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Novel Reactions of Donor-Acceptor Cyclopropanes, and Diels-Alder Approach Towards Fargesine and Fumimycin

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

Abstract

The first chapter of this thesis consists of two related projects that explore novel reactivity of donor-acceptor cyclopropanes, specifically 2-substituted cyclopropane 1,1-diesters. The first project involves the nucleophilic ring opening of donor-acceptor cyclopropanes with potassium organotrifluoroborates. It was found that during the ring opening of the cyclopropane, the diesters of the cyclopropane formed a malonyl-BF_2 complex. The complex could then be hydrolyzed to afford substituted malonates. The reaction was limited to aryl cyclopropanes and potassium alkynyltrifluoroborates. The second project in this chapter explores modifying the Kerr group's previous synthesis of tetrahydro-1,2-oxazines, such that geminal allyl, methyl esters are now on the tetrahydro-1,2-oxazine. This allows for a one-pot dehydrocarbonylation/dehydration procedure to access pyrroles.

The second chapter of this thesis describes efforts towards the total synthesis of two natural products via Diels-Alder of quinoid species. The first project describes the formal synthesis of indole containing fargesine utilizing the Kerr group's Diels-Alder/Plieninger indolization sequence. A Pinnick oxidation, followed by a Curtius rearrangement was required to complete the formal synthesis. The second project describes efforts towards benzofuranone containing fumimycin. The benzofuranone would be accessed by the Diels-Alder of requisite benzoquinone ketal and diene. Following a similar protocol to the Kerr group's modified Plieninger indolization sequence could allow access to the core of fumimycin. Despite many alternative routes, formation of the benzofuranone core eluded this study.

Keywords: donor-acceptor cyclopropanes, nucleophilic ring opening, potassium organotrifluoroborates, annulation, tetrahydro-1,2-oxazines, pyrroles, total synthesis, Diels-Alder, Plieninger indolization sequence, fargesine, fumimycin

Co-Authorship Statement

The results in section 1.5.4 were done in collaboration with William J. Humenny, Katarina Sapeta, and Avedis Karadeolian. Avedis's contribution was developing conditions to convert tetrahydro-1,2-oxazines to 3,4-dihydro-1,2-oxazines. Optimizing the pyrrole protocol was done by myself, William, and Katarina. The scope of the reaction was divided such that cyclopropanes bearing phenyl, or ethyl substituents were worked on by William, cyclopropanes bearing furanyl, or vinyl substituents were worked on by myself, and cyclopropanes with no substitution was worked on by Katarina. Progress towards atorvastatin (Lipitor) was completed solely by William but was included in the thesis to highlight the application of the methodology.

The results in section 2.4.2 were done in collaboration with Sharon E. Michalak. Sharon performed the initial model study, and carried out the Kerr group's Diels-Alder/Plieninger indolization protocol. She then performed the Pinnick oxidation, and attempted the Curtius rearrangement. Further optimization of the Pinnick oxidation and Curtius rearrangement, and completion of the formal synthesis of fargesine was completed by myself.

Acknowledgments

Firstly, I must thank my parents. They have always been supportive of whatever decisions I made in life, and for that I am very grateful. Without their constant love and support (sometimes financially), I do not think I would have been able to get through all these years. They were always a phone call away to offer advice, hear my rants, or cheer me up.

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Of course I must thank all the members of the Kerr group, past and present. You have made my time in lab much more enjoyable. To my early mentors – Dr. Terry Lebold, Dr. Mike Johansen, Dr. Avedis Karadeolian, Katarina Sapeta, and Dr. Dwayne Dias, thank you for everything. Your guidance was exemplary and I am always trying to lead by your example. To 'the boys' – Mike Emmett, Huck Grover, and B-ryan Landschoot – it was really fun working along you, and I will greatly miss our Euchre games that always ended in near fisticuffs. A special thank you to Joanne Curiel-Tejeda for putting up with me during my final years in the group. Your patience and support is what carried in me in the final months of the program. I would also like to thank members of the Pagenkopf group for their guidance throughout the years, especially Andrew Stevens, Cory Palmer, and Naresh Vemula.

Lastly, I I'd like to thank all my family and friends. Your support has definitely made my time in graduate school more enjoyable.

To Maria and Charalambos Kyriacou

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List of Schemes

List of Abbreviations

Å	angstrom
A	acceptor
Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazolines
BHT	dibutylhydroxytoluene
Bu	butyl
Bz	benzoyl
Cp*	pentamethylcyclopentadiene
CSA	camphorsulfonic acid
D	donor
DA	donor-acceptor
dba	dibenzylideneacetone
DBE	dibromoethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
DyKAT	dynamic kinetic asymmetric transformations
E^+	electrophile
ee	enantiomeric excess
er	enantiomeric ratio

Et	ethyl
EDG	electron donating group
EWG	electron withdrawing group
FMO	frontier molecular orbital
gCOSY	gradient correlation spectroscopy
gHMBCAD	gradient heteronuclear multiple-bond correlation spectroscopy adiabatic
gHSQC	gradient heteronuclear single-quantum correlation spectroscopy
Gly	glycine
HOMO	highest occupied molecular orbital
Ile	isoleucine
IR	infrared
LAH	lithium aluminum hydride
LUMO	lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mol	mole(s)
MS	molecular sieve
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu^-	nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
PDC	pyridinium dichromate
Ph	phenyl
PhTh	phthalimide
ppy	phenylpyridine
PTSA	*p*-toluenesulfonic acid
RT	room temperature
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine

TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilane
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMM	trimethylenemethane
TMS	trimethylsilyl
Tf	trifluoromethylsulfonate
Ts	*para*-toluenesulfonyl

Chapter 1 - Novel Reactions of Donor-Acceptor Cyclopropanes

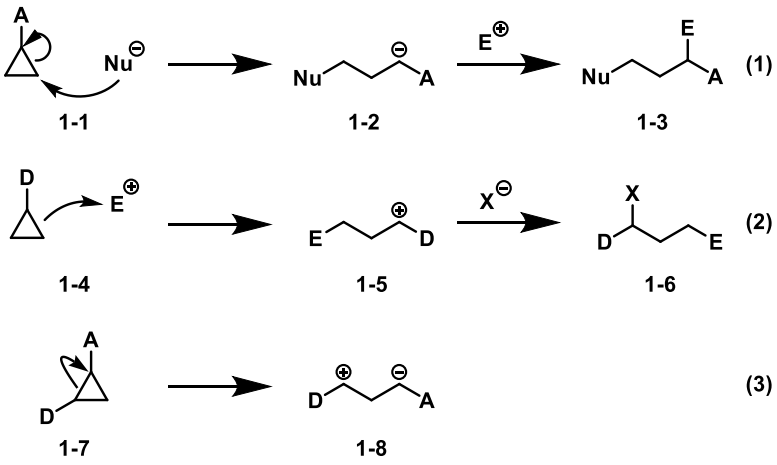
1 Chapter introduction

Chapter one explores new reactivity of donor-acceptor cyclopropanes and is divided into two sections: the ring opening of donor-acceptor cyclopropanes by organotrifluoroborate salts, and the synthesis of pyrroles from the annulation reaction between donor-acceptor cyclopropanes, and nitrones. A general introduction to donor-acceptor cyclopropanes is discussed followed by the introduction and results for each section. The work towards the ring opening of donor-acceptor cyclopropanes by organotrifluoroborate salts was developed independently, while the pyrrole synthesis was done in collaboration with William Humenny, Katarina Sapeta, and Avedis Karadeolian. The results in Section 1.5.4 have been published in a peer reviewed journal.[1] Reproduced in part with permission from Humenny, W.J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M.A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11088-11091. Copyright 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

1.1 Introduction to donor-acceptor cyclopropanes

1.1.1 Structure and reactivity of cyclopropanes

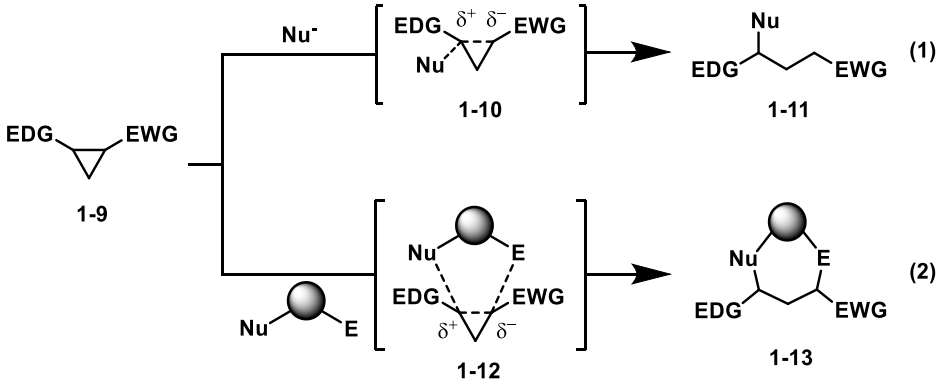
The goal of a synthetic chemist is to access complex molecules, ideally from inexpensive and simple starting materials. Cyclopropanes, while structurally simple, have proven to be an important tool for chemists to accomplish this goal.[2] Due to the high ring strain of cyclopropanes (115 kJ/mol),[3] they react similarly to olefins than other cycloalkanes.[4] The high ring strain of a cyclopropane can further be exploited by the addition of acceptor, donor, or donor and acceptor substituents on the cyclopropane (Scheme 1-1).



Scheme 1-1 The reactivity of acceptor (1), donor (2), and donor-acceptor (3) cyclopropanes

Acceptor substituted cyclopropanes (acceptor = electron withdrawing group (EWG)) are activated by increasing the electrophilic nature of the cyclopropane, allowing for homo-Michael addition ring opening reactions (Scheme 1-1, entry 1). The incipient anion formed upon bond cleavage is also stabilized by the acceptor group. When a donating substituent (donor = electron donating group (EDG)) is on a cyclopropane, the nucleophilic nature of the cyclopropane increases, allowing for reactions with electrophiles (Scheme 1-1, entry 2). The subsequent carbocation formed is also stabilized by the donating substituent. Lastly, in the case of cyclopropanes substituted with donor-acceptor (DA) groups (Scheme 1-1, entry 3), a synergistic effect occurs due to the 'push-pull effect' of both substituents. Polarization of the bond between the two groups leads to a 1,3 diploe (**1-8**), where each charge is stabilized by their respective group. While the position of the donor and acceptor groups can be geminal (on the same carbon), they do not contribute to the synergistic effect and only vicinally disubstituted DA cyclopropanes (on adjacent carbon atoms) will be discussed.

Vicinally substituted donor-acceptor cyclopropanes display different modes of reactivity based on its reacting partner; of particular interest, nucleophiles can react to form acyclic products (Scheme 1-2, entry 1), or dipoles can react to form annulation products (Scheme 1-2, entry 2).



Scheme 1-2 Formation of acyclic (1), or cyclic (2) products from cyclopropanes

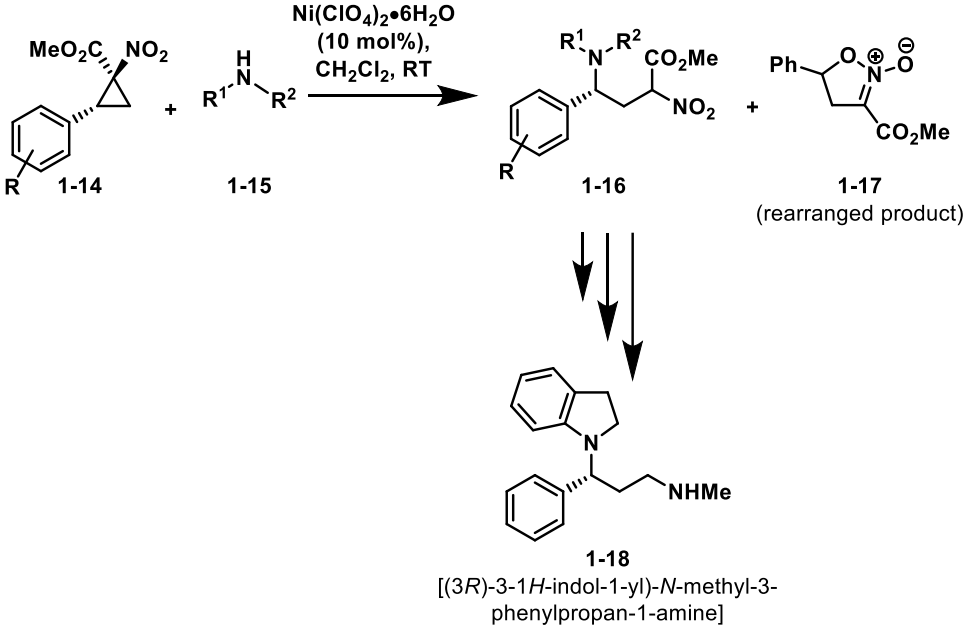
One of the earliest examples of cyclopropane reactivity comes from Bone and Perkin's work on the nucleophilic ring opening of cyclopropanes with ethyl malonate in 1885.[5] There was a resurgence in the studies of cyclopropanes in the 1960's and 1970's with the work done by Stork[6] and Danishefsky,[7] but all of these examples focused on the reactivity of acceptor cyclopropanes. It was not until the 1980's with the work of Wenkert[8] and Reissig[9] that studies on DA cyclopropanes began.

1.2 Ring opening of DA cyclopropanes

1.2.1 Ring opening of DA cyclopropanes with heteroatom nucleophiles

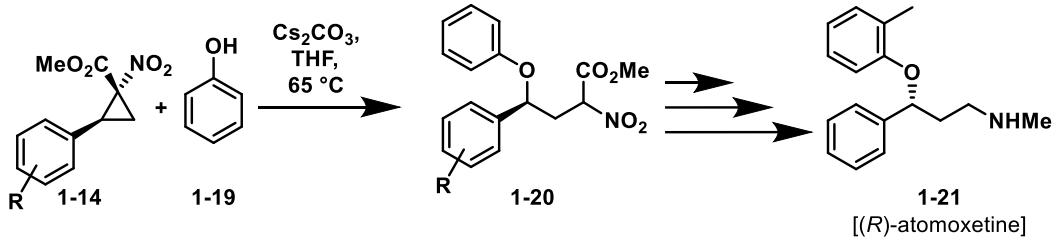
Donor-acceptor cyclopropanes can react with various nucleophiles to undergo ring opening reactions that can be useful for accessing natural products/drug targets. For example, the synthesis of a dual serotonin/norepinephrine reuptake inhibitor (3*R*)-3-(1*H*-indol-1-yl)-*N*-methyl-3-phenylpropan-1-amine (**1-18**) was highlighted during Lifchits and Charette's methodology of amines opening DA cyclopropanes.[10] During their optimization they found that $AlCl_3$, $SnCl_4$, and BF_3•OEt_2 gave the intramolecular rearranged product **1-17**, whereby the nitro group opened the cyclopropane. It was then found that $Ni(ClO_4)_2$•$6H_2O$ gave the best yield of the acyclic product (**1-16**). Various anilines were used in the scope of the reaction, but due to the high basicity of aliphatic amines, complexation with Lewis acid occurred resulting in very sluggish reaction times.

Thus, only pyrrolidine and piperidine were shown to give useful yields, albeit with slow reaction times.



Scheme 1-3 Charette group's opening of cyclopropanes by amines

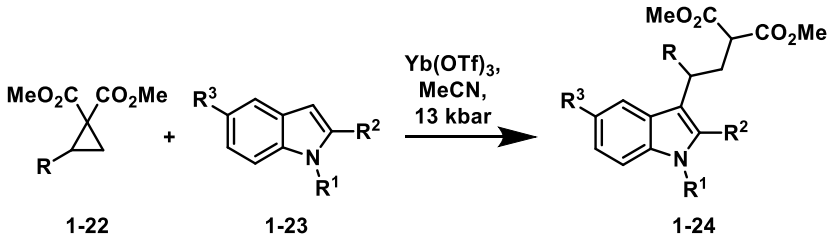
The Charette group were then able to use their cyclopropane and react it with phenol to access (*R*)-atomoxetine (**1-21**, Strattera), which is used to treat anxiety and depression.[11] Electron rich and poor phenols were tolerated (59-84%), although low yields were obtained with *m*-chlorophenol (57%) and 1-naphthol (53%). When enantioenriched cyclopropanes were used, the *ee* of the product was preserved (90-95% *ee*).



Scheme 1-4 Charette group's opening of cyclopropanes by phenols

1.2.2 Ring opening of DA cyclopropanes with indoles

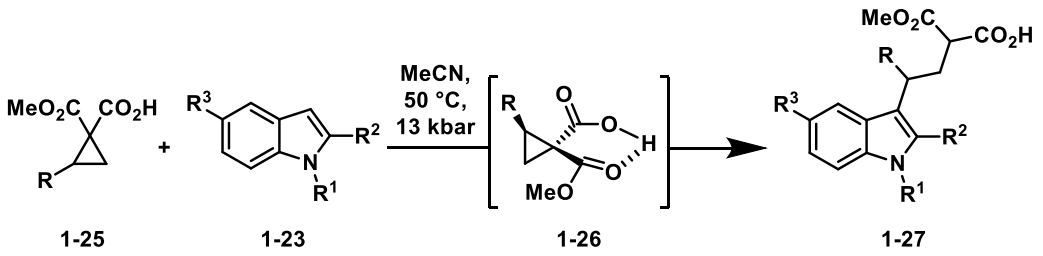
An early example of donor-acceptor cyclopropanes being utilized with carbon nucleophiles to give acyclic products was developed by Harrington and Kerr in 1997.[12] Inspired by their work on alkylating indoles with Michael acceptors,[13] they found that a Friedel-Crafts alkylation of indole **1-23** occurred with cyclopropane **1-22** to give the homo-Michael adduct **1-24** (Scheme 1-5). The reaction occurred under hyperbaric conditions (13 kbar), in dry acetonitrile, under $Yb(OTf)_3$ catalysis; addition of small amounts of water resulted in no reaction, which contradicted literature precedence that water was a good co-solvent with acetonitrile at hyperbaric conditions,[14] and that $Yb(OTf)_3$ retained activity under aqueous conditions.[15] The reaction was tolerant of cyclopropanes substituted with H, Me, or Ph, and *N*-methyl or *N*-*p*-bromobenzyl indoles.



1-22 1-23 1-24

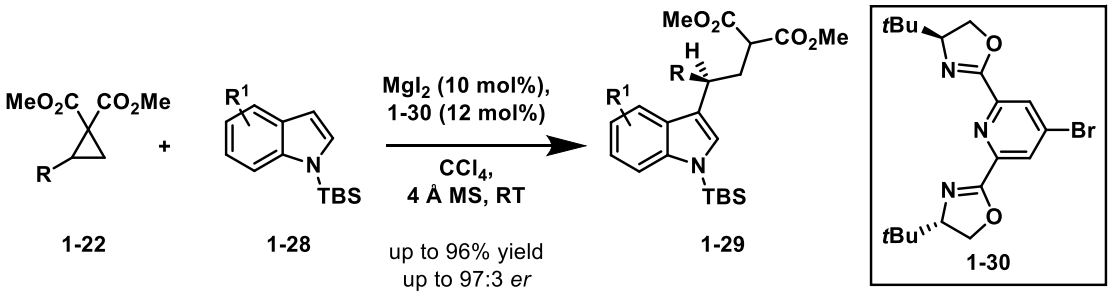
Scheme 1-5 Kerr group's opening of cyclopropanes by indoles

The Kerr group later revisited the Friedel-Crafts alkylation of indoles with donor-acceptor cyclopropanes at hyperbaric conditions when they showed that cyclopropanes **1-25** (geminally disubstituted with one carboalkoxy, and one carbohydroxy group) could under go the same reaction with no catalyst (Scheme 1-6).[16] Thermal conditions were unsuccessful in the transformation to the desired product, and it was also shown that both ester and acid were required for the transformation to occur. The optimization results suggest that hyperbaric conditions induce hydrogen bonding to activate the cyclopropane (**1-26**). Various 3 and 5-substituted indoles, along with aryl and heteroaryl substituted cyclopropanes were successful in the transformation, resulting in alkylated indoles (**1-27**) in 50-97%.



Scheme 1-6 Kerr group's catalyst free opening of cyclopropanes by indoles

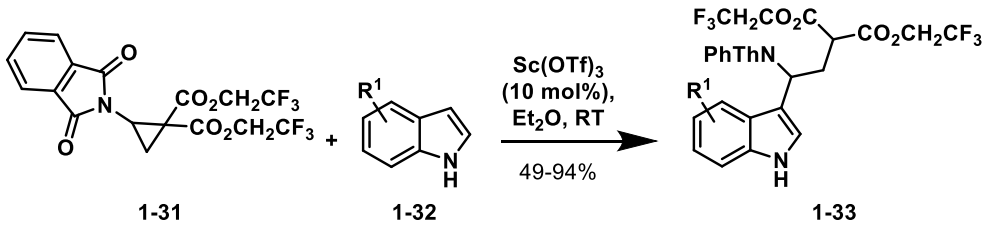
In 2013, the Johnson group applied their previous studies on dynamic kinetic asymmetric transformations (DyKAT)[17] for annulations of racemic donor-acceptor cyclopropanes[18] to the Friedel-Crafts alkylation of indoles with cyclopropanes (Scheme 1-7).[19] Through optimization studies, it was found that an electron deficient indole such as **1-28** was required as electron rich indoles would react with cyclopropanes before the cyclopropane epimerization process occurred. The scope of this reaction was excellent, and various racemic cyclopropanes, and indoles, were used with good yields (up to 96% yield) and high *er* (up to 97:3) to obtain alkylated indole **1-29**.



Scheme 1-7 Johnson group's asymmetric opening of cyclopropanes by indoles

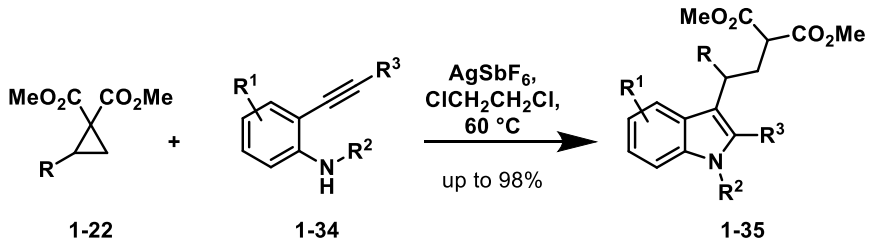
While most groups focused on carbon based donor groups (on cyclopropanes) for the Friedel-Crafts alkylation of indoles, Waser's group showed that aminocyclopropane **1-31** was able to undergo this transformation by modifying the acceptor group.[20] In order for this reaction to proceed, the typical dimethyl-1,1-cyclopropanedicarboxylate acceptor group had to be modified to a more activated *bis*(2,2,2-trifluoroethyl)cyclopropane-1,1-dicarboxylate group (Scheme 1-8). Many cyclopropanes and indoles were used in the reaction and alkylated indole **1-33** was obtained in 49-94% yield; however, when indoles substituted at the 3 position were used, a *C*-3 to *C*-2 alkyl migration was observed. Waser

also showed that aminocyclopropanes could be opened with other aromatic compounds besides indoles, such as pyrroles and phenols.



Scheme 1-8 Waser group's opening of aminocyclopropanes by indoles

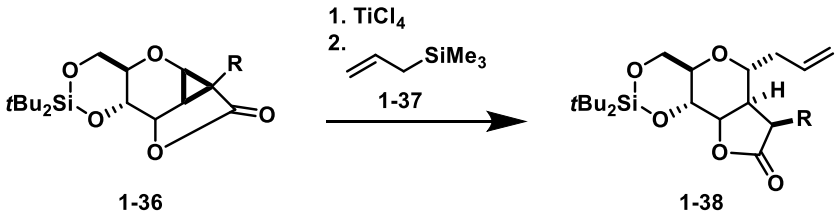
A two-step cascade was developed by the Singh group in 2016, whereby indoles were formed in situ, and then underwent Friedel-Crafts alkylation with donor-acceptor cyclopropanes (Scheme 1-9).[21] Aniline **1-34** was able to undergo alkyne activation/cyclization with $AgSbF_6$, which was also able to catalyze the alkylation to form alkylated indole **1-35**. This is unique to other thermal conditions whereby typical catalysts are Cu, Zn, Sc, In, Mg, or Yb based. Cyclopropanes substituted with aryl, heteroaryl, amino, and styrenyl groups could undergo the transformation.



Scheme 1-9 Singh group's two-step cascade - formation of indole and ring opening of cyclopropane

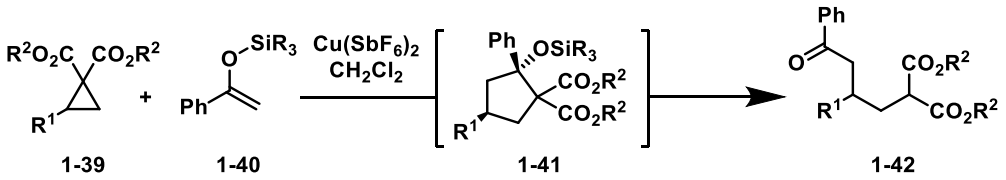
1.2.3 Ring opening of DA cyclopropanes with non-aromatic carbon nucleophiles

As shown above, indoles are very effective at opening donor-acceptor cyclopropanes to result in acyclic products, but non-aromatic carbon nucleophiles are also capable in the acyclic opening of cyclopropanes. In 2003, Yu and Pagenkopf showed that glycal-derived donor-acceptor cyclopropanes (**1-36**) could be opened with allyl silane **1-37**, to allow a simple route to modified glycals (**1-38**) (Scheme 1-10).[22] Using their procedure for the cyclopropanation of glycals,[23] a variety of modified glycals were made that could be ring opened with $TiCl_4$ and allyl silane. It should be noted that if $TiCl_4$ was added after the allyl silane, decomposition of the starting material was observed.



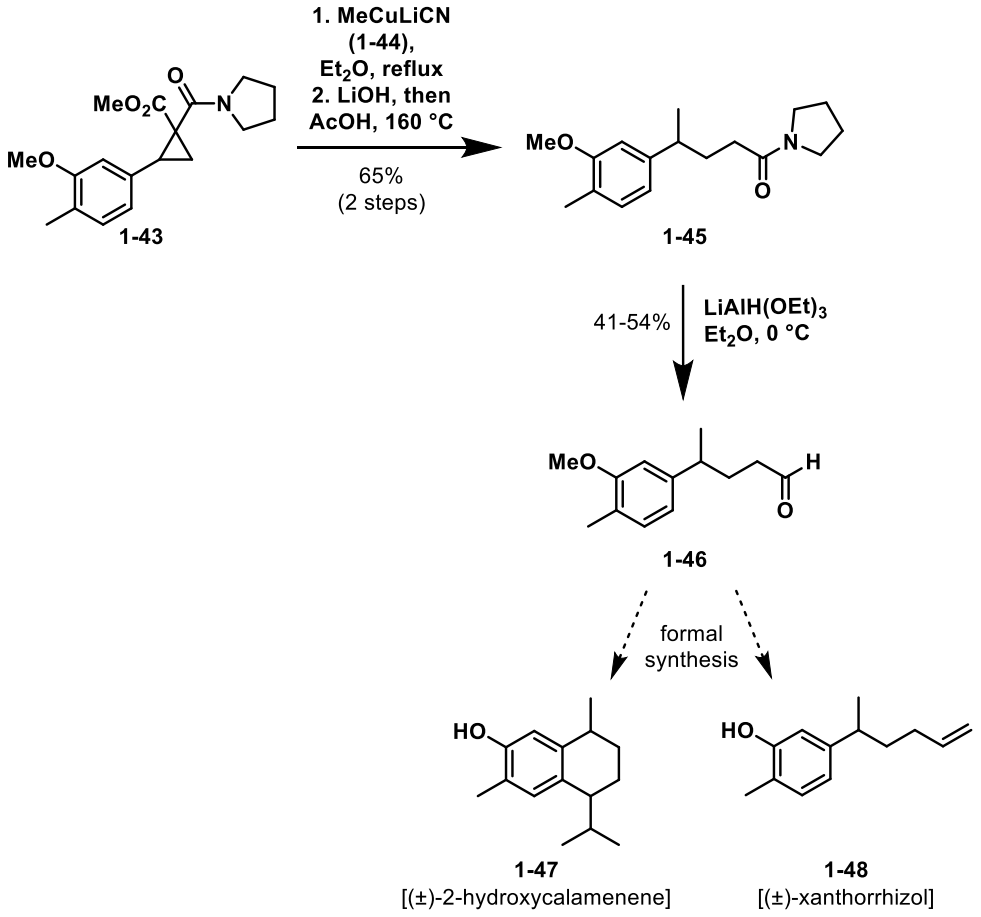
Scheme 1-10 Pagenkopf group's opening of cyclopropanes by allyl silane

Silyl enol ethers **1-40** were used by the Tang group in 2009 to open donor-acceptor cyclopropanes (Scheme 1-11).[24] During their Lewis acid screening, they found that $Yb(OTf)_3$ favoured the cyclic product (**1-41**), while other triflates (Sc, In, Ga, Sn, Cu) favoured the acyclic product (**1-42**). It was then found that $Cu(SbF_6)_2$ gave the best selectivity and highest conversion towards the acyclic product, so it became the Lewis acid of choice. In an effort to gain further understanding of the mechanism, *O*-TMS and *O*-TBS silyl enol ethers were compared in the ring opening of cyclopropane **1-39** and it was found that the cyclic product became favoured with increased bulk around the silane. NMR experiments then confirmed that the cyclic product is actually formed first, and under prolonged stirring with Lewis acid, formation of the acyclic product occurred. The reaction worked well when aryl substituted cyclopropanes were used (64-92%), but were not very effective for styrenyl (49%), vinyl (28%), or 2-furanyl (15%).



Scheme 1-11 Tang group's opening of cyclopropanes by silyl enol ethers

One of the few examples that results in the direct alkylation/ring opening of donor acceptor cyclopropanes was highlighted by the Charette group in the formal synthesis of (±)-2-hydroxycalamenene (**1-47**) and (±)-xanthorrhizol (**1-48**).[25] They were able to show that cyclopropane **1-43** could be opened with organocuprate **1-44**, and then decarboxylated to give **1-45** in 65% yield over the two steps (Scheme 1-12). Compound **1-45** was then taken to **1-46** to complete the formal synthesis. Organocuprates were also used by Corey to open a donor-acceptor cyclopropane towards the synthesis of the antidepressant Sertraline.[26]

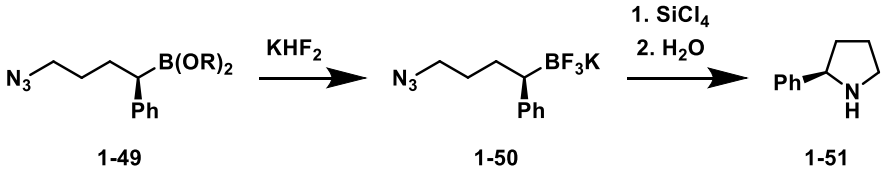


Scheme 1-12 Charette group's opening of cyclopropane with organocuprate towards the formal synthesis of **(±)-**2-hydroxycalamenene and **(±)-**xanthorrhizol

1.3 Ring opening of DA cyclopropanes with potassium organotrifluoroborates

1.3.1 Introduction to potassium organotrifluoroborates

Organoboron compounds have become popular reagents in carbon-carbon bond formation chemistry.[27] Reactions include various coupling reactions (example: Suzuki reaction[28]), and conjugate additions. Originally these reactions have been done using boronic acids and boronate esters; however, these compounds have some limitations: they have low stability, high prices, and some reagents are highly sensitive towards air and moisture. To mitigate these issues, boronic acids and boronate esters have been replaced by potassium organotrifluoroborate salts (RBF_3K). The crystalline salts are easily prepared from inexpensive starting materials, show greater nucleophilicity compared to boronic acids or boronate esters, and are air and moisture stable.[29] While the aforementioned reactions contain a metal catalyst, it was not until 2002 with the work of Matteson and Kim that a metal free approach was undertaken. They were able to convert boronate ester **1-49** to the trifluoroborate salt **1-50**, which then cyclized under $SiCl_4$ mediated conditions to give pyrrolidine **151** (Scheme 1-13).[30] While many others explored the utility of RBF_3K in non-metal-catalyzed reactions, only a select few are discussed below.



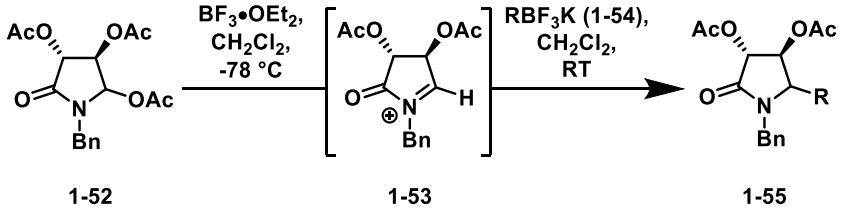
1-49 **1-50** **1-51**

Scheme 1-13 Matteson and Kim's pyrrolidine synthesis by RBF_3K

1.3.2 Organotrifluoroborate salts as nucleophiles

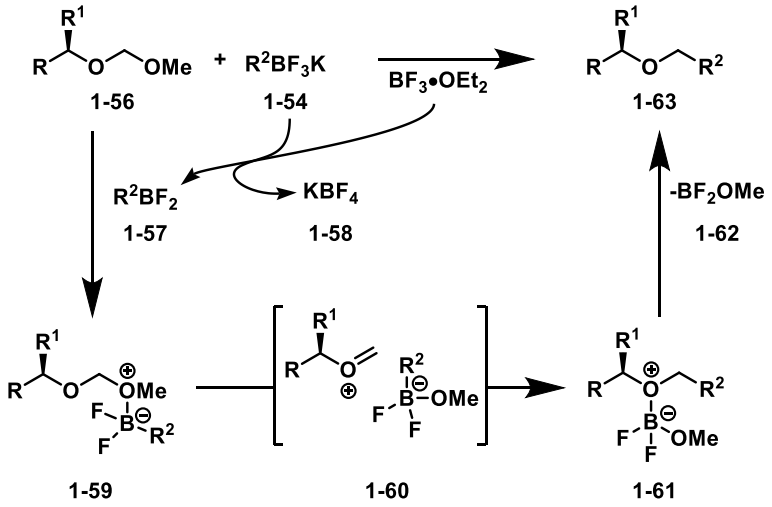
In 2008, the Stefani group wanted to find mild conditions for α-functionalization of *N*-acyliminium ions, as these are important in the preparation of alkaloids and other biologically active nitrogen heterocycles.[31] They were able to show that *N*-benzyl-3,4,5-triacetoxy-2-pyrrolidinone (**1-52**) was able to undergo nucleophilic addition by organotrifluroborate **1-54** under Lewis acidic conditions to form pyrrolidinone **1-55**

(Scheme 1-14).[32] The reaction was unable to proceed without a Lewis acid, suggesting that the reaction proceeds via *N*-acyliminium ion intermediate **1-53** (Scheme 1-14). During their optimization of the reaction they found that four equivalents of Lewis acid, BF_3•OEt_2, was required to obtain good yields and increasing the Lewis acid loading did not give better yields. They also found that modifying the organotrifluoroborate counter ion, and changing the solvent from DCM to DCE had no effect on the reaction. They were able to show that aryl, heteroaryl, and alkynyl substituted trifluoroborate salts were effective nucleophiles towards pyrrolidinone **1-55**.



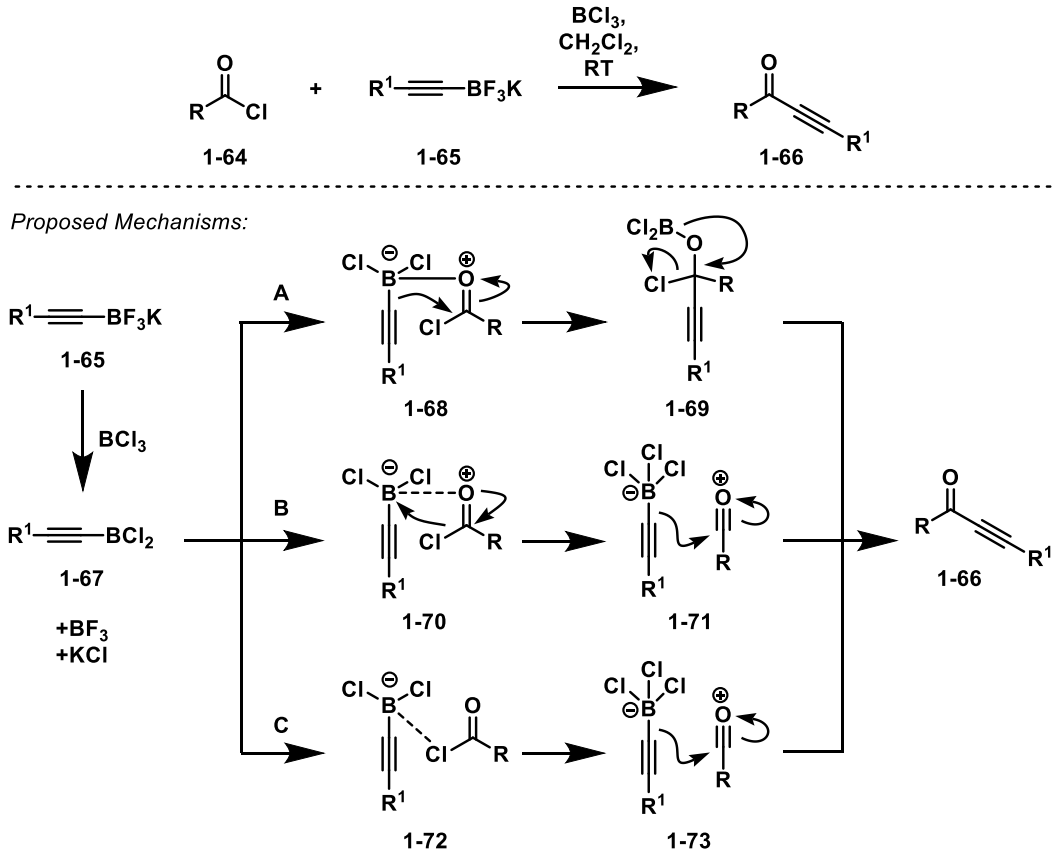
Scheme 1-14 Stefani group's pyrrolidinone alkylation with organotrifluoroborate salts

Mitchell and Bode, in 2009, found that organotrifluoroborate salts **1-54** react as nucleophiles with acetals **1-56** to access a variety of ethers (**1-63**, Scheme 1-15).[33] The ability to circumvent the common way to synthesize ethers, typically a harsh process involving reaction of alkoxides with alkyl halides (Williamson ether synthesis), can minimize potential side reactions. They were effective in showing the synthesis of ethers from aryl, ally, alkynyl, and styrenyl organotrifluroborates reacting with various acetals. The reaction is proposed to proceed by the activated RBF_2 nucleophile (**1-57**, which is also ^{11}B NMR active)[34,35] complexing with the acetal to form zwitterion **1-59**, which collapses to oxocarbenium **1-60**. Addition of the alkyl group to the oxocarbenium intermediate (**1-61**) would result in the desired ether (**1-63**) upon work up.



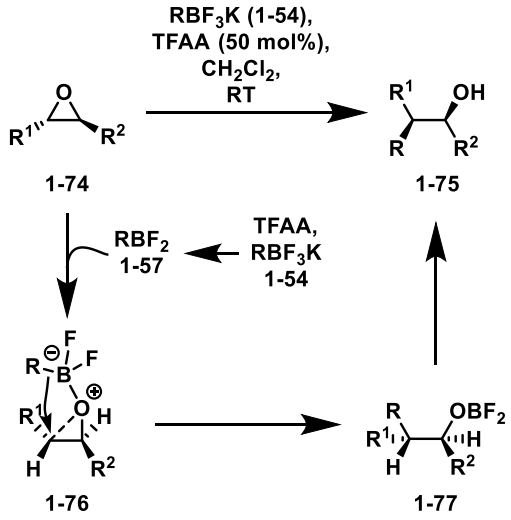
Scheme 1-15 Bode group's synthesis of ethers from organotrifluoroborate salts

In 2014, Taylor and Bolshan showed that they could access a variety of ynones (**1-66**) by the nucleophilic addition of alkynyl organotrifluoroborate salts (**1-65**) to acyl chlorides (**1-64**).[36] Ynones were accessed from aryl or alkyl acyl chlorides reacting with aryl, or alkyl substituted alkynyl trifluoroborate salts in 39-99% yields (Scheme 1-16). Three mechanisms were proposed for the synthesis of the ynones. In pathway A, the BCl_2 nucleophile coordinates with the acyl chloride (**1-68**), activating the carbonyl for nucleophilic attack by the alkynl moiety. In pathway B, alkynyl transfer occurs to an oxocarbenium intermediate (**1-71**) which is formed by intramolecular chloride transfer of coordination complex **1-70**. Lastly, a Friedel-Crafts alkylation type mechanism (**1-72**) can occur to give ynone, as shown in pathway C. It should be noted that pathway B and C are unlikely the route due to the highly unfavourable oxygen species proposed in the mechanism.



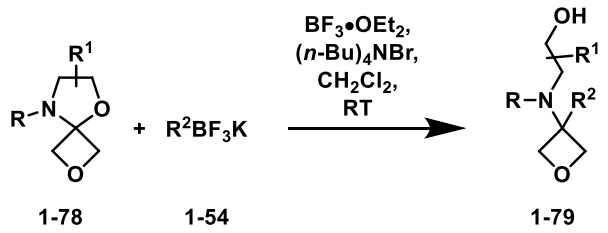
Scheme 1-16 Bolshan group's synthesis of ynones from organotrifluoroborate salts

Also in 2014, Roscales and Csáky found that trifluoroborate salts **1-54** could be used in the ring opening of epoxide **1-74** to form alcohol **1-75** (Scheme 1-17).[37] Surprisingly, unlike the previous examples listed above, boron Lewis acids were not very effective in the transformation, and it was found that TFAA had the highest yields in acting as the fluoride acceptor to form the BF_2 nucleophile, and promoting epoxide opening. Various epoxides reacted with aryl and alkenyl trifluoroborate salts to afford alcohol **1-75** in good yields (52-83%), and as single diastereomers. To explain the diastereoselectivity of the reaction, they proposed that the reaction proceeds similarly to a substitution nucleophilic internal (S_Ni) mechanism, whereby coordination of the BF_2 nucleophile to the epoxide (**1-76**) would allow for stereospecific addition of the R group to the polarized *C-O* bond.



Scheme 1-17 Csáky group's ring opening of epoxides with trifluoroborate salts

In 2015, Brady and Carreira, wanting to expand the work of oxetanes as useful synthetic intermediates,[38] found that potassium organotrifluoroborates were effective in the nucleophilic ring opening of *N*,*O*-acetals (Scheme 1-18).[39] Substituted *N*,*O*-acetals underwent addition reactions with alkynyl, allyl, allenyl, and vinyl potassium trifluoroborates in moderate yields.

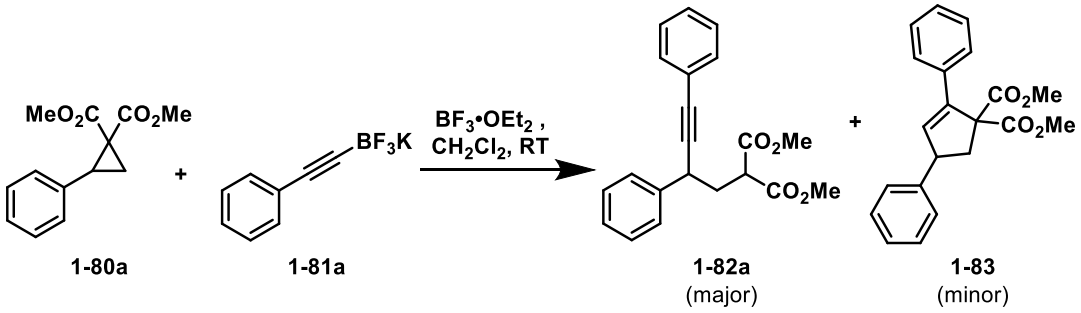


Scheme 1-18 Carreira group's addition of trifluoroborate salts to oxetanyl *N*,*O*-acetals

1.3.3 Results and discussion

1.3.3.1 Discovery of a novel nucleophilic ring opening of DA cyclopropanes by RBF_3K

With hopes of developing a new methodology for DA cyclopropanes, nucleophilic ring opening of cyclopropane **1-80a** by potassium 2-phenyl-1-ethynyltrifluoroborate (**1-81a**) was pursued following similar conditions to the reports presented above. Gratifyingly, the initial test reaction proceeded cleanly (based on loss of starting material by TLC); however, upon further analysis (by ^{1}H NMR spectroscopy) it was found that two inseparable compounds were isolated. It was speculated that acyclic **1-82a**, and cyclic **1-83** products were obtained (Scheme 1-19).

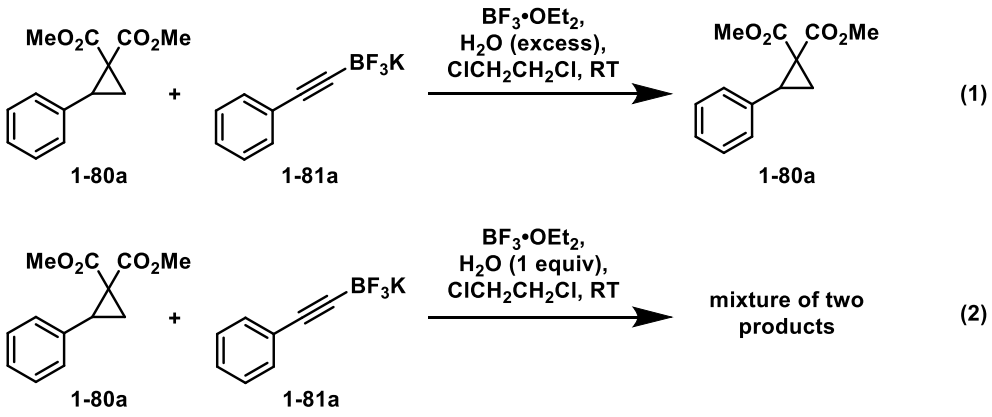


Scheme 1-19 Assumed products of the reaction

While the major product was initially assumed to be acyclic **1-82a**, it soon became apparent that the ^{1}H NMR spectral data did not support the structure; 20 protons were expected for the product, but only 19 were accounted for. Another puzzling piece of information was a single peak observed for both methoxy groups. Since the esters would be diastereotopic, it would be expected that the methoxy groups would not have the same chemical shift (though this phenomenon could be explained by coincidental chemical shifts, the result would be apparent when the structure was solved). Efforts were then taken to find conditions that favoured one product over the mixture, in order to obtain full characterization data. The cyclic product was never isolated or fully characterized, since it was always obtained in relatively minor amounts, but evidence towards **1-83** was due to the presence of a signal in the ^{1}H NMR spectrum as a doublet at 6.37 ppm (J = 2.3 Hz).

1.3.3.2 Efforts towards obtaining a single product

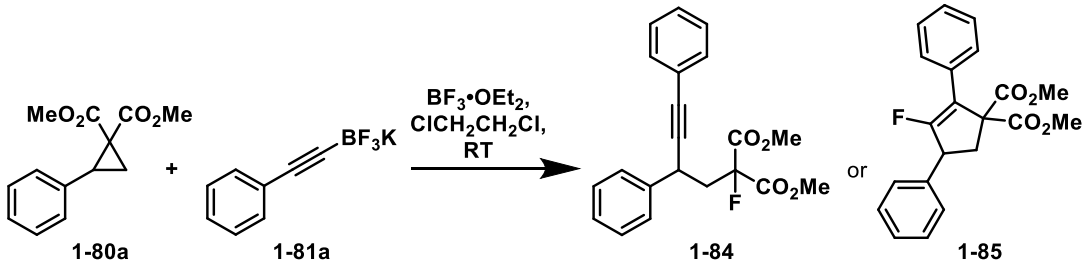
Taking into consideration the proposed mechanism of potassium trifluoroborates behaving as nucleophiles from the literature, varying equivalents of BF_3•OEt_2 and potassium trifluoroborate **1-81a** were used in the optimization, as well as varying temperatures of the solvents DCM, or DCE. DCE was quickly favoured over DCM as the cyclopropane was consumed faster, all other variables equal. Despite many attempts, both products were always formed in an inconsistent ratio, with the alleged cyclized product always being the minor component. NMR experiments were also conducted to determine the ratio of products formed throughout the reaction, but were inconclusive as there was no obvious pattern to the results. It wasn't until a new bottle of DCE was purchased that the cyclized product was no longer formed. With this insight, it was speculated that the reaction is fairly sensitive to water so an experiment was done to confirm this hypothesis. A reflux still for DCE (over calcium hydride) was assembled, and with dry DCE at hand, the same results were obtained as the new DCE bottle. Two water spike experiments were now done to confirm whether or not water was a factor (Scheme 1-20): one reaction involved using excess water (entry 1), while the other reaction used one equivalent of water (entry 2). When excess water was used in the reaction, only unreacted cyclopropane **1-80a** was obtained. When one equivalent of water was added to the reaction, the same mixture of two compounds previously seen were formed (Scheme 1-19), again in a relatively minor ratio for the cyclic product (<10%). Full characterization of the product, followed by optimization studies could now begin.



Scheme 1-20 Water spike experiments

1.3.3.3 Characterization of unknown product

To account for the missing proton, it was speculated that perhaps a fluorine was added to the molecule, which was then confirmed by ^{19}F NMR spectrum, although we were slightly puzzled as to why there were two singlets (See Appendix I). An IR spectrum was also obtained to ensure that an alkyne was there, but there was no indication of a signal. The lack of alkyne signal could be interpreted in two ways: 1) the malonyl anion cyclized onto the alkyne to form a cyclic compound, or 2) since IR spectroscopy relies on changes in dipole moments, internal alkynes may not show a signal as they are pseudo symmetrical. Based on these results two structures (**1-84** and **1-85**) were proposed as shown in Scheme 1-21.



Scheme 1-21 Revised structural assembly of the unknown compound

Two dimensional NMR data were obtained (^{1}H-^{1}H gCOSY, ^{1}H-^{13}C gHSQC, ^{1}H-^{13}C gHMBCAD) in order to corroborate either structure, but the data did not provide enough evidence to either structure. Also, if indeed there was a fluorine attached to a carbon, we would have expected to see C-F coupling in the ^{13}C NMR spectrum; however, the only C-F coupling found in the ^{13}C NMR spectrum was for the carbonyl carbon which did not really support our revised structures. Due to these results, it was proposed that perhaps boron may also be involved in the product. An ^{11}B NMR spectrum confirmed the presence of boron on the molecule; however, the structure still eluded us.

At this point it was decided that single crystal x-ray diffraction spectroscopy data would be useful as the NMR spectroscopy data was too perplexing. After some time, suitable crystals were grown for an X-ray structure and a surprising structure was elucidated (Figure 1-1); the carbonyls of the ester coordinated to form an aromatic like malonyl-BF_2

complex. The two singlets in the ^{19}F NMR could now be rationalized by B-F splitting. Boron is composed of two NMR active isotopes in a 1:4 ratios (^{10}B to ^{11}B) and each of these isotopes were coupling with fluorine to give a signal. The isotope difference is shown in the integration and intensity of the signals in the ^{11}B NMR spectrum (See Appendix I). Although a quartet would be expected for the ^{11}B-^{19}F coupling, diketone-BF_2 complexes exhibit similar spectral properties, due to the fast relaxation time of boron in this system.[40]

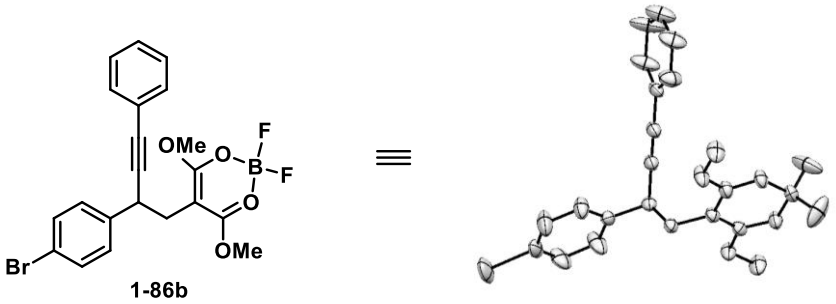
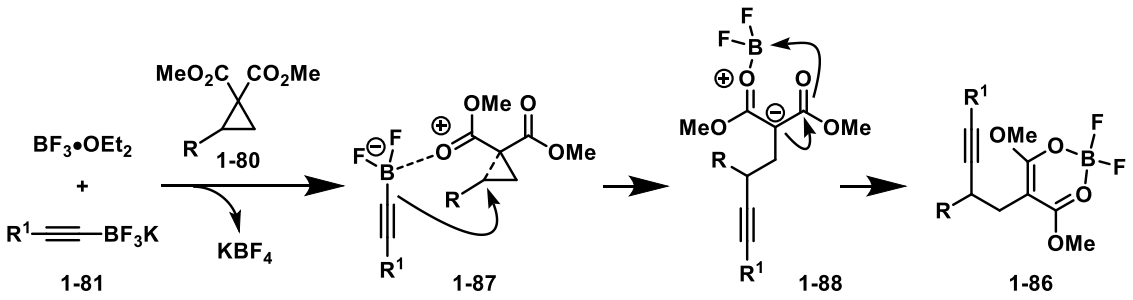


Figure 1-1 Oak ridge thermal ellipsoid plot (ORTEP) representation of malonyl-BF_2 complex

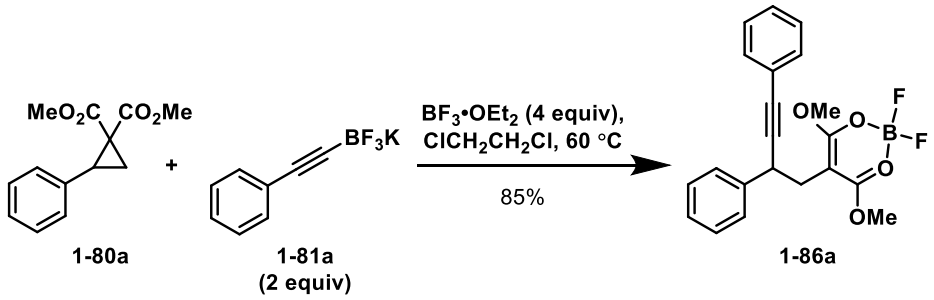
The malonyl-BF_2 complex could be formed as shown in Scheme 1-22. Organotrifluoroborate **1-81** reacts with BF_3•OEt_2 to form the BF_2 nucleophile. Coordination to one of the carbonyls by the BF_2 can allow for nucleophilic addition of the alkynyl moiety (**1-87**). It should be noted that BF_3•OEt_2 could also be contributing to the activation of the cyclopropane. After alkynyl addition, enolization of the malonyl anion (**1-86**) can trap the BF_2 to form malonyl-BF_2 complex **1-86**.



Scheme 1-22 Proposed mechanism to access malonyl-BF_2 complex

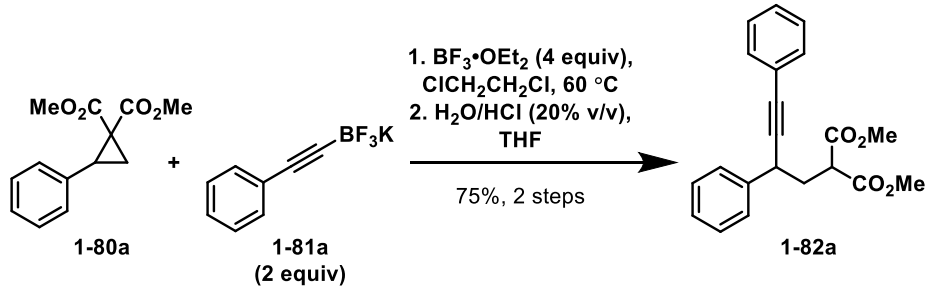
1.3.3.4 Optimization of BF_2-complex

A short optimization of the reaction was done after the characterization of the compound. Initially, a 1:4:8 cyclopropane **1-80a** to trifluoroborate salt **1-81a** to BF_3•OEt_2 at room temperature for 24 hours was used, but equivalents could be lowered to 1:2:4 without a loss in yield (85%). As the reaction did not always go to completion after 24 hours, instead the reaction could be heated to 60 °C for 12 hours for full conversion of the starting material, again without a loss in yield (Scheme 1-23). To determine if BF_3•OEt_2 was required, typical Lewis acids involved in nucleophilic ring opening of cyclopropanes were used: neither $Yb(OTf)_3$, Et_2AlCl, or $TiCl_4$, or removal of Lewis acid were successful in the transformation. While $Yb(OTf)_3$ resulted in no reaction, Et_2AlCl and $TiCl_4$ resulted in decomposition of starting material.



Scheme 1-23 Optimized conditions for formation of malonyl-BF_2 complex

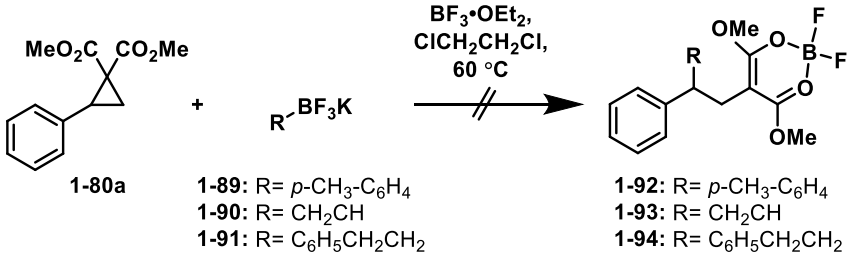
It was then shown that the BF_2 complex can be hydrolyzed efficiently with aqueous HCl in THF overnight to give the originally proposed malonate **1-82a** (Scheme 1-24).



Scheme 1-24 Acid hydrolysis of complex to form malonates

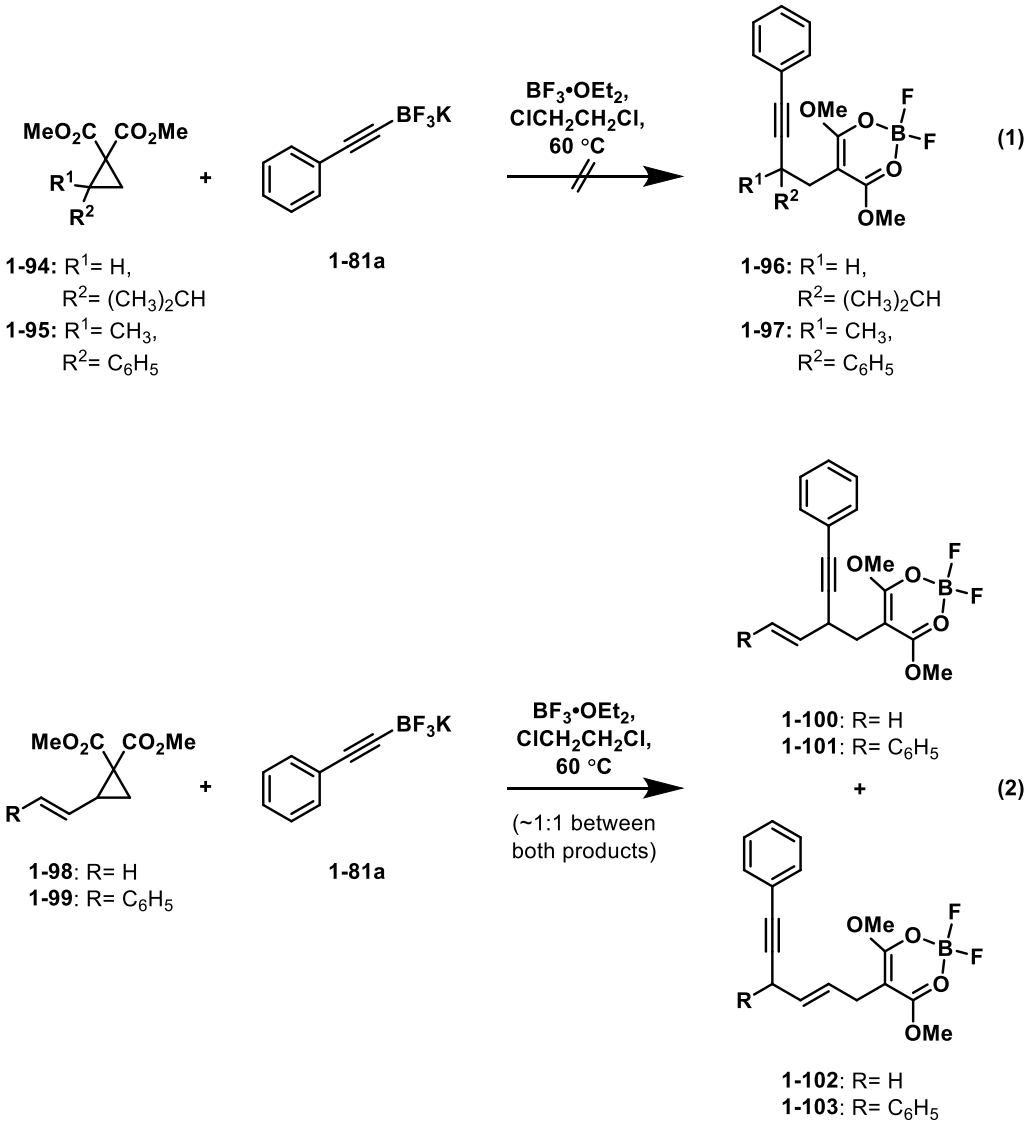
1.3.3.5 Synthesis of malonates

Using the optimized conditions, the scope of organotrifluroborate salts were explored. Aryl (**1-89**), vinyl (**1-90**), and alkyl (**1-91**) trifluoroborate salts were used; however, none of these were able to open the cyclopropane (Scheme 1-25) and only decomposition of the starting material was recovered.



Scheme 1-25 Trifluroborate salt scope to form malonyl-BF_2 complex

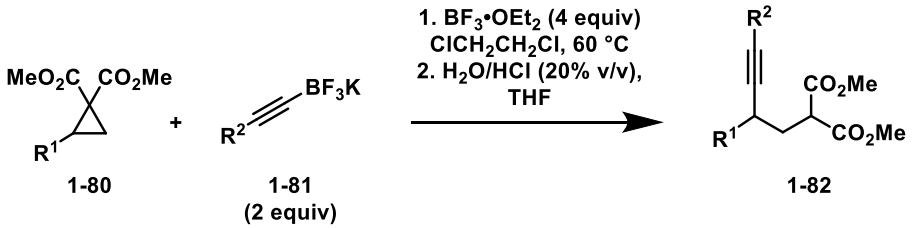
A substrate scope for cyclopropanes was then explored, each of them using potassium 2-phenyl-1-ethynyltrifluoroborate as the RBF_3K for the reaction. With isobutyl cyclopropane **1-94** or di-substituted cyclopropane **1-95** (Scheme 1-26, entry 1), again the desired product was not obtained and only decomposition of the starting material was recovered. When vinyl (**1-98**) or styrenyl (**1-99**) cyclopropane were used (Scheme 1-26, entry 2), ring opening of cyclopropane occurred; however, this was always found in an approximate 1:1 mixture with the S_N2' product. Efforts to favour one product over the other were unsuccessful.



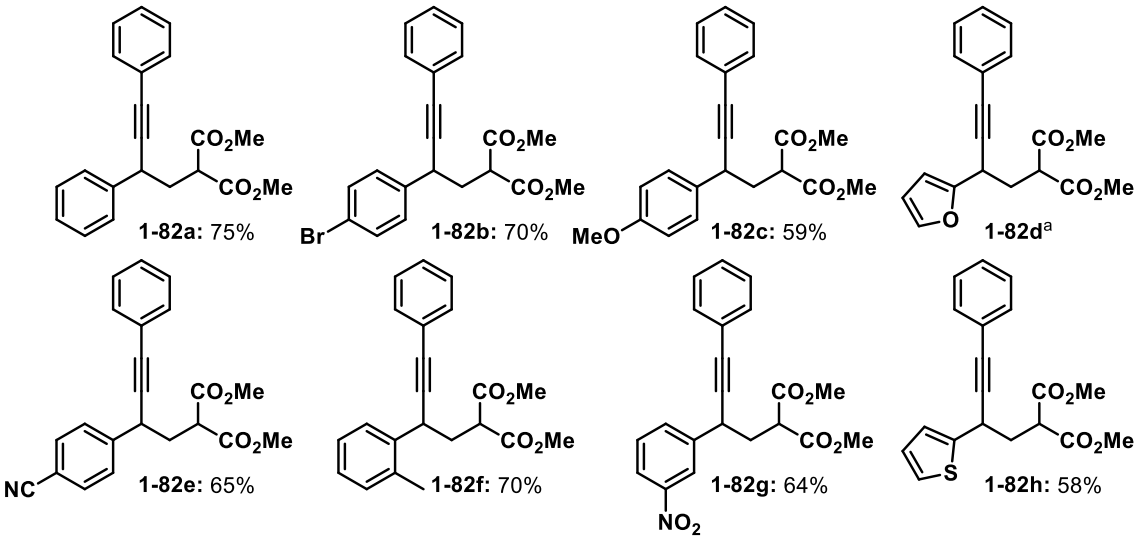
Scheme 1-26 Cyclopropane scope to form malonyl-BF_2 complex

Based on the results discussed above, it was decided that the scope would involve potassium 2-phenyl-1-ethynyltrifluoroborate (**1-81a**) reacting with various aryl cyclopropanes (**1-80**), and dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1-80a**) reacting with various alkynyl potassium trifluoroborate salts (**1-81**). The decision to use both of these compounds was due to their availability of starting material and ease of synthesis.

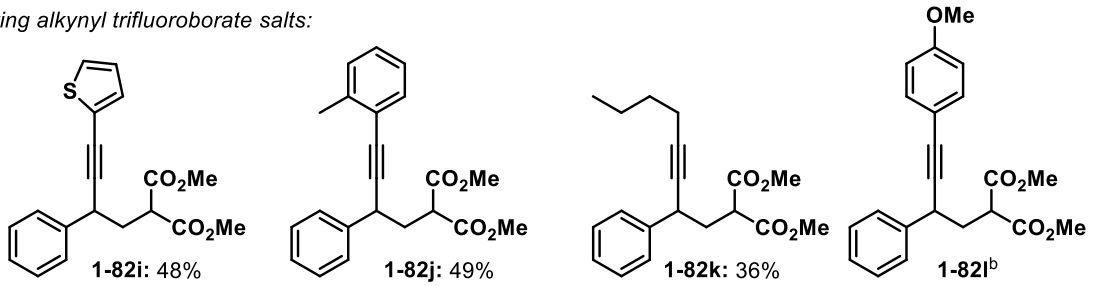
Table 1-1 Substrate scopes of aryl cyclopropanes with alkynyl trifluoroborate salts



varying cyclopropanes:



varying alkynyl trifluoroborate salts:



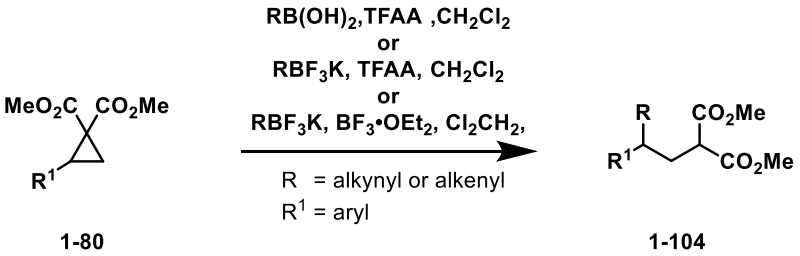
[a]decomposition; [b]inseparable mixture between product and decomposition of starting material

The scope of the reaction is displayed in Table 1-1. The reaction was tolerant of various aryl substituted cyclopropanes and malonates could be made with EDG (**1-82c**) or EWG (**1-82e**) at that position. Heteroaryl substituted cyclopropane worked, as in the case of thiophenyl (**1-82i**); however, the reaction did not work when a furanyl cyclopropane was used (**1-82d**). The decomposition of material from the furanyl cyclopropane could possibly be contributed to side reactions that may occur if the BF_2 nucleophile, or Lewis acid, coordinated to the furanyl oxygen (although no analysis of the decomposition

products was done to confirm this). In terms of the alkynyl organotrifluoroborate salt, heteroaryl, aryl, and alkyl substituents were tolerated. When the RBF_3K required to make malonate **1-82l** was attempted, an inseparable mixture between product and decomposition was obtained. This may be contributed to the nucleophile being more reactive due to the EDG effects of the methoxy group, thus leading to more side reactions.

1.3.3.6 Csákÿ's ring opening of DA cyclopropanes by RBF_3K

In 2016, shortly after the results in Section 1.3 were finished and ready for publication, similar developments were published by Ortega and Csákÿ. They were able to open DA cyclopropanes by boronic acids or potassium organotrifluoroborates, under TFAA or BF_3•OEt_2 mediated conditions (Scheme 1-27).[41]



Scheme 1-27 Csákÿ group's ring opening of DA cyclopropanes by RBF_3K or $RB(OH)_2$

Despite being very similar to the work discussed above, they never isolated the malonyl-BF_2 complex. Differences between the two procedures were: 1) they used their cyclopropane, RBF_3K, and BF_3•OEt_2 in a 1:2:2 ratio (0.5 equivalents of TFAA was used), while the Lewis acid was always in excess in our studies; 2) their solvent was DCM, while we used DCE (DCE and DCM gave us the same results during optimization, but DCE was favoured due to faster reaction times); 3) they added their Lewis acid to a solution of RBF_3K and cyclopropane, while we added the cyclopropane to a solution of Lewis acid and RBF_3K; 4) and lastly, a basic work up was done prior to purification of their compounds while only an aqueous work up was done for the malonyl-BF_2 complex (when a base wash was performed on the malonyl-BF_2 complex, only slight decomplexation occurred). Despite these differences, they were able to open DA

cyclopropanes with alkynyl, styrenyl, vinyl, and allyl trifluoroborate salts in 49-81% yield (only alkynyl trifluoroborate salts were only compatible with the results discussed above).

Ortega and Csákÿ's results raise questions to the mechanism and reactivity of DA cyclopropanes towards RBF_3K. It is apparent that the only real differences between the two procedures are equivalents of BF_3•OEt_2 and order of addition. As it is clear that excess BF_3•OEt_2 results in a malonyl-BF_2 complex, perhaps there is more to the Lewis acid's role than portrayed in Scheme 1-22, and further investigation would be required to determine where the BF_2 source is coming from. The order of addition could explain why Ortega and Csákÿ were able to perform their reaction with alkenyl trifluoroborates, while we were unable to obtain the product. In our procedure, we forming the nucleophilic BF_2 species prior to cyclopropane addition. Since alkenyl trifluoroborates are more reactive than alkynyl trifluoroborates (due to less stabilization), it is possible that my nucleophile had decomposed before the cyclopropane was added. Changing the sequence of addition for my procedure could result in ring opening of cyclopropanes by alkenyl trifluoroborates to form malonyl-BF_2 complexes.

Lastly, although there is only one overlapping example (**1**-**82c**), there is a significant yield increase from our results to Ortega and Csákÿ (59-81%). Since there is a lower yield with our conditions, the Lewis acid could also be decomposing the cyclopropane, in addition to contributing to the malonyl-BF_2 complex.

1.3.4 Conclusions

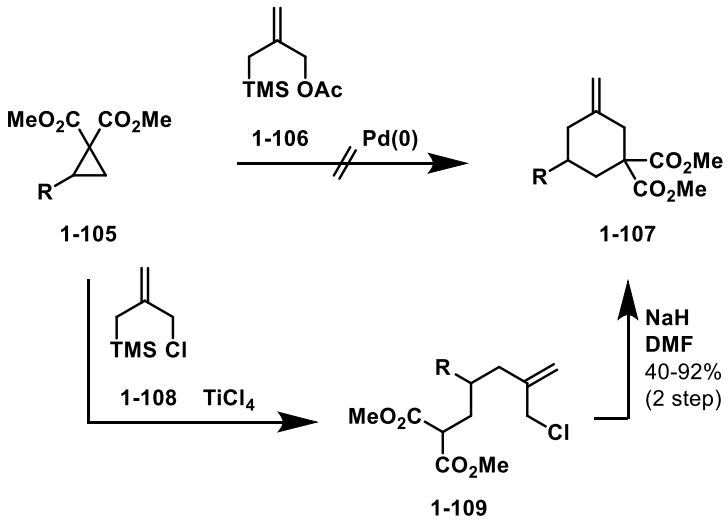
A novel method to the acyclic opening of donor-acceptor cyclopropanes has been discovered using alkynyl trifluoroborate salts under BF_3•OEt_2 mediated conditions. Products were obtained as malonyl-BF_2 complexes and then hydrolyzed with HCl to obtain substituted malonates in 36-75% yield in two steps. Unfortunately, just as the project came to an end, similar results were obtained by Ortega and Csákÿ. They were able to use organotrifluoroborate salts (alkynyl, alkenyl, allyl), but they were unable to access malonyl-BF_2 complexes. A major factor to the difference in products could be because an excess amount of Lewis acid was used in our results, while Lewis acid was used in a 1:1 ratio with the organotrifluroborate salt in Ortega and Csákÿ's results. While this could be contributing to the formation of the malonyl-BF2 complex, it could also be contributing to decomposition of the cyclopropane, and thus lower yields (as shown in the yield difference between **1**-**82c**). Although there were no other overlapping products, an ~40% yield difference was found between product **1**-**82k** and when Ortega and Csákÿ used the same trifluoroborate salt but used a different aryl cyclopropane (dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate), which could also be explained by the excess Lewis acid.

1.4 Annulation reactions with DA cyclopropanes

1.4.1 Formation of carbocycles

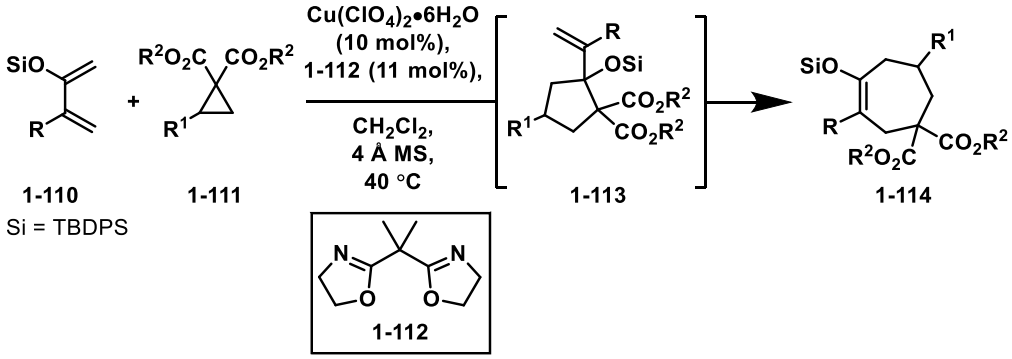
As shown in Scheme 1-2, cyclopropanes can undergo ring opening with nucleophiles to form acyclic products, or can form annulation products in the presence of a nucleophile and electrophile tethered together. This section will give a brief review towards annulation reactions with DA cyclopropanes.

In 2009, Sapeta and Kerr – inspired by Trost and Chan's work[42] on [3+2] cycloadditions of Pd-trimethylenemethane (TMM) complexes with olefins – wanted to apply the concept to a formal [3+3] cycloaddition with cyclopropane **1-105** to form *exo*-methylenecyclohexanes **1-107**.[43] Initially, they attempted using a TMM (**1-106**) precursor under Pd catalysis; however, this did not afford the desired [3+3] annulated product and the reaction needed to be slightly modified. It was then found that $TiCl_4$ would react with **1-108** and cyclopropane **1-105** to give ring open product **1-109**. Despite trying numerous additives, the cyclization was unable to occur as a one-pot procedure. Instead, a two-step process was required, and NaH in DMF was successful in completing the formal annulation. The reaction was viable with the use of aryl, heteroaryl, spiro, and vinyl substituted cyclopropanes, and in total nine examples were made with a two step yield of 40-92%.



Scheme 1-28 Kerr group's synthesis of cyclohexanes from cyclopropanes

In 2015 the Tang group showed that diene **1-110** can undergo an annulation with cyclopropane **1-111** to afford cycloheptanes **1-114** (Scheme 1-29).[44] During their optimization they found that cyclopentane **1-113** was a competing product with their desired cycloheptane product. Increasing the bulk of the ester allowed for cycloheptane to be formed almost exclusively (adamantly esters were ideal, but benzyl esters could also be used). Through their optimization, they also found that 10 mol% ligand **1-112** and $Cu(SbF_6)_2$ were the best conditions to facilitate the transformation. The reaction was tolerant of aryl, heteroaryl, and styrenyl cyclopropanes (68-96% yield), although vinyl cyclopropane had a low 52% yield. In an effort to further understand the reaction mechanism, they monitored the reaction by ^{1}H NMR spectroscopy and they found that cyclopentane **1-113** is actually formed first, and over time, the cyclopentane rearranges to the cycloheptane product (**1-114**). Thus, they concluded that cyclopentane is actually the kinetic product and cycloheptane is the thermodynamic product.

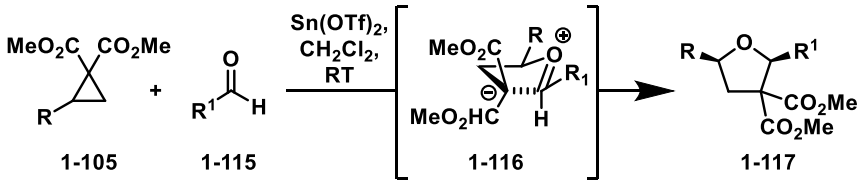


Scheme 1-29 Tang group's synthesis of cycloheptanes from cyclopropanes

1.4.2 Formation of heterocycles

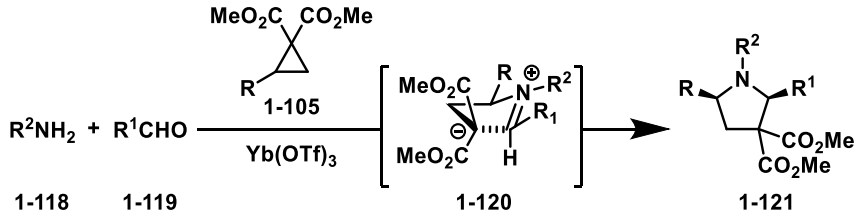
Heterocycles are molecules of interest for organic chemists as they are found in many natural products/drug targets. Developing methods to allow ease of access to these class of molecules is an important undertaking. The Johnson group envisioned that they could access tetrahydrofuran **1-117** by the cycloaddition of donor-acceptor cyclopropane **1-105** with aldehydes **1-115** (Scheme 1-30).[45] Initial attempts to promote a cyclization with $TiCl_4$, $AlCl_3$, $Mg(OTf)_2$, or $La(OTf)_3$ resulted in decomposition or no reactivity. When $Cu(OTf)_2$, $Sc(OTf)_3$, or $SnCl_4$ were used they were able to obtain tetrahydrofurans in

59:1, 3.1:1, and 31:1 diastereomeric ratios (*cis*:*trans*) respectively. It was then found that $Sn(OTf)_2$ was able to give >100:1 *cis*:*trans* selectivity, and was therefore the catalyst of choice for their scope. The reaction was susceptible to electron-rich, electron-neutral, electron poor, heterocyclic, and *α*,*β*-unsaturated aldehydes (89-100% yield, >17:1 *dr*). To account for the *cis* selectivity in the reaction, Johnson proposed that the reaction proceeds through transition state **1-116**, whereby after nucleophilic attack of the aldehyde to the cyclopropane, the substituents are placed pseudoequatorial to minimize unfavourable interactions.



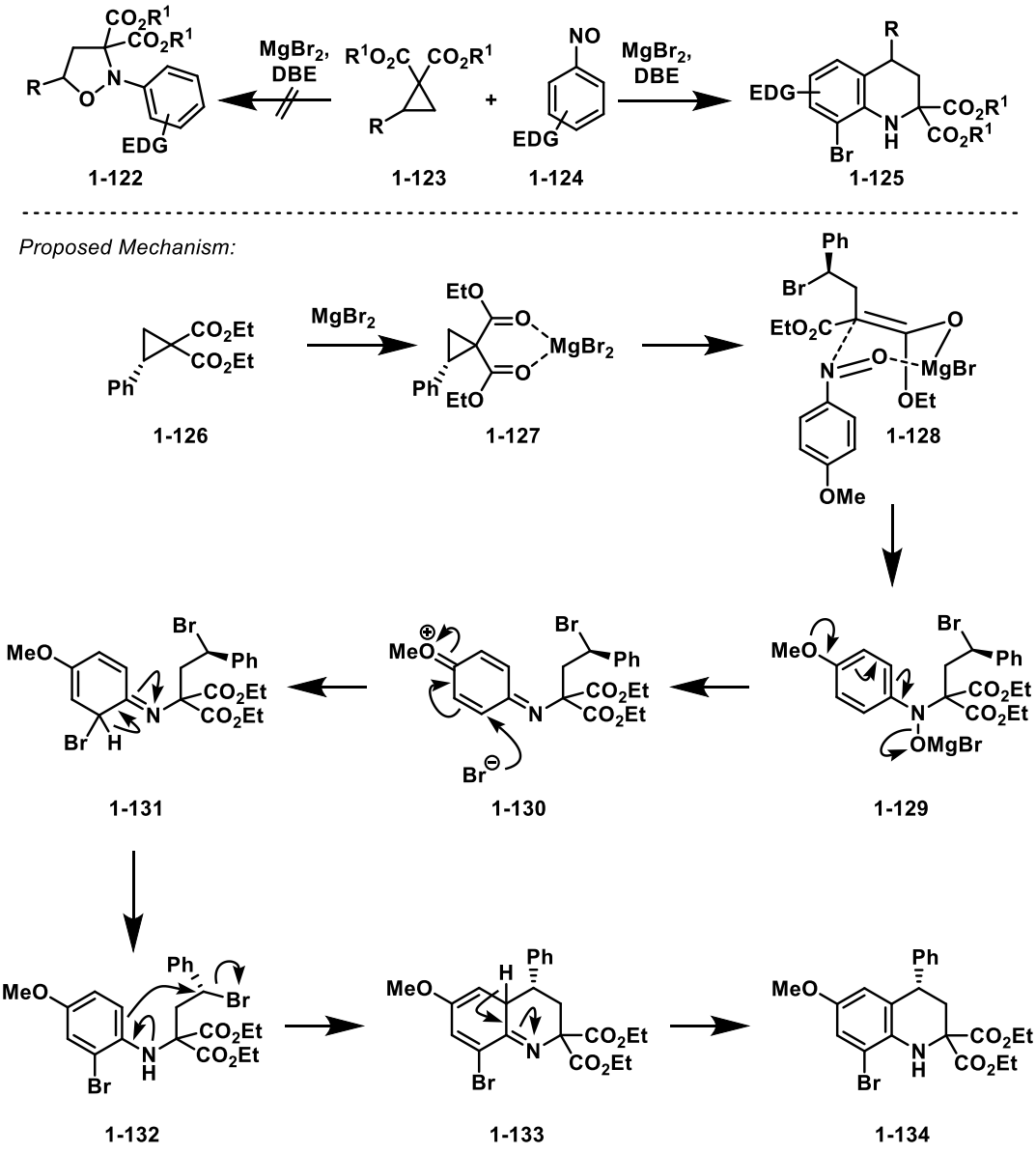
Scheme 1-30 Johnson group's synthesis of tetrahydrofurans from cyclopropanes

In a similar manner to Johnson's works,[45] Carson and Kerr showed that they can form pyrrolidine **1-121** by the three-component reaction of amine **1-118**, aldehyde **1-119**, and cyclopropane **1-105** (Scheme 1-31).[46] They found that $Yb(OTf)_3$ was the best Lewis acid, and it was imperative that the catalyst be added after the formation of the aldimine, since both amines[10] and aldehydes[45] have been shown to open cyclopropanes. For the scope, they showed that primary alkylamines and primary anilines were tolerated in the reaction; however, when modifying the aldehydes, only aryl and heteroaryl aldehydes were tolerated (aliphatic aldehydes gave poor results). The *cis* diastereomer was favoured in all cases, and is explained by intermediate **1-120**, where the substituents would be placed pseudoequatorial to avoid steric interactions.



Scheme 1-31 Kerr group's synthesis of pyrrolidines from cyclopropanes

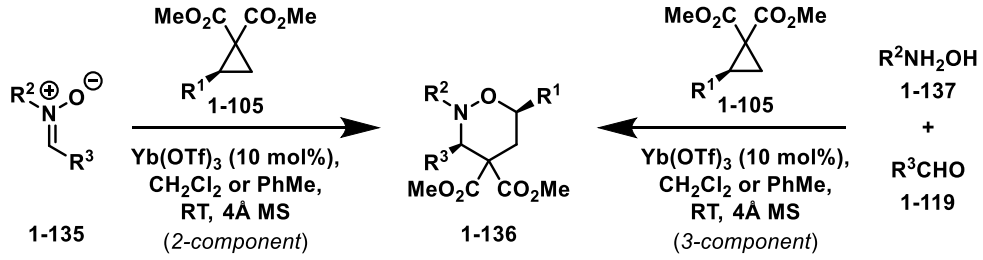
Following up on their 2014 publication of formal [2+3] formal addition with nitroarenes and cyclopropanes to afford isoxazolidines,[47] Das, *et al.* found that the use of electron rich nitrosoarene **1-124** did not react to form isoxazolidine **1-122**, but instead formed *C*-8-brominated tetrahydroquinoline **1-125** (Scheme 1-32).[48] While this reaction was able to proceed with aryl and alkenyl substituted cyclopropanes in yields ranging from 41-63%, perhaps more interesting is the mechanism to obtain tetrahydroquinolines. When an enantioenriched cyclopropane was put through their reaction conditions, they found that the annulation occurred with retention at the stereogenic center (absolute configuration confirmed by X-ray analysis). To account for the stereochemistry they proposed the following mechanism. Cyclopropane **1-126** is activated by $MgBr_2$ (**1-127**) which is then stereoselectively opened by a bromide anion, generating an enolate. The enolate then reacts with nitrosobenzene to form the six membered ring transition state (**1-128**), which then gives magnesiated hydroxylamine **1-129**.[49] Due to the presence of the methoxy group, *N-O* bond cleavage can occur (**1-129**) to form an iminoquinone-type species (**1-130**), which is attacked by a bromide anion. Tautomerization (**1-131**) followed by stereoselective intramolecular Friedel-Crafts type alkylation (**1-132**) gives intermediate **1-133**. A final tautomerization results in tetrahydroquinoline **1-134.**



Scheme 1-32 Studer group's synthesis of tetrahydroquinolines

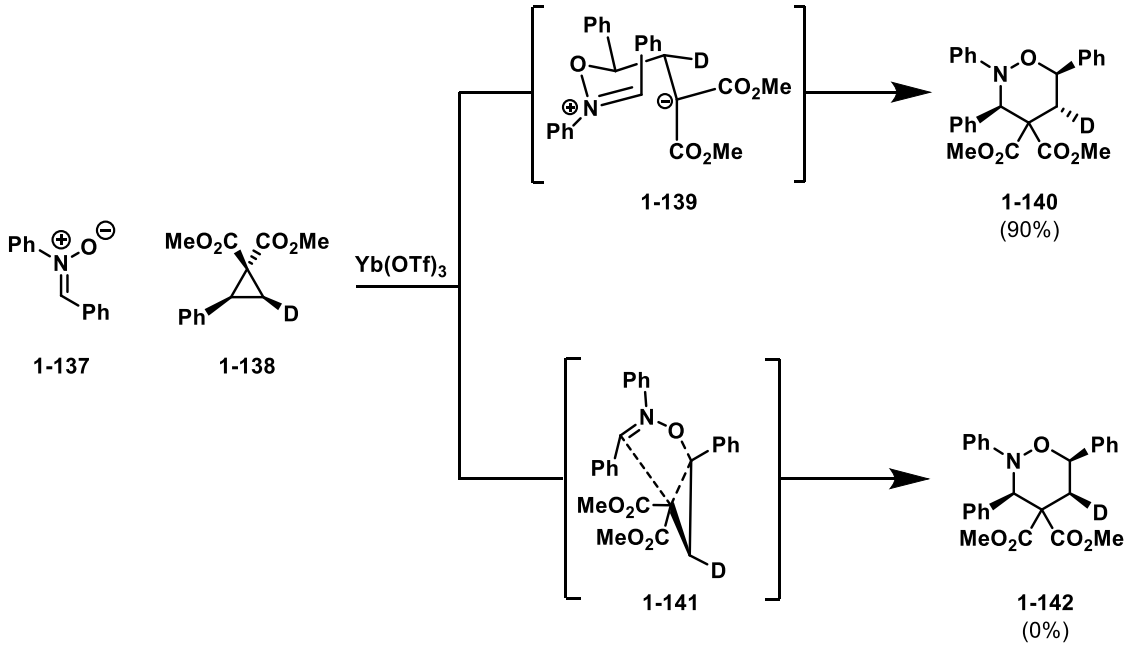
1.4.3 Formation of tetrahydro-1,2-oxazines

Perhaps one of the more important discoveries of donor-acceptor cyclopropane reactivity comes from Young and Kerr in 2003. They were able to form tetrahydro-1,2-oxazines from the formal [3+3] cycloaddition of nitrones (**1-135**) and donor-acceptor cyclopropanes (Scheme 1-33).[50] The reaction worked optimally using $Yb(OTf)_3$, and nitrones bearing *C*-aryl, and *N*-aryl or *N*-alkyl. Cyclopropanes bearing phenyl, styrenyl, or vinyl substituents were also tolerated and yields of tetrahydro-1,2-oxazines were obtained between 50-96%. Shortly after their original publication, Young and Kerr expanded on the methodology when they showed that a three-component process can occur to access tetrahydro-1,2-oxazines.[51] Aldehyde **1-119** and hydroxylamine **1-137** reacted to form the nitrone in situ, prior to the addition of the cyclopropane. The procedure was favourable as nitrones did not need to be made in advance.



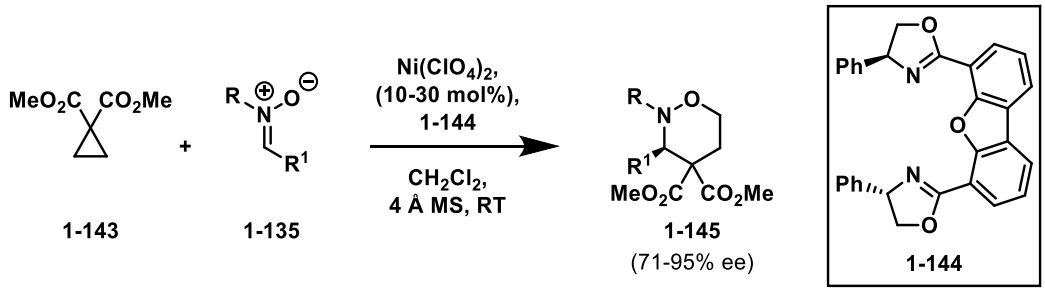
Scheme 1-33 Kerr group's synthesis of tetrahydro-1,2-oxazines

While both methodologies gave a *cis* relationship between *C*-3 and *C*-6 of tetrahydro-1,2-oxazine, they were uncertain of the mechanistic pathway. They speculated that it could occur through either a stepwise mechanism or concerted mechanism. It wasn't until 2007 that studies were undertaken to explore the mechanism.[52] To this end, 2,3-disubstituted-1,1-cyclopropanediester **1-138** was synthesized to undergo ring opening by nitrone **1-137**. In a cycloaddition mechanism, the relationship between the two substituents on the cyclopropane would be preserved in the transition state (Scheme 1-34, **1-141**). This would not be the case in a step-wise mechanism due to an inversion at *C*-5 when the malonyl anion undergoes Mannich-type ring closure (**1-139**). Since only product **1-140** was obtained, and not **1-142**, it was concluded that a step-wise mechanism had to be occurring.



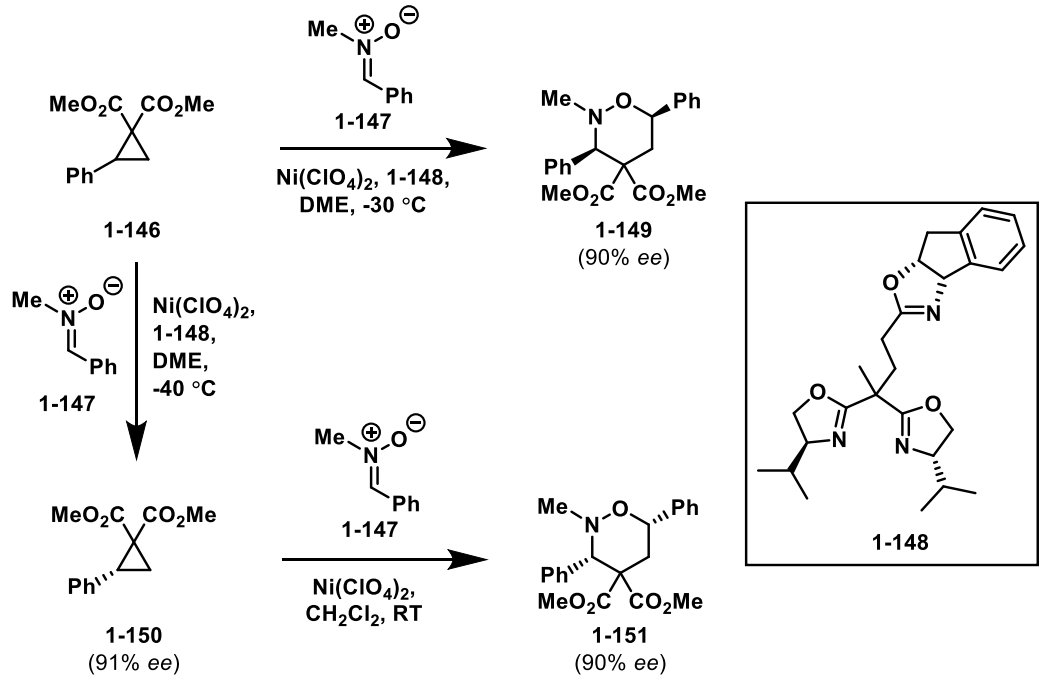
Scheme 1-34 Mechanistic studies for the synthesis of tetrahydro-1,2-oxazines

In 2005, the Sibi group showed how tetrahyrdo-1,2-oxazines could be synthesized enantioselectively by using $Ni(ClO_4)_2$ and ligand **1-144**.[53] The methodology was successful in producing high *ee* (71-95%) tetrahydro,1-2,oxazines (**1-145**) when dimethyl cyclopropane-1,1-dicarboxylate (**1-143**) was utilized. Unfortunately, the methodology was not very useful for substituted cyclopropanes, as the diastereoselectivity was quite low. Despite poor diastereoselectivity, the *ee*'s for tetrahydro-1,2-oxazines derived from substituted cyclopropanes was still high.



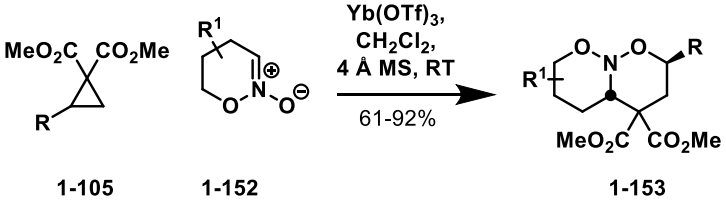
Scheme 1-35 Sibi group's enantioselective synthesis of tetrahydro-1,2-oxazines from dimethyl cyclopropane-1,1-dicarboxylate

It wasn't until 2007 that a protocol was developed to access tetrahydro-1,2-oxazines from substituted cyclopropanes and nitrones with high *ee*, and *dr*, by the Tang group.[54] Their optimized conditions involved using trisoxazoline derived ligand **1-148**, and $Ni(ClO_4)_2$. During their optimization they also found that the ester groups of the cyclopropane had an effect on *ee*: changing the methyl to ethyl esters raised the *ee* from 90 to 95%. The scope involved phenyl, styrenyl, and vinyl substituted cyclopropanes reacting with *N*-methy, and *C*-aryl, *C*-heteroaryl, or *C*-styrenyl nitrones. When racemic dimethyl-2-phenylcyclopropane-1,1-dicarbocylate was used in excess, it was discovered that the unreacted cyclopropane was enantioenriched (*R* in excess). These results prompted them to do kinetic resolution studies, and they found that under their conditions, various aryl substituted cyclopropanes were resolved with high *ee*. Due to this insight, they could form both enantiomers of tetrahydro-1,2-oxazine, based on the sequence of the reaction (Scheme 1-36). In the first pathway, racemic cyclopropane **1-146** is reacted under their normal conditions to obtain (+)-tetrahydro-1,2-oxazine **1-149**. To obtain the enantiomer, excess racemic cyclopropane **1-146** is reacted with nitrone **1-147** such that unreacted *R*-substituted cyclopropane **1-150** can be isolated as the undesired *S*-cyclopropane reacts to form tetrahydro-1,2-oxazine **1-149**. Cyclopropane **1-150** can then be taken up under their standard conditions again to obtain (-)-tetrahydro-1,2-oxazine **1-151**.



Scheme 1-36 Tang group's enantio- and diastereoselective synthesis of tetrahydro-1,2-oxazines from substituted cyclopropanes

More recently, the Ioffe group developed a cyclic nitrone that reacts with donor-acceptor cyclopropanes to access a previously unknown heterobicycle (**1-153**, Scheme 1-37).[55] Using cyclic nitronate **1-152** with cyclopropane **1-105** and typical $Yb(OTf)_3$ conditions allowed them to access a variety of bicycles in yields ranging from 61-92%.

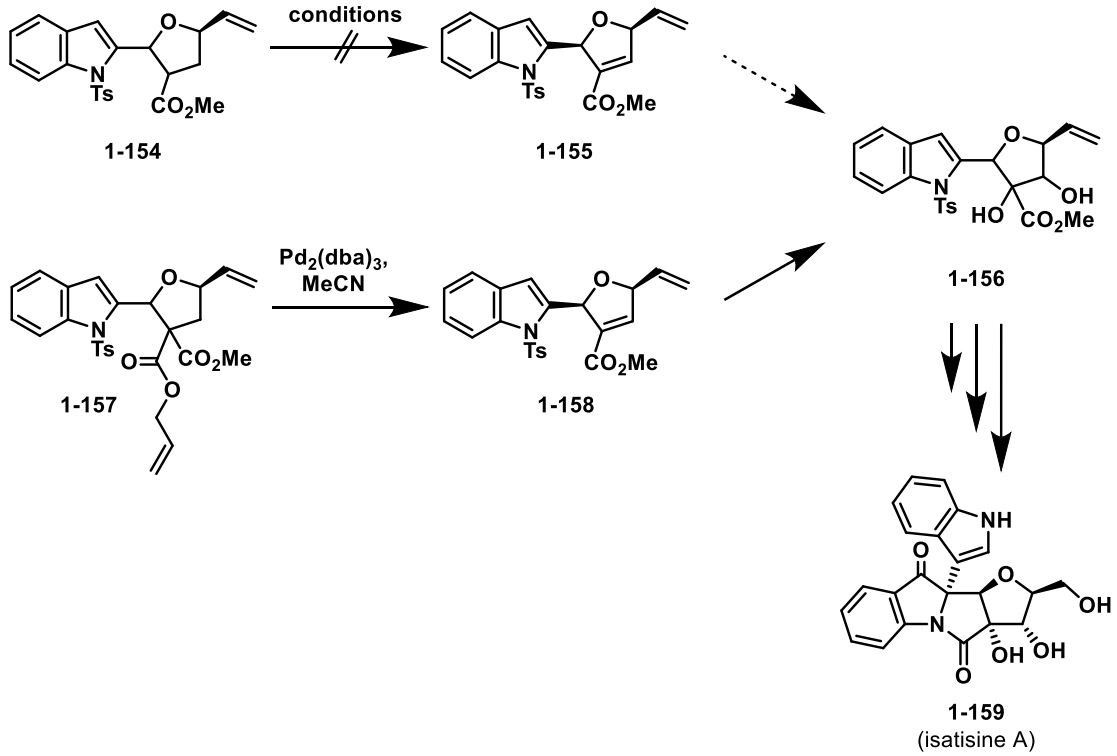


Scheme 1-37 Ioffe group's synthesis of a new type of bicyclic nitrosoacetal from cyclopropanes

1.4.4 Functionalization of tetrahydro-1,2-oxazines

1.4.4.1 Total synthesis of isatisine A

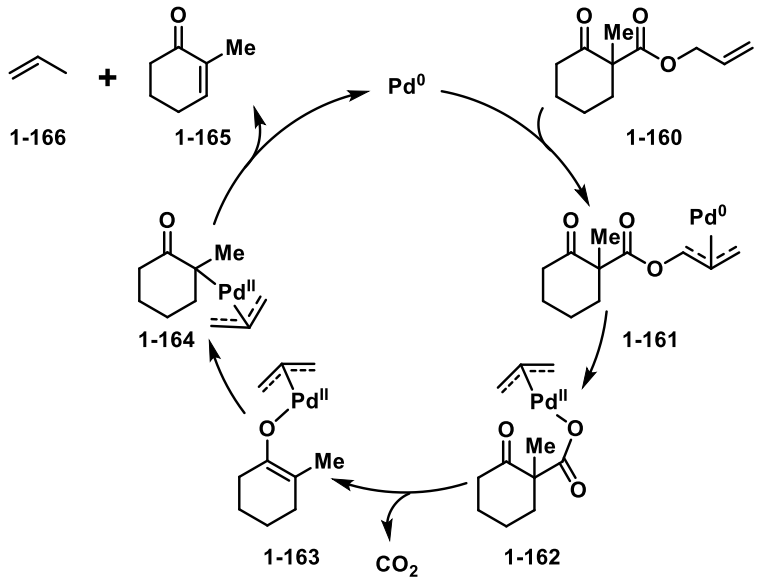
Despite the elegance of the cycloaddition between nitrones and cyclopropanes, a major downfall of the methodology is its lack of regioselectivity when a 2,3-disubstituted cyclopropane is used.[52] As a result, most syntheses of tetrahydro-1,2-oxazines lack functionality at the C5 position. Our group was inspired to tackle this issue after Avedis Karadeolian solved a similar problem during his total synthesis of isatisine A.[56] A key step of his synthesis required accessing hydroxyl-tetrahydrofuran **1-156** (Scheme 1-38); however, attempts to convert tetrahydrofuran **1-154** to dihydrofuran **1-155** for further functionalization proved fruitless. After much deliberation it was found that a THF ring functionalized with a geminal allyl, methyl diester (**1-157**) would undergo a palladium(0) catalyzed dehydrogenative decarbonylation (dehydrocarbonylation) to form dihydrofuran **1-158**, which was dihydroxylated, and further manipulated to isatisine A (**1-159**).



Scheme 1-38 Kerr group's synthesis of isatisine A

1.4.4.2 Dehydrocarbonylation mechanism

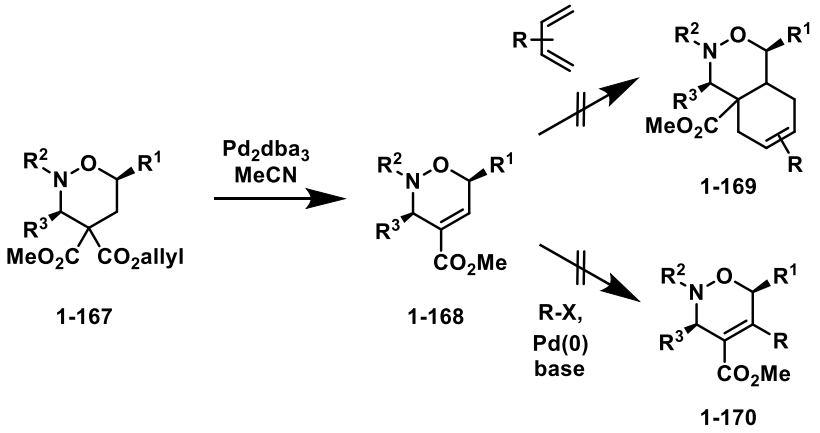
The dehydrocarbonylation reaction Avedis used in isatisine A was originally developed by Tsuji and Shimizu to produce *α*,*β*-unsaturated ketones (**1-165**) from allyl *β*-esters (**1-160**). The proposed mechanism for the dehydrocarbonylation is shown in Scheme 1-39. Coordination of the metal to the allyl ester (**1-161**), followed by an oxidative insertion gives intermediate **1-162**. Dehydrocarbonylation of **1-162** occurs, which results in the palladium being coordinated to the enolate oxygen in **1-163**. Tautomerization of the enolate, and migration of the palladium complex results in intermediate **1-164**, which is then followed by a β-hydride elimination to produce the desired *α*,*β*-unsaturated ketone (**1-165**).



Scheme 1-39 Tsuji and Shimizu's synthesis of *α*,*β*-unsaturated ketones

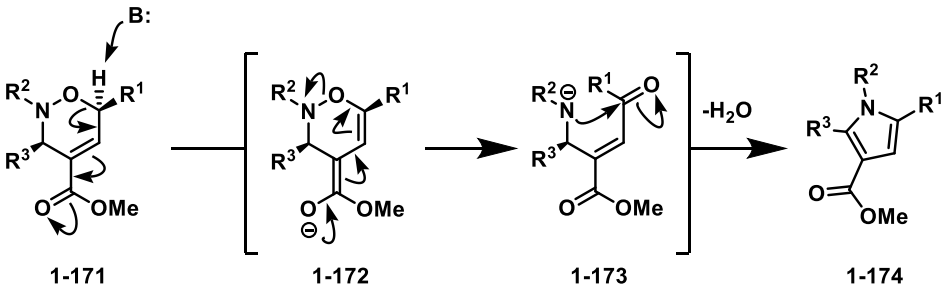
1.4.4.3 4,5-Dihydro-1,2-oxazines and synthesis of pyrroles

With a method to install olefins, it was postulated that tetrahydro-1,2-oxazines can be modified to undergo the Tsuji reaction to give 3,4-dihydro-1,2-oxazines (**1-168**), which can then be manipulated to functionalize C5. We envisioned that C5 functionalization could then occur on **1-168** by the means of Diels-Alder chemistry (**1-169**), or by a coupling reaction (**1-170**, Scheme 1-40).



Scheme 1-40 Attempts to functionalize C5 from 3,4-dihydro,1-2,oxazine

While the route to access 3,4-dihydro-1,2-oxazines was a success, functionalization at the C5 postion was not. In both Diels-Alder and Heck coupling attempts for C5 functionalization, recovery of starting material was observed along with a minor undesired product (being more prominent as a by-product in the Heck reaction). Upon further investigation of the undesired product it was determined that it was a pyrrole (**1-174**). The proposed mechanism of this transformation proceeds as shown in Scheme 1-41.



Scheme 1-41 Proposed mechanism to access pyrroles from 3,4-dihydro-1,2-oxazines

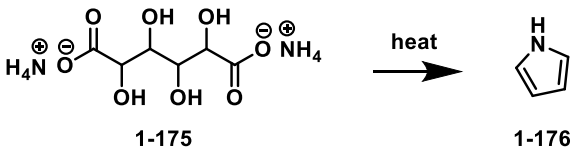
Deprotonation of C6 in compound **1-171** would result in an enolate species (**1-172**), which then undergoes an E1cb mechanism resulting in an *N-O* bond cleavage (**1-173**). Acyl addition by the amide to form the hemiaminal could then undergo dehydration to form the pyrrole (**1-174**). While the mechanism is not certain, similar transformations have been reported in the literature.[57] With these insights into 3,4-dihydro-1,2-oxazine

reactivity, a methodology to access pyrroles from DA cyclopropanes was pursued. Prior to the results, the importance of pyrroles and previous syntheses will be discussed.

1.5 Synthesis of pyrroles from DA cyclopropanes

1.5.1 Introduction to pyrroles

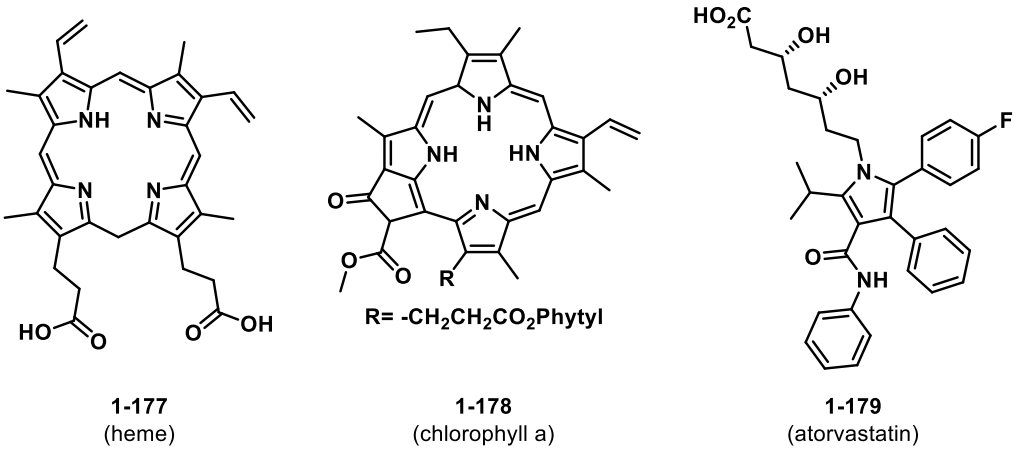
Pyrrole was discovered in coal tar (and later bone oil) by Runge in 1834. It was named pyrrole after the Greek word for ‘red oil’ due to the colour that forms when its vapour acts on pine wood soaked with hydrochloric acid. Despite recognizing a new molecule, the structure was elucidated approximately 20 years later by Thomas Anderson. Anderson distilled over a ton of ivory oil to isolate a colourless oil with a boiling point of 134-138 °C, which also had a “a hot pungent taste”. The first synthesis of pyrrole was in 1860 when Schwanert heated ammonium mucate **1-175** (Scheme 1-42).[58]



1-175 **1-176**

Scheme 1-42 Schwanert’s synthesis of pyrrole

The pyrrole heterocycle is one of, if not the most, important heterocycle known. It is found in natural products from much of the world’s flora and fauna,[59] and is present in many pharmaceutical drugs.[60] The presence of pyrroles, as a tetramer, in two molecules necessary for most life on earth speaks of their importance: heme, found in blood and used to transport oxygen (Figure 1-2, **1-177**); and chlorophyll, essential in photosynthesis of plants (Figure 1-2, **1-178**).[61] An important pyrrole containing pharmaceutical is atorvastatin (Lipitor) (Figure 1-2, **1-179**). Atorvastatin belongs to a family of compounds called statins which are used as a lipid-lowering agent, and are used for the prevention of symptoms associated with cardiovascular disease. Developed in 1985, it went on to be one the highest selling drugs of all time.[62]



1-177 (heme) **1-178** (chlorophyll a) **1-179** (atorvastatin)

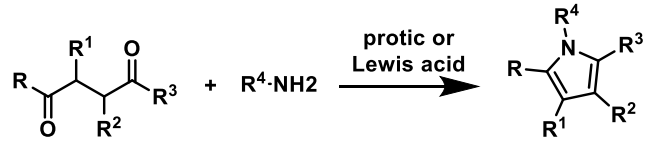
Figure 1-2 Structure of heme, chlorphyll a, and atorvastatin

1.5.2 Various syntheses of pyrroles

Due to the importance of pyrroles, there have been many methodologies developed to access them,[63] and as such, only a select few examples will be highlighted in this section.

1.5.2.1 Paal-Knorr pyrrole synthesis

One of the earliest and most well known synthesis of pyrroles is the classic Paal-Knorr synthesis (Scheme 1-43). In 1884, Paal and Knorr independently found that 1,4-diketone **1-180** can react with ammonia or primary amine **1-118** to access pyrrole **1-181** (Scheme 1-43). The reaction has been greatly studied with many modifications discovered.[64] The amine can be varied greatly, but generally a diketone is required as 1,4-dialdehydes or keto aldehydes are unstable.

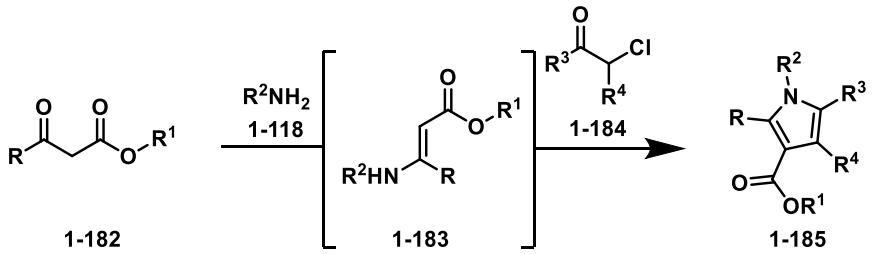


1-180 **1-118** **1-181**

Scheme 1-43 General Paal-Knorr pyrrole synthesis

1.5.2.2 Hantzsch pyrrole synthesis

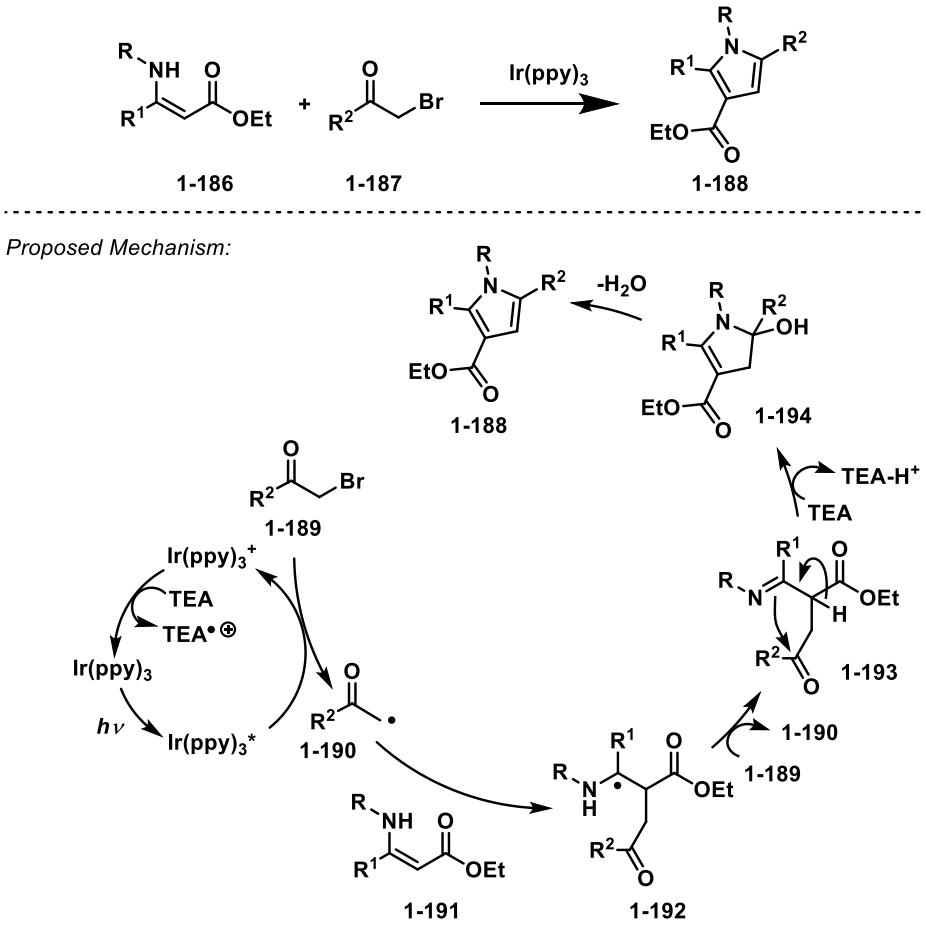
A few years later, one of the earliest multi-component synthesis of pyrroles was developed by Arthur Hantzsch (Scheme 1-44).[65] Addition of α-haloketone **1-184**, β-keto ester **1-182** and ammonia, or a primary amine, give pyrrole **1-185**. A key mechanistic feature of the reaction is the enamine intermediate (**1-183**) attacking the α-haloketone. As this has become another classic pyrrole synthesis, many modifications of this procedure have been developed.



Scheme 1-44 General Hantzsch pyrrole synthesis

One recent example of a Hantzsch type pyrrole synthesis comes from the Wu group. They were able to access polysubstituted pyrroles (**1-188**) in a one pot procedure from enamines (**1-186**) and α-bromo ketones (**1-187**); however, unlike the traditional mechanism, the pyrrole synthesis is initiated through a photoinduced electron transfer from $Ir(ppy)_3$ (Scheme 1-45).[66] In their optimization, they were fortunate to obtain a 92% yield of pyrrole when a mixture of enamine, ketone, and $Ir(ppy)_3$ in DMSO were irradiated with visible light; failure to include one of these components resulted in no pyrrole. To confirm a radical process, TEMPO was placed into the reaction mixture and a significant drop in yield occurred (29%). With a relatively short optimization, they were then able to expand the scope of the methodology to access a variety of pyrroles. Unfortunately, only aryl substituents on the enamine and the α-bromo ketone were tested. Moderate yields were obtained for their pyrroles, but generally electron donating substituents offered greater yields than electron withdrawing, for example when R^1 = *p*-NO_2-C_6H_4 there was a 57% yield of pyrrole, but when R^1 = *p*-OMe-C_6H_4 there was an 84% yield. The proposed mechanism begins with the excitation of $Ir(ppy)_3$ to $Ir(ppy)_3$*, which then undergoes a single electron transfer oxidation by α-bromo ketone, to generate

$Ir(ppy)_3^+$ and the reduced carbonyl. Reduced **1-189** then gets debrominated to give radical **1-190**. Radical **1-190** reacts with the enamine to form intermediate **1-192**, which then self catalyzes the reaction by reducing ketone **1-189**. Cyclization of **1-193**, followed by dehydration of **1-194** leads to the pyrrole **1-188**.

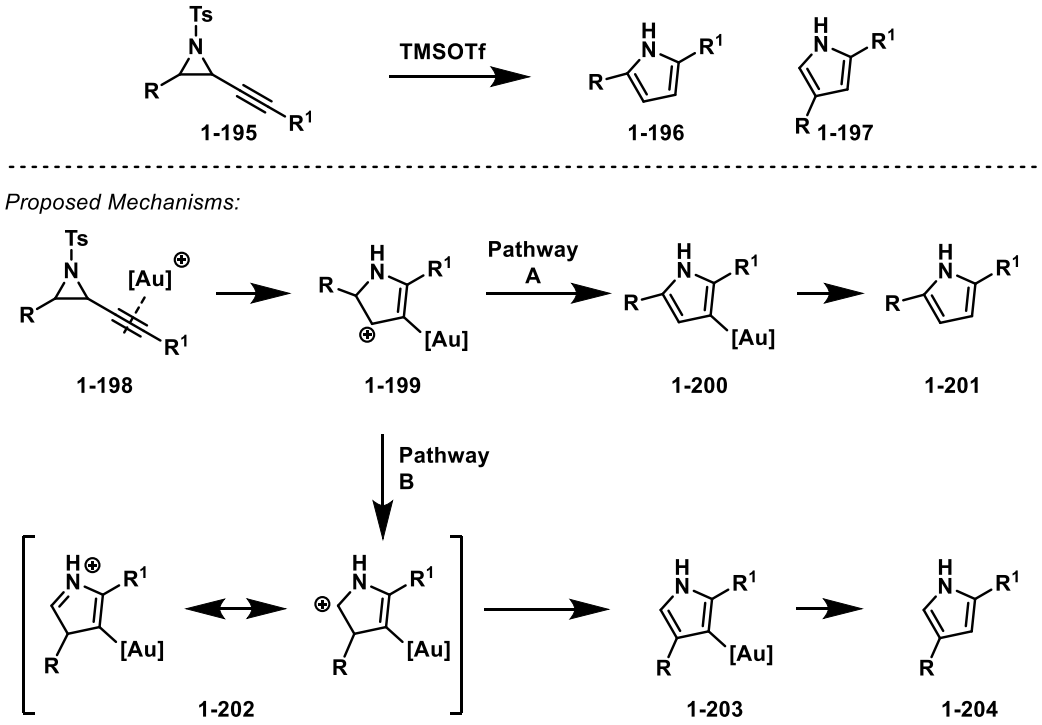


Scheme 1-45 Wu group's light initiated Hantzsch synthesis of pyrroles

1.5.2.3 Davies pyrrole synthesis

Among the classics, modern ways have also been developed to access pyrroles. Inspired by the process developed by the Hashmi *et al.*[67] to access furans from alkynyl epoxides, the Davies group set out to develop conditions to obtain pyrroles from a gold catalyzed, ring expansion of *N*-tosyl alkynyl aziridines (**1-195**) (Scheme 1-46).[68] They found during their optimization that they could influence the pyrrole regioisomer by modifying the solvent, and the counter ion of the gold catalyst (PPh_3AuCl). When AgOTs in DCE was

used, 2-5 substituted pyrrole **1-196** was formed exclusively. When AgOTf in dichloromethane was used, the 2-4 substituted pyrrole **1-197** was the major, or sole product. Lastly, when AgOTf in toluene was used it resulted in a mixture of regioisomers. The regioselectivity can be explained by intermediate **1-199** in the proposed mechanism. A basic counter ion, such as AgOTs, would facilitate in the elimination to form 2,5-disubstituted pyrroles (pathway A). The lack of a basic counter ion would require a Lewis basic solvent to facilitate in this role, as seen in the case with AgOTf, and toluene. Absence of either a basic counter ion or solvent would result in sole formation of the rearranged product (pathway B). The effect of the counter ion on gold catalyst is not surprising to this case, as it has previously been reported in the literature.[69]

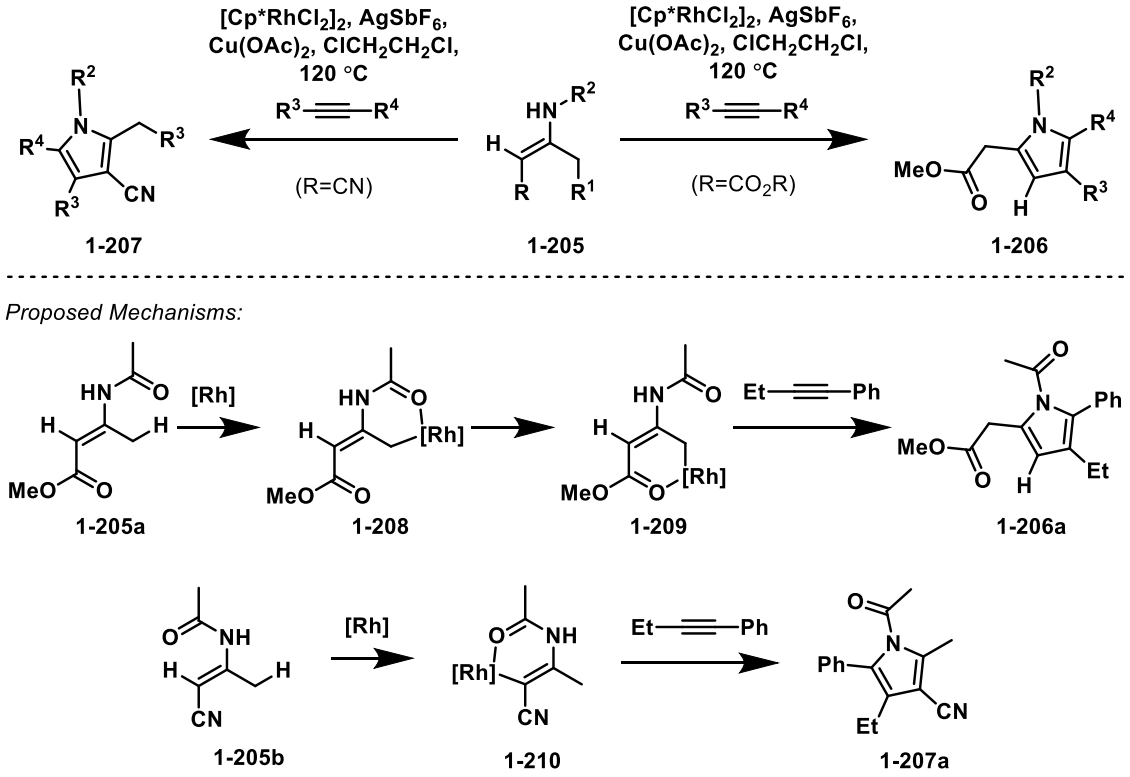


Scheme 1-46 Davies group's synthesis of pyrroles from alkynyl aziridines

1.5.2.4 Glorius pyrrole synthesis

In 2010, the Glorius group expanded on the work developed by Dr. Keith Fagnou's indole synthesis,[70] to access pyrroles by a allylic sp^3 C-H activation, or vinylic sp^2 C-H activation, of enamines and their subsequent coupling with alkynes (Scheme 1-47).[71] The optimized conditions were found to be $[Cp^*RhCl_2]_2$, $AgSbF_6$, and $Cu(OAc)_2$ in DCE; a

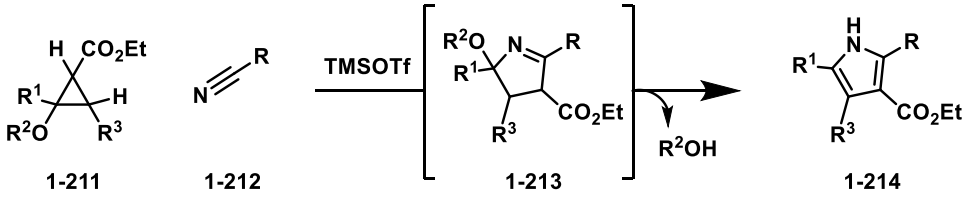
non-coordinating solvent, and choice of oxidant were important to the reaction (many Cu salts were not tolerable of the reaction conditions). The requirement for $Cu(OAc)_2$ was confirmed whereby a reaction without copper gave a 2% yield (^{1}H NMR yield), which then increased to 48% after addition of $Cu(OAc)_2$ (^{1}H NMR yield). It was also found that SbF_6 was the superior counter ion, and some anions, such as chloride anion, resulted in no reaction. The reaction scope was tolerable of various aryl internal alkynes with *N*-acetyl enamine (R= CO_2Me; R^1= H; R^2= Ac) in 38-70% yields, and of various enamines with 1-phenyl-1-butyne, or diphenylacetylene. Since only one regioisomer was formed when R=CO_2Me (**1-206a**), it was speculated that the reaction must be proceeded through intermediate **1-209** (whereby the rhodium coordinates with the carbonyl of the ester). This was confirmed when an enamine with R=CN was used. Since there is only one mode for coordination (as seen in intermediate **1-210**), pyrrole **1-207a** was formed exclusively.



Scheme 1-47 Glorius group's synthesis of pyrroles from C-H activation of enamines

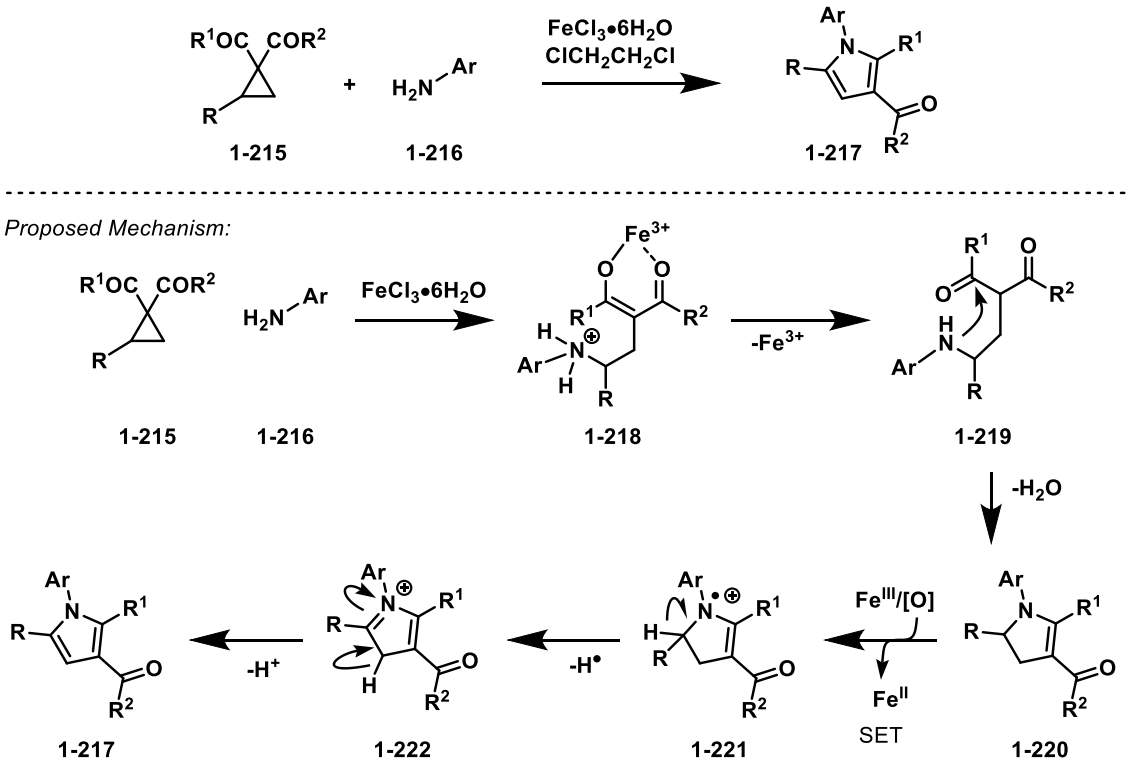
1.5.3 Synthesis of pyrroles from DA cyclopropane

In 2003, the Pagenkopf group showed that they can access pyrroles from donor-acceptor cyclopropanes. Their methodology consisted of the Lewis activated [3+2] cycloaddition between cyclopropane **1-211** and nitriles (**1-212**), followed by dehydration and tautomerization of intermediate **1-213** (Scheme 1-48).[72] Alkyl, vinyl nitriles accessed pyrroles in good yields (77-91%), however aryl nitriles gave low yields (35-55%).



Scheme 1-48 Pagenkopf group's synthesis of pyrroles from cyclopropanes

More recently, in 2014 the Zhang group showed that they can access pyrroles from donor-accepted cyclopropanes and anilines using an iron-mediated oxidation domino reaction (Scheme 1-49).[73] Originally trying to access dihydropyrrole **1-220** from cyclopropane **1-215** and aniline **1-216**, they thought that an iron catalyst would increase the rate of the reaction, but instead they discovered that they had isolated pyrrole **1-217**. As seen in the proposed mechanism in Scheme 1-49, the iron catalyst facilitates in the ring opening of the cyclopropane by the aniline to form dihydropyrrole **1-220**; however, subsequent single electron transfer oxidation of **1-220** by iron and oxygen, generate radical intermediate **1-221**. The intermediate then becomes pyrrole **1-217** through radical dehydrogenation and deprotonation reactions. Radical trapping experiments were undertaken to confirm the conversion of **1-220** to **1-221** by single electron transfer (SET). Three radical scavengers were independently added to the reaction, and in each case the yield of pyrrole **1-217** decreased, while the yield of dihydropyrrole **1-220** increased. They were successful in forming various pyrroles from a variety of anilines and cyclopropanes in moderate yields.

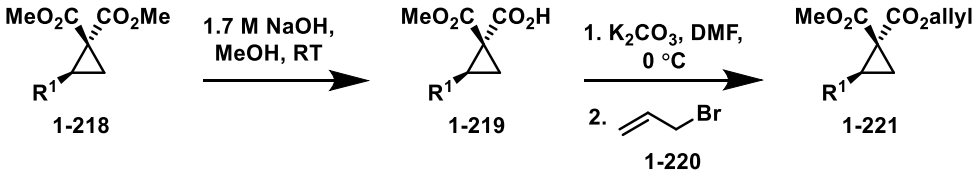


Scheme 1-49 Zhang group's synthesis of pyrroles from cyclopropanes

1.5.4 Results and discussion

1.5.4.1 Synthesis of 1-allyl-1-methylcyclopropane-1,1-dicarboxylate

In order to access pyrroles from DA cyclopropanes, via 4,5-dihydro-1,2-oxazines, various cyclopropanes containing an ally ester moiety first needed to be synthesized. A two-step procedure was undertaken to convert a methyl ester in cyclopropane **1-218** to an allyl ester (Scheme 1-50, **1-221**). This involved monosaponification of an ester, followed by a substitution reaction with allyl bromide. Using dimethylcyclopropane-1,1-dicarboxylate **1-218** in sodium hydroxide and methanol allowed for monosaponification of the geminal ester trans to the substituent on the cyclopropane (**1-219**). Monosaponification of the trans ester occurs as it is the least hindered ester.[74] Reacting the newly formed acid with allyl bromide through an S_N2 or S_N2' mechanism afforded the required 1-allyl-1-methylcyclopropane-1,1-dicarboxylate (**1-221**).



Scheme 1-50 Synthesis of 1-allyl-1-methylcyclopropane-1,1-dicarboxylate

Despite the stereoselective nature of the saponification reaction, the chirality will become inconsequential when tetrahydro-1,2-oxazine undergoes a Tsuji reaction, as this position becomes sp^2 hybridized. The various cyclopropanes that underwent this transformation are shown in Figure 1-3. Pyrroles derived from cyclopropanes **1-221a** and **1-221b** were worked on by William Humenny, **1-221c** and **1-221d** by myself, and lastly **1-221e** by Katarina Sapeta.

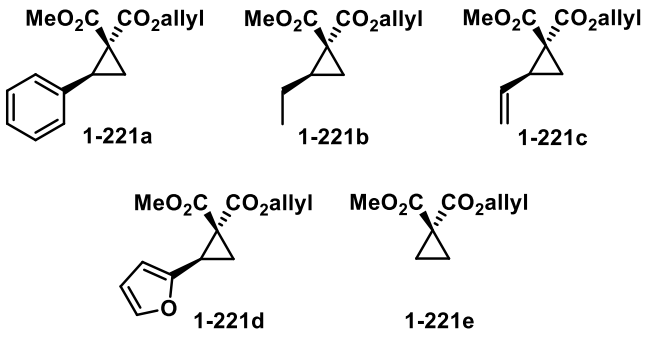
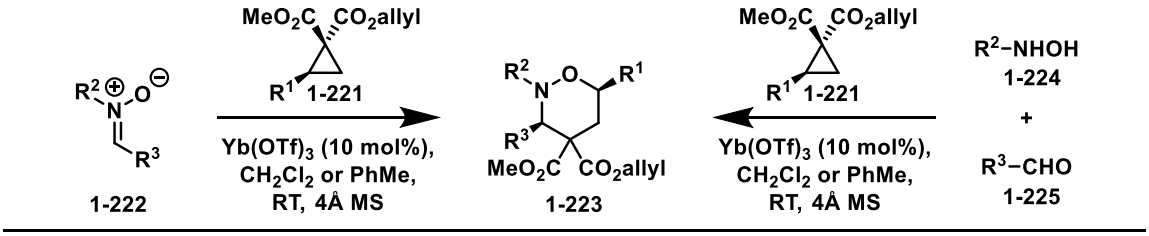


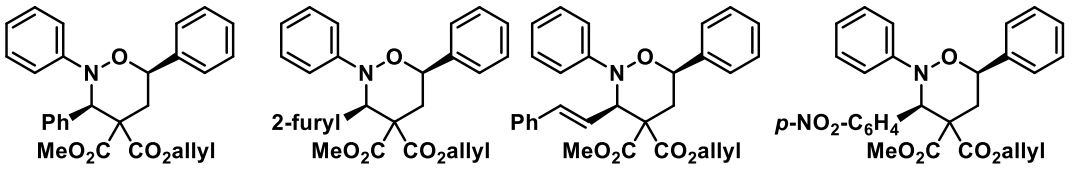
Figure 1-3 Library of 1-allyl-1methylcyclopropane-1,1-dicarboxylate

1.5.4.2 Synthesis of tetrahydro-1,2-oxazine

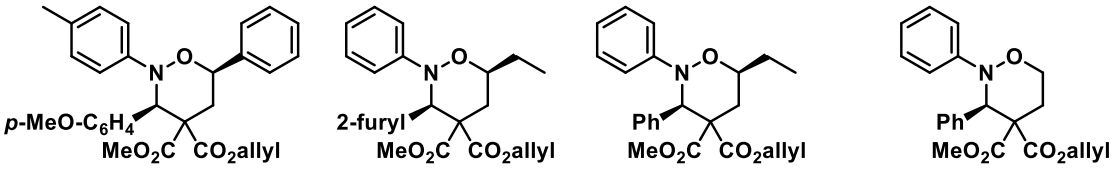
Each of the cyclopropanes in Figure 1 were reacted with various nitrones in order to obtain tetrahydro-1,2-oxazines (Table 1-2) following methods previously described in the literature.[50,51] The nitrones utilized for the reaction were either developed in situ or isolated prior to use, and the decision to use one method versus the other was mostly decided by chemical availability.

Table 1-2 Synthesis of tetrahydro-1,2-oxazines

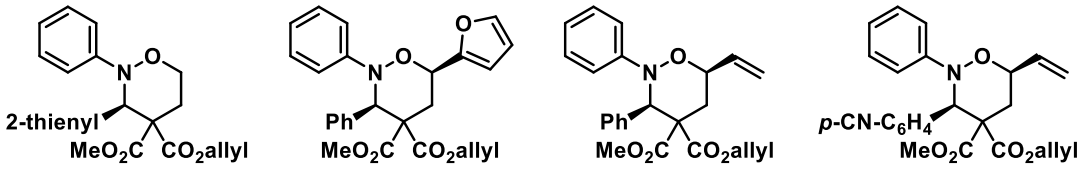




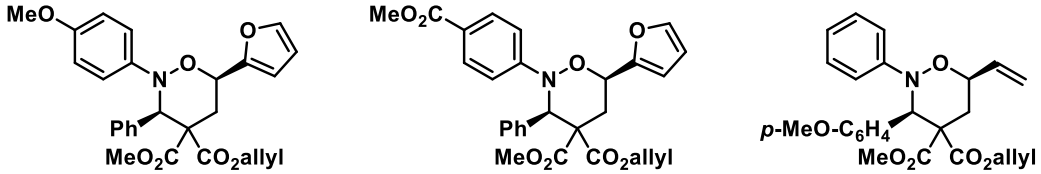
1-223a: 91%[a] **1-223b:** 93%[a] **1-223c:** 89%[a] **1-223d:** 94%[b]



1-223e: 96%[b] **1-223f:** 89%[ac] **1-223g:** 84%[ac] **1-223h:** 68%[a]



1-223i: 99%[a] **1-223j:** 88%[b] **1-223k:** 83%[b] **1-223l:** 63%[b]



1-223m: 90%[b] **1-223n:** 91%[b] **1-223o:** 80%[b]

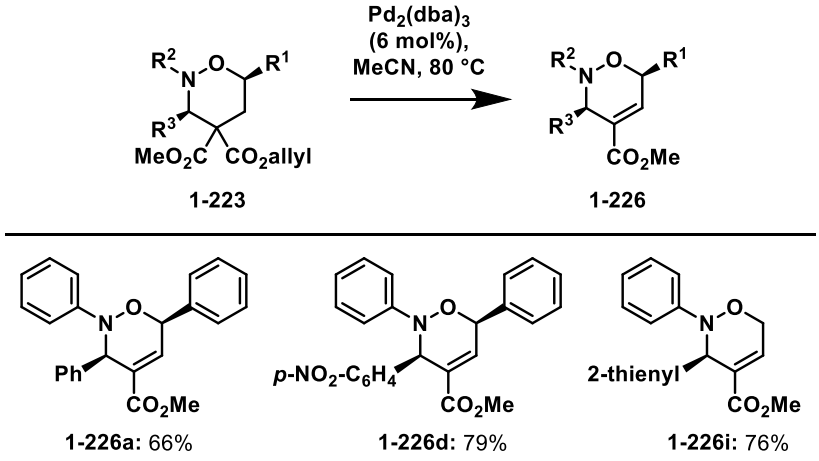
[a]three-component, [b]two-component, [c]required $Sc(OTf)_3$

The formation of tetrahydro-1,2-oxazine (**1-223**) proceeded smoothly and were obtained in very good yields (63-96%). While most of the reactions were carried out in DCM, or toluene, under catalytic Lewis acid conditions (10 mol % of $Yb(OTf)_3$), compounds **1-223f** and **1-223g** had to be carried out with 10 mol% of $Sc(OTf)_3$; due to the slightly more Lewis acidity of the catalyst, it's more effective in reactions containing weak donor groups. The relationship of the substituents on carbons 3 and 6 were assumed to be in a *cis* relationship due to literature precedence.[52]

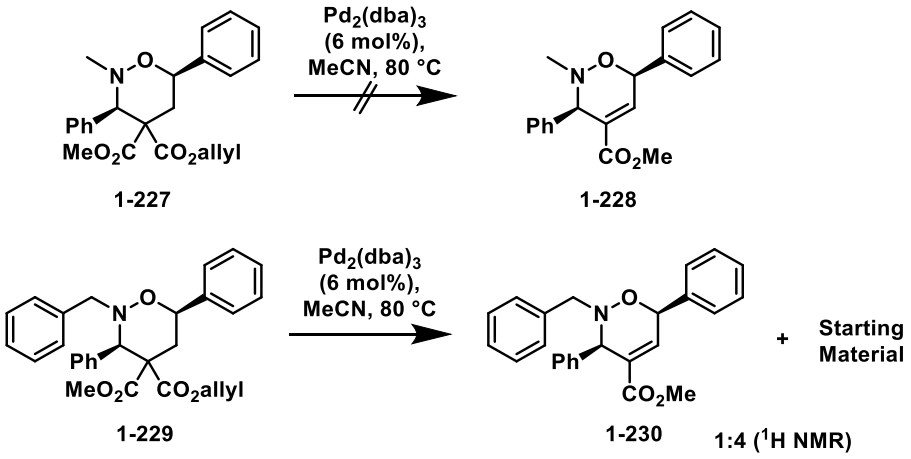
1.5.4.3 Synthesis of 4,5-dihydro-1,2-oxazine

With a process to develop tetrahydro-1,2-oxazine containing a geminal allyl, methyl ester, the dehydrocarbonylation procedure to form 4,5-dihydro-1,2-oxazine (**1-226**) was undertaken. Optimal reaction conditions determined by Avedis Karadolean were found to be heating **1-223** with 6 mol% $Pd_2(dba)_3$ in acetonitrile (Table 1-3).

Table 1-3. Dehydrocarbonylation of tetrahydro-1,2-oxazines



A limitation of this reaction is that only aniline derived nitrones are able to undergo this transformation, as *N*-alkyl or *N*-benzyl resulted in no reaction or partial conversion respectively (Scheme 1-51). Since *N*-alkyl and *N*-benzyl amines are more basic then aniline derived nitrones – because the lone pair in *N*-aryl nitrones are delocalized by the aromatic ring – catalyst poisoning can occur, thus limiting the reaction. Attempts to quaternerize the amine did not aid in the transformation.

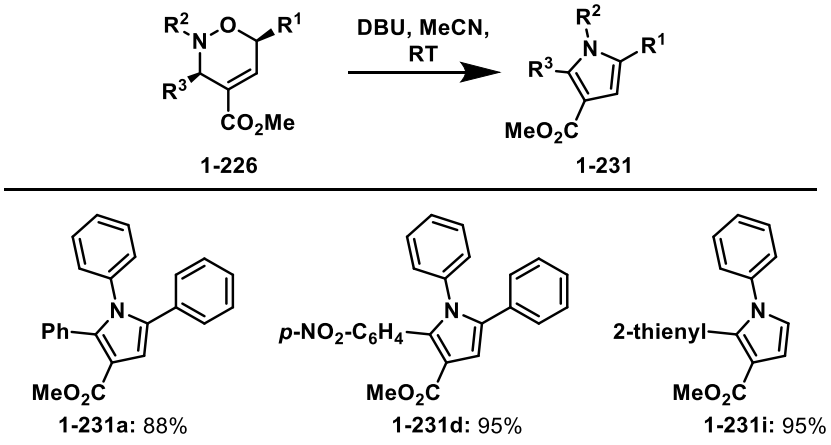


Scheme 1-51. Limitations of dehydrocarbonylation

1.5.4.4 Synthesis of pyrroles

With 4,5-dihydro-1,2-oxazines at hand, we were now able to access pyrroles. Triethylamine was found to successfully convert 4,5-dihydro-1,2-oxazines to pyrroles at room temperature in 24 hours; however, the yields and time were improved when the reaction stirred for five minutes at room temperature with DBU (Table 1-4). Prolonged reaction times (greater than five minutes) resulted in the product decomposing.

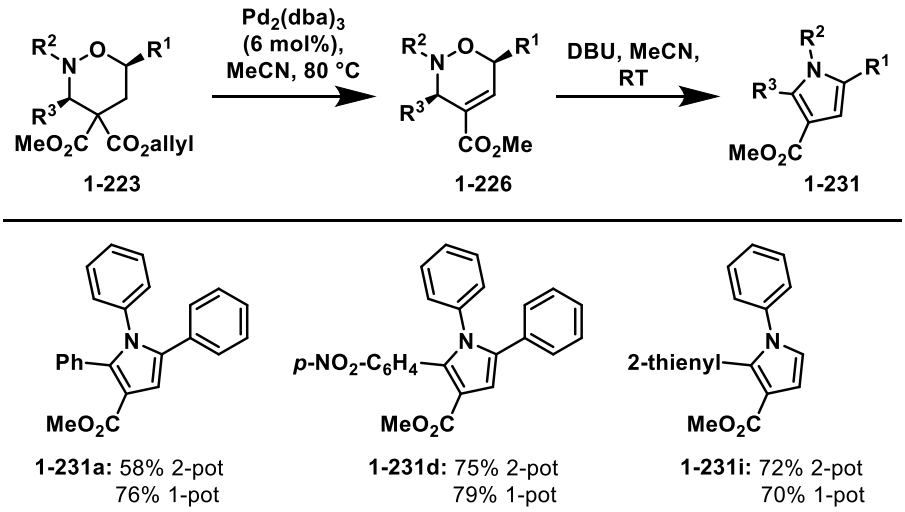
Table 1-4 Dehydration of 4,5-dihydro-1,2-oxazines



As both dehydrocarbonylation and dehydration reactions occurred in acetonitrile, a one-pot procedure was then explored to convert tetrahydro-1,2-oxazine (**1-223**) directly to

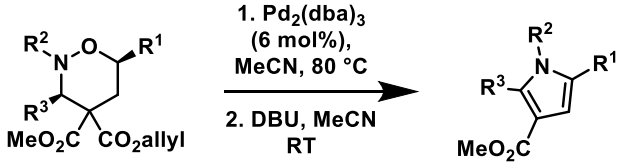
pyrrole (**1-231**). These efforts were successful and it was found that yields were similar, or vastly improved with the one pot procedure (Table 1-5).

Table 1-5 Comparison between one-pot and two-pot procedure to pyrroles

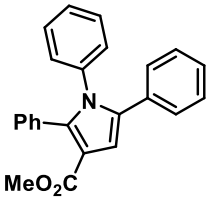


With a library of various 1-allyl-1methylcyclopropane-1,1-dicarboxylates (Figure 1-3) and an optimized route to pyrroles from tetrahydro-1,2-oxazines (Table 1-5), a substrate scope was explored (Table 1-6). Most pyrroles were formed in good yield using the optimized conditions but a few modifications needed to be done. Compound **1-231d** required the use of NEt_3 (and 24 hour reaction time), instead of five minutes with DBU, presumably because C6 proton was very acidic and lead to decomposition of starting material. Also, tetrahydro-1,2-oxazines **1-231f-i** did not proceed under the optimized conditions, and it was required that the reactions be heated in order to proceed. The need for heat was presumably due to the decreased acidity of the proton on C6 due to lack of donor substituent on the cyclopropane. The synthesis of pyrroles is also tolerable of aniline derived nitrones with electron donating and withdrawing groups on the aniline (pyrrole **1-231m** and **1-231n** respectively), benzaldehyde derived nitrones with electron donating (pyrroles **1-231e**, **1-231o**) and withdrawing groups from benzaldehyde (pyrroles **1-231d**, **1-231l**).

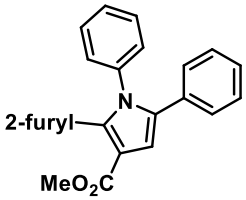
Table 1-6 One-pot procedure to pyrroles from tetrahydro-1,2-oxazines



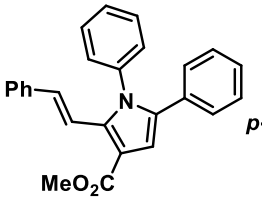
1-223 → **1-231**



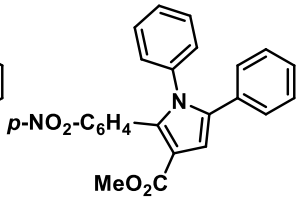
1-231a: 76%



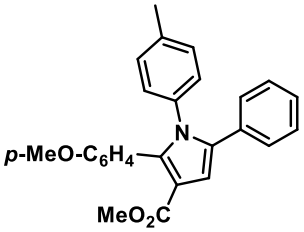
1-231b: 69%



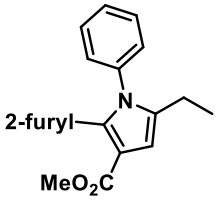
1-231c: 48%



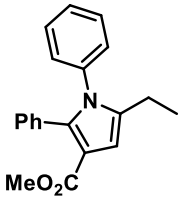
1-231d: 79%[a]



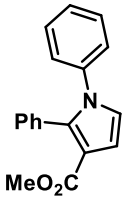
1-231e: 95%



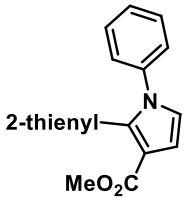
1-231f: 50%[b]



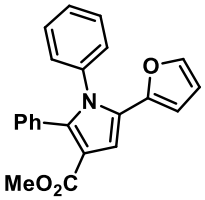
1-231g: 73%[b]



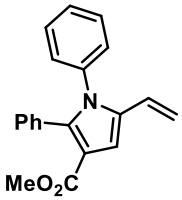
1-231h: 82%[b]



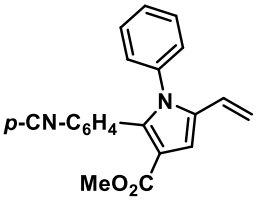
1-231i: 70%[b]



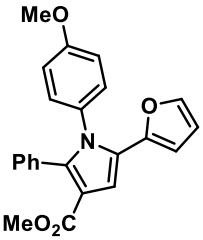
1-231j: 60%



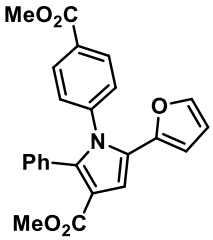
1-231k: 61%



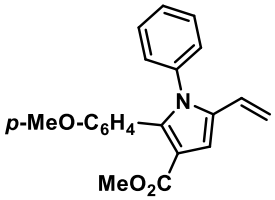
1-231l: 58%



1-231m: 61%



1-231n: 71%

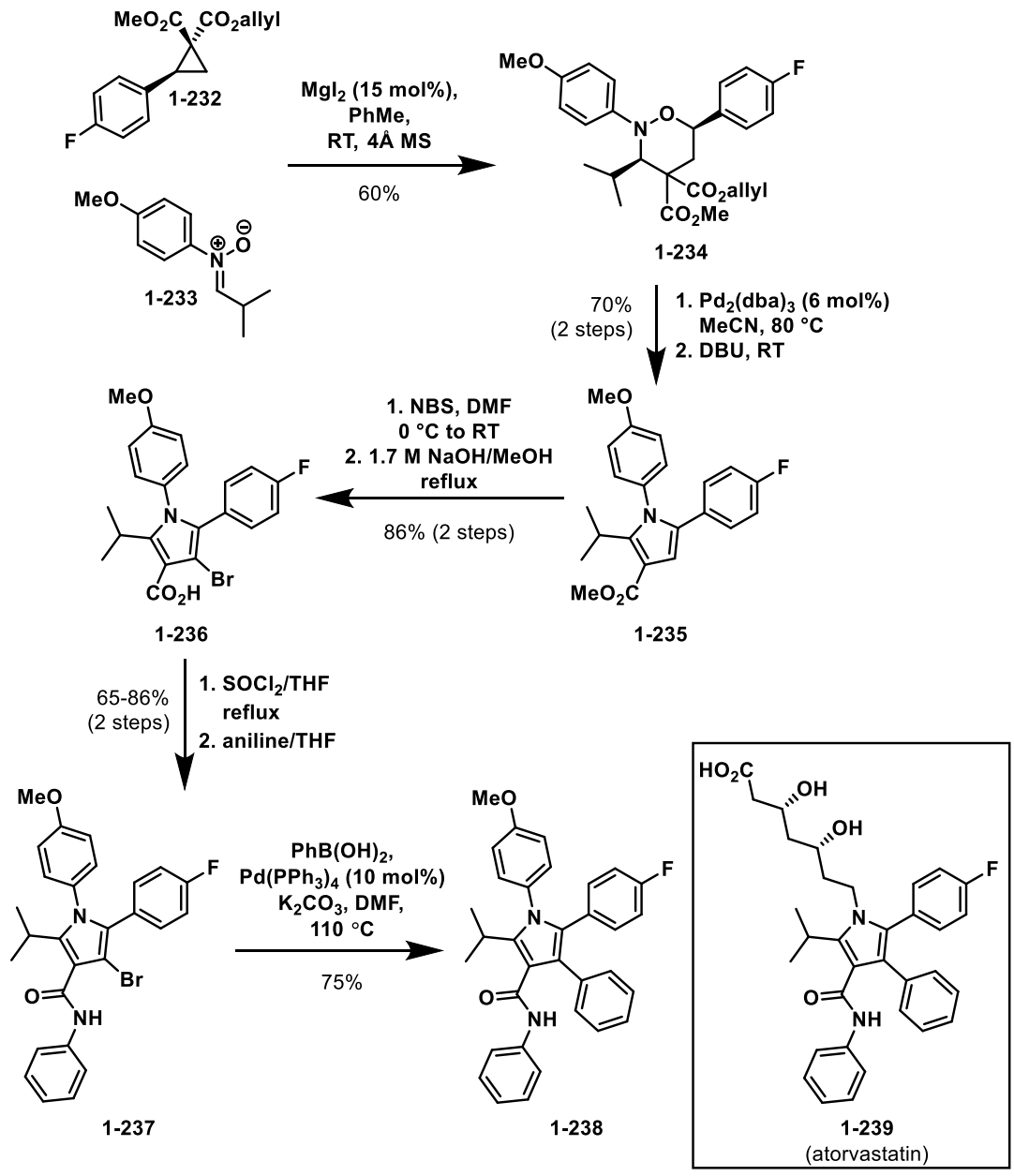


1-231o: 70%

[a]required Et_3N, [b]required heating at 40 °C overnight

1.5.4.5 Progress towards atorvastatin

To highlight the utility of the pyrrole synthesis, progress towards the total synthesis of atorvastatin was undertaken by William Humenny (Scheme 1-52). Reacting nitrone **1-233** with cyclopropane **1-232** gave tetrahydro-1,2-oxazine **1-234** but it should be noted that MgI_2[75] was needed as the standard $Yb(OTf)_3$ or $Sc(OTf)_3$ would not work for this transformation. Pyrrole **1-235** was then accessed through the two-pot dehydrocarbonylation/dehydration in 70% yield over two steps. As atorvastatin contains a phenyl substituent at the two position of the pyrrole, bromination was carried out at this position in order to be a coupling partner later in the synthesis. Hydrolysis of the ester on **1-235** was also formed to give compound **1-236** in 86% over two steps. Conversion of the acid to anilide **1-237** via the acyl chloride was obtained in variable yields (65-86%). Lastly, a Suzuki coupling with phenylboronic acid and pyrrole **1-237** gave pyrrole **1-238** in a 75% yield. Pyrrole **1-238** could then be deprotected to access atorvastatin, however attempts with ceric ammonium nitrate were unsuccessful before William Humenny graduated.



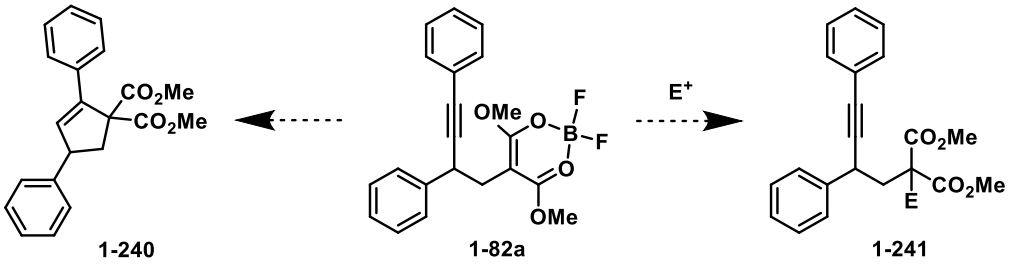
Scheme 1-52 Progress towards atorvastatin

1.5.5 Conclusions

Efforts were undertaken to functionalize the *C*5 position of tetrahydro-1,2-oxazines, via 4,5-dihydro-1,2-oxazines. The 4,5-dihydro-1,2-oxazines were synthesized via a Tsuji dehydro/decarbonylation of an allyl ester on tetrahydro-1,2-oxazines. Attempts to add functionality on the olefin with Diels-Alder, or Heck coupling chemistry were unsuccessful; they formed pyrroles instead. Fifteen examples of tetrahydro-1,2-oxazines were converted to pyrroles in yields ranging from 48-95%. Although the method may be inferior to other pyrrole synthesis, it is nonetheless an interesting reaction that explores further manipulation of the easily prepared tetrahydro-1,2-oxazines heterocycle.

1.6 Summary and future work

In summary, a new method to ring opening of DA cyclopropanes has been accessed, through the use of organotrifluoroborate salts. The methodology was only compatible with alkynyl trifluoroborate salts reacting with aryl substituted DA cyclopropanes. Each example was isolated as a malonyl-BF_2 complex, which then went acid hydrolysis to access the desired malonate species. Examples were made in 36-75% yield over the two steps. Future work will look into the reactivity of the malonyl-BF_2 complex and efforts will be undertaken to develop conditions that can undergo *5-endo-dig* cyclization (**1-240**), or to react the complex with an electrophile (**1-241**). Near the completion of this project, similar work was published by Ortega and Csákÿ.[41]



Scheme 1-53 Studying the reactivity of malonyl-BF_2 complexes

The work described in this chapter also expanded the Kerr group's synthesis of tetrahydro-1,2-oxazines to access pyrroles. Modified cyclopropanes containing geminal allyl and methyl esters underwent an annulation reaction, with nitrones, to form tetrahydro-1,2-oxazines. These were then converted to pyrroles by a one-pot dehydrocarbonylation/dehydration procedure. Various pyrroles were accessed in 48-95% yield from the tetrahydro-1,2-oxazines. A limitation of this reaction is that only nitrones derived from anilines could be used for the reaction. Further exploration is required to find conditions compatible with *N*-alkyl nitrones, which would greatly open the utility of the methodology. The value of the methodology was then applied towards the total synthesis of atorvastatin by William Humenny.

1.7 Experimental

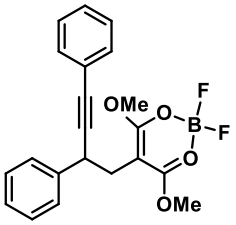
1.7.1 Ring opening of DA cyclopropanes with RBF_3K

General considerations:

All reactions were performed under an atmosphere of argon unless otherwise indicated. Dichloroethane was distilled over calcium hydride, boron trifluoride diethyl etherate was distilled over calcium hydride and diethyl ether under reduced pressure. All other reagents and solvents were used as purchased from Sigma Aldrich, Alfa Aesar, or VWR and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F254), visualizing with UV light, and the plates developed with *p*-anisaldehyde. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc). NMR experiments were performed on Varian Mercury 400, and Inova 400 MHz instruments with ^{13}C operating frequency of 100 MHz, ^{11}B operating frequency of 128 MHz, and ^{19}F operating frequency of 376 MHz. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (*J*) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, app = apparent. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS™ Magnetic Sector Electron Ionization GC-HRMS. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}).

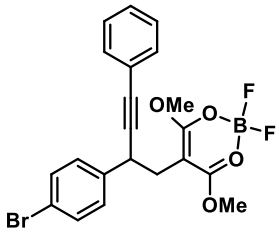
General procedure and spectral data for dimethyl malonates:

To a solution of organo trifluoroborate salt (2.5 equiv) in dry dichloroethane (0.5 mol/L), cooled to 0 °C, was added BF_3•OEt_2 (4.55 equiv) dropwise. The reaction stirred for 20 minutes at 0 °C, at which point cyclopropane (1 equiv) in dichloroethane (0.8 mol/L) was added. The reaction stirred at 0 °C for 5 minutes, 5 minutes at room temperature, and then the reaction flask was placed in a 65 °C oil bath for 16 hours. After this time, water was added to the reaction flask, and the contents were extracted with dichloromethane. The combined organic layers were washed with brine, and dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave the crude malonyl-BF2 complex. The crude material was dissolved in tetrahydrofuran (0.1 mol/L) and to the reaction was added half the volume of a 20% HCl/H_2O (v/v) solution, dropwise, at room temperature. The reaction stirred at room temperature for 12 hours. After this time, the contents were diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with aqueous sodium bicarbonate, brine, and then dried with anhydrous $MgSO_4$. The malonates were then purified by flash column chromatography on silica gel (15% EtOAc/hexanes).

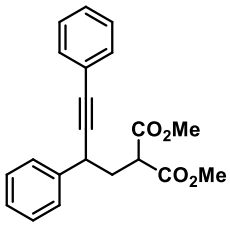


dimethyl 2-(2,4-diphenylbut-3-yn-1-yl)malonyl-BF_2 complex (1-86a): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (94 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the flask. The reaction was then diluted with water and the contents extracted with dichloromethane. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and removal of the solvent *in vacuo* gave **1-86a**. Normally these compounds are carried through crude, but can be purified for characterization by flash column chromatography on silica gel (15% EtOAc/hexanes); **Rf** = 0.56 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 - 7.24 (m, 10 H), 3.88 (X of ABX, J_{AX}=7.5 Hz, J_{BX}=7.4 Hz, 1 H), 3.85 (s, 3 H), 2.74 (A of ABX, J_{AB}=14.2 Hz, J_{AX}=7.5 Hz, 1 H), 2.62 (B of ABX, J_{AB}=14.2 Hz, J_{BX}=7.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6 (t, $J_{(C-F)}$=2.3 Hz), 140.8, 131.5, 128.3, 128.3, 127.9,

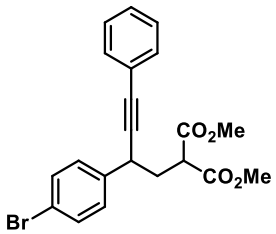
127.6, 127.0, 123.4, 90.4, 83.6, 77.5, 55.5, 38.1, 30.6; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 0.80 (s); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -142.8 (s), -142.9 (s); **FT-IR** (thin film, cm-1) νmax 2950, 1608, 1514, 1448, 1379, 1209, 1121, 1045, 913, 744; **HRMS** calc'd for $C_{21}H_{19}BF_2O_4$ [M+] 384.1344; found 384.1350.



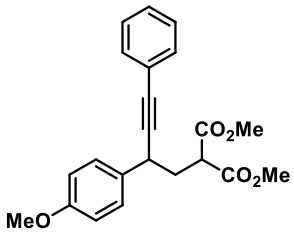
dimethyl 2-(2-(4-bromophenyl)-4-phenylbut-3-yn-1-yl)malonyl-BF_2 complex (1-86b): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (125 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the flask. The reaction was then diluted with water and the contents extracted with dichloromethane. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and removal of the solvent *in vacuo* gave the crude **1-86b**. Normally these compounds are carried through crude, but can be purified for characterization by flash column chromatography on silica gel (15% EtOAc/hexanes); **Rf** = 0.53 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.47 (app d, *J*=8.6 Hz, 2 H), 7.42 - 7.40 (m, 2 H), 7.32 - 7.28 (m, 3 H), 7.27 (app d, *J*=8.6 Hz, 2 H), 3.86 (s, 6 H), 3.89 - 3.85 (X of ABX, J_{AX}=7.7 Hz, J_{BX}=7.2 Hz, 1 H), 2.75 (A of ABX, J_{AB}=14.3 Hz, J_{AX}=7.7 Hz, 1 H), 2.62 (B of ABX, J_{AB}=14.3 Hz, J_{BX}=7.2 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6 (t, $J_{(C-F)}$=2.3 Hz), 139.9, 131.5, 131.4, 129.4, 128.3, 128.1, 123.1, 120.8, 89.7, 83.9, 77.2, 55.5, 37.7, 30.5; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 0.78 (s); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -142.8 (s), -142.9 (s); **FT-IR** (thin film, cm-1) νmax 2950, 1609, 1516, 1448, 1380, 1208, 1123, 1046, 912, 736; **HRMS** calc'd for $C_{21}H_{18}BBrF_2O_4$ [M+] 462.0450; found 462.0437.



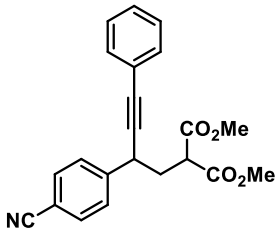
dimethyl 2-(2,4-diphenylbut-3-yn-1-yl)malonate (1-82a): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (94 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82a** (75%, 100 mg, 0.3 mmol) as a yellow oil; **Rf** = 0.72 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 - 7.44 (m, 4 H), 7.36 (app t, *J*=7.6 Hz, 2 H), 7.33 - 7.27 (m, 4 H), 3.97 (app dd, *J*=9.8, 5.9 Hz, 1 H), 3.79 - 3.74 (m, 1 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.53 - 2.34 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 169.4, 140.5, 131.7, 128.7, 128.2, 128.0, 127.5, 127.2, 123.2, 89.3, 84.6, 52.6, 52.6, 49.9, 37.2, 36.3; **FT-IR** (thin film, cm-1) νmax 3029, 2952, 1751, 1736, 1490, 1436, 1226, 1152, 1030, 758, 693; **HRMS** calc'd for $C_{21}H_{20}O_4$ [M+] 336.1362; found 336.1358.



dimethyl 2-(2-(4-bromophenyl)-4-phenylbut-3-yn-1-yl)malonate (1-82b): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (125 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82b** (70%, 116 mg, 0.28 mmol) as an orange oil; **Rf** = 0.50 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (app d, 2 H), 7.45 - 7.43 (m, 2 H), 7.34 - 7.30 (m, 5 H), 3.93 (app dd, *J*=9.6, 5.7 Hz, 1 H), 3.76 (s, 3 H), 3.73 (app dd, *J*=8.8, 5.7 Hz, 1 H), 3.70 (s, 3 H), 2.48 - 2.29 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 169.3, 139.6, 131.7, 131.7, 129.2, 128.3, 128.2, 122.9, 121.1, 88.6, 84.9, 52.7, 52.7, 49.7, 37.0, 35.8; **FT-IR** (thin film, cm-1) νmax 3055, 2952, 2845, 1735, 1488, 1436, 1155, 1012, 913, 826, 758, 692; **HRMS** calc'd for $C_{21}H_{19}BrO_4$ [M+] 414.0467; found 414.0476.

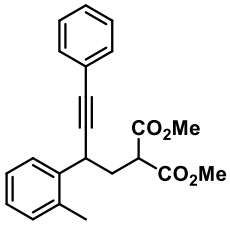


dimethyl 2-(2-(4-methoxyphenyl)-4-phenylbut-3-yn-1-yl)malonate (1-82c): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (106 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82c** (59%, 87 mg, 0.24 mmol) as an orange oil; **Rf** = 0.43 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 - 7.43 (m, 2 H), 7.36 (app d, *J*=8.6 Hz, 2 H), 7.32 - 7.28 (m, 3 H), 6.89 (app d, *J*=8.6 Hz, 2 H), 3.91 (app dd, *J*=9.4, 6.3 Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.76-3.73 (m, 1 H), 3.71 (s, 3 H), 2.49 - 2.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 169.4, 158.7, 132.6, 131.6, 128.5, 128.2, 128.0, 123.2, 114.0, 89.7, 84.3, 55.3, 52.6, 52.6, 49.8, 37.3, 35.5; **FT-IR** (thin film, cm-1) νmax 3032, 2953, 2837, 1735, 1609, 1512, 1437, 1035, 832, 759, 696, 563; **HRMS** calc'd for $C_{22}H_{22}O_5$ [M+] 366.1467; found 366.1453.

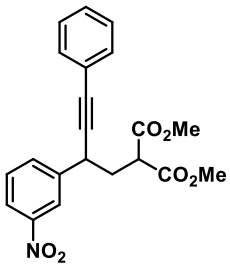


dimethyl 2-(2-(4-cyanophenyl)-4-phenylbut-3-yn-1-yl)malonate (1-82e): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(4-cyanophenyl)cyclopropane-1,1-dicarboxylate (104 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82e** (65%, 93 mg, 0.26 mmol) as an orange oil; **Rf** = 0.36 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 - 7.63 (m, 2 H), 7.60 - 7.55 (m, 2 H), 7.46 - 7.43 (m, 2 H), 7.35 - 7.30 (m, 3 H), 4.04 (app dd, *J*=10.0, 5.3 Hz, 1 H), 3.79 - 3.76 (m, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 2.27 - 2.51 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 169.1, 146.0, 132.5, 131.7, 128.5, 128.5, 128.3, 128.3, 122.5, 118.6, 111.2, 87.5, 85.7, 52.8, 52.8, 49.7, 36.8, 36.4; **FT-IR** (thin film, cm-1) νmax 3002, 2954,

2229, 1735, 1608,1437, 1154, 913, 837, 759, 693, 572 ; **HRMS** calc'd for $C_{22}H_{19}NO_4$ [M+] 361.1314; found 361.1311.

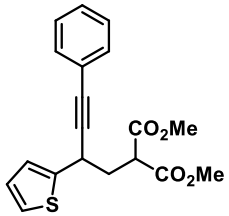


dimethyl 2-(4-phenyl-2-(o-tolyl)but-3-yn-1-yl)malonate (1-82f): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(o-tolyl)cyclopropane-1,1-dicarboxylate (99 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82f** (70%, 97 mg, 0.28 mmol) as a yellow oil; **Rf** = 0.5 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (app d, *J*=7.4 Hz, 1 H), 7.49 - 7.44 (m, 2 H), 7.34 - 7.29 (m, 3 H), 7.26 - 7.17 (m, 3 H), 4.18 (app dd, *J*=10.6, 4.7 Hz, 1 H), 3.91 (app dd, *J*=10.0, 4.9 Hz, 1 H), 3.81 (s, 3 H), 3.71 (s, 3 H), 2.43 (s, 3 H), 2.48 - 2.22 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 169.4, 138.8, 135.1, 131.6, 130.6, 128.2, 128.0, 127.5, 127.1, 126.4, 123.2, 89.7, 84.1, 52.6, 50.0, 35.7, 33.0, 19.0; **FT-IR** (thin film, cm-1) νmax 3021, 2953, 1752, 1736, 1490, 1436, 1284, 1154, 914, 745, 692; **HRMS** calc'd for $C_{22}H_{22}O_4$ [M+] 350.1518; found 350.1503.

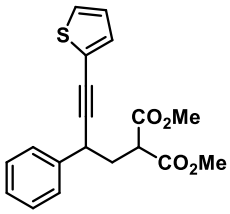


dimethyl 2-(2-(3-nitrophenyl)-4-phenylbut-3-yn-1-yl)malonate (1-82g): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (112 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82g** (64%, 97 mg, 0.25 mmol) as an orange oil; **Rf** = 0.39 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (app t, *J*=2.0 Hz, 1 H), 8.15 (app dt, *J*=8.2, 1.0 Hz, 1 H), 7.80 (app d, *J*=7.8 Hz, 1 H), 7.54 (app t, *J*=8.0 Hz, 1 H), 7.49 - 7.43 (m, 2 H), 7.38 - 7.29 (m, 3 H), 4.11 (app dd, *J*=10.2, 5.1 Hz, 1 H), 3.81 - 3.77 (m, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.55 - 2.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 169.1, 148.5, 142.8, 133.7, 131.7, 129.6, 128.5, 128.3, 122.5,

122.5, 122.4, 87.5, 85.8, 52.8, 52.8, 49.7, 36.9, 36.0; **FT-IR** (thin film, cm-1) νmax 3067, 2953, 2874, 1751, 1532, 1490, 912, 759, 692, 414; **HRMS** calc'd for $C_{21}H_{19}NO_6$ [M+] 381.1212; found 381.1210.

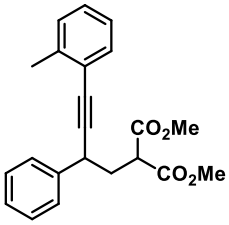


dimethyl 2-(4-phenyl-2-(thiophen-2-yl)but-3-yn-1-yl)malonate (1-82h): Following the general procedure, to a chilled solution of potassium 2-phenyl-1-ethynyltrifluoroborate (208 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (96 mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82h** (58%, 80 mg, 0.23 mmol) as an orange oil; **Rf** = 0.5 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 - 7.42 (m, 1 H), 7.35 - 7.29 (m, 3 H), 7.22 (app dd, *J*=5.1, 1.2 Hz, 1 H), 7.05 (app d, *J*=3.5 Hz, 1 H), 6.96 (app dd, *J*=5.1, 3.5 Hz, 1 H), 4.26 (app dd, *J*=9.0, 5.9 Hz, 1 H), 3.79 - 3.75 (m, 1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 2.62 - 2.43 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 169.3, 143.9, 131.7, 128.2, 126.7, 124.9, 124.4, 122.8, 88.7, 84.2, 52.7, 52.7, 49.6, 37.1, 31.6; **FT-IR** (thin film, cm-1) νmax; 3105, 2952, 2848, 1735, 1598, 1490, 1436, 1156, 1039, 850, 758, 692; **HRMS** calc'd for $C_{19}H_{18}O_4S$ [M+] 342.0926; found 342.0920.

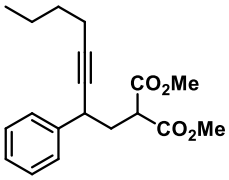


dimethyl 2-(2-phenyl-4-(thiophen-2-yl)but-3-yn-1-yl)malonate (1-82i): Following the general procedure, to a chilled solution of potassium 2-thiophenyl-1-ethynyltrifluoroborate (214 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (94mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82i** (48%, 66 mg, 0.19 mmol) as an orange oil; **Rf** = 0.46 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 - 7.36 (m, 2 H), 7.35 - 7.28 (m, 2 H), 7.27 - 7.21 (m, 1 H), 7.20 - 7.14 (m, 2 H), 6.93 (app dd, *J*=5.1, 3.9 Hz, 1 H), 3.95 (app dd, *J*=9.4, 5.9 Hz, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 3.67 (app dd, *J*=8.6, 6.2 Hz, 1 H), 2.48 - 2.32 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.4, 169.3, 140.1, 131.7,

128.7, 127.5, 127.3, 126.8, 126.6, 123.1, 93.3, 77.6, 52.6, 49.8, 49.8, 36.9, 36.6; **FT-IR** (thin film, cm-1) νmax 2952, 1750, 1734, 1493, 1435, 1152, 913, 743, 700, 553; **HRMS** calc'd for $C_{19}H_{18}O_4S$ [M+] 342.0926; found 342.0936.



dimethyl 2-(2-phenyl-4-(o-tolyl)but-3-yn-1-yl)malonate (1-82j): Following the general procedure, to a chilled solution of potassium 2-methylphenyltrifluoroborate (222 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (94mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82j** (49%, 69 mg, 0.24 mmol) as a yellow oil; **Rf** = 0.49 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 - 7.42 (m, 3 H), 7.37 (app t, *J*=7.6 Hz, 2 H), 7.32 - 7.25 (m, 1 H), 7.24 - 7.20 (m, 2 H), 7.18 - 7.12 (m, 1 H), 4.03 (app dd, *J*=9.8, 5.9 Hz, 1 H), 3.83 (dd, *J*=9.0, 5.5 Hz, 1 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 2.56 - 2.35 (m, 1 H), 2.47 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.5, 169.4, 140.6, 140.0, 132.0, 129.3, 128.6, 128.0, 127.4, 127.1, 125.4, 122.9, 93.2, 83.5, 52.6, 49.9, 37.4, 36.5, 20.8; **FT-IR** (thin film, cm-1) νmax 3061, 2952, 2849, 1752, 1736, 1600, 1493, 1453, 1154, 760, 700, 562; **HRMS** calc'd for $C_{22}H_{22}O_4$ [M+] 350.1518; found 350.1512.



dimethyl 2-(2-phenyloct-3-yn-1-yl)malonate (1-82k): Following the general procedure, to a chilled solution of potassium 2-butyl-1-ethynyltrifluoroborate (188 mg, 1 mmol) in dry dichloroethane (2 mL), was added BF_3•OEt_2 (225 µL, 1.82 mmol). Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (94mg, 0.4 mmol) in dry dichloroethane (0.5 mL) was then added to the reaction. Hydrolysis of the crude material in tetrahydrofuran (4 mL) by 20% HCl/H_2O (v/v) (2 ml), and purification, afforded dimethyl malonate **1-82k** (36%, 46 mg, 0.15 mmol) as a yellow oil; **Rf** = 0.63 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.29 (m, 4 H), 7.26 - 7.20 (m, 1 H), 3.77 - 3.68 (m, 2 H), 3.76 (s, 3 H), 3.70 (s, 3 H), 2.40 - 2.15 (m, 2 H), 2.23 (dt, *J*=7.0, 2.3 Hz, 2 H), 1.56 - 1.37 (m, 4 H), 0.92 (t, *J*=7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.6, 169.5, 141.3, 128.5, 127.4, 126.9, 84.8, 79.6, 52.5, 49.9, 37.5, 35.8, 31.0, 21.9, 18.5, 13.6; **FT-IR** (thin film,

cm-1) νmax 2955, 2872, 1753, 1737, 1494, 1434, 1252, 1154, 1042, 913, 744, 700; **HRMS** calc'd for $C_{19}H_{24}O_4$ [M+] 316.1675; found 316.1662.

1.7.2 Synthesis of pyrroles from DA cyclopropanes

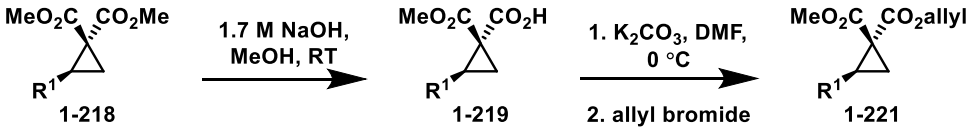
General considerations:

All reactions were performed under an atmosphere of Ar unless otherwise indicated. Toluene, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dichloromethane 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, Alfa Aesar, Caledon, Strem or VWR and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F_{254}), visualizing with UV light, and the plates developed with *p*-anisaldehyde, vanillin, or basic potassium permanganate stains. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

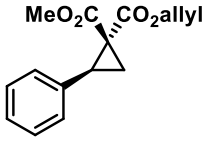
NMR experiments were performed on Varian Mercury 400, Inova 400 and Inova 600 MHz instruments with ^{13}C operating frequencies of 100, 100 and 125 MHz respectively. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (*J*) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 or 8400 mass spectrometer at an ionizing voltage of 70 eV. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}).

As this was a collaborative effort, only compounds I synthesized are included in the experimental.

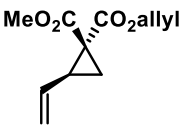
General procedure and spectral data for 1-allyl-1-methylcyclopropane-1,1-dicarboxylate (1-221):



To a 1.7 M solution of NaOH (1.2 equiv) in an equal volume of MeOH was added the desired dimethylcyclopropane-1,1-dicarboxylate (**1-218**). Upon complete saponification of one ester based on TLC analysis the reaction was acidified to pH 4 with 4 M HCl and the cyclopropane was extracted with Et_2O. Removal of solvent under reduced pressure afforded the cyclopropane ester acid (**1-219**). The ester acid was then dissolved in DMF and cooled to 0 °C. At this point 1.1 equiv of K_2CO_3 was added in and the solution was stirred for 30 minutes. After which time allyl bromide was added dropwise and the reaction mixture continued to stir until the ester acid was consumed based on TLC analysis. From here H_2O was added to the reaction flask and the organics were extracted with Et_2O and the 1-allyl-1-methylcyclopropane-1,1-dicarboxylate (**1-221**) were purified by flash column chromatography (EtOAc/hexanes 1:10).

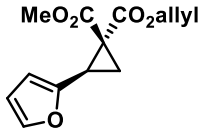


(1*R,2*S**)-1-allyl 1-methyl 2-phenylcyclopropane-1,1dicarboxylate (1-221a)** : yellow oil; $\mathbf{R_f}$ = 0.50 (30% EtOAc/hexanes); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28−7.19 (m, 5H), 5.98-5.88 (m, 1H), 5.35 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.25 (dd, *J* = 10.6, 1.2 Hz, 1H), 4.69 (m, 2H), 3.37 (s, 3H), 3.25 (app t, *J* = 8.6 Hz, 1H), 2.21 (dd, *J* = 7.8, 5.1 Hz, 1H), 1.76 (dd, *J* = 9.4, 5.1 Hz, 1H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 169.4, 166.9, 134.5, 131.6, 128.4, 128.1, 127.4, 118.2, 110.8, 66.1, 52.1, 42.1, 37.3, 32.5, 19.1; **FT-IR** (thin film, cm^{-1}) ν_{max} 2951, 1728 , 1500, 1437, 1382, 1333, 1274, 1217, 1180, 1130, 984, 933, 793, 750, 698, 453, 418; **HRMS** calc'd for $C_{15}H_{16}O_4$ [M+] 260.1049, found 260.1042.



(1*R,2S*)-1-allyl 1-methyl 2-(furan-2-yl)cyclopropane-1,1 dicarboxylate (1-221c)**: colourless oil; $\mathbf{R_f}$ = 0.51 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.89-5.79 (m, 1H), 5.42-5.07 (m, 5H), 4.64-4.51 (m, 2H), 3.68 (s, 3H), 2.54 (app q, *J* = 8.2 Hz, 1 H), 1.68 (dd, *J* = 7.6, 4.9 Hz,

1H), 1.53 (dd, *J* = 9.0, 4.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 167.6, 132.8, 131.5, 118.5, 118.0, 65.9, 52.4, 35.7, 31.2, 20.4; **FT-IR** (thin film, cm^{-1}) ν_{max} 3452, 3088, 2992, 2954, 1732, 1639, 1438, 1389, 1332, 1227, 1208, 1134, 960, 922, 787, 747, 710, 669, 556; **HRMS** calc'd for $C_{11}H_{14}O_4$ [M+] 210.0892, found 210.0892.



(1*R,2S*)-1-allyl 1-methyl 2-(furan-2-yl)cyclopropane-1,1-dicarboxylate (1-221d)**: yellow oil; $\mathbf{R_f}$ = 0.40 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.28 (app dd, *J* = 3.1, 2.0 Hz, 1H), 6.12 (app d, *J* = 3.5 Hz, 1H), 5.95-5.86 (m, 1H), 5.36-5.31 (m, 1H), 5.27-5.23 (m, 1H), 4.72-4.60 (m, 2H), 3.55 (s, 3H), 3.11 (dd, J = 9.2, 8.0 Hz, 1 H), 2.09 (dd, *J* = 7.9, 5.1 Hz, 1H), 1.79 (dd, *J* = 9.8, 5.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 166.7, 149.4, 142.1, 131.3, 118.1, 110.3, 107.4, 66.0, 52.3, 36.4, 25.2, 18.6; **FT-IR** (thin film, cm^{-1}) ν_{max} 3453, 3121, 2995, 2952, 2887, 1731, 1649, 1600, 1505, 1438, 1367, 1332, 1275, 1208, 1130, 1099, 1010, 943, 884, 741, 599, 416; **HRMS** calc'd for $C_{13}H_{14}O_5$ [M+] 250.0841, found 250.0839.

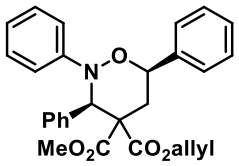
Experimental procedure and spectral data for preparation of tetrahydro-1,2-oxazines (1-223):

General method A – two-component coupling

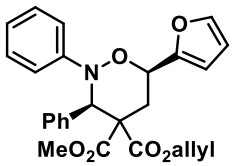
To a solution of 1-allyl-1-methylcyclopropane-1,1-dicarboxylate **1-221** (1.0 equiv), $Yb(OTf)_3$ (10 mol%) in either CH_2Cl_2 or toluene (5−10 mL) was added in one portion the desired nitrone **1-222** (1.3 equiv). The reaction was stirred at the temperature indicated, for the time indicated, under an atmosphere of argon. On completion, the reaction mixture was filtered through celite, pre-adsorbed onto silica gel, and purified by column chromatograpy (silica gel, EtOAc/hexanes).

General method B – three-component coupling

Hydroxylamine **1-224** (1.3 equiv), aldehyde **1-225** (1.4 equiv) and $Yb(OTf)_3$ (10 mol%) were stirred under an atmosphere of argon at ambient temperature in the presence of 4 Å molecular sieves in either toluene or CH_2Cl_2 (5−10 mL) for 0.5 h. Once the nitrone was formed in situ, 1-allyl-1-methylcyclopropane-1,1-dicarboxylate **1-221** (1.0 equiv), dissolved in 1−2 mL of the appropriate solvent, was added to the reaction mixture in one portion. The reaction was stirred at the temperature indicated, for the time indicated, under an atmosphere of argon. On completion, the reaction mixture was filtered through celite, pre-adsorbed onto silica gel, and purified by column chromatograpy (silica gel, EtOAc/hexanes).

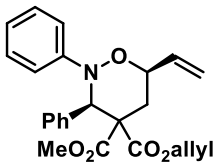


4-allyl 4-methyl 2,3,6-triphenyl-1,2-oxazine-4,4-dicarboxylate (1-223a): Following general method B, phenylhydroxylamine (55 mg, 0.50 mmol), benzaldehyde (57 mg, 0.54 mmol), cyclopropane **1-221a** (100 mg, 0.38 mmol), and $Yb(OTf)_3$ (24 mg, 0.038 mmol) were stirred in toluene (5 mL) for 20 h; affording **1-223a**, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) as a pale yellow viscous oil (91 %, 160 mg, 0.35 mmol, 1.7:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.47 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 5.69-5.57 (m, 1H) 5.18 (app dd, *J* = 10.6, 1.2 Hz, 1H), 5.16-5.13 (m, 1H), 3.93 (s, 3H); Diastereomer B: δ 6.04-5.93 (m, 1H), 5.41 (app dd, *J* = 17.2, 1.2 Hz, 1H), 5.30 (app dd, *J* = 10.2, 1.2 Hz, 1H), 3.48 (s, 3H); Diastereomeric Mixture: δ 7.62−7.54 (m, 7H), 7.47 (t, *J* = 7.0 Hz, 3H), 7.42−7.37 (m, 2H), 7.22−7.16 (m, 6H), 7.15−7.08 (m, 6H), 6.84−6.79 (m, 2H), 5.81 (s, 2H), 5.05 (app dt, *J* = 12.1, 2.7 Hz, 2H), 4.84 (app dt, *J* = 5.9, 1.2 Hz, 1H), 4.39-4.28 (m, 2H), 2.94−2.77 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ 170.0, 169.1, 168.1, 167.4, 148.5, 139.4, 135.0, 134.8, 131.4, 131.0, 130.6, 130.3, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9 (x2), 127.3, 126.4, 126.3 78.8, 66.7, 66.2, 65.8, 59.5, 53.4, 52.5, 37.3, 32.4, 31.7, 31.6, 19.0; **FT-IR** (thin film, cm^{-1}) ν_{max} 3030, 2952, 1732, 1599, 1942, 1453, 1228, 1064, 988, 944, 911, 810, 734, 700, 650, 600; **HRMS** calc'd for $C_{28}H_{27}NO_5$ [M+] 457.1889, found 457.1886.

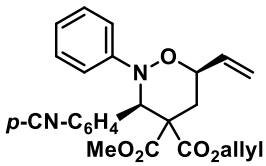


4-allyl 4-methyl 6-(furan-2-yl)-2,3-diphenylmorpholine-4,4-dicarboxylate (1-223j): Following general method A, requisite (150 mg, 0.75 mmol), cyclopropane **1-221d** (160 mg, 0.63 mmol), and $Yb(OTf)_3$ (40 mg, 0.063 mmol) stirred in room temperature dichloromethane (10 mL) for 20 hours, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223j** as a white viscous oil (88%, 250 mg, 0.55 mmol, 1:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.56 (30%, EtOAc/hexanes); **^{1}H NMR** (600 MHz, $CDCl_3$) Diastereomer A: δ 6.60 (d, *J* = 2.9 Hz, 2H), 6.02-5.96 (m, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 4.88-4.80 (m, 2H), 3.90 (s, 3H); Diastereomer B: δ 6.47 (s, 2H), 5.71-5.65 (m, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.45-4.30 (m, 2H), 3.50 (s, 3H); Diastereomeric Mixture: δ 7.64 (d, *J* = 7.0 Hz, 4H), 7.55 (s, 2H), 7.23-7.11 (m, 15H), 6.85 (t, *J* = 7.3 Hz, 2H), 5.81 (s, 2H), 5.23-5.15 (m, 4H), 3.2 (apt dt, *J* = 13.5, 6.4 Hz, 2H), 2.81 (app d, *J* = 14.6 Hz, 2H); **^{13}C NMR** (100

MHz, $CDCl_3$) Diastereomeric Mixture: δ 169.7, 168.8, 167.9, 167.2, 151.7, 148.3, 143.0, 134.7, 134.5, 131.3, 130.9, 130.6, 130.4, 128.3, 128.0, 127.8 (x2), 121.6, 118.7, 118.5, 115.9, 110.3, 108.9, 72.2 (x2), 66.7, 66.2, 66.1, 59.1 (x2), 53.3, 52.4, 28.2; **FT-IR** (thin film, cm^{-1}) ν_{max} 2952, 1740, 1597, 1492, 1452, 1232, 1197, 1151, 1069, 1013, 921, 820, 750, 701, 599; **HRMS** calc'd for $C_{26}H_{25}NO_6$ [M+] 447.1682; found 447.1678.

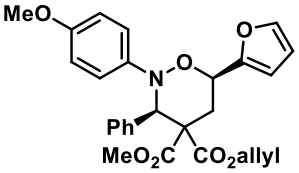


4-allyl 4-methyl 2,3-diphenyl-6-vinylmorpholine-4,4-dicarboxylate (1-223k): Following general method A, requisite nitrone (360 mg, 1.8 mmol), cyclopropane **1-221c** (330 mg, 1.5 mmol), and $Yb(OTf)_3$ (90 mg, 0.15 mmol) stirred in room temperature dichloromethane (10 mL) for 20 hours, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223k** as a pale yellow viscous oil (83%, 510 mg, 1.2 mmol, 1:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.40 (30%, EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 5.95 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.54-5.52 (m, 1H), 3.47 (s, 3H): Diastereomer B: δ 5.63 (ddt, *J* = 17.2, 10.5, 6 Hz, 1H), 5.50-5.48 (m, 1H), 3.89 (s, 3H): Diastereomeric Mixture: δ 7.53-7.50 (m, 4H), 7.19-7.12 (m, 10H), 7.08-7.06 (m, 4H), 6.84-6.79 (m, 2H), 6.08 (ddd, *J* = 17.4, 10.8, 5.5 Hz, 2H), 5.70 (s, 2H), 5.41-5.34 (m, 3H), 5.28 (dq, *J* = 10.6, 1.2 Hz, 1H), 5.20-5.14 (m, 2H), 4.84-4.75 (m, 2H), 4.54-4.48 (m, 2H), 4.40-4.22 (m, 3H), 2.61-2.59 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ 170.0, 169.1, 168.2, 167.5, 148.6 (x 2), 135.9, 134.9, 134.8, 131.5, 131.1, 130.6, 130.4, 128.5, 128.0, 127.9 (x 2), 121.6 (x 2), 118.8, 118.7, 117.3, 115.9 (x 2), 77.1, 66.7, 66.3, 66.0 (x 2), 59.1 (x 2), 53.4, 52.5, 41.8, 30.4 (x 2); **FT-IR** (thin film, cm^{-1}) ν_{max} 3092, 3061, 3028, 2988, 2952, 1740, 1648, 1598, 1493, 1453, 1435, 1229, 1198, 1153, 1085, 1031, 990, 916, 810, 755, 734, 701, 662, 597, 549; **HRMS** calc'd for $C_{24}H_{25}NO_5$ [M+] 407.1733; found 407.1731.



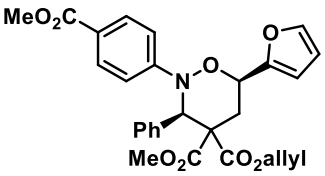
4-allyl 4-methyl 3-(4-cyanophenyl)-2-phenyl-6-vinylmorpholine-4,4-dicarboxylate (1-223l): Following general method A, requisite nitrone (260 mg, 1.2 mmol), cyclopropane **1-221c** (200 mg, 0.97 mmol), and $Yb(OTf)_3$ (60 mg, 0.097 mmol) stirred in room temperature dichloromethane (10 mL) for 20 h, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223l** as a pale yellow

viscous oil (63%, 260 mg, 0.61 mmol, 1.75:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.34 (30%, EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 5.95 (ddt, *J* = 17.0, 11.0, 5.7 Hz, 1H), 5.53-5.52 (m, 1H), 3.9 (s, 3H): Diastereomer B: δ 5.63 (ddt, *J* = 17.4, 10.1, 5.8 Hz, 1H), 5.49-5.48 (m, 1H), 3.50 (s, 3H): Diastereomeric Mixture: δ 7.65-7.62 (m, 4H), 7.483-7.45 (m, 3H), 7.18-7.14 (m, 3H), 7.03 (d, *J* = 8.2 Hz, 3H), 6.85 (t, *J* = 7.2 Hz, 2H), 6.05 (ddd, *J* = 17.4, 10.9, 5.3 Hz, 1H), 5.73 (s, 2H), 5.40-5.16 (m, 5H), 4.85-4.76 (m, 1H), 4.55-4.51 (m, 2H), 4.42-4.27 (m, 2H), 2.67-2.63 (m, 2H), 2.53-2.45 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ 169.4, 168.5, 167.9, 167.1, 148.1, 140.4, 140.3, 135.4, 131.6, 131.5, 131.4, 131.2, 131.1, 130.6, 128.7, 122.3, 119.3, 119.2, 118.4, 117.7, 115.8, 112.0, 77.1, 67.0, 66.5, 65.9, 58.8, 58.7, 30.4, ; **FT-IR** (thin film, cm^{-1}) ν_{max} 2953, 2229, 1740, 1708, 1648, 1597, 1493, 1436, 1254, 1227, 1201, 1152, 1074, 991, 941, 831, 758, 693, 605, 548, 500; **HRMS** calc'd for $C_{25}H_{24}N_2O_5$ [M+] 432.1685; found 432.1684.

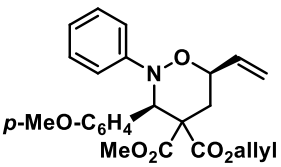


4-allyl 4-methyl 6-(furan-2-yl)-2-(4-methoxyphenyl)-3-phenylmorpholine-4,4-dicarboxylate (1-223m): Following general method A, requisite nitrone (850 mg, 1.2 mmol), cyclopropane **1-221d** (180 mg, 0.71 mmol), and $Yb(OTf)_3$ (44 mg, 0.071 mmol) stirred in room temperature dichloromethane (10 mL) for 20 h, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223m** as a colourless viscous oil (90%, 300 mg, 0.64 mmol, 1:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.28 (30%, EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 6.64 (dd, *J* = 9.0, 1.2 Hz, 4H), 5.25 (dq, *J* = 10.3, 1.2 Hz, 1 H) 3.88 (s, 3H): Diastereomer B: δ 6.93 (app d, *J* = 9.0 Hz, 4H), 5.36 (dq, *J* = 17.2, 1.6 Hz, 1H), 3.51 (s, 3H): Diastereomeric Mixture: δ 7.56-7.52 (m, 4H), 7.49-7.48 (m, 2H), 7.17-7.15 (m, 6H), 6.52 (d, *J* = 3.1 Hz, 2H), 6.41 (dd, *J* = 3.1, 2.0 Hz, 2H), 5.99-5.89 (m, 1H), 5.65-5.55 (m, 3H), 5.17-5.06 (m, 5H), 4.85-4.73 (m, 3H), 4.38-4.20 (m, 3H), 3.11 (ddd, *J* = 14.4, 12.5, 3.9 Hz, 2H), 2.71 (dd, *J* = 14.5, 2.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ 170.0, 169.1, 168.1, 167.4, 155.1, 152.1, 143.0, 142.2 (x 2), 134.9, 134.7, 131.5, 131.1, 130.9, 130.7, 128.1, 127.9 (x 2), 118.9, 118.7, 118.4, 113.7, 110.3, 108.9, 72.3, 72.2, 67.5, 67.4, 66.8, 66.3, 59.4, 59.3, 55.3, 53.4, 52.6, 29.7, 28.2; **FT-IR** (thin film, cm^{-1}) ν_{max} 2298, 2953, 2836, 1740, 1648, 1611, 1508, 1453, 1363, 1245, 1199, 1177, 1151,

1034, 1013, 985, 945, 917, 828, 787, 735, 702, 648, 599, 557; **HRMS** calc'd for $C_{27}H_{27}NO_7$ [M+] 477.1788; found 477.1776.



4-allyl 4-methyl 6-(furan-2-yl)-2-(4 (methoxycarbonyl)phenyl)-3-phenylmorpholine-4,4-dicarboxylate (1-223n): Following general method A, requisite nitrone (190 mg, 0.75 mmol), cyclopropane **1-221d** (160 mg, 0.63 mmol), and $Yb(OTf)_3$ (40 mg, 0.063 mmol) stirred in room temperature dichloromethane (10 mL) for 20 h, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223n** as a white viscous oil (91%, 290 mg, 0.57 mmol, 1.5:1diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.28 (30%, EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 5.71-5.61 (m,1H), 3.88 (s, 3H); Diastereomer B: δ 3.51 (s, 3H); Diastereomeric Mixture: δ 7.83 (app d, *J* = 8.6 Hz, 4H), 7.60-7.54 (m, 6H), 7.21-7.19 (m, 5H), 7.09 (dd, *J* = 8.8, 1.8 Hz, 4H), 6.60 (app d, *J* = 3.5 Hz, 2H), 6.47 (dd, *J* = 3.3, 1.8 Hz, 2H), 5.98 (m, 3H), 5.36 (dd, *J* =17.2, 1.6 Hz, 1H), 5.27 (dd, *J* = 10.6, 0.8 Hz), 5.22-5.17 (m. 2H), 5.07 (dt, *J* = 12.7, 2.9, 2.7 Hz, 2H), 4.85-4.73 (m, 2H), 4.45-4.27 (m, 3H), 3.81 (s, 6H), 3.21-3.13 (m, 2H), 2.76 (dd, *J* = 14.5, 2.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ169.6, 168.8, 167.7, 167.0, 166.8, 151.8, 151.2, 143.3, 134.4, 134.3, 131.2, 130.9, 130.5, 130.4, 130.2, 128.4, 128.1 (x2), 122.6, 119.1, 118.9, 114.3, 114.3, 110.4, 109.3, 72.5, 72.5, 66.9, 68.5, 64.7 (x2), 58.9 (x2), 53.5, 52.7, 51.6, 41.8, 28.3; **FT-IR** (thin film, cm^{-1}) ν_{max} 2952, 1741, 1717, 1605, 1508, 1435, 1363, 1282, 1253, 1178, 1152, 1113, 1090, 1067, 946, 914, 885, 776, 736, 702, 618, 599, 550; **HRMS** calc'd for $C_{28}H_{27}NO_8$ [M+] 505.1737; found 505.1732.

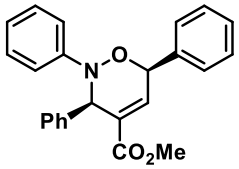


4-allyl 4-methyl 3-(4-methoxyphenyl)-2-phenyl-6-vinylmorpholine-4,4-dicarboxylate (1-223o): Following general method A, requisite nitrone (220 mg, 0.98 mmol), cyclopropane **1-221c** (150 mg, 0.82 mmol), and $Yb(OTf)_3$ (50 mg, 0.082 mmol) stirred in room temperature dichloromethane (10 mL) for 20 h, gave, after filtration and purification (column chromatography, EtOAc/hexanes 1:20) **1-223o** as a colourless viscous oil (80%, 290 mg, 0.66 mmol, 1:1 diastereomeric mixture at C4); $\mathbf{R_f}$ = 0.37 (30%, EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) Diastereomer A: δ 5.53 (dt,

J = 3.03, 1.42 Hz, 1H), 3.88 (s, 3H): Diastereomer B: δ 5.50 (dt, *J* = 3.03, 1.42 Hz, 1H), 3.49 (s, 3H): Diastereomeric Mixture: δ 7.46-7.44 (m, 4H), 7.18-7.14 (m, 4H), 7.09 (s, 2H), 7.07 (d, *J* = 0.4 Hz, 2H), 6.82 (td, *J* = 7.2, 1.2 Hz, 2H), 6.71-6.68 (m, 4H), 6.00 (ddd, *J* = 17.4, 10.9, 5.3, 2H), 6.00-5.90 (m, 1H), 5.73-5.63 (m, 3H), 5.40-5.34 (m, 3H), 5.28 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.22-5.16 (m, 2H), 4.84-4.75 (m, 2H), 4.55-4.49 (m, 2H), 4.44-4.25 (m, 3H), 3.69 (s, 6H), 2.61-2.59 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) Diastereomeric Mixture: δ 170.0, 169.1, 168.2, 167.5, 159.1 (x 2), 148.6 (x 2), 136.0, 131.8, 131.6, 131.5, 131.1, 128.4, 126.8, 126.7, 121.6, 121.5, 118.7, 118.6, 117.2, 115.9 (x 2), 113.2 (x 2), 77.1, 66.7, 66.2, 65.5, 59.1, 54.9 (x 2), 53.3, 52.5, 41.7, 30.4, 30.3, 29.7; **FT-IR** (thin film, cm^{-1}) ν_{max} 2996, 2953, 2837, 1741, 1648, 1600, 1512, 1491, 1453, 1254, 1200 ,1181, 1154, 1116, 1075, 1033, 991, 936, 840, 753, 730, 693, 613, 538; **HRMS** calc'd for $C_{25}H_{27}NO_6$ [M+] 437.1838; found 437.1836.

Experimental procedure and spectral data for dihydro-1,2-oxazines (1-226)

To a solution of tetrahydro-1,2-oxazine (**1-223**, 1 mmol) in CH_3CN (3−5 mL) was added $Pd_2(dba)_3$ (6 mol%). The solution was placed under Ar and brought to reflux (80 °C) for three hours. At this time, the reaction was cooled to RT and filtered through celite. The extract was absorbed onto silca and the solvent was removed by reduced pressure. Pure product was obtained by flash column chromatography on silica gel (eluent: EtOAc in hexanes).



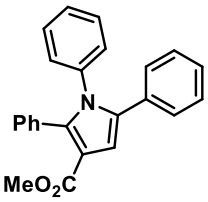
methyl 2,3,6-triphenyl-3,6-dihydro-2*H*-1,2-oxazine-4-carboxylate (1-226a): Following the general procedure, tetrahydro-1,2-oxazine **1-223a** (190 mg, 0.74 mmol) and $Pd_2(dba)_3$ (40 mg, 0.044 mmol) were brought to reflux in CH_3CN (5 mL) for 3 h. Filtration and purification (silica gel column chromatography, EtOAc/hexanes 1:20) provided dihydro-1,2-oxazine **1-226** (66%, 100 mg, 0.28 mmol) as a white powder; $\mathbf{R_f}$ = 0.43 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56−7.51 (m, 2H), 7.50−7.40 (m, 3H), 7.37−7.30 (m, 3H), 7.23−7.16 (m, 5H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.91 (dd, *J* = 7.0 Hz, 1H), 5.75 (s, 1H), 5.58 (s, 1H), 3.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.3 165.2, 148.0, 139.7, 136.7, 136.5, 131.1, 129.5, 128.9, 128.9, 128.6, 127.9, 127.7, 122.3, 117.0, 78.6, 62.9, 52.0; **FT-IR** (thin film, cm^{-1}) ν_{max} 3061, 3031, 2951, 2846, 2360, 1719, 1598, 1493, 1453, 1436, 1245, 1078, 1029, 909, 735, 696, 667, 627, 696; HRMS calc'd for $C_{24}H_{21}NO_3$ [M+] 371.1521, found 371.1519.

Experimental procedure and spectral data for preparation of pyrroles (1-231)

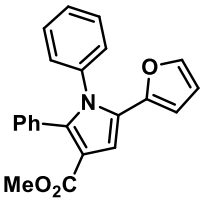
General method A: To a solution of dihydro-1,2-oxazine **1-226** (1 equiv) in CH_3CN (3−5 mL) was added DBU (3 equiv) and stirred under Ar at the indicated temperature for the indicated time. Upon completion (TLC analysis), the solution was filtered through celite and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexanes 1:20) gave the desired pyrroles (**1-231**).

General method B – one-pot procedure: To a solution of tetrahydro-1,2-oxazine (**1-223**, 1 equiv) in CH_3CN (3−5 mL) was added $Pd_2(dba)_3$ (6 mol %). The solution was placed under Ar and brought to reflux (80 °C) for 3 h. At this time, the reaction was cooled to 40 °C and either NEt_3 or DBU (3 equiv) was added in one portion, and the reaction was stirred further for the time indicated. Upon completion (TLC analysis), the solution was filtered through celite and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, EtOAc/hexanes 1:20) gave the desired pyrroles (**1-231**).

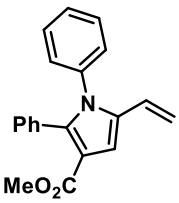
Note: for compounds that co-elute with dba, the following work-up procedure was used: the reaction residue was dissolved in MeOH (3 mL) and $NaBH_4$ (1.2 equiv/ mmol dba) was slowly added. After dba reduction (as based on TLC analysis), the mixture the organics were collected via extraction with Et_2O. The extract was absorbed onto silca and the solvent was removed by reduced pressure. Purification was then effected by the above methods.



methyl 1,2,5-triphenyl-1*H*-pyrrole-3-carboxylate (1-231a): Following general method A, dihydro-1,2-oxazine **1-226a** (38 mg, 0.10 mmol) and DBU (45 μL, 0.30 mmol) in CH_3CN (4 mL, 25 °C, 5 min) gave **1-231a** (79%, 28 mg, 0.079 mmol). Following general method B (one-pot procedure), tetrahydro-1,2-oxazine **1-223a** (57 mg, 0.12 mmol), $Pd_2(dba)_3$ (7 mg, .0072 mmol) in CH_3CN (5 mL), followed by DBU (54 μL, 0.36 mmol) at room temperature (5 min) gave **1-231a** (76%, 28 mg, 0.080 mmol) as a white powder; $\mathbf{R_f}$ = 0.45 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25−7.12 (m, 11H), 7.11−7.07 (m, 2H), 6.95 (s, 1H), 6.94−6.91 (m, 2H), 3.73 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1, 139.9, 137.8, 134.7, 132.1, 131.4, 131.2, 128.8, 128.6, 128.5, 128.0, 127.8, 127.6, 127.2, 126.8, 113.8, 110.8, 51.0; **FT-IR** (thin film, cm^{-1}) ν_{max} 3061, 2948, 2251, 1714, 1599, 1559, 1496, 1474, 1439, 1404, 1274, 1223, 1183, 1113, 912, 777, 760, 731, 696, 542; **HRMS** calc'd for $C_{24}H_{19}NO_2$ [M+] 353.1416, found 353.1424.

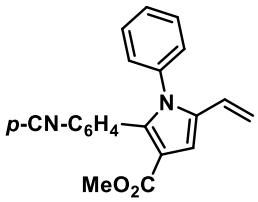


methyl 5-(furan-2-yl)-1,2-diphenyl-1H-pyrrole-3-carboxylate (1-231j): Following general method B, tetrahydro-1,2-oxazine **1-223j** (110 mg, 0.23 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol) in CH_3CN (5 mL, 3 h), followed by DBU (110 μL, 0.70 mmol) at RT (5 minutes) gave **1-231j** (60%, 50 mg, 0.14 mmol); white powder; $\mathbf{R_f}$ = 0.45 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 4H), 7.22-7.18 (m, 5H), 7.23-7.10 (m, 3H), 6.19 (dd, *J* = 5.6, 2.0 Hz, 1H), 5.30 (d, *J* = 3.2 Hz, 1H), 3.72 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.9, 146.5, 141.29, 137.8, 131.1, 130.9, 129.0, 128.8, 128.5, 127.9, 127.3, 126.3, 110.8, 110.0, 109.6, 106.0, 51.0, 41.8; **FT-IR** (thin film, cm^{-1}) 1701, 1496, 1437, 1238, 1210, 1134, 1034, 913, 744, 700, 668; **HRMS** for $C_{22}H_{17}NO_3$ [M+] calc'd 343.1208; found 343.1206.

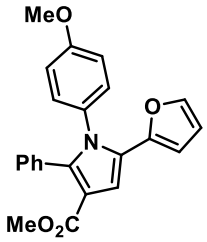


methyl 1,2-diphenyl-5-vinyl-1H-pyrrole-3-carboxylate (1-231k): Following general method B, tetrahydro-1,2-oxazine **1-223k** (150 mg, 0.36 mmol), $Pd_2(dba)_3$ (20 mg, 0.021 mmol) in CH_3CN (5 mL, 3 h), followed by DBU (160 μL, 1.1 mmol) at RT (5 minutes) gave **1-231k** (61%, 66 mg, 0.22 mmol); white powder; $\mathbf{R_f}$ = 0.45 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 3H), 7.18-7.13 (m, 5H), 7.04 (dd, *J* = 6.6, 3.6 Hz,

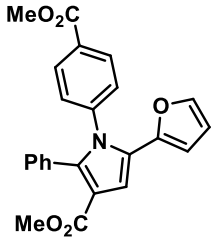
2H), 7.01 (s, 1H), 6.18 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.53 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.00 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.69 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.0, 139.4, 137.1, 133.2, 131.2, 131.0, 128.8, 128.1, 127.8, 127.3, 125.7, 113.7, 113.0, 110.0, 107.7, 50.97; **FT-IR** (thin film, cm^{-1}) 3060, 2924, 1713, 1673, 1652, 1621, 1596, 1557, 1497, 1477, 1425, 1338, 1245, 1218, 1188, 1113, 991, 778, 764, 697; **HRMS** for $C_{20}H_{17}NO_2$ [M+] calc'd 303.1259; found 303.1252.



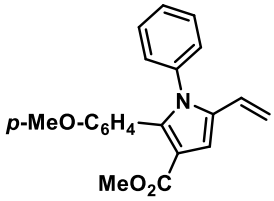
methyl 2-(4-cyanophenyl)-1-phenyl-5-vinyl-1H-pyrrole-3-carboxylate (1-231l): Following general method B, tetrahydro-1,2-oxazine **1-223l** (110 mg, 0.24 mmol), $Pd_2(dba)_3$ (13 mg, 0.015 mmol) in CH_3CN (5 mL, 3 h), followed by DBU (110 μL, 0.11 mmol) at RT (5 minutes) gave **1-231l** (58%, 47 mg, 0.73 mmol); yellow powder; $\mathbf{R_f}$ = 0.33 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.18 (m, 7H), 6.96 (s, 1H), 6.12 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.51 (d, *J* = 17.6 Hz, 1H), 5.00 (d. *J* = 11.2 Hz, 1H), 3.66 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6, 136.6, 136.5, 135.9, 134.3, 131.7, 131.0, 129.1, 128.6, 125.2, 118.6, 114.6, 114.1, 111.3, 108.1, 51.11, 41.8; **FT-IR** (thin film, cm^{-1}) 2922, 2228, 1715, 1495, 1436, 1249, 1220, 1115, 1029, 913.2, 850, 743, 700, 668; **HRMS** for $C_{21}H_{16}N_2O_2$ [M+] calc'd 328.1212; found 328.1209.



methyl 5-(furan-2-yl)-1-(4-methoxyphenyl)-2-phenyl-1H-pyrrole-3-carboxylate (1-231m): Following general method B, tetrahydro-1,2-oxazine **1-223m** (100 mg, 0.21 mmol), Pd2(dba)3 (11 mg, 0.013 mmol) in CH3CN (5 mL, 80 °C, 3 h), followed by DBU (94 μL, 0.63 mmol) at room temperature (5 min) gave **1-231m** (61%, 50 mg, 0.13 mmol) as a white powder; Rf = 0.29 (30% EtOAc/hexanes); **^{1}H NMR** (600 MHz, CDCl3) δ 7.30 (d, J = 1.2 Hz, 1H), 7.22-7.18 (m, 5H), 7.09 (s, 1H), 7.03 (app d, J = 8.8 Hz, 2H), 6.78 (app d, J = 9.4 Hz, 2H), 6.20 (app q, J = 1.8, 1H), 5.29 (d, J = 3.5 Hz, 1H) 3.78 (s, 3H), 3.71 (s, 3H); **^{13}C NMR** (100 MHz, CDCl3) δ 165.0, 159.3, 146.6, 141.2, 140.6, 131.1, 131.0, 129.9, 127.8, 127.3, 126.6, 113.9, 113.7, 109.2, 105.8, 52.3, 50.0; **FT-IR** (thin film, cm-1) 1716, 1514, 1489, 1437, 1382, 1234, 1189, 1109, 1030, 913, 840, 748, 699; **HRMS** for $C_{23}H_{19}NO_4$ [M+] calc'd 373.1314; found 373.1315.



methyl 5-(furan-2-yl)-1-(4-(methoxycarbonyl)phenyl)-2-phenyl-1H-pyrrole-3-carboxylate (1-231n): Following general method B, tetrahydro-1,2-oxazine **1-223n** (93 mg, 0.18 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol) in CH_3CN (5 mL, 3 h), followed by DBU (80 μL, 0.55 mmol) at RT (5 minutes) gave **1-231n** (71%, 48 mg, 0.13 mmol); white powder; $\mathbf{R_f}$ = 0.45 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.22-7.15 (m, 7H), 7.10 (s, 1H), 6.21 (dd, *J* = 3, 2 Hz, 1H), 5.50 (d, *J* = 3.6 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1, 164.7, 146.0, 141.9, 141.7, 140.1, 131.1, 130.5, 130.1, 130.0, 128.9, 128.2, 127.5, 126.0, 110.9, 110.5, 110.0, 106.8, 52.3, 51.1, 41.8, ; **FT-IR** (thin film, cm^{-1}) 1716, 1514, 1489, 1436, 1382, 1234, 1189, 1109, 1030, 913, 840, 743, 699; **HRMS** for $C_{24}H_{19}NO_5$ [M+] calc'd 401.1263; found 401.1253.



methyl 2-(4-methoxyphenyl)-1-phenyl-5-vinyl-1H-pyrrole-3-carboxylate (1-231o): Following general method B, tetrahydro-1,2-oxazine **1-223o** (86 mg, 0.20 mmol), $Pd_2(dba)_3$ (11 mg, 0.012 mmol) in CH_3CN (5 mL, 3 h), followed by DBU (90 μL, 0.59 mmol) at RT (5 minutes) gave **1-231o** (70%, 46 mg, 0.14 mmol); white powder; $\mathbf{R_f}$ = 0.39 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 3H), 7.09-7.04 (m, 4H), 7.00 (s, 1H), 6.72 (d, *J* = 8.4 Hz, 2H), 6.19 (dd, *J* = 17.4, 11.2 Hz, 1H), 5.52 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.00 (dd, *J* = 11.4, 0.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1, 159.0, 137.3, 133.0, 132.2, 128.9, 128.8, 128.1, 125.8, 112.9, 112.8, 107.7, 55.1, 51.0, 41.9; **FT-IR** (thin film, cm^{-1}) 2924, 2853, 1714, 1611, 1597, 1558, 1487, 1440, 1290, 1249, 1217, 1178, 1114, 1036, 944, 906, 839, 776, 699, 517; **HRMS** for $C_{21}H_{19}NO_3$ [M+] calc'd 333.1365; found 333.1361.

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Chapter 2 - Diels-Alder Approach Towards Fargesine and Fumimycin

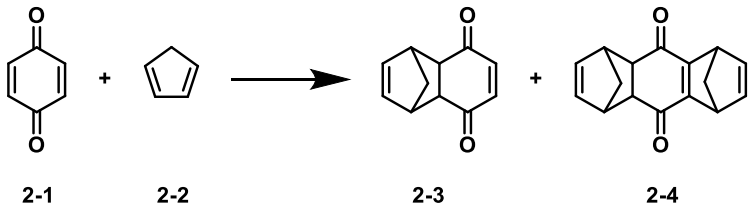
2 Chapter introduction

Chapter two describes the formal synthesis of the indole containing natural product fargesine, and efforts towards the total synthesis of benzofuranone containing natural product fumimycin. Both of these syntheses are dependent on the Diels-Alder reaction of quinoid species, and as such are presented together in this chapter. A general description of Diels-Alder chemistry and its application in total synthesis preludes the chapter, followed by an introduction to indoles, and lastly the introduction and results for each natural product. The work on the formal synthesis of fargesine was developed in collaboration with Sharon Michalak, while efforts towards the total synthesis of fumimycin was independent.

2.1 Diels-Alder reaction

2.1.1 Overview

With the ability to form two new carbon-carbon bonds, the potential to set four contiguous stereocenters in one step, and with predictive regioselectivity, the Diels-Alder reaction is one of the most powerful reactions to chemists.[1] The reaction involves a [4π+2π] cycloaddition between a diene, and an olefin (dienophile). Although the cycloaddition had been previously reported by Wieland,[2] Albrecht,[3] and Euler,[4] they had incorrectly assigned their products. It was not until 1928 that Otto Diels and his student Kurt Alder were able to successfully elucidate the products between 1,4-benzoquinone and cyclopentadiene (Scheme 2-1).[5] Through their subsequent studies on the mechanism, they were awarded the Nobel Prize in Chemistry in 1950 “for their discovery and development of the diene synthesis”.[6]



Scheme 2-1 Diels and Alder's reaction [4π+2π] cycloaddition

The mechanism is often explained with Frontier Molecular Orbital theory (FMO theory).[7] According to FMO theory, the full orbitals of one reactant must have the same symmetry, and similar energy level, with the empty orbitals of another reactant in order for the reaction to proceed. In the Diels-Alder reaction, the highest occupied molecular orbital (HOMO) of the diene, and the lowest unoccupied molecular orbital (LUMO) of the dienophile interact as they are symmetrical and relatively close in energy (Figure 2-1, Standard Diels-Alder). The reaction can be made more favourable by decreasing the energy gap between the HOMO and the LUMO. For example, addition of electron donating groups to the diene increases the energy of the system, while electron withdrawing groups on the dienophile decrease the energy of the system, thus minimizing the energy gap (Figure 2-1, Diels-Alder with EDG/EWG).[8]

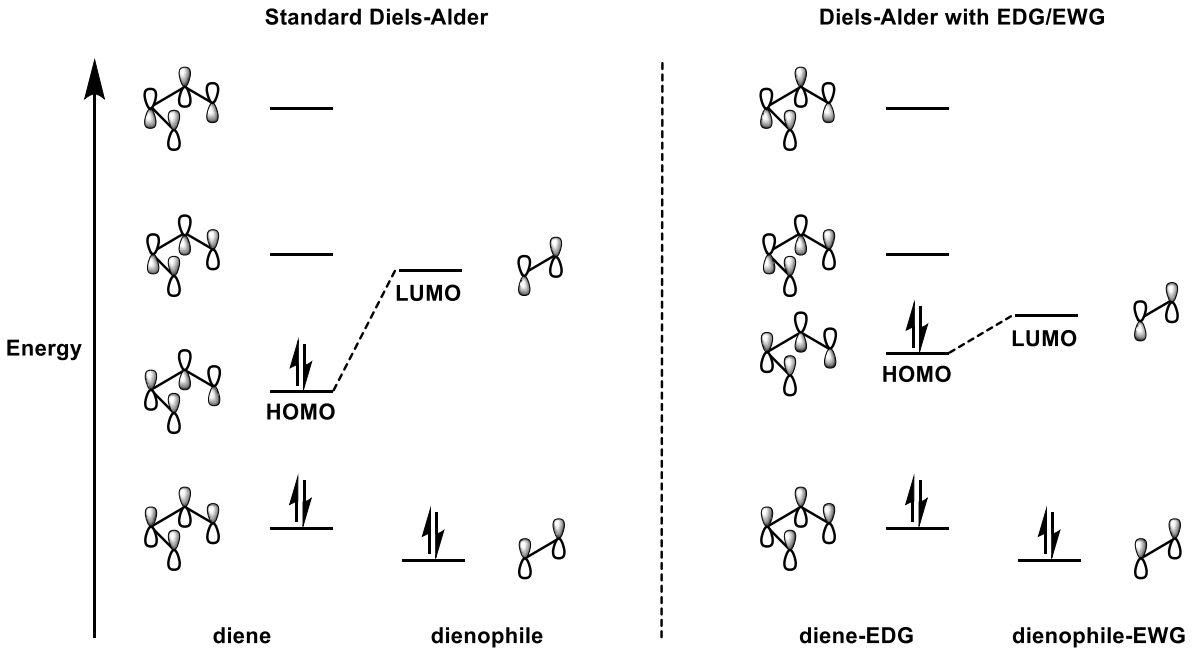
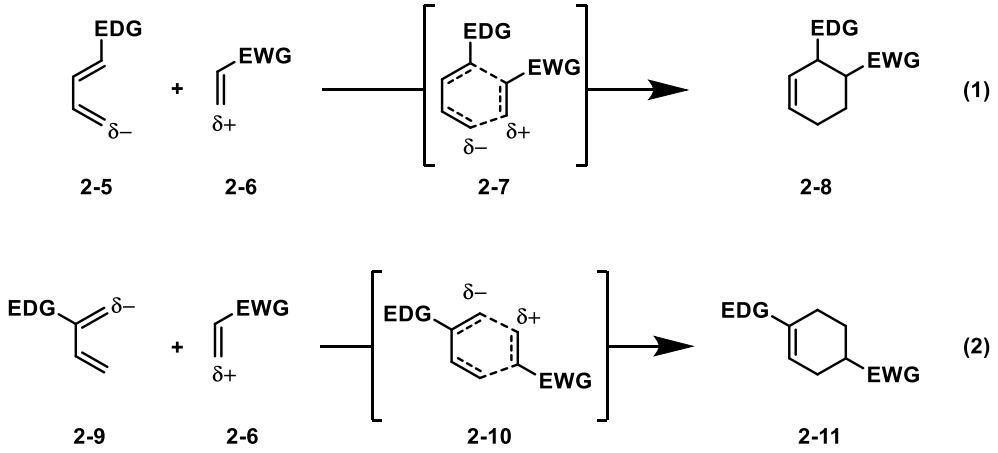


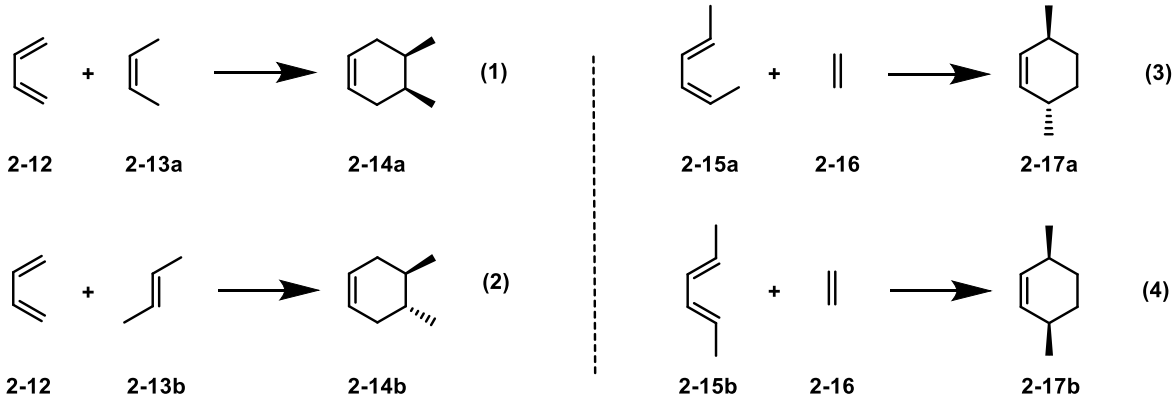
Figure 2-1 FMO representation of the Diels-Alder reaction

As FMO theory involves full orbitals of the diene interacting with the empty orbitals of the dienophile, regioselectivity can be predicted simply by resonance to find the most electron rich sites of the diene, and the most electron deficient site of the dienophile. These will react through a cyclic transition state to form the product (Scheme 2-2).



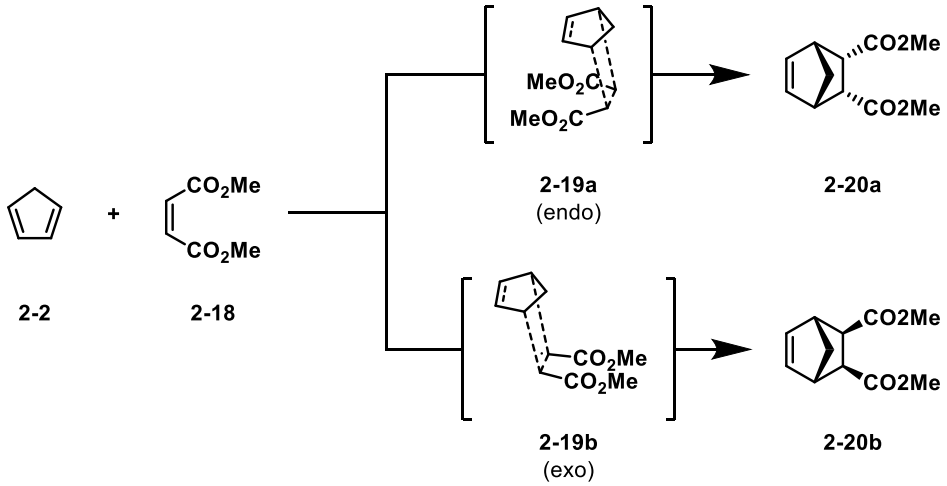
Scheme 2-2 Regioselectivity of the Diels-Alder reaction

For substituted dienes or dienophiles, the relative stereochemistry of the olefins in either reacting partner will be maintained in the cycloadduct. For example, *cis* olefins in the dienophile will result in substituents on the cycloadduct with a *cis* relationship (Scheme 2-3, entry 1), similarly *trans* olefins in the dienophile will give *trans* substituents in the product (Scheme 2-3, entry 2). For dienes composed of olefins with different stereoisomers (*cis* and *trans*), the substituents on the cycloadduct will have a *trans* relationship (Scheme 2-3, entry 3), and dienes composed of olefins with the same stereoisomers will result in products containing substituents with a *cis* relationship (Scheme 2-3, entry 4).[8]



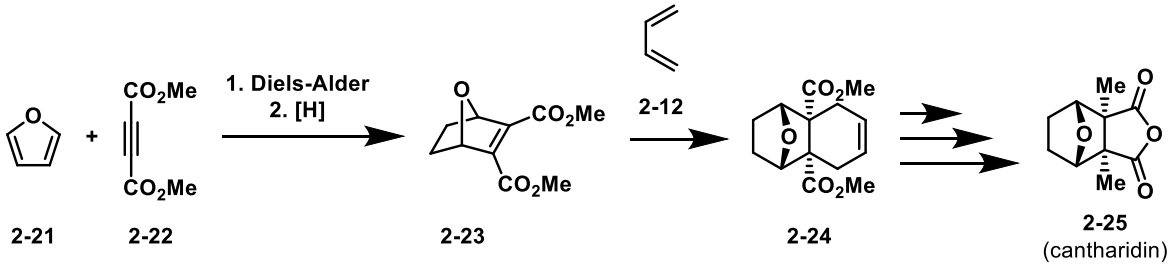
Scheme 2-3 Stereospecificity of the Diels-Alder reaction

As can be seen in Scheme 2-4, a simple Diels-Alder reaction can result in two possible products with differing stereoselectivity which are titled *endo* or *exo* products. The two outcomes for the reaction are due to the relative stabilities in the transition states for either product. The *endo* product involves secondary orbital interactions in the transition state, while the *exo* product does not contain these interactions. Since secondary orbital interactions allow for a more stable transition state, the *endo* product is the kinetic product, and is usually the favoured product unless steric interactions prohibit forming an *endo* transition state.[8]



Scheme 2-4 *Endo* and *exo* transition states of the Diels-Alder reaction

Due to the great insight of the Diels-Alder mechanism, it provides chemists with an invaluable tool in total synthesis. The earliest example of the reaction being used in a total synthesis was by the Stork group on their synthesis of cantharidin in 1951 (Scheme 2-5).[9]



Scheme 2-5 Stork group's synthesis of cantharidin

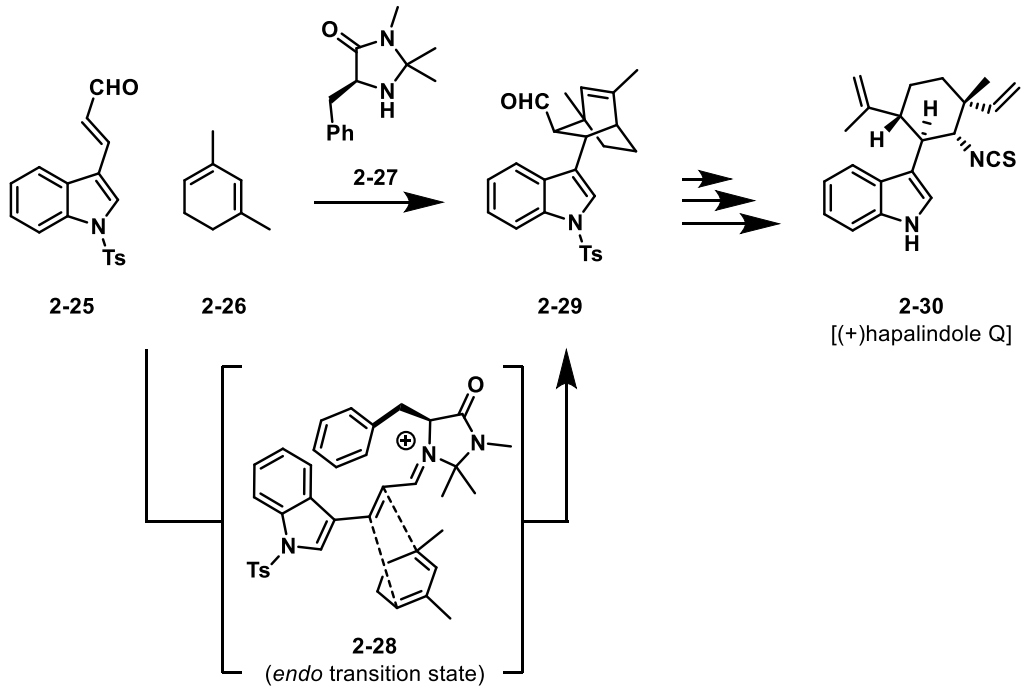
2.1.2 Hyperbaric Diels-Alder

As the Diels-Alder reaction has been around for over 100 years, many conditions have been developed for it. Simply heating the diene and dienophile can be enough for the reaction to proceed and catalytic systems have also been developed to form adducts enantioselectively. However, another method to facilitate the reaction is through the use of hyperbaric conditions. A reaction will proceed if the reactants are in close proximity (omitting other factors such as temperature, solvent, etc); therefore, hyperbaric conditions promote reactions by forcing strong intermolecular interactions.[10] The effect of pressure on a reaction was described by Evans and Polanyi using transition-state theory.[11] In transition-state theory, molecules interact to form an unstable intermediate (transition state), which then can form a stable product. The derived formula of their work is $(\partial \ln k/\partial P)_T = -\Delta V^{\ddagger}/RT$; where k is the rate of a reaction, P is the pressure, R is the gas constant, T is temperature, and $\Delta V^{\ddagger}$ is the difference in 'volume of activation'. The volume of activation is the difference between the volume of the transition state species, and the volume of the reactant molecules. It can be seen from the formula that if $\Delta V^{\ddagger}$ is negative, then the rate will increase with pressure. Generally speaking, reactions that are bond forming result in a negative volume of activation, and reactions that are bond breaking result in a positive volume of activation. Thus, the Diels-Alder reaction is favourable under hyperbaric conditions. In order for the rate to significantly change, several hundred bars of pressure must be applied to the reaction, and approximately 700 bar is required to increase the reaction rate by a factor of two or four.[12] The hyperbaric Diels-Alder will be further discussed later in this chapter (Section 2.6, Progress towards the total synthesis of fumimycin).

2.1.3 Diels-Alder reaction in natural product synthesis

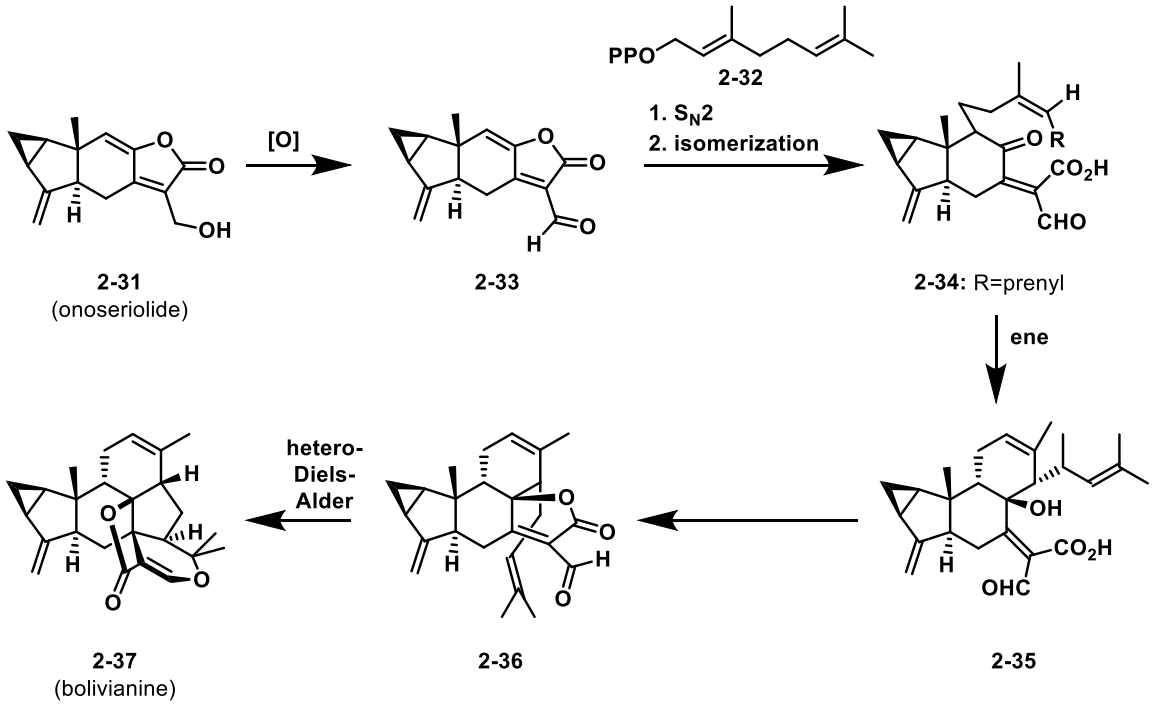
The use of the Diels-Alder reaction in total synthesis grew substantially after Stork's synthesis of cantharidin and many classic targets were accessed this way including Gates' morphine synthesis,[13] and Woodward's steroid syntheses.[14] Several variations of the Diels-Alder reaction have been extensively studied and widely used in the synthesis of natural products and pharmaceuticals, and due to vast amount of information on the topic, only a few recent examples that showcase the transformation of simple starting material to complex natural products will be discussed below.

In memory of Aaron C. Kinsman, the total synthesis of (+)-haplindole Q will be discussed. In 2003, Kinsman and Kerr were able to access the four contiguous stereocenters required for (+)-hapalindole Q through a Diels-Alder reaction between achiral indole **2-25** and cyclohexadiene **2-26** (Scheme 2-6).[15] Stereoselective control in the reaction was brought about with MacMillan's chiral organocatalyst (**2-27**). MacMillian's chiral amine catalyst reacts with *α,β*-unsaturated aldehydes to form an iminium ion which effectively lowers the LUMO of the dienophile, due to the amplified electron withdrawing effect of the iminium ion.[16] Since the catalyst is chiral, it allows for a highly enantioselective Diel-Alder reaction to occur. As shown in the transition state **2-28**, the top face of the molecule is blocked, thus favouring only one enantiomer. Although the Diels-Alder cycloadduct was formed in a low 35% yield, they were able to obtain the product with high *endo* selectivity (70%) and a high *ee* of 93%. Further manipulations were done to complete the total synthesis of (+)-haplindole Q in a total 12 steps from indole **2-25** in a 1.7% overall yield.



Scheme 2-6 Kinsman and Kerr's synthesis of (+)-hapalindole Q

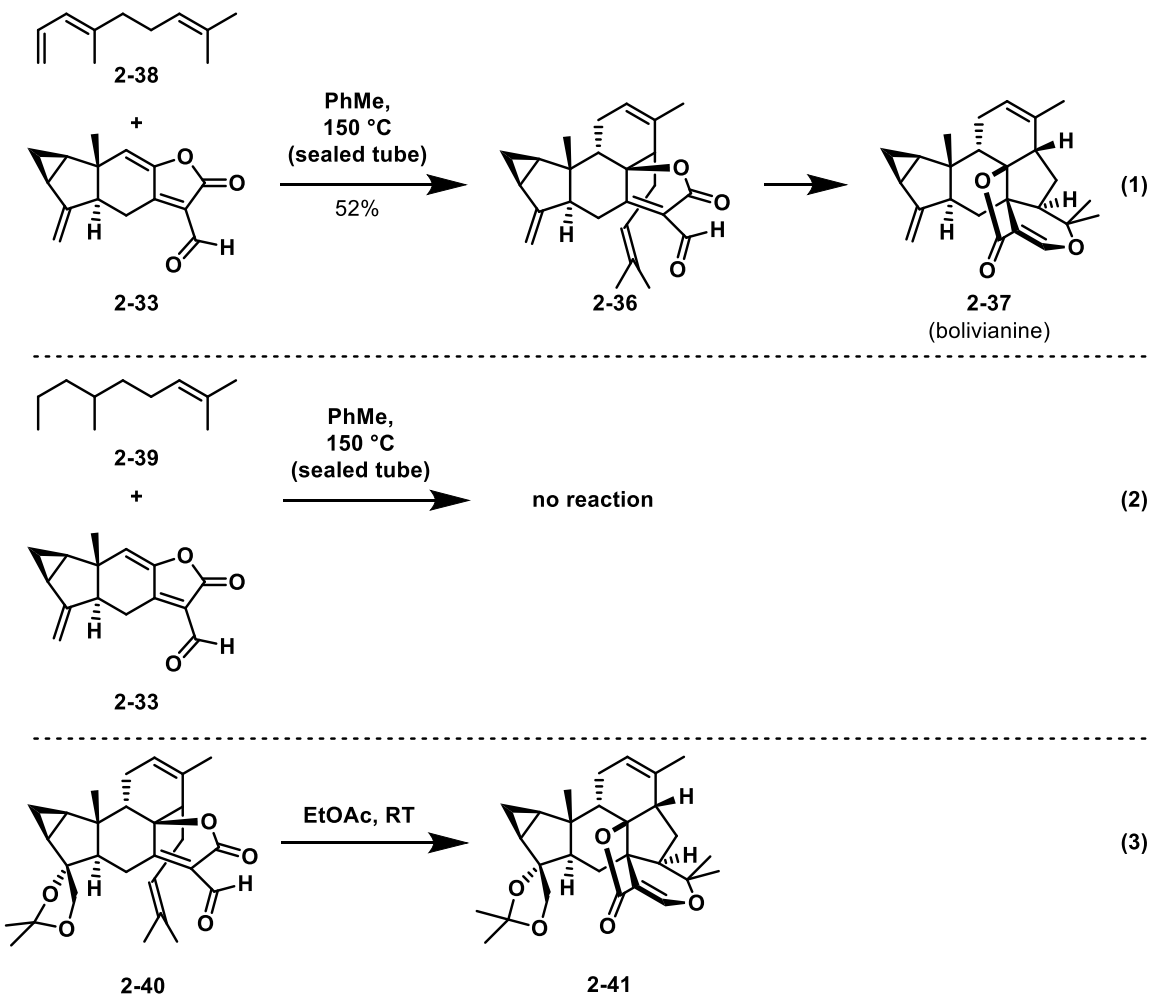
In 2007 the Jullian group isolated the sesterterpenoid bolivianine (**2-37**) from *Hedyosmum angustifolium* (Chloranthaceae).[17] Jullian hypothesized that bolivianine is synthesized within the organism from: 1) allylic oxidation of onoseriolide (**2-31,** Scheme 2-7), 2) nucleophilic attack to geranylpyrophosphate (**2-32**, GPP), and lastly 3) an annulation and hetero-Diels-Alder to form the remaining rings.



Scheme 2-7 Jullian's proposed biosynthesis of bolivianine

Inspired by the proposed biogenesis of bolivianine by Jullian, the Liu group thought they could synthesize onoseriolide, and then access bolivianine from a Diels-Alder/intramolecular hetero-Diels-Alder cascade between oxidized onoseriolide and GPP related terpene, *β*-*E*-ocimene (**2-38**).[18] As seen in Scheme 2-8, entry 1, oxidized onoseriolide and terpene **2-38** were heated to 150 °C in toluene (sealed tube), and remarkably they were able to access bolivianine in a 52% yield. Through their Diels-Alder/intramolecular hetero-Diels-Alder cascade they were able to generate three new rings, four C-C bonds, and five sterogenic centers with excellent selectivity. To determine if the hetero-Diels-Alder reaction initiates the cascade, the Liu group attempted a Diels-Alder between **2-33** and dienophile **2-39** (Scheme 2-8, entry 2). Despite many attempts, the reaction did not work suggesting that the hetero-Diels-Alder reaction only occurs once the proper orientation is set from the initial Diels-Alder reaction. They were able to show that this was indeed the case as a hetero-Diels-Alder occurred at room temperature for compound **2-40** (Scheme 2-8, entry 3), which was already in the proper orientation. Based on their findings they can explain the high selectivity of their Diels-Alder cascade due to: 1) diene **2-38** will react with dienophile **2-33** from the least

hindered face to form *endo* product **2-36**, and as a result 2) the orientation of the dienophile for the hetero-Diels-Alder is aligned to react at the *a*-face of the diene, yielding bolivianine.



Scheme 2-8 Liu group's total synthesis of bolivianine (1), and mechanism investigations (2 and 3)

One of the most famous natural product targets known is the anti-cancer drug paclitaxel (Taxol, **2-42**, Figure 2-2).[19] Taxol comes from a family of terpenes called taxanes, which contain at least 350 members with varying oxidation states, including decinnamoyltaxinine E (**2-43**), taxabaccatin III (**2-44**), taxusin (**2-45**), taxadienone (**2-46**). A parent molecule of the taxanes is taxadiene (**2-47**); this minimally oxidized natural product has functional group handles for further oxidation.

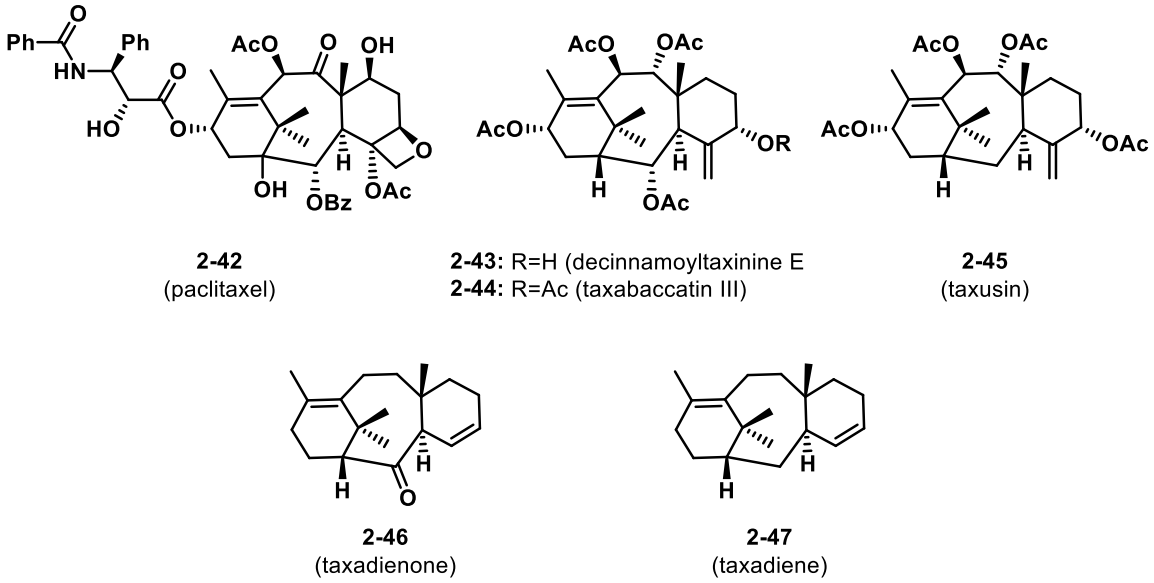
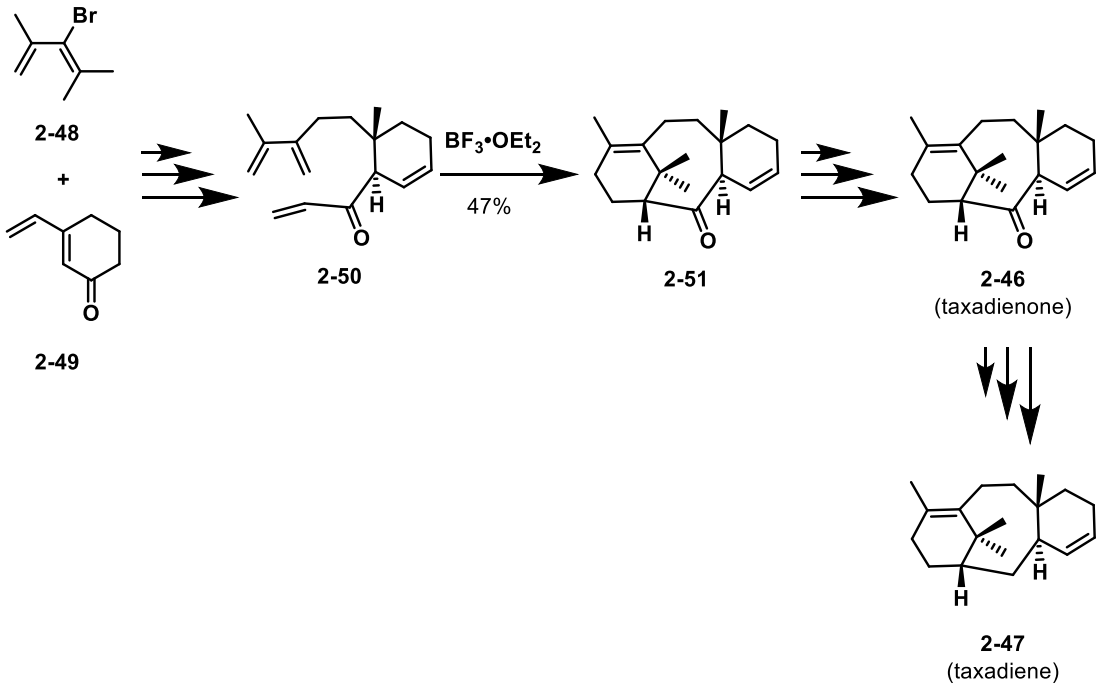


Figure 2-2 Examples of taxanes

Taxadiene is produced in extremely small quantities in nature (less than 1 mg from 750 kg of tree bark from *T. brevifolia*),[20] thus developing a method to access it would allow the synthesis of various taxanes and derivatives for further pharmaceutical testing. In 2012, the Baran group completed a gram-scale synthesis of the taxadiene, with a Diels-Alder reaction detrimental to their synthetic route (Scheme 2-9).[21] Starting from known diene **2-48** and ketone **2-49**, they were able to access intermediate **2-50** in three steps. An intramolecular Diels-Alder reaction formed compound **2-51** with a 47% yield of the desired diastereomer. Compound **2-51** was then converted to taxadienone (**2-46**) in two steps, which could then be converted to taxadiene (**2-47**) in three more steps. More recently, the Baran group was able to highlight the utility of their taxadienone synthesis in the first total synthesis of decinnamoyltaxinine E (18 steps from **2-46**) and taxabaccatin III (19 steps from **2-46**).[22] Although the key Diels-Alder step in Baran's synthesis looks fairly simple, Williams[23] had accessed (±)-taxadiene with a Diels-Alder reaction; however, his synthesis had 26 steps, while Baran's synthesis had 10 steps. The difference in the amount of synthetic steps goes to show how powerful the Diels-Alder can be given the right substrates.



Scheme 2-9 Baran group's synthesis of taxadienone and taxadiene

2.2 Introduction to indoles and their syntheses

2.2.1 Introduction to indoles

Indole is an aromatic heterocycle consisting of a benzene ring fused to a pyrrole ring. It was first isolated from the treatment of indigo with oleum, hence how the name was derived. In 1866, Adolf von Baeyer synthesized indole by the zinc reduction of oxindole,[24] but it was not until 1869 that he was able to correctly elucidate the structure.[25] The indole moiety is one of the largest classes of heterocycles, with indole containing compounds found in many natural products, and pharmaceuticals,[26] and a few examples are shown below in Figure 2-3.

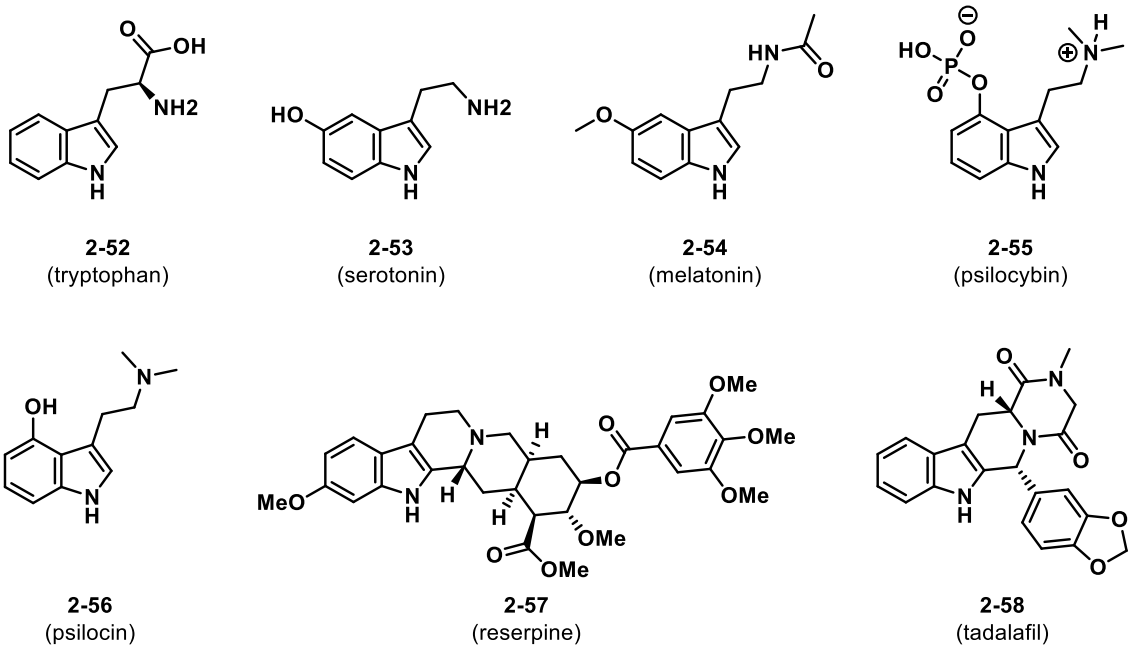


Figure 2-3 Various indole containing natural products, and pharmaceuticals

One of the more important indole containing natural products known is tryptophan (**2-52**), which is an essential amino acid for humans. Tryptophan is also a precursor to serotonin (**2-53**; a neurotransmitter known to be associated with feelings of happiness), and melatonin (**2-54**; involved with the circadian rhythms). Commonly used today for recreation, the Aztecs used psilocybin mushrooms in ceremonies, which contained psychedelics psilocybin (**2-55**) and psilocin (**2-56**). In ancient India, the flower

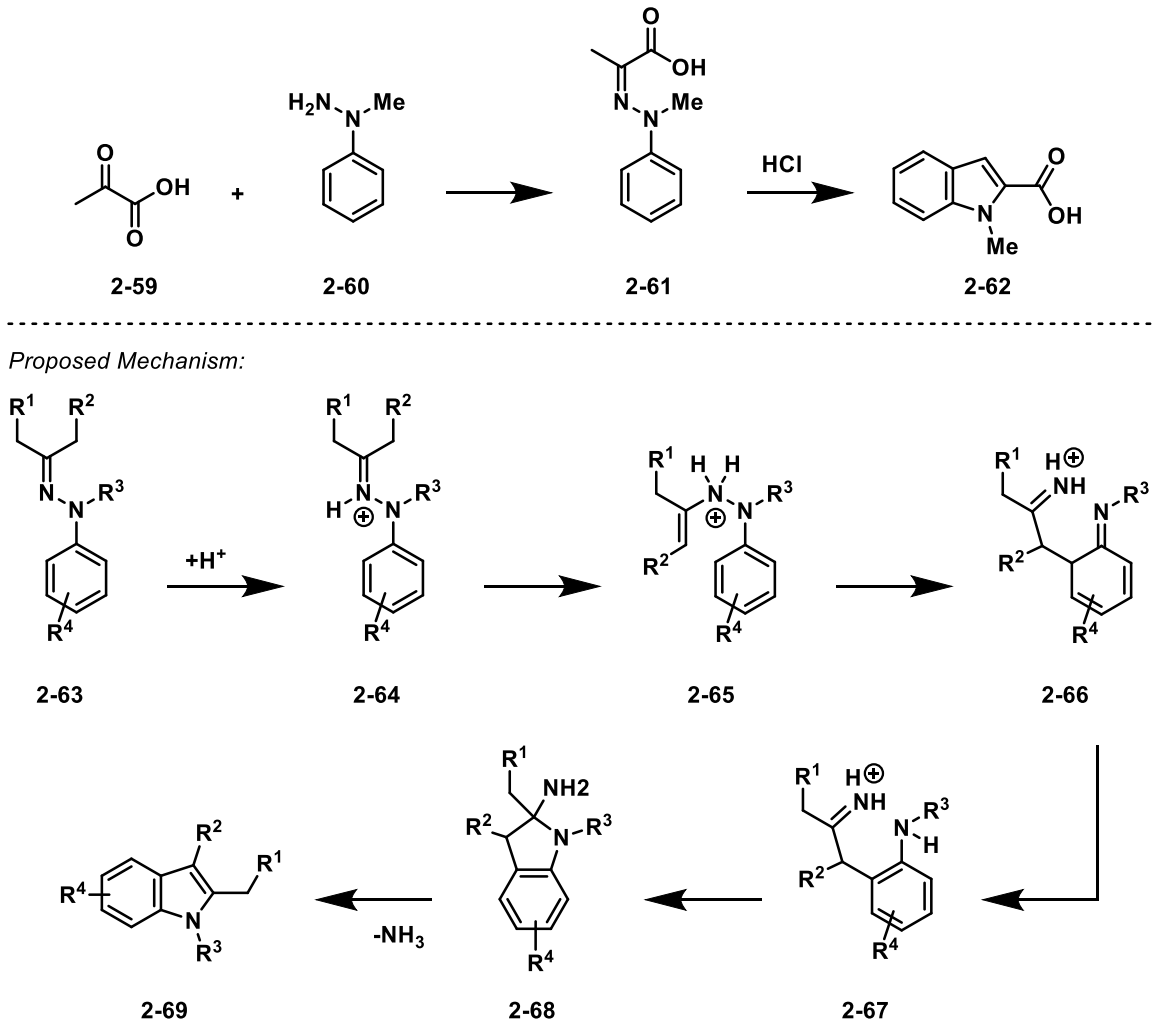
Rauwolfia serpentine was a common medicine for stomach pains, fever, and vomiting, and also contained reserpine (**2-57**), which is more commonly used today to treat high blood pressure.[27] More recently, an important indole containing pharmaceutical is Tadalafil (**2-58**, Cialis), which is a PDE5 inhibitor. As of 2013, Tadalafil (Cialis) was the 51st top selling drug in the US,[28] and is expected to keep rising.

2.2.2 Syntheses of indoles

Given the importance of indoles, there have been a vast amount of research dedicated to their synthesis. A few researchers who worked in the field include Leimgruber-Batcho,[29] Fischer,[30] Bartoli,[31] Bischler-Möhlau,[32] Fukuyama,[33] Gassman,[34] Larock,[35] Madelung,[36] Nenitzescu,[37] Reissert,[38] and Plieninger.[39] Due to amount of work dedicated to this field, only a small subset will be discussed.

2.2.2.1 Fischer indole synthesis

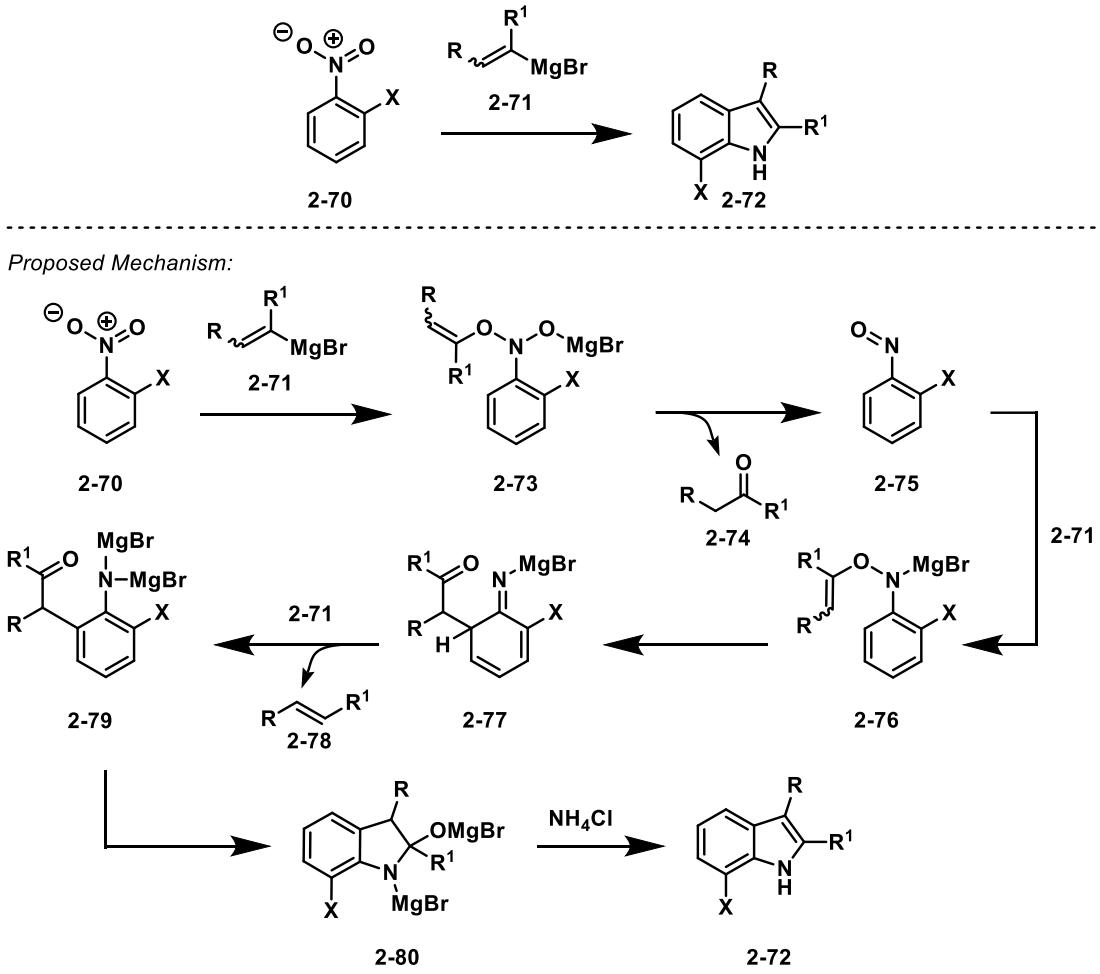
One of the most well-known indole synthesis was developed in 1883 by Fischer and Jourdan. As seen in Scheme 2-10, they reacted pyruvic acid 1-methylphenylhydrazone (**2-61**, derived from ketone **2-59** and phenylhydrazine **2-60**) with HCl and isolated 1-methylindole-2-carboxylic acid (**2-62**).[40] The reaction is tolerant of many protic or Lewis acids, although Lewis acids generally allow for cooler reaction temperatures. For the indolization of unsymmetrical ketones with phenylhydrazines, when a strong acid is used indolization usually occurs at the least substituted α-carbon, and at the more substituted α-carbon under weakly acidic conditions.[41] The mechanism of the reaction, originally proposed by Robinson in 1924,[42] first involves protonation of imine **2-63**, which its self is made from a condensation between a ketone and phenylhydrazine. Tautomerization of **2-63** to form ene-hydrazine **2-65**, followed by a [3,3]-sigmatropic rearrangement results in di-imine **2-66**. Another tautomerization occurs to form enamine **2-67**, which immediately cyclizes to aminal **2-68**. Indole **2-69** is finally produced by the elimination of ammonia.



Scheme 2-10 Fischer indole synthesis

2.2.2.2 Bartoli indole synthesis

Many naturally occurring indoles, and therapeutics, possess substitution at C7; however, synthesis of these indoles can be troublesome. In 1989, the Bartoli group developed an efficient protocol to access C7-substituted indoles through the reaction of substituted nitro groups with substituted vinyl Grignard reagents (Scheme 2-11).[31] The first step of the mechanism involves a reduction of the nitro group in **2-70**, by a Grignard reagent, to form nitroso **2-75**. Confirmation of the initial reduction was done by obtaining **2-74** as a by-product, and also because indoles could be formed straight from nitrosoarene **2-75**.

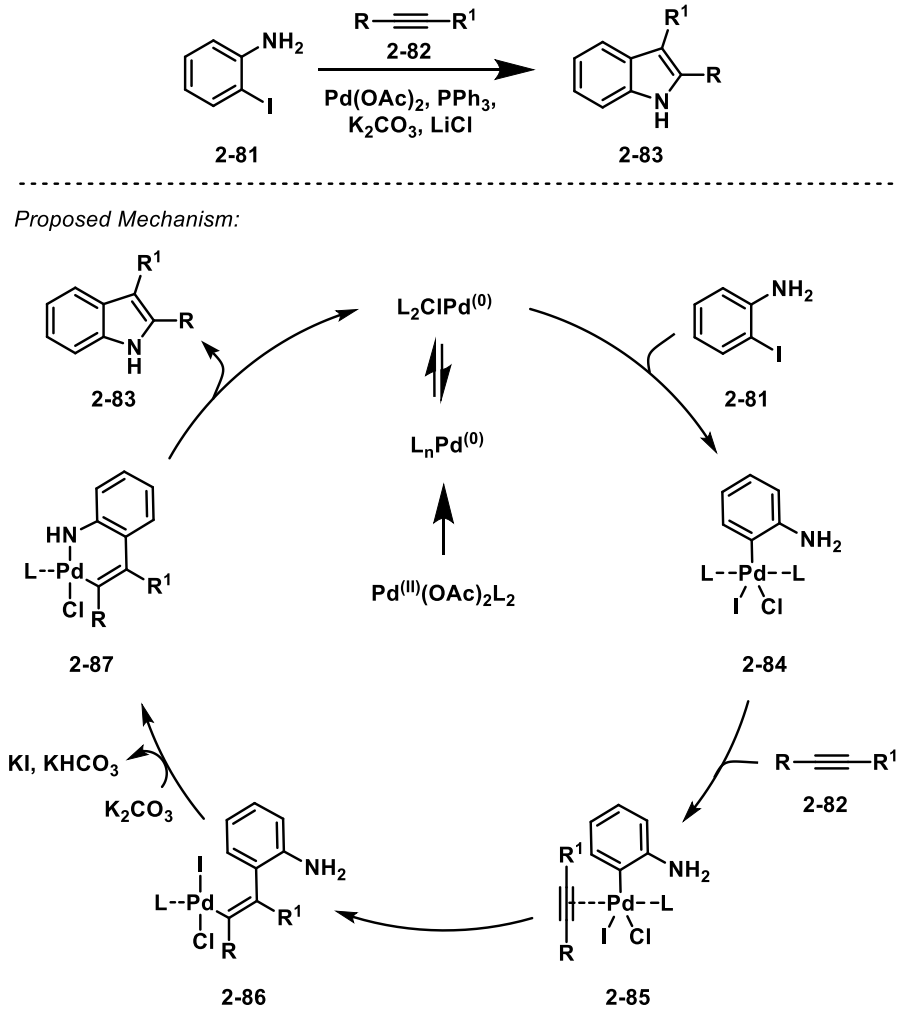


Scheme 2-11 Bartoli indole synthesis

Another Grignard addition, this time to nitrosoarene **2-75**, gives intermediate **2-76** which then undergoes a [3,3] sigmatropic rearrangement to give imine **2-77**. A third Grignard reagent is used to deprotonate **2-77**, which results in re-aromatization of the six membered ring to give **2-79**, and by product **2-78**. Aniline **2-79** then undergoes a cyclization reaction, and subsequent dehydration to give indole **2-72**. If X=Br then a plethora of modifications at the C7 of the indole can occur via various coupling reactions. A few more benefits of the Bartoli indole synthesis include: 1) nitroarenes are commercially available, or can be easily synthesized;[43] 2) the reaction is usually very fast and can easily be scaled up; and lastly, 3) nitro and nitrosoarenes are more reactive than many functional groups towards Grignard reagents, thus alleviated the necessity for protecting groups.[44]

2.2.2.3 Larock indole synthesis

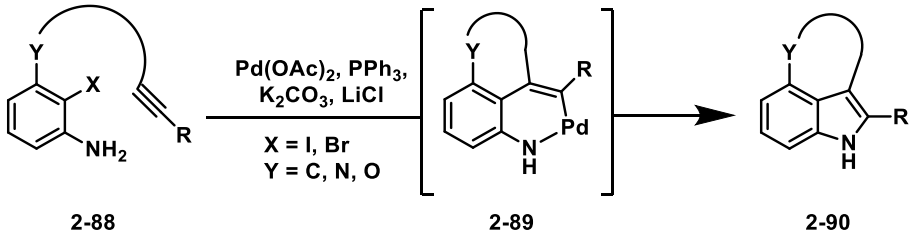
In 1991, Larock developed an indolization sequence from the Pd-catalyzed coupling of 2-iodoanilines (**2-81**) and disubstituted alkynes (**2-82**, Scheme 2-12).[45] The reaction is tolerant to many different substituents on the aniline, or the alkyne, and the coupling is also fairly regioselective – with larger substituents located at the 2-position of the indole.[46] The rationale for the regioselectivity could be explained by sterics in intermediate **2-85**, whereby larger functional groups would avoid the arene.



Scheme 2-12 Larock indole synthesis

The proposed mechanism is highlighted in Scheme 2-12. To begin the synthesis, the Pd(II) source is reduced to Pd(0), which then undergoes an oxidative addition with aniline **2-84**. The alkyne then undergoes a ligand exchange with the palladium complex to form **2-85**, followed by a *syn*-insertion to the arylpalladium bond (**2-86**). The amine then displaces the halide to form the six-membered, heteroatom-containing palladacycle **2-87**, which then undergoes a reductive elimination to regenerate the Pd(0) species, and to form indole **2-83**.

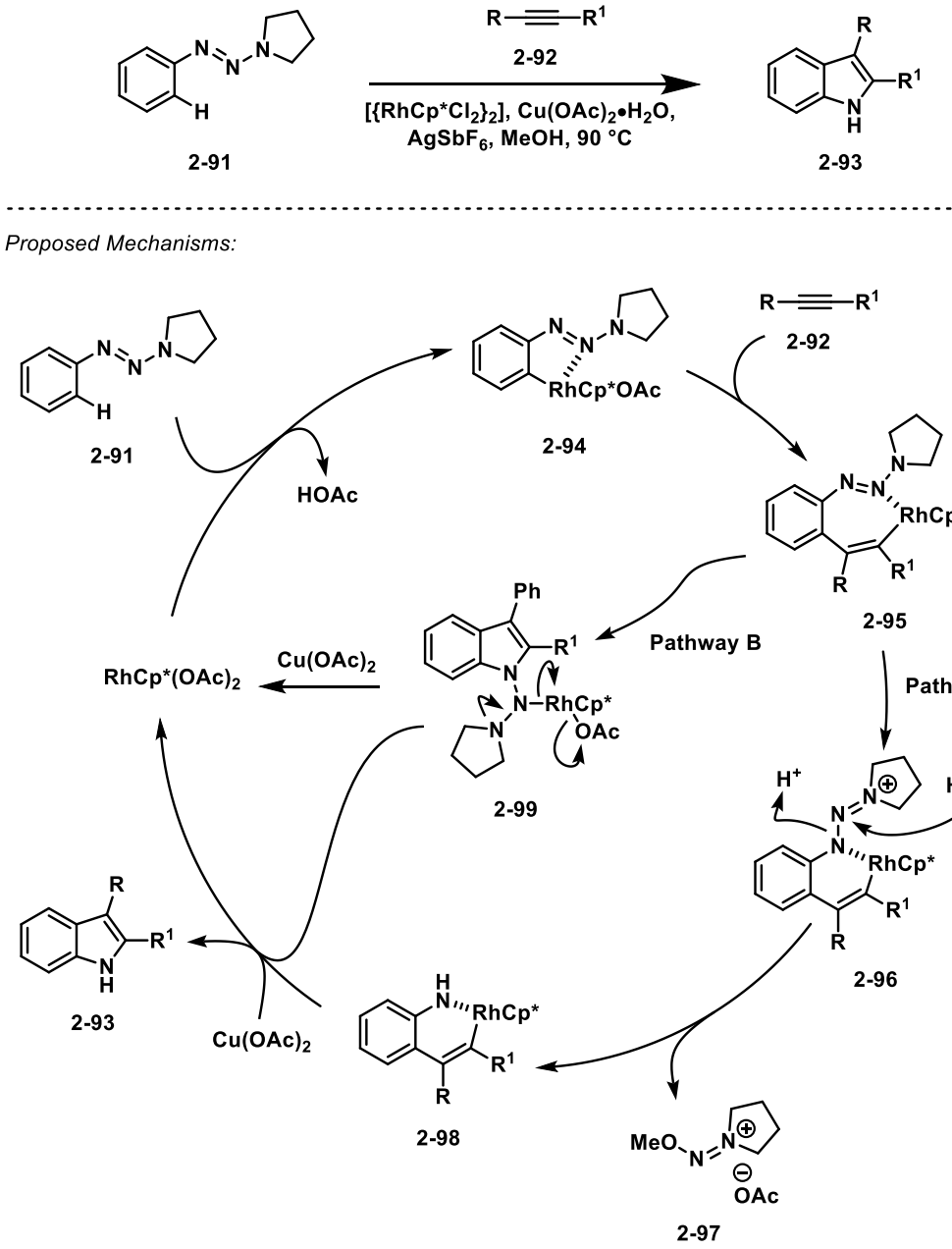
In 2013, the Jia group modified the Larock indole synthesis to access 3,4-fused tricyclic indole **2-90** from an intramolecular Larock indole synthesis of aniline **2-88** (Scheme 2-13).[47] Various atoms in the tether (Y= C, N, or O) could be utilized, and many different sized rings (6, 9, 10, 11, 18) were synthesized.



Scheme 2-13 Jia group's intramolecular Larock indole synthesis

2.2.2.4 Huang indole synthesis

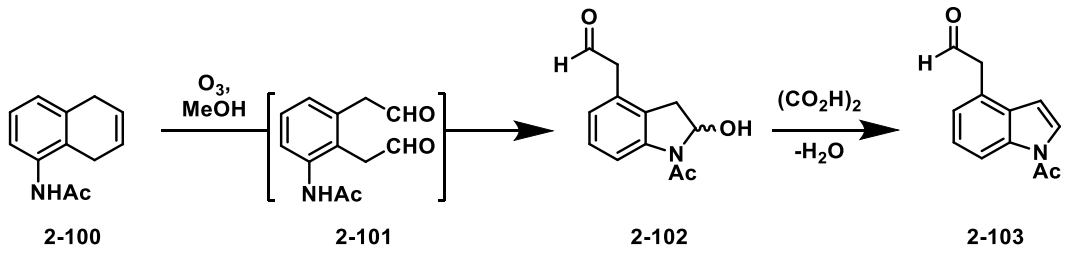
More recently, in 2013, the Huang group found that they could access indoles through a triazene-directed (**2-91**) C-H annulation with alkyne **2-92** (Scheme 2-14).[48] During their optimization they found that [{RhCp*Cl_2}$_2$] and methanol were required, as other catalysts or solvents did not form the indole. Also necessary was a stoichiometric amount of copper oxidant, and catalytic amounts of a non-coordinating silver counter ion. Triazenyl arenes substituted with alkyl, EWG, and halides were able to undergo the indolization sequence, however arenes with EDG resulted in decomposition. Alkynes had either aryl or alkyl substituents, while terminal alkynes could not be used as they lead to dimerization. The proposed mechanism is seen below in Scheme 2-14. After the formation of the active Rh^{3+} acetate species, a directed C-H bond insertion occurs (**2-94**). Insertion of the alkyne results in seven-membered metallacycle **2-95**, which can rearrange to the more stable six-membered metallacycle (**2-96**, Pathway A). Solvolysis of the triazene by methanol (**2-96**), followed by reductive elimination of **2-98** results in indole **2-93**. Alternatively, after the formation of the seven-membered metallacycle **2-95**, N=N insertion to the Rh-C bond forms intermediate **2-99** (Pathway B). Reduction of the Rh catalyst, results in an intermediate similar to **2-96**, which also undergoes solvolysis to access indole **2-93**.



Scheme 2-14 Huang group's synthesis of indoles through triazene directed C-H annulation

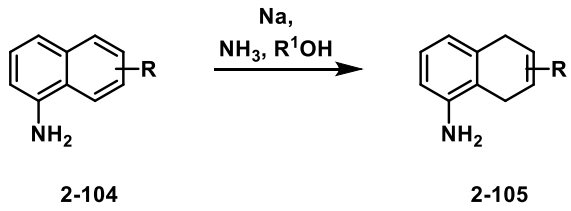
2.2.2.5 Plieninger indolization sequence

In 1956, the Plieninger group were able to convert dihydronaphthalenamine **2-100** to indole **2-103** through an ozonolytic cleavage/dehydration procedure (Scheme 2-15).[49]



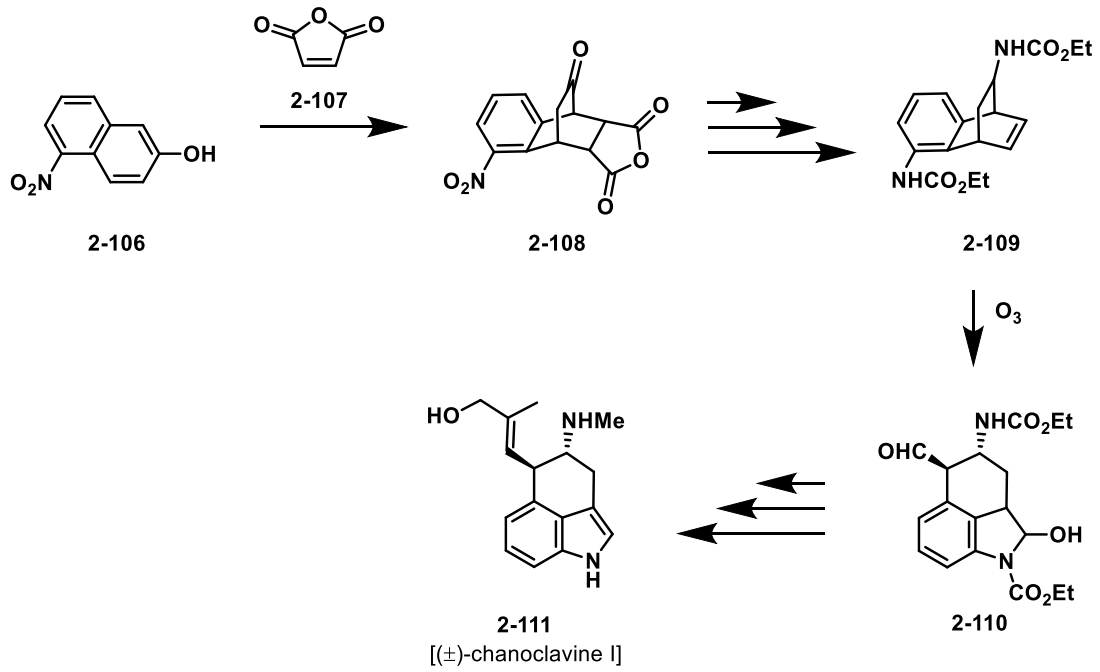
Scheme 2-15 Plieninger's indole synthesis

Despite the relative simplicity of the reaction, the indolization sequence did not build much traction within the synthetic community, likely because the indoles were obtained in low yields and dihydronaphthalenamines were not easily accessible at the time. A Birch reduction of 2-aminonaphthalene **2-104** was commonly employed to access dihydronaphthalenamines (Scheme 2-16); however, many functional groups are not tolerated by the reducing conditions. Nevertheless, the protocol was used in a total synthesis by Plieninger, 20 years later, to access (±)-chanoclavine I.[50]



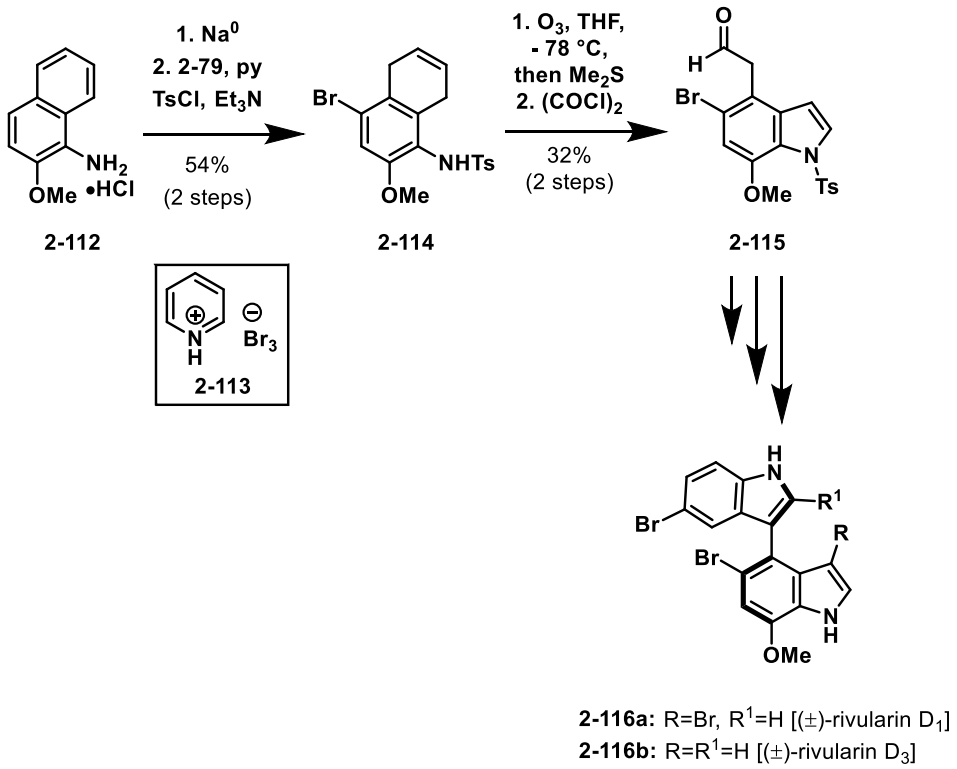
Scheme 2-16 Accessing dihydronapthalenamine via Birch reduction

In the synthesis of (±)-chanoclavine I (Scheme 2-17, **2-111**), the dihydronapthalenamine was not accessed through a Birch reaction, but instead from a Diels-Alder reaction between diene **2-106** and maleic anyhydride (**2-107**). After some further manipulations Plieninger had requisite dihydronapthalenamine **2-109**, which underwent the Plieninger indolization sequence. After a few more synthetic steps, he was able to complete the total synthesis of (±)-chanoclavine I.



Scheme 2-17 Plieninger group's total synthesis of (±)-chanoclavine I

The indolization sequence was also used by Maehr and Smallheer nine years later in their total synthesis of (±)-rivularin D_1 (**2-116a**) and (±)-rivularin D_3 (**2-116b**) (Scheme 2-18).[51] A Birch reduction of aminonaphthalene hydrochloride **2-112**, followed by bromination by pyridinium tribromide (**2-113**), and lastly tosylation of the amine gave access to dihydronaphthalenamine **2-114**. Submitting **2-114** to the Plieninger indolization sequence afforded indole **2-115** in a 32% yield over two steps. The indole then underwent a Fischer indole synthesis to install the other indole moiety, followed by some final manipulations to form (±)-rivularin D_1 and (±)-rivularin D_3.

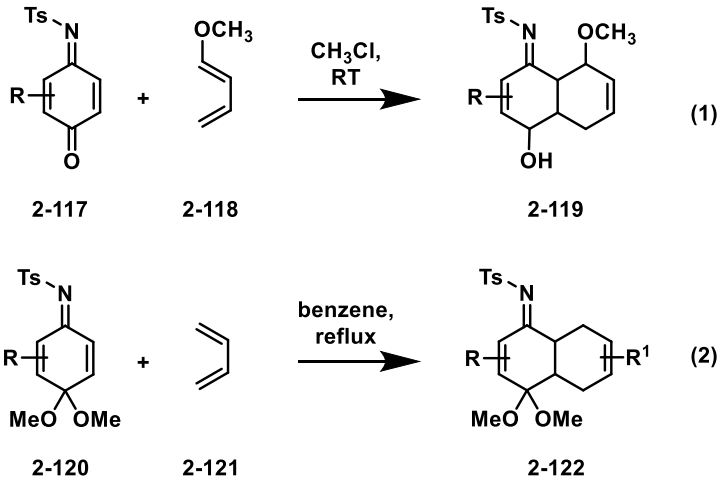


Scheme 2-18 Maehr and Smallheer's total synthesis of (±)-rivularin D_1 and D_3

2.3 Diels-Alder/Plieninger indolization sequence

2.3.1 Accesing dihydronaphthalenamines

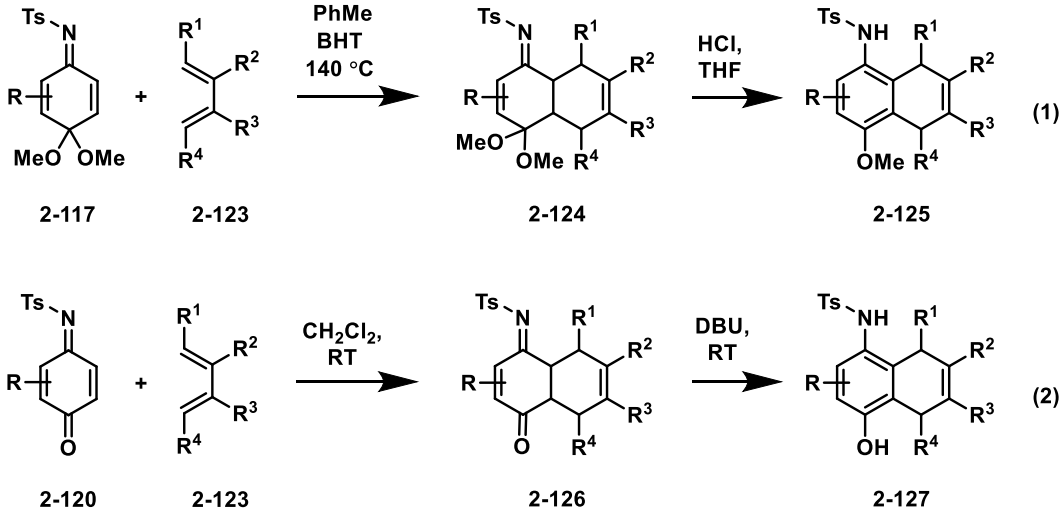
The Kerr group recognized that the Plieninger indolization sequence can be a useful tool to natural product synthesis, and set out to improve the protocol. Inspired by the work of Moore[52] (Scheme 2-19, entry 1) and Coutts[53] (Scheme 2-19, entry 2) on the Diels-Alder of quinone imines (**2-117**) and quinone imine ketals (**2-120**) respectively, the Kerr group realized they could use these Diels-Alder adducts and convert them to dihydronaphthalenamines by acid promoted aromatization.



Scheme 2-19 Moore (1), and Coutts (2) Diels-Alder of imine quinoid species

Originally, the Kerr group used hyperbaric conditions to access their Diels-Alder adducts; however, one of the main issues with this protocol was limited scalability.[54] It was then found that quinone imine ketal **2-117** and diene **2-123** in toluene at 140 °C (sealed tube) can effectively form Diels-Alder adduct **2-124** (Scheme 2-20, entry 1).[55] These adducts were then efficiently converted to dihydronaphthalenamine **2-125** with the use of catalytic HCl in THF.[54b] The scope of the reaction is excellent and various quinone imine ketals and dienes were converted to dihydronaphthalenamine in high yields (85-99%). One downfall of this protocol is that R^1,R^4-disubstituted dienes are not tolerant of the Diels Alder reaction. Steric interactions can occur between the substituent of the diene and the ketal of the dienophile, preventing a cycoaddtion; however, a corollary of the

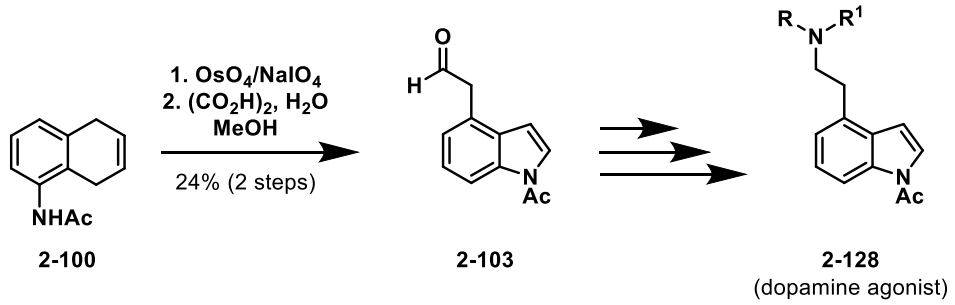
steric effect means that dienes that are R^1 substituted will be regioselective in the Diels-Alder reaction. The Kerr group later showed that they could also form dihydronaphthalenamines from the Diels-Alder reaction of *N*-arylsulfonyl quinone imine (**2-120**) and various dienes (Scheme 2-20, entry 2).[56] These dienophiles were found to be more reactive than quinone imine ketals, and the cycloaddition could effectively proceed at room temperature.



Scheme 2-20 Kerr group's Diels-Alder approach to dihydronaphthalenamines

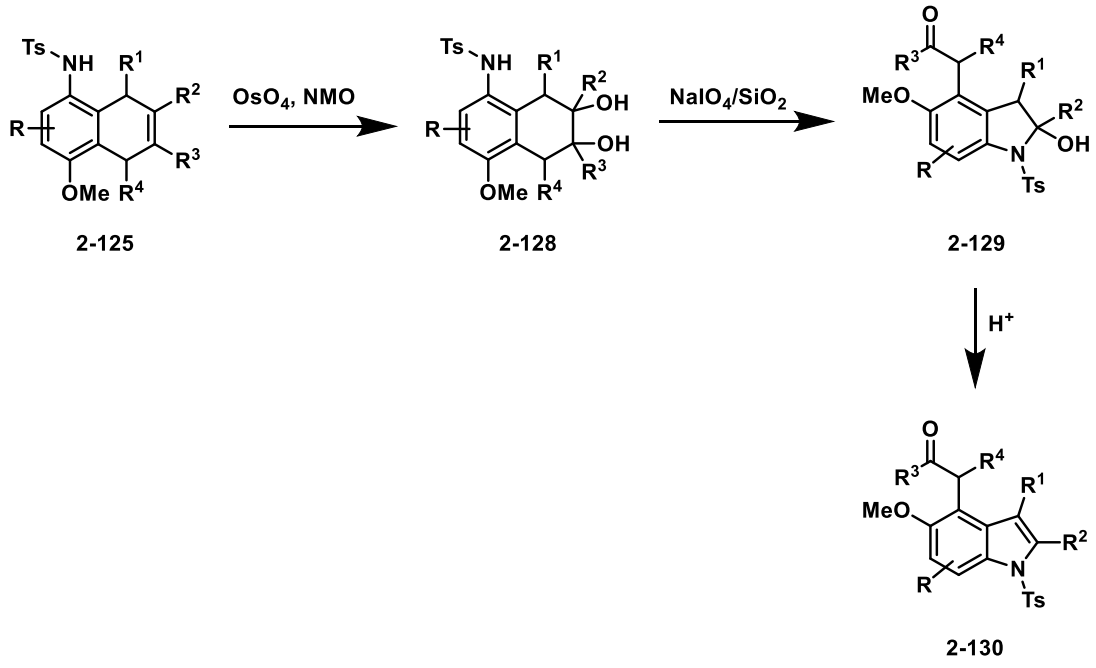
2.3.2 Accessing indoles

With a protocol developed to efficiently access dihydronaphthalenamines, efforts were then taken to develop better conditions for the indolization sequence, as these often gave poor yields under the standard Plieninger indolization sequence. The Kerr group was inspired to tackle this issue after work done in Pearson *et al*. in 1991. In an effort to make 4-(2-*N*,*N*-dialkylaminoethyl)indole (**2-128**) dopamine agonists, Persons *et al.* used a modified Plieininger indolization sequence to access indole **2-103** from the oxidative cleavage of **2-100** by OsO_4 and $NaIO_4$, in a 24% yield (Scheme 2-21).[57]



Scheme 2-21 Persons group's synthesis of dopamine agonists

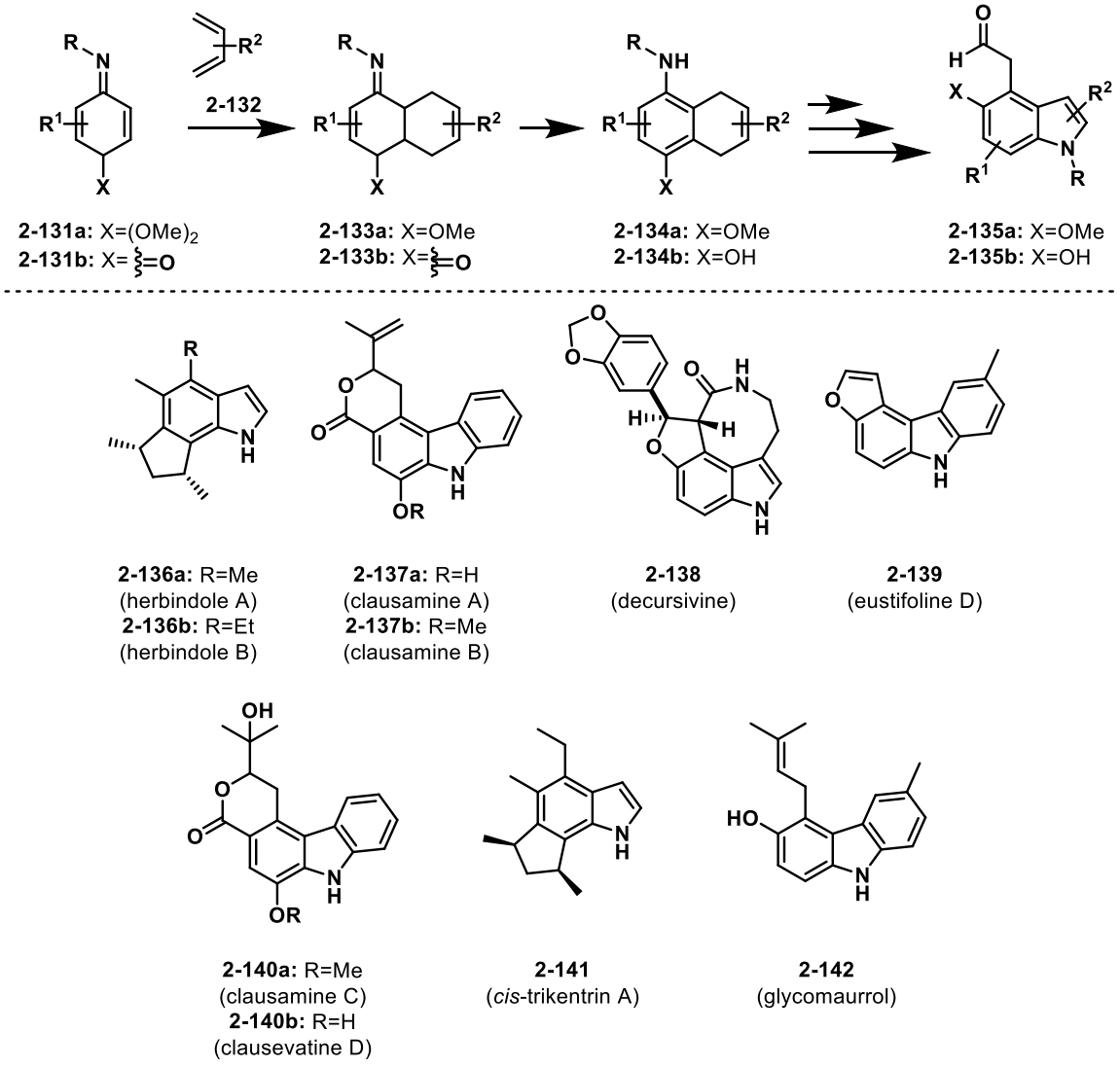
Although the yield was poor, the Kerr group decided to use these conditions as a starting point to optimize the indolization sequence. Johnson Lemieux oxidation[58] resulted in extensive decomposition, and ultimately it was found that a two-step procedure required in order for the indolization to be effective (Scheme 2-22). The protocol involved dihydroxylation of the olefin in **2-125** by NMO and catalytic OsO_4, followed by oxidative cleavage by silica-supported $NaIO_4$ to give hemiaminal **2-129**.



Scheme 2-22 Kerr group's modified Plieninger indolization sequence

Silica-supported $NaIO_4$ was used as diol **2-128** had poor solubility in aqueous solvents normally used for oxidative cleavage allowing the use of organic solvents such as THF or

DCM.[59] Also, purification of the crude material was made extremely easy as only a filtration was required to remove the $NaIO_4/SiO_2$. The indole could then be accessed by an acid promoted dehydration of hemiaminal **2-129** with HCl, PTSA, or H_2SO_4. With a revised Plieininger indolization sequence at hand, the Kerr group was able to access many indole containing natural products (Scheme 2-23).[60]



Scheme 2-23 Kerr group Diels-Alder/Plieninger indolization sequence

2.3.3 Project goal

While the Kerr group provided an efficient route to indoles and utilized the procedure for the total synthesis of indole containing natural products, it was thought that the methodology can be expanded to access benzylamine containing indoles such as: PD 102807 (**2-143**), which is a selective antagonist for an acetylcholine (a neurotransmitter) receptor;[61] fargesine (**2-144**), a natural product;[62] and umifenovir (**2-145**), a therapeutic for influenza (Figure 2-4).[63]

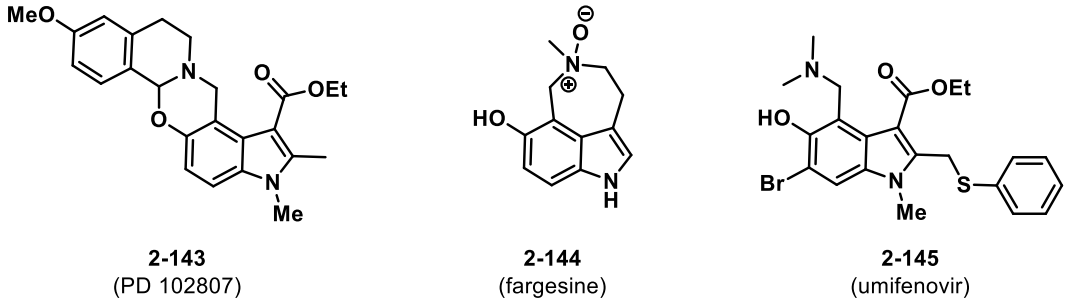
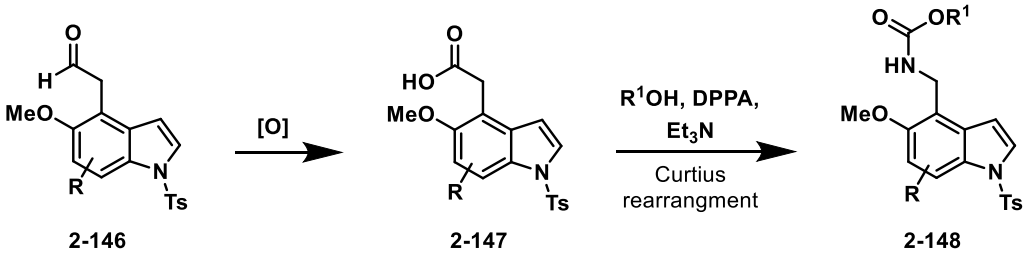


Figure 2-4 Benzylamine containg indoles

As a benzylic aldehyde is normally present in indoles synthesized via the Diels-Alder/Plieninger indolization sequence, a loss of one carbon was required. We envisioned that oxidation of aldehyde **2-146** to acid **2-147**, followed by a Curtius rearrangement (Scheme 2-24) would be an effective procedure to access the molecules in Figure 2-4. We were particularly interested in fargesine, and the following section will discuss its formal synthesis.

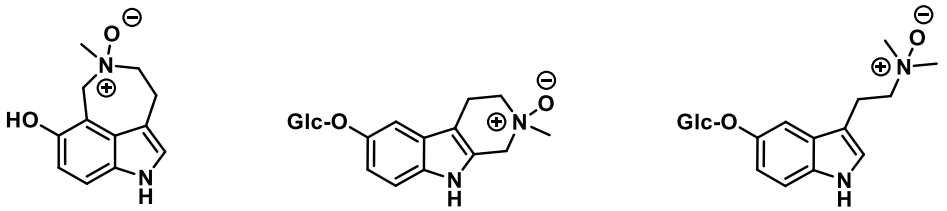


Scheme 2-24 Two-step procedure to access benzylamine containing indoles

2.4 Formal synthesis of fargesine

2.4.1 Introduction to fargesine

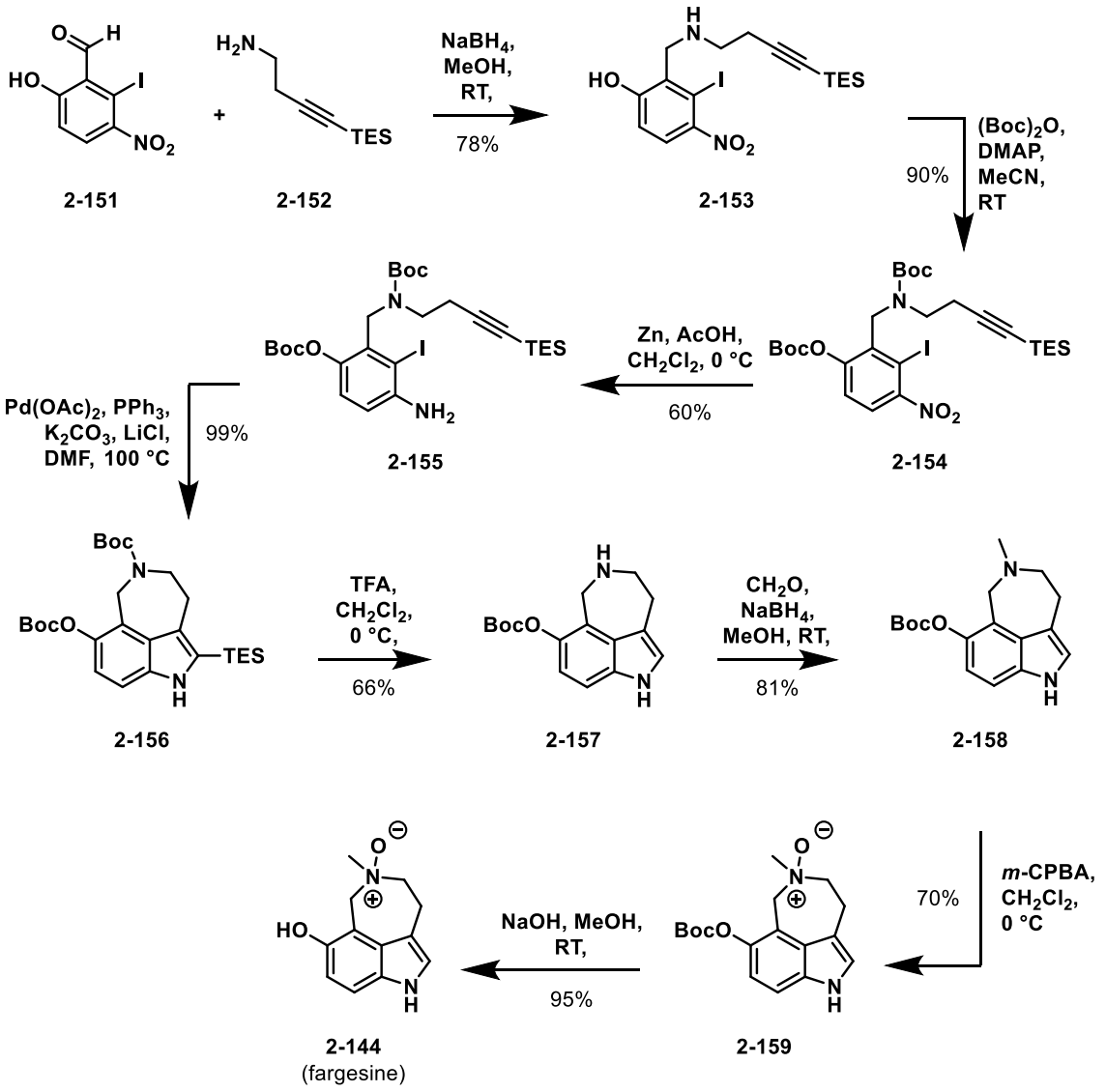
In 2006, the Zhu group isolated three novel alkaloids from the plant *Evodia fargesii* (Figure 2-5); fargesine (**2-144**), plectocomine 12-methyl-5-*O*-β-$_D$-glucopyranoside *N*-oxide (**2-149**), and bufotenine 12-5-*O*-β-$_D$-glucopyranoside *N*-oxide (**2-150**).[62] The fruit of the plant is used as folk medicine in the Jiangxi province of China to relieve cough after measles, and for abdominal pains.



2-144 (fargesine) **2-149** (plectocomine) **2-150** (bufotenine)

Figure 2-5 Isolation of three alkaloids from *Evodia fargesii*

To date there has only been one synthesis of fargesine by the Jia group, which utilized their 3,4-fused tricyclic Larock indole synthesis.[47] The total synthesis can be seen in Scheme 2-25. To begin the synthesis, a reductive amination between known aldehyde **2-151**[64] and amine **2-152** was undertaken to afford secondary amine **2-153**. A Boc protection on the phenol and amine proceeded nicely with a 90% yield to give **2-154**. Reduction of the nitro group with Zn in acetic acid afforded the precursor for the intramolecular Larock indolization in a 60% yield (**2-155**). Gratifyingly, they were able to perform their intramolecular Larock indolization in a quantitative yield to obtain indole **2-156**. To finish the total synthesis, TFA was used to deprotect the TES group and the *N*-Boc in a 66% yield to access compound **2-157**. Reductive amination of **2-157** with formaldehyde (81% yield), followed by *m*-CPBA oxidation of the amine afforded *N*-oxide **2-159** in 70% yield. The total synthesis of fargesine was completed by the deprotection of the *O*-Boc in sodium methoxide.

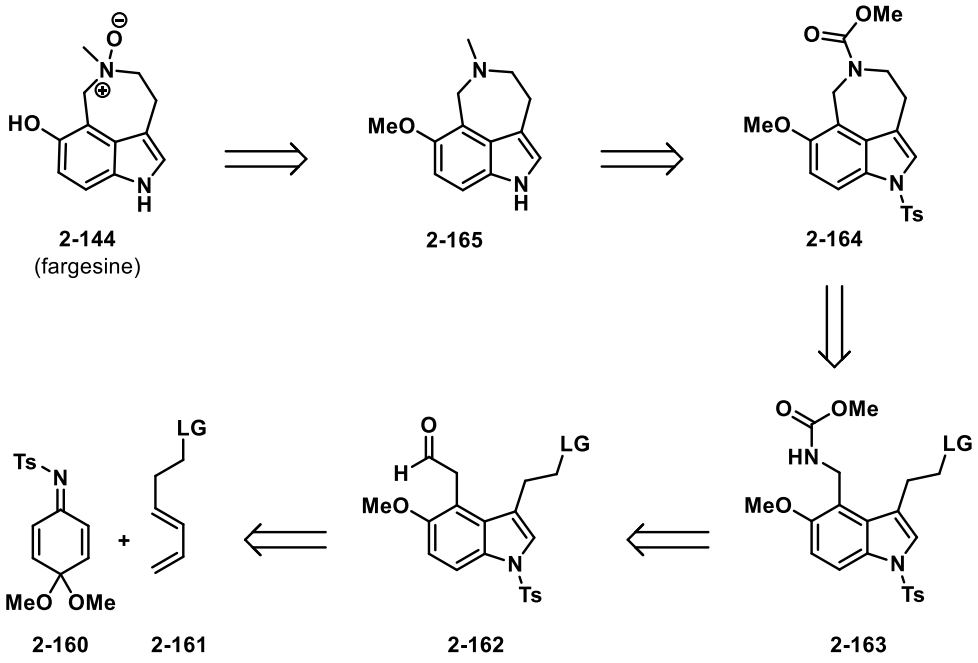


Scheme 2-25 Jia group's total synthesis of fargesine

2.4.2 Results and discussion

2.4.2.1 Retrosynthesis

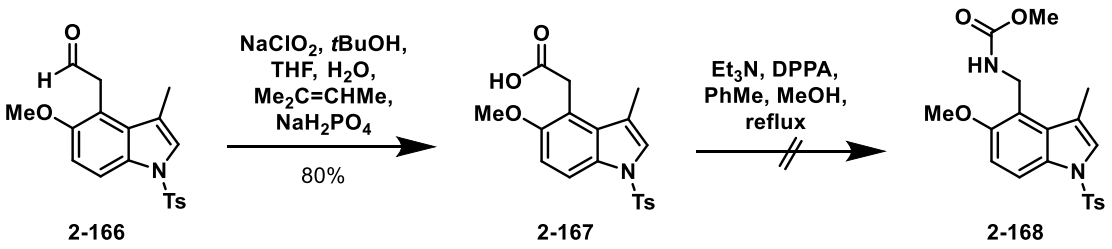
To access fargesine (**2-144**), we proposed (Scheme 2-26) that the last two steps would come about similarly to the literature synthesis: *N*-oxidation, and deprotection of the 5-hydroxy indole. Methylamine indole **2-165** would come from the reduction of methyl carbamate, and detosylation of 3,4-fused indole **2-164**. Fused indole **2-164** would be obtained through the cyclization between methyl carbamate and a leaving group in indole **2-163**. Oxidation of aldehyde indole **2-162** followed by a Curtius rearrangement would give carbamate indole **2-163**. Lastly, indole **2-162** would be developed using the Kerr group's Diels Alder/Plieninger indolization sequence of quinone imine ketal **2-160** and diene **2-161**.



Scheme 2-26 Retrosynthetic pathway for fargesine.

2.4.2.2 Formal synthesis of fargesine

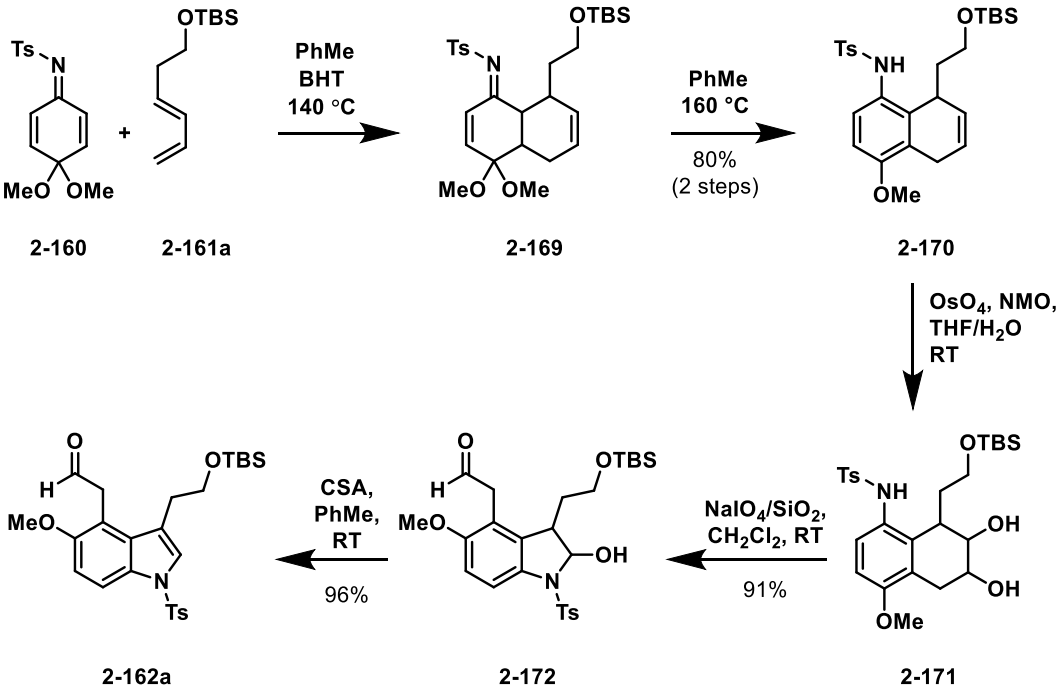
A model study was undertaken by Sharon Michalak with readily available indole **2-166**,[54b] in order to validate our key oxidation/Curtius rearrangement steps required for fargesine (Scheme 2-27). Gratifyingly, oxidation of the aldehyde by a Pinnick oxidation,[65] resulted in an 80% yield of acid indole **2-167**. A Curtius rearrangement was then attempted on the acid following a literature protocol,[66] however the desired product (**2-168**) was not obtained. Despite being unsuccessful on the first attempt of the rearrangement, it was decided that no further exploration of the reaction would happen as it would be more efficient to optimize the rearrangement on the requisite substrate for fargesine.



Scheme 2-27 Model study for the oxidation/Curtius rearrangement protocol

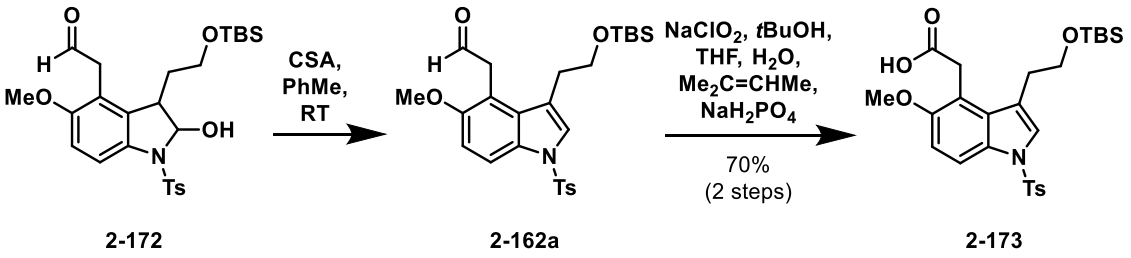
To commence the synthesis of fargesine, Sharon synthesized quinone imine ketal **2-160**[54a] and diene **2-161a**[67] using literature procedures. She then heated the reactants to 140 °C in toluene for 24 hours, with catalytic amounts of BHT, to undergo the Diels-Alder reaction per the protocol developed by Kerr.[55] While these reaction conditions sometimes resulted in partial aromatization to form dihydronaphthalenamine **2-170**, reheating the Diels-Alder adduct in toluene at 160 °C for 12 hours was an effective method for full aromatization. Thus, **2-164** was obtained in an 80% yield over the two steps (Scheme 2-28). With dihydronaphthalenamine **2-170** at hand, the modified Plieninger indolization sequence could begin. Dihydroxylation of the olefin proceeded cleanly (based on a crude ^{1}H NMR spectrum), and did not require further purification. Oxidative cleavage of diol **2-171** with $NaIO_4/SiO_2$ formed the dialdehyde species which immediately cyclized in situ to give hemiaminal **2-172** in a 91% yield over two steps. Despite the crude ^{1}H NMR of hemiaminal **2-172** appearing to be clean, it required

purification by flash column chromatography in order for the acid mediated dehydration to proceed effectively. Camphor sulfonic acid was used for this transformation as it provided higher yields than other acids previously used in the modified Plieninger indolization sequence. Indole **2-162a** was then obtained in 96% yield if isolated, but most of the time was used crude.



Scheme 2-28 Diels Alder, Plieninger indolization sequence

With the modified Plieninger indolization sequence complete, it was now time to attempt the key reactions to the synthesis. Using the Pinnick oxidation conditions from the model study, aldehyde indole **2-162a** was able to be fully converted to acid **2-173** (based on TLC analysis), but low yields were obtained during purification of the acid by flash column chromatography. Despite many eluents being used for the purification, it was found that the crude acid was best purified by crystallization in DCM and hexanes. Thus, acid indole **2-167** was obtained in a 70% yield from hemiaminal **2-172** (Scheme 2-29).

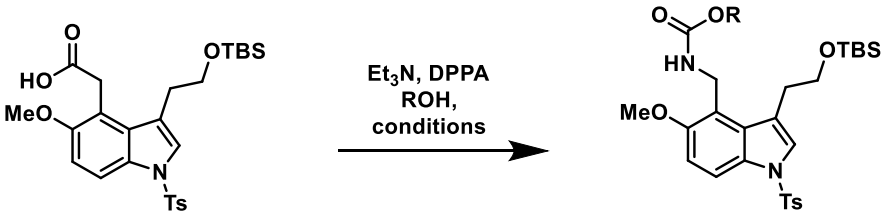


2-172 2-162a 2-173

Scheme 2-29 Pinnick oxidation to access acid for the required Curtius rearrangement

With the requisite acid at hand, the Curtius rearrangement could now be attempted. Efforts towards optimizing the Curtius rearrangement by Sharon are shown below in Table 2-1.

Table 2-1 Initial attempts at the Curtius rearrangement

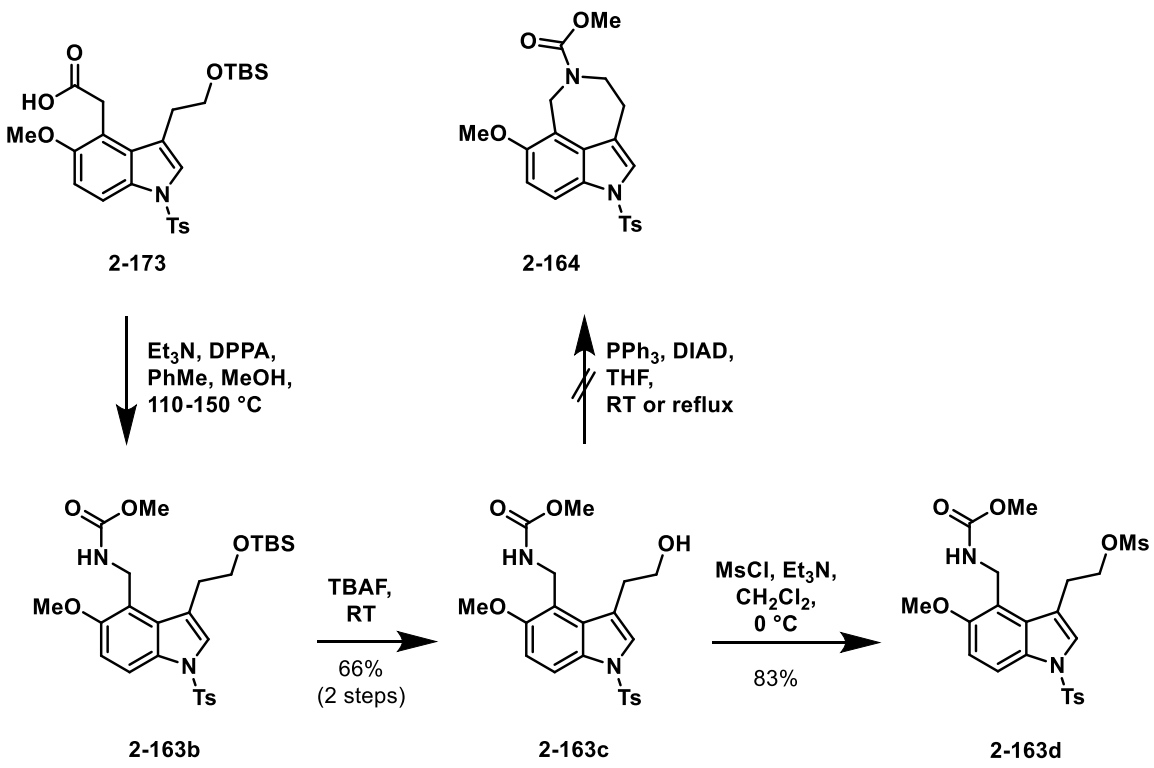


2-173 2-163a

Entry	ROH	Time (h)	Temperature (°C)	Solvent	Yield (%)
1	MeOH	17	110	toluene	18
2	MeOH	24	110	toluene	28
3	MeOH	48	110	toluene	30
4	MeOH	24	80	toluene	43
5	EtOH	22	80	toluene	19
6	MeOH	36	80	benzene	23
7	---	57	60	methanol	45

Each of the examples shown in Table 2-1 involved a one-pot procedure containing acid indole **2-173** in a solvent, along with triethylamine, diphenylphosphoryl azide (DPPA), and an alcohol. Unlike the model study, the initial attempt at the Curtius rearrangement of **2-173** resulted in a low 18% yield of the product (Table 2-1, entry 1). Attempts to increase the yield involved modifying the temperature and reaction time (entry 2-5). It was found that doing the reaction in toluene at lower temperatures, with methanol as the alcohol, resulted in an increased yield of 43% (entry 4). As entry 4 provided the highest yield, a solvent screening was then undertaken. When the reaction was performed in benzene, a lower yield was obtained (entry 6); however, when the reaction was done with methanol as the solvent,[68] a 45% yield (entry 7) was obtained.

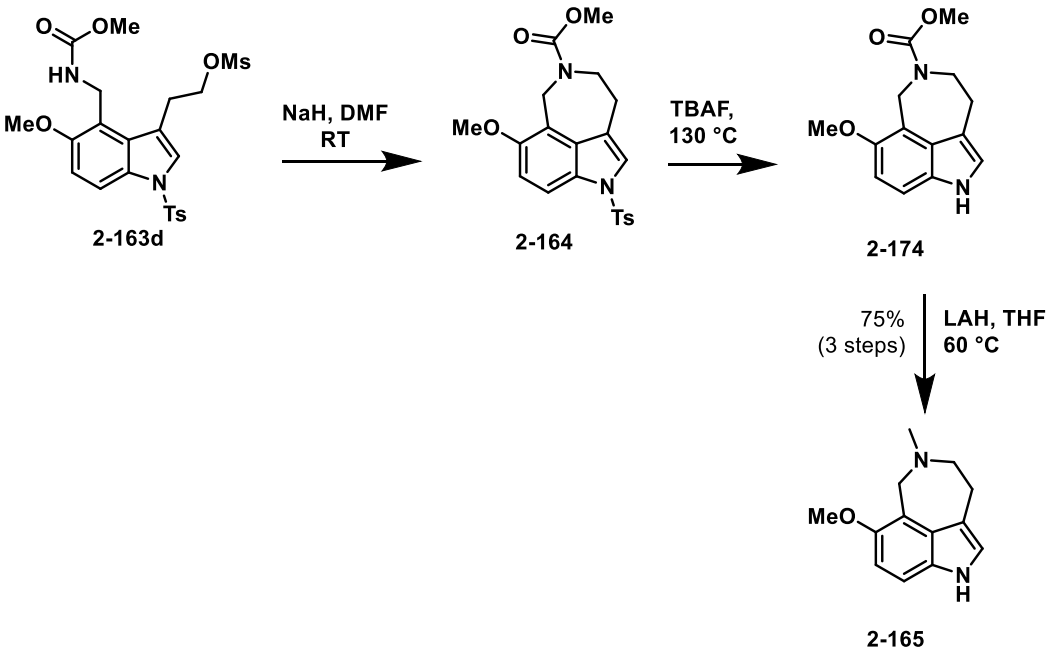
With Sharon's contributions to the synthesis complete, it was found that the Curtius rearrangement required that the isocyanate be formed in situ, followed by subsequent addition of methanol to form the carbamate. Due to the purification (by flash column chromatography) of the Curtius product being somewhat tedious, the process could be simplified by conversion of **2-163b** to **2-163c** since there was a major change in retention factor. Thus, deprotection of the TBS group in **2-163b** occurred effortlessly in TBAF at room temperature overnight to give deprotected alcohol indole **2-163c** in a 66% yield over the two steps (Scheme 2-30). Attempts to form the cyclic carbamate under Mitsunobu[69] conditions were unfruitful; the reaction showed miniscule amounts of the desired product and excessive decomposition. It was decided that mesylation of the alcohol, followed by substitution with the carbamate could afford the desired 3,4-fused tricyclic indole. Mesylation of the primary alcohol with methanesulfonyl chloride at 0 °C formed indole **2-163d** in an 83% yield.



Scheme 2-30 Synthesis of the cyclic precursor

Efforts to form 3,4-fused tricyclic indole **2-164** with *t*BuOK, K_2CO_3, or just thermal conditions did not yield the desired product. Eventually it was found that sodium hydride in DMF (for three hours) could promote cyclization of **2-163d** to indole **2-164** (Scheme 2-31); however, a minor amount of detosylated indole **2-174** was also formed. Longer reaction times (16 hours) did not result in full detosylation so another deprotection method was explored. Indole **2-164** was added to tetrabutyl ammonium fluoride (TBAF) and heated to 130 °C in the microwave for 20 minutes, which gave detosylated indole **2-174**, and a minor amount of unreacted indole.[70] Resubmitting the crude material to the reaction conditions allowed for full detosylation, but since it was already known that tosyl indole was hydride labile, it was decided to carry the crude material forward to the reduction of the carbamate. Thus, the crude mixture of detosylated indole **2-174** was added to a solution of LAH in THF and stirred at room temperature. Surprisingly, these conditions only resulted in full detosylation of the indole (no reduction of the carbamate occurred) but reduction was possible when the THF was heated to 60 °C. Therefore,

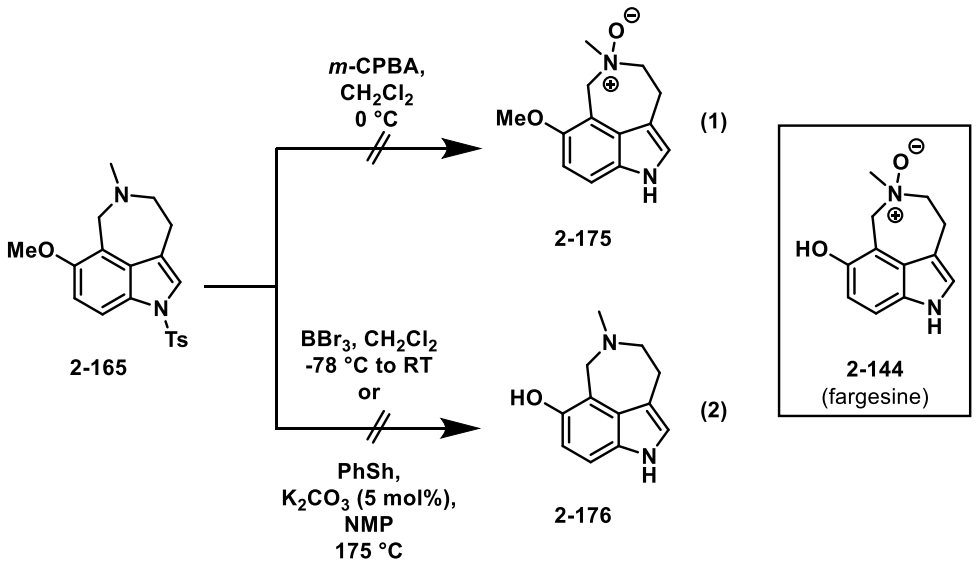
methyl amine indole **2-165** could be quickly accessed over three steps from indole **2-163d** by: 1) cyclization with NaH 2) submitting the crude material from step 1 to detosylation conditions with TBAF, and finally 3) submitting the crude material from step 2 to reducing conditions, which afford methyl amine indole **2-165** with an overall 75% yield. Attempts to go directly from **2-164** to **2-165** with LAH resulted in a mixture between **2-165**, and tosylated **2-165**. Since an optimized route to form **2-165** was already developed, efforts towards a one-pot procedure were abandoned.



Scheme 2-31 Synthesis of *N*-reduced methoxy fargesine **2-159**

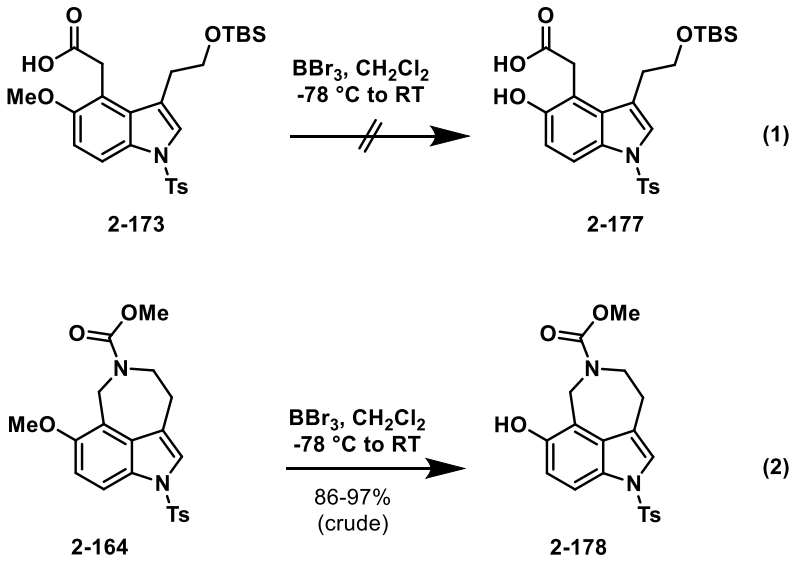
With methyl amine indole **2-157** at hand, only two more steps were required to access fargesine: oxidation of the amine, and subsequent deprotection of the methoxy goup. Despite many attempts to oxidize the amine with *m*-CPBA, following Jia's procedure,[47] only decomposition was obtained (Scheme 2-32, entry 1). Modifying the procedure to shorter reaction times, slow addition of the indole, or cooler temperatures also resulted in decomposition, and no other oxidants were attempted. As the only difference between Jia's indole and our indole at this stage was the protecting group on the 5-hydroxy indole (Jia protected the alcohol with a Boc group), it was speculated that the amine in indole **2-165** was not as delocalized and was therefore more reactive, leading to decomposition.

To circumvent the oxidation issues, it was decided to deprotect the methoxy group prior to *N*-oxidation. Attempts at methoxy deprotection with typical BBr_3 conditions (3, 9.5, or 47 equivalents with temperatures ranging from -78 °C to RT) resulted in decomposition. An attempt at methoxy deprotection using thiophenol and K_2CO_3 also lead to decomposition (Scheme 2-32, entry 2).[71]



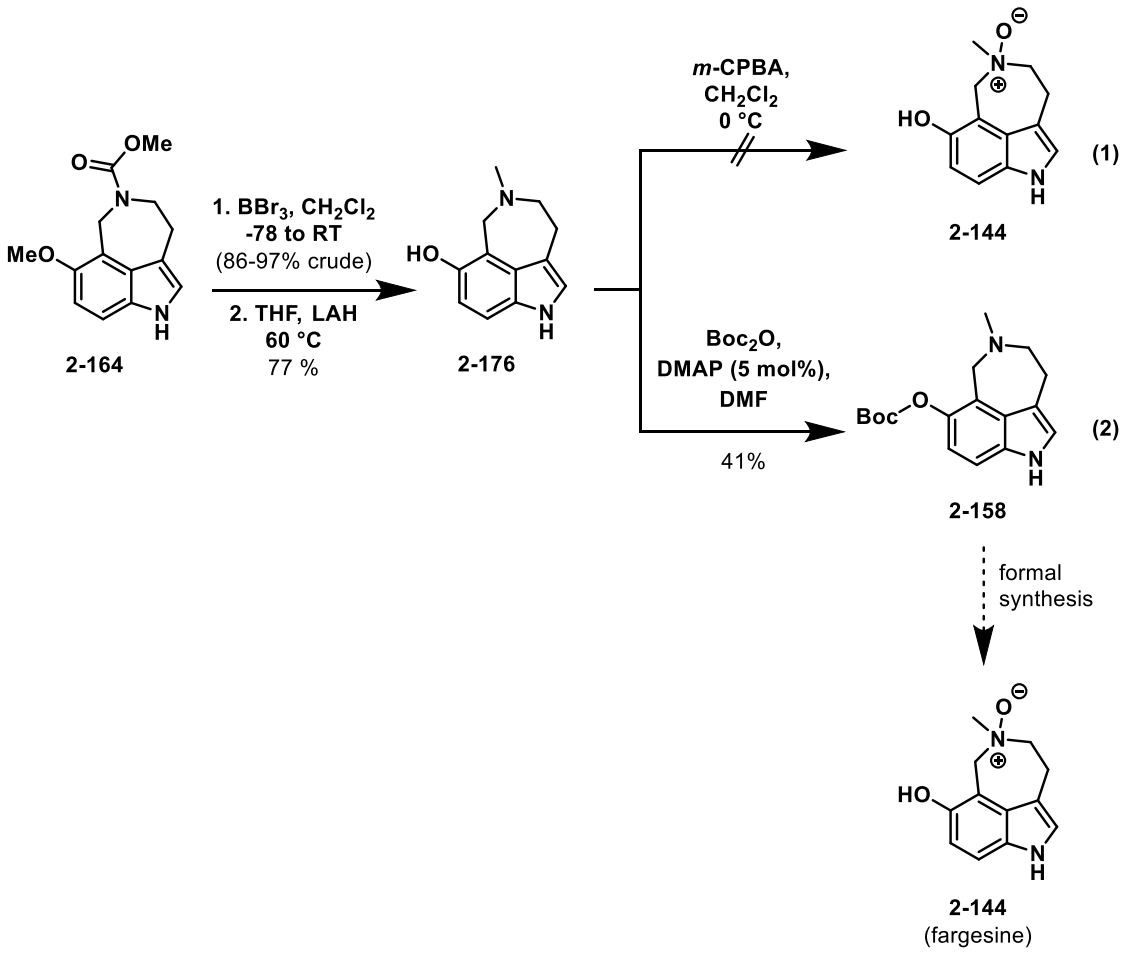
Scheme 2-32 Attempts to oxidize or deprotect indole **2-165** towards fargesine

As it was becoming apparent that the route above would not be viable, it was decided to attempt the methoxy deprotection at an earlier stage of the synthesis. When indole acid **2-173** (Scheme 2-33, entry 1) was reacted with BBr_3, decomposition was obtained; however, when cyclic indole **2-164** was taken up in DCM and BBr_3 (3 equivalents, at -78 C to RT) 5-hydroxyindole **2-178** was accessed (Scheme 2-33, entry 2). After liquid-liquid extraction (EtOAc/H_2O), the crude yield of this reaction was very good (97% yield on 200 mg scale, and 86% yield on 345 mg scale); however, when the material was purified by flash column chromatography, approximately 50% of the mass was lost. It was also found that if the crude material, or purified material, was left alone for a short period of time, the material would begin to become insoluble in many solvents. As the crude and purified ^1H NMR spectra looked the same, it was concluded that the material decomposed and had to be quickly used for the next step.



Scheme 2-33 Earlier stage methoxy deprotection by BBr_3

Recalling that that tosyl indole is hydride labile (Scheme 2-31, **2-163d** to **2-165**), crude indole **2-178** was then taken up in THF and LAH at 60 °C in hopes of detosylating, and reducing the carbamate in a one-pot procedure. Gratifyingly, the one-pot procedure worked and methyl amine indole **2-176** was obtained in a 77% yield. As time and material were running low at this stage, only one amine oxidation was attempted to complete the synthesis of fargesine; however, only decomposition was obtained (Scheme 2-34, entry 1). It was then decided to Boc protect the alcohol as this would then converge with Jia's total synthesis of fargesine. The Boc protection was successfully performed in DMF, as the indole was fairly insoluble in other solvents, to obtain Jia's indole intermediate (**2-158**) in a 41% yield, thus completing the formal synthesis of fargesine (Scheme 2-34, entry 2).



Scheme 2-34 Completing Jia's intermediate for a formal synthesis of fargesine

2.4.3 Conclusions

Efforts towards the total synthesis of fargesine were undertaken utilizing a Diels-Alder, Plieninger indolization sequence. Despite advancing to a late stage intermediate that only required an oxidation and methoxy ether deprotection, the route was not viable in the sysnthesis of fargesine and an alternative route was carried out that converged with Jia's synthesis of fargesine. Although the Jia group synthesis of fargesine is shorter (14 versus 6 steps - from literature compounds) to obtain the same intermediate, many steps in our synthesis can be done on multi-gram scale, and only four purifications by flash column chromatography are required (most reactions are carried forward crude).

2.5 Accessing oxygen analogues of indole: benzofuran, and derivatives

2.5.1 Introduction to benzofuran and derivatives

Despite indoles having a vast amount of research dedicated towards their synthesis, the oxygen analogue benzofuran (Figure 2-6, **2-179**) does not.[72] Nevertheless, it is still an important molecule for chemists as benzofurans and its derivatives exhibit many biological activity including antifungal,[73] antitubercular,[74] anticonvulsant,[75] anticancer,[76] analgesic,[77] antidiabetic,[78] and anti-Alzheimer's properties.[79] Benzofurans are also utilized in polymer chemistry[80] and the dye industry.[81]

2-179 **2-180**

Figure 2-6 Depiction of benzofuran (**2-179**), and benzofuranone (**2-180**)

A derivative of benzofuran is the benzofuranone (Figure 2-6, **2-180**), which is simply a lactone of dihydrobenzofuran. Some examples include: rhuscholide A (Figure 2-7, **2-181**), which shows anti-HIV properties;[82] fumimycin (**2-182**), which has bacterial peptide deformylase inhibitor properties;[83] abiesinol E (**2-183**), which shows antitumor-initiating effects;[84] and lastly, ferrubietolide (**2-184**), which is used as a pesticide.[85]

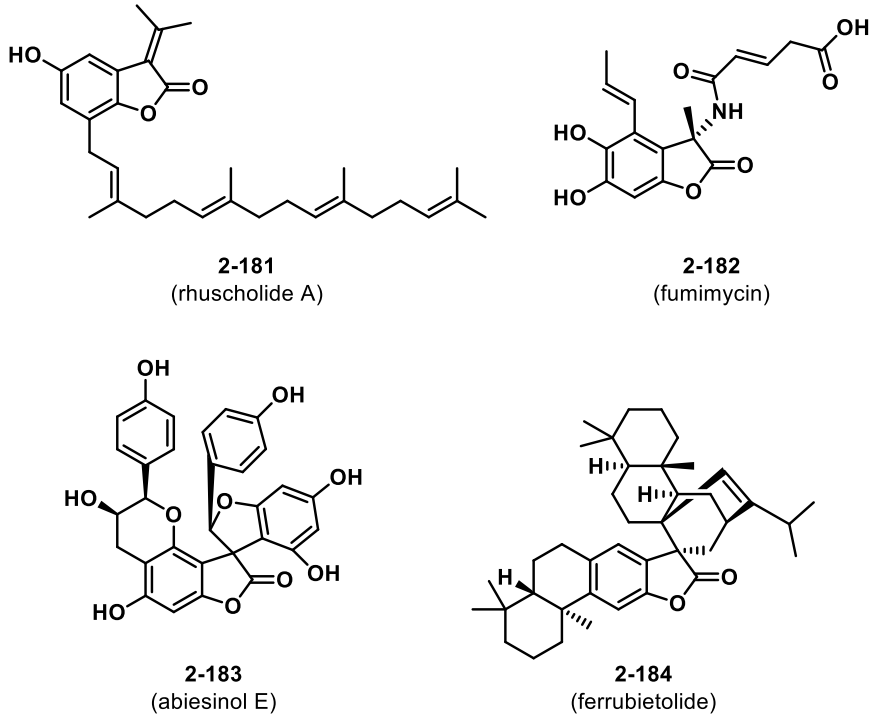
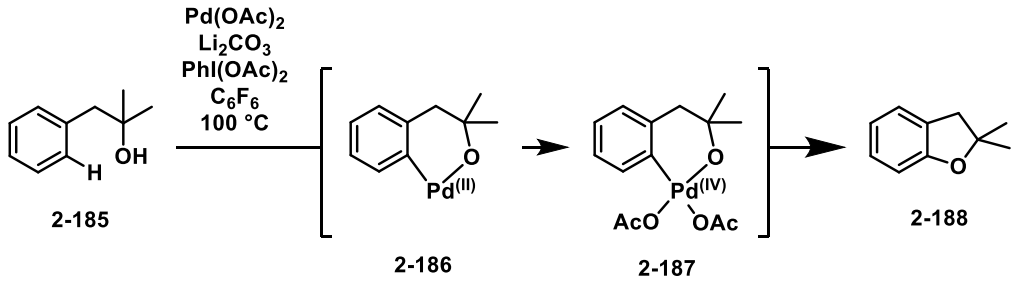


Figure 2-7 Benzofuranone containing natural products

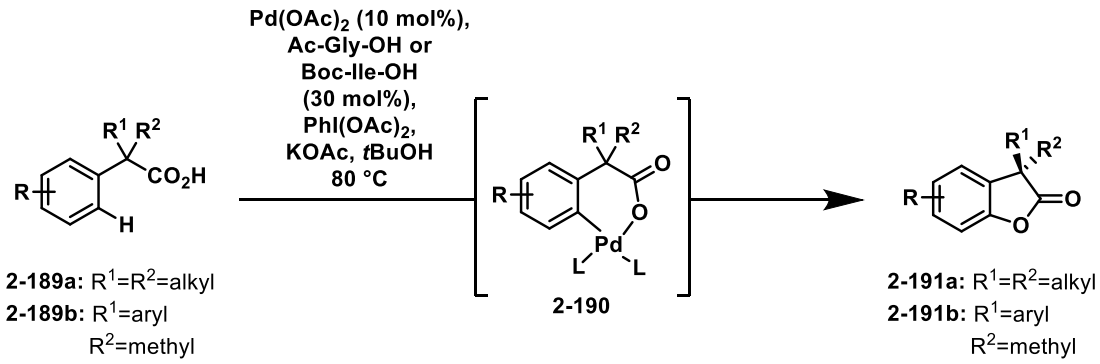
2.5.2 Accessing benzofuranones

In 2010, the Yu group developed a two-step C-H activation/C-O bond formation procedure to convert alcohol **2-185** to 2,3-dihydrobenzofurans **2-188** (Scheme 2-35).[86] A key step to the procedure involves oxidation of the Pd(II) palladacycle **2-186** to Pd(IV) **2-187** by a 'bystanding oxidant' to facilitate reductive elimination.[87] Through careful selection of oxidant, a higher energy metallic species forms to make the reductive elimination favourable, while minimizing potential side reactions.



Scheme 2-35 Yu group's synthesis of 2,3-dihydrobenzofurans

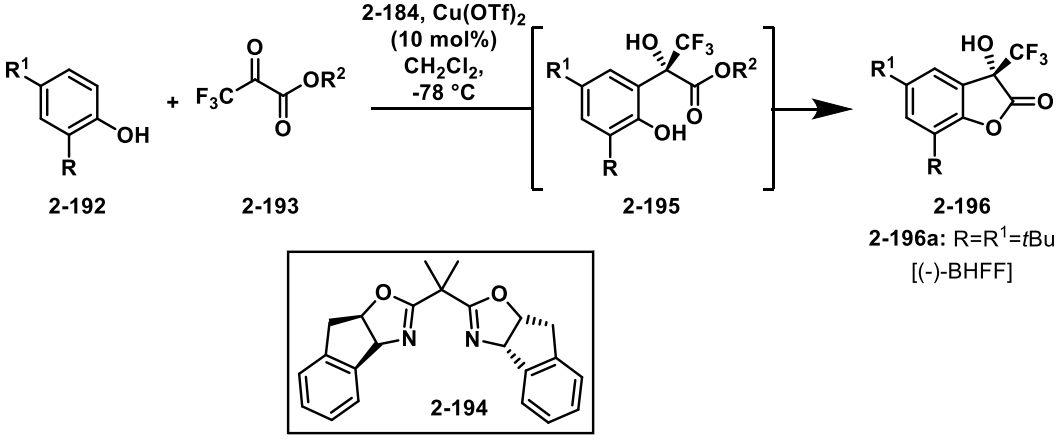
In 2013, the Yu group further developed their protocol to include the synthesis of benzofuranones from phenylacetic acid **2-189** (Scheme 2-36).[88] During their optimization for synthesizing benzofuranones, they found that $PhI(OAc)_2$ was the best oxidant to promote lactonization, but the highest yield obtained was only 42%. Despite various additives and ligands tested, they were unable to obtain benzofuranones in higher yields. They then tried *N*-protected amino acids as ligands since the Yu group had previously shown they can promote C-H activation.[89] When *N*-acetylated glycine was used as a ligand, they were able to obtain various benzofuranones (**2-191a**) in moderate to excellent yields (56-94%); although the substrate scope was somewhat limited because R^1=R^2=Me if there was substitution on the phenyl ring. The enantioselective synthesis of benzofuranones was then explored through the desymmetrization[90] process of diaryl acetic acid **2-189b**. Isoleucine (*N*-Boc protected) gave the best results in the desymmetrization process, obtaining benzofuranone **2-191b** in moderate yields and high *ee* (89-96%)



Scheme 2-36 Yu group's synthesis of benzofuranones

Recently, benzofuranones with 3-hydroxy, 3-trifluromethyl substitution have been shown to exhibit great biological activity and are being explored as potential therapeutics.[91] For example, racemic *bis*(1,1-dimethylethyl)-3-hydroxy3(trifluoromethyl)-2(3*H*)benzo-furanone (BHFF) has potential to treat nervous system disorders, and furthermore, it has been shown that (-)-BHFF is more robust than racemic or (+)-BHFF in animal studies.[92] The Tang group set out to access these therapeutically interesting class of benzofuranones through a catalytic and asymmetric tandem Friedel-Crafts/lactonization between phenol

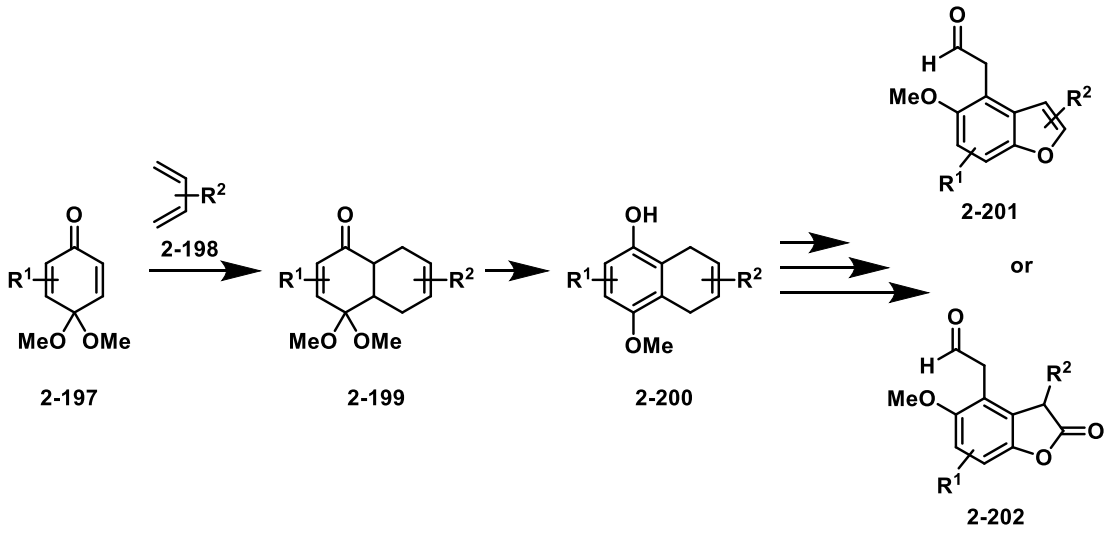
2-192 and trifluoropyruvate **2-193** (Scheme 2-37).[93] While the tandem Friedel-Crafts/lactonization sequence has been known since 1980, reaction conditions typically require strong organic acids as solvents, high temperatures, stoichiometric amounts of Lewis Acid, and were never performed enantioselectively.[94] The Tang group were able to achieve their goal through the use of chiral BOX/Cu(II) system, developed by Jørgensen.[95] Specifically, the Tang group found that BOX derived ligand **2-194** was able to access benzofuranone **2-196** with the best yields and *ee* (80-94%). They were also able to synthesize (-)-BHFF (**2-196a**) in a 62% yield, and >99% *ee* (after recrystallization). Mechanistic studies confirmed that the phenol was important for the regioselectivity of the Friedel-Crafts reaction, as C4 alkylation was more prominent when methyl ethers were utilized.



Scheme 2-37 Tang group's synthesis of benzofuranones and (-)-BHFF (**2-196a**)

2.5.3 Project goal

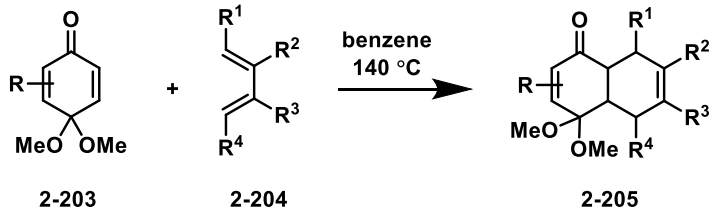
Since the Kerr group had previously shown that they were able to convert dihydronaphthalenamines to indoles (Scheme 2-23), it was speculated that we would be able to convert the oxygen equivalent – dihydronaphthalenol (**2-200**) – into benzofuran and derivatives (**2-201** or **2-202**, Scheme 2-38). The dihydronaphthalenol would come from the Diels-Alder between quinone ketal **2-197** and diene **2-198**. Efforts to develop a methodology and its application towards the total synthesis of fumimycin (**2-182**) are discussed below.



Scheme 2-38 Proposed route towards benzofurans (**2-201**) or benzofuranones (**2-202**)

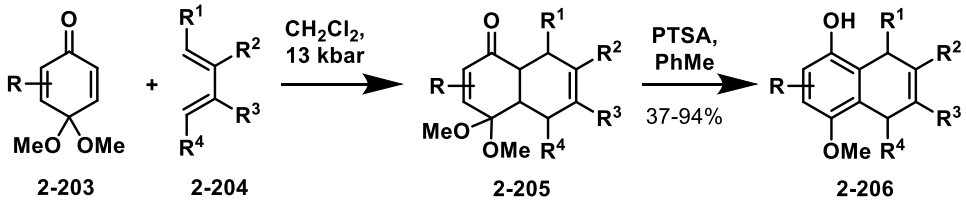
2.5.4 Diels-Alder reaction of quinone ketals

The use of quinone ketals as dienophiles had previously been shown to proceed thermally by Farina and co-workers (Scheme 2-39), but not without many limitations: only reactive dienes could be used, extreme temperatures were required, long reaction times were necessary, and poor yields were obtained for the products.[96] For example, when isoprene was reacted with *p*-benzoquinone ketal in benzene at 140 °C for 160 hours, only a 32% yield of the Diels Alder adduct was obtained.



Scheme 2-39 Farina group's Diels-Alder of quinone ketals

The Kerr group suspected that hyperbaric conditions could improve Farina's work, and would also serve as an expansion of Kerr's hyperbaric Diels-Alder of quinone imine ketals.[54a] They were able to effectively promote the cycloaddition of various dienes with quinone ketal **2-203**, in moderate yields and a 72 hour average reaction time (Scheme 2-40).[97] As noted in Section 2.3.1, dienes with R^1 and R^4 substitution were unable to react due to steric interactions with the acetal. The Diels-Alder adducts were aromatized to their corresponding dihydronaphthalenol **2-206** in moderate yields ranging from 37-94%, with PTSA in dry toluene. With the use of hyperbaric conditions, the Kerr group had successfully overcome the limitations of the Diels-Alder reactions of quinone ketals.



Scheme 2-40 Kerr group's hyperbaric Diels-Alder of quinone ketals

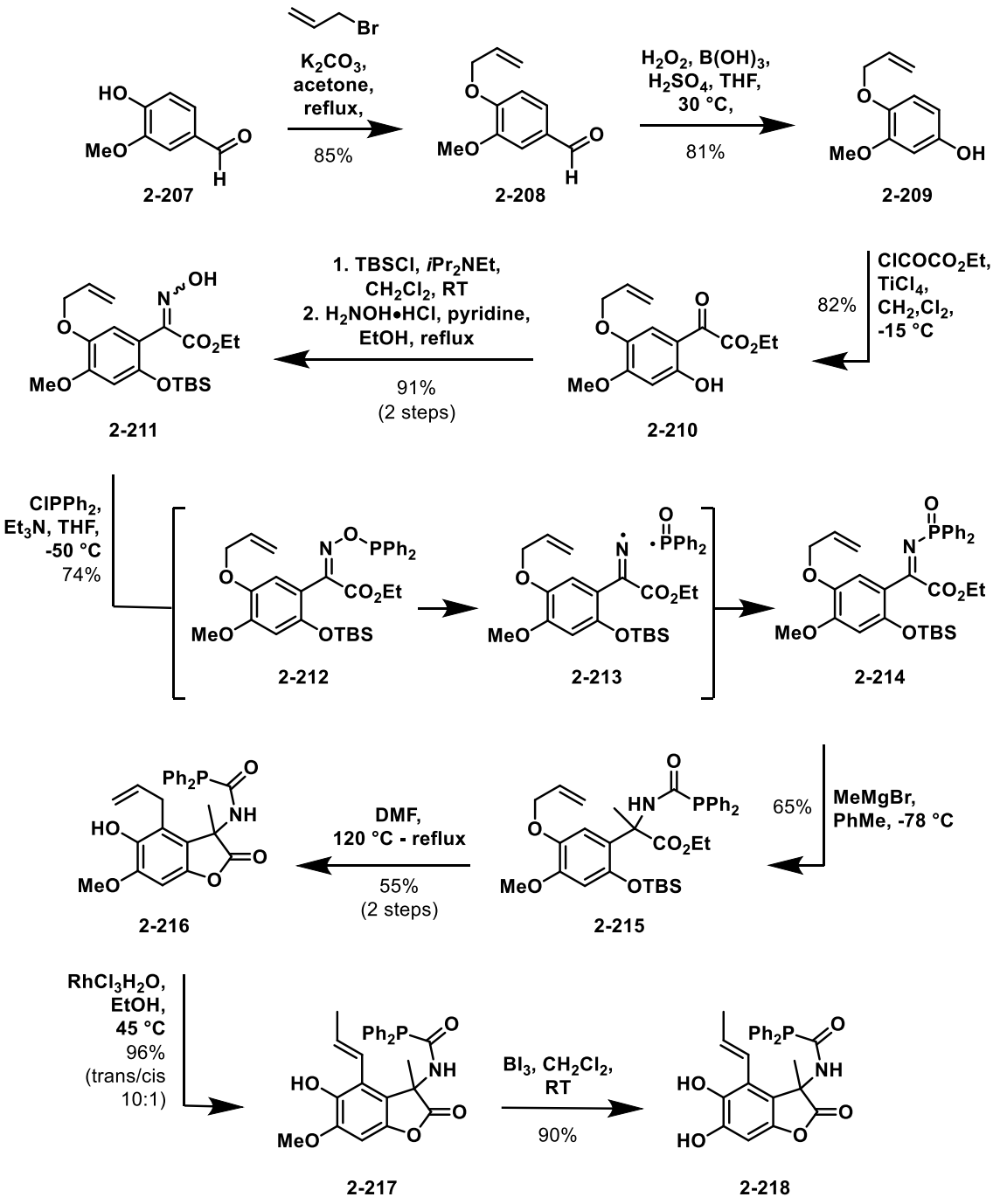
2.6 Progress towards the total synthesis of fumimycin

2.6.1 Introduction to fumimycin and previous synthesis

Fumimycin was isolated from the fermentation broth of *Aspergillus fumisynnematus* F746, a fungus collected from a Korean soil sample by Kim and co-workers in 2007.[83] Fumimycin displays high inhibition of peptide deformylase (PDF),[98] which is an enzyme involved in the removal of formyl groups at the *N*-terminus of bacterial proteins and essential for prokaryotic growth.[99] As this process is not important for mammalian cells, PDF inhibitors represent a class of antibacterial agents which may have very little side effects in humans. To date, there has only been one total synthesis of fumimycin, and this was done by Gross and Bräse in 2010. They were able to access (±)-fumimycin in 18 steps (16 step longest linear sequence) in a 2.2% overall yield.

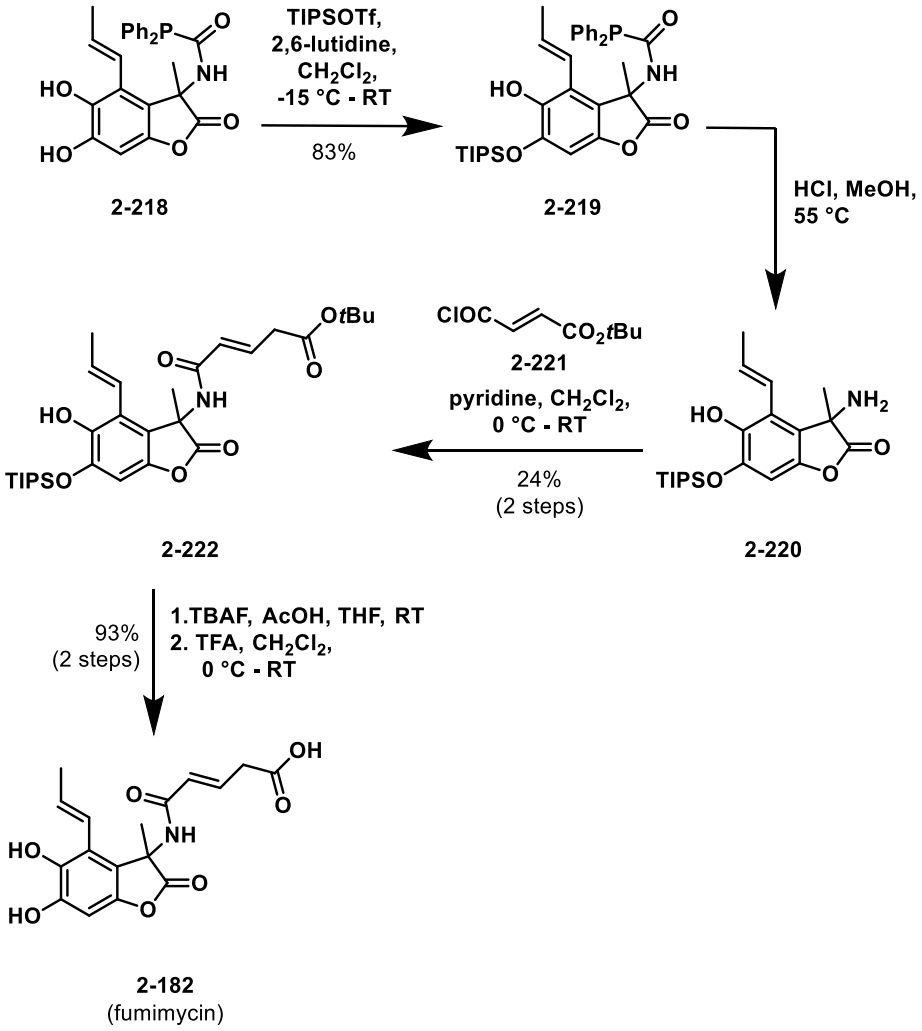
To begin the synthesis of fumimycin, vanillin was allylated and then converted to phenol **2-209** by a Dakin oxidation using $H_2O_2/B(OH)_3/H_2SO_4$.[100] Friedel-Crafts acylation with ethyl 2-chloro-2-oxoacetate afforded **2-210** in an 82% yield. TBS protection of the phenol, followed by a condensation reaction with hydroxylamine gave oxime **2-211** (91% yields over two steps), which was then converted to ketimine **2-214** with chlorodiphenylphospine. The mechanism for this transformation occurs as follows: 1) nucleophilic attack of the oxygen in oxime **2-211** to the phosphine gives intermediate **2-212**; 2) thermally induced homolytic *N-O* bond cleavage occurs to give the two radical species shown in intermediate **2-213**; and lastly, 3) recombination of the radicals forms ketimine **2-214**.[101] The decision to form ketimine **2-214** served two purposes: 1) due to the EWG effects of acyl group, it would promote Grignard addition to the imine, and 2) it would provide a mild protecting group for the amine after Grignard addition to ketimine **2-214**. The aforementioned Grignard addition into the amine gave compound **2-215** in 65%. TBS ether was then deprotected by heating the compound to 120 °C in DMF, which also promoted formation of the benzofuranone core, and continued heating in DMF resulted in a Claisen rearrangement to give benzofuranone **2-216**. Isomerization of the terminal olefin under rhodium catalysis[102] occurred in near quantitative yield with 10:1 selectivity towards the desired *trans* isomer. From here, Gross and Bräse decided a protecting group change on the alcohol was in order as deprotection of the methoxy later

on was unsuccessful. After many attempts, it was found that BI_3 allowed for isolation of diol **2-218** in a 90% yield.[103]



Scheme 2-41 Gross and Bräse's total synthesis of fumimycin

Mono-protection of diol **2-218** with TIPSOTf afforded **2-219** in an 83% yield. Deprotection of the amine and subsequent acylation with **2-221** gave benzofuranone **2-222** in a 24% yield over two steps. Fumimycin (**2-182**) was then accessed by TBAF deprotection of the TIPS ether, and TFA promoted cleavage of the *t*-butyl ester.

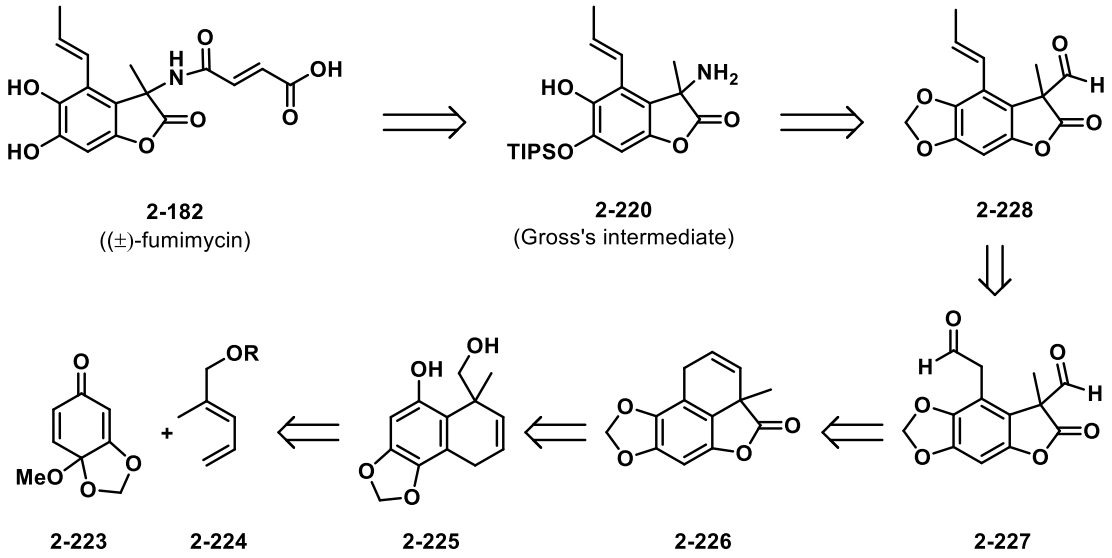


Scheme 2-42 Completing Gross and Bräse's total synthesis of fumimycin

2.6.2 Results and discussion

2.6.2.1 Retrosynthesis

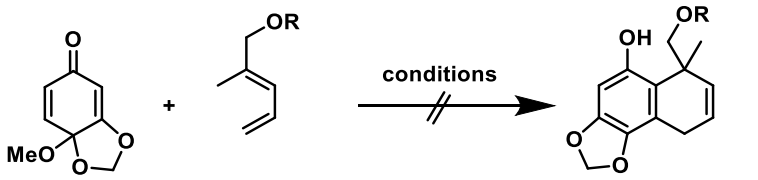
As shown in the retrosynthesis below, we planned to complete our synthesis of fumimycin by converging with Gross and Bräse's synthesis by accessing intermediate **2-220**. The amine in Gross's intermediate would come from a similar protocol to fargesine, which involved an oxidation of benzofuranone aldehyde **2-228** to an acid followed by a Curtius rearrangement, and subsequent hydrolysis of the isocyanate. The other half of Gross's intermediate would arise from a deprotection of the acetal and subsequent mono-protection of the diol with TIPS. The olefin in compound **2-228** could be accessed from a Grignard addition to the least hindered carbonyl of **2-227** followed by a dehydration reaction. Benzofuranone dialdehyde **2-227** would come about from an oxidative cleavage of the olefin in benzofuranone **2-226**, which would have come from the oxidative lactonization of **2-225**. Lastly, dihydronaphthalenol **2-225** would have come about through the Kerr group's Diels-Alder between diene **2-224** and dienophile **2-223**.



Scheme 2-43 Retrosynthesis of fumimycin

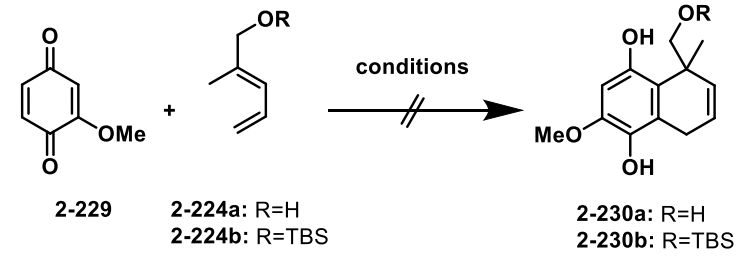
2.6.2.2 Forward synthesis

To begin our studies, a Diels-Alder reaction between known diene **2-224a**[104] or **2-224b**,[105] and quinone ketal **2-223**[106] were attempted to access dihydronaphthalenol **2-225**. However, attempts at forming the Diels-Alder adduct under hyperbaric conditions (13 kbar at RT or 30 °C), thermal conditions (toluene heated to reflux), or Lewis acid catalysis ($TiCl_2(OiPr)_2$ with BINOL,[107] or with BF_3•OEt_2) resulted in no product (Scheme 2-44).



Scheme 2-44 Initial Diels-Alder attempts

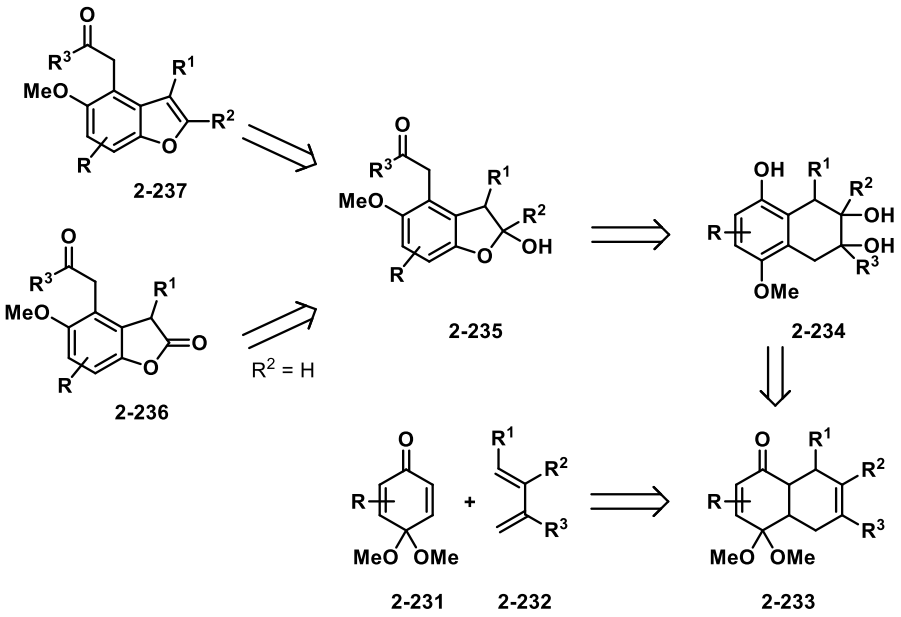
It was thought that perhaps the dienophile could be made more reactive by using a 1,4-benzoquinone **2-229** as the reacting partner. These have a stronger electron withdrawing effect on the dienophile, lowering the energy level of the LUMO, and thus making them more suitable for Diels-Alder chemistry. When similar Diels-Alder conditions from above were done on 1,4-benzoquinone **2-229** and diene **2-224**, again no product was obtained (Scheme 2-45), and it is clear that the diene is too sterically encumbered to react. Due to these results a revised retro synthesis had to be arranged.



Scheme 2-45 Utilizing 1,4-benzoquinone **2-223** to access dihydronaphthalenol **2-224**

2.6.2.3 Revised retrosynthesis

It was thought that Kerr's Diels-Alder/Plieninger indolization sequence could be modified as a methodology to access benzofurans, or benzofuranones (Scheme 2-46).

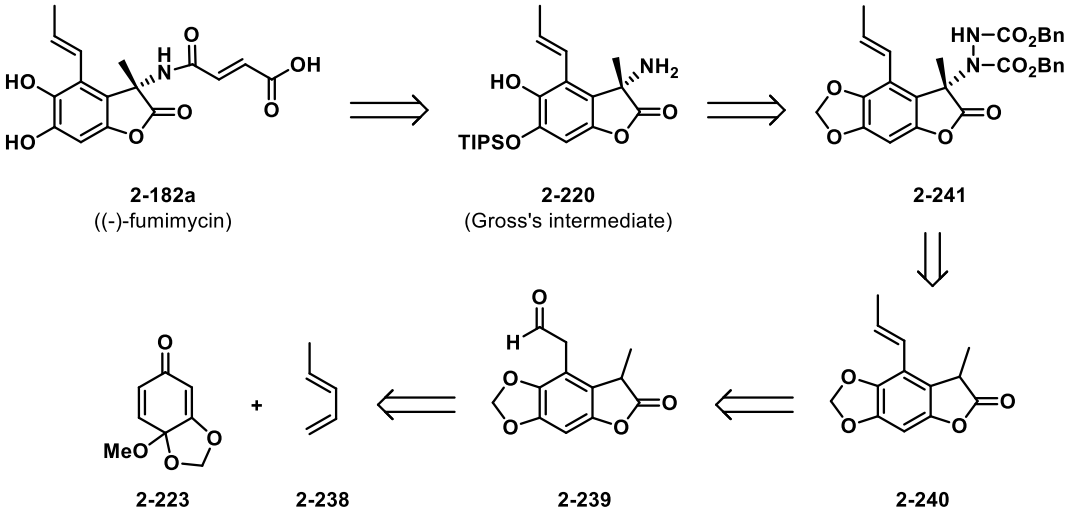


Scheme 2-46 Divergent methodology towards benzofurans and benzofuranones

The modification of the indolization protocol relies on utilizing quinone ketal **2-231** instead of quinone imine ketal for the Diels-Alder reaction. Under the standard Plieninger indolization sequence one would obtain a hemiacetal, and then a dehydration would allow for an indole; however, due to this route being the oxygen analogue, we would access hemiacetal **2-235**, which can then get oxidized to benzofuranone **2-236**, or dehydrated to form benzofuran **2-237**.

The revised retrosynthetic plan is shown below in Scheme 2-47. Again, fumimycin would be derived from Gross's intermediate; however, a new approach would be required to access the amine. A stereoselective amination protocol of benzofuranones would install Boc-protected hydrazine alpha to the carbonyl (**2-241**).[108] Due to the stereoselective control of this reaction, it would allow for the synthesis of naturally occurring fumimycin (**2-182a**). The required amine in Gross's intermediate can then be accessed by reduction of the Boc-protected hydrazine.[109] The olefin in benzofuranone **2-240** would come from a

Grignard addition/dehydration procedure from the aldehyde in **2-239**. Lastly, the modified Diels Alder/Plieninger sequence of piperylene and quinone ketal **2-223** can access benzofuranone **2-239**.

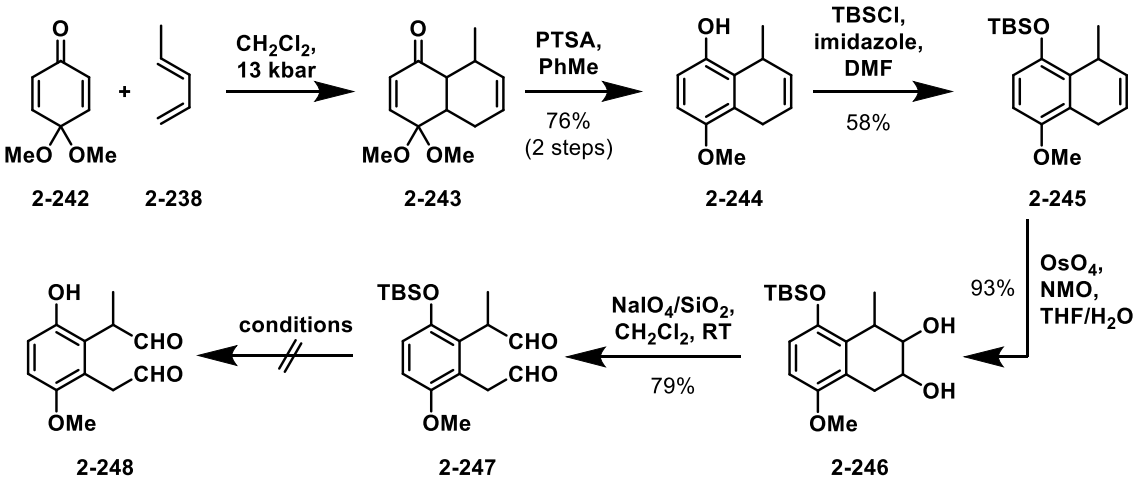


Scheme 2-47 Modified retrosynthesis towards natural (-)-fumimycin

2.6.2.4 Model study I - towards modified Diels-Alder, Plieninger protocol

A model study was attempted to determine conditions for the modified Diels-Alder/ Plieninger protocol using quinone imine ketal **2-242** (Scheme 2-48). To this end, piperylene and quinone imine ketal were reacted under hyperbaric conditions (13 kbar) for 12 hours to afford **2-243**. Aromatization of the crude adduct could then be performed with PTSA in toluene to obtain **2-244** in a 76% yield over the two steps. Attempts to promote the cycloaddition under thermal conditions (toluene heated to 140 °C in a sealed tube, with BHT, for 18 hours), resulted in an approximate ratio of 3:2 between product and unreacted starting material, and it was decided to continue to use hyperbaric conditions. At this stage, we protected phenol **2-244** as a TBS ether to avoid complications that may arise from the phenol in subsequent steps; thus, TBS ether **2-245** was formed in a 58% yield. TBS protected phenol was then dihydroxylated with OsO_4 and NMO to give diol **2-245** in a 93% yield, and was used crude to obtain dial **2-241** in a

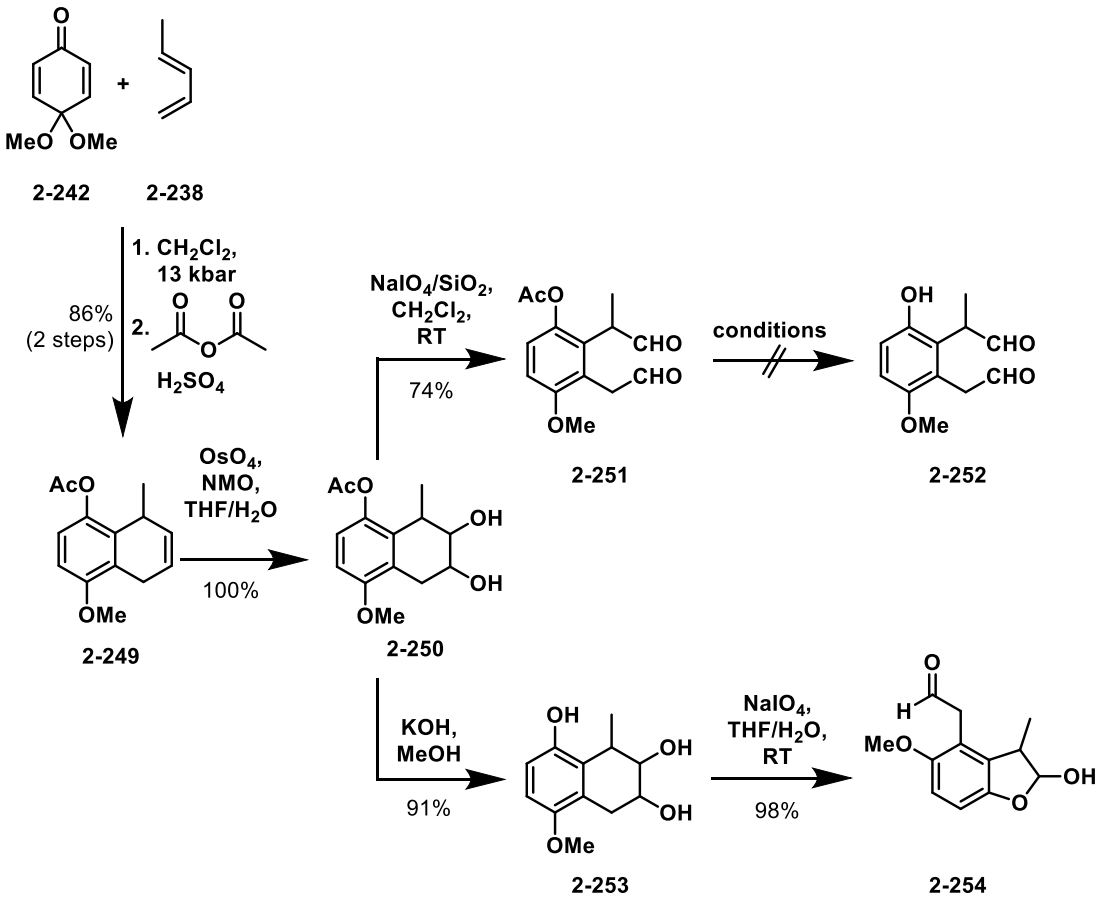
79% yield. Despite the yields in the pathway being moderate, the route became problematic as there was difficulty in removing the TBS group. Attempts with HCl, HF, and TBAF were unsuccessful as they did not promote deprotection but rather decomposed the material (based on crude ^{1}H NMR).



Scheme 2-48 Model study I - towards the modified Diels-Alder/Plieninger protocol towards benzofuranones

2.6.2.5 Model study II - towards modified Diels-Alder, Plieninger protocol

As the deprotection of TBS ether was proving to be difficult, an alternative protecting group was used. We decided that isolation of dihydronaphthalenol **2-244** was unnecessary, and a protected phenol can easily be accessed by a one-pot aromatization/alcohol protection to afford dihydronaphthalenyl acetate **2-249**. To this end, crude Diels-Alder adduct was taken up in acetic anhydride and a catalytic amount of sulfuric acid was added to give dihydronaphthalenyl acetate **2-249** in an 86% yield over two steps. Dihydroxylation of dihydronaphthalenyl acetate afforded diol **2-250** in a quantitative yield, which then underwent oxidative cleave to give dialdehyde species **2-251** in a 74% yield.

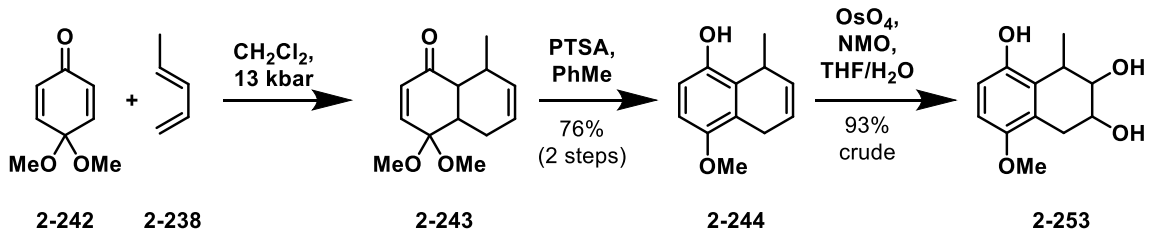


Scheme 2-49 Model study II - towards the modified Diels-Alder/Plieninger protocol towards benzofuranones

Unfortunately, deprotection of the acetate was unsuccessful at this stage, and it was decided to remove the acetyl group at an earlier stage. Deprotection of the acetyl group in diol **2-50** went smoothly and did not require further purification to give triol **2-253**. The crude triol was then submitted to oxidative cleavage conditions with $NaIO_4$, which immediately cyzclized in situ to hemiacetal **2-248** in a 98% yield. The cleavage did not with the previously used $NaIO_4/SiO_2/CH_2Cl_2$ conditions as the triol was not soluble in dichloromethane.

As shown above, it became apparent that the phenol did not need to be protected for the oxidative cleavage, so we set out to determine if protection of dihydronaphthalenol **2-238** was required at all. To this end, dihydronaphthalenol **2-244** was submitted to dihydroxylation conditions and triol **2-247** was obtained in a 93% crude yield. Since the

overall yield to access the triol was higher via the acetylation route, it became the preferred route to access hemiacetal **2-248**.

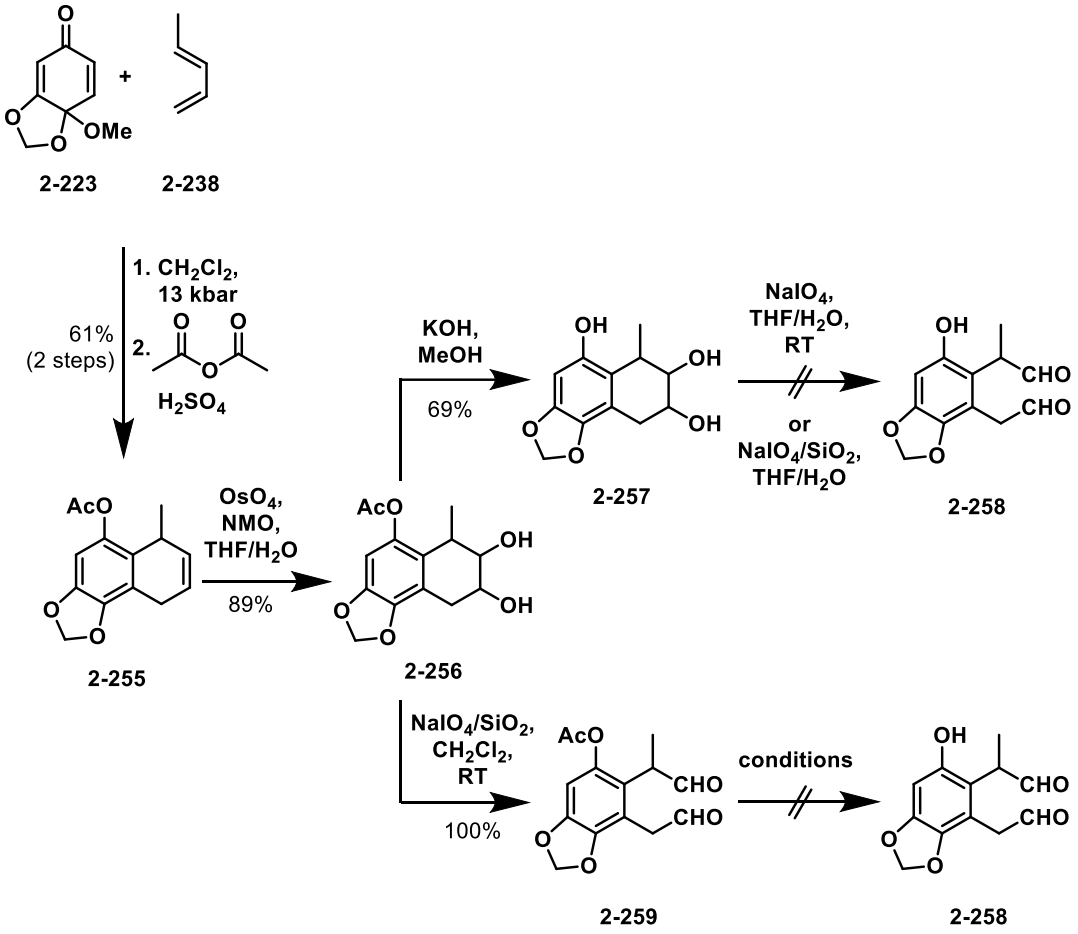


Scheme 2-50 Accessing triol **2-247** without a protecting group

With hemiacetal **2-254** at hand, attempts to oxidize the alcohol with IBX or Fetizon's reagent[110] (Ag_2CO_3/celite) were unsuccessful. Attempts to dehydrate the alcohol with $KHSO_4$, PTSA, and H_3PO_4 were also unsuccessful. Despite being unable to access a benzofuran, or benzofuranone, we were not discouraged as this was only a model study, and hoped that we would be able perform the oxidation on the requisite hemiacetal for fumimycin.

2.6.2.6 Progress towards the total synthesis of fumimycin

Efforts towards the total synthesis of fumimycin followed conditions optimized in the model study. To begin, a Diels-Alder reaction between quinone ketal **2-223**, and piperylene was performed, which then underwent aromatization/alcohol protection to give **2-255** in 61% yield over two steps (Scheme 2-51). Dihydroxylation of the dihydronaphthalenyl acetate gave diol **2-256** in 89% yield, and subsequent deprotection of the acetate afforded triol **2-257** in a 69% yield. Unfortunately, when periodate cleavage was attempted on triol **2-57**, a substantial amount of decomposition was obtained and only a minor amount of product could be seen in the crude ^{1}H NMR spectrum.

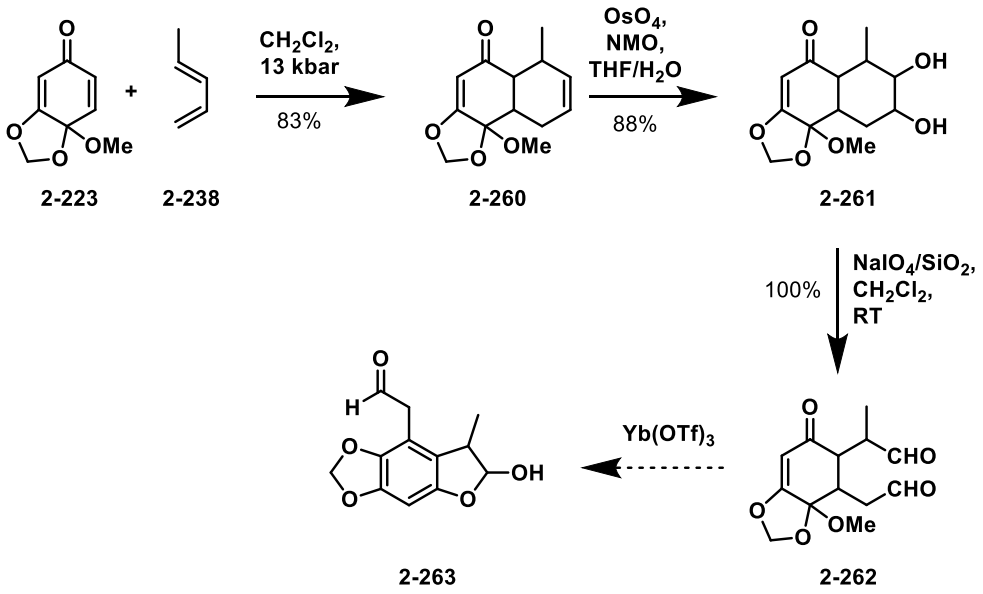


Scheme 2-51 Attempts to access benzofuranone core for fumimycin

An alternative route was required, and despite failing in the model study, it was decided to keep the phenol protected for the periodate cleavage. Di-aldehyde species **2-259** was formed in a quantitative yield, however once again this route was unsuccessful as deprotection conditions were decomposing the molecule. Efforts were then attempted to reduce the aldehyde with $NaBH_4$, or oxidize the aldehydes via Pinnick or PDC oxidation, but to no avail.

One last approach towards fumimycin was attempted. A Diels-Alder reaction was performed between quinone ketal **2-223** and **2-238** to give **2-260** in an 83% yield, but instead of aromatizing the Diels-Alder adduct, it was decided to attempt the dihydroxylation on this intermediate. Dihydroxylation with OsO_4 and NMO afforded diol **2-261** in an 88% yield; dihydroxylation only occurred on the olefin derived from

piperylene as it is not as delocalized as the other olefin. From diol **2-261** periodate cleavage gave dial **2-262** in a quantitative yield. Efforts to promote cyclization under protic acids or BF_3•OEt_2 gave decomposition; however, preliminary studies to promote the cyclization under $Yb(OTf)_3$ mediated conditions appear to have formed hemiacetal **2-263**, (based on crude ^1H NMR of a test reaction). Unfortunately, no other trials could be done on this intermediate, and we were unsuccessful in forming the benzofuranone core to fumimycin. Nevertheless, future work is needed to optimize the cyclization, and further investigation is required to oxidize **2-263** to a benzofuranone. With optimized conditions to access benzofuranone, very few synthetic steps are required to access fumimycin.



Scheme 2-52 Attempt at accessing benzofuranone core for fumimycin

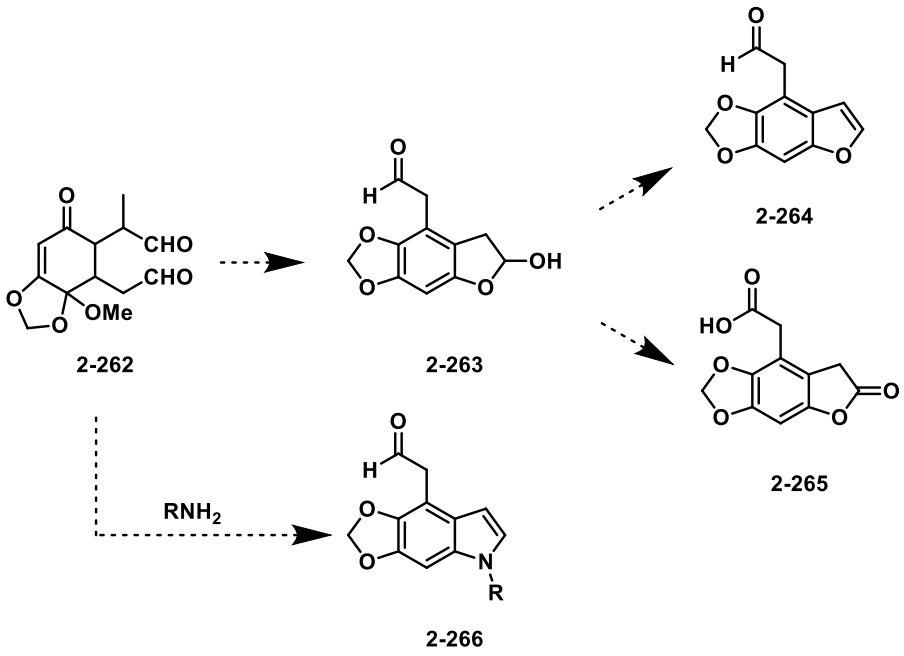
2.6.3 Conclusions

Multiple attempts were taken to modify the Diels-Alder, Plieninger indolization sequence, in an effort to access benzofuranones; however, none were successful. The probable reason to the demise of the route is oxidation of the phenol in late stage intermediates. A final route was devised that avoided phenol synthesis; however, more work is required to determine if the route is a viable method to access benzofuranones.

2.7 Summary and future work

In summary, this chapter showed the trials and tribulations involved in research dedicated to the total synthesis of natural products. The first section of this chapter showed the successful formal synthesis of fargesine. The indole in fargesine was accessed using the Kerr group's Diels-Alder/Plieninger indolization sequence. A two-step procedure was then carried out to convert the benzylic aldehyde to a benzylamine, as required in fargesine. As can be seen during the formal synthesis of fargesine, similar synthetic strategies are not always viable, and alternative routes must be explored (as seen in attempts reproduce Jia's *N*-oxidation conditions in intermediate **2-165**).

The second half of the chapter discussed attempts towards fumimycin. Fumimycin was going to be accessed through a modified Diels-Alder/Plieninger indolization sequence however many attempts to form a benzofuranone failed. A potentially viable route has been found through compound **2-262**. Lewis acid promoted cyclization could afford hemiacetal **2-263** which can then undergo a reduction to form benzofuran **2-264**, or benzofuranone **2-265**. This intermediate is also useful as a Paal-Knorr type procedure could also potentially be utilized to access indole **2-266**.



Scheme 2-53 Future work to access benzofurans, benzofuranones, or indoles

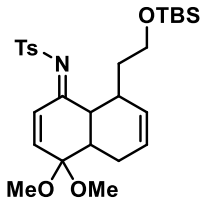
2.8 Experimental

2.8.1 Formal synthesis of fargesine

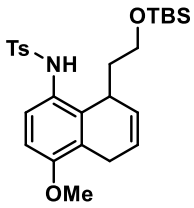
General considerations:

All reactions were performed under an atmosphere of Ar unless otherwise indicated. Toluene, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dichloromethane 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, Alfa Aesar, Caledon, Strem or VWR and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F_{254}), visualizing with UV light, and the plates developed with *p*-anisaldehyde stain. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

NMR experiments were performed on Varian Mercury 400, Inova 400 MHz instruments with ^{13}C operating frequencies of 100 MHz. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (*J*) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS™ Magnetic Sector GC-HRMS. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}).

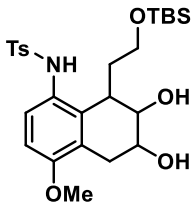


N-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4,4-dimethoxy-4a,5,8,8a-tetra-hydronaphthalen-1(4H)-ylidene)-4-methylbenzenesulfonamide (2-169): N-(4,4-dimethoxycyclohexa-2,5-dien-1-ylidene)-4-methyl -benzenesulfonamide (**2-160**) (6.14 g, 20 mmol), tert-butyl(hexa-3,5-dien-1-yloxy)dimethylsilane (**2-161a**) (12.74g, 60 mmol), toluene (20 mL, 1 mol/L), and butylated hydroxytoluene (< 10 mg) were placed into a glass pressure tube, and then the tube placed into a 140 °C oil bath. The reaction stirred for 24 hours, and the solvent removed *in vacuo*. The product was purified by trituration with cold hexanes, and isolated by filtration. Diels-Alder adduct **2-169** was then obtained (85%, 8.84 g, 17 mmol) as a white solid (melting point: 97-98 °C); **Rf** = 0.56 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (app d, *J*=8.6 Hz, 2 H), 7.30 - 7.22 (m, 3 H), 6.41 (app dd, *J*=10.6, 2.3 Hz, 1 H), 5.46 (s, 2 H), 3.56 (t, *J*=6.3 Hz, 2 H), 3.35 (t, *J*=3.7 Hz, 1 H), 3.30 (s, 3 H), 3.25 (s, 3 H), 2.70 - 2.61 (m, 1 H), 2.55 - 2.46 (m, 1 H), 2.41 (s, 3 H), 2.09 - 2.00 (m, 1 H), 1.95 - 1.83 (m, 2 H), 1.80 - 1.70 (m, 1 H), 0.85 (s, 9 H), -0.02 (s, 3 H), -0.02 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.0, 143.2, 142.1, 138.7, 130.4, 129.3, 126.8, 124.8, 123.7, 99.0, 61.6, 49.6, 47.6, 44.8, 44.8, 36.8, 35.4, 25.9, 24.3, 21.6, 18.2, -5.4, -5.4; **FT-IR** (thin film, cm-1) νmax 3024, 2953, 2928, 2855, 1588, 1471, 1319, 1254, 1156, 1091, 1053, 829, 777, 681, 561; **HRMS** calc'd for $C_{27}H_{41}NO_5SSi$ [M+] 519.2475; found 519.2492.

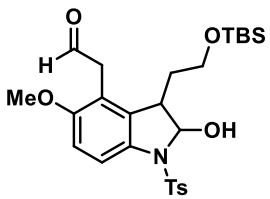


N-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-methoxy-5,8-dihydro-naphthalen-1-yl)-4-methylbenzenesulfonamide (2-170): Diels-Alder adduct **2-169** (8.84 g, 17 mmol) in toluene (20 mL, 0.85 mol/L), and butylated hydroxytoluene (<10 mg) were placed into a glass pressure tube, and then the tube was placed into a 160 °C oil bath. The reaction stirred for 24 hours, and then the solvent removed *in vacuo*. The product was purified by trituration with cold hexanes, and isolated by filtration. Dihydronaphthalenamine **2-170** was obtained (94%, 7.79 g, 15.98 mmol) as a beige solid (melting point: 126-127); **Rf** = 0.58 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.42 - 7.35 (m, 3 H), 7.11 (app d, *J*=8.2 Hz, 2 H), 6.75 (app d, *J*=8.6 Hz, 1 H), 5.80 (m, 1 H), 5.49 (ddd, *J*=9.5, 6.0, 3.3 Hz, 1 H), 3.82 (s, 3 H), 3.58 (dt, *J*=11.3, 3.9 Hz, 1 H), 3.44 (dd, *J*=20.3, 5.9 Hz, 1

H), 3.21 (td, *J*=11.3, 2.3 Hz, 1 H), 2.88 - 2.75 (m, 2 H), 2.35 (s, 3 H), 1.63 - 1.51 (m, 1 H), 1.15 - 1.04 (m, 1 H), 0.96 (s, 9 H), 0.20 (s, 3 H), 0.18 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.0, 142.7, 137.1, 135.1, 130.2, 129.2, 127.4, 126.8, 125.7, 124.9, 124.8, 107.9, 60.4, 55.4, 38.6, 30.9, 26.1, 24.1, 21.4, 18.7, -4.9, -5.4; **FT-IR** (thin film, cm-1) νmax 3185, 3034, 2953, 2929, 2857, 1481, 1256, 1164, 1092, 1060, 838, 811, 668; **HRMS** calc'd for $C_{26}H_{37}NO_4SSi$ [M+] 487.2213; found 487.2215.

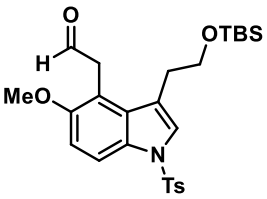


N-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6,7-dihydroxy-4methoxy -5,6, 7,8 -tetrahydronaphthalen-1-yl)-4-methylbenzenesulfonamide (2-171): Dihydronaphthalenamine **2-170** (9.75 g, 20 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (114:86 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (2.81 g, 24 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (9.08 g, 72 mmol) was added and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave crude diol **2-171** as a brown foam that did not require further purification for the next step (a quantitative yield was assumed for next step); **Rf** = 0.03 (30% EtOAc/hexanes); **HRMS** calc'd for $C_{26}H_{39}NO_6SSi$ [M+] 521.2267; found 521.2253.

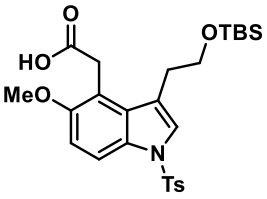


2-(3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-hydroxy-5-meth-oxy-1-tosylindolin-4-yl)acetaldehyde (2-172): To a vigorously stirred slurry of $NaIO_4/SiO_2$ (42.86 g, 30 mmol) in dichloromethane (92 mL, 0.33 mol/L) was added a solution of crude diol **2-171** (assumed 20 mmol) in dichloromethane (480 mL, 0.04 mol/L) dropwise at room temperature over 30 minutes. After 2 hours of stirring, the solution was filtered to remove $NaIO_4/SiO_2$, and the solvent removed *in vacuo*. The crude material was then purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to give hemiaminal **2-172** (91%, 9.48 g, 18.20 mmol) as a yellow foam; **Rf** = 0.33 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.62 (t, *J*=1.8 Hz, 1 H), 7.72 (app d,

J=8.2 Hz, 2 H), 7.45 (app d, *J*=9.0 Hz, 1 H), 7.23 (app d, *J*=8.2 Hz, 2 H), 6.76 (app d, *J*=9.0 Hz, 1 H), 5.64 (d, *J*=3.9 Hz, 1 H), 3.77 (s, 3 H), 3.64 - 3.45 (m, 4 H), 3.13 (dd, *J*=10.9, 2.7 Hz, 1 H), 3.03 (d, *J*=3.5 Hz, 1 H), 2.37 (s, 3 H), 1.34 (dtd, *J*=14.8, 6.3, 6.3, 2.7 Hz, 1 H), 0.91 (s, 9 H), 0.78 - 0.68 (m, 1 H), 0.06 (s, 3 H), 0.05 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.2, 154.9, 144.2, 136.0, 134.9, 132.9, 129.8, 126.8, 118.7, 114.0, 109.9, 90.6, 60.5, 55.9, 45.6, 41.9, 41.9, 35.7, 25.8, 21.5, 18.2, -5.5, -5.5; **FT-IR** (thin film, cm-1) νmax 3483, 2952, 2929, 2856, 1724, 1480, 1353, 1249, 1166, 1093, 1006, 913, 837, 743, 667; **HRMS** calc'd for $C_{26}H_{37}NO_6SSi$ [M+] 519.2111; found 519.2111.

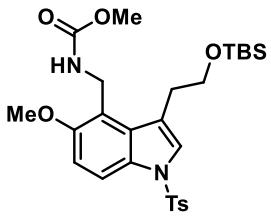


2-(3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-1-tosyl-1H-indol-4-yl)acetaldehyde (2-162a): Hemiaminal **2-172** (1.5 g, 2.88 mmol) and camphorsulfonic acid (689 mg, 2.96 mmol) in toluene (25 mL, 0.12 mol/L) were stirred at room temperature for 1 hour. After which sodium bicarbonate (1.12 g, 8.88 mmol) was added to the mixture and the reaction was stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Indole **2-162a** did not require further purification for the next step (a quantitative yield was assumed for next step) However, the indole can be purified by flash column chromatography on silica gel (30% EtOAc/hexanes) to give the indole **2-162a** (96%, 1.39 g, 2.76 mmol) as a light brown foam; **Rf** = 0.46 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.64 (t, *J*=1.8 Hz, 1 H), 7.91 (app d, *J*=9.0 Hz, 1 H), 7.72 (app d, *J*=8.2 Hz, 2 H), 7.40 (s, 1 H), 7.20 (app d, *J*=8.2 Hz, 2 H), 6.94 (app d, *J*=9.0 Hz, 1 H), 4.00 (d, *J*=2.0 Hz, 2 H), 3.87 (t, *J*=6.4 Hz, 2 H), 3.83 (s, 3 H), 2.91 (td, *J*=6.5, 1.0 Hz, 2 H), 2.34 (s, 3 H), 0.87 (s, 9 H), 0.01 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.1, 154.0, 144.7, 135.2, 131.0, 130.6, 129.8, 126.8, 125.7, 119.8, 113.3, 113.1, 108.7, 62.6, 56.4, 41.1, 30.6, 25.9, 21.5, 18.2, -5.4; **FT-IR** (thin film, cm-1) νmax 2953, 2928, 2856, 1723, 1463, 1422, 1255, 1174, 1094, 913, 837, 743, 666; **HRMS** calc'd for $C_{26}H_{35}NO_5SSi$ [M+] 501.2005; found 501.2020.



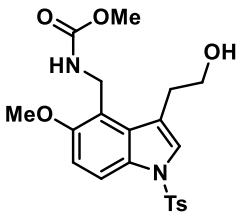
2-(3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-1-tosyl-1H-indol-4-yl)acetic acid (2-173): Crude indole **2-162a** was

dissolved in a 8:3:1 tetrahydrofuran/t-butanol/water mixture (14:5.25:1.75 mL, 0.14 mol/L total). At room temperature, sodium dihydrogen phosphate (1.04 g, 8.64 mmol) and 2-methyl-2-butene (2.44 mL, 23.04 mmol) were added to the reaction mixture, followed by sodium chlorite (781 mg, 8.64 mmol). The reaction stirred for 3 hours and then diluted with a saturated aqueous solution of sodium bisulfite (pre-chilled to 0 °C). The mixture was then extracted with diethyl ether, and the combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the product was purified by crystallization (DCM/hexanes) and filtered to obtain indole acid **2-173** as a white solid (melting point: 127-128 °C) in a 70% yield over two steps (1.04 g, 2.00 mmol); **Rf** = 0.03 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (app d, *J*=9.4 Hz, 1 H), 7.71 (app d, *J*=8.6 Hz, 2 H), 7.39 (s, 1 H), 7.19 (app d, *J*=8.2 Hz, 2 H), 6.92 (app d, *J*=9.4 Hz, 1 H), 4.00 (s, 2 H), 3.88 (t, *J*=6.6 Hz, 2 H), 3.82 (s, 3 H), 2.94 (t, *J*=6.3 Hz, 2 H), 2.33 (s, 3 H), 0.86 (s, 9 H), -0.01 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.3, 154.0, 144.7, 135.2, 130.7, 130.4, 129.8, 126.7, 125.6, 119.8, 114.3, 113.2, 108.9, 62.8, 56.6, 31.5, 30.3, 25.9, 21.5, 18.2, -5.5; **FT-IR** (thin film, cm-1) νmax 2953, 2940, 2857, 1710, 1653, 1423, 1368, 1257, 1174, 1094, 913, 835, 740, 667, 542; **HRMS** calc'd for $C_{26}H_{35}NO_6SSi$ [M+] 517.1954; found 517.1928.

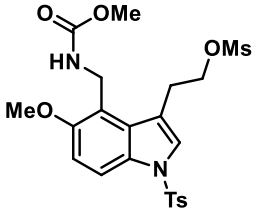


methyl ((3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-methoxy-1-tosyl-1H-indol-4-yl)methyl)carbamate (2-163b): Indole acid **2-173** (1g, 1.93 mmol) was placed in dry toluene (7.7 mL, 0.25 mol/L), along with triethylamine (400 μL, 2.9 mmol) and diphenylphosphoryl azide (622 μL, 2.9 mmol), and heated to reflux for 30 minutes. The reaction was then cooled for a few minutes and methanol was slowly added to the reaction flask (3.9 mL, 0.13 mol/L). The reaction was heated to reflux again for another 30 minutes, and then the contents of the flask were transferred to a sealed tube (another 3.9 mL of methanol were used to rinse the original flask) and heated to 155 °C for 16 hours. The contents of the sealed tube were diluted with saturated $NaHCO_{3(aq)}$, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave crude Curtius

product **2-163b** (1.01 g) as a brown oil that was used crude for the next step; **HRMS** calc'd for $C_{27}H_{38}N_2O_6SSi$ [M+] 546.2220; found 546.2215.

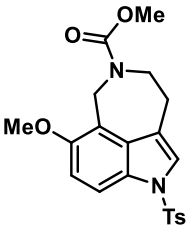


methyl((3-(2-hydroxyethyl)-5-methoxy-1-tosyl-1H-indol-4-yl)methyl) carbamate (2-163c): Crude **2-163b** (1.01 g) was dissolved in 1.0 molar tetrabutylammonium fluoride solution in THF (7.4 mL, 3.83 mmol), and stirred at room temperature for 20 hours. The reaction was then diluted in water, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. The product was then purified by flash column chromatography on silica gel (100% EtOAc) to give indole **2-163c** in 66% yield over the two steps (554 mg, 1.27 mmol) as a white solid; **Rf** = 0.31 (100% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (app d, *J*=9.0 Hz, 1 H), 7.71 (app d, *J*=8.2 Hz, 2 H), 7.41 (s, 1 H), 7.20 (app d, *J*=8.2 Hz, 2 H), 6.92 (app d, *J*=9.0 Hz, 1 H), 5.39 (br s, 1 H), 4.64 (br d, *J*=5.9 Hz, 2 H), 3.87 (s, 3 H), 3.81 (br s, 2 H), 3.63 (s, 3 H), 3.18 (br t, *J*=6.8 Hz, 2 H), 2.33 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.1, 154.8, 144.8, 135.0, 130.8, 129.8, 129.6, 126.7, 126.3, 119.3, 117.9, 113.8, 108.6, 62.4, 56.3, 52.2, 36.5, 30.6, 21.6; **FT-IR** (thin film, cm-1) νmax 3407, 2953, 1701, 1519, 1458, 1422, 1364, 1257, 1173, 1062, 913, 736, 668; **HRMS** calc'd for $C_{21}H_{24}N_2O_6S$ [M+] 432.1355; found 432.1349.

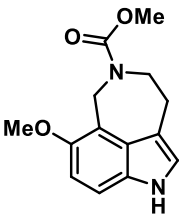


2-(5-methoxy-4-(((methoxycarbonyl)amino)methyl)-1-tosyl-1H-indol-3-yl)ethyl methanesulfonate (2-163d): Indole **2-163c** (200 mg, 0.46 mmol) was dissolved in dichloromethane (15 ml, 0.03 mol/L) and cooled to 0 °C. A few crystals of DMAP were added along with triethylamine (194 µL, 1.4 mmol). Methanesulfonyl chloride (143 µL, 1.85 mmol) was added drop wise. The reaction stirred at 0 °C for 30 minutes and then diluted with water. The mixture was then extracted with dichrlomethane, and the combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the product was purified by crystallization (DCM/hexanes) and filtered to obtain indole **2-163d** (83%, 196 mg, 0.38 mmol) as a

white solid (melting point: 127-128 °C); **Rf** = 0.49 (100% EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (app d, *J*=9.0 Hz, 1 H), 7.72 (app d, *J*=8.2 Hz, 2 H), 7.45 (s, 1 H), 7.21 (app d, *J*=8.2 Hz, 2 H), 6.93 (app d, *J*=9.4 Hz, 1 H), 5.32 (br s, 1 H), 4.57 (br d, *J*=5.9 Hz, 2 H), 4.52 (br t, *J*=6.3 Hz, 2 H), 3.86 (s, 3 H), 3.60 (s, 3 H), 3.46 (br t, *J*=6.3 Hz, 2 H), 2.93 (s, 3 H), 2.33 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.8, 154.7, 144.9, 134.8, 130.5, 129.9, 129.1, 126.8, 126.5, 118.0, 117.4, 113.7, 108.8, 68.7, 56.3, 52.1, 37.4, 36.6, 26.7, 21.5; **FT-IR** (thin film, cm-1) νmax 3399, 2938, 1717, 1558, 1423, 1354, 1258, 1173, 1131, 985, 913, 743, 668; **HRMS** calc'd for $C_{22}H_{26}N_2O_8S_2$ [M+] 510.1131; found 510.1133.

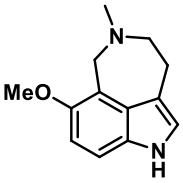


methyl 9-methoxy-6-tosyl-1,3,4,6-tetrahydro-2H-azepino[5,4,3-cd]indole-2-carboxylate (2-164): Indole **2-163d** (840 mg, 1.65 mmol) was dissolved in dry DMF (6.6 ml, 0.25 mol/L), and added dropwise to a room temperature solution of NaH (60% NaH in mineral oil) (197 mg, 4.94 mmol) in dry DMF (7.9 mL, 0.62 mol/L). After the reaction stirred for three hours at room temperature, the mixture was diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave crude **2-164** (600 mg) as a brown oil that was used crude for the next step; **Rf** = 0.65 (100% EtOAc); **HRMS** calc'd for $C_{21}H_{22}N_2O_5S$ [M+] 414.1249; found 414.1256. A crude ^{1}H NMR spectrum is provided as a reference: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (t, *J*=8.8 Hz, 1H), 7.71 (t, *J*=7.6 Hz, 2H), 7.31 (d, *J*=10.6 Hz, 1H), 7.19 (d, *J*=8.2 Hz, 2H), 6.89 (dd, *J*=9.0, 7.0 Hz, 1H), 4.83 (d, *J*=20.7 Hz, 2H), 3.84 (d, *J*=3.8 Hz, 3H), 3.70-3.63 (m, 6H), 3.10-3.01 (m, 2H), 2.33 (s, 3H).

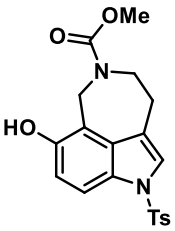


methyl 9-methoxy-1,3,4,6-tetrahydro-2H-azepino[5,4,3-cd]indole-2-carboxylate (2-174): Crude indole **2-164** (600 mg) was dissolved in 1.0 molar tetrabutylammonium fluoride solution in THF (10 mL, 6.9 mmol) and heated to 130 °C in a microwave reactor for 25 minutes. The reaction mixture was diluted with water, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous MgSO4.

Removal of the solvent *in vacuo* gave crude **2-168** which was not further purified for the next step (a quantitative yield was assumed for next step); **HRMS** calc'd for $C_{14}H_{16}N_2O_3$ [M+] 260.1161; found 260.1152.

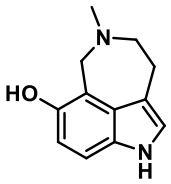


9-methoxy-2-methyl-2,3,4,6-tetrahydro-1H- azepino [5,4,3-cd]indole (2-165): Crude indole **2-1174** (assumed 1.45 mmol) was dissolved in dry THF (29 mL, 0.05 mol/L), and to the reaction flask at room temperature was added LAH (549 mg, 14.5 mol). The reaction was then heated to reflux, and continued heating for three hours. After this time the reaction was cooled to 0 °C, and to the reaction flask was added (drop-wise) for every gram of LAH, a milliliter of water, a milliliter of 20% $NaOH_{(aq)}$, and lastly three milliliters of water. The reaction was allowed to cool to room temperature for 30 minutes, and then filtered through celite. Further purification of the product by flash column chromatography (100% EtOAc) afforded indole **2-165** as a yellow solid in a 75% yield over the three steps (265 mg, 1.22 mmol); **Rf** = 0.63 (100% EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (br s, 1 H), 7.16 (d, *J*=9.0 Hz, 1 H), 6.97 (d, *J*=2.0 Hz, 1 H), 6.87 (d, *J*=8.6 Hz, 1 H), 4.18 (s, 2 H), 3.84 (s, 3 H), 3.07 (s, 4 H), 2.61 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.9, 133.4, 127.8, 123.8, 114.3, 113.6, 112.5, 111.5, 59.6, 59.4, 45.7, 27.1; **FT-IR** (thin film, cm-1) νmax 3049, 2919, 2771, 1579, 1458, 1369,1265, 1236, 1130, 1055, 972, 902, 782; **HRMS** calc'd for $C_{13}H_{16}N_2O$ [M+] 216.1263; found 216.1256.

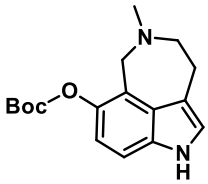


methyl 9-hydroxy-6-tosyl-1,3,4,6-tetrahydro-2H-azepino[5,4,3-cd]indole-2-carboxylate (2-178): Crude indole **2-164** (200 mg, 0.48 mmol) was dissolved in dry dichloromethane (12 mL, 0.04 mol/L) and cooled to -78 °C. To this solution was added 1.0 molar boron tribromide in dichloromethane (1.45 mL, 1.45 mmol) drop wise. The reaction was then allowed to stir to room temperature over 12 hours. After this time the reaction was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave crude **2-178** (188 mg) as a purple solid. The crude material must be immediately carried forward to the next step; **Rf** = 0.62 (100% EtOAc); A crude ^{1}H

NMR spectrum is provided as a reference: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (br t, *J*=8.5 Hz, 2 H), 7.31 (br d, *J*=18.8 Hz, 1 H), 7.21 (br d, *J*=6.5 Hz, 2 H), 6.74 (br dd, *J*=13.2, 8.5 Hz, 1 H), 4.85 (br d, *J*=16.4 Hz, 2 H), 3.73-3.65 (m, 6 H), 3.10-3.03 (m, 2 H), 2.35 (s, 3 H)



2-methyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-9-ol (2-176): Crude indole **2-178** (75 mg, 0.19 mmol) was dissolved in dry THF (3.75 mL, 0.05 mol/L), and to this was added LAH (71 mg, 1.88 mmol). The reaction was heated at 60 °C in the microwave for three hours. After this time the reaction was cooled to 0 °C, and to the reaction flask was added (drop-wise) for every gram of LAH, a milliliter of water, a milliliter of 20% $NaOH_{(aq)}$, and lastly three milliliters of water. The reaction was allowed to cool to room temperature for 30 minutes, and then filtered through celite. Further purification of the product by flash column chromatography (75% DCM/Methanol, and 5% NH_4OH) afforded indole **2-176** (77%, 29 mg, 1.44 mmol)as a yellow oil; **Rf** = 0.5 (75% DCM/Methanol, and 5% NH_4OH); **^{1}H NMR** (400 MHz, CD_3OD) δ 7.08 (app d, *J*=8.6 Hz, 1 H), 6.99 (s, 1 H), 6.67 (app d, *J*=8.6 Hz, 1 H), 4.92 (s, 3 H), 4.24 (s, 2 H), 3.20 - 3.17 (m, 2 H), 3.14 - 3.07 (m, 2 H), 2.66 (s, 3 H); **^{13}C NMR** (100 MHz, CD_3OD) δ 147.9, 133.4, 127.8, 123.8, 114.3, 113.6, 112.5, 111.5, 59.6, 59.4, 45.7, 27.1; **FT-IR** (thin film, cm-1) νmax 3393, 2922, 2532, 1684, 1646, 1436, 1363, 1243, 793; **HRMS** calc'd for $C_{12}H_{14}N_2O$ [M+] 202.1106; found 202.1098.



tert-butyl (2-methyl-2,3,4,6-tetrahydro-1H-azepino[5,4,3-cd]indol-9-yl) carbonate (2-158): Crude indole **2-172** (10 mg, 0.05 mmol), and DMAP (3 mg, 0.03 mmol), were dissolved in dry DMF (3 mL, 0.02 mol/L). Di-tert-butyl dicarbonate (13 mg, 0.06 mmol) was added and the reaction stirred for 16 hours and then diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$ and the solvent removed *in vacuo* gave crude **2-158** which was further purification was done by flash column chromatography (95% DCM/Methanol) afforded **2-158** (41%, 6 mg, 0.02 mmol) as a yellow oil, with ^{1}H NMR spectral data matching the

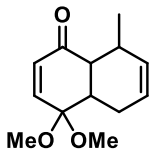
literature;[47] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (br s, 1 H), 7.19 (d, *J*=8.6 Hz, 1 H), 7.01 (d, *J*=1.2 Hz, 1 H), 6.91 (d, *J*=8.6 Hz, 1 H), 4.18 (s, 2 H), 3.19 (t, *J*=5.1 Hz, 2 H), 3.10 (t, *J*=5.1 Hz, 2 H), 2.57 (s, 3 H), 1.56 (s, 9 H).

2.8.2 Progress towards the total synthesis of fumimycin

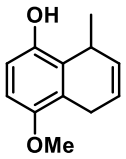
General considerations:

All reactions were performed under an atmosphere of Ar unless otherwise indicated. Toluene, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dichloromethane 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, Alfa Aesar, Caledon, Strem or VWR and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F_{254}), visualizing with UV light, and the plates developed with *p*-anisaldehyde stain. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc).

NMR experiments were performed on Varian Mercury 400, Inova 400 MHz instruments with ^{13}C operating frequencies of 100 MHz. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (*J*) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS™ Magnetic Sector GC-HRMS. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}). High-pressure reactions were carried out on a LECOTM Tempres High-Pressure chemical reactor.

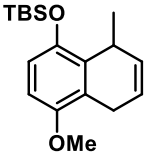


4,4-dimethoxy-8-methyl-4a,5,8,8a-tetrahydronaphthalen-1(4H)-one (2-243): Quinone ketal **2-242** (462.5 mg, 3 mmol) and piperylene (613 mg, 9 mmol) were measured into a length of heat shrinkable Teflon tubing, which was closed at one end with a brass clamp. Dichloromethane (2 mL, 1.5 mol/L) was then added to the mixture and the tube was sealed with another clamp and placed in a LECO Tempres high-pressure chemical reactor, and pressurized at room temperature. After 12 hours the mixture was depressurized and the solvent removed. The crude **2-243** white solid material could be used without further purification for the subsequent step; **Rf** = 0.53 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.48 (dd, *J*=10.6, 2.3 Hz, 1 H), 5.87 (d, *J*=10.2 Hz, 1 H), 5.63 - 5.43 (m, 2 H), 3.33 (s, 3 H), 3.26 (s, 3 H), 3.04 (t, *J*=3.9 Hz, 1 H), 2.74 - 2.63 (m, 1 H), 2.50 - 2.37 (m, 1 H), 2.11 - 1.85 (m, 2 H), 1.39 (d, *J*=7.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.5, 142.3, 132.3, 130.9, 123.7, 99.6, 49.7, 48.1, 47.6, 43.7, 33.8, 24.1, 18.6; **FT-IR** (thin film, cm-1) νmax 3021, 2933, 2831, 1690, 1454, 1377, 1193, 1107, 938, 601, 561, 435; **HRMS** calc'd for $C_{13}H_{18}O_3$ [M+] 222.1256; found 222.1265.

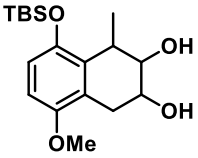


4-methoxy-8-methyl-5,8-dihydronaphthalen-1-ol (2-244): The crude mixture of **2-243**, was assumed to be a quantitative yield (3 mmol) and was dissolved in dry toluene (30 mL, 0.1 mol/L). To the reaction flask was added p-Toluenesulfonic acid (< 10 mg), and the reaction stirred for 30 minutes at room temperature. After this time, solid $NaHCO_3$ (1 g) was added to the flask and was stirred for another 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) gave **2-244** (76% two steps, 431 mg, 2.26 mmol) as an orange solid; **Rf** = 0.50 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.64 - 6.57 (m, 2 H), 5.95 - 5.86 (m, 2 H), 4.54 (d, *J*=1.6 Hz, 1 H), 3.79 (s, 3 H), 3.66 - 3.53 (m, 1 H), 3.43 - 3.34 (m, 1 H), 3.19 - 3.08 (m, 1 H), 1.28 (d, *J*=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.9, 146.6, 130.5, 128.3, 124.5, 122.9, 112.2, 107.7, 55.7, 29.3, 24.3, 22.0; **FT-IR** (thin

film, cm-1) νmax 3413, 3027, 2957, 2925, 2866, 1488, 1460, 1257, 1108, 1074, 799, 724, 704; **HRMS** calc'd for $C_{12}H_{14}O_3$ [M+] 190.0994; found 190.0997.

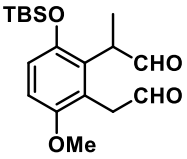


tert-butyl((4-methoxy-8-methyl-5,8-dihydronaphthalen-1-yl)oxy)dimethylsilane (2-245): Compound **2-244** (813 mg, 4.3 mmol) and imidazole (350 mg, 5.13 mmol) were dissolved in dimethylformamide (10.5 mL, 0.25 mol/L). Slowly, tert-butyldimethylsilyl chloride (804 mg, 5.13 mmol) was added to the reaction flask and the mixture stirred for 12 hours at room temperature. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) gave **2-245** (58%, 759 mg, 2.59 mmol) as a yellow oil; **Rf** = 0.63 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.64-6.56 (m, 2H), 5.92-5.85 (m, 2H), 3.77 (s, 3H), 3.59-3.54 (m, 1 H), 3.38-3.08 (m, 2H), 1.22 (d, *J*=7.0 Hz, 3H), 1.02 (s, 9H), 0.27 (s, 3H), 0.18 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.9, 146.6, 132.2, 131.0, 124.5, 122.8, 115.0, 107.1, 55.5, 29.8, 25.9, 24.5, 22.2, 18.2, -3.8, -4.3; **FT-IR** (thin film, cm-1) νmax 3027, 2956, 2929, 2851, 1594, 1479, 1255, 1110, 1075, 1044, 862, 839, 779, 734, 698; **HRMS** calc'd for $C_{18}H_{28}O_2Si$ [M+] 304.1859; found 304.1873.

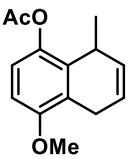


8-((tert-butyldimethylsilyl)oxy)-5-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene-2,3-diol (2-246): Compound **2-245** (748 mg, 2.46 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (14:11 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (345 mg, 2.95 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (1.12 g, 8.85 mmol) was added and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-246** (93%, 774 mg, 2.30

mmol), with no further purification required, as a white solid; **Rf** = 0.16 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.59 (app dd, *J*=23.8, 8.6 Hz, 2 H), 4.12 (ddd, *J*=10.3, 6.9, 2.3 Hz, 1 H), 3.96 (dd, *J*=2.3, 2.3 Hz, 1 H), 3.76 (s, 3 H), 3.30 (qd, *J*=7.2, 2.5 Hz, 1 H), 3.16 (dd, *J*=17.2, 6.6 Hz, 1 H), 2.53 (dd, *J*=17.4, 10.4 Hz, 1 H), 1.20 (d, *J*=7.4 Hz, 3 H), 1.01 (s, 9 H), 0.26 (s, 3 H), 0.20 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.0, 147.7, 129.7, 123.4, 115.3, 107.8, 74.2, 66.0, 55.5, 37.0, 27.6, 25.8, 19.1, 18.2, -3.9, -4.4; **FT-IR** (thin film, cm-1) νmax 3382 2957, 2930, 2856, 1477, 1252, 1103, 1058, 1029, 913, 861, 839, 743; **HRMS** calc'd for $C_{18}H_{30}O_4Si$ [M+] 338.1913; found 338.1924.

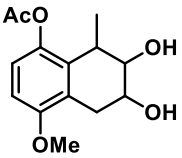


2-(6-((tert-butyldimethylsilyl)oxy)-3-methoxy-2-(2 oxoethyl)phenyl) propanal (2-247): To a vigorously stirred slurry of $NaIO_4/SiO_2$ (5.06 g, 3.5 mmol) in dichloromethane (16 mL, 0.22 mol/L) was added a solution of diol **2-246** (800 mg, 2.36 mmol) in dichloromethane (44 mL, 0.05 mol/L) dropwise at room temperature over 30 minutes. After 2 hours of stirring, the solution was filtered to remove $NaIO_4/SiO_2$, and the solvent removed *in vacuo*. The crude material was then purified by flash chromatography on silica gel (30% EtOAc/hexanes) to give **2-247** (79%, 627 mg, 1.86 mmol) as a yellow oil; **Rf** = 0.46 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.66 - 9.64 (two overlapping aldehyde peaks, 2 H), 6.78 (app dd, *J*=24.2, 9.0 Hz, 2 H), 3.78 (s, 3 H), 3.74 - 3.60 (m, 2 H), 3.52 (q, *J*=7.0 Hz, 1 H), 1.33 (d, *J*=7.0 Hz, 3 H), 0.96 (s, 9 H), 0.25 (s, 3 H), 0.22 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.6, 199.3, 151.9, 147.5, 130.9, 121.7, 117.0, 109.8, 55.9, 46.5, 41.9, 25.9, 18.5, 13.3, -4.0, -4.2; **FT-IR** (thin film, cm-1) νmax 2932, 2886, 2858, 1727, 1592, 1477, 1248, 1211, 1051, 840, 782; **HRMS** calc'd for $C_{18}H_{28}O_4Si$ [M+] 336.1757; found 336.1766.

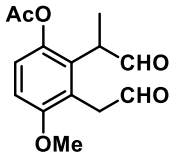


4-methoxy-8-methyl-5,8-dihydronaphthalen-1-yl acetate (2-249): The crude mixture of **2-243**, was assumed to be a quantitative yield (3 mmol) and was dissolved in acetic anhydride (3 mL, 1 mol/L). One drop of sulfuric acid was then added at room temperature and the reaction stirred for 1 minute. The reaction

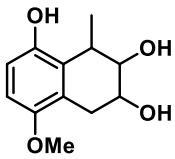
mixture was then placed into an aqueous NaOH solution (0.1 mol/L), and then extracted with diethyl ether. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-249** (86%, 600 mg, 2.58 mmol), with no further purification required, as a white foam; **Rf** = 0.47 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (d, *J*=9.0 Hz, 1 H), 6.73 (d, *J*=9.0 Hz, 1 H), 5.95 - 5.85 (m, 2 H), 3.83 (s, 3 H), 3.50 - 3.36 (m, 2 H), 3.20 - 3.10 (m, 1 H), 2.34 (s, 3 H), 1.24 (d, *J*=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 154.2, 141.6, 132.9, 129.9, 124.3, 122.7, 119.8, 107.2, 55.3, 29.5, 24.1, 22.3, 20.8; **FT-IR** (thin film, cm-1) νmax 3029, 2960, 2934, 2837, 1758, 1589, 1479, 1368, 1338, 1253, 1209, 1108, 1074, 1029, 885, 807, 203; **HRMS** calc'd for $C_{14}H_{16}O_3$ [M+] 232.1099; found 232.1106.



6,7-dihydroxy-4-methoxy-8-methyl-5,6,7,8-tetrahydronaphthalen-1-yl acetate (2-250): Compound **2-249** (307 mg, 1.32 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (7.5:5.5 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (185 mg, 1.59 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (601 mg, 4.77 mmol) was added and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-250** (100%, 350 mg, 1.32 mmol), with no further purification required, as a white foam; **Rf** = 0.03 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.89 (app d, *J*=8.6 Hz, 1 H), 6.70 (app d, *J*=9.0 Hz, 1 H), 4.08 (ddd, *J*=10.1, 6.7, 2.3 Hz, 1 H), 3.90 (dd, *J*=2.3 Hz, 1 H), 3.81 (s, 3 H), 3.18 - 3.07 (m, 2 H), 2.52 (dd, *J*=17.2, 10.2 Hz, 1 H), 2.30 (s, 4 H), 1.17 (d, *J*=7.4 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 154.6, 142.7, 130.9, 123.7, 120.4, 107.9, 73.7, 65.7, 55.5, 36.9, 27.6, 21.0, 19.4; **FT-IR** (thin film, cm-1) νmax 3404, 2935, 2837, 1751, 1590, 1478, 1369, 1207, 1055, 913, 742; **HRMS** calc'd for $C_{14}H_{18}O_5$ [M+] 266.1154; found 266.1149.



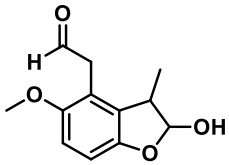
4-methoxy-3-(2-oxoethyl)-2-(1-oxopropan-2-yl)phenyl acetate (2-251): To a vigorously stirred slurry of $NaIO_4/SiO_2$ (2.33 g, 1.63 mmol) in dichloromethane (7 mL, 0.23 mol/L) was added a solution of diol **2-250** (290 mg, 1.09 mmol) in dichloromethane (20 mL, 0.05 mol/L) dropwise at room temperature over 30 minutes. After 2 hours of stirring, the solution was filtered to remove $NaIO_4/SiO_2$, and the solvent removed *in vacuo*. The crude material was then purified by flash chromatography on silica gel (50% EtOAc/hexanes) to give **2-251** (74%, 563 mg, 0.81 mmol) as a yellow oil; **Rf** = 0.20 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.66 (X of ABX, J_{AX}=1.5 Hz, J_{BX}=1.6 Hz, 1 H), 9.61 (s, 1 H), 7.05 (app d, J=9.0 Hz, 1 H), 6.89 (app d, J=9.0 Hz, 1 H), 3.82 (s, 3 H), 3.86 (A of ABX, J_{AB}=17.1 Hz, J_{AX}=1.5 Hz, 1 H), 3.68 (B of ABX, J_{AB}=17.1 Hz, J_{BX}=1.6 Hz, 1 H), 3.47 (q, J=6.8 Hz, 1 H), 2.16 (s, 3 H), 1.25 (d, J=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.1, 198.7, 169.6, 155.5, 142.3, 131.8, 122.9, 121.6, 110.1, 55.9, 47.0, 41.5, 20.7, 13.0; **FT-IR** (thin film, cm-1) νmax 2981, 2940, 2839, 2726, 1763, 1725, 1590, 1477, 1370, 1271, 1199, 1182, 1045, 815, 732; **HRMS** calc'd for $C_{14}H_{16}O_5$ [M+] 264.0998; found 264.0992.



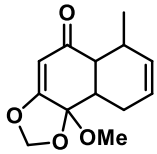
4-methoxy-8-methyl-5,6,7,8-tetrahydronaphthalene-1,6,7-triol (2-253): From acetate **2-250**: Compound **2-250** (572 mg, 2.15 mmol) was dissolved in methanol (27 mL, 0.08 mol/L) at room temperature, and then potassium hydroxide (200 mg, 3.57 mmol) was added to the reaction flask. The reaction stirred for two hours. After this time, the mixture was diluted with brine, and then extracted with diethyl ether. The combined organic layers were then dried with anhydrous $MgSO_4$, and removal of the solvent *in vacuo* gave **2-250** (88%, 422 mg, 1.88 mmol), with no further purification required, as a brown foam; **Rf** = 0.0 (30% EtOAc/hexanes).

From **2-244**: Compound **2-244** (242 mg, 1.27 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (7.5:5.5 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (176 mg, 1.5 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (1.9 mg, 15 mmol) was added

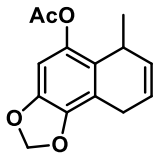
and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-253** (93%, 266 mg, 1.19 mmol), with no further purification required, as a brown foam; **Rf** = 0.0 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, CD_3OD) δ 6.59 (app dd, *J*=11.5, 8.8 Hz, 2 H), 4.06 (ddd, *J*=10.7, 6.4, 2.0 Hz, 1 H), 3.90 (dd, *J*=2.3 Hz, 1 H), 3.76 (s, 3 H), 3.29 (qd, *J*=7.2, 2.7 Hz, 1 H), 3.03 (dd, *J*=17.0, 6.4 Hz, 1 H), 2.58 (dd, *J*=17.2, 10.9 Hz, 1 H), 1.24 (d, *J*=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, CD_3OD) δ 152.5, 151.4, 128.8, 125.9, 113.8, 110.0, 76.2, 67.8, 57.0, 39.1, 28.9, 20.4; **FT-IR** (thin film, cm-1) νmax 3349, 2912, 2486, 1481, 1436, 1255, 1089, 1054, 984; **HRMS** calc'd for $C_{12}H_{16}O_4$ [M+] 224.1049; found 224.1048.



2-(2-hydroxy-5-methoxy-3-methyl-2,3-dihydrobenzofuran-4-yl)acetaldehyde (2-254): Triol **2-253** (427 mg, 1.9 mmol) was dissolved in a 3.4:1 tetrahydrofuran/water mixture (135:40 mL, 0.01 mol/L total) at room temperature, and to this was added $NaIO_4$ (6.1 g, 28.6 mmol). The reaction was stirred at room temperature for 16 hours. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-254** (99%, 417 mg, 1.88 mmol), with no further purification required, as a yellow oil; **Rf** = 0.65 (100% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (t, *J*=2.0 Hz, 1 H), 6.75 (app d, *J*=20.7, 8.6 Hz, 2 H), 5.56 (d, *J*=3.1 Hz, 1 H), 3.77 (s, 3 H), 3.69 - 3.54 (m, 2 H), 3.19 (q, *J*=7.3 Hz, 1 H), 3.11 (br d, *J*=4.3 Hz, 1 H), 1.59 (s, 3 H), 1.21 (d, *J*=7.4 Hz, 3 H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.7, 152.7, 151.2, 131.9, 118.3, 110.1, 109.0, 107.0, 56.1, 44.0, 29.7, 17.9; **FT-IR** (thin film, cm-1) νmax 3399, 2919, 2849, 2340, 1719, 1480, 1463, 1439, 1227, 1078, 1035, 913, 804, 743; **HRMS** calc'd for $C_{12}H_{14}O_4$ [M+] 222.0892; found 222.0895.

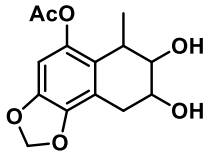


9b-methoxy-6-methyl-6,9,9a,9b-tetrahydronaphtho[1,2-d][1,3]dioxol-5(5aH)-one (2-260): Quinone ketal **2-223** (504.45 mg, 3 mmol) and piperylene (613 mg, 9 mmol) were measured into a length of heat shrinkable Teflon tubing, which was closed at one end with a brass clamp. Dichloromethane (3 mL, 1 mol/L) was then added to the mixture and the tube was sealed with another clamp and placed in a LECO Tempres high-pressure chemical reactor, and pressurized at room temperature. After 19 hours the mixture was depressurized and the solvent removed. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) gave **2-260** (83%, 616 mg, 2.50 mmol) as a white solid; **Rf** = 0.52 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 5.64 - 5.58 (m, 1 H), 5.55 - 5.48 (m, 3 H), 5.28 (s, 1 H), 3.44 (s, 3 H), 3.00 (ddd, *J*=10.6, 6.7, 3.7 Hz, 1 H), 2.88 (dd, *J*=4.1 Hz, 1 H), 2.47 - 2.58 (m, 1 H), 2.17 - 2.08 (m, 1 H), 1.95 - 1.83 (m, 1 H), 1.46 (d, *J*=7.4 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.7, 166.2, 132.7, 123.7, 105.1, 100.4, 98.2, 50.2, 45.4, 38.6, 33.9, 24.2, 19.1; **FT-IR** (thin film, cm-1) νmax 3021, 2926, 2845, 1666, 1462, 1405, 1352, 1305, 1253, 1179, 1098, 1029, 938, 917, 653; **HRMS** calc'd for $C_{13}H_{16}O_4$ [M+] 236.1049; found 236.1050.

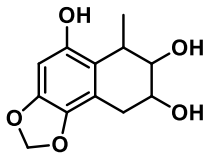


6-methyl-6,9-dihydronaphtho[1,2-d][1,3]dioxol-5-yl acetate (2-255): Diels-Alder adduct **2-260** (2.1 g, 8.88 mmol) was dissolved in acetic anhydride (8.9 mL, 1 mol/L). Three drops of sulfuric acid was then added at room temperature and the reaction stirred for 16 hours**.** The reaction mixture was then placed into an aqueous NaOH solution (0.1 mol/L), and then extracted with diethyl ether. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) gave **2-255** (73%, 1.59 g, 6.48 mmol) as a brown oil; **Rf** = 0.58 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 5.97 (A of AB, *J*=8.1 Hz, 1 H), 5.95 (B of AB, *J*=8.1 Hz, 1 H), 5.91-5.81 (m, 2 H), 3.39-3.10 (m, 3 H), 2.31 (s, 3 H), 1.17 (d, *J*=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 144.8, 142.5, 141.8, 131.1, 125.3, 121.5, 116.9, 102.1, 101.5, 29.3, 23.5, 22.3, 20.9; **FT-IR** (thin film, cm-1) νmax 2963, 2871,

1761, 1646, 1469, 1370, 1334, 1203, 1174, 1057, 957, 893, 706; **HRMS** calc'd for $C_{14}H_{14}O_4$ [M+] 246.0892; found 246.0898.

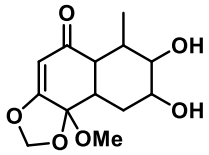


7,8-dihydroxy-6-methyl-6,7,8,9-tetrahydronaphtho[1,2-d][1,3]dioxol-5-yl acetate (2-256): Acetate **2-255** (738 mg, 3 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (17:13 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (527 mg, 4.5 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (1.13 g, 9 mmol) was added and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-256** (89%, 749 mg, 2.67 mmol), with no further purification required, as a orange foam; **Rf** = 0.0 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 5.97 (A of AB, *J*=6.5 Hz, 1 H), 5.95 (B of AB, *J*=6.5 Hz, 1 H), 4.12 (ddd, *J*=10.2, 6.8, 2.1 Hz, 1 H), 3.93 (dd, *J*=2.3 Hz, 1 H), 3.07 (qd, *J*=7.4, 3.1 Hz, 1 H), 3.03 (dd, *J*=16.8, 6.6 Hz, 1 H), 2.64 (dd, *J*=16.8, 10.2 Hz, 1 H), 2.29 (s, 3 H), 1.14 (d, *J*=7.4 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.9, 145.3, 143.1, 142.8, 122.9, 116.0, 102.6, 101.6, 74.0, 65.1, 36.7, 27.0, 20.9, 19.5; **FT-IR** (thin film, cm-1) νmax 3372, 2901, 1755, 1634, 1468, 1369, 1283, 1200, 1167, 1076, 1052, 905, 734; **HRMS** calc'd for $C_{14}H_{16}O_6$ [M+] 280.0947; found 280.0944.

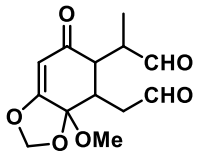


6-methyl-6,7,8,9-tetrahydronaphtho[1,2-d][1,3]dioxole-5,7,8-triol (2-257): Acetate **2-256** (750 mg, 2.68 mmol) was dissolved in methanol (34 mL, 0.08 mol/L) at room temperature, and then potassium hydroxide (250 mg, 4.45 mmol) was added to the reaction flask. The reaction stirred for two hours. After this time, the mixture was diluted with brine, and then extracted with ethyl acetate. The combined organic layers were then dried with anhydrous $MgSO_4$, and removal of the solvent *in vacuo* gave **2-257** (69%, 436 mg, 1.84

mmol), with no further purification required, as a white foam; **Rf** = 0.03 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, CD_3OD) δ 6.23 (s, 1 H), 5.80 (app dd, *J*=14.5, 1.2 Hz, 2 H), 4.05 (ddd, *J*=10.8, 6.4, 2.0 Hz, 1 H), 3.86 (dd, *J*=2.2, 2.1 Hz, 1 H), 3.21 (qd, *J*=7.2, 2.7 Hz, 1 H), 2.90 - 2.60 (m, 2 H), 1.18 (d, *J*=7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, CD_3OD) δ 152.0, 147.1, 139.9, 119.8, 118.7, 102.6, 97.3, 76.5, 67.2, 38.8, 28.4, 20.4; **FT-IR** (thin film, cm-1) νmax 3407, 2914, 2510, 2244, 2074, 1643, 1471, 1366, 1296, 1216, 1182, 1119, 1057, 973; **HRMS** calc'd for $C_{12}H_{14}O_5$ [M+] 238.0841; found 238.0838.



7,8-dihydroxy-9b-methoxy-6-methyl-6,7,8,9,9a,9b-hexahydronaphtho[1,2-d][1,3]dioxol-5(5aH)-one (2-261): Diels-Alder adduct **2-260** (100 mg, 0.42 mmol) was dissolved in a 4:3 tetrahydrofuran/water mixture (2.8:2.2 mL, 0.1 mol/L total), and a small crystal of osmium tetroxide was added. The reaction mixture was stirred for 5 minutes at room temperature, and then N-methylmorpholine-N-oxide (60 mg, 0.51 mmol) was added. The reaction stirred for 16 hours before solid sodium sulfite (128 mg, 1.02 mmol) was added and stirred for an additional 10 minutes. The mixture was diluted with H_2O, and then extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave **2-261** (88%, 100 mg, 0.37 mmol), with no further purification required, as a brown foam; **Rf** = 0.03 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.51 (d, *J*=10.9 Hz, 2 H), 5.33 (s, 1 H), 3.99 (br d, *J*=2.3 Hz, 1 H), 3.65 (dd, *J*=11.3, 2.7 Hz, 1 H), 3.42 (s, 3 H), 3.11 (dt, *J*=12.5, 3.5 Hz, 1 H), 2.84 - 2.76 (m, 1 H), 2.17 - 1.98 (m, 2 H), 1.42 (d, *J*=7.0 Hz, 3 H), 1.34 (td, *J*=13.7, 2.3 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.9, 166.7, 104.3, 100.9, 98.1, 72.2, 68.6, 50.0, 47.5, 35.4, 34.7, 29.4, 15.6; **FT-IR** (thin film, cm-1) νmax 3391, 2965, 2915, 1676, 1655, 1407, 1355, 1254, 1181, 1072, 1047, 1030, 914, 731; **HRMS** calc'd for $C_{13}H_{18}O_6$ [M+] 270.1103; found 270.1098.



2-(3a-methoxy-6-oxo-4-(2-oxoethyl)-3a,4,5,6-tetrahydrobenzo[d][1,3]dioxol -5-yl)propanal (2-262): To a vigorously stirred slurry of $NaIO_4/SiO_2$ (1.4 g, 1.11 mmol, 0.8 mmol/g) in dichloromethane (5 mL, 0.23 mol/L) was added a solution of diol **2-261** (200 mg, 0.74 mmol) in dichloromethane (20 mL, 0.05 mol/L) dropwise at room temperature over 30 minutes. After 2 hours of stirring, the solution was filtered to remove $NaIO_4/SiO_2$, and the solvent removed *in vacuo* to give **2-262** (100%, 198 mg, 0.74 mmol) as a yellow foam; **Rf** = 0.0 (30% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 9.86 (d, *J*=2.3 Hz, 1 H), 9.75 (d, *J*=1.6 Hz, 1 H), 5.54 (d, *J*=1.2 Hz, 2 H), 5.48 (s, 1 H), 3.62 (ddd, *J*=9.8, 4.3, 2.7 Hz, 1 H), 3.50 (s, 3 H), 3.37 (dd, *J*=10.7, 4.1 Hz, 1 H), 2.61 - 2.51 (m, 1 H), 2.47 (ddd, *J*=18.0, 9.8, 2.0 Hz, 1 H), 2.20 (dd, *J*=18.0, 2.7 Hz, 1 H), 1.05 (d, *J*=7.4 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.6, 198.7, 196.2, 167.8, 104.8, 99.8, 98.5, 50.5, 48.4, 42.4, 38.9, 12.0; **FT-IR** (thin film, cm-1) νmax 3405, 2971, 2917, 2838, 2730, 1720, 1655, 1460, 1408, 1186, 1097, 903; **HRMS** calc'd for $C_{13}H_{16}O_6$ [M+] 268.0947; found 268.0937.

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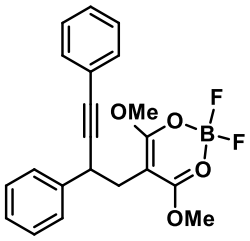
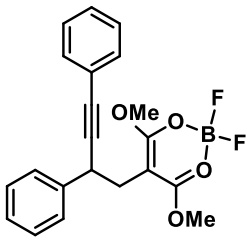
Appendix I – Ring opening of DA cyclopropanes with potassium organotrifluoroborates



Compound **1-86a**

^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-86a**

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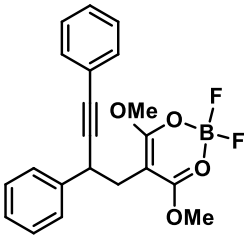
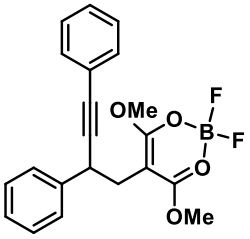


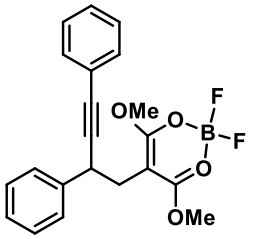
Compound **1-86a**

^{11}B NMR ($CDCl_3$, 128 MHz)

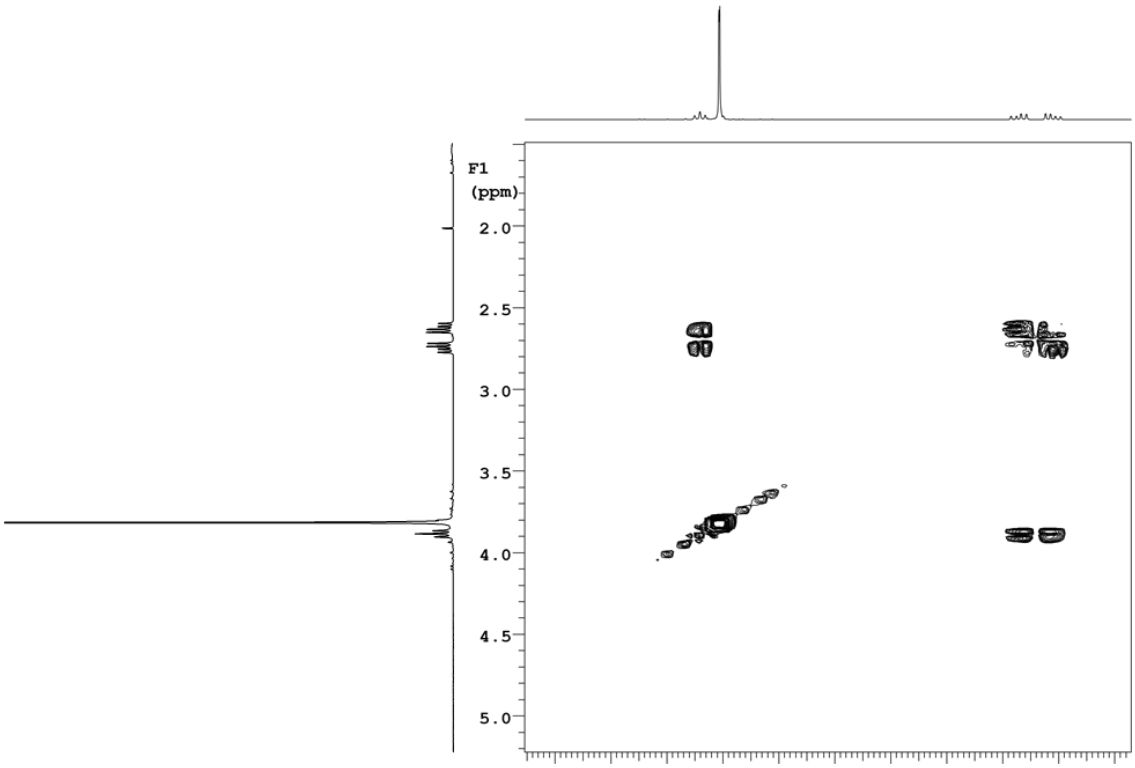


Compound **1-86a**

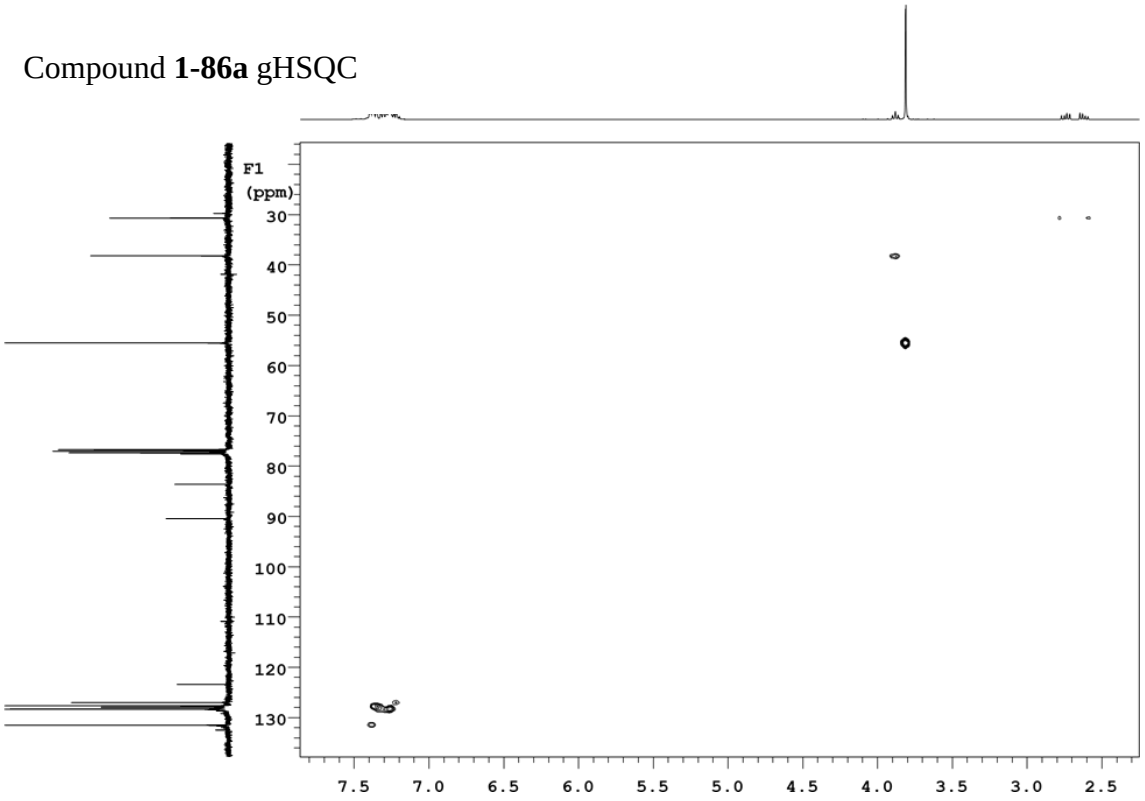
^{19}F NMR ($CDCl_3$, 376 MHz)



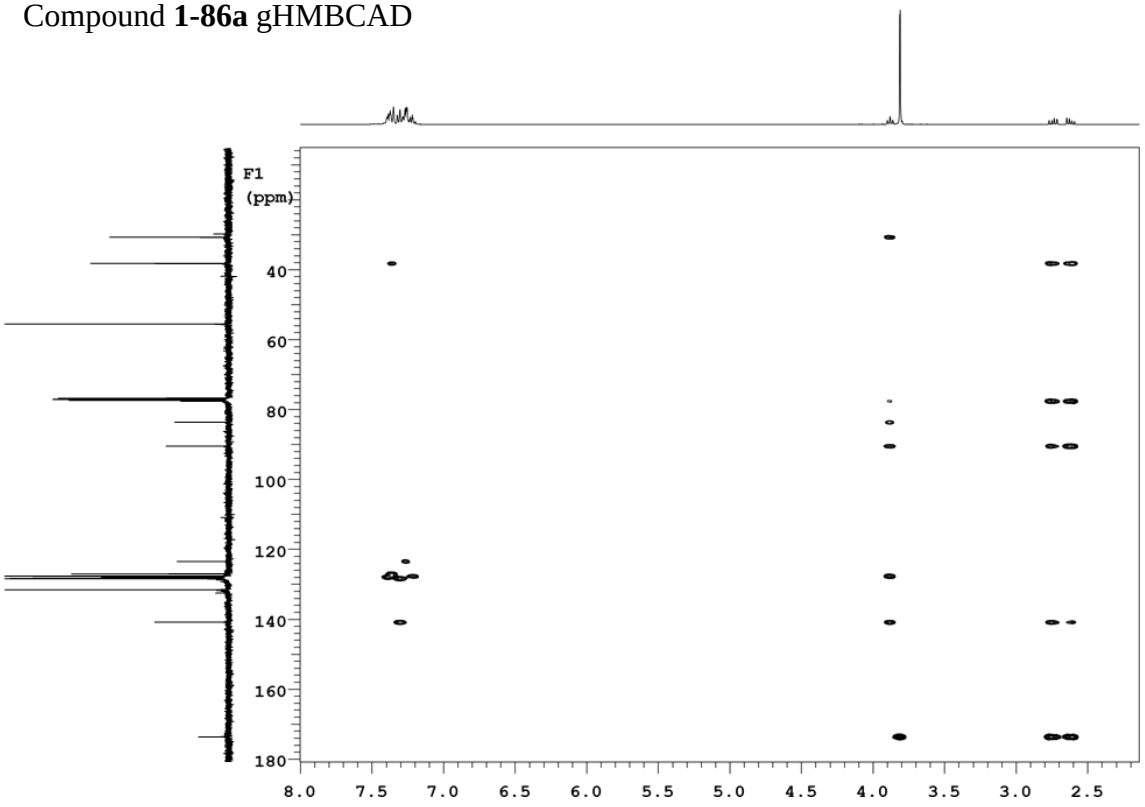
Compound **1-86a** gCOSY

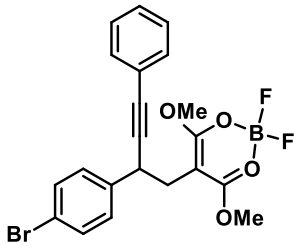


Compound **1-86a** gHSQC



Compound **1-86a** gHMBCAD





Compound **1-86b**

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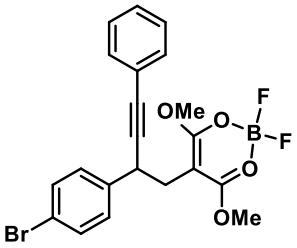
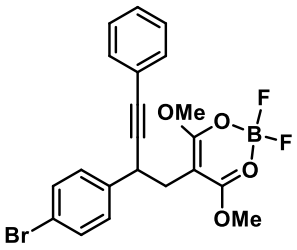


Compound **1-86b**

^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **1-86b**

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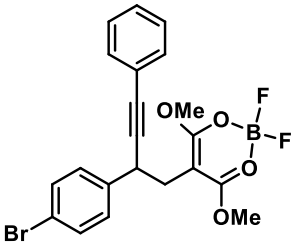

Compound **1-86b**

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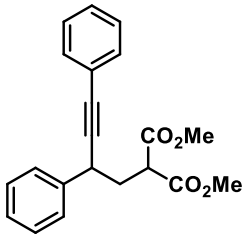

Compound **1-82a**

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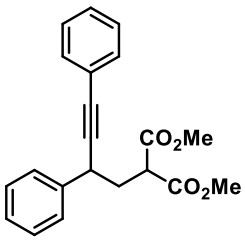
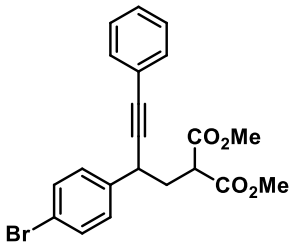


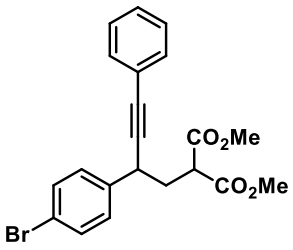
Compound **1-82a**

^{13}C NMR ($CDCl_3$, 100 MHz)



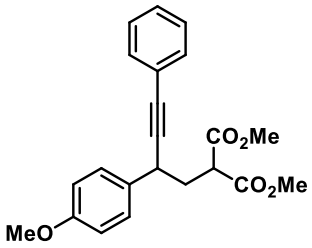
Compound **1-82b**

^{1}H NMR ($CDCl_3$, 400 MHz)



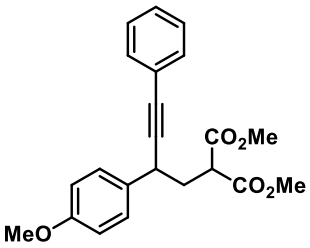
Compound **1-82b**

^{13}C NMR ($CDCl_3$, 100 MHz)



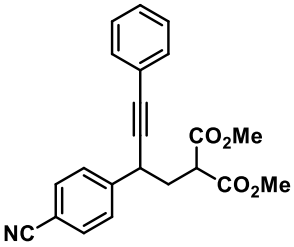
Compound **1-82c**

^{1}H NMR ($CDCl_3$, 400 MHz)



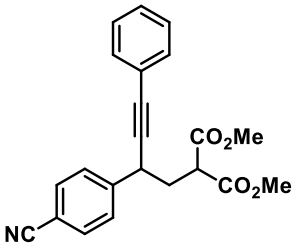
Compound **1-82c**

^{13}C NMR ($CDCl_3$, 100 MHz)



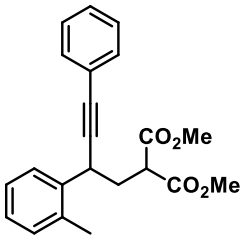
Compound **1-82e**

^{1}H NMR ($CDCl_3$, 400 MHz)



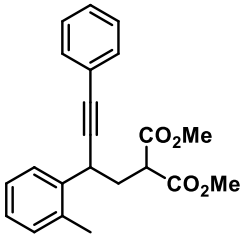
Compound **1-82e**

^{13}C NMR ($CDCl_3$, 100 MHz)



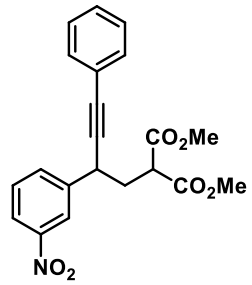
Compound **1-82f**

^{1}H NMR ($CDCl_3$, 400 MHz)



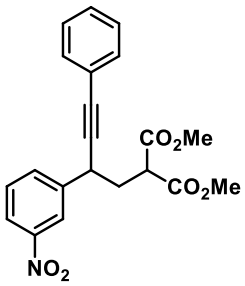
Compound **1-82f**

^{13}C NMR ($CDCl_3$, 100 MHz)



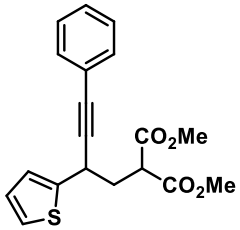
Compound **1-82g**

^{1}H NMR ($CDCl_3$, 400 MHz)



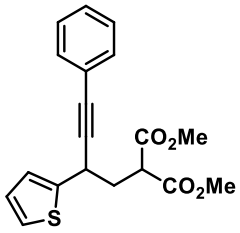
Compound **1-82g**

^{13}C NMR ($CDCl_3$, 100 MHz)



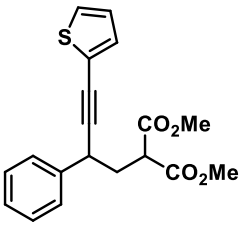
Compound **1-82h**

^{1}H NMR ($CDCl_3$, 400 MHz)



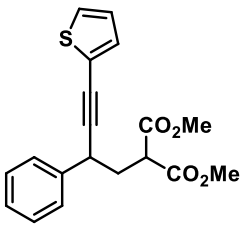
Compound **1-82h**

^{13}C NMR ($CDCl_3$, 100 MHz)



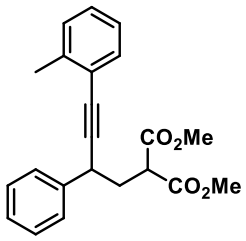
Compound **1-82i**

^{1}H NMR ($CDCl_3$, 400 MHz)



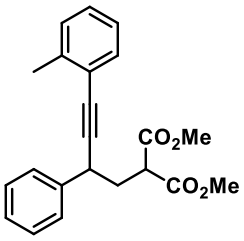
Compound **1-82i**

^{13}C NMR ($CDCl_3$, 100 MHz)



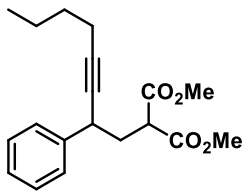
Compound **1-82j**

^{1}H NMR ($CDCl_3$, 400 MHz)



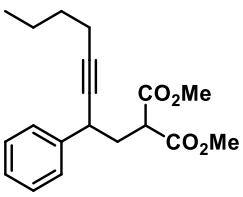
Compound **1-82j**

^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **1-82k**

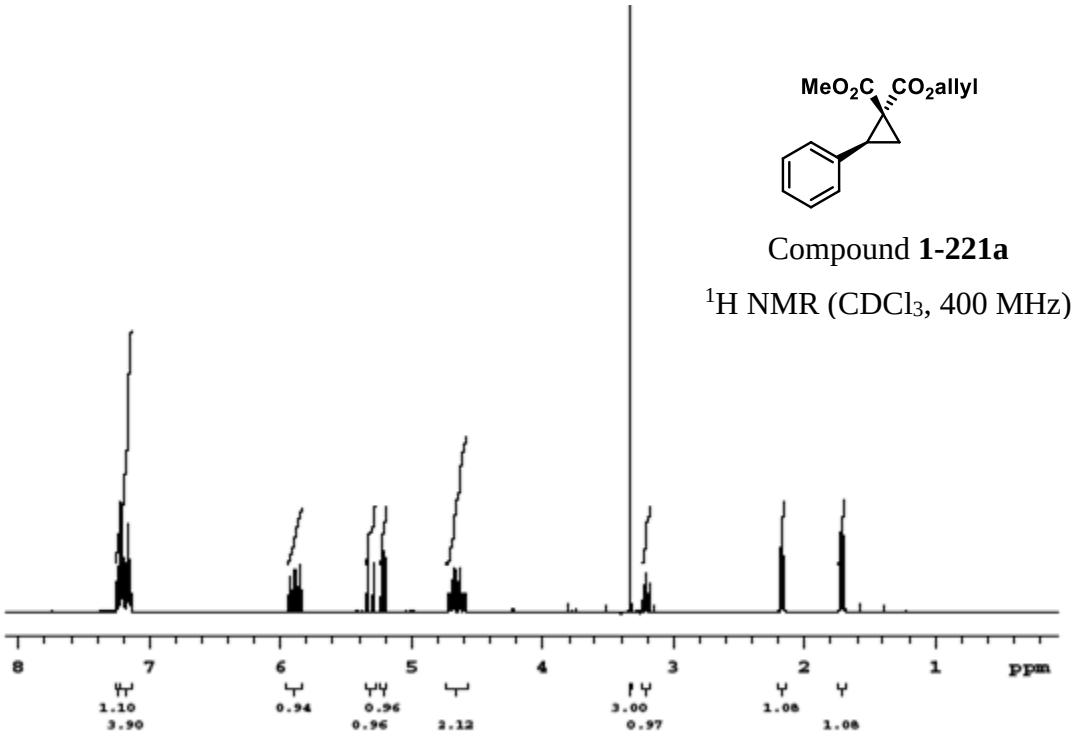
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-82k**

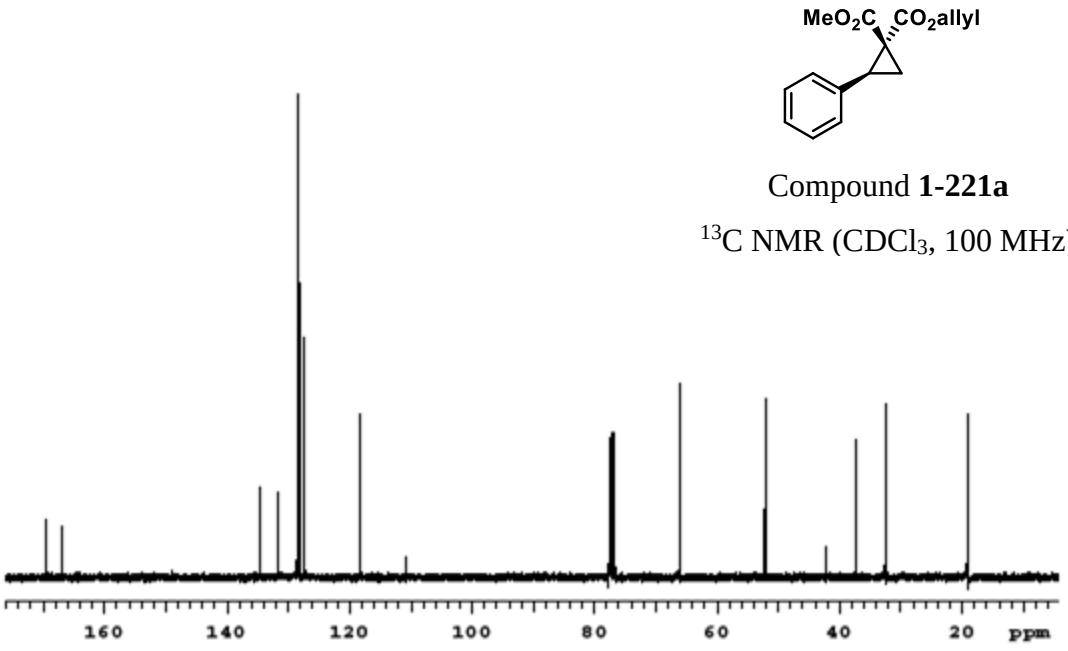
^{13}C NMR ($CDCl_3$, 100 MHz)

Appendix II – Synthesis of pyrroles from DA cyclopropane



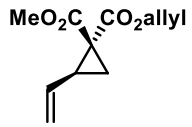
Compound **1-221a**

^{1}H NMR ($CDCl_3$, 400 MHz)



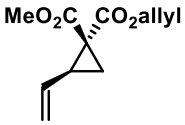
Compound **1-221a**

^{13}C NMR ($CDCl_3$, 100 MHz)



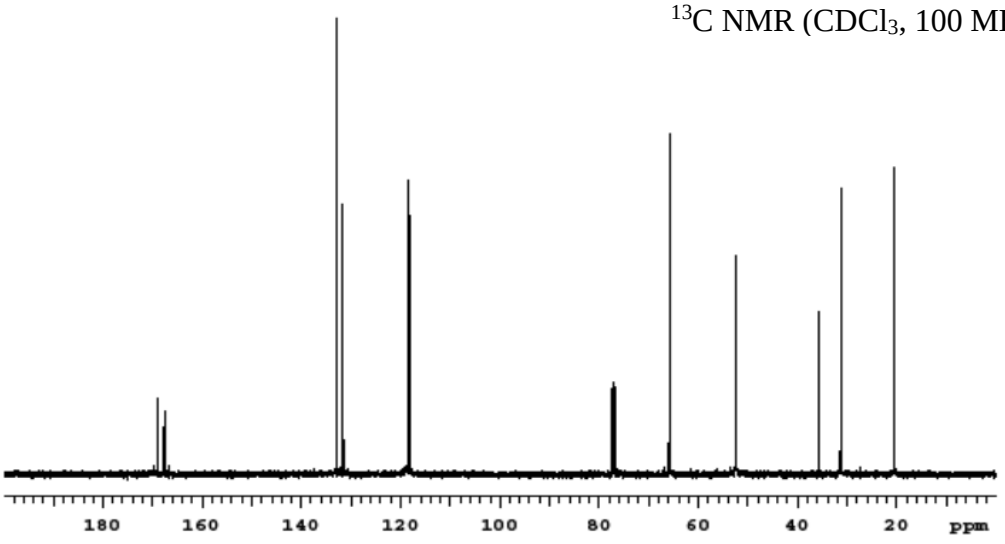
Compound **1-221c**

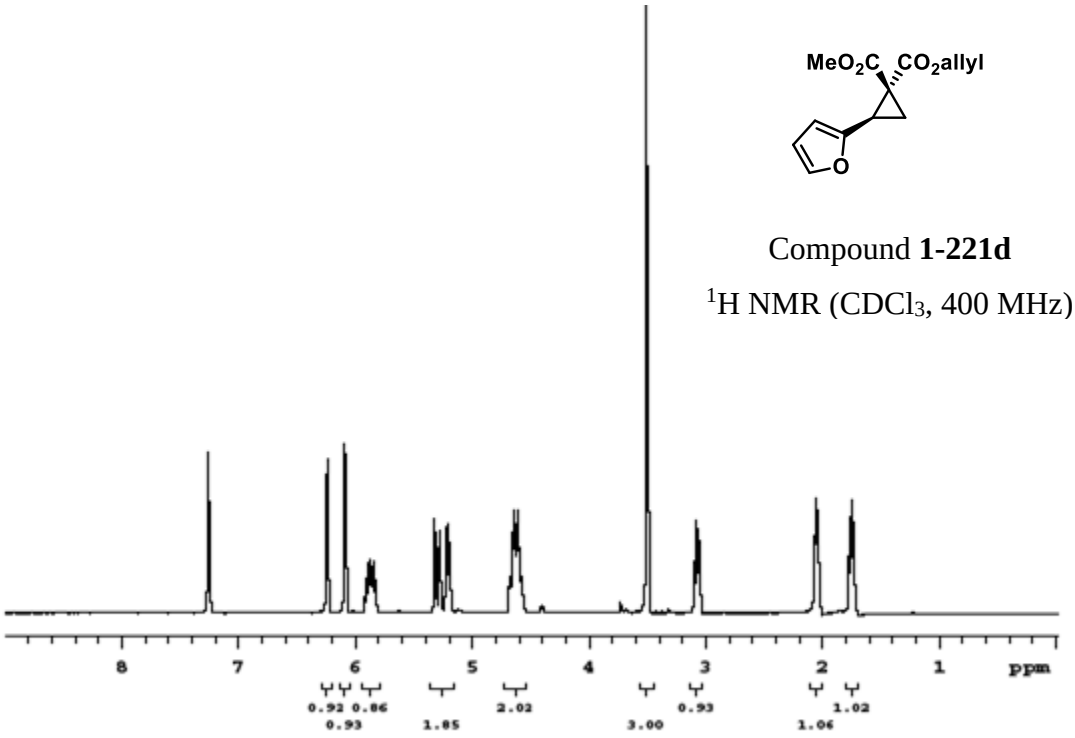
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-221c**

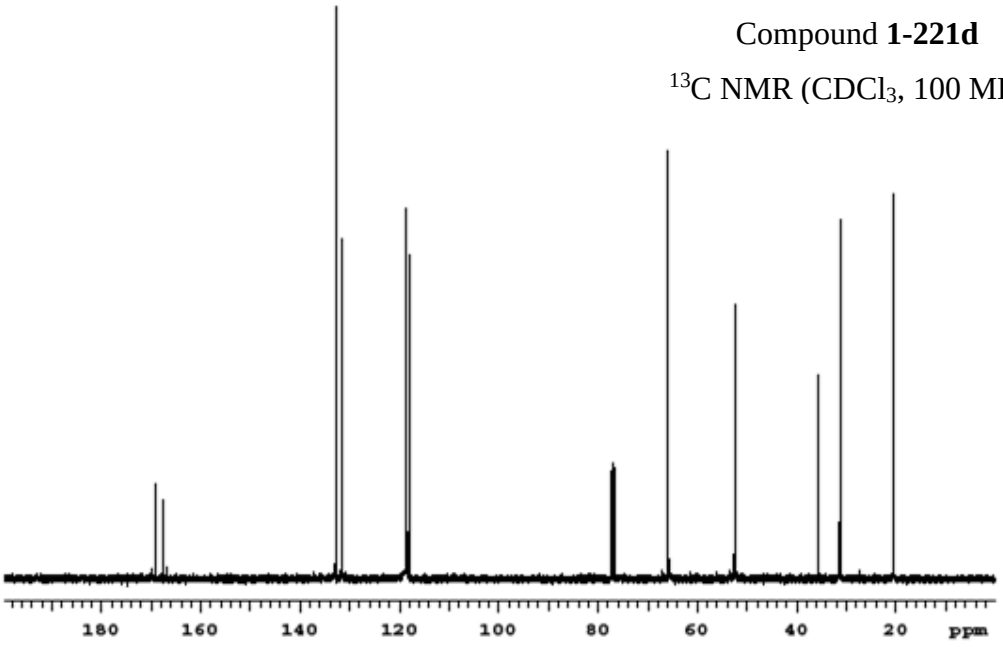
^{13}C NMR ($CDCl_3$, 100 MHz)





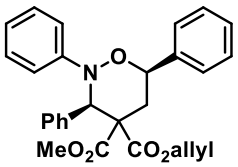
Compound **1-221d**

^{1}H NMR ($CDCl_3$, 400 MHz)



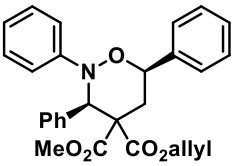
Compound **1-221d**

^{13}C NMR ($CDCl_3$, 100 MHz)



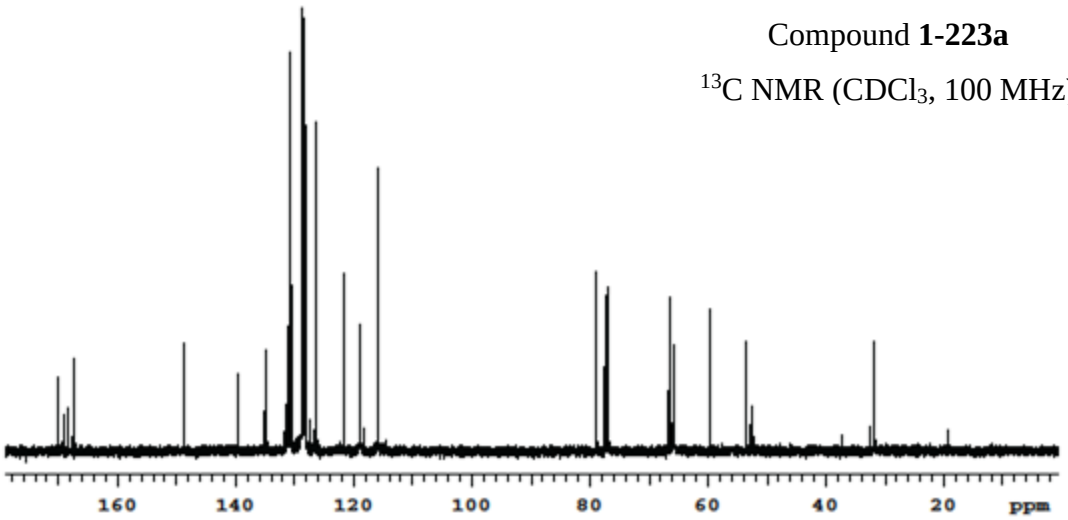
Compound **1-223a**

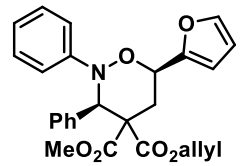
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-223a**

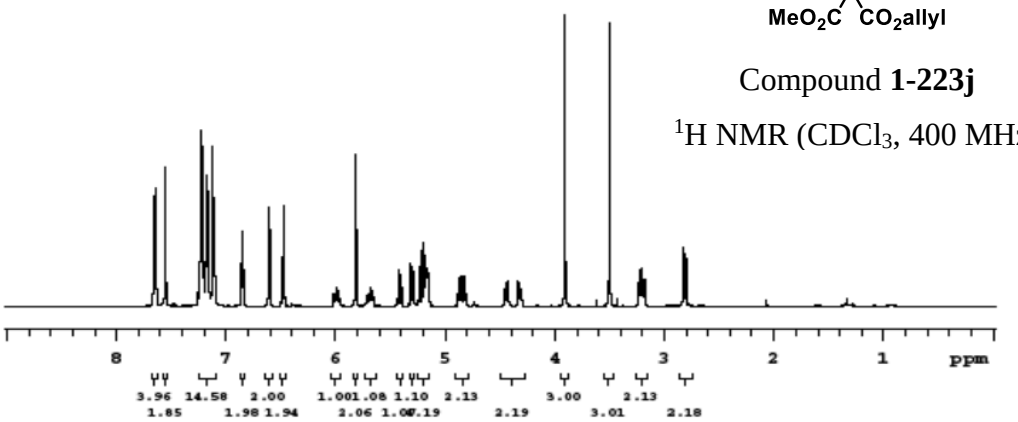
^{13}C NMR ($CDCl_3$, 100 MHz)

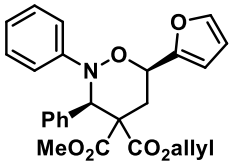




Compound **1-223j**

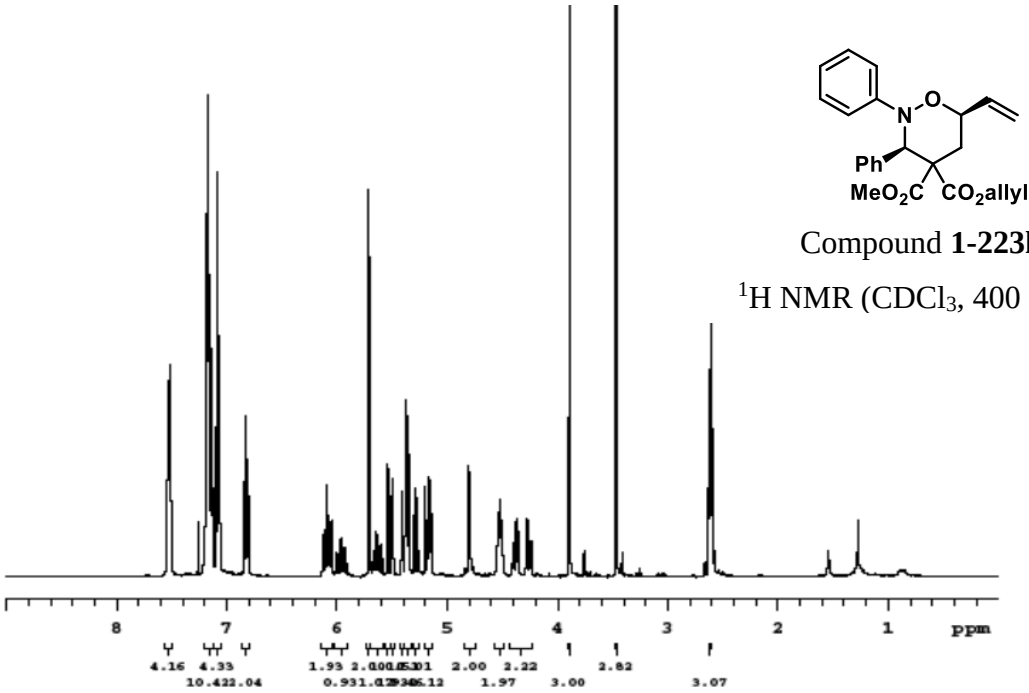
^{1}H NMR ($CDCl_3$, 400 MHz)





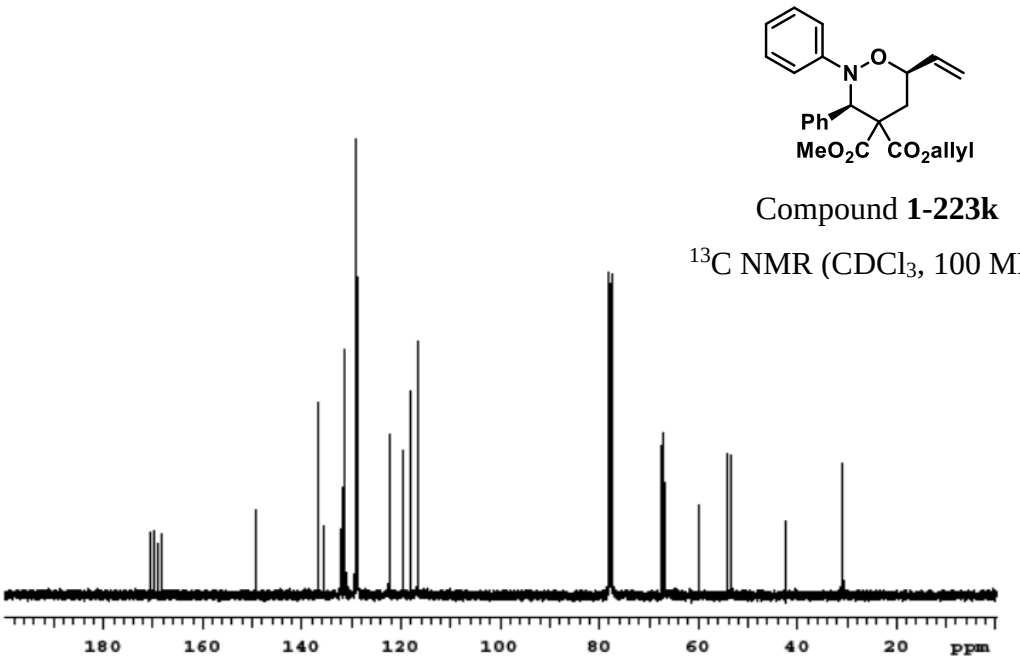
Compound **1-223j**

^{13}C NMR ($CDCl_3$, 100 MHz)



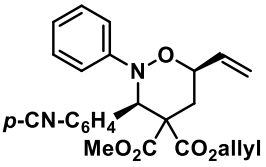
Compound **1-223k**

^{1}H NMR ($CDCl_3$, 400 MHz)



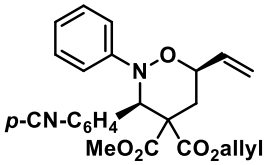
Compound **1-223k**

^{13}C NMR ($CDCl_3$, 100 MHz)



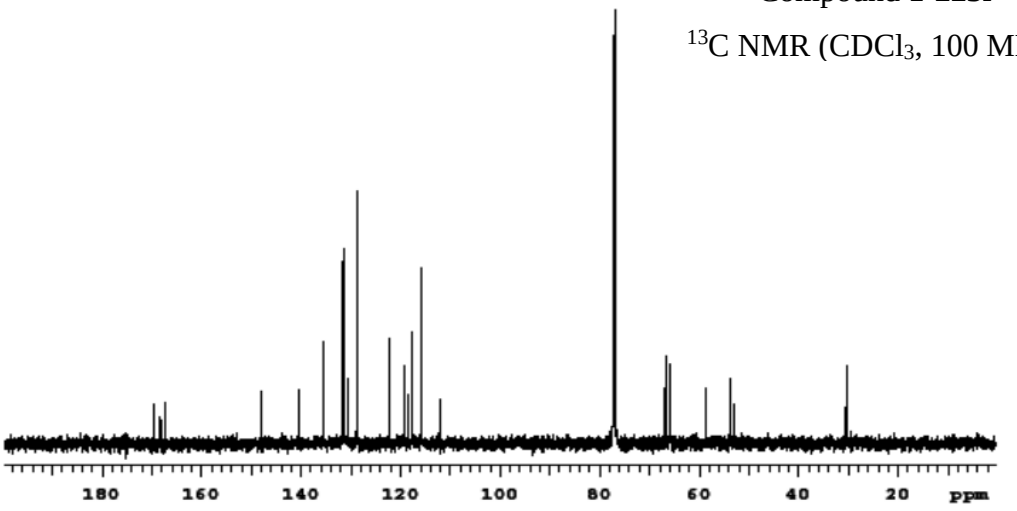
Compound **1-223l**

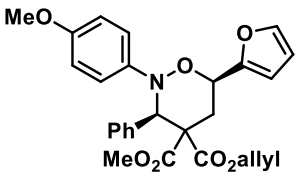
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-223l**

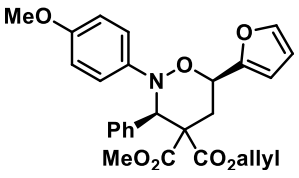
^{13}C NMR ($CDCl_3$, 100 MHz)





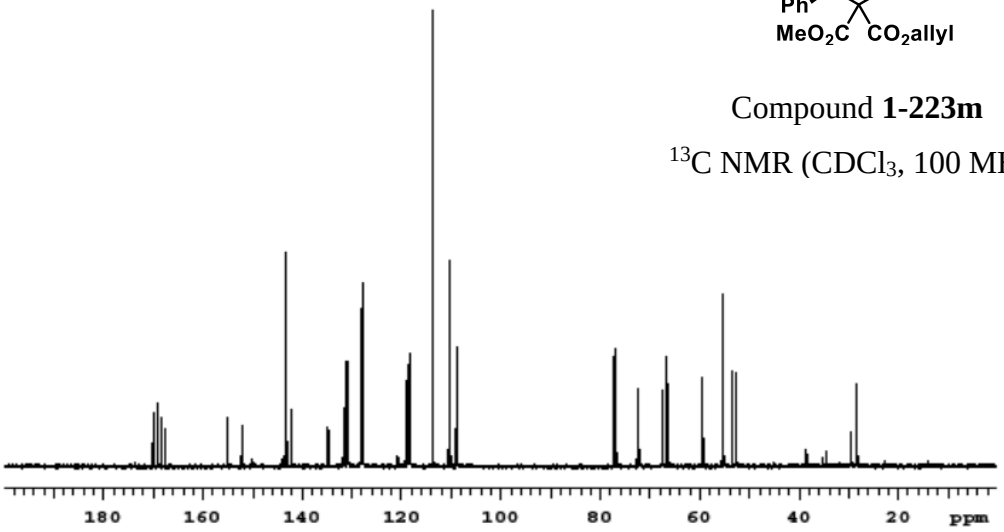
Compound **1-223m**

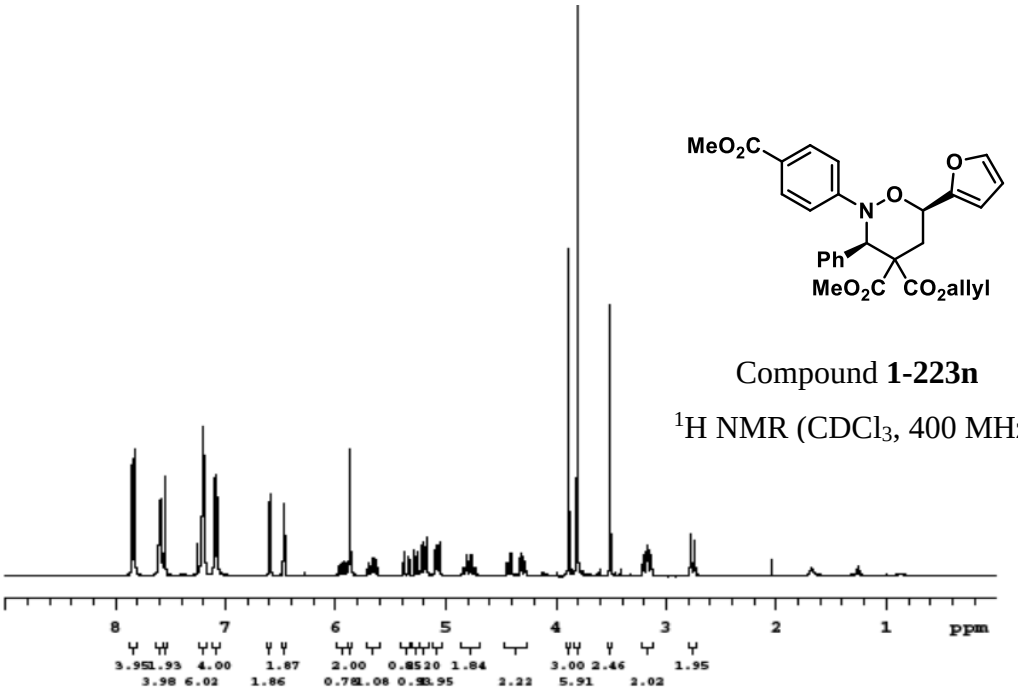
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-223m**

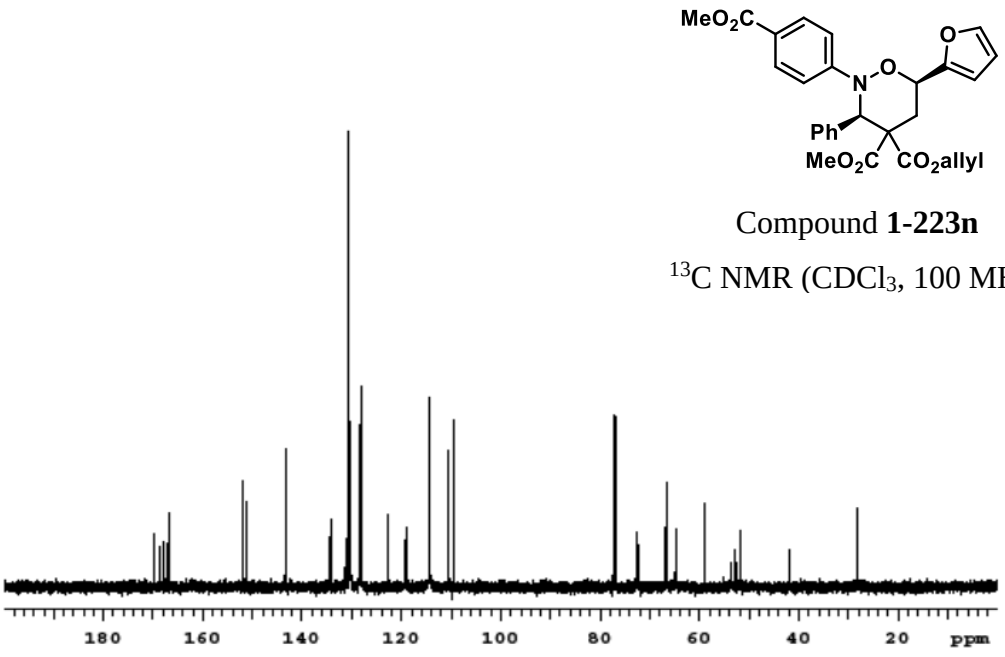
^{13}C NMR ($CDCl_3$, 100 MHz)





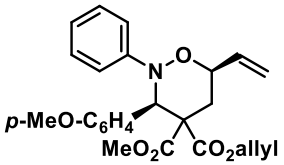
Compound **1-223n**

^{1}H NMR ($CDCl_3$, 400 MHz)



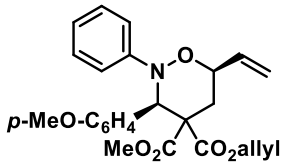
Compound **1-223n**

^{13}C NMR ($CDCl_3$, 100 MHz)



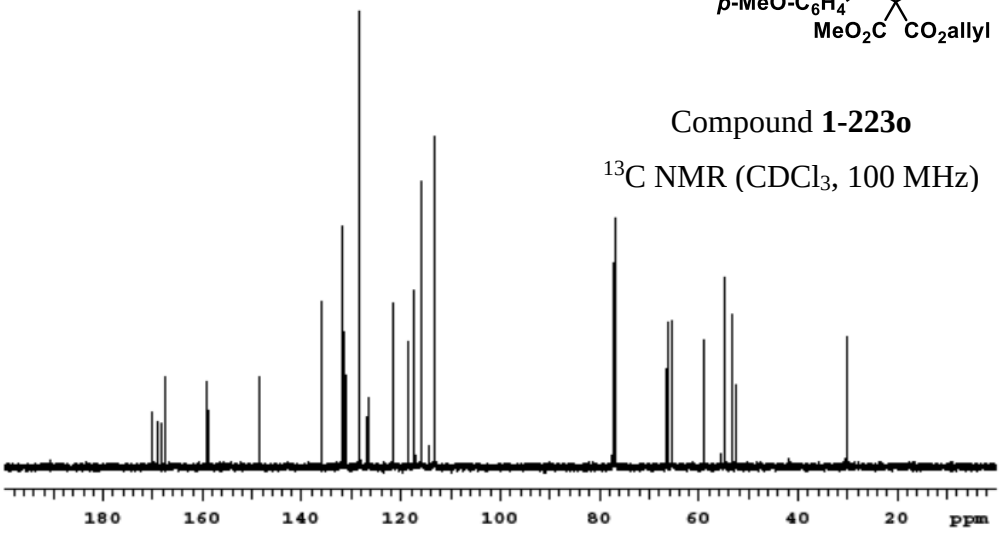
Compound **1-223o**

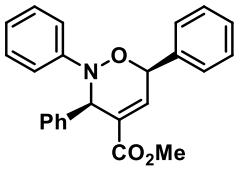
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-223o**

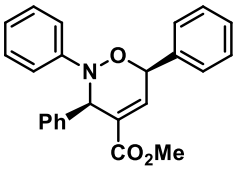
^{13}C NMR ($CDCl_3$, 100 MHz)





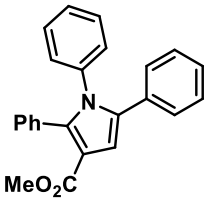
Compound **1-226a**

^{1}H NMR ($CDCl_3$, 400 MHz)



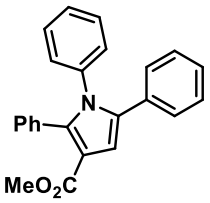
Compound **1-226a**

^{13}C NMR ($CDCl_3$, 100 MHz)



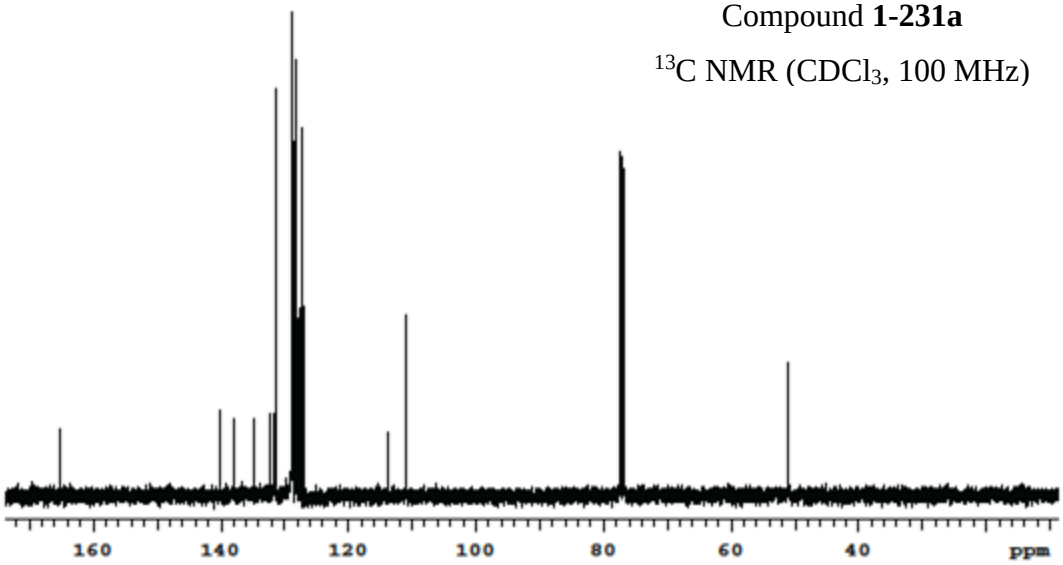
Compound **1-231a**

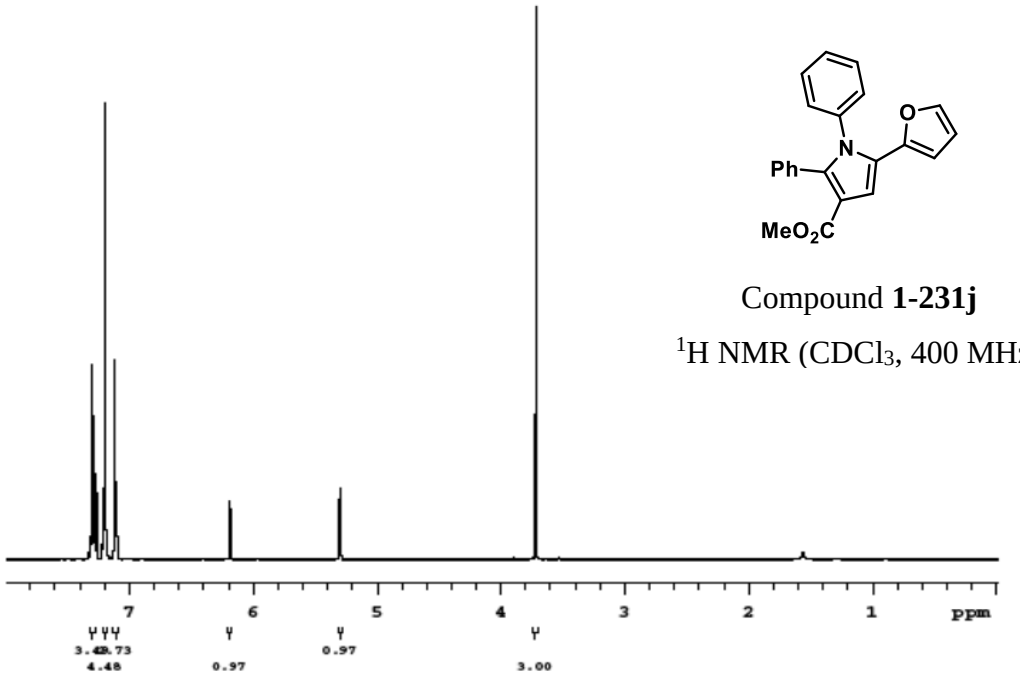
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-231a**

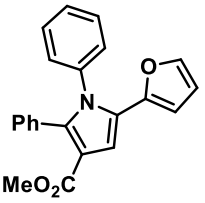
^{13}C NMR ($CDCl_3$, 100 MHz)





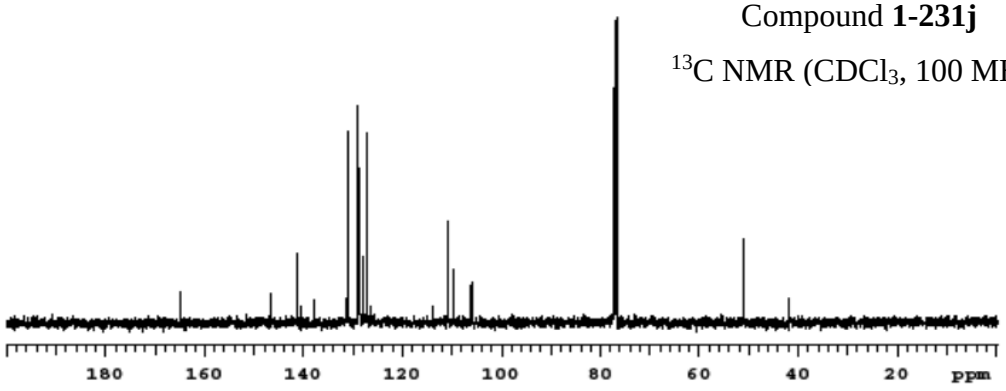
Compound **1-231j**

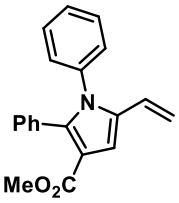
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **1-231j**

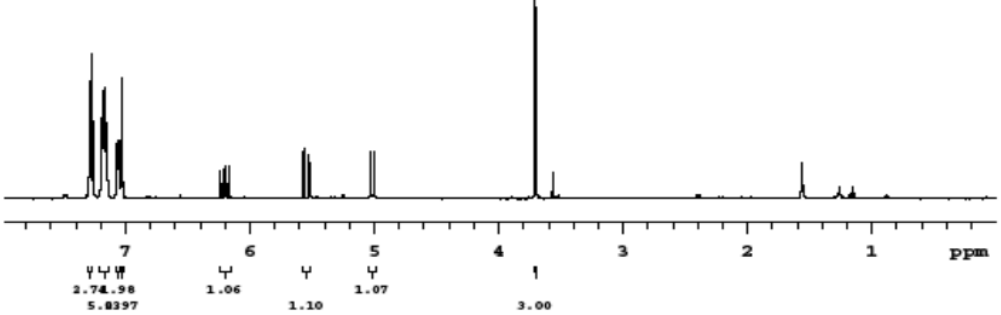
^{13}C NMR ($CDCl_3$, 100 MHz)

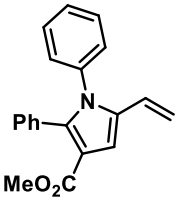




Compound **1-231k**

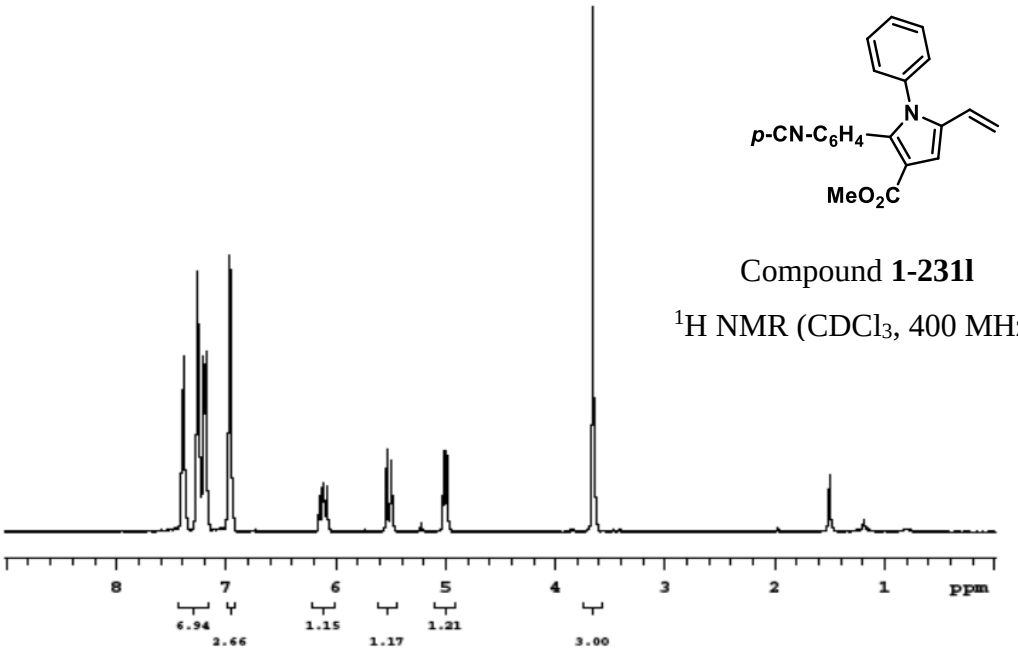
^{1}H NMR ($CDCl_3$, 400 MHz)





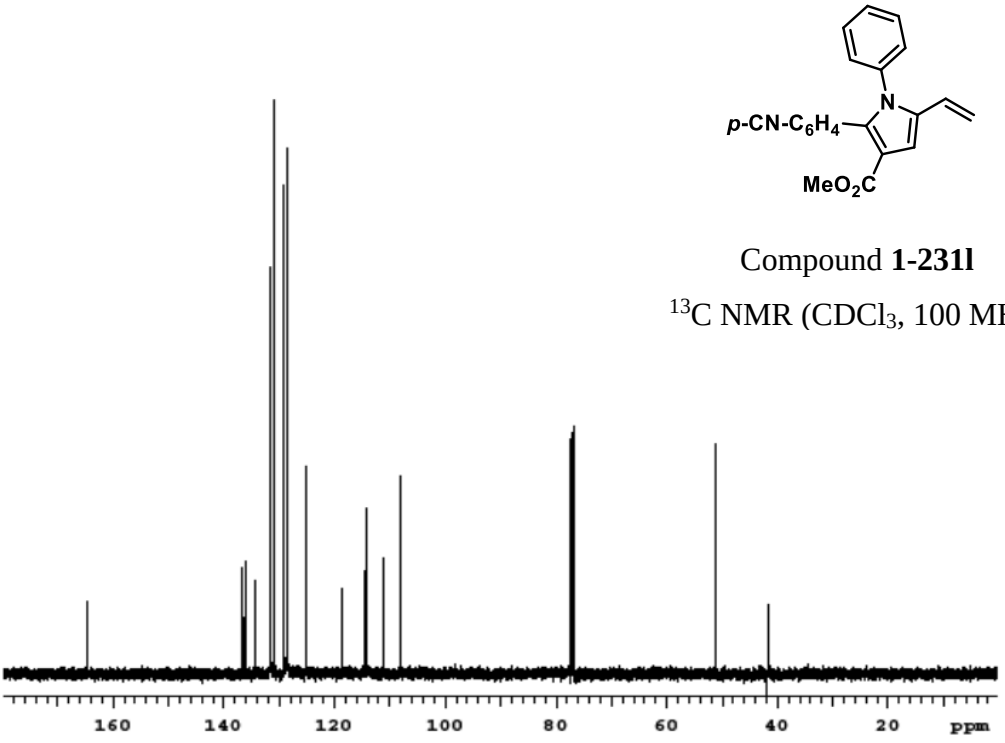
Compound **1-231k**

^{13}C NMR ($CDCl_3$, 100 MHz)



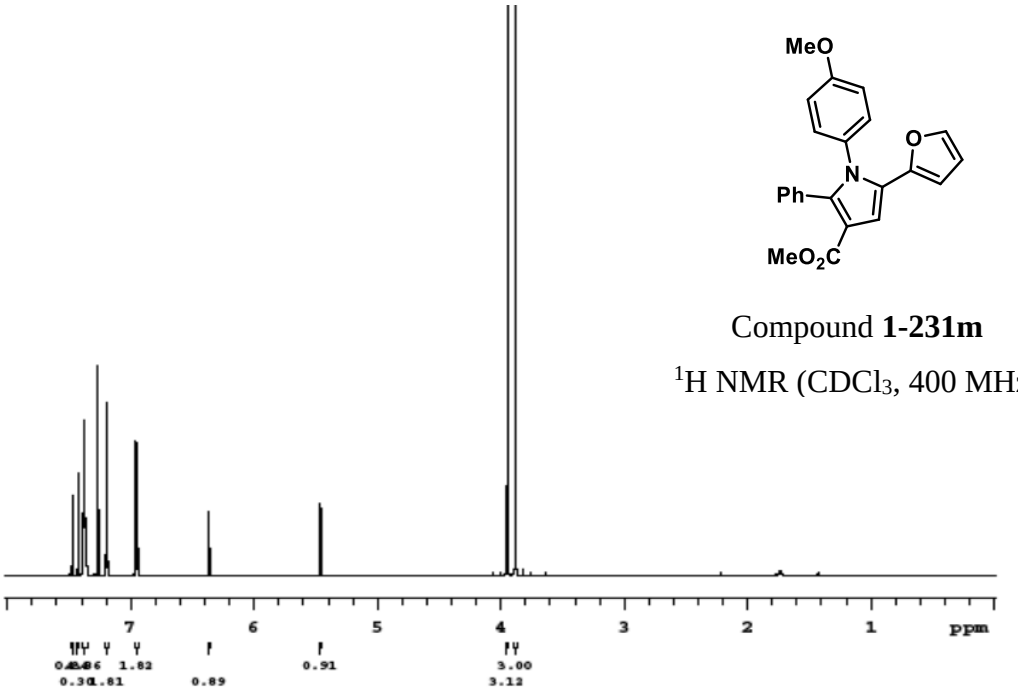
Compound **1-231l**

^{1}H NMR ($CDCl_3$, 400 MHz)



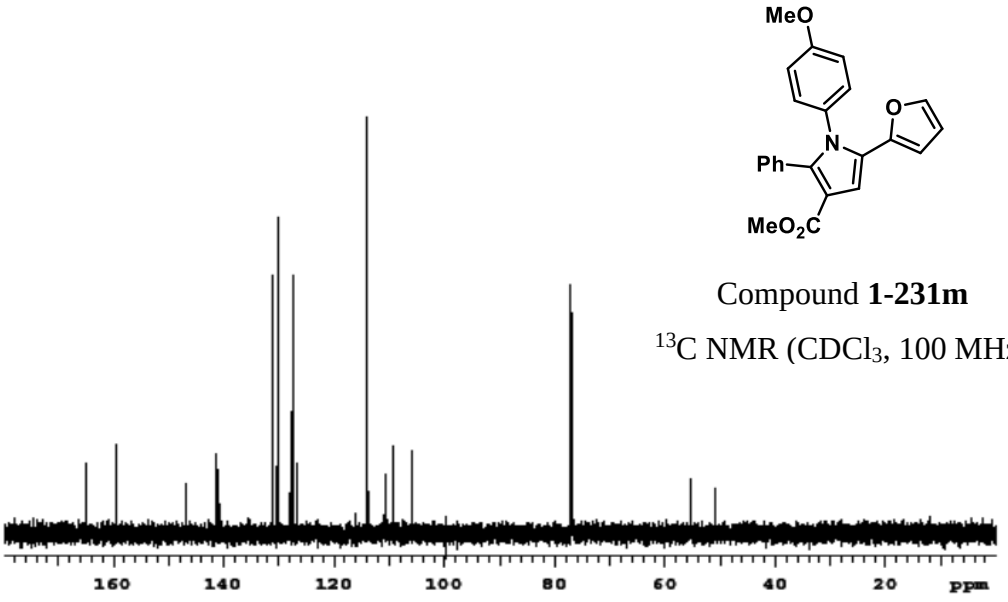
Compound **1-231l**

^{13}C NMR ($CDCl_3$, 100 MHz)



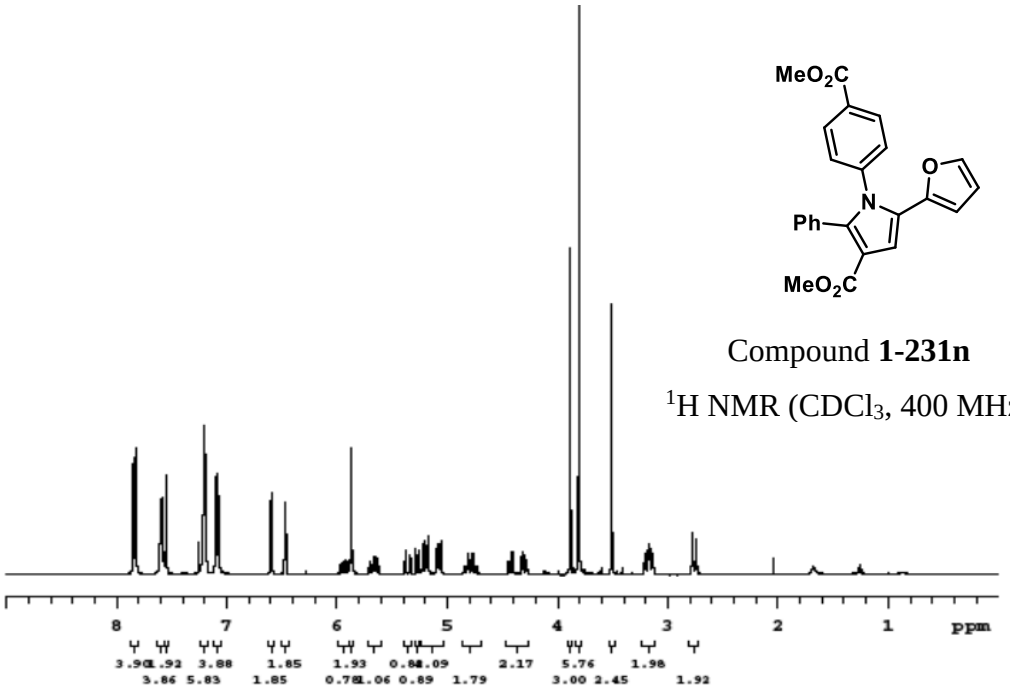
Compound **1-231m**

^{1}H NMR ($CDCl_3$, 400 MHz)



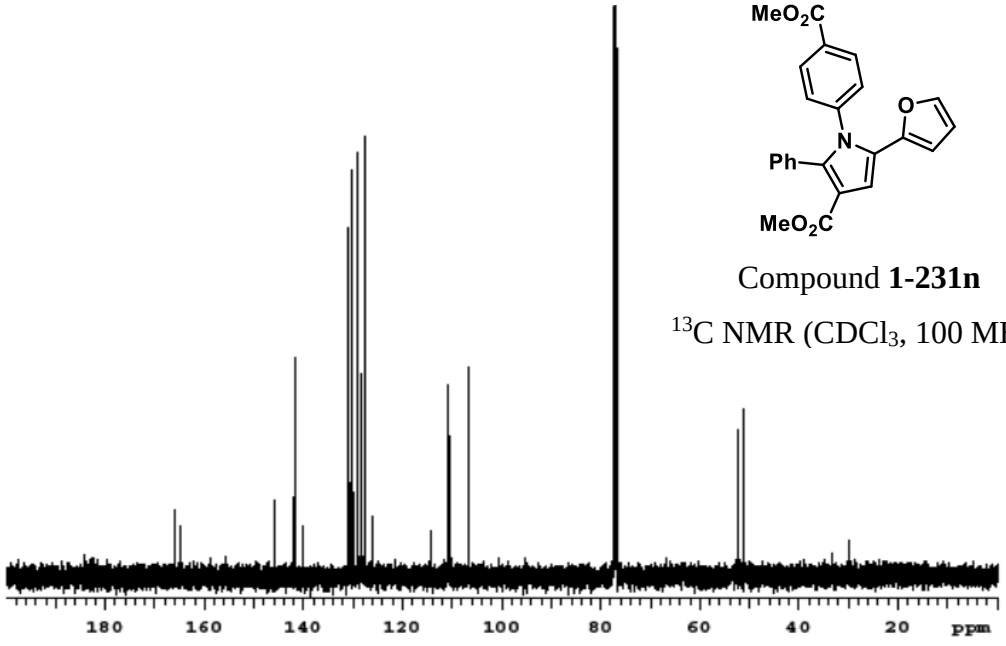
Compound **1-231m**

^{13}C NMR ($CDCl_3$, 100 MHz)



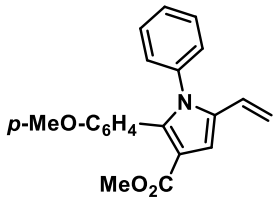
Compound **1-231n**

^{1}H NMR ($CDCl_3$, 400 MHz)



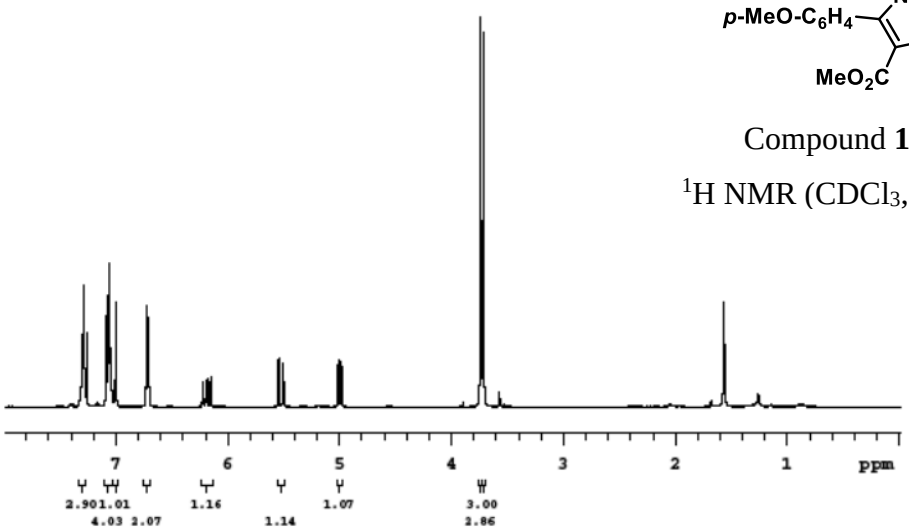
Compound **1-231n**

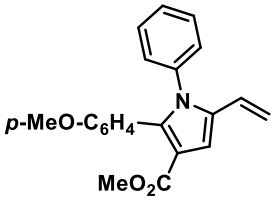
^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **1-231n**

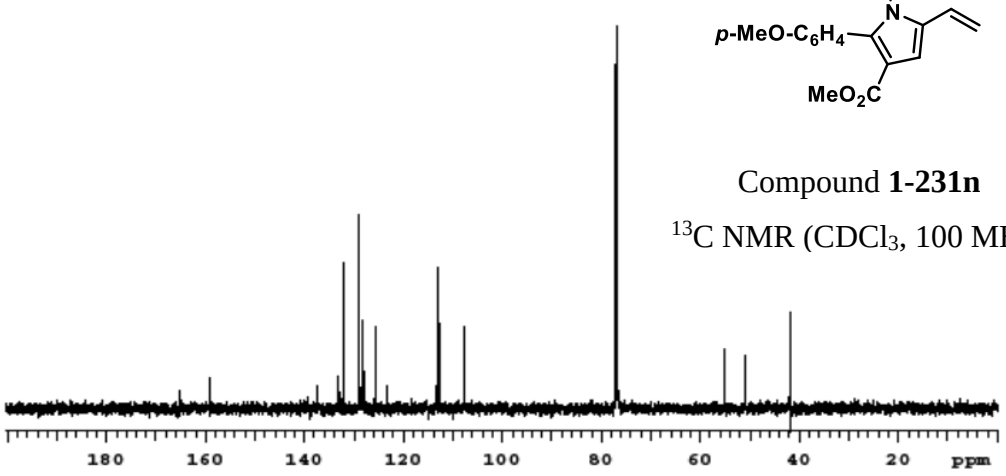
^{1}H NMR ($CDCl_3$, 400 MHz)



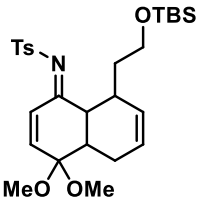


Compound **1-231n**

^{13}C NMR ($CDCl_3$, 100 MHz)

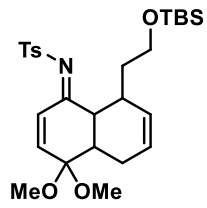


Appendix III – Formal synthesis of fargesine



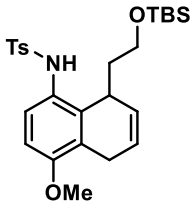
Compound **2-169**

^{1}H NMR ($CDCl_3$, 400 MHz)



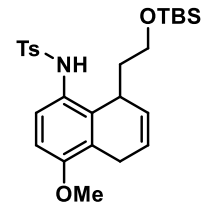
Compound **2-169**

^{13}C NMR ($CDCl_3$, 100 MHz)



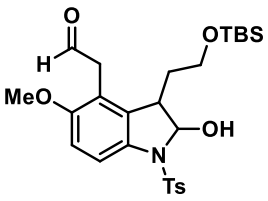
Compound **2-170**

^{1}H NMR ($CDCl_3$, 400 MHz)



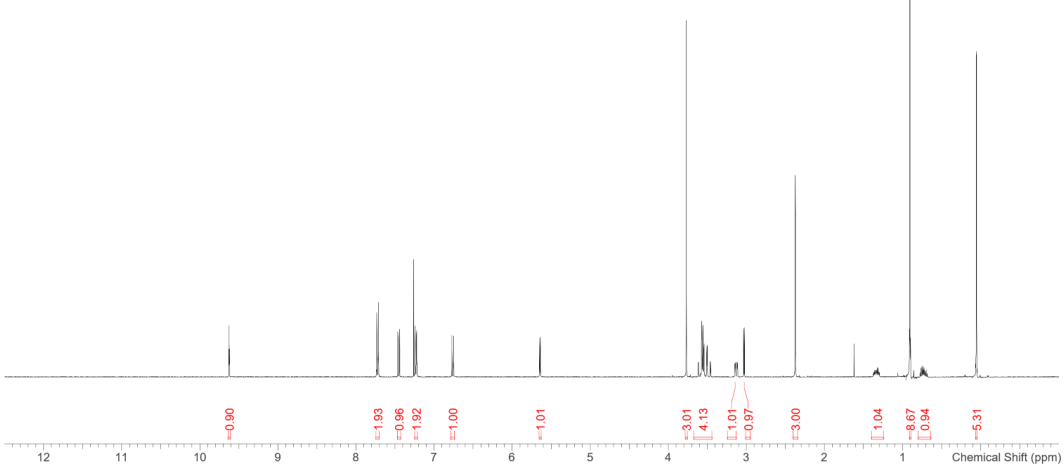
Compound **2-170**

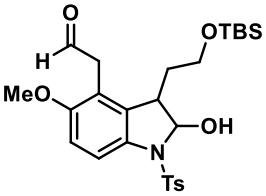
^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **2-172**

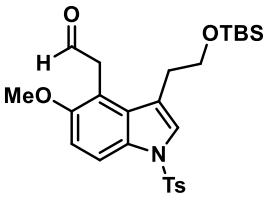
^{1}H NMR ($CDCl_3$, 400 MHz)





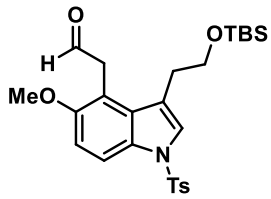
Compound **2-172**

^{13}C NMR ($CDCl_3$, 100 MHz)



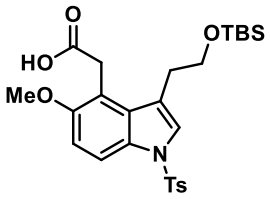
Compound **2-162a**

^{1}H NMR ($CDCl_3$, 400 MHz)



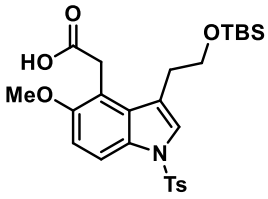
Compound **2-162a**

^{13}C NMR ($CDCl_3$, 100 MHz)



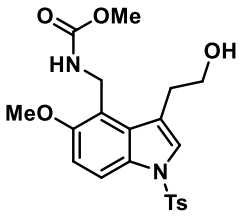
Compound **2-173**

^{1}H NMR ($CDCl_3$, 400 MHz)



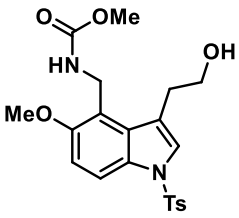
Compound **2-173**

^{13}C NMR ($CDCl_3$, 100 MHz)



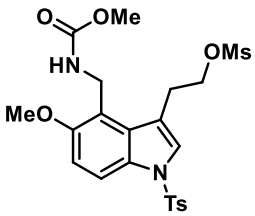
Compound **2-163c**

^{1}H NMR ($CDCl_3$, 400 MHz)



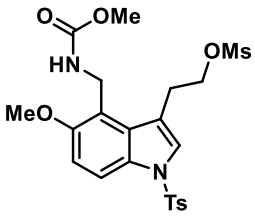
Compound **2-163c**

^{13}C NMR ($CDCl_3$, 100 MHz)



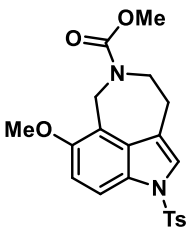
Compound **2-163d**

^{1}H NMR ($CDCl_3$, 400 MHz)



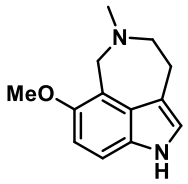
Compound **2-163d**

^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **2-164**

^{1}H NMR ($CDCl_3$, 400 MHz)

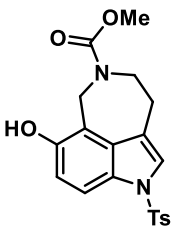


Compound **2-165**

^{1}H NMR ($CDCl_3$, 400 MHz)

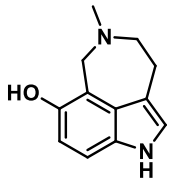
Compound **2-165**

^{13}C NMR ($CDCl_3$, 100 MHz)



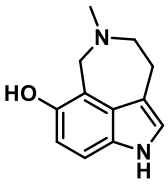
Compound **2-178**

^{1}H NMR ($CDCl_3$, 600 MHz)



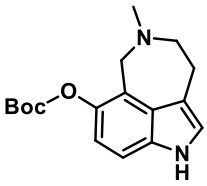
Compound **2-176**

^{1}H NMR (CD_3OD, 400 MHz)



Compound **2-176**

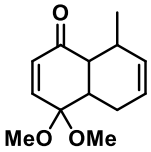
^{13}C NMR (CD_3OD, 100 MHz)



Compound **2-158**

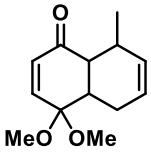
^{1}H NMR ($CDCl_3$, 400 MHz)

Appendix IV – Progress towards the total synthesis of fumimycin



Compound **2-243**

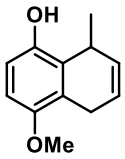
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **2-243**

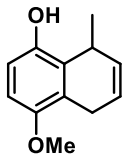
^{13}C NMR

($CDCl_3$, 100 MHz)



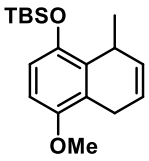
Compound **2-244**

^{1}H NMR ($CDCl_3$, 400 MHz)



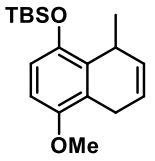
Compound **2-244**

^{13}C NMR ($CDCl_3$, 100 MHz)



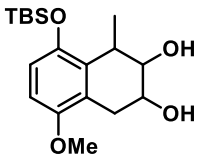
Compound **2-245**

^{1}H NMR ($CDCl_3$, 400 MHz)



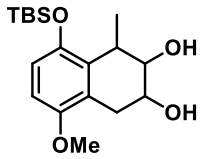
Compound **2-245**

^{13}C NMR ($CDCl_3$, 100 MHz)



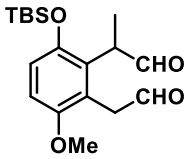
Compound **2-246**

^{1}H NMR ($CDCl_3$, 400 MHz)



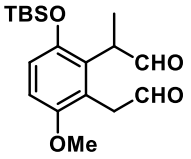
Compound **2-246**

^{13}C NMR ($CDCl_3$, 100 MHz)



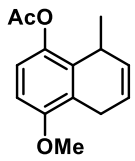
Compound **2-247**

^{1}H NMR ($CDCl_3$, 400 MHz)



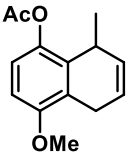
Compound **2-247**

^{13}C NMR ($CDCl_3$, 100 MHz)



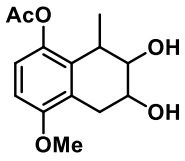
Compound **2-249**

^{1}H NMR ($CDCl_3$, 400 MHz)



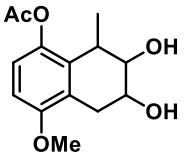
Compound **2-249**

^{13}C NMR ($CDCl_3$, 100 MHz)



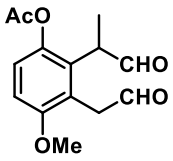
Compound **2-250**

^{1}H NMR ($CDCl_3$, 400 MHz)



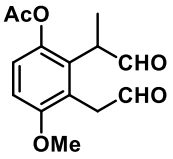
Compound **2-250**

^{13}C NMR ($CDCl_3$, 100 MHz)



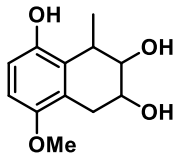
Compound **2-251**

^{1}H NMR ($CDCl_3$, 400 MHz)



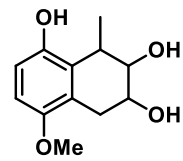
Compound **2-251**

^{13}C NMR ($CDCl_3$, 100 MHz)



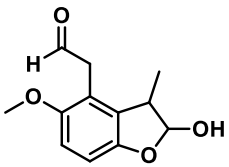
Compound **2-253**

^{1}H NMR (CD_3OD, 400 MHz)



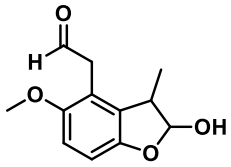
Compound **2-253**

^{13}C NMR (CD_3OD, 100 MHz)



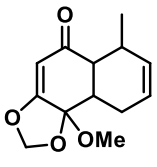
Compound **2-254**

^{1}H NMR ($CDCl_3$, 400 MHz)



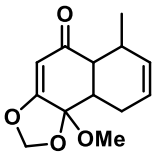
Compound **2-254**

^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **2-260**

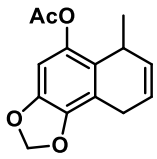
^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **2-260**

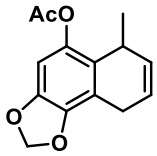
^{13}C NMR ($CDCl_3$,

100 MHz)



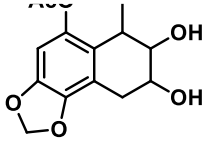
Compound **2-255**

^{1}H NMR ($CDCl_3$, 400 MHz)



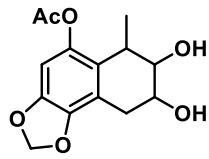
Compound **2-255**

^{13}C NMR ($CDCl_3$, 100 MHz)



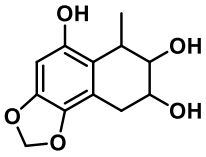
Compound **2-256**

^{1}H NMR ($CDCl_3$, 400 MHz)



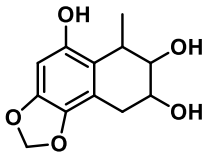
Compound **2-256**

^{13}C NMR ($CDCl_3$, 100 MHz)



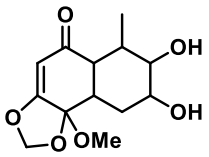
Compound **2-257**

^{1}H NMR (CD_3OD, 400 MHz)



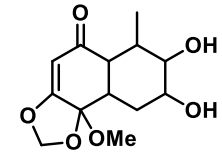
Compound **2-257**

^{13}C NMR (CD_3OD, 100 MHz)



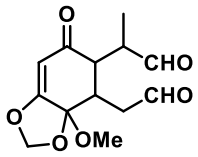
Compound **2-261**

^{1}H NMR ($CDCl_3$, 400 MHz)



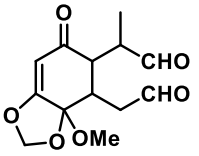
Compound **2-261**

^{13}C NMR ($CDCl_3$, 100 MHz)



Compound **2-262**

^{1}H NMR ($CDCl_3$, 400 MHz)



Compound **2-262**

^{13}C NMR ($CDCl_3$, 100 MHz)

Curriculum Vitae

ACADEMIC INFORMATION

Doctor of Philosophy (Synthetic Organic Chemistry) **Jan 2011 – Sep 2016**
University of Western Ontario, London, Ontario
Research Advisor: Dr. Michael A. Kerr

Doctoral Thesis:
Novel Reactions of Donor-Acceptor Cyclopropanes, and
Diels-Alder Approach Towards Fargesine and Fumimycin

Bachelor of Science **Sept 2005 – Aug 2010**
Honors Specialization Biochemistry and Chemistry
University of Western Ontario, London, Ontario

- Dean's Honor List
- Graduated with Distinction

***Undergraduate Research Thesis*:**
Functionalization of dihydro-1,2-oxazines by Diels-Alder
Research Advisor: Prof. Michael A. Kerr

High School Diploma **Sept 2001 – Aug 2005**
St. Paul Catholic High School
Niagara Falls, Ontario

- Ontario Scholar
- Area of concentration in math and science

RESEARCH AND RELEVANT WORK EXPERIENCE

Graduate Student Researcher **Jan 2011 – Sep 2016**
The University of Western Ontario, London, Ontario
Supervisor: Dr. Michael A. Kerr

- Successfully utilized the Kerr group's nitrone/cyclopropane reaction to make tetrahydro-1,2-oxazines, which were then converted to pyrroles with a one-pot dehydrocarbonylation/dehydration protocol
- Enthusiastically presented research results at national and international conferences
- Composed manuscript for publication upon project completion
- Supervised and trained various junior graduate and undergraduate members within the Kerr group

- Actively contributed to joint meetings of the Kerr/Pagenkopf groups by presenting research findings, reviewing pertinent chemical literature, and by developing interactive learning sessions

Undergraduate Student Supervisor **May 2012 – April 2014**
The University of Western Ontario, London, Ontario

- Mentored and supervised three undergraduate summer students, and one fourth year research thesis student
- Trained students to execute a variety of common organic synthesis laboratory techniques effectively and
  safely, as well as to understand the concepts behind each technique
- Assisted students in understanding mechanisms to reactions they were performing, and in data analysis
- Prepared daily plans for the students

Graduate Teaching Assistant **Jan 2011 – Dec 2015**
The University of Western Ontario, London, Ontario

- Enthusiastically served as a lab demonstrator/instructor for many undergraduate chemistry courses (Chemistry 2273a: Organic Chemistry I – Structure & Spectroscopy; Chemistry 2283b: Organic Chemistry II: Mechanisms and Reactivity; Chemistry 3373f: Organic Chemistry III: Reactions and Strategies for Synthesis; Chemistry 1024b: Chemistry for Engineers; Chemistry 2213a: Organic Chemistry for Life Sciences; Chemistry 2223b: Organic Chemistry for Biological Molecules)
- Performed a pre-laboratory lesson, outlining safety precautions, theoretical concepts, and proper techniques relevant to each experiment
- Evaluated reports and examinations
- Tutored students outside of the laboratory on lecture and laboratory content

Organic Chemistry Research Assistant **May 2009 – Aug 2009**
The University of Western Ontario, London, Ontario
Supervisor: Dr. Michael A. Kerr

- Investigated a novel Friedel-Crafts Alkylation of phenols with donor/acceptor cyclopropanes

Organic Chemistry Research Assistant **May 2006 – Aug 2006**
Brock University, St. Catharines, Ontario **and May 2007 – Aug 2007**
Supervisor: Dr. Travis Dudding

- Trained in organic synthesis laboratory techniques

- Applied techniques learned to the synthesis of 6-acetoxyhexadecan-5-olide, a pheromone for mosquitoes, for biological testing at Brock University

PUBLICATIONS

1. Untargeted plasma and tissue metabolomics in rats with chronic kidney disease given AST-120. Thomas J. Velenosi, Anzel Hennop, David A. Feere, Alvin Tieu, Andrew S. Kucey, Polydoros Kyriacou, Laura E. McCuaig, Stephanie E. Nevison, Michael A. Kerr, and Bradley L. Urquhart. *Sci. Rep.* **2016**, *6*, 22526.

2. Multicomponent synthesis of pyrroles from cyclopropanes: A one-pot palladium(0)-catalyzed dehydrocarbonylation/dehydration. William J. Humenny, Polydoros Kyriacou, Katarina Sapeta, Avedis Karadeolian and Michael A. Kerr. *Angew. Chem. Int. Ed.* **2012**, *51*, 11088.

3. Functionalization of dihydro-1,2-oxazines by Diels-Alder. Polydoros Kyriacou. B.Sc. thesis, University of Western Ontario, **2010.** (non-refereed)

PRESENTATIONS

1. Polydoros Kyriacou, Michael Kerr *Nucleophilic ring opening of donor-acceptor cyclopropanes by potassium organotrifluoroborates*; 99th Canadian Chemistry Conference, Halifax, Nova Scotia, June **2016** (poster presentation).

2. Polydoros Kyriacou, Sharon Michalak, and Michael Kerr *Progress Towards the Total Synthesis of Fargesine via Diels-Alder/Plieninger Indolization Sequence*; 16th Symposium on the Latest Trends in Organic Synthesis, St. Catharines, Ontario, August **2014** (poster presentation)

3. Polydoros Kyriacou, Will Humenny, Katerina Sapeta, Avedis Karadeolian, and Michael Kerr *Multicomponent Synthesis of Pyrroles from Cyclopropanes: A One-Pot Palladium(0)-Catalyzed Dehydrocarbonylation/Dehydration*; 15th Symposium on the Latest Trends in Organic Synthesis, St. Catharines, Ontario, August **2012** (poster presentation).

4. Polydoros Kyriacou, Will Humenny, Katerina Sapeta, Avedis Karadeolian, and Michael Kerr *One Pot Synthesis of Highly Functionalized Pyrroles from Tetrahydro-1,2-oxazines*; 94th Canadian Chemistry Conference, Montreal, Quebec, June **2011** (poster presentation).

5. Polydoros Kyriacou, Will Humenny, Katerina Sapeta, and Michael Kerr *Synthesis of Dihydro-1,2-oxazines*; 21st Quebec and Ontario Mini-Symposium on Biological and Organic Chemistry, London, Ontario, November **2010** (poster presentation).

6. Polydoros Kyriacou, and Michael Kerr *Functionalization of Dihydro-1,2-oxaines via Diels-Alder*; 38th Southern Ontario Undergraduate Student Chemistry Conference, London, Ontario, March **2010** (oral presentation).

SCHOLARSHIPS AND AWARDS

1. Ontario Graduate Scholarship. Value: $15 000. **Sept 2013-May 2014**.

2. University of Western Ontario Teaching Assistant Award. Nominated **Sept 2012-May 2014**

3. James and Dorothy Burns Award. Value: $750. **Nov. 2006**

4. Western Admission Scholarship. Value: $1 000. **Sept 2005**.