October 2017

Synthesis of N-Heterocycles from Donor Acceptor Cyclopropanes and Progress towards Flinderole A, B, and C

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Graduate Program in Chemistry

A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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Abstract

The first chapter of this thesis describes two projects, one explores the novel reactivity of quaternary donor acceptor cyclopropanes and the second one involves progress toward the total synthesis of the flinderoles A, B, and C. The first project involves the Lewis acid catalyzed nucleophilic ring opening of quaternary donor acceptor cyclopropanes with indoline. It was found that the ring opening reaction worked well with either Sc(OTf)$_3$ or Yb(OTf)$_3$ as the Lewis acids. The ring opened products were also able to be converted into pyrroloindoles via a manganese (III) oxidative radical cyclization reaction. Cyclopropanes bearing alkynyl, vinyl, and aryl substituents were well tolerated as well as indolines bearing substitution at the 3-position. The second project involves the application of the ring opening/cyclization reaction to synthesize the pyrroloindole scaffold of the flinderoles. The chapter also describes our efforts to complete the synthesis of the natural products, and despite many alternative routes, we were not able to access the flinderoles.

The second chapter describes the Lewis acid catalyzed annulation reactions of donor acceptor cyclopropanes with vinyl azide and 2$H$-azirine. Surprisingly, the reaction with either the vinyl azide or 2$H$-azirine gave the same azabicyclic product. The reaction was also limited to cyclopropanes bearing trifluoroethyl esters instead of the common methyl esters. The reaction scope with respect to the cyclopropanes tolerated aryl, heteroaryl, vinyl, alkynyl and quaternary substituents on the cyclopropane. In both reactions, the azabicycle was obtained as a single diastereomer, which was confirmed by x-ray crystallography.

**Keywords:** donor acceptor cyclopropanes, nucleophilic ring opening, quaternary cyclopropanes, pyrroloindoles, flinderoles, trifluoroethyl esters, azabicycles, annulation reaction, total synthesis, phosphine gas, organophosphines.
Co-Authorship Statement

The results for the ring opening and Mn(OAc)$_3$ mediated oxidative radical cyclization of quaternary donor acceptor cyclopropanes for the synthesis of pyrroloindoles (Section 1.5.1) were worked on by myself. The progress towards the total synthesis of flinderoles A, B, and C (Section 1.5.2) was also worked on by myself.

The results in Section 2.4 were done in collaboration with Lauren C. Irwin. Lauren’s contributed to the project through the synthesis of $p$-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, thiophene and phthalimide substituted $bis(2,2,2$-trifluoroethyl)cyclopropane-1,1-dicarboxylates. The rest of the $bis(2,2,2$-trifluoroethyl)cyclopropane-1,1-dicarboxylates, reaction optimization, reaction scope, mechanistic studies, and crystal suitable for x-ray diffraction studies were worked on by myself.
Acknowledgments

In the last four years, I had the opportunity to: develop new skills as a synthetic chemist, attend both national and international conferences, meet new people, and make a lot of new friends. Many of my accomplishments during my graduate studies would not have been possible without the support and guidance of my supervisor Dr. Michael Kerr. I would like to thank Dr. Kerr for giving me the opportunity to join his research group, allowing me to be creative in the lab, and always encouraging me to achieve my best.

Next, I would like to thank all the members of the Kerr group, past and present, for all their help and support. You all made working in the lab enjoyable and fun. I would like to thank the past members of the group Mike Emmet, Huck Grover, Matt Vriesen, and Bryan Landschoot for their guidance and help during my early years in the lab. A special thanks to Michelle Flisar for her unconditional support and friendship that extended after graduated school. I would also like to thank Poly Kyriacou for his friendship and support in the last four years at western; thank you for all your advice and guidance and for always reminding me to stay positive. To the current members of the Kerr group, Lauren Irwin for their input and suggestions during group meetings, and to Mathew Piotrowski for the wonderful chemistry discussions and for always keeping it fun while working in the old 217 lab. I would like also to like to thank Dr. Pagenkopf and Naresh Vemula, for their input and guidance during our group meetings and general discussions in chemistry.

My graduate studies would not have been possible without the help from the support staff from Western’s Chemistry department, especially Mathew Willans for his help with NMRs, and to our graduate assistant Darlene McDonald. My sincere thank you to all the ladies in the ChemBio Stores: Marylou Hart, Monica Chirigel, Yuhua Chen, and Sherie McPhee.

Many thanks to Sara and Samantha Pauli from Sugar & Co. for giving me the opportunity to work with them as a cosmetic chemist during my graduate studies Mitacs internship program, and for always believing in my capabilities as chemist.
To my family and friends, thank you for your love and support throughout the good and stressful times of my graduate studies. A special thanks to my friend Ivona Zepic who always stood by my side, despite living in different cities, for always reminding me to stay focused and positive. To my parents Paul and Josie Gelineau, and my manistica Eli Curiel, thank you for your unconditional love and support, for always encouraging me to be independent and free spirited, and to pursue all my dreams and goals. Finally, I would like to thank my grandma Antonia Duran. Since I was young she has been my greatest inspiration and has been such a strong role model in my life. Gracias abuela, por siempre recordarme de que sin importar los obstáculos en la vida, una debe de mantener la fe y la cabeza en alto porque Dios tiene un plan para todos.
Para mi abuela Antonia Duran
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
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<tr>
<td>A</td>
<td>acceptor</td>
</tr>
<tr>
<td>Ad</td>
<td>adamantly</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>ACHN</td>
<td>azobis(cyclohexanecarbonitrile)</td>
</tr>
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<td>Bz</td>
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<td>Bn</td>
<td>benzyl</td>
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<td>BOX</td>
<td>bisoxazoline</td>
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<td>NBS</td>
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<td>butyl</td>
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<tr>
<td>DMSO</td>
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<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMT</td>
<td>dimethyltryptamine</td>
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<tr>
<td>D</td>
<td>donor</td>
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<tr>
<td>DA</td>
<td>donor acceptor</td>
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<tr>
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<td>1,2-dichloroethane</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<td>DFS</td>
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<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectroscopy</td>
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<tr>
<td>GHB</td>
<td>gamma-hydroxybutyric acid</td>
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<td>HMBC</td>
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<td>2-iodoxybenzoic acid</td>
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Chapter 1: Synthesis of Pyrroloindoles from Donor Acceptor Cyclopropanes and their application towards the Total Synthesis of Flinderoles A, B, and C

1 Chapter Introduction

Chapter one explores the new reactivity of donor acceptor (DA) cyclopropanes with a quaternary donor center. The chapter is divided into two projects: 1) the synthesis of pyrroloindoles from the nucleophilic ring opening of quaternary DA cyclopropanes with indoline followed by a Mn(OAc)$_3$ mediated oxidative radical cyclization, and 2) the progress towards the total synthesis of Flinderoles A, B, and C. The work towards the synthesis of pyrroloindoles from quaternary DA cyclopropanes and the progress towards the total synthesis of the Flinderoles A, B, and C was worked independently. The results in Section 1.5.1, Section 1.5.2, and Section 1.5.2.1 have been published in a peer review journal and reproduced in part with permission from Curiel Tejeda, J.E.; Landschoot, B.K.; Kerr, M.A. *Org. Lett.* **2016**, *18*, 2142-2145. Copyright © 2016 American Chemical Society.

1.1 Structure and Reactivity Donor Acceptor Cyclopropanes

One of the goals of an organic chemist is to develop new reactive molecules for the construction of complex compounds. In this light, donor acceptor (DA) cyclopropanes have emerged as useful synthetic blocks that have allowed organic chemists to accomplish their goal of synthesizing complex scaffolds. The reactivity of DA cyclopropanes has been widely used in the development of novel methodologies, and in the total synthesis of natural and unnatural compounds.$^1$ Cyclopropanes are simply three-membered carbocycles characterized by their inherent angle strain, and intrinsic torsional strain.$^2$ Cyclopropanes have a significantly high strain energy of 115 kcal/mol, since they have 60° bond angles which deviates considerably from the ideal 109.5° for $sp^3$-hybridized orbitals. Due to the high ring strain, cyclopropanes react similarly to olefins
rather than cycloalkane. The reactivity of cyclopropanes can be further enhanced by incorporating activating groups which induce bond polarization.\textsuperscript{1,2}

Bond polarization of a C-C bond in the cyclopropane ring can be accomplished through the attachment of an electron donating group (EDG), also known as donor groups (D), (ex: methoxy, methyl, aryl, etc.) or the attachment of an electron withdrawing groups (EWG), also known as acceptor groups (A), (ex: CO\textsubscript{2}R, CN, C(O)R, SO\textsubscript{2}R, etc.).\textsuperscript{1b} When D and A groups are vicinally positioned on the cyclopropane, herein described as donor acceptor (DA) cyclopropanes, they act in a push-pull fashion, which results in an enhanced polarization of the corresponding C-C bond (1-2, Figure 1-1). The enhanced bond polarization facilitates the ring opening reactions of DA cyclopropanes 1-1 with various nucleophiles.\textsuperscript{1b} The charge separation in DA cyclopropanes can be further enhanced in the presence of a Lewis acid, heat, or pressure, allowing the DA cyclopropane to undergo nucleophilic ring opening to give a homo-Michael addition product 1-3. The next section focuses on a few literature examples showcasing this type of transformation. The examples covered in the literature review only focus on the use of DA cyclopropanes with \textit{di}-carboxylate acceptor groups and their equivalents.

![Figure 1-1. Reactivity of DA cyclopropane with a nucleophile.](image)

1.2 Ring Opening of Donor Acceptor Cyclopropanes

One of the earliest examples of nucleophilic ring opening reactions of cyclopropanes comes from the work of Bone and Perkin in 1895, where homo-Michael addition of a malonate nucleophile to a cyclopropane carboxylate was studied.\textsuperscript{3} The field of cyclopropane studies had a resurgence in the 1960s and 1970s with the work of Stork\textsuperscript{4} and Danishefsky\textsuperscript{5}, which only focused on the use of acceptor substituted cyclopropanes.
It was not until the late 1970s and 1980s that the synthetic utility of DA cyclopropanes was demonstrated, in what is considered the modern age of DA cyclopropanes, in the work done by Wenkert\(^6\) and Reissing\(^7\).

### 1.2.1 Ring Opening of Donor Acceptor Cyclopropanes with Indoles

In 1997, Harrington and Kerr showed the hyperbaric (13 kbar) homo-Michael addition of indole \(1-4\) onto DA cyclopropane \(1-5\), catalytic \(\text{Yb(OTf)}_3\) (5 mol%), to give alkylated indole \(1-6\) in a 27-97% yield (Scheme 1-1).\(^8\) The reaction was versatile in the substitution for both the cyclopropane (\(R = \text{H, Ph, Me}\)), and \(N\)-protected indole. When \(R^1 = \text{TIPS}\), the reaction was somewhat problematic in that the addition reaction proceeded with partial desilylation, while with \(R^1 = \text{H}\), the yield of the product was drastically lowered, due to the formation of product \(1-7\).

![Scheme 1-1](image)

**Scheme 1-1.** Harrington and Kerr’s ring opening of DA cyclopropanes with indoles.

In 2011, Kerr and co-workers found that cyclopropane hemimalonate \(1-9\) (geminally disubstituted with one carboxyl ester and one carboxylic acid) could undergo nucleophilic ring opening with indole \(1-8\) at hyperbaric (13 kbar) conditions and catalyst free conditions (Scheme 1-2).\(^9\) The mode of reactivity of cyclopropane hemimalonate \(1-9\) was postulated to be a result of the carboxylic acid moiety forming a favourable hydrogen bond \(1-10\) intermediate.
Scheme 1-2. Kerr group ring opening of cyclopropane hemimalonate with indole.

The hydrogen bond stereoelectronically aligns the two carbonyl groups to receive electron density in the ring opening event, since the resulting zwitterion would be a highly delocalized six-electron species. It is notable to mention that the reaction scope tolerated R = aryl, naphthyl, and heteroaryl substitution on the cyclopropane, but not R = H, isopropyl, and alkenyl substituents. For the indoles, N-substituted R\(^1\) = H, Me, and Bn were well tolerated to give product 1-11 in good yields (68-81%).

An enantioconvergent homo-Michael addition of indoles with DA cyclopropanes was presented by the Johnson group in 2013.\(^{10}\) The reaction proceeded via a dynamic kinetic asymmetric transformation (DyKAT) with a pybox•MgI\(_2\) catalyst system (Scheme 1-3). Steinreiber and co-workers define DyKAT as “the de-symmetrization of racemic or diastereomeric mixtures involving interconverting diastereomeric intermediates”.\(^{11}\) Johnson and co-workers showed that the pybox (1-15)•MgI\(_2\) catalyst selectively activates the (S)-cyclopropane to give the homo-Michael addition product 1-14 with good enantiomeric ratio (er), up to 93:7. The reaction scope was favourable towards electronically diverse indoles bearing a N-TBS protecting group and, in general, the yields were good (68-96%), except for electron deficient indoles bearing halogen or ester substituents (38-40% yield).

In 2016, Singh and co-workers presented a one-pot formation of 2,3-disubstituted indole 1-18 from aniline 1-16 and cyclopropane 1-17 (Scheme 1-4).\(^{12}\) A highlight of the reaction is the use of catalytic AgSbF\(_6\) which triggers the ring opening of DA cyclopropane 1-17 by aniline 1-16 preceded by the cyclization reaction upon alkyne activation to give 1-18 in a 41-98% yield.

Scheme 1-4. Singh group AgSbF\(_6\) catalyzed indolization/C\(_3\)-functionalization cascade of 2-ethynylanilines via ring opening of DA cyclopropanes.

1.2.2 Ring Opening of Donor Acceptor Cyclopropanes with Heteroatom Nucleophiles

Another type of nucleophilic partner for the ring opening of DA cyclopropanes involve the use of heteroatoms. Heteroatom nucleophiles offer easy access to a variety of homo-Michael addition products and heterocycles. One of the first examples of nucleophilic ring opening reactions of DA cyclopropanes with amine nucleophiles was done in 1986 by Blanchard and Schneider (Scheme 1-5).\(^{13}\) Pyrrolidine 1-19 was shown to open DA
cyclopropane 1-20 in the presence of catalytic Et₂AlCl to yield a variety N-alkylated pyrrolidine 1-21 in yields ranging from 30-91%.

Scheme 1-5. Blanchard and Schneider’s ring opening of DA cyclopropanes with pyrrolidine.

In 2008, Charette and co-workers developed a protocol for the Lewis acid catalyzed ring opening of enantiopure methyl 1-nitrocyclopropanecarboxylate 1-22 with amine 1-23 to give homo-Michael addition product 1-24 (Scheme 1-6). Preliminary studies showed that AlCl₃, SnCl₄, and BF₃·OEt₂ Lewis acids generated the ring opening product as well as a mixture of unidentified products. Weakly activating Lewis acids such as Cu(O Tf)₂, ZnCl₂, and Ti(OiPr)₄ gave products in high enantiomeric excess (ee) but in low yields. Optimal results were obtained with NiClO₄·6H₂O, which gave 1-24 in good yields (66-94%) and high ee (90-92%).

Scheme 1-6 Charette and co-workers’ ring opening of DA cyclopropanes with amines.

Furthermore, Tang and co-workers published an asymmetric version of Charette’s work by employing Ni-catalyzed asymmetric ring opening reaction of racemic DA cyclopropane 1-26 with aliphatic amine 1-25 using the chiral indane-trisoxazoline (INTOX) ligand 1-28 (Scheme 1-7). The reaction performed well with a series of substrates which gave a variety of chiral γ-substituted γ-amino acid derivatives 1-27 in yields up to 99%, and enantioselectivity up to 98% ee.
Scheme 1-7. Tang and co-workers’ Ni/(In-TOX) catalyzed asymmetric ring opening of DA cyclopropanes with amines.

Tang and co-workers also showed the first catalytic enantioselective ring opening of DA cyclopropane 1-29 with water (Scheme 1-8).\(^\text{16}\) Cy-TOX/Cu(\(\text{ClO}_4\)\(_2\))\cdot6\(\text{H}_2\)\(^{18}\)\O was employed, where the copper hydrate acted both as the Lewis acid and nucleophile. The reaction performed very well over a broad range of substituted cyclopropanes including aryl, furyl, indolyl, and cinnamyl, leading to \(\gamma\)-hydroxybutyric acid (GHB) derivatives 1-30 in 70-96% yields with up to 96% ee.

Scheme 1-8. Tang and co-workers’ enantioselective ring opening of DA cyclopropanes with water.

Lastly, an efficient regioselective ring opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes 1-32 with primary amines was developed by Yakura and co-workers (Scheme 1-9).\(^\text{17}\) The reaction proceeded at room temperature without any Lewis acid or additives to provide tetrahydroindol-4-ones 1-33 in yields ranging from 86-97%, which were further converted to highly substituted indoles 1-34 in yields up to 87%.
Scheme 1-9. Yakura and co-workers’ ring opening of spirocyclopropane with primary amines.

Yakura and co-workers proposed two plausible routes for the formation of 1-33 (Scheme 1-10). In route a, nucleophilic ring opening of spirocyclopropane 1-32 at the more electrophilic substituted carbon on the cyclopropane, leads to γ-amino ketone A, regioselectivity. Nucleophilic attack of the amine to the carbonyl carbon followed by dehydration of hemiaminal B gives indoline 1-33. An alternative route, route b, involving imine formation and a cyclopropylamine rearrangement (C), was also proposed by Yakura and co-workers. The synthesis of substituted indoline is significant in the field of organic synthesis, as they are often the precursors in the synthesis of biologically active indole alkaloids.

Scheme 1-10. Yakura and co-workers proposed mechanism for the formation of indoline.

1.2.3 Ring Opening of Donor Acceptor Cyclopropanes with Indoline

Another direct method to synthesize functionalized indolines was published by Magolan and Kerr in 2006 where DA cyclopropanes were opened with indoline.\textsuperscript{18} Commercially
available 1,1-carbomethoxycyclopropane 1-36a or dimethyl 2-phenylcyclopropane-1,1-
dicarboxylate (1-36b) reacted with indoline 1-35, under Lewis acidic conditions, to give
N-alkylindolines 1-36a or 1-36b in 80% and 74% yield respectively (Scheme 1-11).


After a six-year hiatus, the scope for the nucleophilic ring opening reaction of DA
cyclopropanes with indoline was studied, employing the same conditions as above to
produce N-alkylindolines (1-37a-i) (Figure 1-2).\textsuperscript{19}
Figure 1-2. Reaction scope for the nucleophilic ring opening of DA cyclopropanes with indoline.

The reactivity of the cyclopropanes toward nucleophilic ring opening is, to a large degree, influenced by the ability of the donor groups to stabilize the developing positive charge during the ring opening event which is reflected in the variation of the reaction times as well as the yields. Good yields (63-80%) were obtained with cyclopropanes bearing aryl, heteroaryl, and vinyl substituents, but not for the isopropyl substituted cyclopropane 1-36h, which required 24 hours to reach completion and only gave 1-37h in 24% yield (Figure 1-2). It was postulated that the steric effect of the isopropyl moiety interfered with indoline during the ring opening event, since unreacted cyclopropane was recovered and thus explaining why 1-37h was obtained in such a low yield.

1.2.3.1 Mn(OAc)$_3$ Mediated Radical Cyclizations of $N$-alkylindolines

In addition to the ring opening of DA cyclopropanes with indoline, in 2006, Magolan and Kerr showed the conversion of $N$-alkylindolines 1-37a and 1-37b into pyrroloindoles 1-
Scheme 1-12. Initial examples of the Mn(OAc)₃ mediated oxidative radical cyclization of N-alkylindolines.

The Mn(OAc)₃ mediated radical cyclization mechanism is shown below in Figure 1-3.¹⁸ The reaction begins with the oxidation of N-alkylindoline 1-37a to indole 1-39, followed by the oxidation of a malonic enolate to give malonic radical 1-40. Cyclization at the two-position of the indole gives benzylic radical 1-41, which can then undergo further oxidation to form carbenium ion 1-42. Aromatization by loss of a proton gave pyrroloindole 1-38a.

Figure 1-3. Reaction mechanism for the Mn(OAc)₃ mediated oxidative radical cyclization.
In addition to Magolan and Kerr’s work in 2006, \(N\)-alkylindolines 1-37a-i were converted to pyrroloindoles 1-38a-i in good yields (61-92%) by treating them with five equivalents of \(\text{Mn(OAc)}_3\) in methanol at a heated to 70 °C (Figure 1-4).

![Chemical Structures](image)

**Figure 1-4.** Reaction Scope for the \(\text{Mn(OAc)}_3\) mediated oxidative radical cyclization of \(N\)-alkylindolines 1-38a-i.

### 1.2.4 Ring Opening of Donor Acceptor Cyclopropanes at Quaternary Donor Sites

Despite the many examples published over the years in the field of nucleophilic ring opening reactions of DA cyclopropanes, the methodologies have predominantly used cyclopropanes with one donating group. The ring opening of cyclopropanes bearing a quaternary donor site vicinal to the diester moiety - also known as quaternary DA cyclopropane - have not been fully explored, and only a few examples exist in the literature. Schneider\(^{13}\) and Kotsuki\(^{21}\) opened DA cyclopropanes at the quaternary donor
site, with pyrrolidine 1-43 and 1H-pyrazole 1-46, respectively, to give ring open products 1-45 and 1-48 in 34% and 83% yield (Scheme 1-13).

Scheme 1-13. Schneider (1) and Kotsuki (2) examples of ring opening of quaternary DA cyclopropanes.

Recently in 2014, Ivanov and co-workers showed that cyclopropane 1-49 bearing quaternary donor site could undergo ring opening with sodium azide in the presence of Et₃N•HCl in DMF heated to 135 °C (Scheme 1-14). Due to the elevated reaction temperature, the nucleophilic ring opening reaction was accompanied by a dealkoxy carbonylation, leading to the formation of azidobutyrate 1-50 in a 48% yield. The reaction also formed benzophenone 1-51 as a side product, via the generation of nitrene, and subsequent rearrangement of the ring open product 1-50.


1.3 Project Goal

Given the limited protocols on the nucleophilic ring opening of DA cyclopropanes at quaternary donor sites, we envisioned a simple extension of Magolan and Kerr’s protocol by reacting quaternary DA cyclopropane 1-52 with indoline 1-35 (Scheme 1-15). The result of this reaction would give N-alkylindoline 1-53 that subsequently can be treated
with Mn(OAc)$_3$ to give pyrroloindole 1-54. The methodology could then be used to access pyrroloindole containing natural products such as the flinderoles A (1-55), B (1-56), and C (1-57). The quaternary stereocenter (carbon with asterisk) of the flinderoles pyrroloindole moiety would be derived from the quaternary cyclopropane.

**Scheme 1-15.** Envisioned application of ring opening/radical cyclization protocol for the synthesis of flinderoles A, B, and C.

### 1.4 Introduction to the Flinderoles A, B, and C

The flinderoles A-C$^{23}$ (Scheme 1-15) are a group of *bis*-indole alkaloids isolated in 2009 from the *Flindersia* plant species in Australia and New Papua Guinea. The flinderoles have been shown to exert impressive antimalarial activity against the parasite *P. falciparum*. Since the commonly used treatment of the *P. falciparum* infection, which causes the most severe malaria infection, have been affected by the presence of multidrug-resistant parasites, the new molecular scaffold of the flinderoles makes them an attractive synthetic target for antimalarial drug discovery. To date, there have been three reported total syntheses of the flinderoles.
1.4.1 Dethe’s Biomimetic Total Synthesis of Flinderole B and C

The first total synthesis of flinderole B and C was done by Dethe and co-workers in 2011. The synthesis showcased a simple and efficient biomimetic approach in which pyrrole[1,2-a] indoles 1-60 and 1-61 were synthesized using a highly stereo- and regioselective [3+2] reaction cascade (Scheme 1-16).

The synthesis begins with the Wittig olefination of aldehyde 1-58 to generate the unsaturated ester, which upon treatment with methyl magnesium iodide gave tertiary alcohol 1-59 in an 81% overall yield (Scheme 1-16). Indole 1-59 could then be used to form the two intermediate indole moieties for the skeleton of flinderole B and C. The first intermediate was made by dehydration of the hydroxyl group of indole 1-59, via mesylation followed by elimination, to give olefin 1-61 in an 81% yield. The use of sodium amalgam to deprotect the phenyl sulphonyl group of 1-59 gave the other coupling partner, alcohol 1-60 in a 91% yield. With 1-60 and 1-61 formed, the stage was set for the key [3+2] reaction. Treatment of 1-60 and 1-61 with an excess of BF₃•OEt₂ promoted the [3+2] cycloaddition reaction and subsequent deprotection of the tert-butyldimethylsilyl (TBS) group gave diol 1-62 in a 78% yield, and good diastereoselectivity (4:1). Oxidation of 1-62 using IBX, followed by a reductive amination of the resulting bisaldehyde, and deprotection of the tryptamine nitrogens gave flinderole B (1-56) as the major product in a 47% yield, and flinderole C (1-57) as the minor product in 11% yield, over the last three steps. Overall, Dethe and co-workers’ synthesis proceeded in an overall 17% combined yield, which involves 11 steps in the longest linear sequence.
Scheme 1-16. Dethe and co-workers’ synthesis of flinderole B and C.

1.4.2  Toste’s Total Synthesis of Flinderoles B and C

The second synthesis of the flinderoles B and C was reported by Toste and co-workers in 2011. Toste’s approach to flinderoles B and C involved the synthesis of two important fragments: indole 1-70 (Scheme 1-17) and indole 1-74 (Scheme 1-18). The two indole fragments would then be united by a Horner-Wadsworth-Emmons (HWE) olefination to obtain the bis-indole framework of the natural products.
Scheme 1-17. Synthesis of Toste and co-workers pyrroloindole fragment 1-70.

To begin the synthesis of indole 1-70, Toste and co-workers protected commercially available tryptophol (1-63) as the tert-butyldiphenylsilyl (TBDPS) ether, followed by N-alkylation with methyl bromoacetate to give indole 1-64 in a 45% (2 steps), which was then converted to amino alcohol 1-66 in a 73% yield (Scheme 1-17). Alkylation of N-methyl-N-ethanolamide 1-66 using lithium diisopropylamide (LDA) and LiCl followed by deprotection with sodium methoxide and an excess of dimethyl carbonate (to remove the amide auxiliary) gave allene 1-67 in an 89% yield, over two steps. Allene 1-67 was then subjected to the key gold(I)-catalyzed hydroarylation by reacting it with 5 mol% of IPrAuCl and 5 mol% AgSbF$_6$ to afford pyrroloindole 1-68 in an 88% yield. Methylation of indole 1-68 gave pyrroloindole 1-69 in a 94% yield and a 2:1 dr. DIBAL-H reduction of the methyl ester on 1-69, and subsequent Parikh-Doering oxidation yielded aldehyde 1-70 in a 68% yield over two steps, thus completing the synthesis of the first indole fragment.

The second fragment (1-74, Scheme 1-18) was synthesized by treating TBS-protected pentyn-4-ol 1-71 with phenylhydrazine and an excess of ZnCl$_2$ to give the desired TBS-protected-2-methyltryptophol 1-72 in a 76% yield. N-Protection with phenylsulfonyl chloride and potassium hydroxide gave indole 1-73 in a 68% yield. A radical bromination/Arbuzov sequence was then performed to afford phosphonate 1-74 in a 77% yield, thus completing the synthesis of the second indole fragment.
Scheme 1-18. Toste’s synthesis of indole fragment 1-74.

A HWE olefination between 1-70 and 1-74 provided the bis-indole skeleton for the flinderoles (Scheme 1-19). Olefin 1-75a was obtained in a 36% yield and its 3'-epimer 1-75b in a 33% yield. From this point on, both bis-indole skeletons were carried forward separately towards flinderoles B and C; thus, tetrabutylammonium fluoride (TBAF) deprotection of the silyl ethers gave compounds 1-76a and 1-76b in 79% and 74% yield, respectively. To finish their synthesis, Toste and co-workers followed Dethe’s final sequence to obtain the flinderoles (Scheme 1-16).24 Flinderole B, 1-56, was obtained in a 62% yield and flinderole C, 1-57, in a 66% yield over three steps. Flinderoles B and C were successfully synthesized in an overall 4% combined yield from the commercially available tryptophol 1-63 in 18 steps (14 steps longest linear sequence).
**Scheme 1-19. Toste's final steps towards the flinderoles B and C.**

1.4.3  Vallakati and May's Biomimetic Synthesis of Flinderoles A, B, and C

The most recent synthesis of flinderoles A, B, and C, was presented by Vallakati and May in 2014.⁵⁶ Vallakati and May’s synthesis was also a biomimetic synthesis of the flinderoles, which in comparison with Dethe and co-workers biomimetic synthesis,¹⁴ Vallakati and May synthesized flinderoles A, B, and C, while Dethe only synthesized flinderoles B and C. The key step of Vallakati and May’s procedure is an acid-promoted dimerization of the natural product borrerine (1-81, Scheme 1-20). Borrerine (1-81) was synthesized via a Pictet-Spengler reaction between tryptamine 1-77 and aldehyde 1-78 in the presence of methyl chloroformate (1-79)²⁷ to give indole 1-80 in an 87% yield. Treatment of 1-80 with lithium aluminium hydride reduced the N-methyl ester to afford Borrerine in an 86% yield. Reacting of borrerine (1-81) with MeOTf in chloroform, followed by trifluoroacetic acid afforded flinderoles B (1-56) and C (1-57) in 21% and 19% yield, respectively. Treatment of borrerine with acetic acid (AcOH), afforded flinderoles A (1-55) in 38% yield.
**Scheme 1-20.** Vallakati and May's biomimetic total synthesis towards the flinderoles A, B, and C.

### 1.5 Results and Discussion

#### 1.5.1 Methodology

Before tackling the flinderoles, the nucleophilic ring opening reaction of quaternary DA cyclopropanes with indolines had to be investigated. We commenced this stage of the project by synthesizing a library of DA cyclopropane containing quaternary donor sites. Aside from cyclopropanes 1-52d and 1-52e, which have been prepared previously, cyclopropanes 1-52a-c are novel. All the cyclopropanes were obtained via a Rh2(esp)2 catalyzed cyclopropanation between the corresponding alkene 1-83 and diazomalonate 1-82 (Figure 1-5). Cyclopropanes 1-52a and 1-52d were obtained in lower yields due to the formation of undesired isomers, by-products, and decomposition of starting material. Cyclopropane 1-52d was obtained in a 9:1 inseparable mixture with its regioisomer in a 52% yield. The mixture of isomers was to be used as is with the hope of separating each isomer at a later stage in the methodology.
Figure 1-5. Rhodium catalyzed synthesis of quaternary DA cyclopropanes 1-52a-e.

After synthesizing a library of quaternary DA cyclopropanes, the next step was to optimize the nucleophilic ring opening of quaternary DA cyclopropanes with indoline. Initially, when the reaction was performed using DCE as the solvent (entries 1 and 2, Table 1-1), the desired product was not obtained, and instead, the DCE reacted with indoline 1-35a to give N-alkylindoline 1-84. Exchanging the solvent to toluene (entry 3) gave the desired N-alkylindoline 1-53c in a 60% yield; however, some decomposition of starting materials was obtained resulting in the low yield. Lowering the reaction temperature to 100 °C and shortening the reaction time from 3 to 1.5 hours (entry 4) resulted in higher yields with little to no decomposition of starting material.
Table 1-1. Optimization conditions for the nucleophilic ring opening of quaternary DA cyclopropanes with indoline.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)₃</td>
<td>DCE, 84 °C</td>
<td>compound 1-84</td>
</tr>
<tr>
<td></td>
<td>(10 mol%)</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ca(NO₃)₂</td>
<td>DCE, 84 °C</td>
<td>compound 1-84</td>
</tr>
<tr>
<td></td>
<td>(5 mol%)</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bu₄NPF₆</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)₃</td>
<td>toluene, 110 °C</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>(10 mol%)</td>
<td>3 h</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)₃</td>
<td>toluene, 100 °C</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>(10 mol%)</td>
<td>1.5 h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)₃</td>
<td>toluene, 100 °C</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>(5 mol%)</td>
<td>1.5 h</td>
<td></td>
</tr>
</tbody>
</table>

It was later found that Yb(OTf)₃ (entry 5, Table 1-1) was a better promoter for the reaction, as less catalyst was required to give product 1-53c with the same reaction time and yield as entry 4. The scope of the ring opening reaction was studied employing conditions in entries 4 and 5.

Results for the ring opening reactions of DA cyclopropanes 1-52a-e (Figure 1-5) with indolines 1-35a, 1-35c - 1-35d are summarized in Figure 1-6. Cyclopropanes bearing acetylenic substituents, 1-52a-c, reacted smoothly with either Sc(OTf)₃ and Yb(OTf)₃ to give N-alkylindolines 1-53a-c in good yields (72-88%). N-Alkylindolone 1-53a was obtained in higher yields when the reaction was performed with Sc(OTf)₃, 88% yield, versus a 77% yield with Yb(OTf)₃; this is the only example were the ring opening
reaction catalyzed by Sc(OTf)$_3$ gave superior results to Yb(OTf)$_3$. The lower yields observed for $N$-alkyindoline 1-53d (44-50% yield) are most likely a result of the vinyl cyclopropane 1-52d undergoing competitive polymerization. Indolines bearing a side chain, 1-35c and 1-35d, also performed well in this reaction yielding a 1:1 mixture of diastereomers. Since the indolines were to be oxidized to indoles in the next step, the mixture of diastereomers was inconsequential.

Figure 1-6. Reaction scope for the nucleophilic ring opening of quaternary DA cyclopropanes with indoline.
The $N$-alkylindolines 1-53a-g were then subjected to the Mn(OAc)$_3$ mediated oxidative radical cyclization to synthesize the corresponding 1,2-pyrroloindoles (Figure 1-7). Initially, the Mn(OAc)$_3$ mediated radical cyclization of $N$-alkylindolines with acetylenic was worrisome to us given that the malonic radical may react in some way with the pendant alkynyl moiety.\textsuperscript{28} However, this was found to not be the case as pyrroloindoles 1-54a-c were obtained in yields ranging from 61-65%.

![Chemical Structures](image1)

**Figure 1-7. Reaction scope for the Mn(OAc)$_3$ mediated oxidative radical cyclization of $N$-alkylindolines 1-53a-g.**

The vinyl substituted pyrroloindole 1-54d was obtained in a low 40% yield, perhaps due to competing polymerization or side reactions upon treatment with Mn(OAc)$_3$. It was interesting to see the difference in yields obtained for pyrroloindoles having substituents at the three-position of the indole 1-54f and 1-54g, 80% versus 63% yield. It is postulated that during the ring closure process, the formation of the allylic cation (1-59, Figure 1-3)
is less favoured from the electron withdrawing effects of the CN group, resulting in lower yields. Results of both the nucleophilic ring opening of DA cyclopropanes at quaternary donor centers with indoline and the Mn(OAc)$_3$ mediated oxidative radical cyclization of the resulting $N$-alkyldiindoles to give pyrroloindoles, shows paralleled yields to their less substituted counterparts in Figure 1-2 and Figure 1-4.

1.5.2 Progress towards the Total Synthesis of the Flinderoles

With the success of our methodology presented in Section 1.5.1, the next step was to apply it in the synthesis of the flinderoles. Retrosynthetically (Scheme 1-21) we envisioned that flinderole B or C - the synthesis will be done using racemic starting materials - can originate from a Wittig reaction with aldehyde 1-88, followed by functional group manipulation to afford the $N$-dimethyltryptamine (DMT) side chains.

![Scheme 1-21. Retrosynthetic plan towards the synthesis of flinderole B or C.](image)

Aldehyde 1-88 could arise from a Krapcho decarboxylation followed by reduction of the esters in compound 1-87 (Scheme 1-21). Intermediate 1-87 would be made by the cross-coupling reaction between a 2-bromoindole derivative 1-86 and pyrroloindole 1-85, the later derived from a hydrostannylation reaction of 1-54a. Pyrroloindole 1-53a can be synthesized in two steps by employing our nucleophilic ring opening of DA cyclopropane 1-52a with indoline 1-35, followed by an oxidative cyclization with Mn(OAc)$_3$. 
1.5.2.1 Synthesis of \textit{bis}-Indole Framework

We commenced our synthesis with a model study to build the \textit{bis}-indole framework of the flinderoles skeleton (Scheme 1-22). To this end, the alkynyl moiety of 1-54f was hydrostannylated to yield vinylstannane 1-89 in an 85% yield. Compound 1-89 was then subjected to Stille coupling conditions with \textit{N}-tosylated 2-bromoindole 1-90 to yield \textit{bis}-indole 1-91 in an 85% yield.

During the Stille coupling reaction, it was noticed that higher yields were obtained with a prolonged reaction time, as well as higher solvent temperatures 110°C; however, the highest yield obtained was 58%. With the skeletal structure of the flinderoles secured in four steps, we then set our sights on developing the isobutylene side chain.

1.5.2.2 Attempts to Synthesis Isobutylene Side Chain of the Flinderoles

Moving forward again with another model study, we wanted to see if our proposed reduction/Wittig olefination would allow access to the isobutylene side chain of the flinderoles. Starting with a Krapcho decarboxylation of 1-54e gave \textit{mono}-ester 1-92 in 74% yield and a \textit{dr} 1:1.3 (Scheme 1-23). DIBAL-H reduction of ester 1-92 yielded aldehyde 1-93 in 87% yield with minimal loss in \textit{dr} (1:1.1). We soon found that aldehyde 1-93 was highly unstable to purification by flash column chromatography, and thus, it was used immediately in the next reaction as a crude mixture.
Scheme 1-23. Synthesis of 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole-1-carbaldehyde 1-93.

Attempts for the Wittig olefination of 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole-1-carbaldehyde (1-93) to access isobutylene side chain are shown in Table 1-2. Initially, t-BuOK was used as the base (entries 1 and 2); however, there were no signs of ylide formation in either tetrahydrofuran or diethyl ether and so a new base was used.

Table 1-2. Wittig olefination attempts towards compound 3-methyl-1-(2-methylprop-1-en-1-yl)-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (1-95).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of phosphonium salt</th>
<th>Base</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>t-BuOK (4.4 equiv)</td>
<td>THF, 0 °C - RT 2 h</td>
<td>Ylide does not form</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>t-BuOK (2.2 equiv)</td>
<td>Ether, 0 °C - RT 2 h</td>
<td>Ylide does not form</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>n-BuLi (1.3 equiv)</td>
<td>Ether, 0 °C - RT 3.5 h</td>
<td>7% product + compound 1-96</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>n-BuLi (1.4 equiv)</td>
<td>Ether, 0 °C - RT 8 h</td>
<td>6% product + compound 1-96</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>n-BuLi (1.2 equiv)</td>
<td>Ether, -78 - 0 °C, -78 °C - RT 8 h</td>
<td>4% product + compound 1-96</td>
</tr>
</tbody>
</table>

Changing the base to n-BuLi (entry 3 and 4, Table 1-2) to promote the olefination was a minor success as the product was formed, but in an undesirable 6-7% yield. In both cases
it appeared (by $^1$H NMR and HRMS) that deformylated 1-96 was being produced as a major by-product. It should be noted that 1-96 is only postulated as it was not fully characterized, but will be discussed in more detail below. Attempts to minimize by-product formation, by cooling the reaction, only resulted in a lower yield of the desired 3-methyl-1-(2-methylprop-1-en-1-yl)-3-phenyl-2,3-dihydro-1$^H$-pyrrolo[1,2-a]indole (1-92) (Table 1-2).

1.5.2.2.1 Investigating the Stability of 3-methyl-3-phenyl-2,3-dihydro-1$^H$-pyrrolo[1,2-a]indole-1-carbaldehyde (1-93)

Since a by-product was being formed during the Wittig olefination, we wanted to test the stability of 3-methyl-3-phenyl-2,3-dihydro-1$^H$-pyrrolo[1,2-a]indole-1-carbaldehyde (1-93) (Scheme 1-23). When a small sample of aldehyde 1-93 was dissolved in an NMR tube with CDCl$_3$, and stirred for 8 h at room temperature, the crude $^1$H NMR showed that the aldehyde signal was completely gone, and the resulting $^1$H NMR suggested that 1-96 (Table 1-2) was being formed. Attempts to characterize compound 1-96 using COSY, HSQC, and HMBC was troublesome as the data was not very clear. Efforts to further characterize the compound by x-ray crystallography was not successful suitable, since crystal was not obtained. Although additional evidence for the structural elucidation of the by-product 1-96 is required, we are basing the formation of 1-96 based on $^1$H NMR, $^{13}$C NMR, and HRMS. Compound 1-96 is believed to be formed by an oxidative deformylation of aldehyde 1-93. Similar aldehydes were also shown to undergo this transformation in the presence of O$_2$. Attempts to deoxygenate the solvent by purging the solvent with argon were unfruitful in preventing the conversion of 1-93 to 1-96. Since it became apparent the aldehyde 1-93, we decided to re-visit our retrosynthetic plan and approach the synthesis of the isobutylene chain in a different manner.

1.5.2.3 Revised Retrosynthetic Plan A

As the Stille coupling for the bis-indole framework was still a viable route, we needed a new route to access the isobutylene side chain. In the revised retrosynthesis (Scheme 1-24), we focused on converting the diester moiety of pyrroloindole 1-87 to alcohol 1-98 via a mono-Grignard addition to one of the diesters of compound 1-87. The resulting
ester on compound 1-97 would be cleaved by a Krapcho decarboxylation and reduction of the resulting ketone would give alcohol 1-98. Dehydration of alcohol 1-98 would yield the desired isobutylene side chain of the flinderoles. It is important to note that in the dehydration step, we run into the possibility of forming the two alkenes: (1) the isolated alkene giving the isobutylene side chain, and (2) the conjugated alkene to the indole. It is most likely that the alkene formed will be the conjugated product, but at this point in the synthesis, we are interested in investigating the chemistry to functionalize the diester moiety of the pyrroloindole. In the dehydration step, we would be employing various dehydration methods and dehydrating agents, such as the Burgess reagent, to form the desired alkene.

Scheme 1-24. Revised retrosynthetic plan A- for the synthesis of flinderole B or C.

Again, a model study was used to explore the optimal conditions required to synthesize the desired isobutylene side chain. By following a protocol published by France and co-workers - where a mono-addition of a Grignard reagent was accomplished to the one of the esters in a DA cyclopropane - pyrroloindole 1-54e was reacted with isopropylmagnesium chloride (1-99) in THF cooled to -78 °C and warmed to room temperature (Scheme 1-25); however, the isolated product of the reaction was the monoester 1-92, which was previously obtained via a Krapcho decarboxylation reaction (Scheme 1-23).
Since the Grignard reaction presented in Scheme 1-25 failed, we hoped that the reaction of pyrroloindole 1-54e with isopropylmagnesium chloride.

Scheme 1-25. Grignard reaction of pyrroloindole 1-54e with isopropylmagnesium chloride.

Since the Grignard reaction presented in Scheme 1-25 failed, we hoped that the reaction of pyrroloindole 1-54e with isopropylmagnesium bromide 1-100 (Scheme 1-26) would yield the single addition product. By following the same conditions as above, compound 1-101 was not produced, and instead, a mixture of side products and decomposition of the starting material was obtained.

Scheme 1-26. Attempts towards the synthesis of 1-101 via a mono-Grignard addition.

With the failed Grignard reactions with pyrroloindole 1-54e (Scheme 1-25 and Scheme 1-26), we decided to attempt the Grignard reaction via a Weinreb amide as it might favour single addition product and prevent starting material decomposition. To begin the conversion to Weinreb amide 1-103 (Scheme 1-27), pyrroloindole 1-92 was treated with 1.7 M NaOH in MeOH at room temperature to obtain acid 1-102 in a quantitative yield. The resulting acid was then treated with mesityl chloride to form the acid chloride, \textit{in situ}, which was then added to a solution of \textit{N,O}-dimethylhydroxylammonium chloride, free-based with triethylamine (Et\textsubscript{3}N), in CH\textsubscript{2}Cl\textsubscript{2}. Unfortunately, the reaction gave only decomposition of the starting material and no significant yield of Weinreb 1-103 was obtained.
A pattern observed in each of the reactions tested above is that either mono-ester 1-92 or the carboxylic acid 1-102 always seemed to decompose to many unresolved compounds during the reaction. The decomposition was a bit worrisome as we observed a similar outcome with aldehyde 1-93 (Scheme 1-23). A similar test to aldehyde 1-93 was performed on compounds 1-92 and 1-102. Test results showed significant decomposition of the starting material and the appearance of 1-96 (Table 1-2). Since the route showed no promise, an alternative route was proposed for the synthesis of the isobutylene side chain of the flinderoles.

### 1.5.2.4 Revised Retrosynthesis Plan B

Our last attempt towards the flinderoles can be seen in the revised retrosynthesis below (Scheme 1-28). The major difference in this approach is the use of methyl 1-isobutyrylcyclopropanecarboxylate 1-104. Since the alcohol will be pre-installed in the cyclopropane, all that would be required is removal of the ester by Krapcho decarboxylation in 1-97. Dehydration of 1-98 would yield isobutylene side chain of the flinderoles, or as previously stated in Section 1.5.2.3, we could also obtain the conjugated alkene.
Scheme 1-28. Revised retrosynthesis B.

As a model study, we sought out to synthesize cyclopropane 1-104, since the starting materials to synthesize of cyclopropane 1-104 are more expensive, and during the cyclopropanation reaction, by-products are often formed, resulting in low yields. (Table 1-3). Reacting phenyl styrene 1-108 and methyl 2-diazo-4-methyl-3-oxopentanoate\textsuperscript{31,32} 1-107 under Rh\textsubscript{2}(esp)\textsubscript{2} catalyzed cyclopropanation conditions (entries 1-2, Table 1-3) did not yield any of the desired product. Changing the catalyst to Rh\textsubscript{2}(OAc)\textsubscript{4} in toluene heated to 110 °C (entries 3 and 4,Table 1-3) with varying equivalents of the diazo compound 1-107 resulted in no reaction and only starting material was recovered. Changing the solvent to benzene heated to 80 °C also resulted in the full recovery of the starting materials.
Table 1-3. Rhodium catalyzed reactions attempted to synthesize methyl 1-isobutyryl-2-methyl-2-phenylcyclopropane-1-carboxylate (1-104).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo compound (equiv)</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>Rh₂(esp)₂ (0.1 mol%)</td>
<td>CH₂Cl₂, RT 18h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>Rh₂(esp)₂ (0.1 mol%)</td>
<td>CH₂Cl₂, 40 °C 18h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Rh₂(OAc)₄ (1 mol%)</td>
<td>toluene, 110 °C, 12h</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>1.3</td>
<td>Rh₂(OAc)₄ (1 mol%)</td>
<td>toluene, 110 °C, 24h</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>Rh₂(OAc)₄ (1 mol%)</td>
<td>benzene, 80 °C, 24h</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

We next thought to employ France and co-workers method of the mono-addition reaction of a Grignard reagent to one of the ester moiety of a DA cyclopropane.³⁰ In turn, dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (1-52e) was reacted with isopropylmagnesium chloride (1-99) in THF cooled to -78 °C and then warmed to room temperature (Scheme 1-29). Unfortunately, the reaction only gave some recovered starting material cyclopropane, and other side products, with signs of ketone 1-104.

Scheme 1-29. Attempts to synthesize methyl 1-isobutyryl-2-methyl-2-phenylcyclopropane-1-carboxylate 1-104.
In the hopes to obtain DA cyclopropane in one step, we decided to approach the Grignard addition via an acid chloride or Weinreb amide intermediate (Scheme 1-30). Were also attempted, but did not work, despite being able to access cyclopropane hemimalonate 1-109.

Scheme 1-30. Attempts to synthesize acid chloride and Weinreb amide for the formation of 1-110 and 1-111, respectively.

It was not until cyclopropane 1-52e was reacted with isopropenylmagnesium bromide 1-100 that an appreciable amount, 33%, of cyclopropane 1-112 was obtained (Scheme 1-31).

Scheme 1-31. Synthesis of cyclopropane 1-112 via a mono-Grignard addition.

With cyclopropane 1-112 in hand, we then proceeded to reduce the alkene. Reacting cyclopropane 1-112 with tosylhydrazide and sodium acetate (NaOAc) in a 1:1 mixture of THF/H₂O heated to 70 °C for 18 h (Scheme 1-32), gave compound 1-104 in a 36% yield and a 5:1 dr. The low yield of this reaction is due to the formation of multiple unidentified by-products in the reaction and difficulty to obtain a single clean product during purification by flash column chromatography. Following our general reaction conditions for ring opening and oxidative cyclization methodology, we obtained
pyrroloindole 1-113 in a 23% overall yield and a 1.6:1 dr. Krapcho decarboxylation of 1-113 gave ketone 1-114 in a 35% yield, which was then reduced to the secondary alcohol 1-115 by employing Luche reducing conditions in a 40% yield.\(^{34}\)

**Scheme 1-32.** Reaction sequence towards the synthesis of alcohol 1-115.

With the alcohol finally obtained, we could now test the dehydration reaction, with the model study, to synthesize the isobutylene side chain (Scheme 1-33). Dehydration conditions to synthesize the isobutylene moiety included treatment of the secondary alcohol with either SOCl\(_2\) and pyridine\(^ {35}\) or Burgess reagent\(^ {36}\). While the use SOCl\(_2\) resulted in decomposition of the starting material, the reaction with the Burgess reagent gave traces of the desired product, but the major product was alkene 1-116, based on the crude mixture \(^1\)H NMR.
Scheme 1-33. Dehydration attempts on alcohol 1-115.

As only a small amount of the two mixed products was obtained (~4 mg), the difficulty by which product 1-117 was formed (8 steps), and the fact that our proposed synthesis was not any more efficient than the already published protocols, we decided to terminate the project.

1.6 Summary and Future Work

The reactivity and use of quaternary DA cyclopropanes for the synthesis of pyrroloindoles is highly valuable and a growing approach towards the synthesis of pyrroloindole natural products. The work presented in chapter one is of foremost importance to the synthetic community as it provides a new method for the development of highly functionalized pyrroloindole scaffolds. The developed methodology has allowed us to synthesize over 7 pyrroloindole scaffolds with varying substitution and a quaternary centre in two steps. The application of the methodology for the total synthesis of the flinderoles A, B, and C has been showcased. During this study, the bis-indole scaffold of the flinderoles was successfully synthesized, however, we encountered multiple issues during the synthesis of the isobutylene side chain. Despite our failed efforts to complete the total synthesis of the flinderoles, our proposed method for the synthesis of the pyrroloindole scaffold of the flinderoles is nonetheless an interesting reaction that explores further manipulation of the easily prepared heterocycle. The newly
methodology provides chemists with the opportunity to synthesize flinderole derivatives for drug development.

1.7 Experimental

All reactions were carried under an Argon atmosphere unless indicated. Toluene, tetrahydrofuran (THF), N,N-dimethylformamide (DMF), and dichloromethane (CH₂Cl₂) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Sigma Aldrich, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F₂₅₄) visualizing with UV light, and the plates were developed using acidic anisaldehyde. Flash column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

NMR experiments were performed on the Varian Mercury 400 and Inova 400 instruments; samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 ppm for ¹³C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Infrared spectra were obtained as thin films on NaCl plates using the Bruker Vector 33 FT-IR instrument. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS (Double Focusing Sector). Melting points were determined using a Gallenkamp melting point apparatus and were uncorrected. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor.

Synthesis of compound 1-83c

![3-methylbut-3-en-1-yn-1-yl]benzene (1-83c).

Commercially available phenylacetylene (100 mg, 0.980 mmol, 1 equiv) was dissolved in 5 mL of dry Et₃N, followed by the addition of commercially available 2-bromoprop-1-ene (142 mg, 1.18 mmol, 1.2 equivs), copper iodide (CuI) (95
mg, 0.050 mmol, 5 mol %), and Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol, 2.5 mol %). The reaction mixture was heated to 90 °C for 12 hours. The reaction was cooled to room temperature and the solvent was removed in vacuo. The crude product was dissolved in 20 mL of CH$_2$Cl$_2$ and washed with water (2 x 10 mL). The organic portion was dried over MgSO$_4$, filtered, and concentrated. Purification of the crude reaction mixture by column chromatography gave the title compound (84 mg, 0.587 mmol, 60%) as colourless oil. Spectral data for this compound matched the previously reported.\(^{37}\)

**Experimental Procedure A: Synthesis of quaternary donor acceptor cyclopropanes.**

![Chemical reaction diagram]

Cyclopropanes **1-52a-e** were prepared according to the following procedure. In a 10 mL or 25 mL round-bottomed flask was added the corresponding alkene **1-83** derivative (1.0 equiv), CH$_2$Cl$_2$ (4 mL - 8 mL) and Rh$_2$(esp)$_2$ catalyst (0.1 mol %). The diazomalonate (**1-82a**) (1.3 equiv) was dissolved in CH$_2$Cl$_2$ (3 mL) and added dropwise over a period of 45 mins - 1 h at room temperature. The reaction was stirred at room temperature for 1.5 - 3 h (monitored by TLC). The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in Hexanes).

**Dimethyl 2-ethynyl-2-methylcyclopropane-1,1-dicarboxylate (1-52a).**

Following experimental procedure A, cyclopropane **1-52a** was prepared by dissolving commercially available 2-methylbut-1-en-3-yne (**1-83a**) (500 mg, 7.56 mmol) and Rh$_2$(esp)$_2$ (5.73 mg, 0.008 mmol) in 5 mL of CH$_2$Cl$_2$ followed by the addition of diazomalonate (**1-82a**) (1055 mg, 9.82 mmol) dissolved in 3 mL of CH$_2$Cl$_2$. The reaction was stirred at room temperature for 2.5 h. Cyclopropane **1-52a** (518 mg, 2.64 mmol, 35%) was obtained as a colourless oil. Rf = 0.47 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.78 (s, 6H), 2.09 (s, 1H), 1.94 (d, $J$ = 5.0 Hz, 1H), 1.60 (d, $J$ = 5.0 Hz, 1H), 1.47 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 167.1, 167.0, 83.5,
68.3, 52.5, 39.9, 26.8, 22.8, 19.9. **FT-IR** (thin film, cm$^{-1}$): 3280, 3001, 2954, 2117, 1738, 1436, 1355, 1250, 1118. **HRMS** calc'd for C$_{10}$H$_{12}$O$_4$ [M$^+$]: 196.0736; found: 196.0733.

**Dimethyl 2-(but-1-ynyl)-2-methylcyclopropane-1,1-dicarboxylate (1-52b).**

Following experimental procedure A, cyclopropane 1-52a was prepared by dissolving commercially available 2-methylhex-1-en-3-yne (1-83b) (500 mg, 5.31 mmol) and Rh$_2$(esp)$_2$ (4.02 mg, 0.005 mmol) in 5 mL of CH$_2$Cl$_2$ followed by the addition of diazomalonate (1-82a) (1090 mg, 6.90 mmol) dissolved in 3 mL of CH$_2$Cl$_2$. The reaction was stirred at room temperature for 3 h. Cyclopropane 1-52b (1010 mg, 4.50 mmol, 85%) was obtained as a colourless oil. Rf = 0.51 (30% EtOAc in hexanes).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 3.68 (s, 3H), 3.67 (s, 3H), 2.04 (q, $J$ = 7.8 Hz, 2H), 1.79 (d, $J$ = 4.7 Hz, 1H), 1.47 (d, $J$ = 4.7 Hz, 1H), 1.35 (s, 3H), 0.99 (t, $J$ = 7.8 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 167.6, 167.3, 82.0, 79.2, 52.5, 52.4, 40.3, 27.1, 23.9, 20.4, 13.7, 12.1. **FT-IR** (thin film, cm$^{-1}$): 2976, 2933, 2128, 1739, 1436, 1329, 1234, 1119. **HRMS** calc'd for C$_{12}$H$_{16}$O$_4$ [M$^+$]: 224.1049; found: 224.1053.

**Dimethyl 2-methyl-2-(phenylethynyl)cyclopropane-1,1-dicarboxylate (1-52c).**

Following experimental procedure A, cyclopropane 1-52c was prepared by dissolving (3-methylbut-3-en-1-yn-1-yl) benzene (1-83c) (395 mg, 2.78 mmol) and Rh$_2$(esp)$_2$ (2.10 mg, 0.003 mmol) in 3 mL of CH$_2$Cl$_2$ followed by the addition of diazomalonate (1-82a) (571 mg, 3.61 mmol) dissolved in 3 mL of CH$_2$Cl$_2$. The reaction was stirred at room temperature for 1.5 h. Cyclopropane 1-52c (707 mg, 2.59 mmol, 93%) was obtained as a colourless oil. Rf = 0.51 (30% EtOAc in hexanes).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 7.35 (dd, $J$ = 5.9, 2.3 Hz, 2H), 7.25 (m, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 2.03 (d, $J$ = 5.0 Hz, 1H), 1.69 (d, $J$ = 5.0 Hz, 1H), 1.54 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 167.7, 167.4, 131.6, 128.2, 128.0, 122.8, 89.5, 80.5, 52.8, 40.9, 27.5, 24.3, 20.2. **FT-IR** (thin film, cm$^{-1}$): 2978, 2952, 2198, 1739, 1436, 1237, 1116. **HRMS** calc'd for C$_{16}$H$_{16}$O$_4$ [M$^+$]: 272.1049; found: 272.1056.
Dimethyl 2-methyl-2-vinylcyclopropane-1,1-dicarboxylate (1-52d).

Following experimental procedure A, cyclopropane 1-52d was prepared by dissolving commercially available isoprene (1-83d) (500 mg, 7.34 mmol) and Rh₂(esp)₂ (5.57 mg, 0.007 mmol) in 5 mL of CH₂Cl₂ followed by the addition of diazomalonate (1-82a) (1740 mg, 11.01 mmol) dissolved in 3 mL of CH₂Cl₂. The reaction was stirred at room temperature for 3 h. Cyclopropane 1-52d (754 mg, 3.80 mmol, 52%) was obtained as a 67:33 inseparable mixture of isomers and as a colourless oil. Rf = 0.56 (30% EtOAc in hexanes). Spectral data for this compound matched the previously reported.³⁸

Dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (1-52e).

Following experimental procedure A, cyclopropane 1-52e was prepared by dissolving commercially available α-methylstyrene (1-83e) (500 mg, 4.23 mmol) and Rh₂(esp)₂ (3.20 mg, 0.004 mmol) in 5 mL of CH₂Cl₂ followed by the addition of diazomalonate (1-82a) (1030 mg, 6.34 mmol) dissolved in 3 mL of CH₂Cl₂. The reaction was stirred at room temperature for 3 h. Cyclopropane 1-52e (1030 mg, 4.15 mmol, 98%) was obtained as colourless oil. Rf = 0.56 (30% EtOAc in hexanes). Spectral data for this compound matched the previously reported.³⁸

Experimental procedure B: Lewis acid catalyzed nucleophilic ring opening of quaternary DA cyclopropanes with indoline.

Compounds 1-53a-g were prepared according to the following procedure. To a solution of the cyclopropane 1-5a-e (1 equiv) in 5 – 10 mL of toluene, indoline 1-35a, 1-35c, 1-
35d (2 equiv) and Sc(OTf)₃ catalyst (10 mol %) (Method A) or Yb(OTf)₃ catalyst (5 mol %) (Method B) were added. The reaction mixture was heated to 100 °C for 1.5 -3 hours (monitored by TLC). The mixture was then cooled to room temperature and diluted with 1M HCl (20 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic layers were combined, washed once with brine, dried over MgSO₄, and filtered. The filtrate was concentrated and purified by column chromatography (EtOAc in Hexanes).

**Dimethyl-2-(2-(indolin-1-yl)-2-methylbut-3-ynyl)malonate (1-53a).**

Following experimental procedure B (Method A), N-alkyindoline 1-53a was prepared by dissolving cyclopropane 1-52a (200 mg, 1.02 mmol), Sc(OTf)₃ (50 mg, 0.102 mmol), and indoline 1-35a (243 mg, 2.04 mmol) in 8 mL of toluene. The reaction was heated to 100 °C for 2 h. Compound 1-53a (285 g, 0.903 mmol, 88%) was obtained as a brown oil. Rf = 0.47 (30% EtOAc in hexanes).

Following experimental procedure B (Method B), N-alkyindoline 1-53a was prepared by dissolving cyclopropane 1-52a (169 mg, 0.861 mmol), Yb(OTf)₃ (27 mg, 0.043 mmol), and indoline 1-35a (204 mg, 1.72 mmol) in 5 mL of toluene. The reaction was heated to 100 °C for 2 h. Compound 1-53a (209 mg, 0.680 mmol, 77%) was obtained as a brown oil.

**1H NMR** (400 MHz, CDCl₃): δ = 7.10 (m, 3H), 6.70 (m, 1H), 3.86 (t, J = 5.9 Hz, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.43 (td, J = 7.8, 1.9 Hz, 1H), 2.88 (t, J = 7.8 Hz, 2H), 2.73 (dd, J = 14.4, 5.8 Hz, 1H), 2.55 (dd, J = 14.4, 7.0 Hz, 1H), 2.44 (s, 1H), 1.55 (s, 3H).

**13C NMR** (100 MHz, CDCl₃): δ = 169.7, 169.6, 148.9, 126.6, 124.3, 118.5, 111.6, 84.9, 73.3, 54.1, 52.4, 49.9, 48.5, 37.9, 27.9, 23.4. **FT-IR** (thin film, cm⁻¹): 3272, 2990, 2952, 2844, 1732, 1605, 1483, 1331, 1263, 1155, 750, 655. **HRMS** calc’d for C₁₈H₂₁NO₄ [M⁺]: 315.1471; found: 315.1474.

**Dimethyl 2-(2-(indolin-1-yl)-2-methylhex-3-ynyl)malonate (1-53b).**

Following experimental procedure D (Method A), N-alkyindoline 1-
was prepared by dissolving cyclopropane 1-52b (332 mg, 1.48 mmol), Sc(OTf)₃ (73 mg, 0.148 mmol), and indoline 1-35a (353 mg, 2.96 mmol) in 10 mL toluene. The reaction was heated to 100 °C for 2 h. Compound 1-53b was obtained as a yellow oil (365 mg, 1.06 mmol, 72%). Rf = 0.50 (30% EtOAc in hexanes).

Following experimental procedure D (Method B), N-alkylindoline 1-53b was prepared by dissolving cyclopropane 1-52b (100 mg, 0.446 mmol), Yb(OTf)₃ (14 mg, 0.022 mmol), and indoline 1-35a (106 mg, 0.892 mmol) in 5 mL of toluene. The reaction was heated to 100 °C for 2 h. Compound x (122 mg, 0.356 mmol, 80%) was obtained as a yellow oil.

1H NMR (400 MHz, CDCl₃): δ = 7.13 (d, J = 7.8 Hz, 2H), 7.04 (dd, J = 7.8, 2.4 Hz, 2H), 6.67, (m, 1H), 3.86 (t, J = 6.6 Hz, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 3.38-3.44 (m, 2H), 2.86 (t, J = 8.9 Hz, 2H), 2.68 (dd, J = 14.4, 5.5 Hz, 1H), 2.46 (dd, J = 14.1, 6.6 Hz, 1H), 2.20 (q, J = 7.4 Hz, 2H), 1.49 (s, 3H), 1.13 (t, J = 7.4 Hz, 3H). 13C NMR (100 MHz, CDCl₃): δ = 169.9, 169.6, 149.2, 131.5, 126.4, 124.0, 117.9, 111.6, 86.8, 80.2, 54.0, 52.4, 49.6, 48.6, 38.0, 27.8, 23.3, 13.6, 12.2. FT-IR (thin film, cm⁻¹): 3102, 3043, 2978, 2951, 2844, 2245, 1735, 1604, 1483, 1435, 1330, 1244, 1149, 748. HRMS calc'd for C₂₀H₂₅NO₄ [M+]: 343.1784; found: 343.1772.

Dimethyl 2-(2-(indolin-1-yl)-2-methyl-4-phenylbut-3-ynyl)malonate (1-53c).

Following experimental procedure B (Method A), N-alkylindoline 1-53c was prepared by dissolving cyclopropane 1-52c (378 mg, 1.39 mmol), Sc(OTf)₃ (68 mg, 0.139 mmol), and indoline 1-35a (331 mg, 2.78 mmol) in 10 mL of toluene. The reaction was heated to 100 °C for 3 h. Compound x (428 mg, 1.09 mmol, 79%) was obtained as a yellow oil. Rf = 0.55 (30% EtOAc in hexanes).

Following experimental procedure B (Method B), N-alkylindoline 1-53c was prepared by dissolving cyclopropane 1-52c (234 mg, 0.858 mmol), Yb(OTf)₃ (27 mg, 0.043 mmol), and indoline 1-35a (204 mg, 1.72 mmol) in 10 mL of toluene. The reaction was
hated to 100 °C for 3 h. Compound 1-53c (122 mg, 0.356 mmol, 79%) was obtained as a yellow oil.

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3); \delta = 7.43 \ (dd, J = 7.3, 2.7 \text{ Hz, } 2H), 7.32-7.28 \ (m, 3H), 7.23 \ (d, J = 8.2 \text{ Hz, } 1H), 7.08 \ (dd, J = 7.4, 2.7 \text{ Hz, } 1H), 6.71 \ (m, 1H), 3.94 \ (dd, J = 7.0, 5.5 \text{ Hz, } 1H), 3.62 \ (s, 3H), 3.58 \ (s, 3H), 3.50-3.42 \ (m, 2H), 2.94-2.89 \ (m, 2H), 2.79 \ (dd, J = 14.5, 5.5 \text{ Hz, } 1H), 2.61 \ (dd, J = 14.5, 5.5 \text{ Hz, } 1H), 1.61 \ (s, 3H). \]

\[ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3); \delta = 169.9, 169.7, 149.3, 131.6, 128.2, 126.7, 124.3, 122.6, 118.4, 111.7, 90.7, 85.2, 54.6, 52.6, 49.7, 48.6, 38.3, 28.0, 23.0. \]

\[ \text{FT-IR (thin film, cm}^{-1}) \: 3021, 2951, 2843, 1735, 1604. \]

\[ \text{HRMS calc'd for C}_{24}\text{H}_{25}\text{NO}_4 [M^+]: 391.1784; \text{found: 391.1770.} \]

Dimethyl 2-(2-(indolin-1-yl)-2-methylbut-3-enyl)malonate (1-53d).

Following experimental procedure B (Method A), N-alkylindoline x was prepared by dissolving cyclopropane 1-52d (200 mg, 1.00 mmol), Sc(OTf)\(_3\) (49 mg, 0.101 mmol), and indoline 1-35a (240 mg, 2.00 mmol) in 8 mL of toluene. The reaction was hated to 100 °C for 3 h. Compound 1-53d (135 mg, 0.444 mmol, 44%) was obtained as a brown oil. Rf = 0.55 (30% EtOAc in hexanes).

Following experimental procedure B (Method B), N-alkylindoline 1-53d was prepared by dissolving cyclopropane 1-52d (436 mg, 2.20 mmol), Yb(OTf)\(_3\) (68 mg, 0.110 mmol), and indoline 1-35a (525 mg, 4.40 mmol) in 10 mL toluene. The reaction was hated to 100 °C for 3 h. Compound 1-53d (334 mg, 1.09 mmol, 50%) was obtained as a brown oil.

\[ ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3); \delta = 7.04 \ (d, J = 8.2 \text{ Hz, } 1H), 6.93 \ (m, 1H), 6.73 \ (m, J = 7.8 \text{ Hz, } 1H), 6.63 \ (m, 1H), 5.96 \ (dd, J = 18.0, 10.9 \text{ Hz, } 1H), 5.19 \ (dd, J = 11.7, 9.7 \text{ Hz, } 2H), 3.71 \ (s, 3H), 3.68 \ (dd, J = 8.2, 4.3 \text{ Hz, } 1H), 3.59 \ (s, 3H), 3.52-3.47 \ (m, 1H), 3.35-3.28 \ (m, 1H), 2.95-2.83 \ (m, 2H), 2.53 \ (dd, J = 14.8, 8.2 \text{ Hz, } 1H), 2.43 \ (dd, J = 14.8, 4.3 \text{ Hz, } 1H), 1.29 \ (s, 3H). \]

\[ ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3); \delta = 170.2, 170.1, 150.0, 142.8, 131.5, 126.4, 124.2, 117.6, 114.7, 111.7, 59.4, 52.7, 52.3, 49.2, 47.7, 38.6, 28.0, 19.1. \]

\[ \text{FT-IR (thin film, cm}^{-1}) \: 3272, 2990, 2952, 2844, 1732, 1605, 1483, 1263, 1155. \]

\[ \text{HRMS calc'd for C}_{18}\text{H}_{23}\text{NO}_4 [M^+]: 315.1471; \text{found: 315.1474.} \]
Dimethyl 2-(2-(indolin-1-yl)-2-phenylpropyl)malonate (1-53e).

Following experimental procedure B (Method A), N-alkylindoline 1-53e was prepared by dissolving cyclopropane 1-52e (219 mg, 0.881 mmol), Sc(OTf)₃ (43 mg, 0.088 mmol), and indoline 1-35a (210 mg, 1.76 mmol) in 8 mL of toluene. The reaction was heated to 100 °C for 2.5 h. Compound 1-53e (246 mg, 0.670 mmol, 76%) was obtained as a white solid. Mp = 126-128 °C. Rf = 0.57 (30% EtOAc in hexanes).

Following experimental procedure B (Method B), N-alkylindoline 1-53e was prepared by dissolving cyclopropane 1-52e (100 mg, 0.402 mmol), Yb(OTf)₃ (13 mg, 0.020 mmol), and indoline 1-35a (96 mg, 0.805 mmol) in 5 mL of toluene. The reaction was heated to 100 °C for 2.5 h. Compound 1-53e (140 mg, 0.380 mmol, 85%) was obtained as a white solid.

1H NMR (400 MHz, CDCl₃): δ = 7.47 (d, J = 8.6 Hz, 2H), 7.30 (m, 2H), 7.23 (m, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.67 (m, 1H), 6.56 (m, 1H), 5.69 (d, J = 7.8 Hz, 1H), 3.78-3.73 (td, J = 8.6, 2.4 Hz, 1H), 3.61 (s, 3H), 3.56 (t, J = 5.8 Hz, 1H), 3.52-3.44 (m, 1H), 3.39 (s, 3H), 3.05-2.97 (m, 2H), 2.64 (d, J = 5.8 Hz, 2H), 1.53 (s, 3H). 13C NMR (100 MHz, CDCl₃): δ = 170.0 169.4, 149.6, 143.8, 131.4, 126.4, 126.8, 126.2, 124.1, 117.5, 112.0, 60.7, 52.7, 52.3, 49.1, 47.7, 41.5, 28.3, 18.4. FT-IR (thin film, cm⁻¹): 2951, 2842, 1752, 1734, 1604, 1484, 1435, 1244, 1202, 1158, 748, 702. HRMS calc'd for C₂₂H₂₅NO₄ [M⁺]: 367.1784; found: 367.1785.

Dimethyl 2-(2-(3-(2-(tert-butyldimethylsilyloxy)ethyl)indolin-1-yl)-2-methylbut-3-enyl)malonate (1-53f).

Following experimental procedure B (Method A), N-alkylindoline 1-53f was prepared by dissolving cyclopropane 1-52a (100 mg, 0.510 mmol), Sc(OTf)₃ (25 mg, 0.051 mmol), and 3-(2-(tert-butyldimethylsilyloxy)ethyl)indoline 1-35c (282 mg, 1.01 mmol) in 5 mL of toluene. The reaction was heated to 100 °C for 1.5 h. Compound 1-53f (211 mg, 0.448 mmol, 80%)
was obtained in a 1:1 mixture of diastereomers and as a brown oil. Rf = 0.51 (30% EtOAc in hexanes).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) (mixture of diastereomers): \(\delta = 7.10\text{-}7.07\) (m, 2H), 7.05 (d, \(J = 5.1\) Hz, 4H), 6.75-6.70 (m, 2H), 3.86-3.82 (m, 2H), 3.73 (td, \(J = 6.3, 3.1\) Hz, 4H), 3.68 (s, 3H), 3.65 (s, 3H), 3.62 (s, 4H), 3.59 (s, 4H), 3.23-3.19 (m, 2H), 3.13 (t, \(J = 8.21\) Hz, 1H), 3.08 (t, \(J = 8.21\) Hz, 1H), 2.80-2.67 (m, 2H), 2.63-2.46 (m, 2H), 2.44 (s, 1H), 2.42 (s, 1H), 2.09-1.98 (m, 2H), 1.76-1.68 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H), 0.91 (s, 18H), 0.08 (s, 12H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}): \(\delta = 169.9, 169.8, 169.6, 169.5, 148.7, 148.5, 135.3, 126.8, 126.7, 123.5, 123.2, 118.5, 118.4, 111.7, 111.6, 85.1, 84.9, 73.3, 61.5, 61.4, 56.4, 56.3, 54.2, 53.9, 52.6, 52.4, 48.6, 48.4, 38.4, 37.5, 36.9, 36.8, 36.7, 36.6, 25.9, 23.6, 23.5, 18.3, 18.2, -5.3, -5.2. \textbf{FT-IR} (thin film, cm\textsuperscript{-1}): 3273, 2952, 2930, 2856, 1736, 1482, 1436, 1256, 1094. \textbf{HRMS} calc'd for C\textsubscript{26}H\textsubscript{39}NO\textsubscript{5}Si [M\textsuperscript{+}]: 473.2597; found: 473.2599.

\begin{center}
\includegraphics[width=0.5\textwidth]{diagram}
\end{center}

**Dimethyl 2-(2-(3-(cyanomethyl)indolin-1-yl)-2-methylbut-3-ynyl)malonate (1-53g).**

Following experimental procedure B (Method A), N-alkylindoline 1-53g was prepared by dissolving cyclopropane 1-52a (390 mg, 1.98 mmol, 1 equiv), Sc(OTf)\textsubscript{3} (97 mg, 0.198 mmol, 10 mol %), and 2-(indolin-3-yl)acetonitrile 1-35d\textsuperscript{40} (314 mg, 1.98 mmol, 1 equiv) in 10 mL of toluene. The reaction mixture was heated to 100 °C for 3 hours. Compound 1-53g (445 mg, 1.25 mmol, 63%) in a 1:1 mixture of diastereomers and as yellow oil. Rf = 0.24 (30% EtOAc in hexanes).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) (mixture of diastereomers): \(\delta = 7.19\) (d, \(J = 7.4\) Hz, 2H), 7.15-7.11 (m, 3H), 7.02 (d, \(J = 7.8\) Hz, 1H), 6.81-6.78 (m, 2H), 3.83 (t, \(J = 6.3\) Hz, 1H), 3.79 (t, \(J = 6.6\) Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 3.50 (s, 3H), 3.47-3.42 (m, 2H). 3.39-3.31 (m, 2H), 2.83 (dd, \(J = 14.0, 7.0\) Hz, 1H), 2.69-2.64 (m, 2H), 2.64 (s, 2H), 2.62 (s, 1H), 2.49 (s, 2H), 2.46 (s, 1H), 1.59 (s, 3H0, 1.57 (s, 3H). \textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}): \(\delta = 169.6, 169.6, 169.5, 169.3, 148.3, 147.9, 131.5, 131.2, 128.3, 128.2, 123.9, 123.8, 119.2, 119.1, 118.5, 112.3, 112.1, 84.6, 84.2, 73.7, 55.8, 54.9, 54.6, 53.9, 52.7, 52.6, 52.5, 52.4, 48.8, 48.3, 38.4, 38.0, 36.6, 36.5, 23.8, 23.2, 21.8, 21.9. \textbf{FT-IR}
Experimental procedure C: Mn(OAc)$_3$ mediated radical oxidative cyclizations of N-alkylindolines to pyrroloindoles.

Compounds 1-54a-g were prepared according to the following procedure. To a solution of N-alkylindoline 1-53a-g (1 equiv) in 8 - 15 mL of MeOH was added Mn(OAc)$_3$ (5 equiv). The reaction mixture was heated to 70 °C for 1 - 3 hours (monitored by TLC). The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in Hexanes).

Dimethyl 3-ethynyl-3-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-54a).

Following experimental procedure C, pyrroloindole 1-54a was prepared by dissolving N-alkylindoline 1-53a (618 mg, 1.96 mmol) and Mn(OAc)$_3$ (2620 mg, 9.79 mmol) in 15 mL of MeOH. The reaction was heated to 70 °C for 1 h. Compound 1-54a (397 mg, 1.28 mmol, 65%) was obtained as a brown solid. Mp = 82-84 °C. Rf = 0.53 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.62 (d, $J$ = 7.8 Hz, 1H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.21 (m, 1H), 7.13 (m, 1H), 6.51 (s, 3H), 3.82 (s, 6H), 3.63 (d, $J$ = 13.6 Hz, 1H), 3.37 (d, $J$ = 13.6 Hz, 1H), 2.54 (s, 1H), 1.90 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 169.3, 168.9, 137.6, 133.0, 131.2, 121.8, 121.7, 120.1, 110.3, 97.3, 83.9, 72.4, 58.2, 55.1, 53.5, 51.7, 28.1. FT-IR (thin film, cm$^{-1}$): 3275, 2953, 2112, 7.8 Hz, 1H), 7.21 (m, 1H), 7.13 (m, 1H), 6.51 (s, 3H), 3.82 (s, 6H), 3.63 (d, $J$ = 13.6 Hz, 1H), 3.37 (d, $J$ = 13.6 Hz, 1H), 2.54 (s, 1H), 1.90 (s, 3H). $^{13}$C NMR

(100 MHz, CDCl$_3$): $\delta$ = 169.3, 168.9, 137.6, 133.0, 131.2, 121.8, 121.7, 120.1, 110.3, 97.3, 83.9, 72.4, 58.2, 55.1, 53.5, 51.7, 28.1. FT-IR (thin film, cm$^{-1}$): 3275, 2953, 2112, 1741, 1449, 1256, 1159. HRMS calc'd for C$_{18}$H$_{17}$NO$_4$ [M$^+$]: 311.1158; found: 311.1153.
Dimethyl 3-(but-1-ynyl)-3-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-54b).

Following experimental procedure C, pyrroloindole 1-54b was prepared by dissolving N-alkylindoline 1-53b (276 mg, 0.804 mmol) and Mn(OAc)$_3$ (1070 mg, 4.02 mmol) in 8 mL of MeOH. The reaction was heated to 70 °C for 1.5 h. Compound 1-54b (177 mg, 0.523 mmol, 65%) was obtained as a yellow oil. Rf = 0.51 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.59 (m, 2H), 7.18 (m, 1H), 7.10 (m, 1H), 6.47 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.55 (d, $J$ = 13.7 Hz, 1H), 3.32 (d, $J$ = 13.7 Hz, 1H), 2.20 (q, $J$ = 7.4 Hz, 2H), 1.81 (s, 3H), 1.12 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 169.5, 169.0, 137.5, 132.9, 131.2, 121.5, 119.8, 110.5, 96.8, 86.2, 79.9, 58.3, 55.5, 53.5, 52.0, 28.6, 13.7, 12.3. FT-IR (thin film, cm$^{-1}$): 2978, 2952, 2845, 2242, 1742, 1449, 1254, 1161. HRMS calc'd for C$_{20}$H$_{21}$NO$_4$ [M$^+$]: 339.1471; found: 339.1458.

Dimethyl 3-methyl-3-(phenylethynyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-54c).

Following experimental procedure C, pyrroloindole 1-54c was prepared by dissolving N-alkylindoline 1-53c (369 mg, 0.943 mmol) and Mn(OAc)$_3$ (1260 mg, 4.72 mmol) in 10 mL of MeOH. The reaction was heated to 70 °C for 1.5 h. Compound 1-54c (225 mg, 0.581 mmol) was obtained as a yellow solid (61%). Mp = 108-110 °C Rf = 0.48 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.65-7.62 (m, 2H), 7.42-7.39 (m, 2H), 7.32-7.27 (m, 3H), 7.21 (m, 1H), 7.13 (td, $J$ = 7.0, 1.2 Hz, 1H), 6.52 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (d, $J$ = 13.6 Hz, 1H), 3.44 (d, $J$ = 13.6 Hz, 1H), 1.96 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 169.4, 168.9, 137.5, 132.9, 131.7, 131.3, 128.5, 128.3, 122.2, 121.7, 121.5, 120.0, 110.4, 97.1, 89.3, 84.2, 58.3, 55.8, 53.6, 53.5, 51.9, 28.3. FT-IR (thin film, cm$^{-1}$): 2996, 2952, 2845, 2242, 1742, 1449, 1254, 1161. HRMS calc'd for C$_{24}$H$_{21}$NO$_4$ [M$^+$]: 387.1471; found: 387.1475.
Dimethyl 3-methyl-3-vinyl-2,3-dihydro-1H-pyrrolo[1,2-\(a\)]indole-1,1-dicarboxylate (1-54d).

Following experimental procedure C, pyrroloindole 1-54d was prepared by dissolving \(N\)-alkylindoline 1-53d (398 mg, 1.31 mmol) and Mn(OAc)\(_3\) (1750 mg, 6.53 mmol) in 10 mL of MeOH. The reaction was heated to 70 °C for 1 h. Compound 1-54d (176 mg, 0.563 mmol, 43%) was obtained as a colourless oil. Rf = 0.57 (30% EtOAc in hexanes). \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.61\) (d, \(J = 8.2\) Hz, 1H), 7.30 (d, \(J = 8.2\) Hz, 1H), 7.14-7.07 (m, 2H), 6.50 (s, 1H), 6.08 (dd, \(J = 17.5, 10.5\) Hz, 1H), 5.18 (d, \(J = 10.5\) Hz, 1H), 5.02 (d, \(J = 17.2\) Hz, 1H) 3.82 (s, 3H), 3.77 (s, 3H), 3.24 (d, \(J = 13.6\) Hz, 1H), 3.18 (d, \(J = 13.6\) Hz, 1H) 1.76 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 169.6, 169.5, 141.2, 138.5, 132.6, 131.6, 121.4, 121.3, 119.6, 114.4, 110.5, 96.6, 63.3, 58.3, 53.5, 53.4, 50.9, 24.2. FT-IR (thin film, cm\(^{-1}\)): 2986, 2953, 2881, 1741, 1447, 1259, 1144, 1095. HRMS calc'd for C\(_{18}\)H\(_{19}\)NO\(_4\) [M\(^+\)]: 313.1314; found: 313.1315.

Dimethyl 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-\(a\)]indole-1,1-dicarboxylate (1-54e).

Following experimental procedure C, pyrroloindole 1-54e was prepared by dissolving \(N\)-alkylindoline 1-53e (344 mg, 0.936 mmol) and Mn(OAc)\(_3\) (1250 mg, 4.68 mmol) in 10 mL of MeOH. The reaction was heated to 70 °C for 2 h. Compound x (284 mg, 0.781 mmol, 83%) was obtained as colourless oil. Rf = 0.53 (30% EtOAc in hexanes). \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.67\) (d, \(J = 7.8\) Hz, 1H), 7.32-7.27 (m, 3H), 7.12 (m, 3H), 7.02 (dd, \(J = 8.2, 1.1\) Hz, 1H), 6.94 (d, \(J = 8.2\) Hz, 1H) 6.60 (s, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 3.51 (d, \(J = 13.6\) Hz, 1H), 3.42 (d, \(J = 13.6\) Hz, 1H) 2.02 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 169.4, 169.3, 144.4, 139.1, 133.0, 131.6, 128.6, 127.4, 125.3, 121.5, 119.8, 110.9, 96.8, 65.2, 58.5, 54.5, 53.5, 53.2, 26.2. FT-IR (thin film, cm\(^{-1}\)): 3056, 2982, 2952, 2842, 1739, 1610, 1448, 1257, 1165, 1094. HRMS calc'd for C\(_{22}\)H\(_{21}\)NO\(_4\) [M\(^+\)]: 363.1471; found: 363.1466.
Dimethyl 9-(2-(tert-butyldimethylsilyloxy)ethyl)-3-ethynyl-3-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-54f).

Following experimental procedure C, pyrroloindole 1-54f was prepared by dissolving N-alkylindoline 1-53f (198 mg, 0.377 mmol) and Mn(OAc)_3 (506 mg, 1.88 mmol) in 8 mL of MeOH. The reaction was heated to 70 °C for 3 h. Compound 1-54f (142 mg, 0.302 mmol, 80%) was obtained as a colourless oil. Rf = 0.57 (30% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.22 m, 1H), 7.14 (m, 1H), 3.85 (dd, J = 7.0, 3.9 Hz, 2H), 3.82 (s, 6H), 3.59 (d, J = 13.2 Hz, 1H), 3.40 (d, J = 13.2 Hz, 1H) 3.06 (dd, J = 7.0, 3.9 Hz, 2H), 2.52 (s, 1H), 1.87 (s, 3H), 0.93 (s, 9H), 0.08 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ = 169.4, 169.0, 134.0, 133.2, 130.1, 121.8, 120.2, 119.6, 110.2, 107.3, 83.9, 72.4, 58.3, 54.6, 53.4, 53.3, 52.5, 28.2, 27.9, 26.0. 18.4. FT-IR (thin film, cm⁻¹): 3279, 2954, 2930, 2856, 1742, 1453, 1434, 1253, 1152, 1090. HRMS calc'd for C₂₆H₃₅NO₅Si [M⁺]: 469.2284; found: 469.2283.

Dimethyl 9-(cyanomethyl)-3-ethynyl-3-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-54g).

Following experimental procedure C, pyrroloindole 1-54g was prepared by dissolving N-alkylindoline 1-53f (444 mg, 1.25 mmol) and Mn(OAc)_3 (1675 mg, 6.25 mmol) in 10 mL of MeOH. The reaction was heated to 70 °C for 3 h. Compound 1-54f (150 mg, 0.428 mmol, 35%) was obtained as a yellow solid. Mp = 88–90 °C. Rf = 0.31 (30% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.30 (m, 1H), 7.24 (m, 1H), 3.97 (d, J = 8.2 Hz, 2H), 3.88 (d, 6H), 3.59 (d, J = 13.6 Hz, 1H), 3.47 (d, J = 13.6 Hz, 1H), 2.59 (s, 1H), 1.90 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.7, 168.5, 134.8, 131.9, 131.1, 123.1, 120.9, 119.3, 118.4, 110.9, 99.3, 83.8, 73.2, 58.7, 55.5, 54.2, 54.0, 51.6, 28.4, 13.3. FT-IR (thin film, cm⁻¹): 3271, 2988, 2951, 1731, 1453, 1348, 1254, 1149, 1096, 745. HRMS calc'd for C₂₀H₁₈N₂O₄ [M⁺]: 350.1267; found: 350.1278.
Hydrostannylation of dimethyl 9-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methyl-3-(2-(tributylstannyl)vinyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1,1-dicarboxylate (1-89).

To a solution of compound 1-54f (50 mg, 0.106 mmol, 1 equiv) in 5 mL of THF, PdCl₂(PPh₃)₂ (3.72 mg, 0.005 mmol, 5 mol %) was added and the mixture was cooled to 0 °C. Bu₃SH (34 mg, 0.117 mmol, 1.1 equiv) was then added dropwise over a 5-minute period. The mixture was stirred at 0 °C for 10 minutes and then at room temperature for 30 minutes. The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in hexanes). Compound 1-89 (68 mg, 0.089 mmol, 85%) was obtained as a colourless oil. Rf = 0.77 (30% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 7.64 (m, 1H), 7.22 (m, 1H), 7.08 (dd, J = 4.7, 4.3 Hz, 2H), 6.18 (d, J = 19.5 Hz, 1H), 6.07 (d, J = 19.5 Hz, 1H), 3.87-3.82 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.19 (s, 1H), 3.06 (dd, J = 6.6 Hz, 2H), 1.68 (s, 3H), 1.51-1.38 (m, 6H), 1.30 (m, 6H), 0.93 (s, 9H), 0.90-0.85 (m, 15H), 0.07 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ = 169.9, 169.6, 150.1, 135.2, 132.9, 131.4, 131.3, 128.0, 121.3, 119.9, 118.9, 110.5, 106.3, 102.8, 101.4, 64.3, 63.3, 58.5, 58.3, 53.2, 53.1, 52.1, 29.1, 29.0, 28.8, 28.3, 37.3, 27.2, 26.0, 23.8, 18.5, 13.7, 13.6, 10.3, 9.5, -5.2. FT-IR (thin film, cm⁻¹): 2954, 2927, 2854, 1743, 1454, 1251, 1150, 1090. HRMS calc'd for C₃₈H₆₅NO₅SiSn [M⁺]: 761.3497; found: 761.3587.
Synthesis of dimethyl 9-(2-(tert-butyldimethylsilyloxy)ethyl)-3-methyl-3-(2-(1-tosyl-1H-indol-2-yl)vinyl)-2,3-dihydro-1H-pyrrolo[1,2-α]indole-1,1-dicarboxylate (1-91).

To a solution of compound **1-89** (39 mg, 0.051 mmol, 1.1 equivs) in 5 mL of toluene were added Pd(PPh₃)₄ (1.76 mg, 0.001 mmol, 3 mol %) and 2-bromo-1-tosyl-1H-indole **1-90** (16 mg, 0.046 mmol, 1 equiv). The reaction mixture was heated to 110 °C for 24 hours. The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in hexanes). **Compound 1-91** (20 mg, 0.026 mmol, 58%) was obtained as a colourless oil. Rf = 0.31 (30% EtOAc in hexanes).

**1H NMR** (400 MHz, CDCl₃): δ = 8.17 (d, J = 8.6 Hz, 1H), 7.71-7.69 (m 1H), 7.45 (d, 8.6 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.37-7.35 (m, 1H), 7.30 (d, J = 8.2 Hz, 1H) 7.21 (d, J = 7.8 Hz, 1H), 7.14-7.12 (m, 2H), 7.07 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 16.0 Hz, 1H), 6.66 (s, 1H), 6.36 (d, J = 16.0 Hz, 1H), 3.90 (t, J = 8.2 Hz, 2H) 3.85 (s, 3H), 3.74 (s, 3H), 3.40 (d, J = 13.4 Hz, 1H), 3.27 (d, J = 13.4 Hz, 1H), 3.10 (t, J = 8.2 Hz, 2H), 2.31 (s, 3H), 1.94 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H).

**13C NMR** (100 MHz, CDCl₃): δ = 169.8, 169.6, 144.6, 137.9, 137.3, 136.7, 135.5, 134.9, 133.1, 131.3, 129.6, 126.5, 124.7, 123.8, 121.7, 120.7, 120.4, 120.1, 119.3, 114.9, 110.3, 109.1, 106.8, 63.2, 62.6, 58.4, 53.4, 53.3, 52.2, 28.4, 26.1, 24.3, 21.5, 18.5, -5.2. **FT-IR** (thin film, cm⁻¹): 2954, 2929, 2856, 1740, 1597, 1451, 1373, 1255, 1174, 1090. **HRMS** calc'd for C₄₁H₄₈N₂O₇Si [M⁺]: 740.2951; found: 740.2961.
Synthesis of methyl 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1-carboxylate (1-92).

In a microwave vial, pyrroloindole 1-54e (275 mg, 0.757 mmol, 1 equiv) was dissolve in DMF (8 mL), followed by the addition of LiCl (64 mg, 1.51 mmol, 2 equiv) and Me$_3$NHCl (72 mg, 0.757 mmol, 1 equiv). The reaction mixture was placed in the microwave reactor and heated to 120 °C for 3 hours. The mixture was diluted with 15 mL of distilled water and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed once with brine, dried over MgSO$_4$, and filtered. The filtrate was concentrated and purified by column chromatography. Compound 1-92 (169 mg, 0.554 mmol, 74%) was obtained in a 1:1.3 mixture of diastereomers and as a yellow oil. Rf = 0.58 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereomers): $\delta$ = 7.64 (d, $J = 7.6$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H) 7.37-7.31 (m, 2H) 7.30-7.24 (m, 5H), 7.12-7.10 (m, 2H), 7.07-7.03 (m, 1H), 6.96 (d, $J = 8.2$ Hz, 1H), 6.92 (dd, $J = 7.8$, 1.5 Hz, 2H), 6.74 (d, $J = 8.2$ Hz, 1H) 4.34 (t, $J = 8.6$ Hz, 1H), 4.17 (t, $J = 7.4$ Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H) 3.19-3.11 (m, 2H), 2.96-2.90 (m, 2H), 2.16 (s, 3H), 1.92 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 171.8, 171.6, 144.9, 144.1, 140.8, 133.4, 133.1, 132.0, 131.5, 128.7, 128.6, 127.4, 127.2, 125.7, 124.9, 121.0, 120.9, 120.8, 120.7, 119.5, 119.4, 110.7, 94.7, 94.5, 65.8, 65.0, 52.5, 52.4, 49.7, 49.5, 41.9, 41.4, 26.6, 24.7. FT-IR (thin film, cm$^{-1}$): 2981, 2951, 1740, 1683, 15557, 1449, 1199, 1167, 1029. HRMS calc'd for C$_{20}$H$_{19}$NO$_2$ [M$^+$]: 305.1416; found: 305.1413.
Synthesis of 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-1-carbaldehyde (1-93).

To a solution of pyrroloindole 1-92 (200 mg, 0.655 mmol, 1 equiv) in toluene chilled to -78 °C was added a 1M solution of DIBAL-H (3.50 mL, 3.48 mmol, 5.3 equiv) dropwise for 20 minutes. The reaction mixture was stirred for 1 hour at which time the reaction flask was removed from the cold bath. Immediately after, the reaction mixture was quenched MeOH (1.5 mL) and the mixture was stirred for an additional 30 minutes. The reaction mixture was then diluted with 5% HCl (20 mL) and extracted with CH₂Cl₂ (20 mL x 3). The combined organic layers were washed with an additional 5% HCl (20 mL), water (20 mL), and brine (20 mL) and dried with MgSO₄. The crude reaction mixture was concentrated to give aldehyde 1-93 was obtained as a yellow foam (157 mg, 0.570 mmol, 87%) and a 1:1.1 mixture of diastereomers. The crude product was used immediately without further purification. H NMR (400 MHz, CDCl₃) (mixture of diastereomers): δ = 9.80 (d, J = 2.3 Hz, 1H), 9.60 (d, J = 2.7 Hz, 1H), 7.67 (m, 1H), 7.65 (m, 1H), 7.34-7.26 (m, 6H), 7.24-7.17 (m, 2H), 7.12-7.02 (m, 4H), 7.09-7.05 (m, 2H), 7.00-6.98 (m, 2H), 6.90 (d, J = 7.4 Hz, 1H), 6.46 (s, 1H), 4.16-4.11 (m, 1H), 4.09-4.04 (m, 1H), 3.13 (dd, J = 2.7, 7.0 Hz, 1H), 3.08 (dd, J = 3.1, 7.0 Hz, 1H), 2.93 (dd, J = 8.9, 13.2 Hz, 1H), 2.89 (dd, J = 6.3, 10.5 Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H).
Experimental data for by product 3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-α]indol-1-one (1-96). $^1$H NMR (400 MHz, CDCl$_3$): \( \delta = 7.82 \text{ (d, } J = 7.4 \text{ Hz, } 1\text{H}), \ 7.36-7.31 \text{ (m, } 3\text{H}), \ 7.22-7.17 \text{ (m, } 2\text{H}), \ 7.5-7.12 \text{ (m, } 2\text{H}), \ 7.12 \text{ (s, } 1\text{H}), \ 3.98 \text{ (d, } J = 8.2 \text{ Hz, } 1\text{H}), \ 3.34 \text{ (s, } 2\text{H}), \ 2.14 \text{ (s, } 3\text{H}).

$^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 191.9, 143.6, 136.4, 134.0, 132.6, 129.0, 127.8, 125.3, 124.9, 124.4, 121.4, 112.6, 99.2, 62.7, 58.9, 26.3. \) HRMS calc'd for $C_{18}H_{15}NO \ [M^+]$: 261.1154; found: 261.1150.

Synthesis of 1-(methoxycarbonyl)-2-methyl-2-phenylcyclopropane-1-carboxylic acid (1-109).

![Synthesis of 1-(methoxycarbonyl)-2-methyl-2-phenylcyclopropane-1-carboxylic acid (1-109).](Image)

To a solution of cyclopropane 1-52e (300 mg, 1.16 mmol, 1 equiv) in MeOH (1.5 mL), 1.7 M NaOH (1.5 mL, 2 equiv) was added and was stirred at room temperature for 8 hours. The reaction mixture was then diluted with EtOAc and water to separate the layers. The quelus layer was acidified with 5% HCl to reach a PH 2, and then extracted with EtOAc (8 mL x 3). The combined organic layers were washed with brine and dried with MgSO$_4$. The crude reaction mixture was concentrated to give cyclopropane 1-109 as a colourless oil (272 mg, 1.16 mmol, quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$): \( \delta = 7.36-7.32 \text{ (m, } 2\text{H}), \ 7.28-7.24 \text{ (m, } 3\text{H}), \ 3.08 \text{ (s, } 3\text{H}), \ 2.49 \text{ (d, } J = 5.2 \text{ Hz, } 1\text{H}), \ 2.24 \text{ (d, } J = 5.2 \text{ Hz, } 1\text{H}), \ 1.66 \text{ (s, } 3\text{H}). \) $^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 174.0, 167.9, 128.8, 128.5, 127.8, 127.5, 52.5, 24.6, 22.4.

Synthesis of methyl 1-isobutyryl-2-methyl-2-phenylcyclopropane-1-carboxylate (1-104).

![Synthesis of methyl 1-isobutyryl-2-methyl-2-phenylcyclopropane-1-carboxylate (1-104).](Image)
To a solution of cyclopropane 1-112 (250 mg, 0.968, 1 equiv) in THF (5 mL) and water (5 mL) was added sodium acetate (397 mg, 4.84 mmol, 5 equiv) and p-toluenesulfonyl-hydrazide (631 mg, 3.38 mmol, 3.5 equiv). The reaction mixture was heated to 70 °C for 18 hours. The reaction was cooled to room temperature and the THF was removed under reduced pressure. The resulting slurry was extracted with Et2O (10 mL x 3), and the combined organic layers were washed with water (30 mL), brine (30 mL) and dried with MgSO4. The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in Hexanes) to give 1-104 as a colourless oil (70 mg, 0.345 mmol, 36%) and a 1:1 mixture of diastereomers. Rf = 0.60 (30% EtOAc in hexanes). 1H NMR (400 MHz, CDCl3) (mixture of diastereomers): δ = 7.27-7.25 (m, 3H), 7.21-7.14 (m, 3H), 3.83 (s, 3H), 3.05 (s, 3H), 2.98-2.92 (m, 1H), 2.32 (d, J = 5.1 Hz, 1H), 2.19 (d, J = 5.5 Hz, 1H), 1.94-1.88 (m, 1H), 1.64 (d, J = 5.1 Hz, 1H), 1.63 (s, 3H), 1.48 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 5.5 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H).

Synthesis of methyl 1-isobutyryl-3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole-1-carboxylate (1-113).

Following experimental procedure B (Method B), cyclopropane 1-104 (90 mg, 0.345 mmol), Yb(OTf)3 (22 mg, 0.035 mmol), and indoline 1-35a (82 mg, 0.690 mmol) were dissolved in 3 mL toluene. The reaction was heated to 100 °C for 6 h. The mixture was then cooled to room temperature and diluted with 1M HCl (10 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed once with brine, dried over MgSO4, and filtered. The filtrate was concentrated and purified by column chromatography (EtOAc in Hexanes). The N-alkylindoline was as a brown foam (Rf = 0.68 in 30% EtOAc in hexanes), and was used immediately in the next step. The resulting N-alkylindoline was dissolved in MeOH
and was added Mn(OAc)_3 (5 equivs). The reaction mixture was heated to 70 °C for 6 hours (monitored by TLC). The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in Hexanes). Pyrroloindole 1-113 was obtained as a yellow foam (20 mg, 0.053 mmol, 23%) 1:1.6 mixture of diastereomers. Rf = 0.59 in 30% EtOAc in hexanes. \(^1H\) NMR (400 MHz, CDCl\(_3\)) (mixture of diastereomers): 7.66 (m, 2H), 7.31-7.25 (m, 7H), 7.15-7.11 (m, 3H), 7.09-7.05 (m, 3H), 7.01 (m, 2H), 6.84 (d, \(J = 8.2\) Hz, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.52 (d, \(J = 14.1\) Hz, 1H), 3.46 (d, \(J = 13.5\) Hz, 1H), 3.38 (d, \(J = 13.5\) Hz, 1H) 3.38-3.33 (m, 1H), 3.29 (d, \(J = 14.1\) Hz, 1H), 3.10-3.14 (m, 1H), 1.99 (s, 3H), 1.98 (s, 3H), 1.20 (d, \(J = 6.5\) Hz, 3H), 1.05 (d, \(J = 6.5\) Hz, 3H), 1.05 (d, \(J = 6.5\) Hz, 3H), 0.77 (d, \(J = 6.5\) Hz, 3H).

**Synthesis of 2-methyl-1-(3-methyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)propan-1-one (1-114).**

![Chemical Structure](image)

In a microwave vial, pyrroloindole 1-113 (80 mg, 0.213 mmol, 1 equiv) was dissolve in DMF (5 mL), followed by the addition of LiCl (18 mg, 0.426 mmol, 2 equiv) and NE\(_3\)-HCl (20 mg, 0.213 mmol, 1 equiv). The reaction mixture was placed in the microwave reactor and heated to 120 °C for 3 hours. The mixture was diluted with 15 mL of distilled water and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed once with brine, dried over MgSO\(_4\), and filtered. The filtrate was concentrated and purified by column chromatography. Compound 1-114 (28 mg, 0.088 mmol, 35%) was obtained as a yellow oil in a 1:2.25 mixture of diastereomers. Rf = 0.58 (30% EtOAc in hexanes). \(^1H\) NMR (400 MHz, CDCl\(_3\)) (mixture of diastereomers): 7.62-7.59 (m, 2H), 7.34-7.32 (m, 2H), 7.30-7.27 (m, 4H), 7.25-7.23 (m, 2H), 7.10-7.06 (m, 2H), 7.04-7.01 (m, 2H), 6.98-6.96 (m, 1H), 6.95-6.93 (m, 2H), 6.78 (d, \(J = 8.2\) Hz, 1H), 6.38 (s, 1H), 6.36 (s, 1H), 4.46 (t, \(J = 8.2\) Hz, 1H), 4.37 (t, \(J = 8.2\) Hz, 1H), 3.23-3.12 (m, 4H), 2.82-
2.77 (m, 2H), 2.06 (s, 3H), 1.92 (s, 3H), 1.23 (d, \(J = 7.0 \text{ Hz}, 3\text{H}\)), 1.22 (d, \(J = 7.0 \text{ Hz}, 3\text{H}\)), 1.18 (d, \(J = 6.5 \text{ Hz}, 3\text{H}\)), 1.09 (d, \(J = 6.5 \text{ Hz}, 3\text{H}\)).

1.8 References


Chapter 2: Annulation Reactions of Donor Acceptor Cyclopropanes with Vinyl Azide and 2H-azirine

2 Chapter introduction

Chapter two describes the annulation reaction of DA cyclopropanes with vinyl azide or 2H-azirine for the formation of 1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates. Throughout the chapter, a general description of annulation reactions between DA cyclopropanes with dipolarophiles to give heterocycles is described. The work presented in this chapter was done in collaboration with Lauren C. Irwin, who synthesized cyclopropanes 2-99c-f and 2-99h. Reaction optimization, reaction scope, mechanistic studies, and crystal suitable for x-ray diffraction studies were developed independently. The results presented in Section 2.4 have been published in a peer review journal and reproduced in part with permission from Curiel Tejeda, J.E.; Irwin, L.C.; Kerr, M.A. *Org. Lett.* **2016**, *18*, 4738-4741. Copyright © 2016 American Chemical Society.

2.1 Annulations of Donor Acceptor cyclopropanes

In Chapter 1, it was shown that when a DA cyclopropane reacts with a nucleophile, a homo-Michael product is formed. If a nucleophile and an electrophile are tethered together (2-2) and react with a DA cyclopropane (2-1), a ring is formed as the product (2-4, Figure 2-1). The new ring is a result of a cycloaddition or an annulation reaction which are characterized by two components coming together to form two new \( \sigma \)-bonds and make a ring.\(^1\) A reaction is classified as a cycloaddition reaction when the ring product is formed \textit{via} a concerted mechanism, while annulation reactions involve a step-wise mechanism. Throughout the chapter, the reactions of DA cyclopropanes for ring formation will be referred to as annulation reactions, as many of their mechanisms are step-wise, rather than concerted. The annulation reactions of DA cyclopropanes are postulated to follow an intermediate (2-3) where the charge separation is enhanced by a Lewis acid, heat, or pressure. The majority of the annulation reactions of activated DA cyclopropanes with dipolarophiles, involve the formation of heterocycles; this is due to the initial ring opening event being more facile with heteroatom based nucleophilic
However, there have been some cases where all-carbon partners are used resulting in the formation of carbocycles.\textsuperscript{2c} Annulation reactions often provide high atom economy, and excellent regio- and stereoselectivities observed in the products. In this chapter, a few examples of cycloaddition/annulation reactions of DA cyclopropanes with varying partners will be discussed as there are many examples in the literature.\textsuperscript{2}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2-1.png}
\caption{Annulation reaction of DA cyclopropanes.}
\end{figure}

### 2.1.1 Annulation Reactions of DA Cyclopropanes to form Carbocycles

In 2009, Sapeta and Kerr reported the Lewis acid catalyzed [3+3] hexannulation of DA cyclopropane 2-5 with 2-(chloromethyl)-3-trimethyl-silyl-1-propane (2-8) to afford exo-methylenecyclohexane 2-7 (Scheme 2-1).\textsuperscript{3} The methodology was inspired by the work of Trost and Chan in which Pd-trimethylenemethane (Pd-TMM) was used as a 3-carbon synthon in a [3 + 2] cycloaddition with olefins.\textsuperscript{4} Since DA cyclopropanes are known to behave similar to alkenes\textsuperscript{2d,e}, attempts towards the one-pot annulation of DA cyclopropane 2-5 with TMM 2-6 failed with various Pd(0) sources. It was later found that the reaction between DA cyclopropane 2-5 and 2-(chloromethyl)-3-trimethyl-silyl-1-propane (2-8), in the presence of TiCl\textsubscript{4}, gave the ring open product 2-9 in yields ranging from 62-92%. Treatment of compound 2-9 with NaH gave the desired exo-methylenecyclohexane product 2-7, in 75-97% yield. Although a two-step protocol was accomplished, attempts to a one-pot procedure by screening of several organic and inorganic additives, Ag(0) sources, and other bases, failed. Substrate scope for the reaction was limited to the use of aromatic, heteroaromatic, vinyl, and spiro-fused cyclopropanes and the utility of the reaction was displayed in the synthesis of the core of the natural product tronocarpine 2-10.
Scheme 2-1. Sapeta and Kerr’s synthesis of \textit{exo}-methylenecyclohexanes.

Later in 2011, Kerr and co-workers developed a tandem cyclopropane ring opening/Conia-ene reaction, catalyzed by Zn(NTf$_2$)$_2$, reaction to give the cyclohexane ring of 2-13 (Scheme 2-2).\textsuperscript{5} The scope of the reaction was investigated and styrenyl, vinyl, heteroaryl, and electron rich and electron poor aryl substituted cyclopropanes afforded 2-11 in yields ranging from 61-90%. The reaction was also limited to the use of terminal alkynes as any internal alkyne inhibited the Conia-ene reaction and only ring open product was isolated.

Scheme 2-2. Kerr and co-workers’ tandem ring opening/Conia-ene annulation reaction to form tetrahydrocarbazole.

In 2015, an efficient [4+3] annulation reaction between dienolsylic ether 2-14 and DA cyclopropane 2-15 in the presence of a Cu(ClO$_4$)$_2$•6H$_2$O to give a variety of cycloheptene or [n,5,0]carbobicycle 2-18 in a 58-96% yield (Scheme 2-3).\textsuperscript{6} An asymmetric version of the reaction was also developed by employing a chiral Cy-TOX ligand (2-16), which provided an innovative approach accessing optically active cycloheptene or
[n,5,0]carbobicycle 2-18 in excellent ee (88-98%). Mechanistic studies showed that the reaction involves a stepwise pathway involving an unusual ring opening of a 5-membered intermediate (2-17), formed by a [3+2] annulation, followed by an intramolecular cyclization to afford the thermodynamically stable [4+3] annulation product.

**Scheme 2-3.** Tang and co-workers’ [4+3] annulation of DA cycloproanes with dienes.

Also in 2015, Tomilov and co-workers published a unique process where DA cyclopropane 2-19 was used as a source of a formal 1,2-dipole in a GaCl₃ mediated [4+2] annulation reaction with alkene 2-22 to access tetralin 2-24 (Scheme 2-4). To form 1,2-dipole (2-21), 1,3-dipole 2-20 which is formed by the typical bond polarization of DA cyclopropane 2-19. A 1,2-hydride shift occurs at the benzyl position and is promoted by the presence of anhydrous GaCl₃. The addition of alkene 2-22 to the 1,2-dipolar gallium complex (2-21) results in intermediate 2-23, which then undergoes an intramolecular electrophilic aromatic substitution to give tetralin 2-24 in yields up to 90%. The reaction was tolerable of a diverse number of unsaturated compounds, with both aryl and alkyl substitutes about the double bond, as well as DA cycloproanes with various substitution patterns on the aromatic ring.

2.1.2 Annulation Reactions of DA Cyclopropanes to form Heterocycles

2.1.2.1 Annulations Reactions with Nitrones

The first example of a dipolar [3+2] annulation reaction between DA cyclopropanes and nitrones was published by Young and Kerr in 2003.¹⁰ Tetrahydro-1,2-oxazine 2-25 was synthesized from the reaction between cyclopropane 2-26, nitron 2-27, and catalytic amounts of Yb(OTf)₃ (5 mol%) (Scheme 2-5). The reaction tolerated a wide range of nitrones; N-tolyl protected nitrones were significantly more reactive than their N-Me protected counterpart, and proceeded to give products in higher yields (73-96% and 50-84%), respectively. Cyclopropanes with a phenyl- or styryl- substituent greatly reduced the reaction times, and cycloadducts were obtained in yields ranging from 74-95%. Lower yields were obtained for vinyl substituted cyclopropanes because of a competing polymerization side reaction. In all cases of the [3+2] annulation, the sole regioisomer isolated had the oxygen atom of the nitrone proximal to the diester moiety of the cyclopropane. A single diastereomer was also formed, with substituents at the C₃ and C₆ cis to each other. In 2004, Young and Kerr expanded on the methodology by showing a three-component process in which hydroxylamine 2-28 reacted with aldehyde 2-29 to give the nitron in situ to yield a diverse array of tetrahydro-1,2-oxazines 2-25 in good yields (66-96%) and diastereoselectivity (>95%) (Scheme 2-5).¹¹
Scheme 2-5. Kerr group synthesis of tetrahydro-1,2-oxazines.

More recently, Ioffe and co-workers developed the first [3+3] annulation of nitronate 2-30 with DA cyclopropane 2-31 to access previously unknown bicyclic nitrosoacetal 2-32 (Scheme 2-6).\textsuperscript{12} The reaction proceeded under catalytic Yb(OTf)\textsubscript{3} (5 mol\%) conditions to give bicycle2-32 in yields ranging from 61-92%.

Scheme 2-6. Ioffe and co-workers' synthesis of bicyclic nitrosoacetal from DA cyclopropanes.

2.1.2.2 Annulation Reactions with Aromatic Azomethine Imines

Another 1,3-dipole used as nucleophiles in the annulation of DA cyclopropanes are azomethine imines. In 2008, Charette and co-workers described the formation of tricyclic dihydroquinoline 2-35 in the first annulation reaction of aromatic azomethine imine 2-33 with DA cyclopropane 2-34 (Scheme 2-7).\textsuperscript{13} Catalyst screening showed that Sc(OTf)\textsubscript{3}, Mg(ClO\textsubscript{4})\textsubscript{2}, and Ni(ClO\textsubscript{4})\textsubscript{2} were suitable catalysts for the reaction, but of the three, Ni(ClO\textsubscript{4})\textsubscript{2} was found to be the best. A benzoyl protected quinolinium ylide showed to be the most effective in the annulation reaction, when compared to its pivaloyl- or triflyl-protected counterparts. Substitution on the benzoyl protecting group showed that the placement of an EWG gave tricyclic dihydroquinoline 2-35 in an 84\% yield (p-CF\textsubscript{3}Bz), while an EDG group gave the annulation product in a lower yield of 54\% (p-OMeBz). The scope of the reaction, with respect to the cyclopropane, showed that electron rich substituted DA cyclopropanes gave cycloadducts in moderate yields (32-87\%) and dr up
to 6.6:1. Electron poor substituents on the cyclopropanes, such as the $p$-NO$_2$ aryl substituted, gave the product in lower yields, 11%, but still a good $dr$ of 5.9:1. A stereochemical analysis of the reaction led to a proposed stepwise mechanism that consists of a nucleophilic ring opening of the DA cyclopropane (2-36) followed by a diastereoselective ring-closing reaction (2-37) to yield tricyclic dihydroquinoline 2-35.

![Scheme 2-7](image)

**Scheme 2-7.** Charette and co-workers’ annulation reaction of DA cyclopropane and aromatic azomethine imine.

Later, in 2013, Tang’s group published a highly enantioselective [3+3] annulation reaction of isoquinoline azomethine imine 2-38 with DA cyclopropane 2-39 catalyzed by a In-TOX 2-41/Ni(ClO$_4$)$_2$ system (Scheme 2-8). The reaction provided the formation of 6,6,6-tricyclic dihydroisoquinoline 2-40 in yields up to 99% with good diastereo- and enantioselectivity ($>20:1$ $dr$ and up to 98% $ee$).
2.1.2.3 Annulation Reactions with Nitriles

In 2003, Yu and Pagenkopf published the first highly stereoselective [3+2] annulation of glycal derived DA cyclopropane 2-43 with nitrile 2-43 to afford dihydropyrroles 2-44, in the presence of Me$_3$SiOTf (Scheme 2-9). The reaction worked well with aliphatic nitriles (such as acetonitrile and pivalonitrile). Aromatic, and α, β-unsaturated nitriles also underwent efficient cyclization to afford dihydropyrrole 2-44 in a 43-96% yield and as a single diastereomer with high stereoselectivity.

Furthermore, Srinivasan and co-workers published a SnCl$_4$ promoted [3+2] annulation between activated DA cyclopropane 2-45 and nitrile 2-46 (Scheme 2-10). The reaction proceeded well with both alkyl and aryl nitriles, which underwent cyclization to give 1-pyrrolines 2-48 in a 48-90% yield. Srinivasan and coworkers postulated that the reaction proceeded via a 1,5-dipole (2-47) with C$_1$ and C$_3$ substituents positioned in a cis-orientation, despite steric crowding, nucleophilic attack ensued by the malonate carbanion to the nitrile carbon to form 1-pyrrolidine 2-48.
Scheme 2-10. Srinivasan’s SnCl$_4$ catalyzed [3+2] annulation reaction of DA cyclopropanes and nitriles.

2.1.2.4 Annulation Reactions with Aldehydes

Pohlhaus and Johnson published a protocol where DA cyclopropane 2-49 and aldehyde 2-50 reacted in the presence of a Lewis acid to give 2,5-\textit{cis}-tetrahydrofuran 2-52 (Scheme 2-11). Initial catalyst screening showed that strong Lewis acids such as TiCl$_4$ and AlCl$_3$ gave significant decomposition of the DA cyclopropane, while milder Lewis acids like SnCl$_2$, ZnCl$_2$, Mg(OTf)$_2$ and La(OTf)$_3$ exhibited no reactivity. While Cu(OTf)$_3$, Sc(OTf)$_3$, and SnCl$_4$ gave clean cycloadducts with low \textit{cis}:\textit{trans} diastereoselectivity, 59:1, 3.1:1, and 3.1:1, respectively.

Scheme 2-11. Pohlhaus and Johnson’s synthesis of 2,5-\textit{cis}-tetrahydrofurans.

The catalyst of choice was found to be Sn(OTf)$_2$ which showed excellent conversion to the 2,5-\textit{cis}-THF 2-52 in excellent yields (82-100%) and $dr \leq 100:1$ (Scheme 2-11). Substrate scope of the aldehydes showed the reaction proceeded smoothly in the presence of electron rich, electron neutral, electron poor, and heterocyclic substituted aldehydes. Pohlhaus and Johnson hypothesized that the stereochemical outcome of the product is due to the placement of the larger group of the aldehyde in a pseudo-equatorial position (2-51) which is more sterically favoured, leading to 2,5-\textit{cis}-THF 2-52.
2.1.2.5 Annulations with Aldimines

Like Pohlhaus and Johnson’s work, Carson and Kerr showed a diastereoselective synthesis of 2,5-cis-pyrrolidine 2-58 from the reaction of aldimine 2-55 and DA cyclopropane 2-56, under catalytic Yb(OTf)₃ conditions (Scheme 2-12). During the initial trials, the aldimines were prepared and isolated prior to the reaction, and although isolated aldimines worked well, aldimines generated in situ were found to be more efficient as fewer side products and higher yields were obtained.

![Scheme 2-12. Carson and Kerr’s synthesis of 2,5-cis-pyrrolidines.](image)

In the one-pot reaction, the Yb(OTf)₃ catalyst and DA cyclopropane 2-56 had to be added after the formation of aldimine 2-55, to avoid either the amine (2-53) or the aldehyde (2-54) from reacting with the DA cyclopropane (Scheme 2-12). The scope of the reaction showed that primary alkylamines and primary anilines were well suited for the reaction; however, the scope of the aldehydes employed was limited to aryl or heteroaryl substituents. Like Pohlhaus and Johnson’s work, the proposed transition state (2-57) for the reaction shows the larger groups of the aldimine in a pseudo-equatorial position, which gives the observed 2,5-cis-pyrrolidine 2-58.
2.2 Project Goal

To expand the work of Carson and Kerr involving the annulation of DA cyclopropanes with aldimines, it was postulated that 2H-azirine 2-59 could react with cyclopropane 2-60 in the presence of a Lewis acid to form pyrrolidine 2-61, with an aziridine imbedded in the ring structure (Scheme 2-13). The motivation for this work is also based on the potentially interesting transformations of the adducts via aziridine ring opening by quaternization followed by a Krapcho decarboxylation of 2-62 to yield piperidine 2-63.

Scheme 2-13. Proposed reaction of DA cyclopropanes with 2H-azirine.

2.3 The Chemistry of 2H-Azirines and Vinyl Azides

2.3.1 Synthesis and Reactivity of 2H-azirines

2H-Azirines (2-66, Scheme 2-14) are compounds with a three-membered heterocycle, consisting of one nitrogen and two carbon atoms. 20 2H-azirines are commonly synthesized by the thermal and/or photochemical treatment of vinyl azides (2-64) and there are two proposed mechanisms for the formation of 2H-azirines (Scheme 2-14). 21,22,23 The first accepted mechanism (A) involves the concerted cyclization-elimination of N\textsubscript{2} gas assisted by the π-bond (2-65) to form 2H-azirine 2-66; the second accepted mechanism (B) involves the participation of a vinylnitrene intermediate 2-67 for the formation of 2H-azirine 2-64. 24 The formation of 2H-azirines by thermolysis of vinyl azides is highly dependent on the structure of the vinyl azide. Azides, where R\textsuperscript{1} = aryl,
alkyl, alkoxy, amine, or carboxylic groups often give stable azirines, while hydrogen or carbonyl substitution leads to nitriles or other heterocyclic products.\textsuperscript{20}

\begin{align*}
\text{A)} & : & \text{heat or } h\nu & \text{concerted} & \text{-N}_2 & \rightarrow & 2-66 \\
2-64 & & & & & & \\
\text{B)} & : & \text{heat or } h\nu & \text{-N}_2 & \rightarrow & 2-66 \\
2-64 & & & & & & \\
\end{align*}

\textbf{Scheme 2-14.} Synthesis of 2H-azirines from vinyl azides.

The chemical reactivity of 2H-azirines is mostly a consequence of their ring strain (48 kcal/mol), reactive $\pi$-bond, and their ability to undergo regioselectivity ring cleavage.\textsuperscript{20,25} 2H-azirines are not only capable of acting as nucleophiles and electrophiles in organic reaction, but they can also act as dienophiles and dipolarophiles in cycloaddition reactions.\textsuperscript{26}

\subsection{2.3.1.1 Reactions of 2H-azirines}

The synthetic utility of 2H-azirines has led them to be useful precursors in the synthesis of a variety of nitrogen-containing heterocyclic systems such as indoles,\textsuperscript{27} pyrroles,\textsuperscript{28} pyridines,\textsuperscript{29} oxazoles,\textsuperscript{30} pyrazines,\textsuperscript{31} and many others.\textsuperscript{32} In 2001, Somfai’s group published a protocol describing the Lewis acid catalyzed hetero Diels-Alder reaction of 2H-azirine 2-68 with Danishefsky’s diene (2-69) or cyclopentadiene (2-71) (Scheme 2-15).\textsuperscript{33} The reaction of 2H-azirine 2-68 with Danishefsky’s diene (2-69) gave the endo-cycloadduct 2-70 in a 55% yield using 30 mol% of either ZnCl\textsubscript{2}, YbCl\textsubscript{3}, CuCl\textsubscript{2}. The reaction of 2H-azirine 2-68 with cyclopentadiene (2-71), also gave the endo-cycloadduct product 2-72 in a 45% yield in the presence of catalytic YbCl\textsubscript{3}.
Scheme 2-15. Somafi’s hetero-Diels alder reactions with 2H-azirine.

Buji and co-workers reported a transition-metal-free and highly selective synthesis of either N-unsubstituted or N-arylidole, 2-75 and 2-76, respectively, by reacting aryne precursor 2-74 and 2H-azirine 2-723 in the presence of 18-crown-6 and potassium fluoride (Scheme 2-16). During preliminary studies, Buji and co-workers found that product selectivity was highly dependent on temperature. When the reaction was performed in THF cooled to -10 °C, N-arylidole 2-76 was formed in a 41-95% yield. On the other hand, when the same reaction was performed in THF heated to 60 °C, the aryne, generated from 2-74, smoothly insert into the 2H-azirine 2-73 to form 2,3-diarylidole 2-75 in a 40-83% yield.

Scheme 2-16. Buji and co-workers synthesis of N-unsubstituted or N-arylidoles.

In 2016, Li and co-workers published a ruthenium-catalyzed intermolecular [3+2] annulation reaction between 2H-azirine 2-77 and activated alkyne 2-78 to afford polysubstituted pyrrole 2-60 (Scheme 2-17). The scope of the reaction with respect to 2H-azirine (2-77) was well tolerated for alkyl, aryl and heteroatom substituents. The reaction also proceeded smoothly with ester- and ketone-derived alkynes; however, when the alkyne was substituted with groups such as carboxylic acids, nitriles, and amides...
pyrrole \(2-60\) was not formed. The postulated reaction mechanism features a C-N bond cleavage of the \(2H\)-azirine by the ruthenium catalyst to give a azaruthenacyclobutene intermediate \(2-79\) for the generation of desired products and specific selectivity of the pyrroles.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 \\
\text{N} & \quad \text{N} & \quad \text{Ru} & \quad \text{EWG}
\end{align*}
\]

Scheme 2-17. Li and co-workers’ ruthenium-catalyzed \([3+2]\) annulation reaction of \(2H\)-azirines and alkynes.

2.4 Results and Discussion

2.4.1 Initial results

To begin our investigation on the reaction of DA cyclopropanes with \(2H\)-azirines, we decided to use readily available, and highly studied,\(^2\) 3-phenyl-\(2H\)-azirine (\(2-81\)), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (\(2-82\)) since the DA cyclopropane is prepared from inexpensive starting materials and has been used in annulation reactions with nitrones, azomethine imines, aldehydes, and iminines.\(^2\) We envisioned that the reaction could be formed via nucleophilic ring opening of DA cyclopropane \(2-82\) by \(2H\)-azirine to give intermediate \(2-83\), which would then form azabicycle \(2-84\) via a Mannich-type ring closure (Scheme 2-18).

\[
\begin{align*}
\text{N} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Ph} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} & \quad \text{Lewis Acid}
\end{align*}
\]

Scheme 2-18. Initial studies of the reaction between \(2H\)-azirine and DA cyclopropane towards the synthesis of azabicycle \(2-84\).
At first, Carson and Kerr’s previously defined conditions were tested, which involved dissolving DA cyclopropane 2-82, 2H-azirine 2-81, and catalytic Yb(OTf)₃ (10 mol%) in toluene heated to 110 °C, but this failed to yield any appreciable amount of a compound resembling 2-84. A brief survey of commonly used Lewis acids such as Sc(OTf)₃, Dy(OTf)₃, and AlCl₃ also failed to give desirable results. A screening of solvents, such as benzene and CH₂Cl₂ at various temperatures (room temperature, 40, 80, 100 °C) did not change the outcome of the reaction.

After much frustration at what seemed to be a straightforward extension of Carson and Kerr’s work, to instead change the course of our study and investigate the reaction of (1-azidovinyl)benzene (2-85) with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (2-82), since vinyl azides are precursors to 2H-azirines, and have been used as 1,3-dipoles in annulation reactions.²³, thirty-six. The potential result of the reaction is outlined on Scheme 2-19. Under Lewis acidic conditions, attack by the nitrogen anion of the vinyl azide 2-85 would yield intermediate 2-87, which may undergo a formal S₅' attack with loss of nitrogen gas resulting in dehydropiperidine 2-86.

![Scheme 2-19. Proposed reaction of (1-azidovinyl)benzene with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate.](image)

Again, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (2-82) was used due to its availability, and along with vinyl azide 2-85, and a catalytic amount of Yb(OTf)₃ (5 mol%) were dissolved in toluene heated to 110 °C. To our enjoyment, we obtained what appeared to be 2-86 in a 26% yield; the reaction also showed that a proof of principle was achieved and we had high hopes that the yields could be improved. Although the ¹H
NMR spectrum, at first glance, looked consistent with 2-86, several aspects of the data soon became worrisome. We noticed that the germinal coupling on the $^1$H NMR of the methylene carbon (a), and the imine resonance in the $^{13}$C NMR spectrum, were missing. In addition, the protons on carbons labelled a and b could not be connect by HMBC. Upon closer inspection of the $^1$H NMR, $^{13}$C NMR, as well as COSY, HSQC, HMBC, it was determined that the product was not 2-86 but in fact 2-84, the azabicycle we initially hoped to obtain from the reaction with DA cyclopropane and 2H-azirine (Scheme 2-20).

![Scheme 2-20. Discovery of dimethyl 2,5-diphenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-84).](image)

A possible mechanistic explanation for the formation of azabicycle 2-84 is shown in Scheme 2-21. Formation of compound 2-84 involves a nucleophilic attack by vinyl azide 2-85 to open DA cyclopropane 2-82 to yield intermediate x. Upon loss of nitrogen gas, stable iminium ion intermediate (x) is formed and subsequent Mannich-type ring closure, gives azabicycle 2-84.

![Scheme 2-21. Possible reaction mechanism for the formation of compound 2-84.](image)
2.4.2 Reaction Optimization

With compound 2-84 characterized, efforts were undertaken to optimize the reaction conditions for the formation of the azabicycle. The major obstacle that we had to overcome was the tendency of vinyl azide 2-85 to dimerize (2-89, Scheme 2-22). Attempts to suppress dimerization by changing solvents (CH₂Cl₂, benzene or toluene), temperature, and catalyst loading, were unsuccessful. Attempting to slowly add the vinyl azide via syringe pump, to lower its concentration, also failed to improve the yields. Catalysts screened during reaction optimization included Yb(OTf)₃, Sc(OTf)₃, AlCl₃, and Dy(OTf)₃, and it was found that Dy(OTf)₃ was the most suitable catalyst for the reaction as it minimized dimerization of the vinyl azide.

![Scheme 2-22. Formation of 2-84 and dimerization product 2-89.](image)

Despite optimization to the best of our abilities, dimerization persisted and the maximum yield of azabicycle 2-90 was only 30% (Scheme 2-22). It was not until later that we became familiar with the work of Professor Jérôme Waser and his use of DA cyclopropanes bearing trifluoroethyl ester in place of the common methyl esters, that the fate of the project began to change. By changing the methyl esters to fluoroethyl ester, the cyclopropane becomes more electrophilic due to the enhanced electron withdrawing effect of the fluoroesters, thus increasing the susceptibility of the cyclopropane to undergo ring opening when exposed to a Lewis acid. When the reaction between (1-azidovinyl) benzene (2-85) and bis(2,2,2-trifluoroethyl) 2-phenylcyclopropane-1,1-dicarboxylate (2-90a) were reacted under catalytic Dy(OTf)₃ (10 mol%) in toluene at 110 °C, the yield of azabicycle 2-90 was significantly improved.
mol%) in toluene and heated to 110 °C, azabicycle \textbf{2-91a} was obtained in a significantly higher yield of 55%, with little dimerization product \textbf{2-89} (Scheme 2-23). We were delighted with the outcome of the reaction, so we decided to explore the scope.

\begin{center}
\begin{tikzpicture}
  \node [draw, align=center] at (0,0) {
    Ph\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CF\textsubscript{3} + Ph\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CF\textsubscript{3} \quad \text{Dy(OTf)}\textsubscript{3} (10 mol\%) \quad \text{toluene, 110 °C}
  \rightarrow \quad \text{Ph\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CF\textsubscript{3} \quad \text{N}}\textsubscript{3} \quad \text{Ph\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CF\textsubscript{3} \quad \text{2-91a}}
  \end{tikzpicture}
\end{center}

\textbf{Scheme 2-23.} Reaction of vinyl azide \textbf{2-85} with DA cyclopropane \textbf{2-90a} bearing trifluoroethyl esters.

\subsection*{2.4.3 Reaction Scope}

Having developed a new efficient set of conditions to favour the annulation reaction for the formation of azabicycle \textbf{2-91a}, the scope of the reaction was investigated by varying the substituents on DA cyclopropane \textbf{2-90}. The results are shown in Scheme 2-24.
Scheme 2-24. Reaction scope for the annulation reaction of vinyl azide 2-85 and DA cyclopropanes 2-90a-j to give azabicycles 2-91a-j.

Several observations are worthy of note. First, the optimized conditions worked reasonably well, producing adducts in yields ranging from 0-82%. The range of cyclopropanes was wide with aryl, heteroaryl, vinyl, alkynyl and phthalimido substituents being tolerated well but cyclopropanes bearing an aryl moiety with an electron withdrawing group such as an ester, nitrile, or nitro group failed to undergo a successful reaction. The difference between EWG and EDG on the aryl ring is that the EDG is better at stabilizing the developing positive charge on the DA cyclopropane during the annulation process. The inductive effect became more apparent with di- and tri-substituted groups, as the cyclopropane was now less reactive due to the electron withdrawing effect of the meta-substituted OMe’s resulting in diminished yields of the
azabicycles, when compared to the *mono*-substituted azabicycle. Despite the minor electron donating effect of the ester on *bis*(2,2,2-trifluoroethyl) 2-acetoxy cyclopropane-1,1-dicarboxylate (2-90g), no annulation product was obtained, and instead, only dimerization of vinyl azide was observed. The methodology was not limited to *mono*-donor substituted DA cyclopropanes; DA cyclopropanes with a quaternary donor center also produced the expected azabicycles 2-91i and 2-91j. Except for 2-91i, all adducts were produced as single diastereomer, which was later confirmed by x-ray crystallography to have the substituent from the cyclopropane and the vinyl azide *trans* to each other (Figure 2-2).

![Figure 2-2. Solid state structure of 2-91a.](image)

### 2.4.4 Rationale for the observed diastereoselectivity

A concrete explanation for the observed diastereoselectivity is somewhat unclear; however, a rationale which predicts the observed results is shown in Scheme 2-25. Zwitterionic species **I** may undergo Mannich-style ring closure *via* transition state **II** resulting in the formation of the observed diastereomer **III**. Transition state **II** would have the R² in a pseudo-equatorial position in the newly formed five-membered ring.
2.4.5 Reactions with 2H-azirine

Given the success for the reaction of vinyl azides with bis(2,2,2-trifluoroethyl) cyclopropane-1,1-dicarboxylates, it was decided to reinvestigate the reaction of 2H-azirine. With the more activated DA cyclopropanes, azabicycles were now being formed, and thus, a new scope was developed for DA cyclopropanes 2-90a-j with 2H-azirine 2-81 (Scheme 2-26). For the most part, the azabicycles were formed in higher yields, and with reduced dimerization compared to the reaction of DA cyclopropanes with vinyl azide (25-92% vs. 27-82% yield). Interestingly, the reaction between 2H-azirine 2-81 with cyclopropane 2-90g proceeded to give azabicycle 2-91g in 34% but in the reaction with the vinyl azide, the annulation product was not observed. The reason for the different reactivity with DA cyclopropane 2-90g is still unclear, and studies into the potential mechanism of the reaction is required for further insight. As previously observed, azabicycles were also formed as a single diastereomer, except for compound 2-91j.

Scheme 2-25. Proposed transition state for the observed diastereoselectivity.
Scheme 2-26. Reaction scope for the annulation reaction between $2H$-azirine 2-81 and DA cycloproanes 2-90a-j to give azabicycles 2-91a-j.

Although the enhanced electrophilicity of the DA cyclopropane now favoured the formation of azabicycles with $2H$-azirine, a significant difference between the use of $2H$-azirine and vinyl azide is their reaction times; azabicycles were formed faster with vinyl azide 2-9 (Scheme 2-24) vs. $2H$-azirine 2-81 (Scheme 2-26). We were intrigued by the difference, so we postulated that the bis(2,2,2-trifluoroethyl)1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates (2-91a-j) could be formed via a vinyl nitrene intermediate.

2.4.6 Postulated Reaction Mechanism

The formation of vinyl nitrenes from the thermal decomposition of vinyl azide and $2H$-azirines has been well documented in the literature. It is our working hypothesis...
that in the reaction of cyclopropane 2-90a and vinyl azide 2-85 (Scheme 2-27), the formation of the vinyl nitrene (2-92) is fast, resulting in a high concentration in solution; consequently, the vinyl nitrene might engage in a ring opening reaction of DA cyclopropane 2-90a to give intermediate 2-93, which rearranges to the stable imminium ion (2-94). A Mannich-type ring closure will then afford azabicycle 2-91a. In the case of the reaction with the 2H-azirine, the vinyl nitrene may be forming at a slower rate, resulting in a lower concentration in solution, thus suppressing dimerization and favouring the reaction with the cyclopropane. It is also important to note that perhaps in the both reactions, the vinyl azide (Scheme 2-21) and the 2H-azirine (Scheme 2-18) are, independently, the reactive species for both reactions. The vinyl azide perhaps is more nucleophilic than the 2H-azirine, which would explain why the formation of the azabicycles is faster (shorter reaction times) than in the reaction with the 2H-azirine. Nonetheless, further experimental data, such as reaction kinetics, is required to gain more insight on the mechanism of the reaction.

Scheme 2-27. Possible mechanistic pathway for the formation of bis(2,2,2-trifluoroethyl)-2,5-diphenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91a).
2.5 Recent Advances in this Field

Shortly after the publication of this work, Dey and Banerjee published the Lewis acid-catalyzed [3+2] annulation reaction of DA cyclopropane 2-95 with vinyl azide 2-96 to give azidocyclopentane 2-97 (Scheme 2-28). The reactions were carried out by employing two sets of reaction conditions. Method A used MgI₂ (20 mol%) as the Lewis acid in CH₂Cl₂ and the products were obtained with excellent diastereoselectivity (up to 94:6 dr) but it required longer reaction times (>20 h) and lower yields (up to 78% yield). Method B employed the use of InCl₃ (20 mol%) in CH₂Cl₂ which gave the product in good yields (>88 % yield), shorter reaction times (< 3 h) but low diastereoselectivity (up to 78:22 dr). The reaction proceeded well with a mono-, di-, and tri-substituted methoxy aryl groups on the DA cyclopropane as well as 2-furyl substituted DA cyclopropane. The reaction did not work with DA cyclopropanes bearing p-tolyl or o-tolyl substituents. Dey and Banerjee could react azidocyclopentane 2-97 with InCl₃ in xylene heated to 140 °C to afford tetrahydropyridine 2-98.

![Scheme 2-28](image)

**Scheme 2-28.** Dey and Banerjee’s [3+2] annulation of DA cyclopropane with vinyl azide.

Comparable results to this methodology were obtained by Chiba and co-workers where the azidocyclopentane derivatives were synthesized using Sc(OTf)₃ as the Lewis acid.

2.6 Summary and Future Work

The annulation of DA cyclopropanes with dipolarophiles provides organic chemists an easy approach to a variety of interesting heterocycles, many of which possessing biological properties. Our contribution to this area of research is characterized by a new annulation reaction between a vinyl azide or 2H-azirine with DA cyclopropanes to produce 1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates (Scheme 2-29).
Scheme 2-29. Reaction summary for the synthesis of 1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates.

During this study, it was found that the replacement of the common methyl ester on the cyclopropane to a more electrophilic fluoroester favoured the annulation reaction to form the observed azabicycle, which consequently reduce the formation of side products, such as the dimerization of the vinyl azide. We postulate that the reaction mechanism might involve a vinyl nitrene intermediate, which forms upon heating the vinyl azide or 2H-azirine, as the reacting partner in the annulation reaction. Further studies, such as reaction kinetics, are required to gain more insight into the mechanism of the reaction.

Future directions for this project would involve the study of the reactivity of the azabicycle towards ring opening of the aziridine ring (Scheme 2-30). In that matter, quaternization of azabicycle 2-99 followed by a Krapcho decarboxylation could yield tetrahydropyridine 2-101. Alternatively, quaternization of azabicycle 2-99 followed by the reaction with a nucleophile could give two potential products; pathway a could yield pyrrolidine 2-103 upon nucleophilic ring opening at the least substituted carbon of the
activated aziridine 2-102, and pathway b could yield piperidine 2-104 could be obtained from the nucleophilic ring opening of the activated aziridine 2-102 at the most substituted carbon.

Scheme 2-30. Possible pathways for ring expansion of azabicycle 2-100.

2.7 Experimental

General information

All reactions were carried under an Argon atmosphere unless indicated. Toluene, benzene, and dichloromethane (CH₂Cl₂) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Sigma Aldrich, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F₂₅₄) visualizing with UV light, and the plates were developed using acidic anisaldehyde or KMnO₄ stain. Flash column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

NMR experiments were performed on the Varian Mercury 400, Inova 400 and Inova 600 instruments; samples were obtained in CDCl₃ (referenced to 7.26 ppm for H and 77.0
ppm for $^{13}$C. Coupling constants ($J$) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dq= doublet of quartets, m = multiplet, b = broad. Infrared spectra were obtained as thin films on NaCl plates using the Bruker Vector 33 FT-IR instrument. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS (Double Focusing Sector). Melting points were determined using a Gallenkamp melting point apparatus and were uncorrected.

**Experimental Procedure A:** Synthesis of bis(2,2,2-trifluoroethyl)cyclopropane-1,1-dicarboxylates (2-90g-i).

Cyclopropanes 2-90g-i were prepared according to the following procedure. To a 10 mL or 25 mL round-bottomed flask was added the corresponding alkene (2-90gg-ii) derivative (1.0 equiv), CH$_2$Cl$_2$ (4 mL - 8 mL) and Rh$_2$(esp)$_2$ catalyst (0.1 mol %). The bis(2,2,2-trifluoroethyl)2-diazomalonate$^{37c}$ (2-106) (1.3 equiv) was dissolved in CH$_2$Cl$_2$ (3 mL) and added dropwise over a period of 45 mins - 1 h at room temperature. The reaction was stirred at room temperature for 1.5 - 3 h (monitored by TLC). The crude reaction mixture was concentrated, pre-absorbed onto silica gel, and purified by column chromatography (EtOAc in Hexanes).

* Bis(2,2,2-trifluoroethyl) 2-acetoxycyclopropane-1,1-dicarboxylate (2-90g).

Following experimental procedure A, cyclopropane 2-90g was prepared by dissolving commercially available vinyl acetate (2-90gg) (200 mg, 2.32 mmol) and Rh$_2$(esp)$_2$ (2.0 mg, 0.002 mmol) in 5 mL of CH$_2$Cl$_2$ followed by the addition of bis(2,2,2-trifluoroethyl)2-diazomalonate (2-106) (887 mg, 3.02 mmol) dissolved in 3 mL of CH$_2$Cl$_2$. The reaction was stirred at room temperature for 8 hours. Cyclopropane 1-52a (711 g, 2.02 mmol, 87 % yield) was obtained as a colourless oil. Rf = 0.49 (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ = 4.89 (dd, $J = 7.0, 5.5$ Hz, 1H) 4.42 -
4.71 (m, 4H) 2.14 (dd, \( J = 6.6, 5.5 \) Hz, 1H) 2.04 (s, 3H) 1.87 (dd, \( J = 7.0, 5.5 \) Hz, 1H).

\(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \( \delta = -73.8 \) (t, \( J = 7.9 \) Hz, 3F), -73.9 (t, \( J = 7.9 \) Hz, 3F). \(^{13}\text{C NMR}\) (150 MHz, CDCl\(_3\)) \( \delta = 169.9, 165.9, 163.3, 122.4 \) (d, \( \text{J}_{\text{C-F}} = 277 \) Hz, 1C), 122.3 (d, \( \text{J}_{\text{C-F}} = 277 \) Hz, 1C), 61.4 (q, \( \text{J}_{\text{C-F}} = 37 \) Hz, 1C), 61.2 (d, \( \text{J}_{\text{C-F}} = 37 \) Hz, 1C), 57.5, 33.4, 20.5, 20.2. \text{FT-IR} (thin film, cm\(^{-1}\)): 3114, 3030, 2982, 1765, 1415, 1366, 1279, 1227, 1170, 1117, 976. \text{HRMS calc’d for C}_{11}H_{10}F_{6}O_{6} [M\text{+}]: 352.0382; found: 352.0460.

\text{Bis}(2,2,2-trifluoroethyl)2-methyl-2-phenylcyclopropane-1,1-dicarboxylate (2-90i).

Following experimental procedure A, cyclopropane 2-91i was prepared by dissolving commercially available \( \alpha \)-methylstyrene (2-90ii) (200 mg, 1.70 mmol) and Rh\(_2\)(esp)\(_2\) (1.50 mg, 0.002 mmol) in 5 mL of CH\(_2\)Cl\(_2\) followed by the addition of \( \text{bis}(2,2,2\text{-trifluoroethyl})2\text{-diazomalonate} \) (2-106) (647 mg, 2.20 mmol) dissolved in 3 mL of CH\(_2\)Cl\(_2\). The reaction was stirred at room temperature for 12 hours. Cyclopropane 2-91i (648 mg, 1.70 mmol, quantitative yield) was obtained as a clear oil. R\(_f\) = 0.60 (30% EtOAc in hexanes). \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta = 7.32 - 7.23 \) (m, 5H), 4.73 - 4.52 (m, 2H), 4.16 (dq, \( J = 12.7, 8.3 \) Hz, 1H), 3.99 (dq, \( J = 12.7, 8.3 \) Hz, 1H), 2.35 (d, \( J = 5.9 \) Hz, 1H), 1.86 (d, \( J = 5.5 \) Hz, 1H), 1.58 (s, 3H). \(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \( \delta = -73.6 \) (t, \( J = 7.9 \) Hz, 3F), -73.8 (t, \( J = 7.9 \) Hz, 3F). \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \( \delta = 166.2, 165.5, 139.8, 128.5, 128.1, 127.6, 122.5 \) (d, \( \text{J}_{\text{C-F}} = 277 \) Hz, 1C), 122.0 (d, \( \text{J}_{\text{C-F}} = 277 \) Hz, 1C), 61.2 (q, \( \text{J}_{\text{C-F}} = 37 \) Hz, 1C), 60.9 (q, \( \text{J}_{\text{C-F}} = 37 \) Hz, 1C), 40.1, 39.6, 25.7, 24.1. \text{FT-IR} (thin film, cm\(^{-1}\)): 3063, 2975, 2935, 1751, 1498, 1448, 1412, 1286, 1168, 1103, 977. \text{HRMS calc’d for C}_{16}H_{14}F_{6}O_{4} [M\text{+}]: 384.0796; found: 384.0787.

\text{Bis}(2,2,2-trifluoroethyl)2-(but-1-ynyl)-2-methylcyclopropane-1,1-dicarboxylate (2-90j).

Following experimental procedure A, cyclopropane 2-90j was prepared by dissolving commercially available 2-methylhex-1-en-3-yne (2-90jj) (500 mg, 5.30 mmol) and Rh\(_2\)(esp)\(_2\) (4.02 mg, 0.005 mmol) in 7 mL of CH\(_2\)Cl\(_2\) followed by the addition of \( \text{bis}(2,2,2\text{-trifluoroethyl})2\text{-diazomalonate} \) (2-106) (2.03 g, 6.90 mmol)
dissolved in 3 mL of CH₂Cl₂. The reaction was stirred at room temperature for 8 hours. Cyclopropane 2k (1.90 g, quantitative yield) was obtained as a colourless oil. Rf = 0.40 (10% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ = 4.54 (m, 4H), 2.13 (q, J = 7.42, 2H), 2.01 (d, J = 5.1 Hz, 1H), 1.69 (d, J = 5.4 Hz, 1H), 1.49 (s, 3H), 1.06 (t, J = 7.4 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ = -73.8 (t, J = 8.6 Hz, 3F), -73.8 (t, J = 8.6 Hz, 3F). ¹³C NMR (100 MHz, CDCl₃) δ = 165.8, 165.5, 121.6 (q, Jₐₚ = 377 Hz, 1C), 121.5 (q, J = 277 Hz, 1C), 83.8, 78.4, 61.5 (q, Jₐₚ = 37 Hz, 1C), 61.3 (q, Jₐₚ = 37 Hz, 1C), 40.0, 28.6, 26.6, 20.8, 14.0, 12.5. FT-IR (thin film, cm⁻¹): 2981, 2944, 2884, 2247, 2131, 1748, 1410, 1280, 1160, 1105. HRMS calc’d for C₁₄H₁₄F₄O₄ [M⁺]: 360.0796; found: 360.0789.

**Experimental procedure B:** Synthesis of azabicyclo[3.1.0]hexane-4,4-dicarboxylates (2-91a-j).

**Caution!** Although we have never had any incidents, organic azides are potentially explosive substances that can decompose upon the exposure to heat, light, and pressure. Any azide synthesized should be stored in the freezer and in the dark. In addition, molecules containing the azido moiety can decompose violently which may result in injury if proper safety precautions are not taken. Reactions were performed with a blast shield.

![Diagram](image)

In a 10 mL round-bottomed flask, the appropriate bis(2,2,2-trifluoroethyl) cyclopropane-1,1-dicarboxylate (2-90a-j) (1.0 equiv) and Dy(OTf)₃ (10 mol%) catalyst were dissolved in 6 mL of toluene. The reaction flask was fitted with a condenser and heated to 110 °C. To this mixture, (1-azidovinyl)benzene⁴⁰ (2-85) (2.0 equiv) (Method A) or 3-phenyl-2H-azirine⁴⁰ (2-81) (2.0 equiv) (Method B), diluted in 1 mL of toluene, was added dropwise over a period of 10-15 mins. The reaction was heated to 110 °C for 3-20 hours (monitored by TLC). The reaction flask was cooled to room temperature and the toluene was removed in vacuo. The crude reaction mixture was then pre-absorbed onto silica gel and purified by column chromatography (EtOAc in Hexanes).
Bis(2,2,2-trifluoroethyl) 2,5-diphenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91a).

Following experimental procedure B Method A compound 2-91a was prepared by dissolving bis(2,2,2-trifluoroethyl) 2-phenylcyclopropane-1,1-dicarboxylate \(^\text{37a} \) (2-90a) (100 mg, 0.270 mmol) and Dy(OTf)\(_3\) (16.8 mg, 0.027 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (78.3 mg, 0.540 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated to 110 °C for 3.5 hours. Compound 2-91a (72 mg, 0.147 mmol, 55 %) was obtained as a clear oil. \( R_f = 0.62 \) (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91a was prepared by dissolving bis(2,2,2-trifluoroethyl)2-phenylcyclopropane-1,1-dicarboxylate (2-90a) (150 mg, 0.405 mmol) and Dy(OTf)\(_3\) (25.0 mg, 0.041 mmol) in 6 mL of toluene. 3-phenyl-2\(H\)-azirine (2-81) (95.0 mg, 0.810 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated to 110 °C for 10 hours. Compound 2-91a (124 mg, 0.254 mmol, 63 %) was obtained as a clear oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\) \( \delta = 7.61 \) (d, \( J = 1.0 \) Hz, 2\( H \)), 7.47 (d, \( J = 1.0 \) Hz, 2\( H \)), 7.40 (m, 2\( H \)), 7.36 - 7.28 (m, 4\( H \)), 5.35 (dd, \( J = 10.9 \), 7.0 Hz, 1\( H \)), 4.64 (dq, \( J = 14.1 \), 7.0 Hz, 1\( H \)), 4.52 (dq, \( J = 12.5 \), 8.2 Hz, 1\( H \)), 4.39 (dq, \( J = 12.5 \), 8.2 Hz, 1\( H \)), 3.77 (dq, \( J = 12.5 \), 8.2 Hz, 1\( H \)), 3.05 (dd, \( J = 14.1 \), 7.0 Hz, 1\( H \)), 2.23 (dd, \( J = 13.9 \), 11.1 Hz, 1\( H \)), 2.16 (s, 1\( H \)), 2.15 (s, 1\( H \)). \(^19\)F NMR (376 MHz, CDCl\(_3\) \( \delta = -73.7 \) (t, \( J = 8.6 \) Hz, 3\( F \)), -73.9 (t, \( J = 8.6 \) Hz, 3\( F \)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\) \( \delta = 168.1 \), 167.9, 139.7, 136.8, 128.7, 128.5, 128.1, 128.1, 128.7, 126.1, 126.3, 123.7 (d, \( J_{C-F} = 277 \) Hz, 1\( C \)), 120.9 (d, \( J_{C-F} = 277 \) Hz, 1\( C \)), 66.2, 65.1, 61.3 (q, \( J_{C-F} = 37 \) Hz, 1\( C \)), 61.2 (q, \( J_{C-F} = 37 \) Hz, 1\( C \)), 54.9, 37.7, 32.8. FT-IR (thin film, cm\(^{-1}\) ): 3062, 3031, 1754, 1604, 1496, 1448, 1413, 1286, 1169, 1104, 980, 700. HRMS calc’d for C\(_{23}\)H\(_{19}\)F\(_6\)NO\(_4\) [M\(^+\)]: 487.1218; found: 487.1144.

Bis(2,2,2-trifluoroethyl)2-(4-methoxyphenyl)-5-phenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91b).
Following experimental procedure B Method A, compound 2-91b was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate\(^{37a}\)(2-90b) (150 mg, 0.375 mmol) and Dy(OTf)\(_3\) (23.0 mg, 0.037 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (108 mg, 0.750 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 3 hours. Compound 2-91b (140 mg, 72 %) was obtained as a white solid. MP = 98-100 °C. Rf = 0.56 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91b was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (2-90b) (150 mg, 0.375 mmol) and Dy(OTf)\(_3\) (23.0 mg, 0.037 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (87.8 mg, 0.750 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 14 hours. Compound 2-91c (179 mg, 0.346 mmol, 92 %) was obtained as a white solid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.60\) (dd, J = 6.6, 1.9 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.24 - 7.34 (m, 3H), 6.93 (d, J = 8.9 Hz, 2H), 5.27 (dd, J = 11.1, 7.2 Hz, 1H), 4.63 (dq, J = 12.8, 8.2 Hz, 1H), 4.52 (dq, J = 12.8, 8.2 Hz, 1H), 4.37 (dq, J = 12.5, 8.2 Hz, 1H), 3.82 (s, 3H), 3.76 (dq, J = 12.8, 8.2 Hz, 1H), 2.98 (dd, J = 14.1, 7.0 Hz, 1H), 2.20 (dd, J = 13.9, 11.1 Hz, 1H), 2.14 (s, 1 H), 2.09 (s, 1H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -73.74\) (t, J = 8.6 Hz, 3F), -73.94 (t, J = 8.6 Hz, 3F). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 168.2, 167.9, 158.8, 136.8, 131.5, 128.7, 128.0, 127.8, 123.7\) (d, J\(_{C-F} = 277\) Hz, 1C), 120.9 (d, J\(_{C-F} = 277\) Hz, 1C), 113.8, 66.2, 64.6, 61.3 (q, J\(_{C-F} = 37\) Hz, 1C), 61.2 (q, J\(_{C-F} = 37\) Hz, 1C), 55.3, 54.8, 37.7, 32.6, 30.8. FT-IR (thin film, cm\(^{-1}\) ): 2969, 2838, 1753, 1612, 1514, 1413, 1287, 1249, 1170, 1103, 981, 701. HRMS calc’d for C\(_{24}\)H\(_{21}\)F\(_6\)NO\(_5\) [M\(^+\)]: 517.1324; found: 517.1230.

\(\text{Bis}(2,2,2\text{-trifluoroethyl})\) 2-(3,4-dimethoxyphenyl)-5-phenyl-1-azabicyclo[3.1.0] hexane-4,4-dicarboxylate (2-91c).
Following experimental procedure B Method A, compound 2-91c was prepared by dissolving bis(2,2,2-trifluoroethyl) 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate\(^\text{41}\) (2-90c) (155 mg, 0.360 mmol) and Dy(OTf)\(_3\) (22 mg, 0.036 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (104 mg, 0.720 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 8 hours. Compound 2-91c (78 mg, 0.142 mmol, 40%) was obtained as a yellow oil. Rf = 0.20 (30% EtOAc in hexanes).

Following experimental procedure C Method B, compound 2-91c was prepared by dissolving bis(2,2,2-trifluoroethyl) 2- (3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (2-90c) (150 mg, 0.348 mmol) and Dy(OTf)\(_3\) (21 mg, 0.035 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (81.7 mg, 0.697 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 16 hours. Compound 2-91c (148 mg, 0.270 mmol, 78 %) was obtained as a yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.56\) (dd, \(J = 8.2, 1.9\) Hz, 2H), 7.31 - 7.21 (m, 3H), 6.99 (d, \(J = 2.0\) Hz, 1H), 6.89 (dd, \(J = 8.2, 1.9\) Hz, 1H), 6.84 (s, 1H), 5.24 (dd, \(J = 10.9, 7.4\) Hz, 1H), 4.60 (dq, \(J = 16.4, 8.2\) Hz, 1H), 4.49 (dq, \(J = 16.4, 8.2\) Hz, 1H), 4.35 (dq, \(J = 12.5, 8.2\) Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72 (dq, \(J = 12.5, 8.2\) Hz, 1H), 2.96 (dd, \(J = 14.1, 7.0\) Hz, 1H), 2.18 (dd, \(J = 13.9, 11.1\) Hz, 1H), 2.11 (s, 1H), 2.07 (s, 1H). \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -73.7\) (t, \(J = 8.6\) Hz, 3F), -73.9 (t, \(J = 8.6\) Hz, 3F). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 168.2, 167.8, 148.9, 148.3, 136.8, 132.2, 128.7, 128.1, 122.5\) (q, \(J_{C-F} = 277\) Hz, 1C), 122.1 (q, \(J_{C-F} = 277\) Hz, 1C), 118.3, 111.0, 110.5, 66.2, 64.8, 61.3 (q, \(J_{C-F} = 37\) Hz, 1C), 63.2 (q, \(J_{C-F} = 37\) Hz, 1C), 56.0, 55.9, 54.8, 37.6, 32.6. FT-IR (thin film, cm\(^{-1}\)):\ 3062, 3004, 2965, 2838, 1753, 1518, 1414, 1285, 1242, 1168, 1103, 1028, 975. HRMS calc’d for C\(_{25}\)H\(_{23}\)F\(_6\)NO\(_6\) [M\(^+\)]: 547.1430 found; 547.1451.

**Bis(2,2,2-trifluoroethyl) 5-phenyl-2-(3,4,5-trimethoxyphenyl)-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91d).**
Following experimental procedure B **Method A**, compound 2-91d was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate41 (2-90d) (150 mg, 0.326 mmol) and Dy(OTf)$_3$ (20 mg, 0.033 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (94.5 mg, 0.652 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 8 hours. Compound 2-90d (96 mg, 0.166 mmol, 51%) was obtained as a white solid. MP = 111-113 °C. Rf = 0.24 (30% EtOAc in hexanes).

Following experimental procedure C **Method B**, compound 2-91d was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (2-90d) (150 mg, 0.326 mmol) and Dy(OTf)$_3$ (20 mg, 0.033 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (76.3 mg, 0.652 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 18 hours. Compound 2-91d (158 mg, 84%) was obtained as a white solid.

**1H NMR** (400 MHz, CDCl$_3$) $\delta$ = 7.56 - 7.60 (m, 2H), 7.34 - 7.24 (m, 3H), 6.64 (d, $J = 0.8$ Hz, 2H), 5.26 (dd, $J = 10.9$, 7.4 Hz, 1H), 4.62 (qd, $J = 16.4$, 8.2 Hz, 1H), 4.52 (dq, $J = 16.4$, 8.2 Hz, 1H), 4.38 (dq, $J = 12.6$, 8.3 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3 H), 3.75 (dq, $J = 12.5$, 8.2 Hz, 1H), 3.00 (dd, $J = 13.9$, 7.2 Hz, 1H), 2.19 (dd, $J = 14.0$, 10.9 Hz, 1H), 2.15 (s, 3H), 2.14 (d, $J = 3.1$ Hz, 2H). **19F NMR** (376 MHz, CDCl$_3$) $\delta$ = -73.7 (t, $J = 8.6$ Hz, 3F), -73.9 (t, $J = 8.6$ Hz, 3F). **13C NMR** (100MHz, CDCl$_3$) $\delta$ = 168.0, 167.7, 153.2, 137.2, 136.6, 135.4, 128.7, 128.1, 122.4 (q, $J_{C-F} = 277$ Hz, 1C), 122.0 (q, $J_{C-F} = 277$ Hz, 1C), 103.8, 66.7, 65.1, 61.3 (q, $J_{C-F} = 37$ Hz, 1C), 61.2 (q, $J_{C-F} = 37$ Hz, 1C), 60.7, 56.2, 54.8, 37.7, 32.8. **FT-IR** (thin film, cm$^{-1}$): 3061, 2969, 2942, 1753, 1589, 1509, 1286, 1241, 1168, 1128, 977, 701. **HRMS** calc’d for C$_{26}$H$_{25}$F$_6$NO$_7$ [M$^+$]: 577.1535; found: 577.1560.

**Bis**(2,2,2-trifluoroethyl)-5-phenyl-2-(thiophen-2-yl)-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91e).

Following experimental procedure B **Method A**, compound 2-91e was prepared by dissolving *bis*(2,2,2-trifluoroethyl)2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate41 (2-90e) (150 mg, 0.399 mmol) and Dy(OTf)$_3$ (24 mg, 0.039 mmol) in 6
mL of toluene. (1-azidovinyl)benzene (2-85) (115 mg, 0.798 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 12 hours Compound 2-91e (155 mg, 0.314 mmol, 80%) was obtained as a yellow oil. Rf = 0.48 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91e was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (2-90e) (150 mg, 0.399 mmol) and Dy(OTf)$_3$ (24 mg, 0.039 mmol) in 6 mL of toluene. 3-phenyl-2*H*-azirine (2-81) (93.4 mg, 0.798 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 18 hours. Compound 8f (157 mg, 80 %) was obtained as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.59 - 7.55$ (m, 2H), 7. 32 - 7.23 (m, 4H), 7.05-6.98 (m, 2H), 5.43 (dd, $J = 10.7$, 6.8 Hz, 1H), 4.64 (dq, $J = 12.5$, 8.2 Hz, 1H), 4.52 (dq, $J = 16.4$, 8.2 Hz, 1H), 4.35 (dq, $J = 12.5$, 8.2 Hz, 1H), 3.75 (dq, $J = 16.4$, 8.2 Hz, 1H), 2.98 (dd, $J = 14.1$, 7.0 Hz, 1H), 2.28 (dd, $J = 14.1$, 7.0 Hz, 1H), 2.26 (d, $J = 1.2$ Hz, 1H), 2.06 (d, $J = 1.2$ Hz, 1H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -73.74$ (t, $J = 8.6$ Hz, 3F), -73.94 (t, $J = 8.6$ Hz, 3F). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 168.0$, 167.6, 142.1, 136.5, 128.6, 128.2, 128.1, 126.7, 124.9, 124.8, 122.5 (q, $J_{C-F} = 277$ Hz, 1C), 122.1 (q, $J_{C-F} = 277$ Hz, 1C), 66.2, 62.0, 61.3 (q, $J_{C-F} = 37$ Hz, 1C), 63.2 (q, $J_{C-F} = 37$ Hz, 1C), 55.4, 38.6, 32.8. FT-IR (thin film, cm$^{-1}$): 3064, 2973, 1754, 1448, 1414, 1286, 1247, 1170, 1103, 978, 701. HRMS calc’d for C$_{21}$H$_{17}$F$_6$NO$_4$S[M$^+$] : 493.0782; found: 493.0721.

Following experimental procedure B Method A, compound 2-91f was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(1,3-dioxoisindolin-2-yl)-5-phenyl-1-azabicyclo[3.1.0] hexane-4,4-dicarboxylate (2-91f).

$^{Bis}(2,2,2$-trifluoroethyl) 2-(1,3-dioxoisindolin-2-yl)-5-phenyl-1-azabicyclo[3.1.0] hexane-4,4-dicarboxylate (2-91f).

Following experimental procedure B Method A, compound 2-91f was prepared by dissolving *bis*(2,2,2-trifluoroethyl) 2-(1,3-dioxoisindolin-2-yl) cyclopropane-1,1-dicarboxylate$^{41}$ (2-90f) (150 mg, 0.342 mmol) and Dy(OTf)$_3$ (21
mg, 0.034 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (99 mg, 0.684 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 16 hours. Compound 2-91f (70 mg, 0.126 mmol, 37%) was obtained as a yellow solid. MP = 151-153 °C. Rf = 0.41 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91f was prepared by dissolving bis(2,2,2-trifluoroethyl) 2-(1,3-dioxoisindolin-2-yl)cyclopropane-1,1-dicarboxylate41 (2-90f) (150 mg, 0.342 mmol) and Dy(OTf)3 (21 mg, 0.034 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (80 mg, 0.684 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 20 hours. Compound 2-91f (140 mg, 0.252 mmol, 74%) was obtained as a yellow solid.

1H NMR (400 MHz, CDCl3) δ = 7.92 (d, J = 2.7 Hz, 1H), 7.90 (d, J = 3.1 Hz, 1H), 7.79 (d, J = 3.1 Hz, 1H), 7.77 (d, J = 3.1 Hz, 1H), 7.61 - 7.57 (m, 2H), 7.34 - 7.25 (m, 5H), 6.36 (dd, J = 10.9, 7.0 Hz, 1H), 4.71 - 4.55 (m, 2H), 4.35 (dq, J = 12.5, 8.3 Hz, 1H), 3.73 (dq, J = 12.5, 8.2 Hz, 1H), 3.48 (dd, J = 14.1, 10.9 Hz, 1H), 3.20 (d, J = 1.2 Hz, 1H) 2.68 (dd, J = 14.1, 7.0 Hz, 1H) 2.15 (d, J = 1.6 Hz, 1H). 19F NMR (376 MHz, CDCl3) δ = -73.74 (t, J = 8.6 Hz, 3F), -73.94 (t, J = 8.6 Hz, 3F). 13C NMR (100 MHz, CDCl3) δ = 168.2, 167.8, 167.3, 135.8, 134.5, 131.5, 128.6, 128.3, 128.1, 123.8, 123.6, 68.8, 64.9, 61.4 (q, Jc-F = 37 Hz, 1C), 61.3 (q, Jc-F = 37 Hz, 1C), 52.9, 35.1, 30.7. FT-IR (thin film, cm⁻¹): 3030, 2979, 2880, 1777, 1719, 1604, 1448, 1373, 1284, 1169, 996, 717. HRMS calc’d for C25H18F6N2O6 [M⁺]: 556.1069; found: 556.1005.

Following experimental procedure B Method B, compound 2-91g was prepared by dissolving cyclopropane 2-90 (150 mg, 0.426 mmol) and Dy(OTf)3 (26 mg, 0.043 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-85) (100 mg, 0.852 mmol), in 1
mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 16 hours. Compound 2-91g (67 mg, 0.143 mmol, 34%) was obtained as a yellow oil. Rf = 0.3 (30% EtOAc in hexanes).

\[ ^1H \text{ NMR} \] (400 MHz, CDCl\textsubscript{3}) \( \delta = 7.54 - 7.50 \) (m, 2H), 7.30 - 7.23 (m, 3H), 6.47 (dd, \( J = 7.9, 6.7 \) Hz, 1H), 4.65 (dq, \( J = 12.5, 8.3 \) Hz, 1H), 4.49 (dq, \( J = 12.5, 8.3 \) Hz, 1H), 4.29 (dq, \( J = 12.5, 8.2 \) Hz, 1H), 3.71 (dq, \( J = 12.5, 8.2 \) Hz, 1H), 2.97 (dd, \( J = 14.4, 6.7 \) Hz, 1H), 2.13 (d, \( J = 1.8 \) Hz, 1H), 2.12 (s, 3H), 2.04 (dd, \( J = 14.4, 8.5 \) Hz, 1H). \[ ^19F \text{ NMR} \] (376 MHz, CDCl\textsubscript{3}) \( \delta = -73.74 \) (t, \( J = 8.6 \) Hz, 3F), -73.94 (t, \( J = 8.6 \) Hz, 3F). \[ ^{13}C \text{ NMR} \] (100 MHz, CDCl\textsubscript{3}) \( \delta = 169.4, 167.5, 167.2, 135.7, 128.5, 128.1, 122.4 \) (q, \( J_{C-F} = 277 \) Hz, 1C), 121.9 (q, \( J_{C-F} = 277 \) Hz, 1C), 87.6, 64.5, 61.4 (q, \( J_{C-F} = 37 \) Hz, 1C), 61.3 (q, \( J_{C-F} = 37 \) Hz, 1C), 54.2, 36.3, 33.0, 20.8. \[ FT-IR \] (thin film, cm\textsuperscript{-1}): 3064, 3031, 2975, 1755, 1496, 1448, 1413, 1285, 1111, 1031, 979. \[ HRMS \] calc’d for C\textsubscript{19}H\textsubscript{17}F\textsubscript{6}NO\textsubscript{4} [M\textsuperscript{+}]: 469.0960; found: 469.0899.

\[
\text{Bis}(2,2,2\text{-trifluoroethyl}) \ 5\text{-phenyl}-2\text{-vinyl}-1\text{-azabicyclo}[3.1.0]\text{hexane}-4,4\text{-dicarboxylate (2-91h).}
\]

Following experimental procedure B Method A, compound 2-91h was prepared by dissolving \( \text{bis}(2,2,2\text{-trifluoroethyl}) \) 2-vinylcyclopropane-1,1-dicarboxylate\textsuperscript{41} (2-90h) (123 mg, 0.384 mmol) and \( \text{Dy(OTf)}_3 \) (23 mg, 0.040 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (112 mg, 0.768 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 12 hours. Compound 2-91h (45 mg, 0.102 mmol, 27%) was obtained as a clear oil. Rf = 0.52 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91h was prepared by dissolving \( \text{bis}(2,2,2\text{-trifluoroethyl}) \) 2-vinylcyclopropane-1,1-dicarboxylate (2-90h) (128 mg, 0.400 mmol) and \( \text{Dy(OTf)}_3 \) (24 mg, 0.040 mmol) in 6 mL of toluene. 3-phenyl-2\text{H}-azirine (2-81) (93.6 mg, 0.833 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 15 hours. Compound 2-91h (44 mg, 25%) was obtained as a clear oil.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.56 - 7.52 (m, 2H), 7.32 - 7.25 (m, 3H), 6.00 - 5.91 (m, 1H), 5.36 (dt, $J$ = 17.2, 1.4 Hz, 1H), 5.26 (dt, $J$ = 10.6, 1.4 Hz, 1H), 4.65 (dq, $J$ = 12.5, 8.3 Hz, 2H), 4.50 (dq, $J$ = 12.5, 8.2 Hz, 1H), 4.33 (dq, $J$ = 2.5, 8.3 Hz, 1H), 3.74 (dq, $J$ = 12.7, 8.3 Hz, 1H), 2.67 (dd, $J$ = 14.5, 7.0 Hz, 1H), 2.13 (s, 1H), 2.01 (s, 1H), 1.96 (dd, $J$ = 14.1, 10.9 Hz, 1H).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -73.77 (t, $J$ = 8.6 Hz, 3F), -73.99 (t, $J$ = 8.6 Hz, 3F).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 168.0, 167.9, 136.7, 135.3, 128.6, 128.0, 122.5 (q, $J_{C-F}$ = 277 Hz, 1C), 122.1 (q, $J_{C-F}$ = 277 Hz, 1C), 117.3, 65.9, 64.6, 61.2 (q, $J_{C-F}$ = 36 Hz, 1C), 61.1 (q, $J_{C-F}$ = 37 Hz, 1C), 54.5, 36.9, 32.2.

FT-IR (thin film, cm$^{-1}$): 3063, 2976, 1754, 1496, 1448, 1413, 1286, 1233, 1170, 1103, 977, 701.

HRMS calc’d for C$_{19}$H$_{17}$F$_6$NO$_4$ [M$^+$]: 437.1062; found: 437.0990.

**Bis(2,2,2-trifluoroethyl) 2-methyl-2,5-diphenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91i).**

Following experimental procedure B Method A, compound 2-91i was prepared by dissolving cyclopropane 2-90i (150 mg, 0.390 mmol) and Dy(OTf)$_3$ (24 mg, 0.039 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (113 mg, 0.781 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 12 hours. Compound 2-91i (160 mg, 0.319 mmol, 82%) was obtained as a yellow semi-solid in a 1:1 mixture of diastereomers. Rf = 0.80 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91i was prepared by dissolving cyclopropane 2-90i (150 mg, 0.390 mmol) and Dy(OTf)$_3$ (24 mg, 0.039 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (91 mg, 0.781 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 18 hours. Compound 8j (169 mg, 0.337 mmol, 87%) was obtained as a yellow semi-solid in a 1:1 mixture of diastereomers.

$^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereomers) $\delta$ = 7.83 (d, $J$ = 8.6 Hz, 2H), 7.62 (d, $J$ = 8.6 Hz, 2H), 7.53 (d, $J$ = 8.2 Hz, 2H), 7.46 (m, 2H), 7.43 - 7.36 (m, 5 H), 7.35- 7.23 (m, 7H), 4.76 - 4.63 (m, 1H), 4.62 - 4.41 (m, 4H), 3.94 (dq, $J$ = 16.4, 8.2 Hz, 1H), 3.68 (dq, $J$ = 12.6, 8.3 Hz, 1H), 3.46 (dq, $J$ = 12.5, 8.4 Hz, 1H), 3.31 (d, $J$ = 14.8 Hz, 1H), 3.25 (d, $J$ = 14.5 Hz, 1H), 2.64 (d, $J$ = 14.5 Hz, 1H), 2.59 (d, $J$ = 14.5 Hz, 1H), 2.41
Bis(2,2,2-trifluoroethyl)2-(but-1-ynyl)-2-methyl-5-phenyl-1-azabicyclo[3.1.0]hexane-4,4-dicarboxylate (2-91j).

Following experimental procedure B Method A, compound 2-91j was prepared by dissolving cyclopropane 2-90j (150 mg, 0.417 mmol) and Dy(OTf)₃ (25 mg, 0.042 mmol) in 6 mL of toluene. (1-azidovinyl)benzene (2-85) (121 mg, 0.833 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 18 hours. Compound 2-91j (103 mg, 52%) was obtained as a clear oil. Rf = 0.44 (30% EtOAc in hexanes).

Following experimental procedure B Method B, compound 2-91j was prepared by dissolving cyclopropane 2-90j (150 mg, 0.417 mmol) and Dy(OTf)₃ (25 mg, 0.042 mmol) in 6 mL of toluene. 3-phenyl-2H-azirine (2-81) (97 mg, 0.833 mmol), in 1 mL of toluene, was then added dropwise. The reaction was heated at 110 °C for 20 hours. Compound 2-91j (105 mg, 53%) was obtained as a clear oil.
(q, $J_{C-F} = 277$ Hz, 1C), 122.2 (q, $J_{C-F} = 277$ Hz, 1C), 85.2, 82.6, 65.8, 61.3 (q, $J_{C-F} = 37$ Hz, 1C), 61.2, 61.0 (q, $J_{C-F} = 37$ Hz, 1C), 55.7, 45.3, 32.9, 25.8, 13.6, 12.3. **FT-IR** (thin film, cm$^{-1}$): 3062, 3030, 2978, 2939, 2881, 2248, 1759, 1497, 1448, 1411, 1285, 1229, 1170, 1129, 974, 701. **HRMS** calc’d for C$_{22}$H$_{21}$F$_6$NO$_4$ [M$^+$]: 477.1375; found: 477.1303.

**X-Ray Crystallography Data of 8b (CDCD 1486123)**

X-ray quality crystals were prepared by vapor diffusion of cyclohexane into a solution of 2-91a in minimal dichloromethane. All x-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K.

![Crystal Structure Image](image)

**Table S1. Summary of Crystal Data for 2-91a**

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\( b, \, \text{Å} \)
\( c, \, \text{Å} \)
\( \alpha,^\circ \)
\( \beta,^\circ \)
\( \gamma,^\circ \)
\( V, \, \text{Å}^3 \)
Number of reflections to determine final unit cell
Min and Max 2\( \theta \) for cell determination,  \( ^\circ \)
Z
F(000)
\( \rho \) (g/cm\(^3\))
\( \lambda, \, \text{Å}, \, (\text{MoK}\alpha) \)
\( \mu, \, (\text{cm}^{-1}) \)
Diffractometer Type
Scan Type(s)
Max 2\( \theta \) for data collection, \( ^\circ \)
Measured fraction of data
Number of reflections measured
Unique reflections measured
R\(_{\text{merge}}\)
Number of reflections included in refinement
Cut off Threshold Expression
Structure refined using
Weighting Scheme
Number of parameters in least-squares
R\(_1\)
wR\(_2\)
R\(_1\) (all data)
wR\(_2\) (all data)
X-Ray Crystallography Data of 2-91f (CDCD 1486124)

X-ray quality crystals were prepared by vapor diffusion of cyclohexane into a solution of 2-91f in minimal dichloromethane. All x-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K.

Table 1. Summary of Crystal Data for n16035

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102
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Min & Max peak heights on final ∆F Map (e/A)  
-0.432, 0.572

Where:
R₁ = Σ(|F₀| - |Fₐ|) / ΣF₀

wR₂ = [Σ(w( F₀² - Fₐ² )²) / Σ(w F₀⁴)]⁰⁵

GOF = [Σ(w( F₀² - Fₐ² )²) / (No. of reflns. - No. of params. )]⁰⁵

### 2.8 References


For studies on the use of GaCl$_3$ in DA cyclopropane chemistry, see selected examples:

(b) Tomilov, Y.V.; Novikov, R.A.; Nefedov, O.M. *Tetrahedron* **2010**, 66, 9151-9158;


3 Conclusions

The two chapters discussed in this thesis are related to each other as they both explored the synthetic utility of donor acceptor (DA) cyclopropanes for the synthesis of N-containing heterocycles. Furthermore, a common theme which ties the two chapters together are the synthetic challenges associated with the development of new synthetic methodologies and their application towards the synthesis of pharmaceuticals or natural products. Often, these types of projects give students the opportunity to gain valuable troubleshooting ability, improve oral and written communication skills, effective time management and organization skills, as well as test their ability to perform efficiently and multi-task in a fast-paced environment.

In chapter one, we studied the ability of quaternary DA cyclopropanes to undergo a nucleophilic ring opening reaction to afford Homo-Michael addition products. The new synthetic protocol described in this chapter was utilized in the synthesis of pyrroloindoles bearing a quaternary centre (Scheme 3-1). The reaction involves a Lewis acid catalyzed nucleophilic ring opening of quaternary DA cyclopropanes with indoline to yield N-alkylated indolines in yields ranging from 44-88%. The resulting ring opened products were then subjected to a Mn(OAc)$_3$ mediated radical oxidative cyclization to afford the corresponding pyrroloindoles with varying substitution in yields ranging from 40-83%, this making them attractive synthetic intermediates in the synthesis of natural products and pharmaceuticals.

![Scheme 3-1](image)

**Scheme 3-1.** Synthesis of pyrroloindoles via a Lewis acid catalyzed nucleophilic ring opening and oxidative radical cyclization of quaternary DA cyclopropanes.
Also in chapter one, the aforementioned methodology was then applied toward the total synthesis of the natural products flinderoles A, B, and C. Although we were not able to synthesize the natural products, we were able to obtain optimized reaction conditions for the synthesis of the \textit{bis}-indole moiety \textit{3-9} (Scheme 3-2) of the natural products, which could be a synthetic method for the synthesis of flinderole analogues for drug development. Furthermore, the project highlights all the struggles and troubleshooting/problem solving associated in natural product synthesis, as shown in our many attempts and revisions to complete the total synthesis of the flinderoles.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme32.png}
\end{center}

\textbf{Scheme 3-2.} Synthesis of \textit{bis}-indole moiety of the flinderoles.

The second chapter of this thesis described the reactivity of DA cyclopropane \textit{3-12} towards the Lewis acid catalyzed annulation reaction with vinyl azide \textit{3-13} or 2\textit{H}-azirine \textit{3-15} to give 1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates \textit{3-14} (Scheme 3-3). During the reaction optimization, it was found that the replacement of the commonly used dimethyl
esters on the DA cyclopropane with the more electrophilic bis-trifluoroethyl esters diminished the formation of side products and gave the desired azabicycle. The reaction of DA cyclopropane 3-12 and 2H-azirine 3-15 had higher yields (25-92% vs 27-82%), but slower reaction times. Mechanistically, we have postulated that the observed 1-azabicyclo[3.1.0]hexane-4,4-dicarboxylates are being formed via a vinyl nitrene intermediate, which forms upon heating the vinyl azide or 2H-azirine. Further studies are required to gain more insight into the mechanism of the reaction.

**Scheme 3-3.** Lewis acid catalyzed annulation reaction of DA cyclopropane 3-12 with vinyl azide 3-13 or 2H-azirine 3-15 for the synthesis of azabicycles 3-14. The envisioned future work for this project will focus on exploring the reactivity of the azabicycles for the conversion to useful heterocyclic motifs.

**Scheme 3-4.** Envisioned transformations azabicycle (x) into useful heterocyclic motifs.
Appendix I- Synthesis of Pyrroloindoles from Donor Acceptor Cyclopropanes and their application towards the Total Synthesis of Flinderoles A, B, and C- $^1$H NMR and $^{13}$C NMR
$^{13}$C NMR of 1-52a
$\text{Me}$

$\text{MeO}_2\text{C}$

$\text{CO}_2\text{Me}$

$^1\text{H NMR of 1-52b}$
$^{13}$C NMR of 1-52b
$^1$H NMR of 1-52c
$^1$H NMR of 1-53a
$^{13}$C NMR of 1-53b
$^{13}\text{C NMR of } 1-53\text{c}$
\[
{^{13}}C \text{ NMR of 1-53e}
\]
$^1\text{H NMR of 1-53g}$
$^{13}$C NMR of 1-53g
$^{13}$C NMR of 1-54a
$^{13}$C NMR of 1-54c
$^1$H NMR of 1-54d
$^{13}$C NMR of 1-54d
$^{13}$C NMR of 1-54e
$^1\text{H} \text{NMR of } 1-54g$
\[ ^1H \text{NMR of 1-89} \]
$^1$H NMR of 1-91
$^1$H NMR of 1-92
$^{13}$C NMR of 1-92
$^1$H NMR of 1-93
$^{13}$C NMR of 1-96
$^{13}$C NMR of 1-109
$^1$H NMR of 1-113
Appendix II- Annulation Reactions of Donor Acceptor Cyclopropanes with vinyl azide and 2H-azirine - $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR
$^{1} \text{H NMR of 2-90g}$
$^{13}$C NMR of 2-90g
$^{13}$C NMR of 2-90i
"H NMR of 2:91a
$^{19}F$ NMR of 2-91a
$^{13}$C NMR of 2-91a
$^1$H NMR of 2-91b
$^{19}$F NMR of 2-91b
$^{13}$C NMR of 2-91b
$\text{H NMR of 2-91c}$
$^{13}$C NMR of 2-91d
$^{13}$C NMR of 2-91f
$^{19}$F NMR of 2-91j
$^{13}$CNMR of 2-91j
Curriculum Vitae

Education

Ph.D. Organic Chemistry
Western University, London, Ontario
Supervisor: Dr. Michael Kerr

Research focus:
- Radical cyclizations for the synthesis of pyrroloindoles: Progress towards the flinderoles.
- Annulation Reactions of Donor–Acceptor Cyclopropanes with (1-azidovinyl)benzene and 3-phenyl-2H-azirine.
- Lewis acid catalyzed reactions of phosphine gas.

B. Sc. (Honours) Biochemistry with First-Class Honours Standing
Brock University, St. Catharines, Ontario
Supervisor: Dr. Travis Dudding


Awards and Scholarships

- Accelerate Mitacs and Sugar & Co. Internship, April 2015-September 2017
- Ontario Graduate Scholarship (OGS), September 2013-May 2014
- Distinguished Graduating Student Award-Biochemistry, June 2013
- E A Cherniak Founders Prize, June 2013
- Society of Chemical Industry Merit Award (Chemistry), June 2013
- Dean’s Honours List, Brock University, 2010-2013
- Queen Elizabeth II Aiming for the top Scholarship, 2009-2012
- Brock University Entrance Scholarship, 2009-2012
- Math and Science Entrance Scholarship, 2009

Publications


Oral presentations


Poster presentation


Academic and Research Experience

Formulation Cosmetic Chemist
Department of Chemistry, Western University, London, Ontario
Accelerate Mitacs, Western University, London, Ontario
Sugar & Company, London, Ontario

- Mitacs accelerate internship with Sugar & Co. and the Department of Chemistry at Western University to synthesize a new product for body sugaring;
- Became familiar with the art of body sugaring and the chemistry of sugaring;
- Worked alongside with Sugar & Co. to formulate new sugaring products that can withstand elevated temperatures and humidity as well as a sugar product that can withstand low temperature and low humidity;
• Ensured that reagents in the new products were within the limits provided by to the Food and Drug Regulation and the Natural Health Product Regulations of Canada;
• Became proficient with the use of a 10 L and 50 L Chemglass unjacketed chemical processors;
• Gained the ability to troubleshoot and to improve the formulation of the already existing sugar products when carrying the reactions in a larger scale;
• Ensure that sugar batches were synthesized in a cost-efficient manner.

**Teaching Assistant** January 2014-April 2015
Department of Chemistry, Western University, London, Ontario

Courses: 2283 Organic Chemistry II: Mechanisms and Reactivity
3373 Organic Chemistry II: Mechanisms and Strategies for Synthesis

• Responsible for imparting pre-lab discussions in safety, proper laboratory techniques, and experiment information;
• Evaluated laboratory reports, mid-terms, and final exams;
• Assisted students with answering questions about course material and experiments.

**Scientifically Yours and Bringing Our World through Science (BOWS)-Teaching Assistant** May 2013
Brock University, St. Catharines, Ontario

• Responsible enhancing laboratory safety during experiments;
• Assisted students with answering questions about experiments and related topics;
• Gain the ability to monitor and mediate educational discussion related to the topics being studied.

**Research Assistant** May-August 2012
Department of Chemistry, Brock University, St. Catharines, Ontario

Supervisor: Dr. Travis Dudding
Research focus: Synthesis of methyl 2-formylbenzoate derivatives.

• Assisted Ph.D. candidate with the preparation of 5-substituted methyl 2-formylbenzoate starting materials used for the enantioselective synthesis of C(3)-chiral phthalides.

**Computational Chemistry- Theorist Assistant** November 2011- May 2012
Department of Chemistry, Brock University, St. Catharines, Ontario

Supervisor: Dr. Travis Dudding
Research focus:
1. Computational study of the origins of selectivity and the reaction mechanism of the
Brønsted acid promoted aza-Darzens Aziridine Reaction.
  • Investigated stereochemistry-determining transition states for the reaction mechanism using Gaussian 09 suite of programs.
2. Study of 1,3-dipolar cycloaddition of münchnones with β-nitrostyrenes.
  • Carried out transition state calculations and natural bond order (NBO) calculations for the analysis of structural critical points.