STRESS RELIEF: EXERCISING LEWIS ACID CATALYSIS FOR DONOR-ACCEPTOR CYCLOPROPANE RING-OPENING ANNULATIONS, A BASIS FOR NEW REACTION METHODOLOGIES

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STRESS RELIEF: EXERCISING LEWIS ACID CATALYSIS FOR DONOR-ACCEPTOR CYCLOPROPANE RING-OPENING ANNULATIONS, A BASIS FOR NEW REACTION METHODOLOGIES

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This dissertation is dedicated in loving memory to my great grandmother, Thelma Cavitt, grandmother, Mary Cavitt, and great aunt, Marie McPherson, who reared me in the absence of my parents. Despite their hardships and economic challenges, they endured and remained diligent in instilling the importance of education, perseverance, and integrity in me. For their love, support, and sacrifices made on behalf of my sisters and me, I will forever be grateful.

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LIST OF SYMBOLS AND ABBREVIATIONS

A	Acceptor
ACN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Ad-1-COOH	1-Adamantanecarboxylic acid
Å	Angstrom
$AgSbF_6$	Silver hexafluoroantimonate
AIBN	Azobisisobutyronitrile
$Al(OTf)_3$	Aluminum(III) trifluoromethanesulfonate
AO	Atomic orbital
Ar	Aryl
$AuBr_3$	Gold(III) bromide
β	Beta
BF_3•Et_2O	Boron trifluoride diethyl etherate
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
bs	Broad singlet
bt	Broad triplet
n-Bu	n-Butyl
Bu_3SnH	Tributyltin hydride
$Bu_4N(PF_6)$	Tetra(*n*-butyl)ammonium hexafluorophosphate
CaH_2	Calcium hydride
Calc.	Calculated
cat.	Catalytic
$Ca(NTf_2)_2$	Calcium triflimide
CARS	Chemical assay for restabilization
^{13}C	Carbon-13
Cbz	Carboxybenzyl
CCl_4	Carbon tetrachloride
$CDCl_3$	Chloroform-d
CDI	1,1'-Carbonyldiimidazole
CF_3COOH	Trifluoroacetic acid
$Co_2(CO)_8$	Dicobalt octacarbonyl
CO	Carbon monoxide
CsOAc	Cesium acetate
$Cu(OAc)_2$	Cupric Acetate
CuI	Copper(I) iodide
$Cu(OTf)_2$	Copper(II) triflate
$CuSO_4$	Copper(II) sulfate
δ	Delta or chemical shift
D	Donor
D-A	Donor-acceptor
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane

D-A-A	Donor-acceptor-acceptor
D-D-A-A	Donor-donor-acceptor-acceptor
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
dtd	Doublet of triplet of doublets
DMAC	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNP	Dinitrophenylhydrazine
dr	Diastereomeric ratio
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
$EtAlCl_2$	Ethylaluminum dichloride
Et_2AlCl	Diethylaluminum chloride
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
F-C	Friedel-Crafts
FMO	Frontier molecular orbital
γ	Gamma
g	Grams
$Ga(OTf)_3$	Gallium(III) trifluoromethanesulfonate
h	Hour
HA	Brønsted acid
^1H	Proton-NMR
H_2	Hydrogen
H_2O_2	Hydrogen peroxide
Hex	Hexane
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
$Hf(OTf)_4$	Hafnium(IV) triflate
$Hg(OTf)_2$	Mercury(II) trifluoromethanesulfonate
HRMS	High resolution mass spectrometry
Hz	Hertz
IEDDA	Inverse electron demand Diels-Alder
$InCl_3$	Indium(III) chloride
$In(OTf)_3$	Indium(III) trifluoromethanesulfonate
i-Pr	Isopropyl
IR	Infrared spectroscopy
K_2CO_3	Potassium carbonate
$KMnO_4$	Potassium permanganate
LA	Lewis acid
$La(OTf)_3$	Lanthanum(III) triflate
LDA	Lithium diisopropylamide

$LiClO_4$	Lithium perchlorate
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Meta
m	Medium or multiplet
M	Molarity
MeOH	Methanol
$Mg(OTf)_2$	Magnesium triflate
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
mL	Milliliter
MMC	Methyl malonyl chloride
mmol	Millimole
$Mn(OAc)_3$	Manganese(III) acetate
MO	Molecular orbital
MS	Molecular sieves
MsOAc	Methanesulfonyl acetate
Myoc-OLF	Myocilin olfactomedin domain
N_2	Nitrogen
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NaOAc	Sodium acetate
Na_2SO_4	Sodium sulfate
Naphth	Naphthalene
NEt_3	Triethylamine
$Ni(OTf)_2$	Nickel(II) trifluoromethanesulfonate
NMR	Nuclear magnetic resonance
Nphth	Phthalimido
o	Ortho
O_2	Oxygen
Obs.	Observed
OLED	Organic light-emitting diode
p	Para
PAF	Platelet activating factor
PAA	*p*-Anisaldehyde
Pd	Palladium
Pd/C	Palladium on carbon
$PdCl_2$	Palladium(II) chloride
$Pd(OAc)_2$	Palladium(II) acetate
PFK	Perfluorokerosene
Ph	Phenyl
Pip	Piperdine
PKCβ	Protein kinase Cβ
PMA	Phosphomolybdic acid
$POCl_3$	Phosphoryl trichloride
PPA	Polyphosphoric acid

ppm	Parts-per-million
PQ	Pyrrolo[3,2,1-*ij*]quinoline
Pr	Propyl
$PtCl_2$	Platinum(II) chloride
$PtCl_4$	Platinum(IV) chloride
PtO_2	Platinum(IV) oxide
q	Quartet
qd	Quartet of doublets
qn	Quintet
R_f	Retention factor
Rh_2esp_2	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
$[RhCl_2(Cp^*)]_2$	Dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer
RT	Room temperature
$Ru_3(CO)_{12}$	Triruthenium dodecacarbonyl
s	Singlet or strong
SAR	Structure-activity relationship
$Sc(OTf)_3$	Scandium(III) triflate
SIRT1	Sirtuin 1
$SnCl_4$	Tin(IV) chloride
SO	Spyro Orange
SPR	Surface Plasmon Resonance
t	Triplet
t-Butyl	Tert-butyl
t-BuOOH	Tert-butyl hydroperoxide
td	Triplet of doublets
TBDPS	Tert-butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THI	Tetrahydroindolizine
THQ	Tetrahydroquinoline
$Ti(i\text{-}PrO)_3Cl$	Chlorotitanium triisopropoxide
TIPB	1,3,5-triisopropylbenzene
TLC	Thin-layer chromatography
p-TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
w	weak
$Yb(OTf)_3$	Ytterbium(III) trifluoromethanesulfonate
$Y(OTf)_3$	Yttrium(III) triflate
ZnI_2	Zinc iodide
$Zn(OTf)_2$	Zinc(II) Triflate

SUMMARY

Nature's biodiversity is complex and filled with beauty and wonder which are all observable on the macroscopic scale. This exquisiteness of nature's intricacies are mirrored on the molecular level such that substances, large or small, are assembled to serve as signaling molecules, protective agents, and fundamental composites of higher-order frameworks for the operation and survival of life. Over the years, chemists have isolated and synthesized these molecules, known as natural products,[1] to understand and evaluate their functions in biology[2–10] and potential for medicinal applications.[11–20]

Although bioactive natural products demonstrate medicinal promise,[21] poor pharmacological effects require further derivatization because semisynthesis is not sufficient to refine adverse pharmacokinetics. For some active molecules, isolation results in poor yields.[22] In addition to small quantity isolation, many natural products, reflecting the immense complexity of biology itself, pose difficult synthetic challenges to organic chemists because of skeletal heterogeneity, stereochemical complexity, and substitution divergence.[23,24] As a result of these synthetic obstacles to natural product utilization, improvements are needed in current chemical approaches, and new innovative methodologies for synthesis and chemical space exploration are necessary.

Pharmaceutically relevant frameworks, natural products, and synthetic biologically active molecules are comprised of polycarbocyclic and heterocyclic scaffolds. Traditionally, cycloadditions, transannular transformations, and annulation reactions serve as powerful methods for polycyclic formation. In order to assemble diverse polycycles, donor-acceptor cyclopropanes are useful, versatile synthetic equivalents for C-C bond formations. By taking advantage of the strain within these unique polarized systems, differing molecular architectures can be accessed directly to perform contemporary organic synthesis. Moreover, the donor-acceptor cyclopropanes initially utilized in these studies provided a fundamental basis for new methods to synthesize other relevant scaffolds. Unique, efficient, Lewis acid-catalyzed intramolecular cyclization strategies for the

construction of functionalized polycycles using Friedel-Crafts-type alkylation sequences are presented to expand the reaction repertoire of the molecular architect. Generally, products were formed from commercially-available starting materials in high yields with broad scope. The methodologies were demonstrated to be modular, operationally simple, and amenable to different substitution patterns and functional groups to afford tetrahydroindolizines, heteroaromatic cyclohexenones, hydropyrido[1,2-*a*]indoles, pyrrolo[1,2-*a*]indoles, pyrrolo[3,2,1-*ij*]quinolines, pyrrolizines, and tetrahydrobenzo[*ij*]quinolizines. To demonstrate the utility of the methodologies devised, progress toward, (±)-rhazinicine, a natural product, is discussed.

This dissertation is organized into six chapters: (1) an introduction, paradoxical stress and molecular strain's utility in synthesis; (2) annulation reactions for the formation of heteroaromatic cyclohexenones; (3) hydropyrido[1,2-*a*]indole formation via an In(III)-catalyzed cyclopropane ring-opening/Friedel-Crafts alkylation sequence; (4) tetrahydroindolizine formation and progress toward the total synthesis of (±)-rhazinicine (5) pyrrolo[1,2-*a*]indole synthesis using a Michael-type Friedel-Crafts cyclization approach; and (6) a versatile protocol for the intramolecular formation of functionalized pyrrolo[3,2,1-*ij*]quinolines.

CHAPTER 1 PARADOXICAL STRESS: EXPLOITING STRAIN FOR SYNTHETIC UTILITY

Stress is an inevitable part of life that results from an adaptive response to the pressures of work, family, environment, and any threat that induces disharmony or dysphoria. Defined by Hans Selye in 1936 as "the non-specific response of the body to any demand for change," stress can arise as a psychological phenomenon that is counter to completing tasks and goals, whether it is a real or perceived change.[25–27] The mere mention of the word stress can induce neurosis! Ask anyone about his or her personal experiences, and he or she will quickly be capable of conjuring a stressful memory or experience. Unique to its peculiar nature, stress is paradoxical,[28] a combination of a psychological positives and negatives. Distress, the negative concept, can debilitate, impair, and stymie overall performance and productivity, but eustress, the positive equivalent, can improve performance, productivity, creativity, self-esteem and health.[29,30] While one's response to his/her environment is not always predictable, it is previous experiences, anecdotal evidence, and drive for inner harmonic balance that increases the eustress to distress ratio and improve the odds of success. If one desires to succeed in an ever-changing society, stress management is critical to the daily functions and interactions of the individual. Harnessing and relieving this psychophysiological tension can foster accomplishment, productivity, and drive, consequently, turning something unfortunate into an opportunity. To alleviate strain, "the stressee" can meditate, involve himself or herself in enjoyment, express his/her feelings, relax, and exercise to promote calmness and stability. Interestingly, this human experience is relatable to the molecular world.

1.1 Molecular Stress

Molecules can be examined through the eyes of anthropomorphism. When molecular structure is probed, bonded electrons constitute the skeleton/framework of

molecules. As suggested by Kirby, bonding electrons act as a "rudimentary nervous system" and respond to perturbations caused by other atoms; therefore, this relay of perturbation is governed by distance and geometry at local centers.[31] Hence, molecules can inherently react and acknowledge external pressures contained within their environment through vibrational degrees of freedom, angle alteration, bond scission, bond formation, and polarization. Moreover, molecules cope with strain induced by themselves, which is characterized by less than optimal geometric arrangement(s)—the individualized, "internal pressure" caused by molecular movement and steric relationships that induces strained forms, conformational isomerism, and instability when a higher energy conformer is compared to the ground state. As a direct result, in accordance with the eustress perspective, chemists can exploit this stress for beneficial synthetic outcomes to discover new reactivity for strained molecules.

1.2 Eustress from the Chemical Perspective

Methodologies can be designed to improve performance and productivity. To the chemist, improved performance and productivity translates into mild conditions, high yields, chemoselectivity, regioselectivity, regiospecificity, diastereoselectivity, diastereospecificity, enantioselectivity, enantiospecificity, and atom economy. For synthetic creativity and molecular design, the use of strained systems may enhance modularity development, diversification in coverage of chemical space, and simplicity. Chemists employ these fundamental tenets of organic synthesis when applying catalysts and reagents to relieve stress in strained carbocyclic and heterocyclic systems to access new reactivity and diverse structures that are often difficult to obtain through traditional routes. Depending on the molecular architecture, selectivity, and amenability of a synthetic step, the reactivity is predicated on an exercise the molecule undergoes to achieve greater structural relaxation and stability. It is this dominant thermodynamic driving force and propensity that is one of the underlying principles observed in ring strained compounds.

1.3 Ring Strain in Cycloalkanes

Chemists view strain as structural stress that raises the internal energy of a compound when the strained molecule is compared to a reference state.[32] This increased energy may be a direct consequence of conformational distortions, nonoptimal bonding, and nonideal angles that are absent from the reference. Most of the research presented in this dissertation explores the reactivity of the most strained cycloalkane—cyclopropane. Understanding its unique reactivity as it pertains to other strained carbocycles requires an understanding of cyclopropane's structure because thermodynamics alone is inadequate to explain the reactivity of cyclopropanes and strain energy similar to that in cyclobutane.[33] Below are basic cycloalkane systems with corresponding strain energies in Figure 1.1.[34–36]

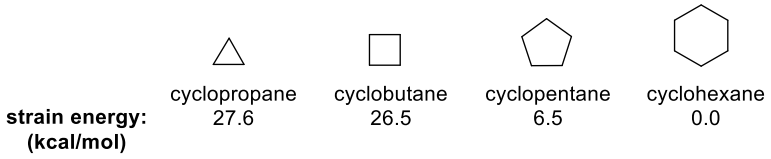


Figure 1.1: Strain energies of cycloalkanes

Because of the cyclic arrangement of cycloalkanes, the stress that these systems experience contribute substantially to ring strain, which is described by its subcomponents, Baeyer strain (angle strain) and Pitzer strain (torsional strain in the context of a ring).[37] Staggered and anti-orientations are the preferable spatial orientations and can result low in torsional strain energy. Out of all the alkanes represented in Figure 1.1, only cyclohexane achieves the staggered, favorable conformation in two chair-like forms as determined by conformational analysis. The chair form's spatial arrangement consists of staggered bonds where the axis of rotation is not aligned such that two atoms or groups have a dihedral angle of 60˚. Large and small angle strain occurs when the C-C-C network deviates from the ideal tetrahedral angle of 109.5˚ for a sp^3 hybridized carbon atom. Interestingly, the cyclohexane chair's carbons adopt an angle close to 109.5˚, ensuing zero strain energy

(Figure 1.2). For cyclopropane, the ring ideality exhibited by the cyclohexane cannot be attained because of planarity.

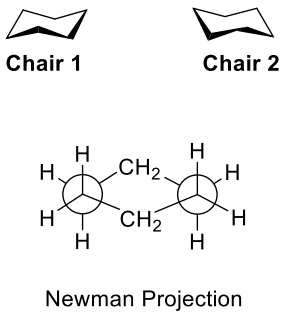


Figure 1.2: Cyclohexane chair forms and Newman projection

The carbon skeleton of cyclopropane is geometrically constrained to a plane, which institutes disfavored coplanar eclipsed C-C bonds (Figure 1.3). Therefore, the majority of cyclopropane's strain arises from its Baeyer strain, since bonds attempt to accommodate three 60˚ angles, ca. 49˚ less than the desired 109.5˚. Because of the equilateral triangle angle constraints, cyclopropane's C-C bonds are *bent* and exist as an intermediate between π- and σ-bonds, known as "τ bonds," since the internuclear angle (<60˚) is substantially less than the 109.5˚ interorbital angle.[38–41] Originally conceived by Förester,[42] the refined valence bond Coulson-Moffitt model advanced this notion by showing a ring constructed from sp^3 hybridized $–CH_2-$ groups 22˚ outward from the C-C nuclear baseline, causing a 20% deficiency in orbital overlap in reference to C-C bonding in ethane (Figure 1.4).[33,39,43–45]

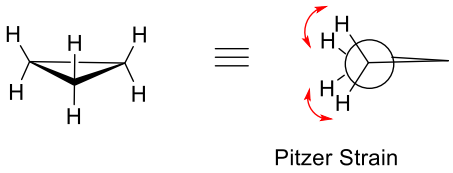


Figure 1.3: Torsional strain in cyclopropane

To accommodate small ring angles, Greenberg et. al [46,47] predicted greater s character (32%) in the C-H bonds in 1978.[48,49] Then, Walsh, in a separate publication,

derived a molecular orbital (MO) picture of cyclopropane that accounts for the unusual reactivity of cyclopropanes not observed in other cycloalkanes (Figure 1.4). Walsh's MO model describes three mathematical linear combinations of sp^2 hybridized atomic orbitals (AO) of lowest energy as the basis set that constitutes the σ-bond network $\boldsymbol{\psi^1}$.[50–53] By using three p-AOs, two other linear combinations of equal energy yield $\boldsymbol{\psi^2}$ and $\boldsymbol{\psi^3}$.

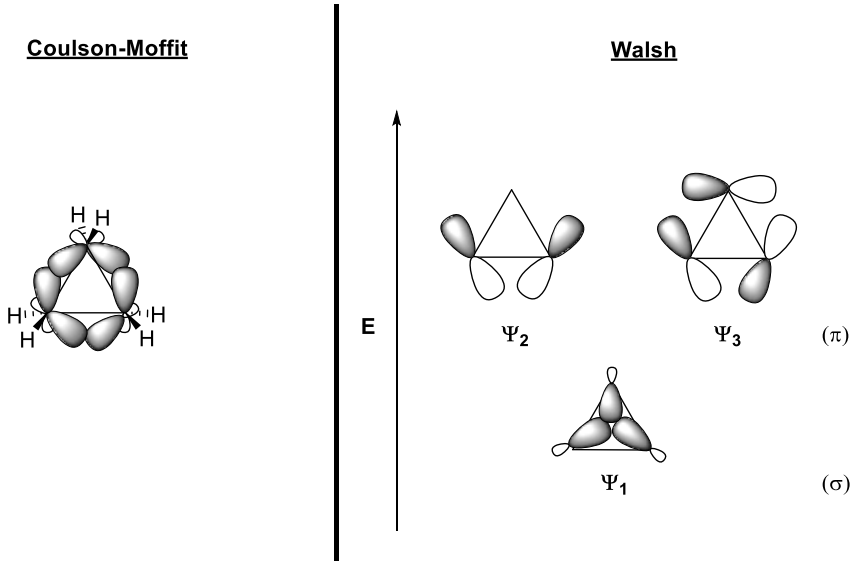


Figure 1.4: Coulson-Moffit and Walsh models for cyclopropane

From the derived combinations, orbital overlap is reduced because of the inward directionality of $\boldsymbol{\psi^1}$, and "quasi π-character" is imparted from $\boldsymbol{\psi^2}$ and $\boldsymbol{\psi^3}$. Both models, Walsh and Coulson-Moffit, account for the substantial angle strain attributed to diminished orbital overlap. For these reasons, a thermodynamic bias for ring-opening is inherent and acts as a driving force for bond cleavage when the cyclopropane is activated. The π-character and large electron density adjacent to the C-C axis[54] makes cyclopropane useful for various transformations with chemical reagents, (e.g., catalysts, nucleophiles, electrophiles, radicals), heat, and light. Presenting a myriad of synthetic opportunities, cyclopropanes are versatile building blocks for organic chemists and can be used to assemble a broad range of carbocyclic and heterocyclic scaffolds.[33,55–59]

1.4 The Push-Pull Effect in Donor-Acceptor Cyclopropanes

Often synthesized from carbenes, carbenoids, or other equivalents and corresponding olefins,[60–62] cyclopropanes are relatively stable and resistant to bond scission unless they are activated. This activation is accomplished by polarizing one or more of the C-C bonds through the attachment of electron-donating (donor, D) and electron accepting (acceptor, A) as substituents (Figure 1.5). Classically, electron-withdrawing functionalities, such as the carbonyl, sulfonyl, and nitro groups, operate as acceptors, and moieties with electron-rich aryl groups, such as heteroatoms, alkyl, or alkenyl groups, act as donors. Common arrangements for the donor and acceptor groups about the cyclopropane ring are shown in Figure 1.5. For this initial discussion, the substituent placement for the donor and acceptor groups to be considered are geminal (**1-1**) and vicinal positioning (**1-2**).

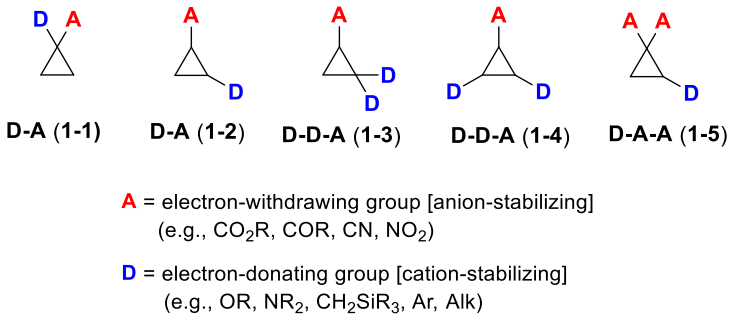


Figure 1.5: Common donor-acceptor arrangements in cyclopropanes

Vicinally-positioned donor and acceptor groups act in a tunable, push-pull fashion, resulting in enhanced polarization of the C-C bond between the donor and acceptor groups (Figure 1.6).[63,64] In contrast, donor and acceptor groups positioned geminally are not as 'synergistic' as vicinal substitution for bond polarization,[56,65] but *gem*-donor-acceptor (D-A) cyclopropanes are very useful for medicinal chemistry[66] and ethylene biosynthesis.[46,47]

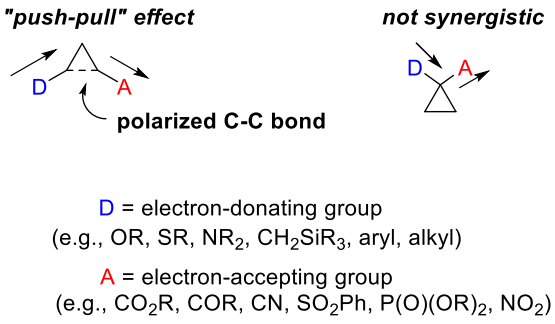


Figure 1.6: Push-pull effect in *vic*- and *gem*-disubstituted cyclopropanes

The push-pull effect induces polarization, resulting in multiple pathways for versatility in product formation. If heterolytic ring opening occurs, a 1,3-zwitterionic intermediate forms such that its stability and reactivity are dependent on the reaction conditions; meaning, this dipole reacts with electrophiles, nucleophiles, and dipolarophiles (Figure 1.7). As a result, donor-acceptor cyclopropanes serve as convenient synthetic equivalents that are purposive for synthesizing compounds with dissonant charge patterns. The *umpolung* of polarity in the carbon center provides an alternative route to complex structures not accessible by other methods.[67] Many donor-acceptor cyclopropane ring-opening reactions proceed through a synchronous route involving nucleophilic attack on the electron-deficient carbon with a concurrent ring-opening. Another pathway for ring-opening is homolytic cleavage via a diradical intermediate that forms independent of a substituents' nature. In the case of dipolarophiles, a formal cycloaddition is purported to proceed through a stepwise polar mechanism. This predictable behavior has led to extensive application of vicinal donor-acceptor cyclopropanes in modern organic chemistry, prompting researchers to better understand the ring polarization.

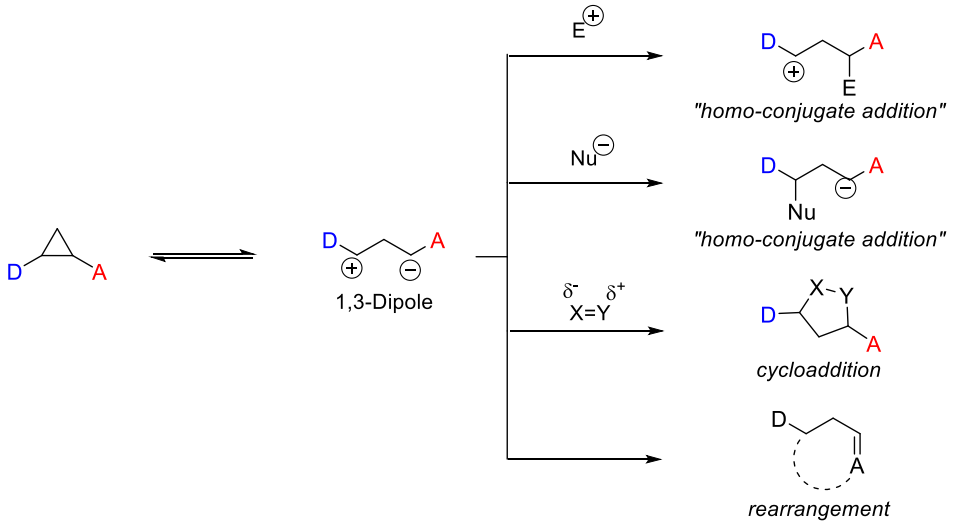


Figure 1.7: Reactivity of *vic*-donor-acceptor cyclopropanes

In order to quantify the polarizing effect of donor and acceptor substituents, Schneider and Werz conducted a systematic theoretical investigation by calculating ring enlargement activation barriers for 72 donor-acceptor cyclopropane combinations (Figure 1.8).[64] As anticipated, smaller transition energies were observed with good donor (e.g., NMe_2, OMe, aryl, alkyl) and acceptor substituents (e.g., NO, CHS, CHO). For most systems, the donor has greater impact on the transition state energy than the acceptor. If an additional acceptor and/or donor group is added geminally, the transition state energies further decrease without significant influence on reaction enthalpies. According to the calculations of Schneider and Werz, increasing solvent polarity (toluene, DCM, DMSO) lowers the activation barrier of their NMe_2/CHO model by 3-10 kcal/mol. Hence, Schneider and Werz predicted that specific combinations of donor and acceptor substituents readily promote ring-expansion with or without catalyst while other combinations offer less C-C bond polarization. Of note, this study involved a synchronous polar ring-enlargement mechanism as opposed to a heterolytic ring-opening that causes larger transition state energies. Similarly, when intermediates involving diradicals were modeled, transition state energies were substantial (Figure 1.8).

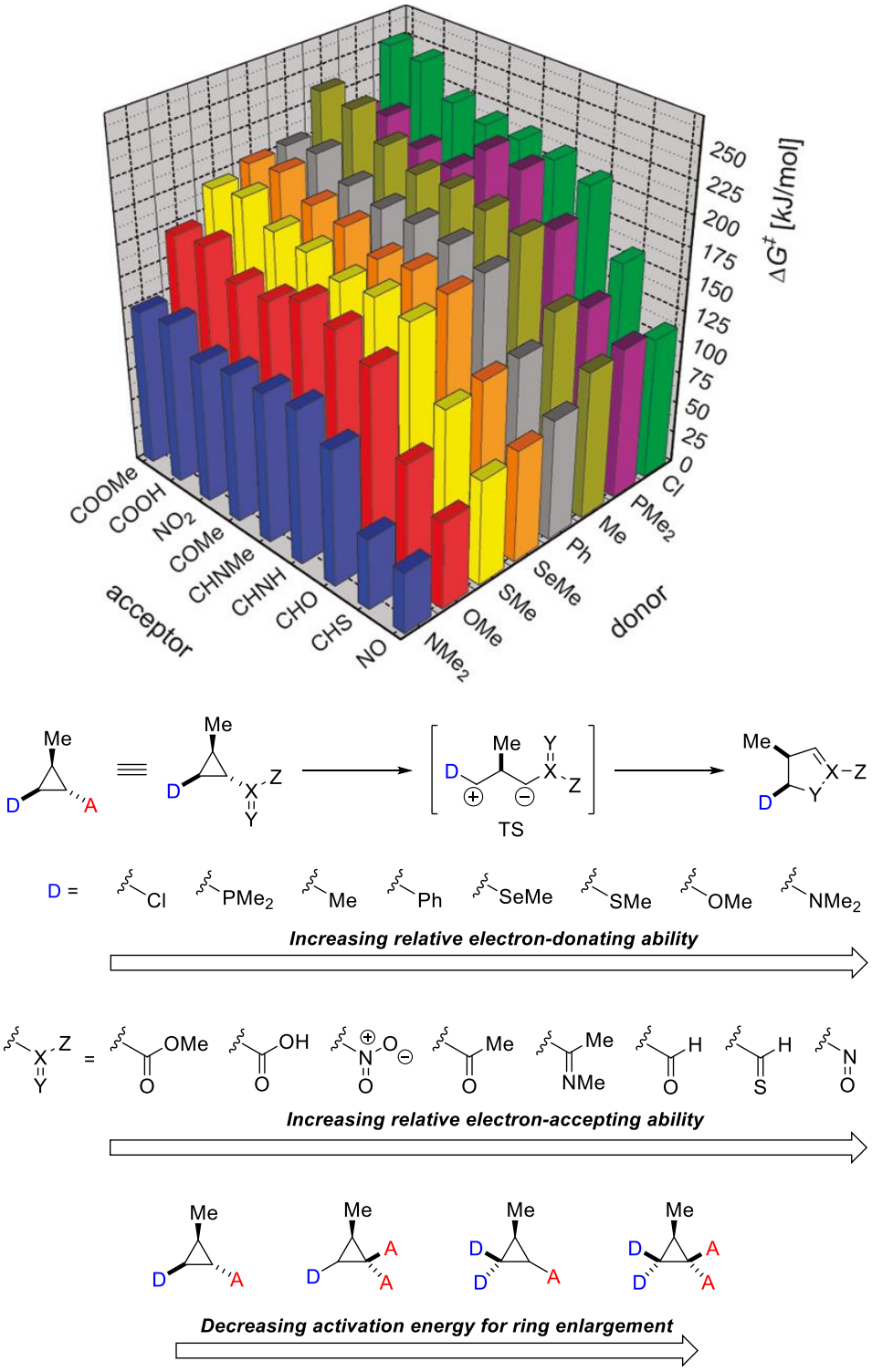


Figure 1.8: Schneider and Werz' donor-acceptor computational insights

1.5 Donor-Acceptor Cyclopropane Design and Synthetic Utility

The incorporation of the intramolecular design for donor-acceptor cyclopropanes was established in the late 1960s and early 1970s. During this period, Stork[68–71] and Grieco[72] pioneered the application of cyclopropyl ketones with alkyl donors as useful precursors for acid-promoted, intramolecular cation-olefin cyclizations. Corey reported the first example of a total synthesis using the Stork cyclopropane cyclization method in the synthesis of (±)-cedrone and (±)-cedrol.[73] Danishefsky published numerous examples of intramolecular nucleophilic ring-opening cyclizations to form functionalized carbocycles and heterocycles.[74] Wenkert later showcased the utility of stronger donor groups, including heteroatom donors,[75] and in 1980, Hirsch and Reissig coined the term "donor-acceptor cyclopropane" for *vic*-structures[76] with both cohorts being recognized for this early renaissance in donor-acceptor cyclopropane chemistry.[77] These seminal examples established a foundation for almost 40 years of work devoted to intramolecular reactions of donor-acceptor cyclopropanes. Trushkov noted this breadth of chemistry in the dedication article to O.M. Nefedov:[78]

"Acceptor and donor together bring a magic force to the three-membered ring. This ring is inimitable under the sky, reacts with radicals, nucleophiles, electrophiles, redox agents, alkenes, imines, aldehydes, conjugated dienes. It dimerizes, reacts with nitrones, nitriles, and alkynes, and so forth, and so on…."

Initially, most of the chemistry encompassed ring cleavage with electrophiles and nucleophiles.[56,65] Within the last 15 years, the number of Lewis acid-catalyzed cycloadditions and annulation transformations with D-A cyclopropanes have soared.[78] Further application of these unique Michael acceptors in [3+2]- and [3+3]-cycloadditions and annulations affirms the proficient production of cyclic compounds intermolecularly with compounds containing double and triple bonds (e.g., allenes, nitrones, alkenes, aldehydes, imines, nitriles, ketones) to afford five- and six-membered constructs.[77,79–81]

Trushkov's outline of important donor-acceptor reactivity before 2008 is presented in Figure 1.9.[78]

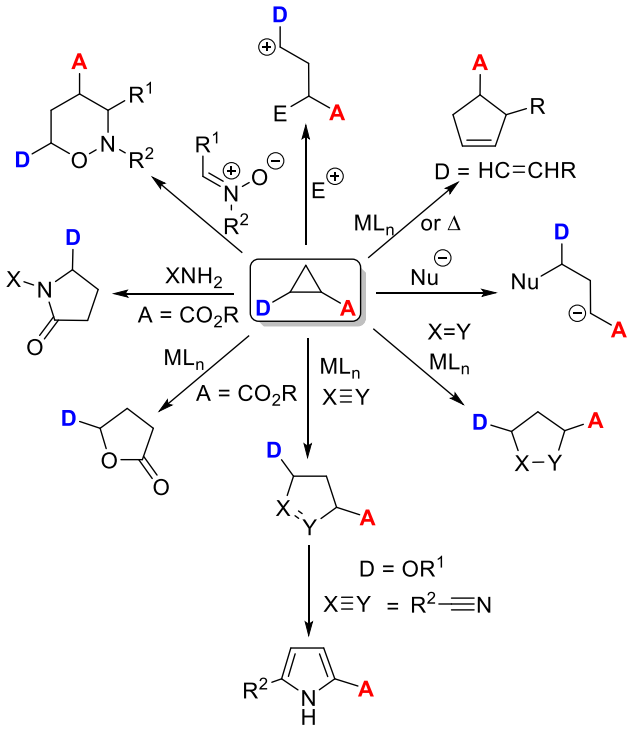


Figure 1.9: Trushkov's overview of donor-acceptor cyclopropane chemistry prior to 2008

These reactive donor-acceptor units can also undergo cycloisomerizations, *umpolung* reactions, rearrangements, ring-opening lactonizations, ring-opening lactamizations, and cyclodimerizations to form diverse scaffolds (Figure 1.10).[82] Some developed asymmetric protocols in which donor-acceptor cyclopropane synthons performed well with high stereoselectivity, regioselectivity, and chemoselectivity and were applied to natural product syntheses.[82–92] Due to the characteristic reactivity and synthetic potential of donor-acceptor cyclopropanes, these polarized carbocycles have garnered a considerable amount of attention and have invigorated a resurgence of the application of donor-acceptor cyclopropane chemical reactivity described by Werz as the "new golden age for donor-acceptor cyclopropanes,"[77] prompting a large number of important extensive reviews on the synthesis and reactivity of D-A cyclopropanes in the last decade.

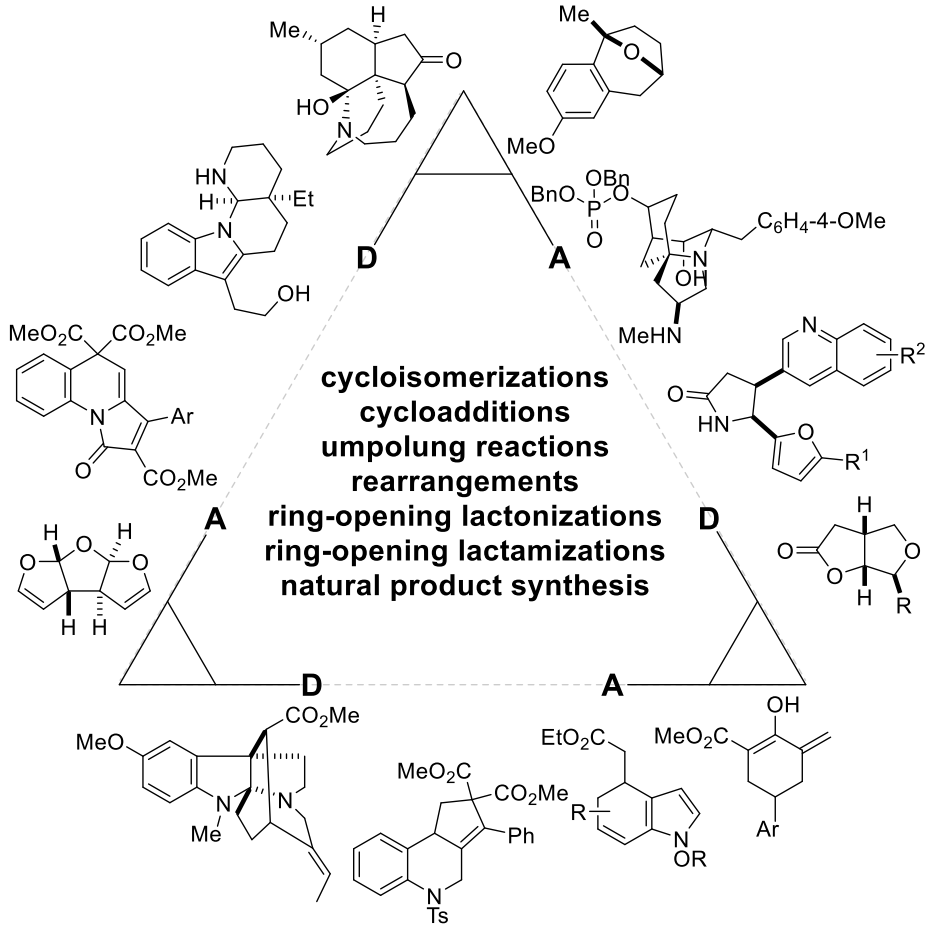


Figure 1.10: Transformations for donor-acceptor cyclopropanes with resulting products formed

1.6 Current Reviews on D-A Cyclopropanes

In 2003, Reissig discussed synthetic applications of vicinally-substituted donor-acceptor cyclopropane derivatives as intermediates in natural product synthesis with an emphasis on cyclopropane bond scission.[56] Subsequently, in 2005, Pagenkopf et al. noted advancements in the formation and usage of donor-acceptor cyclopropanes as dipolarophiles for 1,3-dipolar cycloadditions.[65] In 2009, Waser studied intramolecular ring-opening cyclizations with emphasis on the formal homo-Nazarov cyclization.[93] Likewise, Kerr and Carson published a tutorial review on methods for formation of functionalized heterocycles from ring-expansion reactions of cyclopropanes in 2009.[80]

Then, in 2010, Kerr described intramolecular cycloadditions of donor-acceptor cyclopropanes and transformations of the resulting adducts to natural product targets.[81] In 2011, Trushkov et al. published an account article which included [3+2]-cycloadditions, reductive ring-openings, nucleophilic ring-openings/ring-closures, and acid induced ring-openings.[78] Within the same year, Waser[94] et al. published a paper on the synthesis and reactivity of heteroatom substituted donor-acceptor cyclopropanes while Reisman[95] et al. focused on the application of the Buchner reaction for total synthesis. Moreover in 2012, Qin[96] and Wang[97] separately disclosed an overview of versatile, activated cyclopropanes in natural product synthesis. Afterwards, in 2013, Njardarson and Mack reported new advancements in expansions of three- and four-membered rings by using metal catalysts.[98] In 2014, Cavitt and France[82] reviewed recent intramolecular chemistry for donor-acceptor cyclopropanes; Werz'[77] review justified the assertion of a new forefront for donor-acceptor cyclopropane chemistry; Waser presented more progress in the field and included cyclobutanes; Snieckus[99] reported on the employment of alkenyl and alkylidene substituents; Grandi[100] covered Nazarov-like cyclization reactions reported during 2009-2013. In 2015, Kerr[101] introduced another comprehensive overview of intermolecular and intramolecular annulations using donor-acceptor cyclopropanes to form carbocycles, and Tomilov[102] discussed the dimerization reactions of donor-acceptor cyclopropanes.

1.7 Dissertation Overview

This dissertation centers on novel intramolecular chemistry of *vic*-donor-acceptor-acceptor cyclopropanes (D-A-A) **1-5** and *vic*-donor-donor-acceptor-acceptor cyclopropanes (D-D-A-A) **1-6** to form disparate heterocyclic scaffolds (Figure 1.11). While particular emphasis is placed on intermolecular reactivity in the literature, research studies on intramolecular transformations have recently become more frequent owing to the benefits of intramolecularity for ring-opening cyclization reactions. The advantages of intramolecular reactivity over intermolecular include increased local concentration, milder

reaction conditions, improved control of diastereoselectivity, and rapid formation of polycyclic structures. Notably, the work presented in this dissertation has assisted in ushering in this new golden age and expanding the repertoire of methodologies for the molecular architect by examining the reactivity of different donor-acceptor combinations to construct distinct structures difficult to procure by other synthetic means.

In addition to our contributions to the growing field of donor-acceptor cyclopropane chemistry, we used structural and mechanistic rationale based on donor-acceptor cyclopropane chemistry as a guide and inspiration for new Friedel-Crafts-type alkylation methodologies to access other valuable frameworks. Initially, we were interested in improving protocols reported for our target scaffolds and devising new strategies to access differing molecular skeletons. Because some protocols required harsh reaction conditions, long reaction times, and high temperatures, we sought to reduce the number of cumbersome steps and to incorporate robust transformations using readily accessible, commercially-available, cheap starting materials. If we were to achieve our goals, it was critical to choose reactive systems that were electronically tunable to provide an array of carbocycles and heterocycles. By adding additional polarization to *vic*-donor-acceptor cyclopropanes, we realized or goals, by even more than we had originally anticipated. From the donor-acceptor cyclopropane strategy, we synthesized heteroaromatic ring-fused cyclohexenones **1-8** (Chapter 2), hydropyrido[1,2-*a*]indoles **1-9** (Chapter 3), and tetrahydroindolizines **1-10** (Chapter 4) (Figure 1.11).

As explained earlier, cyclopropanes have an inherent π-character and can be viewed as reactive quasi π-systems. Removing one carbon unit and keeping the double bond character would form Michael-type acceptor compounds **1-7** (Figure 1.11). We inferred that subjecting the polarized Michael-type precursors to Lewis acid would form five-membered constructs (pyrrolo[1,2-*a*]indoles **1-11** and pyrrolizines **1-13**) (Chapter 5). From **1-7**, we postulated that pyrrolo[3,2,1-*ij*]quinolines **1-12** would be synthesized if the indole 2-position were replaced with a poor leaving group such that aromatization could be

established only by electrophilic aromatic substitution at the indole C7-position (Chapter 6). Furthermore, using this same Friedel-Crafts approach tetrahydropyrrolo[3,2,1-*ij*]quinolines **1-14** and tetrahydrobenzo[*ij*]quinolizines **1-15** were hypothesized to form accordingly (Chapter 6). Given the results presented in this dissertation, our diversity-oriented strategy was successful since we covered a significant portion of chemical space from common starting resources. The subsequent chapters will provide a more in-depth analysis that explains the rationale, scope, and other synthetic highlights.

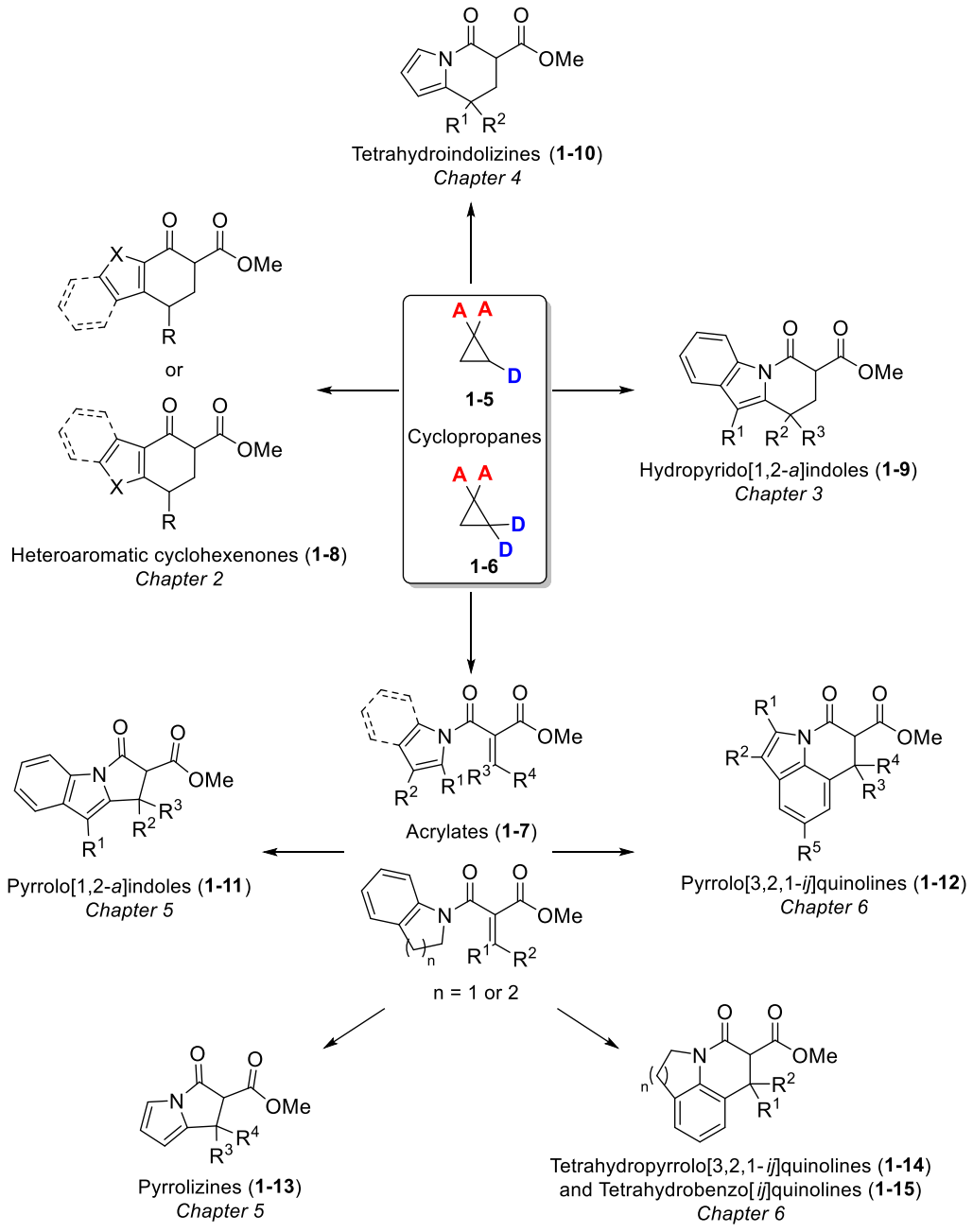


Figure 1.11: Diversity-oriented synthetic strategies originating from donor-acceptor cyclopropanes

CHAPTER 2 SYNTHESIS OF HETEROAROMATIC RING-FUSED CYCLOHEXENONES VIA INDIUM(III) CATALYSIS

The late 20th century work of Corey, Stork, and Danishefsky demonstrated that activated carbonyl cyclopropanes were useful for forming unique polycyclics intramolecularly in one step by ring-opening and subsequent cyclization (Figure 2.1).[71,73,103]

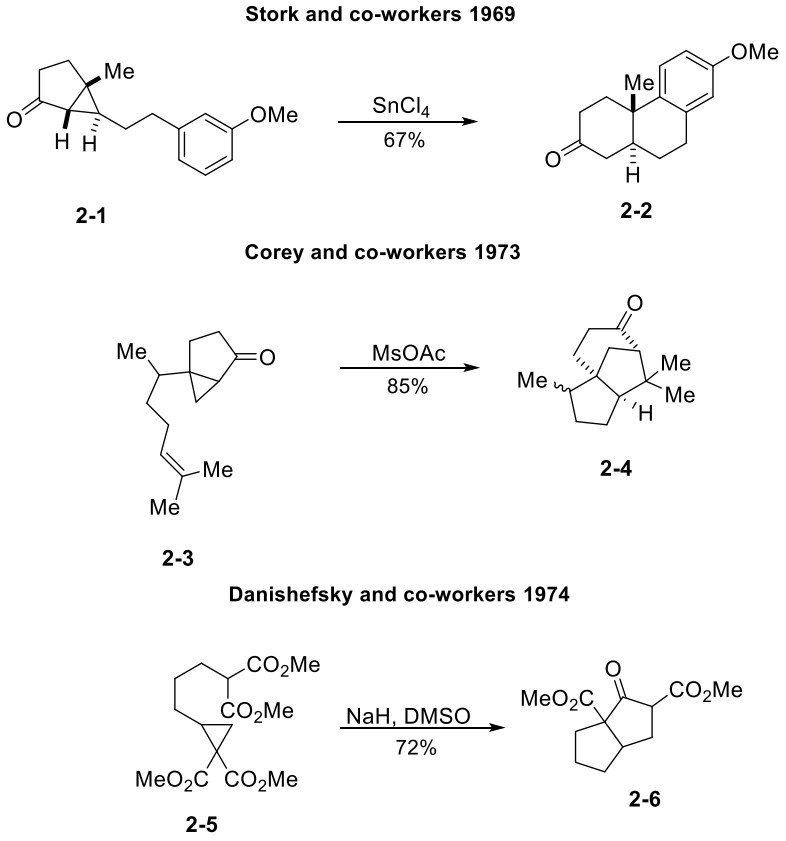


Figure 2.1: Early reports by Stork, Corey, and Danishefsky's including donor-acceptor-acceptor cyclopropanes

For similar transformations, Waser postulated three general ring enlargement modes (Figure 2.2).[93] E*ndo 1* is feasible if the electron withdrawing substituent(s) is outside the ring. After cyclization, two ring carbons form the carbocycle. E*ndo 2* proceeds where all of the ring carbons are amalgamated into the fused system, and finally, *exo* cyclization results from the incorporation of one carbon unit into the cyclized product. Due to poor

orbital alignment, Waser inferred that a concerted process is highly unlikely, but a stepwise mechanism with a dipolar intermediate is more plausible.[104] Given the ring enlargement modes, the *endo(1)* process is considered to be analogous to the well-known Nazarov cyclization if one examines the π-character of vinyl cyclopropyl ketones. The term "homo-Nazarov" was first mentioned in Ra's dissertation outside of the cyclopropane context in 1990.[105] Yadav's synthetic protocol[106] in 2008 coined the ring enlargement with vinyl-type cyclopropyl ketones the "homo-Nazarov" cyclization.

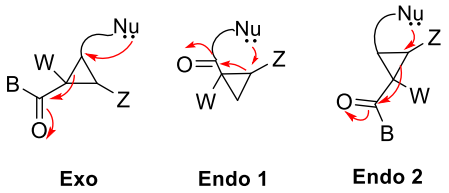


Figure 2.2: Waser's modes of cyclization for substituted cylopropanes

The homo-Nazarov's well-known and highly popular parent reaction, which was discovered in 1941, was named after Ivan Nikolaench Nazarov (1906-1957)—the Nazarov cyclization.[107,108] This concerted electrocyclic reaction, governed by Woodward-Hoffman principles,[109–112] which forms a transient pentadienyl cation under acidic conditions, is recognized as a powerful transformation for synthesizing five-membered rings.[113] Up to 2008, examples of the analogous reaction for six-membered constructs were few. Through the lens of cyclopropanes, the Nazarov reaction converts to the homo-Nazarov reaction because of one additional carbon unit and the differing mechanistic pathway for cyclization. As a result of the versatility of donor-acceptor cyclopropanes as reactive species for C-C bond formation, the application of the homo-Nazarov cyclization for synthesizing cyclic structures has increased the number of routes, approaches, and possibilities to access materials, therapeutics, and natural products difficult to obtain by other means.

Mechanistically, under acidic conditions, carbonyl cyclopropanes **2-9** open to form a cyclic oxyallyl cation in a stepwise manner to afford six-atom cyclic systems **2-10**.

Contrary to the classical Nazarov reaction, the formal homo-Nazarov reaction is not FMO-controlled, but a similar oxyallyl cation is purported to be an intermediate (Figure 2.3).[113,114] The term "formal" is used to indicate that specificity is not imparted by standard Woodward Hoffmann electrocyclic predictions, principles the classic Nazarov reaction adheres to for cyclization. "Formal" would be removed if the cyclopropane system were to cyclize in a manner governed by frontier molecular orbital (FMO) theory to impart stereoselectivity in product formation.[94] Although earlier representative examples of the formal homo-Nazarov methodology underlying principles of ring-enlargements from donor-acceptor cyclopropanes were reported in 1980, the term "formal" was not included in the description of the methodology at that time.

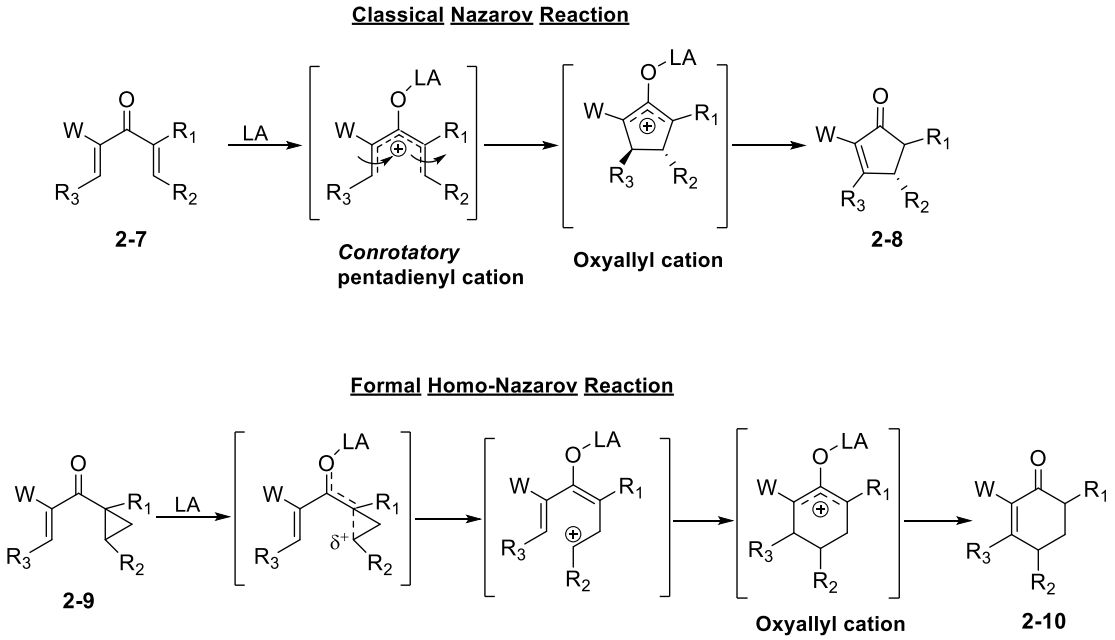


Figure 2.3: The Nazarov reaction and the formal homo-Nazarov reaction

2.1 Earlier Examples of the Formal Homo-Nazarov Reaction

Applying the underlying precept of the formal homo-Nazarov reaction, Murphy and Wattanasin used arylaroyl cyclopropanes **2-11** to synthesize tetralone derivatives **2-12** for a 14-18% yield in 1980. Electron-rich benzenes were ketone substituents on the

cyclopropane. Upon treatment with acid ($SnCl_4$, TFA, or BF_3•Et_2O) at room temperature, ring-opening resulted in the formation of a benzylcarbocation intermediate and ring closure. When electron-donating groups were replaced with hydrogen in either ring, C-C bond scission was slow, and carbinol **2-13** and tetrahydrofuran **2-14** products formed. Adducts were observed when both rings were substituted with donor, activating groups—settling the mechanistic debate at the time. Although this approach was effective for assembling their target compounds, four equivalents of $SnCl_4$ were used, and long reaction times were recorded for product formation (Figure 2.4).[115,116]

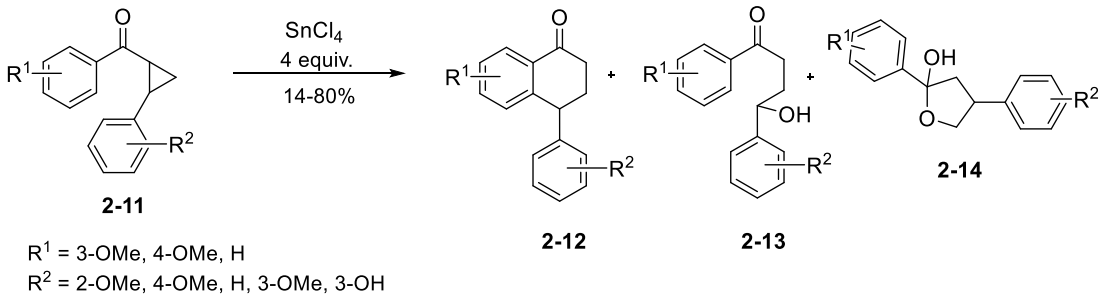


Figure 2.4: Murphy's formation of tetralones

In 1988, further exploration of this chemistry was reported by Tsuge and co-workers, who used 1-alkenyl cyclopropyl ketone **2-15** and excess polyphosphoric acid in benzene under reflux to synthesize 6-membered constructs similar to **2-16** (Figure 2.5).[117] For the representative example, 63% yield was obtained after 30 hours at 80 °C. Depending on the 1-alkenyl cyclopropyl ketones' substitution patterns, the reaction furnished other side products, which may have been a result of the quantity of acid used. Drawbacks for this approach were narrow scope (five out of the sixteen precursors gave the desired cyclohexenones), low to moderate yields (15-63%), and harsh reaction conditions (long reaction times and stoichiometric acid). Hence, the development and application of this methodology was limited.

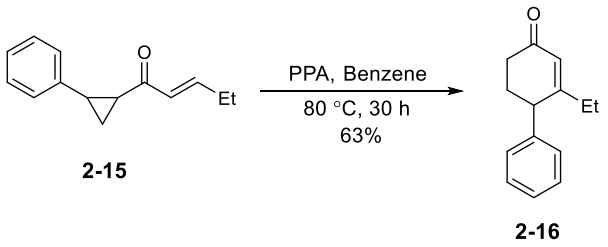


Figure 2.5: A representative example of Tsuge's synthesis of an aryl cyclohexenone

Further expansion of the formal homo-Nazarov methodology occurred in 2005 when Otto et al. reported on heteroaryl-substituted cyclopropyl ketones' reactivity, which was similar to that of 1-alkenyl cyclopropyl ketones (Figure 2.6).[118] This protocol was the first formal homo-Nazarov cyclization example with heteroaryl cyclopropyl ketones to furnish [*b*]-annelated cyclohexenones. 2-Thienyl cyclopropyl ketone **2-17** and 2-furyl cyclopropyl ketone **2-18** yielded 54% and 95%, respectively, when subjected to acidic workup. If 2-furyl and 2-thienyl reactions were exposed to basic conditions, alcohols were obtained in a 40% yield for 2-furyl and a 70% yield for 2-thienyl.

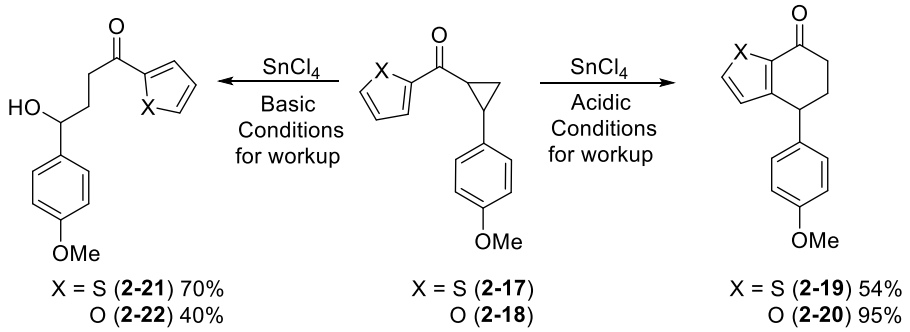


Figure 2.6: Otto's heteroaromatic formal homo-Nazarov reaction

Eventually, in 2008, this six-membered ring annulation was named the heteroaromatic homo-Nazarov cyclization by Kumar and Yadav, and the scope was expanded considerably.[106] Heteroaryl 2-silylmethyl substituted cyclopropanes reacted with 4.0 equiv. of $SnCl_4$ in 1,2-dichloroethane at 80 °C. Precursors **2-23** and **2-24** afforded 2- or 3-substituted heteroaromatic cyclohexenones **2-25** and **2-26** in 80-85% yield (Figure 2.7),

exquisitely establishing β-silyl groups as good stabilizing substituents for carbenium intermediates for this protocol.

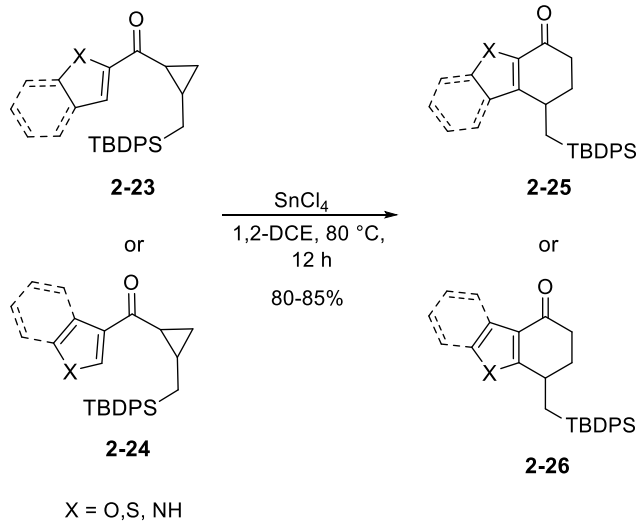


Figure 2.7: Yadav and Kumar's heteroaromatic formal homo-Nazarov reaction

Within the same year, Waser divulged a catalytic formal homo-Nazarov cyclization of activated cyclopropanes using *p*-TsOH to yield fused ring systems, similar to those in Tsuge's report (Figure 2.8).[119]

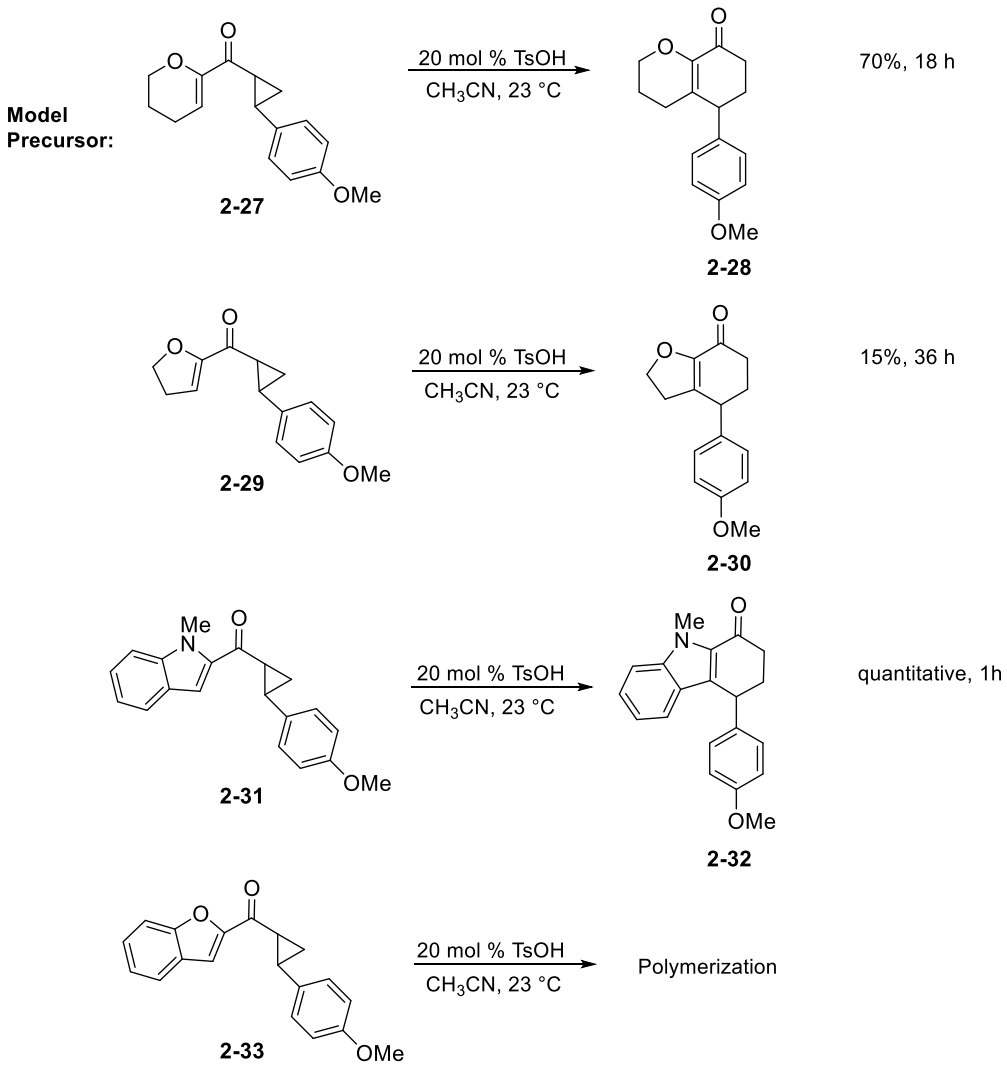


Figure 2.8: Waser's formal homo-Nazarov cyclization

Waser experimentally investigated the mechanism for a Brønsted acid-catalyzed process because a pK_a dependence suggested a stepwise route with cationic intermediates, and Waser wanted to improve the methodology (Figure 2.9). Waser discovered that the reaction was first-order for the acid catalyst concentration, which indicated catalyst involvement in the ring-opening step. However, when attempting to verify this mechanistic postulation, Waser was not initially successful in trapping his model substrate **2-27**, shown in Figure 2.8.

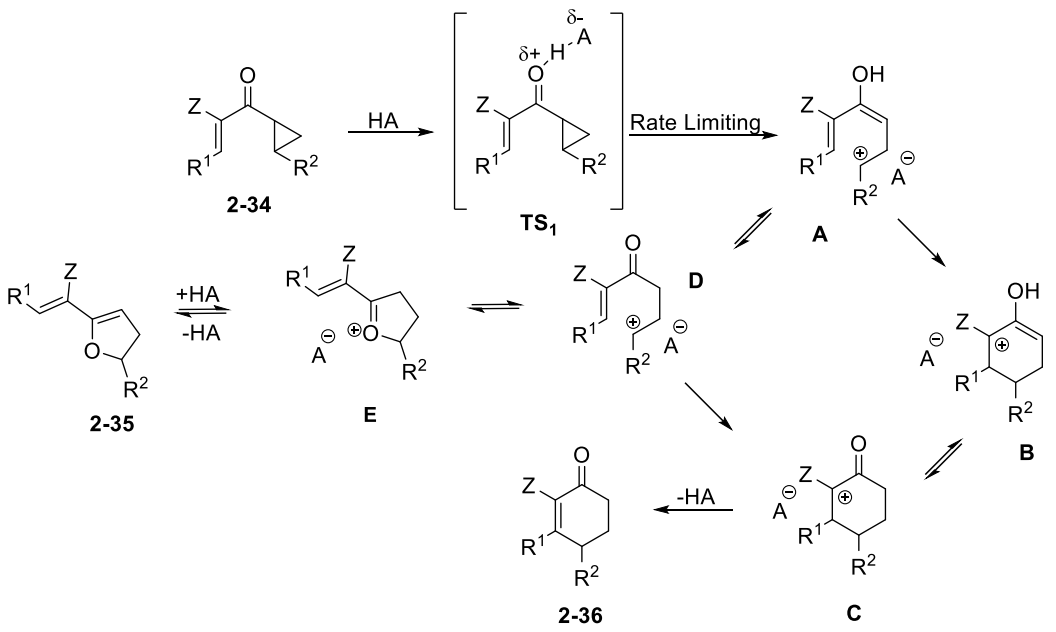


Figure 2.9: Waser's mechanism for the formal homo-Nazarov cyclization

As an alternative to support the formation of the cationic intermediates, Waser treated cyclohexene cyclopropyl ketone **2-27** with water and other nucleophiles, but cyclized **2-28** was observed only. In order to slow the rate, **2-37** was assembled. Standard reaction conditions caused **2-37** to react in a similar time to **2-27**, and no cyclized product for **2-37** was formed. When catalytic TsOH•H_2O (20 mol%) in acetonitrile was used, polymerization occurred (Figure 2.10). Conditions with 5 vol% of water formed carbinol **2-38**; this result supported the plausibility of carbocationic intermediates. Therefore, if ring scission is facile, cyclized products form, but when cleavage is slow, polymerization and nucleophilic attack products becomes more favorable. Following the work of Kumar, Yadav, and Waser, Frontier published a Lewis acid-catalyzed approach to heteroaromatic ring-fused cyclopentanones from heteroaryl vinyl ketones—commonly known as the heteroaromatic Nazarov cyclization.[120] In order to fashion a relatively simple procedure for heteroaryl cyclohexenones assembled in previous protocols, we drew upon Frontier's work for inspiration.

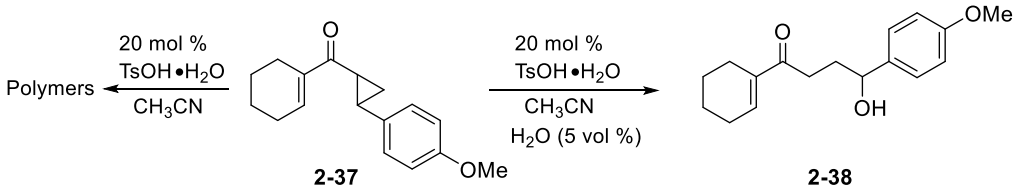


Figure 2.10: Waser's cyclohexene cyclopropyl ketone trials

2.2 Hypothesis and Synthetic Rationale for Heteroaromatic Cyclohexanone Synthesis

Frontier and co-workers explored the effects of tuning the electronics of the Nazarov cyclization reaction. When they placed electron-donating and electron-withdrawing functionalities in different localities on the pentadienone substrates and used a catalytic amount of acid, greater selectivity and reactivity were observed (Figure 2.11).[120]

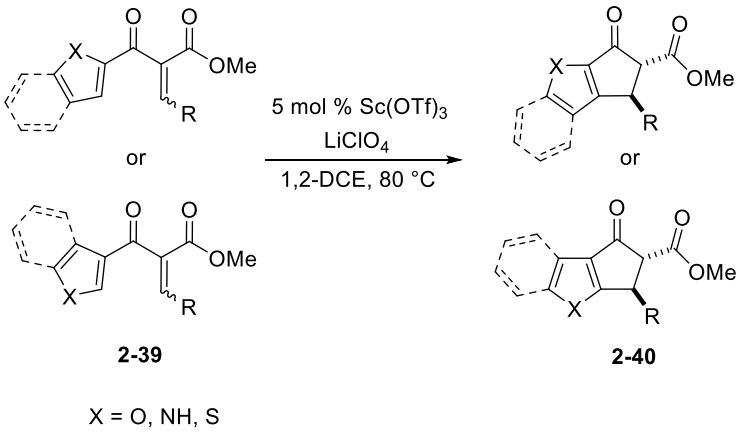


Figure 2.11: Frontier's catalytic Nazarov cyclization of heteroaromatic alkenyl ketones

From Frontier's findings, our group proposed that classical, *vic*-substituted donor-acceptor cyclopropanes could be further polarized with a secondary *gem*-acceptor group and a stabilizing donor group in order to promote the formal homo-Nazarov cyclization.[120–122] The application of donor-acceptor-acceptor (D-A-A) cyclopropanes **2-41** is vast for other chemical transformations (Figure 2.12).[123–135]

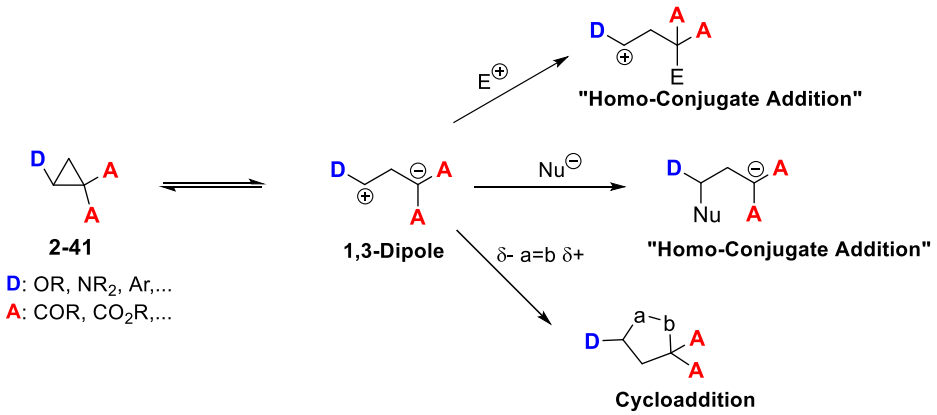


Figure 2.12: *vic*-Donor-acceptor-acceptor cyclopropane reactivity

If a metal coordinating ligand such as an ester in the α-position as the secondary substituent is used, localizing the charge density can further polarize the cyclic oxyallyl cation, which increases the charge predictability and reactivity of intermediate **2-42** designs (Figure 2.13).

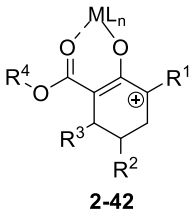


Figure 2.13: Intermediate predictability

For these reasons, milder reaction conditions with good yields are plausible for alkenyl and heteroaryl substituted ketones. The application of this chemistry could lead to a significant expansion in the reaction scope for the formal homo-Nazarov reaction. Consequently, the methods and protocols developed can be utilized for a diverse array of synthetic applications.

The first example as "proof of concept" was reported by France et al. in 2010. Using 30 mol% $In(OTf)_3$ in DCM at 25 °C, Patil and co-workers reported an efficient protocol for the formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones **2-43** which furnished methylene cyclohexenols **2-44** and cyclohexenones **2-45** (Figure 2.14).[136]

For this work, simple alkenes without an α-heteroatom worked, whereas Waser's carbocyclic precursors afforded polymerization or carbinols but not the desired product. The research of Patil et al. was the first publication demonstrating the utility of D-A-A cyclopropanes in which the formal homo-Nazarov cyclization formed cyclohexenones and cyclohexenols using catalytic $In(OTf)_3$. With this concept in mind, the France group published a related method for the heteroaromatic formal homo-Nazarov cyclization.[137]

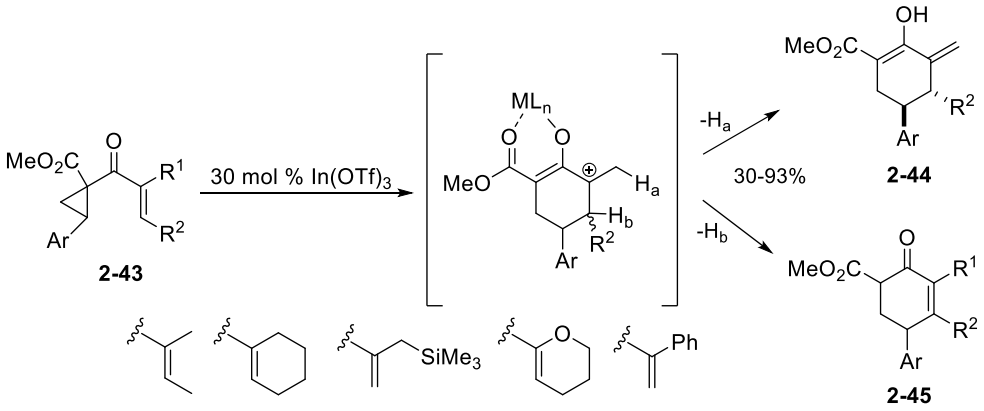


Figure 2.14: France's formal homo-Nazarov cyclization for methylene cyclohexenols and cyclohexenones

Heteroaromatics are key structural components in the core of many natural products, biologics, and medicinally active molecules.[138–143] Given their substantial chemical importance and relevance, heteroaromatics are convenient synthetic equivalents for increasing structural complexity.[144–146] Organic chemists continue to develop efficient methods for their synthesis and incorporation into materials, polymers, and medicines.[147–151] We made use of the underexplored heteroaromatic formal homo-Nazarov ring closure to generate six-membered appendages to form assorted heteroaromatics.

To the best of our knowledge, as mentioned previously, only three examples of the heteroaromatic homo-Nazarov cyclization existed before our published protocol. Yadav[106] synthesized 4-silylmethyl/hydroxymethyl-substituted 2,3-heteroaromatic ring-fused cyclohexanones; Otto[118] made 4,5-dihydrobenzo[*b*]thiophen-7(6*H*)-one and 4,5-dihydrobenzo[*b*]furan-7(*6H*)-one, and Waser[94] cyclized a 2-indolyl substrate with *p*-

TsOH. After a review of the literature mentioned, a rapid method for generating heteroaromatic ring-fused cyclohexanones under mild conditions was warranted for expansion of the reaction scope. Our approach was applied to these donor-acceptor-acceptor cyclopropanes with heteroaromatics **2-46** to generate heteroaryl ring-fused cyclohexanones **2-47**.

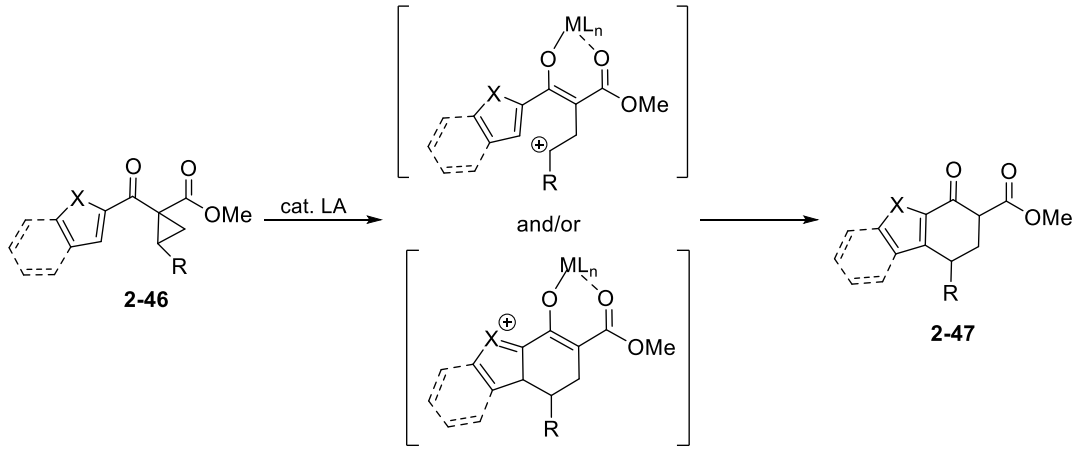


Figure 2.15: Heteroaromatic formal homo-Nazarov cyclization with donor-acceptor-acceptor cyclopropanes

2.3 Precursor Assembly and Reaction Optimization for Heteroaryl Cyclopropyl Ketones

For the initial investigation, we synthesized 2- and 3-heteroaryl cyclopropyl ketone precursors **2-51** in three steps, as shown in Figure 2.16. Prepared from their commercially-available heteroaromatic carboxylic acid *in situ*, 2- and 3-substituted heteroaromatic acid chlorides **2-48** and lithium 1-methoxyethen-1-olate were used to form β-ketoesters **2-49**. Diazotization[61,62,152] generated α-diazoesters **2-50**. Finally, Rh_2esp_2 (dirhodium α,α,α',α'-tetramethyl-1,3-benzenedipropanoate)-catalyzed cyclopropanation[153] with the corresponding olefins afforded heteroaromatic cyclopropyl ketones **2-51**.

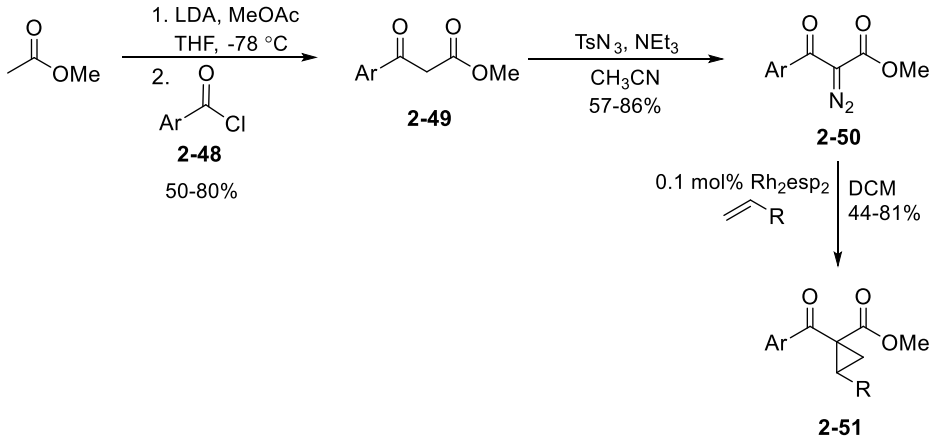
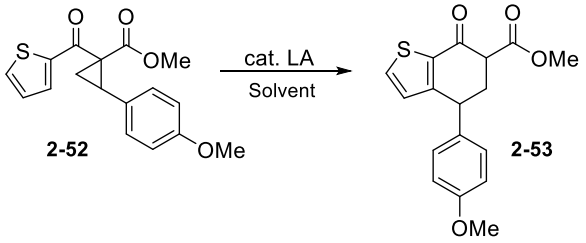


Figure 2.16: Heteroaryl cyclopropyl ketone synthesis

Because thiophene is known for its stability in the presence of Lewis acids and usage in past protocols,[154] 2-thienyl cyclopropyl ketone **2-52** served as the main substrate for optimization using indium(III) catalysis previously reported by the France group for the alkenyl formal homo-Nazarov cyclization.[136] When we subjected **2-52** to 30 mol% $In(OTf)_3$, **2-53** formed with 88% yield in 2.5 hours (Table 2.1, entry 1), affirming our hypothesis for donor-acceptor-acceptor cyclopropanes as feasible participants in the heteroaromatic formal homo-Nazarov cyclization. Markedly, catalyst loading was lowered to 1 mol% and yielded 77% of the product with an increased reaction time of 6.5 hours (Table 2.1, entry 3). In the same manner, $InCl_3$ furnished the product, although the reaction time was longer (4.5 hours), and the yield was lower (78%) (Table 2.1, entry 4). In the end, 5 mol% $In(OTf)_3$ resulted in the 2,3-ringfused cyclohexanone **2-53** having a yield of 86%, a yield comparable to that of (achieved by) the 30 mol% loading (Table 2.1, entry 2). In order to improve the reaction outcomes, we examined the effects of $LiClO_4$ as an additive because previous protocols had successfully implemented the reagent in $Sc(OTf)_3$- and $In(OTf)_3$-catalyzed Friedel-Crafts acylations[155–157] and Nazarov cyclizations[120,122]. This proved to be futile since 1.0 equiv. of $LiClO_4$ with $InCl_3$ and $In(OTf)_3$ salts resulted in poor conversion. Ultimately, 5 mol% $In(OTf)_3$ in dichloromethane (DCM) at room temperature was chosen as the optimal condition.

Table 2.1: Reaction Optimization for Heteroaryl Cyclohexenones



Entry	LA Loading	Solvent	Temp.	Time (h)	Yield[a]
1	30 mol % $In(OTf)_3$	DCM	25 °C	2.5	88%
2	5 mol % $In(OTf)_3$	DCM	25 °C	4.5	86%
3	1 mol % $In(OTf)_3$	DCM	25 °C	6.5	77%
4	5 mol % $InCl_3$	DCM	25 °C	4.5	78%

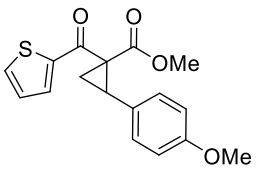
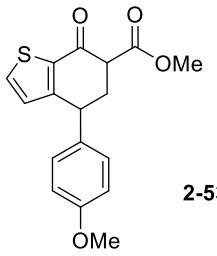
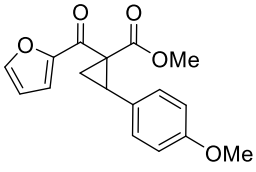
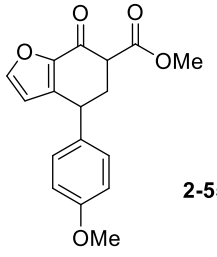
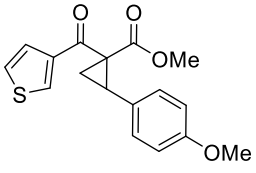
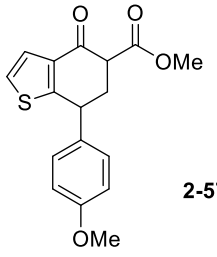
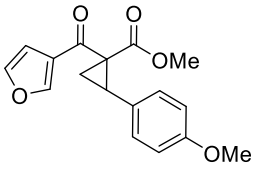
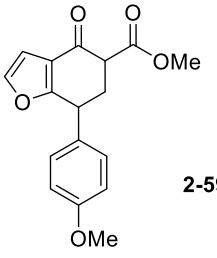
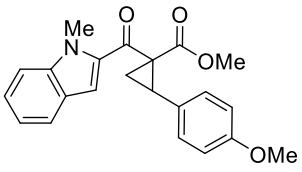
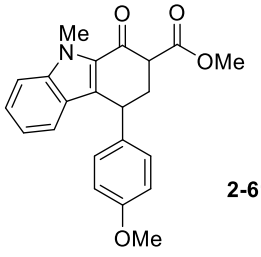
[a] Conversion ascertained by crude ^{1}H NMR. [b] Reaction stopped after the time indicated. [c] No reaction observed.

2.4 Results and Discussion

With the optimized reaction conditions established, we investigated 2- and 3-substituted heteroaryl cyclopropyl ketones for their reactivity for indium(III) catalysis to ascertain scope and reactivity limits. In order to probe the 2-position versus the 3-position for thiophene precursors **2-52** and **2-56**, we subjected 3-thienyl precursor **2-56** to the optimized conditions, which afforded cyclohexanone **2-57** in 73% yield with 1.7:1 *dr* (Table 2.2, entry 3). The diastereomeric ratios were based off of *cis/trans* isomers. Comparatively, this yield was lower than its 2-thienyl cogener **2-53** (86% with 1.5:1 *dr*) (Table 2.2, entry 1). Conversely, 3-furanyl substrate **2-58** (Table 2.2, entry 4) produced cyclohexanone **2-59** in 73% yield with 1.1:1 *dr* as opposed to its 2-substituted counterpart **2-55** in 67% yield with 1.1:1 *dr* (Table 2.2, entry 2). However, 2-substituted furyl precursor was heated to reflux in 1,2-dichloroethane at 84 ˚C because room temperature conditions gave a 28% yield with other side-products not observable at the elevated temperature. It is likely that the additional heat provided enough energy for the desired transition state barrier to be surpassed for the six-membered product. In the case of the 2-thienyl and 2-furyl

substrates, electrophilic aromatic substitution readily occurs at the 3-position, which is typically uncommon for these heteroaromatics, but not for systems with this particular arrangement. The *N*-methyl-2-indolyl cyclopropane **2-60** and *N*-methyl-3-indolyl **2-64** substrates formed their corresponding annulated products **2-61** and **2-62** in 63% yield with 1.2:1 *dr* (Table 2.2, entry 5) and 61% yield with 1.2:1 *dr* (Table 2.3, entry 2) respectively.

Table 2.2: Heteroaromatic Formal Homo-Nazarov Cyclizations

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **2-52**	 **2-53**	4.5	86%	1.5:1
2[d]	 **2-54**	 **2-55**	6.0	67%	1.1:1
3	 **2-56**	 **2-57**	5.0	73%	1.7:1
4	 **2-58**	 **2-59**	6.0	73%	1.1:1
5	 **2-60**	 **2-61**	5.5	63%	1.2:1

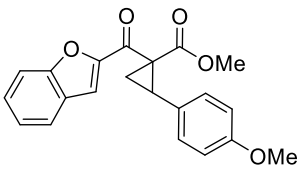
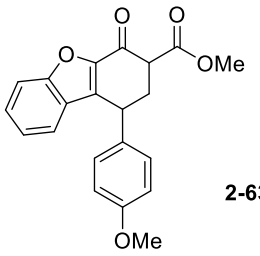
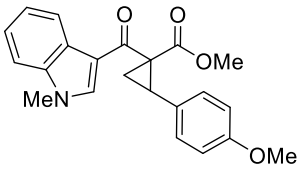
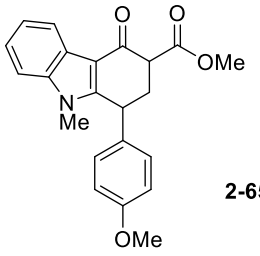
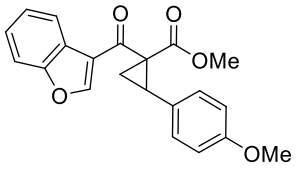
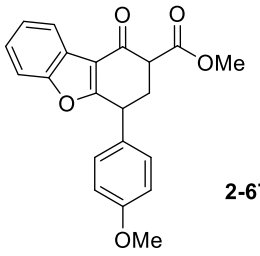
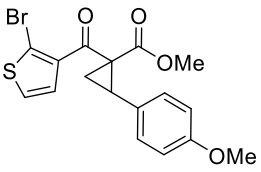
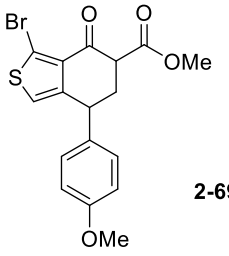
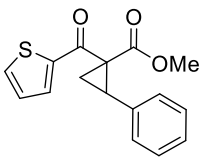
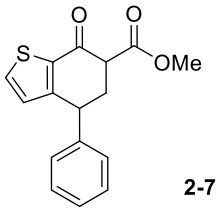
[a] Reactions run with 1.0 equiv. of the precursor and 5 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture. [d] Reaction performed in 1,2-dichloroethane at 84 °C.

To our delight, 2-benzofuran **2-62** cyclized in 91% yield with 1.4:1 *dr* (Table 2.3, entry 1), and 3-benzofuran **2-66** cyclized in 71% yield with 1.2:1 *dr* (Table 2.3, entry 3). Attributable

to mild reaction conditions, competing polymerization of the benzofurans was minimized or avoided, highlighting the versatility of our protocol when matched to other reports in which benzofuran-derived substrates were unsuccessful for the ring closure under acidic conditions.

Until this work, 2,3-ring-fused heteroaromatics were investigated only for formal homo-Nazarov ring enlargement. According to our postulation, we envisioned that 3,4-heteroaryl cyclohexanones could be formed as well. Therefore, we designed a 3-substituted cyclopropyl ketone with the 2-position blocked, as in 2-bromo thienyl cyclopropane **2-68,** such that the 4-position is available for electrophilic attack. As anticipated, 3,4-fused heteroaryl cyclohexanone **2-69** formed in 56% yield (Table 2.3, entry 4) and represents the first example of its kind using a donor-acceptor-acceptor cyclopropane precursor.

Table 2.3: Heteroaromatic Formal Homo-Nazarov Cyclizations

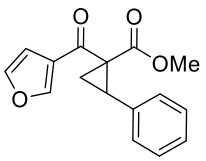
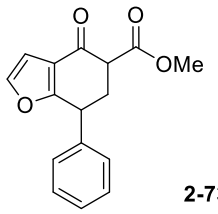
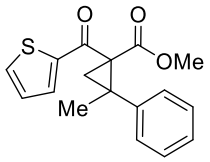
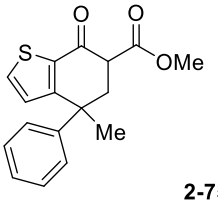
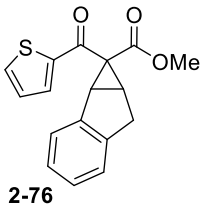
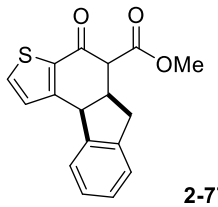
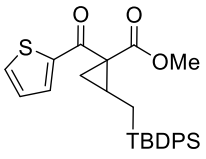
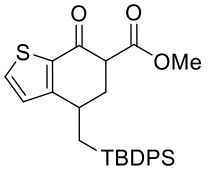
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **2-62**	 **2-63**	5.0	91%	1.4:1
2	 **2-64**	 **2-65**	6.0	61%	1.2:1
3	 **2-66**	 **2-67**	5.5	71%	1.2:1
4	 **2-68**	 **2-69**	8.0	56%	--[e]
5[d]	 **2-70**	 **2-71**	6.0	81%	2.3:1

[a] Reactions run with 1.0 equiv. of the precursor and 5 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture. [d] Reaction performed in 1,2-dichloroethane at 84 °C. [e] 2:1 mixture of keto and enol forms.

Continuing to expand the reaction scope, we examined donor substituents which stabilize positive charge build-up. Phenyl precursors **2-70** and **2-72** formed ring-fused cyclohexanones **2-71** and **2-73** in 81% with 2.3:1 *dr* and 83% yield with 1.2:1 *dr*,

respectively (Table 2.3, entry 5 and Table 2.4, entry 1), with the elevated temperature. When we increased the donation with an additional *gem*-methyl group at the benzylic position to form a tertiary stabilized center, as in α-methyl styrene derivative **2-74**, the **2-75** product was formed in 71% yield with 2.0:1 *dr* (Table 2.4, entry 2) under standard conditions (no heat) with a shorter reaction time (4.5 hours). Presumably, in addition to the electronic effect described, a steric effect could have also contributed to the cyclization result, unlike the phenyl substrate **2-70** which required heating for product formation. Likewise, indanyl precursor **2-76** afforded tetracycle **2-77** in 87% yield (Table 2.4, entry 3). Enlightened by Yadav's report that silyl moieties provide additional stability through the donating β-silyl effect for the formal homo-Nazarov cyclization,[106] we synthesized TBDPS substrate **2-78**; the methylsilyl cyclopropane furnished **2-79** in 71% yield with 2.4:1 *dr* (Table 2.4, entry 4).

Table 2.4: Effects of Cyclopropyl Substituents on the Cyclization

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1[d]	 **2-72**	 **2-73**	6.0	83%	1.2:1
2	 **2-74**	 **2-75**	4.5	71%	2.0:1
3	 **2-76**	 **2-77**	6.0	87%	--[e]
4	 **2-78**	 **2-79**	6.0	71%	2.4:1

[a] Reactions run with 1.0 equiv. of the precursor and 5 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture. [d] Reaction performed in 1,2-dichloroethane at 84 °C. [e] 2:1 mixture of keto and enol forms.

After demonstrating that heteroaryl donor-acceptor-acceptor cyclopropanes are adequate reactants for the homo-Nazarov cyclization in which disparate heteroaromatic ring-fused cyclohexanones are generated, we sought to decrease the number of steps for product formation. Since the Rh(II)-catalyzed cyclopropanation and In(III)-catalyzed ring enlargement readily proceed in dichloromethane at room temperature, we explored a one-pot procedure by conducting two control reactions. We stirred α-diazoester **2-80** with 5 mol% $In(OTf)_3$; the diazo was stable and degradation was minimal in the presence of the

Lewis acid. Then, we monitored 4-methoxy styrene stability with Rh_2esp_2 and $In(OTf)_3$. For an active ~20 mol% indium catalyst loading, 1 mol% of Rh_2esp_2 and 0.2 mol% of $In(OTf)_3$ in dichloromethane at 0 °C as the initial reaction conditions gave a 56% yield of the desired ring-fused cyclohexanone **2-82**, which is higher than the two-step process and equates to a yield of approximately 75% for each individual step (Figure 2.17).

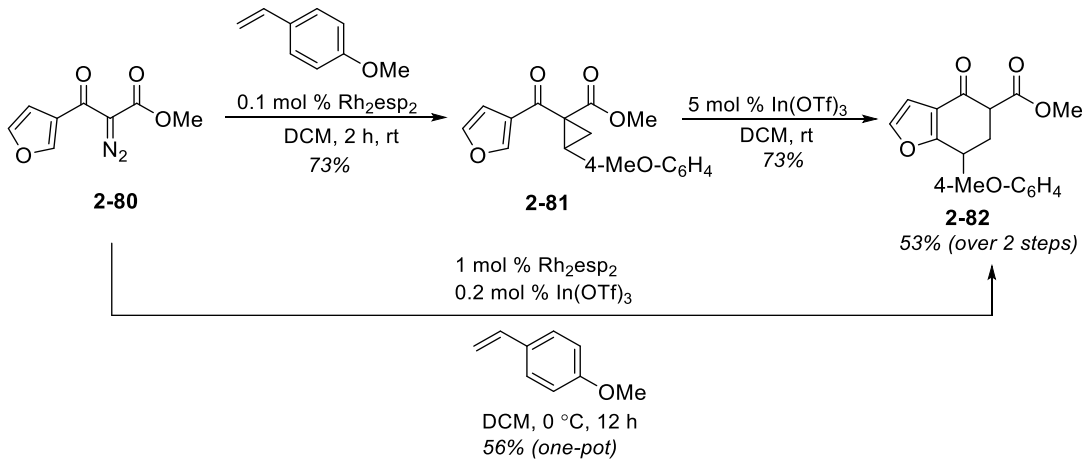


Figure 2.17: One-pot procedure for the heteroaromatic formal homo-Nazarov cyclization

2.5 Conclusion

In summary, the original hypothesis for the heteroaromatic formal homo-Nazarov reaction using donor-acceptor-acceptor cyclopropanes was verified through experimental results. Heteroaryl donor-acceptor-acceptor cyclopropanes gave better yields (56-91%) under milder conditions to form functionalized heteroaryl ring-fused cyclohexenones. Furthermore, we demonstrated the viability of a one-pot protocol. As a consequence of the ubiquity of heteroaromatics in natural products and medicinally relevant compounds, this efficient methodology could be utilized and included in synthetic routes for compounds containing fused heteroaromatic cyclohexenones.

2.6 Research Participants

This research was conducted with Dr. Lien H. Phun and Dr. Dadasaheb V. Patil. They made the precursors and the final products.

This work was published in *Organic Letters*: Phun, L. H.; Patil, D. V.; Cavitt, M. A.; France, S. A Catalytic Homo-Nazarov Cyclization Protocol for the Synthesis of Heteroaromatic Ring-Fused Cyclohexanones. *Org. Lett.* **2011**, *13*, 1952–1955.

2.7 Experimental Information

2.7.1 Synthetic Methods for Heteroaromatic Cyclohexenone Preparation

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, t = triplet, bt = broad triplet, td = triplet of doublets, q = quartet, qd = quartet of doublets, qn = quintet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained with a VG-70SE instrument.

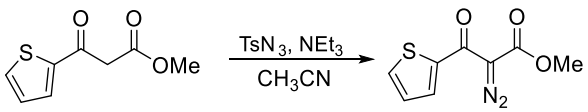
Chromatographic purification was performed as flash chromatography using Dynamic Adsorbents silica gel (32-65μm), using the solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography technical grades solvents were used. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating.

Yields refer to isolated yields of analytically pure material unless otherwise noted. All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-Dichloroethane and dichloromethane were purified by distillation from calcium hydride under N_2 prior to

use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. Lithium bis(trimethylsilyl)amide (LiHMDS) was purchased from Sigma-Aldrich as a 1.0 M solution in THF. *N*-Butyllithium was purchased from Sigma-Aldrich as a 2.5 M solution in hexanes. *T*-Butyllithium was purchased from Sigma-Aldrich as a 1.0 M solution in hexanes. Nitromethane was distilled over CaH_2 and stored under nitrogen under 4 Å molecular sieves. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted. Compounds **2-49** were made with a modified Warner's method.[158] β-Ketoester for compound **2-58** was prepared with a modified version of Frontier's method.[120] Compound **2-66** was prepared with Kanda's protocol.[159] *Compounds synthesized and not reported in the literature until our publication are listed below. Dr. Lien H. Phun and Dr. Dadasaheb V. Patil synthesized the precursors as well.*

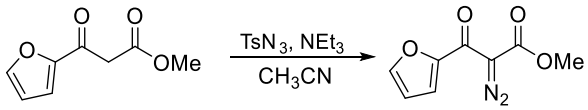
2.7.2 General Procedure for α-Diazo Esters

In a flame dried flask containing a solution of the β-ketoester in acetonitrile (0.2 M), NEt_3 (1.2 equiv.) was added. After vigorous stirring for 5 minutes, tosyl azide (1.2 equiv.) was added, and the reaction was stirred for 3 hours. After complete disappearance of the starting material, the mixture was concentrated *in vacuo* and purified by column chromatography, which furnished the desired diazo compound.[136]

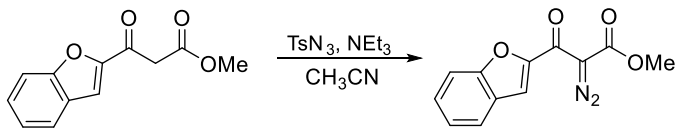


Methyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate (2-50a): According to the general procedure, to a solution of the 2-thienyl β-ketoester (1.50 g, 8.14 mmol) in acetonitrile, NEt_3 (1.4 mL, 9.77 mmol) and tosyl azide (1.93 g, 9.77 mmol) were added. Column chromatography (10% EtOAc/Hex, R_f= 0.25) furnished the diazo as a bright yellow oil

(1.20 g, 69.5%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 8.06 (dd, *J* = 3.91, 1.12 Hz, 1H), 7.66 (dd, *J* = 4.99, 1.12 Hz, 1H), 7.26 (s, 1H), 7.12 (dd, *J* = 4.98, 3.92 Hz, 1H), 3.92-3.82 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 176.3, 161.1, 141.2, 133.8, 127.6, 52.2 ppm. IR: 3100 (m), 2947 (m), 2146 (s, N_2 stretch), 1721 (s), 1712 (s), 1692 (s), 1617 (s), 1604 (s), 1433 (m), 1299 (s) cm^{-1}. HRMS(ESI) M/Z+ Calc. 210.0099, Obs. 210.0095.



Methyl 2-diazo-3-(furan-2-yl)-3-oxopropanoate (2-50b): According to the general procedure, to a solution of the 2-furyl β-ketoester (0.75 g, 4.46 mmol) in acetonitrile NEt_3 (0.75 mL, 5.35 mmol) and tosyl azide (1.06 g, 5.35 mmol) were added. Column chromatography (10% EtOAc/Hex, R_f = 0.20) gave the diazo as a bright yellow oil (0.614 g, 71.0%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.62-7.44 (m, 1H), 7.28-7.20 (m, 1H), 6.72-6.19 (m, 1H) 3.90-3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 170.7, 161.5, 150.4, 146.0, 145.9, 119.4, 112.3, 52.5. IR: 3102 (w), 2953 (w), 2140 (s, N2), 1717 (s), 1584 (s), 1514 (m), 1434 (m), 1410 (w) cm^{-1}. HRMS(ESI) M/Z+ Calc. 194.0328, Obs. 194.0323.

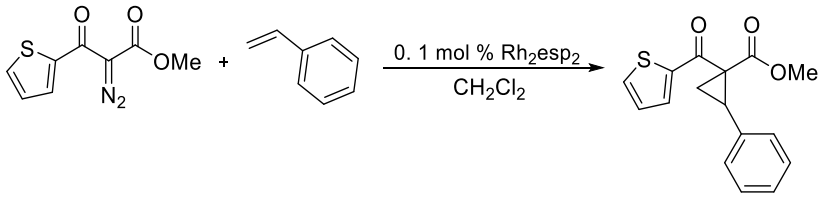


Methyl 3-(benzofuran-2-yl)-2-diazo-3-oxopropanoate (2-50c): According to the general procedure, to a solution of the 2-benzofuryl β-ketoester (0.76 g, 3.50 mmol) in acetonitrile NEt_3 (0.60 mL, 4.22 mmol) and tosyl azide (0.81 g, 4.22 mmol) were added. Column chromatography (10% EtOAc/Hex, R_f = 0.20) afforded the diazo as a bright yellow oil (0.48 g, 57.0%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 8.77 (s, 1H), 8.17 (ddd, *J* = 4.15, 2.91, 0.69 Hz, 1H), 7.83 (d, *J* = 8.34 Hz, 1H), 7.65-7.45 (m, 1H), 7.42-7.28 (m, 1H), 3.93-3.80 (m, 1H) ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 172.1, 161.4, 155.0, 150.5, 128.3, 126.8,

123.9, 123.4, 115.1, 112.2, 52.6. IR: 3129 (w), 2950 (w), 1737 (s), 1671 (s), 1555 (s), 1446 (m), 1316 (w), 1246 (m), 1123 (s), 1088 (m) cm^{-1}. HRMS(ESI) M/Z+ Calc. 244.0484, Obs. 244.0479.

2.7.3 General Procedure for Heteroaryl Cyclopropyl Ketones

In a flame dried flask containing a solution of Rh_2esp_2 (0.1 mol%) in DCM (0.2 M) at 0 °C the corresponding alkene (1.0 equiv.). After stirring the catalyst and olefin for 5 minutes, a solution of the α-diazo ester (0.2 M) was added in one shot, and the mixture was then stirred for an additional 10 minutes at 0 °C. At this time, the ice bath was removed, and the reaction was allowed to warm up to room temperature. After two hours, the reaction was quenched with saturated thiourea (aqueous) and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3x). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated, and column chromatography afforded the desired cyclopropyl heteroaryl ketones.



Methyl 2-phenyl-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (2-70): According to the general procedure, to a solution of Rh_2esp_2 (0.83 mg, 0.1 mol%) in dichloromethane, styrene (0.113 g, 1.09 mmol) was added, followed by a solution of the α-diazo ester (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **2-70** as a solid (0.198 g, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 7.72 (d, *J* = 1.13 Hz, 1H), 7.71 (d, *J* = 1.13 Hz, 1H), 7.67 (d, *J* = 1.12 Hz, 1H), 7.65 (d, *J* = 1.12 Hz, 1H), 3.49 (dd, *J* = 8.98, 8.32 Hz, 1H), 3.30 (s, 3H), 2.38 (dd, *J* = 8.10, 5.05 Hz, 1H), 1.67 (dd, *J* = 9.17, 5.04 Hz, 1H) ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm 186.2, 168.7, 143.0, 134.7, 133.9, 132.5, 129.0, 128.1, 127.5, 127.2, 52.3,

42.5, 30.4, 19.4 ppm. IR: 3036 (w), 2947 (w), 1745 (s), 1656 (s), 1409 (s), 1271 (s), 1141 (s), 1197 (s), 1040 (s), 957 (s) cm^{-1}. HRMS(ESI) M/Z+ Calc. 286.0670, Obs. 286.0697.

2.7.4 Catalyst Screening for Heteroaromatic Cyclohexenone Formation

To a flame dried flask containing the indium catalyst with the appropriate loading (1, 5, or 30 mol%) in anhydrous CH_2Cl_2 (0.2 M) was added cyclopropane **2-52**. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4, and column chromatography (10% EtOAc/Hex) provided **2-53**.

2.7.5 General Procedure for the Lewis Acid-catalyzed Formal Homo-Nazarov Cyclization for Heteroaromatic Cyclopropyl Ketones

To a flame dried flask containing $In(OTf)_3$ (5 mol%) in anhydrous CH_2Cl_2 (0.2M) was added the corresponding cyclopropane. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2 and dried with Na_2SO_4, and column chromatography provided the fused heteroaromatic cyclohexanones.

Dr. Lien H. Phun and Dr. Dadasaheb V. Patil synthesized the cyclized products.

CHAPTER 3 IN(III)-CATALYZED RING-OPENING/FRIEDEL-CRAFTS ALKYLATION SEQUENCE FOR HYDROPYRIDO[1,2-*A*]INDOLE ASSEMBLY

The hydropyrido-[1,2-*a*]indole core, a 6-5-6 tricycle, is arguably one of the most privileged scaffolds in the indole alkaloid family. This 6-5-6 indolic skeleton and its C(6)-oxidized cogeners **3-7** are common structural motifs in natural products, marketed therapeutics, and other useful compounds (Figure 3.1).[142,148,160–167] Organic chemists have devised numerous approaches and strategies to specifically construct the indole derivatives.[168–172] Typically, routes append a piperidine ring onto an indole framework to form the hydropyrido-[1,2-*a*]indole tricycle through the following synthetic means:[173] acid-promoted cyclizations,[174,175] cycloadditions,[176–180] Pauson-Khand reactions,[181] radical cyclizations,[162,182–186] nucleophilic substitutions,[187,188] transition metal-catalyzed C-C bond formations,[189–195] transition metal-catalyzed oxidative C-H/N-H cyclizations,[196] condensations,[197–201] and domino reactions.[173] Depictive examples of each reaction type are presented below.

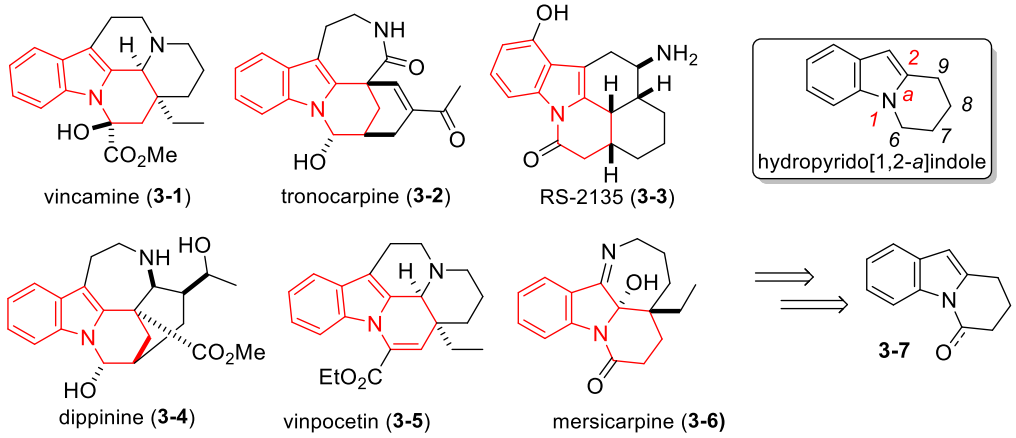


Figure 3.1: Hydropyrido[1,2-*a*]indole core in natural products

3.1 Common Transformations for Pyridoindole Formation

In 2004, Letica Perez-Serrano et al. published the first examples of using the Pauson-Khand reaction for indole chemistry in order to synthesize diverse tetracyclics **3-9**, **3-10**, and **3-11** in a small number of steps (Figure 3.2). With $Co_2(CO)_8$ as the active catalyst over molecular sieves, 1,2-fused, 2,3-fused and 3,3a,4-fused systems were constructed. Various reaction conditions were explored to give good yields of intermediates potentially applicable for natural alkaloid synthesis and derivatization.[181]

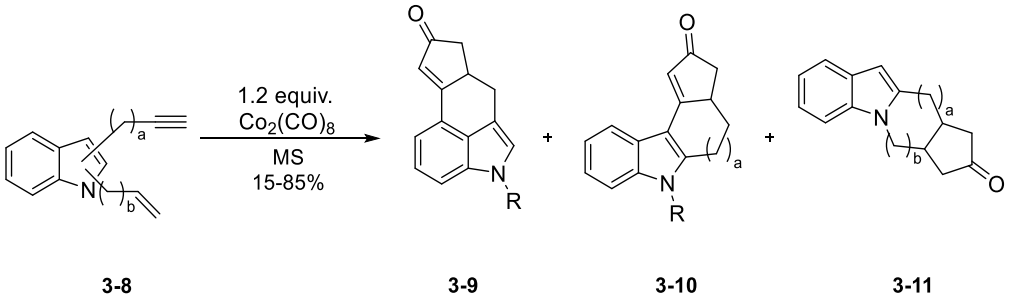


Figure 3.2: Pauson-Khand ring closure for pyridoindole derivatives

Haider and Käferböck published a method on the construction of annulated carbazoles **3-13** by intramolecular, inverse electron demand Diels-Alder (IEDDA) reactions in 2004 (Figure 3.3). Educts **3-12** were synthesized and heated in 1,3,5-triisopropylbenzene (TIPB) at 232 °C for 15 hours to 14 days. After [4+2] cycloaddition, nitrogen extrusion via cycloreversion, and dehydrogenation, products were furnished in 8-75% yield.[176]

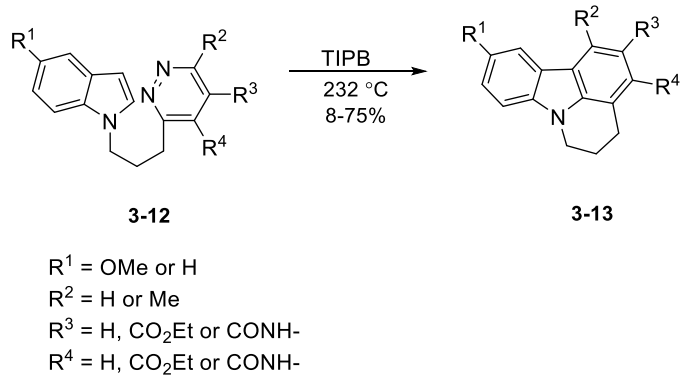


Figure 3.3: Inverse-electron-demand Diels-Alder reaction for annulated carbazoles

In 2006, Tanaka et al. synthesized 3-anilino-4-(3-indolyl)maleimide derivative **3-16** for inhibition of protein kinase Cβ (PKCβ) for diabetes studies (Figure 3.4). To obtain a more potent and selective inhibitor, they assembled conformationally-restricted tetrahydropyrido[1,2-*a*]indole **3-16**. Acetal **3-14** underwent an acid-catalyzed ring closure to form pyrido[1,2-*a*]indole **3-15** in 95% yield after trifluoroacetic acid (TFA) exposure in water and hydrogenation with palladium on carbon.[174]

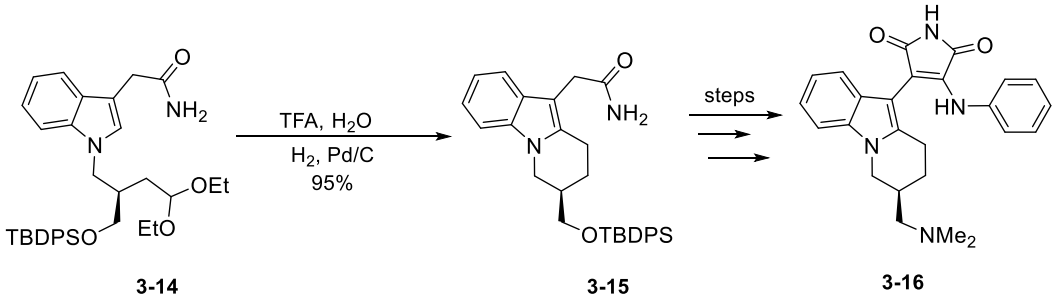


Figure 3.4: Oxa-Pictet-Spengler-type reaction for tetrahydropyrido[1,2-*a*]indole synthesis

Khdour et al. designed a new methide reductive alkylating agent **3-17** to study quinone methide chemistry in 2006 (Figure 3.5). Cyclopropyl quinone methide **3-17** was formed from pyrido[1,2-*a*]indole **3-18**. In the synthetic route, one of the important steps to generating the pyrido[1,2-*a*]indole arose from condensation of indole **3-19** under basic conditions with γ-butyrolactone followed by acidification with polyphosphoric acid to

afford **3-20**, a necessary precursor for the synthesis of **3-18**. The condensation provided a direct route for appending the six-membered piperidine ring to the indole.[198]

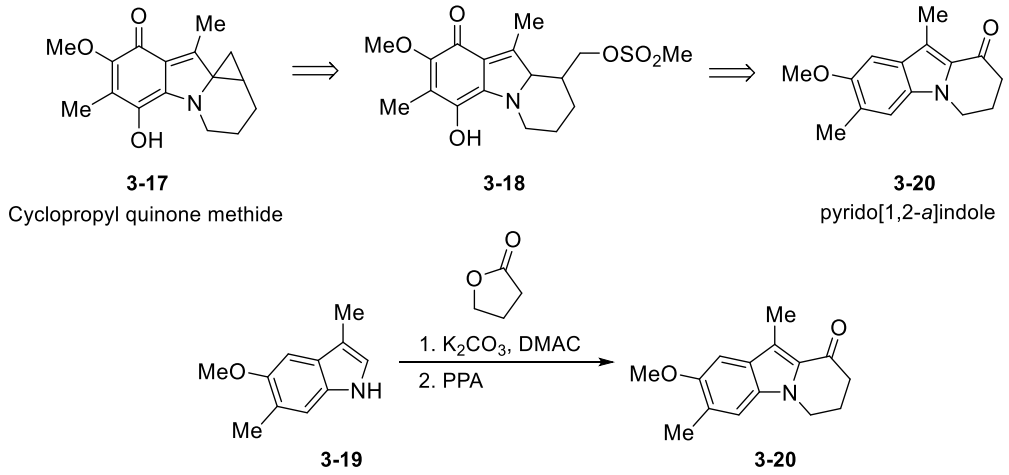


Figure 3.5: Intermolecular condensation for cyclopropyl quinone methide synthesis

In 2008, Kerr reported the first total synthesis of (±)-mersicarpine **3-23**. In order to assemble the hydropyrido[1,2-*a*]indole framework, he implemented a malonic radical ring closure (Figure 3.6). **3-21** was subjected to $Mn(OAc)_3$ in acetic acid at reflux after 1,4-addition to give a 60% yield of **3-22**. Other substrates and conditions were examined for optimization of the radical cyclization. With this cyclization method, Kerr and co-workers were able to rapidly assemble the desired skeleton for the natural product.[162]

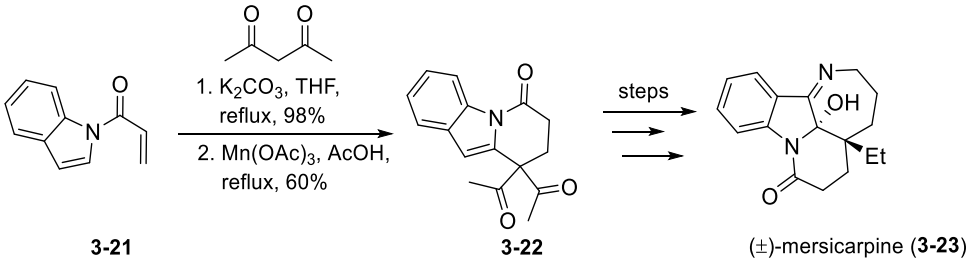


Figure 3.6: Kerr's Mn(III)-radical cyclization for the synthesis of (±)-mersicarpine

In the same year as Kerr's mersicarpine report, Morales and Pagenkopf published the shortest total synthesis of (±)-goniomitine **3-26** using a donor-acceptor cyclopropane [3+2] cyclization to give 5.2% yield of the target in 17 steps (Figure 3.7). This report

highlighted the fact that microwaves could be used to enhance reactivity to decrease reaction times. In order to form tetracycle **3-25**, Kerr subjected nitrile **3-24** to $POCl_3$ in toluene followed by sodium borohydride in methanol. Nitrile **3-25** was afforded in 84% yield.[187]

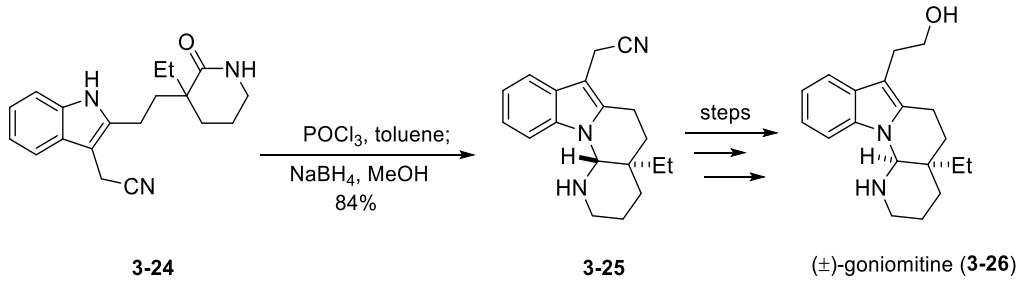
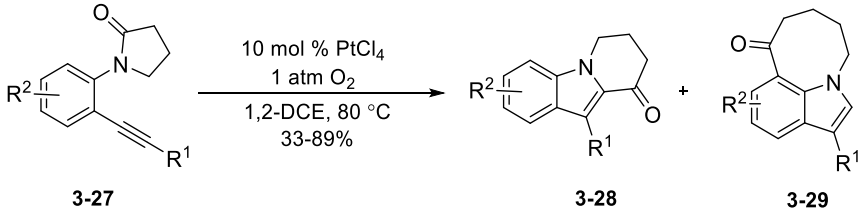


Figure 3.7: Morales and Pagenkopf's nucleophilic substitution for tetracycle formation

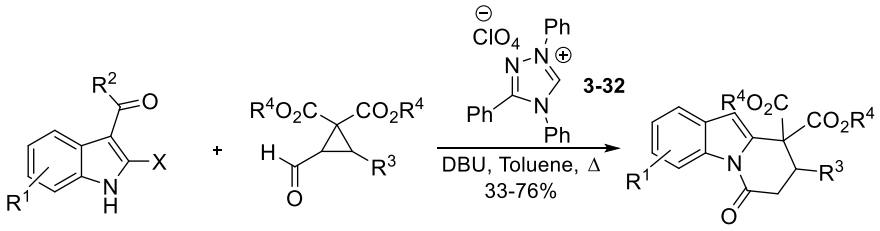
In 2008, Li et al. published a protocol for the synthesis of fused substituted indoles from *N*-(2-alkynylphenyl)lactams **3-27** by using a $PtCl_4/PtCl_2$-catalyzed cylcoisomerization with molecular oxygen in 1,2-dichloroethane at reflux (Figure 3.8). Various moieties were tolerated at the terminus of the γ-lactam precursors and benzene ring to furnish differing sizes and substitutions for the indoles in 33-89% yield. For the transformation, a Pt-catalyzed cyclization, 1,2-acyl migration, and 1,2-migration of R^1 to the platinum carbenoid formed indoles **3-28** and **3-29**.[189]



R^1 = H, Me, cyclopropyl, $(CH_2)_3$
$(CH_2)_3OBn$, Ph, 4-OMe-C_6H_4,
4-CHO-C_6H_4, $CH{=}CH(CH_2)_3CH_3$
or *n*-Bu
R^2 = H, 6-OMe, 4-Br or 4-CO_2Et

Figure 3.8: $PtCl_4/PtCl_2$-catalyzed cycloisomerization for hydropyrido[1,2-*a*]indole synthesis

In 2009, Du et al. reported a unique *N*-heterocyclic carbene-catalyzed domino cyclization to generate 6-5-6 tricyclic hydropyrido[1,2-*a*]indoles (Figure 3.9). Using formylcyclopropane 1,1-diesters **3-31**, they formed hydropyrido[1,2-*a*]indoles **3-33** from halogenated indoles **3-30** and *N*-heterocyclic carbene **3-32** by using a domino ring-opening/redox amidation/cyclization sequence. Aryl and alkyl groups were tolerated about the cyclopropane ring, and halogens, donating alkyl and methoxy groups were substituted on the indole's benzene ring. Although the conversions were high for **3-30**, the isolated yields were lower (33-76%).[173]

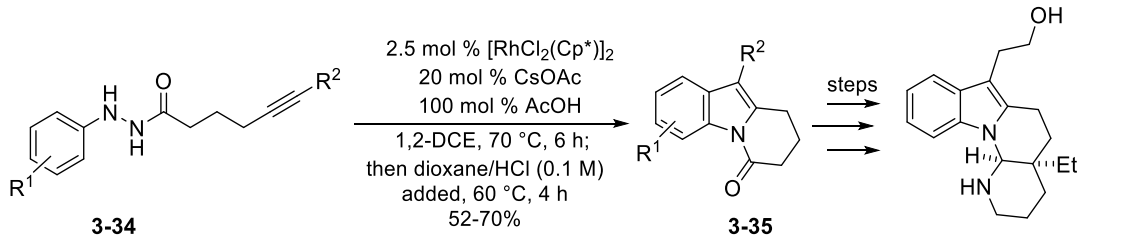


R^1 = H, 5-Cl, 5-Br, 5-I, 6-Cl, 5-Me, 5-Et, 5-*i*-Pr, 5-OMe, 7-Me, 4,6-Me_2,
R^2 = H, OMe or CO_2Me
R^3 = H, Me or Ph
R^4 = Et, Me or *i*-Pr
X = Br or Cl

Figure 3.9: Wang's *N*-heterocyclic carbene-catalyzed domino ring-opening/redox amidation/cyclization reaction

In 2015, Zhou et al. published a one-pot rhodium(III)-catalyzed intramolecular redox-neutral annulation of tethered alkynes formed pyrido[1,2-*a*]indoles **3-35** (Figure 3.10). Alkyne **3-34** was treated with a dirhodium catalyst with cesium acetate, acetic acid, and 1,2-dichloroethane at 70 ˚C reacted for 6 hours; then, dioxane/HCl mixture was added and reacted at 60 ˚C for an additional 4 hours to give pyridoindoles **3-35** in 52-70% yield. This redox-neutral protocol utilized mild reaction conditions and encompassed a broad substrate scope since electron-releasing and electron-accepting groups were well tolerated. Without any oxidant, the reactivity occurs with a reversal in regioselectivity for the

pyrido[1,2-*a*]indole systems. To demonstrate that the method was translational, the group applied the rhodium(III)-catalyzed C-H activation/annulation protocol for the formal total synthesis of (±)-goniomitine **3-26**.[196]



R^1 = H, 4-Me, 4-Br, 3-Me, 3-Cl or 2-F

R^2 = 2-F-C_6H_4, 2-Me-C_6H_4, 3-Me-C_6H_4, 3-CO_2Me-C_6H_4, 3-Cl-C_6H_4, 4-CF_3-C_6H_4, 4-OMe-C_6H_4, $(CH_2)_2$OBn or Ph

Figure 3.10: Li's rhodium(III)-catalyzed redox-neutral annulation protocol

3.2 Hypothesis and Synthetic Rationale for Hydropyrido[1,2-*a*]indole Synthesis

Many of the strategies above require multistep processes to obtain the hydropyrido[1,2-*a*]indole framework because the reaction scope maybe limited due to the reagents employed for the transformation. Therefore, the discovery of a new, efficient method for a facile chemical process for the construction of hydropyrido[1,2-*a*]indoles is a formidable challenge for synthetic chemists. From our previous protocols, we envisaged the rapid formation of the 6-5-6 tricycle using donor-acceptor-acceptor and donor-donor-acceptor-acceptor cyclopropanes.

In a previous publication, Patil et al. disclosed the synthesis of methylene cyclohexenols and cyclohexenones in good to high yields (up to 93%) from alkenyl cyclopropyl ketones that bore an additional α-coordinating electron withdrawing group (such as an ester) as reactive donor-acceptor-acceptor cyclopropanes for the formal homo-Nazarov cyclization (Figure 3.11, Scheme 1).[136] Later, the France group divulged another

Lewis acid-catalyzed approach for heteroaromatic ring-fused cyclohexanones in moderate to good yields (56-91%) via the formal homo-Nazarov cyclization by using heteroaryl cyclopropyl ketones (Figure 3.11, Scheme 2).[137]

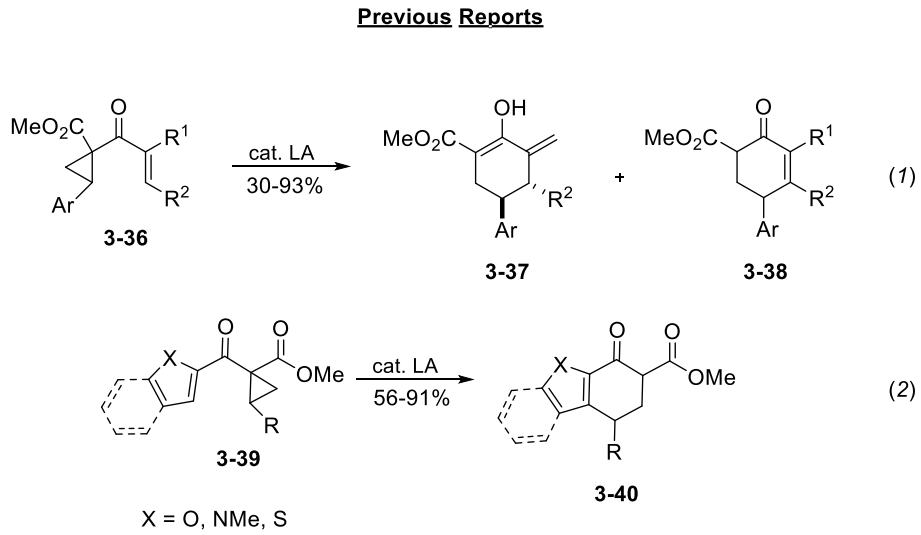


Figure 3.11: France's Lewis acid-catalyzed cyclopropane ring-opening/cyclization earlier reports

As a direct result of this unique reactivity for cyclopropyl ketone donor-acceptor-acceptor cyclopropanes, the synthesis of hydropyrido[1,2-*a*]indoles **3-42** was envisioned to arise from a Lewis acid-catalyzed ring enlargement (Figure 3.12). We aimed to construct hydropyrido[1,2-*a*]indoles from indolyl-donor-acceptor-acceptor cyclopropanes **3-41** such that the indole would act as a π-nucleophile upon Lewis acid activation of the cyclopropanes. Therefore, cyclopropane bond scission would afford an aza-cationic intermediate to give annelated six-membered lactams. Precursor **3-43** was used as the model substrate. We supposed that the *p*-methoxyaryl group would stabilize charge buildup at the benzylic position upon ring-opening. If bond scission occurred heterolytically, as in Figure 3.12, the indole would participate as a π-nucleophile[202] for an intramolecular Friedel-Crafts alkylation.[123] Subsequent rearomatization would form **3-42**, incorporating a nitrogen atom into the newly formed ring, generating the lactam functionality of hydropyrido[1,2-*a*]indole-6(7*H*)-ones **3-42**. Given our previous successful protocols, we

anticipated high yields, mild reaction conditions, and variety in functionalization. We synthesized precursors, optimized the reaction conditions, and determined the reaction scope.

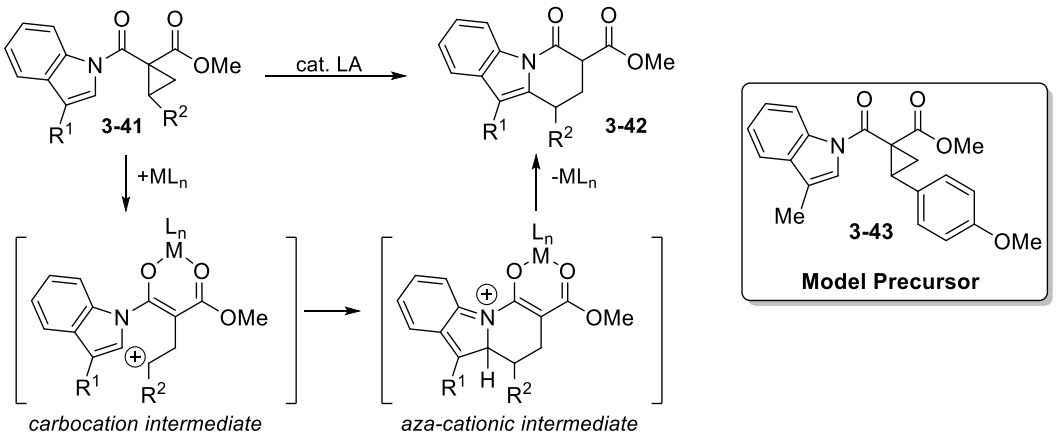


Figure 3.12: Hypothesis and mechanistic rationale for the formation of hydropyrido[1,2-*a*]indoles

3.3 Precursor Assembly and Reaction Conditions for Hydropyrido[1,2-*a*]indoles

We prepared the cyclization precursors in three steps starting with commercially-available indoles **3-44** and methyl malonyl chloride (MMC). *N*-Acylation under basic conditions afforded β-amidoesters **3-45**. Subsequent diazo transfer[62,152,153] gave 1,3-dicarbonyl compound **3-46**. Rh(II)-catalyzed cyclopropanation[62,153] with Rh_2esp_2 in the presence of the requisite alkene afforded methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates **3-47** in good yields (up to 70%) over three steps. Since $In(OTf)_3$ was an effective catalyst for ring-opening cyclizations in our previous report, 30 mol% $In(OTf)_3$ in dichloromethane at room temperature was implemented as the initial reaction condition. To our delight, **3-48** was formed in 99% yield with 2.6:1 *trans:cis dr* (as determined by NMR spectroscopy) in two hours (Table 3.1, entry 1).

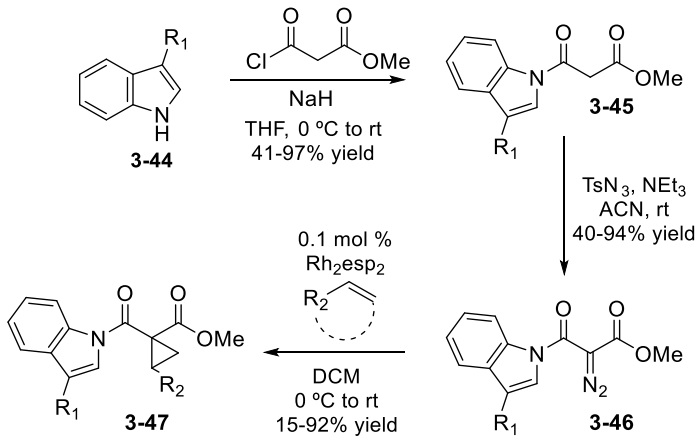


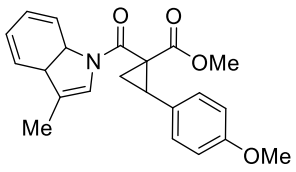
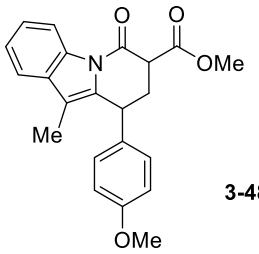
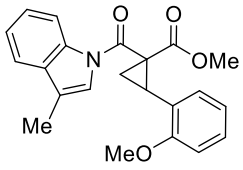
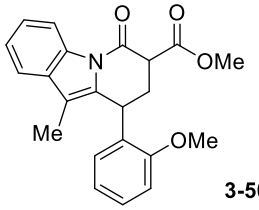
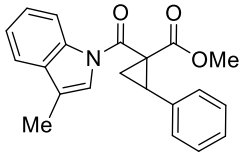
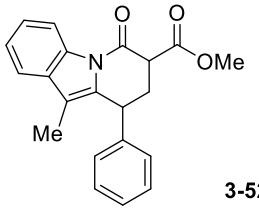
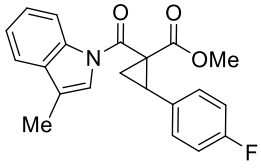
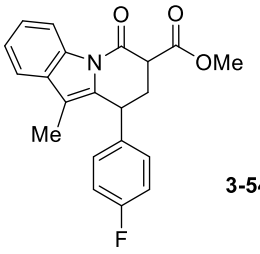
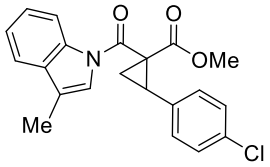
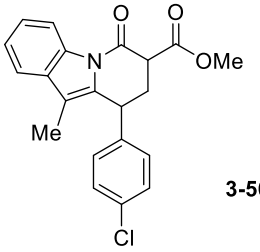
Figure 3.13: Precursor assembly for hydropyrido[1,2-*a*]indoles

3.4 Results and Discussion

To probe electronic effects, we examined differing donors and electron-withdrawing moieties about the aryl ring of the cyclopropane. Like precursor **3-43**, 2-methoxy phenyl precursor **3-49** provided **3-50** in 95% yield with 3.2:1 *dr* (*trans:cis* ratio) (Table 3.1, entry 2). When phenyl derivative **3-51** was subjected to the same reaction conditions at room temperature, starting material was recovered after t>24 hours, and none of the desired product **3-52** was formed. Upon reflux in 1,2-dichloroethane with 30 mol% $In(OTf)_3$, **3-51** furnished **3-52** in 52% yield with 2.6:1 *dr* (Table 3.1, entry 3). Other withdrawing-substituted precursors **3-53**, **3-55**, and **3-57** did not cyclize at room temperature either, but the desired product was observed in 1,2-dichloroethane after reflux. 4-Fluorophenyl **3-53** and 4-chlorophenyl **3-55** cyclopropanes gave tricycles **3-54** and **3-56** in 48% yield with 2.6:1 *dr* and 50% yield with 1.9:1 *dr*, respectively (Table 3.1, entries 4 and 5). 4-Nitro derivative **3-57** formed trace amounts of cyclized product **3-58** as determined by crude ^{1}H NMR (Table 3.2, entry 1). From these observations, *ortho*- and *para*-substituted donors are favorable substituents for the ring-opening/Friedel-Crafts alkylation sequence. As we anticipated, deactivating, electron-withdrawing substituents, viz. fluoro, chloro, and nitro had lower yields, whereas the activating substituents (*o*-and-

p-methoxy subunits) have a higher yields and a greater stabilizing effect. Some of these results reflect the stabilities of benzylic carbocations.[203,204] Although nitro is too withdrawing, the fluoro and chloro product yields are reasonable, and these halogens provide a chemical handle for further derivatization.

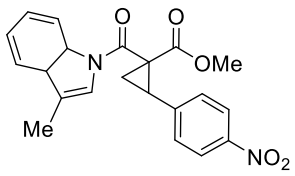
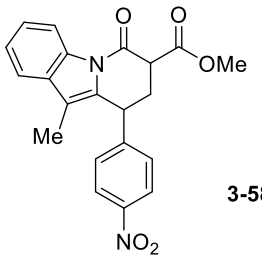
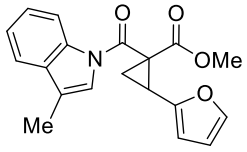
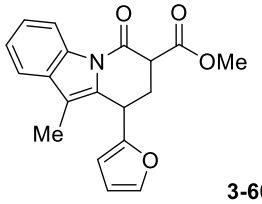
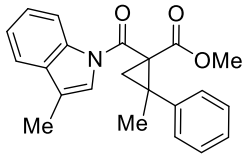
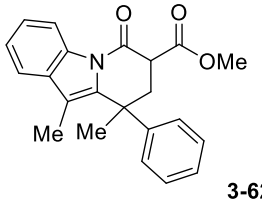
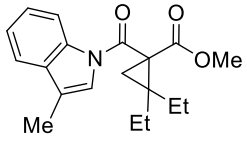
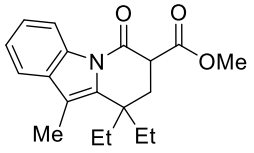
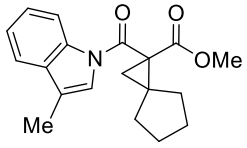
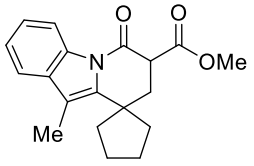
Table 3.1: Electronic Effects with Differing Benzenoids

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **3-43**	 **3-48**	2.0	99%	2.6:1
2	 **3-49**	 **3-50**	3.0	95%	3.2:1
3[d]	 **3-51**	 **3-52**	8.0	52%	2.6:1
4[d]	 **3-53**	 **3-54**	8.0	48%	2.6:1
5[d]	 **3-55**	 **3-56**	12.0	50%	1.9:1

[a] Reactions run with 1.0 equiv. of the precursor and 30 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^{1}H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratios. [d] Reaction performed in 1,2-dichloroethane at 84 °C. [e] Relative configurational assignment not determined. [f] Only one diastereomer visible by ^{1}H NMR.

The next step to exploring the reactivity was to utilize a heteroaromatic as a donor substituent. Furyl cyclopropane **3-59** gave cyclized product **3-60** in near quantitative yield (99%) with 4.5:1 *dr* (Table 3.2, entry 2) at room temperature. This was an exciting finding because furyl-based products had formerly been shown to polymerize. Other donor groups were investigated. α-Methyl styrene **3-61** readily reacted at room temperature as well to afford **3-62** in 94% with 1.1:1 *dr* (Table 3.2, entry 3) with a greater accelerating effect. Compared to the phenyl derivative **3-51**, **3-61** displayed enhanced reactivity, presumably due to the additional strain caused by the methyl group and the increased stability from a benzylic carbocation to a 3˚ benzylic carbocation. Moreover, a quaternary stereocenter was formed in the process, increasing stereocomplexity.

Table 3.2: Donor and Acceptor Effects

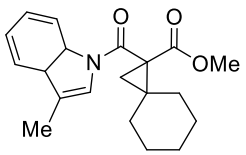
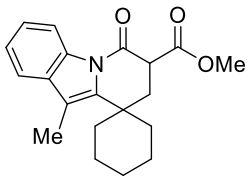
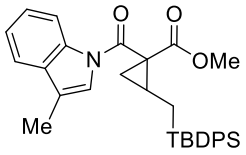
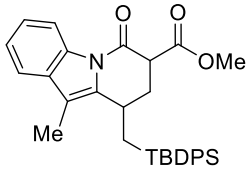
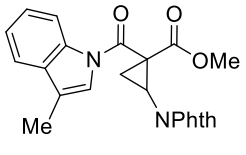
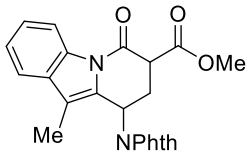
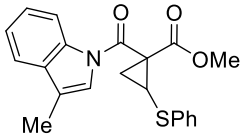
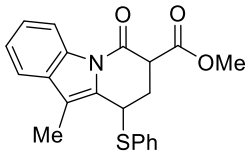
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **3-57**	 **3-58**	20.0	*trace*	--
2	 **3-59**	 **3-60**	2.0	99%	4.5:1
3[d]	 **3-61**	 **3-62**	2.0	94%	1.1:1
4[d]	 **3-63**	 **3-64**	6.0	85%	--
5[d]	 **3-65**	 **3-66**	6.0	88%	--

[a] Reactions run with 1.0 equiv. of the precursor and 30 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratios. [d] Reaction performed in 1,2-dichloroethane at 84 °C. [e] Relative configurational assignment not determined. [f] Only one diastereomer visible by ^1H NMR.

In accordance with the increased reaction rate, high yield, and additional stability provided by alkyl donation to an intermittent benzylic carbonium, *gem*-disubstituted alkyl groups at the donor position of the cyclopropane were employed. Since 3˚ carbocations and benzylic carbocations are proportional in energy, cyclized products should be formed from the geminal precursors. To explore this premise, we assembled **3-63** (2-ethyl-butene derivative), **3-65** (methylene cyclopentane), and **3-67** (methylene cyclohexane) and subjected **3-63** to 30 mol% $In(OTf)_3$ at room temperature, but no product was afforded. When heated in 1,2-dichloroethane at reflux with 30 mol% $In(OTf)_3$, **3-63**, **3-65**, and **3-67** afforded hydropyrido[1,2-*a*]indoles **3-64** (85% yield, Table 3.2, entry 4), **3-66** (88% yield, Table 3.2, entry 5), and **3-68** (79% yield, Table 3.3, entry 1). The products mentioned so far are synthetic accomplishments in that 1) spirocyclics (e.g., **3-66** and **3-68**) can be made from 1,1-disubstituted alkenes, 2) alkyl group utilization for this methodology used to be limited to Tsuge's protocol,[117] and 3) many hydropyrido[1,2-*a*]indole natural products have *gem*-dialkyl substituents at C(*9*).

Continuing with donor group examinations, we investigated the use of a 2-silymethyl group for additional stabilization as reported in Yadav's recent work[106] which used 2-silylmethyl-substituted heteroaromatic cyclopropanes for the formation of tricyclo-2,3-heteroaromatics. 2-silylmethyl cyclopropane **3-69** reacted to form **3-70** in 82% with one observable diastereomer (Table 3.3, entry 2). According to Yadav's postulation,[106] the silyl group stabilized the carbocation upon ring-opening through anchimeric assistance from a silyl group.[205–208] This stabilizing hyperconjugative effect promoted ring enlargement in Yadav's case, and we postulated that it would be effective in our case.

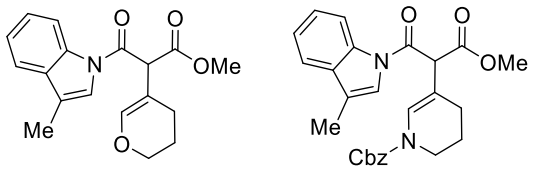
Table 3.3: Substrate Scope

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1[d]	 **3-67**	 **3-68**	6.0	79%	--
2[d]	 **3-69**	 **3-70**	16.0	82%	--[f]
3[d]	 **3-71**	 **3-72**	8.0	55%	4.8:1
4[d]	 **3-73**	 **3-74**	7.0	81%	6.3:1

[a] Reactions run with 1.0 equiv. of the precursor and 30 mol % $In(OTf)_3$ in dichloromethane at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratios. [d] Reaction performed in 1,2-dichloroethane at 84 °C. [e] Relative configurational assignment not determined. [f] Only one diastereomer visible by ^1H NMR.

After investigating aryl, alkyl, and silyl moieties as reactive subunits, we probed heteroatom-donating groups, in particular, oxygen, sulfur, nitrogen groups, for their effectiveness. When phthalimido **3-71**, a masked amine, was substituted as the stabilizing group, **3-72** was obtained in 55% yield with 4.8:1 *dr* (Table 3.3, entry 3). Vinyl phenyl thioether derivative **3-73** gave **3-74** in 81% yield with 6.3:1 *dr* (Table 3.3, entry 4). Unfortunately, when we attempted to synthesize the dihydrofuran and Cbz-protected ring-

fused piperdinyl cyclopropanes, cyclopropanes were not synthesized with our Rh(II)-catalyzed cyclopropanation general procedure. β,γ-unsaturated carbonyl compounds **3-75** and **3-76** in Figure 3.14 were obtained for dihydropyran and Cbz-protected tetrahydropyridine. Therefore, we were not able to investigate the reactivity of the desired cyclopropane precursors for our protocol.

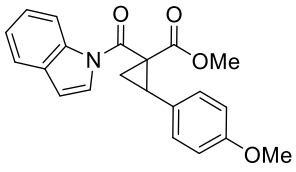
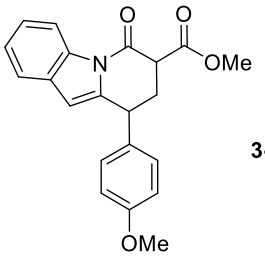
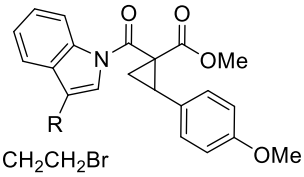
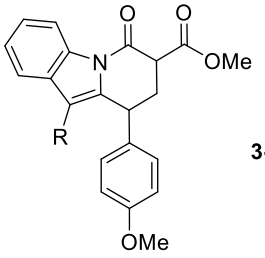
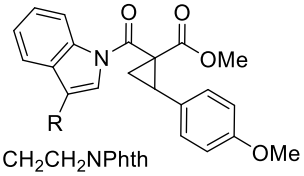
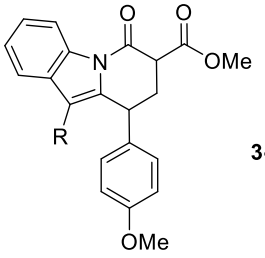
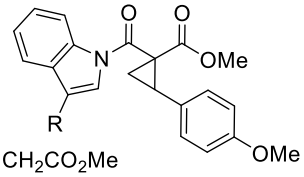
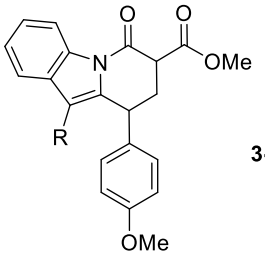


3-75 **3-76**

Figure 3.14: β,γ-unsaturated-δ-heteroatom 1,3-dicarbonyl amides obtained from the Rh(II)-catalyzed method

Given these findings, we attempted to ascertain the flexibility of our protocol if the 3-methyl indole were altered to other tolerable moieties that would be useful for natural product applications. **3-77** (derived from 1*H*-indole) affirmed that 3-substitution on the indole was not necessary for cyclization because **3-78** was formed in 99% yield with 1.1:1 *dr* (Table 3.4, entry 1). 3-(2-Bromoethyl)-1-*H*-indole cyclopropane **3-79** afforded **3-80** in 99% yield with 2.7:1 *dr* (Table 3.4, entry 2) with the bromine remaining intact throughout the cyclization and workup. This bromine group provides another chemical site for further functionalization. Similarly, phthalimid-protected tryptamine derivative **3-81** generated **3-82** in 76% yield with 2.8:1 *dr* (Table 3.4, entry 3), which can be deprotected to give a free amine. Finally, methyl 3-(1*H*-indol-3-yl)propanoate derivative **3-83** provided **3-84** in 88% yield with 2.0:1 *dr* (Table 3.4, entry 4).

Table 3.4: Varying the Indole Substitution

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **3-77**	 **3-78**	0.75	99%	1.1:1
2	 R = CH_2CH_2Br **3-79**	 **3-80**	1.0	99%	2.7:1
3	 R = CH_2CH_2NPhth **3-81**	 **3-82**	2.0	76%	2.8:1
4	 R = CH_2CO_2Me **3-83**	 **3-84**	3.0	88%	2.0:1

[a]Reactions run with the precursor (1.0 equiv.) and 10 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b]Isolated yields after column chromatography. [c]Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*/*cis* diastereomeric ratio.

3.5 Conclusion

In summary, an efficient catalytic ring-opening/Friedel-Crafts alkylation sequence procedure for hydropyrido[1,2-*a*]indole-6(7*H*)-ones was designed. Product yields ranged from 48-99% in four steps from readily accessible indoles and olefins. This Friedel-Crafts alkylation transformation is modular, atom economical, and robust, allowing for a variety of functionalized products to be formed. Attributable to the valued products formed, our method is applicable to highly efficient constructions of complex skeletons of natural products and biologically-active molecules.

3.6 Research Participants

This research was conducted with Dr. Dadasaheb V. Patil and Paul Grzybowski. They made the precursors and the final products.

This work was published in *Chemical Communications*: Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. An Efficient Synthesis of hydropyrido[1,2-*a*]indole-6(7*H*)-Ones via an In(III)-Catalyzed Tandem Cyclopropane Ring-opening/Friedel-Crafts Alkylation Sequence. *Chem. Commun. Camb. U. K.* **2011**, *47*, 10278–10280.

3.7 Experimental Information

3.7.1 Synthetic Methods for Hydropyrido[1,2-*a*]indole Preparation

All reactions were carried out in pre-dried glassware from the oven, and any additional moisture was removed by flame drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere, and dry solvents were used, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. 1,2-Dichloroethane and dichloromethane were purified by distillation from calcium hydride under N_2 prior to use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification.

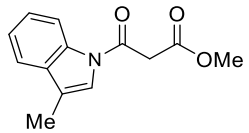
Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to isolated analytically pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer or a Varian Mercury Vx 400 spectrometer with solvent resonances as the internal standard

(^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. *Compounds synthesized and not reported in the literature until our publication are listed below. Dr. Dadasaheb V. Patil and Paul Grzybowski synthesized the precursors and the final products as well.*

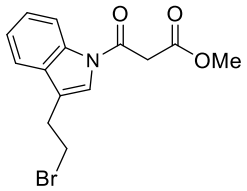
3.7.2 Preparation of β-Amide Esters 3-45

A heterogeneous solution of sodium hydride (1.1 equiv.) and THF (20 mL) was formed and cooled to 0 °C. In a separate flask, the desired indole (1.0 equiv.) was dissolved in 30 mL of THF and syringed into the basic solution. After 30 minutes, methyl-3-chloro-3-oxopropanoate (1.1 equiv.) was slowly added. The reaction was stirred for 14 hours at room temperature. The reaction mixture was quenched with water. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography for product isolation.

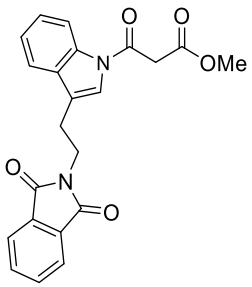


Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (3-45a): The general procedure was followed using sodium hydride (0.624 g, 26.0 mmol), 3-methyl-1H-indole (3.01 g, 22.9 mmol), methyl-3-chloro-3-oxopropanoate (3.0 mL, 28.0 mmol), and THF (120 mL). After 12 hours, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f = 0.26 and R_f = 0.15 for keto and enol tautomers) gave **3-45a** as a light brown solid (3.60

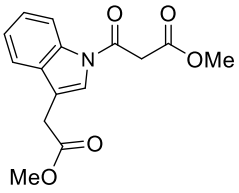
g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (d, *J* = 7.1 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.41 – 7.28 (m, 2H), 7.10 (s, 1H), 3.92 (s, 2H), 3.79 (s, 3H), 2.27 (s, *J* = 1.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8, 163.4, 136.0, 131.5, 125.5, 124.0, 121.4, 119.7, 118.9, 116.7, 52.9, 43.6, 9.7. IR: 3051.9 (w), 2937.6 (w), 1747.0 (s), 1685.1 (s), 1604.1 (w), 1447.0 (s), 1375.5 (s), 1232.6 (m), 1070.7 (m), 913.5 (m), 732.6 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 231.0895, Obs. 231.0895.



Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (3-45b):[209] A mixture of potassium carbonate (0.116 g, 0.840 mmol) and 3-(2-bromoethyl)-1*H*-indole (0.400 g, 1.78 mmol), methyl-3-chloro-3-oxopropanoate (0.30 mL, 2.80 mmol) and acetonitrile (25 mL) were heated to reflux. After 12 hours, the reaction mixture was cooled, filtered and dried *in vacuo.* The residue was dissolved in EtOAc/Hex (1:2.5). The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (20% EtOAc/Hex, R_f = 0.35) formed **3-45b** as a yellowish brown solid (0.559 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.41 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.24 (m, 2H), 7.22 (s, 1H), 3.92 (s, 2H), 3.76 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.5, 163.5, 135.7, 129.8, 125.6, 123.9, 122.1, 120.4, 118.4, 116.7, 52.7, 43.3, 31.1, 28.5. IR: 3091.7 (w), 2940.7 (w), 2878.8 (w), 1760.1 (s), 1657.8 (s), 1615.6 (s), 1535.5 (s), 1440.9 (s), 1239.4 (s), 1191.4 (s), 1040.8 (m), 820.8 (m), 777.4 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 323.0157, Obs. 323.0162.

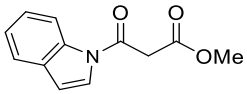


Methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (3-45c): The general procedure was followed using sodium hydride (0.298 g, 12.4 mmol), 2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione[210] (2.23 g, 7.69 mmol), methyl-3-chloro-3-oxopropanoate (1.4 mL, 13.1 mmol), and THF (10 mL). After 12 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f = 0.17) generated **3-45c** as a brown solid (1.84 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.41 (d, *J* = 7.7 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.75 – 7.67 (m, 2H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.27 (m, 3H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.96 (s, 2H), 3.78 (s, 3H), 3.10 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.0, 168.3, 167.2, 166.7, 163.7, 136.0, 134.1, 131.9, 130.4, 125.7, 124.2, 123.3, 121.9, 120.0, 118.9, 116.8, 52.9, 52.8, 43.4, 40.5, 37.2, 24.1. IR: 2937.6 (w), 1742.2 (s), 1703.2 (s), 1691.8 (s), 1599.3 (w), 1456.5 (m), 1383.6 (m), 1329.9 (m), 1210.0 (m), 1153.5 (s), 1008.8 (m), 923.1 (w), 719.7 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 390.1216, Obs. 390.1213.



Methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (3-45d): The general procedure was followed with sodium hydride (0.460 g, 19.2 mmol), methyl 2-(1*H*-indol-3-yl)acetate (2.92 g, 15.4 mmol), methyl-3-chloro-3-oxopropanoate (2.0 mL, 18.7 mmol), and THF (90 mL). After 12 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f = 0.24) afforded **3-45d** as a dark brown solid (2.36

g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.43 – 7.27 (m, 3H), 3.96 (s, 2H), 3.79 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.0, 166.6, 163.6, 135.8, 130.1, 125.8, 124.2, 123.1, 118.9, 116.8, 116.0, 52.8, 52.2, 43.4, 30.6. IR: 3009.3 (w), 2952.1 (w), 1737.4 (s), 1703.2 (s), 1595.1 (m), 1366.0 (s), 1265.7 9 (m), 1204.7 (s), 1148.4 (s), 1015.7 (m), 909.4 (m), 728.3 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 289.0950, Obs. 289.0945.

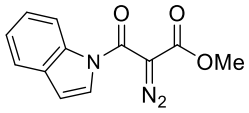


Methyl 3-(1*H*-indol-1-yl)-3-oxopropanoate (3-45e): 1*H*-Indole (503 mg, 4.30 mmol), methyl 3-chloro-3-oxopropanoate (620 uL, 5.61 mmol), and toluene (15 mL) were charged to a round bottom flask equipped with a stir bar. The reaction mixture was heated to a reflux for 12 hours. The toluene was removed by vacuum, and the crude material was purified directly by flash column chromatography (15% EtOAc/Hex, R_f= 0.35), yielding **3-45e** as a yellow-brown oil (550 mg, 59%). ^{1}H NMR (300 MHz, CDCl3) δ ppm 8.44 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.38 – 7.23 (m, 3H), 6.61 (dd, *J* = 3.8, 0.8 Hz, 1H), 3.91 (s,2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.5, 163.8, 135.4, 130.2, 125.1, 124.5, 123.9, 120.7,116.3, 109.8, 52.6, 43.1. IR: 3109.7 (w), 3152.9 (w), 3036.6 (w), 2953.6 (w), 2850.7 (w), 1737.9 (m), 1703.1 (s), 1691.8 (m), 1529.04 (w), 1472.2 (w), 1450.6 (m), 1383.1 (m), 1346.9 (s), 1261.2 (m), 1204.9 (s), 1150.2 (s), 1015.7 (m), 925.7 (m), 747.3 (s), 715.2 (m), 689.3 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc.217.0739, Obs. 217.0738.

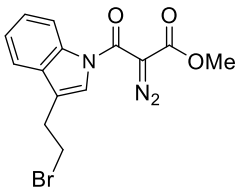
3.7.3 Formation of Diazo Compounds 3-46

The β-amide ester (1.0 equiv.) was dissolved in acetonitrile. Triethylamine (1.2 equiv.) was added to the reaction mixture and stirred for 10 minutes. Tosyl azide (1.2 equiv) was placed in the reaction flask. The mixture was stirred at room temperature for 12 hours and concentrated under reduced pressure. The resulting residue was purified by silica gel

flash chromatography to afford the diazo compound.

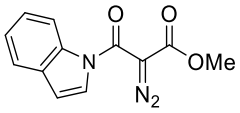


Methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (3-46a): The general procedure was followed using methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1.50 g, 6.49 mmol), triethylamine (1.2 mL, 8.61 mmol), tosyl azide (1.55 g. 7.86 mmol), and acetonitrile (15 mL). After 24 hours, the reaction mixture was concentrated, and column chromatography (20% EtOAc/Hex, R_f= 0.41) afforded **3-46a** as a yellow solid (1.55 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.17 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.39 – 7.26 (m, 2H), 7.11 (s, 1H), 3.85 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.5, 158.9, 136.0, 131.7, 124.8, 123.7, 123.3, 118.9, 117.7, 115.7, 69.7, 52.6, 9.7. IR: 3047.1 (w), 2956.6 (w), 2918.5 (w), 2132.7 (s), 1708.9 (s), 1651.7 (s), 1601.0 (m), 1466.0 (s), 1349.6 (s), 1302.9 (s), 1254.3(s), 1127.9(s), 1046.9 (s), 865.9 (m), 732.7 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 257.0800, Obs. 257.0805.



Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate (3-46b): The general procedure was followed using methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.679 g, 2.09 mmol), triethylamine (0.350 g, 2.51 mmol), tosyl azide (0.561 g, 2.85 mmol), and acetonitrile (15 mL). After 10 hours, the reaction mixture was concentrated, and column chromatography (20% EtOAc/Hex, R_f= 0.50) gave **3-46b** as a yellow oil (0.540 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.22 (s, 1H), 3.81 (s, 3H), 3.61 (t, *J* = 7.3 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 159.1, 136.0, 130.1, 125.0, 124.2, 123.8, 118.7, 118.5, 115.8, 70.1, 52.7, 31.2, 28.7. IR: 3018.6 (w), 2947.1, (w),

2142.0 (s), 1732.7 (s), 1656.5 (s), 1604.1 (w), 1451.7 (s), 1380.4 (s), 1306.8 (s), 1251. 7 (m), 1056. 4 (m), 861.2 (w), 734.3 (s), 708. 8 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 349.0062, Obs. 349.0061.

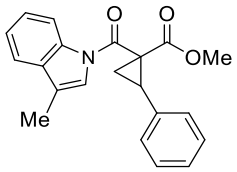


Methyl 2-diazo-3-(1*H*-indol-1-yl)-3-oxopropanoate (3-46c): The general procedure was followed using methyl 3-(1*H*-indol-1-yl)-3-oxopropanoate (3.00 g, 13.8 mmol), triethylamine (2.6 mL, 18.5 mmol), tosyl azide (3.69 g, 18.7 mmol), and acetonitrile (50 mL). After 18 hours, the reaction mixture was concentrated, and column chromatography (10% EtOAc/Hex, R*f*= 0.35) afforded **3-46c** as a yellow oil (3.15 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.22 – 8.16 (m, 1H), 7.59 – 7.53 (m, 1H), 7.40 – 7.23 (m, 3H), 6.61 (dd, *J* = 3.8, 0.7 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 161.3, 159.5, 135.7, 130.6, 127.4, 126.7, 124.7, 123.8, 120.9, 115.5, 108.2, 52.7. IR: 3162.8 (w), 3053.2 (w), 2953.6 (w), 2140.3 (s), 1710.8 (s), 1721.3 (s), 1657.8 (s), 1649.7 (s), 1529.0 (w), 1451.1 (s), 1380.5 (s), 1342.4 (s), 1298.4 (s), 1244.9 (m), 1139.5 (m), 1121.6 (m), 1090.6 (m), 1067.0 (m), 945.5 (w), 883.1 (m), 859.7 (m), 746.5 (s), 640.3 (w) cm^{-1}. HRMS (ESI) M/Z+ Calc. 243.0644, Obs. 243.0640.

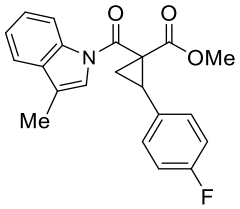
3.7.4 Cyclopropane Synthesis and β,γ-Unsaturated-δ-Heteroatom 1,3-Dicarbonyl Amides

The cyclopropanes were prepared using a modified version of Soumeillant's protocol:[153] A round bottom flask was charged with Rh_2esp_2 (0.1 mol%) and a magnetic stir bar. DCM (2.0 mL) was added to the flask. The reaction vessel was cooled to 0 °C, and the corresponding alkene (1.0 equiv) was added. After 10 minutes, the diazo reagent (1.3 equiv.) was dissolved in DCM (5 mL) and syringed into the reaction mixture. After 10 minutes, the ice bath was removed, and the reaction proceeded at room temperature. Upon completion (monitored by TLC) or 12 hours of reactivity, the solution was quenched with

saturated thiourea and stirred for 30 minutes. The organic layer was separated, and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography.

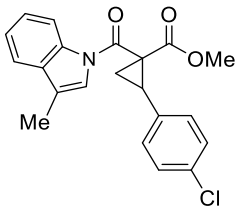


Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropanecarboxylate (3-51): The general procedure was followed using styrene (0.100 g, 0.960 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.329 g, 1.28 mmol), Rh_2esp_2 (1.0 mg, 1.32 μmol), and DCM (13 mL). After 15 hours, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f= 0.60) gave **3-51** as a white solid (0.273 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.45 – 7.26 (m, 8H), 3.48 (t, *J* = 8.8 Hz, 1H), 3.40 (s, 3H), 2.46 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.29 (s, 3H), 1.84 (dd, *J* = 9.3, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.9, 165.6, 136.0, 134.2, 131.5, 129.1, 128.2, 127.4, 125.4, 123.8, 121.4, 119.2, 118.9, 116.5, 52.8, 39.5, 31.5, 18.5, 9.8. IR: 3037.6 (w), 2951.9 (w), 2918.5 (w), 1732.7 (s), 1692.0 (s), 1446.9 (s), 1390.8 (s), 1348.3 (s), 1208.8 (m), 1051.6 (m), 742.1 (m), 684.9 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 333.1365, Obs. 333.1367.

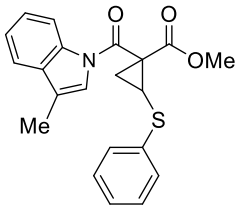


Methyl 2-(4-fluorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (3-53): The general procedure was followed using 4-fluorostyrene (0.311 g, 2.55 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.655 g, 2.55 mmol), Rh_2esp_2 (1.00 mg, 1.32 μmol), and DCM (8 mL). After 12 hours, the reaction was

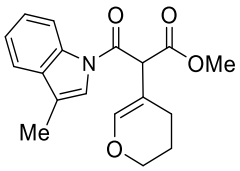
quenched, and column chromatography (20% EtOAc/Hex, R_f= 0.64) afforded **3-53** as a pale green solid (0.757 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.45 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.29 (m, 4H), 7.25 (s, 1H), 7.07 – 6.98 (m, 2H), 3.46 (t, *J* = 8.5 Hz, 1H), 3.42 (s, 3H), 2.42 (dd, *J* = 8.2, 5.3 Hz, 1H), 2.29 (s, 3H), 1.84 (dd, *J* = 9.3, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.8, 165.4, 163.8, 160.5, 136.0, 131.5, 130.7, 130.0, 125.4, 123.9, 121.3, 119.4, 118.9, 116.5, 115.3, 115.0, 52.9, 39.5, 30.8, 18.7, 9.8. IR: 3010.0 (w), 2947.1 (w), 2904.3 (w), 1727.9 (m), 1685.1 (s), 1518.4 (s), 1456.5 (s), 1399.3 (s), 1337.4 (s), 1215.2 (s), 1146.9 (s), 1051.7 (m), 846.9 (m), 723.1 (s), 608.7 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 351.1271, Obs. 351.1268.



Methyl 2-(4-chlorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (3-55): The general procedure was followed using 4-chlorostyrene (0.138 g, 0.994 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.268 g, 1.04 mmol), Rh_2esp_2 (1.4 mg, 1.85 μmol), and DCM (8 mL). After 12 hours, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f= 0.64) furnished **3-55** as a white solid (0.338 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.45 – 7.29 (m, 6H), 7.26 (d, *J* = 1.3 Hz, 1H), 3.44 (t, J = 6.8 Hz, 1H), 3.44 (s, 3H), 2.43 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.30 (s, 3H), 1.86 (dd, *J* = 9.3, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.7, 165.3, 136.0, 133.3, 132.8, 131.5, 130.4, 128.3, 125.4, 123.9, 121.2, 119.4, 118.9, 116.5, 52.9, 39.5, 30.8, 18.6, 9.7. IR: 3010.0 (w), 2951.9 (w), 2913.8 (w), 1727.9 (s), 1691.9 (s), 1485.0 (m), 1451.0 (s), 1389.9 (s), 1347.9 (s), 1218.3 (m), 1156.4 (m), 1080.2 (m), 842.1 (m), 742.1 (m) 708.7 (w) cm^{-1}. HRMS (ESI) M/Z+ Calc. 367.0975, Obs. 367.0981.

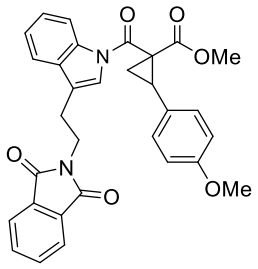


Methyl 1-(3-methyl-1H-indole-1-carbonyl)-2-(phenylthio)cyclopropanecarboxylate (3-73): The general procedure was followed using phenyl(vinyl)sulfane (0.311 g, 2.29 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.723 g, 2.81 mmol), Rh_2esp_2 (1.8 mg, 2.4 μmol), and DCM (13 mL). After 15 hours, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f= 0.40) afforded **3-73** as a colorless oil (0.125 g, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.44 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.43 – 7.28 (m, 4H), 7.23 – 7.16 (m, 2H), 3.56 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.52 (s, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 2.15 (dd, *J* = 7.3, 5.7 Hz, 1H), 1.92 (dd, *J* = 9.2, 5.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3, 164.6, 135.9, 135.4, 131.6, 129.0, 127.7, 126.0, 125.7, 124.0, 121.1, 119.7, 119.0, 116.6, 53.1, 39.8, 28.2, 20.0, 9.7. IR: 3080.6 (w), 2939.6 (w), 2896.9 (w), 1724.3 (s), 1657.6 (s), 1421.8 (s), 1382.7 (s), 1267.7 (s), 789.5 (s), 664.3 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 365.1079, Obs. 365.1083.



Methyl 7-(3-methyl-1*H*-indole-1-carbonyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate (3-75): The general procedure was followed using 2,3-dihydropyran (95 μL, 1.04 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.36 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (8 mL). After 12 hours, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f = 0.40) generated **3-75** as a white solid (0.189 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.45 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.42 – 7.22 (m, 2H), 7.17 (s, 1H), 6.54 (s, 1H), 4.60 (s, 1H), 4.00 – 3.87 (m, 2H), 3.77 (s, 3H), 2.39 – 2.27 (m, 1H), 2.26 (s, 3H), 2.14 – 2.02 (m, 1H), 1.97 – 1.77 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.8, 165.6, 144.5, 136.0, 131.2, 125.3, 123.8, 121.1, 119.2, 118.7, 116.7, 106.4, 80.77, 65.6, 56.0, 52.6, 21.8, 21.5, 9.6. IR: 2942.4 (w), 2866.2 (w), 1756.5 (s), 1694.6 (s), 1651.7 (s), 1608.9 (w), 1451.7 (s), 1385.0 (s), 1349.3 (s), 1140.7 (s), 1065.9 (s), 1018.3 (m), 937.4 (m), 745.4 9 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 313.1314, Obs. 313.1312.

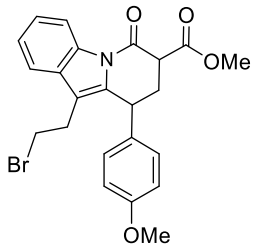


Methyl 1-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxy phenyl)cyclopropanecarboxylate (3-81): The general procedure was followed using 4-methoxystyrene (0.168 g, 1.25 mmol), methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.610 g, 1.46 mmol), Rh_2esp_2 (1.6 mg, 2.11 μmol), and DCM (13 mL). After 12 hours, the reaction was quenched, and column chromatography (40% EtOAc/Hex, R_f = 0.38) afforded **3-81** as a pale brown solid (0.108 g, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.44 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.78 – 7.65 (m, 3H), 7.44 – 7.24 (m, 5H), 6.92 – 6.83 (m, 2H), 4.02 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.39 (t, J = 9.0, 1H), 3.38 (s, 3H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.41 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.79 (dd, *J* = 9.4, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) (Rotamers) δ ppm 168.2, 167.7, 166.0, 158.9, 136.1, 134.0, 133.8, 132.0, 130.4, 130.2, 126.0, 125.6, 124.0, 123.3, 123.2, 122.1, 122.0, 119.6, 119.5, 119.0, 118.9, 116.6, 113.6, 55.2, 53.4, 52.7, 39.6, 38.5, 37.4, 31.3, 24.3, 18.9. IR: 3051.9 (w), 2942.4 (w), 1760.0 (w), 1708.8 (s), 1685.1 (s), 1594.6 (m), 1513.6 (m), 1442.2 (m), 1375.5 (m), 1242.2 (m), 1104.0 (w), 832.6 (m), 732.8 (s), cm^{-1}. HRMS (ESI) M/Z+ Calc. 522.1791, Obs. 522.1777.

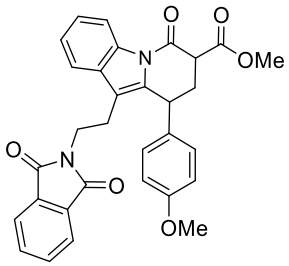
3.7.5 In(OTf)$_3$-Catalyzed Ring-opening/Friedel-Crafts Alkylation Sequence

3.7.5.1 General Method A

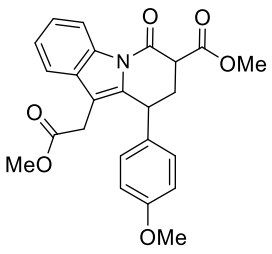
The cyclopropyl β-amide ester (1.0 equiv) was added to a solution of In(OTf)$_3$ (0.30 equiv.) in anhydrous dichloromethane (2 mL) at room temperature. Upon completion, the reaction mixture was quenched with water, and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic layers were concentrated for silica gel flash column chromatography.



Methyl 10-(2-bromoethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (3-80): Methyl 1-(3-(2-bromoethyl)-1H-indole-1-carbonyl)-2-(4-methoxyphenyl)cyclopropane carboxylate (0.050 g, 0.109 mmol), In(OTf)$_3$ (0.018 g, 0.032 mmol) and DCM (3 mL) were mixed according to general method A to afford **3-80** as a colorless oil (0.049 g, 98%) after 1 hour. R_f= 0.35 (20% EtOAc/Hex). *Diastereomeric ratio*: (3.4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.54 (ddd, *J* = 10.3, 6.9, 1.4 Hz, 1.29), 7.53 – 7.42 (m, 1.52), 7.41 – 7.29 (m, 2.75), 7.16 – 7.11 (m, 0.72), 6.95 (dd, *J* = 6.9, 4.7 Hz, 2.19), 6.89 – 6.80 (m, 2.82), 4.68 (t, *J* = 4.2 Hz, 1), 4.43 (dd, *J* = 8.8, 5.3 Hz, 0.29), 3.86 – 3.77 (m, 7.56), 3.69 (dd, *J* = 12.2, 4.6 Hz, 1.48), 3.57 (d, *J* = 3.5 Hz, 1.04), 3.53 – 3.05 (m, 4.53), 3.03 – 2.73 (m, 3.48), 2.66 – 2.37 (m, 2.06). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.47, 165.25, 158.87, 135.52, 134.75, 132.33, 129.66, 129.12, 128.35, 125.22, 124.46, 118.03, 116.94, 116.04, 114.37, 114.18, 55.29, 52.72, 47.11, 35.45, 33.09, 30.91, 27.71. IR: 3023.9 (w), 2918.9 (w), 1725.1 (s), 1658.6 (s), 1591.0 (m), 1493.2 (s), 1349.0 (m), 993.6(s), 725.0 s), 663.0 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 455.0708, Obs. 455.0734.



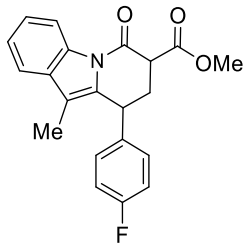
Methyl 10-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indole-7-carboxylate (3-82): Methyl 1-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (0.050 g, 0.096 mmol), $In(OTf)_3$ (0.016 g, 0.028 mmol) and DCM (6 mL) were mixed according to general method A to yield **3-82** as a brown oil (0.038 g, 76.0%) after 2 hours. R_f= 0.38 (40% EtOAc/Hex). *Diastereomeric ratio*: (3.4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.52 – 8.46 (m, 1.26), 7.79 – 7.58 (m, 7.02), 7.41 – 7.26 (m, 2.66), 7.18 – 7.13 (m, 0.75), 7.00 – 6.93 (m, 2.16), 6.86 - 6.72 (m, 2.79), 4.70 (t, *J* = 4.1 Hz, 1), 4.48 (dd, *J* = 8.3, 5.1 Hz, 0.27), 3.85 – 3.80 (m, 0.50), 3.79 - 3.77 (m, 4.32), 3.76 – 3.74 (m, 0.89), 3.74-3.72 (m, 3.51), 3.70 – 3.63 (m, 2.36), 3.54 (s, 0.89), 3.02 – 2.90 (m, 1.09), 2.88 – 2.71 (m, 2.78), 2.61 – 2.50 (m, 0.36), 2.44 – 2.33 (m, 1.38). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.6, 169.2, 168.0, 165.3, 165.1, 158.8, 158.7, 135.6, 135.3, 134.7, 134.6, 133.9, 132.6, 131.9, 131.9, 130.5, 130.1, 129.1, 128.3, 125.2, 125.1, 124.5, 124.4, 123.1, 123.1, 118.4, 118.2, 116.8, 116.8, 115.7, 115.2, 114.3, 114.1, 55.2, 55.2, 52.7, 52.6, 49.7, 47.1, 37.8, 37.0, 36.9, 35.3, 33.7, 33.2, 23.2, 22.9. IR: 3047.1 (w), 2947.1 (w), 2847.1 (w), 1766.03 (w), 1751.74 (m), 1708.8 (s), 1618.4 (m), 1504.1 (m), 1451.7 (m), 1376.6 (s), 1245.9 (s), 1032.6 (s), 837.3 (m), 715.9 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 522.1791, Obs. 522.1791.



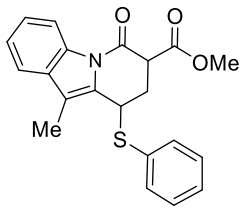
Methyl 10-(2-methoxy-2-oxoethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (3-84): Methyl 1-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (0.070 g, 0.167 mmol), $In(OTf)_3$ (0.028 g, 0.049 mmol) and DCM (6 mL) were combined according to general method A to afford **3-84** as a brown oil (0.062 g, 88.0%) after 3 hours. R_f= 0.45 (40% EtOAc/hex). *Diastereomeric ratio*: (2.0:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.56 – 8.47 (m, 1.45), 7.56 – 7.48 (m, 1.05), 7.44 – 7.28 (m, 3.67), 7.18 – 7.11 (m, 1.06), 7.01 – 6.90 (m, 2.29), 6.88 – 6.78 (m, 3.02), 4.66 (t, *J* = 4.5 Hz, 1), 4.40 (dd, *J* = 9.7, 5.1 Hz, 0.48), 3.90 – 3.81 (m, 1.32), 3.81 – 3.78 (m, 7.54), 3.73 – 3.67 (m, 1.32), 3.64 (s, 1.44), 3.55 (s, 1.42), 3.53 (s, 2.98), 3.52 (s, 0.31), 3.43 (d, *J* = 17.3 Hz, 1.59), 3.32 (d, *J* = 17.7 Hz, 0.85), 3.02 – 2.69 (m, 2.34), 2.58 – 2.38 (m, 1.62). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 170.8, 170.7, 169.5, 169.2, 165.2, 158.9, 158.8, 136.3, 135.8, 134.6, 134.5, 132.3, 131.9, 130.3, 130.0, 129.2, 128.5, 125.3, 125.2, 124.5, 124.4, 118.5, 118.0, 116.8, 114.3, 114.2, 112.4, 112.0, 55.3, 52.8, 52.6, 52.0, 51.9, 50.1, 47.3, 38.5, 35.4, 34.1, 33.2, 29.7, 29.5. IR: 3013.8 (w), 2918.6 (w), 2832.8 (w), 1747.0 (s), 1737.7 (s), 1699.3 (s), 1613.6 (m), 1518.4 (m), 1456.5 (s), 1366.0 (s), 1245.6 (s), 1152.1 (s), 1032.6 (s), 837.3 (m), 731.8 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 421.1525, Obs. 421.1522.

3.7.5.2 General Method B

Into a mixture of $In(OTf)_3$ (0.30 equiv.) in anhydrous 1,2-dichloroethane heated to a reflux, the dissolved cyclopropyl β-amide ester (1.0 equiv) was syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated for silica gel flash column chromatography.



Methyl 9-(4-fluorophenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (3-54): Methyl 2-(4-fluorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropane carboxylate (0.100 g, 0.285 mmol), $In(OTf)_3$ (0.047 g, 0.085 mmol, 30 mol%) and 1,2-dichloroethane (3 mL) were combined according to general method B to give **3-54** as a brown oil (0.048 g, 48%) after 8 hours. R_f= 0.28 (20% EtOAc/Hex). *Diastereomeric ratio*: (2.6:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 – 8.46 (m, 1.37), 7.76 (d, *J* = 8.1 Hz, 0.68), 7.53 – 7.29 (m, 5.16), 7.26 – 6.77 (m, 12.82), 5.75 (s, 0.62), 4.62 (t, *J* = 4.4 Hz, 1.00), 4.39 (dd, *J* = 8.2, 5.3 Hz, 0.35), 3.80 (s, 3.03), 3.65 (dd, *J* = 11.8, 4.5 Hz, 1.24), 3.55 (s, 1.24), 2.93 – 2.79 (m, 2.17), 2.61 – 2.38 (m, 1.87), 2.00 (s, 3.18), 1.76 (s, 1.43). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 169.2, 164.8, 160.2, 136.2, 134.6,132.9, 131.0, 129.6, 129.5, 129.0, 128.8, 125.1, 124.3, 124.2, 118.3, 118.1, 116.7, 116.0, 115.7, 115.4, 115.2, 52.8, 52.5, 49.7, 47.8, 47.1, 35.9, 35.5, 33.8, 33.0, 33.0, 8.5. IR: 3051.9 (w), 2932.8 (w), 2861.4 (w), 1738.3 (m), 1664.6 (m), 1604.1 (m), 1535.1 (m), 1508.3 (m), 1314.8 (m), 1250.8 (s), 1209.5 (s), 1097.4 (m), 989.0 (w), 832.4 (m), 736.0 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 351.1271, Obs. 351.1272.



Methyl 10-methyl-6-oxo-9-(phenylthio)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (3-74): Methyl 1-(3-methyl-1H-indole-1-carbonyl)-2-(phenylthio)cyclopropane carboxylate (0.018 g, 0.049 mmol), $In(OTf)_3$ (0.008 g, 0.014 mmol) and 1,2-dichloroethane (3 mL) were mixed according to general method B to yield

3-74 as a colorless oil (0.014 g, 81%) after 7 hours. R_f= 0.30 (20% EtOAc/Hex). *Diastereomeric ratio*: (10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.54 (d, *J* = 8.6 Hz, 0.10), 8.47 – 8.40 (m, 1), 7.54 – 7.29 (m, 9.0), 4.91 – 4.84 (m, 1.06), 4.48 (dd, *J* = 13.1, 4.8 Hz, 1.04), 3.94 – 3.76 (m, 3.80), 2.72 (td, *J* = 13.6, 3.9 Hz, 1.19), 2.42 – 2.32 (m, 1.42), 2.20 (s, 0.31), 2.04 (s, 3.10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.6, 164.5, 134.7, 134.5, 132.6, 130.6, 130.5, 129.4, 129.2, 128.8, 128.6, 125.6, 124.3, 118.6, 116.6, 52.8, 46.9, 40.0, 29.7, 8.3. IR: 2997.7 (w), 2890.9 (w), 1766.6 (m), 1711.7 (m), 1468.2 (m), 1269.7 (s), 760.1 (s), 663.0 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 365.1119, Obs. 365.1089.

CHAPTER 4 ALUMINUM(III)-CATALYZED TANDEM RING-OPENING/FRIEDEL-CRAFTS CYCLIZATION METHOD FOR 5,6,7,8-TETRAHYDROINDOLIZINE SYNTHESIS

Indolizines and tetrahydroindolizines are key structural motifs in compounds considered to be potential candidates for medicinal purposes.[211–222] Indolizine (**4-1**) and tetrahydroindolizine (THI) (**4-2**) along with quinolizidine cores are reported to exist in 25-30% of identified alkaloids.[223–225] Specifically, the 5,6,7,8-tetrahydroindolize core is found in antimicrobials polygonatine A (**4-3**), polygonatine B (**4-4**), kinganone (**4-5**), and the anticancer natural products rhazinicine (**4-6**) and rhazinilam (**4-7**).[217,220,221,226] For human cytomegalovirus (HCMV) therapeutics, antiviral CMV423 (**4-8**) is effective and serves as a basis for other structure activity relationship inquiries (Figure 4.1).[222,227]

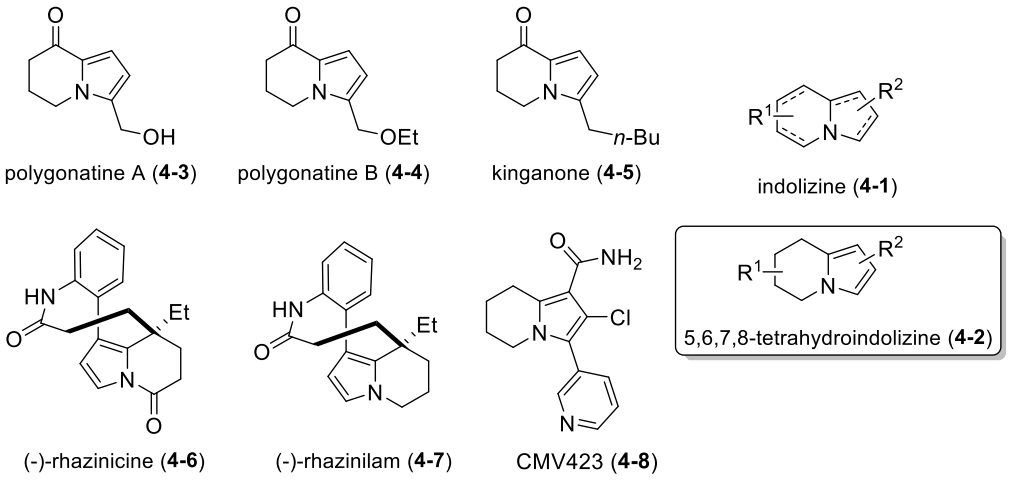
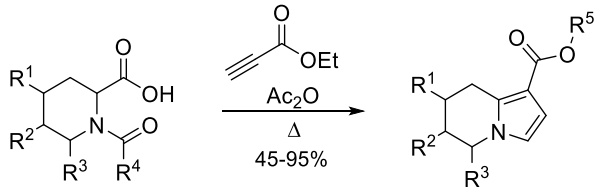


Figure 4.1: Biologically-active tetrahydroindolizines

4.1 5,6,7,8-Tetrahydroindolizine Synthesis Representative Examples

To date, there have been many approaches reported for the preparation of 5,6,7,8-tetrahydroindolizines with varying substitution arrangements involving transition-metal catalysis to nucleophilic ring-opening reactions.[223,226–242] This chapter reviews several approaches used to synthesize 5,6,7,8-tetrahydroindolizines.

In 1977, Pizzorno and Albonico reported a cycloaddition route using ethyl propiolate to *N*-acyl-2-pieridinecarboxylic acids **4-9** in acetic anhydride with heat to give substituted tetrahydroindolizines **4-10** in 45-95% yield.[243] After synthesizing different products, they determined that the reaction was regiospecific since only one isomer was observed. Although the scope was limited, the transformation worked well (Figure 4.2).

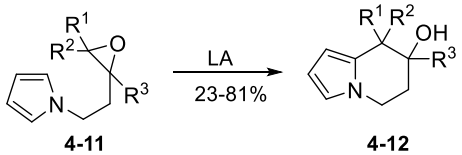


4-9 **4-10**

R^1 = H
R^1-R^2 = C_6H_4
R^2 = H
R^3 = H or CO_2Et
R^4 = H or Me
R^5 = Et or H

Figure 4.2: Pizzorno and Albonico's cycloaddition method

Tanis and Raggon used *N*-(epoxyalkyl)pyrroles (**4-11**) to form 5,6,7,8-tetrahydroindolizidines (**4-12**) with stoichiometric amounts of Lewis acids (e.g., BF_3**.**OEt_2, $EtAlCl_2$, Et_2AlCl, Ti(O-*i*-Pr)$_3$Cl and ZnI_2). The group was guided by their success in using furans for terminating cation cyclizations.[234,244–247] Logically, it followed that a pyrrole unit could participate in the same manner if the epoxide was used as both a metal binding site and as an initiator for ring-opening and ring-closure to form bioactive alkaloids.[234] The predictable cyclization substrates **4-11** were access points for 5-,6-, or 7-membered rings, and tetrahydroindolizines **4-12** depicted in Figure 4.3 were afforded in 23-81% yield.



4-11 **4-12**

R^1 = H, Me
R^2 = H, Me
R^3 = H, Me

Figure 4.3: Tanis and Raggon's cationic cyclization

In 1995, Wang and Alper synthesized 5,6,7,8-tetrahydroindolizines from 2-methyl (or 2,6-dimethyl)piperidinyl ketones **4-13** by using $Co_2(CO)_8$ or $Ru_3(CO)_{12}$.[233] With their metal-catalyzed cyclization, Wang and Alper were interested in including molecular oxygen to oxidize organic compounds. By using $Co_2(CO)_8$ and oxygen, they found that 2-aryl-5,6,7,8-tetrahydroindolizines gave 8a-hydroxy-6,7,8,8a-tetrahydro-3(5*H*)indolizinones **4-15** in fair to good yields (63-76%) Figure 4.4.

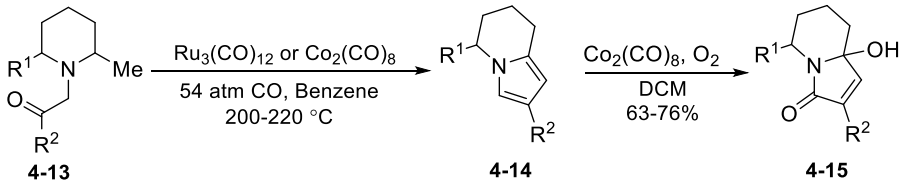


Figure 4.4: Ruthenium and cobalt-catalyzed cyclization

In 2001, Marchalín et al. sought to make azabicyclics that could be screened for biological activity.[230] They synthesized tetrahydroindolizines **4-17** by using a one-pot procedure with 2-formyl-1,4-dihydropyridine derivatives **4-16** and malonitrile as reagents to afford the desired products **4-17** in 57-69% yield. This protocol was short and involved a cascade pathway for product formation via a tandem Knoevenagel reaction/amino-nitrile cyclization (Figure 4.5).

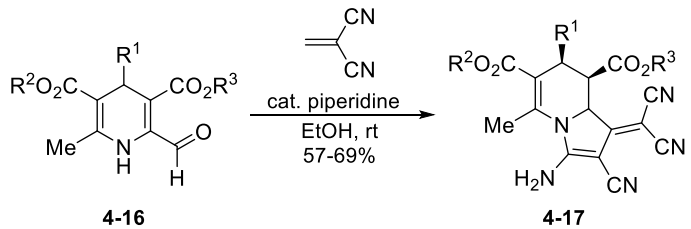


Figure 4.5: One-pot Knoevenagel reaction/amino-nitrile cyclization

In 2009, Bowie and Trauner reported on the total synthesis of (±)-rhazinal **4-20**. In order to assemble the tetrahydroindolizine framework, they performed an oxidative Heck cyclization with 10 mol% $Pd(OAc)_2$ and t-BuOOH.[226] The desired stereochemistry was installed within this intramolecular step. Incorporating the palladium-catalyzed intramolecular ring closure made the route more concise, providing chemists with a direct approach to tetrahydroindolizine **4-19**. Other subsequent steps afforded (±)-rhazinal **4-20**.

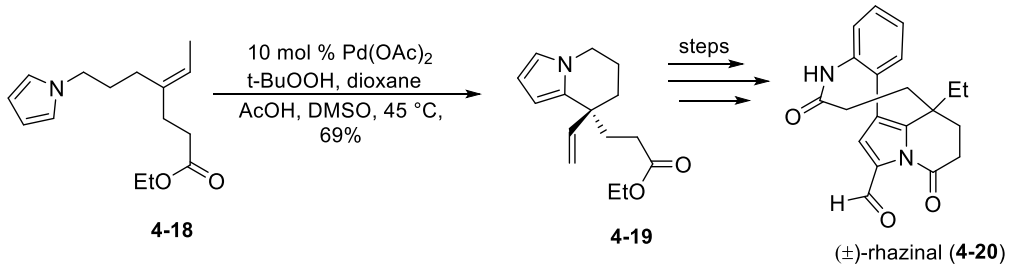


Figure 4.6: Oxidative Heck cyclization for the rhazinal framework

In 2015, Teodoro et al. published a procedure for tetrahydroindolizines from Morita-Baylis-Hillman adducts.[223] The group strategically used Morita-Baylis-Hillman adducts because of the simplicity of using acrylates or α,β-unsaturated ketones and 2-pyridinecarboxaldehydes. From indolizines **4-21**, tetrahydroindolizines **4-22** were formed through a PtO_2 partial hydrogenation under neutral conditions. This method employed commercially available catalysts, low temperatures, and low pressure conditions, resulting in yields ranging from 40-95%.

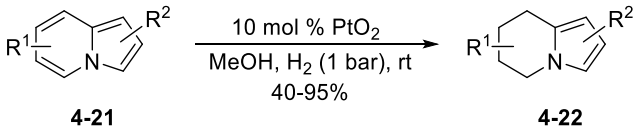


Figure 4.7: Partial hydrogenation of indolizines

4.2 Hypothesis and Synthetic Rationale for 5,6,7,8-Tetrahydroindolizine Assembly

While various procedures have been developed for the designing of 5,6,7,8-tetrahydroindolizine, some representative protocols require long reaction times, high pressure flammable gases,[223] high temperatures,[238,248] and large excess of base[149]. Moreover, some protocols require multistep operations[249–251] and give low overall yields[238,252,253]. Our recent work utilizing Lewis acid-catalyzed intramolecular Friedel-Crafts (F-C) annulations[137,254] has led us to envision another simple protocol for the formation of 5,6,7,8-tetrahydroindolizines **4-28** from methyl 1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylates **4-26**. Analogous to the tandem ring-opening/Friedel-Crafts alkylation for hydropyrido[1,2-*a*]indoles formation (Figure 4.8, scheme 1), the pyrrole substitution would afford 5,6,7,8-tetrahydroindolizines (Figure 4.8, scheme 2).

When D-A-A cyclopropane **4-26** is subjected to catalytic Lewis acid, the carbocycle opens promoting an intramolecular Friedel-Crafts alkylation. We propose the formation of aza-cationic intermediate **4-27** which can generate a new lactam ring for the bicyclic scaffold to afford 5,6,7,8-tetrahydroindolizines **4-28 (**Figure 4.8, scheme 2). Pyrroles are reactive π-nucleophiles capable of participating in this Friedel-Crafts-type chemistry. Some pyrroles are not stable to oxygen, silica, or alumina.[227] Hence, possible degradation of the products and starting materials is of concern. Regardless of the potential drawbacks, this goal is synthetically important to pursue because our method is the first example of employing donor-acceptor-acceptor or donor-donor-acceptor-acceptor cyclopropanes to form diverse methyl oxo-5,6,7,8,tetrahydroindolizine-6-carboxylates. Furthermore, the method allows for facile functionalization around the tetrahydroindolizine ring. To investigate this, we synthesized pyrrole cyclopropanes.

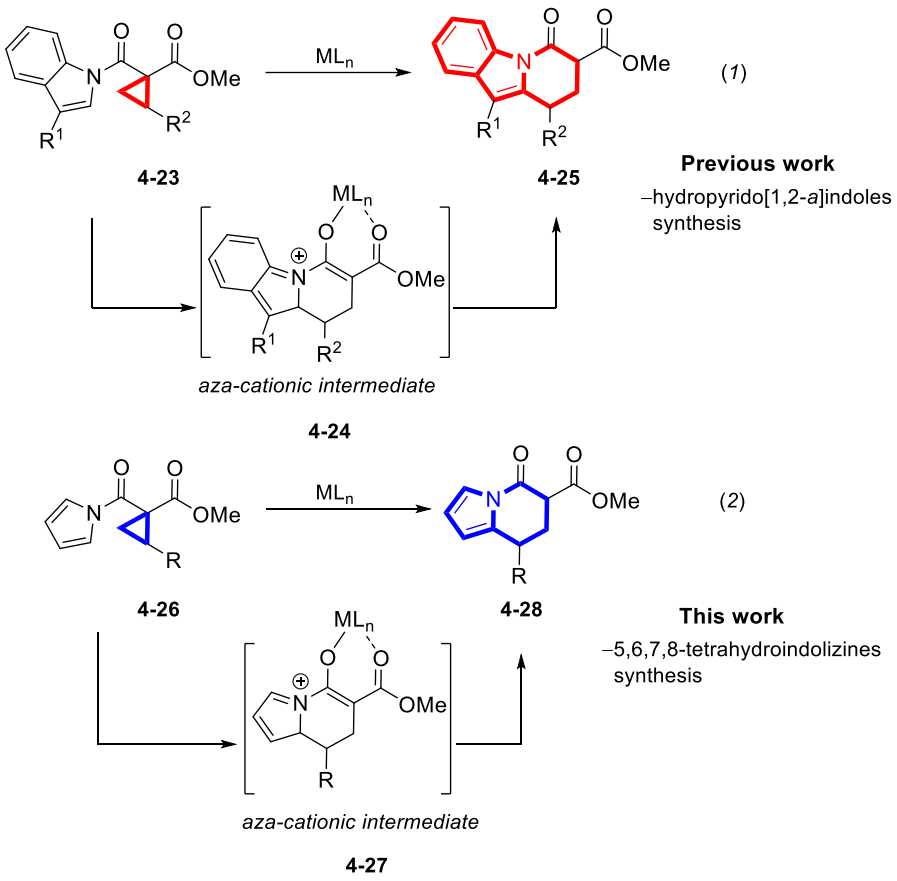


Figure 4.8: Rationale for 5,6,7,8-tetrahydroindolizine formation

4.3 Precursor Assembly and Reaction Optimization for 5,6,7,8-Tetrahydroindolizine Formation

Methyl 1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylates **4-33** were prepared according to Figure 4.9. First, commercially-available starting materials were used to form β-amidoester **4-31** over two linear steps.[255] Diazo transfer[152] gave precursor **4-32**[256] for cyclopropanation with Rh_2esp_2 [bis(rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)][153,257–260] and the requisite alkene to form cyclopropanes **4-33** in moderate to good yields (up to 81 %).

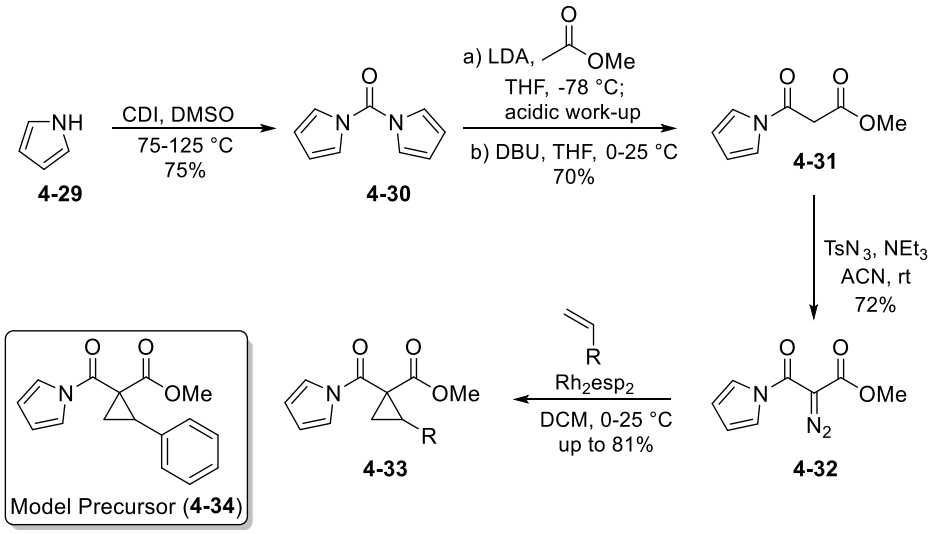


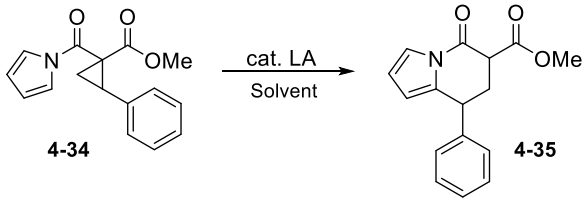
Figure 4.9: Cyclopropane synthesis for 5,6,7,8-tetrahydroindolizine assembly

Exploring the reaction scope for this annulation methodology required the use of methyl 2-phenyl-1-(1*H*-pyrrole-1-carbonyl)cyclopropane-1-carboxylate **4-34**, which served as the model substrate for the reaction optimization. In accordance with our previous In(III)-mediated ring-opening annulations,[136,137,254] we utilized $In(OTf)_3$ as an initial Lewis acid to investigate the relative reactivity for the transformation at different temperatures, concentrations, and catalyst loadings.

The optimization study commenced by subjecting pyrrole cyclopropane **4-34** to 17 mol% $In(OTf)_3$ in acetonitrile (ACN) 0.1 M at 52 ˚C for 15 hours (Table 4.1, entry 1). No cyclized product was formed. To push the reaction forward, we increased the catalyst loading to 22 mol% $In(OTf)_3$ in toluene 0.2 M at reflux for 30 minutes to give 36% yield of the desired diastereomers (Table 4.1, entry 2). The loading was changed to 31 mol% $In(OTf)_3$ in toluene 0.2 M at reflux for 30 minutes, which furnished 42% of the cyclized material (Table 4.1, entry 3). With the same concentration of 0.2 M, trials using 21 mol% and 30 mol% indium gave yields of **4-35** in 46% (Table 4.1, entry 4) and 47% (Table 4.1, entry 5) respectively, the highest yields so far. We sought to lower the temperature by using dichloromethane as a solvent either at room temperature (Table 4.1, entry 6) or reflux

(Table 4.1, entry 7); however, the outcomes were not better even when the Lewis acid loading was increased to 28 mol% at reflux (Table 4.1, entry 10). Although acetonitrile has the advantage of being a cheap, "greener" solvent, 1,2-dichloroethane was employed to strike a good balance in temperature such that the reaction would not proceed at high temperatures, which could cause degradation of the starting materials and products. Furthermore, because we understood that 1,2-dichloroethane was effective for hydropyrido[1,2-*a*]indole synthesis, we altered the loading for the catalyst and reaction concentration to identify an optimal condition (Table 4.1, entry 8, 9, and 11). Since increasing the concentration from 0.1 M to 0.2 M had a deleterious outcome, 0.1 M was chosen as the reaction concentration. In the end, 21 mol% $In(OTf)_3$ at 0.1 M in 1,2-dichloroethane at reflux formed 51% of tetrahydroindolizine **4-35**, the best outcome to this point. Given these results, we then screened typical Lewis acid catalysts used for cyclopropane ring-openings to examine the Lewis acid effects on the Friedel-Crafts alkylation and to improve the yield.

Table 4.1: Indium(III) Triflate Screening for Reaction Optimization



4-34 **4-35**

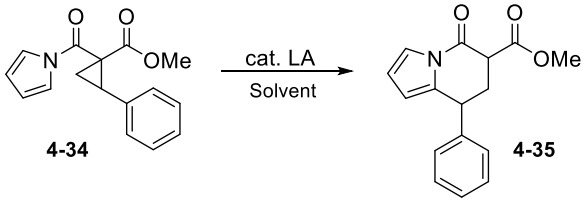
Entry[a]	LA Loading	Solvent	[M]	Temp.	Time (h)	Yield[b]
1	17 mol % $In(OTf)_3$	ACN	0.1	52 °C	15	0%
2	22 mol % $In(OTf)_3$	Toluene	0.2	111 °C	0.5	36%
3	31 mol % $In(OTf)_3$	Toluene	0.2	111 °C	0.5	42%
4	21 mol % $In(OTf)_3$	ACN	0.2	82 °C	2.0	46%
5	30 mol % $In(OTf)_3$	ACN	0.2	82 °C	2.0	47%
6	30 mol % $In(OTf)_3$	DCM	0.2	25 °C	72	0%
7	32 mol % $In(OTf)_3$	DCM	0.2	40 °C	3.5	17%
8	20 mol % $In(OTf)_3$	1,2-DCE	0.2	84 °C	1.0	34%
9	21 mol % $In(OTf)_3$	1,2-DCE	0.1	84 °C	1.0	51%
10	28 mol % $In(OTf)_3$	DCM	0.2	40 °C	4.0	19%
11	21 mol % $In(OTf)_3$	1,2-DCE	0.2	84 °C	0.5	43%
12	22 mol % $In(OTf)_3$	Toluene	0.1	85 °C	1.5	0%
13	22 mol % $In(OTf)_3$	ACN	0.1	82 °C	5.5	49%
14	22 mol % $In(OTf)_3$	Toluene	0.2	87 °C	3.5	33%

[a] Reactions run with 1.0 equiv. of precursor. [b] Isolated yields after column chromatography.

Zinc(II) triflate [$Zn(OTf)_2$], nickel(II) triflate [$Ni(OTf)_2$], magnesium(II) triflate [$Mg(OTf)_2$], and lanthanum(III) triflate [$La(OTf)_3$] did not afford a significant amount of desired product with 20 mol% catalyst loading at reaction times 21 hours or above at 0.1 M (Table 4.2, entries 1, 3, 4, and 9). Initially, indium(III) salts remained the best catalysts for the transformation (Table 4.2, entries 11 and 12). When 20 mol% aluminum(III) triflate at 0.1 M in 1,2-dichloroethane at reflux was employed as the reaction conditions, the product was formed in 56% yield (Table 4.2, entry 14), a 5% improvement over the yield achieved by using $In(OTf)_3$. As already reported in various Friedel-Crafts reactions,

aluminum(III) salts are prime Lewis acceptors which can be used for this transformation.[261–269] From the data, we speculated that the aluminum would be sufficient for apt ring activation through metal chelation and that it could accommodate a six membered-coordinating transition state where the pyrrole is poised to quench the charge build up. We further hypothesize that a balance could be attained in which the reaction conditions are not too acidic or harsh and in which the starting material and product stabilities are not compromised. Next, catalyst loading and solvent effects were examined under the higher yielding conditions.

Table 4.2: Lewis Acid Screen for 5,6,7,8-Tetrahydroindolizines



4-34 **4-35**

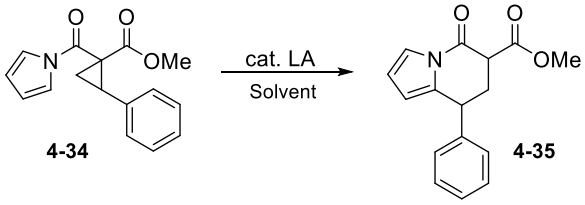
Entry[a]	LA Loading	Time (h)	Yield[b]
1	20 mol % $Zn(OTf)_2$	21.0	0%
2	20 mol % $Hg(OTf)_2$	1.25	30%
3	20 mol % $Ni(OTf)_2$	23.0	0%
4	20 mol % $Mg(OTf)_2$	21.0	0%
5	20 mol % $Cu(OTf)_2$	1.5	22%
6	20 mol % $Yb(OTf)_3$	21.0	28%
7	20 mol % $Bi(OTf)_3$	2.5	39%
8	20 mol % $Y(OTf)_3$	23.0	17%
9	20 mol % $La(OTf)_3$	23.0	0%
10	21 mol % $Ga(OTf)_3$	0.5	38%
11	20 mol % $InCl_3$	17	47%
12	21 mol % $In(OTf)_3$	1.0	51%
13	20 mol % $Sc(OTf)_3$	1.75	42%
14	20 mol % $Al(OTf)_3$	4.0	56%
15	20 mol% $Hf(OTf)_4$	1.5	38%

[a] Reactions run with 1.0 equiv. of precursor 0.1 M in 1,2-DCE at reflux.
[b] Isolated yields after column chromatography.

As a result of the higher yield obtained using 1,2-dichloromethane at reflux, the catalyst loading was lowered to 10 mol% for $Al(OTf)_3$ and $In(OTf)_3$. $In(OTf)_3$ gave 49% (Table 4.3, entry 2) versus 46% with $Al(OTf)_3$ (Table 4.3, entry 1) with similar reaction times. In order to take into account the findings published by Davies and Leonori in their paper on using calcium for the Nazarov cyclization, we included 10 mol% $Ca(NTf_2)_2$ with $(Bu)_4N(PF)_6$ as an additive to test the success of this reaction trial.[270] We obtained a 42%

yield of **4-35** after 15 hours (Table 4.3, entry 3). Since 20 mol% $Al(OTf)_3$ was superior to 10 mol% loading, a concentration effect was explored again. The concentration was changed to 0.2 M, and once again, a lower product yield was obtained. We then examined the reaction's sensitivity to solvent effects at reflux by using 19-20 mol% $Al(OTf)_3$. Ethyl acetate (EtOAc) afforded 40% of the product after 17.5 hours (Table 4.3, entry 5), and toluene gave 48% yield after 2 hours (Table 4.3, entry 6); acetonitrile afforded 64% after 2 hours with 1.5:1 *dr* (Table 4.3, entry 7). In our previous studies, the *trans* diastereomer was the more thermodynamically stable diastereomer than the *cis*. NMR experiments are underway for further verification of this stereochemical relationship. Benzene furnished a 29% yield after 18.0 hours (Table 4.3, entry 8). The reaction may proceed better in acetonitrile because of the solubility of the catalyst, the lower reaction temperature, and the solvent stability of the charged intermediates that may form; moreover, acetonitrile was shown to be a good solvent for rendering hydropyrido[1,2-*a*]indoles in batch and continuous flow operations.[271] The appropriate controls revealed that heat is required for ring-opening (Table 4.3, entry 9) and that an appropriate Lewis acid is necessary for product formation in a reasonable time (Table 4.3, entry 10). Hence, the final optimized conditions were 1.0 equivalent of precursor (0.1 M) and 20 mol% $Al(OTf)_3$ in acetonitrile at reflux.

Table 4.3: Further Lewis Acid Screening for Optimization



4-34 **4-35**

Entry[a]	LA Loading	Solvent	[M]	Temp.	Time (h)	Yield[b]
1	10 mol % $Al(OTf)_3$	1,2-DCE	0.1	84 °C	5.0	46%
2	10 mol % $In(OTf)_3$	1,2-DCE	0.1	84 °C	5.25	49%
3	10 mol % $Ca(NTf_2)_2$ 10 mol % $(Bu)_4N(PF_6)$	1,2-DCE	0.1	84 °C	15	42%
4	20 mol % $Al(OTf)_3$	1,2-DCE	0.2	84 °C	3.5	37%
5	20 mol % $Al(OTf)_3$	EtOAc	0.1	77 °C	17.5	40%
6	19 mol % $Al(OTf)_3$	Toluene	0.1	111 °C	2.0	48%
7	20 mol % $Al(OTf)_3$	ACN	0.1	82 °C	2.0	64%
8	20 mol % $Al(OTf)_3$	Benzene	0.1	80 °C	18.0	29%
9	20 mol % $Al(OTf)_3$	ACN	0.1	25 °C	24.0	0%
10	0 mol % $Al(OTf)_3$	ACN	0.1	84 °C	24.0	0%

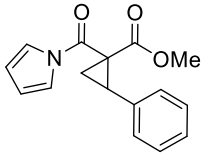
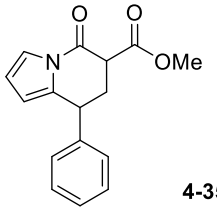
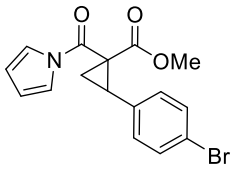
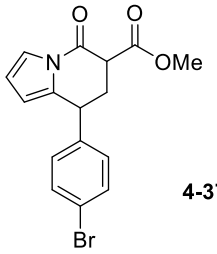
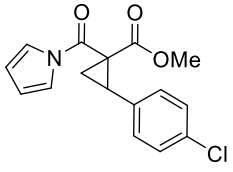
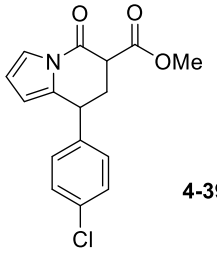
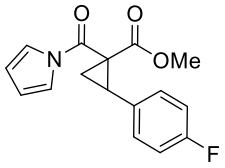
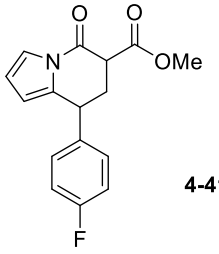
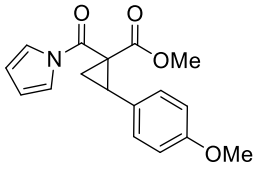
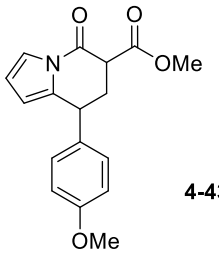
[a] Reactions run with 1.0 equiv. of precursor at 0.1 M.
[b] Isolated yields after column chromatography.

4.4 Results and Discussion

Within the model precursor, a phenyl group serves as the aryl donor substituent. In order to explore the electronic effects of aryl substituents, we investigated differing *para*-substituted electron-donating and electron-withdrawing groups. 4-Bromo phenyl cyclopropane **4-36** gave cyclized tetrahydroindolizine **4-37** in 51% yield with 1.8:1 *dr* (Table 4.4, entry 2). In the same manner, 4-chloro phenyl substrate **4-38** generated **4-39** in 54% yield with 1.8:1 *dr* in the same reaction time of 3 hours as bromo aryl **4-35** (Table 4.4, entry 3). In contrast to the cyclization that results from the use of the phenyl precursor, the halogenated precursors have longer reaction times and lower yields for the cyclization. F-phenyl precursor **4-40** afforded bicycle **4-41** after 1 hour in 71% yield with 1.5:1 *dr* (Table 4.4, entry 4). When a donating group, such as the OMe moiety in **4-42** was added, the yield

increased to 97% for **4-43** with 1.3:1 *dr* in 20 minutes (Table 4.4, entry 5). Since the ring becomes more donating by adding an OMe, the positive charge build up is more stabilized. In comparison to the bromo, chloro, and fluoro cases, reaction times increase and lower yields are obtained. The bromo and chloro aryls have similar product outcomes owing to less stabilization of the benzylic position. Interestingly, the fluoro product was obtained in a higher yield. If our mechanistic thinking is plausible, increasing stability at the benzylic position should promote reactivity; this notion was tested by synthesizing α -methyl styrene derivative **4-44**.

Table 4.4: $Al(OTf)_3$-Catalyzed Friedel-Crafts Alkylation of Pyrrole Cyclopropyl Amides

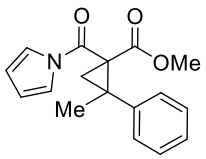
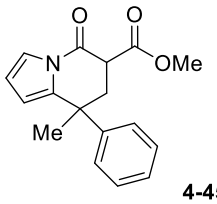
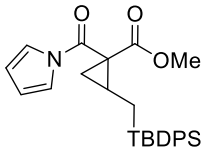
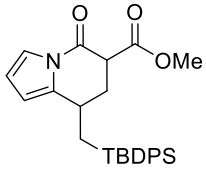
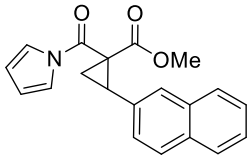
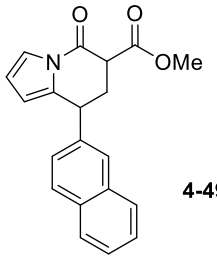
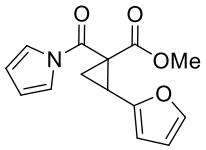
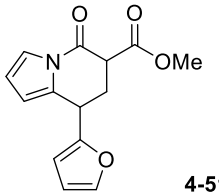
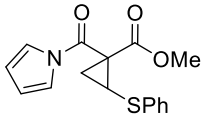
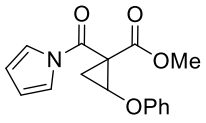
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **4-34**	 **4-35**	2.0	64%	1.5:1
2	 **4-36**	 **4-37**	3.0	51%	1.8:1
3	 **4-38**	 **4-39**	3.0	54%	1.8:1
4	 **4-40**	 **4-41**	1.0	71%	1.5:1
5	 **4-42**	 **4-43**	0.33	97%	1.3:1

[a] Reactions run with 1.0 equiv. of the precursor and 20 mol % $Al(OTf)_3$ in acetonitrile at 82 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans* and *cis* diastereomeric ratios.

We sought to test the stabilizing effect of adding another donor group. α-Methyl styrene derivative **4-44** was placed under the reaction conditions to yield bicycle **4-45** in

95% yield with 4.0:1.0 *dr* in 30 minutes (Table 4.5, entry 1). Adding another donor group improved the product outcome in comparison to the outcome achieved by using only one phenyl group for stabilization, as in precursor **4-34** (Table 4.4, entry 1). Of note, this protocol affords a quaternary center directly, increasing product complexity. In accordance with Yadav's previous disclosure[106] where he used methylsilyl groups for β-cation stability, precursor **4-46** was synthesized, and it reacted to form **4-47** in 72% yield with 1.5:1 *dr* (Table 4.5, entry 2). Pleased so far with our product outcomes, we examined the effects of other aryl groups and heteroatoms as donor groups.

Table 4.5: Donor Effects on the Cyclization

Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **4-44**	 **4-45**	0.5	95%	4.0:1
2	 **4-46**	 **4-47**	0.5	72%	1.5:1
3	 **4-48**	 **4-49**	0.5	69%	1.3:1
4	 **4-50**	 **4-51**	0.5	78%	1.2:1
5	 **4-52**	--			
6	 **4-53**	--			

[a] Reactions run with 1.0 equiv. of the precursor and 20 mol % $Al(OTf)_3$ in acetonitrile at 82 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans* and *cis* diastereomeric ratios.

Naphthalene derivative **4-48** afforded tetrahydroindolizine **4-49** in 69% with 1.3:1 *dr* in 30 minutes (Table 4.5, entry 3). 2-Furyl **4-50** gave **4-51** in 78% yield with 1.2:1 *dr* in

30 minutes as well. The furan did not degrade under the reaction conditions. Hence, the aromatic groups acted as a good donor for this methodology. However, when vinyl phenyl sulfide derivative **4-52** was subjected to the reaction conditions, the reaction proceeded very rapidly rendering 100% conversion of the starting material to other compounds. According to TLC, multiple side-products appeared to form. Although the desired products were evident by NMR, more purification was necessary. For this thioether substrate, heating may not have been necessary because of the donating ability and polarizability of the sulfur, but this assertion has yet to be affirmed. Vinyl phenyl ether derivative **4-53** did not give any appreciable product. Despite the setbacks with heteroatom donors, the other donor-acceptor-acceptor cyclopropanes formed their desired tetrahydroindolizines. Moreover, the yields obtained are comparable if not better than the reported protocols to date. To apply this methodology in natural product synthesis, rhazinicine **4-6** was chosen as an initial target compound.

4.5 *rac*-Rhazinicine Synthesis

Rhazinicine, a member of the rhazinilam family, has garnered considerable attention from synthetic and medicinal chemists as a potential lead antitumor compound as a result of its *in vitro* cytotoxic activity against human promyelocytic leukemia cells (CD_{50} >60 μg/mL), human cervical cancer cells (CD_{50} 2.9 μg/mL), and vincristine-resistant human oral epidermoid carcinoma cells (IC_{50} 4.06 μM).[272,273] Originally reported in a hemisynthesis by Guénard, this Malaysian *Apocynaceae* alkaloid was isolated from *Kopsia dasyrachis* and *Kopsia singapurensis* stem extract.[215,272] Although the natural product's anticancer activity afforded promising medicinal results, rhazinicine exhibited harmful cytotoxic effects on normal mouse fibroblast cells (CD_{50} 20.8 μg/mL), warranting further SAR studies and derivatives to improve its efficacy and selectivity for cancer cells over adherent cells.[273] The devised modular ring-opening/Friedel-Crafts cyclization sequence

could be used to complete the total synthesis of rhazinicine and synthesized derivatives for medicinal testing.

Structurally, rhazinicine contains a nine-membered lactam flanked by a heterobiaryl unit with a 5,6,7,8-tetrahydroindolizine skeleton encompassing a stereogenic quaternary center. As a result of these architectural features, Gaunt, using Ir^{I}- and Pd^{II}-catalyzed C-H functionalizations, and Tokuyama, employing a gold-catalyzed cascade cyclization, published elegant syntheses of the target molecule.[217,274] Tokuyama synthesized rhazinicine in 14 steps whereas Gaunt trimmed the total synthesis to 10 linear steps. In contrast to Gaunt's approach, we envisioned an early construction of the 5,6,7,8-tetrahydroindolizinone moiety through a unique Lewis acid-catalyzed ring-opening/Friedel-Crafts alkylation sequence of a donor-donor-acceptor-acceptor cyclopropane synthetic equivalent without an extensive 10 step precursor preparation as in Tokuyama's report. Our retrosynthetic analysis is displayed in Figure 4.10.

In the final stages of the synthesis, we intended to form the heterobiaryl unit and nine-membered lactam using a late-stage C-H functionalization. Before amide formation with a *N*-protected-2-iodoaniline, we planned to install the 5,6,7,8-tetrahydroindolizine framework from a polarized donor-donor-acceptor-acceptor (D-D-A-A) cyclopropane.

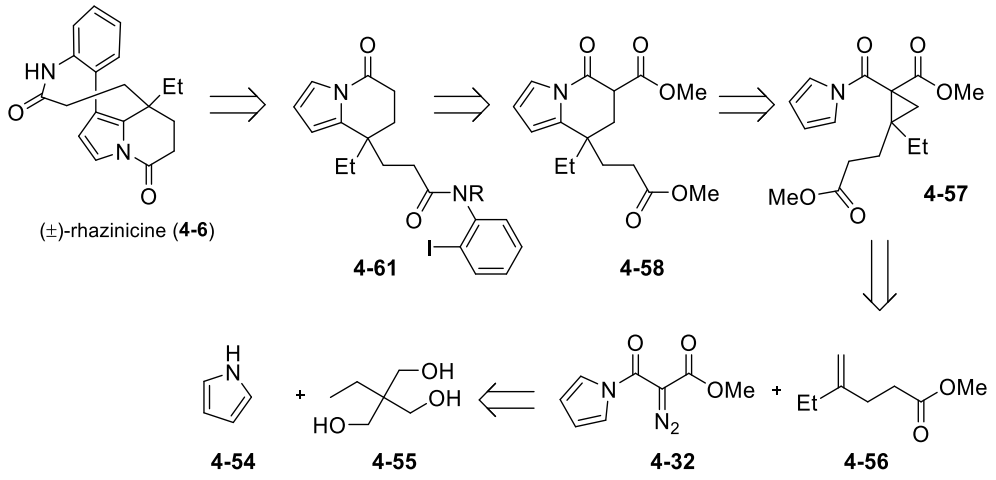


Figure 4.10: Retrosynthetic analysis for rhazinicine

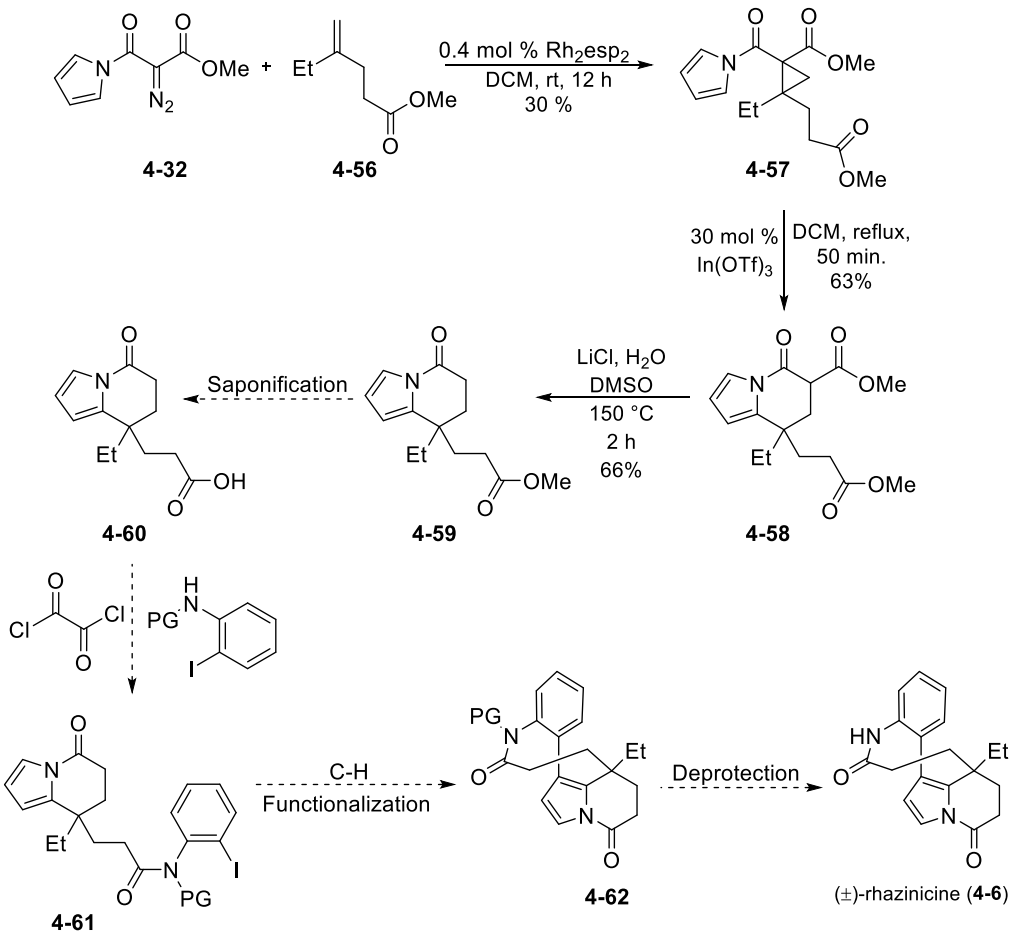


Figure 4.11: Synthetic route for rhazinicine

In the forward synthesis, Rh(II)-catalyzed cyclopropanation with diazo **4-32** and alkene **4-56** gave cyclopropane **4-57** in 30% yield in an unoptimized step. Tandem ring-opening/Friedel-Crafts alkylation sequence with $In(OTf)_3$ produced tetrahydroindolizine **4-58** in 63% yield with 1.1:1 *dr*. Krapcho[275] decarbalkoxylation with lithium chloride gave a 66% yield of **4-59**. To finish the natural product, future steps would include saponification to afford **4-60** or a direct amide coupling with the ester **4-59**. After saponification, amide formation via acyl chloride would furnish **4-61**. Direct C-C coupling with the pyrrole through a $C(sp^2)$-H functionalization step would give **4-62**. Deprotection would afford *rac*-rhazinicine **4-6 (**Figure 4.11). With our method, this total synthesis would showcase the use a donor-acceptor cyclopropane to access the 5,6,7,8-tetrahydroindolizine

core for rhazinicine. Thus, our synthetic route would form the target in 10 steps with a more direct approach.

4.6 Conclusion

In summary, an Al(III)-catalyzed tandem ring-opening/Friedel-Crafts cyclization method was designed to afford functionalized 5,6,7,8-tetrahydroindolizines in yields up to 95%. The protocol is amenable, atom economical, and useful for assembling diverse tetrahydroindolizines. Products obtained for this protocol were obtained quickly and were stable on silica gel. Further utility of this method was applied toward the total synthesis of *rac*-rhazinicine such that the tetrahydroindolizine core was obtained in good yield, affirming the importance of donor-acceptor cyclopropanes as synthetic equivalents for C-C bond formation.

4.7 Research Participants

This work was conducted by Marchello Cavitt.

4.8 Experimental Information

4.8.1 Synthetic Methods for Tetrahydroindolizine Preparation

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification.

Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm). For quantitative flash chromatography, technical grades

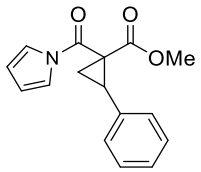
solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Dynamic Absorbents, Inc. silica gel F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic p-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (1H NMR: CDCl3 at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Diastereomeric ratios for the cyclized products were determined by ^{1}H NMR based on a comparison of the signal ratios of the benzylic protons (~4.0-5.0 ppm) for the two diastereomeric protons or other signals displaying clear separation. These assignments are based on the coupling constants. A single observable diastereomer corresponds to >99:1 *dr*. Mass spectra were obtained using a MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. Compound **4-31**[255] and **4-32**[276] were synthesized according to previous reports. *Compounds synthesized and not reported in the literature are listed below.*

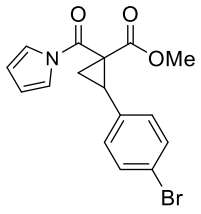
4.8.2 Cyclopropane Synthesis for Tetrahydroindolizine Formation

The cyclopropanes were prepared using a modified version of Soumeillant's

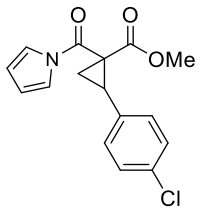
protocol:[153] A round bottom flask was charged with Rh_2esp_2 and a magnetic stir bar. DCM (2.0 mL) was added to the flask. The reaction vessel was cooled to 0˚C, and the corresponding alkene (1.0-3.0 equiv) was added. After 10 minutes, the diazo reagent[256] **4-32** (1.0-2.0 equiv.) was dissolved in DCM (5 mL) and syringed into the reaction mixture. After 10 minutes, the ice bath was removed and the reaction proceeded at room temperature. Upon completion (monitored by TLC) or 12 hours of reactivity, the solution was quenched with saturated thiourea and stirred for 30 minutes. The organic layer was separated, and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography.



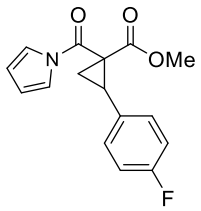
Methyl 2-phenyl-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-34): The general procedure was followed using styrene (650 µL, 5.67 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (538.8 mg, 2.79 mmol), Rh_2esp_2 (4 mg, 5.06 µmol), and DCM (12.5 mL). After 7 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f= 0.66) afforded **4-34** as a white solid (605.7 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 – 7.30 (m, 6H), 7.29 – 7.26 (m, 1H), 6.33 – 6.29 (m, 2H), 3.44 (dd, J_1=J_2= 9.5 Hz, 1H), 3.39 (s, 3H), 2.41 (dd, J = 8.3, 5.3 Hz, 1H), 1.80 (dd, J = 9.3, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.6, 165.6, 133.9, 129.1, 128.2, 127.5, 119.5, 113.4, 52.7, 38.4, 31.2, 18.6. HRMS (ESI) M/Z+ Calc.269.1052, Obs. 269.1043.



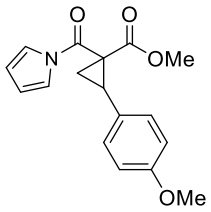
Methyl 2-(4-bromophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-36): The general procedure was followed using 1-bromo-4-vinylbenzene (105 mg, 0.574 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (159.8 mg, 0.827 mmol), Rh_2esp_2 (1.0 mg, 1.266 µmol), and DCM (5.5 mL). After 7 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f= 0.66) gave **4-36** as a white solid (87.8 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.50 – 7.39 (m, 2H), 7.31 (t, *J* = 2.4 Hz, 2H), 7.24 – 7.16 (m, 2H), 6.35 – 6.28 (m, 2H), 3.43 (s, 3H), 3.36 (dd, J_1=J_2= 8.8 Hz, 1H), 2.37 (dd, *J* = 8.3, 5.4 Hz, 1H), 1.81 (dd, *J* = 9.3, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.4, 165.3, 133.0, 131.3, 130.8, 121.6, 119.5, 113.6, 52.9, 38.4, 30.5, 18.6. HRMS (ESI) M/Z+ Calc. 347.0157, Obs. 347.0169.



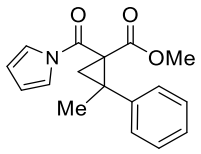
Methyl 2-(4-chlorophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-38): The general procedure was followed using 1-chloro-4-vinylbenzene (88 µL, 0.726 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (187.6 mg, 0.971 mmol), Rh_2esp_2 (1.2 mg, 1.519 µmol), and DCM (7 mL). After 8 hours, the reaction was quenched, and column chromatography furnished **4-38** as a white solid (105.3 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.32 – 7.27 (m, 2H), 7.28 – 7.20 (m, 4H), 6.29 (dd, *J* = 2.7, 2.0 Hz, 2H), 3.41 – 3.33 (m, 4H), 2.35 (dd, *J* = 8.3, 5.4 Hz, 1H), 1.79 (dd, *J* = 9.3, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.3, 165.3, 133.4, 132.4, 130.4, 128.4, 119.4, 113.5, 52.8, 38.4, 30.4, 18.6. HRMS (ESI) M/Z+ Calc. 303.0662, Obs. 303.0674.



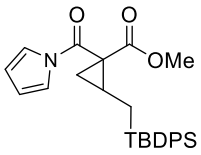
Methyl 2-(4-fluorophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-40): The general procedure was followed using 1-fluoro-4-vinylbenzene (100 µL, 0.822 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (216.4 mg, 1.120 mmol), Rh_2esp_2 (1.2 mg, 1.519 µmol), and DCM (8.2 mL). After 7 hours, the reaction was quenched, and column chromatography rendered **4-40** as a white solid (131.8 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.37 – 7.26 (m, 4H), 7.09 – 6.88 (m, 2H), 6.32 (dd, *J* = 2.7, 2.0 Hz, 2H), 3.45 – 3.36 (m, 4H), 2.38 (dd, *J* = 8.3, 5.4 Hz, 1H), 1.80 (dd, *J* = 9.3, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.4, 165.4, 163.7, 160.5, 130.7and 130.6 (^{13}C-^{19}F coupling, *J* = 8.1 Hz), 129.7 and 129.6 (^{13}C-^{19}F coupling, *J* = 3.4 Hz), 119.4, 115.2, 114.9, 113.4, 52.8, 38.3, 30.3, 18.7. HRMS (ESI) M/Z+ Calc. 287.0958, Obs. 287.0967.



Methyl 2-(4-methoxyphenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-42): The general procedure was followed using 1-methoxy-4-vinylbenzene (104 µL, 0.742 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (192.7 mg, 0.998 mmol), Rh_2esp_2 (1.1 mg, 1.392 µmol), and DCM (7.5 mL). After 12 hours, the reaction was quenched, and column chromatography afforded **4-42** as a white solid (0.134 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.37 – 7.30 (m, 2H), 7.30 – 7.20 (m, 2H), 6.91 – 6.80 (m, 2H), 6.35 – 6.27 (m, 2H), 3.79 (s, 3H), 3.46 – 3.32 (m, 4H), 2.36 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.78 (dd, *J* = 9.4, 5.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.6, 165.7, 158.9, 130.1, 125.7, 119.4, 113.5, 113.3, 104.9, 55.1, 52.7, 38.3, 30.7, 18.7. HRMS (ESI) M/Z+ Calc. 299.1158, Obs. 299.1154.

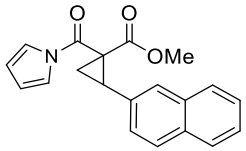


Methyl 2-methyl-2-phenyl-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-44): The general procedure was followed using prop-1-en-2-ylbenzene (110 µL, 0.838 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (247.5 mg, 1.281 mmol), Rh_2esp_2 (1.2 mg, 1.519 µmol), and DCM (6 mL). After 12 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f= 0.68) gave **4-44** as a white solid (176 mg, 74%). *Diastereomeric ratio:* (14.7:1) (^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.46 – 7.27 (m, 7.25), 7.21 – 7.11 (m, 0.56), 7.09 – 7.03 (m, 0.16), 6.34 (dd, *J* = 2.7, 2.1 Hz, 1.91), 6.15 – 6.12 (m, 0.14), 3.71 (s, 0.18), 3.41 (s, 2.94), 2.60 (d, *J* = 5.5 Hz, 0.07), 2.42 (d, *J* = 5.1 Hz, 1.03), 1.91 – 1.86 (m, 0.30), 1.81 (d, *J* = 5.2 Hz, 1.00), 1.49 (s, 3.11). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 168.0, 164.8, 140.4, 128.4, 128.1, 127.3, 119.9, 113.3, 52.6, 40.8, 38.1, 25.9, 25.5. HRMS (ESI) M/Z+ Calc. 283.1208, Obs. 283.1208.

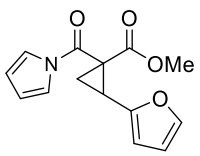


Methyl 2-((tert-butyldiphenylsilyl)methyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate 4-46): The general procedure was followed using allyl(tert-butyl)diphenylsilane (1.17 g, 4.17 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (399.2 mg, 2.067 mmol), Rh_2esp_2 (3.4 mg, 4.30 µmol), and DCM (10 mL). After 12 hours, the reaction was quenched, and column chromatography furnished **4-46** as a white solid (129 mg, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 – 7.63 (m, 4.02), 7.63 – 7.59 (m, 0.85), 7.60 – 7.56 (m, 4.52), 7.45 – 7.31 (m, 14.58), 7.21 – 7.17 (m, 2.30), 6.32 (t, *J* = 2.3 Hz, 2.21), 6.24 (t, *J* = 2.4 Hz, 2.13), 3.67 (s, 2.74), 3.59 (s, 3.00), 2.21 –

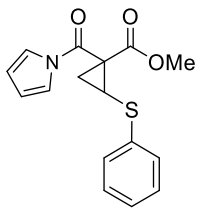
2.16 (m, 0.40), 2.13 – 1.96 (m, 2.42), 1.63 – 1.57 (m, 2.28), 1.45 – 1.32 (m, 2.41), 1.30 – 1.16 (m, 4.20), 1.11 – 1.05 (m, 11.53), 1.00 (s, 11.29), 0.50 (dd, *J* = 14.7, 12.5 Hz, 1.41). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 170.9, 169.3, 166.2, 165.2, 136.1, 136.0, 135.9 (2C), 134.1, 133.7 (2C), 133.6, 129.4, 129.3 (2C), 129.0, 127.8, 127.7 (2C), 127.6, 127.5, 119.6, 119.4, 113.3, 113.0, 52.8, 52.8, 36.2, 35.9, 27.8 (2C), 27.7, 26.2, 25.4, 23.8, 22.98, 18.7, 18.1, 18.0, 10.61, 7.87. HRMS (ESI) M/Z+ Calc. 445.2064, Obs. 445.2063.



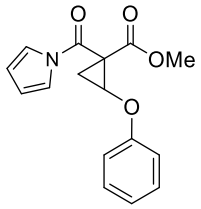
Methyl 2-(naphthalen-2-yl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate 4-48: The general procedure was followed using 2-vinylnaphthalene (0.5824 g, 3.66 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (402.0 mg, 2.081 mmol), Rh_2esp_2 (3.8 mg, 4.81 μmol), and DCM (11 mL). After 15 hours, the reaction was quenched, and column chromatography rendered **4-48** as a yellow solid (412 mg, 62%). Diastereomeric ratio: (4.7:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 – 7.77 (m, 4.12), 7.74 – 7.69 (m, 0.48), 7.65 – 7.61 (m, 0.34), 7.57 – 7.55 (m, 0.29), 7.52 – 7.43 (m, 3.14), 7.44 – 7.39 (m, 0.51), 7.38 (s, 1.85), 7.20 (dd, *J* = 8.5, 1.9 Hz, 0.25), 7.05 (s, 0.39), 6.35 – 6.28 (m, 1.98), 6.04 – 5.98 (m, 0.42), 3.73 (s, 0.61), 3.60 (dd, J_1=J_2= 8.8 Hz, 0.97), 3.54 (dd, J_1=J_2= 8.7 Hz, 0.25), 3.35 (s, 2.91), 2.56 (dd, *J* = 8.3, 5.3 Hz, 1.00), 2.50 (dd, *J* = 8.0, 5.4 Hz, 0.26), 2.00 (dd, *J* = 9.3, 5.4 Hz, 0.22), 1.89 (dd, *J* = 9.3, 5.3 Hz, 1.01). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 167.5, 165.6, 133.1, 133.0, 132.7, 131.4, 128.1, 128.0, 127.8 (2C), 127.7, 127.6, 127.5, 126.9, 126.5, 126.2, 126.0, 125.9, 119.5, 119.4, 113.5, 112.9, 53.1, 52.8, 38.9, 38.6, 33.5, 31.4, 19.9, 18.8. HRMS (ESI) M/Z+ Calc. 319.1208, Obs. 319.1215.



Methyl 2-(furan-2-yl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-50): The general procedure was followed using 2-vinylfuran (1.79 g, 9.51 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (600 mg, 3.11 mmol), Rh_2esp_2 (11.2 mg, 0.014 mmol), and DCM (10 mL). After 15 hours, the reaction was quenched, and column chromatography afforded **4-50** as a yellow solid (382 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 – 7.35 (m, 3H), 6.36 – 6.30 (m, 3H), 6.27 – 6.25 (m, 1H), 3.53 (s, 3H), 3.21 (d, J_1=J_2= 8.8 Hz, 1H), 2.28 (dd, J = 8.0, 5.3 Hz, 1H), 1.90 (dd, J = 9.5, 5.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 167.3, 165.0, 148.8, 142.4, 119.7, 113.5, 110.5, 108.8, 52.9, 37.2, 24.4, 18.6. HRMS (ESI) M/Z+ Calc. 259.0845, Obs. 259.0844.



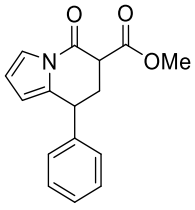
Methyl 2-(phenylthio)-1-(1H-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-52): The general procedure was followed using phenyl(vinyl)sulfane (97 µL, 0.720 mmol), methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (214.1 mg, 1.108 mmol), Rh_2esp_2 (1.1 mg, 1.392 µmol), and DCM (7.3 mL). After 12 hours, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f= 0.69) afforded **4-52** as a brown solid (14 mg, 6.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 – 7.43 (m, 2H), 7.34 – 7.27 (m, 4H), 7.21 – 7.16 (m, 1H), 6.31 – 6.29 (m, 2H), 3.55 – 3.50 (m, 4H), 2.13 (dd, J = 7.4, 5.8 Hz, 1H), 1.88 (dd, J = 9.3, 5.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.9, 164.7, 135.3, 128.9, 127.6, 126.0, 119.4, 113.8, 53.1, 38.8, 27.8, 20.0. HRMS (ESI) M/Z+ Calc. 301.0773, Obs. 301.0768.



Methyl 2-(furan-2-yl)-1-(1H-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-53): The general procedure was followed using 2-vinylfuran (1.79 g, 9.51 mmol), methyl 2-diazo-3-oxo-3-(1H-pyrrol-1-yl)propanoate (600 mg, 3.11 mmol), Rh_2esp_2 (11.2 mg, 0.014 mmol), and DCM (10 mL). After 15 hours, the reaction was quenched, and column chromatography formed **4-53** as a yellow solid (382 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.34 – 7.27 (m, 4H), 7.20 – 7.16 (m, 2H), 7.03 – 6.99 (m, 1H), 6.32 – 6.30 (m, 2H), 4.67 (dd, *J* = 7.1, 5.4 Hz, 1H), 3.45 (s, 3H), 2.53 (dd, *J* = 6.7, 5.3 Hz, 1H), 1.80 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ ppm 167.3, 165.0, 148.8, 142.4, 119.7, 113.5, 110.5, 108.8, 52.9, 37.2, 24.4, 18.6. HRMS (ESI) M/Z+ Calc. 259.0845, Obs. 259.0844.

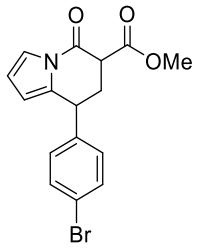
4.8.3 Al(OTf)$_3$-Catalyzed Ring-opening/Friedel-Crafts Alkylation Sequence

The $Al(OTf)_3$, cyclopropyl β-amide ester (1.0 equiv) and dichloromethane needed for 0.1 M at room temperature were combined in a round bottom flask. Upon completion, the reaction mixture was purified directly by silica gel flash column chromatography. Products were shown by 2-D thin layer chromatography to be stable on silica gel.



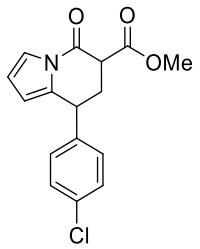
Methyl 5-oxo-8-phenyl-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-35): Methyl 2-phenyl-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.1 mg, 0.186 mmol), $Al(OTf)_3$ (17.6 mg, 0.037 mmol) and ACN (2.0 mL) were combined according to the

general method to give **4-35** as a green oil (32 mg, 64%) after 3 hours. *Diastereomeric ratio*: (1.54:1.0) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.47 – 7.43 (m, 0.89), 7.41 (dt, *J* = 3.5, 1.3 Hz, 1.13), 7.39 – 7.27 (m, 8.68), 7.20 – 7.15 (m, 1.98), 6.27 (t, *J* = 3.3 Hz, 0.88), 6.23 (t, *J* = 3.3 Hz, 1.07), 5.79 (m, 0.90), 5.64 (m, 1.04), 4.28 (dd, *J* = 9.4, 4.5 Hz, 1.00), 4.08 (dd, *J* = 12.5, 4.5 Hz, 1.16), 3.89 – 3.68 (m, 8.30), 2.76 – 2.60 (m, 2.05), 2.49 – 2.36 (m, 2.12). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.2, 169.1, 164.4, 164.0, 141.3, 140.9, 136.0, 135.0, 128.7, 128.7, 128.2, 127.8, 127.6, 127.4, 117.0, 116.9, 113.4, 113.3, 111.3, 52.9, 52.7, 50.7, 48.1, 40.5, 37.6, 34.4, 34.0. HRMS (ESI) M/Z+ Calc. 269.1052, Obs. 269.1058.

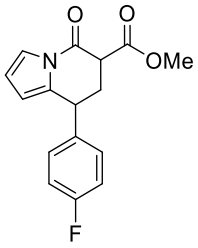


Methyl 8-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-37): Methyl 2-(4-bromophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.0 mg, 0.144 mmol), $Al(OTf)_3$ (13.8 mg, 0.029 mmol) and ACN (1.5 mL) were combined according to the general method to furnish **4-37** as a green oil (25.6 mg, 51%) after 3 hours. *Diastereomeric ratio*: (1.79:1.0) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.52 – 7.45 (m, 4.22), 7.44 (ddd, *J* = 3.4, 1.6, 0.7 Hz, 0.91), 7.41 (dt, *J* = 3.4, 1.3 Hz, 1.02), 7.21 – 7.16 (m, 2.25), 7.10 – 7.05 (m, 1.83), 6.26 (t, *J* = 3.3 Hz, 0.89), 6.23 (t, *J* = 3.3 Hz, 1.01), 5.77 – 5.74 (m, 0.83), 5.65 – 5.61 (m, 1.00), 4.24 (dd, *J* = 9.5, 4.3 Hz, 0.88), 4.05 (dd, *J* = 12.5, 4.4 Hz, 1.04), 3.84 – 3.78 (m, 7.30), 3.76 (t, *J* = 5.5 Hz, 1.12), 2.70 – 2.56 (m, 2.00), 2.44 – 2.34 (m, 1.97). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.0, 168.9, 164.2, 163.6, 140.4, 139.9, 135.4, 134.5, 131.9, 131.7, 129.9, 129.6, 121.5, 121.3, 117.2, 117.1, 113.4, 1113.3,

111.5, 111.4, 53.0, 52.8, 50.6, 48.1, 39.9, 37.2, 34.3, 33.9. HRMS (ESI) M/Z+ Calc. 347.0157, Obs. 347.0165.

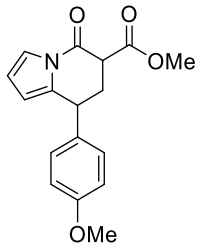


Methyl 8-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-39): Methyl 2-(4-chlorophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.5 mg, 0.166 mmol), $Al(OTf)_3$ (17.3 mg, 0.036 mmol) and ACN (1.8 mL) were combined according to the general method to furnish **4-39** as a green oil (27.3 mg, 54%) after 20 minutes. *Diastereomeric ratio*: (1.75:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.46 – 7.43 (m, 0.87), 7.42 – 7.39 (m, 1.09), 7.36 – 7.29 (m, 4.34), 7.27 – 7.22 (m, 2.93), 7.15 – 7.11 (m, 2.13), 6.26 (t, *J* = 3.3 Hz, 0.96), 6.23 (t, *J* = 3.3 Hz, 1.05), 5.77 – 5.74 (m, 0.83), 5.65 – 5.61 (m, 1.00), 4.25 (dd, *J* = 9.3, 4.4 Hz, 0.94), 4.06 (dd, *J* = 12.5, 4.4 Hz, 1.10), 3.85 – 3.74 (m, 9.01), 2.72 – 2.52 (m, 2.13), 2.47 – 2.34 (m, 2.14). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.0, 168.9, 164.1, 163.7, 139.9, 139.4, 135.5, 134.6, 133.4, 133.2, 129.5, 129.3, 128.9, 117.2, 117.1, 113.4, 113.3, 111.5, 111.4, 53.0, 52.8, 50.6, 48.1, 39.9, 37.1, 34.3, 33.9. HRMS (ESI) M/Z+ Calc. 303.0667, Obs. 303.0671.



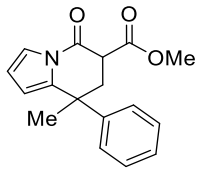
Methyl 8-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-41): Methyl 2-(4-fluorophenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.2 mg,

0.175 mmol), $Al(OTf)_3$ (16.8 mg, 0.035 mmol) and ACN (1.9 mL) were combined according to the general method to render **4-41** as a green oil (35.6 mg, 71%) after 20 minutes. *Diastereomeric ratio*: (1.47:1.0) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 1.00), 7.42 – 7.39 (m, 0.96), 7.29 – 7.26 (m, 1.56), 7.18 – 7.14 (m, 2.06), 7.08 – 6.99 (m, 4.21), 6.26 (t, *J* = 3.3 Hz, 0.92), 6.23 (t, *J* = 3.3 Hz, 0.94), 5.80 – 5.72 (m, 0.88), 5.66 – 5.58 (m, 0.90), 4.25 (dd, *J* = 10.2, 4.5 Hz, 1.09), 4.07 (dd, *J* = 12.5, 4.4 Hz, 1.04), 3.85 – 3.74 (m, 9.14), 2.72 – 2.56 (m, 2.13), 2.46 – 2.32 (m, 2.07). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.1, 169.0, 164.3, 163.8, 162.8, 161.1, 161.0, 137.0, 136.7, 136.6, 135.9, 134.9, 129.7, 129.6, 129.5, 129.4, 128.2, 117.2, 117.0, 116.6, 115.7, 115.6, 115.4, 113.4, 113.3, 113.2, 111.4, 111.3, 53.0, 52.8, 50.6, 48.2, 39.8, 37.0, 34.6, 34.1, which includes ^{13}C-^{19}F coupled peaks. HRMS (ESI) M/Z+ Calc. 287.0946, Obs. 287.0949.

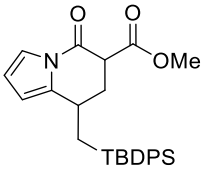


Methyl 8-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-43): Methyl 2-(4-methoxyphenyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.1 mg, 0.167 mmol), $Al(OTf)_3$ (16.0 mg, 0.033 mmol) and ACN (1.8 mL) were combined according to the general method to afford **4-43** as a green oil (48.6 mg, 97%) after 20 minutes. *Diastereomeric ratio*: (1.25:1.0) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.44 – 7.41 (m, 0.99), 7.40 – 7.38 (m, 1.05), 7.24 – 7.19 (m, 2.21), 7.12 – 7.07 (m, 1.93), 6.92 – 6.83 (m, 4.51), 6.25 (t, *J* = 3.3 Hz, 1.00), 6.22 (t, *J* = 3.3 Hz, 1.08), 5.78 – 5.75 (m, 0.87), 5.64 – 5.62 (m, 1.00), 4.22 (dd, *J* = 9.4, 4.4 Hz, 0.97), 4.02 (dd, *J* = 12.6, 3.7 Hz, 1.14), 3.85 – 3.74 (m, 16.87), 2.71 – 2.52 (m, 2.17), 2.45 – 2.30 (m, 2.23). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.2, 169.1, 164.4, 163.9, 158.9, 158.8, 136.5, 135.5, 133.3, 132.9, 129.1,

128.8, 116.9, 116.8, 114.1, 114.0, 113.4,113.3, 111.2, 55.2, 52.9, 52.7, 50.8, 48.2, 39.7, 36.8, 34.6, 34.1. HRMS (ESI) M/Z+ Calc. 299.1158, Obs. 299.1165.

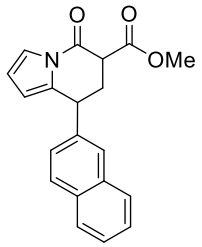


Methyl 8-methyl-5-oxo-8-phenyl-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-45): Methyl 2-methyl-2-phenyl-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (49.8 mg, 0.176 mmol), $Al(OTf)_3$ (16.7 mg, 0.035 mmol) and ACN (1.9 mL) were combined according to the general method to give **4-45** as an off-white solid (47 mg, 95%) after 30 minutes. *Diastereomeric ratio*: (4.0:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.50 (dd, *J* = 3.4, 1.6 Hz, 0.15), 7.44 (dd, *J* = 3.4, 1.6 Hz, 0.97), 7.31 – 7.26 (m, 2.26), 7.24 – 7.19 (m, 1.27), 7.16 – 7.12 (m, 0.36), 6.99 – 6.95 (m, 2.11), 6.38 (t, *J* = 3.3 Hz, 0.97), 6.35 (t, *J* = 3.3 Hz, 0.18), 6.21 (dd, *J* = 3.2, 1.5 Hz, 0.99), 6.04 (dd, *J* = 3.2, 1.6 Hz, 0.17), 3.76 (s, 2.67), 3.32 (dd, *J* = 13.2, 4.6 Hz, 1.04), 3.22 (s, 0.49), 2.97 (dd, *J* = 13.9, 5.3 Hz, 0.20), 2.64 (t, *J* = 13.2 Hz, 1.10), 2.56 (dd, *J* = 13.2, 4.7 Hz, 1.11), 2.41 (dd, *J* = 13.9, 6.2 Hz, 0.22), 1.74 (s, 3.00), 1.71 (s, 0.53).^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.4, 164.5, 144.9, 138.3, 128.7, 128.0, 127.0, 126.9, 125.9, 117.2, 117.1, 113.3, 113.2, 110.9, 110.7, 52.6, 52.3, 47.9, 40.1, 39.9, 39.7, 29.3, 29.1. HRMS (ESI) M/Z+ Calc. 283.1208, Obs. 283.1206.



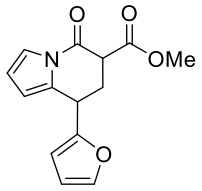
Methyl 8-((*tert*-butyldiphenylsilyl)methyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-47): Methyl 2-((*tert*-butyldiphenylsilyl)methyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (49.8 mg, 0.112 mmol), $Al(OTf)_3$ (10.8 mg, 0.023 mmol) and ACN (1.2 mL) were combined according to the general method to furnish **4-47**

as an off-white solid (35.7 mg, 72%) after 30 minutes. *Diastereomeric ratio*: (1.45:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.74 – 7.70 (m, 0.84), 7.69 – 7.64 (m, 7.77), 7.46 – 7.35 (m, 13.33), 7.33 – 7.27 (m, 1.99), 6.24 (t, *J* = 3.3 Hz, 0.86), 6.21 (t, *J* = 3.3 Hz, 1.01), 6.13 – 6.09 (m, 0.84), 6.00 – 5.97 (m, 1.00), 3.68 (s, 2.54), 3.58 (t, *J* = 5.0 Hz, 1.02), 3.47 (s, 3.09), 3.23 (dd, *J* = 13.0, 4.6 Hz, 0.85), 3.02 – 2.92 (m, 1.06), 2.85 – 2.75 (m, 1.03), 2.10 – 2.01 (m, 1.14), 1.93 (dd, *J* = 15.4, 3.1 Hz, 0.91), 1.89 – 1.81 (m, 1.86), 1.81 – 1.71 (m, 1.36), 1.69 – 1.62 (m, 1.04), 1.47 – 1.31 (m, 2.25), 1.10 – 1.06 (m, 10.01), 1.05 (s, 9.59). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.1, 169.0, 164.6, 164.0, 139.0, 138.9, 136.0 (2C), 135.9. 135.8, 134.8, 134.2, 133.5, 133.3, 129.6, 129.5 (2C), 129.4, 129.3, 127.9 (2C), 127.8, 127.7 (2C), 116.8 (2C), 113.0, 108.9, 108.8, 52.6, 52.5, 50.8, 48.8, 34.0, 33.4, 29.9, 27.8, 27.7, 27.4, 26.5, 18.2 (2C), 14.4, 13.8. HRMS (ESI) M/Z+ Calc. 445.2073, Obs. 445.2075.



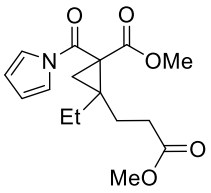
Methyl 8-(naphthalen-2-yl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-49): Methyl 2-(naphthalen-2-yl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (49.9 mg, 0.156 mmol), $Al(OTf)_3$ (14.8 mg, 0.031 mmol) and ACN (1.7 mL) were mixed according to the general method to render **4-49** as an off-white solid (34.6 mg, 69%) after 30 minutes. *Diastereomeric ratio*: (1.31:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 – 7.73 (m, 7.19), 7.61 (s, 0.82), 7.54 – 7.46 (m, 5.96), 7.46 – 7.38 (m, 1.09), 7.34 (dd, *J* = 8.5, 1.8 Hz, 0.80), 6.29 (t, *J* = 3.3 Hz, 0.74), 6.24 (t, *J* = 3.3 Hz, 0.97), 5.83 – 5.80 (m, 0.78), 5.67 – 5.64 (m, 1.00), 4.46 (dd, *J* = 9.2, 4.0 Hz, 0.81), 4.25 (dd, *J* = 12.3, 4.3 Hz, 1.04), 3.88 (dd, *J* = 12.7, 4.6 Hz, 1.19), 3.85 – 3.73 (m, 6.69), 2.83 – 2.72 (m, 1.89), 2.60 – 2.51 (m, 0.85), 2.52 – 2.43 (m, 1.11). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.2, 169.1, 164.4, 163.9, 138.7,

138.2, 135.9, 135.0, 133.4, 133.3, 132.8, 132.6, 128.6, 128.5, 127.7 (2C), 127.6, 127.1, 126.8, 126.3 (2C), 126.0 (2C), 125.9, 125.7, 117.1, 116.9, 113.4, 111.5, 111.5, 52.9, 52.7, 50.7, 48.1, 40.6, 37.8, 34.3, 33.9. HRMS (ESI) M/Z+ Calc. 319.1208, Obs. 319.1201.

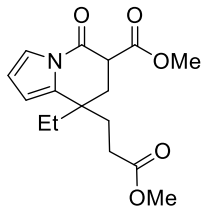


Methyl 8-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-51): Methyl 2-(furan-2-yl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (50.0 mg, 0.193 mmol), $Al(OTf)_3$ (18.5 mg, 0.039 mmol) and ACN (2.0 mL) were combined according to the general method to give **4-51** as an off-white solid (34.6 mg, 69%) after 30 minutes. *Diastereomeric ratio:* (1.15:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.43 – 7.39 (m, 2.72), 7.37 (dd, *J* = 1.9, 0.9 Hz, 0.90), 6.35 (dd, *J* = 3.2, 1.8 Hz, 0.97), 6.31 (dd, *J* = 3.2, 1.9 Hz, 0.94), 6.27 (dt, *J* = 6.4, 3.3 Hz, 1.86), 6.18 – 6.16 (m, 0.92), 6.04 – 6.01 (m, 1.81), 5.98 – 5.95 (m, 0.90), 4.45 – 4.41 (m, 0.95), 4.29 (dd, *J* = 10.3, 4.4 Hz, 1.00), 3.83 – 3.73 (m, 7.54), 2.80 – 2.66 (m, 2.04), 2.60 (ddd, *J* = 13.5, 7.4, 5.0 Hz, 0.99), 2.54 – 2.46 (m, 1.00). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.1, 168.8, 164.0, 163.8, 153.6, 153.4, 142.2, 142.1, 132.5, 131.9, 117.2, 117.1, 113.4, 113.3, 111.2, 111.1, 110.3, 107.0, 106.8, 52.9, 52.8, 49.8, 47.8, 33.4, 31.5, 31.1, 30.4. HRMS (ESI) M/Z+ Calc. 259.0845, Obs. 259.0844.

4.8.4 Rhazinicine Precursor Synthesis

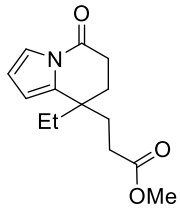


Methyl 2-ethyl-2-(3-methoxy-3-oxopropyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (4-57): Rh_2esp_2 (1.9 mg, 2.405 µmol) was added to a dry flask equipped with a stir bar under nitrogen. 2 mL of DCM was added. Methyl 2-diazo-3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (124.7 mg, 0.646 mmol) was dissolved in 4.0 mL of DCM. Methyl 4-methylenehexanoate (298.5 mg, 2.099 mmol) was added to the reaction pot followed by slow addition of the diazo at 0.5 mL/h (2 mL/4h). The reaction proceeded for 12 hours. The reaction was quenched with saturated thiourea. The organic phase was collected. The aqueous phase was extracted three times with DCM. The combined layers were dried over sodium sulfate, filtered, concentrated and purified using silica gel column chromatography (10%EtOAc/Hex). **4-57** was obtained as a yellow oil (59.8 mg, 30%). *Diastereomeric ratio:* (1.15:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 – 7.26 (m, 1.63), 6.28 – 6.25 (m, 1.85), 3.69 (s, 1.01), 3.68 – 3.65 (m, 2.68), 3.63 (s, 1.60), 2.58 – 2.45 (m, 1.00), 2.41 – 2.23 (m, 1.41), 2.17 – 2.03 (m, 1.01), 1.87 – 1.76 (m, 1.26), 1.76 – 1.65 (m, 1.46), 1.57 – 1.49 (m, 1.00), 1.35 – 1.21 (m, 0.93), 1.00 (t, *J* = 7.5 Hz, 1.92), 0.95 (t, *J* = 7.0 Hz, 1.11), 0.92 – 0.86 (m, 0.48).^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.2, 173.1, 169.2, 169.1, 165.0, 164.9, 119.8, 119.7, 113.2, 113.1, 53.0, 52.9, 51.7 (2C), 40.3, 40.0, 37.7 (2C), 31.2, 31.1, 28.4, 27.1, 27.0, 26.7, 24.0, 21.9, 10.6, 10.5. HRMS (ESI) M/Z+ Calc. 307.1420, Obs. 307.1419.



Methyl 8-ethyl-8-(3-methoxy-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (4-58): Indium(III) trifluoromethanesulfonate (84.1 mg, 0.150 mmol) was charged to a flame-dried flask. Methyl 2-ethyl-2-(3-methoxy-3-oxopropyl)-1-(1*H*-pyrrole-1-carbonyl)cyclopropanecarboxylate (153.3 mg, 0.499 mmol) was dissolved in 3 mL of

DCM and added to the flask. The reaction mixture turned a brown color. 2 mL of DCM was used to rinse the flask containing the starting material and syringed into the reaction pot. The flask was placed in an oil bath, and the temperature was 50 °C. The reaction heated at reflux for 50 min. and cooled to room temperature. The crude was purified directly to obtain **4-58** as a brown oil (95.8 mg, 65%). *Diastereomeric ratio*: (1.1:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.30 (m, 1.90), 6.22 (t, *J* = 3.3 Hz, 0.91), 6.20 (t, *J* = 3.3 Hz, 0.99), 5.97 (dd, *J* = 3.3, 1.5 Hz, 0.93), 5.94 (dd, *J* = 3.3, 1.5 Hz, 1.00), 3.93 (dd, *J* = 13.0, 5.1 Hz, 1.07), 3.85 (dd, *J* = 12.8, 5.1 Hz, 1.13), 3.81 – 3.77 (m, 6.10), 3.64 (s, 2.94), 3.57 (s, 3.05), 2.44 – 2.26 (m, 5.23), 2.25 – 2.17 (m, 1.25), 2.11 – 1.88 (m, 5.58), 1.83 – 1.74 (m, 1.47), 1.71 (q, *J* = 7.5 Hz, 2.17), 1.65 – 1.46 (m, 2.20), 0.91 – 0.82 (m, 6.50). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 173.7, 173.4, 169.8, 169.7, 164.0, 163.9, 137.0, 136.9, 117.1, 117.0, 113.1, 112.9, 109.9, 109.7, 52.7 (2C), 51.6 (2C), 46.9, 46.8, 36.8, 36.5, 34.8, 34.2, 31.7, 31.3, 31.1, 29.7, 28.9, 28.7, 8.12, 7.7. HRMS (ESI) M/Z+ Calc. 307.1420, Obs. 307.1427.



Methyl 3-(8-ethyl-5-oxo-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (4-59): Methyl 8-ethyl-8-(3-methoxy-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroindolizine-6-carboxylate (95.8 mg, 0.312 mmol), LiCl (30.9 mg, 0.729 mmol), water 1 (drop), and DMSO (Anh) was charged to a round bottom flask equipped with a stir bar. The air was removed and replaced with nitrogen, and the flask was heated at 150 °C for 2 hours. The pot was cooled at room temperature and poured onto water. Ethyl Ether was added and the aqueous phase was extracted three times with Ethyl ether. The combined organic layers were dried with sodium sulfate, filtered, concentrated and purified with silica gel column chromatography to afford **4-59** as a brown oil (51 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 (dd,

J = 3.4, 1.5 Hz, 1H), 6.18 (t, *J* = 3.3 Hz, 1H), 5.93 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.61 (s, 3H), 2.82 – 2.67 (m, 2H), 2.36 – 2.26 (m, 1H), 2.26 – 2.17 (m, 1H), 2.03 – 1.93 (m, 1H), 1.94 – 1.82 (m, 3H), 1.73 – 1.63 (m, 1H), 1.63 – 1.55 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm173.8, 167.7, 137.6, 116.6, 112.2, 109.3, 51.6, 36.7, 31.1, 30.5, 30.0, 28.9, 7.92. HRMS (ESI) M/Z+ Calc. 249.1365, Obs. 249.1358.

CHAPTER 5 FRIEDEL-CRAFTS CYCLIZATIONS OF REACTIVE MICHAEL-ACCEPTORS: AN INTRAMOLECULAR, DIASTEREOSELECTIVE SYNTHESIS OF FUNCTIONALIZED 1*H*-PYRROLO[1,2-*A*]INDOLES

Pyrroloindoles are of great interest to synthetic chemists for their medical value and structural diversity.[277–280] If described, these [*a*]-annelated heterocycles are comprised of an indole ring and pyrrole ring fused along a C-N bond "a" connector. The pyrrolo[1,2-*a*]indole is classified by its subclasses which differ in degrees of unsaturation or isomeric locales of π-bonds about the tricyclic core. Below are common scaffolds, 9*H*-pyrrolo[1,2-*a*]indole **5-1**, 3*H*-pyrrolo[1,2-*a*]indole **5-2**, 1*H*-pyrrolo[1,2-*a*]indole **5-3**, 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **5-4**, and 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole **5-5**, displayed in Figure 5.1.

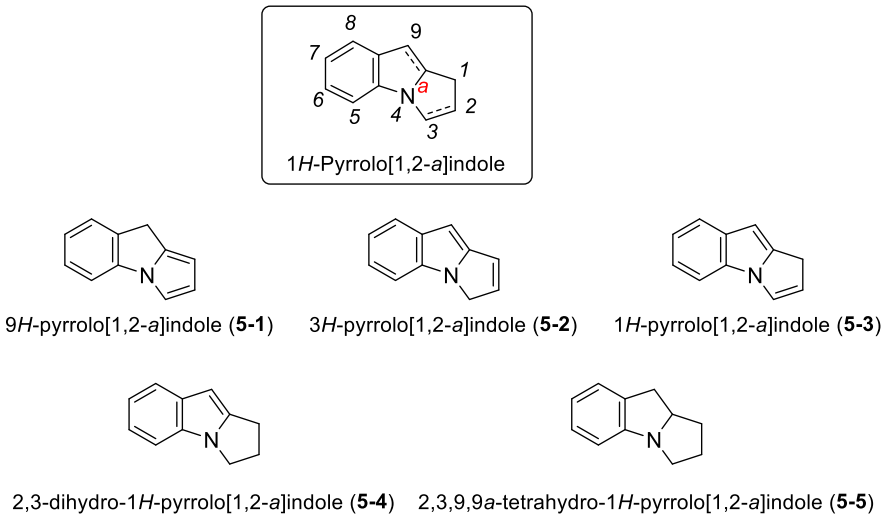


Figure 5.1: Pyrrolo[1,2-*a*]indole numbering and representative scaffolds

Unique to the pyrroloindole framework, compounds consisting of this specific molecular stature are biologically active and useful for combating human diseases.[174,281] In particular, flinderole C[282] **5-6** and isoborreverine[283] **5-7** have selective antimalarial activity;

isatisine A[284] **5-8** is an antiviral; and mitomycin C[285] **5-9** acts as an anticancer agent (Figure 5.2).

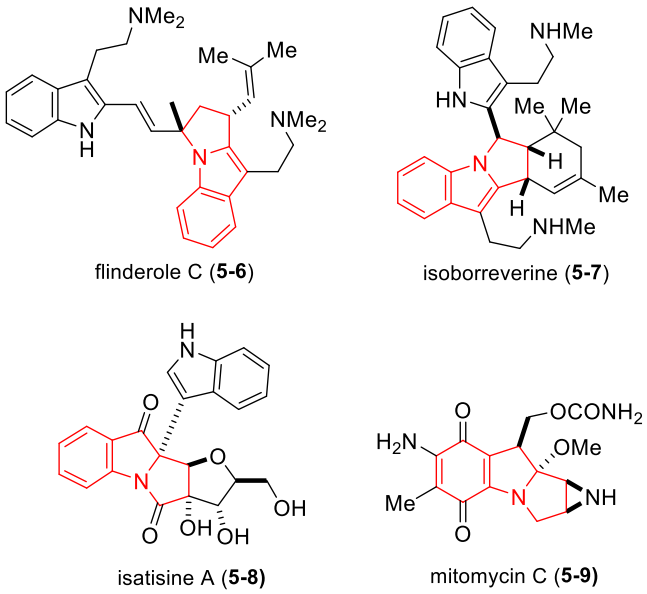


Figure 5.2: Bioactive pyrrolo[1,2-*a*]indole-based natural products

5.1 Pyrrolo[1,2-*a*]indole Synthesis

To date, a plethora of reports for the synthesis of pyrrolo[1,2-*a*]indoles is in the chemical literature,[286–294] signifying the general interest and importance of this alkaloid group.[295,296] Given the large number of routes, complete coverage of all syntheses will not be reviewed in this dissertation, but representative examples are presented (vide infra). Typically, as described by Makarov in a recent review, pyrrolo[1,2-*a*]indoles are synthesized by annulation of a pyrrole onto an indole, annealation of a pyrrole ring to benzene and pyrrole rings, concomitant addition of two pyrroles or pyrrole-type units to a benzene unit, and chemical manipulation of related heterocycles.[296]

5.1.1 Annealation of Pyrrole to Benzene and Pyrrole Rings

In 1995, Moody and Norton[297] reported a radical cyclization of 1-(ω-iodoalkyl)indole-3-carboxaldehydes **5-10** with excess tributyltin hydride and 1.0 equivalent azobisisobutyronitrile (AIBN) in toluene. In contrast to an oxidative protocol[298]

using H_2O_2, Fe(II), and DMSO, the yields (64% and 47%) for Norton's transformation were higher for 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **5-11** (Figure 5.3).

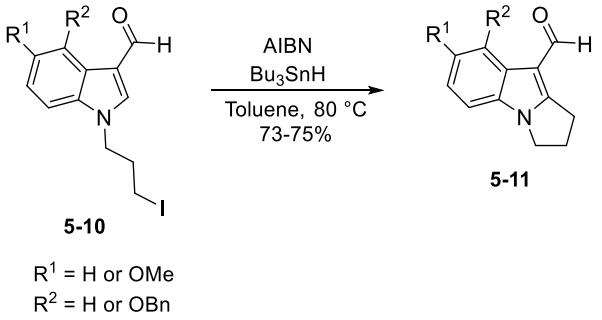


Figure 5.3: Radical cyclization for 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles

5.1.2 Annealation of a Pyrrole to Benzene and Pyrrole Rings

Knochel and Ren[299] published a chemoselective palladium-catalyzed cyclization of *N*-(2-haloaryl)pyrroles **5-12** to form 9*H*-pyrrolo[1,2-*a*]indoles **5-13**. For the mechanism, the substrate undergoes an oxidative addition to generate palladium(II*) in situ*. Subsequent C-H activation and HX elimination forms a palladacycle where reductive elimination generates pyrroloindoles **5-13** (Figure 5.4).

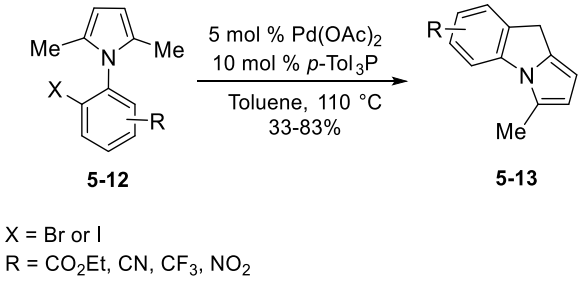


Figure 5.4: Palladium-catalyzed cyclization for 9*H*-pyrrolo[1,2-*a*]indoles

5.1.3 Concomitant Addition of Two Pyrrole Units to a Benzene Unit

Synthetically, the simultaneous addition of two pyrrole rings to a benzene unit to form pyrrolo[1,2-*a*]indoles is advantageous if the number of steps to form the framework is considered. Iwasawa et al. published a Pt(II)/Au(III)-catalyzed [3+2] cycloaddition protocol for 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **5-15** from *N*-(*o*-alkynylphenyl)imines **5-14** containing an internal alkyne (Figure 5.5).[300] These tricyclic indoles are postulated to form from a platinum or gold azomethine ylide which undergoes a [3+2] cycloaddition with a vinyl ether followed by a 1,2-migration to afford 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **5-15** in good yields (60-95%).

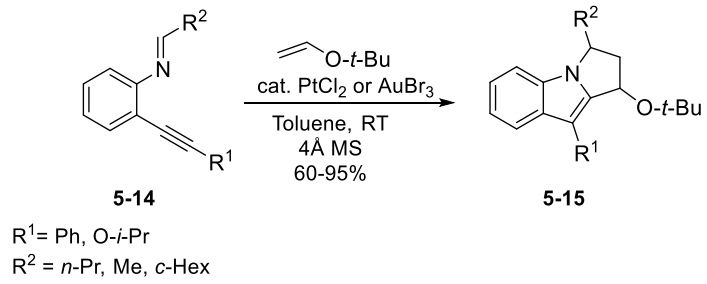


Figure 5.5: Pt(II)- or Au(III)-catalyzed [3+2] cycloaddition for 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles

5.1.4 Rearrangement of Heterocycles

In order to transform heterocycles into pyrrolo[1,2-*a*]indoles, rearrangement occurs with precursors containing an annelated benzene ring. With this in mind, in an effort to assemble an aziridinomitosene skeleton, Miller et al. designed a precursor, specifically **5-16**, capable of undergoing a tandem deprotection/transannular cyclization/dehydration sequence with trifluoroacetic acid in dichloromethane at room temperature, and within five minutes, **5-17** was generated in 92% yield (Figure 5.6).[301] If the retrosynthetic analysis were assessed, it is evident that the reaction sequence was key to form the desired pyrroloindole core of the aziridinomitosene.

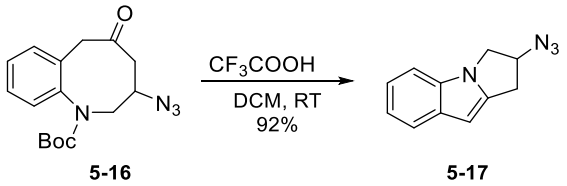


Figure 5.6: Deprotection/transannular cyclization/dehydration sequence for pyrrolo[1,2-*a*]indole

5.2 Hypothesis and Synthetic Rationale for Pyrrolo[1,2-*a*]indole Synthesis

Until our work, a broad, efficient intramolecular approach to install disparate functionality around the 1*H*-pyrrolo[1,2-*a*]indole skeleton had not been attained. In 2011, we disclosed a modular synthesis of hydropyrido[1,2-*a*]indole-6(7*H*)-ones **5-20** using an $In(OTf)_3$-catalyzed tandem cyclopropane ring-opening/intramolecular Friedel-Crafts alkylation sequence from D-A-A cyclopropanes **5-18**.[302] In this report, six-membered constructs were synthesized; for a new methodology, we sought to construct similar five-membered indolic systems. Our rationale emanated from the reactivity exhibited by D-A-A cyclopropanes. According to Walsh, electronically, cyclopropanes have inherent π-character which is influenced by ring substitution—meaning donating and withdrawing moieties alter bond polarization and bond strength.[51,53,303] Therefore, polarized alkylidene malonate monoamide or acrylate **5-21** containing an indoyl moeity would be prone to an intramolecular annulation to form a new five-membered lactam via a different mechanistic pathway with an identical π-nucleophile and akin aza-cationionic intermediate (comparatively, **5-19** and **5-22**, Figure 5.7). Hence, precursors with this Michael-type design would be good conduits to interesting and useful pyrrolo[1,2-*a*]indoles.

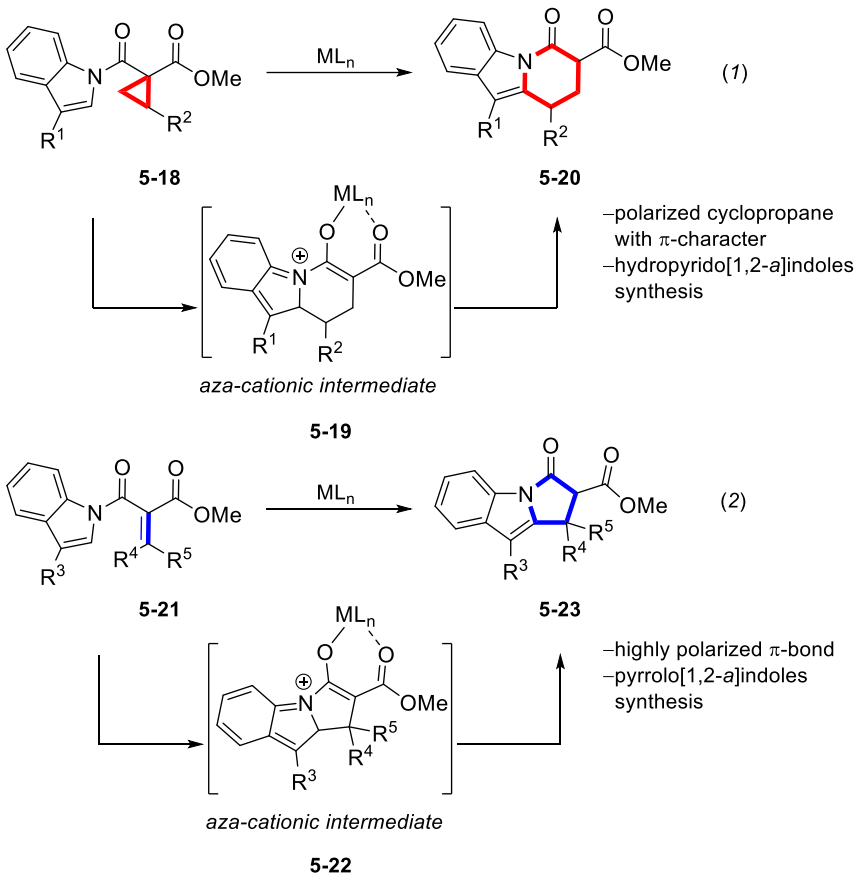


Figure 5.7: Cyclopropane and alkylidene malonate monoamide reactivity

By utilizing this Michael-type setup, Friedel-Crafts alkylation chemistry becomes a viable alternative for pyrroloindole formation. If recognized, employing this approach with an α,β-unsaturated carbonyl can be a powerful strategy for natural product synthesis.[304] Although intermolecular reactions are prevalent,[305,306] intramolecular variants would be more beneficial for the assembly of complex indole polycycles.[120,307–310] In affirmation of our proposed aim, a literature search was conducted; in 2010, Hadjipavolou-Litina reported the unexpected formation of a 1*H*-pyrrolo[1,2-*a*]indole-3(2*H*)-one **5-25** from *N*-cinnamoyl indole derivative **5-24** with stoichiometric trifluoracetic acid in dichloromethane.[311] Without donating groups located in both *ortho*- and *para*-positions, **5-24** does not form **5-25**. However, if an additional acceptor group, such as an ester, were positioned α to the indolic amide to form a more polarized conjugated arrangement,

alkylidene malonate monoamides **5-21** would become more reactive units than their simple α,β-unsaturated counterparts,[312] leading to the prospect that our proposed hypothesis was more plausible.

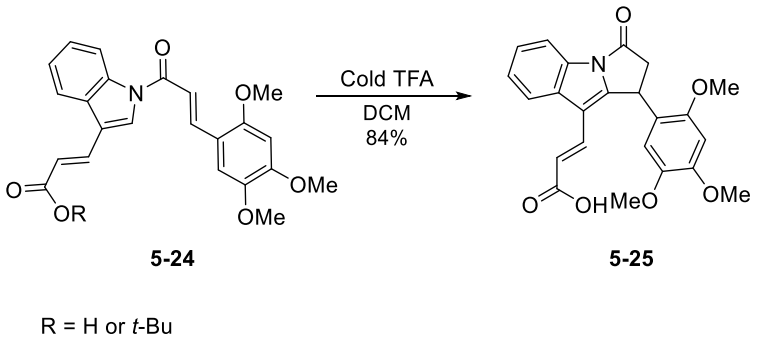


Figure 5.8: Hadjipavolou-Litina and Papaioannour's TFA-promoted annulation

5.3 Precursor Assembly and Reaction Optimization for Pyrrolo[1,2-*a*]indole Synthesis

To begin our study, model precursor 4-OMe-phenyl derivative **5-29**, shown in Table 5.1, was prepared in the following manner (Figure 5.9). *N*-acylated indoles **5-27** were synthesized according to our previous preparation from indoles **5-26** with methyl malonyl chloride (MMC). Base-promoted acylation gave β-amidoesters **5-27**. Knoevenagel condensation with the appropriate aldehyde or ketone afforded the desired acrylates **5-28** in 40-95% yields. Overall, a majority of our precursors were prepared according to the Figure 5.9; alkylidene malonate monoamides derived from ketones were prepared using $TiCl_4$ (General Procedure 5.7.2.2). After synthesis of model precursor **5-29** in Table 5.1, several Lewis acids were selected for screening.

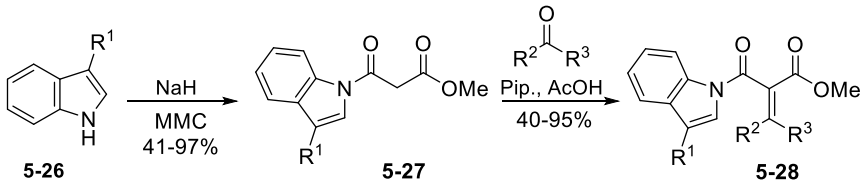


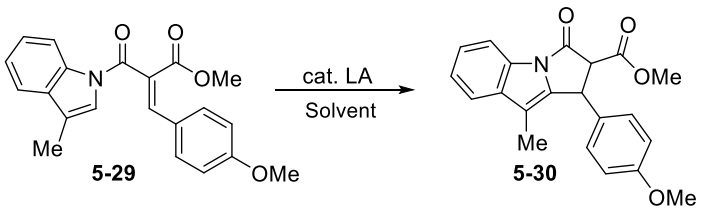
Figure 5.9: Alkylidene malonate monoamide synthesis for pyrrolo[1,2-*a*]indole synthesis

Given our past successes with indium, we chose $In(OTf)_3$ as the starting Lewis acid for our initial cyclization study with model substrate **5-29**. After 48 hours, 30 mol% $In(OTf)_3$ at room temperature and 50 °C in dichloromethane (Table 5.1, entry 1 and 2) did not yield any of the desired product as indicated by ^1H NMR, but toluene at 111 °C with 30 mol% $In(OTf)_3$ gave 100% conversion to product **5-30** after 30 minutes (Table 5.1, entry 3) with a high *trans:cis* diastereomeric ratio (*dr*) determined by ^1H NMR (5.7.3.2 Rationale for *cis/trans* assignment). Of note, the large diastereoselectivities may be associated from a post-cyclization thermodynamic equilibration of the product.

Then, the solvent was changed from toluene to 1,2-dichloroethane to increase polarity and decrease temperature. 30 mol% $In(OTf)_3$ at 84 ˚C afforded full conversion after 45 minutes (Table 5.1, entry 4). Next, the catalyst loading was reduced to 10 mol% $In(OTf)_3$ and complete conversion was observed after 1 hour in 1,2-dichloroethane at reflux (Table 5.1, entry 5). Other Lewis acids with varying Z-effectives at 10 mol% were examined in 1,2-dichloroethane at reflux. $Sc(OTf)_3$ and $Al(OTf)_3$ gave quantitative conversion to product after 1.5 hours (Table 5.1, entries 6 and 7). $Cu(OTf)_2$ (100% conversion, Table 5.1, entry 8), $Yb(OTf)_2$ (100% conversion, Table 5.1, entry 9), and $Zn(OTf)_2$ (45% conversion, Table 5.1, entry 10) usage resulted in longer reaction times, 9, 10, and 48 hours respectively. Due to short reaction times for indium, catalyst loading was lowered to 5 mol% in 1,2-dichloroethane at 84 ˚C to give full conversion after 2 hours (Table 5.1, entry 11). When 5 mol% $In(OTf)_3$ was used for other precursors, reaction completion was not attained. Consequently, 10 mol% $In(OTf)_3$ in 1,2-dichloroethane at

reflux formed most of the products in a timely and efficient manner. With these optimized conditions on hand, reaction extent and scope were examined for the Friedel-Crafts alkylation.

Table 5.1: Reaction Optimization for Pyrrolo[1,2-*a*]indoles



Entry[d]	LA Loading	Solvent	Temp.	Time (h)	Conversion[a]
1	30 mol % $In(OTf)_3$	DCM	25 °C	48.0[b]	--[c]
2	30 mol % $In(OTf)_3$	DCM	50 °C	48.0[b]	--[c]
3	30 mol % $In(OTf)_3$	Toluene	111 °C	0.5	100%
4	30 mol % $In(OTf)_3$	1,2-DCE	84 °C	0.75	100%
5	10 mol % $In(OTf)_3$	1,2-DCE	84 °C	1.0	100%
6	10 mol % $Sc(OTf)_3$	1,2-DCE	84 °C	1.5	100%
7	10 mol % $Al(OTf)_3$	1,2-DCE	84 °C	1.5	100%
8	10 mol % $Cu(OTf)_2$	1,2-DCE	84 °C	9.0	100%
9	10 mol % $Yb(OTf)_3$	1,2-DCE	84 °C	10.0	100%
10	10 mol % $Zn(OTf)_2$	1,2-DCE	84 °C	48.0[b]	45%
11	5 mol % $In(OTf)_3$	1,2-DCE	84 °C	2.0	100%

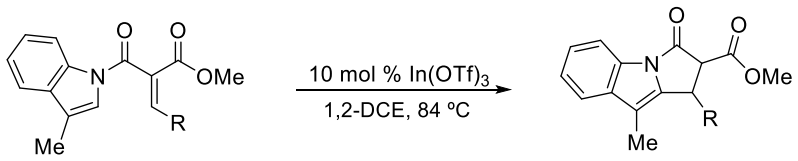
[a] Conversion ascertained by crude ^{1}H NMR. [b] Reaction stopped after the time indicated. [c] No reaction observed. [d] Concentration of 0.06 M.

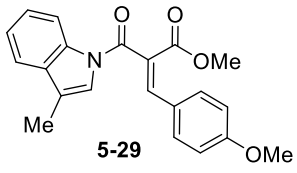
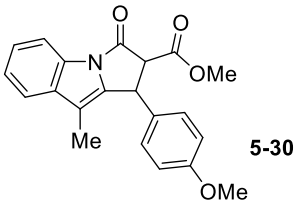
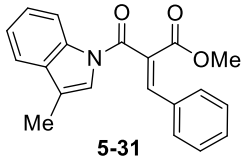
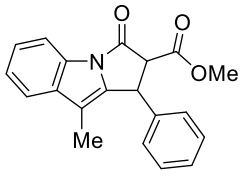
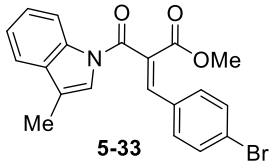
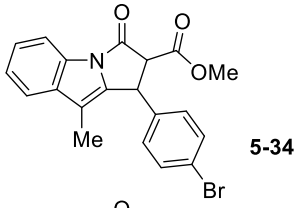
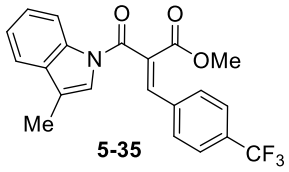
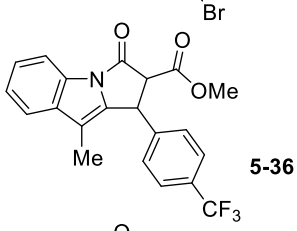
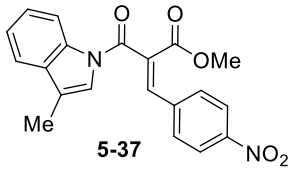
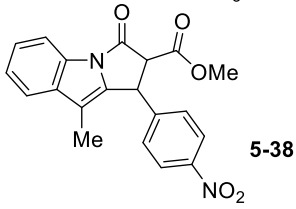
5.4 Results and Discussion

Aryl groups on the acrylates were altered using electron-donating and electron-withdrawing groups (Table 5.2). 4-Methoxy aryl derivative **5-29** gave 1*H*-pyrrolo[1,2-*a*]indole **5-30** in 95% yield with 15:1 *dr* in 1 hour (Table 5.2, entry 1). Substitution was made from a more activated 4-OMe precursor **5-29** to a less activated one **5-31**. Indole **5-**

32 was obtained in 97% with 16:1 *dr* (Table 5.2, entry 2) with the same reaction time. 4-Br-C_6H_5 derivative **5-33** was subjected to the reaction conditions and afforded **5-34** in 93% yield with 16:1 *dr* (Table 5.2, entry 3) albeit with a longer reaction time. More electron deficient aryls such as 4-CF_3-C_6H_5 **5-35** and 4-NO_2-C_6H_5 **5-37** were reacted to form pyrrolo[1,2-*a*]indoles **5-36** and **5-38** in 92% yield with 20:1 *dr* (Table 5.2, entry 4) and 84% with 19:1 *dr* (Table 5.2, entry 5) respectively. These findings suggest the electronics of the aryl substituents does not affect product outcomes significantly, but the reaction times change depending on substitution. Moreover, the more stable *trans* isomer is thermodynamically more favorable over its *cis* version because of the repeated high diastereoselectivities. This reaction success of aryl precursors then led us to investigate electron-rich heteroaromatics.

Table 5.2: Friedel-Crafts Alkylation with Aromatic Alkylidiene Malonate Monoamides



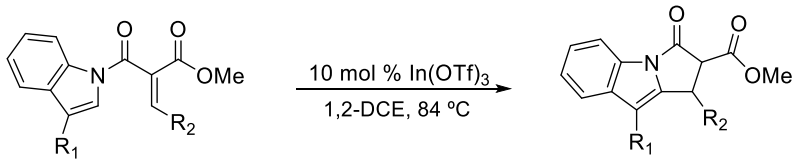
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **5-29**	 **5-30**	1.0	95%	15:1
2	 **5-31**	 **5-32**	1.0	97%	16:1
3	 **5-33**	 **5-34**	3.0	93%	16:1
4	 **5-35**	 **5-36**	3.0	92%	20:1
5	 **5-37**	 **5-38**	2.5	84%	19:1

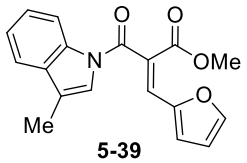
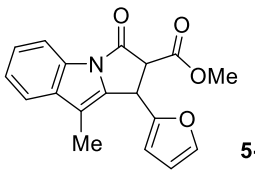
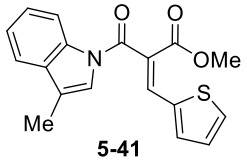
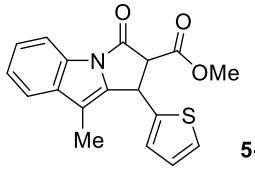
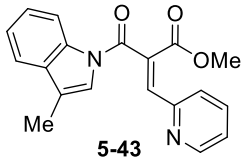
[a] Reactions run with the precursor (1.0 equiv.) and 10 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio.

With this intention, 2-furyl acrylate **5-39**, 2-thienyl acrylate **5-41**, and 2-pyridyl acrylate **5-43** were synthesized. The furyl derivative cyclized to **5-40** in 97% yield with 18:1 *dr* (Table 5.3, entry 1), and the 2-thienyl derivative formed **5-42** in 98% with 24:1 *dr*

(Table 5.3, entry 2). 2-Pyridyl precursor **5-43** did not form the desired 1*H*-pyrrolo[1,2-*a*]indole (Table 5.3, entry 3). Presumably, the lack of reactivity is attributed to the coordinating nitrogen forms a complex with the indium catalyst, preventing product formation. Once establishing differing aryls work, substituent changes were made at the 3-position of the indole.

Table 5.3: Heteroaromatic Donor Group Reaction Scope



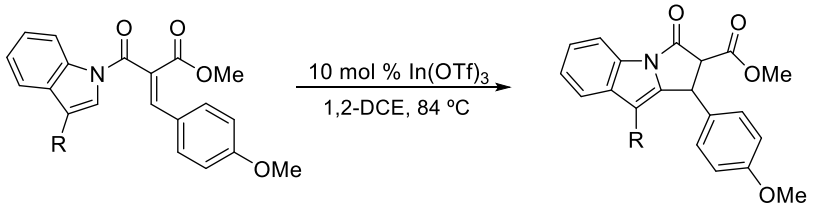
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **5-39**	 **5-40**	2.0	97	18:1
2	 **5-41**	 **5-42**	2.0	98	24:1
3	 **5-43**	--	--	NR	--

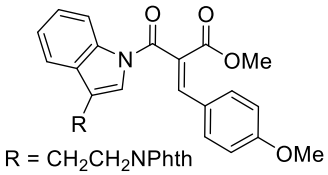
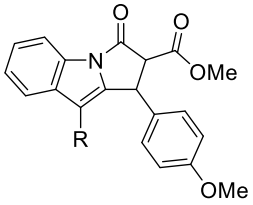
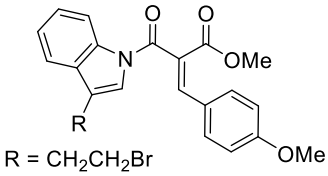
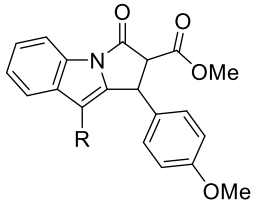
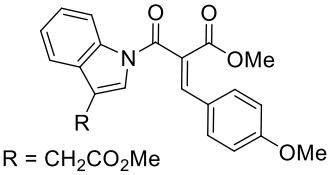
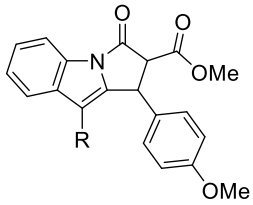
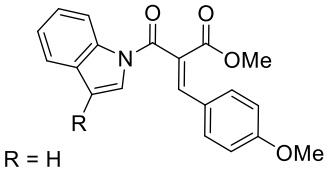
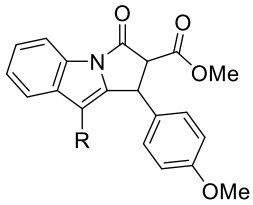
[a] Reactions run with the precursor (1.0 equiv.) and 10 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio.

Phthalimido precursor **5-44** was subjected to the optimized conditions to give **5-45** in 96% yield with 14:1 *dr* (Table 5.4, entry 1). Deprotection of **5-45** furnishes the primary amine which is synthetically appealing for the construction of natural products, such as flinderole C **5-6**. Bromo substrate **5-46** provided **5-47** in 69% yield with 25:1 *dr* (Table 5.4, entry 2). Likewise, methyl acetate derivative **5-48** generates **5-49** in 93% yield with 13:1

dr (Table 5.4, entry 3). Then, indole acrylate **5-50**, having no substituent in the 3-position, was assembled and generated **5-51** in 98% yield with 10:1 *dr* (Table 5.4, entry 4), demonstrating substitution at the 3-position is not crucial for product formation, and the reaction time is not extended substantially. As a part of the scope investigation, the alkylidene malonate monoamides were changed to nonaromatic groups that represent moieties derived from alkyl aldehydes and cinnamaldehyde.

Table 5.4: Alterations at the 3-Position on the Indole



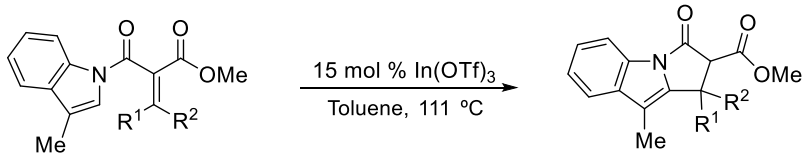
Entry[a]	Precursor	Product	time (h)	Yield[b]	dr[c]
1	 R = CH_2CH_2NPhth **5-44**	 **5-45**	4.0	96%	14:1
2	 R = CH_2CH_2Br **5-46**	 **5-47**	12.0	69%	25:1
3	 R = CH_2CO_2Me **5-48**	 **5-49**	3.0	93%	13:1
4	 R = H **5-50**	 **5-51**	1.0	98%	10:1

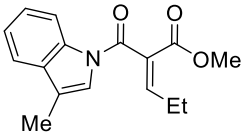
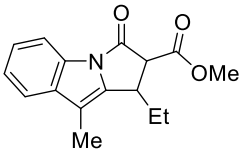
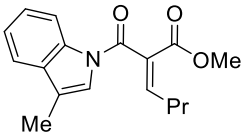
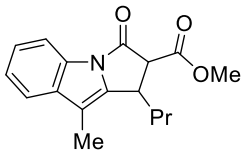
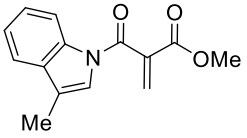
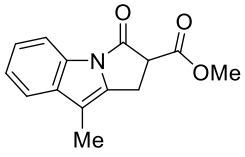
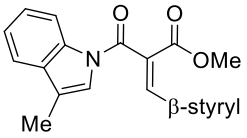
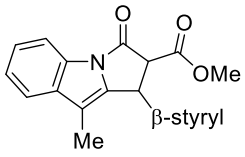
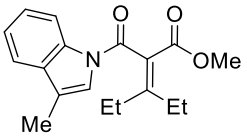
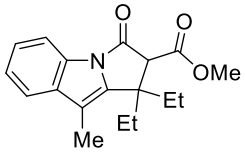
[a] Reactions run with the precursor (1.0 equiv.) and 10 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio.

The ethyl substituted alkylidene malonate monoamide **5-52** under the optimized reaction conditions did not yield product after >24 hours. After some further optimization, the catalyst loading was increased to 15 mol% $In(OTf)_3$ with a higher boiling solvent (toluene) and heated to reflux. **5-52** was subjected to the new conditions and formed **5-53** in 89% yield as the *trans* isomer exclusively (Table 5.5, entry 1). Propyl precursor **5-54**

gave **5-55** in 84% yield (Table 5.5, entry 2) with one observable diastereomer. When formaldehyde derived substrate **5-56** was subjected to the reaction conditions, **5-57** formed in 47% yield (Table 5.5, entry 3); degradation was observed due to the stability of the starting material and product under the higher temperature and catalyst loading. Conjugated cinnamate **5-58** afforded **5-59** in 71% yield with 8:1 *dr* (Table 5.5, entry 4). 2,2-Disubstituted acrylate **5-60** cyclized to form **5-61** in 98% yield (Table 5.5, entry 5) with a quaternary center. As a direct consequence of this new finding, our methodology is useful for installing quaternary centers, chiral or achiral, derived from ketones. With all the data so far, we predicted indole could be exchanged for pyrrole on the alkylidene malonate monoamide to an entirely new scaffold.

Table 5.5: Reaction Scope of Nonaromatic Alkylidene Malonate Monoamides

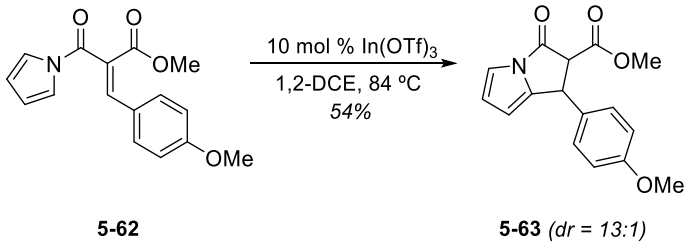


Entry[a]	Precursor	Product	time (h)	Yield[b]	dr[c]
1	 **5-52**	 **5-53**	12.0	89%	--[d]
2	 **5-54**	 **5-55**	12.0	84%	--[d]
3	 **5-56**	 **5-57**	1.0	47%	--
4	 **5-58**	 **5-59**	12.0	71%	8:1
5	 **5-60**	 **5-61**	1.0	98%	--

[a] Reactions run with the precursor (1.0 equiv.) and 15 mol % $In(OTf)_3$ in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*/*cis* diastereomeric ratio. [d] One diastereomer observable by crude NMR.

Consequently, if pyrrole is used, our methodology would furnish 1*H*-pyrrolizin-3(2*H*)-ones. Pyrrolizines, naturally occurring compounds, have unique synthetic and medicinal potential due to their therapeutic and biological activities.[313–320] Excitingly, when acrylate **5-62** was treated with 10 mol% $In(OTf)_3$ in 1,2-dichloroethane at reflux,

desired pyrrolizine **5-63** was recovered in 54% yield with 13:1 *dr* (Figure 5.10). Unfortunately, product degradation under the reaction conditions attenuated the isolated yield.



5-62 **5-63** *(dr = 13:1)*

Figure 5.10: Reaction assessment for 1*H*-pyrrolizin-3(2*H*)-one formation

5.5 Conclusion

In brief, the reactivity of donor-acceptor-acceptor cyclopropane systems explored previously evolved into the development of a new intramolecular route for pyrrolo[1,2-*a*]indoles. This amenable, efficient protocol was devised using a diastereoselective, Lewis acid-catalyzed intramolecular Friedel-Crafts reaction. The protocol gives high yields (up to 98%) of five-membered lactams with high diastereoselectivities (up to 25:1 *dr*), and precursors were built from cheap, commercially-available reagents in two steps. The scope was broadened using heteroaromatics, halogens, and a *N*-phthalimide, providing access to functional groups typically incapable of direct installation due to Lewis basicity (e.g. amine). Moreover, quaternary center incorporation is simple to install with high yields; notably, removal of the indole and installment of a pyrrole resulted in 1*H*-pyrrolizin-3(2*H*)-one formation, opening a new avenue for the synthesis of functionalized pyrrolizines and verifying the fundamental rationale for the methodological development.

5.6 Research Participants

This research was conducted with Dr. Dadasaheb V. Patil. He made the precursors and the final products.

This work was published in Chemical Communications: Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. An Efficient Synthesis of hydropyrido[1,2-*a*]indole-6(7*H*)-ones via an In(III)-Catalyzed Tandem Cyclopropane Ring-opening/Friedel-Crafts Alkylation Sequence. Chem. Commun. Camb. U. K. 2011, 47, 10278–10280.

5.7 Experimental Information

5.7.1 Synthetic Methods for Pyrrolo[1,2-*a*]indole Preparation

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane, and dichloromethane were purified by distillation from calcium hydride. Acetonitrile was dried by fractional distillation over CaH_2. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI, and Strem (for metal catalysts). These reagents were used without further purification. All methyl 3-(1*H*-indol-1-yl)-3-oxopropanoates **5-27** were synthesized as previously reported.[302]

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic p-anisaldehyde (PAA) solution, and an ethanol solution of

phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration values. Mass spectra were obtained by the Georgia Institute of Technology Bioanalytical Mass Spectrometry Facility using a VG-70SE instrument. *Compounds synthesized and not reported in the literature until our publication are listed below. Dr. Dadasaheb V. Patil synthesized the precursors and the final products as well.*

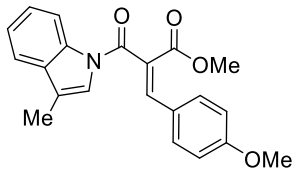
5.7.2 Alkylidene Malonate Monoamide Preparation for Pyrrolo[1,2-*a*]indole Synthesis

5.7.2.1 General Procedure A[321]

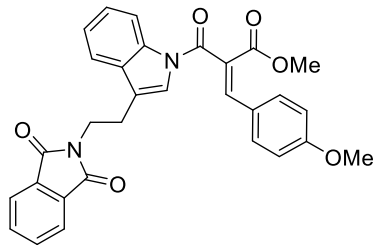
The β-esteramide (1.0 equiv.), aldehyde (1.3 equiv.), glacial acetic acid (0.5 equiv.), and piperidine (0.1 equiv.) were heated to a reflux in benzene using a Dean-Stark trap for 12 hours. After cooling the reaction mixture to room temperature, water was added to the reaction vessel, and the organic layer was collected. Subsequently, the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with 1 M HCl and saturated sodium bicarbonate. The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

5.7.2.2 General Procedure B[322]

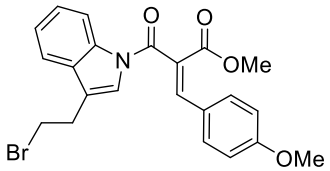
A round bottom flask was charged with the β-esteramide (1.0 equiv.) and THF (25 mL). After cooling the solution to 0 ˚C, titanium(IV) chloride tetrahydrofuran complex (2.0 equiv.) and CCl_4 (2.0 equiv.) were added to the reaction vessel. After 1 hour at 0 ˚C, the aldehyde (1.0 equiv.) was added slowly, and the reaction was stirred for an hour. Then, pyridine (4.0 equiv.) was added to the solution dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 14 hours. The reaction was quenched with water and the organic layer was collected. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).



Methyl 3-(4-methoxyphenyl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (5-29): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1.04 g, 4.50 mmol), 4-methoxybenzaldehyde (0.65 mL, 5.34 mmol), glacial acetic acid (0.126 g, 2.10 mmol), piperidine (0.0780 g, 0.911 mmol) and benzene (15 mL) were mixed according to general procedure A to afford **5-29** as a white solid (1.32 g, 84%) after 12 hours. R_f= 0.30 (20% EtOAc/Hex). [m.p. 138-140 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.69 (d, *J* = 8.1 Hz, 1H), 7.94 (s, 1H), 7.53 – 7.32 (m, 5H), 7.01 (s, 1H), 6.79 – 6.72 (m, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 2.18 (d, *J* = 0.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.2, 164.9, 161.7, 142.9, 135.3, 132.1, 131.9, 125.2, 124.6, 124.1, 123.3, 122.4, 119.1, 118.8, 116.7, 114.5, 55.1, 52.6, 9.5. IR: 3070.1 (w), 3007.0 (w), 2930.6 (w), 2824.4 (w), 1715.1 (m), 1678.1 (s), 1598.3 (s), 1511.9 (m), 1448.1 (m), 1395.8 (m), 1341.2 (m), 1254.3 (s), 1170.5 (s), 1047.5 (s), 874.9 (m), 732.2 (s), 698.5 (m), 536.2 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 349.1314, Obs. 349.1314.

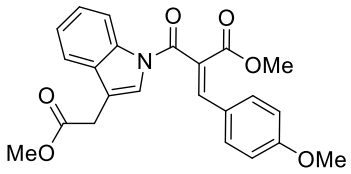


Methyl 2-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (5-44): Methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.08 g, 2.77 mmol), 4-methoxybenzaldehyde (0.459 g, 3.37 mmol), glacial acetic acid (0.0940 g, 1.57 mmol), piperidine (0.022 g, 0.253 mmol) and benzene (150 mL) were mixed according to general procedure A to yield **5-44** as a light yellow solid (0.569 g, 40%) after 16 hours. R_f= 0.40 (40% EtOAc/Hex). [m.p. 147-149 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.64 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 7.78 – 7.72 (m, 2H), 7.71 – 7.64 (m, 3H), 7.48 – 7.31 (m, 4H), 7.13 (s, 1H), 6.79 – 6.71 (m, 2H), 3.95 – 3.88 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.05 – 2.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.1, 165.5, 164.9, 161.9, 143.3, 135.5, 133.9, 132.1, 131.9, 131.1, 125.6, 124.8, 124.4, 123.2, 122.9, 119.7, 118.9, 117.0, 114.6, 55.3, 52.7, 37.1, 24.1. IR: 3120.0 (w), 3060.2 (w), 2950.6 (w), 2844.3 (w), 1790.2 (s), 1691.8 (s), 1678.5 (s), 1652.9 (s), 1598.7 (s), 1434.3 (m), 1390.0 (s), 1256.0 (s), 1203.9 (s), 1172.7 (s), 1121.3 (m), 1019.5 (m), 888.2 (m), 750.6 (m), 718.5 (s), 529.5 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 508.1634, Obs. 508.1638.



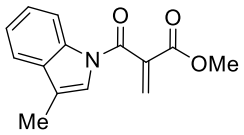
Methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (5-46): Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.345 g, 1.06 mmol), 4-methoxybenzaldehyde (0.244 g, 1.64 mmol), glacial acetic acid (0.0315 g, 0.524 mmol), piperidine (0.0172 g, 0.202 mmol) and benzene (30 mL) were combined according to

general procedure A to afford **5-46** as a yellowish orange solid (0.384 g, 82%) after 14 hours. R_f= 0.31 (20% EtOAc/Hex). [m.p. 90-92 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.67 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.55 – 7.42 (m, 2H), 7.42 – 7.34 (m, 3H), 7.07 (s, 1H), 6.79 – 6.73 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (t, *J* = 7.2 Hz, 1H), 3.52 (t, *J* = 7.3 Hz, 1H), 3.16 (t, *J* = 7.3 Hz, 1H), 3.06 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 165.5, 165.0, 162.0, 143.6, 135.5, 132.1, 130.6, 125.7, 124.7, 124.3, 123.6, 123.4, 123.2, 120.3, 118.5, 117.2, 114.7, 77.2 (Rotamers), 55.4, 52.8, 43.1 (Rotamers), 31.0, 28.7, 28.5. IR: 3060.2 (w), 3007.0 (w), 2957.2 (w), 2834.3 (w), 1708.5 (m), 1691.0 (m), 1598.9 (s), 1512.2 (m), 1450.9 (m), 1392.8 (m), 1256.3 (s), 1203.1 (s), 1172.6 (s), 1026.8 (m), 878.2 (w), 830.6 (m), 730.4 (s), 700.6 (s), 539.5 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 441.0576, Obs. 441.0580.

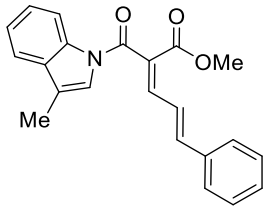


Methyl 2-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (5-48): Methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.01 g, 3.50 mmol), 4-methoxybenzaldehyde (0.615 g, 4.52 mmol), glacial acetic acid (0.105 g, 1.75 mmol), piperidine (0.043 g, 0.506 mmol) and benzene (150 mL) were combined according to general procedure A to generate **5-48** as a light yellow solid (0.568 g, 40%) after 16 hours. R_f= 0.26 (40% EtOAc/Hex). [m.p. 147-149 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.66 (d, *J* = 8.1 Hz, 1H), 7.93 (s, 1H), 7.57 – 7.42 (m, 3H), 7.42 – 7.33 (m, 2H), 7.20 (s, 1H), 6.80 – 6.74 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.63 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 170.8, 165.6, 164.9, 161.9, 143.5, 135.4, 132.1, 130.8, 125.6, 124.7, 124.4, 124.2, 123.1, 119.0, 117.0, 115.8, 114.6, 55.3, 52.8, 52.1, 30.7. IR: 3050.2 (w), 3003.7 (w), 2953.9 (w), 2841.0 (w), 1737.6 (m), 1722.3 (m), 1710.6 (m), 1691.1 (m), 1598.9 (s), 1512.4 (m), 1450.7 (m), 1392.8 (m), 1256.2 (s), 1202.3 (m),

1172.0 (s), 1045.5 (m), 1026.7 (m), 888.2 (w), 730.4 (s), 700.4 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 407.1369, Obs. 407.1389.



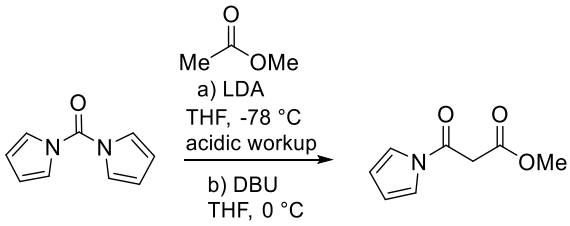
Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (5-56): Using conditions established by Yiotakis[323], a round bottom flask was charged with acetic acid (12 mL), methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.602 g, 2.60 mmol), formaldehyde (0.0708 g, 2.359 mmol), and $Cu(OAc)_2$ (0.0416 g, 0.229 mmol) and the mixture was heated at reflux for 3 hours. The solvent was removed *in vacuo* and diethyl ether was added. The mixture was filtered and the filtrate was washed successively with 1 M HCl, dilute $NaHCO_3$, 1 M HCl, and brine. The organics were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified using silica gel flash chromatography to yield **5-56** as a brown oil (0.470 g, 74%). R_f = 0.37 (20% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.44 (d, *J* = 7.3 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.44 – 7.30 (m, 2H), 6.99 (s, 1H), 6.79 (d, *J* = 0.4 Hz, 1H), 6.15 (s, 1H), 3.81 (d, *J* = 0.8 Hz, 3H), 2.27 – 2.25 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.8, 163.6, 137.3, 135.7, 132.0, 131.7, 125.4, 124.1, 122.7, 119.2, 119.0, 116.6, 52.8, 9.7. IR: 3119.9 (w), 3060.2 (w), 2960.5 (w), 2914.0 (w), 1736.9 (s), 1728.1 (s), 1690.8 (s), 1678.3 (s), 1449.6 (s), 1387.6 (m), 1343.5 (m), 1235.7 (m), 1170.7 (m), 1151.2 (m), 1061.6 (m), 931.4 (w), 881.6 (m), 735.1 (s), 701.4 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 243.0895, Obs. 243.0891.



Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (5-58): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.201 g, 0.868 mmol), cinnamaldehyde (0.158 g, 1.19 mmol), glacial acetic acid (0.0525 g, 0.873 mmol),

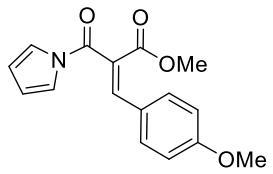
piperidine (0.0259 g, 0.304 mmol) and benzene (15 mL) were combined according to general method A to yield **5-58** as a red solid (0.280 g, 93%) after 12 hours. R_f = 0.40 (20% EtOAc/Hex). [m.p. 108-110 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.65 (s, 1H), 7.76 (d, *J* = 11.8 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 – 7.27 (m, 7H), 7.12 (d, *J* = 15.3 Hz, 1H), 6.97 (s, 1H), 6.89 – 6.76 (m, 1H), 3.79 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (Isomers) δ ppm 164.6, 145.0, 144.2, 135.6, 135.1, 132.1, 130.0, 128.8, 127.8, 126.7, 125.3, 124.1, 122.8, 122.2, 119.2, 119.0,116.8, 52.6, 34.5, 31.5, 25.1, 22.5, 14.1, 9.7. IR: 3123.3 (w), 3036.9 (w), 2953.9 (w), 2841.0 (w), 1710.8 (s), 1720.8 (s), 1678.1 (s), 1611.5 (s), 1589.9 (s), 1434.0 (s), 1392.4 (m), 1340.6 (m), 1236.3 (s), 1210.4 (s), 1154.0 (m), 1080.2 (m), 1047.9 (m), 974.9 (w), 888.2 (w), 746.8 (s), 689.0 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 345.1365, Obs. 345.1367.

Preparation of Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (5-62):



Methyl 3-oxo-3-(1H-pyrrol-1-yl)propanoate: Following a modification of Evans' reported procedure[324]: *n*-BuLi (10M in hexanes, 36 mmol) was added to a solution of diisopropylamine (3.13 mL, 22.16 mmol) in THF (40 mL) at -78 °C. After 30 minutes, methyl acetate (2.9 mL, 36.5 mmol) was added slowly and the mixture was stirred for another 30 minutes. A solution of di(1*H*-pyrrol-1-yl)methanone[325] (3.55 g, 22.16 mmol) in THF (10 mL) was added to the reaction vessel. After 1 hour, the reaction was quenched with AcOH and washed with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was washed with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF, and 1,8-

diazabicyclo[5.4.0]undec-7-ene (500 µL, 3.34 mmol) was added. After 1 hour, ethyl acetate was added to the reaction flask. The mixture was washed with 0.5 M $CuSO_4$, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified to afford the desired product as a brown oil (2.92g, 79%). R_f = 0.28 (20% EtOAc/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.23 (s, 2H), 6.31 – 6.22 (m, 2H), 3.83 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.2, 163.1, 119.1, 113.7, 52.6, 41.8. IR: 3143.2 (w), 3000.4 (w), 2950.6 (w), 1742.1 (s), 1709.9 (s), 1469.4 (m), 1343.4 (s), 1249.2 (s), 1208.0 (m), 1160.0 (m), 1115.1 (s), 1076.0 (m), 994.5 (m), 917.8 (s), 738.5 (s), 675.7 (m), 610.0 (m), 597.7 (m), 519.6 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 167.0582, Obs. 167.0596.



Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (5-62):

Methyl 3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (0.500 g, 2.99 mmol), 4-methoxybenzaldehyde (0.560 g, 4.11 mmol), glacial acetic acid (0.105 g, 1.75 mmol), piperidine (0.0431 g, 0.506 mmol) and benzene (25 mL) were combined according to general method A to afford **5-62** as a brown solid (0.780 g, 91%) after 12 hours. R_f = 0.25 (20% EtOAc/Hex). [m.p. 79-81 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.91 (s, 1H), 7.37 – 7.29 (m, 3H), 6.85 – 6.78 (m, 3H), 6.27 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.2, 164.7, 162.0, 144.0, 132.0, 124.6, 122.3, 114.6, 114.1, 55.3, 52.8. IR: 3143.2 (w), 3073.4 (w), 2960.5 (w), 2837.6 (w), 1709.6 (s), 1678.6 (s), 1598.3 (s), 1512.6 (s), 1451.8 (m), 1288.9 (m), 1253.2 (m), 1202.3 (m), 1173.4 (s), 1126.4 (m), 1069.3 (m), 1017.7 (m), 884.9 (m), 825.1 (m), 730.3 (s), 700.5 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 285.1001, Obs. 285.0997.

5.7.3 In(III)-catalyzed Cyclizations

5.7.3.1 General Procedure for Friedel-Crafts Cyclizations

To a mixture of $In(OTf)_3$ (0.10 equiv) in 1,2-dichloroethane or toluene heated to a reflux, dissolved acrylates **5-28** (1.0 equiv) were syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated for column chromatography using silica gel.

5.7.3.2 Rationale for *cis/trans* assignment

The major diastereomer is *trans* in spatial orientation based on a correlation between the calculated dihedral angle between H_a and H_b for both the *cis*- and *trans*-isomers and the expected Karplus[326,327] coupling constant. This value was compared to the experimental value using ^1H NMR (Table 5.6). Diastereomeric ratios are reported where applicable, and the integral value for each signal is noted.

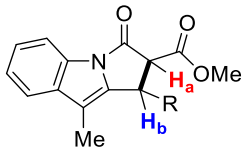
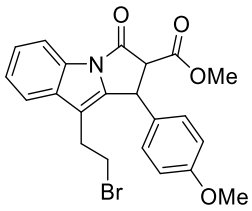


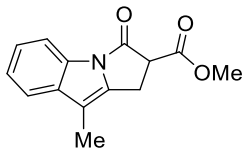
Table 5.6 *Cis/Trans* Assessment for Spatial Orientation

Diastereomer	Dihedral Angle[a]	Predicted Karplus *J*-Value (Hz)[b]	Observed *J*-Value (Hz)[c]
cis	8.5˚	~7-8	9-10
trans	125.8˚	~5-6	5-6

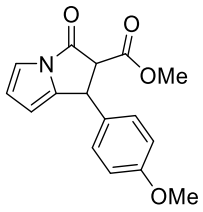
[a]Determined from energy minimizations using Trident software from Schrodinger, Inc.
[b]Determined from Karplus coupling constant chart
[c]Determined by ^1H NMR spectroscopy



Methyl 9-(2-bromoethyl)-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (5-47): Methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.061 g, 0.138 mmol), $In(OTf)_3$ (0.0081 g, 0.014 mmol) and 1,2-DCE (7 mL) were combined according to the general procedure to afford **5-47** as a brown oil (0.0418 g, 69%) after 12 hours. R_f= 0.24 (30% EtOAc/Hex). *Diastereomeric ratio*: (25:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.20 – 8.14 (m, 0.17), 8.12 – 8.06 (m, 0.95), 7.71 (s, 0.07), 7.52 – 7.44 (m, 1.30), 7.42 – 7.29 (m, 2.54), 7.21 – 7.14 (m, 2.08), 7.10 – 7.14 (m, 0.31), 6.93 – 6.80 (m, 2.44), 5.06 (d, *J* = 4.9 Hz, 1.00), 4.52 – 4.45 (m, 0.04), 4.06 – 4.01 (m, 0.98), 3.90 – 3.77 (m, 6.82), 3.56 – 3.21 (m, 3.42H), 3.12 – 2.64 (m, 3.54). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.8, 164.7, 159.4, 141.1, 140.9, 135.2, 135.0, 131.5, 131.1, 131.0, 130.2, 130.0, 128.3, 124.6, 124.3, 118.8, 114.7, 114.4, 114.2, 113.9, 112.2, 111.3, 62.6, 55.3, 53.3, 43.2, 42.3, 31.1, 27.3, 27.2. IR: 3017.0 (w), 2953.9 (w), 2927.3 (w), 2831.0 (w), 1737.2 (s), 1726.3 (s), 1712.0 (s), 1610.9 (m), 1452.8 (s), 1392.3 (m), 1365.0 (m), 1317.0 (m), 1245.5 (s), 1173.6 (s), 1028.3 (m), 931.4 (w), 831.0 (m), 747.6 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 441.0576, Obs. 441.0575.



Methyl 9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate(5-57): Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (0.100 g, 0.411 mmol), $In(OTf)_3$ (0.0355 g, 0.0632 mmol) and toluene (5 mL) were combined according to the general procedure to afford **5-57** as a pale yellow solid (0.0471 g, 47%) after 1 hour. R_f= 0.34 (20% EtOAc/Hex). [m.p. 95-97 ˚C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.04 – 7.97 (m, 1H), 7.49 – 7.41 (m, 1H), 7.35 – 7.27 (m, 2H), 4.15 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.84 (s, 3H), 3.54 – 3.44 (m, 1H), 3.33 (ddd, *J* = 17.2, 9.3, 1.3 Hz, 1H), 2.20 (t, *J* = 1.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 165.5, 136.4, 136.3, 130.4, 124.3, 123.6, 118.7, 113.8, 109.7, 53.2, 52.5, 23.0, 8.3. HRMS (ESI) M/Z+ Calc. 243.0895, Obs. 243.0897.



Methyl 1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (5-63): Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (0.152 g, 0.531 mmol), $In(OTf)_3$ (0.0308 g, 0.055 mmol) and 1,2-DCE (13 mL) were combined according to the general procedure to afford **5-63** as a red oil (0.0817 g, 54%) after 12 hours. R_f= 0.35 (20% EtOAc/Hex). *Diastereomeric ratio*: (13:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.06 (m, 3.27), 6.91 – 6.78 (m, 2.20), 6.53 (t, *J* = 3.1 Hz, 0.10), 6.36 – 6.29 (m, 0.96), 6.02 – 6.00 (m, 0.08), 5.99 – 5.94 (m, 0.95), 4.87 (d, *J* = 3.9 Hz, 1.01), 4.40 (d, *J* = 9.1 Hz, 0.07), 3.92 (d, *J* = 5.1 Hz, 0.91), 3.85 (s, 2.96), 3.80 (s, 3.00), 3.79 (s, 0.67), 3.24 (s, 0.26). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 165.5, 159.2, 140.5, 131.9, 128.4, 120.0, 114.4, 113.6, 111.7, 106.2, 105.0, 62.5, 55.3, 53.2, 42.4. IR: 3143.2 (w), 3106.6 (w), 3000.4 (w), 2957.2 (w), 2910.7 (w), 2837.6 (w), 1754.8 (s), 1737.3 (s), 1727.2 (s), 1608.9 (w), 1512.0 (m), 1401.6 (m), 1291.3 (m), 1242.7 (m), 1161.7 (m), 1080.8 (m), 974.5 (w), 901.5 (w), 833.4 (w), 719.4 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 285.1001, Obs. 285.1004.

CHAPTER 6 PYRROLO[3,2,1-*IJ*]QUINOLINE SYNTHESIS VIA IN(III)-CATALYZED FRIEDEL-CRAFTS CYCLIZATIONS

Along with the theme of heterocycle synthesis, another class of compounds, the pyrroloquinolines, was targeted. This class contains in its molecular skeleton the 1,2,3,4-tetrahydroquinoline skeleton (THQ) (**6-1**). Prevalent in nature, the 1,2,3,4-tetrahydroquinoline framework is one of the most valued nitrogen-containing architectures because it is used in medicinal, biological, and agrochemical research.[328] As a subgroup within the THQ class, pyrrolo[3,2,1-*ij*]quinolines (PQ, **2**) and their reduced and oxidized derivatives have become of great interest in the area of drug discovery, agrochemistry, and materials science.[329–338] For example, PHA-529311 (**6-3**) demonstrates inhibitory activity against herpesvirus DNA polymerases,[332,339] and **6-4** strongly activates sirtuin 1 (SIRT1).[340] KC 11404 (**6-5**), a promising molecule for asthma, has potent histamine and platelet activating factor (PAF) antagonism along with strong inhibition of 5-lipoxygenase activities.[335] Pyrrolo[3,2,1-*ij*]quinoline **6-6** was reported as a good agonist for the 5-hydroxytryptamine receptor (5-HT_{2c}) with greater selectivity for the 5-HT_{2a} isoform, becoming a possible therapeutic candidate for epilepsy and obesity.[334] In several cases, PQ derivatives exhibited high diuretic,[341] melatoninergic,[337] and anti-acetylcholinesterase activity.[338] Moreover, PQs were reported as key intermediates towards the synthesis of other bioactive compounds and natural products.[225,342,342,343] Lastly, the 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline system comprises the central core of lilolidine (**6-7**) alkaloids,[344] which have been explored as therapeutics, fungicides (i.e., lilolidone **6-8**),[345] and as red-light-emitting dopants in organic light-emitting diodes (OLEDs) (**6-9**).[333]

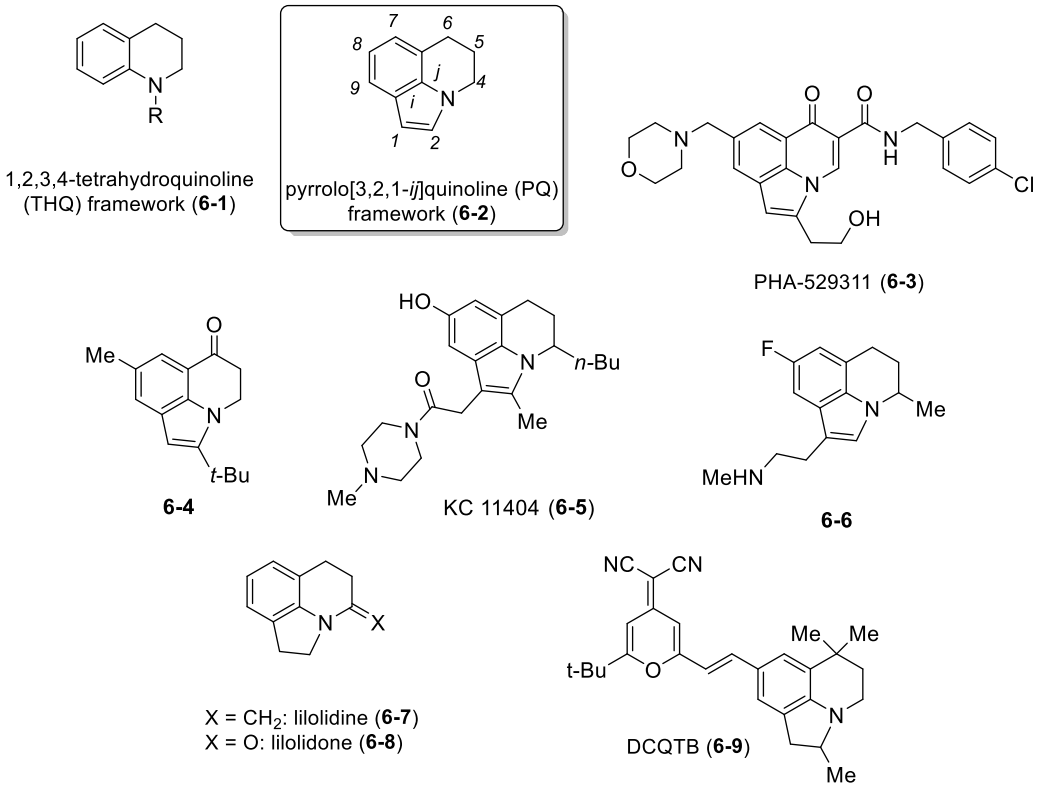


Figure 6.1: Molecules containing the pyrroloquinoline framework

6.1 Syntheses of Pyrroloquinolines

Many methods have been reported for the synthesis of pyrrolo[3,2,1-*ij*]quinoline derivatives. Most methodologies involve the annellation of a six-membered construct onto an indolic-type structural analog or that of five-membered ring construction onto a quinoline molecule. Other transformations include free radical cyclizations,[185,346–351] sigmatropic reactions,[352–355] Wittig-type,[356] Michael-type annulations,[330,357] Fischer indolization,[358] Friedel-Crafts reactions,[359–361] multicomponent reactions,[356] transition metal-catalyzed annulations,[293,362–366] and C-H functionalization.[364,366–368] In light of the numerous approaches, interesting, recent advances are discussed below.

In 2014, Xiao-Ming et al. published a cyclodehydration of α-amino carbonyl molecules **6-10** to form pyrrolo[3,2,1-*ij*]quinolines **6-11**.[369] The authors implemented the Bischler[370,371] reaction as their guide to design a green synthesis for quinolines and indoles. To become more eco-friendly, the group used inorganic salts—not corrosive

acids or heavy metals. Settling on NH_4PF_6 in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) at 110 ˚C, they obtained pyrrolo[3,2,1-*ij*]quinolines **6-11** in 61-92% yield. The ammonium group was hypothesized to activate the carbonyl for a nucleophilic ring attack followed by dehydration to afford the desired products. Alkyls, methy esters, and aryl containing methoxy, chloro, bromo, and trifluormethyl moieties were compatabile, and the reactions proceeded smoothly (Figure 6.2).

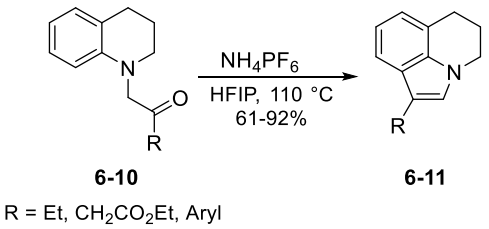


Figure 6.2: Xiao-Ming's cyclodehydration for pyrroloquinolines

Within the same year as Xiao-Ming's protocol, Mphahlele and Oyeyiola disclosed a method for the synthesis of 2-substituted 4-aryl-8-bromo-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6-ones **6-13** from 2-aryl-6,8-dibromoquinolin-4(1*H*)-ones **6-12** via a site-selective Sonogashira[372] cross-coupling with Pd/C-PPh_3, copper(I) iodide, and potassium carbonate in DMF:H_2O at 110 ˚C.[365] Using a bromine at the C6 position for the Sonogashira coupling with phenylacetylene, the Pd/C-PPh_3-CuI pre-catalyst mixture performed the oxidative addition to install an alkyne. Deprotonation of the nitrogen caused a base-promoted cyclization to afford compounds **6-13** in 62-68% yield (Figure 6.3). Four substrates were shown to display reactivity. Final Suzuki-Miyaura[373] cross coupling with 4-flurophenylboronic acid afforded derivatives of compounds **6-13**.

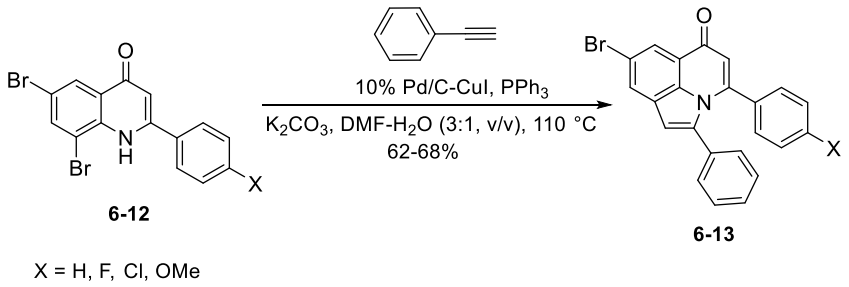
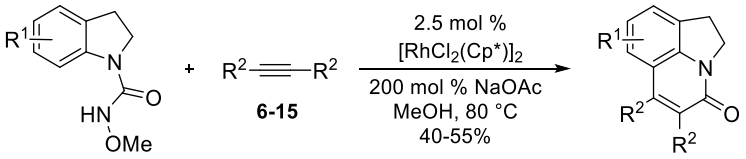


Figure 6.3: Mphahlele's one-pot site-selective Sonogashira cross-coupling heteroannulation

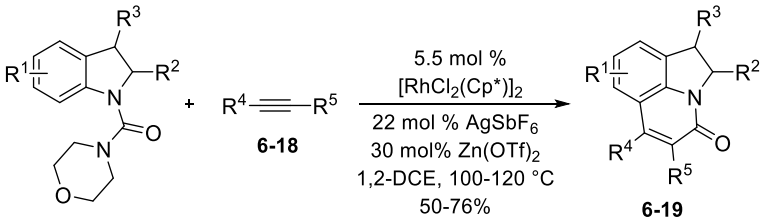
Recently, transition metal-catalyzed protocols to form pyrroloquinolines were reported by Wang, Manoharan, and Yang in 2015 (Figure 6.4). Wang et. al. divulged a Rh(III)-catalyzed redox-neutral C-H functionalization of indolines **6-14** with alkynes.[374] Noticing that indoles can be functionalized at the C2-H and C3-H, they designed a method such that C-H functionalization would provide access to the pyrrolo[3,2,1-*ij*]quinolin-4-one framework. Using electron-releasing and electron-accepting indolines, $[RhCl_2(Cp^*)]_2$, sodium acetate (NaOAc), and methanol heated to 80 ˚C for 24 hours, they generated 1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]-quinoline-4-ones **6-16** in 40-55% yield. The conditions were compatible with methoxy groups, esters, and halogens, but propargyl acetates and propargyl alcohols did not form any of the desired products, and the reaction was not affected by substitution on the indoline. For the mechanism, the group suggested a rhodium(III) reversible C-H cleavage at C7 to form a six-membered rhodacycle after proton removal. Alkyne insertion formed an expanded rhodacycle (8-membered). Intramolecular nucleophilic addition and subsequent elimination formed **6-16**.

Wang et al.



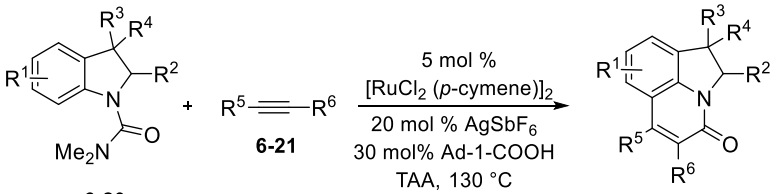
R^1 = Me, OMe, F, Cl, Br, CO_2Me
R^2 = Me, *n*-Bu, *n*-Pr

Yang et al.



R^1 = H, Br, Cl, F, Me
R^2 = H or Me
R^3 = H or Me
R^4 = Ar, Me, Et, *n*-Pr, 4-OMe-C_6H_4, Ph, 4-Br-C_6H_4
R^5 = Ar, 2-Naphth, Ph, Et, 4-Br-C_6H_4

Manoharan and Jeganmohan



R^1 = Br, H, OMe
R^2 = H or Me
R^3 = H, Me, Ph
R^4 = H or Me
R^3-R^4 = -$(CH_2)_5$-
R^5 = Et, *n*-Bu, Me, Ph, 4-OMe-C_6H_4, CH_2OMe
R^6 = Ph, 2-thienyl, CO_2Et, CO_2Me 4-OMe-C_6H_4, Me, Et, CH_2OMe

Figure 6.4: Transition metal-catalyzed C-H functionalization reactions

Yang et al. developed a Rh(III)-catalyzed approach to the indoline skeleton for a C-H functionalization/annulation sequence to assemble pyrroloquinolinone derivatives **6-19** in 2015 as well (Figure 6.4).[364] As a part of the strategy, the group incorporated a morpholine moiety to act as a directing group such that the C-H and C-N bond cleavages would occur. $[RhCl_2(Cp^*)]_2$, $AgSbF_6$, alkynes, and $Zn(OTf)_2$ in 1,2-dichloroethane at 100-120 ˚C gave pyrroloquinolines **6-19** in moderate to good yields (50-76%) after 18-24 hours. Similar to the previous protocol mentioned above, halogens, aryls, and alkyl groups were tolerated. Accordingly, if the electronics were tuned appropriately such that the directing ability and carbamoyl moiety were balanced, the annulation reactions worked well. Furthermore, since the redox was neutral, the asymmetric alkynes afforded good regioselectivity.

Manoharan and Jeganmohan reported another route to pyrroloquinolinones using **6-20**, alkynes, $\{RuCl_2(p\text{-cymene})\}_2$, $AgSbF_6$, and Ad-1-COOH in tert-amyl alcohol at 130 ˚C for 24 hours (Figure 6.4).[366] Aryl, alky, and ether-based alkynes were reported to form pyrroloquinolinones **6-22** in 47-79% yield. Mechanistically, they hypothesized that the products would form along a similar pathway as the route outlined by Wang except that a ligand exchange would occur between the catalyst and $AgSbF_6$. Chelation and deprotonation at C7-H formed a six-membered ruthenacycle. Insertion of the alkyne into the Ru-C connectivity was postulated to occur. Then, protonation and elimination of dimethyl amine furnished the desired pyrroloquinolines. The method was regioselective and tolerable of various functional groups.

Despite the broad applicability and rising interest among synthetic chemists, reported methods for the preparation of pyrrolo[3,2,1-*ij*]quinolines exhibit major drawbacks. Harsh reaction conditions, high catalyst loadings, lengthy synthetic protocols, poor atom economy, and/or functional group intolerance were complications for previous approaches. For example, methods that involved the formation of the PQ

framework via Fischer indolization were limited by the preparation of the 1-amino-THQs.[334,335,337] Likewise, transition metal-catalyzed annulations that were used to form PQs tended to use high catalyst loadings with expensive catalysts.[293,362,363] In one report, 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones were obtained by appending a pyrrole ring onto 2,3-dihydroquinolin-4(1*H*)-ones by using a Sonogashira coupling with 10% Pd/C followed by an intramolecular C-N bond formation reaction using 5 mol% $PdCl_2$.[340] Another representative example involved Friedel-Crafts annulations on indoles to form a PQ tricycle,[359–361,375] but unfortunately, stoichiometric amounts of protic or Lewis acids were required for cyclization. Finally, other examples involving either multicomponent reactions,[356] free radical cyclizations,[346,347] sigmatropic rearrangements[352,353] and Michael-type annulations[357] had a narrow substrate scope. In general, efficient syntheses for the assembly of functionalized pyrrolo[3,2,1-*ij*]quinolines for greater selectivity, economic viability, and operational simplicity are needed.

6.2 Hypothesis and Synthetic Rationale for the Synthesis of Pyrrolo[3,2,1-*ij*]quinolin-4-ones

In conjuction with our previous efforts to develop routes that readily tap into broad skeletal diversity for *N*-annelated polycycles,[254,255] we sought to prepare pyrrolo[3,2,1-*ij*]quinolines. We devised an $In(OTf)_3$-catalyzed intramolecular Friedel-Crafts alkylation of methyl 2-(1*H*-indole-1-carbonyl)acrylates **6-23** (Figure 6.5, scheme 1) as a highly efficient and diastereoselective approach to functionalized 1*H*-pyrrolo[1,2-*a*]-indole-3(2*H*)-ones **6-24** under mild conditions.[255] Using similar chemistry, we predicted that Freidel-Crafts alkylation chemistry would afford pyrrolo[3,2,1-*ij*]quinolines by employing a substrate with the indole 2-position blocked, as in the methyl 2-(2-methyl-1*H*-indole-carbonyl)acrylate **6-25** (Figure 6.5, scheme 2). With the 2-position unavailable, electrophilic attack would be feasible at

the indole 7-position, yielding pyrrolo[3,2,1-*ij*] quinolin-4-ones **6-26**.

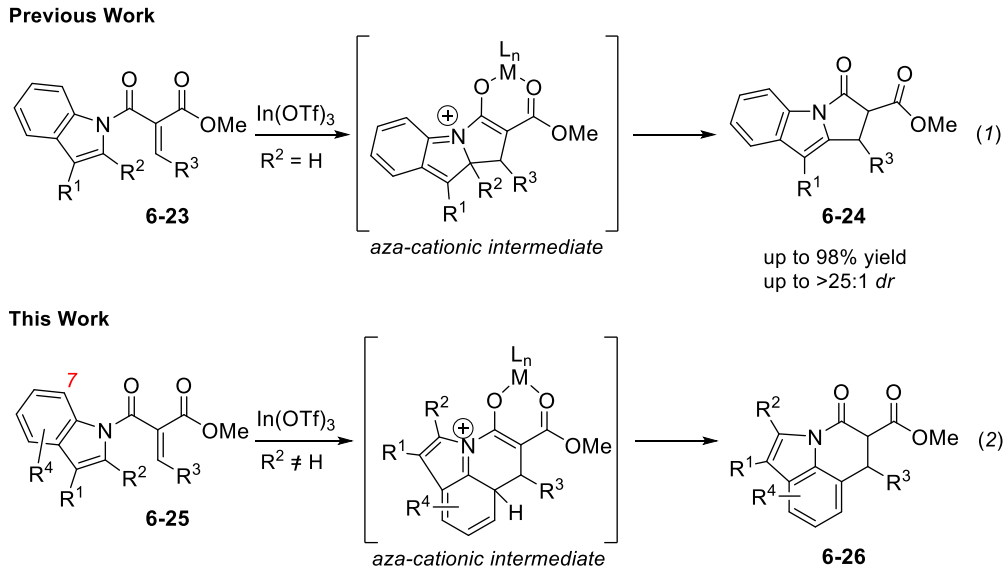


Figure 6.5: Rationale for pyrroloquinoline formation

6.3 Precursor Assembly for Pyrroloquinoline Synthesis

Testing this rationale required synthesizing the desired alkylidene malonate monoamides as previously reported in the literature.[255] Treatment of an indole with methyl malonyl chloride afforded β-amide esters **6-28**. Knoevenagel condensation[376] with the appropriate aldehydes formed the appropriate alkylidene malonate monoamides **6-29**.

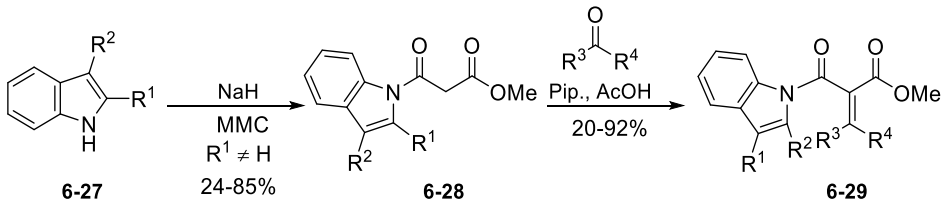


Figure 6.6: Alkylidene malonate monoamide synthesis for pyrroloquinoline assembly

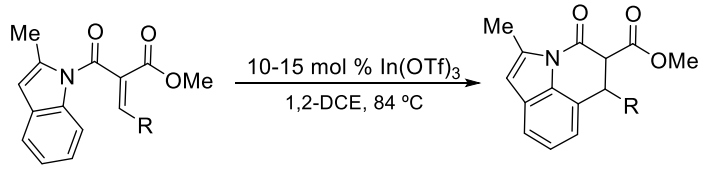
6.4 Results and Discussion

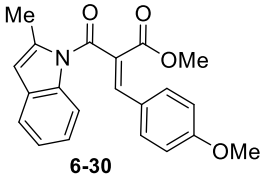
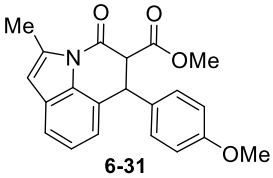
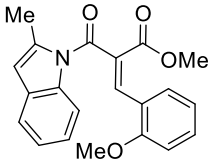
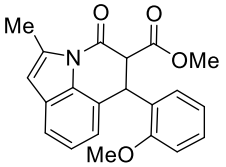
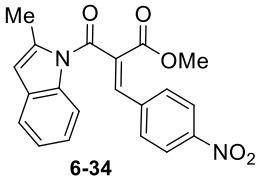
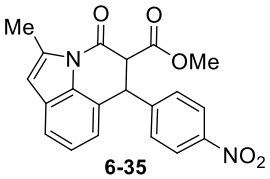
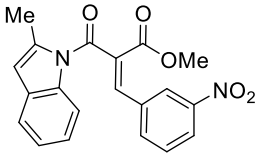
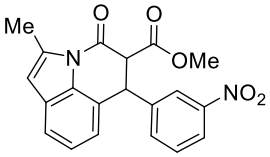
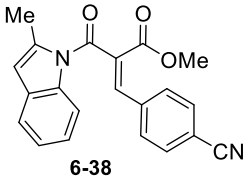
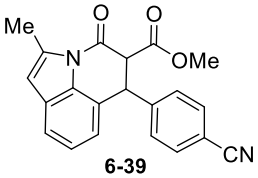
For our first trial run, **6-30** (derived from 2-methyl indole and *p*-anisaldehyde)

was subjected to 15 mol% $In(OTf)_3$ in refluxing 1,2-dichloroethane. As anticipated, **6-30** cyclized to form the desired pyrrolo[3,2,1-*ij*]quinolin-4-one product **6-31** in 63% yield with 50:1 *trans*:*cis dr* (Table 6.1, entry 1). With the same donating group as **6-30**, 2-methoxyphenyl derivative **6-32** generated its PQ product **6-33** in 87% yield with a 3.7:1 *dr* (Table 6.1, entry 2).

We then sought to probe the electronic effects of the transformation and discovered a strong electronic influence on the reaction when the aryl substituent was changed to a strong electron-withdrawing group (Table 6.1, entries 3-5). Although the 4-nitro-, 3-nitro-, and 4-cyano-aryl substituted alkylidene malonate monoamides formed products **6-35**, **6-37**, and **6-39** in good yields (78%, 86%, and 78%, respectively), low diastereoselectivities were observed (~2:1 *dr*). When halogens were used (F or Br, Table 6.2, entries 1 and 2), both produced their respective products **6-41** and **6-43** in 94% and 61% yield. Although *m*-bromo gave an 8.3:1 *dr*, the *p*-fluoro gave a 2.6:1 *dr*. Given fluorine's high electronegativity, an akin electronic effect may have influences like those in the nitro and cyano groups. We then substituted a heteroaromatic group on the alkylidiene malonate monoamide. 2-Thienyl derivative **6-44** cyclized to afford **6-45** as a single observable diastereomer in 51% yield with *dr* >99:1 (Table 6.2, entry 3).

Table 6.1: Alkene Substituent Effect on Reactivity



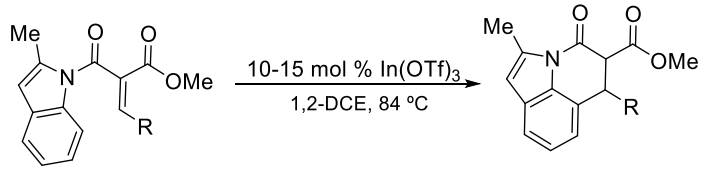
Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **6-30**	 **6-31**	3.0	63%	50:1
2[d,e]	 **6-32**	 **6-33**	3.0	87%	3.7:1
3[d,e]	 **6-34**	 **6-35**	3.0	78%	2.4:1
4[e]	 **6-36**	 **6-37**	13.0	86%	2.2:1
5[e]	 **6-38**	 **6-39**	14.0	78%	1.9:1

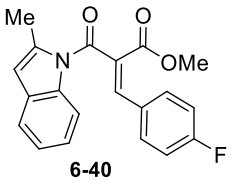
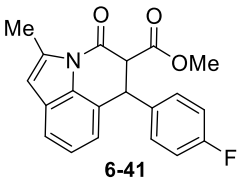
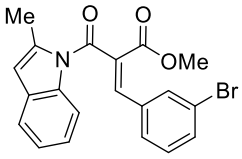
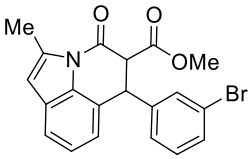
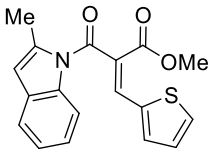
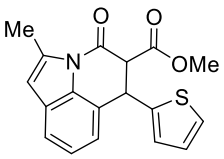
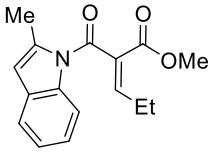
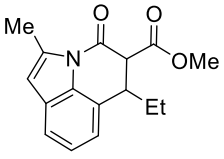
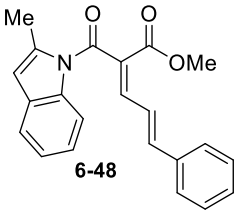
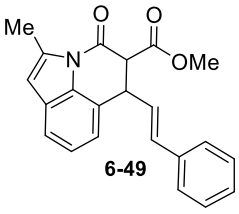
[a] Reactions run with the precursor (1.0 equiv.) and 10-15 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio. [d] The reaction was performed in toluene at reflux. [e] Yield represents a combined cis-trans mixture. [f] The reaction was performed with 30 mol % $In(OTf)_3$ in toluene at reflux.

As a result of the data obtained from aromatic substituents, the precursor scope was expanded to include nonaromatic substrates. In particular, alkylidiene malonate monoamides derived from alkyl aldehydes and cinnamaldehyde were investigated.

When the ethyl-substituted alkylidiene malonate monoamide **6-46** was subjected to the reaction conditions, no conversion was observed after 24 hours. Further optimization with a higher catalyst loading (30 mol%) in toluene at reflux gave pyrroloquinoline **6-47** in 84% yield with 25:1 *dr* (Table 6.2, entry 4). After treatment of cinnamaldehyde-derived alkylidiene malonate monoamide **6-48** under the same conditions, **6-49** was formed in 65% yield with 20:1 *dr* (Table 6.2, entry 5).

Table 6.2: Alkene Substituent Effect on Reactivity



Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1[e]	 **6-40**	 **6-41**	1.0	94%	2.6:1
2	 **6-42**	 **6-43**	14.0	61%	8.3:1
3	 **6-44**	 **6-45**	14.0	51%	>99:1
4[f]	 **6-46**	 **6-47**	12.0	84%	25:1
5[f]	 **6-48**	 **6-49**	14.0	65%	20:1

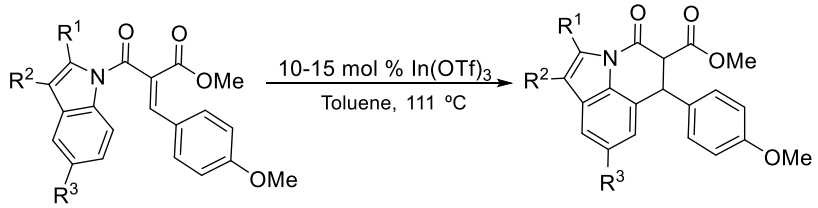
[a] Reactions run with the precursor (1.0 equiv.) and 10-15 mol % $In(OTf)_3$ in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio. [d] The reaction was performed in toluene at reflux. [e] Yield represents a combined cis-trans mixture. [f] The reaction was performed with 30 mol % $In(OTf)_3$ in toluene at reflux.

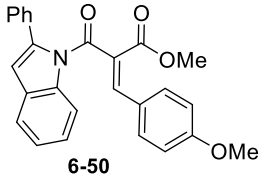
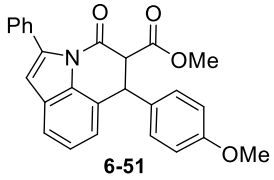
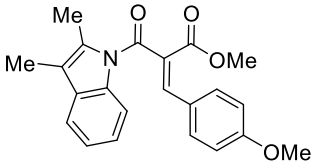
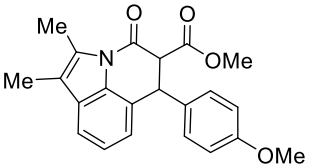
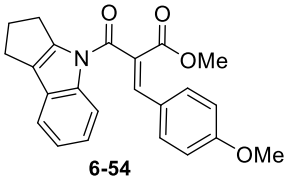
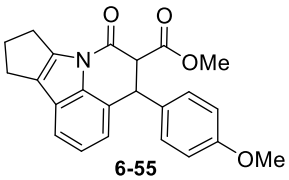
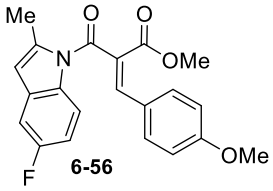
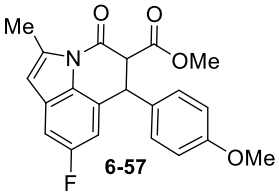
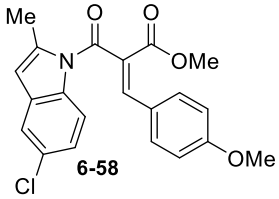
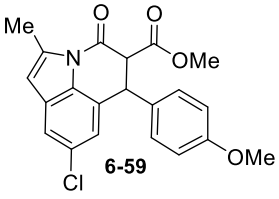
Next, differing substitutions were made around the indole ring (Table 6.3). When 2-phenyl indolyl alkylidiene malonate monoamide **6-50** was subjected to the reaction conditions, pyrrolo[3,2,1-*ij*]quinolin-4-one **6-51** was obtained in 97% yield

with 17:1 *dr* (Table 6.3, entry 1). 2,3-Disubstituted indoles also cyclized. 2,3-Dimethyl indolyl alkylidiene malonate monoamide **6-52** formed **6-53** in 86% yield with >99:1 *dr* (Table 6.3, entry 2). Similarly, the tetrahydrocyclopenta[*b*]indole based alkylidiene malonate monoamide **6-54** furnished tetracyclic product **6-55** in 82% yield as a single observable diastereomer (Table 6.3, entry 3).

Installing substituents on the benzenoid portion of indole was tolerated and did not inhibit the transformation from ocurring (Table 6.3, entries 4 and 5). Specifically, the 5-fluoro- and 5-chloro-2-methyl indole derivatives **6-56** and **6-58** produced pyrrolo[3,2,1-*ij*]-quinolin-4-ones **6-57** and **6-59** in high yields (88% and 90%), respectively, with high diastereoselectivities (>99:1 *dr*).

Table 6.3: Indole Substituent Effect on Reactivity



Entry[a]	Precursor	Product	Time (h)	Yield[b]	dr[c]
1	 **6-50**	 **6-51**	3.0	97%	17:1
2	 **6-52**	 **6-53**	4.0	86%	>99:1
3	 **6-54**	 **6-55**	12.0	82%	>99:1
4[d]	 **6-56**	 **6-57**	12.0	88%	>99:1
5	 **6-58**	 **6-59**	4.0	90%	>99:1

[a] Reactions run with the precursor (1.0 equiv.) and 10-15 mol % $In(OTf)_3$ in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities were determined from ^1H NMR of crude reaction mixture and represent *trans*:*cis* diastereomeric ratio. [d] The reaction was performed in 1,2-dichloroethane at reflux.

As previously mentioned, the tricyclic skeletons of the 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (lilolidines, **6-7** and **6-8**) have been shown to have various applications.[333,344,345] We investigated the reactivity of the indoline-derived substrate **6-**

60 to ascertain its compatibility in the intramolecular Friedel-Crafts annulation (Figure 6.7). Subjecting **6-60** to the reaction conditions provided the lilolidine derivative **6-62** in 81% yield as one observable diastereomer in a mixture with its decarboxylated product.

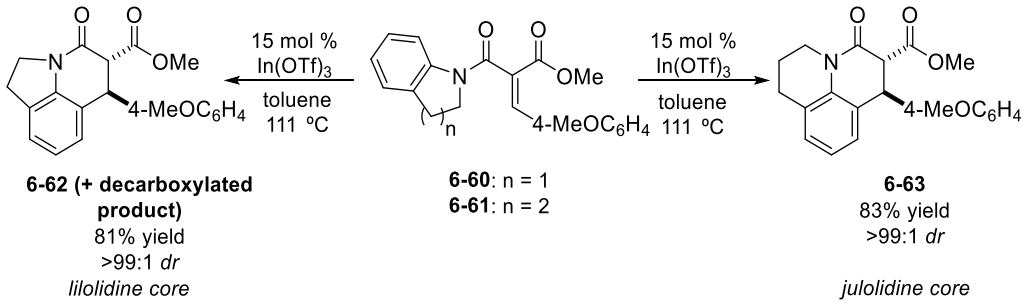


Figure 6.7: Lilolidine and julolidine alkaloid skeleton synthesis

Because of the success of indoline, we also employed the substrate **6-61** (derived from tetrahydroquinoline) in the cyclization (Figure 6.7). The resulting product encompassed the 1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinoline core, which is central in the julolidine class of alkaloids. Julolidine derivatives have attracted considerable attention due to their wide-ranging biological activities, including their role as bifunctional intercalators for DNA.[377] As expected, **6-61** readily cyclized, and it formed the expected tricyclic product **6-63** in 83% yield as the *trans*-diastereomer.

6.5 Conclusion

In conclusion, we have devised a general route for the efficient construction of a variety of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-ones. This transformation involves an $In(OTf)_3$-catalyzed diastereoselective Friedel-Crafts alkylation of methyl 2-(2-methyl-1*H*-indole-carbonyl)acrylates. One simple hydrogen replacement with a poor leaving group at the 2-position of the indole resulted in pyrroloquinolines. The products were formed in good to high yields with diastereoselectivities up to >99:1 *dr*. This protocol also provided a convenient route to the lilolidine and julolidine family of

alkaloids.

6.6 Research Participants

This research was conducted with Dr. Dadasaheb V. Patil and Paul Grzybowski. They made the precursors and the final products.

This work was published in *Chemical Communications*: Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. A General Intramolecular Friedel-Crafts Approach to Functionalized Pyrrolo[3,2,1-*ij*]quinolin-4-ones. *Chem. Commun. Camb. U. K.* **2012**, *48*, 10337–10339.

6.7 Experimental Information

6.7.1 Synthetic Methods for Pyrrolo[3,2,1-*ij*]quinolines Preparation

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. Compounds **6-28** and **6-29** were synthesized according to our reported protocol.[302]

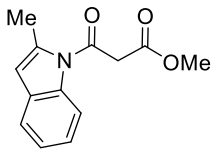
Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm). For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Dynamic Absorbents, Inc. silica gel F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic p-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (1H NMR: CDCl3 at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm),

multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Diastereomeric ratios for the cyclized products were determined by ^{1}H NMR based on a comparison of the signal ratios of the benzylic protons (~4.0-5.0 ppm) for the two diastereomeric protons or other signals displaying clear separation. These assignments are based on the coupling constants. A single observable diastereomer corresponds to >99:1 *dr*. Mass spectra were obtained using a MicroMass Autospec M. The accurate mass analyses were run in EI mode at a mass resolution of 10,000 using PFK (perfluorokerosene) as an internal calibrant. *Compounds synthesized and not reported in the literature until our publication are listed below. Dr. Dadasaheb V. Patil and Paul Grzybowski synthesized the precursors and the final products as well.*

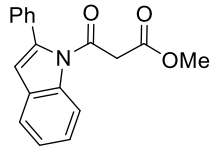
6.7.2 Synthesis of β-Amide Esters 6-27 for Pyrrolo[3,2,1-*ij*]quinoline Assembly

Sodium hydride (1.2 equiv.) was suspended in tetrahydrofuran and cooled to 0 °C. In a separate flask, the desired *N*-heterocycle (1.0 equiv.) was dissolved in tetrahydrofuran and syringed into the reaction vessel. After 30 minutes, methyl-3-chloro-3-oxopropanoate (1.25 equiv.) was added quickly. The reaction was stirred for 14 hours at room temperature. The reaction mixture was quenched with water. The organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography for product isolation.

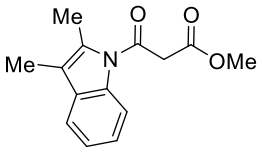


Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (6-28a): The general procedure was followed using sodium hydride (0.636 g, 26.5 mmol), 2-methyl-1*H*-indole (3.00 g,

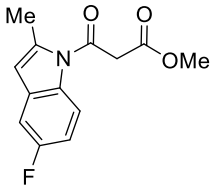
22.9 mmol), methyl-3-chloro-3-oxopropanoate (3.0 mL, 28.0 mmol), and THF (120 mL). After 5 hours, the reaction was quenched, and column chromatography formed **6-28a** as a red solid (1.80 g, 34%). (R_f = 0.40, 30% EtOAc/Hex) [m.p. 74-76°C] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 - 7.92 (m, 1H), 7.43 - 7.48 (m, 1H), 7.21 - 7.28 (m, 2H), 6.39 (s, 1H), 4.07 (s, 2H), 3.81 (s, 3H), 2.61 (d, *J* = 1.12 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 166.9, 165.9, 137.0, 136.3, 129.8, 123.9, 123.6, 120.0, 114.9, 110.6, 52.7, 45.6, 17.3. IR: 3022.4 (w), 2953.1 (w), 1733.8 (s), 1700.1 (s), 1684.4 (s), 1606.3 (m), 1588.1 (m), 1526.9 (m), 1450.5 (m), 1374.4 (m), 1300.3 (m), 1235.7 (s), 1162.5 (m), 1085.2 (w), 758.3 (s), 668.5 (w), 649.4 (w) cm^{-1}. HRMS (ESI) M/Z+ Calc. 231.0895, Obs. 231.0894.



Methyl 3-oxo-3-(2-phenyl-1*H*-indol-1-yl)propanoate (6-28b): The general procedure was followed using sodium hydride (0.414 g, 17.3 mmol), 2-phenyl-1*H*-indole (3.00 g, 15.5 mmol), methyl-3-chloro-3-oxopropanoate (2.0 mL, 18.7 mmol), and THF (140 mL). After 5 hours, the reaction was quenched, and column chromatography afforded **6-28b** as a orange oil (1.28 g, 28%). (R_f = 0.48, 30% EtOAc/Hex) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (qd, *J* = 0.84, 8.28 Hz, 1H), 7.55 - 7.59 (m, 1H), 7.44 - 7.49 (m, 5H), 7.36 - 7.41 (m, 1H), 7.29 - 7.34 (m, 1H), 6.64 (d, *J* = 0.69 Hz, 1H), 3.63 (s, 3H), 3.39 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 166.8, 166.7, 139.0, 137.9, 133.3, 129.1, 129.0, 129.0, 125.5, 124.2, 120.5, 120.4, 116.3, 112.5, 52.4, 45.9. IR: 3029.5 (w), 2958.2 (s), 2925.4 (s), 2852.3 (s), 1745.4 (s), 1715.4 (s), 1604.8 (w), 1470.7 (m), 1451.8 (w), 1406.9 (m), 1359.4 (m), 1341.8 (w), 1301.7 (m), 1253.6 (w), 1205.1 (m), 1155.5 (m), 1117.3 (w), 1076.5 (m), 1056.7 (w), 1020.7 (w), 970.1 (m), 919.4 (w), 821.1 (w), 747.8 (m), 700.7 (w) cm^{-1}. HRMS (ESI) M/Z+ Calc. 293.1052, Obs. 293.1053.



Methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (6-28c): The general procedure was followed using sodium hydride (2.41 g, 18.1 mmol), 2,3-dimethyl-1*H*-indole (2.02 g, 13.9 mmol), methyl-3-chloro-3-oxopropanoate (1.94 mL, 18.1 mmol), and THF (15 mL). After 14 hours, the reaction was quenched, and column chromatography afforded **6-28c** as a pale yellow solid (1.55 g, 56%). (R_f = 0.26, 20% EtOAc/Hex) [m.p. 75-77°C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.77-7.84 (m, 1H), 7.26-7.32 (m, 1H), 7.17 (m, 2H), 3.88 (s, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 8.2, 13.5, 45.2, 52.1, 114.5, 115.8, 117.7, 122.9, 123.6, 130.8, 131.6, 135.0, 165.3, 166.7. IR: 2989.2 (w), 2959.3 (w), 2925.6 (w), 1741.6 (s), 1681.3 (s), 1615.5 (w), 1449.6 (m), 1433.5 (m), 1361.6 (s), 1329.6 (m), 1259.5 (s), 1229.0 (w), 1162.2 (s), 1127.1 (m), 1100.2 (w), 1069.9 (w), 1019.5 (s), 928.9 (m), 833.2 (w), 759.5 (s), 691.3 (m), 613.1 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 245.1052, Obs. 245.1053.



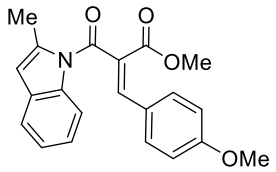
Methyl 3-(5-fluoro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (6-28d): The general procedure was followed using potassium hydride (0.711 g, 17.7 mmol), 5-fluoro-2-methyl-1*H*-indole (2.03 g, 13.6 mmol), methyl-3-chloro-3-oxopropanoate (1.9 mL, 17.7 mmol), and THF (18 mL). After 14 hours, the reaction was quenched, and column chromatography afforded **6-28d** as a red solid (0.805 g, 24%). (R_f = 0.20, 20% EtOAc/Hex) [m.p. 80-82°C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.96 (dd, *J* = 4.45, 9.11 Hz, 1H), 7.08 (dd, *J* = 2.60, 8.54 Hz, 1H), 6.95 (dt, *J* = 2.64, 9.09 Hz, 1H), 6.35 (s, 1H), 4.03 (s, 2H), 3.80 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8, 165.6, 161.2, 158.0, 138.1, 133.0, 130.9,

130.8, 116.5 and 116.4 (doublet), 111.6, 111.3, 110.6 and 110.5 (doublet), 105.8, 105.4, 52.8, 45.4, 17.3. IR: 3013.0 (w), 2956.9 (w), 1752.2 (s), 1682.4 (s), 1603.6 (m), 1476.2 (m), 1438.8 (m), 1376.3 (m), 1301.9 (w), 1259.5 (w), 1187.8 (m), 1157.8 (s), 1129.8 (m), 1000.5 (m), 958.5 (m), 870.7 (m), 797.1 (m), 780.4 (m), 668.4 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 249.0801, Obs. 249.0809.

6.7.3 Preparation of Alkylidene Malonate Monoamides for Pyrrolo[3,2,1-*ij*]quinolone Formation

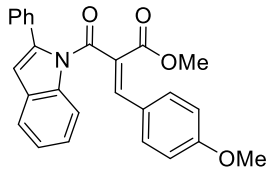
6.7.3.1 General Method A[321]

The β-amide ester (1.0 equiv.), aldehyde (1.3 equiv.), glacial acetic acid (0.5 equiv.), and piperidine (0.1 equiv.) were heated to a reflux in benzene with the use of a Dean-Stark trap for 14 hours. After the reaction mixture was cooled to room temperature, water was added to the reaction vessel, and the organic layer was collected. Subsequently, the aqueous phase was extracted with ethyl acetate three times. The combined organic layers were washed with 1M HCl and saturated sodium bicarbonate. The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

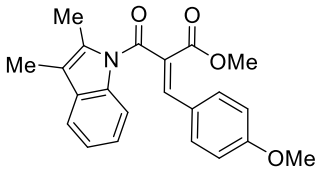


Methyl 3-(4-methoxyphenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (6-30): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1.80 g, 7.78 mmol), 4-methoxybenzaldehyde (1.2 mL, 10.1 mmol), glacial acetic acid (0.262 g, 4.37 mmol), piperidine (80 µL , 0.810 mmol) and benzene (120 mL) were mixed according to general method A to afford **6-30** as an orange oil (2.50 g, 92%) after 18 hours. (R_f = 0.24, 20% EtOAc/Hex) (*Diastereomer*) ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (br. s., 0.81), 7.87

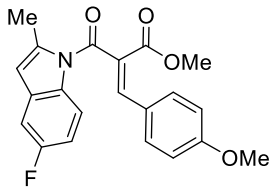
(s, 1.13), 7.72 (s, 0.15), 7.33 - 7.47 (m, 3.50), 7.21 - 7.30 (m, 2.08), 6.89 (d, *J* = 8.79 Hz, 0.27), 6.75 (d, *J* = 8.76 Hz, 2.10), 6.35 (s, 1.00), 3.87 (d, *J* = 0.70 Hz, 0.25), 3.83 (s, 0.26), 3.81 (s, 0.31), 3.77 (s, 2.63), 3.72 (s, 2.94), 2.48 (br. s., 2.87). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.3, 165.1, 161.8, 142.9, 142.5, 131.9, 131.4, 129.8, 125.6, 124.7, 119.6, 114.5, 114.3, 55.2, 52.7, 16.7. IR: 3065.3 (w), 2951.7 (w), 2939.1 (w), 1720.6 (s), 1682.4 (s), 1600.9 (s), 1511.8 (s), 1452.5 (s), 1385.8 (m), 1321.3 (m), 1290.4 (m), 1258.9 (s), 1203.7 (m), 1172.3 (s), 1123.0 (m), 1056.1 (w), 1027.6 (m), 917.2 (w), 831.4 (m), 763.9 (s), 751.0 (s), 700.6 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 349.1314, Obs. 349.1319.



Methyl 3-(4-methoxyphenyl)-2-(2-phenyl-1*H*-indole-1-carbonyl)acrylate (6-50): Methyl 3-oxo-3-(2-phenyl-1*H*-indol-1-yl)propanoate (1.28 g, 4.36 mmol), 4-methoxybenzaldehyde (0.70 mL, 5.75 mmol), glacial acetic acid (0.131 g, 2.18 mmol), piperidine (50 µL , 0.506 mmol) and benzene (120 mL) were mixed according to general method A to afford **6-50** as a dark brown solid (0.457 g, 25%) after 18 hours. (R_f = 0.37, 20% EtOAc/Hex) [m.p. 105-107 °C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.63 (d, *J* = 8.17 Hz, 1H), 7.40 - 7.51 (m, 2H), 7.29 - 7.38 (m, 2H), 7.19 - 7.27 (m, 2H), 7.16 (s, 1H), 7.00 - 7.13 (m, 4H), 6.54 - 6.61 (m, 2H), 6.34 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8, 164.4, 161.5, 143.1, 139.8, 138.2, 133.4, 131.6, 129.6, 128.6, 127.8, 125.4, 125.2, 125.0, 124.3, 120.2, 116.6, 114.0, 111.9, 55.3, 52.3. IR: 3065.3 (w), 2951.7 (w), 2939.1 (w), 1720.6 (s), 1682.4 (s), 1600.9 (s), 1511.8 (s), 1452.5 (s), 1385.8 (m), 1321.3 (m), 1290.4 (m), 1258.9 (s), 1203.7 (m), 1172.3 (s), 1123.0 (m), 1056.1 (w), 1027.6 (m), 917.2 (w), 831.4 (m), 763.9 (s), 751.0 (s), 700.6 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 411.1471, Obs. 411.1480.



Methyl 2-(2,3-dimethyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (6-52): Methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (0.501 g, 2.04 mmol), 4-methoxybenzaldehyde (0.300 mL, 2.47 mmol), glacial acetic acid (0.094 g, 1.57 mmol), piperidine (0.043 g, 0.506 mmol) and benzene (30 mL) were mixed according to general method A to form **6-52** as a yellow solid (0.661 g, 89%) after 18 hours. (R_f = 0.25, 20% EtOAc/Hex) [m.p. 94-96°C] ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.63 (br. s, 1H), 7.87 (br. s., 1H), 7.33 - 7.48 (m, 3H), 7.28 (br. s., 2H), 6.73 (d, *J* = 8.50 Hz, 2H), 3.77 (s, 3H), 3.67 (d, *J* = 1.21 Hz, 3H), 2.25 - 2.53 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.9, 165.2, 161.9, 142.5, 136.1, 131.8, 131.5, 126.6, 125.3, 124.3, 123.6, 117.9, 116.5, 114.6, 55.2, 52.4, 13.4, 8.6. IR: 3008.4 (w), 2933.3 (w), 2839.7 (w), 1721.5 (s), 1675.4 (s), 1601.6 (s), 1513.5 (s), 1458.5 (s), 1396.3 (m), 1306.8 (s), 1258.4 (s), 1203.4 (m), 1174.8 (s), 1133.5 (w), 1028.0 (w), 907.9 (w), 832.0 (w), 750.0 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 363.1471, Obs. 363.1470.



Methyl 2-(5-fluoro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (6-56): Methyl 3-(5-fluoro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.301 g, 1.21 mmol), 4-methoxybenzaldehyde (0.180 mL, 1.48 mmol), glacial acetic acid (0.0520 g, 0.873 mmol), piperidine (25 µL , 0.253 mmol) and benzene (30 mL) were mixed according to general method A to afford **6-56** as a red solid (0.382 g, 86%) after 18 hours. (R_f = 0.43, 30% EtOAc/Hex) [m.p. 95-97 °C] (*Temperature for the ^{1}H NMR and ^{13}C NMR = 60 °C)* ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.25 (br s, 1H), 7.85 (s, 1H), 7.28 - 7.39 (m, 2H), 7.05

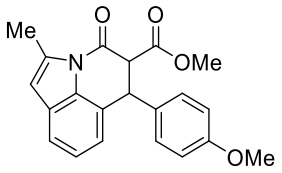
(dd, *J* = 2.57, 8.61 Hz, 1H), 6.95 (dt, *J* = 2.58, 9.12 Hz, 1H), 6.70 - 6.79 (m, 2H), 6.27 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.0, 165.0, 162.1, 161.5, 158.3, 143.0, 133.3, 131.8, 131.1 and 131.0 (doublet), 125.8, 124.9, 116.9, 114.6, 111.5, 111.2, 110.3, 105.5, 105.2, 55.2, 52.5, 16.5. IR: 2948.8 (w), 2903.6 (w), 1720.7 (m), 1685.4 (m), 1602.5 (s), 1513.7 (s), 1472.7 (m), 1448.5 (m), 1389.2 (m), 1301.5 (m), 1274.6 (s), 1260.5 (s), 1176.5 (s), 995.0 (w), 957.3 (w), 832.8 (w), 764.3 (s), 750.0 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 367.1220, Obs. 367.1226.

6.7.3.2 General Method B[322]

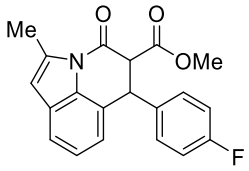
A round bottom flask was charged with the β-amide ester (1.0 equiv.) and THF (25 mL). After the solution was cooled to 0 °C, titanium(IV) chloride tetrahydrofuran complex (2.0 equiv.) and CCl_4 (2.0 equiv.) were added to the reaction vessel. After 1 hour at 0 °C, the aldehyde (1.0 equiv.) was added slowly, and the reaction was stirred for an hour. Then, pyridine (4.0 equiv.) was added to the solution dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 14 hours. The reaction was quenched with water and the organic layer was collected. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine. The organic layer was dried with Mg_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

6.7.4 In(OTf)$_3$-Catalyzed Annulations for Pyrrolo[3,2,1-*ij*]quinoline Assembly

To a mixture of $In(OTf)_3$ (0.10-0.15 equiv.) in 1,2-dichloroethane (or toluene) heated to a reflux, dissolved alkylidene malonate monoamides (1.0 equiv) were syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with DCM. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered. After concentration of the crude mixture, silica gel column chromatography was used for purification.

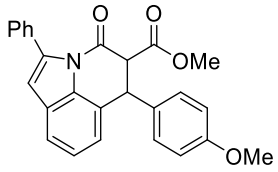


Methyl 6-(4-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (6-31): Methyl 3-(4-methoxyphenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.258 g, 0.739 mmol), $In(OTf)_3$ (0.0428 g, 0.0760 mmol) and 1,2-dichloroethane (13 mL) were combined according to the general procedure to render **6-31** as a brown solid (0.161 g, 63%) after 3 hours. (R_f = 0.35, 20% EtOAc/Hex) [m.p. 122-124 °C] *Diastereomeric ratio*: (50:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31 - 7.37 (m, 1H), 7.14 - 7.20 (m, 2H), 7.08 - 7.13 (m, 1H), 6.84 - 6.92 (m, 2H), 6.71 (d, *J* = 7.48 Hz, 1H), 6.41 (d, *J* = 1.25 Hz, 1H), 4.96 (d, *J* = 10.85 Hz, 1H), 4.19 (d, *J* = 10.88 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.71 (d, *J* = 1.03 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.0, 164.0, 159.0, 137.2, 134.9, 130.9, 129.6, 127.4, 124.0, 122.7, 121.0, 118.4, 114.3, 109.4, 58.8, 55.2, 52.6, 45.3, 15.2. IR: 2954.7 (w), 2922.5 (w), 2850.5 (w), 1749.6 (s), 1709.3 (s), 1611.6 (w), 1513.5 (s), 1443.5 (s), 1381.8 (s), 1340.9 (s), 1252.6 (s), 1178.9 (w), 1153.2 (m), 1032.8 (m), 818.6 (m), 764.7 (m), 749.1 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 349.1314, Obs. 349.1310.

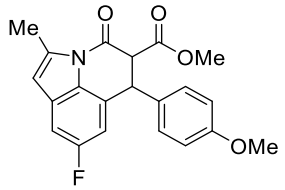


Methyl 6-(4-fluorophenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (6-41): Methyl 3-(4-fluorophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.0760 g, 0.225 mmol), $In(OTf)_3$ (0.0188 g, 0.0330 mmol) and 1,2-dichloroethane (8 mL) were combined according to the general procedure to afford **6-41** as a yellow solid (0.0716 g, 94% for combined *cis* and *trans* isomers) after 1 hour. (R_f = 0.68, 30% EtOAc/Hex) [m.p. 153-155 °C] *Diastereomeric ratio*: (2.6:1) (*trans*-

Diastereomer chemical shifts reported) ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.36 (d, *J* = 7.77 Hz, 1H), 7.19 - 7.25 (m, 2H), 7.13 (t, *J* = 7.62 Hz, 1H), 7.00 - 7.09 (m, 2H), 6.68 (d, *J* = 7.44 Hz, 1H), 6.42 (d, *J* = 1.17 Hz, 1H), 5.01 (d, *J* = 10.85 Hz, 1H), 4.18 (d, *J* = 10.85 Hz, 1H), 3.68 (s, 3H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.8, 163.7, 137.3, 134.8, 130.2 and 130.1 (doublet), 127.5, 124.2, 122.1, 120.9, 118.7, 116.1, 115.8, 109.5, 77.2, 58.7, 52.7, 45.4, 15.2. IR: 3058.4 (w), 2954.5 (w), 2923.0 (w), 1746.8 (s), 1708.7 (s), 1605.3 (w), 1509.8 (s), 1443.8 (s), 1380.9 (s), 1340.0 (s), 1267.9 (m), 1224.3 (s), 1159.1 (s), 1097.6 (w), 1051.5 (w), 1010.0 (w), 967.1 (w), 818.5 (m), 748.7 (s) cm^{-1}. HRMS (ESI) M/Z+ Calc. 337.1114, Obs. 337.1115.



Methyl 6-(4-methoxyphenyl)-4-oxo-2-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (6-51): Methyl 3-(4-methoxyphenyl)-2-(2-phenyl-1*H*-indole-1-carbonyl)acrylate (0.160 g, 0.390 mmol), $In(OTf)_3$ (0.0223 g, 0.0400 mmol) and 1,2-dichloroethane (13 mL) were combined according to the general procedure to afford **6-51** as a reddish orange solid (0.155 g, 97%) after 3 hours. (R_f = 0.33, 20% EtOAc/Hex) [m.p. 108-110 °C] *Diastereomeric ratio*: (17.3:1). (*trans*-Diastereomer chemical shifts reported) ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.16 - 8.22 (m, 1H), 7.71 - 7.76 (m, 1H), 7.16 - 7.45 (m, 7H), 7.02 - 7.09 (m, 2H), 6.71 - 6.77 (m, 2H), 5.19 (d, *J* = 4.40 Hz, 1H), 4.05 (d, *J* = 4.43 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.0, 164.9, 158.9, 139.4, 134.4, 132.0, 131.7, 130.5, 128.4, 128.4, 128.4, 127.0, 124.9, 124.5, 120.2, 116.7, 114.3, 114.1, 63.0, 55.2, 53.3, 42.7. IR: 3056.9 (w), 2953.2 (w), 2837.9 (w), 1730.5 (s), 1610.2 (s), 1511.9 (s), 1454.6 (s), 1392.4 (s), 1345.1 (m), 1305.2 (m), 1246.7 (s), 1145.4 (s), 1103.0 (w), 1029.6 (s), 830.8 (m), 748.6 (s), 699.8 (s), 628.6 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 411.1471, Obs. 411.1470.



Methyl 8-fluoro-6-(4-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (6-57): Methyl 2-(5-fluoro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0750 g, 0.204 mmol), $In(OTf)_3$ (0.0180 g, 0.0320 mmol) and 1,2-dichloroethane (7 mL) were combined according to the general procedure to afford **6-57** as a yellow solid (0.660 g, 88%) after 12 hours. (R_f = 0.40, 20% EtOAc/Hex) [m.p. 106-108 °C] *(Single Diastereomer Observed)* ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.13 - 7.18 (m, 2H), 7.01 (ddd, *J* = 0.63, 2.21, 8.96 Hz, 1H), 6.86 - 6.91 (m, 2H), 6.43 - 6.48 (m, 1H), 6.37 - 6.39 (m, 1H), 4.92 (d, *J* = 10.79 Hz, 1H), 4.17 (d, *J* = 10.85 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.70 (d, *J* = 1.19 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.8, 163.7, 161.7, 159.3, 159.2, 138.7, 131.1, 130.3, 129.5, 128.1 and 128.0 (doublet), 124.0 and 123.9 (doublet), 114.4, 109.2, 109.2, 109.1, 108.9, 104.7, 104.4, 58.5, 55.2, 52.7, 45.3, 15.2. IR: 3001.9 (w), 2954.8 (w), 2838.9 (w), 1747.3 (s), 1709.5 (s), 1632.7 (m), 1610.7 (m), 1513.3 (s), 1479.6 (s), 1435.4 (s), 1381.4 (s), 1327.8 (m), 1254.6 (s), 1210.5 (s), 1156.7 (s), 1112.8 (s), 1031.8 (s), 961.2 (m), 852.7 (s), 832.2 (s), 741.1 (s), 714.0 (m), 619.6 (m) cm^{-1}. HRMS (ESI) M/Z+ Calc. 367.1220, Obs. 367.1227.

6.7.5 Control Reactions for Pyrroloquinolines

6.7.5.1 Trifluoromethanesulfonic Acid Reaction

To a mixture of trifluoromethanesulfonic acid (TfOH) (0.0010 g, 0.0068 mmol) in 1,2-dichloroethane heated to a reflux, dissolved methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(4-nitrophenyl)acrylate (0.250 g, 0.6866 mmol) was syringed into the reaction vessel. The reaction mixture was stirred at reflux for 16 hours. The reaction afforded only starting material as observed by crude ^{1}H NMR.

6.7.5.2 1,8-Diazabicyclo[5.4.0]undec-7-ene Epimerization Reaction

The diastereomeric mixture of Methyl 2-methyl-6-(4-nitrophenyl)-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (0.06 g, 0.16478 mmol), DBU (0.0075 g, 0.0494 mmol) and 1,2-dichloroethane (3 mL) were combined and stirred at room temperature for 14 hours. The reaction afforded the *trans* isomer as a single observable diastereomer (>99:1 *dr*) from ^{1}H NMR of the crude reaction mixture.

APPENDIX

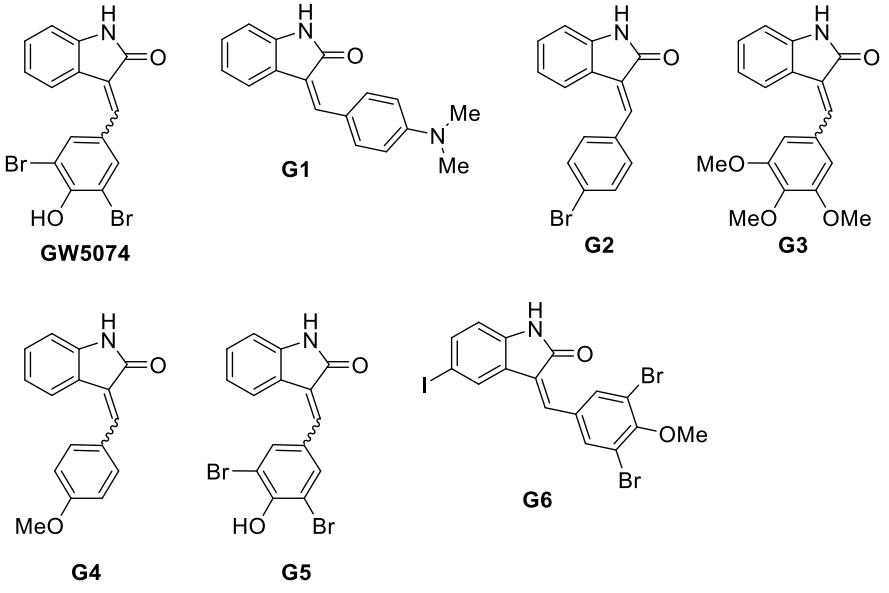
Glaucoma is a serious disease that can wreak havoc on one's quality of life and affects over three million Americans and 60.5 million individuals worldwide according to a 2010 study.[378] Being an impairing ailment, glaucoma threatens the sense held most sacred...sight. Given the urgency for a cure, many studies have been conducted to understand the pathogenesis for open-angle and angle-closure glaucoma.[379–387] Research has shown that mutations in the olfactomedin domain of myocilin are plausible causes for inherited open angle glaucoma.[380,388,389] Mutations in the domain causes protein misfolding, promoting aggregation of myocilin protein in the trebecular meshwork, which is responsible for draining aqueous humor in the space between the lens and the cornea of the eye.[380,390] The aggregation of mutant myocilin may predispose the host to increased intraocular pressure,[391] which is a marker for glaucoma.[392] Despite strides made in combating this disorder, myocilin remains a domain of unknown structure and function. Lieberman et al. sought to evaluate chemical probes to gain insight into the functional niche of myocilin and potentially identify targeted molecules to inhibit mutant myocilin aggregation. To this end, compounds were ordered and synthesized for screening.

A.1. Chemical Probes for Myocilin Studies

Fourteen compounds were identified in our myocilin olfactomedin domain (myoc-OLF) pilot screen by chemical assay for restabilization (CARS), which resulted in a 50% or better decrease in spyro orange (SO) fluorescence. This study proceeded with eleven hit compounds, dismissing several compounds due to an increase in SO florescence because of interference with SO or destabilizing effects. The ligands were then evaluated for inhibition of myoc-OLF fibrillization, which is responsible for aggregation. A fluorescence plate reader-based assay combined with atomic force microscopy was developed to evaluate the extent of fibrillization upon the addition of a compound. GW5074 bound to myoc-OLF stoichiometrically with micromolar affinity and was

determined to cause a decrease in myoc-OLF fibrillization in a dose dependent manner. Based on the results from surface plasmon resonance (SPR) and the fibrillization assay, several derivatives of GW5074 were synthesized. Of the derivatives, G5 was a potent inhibitor of amyloidogenesis *in vitro*.

Next, the ligands were evaluated with the use of a mutant myocilin cellular secretion assay which tested the ability of the ligand to rescue mutant myocilin secretion (1477 mutant myocilin represents one of the least stable glaucoma causing OLF variants) and prevent glaucoma associated HTM cell death. The results indicated that GW5074 was not suitable because it precipitated when it was added to the aqueous cell media. Second generation G2 and G5 both exhibited adequate solubility and a good cellular toxicity profile. A dose dependent increase in 1477N mutant myocilin was found with G5 though G2 did not enhance secretion. From this study, it was concluded that G5 has great promise for development into target molecules to reduce mutant myocilin aggregation.



A.2. Research Participants

All biological studies were conducted by Dr. Susan Orwig, Pamela Chi, Yuhong Du, Dr. Shannon E. Hill, Amrithaa Suntharalingam, Katherine Turnage, Chad Dickey, Haian Fu,

and Professor Raquel Lieberman. Compounds not commercially available were synthesized by Marchello Cavitt. This research was published in *ACS Chemical Biology*: Orwig, S. D.; Chi, P. V.; Du, Y.; Hill, S. E.; Cavitt, M. A.; Suntharalingam, A.; Turnage, K. C.; Dickey, C. A.; France, S.; Fu, H.; Lieberman, R. L. Ligands for Glaucoma-Associated Myocilin Discovered by a Generic Binding Assay. *ACS Chem. Biol.* **2014**, *9*, 517–525.

A.3. Synthetic Methods

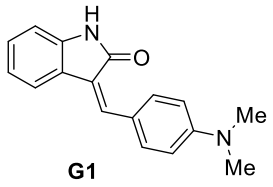
Compounds were either purchased (GW5074, Sigma Aldrich), TCI chemicals, or synthesized as follows. All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel under vacuum. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Absolute ethanol was used. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification.

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Melting points were determined by an Electrothermal Mel-Temp. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained with a Shimadzu IR Prestige 21 FTIR instrument. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were

recorded on a Varian Mercury Vx 300 MHz spectrometer, a Varian Mercury Vx 400 MHz spectrometer, Bruker 400 MHz spectrometer, or Bruker 500 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.50 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160). *Compounds synthesized and not reported in the literature until our publication are listed below. Some data may be missing because the compound(s) matched the data in the literature. Only new data that was not reported in the literature is shown below.*

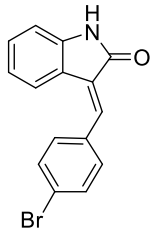
General Procedure: 2-Indolinone (1.0 equiv.), aldehyde (1.0-1.2 equiv.), piperidine (0.2-2 equiv.), and absolute ethanol (10 mL) were charged to a flask equipped with a condenser and stir bar. The mixture was heated to a reflux for 16 hours. The resulting solid was filtered, washed repeatedly with low boiling petroleum ether, collected, and dried *in vacuo* overnight. Each sample was characterized, examined for purity by NMR, and compared to the data in the literature.



G1

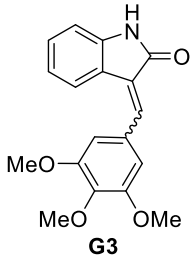
(Z)-3-[4-(Dimethylamino)benzylidene]indolin-2-one (**G1**)**:** The general procedure that was followed used indolin-2-one (415 mg, 3.12 mmol), 4-(dimethylamino)benzaldehyde (541 mg, 3.63 mmol), piperidine (517 mg, 6.07 mmol), and ethanol (15 mL). The reaction proceeded for 16 hours. ^{13}C NMR (75MHz, DMSO-d_6) δ ppm = 167.6, 151.7, 139.5, 138.0,

134.7, 127.0, 126.1, 122.1, 120.6, 120.3, 118.4, 111.0, 108.9. The characterization of the compound was in accordance with reported data.[393,394]



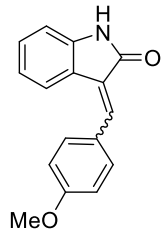
G2

(*E*)-3-(4-Bromobenzylidene)indolin-2-one (G2): The general procedure that was followed used indolin-2-one (415 mg, 3.11 mmol), 4-bromobenzaldehyde (668 mg, 3.61 mmol), piperidine (517 mg, 6.07 mmol), and ethanol (15 mL). The reaction proceeded for 12 hours. The characterization of the compound was in accordance with the reported data. The ^{1}H NMR matched the literature values for the *E* isomer. No *Z* isomer was initially detected. However, over the collection time of the carbon-13 spectrum, isomerization occurred. ^{13}C NMR (101MHz, DMSO-d_6) δ ppm = 168.4, 167.0, 143.1, 140.9, 135.2, 134.3, 133.7, 133.1, 131.8, 131.7, 131.3, 131.3, 130.3, 129.3, 128.2, 127.5, 124.7, 123.8, 122.8, 122.5, 121.2, 120.6, 119.9, 119.9, 110.2, 109.4, 105.5. The other characterization was in accordance with the reported data.[395]



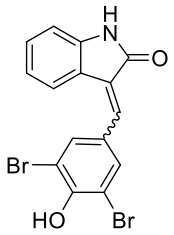
G3

(*E*)-3-(3,4,5,-trimethoxybenzylidene)indolin-2-one (G3): The general procedure was followed with the use of indolin-2-one (301 mg, 2.26 mmol), 3,4,5-trimethoxybenzaldehyde (488 mg, 2.49 mmol), piperidine (431 mg, 5.06 mmol), and ethanol (15 mL). The reaction proceeded for 12 hours. The characterization of the compound was in accordance with the reported data.[396,397]



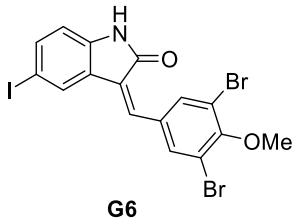
G4

3-(4-Methoxybenzylidene)indolin-2-one (G4): [(E:Z ratio) = 6.3:1] The general procedure was followed with the use of indolin-2-one (499 mg, 3.75 mmol), 4-methoxybenzaldehyde (615 mg, 4.52 mmol), piperidine (34 mg, 0.405 mmol), and ethanol (10 mL). The reaction proceeded for 6.5 hours. ^{13}C NMR (75MHz, $CDCl_3$) δ ppm = 170.8, 168.4, 161.7, 161.0, 141.7, 139.5, 137.6, 137.5, 134.4, 131.5, 129.4, 128.2, 127.4, 127.1, 126.0, 124.0, 122.7, 122.1, 121.6, 121.6, 118.8, 114.2, 113.8, 110.2, 109.5, 55.4. The other characterization was in accordance with the reported data.[398,399]



G5

3-(3,5-Dibromo-4-hydroxy-benzylidene)-1,3-dihydro-indol-2-one (G5): Indolin-2-one (302 mg, 2.27 mmol), 3,5-dibromo-4-hydroxybenzaldehyde (636 mg, 2.27 mmol), p-toluenesulfonic acid monohydrate (51 mg, 0.269 mmol), and ethanol (15 mL) were heated to a reflux. The reaction proceeded for 16 hours. [(E:Z ratio) = 1:1.1] ^{1}H NMR (300MHz, DMSO-d_6) δ ppm = 10.66-10.60 (broad singlets, 3.54), 8.79 (s, 2.19), 7.90 (s, 2.00), 7.69 (s, 1.10), 7.63 (d, *J* = 7.5 Hz, 1.16), 7.51 - 7.45 (m, 2.16), 7.27 - 7.16 (m, 2.26), 6.98 (t, *J* = 7.6 Hz, 1.15), 6.92 - 6.79 (m, 3.21), 3.63 (br s, 1.63). ^{13}C NMR (75MHz, DMSO-d_6) δ ppm = 168.5, 167.3, 152.5, 151.9, 143.1, 140.7, 136.1, 133.9, 133.2, 133.1, 130.3, 128.9, 128.7, 128.2, 127.6, 126.1, 125.6, 124.9, 122.0, 121.2, 120.7, 119.6, 111.8, 111.1, 110.3, 109.5.



G6

(*Z*)-3-(3,5-dibromo-4-methoxybenzylidene)-5-iodoindolin-2-one (G6): Piperidine (0.091 mmol, 7.7 mg), 3,5-dibromo-4-methoxybenzaldehyde: (0.49 mmol, 0.145 mg), 5-iodoindolin-2-one (0.45 mmol, 0.118 mg), and ethanol (10 mL) were charged to a flask with a condenser. The mixture was heated to a reflux for 16 hours. The orange solid was collected and washed repeatedly with petroleum ether and afforded 0.1509 g (62%) of the desired product. (R_f = 0.73, 1% MeOH/DCM) [(E:Z ratio) = 1:2.8] [m.p. 273-275 °C] (Z isomer NMR data) ^{1}H NMR (500MHz, DMSO-d_6) δ ppm = 10.83 (s, 1 H), 8.78 (s, 2 H), 8.04 (d, *J* = 1.7 Hz, 1 H), 7.85 (s, 1 H), 7.55 (dd, *J* = 1.7, 8.1 Hz, 1 H), 6.68 (d, *J* = 8.1 Hz, 1 H), 3.86 (s, 3 H). ^{13}C NMR (126MHz, DMSO-d_6) δ ppm = 166.5, 154.8, 140.5, 137.5, 136.2, 134.5, 132.9, 128.4, 127.1, 126.8, 117.1, 112.0, 84.2, 60.7. IR: 3149.8 (m), 3080.3 (w), 3024.4 (w), 2866.2 (w), 1701.2 (s), 1604.8 (s), 1525.7 (m), 1475.5 (m), 1465.9 (m), 1361.7 (m), 1273.0 (s), 1201.7 (s), 985.6 (s), 804.3 (s) cm^{-1}. HRMS (ESI) Calc. 532.8123 Obs. 532.8118.

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