3,4-Annulated Indoles via Tandem Cyclopropane Ring-Opening/Conia-ene and Michael Addition/Conia-ene Reactions

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Abstract

The indole moiety is ubiquitous in natural products, and as such their reactions and syntheses are a high priority for organic chemists. The use of tandem reactions is an excellent strategy to optimize the efficiency of chemical processes. This thesis details the process of designing and implementing of strategies for the syntheses of 3,4-annulated indoles from 4-ethynylindoles via tandem cyclopropane ring-opening/Conia-ene and Michael addition/Conia-ene reactions. It was discovered through optimization experiments that the reactions are highest yielding using superstoichiometric amounts of Lewis acidic zinc halides. The cyclopropane variant of the reaction was applied to successfully synthesize 23 new 3,4-cycloheptannoindoles products. The Michael addition variant was used to synthesize 14 new 3,4-cyclohexannoindoles. Both reactions tolerated electron withdrawing and electron donating aryl groups on the electrophilic substrates. Yields were generally higher using cyclopropane substrates compared to Michael-acceptors. In both cases 4-ethynyl-1-methylindole performed significantly better than unprotected 4-ethynylindole.

**Keywords:** Conia-ene reaction, cyclopropane annulation, donor-acceptor cyclopropane, fused tricycle, indole annulation, Michael addition, nucleophilic ring-opening, tandem reaction.
Summary for Lay Audience

A vast number of pharmaceuticals are derived from molecules obtained from natural sources like plants and fungi. Some of these natural products can be efficiently harvested and used directly, however many cannot be obtained in significant amounts. For these cases, synthetic organic chemists are employed to replicate the natural products and similar molecules so that they can eventually be used for treatment of ailments. It is important to note that not all synthetic organic chemists focus directly on the synthesis of drugs or natural products; this type of research is known as target-oriented synthesis. Many chemists focus on the development and optimization of different chemical reactions (this type of research is known as methodology-oriented synthesis) which increases the collective knowledge of organic chemists. While methodology-oriented synthesis typically does not produce potentially useful compounds, it creates a plethora of new options for target-oriented researchers to use.

This thesis focuses on the design, and implementation of two new chemical methodologies. These methodologies were constructed using a strategy known as a tandem process. A tandem process is when two or more reactions happen sequentially in one container without needing to add more chemicals or change the temperature or pressure. This strategy can greatly improve the overall efficiency of chemical processes by reducing waste and lowering labour requirements by reducing the need for purifications.
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List of Abbreviations

Å – angstroms
Ar – aryl
atm – atmospheres
ATR-IR – Attenuated Total Reflectance Infrared Spectroscopy
Bn – benzyl
Bu – butyl
cat. – catalytic
Cbz – benzyl chloroformate
d – days
DAC – donor-acceptor cyclopropane
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE – 1,2-dichloroethane
DCM – dichloromethane
DIBAL – diisobutylaluminum hydride
DMF – dimethyl formamide
DMSO – dimethyl sulfoxide
dr – diastereomeric ratio
E – electrophile
ee – enantiomeric excess
eq – equivalents
ESI – electrospray ionization
esp – Espino ligand (m-benzenedipropionic acid)
Et – ethyl
EtOH – ethanol
g – grams
h – hours
HRMS – high-resolution mass spectrometry
iPr – isopropyl
IR – infrared spectroscopy
LDA – lithium diisopropylamide
Me – methyl
MeCN – acetonitrile
MeOH – methanol
mg – milligrams
min – minutes
mL – millilitres
mmol – millimole
MS – molecular sieves
NMR – nuclear magnetic resonance
NTf₂ – bistriflimide
Nu – nucleophile
OTf – trifluromethanesulfonate
p.t. – proton transfer
Ph – phenyl
ppm – parts per million
Pr – propyl
r.t. – room temperature
SN1 – unimolecular nucleophilic substitution
SN2 – bimolecular nucleophilic substitution
TBDPS – tert-butyldiphenylsilyl
t-Bu – tert-butyl
Temp. – temperature
THF – tetrahydrofuran
TLC – thin-layer chromatography
TMS – trimethyl silyl
Ts – toluenesulfonyl
v – volume
1 Introduction

1.1 Indoles in Natural Products

Indole is a bicyclic aromatic compound whose basic structure is among the most common moieties found in natural products, and by extension, pharmaceuticals. For example, methylergometrine is a medication on the World Health Organization list of essential medicines used to treat post-partum hemorrhaging.\(^{[1]}\) Oxypertine is an antipsychotic drug, and tadalafil (better known as Cialis®) is a medication used for the treatment of erectile dysfunction (Figure 1.1). Their widespread appearance in biologically-active molecules makes the synthesis and reactions of indoles a perpetually relevant topic of organic chemistry.

![Figure 1.1. Indole and indole-containing drugs.](image)

1.2 One-pot Procedures

Some drugs can be directly harvested from nature or can be made by modifying natural products, but many cannot be obtained from nature in useful quantities for clinical testing and manufacturing. Many biologically-active molecules are present in nature in such low quantities that large amounts of organisms need to be harvested to acquire a usable amount the natural product. Synthetic chemists seek to make these natural products from commercially available materials.

A useful strategy for synthesizing natural products efficiently is to do two or more reactions in the same reaction vessel (Scheme 1.1). The reactions need to be carefully chosen so that conditions and by-products of earlier steps do not interfere with subsequent steps. If the reactivities are compatible, then a one-pot procedure can significantly improve the overall
efficiency of syntheses as one purification step per transformation is eliminated. Reducing the need for purification reduces opportunities for yield loss and makes the overall process less labour-intensive.\textsuperscript{[2]}

A subset of one-pot procedures is the tandem reaction; this is a procedure where all reagents are added at once and conditions are kept constant. In tandem reactions, each step produces the requisite functionality of the next. The more reactions that are involved in a tandem process the more efficient it becomes compared to doing each step individually. For example, a tandem process of four reactions only needs to give a yield of 66\% to be equivalent to 4 discreet steps of 90\% yield each \((0.9^4 = 0.656)\). Additionally removing 3 of the 4 purifications steps is guaranteed to improve the yield, reduce the amount of wasted solvents, and reduce the labour requirement.

Scheme 1.1. Comparison of stepwise, one-pot, and tandem procedures.

A classic example of a tandem reaction is Robinson’s 1917 synthesis of tropinone \textsuperscript{1.3} from 3-oxo-glutaric acid \textsuperscript{1.1}, succinaldehyde \textsuperscript{1.2}, and methylamine hydrochloride (Scheme 1.2). Robinson successfully synthesized tropinone in one step with a yield of 42\%\textsuperscript{[3]} The original synthesis of tropinone from cycloheptanone by Willstätter in 1901 had taken 21 distinct steps and had an overall yield of less than 1\%.\textsuperscript{[4]}
Scheme 1.2. Robinson’s tandem synthesis of tropinone.

1.3 Background of Donor-Acceptor Cyclopropanes

Cyclopropane is the simplest cycloalkane, consisting of 3 carbon-carbon σ-sigma bonds forming a perfect equilateral triangle. The bond angles of cyclopropane are all 60° which deviate significantly from the ideal 109.5° of tetrahedral sp³ carbons. The large disparity between optimal and observed angles in the cyclopropane ring produces a very large ring strain of approximately 115.2 kJ/mol. For comparison, the ring strain of cyclohexane is only 0.6 kJ/mol (Table 1). [5] In addition to the large ring strain caused by the bond angles, cyclopropane also experiences high torsional strain as all substituents are permanently in eclipsed conformations because 3-membered rings cannot be distorted from flat shapes like larger rings can.

Table 1.1. Comparison of the ring strain of cycloalkanes.

<table>
<thead>
<tr>
<th>Ring</th>
<th>Strain (kJ/mol)</th>
<th>Strain per C (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>△</td>
<td>115.2</td>
<td>38.4</td>
</tr>
<tr>
<td>□</td>
<td>109.1</td>
<td>27.3</td>
</tr>
<tr>
<td>⬤</td>
<td>25.9</td>
<td>5.2</td>
</tr>
<tr>
<td>⬤</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>⬤</td>
<td>39.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Despite its high ring-strain, cyclopropane is relatively unreactive due to the strength of carbon-carbon bonds. However, there is a class of cyclopropanes known as donor-acceptor cyclopropanes (DAC) (1.4) that are vicinally disubstituted with a donor group and an acceptor group. Donor groups refer to groups that can stabilize a developing positive charge (such as methoxy or phenyl groups) and acceptor groups are groups that can stabilize a developing negative charge (typically a carbonyl). The donor and acceptor groups create a push-pull effect along the carbon-carbon bond between them, giving it a unique 1,3-zwitterionic reactivity (1.5). A Lewis acid is typically also required to bind to the acceptor group carbonyl oxygen to further activate the cyclopropane. Although cyclopropane ring-opening reactions are concerted reactions, it is helpful to depict them as stepwise to show the reactivity of the donor-acceptor cyclopropane (Scheme 1.3). The zwitterionic “intermediate” 1.5 can be trapped by either a nucleophile at the positive carbon (1.6a) or an electrophile at the negative carbon (1.6b). A molecule with both an electrophilic moiety and a nucleophilic moiety can form rings 1.6c. Additionally, a dipolar species can undergo cycloaddition reactions forming new five-membered heterocycles 1.6d.[6]

\[
\text{Scheme 1.3. Extreme case of the reactivity of donor-acceptor cyclopropanes.}
\]

The most encountered reaction is the nucleophilic ring-opening reaction (Scheme 1.4). The mechanism is like both S_N1 and S_N2 reactions as the nucleophile attacks the more substituted carbon of cyclopropanes 1.7 like an S_N1 reaction, but complete inversion of stereochemistry is typically observed in ring-opened adducts 1.8 which would be expected for an S_N2 reaction mechanism.
Seminal work on the reactions of DACs was done by Stork in the 1960s. Stork discovered that α-keto bicyclic cyclopropane 1.9 can be made to open, and give a mixture of 1.10, 1.11, and 1.12 in a ratio of (1:5:3).\[^7\] Stork determined that compounds 1.10 and 1.12 resulted from the involvement of the external alkene in the ring-opening, and compound 1.11 is the result of the ring-opening without the alkene’s involvement. This was determined by subjecting 1.11 to cyclization conditions, and neither 1.10 nor 1.12 were formed, indicating that 1.11 cannot be an intermediate in the formations of 1.10 and 1.12.

To determine if the involvement of the external alkene is concerted or stepwise, another experiment was done by treating trans-cyclopropyl ketone 1.13 with SnCl\(_4\) which produced cyclopropyl ketone. Since trans-cyclopropyl ketones gave only trans-cyclized products, and cis-cyclopropyl ketones gave only cis-cyclized products the mechanism must be concerted. A stepwise mechanism would have to go through a carbocation intermediate that could produce both isomers.

### Scheme 1.5. Stork’s seminal work on cyclopropane ring-opening.

### Scheme 1.6. Proof of the concerted nature of cyclopropane ring-openings.
An early example of a donor-acceptor cyclopropane being used as they typically are today, is work from Danishefsky in 1972 (Scheme 1.7). He demonstrated that dimethyl 2-vinylcyclopropane-1,1-dicarboxylate undergoes nucleophilic ring-opening at the more substituted cyclopropyl carbon with complete inversion of stereochemistry. He demonstrated that the reaction proceeds through an S_N2-type mechanism by opening cyclopropane 1.16 with pyrrolidine to give the adduct 1.17, which could be alkylated to quaternary ammonium salt 1.18. The malonate group could then be deprotonated with NaOH. The resulting malonate ion could reform the cyclopropane ring using the pyrrolidine group as a leaving group. The reaction of 1.18 to 1.16 generated the original enantiomer of the vinyl cyclopropane (and this reaction is known to undergo an S_N2 mechanism), which suggests 1.16 to 1.17 must also involve a complete inversion of stereochemistry, and therefore follow a traditional S_N2 mechanism.

Scheme 1.7. Proof that cyclopropanes can be opened through an S_N2 mechanism.

1.4 Syntheses of Cyclopropanes

1.4.1 Corey-Chaykovsky Reaction

There are a multitude of synthetic pathways to donor-acceptor cyclopropanes. Two common methods are the Johnson-Corey-Chaykovsky reaction, and metal carbenoid chemistry. The Johnson-Corey-Chaykovsky reaction (usually shortened to Corey-Chaykovsky reaction) is a classic reaction discovered by A.W. Johnson in 1961 while attempting a Wittig reaction on benzaldehydes 1.19 using 9-dimethylsulfonium fluorenylde (Scheme 1.8). He discovered that rather than producing the desired 9-benzalfluorenes 1.20, the reaction produced epoxides

\[ \text{NaOH} \]

\[ \begin{array}{c}
\text{H} \quad \text{CO}_2\text{Me} \\
\text{C}_2\text{H}_4 \text{CO}_2\text{Me} \\
\end{array} \xrightarrow{\text{pyrrolidine}, 100^\circ C} \begin{array}{c}
\text{N} \quad \text{CO}_2\text{Me} \\
\text{C}_2\text{H}_4 \text{CO}_2\text{Me} \\
\end{array} \xrightarrow{\text{Me}_3\text{O}^+\text{BF}_4^-} \begin{array}{c}
\text{N} \quad \text{BF}_4^- \quad \text{H} \\
\text{CO}_2\text{Me} \\
\end{array} \]

\[ [\alpha]_2 (\text{CCl}_4) +55.2^\circ \quad [\alpha]_2 (\text{CCl}_4) +4.4^\circ \quad 1.18 \]

1.16 1.17 1.18
Johnson found that the reaction worked in reasonable yields (30-40%) in DCM in the cases of R = p-NO₂, m-NO₂, o-NO₂, p-CN, or 2,4-dichloro.

Scheme 1.8. Johnson’s discovery of the epoxidation of benzaldehydes with sulfur ylides.

This reaction was greatly refined and expanded on by E.J. Corey, and Michael Chaykovsky to get better yields and selectivity, and include enones 1.22 as starting materials which can be converted to cyclopropanes 1.23 (Scheme 1.9). It was found that using dimethylsulfoxonium methylide would selectively react at the α,β-alkene to produce a cyclopropane whereas dimethylsulphonium methylide would also epoxidize the carbonyl. Dimethylsulfoxonium methylide has since become a ubiquitous reagent for synthetic organic chemists to make cyclopropanes from α,β-unsaturated ketones, esters, and amides.

Scheme 1.9. Cyclopropanation of chalcone with dimethylsulfoxonium methylide.

1.4.2 Metal-Carbenoid Chemistry

Another robust method of making cyclopropanes is metal-carbenoid chemistry. Metal catalysts, typically Rh(II) dimers, can complex to diazo compounds 1.25 to generate carbenoid species that can be inserted into C-H bonds, or can be inserted across electron-deficient alkenes or alkynes to generate cyclopropanes or cyclopropenes, respectively (Scheme 1.10). Cyclopropanes 1.26 are commonly made from styrenes 1.24 as their wide availabilities make them practical starting points of substrate scopes, in addition there are no C-H bonds that the carbenoid would preferentially add into, which can be a problem with aliphatic alkenes.
Scheme 1.10. Cyclopropanation using Rh$_2$(esp)$_2$ and dimethyl diazoacetate.

1.5 Reactions of Donor-Acceptor Cyclopropanes

1.5.1 Ring-Opening Reactions Generating Carbocycles

Donor-acceptor cyclopropanes have become a useful for synthesizing new carbocycles. In 2008 Ivanova$^{[18]}$ described a rare method for the synthesis of 7-membered cycloaddition products using donor-acceptor cyclopropanes and a 1,4-dipole. This is not a commonly observed reaction type as most 1,4-dipoles are also 1,2-dipoles and undergo (3+2) annulations much more easily.$^{[19]}$ To achieve this unusual reactivity Ivanova used the reactive diene, 1,3-diphenylisobenzofuran 1.28, to perform (4+3) annulation on various 2-arylcylopropane-1,1-diesters 1.27. The yields of these reactions were all very high but came with generally low diastereoselectivities. Substrates with electron-rich aryl substituents gave better selectivities (3:1 to 6:1), favouring the exo products 1.29. This reaction is analogous to the classic Diels-Alder reaction, in that it uses a diene and dienophile. The reported reactions were done using cyclopropanes as the dienophile rather than alkenes which produced rings one carbon larger. The authors proposed that the mechanism is concerted like the Diels-Alder rather than stepwise because the less stable exo products 1.29 are formed as the major product. A stepwise mechanism involving separate steps of ring-opening followed by a cyclization would likely result in the more stable endo products 1.30 being the major product.
Donor acceptor-cyclopropanes can also be used to form polycyclic carbocycles by reactions with allenes (Scheme 1.11). Wang published a methodology for synthesizing [4.3.0]nonanes 1.33 and [3.2.1]octanes 1.32 using an intramolecular formal cycloaddition of a donor-acceptor cyclopropane with an appended allene. Cross cycloadducts 1.32 were generated from a ring-opening by the internal \( \pi \)-bond followed by cyclization at the resulting allylic cation. The intermediate also has a resonance structure that puts the cation at the terminus of the external \( \pi \)-bond. Cyclization at this position gave parallel cycloadducts 1.33. It was found that using \( \text{Sc(OTf)}_3 \) in refluxing DCE would almost exclusively form parallel cycloadducts 1.33 in excellent yields. In only one case was the cross cycloadduct formed (\( R^1 = \text{Me}, R^2/R^3 = \text{Ph/Me}, R^4 = \text{H}, R^5 = \text{H} \)). The authors then attempted to develop a method for preferentially forming the cross products 1.32 but were initially unable to prevent the partial formation of the corresponding parallel products. Using \( \text{Yb(OTf)}_3 \) modest preference for the cross products was achieved with isomeric ratios up to 2.2:1. The lack of selectivity for the cross product is likely due to the lower stability of its intermediate cation compared to the cation preceding the parallel product. To improve the selectivity for cross isomers, the authors installed halogens on the terminus of the allene to destabilize the parallel cation. This effectively eliminated the formation of parallel products for most reactions and gave yields of 40-74% with roughly equal amounts of \( E \) and \( Z \) isomers.
Intramolecular cross and parallel cycloadditions of allenes and DACs.

**Scheme 1.12.** Intramolecular cross and parallel cycloadditions of allenes and DACs.

1.5.2 Ring-Opening Reactions Generating Heterocycles

Heterocycles can also be synthesized from donor-acceptor cyclopropanes. Charette reported a Ni(ClO$_4$)$_2$-catalyzed protocol of synthesizing [6,6,6]-fused tricyclic dihydroquinoline derivatives 1.36 from azomethine imines 1.34 and cyclopropane-1,1-diesters 1.35 (**Scheme 1.12**).[20] The reaction was found to proceed in a stepwise manner beginning with a nucleophilic attack from the negatively charged nitrogen on the cyclopropane, followed by an attack from the malonic enolate at the 2-position of the quinoline forming a 6-membered ring. This transformation gave products in poor to great yields with modest selectivity in favour of the isomer with R$^2$ cis to the junction proton. The reaction tolerated a variety of cyclopropanes 1.35, as well as electron-poor and electron-rich benzoyl substituents on 1.34. The greatest yield (87%) and selectivity (6.6:1) were achieved with N-(4-methoxybenzoyl)iminoquinolinium ylide (R$^1$ = 4-OMe-Ph). The authors also tested the conditions on an isoquinolinium analogue of 1.34 (R$^1$ = Ph) with 2-phenylcyclopropane-1,1-diester and reported a 21% yield of the cis diastereomer and [α]-fused regioisomer.
Scheme 1.13. Reaction generating tricyclic dihydroquinolines from donor-acceptor cyclopropanes and N-benzylliminoquinolinium ylides.

Mattson reported a urea-catalyzed synthesis of 1,2-oxazines 1.39 from a [3+3]-cycloaddition of nitro-cyclopropanes 1.37 with aryl nitrones 1.38 (Scheme 1.14). Ureas were found to be effective at activating the cyclopropanes via hydrogen bonding through the nitro group. 14 examples of oxazines 1.39 were synthesized with generally high yields, and diastereomeric ratios were mostly 2:1 in favour of the isomer with the nitro group cis to R1 and R2. The reaction worked with a variety of aryl substituents on the cyclopropane, however using a vinyl group significantly hindered the reaction giving a 25% yield. Similarly, different aryl groups at both positions of the nitrone were tolerated well. Enantioenriched methyl (1R,2S)-1-nitro-2-phenylcyclopropane-1-carboxylate (89% ee) demonstrated complete transfer of chirality, giving the corresponding product with 91% enantiomeric excess.

Scheme 1.14. [3+3]-cycloaddition of DACs with nitrones generating 1,2-oxazines.

The Kerr group has also done significant work in this area. Recently, it was discovered that cyclopropanes 1.42 (generated in situ from 1,3-diienes 1.41 and ethyl 2-formyldiazoacetate 1.40) underwent a vinylogous Cloke-Wilson rearrangement to 2,5-dihydrooxepins 1.43 if a
cyclic diene or 2-substituted butadienes were used (Scheme 1.15).\textsuperscript{22} Alternatively, if a 1-arylbutadiene was used, a Cloke-Wilson rearrangement happened generating dihydrofurans 1.44. Dihydrooxepins 1.43 could also be converted to dihydrofurans using catalytic Sc(OTf)\textsubscript{3} (5 mol\%) in refluxing DCM. The vinylogous Cloke-Wilson variant was successful in converting 4 dienes to 2,5-dihydrooxepins in modest yields, and the Cloke-Wilson reaction was applied to 6 examples of 1-arylbutadienes in low to modest yields.

![Scheme 1.15. Tandem cyclopropanation/Cloke-Wilson rearrangement and vinylogous variant.](image)

Other examples from the Kerr group include the synthesis of butanolides from cyclopropane hemimalonates;\textsuperscript{23} the one-pot synthesis of pyrroles from cyclopropane diesters and \textit{in situ}-generated nitrones;\textsuperscript{24} and the three-component synthesis of pyrrolidines from aldehydes, amines, and cyclopropane diesters,\textsuperscript{25} among many others.

### 1.6 Reactivity of Indoles

Indole is an electron rich aromatic system that undergoes \textit{S_E}Ar reactions up to 10\textsuperscript{13} times faster than benzene.\textsuperscript{26} These reactions happen preferentially at the C3 position because of the participation of the nitrogen in the resulting \textit{σ}-complex 1.46 (Scheme 1.16), whereas all resonance structures of 1.45 have the positive charge on a carbon. In cases where C3 is blocked prior to a \textit{S_E}Ar reaction, the electrophile will still be added at C3, then the more electron rich C3 substituent will migrate to C2 to restore the aromaticity of the indole.\textsuperscript{27} C2 is the next most reactive site after C3 and is the most acidic site after N1. C2 substitution is typically done by 2-lithiating \textit{N}-protected indoles with LDA or BuLi and quenching with an electrophile.
1.6.1 Ring-Opening Reactions with Indole Nucleophiles

The high reactivity toward $S_{E}$Ar reactions make indoles strong nucleophiles to be used in a wide variety of reactions such as, Michael additions, additions to allenes, and cyclopropane ring-openings. The first successful cyclopropane ring-opening using an indole as a nucleophile was done by Kerr and Harrington in 1997 (Scheme 1.17). The indole systems were shown to be good nucleophiles for opening cyclopropanes under high pressure (13 kbar) in the presence of Yb(OTf)$_3$ as a Lewis acid catalyst. The substrate scope tested was limited but 5 examples of ring-opened adducts were synthesized. The reaction was successful with N-methylated and N-silylated indoles as well as 2-methyl-, 2-phenyl-, and unsubstituted cyclopropane-1,1-diesters.

However, using unprotected indole drastically lowered the yield and produced a substantial amount of by-product (Scheme 1.18). Presumably the by-product forms from an intramolecular attack by a malonic enolate on iminium intermediate 1.51.
1.6.2 Annulation Reactions with Indoles

A follow-up study to the work by Kerr and Harrington from 1997 (and 1999 \[32\]) was done to optimize and test the substrate scope of the by-reaction with unprotected indoles (Scheme 1.19). It was found that this reaction is quite robust for providing 2,3-cyclopentannindolines 1.55 from a variety of skatole derivatives 1.53 and cyclopropane-1,1-diesters 1.54. Yields were all modest to great, and in cases where diastereomers could be formed, the isomer that had R\(^4\) trans to R\(^1\) always predominated to a varying degree. The best yield was obtained using N-methylskatole with cyclopropane 1.54 (R\(^4\) = Ph, R\(^5\) = Et), which gave a total yield of 89%, with a diastereomeric ratio of 8:1. This reaction proved to be among the most facile, proceeding in 6 h at 0°C and 1 atm. The best selectivity was achieved using 1,2-dimethylskatole and a vinylcyclopropane substrate (R\(^4\) = vinyl, R\(^5\) = Et) which only gave a combined yield of 39%, but produced diastereomers in a ratio of 12:1. Some substrates required extreme pressure to attain appreciable yields.

Scheme 1.19. 2,3-Cyclopentannulation of 3-methylindoles.

In the cases where R\(^1\) ≠ H, 2-alkylation adducts 1.57 were formed as by-products with the desired 2,3-cyclopentanoindolines 1.55 (Scheme 1.20). These were formed in small amounts (≤ 5%) via an alkyl shift of ring-opened intermediates 1.56.
Scheme 1.20. Formation of 2-alkylindole 1.57 as a result of an alkyl shift.

In 2011, France reported a method of synthesizing 1,2-annulated indoles 1.59 via an intramolecular tandem cyclopropane ring-opening/Friedel-Crafts alkylation (Scheme 1.21).\[33\] Indoles 1.58 that had pendant cyclopropanes were made in three steps by ⁷-acylation of indoles with methyl malonyl chloride, followed by a Regitz diazo transfer to get an α-diazoester, which could finally be cyclopropanated with a variety of alkenes using Rh₂(esp)₂. The resulting cyclopropanes were then catalytically opened using In(OTf)₃ generating a carbocation that could be easily trapped by attack from the indole. The authors describe this as a stepwise process rather than the typical concerted mechanism of cyclopropane ring-openings. This reaction proved to be quite robust, allowing a large variety of substituents on the cyclopropane including alkyl, aryl, heterocyclic, fusedbicyclic and spirocyclic groups. Yields up to 99\% were achieved, typically with poor to good diastereoselectivity for trans isomers. The trans isomer was exclusively observed using the bulkiest acyclic substrate (R² = TBDPS).

Scheme 1.21. Intramolecular tandem cyclopropane ring-opening/Friedel-Crafts alkylation.

Some donor-acceptor cyclopropanes can dimerize to form larger rings. Ivanova reported that 2-(3-indolyl)cyclopropane-1,1-diesters 1.60 reacted with themselves to form a [5,5]-fused ring systems 1.61 using a super stoichiometric amount of SnCl₄ in nitromethane (Scheme 1.22).\[34\] The reactions formed only one isomer in yields of 57-75\%. The reaction was tolerated well by substrates with electron-withdrawing groups at the 5-position of the indole and alkyl
substituents at the 1-position. Substituting the indole at the 2-position caused the reaction to fail outright. Likewise, an electron-withdrawing tosyl group on the nitrogen prevented the reaction from proceeding. These are both expected outcomes as blocking the 2-position increases steric hindrance and N-substituting indoles with electron-withdrawing groups make the C3 position significantly less electron-rich, and therefore less nucleophilic.

Scheme 1.22. Tandem cyclodimerization of 2-(3-indolyl)cyclopropane-1,1-diesters.

1.7 Cyclopropane Ring-Opening Reactions in Total Syntheses

Cyclopropane ring-opening reactions are popular tools in total syntheses, in part due to the stereochemical control they can impart on reactions. Jung used a donor acceptor-cyclopropane ring-opening reaction of 1.62 to form bicyclic intermediate 1.63 in the synthesis of (+)-Fawcettimine (Scheme 1.23), an alkaloid isolated from club grass of the genus *Lycopodium*.\(^{[35]}\) One step of this synthesis was the first reported intramolecular nucleophilic ring-opening of a cyclopropane by an enol ether. Using a catalytic amount of Sc(OTf)\(_3\) the reaction went smoothly in 77% yield and gave only one regioisomer due to the stereospecific nature of S\(_{N}\)2-type reactions.

Scheme 1.23. Ring-opening step in the synthesis of (+)-Fawcettimine.
Another example of a cyclopropane ring-opening being used in total synthesis is Pagenkopf’s synthesis of aspidosperma alkaloid, (±)-goniomitine (Scheme 1.24).[^36] The key step of this synthesis was the one-pot ring-opening of 1.64 with TMSOTf followed by attack from a heavily substituted nitrile on the oxocarbenium ion. The nitrilium intermediate 1.65 then cyclized to a dihydroindole, and upon aromatization gave tetrahydroindole 1.66 in 74% yield.

![Scheme 1.24. Pagenkopf’s total synthesis of (±)-goniomitine.](image)

Ring-opening reactions of cyclopropanes have also been employed by the Kerr group for the total syntheses of a multitude of natural products, such as (−)-allosecurinine,[^37] FR901483,[^38] and (+)-isatisine[^39] (Scheme 1.25). (−)-Allosecurinine was made in 15 synthetic steps in an overall yield of 5%. A key ring-forming step in this synthesis was cycloaddition of cyclopropane 1.67 with aldehyde 1.68 under Lewis acidic conditions to give bicyclic intermediate 1.69. The total synthesis of FR901483 was achieved using a convergent synthetic pathway. The most important step in the synthesis was the intramolecular ring-opening of spirocyclic cyclopropane 1.70 to form the [6,6,5]-fused tricyclic framework of 1.71. This step was accomplished by first condensing the amine of 1.70 with paraformaldehyde to form an imine. The imine nitrogen then opened the cyclopropane, and the resulting carbanion attacked the iminium ion to form the 5-membered ring. (+)-Isatisine was synthesized in 14-steps from homochiral cyclopropane 1.73 and protected indole 1.72 with an overall yield of 6%. The first step of this synthesis was the cycloaddition of the aldehyde of 1.72 with the cyclopropane. This
produced adduct 1.74 as a pair of inseparable diastereomers, but they were resolved in a later step.

Scheme 1.25. Total syntheses of (−)-allosecurinine, FR901483, and (+)-isatisine accomplished in the Kerr group.

1.8 Conia-ene Chemistry

1.8.1 Alder-ene and Thermal Conia-ene Reaction

The Alder-ene reaction is a classic reaction involving the allylic hydrogen of an alkene 1.75 and an enophile 1.76, which are typically carbonyls, imines, or activated alkenes such as benzylidene malonates (Scheme 1.26). These reactions typically require heat and/or Lewis acid catalysts. Ene reactions are also commonly used for annulations if they are done intramolecularly.
A modification of the Alder-ene reaction called the Conia-ene reaction was developed in the 1970s by its namesake.\textsuperscript{[41]} The original thermal form of the Conia-ene reaction is an annulation reaction of an enol 1.77 with a pendant alkene or alkyne. The reaction is typically used to form 5- and 6-membered rings 1.78 with exocyclic methyl (from alkenes) or methylene (from alkynes) groups.

**Scheme 1.26.** General examples of the Alder-ene reaction.

**Scheme 1.27.** General thermal Conia-ene reaction.

### 1.8.2 Catalytic Conia-ene Chemistry

The major downside of the thermal Conia-ene reaction is that the very high temperature required is not compatible with a variety of organic functional groups. For this reason, much work has been done to develop milder conditions for similar reactions to work. The catalytic Conia-ene reaction uses a Lewis acid to promote the cyclization rather than extreme heat. Although some heating and a base are commonly used to get the reaction to proceed more quickly and with higher yields. Conia-ene type reactions can be promoted by a great number of Lewis acids, and the mode of activation depends on the metal chosen (Figure 1.2). Nakamura has proposed five mechanisms of Lewis-acid binding.\textsuperscript{[42]} Hard metals such as sodium, tin, and lithium are oxophilic and can bind the ester moieties of the substrate to hold the molecule in an enolate configuration (Figure 1.2A). Soft metals like gold, silver, and platinum can bind the soft $\pi$-electrons of the multiple bond moiety causing it to be more susceptible to attack by the enol (Figure 1.2B). Some metals of intermediate hardness like
nickel and rhenium will bind to the multiple-bond and the enol π-electrons (Figure 1.2C). Other moderately hard metals like zinc and copper bind the multiple-bond and the carbonyl(s) (Figure 1.2D). Alternatively, this double activation at the carbonyl(s) and the alkyne can also be done using two discrete metals – one hard and one soft (Figure 1.2E).

**Figure 1.2.** Nakamura’s five proposed mechanisms for the activation of Conia-ene substrates by Lewis acids.

The catalytic Conia-ene reaction is most used with alkynes rather than alkenes as the reactions with alkenes produce less useful alkyl functional groups compared to the alkenyl groups produced by reactions with alkynes. Additionally, terminal alkyne substrates are often more practical than internal alkynes as typically only one product is formed. Substrate 1.79 for example could in theory undergo 2 different cyclizations (Scheme 1.28). A 6-endo-dig cyclization would result in 1.81 and a 5-exo-dig cyclization would result in 1.80. According to Baldwin’s rules these are both favoured cyclizations, but the 5-exo-dig is almost exclusively observed from reactions using alkynes. The regioselectivity comes from the transition state of the 5-exo-dig cyclization being better stabilized as it has a “tertiary” δ+ charge compared to the “secondary” δ+ charge of the transition state of the 6-endo-dig cyclization. This preference for exo-cyclization extends to larger ring sizes, but 4-exo-dig transformations are disfavoured so 5-endo-dig is preferred. Using an internal alkyne for this transformation will often result in a mixture of 5-exo-dig and 6-endo-dig products (or preference for 6-endo-dig) depending on the steric and electronic effects of the other group on the alkyne.[43]
1.8.3 Exo-dig Conia-ene Cyclizations Generating Carbocycles

An early example of the catalytic Conia-ene reaction is from research published by Toste (Scheme 1.29). It was found that a combination of (PPh$_3$)AuCl and AgOTf in small catalyst loadings could promote the cyclization of ω-ethynyl-β-ketoesters 1.82 to cyclopentanes 1.83 with exocyclic alkenes. The reaction worked in very high yields for a large variety of substrates. In cases where R$^1$ and R$^2$ are joined in a ring, only cis-fused bicyclic systems were produced. Ketoesters substituted at the β-, γ-, or δ-positions generated a mixture of diastereomers with a preference for the substituent being cis relative to the ester group. The diastereoselectivity was the highest for the β-ethyl ketoester substrate (R$^2$ = Et) with a $dr$ of 17:1. The $dr$ was reduced to 4.2:1 for the β-phenyl ketoester substrate (R$^2$ = Ph), 4:1 for the γ-benzyl ketoester substrate (R$^4$ = Bn), and 2.9:1 for the δ-propyl ketoester substrate (R$^5$ = nPr).

The Conia-ene reaction is also useful for forming rings larger than 6 carbons. Nakamura
developed a method of synthesizing rings of 6 or more carbons using In(NTf₂)₂ as a catalyst (Scheme 1.30).\textsuperscript{[45]} In their initial study of ring sizes, they found the reaction to proceed with high yields when forming 6- and 7-membered rings, moderate yield for 8-membered rings, and low yield for 9-membered rings. The expected product 1.85 was never isolated due to the isomerization to 1.86 and 1.87. For the 6-membered rings only the enone product 1.86 was observed. 7-membered rings were observed as a mixture of enone (1.86) and enol (1.87) tautomers, and larger rings were only observed in the enol form (1.87). Using carefully chosen substrates they were able to form some 8-, 9-, and 10-membered rings in yields of 74-89%. Products 1.88 and 1.89 were formed as a mixture, with the fully conjugated isomer 1.89 predominating. Biphenyl substrates gave enols 1.90.

\begin{center}
\begin{tikzpicture}
\node[draw, shape=rectangle, rounded corners] (a) at (0,0) {\includegraphics[width=\textwidth]{diagram.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.30.} Formation of larger carbocycles using Conia-ene chemistry.

1.8.4 \textit{Exo-dig} Conia-ene Cyclizations Generating Heterocycles

In addition to carbocycles, catalytic Conia-ene chemistry has been successfully used to make new heterocyclic structures. Nakamura used In(OTf)₃ and DBU to produce heterocycles 1.92 from alkynes 1.91 (Scheme 1.31). The reactions gave generally high yields for the synthesis of lactams, pyrrolidines, piperidines, and tetrahydrofurans.
Scheme 1.31. Synthesis of nitrogen and oxygen heterocycles using Conia-ene reaction.

The authors then used these conditions to form the pyrroldinone ring of salinosporamide A (Scheme 1.32). This step of the total synthesis converted alkyne 1.93 to pyrrolidinone 1.94 in 96% yield with complete retention of stereochemistry.

Scheme 1.32. Conia-ene step in the total synthesis of salinosporamide A.

1.8.5 Tandem Conia-ene Chemistry

The catalytic Conia-ene reaction has been used in a variety of tandem processes, especially with other reactions that require Lewis acid catalysts like Michael-additions and cyclopropane ring-openings. Nakamura reported a tandem Michael-addition/Conia-ene protocol for the synthesis of tetrahydrofurans 1.96 from propargyl alcohol and activated alkenes 1.95 (Scheme 1.33).[^46] The reaction was conducted neat with 20 mol% Zn(OTf)₂ and triethylamine. Yields were consistently high for a variety of benzylidene and alkylidene malonates. When E and Z isomers of an unsymmetrical β-ketoester were used as substrates, a mixture of diastereomers

was produced (2:1 in favour of the isomer with R\textsuperscript{3} trans to the ester group). The ratio of isomers was identical whether starting with an E or Z alkene, suggesting that the initial 1,4-addition step is reversible.

\[ \text{HO}=\text{CH}^\downarrow_{\text{trans}} \text{O} \text{Zn(OTf)}_2/\text{Et}_3\text{N} \text{ (20 mol\%)} \rightarrow \text{neat, r.t.} \]

**Scheme 1.33.** Synthesis of tetrahydropyrans from propargyl alcohol and activated olefins.

Kerr reported similar work synthesizing piperidines from N-benzylpropargylamines 1.98 and donor-acceptor cyclopropanes 1.97 (Scheme 1.34).

The reaction proceeded by a nucleophilic ring-opening by the amine followed by a Conia-ene cyclization to give piperidine 1.99. Optimization led to conditions of 10 mol\% Zn(NTf\textsubscript{2})\textsubscript{2} in refluxing benzene. Sc(OTf\textsubscript{3}) was also a suitable catalyst, but In(OTf\textsubscript{3}) failed to promote the reaction. Yields were generally very high; most were at least 90\%. The reaction was somewhat hindered using dimethyl methylcyclopropane-1,1-diester (R\textsuperscript{1} = Me) and the parent dimethyl cyclopropane-1,1-diester (R\textsuperscript{1} = H). The (2-furyl)-bearing product demonstrated decomposition; this was alleviated by the addition of more catalyst and some amine. The authors then demonstrated the stereochemical outcomes of this reaction using 2-methyl-N-benzylpropargylamine (R\textsuperscript{2} = Me). Racemic starting materials gave an equal distribution of all 4 stereoisomers (RR,SS,SR,RS). Using enantiomerically pure substrates gave a single diastereomer (>97\% purity), with ee of 95-95\%. The chiral centre of the propargylamine was retained through the reaction, and the chiral centre of the cyclopropane was inverted.
Scheme 1.34. Tandem ring-opening/Conia-ene procedures for the synthesis of piperidines.

The Kerr group then investigated the analogous transformation with propargyl alcohol to produce tetrahydropyrans 1.102 using a tandem cyclopropane ring-opening/Conia-ene protocol (Scheme 1.35).[48] Like in the previous work, this reaction involves the opening of cyclopropanes 1.100 with propargyl alcohols 1.101 followed by a Conia-ene cyclization to the final THP product. This reaction was done with 2 slightly different sets of conditions. Conditions A were 20 mol% In(OTf)$_3$ with 10 mol% $N,N$-dimethylaniline in refluxing toluene. Conditions B were 20 mol% In(OTf)$_3$ in toluene at room temperature followed by a separate addition of 3 equivalents of ZnBr$_2$ and an equivalent of triethylamine. Conditions A gave good yields with a limited scope, as the substrates required electron-withdrawing aryl substituents. Conditions B gave equal or better yields for a larger variety of cyclopropanes. In the case of $R^1 = H$, a yield of only 27% was obtained, which is somewhat expected as the parent cyclopropane-1,1-diester is typically a poor DAC due to its lack of donor group. Using a single enantiomer of the cyclopropane gave a product with ee of 97% for $R^1 = Ph$, and 98% for $R^1 = 4$-Cl-Ph. When the reaction was tested with racemic 3-butyn-2-ol ($R^2 = Me$) and racemic dimethyl 2-phenyl-1,1-cyclopropanediester a 1:1 mixture of cis and trans tetrahydropyrans was generated.
Scheme 1.35. One-pot ring-opening/Conia-ene procedures for the synthesis of THPs.

Kerr has also described the synthesis of tetrahydrocarbazoles 1.105 via a tandem cyclopropane ring-opening/Conia-ene reaction using 2-ethynyl indoles 1.104 as nucleophiles (Scheme 1.36). The optimized conditions of this reaction were 5 mol% Zn(NTf₂)₂ in refluxing DCE. A non-tandem process of 10 mol% Sc(OTf)₃ followed by 3 equivalents of ZnBr₂ and one equivalent of triethylamine was also found to promote the reaction, but with less efficiency. The tandem process gave high yields using N-methylindoles (R² = Me) and donor-acceptor cyclopropanes 1.103 with aryl substituents. The yields were harmed by using unprotected indole substrates (R² = Me) and the parent cyclopropane-1,1-diester substrate (R¹ = H). Interestingly, N-methylindoles with electron withdrawing substituents at the 6-position produced the largest yields (R³ = CF₃, 93%; CO₂Me, 92%). The reaction was then tested with internal alkyne substrates, and it failed to produce any Conia-ene products. Rather, the ring-opened adducts were isolated in good yields (72-97%). A deuterium labelling study was conducted to demonstrate the mechanism of this transformation. It was found that a deuterated alkyne produces an alkene with the deuterium proximal to the nitrogen of the indole and the proton proximal to the esters. This suggests that the zinc binds both the esters and the alkyne during the Conia-ene step. This is consistent with the behaviour of zinc reported by Nakamura.
Scheme 1.36. Tandem cyclopropane ring-opening/Conia-ene reaction using indoles as nucleophiles.

1.9 Scope of Thesis

The previous success of using 2-ethynyl indoles in tandem ring-opening/Conia-ene reactions inspired the investigation of similar chemistry with different ethynylindoles (Scheme 1.37). This thesis will primarily focus on the reactions of 4-ethynylindoles 1.106 with donor-acceptor cyclopropanes 1.107 or Michael-acceptors 1.109 which generate 3,4-annulated indoles 1.108 and 1.110 via tandem Conia-ene cyclizations. Included herein are optimizations, and substrate scopes of both tandem reactions.

Scheme 1.37. Tandem Michael addition/Conia-ene and ring-opening/Conia-ene reactions.
2 Results and Discussion

2.1 Tandem Cyclopropane Ring-opening/Conia-ene Methodology

In previously published work Kerr outlined the synthesis of tetrahydrocarbazoles via a tandem cyclopropane ring-opening/Conia-ene reaction with 2-ethynyl indoles as nucleophiles. Based on this work,[49] and other research done on tandem ring-opening/Conia-ene processes,[47,48] it was imagined that moving the alkyne group around the indole frame would give different annulated indoles. For example, 4-ethynylindoles 2.1 would produce 3,4-cycloheptannulated indoles 2.4. Additionally, replacing a cyclopropane 2.2 with a Michael acceptor 2.5 would give rings one carbon smaller (2.7) (Scheme 2.1).

Scheme 2.1. Hypothesized tandem ring-opening/Conia-ene transformations.

2.1.1 Model Substrates

To begin testing our hypothesis, model substrates needed to be chosen. Dimethyl phenylcyclopropane-1,1-diester 2.2a was selected as it is known to be a reliable substrate from previous research in the Kerr group,[49,50] and was easily available in a single step by cyclopropanating styrene with dimethyl diazomalonate and catalytic Rh$_2$(esp)$_2$. Unprotected 4-ethynylindole 2.1b and its N-methyl derivative 2.1a were both considered as model substrates. Since neither of them are commercially available, they needed to be synthesized. The first attempted synthetic pathway was to make 4-bromoindole using a Fischer indole synthesis from $m$-bromoaniline followed by a Sonogashira coupling with
trimethylsilylacetylene. Then the trimethylsilyl (TMS) group would have been removed with a fluoride source such as tetrabutylammonium fluoride (Scheme 2.2).

![Diagram of retrosynthetic pathway to 4-ethynylindoles.]

Scheme 2.2. Retrosynthetic pathway to 4-ethynylindoles.

3-Bromophenylhydrazine 2.10 was made in 60% yield from 3-bromoaniline 2.11 by diazotization with NaNO₂ and HCl, followed by reduction with SnCl₂. The subsequent indole forming step was unsuccessful, likely due to an impure source of acetaldehyde. In hindsight the reaction was not ideal, as an inconvenient mixture of 4-bromoindole and 6-bromoindole would likely be formed. Luckily, 4-bromoindole 2.9 was found from a niche retailer, so the Sonogashira step could be tested. Multiple attempts were made with TMS-acetylene, Pd(PPh₃)₄, triethylamine, and CuI or CuCN at various temperatures, but in all cases starting material was recovered with moderate decomposition and no signs of alkynylindole 2.8 in the ¹H NMR spectrum. A likely issue with this reaction was the lower reactivity of arylbromides compared to aryliodides and aryltriflates. Neither of these alternatives were readily available, so a different synthetic route was sought.

The next plan for synthesizing 4-ethynylindoles was to use the Corey-Fuchs reaction on 4-formylindoles. 4-Formylindole is commercially available but was prohibitively expensive at the time this project began, so it needed to be made as well. By combining the procedures of two literature syntheses, 4-ethyl-1-methylindole 2.1a was made in 5 steps from 4-cyanoindole 2.10 (Scheme 2.3). 4-Cyanoindole was N-methylated with NaH and MeI in 67% yield. The resulting N-protected cyanoindole 2.12 was reduced with DIBAL to give 4-formyl-1-methylindole 2.13 in quantitative yield. Formylindole 2.13 was treated with 3 equivalents of
CB\textsubscript{4} and 6 equivalents of PPh\textsubscript{3} in THF to produce (2,2-dibromo)ethenylindole 2.14 in 83\% yield. The dibromoalkene was then treated with BuLi to give the desired 4-ethynyl-1-methylindole in 83\% yield. Fortunately, during the course of this project 4-formylindole 2.12 became affordable from Oakwood chemicals. This eliminated the need for the DIBAL reduction step of the synthesis, but the indole still needed methylating to be compatible with the highly basic BuLi used in the final step.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {2.10};
\node (b) at (2,0) {2.12};
\node (c) at (4,0) {2.13a};
\node (d) at (0,-2) {2.14};
\node (e) at (2,-2) {2.1a};
\node (f) at (1,-1) {NaH, Mol}
\node (g) at (1,-1.5) {THF, 0\degree C}
\node (h) at (1,-2) {67\%}
\node (i) at (3,-1) {DIBAL-H}
\node (j) at (3,-1.5) {THF, -78\degree C}
\node (k) at (3,-2) {quant.}
\node (l) at (0,-3) {PPh\textsubscript{3}, CBr\textsubscript{4}}
\node (m) at (0,-3.5) {THF, -20\degree C}
\node (n) at (0,-4) {83\%}
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.3.} First successful synthesis of 4-ethynyl-1-methylindole.

2.1.2 Initial Testing

With model substrates in hand, the desired reactivity could be probed. The logical starting point was to test the optimized conditions used for the synthesis of tetrahydrocarbazoles from 2-ethynylindoles.\textsuperscript{[49]} The conditions used were 5 mol\% Zn(NTf\textsubscript{2})\textsubscript{2} in refluxing 1,2-dichloroethane, with 0.4 equivalents excess of indole 2.1a (\textbf{Scheme 2.4}). The reaction was monitored via TLC until the complete consumption of cyclopropane 2.2a after 1 day. These conditions immediately produced positive results. Conia-ene cyclization product 2.4a was not produced, however the ring-opened intermediate 2.3a was obtained in 52\% isolated yield with some unidentified impurities.
Scheme 2.4. Initial attempt to synthesize 3,4-cycloheptanooindole 2.4aa.

The production of the intermediate was evidenced by the $^1$H NMR spectrum (Figure 2.1). There was a singlet at 3.33 ppm, indicative of a terminal alkyne, and a 4-proton spin system (2.70, 3.52, 5.17 ppm) that corresponded to the new alkyl chain. The triplet at 5.17 ppm could be justified as the methine proton proximal to the electron-withdrawing indole and phenyl moieties. Additionally, there were no singlets (or small $J$-value doublets) at approximately 5-6 ppm to indicate the alkene protons that would be expected from the Conia-ene cyclization.

Figure 2.1. 400 MHz $^1$H NMR (CDCl$_3$) spectrum of ring-opened intermediate 2.3a.

This intermediate was treated with a variety of different Lewis acids to promote the Conia-ene cyclization step. For the first attempt, conditions from work published by Toste were tested (Scheme 2.5). The ring-opened intermediate 2.3a (0.12 mmol) was dissolved in DCM (0.3 mL) in a pressure tube and to it was added PPh$_3$AuNTf$_2$ (1 mg, 1 mol %). The mixture was stirred under argon in the dark for 16 hours, with TLC monitoring. No reaction was observed in 16 hours, so the starting material was repurified and used again.
**Scheme 2.5.** First attempted Conia-ene cyclization of ring-opened adduct 2.3a.

The second attempt was made using another set of Toste’s conditions (Scheme 2.6).[44] The ring-opened intermediate 2.3a was dissolved in DCM (0.2 mL) and to it was added Ph₃PAuCl (2 mg, 5 mol %) and AgOTf (1 mg, 5 mol %). This was stirred at room temperature and monitored via TLC, however after 16 hours, again no Conia-ene product 2.4a formed. These negative results indicated that soft metals like silver and gold were likely not suitable for the desired transformation.

**Scheme 2.6.** Second attempted Conia-ene cyclization of 2.3a.

The next attempt was to use 2 equivalents of ZnBr₂ for the Lewis acid (Scheme 2.7) as has been previously done in the Kerr group for Conia-ene reactions.[49] The ring-opened product 2.3a (0.13 mmol) was put in a pressure tube and to it was added DCE (0.45 mL) and ZnBr₂ (0.26 mmol). The reaction mixture was sealed under argon and heated to 90°C until the starting material 2.3a was determined to be used up via TLC. The material was separated and purified by flash chromatography (40% EtOAc in hexanes) and analyzed via ¹H NMR (Figure 2.2). Gratifyingly, the desired Conia-ene cyclization product 2.4aa was confirmed to have been synthesized.
Scheme 2.7. Third attempted Conia-ene cyclization of 2.3a.

This determination was made based on the presence of 2 singlets at 5.18 and 5.55 ppm which are in the typical range of terminal alkene protons. The characterization was further supported by the disappearance of the alkyne peak at 3.33 ppm and the 4-proton spin system was replaced by a 3-proton spin system of peaks at 4.43, 2.95, and 2.75 ppm. High-resolution mass spectrometry (Electrospray Ionization) was used to verify the molecular weight.

Figure 2.2. 400 MHz 1H NMR spectrum of Conia-ene cyclization product 2.4aa.

With a Lewis acid capable of promoting this Conia-ene reaction, it was thought that ZnBr$_2$ might also promote the ring-opening step thereby making the overall process from 4-ethynyl-1-methylindole to 3,4-annulated indoles a tandem reaction (Scheme 2.8). To attempt the reaction, a pressure tube was charged with a stir bar and to it was added 4-ethynyl-1-methylindole 2.1a (0.32 mmol), cyclopropane 2.2a (0.23 mmol), DCE (0.6 mL), and ZnBr$_2$ (0.46 mmol). The reaction was sealed under argon and heated to 90°C overnight. The mixture was separated and purified via flash chromatography (40% EtOAc in hexanes) and analyzed by $^1$H NMR. The NMR spectrum of the product matched that from the 2-step process, therefore
it was concluded that ZnBr$_2$ was suitable to promote the desired tandem ring-opening/Conia-ene reaction.

**Scheme 2.8.** Attempted tandem ring-opening/Conia-ene reaction with ZnBr$_2$.

2.1.3 Tandem Ring-opening/Conia-ene Optimization

With preliminary conditions in hand, it was then necessary to optimize the reaction conditions to attain good yields for an eventual substrate scope. The data for the optimization reactions are reported in Table 2.1. All tests were conducted based on 50 mg of cyclopropane 2.2a. The optimal conditions were chosen to be 2 equivalents of ZnBr$_2$ and 1 equivalent of 2,6-lutidine in refluxing benzene for 22 hours (Entry 12). Ambient temperature proved to be too low to promote the Conia-ene step (Entries 2,3,6), and 60 °C gave poor yield (Entry 4). Adding triethylamine significantly improved yield (Entry 5), presumably by stabilizing the malonate intermediate. The reaction was attempted for a shorter time, but it did not reach completion (Entry 7). A catalytic amount of ScOTf$_3$ was tried as a replacement for ZnBr$_2$, which furnished the Conia-ene product with poor efficiency (Entry 8). Replacing triethylamine with DBU (Entry 9) had a negative impact on the yield, but 2,6-lutidine (Entry 10) substantially improved it. Benzene was shown to be a marginally more suitable solvent than DCE (Entry 11). Lastly, the most effective solvent and base were combined to give a marginally better yield (Entry 12).
Table 2.1. Optimization data for tandem ring-opening/Conia-ene reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Lewis Acid</th>
<th>Base (1 eq.)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield 2.4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>none</td>
<td>90</td>
<td>22</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>none</td>
<td>rt</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>none</td>
<td>rt</td>
<td>94</td>
<td>2.3aa</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>none</td>
<td>60</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>Et$_3$N</td>
<td>90</td>
<td>22</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>Et$_3$N</td>
<td>rt</td>
<td>22</td>
<td>2.3aa</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>Et$_3$N</td>
<td>90</td>
<td>6</td>
<td>Incomplete</td>
</tr>
<tr>
<td>8</td>
<td>DCE</td>
<td>20 mol % Et$_3$N</td>
<td>90</td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>DBU</td>
<td>90</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>DCE</td>
<td>2 eq. ZnBr$_2$</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>benzene</td>
<td>2 eq. ZnBr$_2$</td>
<td>Et$_3$N</td>
<td>90</td>
<td>22</td>
<td>74</td>
</tr>
<tr>
<td>12</td>
<td>benzene</td>
<td>2 eq. ZnBr$_2$</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>82</td>
</tr>
</tbody>
</table>

2.1.4 Synthesis of Substrates

The original pathway to 4-ethynyl-1-methylindole was successful but could not be expanded to differently $N$-protected indoles. Additionally, the process produced 6 equivalents of triphenylphosphine oxide which is both extraordinarily wasteful and labourious to remove. An alternate pathway was sought out. The Seyferth-Gilbert homologation using the Ohira-Bestmann reagent proved to be a simple and comparatively atom-economical alternative for
the synthesis of the desired 4-ethynylindoles 2.1 (Scheme 2.9).\textsuperscript{[56–58]} 4-Ethynyl-1-methylindole 2.1a and unprotected 4-ethynylindole 2.1b were both made in 75% yields and 95% conversions after 5 days at room temperature. In the case of 4-ethynyl-1-methylindole, 4-formylindole 2.13b was first methylated to 2.13a with NaH and MeI. This synthetic route was used for the remainder of the project.

Scheme 2.9. Synthesis of 4-ethynylindoles with the Ohira-Bestmann reagent.

Most cyclopropane substrates were made by Knoevenagel condensations of arylaldehydes 2.15 followed by Corey-Chaykovsky cyclopropanation (Scheme 2.10).\textsuperscript{[59]} This pathway was chosen over directly cyclopropanating styrene with Rh\textsubscript{2}(esp)\textsubscript{2} because the benzylidene malonate intermediates themselves were recognized as potential substrates to make 3,4-cyclohexannoindoles. Knoevenagel products 2.5 were made in yields of 70-80% and cyclopropanes 2.2 were produced in yields of 40-80%.

Scheme 2.10. Synthesis of benzylidene malonate and cyclopropane substrates.

4-Ethynyl-1,2-dimethylindole was made in 6 steps from 4-formylindole (Scheme 2.11). First the indole was protected with benzenesulfonyl chloride (2.16), in 81% yield. Initially, a protection was attempted with toluenesulfonyl chloride, but the yield was very poor. The aldehyde was then protected by conversion to acetal 2.17 with propanediol and catalytic 4-toluenesulfonic acid in 81% yield. The indole was then methylated at the 2-position by lithiation with LDA followed by quenching with methyl iodide. Early attempts at this step used 1.05 equivalents of LDA and 1.1 equivalents of methyl iodide. This gave mediocre conversions
on the order of 60%, and the methylated product 2.18 was inseparable from the starting material 2.17, so higher equivalents were subsequently used. 80% conversion was achieved by using 1.4 equivalents of LDA and 1.65 equivalents of methyl iodide. 4.5 equivalents of LDA and 10 equivalents of methyl iodide were needed to obtain a conversion of 94% and a yield of 91%. Then methylated species 2.18 was doubly deprotected in one pot to give 2.19 in 70% yield. This was done using KOH in refluxing EtOH to remove the sulfonyl protecting group, and presumably upon acidifying the resulting benzenesulfonic acid rapidly hydrolysed the acetal to an aldehyde. Fortunately, at this point the small amount of unmethylated material could be removed via flash chromatography. Indole 2.19 was then N-methylated using NaH and MeI giving 2.20 in 69% yield, and finally a Seyferth-Gilbert homologation gave 4-ethynyl-1,2-dimethylindole 2.1c in 78% yield.

Scheme 2.11. Synthetic pathway for the synthesis of 4-ethynyl-1,2-dimethylindole.

2.1.5 Tandem Ring-Opening/Conia-ene Substrate Scope

With optimized conditions and starting materials in hand, a substrate scope could be tested. The results are tabulated in Table 2.2. It was found that the reaction conditions furnished a wide variety of 3,4-cycloheptannulated indoles from unprotected 4-ethynylindole 2.1b and 4-ethynyl-1-methylindole 2.1a. Yields were consistently higher using 4-ethynyl-1-methylindole 2.1a. The higher yields can likely be attributed to 2 factors. The first is that N-methylindole is more electron rich, and therefore more nucleophilic than unprotected indole. The second factor is that the unprotected indole 2.1b can undergo a 1-alkylation side reaction. The difference in yields generated from 4-ethynyl-1-methylindole and 4-ethynylindole varied from marginal (2.4aa vs. 2.4ba) to substantial (2.4aj vs. 2.4bj). The highest yields of Conia-ene products
were those with electron rich aryl substrates such as phenylcyclopropane 2.2a, 4-methoxyphenylcyclopropane 2.2b, and (2-furyl)cyclopropane 2.2g. Electron deficient aryl substituents (2.4ac and 2.4ad) were also tolerated well. However, 4-cyanophenyl-bearing product 2.4ae was produced with substantially lower efficiency. Heterocyclic compounds 2.4af, 2.4ah, and 2.4ai were synthesized in yields comparable to the model 2.4aa. Styryl substrate 2.2j performed well with methylated indole, but vinyl substrate 2.2k did not. In fact, product 2.2ak experienced rapid decomposition, therefore a clean mass spectrum could not be obtained. 4-Ethynyl-1,2-dimethylindole 2.1c produced the corresponding product 2.4ca in 70% yield. It was thought that the extra methyl group of 2.1c might have further increased the nucleophilicity of the indole and produce a higher yield than model substrate 2.1a. The marginally lower yield of 2.4ca compared to model 2.4aa is likely due to some steric clash between its methyl and phenyl groups.

Table 2.2. Tandem cyclopropane ring-opening/Conia-ene substrate scope.

<table>
<thead>
<tr>
<th>Product</th>
<th>Structure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4aa</td>
<td><img src="image1.png" alt="Image" /></td>
<td>(86%)</td>
</tr>
<tr>
<td>2.4ab</td>
<td><img src="image2.png" alt="Image" /></td>
<td>(82%)</td>
</tr>
<tr>
<td>2.4ac</td>
<td><img src="image3.png" alt="Image" /></td>
<td>(75%)</td>
</tr>
<tr>
<td>2.4ad</td>
<td><img src="image4.png" alt="Image" /></td>
<td>(72%)</td>
</tr>
<tr>
<td>2.4ae</td>
<td><img src="image5.png" alt="Image" /></td>
<td>(38%)</td>
</tr>
<tr>
<td>2.4af</td>
<td><img src="image6.png" alt="Image" /></td>
<td>(72%)</td>
</tr>
<tr>
<td>2.4ag</td>
<td><img src="image7.png" alt="Image" /></td>
<td>(88%)</td>
</tr>
<tr>
<td>2.4ah</td>
<td><img src="image8.png" alt="Image" /></td>
<td>(72%)</td>
</tr>
<tr>
<td>2.4ai</td>
<td><img src="image9.png" alt="Image" /></td>
<td>(73%)</td>
</tr>
<tr>
<td>2.4aj</td>
<td><img src="image10.png" alt="Image" /></td>
<td>(67%)</td>
</tr>
<tr>
<td>2.4ak</td>
<td><img src="image11.png" alt="Image" /></td>
<td>(38%)</td>
</tr>
<tr>
<td>2.4al</td>
<td><img src="image12.png" alt="Image" /></td>
<td>(58%)</td>
</tr>
<tr>
<td>2.4bj</td>
<td><img src="image13.png" alt="Image" /></td>
<td>(38%)</td>
</tr>
<tr>
<td>2.4bk</td>
<td><img src="image14.png" alt="Image" /></td>
<td>(22%)</td>
</tr>
<tr>
<td>2.4ca</td>
<td><img src="image15.png" alt="Image" /></td>
<td>(70%)</td>
</tr>
</tbody>
</table>
2.2 Tandem Michael Addition/Conia-ene Methodology

2.2.1 Initial Testing

With the success of the methodology for the synthesis of 3,4-cycloheptannulated indoles 2.4, it was imagined that the same strategy could be applied to produce 3,4-cyclohexannulated indoles 2.7 if the cyclopropanes were replaced with Michael acceptors. The logical starting point for this phase of the project was to try the same conditions as previous (Scheme 2.12). Using 2 equivalents of ZnBr$_2$, 1 equivalent of 2,6-lutidine, and excess indole in refluxing benzene for a day gave the desired Conia-ene product 2.7aa in 6% yield.

Scheme 2.12. Initial attempted synthesis of 3,4-cyclohexannoindole 2.7aa.

The synthesis of 2.7aa was confirmed by diagnostic singlets at 5.21, 5.79, 6.23, and 6.78 ppm in the $^1$H NMR spectrum (Figure 2.3). These signals were not assigned to specific protons, however 3 of their shifts agreed with those of a 2-indolyl proton and exocyclic methylene protons. The final proton shift could be justified by proximity to a phenyl group, indole moiety and a malonic ester. In contrast to the spectrum of 3,4-cycloheptannulated indole 2.4aa (Figure 2.2), there was no alkyl spin system due to the lack of methylene linker between the benzylic and malonic carbons. High-resolution mass spectrometry (electrospray ionization) was used to verify the molecular weight of 2.7aa.
Figure 2.3. 400 MHz $^1$H NMR (CDCl$_3$) spectrum of Conia-ene cyclization product 2.7aa.

With a proof of concept, the reaction conditions were tuned to improve yields. The results are reported in Table 2.3. After many iterations, the optimized conditions were determined to be 3 equivalents of benzylidene malonate, 3 equivalents of ZnI$_2$, and 2 equivalents of 2,6-lutidine in 1,4-dioxane at 75 °C for 22 h (Entry 23). All tests were conducted using 50 mg of the limiting reagent. From the optimization trials it was found that ZnI$_2$ was the only reasonable Lewis acid for this reaction. A variety of triflate and bistriflimide salts were screened for this transformation (Entries 3-7, 15). In all cases starting material was recovered with no sign of Michael adduct or Conia-ene product. ZnCl$_2$ also failed to promote any reaction (Entry 14).

Many solvents were tested, and it was found that 1,4-dioxane was the most suitable (Entry 13), and benzene could be a reasonable alternative (Entry 10). Acetonitrile (Entry 8) and toluene (Entry 11) gave very low yields with substantial decomposition. Only starting material was recovered using 1,2-dichloroethane (Entry 9), and THF (Entry 12). Lowering the temperature from 90 °C to 75 °C gave a marked increase in yield but required longer reaction time (Entry 10). Multiple attempts were made to reduce the reaction time, such as higher temperature in dioxane. Reasonable yield in 1 day was attained at 90 °C (Entry 19), but 110°C gave significantly lower yield in 4 h (Entry 20). Increasing the equivalents of Lewis acid (Entry 21), base (Entry 22), and both (Entry 23) successfully reduced the reaction time from 2 days to 1 day.
Table 2.3. Tandem Michael addition/Conia-ene substrate scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Eq. 2.5</th>
<th>Lewis Acid</th>
<th>Base (1 eq.)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield 2.7aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzene</td>
<td>0.8</td>
<td>2 eq. ZnBr₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>benzene</td>
<td>0.8</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>benzene</td>
<td>0.8</td>
<td>20 mol % Zn(OTf)₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>0.8</td>
<td>20 mol % Zn(NTf)₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>benzene</td>
<td>0.8</td>
<td>20 mol % In(OTf)₃</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>benzene</td>
<td>0.8</td>
<td>20 mol % Cu(OTf)₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>benzene</td>
<td>0.8</td>
<td>20 mol % Yb(OTf)₃</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
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<tr>
<td>8</td>
<td>MeCN</td>
<td>0.8</td>
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<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>0.8</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>benzene</td>
<td>0.8</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>75</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>toluene</td>
<td>0.8</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>75</td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>0.8</td>
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<td>2,6-lutidine</td>
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<tr>
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<td>1,4-dioxane</td>
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<td>61</td>
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<tr>
<td>15</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>20 mol % Sc(OTf)₃</td>
<td>2,6-lutidine</td>
<td>75</td>
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<td>0</td>
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<tr>
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<td>1,4-dioxane</td>
<td>2</td>
<td>2 eq. ZnI₂</td>
<td>DBU</td>
<td>75</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>2 eq. ZnI₂</td>
<td>NEt₃</td>
<td>75</td>
<td>46</td>
<td>30</td>
</tr>
<tr>
<td>18</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>2 eq. ZnI₂</td>
<td>NEt₃</td>
<td>50</td>
<td>94</td>
<td>incomplete</td>
</tr>
<tr>
<td>19</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>90</td>
<td>22</td>
<td>50</td>
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<tr>
<td>20</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>110</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>21</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>3 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>75</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>22</td>
<td>1,4-dioxane</td>
<td>4</td>
<td>2 eq. ZnI₂</td>
<td>2,6-lutidine</td>
<td>75</td>
<td>22</td>
<td>58</td>
</tr>
<tr>
<td>23</td>
<td>1,4-dioxane</td>
<td>3</td>
<td>3 eq. ZnI₂</td>
<td>2 eq. 2,6-lutidine</td>
<td>75</td>
<td>22</td>
<td>62</td>
</tr>
</tbody>
</table>
2.2.2 Tandem Michael addition/Conia-ene Substrate Scope

Using the optimized conditions, a substrate scope could be investigated. The findings are reported in Table 2.4. The reaction conditions tolerated a variety of benzylidene malonates 2.5 with 4-ethynyl-1-methylindole 2.1a. The highest yields were achieved with carbomethoxy- and cyano-bearing substrates 2.5b and 2.5d. 4-Halophenyl products 2.7ag-ai were synthesized in yields comparable to the model 2.7aa. Interestingly pentafluorophenyl substrate 2.7j was not tolerated as well as its 4-fluorophenyl counterpart 2.7g. Heterocyclic substrates were generally not tolerated well. Thiethyl product 2.7af was furnished in moderate yield, but furyl- and indolyl-bearing Conia-ene adducts 2.7ae and 2.7al were synthesized in low yields and experienced some decomposition. Methylenedioxyphenyl product 2.7ak was furnished in good yield. Since electron-withdrawing substituents seemed to perform better than electron-donating substituents, substrate 2.5m was chosen as an easily accessible source of an electron-withdrawing alkyl group. Unfortunately, it was unsuccessful in furnishing the Conia-ene product 2.7am, and experienced complete decomposition. A potential route of decomposition is via a gramine-type fragmentation as CCl₃ units are sufficiently good leaving groups. Lastly, it was anticipated that the performance of unprotected indole 2.1b would be poor, like it was for the synthesis of 3,4-cycloheptanonoindoles. Unsurprisingly, Conia-ene products 2.7ba and 2.7bb were furnished in substantially lower yields than 2.7aa and 2.7ab, respectively. In addition to low yields as compared to the N-methyl substrate, the reactions with 4-ethynylindole produced an unidentified and inseparable by-product that gave signals at 4.12 and 4.24 ppm in the ¹H NMR spectrum (see Appendix).
Table 2.4. Tandem Michael addition/Conia-ene substrate scope.

![Diagram showing synthetic reaction]

2.3 Large Scale Reactions

To determine the synthetic utility of the proposed methodologies, the cyclopropane ring-opening/Conia-ene and Michael addition/Conia-ene tandem reactions were attempted on a gram scale (Scheme 2.13). Delightfully, both reactions were found to scale up well. The cyclopropane ring-opening/Conia-ene methodology showed a modest decline in yield of 2.4aa from 86% based on 50 mg of cyclopropane to 73% with 600 mg. The Michael addition/Conia-ene methodology showed a similar decline in yield of 2.7aa from 62% based on 50 mg of indole to 48% with 410 mg.
Scheme 2.13. Larger scale synthesis of 3,4-cycloheptannioindoles and 3,4-cyclohexannioindoles.
3 Conclusions and Future Work

3.1 Conclusions

Based on previous work in the Kerr group\textsuperscript{[49]}, a synthetic strategy for the tandem cyclopropane ring-opening/Conia-ene synthesis of 3,4-cycloheptannioindoles 2.4 from 4-ethynylindoles was designed and successfully applied to synthesize 23 new compounds 2.4 (Scheme 3.1). These are two new reactions that can be drawn upon in future total syntheses of natural products. The initial attempt with previous conditions yielded the intermediate 2.3aa. After screening a handful of Lewis acids, the desired 3,4-cycloheptannioindole structure was successfully obtained. Further testing demonstrated that the overall process from 4-ethynylindoles 2.1 to 3,4-cycloheptannioindoles 2.4 can be done as a tandem reaction. Altering this reaction with new solvents, Lewis acids, and bases lead to optimized conditions. ZnBr\textsubscript{2} was ultimately the Lewis acid of choice for this reaction. Investigating the substrate scope revealed the highest yielding reactions were those done using methylated indole 2.1a with cyclopropanes 2.2 bearing an electron-rich aryl group.

![Scheme 3.1. Tandem synthesis of 3,4-cycloheptannioindoles from DA cyclopropanes and 4-ethynylindoles.](image)

A similar strategy was then successfully applied to synthesize 3,4-cyclohexannoindoles 2.7 from benzylidene malonates 2.5 and ethynylindoles 2.1 via tandem Michael addition/Conia-ene reactions (Scheme 3.2). 14 new compounds were obtained using this strategy. Initially the previous conditions were tested, which produced the desired [6,6,5]-fused tricyclic system in low yields. Many attempts to optimize this transformation finally gave the desired product 2.7aa in a modest 62% yield. ZnI\textsubscript{2} was the Lewis acid of choice for this tandem process, many others failed to promote the reaction. The highest performing substrates were generally
benzylidene malonates with electron-withdrawing substituents. Like the reactions with cyclopropanes, methylated indole 2.1a performed significantly better than unprotected 2.1b.

![Scheme 3.2. Tandem synthesis of 3,4-cyclohexannoindoles from Michael acceptors and 4-ethynylindoles.](image)

### 3.2 Future work

While these projects reached a satisfying endpoint, there is potential for the work to be expanded even further. The obvious direction would be to revisit a previously unsuccessful synthesis of 1,2-annulated indole 3.2 from the tandem ring-opening/Conia-ene reaction of N-propargyl skatole 3.1 and DAC 2.2a. Attempting the successful conditions of the presented methodologies would be a good place to start. The knowledge gained through these projects gives new hope that this previously unfruitful project could still be seen to a successful conclusion.

![Scheme 3.3. Potential revisit of the previously unsuccessful synthesis of 1,2-cycloheptannoindole 2.22.](image)

Another possible derivation of this work could be the synthesis of 1,7-annulated indoles 3.5 and 3.7 from 7-ethynylindoles 3.3. This could plausibly be achieved using the deprotonated form of indole 3.3 as a nucleophile for a ring-opening reaction or Michael addition. 1-Alkylation should be achieved if NaH is used as a base. Adducts 3.4 and 3.6 should be able to undergo a Conia-ene cyclization to give the desired ring systems (Scheme 3.4).
Scheme 3.4. Hypothetical strategy for the synthesis of 1,7-annulated indoles.

There is limited precedence for alkylating indoles at the nitrogen via cyclopropane ring-opening, however it has been accomplished by Inaba (Scheme 3.5).[60] They successfully ring-opened diethyl cyclopropane-1,1-diester 3.9 with 2-chloroindole 3.10 in 18% yield. Optimization of a similar reaction with 7-ethynylindoles 3.3, particularly by using a better donor-acceptor cyclopropane 2.2, should give adducts 3.4 in good yields. A potential hurdle for this reaction is that alkynes are also sufficiently acidic to be deprotonated by NaH, but careful control of the equivalents should give deprotonation at only the nitrogen. An alternate circumvention to the acidity is to install a protecting group, such as TMS, on the alkyne before the alkylation step.

Scheme 3.5. Precedence for N-alkylation of indoles via cyclopropane ring-opening.

There is also some precedence for the alkylation of indoles at the N-position via Michael additions (Scheme 3.6).[61] Work done by Wu demonstrated a tandem reaction similar to the desired reaction. They successfully synthesized intermediates 3.13 from indoles 3.11 and
benzylidene malonates 3.12. The intermediated then underwent a cyclization resulting in cyclization product 3.14 which resembled those of Conia-ene reactions.

Scheme 3.6. Precedence for N-alkylation of indoles via Michael addition.

The newly developed methodologies also have potential to be used in total syntheses as there are a variety of natural products that contain a 3,4-annulated indole framework (Figure 3.1). Although the tested substrates are unlikely to be directly useful, the methodologies are likely suitable with valid substrates. Additionally, the simplicity of the substrates (indoles, cyclopropanes, and benzylidene malonates), should allow for their relatively facile syntheses.

Figure 3.1. Potential natural product targets.
4 Experimental

4.1 General Information

Unless otherwise stated all reactions were conducted under an inert atmosphere of argon, and in vessels oven dried above 110°C. Dichloromethane (DCM), tetrahydrofuran (THF), toluene, and 1,4-dioxane were dried over an alumina column, and toluene and benzene were also deoxygenated over a column of copper catalyst. Dimethyl formamide (DMF) was dried on a column of 5Å molecular sieves. 1,2-Dichloroethane (DCE) was purchased from Sigma-Aldrich and stored on 4Å molecular sieves. All other commercial reagents were purchased from Sigma-Aldrich, Oakwood, and Alfa-Aesar and used without further purification. Flash chromatography was performed using silica gel P60 from SiliCycle. Proton nuclear magnetic resonance (1H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) were collected using Bruker-400 (400 MHz) and Inova-600 (600 MHz) spectrometers. Chemical shifts of protons are referenced to CDCl3 δ (7.26 ppm). Chemical shifts of carbon are referenced to CDCl3 (δ 77.0 ppm). NMR data are presented in the following order: chemical shift, multiplicity, coupling constants, integration. Infrared spectra were collected with a Bruker Alpha II ATR-IR spectrometer. Mass spectra were collected using a Waters High-Definition Mass Spectrometer and a Bruker micrOTOF 11, both in positive mode.

4.2 General Procedures

General procedure A: Synthesis of Michael acceptor substrates (2.5a-m).

A literature procedure was followed. A reaction flask equipped with a Dean-Stark apparatus was charged with a stir bar, benzene (40 mL) and aldehyde 2.15 (10 mmol). To the solution of aldehyde in benzene was added dimethyl malonate (12 mmol) followed by piperidine (1 mmol) and glacial acetic acid (1 mmol). The mixture was refluxed overnight then filtered, concentrated in vacuo, and purified via flash chromatography (30% v/v ethyl acetate in hexanes). The 1H NMR spectra matched literature spectra.

General procedure B: Synthesis of donor-acceptor cyclopropane substrates (2.2a-k).
A modified literature procedure was followed. A reaction flask was charged with a stir bar and DMF (8 mL). NaH (4.8 mmol) was added and stirred for 5 min. Trimethylsulfoxonium iodide (4.8 mmol) was added and allowed to stir for 1 h. A solution of benzylidene malonate 2.5 (4 mmol, 1M) was added and the reaction was stirred until completion as judged by TLC monitoring. The mixture was then poured onto ice and 5% HCl (total volume of 30 mL), extracted with diethyl ether, dried on MgSO₄, concentrated in vacuo, then purified via flash chromatography (20% v/v ethyl acetate in hexanes). The ¹H NMR spectra matched literature spectra.

**General procedure C: Seyferth-Gilbert homologation of 4-formylindoles.** A modified literature procedure was followed. A reaction flask was charged with a stir bar, MeOH, and 4-formylindole 2.1a, 2.1b, or 2.1c (1 eq.). To this was added K₂CO₃ (2 eq.) and diethyl 1-diazo-2-oxopropylphosphonate (2 eq.) and the reaction was stirred overnight. 4 days of reaction time gave conversions of >95%. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, then concentrated in vacuo. The resulting oil was then purified via flash chromatography (25% v/v ethyl acetate in hexanes).

**General procedure D: Synthesis of 3,4-cycloheptannoindoles (2.4aa-2.4ca).** To a pressure tube equipped with a stir bar was added 4-ethynylindole 2.1a, 2.1b or 2.1c (1.4 eq) followed by benzene (0.75mL) and cyclopropane diester 2.2 (1 eq). Once this mixture was homogeneous, 2,6-lutidine (1 eq) was added followed by ZnBr₂ (2 eq). The pressure tube was then purged with argon and sealed using a Teflon cap and crimped aluminum ring. The reaction was heated overnight at 90-100°C. Then the supernatant liquid was transferred to a separatory funnel via Pasteur pipette and the reaction flask was rinsed with DCM 3 times and these washing were added to the separatory funnel. This was then washed with dilute HCl (approx. 2%), saturated NaHCO₃, water, and brine then dried on NaSO₄, filtered, and concentrated in vacuo. The resulting oil or foam was purified via flash chromatography (25% v/v ethyl acetate in hexanes). Some products required further purification, to do so the sample was dissolved in DCM and adsorbed on to silica gel. The silica was then dried to a free-flowing powder. The impregnated silica was then put on top of a small layer of fresh silica in a pipette and flushed with hexanes. Then the sample was desorbed from the silica by flushing with DCM and/or ethyl acetate and was concentrated in vacuo.
General procedure E: Synthesis of 3,4-cyclohexannoindoles (2.7aa-2.7am). To a pressure tube equipped with a stir bar was added 4-ethynylindole 2.1a or 2.1b (1 eq) followed by 1,4-dioxane (1 mL) and benzylidene malonate (2 eq). Once this mixture was homogeneous, 2,6-lutidine (2 eq) was added followed by ZnI$_2$ (3 eq). The pressure tube was then purged with argon and sealed using a Teflon cap and a crimped aluminum ring. The reaction was heated for 22 h at 75°C. Then the supernatant liquid was transferred to a separatory funnel via Pasteur pipette and the reaction flask was rinsed with DCM 3 times and these washing were added to the separatory funnel. The mixture was then washed with dilute HCl (approx. 2%), saturated NaHCO$_3$, water, and brine then dried on Na$_2$SO$_4$, filtered and concentrated in vacuo. The resulting oil or foam was purified via flash chromatography (15-35% v/v ethyl acetate in hexanes).

4.3 Synthesis and Characterization of Substrates

4-formyl-1-methyl-1H-indole (2.13a)

A reaction flask was charged with a stir bar, DMF (15 mL), and 4-formyl-1H-indole (6.9 mmol). This was cooled to 0°C and to it was added NaH (10.4 mmol). After stirring at 0°C for 15 minutes, MeI (13.8 mmol) was slowly added. The reaction was allowed to warm to room temperature and stirred for 2h. Then it was quenched with saturated NH$_4$Cl at 0°C. The mixture was then extracted with ether and the combined organic layers were washed with water and brine, dried on MgSO$_4$ and concentrated in vacuo. The $^1$H NMR spectrum matched a literature spectrum.$^{[54]}$
4-ethynyl-1-methyl-1H-indole (2.1a)

Following General Procedure C, a reaction flask was charged with a stir bar, MeOH (100 mL), and 4-formylindole 2.13a (5.5 mmol). To this was added K$_2$CO$_3$ (11 mmol) and diethyl 1-diazo-2-oxopropylphosphonate (11 mmol) and the reaction was stirred overnight. After 4 days there was a conversion of about 95%, determined via $^1$H NMR of the crude material. The mixture was diluted with water and extracted with ethyl acetate. The combine organic layers were washed with water and brine, then concentrated in vacuo. The resulting oil was then purified via flash chromatography (25% v/v ethyl acetate in hexanes). The $^1$H NMR spectrum matched a literature spectrum.[55]

![4-ethynyl-1-methyl-1H-indole](image)

4-ethynyl-1-methyl-1H-indole (2.1b)

Following General Procedure C, a reaction flask was charged with a stir bar, MeOH (100 mL), and 4-formyl-1H-indole (6.9 mmol). To this was added K$_2$CO$_3$ (13.7 mmol) and diethyl 1-diazo-2-oxopropylphosphonate (13.7 mmol) and the reaction was stirred overnight. After 4 days there was a conversion of about 95%, determined via $^1$H NMR of the crude material. The mixture was diluted with water and extracted with ethyl acetate. The combine organic layers were washed with water and brine, then concentrated in vacuo. The resulting oil was then purified via flash chromatography (25% v/v ethyl acetate in hexanes). The $^1$H NMR spectrum matched a literature spectrum.[55]

![4-ethynyl-1-methyl-1H-indole](image)

1-(4-methylbenzenesulfonyl)-1H-indole-4-carbaldehyde (2.16)

4-Formylindole (13.8 mmol) was dissolved in DMF (40 mL) and cooled to 0°C. NaH (20.7
mmol) was added slowly and the mixture was allowed to stir for 5 min. Benzenesulfonyl chloride (27.6 mmol) was then added at 0°C and the reaction was allowed to warm to rt and stirred overnight. The reaction mixture was then poured on a mixture of sat. NH₄Cl and ice (total volume approx. 60 mL) and extracted 3 times with ethyl acetate. The organic layers were collected and concentrated in vacuo. The crude material was then purified via flash chromatography (25% EtOAc/hexanes). The protected indole was recovered in 81% yield and the ¹H NMR spectrum matched the literature.¹⁶³

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{SO₂Ph} & \quad \text{N-protected indole 2.16 (11.2 mmol) was dissolved in toluene (50 mL), and to it was added toluenesulfonic acid (1.1 mmol) and propanediol (33.7 mmol). A Dean-Stark apparatus was attached, and the reaction mixture was heated to reflux until the evolution of water subsided. The reaction mixture was then cooled to rt and washed with sat. NaHCO₃ and brine then dried on MgSO₄ and concentrated in vacuo. The crude material was then purified via flash chromatography (25% EtOAc/hexanes). Doubly protected indole 2.17 was collected in 81% yield. ¹H NMR (400 MHz, Chloroform-\text{d}) \delta 8.01 (dd, J = 8.2, 1.0 Hz, 1H), 7.86 (dd, J = 8.5, 1.3 Hz, 2H), 7.59 (d, J = 3.7 Hz, 1H), 7.56 – 7.46 (m, 1H), 7.41 (dd, J = 8.6, 7.2 Hz, 2H), 7.37 – 7.27 (m, 2H), 6.97 (dd, J = 3.7, 0.9 Hz, 1H), 5.73 (s, 1H), 4.29 (ddd, J = 12.1, 5.0, 1.5 Hz, 2H), 4.14 – 3.84 (m, 2H), 2.27 (dtt, J = 13.5, 12.4, 5.0 Hz, 1H), 1.49 (ddt, J = 13.5, 2.6, 1.2 Hz, 1H).; ¹³C NMR (101 MHz, CDCl₃) \delta 138.2, 135.3, 133.9, 131.0, 129.3, 128.3, 128.3, 126.8, 126.3, 124.4, 121.2, 114.2, 108.5, 101.5, 77.4, 77.3, 77.0, 76.9, 76.7, 67.5, 25.9.; IR (ATR): 2965, 2854, 1448, 1426, 1371, 1282, 1237, 1186, 1166, 1141, 1100, 992, 764, 726, 686, 659, 583, 563.
\end{align*}
\]
4-(1,3-dioxan-2-yl)-2-methyl-1-(4-methylbenzenesulfonyl)-1H-indole (2.18)

A literature procedure was followed. Diisopropylamine (45 mmol) was dissolved in THF (150 mL) and cooled to -78°C. Then BuLi (41 mmol) was slowly added, and the mixture was stirred for 10 min. To the resulting solution of lithium diisopropylamide was added a 0.5 M solution of doubly protected indole 2.17 (9 mmol) in THF. The reaction was allowed to stir at -78°C for 15 min. The reaction was then warmed to 0°C for 1 h. Then the reaction was warmed to rt and stirred overnight. The reaction was quenched with sat. NH₄Cl, extracted 3 times with ethyl acetate, and dried on MgSO₄. A 94/6 mixture of product/starting material was obtained in a yield of 91%. The starting material was inseparable via flash chromatography. The material was then carried forward without further purification.  

\[^1\text{H NMR}\] (400 MHz, Chloroform-
\[^d\]) \(\delta\) 8.17 (dt, \(J = 8.4, 0.9\) Hz, 1H), 7.80 – 7.74 (m, 2H), 7.56 – 7.47 (m, 1H), 7.40 (ddt, \(J = 8.1, 6.8, 0.6\) Hz, 2H), 7.32 (dt, \(J = 7.4, 0.7\) Hz, 1H), 7.27 – 7.22 (m, 1H), 6.68 – 6.66 (m, 1H), 5.69 (s, 1H), 5.30 (s, 1H), 4.29 (ddd, \(J = 11.9, 5.0, 1.4\) Hz, 2H), 4.07 – 3.95 (m, 2H), 2.62 (d, \(J = 1.1\) Hz, 3H), 2.36 – 2.21 (m, 1H);  \[^13\text{C NMR}\] (101 MHz, CDCl\(_3\)) \(\delta\) 139.2, 137.5, 133.7, 129.3, 126.8, 126.4, 123.5, 121.4, 115.1, 108.7, 101.8, 67.6, 25.9, 15.8. \[^\text{IR (ATR)}\]: 2963, 2923, 2855, 1755, 1670, 1591, 1532, 1448, 1369, 1186, 1170, 1095, 999, 729, 591.

2-methyl-1H-indole-4-carbaldehyde (2.19)

A modified procedure for deprotection of indoles was used.\[^{[64]}\] The doubly protected indole (1.0 mmol) was dissolved in ethanol and to it was added powdered KOH (10.2 mmol). The reaction mixture was heated to reflux overnight. The reaction mixture was then cooled and partitioned between 1 M HCl and ether and shaken for 5 minutes. The organic layer was then
separated, and the aqueous layer was extracted 3 times with ether. The combined organic layers were dried on MgSO₄ and concentrated in vacuo. The crude material was purified via flash chromatography (25% EtOAc/hexanes). 113 mg (70%) of pure material was obtained. The 1H NMR spectrum matched a literature spectrum.[65]

1,2-dimethyl-1H-indole-4-carbaldehyde (2.20)

A reaction flask was charged with a stir bar, DMF (10 mL), and 4-formyl-1H-indole (2.7 mmol). This was cooled to 0°C and to it was added NaH (4.0 mmol). After stirring at 0°C for 15 minutes, MeI (5.33 mmol) was slowly added. The reaction was allowed to warm to room temperature and stirred for 2h. Then it was quenched with saturated NH₄Cl at 0°C. The mixture was then extracted with ether and the combined organic layers were washed with water and brine, dried on MgSO₄ and concentrated in vacuo. The crude material was purified via flash chromatography (25% EtOAc/hexanes) to afford 2.20 (317 mg, 69%). 1H NMR (400 MHz, Chloroform-d) δ 10.22 (s, 1H), 7.63 – 7.55 (m, 1H), 7.52 – 7.46 (m, 1H), 7.34 – 7.16 (m, 1H), 7.05 (q, J = 0.9 Hz, 1H), 3.79 – 3.58 (m, 3H), 2.46 (dd, J = 1.8, 0.9 Hz, 3H); 13C NMR (101 MHz, CDCl₃) δ 193.3, 168.2, 141.3, 138.2, 127.2, 127.0, 126.1, 119.7, 114.9, 114.9, 100.6, 29.7, 29.6, 29.6, 13.0, 13.0.; IR (ATR): 2924, 2845, 2805, 2720, 1673, 1605, 1568, 1539, 1460, 1384, 1359, 1343, 1294, 1275, 1225, 1182, 1137, 1012, 881, 818, 770, 738, 648.

4-ethynyl-1,2-dimethyl-1H-indole (2.1c)

General procedure C was followed without alteration. Reagents employed: 2.20 (317 mg, 1.8 mmol), MeOH (30 mL), K₂CO₃ (632 mg, 4.6 mmol), and diethyl 1-diazo-2-oxopropylphosphonate (1.0 g, 4.6 mmol). 243 mg (78%) of white solid was collected. 1H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.26 (m, 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.45 (d, J =
1.3 Hz, 1H), 3.69 (s, 3H), 3.29 (s, 1H), 2.47 (d, J = 1.0 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.0, 136.9, 129.9, 123.8, 120.1, 112.3, 109.7, 99.4, 83.0, 78.8, 29.7, 29.6, 12.8.; IR (ATR): 3278, 2921, 2853, 2096, 1545, 1424, 1392, 1335, 1274, 1133, 1054, 976, 758, 664, 628, 594.; HRMS (ESI+) calc’d for C$_{12}$H$_{12}$N [M+H]$^+$ = 170.0964, found = 170.0975.

4.4 Characterization of 3,4-cycloheptannindoles

![Chemical Structure of 10,10-dimethyl 3-methyl-9-methylidene-12-phenyl-3-azatricyclo[6.4.1.0$^{4,13}$]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4aa)](image)

2.4aa was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 2.2a (54 mg, 0.23 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr$_2$ (104 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.23 mmol), and benzene (0.75 mL). 2.4aa (77 mg, 86%) was obtained as a red oil: R$_f$ = 0.43, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 7.51 – 6.97 (m, 8H), 6.25 (d, J = 1.5 Hz, 1H), 5.55 (s, 1H), 5.18 (s, 1H), 4.43 (dd, J = 12.0, 3.4, 1.5 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 2.95 (dd, J = 14.2, 3.4 Hz, 1H), 2.75 (dd, J = 14.2, 12.1 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.7, 170.9, 147.5, 145.9, 136.5, 133.9, 128.5, 128.4, 127.2, 126.6, 124.6, 122.0, 119.7, 118.7, 117.7, 108.9, 65.0, 52.9, 52.6, 44.2, 40.8, 32.7.; IR (ATR): 3058, 3027, 2950, 2255, 1732, 160, 1493, 1452, 1266, 1220, 1062, 906, 725, 699, 647; HRMS (ESI+) calc’d for C$_{24}$H$_{24}$NO$_4$ [M+H]$^+$ = 390.1705, found = 390.1704.
10,10-dimethyl 9-methylidene-12-phenyl-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ba)

2.4ba was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 2.2a (59 mg, 0.25 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr₂ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4ba (64 mg, 77%) was obtained as a pale yellow oil: Rᵥ = 0.54, 25% EtOAc in hexanes; ¹H NMR (400 MHz, Chloroform-d) δ 8.03 (d, J = 10.1 Hz, 1H), 7.50 – 6.97 (m, 8H), 6.43 – 6.24 (m, 1H), 5.57 (s, 1H), 5.22 (s, 1H), 4.53 – 4.36 (m, 1H), 3.85 – 3.69 (m, 6H), 2.97 (dd, J = 14.3, 3.2 Hz, 1H), 2.88 – 2.73 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.7, 171.7, 147.2, 147.2, 145.7, 145.7, 135.8, 133.7, 133.7, 128.6, 128.5, 128.4, 126.6, 124.3, 122.5, 122.4, 122.4, 121.4, 119.2, 118.1, 110.9, 110.8, 65.1, 52.9, 52.6, 44.1, 40.7.; IR (ATR): 3410, 3059, 3028, 2951, 2254, 1729, 1600, 1494, 1453, 1433, 1266, 1216, 1062, 907, 728, 700; HRMS (ESI+) calc’d for C₂₃H₂₂NO₄ [M+H]^+ = 376.1549, found = 376.1548.

10,10-dimethyl 3-methyl-9-methylidene-12-(4-methoxyphenyl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ab)

2.4ab was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate 2.2b (65 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr₂ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4ab (87 mg, 82%) was obtained as a tan foam/powder: Rᵥ = 0.37, 25% EtOAc in hexanes; ¹H NMR (400 MHz, Chloroform-d) δ 7.31 – 7.16 (m, 5H), 6.89 (d, J = 8.6 Hz, 2H), 6.24 (d, J = 1.5 Hz, 1H), 5.52 (s, 1H), 5.15 (s, 1H), 4.40 – 4.30 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 2.89 (dd, J = 14.2, 3.4 Hz, 1H), 2.69 (dd, J = 14.2, 12.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.8, 171.0, 158.4, 147.6, 138.2, 136.7, 134.0, 129.4, 127.3, 124.7, 122.1, 120.2, 118.7, 117.8, 114.0, 108.9, 77.5, 77.4, 77.2, 76.8, 65.1, 55.4, 53.0, 52.7, 44.5, 40.0, 32.8.; IR (ATR): 2950, 1736, 1510, 1246, 1225; HRMS (ESI+) calc’d for C₂₅H₂₆NO₅ [M+H]^+ = 420.1811, found = 420.1802.
2.4bb was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate 2.2b (71 mg, 0.27 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr₂ (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 2.4bb (50 mg, 46%) was obtained as a white solid: R₁ = 0.16, 25% EtOAc in hexanes; ¹H NMR (400 MHz, Chloroform-d) δ 7.99 (s, 1H), 7.43 – 7.08 (m, 3H), 6.92 (d, J = 8.7 Hz, 1H), 6.37 (dd, J = 2.5, 1.6 Hz, 1H), 5.55 (s, 1H), 5.21 (s, 1H), 4.42 (ddd, J = 11.9, 3.2, 1.6 Hz, 1H), 3.85 (s, 3H), 3.78 – 3.64 (m, 6H), 2.92 (dd, J = 14.3, 3.2 Hz, 1H), 2.75 (dd, J = 14.3, 11.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 171.1, 158.3, 147.1, 137.8, 135.8, 133.9, 129.3, 124.3, 122.5, 122.2, 121.9, 119.2, 118.1, 113.9, 110.7, 65.1, 55.3, 52.8, 52.6, 44.3, 39.8; IR (ATR): 3410, 2952, 2837, 1732, 1609, 1510, 1433, 1243, 1175, 1071, 1032, 909, 731; HRMS (ESI+) calc’d for C₂₄H₂₄NO₅ [M+H]⁺ = 406.1654, found = 406.1637.

2.4ac was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate 2.2c (67 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr₂ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4ac (38 mg, 38%) was obtained as an oil: R₁ = 0.69, 25% EtOAc in hexanes; ¹H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.04 (m, 7H), 6.23 (d, J = 1.5 Hz, 1H), 5.54 (s, 1H), 5.17 (s, 1H), 4.43 (ddd, J = 12.0, 3.5, 1.5 Hz, 1H), 3.75 (s, 3H), 3.71 (s,
3H), 3.64 (s, 3H), 2.91 (dd, J = 14.2, 3.4 Hz, 1H), 2.69 (dd, J = 14.2, 12.1 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.6, 170.9, 147.4, 144.4, 136.6, 133.9, 132.3, 129.8, 128.8, 127.2, 124.5, 122.2, 119.4, 118.9, 117.9, 109.0, 77.5, 77.2, 76.8, 65.0, 53.0, 52.7, 44.2, 40.2, 32.8.; IR (ATR): 2950, 1732, 1221, 906, 727; HRMS (ESI+) calc’d for C24H23NO4Cl [M+H]+ = 424.1315, found = 424.1315.

10,10-dimethyl 9-methylidene-12-(4-chlorophenyl)-3-azatricyclo[6.4.1.04,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4bc)

2.4bc was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate 2.2c (72 mg, 0.27 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr2 (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 2.4bc (64 mg, 58%) was obtained as an orange oil: Rf = 0.38, 25% EtOAc in hexanes; 1H NMR (400 MHz, Chloroform-d) δ 8.00 (s, 1H), 7.55 – 7.01 (m, 7H), 6.31 (t, J = 2.0 Hz, 1H), 5.53 (s, 1H), 5.19 (s, 1H), 4.64 – 4.30 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.89 (dd, J = 14.3, 3.2 Hz, 1H), 2.71 (dd, J = 14.3, 11.9 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.5, 171.0, 147.0, 144.1, 135.8, 133.7, 132.3, 129.7, 128.7, 124.2, 122.6, 122.1, 121.1, 119.3, 118.3, 110.9, 65.0, 52.9, 52.7, 44.0, 40.1.; IR (ATR): 3407, 2951, 1730, 1489, 1433, 1268, 1233, 1216, 1090, 1070, 1014, 909, 731; HRMS (ESI+) calc’d for C23H21NO4Cl [M+H]+ = 410.1159, found = 410.1162.

10,10-dimethyl 3-methyl-9-methylidene-12-[4-(methoxycarbonyl)phenyl]-3-azatricyclo[6.4.1.04,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ad)
2.4ad was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[4-(methoxycarbonyl)phenyl]cyclopropane-1,1-dicarboxylate 2.2d (73 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.2a (50 mg, 0.32 mmol), ZnBr2 (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4ad (81 mg, 72%) was obtained as a yellow oil: Rf = 0.24, 25% EtOAc in hexanes; 1H NMR (400 MHz, Chloroform-d) δ 8.06 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.39 – 7.14 (m, 3H), 6.21 (d, J = 1.5 Hz, 1H), 5.57 (s, 1H), 5.19 (s, 1H), 4.53 (ddd, J = 11.9, 3.5, 1.5 Hz, 1H), 3.96 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 2.95 (dd, J = 14.2, 3.4 Hz, 1H), 2.75 (dd, J = 14.2, 12.0 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.5, 170.7, 167.1, 151.2, 147.3, 136.5, 133.8, 129.9, 128.6, 128.5, 127.1, 124.5, 122.2, 118.9, 118.8, 117.8, 108.9, 64.9, 52.9, 52.6, 52.1, 43.8, 40.7, 32.8; IR (ATR): 2951, 2255, 1718, 1609, 1434, 1277, 1111, 1070, 1020, 909, 729; HRMS (ESI+) calc’d for C26H26NO6 [M+H]+ = 448.1760, found = 448.1773.

10,10-dimethyl 9-methylidene-12-[4-(methoxycarbonyl)phenyl]-3-azatricyclo[6.4.1.04,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4bd)

2.4bd was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[4-(methoxycarbonyl)phenyl]cyclopropane-1,1-dicarboxylate 2.2d (79 mg, 0.27 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr2 (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 2.4bd (57 mg, 49%) was obtained as an orange oil: Rf = 0.28, 25% EtOAc in hexanes; 1H NMR (400 MHz, Chloroform-d) δ 8.05 (d, J = 8.3 Hz, 3H), 7.45 (d, J = 8.3 Hz, 2H), 7.35 – 7.11 (m, 3H), 6.32 (ddd, J = 2.5, 1.5 Hz, 1H), 5.56 (s, 1H), 5.21 (s, 1H), 4.55 (ddd, J = 11.8, 3.2, 1.5 Hz, 1H), 3.95 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 2.94 (dd, J = 14.3, 3.2 Hz, 1H), 2.77 (dd, J = 14.3, 11.8 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.5, 170.9, 167.1, 150.9, 146.9, 135.7, 133.7, 129.9, 128.6, 128.5, 124.2, 122.7, 122.1, 120.8, 119.4, 118.3, 110.8, 65.0, 52.9, 52.7, 52.1, 43.7, 40.7; IR (ATR): 3403, 2950, 1718, 1609, 1433, 1277, 1111, 1070, 1020, 909, 729; HRMS (ESI+) calc’d for C25H24NO6 [M+H]+ = 434.1604, found = 434.1596.
10,10-dimethyl 3-methyl-9-methylidene-12-(4-cyanophenyl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4ae)

2.4ae was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-cyanophenyl)cyclopropane-1,1-dicarboxylate 2.2e (60 mg, 0.23 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr$_2$ (104 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.23 mmol), and benzene (0.75 mL). 2.4ae (45 mg, 38%) was obtained as a colourless oil: R$_f$ = 0.30, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 7.67 (d, $J$ = 8.3 Hz, 2H), 7.49 (d, $J$ = 8.1 Hz, 2H), 7.39 – 7.18 (m, 2H), 6.26 – 6.13 (m, 1H), 5.57 (d, $J$ = 1.3 Hz, 1H), 5.19 (s, 1H), 4.66 – 4.45 (m, 1H), 2.93 (ddd, $J$ = 14.2, 3.5, 2.0 Hz, 1H), 2.70 (ddd, $J$ = 14.1, 12.0, 1.8 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 170.7, 151.5, 147.2, 136.6, 133.7, 132.5, 129.3, 127.0, 124.4, 122.4, 119.1, 119.0, 118.4, 118.0, 110.6, 109.1, 77.5, 77.2, 76.8, 64.8, 53.1, 52.8, 43.9, 40.9, 32.9.; IR (ATR): 2951, 2226, 1732, 1221, 728; HRMS (ESI+) calc’d for C$_{25}$H$_{23}$N$_2$O$_4$ [M+H]$^+$ = 415.1658, found = 415.1656.

10,10-dimethyl 9-methylidene-12-(4-cyanophenyl)-3-azatricyclo [6.4.1.0^4,13]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4be)

2.4be was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(4-cyanophenyl)cyclopropane-1,1-dicarboxylate 2.2e (65 mg, 0.25 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr$_2$ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4be (25 mg, 28%) was obtained as a tan foam: R$_f$ = 0.17, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 8.05 (s, 1H), 7.67 (d, $J$ = 8.4 Hz, 2H), 7.49 (d, $J$ = 8.2 Hz, 2H), 7.36 – 7.12 (m, 3H), 6.32 (dd, $J$ = 2.5, 1.5 Hz, 1H), 5.56 (s, 1H), 5.21 (s, 1H), 5.19 (s, 1H), 4.66 – 4.45 (m, 1H), 2.93 (ddd, $J$ = 14.2, 3.5, 2.0 Hz, 1H), 2.70 (ddd, $J$ = 14.1, 12.0, 1.8 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 170.7, 151.5, 147.2, 136.6, 133.7, 132.5, 129.3, 127.0, 124.4, 122.4, 119.1, 119.0, 118.4, 118.0, 110.6, 109.1, 77.5, 77.2, 76.8, 64.8, 53.1, 52.8, 43.9, 40.9, 32.9.; IR (ATR): 2951, 2226, 1732, 1221, 728; HRMS (ESI+) calc’d for C$_{25}$H$_{23}$N$_2$O$_4$ [M+H]$^+$ = 415.1658, found = 415.1656.
4.58 (ddd, J = 11.7, 3.2, 1.5 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 2.91 (dd, J = 14.3, 3.3 Hz, 1H), 2.73 (dd, J = 14.3, 11.8 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.3, 170.9, 151.1, 146.7, 135.7, 133.7, 132.5, 129.2, 124.1, 122.9, 121.9, 120.3, 119.5, 119.0, 118.4, 110.9, 110.6, 64.8, 53.0, 52.7, 43.7, 40.8.; IR (ATR): 3403, 2952, 2227, 1729, 1605, 1502, 1433, 1217, 1070, 909, 729; HRMS (ESI+) calc’d for C24H21N2O4 [M+H]+ = 401.1501, found = 401.1513.

10,10-dimethyl 3-methyl-9-methylidene-12-(thiophene-2-yl)-3-azatricyclo[6.4.1.04.13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4af)

2.4af was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate 2.2f (60 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr2 (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4af (72 mg, 72%) was obtained as a red solid: Rf = 0.47, 25% EtOAc in hexanes; 1H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.21 (m, 4H), 7.14 – 6.93 (m, 2H), 6.57 (s, 1H), 5.57 (s, 1H), 5.21 (s, 1H), 4.93 – 4.81 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.16 – 2.99 (m, 1H), 2.80 (ddd, J = 14.0, 11.8, 1.9 Hz, 1H); 13C NMR (101 MHz, CDCl3) δ 171.4, 170.8, 149.0, 147.2, 147.2, 136.6, 133.8, 127.3, 126.5, 124.5, 124.1, 123.5, 122.1, 119.1, 118.8, 117.8, 109.0, 109.0, 64.9, 52.9, 52.7, 45.3, 35.9, 32.8.; IR (ATR): 2950, 2254, 1732, 1434, 1220, 1070, 905, 725, 697, 647; HRMS (ESI+) calc’d for C22H22NO4S [M+H]+ = 396.1269, found = 396.1282.
10,10-dimethyl 9-methylidene-12-(thiophene-2-yl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4bf)

**2.4bf** was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate **2.2f** (65 mg, 0.27 mmol), 4-ethynylindole **2.1b** (50 mg, 0.35 mmol), ZnBr₂ (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). **2.4bf** (63 mg, 61%) was obtained as a yellow solid: Rf = 0.32, 30% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-d) δ 8.05 (s, 1H), 7.41 – 7.12 (m, 4H), 7.12 – 6.92 (m, 2H), 6.61 (s, 1H), 5.54 (s, 1H), 5.20 (s, 1H), 3.86 – 3.58 (m, 6H), 3.05 (dd, J = 14.3, 3.2 Hz, 1H), 2.79 (dd, J = 14.3, 11.8 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl₃) δ 171.5, 171.1, 148.8, 146.9, 135.8, 133.7, 126.6, 124.6, 123.9, 123.6, 122.6, 122.5, 122.5, 120.8, 119.4, 119.3, 111.0, 111.0, 65.1, 53.0, 52.8, 45.3, 35.9.; IR (ATR): 3406, 2951, 2250, 1728, 1432, 1210, 1069, 906, 726, 696; HRMS (ESI+) calc’d for C₂₁H₂₀NO₄S [M+H]^+ = 382.1113, found = 382.1105.

![](image.png)

10,10-dimethyl 3-methyl-9-methylidene-12-(furan-2-yl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ag)

**2.4ag** was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate **2.2g** (56 mg, 0.25 mmol), 4-ethynyl-1-methylindole **2.1a** (50 mg, 0.32 mmol), ZnBr₂ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). **2.4ag** (77 mg, 88%) was obtained a yellow oil: Rf = 0.56, 25% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.42 (dd, J = 1.9, 0.9 Hz, 1H), 7.35 – 7.12 (m, 3H), 6.61 (d, J = 1.5 Hz, 1H), 6.40 (dd, J = 3.2, 1.9 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 5.55 (s, 1H), 5.17 (s, 1H), 4.66 (dd, J = 11.9, 3.5, 1.4 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.07 (dd, J = 14.3, 3.5 Hz, 1H), 2.78 (dd, J = 14.3, 12.0 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl₃) δ 171.5, 170.7, 158.0, 147.4, 141.2, 136.5, 133.6, 126.6, 124.1, 122.0, 118.7, 117.4, 116.1, 110.1, 108.9, 105.2, 64.6, 52.9, 52.6, 41.4, 33.9, 32.8.; IR (ATR): 2951, 1736, 1600, 1505, 1435, 1266, 1222, 1066, 1009, 914, 797, 735; HRMS (ESI+) calc’d for
C$_{22}$H$_{22}$NO$_5$ [M+H]$^+$ = 380.1498, found = 380.1509.

10,10-dimethyl 9-methylidene-12-(furan-2-yl)-3-azatricyclo [6.4.1.0$^{4,13}$]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4bg)

2.4bg was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate 2.2g (51 mg, 0.23 mmol), 4-ethynylindole 2.1b (46 mg, 0.30 mmol), ZnBr$_2$ (104 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.23 mmol), and benzene (0.75 mL). 2.4bg (34 mg, 41%) was obtained as a pale yellow oil: R$_f$ = 0.24, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.02 (s, 1H), 7.41 (dd, $J = 1.9, 0.9$ Hz, 1H), 7.33 – 7.11 (m, 4H), 6.72 (dd, $J = 2.5, 1.5$ Hz, 1H), 6.39 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.24 (dd, $J = 3.2, 0.7$ Hz, 1H), 5.54 (s, 1H), 5.19 (s, 1H), 4.68 (ddd, $J = 11.8, 3.4, 1.5$ Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.05 (dd, $J = 14.4, 3.3$ Hz, 1H), 2.78 (dd, $J = 14.4, 11.8$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 170.9, 157.8, 147.0, 141.2, 135.7, 133.6, 123.9, 122.5, 121.7, 119.3, 118.1, 117.9, 110.8, 110.1, 105.3, 64.7, 52.9, 52.7, 41.3, 33.9.; IR (ATR): 3408, 2951, 1732, 1603, 1504, 1433, 1268, 1240, 1216, 1066, 1009, 912, 731; HRMS (ESI+) calc’d for C$_{21}$H$_{20}$NO$_5$ [M+H]$^+$ = 366.1341, found = 366.1347.

10,10-dimethyl 3-methyl-9-methylidene-12-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]-3-azatricyclo [6.4.1.0$^{4,13}$]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ah)

2.4ah was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[1-(tosyl)-1H-indol-3-yl]cyclopropane-1,1-dicarboxylate 2.2h (106 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr$_2$ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL,
0.25 mmol), and benzene (0.75 mL). **2.4ah** (81 mg, 72%) was obtained as red a solid: \( R_f = 0.23 \), 30% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 8.06 (d, \( J = 8.0 \) Hz, 1H), 7.82 (d, \( J = 7.8 \) Hz, 2H), 7.64 – 7.53 (m, 1H), 7.44 (d, \( J = 7.8 \) Hz, 1H), 7.39 – 7.22 (m, 6H), 7.16 (t, \( J = 7.6 \) Hz, 1H), 6.33 (s, 1H), 5.59 (s, 1H), 5.20 (s, 1H), 4.75 (d, \( J = 10.7 \) Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.60 (s, 3H), 3.11 – 2.93 (m, 1H), 2.92 – 2.77 (m, 1H), 2.39 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 171.6, 170.7, 147.4, 144.9, 136.6, 135.7, 135.3, 133.8, 130.0, 130.0, 127.0, 126.9, 126.7, 124.7, 124.3, 123.3, 123.0, 122.1, 120.9, 118.8, 117.6, 116.8, 113.9, 109.0, 65.0, 52.9, 52.7, 42.8, 32.8, 31.6, 21.6.; IR (ATR): 2952, 2255, 1733, 1598, 1446, 1368, 1172, 905, 724, 573, 536; HRMS (ESI+) calc’d for C\(_{33}\)H\(_{31}\)N\(_2\)O\(_6\)S \([\text{M+H}]^+\) = 583.1903, found = 583.1905.

![Molecular structure](image)

**10,10-dimethyl 9-methylidene-12-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]-3-azatricyclo [6.4.1.0\(^4,13\)]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4bh)**

**2.4bh** was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[1-(tosyl)-1H-indol-3-yl]cyclopropane-1,1-dicarboxylate **2.2h** (116 mg, 0.27 mmol), 4-ethynyldindole **2.1b** (50 mg, 0.35 mmol), ZnBr\(_2\) (121 mg, 0.54 mmol), 2,6-lutidine (30 \( \mu \)L, 0.27 mmol), and benzene (0.75 mL). **2.4bh** (64 mg, 41%) was obtained as red a solid: \( R_f = 0.20 \), 30% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 8.09 – 7.96 (m, 2H), 7.82 (d, \( J = 8.3 \) Hz, 2H), 7.59 (s, 1H), 7.50 – 7.04 (m, 8H), 6.41 (d, \( J = 2.3 \) Hz, 1H), 5.59 (s, 1H), 5.22 (s, 1H), 4.87 – 4.65 (m, 1H), 3.80 – 3.65 (m, 6H), 2.99 (dd, \( J = 14.3, 3.6 \) Hz, 1H), 2.87 (dd, \( J = 14.3, 11.9 \) Hz, 1H), 2.39 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 171.5, 170.8, 147.1, 145.0, 144.9, 135.9, 135.6, 135.3, 133.6, 133.6, 130.0, 126.9, 126.4, 124.7, 124.0, 123.3, 122.9, 122.5, 122.2, 120.9, 119.2, 118.3, 117.9, 113.8, 110.9, 65.0, 52.9, 52.7, 42.7, 31.7, 21.6.; IR (ATR): 3410, 2951, 1731, 1445, 1366, 1171, 906, 727, 572; HRMS (ESI+) calc’d for C\(_{32}\)H\(_{29}\)N\(_2\)O\(_6\)S \([\text{M+H}]^+\) = 569.1746, found = 569.1724.
10,10-dimethyl 3-methyl-9-methylidene-12-(2H-1,3-benzodioxol-5-yl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4ai)

2.4ai was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(2H-1,3-benzodioxol-5-yl)cyclopropane-1,1-dicarboxylate 2.2i (72 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr$_2$ (112 mg, 0.50 mmol), 2,6-lutidine (30 μL, 0.25 mmol), and benzene (0.75 mL). 2.4ai (82 mg, 73%) was obtained as a yellow oil: R$_f$ = 0.31, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.19 (m, 3H), 6.94 – 6.81 (m, 3H), 6.37 (s, 1H), 6.04 – 5.93 (m, 2H), 5.58 (s, 1H), 5.20 (s, 1H), 4.44 – 4.37 (m, 1H), 2.96 (dd, J = 14.2, 3.4 Hz, 1H), 2.72 (ddd, J = 14.2, 12.1, 1.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.6, 170.8, 147.7, 147.5, 146.2, 139.9, 136.6, 133.8, 127.3, 124.5, 122.0, 121.3, 119.6, 118.7, 117.6, 108.9, 108.8, 108.2, 100.9, 64.9, 52.9, 52.6, 44.5, 40.5, 32.8.; IR (ATR): 2951, 2253, 1731, 1485, 1438, 1223, 1036, 906, 725; HRMS (ESI+) calc’d for C$_{25}$H$_{24}$NO$_6$ [M+H]$^+$ = 434.1603, found = 434.1603.

10,10-dimethyl 9-methylidene-12-(2H-1,3-benzodioxol-5-yl)-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4bi)

2.4bi was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-(2H-1,3-benzodioxol-5-yl)cyclopropane-1,1-dicarboxylate 2.2i (78 mg, 0.27 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr$_2$ (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 5k (67 mg, 58%) was obtained as a white solid: R$_f$ = 0.17,
25% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.92 (s, 1H), 7.35 – 7.09 (m, 5H), 6.91 – 6.73 (m, 3H), 6.44 (dd, \(J = 2.4, 1.6\) Hz, 1H), 5.95 (q, \(J = 1.4\) Hz, 2H), 5.52 (s, 1H), 5.17 (s, 1H), 4.38 (ddd, \(J = 11.9, 3.2, 1.6\) Hz, 1H), 2.88 (dd, \(J = 14.3, 3.2\) Hz, 1H), 2.68 (dd, \(J = 14.3, 11.9\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.7, 171.1, 147.8, 147.2, 146.3, 139.7, 135.9, 134.0, 124.4, 122.7, 122.3, 121.7, 121.5, 119.4, 118.3, 110.9, 108.9, 108.3, 101.0, 77.5, 77.4, 77.2, 77.1, 76.8, 65.1, 53.0, 52.7, 44.5, 40.5; IR (ATR): 3411, 2951, 1732, 1485, 1245, 1037, 911; HRMS (ESI+) calc’d for C\(_{24}\)H\(_{22}\)NO\(_6\) [M+H]\(^+\) = 420.1447, found = 420.1448.

![Diagram](image1.png)

10,10-dimethyl 3-methyl-9-methylidene-12-[(1E)-2-[phenylethenyl]-3-azatricyclo [6.4.1.0\(^4\)13]trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4aj)

2.4aj was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[(1E)-2-phenylethenyl]-1,1-dicarboxylate 2.2j (65 mg, 0.25 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnBr\(_2\) (112 mg, 0.50 mmol), 2,6-lutidine (30 \(\mu\)L, 0.25 mmol), and benzene (0.75 mL). 2.4aj (67 mg, 88%) was obtained a red oil: \(R_f = 0.50, 25\%\) EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.62 – 7.20 (m, 7H), 6.82 (d, \(J = 1.5\) Hz, 1H), 6.66 (d, \(J = 15.7\) Hz, 1H), 6.38 (dd, \(J = 15.7, 8.9\) Hz, 1H), 5.56 (s, 1H), 5.15 (s, 1H), 4.09 – 3.96 (m, 1H), 3.82 (s, 3H), 3.77 – 3.68 (m, 6H), 2.98 (dd, \(J = 14.2, 4.0\) Hz, 1H), 2.52 (dd, \(J = 14.2, 12.1\) Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.7, 170.6, 147.9, 137.4, 136.9, 133.6, 132.8, 129.9, 128.6, 127.3, 127.2, 126.3, 123.9, 122.0, 118.5, 117.1, 116.8, 108.9, 64.7, 52.9, 52.6, 42.3, 38.2, 32.8; IR (ATR): 2950, 2262, 1732, 1599, 1447, 1266, 1218, 1068, 906, 725; HRMS (ESI+) calc’d for C\(_{26}\)H\(_{26}\)NO\(_4\) [M+H]\(^+\) = 416.1862, found = 416.1864.
10,10-dimethyl 9-methylidene-12-[(1E)-2-[phenylethenyl]-3-azatricyclo [6.4.1.0^{4,13}] trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4bj)

2.4bj was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-[(1E)-2-phenylethenyl]-1,1-dicarboxylate 2.2j (71 mg, 0.27 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnBr$_2$ (121 mg, 0.54 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 2.4bj (19 mg, 24%) was obtained a yellow solid: R$_f$ = 0.50, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 8.05 (s, 1H), 7.57 – 7.08 (m, 8H), 6.92 (dd, J = 2.5, 1.4 Hz, 1H), 6.64 (d, J = 15.7 Hz, 1H), 6.37 (dd, J = 15.7, 8.8 Hz, 1H), 5.53 (s, 1H), 5.16 (s, 1H), 4.11 – 3.92 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.93 (dd, J = 14.2, 3.7 Hz, 1H), 2.51 (dd, J = 14.3, 11.9 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.6, 170.7, 147.5, 137.4, 136.1, 133.6, 132.6, 130.1, 128.6, 127.3, 126.3, 123.7, 122.5, 122.0, 119.1, 119.0, 117.3, 110.7, 64.7, 52.9, 52.6, 42.2, 38.1.; IR (ATR): 3411, 3026, 2952, 2928, 1730, 1699, 1495, 1433, 1217, 1069, 906, 727; HRMS (ESI+) calc’d for C$_{25}$H$_{24}$NO$_4$ [M+H]$^+$ = 402.1705, found = 402.1711.

![Chemical Structure](image)

10,10-dimethyl 3-methyl-9-methylidene-12-ethenyl-3-azatricyclo [6.4.1.0^{4,13}] trideca-1,4(13),5,7- tetraene-10,10-dicarboxylate (2.4ak)

2.4ak was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate 2.2k (42 mg, 0.23 mmol), 4-ethynyl-1-methylindole 2.1a (46 mg, 0.30 mmol), ZnBr$_2$ (104 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.23 mmol), and benzene (0.75 mL). 2.4ak (30 mg, 38%) was obtained as a red oil: R$_f$ = 0.41, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.18 (m, 3H), 6.75 (d, J = 1.6 Hz, 1H), 6.05 – 5.78 (m, 1H), 5.49 (d, J = 1.0 Hz, 1H), 5.34 – 5.20 (m, 1H), 5.19 – 5.11 (m, 1H), 5.09 (d, J = 0.8 Hz, 1H), 3.77 (d, J = 0.9 Hz, 3H), 3.73 (d, J = 0.9 Hz, 3H), 3.67 (d, J = 0.9 Hz, 3H), 2.84 (dd, J = 14.4, 3.9 Hz, 1H), 2.51 – 2.31 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.7, 170.6, 147.7, 141.1, 136.8, 133.6, 126.9, 123.9, 121.9, 118.4, 117.0, 116.8, 114.6, 108.8, 64.7, 52.8, 52.5, 42.0, 39.0, 32.8, 30.0, 29.7.; IR (ATR): 2950, 2925, 1737, 1454, 1435, 1418, 1309, 1267, 1220, 1071, 912, 745; HRMS (ESI+) calc’d for C$_{20}$H$_{22}$NO$_4$ [M+H]$^+$ = 340.1549, found = 340.1548.
could not obtain a good signal.

![Chemical structure](image)

10,10-dimethyl 9-methylidene-12-ethenyl-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4bk)

2.4bk was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate 2.2k (46 mg, 0.23 mmol), 4-ethynylindole 2.1b (42 mg, 0.30 mmol), ZnBr₂ (104 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.23 mmol), and benzene (0.75 mL). 2.4bk (17 mg, 22%) was obtained as a red oil: R<br>ₐ = 0.48, 25% EtOAc in hexanes; ¹H NMR (400 MHz, Chloroform-d) δ 8.08 (s, 1H), 7.38 – 7.07 (m, 3H), 6.86 (t, J = 2.0 Hz, 1H), 5.96 (ddd, J = 17.0, 10.0, 8.6 Hz, 1H), 5.49 (s, 1H), 5.29 – 5.21 (m, 1H), 5.15 (dd, J = 9.9, 1.8 Hz, 1H), 5.11 (s, 1H), 3.89 – 3.78 (m, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.83 (dd, J = 14.3, 3.6 Hz, 1H), 2.40 (dd, J = 14.3, 11.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.7, 170.8, 147.5, 140.9, 136.0, 133.6, 123.8, 122.4, 121.9, 119.0, 118.9, 118.9, 117.3, 114.8, 110.7, 64.8, 52.9, 52.5, 42.0, 39.0.; IR (ATR): 3406, 2952, 1728, 1432, 1215, 910, 730; HRMS (ESI⁺) calc’d for C₁₉H₂₀N⁴O₄ [M+H]^⁺ = 326.1392, found = 326.1386.

![Chemical structure](image)

10,10-dimethyl 2,3-dimethyl-9-methylidene-12-phenyl-3-azatricyclo[6.4.1.0^4,13]trideca-1,4(13),5,7-tetraene-10,10-dicarboxylate (2.4ca)

2.4ca was prepared following General Procedure D. Reagents employed: 1,1-dimethyl 2-phenylecyclopropane-1,1-dicarboxylate 2.2a (53 mg, 0.23 mmol), 4-ethynylindole 2.1c (50 mg, 0.30 mmol), ZnBr₂ (121 mg, 0.46 mmol), 2,6-lutidine (30 μL, 0.27 mmol), and benzene (0.75 mL). 2.4ca (65 mg, 70%) was obtained as a white solid: R<br>ₐ = 0.37, 25% EtOAc in hexanes; ¹H
NMR (599 MHz, Chloroform-d) δ 7.34 (dd, J = 7.3, 1.2 Hz, 1H), 7.26 – 7.21 (m, 3H), 7.20 – 7.14 (m, 4H), 5.59 (d, J = 1.3 Hz, 1H), 4.98 (d, J = 1.4 Hz, 1H), 4.49 (ddd, J = 11.8, 6.2 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 3.52 (d, J = 1.2 Hz, 3H), 3.24 – 3.08 (m, 1H), 2.53 (ddd, J = 14.8, 11.7, 1.5 Hz, 1H), 1.76 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 171.5, 170.0, 149.6, 148.1, 136.1, 134.6, 131.6, 128.5, 128.1, 125.9, 124.2, 120.3, 118.7, 113.4, 112.5, 108.3, 64.1, 52.9, 52.4, 45.8, 41.0, 29.6, 11.6.; IR (ATR): 3057, 3024, 2999, 2950, 2250, 1734, 1600, 1543, 1490, 1434, 1408, 1305, 1271, 1220, 1175, 1093, 1060, 908, 772, 727, 700, 648.; HRMS (ESI+) calc’d for C25H25NNaO4 [M+Na]+ = 426.1676, found = 426.1679.

4.5 Characterization of 3,4-cyclohexanninoindoles

![Chemical Structure](image)

6,6-dimethyl 2-methyl-7-methylidene-5-phenyl-2-azatricyclo[6.3.1.04,12]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7aa)

2.7aa was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-(phenylmethylidene)malonate 2.5a (142 mg, 0.64 mmol), 4-ethynyl-1-methyldione 2.1a (50 mg, 0.32 mmol), ZnI2 (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (15% EtOAc/hexanes), 2.7aa (74 mg, 62%) was obtained as an oil: Rf = 0.21, 15% EtOAc in hexanes; 1H NMR (400 MHz, Chloroform-d) δ 7.64 – 6.92 (m, 8H), 6.80 (s, 1H), 6.25 (s, 1H), 6.25 (s, 1H), 5.81 (s, 1H), 5.24 (s, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.58 (s, 3H); 13C NMR (101 MHz, CDCl3) δ 170.4, 168.9, 142.1, 137.4, 134.9, 128.8, 128.0, 127.9, 127.0, 125.1, 124.0, 122.8, 116.5, 113.5, 112.8, 108.6, 66.4, 53.0, 52.2, 46.9, 33.0.; IR (ATR): 2950, 2251, 1735, 1601, 1494, 1466, 1432, 1302, 1230, 1037, 908, 729, 700.; HRMS (ESI+) calc’d for C23H21NNaO4 [M+Na]+ = 398.1363, found = 398.1362.
6,6-dimethyl 7-methylidene-5-phenyl-2-azatricyclo[6.3.1.0\(^{4,12}\)]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ba)

2.7ba was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-(phenylmethylidene)malonate 2.5a (154 mg, 0.70 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnI\(^2\) (345 mg, 1.05 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). The material was partially purified via flash chromatography (15% EtOAc/hexanes). There was an impurity that could not be removed. Impure 2.7ba (41 mg, 32%) was obtained as an oil: R\(_f\) = 0.20, 25% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) δ 7.99 (s, 1H), 7.37 (dd, \(J = 6.1, 1.9\) Hz, 1H), 7.33 – 7.20 (m, 2H), 7.19 – 7.15 (m, 3H), 7.11 – 7.01 (m, 2H), 6.88 (dd, \(J = 2.2, 0.8\) Hz, 1H), 6.20 (d, \(J = 0.6\) Hz, 1H), 5.77 (s, 1H), 5.20 (s, 1H), 3.57 (s, 3H), 3.54 (s, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) δ 170.3, 168.8, 168.4, 167.9, 141.8, 137.4, 137.3, 133.8, 129.0, 128.8, 128.3, 127.9, 127.8, 127.1, 127.0, 124.8, 123.3, 119.4, 116.5, 114.8, 113.4, 110.3, 77.4, 77.2, 77.0, 76.7, 66.3, 55.0, 53.4, 53.0, 52.7, 52.4, 52.1, 46.9, 44.1.; IR (ATR): 3405, 3030, 3005, 2953, 1734, 1601, 1496, 1236, 1156, 1034, 914, 752, 702.; HRMS (ESI+) calc’d for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_4\) [M+Na\(^+\)] = 384.1206, found = 384.1210.

6,6-dimethyl 2-methyl-7-methylidene-5-(4-cyanophenyl)-2-azatricyclo[6.3.1.0\(^{4,12}\)]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ab)

2.7ab was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-cyanophenyl)methylidene]malonate 2.5b (157 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI\(^2\) (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7ab (97 mg, 75%) was obtained as an oil: R\(_f\) = 0.12, 20% EtOAc in hexanes; \(^1\)H NMR (599 MHz, 71
Chloroform-$d$) $\delta$ 7.44 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 7.3$ Hz, 1H), 7.29 (t, $J = 7.7$ Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 1H), 7.18 (d, $J = 8.1$ Hz, 2H), 6.74 (s, 1H), 6.18 (s, 1H), 5.58 (s, 1H), 5.23 (s, 1H), 3.73 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 168.7, 147.9, 137.4, 134.9, 131.7, 129.6, 127.9, 124.7, 124.2, 123.2, 119.0, 116.5, 113.2, 112.2, 110.5, 108.9, 66.4, 53.2, 52.4, 46.6, 33.0; IR (ATR): 2951, 2228, 2127, 1731, 1606, 1503, 1434, 1239, 1043, 912, 757, 732, 351.; HRMS (ESI+) calc’d for C$_{24}$H$_{20}$N$_2$O$_4$ [M+Na]$^+$ = 423.1315, found = 423.1293.

6,6-dimethyl 7-methylidene-5-(4-cyanophenyl)-2-azatricyclo[6.3.1.0$^{4,12}$]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7bb)

2.7bb was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-cyanophenyl)methylidene]malonate 2.5b (172 mg, 0.70 mmol), 4-ethynylindole 2.1b (50 mg, 0.35 mmol), ZnI$_2$ (335 mg, 1.05 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). The material was partially purified via flash chromatography (35% EtOAc/hexanes). There was an impurity that could not be removed. Impure 2.7bb (43 mg, 32%) was obtained as an oil: $R_f = 0.20$, 35% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.12 (d, $J = 12.0$ Hz, 1H), 7.68 – 7.54 (m, 1H), 7.48 (dd, $J = 8.5$, 6.6 Hz, 2H), 7.41 (dd, $J = 5.1$, 2.9 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 1H), 6.89 (dd, $J = 2.2$, 0.7 Hz, 1H), 6.25 – 6.12 (m, 1H), 5.61 (s, 1H), 5.27 (s, 1H), 3.64 (s, 3H), 3.55 (s, 3H). $^{13}$C NMR (including impurities): $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.0, 168.8, 168.0, 167.6, 147.7, 142.9, 137.5, 133.9, 132.1, 131.8, 130.3, 129.7, 124.5, 124.5, 123.7, 119.7, 119.1, 116.6, 113.8, 113.5, 110.8, 110.6, 77.5, 77.2, 76.8, 66.5, 60.5, 54.3, 53.3, 53.0, 52.8, 52.5, 46.7, 44.0, 21.2, 14.3. IR (ATR): 3405, 2953, 2228, 1731, 1606, 1503, 1434, 1239, 1043, 912, 757, 732, 581.; HRMS (ESI+) calc’d for C$_{23}$H$_{28}$N$_2$O$_4$ [M+Na]$^+$ = 409.1159, found = 409.1164.
6,6-dimethyl 2-methyl-7-methylidene-5-(4-methoxyphenyl)-2-azatricyclo[6.3.1.0^4,12]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ac)

2.7ac was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-methoxyphenyl)methylidene]malonate 2.5c (160 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (25% EtOAc/hexanes), 2.7ac (41 mg, 30%) was obtained as a yellow oil: $R_f = 0.35$, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.36 (d, $J = 7.2$ Hz, 1H), 7.28 (d, $J = 1.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.78 (s, 1H), 6.73 (d, $J = 8.5$ Hz, 2H), 6.21 (s, 1H), 5.78 (d, $J = 0.9$ Hz, 1H), 5.16 (s, 1H), 3.76 – 3.74 (m, 6H), 3.61 (s, 3H), 3.56 (d, $J = 1.0$ Hz, 3H).; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.4, 168.9, 158.5, 137.6, 134.9, 134.0, 129.8, 128.0, 125.1, 123.8, 122.8, 116.3, 113.8, 113.2, 112.8, 108.5, 66.5, 55.0, 52.9, 52.1, 46.2, 33.0.; IR (ATR): 2998, 2950, 2837, 1737, 1608, 1510, 1466, 1301, 1236, 1177, 1035, 911, 800.; HRMS (ESI+) calc’d for C$_{24}$H$_{23}$NNaO$_5$ [M+Na]$^+$ = 428.1468, found = 428.1455.

![Chemical structure image]

6,6-dimethyl 2-methyl-7-methylidene-5-[4-(methoxycarbonyl)phenyl]-2-azatricyclo[6.3.1.0^4,12]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ad)

2.7ad was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-methoxyphenyl)methylidene]malonate 2.5d (178 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (25% EtOAc/hexanes), 2.7ad (121 mg, 87%) was obtained as an oil: $R_f = 0.33$, 25% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.87 (d, $J = 8.3$ Hz, 2H), 7.39 (d, $J = 7.2$ Hz, 1H), 7.35 – 7.27 (m, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 6.78 (s, 1H), 6.23 (s, 1H), 5.70 (s, 1H), 5.28 (s,
1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.60 (s, 3H), 3.56 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 170.1, 168.7, 167.0, 147.5, 137.4, 134.9, 129.3, 128.8, 128.6, 127.9, 124.9, 124.1, 123.0, 116.5, 113.0, 112.7, 108.7, 66.3, 53.1, 52.3, 52.0, 46.7, 33.0; IR (ATR): 3057, 2949, 1734, 1717, 1608, 1466, 1434, 1280, 1236, 1210, 1104, 1036, 948, 916, 796, 766, 744, 727, 704, 652, 571.

HRMS (ESI+) calc’d for C\(_{25}\)H\(_{23}\)NNaO\(_6\) [M+Na]\(^+\) = 456.1418, found = 456.1420.

6,6-dimethyl 2-methyl-7-methylidene-5-(2-furan-2-yl)-2-azatricyclo[6.3.1.0\(_4\)\(_1\)2]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ae)

2.7ae was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[furan-2-yl]methylidene]malonate 2.5e (134 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI\(_2\) (305 mg, 0.96 mmol), 2,6-lutidine (60 \(\mu\)L, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (15% EtOAc/hexanes), 2.7ae (41 mg, 35%) was obtained as an oil: R\(_f\) = 0.13, 15% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.31 (dd, \(J\) = 1.9, 0.9 Hz, 1H), 7.29 (d, \(J\) = 0.9 Hz, 1H), 7.23 (d, \(J\) = 7.2 Hz, 1H), 7.18 (dd, \(J\) = 8.0, 0.9 Hz, 1H), 6.88 (d, \(J\) = 1.0 Hz, 1H), 6.28 (dd, \(J\) = 3.2, 1.8 Hz, 1H), 6.08 (d, \(J\) = 2.4 Hz, 2H), 5.48 (s, 1H), 5.33 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.59 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 170.1, 168.9, 154.2, 141.0, 139.2, 135.0, 128.0, 125.1, 124.2, 123.0, 114.7, 112.8, 110.4, 110.2, 108.6, 107.5, 66.4, 53.0, 52.6, 41.0, 33.0; IR (ATR): 2954, 2924, 2854, 1736, 1603, 1252, 1048, 912, 752, 735.; HRMS (ESI+) calc’d for C\(_{21}\)H\(_{19}\)NNaO\(_5\) [M+Na]\(^+\) = 388.1155, found = 388.1172.

6,6-dimethyl 2-methyl-7-methylidene-5-(2-thiophene-2-yl)-2-azatricyclo[6.3.1.0\(_4\)\(_1\)2]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7af)
2.7af was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(thiophen-2-yl)methylidene]malonate 2.5f (145 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI₂ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (15% EtOAc/hexanes), 2.7af (53 mg, 44%) was obtained as an oil: Rᵣ = 0.17, 15% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.12 (m, 4H), 6.97 – 6.88 (m, 2H), 6.87 (d, J = 1.0 Hz, 1H), 6.17 (s, 1H), 5.71 (s, 1H), 5.52 (s, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 3.62 (s, 3H); \(^13\)C NMR (101 MHz, CDCl₃) δ 170.0, 168.7, 143.8, 138.6, 135.0, 127.9, 126.4, 126.0, 124.8, 124.7, 124.2, 123.0, 115.8, 113.6, 112.9, 108.6, 67.2, 52.9, 52.4, 42.9, 33.0.; IR (ATR): 2950, 1736, 1602, 1466, 1432, 1358, 1302, 1230, 1207, 1046, 910, 755, 731, 704.; HRMS (ESI+) calc'd for C\textsubscript{21}H\textsubscript{19}N\textsubscript{4}NaO\textsubscript{4} \([M+Na]^+\) = 404.0927, found = 404.0914.

![Image of 6,6-dimethyl 2-methyl-7-methylidene-5-(4-fluorophenyl)-2-azatricyclo[6.3.1.0\textsubscript{4,12}]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ag)](image)

2.7ag was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-fluorophenyl)methylidene]malonate 2.5g (153 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI₂ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7ag (73 mg, 58%) was obtained as an oil: Rᵣ = 0.20, 20% EtOAc in hexanes; \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.35 (m, 1H), 7.33 – 7.26 (m, 1H), 7.23 (dd, J = 8.1, 0.8 Hz, 1H), 7.09 (dd, J = 8.7, 5.4 Hz, 2H), 6.89 (t, J = 8.7 Hz, 2H), 6.78 (s, 1H), 6.23 (s, 1H), 5.76 (d, J = 1.4 Hz, 1H), 5.22 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H); \(^13\)C NMR (101 MHz, CDCl₃) δ 170.3, 168.9, 163.1, 160.6, 137.8, 137.8, 137.5, 134.9, 130.4, 130.3, 127.9, 125.0, 124.0, 123.0, 116.5, 114.8, 114.6, 113.4, 112.9, 108.7, 66.5, 53.0, 52.2, 46.2, 33.0.; IR (ATR): 2951, 2926, 1735, 1602, 1507, 1466, 1433, 1302, 1219, 1158, 1045, 907, 850, 806, 726, 649, 574, 523.; HRMS (ESI+) calc’d for C\textsubscript{24}H\textsubscript{20}FN\textsubscript{4}NaO\textsubscript{4} \([M+Na]^+\) = 416.1269, found = 416.1282.
6,6-dimethyl 2-methyl-7-methylidene-5-(4-chlorophenyl)-2-azatricyclo[6.3.1.0^{4,12}]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ah)

2.7ah was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-chlorophenyl)methylidene]malonate 2.5h (163 mg, 0.64 mmol), 4-ethyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7ah (85 mg, 65%) was obtained as an oil: R$_f$ = 0.31, 20% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.38 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.29 (d, $J = 4.8$ Hz, 1H), 7.23 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.16 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.5$ Hz, 2H), 6.77 (d, $J = 0.7$ Hz, 1H), 6.21 (s, 1H), 5.72 (s, 1H), 5.19 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.2, 168.8, 140.6, 137.5, 134.9, 132.7, 130.2, 128.1, 127.9, 124.9, 124.0, 123.0, 116.4, 113.1, 113.0, 108.7, 66.4, 53.1, 52.3, 46.2, 33.0.; IR (ATR): 2950, 2254, 1735, 1601, 1489, 1466, 1432, 1301, 1233, 1088, 1044, 1015, 909, 790, 729, 650.; HRMS (ESI+) calc’d for C$_{23}$H$_{20}$NNaO$_4$Cl [M+Na]$^+$ = 432.0973, found = 432.0965.

6,6-dimethyl 2-methyl-7-methylidene-5-(4-bromophenyl)-2-azatricyclo[6.3.1.0^{4,12}]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ai)

2.7ai was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(4-bromophenyl)methylidene]malonate 2.5i (190 mg, 0.64 mmol), 4-ethyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7ai (80 mg, 55%) was obtained as an oil: R$_f$ = 0.19, 20% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.39 (d, $J = 7.2$ Hz, 1H), 7.34 – 7.18 (m, 5H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.78
(s, 1H), 6.23 (s, 1H), 5.73 (s, 1H), 5.20 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 170.2, 168.8, 141.2, 137.5, 134.9, 131.0, 130.6, 127.9, 124.9, 124.0, 123.0, 120.9, 116.4, 113.0, 113.0, 108.7, 66.3, 53.1, 52.3, 46.3, 33.0; \textbf{IR (ATR)}: 2950, 2255, 1735, 1601, 1487, 1466, 1432, 1231, 1037, 1010, 907, 788, 726, 648; \textbf{HRMS (ESI+)} calc’d for C\textsubscript{23}H\textsubscript{20}NNaO\textsubscript{4}Br [M+Na]\textsuperscript{+} = 476.0468, found = 476.0458.

6,6-dimethyl 2-methyl-7-methylidene-5-(2,3,4,5,6-pentafluorophenyl)-2-azatricyclo[6.3.1.0\textsuperscript{4,12}]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7aj)

\textbf{2.7aj} was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(2,3,4,5,6-pentafluorophenyl)methylidene]malonate \textbf{2.5j} (153 mg, 0.64 mmol), 4-ethynyl-1-methylindole \textbf{2.1a} (50 mg, 0.32 mmol), ZnI\textsubscript{2} (305 mg, 0.96 mmol), 2,6-lutidine (60 \(\mu\)L, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (25% EtOAc/hexanes), \textbf{2.7aj} (60 mg, 40%) was obtained as an oil: \(R_f = 0.58\), 25% EtOAc in hexanes; \textbf{\textsuperscript{1}H NMR} (400 MHz, Chloroform-\textit{d}) \(\delta\) 7.36 (dd, \(J = 7.2, 0.8\) Hz, 1H), 7.32 – 7.25 (m, 1H), 7.22 (dd, \(J = 8.1, 0.8\) Hz, 1H), 6.84 – 6.79 (m, 1H), 6.10 (s, 1H), 5.86 (s, 1H), 5.47 (s, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.57 (s, 3H); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 169.9, 168.7, 137.8, 134.6, 128.1, 125.4, 124.3, 123.1, 114.4, 113.2, 108.7, 65.6, 53.4, 52.8, 35.6, 33.0; \textbf{IR (ATR)}: 2954, 1733, 1521, 1497, 1467, 1304, 1242, 1121, 1092, 1045, 991, 967, 909, 731, 649; \textbf{HRMS (ESI+)} calc’d for C\textsubscript{23}H\textsubscript{16}NNaO\textsubscript{5}F\textsubscript{5} [M+Na]\textsuperscript{+} = 488.0892, found = 488.0903.

6,6-dimethyl 2-methyl-7-methylidene-5-(2H-1,3-benzodioxol-5-yl)-1H-indol-3-yl]-2-azatricyclo[6.3.1.0\textsuperscript{4,12}]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7ak)
2.7ak was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[(2H-1,3-benzodioxol-5-yl)methylidene]malonate 2.5k (169 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7ak (89 mg, 66%) was obtained as an oil: $R_f = 0.15$, 20% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 7.35 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.28 (m, 1H), 7.21 (dd, $J = 8.1, 0.8$ Hz, 1H), 6.79 (d, $J = 0.7$ Hz, 1H), 6.71 – 6.59 (m, 2H), 6.52 (d, $J = 1.6$ Hz, 1H), 6.22 (d, $J = 0.6$ Hz, 1H), 5.88 (dd, $J = 8.8, 1.5$ Hz, 2H), 5.82 (s, 1H), 5.14 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.3, 168.8, 147.2, 146.4, 137.2, 136.0, 134.9, 127.8, 125.0, 123.8, 122.8, 121.8, 116.6, 113.6, 112.9, 110.2, 108.5, 107.5, 100.8, 66.3, 53.0, 52.2, 46.6, 33.0.; IR (ATR): 2950, 1737, 1602, 1488, 1441, 1232, 1039, 914, 731.; HRMS (ESI+) calc’d for C$_{24}$H$_{21}$N$_2$NaO$_4$ [M+Na]$^+$ = 384.1206, found = 384.1210.

6,6-dimethyl 2-methyl-7-methylidene-5-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]-2-azatricyclo[6.3.1.0$^{4,12}$]dodeca-1(12),3,8,10-tetraene-6,6-dicarboxylate (2.7al)

2.7al was prepared following General Procedure E. Reagents employed: 1,3-dimethyl 2-[[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]methylidene]malonate 2.5l (264 mg, 0.64 mmol), 4-ethynyl-1-methylindole 2.1a (50 mg, 0.32 mmol), ZnI$_2$ (305 mg, 0.96 mmol), 2,6-lutidine (60 μL, 0.64 mmol), and 1,4-dioxane (1 mL). After purification via flash chromatography (20% EtOAc/hexanes), 2.7al (32 mg, 18%) was obtained as an oil: $R_f = 0.15$, 20% EtOAc in hexanes; $^1$H NMR (400 MHz, Chloroform-d) δ 8.00 – 7.88 (m, 1H), 7.67 (d, $J = 8.3$ Hz, 2H), 7.57 – 7.51 (m, 1H), 7.45 – 7.08 (m, 8H), 6.69 (d, $J = 0.9$ Hz, 1H), 6.19 (s, 1H), 5.63 (s, 1H), 5.46 (s, 1H), 3.73 (s, 3H), 3.46 (s, 3H), 3.26 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.1, 168.8, 144.5, 139.1, 135.3, 135.1, 134.7, 131.0, 129.6, 127.8, 126.8, 126.1, 124.9, 124.4, 123.6, 123.1, 123.0, 122.9, 119.7, 115.3, 113.8, 113.1, 112.8, 108.8, 66.3, 52.8, 52.1, 37.7,
33.0, 21.6.; IR (ATR): 2951, 1737, 1447, 1366, 1238, 1174, 1121, 1091, 1048, 973, 748, 668, 575, 538.; HRMS (ESI+) calc’d for C_{32}H_{28}N_{2}O_{6}S_{2}Na [M+Na]^+ = 591.1560, found = 591.1557.

References

Appendix – $^1$H NMR, $^{13}$C NMR
1H NMR (400 MHz, Chloroform-d) δ 10.22 (s, 1H), 7.63 – 7.55 (m, 1H), 7.52 – 7.46 (m, 1H), 7.34 – 7.16 (m, 1H), 7.05 (q, J ≈ 9.0 Hz, 1H), 3.79 – 3.58 (m, 3H), 2.46 (dd, J ≈ 1.8, 9.0 Hz, 3H).

13C NMR (100 MHz, CDCl3) δ 193.3, 168.2, 141.3, 138.2, 127.2, 127.0, 126.1, 119.7, 114.9, 114.9, 109.6, 29.7, 29.6, 29.6, 13.0, 13.0.
\[ ^{1}H\text{NMR (400 MHz, Chloroform-d):} \delta 7.32 - 7.26 (m, 2H), 7.11 (t, J = 7.8 Hz, 2H), 6.45 (d, J = 1.3 Hz, 1H), 3.69 (s, 3H), 3.29 (s, 1H), 2.47 (d, J = 1.9 Hz, 3H). \]

\[ ^{13}C\text{NMR (101 MHz, CDCl}_3): \delta 138.0, 156.9, 129.9, 123.3, 112.4, 109.7, 99.4, 83.0, 78.8, 59.7, 29.0, 12.8. \]
1H NMR (400 MHz, Chloroform-d): δ 7.51 – 6.97 (m, 8H), 6.25 (d, J = 1.5 Hz, 1H), 5.55 (s, 1H), 5.18 (s, 1H), 4.41 (dd, J = 12.0, 3.4 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 2.95 (dd, J = 14.2, 3.4 Hz, 1H), 2.75 (dd, J = 14.2, 12.1 Hz, 1H).
$^{13}C$ NMR (100 MHz, CDCl$_3$): 0.171, 1.71, 17.0, 147.5, 145.9, 136.5, 133.9, 138.5, 128.4, 127.7, 126.8, 124.6, 122.0, 119.7, 118.7, 117.7, 108.8, 65.0, 53.9, 52.6, 44.2, 40.8, 32.7.
PROTON-1H CDCl₃ /home/nmr-data/Kerr/Shane/9406 Kerr 23

1H NMR (500 MHz, CDCl₃): δ 7.96, 7.23, 6.39, 4.42.

13C NMR (125 MHz, CDCl₃): δ 171.6, 171.3, 158.3, 147.1, 137.8, 135.8, 133.0, 129.3, 124.3, 122.5, 122.2, 121.9, 110.2, 118.1, 113.9, 110.7, 65.1, 55.3, 52.8, 52.5, 44.3, 39.8.
\begin{align*}
\text{H NMR} (400 MHz, Chloroform-d$_6$): & 7.31 – 7.14 (m, 3H), 6.89 (d, J = 8.6 Hz, 2H), 6.24 (d, J = 1.5 Hz, 1H), 5.52 (s, 1H), 5.15 (s, 1H), 4.40 – 4.30 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 2.89 (d, J = 14.2 Hz, 1H), 2.69 (d, J = 14.2 Hz, 1H).
\end{align*}
$^{13}$C NMR (101 MHz, CDCl$_3$): 61.71, 171.0, 158.4, 147.6, 135.2, 138.7, 134.0, 129.4, 127.3, 124.7, 122.1, 120.2, 118.7, 113.8, 114.0, 108.9, 77.5, 77.4, 77.2, 76.8, 65.1, 53.4, 53.0, 52.7, 44.5, 40.0, 32.8
$^1$H NMR (400 MHz, Chloroform-d): δ 7.67 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.39–7.19 (m, 2H), 6.38–6.13 (m, 3H), 3.57 (q, J = 1.3 Hz, 1H), 2.31 (dd, J = 14.2, 3.5, 2.0 Hz, 1H), 2.70 (dd, J = 14.1, 3.5, 1.4 Hz, 1H).

$^1$C NMR (100 MHz, CDCl$_3$): δ 171.3, 170.9, 151.1, 146.7, 135.7, 133.7, 132.5, 129.2, 124.1, 122.9, 121.9, 120.3, 119.5, 119.0, 118.4, 110.9, 110.6, 64.8, 53.0, 52.7, 43.7, 40.8.
$^13$C NMR (101 MHz, CDCl$_3$): 157.4, 170.0, 157.8, 147.0, 141.2, 135.7, 133.6, 123.0, 122.5, 121.7, 119.3, 118.1, 117.9, 110.8, 110.1, 105.3, 84.7, 52.0, 52.7, 48.3, 33.9.
C-13 (H-1) using the Bruker 400 MHz.

H-COSY (101 MHz, CDCl3) δ 171.7, 170.4, 147.9, 137.4, 136.9, 133.6, 132.8, 129.9, 128.6, 127.3, 127.2, 126.9, 125.9, 122.0, 118.5, 117.1, 116.8, 108.9, 84.7, 52.5, 52.6, 42.3, 38.2, 32.8.
$^1$H NMR (400 MHz, Chloroform-d): δ 8.06 (s, 1H), 7.38 – 7.17 (m, 18H), 6.87 (s, 1H), $J = 2$ Hz. (III), 5.84 (dd, $J = 7.0, 10.0$, 8 Hz, III), 5.40 (d, $J = 5.2$ Hz, III), 5.29 – 5.21 (m, III), 5.15 (dd, $J = 0.8$, 1.8 Hz, III), 5.11 (s, III), 3.89 – 3.78 (m, III), 3.73 (s, III), 3.68 (s, III), 2.83 (m, $J = 14.3$, 3.5 Hz, III), 2.40 (dd, $J = 14.3$, 11.0 Hz, III).

$^1$C NMR (101 MHz, CDCl$_3$): δ 171.7, 170.8, 147.5, 140.9, 138.0, 133.6, 123.8, 122.4, 121.9, 119.0, 118.9, 118.9, 117.3, 114.8, 110.7, 64.8, 52.9, 52.5, 42.0, 39.9.
$^1$H NMR (400 MHz, Chloroform-d) δ 8.05 (s, 3H), 7.45 (d, $J = 8.3$ Hz, 3H), 7.35 (t, 3H), 6.32 (s, 1H), 5.66 (s, 1H), 3.21 (s, 3H), 4.55 (s, 1H), 1.5 Hz, 1H), 3.95 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 2.94 (s, 3H), 1.43 (s, 3H), 1.1 (1H).

$^1$C NMR (101 MHz, CDCl$_3$) δ 171.5, 170.1, 167.1, 167.4, 164.9, 146.2, 135.7, 133.7, 132.9, 128.6, 128.2, 122.7, 122.1, 120.9, 119.4, 118.9, 110.8, 65.9, 52.6, 52.7, 52.1, 43.7, 40.7.
PROTON-UNO CDCl3 /home/nmr-data/Kent/Shane/8400 Kent 15

1H NMR (400 MHz, Chloroform-d) 8 8.09 - 7.96 (m, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 7.50 - 7.04 (m, 3H), 6.41 (d, J = 2.3 Hz, 1H), 5.59 (s, 1H), 5.22 (s, 1H), 4.87 - 4.65 (m, 1H), 3.80 - 3.65 (m, 6H), 2.99 (dd, J = 14.3, 3.6 Hz, 1H), 2.87 (dd, J = 14.3, 11.9 Hz, 1H), 2.39 (s, 3H).

SCS-1290H-2.2hd C-13 (1H) using the Bruker 400

CARBON-nboe CDCl3 /home/nmr-data/Kent/Shane/8400 Kent 6

13C NMR (101 MHz, CDCl3) 5 171.5, 170.8, 147.1, 146.0, 144.9, 135.9, 135.6, 135.3, 133.6, 133.6, 130.0, 126.6, 126.4, 124.7, 124.0, 122.3, 122.9, 122.5, 122.2, 120.0, 119.2, 118.3, 117.9, 113.8, 110.9, 66.8, 52.9, 52.7, 42.7, 34.7, 21.6.
H NMR (400 MHz, Chloroform-δ): δ 8.06 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 7.8 Hz, 2H), 7.54 (m, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.39 – 7.22 (m, 6H), 7.16 (t, J = 7.8 Hz, 1H), 6.33 (s, 1H), 5.19 (s, 2H), 2.70 (s, 2H), 3.73 (d, J = 10.7 Hz, 1H), 3.75 (s, 2H), 3.25 (s, 3H), 3.11 – 2.91 (m, 13H), 2.92 – 2.77 (m, 18H), 2.30 (s, 3H).

C-12 (H-1) using the Bruker 400

1H NMR (400 MHz, CDCl3): δ 171.6, 170.7, 147.4, 144.9, 136.6, 135.7, 135.3, 133.8, 130.0, 130.0, 127.0, 125.6, 125.7, 124.7, 124.3, 123.3, 123.0, 122.1, 120.6, 118.8, 117.6, 118.8, 112.9, 109.9, 65.0, 62.9, 22.7, 21.8, 21.6.
$^{1}H$ NMR (400 MHz, Chloroform-d): δ 7.92 (s, 1H), 7.35 - 7.39 (m, 3H), 6.94 - 6.71 (m, 3H), 6.44 (d, J = 2.4, 1H Hz, 1H), 5.96 (d, J = 1.4 Hz, 2H), 5.52 (s, 1H), 5.17 (c, 1H), 4.38 (d, J = -11.9 Hz, 2H), 2.88 (s, J = 14.3, 3.2 Hz, 2H), 2.66 (d, J = 14.3 Hz, 2H).}

$^{13}C$ NMR (101 MHz, CDCl3): δ 171.1, 171.1, 171.1, 147.8, 147.9, 148.6, 139.7, 135.9, 134.6, 124.4, 122.7, 122.7, 121.7, 121.5, 119.4, 118.3, 110.9, 108.9, 108.3, 101.6, 77.5, 77.4, 77.2, 77.1, 78.8, 65.1, 53.0, 52.7, 44.5, 40.5.
H NMR (400 MHz, CDCl₃): δ 7.38 – 7.19 (m, 3H), 6.94 – 6.81 (m, 3H), 6.37 (t, 1H), 6.04 – 5.93 (m, 3H), 5.58 (s, 1H), 5.20 (s, 1H), 4.44 – 4.37 (m, 1H), 2.00 (s, 1H), 1.76 (d, J = 14.2 Hz, 1H), 1.73 (d, J = 14.2 Hz, 1H).

(C) NMR (1H MHz, CDCl₃): δ 171.6, 170.8, 147.3, 147.5, 146.2, 139.0, 136.6, 133.8, 127.3, 124.2, 122.0, 121.3, 119.4, 118.7, 117.6, 108.9, 108.8, 108.2, 100.9, 94.9, 22.9, 22.6, 44.5, 40.5, 32.8.
$^1$H NMR (599 MHz, Chloroform-d) δ 7.54 (dd, J = 7.3, 1.2 Hz, 1H), 7.26 – 7.21 (m, 3H), 7.20 – 7.14 (m, 4H), 5.59 (d, J = 1.3 Hz, 1H), 4.98 (d, J = 1.4 Hz, 1H), 4.49 (dd, J = 11.8, 2 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 3.52 (d, J = 1.2 Hz, 3H), 3.24 – 3.08 (m, 1H), 2.53 (dd, J = 14.8, 11.7, 12.5 Hz, 1H), 1.74 (s, 3H).

$^1$C NMR (101 MHz, CDCl$_3$) δ 171.5, 170.0, 140.6, 148.1, 136.1, 134.6, 131.6, 129.5, 128.1, 125.9, 124.2, 135.3, 138.7, 133.4, 125.3, 108.5, 64.1, 52.3, 32.4, 45.4, 41.0, 29.0, 11.6.
$^{1}H$ NMR (400 MHz, Chloroform-$d$): δ 8.87 (d, $J = 8.3$ Hz, 2H), 7.39 (d, $J = 7.1$ Hz, 3H), 7.35 – 7.27 (m, 3H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 4.4$ Hz, 3H), 7.68 (s, 1H), 6.23 (s, 1H), 5.70 (s, 1H), 5.28 (s, 3H), 3.87 (s, 3H), 3.74 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H).

$^{13}C$ NMR (101 MHz, CDCl$_3$): δ 170.1, 168.7, 167.9, 147.5, 137.4, 134.9, 129.3, 128.8, 128.6, 127.9, 124.9, 124.1, 123.0, 118.5, 113.0, 112.7, 108.7, 66.3, 53.1, 52.3, 52.0, 46.7, 33.0.
**H NMR (400 MHz, Chloroform-d):** 8.00 - 7.88 (m, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.57 - 7.51 (m, 1H), 7.45 - 7.40 (m, 1H), 7.19 (d, J = 9.0 Hz, 1H), 5.19 (s, 1H), 5.03 (s, 1H), 3.48 (s, 1H), 3.25 (q, 2H), 2.56 (s, 3H).

**C NMR (101 MHz, CDCl3):** 170.1, 168.8, 144.5, 139.1, 135.3, 135.1, 134.7, 131.0, 129.6, 127.8, 126.8, 125.1, 124.9, 124.4, 123.6, 123.1, 123.0, 122.0, 130.7, 115.3, 113.3, 113.1, 112.8, 108.8, 68.3, 62.8, 52.1, 37.7, 33.0, 21.6.
$^1$H NMR (400 MHz, Chloroform-d) δ 7.35 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.31 (m, 1H), 7.21 (dd, $J = 8.1, 0.8$ Hz, 1H), 6.79 (d, $J = 7.0$ Hz, 1H), 6.51 (m, 2H), 6.52 (d, $J = 8.8, 1.3$ Hz, 2H), 5.82 (s, 1H), 3.14 (s, 3H), 3.06 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl3) δ 170.3, 168.8, 147.3, 144.4, 137.2, 136.9, 134.9, 127.8, 125.0, 123.8, 122.8, 121.8, 116.9, 113.6, 112.0, 109.2, 108.5, 107.5, 100.8, 68.3, 53.0, 52.2, 45.6, 33.0.

COOMe
**PROTON 1H (CDCl3)**

H NMR (400 MHz, CDCl3): δ 7.39 (d, J = 7.2 Hz, 1H), 7.34 – 7.18 (m, 3H), 7.01 (d, J = 8.3 Hz, 1H), 6.78 (s, 1H), 6.23 (s, 1H), 5.73 (s, 1H), 5.20 (s, 1H), 3.75 (s, 1H), 2.64 (s, 3H), 3.58 (s, 3H).

**CARBON 13C (CDCl3)**

13C NMR (101 MHz, CDCl3): δ 170.2, 168.8, 141.2, 137.5, 134.0, 131.0, 130.6, 127.9, 124.9, 124.0, 123.0, 120.9, 116.4, 113.6, 113.0, 108.7, 66.3, 33.1, 32.3, 46.3, 33.0.
PROTON: UVO CDCl3

$^1$H NMR (400 MHz, Chloroform-d): δ 3.71 - 7.35 (m, 1H), 7.33 - 7.36 (m, 1H), 7.23 (d, J = 8.1, 0.8 Hz, 1H), 7.00 (d, J = 8.7, 5.4 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.78 (s, 1H), 6.23 (s, 1H), 5.78 (d, J = 1.4 Hz, 1H), 5.23 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl3): δ 170.3, 168.9, 163.1, 166.6, 137.8, 137.5, 134.9, 130.4, 130.3, 127.9, 125.0, 124.0, 123.0, 116.5, 114.8, 114.6, 113.4, 113.9, 108.7, 86.5, 53.0, 52.2, 46.2, 33.5.
$^1$H NMR (400 MHz, Chloroform-d): δ 7.36 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.32 - 7.25 (m, 2H), 7.22 (dd, $J = 8.1, 0.8$ Hz, 1H), 6.84 - 6.79 (m, 1H), 6.10 (s, 1H), 5.48 (s, 1H), 5.47 (s, 1H), 7.10 (s, 1H), 3.71 (s, 1H), 3.57 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.9, 168.7, 137.8, 134.6, 128.1, 124.3, 123.1, 114.4, 113.2, 108.7, 65.6, 53.4, 52.8, 51.6, 33.0.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.23 (dd, J = 8.0, 0.8 Hz, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.05 (dd, J = 8.5 Hz, 2H), 6.77 (d, J = 0.7 Hz, 1H), 6.21 (s, 1H), 5.72 (s, 1H), 5.19 (s, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.2, 168.8, 140.6, 137.5, 134.0, 132.7, 130.2, 128.3, 127.9, 124.9, 124.0, 123.0, 118.4, 113.1, 113.0, 108.7, 68.4, 53.1, 52.3, 46.2, 33.0.
**H NMR (400 MHz, CDCl₃)**  δ 7.54 - 6.92 (m, 8H), 6.80 (s, 1H), 6.25 (s, 1H), 5.81 (s, 1H), 5.24 (s, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.58 (s, 3H).

**13C NMR (101 MHz, CDCl₃)** δ 170.4, 168.9, 142.1, 137.4, 134.9, 128.8, 128.0, 127.9, 127.0, 125.1, 124.0, 122.8, 116.5, 113.5, 112.8, 108.0, 66.4, 53.0, 52.2, 46.9, 33.0.
$\text{H NMR (599 MHz, Chloroform-d): s 8.3 Hz, 2H), 7.37 (d, } J = 7.3 \text{ Hz, 1H), 7.29 (d, } J = 7.7 \text{ Hz, 2H), 7.22 (d, } J = 8.1 \text{ Hz, 1H), 7.18 (d, } J = 8.1 \text{ Hz, 1H), 6.74 (s, 1H), 6.18 (s, 1H), 5.58 (s, 1H), 3.25 (s, 1H), 3.73 (s, 1H), 3.81 (s, 3H), 3.53 (s, 3H).}$

$\text{13C NMR (101 MHz, CDCl$_3$): s 170.0, 168.7, 147.9, 137.4, 134.9, 131.7, 129.6, 127.9, 124.7, 124.2, 123.2, 119.0, 116.5, 113.2, 112.2, 110.5, 108.9, 73.2, 52.4, 46.6, 33.0.}$
Curriculum Vitae

EDUCATION

Bachelor of Science, Honours Specialization in Chemistry
*The University of Western Ontario, London, Ontario*
Sept. 2015 – April 2020

Master of Science, Organic Chemistry
*The University of Western Ontario, London, Ontario*
May 2020 – present

RESEARCH EXPERIENCE

Masters Student
*The University of Western Ontario, London, Ontario*
Research Supervisor: M. A. Kerr
May 2020 – present

- Developed new synthetic methodologies for the synthesis of 3,4-annulated indole via tandem Michael addition/Conia-ene and cyclopropane ring-opening/Conia-ene reactions
- Gained first-hand experience with named reactions such as: the Knoevenagel condensation, Swern oxidation, and Corey-Chaykovsky cyclopropanation

Undergraduate Chemistry Thesis Project
*The University of Western Ontario, London, Ontario*
Research Supervisor: M. A. Kerr
Sept. 2019 – April 2020

- Attempted synthesis of alkyl diazo compounds by diazotization of aminocyclopropanes
- Attempted synthesis of piperidines via a one-pot cyclopropane ring-opening/ene-yne metathesis reaction
- Attempted synthesis of pyrrolidines via ring-opening reactions of donor-acceptor cyclopropanes with aryl azides

Science Internship Program
*BioLiNE Corp., Alvinston, Ontario*
May 2018 – August 2019

- Carried out many gravimetric analyses of aqueous samples for the purposes of quality assurance
- Designed and carried out a multitude of experiments to gain insight into fulvic acid, and to improve the fulvic acid product
- Assisted with bench and pilot scale experiments for the implementation of new chemical processes on a plant scale
AWARDS

- Dean’s list, *The University of Western Ontario*, London, Ontario

EMPLOYMENT

**Teaching Assistant – Western University**

- Chemistry 1302B: Assisted students with homework problems and answered questions about testable material
- Chemistry 2273A: Graded laboratory reports as well as midterm and final exams
- Solvent Purification System Manager: Refilled solvents, replaced nitrogen tanks, and ensured proper maintenance of equipment

**Associate Scientist – Paraza Pharma**

- May 2020 – present
- June 2022