INNOVATIVE APPROACHES TO CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS USING STRAINED CARBOCYCLES

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INNOVATIVE APPROACHES TO CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS USING STRAINED CARBOCYCLES

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This thesis is dedicated to my father, Cau A Phun, and my mother, the late Cu Chang Vong. Thank you for making the sacrifices in order for me to have a brighter future.
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## Nomenclature

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Summary

Natural products and small molecules play a major role in drug development. Using natural products as a source of medicine comes with many challenges. Some of the challenges include lack of natural abundance and difficulty in isolation. Consequently, synthetic organic chemistry is a solution to providing these compounds for further exploration and aiding in structure-activity-relationship studies. However, synthetic chemistry comes with its own challenges such as efficiency, chemoselectivity, stereoselectivity and enantioselectivity. As a result, synthetic tools that addresses these challenges are required solve these difficult synthetic limitations. These tools can be new catalysts, new instruments, or innovative methodologies that can permit new chemical transformations and facilitate in the total synthesis of complex natural products. Therefore, organic chemists are in search of new tools to aid in the pursuits of total syntheses of natural products for further biological studies.

In this thesis, new synthetic methodologies using cyclopropanes, cyclopropenes and furan derivatives are used as building blocks in order to access scaffolds that are present in many natural products. As a result, Chapter One provides an all-encompassing discussion on the properties of cyclopropanes, cyclopropenes and furans. One central example that is discussed herein is the cyclization of donor-acceptor cyclopropyl ketones to generate substituted cyclohexenones, also known as the formal homo-Nazarov cyclization. Chapter One discusses the limitations of the homo-Nazarov cyclization. These challenges include excess Lewis acid (SnCl₄), lack of generality, high temperature and long reaction time. Chapter Two of this thesis discusses the homo-Nazarov cyclization using two different reactive pi system. The first part will discuss the alkenyl
homo-Nazarov cyclization, in which a simple vinyl system was employed as the reactive π-unit. This methodology used a catalytic amount of Lewis acid (30 mol % of In(OTf)_3) to promote the cyclization. Eight different alkene derivatives were shown to undergo cyclization to provide methylene cyclohexenols and cyclohexanones in 30-93% yields. Utility of these products as building blocks was demonstrated by addition of thiophenol to the exocyclic alkene of the methylene cyclohexenols to form a thioether, and Krapcho decarbalkoxylation cleaved the carboxylate group on the cyclohexenone. After the success of the alkenyl homo-Nazarov cyclization, an interest in using the π-system of heteroaromatic compounds led us to develop the heteroaryl homo-Nazarov cyclization. In this protocol, 14 substrates were shown to undergo the homo-Nazarov cyclization to provide heteroaryl ring-fused cyclohexenones in 56-91% yield. A tandem cyclopropanation/homo-Nazarov protocol was also demonstrated in which the one pot yield was higher than the two individual steps alone. This report also showed that cyclopropanes with an alkoxy donor group readily rearranged to dihydrofurans. This concept will be expanded upon in Chapter Three of this thesis.

Chapter Three exhibits a robust method to generate a library of dihydrofuran acetals from the rearrangement of electron rich cyclopropanes. Trisubstituted and tetrasubstituted dihydrofuran acetals were generated in 45-78% yield. These dihydrofuran acetals were readily transformed into benzofused heteroaromatic compounds via a ring-opening/Prins-type cyclization and elimination using In(OTf)_3. Furans were obtained using sterically hindered dihydrofuran acetals by elimination of the alkoxy group while silyl orthoacetates provided furanones.
A continued interest in developing methodologies using strained carbocycles led us to examine cyclopropene-3,3’-dicarboxyls as the reactive subunit. Chapter Four will discuss the use of these cyclopropenes with a tethered heteroaryl group as a new strategy for the synthesis of benzofused heteroaromatic compounds. In this report, a catalytic amount of In(OTf)$_3$ was used in order to obtain 15 benzofused heteroaromatic products in 25-86% yield. The mechanistic rationale of the cycloisomerization was also examined.

Chapter Five highlights the formation of furan-3-carboxylates via decomposition of α-diazo compounds. These furan carboxylates were then converted to the benzofused heteroaromatic compounds using 5 mol % of In(OTf)$_3$. This methodology allowed for the formation of benzo[b]thiophenes, benzo[c]thiophenes, benzofurans, dibenzofurans, indoles, indolizines and pyrido[1,2,a]indoles in 31-86% yield.

Finally, Chapter Six will summarize the thesis and provide future outlook for each individual project pursued.
Chapter One: Introduction

1.1 Challenges in Synthetic Chemistry

Natural products play a vital role in the pharmaceutical industry, serving as a major source for drug development. Often, the pharmacophore of potent drugs are natural product inspired. Semisynthesis of these natural products have also provided potent leads for the pharmaceutical industry.\textsuperscript{1,2} Unfortunately, many of these natural products pose serious challenges in isolation due to low abundance or compound stability. As a result, synthetic chemistry has played a vital role in filling this gap in order to generate more products or aid in structure activity relationship studies. Since the turn of the century, synthetic chemistry has reached an unprecedented level of sophistication and execution.\textsuperscript{3} The current tools available to chemists provide them with the confidence to solve interesting synthetic shortcomings. These tools include new catalysts, new instruments and synthetic methodologies which permit new chemical transformations and facilitate the total synthesis of complex natural products. However, many challenges exist in synthetic organic chemistry. These challenges include efficiency, chemoselectivity, regioselectivity and stereoselectivity.\textsuperscript{4} Therefore, organic chemists are in search of new tools to address these limitations. Along the same line, an interest in developing new tools that will aid in total syntheses of natural product endeavours led us to develop the different methodologies using strained carbocycles as the reactive subunit. In this thesis, new synthetic methodologies using cyclopropanes, cyclopropenes and furan derivatives contribute to this toolbox in order to address current synthetic limitations.

1.2 Cyclopropanes and Their Properties

Cyclopropane has attracted great attention since its discovery by William Henry Perkin in 1884.\textsuperscript{5-7} The reactivity of this three-membered carbocycle can be explained by comparing it with
its acyclic counterpart.\textsuperscript{8,9} Contrary to acyclic hydrocarbons, cyclic hydrocarbons have inherent ring strain energy. This strain energy primarily consists of two types: (1) torsional strain and (2) angle strain (Figure 1.1).\textsuperscript{10} Torsional strain emerges when bonds are not ideally staggered. Angle strain ensues when the C-C-C bond angle of the ring deviates from the ideal angle of 109.5°, which is preferred for an sp\textsuperscript{3} carbon.\textsuperscript{11}

**Torsional Strain**

\[
\begin{align*}
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H}
\end{align*}
\]

**Angle Strain**

\[
60°
\]

**Figure 1.1**: Cyclopropane Torsional Strain and Angle Strain

The typical C-C bond of an acyclic hydrocarbon is 88 kcal/mol, while the C-C bonds of a cyclopropane is 60.9 kcal/mol, making it much weaker than the acyclic C-C bond.\textsuperscript{12} This leads to the cyclopropane being more reactive than acyclic alkanes and other cycloalkanes that have less ring strain (e.g. cyclohexane and cyclopentane). The estimated total ring strain (combined torsional and angle strain) in a cyclopropane is \(\sim28\) kcal/mol. The carbon framework of a cyclopropane is planar with only one possible conformation where all the substituents are eclipsed, providing only 9 kcal/mol of torsional strain.\textsuperscript{12} This means that the majority of the ring strain is from angle strain, which arises from its geometry. An equilateral triangle prefers a C-C-C bond angle of 60° which is analogous to the angle of the cyclopropane. Consequently, the cyclopropane bond angles are 49.5° less than the desired C-C-C angle for the typical sp\textsuperscript{3} hybridization (109.5°). Since the bond angle is constrained to 60° and the desired interorbital angle is 109.5°, the orbital overlap is diminished by 20% relative to the orbital overlap in the C-
C bond of propane. This accounts for the remaining 19 kcal/mol of strain.\textsuperscript{13} The Coulson-Moffitt model demonstrates that the cyclopropane can arise from three \(sp^3\)-hydridized \(-\text{CH}_2\)-groups.\textsuperscript{13,14} These \(sp^3\) hybrids are pointed about 22° outward from the imaginary line connecting the nuclei. Consequently, there is a 20% reduction in the effective overlap of the C-C bond of ethane. As a result, this reduction in effective overlap of the C-C bond is reckoned as the source of the angle strain. The C-C bonds of the cyclopropane are "bent", and these bonds are often referred to as "banana bonds" (Figure I-2).\textsuperscript{13,15}

![Image of banana bonds](image)

**Figure 1.2:** “Banana Bonds” of Cyclopropanes: Coulson-Moffitt Model

Another model, the Walsh model, constructs the cyclopropane from three \(sp^2\)-hydridized methylenes (\(\text{CH}_2\)s) oriented radially toward the center of the cyclopropane ring (Figure 1.3).\textsuperscript{14} This model depicts angle strain as a result of poor overlap. The orbital overlap in \(\psi1\) is diminished due to the lobes of the \(sp^2\) hybrids oriented inward from the imaginary lines connecting the carbon atoms. Alternatively, \(\psi2\) can be viewed as a distorted \(\pi\)-bond. Therefore, the optimal bonding overlap occurs when the orbitals are all pointed towards the center of the ring, and allows for the delocalization of the electron density into the ring.
Despite the ring strain, cyclopropanes are often chemically inert and require electron-donating or accepting substituents to activate them towards polar reactions. Strategic substitution on the cyclopropane allows for facile ring opening. 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 1.4). Classically, electron-withdrawing functionalities such as the carbonyl group serve as the acceptors, and moieties with electron-rich aryl groups, heteroatoms, alkyl or alkenyl groups act as donors. 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). Recent D-D-A cyclopropane’s reactivity has been shown extensively by Davies\textsuperscript{18} and Doyle\textsuperscript{19}, while reactivity of D-A-A cyclopropanes are shown by Johnson\textsuperscript{20,21}, Charette\textsuperscript{22} and Kerr\textsuperscript{23}. Despite the extensive literature on the utility of these cyclopropanes, this thesis will only highlight D-A-A cyclopropane chemistry.

1.4 Donor-Acceptor Cyclopropanes

Given the diverse utility of these cycloproducts, extensive protocols for their synthesis have been disclosed as well. Examples of these include the halomethyl-mediated cyclopropanation reactions (Scheme 1.1, equation 1), metal-mediated diazo decomposition (Scheme 1.1, equation 2), and nucleophilic addition-ring closures (Scheme 1.1, equation 3). Metal-mediated decomposition of diazo compounds is one of the most popular method of D-A cyclopropane synthesis.\textsuperscript{19,24-26}

![Scheme 1.1: Different Routes for Cyclopropane Synthesis](image)

Geminally-substituted D-A cyclopropanes (I) and vicinally-substituted D-A cyclopropanes (II) are the two most common modes of activation (Scheme 1.2, equation 1). Geminal D-A cyclopropanes do not behave synergistically, and have limited examples with respect to vicinal D-A cyclopropanes. In contrast, vicinally-substituted donor and acceptor groups act synergistically in a controllable fashion due to the polarization of the C-C bond.
between the vicinal groups. As a result, these D-A cycloproanes provide predictable reaction outcome (Scheme 1.2, equation 2).

\[ \text{(1)} \]

\[ \text{(2)} \]

\[ D = \text{electron-donating (cation-stabilizing) group} \]
\[ \text{OR, NR}_2, \text{CH}_2\text{SiR}_3, \text{Ar, Alk etc.} \]
\[ A = \text{electron-withdrawing (anion-stabilizing) group} \]
\[ \text{CO}_2\text{R, COR, CN, NO}_2 \text{ etc.} \]

**Scheme 1.2**: Donor-Acceptor (D-A) Cycloproanes

This predictable substituent effect and reactivity have led to the extensive application of vicinal donor-acceptor (D-A) cycloproanes (termed D-A cycloproanes) as chemical building blocks.\textsuperscript{27} Upon ring opening, a 1,3-dipole is formed with both cationic and anionic centers.\textsuperscript{28,29} This intermediate is reactive towards electrophiles and nucleophiles in homo-conjugate addition reactions (pathways a and b) and dipolarophiles in cycloaddition reactions (pathway c) (Scheme 1.3). Donor-acceptor cycloproanes are often viewed as analogs of olefin double bonds due to the deviation from the ideal tetrahedral sp\textsuperscript{3} hybrid orbitals to bent bonds with more p character. Consequently, D-A cycloproanes are able to react with nucleophiles and electrophiles and can participate in reactions similar to olefins.\textsuperscript{11}

**Scheme 1.3**: Reactivity of D-A Cycloproanes
1.5 Intramolecular Lewis Acid-Catalyzed Cyclizations of Cyclopropanes

D-A cyclopropanes participate in intramolecular and intermolecular reactions with electrophiles, nucleophiles, and dipolarophiles. Given the vast quantity of antecedent examples, only examples of Lewis acid-catalyzed cyclizations since 2007 will be discussed in this section to be in line with the theme of this thesis.

In 2009, Werz and co-workers reported an approach for the formation of \([n,5]\)-spiroketals 3 \((n = 5 \text{ and } 6)\) in moderate to good yields \((ca. 26-87\%)\).\(^{30}\) Reduction of the ester on spiroannelated-substituted cyclopropanes 1 with LiAlH\(_4\) to its corresponding alcohol 2, followed by treatment with IBX and Yb(OTf)\(_3\) formed five-membered enol ether compounds 3 (Scheme 1.4).

\[
\begin{align*}
1 & \xrightarrow{\text{LiAlH}_4/\text{THF}} 2 \xrightarrow{\text{IBX/Yb(OTf)}_3} 3
\end{align*}
\]

**Scheme 1.4:** Werz’s Spiroketal Formation

With this procedure, various monosaccharide-derived spiroketals 4, 5 and 6 were synthesized (Scheme 1.5). After having success with IBX alone, IBX with Lewis acids were screened. Yb(OTf)\(_3\) was ascertained to be optimal to improve the yields. From product analysis, it was observed that the configuration of the spirocenter was not conserved in the transformation with IBX and Yb(OTf)\(_3\). As a result, the main reaction pathway for most of the substrates entailed the formation of a zwitterionic intermediate, resulting in a loss of stereochemistry at the spirocenter (Scheme 1.5, pathway b). However, Dess-Martin periodinane preserved the stereochemistry by proceeding through a concerted mechanism (Scheme 1.5, pathway a).
Overall, the three-step approach is an innovative way to form spiroke tals when compared to known approaches.

**Scheme 1.5: Ring Enlargement of Spiroke tals Mechanism**

### 1.5.1 Lewis Acid-Catalyzed Ring Expansion of Cyclopropanes

Suzuki and co-workers were interested in developing a protocol for the acid-catalyzed ring opening of 1-alkenyl cyclopropyl ketones.\(^1\) They were able to show a Cope rearrangement of \textit{vic}-divinylcyclopropanes 7 and 9 to form seven-membered ring frameworks 8 and 10 (Scheme 1.6).\(^1\) Suzuki and colleagues focused their attention on the benzosurrograte 11 with the hope that the model diene moiety in A is reactive enough to participate in the projected reaction to provide 12 (Scheme 1.6).
The model substrate, mono-substituted cyclopropane 11, was subjected to heating in 1,2-dichlorobenzene at 180 °C. The reaction did not furnish the desired product but provided a mixture of unidentified products. When a second substituent was introduced vicinally on the cyclopropane, such as a silyl group in cyclopropanes 12, only trace amounts of benzocycloheptenes 13 were detected under thermal conditions (Scheme 1.7). Introduction of a formyl group (an acceptor group) vicinally on the cyclopropane led to a dramatic effect on the reactivity, and the cycloheptene was afforded in high yields. The authors noted that an electron-withdrawing group is necessary for the ease of bond cleavage of the cyclopropane ring, and a more activating group such as phenyl at the vicinal position provided the benzocycloheptene in high yield (ca. 87%). Suzuki and coworkers noted that if the second activating group was more electronegative, further polarization of the C-C bond will allow for milder reaction conditions and shorter reaction times.

Scheme 1.7: Ring Expansion of Cyclopropane Under Thermal Conditions

1.5.2 Lewis Acid-catalyzed Cycloisomerization of Cyclopropanes

Cycloisomerization of cyclopropanes (rearrangements of cyclopropanes into polycycles) is another mode of ring-forming reactions. This strategy utilizes both Brønsted and Lewis acids to promote ring opening. Delocalization of the dipolar intermediate allows for the construction of cyclohexenes, furans, γ-lactones, and styrylmalonates.27
**Scheme 1.8**: Ring-Expansion of Methyl (Arylhydroxymethyl) Cyclopropanecarboxylates and Methyl (Diarylhydroxymethyl) Cyclopropanecarboxylates

Nishii and co-workers reported a strategy for the formation of 1-aryl-1,2-dihyronaphthalene-3-carboxylic acid esters 15 from methyl (arylhydroxymethyl)cyclopropane carboxylates 14 with Lewis acids (110 mol%) (Scheme 1.8). Various Lewis acids were used for the regioselective ring expansion reaction. For this transformation, Sc(OTf)_3 was the best Lewis acid. Electron donating and electron withdrawing substituents were well-tolerated to produce dihyronaphthalene products in good to high yields (ca. 60-80%). Also, the protocol afforded products 17 from the cyclization of methyl (diarylhydroxymethyl)cyclopropane carboxylates 16 in good to excellent yields (ca. 71-99%).
Scheme 1.9: Intermediates for 1-Aryl-1,2-Dihydronaphthalene-3-carboxylic Acid Esters

The mechanism begins with the chelation of Sc(OTf)$_3$ to the hydroxyl $\text{Ia}$ and the carbonyl ester of $\text{18}$ to form cation $\text{Ib}$ (Scheme 1.9). Ring-opening and intramolecular Friedel-Crafts alkylation forms the dihydronaphthalene $\text{19}$. If the $\text{Z}$-intermediate $\text{Id}$ is produced, the cyclization proceeded readily; however, the $\text{E}$-intermediate $\text{Ic}$ slows the conversion. The influence of steric was probed by substituting a bulky group for $R_3$, and the authors found that the size of $R_3$ had minimal influence on the reaction outcome. Furthermore, the use of halogenated acids such as TiCl$_4$ and SnCl$_4$ resulted in chlorination of the benzylic cation.

Scheme 1.10: Observed Products for the Transformations of Cyclopropane 20

Melnikov and co-workers reported a chemo-, regio-, and stereoselective protocol for the isomerization of 2-arylcyclopropane-1,1-dicarboxylate $\text{20}$ into 2-styrylmalonate $\text{22}$ (Scheme
Using Lewis acids to control the chemoselectivity, the group found that these cyclopropanes furnished lactones 21 as well as chloro homo-malonate 23. Moderately activating Lewis acids did not afford products with substrate 20; hence, strong Lewis acids (TiCl₄, SnCl₄, AlCl₃, BF₃·Et₂O, TMSOTf) were used to furnish the desired products in fair to good yields (26-88%).

**Scheme 1.11:** Observed Products from Isomerization of 2-Arylcyclopropane-1,1-dicarboxylates

The postulated mechanism begins with the Lewis acid binding to 24 to form 1,3-dipole IIa (Scheme 1.11). Afterwards, lactone IIb is formed by an intramolecular attack of the enolate oxygen IIb onto the benzylic carbon. Subsequent hydrolysis affords furanone 21a (Scheme 1.11, path a). If the alkoxide deprotonates the β-hydrogen, styrylmalonate IIc is formed as the intermediate, IIc then tautomerizes to 22a (Scheme 1.11, path b). Lastly, halide attack onto the benzylic cation followed by hydrolysis affords chloropropane 23a (Scheme 1.11, path c). Thus, three different mechanistic pathways afford three different products.
1.5.3 [3+\(n\)] Cycloadditions of Donor-Acceptor Cyclopropanes

**Scheme 1.12:** Johnson’s Cyclopropane-Aldehyde Annulations at Quaternary Donor Sites

Donor-acceptor cyclopropanes undergo [3+\(n\)] annulations in the presence of a promoter. Johnson and co-workers elegantly demonstrated an example of a diastereoselective cyclopropane-aldehyde [3+2] annulation to provide tetrahydrofurans with high cis-diastereoselectivity (Scheme 1.12).\(^{34}\) Using Sn(OTf)\(_2\) as the Lewis acid promoter, alkyl and aryl substituted cyclopropanes 24 readily underwent cycloaddition with alkyl and aryl aldehydes 25 to provide highly substituted cis-tetrahydrofurans 26 in high yields (up to 95\%) and high diastereoselectivity (up to 99:1 \(dr\)). If the cyclopropane were enantioenriched, chirality was completely transferred under these conditions.

**Scheme 1.13:** Melnikov’s [3+3] Dimerization of D-A Cyclopropanes

Melnikov and co-workers showed examples of [3+3]-dimerization of donor-acceptor cyclopropanes 27 to generate substituted cyclohexanes 28 (Scheme 1.13).\(^{33}\) Excess SnCl\(_4\) (1.2 equiv) promoted ring opening of cyclopropanes 27 to form 1,3-dipoles. Dimerization of the 1,3-dipoles afforded cyclodimers 28. 2-Aryl and 2-heteroarylcyclopropane-1,1-dicarboxylates were used, rapidly generating these symmetrically substituted cyclohexanes in modest yields (up to 88\%).
D-A cyclopropanes are viewed as analogs of olefins and can react with electrophiles and nucleophiles. Ivanova and co-workers beautifully utilized this intrinsic property to promote a [4+3] cycloaddition of 2-aryl-1,1-cyclopropane diesters 29 with 1,3-diphenylisobenzofuran 30 as the diene (Scheme 1.14). A catalytic amount of Yb(OTf)₃ (5 mol%) was effective to catalyze the cycloaddition, providing cycloadducts 31 in 84-92% yield.

An interested in the pyrazolidine structure led Kerr and co-workers to develop a Lewis acid-catalyzed annulation of donor-acceptor cyclopropanes. In Kerr’s report, a diastereoselective synthesis of bicyclopypyrazolidines were achieved using hydrazinoethyl 1,1-cyclopropanediesters, aldehydes and Yb(OTf)₃ (Scheme 1.15). Depending on the addition of the Lewis acid and aldehyde, different isomeric ratios of product were observed. If the aldehyde were added and then ytterbium (III), the trans-adduct 33 was the major product via an E-aza-iminium intermediate (Scheme 1.15). Inversely, alteration in the addition formed the Z-aza-iminium intermediate, and the cis-adduct 34 was obtained as the minor product. The mechanistic details were reflective of their previous work, and the products were obtained in good to excellent yields (ca. 16-90%). It is worthwhile to mention that some of the adducts’ ee were greater than 99%. Moreover, when the Boc group was replaced with a methyl carbamate, the selectivity was improved for the 2,5-cis-pyrazolidines significantly.
1.5.4 Reactivity of Donor-Acceptor Cyclopropanes

Vijayasree and co-workers reported unique procedures for accessing tetrahydrofuran-3-one 37, tetrahydropyran-3-one 36 and lactones 38 and 39 with regiocontrol through the cleavage of each D-A-A cyclopropane bond of 35 (Scheme 1.16).37 The group envisioned that different compounds could be obtained by chemoselective modification of the CO and CO₂Et acceptors and by regioselective cleavage of each cyclopropyl bond. After having prepared the cyclopropylfuranones in their enantiopure forms, the group subjected 40 to $n$-Bu₃SnH and AIBN to afford 41 in near quantitative yield (Scheme 1.17). Next, the second cyclopropyl bond cleavage was attained when TMSOTf with triethylsilane were the reagents used, and upon PCC oxidation, keto-esters 43a and 43b were formed in 66% or 62% yield, respectively. Further
treatment of 40 with allyltributyltin furnished trisubstituted tetrahydropyran-3-one 42 in 81% yield. For the third cleavage, the group reduced the ketone carbonyl to alcohol 44. Upon treatment of TMSOTf and Et₃SiH, tandem lactonization with the ester in situ formed the furofuranone 45 and 46 in 64%-89% yield.

Scheme 1.17: Reaction of Cyclopropanes to Furanones

The tandem ring-opening-lactonization sequence was general and various nucleophiles could be used to access THF, THP, and lactone derivatives (Scheme 1.18). Treatment of cyclopropane 47 with TMSOTf followed by PhSH provided thioether 48 in 85% yield, while dithiane derivative 50 was obtained in 78% using ethanedithiol. Lactone 51 was observed in 88% using TMSOTf and 1,3,4-(MeO)₃C₆H₃. Using a Brønsted acid mixture, H₂SO₄ and MeOH, tetrahydrofuran acetal 49 was observed in 69% yield.
1.6 Summary of Cyclopropanes and Its Reactivity

In summary, cyclopropanes are very useful synthetic subunits, in particular, vicinal D-A cyclopropanes as they behave similarly to 1,3-dipoles. These D-A cyclopropanes have participated in cycloaddition reactions, cycloisomerization reactions, ring expansion reactions, and intramolecular cyclization reactions. The previous examples on Lewis acid promoted transformations of cyclopropanes to afford a diverse array of scaffolds demonstrated the vast potential of these cyclopropanes as reactive subunits. These examples gave us insight on the effects of the promoter on product formation and the stereoselectivity of the reaction. Furthermore, the order of addition in the reaction may play a role on product formation. The lessons learned here provided us with more confidence to use D-A-A cyclopropanes as reactive subunits and to explore reactions using these products. The alkenyl homo-Nazarov cyclization is the cyclization of alkenyl cyclopropyl ketones to afford cyclohexenones and methylene cyclohexenols. Chapter Two will discuss the current limitations of the alkenyl homo-Nazarov cyclization as well as our solutions to some of these challenges. Chapter Two will also highlight our contribution to the heteroaryl homo-Nazarov cyclization (using the π-system of the heteroaromatics) to form heteroaryl ring-fused cyclohexanones. Chapter Three will discuss the
formation of 5-heteroaryl-2,3-dihydrofuran acetals and its utility for the formation of benzofused heteroaromatic compounds.

1.7 Cyclopropene and Its Properties

Since Freundler’s initial synthetic report of cyclopropene from the pyrrolysis of barium furoate in 1897, the strained carbocycle has garnered a tremendous amount of attention from synthetic chemists. Cyclopropene has a strain energy of approximately ~53 kcal/mol in the ground state, mainly attributed to the strain in the σ framework. Walsh’s model of cyclopropene’s bonding (Fig. 1.6) showed two $sp$-hybridized vinylic carbon atoms, in which one $p$-orbital on each carbon is responsible for the double formation, while the other orbitals contributes to the ring. The remaining carbon atom is $sp^2$ hybridized, resembling its saturated counterpart’s model, the cyclopropanes. The hybridization of the alkene carbons on the cyclopropene is closer to that of an alkyne rather than an alkene, further supporting the unusual reactivity of the cyclopropene ring. This is evident, as the addition across the double bond in cyclopropene proceeds readily to release ~26 kcal/mol of energy.

![Figure 1.6: Walsh Model of Cyclopropene](image)

1.8 Synthesis of Cyclopropenes
Freundler’s method did not provide appreciable amounts of cyclopropene due to its volatility and the high temperature necessary to distill the product. The first confirmed report for the synthesis of cyclopropene was by Dem’yanov and Doarenko in 1922. This report showed that cyclopropene \( 54 \) was achieved from the thermal decomposition of trimethylcyclopropylammonium hydroxide (generated from trimethylcyclopropylammonium iodide \( 52 \) and AgOH) on platinized clay at \( \sim 300 \) °C (Scheme 1.19). A byproduct of this reaction was the formation of dimethylaminocyclopropane \( 53 \).

![Scheme 1.19: Dem’yanov and Doyarenko’s Synthesis of Cyclopropene](image)

Since then, reports of the preparation of cyclopropenes from their corresponding cyclopropane precursors through elimination reactions which have been extensively reviewed. New advances from Davies, Fox and Gevorgyan for the synthesis of both racemic and stereoselective cyclopropenes through catalytic cyclopropenation of alkynes with diazo compounds in the presence of a rhodium catalyst have also been highlighted. In 2011, Shi summarized recent advances in cyclopropenation reactions.

1.9 Reactions of Cyclopropenes

This section will encompass relevant examples of transformations of cyclopropenes. Emphasis will be placed on metal catalyzed cycloisomerizations of cyclopropenes from 2007 to date. Other examples will focus on the formation of benzenoid products.

1.9.1 Thermal Expansion of Cyclopropenes
Cyclopropenes are highly strained subunits, and often participate in ring-opening reactions in order to release this ring strain. For example, irradiation of 1,2-diphenyl-3,3-dimethylcyclopropene 55 produced carbene 56, which then gave two isomeric dienes 57 and 58 in a 3:1 ratio (Scheme 1.20, equation a). Tetramethylcyclopropene 59 in the presence of high heat, 490 °C or 260-298 °C led to dimethylpenta-1,3-dienes 60 and 61 (Scheme 1.20, equation b). However, if there was a mono-methylsubstituted 65 or unsubstituted cyclopropene 52 (via diradical 63), alkyne products 64 and 66 were formed after pyrolysis as well as diene 67 (Scheme 1.20, equation c and d). When a trimethylsilyl (-TMS) group was used to stabilize the β-cationic center 69, Brønsted acid (p-TsOH) was able to promote the ring opening reaction of cyclopropene 68 to provide 1,3-diene product 70 (Scheme 1.20, equation e).

Scheme 1.20: Ring-Opening Reactions of Cyclopropenes

1.9.2 Gold Catalyzed Reactions with Cyclopropenes
Lee and coworkers reported a regioselective gold (I)-catalyzed ring-opening of cyclopropenes to generate substituted furanones and indenes. In this report, gold (I) activated the double bond of cyclopropene 71 as shown in 72. This activation caused the bond to break to form cationic/carbenoid complex 73 that may be subsequently trapped by nucleophiles (Scheme 1.21). This report showed that they were able to trap various alcohols to generate highly substituted enols. They further elaborated on the interaction of gold and the cyclopropene by having a phenyl and a carbonyl group substituted at the geminal position, initiating an intramolecular attack of the proposed vinyl cation/carbenoid complex.

Intramolecular attack of the ester carbonyl oxygen moiety on to C-1 of the vinyl cation/carbenoid intermediate and hydrolysis provided furanones 75a-c (Scheme 1.22). Indene 76a-c and 77a-c were formed as a result of the intramolecular attack of the Ph substituent in a Friedel Crafts type mechanism, further validating the proposed vinyl carbenoid/cationic intermediate. This report showed the use of three different substituents on the cyclopropene, with only one example of an electron donating and an electron withdrawing substituent. Further exploration of the reaction concluded that electronics did not play a major role in the product formation.
Scheme 1.23: Wang’s Strategy for Furanone Synthesis

Wang and coworkers demonstrated that AuPPh₃Cl/AgOTf in CH₂Cl₂ was an efficient promoter of the cycloisomerization of cyclopropenes 74a (Scheme 1.23). This example showed that furanone 75a was obtained in 40% yield in 1 h at room temperature. The furanone was formed due to the interaction of the intermediate vinyl-Au carbene with the carbonyl oxygen.

Scheme 1.24: Halide Triggered Cyclization of Cyclopropenyl-Substituted Alkyl Halides

Ma and coworkers reported a method for the synthesis of polyfunctionalized (E)-haloalkylidene cyclic products via a regio- and stereoselective halide triggered (X = I or Br) ring-opening/intramolecular trapping of cyclopropenes (Scheme 1.24). Dimethyl 2-(3-bromopropyl)-3-phenylcycloprop-2-ene-1,1-dicarboxylate 78 was subjected to 1.5 equiv of NaI and 0.5 equiv of Na₂CO₃ in acetone under reflux to probe the reaction. Only the (E)-iodobenzylidenecylopentane 79 derivatives were observed and none of the six membered ring was formed. In the mechanism, the halide attacked the adjacent position to the phenyl group. Upon cleavage of the cyclopropene’s C-C bond, the vinylic cation is quickly trapped by the iodide. This observation validated the mechanism by showing that the iodide anion only attacks regioselectively at the sp²-carbon adjacent to the phenyl group. They further applied the reaction to 5-(3’3’-bis(methoxycarbonyl)-cyclopropenyl)pentyl bromide and was able to isolate the 7-
membered product 80 in 57% yield. This protocol permits cyclopropenes with chain lengths of 2-4 carbons to provide products in 22-96% yield.

![Scheme 1.25: Plausible Mechanism for the Ring-Opening Cyclization Reaction](image)

Product formation seemingly arises from ring opening of cyclopropene 81 to generate a stabilized anion 82. This anion attacks and displaces the leaving group to form carbocycle 83 (Scheme 1.25). The regioselectivity is high, as the iodide anion only attacks the less substituted sp<sup>2</sup> carbon atom. The method’s versatility was demonstrated by construction of four- to seven-membered ring products. They further validate the method’s utility by preparing several different substituted cyclic products where the sp<sup>2</sup>-sp<sup>2</sup> C-bond was stereodefined.

### 1.10 Summary of Cyclopropenes and Their Transformations

In summary, cyclopropenes are highly strained and high energy species that readily ring open to release its ring strain. Examples shown include thermal rearrangements of cyclopropenes, halide triggered rearrangements of cyclopropenes, and gold catalyzed transformations of cyclopropenes in order to generate furanones and indenes. Lee’s success of using a gold complex as the catalyst to promote indene formation provided confirmation that a Lewis acid can promote rearrangements of cyclopropenes to form different benzenoid isomers. This further strengthens our hypothesis that a cyclopropene with a tethered heteroaromatic can provide benzofused heteroaromatics under the right conditions. Chapter Four will discuss our efforts in using 3,3’-dicarbonylcyclopropenes as the reactive subunit to generate benzofused heteroaromatic compounds. The reaction scope, mechanistic rationale and utility will be discussed in greater details.
1.11 Furan and Its Properties

Furan is a five membered heteroaromatic compound that is prevalent in naturally occurring and biologically active compounds. Furan has also found a major role in the backbone of many polymers.\textsuperscript{53,54} Industrially, furan is used as a solvent for resins, formation of lacquers and chemical intermediates for organic syntheses. Furan exists as a clear, colorless liquid, which turns brown upon standing.\textsuperscript{55}

Furan is planar, aromatic and contains $6\pi$ electrons. It is isoelectronic with the cyclopentadienyl anion. Furan has three major resonance contributors, and the charge distribution depicts the 2 and 5 position to be more nucleophilic as compared to the 3 and 4 position of the furan (Figure 1.7).\textsuperscript{56} Furan is sensitive to strong protic acids and Lewis acids, as ring opening reactions of furans have been demonstrated. Consequently, the methodology considered in this thesis takes into account this intrinsic property and further exploit it for construction of benzofused heteroaromatic compounds.

![Figure 1.7: Resonance Contributors of Furan and Charge Distribution](image)

1.12 Synthesis of Furans

One of the most well known strategies to access furans synthetically is via the Paal Knorr furan synthesis.\textsuperscript{57,58} In this reaction, 1,4-dicarbonyl systems undergo an intramolecular condensation promoted by acid and heat, followed by dehydration to provide substituted furans. This transformation is reversible, as furans can be converted back to 1,4-diketones. Feist-Benary synthesis of furan occurs when an alpha halocarbonyl reacts with a beta-dicarbonyl in the presence of base via an aldol condensation, followed by an intramolecular $O$-alkylation and
dehydration to furnish the furan product. Modified versions of these syntheses have proven to be the most powerful method for the synthesis of furans. However, these approaches are unsuitable for acid-sensitive substrates and require substitution on C-2 of the heterocycles due to instability of the precursors.

Figure 1.8: General Metal Catalyzed Cycloisomerization of Alkynyl Ketones and Imines

Therefore, catalytic approaches toward furans using milder conditions provided rapid access to multisubstituted furans. For example, transition metal-catalyzed cycloisomerizations of allenyl ketones are highly attractive (Figure 1.8). Marshall\textsuperscript{59-61} introduced Ag as the metal to promote the reaction, and it was elaborated by Hashmi\textsuperscript{62} using gold as the catalyst. Gevorgyan expanded on these methods by using copper as the catalyst for the cycloisomerization.\textsuperscript{63,64} He also revealed that the reaction proceeds through an allenylimine or ketone intermediate and the propargylic protons generally reside at the C-3 and C-4 positions of the ring. Despite a number of advantages for these protocols, the scope was limited to only the preparation of C-3 and C-4 unsubstituted heterocycles. Gevorgyan became interested in expanding the scope of the migratory group and they followed up with a general method for the 1,2-migration/cycloisomerization toward polysubstituted furans as well as multisubstituted 3-thio-, seleno-, halo-, aryl-, and alkyl-furans and pyrroles.\textsuperscript{65}

Polysubstituted furans are prepared from simple furans, with easy access to substitution at the 2- and 5- positions as compared to the 3- and 4- positions.\textsuperscript{66} Highly selective cyclization reactions from nonfuran starting materials are also efficient for the synthesis of polysubstituted furans.
1.13 Benzofused Heteroaromatic Compounds from Furans

Butin and coworkers developed a simple approach to 3-(2-acylvinyl)-2-(hetero)aryl-indoles 86 using an acid-catalyzed cyclization of 2-(2-aminophenyl)furans 84 with (hetero)aromatic aldehydes 85 (Scheme 1.26). This reaction proceeded via mild acid and provided indoles containing a reactive α,β-unsaturated ketone moiety. This ketone moiety served as a point of functionalization for further elongation. The scope of the reaction was examined using alkyl and halo substituted anilines and alkyl substitution on the furan along with electron rich and electron poor aldehydes. The substitution about the furan and aniline did not play a role in product yield. However, electron rich aldehydes gave slightly higher yields.

Scheme 1.27: Butin’s Furan Ring Opening-Indole Ring Closure Protocol

Butin and coworkers showcased a simple and efficient method for the synthesis of 2-(2-acetylvinyl)-3-(5-alkyl-2-furyl)indoles 88a by reductive cyclization of bis(5-alkyl-2-furyl)(2-
nitroaryl)methanes 87a in ethanol (Scheme 1.27). This protocol involved heating the furan substrates with SnCl$_2$·2H$_2$O in ethanol. The reaction proceeded via a nitrosoarene intermediate, which interacted with the furan ring via electrophilic nitrogen attack onto the C(2) position of the furan ring. Indole products were isolated in 30-73% yields. Electron rich aryl ring (p-methoxy) lowered the yields due to a decrease in the electrophilicity of the nitrosoarene nitrogen, as a result only provided aniline products. Further attempts to use related bis(5-alkyl-2-thienyl)(2-nitroaryl)methanes 87b under the same reaction conditions failed to undergo the analogous recyclization and were transformed into bis(5-alkyl-2-thienyl)(2-aminoaryl)methanes 89b instead.

![Scheme 1.28: Yin’s Pd-Catalyzed Arylative Dearomatization of Furans](image)

Yin and coworkers developed a Pd(0)-catalyzed dearomatization/intramolecular arylation of furan 90a-b to furnish functionalized benzofurans 91a and indoles 91b in moderate to good yields (Scheme 1.28). This involved the formation of a π-allylic palladium complex, furan ring opening, and a β-hydride elimination sequence. Careful optimization led to a mixture of Pd(PPh$_3$)$_4$ (5 mol%), PPh$_3$ (10 mol%) and K$_2$CO$_3$ (2 equiv) as the optimal conditions. Electron donating groups on the aryl ring (R$_3$) had a positive influence on the yield, while electron withdrawing groups (CF$_3$) did not provide any desired product. The authors rationalized that this may be due to the leaving group ability of the 4-CF$_3$-phenoxy group which resulted in the cleavage of the C-O bond in the presence of Pd(0).

1.14 Summary of the Reactions of Furans
As showcased, furans can be used as a reactive subunit in order to generate complex scaffolds such as benzofused heteroaromatics. In particular, metal catalyzed dearomatization and acid promoted cyclizations were shown in the examples above. Chapter Six of this thesis details the metal catalyzed ring opening of furans to form interesting benzenoid scaffolds. This will include the contributions made to the areas of Lewis acid catalyzed cycloisomerization of furan-3-carboxylates for benzofused heteroaromatic compounds. Relevant literatures will be discussed therein.

1.15 Outline of Thesis

In this thesis, five different methodologies using cyclopropanes and cyclopropenes as reactive subunits will be showcased. The goals of these methodologies are to address the current synthetic limitations (i.e. substrate scope, efficiency, and harsh reaction conditions) associated with them. Chapter Two will illustrate our efforts to solve the current limitations of the alkenyl and heteroaryl homo-Nazarov cyclization (cyclization of cyclopropyl ketones). The alkenyl homo-Nazarov cyclization’s (using simple vinyl π-systems) reaction optimizations, product characterizations, and scope and utility will be discussed. Based on the success of the alkenyl homo-Nazarov cyclization, the heteroaryl homo-Nazarov methodology was developed. In this methodology, the reactive π-unit is from the heteroaromatic, allowing for the formation of heteroaryl ring-fused cyclohexanones. A tandem cyclopropanation/homo-Nazarov protocol was demonstrated in which the one pot yield is higher than the two individual steps alone. Chapter Three will exhibit a method to generate a library of dihydrofurans from rearrangements of electron rich cyclopropanes. In this chapter, the utility of these dihydrofurans to generate benzofused heteroaromatic compounds, furans, and furanones will be shown. Chapter Four unveils the formation of cyclopropene-3,3’-dicarbonyl compounds from a rhodium catalyzed
decomposition of α-diazo compounds. These cyclopropenes are transformed into benzofused heteroaromatics via a catalytic amount of In(OTf)$_3$. Extensive discussion on the starting material formation and cycloisomerization of these building blocks to the benzofused heteroaromatic products is relayed. Mechanistic discussion of the cycloisomerization and protodesilylation will also be shown. Chapter Five highlights the formation of furan-3-carboxylates from α-diazo compounds. These furan carboxylates are able to convert to benzofused heteroaromatic compounds. Finally, Chapter Six will summarize all of research findings as well as outline several future directions.
Chapter Two: The Formal Homo-Nazarov Cyclization

2.1 Biologically Relevant Compounds with a Cyclohexenone Core

Organic structures containing cyclohexenones and heterocycles are of great importance in drug development. These architectures occur in many potent bioactive natural products and synthetic drugs, and can serve as important intermediates in organic synthesis. For example, jesterone 1 is an epoxyquinone natural product isolated from Pestalotiopsis jesteri which shows micromolar activity against the oomycetous fungi (Figure 2.1). Jesterone also shows activity against human breast and human cancer cell lines. Sarcodictyenone 2, extracted from the Mediterranean stolonifer Sarcodictyon roseum, displays cytotoxicity for HeLa cancer cell lines. Meanwhile, actinobolin 3, isolated from Streptomyces griseoviridus, has garnered much interest due to its broad-spectrum antibiotic activity as well as reasonable antileukemic activity. Viridin 4, a furanosteroid, has antibacterial and antifungal activity. Taberhanine 5 has anticancer activity. Morphine 6, the most abundant alkaloid found in opium, is a potent analgesic agent. Given that these cyclohexenone-containing natural products have a diverse activity profile, new methodologies to access them are of importance.

Figure 2.1: Examples of Cyclohexenone Containing Natural Products
2.2 Selected Methods for Cyclohexenone Preparation

Industrially, simple cyclohexenones are prepared from the Birch reduction of phenol, although many methods exist for their construction. Given the expansive quantity of strategies for their construction, selected metal-catalyzed examples that were disclosed in the last ten years will be discussed. Efforts towards the synthesis of the indole alkaloid welwitindolinones led Tang and co-workers to disclose a Rh(I)-catalyzed [5+1] cycloaddition of allenyl cyclopropanes 7 to generate the cyclohexenone core 8 (Scheme 2.1).75 Only one example of the [5+1] cycloaddition was shown, and no other reports have ensued.

Scheme 2.1: Tang’s Rh(I) Catalyzed [5+1] Cycloaddition of Allenyl Cyclopropanes

Wang and co-workers disclosed a platinum-catalyzed hydrative cyclization of 1,5-diynes 9 to generate cyclohexenones 10 (Scheme 2.2).76 This newly developed metal-catalyzed hydrative cyclization reaction is not only an attractive “green” hydrodemetalation procedure, but also an ideal synthetic method for preparing cyclic enone compounds. In this protocol, various electron withdrawing groups (esters, phosphonates, carbonyls) were tolerated. The reaction mechanism involves initial coordination of the metal to alkyne 11 to form intermediate A, followed by a Markovnikov addition of water gave enol B and tautomerization furnished the 1,5-diketo platinate (C) (Scheme 2.3). Cleavage of the metal generated the ketone intermediate D,
followed by an aldol condensation formed the cyclohexenone product 12. Alternatively, tautomerization of the enol promoted the attack on to the alkyne and facilitated the insertion of platinum into the alkyne to form intermediate E. Final demetalation of intermediate F provided cyclohexenone 12.

![Scheme 2.3: Proposed Mechanism of Pt-Catalyzed Hydrative Cyclization of 1,6-Diynes](image)

Taber and co-workers reported the ring expansion of vinyl cyclopropane 13 to enone 14 using UV irradiation in the presence of Fe(CO)₃. This methodology permits the synthesis of steroidal cyclohexanones 15 (Scheme 2.4).⁷⁷ In this methodology, using less than 1 equivalent of Fe(CO)₃ reduced the conversion rate, while increasing the loading to more than 2 equivalents did not provide significant improvements in product formation. Higher yields were obtained by periodic agitation of the reaction mixture which increased the irradiation of the film formed between the product and the starting material. This methodology was highly efficient, as products were obtained in good to high yields (72-89%).

![Scheme 2.4: Taber’s Cyclohexanone Synthesis](image)
Widenhoefer and co-workers developed a Pd-catalyzed intramolecular oxidative alkylation of unactivated olefin 16 to form cyclohexenone 17 (Scheme 2.5).\textsuperscript{78,79} In this report, 11 examples of various 1,3-dicarboxyls were shown. This methodology tolerated a variety of acyl groups, including ethyl, propionyl, \textit{tert}-butyl, as well as cyclohexyl in excellent yields (70-85% yield).

\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{Ac} \\
\text{Me} & \quad \text{O} & \quad \text{Ac} \\
\text{16} & & \text{17}
\end{align*}

\textbf{Scheme 2.5:} Widenhoefer’s Approach Towards Cyclohexenones

Li showed a Lewis acid-catalyzed Conia-ene rearrangement of \(\beta\)-alkynic-\(\beta\)-dicarboxyls 18 as a method to form cyclohexenones 19 in 52-80% yield (Scheme 2.6).\textsuperscript{80,81} Activation of the 1,3-dicarboxyl system by Yb(OTf)\(_3\), followed by coordination of ZnCl\(_2\) to the alkyne promoted the alkylation. This methodology tolerated both terminal and internal alkynes, as well as sterically hindered alkynes. Cyclohexenones were formed in fair to good yields (36-80%).

\begin{align*}
\text{O} & \quad \text{O} & \quad \text{OEt} \\
\text{18} & & \text{Yb(OTf)}_3 (1 \text{ equiv}) & \text{ZnCl}_2 (10 \text{ mol} \%) \\
\text{R} & & 52-80\% & \text{R=H, Me, Ar} \\
\text{19} & & 
\end{align*}

\textbf{Scheme 2.6:} Li’s Conia-Ene Reaction of \(\beta\)-Alkynic-\(\beta\)-Dicarboxyls

Yu and coworkers developed a method utilizing Rh(I) to catalyze the [5+1] cycloaddition of vinylcyclopropanes 20 and CO to generate cyclohexenones (Scheme 2.7).\textsuperscript{81} After screening various conditions and Rh(I) catalysts, it was found that treating vinyl cyclopropanes in the presence of 10 mol% of [Rh(dppp)]OTf in 1,2-DCE at reflux provided a mixture of \(\alpha,\beta\)- and \(\beta,\gamma\)-
cyclohexenones 21 (41-74% yield) and 22 (7-43% yields). Using [Rh(dppp)]OTf afforded the \( \beta,\gamma \)-cyclohexenones 21 as the major product whereas treatment of vinylecyclopropanes with [Rh(dppp)]SbF\(_6\) followed by DBU gave the \( \alpha,\beta \)-cyclohexenones 23 as the major product (43-85% yield). The scope of this methodology was significant, as alkyl substituents, alkenyl substituents, ethers, and even unprotected alcohols were tolerated.

\[ \text{Scheme 2.7: Yu’s Rh(I)-Catalyzed [5+1] Cycloaddition of Vinylecyclopropanes and CO} \]

2.3 Introduction to the Formal Homo-Nazarov Cyclization

Given that cyclohexenone natural products are highly prevalent and are difficult to isolate, synthetic organic chemistry can be an alternative to access these natural products. This complements the goal of synthetic chemists to develop efficient, cost-effective and new approaches towards the formation of the cyclohexenone core. Since the discovery of the predictable reactivity of D-A cyclopropanes, synthetic chemists have exploited these building blocks for the formation of different core scaffolds. In line with this would be the formal homo-Nazarov cyclization reaction, in which D-A cyclopropanes were used to construct cyclohexenones. Despite the incommensurable number of approaches towards the synthesis of cyclohexenones, the need for a facile and rapid method for the formation of these structures still exists. The homo-Nazarov cyclization is an alternative strategy to address some of the challenges.
2.4 The Homo-Nazarov Cyclization versus the Nazarov Cyclization

In the presence of acid promoters, cyclopropyl aryl (or heteroaryl) ketones and cyclopropyl vinyl ketones undergo ring-opening/Friedel-Crafts annulations to generate α-tetralones, cyclohexenones, and heteroaryl-fused cyclohexanones (Fig. 2.2). The mechanistic pathway involves cyclopropane ring-opening to afford a 1,3-dipole, followed by adjacent π-attack to form a six-membered oxyallyl cation. Tautomerization upon work-up generates cyclohexenone. Due to the homology with the classic Nazarov cyclization, in which Brønsted or Lewis acids can promote the cyclization of divinyl ketones (via the formation of a five-membered oxyallyl cation) to generate cyclopentenones, these transformations have been termed by Tsuge as homo-Nazarov cyclizations. However, it should be noted that the mechanism is not the same. The Nazarov cyclization is governed by the Woodward-Hoffmann rules (FMO-4π-conrotatory cyclization) while the homo-Nazarov is not. The homo-Nazarov is a polar mechanism via the generation of an acyclic cation followed by the formation of an oxyallyl cation intermediate. Unlike the well-studied Nazarov cyclization, the homo-Nazarov reaction has been relatively underexplored in the literature (Figure 2.2).

![Diagram of Nazarov Cyclization and Formal Homo-Nazarov Cyclization](image_url)

**Figure 2.2:** The Nazarov Cyclization versus the Formal Homo-Nazarov Cyclization
2.4.1 Stoichiometric Homo-Nazarov Cyclization

Newman reported that the treatment of aryl aroyl cyclopropanes with PCl\textsubscript{5} readily forms 1-aryl-naphthalenes,\textsuperscript{86} while rigid cyclopropyl ketones were used by Stork for the synthesis of benzodecalones.\textsuperscript{87} Grieco was able to use non-rigid alkylcyclopropylketones to generate benzodecalones.\textsuperscript{88} However, it was Murphy and co-workers that followed with a report on the use of aryl aroyl cyclopropanes as versatile building blocks to cyclohexanones.\textsuperscript{89} In Murphy’s example, cyclopropyl ketones 31 were treated with stannic chloride (SnCl\textsubscript{4}) in benzene at room temperature to afford tetralones 32 in 15-80% yield (Scheme 2.8). Murphy disclosed that the cyclization was influenced by both the solvent and catalyst. Murphy also found evidence of a cationic intermediate for the cyclization. Even though this report provided a lot of information for the homo-Nazarov cyclization, it had many limitations. For example, Murphy’s protocol only worked for activated cyclopropanes, and dihydrofuran products were observed in 8 out of the 20 cases due to the attack of the enolate onto the carbocation. Murphy’s protocol also required long reaction time ( >8 h) and a large excess of SnCl\textsubscript{4}.

\[
\begin{align*}
\text{SnCl}_4 \, \text{(4 equiv.)} &\quad \text{benzene, rt} \\
15-80\% &\quad \text{SnCl}_4 \rightarrow \text{32} \\
\end{align*}
\]

\( R_1 = 3\text{-OMe}, 4\text{-OMe}, H \)
\( R_2 = 2\text{-OMe}, 4\text{-OMe}, H, 3\text{-OMe}, 3\text{-OH} \)

**Scheme 2.8**: Murphy’s Homo-Nazarov Cyclization Protocol

Tsuge and co-workers disclosed a report on the cyclization of 1-alkenyl cyclopropyl ketones 33 in presence of excess acid (Scheme 2.9).\textsuperscript{85} In this report, an example of the homo-Nazarov cyclization was achieved using vinyl cyclopropyl ketones in the presence of excess polyphosphoric acid. Heating at reflux in benzene afforded the cyclohexanone derivative 34 in
63% yield. However, Tsuge’s protocol was extremely limited, as only 5 out of the 16 cyclopropane precursors actually provided the desired cyclohexenones. In addition, Tsuge’s protocol required a large excess of SnCl₄ (4 equiv), long reaction times (24 h to 10 d) and high temperature (80 °C).

Scheme 2.9: Tsuge’s homo-Nazarov Cyclization Protocol

In 2005, with an interest in thienyl and furyl propenones and their reactions with malonates, cyanoacetates, and malononitrile, Otto and co-workers synthesized heteroaryl cyclopropyl ketones. These heteroaryl cyclopropyl ketones generated heteroaryl ring-fused cyclohexanones in the presence of excess SnCl₄ in 54% to 90% yield (Scheme 2.10). However, only the furanyl (90% yield) and thienyl (54% yield) derivatives were explored.

Scheme 2.10: Otto’s Homo-Nazarov Cyclization Protocol

In 2008, Yadav and co-workers reported a homo-Nazarov cyclization protocol for the synthesis of 4-silylmethyl-substituted 2,3-heteroaromatic ring-fused cyclohexenones (Scheme 2.11). Using 4 equivalents of SnCl₄ in 1,2-dichloroethane at reflux, 2-t-butyl diphenylsilylmethyl-substituted cyclopropyl heteroaryl ketones 37 and 40 cyclized to furnish 2,3-heteroaromatic ring-fused cyclohexenones 39 and 42 in 70-85% yield, respectively. The reaction design was applicable for furans, pyrroles, thiophenes, and indoles. The silylmethyl
group served as a competent donor compared to a simple alkyl substituent due to stabilization of
the transient six-membered carbocationic intermediates $38$ and $41$ (formed upon ring opening)
through the $\beta$-silyl effect. Furthermore, the group acted as a chemical handle for further
derivatization by conversion to alcohols under Fleming oxidation conditions. Finally, the use of
an ether as a donor group was also successfully demonstrated for the first time. Yadav’s protocol
provided a lot of insight into the heteroaryl homo-Nazarov cyclization; however, only TBDPS-
based cyclopropanes worked.

\[
\begin{align*}
X = & \begin{array}{c}
\text{O, S, NH} \text{ (37)}
\end{array} \\
\text{SnCl}_4 & \xrightarrow{\text{1,2 DCE, 80 oC}} \text{SiPh}_2\text{-Bu} \\
\text{38} & \rightarrow \text{39}
\end{align*}
\]

\[
\begin{align*}
X = & \begin{array}{c}
\text{O} \text{ (40)}
\end{array} \\
\text{SnCl}_4 & \xrightarrow{\text{1,2 DCE, 80 oC}} \text{SiPh}_2\text{-Bu} \\
\text{41} & \rightarrow \text{42}
\end{align*}
\]

**Scheme 2.11:** Yadav’s Homo-Nazarov Cyclizations with 2-Silylmethyl Donor Groups

### 2.4.2 Catalytic Homo-Nazarov Cyclization

\[
\begin{align*}
\text{R}_1 & \xrightarrow{\text{20 mol % $p$-TsOH}} \text{CH}_3\text{CN} \\
\text{X} = & \begin{array}{c}
\text{CHTMS} \text{ (43)}
\end{array} \\
\text{R}_2 & \xrightarrow{\text{20 mol % $p$-TsOH}} \text{CH}_3\text{CN} \\
\text{R}_1 & \xrightarrow{\text{20 mol % $p$-TsOH}} \text{CH}_3\text{CN} \\
\text{44} & \rightarrow \text{45}
\end{align*}
\]

**Scheme 2.12:** Waser’s Brønsted Acid-Catalyzed Formal Homo-Nazarov Cyclization

Historically, all previous examples of the homo-Nazarov cyclization used stoichiometric
amounts of Brønsted or Lewis acids in order to promote reactivity. This requirement has,
ultimately, resulted in limited application of the methodology. To address this issue, Waser
reported the first example of a catalytic homo-Nazarov cyclization using dihydropyran- and dihydrofuran-substituted cyclopropyl ketones 43 to generate cyclohexenones 44 and 45 (Scheme 2.12).\textsuperscript{82,93} He observed that while most Lewis acids led to polymerization of the dihydropyran substrate, certain Brønsted acids were a viable alternative. The $p$Ka of the catalyst appeared to have a strong influence on the outcome of the reaction; sulfonic acids were optimal. Stronger acids led to decomposition of the starting material, while weaker acids were unable to achieve full conversion. The optimized conditions of $p$-TsOH (20 mol\%) in acetonitrile at room temperature afforded the desired cyclohexenones in 15-99\% yield. To achieve the desired cyclization, electron-rich aromatic donor substituents were necessary. Similarly, without the heteroatom donor in the $\alpha$-position, no reaction was observed unless a silyl directing group was present at the $\beta'$-position.

\textbf{Scheme 2.13:} Waser’s Postulated Mechanism for the Homo-Nazarov Cyclization

A stepwise mechanism was proposed where ring-opening is the rate-determining step, followed by a rapid cyclization event (Scheme 2.13). Protonation of cyclopropane 46 formed TS1, followed by ring opening to form carbocation 47. Attack of the adjacent $\pi$-system formed 48. Tautomerization of the enol intermediate to 49 followed by a Nazarov type elimination
provides cyclohexenone 53. Carbocation intermediate 47 could also undergo enolization to intermediate 50. Trapping of the π-system furnished intermediate 49 and elimination formed product 53. Carbocation 50 can be attacked by the enolate oxygen to form 51. Tautomerization provides dihydrofuran 52, which is the result of an unproductive pathway.

Waser also probed the reaction by using the π-system of a heteroaryl substituent as the pendant nucleophile. When the heteroaryl subunit was a protected or unprotected 2-indole as in cyclopropane 54, cyclization readily occurred to provide the desired fused cyclohexenone 55 in quantitative yield (Scheme 2.14). However, when other heteroaryl groups were employed, no desired cyclization was observed.

**Scheme 2.14:** Brønsted Acid-Catalyzed Heteroaromatic Homo-Nazarov Cyclization

An interest in accessing the *Aspidosperma* indole alkaloid core led Waser to explore amino groups as donor substituents for the homo-Nazarov cyclization. Using cyclopropanes 56 as the substrate, and upon cyclopropane ring-opening, a transient iminium ion was formed. This ion is readily attacked by the adjacent π-system. Interestingly, when the indole nitrogen is unprotected, catalyst and solvent selections have a direct impact on the outcome (Scheme 2.15). With Cu(OTf)₂ (15-25 mol%) in acetonitrile, the anticipated homo-Nazarov product 57 was formed in high yield (88-95%). In contrast, with catalytic p-TsOH in CH₂Cl₂, the N,N-acetal product 58 was observed as a result of attack of the indole nitrogen on the iminium intermediate.
Next, Waser and co-workers used this protocol for the synthesis two *Aspidosperma* alkaloids, the total synthesis of Goniomitine 60 (Scheme 2.16, equation 1) and a formal synthesis of Aspidospermidine 62 (Scheme 2.16, equation 2). Cyclopropane 60, bearing a 3-(siloxyethyl)indole moiety, was cyclized in the presence of a catalytic amount of \( p \)-TsOH, provided the tetracyclic core 58 of goniomitine in 93% yield. A sequence of reduction, acetylation, and deprotection afforded goniomitine 60 in 13 linear steps and an overall yield of 11% starting from \( \delta \)-valerolactam.

The formal synthesis of Aspidospermidine 62 was achieved using Cu(OTf)\(_2\) (15 mol%) to promote the cyclization of aminocyclopropane 61 to form heterocycle 57 (Scheme 2.16). Heterocycle 57 was the intermediate reported by Wenkert and Hudlicky in their total synthesis of Aspidospermidine.\(^{28}\) Waser and co-workers demonstrated that the utility of this methodology is high by these two synthetic examples; however, his catalytic heteroaryl homo-Nazarov cyclization remained underexplored and was not amenable to acid sensitive substrates.
These early examples showed that excess Lewis acid can promote the homo-Nazarov cyclization. Using a strong donor group and activated alkenes, a catalytic amount of Brønsted acid can also promote the cyclization. Utility of this protocol for total syntheses of alkaloid natural products were also shown. Despite these seminal contributions, many limitations still exist for the protocol, such as long reaction times, high temperature and limited scope. Therefore, a need for the development of a catalytic homo-Nazarov cyclization that will be amenable to simple, unactivated alkenes and expansion of heteroaromatics still exists.

### 2.5 Alkenyl Homo-Nazarov Cyclization Project Objective

D-A cyclopropanes undergo ring opening in the presence of a Lewis acid in a predictable manner to provide 1,3-dipoles that react in cycloaddition and cyclization reactions. With the limited number of examples in the literature about the alkenyl homo-Nazarov cyclization, we were extremely interested in expanding the scope and utility of this methodology. This facilitated our goal of developing a catalytic alkenyl homo-Nazarov cyclization to form functionalized six-membered rings.
2.6 Hypothesis and Rationale for the Methodology

We envisioned using vinyl cyclopropyl ketones bearing a secondary acceptor (such as an ester or ketone) in the α’-position would promote the cyclization (Scheme 2.17). The additional acceptor group in the α’-position to form a donor-acceptor-acceptor (D-A-A) cyclopropanes will allow for a bidentate coordination to the Lewis acid and further “polarize” the C1-C3 bond, which will lower the activation barrier for this C1-C3 bond cleavage. This allows for rapid ring opening of the cyclopropanes to the cation, which then can be trapped by any π-system. By facilitating the rapid ring opening, the nucleophilicity of the π-system will not play a role in the rate-determining step (RDS), hence simple unactivated alkenes will work. Upon π-attack, the acceptor group will polarize the resulting cyclic oxyallyl cation by localizing charge density on the α-carbon, providing predictable reaction outcomes.

Scheme 2.17: Homo-Nazarov Cyclization of Cyclopropane with Secondary Acceptor

2.7 Development of the Methodology

We began our study with cyclopropyl vinyl β-ketoesters containing an electron-rich aromatic donor group and an unactivated alkene. The model substrate can rapidly be prepared from the formation of a β-ester weinreb amide 63, followed by a diazo transfer in order to furnish the bench stable α-diazo compound 64. Diazo 64 was subjected to a rhodium catalyzed cyclopropanation with 4-methoxystyrene to generate the cyclopropane precursor 65 with the donor group installed. Treatment of our cyclopropane with the vinylgrignard reagent readily
furnished the necessary alkenyl cyclopropyl ketone 66a as our model substrate (Scheme 2.18). This model substrate was chosen due to the ease of characterization in the NMR.

Scheme 2.18: Synthesis of the Model Substrate

Using the model substrate 66a, various Lewis acids were used to promote the cyclization. Upon generation of the acyclic carbocation, trapping by the pendant vinyl system yields a six-membered oxyallyl cation. Attack of the π-system onto the carbocation, followed by work-up provided cyclohexenone 68a and methylene cyclohexanol 67a (Scheme 2.19).

Scheme 2.19: Initial Lewis Acid Screen for the Alkenyl Homo-Nazarov Cyclization

Upon ring opening of the cyclopropane to generate carbocation intermediate 70, another product could be formed. The undesired dihydrofuran 69a can result from the attack of the enolate (shown in 72) on the acyclic benzylic cation intermediate 71 (Scheme 2.20). This is a result of a less tightly bound Lewis acid to the two carbonyls. Hence, a Lewis acid that can tightly bind to the dicarbonyl will be able to circumvent this undesired product formation.
Scheme 2.20: Mechanism for Dihydrofuran Formation

Cyclopropane 66a (derived from 2-butenes) was subjected to 30 mol% of each Lewis acid, Sc(OTf)3, In(OTf)3, Al(OTf)3, Zn(OTf)2, Cu(OTf)2, Ag(OTf), Mg(OTf)2, Yb(OTf)3, Pd(PPh3)4, Pd(OAc)2, and Pd(PPh3)2Cl2, as well as investigating various solvents and temperature to determine the best reaction condition. Using crude NMR*, it was determined that only In(OTf)3 in dichloromethane at room temperature was able to selectively generate the desired cyclohexenone and methylene cyclohexanol (Figure 2.3).

![Lewis Acid Screen](image)

**Figure 2.3**: Lewis Acid Screen for the Alkenyl Homo-Nazarov Cyclization

* See Experimental Section
The two possible homo-Nazarov products, cyclohexenones 68 and methylene cyclohexenols 67, can form from carbocation intermediate 73, which is the intermediate from subjecting cyclopropane 66 to 30 mol% of In(OTf)₃ (Scheme 2.21). The expected homo-Nazarov product, cyclohexenone 68, arises from the standard Nazarov-type eliminative pathway. Unexpectedly, a cross-conjugated enol (methylene cyclohexenol 67) was also observed. This product is formed from the elimination of Hₐ.

Scheme 2.21: Possible Pathways for Product Formation

Cyclohexenones 68 and methylene cyclohexenol 67 (the homo-Nazarov products) are formed in 75% combined yield in a 3:2 ratio of the exocyclic to endocyclic alkene product, which are separable via column chromatography (Table 2.1, entry 1). Cyclopropane 66b derived from cyclohexene was used to form bicyclic products, and this also provided the mixture of exocyclic product 67b in 45% yield, and endocyclic product 68b in 30% yield (Table 2.1, entry 2). Next, the effects of the simple vinyl system was explored, and a mixture of the exocyclic product 67c in 46% yield (80% BRSM) and the endocyclic product 68c in 31% yield was achieved (Table 2.1, entry 3). The effects of the donor group was investigated by using the phenyl group as the donor group. Only one product, methylene cyclohexenol 67d was isolated in 46% yield (Table 2.1, entry 4). When a poor donor group was used, such as cyclopropane 66e, derived from 4-fluoro styrene, the homo-Nazarov cyclization produced methylene cyclohexenol
67e in 55% yield (77% BRSM) (Table 2.1, entry 5). However, the reaction did not go to completion after 24 hours. The product ratio can be influenced through strategic installation of the silyl group. For instance, presence of a β'-silyl group (as in 66f) results in the formation of only the exocyclic alkene product 67e in 92% yield. (Table 2.1, entry 6).
Table 2.1: In(OTf)$_3$-Catalyzed Homo-Nazarov Cyclization of Alkenyl Cyclopropyl Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product(s) (%) yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image]</td>
<td>![Image] 66a (45%) ![Image] 66a (30%)</td>
</tr>
<tr>
<td>2</td>
<td>![Image]</td>
<td>![Image] 66b (45%) ![Image] 66b (30%)</td>
</tr>
<tr>
<td>3</td>
<td>![Image]</td>
<td>![Image] 66c (48%) ![Image] 66c (31%)</td>
</tr>
<tr>
<td>4</td>
<td>![Image]</td>
<td>![Image] 66d (46%)$^d$</td>
</tr>
<tr>
<td>5$^c$</td>
<td>![Image]</td>
<td>![Image] 66e (55%)$^d$</td>
</tr>
<tr>
<td>6</td>
<td>![Image]</td>
<td>![Image] 66f (92%)</td>
</tr>
<tr>
<td>7</td>
<td>![Image]</td>
<td>![Image] 66g (93%)</td>
</tr>
<tr>
<td>8$^c$</td>
<td>![Image]</td>
<td>![Image] 66h (29%)$^d$</td>
</tr>
</tbody>
</table>

$^a$ Reactions run with 1 equiv of substrate 4 and 30 mol % In(OTf)$_3$ in CH$_2$Cl$_2$ at 25 °C and complete within 1h. $^b$ Isolated yields after column chromatography. $^c$ Reaction did not go to completion over 24h. $^d$ Yields based on recovered starting material are as follows: 67d (80%); 67e (77%); and 68h (50%).

Other unactivated alkenes demonstrate similar reactivity (~75% yield, 3:2 ratio), while activation of the alkene with an $\alpha'$-oxygen allows for efficient cyclization (Table 2.1, entry 1-3). This was demonstrated via cyclopropane 66g undergoing cyclization to provide cyclohexenone.
68g in 93% yield (Table 2.1, entry 7). When an α-aryl substituted alkene was employed, in the case of cyclopropane 66h, the dienol 68h was isolated in 29% yield (50 % BRSM) (Table 2.1, entry 8). The low yield could be attributed to the fact that along with unreacted starting material, the major component was the dihydrofuran byproduct. This is the only example in which the homo-Nazarov product is the minor product in the presence of In(OTf)$_3$. A possible explanation for this is if 66h exists as the less reactive s-cis enone, a bond rotation may be required to attack the carbocation generated. MMFF calculations were used to validate this rationale, and confirmed that the s-cis conformation is more stable than the s-trans conformation by 6 kcal/mol due to the stabilizing π-interactions between the α-phenyl substituent and the oxygen lone pairs of the adjacent ester group. Consequently, the trapping of the acyclic cation by the enolate upon ring opening is much faster than the attack of the π-system due to difficulty in rotation.

Further illustration of the utility of the reaction was confirmed by using methylene cyclohexenols 67c and cyclohexenones 68a as synthetic building blocks (Scheme 2.22). Addition across the exocyclic double bond using Et$_3$N and PhSH converted cyclohexenol 67c into a 1:1 diastereomeric mixture of thioether 73. Krapcho decarbalkoxylation of cyclohexenone 68a was performed to furnish 74 in 74% yield.

![Scheme 2.22: Functionalization of the Homo-Nazarov Products](image-url)
2.8 Heteroaryl Homo-Nazarov Cyclization

In efforts to expand the scope and utility of the homo-Nazarov cyclization, we were interested in using of the reactive π-unit derived from a heteroaromatic ring. This expansion in scope can serve as an efficient methodology for the construction of heteroaryl ring-fused cyclohexanones and its natural products.

With this concept in mind, we envisioned employing these donor-acceptor-acceptor (D-A-A) cyclopropanes with heteroaromatics as reactive π-systems in order to generate heteroaryl ring-fused cyclohexanones 77 from the homo-Nazarov cyclization of cyclopropyl heteroaryl ketones 75 (Scheme 2.23). The hypothesis includes the generation of carbocation intermediate 76 in order to promote the cyclization.

![Scheme 2.23: France’s Approach to Heteroaryl Homo-Nazarov Cyclization](image)

2.9 Development of the Methodology

Cyclopropane precursors were synthesized according to the general scheme 2.24. Addition of the enolate of methyl acetate to the appropriate 2- or 3-substituted heteroaromatic acid chloride 78 (freshly prepared from heteroaryl acid and oxalyl chloride) provided β-ketoesters 79 (Scheme 2.24). Diazo transfer with TsN₃ and Et₃N then provided α-diazo esters 80. Finally, treatment of the diazo 80 with Rh₂esp₂ (dirhodium α,α,α’,α’-tetramethyl-1,3-benzenedipropanoate) in the presence of the requisite alkene provided cyclopropanes 81 as the homo-Nazarov precursors.
Thiophene was chosen as the first heteroaromatic moiety examined for optimizing our protocol due to its stability in presence of Lewis acids\textsuperscript{98} and ease of commercial availability. The 2-thienyl cyclopropane 81\textsubscript{a} was synthesized and used as the substrate for catalyst screening (Table 2.2). Influenced by the success of the alkenyl homo-Nazarov cyclization,\textsuperscript{99} we began by screening In(OTf)\textsubscript{3}. When subjected to 30 mol\% of In(OTf)\textsubscript{3}, cyclopropane 81\textsubscript{a} successfully cyclized to give the 2,3-thienyl ring fused cyclohexanone 82\textsubscript{a} in 88\% yield in less than 3 h (Table 2.2, entry 1). Despite this great result, we wanted to develop a more robust and efficient protocol. Therefore, the first factor we were interested in was the effects of lowering the amount of catalyst. With the initial starting point of 30 mol\%, the loading was gradually decreased to 1 mol\%. As the catalyst loading was decreased, unsurprisingly, the reaction time increased. This is due to the fact that the rate determining step is the generation of the necessary acyclic carbocation intermediate. A catalyst loading of 5 mol\% of In(OTf)\textsubscript{3} provided the homo-Nazarov product in 86\% yield after 5 h (Table 2.2, entry 2), which was highly comparable to the results with 30 mol\% catalyst. Notably, 1 mol \% In(OTf)\textsubscript{3} efficiently catalyzes the reaction, albeit with a lower yield of 77\% after 6.5 h (Table 2.2, entry 3). Similarly, 5 mol\% of InCl\textsubscript{3} catalyzes the cyclization in comparable time (4.5 h) to In(OTf)\textsubscript{3} (5 h), but with a significant decrease in yield 78\% vs. 86\% (Table 2.2, entry 4). Inspired by its successful use in Sc(OTf)\textsubscript{3}- and In(OTf)\textsubscript{3}- catalyzed Friedel-Crafts acylations and Nazarov cyclizations, LiClO\textsubscript{4} was explored as an additive.\textsuperscript{100} However, when 1 equiv of LiClO\textsubscript{4} was used with either In\textsuperscript{3+} salt, very low conversion was observed. Thus, In(OTf)\textsubscript{3} at 5 mol \% loading in dichloromethane at room

\textbf{Scheme 2.24: Synthesis of Heteroaryl Cyclopropanes}
temperature was chosen as the final protocol due to the isolated yield and reasonable reaction time. After determining the best Lewis acid and Lewis acid loading, we also screened different solvents (dichloromethane, benzene, tetrahydrofuran and acetonitrile) to determine the best solvent system; however, it was determined that CH₂Cl₂ was the best solvent for the cyclization.

**Table 2.2: Effect of Catalyst Loading**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Loading (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In(OTf)₃</td>
<td>30</td>
<td>2.5</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)₃</td>
<td>5</td>
<td>5</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)₃</td>
<td>1</td>
<td>6.5</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>InCl₃</td>
<td>5</td>
<td>4.5</td>
<td>78%</td>
</tr>
</tbody>
</table>

With optimized conditions for the cyclization obtained and in line with our interest of developing a modular approach, a diverse set of heteroaryl substrates was examined to determine the reaction scope and limitations (Table 2.3). In direct comparison to the 2-thienyl cyclopropane 81a which afforded 82a in 86% yield as a 1.5/1 mixture of trans:cis diastereomers (Table 2.3, entry 1), the 3-thienyl substrate 81c provided cyclohexanone 82c in 73% yield (1.7:1 dr) (Table 2.3, entry 3). In contrast, the 3-furanyl substrate 81d (Table 2.3, entry 4) provided its product 82d (1.1:1 dr) in a higher yield (73% vs. 67%) than that of its 2-furyl counterpart 82b (1.1:1 dr) from cyclopropane 81b (Table 2.3, entry 2). The 2-furyl yield was slightly lower perhaps due to degradation of the starting material in the presence of the Lewis acid. The 2-indolyl cyclopropane 81e afforded cyclized product 82e in 63% yield (1.2:1 dr) (Table 2.3, entry 5), and 3-indole 81g gave product 82g in a comparable yield of 61% (1.2:1 dr) (Table 2.3, entry 7). This provides a new route to generate indole fused cyclohexanones, which are of great interest in
alkaloid natural products. Similarly, the 2-benzofuran 81f cleanly cyclized to give 82f in 91% yield (1.2:1 $dr$) (Table 2.3, entry 6) and 3-benzofuran 81h afforded the desired product 82h in 71% yield (1.2:1 $dr$) (Table 2.3, entry 8). This is noteworthy because the benzofuran had been unsuccessful as a homo-Nazarov substrate due to issues with competing polymerization.\(^{101}\) Using this methodology, both the 2- and 3-benzofuran fused products were formed in high yields.

To date, only 2,3-ring-fused heteroaromatics had been synthesized using homo-Nazarov cyclizations.\(^{91}\) Therefore, as an expansion of the scope of this reaction, we were interested in developing a method that would allow for formation of 3,4-ring-fused compounds as well. We hypothesized that if we employed a 3-substituted substrate with the 2-position blocked, as in the 2-bromo thienyl cyclopropanes 81i, then the 3,4-ring-fused cyclohexanones can be achieved. With the 2-position unavailable, the only site for nucleophilic attack would be the 4-position. Thus, cyclization of 81i should produce the 3,4-fused heteroaryl cyclohexanone 82i. As anticipated, when subjected to the reaction conditions, 81i generated the desired product 82i in 56% yield (Table 2.3, entry 9).
Table 2.3: Heteroaromatic Homo-Nazarov Cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>dr (trans/cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81a X=S</td>
<td>82a</td>
<td>86%</td>
<td>1.5/1</td>
</tr>
<tr>
<td>2</td>
<td>81b X=O</td>
<td>82b</td>
<td>67%</td>
<td>1.1/1</td>
</tr>
<tr>
<td>3</td>
<td>81c X=S</td>
<td>82c</td>
<td>73%</td>
<td>1.7/1</td>
</tr>
<tr>
<td>4</td>
<td>81d X=O</td>
<td>82d</td>
<td>73%</td>
<td>1.1/1</td>
</tr>
<tr>
<td>5</td>
<td>81e X=NM</td>
<td>82e</td>
<td>63%</td>
<td>1.2/1</td>
</tr>
<tr>
<td>6</td>
<td>81f X=O</td>
<td>82f</td>
<td>91%</td>
<td>1.4/1</td>
</tr>
<tr>
<td>7</td>
<td>81g X=NM</td>
<td>82g</td>
<td>61%</td>
<td>1.2/1</td>
</tr>
<tr>
<td>8</td>
<td>81h X=O</td>
<td>82h</td>
<td>71%</td>
<td>1.2/1</td>
</tr>
<tr>
<td>9</td>
<td>81i</td>
<td>82i</td>
<td>56%</td>
<td>—a</td>
</tr>
</tbody>
</table>

*a Reactions run with 1equiv of substrate and 5 mol % of In(OTf)3 in CH2Cl2 at 25 °C and complete within 6h. *Isolated yields after column chromatography. *Diastereoselectivities as determined by crude 1H NMR. *Reaction performed in 1,2-DCE at 80 °C. * 2:1 mixture of keto and enol forms.

Next, other donor substituents about the cyclopropanes were examined (Table 2.4). Phenyl derivatives 81j and 81k provided the desired ring-fused cyclohexanones 82j (2.3:1 dr) and 82k (1.2:1 dr) in 81% and 83% yield, respectively (Table 2.4, entry 1 and 2). When α-methyl styrene was used to generate cyclopropane 81l, product 82l was obtained in 71% yield (2:1 dr) (Table 2.4, entry 3). This allowed us to install a challenging quaternary center in one
Similarly, the indanyl substrate 81m gave tetracycle 82m in 87% yield (Table 2.4, entry 4). Inspired by Yadav’s report, silyl derivative 81n was synthesized and cyclized to afford 82n in 72% yield (2.4:1 dr) (Table 2.4, entry 5).

**Table 2.4:** Heteroaryl Homo-Nazarov Cyclization Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr (trans/cis)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81j</td>
<td>82j</td>
<td>81%</td>
<td>2.3/1</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81k</td>
<td>82k</td>
<td>83%</td>
<td>1.2/1</td>
</tr>
<tr>
<td>3</td>
<td>81l</td>
<td>82l</td>
<td>71%</td>
<td>2/1</td>
</tr>
<tr>
<td>4</td>
<td>81m</td>
<td>82m</td>
<td>87%</td>
<td>...&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>81n</td>
<td>82n</td>
<td>72%</td>
<td>2.4/1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions run with 1equiv of substrate and 5 mol % of Ir(OAc)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C and complete within 6h. <sup>b</sup>Isolated yields after column chromatography. <sup>c</sup>Diastereoselectivities as determined by crude <sup>1</sup>H NMR. <sup>d</sup>Reaction performed in 1,2-dichloroethane at 80 °C. <sup>e</sup>Only one diastereomer visible <sup>1</sup>H NMR.

### 2.10 Tandem Cyclopropanation/Homo-Nazarov Cyclization Protocol

An interest in developing a more efficient, greener protocol led us to attempt to develop a tandem cyclopropanation/homo-Nazarov cyclization protocol. Given that both the cyclopropanation and homo-Nazarov cyclization steps readily occurred in dichloromethane at
room temperature, we envisioned the development of a one-pot procedure that would occur in the presence of both the rhodium (for cyclopropanation) and indium (for cyclization) catalysts (Scheme 2.25). To test the feasibility of this procedure, two key control reactions were conducted. First, the stability of α-diazoester 80d in the presence of In(OTf)_3 (5 mol %) was established by monitoring a stirring mixture of the two components. Next, the stability of the alkene (4-methoxy styrene) was examined in the presence of both Rh$_2$esp$_2$ and In(OTf)$_3$. To achieve an active indium catalyst loading of 20 mol%, 1 mol% of Rh$_2$esp$_2$ and 0.2 mol% of In(OTf)$_3$ in dichloromethane at 0 °C were employed as the initial reaction conditions. We were pleased to find that subjecting α-diazoester 80d to these conditions provided the desired ring-fused cyclohexanone 82d in 56% yield, which is higher than the yield for the two-step process and equates to an average of about 75% yield for each individual step. This one pot is of high value, as less solvent will be used and less waste will be generated. We were able to save time in terms of isolation, minimize labor and overall cost.

Scheme 2.25: Tandem Cyclopropanation-Homo-Nazarov Cyclization Protocol
2.11 Cyclopropane with Oxygen/Ether Substituent

With an interest in expanding the scope of the protocol, we also investigated the effects of having an oxygen donor group on the cyclopropane. Therefore, we synthesized a cyclopropane 81o derived from ethyl vinyl ether. Upon cyclopropanation of diazo 80a and characterization, we discovered that we formed the dihydrofuran product 83 (Scheme 2.26). As noted in the literature, these cyclopropanes are unstable and readily isomerizes to dihydrofuran (DHF) acetal 83 as the more stable isomer.102

\[
\text{Scheme 2.26: Cyclopropanation and Rearrangement to Dihydrofuran}
\]

After the isolation of dihydrofuran acetal 83, we were intrigued as to what would happen if we subjected the dihydrofuran acetal 83 to the cyclization conditions of 5 mol% of In(OTf)₃. Surprisingly, the product formed was the benzo[b]thiophene product 84 in 51% yield (Scheme 2.27). This is notable because it provided an alternative to the formation of the benzofused heteroaromatic products. Detailed discussion of the transformation and scope of this methodology is discussed in Chapter Four of this thesis.

\[
\text{Scheme 2.27: Ring Opening of Dihydrofuran Acetals to Benzofused Heteroaromatics}
\]

Compounds

In summary, cyclopropanes were used as building blocks in order to generate cyclohexanones and cyclohexenols, as they are highly prevalent in many natural products.
Treatment of alkenyl donor-acceptor-acceptor cyclopropanes with 30 mol% of In(OTf)$_3$ promoted the homo-Nazarov cyclization and provided cyclohexenones and methylene cyclohexenols in up to 93% yield. When unactivated or electron-poor aromatic donor groups are used, cyclization proceeds under the reaction conditions, albeit with lower yields and longer reaction times. Utility of these core structures were demonstrated by converting methylene cyclohexenol into a thioether and Krapcho decarbalkoxylation was achieved using a NaCl/DMSO mixture. Future studies include expanding the scope of the vinyl system and effects of having different heteroatoms on the vinyl system. Asymmetric alkenyl homo-Nazarov cyclization as well as further mechanistic investigations will be pursued.

A general protocol for the heteroaromatic homo-Nazarov cyclization has been reported. This protocol was a modular approach to the homo-Nazarov cyclization in which 2,3- and 3,4- heteroaryl ring fused cyclohexanones were achieved. Previously, the method was only limited to 2,3-ring fused products. Therefore this report further expanded the scope and utility of this methodology. Notably, the benzofuran substrates were achieved, as previous reports were not able to generate these products due to polymerization. A tandem cyclopropanation/homo-Nazarov cyclization was also demonstrated in which the one pot yield (56%) was higher than the two individual steps alone (combined 49%). An example of the formation of 5-heteroaryl-2,3-dihydrofuran acetics were also shown. These acetics were converted to benzofused heteroaromatic compounds in one step. Further discussion and scope of this methodology is available in Chapter Four of this thesis.

2.12 Summary of Chapter Two
In this chapter, the alkenyl homo-Nazarov cyclization was disclosed along with the heteroaryl homo-Nazarov cyclization. The alkenyl homo-Nazarov cyclization used 30 mol% of In(OTf)$_3$ as the Lewis acid in order to promote the cyclization of
simple alkenes for the formation of methylene cyclohexenols and cyclohexenones in up to 93% yield. The heteroaryl homo-Nazarov cyclization used the reactive π-system of the heteroaromatics and 5 mol% of In(OTf)$_3$ in order to form heteroaryl ring-fused cyclohexanones in up to 91% yield. Further studies are underway to expand these methods to other heteroaromatics, such as pyrrole, imidazole, oxazole and pyridine. Other projects include optimization and generalization of the one-pot reaction for different heteroaromatics. Reactions examining the transfer of absolute chirality during the cyclization of a chiral cyclopropane are currently being conducted.
**Experimentals**

1. **General Methods**

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. Proton and carbon nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were recorded on a Varian Mercury Vx 300 spectrometer with solvent resonance 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, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, t = triplet, bt = broad triplet, td = triplet of doublets, q = quartet, qd = quartet of doublets, qn = quintet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Chromatographic purification was performed as flash chromatography using Dynamic Adsorbents silica gel (32-65µm), using the solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography technical grades solvents were used. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F$_{254}$ TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate (KMnO$_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic $p$-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating. 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. Acetonitrile was dried by fractional distillation over CaH$_2$. Benzene was purified by drying with CaH$_2$. Lithium bis(trimethylsilyl)amide (LHMDS) was purchased from Sigma-Aldrich as a 1.0 M solution in THF. $n$-Butyllithium was purchased from Sigma-Aldrich as a 2.5 M solution in hexanes. $t$-Butyllithium was purchased from Sigma-Aldrich as a 1.7 M solution in hexanes. Nitromethane was distilled over CaH$_2$ and stored under nitrogen under 4Å molecular sieves. 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. Compounds 64, 65, 66a-66h, 67a-67e, 68a-68h, 69a, 73, 74 were prepared and characterized by Dadasaheb V. Patil. Optimization of the reaction conditions were also performed and discussed by Dadasaheb V. Patil and can be found in the published manuscript. Compounds 79a, 79b, 79c, 79e, 79f, 79g were made via a modified Warner’s method. Compound 79d was prepared by a modified version of Frontier’s method. Compound 79h was prepared based on Kanda’s protocol.

2. General Procedures

A. Formation of β-Keto ester 79i

\[
\begin{align*}
\text{Br} & \quad \text{COH} \\
\text{S} & \quad 1) (\text{COCl})_2, \text{DCM, rt} \\
\text{Br} & \quad 2) \text{LHMDS, MeOAc, THF, -78 °C} \\
\text{79i} & \quad + \\
\text{Me} & \quad \text{COOMe}
\end{align*}
\]

Methyl 3-(2-bromothiophen-3-yl)-3-oxopropanoate (79i). 2-Bromo-3-thiophene carboxylic acid chloride was prepared from a solution of 2-bromo-3-thiophene carboxylic acid (0.50 g, 2.41 mmol) in DCM (0.5M) and was added a catalytic amount of $N,N'$-dimethylformamide (0.2 mL) was added. The solution was cooled to 0 °C, and to it was added oxallyl chloride (0.25 mL 2.9 mmol). LiHMDS (5.1 mL, 5.1 mmol) was added to a solution of methyl acetate (0.21 mL, 2.54 mmol) in THF at -78 °C and allowed to stir for 45 minutes. To the solution of the enolate was
added the 2-bromo-3-thiophene acid chloride in 10 mL of THF. The reaction was allowed to stir for 30 minutes at -78 °C, quenched with saturated ammonium chloride. The reaction was allowed to warm up to room temperature, extracted with Et₂O, washed with brine, and dried with anhydrous Na₂SO₄. The solution was then concentrated and column chromatography (15 % EtOAc/hexane, Rₚ= 0.3) afforded 79i as an oil (0.317 g, 50.4%). (4:1 mixture of ester and enol).

1H NMR (CDCl₃, 300 MHz) δ 12.4 (s, 0.23, enol) 7.34 (d, J = 5.8 Hz, 1), 7.24 (d, J = 5.8 Hz, 1.23), 7.20 (d, J = 5.8 Hz, 0.20), (5.80, s, 0.23, enol), 4.01-3.96 (s, 2), 3.78, (s, 0.78, enol), 3.76-3.69 (s, 3H); 13C NMR (CDCl₃, 75 MHz) δ 186.4, 173.2, 167.4, 166.3, 137.8, 128.9 (2C), 127.7, 126.5 (2C), 119.4, 113.4, 90.1, 52.4, 51.5, 48.1. IR 3103(w), 2940(w), 2021(m), 1957(m), 1731(m), 1658(m), 1512(w), 1402(w), 1309(m), 1213(m) cm⁻¹. HRMS(ESI) M/Z⁺ Calc. 261.9299, Obs. 261.9299.

B. General procedure for the formation of α-diazo-esters (80a-80m)

In a flame dried flask containing a solution of the β-keto ester in acetonitrile (0.2 M) was added Et₃N (1.2 equiv.). After vigorous stirring for 5 minutes, tosyl azide (1.2 equiv.) was added, and the reaction was allowed to stir for 3 hrs. After complete disappearance of starting material, the mixture was concentrated in vacuo, followed by column chromatography to furnish the desired diazo compound.⁹⁹

**Methyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate (80a).** According to the general procedure, to a solution of the β-keto ester 79a (1.50 g, 8.14 mmol) in acetonitrile was added Et₃N (1.4 mL, 9.77 mmol) and tosyl azide (1.93 g, 9.77 mmol). Column chromatography (10%
EtOAc/hexane, Rf = 0.25) furnished compound 80a as a yellow oil (1.20 g, 69.5%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ 8.06 (dd, \(J = 3.9, 1.1\) Hz, 1H), 7.66 (dd, \(J = 4.9, 1.1\) Hz, 1H), 7.12 (dd, \(J = 4.9, 3.9\) Hz, 1H), 3.82 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) δ 176.3, 161.1, 141.2, 133.8 (2C), 127.6 (2C), 52.2. IR 3100(m), 2947(m), 2146(s, N\(_2\) stretch), 1721(s), 1712(s), 1692(s), 1617(s), 1604(s), 1433(m), 1299(s) cm\(^{-1}\). HRMS(ESI) M/Z\(^+\) Calc. 210.0099, Obs. 210.0095.

Methyl 2-diazo-3-(furan-2-yl)-3-oxopropanoate (80b). According to the general procedure, to a solution of the β-keto ester 79b (0.75 g, 4.46 mmol) in acetonitrile was added Et\(_3\)N (0.75 mL, 5.35 mmol) and tosyl azide (1.06 g, 5.35 mmol). Column chromatography (10% EtOAc/hexane, Rf = 0.20) furnished 80b as a bright yellow oil (0.614 g, 71.0%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ 7.59 (dd, \(J = 1.6, 0.8\) Hz, 1H), 7.50 (dd, \(J = 3.6, 0.8\) Hz, 1H), 6.56 (dd, \(J = 3.6, 1.7\) Hz, 1H), 3.82 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) δ 170.7, 161.5, 150.4, 146.0, 145.9, 119.4, 112.3, 52.5. IR 3102(w), 2953(w), 2140(s,N\(_2\)), 1717(s), 1584(s), 1514(m), 1434(m), 1410(w) cm\(^{-1}\). HRMS(ESI) M/Z\(^+\) Calc. 194.0328, Obs. 194.0323.

Methyl 2-diazo-3-oxo-3-(thiophen-3-yl)propanoate (80c). According to the general procedure, to a solution of the β-keto ester 79c (1.50 g, 8.14 mmol) in acetonitrile was added Et\(_3\)N (1.4 mL, 9.77 mmol) and tosyl azide (1.93 g, 9.77 mmol). Column chromatography (10% EtOAc/hexane, Rf = 0.20) furnished 80c as a yellow oil (1.10 g, 64.7%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ 8.17 (dd, \(J = 2.9, 1.2\) Hz, 1H), 7.47 (dd, \(J = 5.1, 1.1\) Hz, 1H), 7.26 (dd, \(J = 5.1, 2.9\) Hz, 1H), 3.84(s, 3H).
$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 179.0, 161.4, 138.9, 132.9, 128.0, 127.9, 124.9, 52.3. IR 3102 (w), 2943(w), 2126 (br s, N$_2$ stretch), 1721(s), 1212(s), 1604(m), 1498(m), 1435(m), 1299(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 210.0101 , Obs. 210.0106.

**Methyl 2-diazo-3-(furan-3-yl)-3-oxopropanoate (80d).** According to the general procedure, to a solution of the β-keto ester 79d (1.50 g, 8.9 mmol) in acetonitrile was added Et$_3$N (1.5 mL, 10.7 mmol) and tosyl azide (2.1 g, 10.7 mmol). Column chromatography (10% EtOAc/Hex, $R_f$ = 0.20) furnished 80d as a bright yellow oil (1.17 g, 68.0%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.44 (dd, $J = 1.4, 0.8$ Hz, 1H), 7.40 (dd, $J = 1.9, 1.5$ Hz, 1H), 6.87 (dd, $J = 1.9, 0.8$ Hz, 1H), 3.84 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 177.5, 161.2, 148.9, 142.7, 130.2, 124.9, 110.2, 52.2. IR 3143(w), 2957(w), 2133(s, N$_2$ stretch), 1721(s), 1711(s), 1604(s), 1509(m), 1369(m), 1323(s), 1284(s), 1178(m), 1119(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 194.0328 , Obs. 194.0323.

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 179.0, 161.4, 138.9, 132.9, 128.0, 127.9, 124.9, 52.3. IR 3102 (w), 2943(w), 2126 (br s, N$_2$ stretch), 1721(s), 1212(s), 1604(m), 1498(m), 1435(m), 1299(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 210.0101 , Obs. 210.0106.

**Methyl 3-(benzofuran-2-yl)-2-diazo-3-oxopropanoate (80f).** According to the general procedure, to a solution of the β-keto ester 79f (0.76 g, 3.50 mmol) in acetonitrile was added Et$_3$N (0.60 mL, 4.22 mmol) and tosyl azide (0.81 g, 4.22 mmol). Column chromatography (10% EtOAc/hexane, $R_f$ = 0.20) furnished 80f as a bright yellow oil (0.48 g, 57.0%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.77 (s, 1H), 7.65 (ddd, $J = 4.1, 2.9, 0.7$ Hz, 1H), 7.65-7.45 (m, 2H), 7.42-7.28 (m, 1H), 3.93-3.80 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 172.1, 161.4, 155.0, 150.5, 128.3, 126.8, 123.9, 123.5, 123.4, 115.1, 112.2, 52.6. IR 3129(w), 2950(w), 1737(s), 1671(s), 1555(s),
1446(m), 1316(w), 1246(m), 1123(s), 1088(m) cm\(^{-1}\). **HRMS(ESI) M/Z**\(^+\) Calc. 244.0484 , Obs. 244.0479.

![Chemical structure](image)

**Methyl 3-(benzofuran-3-yl)-2-diazo-3-oxopropanoate (80h).** According to the general procedure, to a solution of the β-keto ester 79h (0.26 g, 1.18 mmol) in acetonitrile was added Et\(_3\)N (0.2 mL, 1.41 mmol) and tosyl azide (0.28 g, 1.41 mmol). Column chromatography (10% EtOAc/hexane, R\(_f\)= 0.25) furnished 80h as a bright yellow oil (0.25 g, 86.3%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.80-8.71 (s, 1H), 8.24-8.07 (m, 1H), 7.56-7.44 (m, 1H), 7.38-7.28 (m, 2H), 3.87-3.83 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 177.8, 161.5, 154.6, 152.8, 130.2, 127.5, 125.5, 124.4, 122.8, 119.2, 111.4, 52.3. IR 2955(m), 2924(w), 2138(br s, N\(_2\) stretch), 1721(s), 1711(s), 1635(m), 1570(m), 1385(s), 1168(s) cm\(^{-1}\). **HRMS(ESI) M/Z**\(^+\) Calc. 244.0484, Obs. 244.0491.

![Chemical structure](image)

**Methyl 3-(2-bromothiophen-3-yl)-2-diazo-3-oxopropanoate (80i).** According to the general procedure, to a solution of the β-keto ester 79i (0.317 g, 1.21 mmol) in acetonitrile was added Et\(_3\)N (0.20 mL, 1.45 mmol) and tosyl azide (0.285 g, 1.45 mmol). Column chromatography (10% EtOAc/hexane, R\(_f\)= 0.25) furnished 80i as a yellow oil (0.213 g, 61.0%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.25 (d, \(J = 5.4\) Hz, 1H), 7.01 (d, \(J = 5.7\) Hz, 1H), 3.79 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 180.8, 160.8, 138.1, 127.8 (2C), 126.1, 114.9, 52.5. IR 3096(w), 2953(w), 2134(br s, N\(_2\) stretch), 1735(s), 1726(s), 1629(s), 1625(m), 1620(m), 1435(m), 1407(m) cm\(^{-1}\). **HRMS(ESI) M/Z**\(^+\) Calc. 287.9221 , Obs. 287.9204.
C. General procedure for the formation of cyclopropyl heteroaryl ketones (81a-81n)\textsuperscript{97}

In a flame dried flask containing a solution of Rh\textsubscript{2}esp\textsubscript{2} (0.1 mol %) in DCM (0.2M) at 0 °C was added the corresponding alkene (1.0 equiv.). After stirring for 5 minutes, a solution of the α-diazo ester (0.2 M) was added in one shot, and allowed to stir for 10 minutes at 0 °C. At this time, the ice bath was removed and the reaction was allowed to warm up to room temperature. After two hours, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3x). The organic layer was washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, concentrated, and column chromatography afforded the desired cyclopropyl heteroaryl ketones.

\[
\text{Methyl 2-(4-methoxyphenyl)-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (81a).}
\]

According to the general procedure, to a solution of Rh\textsubscript{2}esp\textsubscript{2} (3.8 mg, 5.12 µmol) in DCM was added 4-methoxy styrene (0.68 mL, 5.12 mmol), followed by a solution of α-diazo ester 80a (1.4g, 6.66 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81a as a solid (1.32 g, 82%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) δ 7.70 (dd, \textit{J} = 3.8, 1.1 Hz, 1H), 7.66 (s, \textit{J} = 5.0, 1.1 Hz, 1H), 7.25-7.19 (m, 2H), 7.12 (dd, \textit{J} = 4.9, 3.8 Hz, 1H), 6.87-6.78 (m, 2H), 3.79 (s, 3H), 3.44 (t, \textit{J} = 8.6, 1H), 3.37 (s, 3H), 2.33 (dd, \textit{J} = 8.1, 5.0 Hz, 1H), 1.65 (dd, \textit{J} = 9.2, 5.0 Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) δ 186.4, 168.7, 158.7, 143.1, 133.7, 132.4, 130.0, 128.0, 126.5, 113.5, 104.9, 55.1, 52.3, 42.4, 30.0, 19.6. IR 3002(w),
2951(m), 2923(w), 1721(s), 1682(s), 1661(s), 1558(w), 1444(m), 1430(s), 1386(m) cm$^{-1}$.

**HRMS(ESI) M/Z** \text{Calc. 316.0762, Obs. 316.0769.}

![Methyl 1-(furan-2-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (81b).](image)

According to the general procedure, to a solution of Rh$_2$esp$_2$ (1.8 mg, 2.36 µmol) in DCM was added 4-methoxy styrene (0.32 g, 2.36 mmol), followed by a solution of the α-diazo ester 80b (0.75g, 3.07 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81b as a solid (0.467 g, 66 %). (1.5:1 trans/cis diastereomeric mixture).

**$^1$H NMR** (CDCl$_3$, 300 MHz) δ 7.57 (dd, $J = 1.7, 0.8$ Hz, 0.93), 7.43 (dd, $J = 1.7, 0.8$ Hz, 0.59), 7.25-7.14 (m, 2.98), 6.98-6.93 (m, 1.06), 6.92-6.88 (m,0.70 ), 6.86-6.76 (m, 2.10), 6.66-6.57 (m, 1.15), 6.53 (dd, $J = 3.6, 1.7$ Hz, 1.27), 6.35 (dd, $J = 3.6, 1.7$ Hz, 0.80), 3.76 (s, 3.5), 3.67 (d, $J = 4.9$ Hz, 3.41), 3.45 (dd, $J = 18.0, 8.9$ Hz, 1.74), 3.36 (s, 2.93), 2.40-2.22 (m, 2.40), 1.78-1.50 (m, 2.62).

**$^{13}$C NMR** (CDCl$_3$, 75 MHz) δ 182.4, 168.5, 158.7, 146.4, 130.0 (2C), 129.1, 117.9, 113.4, 112.1, 55.0, 52.4, 41.7, 33.0, 30.0, 20.1, 17.4. **IR** 3139 (w), 2953(w), 2827(w), 1726(s), 1672(s), 1612(m), 1542 (m), 1436(w), 1309(s), 1248( s), 1159(s) cm$^{-1}$. **HRMS(ESI) M/Z** \text{Calc. 300.1004, Obs. 300.0998.}

![Methyl 2-(4-methoxyphenyl)-1-(thiophene-3-carbonyl)cyclopropanecarboxylate (81c).](image)

According to the general procedure, to a solution of Rh$_2$esp$_2$ (3.6 mg, 4.76 µmol) in DCM was
added 4-methoxystyrene (0.49g, 3.65 mmol), followed by a solution of the α-diazo ester 80c (1.0 g, 4.76 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81c as a solid (0.86 g, 75.0%). \(^{1}H\) NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.06 (dd, \(J = 2.9, 1.2\) Hz, 1H), 7.53 (dd, \(J = 5.1, 1.2\) Hz, 1H), 7.32 (dd, \(J = 5.1, 2.9\) Hz, 1H), 7.25-7.14 (m, 2H), 6.87-6.77 (m, 2H), 3.79 (s, 3H), 3.44 (t, \(J = 8.6, 8.6\) Hz, 1H), 3.33 (s, 3H), 2.32 (dd, \(J = 8.0, 4.9\) Hz, 1H), 1.63 (dd, \(J = 9.2, 4.9\) Hz, 1H); \(^{13}C\) NMR (CDCl\(_3\), 75 MHz) \(\delta\) 187.9, 169.0, 158.7, 141.2, 132.1, 130.0 (2C), 128.9, 127.1, 126.6, 126.3, 113.5, 55.2, 52.3, 43.0, 29.8, 19.7. IR 3113(w), 2947(w), 2831(w), 1726(s), 1671(s), 1665(m), 1608(w), 1552(m), 1513(s), 1117(m), 1034(m) cm\(^{-1}\). HRMS(ESI) M/Z \(^{+}\) Calc. 316.0762, Obs. 316.0769.

Methyl 1-(furan-3-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (81d).

According to the general procedure, to a solution of Rh\(_{2}\)esp\(_2\) (3.0 mg, 3.96 µmol) in DCM was added the 4-methoxy styrene (0.53 g, 3.96 mmol), followed by a solution of the α-diazo ester 80d (1.0 g, 5.15 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81d as a yellow solid (0.86 g, 72 %). (2.12:1 trans/cis diastereomeric mixture). \(^{1}H\) NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.01 (dd, \(J = 1.4, 0.8\) Hz, 1.58), 7.73 (dd, \(J = 1.4, 0.8\) Hz, 0.93), 7.42 (dd, \(J = 3.6, 1.6\) Hz, 2.18), 7.26-7.12 (m, 4.66), 6.96 (dd, \(J = 8.6, 1.9\) Hz, 1.05), 6.89-6.71 (m, 15.84), 6.67 (dd, \(J = 8.7, 3.4\) Hz, 1.87), 6.50 (dd, \(J = 3.0, 1.2\) Hz, 0.96), 3.76 (s, 6.07), 3.71-3.64 (m, 5.22), 3.47-3.25 (m, 8.96), 2.36-2.14 (m, 3.0), 1.77-1.67 (m, 1.44), 1.65-1.55 (m, 2.61). \(^{13}C\) NMR (CDCl\(_3\), 75 MHz) \(\delta\) 188.1, 168.8, 158.7, 147.2, 143.9, 141.7, 140.8, 129.9, 128.9, 126.5, 113.5, 109.1, 55.1, 52.3, 32.9, 29.9, 19.7. IR 3139 (w), 2953(w), 2827(w),
1726(s), 1672(s), 1612(m), 1542(w), 1309(s), 1248(s), 1159(s) cm⁻¹.

**HRMS(ESI) M/Z⁺** Calc. 300.1004, Obs. 300.0998.

Methyl 1-(benzofuran-2-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (81f).

According to the general procedure, to a solution of Rh₂esp₂ (1.1 mg, 1.46 µmol) in DCM was added the 4-methoxy styrene (0.2 g, 1.46 mmol), followed by a solution of the α-diazo ester 80f (0.46 g, 1.9 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81f as a solid (0.323 g, 66.0%). (1.7:1 trans/cis diastereomeric mixture). **¹H NMR** (CDCl₃, 300 MHz) δ 7.74-7.69 (m, 1H), 7.63-7.52 (m, 2H), 7.54-7.39 (m, 2H), 7.37-7.27 (m, 1H), 7.30-7.19 (m, 2H), 6.93-6.75 (m, 1H), 3.80 (s, 3H), 3.54 (t, J = 8.7, 1H), 3.39 (s, 3H), 2.38 (dd, J = 8.2, 5.0 Hz, 1H), 1.71 (dd, J = 9.2, 5.0 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz) δ 183.6, 168.5, 158.8, 155.6, 152.1, 130.1, 129.2, 128.3, 128.0, 127.5, 126.4, 123.9, 123.3, 113.4, 112.3, 55.1, 52.6, 42.1, 34.3, 30.2, 20.6. **IR** 2940(w), 2831(w), 1721(s), 1658(s), 1513(s), 1432(m), 1246(s), 1162(m) cm⁻¹. **HRMS(ESI) M/Z⁺** Calc. 350.1154, Obs. 350.1163.

Methyl 1-(benzofuran-3-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (81h).

According to the general procedure, to a solution of Rh₂esp₂ (2.2 mg, 2.9 µmol) in DCM was added the 4-methoxy styrene (0.4 g, 2.92 mmol), followed by a solution of the α-diazo ester 80h
(0.92 g, 3.8 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81h (0.646 g, 66.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.72 (ddd, $J = 8.0, 1.2, 0.6$ Hz, 1.32), 7.64-7.40 (m, 6.54), 7.37-7.25 (m, 1.97), 7.30-7.18 (m, 3.96), 7.09-6.95 (m, 1.28), 6.91-6.76 (m, 2.09), 6.67-6.47 (m, 1.47), 3.79 (s, 1H), 3.68 (s, 1H), 3.61 (s, 1H), 3.52 (m, 1H), 3.39 (s, 1H), 2.55-2.17 (m, 1H), 1.93-1.55 (m, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 184.5, 168.4, 158.8, 155.6, 151.9, 130.1, 129.3, 128.3, 128.0, 123.9, 123.4, 113.6, 113.5, 112.4, 55.2, 55.0, 52.4, 42.0, 33.4, 30.3, 20.5. IR 2940(w), 2840(w), 1729(s), 1737(s), 1672(s), 1553(m), 1514(s), 1442(m), 1305(m), 1282(m), 1248(m) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 350.1154, Obs. 350.1163.

**Methyl-1-(2-bromothiophene-3-carbonyl)-2-(4-methoxyphenyl) cyclopropane carboxylate (81i).** According to the general procedure, to a solution of Rh$_2$esp$_2$ (0.51 mg, 6.65 µmol) in DCM was added the 4-methoxy styrene (0.089 g, 0.665 mmol), followed by a solution of the $\alpha$-diazo ester 80i (0.25 g, 0.864 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81i as a solid (0.15 g, 57.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, $J = 8.7$ Hz, 1H), 7.19-7.12 (m, 2H), 7.03-6.94 (m, 1H), 6.82 (d, $J = 8.7$ Hz, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 3.38 (dd, $J = 15.2, 10.7$ Hz, 1H), 3.03 (dd, $J = 15.2, 8.9$ Hz, 1H), 2.36-2.25 (m, 1H), 1.64 (dd, $J = 8.8, 5.1$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 165.0, 159.6, 133.0, 130.1, 129.1, 128.7, 128.0, 127.5, 126.3, 125.6, 125.5, 114.0, 55.3, 51.2, 38.5, 32.0, 21.5. IR 3103(w), 2933(m), 2827(w), 1688(m), 1602(w), 1512(s), 1429(m), 1245(s), 1167(m), 1110(m), 1088(w), 1031(m) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 393.9841, Obs. 393.9831.
Methyl 2-phenyl-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (81j). According to the general procedure, to a solution of Rh$_2$esp$_2$ (0.83 mg, 0.1 mol %) in DCM was added styrene (0.113 g, 1.09 mmol), followed by a solution of the α-diazo ester 80a (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81j as a solid (0.198 g, 81.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.71 (dd, $J = 1.1$, 3.8 Hz, 1 H), 7.66 (dd, $J = 1.1$, 5.0 Hz, 1 H), 7.32 - 7.22 (m, 5 H), 7.12 (dd, $J = 3.8$, 4.9 Hz, 1 H), 3.49 (t, $J = 8.6$ Hz, 1 H), 3.34 (s, 3 H), 2.38 (dd, $J = 5.1$, 8.1 Hz, 1 H), 1.67 (dd, $J = 5.0$, 9.2 Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 186.2, 168.6, 143.0, 134.6, 133.8, 132.5, 128.9 (2C), 128.1 (2C), 127.5, 127.2, 52.3, 42.5, 30.4, 19.4. IR 3036 (w), 2947 (w), 1745 (s), 1656 (s), 1409 (s), 1271 (s), 1141 (s), 1197 (s), 1040 (s), 957 (s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 286.0670, Obs. 286.0697.

Methyl 1-(furan-3-carbonyl)-2-phenylcyclopropanecarboxylate (81k): According to the general procedure, to a solution of Rh$_2$esp$_2$ (1.1 mg, 1.19 µmol) in DCM was added the styrene (0.154 g, 1.83 mmol), followed by a solution of the α-diazo ester 80d (0.30 g, 1.54 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81k as an oil (0.18 g, 43.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.02 (dd, $J = 1.4$, 0.8 Hz, 1H), 7.43 (dd, $J = 1.9$, 1.4 Hz, 1H), 7.32-7.20 (m, 5H), 6.76 (dd, $J = 1.9$, 0.8 Hz, 1H), 3.55-3.42 (m, 1H), 3.34 (s, 3H), 2.31 (dd, $J = 8.0$, 4.9 Hz, 1H), 1.62 (dd, $J = 9.1$, 4.9 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 187.9, 168.7, 147.2 (2C), 143.9(2C), 134.6, 128.8, 128.1, 127.2, 126.7, 109.0, 52.2, 43.3, 30.2,
According to the general procedure, to a solution of Rh$_2$esp$_2$ (0.83 mg, 1.09 µmol) in DCM was added the alpha methyl styrene (0.13 g, 1.09 mmol), followed by a solution of the α-diazo ester $80a$ (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded $81l$ as a solid (0.21 g, 65.0%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.91 (dd, $J = 3.8$, 1.2 Hz, 1H), 7.66 (dd, $J = 5.0$, 1.2 Hz, 1H), 7.49-7.37 (m, 2H), 7.38-7.28 (m, 2H), 7.30-7.07 (m, 2H), 3.33 (s, 3H), 2.36 (d, $J = 5.0$ Hz, 1H), 1.81 (d, $J = 3.7$ Hz, 1H), 1.42 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 186.1, 169.7, 145.2, 141.4, 134.0, 133.5, 128.3(2C), 128.2(2C), 128.1, 127.1, 52.2, 43.7, 37.8, 25.6, 25.1. IR 3002 (w), 2951(w), 2923(w), 1721(s), 1682(s), 1661(s), 1515(w), 1444(s), 1410(m) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 300.0820, Obs. 300.0830.

According to the general procedure, to a solution of Rh$_2$esp$_2$ (1.08 mg, 1.43 µmol) in DCM was added indene (0.128 g, 1.10 mmol), followed by the α-diazo ester $80a$ (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded $81m$ as an oil (0.20 g, 62%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.77 (dd, $J = 1.0$, 3.9 Hz, 1 H), 7.65 (dd, $J = 1.1$, 5.0 Hz, 1 H), 7.43 - 7.36 (m, 1 H), 7.21 - 7.14 (m, 3 H), 7.10 (dd, $J = 3.9$, 5.0 Hz, 1 H).
H), 3.68 (d, J = 6.5 Hz, 1 H), 3.59 (d, J = 18.0 Hz, 1 H), 3.33 (dd, J = 6.6, 17.8 Hz, 1 H), 3.25 (s, 3 H), 2.68 (t, J = 6.5 Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 186.0, 167.8, 143.6, 143.2, 139.3, 134.0, 132.3, 128.2, 127.1, 126.6, 125.3, 124.4, 52.0, 44.6, 39.5, 33.6, 33.6. IR 3060(w), 2943(m), 1735(s), 1657(s), 1648(s), 1434(w), 1410(s), 1353(m), 1301(s), 1264(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 298.0670, Obs. 298.0697

Methyl 2-((tert-butyldiphenylsilyl)methyl)-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (81n). According to the general procedure, to a solution of Rh$_2$esp$_2$ (1.4 mg, 1.83 µmol) in DCM was added allyl(tert-butyl)diphenylsilane (0.513 g, 1.83 mmol), followed by a solution of the α-diazo ester 80a (0.50 g, 2.40 mmol). The reaction was quenched and column chromatography (10% EtOAc/hexane) afforded 81n as an oil (0.375 g, 44.3 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.66 (dd, J = 7.5, 1.9 Hz, 4H), 7.62-7.54 (m, 3H), 7.45-7.30 (m, 4H), 7.06 (dd, J = 4.8, 3.9 Hz, 1H), 3.66 (s, 3H), 2.20-1.99 (m, 1H), 1.62 (dd, J = 4.8, 3.1 Hz, 1H), 1.45-1.23 (m, 1H), 1.16 (dd, J = 9.1, 4.7 Hz, 1H), 1.10 (s, 9H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 186.9, 170.2, 143.3, 135.9 (2C), 135.9, 134.1, 133.8, 133.2, 131.9, 129.1, 129.1, 127.8, 127.6 (2C), 127.5 (2C), 52.3, 40.2, 27.7, 24.1, 23.4, 18.0, 8.2. IR 3013.6, 2928.5, 2855.8, 1725.4, 1657.7, 1457.5, 1426.9, 1310.2, 1275.3 cm$^{-1}$. HRMS M/Z$^+$ (ESI) Calc. 462.1719, Obs. 462.1681.
Methyl-2-(4-methoxyphenyl)-1-(1-methyl-1H-indole-2-carbonyl) cyclopropane carboxylate (81e). t-BuLi (1.3 mL, 1.70 mmol) was added over 15 minutes to a -78 °C solution of n-methyl indole (0.24 mL, 1.87 mmol) in THF (8.52 mL). After stirring for 45 minutes at -78 °C, a solution of the Weinreb amide cyclopropane\(^4\) (0.250g, 0.852 mmol) in 2 mL THF was added slowly to the reaction and allow to warm up to rt. After 3 hours, the reaction was quenched with saturated aqueous NH\(_4\)Cl, extract 3x with Et\(_2\)O, dried with Na\(_2\)SO\(_4\), and column chromatography (10 % EtOAc/hexane, R\(_f\) = 0.25) afforded cyclopropane 81e (0.21 g, 68%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta 7.68 (dd, J = 0.8, 8.1 \text{ Hz}, 1 \text{ H}), 7.42 - 7.38 (m, 2 \text{ H}), 7.33 - 7.22 (m, 3 \text{ H}), 7.16 (ddd, J = 3.0, 4.9, 8.1 \text{ Hz}, 1 \text{ H}), 6.88 - 6.81 (m, 2 \text{ H}), 4.09 (s, 3 \text{ H}), 3.80 (s, 3 \text{ H}), 3.46 (t, J = 8.5 \text{ Hz}, 1 \text{ H}), 3.32 (s, 3 \text{ H}), 2.41 (dd, J = 5.0, 7.9 \text{ Hz}, 1 \text{ H}), 1.67 (dd, J = 5.0, 9.2 \text{ Hz}, 1 \text{ H}). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta 186.9, 169.2, 158.6, 139.9, 138.7, 130.0, 126.8, 123.0, 122.3, 121.0, 119.8, 113.5, 111.6, 110.3, 103.5, 55.1, 52.4, 43.2, 32.0, 32.0, 29.1, 19.8. IR 2924.2, 1728.3, 1699.8, 1684.1, 1656.3, 1363.5, 1248.3 cm\(^{-1}\). HRMS(ESI) M/Z\(^+\) Calc. 363.1471, Obs. 363.1479.

Compound 79g’ was prepared using a two-step Knoevenagel\(^101\) condensation followed by a Corey-Chaychovsky Cyclopropanation.

![Diagram](image)

Methyl 3-(4-methoxyphenyl)-2-(1-methyl-1H-indole-3-carbonyl)acrylate (79g’). A solution of the \(\beta\)-ketoester 79g (0.75 g, 3.24 mmol), \(p\)-anisaldehyde (0.56 g, 4.09 mmol), glacial acetic acid (80 \(\mu\)L, 1.49 mmol), piperidine (32 \(\mu\)L, 0.324 mmol) was refluxed in benzene (30 mL) using a Dean-Stark apparatus for 16 hours. The residual dark red brown mixture was dissolved in de-ionized water and extracted with ethyl acetate (3x). The combined organic layers were then washed with 1N hydrochloric acid followed by a subsequent wash with saturated sodium
bicarbonate solution. The mixture was concentrated under high vacuum after drying with magnesium sulfate. Column chromatography (25% EtOAc/hexane) furnished the desired alkenyl substrate 79g as an orange oil (0.724 g, 63%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) 8.42 (s, 1H), 7.84 (s, 1H), 7.56-7.48 (m, 1H), 7.50-7.39 (m, 2H), 7.40-7.27 (m, 3H), 6.80-6.61 (m, 2H), 3.74 (m, 9H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) \(\delta\) 189.2, 166.5, 161.1, 141.0, 138.0, 137.8, 132.4 (2C), 129.7, 126.2, 125.7, 123.7, 122.9, 122.6 (2C), 116.3, 114.2, 109.8, 55.2, 52.4, 33.6. IR \(3051.8, 2949.5, 2182.9, 2055.7, 1709.6, 1599.3, 1511.5, 1250.3, 1173.6\) cm\textsuperscript{-1}. HRMS(ESI) M/Z\textsuperscript{+} Calc. 349.1314, Obs. 349.1307.

Methyl 2-(4-methoxyphenyl)-1-(1-methyl-1H-indole-3-carbonyl)cyclopropanecarboxylate (81g).\textsuperscript{101} Following a Waser’s protocol, \(n\)-BuLi (0.858 mmol) was added dropwise to a solution of trimethylsulfoxonium iodide (0.193 g, 0.944 mmol) in anhydrous THF (0.75 M) at 0°C. The solution was allowed to warm to rt and stirring was continued under nitrogen for 1 hour. A solution of the 0.54 M of ylide was obtained. The ylide (1.74 mL, 0.943 mmol) was added dropwise to a solution of the alkene (0.300g, 0.858 mmol) in anhydrous THF (0.10 M) at room temperature and stirred for 3 hours. The reaction was quenched with NaHCO\textsubscript{3} and extracted with Et\textsubscript{2}O (3x). The combined organic layers were washed with brine (2x), dried over MgSO\textsubscript{4}, and the solvent was removed under reduced pressure. Column chromatography (10% EtOAc/hexane, \(R_f= 0.15\)) afforded the indolycyclopropane 81g (0.168 g, 54.0%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \(\delta\) 8.35 (dd, \(J = 5.6, 2.5\) Hz, 1H), 7.70 (s, 1H), 7.36-7.27 (m, 3H), 7.24-7.16 (m, 2H), 6.85-6.70 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.40 (t, \(J = 8.4, 1\)H), 3.30 (s, 3H), 2.26 (dd, \(J = 7.8, 4.9\) Hz, 1H), 2.06 (s, 3H), 1.30 (s, 3H), 0.88 (s, 3H).
1.58 (dd, J = 9.1, 4.9 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 187.5, 169.9, 158.5, 137.3, 135.5, 129.9 (2C), 127.3, 126.6, 123.5, 122.8, 122.5, 115.4, 113.4 (2C), 109.6, 55.1, 52.3, 43.1, 33.6, 28.6, 18.7. IR 2924, 1728, 1699, 1684, 1656, 1363, 1248 cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 363.1471, Obs. 363.1479.

Methyl 5-ethoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (83): According to the general procedure, ethyl vinyl ether (0.132 g, 1.83 mmol) was added to a solution of Rh$_2$esp$_2$ (1.8 mg, 2.37 µmol) in DCM at 0 °C, followed by a solution of the α-diazo ester 80a (0.500 g, 2.37 mmol). The reaction was quenched after 5 hours and purification by column chromatography ($R_f$ = 0.35, 10% EtOAc/hexane) afforded 83 as a colorless oil (0.430 g, 72.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.21 (dd, J=3.9, 1.3 Hz, 1 H), 7.46 (dd, J=5.0, 1.1 Hz, 1 H), 7.06 (dd, J=5.0, 3.9 Hz, 1 H), 5.57 (dd, J=7.2, 2.6 Hz, 1 H), 3.89 (dq, J=9.6, 7.1 Hz, 1 H), 3.71 (s, 3 H), 3.60 (dq, J=9.6, 7.1 Hz, 1 H), 3.20 (dd, J=16.7, 7.1 Hz, 1 H), 2.92 (dd, J=16.7, 2.5 Hz, 1 H), 1.21 (t, J=7.1 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 165.0, 156.6, 132.0, 131.3, 129.9, 126.9, 103.9, 99.7, 64.0, 50.8, 38.1, 14.9. IR 3096.7(m), 2950.9(w), 1736.7(s), 1726.4(s), 1672.2(s), 1506.8(m), 1462.2(m) cm$^{-1}$. HRMS (ESI) Calc. 254.0613, Obs. 254.0462.

D. Procedure for Catalyst Screening

To a flame dried flask containing the indium catalyst with the appropriate loading (1, 5, or 30 mol%) in anhydrous CH$_2$Cl$_2$ (0.2M) was added cyclopropane 81a. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched
with H₂O. The mixture was extracted with CH₂Cl₂, dry with Na₂SO₄, and column chromatography (10% EtOAc/hexane) provided 82a.

E. General Procedure for the Lewis-Acid catalyzed cyclization of heteroaryl cyclopropyl ketones (Products 82a-82n)

To a flame dried flask containing In(OTf)₃ (5 mol %) in anhydrous CH₂Cl₂ (0.2M) was added the corresponding cyclopropane. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H₂O. The mixture was extracted with CH₂Cl₂, dried with Na₂SO₄, and column chromatography provided the fused heteroaromatic cyclohexanones.

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\text{Methyl-4-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo}[b]\text{thiophene-6-carboxylate (82a). According to the general procedure, cyclopropane 81a (0.050 g, 0.17 mmol) was added to a solution of In(OTf)₃ (4.42 mg, 8.33 µmol) in DCM. The reaction was quenched after 4.5 hours, and column chromatography (15% EtOAc/hexane, Rₜ= 0.25) provided 82a as a solid (0.043 g, 86.4 %). (Diastereomeric ratio 1.5:1) }^{1}\text{H NMR (CDCl₃, 300 MHz)} \delta \text{ 7.64 (d, } J = 4.9 \text{ Hz, 0.90), 7.59 (d, } J = 4.9 \text{ Hz, 1.13), 7.13 (d, } J = 8.4 \text{ Hz, 2.82), 7.03 (d, } J = 8.5 \text{ Hz, 2.02), 6.88 (dd, } J = 10.8, 8.5 \text{ Hz, 4.46), 6.71 (d, } J = 5.0 \text{ Hz, 0.90), 6.58 (d, } J = 5.0 \text{ Hz, 1.14), 4.38 (dd, } J = 7.4, 4.8 \text{ Hz, 1.00), 4.10 (dd, } J = 11.8, 4.4 \text{ Hz, 1.52),3.82-3.73 (m, 1.54), 3.68 (dd, } J = 7.1, 4.8 \text{ Hz, 1.00), 2.92-2.62 (m, 2.72), 2.58-2.32 (m, 2.32). }^{13}\text{C NMR (CDCl₃, 75 MHz)} \delta 165.3, 159.8, 133.0, 130.1, 129.1, 127.5(2C), 125.4, 114.0(2C), 113.5, 104.9, 83.7, 55.3, 55.1, 51.2, 38.5. }^{\text{IR}}
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Methyl 4-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzofuran-6-carboxylate (82b). A solution of In(OTf)$_3$ (8.15 mg, 0.015 mmol) in 1,2-DCE was added cyclopropane 81b (0.088 g, 0.29 mmol) and the reaction was heated to reflux. After 6 hours, the reaction was cooled to room temperature, followed by the general work up. Column chromatography (15% EtOAc/hexane, R$_f$ = 0.25) provided 82b as a solid (0.059 g, 67.0%). (Diastereomeric ratio 1.1:1).

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.38-7.30 (m, 1.91), 7.14-7.08 (d, $J = 0.5$ Hz, 1.98), 7.04-7.01 (d, $J = 0.5$ Hz, 2.24), 6.92-6.86 (m, 4.29), 6.76-6.72 (m, 2.02), 4.53-4.39 (m, 1.00), 4.30-4.19 (m, 0.95), 3.82-3.78 (m, 6.23), 3.76-3.70 (m, 6.28), 3.68-3.58 (m, 2.56), 2.91-2.83 (m, 1.23), 2.71-2.50 (m, 2.27), 2.40-2.30 (m, 1.22). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 188.7, 188.4, 170.3, 170.0, 167.2, 167.1, 159.1, 159.0, 146.0, 143.7 (2C), 131.0, 130.9, 129.0, 128.8, 121.2, 121.1, 119.4, 114.4, 114.3, 113.9, 112.3, 110.9, 106.9, 104.8, 55.3, 54.5, 52.5, 52.3, 51.6, 40.4, 37.9, 36.1, 35.5. IR 3116(w), 2947(w), 2824(w), 1735(m), 1685(s), 1602(m), 1525(m), 1439(m), 1247(br s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 300.0998, Obs. 300.1004.
Methyl-7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (82c). According to the general procedure, to a solution containing In(OTf)$_3$ (8.9 mg, 0.158 mmol) was added cyclopropane 81c (0.10 g, 0.316 mmol). The reaction was quenched after 5 hours, and column chromatography (15% EtOAc/hexane, R$_f$ = 0.25) provided 82c as a solid (0.073 g, 73.0 %). (Diastereomeric ratio 1.7:1). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.45-7.36 (m, 1.96), 7.21-7.11 (m, 2.65), 7.10-7.00 (m, 2.67), 6.99-6.80 (m, 3.59), 4.55 (dd, $J =$8.0, 4.6 Hz, 0.58), 4.29 (dd, $J =$ 11.8, 4.3 Hz, 1.00), 3.80-3.56 (m, 13.8), 2.93-2.67 (m, 2.11), 2.62-2.39 (m, 2.04). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 187.6, 170.4, 161.6, 159.2, 135.9, 134.4, 129.1, 128.9, 124.9, 114.2, 55.3, 52.5, 42.4, 42.6, 39.6, 37.0. IR 3086(w), 2950(m), 2827(w), 1736(s), 1664(s), 1602(w), 1510(m), 1413(s), 1244(s), 1175(s), 1151(s), 1014(m) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 316.0769, Obs. 316.0771.

![Chemical structure](image)

Methyl 7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (82d). According to the general procedure, to a solution containing In(OTf)$_3$ (9.36 mg, 0.017 mmol ) was added cyclopropane 81d (0.100 g, 0.33 mmol). The reaction was quenched after 6 hours, and column chromatography (15% EtOAc/hexane, R$_f$ = 0.25) provided 82d as a solid (0.073 g, 73.0 %). (Diastereomeric ratio 1.1:1). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.36 (dd, $J =$ 2.1, 0.5 Hz, 1.03), 7.32 (dd, $J =$ 1.5, 0.6 Hz, 1.12), 7.17-7.07 (m, 2.32), 7.06-6.98 (m, 2.21), 6.96-6.84 (m, 4.31), 6.74-6.70 (m, 2.20), 4.46 (dd, $J =$ 3.7, 3.1 Hz, 1.00), 4.24 (dd, $J =$ 10.5, 5.8 Hz, 1.09), 3.84-3.72 (m, 12.77), 3.72-3.54 (m, 3.25), 2.87 (s, 1.29), 2.75-2.46 (m, 2.61), 2.46-2.26 (m, 1.44). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 188.7, 170.0, 167.2, 159.2, 144.1, 131.0, 129.1, 128.6, 79
121.1, 114.5, 106.8, 55.3, 54.5, 52.6, 52.4, 51.6, 40.5, 37.9, 36.0, 35.5. IR 3060(w), 2947(w), 2834(w), 1745(m), 1687(s), 1679(m), 1442(s), 1264(s), 1249(s), 1180(w), 1117(w), 1027(w) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 300.0998, Obs. 300.0998.

**Methyl-4-(4-methoxyphenyl)-9-methyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (82e).** According to the general procedure, to a solution containing In(OTf)$_3$ (3.85 mg, 6.85 µmol) was added cyclopropane 81e (0.049 g, 0.137 mmol). The reaction was quenched after 5.5 hours, and column chromatography (20% EtOAc/hexane, R$_f$= 0.20) provided 82e as a solid (0.031 g, 63.0 %). (Diastereomeric ratio 1.2:1). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.41-7.33 (m, 3.96), 7.33-7.28 (m, 2.23), 7.16 (m, 2.81), 7.12-7.01 (m, 1.29), 6.96-6.81 (dd, $J$ = 7.9, 4.1 Hz, 4.52), 6.69 (m, 1.06), 4.62 (t, $J$ = 5.6, 5.6 Hz, 1.00), 4.37 (dd, $J$ = 11.2, 4.7 Hz, 1.21), 4.09 (m, 4.97), 3.80-3.60 (m, 12.85), 2.99-2.84 (m, 1.39), 2.60-2.48 (m, 2.52), 2.40 (m, 1.63); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 186.9, 170.7, 158.6, 140.4, 135.2, 134.2, 131.1, 130.3, 127.0, 124.3, 122.9, 120.1, 114.0, 110.3, 55.6, 52.4, 40.4, 38.5, 37.4, 31.6. IR 2941(m), 2834(w), 1736(s), 1610(m), 1511(m), 1468(m), 1245(s), 1021(m), 747(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 363.1471, Obs. 363.1478.
Methyl 1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[b,d]furan-3-carboxylate (82f). According to the general procedure, to a solution containing In(OTf)$_3$ (6.55 mg, 0.017 mmol) was added the cyclopropane 81f (0.078 g, 0.233 mmol). The reaction was quenched after 5 hours, and column chromatography (15% EtOAc/hexane, R$_f$ = 0.25) provided 82f as a solid (0.071 g, 91.0%). (Diastereomeric ratio 1.4:1). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.61 - 7.54 (m, 2.41), 7.49 - 7.39 (m, 2.73), 7.23 - 7.04 (m, 5.41), 6.96 - 6.85 (m, 4.67), 6.74 (d, J = 7.6 Hz, 1.07), 4.60 (dd, J = 4.9, 8.6 Hz, 1.00), 4.38 (dd, J = 4.8, 10.8 Hz, 0.73), 3.88 - 3.70 (m, 12.35), 2.97 - 2.87 (m, 1.19), 2.83 - 2.58 (m, 1.94), 2.55 - 2.44 (m, 1.37); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 224.9, 158.9, 156.4, 133.1, 132.5, 129.4, 128.9, 125.5, 123.5, 123.2, 114.303, 112.8, 55.3, 52.6, 52.3, 39.6, 37.8. IR 2942(w), 2831(w), 1731(s), 1677(s), 1608(s), 1426(m), 1245(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 350.1154, Obs. 350.1163.

Methyl-1-(4-methoxyphenyl)-9-methyl-4-oxo-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate (82g). According to the general procedure, to a solution containing In(OTf)$_3$ (2.86 mg, 5.0 µmol) was added cyclopropane 81g (0.037 g, 0.102 mmol). The reaction was quenched after 6 hours, and column chromatography (20% EtOAc/hexane, R$_f$ = 0.25) provided 82g as a solid (0.022 g, 61.0%). (Diastereomeric ratio 1.2:1) $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.36-7.30 (d, J = 3.3 Hz, 3.71), 7.18-7.10 (d, J = 8.6 Hz, 3.50), 7.07-7.00 (m, J = 8.6 Hz, 2.68), 6.98 (dd, J = 8.0, 3.9 Hz, 0.92), 6.93-6.78 (m, 4.05), 6.74-6.66 (d, J= 8.0 Hz, 0.91), 4.64 (t, J = 5.6, 5.6 Hz, 1.00), 4.38 (dd, J = 10.7, 5.1 Hz, 0.87), 4.12 (m, 4.69), 3.82-3.70 (m, 11.75), 2.93 (ddd, J = 3.5, 8.7, 5.0 Hz, 1.22), 2.49-2.36 (m, 3.16). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 187.1, 171.0, 158.5, 135.2,
134.2, 130.3, 129.2, 127.0, 122.9, 122.3, 120.3, 120.1, 114.0, 110.3, 55.6, 52.2, 40.3, 38.5, 37.4, 36.9, 31.6, 29.6. **IR** 3001(w), 2924(m), 2850(m), 1772(s), 1738(w), 1658(s), 1623(m), 1540(m), 1511(m), 1246(s), 1219(m) cm\(^{-1}\). **HRMS(ESI) M/Z**\(^+\) Calc. 363.1471, Obs. 363.1478.

Methyl 4-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydrodibenzo[\(b,d\)]furan-2-carboxylate (81h). According to the general procedure, to a solution containing In(OTf)\(_3\) (5.8 mg, 0.103 \(\mu\)mol) was added cyclopropane 81h (0.075 g, 0.206 mmol). The reaction was quenched after 5.5 hours, and column chromatography (15% EtOAc/hexane, R\(_f\) = 0.25) provided 82h as a solid (0.053 g, 71.0 %). (Diastereomeric ratio 1.2:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.60 - 7.54 (m, 2.14), 7.48 - 7.38 (m, 2.41), 7.22 - 7.02 (m, 5.36), 6.95 - 6.84 (m, 4.24), 6.73 (d, \(J = 8.0\) Hz, 1.06), 4.60 (dd, \(J = 4.8, 8.5\) Hz, 0.79), 4.37 (dd, \(J = 4.8, 10.9\) Hz, 1.00), 3.87 - 3.71 (m, 12.55), 2.91 (td, \(J = 5.3, 13.8\) Hz, 0.88), 2.82 - 2.58 (m, 2.16), 2.49 (ddd, \(J = 4.8, 8.7, 13.8\) Hz, 0.98); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 182.8, 169.8, 169.6, 159.0, 158.9, 156.4, 146.0, 136.9, 132.6, 129.4, 129.2, 125.6, 123.7, 123.6, 114.3, 112.8, 55.3, 54.5, 52.3, 39.6, 38.0. **IR** 2960(m), 2923(m), 2844(w), 1721(s), 1675(m), 1615(w), 1552(m), 1505(w), 1459(m), 1426(m) cm\(^{-1}\). **HRMS(ESI) M/Z**\(^+\) Calc. 350.1154, Obs. 350.1163.
Methyl 3-bromo-7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-5-carboxylate (82i): According to the general procedure, to a solution containing In(OTf)₃ (3.55 mg, 6.32 µmol) was added cyclopropane 81i (0.050 g, 0.126 mmol). The reaction was quenched after 8 hours, and column chromatography (15% EtOAc/hexane, Rᵢ = 0.25) provided 82i as a solid (0.028 g, 56.0%). (2:1 mixture of keto and enol forms). ¹H NMR (CDCl₃, 300 MHz) δ 12.58 (s, 0.28), 7.78-7.63 (m, 0.42), 7.66-7.48 (m, 0.33), 7.47-7.32 (m, 0.21), 7.30-7.16 (m, 1.07), 7.16-6.95 (m, 0.37), 6.81-6.79 (m, 1.30), 6.45-6.40 (m, 0.56), 3.95-3.60 (m, 3.97), 2.91-2.76 (m, 0.53), 2.70-2.55 (m, 1.00). ¹³C NMR (CDCl₃, 75 MHz) δ 173.0, 163.1, 158.7, 146.7, 144.7, 133.8, 131.8, 130.0, 129.2, 122.7, 121.2, 114.3, 57.4, 56.6, 55.3, 51.8, 43.0, 30.8. IR 2920(m), 2840(m), 1735(m), 1598(m), 1511(s), 1440(m), 1353(m), 1246(s), 1176(m) cm⁻¹. HRMS(ESI) M/Z⁺ Calc. 393.9874, Obs. 393.9869.

Methyl 7-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (82j): A solution containing In(OTf)₃ (5.2 mg, 9.24 µmol) in 1,2-DCE was added cyclopropane 81j (0.050 g, 0.19 mmol) and the reaction was heated to reflux. The reaction was quenched after 6 hours, followed by general work up, and column chromatography (15% EtOAc/hexane, Rᵢ = 0.25) provided 82j as a solid (0.041 g, 81.0%). (Diastereomeric ratio 2.3:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.63 (d, J = 5.0 Hz, 0.29), 7.58 (d, J = 5.0 Hz, 0.42), 7.49-7.38 (m, 1.38), 7.39-7.26 (m, 7.70), 7.21-7.03 (m, 3.44), 6.69 (d, J = 5.0 Hz, 0.27), 6.62-6.44 (d, J = 5.0 Hz, 0.33), 4.59 (dd, J = 7.7, 4.7 Hz, 0.52), 4.32 (dd, J = 11.9, 4.3 Hz, 1.00), 3.89-3.53 (m, 7.90), 3.01-2.60 (m, 2.38), 2.65-2.22 (m, 2.36). ¹³C NMR (CDCl₃, 75 MHz) δ 187.5, 170.3, 160.7, 155.2, 154.3, 142.4,
Methyl 4-oxo-7-phenyl-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (82k). According to the general procedure, to a solution containing In(OTf)₃ (12.4 mg, 0.23 µmol, 5 mol%) was added cyclopropane 81k (0.12 g, 0.44 mmol). The reaction was quenched after 6 hours, and column chromatography (20% EtOAc/hexane, Rᵣ= 0.25) provided 82k as a solid (0.099 g, 82.5 %). (Diastereomeric ratio 1.2:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.20 (m, 4.45), 7.11 (dd, J = 7.9, 1.5 Hz, 1.02), 7.02 (dd, J = 7.7, 1.7 Hz, 1.16), 6.66 (m, 1.0), 4.44 (dd, J = 6.3, 5.9 Hz, 0.62), 4.21 (dd, J = 10.4, 5.7 Hz, 0.54), 3.79-3.70 (m, 3.26), 3.64-3.49 (m, 1.12), 3.00-2.80 (m, 0.67), 2.65-2.47 (m, 0.98), 2.41-2.23 (m, 0.68 ). ¹³C NMR (CDCl₃, 75 MHz) δ 188.4 (2C), 170.2, 170.0, 166.7, 143.9, 143.8, 139.1, 139.0, 129.0, 128.9, 127.8, 127.7, 127.6, 121.4, 106.8, 106.7, 54.4, 52.5, 52.4, 51.5, 41.1, 38.7, 36.0, 35.3. IR 3121(w), 2937(w), 1772(s), 1730(s), 1684(m), 1605(w), 1583(m) cm⁻¹. HRMS(ESI) M/Z⁺ Calc. 270.0892, Obs. 270.0893.

Methyl 4-methyl-7-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (82l). According to the general procedure, to a solution containing In(OTf)₃ (7.06 mg, 0.125 µmol) was added cyclopropane 81l (0.075 g, 0.25 mmol). The reaction was quenched after 4.5 hours, and column chromatography (15% EtOAc/hexane, Rᵣ= 0.25) provided 82l as a solid (0.053 g, 71.0
%). (Diastereomeric ratio 2:1). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.91 (d, $J = 5.0$ Hz, 0.83), 7.64 (d, $J = 5.1$ Hz 0.32), 7.63-7.30 (m, 6.04), 7.28-7.25 (m, 1.17), 7.21-7.09 (m, 2.04), 6.86-6.92 (m, 0.33), 3.98-3.92 (dd, $J = 9.8$, 9.0 Hz, 0.57), 3.92-3.86 (s, 2.83), 3.70-3.68 (s, 0.97), 3.46 (dd, $J = 13.7$, 3.9 Hz, 0.97), 3.12-3.02 (m, 0.36), 2.98-2.88 (m, 1.10), 2.62 (dd, $J = 13.4$, 4.1 Hz, 1.01), 2.52-2.44 (m, 0.37), 1.98-1.92 (s, 2.37), 1.83-1.79 (s, 1.16). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 187.7, 186.8, 170.4, 170.3, 162.9, 159.3, 157.4, 146.5, 144.7, 136.2, 135.5, 128.6, 128.3, 128.0, 127.7, 127.1, 126.9, 126.8, 126.3, 125.2, 124.9, 124.8, 119.1, 115.3, 53.6, 52.3, 52.2, 51.9, 43.8, 43.6, 42.6, 38.1, 31.2, 29.5. IR 3002 (w), 2951(w), 2923(w), 1721(s), 1682(s), 1661(s), 1515(w), 1444(s) 1410(m) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 300.0820, Obs. 300.0830.

Methyl 4-oxo-5,5a,10,10a-tetrahydro-4H-fluoreno[2,1-b]thiophene-5-carboxylate (82m).

According to the general procedure, to a solution containing In(OTf)$_3$ (4.71 mg, 8.38 µmol) was added cyclopropane 81m (0.050 g, 0.17 mmol). The reaction was quenched after 6 hours, and column chromatography (15% EtOAc/hexane, R$_f = 0.25$) provided 82m as a solid (0.043 g, 87.0 %). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.80 (td, $J = 3.8$, 1.1, 1.1 Hz, 0.59), 7.75-7.62 (m, 0.67), 7.50 (td, $J = 8.6$, 3.7, 3.7 Hz, 0.41), 7.45-7.31 (m, 1.57), 7.31-7.05 (m, 2.65), 6.99-6.81 (m, 0.95), 3.92-3.62 (m, 3.24), 3.62-3.41 (m, 1.00). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 185.6, 168.7, 143.9, 142.3, 139.8, 135.1, 133.3, 132.6, 128.4, 126.3, 125.0, 123.6, 121.1, 57.7, 52.8, 40.1. IR 2930 (m), 2847(w), 1737(s), 1664(s), 1959(s), 1595(w), 1413(m), 1254(s), 1207(s), 1147(s), 1087(s) cm$^{-1}$. HRMS(ESI) M/Z$^+$ Calc. 298.0670, Obs. 298.0697.
Methyl 4-((tert-butyldiphenylsilyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (82n). According to the general procedure, to a solution containing In(OTf)₃ (12.1 mg, 0.21 µmol, 30 mol %) was added cyclopropane 81n (0.10 g, 0.429 mmol). The reaction was quenched after 6 hours, and column chromatography (20% EtOAc/hexane, R_f = 0.25) provided 82n as a solid (0.071 g, 71.0 %). (Diastereomeric ratio 2.4:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.76 - 7.64 (m, 8.34), 7.63 - 7.52 (m, 2.15), 7.51 - 7.33 (m, 14.00), 7.14 - 6.99 (m, 1.69), 6.79 (d, J = 5.0 Hz, 0.65), 3.67 (d, J = 4.4 Hz, 2.23), 3.64 - 3.60 (m, 1.09), 3.58 (s, 2.46), 3.54 - 3.42 (m, 1.84), 3.30 - 3.12 (m, 2.00), 3.12 - 2.91 (m, 0.92), 2.37 - 2.17 (m, 1.39), 2.17 - 1.74 (m, 4.81), 1.73 - 1.36 (m, 5.62), 1.13 - 0.97 (m, 18.39). ¹³C NMR (CDCl₃, 75 MHz) δ 187.7, 186.6, 169.9, 159.1, 136.1, 136.0, 135.9, 135.9, 134.9, 129.6, 129.5, 129.4, 128.0, 127.9, 127.8, 127.7, 127.6, 52.2, 51.1, 30.6, 27.8, 27.7, 18.3. IR 2927, 2855, 1742, 1678, 1458, 1427, 1275, 1260 cm⁻¹.


Methyl 4-hydroxybenzofuran-5-carboxylate (83). According to the general procedure, methyl 5-ethoxy-2-((thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate 84 (0.10 g, 0.419 mmol) was added to a solution containing In(OTf)₃ (11.8 mg, 0.21 µmol) in DCM. The reaction was quenched after 24 hours, and purification by column chromatography (R_f = 0.25, 15% EtOAc/hexane,) provided the product 84 as a white solid (0.0445 g, 51 %). All data matches literature.

F. Tandem Cyclopropanation-Homo Nazarov Cyclization
To a flame dried flask containing Rh$_2$esp$_2$ (6.00 mg, 7.93 µmol) and In(OTf)$_3$ (1.01 mg, 1.79 µmol) in DCM (2 mL) was added 4-methoxystyrene (0.106 g, 0.793 mmol) at 0 °C. After 5 minutes, a solution of α-diazo ester 80d (0.200 g, 1.03 mmol) in DCM (2 mL) was added to the flask. The ice bath was removed after 10 minutes and the reaction was allowed to warm up to rt. The reaction was quenched with water after 12 hours, extracted with DCM (3x), dried with Na$_2$SO$_4$, and column chromatography (10% EtOAc/hexane, R$_f$= .15) afforded 82d as a solid (0.060 g, 56.6%).
Chapter Three: Acetal Ring Opening/Prins-type Cyclization/Elimination

Cascade of 5-Heteroaryl-2,3-Dihydrofurans

3.1 Introduction to Dihydrofurans

Dihydrofuran (DHF) is one of the most ubiquitous motifs in natural products possessing biological properties.\(^{106}\) The two isomers of dihydrofurans include 2,3-dihydrofuran and 2,5-dihydrofuran (Figure 3.1).\(^{107}\) In particular, molecules containing the 2,3-dihydrofuran moiety are widely used as medicines, insecticides and/or pesticides.\(^ {108}\) This chapter will only focus on the 2,3-dihydrofuran moiety and its reactivity.

![Figure 3.1: Dihydrofuran Isomers](image)

3.2 Natural Products Containing Dihydrofurans

Natural products containing the 2,3-DHF moiety are highly abundant in nature. For example, aflatoxins (1 and 2) are members of a large family of natural products known as the mycotoxins (Figure 3.2).\(^ {109,110}\) These mycotoxins are toxic and are harmful to agricultural products such as peanuts, rice, wheat, soybeans. Clerodin (3), one of the most active mycotoxins, was first isolated in 1936 from Clerodendron infortunatum. It is a potent insect antifeedant, and thus has potential for use in the protection of crops.\(^ {111-113}\) Norrisolide (4) was isolated by Faulkner and coworkers in 1983 from dorid nudibranch mollusc Chromodoris norrisi.\(^ {114}\) This marine natural product has been shown to inhibit secreted phospholipase A\(_2\) (sPLA\(_2\)).\(^ {115}\) Norrisolide (4) was also shown to induce an irreversible vesiculation of these membranes.\(^ {116}\)

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\(^*\)This work is in collaboration with Joel Aponte-Guzman, Marchello A. Cavitt and Jack C. Davy.
Austocystin (5) was isolated from Aspergillus UGM218 as a potent and selective cytotoxic agent in a 26-cell-line panel.\textsuperscript{117}

![Chemical structures](image)

**Figure 3.2:** Natural Products Containing the Dihydrofuran Scaffold

Given the prevalence of natural products containing the DHF motif and these compounds’ broad biological activity, rapid methods are extremely attractive in order to form these core scaffolds in high yields. As a result, many synthetic approaches for the access of the DHF core have been realized. These methods include the decomposition of diazo ketones\textsuperscript{19} or α-elimination of dibromo ketones in the presence of olefinic trapping agents. Oxidative cycloaddition reactions mediated by metal salts\textsuperscript{118} and iodonium ylides\textsuperscript{119,120} have also been employed as an alternative to diazo compounds without major drawbacks such as explosive and health hazards. Given the extensive literature, only selected examples of metal catalyzed synthesis of 5-substituted 2,3-dihydrofurans will be discussed \textit{vide infra}.

### 3.3 Relevant Examples For the Synthesis of Dihydrofurans

2,3-Dihydrofurans 7 can be formed readily from a thermal rearrangement of vinyl epoxides 6 in the presence of an activator such as heat or acid (Scheme 3.1).\textsuperscript{121} The mechanism of this transformation is via an ylide-type intermediate that undergoes either a $[2\pi_s + 2\sigma_a]$ or $[2\pi_a + 2\sigma_s]$ disrotatory ring closure to afford a mixture of \textit{cis} 9 and \textit{trans} 8 isomers.
The Mn(OAc)$_3$-mediated oxidative free radical addition of acetoacetic esters 10 to alkenes 11 is a useful synthetic method to provide 2,3-dihydrofurans 12 (Scheme 3.2). This was first reported by Dessau and coworkers in 1974, and expanded by several groups, including the Brun group. Brun was interested in developing a stereocontrolled intermolecular dihydrofuran formation. Brun’s strategy used an oxazolidinone as the chiral auxiliary to impart diastereoselectivity. They varied the groups on the esters and the alkenes, and found that they were able to form selectively the trans isomer. This methodology was limited to alkyl β-ketoesters and aryl cinnamoyl esters and provided the 2,3-dihydrofurans in good yields (65-80%).

Ceric ammonium nitrate (CAN) has been shown to facilitate the cycloaddition of 1,3-dicarbonyl compounds to cinnamic esters. Roy and coworkers treated β-ketoesters 13 or β-diketones 16 with cyclic enol ethers 14 to provide fused acetals 15 and 17 in good yields (Scheme 3.3). Roy chose readily available cyclic enol ethers, dihydropyran and dihydrofuran...
as substrates and allowed them to react with different alkyl or cyclic 1,3-dicarbonyl compounds. This method can be performed at low temperature. The protocol provides the acetics 15 and 17 in good yields (60-75%).

**Scheme 3.3:** CAN Mediated Cycloaddition of 1,3-Dicarbonyl Compounds

Functionalized dihydrofurans can be formed via an active methylene compound with olefins as promoted by metal catalysts such as palladium. Cacchi and coworkers designed an innovative palladium-catalyzed oxyarylation of α-allyl-β-ketoesters 18 (oxypalladation/Mizoroki-Heck reaction), furnishing highly substituted dihydrofurans 19 (Scheme 3.4). This report was extremely general, as it was extended to electron rich and electron poor aryl halides and heteroaryl halides. Dihydrofurans were isolated in 10-94% yield.

**Scheme 3.4:** Dihydrofurans from Metal Mediated Diazocomposition

Fallis and coworkers reported dihydrofurans from α-diazoketones via a ring opening-cyclization of donor-acceptor cyclopropanes intermediates. This methodology was initially motivated by their goal towards the synthesis of anti-tumor agent taxol. This report noted that in presence of a catalyst to decompose diazo 20, such as Rh$_2$(OAc)$_4$, Pd(OAc)$_2$, and CuCl in presence of ethyl vinyl ether, dihydrofurans 21 were rapidly generated (Scheme 3.5).
Scheme 3.5: Fallis’ Dihydrofuran Synthesis from α-Diazoketones

The authors rationalized that the dihydrofuran arose from a concerted or stepwise dipolar cycloaddition of α-diazoketone 22 to the enol ether, or that the intermediate cyclopropylketone 23 was an intermediate that undergoes rapid ring opening to enolate 24 and subsequent ring closure gave the product (Scheme 3.6). This spontaneous rearrangement provided dihydrofurans 25 in 10-70%, depending on choice of catalyst. Fallis’ report was limited to cyclic or aryl substituted dihydrofurans.

Scheme 3.6: Fallis’ Mechanistic Rationale for Acetal Formation

Alonso reported that α-diazo-β-ketoesters 27 and enol ethers 26 in presence of copper/bronze formed dihydrofurans 28 in modest yields (6-76%) upon heating in fluorobenzene (Scheme 3.7).\(^{130,131}\) The most vital step in these reports was the generation of β-oxycyclopropylketone intermediate. Alonso’s protocol was limited to cyclic or alkyl 1,3-dicarbonyls.

Scheme 3.7: Alonso’s Cu-Catalyzed Reactions of α-Diazodicarbonyl Compounds

Davies and coworkers developed an asymmetric synthesis of 2,3-dihydrofurans using Rh\(_2\)(Oct)\(_4\) to generate the requisite carbenoid (Scheme 3.8). (R)-pantolactone was used as the
chiral auxiliary to impart enantioselectivity.\textsuperscript{132,133} However, the carbonyl of (R)-pantolactone interfered with the carbenoid, and resulted in low enantioselectivity. Davies then used vinylcarbenoids derived from substrate 29 to react with excess vinyl ether in order to generate the cyclopropane intermediate. Treatment with TBAF at -78 °C provided the dihydrofuran product 30 as a single diastereomer. Presumably, the product would be formed after desilylation of the cyclopropane, followed by ring expansion to form the dihydrofuran. Only alkyl and aryl substituted dihydrofurans were achieved using this protocol.

\begin{figure}
\centering
\includegraphics[scale=0.5]{diagram.png}
\caption{Scheme 3.8: Davies Asymmetric Synthesis of 2,3-Dihydrofurans}
\end{figure}

In 2011, Lyoo and coworkers disclosed an efficient method toward the synthesis of 2,3-dihydrofuran via [3+2] cycloaddition of cyclic diazodicarbonyl compounds catalyzed by AgBF\textsubscript{4}/[Bmim]BF\textsubscript{4} (Scheme 3.9).\textsuperscript{134} Mechanistically, Ag-catalyzed decomposition of the diazo 31 to its carbene 32 in presence of the alkene provides cyclopropane intermediate 33. Bond cleavage of cyclopropane 33 forms the zwitterion 34, which then undergoes ring closure to form dihydrofuran 35. This methodology tolerated both electron rich and electron poor olefins. Moreover, dihydrofuran products can be formed in 54-74\%. 

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Scheme 3.9: Ag(I) Catalyzed [3+2] of Diazocarbonyls

3.4 Dihydrofurans as Useful Synthetic Building Blocks

After developing the formation of these dihydrofurans, Lyoo and coworkers demonstrated further utility by converting these dihydrofurans with an acetate group to the corresponding 3-acyl furans. Treatment of dihydrofuran derivatives with p-TsOH in refluxing toluene gave 3-acylfurans in 80-89% yields (Scheme 3.10).

Scheme 3.10: Lyoo’s Protocol for Dihydrofuran to Furan

Corey and Gosh treated dihydrofuran acetal first with a Brønsted acid (5% aqueous sulfuric acid-THF (20:1)), followed by Brønsted base (10% aqueous potassium hydroxide-methanol (1:1) provided enone in 73% yield (Scheme 3.11). This acetal hydrolysis and base treatment provided fused and/or spiro 2-cyclopentenones via an intramolecular aldol condensation. Protonation of the acetal and ring opening to formed the acyclic ketone. A base-catalyzed aldol condensation afforded the cyclopentenone product.
The examples above showed that 1,3-dicarbonyl compounds can undergo cycloaddition reactions with electron rich olefins to provide dihydrofurans. In Lyoo’s example, treatment of diazo compounds with electron rich olefin can result in the formation of an intermediate cyclopropane, which then can rearrange to its corresponding dihydrofuran. An alternative pathway would be a [3+2] cycloaddition of the diazocarbonyls, and the reactivity of these compounds is substrate dependent. This report validated our hypothesis that we could form a transient cyclopropane which rearranges to the didhydrofuran. Furthermore, Lyoo also showed that treatment of these dihydrofuran acetals to a protic acid is a new method for the formation of substituted furans. Corey’s report showed that dihydrofuran acetals can under ring rearrangement to form furanones. These reports gave us even more reassurance to further examine the dihydrofuran acetal rearrangement and its utility as a building block for benzofused heteroaromatics, furans and furanones.

3.5 Rearrangements of Electron Rich Cyclopropanes

Abdallah and coworkers reported that the equilibrium for these push-pull cyclopropanes 40a, especially those containing two electron withdrawing groups, as well as a heteroatom at the α-position readily leads to the ring expansion to form dihydrofuran 40b (Scheme 3.12). Lund and coworkers also observed the same rearrangement. Extensive NMR studies generated the conclusion that α-diazo-ketone systems react with electron rich olefins such as vinyl ethers form cyclopropyl ketones. However, these cyclopropanes are extremely labile, and do not survive the
standard reaction work up at room temperature. They readily rearrange to their more stable form as a dihydrofuran acetal, which are isolable.\textsuperscript{128,129}

![Scheme 3.12: Equilibrium of Cyclopropanes with Oxygen as Donor Group](image)

### 3.6 Project Objective

In Chapter Two of this thesis, we observed that dihydrofuran acetals were readily formed by treating heteroaryl α-diazo compounds with electron rich olefins. Upon treatment of these dihydrofuran acetals, we were able to form benzofused heteroaromatic compounds. After this observation, we were interested in exploring the full potential of this methodology for the synthesis of different heteroaromatic compounds using dihydrofuran acetals as the reactive subunits.

### 3.7 Project Rationale

Chapter Two of this thesis disclosed the heteroaryl homo-Nazarov cyclization for the rapid generation of heteroaryl ring-fused cyclohexanones. An interest in developing an extremely versatile homo-Nazarov cyclization led us to explore cyclopropanes with a heteroatom as the donor group. In this report, treatment of our model diazo 41 (derived from 2-thiophene carboxylic acid) with Rh\textsubscript{2}esp\textsubscript{2} (dirhodium α,α,α',α'-tetramethyl-1,3-benzenedipropanoate)\textsuperscript{97} in presence of ethyl vinyl ether was predicted to form cyclopropane 42. Yet dihydrofuran 43 was isolated in good yield (72 %) (Scheme 3.13).\textsuperscript{136} This finding was consistent with those in literature. In presence of an extremely good donor group (such as an ether) and two electron-withdrawing groups, cyclopropanes 42 are generated as intermediates which readily rearrange to form the dihydrofuran.\textsuperscript{129}
Scheme 3.13: Ring Expansion of Oxygen Substituted Cyclopropanes with Two Acceptor Groups

Upon the generation of the intermediate heteroaryl D-A-A cyclopropane from the reaction of Rh$_2$esp$_2$ and heteroaryl $\alpha$-diazo-$\beta$-keto esters in presence of ethyl vinyl ether, rearrangement occurs to provide the more stable dihydrofuran products. Upon formation of the ethoxycyclopropane 42, rapid ring opening forms the enolate intermediate 44 (Scheme 3.13). Subsequent attack of the enolate onto the oxonium ion forms dihydrofuran product 43a.

Scheme 3.14: Mechanistic Rationale for Dihydrofuran Formation

3.8 Synthesis of Dihydrofuran Acetals

Our initial goal was to evaluate the feasibility of this method for all vinyl ethers. We subjected different heteroaryl $\alpha$-diazo-$\beta$-keto esters to different vinyl ethers. We were delighted to isolate the dihydrofuran products in high yields. Using the same 2-thiophene $\alpha$-diazo-$\beta$-ketoester 41a and ethyl vinyl ether 52a, dihydrofuran 43a was isolated in 71% yield (Table 3.1, entry 1). As compared to benzylvinyl ether, dihydrofuran product 43g was yielded in 48% (Table 3.1, entry 2). tert-Butylvinyl ether afforded dihydrofuran product 43h in 52% (Table 3.1, entry 3). Dihydrofuran 42i, derived from trimethyl(vinyl)oxy)silane was formed in 35% (Table 3.1, entry 4).
Table 3.1: Synthesis of Dihydrofuran Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
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<td>![Diazol] 41a</td>
<td>![Alkene] 52a</td>
<td>![Product] 43a</td>
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<tr>
<td>2</td>
<td>![Diazol] 41a</td>
<td>![Alkene] 52b</td>
<td>![Product] 43g</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>![Diazol] 41a</td>
<td>![Alkene] 52c</td>
<td>![Product] 43h</td>
<td>52</td>
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<tr>
<td>4</td>
<td>![Diazol] 41a</td>
<td>![Alkene] 52d</td>
<td>![Product] 42i</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields after column chromatography

3-Thiophene α-diazo-β-ketoester 41b was subjected to the standard conditions with ethyl vinyl ether 52a to provide product 43b in 42% (Table 3.2, entry 1). Starting from 2-α-diazofuran-β-ketoester 41c, dihydrofuran 43c was isolated 41% (Table 3.2, entry 2). The low yield could be due to degradation, as for 43d derived from 3-furyl diazo 41d, the yield improved significantly to 78% (Table 3.2, entry 3). Dihydrofuran 43e, derived from 2-bromo-furyl diazo 41e can be formed in 46%, perhaps due to degradation (Table 3.2, entry 4). It is worthwhile to mention that the 2-bromo can serve as a point of functionalization for further complexity. Benzofuran substituted dihydrofuran 43f can be rapidly formed in 71% (Table 3.2, entry 5). Interestingly, when N-methylpyrrole diazo 41g was subjected to the cyclopropanation reaction in presence of heat, only the indole product 49g was observed in 22% yield (Table 3.2, entry 6). This could be attributed to the instability of the dihydrofuran and the reaction conditions.
Table 3.2: Synthesis of Different Heteroaryl Dihydrofuran Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
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</thead>
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<td><img src="image3" alt="Producte" /></td>
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<tr>
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<td><img src="image2" alt="Alkenede" /></td>
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<tr>
<td>5</td>
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<td><img src="image3" alt="Producte" /></td>
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<tr>
<td>6</td>
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<td><img src="image2" alt="Alkenede" /></td>
<td><img src="image3" alt="Producte" /></td>
<td>22</td>
</tr>
</tbody>
</table>

Conditions: Reactions were performed with diazo substrate 41 (1.1-1.3 equiv), vinyl ether 52 (1 equiv), and R̄H₂esp₂ (0.1 mol%) in CH₂Cl₂ at 0°C.

a Isolated yields after column chromatography

b Heating in 1,2-DCE

After determining that this rapid rearrangement was amenable towards different heteroaromatics, we investigated the effects of the donor group. We were able to demonstrate that simple vinyl ethers readily react with the carbenoid to generate trisubstituted dihydrofurans. However, the ability to generate a fully substituted dihydrofuran is of high interest. Using 1-ethoxybut-1-ene 52e, dihydrofuran 43j was formed in 45% (Table 3.3, entry 1), while 2-methoxyprop-1-ene 52f furnished dihydrofuran 43k in 50% (Table 3.3, entry 2). Notably, this is a rapid method to generate a dihydrofuran with a quaternary center. Dihydrofuran 43l formed in 51%, can be readily formed from β-methoxystyrene 52g and diazo 41a (Table 3.3, entry 3), and
dihydrofuran 43m was formed in 61% from the commercially available 2,3-dihydrofuran (Table 3.3, entry 4). Using tert-butyl((1-methoxyvinyl)oxy)dimethylsilane, dihydrofuran 43n can be formed in 70% (Table 3.3, entry 5).

Table 3.3: Synthesis of Different Alkoxy Dihydrofuran Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td><img src="alkene2.png" alt="" /></td>
<td><img src="product2.png" alt="" /></td>
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</tr>
<tr>
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<td><img src="alkene3.png" alt="" /></td>
<td><img src="product3.png" alt="" /></td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td><img src="diazo4.png" alt="" /></td>
<td><img src="alkene4.png" alt="" /></td>
<td><img src="product4.png" alt="" /></td>
<td>61</td>
</tr>
<tr>
<td>5b</td>
<td><img src="diazo5.png" alt="" /></td>
<td><img src="alkene5.png" alt="" /></td>
<td><img src="product5.png" alt="" /></td>
<td>70</td>
</tr>
</tbody>
</table>

Conditions: Reactions were performed with diazo substrate 41(1.1-1.3 equiv), vinyl ether 52 (1 equiv), and Rh2esp2 (0.1 mol%) in CH2Cl2 at 0°C a isolated yields after column chromatography b Rh2(oct)4 (5 mol%) was used

3.9 Ring Opening/Prins-type Cyclization/Elimination of Dihydrofuran Acetals

Following the development of a rapid and facile method for the generation of dihydrofurans, an interest in exploiting these dihydrofurans and their applications led us to our next discoveries. We wanted to probe the reactivity of these dihydrofurans in presence of Lewis acids to determine if we would be able to form benzofused heteroaromatics products.
Scheme 3.15: Proposed Mechanism for the Formation of Benzofused Heteroaromatics

The formation of the benzofused heteroaromatic is as follow: upon chelation with a Lewis acid (as depicted in 43), an acetal ring opening will occur to form oxonium intermediate 46. Intermediate 46 is stabilized by the electrons of the oxygen, and attack by the pendant heteroaromatic π-system generates 47. Elimination of the alkoxy group provides 48 (Scheme 3.15). Using a model dihydrofuran substrate, derived from 2-thiophene and ethyl vinyl ether, different conditions and Lewis acids were screened in order to determine the best conditions for the desired transformation. We found that 5 mol % of In(OTf)₃ can catalyze the acetal ring opening and form the desired benzo[b]thiophene product 49a in 65% yield (Table 3.4, entry 1). Provided that the acetal readily undergoes ring opening, ring closing, followed by elimination to provide the desired benzofused heteroaromatic, we wanted to probe the electronics on the acetal system for the methodology. We synthesized different alkoxy-derivatives and subjected them to In(OTf)₃ at room temperature. When dihydrofuran 43g (with a benzyl group) was used, 49a was formed in 46% (Table 3.4, entry 2). Next, dihydrofuran 43h (from the tert-butyl group) provided 49a in 69% yield (Table 3.4, entry 3). Notably, the O-silyl derivative provided a low yield of 24% (Table 3.4, entry 4), perhaps due to hydrolysis of the labile O-Si bond. The isolation of 49a from all four reactions validates the mechanism, as the alkoxy group does not play a major role in the formation of the product.

Next, we wanted to probe the effects of the heteroaromatics. Various heteroaryl dihydrofurans with an ethoxy acetal were synthesized. These dihydrofurans were also subjected
to 5 mol % of \( \text{In(OTf)}_3 \) at room temperature, and it was found that 3-thienyl dihydrofuran 43b provided benzo[b]thiophene 49b in 58% yield (Table 3.4, entry 5). Substituted benzofurans can be readily accessed by having the furan as the heteroaryl group, and both 2- and 3-furyl dihydrofurans (43c and 43d) provided its corresponding benzofurans 49c and 49d in good yield (67% and 71%, respectively) (Table 3.4, entry 6 and 7). Dibenzofuran 49f can be realized from dihydrofuran 43f (derived from benzofurans \( \alpha \)-diazo) in 62% yield (Table 3.4, entry 8). Overall, we have developed a novel approach towards the synthesis of benzofused heteroaromatic compounds using dihydrofuran acetals.

**Table 3.4**: Generation of Benzofused Heteroaromatics from Dihydrofuran Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R=Et 43a</td>
<td>49a</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>R=Bn 43g</td>
<td>49a</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>R=t-Bu 43h</td>
<td>49a</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>R=TMS 43i</td>
<td>49a</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>R=Et 43b</td>
<td>49b</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>R=Et 43c</td>
<td>49c</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>R=Et 43d</td>
<td>49d</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>R=Et 43f</td>
<td>49f</td>
<td>62</td>
</tr>
</tbody>
</table>

Conditions: Reactions were performed with dihydrofuran substrate 43 (1 equiv) and \( \text{In(OTf)}_3 \) (5 mol%) in \( \text{CH}_2\text{Cl}_2 \) at 25 °C. b Isolated yield after column chromatography.
Consequently, we were interested in building more complex benzofused heteroaromatic compounds, and we envisioned that by having a more substituted dihydrofuran acetal (derived from disubstituted vinyl ethers), upon cyclization and elimination, the substituent will remain intact. However, when the tetrasubstituted dihydrofuran was subjected to the conditions of In(OTf)$_3$ at room temperature, such as in the case of 43k and 43m, we found that the desired benzofused heteroaromatic compounds were not formed. Instead, we isolated the elimination product (Table 3.5, entry 1). This may be due to steric hindrance, and the Lewis acid’s inability to effectively chelate to the oxygen on the dihydrofuran. Consequently, ring opening will not occur to form the necessary intermediate for the Prins-type cyclization. Instead, it chelates to the ethoxy group, and the oxygen on the dihydrofuran promotes the elimination. From our results with N-methylpyrrole, we decided to heat the reaction to promote the acetal ring opening. Upon heating in 1,2-DCE, we observed the formation of a mixture of products. Under elevated temperatures, an inseparable mixture of 49k and 49k’ (1.5:1 ratio) was isolated as the major product. Also an inseparable mixture of 50k and 50k’ (1.5:1 ratio) were obtained as the minor product (Scheme 3.16). This is due to the elimination of the ethoxide, which undergoes transesterification to form 49k’ and 50k’.

![Scheme 3.16: Tetrasubstituted Dihydrofuran Optimization](image)

In the case of the trisubstituted furan 50l, the elimination of the methoxy group from 43l was rapid to provide furan 50l in 82% yield (Table 3.5, entry 2). Furanone 51 arose from the cleavage of the silyl group followed by elimination of the methoxy group in 43p to provide
furanone 51 in 29% (Table 3.5, entry 3). This utility serves as an alternative for the generation of 5-heteroaryl substituted furanones. From these discoveries, substituted dihydrofuran acetals can be used as building blocks to generate substituted furans in modest yields, while orthoacetates form furanones in modest yields.

**Table 3.5**: Reactions of Highly substituted Dihydrofuran Acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dihydrofuran</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

Conditions: Reactions were performed with dihydrofuran substrate 43 (1 equiv) and In(OTf)<sub>3</sub> (5 mol%) in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C. <sup>b</sup> Isolated yield after column chromatography

### 3.10 Summary

In summary, we have successfully demonstrated a rapid and efficient strategy for the construction of dihydrofurans. In this protocol, heteroaryl diazo compounds and electron rich olefins were subjected to a Rh(II)-catalyzed cyclopropanation reaction, which is in equilibrium with the dihydrofuran acetals. These heteroaryl substituted dihydrofuran acetals were generated up to 71% yield, and it tolerated different heteroaromatics as well as functional groups about the dihydrofuran. Utilizing dihydrofurans as building blocks, we formed benzofused heteroaromatic
compounds upon subjection to 5 mol % of In(OTf)$_3$. Trisubstituted dihydrofurans gave furans readily in modest yields. Furanones were achieved using orthoacetates as the starting material.

These dihydrofurans can serve as synthetic precursors or handles for more complex structures such as benzofused heteroatomatics. Future areas of research will include a one pot synthesis of these dihydrofurans into pyrroles. Formation of O,S acetals can be achieved via vinyl thioethers, or even enamines can be employed to generate N,O acetals. Different heteroaromatics will be explored, such as pyridine for the generation of quinolines and indoles for carbazole synthesis. Further optimization of the N-methylpyrrole can be a new strategy for indole synthesis.
Experimentals

1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. 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. α-Diazo compounds 41a-41f were synthesized as previously reported. Benzyl vinyl ether 52b was prepared as according to Nakamura’s protocol and was distilled. β-methoxystyrene 52g was prepared according to Gassman’s procedure. Tert-butyl((1-methoxyvinyl)oxy)dimethylsilane 52i was formed from Heathcock’s procedure. Compounds 43e, 43g, 43i, 43j, 43k, 49k, 49k’, 50k, 50k’ were synthesized and provided by Joel Aponte-Guzman as well as transformations of 43g to 49a, 43i to 49a, 43c to 49c, 43d to 49d and 43f to 49f.

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 F254 TLC glass plates. Visualization was accomplished with 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 (1H
NMR and $^{13}$C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 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).

2. General Procedures

A. Formation of Heteroaryl Dihydrofurans 43a-43n

*General Protocol:* The corresponding alkene (1.0 equiv.) was added to a solution of Rh$_2$esp$_2$ (0.1 mol %) in DCM (1-2 mL) at 0 °C. After stirring for 5 minutes, a solution of the α-diazo ester (1.1-1.3 equiv., 0.2 M) was added in one shot and allowed to stir for 10 minutes at 0 °C. The ice bath was removed, and the reaction was allowed to warm to room temperature. After two hours, the reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The organic layer was collected, and the aqueous layer was extracted with DCM three times. Then, the organic layer was washed with brine, dried with Na$_2$SO$_4$, concentrated, and column chromatography afforded the desired products.

![Chemical Reaction](image)

*Methyl 5-ethoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43a):* According to the general procedure, a solution of α-diazo ester 41a (0.500 g, 2.4 mmol) was added to ethyl vinyl ether
ether (0.132 g, 1.83 mmol) and Rh_{2}esp_{2} (1.8 mg, 2.37 µmol) in DCM at 0 °C. The reaction was quenched after 5 hours and column chromatography (10% EtOAc/hexane) afforded 43a as an oil (0.430 g, 72.0%). \( R_f \) (10% Et\textsubscript{2}O/hexane) = 0.25. All characterization matches previous literature.\textsuperscript{136}

Methyl 5-ethoxy-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (43b): According to the general procedure, a solution of \( \alpha \)-diazo ester 41b (0.515 g, 2.45 mmol) was added to ethyl vinyl ether (0.133 g, 1.83 mmol) and Rh_{2}esp_{2} (1.4 mg, 1.9 µmol) in DCM at 0 °C. The reaction was quenched and column chromatography (7% Et\textsubscript{2}O/hexane) afforded 43b as colorless oil (0.278 g, 59.7%). \( R_f \) (7% Et\textsubscript{2}O/hexane) = 0.20. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) \( \delta \) 8.45 (dd, \( J \)=2.9, 0.7 Hz, 1 H), 7.76 (dd, \( J \)=5.1, 0.9 Hz, 1 H), 7.28 (dd, \( J \)=5.0, 3.1 Hz, 1 H), 5.62 (dd, \( J \)=7.1, 2.5 Hz, 1 H), 3.93 (dq, \( J \)=9.4, 7.1 Hz, 1 H), 3.73 (s, 3 H), 3.65 (dq, \( J \)=9.4, 7.1 Hz, 1 H), 3.23 (dd, \( J \)=16.7, 7.3 Hz, 1 H), 2.94 (dd, \( J \)=16.7, 2.7 Hz, 1 H), 1.25 (t, \( J \)=7.1 Hz, 3 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz) \( \delta \) 165.4, 158.0, 130.8, 130.3, 128.3, 124.4, 103.8, 100.5, 64.1, 51.1, 38.2, 15.1. \textsuperscript{IR} 3132.4(w), 2983.7(m), 2975.2(m), 1700.7(s), 1611.5(s), 1435.9(m), 1251.8(s),1189.5(s), 1064.9(s) cm\textsuperscript{-1}. \textsuperscript{HRMS (ESI)} Calc. 254.0613, Obs. 254.0613.

Methyl 5-ethoxy-4,5-dihydro-[2,2'-bifuran]-3-carboxylate (43c): According to the general procedure, \( \alpha \)-diazo ester 41c (2.50 g, 12.9 mmol) was added to ethyl vinyl ether (0.774 g, 9.90 mmol) and Rh_{2}esp_{2} (7.5 mg, 9.9 µmol) in DCM at 0 °C. The reaction was quenched after 6 hours and column chromatography afforded 43c as yellow solid (1.70 g, 72.0%). \( R_f \) (10%
EtOAc/hexane) = 0.25. **mp**: 75.5-76.3 °C. **1H NMR** (CDCl₃, 300 MHz) δ 7.70 (d, J=3.5 Hz, 1 H), 7.39 (d, J=1.6 Hz, 1 H), 6.37 (dd, J=3.6, 1.7 Hz, 1 H), 5.51 (dd, J=7.2, 2.7 Hz, 1 H), 3.80 (dq, J=9.5, 7.1 Hz, 1 H), 3.57 (s, 3 H), 3.48 (dq, J=9.5, 7.1 Hz, 1 H), 3.06 (dd, J=16.8, 7.2 Hz, 1 H), 2.77 (dd, J=16.7, 2.8 Hz, 1 H), 1.08 (t, J=7.1 Hz, 3 H). **13C NMR** (CDCl₃, 75 MHz) δ 164.3, 152.7, 144.2, 143.8, 117.6, 111.8, 104.5, 100.1, 64.1, 50.7, 37.6, 14.8. **IR** 3134.3(w), 2977.1(w), 2953.6(w), 1725.7(s), 1699.9(s), 1672.1(s), 1665.7(s), 1635.4(w), 1463.2(s), 1436.2(m), 1418.5(s), 1393.4(m), 1255.0(s), 1158.4(m), 1121.7(m), 1055.8(m), 901.5(w), 882.3(m), 764.2(s), 593.1(m) cm⁻¹. **HRMS (ESI)** Calc. 238.0841, Obs. 238.0847.

**Methyl 5-ethoxy-4,5-dihydro-[2,3'-bifuran]-3-carboxylate (43d):** According to the general procedure, α-diazo ester 41d (2.04 g, 10.5 mmol) was added to ethyl vinyl ether (0.58 g, 8.08 mmol) and Rh₂esp₂ (6.12 mg, 2.37 µmol) in DCM at 0 °C. The reaction was quenched after 5 hours and column chromatography afforded 43d as an oil (1.50 g, 77.8%). **Rf** (10% EtOAc/hexane) = 0.25. **1H NMR** (CDCl₃, 300 MHz) δ 8.47 (s, 1 H) 7.41 (dd, J=3.2, 1.6 Hz, 1 H), 7.00 (dd, J=1.9, 0.7 Hz, 1 H), 5.64 - 5.58 (m, 1 H), 3.90 (dq, J=9.5, 7.1 Hz, 1 H), 3.73 (s, 3 H), 3.63 (dq, J=9.5, 7.1 Hz, 1 H), 3.19 (dd, J=16.6, 7.3 Hz, 1 H), 2.90 (dd, J=16.6, 2.6 Hz, 1 H), 1.24 (t, J=7.1 Hz, 3 H). **13C NMR** (CDCl₃, 75 MHz) δ 165.3, 156.7, 146.8, 142.3, 116.4, 110.0, 104.2, 100.5, 64.1, 50.9, 37.8, 15.1. **IR** 3134.3(w), 2977.1(w), 2953.6(w), 1725.7(s), 1699.9(s), 1672.1(s), 1665.7(s), 1635.4(w), 1463.2(s), 1436.2(m), 1418.5(s), 1393.4(m), 1255.0(s), 1158.4(m), 1121.7(m), 1055.8(m), 901.5(w), 882.3(m), 764.2(s), 593.1(m) cm⁻¹. **HRMS (ESI)** Calc. 238.0841, Obs. 238.0847.
Methyl 5-(tert-butoxy)-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43h): According to the general procedure, α-diazo ester 41a (0.300 g, 1.43 mmol) was added to t-butyl vinyl ether (0.112 g, 1.09 mmol) and Rh\textsubscript{2}esp\textsubscript{2} (1.0 mg, 1.1 µmol) in DCM at 0 °C. The reaction was quenched after 4 hours and column chromatography (5% EtOAc/hexane) afforded 43h as an oil (0.430 g, 52.3%). \( R_f \) (5% EtOAc/hexane) = 0.30. \(^1\text{H NMR} \) (CDCl\textsubscript{3}, 300 MHz) δ 8.21 (dd, \( J = 3.8, 1.1 \) Hz, 1 H), 7.47 (dd, \( J = 5.1, 1.1 \) Hz, 1 H), 7.09 (dd, \( J = 5.0, 3.9 \) Hz, 1 H), 5.88 (dd, \( J = 7.4, 3.0 \) Hz, 1 H), 3.74 (s, 3 H), 3.25 (dd, \( J = 16.5, 7.4 \) Hz, 1 H), 2.90 (dd, \( J = 16.5, 3.0 \) Hz, 1 H), 1.33 (s, 9 H). \(^{13}\text{C NMR} \) (CDCl\textsubscript{3}, 75 MHz) δ 165.5, 156.8, 132.1, 131.8, 129.9, 127.1, 99.5, 99.2, 75.8, 51.0, 39.1, 28.8. \(^\text{IR}\) 2973.8(s), 1695.1(s), 1603.0(s), 1247.6(s), 1168.3(m), 1066.3(s) cm\(^{-1}\). \( \text{HRMS (ESI)} \) Calc. 282.0960, Obs. 282.0936.

Methyl 5-methoxy-5-methyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43k): According to the general procedure, α-diazo ester 41a (0.500 g, 2.38 mmol) was added to 2-methoxyprop-1-ene (0.156 g, 2.16 mmol) and Rh\textsubscript{2}esp\textsubscript{2} (1.6 mg, 2.2 µmol) in DCM at 0 °C. The reaction was quenched after 4 hours and column chromatography (10% EtOAc/hexane) afforded 43k as an oil (0.275 g, 50.2%). \( R_f \) (10% EtOAc/hexane) = 0.30. \(^1\text{H NMR} \) (CDCl\textsubscript{3}, 300 MHz) δ 8.20 (dd, \( J = 0.88, 3.81 \) Hz, 1H), 7.51 (dd, \( J = 1.10, 5.06 \) Hz, 1H), 7.11 (dd, \( J = 3.87, 5.04 \) Hz, 1H), 3.76 (s, 3H), 3.36 - 3.32 (m, 3H), 3.15 (d, \( J = 16.9 \) Hz, 1H), 3.03 (d, \( J = 16.9 \) Hz, 1H), 1.66
(s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 165.2, 156.9, 132.2, 131.0, 130.2, 127.1, 109.9, 100.0, 51.1, 49.8, 41.1, 24.7. IR 3103.3(w), 2987.1(w), 2947.8(w), 2834.3(w), 1702.5(s), 1691.7(s), 1678.2(w), 1602.8(s), 1433.3(w), 1421.7(w), 1333.0(w), 1267.1(s), 1228.5(m), 1189.8(m), 1112.7(s), 1070.2(w), 1036.8(s), 933.7(w), 853.0(w), 790.3(m), 759.7(m), 745.9(m), 716.2(m) cm$^{-1}$. HRMS (ESI) Calc. 254.0613, Obs. 254.0600.

Methyl 5-methoxy-4-phenyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43l):

According to the general procedure, α-diazo ester 41a (0.40 g, 1.90 mmol) was added to β-methoxystyrene$^3$ (0.232 g, 1.73 mmol) and Rh$_2$esp$_2$ (1.3 mg, 1.7 µmol) in DCM at 0 °C. The reaction was quenched after 4 hours and column chromatography (10% EtOAc/hexane) afforded 43l as an off-white solid (0.28 g, 51.2%). $R_f$ (15% Et$_2$O/hexane) = 0.25. mp: 97.3-98.9 °C. $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.22 (dd, $J$=3.9, 1.2 Hz, 1 H), 7.49 (dd, $J$=5.1, 1.2 Hz, 1 H), 7.29 - 7.13 (m, 5 H), 7.09 (dd, $J$=5.0, 3.9 Hz, 1 H), 5.66 (d, $J$=1.6 Hz, 1 H), 4.52 (d, $J$=1.5 Hz, 1 H), 3.48 (s, 3 H), 3.41 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 164.9, 157.6, 136.4, 132.5, 130.9, 130.6, 129.0, 127.6, 127.1, 126.8, 107.4, 104.6, 57.3, 53.1, 50.8. IR: 3033.6(w), 2950.6(w), 2827.7(w), 1691.5(s), 1658.7(s), 1598.4(s), 1411.8(s), 1244.4(s), 1222.6(m), 1176.4(m), 1142.9(m), 1071.0(m), 1050.7(m), 1019.1(w), 992.6(m), 936.3(m), 878.2(w), 729.7(m), 697.2(s), 661.3(m), 553.9(m) cm$^{-1}$. HRMS (ESI) Calc. 316.0769, Obs. 316.0769.
Methyl 2-(thiophen-2-yl)-3a,4,5,6a-tetrahydrofuro[2,3-b]furan-3-carboxylate (43m): According to the general procedure, α-diazo ester 41a (0.300 g, 1.43 mmol) was added to dihydrofuran (0.077 g, 1.1 mmol) and Rh₂esp₂ (1.0 mg, 1.1 µmol) in DCM at 0 °C. The reaction was quenched after 8 hours and column chromatography (10% EtOAc/hexane) afforded 43m as a white solid (0.167 g, 61.0%). Rf (10% EtOAc/hexane) = 0.25. mp: 99.1-100.7 °C. ¹H NMR (CDCl₃, 300 MHz) δ 8.17 (dd, J=3.9, 1.2 Hz, 1 H), 7.53 (dd, J=5.1, 1.2 Hz, 1 H), 7.10 (dd, J=5.1, 3.9 Hz, 1 H), 6.21 (d, J=6.4 Hz, 1 H), 4.12 - 4.03 (m, 1 H), 4.01 – 3.93 (m, 1 H), 3.81 - 3.71 (m, 4 H), 2.20 - 2.11 (m, 2 H). ¹³C NMR (CDCl₃, 75 MHz) δ 165.1, 159.2, 132.9, 130.9, 130.5, 127.0, 108.7, 101.5, 66.9, 51.1, 48.6, 32.3. IR 3103.3 (w), 2977.1(w), 2943.9(w), 2870.9(w), 1738.4(m), 1691.5(s), 1678.0(m), 1665.1(m), 1597.9(s), 1411.7(m), 1324.6(m), 1240.0(s), 1190.3(w), 1177.7(w), 1146.6(w), 1103.6(w), 1051.1(m), 1026.1(w), 954.1(m), 925.3(m), 773.2(m), 721.0(m) cm⁻¹. HRMS (ESI) Calc. 252.0456 Obs. 252.0442.

Methyl 5-((tert-butyldimethylsilyl)oxy)-5-methoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43n): To a solution of Rh₂(oct)₄ (55.6 mg, 7.15 x 10⁻² mmol, 0.05 equiv.) in DCM (5 mL) at room temperature was added the tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (0.723 g, 3.58 mmol, 2.5 equiv.). Then, a solution of the α-diazo ester 41a (0.300 g, 1.43 mmol, 1 equiv.) in DCM (2 mL) was added via syringe pump over 3 hours. The reaction was stirred for 12 hours after completion of addition and column chromatography (10% EtOAc/hexane) afforded 43n as an oil (0.282 g, 70.0%). Rf (10% EtOAc/hexane) = 0.35. ¹H NMR (CDCl₃, 300 MHz) δ 8.21 (d, J=3.8 Hz, 1 H), 7.51 (d, J=5.0 Hz, 1 H), 7.11 (dd, J=5.0, 3.9 Hz, 1 H), 3.76 (s, 3 H), 3.43 (s, 3 H), 3.25 (d, J=18.0 Hz, 1 H), 3.07 (d, J=18.0 Hz, 1 H), 0.93 (s, 9 H), 0.24 (s, 3 H),
$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 165.0, 155.3, 132.3, 131.1, 130.3, 127.2, 121.2, 99.9, 51.1, 49.6, 42.4, 25.5, 17.8, -3.4, -4.2. IR 3086.6(w), 2947.2(w), 2857.6(w), 1736.6(s), 1727.0(s), 1700.4(s), 1683.5(s), 1658.6(s), 1435.3(m), 1410.4(s), 1355.0(m), 1337.8(w), 1269.7(m), 1160.1(s), 1110.1(w), 1085.8(w), 851.6(m), 728.1(s) cm$^{-1}$. HRMS (ESI) Calc. 370.1304, Obs. 370.1296.

**B. Synthesis of Benzo-fused Heteroaromatics**

To a flame-dried flask containing In(OTf)$_3$ (5 mol %) in anhydrous DCM (0.2 M) was added the corresponding dihydrofuran. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H$_2$O. The mixture was extracted with DCM, dried with Na$_2$SO$_4$, and column chromatography provided the benzo-fused heteroaromatic.

![Chemical Structure](image)

**Methyl 7-hydroxybenzo[b]thiophene-6-carboxylate (49a):** According to the general procedure, methyl 5-ethoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate 43a (0.100 g, 0.419 mmol) was added to a solution containing In(OTf)$_3$ (11.8 mg, 0.210 μmol) in DCM. The reaction was quenched after 24 hours, and purification by column chromatography ($R_f$= 0.25, 5% EtOAc/hexane,) provided the product 49a as a white solid (0.0565 g, 65.0%). All data matches literature.$^5$
Methyl 7-hydroxybenzo[b]thiophene-6-carboxylate (49a): According to the general procedure, methyl 5-(tert-butoxy)-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43h) (0.100 g, 0.354 mmol) was added to a solution containing In(OTf)$_3$ (9.9 mg, 0.21 µmol) in DCM. The reaction was quenched after 24 hours, and column chromatography (5% Et$_2$O/hexane) provided product 49a as a white solid (0.058 g, 69.0%). All data matches literature.

Methyl 4-hydroxybenzo[b]thiophene-5-carboxylate (49b): According to the general procedure, methyl 5-ethoxy-2-(thiophen-3-yl)-4,5-dihydrofuran-3-carboxylate (43b) (0.167 g, 0.662 mmol) was added to a solution containing In(OTf)$_3$ (18.6 mg, 3.31×10$^{-2}$ mmol) in 10 mL DCM. The reaction was quenched after 4 hours, and column chromatography (2% Et$_2$O/hexane) provided product 49b as a white solid (0.0870 g, 63.0%). $R_f$ (10% Et$_2$O/hexane) = 0.45. All characterization matches literature.

Methyl 7-hydroxy-1-methyl-1H-indole-6-carboxylate (50g): According to the general procedure, to a solution of Rh$_2$esp$_2$ (1.0 mg, 1.32 µmol) in 1,2-DCE at 84 °C was added the ethyl vinyl ether (0.095 g, 1.32 mmol), followed by a solution of the α-diazo ester 41g (0.300 g, 1.45 mmol). The reaction was quenched and column chromatography afforded 49g as a yellow solid.
(59.5 mg, 22.0%). \( R_f \) (15% Et\(_2\)O/hexane) = 0.45. **mp:** 136-138.0. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.40 (s, 1H), 7.64 (d, \( J = 8.6 \) Hz, 1H), 6.90 (d, \( J = 3.2 \) Hz, 1H), 6.78 (d, \( J = 8.6 \) Hz, 1H), 6.46 (d, \( J = 3.2 \) Hz, 1H), 4.01 (s, 3H), 3.74 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 169.9, 159.1, 134.4, 130.5, 128.5, 123.8, 110.3, 102.7, 98.5, 51.7, 38.2. **IR** 2956.8(w), 2951.2(w), 1738.9(m), 1662.5(s), 1611.5(m), 1454.3(s), 1353.8(m), 1227.8(s) cm\(^{-1}\). **HRMS (ESI)** Calc. 205.0739, Obs. 205.0739.

**C. Synthesis of Furans and Furanone**

**Methyl 5-methyl-2-(thiophen-2-yl)furan-3-carboxylate (50l):** According to the general procedure, methyl 5-methoxy-5-methyl-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43l) (0.120 g, 0.473 mmol) was added to a solution containing In(OTf)\(_3\) (13.3 mg, 23.6 \( \mu \)mol) in DCM. The reaction was quenched after 4 hours, and column chromatography (2% Et\(_2\)O/hexane) provided product 50l as a clear oil (0.0865 g, 82.2 %). \( R_f \) (10% Et\(_2\)O/hexane) = 0.54. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 8.00 (dd, \( J = 3.8, 1.2 \) Hz, 1H), 7.38 (dd, \( J = 5.1, 1.2 \) Hz, 1H), 7.09 (dd, \( J = 5.1, 3.8 \) Hz, 1H), 6.37 (s, 1H), 3.85 (s, 3H), 2.32 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \) 163.9, 151.6, 150.6, 133.9, 131.8, 128.0, 127.3, 112.5, 108.3, 51.5, 13.3. **IR** 2976.6(w), 1731.9(s), 1611.1(s), 1410.4(s), 1290.1(m), 1241.9(m), 1159.8(s) cm\(^{-1}\). **HRMS (ESI)** Calc. 222.0351 Obs. 222.0352.
Methyl 5-oxo-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (51): According to the general procedure, methyl 5-((tert-butyldimethylsilyl)oxy)-5-methoxy-2-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (43p) (0.110 g, 0.297 mmol) was added to a solution containing In(OTf)$_3$ (8.2 mg, 0.015 mmol) in DCM. The reaction was quenched after 2 hours, and column chromatography (2% Et$_2$O/hexane) provided product 51 as a clear oil (0.0191 g, 28.7%). $R_f$ (15% EtOAc/hexane) = 0.25. $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.13 (dd, $J = 3.9, 1.2$ Hz, 1H), 7.64 (dd, $J = 5.0, 1.2$ Hz, 1H), 7.16 (dd, $J = 5.0, 3.9$ Hz, 1H), 3.84 (s, 3H), 3.69 (s, 2H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 171.6, 163.1, 155.1, 133.5, 132.6, 128.7, 127.5, 101.7, 51.8, 34.9. IR 3111.2(w), 2955.4(w), 1731.9(s), 1661.1(s), 1519.5(m), 1411.8(s), 1240.5(s), 1162.6(s) cm$^{-1}$. HRMS (ESI) Calc. 224.0143 Obs. 224.0146.
Chapter Four: Cycloisomerization of Cyclopropene-3,3’-Dicarboxyls

4.1 Introduction to Heteroaromatic Compounds

Benzo-fused heteroaromatics and heterobiaryls are common structural motifs termed as “privileged” by medicinal chemists because of their presence in a diverse range of pharmaceutically relevant small molecules and bioactive natural products. They also have found relevance in many pharmacophores of drugs to date. For instance, they can be found in furomollugin(1), karajin (2), cycloclavine (3), naratriptan (4) and many more alkaloid derivatives (Figure 4.1). Furomollugin (1), isolated from several members of the Rubiaceae family, has demonstrated activity against lymphoid leukemia (P338) in mice. Karajin (3) is a flavonoid from the karanja tree that has shown antibacterial activity. Cycloclavine (4) is an alkaloid isolated from seeds of Ipomea hildebrandtii in 1969. Naratriptan (4) is an indole based synthetic drug that acts as a serotonin mimic.

![Figure 4.1: Natural Products Containing Benzofused Heteroaromatics](image)

Benzofused heteroaromatics have also been used as probes to explore biochemical pathways and to understand biological function. Because of their interesting photophysical properties, these compounds have found application in materials science as organic light emitting...
diodes (OLEDs)\textsuperscript{153} and organic photovoltaics (OPVs).\textsuperscript{154} Furthermore, benzofused heteroaromatics can serve as ligands for many metal complexes.\textsuperscript{155}

Benzofused heteroaromatics’ broad activity spectrum motivated scientists to develop efficient methodologies for the construction of these frameworks. Many synthetic strategies have been disclosed for these benzofused heteroaromatic scaffolds.\textsuperscript{156} Cycloaddition and cyclization reactions are two key transformations that contribute to the synthesis of these polycyclic benzofused heteroaromatic compounds.\textsuperscript{144,157-159} Often, these methods require harsh reaction conditions, long reaction time, expensive catalysts, and limited in functional group tolerance. As a result, new methodologies are necessary in order to generate benzofused heteroaromatic compounds in a mild and efficient conditions, as well as in an economical manner.\textsuperscript{160} In line with our interest of developing methods utilizing strained carbocycles, this chapter will focus on our strategies for the formation of benzofused heteroaromatic compounds using cyclopropene-3,3’-dicarboxyls as building blocks. Relevant discussion on properties of cyclopropenes was included in Chapter One of this thesis. This chapter will showcase the first example of a Lewis acid catalyzed cycloisomerization of cyclopropene-3,3’-dicarboxyls.

4.2 Reactions of Cyclopropenes

Due to its high ring strain, cyclopropenes readily participate in ring opening transformation. This section will encompass selected examples of ring opening reactions of cyclopropenes. These examples focuses on cycloisomerization reactions of cyclopropenes by Brønsted acid and Lewis acids. Additionally, examples will focus on the formation of benzenoids products.
4.2.1 Brønsted Acid-Catalyzed Ring Opening Reactions of Cyclopropenes

The initial example of acid-mediated cyclopropene isomerization was reported in 1961 for the polymerization of sterculic acid 5 (Scheme 4.1). Sterculic acid 5 was heated in glacial acetic acid, forming a complex mixture of four unsaturated allylic acetates 10a-10d. The mechanism of this transformation involves the protonation of the cyclopropene to generate cyclopropyl cations 6 and 7. Subsequent ring opening/rearrangement provides the pair of allylic cations 8 and 9. Trapping of acetic acid to either end afforded the four observed allylic acetates 10a-10d.

Scheme 4.2: Breslow’s Formation of Diphenylcrotonolactone
Breslow and co-workers demonstrated two examples of acid-promoted cyclopropene isomerizations. Treatment of diphenylcyclopropene carboxylic acid 11 with a protic acid afforded diphenylcrotonolactone 14 (Scheme 4.2). Protonation of the double bond generated cyclopropyl cation 12 that undergoes electrocyclic ring opening to afford the benzylic cation 13. Intramolecular trapping of the cation by the carboxylic acid yields 14. Even though this was a notable observation, there was no additional discussion of yield or information on the specific reaction conditions. Moreover, the substrate scope was not explored in further details.

Scheme 4.3: Cycloisomerization of 1,2,3-Triphenylcyclopropene

Under similar conditions, indene 18 was formed from 1,2,3-triphenylcyclopropene (Scheme 4.3). Protonation of 15 generated cyclopropyl cation 16 that rearranged to its acyclic isomer 17. Carbocation 17 was trapped by one of the phenyl groups via a Friedel-Crafts-type mechanism, providing 1,2-diphenyl-1H-indene 18 as the observed product. Analogous to the previous case, yields and reaction conditions were not disclosed. Even though these were interesting observations, the reactions were not followed up with a more formal report, and as a result, no other Brønsted acid promoted processes were disclosed for more than 30 years.
In 1987, Padwa and coworkers demonstrated that the addition of 3,3-dimethyl-1-(p-tolylsulfonyl)-2-(trimethylsilyl)cyclopropene 19 to a dilute benzene solution of $p$-TSA resulted in the formation of diene 22 in good yield (Scheme 4.4). Protonation of cyclopropene 19 provides cyclopropyl cation 20 which undergoes ring opening followed by proton loss to give 21. In this report, cyclopropene 19 was the only substrate used for the acid-catalyzed reaction.

**4.2.2 Lewis Acid-Catalyzed Ring Opening Reactions of Cyclopropenes**

After 20 years from the initial report, an acid-promoted cyclopropene isomerization was revisited. In 2007, Shi and coworkers showed that Lewis acids can catalyze the intramolecular Friedel-Crafts rearrangement reactions of vinylcyclopropenes to form naphthalenes or indenes. Lewis acid catalysts played a primary role in the chemoselectivity and product formation. Using BF$_3$·OEt$_2$ with cyclopropene 23, naphthalenes 24 were isolated in 55-70% yield. However, when Cu(OTf)$_2$ was employed, indenes 25 were isolated in 75-98%.
The mechanism for the formation of naphthalene entails the initial generation of HBF$_n$(OH)$_{4-n}$ A, which is formed from the reaction of BF$_3$·OEt$_2$ with trace amounts of water (Scheme 4.6). Protonation of the vinyl cyclopropene 23 produced cyclopropyl cation B, and the cyclopropene ring opened to give the resonance-stabilized intermediate 26. Isomerization of 26 led to intermediate 27, followed by trapping with aryl ring forms 28, subsequent aromatization produced 24.

For indenes 25, the authors suggested that the steric repulsion between the Lewis acid and the aromatic R$_2$ group of zwitterionic intermediate 29 is formed upon the π-attack on the Lewis acid (Scheme 4.7). Ring opening provided cation-delocalized intermediates 30 and 31. Friedel-Crafts trapping of the cation by one of the aryl rings gave the corresponding indene 25.
upon rearomatization of 32. This indene is distinctly different from the indenes 33 formed from carbene mechanisms (Scheme 4.7, inset).

These examples provided insights into the types of catalysts that could promote the ring opening of the cyclopropene to form the vinylic carbocation intermediate. It also provided us with a direction for the choice of catalyst in order to promote the cycloisomerization. Therefore, we must keep in mind that different substituents about the cyclopropene may provide different isomers. Consequently, optimization was necessary in order to be able to develop an efficient cycloisomerization protocol.

4.3 Cycloisomerization of Cyclopropenes

Given this diverse utility, the development of efficient methods for the synthesis of benzo-fused heteroaromatics and heterobiaryls has been an important goal for synthetic chemists. Whereas alkynes have been widely used as reactive units to generate benzo-fused substrates, cyclopropenes have received limited attention in this area despite their unique reactivity that results from their substantial ring strain. Cyclopropenes readily participate in an assortment of additions, substitutions, cycloadditions, and metal-promoted transformations. In particular, the metal-catalyzed rearrangement, or cycloisomerization, of 2-acyl- and 2-iminocyclopropenes to afford heterocyclic compounds has recently garnered a lot of attention from both a synthetic and mechanistic viewpoint. This method has become a powerful way to prepare furans\textsuperscript{162}, indolizines\textsuperscript{49}, imidazopyridines\textsuperscript{144}, and pyrrolo[2,1-b]oxazoles. In contrast, few examples of the analogous metal-catalyzed cycloisomerizations to form benzenoid rings have been disclosed. In a seminal report, Shi and co-workers demonstrated that arylvinylcyclopropenes rearranged in the presence of Lewis acids to give functionalized naphthalenes.\textsuperscript{163} While this example (and subsequent publications) has provided invaluable insight into the potential of using
cyclopropenes as substrates for benzannulation reactions, only carbocyclic products were generated.

4.4 Project Objective

As part of our ongoing efforts towards methods employing small strained rings as the reactive subunit in the presence of Lewis acids, we were keenly interested in utilizing cyclopropene-3,3-dicarbonyl compounds as templates for intramolecular cyclizations. Although this class of cyclopropenes has not been employed as a substrate for cycloisomerizations, it has been shown to undergo ring opening reactions in the presence of halides or organometallic reagents. These reagents serve as nucleophiles to promote a SN₂-like ring-opening of the cyclopropene. To the best of our knowledge, ring opening of cyclopropene-3,3-dicarbonyl compounds promoted by Lewis acids has not been disclosed. The interest in using strained carbocycles as the reactive subunit led us to cyclopropene-3,3'-dicarbonyl as a potential reactive subunit for the formation of benzo fused heteroaromatic compounds.

4.5 Cycloisomerization of Cyclopropenes -3,3’-Dicarbonyl

Herein, first example of a Lewis acid catalyzed cycloisomerization of cyclopropene-3,3-dicarbonyl compounds to give a wide array of benzo fused heteroaromatics and heterobiaryls will be reported.

![Scheme 4.8: Synthesis of Model Cyclopropene Substrate](image)

We began our study with the synthesis of the model cyclopropene, derived from 1-bromo-4-ethynylbenzene and α-diazo derived from 2-thiophene acyl chloride 32. Treatment of acid chloride 32 with the enolate from methyl acetate afforded 33 in 72% yield. Diazo transfer with TsN₃ and Et₃N furnished diazo 34. Cyclopropene-3,3’-dicarbonyl substrates were readily
synthesized by using the general protocol disclosed by Gonzales-Bobes\textsuperscript{97} \textit{et al.} in which the corresponding \(\alpha\)-diazo-\(\beta\)-keto esters were added to solutions of alkynes in the presence of Dubois’ catalyst\textsuperscript{164}, \([\text{Rh}_2\text{esp}_2]\) (dirhodium \(\alpha,\alpha,\alpha',\alpha'\)-tetramethyl-1,3-benzene dipropanoate; Scheme 4.8). Using this scheme, model substrate 35, derived from 2-thiophene \(\alpha\)-diazo 34 and 1-bromo-4-ethynylbenzene, was isolated in 86\% yield. After obtaining the cyclopropene 35, we determined the best Lewis acid for the promotion of the cyclization.

Given our success in the homo-Nazarov cyclizations of heteroaryl cyclopropyl ketones,\textsuperscript{99,136} \(\text{In(OTf)}_3\) was the first Lewis acid screened (Table 4.1). We subjected our model cyclopropene substrate 35 to 30 mol \% of \(\text{In(OTf)}_3\), and we found that the cycloisomerized product can be readily obtained after 2 hours. Meanwhile, \(\text{Sc(OTf)}_3\) was slightly slower, with complete conversion after 3 hours. \(\text{AgOTf}, \text{Al(OTf)}_3\) and \(\text{Zn(OTf)}_2\) did not go to complete conversion of the cyclopropene even after 12 hours. \(\text{Cu(OTf)}_2\) was slightly more efficient as compared to the latter three Lewis acids, complete conversion of the cyclopropene was observed after 8 hours. Ultimately, \(\text{In(OTf)}_3\) was still the best Lewis acid to catalyze the cycloisomerization of cyclopropenes-3,3’-dicarbonyl.
**Table 4.1**: Lewis Acid Screen for Cycloisomerization of Cyclopropenes

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Lewis acid (30 mol %)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>In(OTf)$_3$</td>
<td>2h</td>
</tr>
<tr>
<td>Sc(OTf)$_3$</td>
<td>3h</td>
</tr>
<tr>
<td>AgOTf</td>
<td>&gt;12h</td>
</tr>
<tr>
<td>Al(OTf)$_3$</td>
<td>&gt;12h</td>
</tr>
<tr>
<td>Zn(OTf)$_2$</td>
<td>&gt;12h</td>
</tr>
<tr>
<td>Cu(OTf)$_2$</td>
<td>8h</td>
</tr>
</tbody>
</table>

The fact that In(OTf)$_3$ was the best Lewis acid to promote the cyclization was not a novel realization to us. In fact, we envisioned that this transformation may occur via a similar mechanism as that of the heteroaryl homo-Nazarov cyclization, which was discussed in great lengths in Chapter Two of this thesis (Scheme 4.9, 1). In this protocol, donor-acceptor cyclopropanes 37 with a tethered heteroaryl group were subjected to 5 mol% of Lewis acid, and heteroaryl ring-fused cyclohexanones were obtained. The mechanism of this transformation involves initial chelation of the Lewis acid (intermediate 38) to further polarize the bond and promotes ring opening to form the carbocation 39. Attack of the π-system of the heteroaromatic generated these cyclohexanones. Therefore, we envisioned that the isomerization of the cyclopropene to the acyclic vinylic cation 42 counterpart would occur after the chelation of the Lewis acid to cyclopropene 40 (as shown in 41) (Scheme 4.9, 2).
After we determined the best conditions for the cycloisomerization, we wanted to probe the reactivity of the methodology towards different heteroaromatics; hence, we needed to synthesize a diverse set of heteroaryl cyclopropenes. The 3-thienyl diazo 34b provided cyclopropene 35b in 22% after treatment with alkyne 43a and Rh₂esp₂ (Table 4.2, entry 1). The low yield was attributed to the rapid degradation of the diazo to generate a carbenoid that undergoes side reactions to form uncharacterized products. Cyclopropene 35c, derived from 2-bromo-3-thiophene diazo 34c, was isolated in 40% (Table 4.2, entry 2). 2-Furyl diazo 34d furnished cyclopropene 35d in 42%, while 3-furyl cyclopropene was isolated in only 21% from 3-furyl α-diazo 34e (Table 4.2, entry 3 and 4). 2-Benzofuran diazo 34f provided cyclopropene 35f in 60% (Table 4.2, entry 5) while its N-acyl-indolyl diazo 34g provided cyclopropene 35g in comparable yield of 62% (Table 4.2, entry 6).
These different heteroaryl cyclopropenes allowed us to probe the effects of the heteroaromatics on the cycloisomerization of 3,3’-dicarbonyl cyclopropenes. With our model substrate 35a, derived from 2-thiophene diazo 34a, benzothiophene 36a was afforded in 86% yield (Table 4.3, entry 1). Meanwhile, 3-thienyl cyclopropene 35b participated in the cycloisomerization to furnish benzothiophene product 36b in only 48% yield (Table 4.3, entry 2). 2-Bromo-3-thiophene cyclopropene 35c provided the benzo[c]thiophene 36c in 38.1% with 5 mol % of Lewis acid, however, upon increasing the catalyst loading to 15 mol %, the yield improved significantly to 43.1% (Table 4.3, entry 3). This is presumably due to the difference in
nucleophilicity of the 2 vs. 3 position on the thiophene. Benzofuran 36d, from 2-furyl cyclopropene 35d was afforded in 26%, while 3-furyl cyclopropene 35e afforded its corresponding benzofuran 36e in 45% (Table 4.3, entry 4 and 5). These low yields could be attributed to the degradation of the cyclopropenes in presence of the Lewis acid. Dibenzofuran 36f can be achieved from cyclopropene 35f in 48% yield (Table 4.3, entry 6). Interestingly, N-acyl-3-methylindole cyclopropene 35g provided pyrido[1,2,a]indole 36g in 65% yield (Table 4.3, entry 7). Pyrido[1,2,a]indoles are found in many natural products, and this method may permit easy access to these core structures.165,166
Table 4.3: Cycloisomerization of Cyclopropenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropene</th>
<th>Product</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="35a" alt="" /></td>
<td><img src="36a" alt="" /></td>
<td>86%</td>
</tr>
<tr>
<td>2(^a)</td>
<td><img src="35b" alt="" /></td>
<td><img src="36b" alt="" /></td>
<td>48%</td>
</tr>
<tr>
<td>3(^a)</td>
<td><img src="35c" alt="" /></td>
<td><img src="36c" alt="" /></td>
<td>43%(^d)</td>
</tr>
<tr>
<td>4(^a)</td>
<td><img src="35d" alt="" /></td>
<td><img src="36d" alt="" /></td>
<td>26%</td>
</tr>
<tr>
<td>5(^b)</td>
<td><img src="35e" alt="" /></td>
<td><img src="36e" alt="" /></td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td><img src="35f" alt="" /></td>
<td><img src="36f" alt="" /></td>
<td>48%</td>
</tr>
<tr>
<td>7</td>
<td><img src="35g" alt="" /></td>
<td><img src="36g" alt="" /></td>
<td>65%</td>
</tr>
</tbody>
</table>

\(^a\) performed with 30 mol % In(OTf)\(_3\) \(^b\) performed with 15 mol % In(OTf)\(_3\) \(^c\) isolated after column chromatography \(^d\) Mixture of mono and dibrominated products determined by MS

After establishing amenability for different heteroaromatics, we wanted to investigate the influence of the electronics about the cyclopropene on the cycloisomerization protocol. We synthesized cyclopropene 35h, derived from 2-thiophene and phenylacetylene, and subjected it to our cycloisomerization conditions. Phenyl substituted benzothiophene 36h was achieved in
63% yield (Table 4.4, entry 1). Next, we also wanted to probe the reactivity of the furan to determine if the yield could be improved, and we found that phenyl substituted benzo furans 36i was isolated in 46% yield from cyclopropene 35i (Table 4.4, entry 2). Notably, this yield is significantly higher than the product with 4-bromophenyl substituted 36d. We were interested in having a highly electron withdrawing group on the cyclopropene so we made cyclopropene 35j derived from 4-ethynyl-α,α,α-trifluorotoluene (Table 4.4, entry 3). This cyclopropene 35j was subjected to 5 mol % of In(OTf)₃, and as expected, no product was observed. Attempts to promote the cycloisomerization by increasing the catalyst loading (up to 30 mol %) and heating at high temperature (110 °C in toluene) still did not provide the desired product 36j. This could be attributed to the destabilization of the vinylic carbocation intermediate formed in the cycloisomerization reaction, as the CF₃ group is a highly electron-withdrawing substituent.

Table 4.4: Effects of the Donor Group on Cycloisomerization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropene</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /> 35h</td>
<td><img src="image2.png" alt="Image" /> 36h</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /> 35i</td>
<td><img src="image4.png" alt="Image" /> 36i</td>
<td>46 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /> 35j</td>
<td><img src="image6.png" alt="Image" /> 36j</td>
<td>NR</td>
</tr>
</tbody>
</table>

Surprisingly, during our attempts at making an electron rich cyclopropene, as derived from 4-ethynylanisole 43k, as well as those derived from alkyl groups, we were unable to isolate the cyclopropene product, as consistent with Davies’ report. This led us to develop a tandem
cyclopropenation/cycloisomerization protocol. In this protocol, the diazo, Rh$_2$esp$_2$, and the alkyne were mixed together, and after complete consumption of the diazo (monitored via TLC), In(OTf)$_3$ was added to the reaction flask. Using diazo 34a and alkyne 43a, benzothiophene 36k was isolated in only 15%, perhaps due to the complex mixture present that interfered with the formation of the necessary chelate for effective cycloisomerization (Table 4.5, entry 1). 2-Ethynylthiophene 43l also proved to be problematic in isolation, and was subjected to the tandem protocol to provide the benzothiophene product 36l in 25% yield (Table 4.5, entry 2). Once optimized, this protocol is useful for the formation of heterobiaryl scaffolds. Trimethyl(prop-2-yn-1-yl)silane 43m was employed as the alkyne, and no cyclopropene product was successfully isolated. Using the tandem cyclopropenation/cycloisomerization protocol, benzothiophene product 36m was isolated in 29% yield (Table 4.5, entry 3). Next, we were interested in expanding the scope of our methodology to tolerate alkyl substituents, and we were not able to isolate the cyclopropene intermediate successfully (Table 4.5, entry 4). We determined the formation of the cyclopropene by a crude NMR of the reaction mixture; however, attempts to carry this crude mixture forward were unsuccessful, since no benzofused product 36n was isolated.
Table 4.5: Tandem Cyclopropenation/Cycloisomerization Protocol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkyne</th>
<th>Cyclopropene</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{S-SO}_2\text{O}\text{Me}) 34a</td>
<td>(\equiv\text{Ph-OMe}) 43k</td>
<td>(\text{C}_9\text{H}_6-4\text{-OMe}) 36k</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{S-SO}_2\text{O}\text{Me}) 34a</td>
<td>(\equiv\text{S}) 43l</td>
<td>(\text{C}_9\text{H}_6\text{-OMe}) 36l</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{S-SO}_2\text{O}\text{Me}) 34a</td>
<td>(\equiv\text{TMS}) 43m</td>
<td>(\text{C}_9\text{H}_6\text{-OMe}) 36m</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{S-SO}_2\text{O}\text{Me}) 34a</td>
<td>(\equiv\text{n-Bu}) 43n</td>
<td>(\text{C}_9\text{H}_6\text{-OMe}) 36n</td>
<td>NRb</td>
</tr>
</tbody>
</table>

*a Isolated after column chromatography  b No Reaction*

Mechanistically, we envisioned that the heteroaryl group can serve as an intramolecular nucleophile according to a Friedel-Crafts-type mechanism. The Lewis acid will coordinate with the two carbonyl groups to form a six-membered chelate (45), resulting in an increased polarization of the C1-C3 bond. Subsequently, the pendant heteroaryl moiety will initiate an intramolecular S_N1-like nucleophilic cyclopropene ring-opening, Friedel-Crafts generates 46 and proton transfer provides the cycloisomerized product 47. This reactivity is rather novel, as the reported ring-opening reactions of cyclopropene-3,3-dicarbonyl compounds occur in a S_N2-like manner. Remarkably, when cyclopropene 48, derived from TMS-acetylene, did not undergo cycloisomerization to provide product 52 with the TMS substituted at the 4-position. Instead, benzothiophene 48 was isolated in 58% yield (Scheme 4.10). We postulate that the heteroaryl attack on the cyclopropene occurs with an inverse regioselectivity due to the \(\beta\)-silyl effect to
afford the corresponding TMS-substituted aromatic product 50, followed by protodesilylation under the reaction conditions to provide the benzo[b]thiophene product 51.

Scheme 4.10: Mechanistic Rationale for Indium-catalyzed Cycloisomerization

After fully examining both the heteroaryl effect and the substituent effect, we changed directions and focused on the difference of the acceptor groups. Having a ketone as an acceptor group will provide another chemical handle such as alkylation or condensations after the cycloisomerization. Taking diazo 34p with a ketone as the acceptor group and subjecting it to 4-methoxystyrene 43k, we found that only the benzofused heteroaromatic product 36p was isolated in modest yield of 62% (Table 4.6, entry 1). We wanted to apply this for the formation of benzofurans, and we found that subjecting diazo 34q derived from 3-furan, benzofurans 36q was formed in 31% yield (Table 4.6, entry 2). Changing the acceptor group to an amide, such as the case of N-acylpyrrole diazo 34r, we were able to form indolizine 36r in 51% yield after 2 hours (Table 4.6, entry 3). This strategy allowed us to quickly access substituted benzofused heteroaromatic products in modest yields in a short reaction time.
Table 4.6: Effects of Varying the Acceptor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="34p" /></td>
<td><img src="image2" alt="36p" /></td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="34q" /></td>
<td><img src="image4" alt="36q" /></td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="34r" /></td>
<td><img src="image6" alt="36r" /></td>
<td>51</td>
</tr>
</tbody>
</table>

\(a\) Isolated from column chromatography

4.6 Cycloisomerization of Cyclopropene-3,3’-Dicarbonyl to Furan

It is worthwhile to note that when we warm the reaction up to room temperature immediately after the addition of the diazo, the product isolated was that of a furan 53. This product presumably arises from the intermediate cyclopropene, which is the unstable kinetic product, and rearranges to the more stable furan as the thermodynamic product. Chapter Five of this thesis will discuss the formation and utility of this protocol in more details.

Scheme 4.11: Rearrangement to Furans

4.7 Summary of the Cycloisomerization of Cyclopropene-3,3’-Dicarbonyl

In summary, to the best of our knowledge, we have successfully demonstrated the first example of cycloisomerization of 3,3’-dicarbonylcyclopropenes. We were able to develop a versatile method to provide benzofused heteroaromatic compounds in high yields (up to 86%).
This methodology tolerated electron rich and heteroaryl substituents about the cyclopropene. The benzofused heteroaromatic product was achieved in one step simply by varying the acceptor group to either a ketone or amide. Overall, this methodology allowed for rapid generation of benzothiophenes, benzofurans, dibenzofurans, indolizines, as well as pyrido[1,2,a]indoles.

The formation of the cyclopropenes proves to be troublesome for some substrates, and much optimization is necessary in this aspect. Optimization of the reaction conditions to include a broader substrate scope in terms of the donor group ability. Heteroaryl substrate scope can also be expanded to pyridines, oxazoles, and thiazoles for the formation of quinolines, benzisoxazole and benzothiazole. Utility of these cyclopropenes in the cycloadditions such as [3+2] with various dipolarophiles are of high interest. A full paper is currently being pursued to discuss all the mechanistic aspects and limitations of the protocol. Mechanistic details and kinetic experiments are necessary in order to fully understand the formation of the cyclopropenes as well as cycloisomerization of the cyclopropene-3,3′-dicarboxyls.
Experimentals

1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenoneketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. Anhydrous acetonitrile was purchased from EMD Chemicals and used without further purification. Methyl acetate was fractionally distilled over P₂O₅. 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. α-Diazo compounds 34a-34f were synthesized as previously reported.¹³⁶ α-Diazo compound 34g was synthesized as previously reported.¹⁶⁷ Compounds 35b, 35f, 35g, 36b, 36f, 36g were characterized and provided by Joel Aponte-Guzman. Compounds 35d, 35e, 36d and 36e were characterized and provided by Marchello A. Cavitt.

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 F₂₅₄ TLC glass plates. Visualization was accomplished with 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
(\textsuperscript{1}H NMR and \textsuperscript{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (\textsuperscript{1}H NMR: CDCl\textsubscript{3} at 7.26 ppm; \textsuperscript{13}C NMR: CDCl\textsubscript{3} at 77.0 ppm). \textsuperscript{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).
2. Experimental Procedures

A. Formation of Diazo Compounds

**General Method:** NEt₃ (1.2 equiv.) was added to a flame-dried flask containing a solution of the β-ketoester in acetonitrile (0.2 M). After vigorous stirring for 5 min, tosylazide (1.2 equiv.) was added, and the reaction was allowed to stir for 3 h. After complete disappearance of starting material as determined by TLC, the mixture was concentrated *in vacuo*, followed by column chromatography to furnish the desired diazo compound.

**2-Diazo-1-(thiophen-2-yl)butane-1,3-dione (34p).** 1-(Thiophen-2-yl)butane-1,3-dione (1.00 g, 5.94 mmol), Et₃N (1.0 mL, 7.13 mmol), tosylazide (1.41 g, 7.13 mmol), and acetonitrile (30 mL) were mixed according to the general method to afford 34p as a yellow oil (0.90 g, 78%). Rᵣ = 0.15 (10% EtOAc/hexane). **¹H NMR** (300 MHz, CDCl₃) δ 7.64 (d, J = 4.99 Hz, 1H), 7.56 (ddd, J = 3.87, 1.64, 1.06 Hz, 1H), 7.15-6.99 (m, 1H), 2.52 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 190.6, 175.1, 141.8, 133.5, 130.4, 127.9, 29.2. **IR:** 3094.2(m), 2924.6(w), 2110.1(s, N₂ stretch), 1619.4(s), 1611.6(s), 1429.4(s), 1308.9(s), 1229.9(s), cm⁻¹. **HRMS-ESI** (m/z): Calc. 194.0157, Obs. 194.0159.

**2-Diazo-1-(furan-3-yl)butane-1,3-dione (34q).** 1-(Furan-3-yl)butane-1,3-dione (8.12 g, 53.4 mmol), Et₃N (9.0 mL, 64.0 mmol), tosylazide (12.6 g, 64.0 mmol) and acetonitrile (267 mL) were mixed according to the general method to afford 34q as a yellow oil (7.51 g, 79%). Rᵣ = 0.15 (15% EtOAc/hexane). **¹H NMR** (300 MHz, CDCl₃) δ 7.97 (dd, J = 1.46, 0.90 Hz, 1H), 7.42 (dd, J = 1.93, 1.48 Hz, 1H), 6.67 (ddd, J = 2.84, 1.96, 1.00 Hz, 1H), 2.47 (s, 3H). **¹³C NMR** (75
MHz, CDCl$_3$) δ 190.1, 176.3, 145.9, 143.9, 125.4, 109.1, 29.10. IR: 3133.5 (m), 2120.8 (s), 1772.1 (m), 1695.9 (m), 1657.8 (s), 1649.4 (s), 1641.6 (s), 1630.5 (m) cm$^{-1}$. HRMS-ESI (m/z): Calc. 178.0378, Obs. 178.0386.

**Methyl 2-diazo-3-oxo-3-(1H-pyrrol-1-yl)propanoate (34r).** Methyl 3-oxo-3-(1H-pyrrol-1-yl)propanoate$^2$ (1.03 g, 6.16 mmol), Et$_3$N (1.0 mL, 7.12 mmol), tosylazide (1.41 g, 7.16 mmol) and acetonitrile (31 mL) were mixed according to the general method to afford 34r as a yellow oil (0.86 g, 72%). R$_f$ = 0.44 (gradient from 10% EtOAc/hexane to 20% EtOAc/Hex). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27 (m, 2H), 6.51-5.70 (m, 2H), 3.85 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 224.9, 161.0, 159.4, 129.7, 130.1, 120.6, 112.8, 52.7. IR: 3146.3 (m), 2140.4 (s), 1722.2 (s), 1658.3 (s), 1470.9 (s) cm$^{-1}$. HRMS-ESI (m/z): Calc. 193.0487, Obs. 193.0490.

**B. Formation of Cyclopropenes 35a-35n**

**Procedure A:** A round bottom flask was charged with Rh$_2$esp$_2$ (0.5-1.0 mol %) and CH$_2$Cl$_2$ (0.5 M). After cooling the solution to 0 °C, the corresponding alkyne (1.0 equiv.) was added to the reaction vessel. After stirring for 5 min, a solution of the α-diazo ester (1.3 equiv.) in CH$_2$Cl$_2$ (0.5 M) was added in one shot, and allowed to stir at 0 °C until disappearance of the diazo compound. The reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted 3x with CH$_2$Cl$_2$. The organic layer was washed with brine, dried with Na$_2$SO$_4$, concentrated, and column chromatography afforded the desired cyclopropene 35.$^2$

**Procedure B:** According to Davies’ procedure$^{47}$, to a round bottom flask was charged with the indicated amount of Rh$_2$(S-PTAD)$_4$ (2.0 mol %, 0.02 equiv.) and the corresponding alkyne (1.0
equiv.) in CH₂Cl₂ (0.5 M). After stirring for 5 min at -45 °C bath, α-diazo ester 34a (2 equiv.) in CH₂Cl₂ (0.5 M) was added via syringe pump (0.80 mL/h). After the addition was complete, the mixture was stirred for an additional 1 hr at -45°C, then neutral alumina was added to the reaction, concentrated, and purification by column chromatography afforded the desired cyclopropene.

![Methyl 2-(4-bromophenyl)-1-(thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35a).](image)

**Methyl 2-(4-bromophenyl)-1-(thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35a).** Rh₂esp₂ (8.3 mg, 1.09×10⁻² mmol), α-diazo ester 34a (0.300 g, 1.90 mmol), 1-bromo-4-ethynylbenzene (0.197 g, 1.09 mmol) and CH₂Cl₂ (2.2 mL) were mixed according to general Procedure A to afford 35a as a white solid (0.220 g, 56% yield) after 5 h. Rᵣ = 0.25 (15% EtOAc/hexane) [mp: 148.1-149.5 °C]. ¹H NMR (300 MHz, CDCl₃) δ 7.78 (dd, J = 3.82, 1.11 Hz, 1H), 7.63 (dd, J = 4.95, 1.11 Hz, 1H), 7.57 (d, J = 1.33 Hz, 4H), 7.12 (dd, J = 5.59, 3.19 Hz, 2H), 3.72 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 189.7, 172.3, 142.2, 134.1, 133.1, 132.1(2C), 131.8(2C), 128.1, 125.2, 123.40, 113.7, 98.1, 52.6, 38.2. IR: 3137.1 (m), 2950.6 (m), 1991.2 (m), 1967.0 (m), 1942.3 (w), 1791.8 (w), 1771.8 (s), 1726.4 (s), 1683.8 (s), 1657.4 (s), 1649.2 (s), 1643.0 (s), 1515.9 (w) cm⁻¹. HRMS-ESI (m/z): Calc.361.9646, Obs.361.9622.

![Methyl 2-(4-bromophenyl)-1-(2-bromothiophene-3-carbonyl)cycloprop-2-enecarboxylate (35c).](image)

**Methyl 2-(4-bromophenyl)-1-(2-bromothiophene-3-carbonyl)cycloprop-2-enecarboxylate (35c).** Rh₂esp₂ (9.5 mg, 1.26×10⁻² mmol), α-diazo ester 34c (0.400 g, 1.39 mmol), 1-bromo-4-ethynylbenzene (0.226 g, 1.26 mmol) and CH₂Cl₂ (2.2 mL) were mixed according to Procedure
A to afford 35c as a yellow oil (0.145 g, 40.2% yield) after 2 h. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66-7.51 (m, 4H), 7.34 (d, $J = 5.79$ Hz, 1H), 7.28 (d, $J = 2.66$ Hz, 1H), 7.05 (s, 1H), 3.71 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 192.2, 172.3, 138.5, 132.2 (2C), 131.8 (2C), 129.0, 126.3, 125.2, 123.4, 118.1, 113.5, 97.7, 52.6, 39.3. IR 3152.3, 2954.0, 1729.1, 1671.0, 1552.0, 1254.7, 1176.8 cm$^{-1}$. HRMS (ESI) Calc. 439.8717, Obs. 439.8723.

Methyl 2-phenyl-1-((thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35h). Rh$_2$(S-PTAD)$_4$ (29.6 mg, 1.9*10$^{-2}$ mmol), $\alpha$-diazo ester 34a (0.400 g, 1.90 mmol), phenylacetylene (0.097 g, 0.95 mmol) and CH$_2$Cl$_2$ (3mL) were mixed according to Procedure B to afford 35h as a yellow oil (0.150 g, 55.5% yield) after 3 h. $R_f$ = 0.25 (15% EtOAc/hexane). Isolated as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.79 (m, 1H), 7.72 (dd, $J = 6.93$, 3.17 Hz, 2H), 7.62 (d, $J = 4.68$ Hz, 1H), 7.43 (dd, $J = 5.28$, 2.21 Hz, 3H), 7.15-7.09 (m, 1H), 7.08 (s, 1H), 3.72 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 189.9, 172.5, 142.3, 133.8, 133.0, 130.4 (2C), 128.8 (2C), 127.9, 124.3, 114.4, 97.1, 97.1, 52.4, 38.4. IR 2969.6, 2931.5, 2870.5, 1736.2, 1662.5, 1411.8, 1257.5 cm$^{-1}$. HRMS-ESI (m/z): Calc. 284.0507, Obs. 284.0507.

Methyl 1-(furan-2-carbonyl)-2-phenylcycloprop-2-enecarboxylate (35i). Rh$_2$(S-PTAD)$_4$ (32.12 mg, 2.0*10$^{-2}$ mmol), $\alpha$-diazo ester 34i (0.400 g, 2.06 mmol), phenylacetylene (0.105 g, 1.03 mmol) and CH$_2$Cl$_2$ (2.2 mL) were mixed according to Procedure B to afford 35i as a white solid (0.170 g, 61.5% yield) after 3 h. [mp: 106-108 °C]. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70
(dd, $J = 6.81, 3.29$ Hz, 2H), 7.61 (td, $J = 1.41, 0.71, 0.71$ Hz, 1H), 7.42 (m, 3H), 7.23 (dd, $J = 3.59, 0.75$ Hz, 1H), 7.05 (s, 1H), 6.61-6.48 (m, 1H), 3.71 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 186.1, 172.5, 152.4, 146.2, 130.5, 130.3, 128.8, 124.4, 117.7, 113.7, 112.3 (2C), 96.4, (2C), 52.4, 37.7. IR 3159.4, 2983.7, 2965.3, 1734.7, 1648.4, 1464.3, 1305.6, 1267.4, 1164.0 cm$^{-1}$. HRMS (ESI) Calc.268.0736, Obs. 268.0736.

Methyl 1-(thiophene-2-carbonyl)-2-(4-(trifluoromethyl)phenyl)cycloprop-2-enecarboxylate (35j). Rh$_2$(S-PTAD)$_4$ (29.6 mg, 1.9*10$^{-2}$ mmol), α-diazo ester 34a (0.400 g, 1.90 mmol), 1-ethyl-4-(trifluoromethyl)benzene (0.162 g, 0.95 mmol) and CH$_2$Cl$_2$ (3 mL) were mixed according to Procedure B to afford 35j as an off-white solid (0.179 g, 53.4% yield) after 3 h. R$_f$ = 0.25 (15% EtOAc/hexane) [mp: 122-124 °C]. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (d, $J = 7.98$ Hz, 2H), 7.83 (dd, $J = 3.82, 1.13$ Hz, 1H), 7.73 (d, $J = 8.08$ Hz, 2H), 7.69 (dd, $J = 4.94, 1.13$ Hz, 1H), 7.27 (s, 1H), 7.17 (dd, $J = 4.94, 3.83$ Hz, 1H), 3.76 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 189.4, 172.2, 142.2, 134.2, 133.2, 132.3, 132.0, 130.7, 128.1, 125.9, 125.8, 125.0, 122.3, 113.7, 100.0, 52.6, 38.4. IR 3142.3, 2962.5, 1714.9, 1648.4, 1410.4, 1324.0, 1253.2, 1125.8 cm$^{-1}$. HRMS (ESI) Calc. 352.0415, Obs. 352.0383.

Methyl 2-(4-methoxyphenyl)-1-(thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35k). Rh$_2$(S-PTAD)$_4$ (29.6 mg, 1.9*10$^{-2}$ mmol), α-diazo ester 34a (0.400 g, 1.90 mmol), 4-
ethynylanisole (0.125 g, 0.95 mmol) and \( \text{CH}_2\text{Cl}_2 \) (2.2 mL) were mixed according to Procedure B. However, multiple attempts at purification yielded no product. Hence, a tandem protocol was applied in order to generate the benzo-fused product. The crude cyclopropene mixture containing 35k was carried forward (see cycloisomerization protocol).

Methyl 2-(thiophen-2-yl)-1-(thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35l). \( \text{Rh}_2(\text{S-PTAD})_4 \) (53.9 mg, 3.46*10^{-2} mmol), \( \alpha \)-diazo ester 34a (0.400 g, 1.90 mmol), 2-ethynylthiophene (0.187 g, 1.73 mmol) and \( \text{CH}_2\text{Cl}_2 \) (2.2 mL) were mixed according to Procedure B. However, multiple attempts at purification yielded no isolated product. Hence, a tandem protocol was applied in order to generate the benzo-fused product. The crude cyclopropene mixture containing 35l was carried forward (see cycloisomerization protocol).

Methyl 1-(thiophene-2-carbonyl)-2-((trimethylsilyl)methyl)cycloprop-2-enecarboxylate (35m). \( \text{Rh}_2(\text{S-PTAD})_4 \) (53.9 mg, 3.5*10^{-2} mmol), \( \alpha \)-diazo ester 34a (0.400 g, 1.90 mmol), propargy-TMS (0.194 g, 1.73 mmol) and \( \text{CH}_2\text{Cl}_2 \) (2.2 mL) were mixed according to Procedure B. However, multiple attempts at purification yielded no isolable product. The crude cyclopropene mixture containing 35m was carried forward (see cycloisomerization protocol).
Methyl 2-butyl-1-(thiophene-2-carbonyl)cycloprop-2-enecarboxylate (35n). \( \text{Rh}_2(\text{S-PTAD})_4 \) (29.6 mg, 1.9*10^-2 mmol), \( \alpha \)-diazo ester 34a (0.400 g, 1.90 mmol), 1-Hexyne (0.078 g, 0.951 mmol) and \( \text{CH}_2\text{Cl}_2 \) (2.2 mL)were mixed according to Procedure B. However, multiple attempts at purification yielded no isolable product. The crude cyclopropene mixture containing 35n was carried forward (see cycloisomerization protocol).

Methyl 1-(thiophene-2-carbonyl)-2-(trimethylsilyl)cycloprop-2-enecarboxylate (48). \(^{168}\) \( \text{Rh}_2(\text{OAc})_4 \) (1.58 mg, 3.56*10^-3 mmol, 0.25 mol%), trimethylsilylacetylene (2.86 mmol, 2.0 equiv.), \( \alpha \)-diazo ester 34a (0.300 g, 1.43 mmol, 1 equiv.) and \( \text{CH}_2\text{Cl}_2 \) (3.2 mL) were mixed according to general method B to afford 48 as a pale yellow oil (0.210 g, 52%). \( \text{Rf} \) 0.22 (10% \( \text{Et}_2\text{O/hexane} \)). \(^1\text{H NMR} \) (300 MHz, CDCl\(_3\) ) \( \delta \) 8.06 (dd, \( J = 4.41, \) 1.84 Hz, 1H), 7.42 (dd, \( J = 5.07, \) 1.22 Hz, 1H), 7.11 (t, \( J = 4.43, \) 4.43 Hz, 1H), 6.97 (s, 1H), 3.87 (s, 3H), 0.36 (s, 9H). \(^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\) ) \( \delta \) 190.0, 177.0, 142.5, 132.0, 131.0, 130.0, 116.0, 112.0, 52.0, 00.0. \( \text{IR:} \) 3109.6 (s), 2952.9 (s), 1791.8 (w), 1737.2 (s), 1729.0 (s), 1709.0 (s), 1657.8 (s), 1649.4 (s), 1515.2 (w), 1464.3 (s) cm\(^{-1} \). \( \text{HRMS-ESI} \) (m/z): Calc. 280.0589, Obs. 280.0584.

C. General Procedure for the Lewis-Acid Catalyzed Cycloisomerization of Cyclopropenes

\textbf{Procedure C}: The corresponding cyclopropene was added to a flame dried flask containing \( \text{In(OTf)}_3 \) (5-30 mol %) in anhydrous \( \text{CH}_2\text{Cl}_2 \) (0.2 M). The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with \( \text{H}_2\text{O} \). The mixture was extracted with \( \text{CH}_2\text{Cl}_2 \), dried with \( \text{Na}_2\text{SO}_4 \), and purification by column chromatography provided the benzo-fused heteroaromatic product.
**Procedure D**: A round bottom flask was charged with Rh$_2$esp$_2$ (1 mol %) or Rh$_2$(S-PTAD)$_4$ (2 mol %) and CH$_2$Cl$_2$ (0.5 M). After cooling the solution to 0 °C, the corresponding alkyne (1.0 equiv.) was added to the reaction vessel. After stirring for 5 min, a solution of the α-diazo ester (1.3 equiv.) in CH$_2$Cl$_2$ (0.5 M) was added in one shot, and allowed to stir at 0 °C. Via TLC, after the complete consumption of the diazo, the ice bath was removed and the reaction was allowed to warm up to rt. In(OTf)$_3$ (5-10 mol %) was then added to the reaction mixture. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H$_2$O. The mixture was extracted with CH$_2$Cl$_2$, dried with Na$_2$SO$_4$, and column chromatography provided the benzo-fused heteroaromatic products.

![Diagram](image_url)

**Methyl 4-(4-bromophenyl)-7-hydroxybenzo[b]thiophene-6-carboxylate (36a).** In(OTf)$_3$ (3.8 mg, 6.8*10$^{-3}$ mmol), cyclopropene 35a (0.050 g, 0.137 mmol), and CH$_2$Cl$_2$ (1 mL) were mixed according to the general Procedure C to afford 36a as an off-white solid (0.043g, 86%) after 10h. $R_f = 0.30$ (10% EtOAc/hexane) [mp: 116.7-118.0 °C].$^1$H NMR (300 MHz, CDCl$_3$) δ 11.56 (s, 1H), 7.75 (s, 1H), 7.74-7.68 (m, 1H), 7.66-7.49 (m, 4H), 7.47-7.36 (m, 1H), 4.00 (s, 3H).$^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.3, 167.6, 157.9, 147.3, 145.8, 138.7, 133.9, 131.9, 129.6, 127.8, 126.7, 125.7, 124.2, 122.1, 107.1, 52.3. IR: 3090.9 (w), 2953.3 (m), 2921.7 (s), 2851.2 (s), 1672.3 (s), 1666.1 (s), 1611.1 (m), 1560.6 (m) cm$^{-1}$. HRMS-ESI (m/z): Calc. 361.9646, Obs.361.9616.
Methyl 3-bromo-7-(4-bromophenyl)-4-hydroxybenzo[c]thiophene-5-carboxylate (36c). In(OTf)₃ (2.24 mg, 3.98*10⁻³ mmol), cyclopropene 35c (0.035 g, 0.0797 mmol), and CH₂Cl₂ (2 mL) were mixed according to Procedure C to afford an inseparable mixture of 36c and a debrominated product as a white solid (0.015 g, 43.1%) after 10 h. [mp: 110-112 °C].¹H NMR (300 MHz, CDCl₃) δ 11.55 (s), 7.74 (s), 7.72-7.65 (m), 7.64-7.49 (m), 7.40 (dd), 3.99 (s) ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 171.1, 157.8, 157.3, 145.9, 143.8, 139.0, 138.7, 132.0, 131.8, 131.6, 131.5, 130.6, 130.5, 129.8, 129.1, 128.6, 128.2, 128.1, 126.8, 125.8, 125.3, 124.3, 123.7, 122.1, 121.9, 121.5, 107.2, 106.3, 52.5, 52.4. IR 2956.0, 2924.3, 2854.8, 1741.8, 1669.6, 1440.2, 1247.6 cm⁻¹. HRMS (ESI) Calc. 439.8717, Obs. 439.8714.

Methyl 7-hydroxy-4-phenylbenzo[b]thiophene-6-carboxylate (36h). In(OTf)₃ (4.9 mg, 8.8*10⁻³ mmol), cyclopropene 35h (50.0 mg, 0.176 mmol), and CH₂Cl₂ (2 mL) were mixed according to the general Procedure C to afford 36h as a white solid (31.5 mg, 63%) after 10h. Rf = 0.30 (10% EtOAc/hexane) [mp: 154.0-156.3 °C].¹H NMR (300 MHz, CDCl₃), 11.52 (s, 1H), 7.78 (s, 1H), 7.66 (d, J = 5.83 Hz, 1H), 7.59-7.33 (m, 6H), 3.99 (s, 3H).¹³C NMR (75 MHz, CDCl₃) δ 171.1, 156.9, 144.0, 140.0, 131.1, 129.3, 128.9(2C), 128.5(2C), 128.3, 127.2, 125.3, 124.0, 106.2, 52.3. IR: 2951.6 (m), 2918.5 (s), 2851.4 (s), 1671.7 (s), 1665.6 (s), 1472.0 (s) cm⁻¹. HRMS-ESI (m/z): Calc. 284.0507, Obs. 284.0507.
Methyl 7-hydroxy-4-phenylbenzofuran-6-carboxylate (36i). In(OTf)_3 (5.2 mg, 9.3*10^{-3} mmol), cyclopropene 35i (0.050 g, 0.186 mmol), and CH_2Cl_2 (2 mL) were mixed according to Procedure C to afford 36i as an off-white solid (0.023 g, 46%) after 10 h. \(^1\)H NMR (300 MHz, CDCl_3) δ 11.44 (s, 1H), 7.95 (s, 1H), 7.80 (dd, J = 8.37, 1.26 Hz, 2H), 7.64 (d, J = 2.22 Hz, 1H), 7.47 (m, 2H), 7.37 (m, 1H), 7.05 (d, J = 7.60 Hz, 1H), 3.99 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl_3) δ 171.1, 156.7, 156.7, 144.3, 135.5, 128.6 (2C), 128.1 (2C), 127.4, 124.9, 118.4, 117.6, 106.5, 105.0, 52.2. IR: 3122.6 (w), 3062.3 (w), 2952.2 (w), 2855.5 (w), 1716.9 (w), 1672.0 (s), 1666.4 (s), 1619.9 (m), 1604.9 (s), 1470.0 (s), 1440.5 (s) cm\(^{-1}\). HRMS (ESI) Calc. 268.0736, Obs. 268.0741.

Methyl 7-hydroxy-4-(4-methoxyphenyl)benzo[b]thiophene-6-carboxylate (36k). In(OTf)_3 (53.4 mg, 9.5*10^{-2} mmol) was added to the crude cyclopropene 35k (see cyclopropenation procedure) according to Procedure D to afford 36k as a white solid (0.044 g, 14.7%) after 9 h. R_f 0.30 (5% EtOAc/hexane) [mp: 135.7-137.6 °C]. \(^1\)H NMR (300 MHz, CDCl_3) δ 11.50 (s, 1H), 7.72 (s, 1H), 7.69 (d, J = 5.55 Hz, 1H), 7.60 (d, J = 8.89 Hz, 2H), 7.39 (dd, J = 5.55, 0.57 Hz, 1H), 7.02 (d, J = 8.88 Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl_3) δ 171.3, 159.2, 157.1, 146.2, 132.2, 130.1, 129.1(2C), 127.6, 125.6, 123.8, 121.9, 114.1(2C), 107.0, 55.3, 52.2. IR: 3082.2 (w), 2952.2 (m), 2922.3 (s), 2851.3 (m), 1733.5 (m), 1716.3 (s), 1700.3 (s), 1619.9 (m), 1604.9 (s), 1470.0 (s), 1440.5 (s) cm\(^{-1}\).
1665.4 (s), 1659.4 (m), 1607.8 (m), 1560.1 (m) cm\(^{-1}\). **HRMS-ESI** (m/z): Calc. 314.0613, Obs. 314.0614.

**Methyl 7-hydroxy-4-(thiophen-2-yl)benzo[b]thiophene-6-carboxylate (36l).** According to Procedure D, In(OTf)\(_3\) (145.0 mg, 0.260 mmol), crude cyclopropene 35l (see cyclopropenation procedure), and CH\(_2\)Cl\(_2\) (10 mL) were mixed according to Procedure D to afford 36l as a white solid (0.110 g, 29.5%) after 9 h. \(R_f\) 0.25 (10% EtOAc/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.56 (s, 1H), 7.94 (s, 1H), 7.70 (d, \(J = 5.55\) Hz, 1H), 7.49 (d, \(J = 3.60\) Hz, 1H), 7.44 (d, \(J = 5.55\) Hz, 1H), 7.35 (d, \(J = 4.54\) Hz, 1H), 7.16 (dd, \(J = 5.15, 3.61\) Hz, 1H), 4.00 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.0, 157.5, 145.2, 141.7, 130.5, 127.6, 125.8, 124.8, 124.7, 122.0, 120.9, 107.0, 52.3. **IR:** 3105.9 (w), 3089.0 (m), 2951.6 (m), 2851.1 (w), 1665.1 (s), 1659.0 (s), 1610.9 (m), 1576.1 (s), 1554.1 (m) cm\(^{-1}\). **HRMS-ESI** (m/z): Calc. 290.0071, Obs. 290.0073.

**Methyl 7-hydroxy-4-((trimethylsilyl)methyl)benzo[b]thiophene-6-carboxylate (36m).** In(OTf)\(_3\) (148.6 mg, 8.6*10\(^{-2}\) mmol), crude cyclopropene 35m (see cyclopropenation procedure), and CH\(_2\)Cl\(_2\) (10 mL) were mixed according to Procedure D to afford 36m as a colorless oil (0.086 g, 15%) after 9 h. \(R_f\) = 0.25 (10% Et\(_2\)O/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.29 (s, 1H), 7.63 (d, \(J = 5.58\) Hz, 1H), 7.36 (m, 2H), 3.97 (s, 3H), 2.24 (s, 2H), 0.03 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.4, 155.4, 146.8, 129.4, 125.3, 124.7, 122.1, 122.1, 106.7, 52.1, 24.7, -1.2. **IR:** 3085.6 (m), 2951.5 (s), 2150.2 (m), 1772.1 (w), 1733.6 (m), 1717.0 (m), 1695.8 (m), 1665.8 (s), 1659.4 (m), 1607.8 (m), 1560.1 (m) cm\(^{-1}\).
1665.0 (s), 1609.9 (m), 1575.9 (m), 1600.0 (m) cm\(^{-1}\). **HRMS-ESI** (m/z): Calc. 294.0746, Obs. 294.0742.

1-(7-hydroxy-4-(4-methoxyphenyl)benzo[b]thiophen-6-yl)ethanone (36p). \(\text{Rh}_2\text{esp}_2\) (9.0 mg, 1.19*10^{-2} mmol), \(\alpha\)-diazo ester 34p (0.300 g, 1.54 mmol), 4-ethynylanisole (0.160 g, 1.99 mmol) and CH\(_2\)Cl\(_2\) (8 mL) were mixed according to the general method to afford 36p as an off-white solid (0.183 g, 31%) after 5 h. \(R_f\) 0.20 (15% EtOAc/hexane) [mp: 94.0-96.4 °C]. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 13.32 (s, 1H), 7.72 (d, \(J = 5.55\) Hz, 1H), 7.61 (s, 1H), 7.57 (d, \(J = 5.76\) Hz, 2H), 7.40 (d, \(J = 5.54\) Hz, 1H), 7.04 (d, \(J = 8.78\) Hz, 2H), 3.89 (s, 3H), 2.71 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 204.6, 159.3, 158.3, 148.0, 132.1, 130.6, 129.2 (2C), 128.0, 125.8, 124.6, 122.3, 115.0, 114.2 (2C), 55.3, 27.0 cm\(^{-1}\). IR: 3084.1 (w), 3000.8 (w), 2925.6 (m), 1733.5 (m), 1683.9 (s), 1639.3 (s), 1619.5 (m), 1463.8(s). **HRMS-ESI** (m/z): Calc. 298.0664, Obs. 298.0665.

1-(4-hydroxy-7-(4-methoxyphenyl)benzofuran-5-yl)ethanone (36q). \(\text{Rh}_2\text{esp}_2\) (1.6 mg, 2.16*10^{-3} mmol), \(\alpha\)-diazo ester 34q (0.500 g, 2.81 mmol), 4-ethynylanisole (0.285 g, 2.16 mmol) and CH\(_2\)Cl\(_2\) (10 mL) were mixed according to the general method to afford 36q as an off-white solid (0.326 g, 53%) after 5 h. \(R_f\) 0.30 (15% EtOAc/hexane) [mp: 103.5-105.5 °C]. \(^1\)H NMR
(300 MHz, CDCl) δ13.20 (s, 1H), 7.73-7.67 (m, 3H), 7.63 (d, J = 2.21 Hz, 1H), 6.91 (m, 3H), 3.88 (s, 3H), 2.71 (s, 3H). 13C NMR (75 MHz, CDCl) δ 204.2, 159.2, 157.7, 157.5, 144.5, 129.3 (2C), 128.0, 125.5, 125.0, 118.2, 114.8 (2C), 114.2, 105.2, 55.3, 27.0. IR: 2925.6 (m), 1791.8 (m), 1726.2 (s), 1640.1 (m), 1597.9 (s), 1575.5 (s) cm⁻¹.

Methyl 5-hydroxy-8-(4-methoxyphenyl)indolizine-6-carboxylate (36r). Rh2esp2 (1.9 mg, 2.59*10⁻³ mmol), α-diazo ester 34r (0.500 g, 2.59 mmol), 4-ethynylanisole (0.500 g, 2.59 mmol) and CH₂Cl₂ (4 mL) were mixed according to the general method to afford 36r as an off-white solid (0.302 g, 51%) after 3 h. Rf 0.20 (15% EtOAc/hexane) [mp: 114.9-116.5 °C]. ¹H NMR (300 MHz, CDCl) δ 11.84 (s, 1H), 7.49 (d, J = 8.88 Hz, 2H), 7.38 (dd, J = 2.64, 1.50 Hz, 1H), 7.08-7.03 (m, 1H), 7.01 (d, J = 8.88 Hz, 2H), 6.72 (dd, J = 4.10, 2.68 Hz, 1H), 6.70 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H). 13C NMR (75 MHz, CDCl) δ 170.9, 160.0, 156.4, 130.2(2C), 129.1, 127.1, 116.3, 114.3, 113.5, 108.1, 104.7, 97.0, 55.4, 51.9. IR: 3084.1 (w), 2954.4 (s), 2922.8 (s), 2851.9 (m), 1737.7 (s), 1726.1 (s), 1711.6 (m), 1605.0 (s) cm⁻¹. HRMS-ESI (m/z): Calc. 297.1001, Obs. 297.0998.

Methyl 7-hydroxybenzo[b]thiophene-6-carboxylate (51). In(OTf)₃ (10.2 mg, 1.79x10⁻² mmol), cyclopropene 48 (0.100 g, 0.357 mmol), and CH₂Cl₂ (1.8 mL) were mixed according to the general procedure to afford 51 after 6 h as an off-white solid (0.043 g, 58% yield). All data matches literature.¹⁰⁵
Chapter Five: Cycloisomerization of Furan-3-Carboxylates Into Benzofused Heteroaromatic Compounds*139

5.1 Synthesis of Benzofused Heteroaromatic Compounds from Furans

Benzofused scaffolds and their derivatives represent an important structural motif as they are ubiquitous in numerous natural products with biological activities and pharmaceuticals. Hence, new and efficient methodologies for the synthesis of benzofused derivatives are of high interest, yet, limited reports are available for the preparation of these compounds. In Chapters Three and Four, two methods towards the synthesis of benzofused heteroaromatic compounds were discussed. With a continued interest in developing methods for their synthesis, this chapter will discuss a different approach for their formation. This method employs furans as the reactive intermediate for the construction of benzofused heteroaromatics.

5.2 Synthesis of Furans

The synthesis of furans is of high interest because they can serve as a building block to generate more complex structures. As a result, many strategies have been realized for furan formation. In this section, examples of acid and metal assisted synthesis of 5-substituted furans from 2007 to date will be disclosed. These examples mainly focus on the formation of furans from cyclopropanes.

5.2.1 Furans from Dicarbonyls

\[ \text{Scheme 5.1: Furan Synthesis from Dicarboxyls} \]

* This work is in collaboration with Joel Aponte-Guzman.
A classic way to access furan synthetically is via Paal-Knorr furan synthesis (Scheme 5.1, 1). In this reaction, 1,4-dicarbonyl systems 1 undergo an intramolecular condensation promoted by acid and heat, followed by dehydration to provide substituted furans 2. This transformation is reversible, as furans can be converted back to 1,4-diketones. Feist-Benary synthesis of furan occurs when an α-halocarbonyl 4 reacts with a β-dicarbonyl 3 in presence of base via an aldol condensation, followed by an intramolecular O-alkylation to form dihydrofuran intermediate 5. Subsequent dehydration of 5 furnished furan 6 (Scheme 5.1, 2). Modified versions of these syntheses have proven to be the most powerful method for the synthesis of furans. However, these approaches are unsuitable for acid-sensitive substrates. Due to the instability of the starting materials, all products formed contain a C-2 substitution on the heterocycle. As a result, these strategies are mainly employed for furans with 2-and5-substitution patterns.

5.2.2 Metal Mediated Furan Synthesis

![Scheme 5.2: General Metal Catalyzed Cycloisomerization of Alkynyl Ketones and Imines](image)

Catalytic approaches toward highly substituted furans 9 from acyclic substrates using mild conditions are of great interest. Marshall\textsuperscript{59-61} introduced silver as the metal to promote the reaction, and it was elaborated by Hashmi\textsuperscript{62} using gold. Geovorgyan also showed an example of this using copper as the catalyst (Scheme 5.2).\textsuperscript{45} Polysubstituted furans can be prepared from simple furans, with easy access to substitution at the 2-and 5-positions as compared to the 3-and 4-position.\textsuperscript{66} Highly selective cyclization reactions from nonfuran starting materials are also efficient for the synthesis of polysubstituted furans. Cyclopropenes, with its exceedingly reactive C=C double bond have shown to undergo a variety of addition and ring opening reactions.\textsuperscript{45,46}
Regioselective synthesis of furans from cyclopropenyl ketones have been demonstrated by Padwa and coworkers in 1991. In this report, Padwa noted a Rh-catalyzed ring opening of cyclopropenyl ketones 10 in a highly regiospecific manner and is dependent on the oxidation state of the metal. Rh(II) specifically forms isomer 11, while Rh(I) forms only isomer 12 (Scheme 5.3). They rationalized that the formation of a metallocyclobutene, which then undergoes a reductive elimination to form the observed furan. The formal increase in oxidation state from Rh(I) to Rh(III) is more facile than from Rh(II) to Rh(IV).

![Scheme 5.3: Padwa’s Regioselective Rearrangements of Cyclopropenes](image)

Recently, Ma reported a selective synthesis of substituted 2-alkyloxy-furans 14 and 15 via ring opening cycloisomerization of cyclopropenyl carboxylates 13 (Scheme 5.4). While many catalysts and conditions were tested using the model substrate where R₁ is n-butyl, only 2.6 mol% of RuCl₂(PPh₃)₃ in THF stirring at room temperature for 10 hours gave 15 as the major isomer in 95% yield. Furan 14 was obtained using Cu(acac)₂ in acetonitrile at 100 °C in 88% yield after 48 hours. Other catalysts were screened, and all were found to be ineffective as cycloisomerization catalysts. Trace products were observed using Rh₂(OAc)₄ or Cu(OAc)₂. IrCl(CO)(PPh₃)₂ or CuCl₂ gave a mixture of both isomers 14 and 15.

![Scheme 5.4: Cycloisomerization of Cyclopropenyl Carboxylates](image)

The generality of the reaction was examined, where R₁ was an alkyl, benzyl, aryl, or vinyl. The 2,3,5-trisubstituted furans and 2,3,4-trisubstituted furans could be obtained in good to
excellent yields with >99:1 selectivity (Scheme 5.4). It is worthwhile to note that the two catalyst systems tolerate even a free hydroxyl group to afford the corresponding furans. Furthermore, the benzenesulfonyl group required the reaction had to be heated in toluene at reflux.

Scheme 5.5: Ma’s Regioselective Cycloisomerization of Cyclopropenyl Ketone

The authors also examined the cycloisomerization reaction of cyclopropenyl ketone 16 under the same conditions (Scheme 5.5). These reactions occurred smoothly under the new catalytic conditions, where the RuCl₂(PPh₃)₃ loading was increased to 2.6 mol % in order to provide furan 17 in 83% yield and the Cu(acac)₂ loading was 5.9 mol %. Furan 18 was isolated in 71% yield using Cu(acac)₂.

Scheme 5.6: Plausible Mechanism of Cycloisomerization reactions

In the case of ruthenium, chlorometalation occurs when the chloride anion attacks the less substituted sp²-carbon to generate IIa. In contrast, the intermediate IIb in the Cu(acac)₂ catalytic cycle, the cationic center was stabilized by the R₁ group. The cyclopropane intermediates
undergo a ring-opening isomerization to afford metal carbene intermediates IIIa and IIIb. Subsequent attack by the carbonyl oxygen onto the metal carbene carbon led to a cyclic metal intermediate IVa and IVb, and isomerization furnishes the corresponding substituted furans 19 and 20.

Ma and coworkers developed an efficient approach to benzofused heterocycles from cyclopropene derivatives (Scheme 5.7). Deprotection by organolithiums and subsequent ring opening followed by cyclization of the related 2-cyclopropenyl phenyl 21 or benzyl acetates generate isochromenes 22 and benzofurans 23 in one pot.

Scheme 5.7: Formation of Tetrahydro-2H-pyran and Benzofurans

The initial hypothesis was that after deprotection, the tetrahydro-2H-pyran-and acetoxy-protected phenol-substituted cyclopropenes would form benzofurans (Scheme 5.7). After countless efforts using weak bases such as LiOH, K$_2$CO$_3$, NaHCO$_3$, or PPTS etc. failed, they decided to try stronger bases. Ma and coworkers demonstrated that upon treatment of 4 equiv. of n-BuLi to dimethyl 2-(2-acetoxyphenyl)cyclo-prop-2-ene-1,1-dicarboxylate, the corresponding chromene or benzofuran was achieved in one hour. The scope of this report included geminal diesters, monoester, and sulfonyl as the substituents about C1. The generality for the substrates were explored using different substituents on the aryl ring, and provided affirmation that the electronics did not play a role in the formation of the benzofurans, as both electron rich and electron poor aryl ring gave comparable yields. The benzofurans containing C-Cl bonds could further be transformed into useful substituted aryl compounds via a Suzuki coupling reaction.
Scheme 5.8: Mechanistic Rationale

Ma and coworkers proposed that the reaction of 23 with \( n\)-BuLi forms intermediate A (Scheme 5.8). Attack of the oxygen anion in A onto the cyclopropene generated the benzofuranyl anion C, followed by addition of AcOD to form 24. However, in presence of excess \( n\)-BuLi, A encountered a second deprotonation to generate dianion B. Dianion B attacks the cyclopropene, causing it to ring open followed by cyclization to form the benzofuranyl dianion D. Upon quenching with AcOD, bis-deuterated benzofuran 25 was afforded.

Scheme 5.9: Chan’s Approaches for the Synthesis of Furans

Recently, Chan and coworkers showed that unsaturated alcohols in presence of Brønsted acid can be another strategy for the construction of substituted furans.\textsuperscript{173} Chan developed two cycloisomerization strategies for furan synthesis using propargylic 1,4-diols 26 (Scheme 5.9).
The first report of the cycloisomerization of the 1,4-propargylic diol 26 proceeded via an allenyl ketone intermediate 27, furnishing furans in 42-94% yield (Scheme 5.9, 1). The second strategy employed $p$-TsOH as the promoter for a tandem alkylation/cycloisomerization of but-2-yne-1,4-diols 26 with 1,3-dicarbonyl compounds 29, providing furans 30 in 60-85% yield (Scheme 5.9, 2).

### 5.3 Furans as Reactive Subunits

Furans are used for the generation of 1,4-dicarbonyls via protonation with a strong Brønsted acid. Activation of furan by a Lewis acid could also promote nucleophilic attack at the 2 or 5 position to promote ring cleavage. However, these are very simple transformations in which furans participate. More elaborate uses for furans were shown recently by Liu and coworkers. They disclosed a series of furan/yne cyclizations via gold-catalyzed *endo* cyclization of internal alkynes to furnish aromatic compounds containing enal or enone functionalities, while maintaining excellent stereoselectivity (Scheme 5.10).

In the first report, Liu and colleagues disclosed a domino approach for the synthesis of substituted benzenes 32 containing enone or enal functionalities from alkynyl furans 31 (Scheme 5.10, equation 1). In the second report, in presence of gold, furans containing enynyl 33 can undergo a 6-*endo-dig* cyclization to form...
fulvene derivatives 34 via the π-complex between the gold catalyst and the alkyne (Scheme 5.10, equation 2). In this method, furan rings are introduced to an aryl ring via a metal or Lewis acid catalyzed Friedel-Crafts reactions, or via nucleophilic addition of 2-furanyllithium to an aldehyde. This procedure provided 1-napthol derivatives with enal or enone moiety to provide products in high stereoselectivities, mild reaction conditions, and easily accessible starting materials. Liu’s protocol was accessible for electron rich and electron poor aryl groups, as well as alkyl and aryl groups about the alkyne. Napthol derivatives were provided from 59-99% yield. Liu also disclosed a furan-yne cyclization of furan 35 to napthol intermedium 36, which was then used for the synthesis of 2H-benzo[h]chromen-2-one 37 (Scheme 5.11).

Scheme 5.11: Liu’s Furan/yne Cyclizations

The selected examples showed that cyclopropenes readily rearranges to furans in presence of a Lewis acid. Ma’s examples provided insight into the rearrangement mechanism of the cyclopropenes, and that different isomers were observed based on the choice of the catalyst. Liu’s examples further confirmed that furans can undergo ring opening in presence of a metal catalyst such as gold to provide benzenoid products. These reports further validate that furans can be used as reactive subunits for benzofused heteroaromatic compounds via activation of a Lewis acid.
5.4 Project Hypothesis

During our studies of the cycloisomerization of 3,3’-dicarbonyl cyclopropenes, we observed an interesting product formed while we were attempting the cyclopropenation reaction. Treatment of diazo 38a with 4-ethynylanisole 39a with hopes of isolated cyclopropene 40a was met with futility. We discovered that we actually isolated furan derivative 41a. This was attributed to the fact that the cyclopropene is the kinetic product of the reaction, which is unstable and rearranges to the thermodynamic product, the furan 41a (Scheme 5.12).

![Scheme 5.12: Rearrangement of Cyclopropene](image)

With an overall goal of generating benzofused heteroaromatic compounds, we were interested in the reaction outcome of subjecting this furan to a Lewis acid. Notably, upon treatment of furan 41a with In(OTf)$_3$ (5 mol%), we were able to isolate benzo[b]thiophene product 42a in 86% yield (Scheme 5.13). This was very intriguing to us and provided us with more motivation to continue our pursuit of new methodologies for the formation of benzofused heteroaromatic compounds.

![Scheme 5.13: Ring Opening/Rearrangement of Furan 41a](image)

With this in mind, we wanted to develop a method to access these benzofused heteroaromatic compounds via the furan intermediates which can easily be formed from our
diazo compounds and alkynes. The synthesis of the furan intermediates can be achieved by formation of heteroaryl β-ketoester 44 (from treatment of the enolate of methyl acetate to the acyl chloride 43), followed by diazo transfer to form stable α-diazocarbonyl products 45. The diazo compounds were subjected to Rh$_2$esp$_2$ (1 mol %) in presence of an alkyne to form the tri-substituted furans 46 in good yields (Scheme 5.14).

**Scheme 5.14:** Synthesis of Furans

The scope of the reaction was explored by probing the substituent effect on the alkyne (Table 5.1). Readily available terminal alkynes were used in order to install the substituent at the 5 position. Electron rich aryl alkyne, such as 4-ethynyl anisole 39a, gave furan 41a in 65% yield (Table 5.1, entry 1). Phenylacetylene 39b also provided the furan 41b in 65% yield (Table 5.1, entry 2), while an electron-poor alkyne (1-ethynyl-4-(trifluoromethyl)benzene) furnished the furan 41c in lower yield, only 46% (Table 5.1, entry 3). Furan derived from $n$-hexyne 41d was formed in 67% (Table 5.1, entry 4), while a more volatile alkyne, propargyl-TMS, gave 39e in 36% yield (Table 5.1, entry 5). The TMS group serves as a point of functionalization as it can undergo Fleming oxidation to provide an alcohol.$^{177}$ 2-Ethynylthiophene 39f formed a 2,5-di(thiophen-2-yl)furan product 41f in 68% yield (Table 5.1, entry 6). This scaffold is useful in dendrimers and material science, and this methodology could be applied for their synthesis.
Table 5.1: Substituent Effects for Furan Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>46%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>67%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1" alt="Diazotopic Structure" /></td>
<td><img src="image2" alt="Alkyne Structure" /></td>
<td><img src="image3" alt="Furan Product" /></td>
<td>68%</td>
</tr>
</tbody>
</table>

*a Isolated from column chromatography

Our next goal was to investigate the modularity of this methodology by investigating its amenability towards different heteroaromatics. 3-Thiophene diazo 38b was subjected to Rh2esp2 in presence of 4-ethynylanisole 39a, and surprisingly, furan 41g was isolated in only 31% yield (Table 5.2, entry 1). 2-Bromo-3-thiophene diazo 38c under the standard conditions provided furan product 41h in 65% yield (Table 5.2, entry 2). This substrate is unique, as further elongation or complexity could be generated off of the bromo substituent. Bifuran product 41i was isolated in good yield (87%) starting from 2-furan diazo 38d, while its isomer derived from 3-furan diazo 38e provided the corresponding product 41j in much lower yield, only 32% (Table
5.2, entry 3 and 4). This could be attributed perhaps to the degradation of the product during the transformation. 2-Benzofuran diazo 38f provided the furan product 41k in a modest yield of 65% (Table 5.2, entry 5), while the N-methyl pyrrole diazo 38g gave the furan product 41l in 87% (Table 5.2, entry 6). We were delighted to find that furan 41m derived from N-acyl-indole diazo 38h, as indole is present in many natural products. Overall, this methodology was found to be amenable to a large number of heteroaromatics, and can be used as a general method for the synthesis of 2,3,5-substituted furans.
Table 5.2: 5-Heteroaryl Substituted Furan Synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>31%</td>
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<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>87%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1" alt="Diazobenzene" /></td>
<td><img src="image2" alt="Alkyne" /></td>
<td><img src="image3" alt="Product" /></td>
<td>65%</td>
</tr>
</tbody>
</table>

a Isolated yields after column chromatography

After developing a general method for the formation of furans, we wanted to design a method which utilizes furans as the building blocks in order to generate benzofused heteroaromatic compounds. Given Liu’s success with the formation of naphthols by having a phenyl substituent off of the furan, and our initial observations, we hypothesized that if we
could form the ring opened product, we would be able to generate the same vinylic cation intermediate in the cycloisomerization of cyclopropenes in order to generate the benzofused heteroaromatic products. We envision that once furan 43 chelates to a metal, 44 will undergo ring opening to form the vinylic cation intermediate 45 (the same intermediate in the case of the cycloisomerization of cyclopropene), which then can be trapped by the adjacent heteroaromatic to furnish the benzofused heteroaromatic products 46 (Scheme 5.15).

Scheme 5.15: Mechanism of Furan Ring Opening

To probe our hypothesis, we used furan 41a and screened various Lewis acids at 5 mol %, at room temperature in order to determine the best one for the desired transformation. With the hopes that it will form the same intermediate as in the cycloisomerization of 3,3’-dicarbonyl cyclopropenes, we screened In(OTf)₃ first. We found that In(OTf)₃ readily provided the benzofused heteroaromatic 42a in 4.5 hours, while Sc(OTf)₃ went to complete conversion after 10 hours. Al(OTf)₃ and Zn(OTf)₂ did not provide complete conversion of the furan even after 24 hours, while AgOTf provided the desired benzo[b]thiophene 42a after 8 hours. Overall, In(OTf)₃ was the best catalyst to promote ring opening of the furan and the formation of the benzofused heteroaromatic product 42a in 86% yield (Table 5.3).
Table 5.3: Lewis Acid Screen

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>In(OTf)_3</td>
<td>4.5h</td>
</tr>
<tr>
<td>Sc(OTf)_3</td>
<td>10h</td>
</tr>
<tr>
<td>Al(OTf)_3</td>
<td>+24h</td>
</tr>
<tr>
<td>Zn(OTf)_2</td>
<td>+24h</td>
</tr>
<tr>
<td>AgOTf</td>
<td>8h</td>
</tr>
</tbody>
</table>

After the optimized conditions were attained, we wanted to probe the electronics about the furan and its role in the product formation. The phenyl substituent 41b was tested, and the product 42b was isolated in 86% (Table 5.4, entry 1). Next, an electron poor substituent was tested, using the furan product derived from 4-ethynyl-α,α,α-trifluorotoluene. This furan did not furnish any of the benzofused product 42c, despite harsh conditions of increased catalyst loading and heating to reflux in toluene (Table 5.4, entry 2). This was not surprising, as the substituent destabilizes the vinylic cation intermediate. Alkyl substituents were also investigated, and the same observation was made in regards to the electronics. No product was isolated from furan 41d as the alkyl substituent is too destabilizing to generate the vinylic cation intermediate necessary for cyclization to 42d (Table 5.4, entry 3). If we take into account the case of the vinylic cation and consider reaction enthalpies (energy of stabilization), a phenyl substituent provides ~25 kcal mol\(^{-1}\) of increased stability over a simple \(n\)-alkyl substituent on the positively charged vinylic position. A silyl-based furan 41e, derived from propargyl-TMS, did not undergo cycloisomerization at room temperature. However, upon heating to reflux in 1,2-dichloroethane, cycloisomerization afforded product 42e in 68% yield (Table 5.4, entry 4). This could be attributed to the β-silyl effect onto the carbocation intermediate. Meanwhile, furan 41f readily
undergoes cycloisomerization in presence of In(OTf)$_3$ to provide the heterobiaryl product 42f in high yield of 83 % (Table 5.4, entry 5).

**Table 5.4: Cycloisomerization of Furans for Benzofused Heteroaromatic Compounds**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Structure 9" /></td>
<td><img src="image10.png" alt="Structure 10" /></td>
<td>83</td>
</tr>
</tbody>
</table>

To ensure that this method will be able to form a diverse group of benzofused heteroaromatics, we needed to investigate how the heteroaromatic will affect the cycloisomerization of the furan. We wanted to design a robust method that will allow for generation of diverse set of interesting benzofused heteroaromatic scaffold. Therefore, we needed to probe the effects of the heteroaromatic on the cycloisomerization protocol.
Table 5.5: Cycloisomerization of Various Heteroaryl Furans for Benzofused Heteroaromatics

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="41g" /></td>
<td><img src="image" alt="42g" /></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="41h" /></td>
<td><img src="image" alt="42h" /></td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="41i" /></td>
<td><img src="image" alt="42i" /></td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="41j" /></td>
<td><img src="image" alt="42j" /></td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="41k" /></td>
<td><img src="image" alt="42k" /></td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="41l" /></td>
<td><img src="image" alt="42l" /></td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="41m" /></td>
<td><img src="image" alt="42m" /></td>
<td>69</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated from column chromatography

The 3-thienyl derivative 41g was subjected to In(OTf)<sub>3</sub>, benzo[b]thiophene 42g was formed in 82% (Table 5.5, entry 1). Next we probed the 2-bromo-3-thienyl furan 41h derivative’s reactivity, and found that we were able to make benzo[c]thiophene 42h in 55%, which is extremely useful in material science (Table 5.5, entry 2). We envision that we would be...
able to build upon this scaffold to generate much more complex products. We were also interested in being able to form benzofurans, as they are found in many biologically relevant natural products. Using 2-furyl derivative 41i, benzofuran 42i was formed in 78% yield (Table 5.5, entry 3), while benzofuran 42j was formed in 82% yield from 41j (Table 5.5, entry 4). We were also able to form dibenzofuran 42k in high yield of 69% from furan 41k (Table 5.5, entry 5). Provided that the indole core is often called the “privileged” scaffold as it is found in many potent bioactive natural products, we were interested in a method in which we would be able to form these core skeletons. Using 2-N-methylpyrrole substituted furan, N-methyl indole 42l in 78% yield from furan 41l (Table 5.5, entry 6). N-acyl-indole 41m readily provides pyrido[1,2,a]indole 42m in 69% yield (Table 5.5, entry 7).

5.5 Summary

In summary, we have developed a facile method for the formation of 2,3,5-trisubstituted furans via a Rh(II) catalyzed decomposition of α-diazo-β-ketoesters in presence of a terminal alkyne. This methodology afforded various 2-heteroaryl substituted furans in 36-87% yield. This procedure is amenable to most heteroaromatics, tolerates electron rich, electron-poor, alkyl, as well as heteroaryl substituted alkynes. We were also able to take these furans and use them as versatile building blocks for the formation of benzo fused heteroaromatics. Given that benzofused heteroaromatics are ubiquitous in natural products, medicinal chemistry, material and polymer science, as well as inorganic complexes, this methodology is of great importance. We were able to form benzo[b]thiophenes, benzo[c]thiophenes, benzofurans, dibenzofurans, indoles indolizines, and pyrido[1,2,a]indoles in good to high yields, 55-86%.
Experimentals

1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenoneketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. Anhydrous acetonitrile was purchased from EMD Chemicals and used without further purification. Methyl acetate was fractionally distilled over P$_2$O$_5$. 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. α-Diazo compounds 38a-38g were synthesized as previously reported. α-Diazo compound 38h was synthesized as previously reported.$^{167}$

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 with UV light, aqueous basic potassium permanganate (KMnO$_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic p-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material. Compounds 41e, 41j, 42b, 42g, 42i and 42j were provided by Joel Aponte-Guzman.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment.
from SmartOrbitThermoelectronic Corp. 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, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 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), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160).

2. General Procedures

A. Formation of Furans-3-Carboxylates

General Method A: A round bottom flask was charged with Rh$_2$esp$_2$ (1 mol %) and CH$_2$Cl$_2$ (0.5 M). After cooling the solution to 0 °C, the corresponding alkyne (1.0 equiv.) was added to the reaction vessel. After stirring for 5 min, a solution of the α-diazo ester (1.3 equiv.) in CH$_2$Cl$_2$ (0.5 M) was added in one shot, and allowed to stir for 10 min at 0 °C. At this time, the ice bath was removed and the reaction was allowed to warm up to rt. The reaction was quenched with saturated aqueous thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted 3x with CH$_2$Cl$_2$. The organic layer was washed with brine, dried with Na$_2$SO$_4$, concentrated, and column chromatography afforded the desired cyclopropene.$^2$

General Method B: A round bottom flask was charged with the indicated amount of Rh$_2$(OAc)$_4$ and the corresponding alkyne (2.0 equiv.) in CH$_2$Cl$_2$ (0.5 M). After stirring for 5 min at room temperature, α-diazo ester 38a (1 equiv.) in CH$_2$Cl$_2$ (0.5 M) was added via syringe pump (0.80
mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite (eluting with EtOAc), concentrated, and purification by column chromatography afforded the desired cyclopropene.

**Methyl 5-(4-methoxyphenyl)-2-(thiophen-2-yl)furan-3-carboxylate (41a).** \( \text{Rh}_2 \text{esp}_2 \) (8.33 mg, 1.09*10\(^{-2}\) mmol), \( \alpha \)-diazoe ester 38a (0.300 g, 1.43 mmol), 4-ethynylanisole (0.144 g, 1.09 mmol) and \( \text{CH}_2\text{Cl}_2 \) (2.2 mL) were mixed according to general method A to afford 41a as a white solid (0.222 g, 65% yield) after 4 h. \( R_f \) 0.30 (15% EtOAc/hexane) [mp: 91.8-93.4 °C]. \(^1\text{H NMR} \) (300 MHz, \( \text{CDCl}_3 \)) \( \delta \) 8.10 (dd, \( J = 3.45, 0.83 \text{ Hz}, 1\text{H} \)), 7.65 (d, \( J = 8.43 \text{ Hz}, 2\text{H} \)), 7.44 (dd, \( J = 5.08, 0.49 \text{ Hz}, 1\text{H} \)), 7.14 (dd, \( J = 5.07, 3.81 \text{ Hz}, 1\text{H} \)), 6.96 (d, \( J = 8.47 \text{ Hz}, 2\text{H} \)), 6.90 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H). \(^{13}\text{C NMR} \) (75 MHz, \( \text{CDCl}_3 \)) \( \delta \) 163.8, 159.6, 151.8, 131.5, 129.2, 128.4 (2C), 127.7, 127.4, 125.5, 122.4, 114.2 (2C), 105.7, 55.3, 51.6. \( \text{IR: } 3101.9 \text{ (w)}, 2996.3 \text{ (m)}, 2947.7 \text{ (m)}, 2834.8 \text{ (m)}, 1733.3 \text{ (s)}, 1710.1 \text{ (s)}, 1635.4 \text{ (s)}, 1614.7 \text{ (m)}, 1596.2 \text{ (w) cm}^{-1} \). \( \text{HRMS-ESI} \) (m/z): Calc. 314.0613, Obs. 314.0614.

**Methyl 5-phenyl-2-(thiophen-2-yl)furan-3-carboxylate (42b).** \( \text{Rh}_2 \text{esp}_2 \) (11.0 mg, 1.46*10\(^{-2}\) mmol), \( \alpha \)-diazoe ester 38a (0.300 g, 1.90 mmol), phenylacetylene (0.149 g, 1.46 mmol) and \( \text{CH}_2\text{Cl}_2 \) (3 mL) were mixed according to general method A to afford 41b as a yellow oil (0.197 g, 65% yield) after 4 h. \( R_f \) 0.25 (10% EtOAc/hexane). \(^1\text{H NMR} \) (300 MHz, \( \text{CDCl}_3 \)) \( \delta \) 8.13 (dd, \( J = 3.81, 1.20 \text{ Hz}, 1\text{H} \)), 7.72 (dd, \( J = 8.45, 1.17 \text{ Hz}, 2\text{H} \)), 7.44 (m, 2H), 7.33 (d, \( J = 7.38 \text{ Hz}, 1\text{H} \)),
7.15 (dd, J = 5.07, 3.80 Hz, 1H), 7.04 (s, 1H), 3.92 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.7, 151.7, 131.5, 129.4, 128.8 (2C), 128.7, 128.1 (2C), 128.0 (2C), 127.5, 123.9, 113.7, 107.3, 51.6. IR: 3093.4 (w), 2940.6 (w), 2157.9 (w), 2030.3 (m), 2012.4 (w), 1978.7 (w), 1727.8 (s), 1736.8 (s), 1671.8 (s), 1648.6 (m) cm$^{-1}$. HRMS-ESI (m/z): Calc. 284.0507, Obs. 284.0507.

**Methyl 2-(thiophen-2-yl)-5-(4-(trifluoromethyl)phenyl)furan-3-carboxylate (41c).** Rh$_2$esp$_2$ (11.04 mg, 1.46*10$^{-2}$ mmol), $\alpha$-diazo ester 38a (0.300 g, 1.43 mmol), 1-ethynyl-4-(trifluoromethyl)benzene (0.25 g, 1.46 mmol) and CH$_2$Cl$_2$ (3 mL) were mixed according to general method A to afford 41c as a white solid (0.216 g, 46% yield) after 4 h. R$_f$ 0.30 (5% EtOAc/hexane) [mp: 90.4-93.1°C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (dd, J = 3.81, 1.19 Hz, 1H), 7.83 (dd, J = 9.01, 5.25 Hz, 2H), 7.53 (dd, J = 5.07, 1.19 Hz, 1H), 7.20-7.03 (m, 3H), 7.11 (s, 1H), 3.91 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.8, 153.0, 150.0, 132.6, 131.1, 129.3, 128.6, 128.5, 127.6, 125.9, 125.8, 124.0, 123.9, 113.8, 109.4, 51.7. $^{19}$F NMR (300 MHz, CDCl$_3$) 70.3. IR: 3115.7 (w), 2953.1 (m), 2923.7 (s), 2853.0 (m), 2127.8 (w), 1966.7 (w), 1760.1 (m), 1712.3 (m), 1656.1 (w), 1619.1 (m), 1601.0 (w) cm$^{-1}$. HRMS-ESI (m/z): Calc. 352.04, Obs. 352.04.

**Methyl 5-butyl-2-(thiophen-2-yl)furan-3-carboxylate (41d).** $^3$Rh$_2$(OAc)$_4$ (0.032 g, 7.15*10$^{-2}$ mmol, 5 mol %), 1-hexyne (0.235 g, 2.86 mmol, 2.0 equiv.), $\alpha$-diazo ester 38a (0.300 g, 1.43 mmol, 1 equiv.) and CH$_2$Cl$_2$ (3.2 mL) were mixed according to general method B to afford 41d
as a pale yellow oil (0.254 g, 67% yield). R_f 0.22 (10% Et_2O/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.99 (dd, \(J = 3.78, 1.19\) Hz, 1H), 7.39 (dd, \(J = 5.08, 1.19\) Hz, 1H), 7.10 (dd, \(J = 5.06, 3.79\) Hz, 1H), 6.38 (s, 1H), 3.86 (s, 3H), 2.65 (t, \(J = 7.54, 7.54\) Hz, 2H), 1.65 (dd, \(J = 15.18, 7.62\) Hz, 2H), 1.41 (dd, \(J = 14.97, 7.51\) Hz, 2H), 0.95 (t, \(J = 7.35, 7.35\) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.9, 155.0, 151.4, 131.8, 130.0, 128.0, 127.2, 112.3, 107.7, 51.2, 29.7, 27.3, 22.1, 14.0. IR: 2952.7 (s), 2925.0 (s), 2855.7 (s), 1712.1 (s), 1664.5 (s), 1565.5 (w), 1439.7 (w) cm\(^{-1}\). HRMS-ESI (m/z): Calc. 264.0820, Obs. 264.0819.

Methyl 2,5-di(thiophen-2-yl)furan-3-carboxylate (41f). Rh\(_{2}\)esp\(_2\) (8.33 mg, 1.09*10\(^{-2}\) mmol), \(\alpha\)-diazo ester 38a (0.300 g, 1.43 mmol), 2-ethynylthiophene (0.120 g, 1.09 mmol) and CH\(_2\)Cl\(_2\) (2.2mL) were mixed according to general method A to afford 41f as a pale oil (0.212 g, 68%) after 5 h. R_f 0.30 (15% EtOAc/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.09 (dd, \(J = 3.81, 1.21\) Hz, 1H), 7.45 (dd, \(J = 5.07, 1.21\) Hz, 1H), 7.35 (dd, \(J = 3.64, 1.17\) Hz, 1H), 7.29 (dd, \(J = 5.05, 1.19\) Hz, 1H), 7.14 (dd, \(J = 5.07, 3.81\) Hz, 1H), 7.07 (dd, \(J = 5.05, 3.64\) Hz, 1H), 6.90 (s, 1H), 3.90 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.5, 151.7, 147.3, 132.1, 131.2, 128.8, 128.1, 127.8, 127.4, 125.1, 123.7, 113.5, 107.1, 51.7. IR: 3103.2 (m), 2948.8 (m), 2919.2 (m), 2849.3 (s), 1720.2 (s), 1710.6 (s), 1683.0 (s), 1667.8 (s), 1652.8 (s), 1599.0 (s), 1564.1 (s), 1540.0 (s) cm\(^{-1}\). HRMS-ESI (m/z): Calc. 290.0071, Obs. 290.0073.
Methyl 5-(4-methoxyphenyl)-2-(thiophen-3-yl)furan-3-carboxylate (41g). Rh$_2$esp$_2$ (8.33 mg, 1.09*10$^{-2}$ mmol), α-diazo ester 38b (0.300 g, 1.43 mmol), 4-ethynylanisole (0.145 g, 1.1 mmol) and CH$_2$Cl$_2$ (2.2 mL) were mixed according to general method A to afford 41g as a pale oil (0.108 g, 31%) after 5 h. R$_f$ 0.22 (10% Et$_2$O/hexane) [mp: 112.3-114.4 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.50-8.34 (m, 1H), 7.84 (dd, $J$ = 5.12, 1.17 Hz, 1H), 7.66 (d, $J$ = 8.92 Hz, 2H), 7.37 (dd, $J$ = 5.50, 2.75 Hz, 1H), 6.96 (d, $J$ = 8.93 Hz, 2H), 6.90 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 164.0, 159.5, 152.6, 151.5, 130.7, 127.0, 126.1, 125.4 (2C), 125.1, 122.6 114.2 (2C), 114.1, 105.7, 55.3, 51.6. IR: 3000.2 (m), 2953.1 (m), 2835.2 (m), 1733.7 (w), 1717.0 (s), 1700.0 (m), 1664.8 (m), 1609.0 (w), 1575.4 (w) cm$^{-1}$. HRMS-ESI (m/z): Calc. 314.0613, Obs. 314.0617.

Methyl 2-(2-bromothiophen-3-yl)-5-(4-methoxyphenyl)furan-3-carboxylate (41h). Rh$_2$esp$_2$ (4.44 mg, 5.86*10$^{-3}$ mmol), α-diazo ester 38c (0.300 g, 0.763 mmol), 4-ethynylanisole (0.079 g, 0.586 mmol) and CH$_2$Cl$_2$ (1.4 mL) were mixed according to general method A to afford 41h as a yellow solid (0.150 g, 65%) after 5 h. R$_f$ 0.25 (10% EtOAc/hexane) [mp: 94.0-96.4 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.67 (d, $J$ = 8.56 Hz, 2H), 7.39 (d, $J$ = 5.77 Hz, 1H), 7.30 (d, $J$ = 5.77 Hz, 1H), 7.03-6.88 (m, 3H), 3.84 (s, 3H), 3.83 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.5, 159.7, 153.4, 150.1, 129.6, 125.5, 125.4 (2C),122.5, 117.0, 114.3, 114.2 (2C), 105.0, 104.9, 55.3, 51.7. IR: 2955.0 (m), 2923.5 (m), 1665.9 (s), 1635.6 (s), 1611.3 (m), 1559.4 (m), 1514.2 (w) cm$^{-1}$. HRMS-ESI (m/z): Calc. 391.9752, Obs. 391.9713.
Methyl 5-(4-methoxyphenyl)-[2,2'-bifuran]-3-carboxylate (41i). \( \text{Rh}_2\text{esp}_2 \) (9.02 mg, 1.19*10^-2 mmol), \( \alpha \)-diazo ester 38d (0.300 g, 1.54 mmol), 4-ethynylanisole (0.157 g, 1.19 mmol) and CH\(_2\)Cl\(_2\) (1.4mL) were mixed according to general method A to afford 41i as a white solid (0.310 g, 87% yield) after 5 h. R\(_f\) 0.25 (10% EtOAc/hexane) [mp: 97.4-99.6 °C]. \( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.67 (d, \( J = 8.79 \) Hz, 2H), 7.57 (d, \( J = 1.48 \) Hz, 1H), 7.53 (dd, \( J = 3.53, 0.72 \) Hz, 1H), 6.94 (d, \( J = 8.85 \) Hz, 2H), 6.89 (s, 1H), 6.56 (dd, \( J = 3.53, 1.77 \) Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H). \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 163.3, 159.6, 152.4, 147.5, 144.5, 143.2, 125.6 (2C), 122.4, 114.2 (2C), 114.0, 113.0, 111.9, 105.3, 55.3, 51.6. IR: 2953.5 (m), 2840.3 (m), 1791.7 (w), 1721.2 (s), 1711.9 (s), 1603.5 (s), 1569.8 (s), 1541.8 (m) cm\(^{-1}\). HRMS-ESI (m/z): Calc. 298.0841, Obs. 298.0842.

Methyl 2-(benzofuran-2-yl)-5-(4-methoxyphenyl)furan-3-carboxylate (41k). \( \text{Rh}_2\text{esp}_2 \) (7.20 mg, 9.46*10^-3 mmol), \( \alpha \)-diazo ester 38f (0.300 g, 1.23 mmol), 4-ethynylanisole (0.097 g, 0.946 mmol) and CH\(_2\)Cl\(_2\) (2 mL) were mixed according to general method A to afford 41k as a white solid (0.197 g, 65%) after 3 h. R\(_f\) 0.25 (10% EtOAc/hexane) [mp: 164.2-166.8 °C]. \( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.97 (d, \( J = 0.96 \) Hz, 1H), 7.75 (d, \( J = 8.95 \) Hz, 2H), 7.36 (ddd, \( J = 8.27, 7.25, 1.39 \) Hz, 2H), 7.30 (d, \( J = 1.10 \) Hz, 1H), 7.27 (m, 2H), 7.00 (s, 1H), 6.97 (d, \( J = 1.63 \) Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H). \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 164.1,159.8, 154.7, 153.3, 147.0, 145.8, 128.6, 125.8 (2C), 123.2 (2C), 122.2 (2C), 116.5 (2C), 114.2, 111.3, 108.9, 105.9, 55.3,
Methyl 5-(4-methoxyphenyl)-2-(1-methyl-1H-pyrrol-2-yl)furan-3-carboxylate (41l). To a stirring solution of Rh$_2$esp$_2$ (9.02 mg, 1.19*10$^{-2}$ mmol) in 1,2-dichloroethane (2.4 mL), 4-ethynylanisole (0.157 g, 1.19 mmol) was added. Next, a solution of the α-diazo ester 38g (0.300 g, 1.54 mmol) in 1,2-dichloroethane was added and the mixture heated to reflux. After 6 h, the reaction was cooled to rt. The crude mixture was purified to yield 41l as a white solid (0.310 g, 87.3% yield). R$_f$ 0.25 (10% EtOAc/hexane) [mp: 102.5-103.5 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.60 (d, $J = 8.95$ Hz, 2H), 6.95 (s, 1H), 6.92 (d, $J = 1.97$ Hz, 2H), 6.81-6.73 (m, 2H), 6.23 (dd, $J = 3.86, 2.63$ Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.5, 152.1, 149.9, 125.7(2C), 125.2 (2C), 115.0, 114.7 (2C), 114.6, 114.2, 108.1, 105.2, 55.3, 51.4, 36.2. IR: 2924.2 (s), 2850.3 (s), 2009.8 (m), 1722.0 (s), 1711.4 (m), 1658.5 (s), 1601.8 (m), 1557.9 (s) cm$^{-1}$. HRMS-ESI (m/z): Calc. 348.0998, Obs. 348.1003.

Methyl 5-(4-methoxyphenyl)-2-(3-methyl-1H-indol-1-yl)furan-3-carboxylate (41m). Rh$_2$esp$_2$ (1.01 mg, 8.97*10$^{-3}$ mmol), α-diazo ester 38h (0.300 g, 1.43 mmol), 4-ethynylanisole (0.120 g, 0.897 mmol) and CH$_2$Cl$_2$ (2mL) were mixed according to the general method to afford 41m as a yellow oil (0.233 g, 67% yield) after 3 h. R$_f$ 0.20 (15% EtOAc/hexane). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.65-7.55 (m, 3H), 7.40 (s, 1H), 7.33-7.19 (m, 3H), 6.99-6.89 (m, 3H), 3.84 (s, 3H), 3.83 (s, 3H),
3.78 (s, 3H), 2.37 (s, 3H). $^{13}$C NMR (Bruker 125 MHz, CDCl$_3$): δ 162.8, 159.6, 149.0, 148.0, 136.4, 129.9, 125.5, 125.1, 123.2, 122.3, 121.3, 119.1, 114.5, 111.9, 106.2, 104.6, 55.3, 51.6, 11.0. IR: 3053.3 (m), 2953.0 (m), 2923.9 (s), 2852.3 (m), 1737.3 (m), 1657.1 (s), 1649.2 (s), 1642.5 (m), 1606.3 (m) cm$^{-1}$. HRMS-ESI (m/z): Calc. 361.1274, Obs. 361.1308.

B. General Procedure for the Lewis Acid Catalyzed Cycloisomerization of Furan-3-Carboxylates

Procedure A: The corresponding cyclopropene was added to a flame dried flask containing In(OTf)$_3$ (5 mol %) in anhydrous CH$_2$Cl$_2$ (0.2M). The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H$_2$O. The mixture was extracted with CH$_2$Cl$_2$, dried with Na$_2$SO$_4$, and purification by column chromatography provided the benzo-fused heteroaromatic product.

Methyl 7-hydroxy-4-(4-methoxyphenyl)benzo[b]thiophene-6-carboxylate (42a). In(OTf)$_3$ (8.93 mg, 1.59*10$^{-2}$ mmol), furan 41a (0.100 g, 0.318 mmol), and CH$_2$Cl$_2$ (1.6 mL) were mixed according to the general procedure to afford 42a as a white solid (0.086 g, 86%) after 9 h. R$_f$ 0.30 (5% EtOAc/hexane) [mp: 135.7-137.6 °C]. $^1$H NMR (300 MHz, CDCl$_3$): δ 11.50 (s, 1H), 7.72 (s, 1H), 7.69 (d, $J = 5.55$ Hz, 1H), 7.60 (d, $J = 8.89$ Hz, 2H), 7.39 (dd, $J = 5.55, 0.57$ Hz, 1H), 7.02 (d, $J = 8.88$ Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 171.3, 159.2, 157.1, 146.2, 132.2, 130.1, 129.1 (2C), 127.6, 125.6, 123.8, 121.9, 114.1 (2C), 107.0, 55.3, 52.2. IR: 3082.2 (w), 2952.2 (m), 2922.3 (s), 2851.3 (m), 1733.5 (m), 1716.3 (s), 1700.3
(s), 1665.4 (s), 1659.4 (m), 1607.8 (m), 1560.1 (m) cm$^{-1}$. **HRMS-ESI** (m/z): Calc. 314.0613, Obs. 314.0614.

**Methyl 7-hydroxy-4-((trimethylsilyl)methyl)benzo[b]thiophene-6-carboxylate (42e).** Modification of the general procedure, In(OTf)$_3$ (9.54 mg, 1.67*10$^{-2}$ mmol), furan 41e (0.100 g, 0.339 mmol), and 1,2-dichloroethane (1.7 mL) were heated to reflux to afford 42e as a pale oil (0.83 g, 83%) after 7.5 h. $R_f$ 0.25 (10% Et$_2$O/hexane). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.29 (s, 1H), 7.63 (d, $J = 5.58$ Hz, 1H), 7.36 (m, 2H), 3.97 (s, 3H), 2.24 (s, 2H), 0.03 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.4, 155.4, 146.8, 129.4, 125.3, 124.7, 122.1, 122.1, 106.7, 52.1, 24.7, -1.2. IR: 3085.6 (m), 2951.5 (s), 2150.2 (m), 1772.1 (w), 1733.6 (m), 1717.0 (m), 1695.8 (m), 1665.0 (s), 1609.9 (m), 1575.9 (m), 1600.0 (m) cm$^{-1}$. **HRMS-ESI** (m/z): Calc. 294.0746, Obs. 294.0742.

**Methyl 7-hydroxy-4-((thiophen-2-yl)benzo[b]thiophene-6-carboxylate (42f).** In(OTf)$_3$ (9.54 mg, 1.67*10$^{-2}$ mmol), furan 41f (0.035 g, 0.121 mmol), and CH$_2$Cl$_2$ (1 mL) were mixed according to the general procedure to afford 42f as a pale oil (0.029 g, 83%) after 7 h. $R_f$ 0.25 (10% EtOAc/hexane). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.56 (s, 1H), 7.94 (s, 1H), 7.70 (d, $J = 5.55$ Hz, 1H), 7.49 (d, $J = 3.60$ Hz, 1H), 7.44 (d, $J = 5.55$ Hz, 1H), 7.35 (d, $J = 4.54$ Hz, 1H), 7.16 (dd, $J = 5.15$, 3.61 Hz, 1H), 4.00 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.0, 157.5, 145.2, 141.7, 130.5, 127.6, 125.8, 124.8, 124.7, 124.7, 122.0, 120.9, 107.0, 52.3. IR: 3105.9
Methyl 3-bromo-4-hydroxy-7-(4-methoxyphenyl)benzo[c]thiophene-5-carboxylate (42h).

In(OTf)$_3$ (3.99 mg, 7.09*10$^{-3}$ mmol), furan 41h (0.056 g, 0.142 mmol), and CH$_2$Cl$_2$ (1 mL) were mixed according to the general procedure to afford 42h as a yellow solid (0.031 g, 55%) after 8 h. R$_f$ 0.30 (15% EtOAc/hexane) [mp: 104.8-106.7 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 11.52 (s, 1H), 7.74 (s, 1H), 7.64 (dd, $J$ = 5.41, 0.50 Hz, 1H), 7.63-7.56 (m, 1H), 7.45 (dd, $J$ = 7.10, 4.76 Hz, 2H), 7.01 (dd, $J$ = 8.89, 2.51 Hz, 2H), 3.99 (s, 3H), 3.88 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.9, 156.6, 144.1, 132.5, 130.9, 130.0, 129.1, 129.0, 125.0, 124.1, 123.8, 121.9, 114.1, 113.9, 106.2, 55.3, 52.3. IR: 3085.4 (w), 2997.2 (w), 2953.2 (s), 2835.3 (s), 1733.7 (w), 1717.3 (s), 1700.0 (s), 1665.2 (m), 1609.7 (s), 1575.6 (m), 1540.1 (m) cm$^{-1}$. HRMS-ESI (m/z): Calc. 391.9752, Obs. 391.9713.

Methyl 4-hydroxy-1-(4-methoxyphenyl)dibenzo[b,d]furan-3-carboxylate (42k).

In(OTf)$_3$ (4.41 mg, 7.85*10$^{-3}$ mmol), furan 41k (0.050 g, 0.157 mmol), and CH$_2$Cl$_2$ (1 mL) were mixed according to the general procedure to afford 42k after 12 h as a yellow solid (0.035 g, 69%). R$_f$ 0.30 (15% EtOAc/hexane) [mp: 145.2-147.3 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 11.54 (s, 1H),
8.25 (d, $J = 6.33$ Hz, 1H), 8.04 (s, 1H), 7.78 (d, $J = 8.69$ Hz, 2H), 7.59 (d, $J = 7.41$ Hz, 1H), 7.51-7.35 (m, 2H), 7.06 (d, $J = 8.77$ Hz, 2H), 4.01 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.8, 159.1, 157.7, 155.6, 129.5 (2C), 128.0, 127.6, 126.6 (2C), 123.5 (2C), 123.2, 123.0, 118.0, 114.1 (2C), 111.3, 107.2, 55.3, 52.2. IR: 3079.7 (w), 2953.6 (m), 2835.5 (w), 1672.4 (s), 1633.1 (m), 1611.2 (m), 1576.6 (s), 1539.3 (w), 1518.7 (s) cm$^{-1}$. HRMS-ESI (m/z): Calc. 348.0998, Obs. 348.1003.

Methyl 7-hydroxy-4-(4-methoxyphenyl)-1-methyl-1H-indole-6-carboxylate (42l). In(OTf)$_3$ (3.16 mg, 5.62*10$^{-3}$ mmol), cyclopropene 41l (0.035 g, 0.112 mmol), and CH$_2$Cl$_2$ (1 mL) were mixed according to the general procedure to afford 42l as a brown solid (0.021 g, 78%) after 12 h. $R_f$ 0.20 (15% EtOAc/hexane) [mp: 185.3-187.2 °C]. $^1$H NMR (300 MHz, CDCl$_3$) δ 11.24 (s, 1H), 7.32 (d, $J = 8.16$ Hz, 2H), 7.02 (d, $J = 2.98$ Hz, 1H), 6.96 (d, $J = 8.64$ Hz, 3H), 6.90 (dd, $J = 3.05$, 0.71 Hz, 1H), 4.06 (s, 3H), 3.87 (s, 3H), 3.27 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.3, 159.2, 158.0, 134.8, 132.8, 131.7 (2C), 131.1, 130.4, 128.3, 127.7, 114.7, 113.2 (2C), 102.5, 77.3, 77.2, 76.9, 76.6, 55.3, 51.9, 37.0. IR: 2951.7 (s), 2922.2 (s), 2850.4 (s), 1733.8 (s), 1717.0 (m), 1700.2 (m), 1684.2 (s), 1657.4 (w), 1649.5 (s), 1558.9 (s) cm$^{-1}$. HRMS-ESI (m/z): Calc. 311.1158, Obs. 311.1148.
Methyl 6-hydroxy-9-(4-methoxyphenyl)-10-methylpyrido[1,2-α]indole-7-carboxylate (42m).

In(OTf)₃ (6.06 mg, 1.08*10⁻² mmol), furan 41m (0.075 g, 0.216 mmol), and CH₂Cl₂ (1 mL) were mixed according to the general procedure to afford 42m as a yellow solid (0.052 g, 69% yield) after 6 h. Rᵣ 0.20 (15% EtOAc/hexane) [mp: 175.5-178.5 °C]. ¹H NMR (300 MHz, CDCl₃) δ 12.23 (s, 1H), 7.78 (d, J = 8.20 Hz, 1H), 7.39 (d, J = 8.81 Hz, 2H), 7.25 (ddd, J = 8.11, 6.41, 0.82 Hz, 1H), 7.04 (d, J = 8.80 Hz, 2H), 6.97 (ddd, J = 8.13, 6.86, 1.21 Hz, 1H), 6.56 (d, J = 8.77 Hz, 1H), 6.44 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.90 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 160.1, 159.6, 131.4, 131.4, 130.7 (2C), 129.6, 128.7, 126.8, 121.7, 121.5, 119.4, 114.8, 114.1 (2C), 109.8, 106.3, 98.3, 55.4, 52.0, 10.0. IR: 3053.3 (m), 2953.0 (m), 2923.9 (s), 2852.3 (m), 1737.3 (m), 1657.1 (s), 1649.2 (s), 1642.5 (m), 1606.3 (m) cm⁻¹. HRMS-ESI (m/z): Calc. 361.1314, Obs. 361.1307.
Chapter VI: Conclusions and Future Outlook

Chapter II: The Alkenyl and Heteroaryl Homo-Nazarov Cyclization

The cyclohexenone and cyclohexenols moieties are extremely important in natural products and medicinal chemistry. The alkenyl homo-Nazarov cyclization disclosed in this thesis demonstrates that a catalytic amount of Lewis acid, in particular In(OTf)$_3$, can promote the cyclization of simple alkenes. In this protocol, eight alkenyl cyclopropyl ketone examples were shown to undergo cyclization to afford cyclohexenones in 29-93% yield. The scope of the alkenyl derivatives can be expanded upon, as well as varying the different acceptor groups to include sulfonates, phosphonates and ketones. Further studies of the reaction kinetics and full elucidation of the substituent effects on the reaction mechanism is crucial. Lastly, chiral Lewis acids can be employed in order to develop an enantioselective alkenyl homo-Nazarov cyclization. Further exploration using chiral Brønsted acids to catalyze the cyclization is also possible. The heteroaryl homo-Nazarov cyclization expanded the scope of this protocol to be amenable for most heteroaromatics. These heteroaryl ring-fused products are exceptionally useful, as they are found in many natural products that are highly potent. This protocol also generated products with multiple stereogenic centers. Future development includes an asymmetric heteroaryl homo-Nazarov cyclization protocol, as well as application of these ring-fused cyclohexanones as building blocks for the total synthesis of natural products. *In-situ* trapping of the carbocation with a nucleophile could be achieved. These nucleophiles can include indoles, amines, alcohols and thiols. These cyclopropanes can also participate in 3+$n$ cycloadditions reactions with aldehydes, nitrones, imines and alkenes.
Chapter III: Dihydrofuran Formation Future Outlook

Dihydrofurans were accessed via a Rh(II) decomposition of diazo compounds and electron rich vinyl systems. These dihydrofurans can be used to form different synthetic building blocks such as furans, lactones, and benzofused heteroaromatic compounds. Given the diverse products obtained, this methodology will be further optimized to include tri-and-tetrasubstituted olefins. Further optimization of the indole formation is also a worthwhile pursuit. Natural products such as Clausamine A and Clausevatine D can also be realized using this methodology.

Chapter IV: Cycloisomerization of 3,3’-Dicarbonyl Cyclopropenes

The first Lewis acid catalyzed cycloisomerization of 3,3’-dicarbonyl cyclopropenes were realized by our group. This allowed for the construction substituted benzofused heteroaromatics in modest to high yields. Further studies will include optimizing the conditions for the cyclopropene formation, as well as optimizing the conditions for the cycloisomerization. Application of this protocol for natural product synthesis as well as polymer synthesis will be pursued. The generation of pyrido[1,2,a]indoles can be achieved, and these core scaffolds can be developed into tunable fluorescent probes.

Chapter V: Cycloisomerization of Furans

Ring opening and rearrangement of furans were disclosed, and the formation of these benzofused heteroaromatic compounds are also of great utility. Limited examples of furan ring opening and rearrangement into benzenoid structures have been realized, and this is an innovative strategy for the construction of benzofused heteroaromatic compounds. Further optimization of the conditions will be advantageous. Using heteroaromatics such as pyridines, quinolines can be generated from this methodology. These furan scaffolds can also participate in cycloaddition reactions with dienophiles to generate much more complex products.
Appendix: Synthetic 7,8-Dihydroxyflavone for Potential Antidepressant Effect*

Flavonoids are natural products that are found primarily in plants.\textsuperscript{178,179} Flavonoids have diverse functions for the plants, such as defense, UV protection, auxin transport inhibition, allelopathy, and pigments.\textsuperscript{180} They are low molecular weight secondary metabolites and they are not necessary for plants’ survival. However, much of these flavonoids are bioactive, with more than 9,000 different compounds known.\textsuperscript{181} These flavonoids have a range of bioactivity including anticancer\textsuperscript{182}, weight management,\textsuperscript{183} as antioxidants,\textsuperscript{184} and many more.\textsuperscript{185} Flavonoids are polyphenolic compounds with a C6-C3-C6 backbone. They can be subdivided into five structural categories: flavones, chalcones, flavonols, flavanones, flavan-3-ols (catechins), isoflavone, anthocyanidins and flavanol (Scheme A-1).\textsuperscript{186} These compounds (aglycones) are commonly glycosylated (at one or more sites with a variety of sugars) and may also be alkoxylated or esterified.\textsuperscript{187} Common sources include red wine, stems, flowers, fruits, vegetables, nuts, seeds, herbs, spices, coffee, and teas.\textsuperscript{188}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{flavonoids.png}
\caption{Chemical structures of representative flavonoids}
\end{figure}

Neurotrophins, the growth factors that sustains the development of the peripheral and the central nervous system, including brain-derived neurotrophic factor (BDNF). BDNF is of particular therapeutic interest because of its neurotrophic actions on neuronal populations involved in several disorders, including amyotrophic lateral sclerosis, Parkinson disease and
Alzheimer’s disease. However, clinical trials using recombinant BDNF have been disappointingly negative due to poor delivery, short half-life, and other limitations. Although efforts have been made to circumvent these problems, no flavonoid has been identified as potent and selective in vivo agonists of TrkB.

BDNF functions via tropomyosin kinase receptor (TrkB) by binding to it and triggering TrkB’s dimerization through conformational changes and autophosphorylation of tyrosine residues in its intracellular domain. This resulted in activation of the three major signaling pathways involving mitogen activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), and phospholipase C-γ1. The 7,8-Dihydroxyflavone has been identified as a novel TrkB agonist, as it is suggested that 7,8-dihydroxyflavone binds the extracellular domain of TrkB and triggers its activation and dimerization. This study evaluated different 7,8-dihydroxyflavones 1 in order to determine the best small molecule as a TrkB agonist. This study found that the hydrogen bond acceptor on the 4’-position of the flavones B ring is critical for 7,8-dihydroxyflavone’s TrkB agonistic effect. The synthetic 4’-dimethylamino-7,8-dihydroxyflavone 2 is the most potent agonist for TrkB compared to the lead 7,8-dihydroxyflavone. Both strongly provoked neurogenesis and display robust antidepressant effects in a TrkB-dependent manner.

![Image of 7,8-Dihydroxyflavone and Its Lead Compound](image)

**Figure A.2:** 7,8-Dihydroxyflavone and Its Lead Compound

In this appendix, synthesis of the most potent lead, 4’-dimethylamino-7,8-dihydroxyflavone will be discussed. Starting with 3’,4’-gallacetophenone 3 and 4-
dimethylaminobenzoyl chloride 4 in presence of pyridine, ester 5 was readily formed. Baker-Venkataraman rearrangement of ester 5 in presence of KOH and pyridine affords diketone 6. Treatment of diketone 6 with a mixture of acetic acid and sulfuric acid affords the capped flavones 7 in modest yields. Acid catalyzed deprotection using HBr at reflux readily provides the unprotected flavones 2 in decent yield. Recrystallization of this product in methanol provides the desired product as a crystalline solid (Scheme A-1).

Scheme A.1: Synthesis of Flavones

After obtaining the flavones, they were subjected to structure-activity relationship (SAR) studies to determine the pharmacophore of the flavone. Preliminary SAR supports that the 7,8-catechol moiety is essential for the agonistic effect by 7,8-dihydroxyflavone. To explore the structure activity relationships, the role of different hydroxyl groups in each ring was examined. After further examination, the SAR study suggested that the catechol group was indispensable for the agonistic activity, while the 3’-hydroxy group increased the activity. The lead compound 2 mimicked BDNF and potently activated the TrkB receptor. As a result, evident antidepressant effects of the mice model were shown. While 7,8-dihydroxyflavone requires 5mg/kg of the 7,8-dihydroxyflavone 1 in order to express comparable antidepressant effects as that of 4’-dimethylamino-7,8-dihydroxyflavone 2a, which required only 1mg/kg. As a result, 4’-
dimethylamino-7,8-dihydroxyflavone **2a** is a stronger agonist on TrkB than 7,8-dihydroxyflavone. 4’-Fluoro flavone **2b** was also more active than the parent 7,8-dihydroxyflavone.

**Experimental**

6-Acetyl-2,3-dimethoxyphenyl 4-(dimethylamino)benzoate (5a). To a solution of 1-(2-hydroxy-3,4-dimethoxyphenyl)ethanone **1** (5.831 g, 29.72 mmol) in dry pyridine (25 mL) was added portions of (4-dimethylamino)benzoyl chloride **4a** (8.19 g, 44.58 mmol) over 15 minutes. The mixture is stirred for 2 hours, and reaction progress was monitored based on TLC. Upon complete disappearance of starting material **1**, reaction was acidified with 2M HCl, extracted with ethyl acetate (2X), dichloromethane (3X), wash with brine, dry, and evaporated under reduced pressure. Flash column chromatography (eluant 10% ethyl acetate/hex) afforded pure product **5a** (8.4 g, 82.7%) as a white crystalline solid. mp 102-106 ± 0.5C. 1H NMR (300 MHz,
CDCl$_3$ $\delta$ 2.48 (3H, s), 3.01 (6H, s), 3.80 (3H, s), 3.93 (3H, s), 6.70 (2H, d), 6.90 (1H, d), 7.70 (1H, d), 8.10 (2H, d); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 20, 40 (2C), 56, 61, 109, 111 (2C), 116, 125, 126, 13 (2C), 142, 145, 154, 158, 165, 196. IR (neat) 2990, 2966, 2890, 2823, 1976, 1685, 1603, 1268, 1171, 1059, 976, 828, 799, 759 cm$^{-1}$.

1-(4-(Dimethylamino)phenyl)-3-(2-hydroxy-3,4-dimethoxyphenyl)propane-1,3-dione (6a). A solution containing 6-acetyl-2,3-dimethoxyphenyl 4-(dimethylamino)benzoate 5a (8.45 g, 24.6 mmol), anhydrous powdered potassium hydroxide (2.08 g, 36.9 mmol), and pyridine (50 mL) was heated at 50 °C for 2 h. Reaction was cooled to room temperature, acidified with 2 M HCl, extracted with ethyl acetate, washed with brine, dried with MgSO$_4$, and evaporated under reduced pressure to yield 7.59 g (90%) of crude propanedione 6. The crude reaction mixture was carried forward without further purification.

2-(4-(Dimethylamino)phenyl)-7,8-dimethoxy-4H-chromen-4-one (7a). A solution of 1-(4-(dimethylamino)phenyl)-3-(2-hydroxy-3,4-dimethoxyphenyl)propane-1,3-dione (6a) (11.48 g, 33.45 mmol) in glacial acetic acid (100 mL) and concentrated sulfuric acid (1 mL) was refluxed for 1 hour. Reaction mixture was poured into ice and the precipitate was extracted with ethyl acetate (2X), dichloromethane (3X), washed with brine, and evaporation under reduced pressure to yield a dark solid. The crude mixture was carried forward to the deprotection step.
2-(4-(Dimethylamino)phenyl)-7,8-dihydroxy-4H-chromen-4-one (2a). A solution of 2-(4-(dimethylamino)phenyl)-7,8-dimethoxy-4H-chromen-4-one (7) (0.462 g, 1.42 mmol) in aqueous hydrobromic acid (48%) (10 mL) is refluxed overnight. After cooling, the reaction mixture is diluted with water, neutralized with saturated NaHCO₃, and extracted with 1-butanol. The organic phase is washed with water, dried, and evaporated under reduced pressure. Recrystallized from 50% Methanol/Dichloromethane provided a deep red solid crystals. mp 242-245 +0.5°C. ¹H NMR (300 MHz, DMSO-d₆) δ 3.01(6H, s), 6.65 (1H, s), 6.82 (2H, d), 6.85 (1H, d), 7.35 (1H,d), 7.97 (2H,d); ¹³C NMR (75 MHz, DMSO-d₆) δ 39.5 (2C), 103, 108, 113,114,116,118,119,129,134,151,164, 178; IR (neat) 3371, 3200, 2590, 2171, 1966, 1619, 1566, 1480, 1300 cm⁻¹. MS ESI m/z 298 [(M+H)+]. Yield: 0.221g, 52%.

6-Acetyl-2,3-dimethoxyphenyl 4-fluorobenzoate (5b). To a solution of 1-(2-hydroxy-3,4-dimethoxyphenyl)ethanone 1 (1.86 g, 9.52 mmol) in dry pyridine (19 mL) was added portions of (4-fluoro)benzoyl chloride 4b (2.25 g, 14.28 mmol) over 15 minutes. The mixture is stirred for 2 hours, and reaction progress was monitored based on TLC. Upon complete disappearance of starting material 1, reaction was acidified with 2M HCl, extracted with ethyl acetate (2X), dichloromethane (3X), wash with brine, dry, and evaporated under reduced pressure. Flash column chromatography (eluant 10%ethyl acetate/ hex) afforded pure product 5b as a yellow oil. (2.27g, 48.9%). ¹H NMR (300 MHz, CDCl₃) δ ppm 8.10 (d, J = 9.17 Hz, 1H), 7.68 (d, J = 8.90
Hz, 1H), 6.87 (d, J = 8.96 Hz, 1H), 6.72 (d, J = 9.18 Hz, 1H), 3.08 (s, 6H), 2.49 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 195.7, 167.9, 163.7, 157.2, 144.2, 141.5, 133.0, 132.9, 132.7, 126.1, 125.4, 116.0, 115.8, 115.5, 109.1, 60.9, 56.1. IR 3001, 1599, 1532, 1491, 1202, 1037, 788, 586 cm$^{-1}$.

1-(4-fluorophenyl)-3-(2-hydroxy-3,4-dimethoxyphenyl)propane-1,3-dione (6b). A solution containing 6-acetyl-2,3-dimethoxyphenyl 4-fluorobenzoate 5b (2.27 g, 7.14 mmol), anhydrous powdered potassium hydroxide (0.600 g, 10.7 mmol), and pyridine (50 mL) was heated at 50 °C for 2 h. Reaction was cooled to room temperature, acidified with 2 M HCl, extracted with ethyl acetate, washed with brine, dried with MgSO$_4$, and evaporated under reduced pressure to yield 1.60 g (70%) of crude propanedione 6b. The crude reaction mixture was carried forward without further purification.

2-(4-Fluorophenyl)-7,8-dimethoxy-4H-chromen-4-one (7b). A solution of 1-(4-fluorophenyl)-3-(2-hydroxy-3,4-dimethoxyphenyl)propane-1,3-dione (6b) (1.12 g, 3.52 mmol) in glacial acetic acid (15 mL) and concentrated sulfuric acid (0.2 mL) was refluxed for 1 hour. Reaction mixture was poured into ice and the precipitate was extracted with ethyl acetate (2X), dichloromethane (3X), washed with brine, and evaporation under reduced pressure to yield a dark solid. The crude mixture was carried forward to the deprotection step.
2-(4-Fluorophenyl)-7,8-dihydroxy-4H-chromen-4-one

A solution of 2-(4-Fluorophenyl)-7,8-dimethoxy-4H-chromen-4-one (7b) (0.560 g, 1.42 mmol) in aqueous hydrobromic acid (48%) (10 mL) is refluxed overnight. After cooling, the reaction mixture is diluted with water, neutralized with saturated NaHCO₃, and extracted with 1-butanol. The organic phase is washed with water, dried, and evaporated under reduced pressure. Recrystallized from 50% Methanol/Dichloromethane provided red solid crystals. Yield 0.242 g, 48.0%. mp 212-215 +0.5°C. ¹H NMR (300 MHz, DMSO-d₆) δ 8.20-8.25 (dd, J=8.80, 2H), 7.35 (d, J=8.56, 1H), 6.91 (d, J=8.64,1H), 6.85 (d, J=8.76,2H), 6.64 (s,1H), 3.02 (s, 6H). ¹³C NMR (75 MHz, DMSO-d₆) δ 177.2, 161.2, 151.0, 150.9, 147.0, 133.4, 129.5, 128.4, 117.2, 116.6, 116.3, 115.5, 115.4, 114.5, 106.4, 101.3. IR 3001, 1599, 1532, 1491, 1202, 1037, 788, 586 cm⁻¹. MS ESI m/z 272 [(M+H)⁺].
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