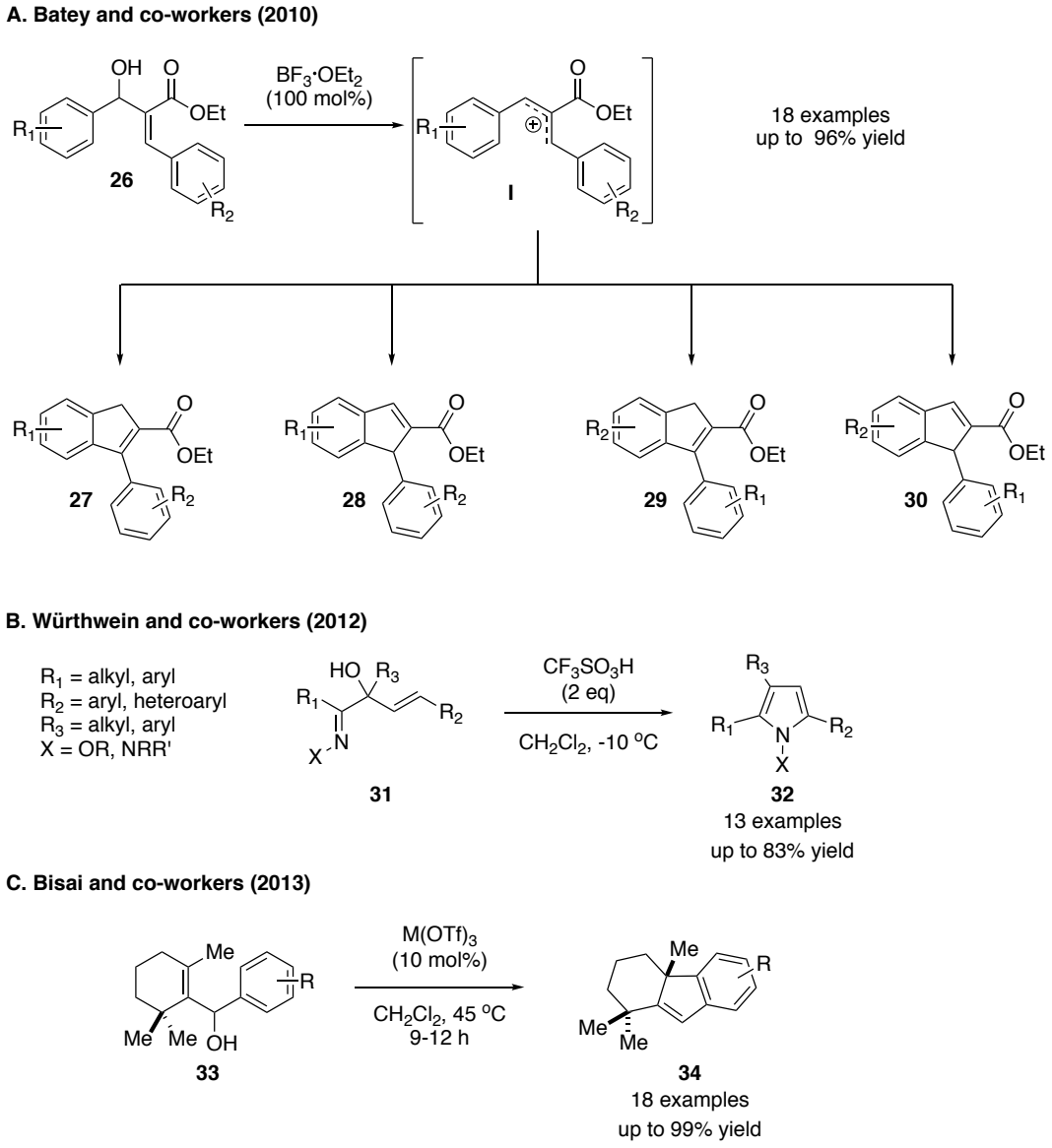
4.4 The Dehydrative, Nazarov-type Cyclization

Interestingly, one of the key features of the Nazarov-type cyclization is the initiation of the 4π-electrocyclization, central to the formation of functionalized cyclopentyl rings. One relevant example is the direct ionization of the C-O bond of divinyl alcohols and (hetero)aryl-substituted allyl alcohols (Scheme 4.4).[9] Explored by several groups, this dehydrative, Nazarov-type approach provides straightforward routes to cyclopentadienes, indenes and heteroaryl-fused cyclopentadienes.



Scheme 4.4. Dehydrative, Nazarov-type Cyclization

In 2010, Batey and co-workers reported an example of dehydrative, Nazarov-type 4π-electrocyclization to access functionalized indenes (Scheme 4.5A).[10] They have comprehensively studied the effects of substituents on the selectivity of the cyclizations of 1,3-diarylallylic cations **I**, derived from the diallyl alcohols using stoichiometric BF_3•OEt_2. Then Würthwein and co-workers in 2012,[11] incorporated a heteroatom (N in this case) in the vinyl moiety of the divinyl alcohol **31**, leading to the synthesis of pyrroles **32** (Scheme 4.5B). This transformation involved formation of highly reactive 1-azapentadienyl cations after protonation at the hydroxyl group of **31** by the super acid and subsequent loss of water. Then the 1-azapentadienyl cations underwent a pericyclic ring-closure reaction leading to the pyrroles **32** after proton loss and aromatization. Finally in 2013, Bisai and co-workers[9g] showcased an example of a metal triflate-catalyzed cyclization of arylvinylcarbinols **33** via an arylallyl carbocation species intermediate, affording synthesis of the carbotricyclic scaffold of natural products, taiwaniaquinoids (Scheme 4.5C).



Scheme 4.5. Examples of Dehydrative Nazarov-type Cyclization in Literature

4.5 Dehydrative, Nazarov-type Electrocyclizations of Alkenyl (Hetero)aryl Carbinols via Calcium Catalysis

4.5.1 Project Rationale and Justification

As mentioned in previous chapters, our lab has developed a variety of Lewis acid-catalyzed protocols toward (hetero)aryl-fused five-, six-, and seven-membered rings using Nazarov-like reactions.[12,13,14] As such, we sought to establish the catalytic, formal homo-Nazarov cyclization as a template for diversity-oriented synthesis (Figure 4.2).[15]

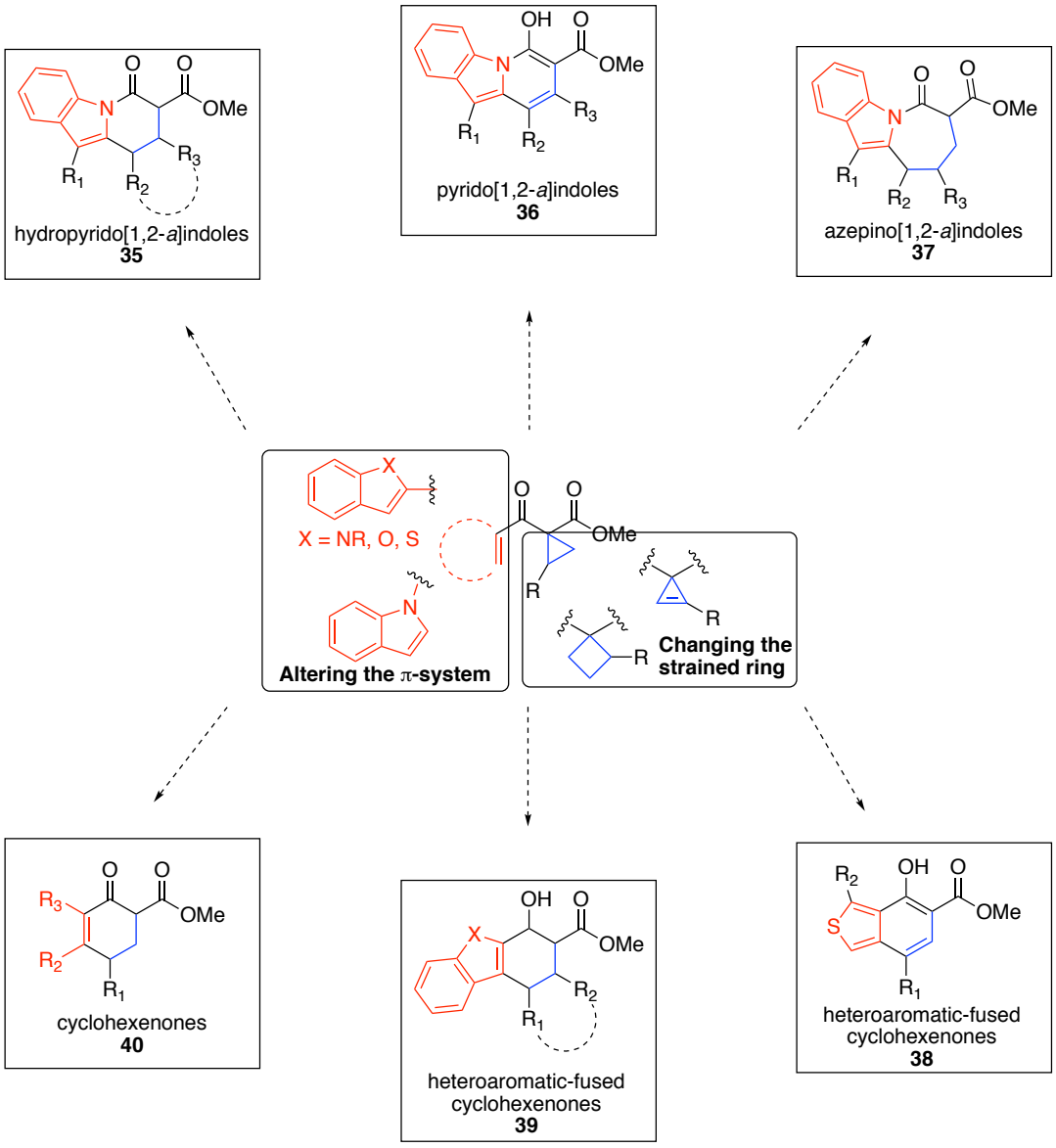
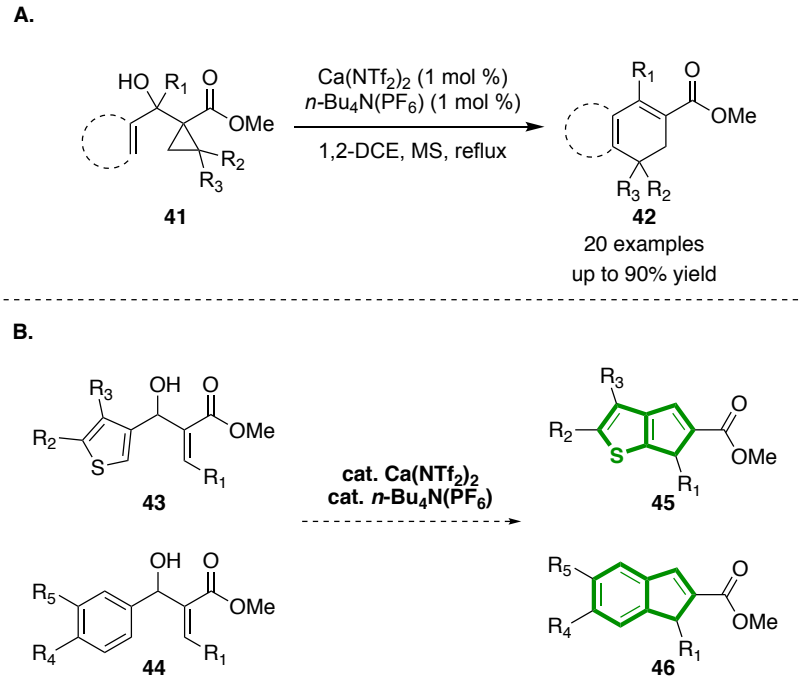


Figure 4.2. Catalytic, Formal Homo-Nazarov Cyclization as a Template for Diversity-Oriented Synthesis

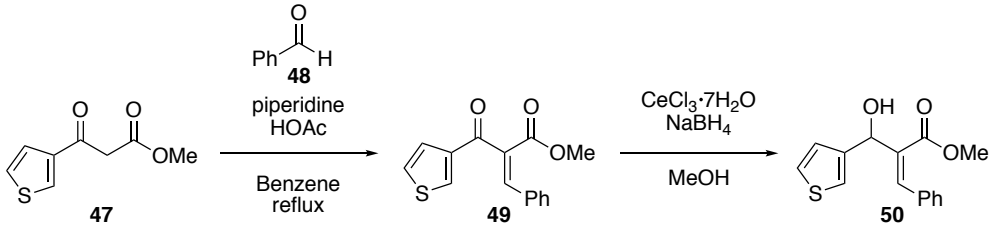
To expand that work on Nazarov-type cyclization, we recently reported a Ca^{2+}-catalyzed, dehydrative, ring-opening cyclization of (hetero)aryl cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes in up to 97% yield (Scheme 4.6A).[16] As a result, replacing the cyclopropane with an alkene would lead to formation of 5-membered rings instead of 6-membered rings. Therefore we pursued to identify catalytic conditions that were amenable for the dehydrative Nazaro-type cyclization of alkenyl (hetero)aryl carbinols that specifically led to the synthesis of functionalized cyclopenta[*b*]thiophenes (Scheme 4.6B).



Scheme 4.6. (A) Ca^{2+}-catalyzed, Dehydrative, Ring-Opening Cyclization of **41**, (B) Analogous Catalytic Approach to Cyclopenta[*b*]thiophenes

4.5.2 Model Substrate Synthesis

The alkenyl (hetero)aryl carbinol **50** was synthesized via a two-step sequence from *β*-ketoester **47** (Scheme 4.7), which was accessed via a two step synthesis from commercially available thiophene-3-carboxylic acid. Knoevenagel condensation of *β*-ketoester **47** with benzaldehyde **48** led to alkylidene *β*-ketoester **49**. Finally subsequent Luche reduction[17] of **49** provided with the desired carbinol **50**.

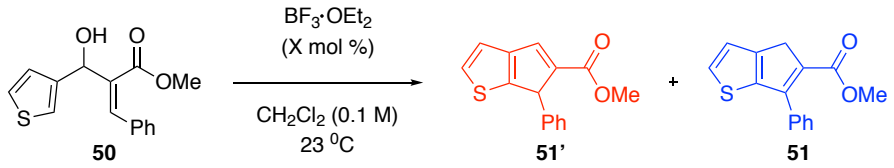


Scheme 4.7. Synthesis of Model alkenyl 3-thiophene Carbinol **49**

4.5.3 Proof of Principle

Initially, we treated carbinol **50** to the same conditions reported by Batey[10] – 100 mol% of BF_3•OEt_2 in CH_2Cl_2 at room temperature (Table 4.1). The transformation successfully led to formation of cyclopenta[*b*]thiophene **51** albeit in low yield (47% yield). Attempt to achieve catalysis by lowering the amount of catalyst loading to 10 mol% did not affect the yield of the reaction but a 2:3 mixture of cyclopenta[*b*]thiophene isomers (**51'**:**51**) were obtained. This showed successful implementation of catalytic conditions to afford the synthesis of cyclopenta[*b*]thiophenes in two different isomeric forms.

Table 4.1. Initial Catalytic Conditions for Cyclopenta[*b*]thiophene Synthesis

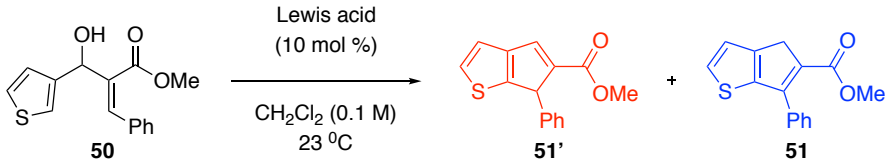


Entry	Loading (mol %)	Time (h)	Yield (%)	**51':51**
1	100	4	47	0:1
2	10	5	43	2:3

4.5.4 Reaction Optimization

From the initial screening, we investigated other Lewis acids than BF_3•OEt_2 such as metal triflate salts (Table 4.2, entries 4, 6 – 13). No desired product was obtained with $La(OTf)_3$, $Yb(OTf)_3$, $Ni(OTf)_2$ and $Dy(OTf)_3$ after 24 h (entries 10-13), while trace amount of cyclopenta[*b*]thiophene was detected with $Al(OTf)_3$ (entry 9). $In(OTf)_3$ and $Ga(OTf)_3$ gave the sole cyclopenta[*b*]thiophene isomer **51** in 51% and 47% yield respectively. Treating carbinol **50** with $Bi(OTf)_3$ led to a mixture of cyclopenta[*b*]thiophenes **51'**:**51** as a 1:2 mixture with an increased yield of 57% (entry 4). Inspired by our previous work on the ring-opening cyclization (Scheme 4.6A), a combination of $Ca(NTf_2)_2$ and additive (n-Bu_4N)(PF_6) was used for this transformation. This combination has been shown to be effective in catalyzing Nazarov cyclization and the reactions of carbinols.[18] Under these conditions, only cyclopenta[*b*]thiophene isomer **51** was obtained in 55% yield in 4 h (entry 2). Attempts to improve the effectiveness of the transformation by carrying the reaction at reflux led to an increase in yield of 65% in 1h 45 min (entry 3).

Table 4.2. Acid Screening for Cyclopenta[*b*]thiophene Synthesis



Entry	Lewis acid	Time (h)	Yield (%)	**51':51**
1	None	24	-	-
2	$Ca(NTf_2)_2$ $(n\text{-}Bu_4N)(PF_6)$	4	55	0:1
3*	$Ca(NTf_2)_2$ $(n\text{-}Bu_4N)(PF_6)$	1.75	65	0:1
4	$Bi(OTf)_3$	4	57	1:2
5*	$Bi(OTf)_3$	1.75	62	1:1
6	$In(OTf)_3$	4	51	0:1
7	$Ga(OTf)_3$	4	47	0:1
8	$Sc(OTf)_3$	24	11	1:1.15
9	$Al(OTf)_3$	20	trace	-
10	$La(OTf)_3$	>24	-	-
11	$Yb(OTf)_3$	>24	-	-
12	$Ni(OTf)_2$	>24	-	-
13	$Dy(OTf)_3$	24	-	-
14	TfOH	0.5	43	2:3

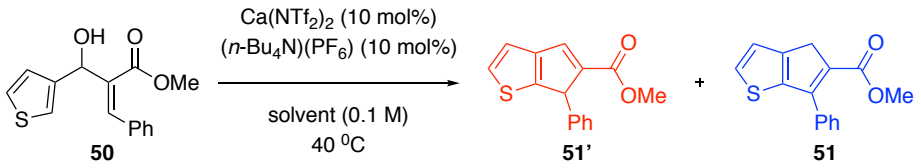
* Reaction run at 40 °C.

Next, we studied the effects of time at reflux on both the yields and product ratios (Table 4.3, entries 1 – 3). At 1h 30 min, the reaction gave a 3:1 mixture of the products with isomer **51'** as the major one, whereas when the reaction was allowed to go longer (2h 30 min), some isomerization was observed as **50'** to **50** ratio eroded to 1:5.5 along with a minor drop in yield (58%), possibly due to product degradation. Therefore to

minimize product degradation while optimizing for yield and product ratios, 1.75 h was selected as the ideal reaction time.

In the final phase of optimizing the conditions for this transformation, we investigated the effects of (1) decreasing catalyst loading, (2) solvent, and (3) reaction concentration. Reducing the catalyst loadings to 5 mol% and 2.5 mol% did not lead to any improvement in yields and was detrimental to the rate of the alkene isomerization. Then, the different solvents were screened while maintaining the temperature at 40 °C to minimize product degradation (Table 4.3). Similar to CH_2Cl_2, both 1,2-DCE and toluene gave only isomer **51** but with reduced yields, 58% and 53% respectively (entries 4 and 5). On the other hand MeCN was incompatible since no desired products were observed (entry 6). This is presumably due to catalyst deactivation through solvent coordination. With THF, we detected a mixture of isomers **51'**:**51** as a 1:6 mixture (entry 7). Interestingly, benzene gave a slight improvement in yield, 67% and when the reaction was diluted (concentration = 0.05 M), the yield was further improved to 70% yield. Therefore, the optimized conditions for this transformation was 10 mol % of $Ca(NTf_2)_2$ and 10 mol% of (n-Bu_4N)(PF_6) in benzene (0.05 M) at 40 °C at 1.75 h.

Table 4.3. Effect of Changing Solvents



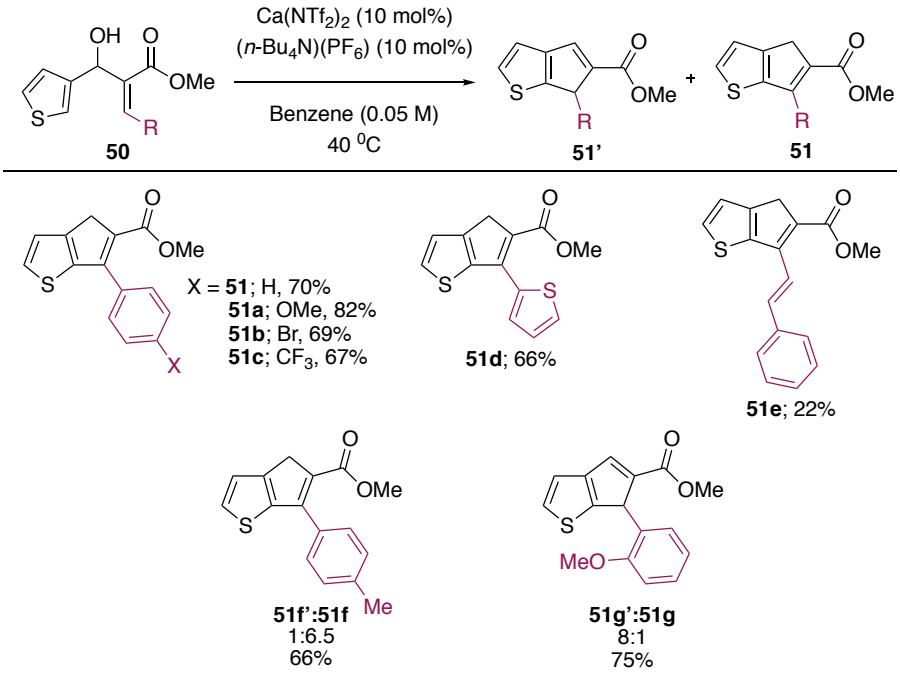
Entry	Solvent	Time (h)	Yield (%)	**51':51**
1	CH_2Cl_2	1.75	65	0:1
2	CH_2Cl_2	1.0	63	3:1
3	CH_2Cl_2	2.5	57	1:5.5
4	1,2-DCE	1.75	58	0:1
5	Toluene	1.75	53	0:1
6	MeCN	>24	-	-
7	THF	1.75	57	1:6
8	Benzene	1.75	67	0:1

4.5.5 Examination of Substrate Scope

With the optimized conditions in hand, we studied the scope for the transformation by investigating the effect of changing the alkenyl substituent of the carbinol **50** (Table 4.4). First, we examined any stereoelectronic effects imparted by substituents on the phenyl ring. When the more electron donating group, *para*-methoxy was used, **51a** was obtained in highest yield, 82%. With a weakly activating *para*-tolyl substituent, a 1:6.5 mixture of cyclopenta[*b*]thiophene isomers was produced with **51f** as major. With a weakly electron-withdrawing group (*para*-bromo) and a strong electron-withdrawing group (*para*-trifluoromethyl), the cyclization led to formation of solely isomer **51b** and

51c in 69% and 67% respectively. Therefore, this study suggested that higher yields are anticipated with strong donor groups on the phenyl ring due to slight inductive effect.

Table 4.4. Scope for Cyclopenta[*b*]thiophene Synthesis

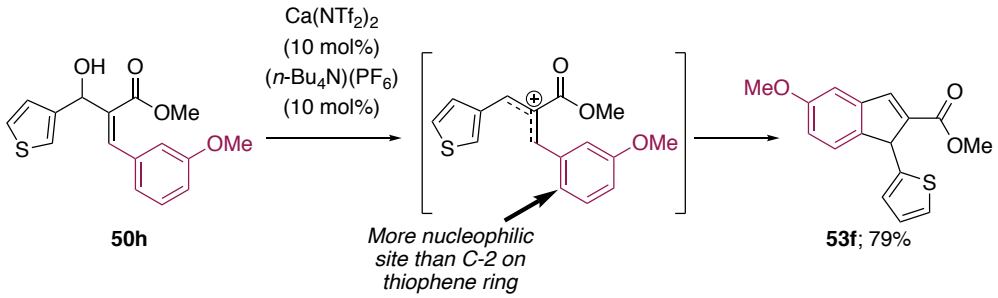


* Synthesis of **51f** and **51g** performed by co-author Matthew Sandridge.

To further probe substituent effects on the cyclization, the *ortho*- and *meta*-methoxyphenyl carbinols **50g** and **50h** were subjected to the reaction conditions. Cyclization of **50g** led to cyclopenta[*b*]thiophene as a 8:1 isomeric mixture with major **51g'** in 75% yield. This unexpected result might presumably be due to steric influences (imparted by the methoxy group), which lowered the rate of alkene isomerization. On the other hand, **50h** did not produce any cyclopenta[*b*thiophene isomers **51h'** or **51h** (Scheme 4.8). Instead, indene **53f** was formed in 79% yield where cyclization occurred onto the aryl group (reaction performed by co-author Matthew Sandridge). This result was consistent with Batey's work[10] in which the location of substituent on the phenyl ring has a direct influence on product outcome, with cyclization onto the more nucleophilic

aromatic ring as the major product.[19] Ring closure is thus expected to occur preferentially on the phenyl ring *para* to the methoxy group – a more nucleophilic position than C-2 on the thiophene ring.

Moreover, other than phenyl substituents, a heteroaryl group such as thiophene was substituted on the alkenyl moiety of carbinol **50d** (Table 4.4). **51d** was generated in 66% yield, as no cyclization onto the 2-thienyl moiety was observed. This outcome agrees with the greater nucleophilicity of the thiophene C-2 vs C-3. For **50e** with a *β*-styryl substituent, only 22% yield of **51e** was isolated along with significant degradation and uncharacterized compound mixtures. Given the added delocalization, multiple cationic intermediates could be formed and might have been involved in competing reactions.



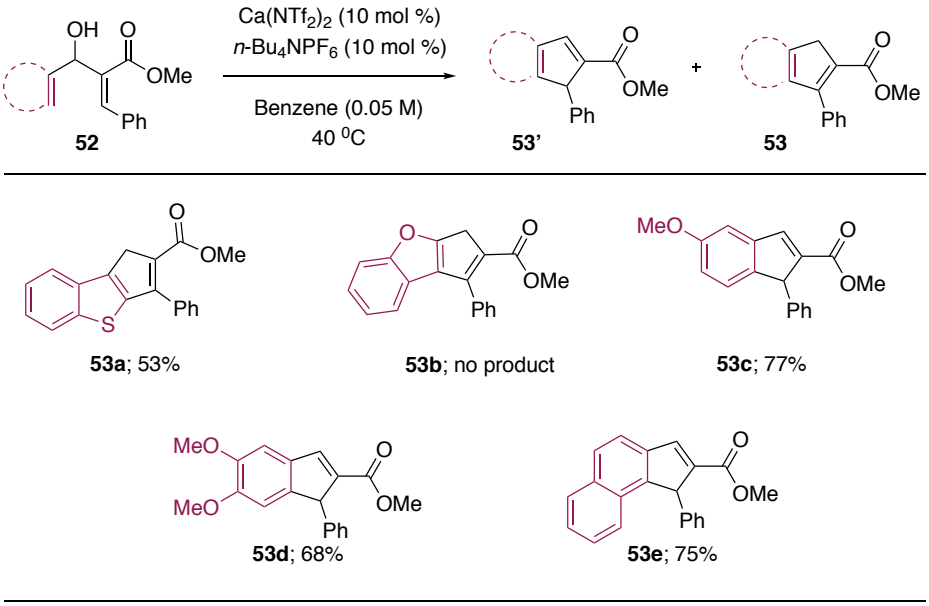
Scheme 4.8. Synthesis of Indene **53f**

Next, the effects of replacing the thienyl group with other (hetero)arenes were studied under the optimized conditions (Table 4.5). 2-Benzothienyl carbinol **52a** cyclized to give benzo[*b*]cyclopenta[*d*]thiophene **53a** in 53% yield. However, 2-benzofuranyl carbinol **52b** did not give any desired product, as significant decomposition was observed. This outcome was consistent with the low yield (10%) observed by Batey[10] for

a similar 3-benzofuranyl derivative.

Finally, we also investigated some examples with phenyl substituent on carbinols **52** in an attempt to synthesize functionalized indenes. *Ortho*-methoxy substituted phenyl carbinol **52c** led to indene **53c** in 77% yield as expected. 2-Naphthyl carbinol **52e** proved a competent substrate (75% yield) with alkylation readily occurring at C-1 to form **53e** as the only detectable product. This outcome was consistent with what Batey[10] obtained for a 2-naphthyl derivative with a methyl group in place of the ester group.

Table 4.5. Effect of Changing the (Hetero)aryl Carbinol Substituents

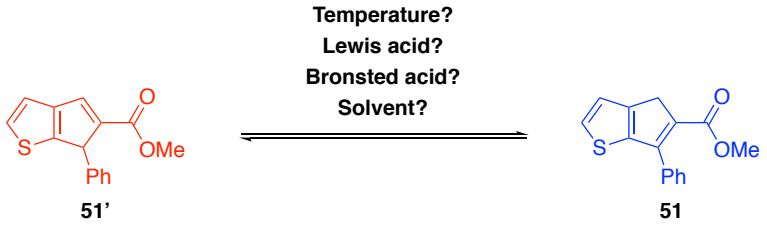


4.5.6 Reaction Mechanism*

After investigating the scope of the transformation, the nature of the isomeric ratios of the products remained puzzling. The reaction appeared to be more complicated than a simple kinetic vs thermodynamic product argument since the ratios fluctuated,

* The mechanistic studies were performed by co-author Matthew Sandridge.

changing in both directions. An understanding of the product ratios for this transformation was extensively investigated through a series of control reactions (Scheme 4.9).



Scheme 4.9. Probing the Interconversion of **51'** and **51**

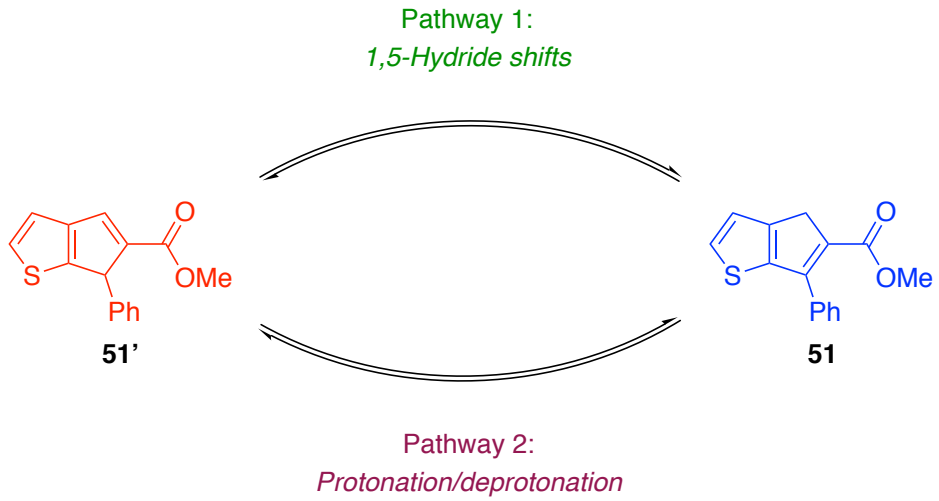
First, before the optimization experiments were finalized, a 1:1.7 isomeric mixture of **51'**:**51** was subjected to the initial reaction conditions (10 mol % of $Ca(NTf_2)_2$ and 10 mol% of (n-Bu_4N)(PF_6) in CH_2Cl_2 (0.1 M) at 40 °C) for 0.5 h and 1 h (Table 4.6). At 0.5 h, the product ratios improved with an increase for **51** (1:15 isomeric mixture) (entry 1). On the other hand, letting the reaction at reflux for 1 h resulted in deterioration of **51'**:**51** isomeric mixture to 1:3.5 (entry 2). Furthermore, in both cases, we observed product degradation as about 65 – 69% of the mixture was recovered. From this first study, we learnt two things: (1) the reflux time affects directly the product ratios, and (2) there is a competing pathway happening resulting in product degradation.

Table 4.6. Control Experiment to Probe the Effect of Temperature

Entry	Time at reflux (h)	% recovery	**51':51**
1	0.5	65	1:15
2	1.0	69	1:3.5

There are two plausible mechanistic pathway for the existence of the interconversion of **51'** and **50** (Scheme 4.10). The first pathway involves two 1,5-H shifts

occurring consecutively (converting from the 4*H*, 5*H* and 6*H*-cyclopenta[*b*]thiophenes and vice versa). Otherwise, the other pathway can be described as an acid/base-mediated protonation/deprotonation mechanism. Finally, a third option could be a combination of the two pathways if they occur concurrently.



Scheme 4.10. Plausible Mechanism for Interconversion

To understand further the effects of heat on the isomeric ratios, a plot of product ratios as a function of time was drawn (Figure 4.3). The blue line indicated significant fluctuations in the isomeric ratios between 60 and 120 min for the optimized reaction starting with **50**. Full conversion of **50** to cyclopenta[*b*]thiophene was observed within 15 min with oscillation in product ratios until 105 min where only isomer **51** was detected. Lastly, product degradation did not seem to aggravate over the time span of 15 min and 120 min.

Two additional experiments involved heating and stirring a 1:2.2 isomeric ratio of **51'**:**51** in benzene either with 10 mol% $HNTf_2$ (purple line) or without (green line). If the

interconversion were the result of purely thermodynamic H-shifts, product fluctuation would be observed with simple heating and stirring over time. If it was following the protonation/deprotonation pathway 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%). As a result, interconversion seemed very slow or the system had reached equilibrium. This result is definitely different from the other data sets involving the calcium catalyst, which appeared to be accountable for the large fluctuations. Therefore, we could presumably think there might be some sort of complex involving the calcium catalyst and the products that facilitated interconversion between **51'** and **51**.

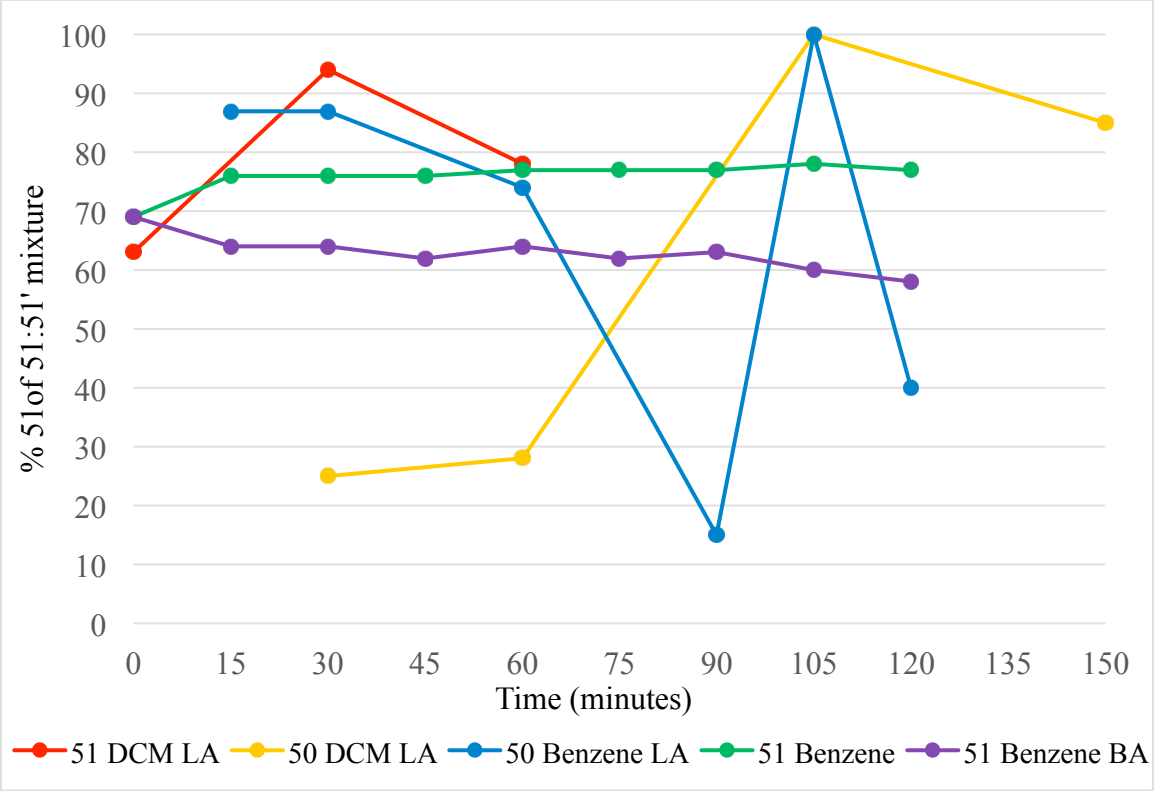
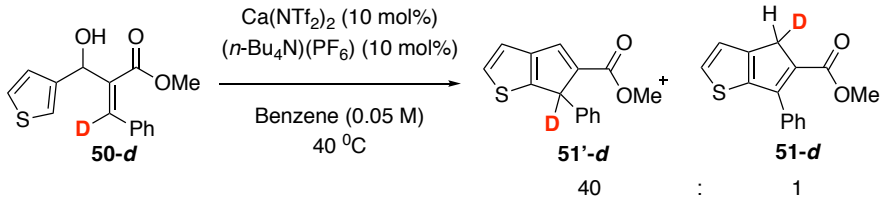


Figure 4.3. Control Reactions as a Function of Time

Finally, we subjected deuterated carbinol **50-*d*** to the reaction conditions in an attempt to investigate the hydride shift mechanism (Scheme 4.11). **51'-*d*** was obtained as the major product in a 40:1 ratio of **51'-*d***:**51-*d***. This experiment was repeated at 30 min and 60 min and gave identical results. Analogously, the control reaction of carbinol **50** in deuterated solvent showed no deuterium incorporation but did indicate a change in isomeric ratio, implying a solvent effect. Therefore the consistency over time and constant prevalence of **51'-*d*** isomer suggested that it formed first in the reaction and presence of the deuterium prevented isomerization, implying a very large kinetic isotope effect. Mechanistically, this meant that cyclopenta[*b*]thiophene **51'** was the first to form in the reaction and subsequently isomerized in the instances we observed isomer **51**.

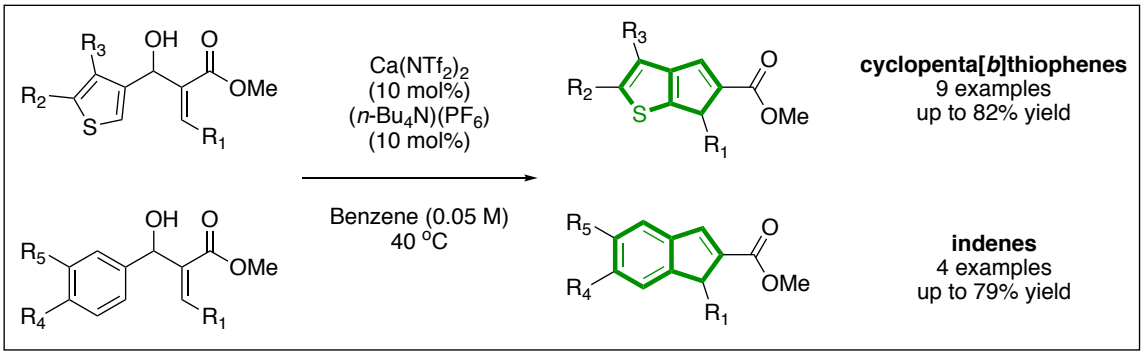


Scheme 4.11. Nazarov Cyclization of Deuterated Carbinol **50-*d***

4.6 Summary

Herein, we revealed a Ca^{2+}-catalyzed protocol for the dehydrative, Nazarov-type electrocyclization of alkenyl (hetero) aryl carbinols that allowed access to functionalized cyclopenta[*b*]thiophenes and indenes (Scheme 4.12). This novel approach provides with milder conditions for the direct synthesis of cyclopenta[*b*]thiophenes, circumventing the need for cyclopenta[*b*]thiophenones as precursors. As a result, high tolerance for aryl and heteroaryl substituents on the alkene moiety of carbinols was shown. Substituent effects on the phenyl ring play a significant role in determining product outcomes and isomeric

ratios. For systems with competing (hetero)aryl substituents, cyclization occurred preferentially on the most nucleophilic ring. In addition, interestingly with the 3-thienyl series (without a competing aryl substituent), the reaction was selective for the thermodynamic alkene isomer in all but one case, whereas the arene series favored the kinetic alkene isomer for the resulting indenes. Lastly, this transformation represents one of the only examples of catalytic, dehydrative, Nazarov-type electrocyclizations in which thiophenes are compatible.



Scheme 4.12. Catalytic Dehydrative Nazarov Cyclization for Cyclopenta[*b*]thiophenes

4.7 Experimental Section

4.7.1 Cyclohepta[*b*]thiophenes and Indenes:

For the Ca^{2+}-catalyzed dehydrative Nazarov-type electrocyclizations for the synthesis of cyclopenta[*b*]thiophene and indene derivatives, the experimental section and characterization can be found in the article: Martin, M. C.; Sandridge, M. J.; Williams, C. W.; Francis, Z. A.; France, S. *Tetrahedron* **2017**, *73*, 4093.

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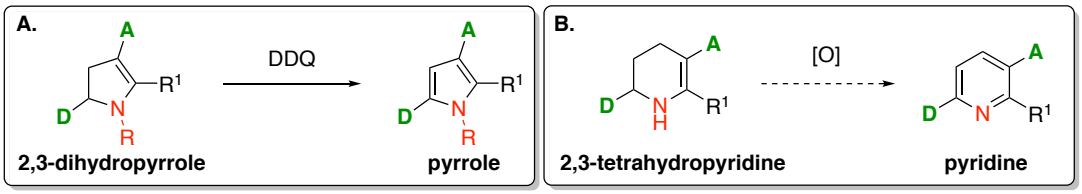
CHAPTER 5. CONCLUSIONS AND FUTURE OUTLOOK

5.1 Conclusion

Highlighted in this thesis are the diversity-oriented synthetic strategies as a gateway to small *N*-heterocyclic and polycyclic scaffolds such as 2,3-dihydropyrroles, 2,3-tetrahydropyridines, azepino[1,2-*a*]indoles, cyclohepta[*b*]indoles, cyclopenta[*b*]thiophenes and indene derivatives. We have developed a general approach using mild Lewis acid-catalyzed amine ring opening cyclization using D-A cyclopropanes and D-A cyclobutanes to access 2,3-dihydropyrroles and 2,3-tetrahydropyridines. The design of a catalytic and diastereoselective formal [5+2] cycloaddition approach to access the azepino[1,2-*a*]indole scaffold found in many natural product targets. Importantly, the first example of Lewis acid-catalyzed intramolecular ring-opening cyclizations of D-A cyclobutanes, have been reported. In addition, this catalytic formal [5+2] cycloaddition has proven to be applicable to the synthesis of another interesting seven-membered ring fused indole, cyclohepta[*b*]indole. Finally, the first example of a Ca^{2+}-catalyzed dehydrative, Nazarov-type cyclization in which thiophenes are compatible, hence providing with a more direct route to the synthesis of cyclopenta[*b*]thiophene and indene derivatives. These frameworks are useful in many applications in the field of inorganic chemistry and material science.

5.2 Lewis Acid-Catalyzed Amine Ring-Opening Cyclizations of Strained Carbocycles

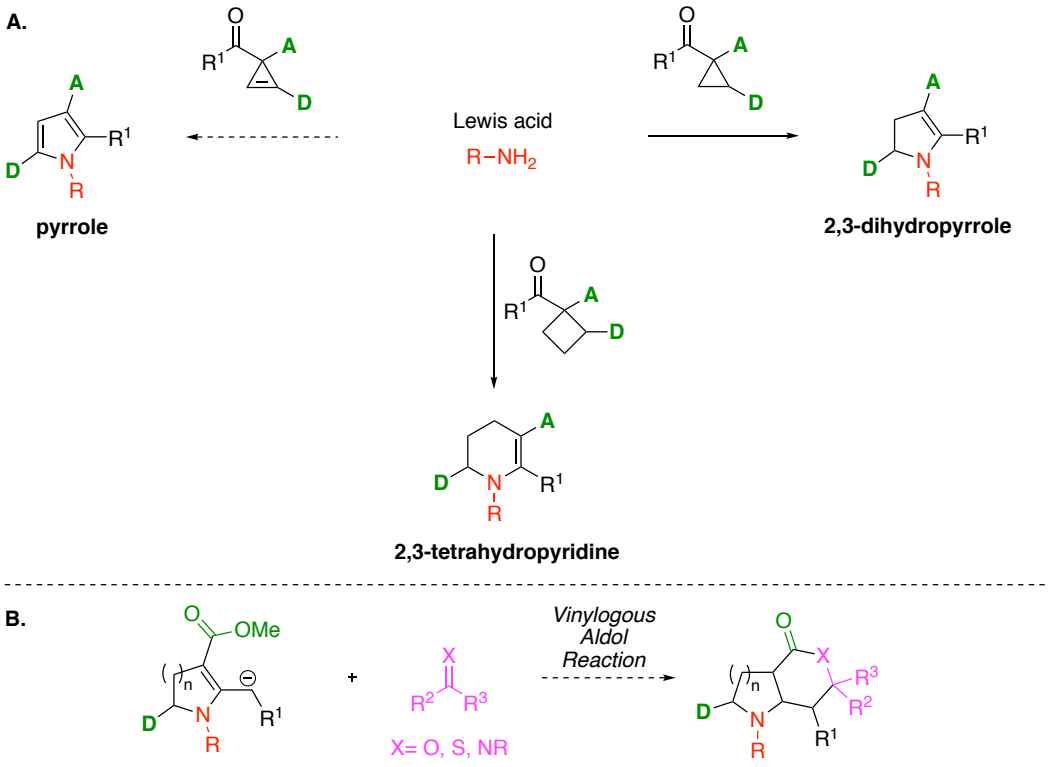
Chapter 2 entailed this Ni-catalyzed amine ring-opening cyclizations of D-A cyclopropanes and D-A cyclobutanes to afford dihydropyrroles and tetrahydropyridine core structures. Interestingly, we have shown treatment of these dihydropyrroles with DDQ led to the formation of another popular nitrogen-containing five-membered ring, the pyrrole (Scheme 5.1A). Once the optimization conditions are finalized with D-A cyclobutanes to access the 2,3-tetrahydropyridines, similar oxidation conditions could be applied to lead to formation of functionalized pyridines, found to be useful in medicinal chemistry.



Scheme 5.1. Oxidation Step to Afford Pyrrole and Pyridine Derivatives

In addition, an alternative route to access functionalized pyrroles is possible by applying the Lewis acid-catalyzed amine ring-opening cyclization protocol to D-A cyclopropenes. This will provide a more straightforward route to pyrroles using the strained polarized carbocycles, D-A cyclopropenes (Scheme 5.2A). Finally, highlighted in chapter 2 was the importance of the extended conjugation with the enamine moiety due to the presence of the EWG (-CO_2R) at the 3-position, leading to potential vinylogous

reactivity in presence of difference electrophiles accessing polycyclic skeletons (Scheme 5.2B)



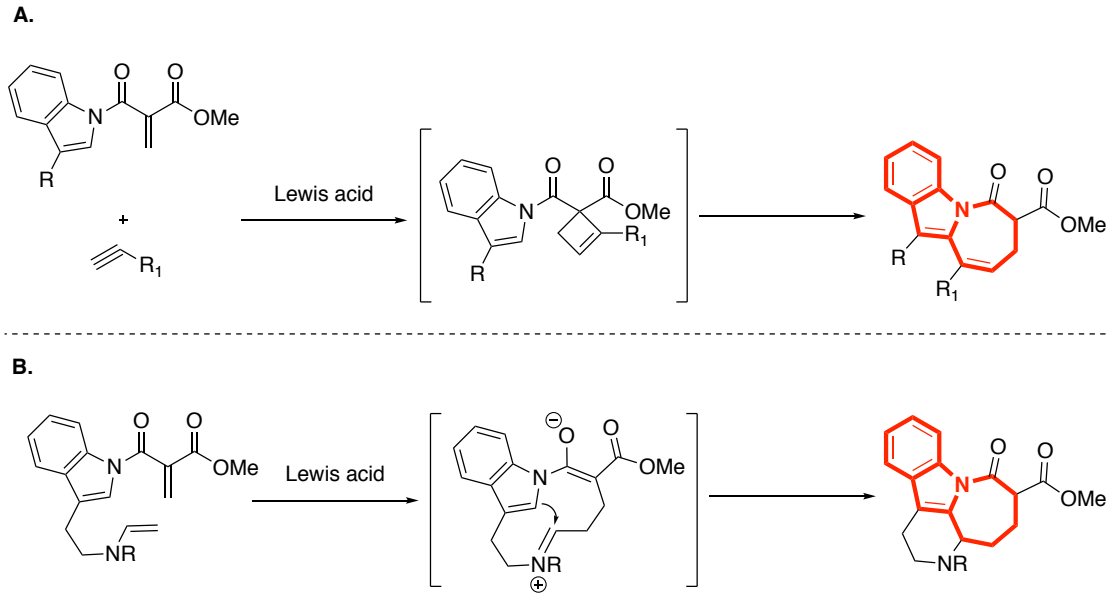
Scheme 5.2. (A) Strained Polarized Carbocycles as a Means to *N*-heterocycles, (B) Further Derivation using Vinylogous Reactivity

5.3 Future Directions with Formal [5+2] Cycloaddition Approach

Chapter 3 highlighted this novel formal [5+2] cycloaddition approach to access the azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles found in many natural products and pharmaceutically-relevant compounds. The catalytic conditions allowed for a broad scope using diverse mono- and multi-substituted alkenes accessing especially highly functionalized azepino[1,2-*a*]indoles in high yields and diastereoselectivities. From these outcomes, it would be interesting to implement this strategy with alkynes (Scheme 5.3A),

hence leading to unsaturation in the seven-membered ring fused indole scaffolds. Moreover, there is the potential formation of D-A cyclobutenes as intermediates, which can undergo intramolecular ring-opening cyclization to form this unsaturated seven-membered ring. This type of chemistry will be very much attractive and novel since no reports of intramolecular ring-opening cyclizations with D-A cyclobutenes exist in the literature.

Moreover, in an attempt to apply this formal [5+2] cycloaddition protocol to the synthesis of certain natural products (Scheme 5.3B), we envisioned intramolecular formal [5+2] cycloadditions of tethered alkylidenes under Lewis acid conditions to access these nitrogen-substituted tetracyclic scaffolds. This can provide a direct synthetic route to these scaffolds. On the other hand, the intermolecular approach developed in chapter 3 did not show successful implementation.



Scheme 5.3. Potential Other Directions with Formal [5+2] Cycloadditions

Finally, with the constant interest with the popular indole alkaloid natural products, we have explored the formal [5+2] cycloaddition reactivity involving mostly indole-type alkylidenes to access the azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles. There is potential to apply this reactivity towards the synthesis of other scaffolds using different heterocyclic-based alkylidenes (Figure 5.1). Therefore, these scaffolds can provide the generality and breadth of scope of formal [5+2] cycloaddition as well as D-A cyclobutane reactivity.

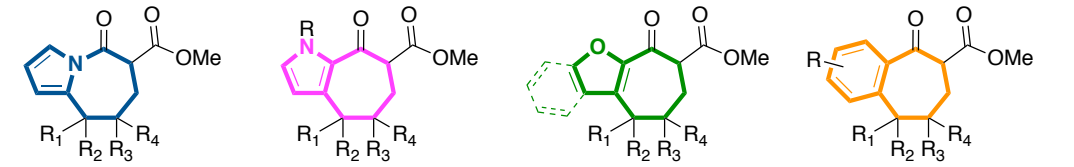


Figure 5.1. Other Potential Scaffolds using Formal [5+2] Cycloadditions