The Development of Synthetic Methods Using Isoindole Chemistry

by

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Abstract

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Thesis directed by Associate Professor Xiang Wang

Isoindoles are very reactive 10π aromatic heterocycles that commonly act as nucleophiles. Isoindole derivatives, which can be accessed via isoindoles, are ubiquitous in natural products and synthetic bioactive molecules. This dissertation presents a review of recent literature involving isoindole chemistry and describes the development of synthetic methods that utilize isoindole chemistry. First, a review of the literature from the past decade (2012-present) pertaining to the synthesis and reactions of isoindoles is given. Second, a novel one-pot synthesis of polycyclic isoindolines is described which employs an innovative isoindole umpolung strategy that allows isoindoles, which typically act as nucleophiles, to be used instead as electrophiles in a Pictet-Spengler-type cyclization. This method extends the scope of the Pictet-Spengler reaction to include isoindoles and affords the polycyclic isoindoline products in good yields. Third, efforts toward the development of two cyclization cascade reactions that involve isoindole chemistry are described, which provide access to analogs of batracylin, a versatile anticancer drug, and tryptanthrin, an antimicrobial and antiviral agent.

Dedication

I dedicate this thesis to all who supported me along the way.

Acknowledgements

Throughout my graduate career, I have been very fortunate to have been surrounded by an incredibly supportive group of people. First, I want to thank my advisor, Professor Xiang Wang, for the wealth of guidance, support, and opportunities that he has provided. He allowed me to do exciting and challenging chemistry, and I am grateful for the knowledge and experience I gained from working for him. I am also very thankful to Professor Tarek Sammakia. He also provided me with a lot of guidance and support throughout my graduate career, and I learned a lot from him.

Next, I want to thank my undergraduate advisor, Professor Katherine Thomas (née Hervert), whose mentorship shaped me as a scientist and gave me the confidence to learn to do things for myself and take great pride in it. It is because of her that I took it upon myself to learn to build computers, wax skis, fix electronic devices, and become proficient at what is now my favorite hobby, wildlife photography. I would also like to thank her and the rest of the Ohio Wesleyan University Chemistry Department of 2005-2009, including Professors Heather Grunkemeyer, Dan Vogt, Dale Brugh, David Lever, and the late Professor Kim Lance, for instilling a love of chemistry within me, teaching me to think on my feet, and preparing me well for graduate school. They were exceptional professors, and their unique combination of warmth and humor, with a healthy dose of cynicism, made my time at OWU a pleasure. I remain incredibly fond of my college days.

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Finally, I want to thank my family and the rest of my friends. I am exceptionally grateful to my parents, Jeff and Cassie, and my brother, Alex, for their unwavering support. They have always believed in me and have been incredibly supportive of me throughout all my endeavors. Without them, this would not have been possible. I would also like to thank my friends Tim

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Abbreviations and Acronyms

3ÅMS	3 Å molecular sieves
[H]	reduction
[O]	oxidation
ABCN	1,1′-Azobis(cyclohexanecarbonitrile)
ACN	acetonitrile
Ac	acetyl
AcOH	acetic acid
AgOAc	silver (I) acetate
AIBN	Azobisisobutyronitrile
app	apparent
A. niger	*Aspergillus niger*
A. fumigates	*Aspergillus fumigates*
aq.	aqueous
Ar	aryl
Bn	benzyl
BODIPY	boron dipyrromethene
BPO	benzoyl peroxide
br	broadened
B. subtilis	*Bacillus subtilis*
Bu	*n*-butyl
BuLi	*n*-butyllithium
C. albicans	*Candida albicans*

CoV	Coronavirus
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenyl phosphate
dppe	1,2-bis(diphenylphosphino)ethane
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
E^+	electrophile (generic)
e^-	electron
E. coli	*Escherichia coli*
EDG	electron-donating group
Equiv.	equivalents
Et	ethyl
Et_3N	triethylamine

Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
FT-IR	Fourier transform infrared spectroscopy
Hex	hexanes
Hν	light
HPLC	high-performance liquid chromatography
H. pylori	*Helicobacter pylori*
HR-MS	high-resolution mass spectrometry
i-Pr	isopropyl
i-PrOH	isopropanol
K. pneumoniae	*Klebsiella pneumoniae*
LC-MS	liquid chromatography-mass spectrometry
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
M	Metal (generic)
m	multiplet
MeCN	acetonitrile
MeOH	methanol
MeOTs	methyl trifluoromethanesulfonate
MRSA	methicillin-resistant *Staphylococcus aureus*

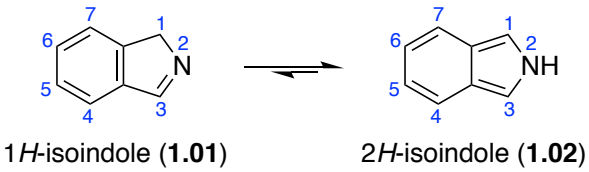
MsOH	methane sulfonic acid
NaOAc	sodium acetate
n-Bu	*n*-butyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
ND	not determined
NMP	*N*-Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	*ortho*
OAc	acetate
oct	octanoate
OPA	*ortho*-phthalaldehyde
Oxone	potassium peroxymonosulfate
p	pentet
p	*para*
Ph	phenyl
P. putida	*Pseudomonas putida*
PTSA	*para*-toluenesulfonic acid
Py	pyrrole
q	quartet
r.t.	room temperature
s	singlet

SARS	severe acute respiratory syndrome
S. aureus	*Staphylococcus aureus*
Sat.	saturated
S_EAr	electrophilic aromatic substitution
S. epidermis	*Staphylococcus epidermis*
S. pyogenes	*Streptococcus pyogenes*
S. typhi	*Salmonella typhi*
t	time
t	triplet (for NMR spectra only)
t-Bu	*tert*-butyl
t-BuOK	potassium *tert*-butoxide
TCA	trichloroacetic acid
TEA	triethylamine
Temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TsOH	*para*-toluenesulfonic acid
T. viridae	*Trichoderma viridae*
V. cholerae	*Vibrio cholerae*

Chapter 1: A Review of Recent Literature on the Chemistry of Isoindoles

1.1 Introduction

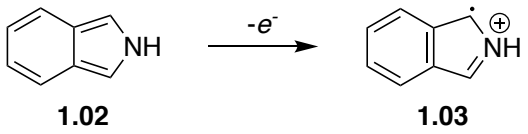
Isoindoles (**1.02**, Scheme 1.1) are aromatic heterocycles[1] consisting of a benzo-fused pyrrole ring system[2] with 10π electrons[1,3].



1*H*-isoindole (**1.01**) 2*H*-isoindole (**1.02**)

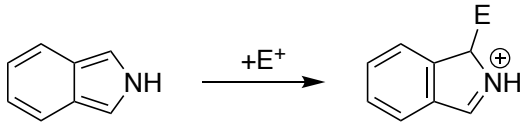
Scheme 1.1. Isoindole tautomeric equilibrium.

Due to the π-excessive nature of the pyrroloid ring and the fact that an aromatic benzenoid ring is formed upon reactions such as one-electron oxidations and 1,3-additions[3] (Scheme 1.2), isoindoles are highly reactive[1,3,4] and thus, difficult to isolate[5].



1.02 **1.03**

one-electron oxidation



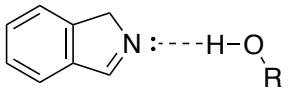
1.02 **1.04**

addition of electrophile to C-1

Scheme 1.2. Examples of reactions that form a complete benzenoid ring.

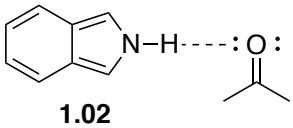
This propensity to restore aromaticity to six-membered ring is also responsible for the tautomeric equilibrium that exists between 2*H*- and 1*H*-isoindoles (Scheme 1.1, *supra*).[4] The 2*H*-isoindole tautomer often predominates, as it is typically more stable due to its higher resonance energy.[2,6] However, the solvent and the substituents can sometimes shift the equilibrium to favor the 1*H*-isoindole tautomer.[3,4] Solvents that serve as hydrogen bond donors tend to stabilize the 1*H*-isoindole form (Figure 1.1A), whereas those that serve as hydrogen bond acceptors tend to stabilize the 2*H*-isoindole form (Figure 1.1B).

(A) Stabilization of 1*H*-Isoindole by Hydrogen Bond Donor



1.01

(B) Stabilization of 2*H*-Isoindole by Hydrogen Bond Acceptor



1.02

Figure 1.1. Effects of solvents on isoindole tautomeric equilibrium.

The presence of an electron-donating group at the C-1 (C-3) position stabilizes the 1*H*-isoindole form, with only this form being detected in the case of strong electron-donating groups (Figure 1.2A), such as alkoxy (**1.05a,b**) and disubstituted amino groups (**1.06a,b**).[3] For monosubstituted and unsubstituted amino groups (**1.07a,b**), the amidine form (**1.07c**) is also possible. Conversely, the presence of an electron-withdrawing group at the C-1 (C-3) position stabilizes the 2*H*-isoindole form (Figure 1.2B). Substitution on the six-membered ring is more complex and is further confounded by the type of solvent used.

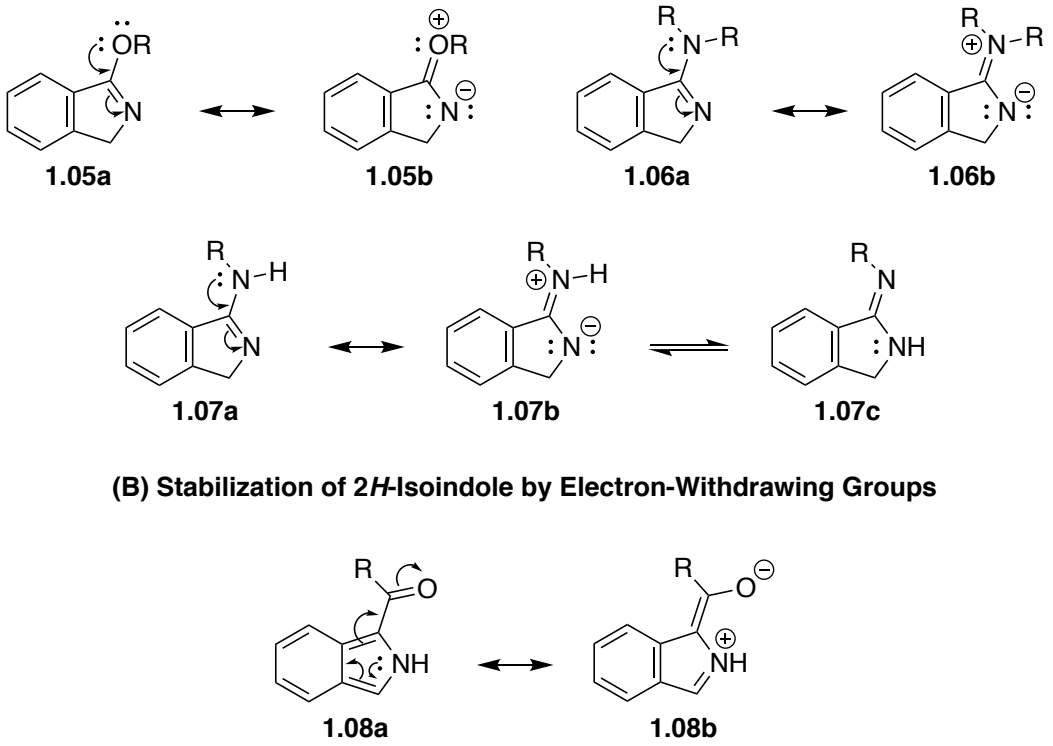


Figure 1.2. Effects of substituents on isoindole tautomeric equilibrium.

Isoindole reactivity can also be explained by electron donation from the lone pair on the isoindole nitrogen via resonance (Figure 1.3). This resonance renders the isoindole nucleophilic at the C-1 (C-3) position[3,7] (**1.02d**), where MO calculations have shown that the ground-state π-electron density is highest[3]. Additional resonance structures can be drawn in which this electron donation places a negative charge on C-5 (C-6) (**1.02b**), where MO calculations have found that the π-electron density is higher than at C-4 (C-7). In addition to the reactions described in this review, numerous cycloaddition[8–16], nucleophilic[12,17–20] and electrophilic[3,15,21] aromatic substitution, Michael[9], intramolecular cyclization[20], redox[6,22–27], and polymerization[15] reactions[1,3] have been reported.

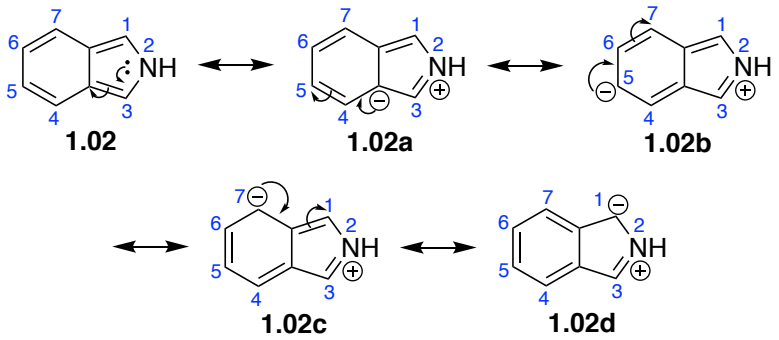


Figure 1.3. Isoindole resonance structures.

Due to their highly reactive nature, isoindoles are important synthetic precursors to isoindole derivatives (Figure 1.4), which include isoindolines (**1.09**), isoindolinones (**1.10**), and phthalimides (**1.11**).

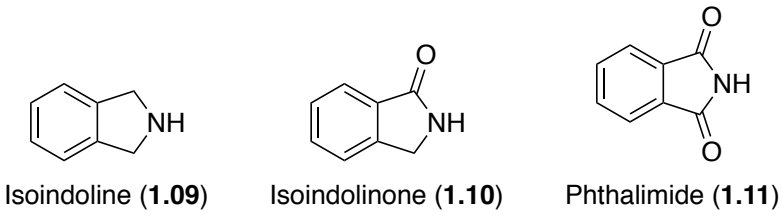


Figure 1.4. Isoindole derivatives.

These derivatives possess a wide range of biological activities and have thus found use in medicine (Figure 1.5).[28] For example, there have been recent reports of isoindolenine-containing compounds with various anticancer activities[29–33], including the clinical candidate[33] navoximod (**1.12**)[31–33], which possess both antineoplastic and immunomodulatory properties. Isoindolinone and phthalimide bioactives are even more prevalent. For example, broad-spectrum antibacterial agents containing the isoindolinone moiety (**1.16a,b**) have recently been discovered.[34] The

phthalimide moiety can be found in potential agents for the treatment of Alzheimer's disease[35,36] (e.g., **1.15**), benign prostatic hyperplasia[37] (BPH) (**1.14**), and inflammation, such as the drug apremilast (**1.13**)[28], which is FDA-approved to treat psoriasis and psoriatic arthritis[38].

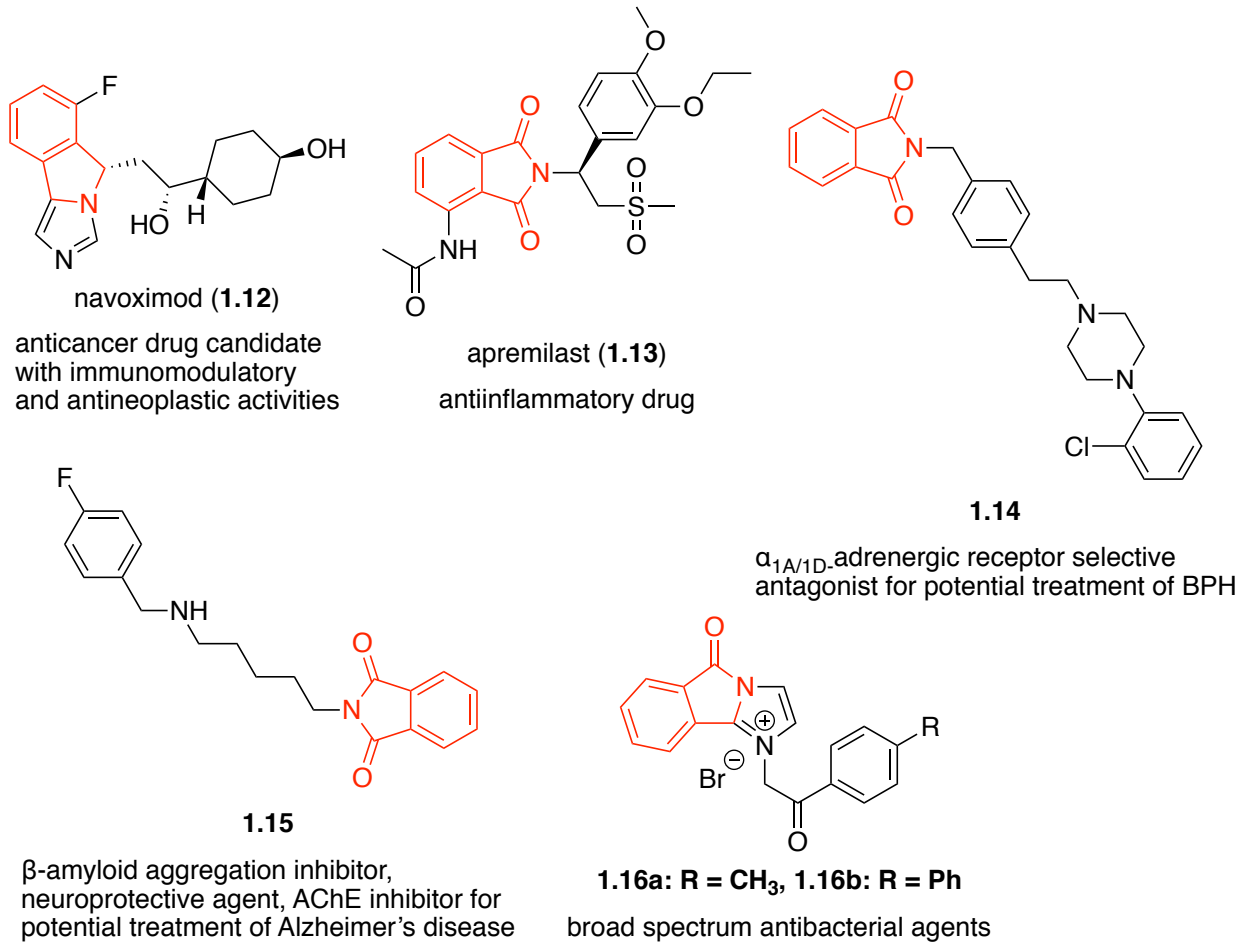
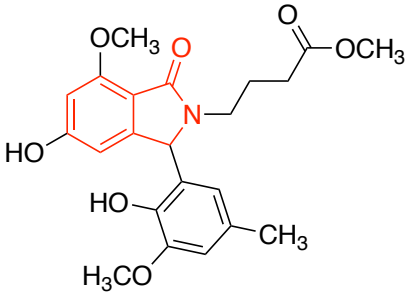


Figure 1.5. Examples of biologically active isoindole derivatives.

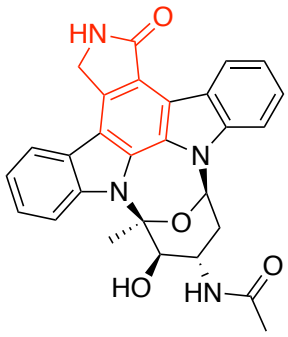
Isoindole derivatives are also prevalent in natural products (Figure 1.6), many of which are also biologically active. Some recent examples include Daldinan A (**1.17**)[39], an antioxidant isolated from the ascomycete *Daldinia concentrica*, the potential anticancer (**1.18**) and anti-fibrotic (**1.19**) agents isolated from marine-derived *Streptomyces* sp. DT-A61[40], and the erinaceolactams (e.g.,

1.20)[41] isolated from the fruiting bodies of the *Hericium erinaceus* mushroom, which may contribute to the antitumor effects of the *H. erinaceus* extract.



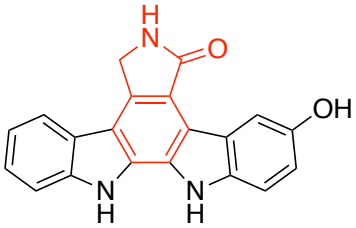
Daldinan A (**1.17**)

antioxidant isolated from the ascomycete *Daldinia concentrica*



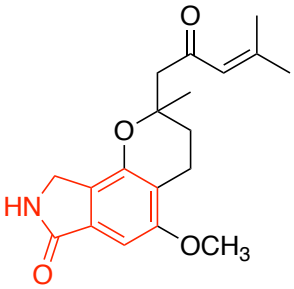
1.18

potential anticancer agent isolated from marine-dervied *Streptomyces* sp. DT-A61



1.19

anti-fibrotic agent isolated from marine-dervied *Streptomyces* sp. DT-A61

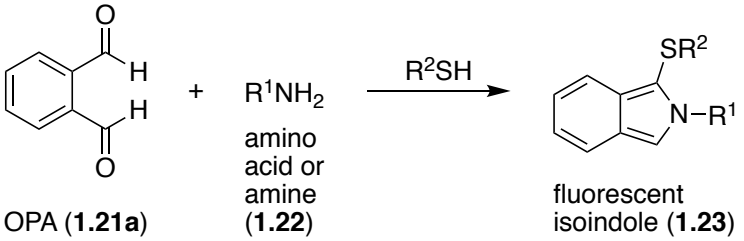


Erinaceolactam C (**1.20**)

possible antitumor agent isolated from the *Hericium erinaceus* mushroom

Figure 1.6. Examples of isoindole natural products.

Isoindoles can also be fluorescent and have found recent and widespread use in analytical methods for the detection of amino acids[42–45] and other amine-containing compounds[46]. In such methods, the amino acids or amines are derivatized as fluorescent isoindoles (**1.23**) via a condensation reaction between their amino groups (**1.22**) and *ortho*-phthalaldehyde (OPA, **1.21**) (Scheme 1.3).



Scheme 1.3. Derivatization of amino acids as fluorescent isoindoles.

Additionally, isoindole-containing structures are used as dyes (Figure 1.7), such as the fluorescent BODIPY dyes (**1.24**-**1.25**)[5,47,48] and the highly pigmented phthalocyanines (**1.26**)[5,49–54]. These dyes have important biomedical applications, including diagnostic techniques, such as photoacoustic imaging[49], and therapeutic applications, such as photodynamic[49] and photothermal[50,51] therapies, which use light energy to destroy cancerous cells. Isoindole-containing dyes have also recently found use in solar cells.[52–54]

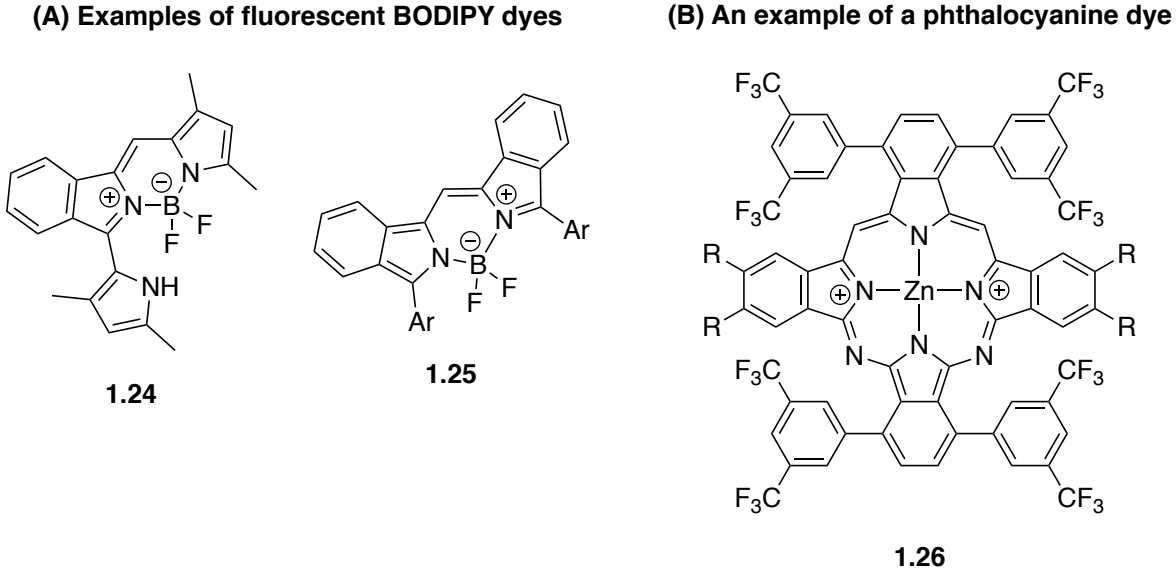


Figure 1.7. Examples of isoindole-containing BODIPY and phthalocyanine dyes.

Due to the reactive nature of isoindoles, as well as the widespread utility and ubiquitous nature of the isoindole scaffold, novel methods for the synthesis and utilization of isoindoles are desired. This review will focus on novel methods for the synthesis of isoindoles, as well as reactions of isoindoles, from the past decade. Only the most relevant and broadly applicable methods and reactions will be included. Accordingly, methods for the synthesis of isoindole-containing BODIPY dyes and phthalocyanines will be excluded. Additionally, where a reference contains multiple related reactions, only those that involve isoindoles will be discussed.

1.2 Synthesis of 2*H*-Isoindoles: Condensation Reactions.

Condensation reactions offer a way to prepare isoindoles from starting materials that are commercially available or that can typically be readily synthesized from inexpensive, commercially available materials. Typically, benzylic dielectrophiles and amine nucleophiles are employed as reacting partners in the intermolecular condensation reactions that are used to prepare isoindoles. The most common dielectrophiles used are *ortho*-bromomethylbenzyl carbonyl species and *ortho*-phthalaldehydes. Conversely, in the intramolecular condensation reactions that are used to prepare isoindoles, the nucleophilic and electrophilic moieties are on the same molecule, so only a single electrophilic center is needed. However, the same types of electrophilic centers used in the intermolecular condensation routes to isoindoles, namely benzylic carbonyl species and benzylic bromomethyl groups, can serve as the electrophilic moiety in an intramolecular condensation approach.

As discussed *supra*, two types of dielectrophiles are commonly used as precursors to isoindoles in intermolecular condensation reactions with amines; however, they cannot be used interchangeably. Approaches that employ 2-(bromomethyl)benzaldehydes or 2-

(bromomethyl)benzyl ketones as precursors are typically used to access either *C*-unsubstituted isoindoles or *C*-alkyl/aryl isoindoles, as neither of the reactants undergoes a redox reaction to get to the isoindole product (Figure 1.8). The carbonyl carbon is reduced by the same amount that the bromomethyl carbon is oxidized and thus, there is no net change in oxidation state for the dielectrophile, and the amine nitrogen maintains the same oxidation state, as well. Conversely, when ortho-phthalaldehydes are converted to *C*-unsubstituted 2*H*-isoindoles, both aldehyde carbons are reduced for a net two-electron reduction for the dielectrophile. Therefore, for *ortho*-phthalaldehydes to be serve as precursors to 2*H*-isoindole derivatives, either a reducing agent must be present or a bond to an atom that is more electronegative than carbon must be formed at either C1 or C3 of the isoindole.

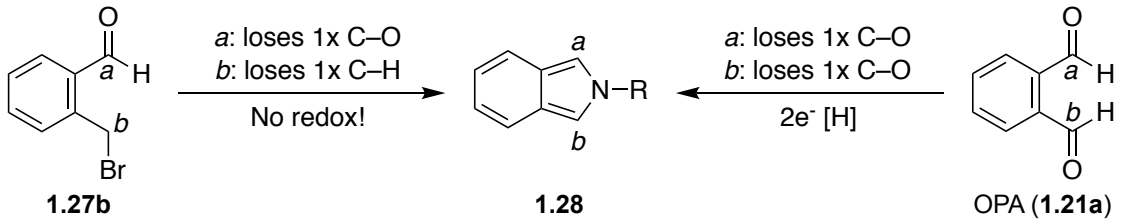
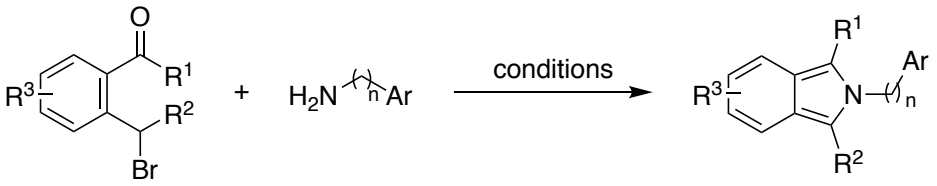


Figure 1.8. Changes in oxidation states for isoindole formation from 2-(bromomethyl)benzaldehyde and *ortho*-phthalaldehyde dielectrophiles.

In 2020, this research group reported a one-pot synthesis of polycyclic isoindolines (Scheme 1.4).[7] This reaction proceeds via an isoindole intermediate (**1.28a**) that is formed *in situ* via a condensation reaction of a 2-(bromomethyl)benzaldehyde (**1.27a**) with a β-arylalkylamine (**1.29a**). This approach to preparing isoindoles was based on previously reported literature[9,55],

such as the method reported by Sypchenko et al.[55] in 2012 for the preparation of *N*-(2-aminophenyl)isoindoles (**1.28b**, Scheme 1.4) via the reaction of *ortho*-(bromomethyl)benzophenones (**1.27c**) with 1,2-phenylenediamines (**1.29b**). However, in this example, triethylamine is used to effect deprotonation of the isoindolium (**1.31**, Scheme 1.5) to form the isoindole (**1.28**), instead an additional equivalent of the amine reacting partner.

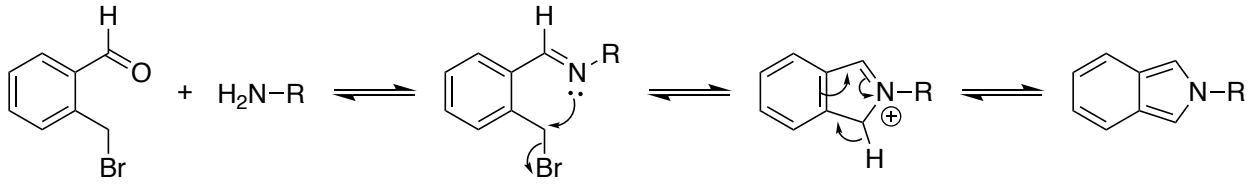


1.27a-c **1.29a-b** **1.28a-b**

Weintraub et al. (ref. 7): R^1 = H; R^2 = H, CH_3; R^3 = H, Cl, F; n = 1,2; Ar = tryptamine derivative, indole derivative, 1-pyrrole; conditions = Et_3N, DCM, 23 °C.

Sypchenko et al. (ref. 55): R^1 = 4-ClC_6H_4; R^2 = H; R^3 = H; n = 0; Ar = 2-aminophenyl, 2-amino-5-nitrophenyl; conditions = EtOH, 50 °C.

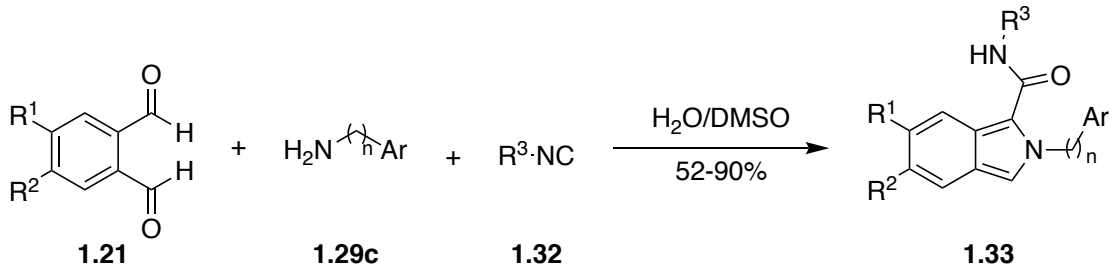
Scheme 1.4. Synthesis of isoindoles via condensation reactions of 2-(bromomethyl)benzylic carbonyl species with amines.



1.27b **1.29** **1.30** **1.31** **1.28**

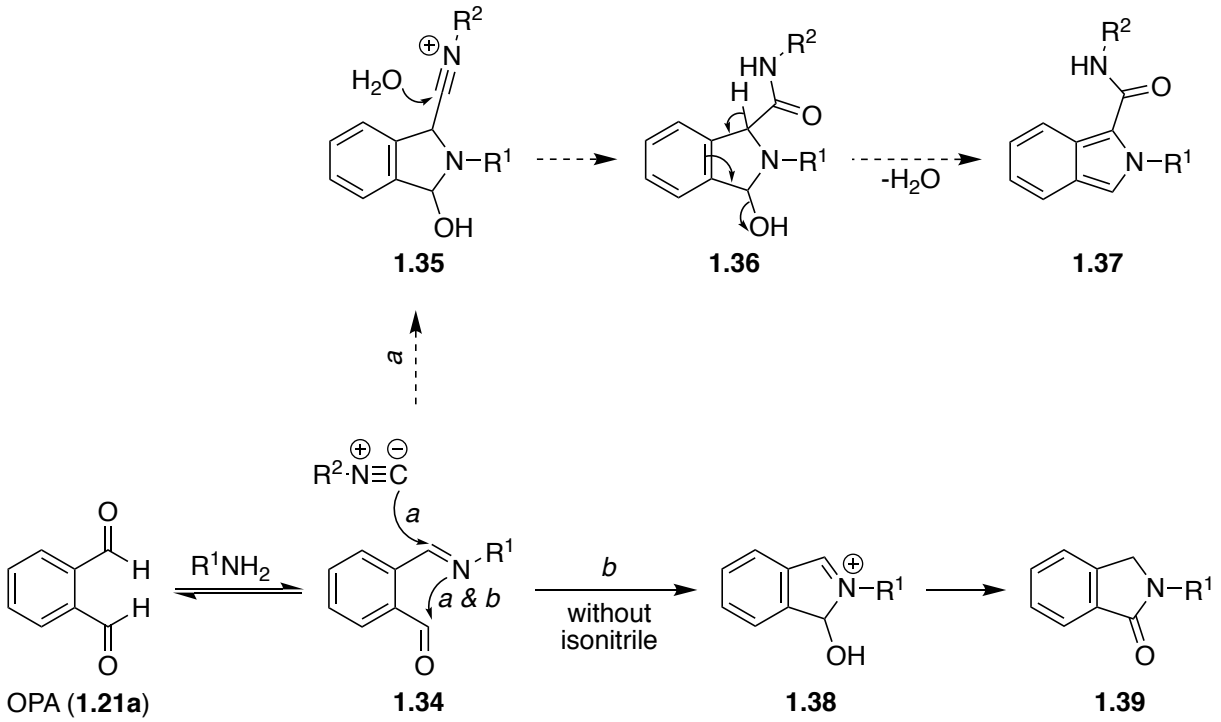
Scheme 1.5. Mechanism for the condensation reaction of 2-(bromomethyl)benzaldehydes and ketones with amines.

In 2012, Zhang et al. reported a three-component reaction between an OPA (**1.21**), a primary amine (**1.29c**), and an isonitrile (**1.32**), in which 1-carboxamido-isoindoles (**1.33**) were formed in moderate-to-good yields (Scheme 1.6).[56] In the envisioned mechanism, the amine reacted with one of the aldehydes in OPA to form a monoimine (**1.34**), which was then attacked by the isonitrile (Scheme 1.7, *infra*). Concurrently, the imine attacked the other aldehyde to form the five-membered ring in intermediate **1.35**. The nitrilium cation was then trapped by water via a Ritter-type mechanism to give intermediate **1.36**, which subsequently underwent dehydration-mediated aromatization to give the isoindole (**1.37**). For the desired reaction to proceed, it was necessary to prevent the competing formation of the isoindolinone (**1.39**) by using sodium bisulfite to form an aldehyde bisulfite adduct. The authors reasoned that this would render the aldehydes less electrophilic, thus slowing the formation of the hydroxyiminium intermediate in the competing pathway and allowing the isonitrile to attack the imine prior to cyclization. The substrates that were investigated were all well-tolerated, although the relative reactivities and electronic effects were variable and did not show many clear trends. For the dialdehyde substrate, OPA and 3,4-dimethoxy OPA were tolerated. Commercially available *tert*-butyl, cyclohexyl, and glycine isonitriles were investigated, all of which worked well. For the amine reacting partner, unsubstituted, electron-rich, and electron-poor benzyl amines were tolerated, as were unsubstituted and electron-rich anilines.



R^1 = R^2 = H or OMe; n = 0 or 1; Ar = Ph, 4-OMe-C_4H_6, 4-Cl-C_4H_6; R^3 = CH_2CO_2Et, *t*-Bu, cyclohexyl

Scheme 1.6. Three-component reaction for the synthesis of 1-carboxamido-isoindoles from *ortho*-phthalaldehyde derivatives.

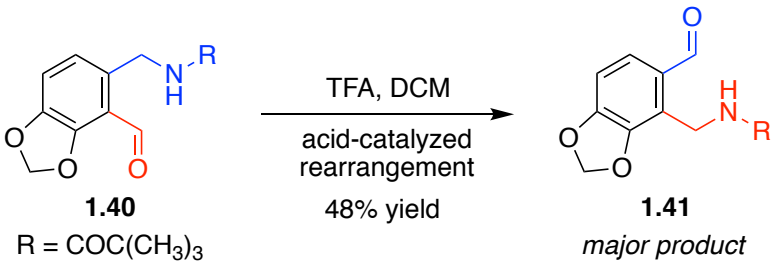


pathway a: envisioned pathway; *pathway b*: mechanism for the reaction in the absence of isonitrile

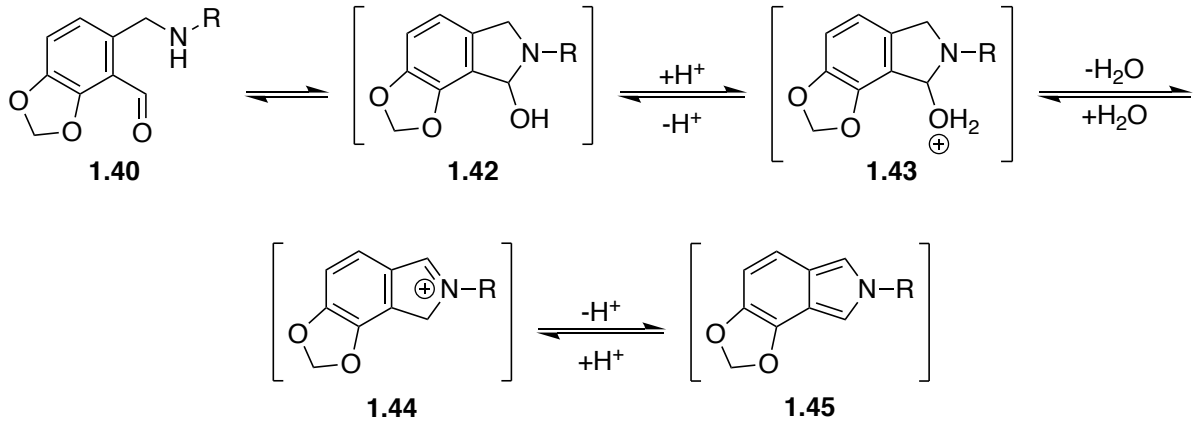
Scheme 1.7. Mechanism for three-component reaction of *ortho*-phthalaldehyde derivatives with amines and isonitriles.

In 2019, Hargitai et al. reported an acid-promoted rearrangement wherein an isoindole intermediate forms via the intramolecular condensation of methylenedioxy-substituted *ortho*-(pivaloylaminomethyl)benzaldehyde (**1.40**, Scheme 1.8).[57] This reaction is mechanistically similar to the reactions discussed *supra*, with the main difference being that there is only one electrophilic site. In the mechanism for this condensation (Scheme 1.9), the amino group attacks the aldehyde to form a hemiaminal (**1.42**). The hydroxyl group is then protonated (**1.43**) and water is subsequently lost to form an isoindolium (**1.44**), which is subsequently deprotonated to

form an isoindole intermediate (**1.45**), as seen in the mechanism for the intermolecular condensations of the *ortho*-(bromomethyl)benzyl carbonyl species described *supra*.



Scheme 1.8. Acid-promoted rearrangement of substituted *ortho*-aminomethylbenzaldehydes.



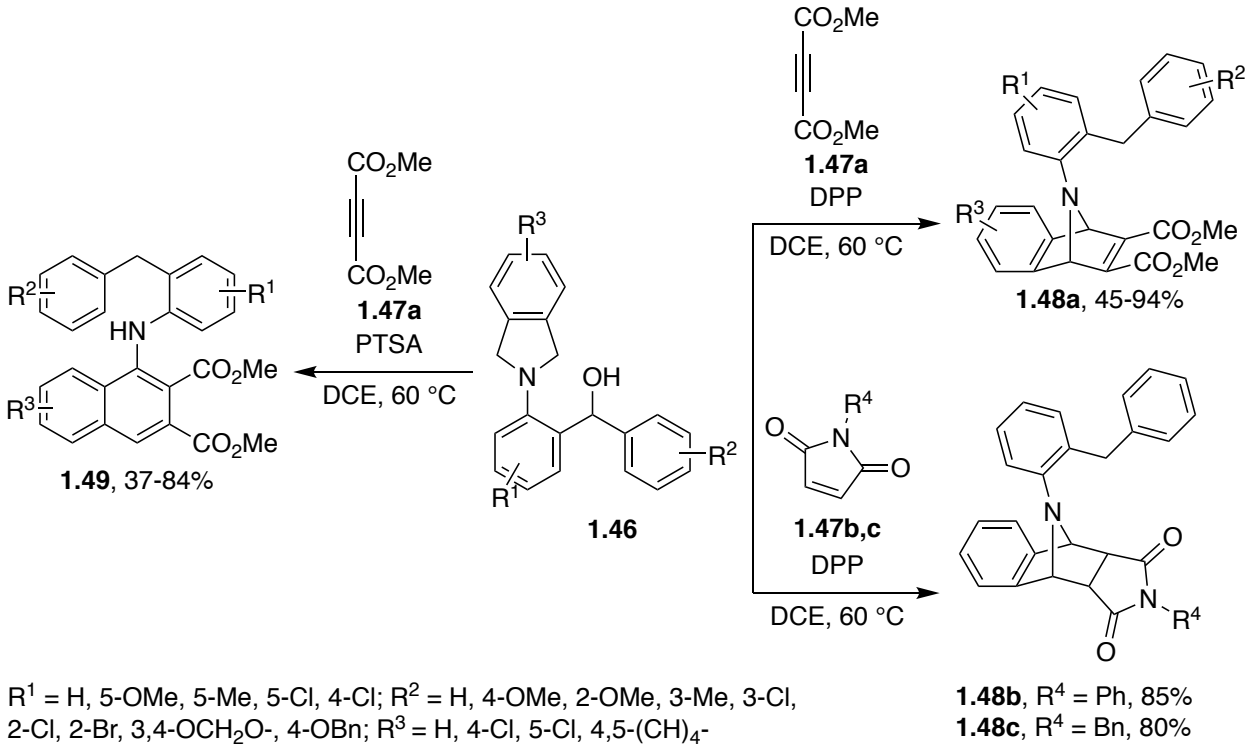
Scheme 1.9. Mechanism for formation of the isoindole intermediate in the acid-promoted rearrangement of substituted *ortho*-aminomethylbenzaldehydes.

The molybdenum-catalyzed formation of pyrido[2,1-*a*]isoindoles by retro-cyclopropanation of pyridyl-bearing cyclopropanes with release of ethylene and subsequent

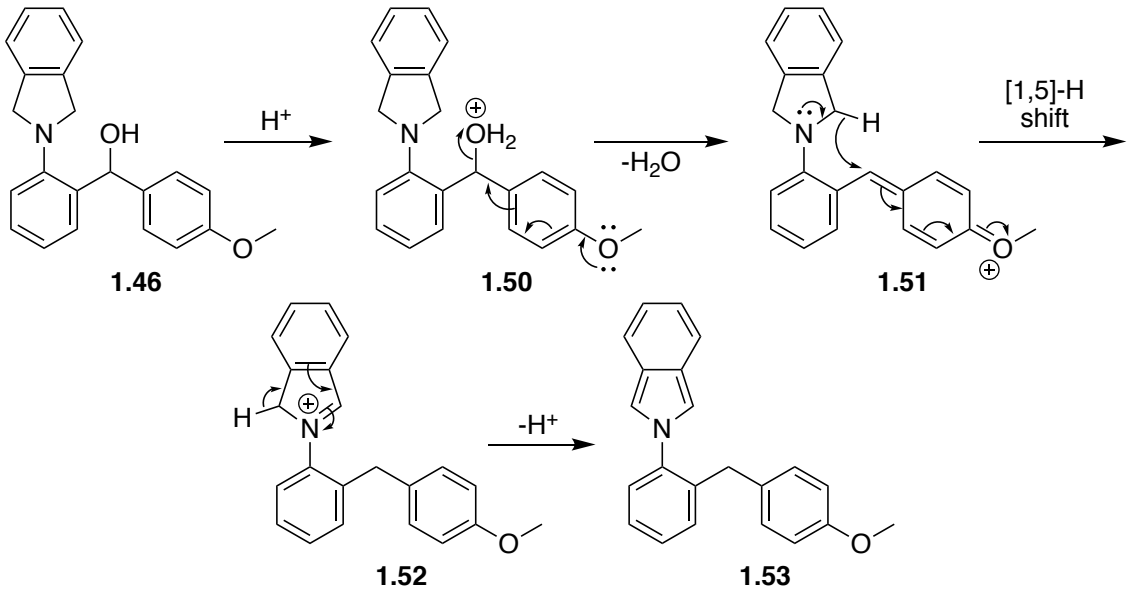
intramolecular cyclization reported by Asako in 2018,[58] which will discussed *infra* in Section 1.7, provides another example of isoindole formation via intramolecular condensation that is very different from the condensations described previously. This example illustrates that condensation methods for the preparation of isoindoles can also be metal-catalyzed.

1.3 Synthesis of 2*H*-Isoindoles from Isoindolines.

The two acid-promoted [1,5]-hydride shift pathways reported by Zhen et al. in 2017 feature an isoindoline starting material and proceed through an isoindole intermediate (Scheme 1.10).[59] In the mechanism proposed by the authors (Scheme 1.11, *infra*), the hydroxyl group of substrate **1.46** was protonated by the acid catalyst (**1.50**), followed by dehydration to form quinone methide intermediate **1.51**. This is followed by a [1,5]-hydride shift of one of the isoindoline α-protons to give isoindolium **1.52**, which is subsequently deprotonated to give isoindole intermediate **1.53**.

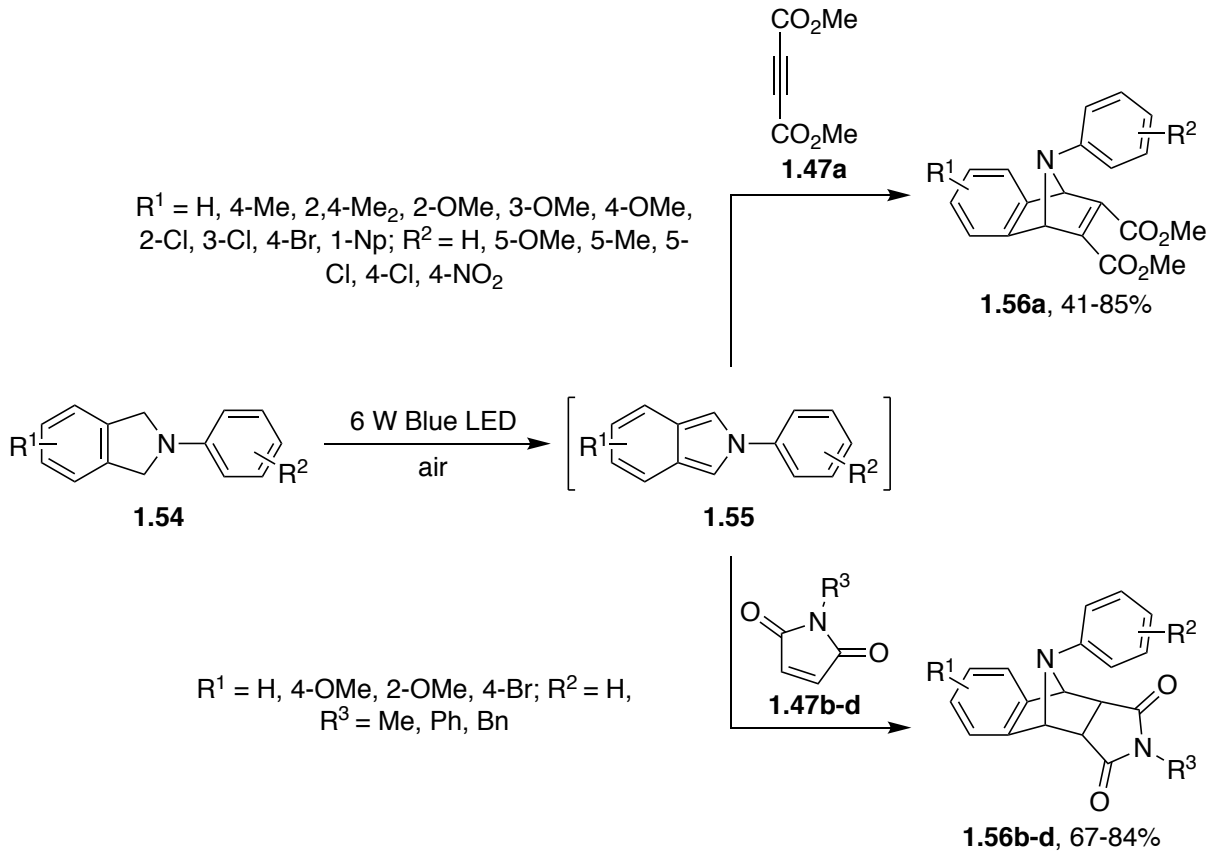


Scheme 1.10. DPP-catalyzed [1,5]-hydride shift/Diels-Alder cascade and PTSA-catalyzed [1,5]-hydride shift/Diels-Alder/isomerization cascade.

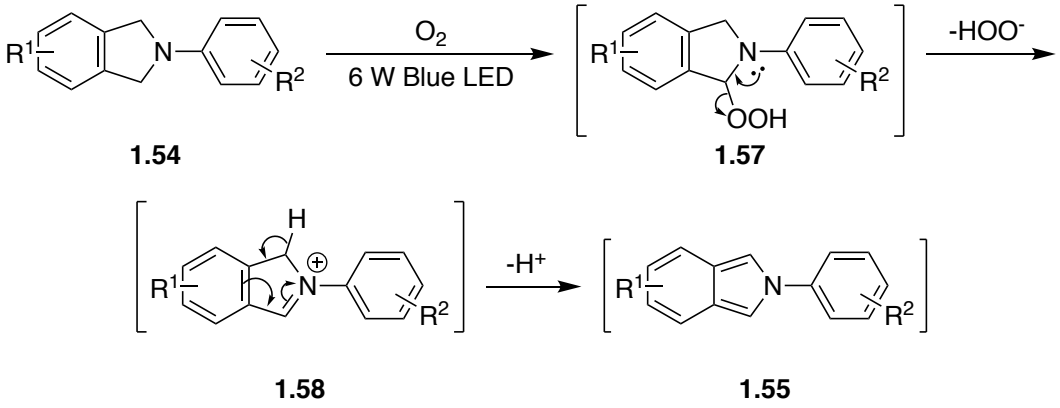


Scheme 1.11. Mechanism for formation of isoindole intermediate in DPP- and PTSA-catalyzed [1,5]-hydride shift/Diels-Alder and [1,5]-hydride shift/Diels-Alder/isomerization cascades.

In 2015, Lin et al. used visible light to convert an *N*-aryl isoindoline to an isoindole in situ in the presence of air, which subsequently underwent an intermolecular Diels-Alder reaction (Scheme 1.12).[60] The authors proposed an autoxidation-type mechanism (Scheme 1.13, *infra*) wherein hydroperoxide formation occurs at the isoindoline α-position (**1.57**). Subsequent elimination of hydrogen peroxide ion gives isoindolium (**1.58**), which is subsequently deprotonated to form the isoindole intermediate (**1.55**). Good yields were obtained for the Diels-Alder reaction products (**1.56a-d**), which indicates that this could be a good way to generate isoindoles under mild conditions.



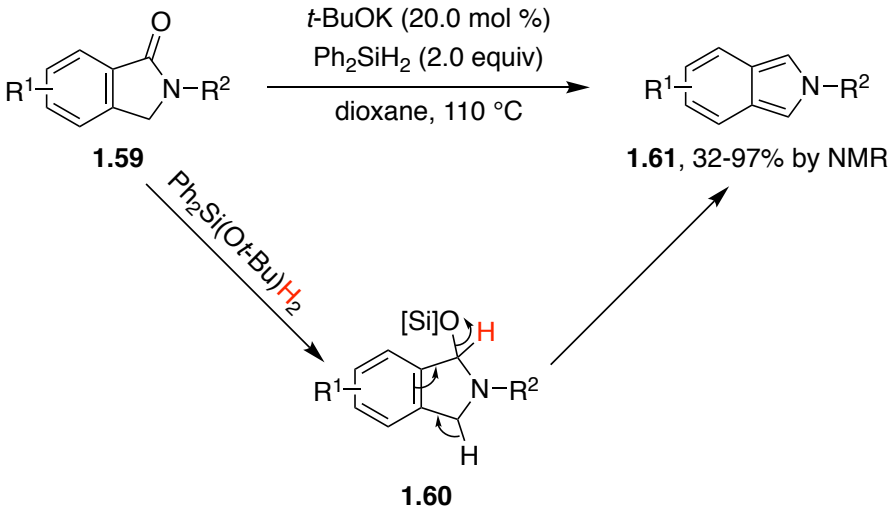
Scheme 1.12. Visible light-induced isoindole formation/Diels-Alder reaction.



Scheme 1.13. Proposed mechanism for the oxidation of isoindolines to isoindoles.

1.4 Synthesis of 2*H*-Isoindoles from Isoindolinones and Phthalimides.

In 2017, Ding et al. reported an alkoxide-catalyzed reduction of isoindolinones to isoindoles using a silane reductant (Scheme 1.14).[61] In the proposed mechanism, the base activates the silane by forming a pentacoordinated intermediate, which facilitates hydride transfer to the carbonyl to form silylhemiaminal intermediate **1.60**. Deprotonation of this intermediate at the 3-position and subsequent elimination of the siloxy moiety gives the isoindole product (**1.61**). The best yields were obtained with *t*-BuOK as the base and Ph_2SiH_2 as the reductant. Due to the instability of isoindoles, the authors reported yields for the Diels-Alder reactions of the formed isoindoles with *N*-phenyl maleimide (**1.47b**). Hydrosilylation of *N*-benzyl, alkyl or aryl substituted benzolactams gave the corresponding isoindoles (**1.61**) in moderate-to-good yields. Excellent yields were obtained for benzolactam substrates with alkylated benzene rings. The reaction tolerated a wide range of functional groups, including halogens, alkenes, naphthalene rings, and carbamic esters. The authors further demonstrated that this reaction is effective on a larger 2.0 g scale. Given its generally good yields, wide functional group tolerance, efficacy upon scale-up, and use of environmentally benign conditions and a readily available catalyst, this reaction represents a promising synthetic method for the preparation of isoindoles.

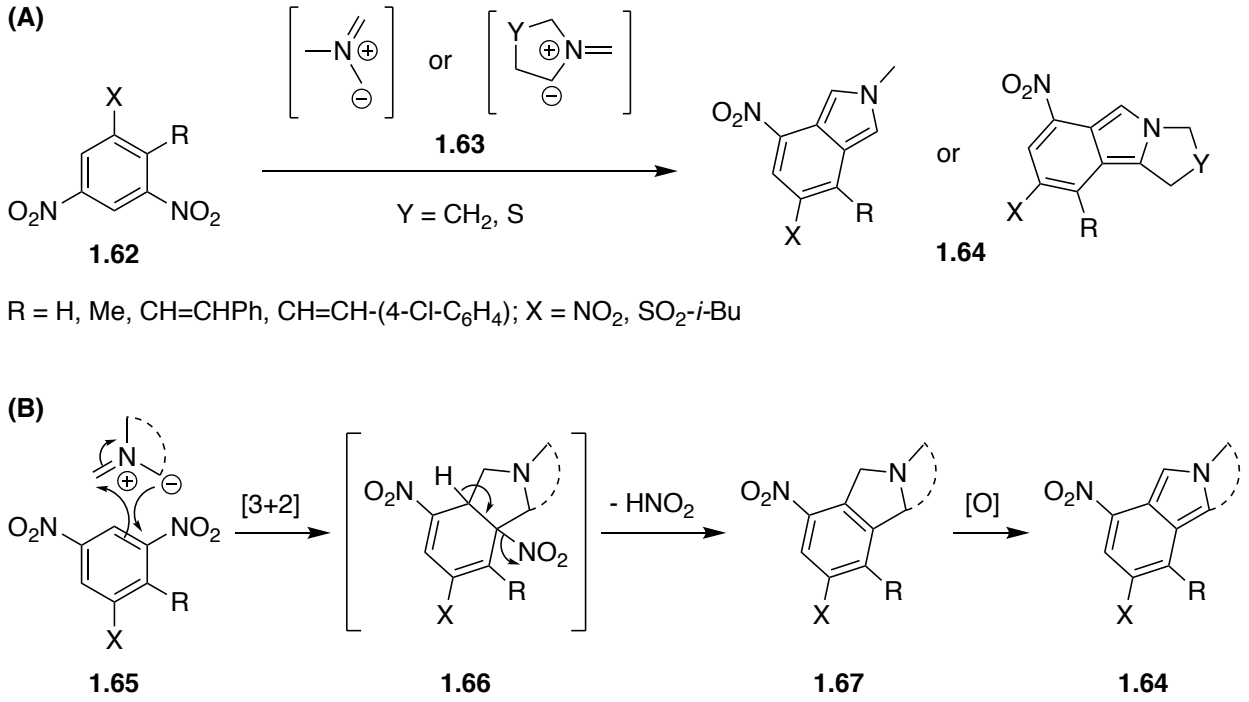


Scheme 1.14. Reduction of isoindolinones to isoindoles via alkoxide-catalyzed hydrosilylation.

1.5 Synthesis of 2*H*-Isoindoles via Cycloaddition and Cycloreversion Reactions.

In 2012, Starosotnikov et al. reported the first example of a one-step isoindole synthesis via a 1,3-dipolar cycloaddition of azomethine ylides and nitroarenes (Scheme 1.15A).[62] The mechanism proposed by the authors starts with a [3+2] cycloaddition of the ylide dipole to the nitroarene (**1.65**, Scheme 1.15B), followed by rearomatization of the benzene ring via loss of nitrous acid to give an isoindoline (**1.67**). The isoindoline pyrroline ring subsequently undergoes oxidative dehydrogenation, possibly with air, but more likely with the starting polynitro compounds, to form the isoindole (**1.64**). Yields were generally moderate (32-58%), except for reactions of 2,4,6-trinitrotoluene (TNT) (X = NO_2, R = Me), which gave low yields of only 11%. The authors hypothesized that this is due to side reactions in which the methyl group of TNT is deprotonated to form a reactive 2,4,6-trinitrobenzyl anion. The authors found that the reaction

proceeded regioselectively at the aromatic C–C bond activated by the nitro group that is *ortho* to the R group. Nitroarene substrates with an external alkene double bond still formed the isoindole as the exclusive product, except for **1.68**, which had an alkene that was activated to behave as a nucleophile by the alkoxy group (Figure 1.9). The reaction was compatible with acyclic and cyclic ylides, except that for the cyclic ylide with Y = S, the isoindoline was not completely converted to the isoindole upon prolonged heating.



Scheme 1.15. (A) Scheme and (B) mechanism for the synthesis of isoindoles via 1,3-dipolar cycloaddition of azomethine ylides and nitroarenes.

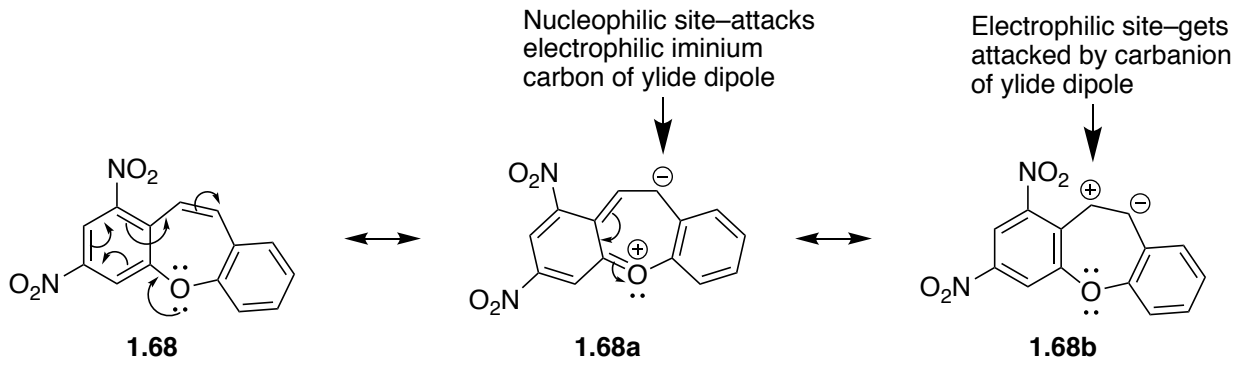
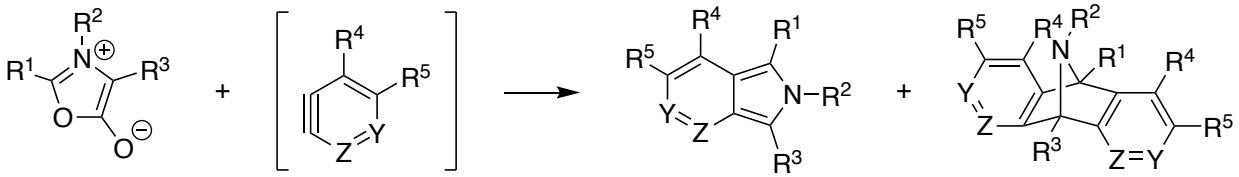


Figure 1.9. Rationale for failure of nitroarene **1.68** in the 1,3-dipolar cycloaddition of azomethine ylides and nitroarenes.

In 2014, Fang et al. reported a cascade of cycloadditions and cycloreversions in which a stable münchnone containing an electron withdrawing group at R^3 underwent a [3+2] cycloaddition with an *in situ*-generated aryne (Scheme 1.16).[63] The adduct that formed then underwent a [4+2] cycloreversion to form an isoindole intermediate (**1.71**) in situ, accompanied by the loss of carbon dioxide (Scheme 1.16B). Attempts by the authors to manipulate the reaction conditions to stop at the isoindole were unsuccessful. However, Lopchuk and Gribble, who reported a very similar reaction in the same year, were able to stop at the isoindole by modifying the conditions for the aryne formation and achieve mostly high yields (Scheme 1.16A).[64] The presence of an electron-donating substituent on the aryne did not materially affect the yield. A slightly higher yield was observed where the electron-donating group was at R^5 rather than R^4. Additionally, the authors prepared two azaisoindoles (Y = CCl, Z = N and Y = N, Z = CH), but obtained only moderate yields.

(A) Scheme for reactions reported by Fang et al. (ref. 63) and Lopchuk and Gribble (ref. 64):



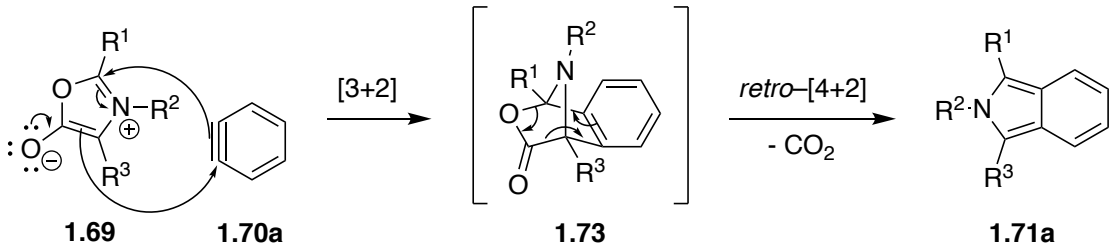
1.69 **1.70** **1.71** **1.72**

isoindole ***benzanthracenimine***

***Fang et al. (ref. 63)*:** R^1 = aryl or heteroaryl; R^2 = Me; R^3 = EWG; R^4 = H; R^5 = H, Me, OMe; Y = CH, CMe, COMe; Z = CH. Prepared benzanthracenimines in 75-92% yields.

Lopchuk and Gribble (ref. 64): R^1,R^3 = Ph, Me; R^2 = Bn, Me; R^4 = H, Me, OMe; R^5 = H, Me; Y = CCl, N; Z = CH, N. Prepared isoindoles in 76-93% yields and azaisoindoles in 41-58% yields.

(B) Mechanism for formation of isoindole products:

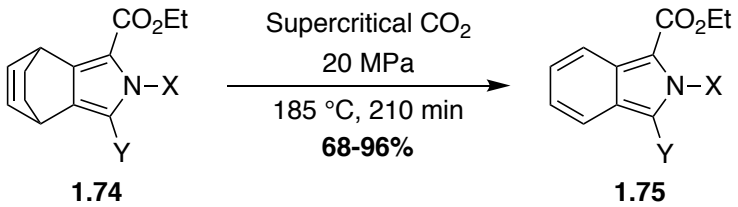


1.69 **1.70a** **1.73** **1.71a**

Scheme 1.16. Formation and reaction of isoindoles via cycloaddition/cycloreversion cascade reactions of münchnones with arynes.

In 2017, Ito et al. reported the conversion of bicyclopyrroles (**1.74**) to isoindoles (**1.75**) via a retro-Diels-Alder reaction that was accompanied by the loss of ethylene in supercritical carbon dioxide (Scheme 1.17).[65] Additional ethylene gas was added to the reaction as an oxygen scavenger to improve the yield. The conditions were harsh, and the investigation of the substrate scope was limited, but most of the yields were high. All substrates that successfully decomposed to the corresponding isoindoles had an ethyl ester at C1, as the conversion of α-unsubstituted bicyclopyrroles to isoindoles was poorly controlled. Several N-unsubstituted substrates were

investigated. While the C3-unsubstituted substrate (X = H) gave only a moderate yield, good-to-excellent yields were obtained for substrates bearing a phenyl group or an electron-withdrawing group at this position. However, substrates bearing a bromine atom at the 3-position (Y = Br) gave only trace yield of the isoindole. The only *N*-substituted substrate that was investigated was the C3-unsubstituted *N*-benzyl substrate, which also gave a good yield.



1.74 **1.75**

X = H, CO_2Ph; Y = H, Ph, CN, CHO

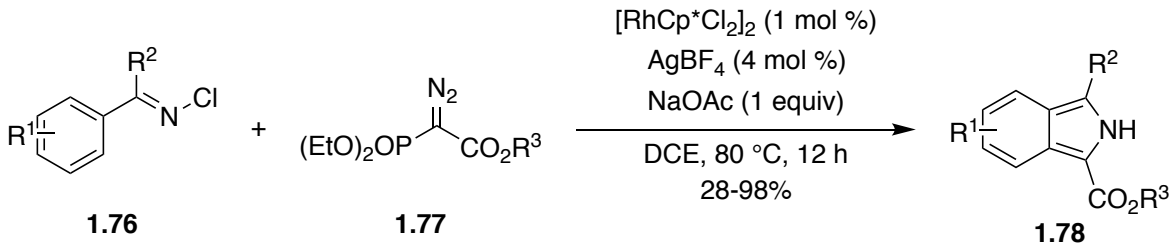
Scheme 1.17. Synthesis of isoindoles from bicyclopyrroles via a retro-Diels-Alder reaction.

1.6 Synthesis of 2*H*-Isoindoles via Transition Metal-Catalyzed Coupling Reactions.

With few exceptions, most of the recently reported transition metal-catalyzed methods for the synthesis of 2*H*-isoindoles are catalyzed by rhodium. In addition to the methods discussed herein, additional examples of pyrido-fused isoindole syntheses that involve transition-metal-catalyzed coupling reactions can be found *infra* in Section 1.7.

Rhodium is the most used metal in the recently reported transition metal-catalyzed coupling reactions used to prepare isoindoles. In 2019, Qi et al. reported a Rh(III)-catalyzed coupling of *N*-chloroimines (**1.76**) with α-diazo-α-phosphonoacetates (**1.77**) that provided

dechlorinative/dephosphonative access to 2H-isoindoles (**1.78**, Scheme 1.18).[66] This was the first reported use of *N*-chloroimines for directed C-H functionalization. To generate a cationic Rh(III) catalyst, $AgBF_4$ was used as a halide–abstraction reagent. The authors reported that this reaction proceeds well with *N*-chloroimines bearing electron-donating and electron-withdrawing groups at the *para* or *meta* positions. *Ortho* substitution resulted in slightly lower yields and disubstitution further hindered the reactivity. Replacing the imino C–Me group with a larger group also reduced the yield, an effect that was magnified with a fused ring system. Substitution of the α-diazo-α-phosphonoacetate ester R group was also tolerated, but slightly reduced the yield. Yields ranged from 28-98%, with most substrates giving moderate-to-high yields. To expand the utility of this method, Ni(II) catalysis was subsequently used to remove the ester from the isoindole C3-position and the isoindole was further derivatized at that position.

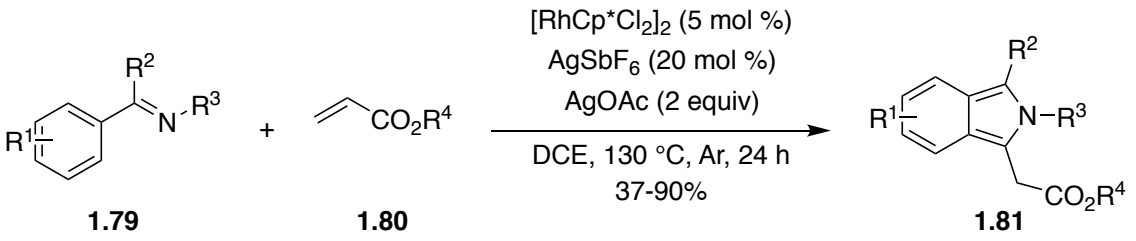


1.76 **1.77** **1.78**

R^1 = H, Ph, alkyl, OMe, halogen, CF_3, CN; R^2 = alkyl, Ph; R^3 = alkyl, phenyl

Scheme 1.18. Synthesis of isoindoles via Rh(III)-catalyzed coupling of *N*-chloroimines with α-diazo-α-phosphonoacetates.

In a similar reaction, Li et al. used a Rh(III) catalyst to effect C–H activation of α-iminonitriles and α-imino esters (**1.79**), coupling them with acrylates (**1.80**) to form 2*H*-isoindoles (**1.81**) in yields of 37-90% (Scheme 1.19).[67] Substitution of the α-iminonitrile *C*-aryl ring with halogens and electron-withdrawing groups at the para position were well-tolerated and electron-donating groups were also tolerated in either the *ortho*, *meta*, or *para* positions. Substitution of the *N*-aryl ring with an electron-withdrawing group or halide at the para or meta position was well tolerated and electron-withdrawing groups were also tolerated at these positions. However, substitution with an *N*-cyclopropyl gave a moderate yield of only 41% and no desired product was obtained with *N*-*n*-Butyl and *N*-isopropyl groups. For the acrylates, substitution with an alkyl, benzyl, phenyl, or naphthyl group was tolerated, giving moderate-to-excellent yields. The authors extended this reaction to α-imino esters and obtained high yields for those substrates, except for the esters that were fused to the *N*-aryl ring, which gave moderate yields. Substitution of the α-imino ester *C*-aryl or *N*-aryl ring with a halogen was well-tolerated, as was substitution of the *C*-aryl ring with a cyano electron-withdrawing group and substitution of the *N*-aryl ring with a methoxy electron-donating group. Comparable yields were obtained for both α-imino methyl and ethyl esters.

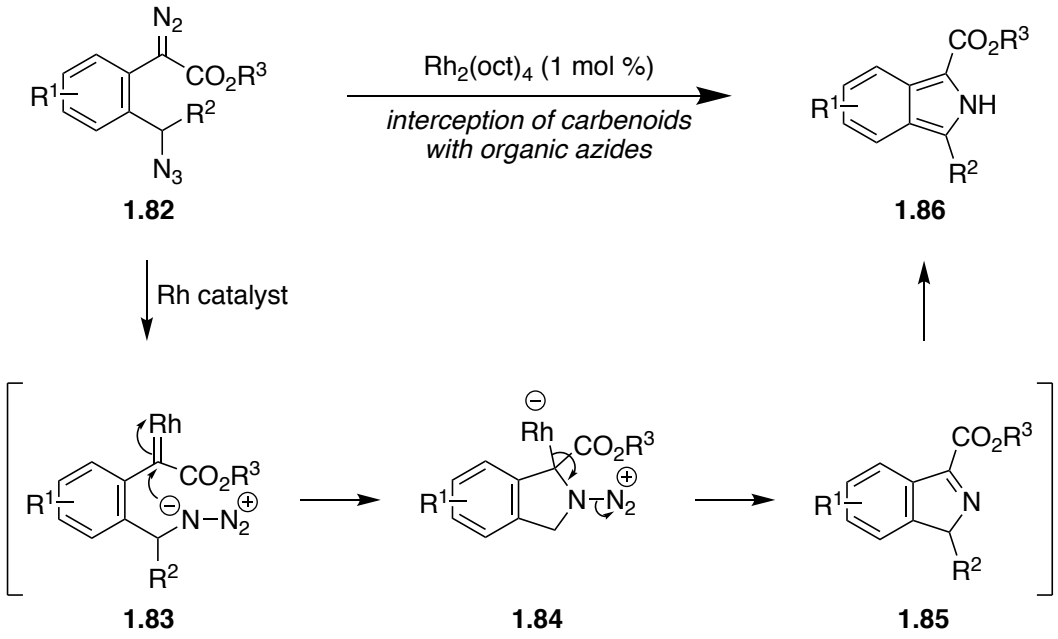


R^1 = H, Me, CF_3, CN, X; R^2 = CN or ester; R^3 = Ar or cyclopropyl; R^4 = Ar or alkyl

Scheme 1.19. Synthesis of isoindoles via Rh(III)-catalyzed coupling of α-iminonitriles or α-imino esters with acrylates.

Unlike the methods described previously, the intramolecular condensation of benzyl azides with α-aryldiazoesters reported by Zhu et al. in 2019 was catalyzed by Rh(II) instead of Rh(III) (Scheme 1.20).[68] This reaction proceeded via a Rh(II)-catalyzed interception of the diazo group by the azide, which began with the formation of carbenoid **1.83** from the diazo group, followed by nucleophilic attack of the carbenoid by the azide to give intermediate **1.84**. Subsequent Rh–C bond cleavage and nitrogen extrusion gave α-imino ester **1.85**, which rapidly tautomerized to isoindole **1.86**. All the examined azides reportedly gave good-to-excellent yields by NMR, with differences in isolated yields being attributed to the stability of the isoindoles during purification. The electronics of the azide benzene ring did not have a substantial effect on the yield and both electron-withdrawing and electron-donating substituents were well-tolerated. Substitutions at the *ortho*, *meta*, and *para* positions with respect to the azidomethyl group all gave similar results. Additionally, methyl and ethyl esters gave comparable results. Substitution at the benzylic position (R^2) was also examined. While a phenyl group resulted in excellent

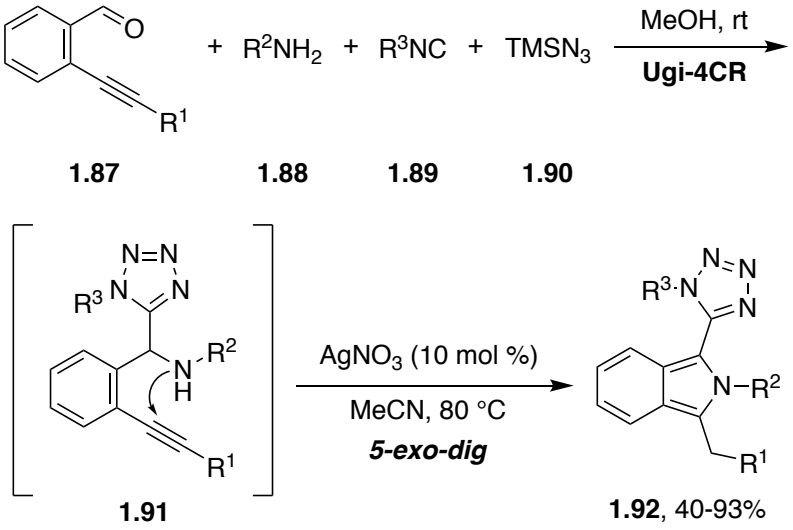
yields, particularly when the amount of the starting material was doubled, substitution with a methyl group slightly reduced the yield.



Scheme 1.20. Rh(II)-catalyzed intramolecular condensation of benzyl azides with α-aryldiazoesters.

In 2014, Wu et al. reported a one-pot, two-step synthesis of 1,2-disubstituted 3-(1*H*-tetrazol-5-yl)-2*H*-isoindoles via a four-component Ugi reaction/silver-catalyzed cyclization cascade (Scheme 1.21).[69] The transformation reportedly begins with the four-component Ugi reaction of the 2-alkynylbenzaldehyde, amine, isonitrile, and trimethylsilyl azide reacting partners, giving tetrazole-substituted intermediate **1.91**, which subsequently undergoes a silver-catalyzed intramolecular cyclization that ultimately leads to isoindole product **1.92**. For the

substrate scope, the authors examined the effects of substitution of the alkyne (R^1), amine (R^2), and isonitrile (R^3). The authors found that the 2-alkynylbenzaldehydes were more reactive and gave higher yields when R^1 was an aryl group versus an alkyl group. Additionally, a good yield was obtained when R^1 was a trimethylsilyl group, and the group remained intact. Aliphatic amines, electron-poor anilines, and electron-rich anilines were all suitable reacting partners. Substitution of the aniline with methyl, methoxy, ethoxy, and halogen groups was well-tolerated. Commercially available isonitriles were used, including (2-isocyanoethyl)benzene and *tert*-butyl, benzyl, and cyclohexyl isocyanides, all of which gave the isoindole products in moderate-to-excellent yields.



1.87 **1.88** **1.89** **1.90**

1.91

1.92, 40-93%

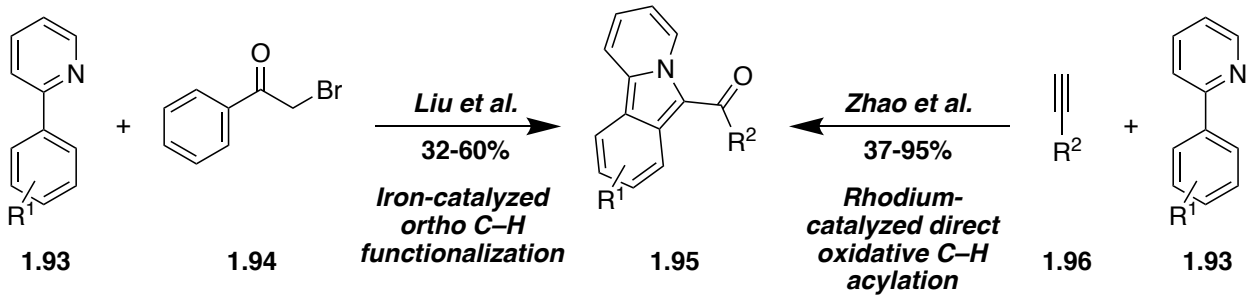
R^1 = aryl, alkyl, cycloalkyl, Me_3Si; R^2 = aryl, benzyl, cycloalkyl;
R^3 = $C_6H_5(CH_2)_2$, benzyl, alkyl, cycloalkyl

Scheme 1.21. One-pot synthesis of isoindoles via silver-catalyzed four-component Ugi reaction/5-exo-dig cyclization.

1.7 Transition Metal-Catalyzed Synthesis of Pyrido-Fused 2*H*-Isoindoles.

There has been a fair amount of recent interest in the preparation of pyrido[2,1-*a*]isoindoles. The approaches reported within the past decade are all transition metal-catalyzed and feature a 2-arylpyridine reacting partner. They can be divided into two categories: intermolecular approaches, which involve the formation of both C–C and C–N bonds, and intramolecular approaches, which only involve C–N bond formation.

In 2013, Liu et al. prepared pyrido[2,1-*a*]isoindoles from 2-arylpyridines in fair-to-moderate yields via an iron-catalyzed *ortho* C–H functionalization reaction with 2-bromoacetophenone in the presence of CsI (Scheme 1.22).[70] This approach was innovative in that it allowed for a fully regioselective synthesis of pyrido[2,1-*a*]isoindoles by leveraging the difference in steric hindrance at the two *ortho* positions of the 2-arylpyridine benzene ring. However, the substrate scope was rather limited and was only investigated for the 2-arylpyridine reacting partner. Electron-donating groups were tolerated, including the bulky *tert*-butyl group. Halogens were also tolerated but gave lower yields that decreased with increasing electronegativity of the halogen. Additionally, substitution at the *ortho* and *meta* positions gave lower yields than *para*-substitution.



***Liu et al. (ref. 70)*:** FeI_2 (25 mol %), CsI (1.25 equiv), toluene–NMP, 150 °C, **32-60%**
***Zhao et al. (ref. 71)*:** $[Rh(OAc)_2]_2$ (5 mmol %), $Cu(OAc)_2$ (1 equiv), CuI (1 equiv), 1:3 *o*-xylene:DMA, 140 °C, air, **37-95%**

Scheme 1.22. Intermolecular approaches for the synthesis of pyrido[2,1-*a*]isoindoles.

In 2014, Zhao et al. prepared 6-acetyl pyrido[2,1-*a*]isoindoles in moderate-to-excellent yields via a rhodium-catalyzed direct oxidative C–H acylation of 2-arylpyridines with terminal alkynes in the presence of copper salts under air (Scheme 1.22, *supra*).[71] Like the approach reported by Liu et al., this approach also appeared to be regioselective due to the differences in steric hindrance at the 2-arylpyridine *ortho* positions, but the yields were significantly higher than those reported by Liu et al. In the model system, 2-phenylpyridine and phenylacetylene were used as the reacting partners. Substitution of the 2-arylpyridine benzene ring with an electron-donating group was well-tolerated and resulted in high yields comparable to that of the unsubstituted product, whereas the presence of an electron-withdrawing group hindered the reaction and reduced the yield. However, chloro, acetyl, ester, and nitro groups were all tolerated. Substitutions at the *ortho*, *meta*, and *para* positions gave similar outcomes. Mostly aryl-substituted terminal acetylenes were investigated. Excellent yields were obtained with a

chlorine or fluorine in the *para* position of the phenyl group. Substitution with an electron-donating group at the *para* position resulted in only moderate yields, whereas an excellent yield was obtained with a methyl group in the *meta* position. Heteroaryl groups gave only moderate yields. The only alkyl group investigated, cyclopropyl, gave a good yield.

Asako et al. have reported two molybdenum-catalyzed methods for the synthesis of 6-aryl and 6-alkyl pyrido[2,1-*a*]isoindoles in good yields from 1-substituted 2-(2-pyridyl)benzenes (Figure 1.10).[58,72] Both methods employ the same general approach of forming a carbene equivalent at the benzylic carbon at the 1-position of the benzene ring, which undergoes a C–N bond-forming intramolecular cyclization.

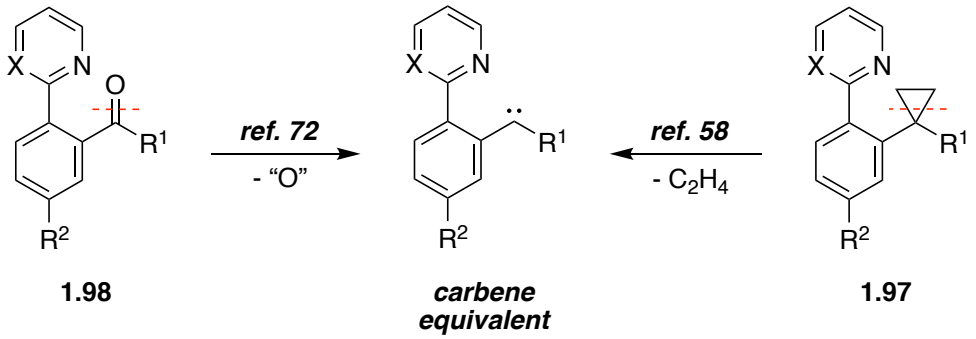
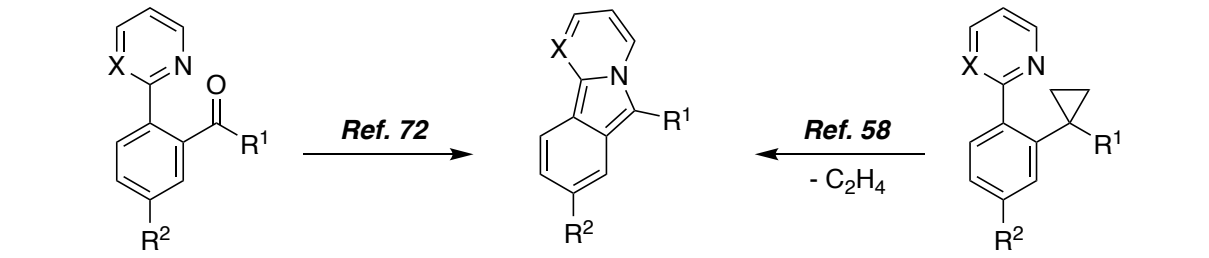


Figure 1.10. Strategy for intramolecular approaches to pyrido[2,1-*a*]isoindoles by Asako et al.

In 2018, the authors reported a Mo(0)/*o*-quinone-catalyzed retro-cyclopropanation of pyridyl-bearing cyclopropanes (**1.97**) with release of ethylene and subsequent intramolecular cyclization (Scheme 1.23).[58] The substrate scope has some limitations, as an aryl or alkyl

substituent was required at the 1-position of the cyclopropane ring, but it complements existing methods, as they are largely limited to the preparation of 6-H, 6-acyl, and 6-alkoxycarbonyl pyrido[2,1-*a*]isoindoles. Aryl substituents generally gave higher yields than alkyl substituents, with phenyl and naphthyl groups giving excellent yields. Additionally, 6-alkylpyrido[2,1-*a*]isoindoles were moderately unstable and were consequently oxidized and isolated as alkyl 2-(2-pyridyl)phenyl ketones. The effect of substitution of the aryl ring was investigated, predominately at the para position. Electron-donating methyl and methoxy groups were tolerated, as were halogens. Substitution at the *ortho* position with a methyl group required a slightly higher temperature, but only a small decrease in yield was observed. Substitution of the 2-phenylpyridine moiety with an electron-donating methoxy group or an electronegative fluorine atom slowed down the reaction and reduced the yield substantially. However, this method is potentially also useful for the preparation of pyrimido[2,1-*a*]isoindoles (X = N), as a nearly quantitative yield was observed for 6-phenyl product.



1.98

R^1 = aryl, alkyl, cycloalkyl;
R^2 = H, Me, OMe; X = CH, N

1.99

Ref. 58: 65-98%
Ref. 72: 69-97%
(isoindolium salts)

1.97

R^1 = aryl, alkyl, cycloalkyl;
R^2 = H, OMe, F; X = CH, N

***Ref. 72*:** $Mo(CO)_6$/*o*-quinone (10 mol %), PPh_3 or dppe (0.6-1.1 equiv), toluene or mesitylene, 140-180 °C, 24 h; then TfOH.
***Ref. 58*:** $Mo(benzene)_2$/*o*-quinone (20 mol %), mesitylene, 160-180 °C, 18-72 h.

Scheme 1.23. Synthesis of pyrido[2,1-*a*]isoindoles via intramolecular deoxygenation and retro-cyclopropanation reactions.

In 2021, the authors also prepared 6-aryl and 6-alkyl pyrido[2,1-*a*]isoindoles (**1.99**, Scheme 1.23) and the corresponding isoindolium salts via the deoxygenation of carbonyl compounds (**1.98**).[72] Like the method described *supra*, this method was catalyzed by a Mo(0)/*o*-quinone system, although this method additionally required a phosphine reductant. The yields for the two methods were comparable, but several were slightly higher with this method than with the retro-cyclopropanation. As with the retro-cyclopropanation, this method could only be used to prepare 6-alkyl or 6-aryl substituted products, with aryl-substituted ketones giving faster reactions and higher yields than alkyl-substituted ketones and ketones with bulky aryl groups. Substitution of the aryl group at the para position with an electron-donating group or a halogen was well-tolerated, giving yields of at least 90%, except for a methyl group. Unlike with the retro-cyclopropanation reaction, substitution of the 2-phenylpyridine moiety (R^2) with an

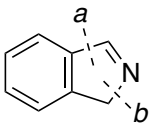
electron-donating group increased the yield slightly, although only methyl and methoxy groups were investigated with this method. Like the retro-cyclopropanation method, this method is potentially also useful for the preparation of pyrimido[2,1-*a*]isoindoles (X = N), although a slightly lower yield was obtained with this method for 6-phenylpyrimido[2,1-*a*]isoindole. The biggest difference in the scopes of these two methods is that with the deoxygenative method, most of the isoindoles were converted to the isoindolium salts by treatment with triflic acid to avoid partial oxidation during the purification process, whereas some of the isoindoles were stable during purification with the retro-cyclopropanation method.

1.8 Synthesis of 1*H*-Isoindoles via Transition Metal-Catalyzed Coupling Reactions.

Isolating 1*H*-isoindoles is a challenge because they readily isomerize into highly labile 2*H*-isoindoles. One strategy for preventing isomerization is to prepare chiral 1*H*-isoindoles bearing a quaternary stereogenic center, for which isomerization is not possible. Many of the methods described herein utilize this approach.

The most used metals for the formation of 1*H*-isoindoles in recent literature are palladium and rhodium, but ruthenium- and lanthanum-catalyzed methods have also been reported. Except for the lanthanum-catalyzed method, all the methods reported herein begin with C–H activation at the *ortho* position. In the Pd-catalyzed methods, cyclization occurs via the formation of the aryl $C(sp^2)$–$C(sp^3)$ bond and in the other methods, cyclization occurs via $C(sp^3)$–N bond formation (Figure 1.11). Most of the methods that fall into the latter category cyclize via an aza-Michael addition of an imine species to an alkene moiety that was installed via *ortho*-vinylation (Scheme 1.25, *infra*); however, the La-catalyzed approach of Ye et al. cyclizes

via the coupling of a nitrile to an internal alkyne (Scheme 1.28, *infra*). These approaches are generally high yielding, with excellent yields being reported for several of them.

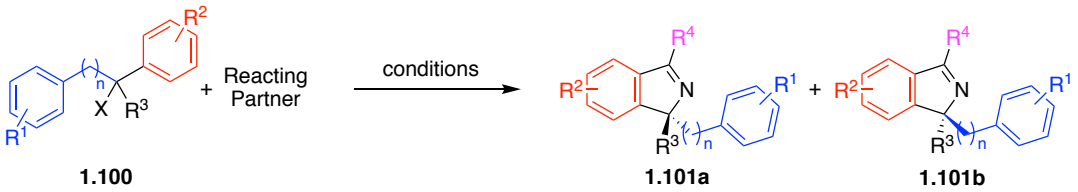


a: Pd-catalyzed approaches: cyclization via C–C formation.
b: Rh-, Ru-, and La-catalyzed approaches: cyclization via C–N formation

Figure 1.11. Summary of transition-metal catalyzed approaches for the formation of 1*H*-isoindoles.

In 2018, Grosheva and Cramer published a palladium(0)-catalyzed enantioselective C–H functionalization approach for the synthesis of chiral 1*H*-isoindoles bearing quaternary stereogenic centers from trifluoroacetimidoyl chlorides that delivers previously inaccessible perfluoroalkylated 1*H*-isoindoles in high yields and enantioselectivities (Scheme 1.24).[73] Most of the catalytic methods reported prior to this publication gave racemic mixtures, so this report filled a gap in the literature. Both electron-poor and electron-rich aryl groups gave high yields and enantioselectivities, and naphthyl groups were also well-tolerated. For larger R groups, the Pd(0) catalyst and readily accessible phosphordiamidite ligands gave high enantioselectivities. However, modifications to the method were needed to improve the enantioselectivities for substrates with smaller R groups, which included the use of larger amounts of a different palladium catalyst and TADDOL-phosphoramidite ligand, as well as a different base. As with the reaction for larger R groups, the yields were high, the electronics of the aryl group largely did

not affect the reaction outcome, and the enantioselectivities for the 1*H*-isoindole products were comparable. Imidoyl chlorides with longer perfluoroalkylated chains were also investigated, but only for the preparation of thienopyrroles, which are not within the scope of this review.



1.100 **1.101a** **1.101b**

Tang et al.	n = 1; X = NC	R_4I	$Pd(MeCN)_2Cl_2$ (10 mol %) DPPB (10 mol %) $CsCO_3$ (1.2 equiv) PivOH (0.6 equiv) $PhCF_3$, 80 °C, 1.5 h, Ar	**a** & **b** (57-95%): R_1 = H, Me, F, Cl, CO_2Me; R_2 = H, OMe, Cl, F; R_3 = CO_2Et; R_4 = aryl
Wang et al.	n = 0; X = NC	R_4I	$Pd(OAc)_2$ (1 or 5 mol %) L* (2 or 10 mol %) Cs_2CO_3 (1.0 equiv) PivOH (0.6 equiv) PhMe, 60 °C, 2 h, Ar	**b** (24-99%; up to 99% ee): R_1 = R_2 = H, Me, OMe, F, Cl, Br; R_3 = CF_3, CF_2H; R_4 = aryl, vinyl
Grosheva et al. (original/larger R_3)	n = 0; X = 	–	$Pd(dba)_2$ (5 mol %) L* (10 mol %) CsOAc PhMe, 40 °C, 36 h	**b** (84-98%; up to 95.5:4.5 *er*): R_1 = R_2 = H, Me, OMe, F, Cl, CF_3, 2-Np; R_3 = Me, $(CH_2)_2OTBS$, cyclopropyl, *N*-Ts azetidinyl, *N*-Ts piperidinyl; R_4 = CF_3
Grosheva et al. (smaller R_3)	n = 0; X = 	–	Pd(allyl)Cp (10 mol %) L* (20 mol %) Cesium *o*-anisate PhMe, 50 °C, 36 h	**a** (92-99%; up to 93:7 *er*): R_1 = R_2 = H, OMe, F; R_3 = Me, $(CH_2)_2Bn$, $(CH_2)_2OBn$; R_4 = CF_3

Scheme 1.24. Palladium-catalyzed approaches for the synthesis of 1*H*-isoindoles bearing quaternary centers.

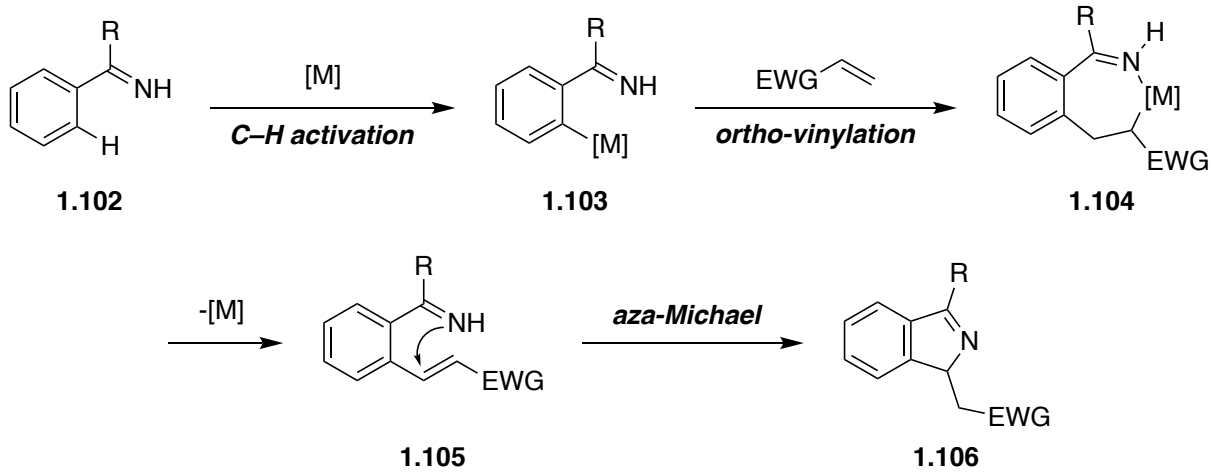
In 2021, Wang et al. reported another palladium-catalyzed enantioselective approach for the synthesis of 1*H*-isoindoles bearing quaternary stereogenic centers and perfluoroalkyl groups (Scheme 1.24, *supra*).[74] However, this approach differed from that of Grosheva and Cramer in that it used α,α-diaryl tri- and difluoromethylated isocyanides and substituted iodides as

precursors, used a Pd(II) catalyst, was intermolecular versus intramolecular, and gave 1*H*-isoindoles with a perfluoroalkyl group at the quaternary center (3-position), rather than at the imino carbon (1-position). The substrate scope was impressive, with a total of 70 examples provided. Alkenyl and aryl iodide substrates were investigated. Both electron-rich and electron-poor aryl iodides gave good-to-excellent yields and high enantioselectivities, and the position of the substituent had no obvious influence on the reaction outcome. Several of the aryl iodides investigated were natural product-, drug-, and functional molecule-derived, for which similar reaction outcomes were achieved. The alkenyl iodides investigated were 3-iodo-2-cyclopentenone and 3-iodo-2-cyclohexenone, both of which gave excellent enantioselectivities. The former gave good yields, but the latter gave only low-to-moderate yields. For the aryl ring on the isocyanide substrate, the electronics did not appear to influence the yield or enantioselectivity, but the effects of changing the position of the aryl substituent were not investigated. Using a difluoromethyl-substituted isocyanide substrate instead of a trifluoromethyl-substituted isocyanide substrate had no obvious influence on the reaction outcome, although an increase in the catalyst loading was required. To further demonstrate the utility of the reaction, the authors also investigated a tandem-cyclization approach using allene-bearing aryl iodides, which resulted in C1-tethered benzofuran-isoindole, indole-isoindole, and isoquinoline-isoindole bisheterocyclic scaffolds.

The Pd(II)-catalyzed C–H activation/cycloimidoylation of 2-isocyano-2,3-diarylpropanoates reported in 2018 by Tang et al. also gave 1*H*-isoindole products bearing C3 quaternary carbon centers; however, it was not enantioselective (Scheme 1.24, *supra*).[75] This approach was similar to the approach later reported by Wang et al. in that it involved the Pd(II)-catalyzed coupling of aryl iodides with substrates bearing an isocyano group and two aryl

groups, although the substrates used in this method were not symmetric as they were in the method reported by Wang et al. and thus, the aryl groups were not identical. Additionally, under alternate conditions, this reaction could be used to preferentially obtain 3,4-dihydroisoquinolines instead of isoindoles. The authors reported optimized conditions for both reactions, but only the reaction that selectively gives the 1*H*-isoindole product will be discussed in this review. Substitutions at R^1 with methyl, halogen, and ester groups all gave good yields. *Ortho*, *meta*, and *para* substitution were all well-tolerated, as was difluoro substitution. For the aryl group at the 2-position of the diarylpropanoate, substitutions with chloro, fluoro, and methoxy groups gave good-to-excellent yields. Similar outcomes were obtained with starting materials bearing ortho and para substitutions at R^2; however, meta substitution gave a mixture of 1*H*-isoindole regioisomers. Sterically hindered aryl iodides enhanced the selectivity for the 1*H*-isoindole product over the 3,4-dihydroisoquinoline product. Conversely, *para* substitution with a smaller chlorine atom reduced the total overall yield slightly and the selectivity significantly.

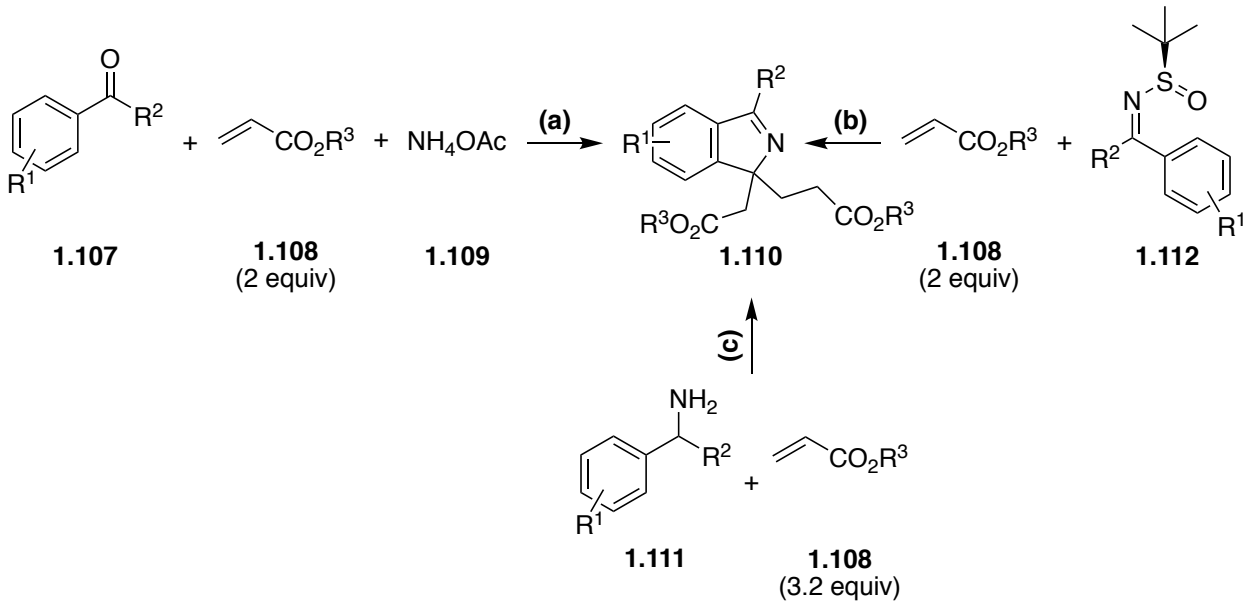
In the Rh-catalyzed processes reported by Wang et al.[76] and Yi et al.[77] in 2016, which were used to prepare 1,3,3-trisubstituted 1*H*-isoindoles, three new bonds were installed around a quaternary carbon (Scheme 1.26, *infra*). All three approaches feature a sequence that consists of C–H activation at the *ortho* position, followed by *ortho*-vinylation to give an intermediate that subsequently cyclizes to form the 1*H*-isoindole, typically via an aza-Michael addition (Scheme 1.25).



Scheme 1.25. General reaction sequence for Rh- and Ru-catalyzed formations of 1*H*-isoindoles.

Wang et al. used *N*-sulfinyl ketoimines as a novel substrate for the redox-neutral coupling with different activated olefins via a Rh-catalyzed C–H activation pathway to prepare 1*H*-isoindoles in moderate-to-excellent yields (Scheme 1.26).[76] A broad substrate scope was established. For the ketoimine substrate, electron-donating methyl and methoxy groups were well-tolerated at R^1, as were halogens. Better yields were obtained for substrates with an aryl group at R^2 than an alkyl group. For substrates with a substituted aryl group at R^2, the same substitutions that were tolerated at R^1 were generally also tolerated at R^2. Substitution with a trifluoromethyl electron-withdrawing group was also well-tolerated, as was disubstitution with methyl groups. Additionally, substitutions with naphthyl groups were well-tolerated at both R^1 and R^2, which means that this method could potentially be used to access benzo-fused 1*H*-isoindoles. Identical aryl groups were often used at R^1 and R^2, so it was hard to draw conclusions about the electronics at those positions independently; however, it appears that substitution at the

ortho and *meta* positions slightly reduced the yield compared to *para* substitution. For the alkene reacting partner, the alkyl and benzyl acrylate esters that were investigated all gave good yields.



(a) ***Yi et al.,*** **56-96%.** R^1 = H, EDG, halogen, EWG; R^2 = alkyl, phenyl, cycloalkyl, cyclic arylketone; R^3 = alkyl; conditions = $[RhCp^*Cl_2]_2$ (5 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), 1,2-DCE, M.W., 130 °C, 10 min.

(b) ***Yi et al.,*** **59-75%.** R^1 = H, OMe; R^2 = alkyl, phenyl, cycloalkyl; R^3 = Et; conditions = $[RhCp^*Cl_2]_2$ (5 mol %), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), 1,2-DCE, M.W., 120 °C, 10 min.

(c) ***Wang et al.,*** **63-95%.** R^1 = H, EDG, halogen, EWG, aryl, benzo-fused naphthalenes; R^2 = aryl, alkyl; R^3 = alkyl, benzyl; conditions = $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Zn(OTf)_2$ (0.1 equiv), DCE/AcOH (10:1), 100 °C, 12 h.

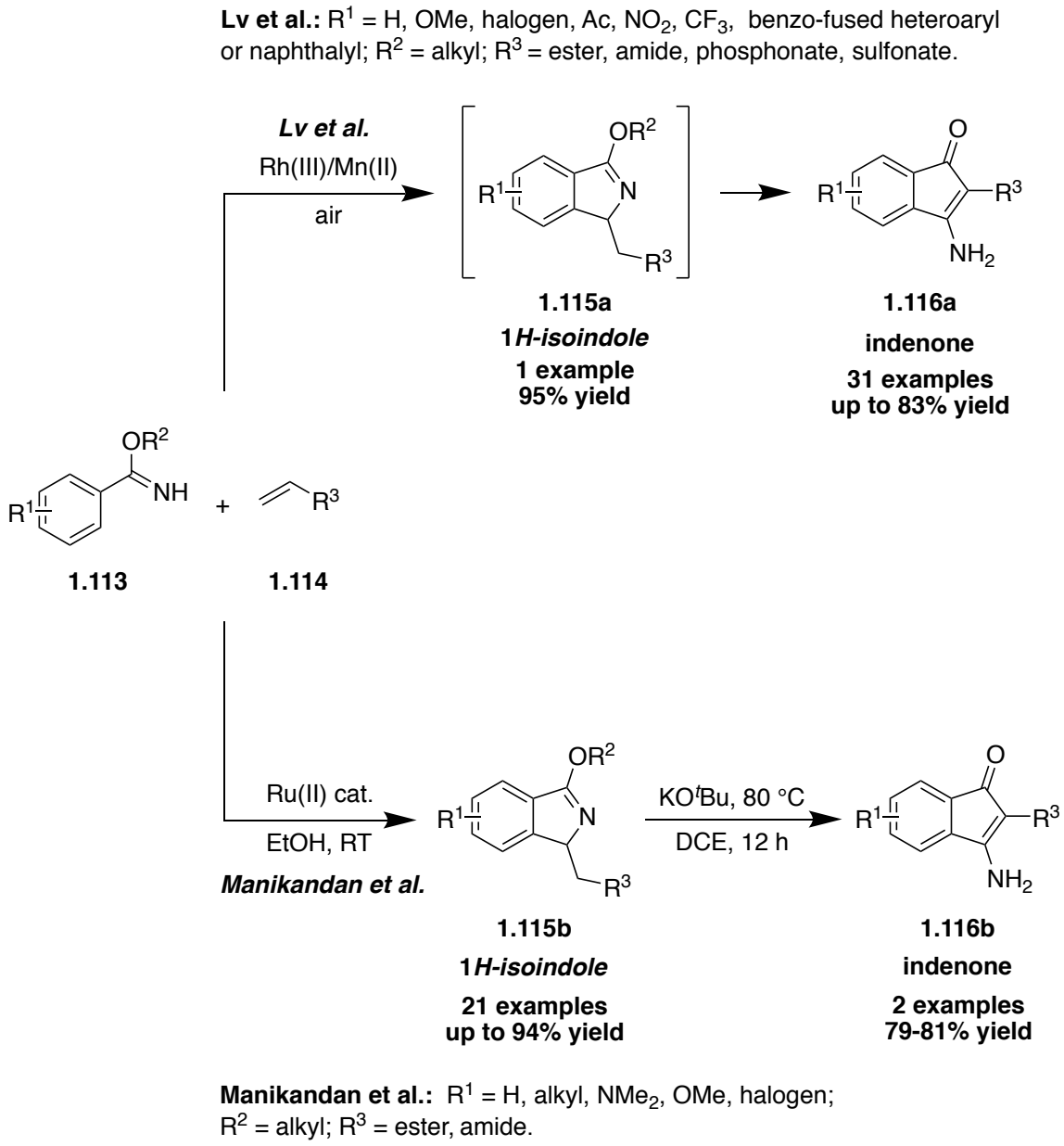
Scheme 1.26. Rh(III)-catalyzed C–H activation/*ortho*-vinylation approaches for the synthesis of substituted 1*H*-isoindoles with a quaternary center.

Yi et al. also prepared similar 1,3,3-trisubstituted 1*H*-isoindoles via two reactions with substituted acrylate alkene reacting partners, both of which were catalyzed by $[RhCp^*Cl_2]_2$ in the

presence of copper (II) acetate monohydrate (Scheme 1.26, *supra*).[77] The first reaction started from aryl ketones and also required ammonium acetate. The yields were moderate-to-excellent, and the substrate scope was broad. For the aryl ketone, electron-donating and electron-withdrawing groups were well-tolerated at R^1, although the presence of an electron-withdrawing group reduced the yield. Substitution with an electron-donating group at the *ortho* and *para* positions gave good yields, but substitution at the *meta* position gave only moderate-to-good yields and regioisomeric mixtures. The strongly electron-donating hydroxy and methoxy groups produced slightly more of the 4-substituted 1*H*-isoindole product than the 6-substituted 1*H*-isoindole product, whereas the more weakly electron-donating acetamide and methyl groups produced little-to-none of the 4-substituted 1*H*-isoindole product. Excellent yields were obtained with a phenyl group at R^2, whereas alkyl groups gave only moderate yields, except for the cyclic arylketone α-tetralone, which gave a good yield. Several alkyl ester reacting partners were screened, all of which were well-tolerated. In the second reaction, the products (**1.110**) were prepared from α-substituted benzylamines (**1.111**) in moderate-to-good yields. Ammonium acetate was not required, but additional equivalents of the copper salt and the alkene reacting partner were needed. The investigation of the substrate scope for this reaction was much narrower, as it was intended only to complement the reaction of aryl ketones. At the R^1-position, only para substitution with a methoxy group was investigated, which reduced the yield. All the same substitutions for the R^2-position were investigated, except for α-tetralone, and all were tolerated, with the phenyl group giving the best yield. Ethyl acrylate was the only alkene reacting partner used in this reaction.

In 2017, Lv et al. reported a rhodium-catalyzed C–H activation and multistep cascade reaction of benzimidates and alkenes (Scheme 1.27).[78] While the purpose of this method is to

prepare indenones, it appears that with shorter reaction times, it may possible to isolate the 1*H*-isoindole intermediates (**1.115a**) in high yields, as the authors reported a 95% yield of the 1*H*-isoindole for their model system after a 3 h reaction time and an 85% yield of the indenone after 24 h. Additionally, when acrylonitrile (R^3 = CN) was used as the alkene reacting partner, only the 1*H*-isoindole was isolated in a 65% yield. The substrate scope will be discussed *infra* in Section 1.17.



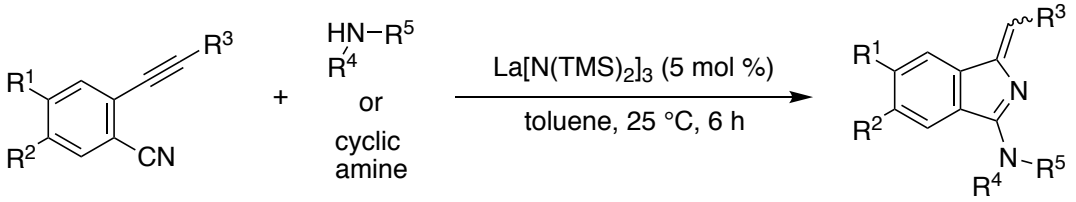
Scheme 1.27. Formation of isoindoles and indenones from benzimidates and alkenes.

The Ru(II)-catalyzed approach used by Manikandan et al.[79] to prepare 1*H*-isoindoles from benzimidates in 2017 is almost functionally identical to the Rh(III)-catalyzed approach reported by Lv et al.[78] in the same year, described *supra* in Section 1.8 (Scheme 1.27). There are

a few key differences, however. Most notably, the approach of Manikandan et al.[79] was optimized to stop at the 1*H*-isoindole product, while the approach of Lv et al.[78] went through a 1*H*-isoindole intermediate (**1.115b**) that could potentially be isolated after a few hours but was optimized to proceed to the indenone product (**1.116b**). Additionally, the approach of Manikandan et al. uses a green solvent, is catalyzed by a different metal, and does not require air or oxygen, as an oxygen source is only needed to convert the 1*H*-isoindole to the isoindolinone or indenone.[79] Given that Lv et al.[78] only isolated the 1*H*-isoindole for one example, it is hard to directly compare the yields of these two reactions; however, the yield reported by Lv et al. is comparable to the yields reported by Manikandan et al.[79], although the yields reported by Manikandan et al. for identical substrates seemed to be slightly lower. For the benzimidate reacting partner, the substrate scope was investigated for the aryl ring and alkoxy groups. For the aryl ring, the presence of a strongly electron-donating alkoxy or tertiary amino group slightly improved the yield and trisubstitution with an alkoxy group gave very good yields. Conversely, substitution with a methyl group did not significantly affect the outcome. Substitution with a halogen was also tolerated, but slightly reduced the yield. The effect of substitution with an electron-withdrawing group was not investigated. The position of the substituent did not significantly affect the outcome of the reaction. For the alkoxy group, methoxy, ethoxy, and isopropoxy groups were all well-tolerated. For the alkene reacting partner, the more strongly electron-withdrawing vinyl esters gave better yields than acrylamide, which gave only a 21% yield, and styrene, which did not cyclize. Various vinyl esters were investigated, and it was found that *n*-alkyl, phenyl, and benzyl esters all gave good yields, and the cyclohexyl ester gave an excellent yield. However, having a bulky *tert*-butyl group on the vinyl ester significantly

reduced the yield, and using 2-phenoxyethyl acrylate as the alkene partner also gave only moderate yields.

In 2018, Ye at al. reported an efficient and atom-economical lanthanum-catalyzed intermolecular hydroamination of 2-alkynylbenzonitriles with secondary amines, which was used to provide 1-amino-1*H*-isoindoles in moderate-to-excellent yields (Scheme 1.28).[80] The substrate scope was reasonably broad. For the 2-(phenylethynyl)benzonitrile substrate, the authors looked at the effects of substitution at three positions. Substrates bearing *para*-substituted electron-rich and electron-poor aryl moieties on the alkyne at R^3 all gave the desired products in good-to-excellent yields, whereas a cyclopropyl group gave only moderate yields and a 2-pyridyl group gave only trace yield. A terminal alkyne (R^3 = H) was found to be incompatible with the reaction conditions, which was attributed to competing deprotonation of the terminal alkyne and the amine by the bis(trimethylsilyl)amido anion and subsequent coordination to the La^{3+} ion. It was found that the presence of either an electron-donating or an electron-withdrawing group on the aryl ring at R^1 decreased the yield somewhat, as did the presence of a moderately electronegative chlorine atom at R^2. For the amine reacting partner, except for the sterically hindered diisopropylethylamine, which did not react, all cyclic and acyclic secondary amines investigated gave the aminoisoindole product in good-to-excellent yields. However, benzylamine gave only trace yield, leading the authors to conclude that primary amines are incompatible with the reaction conditions. Unlike the reaction reported by Yao et al.[81], which will be discussed *infra* in Section 1.9, this reaction is not exclusively selective for one alkene isomer. While high or exclusive *Z*- or *E*-selectivities were observed for certain combinations of substrates, the *Z*/*E* isomeric ratios varied substantially, and both kinetics and thermodynamics were found to be at work.



1.117 **1.118** **1.119**

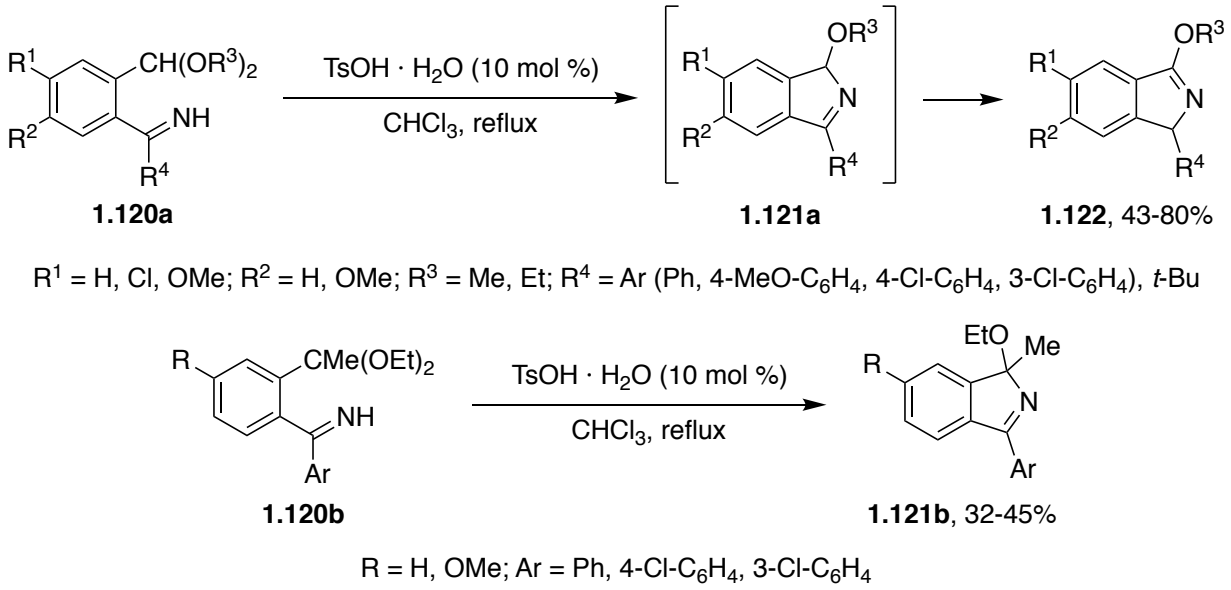
R^1 = H, Me, OMe, CF_3; R^2 = H, Cl; R^3 = Ar (Ph, *p*-OMe-Ph, *p*-Me-Ph, *p*-Br-Ph, *p*-CF_3-Ph), cyclopropyl; R^4 = Bn, Ph, Ar; R^5 = Me; cyclic amine = pyrrolidine, morpholine, 1,3-dihydroindole

Scheme 1.28. Lanthanum-catalyzed hydroamination of 2-alkynylbenzonitriles with secondary amines.

1.9 Transition Metal-Free Synthesis of 1*H*-Isoindoles.

In 2015, Kuroda and Kobayashi reported a procedure wherein 1*H*-isoindoles were prepared from [2-(dialkoxymethyl)phenyl]methanimines (**1.120**) in the presence of a catalytic amount of aqueous TsOH in refluxing $CHCl_3$ (Scheme 1.29).[82] In the proposed mechanism, substitution of one of the alkoxy groups by the imino nitrogen resulted in cyclization to form the strained 3-substituted 1-alkoxy-1*H*-isoindole **1.121**. For the acetal substrates (**1.120a**), this intermediate subsequently underwent double-bond migration to form the less strained 1-substituted 3-alkoxy-1*H*-isoindole **1.122** in fair-to-good yields. For the ketal substrates (**1.120b**), double-bond migration of the 3-substituted 1-alkoxy-1*H*-isoindole (**1.121b**) to relieve strain was not possible due to the lack of a proton at the 1-position. The authors ascribed the comparatively lower yields for these substrates to this fact and to the resulting increase in lability to the reaction conditions. Reactions leading to products containing electron-donating substituents on the 1*H*-

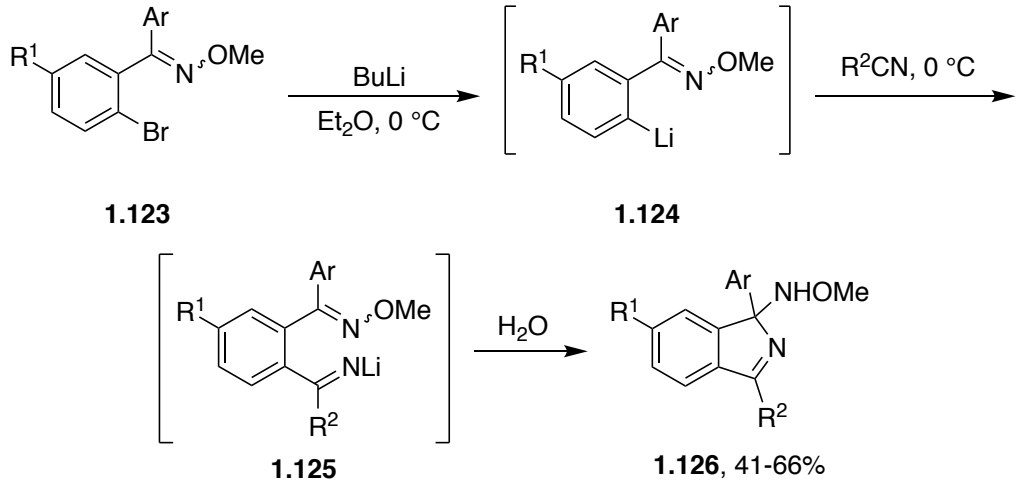
isoindole benzenoid ring and electron-withdrawing substituents on the 1-aryl ring reportedly proceeded more smoothly; however, the electronics at these positions did not noticeably affect the yields. However, owing to their greater lability under acidic conditions, lower yields were observed for the 1-methoxy products than the 1-ethoxy products. To address this issue, the authors proposed using a weaker acid catalyst in place of TsOH, such as camphor sulfonic acid.



Scheme 1.29. Acid-catalyzed synthesis of 1*H*-isoindole derivatives from [2-(dialkoxymethyl)phenyl]methanimines.

The procedure reported by Kuroda and Kobayashi was similar to a reaction that was previously reported by Kobayashi et al. in 2014, in which cyclization to form a 1*H*-isoindole (**1.126**) occurred when the nitrogen of the imido anion of *in situ*-generated intermediate **1.125**

attacked the *O*-methyloxime carbon (Scheme 1.30).[83] The preceding intermediate (**1.124**) was also formed in situ via lithium-halogen exchange and subsequent attack of the arylithium on a nitrile lead to the imido anion. Yields ranged from 41% to 66% and were similar for most of the substrates, regardless of the electronics of the aromatic rings, in cases where the aromatic rings were all phenyl derivatives. Having an isopropyl group instead of a phenyl derivative at R^2 also did not affect the yield. However, yields were slightly lower for reactions of substrates with a thiophen-2-yl group at the *O*-methyloxime carbon. Additionally, while the presence of one α-hydrogen on the nitrile was tolerated with no effect on the yield, nitriles containing two α-hydrogens led to complex mixtures, presumably due to deprotonation by the organolithium species.



1.123 **1.124**

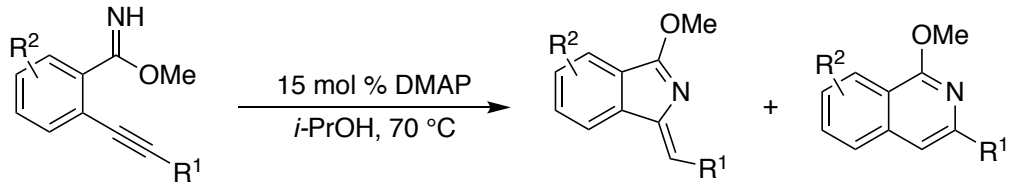
1.125 **1.126**, 41-66%

R^1 = H, Cl, OMe; R^2 = Ar (Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4), *i*-Pr; Ar = Ph, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 2-thiophenyl

Scheme 1.30. Synthesis of novel 1*H*-isoindole derivatives from reaction of aryl(2-lithiophenyl)methanone *O*-methyloximes with nitriles.

In 2019, Yao et al. reported a transition metal-free and highly (*Z*)-stereoselective synthesis of 3-methoxy-1-methyleneisoindoles in moderate-to-good yields from 2-alkynylbenzimidates via a DMAP-catalyzed cyclization under mild conditions (Scheme 1.31).[81] In the reported mechanism for this reaction (Scheme 1.32), DMAP deprotonates the benzimidate N–H to form anion **1.130**. From here, the anion can attack either the proximal alkyne carbon to effect a 5-exo-dig cyclization (path a) or the distal alkyne carbon to effect a 6-endo-dig cyclization (path b). The resulting carbanions **1.131** and **1.132** are then protonated by $DMAPH^+$ to give products **1.128** and **1.129**, respectively. The 5-exo pathway gives the isoindole product (**1.128**), whereas the 6-endo pathway gives the isoquinoline product (**1.129**). The 5-exo pathway was favored for all aryl-substituted alkyne substrates, whereas the 6-endo pathway was favored for alkenyl- and alkyl-substituted alkynes. Since the isoindole (5-exo) products were desired, the authors focused their investigations primarily on alkynes bearing aryl substituents, as those tended to favor the preferred pathway. Both electron-withdrawing and electron-donating groups on the alkyne phenyl ring (R^1) were mostly tolerated. The presence of strongly electron-withdrawing groups slightly reduced the yields relative to the unsubstituted phenyl group but gave only the desired product. Unlike with similar reactions that are transition-metal catalyzed, steric hindrance at the *ortho* position also disfavored the 6-endo pathway. The more strongly electron-donating methoxy group led to an incomplete reaction with a low yield and a comparatively large amount of the minor product. The authors hypothesized that this is due to the carbon–carbon triple bond not being sufficiently polarized due to the presence of a strongly electron-donating group on the terminal aryl group. Many substitutions of the benzimidate aromatic ring (R^2) were also well-tolerated, including halide, alkyl, methoxy, and trifluoromethoxy groups. As with substitution of the alkyne benzene ring, the presence of an

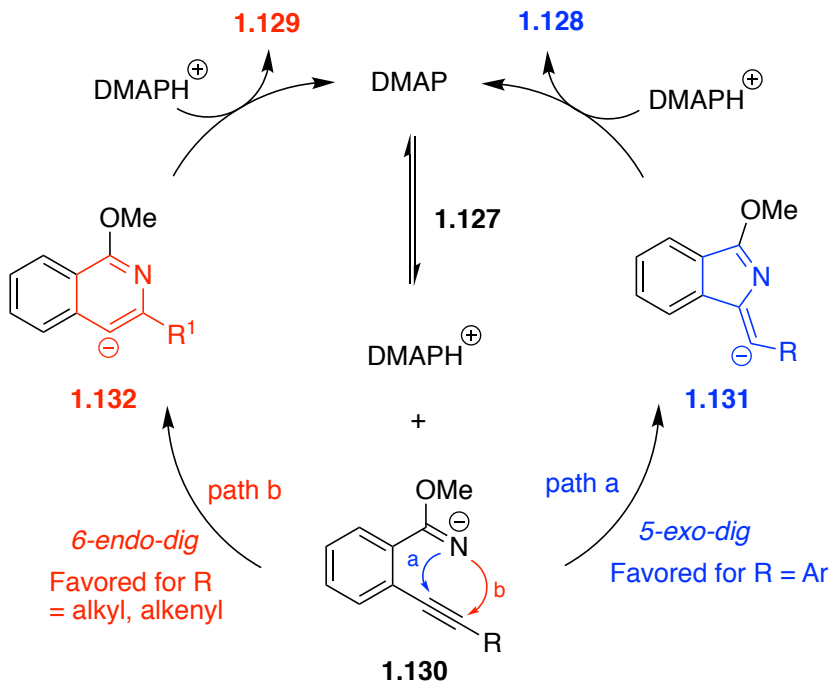
electron-donating group on the benzimidate ring caused the isoquinoline minor products to form in amounts that generally appeared to increase as the electron-donating strength of the group and the number of such groups increased. The positions of the substituents did not materially affect the yields, but substitution at the 6-position improved the selectivity for the desired product.



1.127 **1.128** ***major*** ***Z isomer only*** **1.129** ***minor***

R^1 = Ph, 4-CO_2Et-C_6H_4, 2-CO_2Me-C_6H_4, 4-CF_3-C_6H_4, 4-CN-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, 2-Me-C_6H_4, 2-*i*-Pr-C_6H_4; R^2 = H, 6-F, 5-Me, 4,5-$(OMe)_2$, 5,6-$(OMe)_2$

Scheme 1.31. Synthesis of 3-methoxy-1-methyleneisoindoles from 2-alkynylbenzimidates.

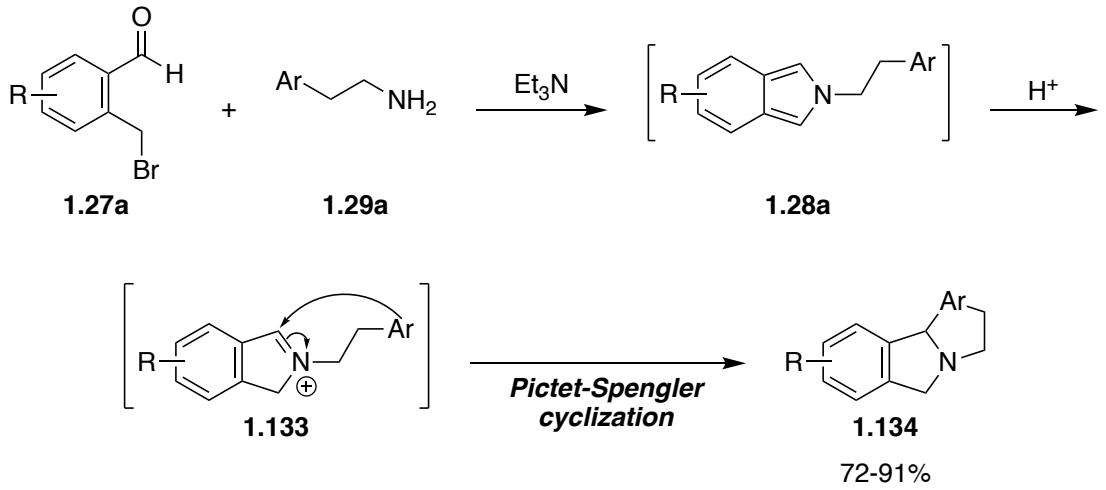


Scheme 1.32. Mechanism for DMAP-catalyzed cyclization of 2-alkynylbenzimidates.

1.10 Reactions of 2*H*-Isoindoles: Cyclization Reactions.

The one-pot synthesis of polycyclic isoindolines reported by this research group, which was introduced *supra* in Section 1.2, employed an isoindole umpolung strategy in which the nucleophilic *in situ*-formed isoindoles (**1.28a**) were protonated by TFA to convert them to the electrophilic isoindolium species (**1.133a**) that subsequently underwent Pictet-Spengler-type cyclizations with the β-arylethylamine moieties to give polycyclic isoindolines (**1.134**) in good yields (Scheme 1.33).[7] In the model reaction with 2-(bromomethyl)benzaldehyde, tryptamine was used as the β-arylethylamine reacting partner, as tryptamines are popular Pictet-Spengler substrates. Electron-rich and electron-poor tryptamines were well-tolerated, and only the latter reduced the yield, as they were worse nucleophiles in the Pictet-Spengler cyclization. *N*-

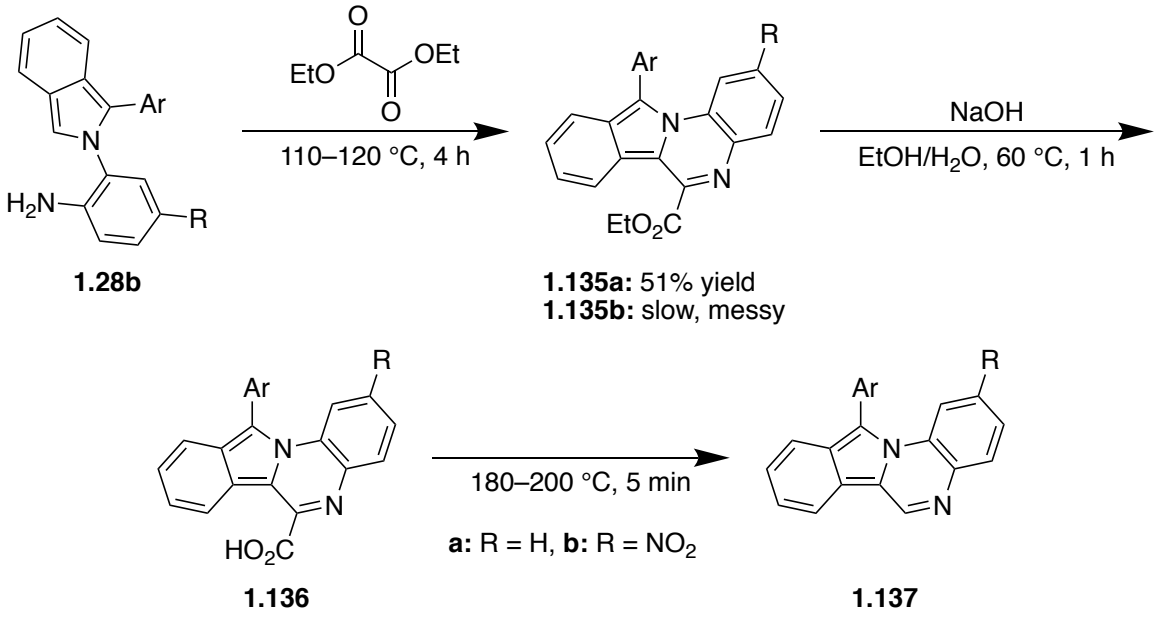
methyltryptamine also gave a high yield. Several other indole-derived β-arylethylamines were investigated, but only 4-(aminomethyl)indole cyclized. This substrate gave a product with a strained geometry in a yield that was slightly lower than that obtained with most of the tryptamines. An N-linked pyrrole aryl group also gave the same high yield as tryptamine. Isoindoles prepared from various substituted phenylethylamines, however, did not cyclize. Substitution of the aldehyde reacting partner with a halogen was well-tolerated but gave regioisomeric mixtures. Similar yields were obtained using *ortho*- vs *meta*-substituted aldehydes; however, for the latter, the regioisomers could not be separated. While the substrate scope has some limitations, this work provides the first known example in which isoindoles are used as electrophiles, thus paving the way for the development of additional methods that employ an isoindole umpolung strategy. Additionally, this work extends the scope of the Pictet-Spengler reaction to include isoindolium electrophiles.



R = H, Cl, F; Ar = tryptamine derivatives, indole derivatives, 1-pyrrole
Conditions: Et_3N, DCM or DCE, 23 °C, 2 h, then TFA, -40 °C → 23 °C or 60 °C, 16 h.

Scheme 1.33. One-pot synthesis of polycyclic isoindolines using isoindole umpolung.

As part of the work by Sypchenko et al., which was introduced *supra* in Section 1.2, the *N*-(2-aminophenyl)isoindoles prepared by the authors were used to investigated multiple reactions, many of which are either variations of published reactions or did not directly involve the isoindole ring.[55] However, the reaction of *N*-(2-aminophenyl)isoindole **1.28b** with diethyloxalate to give the 6-ethoxycarbonyl cyclization product (**1.135**) does not appear to have been published prior to this work (Scheme 1.34). The scope for this reaction is unclear, but it was found to be too slow and messy in the presence of a nitro group on the *N*-(2-aminophenyl) ring. However, since a moderate yield of 51% was obtained for **1.135a**, this reaction may have potential synthetic utility. The authors also demonstrated that the ester can be removed by subsequently hydrolyzing **1.135a** to the acid (**1.136**), which was then subjected to decarboxylation to give **1.137**.

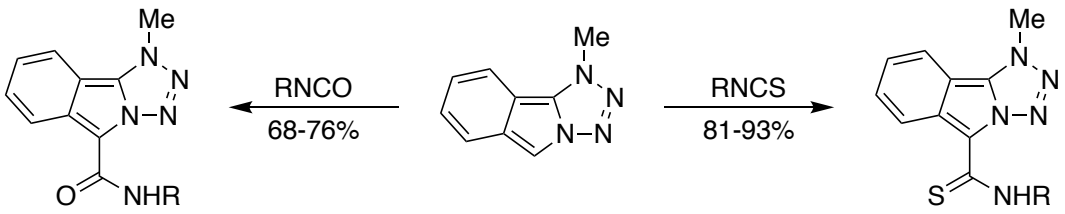


Scheme 1.34. Reaction of *N*-(2-aminophenyl)isoindoles with diethyloxalate and subsequent decarboxylation.

1.11 Reactions of 2*H*-Isoindoles: Reactions with Electrophiles.

In an expanded and optimized procedure analogous to an earlier procedure for the installation of a thioamide at the α-position using an isothiocyanate, Yegorova et al. prepared 1-methyltetrazolo[5,1-*a*]isoindole-derived amides by reacting a fused isoindole (**1.138**) with an isocyanate electrophile to install an amide at the unsubstituted α-position (**1.139**, Scheme 1.35).[84] The thioamides (**1.140**) were also prepared using the optimized procedure. X-ray diffraction studies were conducted on both the amides and thioamides to determine their bond lengths, so

that molecular modeling could then be used to investigate the suitability of these isoindole derivatives as Diels-Alder dienes.

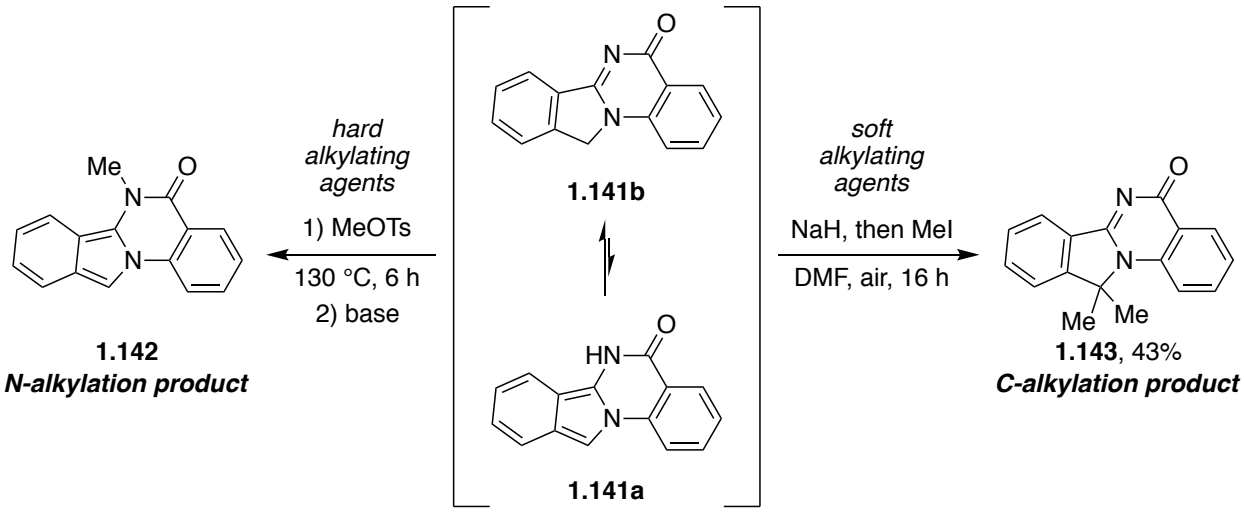


1.139 **1.138** **1.140**

Amides: R = 3-OMe-C_6H_4, 3,5-$(OMe)_2$-C_6H_4, CH_2Ar (Ar = 4-F-C_6H_4, 2-thiophenyl), cyclohexyl.
Thioamides: R = Me, *t*-Bu, cyclohexyl, Ph, Bn, 4-OEt-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 3-CF_3-C_6H_4.

Scheme 1.35. Synthesis of 1-methyltetrazolo[5,1-*a*]isoindole-derived amides and thioamides.

In 2014, Baglai et al. demonstrated that for *C*,*N*-annelated isoindoles, it is possible to control the reaction conditions to preferentially effect alkylation of the isoindole ring over external nitrogen atoms (Scheme 1.36).[85] The authors reported that while the use of the hard alkylating agent methyl tosylate at higher temperatures promoted *N*-alkylation (**1.142**), the initial use of the base NaH and subsequent addition of the soft alkylating agent methyl iodide at room temperature favored *C*-alkylation, giving the *C*,*C*-dimethylated iminoisoindole product (**1.143**) as the major product. Since only the *N*-methylated product was previously observed for these substrates, this discovery expands the potential for the development of new structures and new preparative schemes.



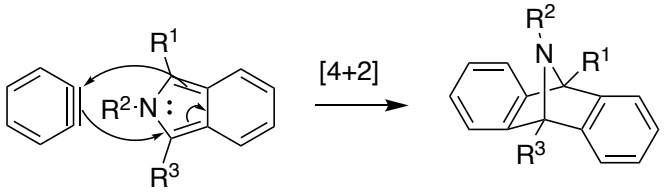
Scheme 1.36. Alkylation of *C*,*N*-annelated isoindoles under soft versus hard conditions.

1.12 Reactions of 2*H*-Isoindoles: Cycloaddition Reactions.

As mentioned *supra* in Section 1.1, cycloaddition reactions of isoindoles are extremely common and have been known in the literature for quite some time, with [4+2]-cycloadditions being the most common. Much of the recent novel cycloaddition chemistry of isoindoles incorporates the Diels-Alder reaction into cascade reactions, as the [4+2]-cycloadditions of isoindoles, themselves, are not novel. Additionally, because the Diels-Alder reaction of isoindoles is so well-established, it is commonly used as a means of trapping and confirming the formation of unstable isoindoles, as was done by Ding et al.[61] and Ito et al.[65], or to establish the compatibility of a method for the formation of isoindoles with subsequent reactions, as was done by Zhang et al.[56]

The isoindole intermediates formed *in situ* in the cascade of cycloaddition and cycloreversion reactions reported by Fang et al., which was described *supra*, subsequently

underwent a [4+2] cycloaddition with a second equivalent of the aryne to give benzanthracenimines in mostly high yields (Scheme 1.37).[63] The authors investigated the scope of the reaction and found it to be tolerant to substitutions on both the münchnone and the aryne reacting partners (Scheme 1.16, *supra*). Where the R^1 substituent on the münchnone was a phenyl derivative, its substitution did not have a large effect on the yield, although the presence of a halogen slightly reduced the yield. However, a significantly lower yield was observed where R^1 was a heteroaryl thiophen-2-yl group. The strength of the electron-withdrawing group at R^3 seemed to have a much greater effect on the yield, as no desired product was obtained with a strongly electron-withdrawing trifluoroacetyl group at this position, yet high yields were obtained with the less strongly electron-withdrawing acetyl and butyryl groups. The authors also looked at the effect of disubstitution of the aryne substituent with electron-donating groups at R^5 and carbon Y. Where there were methyl groups at these positions, the yields did not differ materially from those obtained with the unsubstituted benzyne; however, the presence of two more strongly electron-donating methoxy groups reduced the yield.



1.70a **1.71a** **1.72a**

Scheme 1.37. Formation of benzanthracenimines via [4+2]-cycloaddition of isoindoles with arynes.

Conversely, while Lopchuk and Gribble predominately sought to have their similar reaction stop at the isoindole, they also optimized the aryne formation conditions to give the benzanthracenimine exclusively.[64] Unsurprisingly, the conditions they reported for obtaining the benzanthracenimine product were strikingly similar to those reported by Fang et al.[63]

In the visible-light induced isoindole formation reported by Lin et al., described *supra*, the isoindoles (**1.55**) generated in situ subsequently served as Diels-Alder dienes (Scheme 1.12, *supra*). Dimethyl acetylenedicarboxylate (DMAD, **1.47a**) and *N*-methyl (**1.47d**), *N*-phenyl (**1.47b**), and *N*-benzyl (**1.47c**) maleimides were employed as dienophiles, all of which gave the corresponding cycloadducts (**1.56a-d**) in good yields. The selectivity was only discussed for maleimide dienophiles, which gave perfect endo-selectivity. The authors found that the scope of this reaction was limited to *N*-arylisoindolines. A slightly lower yield was obtained with an *N*-(1-napthyl) substituent relative to the *N*-phenyl substituent. Both electron-donating and electron-withdrawing substituents on the *N*-phenyl ring were well-tolerated. Good yields were also obtained in the presence of chlorine, methyl, and methoxy substituents on the isoindoline benzene ring; however, the presence of a nitro group gave a much lower yield. This reaction worked comparably well on a gram scale.

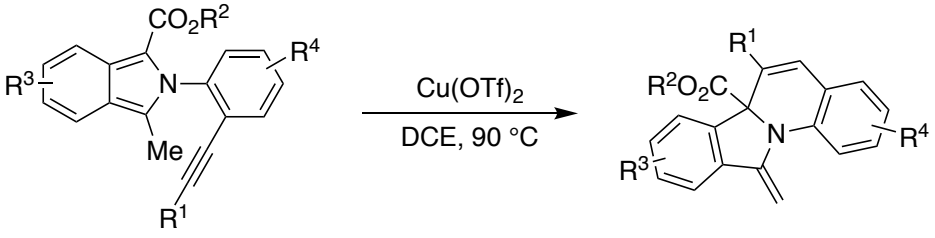
The cycloaddition-based formal C–H alkynylation of isoindoles reported by Ohmura et al. in 2013,[86] which will be discussed *infra* in Section 1.14, also features a [4+2] cycloaddition of isoindoles. The isoindole that forms as an intermediate in the [1,5]-hydride shift/Diels-Alder reaction sequence reported by Zhen et al., which was introduced *supra* in Section 1.3, also includes a [4+2] cycloaddition.[59] While this was the first report of a Diels-Alder reaction of *N*-substituted isoindoles bearing a moiety that forms a quinone-methide ring, what is interesting

about the reaction is not the cycloaddition itself, but the rearrangements that can occur before and after the cycloaddition. Therefore, the cycloaddition reaction of the isoindole intermediate and subsequent rearrangement in the presence of PTSA will be discussed *infra* in Section 1.15.

1.13 Reactions of 2*H*-Isoindoles: Transition Metal-Catalyzed Coupling Reactions.

Yao et al. reported an efficient copper-catalyzed chemo-divergent tandem reaction of *N*-(*ortho*-alkynyl)aryl-pyrroles and isoindoles in 2020, which delivers ring-fused *N*-heterocycles in an atom-economical manner.[87] This review will focus solely on the reaction of *N*-(*ortho*-alkynyl)aryl-2*H*-isoindole-1-carboxylate substrates (**1.144**), which provided ring-fused isoindoline derivatives in good yields (Scheme 1.38). The proposed mechanism for this reaction features a copper-mediated dearomative cyclization of **1.144** to give intermediate **1.146a**, for which resonance structure **1.146b** can also be drawn, which restores aromaticity to the benzenoid ring (Scheme 1.39). Deprotonation of the methyl group adjacent to the tertiary carbocation in **1.146b** gives alkene intermediate **1.147**, which is subsequently protonated to give isoindoline product **1.145**. The substrate scope was not as thoroughly investigated for the isoindole substrates as it was for the pyrrole substrates; however, fifteen examples are provided, and substitutions were investigated at all four positions. At the R^1-position, substitution with an aryl ring was well-tolerated and the outcomes for electron-rich aryl rings bearing a methyl, ethyl, or methoxy group were similar to those observed for an unsubstituted ring and more electron-poor aryl rings bearing a fluorine, chlorine, and bromine. Substitutions at the *para* and *meta* positions gave similar results, but *ortho* substitution reduced the yield. Substitution with a butyl group instead of an aryl ring at the R^1-position slightly improved the yield. For ease of preparation of the starting materials, only isoindole substrates bearing esters at C1 were investigated. Three

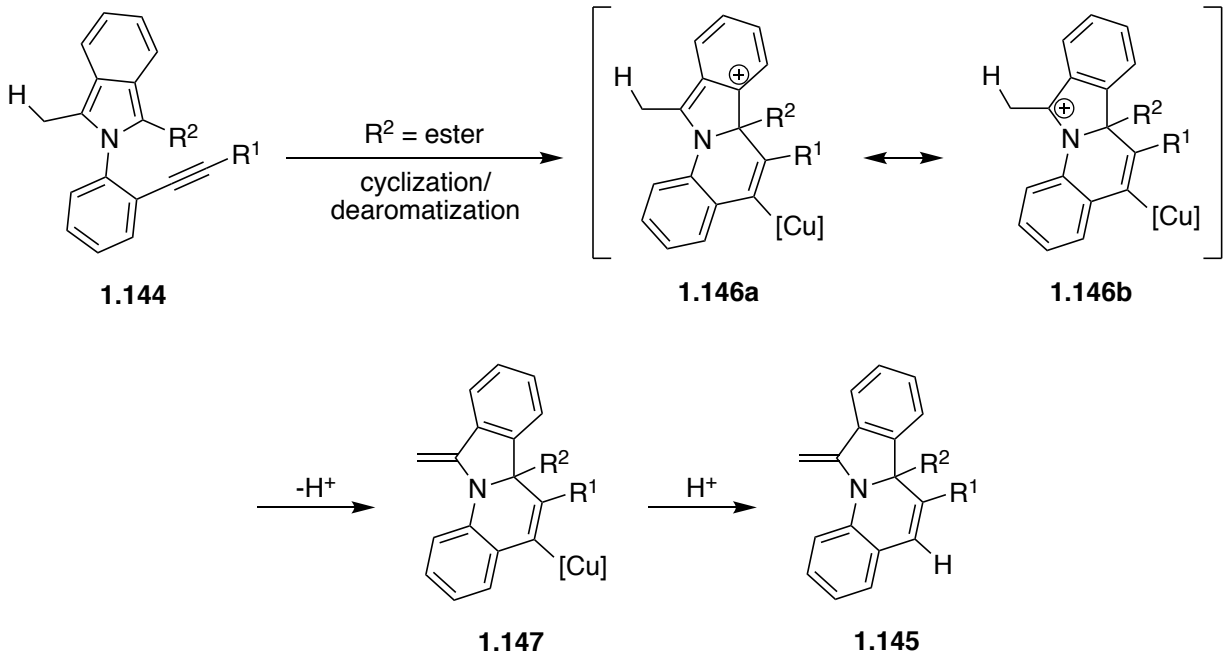
different ester groups were investigated, and it was found that methyl esters gave significantly higher yields than ethyl and isopropyl esters. Only methyl substitution was investigated at the R^3- and R^4-positions, and it was found that it reduced the yield at R^3 but gave a similar yield to the unsubstituted substrate at R^4.



1.144 **1.145**, 67-88%

R^1 = Ar, *n*-Bu; R^2 = alkyl; R^3 = H, Me, Cl; R^4 = H, Me

Scheme 1.38. Copper-catalyzed cyclization of *N*-(*ortho*-alkynyl)aryl-2*H*-isoindoles.

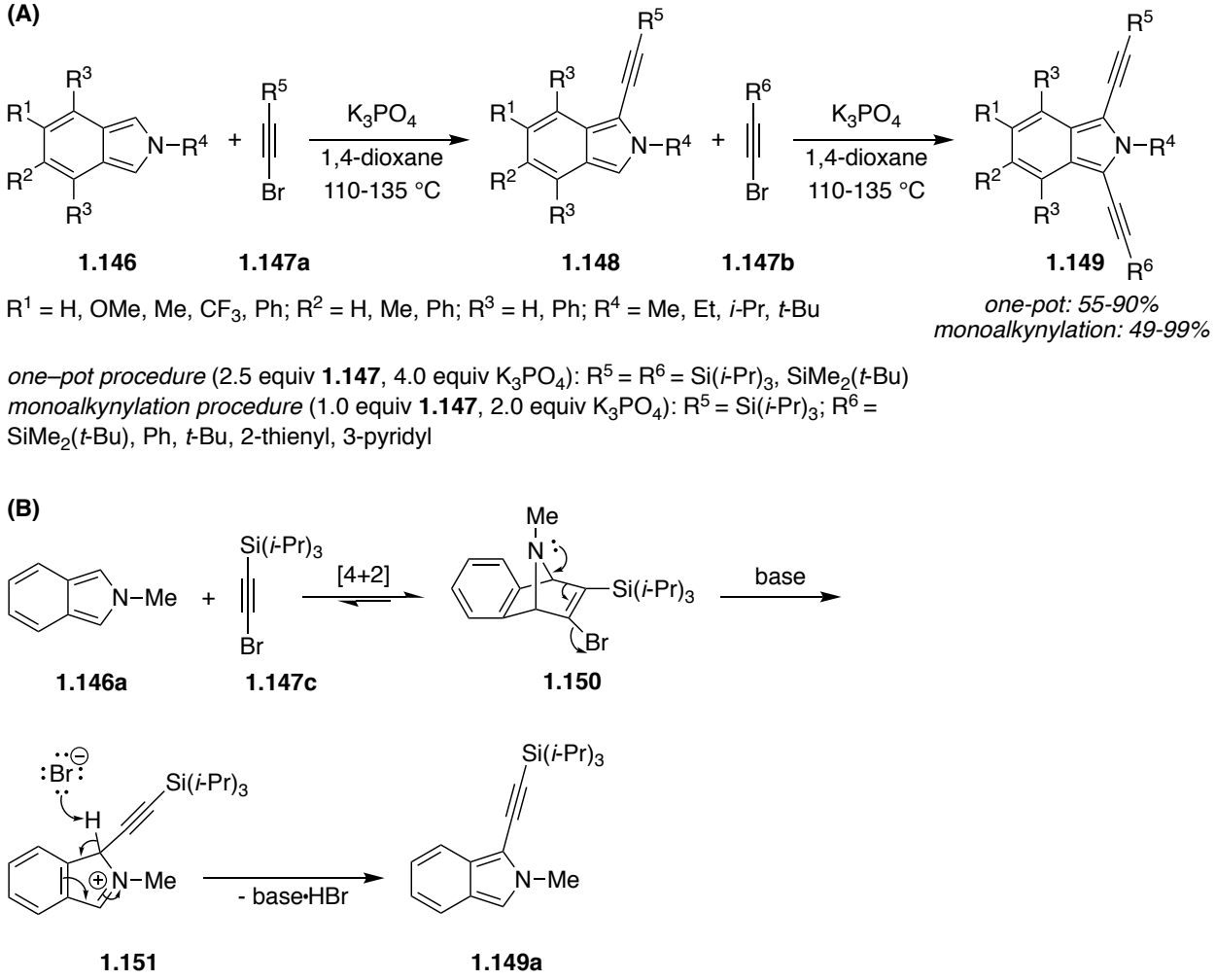


Scheme 1.39. Mechanism for copper-catalyzed cyclization of *N*-(*ortho*-alkynyl)aryl-2*H*-isoindoles.

1.14 Reactions of 2*H*-Isoindoles: Metal-Free Coupling Reactions.

In 2013, Ohmura et al. reported a transition metal-free C–H alkynylation of isoindoles (**1.146**) using (bromoethynyl)triisopropylsilane (**1.147**) in the presence of potassium phosphate, which afforded 1,3-bis(triisopropylsilylethynyl)isoindoles (**1.149**) in high yields (Scheme 1.40A).[86] The reported mechanism proceeded via a [4+2] cycloaddition between the isoindole (**1.146a**) and the 1-bromoalkyne substrate (**1.147c**) to give cycloadduct **1.150**, which subsequently underwent a ring-opening reaction to give intermediate **1.151**, which was then converted back to the isoindole to form **1.149a** with concomitant formation of base hydrobromide salt (Scheme 1.40B). The scope of the synthesis of symmetrical 1,3-

dialkynylisoindoles was limited to 1-bromoalkyne substrates bearing a silyl group at the other end. However, phenyl-, *tert*-butyl-, 2-thienyl-, and 3-pyridyl-substituted bromoalkynes successfully reacted with monoalkynylated isoindoles (**1.148**) bearing a trialkylsilylethynyl group to give nonsymmetrical isoindoles (**1.149**, $R^5 \neq R^6$) in yields of 49-79%. Additionally, 1,4-bis(bromoethynyl)benzene reacted successfully with monoalkynylated isoindole **1.148** to give a phenylene-linked dimer in a 73% yield. However, yields were highest for bis(trialkylsilylethynyl) isoindoles, ranging from 84-85% for one-pot bis-alkynylations and 81-99% for alkynlation of monoalkynylated isoindoles. To overcome this limitation, the authors demonstrated that desilylative derivatizations can be accomplished with excellent yields. Substitutions of the isoindole benzenoid ring and nitrogen were generally well-tolerated, including some sterically hindered substitutions, with yields ranging from 55-88% and 71-90%, respectively.

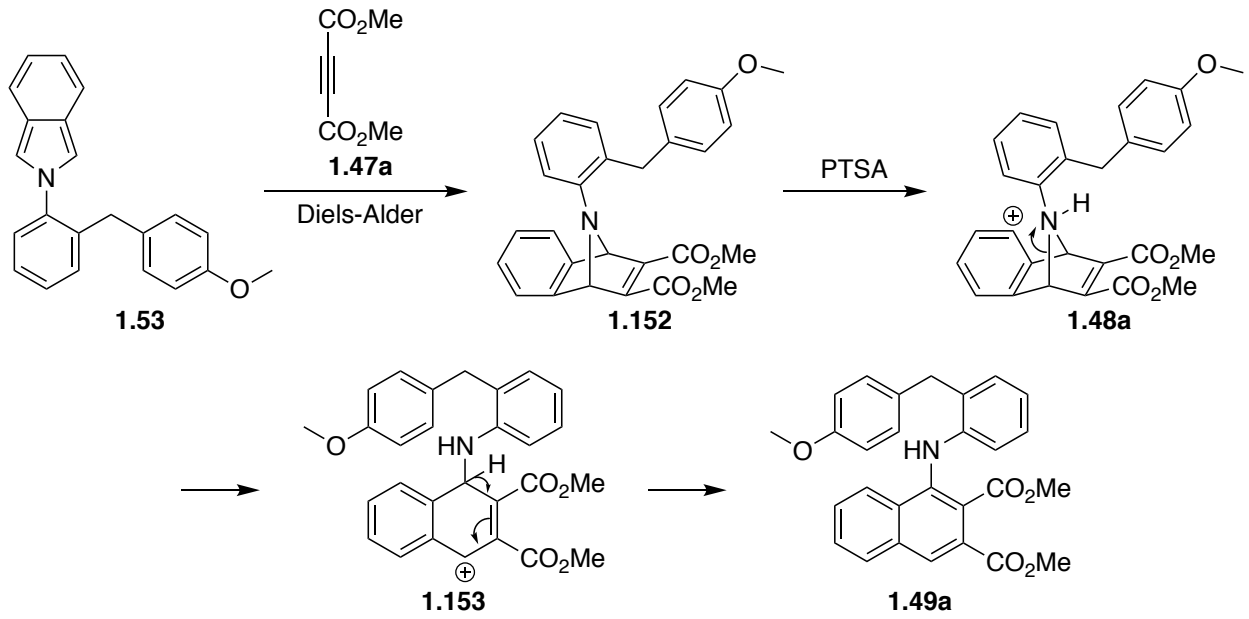


Scheme 1.40. (A) Scheme and (B) mechanism for transition metal-free C–H alkynylation of isoindoles using (bromoethynyl)trialkylsilanes.

1.15 Reactions of 2*H*-Isoindoles: Acid-Promoted Rearrangements.

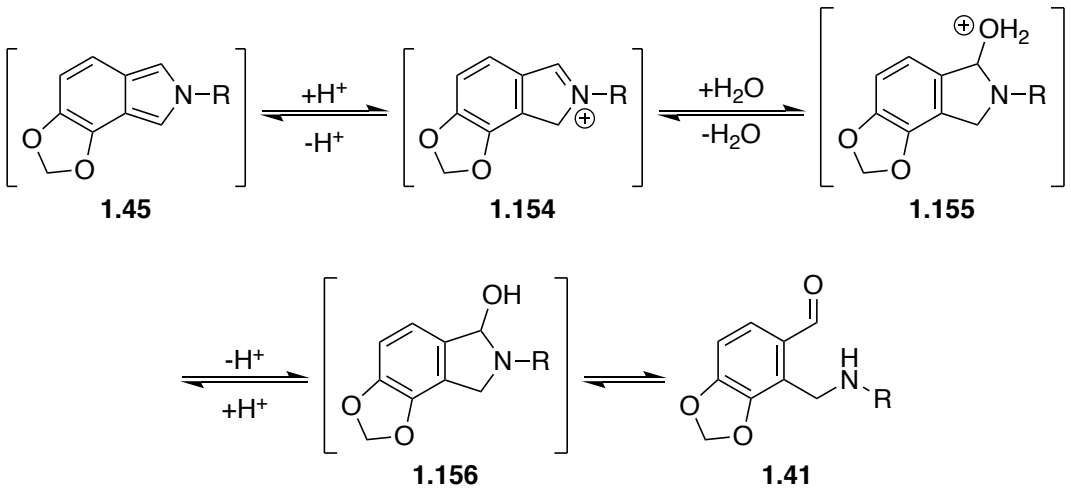
The isoindole intermediate (**1.53**) formed in the acid-promoted [1,5]-hydride shift pathway reported by Zhen et al. in 2017, discussed *supra*, undergoes a Diels-Alder reaction with a dienophile (**1.47**) to form cycloadduct **1.48a-d** (Scheme 1.10, *supra*).[59] When DPP is employed

as the acid catalyst, this bridged-ring heterocycle is the final product. However, when the much stronger acid PTSA is used, cycloadduct **1.48a** is protonated (**1.152**) and subsequently isomerizes (**1.153**) to form a benzenoid ring, leading to polycyclic product **1.49a** (Scheme 1.41). For the DPP- and PTSA-catalyzed pathways, both electron-donating and electron-withdrawing substituents were tolerated on the *N*-benzyl, quinone methide, and isoindolinine rings of **1.46**, giving yields of 45-94% for bridged-ring heterocycle **1.48** and 37-84% for polycycle **1.49** (Scheme 1.10, *supra*). In the absence of any substituents on **1.46**, only modest yields were obtained for both products. In addition to DMAD, *N*-phenylmaleimide (**1.47b**) and *N*-benzylmaleimide (**1.47c**) were also investigated as dienophiles for the DPP-catalyzed pathway and gave good yields. When both reactions were run on a gram scale, the yields remained high, indicating that both pathways are scalable.



Scheme 1.41. Mechanism for formation of cycloadduct from isoindole intermediate and subsequent PTSA-catalyzed rearrangement in [1,5]-hydride shift/Diels-Alder/isomerization cascade.

In the acid-promoted rearrangement reported by Hargitai et al., described *supra* in Section 1.2, after the isoindole formed *in situ*, the reaction essentially reversed course, but with the opposite regioselectivity, to give the regioisomer (**1.41**) of the starting material as the major product (Scheme 1.42).[57] The isoindole (**1.45**) was protonated by TFA to form an isoindolium (**1.154**) at the less sterically hindered α-position. Water subsequently attacked the isoindolium electrophile to give **1.155**, which was then deprotonated to give hydroxyisoindoline **1.156**, followed by tautomerization to aldehyde **1.41**. It should be noted that a polymerization side reaction was observed, but it is already well-established that whenever an nucleophilic isoindole and an electrophilic isoindolium species co-occur, polymerization is a possibility.[7,15]

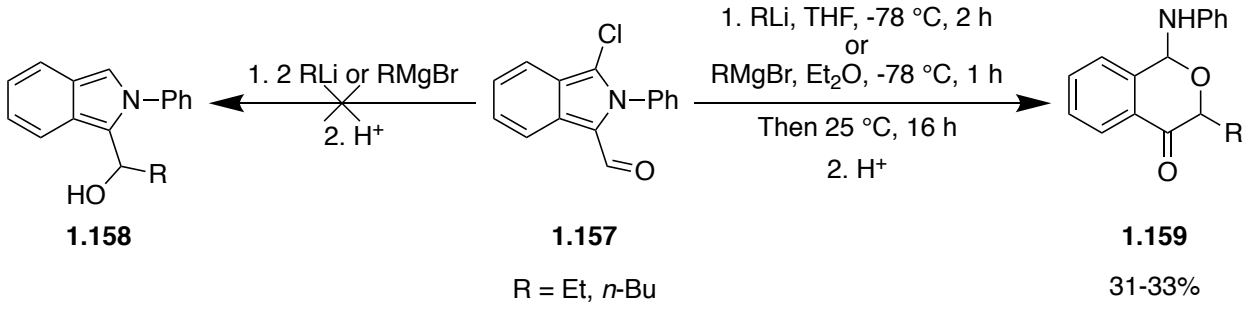


Scheme 1.42. Mechanism for reaction of isoindole intermediate in acid-promoted rearrangement of substituted *ortho*-aminomethylbenzaldehydes.

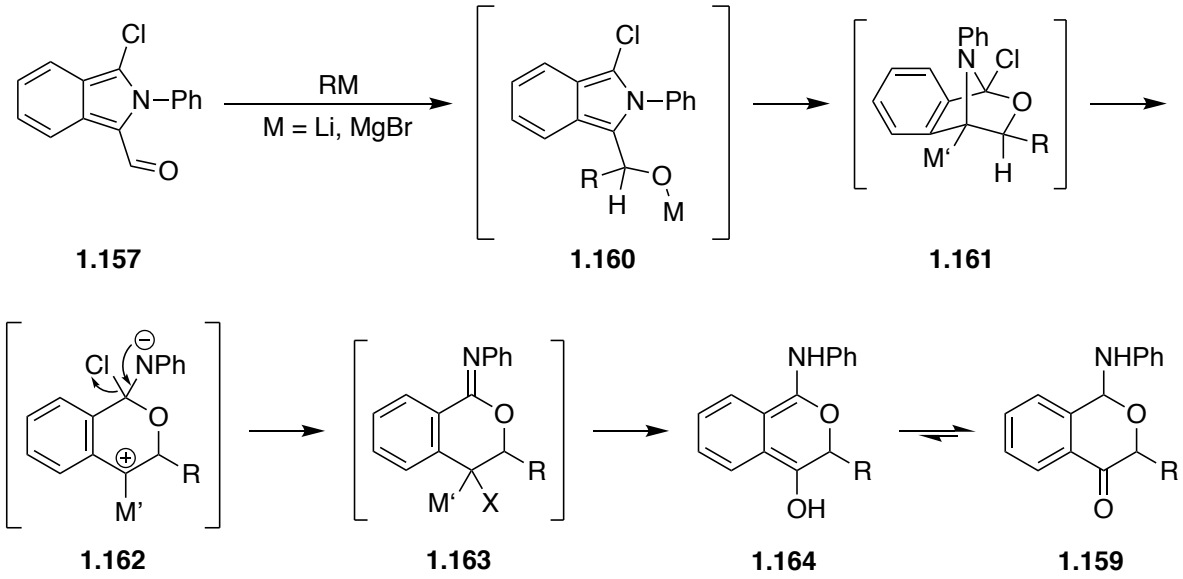
1.16 Reactions of 2*H*-Isoindoles: Alkylating Rearrangements.

In an attempt to perform a one-pot addition of an alkyllithium or Grignard reagent to the aldehyde of 3-chloro-2-phenyl-isoindole-1-carbaldehyde with tandem metal-chlorine exchange, Baglai et al. unexpectedly observed the formation of 1-amino-4-isochromanones (**1.159**), rather than the expected C-3 unsubstituted products (**1.158**), wherein the chlorine is replaced by a proton (Scheme 1.43).[57] In one proposed mechanism for this reaction, the expected addition of the organolithium or Grignard reagent occurs first to give alkoxide adduct **1.160**, but then instead of lithium halogen exchange, the alkoxide attacks the chlorinated C-3 position to form the new bridged bicyclic ring system in **1.161a**, with the possible driving force being the aromatization of the benzenoid ring (Scheme 1.44A, *infra*). Next, the fused pyrrolidine ring is opened by C–N bond cleavage with concomitant formation of a benzylic metal–carbocation center at C-1

(**1.162a**). The tedrahedral center at C-3 then collapses with elimination of a chloride ion as the negatively charged nitrogen atom forms an imino double bond at C-3, giving iminoester **1.163a**. The chloride ion then attacks the carbocation to give **1.164a**, which undergoes subsequent hydrolysis to give the isochromanone product (**1.159**). The alternative proposed mechanism excludes the carbenoid intermediate (**1.164a**), as alkoxide intermediate **1.160** is stable until hydrolysis (Scheme 1.44B, *infra*). The rearrangement could instead be induced by water to give benzylic carbocations **1.162b** and **1.163b**, followed by benzylic alcohol **1.164b**. Due to issues with purification, the isochromanones were only isolated in yields of about 30% as 2:1 mixtures of diastereomers, so the potential for broader synthetically utility is unclear. Nevertheless, the result is interesting and could be used to develop new methods that feature nucleophilic attack on a C–Cl bond at the isoindole α-position by a pendant alkoxide or similar anionic group.



Scheme 1.43. Alkylating rearrangement of 3-chloro-2-phenyl-isoindole-1-carbaldehydes to 1-amino-4-isochromanones.

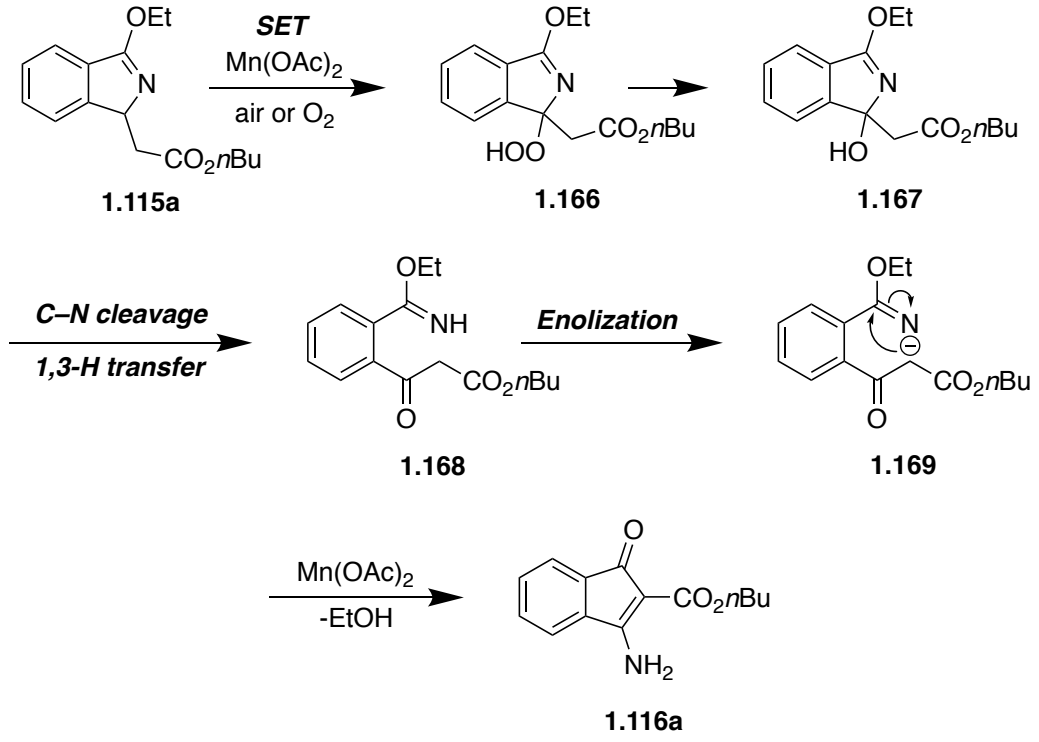


Scheme 1.44. Proposed mechanisms for the alkylating rearrangement of 3-chloro-2-phenyl-isoindole-1-carbaldehydes to 1-amino-4-isochromanones.

1.17 Reactions of 1*H*-Isoindoles: Conversion to Indenones.

In the rhodium-catalyzed synthesis of functionalized indenones from benzimidates and alkenes reported by Lv et al., which was introduced *supra* in Section 1.8, an alkoxy-substituted 1*H*-isoindole (**1.115a**) is formed in situ following C–H activation, alkene insertion, and cyclization, and is subsequently converted to an indenone (**1.116a**) under the reaction conditions.[78] In the proposed mechanism for the conversion of the 1*H*-isoindole to the indenone (Scheme 1.45), 1*H*-isoindole **1.115a** was converted to hydroperoxide **1.166** in the presence of $Mn(OAc)_2$ and either air or oxygen via a Mn(III)-mediated single-electron transfer process. Hydroperoxide **1.166** could then be reduced by Mn(II) or react with the 1*H*-isoindole (**1.115a**) to

give alcohol species **1.167**, which subsequently undergoes $Mn(OAc)_2$-promoted C–N bond cleavage and 1,3-H transfer. The resulting intermediate **1.168** then undergoes enolization and enolate **1.169** subsequently does an intramolecular nucleophilic attack on the imine carbon to give indenone product **1.116a**.

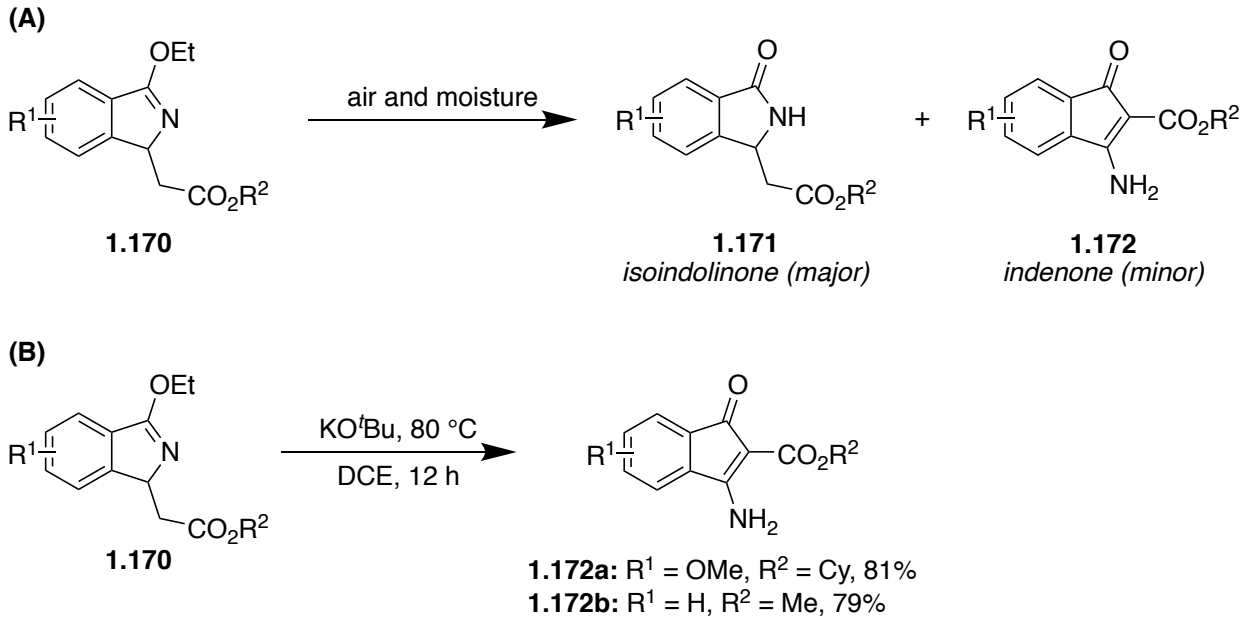


Scheme 1.45. Mechanism for the $Mn(OAc)_2$-promoted conversion of 1*H*-isoindoles to indenones in the presence of air or O_2.

The substrate scope was thoroughly investigated (Scheme 1.27, *supra*). For the benzimidate reacting partner, a variety of electron-donating and electron-withdrawing groups were tolerated at R^1, although slightly lower yields were observed with halogens and electron-withdrawing groups. For electron-donating groups, *para* substitution was slightly preferred over *meta* substitution, and the reverse was observed for electron-withdrawing groups. Substitution with a halogen at various positions was tolerated, although *ortho* substitution reduced the yield. It is also worth noting that a mixture of regioisomers was observed for several *meta*-substituted substrates. A few benzo-fused substrates were also investigated and gave moderate yields. While the best results were obtained with an ethoxy group at R^2, other alkoxy groups were also compatible. For the alkene reacting partner, various electron-withdrawing groups were investigated at R^3, including esters, amides, phosphonates, and sulfonates. Esters generally gave good yields, except for a *tert*-butyl ester, which gave only a 20% yield. Amides and phosphonates gave moderate yields, while sulfonates gave acceptable yields.

However, a 2017 report by Manikandan et al. suggests that this transformation may also be possible under transition metal-free conditions.[79] The authors reported that 1-ethoxyisoindoles **1.170** are unstable to air and water and will spontaneously react to form some of the indenone (**1.172**) as the minor product along with the isoindolinone (**1.171**) major product (Scheme 1.46A). Additionally, Manikandan et al. reportedly prepared the indenones in good yields by heating **1.170** in a sealed tube in the presence of KO*t*-Bu (Scheme 1.46B). This is in apparent contrast to the report by Lv et al.[78], which indicated that a transition metal catalyst and either air oxygen were needed to convert ethoxyisoindole **1.115a** to indenone **1.116a**. However, it does not appear that Lv et al. attempted this reaction in the presence KO*t*-Bu and it is possible that a different mechanism is operative in this case. Notably, the procedure reported by Manikandan et

al.[79] does not clarify whether air was present within the sealed tube, although there is no mention of degassing the solvent or using an inert atmosphere. To understand the mechanism for this reaction, more information and further studies are needed.

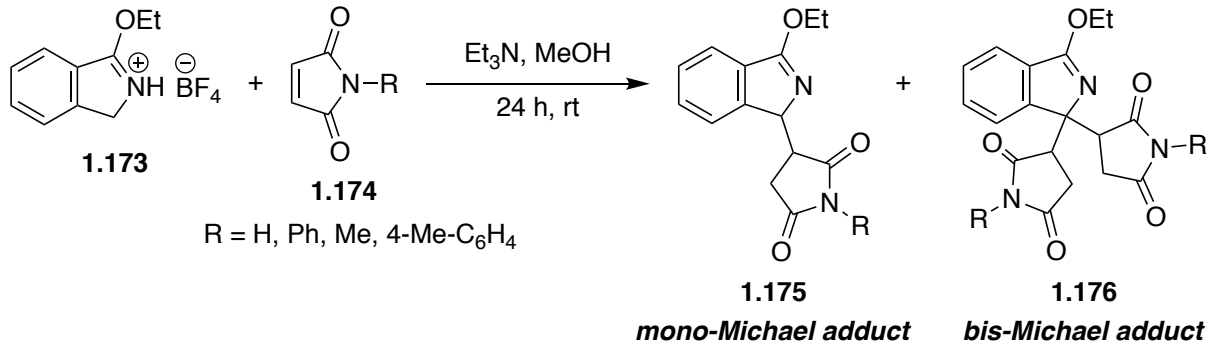


Scheme 1.46. (A) Reaction of C3-substituted 1-ethoxy-1*H*-isoindoles with air and moisture. (B) Transition metal-free synthesis of indenones from 1*H*-isoindoles.

1.18 Reactions of 1*H*-Isoindoles: Michael Addition Reactions.

In 2012, Levkov et al. reported a Michael addition of *N*-substituted maleimides to 1-ethoxyisoindoles in which the ethoxyisoindolium starting material (**1.173**) was deprotonated by triethylamine to form the corresponding isoindole nucleophile, which subsequently attacked the

conjugate position of the maleimide electrophile (**1.174**) to give the mono-Michael adduct (**1.175**, Scheme 1.47).[89] In cases where the mono-Michael adducts were soluble in the reaction solvent, methanol, a second Michael addition occurred to give the bis-Michael adduct (**1.176**) as the major product. Such cases included the reactions of *N*-methyl and *N*-tolyl maleimides, for which yields of 47% and 46%, respectively, were obtained. The mono-Michael adducts for the unsubstituted and *N*-phenyl maleimides were insoluble in methanol and consequently precipitated out and were isolated as the major products in yields of 51% and 53%, respectively. For *N*-phenyl maleimide, the bis-Michael adduct also formed as the minor product in a 9% yield.



Scheme 1.47. Michael addition of *N*-substituted maleimides to 1-ethoxyisoindoles.

1.19 Conclusions.

Numerous novel methods for the formation of 2*H*- and 1*H*-isoindoles have been reported within the past decade, and to a lesser extent, reactions that utilize them. The issue of low reaction yields has largely been overcome, as many of the reactions described herein generally

produce high yields. Additionally, a few unexpected rearrangements have been discovered. However, many of these syntheses focus on fused isoindoles or are otherwise narrow in their applicability. Given the ubiquitous nature of isoindole derivatives in synthetic bioactives and natural products, surprisingly little work has been done that uses isoindoles to directly access these potentially useful compounds. It is also surprising that in the past decade, only a few intramolecular cyclization reactions of isoindoles have been reported, as these reactions often provide an elegant way to access polycyclic isoindole derivatives. The use of isoindoles as electrophilic reacting partners is another exciting avenue that remains largely unexplored. While significant progress has been made in research related to isoindoles, there is still much that remains to be explored.

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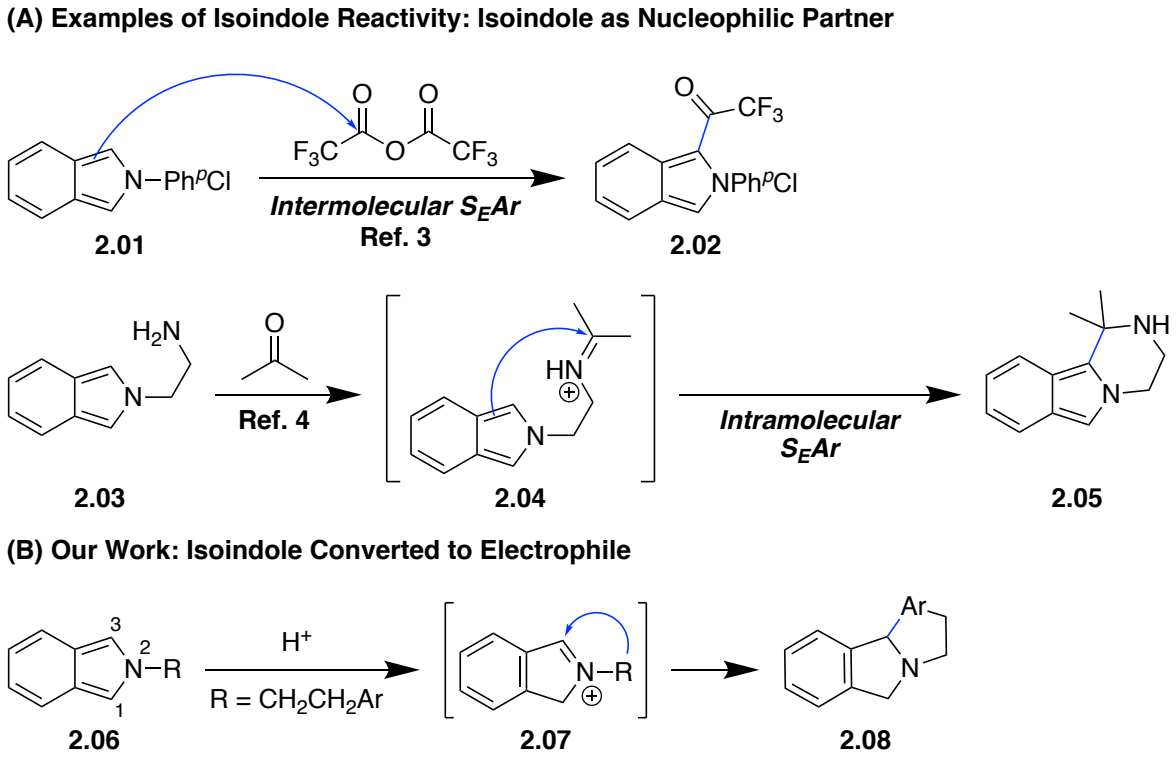
Chapter 2: A One-Pot Synthesis of Polycyclic Isoindolines Using Isoindole Umpolung[1]

2.1. Introduction

As discussed *supra* in Section 1.1, isoindoles are highly reactive moieties that participate in a variety of reactions.[2–5] Resonance donation from the lone pair on the isoindole nitrogen renders the α-position nucleophilic–a feature of isoindole reactivity that has been exploited in electrophilic aromatic substitution reactions,[2–4] Michael reactions,[5] and intramolecular cyclizations[4] (Scheme 2.1A). Isoindoles also often serve as highly reactive electron-sufficient dienes in Diels-Alder reactions.[2,5–10] However, to our knowledge, little work had previously been done to investigate the role of isoindoles as electrophiles. This is because polymerization occurs when the isoindole reacts incompletely with an electrophile to form an electrophilic species, which then reacts with unreacted isoindole.[2] Protonation of an isoindole is known to occur at the 1-position, giving an isolable isoindolium salt,[3] an iminium species, which polymerizes as described. In the Pictet-Spengler reaction, which will be described in detail *infra*, an *in situ*-generated iminium electrophile is attacked by an aromatic nucleophile, resulting in cyclization. This chapter will describe a one-pot synthesis of polycyclic isoindolines that employs an isoindole umpolung approach in which an isoindole is formed *in situ* and subsequently converted to an electrophile by protonating C1 to form the corresponding isoindolium ion. This strategy renders the C3 position electrophilic and opens up the possibility for reactions with various nucleophiles (Scheme 2.1B). Polymerization is avoided by diluting the reaction mixture to favor intramolecular cyclization and using a large excess of acid to ensure complete conversion of the isoindole to the isoindolium. The isoindole subsequently undergoes a Pictet-Spengler-type cyclization to afford polycyclic isoindolines in good yields, as the aromatic nucleophiles used in

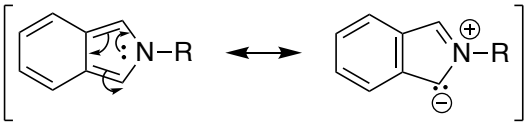
Pictet-Spengler reactions are compatible with the reaction conditions. To provide context for how our work fits into the existing body of knowledge, a brief review of the nucleophilic reactivity of isoindoles and the Pictet-Spengler reaction will be given. The mechanism for the acid-promoted polymerization of isoindoles will also be discussed in greater detail. To provide context for our synthetic strategy, condensation reactions of isoindoles will also be briefly discussed.



Scheme 2.1. (A) Examples of isoindole reactivity. (B) Our approach.

2.2. Nucleophilic Reactivity of Isoindoles

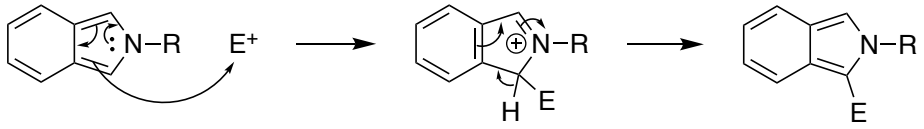
Isoindoles serve as the nucleophilic reacting partner in most of the reactions in which they participate. Resonance donation from the lone pair on the isoindole nitrogen renders the α-position nucleophilic (Figure 2.1).



2.06a **2.06b**

Figure 2.1. Resonance structures showing nucleophilic isoindole α-position.

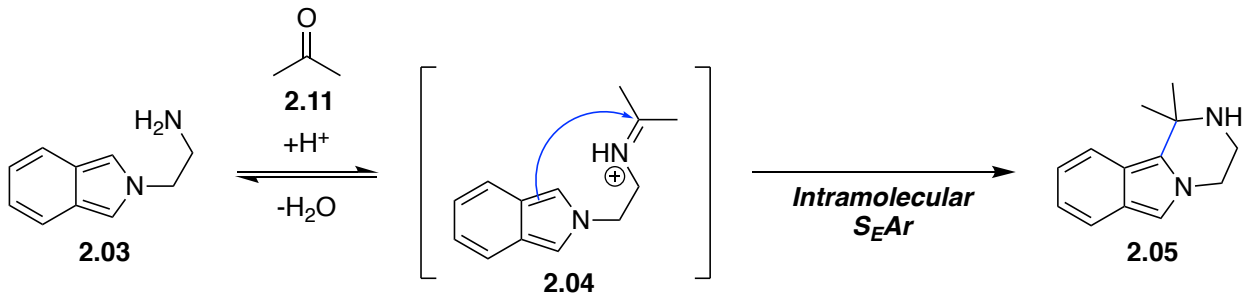
This feature of isoindole reactivity that has been exploited in several types of reactions. In electrophilic aromatic substitution (S_EAr) reactions, which are among the most common reactions of isoindoles, the isoindole attacks an electrophile, forming a bond at the isoindole α-position (Scheme 2.2).[2–4,11] The resulting isoindolium (**2.09**) subsequently rearomatizes back to the *C*-substituted isoindole (**2.10**).



2.06 **2.09** **2.10**

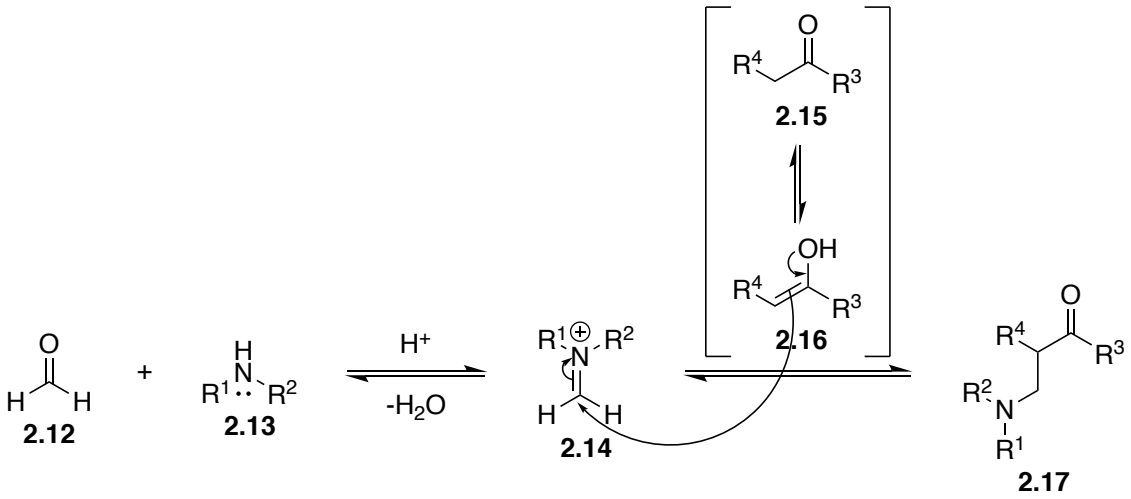
Scheme 2.2. Generic mechanism for intermolecular electrophilic aromatic substitution reactions.

Many of the reported intramolecular cyclizations of isoindoles cyclize via intramolecular electrophilic aromatic substitution reactions (Scheme 2.3).



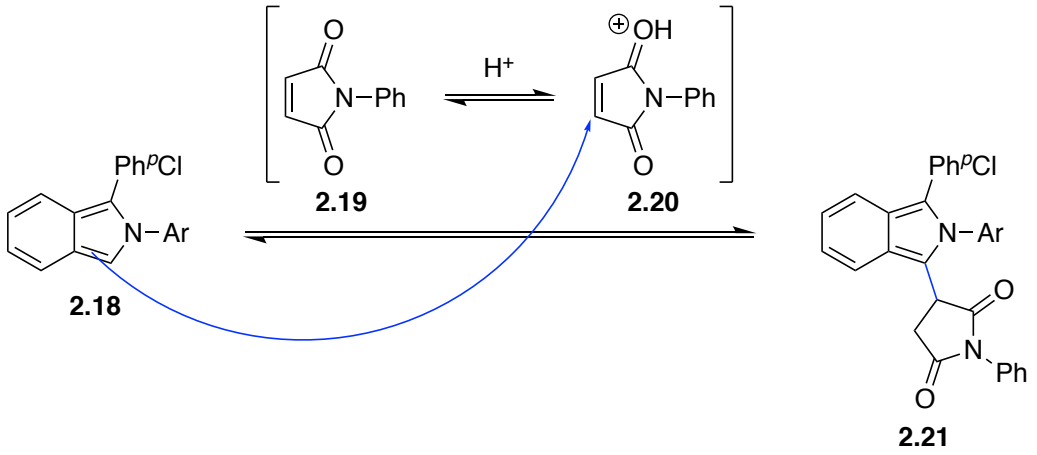
Scheme 2.3. Example of an intramolecular cyclization reaction of an isoindole.[4]

Such reactions are considered variants of the Mannich reaction (Scheme 2.4) because in the first part of the reaction, a pendant amino group reacts with an aldehyde or a ketone to form an iminium ion, which is subsequently attacked by a nucleophile.[12] The only difference is that in the Mannich reaction, an enol or an enolate serves as the nucleophile, whereas in intramolecular cyclizations of isoindoles, the isoindole serves as the nucleophile.



Scheme 2.4. The Mannich reaction.[12]

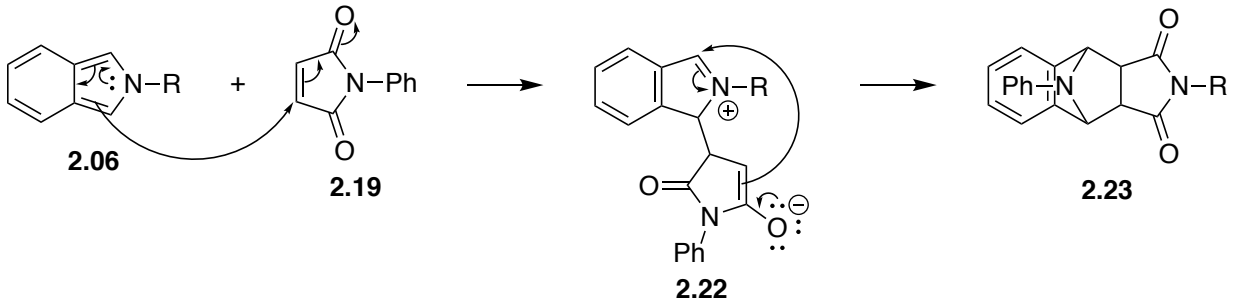
Isoindoles also serve as nucleophiles in Michael additions (Scheme 2.5).[5,13] However, in the case of isoindoles, the Michael addition is simply another example of an electrophilic aromatic substitution reaction with the nuance that the electrophile is an α,β-unsaturated carbonyl species, which gets attacked by the isoindole at the β-position.



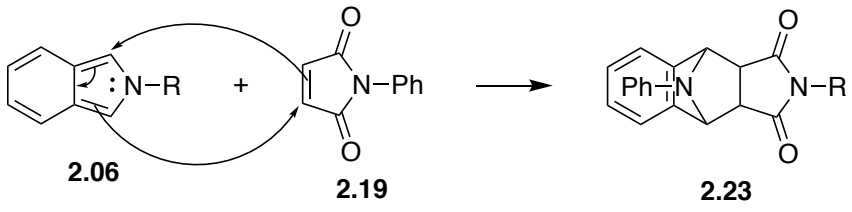
Scheme 2.5. Example of a Michael addition reaction of an isoindole.[5]

Additionally, isoindoles serve as highly reactive electron-sufficient dienes in Diels-Alder and other cycloaddition reactions.[2,5–9] Due to the concerted nature of cycloaddition reactions, the isoindole is not technically a nucleophile; however, the reaction can be considered to start off with the isoindole acting as a nucleophile. Additionally, a stepwise mechanism can be drawn that begins with a Michael addition (**2.22**, Scheme 2.6A), in which the isoindole acts as a nucleophile, followed by an intramolecular nucleophilic attack on the resulting isoindolium by the resulting enolate to give the cycloadduct (**2.23**). Although the true cycloaddition reaction mechanism is as shown in Scheme 2.6B, the stepwise mechanism shown in Scheme 2.6A demonstrates the nucleophilic character of the isoindole diene in cycloaddition reactions.

(A) Stepwise mechanism to demonstrate nucleophilic nature of isoindole in Diels-Alder reactions.



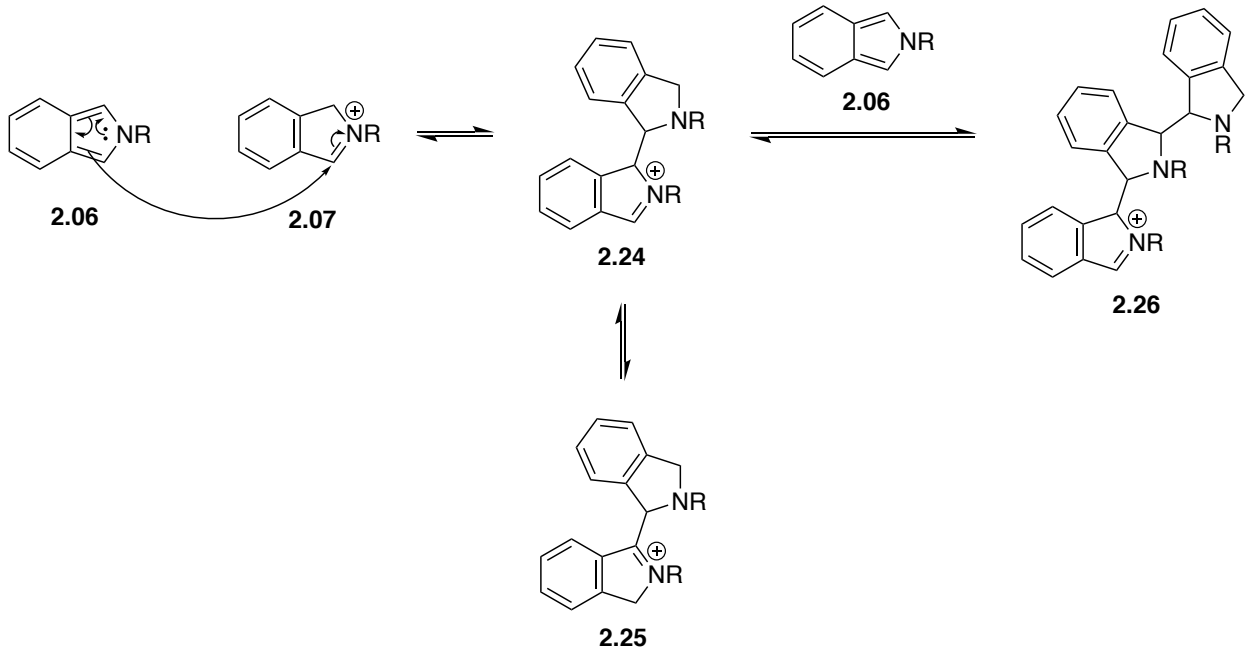
(B) Actual mechanism for Diels-Alder reactions of isoindoles.



Scheme 2.6. Mechanisms demonstrating (A) the nucleophilic character and (B) the actual behavior of isoindoles in Diels-Alder reactions.

2.3. Mechanism for the Acid-Promoted Polymerization of Isoindoles

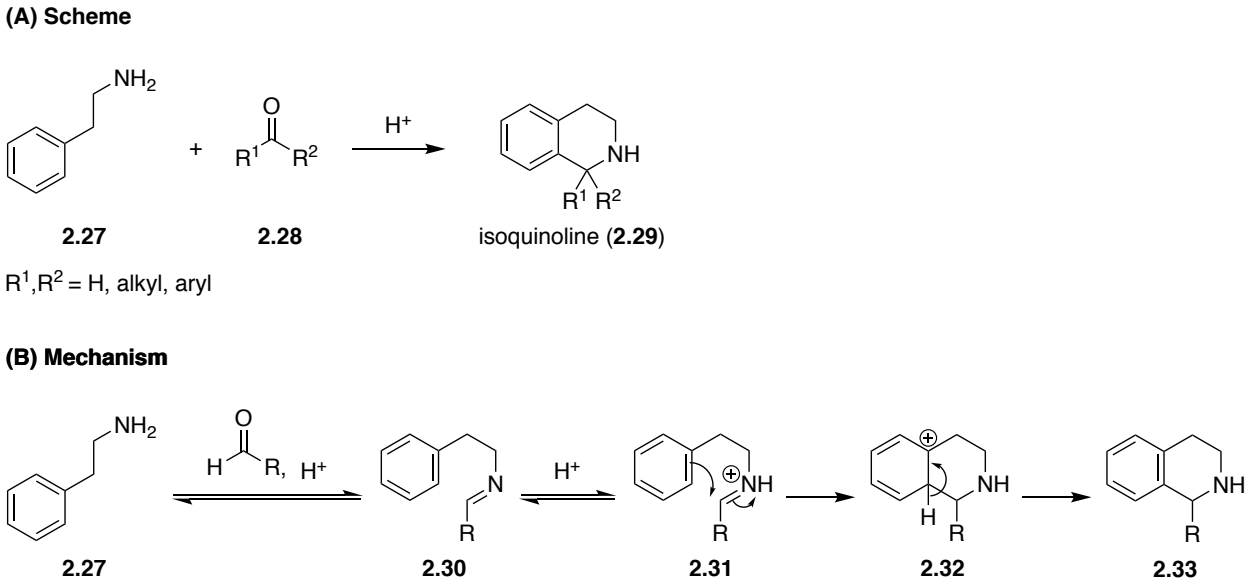
Whenever nucleophilic isoindoles are present at the same time as electrophilic isoindolium species, polymerization can occur (Scheme 2.7).[2] This can happen in the presence of acid, which protonates the isoindole to form the isoindolium, unless the isoindole is completely converted to the isoindolium. In the mechanism for this reaction, the nucleophilic isoindole attacks the electrophilic isoindolium carbon to form dimer species **2.24**, in which they are bonded at the α-position. Depending on the conditions, the newly formed isoindolium carbon of **2.24** can either react with another molecule of the isoindole to give trimer species **2.26** or it can isomerize to the other isoindolium salt (**2.25**).



Scheme 2.7. Mechanism for the acid-promoted polymerization of isoindoles.

2.4. The Pictet-Spengler Reaction and the Tryptamine Modification

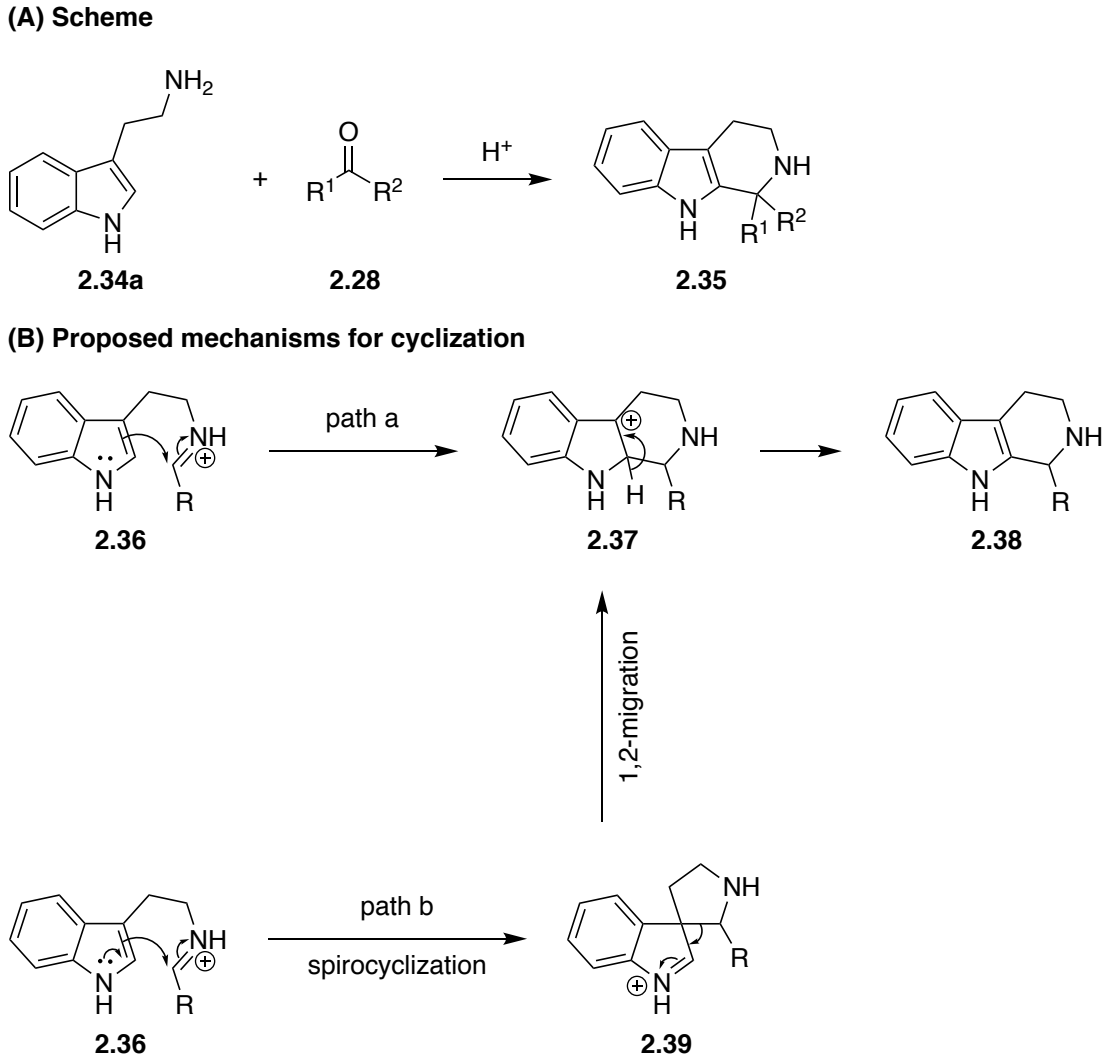
In the Pictet-Spengler reaction, a β-arylethylamine reacts with an aldehyde or a ketone, often in the presence of acid, to provide an isoquinoline derivative (Scheme 2.8A).[14–16] The mechanism for this reaction begins with a condensation reaction between the amine and the aldehyde or ketone (Scheme 2.8B). The resulting imine (**2.30**) is subsequently protonated by the acid to give an iminium electrophile (**2.31**), which then cyclizes via nucleophilic attack by the aryl ring (**2.32**). Subsequent rearomatization gives the isoquinoline product (**2.33**).



Scheme 2.8. Pictet-Spengler reaction (A) scheme and (B) mechanism.[14,16]

A modification originally reported by Tatsui (Scheme 2.9A) uses a tryptamine derivative (**2.34a**) as the β-arylethylamine reacting partner instead of a β-phenylethylamine derivative, which provides a tetrahydro-β-carboline derivative (**2.35**) instead of a tetrahydroisoquinoline

derivative. The tryptamine modification is mechanistically similar to the generic Pictet-Spengler reaction, with the only difference being that there is more of a debate surrounding the mechanism and the occurrence of spirocyclization.[16,18] In one proposed mechanism for the Pictet-Spengler reaction of tryptamines, cyclization initially results in a spiroindole intermediate (**2.39**, Scheme 2.9B), as shown in pathway b, which subsequently undergoes a migration to give the carbocation intermediate (**2.37**). However, this has been heavily debated, and an alternative mechanism has been proposed in which cyclization provides **2.37** directly, as shown in pathway a. Computational evidence suggests that both mechanisms might be operational.



Scheme 2.9. (A) Scheme and (B) proposed cyclization mechanisms for the tryptamine modification to the Pictet-Spengler reaction.

The scope of the Pictet-Spengler reaction has since been extended to include other β-heteroarylethylamine substrates, including other indole (**2.40**)[19–23], pyrrole (**2.34i**, **2.43**-**2.45**)[21,23–28], furan (**2.34j**)[29,30], and thiophene (**2.41**-**2.42**)[24,31–34] derivatives, as well as other heteroarylalkylamines, such as 4-(aminomethyl)indole (**2.34f**)[35] (Figure 2.2).

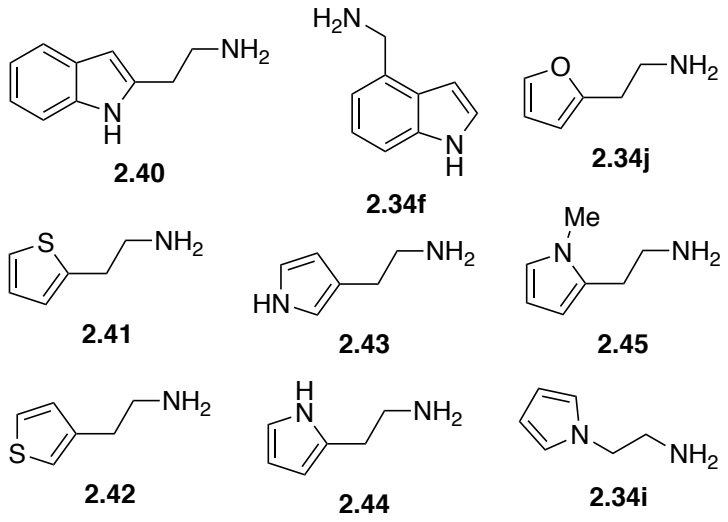


Figure 2.2. Examples of other reported amine reacting partners for the Pictet-Spengler reaction.

2.5. Formation of Isoindoles via Condensation Reactions

As described *supra* in Section 1.2, condensation reactions of benzylic dielectrophiles with amines can provide easy access to isoindoles. These electrophilic sites can either be benzyl bromides[5,36–38] or benzylic carbonyl species[5,38–40], such as benzaldehydes or benzyl ketones. Accessing *C*-unsubstituted 2*H*-isoindoles from symmetric dielectrophiles, in which the two electrophilic sites are of the same type, requires an oxidant or a reductant (Figure 2.3). This is because each aldehyde carbon loses one C–Z bond during the reaction, where Z is a more electronegative atom, and each benzyl bromide carbon loses one C–H bond. Therefore, an *ortho*-phthalaldehyde (**2.52**) dielectrophile loses a total of two C–Z bonds, which amounts to a two-electron reduction, and a 1,2-Bis(bromomethyl)benzene (**2.49**) dielectrophile loses a total of two C–H bonds, which amounts to a two-electron oxidation. Consequently, to avoid using an oxidant or a reductant, a 2-(bromomethyl)benzaldehyde (**2.51**) dielectrophile must be used, as the aldehyde carbon will be reduced by the same amount that the benzyl bromide carbon will be oxidized, which means that no redox reaction will occur.

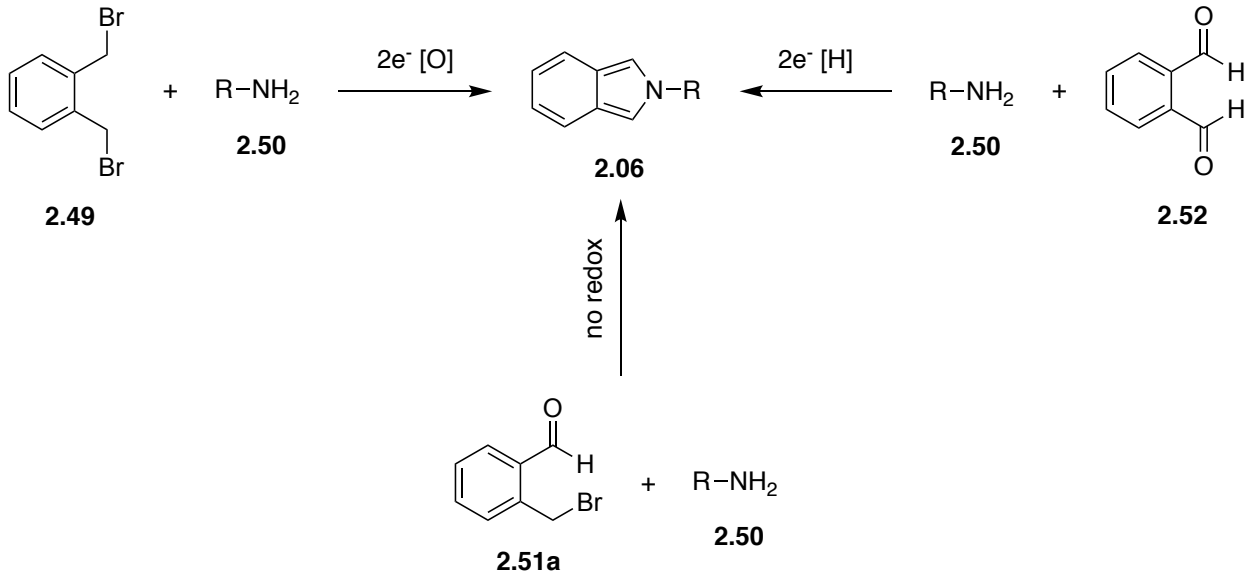
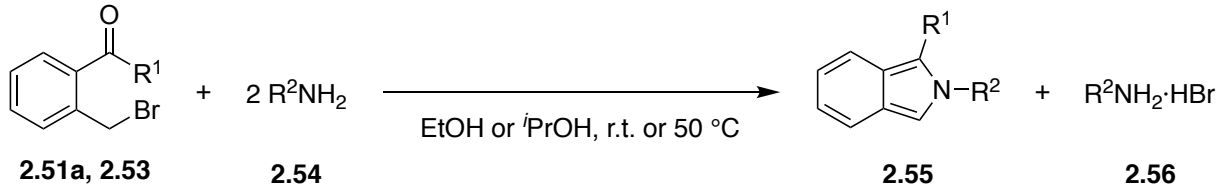


Figure 2.3. Changes in oxidation states for various isoindole precursors in condensation reactions with amines.

Methods reported by Voitenko et al.[5] and Sypchenko et al.[38] in 2011 and 2012, respectively, use 2-(bromomethyl)benzaldehyde (**2.51a**) and 2-(bromomethyl)benzyl ketone derivatives (**2.53**) as precursors (Scheme 2.10). In both methods, the dielectrophile reacts with two equivalents of the amine in a protic solvent to provide one equivalent of the isoindole and one equivalent of the amine HBr salt. When 2-(bromomethyl)benzaldehyde (**2.51a**) was used as the precursor, the reaction proceeded smoothly at room temperature,[5] whereas reactions of 2-(bromomethyl)benzyl ketones required heat and slightly longer reaction times[5,38].

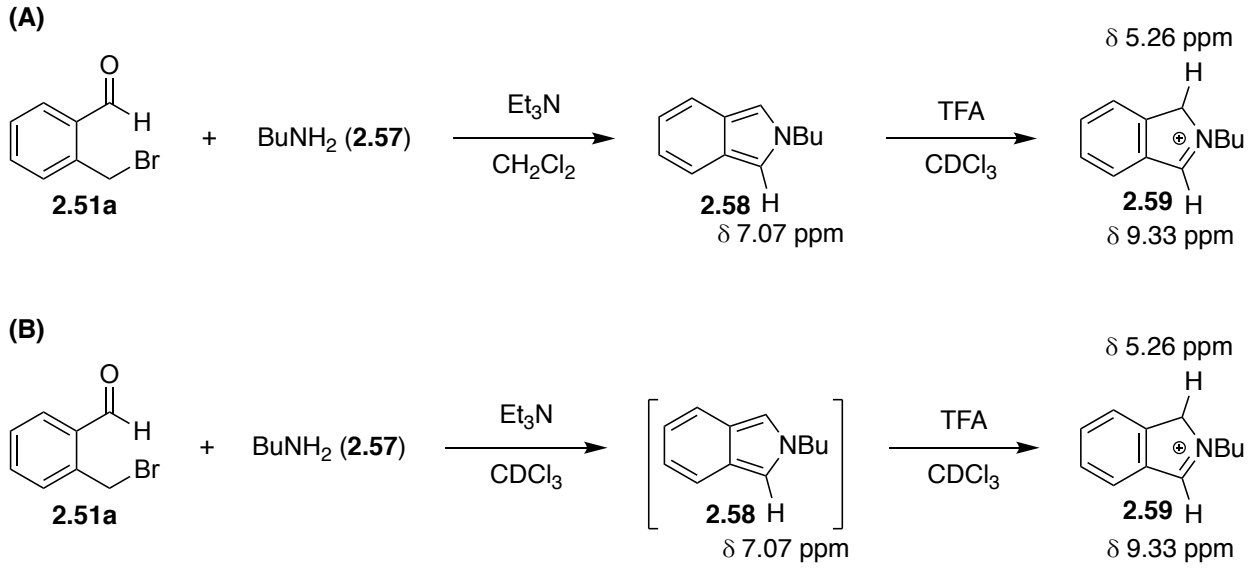


Voitenko et al. (2011): R^1 = H, aryl; R^2 = benzyl, aryl, cyclohexyl; conditions = EtOH or ^{i}PrOH, r.t. or 50 °C
Sypchenko et al. (2012): R^1 = aryl; R^2 = 2-aminoaryl; conditions = EtOH, 50 °C

Scheme 2.10. Synthesis of isoindoles via condensation reactions of 2-(bromomethyl)benzaldehyde and 2-(bromomethyl)benzyl ketones with amines.[5,38]

2.6. One-Pot Synthesis of Polycyclic Isoindolines Using Isoindole Umpolung: Preliminary Studies

We envisioned an approach in which an isoindole could be converted to an electrophile by protonating C1 to form the correponding isoindolium ion, rendering the C3 position electrophilic and opening up the possibility for reactions with various nucleophiles, such as the aromatic nucleophiles employed in the Pictet-Spengler reaction (Scheme 2.1B, *supra*). To avoid decomposition by polymerization and oxidation, we planned to use excess acid to completely convert the isoindole to the isoindolium. In order to prove our hypothesis, we first synthesized *N*-butylisoindole (**2.58**, Scheme 2.11) from 2-(bromomethyl)benzaldehyde (**2.51a**) and butylamine (**2.57**, 1.2 equiv.) in the presence of triethylamine (1.2 equiv.) in dichloromethane by adapting the procedure reported by Voitenko, et al.[5] Following an aqueous workup, the isoindole was isolated and taken up in deuterated chloroform.



Scheme 2.11. Preliminary studies.[41]

The ^{1}H NMR spectrum (Figure 2.4) showed quantitative conversion of aldehyde **2.51a** to the corresponding isoindole **2.58**. The signal at 7.10 ppm, which corresponds to the protons at the 1- and 3-positions, served as the diagnostic peak for the isoindole.

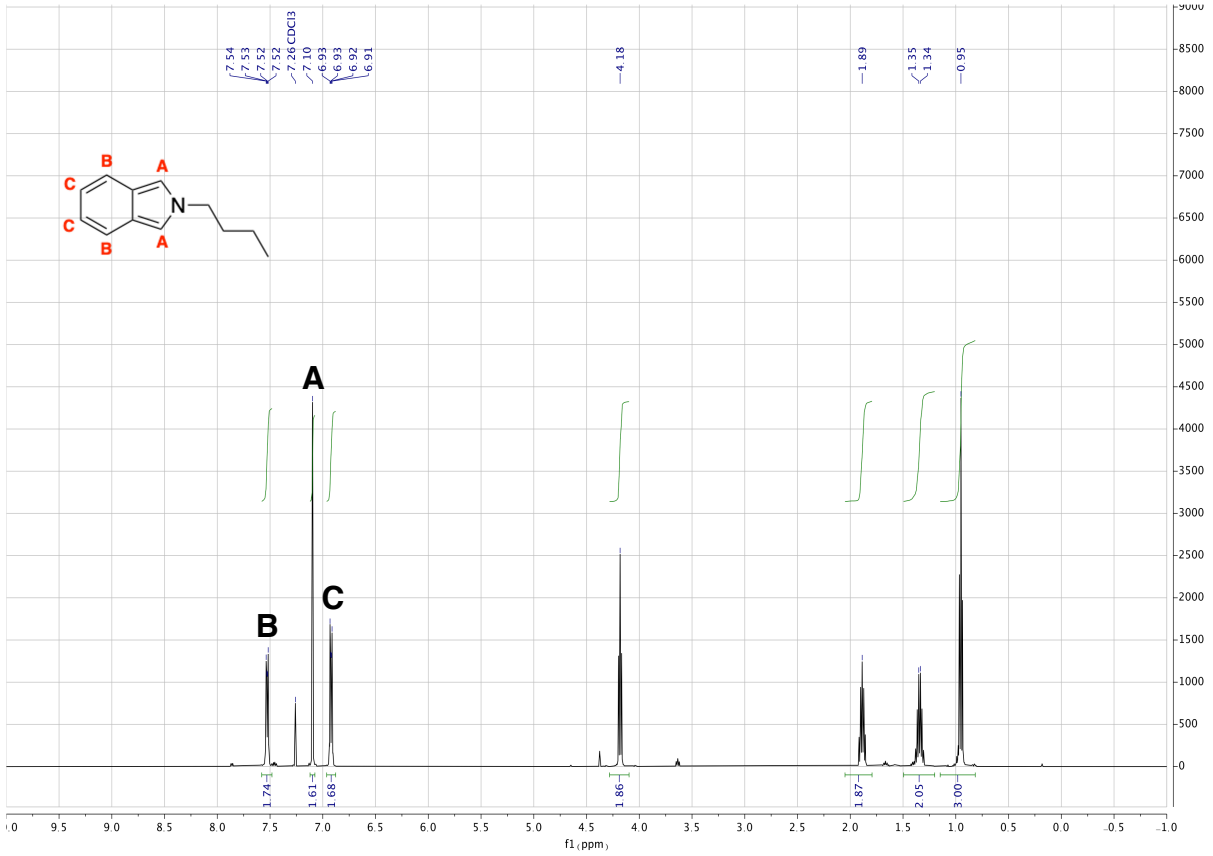


Figure 2.4. ^{1}H NMR spectrum of isoindole **2.58** (from stepwise procedure).

The isoindole was then treated with a large excess of TFA, and quantitative conversion of isoindole **2.58** to isoindolium species **2.59** (Scheme 2.11, *supra*) was observed by ^{1}H NMR (Figure 2.5). The isoindole diagnostic peak at 7.10 ppm disappeared and two new singlets at 9.30 ppm and 5.24 ppm, integrating to one and two protons, respectively, were observed (Figures 2.5-2.6). The former was downfield of the isoindole diagnostic peak, as expected for an iminium C–H, and the latter was 1.86 ppm upfield of the isoindole diagnostic peak, consistent with protonation of the isoindole at the C1-position. Taken together, these indicate quantitative conversion of the isoindole to the isoindolium.

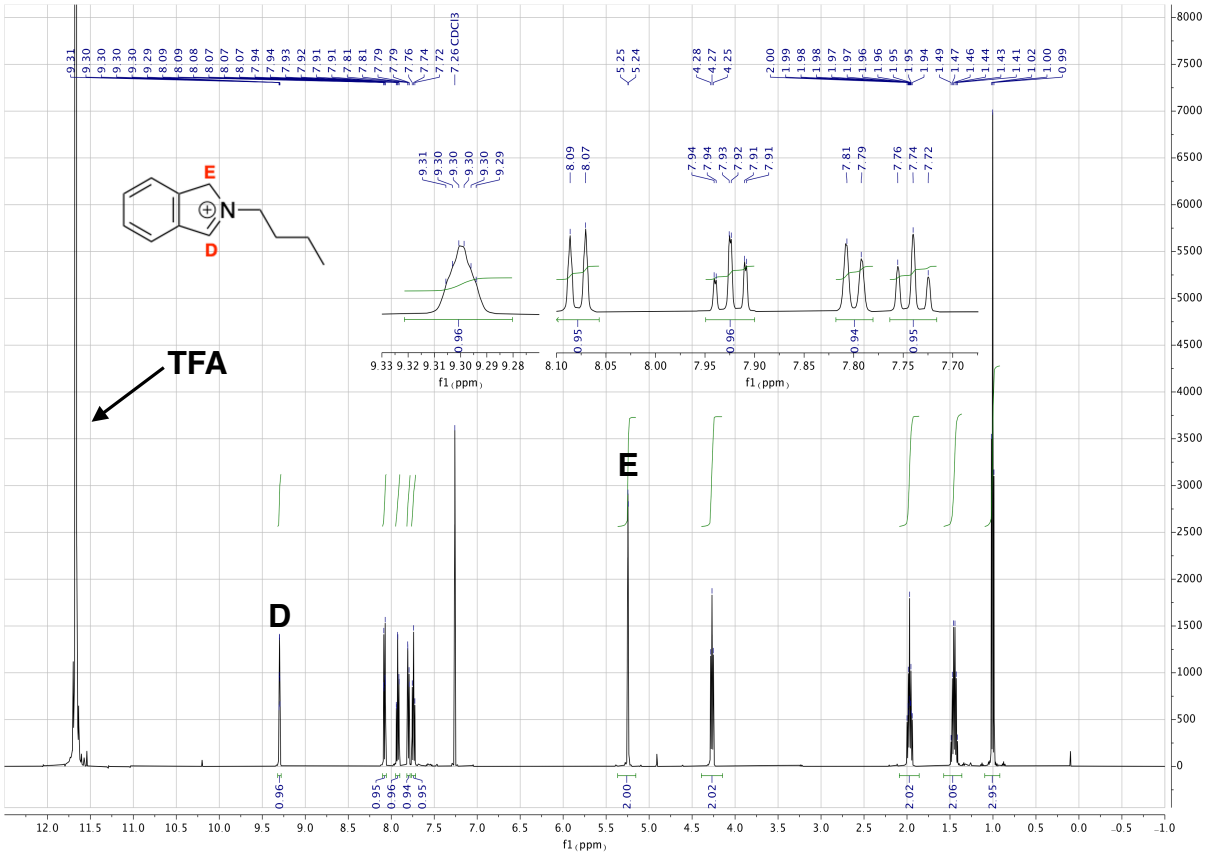


Figure 2.5. ^{1}H NMR spectrum of isoindolium **2.59** (from stepwise procedure).

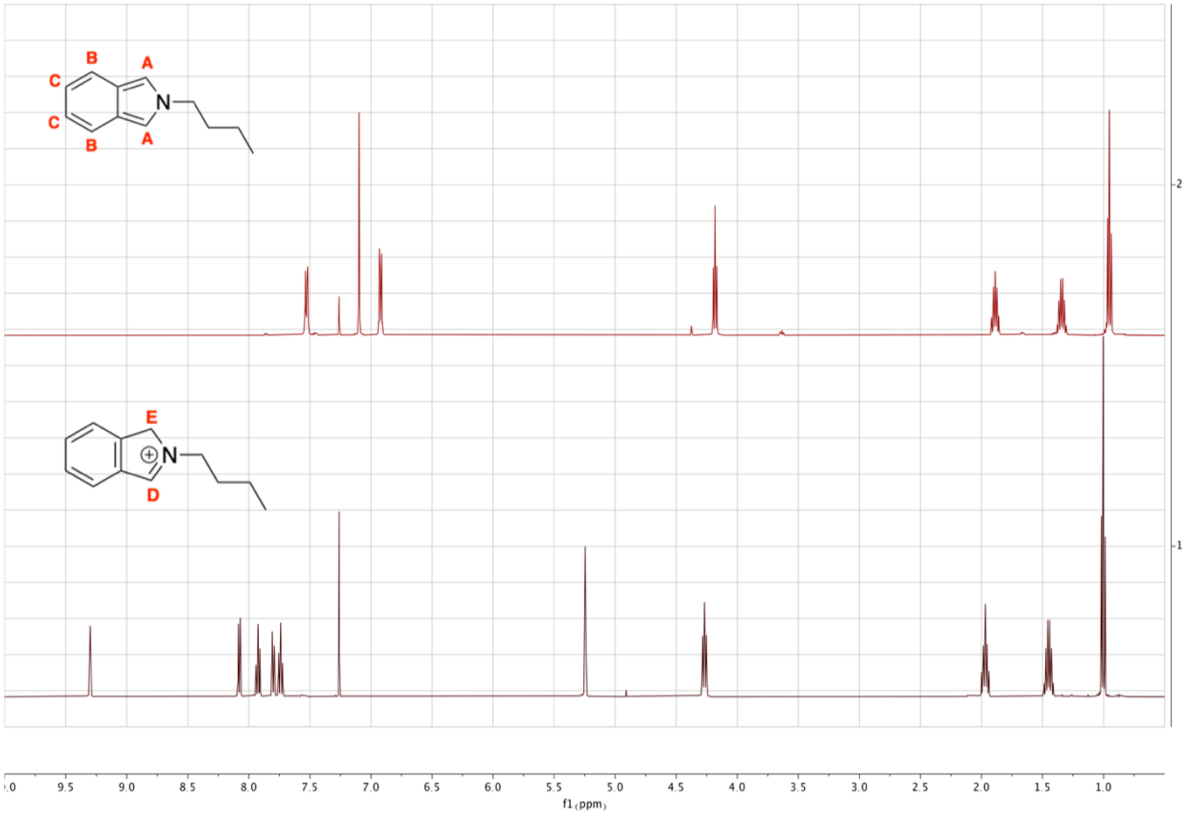


Figure 2.6. Stacked ^{1}H NMR spectra of isoindole **2.58** (top) and isoindolium **2.59** (bottom) (from stepwise procedure).

These studies were then repeated in a one-pot procedure in which the isoindole was formed *in situ* in deuterated chloroform, and then converted to the isoindolium by the addition of excess TFA directly to the ^{1}H NMR sample. Similar results were observed, demonstrating that a one-pot procedure can also be used to quantitatively form the isoindole and isoindolium (Figures 2.7-2.9).

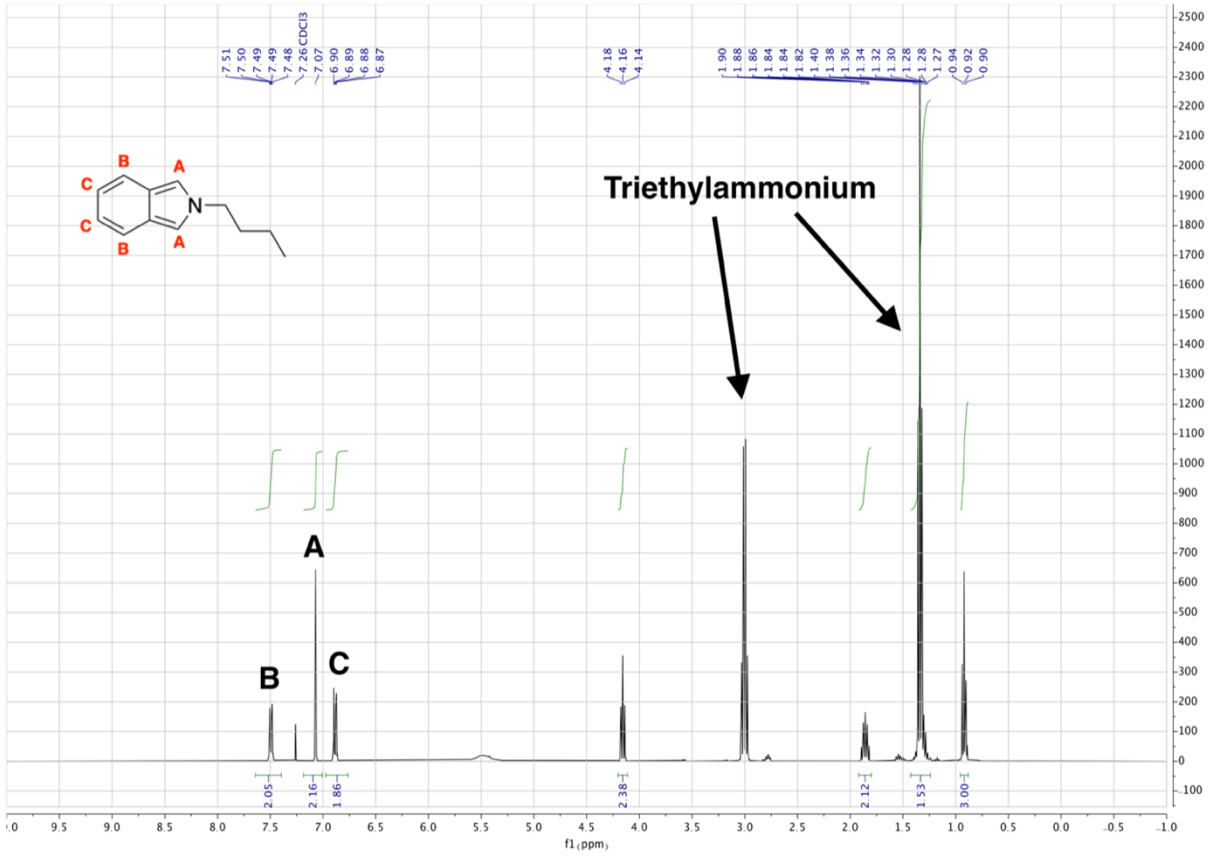


Figure 2.7. ^{1}H NMR spectrum of isoindole **2.58** (synthesized via one-pot procedure).

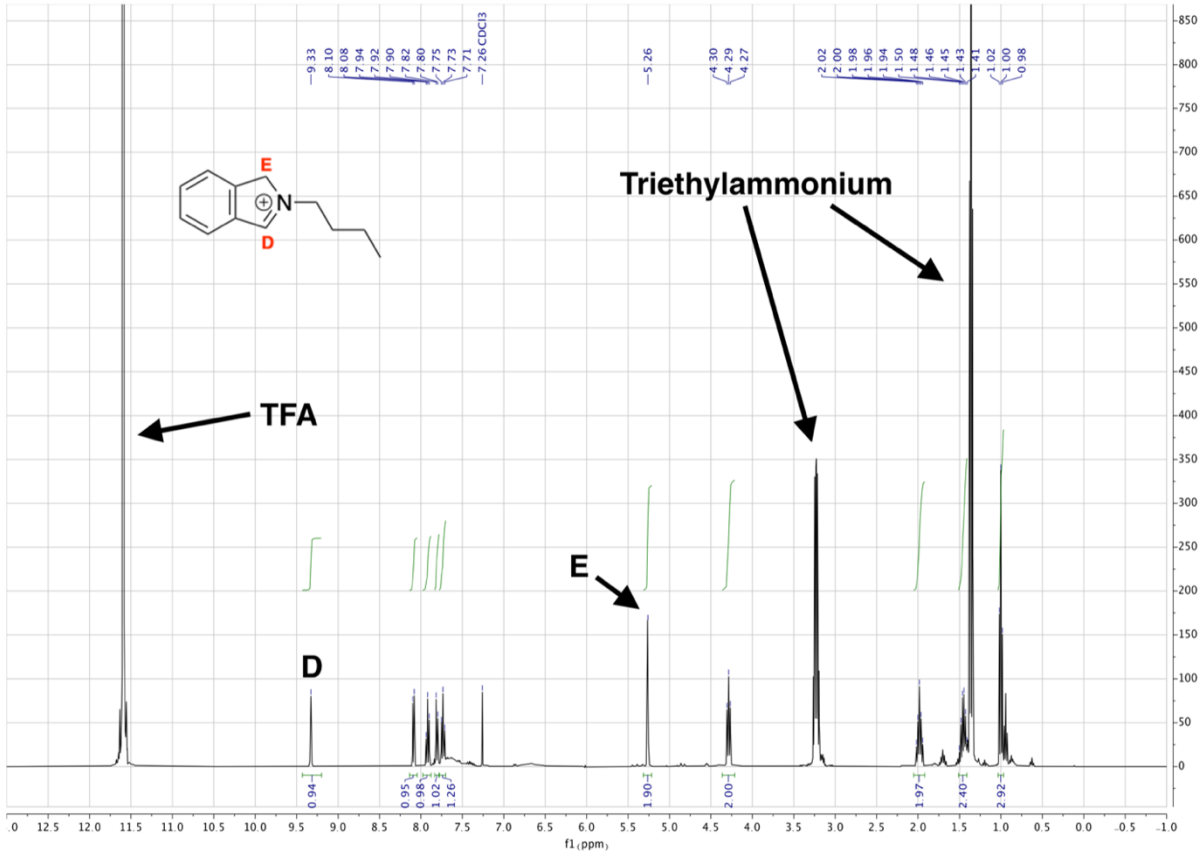


Figure 2.8. ^{1}H NMR spectrum of isoindolium **2.59** (synthesized via one-pot procedure).

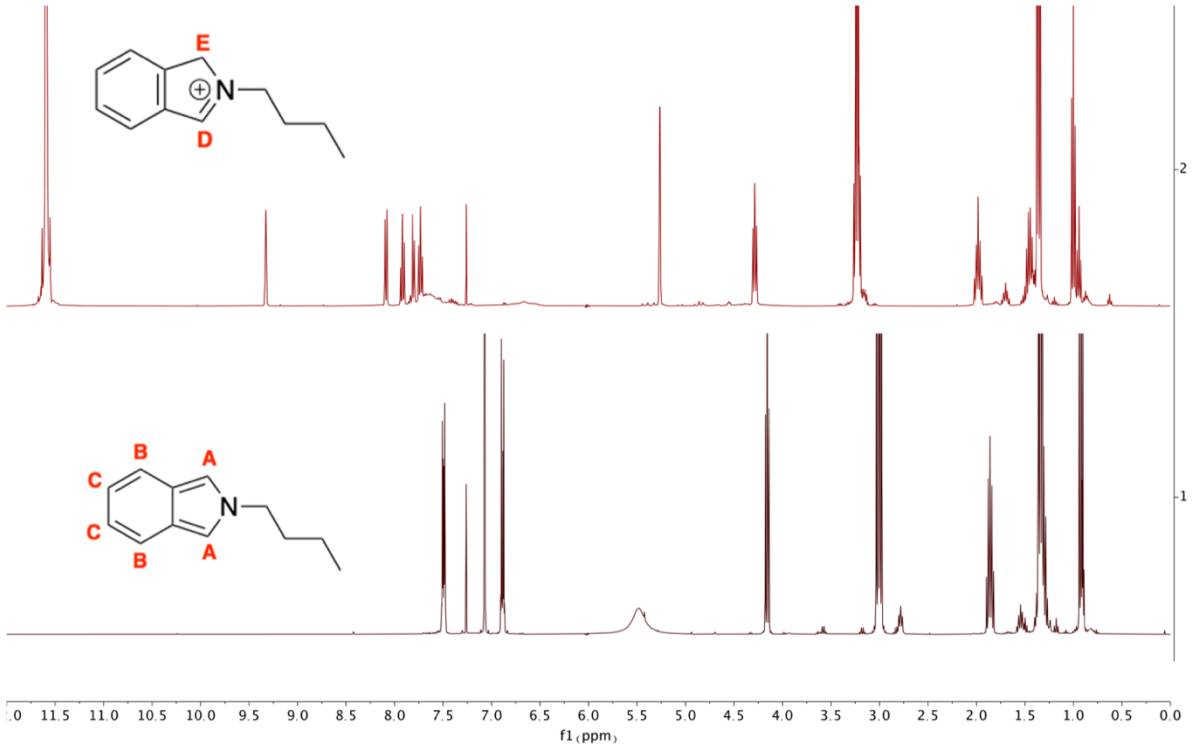


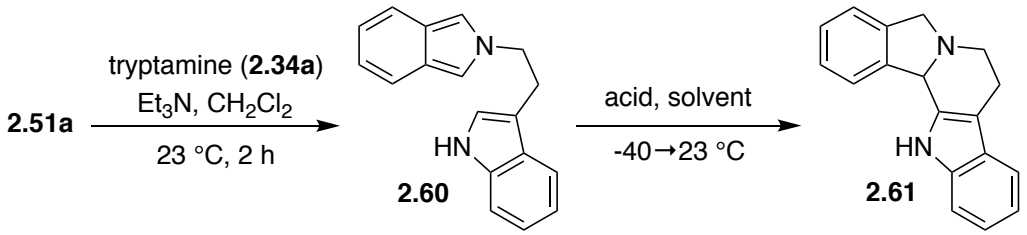
Figure 2.9. Stacked ^{1}H NMR spectra of isoindole **2.58** (bottom) and isoindolium **2.59** (top) (from one-pot procedure).

2.7. One-Pot Synthesis of Polycyclic Isoindolines Using Isoindole Umpolung: Optimization of Reaction Conditions

In the Pictet-Spengler reaction, an iminium ion serves as the electrophile, which is subsequently attacked by an aromatic nucleophile. Hence, we decided to develop a Pictet-Spengler-type reaction to synthesize polycyclic isoindolines reminiscent of the natural product nuevamine.[42] Tryptamines were chosen in our model system, as they have been utilized extensively in Pictet-Spengler cyclizations,[15,17] and the β-carboline structures formed are found in bioactive molecules and hormones[43]. The reaction conditions were optimized systematically (Table 2.1, *infra*). Initially, the isoindole was isolated prior to acidification. Various solvents,

protic acids, and equivalents of acid were investigated. Based on literature precedent, TFA was used as the default protic acid catalyst.[44,45] To avoid polymerization, 10 equivalents of acid was used as the default. The chlorinated solvents (entries 1-3) gave **2.61**[46,47] in very high yields by ^{1}H NMR, with dichloromethane (entry 1) and dichloroethane (entry 2) giving the highest yields. Toluene (entry 4), a nonpolar solvent that would allow for high temperature refluxes, also gave a high yield. Polar solvents and protic solvents were not suitable for this reaction. No desired product was formed in acetonitrile (entry 5). THF (entry 6), 1,4-dioxane (entry 7), MeOH (entry 8), and DMF (entry 9) effected decomposition of the product. The optimal protic acid catalyst was TFA (entry 1). For the acids stronger than TFA, MsOH (entry 11) and HCl (entry 10), the percent yields decreased with increasing acid strength. Weaker acids, such as trichloroacetic acid (entry 12) and AcOH (entry 13), also resulted in lower yields. No product was obtained using AcOH, the weakest acid screened, even with heating. As anticipated, a superstoichiometric amount of acid was needed, as no product was obtained when a single equivalent was added. Increasing the number of equivalents increased the yield dramatically, up to 5.0 equivalents (entries 14–16). Beyond 5.0 equivalents, only a slight increase in the yield was observed (entry 1). For the multistep procedure originally employed, 10 equivalents were optimal. A one-pot procedure was further developed for the ease of the reaction. When 10 equivalents of TFA were added in a one-pot procedure, the yield was substantially lower than for the multistep procedure (entry 17). We hypothesized that residual triethylamine from the isoindole formation consumed some of the acid, forming triethylammonium and decreasing the yield. Increasing the amount of TFA added from 10 to 20 equivalents gave the highest yield (entry 18).

Table 2.1. Optimization of Reaction Conditions.

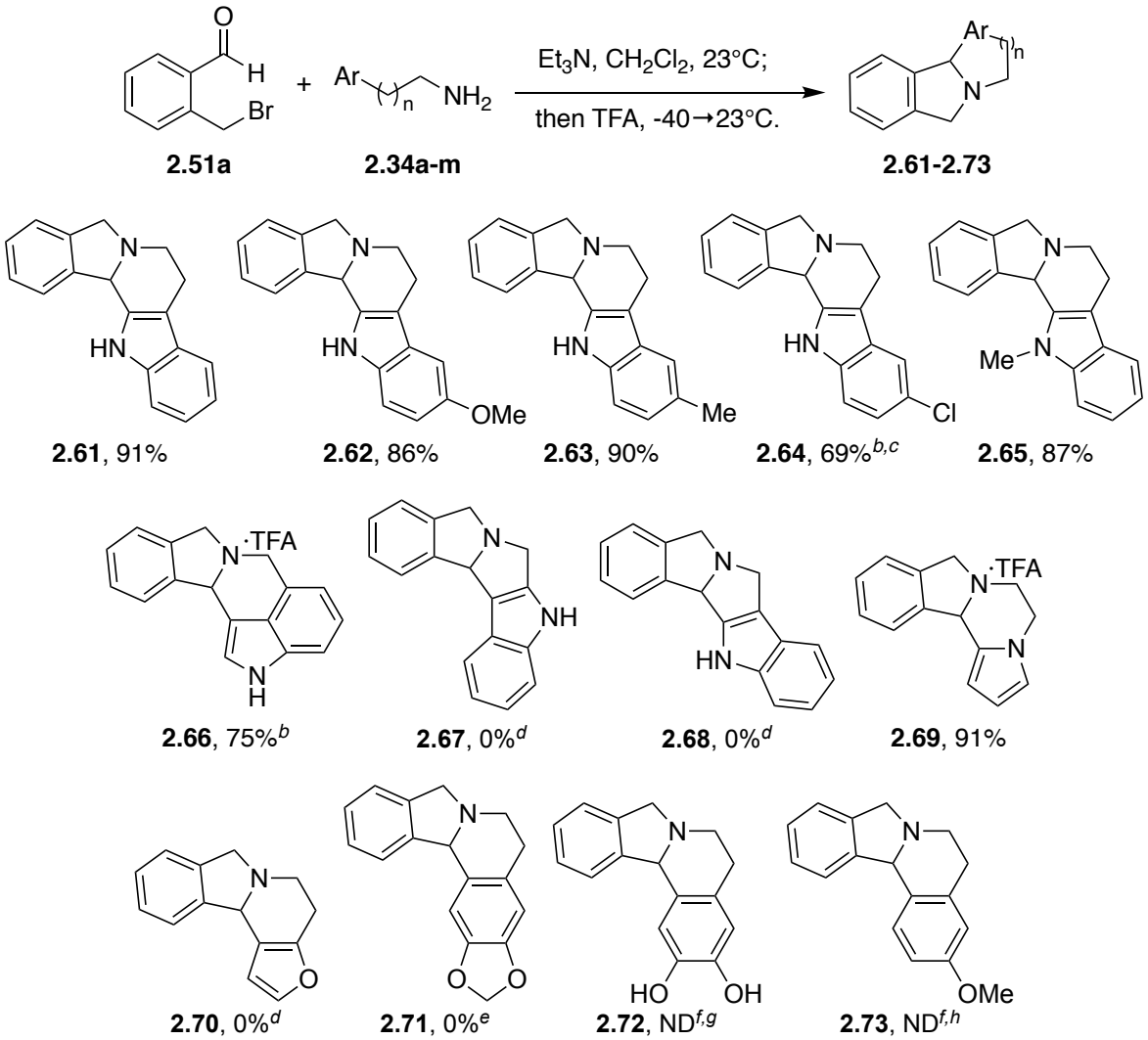


Entry	Solvent[a]	Acid	Equiv.	Yield (%)[b]
1	CH_2Cl_2	CF_3CO_2H	10	>98 (84)
2	$ClCH_2CH_2Cl$	CF_3CO_2H	10	98 (81)
3	$CHCl_3$	CF_3CO_2H	10	91
4	toluene	CF_3CO_2H	10	95 (78)
5	Acetonitrile	CF_3CO_2H	10	0
6	THF	CF_3CO_2H	10	decomposed
7	1,4-dioxane	CF_3CO_2H	10	decomposed
8	MeOH	CF_3CO_2H	10	decomposed
9	DMF	CF_3CO_2H	10	decomposed
10	CH_2Cl_2	HCl	10	48 (18)
11	CH_2Cl_2	MsOH	10	48[c]
12	CH_2Cl_2	CCl_3CO_2H	10	80 (77)
13	CH_2Cl_2	CH_3CO_2H	10	0[d]
14	CH_2Cl_2	CF_3CO_2H	1.0	0
15	CH_2Cl_2	CF_3CO_2H	2.5	23
16	CH_2Cl_2	CF_3CO_2H	5.0	94
17[e]	CH_2Cl_2	CF_3CO_2H	10	67 (63)
18[e]	CH_2Cl_2	CF_3CO_2H	20	100 (91)

[a]For reactions in which **2.60** was isolated, this refers to the cyclization step. [b]Yields were determined by ^{1}H NMR with 1,3,5-Trimethoxybenzene as the internal standard. Isolated yields are shown in parentheses. [c]Purified product was a complex mixture. Isolated yield not determined. [d]No cyclization observed at 23°C or 50°C. [e]A one-pot procedure was used in which the isoindole was formed by the addition of triethylamine (1.2 equiv) to tryptamine (1.2 equiv) and 2-(bromomethyl)benzaldehyde (1.0 equiv, 0.10 M in CH_2Cl_2) at 23°C. After 2 h, sufficient DCM was added to bring the concentration to 0.02 M, and TFA was added at -40°C. The reaction mixture was subsequently allowed to warm to 23°C and stirred for 16 h.

2.8. One-Pot Synthesis of Polycyclic Isoindolines Using Isoindole Umpolung: Scope of the Reaction

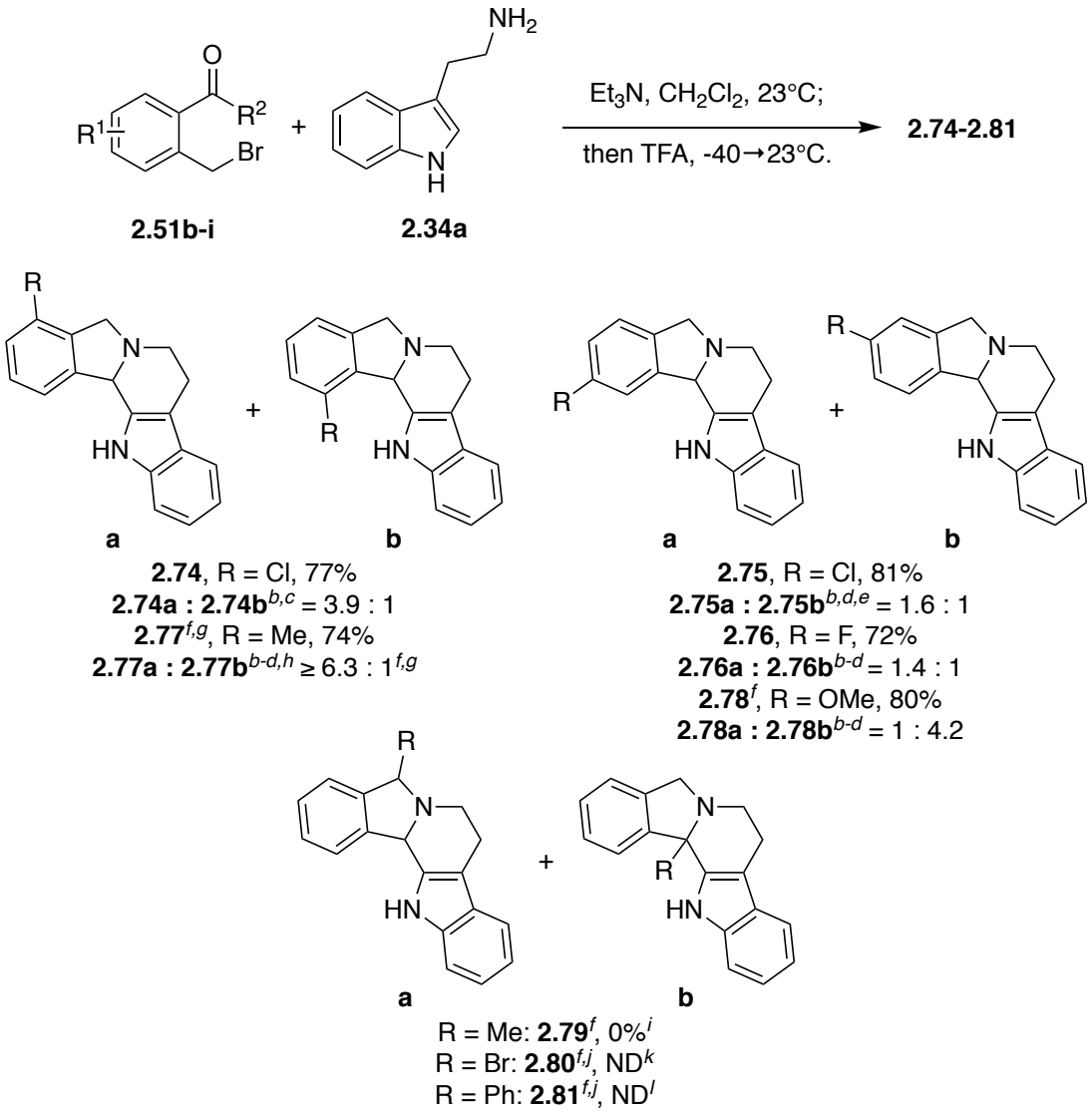
Our optimized conditions were employed to evaluate various β-arylethylamine and arylmethylamine reacting partners (Scheme 2.12, *infra*). First, substituted tryptamines were investigated. To establish the relevance of the β-arylethylamine electronics, electron-rich and electron-poor tryptamines were investigated. Two tryptamines bearing an electron-donating substituent were investigated: 5-methoxytryptamine[48] and 5-methyltryptamine[49] which gave the desired products **2.62** and **2.63**, respectively, in yields comparable to that of **2.61**. Thus, the presence of an electron-donating group did not significantly affect the yield. Increasing the electron-donating group strength, from methyl to methoxy, was associated with a slight decrease in yield. However, the presence of an electron-withdrawing substituent substantially reduced the yield, as can be seen with the 5-chlorotryptamine[50] cyclization product (**2.64**). To effect complete cyclization, a reaction time of three days at 23°C or 16 hours at 60°C was required. To probe the effect of indole *N*-alkylation, 1-methyltryptamine[45] was cyclized to give **2.65**. As anticipated, the *N*-alkyl group slightly decreased the yield. To extend the scope of this reaction beyond tryptamines, 4-(aminomethyl)indole (**2.34f**), an established Pictet-Spengler substrate,[35] was investigated. This substrate was of interest due to the strained geometry of the cyclization product. To reduce the time required for complete cyclization from three days to 16 hours, the reaction mixture was heated to 60°C to give **2.66**. However, attempts to cyclize 2-(aminomethyl)indole and 3-(aminomethyl)indole were unsuccessful, as the isoindoles remained uncyclized, both at room temperature and 60°C. The expected cyclization products (**2.67**-**2.68**) were not observed.



Scheme 2.12.[a] Scope of arylalkylamine reacting partner. (a) Isolated yields, followed by product distribution for regioisomeric mixtures. (b) Heated reaction mixture in DCE to 60°C after TFA addition to promote cyclization. (c) Characterized as TFA salt. (d) Cyclization at 23°C and 70°C gave isoindole after basic aq. workup. (e) Cyclization at 23°C and 80°C gave isoindole after basic aq. workup. (f) Cyclization at 23°C gave isoindole after basic aq. workup. (g) Cyclization at 80°C gave a complex mixture. (h) Cyclization at 80°C gave polymerization.

To expand the scope of this work beyond indole nucleophiles, 1-(2-aminoethyl)pyrrole (**2.34i**) and substituted phenethylamine (**2.34k**-**m**) substrates were investigated. The pyrrole ring is a privileged scaffold found in many bioactive molecules.[51] Furthermore, Pictet-Spengler reactions of 1-(2-aminoethyl)pyrrole have been reported.[23,24,26,28] Purification attempts were

unsuccessful, even following acidification with AcOH or TFA, as the product oxidized readily. Impurities arising from the viscosity of the product were excluded using procedural modifications, giving **2.69**.[52] Attempts to cyclize homopiperonylamine[53], dopamine[54], and 3-methoxyphenethylamine[14,54] substrates from the seminal Pictet-Spengler works[14,15] were unsuccessful. The isoindoles formed cleanly, but homopiperonylamine remained uncyclized (**2.71**), 3-methoxyphenethylamine polymerized (**2.73**), and dopamine[55] gave a complex mixture (**2.72**). Additionally, the isoindole of 2-furan-2-yl-ethylamine also failed to cyclize (**2.70**), both at room temperature and 70°C. While there is literature precedent for the amine as a Pictet-Spengler substrate, one of the reported reactions[30] used HCl, which is a stronger acid catalyst than TFA, and the other used an *N*-acyliminium reacting partner, which is a stronger electrophile than an isoindolium. Therefore, the reaction conditions investigated may have been too mild for this substrate.



Scheme 2.13.[a] Scope of aldehyde reacting partner. (a) Isolated yields followed by product distributions. (b) Determined by ^{1}H NMR. (c) From crude mixture. (d) Expected major and minor products. Identities were not confirmed. (e) From lyophilized pure mixture. (f) Heated to 50°C in DCE to form isoindole. (g) The 2-(chloromethyl)benzaldehyde was used to prepare **2.77**. (h) Possible regioisomeric mixture. (i) No cyclization was observed at 23°C or 70°C. (j) Approximately 80% conversion to the isoindole was achieved. No cyclization was observed at 23°C. (k) A complex mixture was obtained and cyclization may not have occurred at 70°C. (l) Suspected decomposition.

Next, substituted 2-bromomethylbenzaldehydes were screened (Scheme 2.13, *supra*). Reactions of 2-bromomethyl-3-chlorobenzaldehyde, 2-bromomethyl-4-chlorobenzaldehyde, and 2-bromomethyl-4-fluorobenzaldehyde with tryptamine were used to probe the electronics and regioselectivity of the reaction, giving regioisomeric mixtures **2.74**–**2.76**, respectively. Diminished reaction yields were observed for the electron-deficient halogen-substituted aldehydes. Chlorine substitution of the aldehyde decreased the yield by 11-15%, and fluorine substitution decreased the yield by 21%. These data suggest an inverse relationship between the electron deficiency of the substrate and the yield. Chlorine substitution in the 3-position gave over twofold greater regioselectivity than the 4-position. As anticipated, fluorine substitution in the 4-position gave approximately the same regioselectivity as chlorine substitution in the 4-position. Using 1D ^{1}H NOE experiments, **2.74a** was identified as the major product of **2.74** (Figure 2.10). At room temperature, it appears that the less stable isoindolium regioisomer cyclizes to form the major product. The isoindolium that leads to **2.74a** is less stable than the isoindolium leading to **2.74b** because in the latter, chlorine is *ortho* to the iminium and stabilizes it via conjugation, whereas in the former, chlorine is *meta* and thus, not in conjugation with the iminium. While at first glance, this is not consistent with our observations for **2.83** (Scheme 2.15, *infra*) and **2.82** (Scheme 2.14, *infra*), described *infra*, those reactions were heated, which may favor the formation of the more stable isoindolium regioisomer. Regioisomers of **2.75** and **2.76** were not separable by TLC or HPLC.

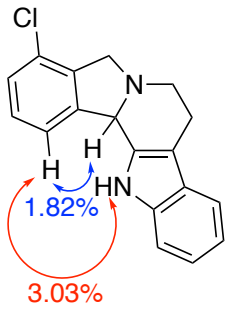
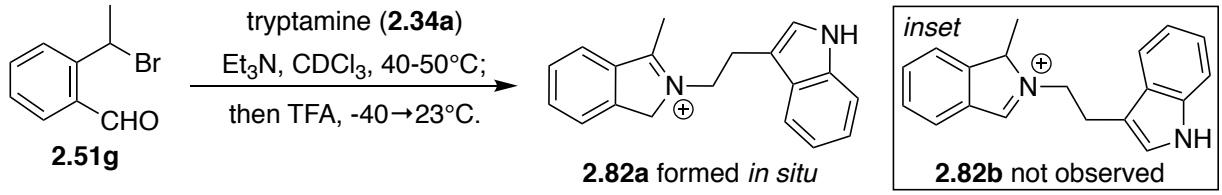


Figure 2.10. Key 1D ^{1}H NOE data for **2.74a**.

The electron-rich aldehydes 2-chloromethyl-6-methylbenzaldehyde (**2.51e**)[56] and 2-bromomethyl-4-methoxybenzaldehyde (**2.51f**) were also investigated and gave products **2.77** and **2.78**, respectively. The comparatively lower yields for **2.77** and **2.78**, the cyclization products of electron-rich aldehydes, can be attributed to the observed instabilities of both the products and their aldehyde precursors. Interestingly, the HPLC and LCMS data suggest that only one regioisomer of **2.77** formed, and the ^{1}H NMR spectrum appears to be consistent with this data. While there is a singlet that could correspond to a methine CH, the integrals for other small peaks in the alkyl region, while potentially too small to be reliable, are not consistent with belonging to a minor regioisomer. Thus, it can only be discerned that the regioselectivity for this substrate is at least 6.3:1. The high regioselectivity for this substrate can potentially be explained by the steric hinderance associated with cyclization through the isoindolium that is *ortho* to the methyl group. The reaction for **2.78** was slightly less regioselective, with a ratio of 4.2:1. Interestingly, for **2.78**, the regioselectivity for the room temperature cyclization favored the regioisomer with the more upfield methine proton in the ^{1}H NMR, which is seemingly more consistent with structure **2.78b**, as the methine proton is farther from the electronegative oxygen atom. This corresponds to the more stable isoindolium but could potentially be attributed to the greater degree of steric hindrance associated with cyclizing through the less substituted

isoindolium. Due to the instabilities of the aldehydes, the associated low yields obtained for these starting materials, and the fact that the regioselectivities could not conclusively be determined, investigations for these substrates were abandoned prior to full characterization of the compounds.

Attempts to investigate the effects of substitution at the isoindolium 1-/3-position, using 2-(bromoethyl)benzaldehyde (**2.51g**), 2-(dibromomethyl)benzaldehyde (**2.51h**), and (2-(bromomethyl)phenyl)(phenyl)methanone (**2.51i**) were unsuccessful. Cyclization was not observed for 2-(bromoethyl)benzaldehyde, even with heating (**2.79**). For **2.51h** and **2.51i**, incomplete conversion to the isoindole was observed, even with heating and long reaction times. Additionally, no cyclization was observed for the reactions of **2.51h** and **2.51i** at room temperature and suspected decomposition was observed for **2.51i** in the presence of gentle heat (**2.81**), whereas **2.51h** gave a complex mixture and possibly remained uncyclized (**2.80**). However, the regioselectivity of the isoindolium formation was determined using **2.51g** (Scheme 2.14, **2.82**). The isoindole and isoindolium were formed *in situ* in $CDCl_3$. Following acidification, a ^1H NMR spectrum of the isoindolium was obtained (Figure 2.11). A peak at 5.15 ppm integrating to two hydrogens was observed, which is close to the chemical shift of the benzylic isoindolium protons from the preliminary studies. The isoindolium C-H singlet was also absent. These findings establish that for **2.82**, the more substituted isoindolium **2.82a** forms exclusively and support our hypothesis that steric hinderance from the methyl group prevented cyclization.



Scheme 2.14. Regioselectivity of isoindolium formation for **2.82**.

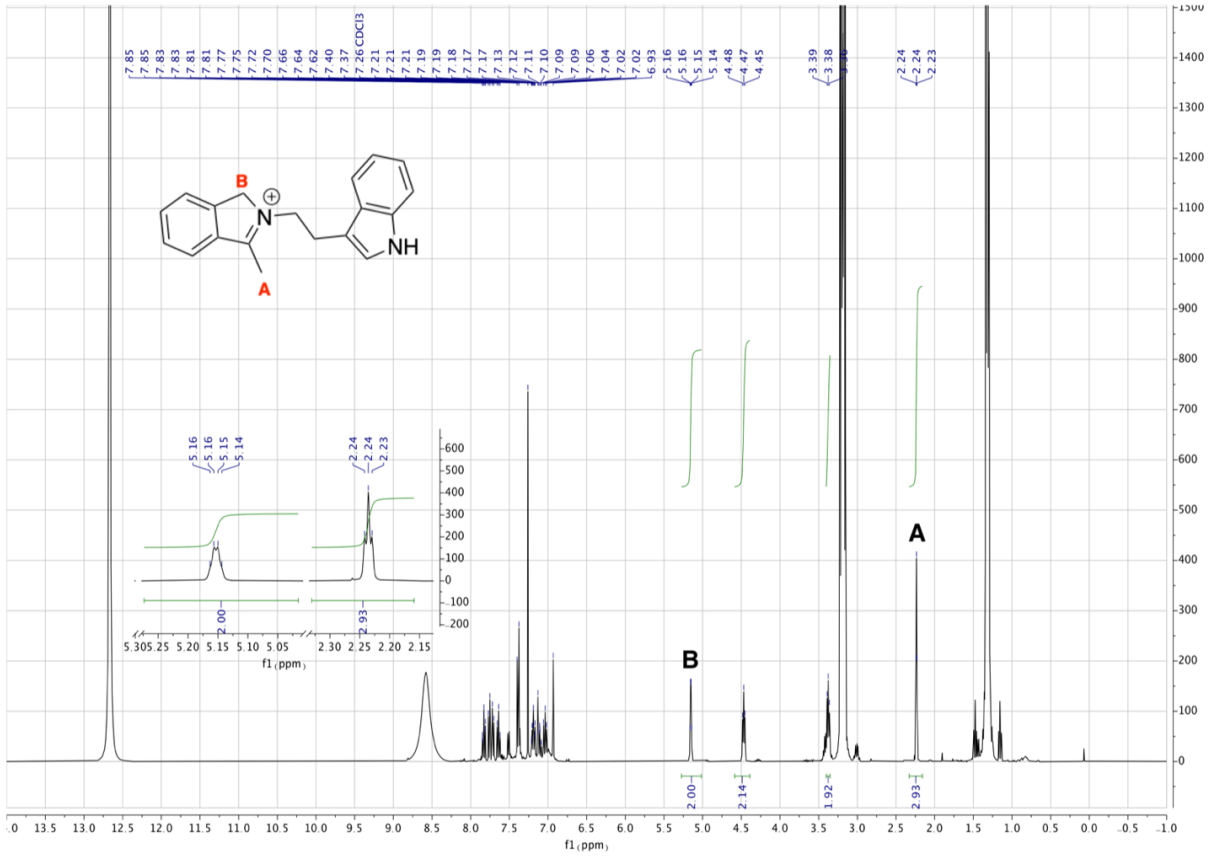
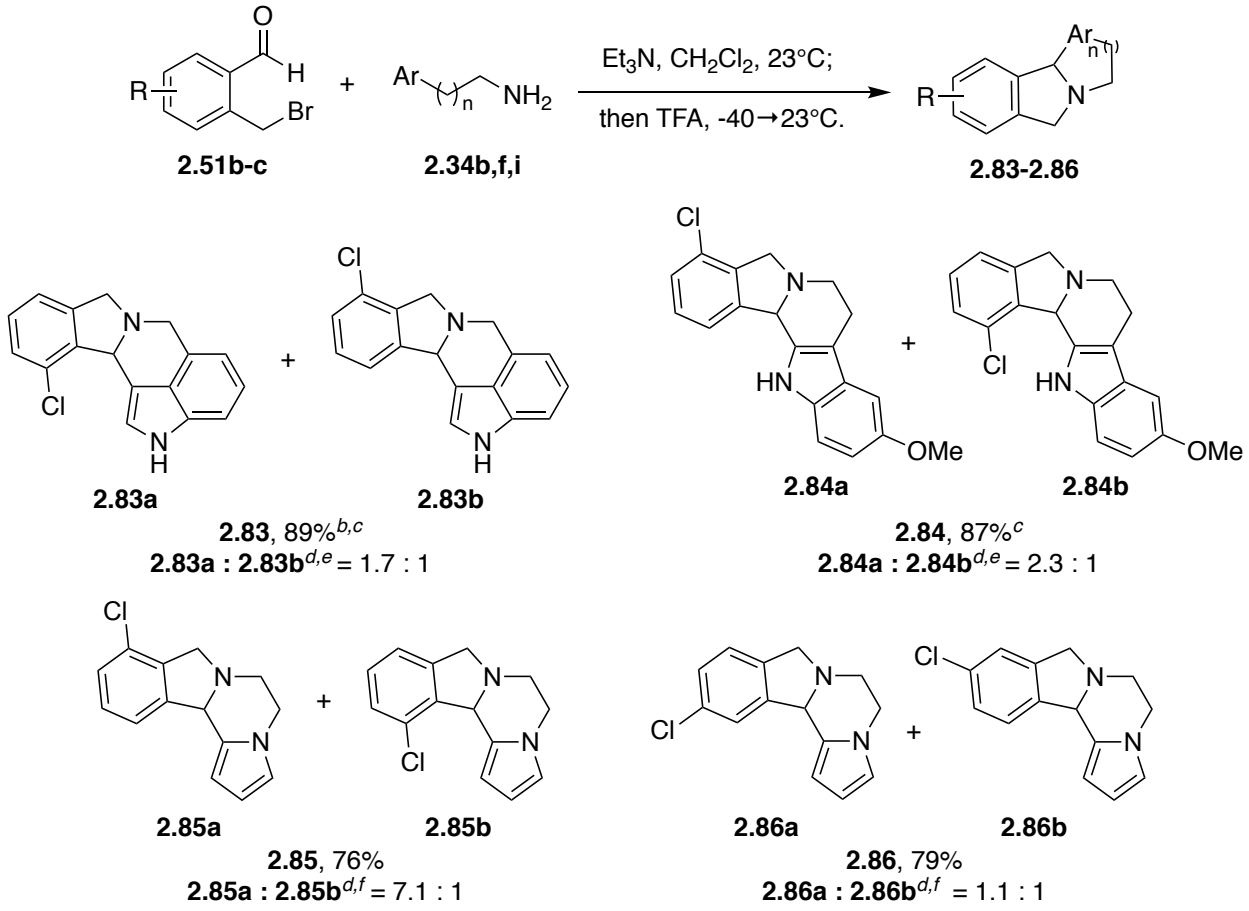


Figure 2.11. ^{1}H NMR spectrum of Isoindolium **2.82**.

Finally, we investigated the effects of combining 2-bromomethyl-3-chlorobenzaldehyde with 4-(aminomethyl)indole (**2.83**) and 5-methoxytryptamine (**2.84**) on the yield and regioselectivity (Scheme 2.15, *infra*). Interestingly, using an electron-poor aldehyde with 4-

(aminomethyl)indole improved the yield considerably. However, the regioselectivity of **2.83** was about half that of **2.74**. The increase in yield with 5-methoxytryptamine, for **2.84** versus **2.62**, was negligible, and the regioselectivity of **2.84** was also substantially lower than **2.74**. While the regioselectivity of **2.84** is expected to be the same as that of **2.74**, with the reaction cyclizing via the less stable isoindolium, the regioselectivity of **2.83** is expected to be the opposite because the reaction required heat. While the structures of the regioisomers were not confirmed due to degradation of the samples in the NMR solvents during the long acquisition times required to obtain clean NMR spectra, the ^{1}H NMR data support this hypothesis. In the major product (**2.83a**), the methine proton is further downfield than in the minor product (**2.83b**), which suggests that it is closer to the chlorine atom in the major product. This is consistent with structure **2.83a** and with our findings for the other reactions that were exposed to heat for which regioisomers were observed. Conversely, the methine proton in **2.74a**, the identity of which was confirmed, was further upfield than that of **2.74b**, which indicates that the chlorine atom is further away from the methine proton in the major product. Similarly, in the ^{1}H NMR for the major regioisomer of **2.84** (**2.84a**), the methine proton is further upfield than it is in the minor regioisomer (**2.84b**). Like **2.74**, **2.84** was not exposed to heat, so these results are consistent with our hypothesis that room temperature cyclizations proceed through the less stable isoindolium ion, whereas reactions that are heated to effect cyclization proceed through the more stable isoindolium ion.



Scheme 2.15.*a* Combinations of substituted aldehydes with various arylalkylamines. (a) Isolated yield followed by product distribution. (b) Heated reaction mixture in DCE to 60°C after TFA addition to promote cyclization. (c) Characterized as HCl salt. (d) Expected major and minor products. Identities were not confirmed. (e) Determined by HPLC from acidified crude mixture. (f) Determined by ^{1}H NMR from crude mixture.

To attempt to address some of the issues observed with the cyclization product of 1-(2-aminoethyl)pyrrole (**2.69**), we investigated the effects of combining it with 2-bromomethyl-3-chlorobenzaldehyde (**2.51b**) and 2-bromomethyl-4-chlorobenzaldehyde (**2.51c**), reasoning that the cyclization products may be stable enough to purify due to the presence of an electronegative chlorine atom and that the regioisomers for **2.86** (Scheme 2.15, *supra*) may be separable, which would allow us to determine the regioselectivity for cyclizations of 2-bromomethyl-4-

chlorobenzaldehyde (**2.51c**). Disappointingly, while both reactions cyclized successfully and gave good yields of 76% and 79% for **2.85** and **2.86**, respectively, the products were not stable to purification and the regioisomers for **2.86** were not separable. From the crude ^{1}H NMR spectra, the respective regioselectivities for **2.85** and **2.86** were approximately 7.1:1 and 1.1:1. Interestingly, while the regioselectivity for **2.86** was slightly worse than that of the tryptamine cyclization product of 2-bromomethyl-4-chlorobenzaldehyde (**2.75**), the regioselectivity for **2.85** was nearly double that of **2.74**.

2.9. Conclusions and Future Work

We have developed an efficient synthesis of polycyclic isoindolines in good yields using a one-pot procedure. The *in situ*-generated nucleophilic isoindoles were converted to electrophilic isoindoliums via protonation, which underwent Pictet-Spengler-type cyclizations to give the polycyclic isoindolines. These results open the door to other reactions that can utilize isoindoliums as electrophiles via isoindole umpolung and extend the scope of the Pictet-Spengler reaction to include isoindolium electrophiles. Efforts toward the development of an additional reaction based on the isoindole umpolung strategy will be discussed in the next chapter. However, it is likely that many others have yet to be discovered. Efforts toward further development of additional reactions that utilize this approach and the biological evaluation of the polycyclic isoindolines are ongoing in this research group and will be reported in due course.

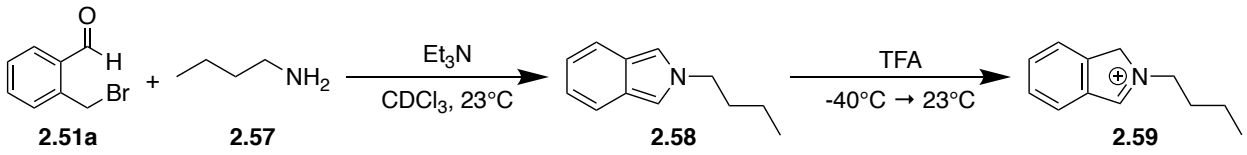
2.10. Experimental

General Considerations. All reactions were performed under argon. Moisture-sensitive reactions were carried out using oven- and vacuum-dried glassware. Dry DCM, THF, MeOH,

and toluene were dried using a PS-MD-5 solvent purification system from Innovative Technology, by passage through columns containing activated alumina and copper. Dry DCE was dried over 3 Å molecular sieves. Dry DCM and DCE used in the synthesis of benzaldehyde substrates and cyclization reactions were stored over 3 Å molecular sieves under argon and degassed prior to use by bubbling argon gas through the solvent. All commercially available reagents were purchased from different suppliers and used as received. Melting points were recorded on a DigiMelt melting point apparatus from Stanford Research Systems. Deuterated solvents for NMR spectroscopy were purchased from different suppliers. All deuterated solvents were dried over 3 Å molecular sieves and anhydrous Na_2SO_4, with the exception of $CDCl_3$, which was dried over 3 Å molecular sieves and oven-dried anhydrous K_2CO_3. NMR spectra were recorded on a Varian INOVA 500 MHz NMR Spectrometer (11.74 T), Varian INOVA 400 MHz NMR Spectrometer (9.39T), or a Bruker Avance-III 300 NMR Spectrometer (7.05 T) at temperatures of 20-25°C and were processed using MestreNova version 14.0.1. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. Unless otherwise noted, proton (^1H) and carbon (^{13}C) NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ = 7.26; 77.16), residual C_3D_5HO in C_3D_6O (δ = 2.05; 29.84), residual CD_2HCN in CD_3CN (δ = 1.94; 1.32), residual CD_2HOD in CD_3OD (δ = 3.31; 49.00), residual C_2D_5HOS in C_2D_6OS (δ = 2.50; 39.52), or residual $CDHCl_2$ in CD_2Cl_2 (δ = 5.32; 54.00). In some cases, due to the proximities of the chemical shifts to other peaks or the desire to do subsequent GSD analyses on the same spectrum, residual HOD in CD_3OD (δ = 4.87) was used as a reference in the ^1H NMR. For ^{13}C NMR spectra taken in CD_3CN, if the solubility of the compound was low, the nitrile carbon was used as a reference, instead (δ = 118.26). Coupling constants (J) are reported in Hertz (Hz) and refer to apparent

multiplicities. The following abbreviations are used for the multiplicities: (s): singlet, (d): doublet, (t): triplet, (q): quartet, (p): pentet, (m): multiplet. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Infrared spectra were recorded on a Cary 360 ATR FT-IR. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. For purifications and determination of product distributions by HPLC, a Zorbax 300 SB-C18 PrepHT (5 µm, 21.2 x 150 mm) column and HPLC-grade solvents were used.

Procedures for the Formation of Isoindoles and Isoindolium Salts for Preliminary Studies.



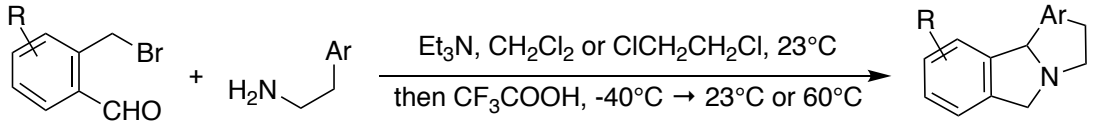
2.51a **2.57** **2.58** **2.59**

Formation of Isoindoles and Isoindolium Salts for Preliminary Studies: Stepwise Procedure. Aldehyde **2.51a** (0.070 mmol, 1.0 equiv) and *n*-butylamine (**2.57**, 0.084 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (0.70 mL, 0.10 M) in a 2-dram teflon-lined screw cap vial equipped with a magnetic stir bar. The reaction mixture was purged with argon and triethylamine (0.084 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then washed twice with water (2 x 0.70 mL), and the organic portion was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give isoindole **2.58**. The residue was taken up in 0.70 mL $CDCl_3$[57], transferred to an NMR tube, and a ^1H NMR spectrum of isoindole **2.58** was recorded. Isoindole **2.58** was then further diluted with $CDCl_3$[57] to a total volume of 1.4 mL and cooled to -40°C. TFA (3-5 drops) was added directly to the reaction mixture at -40°C, the cooling bath was promptly withdrawn, and the NMR tube was shaken

vigorously to mix the reactants. The reaction mixture was allowed to warm to room temperature, sonicated for several minutes, and a ^{1}H NMR spectrum of isoindolium **2.59** was recorded *in situ*.

Formation of Isoindoles and Isoindolium Salts for Preliminary Studies: One-Pot Procedure. Aldehyde **2.51a** (0.070 mmol, 1.0 equiv) and *n*-butylamine (**2.57**, 0.084 mmol, 1.2 equiv) were dissolved in $CDCl_3$[57] (0.70 mL, 0.10 M) in a 2-dram teflon-lined screw cap vial equipped with a magnetic stir bar. The reaction mixture was purged with argon and triethylamine (0.084 mmol, 1.2 equiv) was added. The reaction mixture was stirred at room temperature for 1 h. A 0.5 mL aliquot of isoindole **2.58** was transferred to an NMR tube and a ^{1}H NMR spectrum was recorded *in situ*. The NMR sample was cooled to -40°C and 3-5 drops of TFA were added. The reaction mixture was allowed to warm to room temperature, sonicated for several minutes, and a ^{1}H NMR spectrum of isoindolium **2.59** was recorded *in situ*.

Reaction Scheme and General Procedures for Acid-Catalyzed Cyclization Reactions.



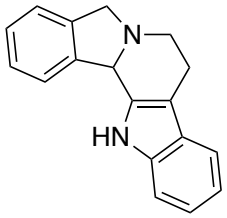
2.51a-f **2.34a-m** **2.61-2.84**

R = H, Cl, F, Me, OMe

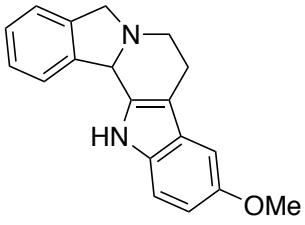
General Procedure A: Cyclization at Room Temperature. The aldehyde (**2.51a-i**) (0.20 mmol, 1.0 equiv) and *β*-arylalkylamine (**2.34a-m**) (0.24 mmol, 1.2 equiv) reacting partners were dissolved in dry DCM (2.0 mL, 0.10 M) in a 25 mL round-bottom flask equipped with a magnetic stir bar. Triethylamine (0.24 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. Upon complete

conversion of the aldehyde to the isoindole (generally between 1.5 and 2.5 h), an additional 8.0 mL of dry DCM was added. The reaction mixture was cooled to -40°C and TFA (4.0 mmol, 20 equiv) was added. The reaction mixture was allowed to warm slowly to room temperature, and the reaction mixture was stirred for 16 h. The reaction mixture was washed once with saturated aqueous K_2CO_3 (5.0 mL). The aqueous portion was then extracted with DCM (10.0 mL). The organic extracts were combined and dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. Products **2.61-2.63, 2.65, 2.69, 2.74-2.78,** and **2.84-2.86** were purified as described *infra*. Product **2.69** was subjected to procedural modifications described *infra* and characterized without further purification.

General Procedure B: Cyclization at Elevated Temperature. The aldehyde (**2.51a-i**) (0.20 mmol, 1.0 equiv) and *β*-arylalkylamine (**2.34a-m**) (0.24 mmol, 1.2 equiv) reacting partners were dissolved in dry DCE (2.0 mL, 0.10 M) in a 35 mL sealed tube equipped with a magnetic stir bar or spin vane. Triethylamine (0.24 mmol, 1.2 equiv) was added, the reaction mixture was returned to an argon atmosphere, and the tube was quickly sealed. The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. Upon complete conversion of the aldehyde to the isoindole (generally between 1.5 and 2.5 h), an additional 8.0 mL of dry DCE was added. The reaction mixture was cooled to -40°C and TFA (4.0 mmol, 20 equiv) was added. The reaction mixture was allowed to warm slowly to room temperature, and then heated to 60°C for 16 h, with stirring. Products **2.64, 2.66,** and **2.83** were subjected to the general work-up described in general procedure A, *supra*, and purified as described *infra*.

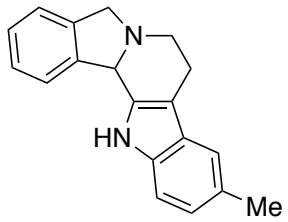


*7,8,13,13b-Tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.61**).* Cyclization product **2.61** was synthesized using general procedure A. Purification using basic alumina flash column chromatography (1:5 Hexanes:EtOAc, then 1:1 DCM:EtOAc) gave 48.0 mg (91% yield) of **2.61** as a tan solid. m.p.: 167.8-172.5°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.52 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.32 – 7.20 (m, 4H), 7.17 – 7.09 (m, 2H), 5.53 (s, 1H), 4.23 (d, *J* = 12.8 Hz, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.47 (ddd, *J* = 13.8, 5.5, 2.1 Hz, 1H), 3.36 (ddd, *J* = 13.8, 10.8, 4.6 Hz, 1H), 3.09 (dddd, *J* = 16.1, 10.8, 5.5, 2.0 Hz, 1H), 2.74 – 2.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.4, 136.4, 133.2, 127.6, 127.3, 127.1, 123.5, 122.1, 121.8, 119.5, 118.4, 111.0, 108.1, 61.8, 54.1, 45.2, 16.7, 15.9 ppm. FTIR (neat): $\tilde{\nu}$ 3149, 3100, 3044, 3071, 2925, 2854, 1446, 1356, 1323, 1282, 1219, 1181, 1144, 1114, 1077, 1010, 976, 935, 898, 865, 801, 742 cm^{-1}. HRMS (ESI^{+}): m/z $[M+H]^{+}$ calculated for $C_{18}H_{16}N_2$: 261.1392; found: 261.1402.



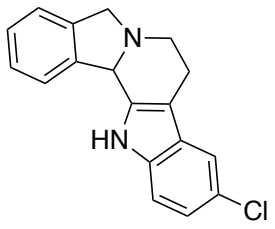
*10-Methoxy-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.62**).* Cyclization product **6** was synthesized using general procedure A. Purification using basic alumina flash column chromatography (EtOAc + 2% TEA) gave 59.6 mg (86% yield) of **2.62** as a yellow-green solid. m.p.: 175.9-180.0°C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (s, 1H), 7.48 (d, *J* =

7.0 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.53 (s, 1H), 4.22 (d, *J* = 12.8 Hz, 1H), 4.15 (d, *J* = 12.6 Hz, 1H), 3.84 (s, 3H), 3.46 (ddd, *J* = 14.1, 5.5, 1.5 Hz, 1H), 3.35 (ddd, *J* = 14.0, 11.1, 4.7 Hz, 1H), 3.06 (dddd, *J* = 16.5, 11.0, 5.6, 1.7 Hz, 1H), 2.69 – 2.56 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 141.0, 140.3, 134.1, 131.5, 127.7, 127.6, 127.1, 123.5, 122.1, 111.7, 111.5, 107.9, 100.7, 61.8, 56.0, 54.1, 45.1, 16.8 ppm. FTIR (neat): $\tilde{\nu}$ 3149, 3059, 2929, 2854, 1673, 1621, 1595, 1476, 1453, 1356, 1301, 1282, 1211, 1137, 1110, 1077, 1028, 999, 935, 909, 891, 846, 820, 790, 745, 704 cm^{-1}. HRMS (ESI$^+$): m/z $[M+H]^+$ calculated for $C_{19}H_{18}N_2O$: 291.1497; found: 291.1502.

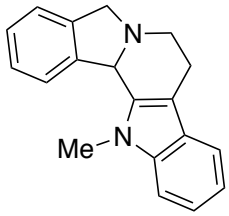


*10-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.63**)*. Cyclization product **2.63** was synthesized using general procedure A. Purification using basic alumina flash column chromatography (EtOAc + 2% TEA) gave 65 mg (90% yield) of a golden-brown solid. m.p.: 128.0-133.6°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.30 (s, 1H), 7.29 – 7.22 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 5.52 (d, *J* = 1.0 Hz, 1H), 4.22 (d, *J* = 13.0 Hz, 1H), 4.16 (d, *J* = 12.8 Hz, 1H), 3.45 (ddd, *J* = 13.8, 5.4, 1.8 Hz, 1H), 3.35 (ddd, *J* = 13.9, 10.9, 4.7 Hz, 1H), 3.06 (dddd, *J* = 16.1, 10.8, 5.4, 1.8 Hz, 1H), 2.70-2.63 (m, 1H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.04, 140.27, 134.71, 133.19, 128.70, 127.59, 127.55, 127.09, 123.42, 123.28, 122.13, 118.10, 110.65, 107.55, 61.82, 54.13, 45.18, 21.55, 16.76 ppm. FTIR (neat): $\tilde{\nu}$ 3398, 3015, 2914, 2843, 1673, 1587, 1457, 1353, 1301,

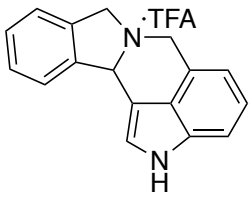
1237, 1118, 1017, 865, 790, 738 cm^{-1}. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{19}H_{18}N_2$: 275.1548; found: 275.1553.



*10-Chloro-5,6,7,8,13,13b-hexahydrobenzo[1,2]indolizino[8,7-b]indol-6-ium (**2.64**).* Cyclization product **2.64**[58] was synthesized using general procedure B. Purification using preparative TLC (silica; EtOAc) gave 49.8 mg (69% yield) of **2.64** as a yellow solid. m.p.: 152.2-155.9°C. ^1H NMR (400 MHz, CD_3CN) δ 9.67 (s, 1H), 7.75 (d, *J* = 6.9 Hz, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.50 – 7.37 (m, 5H), 7.16 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.27 (s, 1H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.57 (d, *J* = 14.4 Hz, 1H), 3.75 – 3.61 (m, 2H), 3.10 (ddd, *J* = 6.9, 5.0, 1.4 Hz, 2H). ^{13}C NMR (101 MHz, CD_3CN) δ 136.7, 136.4, 134.8, 130.3, 129.8, 129.6, 127.8, 125.7, 124.7, 124.2, 123.4, 118.8, 113.7, 106.5, 62.9, 55.6, 46.6, 17.1. FTIR (neat): $\tilde{\nu}$ 3220, 2921, 2854, 1666, 1446, 1315, 1178, 1129, 1058, 1014, 984, 946, 879, 835, 797, 742, 719, 704, 663 cm^{-1}. HRMS (ESI^+): m/z $[M]^+$ calculated for $C_{18}H_{15}ClN_2^+$: 295.1002; found: 295.1006.

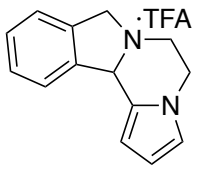


*13-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.65**).* Cyclization product **2.65** was synthesized using general procedure A. Purification using preparative TLC (silica; 4:3 Hexanes:EtOAc + 5% TEA) gave 52.2 mg (87% yield) of **2.65** as a pale yellow to tan-yellow solid. m.p.: 95.1-98.3°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.51 (d, J = 7.8 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.35 – 7.29 (m, 2H), 7.28 – 7.16 (m, 3H), 7.11 (t, J = 7.4 Hz, 1H), 5.50 (s, 1H), 4.35 (d, J = 14.1 Hz, 1H), 4.12 (d, J = 14.2 Hz, 1H), 3.89 (s, 3H), 3.11 – 2.82 (m, 4H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 142.2, 142.1, 138.4, 135.0, 127.8, 127.4, 127.2, 124.2, 124.0, 121.8, 119.5, 118.7, 109.5, 108.7, 62.4, 57.7, 47.3, 31.9, 19.8 ppm. FTIR (neat): $\tilde{\nu}$ 3048, 2951, 2914, 2851, 2813, 2694, 1684, 1614, 1464, 1379, 1341, 1308, 1289, 1263, 1241, 1207, 1181, 1148, 1129, 1114, 1073, 1047, 1010, 958, 913, 846, 771, 738, 701 cm^{-1}. HRMS (ESI^{+}): m/z [M+H]$^{+}$ calculated for $C_{19}H_{18}N_2$: 275.1548; found: 275.1554.



*6,7,8,12b-Tetrahydro-2H-isoindolo[2,1-b]pyrrolo[4,3,2-de]isoquinolin-7-ium (**2.66**).* Cyclization product **2.66** was synthesized using general procedure B, except that EtOAc was substituted for DCM as the extraction solvent in the workup, in order to minimize the presence of triethylammonium salt. The crude product was then lyophilized to remove Et_3N, then taken up in EtOAc and acidified with TFA. The solvent was removed, and the residue was taken up in

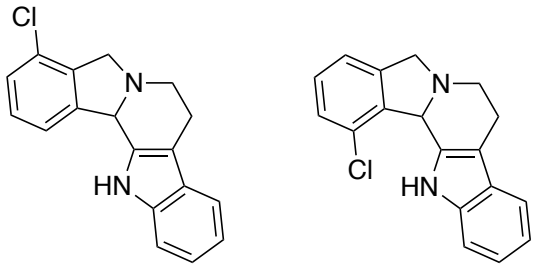
HPLC-grade acetonitrile and filtered using a 0.22 μm syringe filter. The crude TFA salt was purified by preparative HPLC with a gradient of 70-55% A (A: 0.1% TFA in H_2O, B: ACN). Crude material purposefully discarded from the injection syringe to clear air bubbles was recovered via a kimwipe that was subsequently dissolved in methanol, so that an accurate yield could be determined, as attempts to purify the product by silica gel and basic alumina chromatography were unsuccessful. Lyophilization in 1:1 ACN: H_2O gave 54.8 mg (75% yield) of **2.66** as a dark red to dark brown solid. m.p.: 143.9-147.4°C. ^{1}H NMR (400 MHz, CD_3CN) δ 9.54 (s, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 (s, 1H), 7.02 (*br* d, *J* = 7.1 Hz, 1H), 6.41 (s, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.83 (d, *J* = 14.1 Hz, 1H), 4.55 (d, *J* = 15.8 Hz, 1H), 4.26 (d, *J* = 14.1 Hz, 1H). ^{13}C NMR (101 MHz, CD_3CN) δ 139.5, 134.5, 134.1, 130.0, 129.8, 124.6, 124.2, 123.3, 123.1, 122.1, 120.4, 117.0, 111.9, 106.1, 65.0, 56.6, 49.5 ppm. FTIR (neat): $\tilde{\nu}$ 3223, 3119, 3052, 2989, 2948, 2567, 1666, 1591, 1446, 1341, 1178, 1125, 1055, 1017, 913, 835, 797, 745, 719 cm^{-1}. HRMS (ESI$^+$): m/z $[M]^+$ calculated for $C_{17}H_{15}N_2^+$: 247.1235; found: 247.1244.



*6,7,8,12b-Tetrahydro-5H-pyrrolo[2',1':3,4]pyrazino[2,1-a]isoindol-7-ium (**2.69**).* Cyclization product **2.69** was prepared using general procedure A, but with several modifications. The reaction vessel and the isolated products were covered in foil, whenever possible, to prevent any light-catalyzed reactions of the pyrrole ring. The light in the fume hood remained off at all times. The DCM used was degassed several times prior to use, as were the saturated aqueous K_2CO_3 and EtOAc used in the work-up and acidification steps. The cleanest product was obtained when

an excess of 2-(bromomethyl)benzaldehyde (**2.51a**) (1.2 equivalents) was used, instead of 1-(2-aminoethyl)pyrrole. When 1-(2-aminoethyl)pyrrole was used in excess, the viscous crude product trapped the residual 1-(2-aminoethyl)pyrrole. Attempts to remove it *in vacuo*, even for 5-7 days, were unsuccessful, and the product was not stable to lyophilization. When a smaller excess (1.05-1.1 equivalents) of 1-(2-aminoethyl)pyrrole was used, complete conversion was not achieved. Accordingly, the amine reacting partner was weighed out first, and the flask was immediately placed under argon; the aldehyde partner was then weighed out separately, quickly transferred to the reaction flask, and promptly dissolved in DCM. The reaction was allowed to proceed as normal, with the isoindole forming in only 1.25 h. Upon complete cyclization, the solvent was carefully removed *in vacuo*, at ambient temperature. EtOAc was substituted for DCM as the extraction solvent, and the work-up was carried out as previously described, except that the extract was kept under argon while drying over Na_2SO_4. Once isolated, the crude product was covered in foil and allowed to dry *in vacuo* for 48-72 h to remove Et_3N. The residue was then taken up in ethyl acetate and filtered via syringe (0.22 μm filter) to remove any residual Et_3NH^+ salt and any other insoluble impurities. The filter was rinsed with additional ethyl acetate and the filtrate was concentrated to about half its initial volume, and TFA was added dropwise until no more precipitation was observed. To remove residual EtOAc, the residue was taken up in chloroform and concentrated several more times. The residual solvent was then removed *in vacuo* over 2 d, while covered in foil. These modifications gave 57.5 mg (91% yield) of **2.69** as a dark green sticky solid, which was characterized without further purification, due to its tendency to oxidize readily when exposed to air. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.32 (m, 4H), 7.28 – 7.25 (m, 1H), 6.71 – 6.68 (*br* m, 1H), 6.34 – 6.23 (m, 2H), 6.17 (s, 1H), 5.12 (d, J = 14.7 Hz, 1H), 4.43 (ddd, J = 13.9, 10.5, 3.3 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H), 4.12 (dt, J = 13.8, 3.7 Hz,

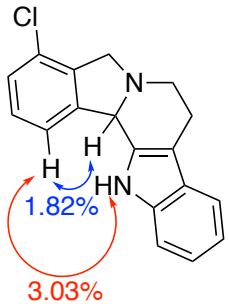
1H), 3.95 (dt, *J* = 12.4, 3.6 Hz, 1H), 3.43 – 3.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 132.1, 129.7, 129.6, 123.8, 123.5, 121.3, 120.8, 109.6, 107.0, 62.9, 58.7, 48.1, 41.1 ppm. FTIR (neat): $\tilde{\nu}$ 2921, 2854, 1666, 1461, 1416, 1341, 1301, 1178, 1118, 999, 961, 920, 827, 794, 745, 719 cm^{-1}. HRMS (ESI$^+$): m/z [M]$^+$ calculated for $C_{14}H_{15}N_2^+$: 211.1235; found: 211.1239.



*4-Chloro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.74a**) and 1-Chloro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.74b**).* Regioisomeric mixture **2.74** was synthesized using general procedure A. A product distribution of 3.9:1 for **2.74a**:**2.74b** was determined by integrating the methine singlets in the crude ^{1}H NMR. Subsequent purification by preparative TLC (silica; EtOAc) gave 59.1 mg (77% yield) of **2.74a** and **2.74b**.

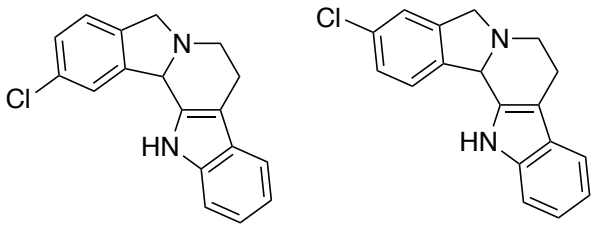
2.74a: Reddish-orange solid. m.p.: 146.0-149.2°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 7.81 (d, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 5.61 (s, 1H), 4.16 (s, 2H), 3.35 – 3.27 (m, 1H), 3.17 – 3.06 (m, 1H), 3.06 – 2.95 (m, 1H), 2.57 – 2.52 (m, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.09 (d, *J* = 1.1 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 6.7 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 5.69 (s, 1H), 4.32 (d, *J* = 13.6 Hz, 1H), 4.21 (d, *J* = 13.6 Hz, 1H), 3.46 (ddd, *J* = 13.7, 5.3, 2.2 Hz, 1H), 3.39 – 3.31 (m, 1H), 3.08 (ddd, *J* = 16.1, 7.0, 3.3 Hz, 1H), 2.77 – 2.69 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 138.1, 136.5, 131.7, 129.8, 129.1, 128.0, 127.0, 122.2, 120.7, 119.7, 118.4,

114.0, 111.2, 108.1, 77.2, 62.7, 53.6, 45.2, 16.7 ppm. FTIR (thin film): $\tilde{\nu}$ 3167, 3059, 2929, 2854, 1685, 1607, 1585, 1566, 1462, 1376, 1350, 1331, 1302, 1268, 1242, 1197, 1182, 1160, 1141, 1112, 1082, 1052, 1011, 981, 925, 907, 892, 873, 840, 810, 795, 743 cm^{-1}. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{18}H_{15}ClN_2$: 295.1002; found: 295.1005.

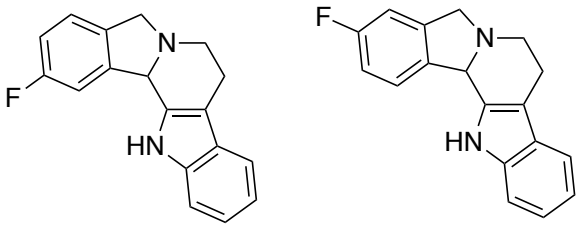


Key 1D ^1H NOE data for **2.74a**.

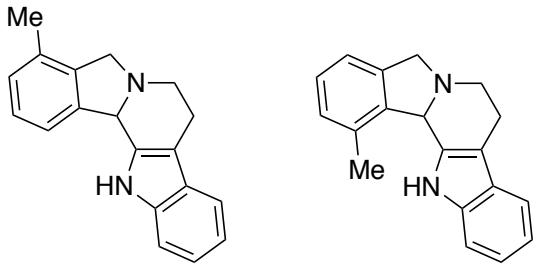
2.74b: Yellow-brown solid. m.p.: 137.5-141.9°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.50 (d, J = 7.7, 1H), 7.34 – 7.30 (m, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.03 (m, 4H), 5.81 (d, J = 2.3 Hz, 1H), 4.32 (d, J = 13.2 Hz, 1H), 4.16 (d, J = 12.8 Hz, 1H), 3.51 (dd, J = 14.1, 5.4 Hz, 1H), 3.38 (ddd, J = 14.1, 11.8, 4.6 Hz, 1H), 3.12 (dddd, J = 15.9, 11.8, 5.6, 2.1 Hz, 1H), 2.73 – 2.64 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 139.6, 135.9, 132.7, 129.4, 128.1, 127.4, 126.9, 122.2, 122.1, 119.6, 118.3, 111.1, 108.3, 61.2, 53.9, 44.7, 16.0 ppm. FTIR (thin film): $\tilde{\nu}$ 3450, 3056, 2925, 2854, 1693, 1626, 1585, 1547, 1491, 1462, 1402, 1376, 1350, 1331, 1302, 1287, 1268, 1242, 1205, 1141, 1112, 1048, 1033, 1015, 974, 899, 858, 810, 776, 736, 706 cm^{-1}. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{18}H_{15}ClN_2$: 295.1002; found: 295.1008.



*2-Chloro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.75a**) and 3-Chloro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.75b**).* Regioisomeric mixture **2.75** was synthesized using general procedure A and subsequently purified by preparative TLC (silica; EtOAc). Lyophilization of the pure product mixture in 1:1 ACN:H_2O gave 53.5 mg (81% yield) of **2.75a** and **2.75b** as a yellow-brown solid. Neither preparative TLC nor HPLC was able to separate **2.75a** and **2.75b**. Due to the proximity to peaks from impurities in the crude ^{1}H NMR, purification and lyophilization were necessary before the product distribution could be determined by integrating the methine proton singlets. The product distribution was determined to be 1.6:1; however, the identities of the major and minor products are not known. The structures above for **2.75a** and **2.75b** represent the predicted major and minor products, respectively. m.p.: 132.5-139.6°C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 10.09 (s, 1H), 10.03 (s, 1H), 7.85 – 7.75 (m, 2H), 7.43 (d, J = 7.8 Hz, 2H), 7.33 – 7.21 (m, 6H), 7.07 – 7.00 (m, 2H), 7.00 – 6.94 (m, 2H), 5.60 (s, 1H), 5.58 (s, 1H), 4.30 – 4.19 (m, 2H), 4.19 – 4.10 (m, 2H), 3.44 – 3.33 (m, 2H), 3.28 – 3.17 (m, 2H), 3.14 – 3.01 (m, 2H), 2.66 – 2.56 (m, 2H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 144.80, 143.94, 141.49, 140.39, 137.67, 137.52, 134.08, 133.83, 133.36, 132.73, 128.13, 128.07, 127.57, 125.41, 125.28, 124.17, 123.99, 122.07, 122.02, 119.60, 119.58, 118.77, 118.75, 111.79, 111.74, 108.41, 108.25, 62.52, 62.19, 54.39, 54.07, 45.68, 45.63, 16.96, 16.93 ppm. FTIR (neat): $\tilde{\nu}$ 3227, 3059, 2921, 285, 1681, 1610, 1584, 1450, 1323, 1237, 1155, 1107, 1073, 1025, 891, 872, 805, 742 cm^{-1}. HRMS (ESI$^+$): m/z $[M+H]^+$ calculated for $C_{18}H_{15}ClN_2$: 295.1002; found: 295.1008.

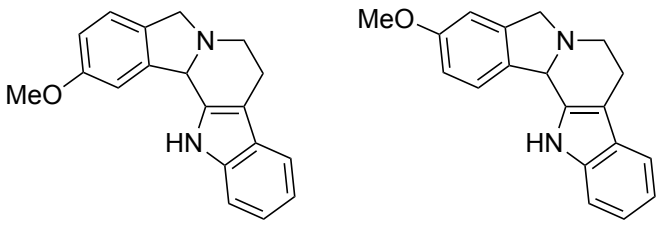


*2-Fluoro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.76a**) and 3-Fluoro-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.76b**).* Regioisomeric mixture **2.76** was synthesized using general procedure A and subsequently purified by preparative TLC (silica; EtOAc) to give 37.8 mg (72% yield) of **2.76a** and **2.76b** as a brown solid. Neither preparative TLC nor HPLC was able to separate **2.76a** and **2.76b**. The product distribution was determined from the crude ^{1}H NMR by integrating the methine proton singlets. The product distribution was determined to be 1.4:1; however, the identities of the major and minor products are not known. The structures above for **2.76a** and **2.76b** represent the predicted major and minor products, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.20 – 7.04 (m, 6H), 7.00 – 6.86 (m, 4H), 5.66 (s, 1H), 5.63 (s, 1H), 4.30 – 4.14 (m, 4H), 3.52 – 3.43 (m, 2H), 3.43 – 3.32 (m, 2H), 3.14 – 3.02 (m, 2H), 2.82 – 2.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.92, 163.50, 161.49, 161.07, 142.82, 142.65, 136.60, 136.40, 135.75, 132.76, 132.20, 127.26, 124.71, 124.62, 123.26, 123.17, 122.14, 122.07, 119.72, 118.45, 114.74, 114.52, 114.24, 114.01, 111.07, 110.81, 109.75, 109.52, 108.45, 108.17, 61.89, 61.22, 54.05, 53.47, 45.13, 16.66.



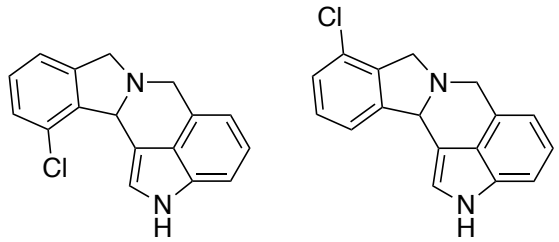
*4-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.77a**) and 1-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.77b**).* Possible regioisomeric mixture **2.77** was synthesized using general procedure A, except that the 2-(chloromethyl)benzaldehyde derivative was used instead of the 2-(bromomethyl)benzaldehyde derivative, DCE was used as the solvent, and the reaction mixture was heated to 50°C during the isoindole formation step only. A product distribution of at least 6.3:1 for **2.77a**: **2.77b** was determined by integrating the methine singlet of the major product and each of the possible methine singlets of the minor product in the crude ^{1}H NMR. Subsequent purification by preparative TLC (silica; 1:4 Hexanes: EtOAc + 2% TEA) gave 30.4 mg[59] (74% yield) of **2.77a** as a yellow-brown solid. All observable fractions from the preparative TLC, as well as a subsequent preparative HPLC conducted for this purpose, were analyzed by LCMS in an effort to locate the minor regioisomer. These efforts were unsuccessful. It is not known whether a minor regioisomer formed. The identity of the major product was not determined, as the amount of material remaining was not sufficient for further NMR experiments. Due to the difficulties associated with synthesizing the aldehyde due to the tendency to undergo dehalogenation during the synthesis of the aldehyde and the observed instability of the aldehyde, further investigations for this substrate were abandoned. The structures above for **2.77a** and **2.77b** represent the predicted major and minor products, respectively. **2.77a:** Yellow-brown solid. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.90 (s, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.27 (d, J =

7.4 Hz, 1H), 7.04 - 6.91 (m, 4H), 5.57 (d, *J* = 1.7 Hz, 1H), 4.17 (d, J = 13.6 Hz, 1H), 4.12 (d, J = 13.0 Hz, 1H), 3.43 (ddd, J = 13.7, 5.1, 1.4 Hz, 1H), 3.24 (ddd, J = 13.8, 11.3, 4.4 Hz, 1H), 3.09 (dddd, J = 15.8, 11.0, 5.0, 1.8 Hz, 1H), 2.61 - 2.55 (m, 1H), 2.20 (s, 3H).



*3-methoxy-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.78a**) and 2-methoxy-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole (**2.78b**).* Regioisomeric mixture **2.78** was synthesized using general procedure A, except that the reaction was run in DCE on a scale of approximately 0.01 mmol and the reaction mixture was heated to 50°C during the isoindole formation only. Subsequent purification by preparative TLC (silica; 15:1 DCM:MeOH) gave 22.1 mg (80% yield) of **2.78** as a golden brown solid. The product distribution was determined by integrating the methine signals in the crude ^{1}H NMR and was found to be 1:4.2; however, the identities of the major and minor products are not known. The structures above for **2.78a** and **2.78b** represent the predicted major and minor products, respectively. Due to the observed instability of the aldehyde and the fact that regioisomers could not be separated, further investigations for this substrate were abandoned. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.81 (s, 1H), 7.48 (app d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.30 (ddd, *J* = 3.0, 1.1, 0.6 Hz, 1H), 7.28 (app ddt, *J* = 8.0, 2.9, 1.1 Hz, 2H), 7.18 – 7.03 (m, 5H), 6.81 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.77 (app q, *J* = 3.0 Hz, 2H), 5.55 (s, 1H), 5.52 (s, 1H), 4.23 – 4.07 (m, 4H), 3.84 (s, 3H),

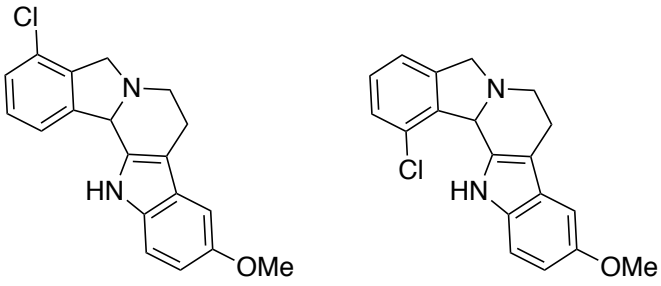
3.77 (s, 3H), 3.46 (ddd, *J* = 13.8, 5.5, 1.8 Hz, 2H), 3.35 (ddd, *J* = 13.6, 11.0, 4.6 Hz, 2H), 3.07 (dddd, *J* = 16.1, 10.5, 5.4, 2.4 Hz, 2H), 2.68 (ddd, *J* = 15.7, 3.2, 1.3 Hz, 2H).



*12-Chloro-6,7,8,12b-tetrahydro-2H-isoindolo[2,1-b]pyrrolo[4,3,2-de]isoquinolin-7-ium (**2.83a**) and 9-Chloro-6,7,8,12b-tetrahydro-2H-isoindolo[2,1-b]pyrrolo[4,3,2-de]isoquinolin-7-ium (**2.83b**).* Regioisomeric mixture **2.83** was synthesized using general procedure B. The product distribution of the crude mixture was found to be 1.7:1 **2.83a**: **2.83b** by HPLC.[60] However, the identities of the major and minor products were not confirmed because the samples had degraded significantly in the NMR solvents before ^{1}H NOE data could be obtained, due to the multiple attempts and long run times required to obtain sufficiently clean spectra. The structures above for **2.83a** and **2.83b** represent the predicted major and minor products, respectively. Purification by preparative TLC (silica; 10:1 DCM:MeOH) gave 59.5 mg (89% yield) of **2.83a** and **2.83b**.

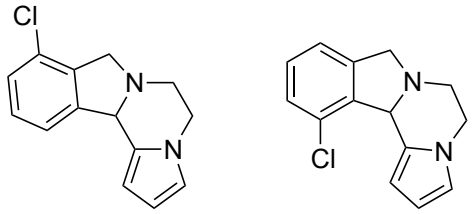
2.83a[61,62]**:** Pale pink solid. m.p.: 170.7-175.8°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.53 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.24 (*br* m, 2H), 7.21 – 7.05 (m, 2H), 6.51 (s, 1H), 5.07 – 4.94 (*br* m, 1H), 4.87 – 4.73 (*br* m, 1H), 4.70 – 4.55 (*br* m, 1H), 4.29 (*br* m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 138.9, 136.9, 134.7, 132.2, 130.7, 129.2, 124.5, 123.5, 122.2, 119.1, 117.6, 112.4, 111.4, 105.0, 65.9, 56.8, 50.1 ppm. FTIR (neat): $\tilde{\nu}$ 3145, 3115, 3037, 2940, 2925, 2847, 2608, 2541, 2489, 2001, 1968, 1655, 1614, 1580, 1535, 1450, 1431, 1379, 1334, 1271, 1233, 1192, 1170, 1144, 1055, 1006, 991, 898, 846, 820, 771, 749, 723, 686 cm^{-1}.

HRMS (ESI$^+$): m/z [M]$^+$ calculated for $C_{17}H_{14}ClN_2^+$: 281.0846; found: 281.0852. **2.83b**[61–63]**:** Brown solid. m.p.: 103.6-108.2°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.94 (s, 1H), 7.50 – 7.30 (m, 4H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.98 (s, 1H), 6.44 (s, 1H), 5.00 – 4.85 (m, 2H), 4.50 (d, *J* = 15.5 Hz, 1H), 4.26 (d, *J* = 14.0 Hz, 1H). FTIR (neat): $\tilde{\nu}$ 3182, 3115, 2921, 2851, 2485, 1997, 1904, 1669, 1621, 1584, 1450, 1375, 1334, 1196, 1140, 1055, 1017, 902, 768, 723, 686 cm^{-1}. HRMS (ESI$^+$): m/z [M]$^+$ calculated for $C_{17}H_{14}ClN_2^+$: 281.0846; found: 281.0855.



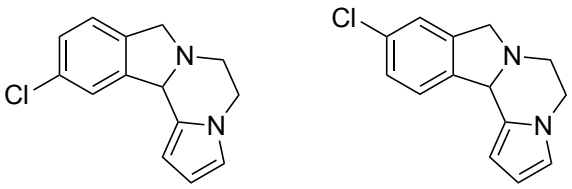
4-Chloro-10-methoxy-5,6,7,8,13,13b-hexahydrobenzo[1,2]indolizino[8,7-b]indol-6-ium ***(2.84a)*** *and 1-Chloro-10-methoxy-5,6,7,8,13,13b-hexahydrobenzo[1,2]indolizino[8,7-b]indol-6-ium* ***(2.84b)****.* Regioisomeric mixture **2.84** was synthesized using general procedure A. The product distribution of the crude mixture was found to be 2.3:1 **2.84a**: **2.84b** by HPLC.[60] Purification by preparative TLC (silica; 10:1-15:1 DCM:EtOAc) gave 63.6 mg (87% yield) of **2.84a** and **2.84b**. **2.84a**[61,62]**:** Yellow-brown solid. m.p.: 119.3-123.5°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.32 (s, 1H), 7.84 – 7.50 (m, 1H), 7.21 (s, 3H), 6.75 (d, *J* = 10.7 Hz, 2H), 6.24 (s, 1H), 4.83 (d, *J* = 14.2 Hz, 1H), 4.41 (d, *J* = 13.7 Hz, 1H), 3.94 (s, 1H), 3.79 (s, 3H), 3.68 – 3.43 (m, 2H), 3.26 – 2.90 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.6, 139.1, 133.8, 133.0, 132.4, 130.7, 127.2, 127.0, 123.2, 114.0, 113.2, 106.3, 101.2, 65.3, 56.1, 48.2, 17.9 ppm. FTIR (neat): $\tilde{\nu}$ 3167, 3071, 2921, 2854, 2832, 2478, 2381, 2359, 2344, 2322, 2159, 2117, 1666, 1625, 1580, 1487, 1457, 1368, 1312, 1289, 1263, 1215, 1148, 1129, 1077, 1032, 943, 920, 898, 794, 760, 719, 686, 648 cm^{-1}.

HRMS (ESI$^+$): m/z [M]$^+$ calculated for $C_{19}H_{18}ClN_2O^+$: 325.1108; found: 325.1108. **2.84b**[61,62]**:** Greenish-brown solid. m.p.: 93.9-96.6°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.52 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.96 (d, *J* = 1.7 Hz, 1H), 6.86 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.31 (s, 1H), 4.84 – 4.50 (m, 2H), 3.82 (s, 3H), 3.73 – 3.62 (m, 2H), 3.27 – 3.03 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.8, 137.8, 135.8, 133.9, 132.8, 130.6, 130.0, 127.3, 126.7, 123.7, 114.3, 113.9, 106.9, 101.1, 63.9, 56.1, 54.7, 46.5, 16.7 ppm. FTIR (neat): $\tilde{\nu}$ 3436, 3346, 3078, 3063, 2921, 2854, 2828, 2653, 2467, 2374, 2344, 2322, 2120, 1994, 1666, 1625, 1580, 1487, 1453, 1353, 1312, 1293, 1215, 1174, 1129, 1084, 1028, 984, 898, 783, 719, 701, 656 cm^{-1}. HRMS (ESI$^+$): m/z [M]$^+$ calculated for $C_{19}H_{18}ClN_2O^+$: 325.1108; found: 325.1115.



*9-chloro-5,6,8,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[2,1-a]isoindole (**2.85a**) and 12-chloro-5,6,8,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[2,1-a]isoindole (**2.85b**).* Regioisomeric mixture **2.85** was synthesized using general procedure A, which gave 32.7 mg (76% yield) of a brown sticky solid. A product distribution of 7.1:1 for **2.85a**: **2.85b** was found by integrating the methine singlets in the crude ^{1}H NMR. Attempts to purify the product via TLC and preparative HPLC were unsuccessful and gave messier products than the crude. This reaction suffered from similar issues as the product of the reaction of 1-(2-aminoethyl)pyrrole with 2-(bromomethyl)benzaldehyde. **2.85:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 6.4 Hz, 1H), 7.20 – 7.16 (m, 2H), 6.56 (s, 1H), 6.19 – 6.13 (m, 1H), 6.08 (s, 1H), 5.55 (s, 1H), 4.33 (d, *J* = 14.3 Hz,

1H), 4.13 (d, *J* = 14.5 Hz, 1H), 4.07 (td, *J* = 7.9, 3.6 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.30 – 3.12 (m, 2H).



*11-chloro-5,6,8,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[2,1-a]isoindole (**2.86a**) and 10-chloro-5,6,8,12b-tetrahydropyrrolo[2',1':3,4]pyrazino[2,1-a]isoindole (**2.86b**).* Regioisomeric mixture **2.86** was synthesized using general procedure A, which gave 32.7 mg (79% yield) of a brown sticky solid. A product distribution of 1.1:1 for **2.86a**:**2.86b** was found by integrating the methine singlets in the crude ^{1}H NMR. Attempts to purify the product via TLC and preparative HPLC were unsuccessful and gave messier products than the crude. This reaction suffered from similar issues as the product of the reaction of 1-(2-aminoethyl)pyrrole with 2-(bromomethyl)benzaldehyde (**2.69**). **2.68:** ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.49 – 7.45 (m, 2H), 7.32 – 7.21 (m, 4H), 6.57 (app ddd, *J* = 3.8, 2.9, 1.9 Hz, 2H), 6.12 – 5.97 (m, 4H), 5.40 (s, 1H), 5.37 (s, 1H), 4.23 – 4.05 (m, 6H), 3.94 – 3.82 (m, 2H), 3.22 (app dddd, *J* = 13.6, 8.1, 5.7, 4.1 Hz, 2H), 3.17 – 3.04 (m, 2H).

Attempted Cyclizations of Arylalkylamines. Attempts were made to cyclize 2-(aminomethyl)indole, 3-(aminomethyl)indole, 2-furan-2-ylethylamine, homopiperonylamine, dopamine hydrochloride, and 3-methoxyphenethylamine with aldehyde **2.51a** by following general procedures A and B. For all reactions of dopamine hydrochloride, 3.2 equivalents of Et_3N were added, instead of the usual 1.2, to effect complete deprotonation of the HCl salt *in*

situ. The isoindoles for all of these substrates formed completely at room temperature. In addition, cyclizations of the phenylethylamine substrates were attempted via a modified version of general procedure B in which the reaction mixture was heated to 80°C, but similar results were observed. LC-MS and ^{1}H NMR spectra recorded for the products of these reactions indicated that cyclization of the isoindolium ions did not occur. For dopamine hydrochloride, the product was a complex mixture. For 3-methoxyphenethylamine, LCMS data indicated that a polymer was also formed.

Regioselectivity of Isoindolium formation: Procedure for Formation of Isoindolium 2.82 and Attempted Cyclizations of Benzaldehyde 2.51g.

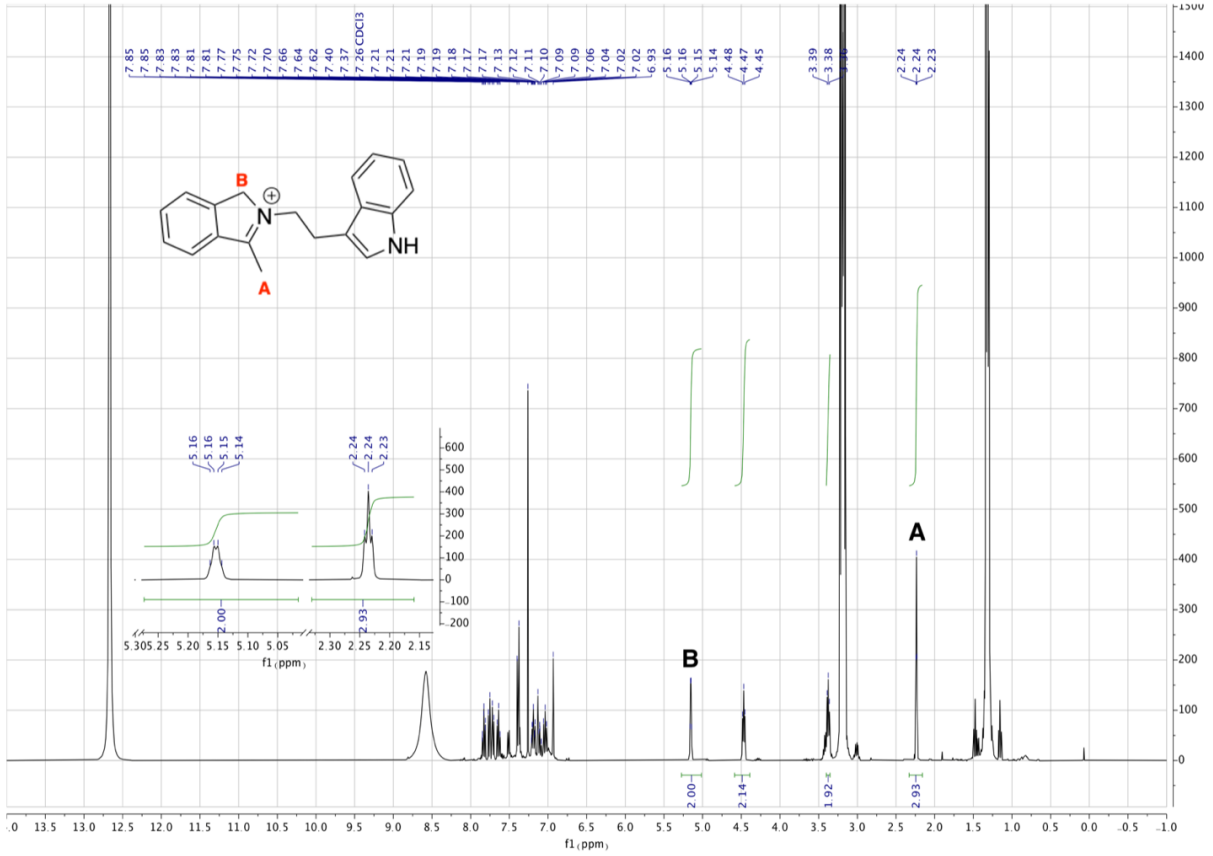
2.51g **2.34a** **2.82a**

Formation of 2-(2-(1H-indol-3-yl)ethyl)-3-methyl-1H-isoindol-2-ium (2.82a). Aldehyde **2.51g** (0.10 mmol, 1.0 equiv) and tryptamine (**2.34a**) (0.12 mmol, 1.2 equiv) were dissolved in $CDCl_3$[57] (1.0 mL, 0.10 M) in a vial equipped with a magnetic stir bar. The reaction mixture was purged with argon and triethylamine (0.12 mmol, 1.2 equiv) was added. The reaction mixture was heated gently to 40-50°C and stirred until the maximum possible conversion of approximately 95% was achieved. An aliquot of the reaction mixture was then transferred to an NMR tube and cooled to -40°C. TFA was added in an amount that was scaled in proportion to the amount

transferred to the NMR tube, such that approximately 20 equivalents were added. The reaction mixture was allowed to warm to room temperature and sonicated to mix the components. A ^{1}H NMR spectrum of **2.82a** was then recorded *in situ*.

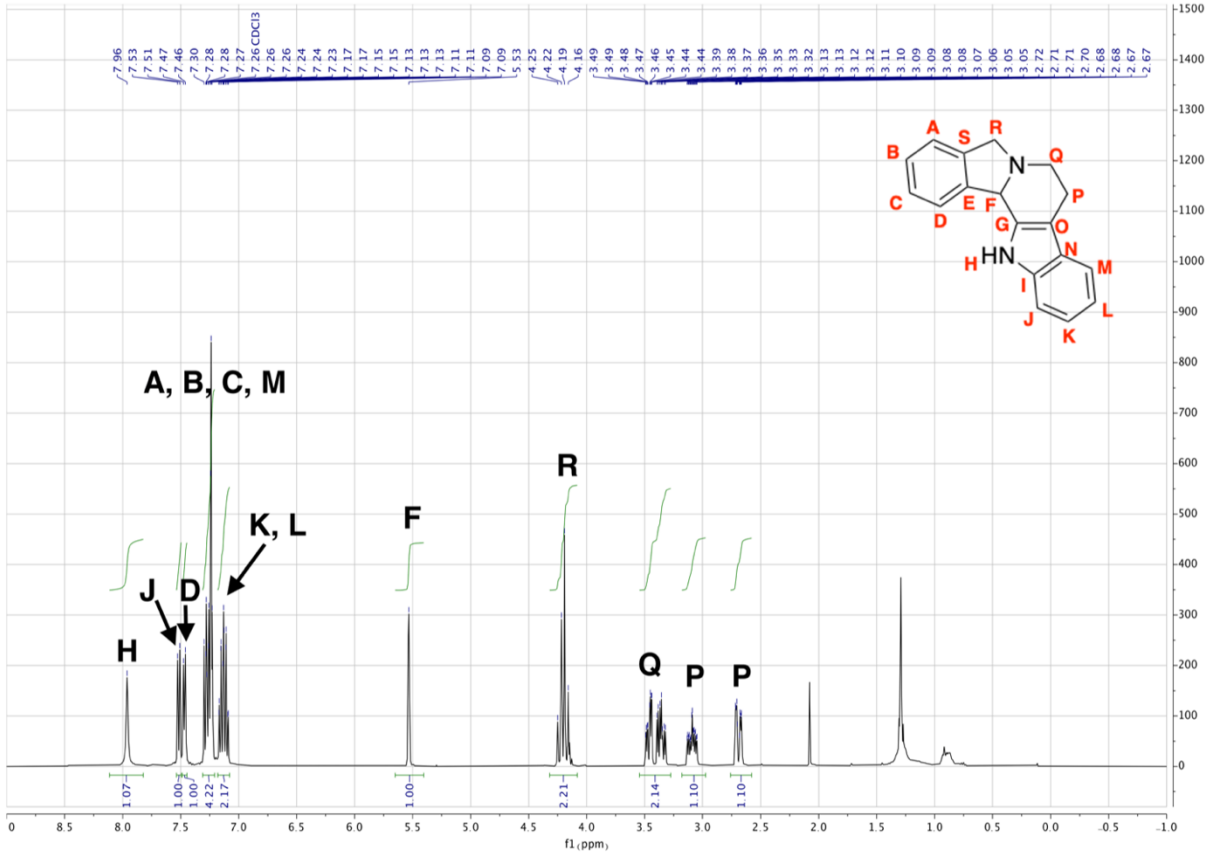
Cyclization Attempts–Benzylic Substitution. Attempts were made to cyclize 2-(bromoethyl)benzaldehyde (**2.51g**) and tryptamine (**2.34a**) via general procedures A and B, except that for both procedures, DCE was used as the solvent and the reaction mixture was heated gently to 40-50°C to form the isoindole. Approximately 95% conversion to the isoindole was achieved, but cyclization of the isoindolium was not observed. Attempts were also made to cyclize 2-(dibromomethyl)benzaldehyde (**2.51h**) and (2-(bromomethyl)phenyl)(phenyl)methanone (**2.51i**) using the same procedures. Approximately 80% conversion to the isoindole was achieved and no cyclization was observed at room temperature. Additionally, suspected decomposition was observed for **2.51i** in the presence of gentle heat (**2.81**), whereas **2.51h** gave a complex mixture and possibly remained uncyclized (**2.80**).

[1]H NMR spectrum of Isoindolium **2.82a.**

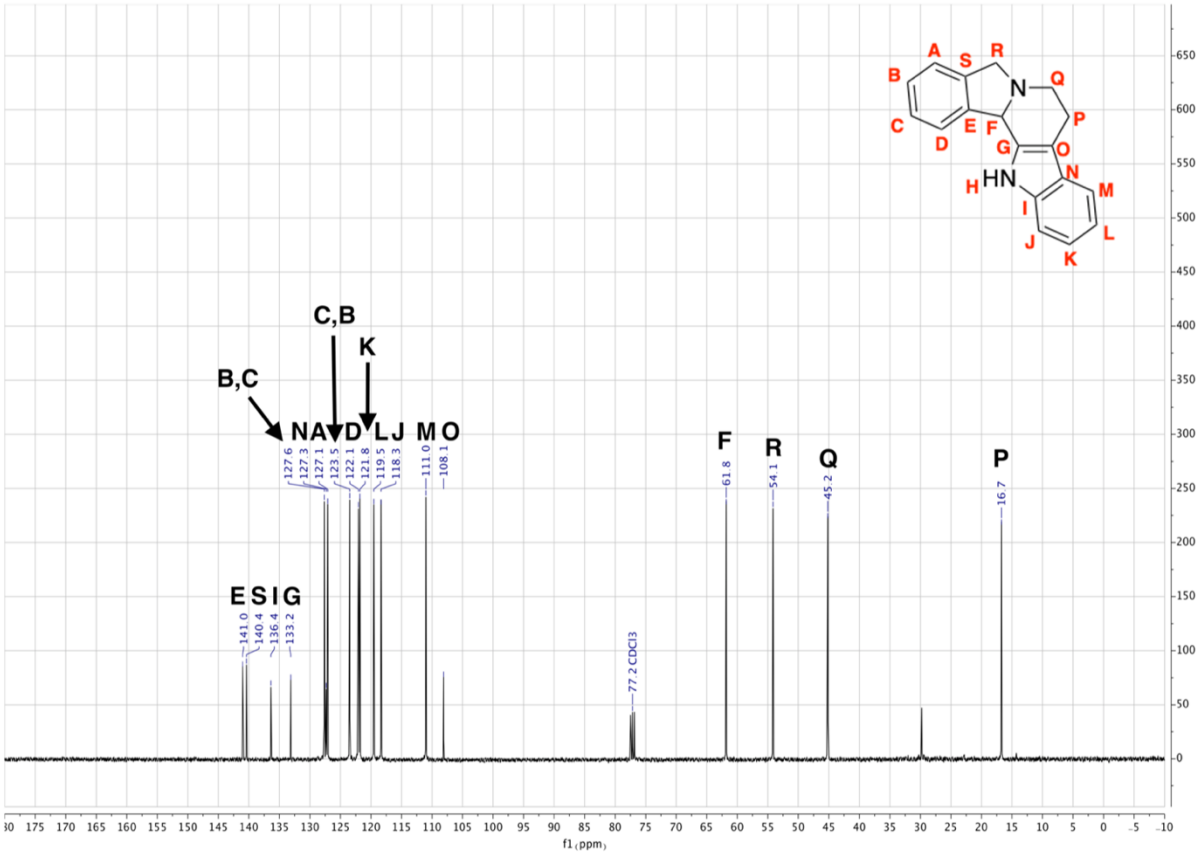


NMR Spectra for the Structural Assignments of 2.61 and 2.74a.

^{1}H NMR spectrum of **2.61**.

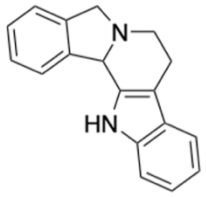


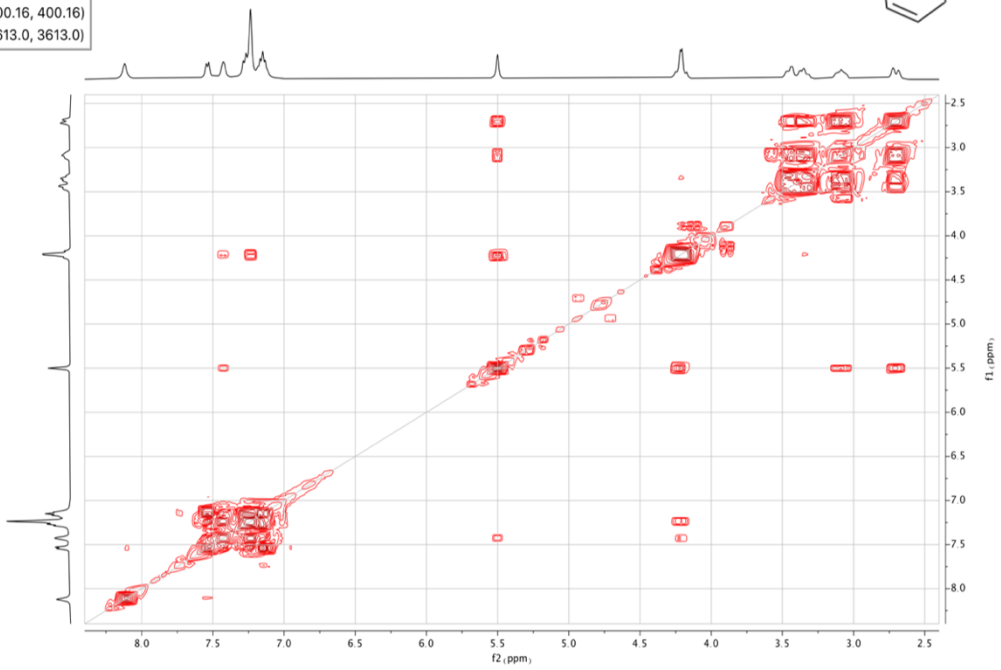
^{13}C NMR spectrum of **2.61**.



^{1}H-^{1}H COSY NMR spectrum of **2.61**.

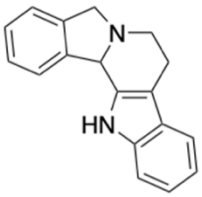
Parameter	Value
1 Solvent	cdcl3
2 Temperature	20.0
3 Pulse Sequence	gCOSY
4 Number of Scans	2
5 Relaxation Delay	1.0000
6 Pulse Width	7.5000
7 Spectrometer Frequency	(400.16, 400.16)
8 Spectral Width	(3613.0, 3613.0)

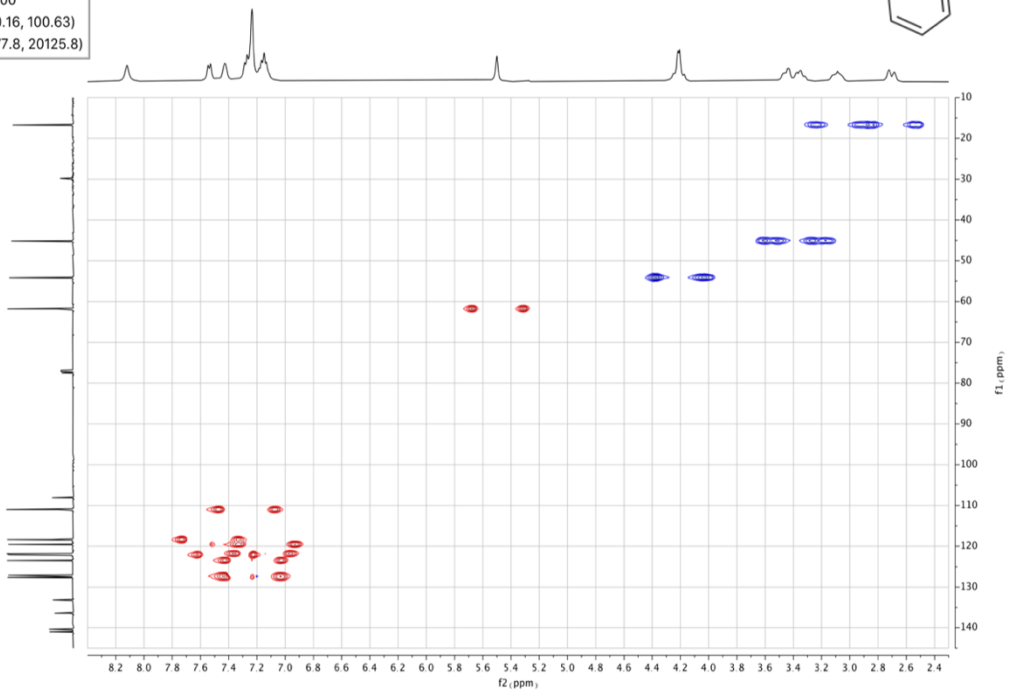




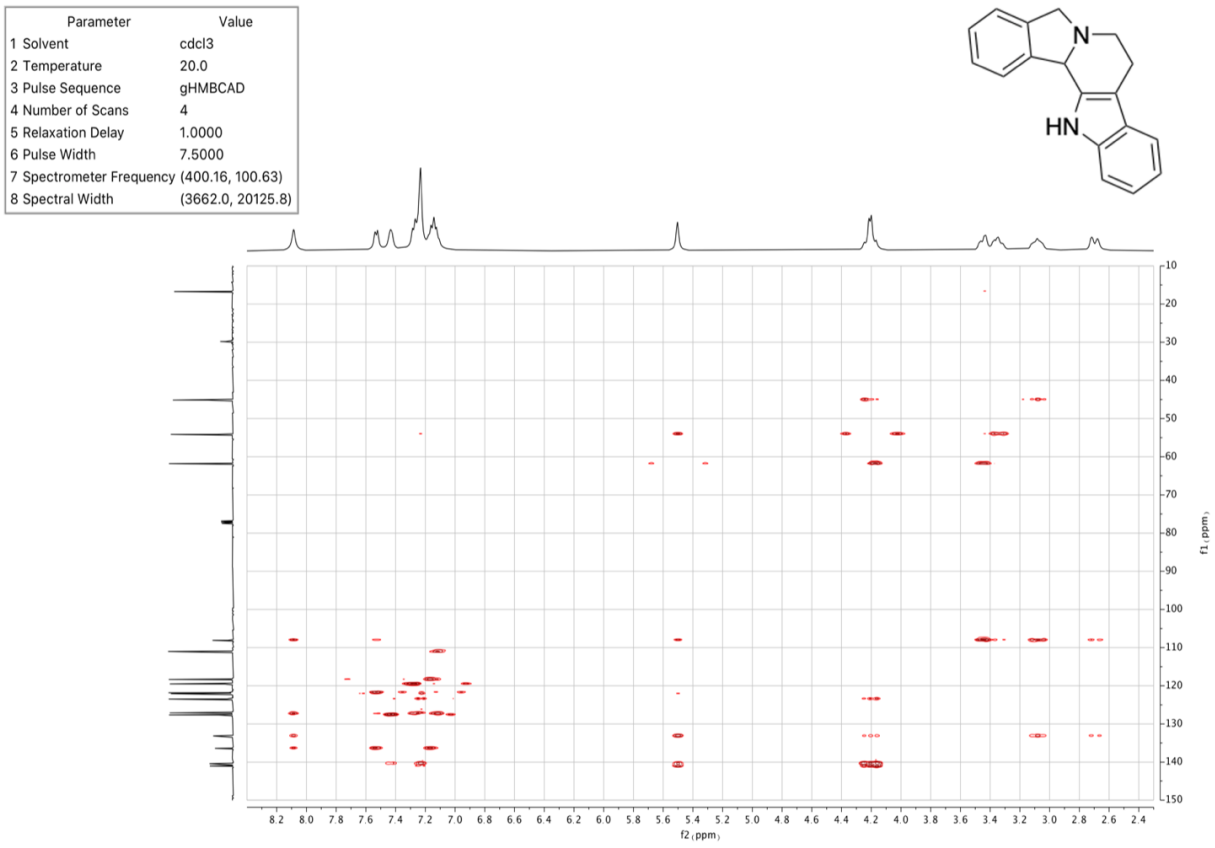
^{1}H-^{13}C HSQC NMR spectrum of **2.61**.

Parameter	Value
1 Solvent	cdcl3
2 Temperature	20.0
3 Pulse Sequence	gHSQCAD
4 Number of Scans	4
5 Relaxation Delay	1.0000
6 Pulse Width	7.5000
7 Spectrometer Frequency	(400.16, 100.63)
8 Spectral Width	(4377.8, 20125.8)

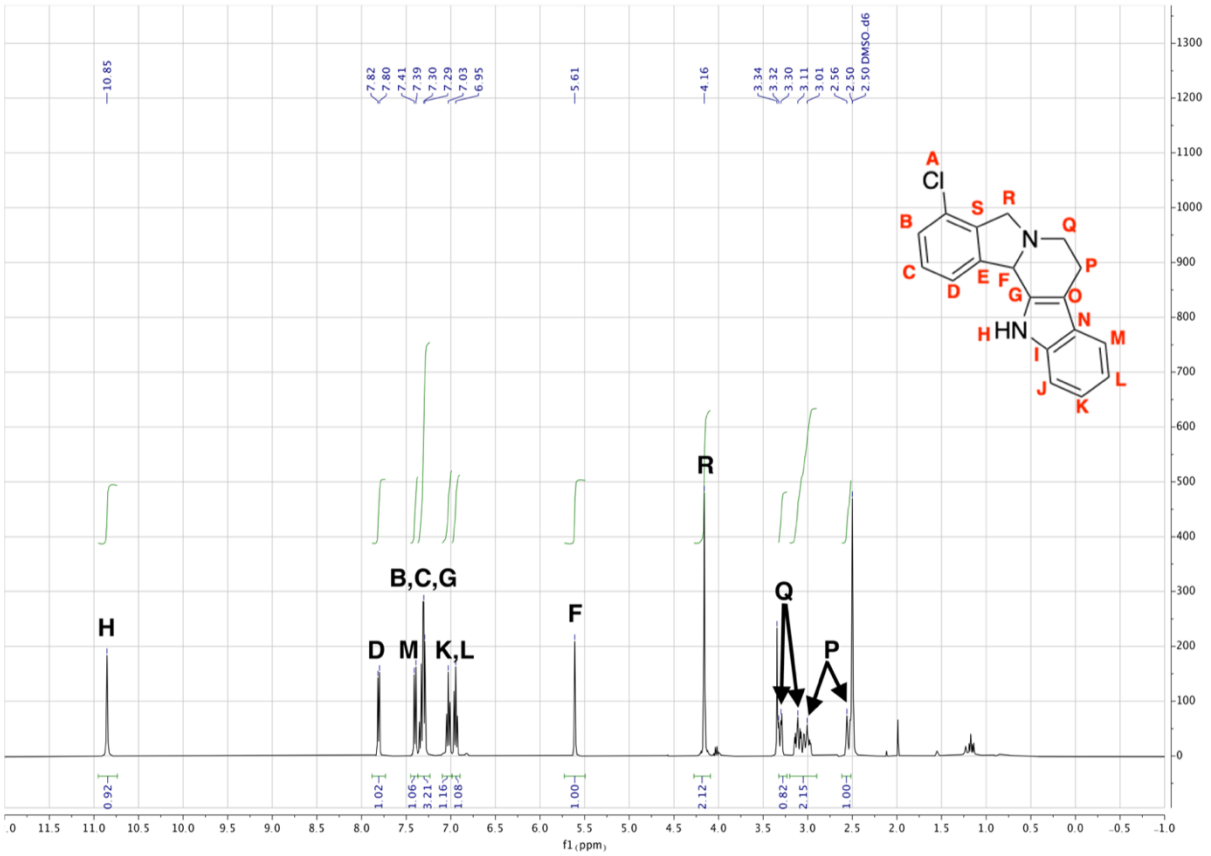




^{1}H-^{13}C HMBC NMR spectrum of **2.61**.



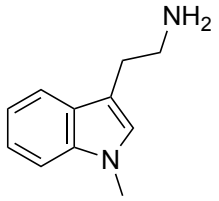
^{1}H NMR spectrum of **2.74a**.



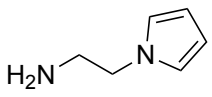
Synthesis of Starting Materials: Amines.

Commercially available amines **2.34a**, **2.34e**, **2.34f-h**, and **2.34j-l** were used as received. The hydrochloride salt of dopamine (**2.34m**) was obtained commercially and used as received.

The hydrochloride salts of **2.34b-d** were also obtained commercially but were converted to the corresponding free amines prior to use via the following procedure: the amine salt was dissolved in DCM and washed with saturated aqueous Na_2CO_3. The organic layer was subsequently dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo* to give the free amine.



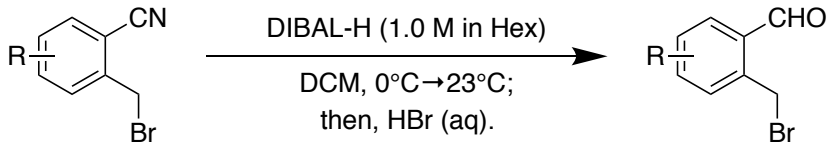
*2-(1-methyl-1H-indol-3-yl)ethan-1-amine (**2.34e**).* The title compound was synthesized according to a procedure reported in the literature, with modifications.[1] A solution of tryptamine (360 mg, 0.92 mmol, 1.0 equiv) in anhydrous THF (3.6 mL) was added dropwise at 0°C to a stirred suspension of NaH (60% dispersion in mineral oil, (44 mg, 1.10 mmol, 1.2 equiv.) in anhydrous THF (1.2 mL). The cold bath was removed and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was then cooled to 0°C and MeI (20. mg, 1.39 mmol, 85 µL, 1.5 equiv) was added dropwise. The resulting mixture was subsequently allowed to warm to stirred room temperature. Since only 40% conversion after 8h, the reaction mixture was again cooled to 0°C and an additional 1.2 equiv. of NaH was added, followed by an additional 3.0 equiv. of MeI (39 mg, 2.76 mmol, 0.17 mL) after 0.5 h. The solvent was then removed *in vacuo* and the residue was dissolved in water (35 mL) and subsequently extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, 3:1 Hexanes:EtOAc) to give 80 mg (50% yield) of the title compound as a yellow oil. The spectra matched those reported in the literature.



*2-(1H-pyrrol-1-yl)ethan-1-amine (**2.34i**).* The title compound was synthesized according to a procedure reported in the literature.[65] Solid NaOH (2.00 g, 50 mmol) and tetrabutylamonium

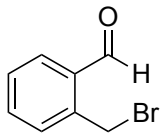
hydrogen sulfate (TBAS) (0.17 g, 0.5 mmol) were added to a solution of pyrrole (10 mmol) in MeCN (30 ml). The solution was stirred at room temperature for 0.5 h and then 2-chloroethylamine hydrochloride (1.39 g, 12 mmol) was added. The reaction mixture was heated to reflux for 24 h.The mixture was then allowed to cool to room temperature and subsequently poured into water (100 mL), extracted with ether, and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the crude product as a yellow oil. The product was then purified by vacuum distillation to give 0.63 g (58% yield) of the title compound as a golden oil. The spectra matched those reported in the literature.

Synthesis of Starting Materials: Aldehydes.

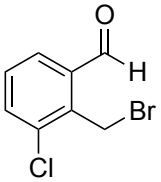


Representative General Procedure for the Synthesis of Aldehydes. Derivatives of 2-(bromomethyl)benzaldehyde were synthesized from the corresponding nitriles according to a procedure reported in the literature, with minor modifications.[66] DIBAL-H (1.0 M in Hexanes, 6.50 mL, 6.50 mmol, 1.3 equiv.) was added dropwise to a solution of the corresponding nitrile (5.00 mmol) in dry DCM (19.2 mL, 0.26 M) under Ar at 0°C via a reduced pressure addition funnel. The cooling bath was removed and the solution was allowed to stir for a period of 3 h. The reaction mixture was then cooled to 0°C and the contents of the reaction flask were subsequently poured into a 500 mL beaker containing crushed ice (20 g) and a precooled aqueous HBr solution (6.0 N, 20 mL). The resulting mixture was vigorously stirred for 1 h without darkening, and then extracted with DCM three times (20 mL twice; 10 mL once). The

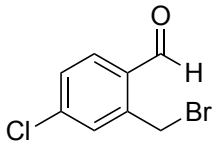
organic fractions were combined, washed once with 1 N $NaHCO_3$ (aq) and twice with H_2O, and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* afforded the aldehyde.



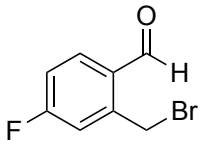
*2-(bromomethyl)benzaldehyde (**2.51a**).* Aldehyde **2.51a** was synthesized on a 5.34 mmol scale according to the representative general procedure for the synthesis of aldehydes. The crude product was purified via flash column chromatography (silica gel, DCM). A brown oil (1.06 g, 96% yield) was obtained, which crystallized upon freezing. The spectra matched those reported in the literature.[66]



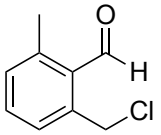
*2-(bromomethyl)-3-chlorobenzaldehyde (**2.51b**)*. Aldehyde **2.51b** was synthesized on a 6.59 mmol scale according to the representative general procedure for the synthesis of aldehydes. A yellow solid (1.22 g) was obtained in a 79% yield and was used without purification. The spectra matched those reported in the literature.[67]



*2-(bromomethyl)-4-chlorobenzaldehyde (**2.51c**)*. Aldehyde **2.51c** was synthesized on a 5.21 mmol scale according to the representative general procedure for the synthesis of aldehydes. A yellow solid (1.01 g, 83% yield) was obtained and was used without purification. The spectra matched those reported in the literature.[68]

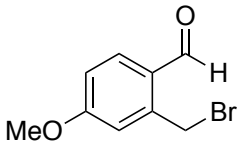


*2-(bromomethyl)-4-fluorobenzaldehyde (**2.51d**)*. Aldehyde **2.51d** was synthesized on a 4.72 mmol scale according to the representative general procedure for the synthesis of aldehydes. The crude product was purified via flash column chromatography (silica gel, 9.5:1 Hexanes:EtOAc). A brown solid (0.80 g, 78% yield) was obtained. The spectra matched those reported in the literature.[68]

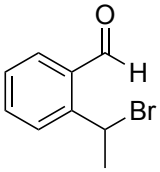


*2-(chloromethyl)-6-methylbenzaldehyde (**2.51e**)*. The 2-(chloromethyl)benzaldehyde **2.51e** was synthesized from the corresponding nitrile on a 0.91 mmol scale according to the representative general procedure for the synthesis of aldehydes. A dark red oil (60 mg, 39% yield) was obtained

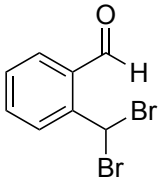
and was used without purification. Due to the relatively low yield and the instability of the aldehyde, the product was solely characterized by ^{1}H NMR. **2.51e**: ^{1}H NMR (400 MHz, cdcl$_3$) δ 10.65 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.98 (s, 2H), 2.66 (s, 3H).



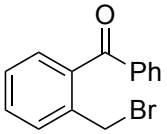
*2-(bromomethyl)-4-methoxybenzaldehyde (**2.51f**)*. Aldehyde **2.51f** was synthesized on a 2.21 mmol scale according to the representative general procedure for the synthesis of aldehydes. The crude product was purified via flash column chromatography (silica gel, 50:1 Hexanes:EtOAc). A white solid (0.36 g, 71% yield) was obtained.[69]



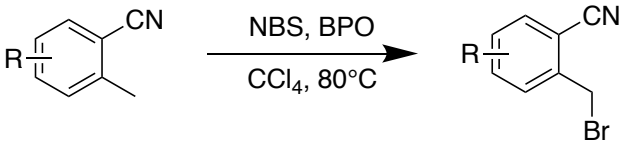
*2-(1-bromoethyl)benzaldehyde (**2.51g**)*. Aldehyde **2.51g** was synthesized on a 16.3 mmol scale according to the representative general procedure for the synthesis of aldehydes. The crude product was purified via flash column chromatography (silica gel, 20:1 Hexanes:EtOAc). A brown solid (1.42 g, 41% yield) was obtained. The spectra matched those reported in the literature.[70]



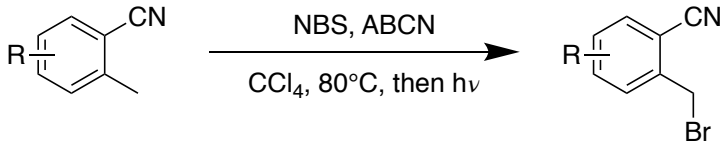
*2-(dibromomethyl)benzaldehyde (**2.51h**)*. Aldehyde **2.51h** was synthesized on a 0.57 mmol scale according to the representative general procedure for the synthesis of aldehydes, except that 1.0 M DIBAL-H in Heptane was used. The crude product was purified via flash column chromatography (silica gel, DCM). A pale pink solid (79 mg, 50% yield) was obtained. The spectra matched those reported in the literature.[71]



*(2-(bromomethyl)phenyl)(phenyl)methanone (**2.51i**)*. Ketone **2.51i** was synthesized via a modified procedure that was devised from procedures reported in the literature.[72,73] Phenyl(*o*-tolyl)methanone (1.48 g, 7.55 mmol, 1.00 equiv) and *N*-bromosuccinimide (1.48 g, 8.31 mmol, 1.10 equiv.) were added to a round-bottom flask containing a magnetic stir bar. CCl_4 (47 mL, 0.16 M) was added, followed by ABCN (37 mg, 0.15 mmol, 0.02 equiv.) was added to the reaction flask and the reaction mixture was heated to reflux for 0.5 h and then removed from heat and irradiated. Shortly thereafter, the reaction mixture began to turn orange. The reaction mixture was allowed to stir at room temperature until the orange color disappeared, at which time it was filtered to remove the succinimide byproduct. The solvent was removed *in vacuo* to provide 0.96 g (46 % yield) of the title compound, which was used without further purification. The spectra matched those reported in the literature.[74]

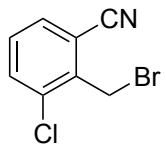


General Procedure for the Benzylic Bromination of Benzonitriles. The 2-(bromomethyl)benzonitrile derivatives were synthesized according to a procedure derived from procedures reported in the literature[68,70], with minor modifications. The nitrile starting material and *N*-bromosuccinimide (1.15 equiv.) were added to a round-bottom flask containing a magnetic stir bar. A sufficient amount of CCl_4 was added to give a concentration of 1.6 M with respect to the nitrile. Benzoyl peroxide (0.02 equiv.) was added to the reaction flask and the reaction mixture was heated to 80°C with stirring for 24 h. The reaction mixture was subsequently allowed to cool to room temperature and then filtered to remove the succinimide byproduct. The solvent was removed *in vacuo* to provide the 2-(bromomethyl)benzonitrile derivative.

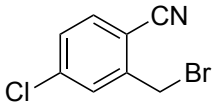


Modified Procedure for the Benzylic Bromination of Benzonitriles. The nitrile starting material and *N*-bromosuccinimide (1.1 equiv.) were added to a round-bottom flask containing a magnetic stir bar. A sufficient amount of CCl_4 was added to give a concentration of 0.36 M with respect to the nitrile. ABCN (0.04 equiv.) was added to the reaction flask and the reaction mixture was heated to reflux for 0.5 h and then removed from heat and irradiated. Shortly thereafter, the reaction mixture began to turn orange. The reaction mixture was allowed to stir at

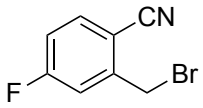
room temperature until the orange color disappeared, at which time it was filtered to remove the succinimide byproduct. The solvent was removed *in vacuo* to provide the 2-(bromomethyl)benzonitrile derivative.



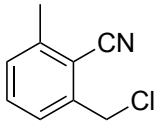
2-(bromomethyl)-3-chlorobenzonitrile. The title compound was synthesized on an 8.45 mmol scale according to the representative general procedure for the benzylic bromination of benzonitriles. The crude product was purified via flash column chromatography (silica gel, 9:1 Hexanes:EtOAc to 8:2 Hexanes:EtOAc). A light pink solid (1.70 g, 87% yield) was obtained. The spectra matched those reported in the literature.[75]



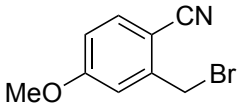
2-(bromomethyl)-4-chlorobenzonitrile. The title compound was synthesized on a 14.5 mmol scale according to the representative general procedure for the benzylic bromination of benzonitriles. The crude product was purified via flash column chromatography (silica gel, 100:1 *n*-pentane:EtOAc). A peach-colored solid (3.01 g, 90% yield) was obtained. The spectra matched those reported in the literature.[68]



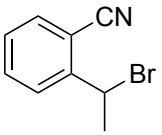
2-(bromomethyl)-4-fluorobenzonitrile. The title compound was obtained commercially and used as received.



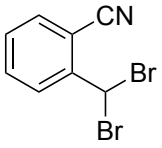
2-(chloromethyl)-6-methylbenzonitrile. The title compound was synthesized on a 31.4 mmol scale according to the modified procedure for the benzylic bromination of benzonitriles, except that *N*-chlorosuccinimide was used instead of *N*-bromosuccinimide, AIBN (0.05 equiv.) was used as the radical initiator, and 2:1 CCl_4:$CHCl_3$ was used as the solvent system. The crude product was purified via flash column chromatography (silica gel, 5:1 Hexanes:Et_2O). A white solid (2.55 g, 49% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 4.75 (s, 2H), 2.58 (s, 3H).



2-(bromomethyl)-4-methoxybenzonitrile. The title compound was synthesized on a 6.11 mmol scale according to the representative general procedure for the benzylic bromination of benzonitriles. The crude product was purified via flash column chromatography (silica gel, 50:1 Hexanes:EtOAc). A white solid (0.87 g, 63 % yield) was obtained. The spectra matched those reported in the literature.[69]



2-(1-bromoethyl)benzonitrile. The title compound was synthesized on a 23.2 mmol scale according to the modified procedure for the benzylic bromination of benzonitriles. The crude product was purified via flash column chromatography (silica gel, 16:1 Hexanes:EtOAc), which gave a white solid (2.91 g, 86% yield). The spectra matched those reported in the literature.[70]



2-(dibromomethyl)benzonitrile. The title compound was synthesized on a 7.90 mmol scale according to the representative general procedure for the benzylic bromination of benzonitriles, except that the concentration of the starting material was 0.85 M and 2.0 equiv. NBS and 0.1 equiv. BPO were used. The crude product was purified via flash column chromatography (silica gel, 15:1 Hexanes:EtOAc), which gave a white solid (1.78 g, 82% yield). The spectra matched those reported in the literature.[76]

2.11. References and Notes

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(55) Due to the water solubility of the free amine and the commercial availability of dopamine HCl, the free amine was not formed. Instead, 3.2 equiv. of Et_3N were used to form the isoindole with complete conversion.

(56) The chloromethyl benzaldehyde was used due to the tendency of the bromomethyl substrate to undergo debromination during the reduction of the corresponding nitrile.

(57) To reduce the size of the HOD peak, the $CDCl_3$ used for reactions was dried over 3Å mol sieves, but no K_2CO_3 was added, as this could react with TFA in the second step. Additionally, Na_2SO_4 was added directly to the NMR tube.

(58) Characterized as the TFA salt.

(59) A portion of the crude material was purified by preparative TLC and used to calculate the percent yield. The amount of pure material reported for the reaction was calculated from the percent yield.

(60) A small amount of the crude mixture was acidified with 4.0 M HCl in dioxane and used to determine the product distribution by HPLC (70-50% A; A: 0.1% HCl in H_2O, B: MeCN)

(61) Characterized as the HCl salt.

(62) The samples degraded significantly in the NMR solvents due to oxidation, which was confirmed using LC-MS. Poor shimming was also observed in the ^1H NMR due to low solubility in CD_2Cl_2. Solubility in CD_3OD was somewhat improved; however, some of the aliphatic proton chemical shifts overlapped with CD_3OD in the ^1H NMR.

(63) Multiple attempts were made to obtain a ^{13}C NMR spectrum of sufficient intensity. However, even a run-time of 36 h failed to give a spectrum of sufficient intensity to visualize all the carbons. We hypothesize that this was due to insufficient solubility in CD_3OD, as much of the compound remained undissolved.

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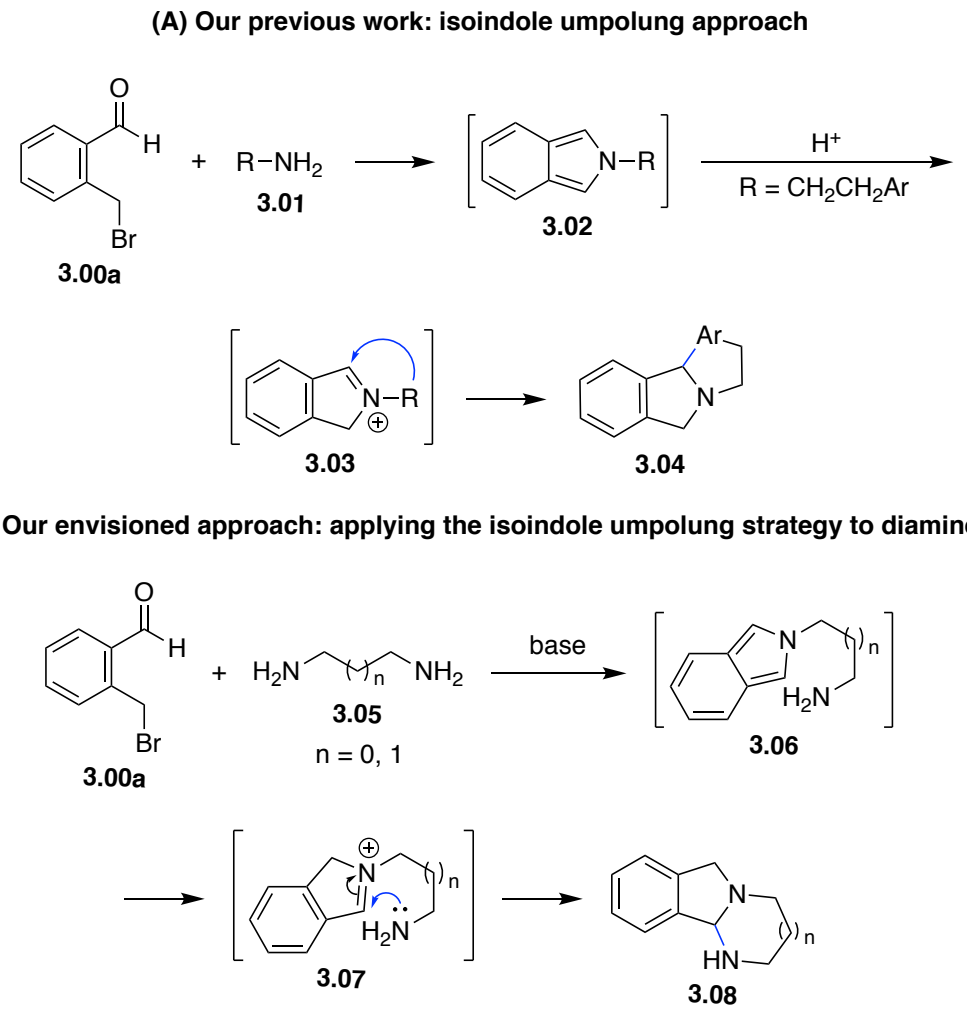
Chapter 3: Efforts Toward the Development of Two Cyclization Cascade Reactions Involving Isoindole Chemistry

3.1. Introduction to the Cascade-Oxidation Approach

We sought to expand the scope of our isoindole umpolung approach[1] by developing additional one–pot reactions that utilize this approach and can be used to prepare pharmaceutically relevant compounds that contain the isoindole scaffold (Scheme 3.1). We sought to form the isoindole (**3.06**) and isoindolium (**3.07**) species in the same manner–specifically, via an *in situ* condensation reaction of a 2-(bromomethyl)benzaldehyde (**3.00a**) with a primary amine (**3.01**). However, a different species of nucleophile would attack the isoindolium electrophile to effect cyclization. Accordingly, we identified readily accessible primary amine reacting partners bearing an additional nucleophilic reactive site that are capable of cyclizing with the isoindolium species formed from the reaction with 2-(bromomethyl)benzaldehyde substrates. We reasoned that *N*-unsubstituted 1,2- and 1,3-diamines (**3.05**) would fit both criteria, as they would cyclize to form 5- and 6-membered rings, respectively (Scheme 3.1B).



Scheme 3.1. (A) Our previous work: the isoindole umpolung approach. (B) Our envisioned approach for the reaction of 2-(bromomethyl)benzaldehyde derivatives with diamines.

Of particular interest were 2-aminobenzylamines, as we reasoned that these could be used to prepare pharmaceutically-relevant analogs of several biologically active compounds, including batracylin (**3.09**), tryptanthrin (**3.10**), and indolo[1,2-*c*]quinazoline derivatives (**3.11**, Figure 3.1). The activities of these compounds and their structural similarities to our targets will be discussed in detail *infra*. Given the pharmaceutical utility of its cyclization products and its commercial

availability, 2-aminobenzylamine (**3.12a**, Scheme 3.2) was used as the amine reacting partner in the model reactions with the unsubstituted aldehyde substrates for both methods described herein.

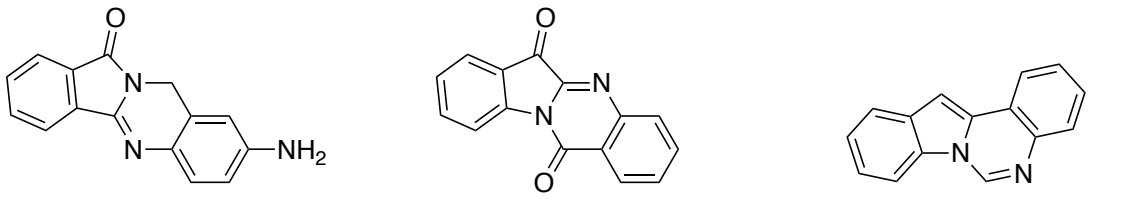
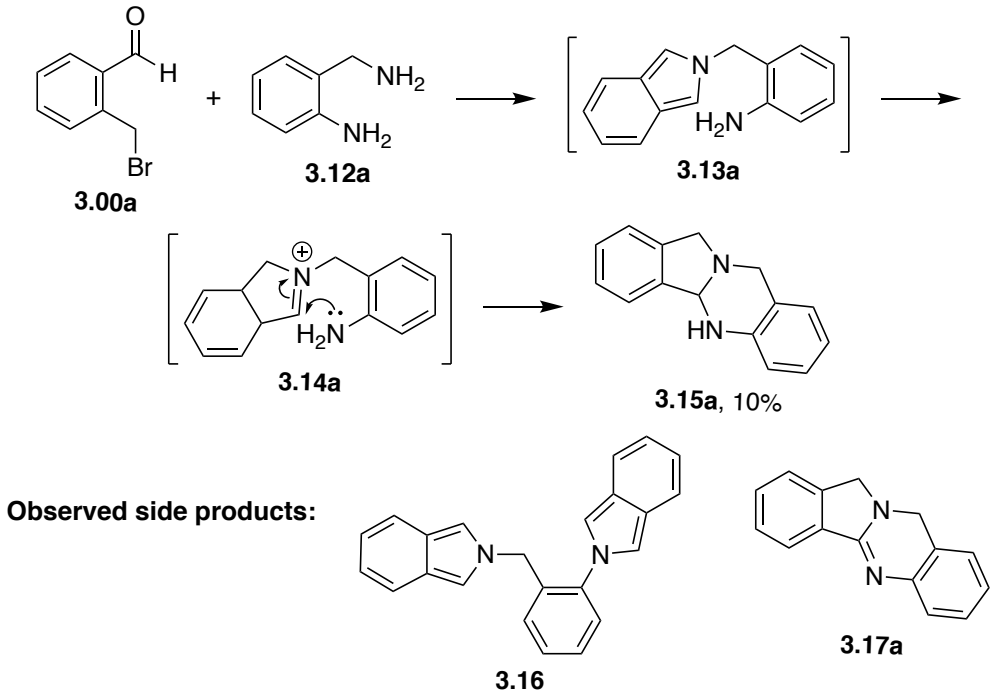


Figure 3.1. Examples of biologically active structural analogs of our proposed targets.

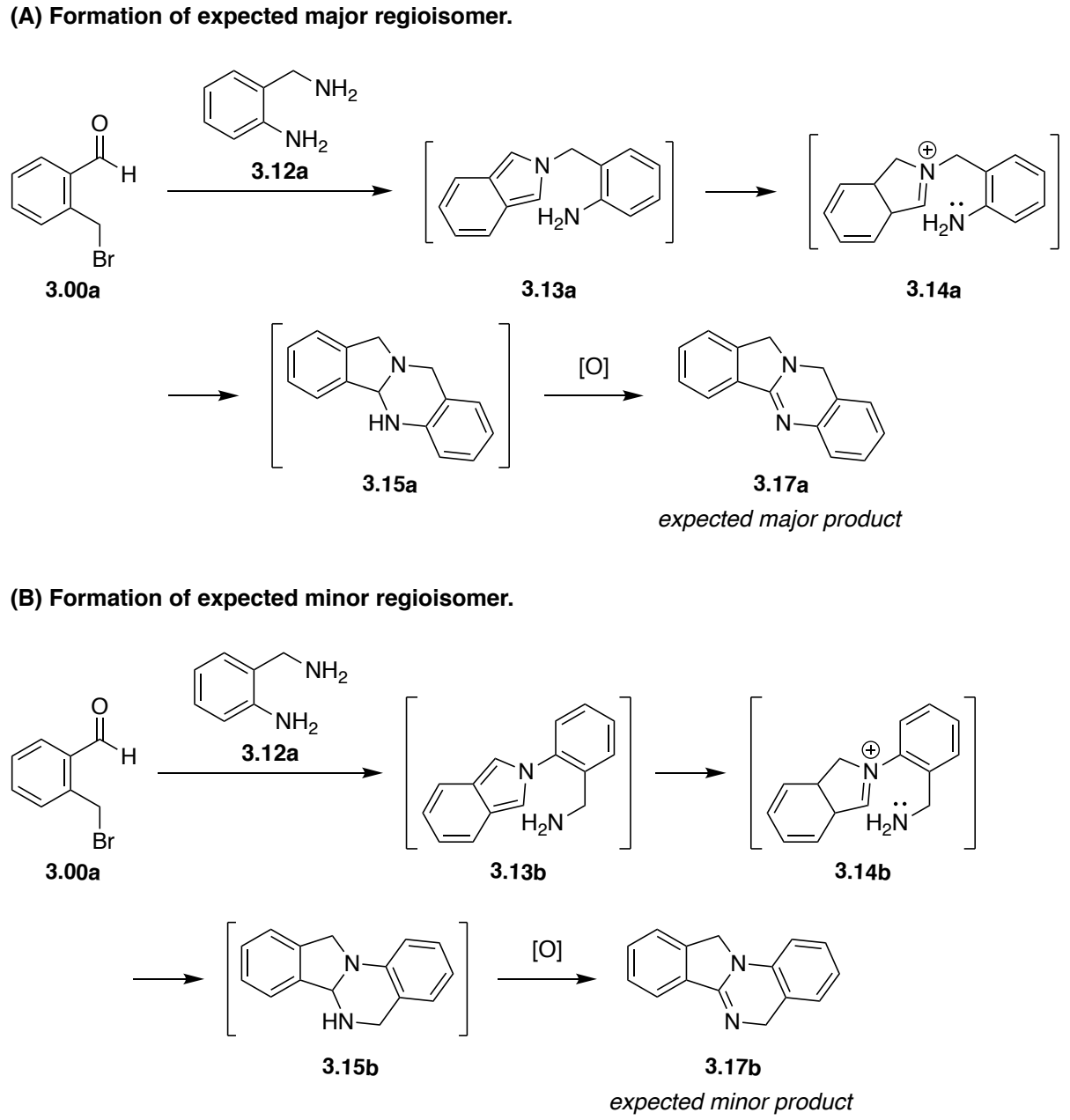


Scheme 3.2. Model system for our approach and observed side products.

However, due to the incompatibility of the pendant amino group in the isoindole (**3.13a**) with the excess acid required to effect cyclization with minimal polymerization of the isoindole, we decided to investigate whether isoindolium formation (**3.14a**) and cyclization (**3.15a**) would still occur in the absence of acid. The *in situ* isoindole formation conditions from the isoindole umpolung approach were adapted to this reaction, except that DIEA was used as the tertiary amine base because it is less nucleophilic than Et_3N, and therefore, less likely to attack the isoindolium species through which cyclization is expected to occur. We found that while cyclization did occur in the absence of acid, the conversion and yield for cyclization product were low. Additionally, two side products were detected via LC-MS. The bis-isoindole (**3.16**) forms from the reaction of each of the free amino group of the aniline in the isoindole with an equivalent of the aldehyde. The amidine product (**3.17a**) likely forms via oxidation of the cyclization product, as the aldehyde carbon from the starting material must undergo a two-electron oxidation to get to the amidine product, while the oxidation state of the bromomethyl carbon remains unchanged. This may happen via autoxidation.

We were particularly intrigued by oxidation side product **3.17a** because of its closer structural similarities to the aforementioned bioactives and reasoned that we could access it by developing a cyclization–oxidation cascade reaction (Scheme 3.3, *infra*). In this approach, an oxidizing agent would be added to the reaction mixture following the formation of the isoindole. We anticipated that the use of asymmetrical dienes will produce a mixture of regioisomers, since the isoindole can form from either of the two amino groups. In the case of our model system, we anticipated that we could obtain **3.17b** as a minor product because it forms via the isoindole of the less nucleophilic aniline amino group (**3.13b**, Scheme 3.3B). Herein, efforts toward the development of the cyclization–oxidation cascade reaction of 2-(bromomethyl)benzaldehyde

derivatives with 1,2-, 1,3-, and 1,4-diamines and other dinucleophilic species will be described. Additionally, our efforts toward the development of a redox-free approach that provides the same products will be presented.



Scheme 3.3. Our envisioned cyclization-oxidation cascade approach: formation of (A) major and (B) minor regioisomers.

3.2. Biological Activities of Batracylin, Tryptanthrin, and Indolo[1,2-*c*]quinazoline Derivatives and Structural Similarities to Our Targets

The target compounds for our model system and their derivatives are analogs of several bioactive compounds. Batracylin (**3.09**), a dual inhibitor of topoisomerases I and II,[2] is a well-established and versatile anticancer agent. Batracylin and its derivatives have been shown to have activity against several types of cancer, including leukemia[2–4], lung cancer[3], melanoma[5], and colon cancer[6]. Derivatives of indolo[1,2-*c*]quinazoline (**3.11**) and tryptanthrin (**3.10**) both possess antimicrobial and antifungal properties. Several indolo[1,2-*c*]quinazoline derivatives exhibited promising activity *in vitro* against the Gram-negative bacteria *Escherichia coli* (*E. coli*), *Pseudomonas putida* (*P. putida*), and *Salmonella typhi* (*S. typhi*), as well as the Gram-positive bacteria *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus* (*S. aureus*).[7] Those same derivatives also showed pronounced antifungal activity *in vitro* against *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*). A similar compound showed potent activity against the Gram-negative bacteria *Klebsiella pneumoniae* (*K. pneumoniae*) and *E. coli*, the Gram-positive bacteria *Streptococcus pyogenes* (*S. pyogenes*), *S. aureus, and B. subtilis*, and the fungal strains *Trichoderma viridae* (*T. viridae*), *A. niger*, and *C. albicans*.[8] Tryptanthrin and its derivatives also showed activity against Gram-negative bacteria, including *Helicobacter pylori* (*H. pylori*)[9,10], *Vibrio cholerae* (*V. cholerae*)[11], and *E. coli*[12], as well as Gram-positive bacteria, including the *Staphylococcus* species *S. aureus*[13], *S. epidermis*[13], and methicillin-resistant *S. aureus* (MRSA)[13–15]. Tryptanthrin has also been identified as a potential biofilm inhibitor against toxic *V. cholerae*.[11] The antifungal activities include anticryptococcal activity, with a synergistic effect when used in combination with calcineurin inhibitors,[16,17] as well as a possible synergistic effect against *Aspergillus fumigates (A. fumigates)* and *C. albicans* when

combined with isatin.[13] Additionally, tryptanthrin derivatives exhibited promising in vitro antidiabetic activity, as well as anticancer activity against lung cancer.[10] Most exciting, however, is that due its potent antiviral activity against a type of human coronavirus, tryptanthrin has been implicated as a promising lead compound for the treatment of SARS-CoV-2, the virus responsible for the current global pandemic.[18]

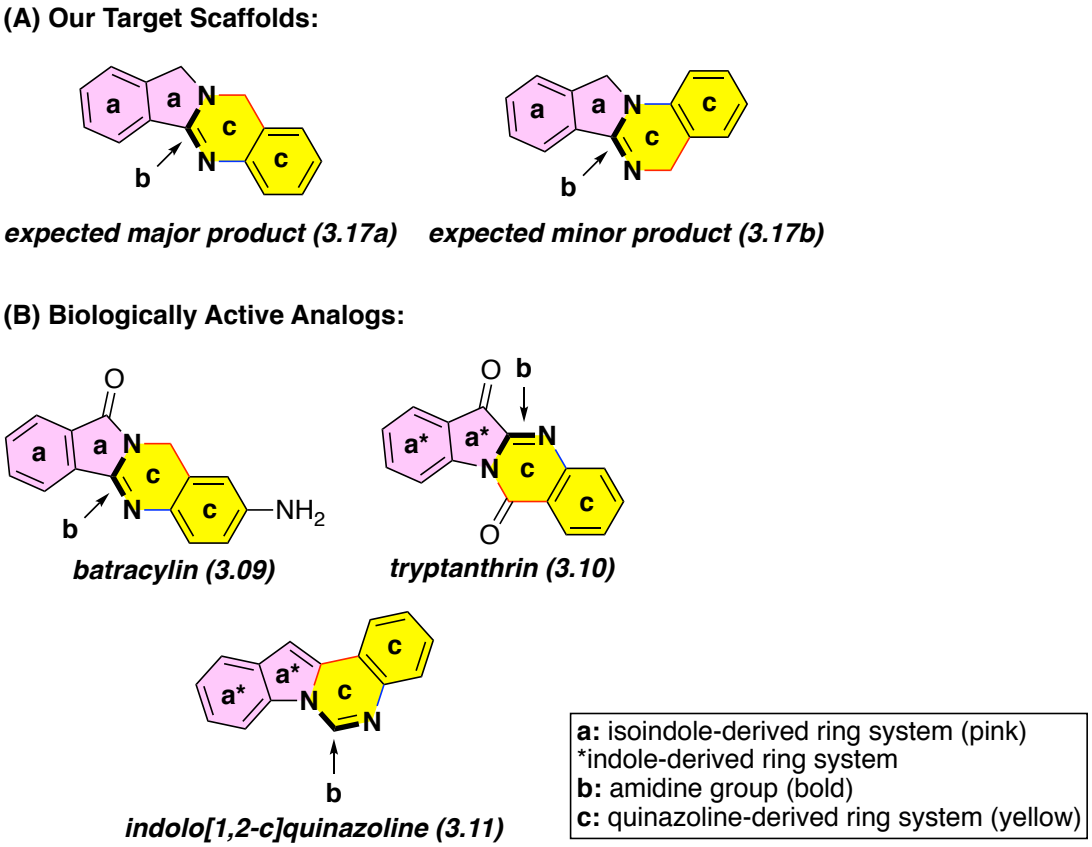


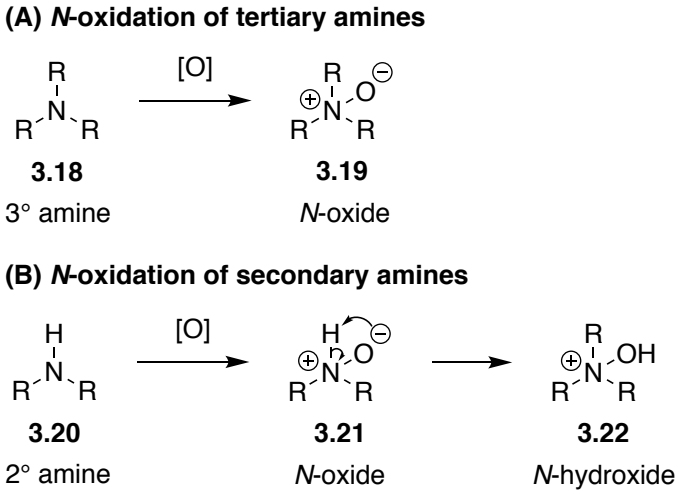
Figure 3.2. Structural features of our target scaffolds and biologically active analogs.

Our expected major (**3.17a**) and minor (**3.17b**) products are analogs of these biologically active compounds. All of these compounds share several structural features, which include either an isoindole- or an indole-derived ring system (**a**, Figure 3.2), an amidine group (**b**), an aniline

moiety (**c**), a benzylamino group (**d**), and a quinazoline-derived ring system (**e**), of which the aniline and benzylamino groups are a part. Batracylin is a derivative of **3.17a**, as it has the same core structure. The only differences are that the benzenoid ring of the quinazoline is substituted with an amino group and the isoindole-derived ring system is an isoindolinone instead of an isoindoline.

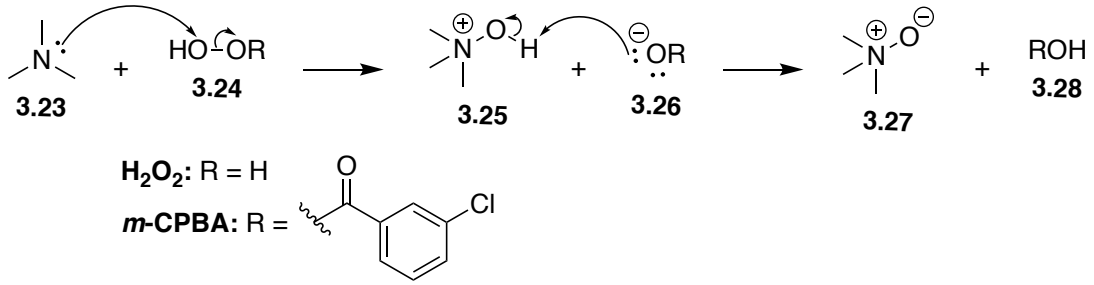
3.3. *N*-Oxidation of Secondary and Tertiary Amines

N-oxidation of secondary and tertiary amines occurs when an oxygen atom is transferred to the nitrogen atom of the amine.[19] For tertiary amines, *N*-oxidation will give the corresponding *N*-oxide (**3.19**), whereas for secondary amines, the oxy anion that forms initially (**3.21**) will deprotonate the resulting ammonium salt to give the *N*-hydroxide (**3.22**, Scheme 3.4). Since amines can act as nucleophiles, the oxygen transfer reagents that are typically used for the *N*-oxidation of amines tend to be electrophilic in nature. For many of these amine *N*-oxidation reagents, including H_2O_2, persulfates, Oxone, and mCPBA, the electrophilic reactive site is an oxygen atom that is part of a weak peroxide bond.



Scheme 3.4. *N*-oxidation of (A) tertiary and (B) secondary amines.

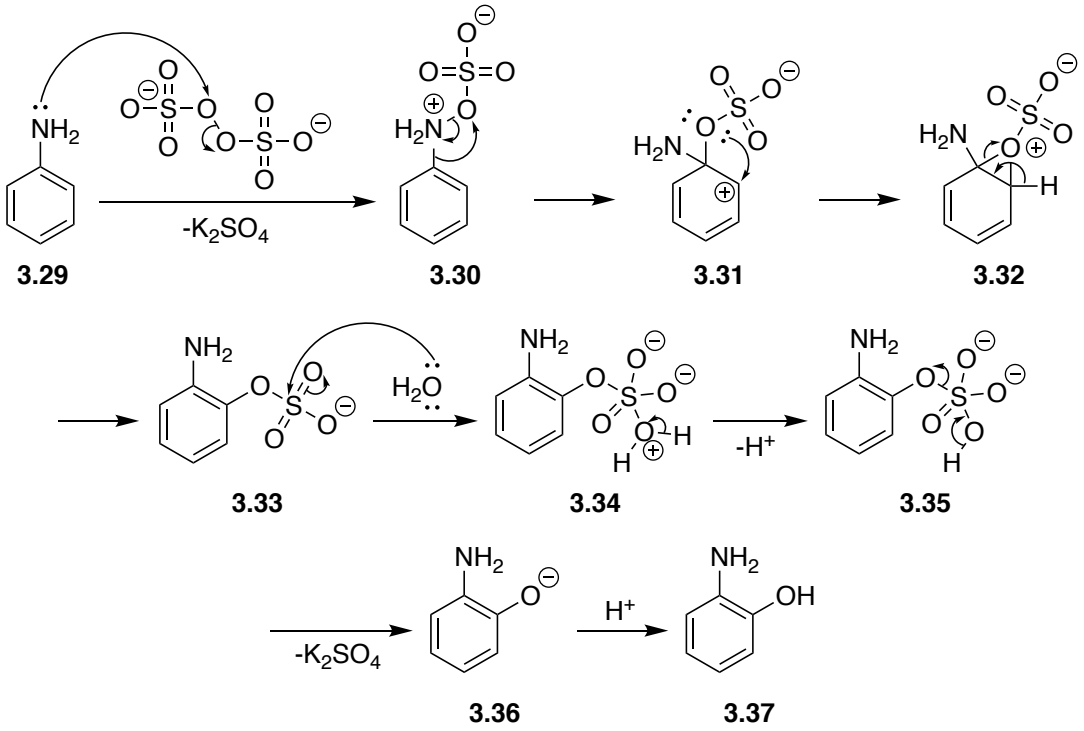
Hydrogen peroxide is one of the most common reagents for the *N*-oxidation of amines[20–26], including isoindolines[27]. In the mechanism for this reaction, the amine attacks one of the oxygen atoms, which causes the weak peroxide bond to break (Scheme 3.5). This results in the formation of ammonium *N*-hydroxide species **3.25** and the hydroxide anion, which subsequently deprotonates the *N*-hydroxide to give *N*-oxide **3.27**. Another commonly used reagent for the *N*-oxidation of secondary and tertiary amines is *m*-CPBA (Scheme 3.5). The reaction of *m*-CPBA with secondary and tertiary amines is thought to be mechanistically similar to the one described *supra* for hydrogen peroxide.[28] The amine nucleophile attacks the protonated peroxide oxygen atom, resulting in the cleavage of the weak peroxide bond (**3.25**). The resulting carboxylate anion then deprotonates the hydroxyl group to give the *N*-oxide (**3.27**).



Scheme 3.5. Mechanism for the oxidation of secondary and tertiary amines using H_2O_2 or *m*-CPBA.

Persulfate salts have not been used as extensively as H_2O_2 for this purpose, but there are a couple of reported examples in which they were used to oxidize amines to the corresponding *N*-oxides. In one example[29], choline peroxydisulfate was used to oxidize secondary amines with very high yields, and in the other example[30], ammonium persulfate was used to oxidize a tertiary amine. Additionally, while there are few examples of amine *N*-oxidation that utilize persulfate

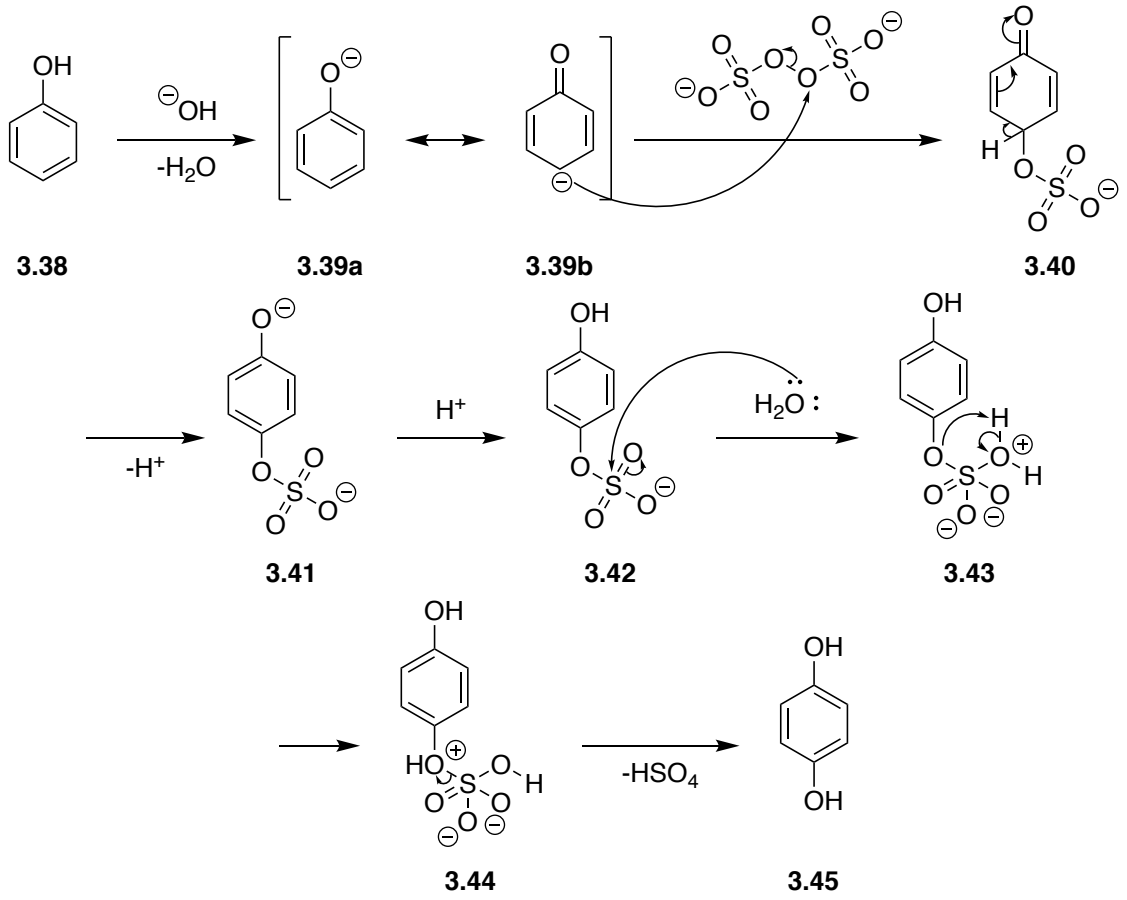
salts, they have been known to act as electrophiles in other reactions. While it does not give the *N*-oxide product, the Boyland-Sims oxidation begins with nucleophilic attack by an aniline on one of the persulfate oxygen atoms, which causes the weak peroxide bond to break (Scheme 3.6).[31,32] The resulting Zwitterionic sulfate species (**3.30**) rearranges, putting the sulfate group in the *ortho* position (**3.33**). Subsequent hydrolysis of the sulfate leaves a hydroxyl group in the *ortho* position (**3.37**).



Scheme 3.6. Mechanism for the Boyland-Sims oxidation.[31,32]

In the Elbs persulfate oxidation, which is mechanistically similar to the Boyland-Sims oxidation, the tautomeric *para* carbanion of a phenolate anion (**3.39b**) acts as the nucleophile, giving sulfate intermediate **3.40** (Scheme 3.7).[33,34] However, in this reaction, the sulfate does not rearrange. Instead, the intermediate tautomerizes back to the phenolate ion (**3.41**), which is then

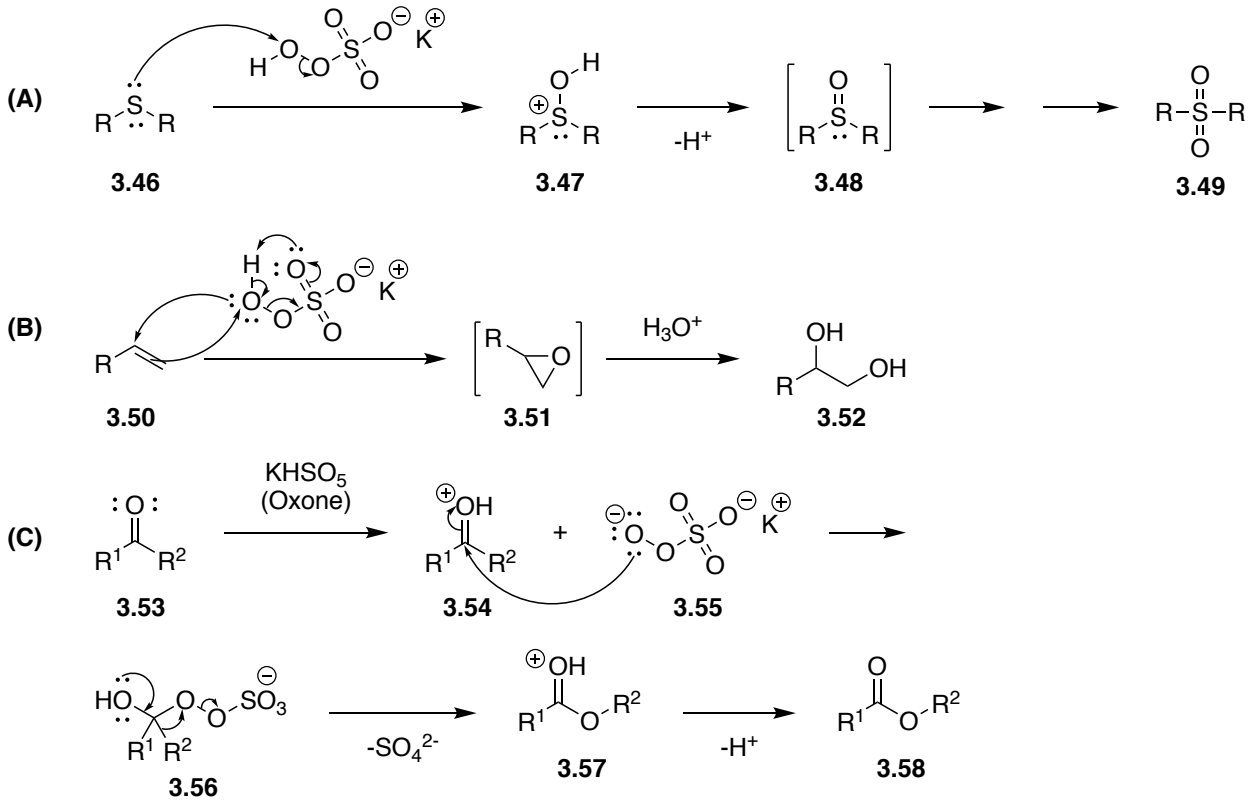
protonated to give the phenol (**3.42**). Subsequent hydrolysis of the sulfate gives a second hydroxyl group (**3.45**), albeit in low yields.



Scheme 3.7. Mechanism for the Elbs persulfate oxidation.[33]

While Oxone is more commonly used to convert amines to the corresponding nitroxide radicals, there are a couple of reported examples in which it has been used to oxidize secondary amines to the corresponding *N*-hydroxides.[35,36] Additionally, there is literature precedent for its use as an electrophilic oxygen transfer reagent. For example, the mechanism for oxidation of sulfides to sulfoxides to sulfones (Scheme 3.8A) begins with nucleophilic attack by the sulfide on the protonated peroxide oxygen.[37] Similarly, the oxidation of aryl iodides begins with the

iodide acting as a nucleophile and attacking at the same position as the sulfide.[38] While concerted in nature, the mechanism for the epoxidation of an alkene using Oxone can also be thought of as beginning with nucleophilic attack by the alkene (Scheme 3.8B).[39] However, it should be noted that upon deprotonation, Oxone can act as a nucleophile, as it does in the Baeyer-Villiger oxidation (Scheme 3.8C).[40]



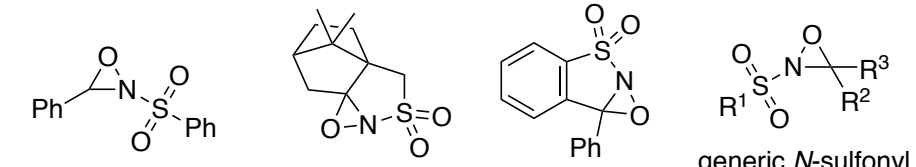
Scheme 3.8. Examples of reactions of Oxone. (A) Oxidation of sulfides to sulfones. (B) Epoxidation of alkenes. (C) Baeyer-Villiger oxidation.

N-sulfonyl oxaziridines are also electrophilic oxidizing agents; however, they do not contain a peroxide bond. These oxidants and the mechanisms for the oxidation reactions that use them will be discussed *infra* in the next section.

3.4. The Davis Oxidation

N-sulfonyl oxaziridines, such as the Davis reagent[41,42], are used as oxygen atom transfer reagents (Figure 3.3A). Although some studies[43,44] of the transition state indicate that oxygen transfer may proceed through an asynchronous concerted mechanism, *N*-sulfonyl oxaziridines can be thought of as electrophilic in nature because of the advanced N–O bond cleavage and consequent buildup of partial negative charge on nitrogen (Figure 3.3B).[45]

(A) Generic *N*-sulfonyl oxaziridine structure and examples



Davis reagent (**3.59**) **3.60** **3.61**

(B) Asynchronous transition state for oxygen atom transfer

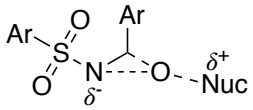
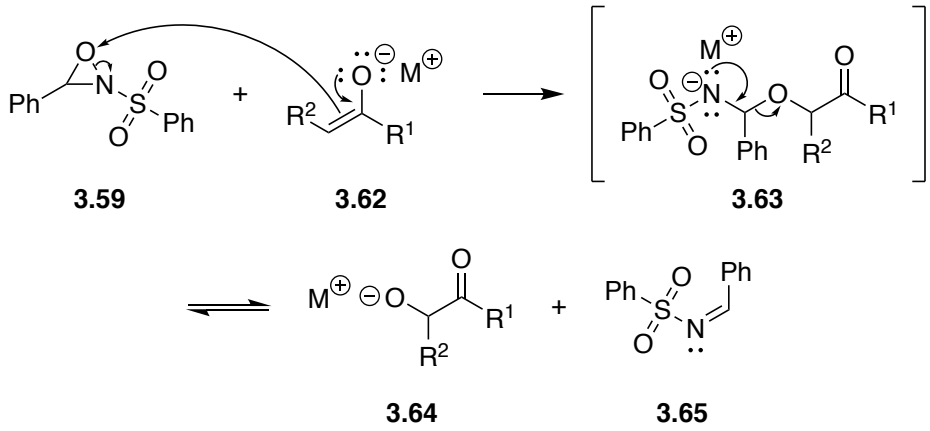


Figure 3.3. (A) *N*-sulfonyl oxaziridine generic structure and examples.[41,46] (B) Asynchronous transition state for oxygen atom transfer by *N*-sulfonyloxaziridines.[43–45,47]

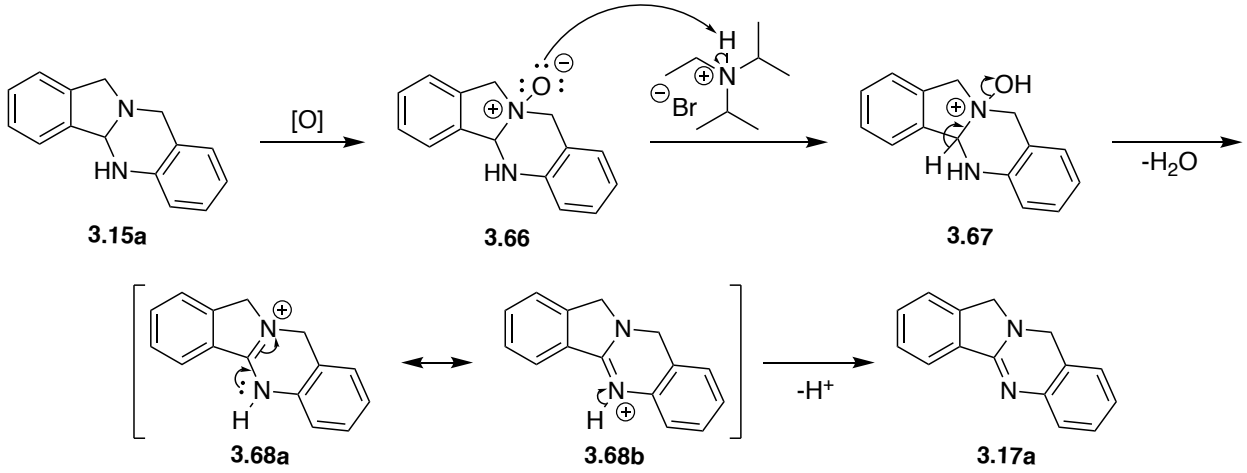
However, other studies support a stepwise S_N2-type mechanism, including studies reported by Davis et al.[46,48], and the mechanism is often shown in a stepwise fashion. For example, in the stepwise mechanism for the oxidation of enolates, the enolate nucleophile (**3.62**) attacks the electrophilic oxaziridine oxygen (**3.59**), which causes the N–O bond to break and places a negative charge on the nitrogen atom (**3.63**, Scheme 3.9). This charge is resonance stabilized, which makes this step favorable. Next, the tetrahedral intermediate collapses to form an imine (**3.65**), eliminating the oxygen atom in the process and providing the oxy anion product (**3.64**).



Scheme 3.9. Stepwise mechanism for the oxidation of enolates using the Davis reagent.[46,48]

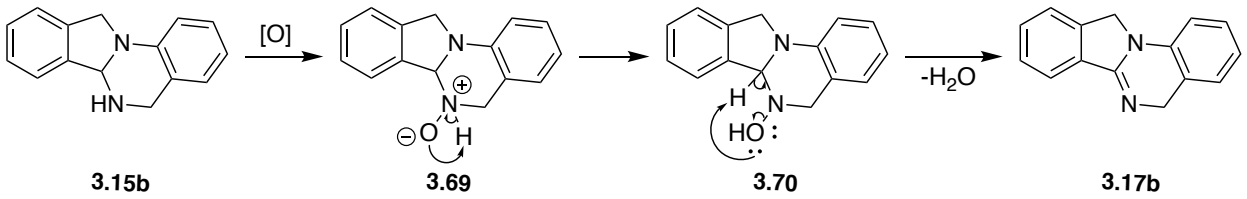
3.5. Proposed Mechanisms for the Oxidation of the Cyclization Products

We reasoned that the major cyclization product **3.15a** could be converted to **3.17a** via *N*-oxidation of the more nucleophilic tertiary amine. In our proposed mechanism (Scheme 3.10), the tertiary amine is oxidized to the *N*-oxide (**3.66**), which is subsequently protonated to form the *N*-hydroxide (**3.67**). The methine proton is subsequently removed in a dehydrative elimination, which gives an amidinium intermediate (**3.68a**) that is in resonance with species **3.68b**. Subsequent deprotonation of **3.68b** gives the amidine product (**3.17a**).



Scheme 3.10. Proposed mechanism for the oxidation of major cyclization product **3.15a** to amidine **3.17a**.

However, for minor cyclization product **3.15b**, the secondary amine is more nucleophilic than the tertiary amine because the latter is in conjugation with the aryl ring. Consequently, our proposed mechanism for the oxidation of **3.15b** to **3.17b** (Scheme 3.11) begins with the *N*-oxidation of the secondary amine to form *N*-oxide species **3.69**. The oxy anion subsequently deprotonates the quaternary ammonium in an intramolecular deprotonation to give the *N*-hydroxide (**3.70**). The hydroxyl group then deprotonates the neighboring methine carbon of the aminal in a dehydrative elimination, which gives amidine product **3.17b**.



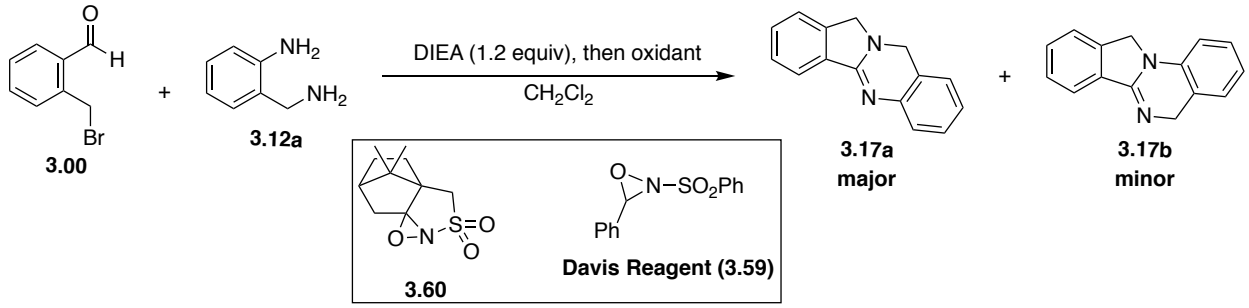
Scheme 3.11. Proposed mechanism for the oxidation of minor cyclization product **3.15b** to amidine **3.17b**.

3.6. Screening of Oxidants and Optimization of Reaction Conditions for Cyclization-Oxidation Cascade

We began our efforts toward the development of a cyclization–oxidation cascade reaction by screening various oxidants (Table 3.1, *infra*). We began by screening oxygen, as we reasoned that the autoxidation of **3.15a** was responsible for the formation of side product **3.17a** in the absence of an added oxidant. However, no reaction occurred under an atmosphere of oxygen (Entry 1). Based on extensive literature precedent supporting its use in the formation of

secondary and tertiary amine *N*-oxides and *N*-hydroxides from the parent amines, hydrogen peroxide was also investigated. Disappointingly, only a 20 % yield was obtained using five equivalents of H_2O_2 (Entry 2). Several persulfate oxidants were investigated, as they can act as electrophiles, such as in the Elbs persulfate oxidation (Scheme 3.7, *supra*),[33] and there is literature precedent for their use in the oxidation of secondary[29] and tertiary[30] amines to the corresponding *N*-hydroxides. However, only trace yield was obtained using $Na_2S_2O_8$, $K_2S_2O_8$, and $(NH_4)_2S_2O_8$ (Entries 4-7). We reasoned that perhaps the single equivalent of water that was generated during the reaction was not sufficient to remove the sulfate group and liberate the *N*-oxide. Additionally, no reaction was observed with Oxone (Entry 3), which has also been used in the literature to convert secondary amines to the corresponding *N*-hydroxides and *N*-oxy radical species. This is not surprising. While Oxone can act as an electrophile when protonated, as in the first step of the oxidation of sulfides (Scheme **3.8A**, *supra*),[37] it can also act as a nucleophile when deprotonated, as in the first step of the Baeyer-Villiger oxidation of 2-arylindoles (Scheme **3.8C**, *supra*)[40]. It is possible that the Oxone was deprotonated by one of the amines present in our reaction, which would likely prevent it from reacting with our cyclization product or the isoindole intermediate, both of which are nucleophilic. Success was finally achieved with *N*-sulfonyl oxaziridine species, which are effective electrophilic oxygen transfer reagents (Scheme 9, *supra*). While the Davis reagent (**3.59**) surprisingly gave only trace yield of the desired product (Entries 8 and 9), (1*S*)-(+)-(10-Camphorsulfonyl)oxaziridine (**3.60**) gave a 45 % yield of major product **3.17a** at room temperature (Entry 10).

Table 3.1. Screening of oxidants and optimization of reaction conditions for cyclization-oxidation cascade.



Entry[a]	Oxidant	Equiv.	Temperature (°C)	Time (h)[b]	Yield (%) 3.17a[c]
1	O_2	–	23	6	NR
2	H_2O_2	5.0	23	6	20
3	Oxone	1.0	23	6	6
4	$Na_2S_2O_8$	2.0	23	6	trace
5[d]	$Na_2S_2O_8$	2.0	23	3	trace
6	$K_2S_2O_8$	2.0	23	6	trace
7	$(NH_4)_2S_2O_8$	2.0	23	6	trace
8	**3.59**	1.1	23	6	trace, complex mixture
9[e]	**3.59**	1.5	23	2	trace, complex mixture
10	**3.60**	1.1	23	6	45
11	**3.60**	1.5	23	1	42
12[d]	**3.60**	1.5	23	2	76
13	**3.60**	1.5	23	2	66 (**3.17a**) & 9 (**3.17b**)
14	**3.60**	1.5	23	4	63
15	**3.60**	1.5	23	6	66
16	**3.60**	1.5	23	22	55
17[d]	**3.60**	1.7	23	2	71
18	**3.60**	2.0	23	6	56
19	**3.60**	3.0	23	6	38
20[d]	**3.60**	3.0	23	2	27
21	**3.60**	1.5	0	2	22

[a]Unless otherwise specified, a one-pot procedure was used in which the isoindole was formed by the addition of DIEA (1.2 equiv) to the diamine (1.1 equiv) and 2-(bromomethyl)benzaldehyde (1.0 equiv, 0.1 M in CH_2Cl_2) at 23 °C. After 1 h, the oxidant was added. [b]Reaction time for oxidation step. [c]Isolated yields. [d]The amounts of DIEA and diamine were increased to 1.3 equivalents and 1.2 equivalents, respectively. The isoindole was allowed to form over a period of 2 h before adding the oxidant, instead of 1 h.

Next, the reaction conditions were optimized using oxidant **3.60** (Table 3.1). Gratifyingly, when the number of equivalents of **3.60** was increased from 1.1 to 1.5 (Entry 15), the yield of **3.17a** increased to 66 %, although the yield decreased proportionally with the addition of 1.7 or more equivalents (Entries 17-20). While a 1 h reaction time led to a reduced yield of only 42 % of **3.17a** (Entry 11), reaction times of 2-6 h gave comparable yields (Entries 13-16). Since the yield of **3.17a** decreased slightly again at 22 h, a reaction time of only 2 h was found to optimal, giving a 66 % yield of the major regioisomer (**3.17a**), in which the isoindole formed from the more nucleophilic benzylic amino group, and a 9 % yield of the minor regioisomer (**3.17b**), in which the isoindole formed from the less nucleophilic aniline (Entry 13). Cooling the reaction to 0 ℃ hindered the reaction and caused the yield of **3.17a** to drop to only 22 % (Entry 21). Slight improvements in the yields were observed when the reaction conditions were further modified to increase the number of equivalents of diamine **3.12a** and DIEA added and to allow more time for full conversion of the starting materials to the isoindole prior to adding the oxidant (Entries 12, 17, and 20), with the modified best conditions giving a 76 % yield of **3.17a** (Entry 12). We also revisited the reaction of the Davis reagent (**3.59**) using our optimized conditions but observed the same perplexing result (Entry 9). We suspect that the relief of ring strain that occurs during oxygen atom transfer, during which one of the three fused rings is broken, could explain the greater reactivity observed with **3.60**.

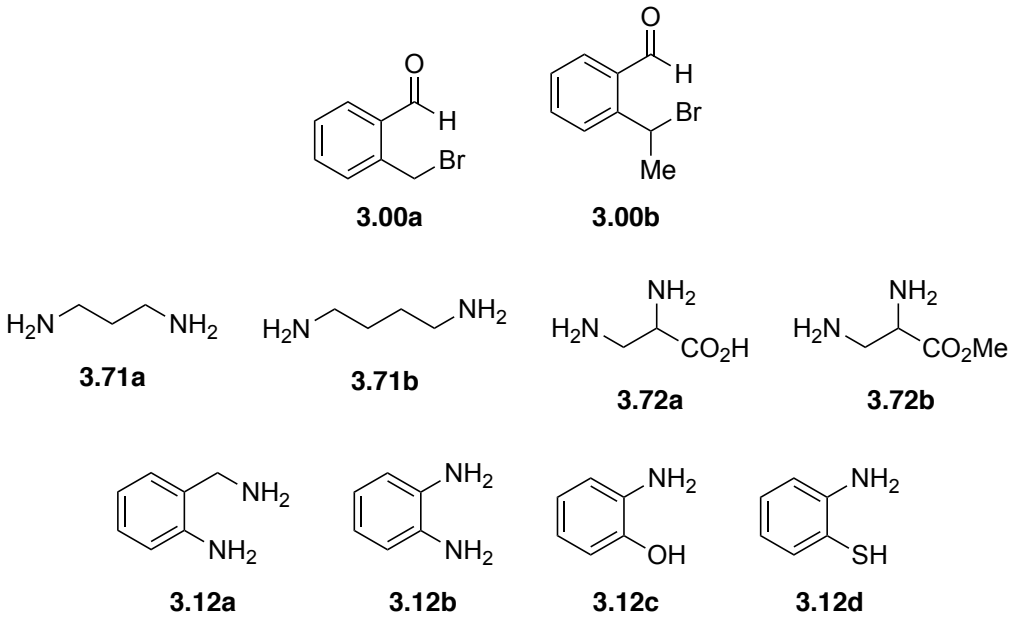
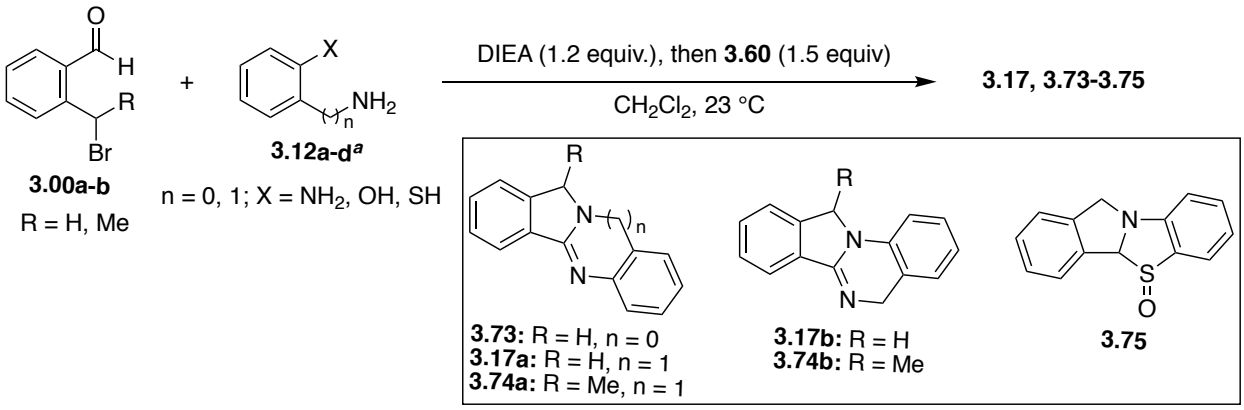


Figure 3.4. Substrates investigated for the cyclization/oxidation cascade reaction.

With our optimized reaction conditions in hand, we then investigated the substrate scope (Figure 3.4, *supra*), starting with the dinucleophilic reacting partner. First, we investigated various aryl dinucleophiles. Unlike the aryl 1,3-diamine species (**3.12a**) used in our model system (Entries 2-3, Table 3.2), the 1,2-diamine species *ortho*-phenylenediamine (**3.12b**) gave a messy reaction with incomplete formation of the isoindole, although some of the desired product (**3.73**) was obtained (Entry 1). This can potentially be attributed to the strained nature of the product, the decreased nucleophilicity of the aniline amino groups, and the incomplete formation of the isoindole. Other aniline 1,2-dinucleophiles (**3.12c-d**) gave mixed results. While no reaction was observed with 2-aminophenol (**3.12c**, Entry 5), 2-aminobenzenethiol (**3.12d**) gave a 96 % yield of sulfoxide product **3.75** (Entry 4), in which sulfur was oxidized instead of carbon. This showed that aminothiols are suitable dinucleophiles for this cascade.

Table 3.2. Substrate scope of aryl diamine reacting partners in cyclization/oxidation cascade reaction.



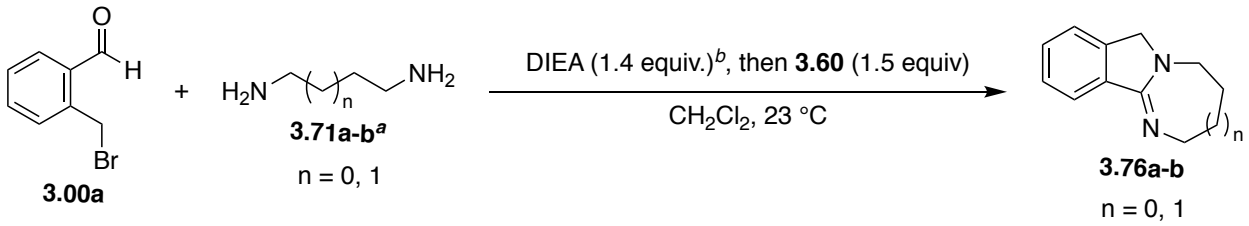
Entry	R	n	X	Products	Yield (%)
1[b]	H	0	NH_2	Complex Mixture[c]	ND
2[d]	H	1	NH_2	**3.17a** (major) & **3.17b** (minor)	76 (**3.17a**)
3	H	1	NH_2	**3.17a** (major) & **3.17b** (minor)	66 (**3.17a**) & 9 (**3.17b**)
4	H	0	SH	Sulfoxide **3.75**	96
5	H	0	OH	–	NR
6	Me	1	NH_2	**3.74a** (major) + **3.74b** (minor)	21 (**3.74a**)[e] & 9 (**3.74b**)

[a]Unless otherwise specified, 1.1 equiv. of **3.12** were added. [b]Similar results were obtained using 1.2 equiv. of **3.12** and 1.4 equiv. of DIEA. [c]Detected by LC-MS. [d]Used 1.2 equiv. of **3.12** and 1.4 equiv. of DIEA. [e]Semi-pure mixture of major product and either the corresponding nitrone or the oxaziridine of desired product, per LC-MS.

Next, we investigated alkyl 1,3- and 1,4-diamines. Disappointingly, 1,3-diaminopropane, an alkyl 1,3-diamine, gave only a 37 % isolated yield of the hydrochloride salt of **3.76a** (Entry 1, Table 3.3, *infra*), which is considerably lower than the yields obtained with the 1,3-diamine from

the model reaction. Additionally, attempts to separate the product from the hydrochloride salt of DIEA via preparative HPLC were unsuccessful. Aqueous and basic aqueous workups were subsequently attempted (Entries 2 and 3, respectively). A series of aqueous and basic aqueous washes of the organic extract followed by lyophilization of the crude product successfully removed all residual DIEA and DIEA hydrobromide (Entry 3). Good crude yields were achieved, but significant impurities remained. As with the other dihydrochloride salts investigated, attempts to react *in situ*-deprotonated putrescine dihydrochloride, a 1,4-diamine species, with the aldehyde from our model reaction were unsuccessful. The isoindole failed to form in the presence of both 3.6 and 7.2 equivalents of DIEA (Entries 4 and 5, respectively), even after several hours, as well as overnight.

Table 3.3. Substrate scope of alkyl diamine reacting partners in cyclization/oxidation cascade reaction.



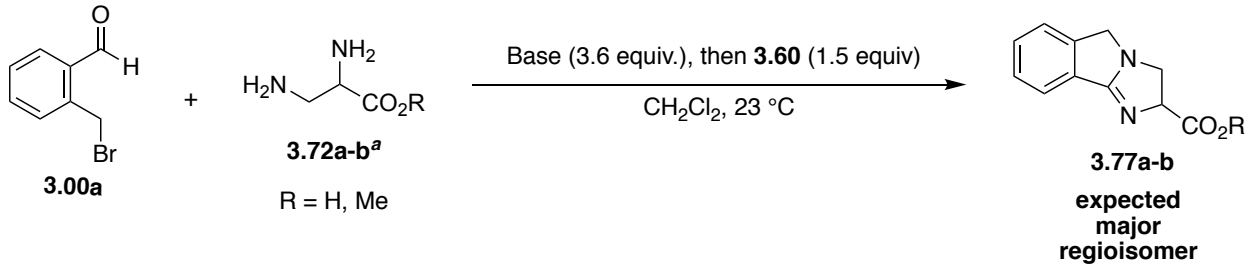
Entry	n	Workup	Yield (%) 3.76
1[a]	0	Removed solvent, acidified to form HCl salt	37 (semi-pure mixture)[c]
2	0	Aqueous workup[d]	82 (crude)[e]
3	0	Basic aqueous workup, then lyophilization[f]	72 (crude)[e]
4[g]	1	–	NR[h]
5[g]	1	–	NR[h]

[a]For entry 1, 1.1 equivalents of the diamine were added. For entries 2-5, 1.2 equivalents were added. [b] For entry 1, 1.2 equivalents of DIEA were added. For entries 2-3, 1.4 equivalents were added. For entry 4, 3.6 equivalents were added. For entry 5, 7.2 equivalents were added. [c]Purification of HCl salt via HPLC gave an inseparable mixture of the HCl salt of **3.76a** and DIEA·HCl. The yield of **3.76a** was calculated from the ^{1}H NMR spectrum of the semi-pure mixture. [d]Crude yield of product isolated following aqueous workup and subsequent extraction with 6:1 ethyl acetate:DCM. Some DIEA·HBr salt remained. Yield was not adjusted to account for impurities. [e]Crude yield was not adjusted to account for impurities. [f]The product was dissolved in 6:1 ethyl acetate:DCM, washed twice with water, and then washed twice with saturated aqueous potassium carbonate. The organic extract was dried over anyhydrous sodium sulfate and solvent was removed via evaporation. Residual DIEA was removed via lyophilization. However, DIEA and DIEA·HBr were successfully removed. [g]The dihydrochloride salt of the diamine was used. Attempts were made to deprotonate the dihydrochloride salt *in situ* using a larger excess of DIEA. [h]No isoindole formation was observed via TLC or LC-MS.

Electron-deficient 1,2-diamines also gave poor results, like due to their reduced nucleophilicities (Table 3.4, *infra*). Reactions of 2,3-diaminopropanoic acid (**3.72a**) and methyl 2,3-diaminopropanoate (**3.72b**), which were formed *in situ* from their dihydrochloride salts using 3.6 equivalents of either DIEA or Et_3N, were not successful. The dihydrochloride salt of 2,3-diaminopropanoic acid (Entry 1) did not react and the dihydrochloride salt of methyl 2,3-diaminopropanoate gave only trace yield when deprotonated with DIEA (Entry 2) and no desired product when deprotonated with Et_3N (Entry 3). While a greater percent conversion was observed for **3.72a-b** than **3.71b**, the isoindoles of these diamines also formed incompletely. While the reduced nucleophilicity of **3.72a-b** may be partly to blame, perhaps a stronger base is needed to protonate the dihydrochloride salts.

Lastly, we investigated the effect of benzylic substitution of the aldehyde reacting partner with a methyl group and found that it hindered the reaction (Entry 6, Table 3.2, *supra*). For the expected major product (**3.74a**), an isolated yield of only 21% was observed. Additionally, the LC-MS spectrum indicated that **3.74a** was part of a mixture with either the corresponding nitrone or the corresponding oxaziridine, which is indicative of overoxidation of the desired product. However, the expected minor product (**3.74b**) was isolated by itself in a 9% yield. A 9% yield was also observed for the minor product of the model reaction (**3.17b**, Entry 3); however, a significantly higher 66% yield was observed for major product **3.17a**, which amounts to a regioselectivity of 7.3:1. Thus, benzylic substitution significantly reduced the regioselectivity, as a ratio of only 2.3:1 was observed for **3.74**. However, since the regioselectivity was determined using isolated yields, it is possible that differences in the separations influenced the results. Further work would be needed to confirm the regioselectivity using the crude reaction mixtures.

Table 3.4. Substrate scope of electron-deficient 1,2-diamine reacting partners in cyclization/oxidation cascade reaction.



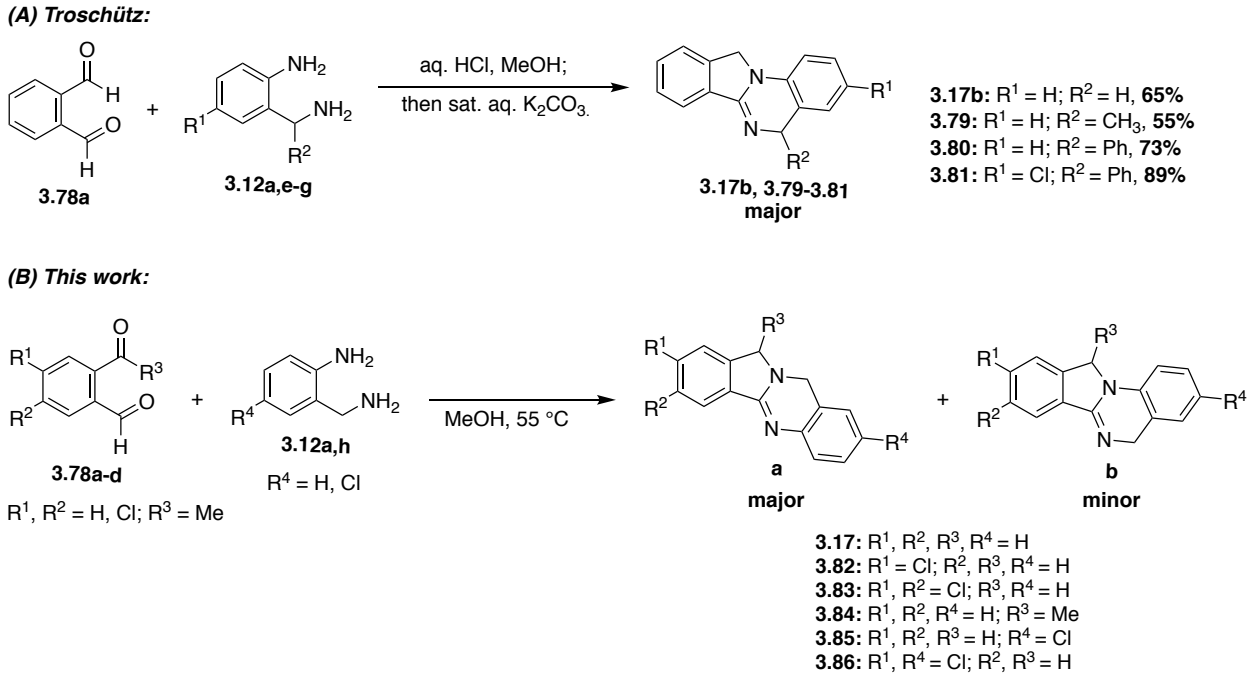
Entry	R	Base	Yield (%) 3.77
1	H	DIEA	NR
2	Me	DIEA	Trace
3	Me	Et_3N	0[b]

[a]The dihydrochloride salts were used. A larger excess of base was used to convert the dihydrochloride salts to the corresponding free amines. [b]The desired product was not detected via LC-MS.

3.7. Condensation/Cyclization Cascade Reactions of *Ortho*-Phthalaldehydes with Diamines: Our Approach and Rationale

Due to the limited shelf life of the oxidant and the difficulty associated with synthesizing *ortho*-substituted electron-rich 2-(bromomethyl)benzaldehydes, we decided to look for dielectrophilic reacting partners that would react with diamines to give the desired products **3.17a** and **3.17b** in the absence of an oxidant. Accordingly, we sought dielectrophiles with the same net oxidation state as the desired products. We identified *ortho*-phthalaldehydes as suitable dielectrophiles, since one aldehyde carbon would undergo a two-electron oxidation and the other would undergo a two-electron reduction, so there would be no net change in the oxidation state

and thus, no redox reaction would occur. Additionally, OPA is commercially available and inexpensive, and substituted phthalaldehydes can be prepared from inexpensive starting materials in only one or two steps. Moreover, there is abundant literature precedent for the synthesis of isoindole derivatives via condensation reactions of OPA with both amines and diamines,[49–53] including a publication by Troschütz[54] (Scheme 3.12) that uses the same diamine that we chose for our model system (**3.12a**).



Scheme 3.12. A comparison of our approach and the work reported by Troschütz[54].

We reasoned that our work would complement the method published by Troschütz[54] nicely, for several reasons. First, the method reported by Troschütz used an extremely large excess of aqueous HCl and consequently gave the opposite regioselectivity of our envisioned

approach. While the authors reportedly obtained our desired major product as the major regioisomer in the absence of HCl, it does not appear that they optimized the reaction conditions, nor did they report a yield for the acid-free reactions. Second, the author did not report screening the conditions for the acid-promoted reaction, as no other solvents or acids were mentioned. Third, the authors only screened three substituted 2-aminobenzylamine derivatives with either a phenyl group or a methyl group at the benzylic position (R^2 = Ph, Me), two of which had an unsubstituted benzene ring (**3.12e-f**) and one of which had a chlorine on the benzene ring and a phenyl group at the benzylic position (**3.72g**). Notably, substituted phthalaldehydes and substituted 2-aminobenzylamine derivatives with an unsubstituted benzylic position (R^2 = H) were not investigated. Finally, only a moderate yield was obtained for the model reaction under acidic conditions. We reasoned that we could expand upon this work by optimizing the reaction conditions for the acid-free condensation-cyclization cascade and potentially improving upon the yield for the acid-promoted reaction, as well as investigating substituted phthalaldehydes (**3.78b-d**), 2-acyl benzaldehydes, and substituted 2-aminobenzylamine derivatives with unsubstituted benzylic positions (**3.12h**, Figure 3.5). Since four regioisomers are possible for reactions of substituted phthalaldehydes as opposed to only two for substituted amines, investigating the substrate scope of the phthalaldehyde will provide useful information to further our understanding of the reaction. It would also be helpful to determine whether 2-acyl benzaldehyde species will cyclize, given the greater degree of steric hindrance and the reduced reactivity of the ketone compared to an aldehyde, and if so, to probe the regioselectivity of that cyclization.

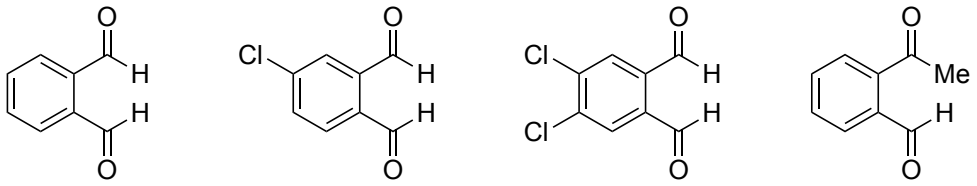
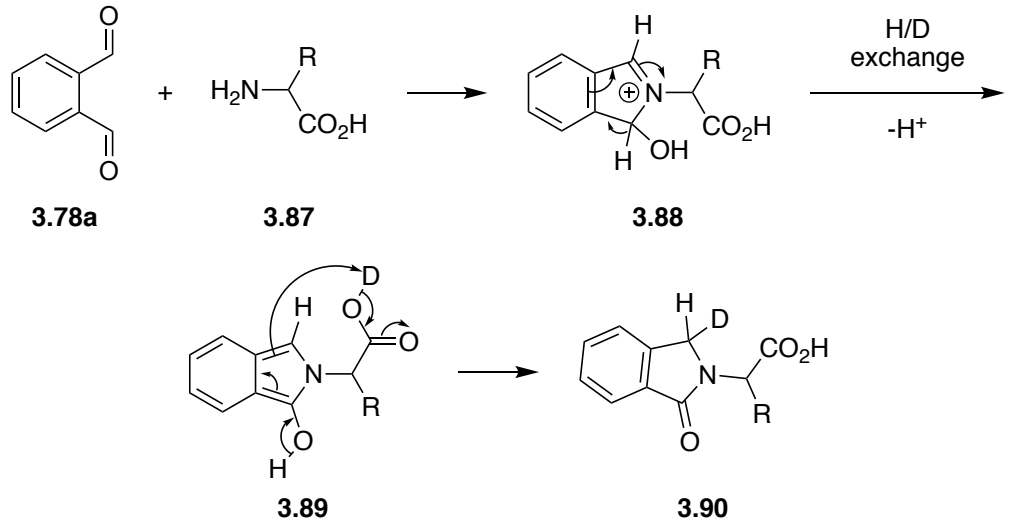


Figure 3.5. Substrates investigated for the condensation/cyclization cascade reactions of *ortho*-phthalaldehydes and 2-acyl benzaldehydes with amines.

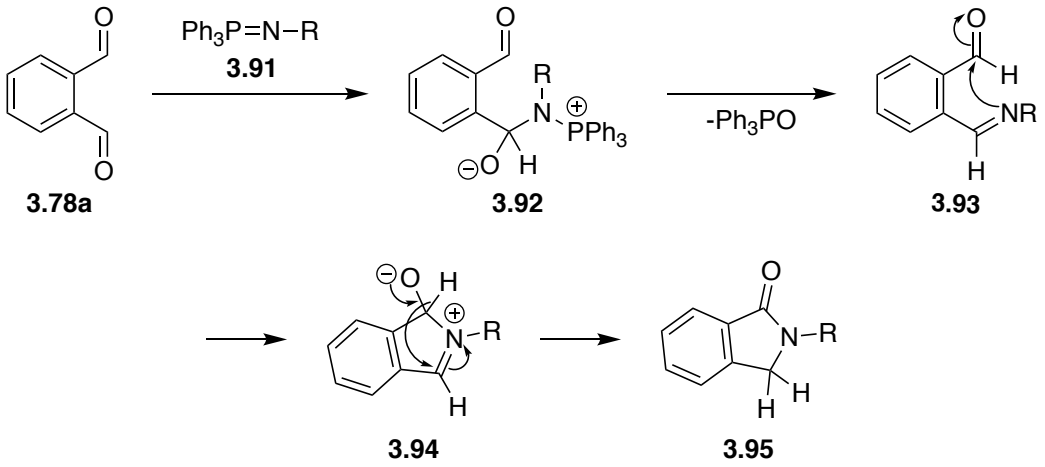
3.8. Proposed Mechanism for the Reaction of *Ortho*-Phthalaldehydes with Diamines

Studies by Grigg et al.[55] and Aubert et al.[56] suggest that the condensation reaction of *ortho*-phthalaldehydes with amines proceeds via a hydroxyiminium intermediate. Grigg et al. studied the formation of isoindolinones (**3.90**) from the condensation reaction of *ortho*-phthalaldehyde (**3.78a**) with α-amino acids (**3.87**, Scheme 3.13).[55] Deuterium labeling of the pendant acid was used to determine whether the suspected hydroxyiminium intermediate (**3.88**) underwent a 1,3-hydride shift or formed an isoindolinol (**3.89**), which subsequently tautomerized to the isoindolinone (**3.90**). Deuterium incorporation was observed at the isoindole α-position with a facial selectivity suggestive of intramolecular protonation, which provides evidence for the existence of isoindolinol **3.89**. This in turn supports the theory that the reaction proceeds through hydroxyisoindolium **3.88**, as it provides a clear pathway to the isoindolinol.



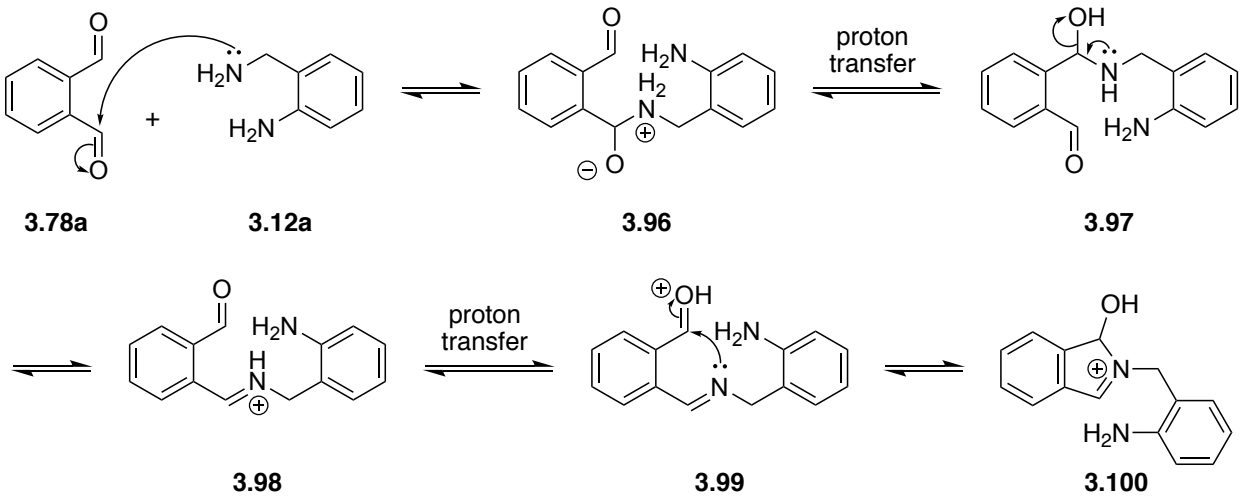
Scheme 3.13. Mechanistic studies by Grigg et al. for the formation of an isoindolinone via the condensation of *ortho*-phthalaldehyde with amino acids.[55]

A hydroxyisoindolium intermediate was also implicated under the basic conditions employed by Aubert et al., who studied the formation of isoindolinones (**3.95**) from the condensation of iminophosphoranes (**3.91**) with *ortho*-phthalaldehyde (**3.78a**, Scheme 3.14). In the proposed mechanism, an imine (**3.93**) forms from the reaction of one of the aldehydes with the iminophosphorane (**3.91**). The nitrogen of the imine attacks the remaining unreacted aldehyde, resulting in cyclization and the formation of an oxy anion isoindolium species (**3.94**). A subsequent oxygen-assisted 1,3-hydride shift provides the isoindolinone (**3.95**).



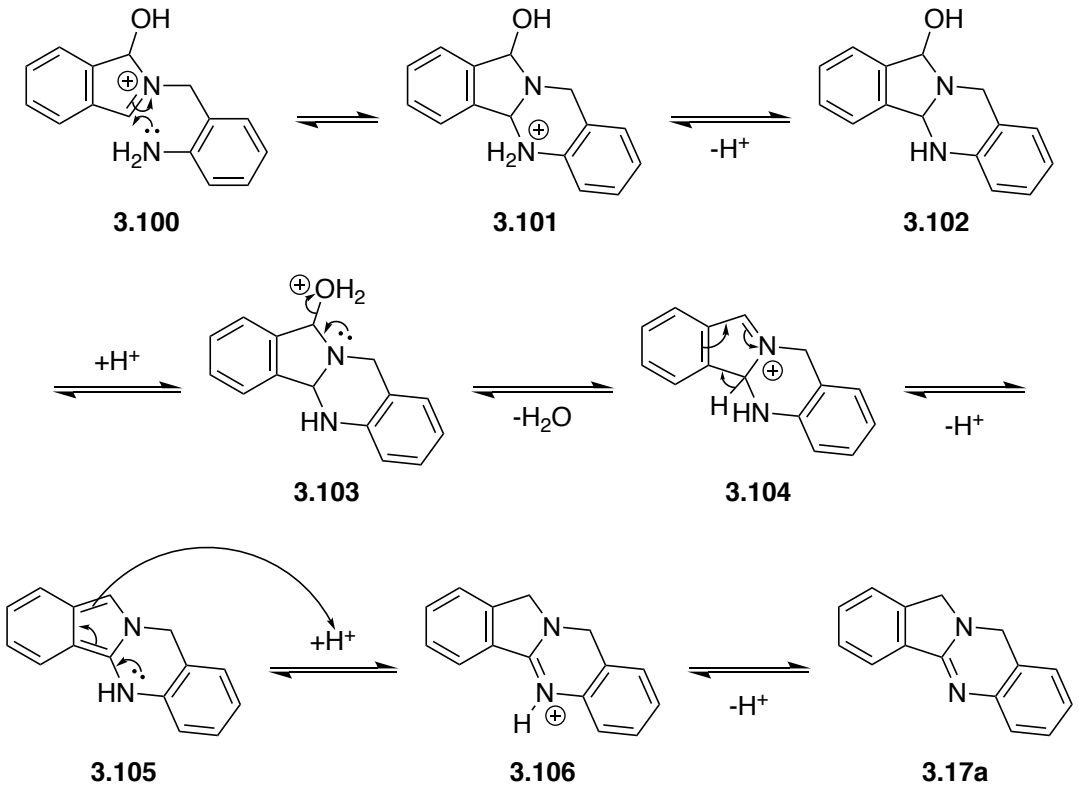
Scheme 3.14. Mechanism proposed by Aubert et al. for the formation of an isoindolinone via the condensation of *ortho*-phthalaldehyde with iminophosphoranes.[56]

We suspect that the reaction of *ortho*-phthalaldehyde derivatives with diamines also proceeds via a hydroxyisoindolium intermediate (**3.100**, Scheme 3.15). Since the pendant diamine is nucleophilic in nature, cyclization must occur via nucleophilic attack on an electrophile that forms *in situ*. The isoindolium carbon of intermediate **3.100** is electrophilic and is thus susceptible to nucleophilic attack by the remaining free amino group of the diamine.



Scheme 3.15. Proposed mechanism for the formation of hydroxyisoindolium intermediate **3.100**.

In our proposed mechanism for the cyclization step, the remaining free amino group of intermediate **3.100** attacks the isoindolium carbon, resulting in cyclization to give **3.101** (Scheme 3.16). After a proton transfer converts the alcohol to a good leaving group (**3.103**), water is lost, giving isoindolium species **3.104**. Subsequent deprotonation at the α-position gives isoindole **3.105**. Electron donation from the aniline nitrogen via resonance results in protonation of the isoindole at the less substituted α-position (**3.106**), which is followed by deprotonation to give the amidine product (**3.17a**).

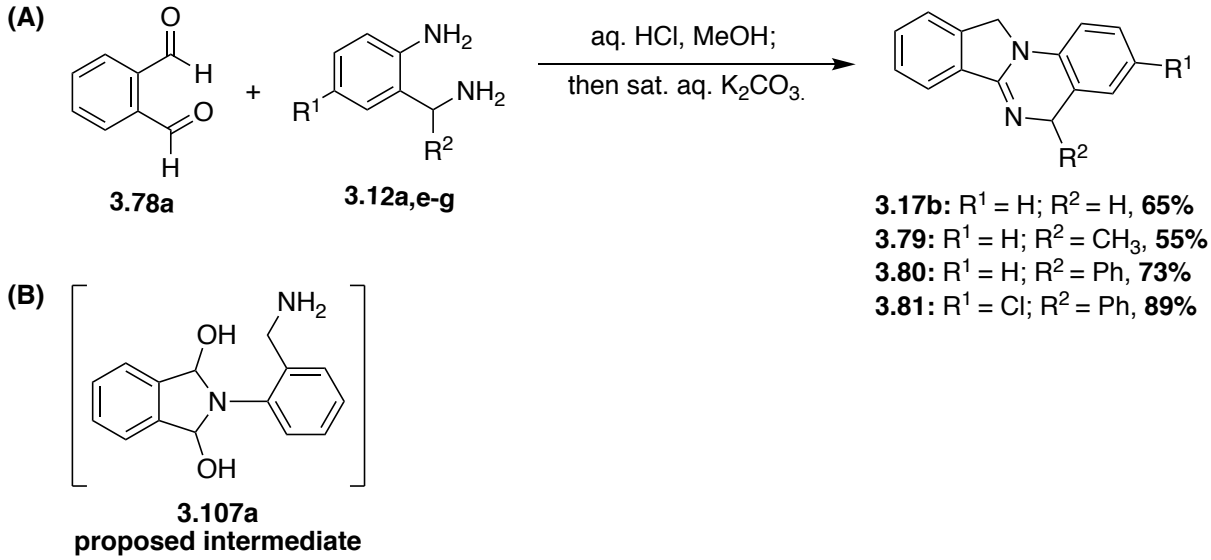


Scheme 3.16. Proposed mechanism for the cyclization of step of the reaction of *ortho*-phthalaldehydes with 2-aminobenzylamines.

3.9. Condensation/Cyclization Cascade Reactions of *Ortho*-Phthalaldehydes and 2-Acyl Benzaldehydes with Diamines: Work Reported by Troschütz.

In 1980, Troschütz reported the reaction of *ortho*-phthalaldehyde with derivatives of 2-aminobenzylamine, primarily in the presence of 140 equivalents of aqueous HCl (Scheme 3.17).[54] A small amount of methanol was added as a cosolvent. After several minutes of stirring at room temperature, the quinazoline cyclization products crystallized out and were isolated in moderate-to-good yields. Under acidic conditions, the observed regioselectivity was such that the less basic aniline amino group of the diamine (**3.12a,e-g**) underwent a condensation reaction with *ortho*-phthalaldehyde (OPA, **3.78a**), and the more basic benzylic amino group subsequently

cyclized. This is presumably due to the fact that under acidic conditions, the more basic benzylic amino group is expected to be protonated before the less basic aniline, and the corresponding ammonium salt that forms, which is less acidic than that of the aniline, is expected to be deprotonated after the aniline. Consequently, at the outset of the reaction, there is expected to be more of the aniline present as the free amino group, which is the form that will act as a nucleophile in the reaction with OPA. The author confirmed this hypothesis by performing the reaction in the absence of acid and characterizing the product, although no yield was determined and no further was done with that reaction. Limited substrate scope investigations were conducted for the diamine substrate only. In addition to the unsubstituted 2-aminobenzylamine (**3.12a**), three derivatives were investigated, two of which have a phenyl group (**3.12f** and **3.12g**) and one of which had a methyl group (**3.12e**) at the benzylic position (R^2). Substrate **3.72g** also had a chlorine at the *para* position relative to the aniline (R^1 = Cl), whereas the phenyl rings of the other three (**3.12a** and **3.12e-f**) were unsubstituted. No mechanistic studies were conducted; however, the author proposed that the reaction proceeds through the dihydroxy isoindoline intermediate **3.107**. It is not clear whether this intermediate was observed by the author or simply predicted based on the abundance of water, which can act as a nucleophile and attack the electrophilic iminium of the hydroxyisoindolium that is expected form, as discussed *supra*.

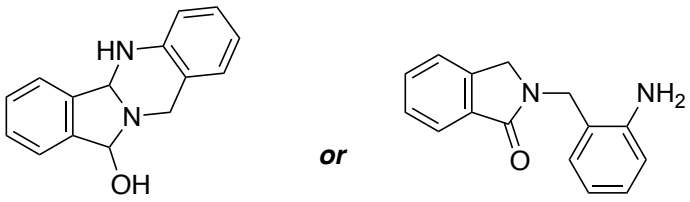


Scheme 3.17. (A) Scheme of the acid-promoted reaction of *ortho*-phthalaldehyde with substituted 2-aminobenzylamines reported by Troschütz. (B) Intermediate proposed by Troschütz.

3.10. Condensation/Cyclization Cascade Reactions of *Ortho*-Phthalaldehydes and 2-Acyl Benzaldehydes with Diamines: Optimization of Reaction Conditions

The reaction conditions were systematically optimized, using the reaction conditions from our cascade-oxidation reaction, which is described earlier in this chapter, as a starting point (Table 3.5, *infra*). While an isoindole is not expected to form until after cyclization when OPA is used as the dielectrophile, we anticipated that the addition of a tertiary amine base might facilitate the eventual formation of an isoindole or other proton transfers that occur. Accordingly, the tertiary amine bases DIEA and Et_3N were investigated as additives. At a concentration of 0.2 M with respect to the phthalaldehyde, the addition of DIEA (Entry 1) improved the yield but reduced the selectivity relative to the same reaction conditions without an additive (Entry 5). At a concentration of 0.05 M with respect to the phthalaldehyde, the addition of DIEA (Entry 2) also

slightly improved the yield with a modest improvement in the selectivity relative to the same reaction conditions without an additive (Entry 7). The addition of TEA (Entry 4) gave a slightly larger improvement in the selectivity than DIEA, but with no improvement in the yield relative to the same reaction conditions without an additive (Entry 7). The addition of a base was also generally associated with a messier reaction with significant amounts of polymerization and the formation of a species that is likely either uncyclized isoindolinone species **3.108**, a possible side product, or cyclized hydroxyaminal species **3.102**, an expected intermediate, being observed via LC-MS (Figure 3.6). Since two equivalents of water are lost during the reaction, we anticipated that the addition of 3 Å molecular sieves might drive the reaction forward by removing the water, potentially improving the yield and reducing the incidence of unwanted side reactions involving water. However, it appears that the sieves hindered the reaction (Entry 3). We reasoned that the water molecules generated may play an essential role in subsequent proton transfer steps, particularly in an aprotic solvent like DCM.

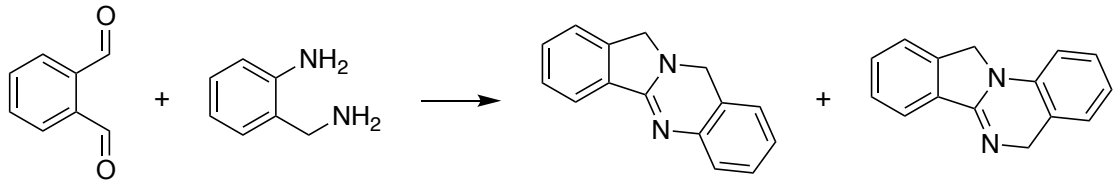


3.102 **3.108**

Calc. Mass: 238.11 **Calc. Mass: 238.11**
Found by LC-MS: 239.1 ($M+H^+$) **Found by LC-MS: 239.1 ($M+H^+$)**

Figure 3.6. Possible structures for the second most abundant species detected via LC-MS for the reaction of *ortho*-phthalaldehydes with diamines.

Table 3.5. Optimization of the reaction conditions for the reaction of *ortho*-phthalaldehydes with diamines.



3.78a **3.12a** **3.17a** **3.17b**

Entry	[3.71a] (M)	Solvent	Additive	Temperature (°C)	Time (h)	Yield (%)[c,d]	Regioselectivity (3.17a:3.17b)[c,d]
1	0.20	CH_2Cl_2	DIEA[a]	23	72	56	2.2:1
2	0.05	CH_2Cl_2	DIEA[a]	23	72	56	2.5:1
3	0.05	CH_2Cl_2	DIEA[a], 3ÅMS	23	72	ND, Complex Mixture[e]	ND[e]
4	0.05	CH_2Cl_2	Et_3N[a]	23	72	47	2.9:1
5	0.20	CH_2Cl_2	–	23	72	41	4.4:1
6	0.10	CH_2Cl_2	–	23	72	41	4.6:1
7	0.05	CH_2Cl_2	–	23	72	49	1.8:1
8	0.01	CH_2Cl_2	–	23	72	85, Complex Mixture	3.2:1
9	0.05	$CHCl_3$	–	23	72	60	4.2:1
10	0.05	CH_3OH	–	23	72	73	6.3:1
11	0.05	CH_3CN	–	23	72	57	3.3:1
12	0.05	THF	–	23	72	23, Complex Mixture	ND
13	0.05	Toluene	–	23	72	42	4.5:1
14	0.05	CH_2Cl_2	TFA[b]	23	72	88	1:101
15	0.05	CH_3OH	–	23	48	79	9.0:1
16	0.05	Toluene	–	100	2	ND, Complex Mixture[f]	ND
17	0.05	CH_3OH	–	60	24	76	1.2:1
18	0.05	CH_3OH	–	55	1	71[g]	1.3:1
19	0.05	CH_3OH	–	55	0.25	81[g]	6.3:1
20	0.05	CH_3CN	–	78	0.5	Oxidized[h]	ND[h]

[a]A quantity of 1.3 equivalents was added. [b]A quantity of 0.55 equivalents was added. [c]Unless otherwise specified, yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. The regioselectivity was determined by integrating the methylene signals for the major and minor regioisomers. [d]ND is shorthand for "not determined". [e]A low percent

conversion was observed by TLC. The product was not characterized. [f]The product mixture was complex and the chemical shifts in the ^{1}H NMR spectrum did not match those of the desired products. [g]Isolated yield. [h]A suspected mixture of the isoindolinone of one of the cyclization products and the possible acid salt of a cyclization product was obtained. The regiochemistry of these products was not determined.

Since LC-MS spectra indicated that polymerization was occurring, we initially tried to implement a strategy like the one we used in our isoindole umpolung approach, described *supra* in Chapter 2, wherein we started with a higher concentration to favor the intermolecular reaction between the dielectrophile and the amine nucleophile and then subsequently added more solvent to reduce the concentration and favor the intramolecular cyclization over subsequent intermolecular reactions. However, this strategy was unsuccessful, and polymerization was still observed.

Next, we decided to investigate the use of TFA as an additive, reasoning that it would facilitate the reaction by activating the aldehyde groups toward nucleophilic attack by the diamine. Additionally, we reasoned that by adding half of an equivalent of TFA relative to the diamine, we could potentially force the amino groups to react sequentially and prevent a single molecule of the diamine from reacting with two molecules of OPA (**3.78a**), thus reducing polymerization. We were delighted to find that the addition of TFA (0.55 equivalents) as an additive gave a very good yield and an extremely clean reaction (entry 14). Additionally, the reaction was nearly perfectly regioselective for **3.17b**, which is observed as the minor product in reactions without TFA. We attributed the reversal in regioselectivity to the fact that the benzylic amino group is more basic than the aniline and will therefore preferentially get protonated by TFA to form a quaternary ammonium salt, which cannot act as a nucleophile. Moreover, the quaternary ammonium salt of the aniline will be more acidic than that of the benzylic amino group, so if both amino groups get protonated, the ammonium salt of the aniline will

preferentially be deprotonated over that of the benzylic amino group. Consequently, under acidic conditions, the aniline will be the first to react with OPA (**3.78a**). Conversely, under neutral or basic conditions **3.17a** is formed as the major product because while both amino groups are free to react, the benzylic amino group is a better nucleophile than the aniline and will therefore preferentially react with OPA over the aniline. These findings and our reasoning were consistent with those of Troschütz, which were discussed *supra* in Section 3.9.

With these optimized conditions in hand for the formation of **3.17b**, we sought to continue to optimize the reaction conditions for the formation of **3.17a** under neutral conditions and decided to forgo the use of an additive. We investigated concentrations of 0.2 M, 0.1 M, 0.05 M, and 0.01 M with respect to the phthalaldehyde. There was no difference in the yields and no significant difference in the regioselectivity between the 0.2 M and 0.1 M concentrations (Entries 5 and 6, respectively), while the 0.05 M concentration (Entry 7) gave a higher yield but was significantly less regioselective. Further reducing the concentration to 0.01 M (Entry 6) gave a significantly higher yield than the higher concentrations. The regioselectivity was higher than the 0.05 M concentration, but lower than the 0.2 M and 0.1 M concentrations. Additionally, the reaction was not as clean as the other concentrations, leading us to continue to use 0.05 M as the default concentration for screening the other conditions.

Next, we screened additional solvents of varying polarities, including chloroform, methanol, acetonitrile, THF, and toluene. We found that chloroform, a chlorinated solvent that is less polar than DCM, gave a higher yield and significantly higher selectivity (Entry 9). The polar protic solvent methanol (Entry 10) gave the highest yield and regioselectivity of the solvents screened, which is possibly due to its ability to act as a proton shuttle and facilitate proton transfers. Polar aprotic solvents gave mixed results, with acetonitrile (Entry 11) giving a

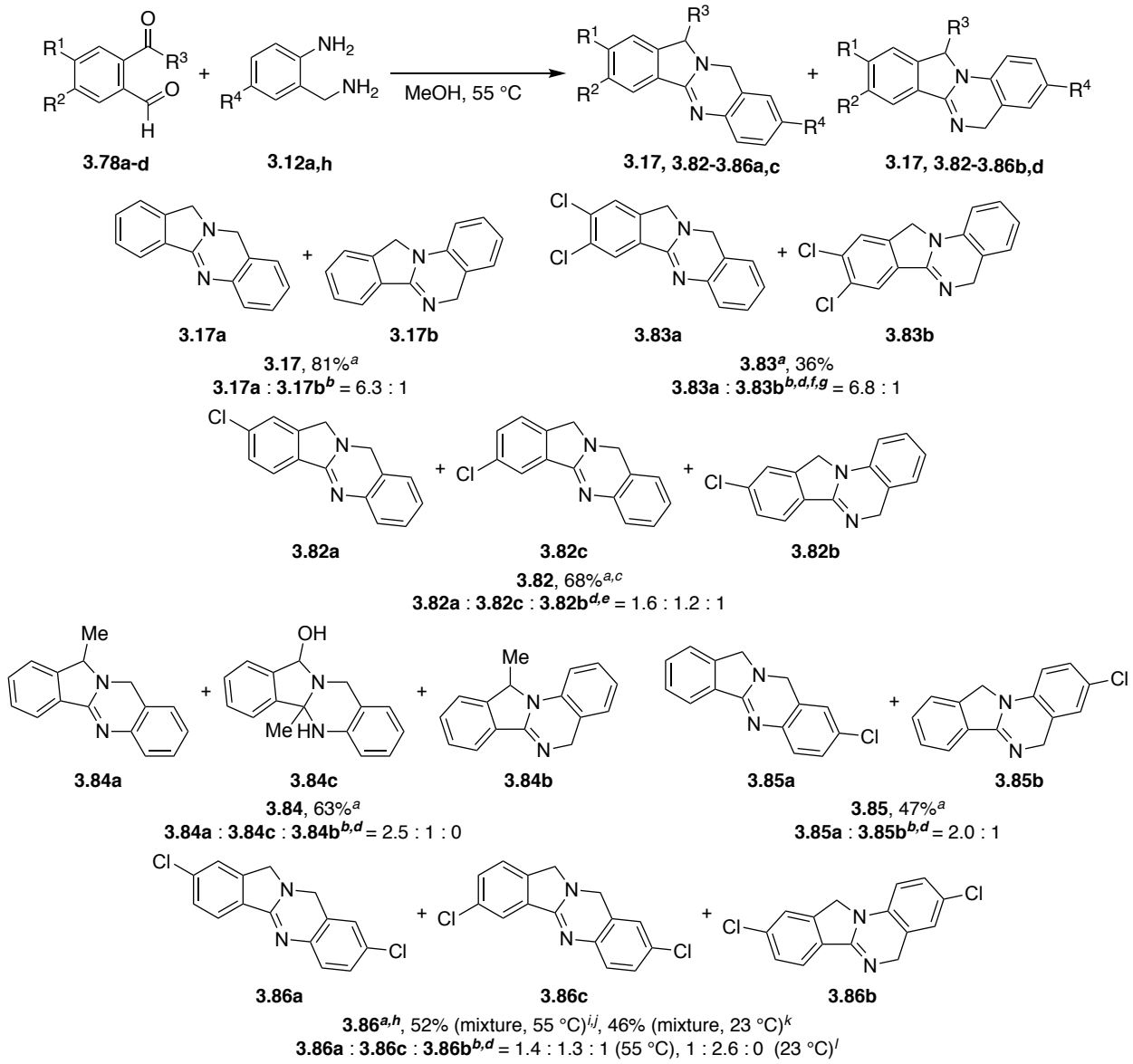
moderate yield and regioselectivity, but THF (Entry 12) giving poor results in terms of both yield and selectivity. Toluene (Entry 13), a non-polar solvent, gave a decent regioselectivity of 4.5:1.0, but only a moderate yield of 42%.

To establish the reaction time, reaction monitoring was initially attempted via TLC and LCMS; however, the results were inconclusive. While a color change was observed within seconds, a promising TLC spot was observed within minutes, and a peak in the LCMS spectrum corresponding to the desired molecular weight was detected in substantial amounts in 0.5 h, the TLC continued to change over the course of 72 h. Therefore, when screening conditions, 72 h was used as the default reaction time for room temperature reactions. We later attempted to monitor the reactions simultaneously by ^{1}H NMR and TLC; however, frequent monitoring resulted in significant chemical shift changes via NMR, and in some cases, a change in the number of methylene peaks, that led us to believe that oxidation was possibly occurring. Accordingly, we decided to try a shorter reaction time of 48 h for the room temperature reaction in methanol (Entry 15). To our delight, the yield improved slightly to 79% and the regioselectivity improved significantly to 9.0:1.0. However, we desired a shorter reaction time and decided to investigate whether the use of heat could shorten the reaction time. When the reactions in methanol were heated to 55-60 ℃, a reaction time of 24 h (Entry 17) or 1 h (Entry 18) gave good isolated yields, but the selectivity was greatly reduced to nearly 1:1. Due to the nearly instant occurrence of a color change, we reasoned that perhaps those reaction times were excessive. Accordingly, we decided to try a significantly shorter reaction time of 0.25 h for the reaction in methanol at 55 ℃ (Entry 19) and were delighted to find that the yield was high and the regioselectivity was comparable to the 72 h room temperature reaction (Entry 10). Concurrently, we decided to investigate whether solvents with higher boiling points than

methanol would give better results. We decided to investigate heating toluene to 100 °C due to its relatively high boiling point and the fact that the room temperature reaction showed acceptable regioselectivity. Based on literature precedent, we also tried heating the reaction in acetonitrile to 78 °C.[57,58] However, both reactions (Entries 16 and 20, respectively) gave inferior results.

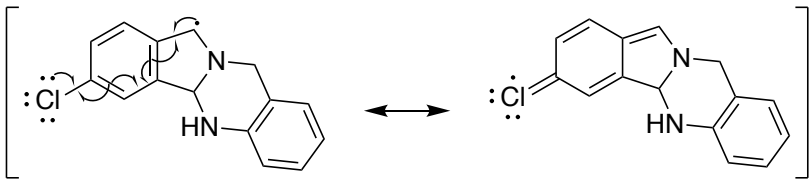
With our optimized conditions in hand, we investigated the scope of the dielectrophilic reacting partner (Scheme 3.18, *infra*). The substituted phthalaldehydes 4-chlorophthalaldehyde (**3.78b**) and 4,5-dichlorophthalaldehyde (**3.78c**) were investigated, as well as 2-acetylbenzaldehyde (**3.71d**). For the reaction of 4-chlorophthalaldehyde (**3.78b**) with 2-aminobenzylamine (**3.12a**), a mixture of regioisomers of the desired product and an isoindolinone species was obtained in an 82% isolated yield (**3.82**).[59] The regioselectivity for the three regioisomers was determined to be 1.6:1.2:1; however, that did not include the isoindolinone. It is not known whether the regioisomer that underwent oxidation was the major regioisomer; however, it is suspected that the isoindolinone species has the chlorine in the *para* position relative to the carbonyl group, as the radical species that would form during autoxidation would be stabilized by the chlorine via resonance (Figure 3.7, *infra*). The reaction of **3.78c** with **3.12a** yielded a mixture of regioisomers of the desired products and the suspected isoindolinones (**3.83**). The crude ^{1}H NMR was complex; however, the regioselectivity was estimated to be 6.8:1 for the suspected desired products and 6.3:1 for the suspected isoindolinones.[60] Attempts to separate and isolate the products via preparative TLC were unsuccessful. On the other hand, the reaction of 2-acetylbenzaldehyde (**3.78d**) with **3.12a** was successful, giving a 63 % yield of **3.84a** (**3.84**). The ^{1}H NMR spectrum is consistent with the expected regioselectivity of cyclization. Cyclization occurred surprisingly quickly, which

suggests that cyclization occurs through the less stable hydroxyisoindolium species to give the major cyclization product **3.84a**. While coincident peaks were present in the crude ^{1}H NMR spectrum, it appears that cyclization through the more substituted isoindolium led to the minor product, with a selectivity of about 2.5:1. Interestingly, the expected minor regioisomer (**3.84b**), in which the aniline forms the isoindolium and the benzylamine moiety subsequently cyclizes, was not observed. Further work on a larger scale will be needed to isolate and characterize the suspected minor product. To examine the scope of the diamine reacting partner, the reaction of 2-(aminomethyl)-4-chloroaniline (**3.12h**) with OPA (**3.78a**) was investigated and was found to be successful, giving a 47 % yield of **3.85** and regioselectivity of 2.0:1 (Entry 5).



Scheme 3.18. Substrate scope of the reaction of *ortho*-phthalaldehyde and 2-acyl benzaldehyde derivatives with diamines. [a]Isolated yield. [b]From crude ^{1}H NMR spectra. [c]Excludes cyclized isoindolinone (14% isolated yield). [d]Predicted structures. Identities were not confirmed. [e]From ^{1}H NMR spectra of **112a** and **112c** (1.3 : 1 mixture, 50%) and pure **112b** (18%). [f]From crude ^{1}H NMR, which showed a mixture of **113a-b** and cyclized isoindolinones. Products were not stable to purification. [g]6.3 : 1 for isoindolinones. [h]Only the major product from each reaction was isolated. [i]From crude ^{1}H NMR, which shows a mixture of **116a-c**. [j]Major: **116a**, 19%. [k]Major: **116c**, 33%. [l]Only two regioisomers formed in significant amounts.

Reactions of substituted phthalaldehydes with substituted diamines were also investigated. The reaction of 4-chlorophthalaldehyde (**3.78b**) with 2-(aminomethyl)-4-chloroaniline (**3.12h**) was successful, both under heated and unheated conditions (**3.86**, Scheme 3.18, *supra*). The yields were fairly close, but the heated reaction gave a regioselectivity of 1.4:1.3:1 **3.86a**:**3.86c**:**3.86b**, whereas the unheated reaction gave a regioselectivity of 2.6:1 **3.86c**:**3.86a**.[61] Attempts to isolate all the individual products for full characterization were unsuccessful, but the major regioisomers were isolated for both the heated and unheated reactions. Based on our observations with the model reaction, it is believed that in both cases, the isoindoline nitrogen came from the benzylic amino group, with the difference between the structures being the position of the chlorine atom on the isoindoline benzene ring. It is suspected that the reaction at room temperature predominately cyclized via the more reactive isoindolium species, which would give rise to product **3.86c**, whereas the heated reaction predominately cyclized via the isoindolium species that is resonance stabilized via electron donation from chlorine (Figure 3.7), which would give product **3.86a**. Alternatively, it is possible that in the presence of heat, product **3.86c** isomerizes to product **3.86a**, in which the amidine is stabilized via electron donation from the chlorine atom via resonance.



3.109a **3.109b**

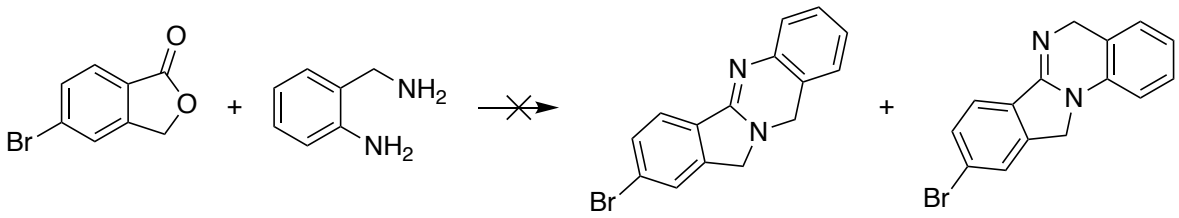
Figure 3.7. Resonance stabilization of benzylic radical by a chlorine atom in the *para* position.

Unsurprisingly, the reaction of 4,5-dichlorophthalaldehyde (**3.78c**) with 2-(aminomethyl)-4-chloroaniline (**3.12h**) was very messy and was consequently not characterized. This was likely due to the propensity of the electron-poor isoindoline benzene ring to promote oxidation at the isoindoline benzylic position coupled with the possibility for oxidation at the dihydroisoquinoline benzylic position, due the presence of an electronegative chlorine atom on that benzene ring, as well. Further studies will be needed to determine whether oxidation occurs during the reaction or the workup step; however, the amount of oxidation generally appeared to increase during purification of the chlorinated reaction products.

Due to the difficulties associated with monitoring the reactions of phthalaldehydes, we decided to concurrently investigate phthalides as the dielectrophilic reacting partners (Table 3.6, *infra*). Since phthalides consist of a benzo-fused lactone ring, they could potentially react with diamines in the absence of an oxidant to give the same products as pthalaldehydes, since the ester carbonyl carbon is at the same oxidation state as the amidine carbon in the product and the methylene carbon that is bonded to the ester oxygen is at the same oxidation state as the isoindoline methylene carbon. We used 5-bromophthalide (**3.110**) in our model reaction with 2-aminobenzylamine (**3.12a**) because we had it on hand and were interested in investigating substituted phthalides; however, our initial attempts to utilize this substrate were unsuccessful. No reaction was observed after 24 h at 140 °C in MeOH or DCE (Entries 1 and 2, respectively). Predictably, subsequent attempts to activate the carbonyl toward nucleophilic attack by the diamine in methanol via the addition of a drop of TFA led to the transesterification product (Entry 3), whereas no reaction was observed in DCE (Entry 4). Based on literature precedent[62] for the synthesis of phthalimidines via condensation reactions of phthalides with benzylamine and aniline derivatives, we also tried to activate the carbonyl using $InCl_3$ as a Lewis acid catalyst,

but this led to a messy reaction with suspected decomposition (Entries 5-8). While this approach seemed promising, it is worth noting that the reactions in that publication were ran neat in the amine, whereas we did not want to use a large excess of the diamine because we desired to effect subsequent intramolecular cyclization and disfavor subsequent intermolecular reactions. Another issue with this approach is that the authors of the literature precedent reported significantly faster reaction times for aniline derivatives than benzylamine derivatives, likely due to the lower basicity of the anilines and consequent reduced affinity for the Lewis acid catalyst. Therefore, even if this approach could be engineered to work, it would likely give the same regioselectivity as our acid-catalyzed reaction of OPA with diamines (**3.111b**), but with harsher conditions and potentially lower yields. Accordingly, we decided to abandon this approach and continue with the phthalaldehyde approach.

Table 3.6. Screening of reaction conditions for the reaction of phthalides with diamines.



3.110 **3.12a** **3.111a** **3.111b**

Entry	Solvent[a]	Additives	Temperature (°C)	Outcome
1	1,2-DCE	–	140	NR
2	CH_3OH	–	140	NR
3	CH_3OH	TFA (cat.)	23 →140	Transesterification
4	1,2-DCE	TFA (cat.)	23 →140	NR
5	1,2-DCE	$InCl_3$ (0.6 equiv.)	215[c]	Decomposition
6	1,2-DCE	$InCl_3$ (0.3 equiv.)[b]	215[c]	Decomposition
7	1,2-DCE	$InCl_3$ (0.6 equiv.)	80	Decomposition
8	1,2-DCE	$InCl_3$ (0.6 equiv.), DMAP (1.0 equiv.)[c]	215[c]	Decomposition

[a]A concentration of 0.05 M with respect to the phthalide was used. [b]Closer to amount of 0.2 equivalents used in literature precedent. [c]Based on literature precedent.

3.11. Future Directions and Conclusions

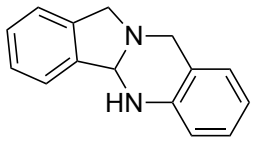
Preliminary studies have been completed and a partial substrate scope has been established for two cyclization cascade reactions that involve isoindole chemistry. These approaches can be used to prepare the same products, namely, isoindoloquinazolines and other isoindole derivatives. However, for both approaches, it would be desirable to broaden the substrate scope. For the cyclization-oxidation cascade reaction, the substrate scope of the aldehyde reacting partner could be expanded to include other electron-poor and electron-rich

aldehydes. Additionally, other benzyl-substituted aldehydes and ketones could be investigated, such as a benzophenone derivative. For the reaction of *ortho*-phthalaldehydes with diamines, the substrate scope of the phthalaldehyde could be expanded to include *ortho*-substituted phthalaldehydes, as well as phthalaldehydes with halogens other than chlorine, as well as electron-withdrawing and electron-donating groups. Additional diamines could also be investigated for both reactions. For the cyclization-oxidation cascade reaction, these could include the corresponding free amines of the diamine dihydrochloride salts that we attempted to deprotonate *in situ*. Additionally, further work will be needed to further probe the regioselectivity for both reactions and conclusively identify the structures of the regioisomers for the substituted compounds. For the reaction of *ortho*-phthalaldehydes with diamines, additional efforts will be needed to further optimize the reaction conditions for chlorinated substrates, with special attention paid to avoiding oxidation. Alternatively, the conditions could be optimized to further oxidize the products to the corresponding isoindolinones. Once this methodological work has been completed, these approaches can be used to prepare compounds which can be screened for some of the biological activities described *supra* in Section 3.2. It would be particularly exciting to screen isoindoloquinazoline derivatives for activity against SARS-CoV-2 because the pandemic is ongoing and as of this writing, there are only two treatment options available that can be administered orally.[63] Efforts toward the further optimization and expansion of these approaches, as well as the biological evaluation of the synthesized compounds, are ongoing in this research group and will be reported in due course.

3.12. Experimental for the Cyclization-Oxidation Cascade Approach

General Considerations. All reactions were performed under argon. Moisture-sensitive reactions were carried out using oven- and vacuum-dried glassware. Dry DCM, THF, MeOH, and toluene were dried using a PS-MD-5 solvent purification system from Innovative Technology, by passage through columns containing activated alumina and copper. Dry DCE was dried over 3 Å molecular sieves. Dry DCM and DCE used in the synthesis of benzaldehyde substrates and cyclization reactions were stored over 3 Å molecular sieves under argon and degassed prior to use by bubbling argon gas through the solvent. All commercially available reagents were purchased from different suppliers and used as received. Melting points were recorded on a DigiMelt melting point apparatus from Stanford Research Systems. Deuterated solvents for NMR spectroscopy were purchased from different suppliers. All deuterated solvents were dried over 3 Å molecular sieves and anhydrous Na_2SO_4, with the exception of $CDCl_3$, which was dried over 3 Å molecular sieves and oven-dried anhydrous K_2CO_3. NMR spectra were recorded on a Varian INOVA 500 MHz NMR Spectrometer (11.74 T), Varian INOVA 400 MHz NMR Spectrometer (9.39T), or a Bruker Avance-III 300 NMR Spectrometer (7.05 T) at temperatures of 20-25°C and were processed using MestreNova version 14.0.1. LC-MS spectra were recorded on an Agilent 6120 small molecule LC-MS. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. Unless otherwise noted, proton (^1H) and carbon (^{13}C) NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ = 7.26; 77.16), residual C_3D_5HO in C_3D_6O (δ = 2.05; 29.84), residual CD_2HCN in CD_3CN (δ = 1.94; 1.32), residual CD_2HOD in CD_3OD (δ = 3.31; 49.00), residual C_2D_5HOS in C_2D_6OS (δ = 2.50; 39.52), or residual $CDHCl_2$ in CD_2Cl_2 (δ = 5.32; 54.00). In some cases, due to the proximities of the chemical shifts to other peaks or the desire to

do subsequent GSD analyses on the same spectrum, residual HOD in CD_3OD ($\delta = 4.87$) was used as a reference in the ^1H NMR. For ^{13}C NMR spectra taken in CD_3CN, if the solubility of the compound was low, the nitrile carbon was used as a reference, instead ($\delta = 118.26$). Coupling constants (J) are reported in Hertz (Hz) and refer to apparent multiplicities. The following abbreviations are used for the multiplicities: (s): singlet, (d): doublet, (t): triplet, (q): quartet, (p): pentet, (m): multiplet. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Infrared spectra were recorded on a Cary 360 ATR FT-IR. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. For purifications and determination of product distributions by HPLC, a Zorbax 300 SB-C18 PrepHT (5 µm, 21.2 x 150 mm) column and HPLC-grade solvents were used.



*4b,5,10,12-tetrahydroisoindolo[1,2-b]quinazoline (**3.15a**).* The aldehyde (**3.00a**) (39.8 mg, 0.20 mmol, 1.0 equiv) and diamine (**3.12a**) (26.9 mg, 0.40, 1.1 equiv) reacting partners were dissolved in dry DCM (2.0 mL, 0.10 M) in a 2-dram scintillation vial equipped with a magnetic stir bar. DIEA (42 µl, 0.24 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. After 6 h of stirring at room temperature, approximately 16% conversion was observed via TLC and LCMS. Approximately half of the original volume of solvent was removed *in vacuo* and the remaining crude reaction mixture was directly purified via preparative TLC on silica (10:1 DCM:MeOH), which gave the suspected regioisomer **3.15a** in a 10% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 1H),

7.40 – 7.31 (m, 3H), 7.18 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.70 (td, J = 7.4, 1.1 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 5.66 (d, J = 3.3 Hz, 1H), 4.82 (d, J = 13.4 Hz, 1H), 4.53 (dd, J = 13.4, 3.4 Hz, 1H), 4.37 (d, J = 16.6 Hz, 1H), 4.08 (d, J = 16.6 Hz, 1H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{15}H_{14}N_2$: 223.12; found: 223.1.

Procedure for Screening Conditions. The aldehyde (**3.00a**) (0.10 mmol, 1.0 equiv) and diamine (**3.12a**) (0.11 or 0.12 mmol, 1.1 or 1.2 equiv) reacting partners were dissolved in dry DCM (1.0 mL, 0.10 M) in a 1- or 2-dram scintillation vial or a 5-10 mL round-bottom flask equipped with a magnetic stir bar. DIEA (0.12 or 0.14 mmol, 1.2 or 1.4 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. After 1 h, the oxidant was added in the amount specified at room temperature or 0°C. The reaction mixture was then stirred for an additional 2 h or until the disappearance of the isoindole was observed. The reaction progress was monitored by TLC and LC-MS. Upon completion of the reaction, the solvent was removed *in vacuo*. For reactions that gave a significant amount of the desired product via LC-MS and ^{1}H NMR, the crude product was purified via preparative TLC on silica.

General Procedure A: General Procedure for Cyclization-Oxidation Cascade Reactions. The aldehyde (**3.00a-b**) (0.10 mmol, 1.0 equiv) and diamine (**3.12a-d**, **3.71a**) (0.11 mmol, 1.1 equiv) reacting partners were dissolved in dry DCM (1.0 mL, 0.10 M) in a 1-dram scintillation vial or a 5 mL round-bottom flask equipped with a magnetic stir bar. DIEA (0.12 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. After 1 h, the oxidant (0.15 mmol, 1.5 equiv) was added at room temperature and the reaction mixture was stirred for an additional 2 h or until the disappearance of the isoindole was observed. The reaction progress was monitored by TLC and

LC-MS. Upon completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified via preparative TLC on silica. Product **3.76a** was instead subjected to one of the three workup and purification procedures described *infra*. For products **3.17** and **3.74**, where LC-MS indicated the successful formation of a relatively clean product, only approximately half of the original volume of solvent was removed *in vacuo* and the remaining crude reaction mixture was directly purified via preparative TLC on silica.

General Procedure B: Modified General Procedure for Cyclization-Oxidation Cascade Reactions. The aldehyde (**3.00a**) (0.10 mmol, 1.0 equiv) and diamine (**3.12a-c, 3.71a**) (0.24 mmol, 1.2 equiv) reacting partners were dissolved in dry DCM (1.0 mL, 0.10 M) in a 1-dram scintillation vial or a 5 mL round-bottom flask equipped with a magnetic stir bar. DIEA (0.28 mmol, 1.4 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. After 2 h, the oxidant (0.15 mmol, 1.5 equiv) was added at room temperature and the reaction mixture was stirred for an additional 2 h or until the disappearance of the isoindole was observed. Upon completion of the reaction, the solvent was removed *in vacuo* and the crude product was purified via preparative TLC on silica. Product **3.76a** was instead subjected to one of the three workup and purification procedures described *infra*. For product **3.17**, where LC-MS indicated the successful formation of a relatively clean product, only approximately half of the original volume of solvent was removed *in vacuo* and the remaining crude reaction mixture was directly purified via preparative TLC on silica.

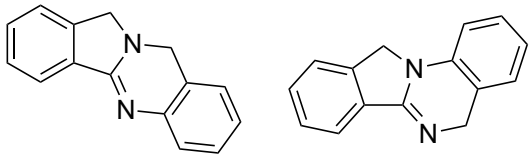
General Procedure C: Procedure for Cyclization-Oxidation Cascade Reactions of Diamine Dihydrochloride Salts. The aldehyde (**3.00a**) (0.10 mmol, 1.0 equiv) and diamine (**3.71b, 3.72b**) (0.11 or 0.12 mmol, 1.1 or 1.2 equiv) reacting partners were dissolved in dry DCM (1.0 mL, 0.10 M) in a 1-dram scintillation vial or a 5 mL round-bottom flask equipped

with a magnetic stir bar. DIEA or Et_3N (0.36 mmol, 3.6 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. The isoindole was allowed to form for up to 3 h, with the exception of the reaction of **3.71b**, for which both 3-6 h and overnight isoindole formations were investigated.[64] The oxidant (0.15 mmol, 1.5 equiv) was then added at room temperature and the reaction mixture was stirred until the disappearance of the isoindole was observed by TLC and LC-MS. Since the LC-MS spectra indicated that very little or none of the desired products had formed for these reactions, the crude products were not isolated or purified.

General Procedure D: Modified Procedure for Cyclization-Oxidation Cascade Reactions of Diamine Dihydrochloride Salts. The aldehyde (**3.00a**) (0.10 mmol, 1.0 equiv) and diamine (**3.71b**) (0.12 mmol, 1.2 equiv) reacting partners were dissolved in dry DCM (1.0 mL, 0.10 M) in a 1-dram scintillation vial or a 5 mL round-bottom flask equipped with a magnetic stir bar. DIEA (0.72 mmol, 7.2 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. The isoindole was allowed to form for up to 3-6 h or overnight; however, no isoindole was detected by TLC. The oxidant (0.15 mmol, 1.5 equiv) was then added at room temperature and the reaction mixture was stirred until the disappearance of the isoindole was observed by TLC and LC-MS. Since the LC-MS spectra indicated that none of the desired products had formed for these reactions, the crude products were not isolated or purified.

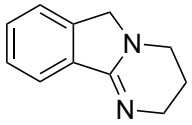
General Procedure E: Modified Procedure for Cyclization-Oxidation Cascade Reactions of Diamine Dihydrochloride Salts. The aldehyde (**3.00a**) (0.20 mmol, 1.0 equiv) and diamine (**3.72a-b**) (0.24 mmol, 1.2 equiv) reacting partners were dissolved in dry DCM (2.0 mL, 0.10 M) in a 2-dram scintillation vial or a 10 mL round-bottom flask equipped with a magnetic

stir bar. DIEA or Et_3N (0.72 mmol, 3.6 equiv) was added and the reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC. The isoindole was allowed to form for up to 3-6 h.[65] The oxidant (0.30 mmol, 1.5 equiv) was then added at room temperature and the reaction mixture was stirred until the disappearance of the isoindole was observed by TLC and LC-MS. Since the LC-MS spectra indicated that very little or none of the desired products had formed for these reactions, the crude products were not isolated or purified.



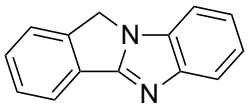
*10,12-dihydroisoindolo[1,2-b]quinazoline (**3.17a**) and 5,11-dihydroisoindolo[2,1-a]quinazoline (**3.17b**).* Regioisomeric mixture **3.17** was synthesized using general procedures A and B. Purification of the regioisomeric mixture synthesized via general procedure A by preparative TLC on silica (10:1 DCM:MeOH) gave 14.5 mg (66% yield) of **3.17a** and 2.0 mg (9% yield) of **3.17b** as orange oils. Purification of the regioisomeric mixture synthesized via general procedure B by preparative TLC on silica (10:1 DCM:MeOH) gave 16.7 mg (76% yield) of **3.17a** as an orange oil. **3.17a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 1H), 7.54 – 7.48 (m, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.17 (m, 2H), 7.02 (ddd, *J* = 7.5, 6.7, 1.7 Hz, 1H), 6.95 (ddq, *J* = 7.5, 1.6, 0.8 Hz, 1H), 4.82 (s, 2H), 4.37 (s, 2H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{15}H_{12}N_2$: 221.11; found: 221.1. **3.17b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.25 – 7.17 (m, 1H), 7.08 – 7.04 (m, 1H), 7.04 – 6.98 (m, 1H), 6.72 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 2H), 4.76 (s, 2H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{15}H_{12}N_2$: 221.11; found: 221.1. Spectra were generally in

agreement with the literature[54] and the desired products were detected as the primary species present via LC-MS. However, in the ^{1}H NMR spectrum for **3.17a**, the chemical shifts of the methylene peaks differed slightly from their reported values of 4.75 ppm and 4.30 ppm, and in the ^{1}H NMR spectrum for **3.17b**, the chemical shifts of the methylene peaks differed slightly from their reported values of 4.90 ppm and 4.68 ppm. To confirm the formation of the desired amidine products, additional NMR spectra were obtained as described in the next section. The spectra were consistent with an approximately equal mixture of the correct products. Taken together with the LC-MS spectra, these data suggest that the structures shown are the correct structures.

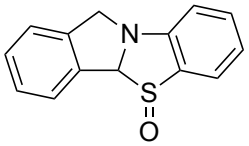


*2,3,4,6-tetrahydropyrimido[2,1-a]isoindole (**3.76a**).* Product **3.76a** was originally synthesized according to general procedure A. Following the removal of the solvent, the product was acidified with HCl (4.0 M in 1,4-dioxane) to convert it to the hydrochloride salt and purified via preparative HPLC (70% A; A: 0.1% HCl in H_2O, B: MeCN) to give 7.7 mg (37 % yield)[66] of the hydrochloride salt of **3.76a** as a yellow solid The product was characterized as the HCl salt. However, attempts to separate the desired product from DIEA hydrochloride via preparative HPLC were unsuccessful. Product **3.76a** was also synthesized via general procedure B. Two alternative workup procedures were investigated. The first was an aqueous workup in which the reaction mixture was taken up in 6:1 ethyl acetate:DCM (2.5 mL) and washed with three 2.5 mL portions of water. The organic extract was subsequently dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give 14.1 mg (82% yield) of a sticky yellow solid. Since

some DIEA still remained, the reaction was repeated and subjected to a basic aqueous workup in which the crude product was taken up in 6:1 ethyl acetate:DCM (2.5 mL) and washed twice with water (2 x 2.5 mL) to remove some of the DIEA hydrobromide and then twice with saturated potassium carbonate (2 x 2.5 mL) to convert the residual DIEA hydrobromide to the free amine. The crude was subsequently subjected to lyophilization to remove the residual DIEA, which gave 12.4 mg (72% yield) of **3.76a** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.70 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.53 – 7.43 (m, 2H), 4.84 (s, 2H), 3.87 (s, 2H), 3.78 – 3.60 (m, 2H), 2.19 (p, *J* = 5.9 Hz, 2H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{11}H_{12}N_2$: 173.11; found: 173.1.

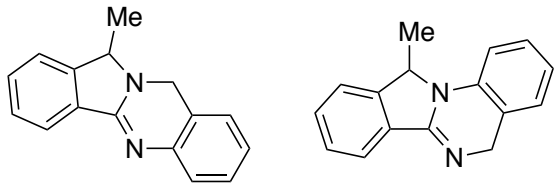


*11H-benzo[4,5]imidazo[2,1-a]isoindole (**3.73**).* Crude product mixture **3.73** was synthesized according to general procedures A and B. Incomplete conversion to the isoindole was observed via TLC and a complex mixture was obtained as a brown solid. The mixture was not subjected to purification and the yield was not determined. One of the compounds observed via ^{1}H NMR and LC-MS matched the reported literature spectra for **3.73**.[67]



4b,11-dihydrobenzo[4,5]thiazolo[2,3-a]isoindole 5-oxide *(**3.75**).* Crude product mixture **3.75** was synthesized using general procedure A, which gave 23.2 mg of **3.75** in a 96% yield. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.84 – 7.79 (m, 1H), 7.54 – 7.48 (m, 2H), 7.25 – 7.17 (m, 1H), 7.02 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.70 – 6.63 (m, 2H), 5.09 (s, 1H), 4.99 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H). LC-MS (ES-API): m/z $[M]^+$ calculated for $C_{14}H_{11}NOS$: 241.06; found: 241.1.



*12-methyl-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.74a**) and 11-methyl-5,11-dihydroisoindolo[2,1-a]quinazoline (**3.74b**).* Regioisomeric mixture **3.74** was synthesized according to general procedure A. The crude reaction mixture was purified via preparative TLC on silica (10:1 DCM:MeOH), giving 4.9 mg (21% yield) of **3.74a** and 2.1 mg (9% yield) of **3.74b** as red solids. Product **3.74a** was isolated in a semi-pure mixture with either the corresponding nitrone or the oxaziridine, per LC–MS. **3.74a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.24 (app d, *J* = 2.0 Hz, 2H), 7.07 – 7.00 (m, 1H), 6.68 (d, *J* = 8.9 Hz, 1H), 4.93 (d, *J* = 13.0 Hz, 1H), 4.72 (d, *J* = 13.0 Hz, 1H), 4.53 (q, *J* = 6.4 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H). **3.74b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.4 Hz, 1H), 7.53 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.04 (q, *J* = 6.6 Hz, 1H), 4.92 (d, *J* = 17.3 Hz, 1H), 4.76 (d, *J* = 17.4 Hz, 1H), 1.71 (d, *J* = 6.6 Hz, 3H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{16}H_{14}N_2$: 235.12; found: 235.1.

Synthesis of Aldehyde Starting Materials. Aldehydes **3.00a** and **3.00b** were prepared as described *supra* in Section 2.10.

Synthesis of Diamine Starting Materials.

Commercially available diamines were used as received. The dihydrochloride salts of diamines **3.71b** and **3.72a-b** were used.

3.13. Experimental for Reaction of *Ortho*-Phthalaldehydes and 2-Acyl Benzaldehydes with Diamines

General Considerations. All reactions were performed under argon. Moisture-sensitive reactions were carried out using oven- and vacuum-dried glassware. Dry DCM, THF, MeOH, and toluene were dried using a PS-MD-5 solvent purification system from Innovative Technology, by passage through columns containing activated alumina and copper. Dry DCE was dried over 3 Å molecular sieves. Dry DCM and DCE used in the synthesis of benzaldehyde substrates and cyclization reactions were stored over 3 Å molecular sieves under argon and degassed prior to use by bubbling argon gas through the solvent. All commercially available reagents were purchased from different suppliers and used as received. Melting points were recorded on a DigiMelt melting point apparatus from Stanford Research Systems. Deuterated solvents for NMR spectroscopy were purchased from different suppliers. All deuterated solvents were dried over 3 Å molecular sieves and anhydrous Na_2SO_4, with the exception of $CDCl_3$, which was dried over 3 Å molecular sieves and oven-dried anhydrous K_2CO_3. NMR spectra were recorded on a Varian INOVA 500 MHz NMR Spectrometer (11.74 T), Varian INOVA 400 MHz NMR Spectrometer (9.39T), or a Bruker Avance-III 300 NMR Spectrometer (7.05 T) at

temperatures of 20-25°C and were processed using MestreNova version 14.0.1. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. Unless otherwise noted, proton (^{1}H) and carbon (^{13}C) NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (δ = 7.26; 77.16), residual C_3D_5HO in C_3D_6O (δ = 2.05; 29.84), residual CD_2HCN in CD_3CN (δ = 1.94; 1.32), residual CD_2HOD in CD_3OD (δ = 3.31; 49.00), residual C_2D_5HOS in C_2D_6OS (δ = 2.50; 39.52), or residual $CDHCl_2$ in CD_2Cl_2 (δ = 5.32; 54.00). In some cases, due to the proximities of the chemical shifts to other peaks or the desire to do subsequent GSD analyses on the same spectrum, residual HOD in CD_3OD (δ = 4.87) was used as a reference in the ^{1}H NMR. For ^{13}C NMR spectra taken in CD_3CN, if the solubility of the compound was low, the nitrile carbon was used as a reference, instead (δ = 118.26). Coupling constants (J) are reported in Hertz (Hz) and refer to apparent multiplicities. The following abbreviations are used for the multiplicities: (s): singlet, (d): doublet, (t): triplet, (q): quartet, (p): pentet, (m): multiplet. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Infrared spectra were recorded on a Cary 360 ATR FT-IR. LC-MS spectra were recorded on an Agilent 6120 small molecule LC-MS. HR-MS analyses were performed by the University of Colorado at Boulder Mass Spectrometry Core Facility. For purifications and determination of product distributions by HPLC, a Zorbax 300 SB-C18 PrepHT (5 μm, 21.2 x 150 mm) column and HPLC-grade solvents were used.

General Procedure A: General Procedure for the Screening of Reaction Conditions. *Ortho*-phthalaldehyde (**3.78**) (0.10 mmol, 1.0 equiv) was added to a stirred solution of the diamine (**3.12a**) (0.11 mmol, 1.1 equiv) and the indicated additive, where applicable, in a sufficient amount of the indicated solvent to give the desired concentration. The reaction mixture

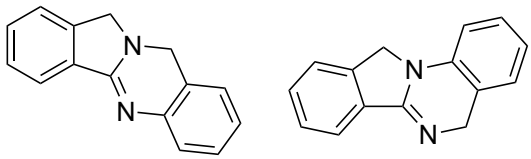
turned red almost immediately but was stirred at room temperature for the specified amount of time. Attempts were also made to monitor the reaction progress by TLC and LC-MS, however, the results were often unclear, as described *supra*. In cases where the reaction was monitored via NMR, the reaction was run on a slightly larger scale and aliquots of the reaction mixture were removed at the specified times. The solvent was removed from the aliquots *in vacuo* and the residue was dissolved in the NMR solvent. Upon suspected completion of the reaction, the solvent was removed *in vacuo*. Where the reaction progress was monitored via TLC or not at all, as indicated *supra* in Section 3.10, the yield was typically determined from the crude NMR using an internal standard. However, in certain cases, as indicated *supra* in Section 3.10, isolated yields were reported instead.

General Procedure B: General Procedure for Unheated Reactions of *Ortho*-Phthalaldehyde Derivatives with 2-Aminobenzylamines: Acid-Free Conditions. The phthalaldehyde derivative (**3.78a,b**) (0.10 mmol, 1.0 equiv) was added to a stirred solution of the diamine (**3.12a,d**) (0.11 mmol, 1.1 equiv) in MeOH (2.00 mL, 0.05 M) in a 2-dram scintillation vial equipped with a magnetic stir bar. The reaction mixture turned red almost immediately but was stirred at room temperature for 48 h. Attempts to monitor the progress of the reaction are described *supra* under general procedure A. Upon completion of the reaction, the solvent was removed *in vacuo*. Where the crude product was not sufficiently pure, it was purified by preparative TLC as described *infra*.

General Procedure C: General Procedure for Heated Reactions of *Ortho*-Phthalaldehyde Derivatives with 2-Aminobenzylamines: Acid-Free Conditions. The phthalaldehyde derivative (**3.78a-d**) (0.10 mmol, 1.0 equiv) was added to a stirred solution of the diamine (**3.12a,h**) (0.11 mmol, 1.1 equiv) in MeOH (2.00 mL, 0.05 M) in a 2-dram scintillation

vial equipped with a magnetic stir bar. The reaction mixture turned red almost immediately but was heated to 55 °C for 0.25 h or until the reaction appeared to have reached completion, as indicated by TLC. Upon completion of the reaction, the solvent was removed *in vacuo*. Where the crude product was not sufficiently pure, it was purified by preparative TLC as described *infra*.

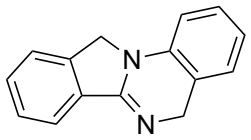
General Procedure D: General Procedure for the Reaction of *Ortho*-Phthalaldehyde Derivatives with 2-Aminobenzylamines: Acidic Conditions. TFA (0.06 mmol, 0.55 equiv) was added to a stirred solution of the diamine (0.11 mmol, 1.1 equiv) in DCM (2.00 mL, 0.05 M) in a 2-dram scintillation vial equipped with a magnetic stir bar. The reaction mixture was stirred at room temperature. After approximately 0.15 h, *ortho*-phthalaldehyde (**3.78a**) (0.10 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 72 h. Upon completion of the reaction, the product was washed with saturated aqueous K_2CO_3, and the organic portion was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the product was further dried *in vacuo*. The yield was determined from the crude ^{1}H NMR relative to a 1,3,5-trimethoxybenzene internal standard.



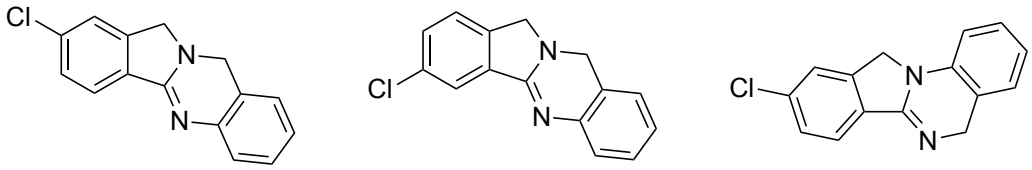
*10,12-dihydroisoindolo[1,2-b]quinazoline (**3.17a**) and 5,11-dihydroisoindolo[2,1-a]quinazoline (**3.17b**).* Regioisomeric mixture **3.17** was synthesized using general procedures A, B, and C. Except where isolated yields were reported, the yield was determined from the crude ^{1}H NMR relative to a 1,3,5-trimethoxybenzene internal standard, as indicated *supra* in Section 3.10. The

regioselectivity was also determined from the crude ^{1}H NMR. The spectra were in accordance with those described in the previous section. **3.17a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 1H), 7.54 – 7.48 (m, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.17 (m, 2H), 7.02 (ddd, *J* = 7.5, 6.7, 1.7 Hz, 1H), 6.95 (ddq, *J* = 7.5, 1.6, 0.8 Hz, 1H), 4.82 (s, 2H), 4.37 (s, 2H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{15}H_{12}N_2$: 221.11; found: 221.1. **3.17b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.25 – 7.17 (m, 1H), 7.08 – 7.04 (m, 1H), 7.04 – 6.98 (m, 1H), 6.72 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.93 (d, *J* = 1.2 Hz, 2H), 4.76 (s, 2H). LC-MS (ES-API): m/z $[M+H]^+$ calculated for $C_{15}H_{12}N_2$: 221.11; found: 221.1. Spectra were generally in agreement with the literature[54] and the desired products were detected as the primary species present via LC-MS. However, in the ^{1}H NMR spectrum for **3.17a**, the chemical shifts of the methylene peaks differed slightly from their reported values of 4.75 ppm and 4.30 ppm, and in the ^{1}H NMR spectrum for **3.17b**, the chemical shifts of the methylene peaks differed slightly from their reported values of 4.90 ppm and 4.68 ppm. To confirm the formation of the desired amidine products, an approximately equal mixture of the two regioisomers was synthesized via general procedure C, except that a longer reaction time of 13 h was used. The product mixture was characterized via ^{13}C NMR and DEPT-135 to ensure that the anticipated types of carbons were present in the expected amounts. The spectra were consistent with an approximately equal mixture of the correct products. Mixture **3.17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 1H), 7.87 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.48 – 7.34 (m, 6H), 7.22 (dd, *J* = 1.4, 0.5 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.00 – 6.97 (m, 2H), 6.96 (dd, *J* = 7.2, 1.4 Hz, 1H), 6.89 (ddq, *J* = 7.5, 1.5, 0.8 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.85 (q, *J* = 1.2 Hz, 2H), 4.73 (t, *J* = 0.7 Hz, 2H), 4.66 (t, *J* = 1.0 Hz, 2H), 4.29 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.92 (C), 156.25 (C), 142.74 (C), 140.38 (C), 140.23 (C), 137.59 (C), 133.55 (C), 133.11 (C), 131.12 (CH),

130.80 (CH), 128.54 (CH), 128.34 (CH), 128.06 (CH), 127.77 (CH), 126.25 (CH), 126.17 (CH), 124.80 (CH), 124.34 (CH), 123.51 (CH), 123.09 (CH), 122.77 (CH), 122.68 (CH), 122.50 (CH), 119.59 (C), 119.48 (C), 111.00 (CH), 54.53 (CH_2), 50.36 (CH_2), 48.83 (CH_2), 46.80 (CH_2). DEPT-135 ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.13 (CH), 130.80 (CH), 128.54 (CH), 128.34 (CH), 128.06 (CH), 127.77 (CH), 126.25 (CH), 126.17 (CH), 124.79 (CH), 124.35 (CH), 123.52 (CH), 123.08 (CH), 122.77 (CH), 122.68 (CH), 122.50 (CH), 111.00 (CH), 54.54 (CH_2), 50.36 (CH_2), 48.83 (CH_2), 46.79 (CH_2).

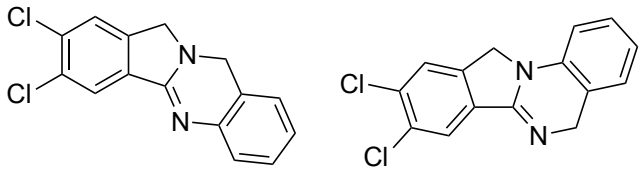


*5,11-dihydroisoindolo[2,1-a]quinazoline (**3.17b**).* Cyclization product **3.17b** was synthesized as the TFA salt via general procedure D, which gave 25.3 mg of a red sticky solid. From the crude ^{1}H NMR, the yield was determined to be 88% and the regioselectivity was found to be 101:1 **3.17b:3.17a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.54 – 7.39 (m, 3H), 7.19 (dddt, *J* = 7.5, 6.7, 2.3, 0.7 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.75 – 6.66 (m, 1H), 4.91 (dd, *J* = 1.5, 0.8 Hz, 2H), 4.73 (dd, *J* = 1.3, 0.7 Hz, 2H). As discussed *supra*, the ^{1}H NMR spectrum is in agreement with the literature[54] and with the other spectra reported herein for **3.17b**.

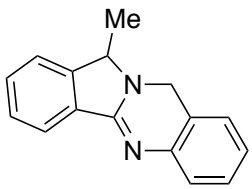


*2-chloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.82a**), 3-chloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.82c**), and 9-chloro-5,11-dihydroisoindolo[2,1-a]quinazoline (**3.82b**).* Regioisomeric mixture **3.82** was synthesized via general procedure C, which gave 21 mg (82% yield) of a dark yellow solid. The crude ^{1}H NMR was a complex mixture, so the crude product was purified via preparative TLC and the yield and regioselectivity[68] were determined from the isolated compounds. Attempts to isolate the products individually were unsuccessful. Following purification via preparative TLC (silica; 10:1 DCM:MeOH), a 12.7 mg (50% yield) of a 1.3:1 mixture of suspected regioisomers **3.82a** and **3.82c** was isolated. Suspected minor regioisomer **3.82b** (4.6 mg, 18% yield) and the suspected

isoindolinone of **3.82c** (3.8 mg, 14% yield) were also isolated. **Mixture of suspected regioisomers 3.82a and 3.82c:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, *J* = 1.5 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.28 (q, *J* = 1.8 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.02 – 6.96 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.85 – 6.79 (m, 3H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.48 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.62 (app d, *J* = 4.7 Hz, 2H), 4.58 (app d, *J* = 3.7 Hz, 2H), 4.49 (s, 2H), 4.15 (s, 2H). **3.82b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.53 (app d, *J* = 12.1 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.03 (s, 2H), 4.92 (s, 2H). HRMS $[M+H]^+$ Calc.: 255.0689, Found: 255.0699.

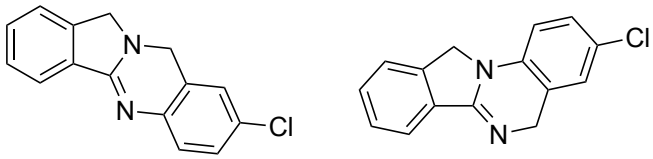


*2,3-dichloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.83a**) and 8,9-dichloro-5,11-dihydroisoindolo[2,1-*a*]quinazoline (**3.83b**).* Synthesis of **3.83** via general procedure C gave 10.4 mg (36 % yield) of a pale-yellow solid that was a mixture of the desired major and minor regioisomers **3.83a** and **3.83b**, as well as the corresponding isoindolinones **3.83a** and **3.83b**. Attempts to separate the products via preparative TLC were unsuccessful.

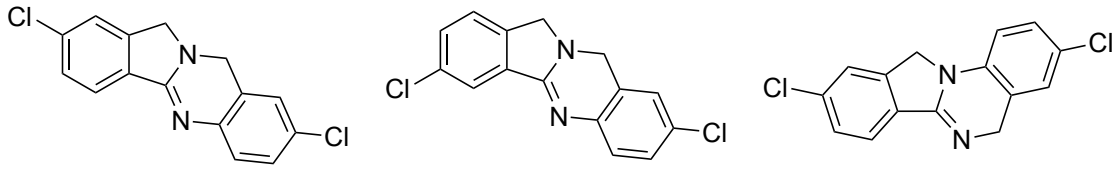


*12-methyl-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.84a**).* Synthesis of **3.84** via general procedure C gave 14.8 mg (63% yield) of a red oil. The crude product mixture was complex, but

it contained some of a compound that is suspected to be minor product **3.84c**, with a regioselectivity of approximately 2.5:1 **3.84a**:**3.84c**. Notably, expected minor regioisomer **3.84b** was not detected. **3.84a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.24 (app d, *J* = 2.0 Hz, 2H), 7.07 – 7.00 (m, 1H), 6.68 (d, *J* = 8.9 Hz, 1H), 4.93 (d, *J* = 13.0 Hz, 1H), 4.72 (d, *J* = 13.0 Hz, 1H), 4.53 (q, *J* = 6.4 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H).



*8-chloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.85a**) and 3-chloro-5,11-dihydroisoindolo[2,1-a]quinazoline (**3.85b**).* Synthesis of **3.85** via general procedure C gave 12.0 mg (47% yield) of a yellow solid. The regioselectivity was determined from the crude ^{1}H NMR to be 2.0:1 **3.85a**:**3.85b**[61]. Purification via preparative TLC (silica; 10:1 DCM:MeOH) gave 2.6 mg of the suspected acid salt of the major product, which is predicted to be **3.85a**. **Mixture of 3.85a and 3.85b**: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.90 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.51 – 7.47 (m, 1H), 7.47 – 7.37 (m, 2H), 7.16 (app ddt, *J* = 8.4, 2.4, 0.7 Hz, 2H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.09 (s, 1H), 6.98 (app ddt, *J* = 9.4, 2.1, 0.9 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.78 (s, 2H), 4.77 (s, 2H), 4.70 (s, 2H), 4.36 (s, 2H). **Acid salt of 3.85a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.75 (s, 1H), 9.08 (d, *J* = 7.7 Hz, 1H), 7.76 (td, *J* = 7.6, 1.1 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.36 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.09 (s, 2H), 5.03 (s, 2H). HRMS $[M+H]^+$ Calc.: 255.0689, Found: 255.0698.

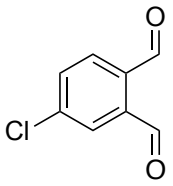


*2,8-dichloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.86a**), 3,8-dichloro-10,12-dihydroisoindolo[1,2-b]quinazoline (**3.86c**), and 3,9-dichloro-5,11-dihydroisoindolo[2,1-a]quinazoline (**3.86b**).* Synthesis of **3.86** via general procedures B and C gave a yellow solid in total yields of 46% (13.3 mg) and 52% (15.0 mg), respectively.[69] The regioselectivity for the product mixture synthesized via general procedure B was determined from the crude ^{1}H NMR to be 2.6:1 **3.86c**:**3.86a**[61] and the regioselectivity for the product mixture synthesized via general procedure C was determined from the crude ^{1}H NMR to be 1.4:1.3:1 for **3.86a**:**3.86c**:**3.86b**[61]. Attempts to isolate all three products were unsuccessful and only the major product was isolated for each reaction. Following purification of the products synthesized using general procedures B and C via preparative TLC (15:1 DCM:MeOH + 1% Et_3N), the major product for the latter, which is predicted to be **3.86a**, was isolated in a 19% yield (5.5 mg), and the major product for the former, which is predicted to be **3.86c**, was isolated in a 33% yield (9.5 mg). **3.86a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.91 (s, 1H), 9.13 (d, *J* = 8.8 Hz, 1H), 7.62 (app dd, *J* = 5.0, 1.9 Hz, 2H), 7.37 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 5.07 (s, 2H), 5.03 (s, 2H). **3.86c:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.73 (s, 1H), 9.03 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.52 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.37 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.17 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 5.15 (s, 2H), 4.95 (s, 2H). HRMS $[M+H]^+$ Calc.: 289.0299, Found: 289.0308.

General Procedure for the Reaction of 5-Bromophthalide with 2-Aminobenzylamine: Acid-Free Conditions. The phthalide (**3.110**) (0.10 mmol, 1.0 equiv) was added to a solution of the

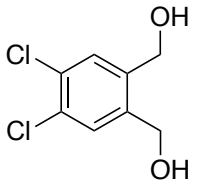
diamine (**3.12a,d**) (0.11 mmol, 1.1 equiv) in the solvent indicated *infra* in Table 3.8 (2.00 mL, 0.05 M) in a 2-dram scintillation vial equipped with a magnetic stir bar. Any additives specified in Table 3.8 were subsequently added and the vial was sealed. The reaction mixture was then heated to the specified temperature with stirring. The reaction progress was monitored via TLC. After 24-48 h at the desired temperature, the reaction mixture was cooled to room temperature, poured onto ice-cold 1% aqueous HCl, and then extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and then filtered. The solvent was removed *in vacuo* and the crude product was analyzed via ^1H NMR.

Synthesis of Phthalaldehyde Starting Materials.

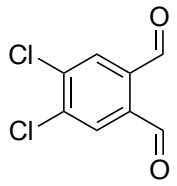


*4-Chlorophthalaldehyde (**3.78b**).* Phthalaldehyde **3.78b** was synthesized based on a modified procedure from the literature.[70] A solution of *N,N,N'*-trimethylethylenediamine (0.35 mL, 2.73 mmol, 1.10 equiv) in THF (6 mL) was cooled to -20 °C, treated with *n*-BuLi (1.6 M in hexanes, 1.65 mL, 2.64 mmol, 1.06 equiv.), and stirred for 15 minutes. A solution of 4-chlorobenzaldehyde (350.6 mg, 2.49 mmol, 1.00 equiv.) in THF (4 mL) was added dropwise and stirred for 15 minutes. A solution of *n*-BuLi (1.6 M in hexanes, 4.70 mL, 7.52 mmol, 3.01 equiv) was added and stirred at –20 °C for 3 h. The reaction mixture was cooled to -42 °C, followed by dropwise addition of anhydrous DMF (1.18 mL, 15.19 mmol, 6.10 equiv). After stirring for 5 min, the reaction mixture was allowed to warm up to room temperature over a period of 1 h and

stirred at room temperature for 1 h. An aqueous solution of 2 N HCl (25 mL) was added, extracted with EtOAc (3 x 25 mL), dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo*. Flash column chromatography on silica (10:1 Hexanes:EtOAc) provided **3.78b** (229 mg, 2.15 mmol) as a yellow solid in a 55% yield. The spectra matched those reported in the literature.



4,5-dichlorobenzene-1,2-dimethanol. The title compound was synthesized via a procedure that was based on the reported literature, with modifications. A solution of $LiAlH_4$ (1.0 M in THF, 3.90 mL, 3.90 mmol, 2.07 equiv) in an additional 2.2 mL of dry THF was added dropwise to a solution of 4,5-dichlorobenzene-1,2-dicarboxylic acid (442.2 mg, 1.882 mmol, 1.00 equiv.) in dry THF (1.70 mL) at -78°C via a reduced-pressure addition funnel. The reaction mixture was subsequently allowed to warm slowly to room temperature over a period of approximately 2 h. The reaction mixture was then heated to reflux overnight. The reaction mixture was then cooled to 0°C and then quenched with cold 15% aq. KOH (1.8 mL) and ice cold water (1.8 mL). The reaction mixture was subsequently diluted with THF (3.6 mL) and the organic layer was separated. The organic extract was washed with brine (3.6 mL), further extracted with Et_2O (3.6 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give 317 mg of 4,5-dichlorobenzene-1,2-dimethanol as a white solid in an 81% yield. The spectra matched those reported in the literature.[71]



*4,5-Dichlorophthalaldehyde (**3.78c**).* Phthalaldehyde **3.78c** was synthesized from the corresponding diol based on a procedure reported in the literature.[71] A solution of oxalyl chloride (0.290 mL, 3.18 mmol, 2.22 equiv.) in dry DCM (3.60 mL) was added to a dry 50 mL three-necked flask equipped with a stir bar and a reduced pressure addition funnel under Ar. The stirred solution was cooled to -78°C and a solution of DMSO (0.490 mL 6.34 mmol, 4.43 equiv.) in dry DCM (0.90 mL) was added dropwise. The solution was stirred for 5 min and a solution of 4,5-dichlorobenzene-1,2-dimethanol (297 mg, 1.43 mmol, 1.00 equiv) in a DCM-DMSO mixture (0.40 mL) was added dropwise the reaction mixture at -78°C. After 0.5 h of stirring, Et_3N (3.60 mL, 25.8 mmol, 18.0 equiv.) was added dropwise at -78°C. The reaction mixture was allowed to stir for 10 min and then slowly warmed to room temperature. Ice-cold water (7.2 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (2 x 4 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified via flash column chromatography (silica; Hexanes, then 7:3 Hexanes:EtOAc) to give 224 mg of phthalaldehyde **3.78c** as a pale-yellow solid in a 77% yield. The spectra matched those reported in the literature.[72]

Synthesis of Diamine Starting Materials.

Commercially available diamines were used as received.

3.14. References and Notes.

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