ASYMMETRIC RADICAL CATALYSIS IN THE SYNTHESIS OF PYRROLOINDOLINE ALKALOIDS

Emily Christine Gentry

A DISSERTATION
PRESENTED TO THE FACULTY
OF PRINCETON UNIVERSITY
IN CANDIDACY FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

RECOMMENDED FOR ACCEPTANCE BY
THE DEPARTMENT OF CHEMISTRY

Advisor: Professor Robert R. Knowles

September 2018
Abstract

In recent years, the use of radicals in catalysis has rapidly expanded in parallel with the development of new methods for their generation. However, the stereochemical fate of these reactions remains difficult to control, as the intermediates formed in such processes are highly reactive. One solution to this challenge would be to couple the redox event to the binding of substrate with a chiral catalyst, ensuring that the radical is formed only as a catalyst-bound adduct. This basic design principle is manifested in a mechanism known as proton-coupled electron transfer (PCET), wherein a hydrogen-bonding interaction between the substrate and Brønsted catalyst is necessary for electron transfer to occur.

This dissertation first details the development of an enantioselective radical reaction using an oxidative PCET mechanism, wherein a chiral phosphate base functions jointly with a photocatalytic oxidant to form an indole radical cation intermediate. The resulting key hydrogen-bonded indole radical cation intermediate is trapped with the persistent radical TEMPO• to generate enantioenriched 3a-TEMPO-substituted pyrroloindolines.

These initial studies then led to the discovery that TEMPO-derived alkoxyamines could undergo subsequent one-electron oxidation to catalytically generate carbocation intermediates via mesolytic C–O bond cleavage. We used this method to access a variety of enantioenriched 3a-functionalized pyrroloindolines from a common synthetic intermediate. The development, mechanistic study, and scope of these reactions are described herein, along with their application in the synthesis of several pyrroloindoline natural products.
Acknowledgements

It is hard to believe that five years have passed so quickly. It seems like just the other day I was moving into Butler, and now, here I am writing my thesis. While I have experienced a roller coaster of emotions during my time here, I will always fondly remember my time here. One of the reasons I chose to come to Princeton was because the people were so welcoming and friendly and this is also the reason why I will deeply miss working here. I would like to return thanks to the many people who have helped me along the way in both overcoming challenges and celebrating successes. I couldn’t have done this without you!

Above all, I would like to thank my advisor Rob who has been the greatest source of knowledge and inspiration over these past five years. Your infectious enthusiasm for chemistry is unrivaled as is the creativity that you bring to organic chemistry. You always encourage us to think outside the box and learn beyond our discipline, which pushes the group’s chemistry in really interesting directions. It has been incredible to see the group transform and grow over the past few years. When I joined, we only had eight members and were frantically trying to get oxidative PCET to work and look at us now. You have taught me so much over the years that I am grateful for, but I am especially thankful to you for teaching me how to effectively communicate my chemistry, which is one of the most valuable skills to possess. I owe my love for sans serif fonts and beautiful slides to you! I am also incredibly grateful for the support you have given me to pursue something different in my post doc and am excited to see where it takes me.

I would also like to thank Erik Sorensen, Abby Doyle, Brad Carrow and Dave MacMillan for generously serving on my committee and providing valuable insight and feedback on my PhD work. I am especially grateful to Erik for taking the time out of his busy schedule to serve as my second reader and also for sharing his extraordinary passion for synthesis. I am very appreciative of Erik, Abby, and Dave for serving as references during my post doc search. I would also like to give a special thanks to Brad for joining my committee for the final stretch.
To my former mentors, Jeff Johnson, Kim Steward, and Jeremy Kister, I wouldn’t be where I am today without you. Thank you for taking a chance on me and believing in me throughout the years. Kim, looking back at how clueless I was as an undergrad, you are truly a saint for putting up with me.

The grad students in the Princeton chemistry department are so blessed to have fantastic facilities and staff. I would especially like to thank John Eng, István Pelzcer, and Ken Conover for keeping all of the instruments in the department running smoothly and helping with compound characterization. I would also like to express my gratitude for Christina Kraml, Laura Wilson, and Neal Byrne who have helped with many separations over the years. I also owe a big thank you to Cherilus, for always working with a smile on his face and making me laugh when I’m stuck in lab late at night.

Most of my time at Princeton was spent in the lab, so the wonderful experience I had in grad school is really because of the entertaining and supportive coworkers I had the privilege of working with, past and present. There is never a dull moment in the Knowles Lab, which I especially appreciated on days when chemistry didn’t go my way. You guys always push me to be the best scientist and person I can. First, I would like to thank my classmates David and Lucas for experiencing the journey with me. David, I have always admired your ability to communicate thoughts and use a vocabulary much bigger than my own, and your dad jokes make me laugh even on the worst of days. Lucas, thank you for sharing your love for good food with me and for generously supplying the lab with chocolates and hot Cheetos.

I also want to give a heartfelt thank you to the former Knowles Lab members who were both fantastic mentors and supportive friends. Lydia, I am so grateful that I had the pleasure to work with you on the pyrroloindoline project and share our hatred for prep plates. You have such a positive attitude and even keeled temperament and you always gave me perspective when I most needed it. You are truly a wonder woman! I will deeply miss our Thursday night shrimp fajita dates. Hattie, I honestly can’t imagine grad school without you. You always lent an ear and provided a helping hand whenever I (or anyone else) needed it and will forever treasure the late-night discussions we shared over wine and cheese. Drew, you bring an unreal amount of positive energy (and volume) to any room you walk into, but above all else, you have a huge heart and understand my need for Bojangles. Gilbert, thank you for being my host on visiting weekend and recruiting me to the Knowles lab with your suave Bert charm. I will always cherish the few
months I got to spend as your deskmate. Brendan, you taught me the importance of always having an opinion, whether it be about chemistry or which cheese is the tastiest, and for that, I am grateful.

To current members of the lab, keep the hard work up and always strive to be the best labmates you can be! Qilei, you are a hardworking, sassy, and compassionate person and I sincerely respect you both as a chemist and a friend. Marty, you are one of the most thoughtful people I know and have a profound opinion on just about everything. You also have an unparalleled amount of happiness and patience that I wish I had. Casey and Hunter, I couldn’t have survived writing this thesis without you and your crazy yoga poses. Casey, even though you are an old soul, you bring a youthful Ruth-like energy to the group. You are a master of asymmetric catalysis and I can’t wait to see where your graduate career takes you. Hunter, my fellow Tarheel, you have the ability to always put a smile on my face, even on the most stressful of days. Guanqi, you are and always will be the wackiest person I know. Su, I am so thankful that we got to be deskmates this past year. You are an incredibly driven and ambitious woman and I know you will have a great graduate career. Your enthusiasm for chemistry hugely helped me finish my final year. Anthony, you are the greatest lab citizen and mentor and I am envious of the younger folks who have the privilege to overlap with you for longer. Thank you for helping edit this thesis and every other document I’ve written in the last year.

I also need to give a big thanks to the people who greatly improved my graduate experience outside of the Knowles lab. Patti and Tracy, you have been fantastic friends to me throughout the years and our Thursday night dinners kept me going and gave me something to look forward to each week. Jesus, thank you for always being there to listen and motivate me to finish the tasks at hand. Michelle, no matter how often we saw each other, we always had the best time and great chats.

To my friends outside of Princeton, thank you for pulling me outside of my grad school bubble every now and then. Although sporadic, weekends away from Princeton always gave me greater perspective and motivation. Macy and Christine, you are two truly inspirational women who have pushed me to be the best person I can be. You both have so much determination, resilience and compassion, and I know you will make the best doctors. You have given me so much love and support throughout the
years, from freshman year at UNC to now, and for that, I can't thank you enough. Julie, I am so thankful for your friendship and for being able to share my gluten troubles with you.

My family deserves huge praise for believing in me all these years, even when I didn’t believe in myself. To my parents, Jeff and Mel, you gave me great freedom to pursue what I’m passionate about, but yet were there to support me every step of the way. Our family vacations were always the highlight of the year and helped me to relax, recharge and finish my Ph.D. Caroline and Logan, thanks for always having an air mattress to sleep on when I needed to get out of Princeton and for distracting me from my lab worries with fun outdoor activities and Banks. To Mimi, Papa and Brent, thank you for sending so much love and thoughtful cards my way. Ian and Kate, I am very grateful for your support throughout this process and for providing a home away from home in Scotland.

Lastly, I want to thank my best friend and golf partner for life, Neil, who has wholeheartedly supported me through the inevitable ups and downs of grad school. You carried me through the tough times with encouraging words and Scottish humor and I couldn’t have endured this journey without you by my side. Thank you for being the kindest and most understanding man I know!
To my parents for their endless love and support
# Table of Contents

Abstract iii  
Acknowledgements iv  
Table of Contents ix  
List of Figures xi  
List of Tables xiv  

## Chapter 1: Catalytic Strategies for Stereoccontrolled Radical Reactions

1. Radicals in Organic Synthesis 1  
2. Organocatalysis 2  
3. Lewis Acid Coordination 10  
4. Non-Covalent Interactions 16  
5. Proton-Coupled Electron Transfer (PCET) 18  
6. Summary of Thesis Work 21  

## Chapter 2: Development of an Asymmetric Proton-Coupled Electron Transfer Reaction to Form Enantioenriched TEMPO-Functionalized Pyrroloindolines

1. Tryptophan PCET 22  
2. Reaction Design and Optimization 23  
3. Reaction Scope 28  
4. Control Reactions and Other Experiments 29  
5. Mechanistic Studies 33  
6. Conclusion 37
Chapter 3: Mesolytic Bond Cleavage of TEMPO-Derived Alkoxyamine Radical Cations

I. Introduction 38

II. Reaction Design and Optimization 40

III. Scope of Mesolytic Bond Cleavage Reaction 46

IV. Conclusion 50

Chapter 4: Asymmetric Total Synthesis of Pyrroloindoline Natural Products

I. Introduction to Pyrroloindoline Natural Products 51

II. Synthetic Approaches to C3a–C3a’ Linkage 54

III. Asymmetric Synthesis of (–)-calycanthidine 57

IV. Asymmetric Synthesis of (–)-chimonanthine 60

V. Asymmetric Synthesis of (–)-psychotriasine 65

VI. Conclusion and Future Directions 66

Supporting Information

Appendix A 67

Appendix B 128

Appendix C 165
List of Figures

Chapter 1: Catalytic Strategies for Stereocontrolled Radical Reactions

Figure 1: Synthesis of triquinanes by tandem radical cyclization. 1
Figure 2: Strategies for enantioselective organocatalysis. 3
Figure 3: Enantioselective radical additions to enamines using photoredox catalysis. 4
Figure 4: Catalytic cycle for asymmetric enamine photoredox catalysis. 5
Figure 5: Organo-SOMO activation for enantioselective radical catalysis. 6
Figure 6: Catalytic cycle for photoredox organo-SOMO catalysis. 7
Figure 7: Asymmetric photochemical α-alkylation of aldehydes. 8
Figure 8: Asymmetric photochemical β-alkylation of aldehydes. 9
Figure 9: General mechanisms for Lewis acid-mediated stereoselective radical reactions. 10
Figure 10: Lewis-acid controlled diastereoselectivity in radical alkylation of chiral oxazolidinones. 11
Figure 11: Diastereoselective alkylation of α, β-unsaturated esters. 12
Figure 12: Enantioselective alkylation of oxazolidinone using chiral Lewis acids. 13
Figure 13: Dual photoredox Lewis acid catalysis in enantioselective [2+2] cycloadditions. 14
Figure 14: Stereoisomers of chiral-at-metal complexes. 15
Figure 15: Asymmetric photoredox Lewis acid catalysis. 16
Figure 16: H-bonding mediated enantioselective radical alkylation of oxime ethers. 17
Figure 17: Enantioselective reductive cyclization using a H-bonding template. 17
Figure 18: Photoexcited electron transfer using a chiral complexing catalyst. 18
Figure 19: Proton-coupled electron transfer mechanisms. 19
Chapter 2: Development of an Asymmetric Proton-Coupled Electron Transfer Reaction to Form Enantioenriched TEMPO-Functionalized Pyrroloindolines

Figure 1: Generation of indole radical cation via PCET mechanism in DNA photolyase. 23
Figure 2: Role of indole PCET in RNR initiation. 23
Figure 3: Reaction design for indole PCET. 24
Figure 4: Proposed catalytic cycle for enantioselective indole PCET reaction. 25
Figure 5: Detrimental role of TEMPO-H in the reaction. 26
Figure 6: Proposed role of iodonium in PCET reaction. 32
Figure 7: Effect of TEMPO on the distribution of byproducts. 32
Figure 8: EPR spectrum on indole radical intermediate. 33
Figure 9: Reduction of TIPS-EBX by Ir(ppy)₃ to form the more oxidizing Ir^{IV} state. 34
Figure 10: Luminescence quenching experiment to support PCET mechanism. 34
Figure 11: Cyclic voltammetry of PCET oxidation of indole by Ir^{IV}(ppy)₃ and phosphate. 35
Figure 12: Modulation of indole redox potential through H-bonding interaction. 36

Chapter 3: Mesolytic Bond Cleavage of TEMPO-Derived Alkoxyamine Radical Cations

Figure 1: Homolytic vs. heterolytic mechanisms of mesolytic bond cleavage. 39
Figure 2: Thermochemical cycle for bond weakening in mesolytic cleavage. 40
Figure 3: Using TEMPO-derived alkoxyamines in mesolytic bond cleavage. 41
Figure 4: TEMPO-functionalized pyrroloindolines as a synthetic intermediate for pyrroloindoline natural products. 42
Figure 5: Bond weakening of C–O bond in alkoxyamine radical cations. 43
Chapter 4: Asymmetric Total Synthesis of Pyrroloindoline Natural Products

Figure 1: Pyrroloindoline natural products. 52
Figure 2: Biosynthetic pathway of chimonanthine and labeling studies. 53
Figure 3: Overman’s asymmetric synthesis of (−)-chimonanthine. 54
Figure 4: Radical-mediated pathways to pyrroloindoline natural products. 55
Figure 5: Movassaghi’s synthesis of heterodimeric pyrroloindolines. 56
Figure 6: Proposed mesolytic cleavage strategy for the synthesis of unsymmetrical dimers. 57
Figure 7: Time course of heterodimerization reaction. 59
Figure 8: Asymmetric synthesis of (−)-calycanthidine. 59
Figure 9: 1H NMR analysis of homodimer diastereoenrichment. 62
Figure 10: Cyclic voltammograms of meso and C₂ homodimers. 63
Figure 11: Stern-Volmer quenching of meso vs. C₂ homodimers. 64
Figure 12: Asymmetric synthesis of (−)-chimonanthine. 65
Figure 13: Asymmetric synthesis of (−)-psychotriasine. 66
List of Tables

Chapter 2: Development of an Asymmetric Proton-Coupled Electron Transfer Reaction to Form Enantioenriched TEMPO-Functionalized Pyrroloindolines

Table 1: Effect of BINOL phosphate backbone on enantioselectivity. 26
Table 2: Optimization of PCET reaction. 27
Table 3: Evaluation of solvents in enantioselective TEMPO trapping. 27
Table 4: Substrate scope of enantioselective PCET reaction. 29
Table 5: Effect of photocatalyst redox potential on enantioselectivity. 31

Chapter 3: Mesolytic Bond Cleavage of TEMPO-Derived Alkoxyamine Radical Cations

Table 1: Optimization of mesolytic bond cleavage reaction. 46
Table 2: Substrate scope of mesolytic bond cleavage with pyrroloindoline alkoxyamines. 47
Table 3: Scope of TEMPO-derived alkoxyamine electrophiles. 48
Table 4: Nucleophile scope in C–O cleavage of secondary benzylic alkoxyamine. 49

Chapter 4: Asymmetric Total Synthesis of Pyrroloindoline Natural Products

Table 1: Optimization of heterodimerization reaction. 58
Table 2: Optimization of homodimerization. 61
Chapter 1: Catalytic Strategies for Stereocontrolled Radical Reactions

I. Radicals in Organic Synthesis

Radical-mediated reactions have vast utility in organic synthesis, as they offer reactivities complementary to, and often completely orthogonal to, that of polar mechanisms. While initially thought to be too highly reactive and uncontrollable for complex target synthesis, radicals are now commonly considered in synthetic planning, especially in the construction of challenging C–C bonds. Perhaps the most notable advantages of using radical-based strategies in synthesis are their ability to form sterically-demanding bonds and participate in elegant cascade reactions.\(^1\) In fact, these features have been exploited in a number of natural product syntheses to assemble complex ring systems in a single chemical step. A classic example of this type of transformation is used in Curran’s synthesis of the triquinanes, in which tandem radical cyclization is used to generate a series of cis-fused five-membered rings with sterically hindered C–C linkages (Figure 1).\(^2\) These key steps are initiated by the traditional tin hydride method for radical generation, which requires the use of toxic reagents in stoichiometric amounts.

---


---

*Figure 1*: Synthesis of triquinanes by tandem radical cyclization.
Since then, there have been tremendous strides in the development of catalytic methods for the
generation of free radicals, particularly over the past decade with the recent advent of photoredox
catalysis. However, while strategies for the catalytic generation of radicals have greatly advanced, there
remains a challenge in controlling the stereochemical fate of these intermediates in subsequent bond
formations due to their high innate reactivity and fast rates of configurational inversion. Many notable
eamples exist for manipulating the diastereoselectivity in radical reactions through either substrate bias
or chiral auxiliaries. However, there are comparatively few catalytic strategies to promote stereocontrolled
radical-mediated mechanisms. This introductory chapter will cover the methods that have been previously
exploited in asymmetric radical catalysis, such as organocatalysis, Lewis acid coordination, and non-
covalent binding. It will then present a new general approach for achieving enantioselective radical
reactivity using proton-coupled electron transfer (PCET). In this mechanism, electron transfer is kinetically
coupled to H-bonding coordination of a substrate to a Brønsted catalyst, ensuring that radical intermediates
are formed exclusively as H-bonded adducts. Following the redox event, the non-covalent associations can
remain intact and affect the stereochemical fate of subsequent bond-forming steps if a chiral Brønsted
catalyst is employed.

II. Organocatalysis

Organocatalysis, or the use of small organic molecules to catalyze chemical transformations, has
emerged as a powerful strategy for performing enantioselective bond formations. While several examples
of organocatalytic reactions were documented throughout the 20th century, the field did not receive

---

widespread recognition until the late 1990s, when a series of studies were published by Shi\textsuperscript{6}, Denmark\textsuperscript{7}, Yang\textsuperscript{8}, Jacobsen\textsuperscript{9}, Corey\textsuperscript{10}, and Miller\textsuperscript{11}, which demonstrated that small organic molecules could catalyze asymmetric transformations. At the turn of the century, List\textsuperscript{12} and MacMillan\textsuperscript{13} made two important contributions to the field when they almost simultaneously reported asymmetric secondary amine-catalyzed aldol and Diels–Alder reactions, respectively. A few years later, Jørgensen designed a more general amine organocatalyst that could catalyze a wide range of aldehyde α-functionalizations, circumventing the need to fine tune catalyst structure for each individual transformation.\textsuperscript{14} Since then, amine-derived organocatalysts have been widely utilized to promote reactivity of carbonyl-containing substrates via three complementary mechanisms known as iminium, enamine, and organo-SOMO activation (Figure 2).\textsuperscript{15}

![Figure 2: Strategies for enantioselective organocatalysis. The MacMillan imidazolidinone organocatalyst](image)

While these three activation strategies are distinct, they are all derived from the parent iminium ion generated through condensation of a secondary amine catalyst onto an aldehyde. An enamine species is then formed through the subsequent deprotonation of the iminium ion to provide a reactive nucleophilic

---

coupling partner. This intermediate has been intercepted with a wide variety of closed shell electrophiles to perform enantioselective polar chemistries. More recently, MacMillan and Nicewicz have further demonstrated that enamine nucleophiles can react asymmetrically with open shell intermediates generated using photoredox catalysis. \(^{16}\) In this system, the enamine serves as a chiral acceptor molecule to provide enantioinduction in the radical addition step (Figure 3).

![Enantioselective radical additions to enamines using photoredox catalysis.](image)

**Figure 3**: Enantioselective radical additions to enamines using photoredox catalysis.

Specifically, the reaction proceeds via initial one-electron reduction and fragmentation of an \(\alpha\)-bromo carbonyl compound by the reduced state of Ru(bpy)\(_3\)Cl\(_2\) to furnish an electron-deficient radical (Figure 4). This reactive species is then intercepted by the nucleophilic chiral enamine in the enantiodetermining alkylation step to generate a \(\beta\)-stereogenic \(\alpha\)-amino radical. This intermediate is subsequently oxidized by the excited state of Ru(bpy)\(_3\)Cl\(_2\) to afford an iminium ion. Hydrolysis of this adduct results in the desired enantioenriched \(\alpha\)-alkylated aldehyde and regenerates the amine catalyst. In this system, the sterically demanding tert-butyl group of the amine catalyst enforces a conformation in which the 2n-electron system is projected away from it. Facial selectivity is proposed to arise from the methyl group blocking the \(re\) face, leaving the \(si\) face exposed for alkylation by the radical intermediate.

Figure 4: Catalytic cycle for asymmetric enamine photoredox catalysis.

Organo-SOMO catalysis provides another straightforward means to generate enantioenriched α-alkylated aldehyde products. In this framework, an electron-rich enamine undergoes one-electron oxidation to provide an electron-deficient radical cation, offering divergent and complementary reactivity to enamine chemistry. The initial report of organo-SOMO catalysis by MacMillan utilized stoichiometric ceric (IV) ammonium nitrate (CAN) as a single electron transfer reagent to generate the desired radical cation intermediate from a transient enamine species (Figure 5a).\(^{17}\) A variety of electron-rich olefins and other ‘SOMO-philes’ were able to be coupled with this radical ion to generate optically-enriched α-alkylated aldehydes.

This process was recently rendered catalytic by interfacing organo-SOMO with photoredox catalysis (Figure 5b).\(^\text{19}\)

**Figure 5:** Organo-SOMO activation for enantioselective radical catalysis.

In this elegant work, the excited state of an iridium-based photocatalyst served as the one-electron oxidant to engender the requisite radical cation species. Upon coupling of this intermediate with an alkene acceptor, the resulting alkyl radical is reduced by a thiol catalyst to produce the enantioenriched α-alkylated adduct. Subsequent reduction of the thyl radical by the reduced state photocatalyst and hydrolysis of the iminium intermediate regenerates all catalytic components (Figure 6).


While the aforementioned examples employ ground state enamine or iminium species, Melchiorre and coworkers have recently demonstrated the synthetic potential of the excited states of these intermediates in enantioselective alkylation chemistries. They discovered that certain iminium and enamine species can undergo photoexcitation to facilitate single electron transfer and generate free radical intermediates. They first reported this mechanism in the context of an enantioselective aldehyde α-alkylation wherein an electron-deficient alkyl halide and electron-rich enamine intermediate form a chiral electron donor-acceptor (EDA) complex in situ (Figure 7). In this system, irradiation of the transient EDA complex induces electron transfer and creates a contact radical ion pair. Spontaneous halide dissociation of the radical anion component reveals an alkyl radical which stereoselectively couples with the chiral enamine radical cation to provide the desired enantioenriched α-alkylation product.

Figure 7: Asymmetric photochemical α-alkylation of aldehydes.

The Melchiorre group has recently extended this concept to chiral iminium ions wherein photoexcitation converts these traditionally electrophilic intermediates into strong one-electron oxidants (Figure 8). In this work, the excited state iminium ion (*E_{red} \sim +2.3 \text{ V vs. Ag/Ag}^+ \text{ in MeCN}) induces oxidation of electron-rich alkyl trimethylsilane substrates (*E_p = +1.74 \text{ V vs. Ag/Ag}^+ \text{ in MeCN}) to furnish a β-enaminyl radical and a silyl radical cation intermediate which undergoes rapid irreversible fragmentation.

---

of the C-Si bond to reveal an alkyl radical. Subsequent stereocontrolled coupling of the chiral $\beta$-enaminyl radical and alkyl radical forms the $\beta$-functionalized product. Together, these studies demonstrate that accessing the excited state of classical intermediates in thermal enantioselective organocatalytic chemistries can uncover new radical-mediated mechanisms for the asymmetric alkylation of aldehydes.

**Figure 8:** Asymmetric photochemical $\beta$-alkylation of aldehydes.
III. Lewis Acid Coordination

Lewis acid coordination is one of the most commonly employed methods to control stereoselectivity in radical-mediated mechanisms. There are two general ways by which Lewis acids can affect the stereochemical outcome of radical reactions. Firstly, an achiral Lewis acid can be chelated to a chiral acceptor or radical precursor to alter the diastereoselectivity of a radical reaction by favoring a certain conformation (Figure 9a). Alternatively, a chiral Lewis acid can bind to an achiral or racemic compound to invoke enantioselectivity in the radical addition step by sterically blocking a particular face of the substrate during bond formation (Figure 9b).

Figure 9: General mechanisms for Lewis acid-mediated stereoselective radical reactions.

Regardless of which Lewis acid-mediated mechanism is employed, a meaningful association needs to be maintained during the bond-forming step to impart enantioselectivity. Typically, this means that high Lewis acid loadings are required to achieve high selectivity due to the presence of racemic background processes and the propensity of the product to unproductively associate with the catalyst. Therefore,

---

judicious choice of both substrate and catalyst is often the key to achieving a highly enantioselective and catalytic radical reaction using this strategy.

While achiral Lewis acids alone cannot affect the stereochemical fate of radical additions, their use in combination with a chiral substrate can lead to diastereoselective radical reactions. One of the first notable examples of this type of stereochemical control was reported by Sibi and coworkers in which the rotation about an oxazolidinone amide bond was restricted by the chelation of a Lewis acid catalyst leading to higher selectivity in the radical addition step (Figure 10).24 Specifically, when a catalyst is present in solution, the doubly-coordinated rotamer featured in Figure 10 is dominant, and the radical is anticipated to mostly react with that conformation.25 Furthermore, the presence of a bulky alkyl group on the oxazolidinone forces addition to the less hindered face, leading to the observed high diastereoselectivity. Using this strategy, an asymmetric α-allylation was achieved wherein the reaction proceeds with no diastereoselectivity in the absence of a Lewis acid catalyst, but reaches near perfect diastereoselectivity in the presence of MgBr$_2$·OEt or Sc(OTf)$_3$.

![Figure 10](image)

**Figure 10**: Lewis-acid controlled diastereoselectivity in radical alkylation of chiral oxazolidinones.

This design principle has been demonstrated in a number of other systems, including the diastereoselective alkylation of α,β-unsaturated esters with α-D-glucopyranoside chiral auxiliaries (Figure 11).26 Namely, the use of four equivalents of Et$_2$AlCl provided highly diastereoselective radical addition into

---

α-D-glucopyranoside-derived Michael acceptors, while the coupling was completely unselective in the absence of a Lewis acid catalyst and only slightly selective with one equivalent of Et₂AlCl. The exact conformation of the substrates in the stereodetermining transition state were not determined, but evaluation of the alcohol protecting groups on the sugar derivative revealed that substrates possessing acyloxy groups or a bulky TBS group at the C2 and C3 positions were required for good enantioselectivity.

![Figure 11](image)

**Figure 11**: Diastereoselective alkylation of α, β-unsaturated esters.

Chiral Lewis acids offer another means to control the stereoselectivity of a radical reaction and do not require the presence of a chiral auxiliary appendage on the substrate itself. This strategy was first reported by Porter, who found that an enantioselective alkylation of an α, β-unsaturated oxazolidinone could be accomplished in the presence of one equivalent Lewis acid and chiral bisoxazoline (BOX) ligand (Figure 12). The selectivity was proposed to arise from a combination of chelation-enforced Z, Z-conformation of the acryloyl oxazolidinone, the preferred cis conformation of the radical intermediate due to steric interactions, and catalyst shielding of the back face by a phenyl substituent on the ligand. While this transformation requires stoichiometric amounts of chiral Lewis acid, it was nonetheless an important breakthrough in asymmetric radical catalysis, as it demonstrated that chirality can be transferred from catalyst to substrate through a transient association.

![Table](table)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piv</td>
<td>84</td>
<td>93:7 (64:36)</td>
</tr>
<tr>
<td>MesCO</td>
<td>100</td>
<td>95:5 (1:1)</td>
</tr>
<tr>
<td>Bn</td>
<td>81</td>
<td>70:30 (61:39)</td>
</tr>
<tr>
<td>TBS</td>
<td>98</td>
<td>90:10 (67:33)</td>
</tr>
</tbody>
</table>

<sup>a</sup> value in parentheses diastereoselectivity using only 1 equiv of LA

Recent work by Yoon and coworkers merged chiral Lewis acid coordination with photoredox catalysis to accomplish asymmetric radical cycloadditions under mild conditions (Figure 13). In this effort, they devised a system that eliminated racemic background reactivity by coupling Lewis acid coordination to the redox event. Specifically, Lewis acid coordination is known to be essential for cycloadditions to proceed via one-electron reduction mechanisms, presumably due to the stabilization that it imparts on the radical anion species.\textsuperscript{28} Therefore, an enantioselective [2+2] cycloaddition between two enone components could be accomplished through a dual catalyst system consisting of a photoredox catalyst and Lewis acid cocatalyst, wherein Lewis acid chelation must occur prior to the electron-transfer event.\textsuperscript{29} They discovered lanthanide triflates, specifically Eu(OTf)\textsubscript{3}, used in conjunction with peptide-based chiral Schiff ligands performed best in the reaction providing up to 92% ee for the model substrate. Interestingly, the catalyst loading could be dropped to as low as 2.5 mol% without erosion in the enantioselectivity, indicating that there is no contribution from a racemic background process.

\textbf{Figure 12:} Enantioselective alkylation of oxazolidinone using chiral Lewis acids.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption{Enantioselective alkylation of oxazolidinone using chiral Lewis acids.}
\end{figure}


Recently, a new class of chiral Lewis acid catalysts were introduced by Meggers and coworkers, in which an octahedral transition metal complex serves as both the reactive center and source of chirality (Figure 14). These ‘chiral-at-metal’ iridium and rhodium complexes have proven to be highly effective in a variety of Lewis acid-catalyzed asymmetric polar reactions including Michael additions, Friedel–Crafts alkylations, cycloadditions, and Mannich reactions. More recently, these chiral-at-metal complexes have also been exploited as photoredox catalysts, in which they not only activate substrates through Lewis acid coordination but they also generate reactive radical intermediates through photoexcited single electron transfer.

---

Figure 14: Stereoisomers of chiral-at-metal complexes.

In the initial studies, 2-acyl imidazoles chelated to the metal center undergo deprotonation to deliver a highly reducing enolate-ligated photoactive iridium catalyst (Figure 15a). Electron transfer from the photoexcited state of this catalyst to an electron-deficient alkyl halide produced an electrophilic radical, which readily coupled with the electron-rich enolate intermediate to form highly enantioenriched α-alkylated 2-acyl imidazole products. Further investigations revealed that this reaction scheme was amenable to a wide range of photocatalytically generated electrophilic radicals. Additionally, they demonstrated that this strategy could be extended to asymmetric radical-radical coupling reactions between trifluoromethyl ketones and tertiary amines to form 1,2-amino alcohols (Figure 15b). This reaction proceeds via initial electron transfer from the ligated ketone to a tertiary amine to form the corresponding Ir-coordinated ketyl radical and aminium ion. Proton transfer between these two intermediates then delivers an electron-deficient ketyl radical and an electron-rich α-aminoalkyl radical, which subsequently couple stereoselectively to furnish the desired product. The stereochemical outcome in both of the aforementioned reactions is controlled by the chiral-at-metal catalyst, which also serves as the photocatalyst. This represents a novel strategy to affect enantioselective radical reactions via the coordination of a chiral catalyst to either an acceptor molecule or the radical species.

IV. Non-Covalent Interactions

An alternative method for achieving catalyst-controlled enantioselectivity in radical-mediated reactions is through non-covalent binding with a chiral template. While this approach is underdeveloped relative to Lewis acid catalysis, there are a handful of notable examples that demonstrate the potential of this strategy. Jang and coworkers reported an interesting system, in which non-covalent interactions between a radical acceptor and chiral quaternary ammonium salt controlled the stereochemistry of alkyl radical addition to oxime ethers to form enantioenriched α-amino acids (Figure 16).\(^{37}\) In this reaction, the ammonium salt serves a dual purpose as both chiral catalyst and phase-transfer reagent. The proposed stereochemical model suggests both H-bonding interactions and \(\pi-\pi\) stacking contribute to the high enantioselectivity, with attack on the \textit{si} face favored due to blocking of the \textit{re} face by the quinoline group.

Figure 16: H-bonding mediated enantioselective radical alkylation of oxime ethers.

Bach and coworkers have perhaps made the most significant contributions to the field of non-covalent stereochemical control of radical reactions. Their debut publication in the area implemented a chiral H-bonding template to affect an enantioselective atom transfer cyclization (Figure 17). While this reaction required a large excess of the chiral template and delivered only modest enantioselectivities, it was an important first step in demonstrating the feasibility of a non-covalent strategy. As shown in the stereochemical model, the re face is shielded by the tetrahydronaphthalene ring system of the catalyst, prompting hydrogen atom transfer to proceed from the more accessible si face.

Figure 17: Enantioselective reductive cyclization using a H-bonding template.

Extending this line of reasoning, Bach and coworkers later developed a dual catalyst that contained both a chiral H-bonding template and a photosensitizer (Figure 18). The utility of this system was demonstrated in the context of an enantioselective intramolecular α-aminoalkyl radical addition to a quinolone. In this process, UV excitation of the photosensitizer induces oxidation and subsequent deprotonation of the amine to generate an α-amino radical. This nucleophilic intermediate then adds to the appended enone, resulting in an α-carbonyl radical that can be readily reduced to the enolate and protonated to furnish the desired product. Importantly, in this system, they are able to use catalytic amount of chiral H-bonding template to achieve high enantioselectivities.

**Figure 18**: Photoexcited electron transfer using a chiral complexing catalyst.

### V. Proton-Coupled Electron Transfer (PCET)

As discussed in a few of the aforementioned examples, one general strategy for controlling the enantioselectivity of radical-mediated reactions is to couple radical generation to the binding of substrate with a chiral catalyst. This basic design principle is well manifested in a mechanism known as proton-coupled electron transfer (PCET), wherein a hydrogen-bonding interaction between the substrate and a Brønsted catalyst is necessary for single electron transfer to occur (Figure 19). PCETs are unconventional redox events in which a proton and electron are exchanged in a single elementary step, and they are known

---

to operate in some of the most important biological redox processes, from photosynthetic water oxidation and ribonucleotide reduction to DNA biosynthesis. Recently, the Knowles group became interested in exploring the application of PCET mechanisms in organic synthesis for the chemoselective generation and enantioselective reactivity of free radical intermediates.\textsuperscript{40}

---

**Figure 19**: Proton-coupled electron transfer mechanisms.

From a macroscopic viewpoint, PCETs appear to be very similar to traditional hydrogen atom transfers (HATs). However, unlike HAT mechanisms, wherein a proton and electron travel concomitantly from a single donor to a single acceptor, the proton and electron in a multisite PCET mechanism can originate from two separate donors, or travel to two distinct acceptors.\textsuperscript{41} This seemingly subtle detail has some very profound synthetic consequences. Specifically, since multisite PCETs are a formally termolecular process, the kinetic feasibility of such an event relies upon the formation of a pre-equilibrium hydrogen bond between the Brønsted base and substrate. In turn, multisite PCET provides a framework for the chemoselective generation of free radicals wherein polarized X–H bonds, such as N–H or O–H bonds, are selectively activated over much weaker, but less polarized, C–H bonds.\textsuperscript{42} More relevant to the contents of this chapter, due to its H-bonding requirement, PCET will only furnish radicals as catalyst-bound adducts

---


and can therefore serve as a unique opportunity for enantioselective radical catalysis, wherein the racemic background processes are eliminated. If these non-covalent associations are sufficiently stabilizing to persist during subsequent bond-forming steps, they can serve as a basis for asymmetric induction when a chiral Brønsted catalyst is employed.

The feasibility of these ideas was recently demonstrated in our group by Lydia Rono and Hattie Yayla in the context of an intramolecular aza-pinacol coupling (Figure 20). In this example, a chiral phosphoric acid and reducing photocatalyst functioned jointly to furnish a ketyl radical intermediate via reductive PCET. This open shell species then reacted with a pendant hydrazone moiety in the enantiodetermining step to generate a hydrazyl radical, which was subsequently reduced by Hantzsch ester to produce an enantioenriched α-amino alcohol. Notably, these studies represent a rare example of a highly enantioselective bond-forming process mediated by a discrete hydrogen-bonding interaction between a chiral anion and a neutral free radical.

![Figure 20: Asymmetric aza-Pinacol coupling via PCET-generated ketyl radical.](image)

VI. Summary of Thesis Work

As illustrated in this first chapter, while the use of radicals in synthesis continues to grow, catalytically controlling enantioselectivity in the reactions of these intermediates remains a challenge. Proton-coupled electron transfer mechanisms provide a unique platform to perform asymmetric radical catalysis wherein non-covalent association of chiral Brønsted catalysts to open-shell intermediates provides a basis for enantioinduction in bond formation. Prior work from our group has demonstrated the viability of this strategy in the context of an enantioselective reductive PCET-mediated aza-pinacol cyclization. This dissertation will describe the development of the first asymmetric oxidative PCET reaction in which a key hydrogen-bonded indolyl radical cation intermediate is trapped with the persistent radical TEMPO• to generate enantioenriched C3a-TEMPO-substituted pyrroloindolines.

Chapter 2 will first detail the biological inspiration for the enantioselective indole radical cation-mediated PCET reaction and then present the optimization and scope of the method. Mechanistic studies are presented to support the proposed PCET mechanism, wherein a phosphate-indole complex is selectively oxidized over unbound indole, ensuring that the indole radical cation is formed only as a catalyst-bound adduct.

In Chapter 3, we describe the development of a mesolytic bond cleavage strategy to derivatize these enantioenriched TEMPO-functionalized products into a variety of valuable pyrroloindoline architectures. In this framework, a catalytic single-electron oxidation/mesolytic cleavage sequence is utilized to furnish transient carbocation intermediates that may be intercepted by a wide range of nucleophiles. Overall, this approach provides a concise route to a variety of enantioenriched C3-functionalized pyrroloindolines from a common synthetic intermediate.

Finally, Chapter 4 presents the application of the two catalytic radical cation chemistries described above in the concise asymmetric total synthesis of several classically targeted pyrroloindoline natural products. In this scheme, a pyrroloindoline carbocation generated via mesolytic cleavage of could be intercepted stereoselectively with prochiral tryptamine to construct the sterically demanding C3a–C3a’ bond.
Chapter 2: Development of an Asymmetric Proton-Coupled Electron Transfer Reaction to Form Enantioenriched TEMPO-Functionalized Pyrroloindolines

I. Tryptophan PCET

Proton-coupled electron transfer (PCET) mechanisms underpin some of the most important radical-mediated reactions in nature including photosynthesis and respiration, DNA biosynthesis, and nitrogen fixation. These processes rely on the intricate coordination of H-bonding and proton motion within protein environments to promote electron transfer processes, often over long distances. Thus, proteins have evolved their structural dynamics to support perfect choreography of proton and electron movement. While redox-active cofactors or metals are commonly responsible for initiating enzymatic redox events, amino acid (AA) residues often gate and control radical propagation. Due to their favorable redox and H-bonding properties, tryptophan and tyrosine are among the most commonly employed AAs in enzymatic charge transfer pathways.

While oxidation of these two aromatic AA residues is relatively facile, charge transfer generally becomes much more viable when accompanied by proton transfer to avoid the formation of high energy charged intermediates. However, in tryptophan PCET, proton transfer does not always occur due to the relatively high $pK_a$ (~4 in H$_2$O) of the radical cation under physiological conditions. Rather, a H-bonding interaction between tryptophan and a nearby H-bonding acceptor provides enough stabilization for facile electron transfer to occur without concurrent proton transfer.

One such example of this tryptophan PCET mechanism is found in the first step of a three-part hole hopping pathway in DNA photolyase wherein Trp382 is oxidized to its corresponding radical cation by photoexcited FADH$^\bullet$ (Figure 1). In this system, Asn378 is implicated as the H-bonding partner that drives PCET oxidation of Trp382, as it is the only polar residue found within a 6Å radius.

---


Figure 1: Generation of indole radical cation via PCET mechanism in DNA photolyase. Furthermore, an indole radical cation is also proposed to be a key intermediate in ribonucleotide reductase (RNR) (Figure 2). Specifically, Trp48 is recognized to initiate RNR activity via one-electron reduction of the diiron center to produce the catalytically active Fe$^{III}$–Fe$^{IV}$ species. This reduced metal complex is then responsible for generating the Tyr122• intermediate, the first step of the 35Å charge transfer pathway.

Figure 2: Role of indole PCET in RNR initiation.

II. Reaction Design and Optimization

While indole PCET-mediated oxidations have been studied extensively in biological and biomimetic systems, their reactivity has been entirely unexplored in a synthetic context. Inspired by the aforementioned examples of tryptophan PCET, we became interested in generating indole radical cations
using a synthetic PCET system adapted from those described in Chapter 1. Specifically, we proposed that a one-electron oxidant could function jointly with a Brønsted base to activate tryptamine in an oxidative PCET mechanism. If a chiral base was employed, we imagined that the stereochemical fate of this indole radical intermediate might be affected.

Prior work by former graduate students Lydia Rono and Hatice Yayla demonstrated that reductive PCET could be used as a platform for asymmetric radical catalysis in the context of an enantioselective aza-pinacol cyclization using ketyl radicals (vide supra). We hypothesized that this strategy could be extended to the oxidative regime, provided that a meaningful H-bonding interaction is maintained between the radical intermediate and Brønsted catalyst following the redox event. With respect to the proposed indole system, we reasoned that the use of a chiral phosphate base in conjunction with a photocatalytic oxidant could provide the ideal framework for enantioselective radical catalysis (Figure 3). Similar to biological PCET of tryptophan, we believed that a chiral phosphate base ($pK_a = 12-13$ in MeCN) could participate in H-bonding with an indole to sufficiently lower the potential required for its one-electron oxidation without deprotonating the resulting indolyl radical cation ($pK_a \sim 14.5$ in MeCN). Furthermore, the radical cation generated from the redox event would remain strongly associated with the phosphate in an ionic hydrogen bond, providing a basis for enantioselectivity in subsequent bond-forming steps.

**Figure 3**: Reaction design for indole PCET.

---


48 Calculated from N-H BDFE = 93 kcal/mol and $E_{1/2} = +0.78$ V vs. Fc+/Fc in MeCN for indole.
We envisioned a catalytic cycle that would be initiated by excitation of a photocatalyst with 470 nm blue light (Figure 4). The excited-state photocatalyst would then act jointly with a chiral anionic phosphate base to oxidize tryptamine in a PCET mechanism. The resulting H-bonded indole radical cation intermediate could be intercepted asymmetrically with the persistent radical TEMPO• to produce a closed-shell intermediate. Subsequent cyclization of the pendant amine onto the iminium moiety would generate the desired enantioenriched 3-TEMPO-substituted pyrroloindoline product. Finally, PCET-mediated reduction of TEMPO• to TEMPO-H would regenerate the catalytic components to turn over the cycle.

Figure 4: Proposed catalytic cycle for enantioselective indole PCET reaction.

Initial investigations of the proposed reaction demonstrated its feasibility. Subjecting N'-Me tryptamine to 2 mol% Ru(bpy)₃(BArF)₂ with 20 mol% (R)-TRIP BINOL phosphate and 2 equivalents of TEMPO• under blue light irradiation yielded the desired product in low yield and enantioselectivity (Table 1). Unfortunately, variation in the BINOL phosphate architecture did not improve the efficiency or enantioselectivity of the reaction. However, changing the protecting group had a dramatic effect on the stereochemical outcome with Cbz protection providing the optimal selectivity of 86% ee. Despite extensive
efforts to improve the efficiency of the reaction, at this point, we were unable to achieve yields higher than 20% (Table 2).

![Diagram](image.jpg)

**Table 1**: Effect of BINOL phosphate backbone on enantioselectivity.

We postulated that these poor yields might be due to the in situ generation of TEMPO-H as a stoichiometric byproduct (Figure 5). More specifically, we reasoned that since TEMPO-H is a well-documented substrate for PCET, it is likely sequestering our catalytic reagents in a kinetically dominant, yet unproductive redox cycle.

![Diagram](image2.jpg)

**Figure 5**: Detrimental role of TEMPO-H in the reaction.
Table 2: Optimization of PCET reaction.

As expected, the reaction completely shut down upon addition of 20 mol% TEMPO-H, confirming our hypothesis (Table 2). To combat this issue, we examined the use of sacrificial oxidants that could also serve as terminal proton acceptors to directly obviate the need for TEMPO-H production. Following extensive screening, we found that use of iodonium oxidants with 0.5 mol% Ir(ppy)$_3$ and 5 mol% TRIP BINOL phosphate greatly improved the overall yield with TIPS-EBX providing optimal levels of reaction efficiency and enantioselectivity. More extensive evaluation of solvents confirmed THF to be superior in both yield and enantioselectivity of the reaction (Table 3).

Table 3: Evaluation of solvents in enantioselective TEMPO trapping.

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>73</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>85</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>dioxane</td>
<td>71</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>MTBE</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>61</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>CH$_2$Cl$_2$</td>
<td>77</td>
<td>52</td>
</tr>
</tbody>
</table>

* with 1.2 equivalents of TIPS-EBX
It is worth noting that TIPS-EBX is a poor one-electron oxidant \((E_{p/2} = -1.50 \text{ V vs. } \text{Fc}^+/\text{Fc})\) and it cannot directly engage in electron transfer reactions with \(N'\text{-Cbz tryptamine 1}\). However, one electron reduction of this reagent by the excited state of the \(\text{Ir(ppy)}_3\) photocatalyst \((\E_{1/2} = -2.11 \text{ V vs. } \text{Fc}^+/\text{Fc})\) is facile and liberates a carboxylate base \((\text{vide infra})\) that can serve as a stoichiometric acceptor for the proton liberated during each revolution of the catalytic cycle, negating the formation of TEMPO-H. Further evaluation revealed that H8-TRIP BINOL phosphate was a more selective catalyst, providing the desired product 2 from \(N'\text{-Cbz tryptamine}\) in 93% ee with phosphate loadings as low as 3 mol%. Under the optimized conditions, the reaction was able to be performed in flow on up to 10mmol of starting material with 81% yield and 93% ee.

III. Reaction Scope

Following optimization, we sought to evaluate the scope of this transformation, focusing on the potential for down-stream derivatization of the products (Table 4). We found that the reaction worked well with a variety of different functional groups on the indole ring. In particular, brominated substrates at the C4, C5, and C6 positions (3–5) were well-tolerated as well as C5-borylated and chlorinated substrates (6 & 7), which provide valuable functional handles for subsequent derivatization. Furthermore, the electronic nature of aryl substitution had no deleterious effect, as substrates with both electron-rich and electron-poor functional groups (8 & 9) worked in the reaction with good yield and high enantioselectivities. With respect to limitations, we found that tryptamines bearing substitution at the C2 and C7 (11 & 12) positions were poor substrates in the reaction, which we attribute to disruption of key H-bonding interactions between the phosphate catalyst and radical cation.
IV. Control Reactions and Other Experiments

We performed several control experiments to support the proposed PCET-mediated reactivity. Firstly, reactions conducted in the absence of photocatalyst or light delivered no desired product or conversion of starting material. However, the reaction provided 41% yield of racemic product when phosphate was omitted. We attribute this background reactivity to the in situ formation of a benzoate base following initial reduction of TIPS-EBX ($E_{1/2} = -1.50 \text{ V vs. } \text{Fc}^+/\text{Fc}$) by Ir(ppy)$_3$ ($E_{1/2} = -2.11 \text{ V vs. } \text{Fc}^+/\text{Fc}$). However, despite the possibility of this racemic background reactivity, a highly enantioselective reaction is

Table 4: Substrate scope of enantioselective PCET reaction.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>81%</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>80%</td>
<td>92%</td>
</tr>
<tr>
<td>5</td>
<td>65%</td>
<td>87%</td>
</tr>
<tr>
<td>6</td>
<td>77%</td>
<td>92%</td>
</tr>
<tr>
<td>7</td>
<td>59%</td>
<td>88%</td>
</tr>
<tr>
<td>8</td>
<td>62%</td>
<td>88%</td>
</tr>
<tr>
<td>9</td>
<td>64%</td>
<td>92%</td>
</tr>
<tr>
<td>10</td>
<td>79%</td>
<td>91%</td>
</tr>
<tr>
<td>11</td>
<td>17%</td>
<td>40%</td>
</tr>
<tr>
<td>12</td>
<td>12%</td>
<td>25%</td>
</tr>
</tbody>
</table>

TEMPO-functionalized pyrroloindolines:

- 3: 79%, 90% ee
- 4: 80%, 92% ee
- 5: 65%, 87% ee
- 6: 77%, 92% ee
- 7: 59%, 88% ee
- 8: 62%, 88% ee
- 9: 64%, 92% ee
- 10: 79%, 91% ee
- 11: 17%, 40% ee
- 12: 12%, 25% ee
achieved in the presence of a chiral phosphate catalyst even at very low catalyst loadings, highlighting the strength of non-covalent association between the tryptamine substrate and phosphate.

To further verify that the reaction proceeds through a phosphate-bound indole radical cation, we replaced the indole N–H bond with an N-alkyl group. We expected that this would disrupt both the H-bond coupled electron transfer and the basis for asymmetric induction. As expected, we observed that a tryptamine substrate bearing an N-Me group on the indole nitrogen did not react at all under the standard reaction conditions and was recovered unchanged. This outcome is notable in the fact that the N-alkyl indole is easier to oxidize via direct outer sphere ET than the N–H compound by more than 70mV. Furthermore, since Ir$^{IV}$(ppy)$_3$ ($E_{1/2} = +0.39 \text{ V vs. Fc}^+/\text{Fc}$) is oxidizing enough to convert TEMPO• ($E_{1/2} = +0.33 \text{ V vs. Fc}^+/\text{Fc}$) to its corresponding oxoammonium ion, we sought to confirm that this was not the predominant pathway in our reaction in analogy to recent asymmetric phase transfer work by Toste.$^{49}$ Control experiments wherein a pre-generated oxoammonium salt derived from TEMPO• was added to the reaction provided only trace quantities of product as a racemic mixture, suggesting that this is not the operative pathway for product formation.

Additionally, we evaluated the enantioselectivity of the reaction as a function of photocatalyst oxidation potential (Table 5). Two interesting observations came from this study. First, high enantioselectivity was maintained over a wide range of photocatalyst redox potentials, even when strongly oxidizing catalysts such as Ru(bpz)$_3$Cl$_2$ were employed. Unlike [Ir$^{IV}$(ppy)$_3$]$^+$, this catalyst does not require H-bond pre-association of the phosphate to oxidize the tryptamine en route to radical cation formation. This observation suggests that the rate of ion pairing between the radical cation and the phosphate is faster than TEMPO• trapping and that the productive reaction proceeds exclusively through the phosphate-bound complex even if they are not complexed during the initial electron transfer event. Next, we discovered that the reaction could be effectively mediated by very weakly oxidizing photocatalysts such as

*Ir(ppy)$_2$(dtbbpy)PF$_6$ (*$E_{1/2} = + 0.27$ V vs. Fc$^+$/Fc), wherein a formally 500mV uphill ET is able to take place. Notably, while the more-oxidizing Ir$^{IV}$ species ($E_{1/2} = + 0.83$ V vs. Fc$^+$/Fc) may contribute to this reactivity, we have independently proved that the excited state of Ir(ppy)$_2$(dtbbpy)PF$_6$ is competent in phosphate-mediated oxidation of $N'$-Cbz-tryptamine using Stern-Volmer luminescence quenching experiments (vide infra).

Table 5: Effect of photocatalyst redox potential on enantioselectivity.

<table>
<thead>
<tr>
<th>photocatalyst</th>
<th>$E^0$ (V vs. Fc$^+$/Fc)</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Ir$^{III}$(ppy)$_2$(dtbbpy)PF$_6$</td>
<td>0.27</td>
<td>72</td>
<td>91</td>
</tr>
<tr>
<td>Ir$^{IV}$(ppy)$_3$</td>
<td>0.39</td>
<td>74</td>
<td>93</td>
</tr>
<tr>
<td>*Ir$^{III}$(dF-Me-ppy)$_2$(dtbbpy)PF$_6$</td>
<td>0.58</td>
<td>74</td>
<td>92</td>
</tr>
<tr>
<td>*Ir$^{III}$(dF-CF$_3$-ppy)$_2$(dtbbpy)PF$_6$</td>
<td>0.83</td>
<td>73</td>
<td>93</td>
</tr>
<tr>
<td>*Ru$^{II}$(bpz)$_3$Cl$_2$</td>
<td>1.06</td>
<td>72</td>
<td>93</td>
</tr>
</tbody>
</table>

To better understand the mechanism of iodonium reactivity, we sought to isolate and identify the byproducts formed by TIPS-EBX. Using $^1$H NMR, $^{13}$C NMR and mass spectrometry, compounds 13, 14 and 15 were confirmed to be the major side products (Figure 6). One electron reduction of the iodonium by Ir(ppy)$_3$ is proposed to trigger fragmentation followed by protonation of the benzoate to generate the alkynyl iodide 13 and aromatic carbon-centered radical. This highly reactive radical can readily undergo hydrogen atom transfer from ethereal solvent (THF) to generate benzoic acid 14. Alternatively, the radical can add to the acetylene iodide. A subsequent loss of iodine generates a carbene capable of 1,2- migration to deliver alkynylated benzoic acid 15.
To probe this hypothesis, we tested the effect of TEMPO• concentration on byproduct distribution. TEMPO• is known to be an efficient radical scavenger and can therefore intercept any radicals that are generated in the reduction of iodonium. In support of our hypothesis, increasing concentrations of TEMPO• led to an increase in the yield of alkynyl iodide 13. Furthermore, increasing [TEMPO•] resulted in decreasing yields of 15 (Figure 7). This is consistent with formation of the side product through radical addition to the iodide. Together these results support the proposed mechanism of EBX-iodonium fragmentation.

**Figure 6:** Proposed role of iodonium in PCET reaction.

**Figure 7:** Effect of TEMPO on the distribution of byproducts.
V. Mechanistic Studies

In an effort to observe the formation of a radical species under our conditions, we performed electron paramagnetic resonance (EPR) spectroscopy experiments. Using a 1:1 mixture of indole and (PhO)₂PO₂NBu₄ in the presence of 2 mol% Ru(bpy)₃(BArF)₂ under visible light irradiation, we were able to observe an EPR signal with a g-value of 2.006 indicating the presence of an organic radical (Figure 8). The signal appears as a triplet with hyperfine coupling constant of 15.5 G due to its coupling with the indole nitrogen as ¹⁴N has a nuclear spin of one. Control experiments confirmed that the radical was not formed in the absence of phosphate. Furthermore, the observed EPR spectrum is nearly identical to that of the simulated spectrum, supporting the intermediacy of an indole radical species generated by the joint action of a photocatalytic oxidant and phosphate base.

![EPR spectrum on indole radical intermediate.](image)

**Figure 8:** EPR spectrum on indole radical intermediate.

Seeking to further demonstrate the feasibility of our proposed mechanism, we elected to study the electron transfer step using a series of Stern–Volmer luminescence quenching and cyclic voltammetry (CV) experiments. Under the oxidizing conditions of the catalytic reaction, we expected that the excited-state of the Ir(ppy)₃ photocatalyst (E_{1/2} = –2.11 V vs Fc⁺/Fc) would first be quenched by the TIPS-EBX iodonium reagent (E_{1/2} = –1.50 V vs Fc⁺/Fc) (Figure 9). It is then this ground state IrIV (E_{1/2} = +0.39 V vs. Fc⁺/Fc) that participates in the oxidation of tryptamine, and thus, the electron transfer step cannot be studied directly by excited-state luminescence quenching with Ir(ppy)₃.
Figure 9: Reduction of TIPS-EBX by Ir(ppy)$_3$ to form the more oxidizing Ir$^{IV}$ state.

Instead, we performed quenching experiments with a surrogate photocatalyst [Ir(ppy)$_2$(dtbbpy)]PF$_6$, whose excited state potential ($E_{1/2} = +0.27$ V vs. Fc$^+$/Fc) is close to that of ground state Ir$^{IV}$(ppy)$_3^+$. In these experiments, we determined that the rate of quenching is first order in both base and substrate with no appreciable quenching observed in the case of substrate or phosphate alone (Figure 10). These results suggest electron transfer from the tryptamine is not favorable in the absence of phosphate; however, the experiment does not wholly depict the kinetic picture of the catalytic reaction as it is mediated by a ground state rather than an excited state oxidant.

Figure 10: Stern-Volmer luminescence quenching experiment to support PCET mechanism.
Therefore, based on prior work by Hatice Yayla, we elected to use CV to better probe the thermal electron transfer between tryptamine and Ir\textsuperscript{IV} in support of the proposed PCET mechanism. Specifically, we found that the Ir\textsuperscript{IV/III} redox couple remains reversible in the presence of phosphate or tryptamine alone. However, it becomes irreversible upon addition of phosphate and tryptamine together producing a large catalytic current. This feature can be attributed to the oxidation of Ir\textsuperscript{III} on the surface of the electrode to form Ir\textsuperscript{IV}, followed by oxidation of the tryptamine-phosphate complex in solution by the Ir\textsuperscript{IV} species. The resulting Ir\textsuperscript{III} complex can undergo a subsequent oxidation on the electrode and the cycle is repeated, generating the observed catalytic wave (Figure 11).

![Cyclic voltammetry of PCET oxidation of indole by Ir\textsuperscript{IV}(ppy)\textsubscript{3} and phosphate.](image)

**Figure 11**: Cyclic voltammetry of PCET oxidation of indole by Ir\textsuperscript{IV}(ppy)\textsubscript{3} and phosphate.

Finally, we endeavored to prove that electron transfer from the phosphate-indole complex was favored over oxidation of the unbound indole due to a favorable shift in redox potential upon coordination. To do so, we performed a second set of CV experiments, in which anodic currents were applied to solutions of tryptamine in the presence of varying amounts of phosphate base (Figure 12).
Figure 12: Modulation of indole redox potential through H-bonding interaction.

These studies revealed that a new peak with earlier onset potential was produced upon addition of base, and the resulting current response increased with increasing concentrations of base. Control experiments revealed that scans of either tryptamine or the phosphate base alone were not responsible for these current features. These results are indicative of a mechanism wherein oxidation of the tryptamine-phosphate H-bonded complex is much more facile than the oxidation of either component independently. This redox behavior is characteristic of a PCET process wherein the potential of the substrate is modulated through H-bonding interactions. Increasing concentrations of the phosphate result in a higher equilibrium concentration of the non-covalently associated complex which leads to a higher current of the peak at a less positive potential.

The above mechanistic studies support selective oxidation of the phosphate-indole complex, but they do not provide insight into the nature of hydrogen bonding in the post-PCET complex, and specifically, where the proton lies within this interface. While pKₐ values suggest the intermediacy of an indole radical cation intermediate in the catalytic reaction, we turned to density functional theory (DFT) calculations to support this hypothesis. A relaxed scan [UB3LYP 6-31G+(d, p) CPCM=THF] of the hydrogen bonding coordinate revealed that the proton prefers to remain covalently bound to the indole nitrogen within the
post-PCET complex, supporting the intermediacy of an indole radical cation rather than a neutral radical in the reaction.

**VI. Conclusion**

Herein, we have reported the group’s first enantioselective oxidative PCET reaction, wherein a one-electron oxidant functioned jointly with a chiral phosphate base to furnish an indole radical cation which coupled with the stable nitroxyl radical TEMPO• to form enantioenriched TEMPO-functionalized pyrroloindolines. This transformation represents a rare example of a highly enantioselective reaction of a radical cation intermediate that is mediated entirely by non-covalent interactions. We are optimistic that this report will facilitate future advances in the asymmetric reactions of radical cation intermediates.
Chapter 3: Mesolytic Bond Cleavage of TEMPO-Derived Alkoxyamine Radical Cations

I. Introduction

Carbocations are classical intermediates in organic chemistry that display a wide range of reactivities. Since their discovery in 1901, carbocations have received great attention from the synthetic community for the remarkable chemistry that they can accomplish. However, their use in complex target synthesis and asymmetric catalysis is still limited by the lack of mild and catalytic methods for their generation. Traditional approaches to generate carbocation intermediates require the use of either strong Lewis or Brønsted acids or stoichiometric silver reagents and thus, limit the scope of nucleophiles and functionalities amenable to reaction conditions. Modern methods have employed hydrogen-bonding catalysts such as thioureas to facilitate ionization under much milder conditions and even offer access to asymmetric carbocation chemistries. However, these non-covalent approaches only work for the formation of stabilized carboxcations and often require high catalyst loadings. Therefore, there remains a need to develop strategies for the catalytic generation of carbocations under mild and neutral conditions.

Seeking to address this challenge, we devised a new method to form carbocation intermediates under mild catalytic conditions using mesolytic bond cleavage, wherein a bond in a radical cation is broken to form a carbocation and a radical species. Mesolytic bond cleavage occurs via either a homolytic or heterolytic process (Figure 1) and the favored pathway depends on which group has a higher oxidation potential and forms a more stabilized radical. In our reaction design, we imagined that the use of TEMPO-

derived alkoxyamine radical cations would favor the heterolytic cleavage pathway to generate the stable nitroxyl radical TEMPO• and a carbocation intermediate.

**Figure 1:** Homolytic vs. heterolytic mechanisms of mesolytic bond cleavage.

Although mesolytic bond cleavage is a well-documented mechanism for the generation of reactive intermediates, it has not been exploited for the catalytic generation of carbocations.\(^{54}\) We envisioned that our method could be a general strategy to perform catalytic carbocation chemistry; however, the success of our protocol hinged on whether the central C–O bond could undergo spontaneous scission following one-electron oxidation of the alkoxyamine. In order for bond breaking to occur, we postulated that the strength of the scissile bond in the radical cation must be reduced to near 0 kcal/mol. The degree of bond weakening that accompanies one-electron oxidation can be conveniently calculated using a simple thermodynamic cycle (Figure 2).

---

Figure 2: Thermochemical cycle for bond weakening in mesolytic bond cleavage.

In this scheme, the difference in bond strengths between the neutral substrate and radical cation is equal to the difference between the redox couples of the substrate (R–X/R–X⁺) and dissociated carbocation (R⁺/R•). Since the potential needed for cation reduction is not dependent upon the dissociated radical fragment, the identity of the radical portion can be adjusted to manipulate the strength of the scissile bond in the radical cation. The BDFE of the scissile bond in the radical cation is a function of both the corresponding bond strength and oxidation potential of the neutral starting material. Specifically, decreasing the BDFE of the scissile bond in the starting material, or increasing the potential required for substrate oxidation would lead to a weaker bond in the radical cation intermediate. However, raising the oxidation potential of the substrate limits functional group tolerance while lowering the BDFE decreases the stability of the starting material. Therefore, a fine balance between these two opposing requirements must be made to develop a synthetically useful system.

II. Reaction Design and Optimization

In an effort to find the ideal carbocation precursor, we became interested in using TEMPO-derived alkoxyamines as substrates for mesolytic bond cleavage (Figure 3). Since TEMPO⁺ is a persistent radical, the C–O bonds in TEMPO-derived alkoxyamines are exceptionally weak. For instance, the C–O BDFE in
cumyl alcohol is 81 kcal/mol while the C–O bond in the corresponding TEMPO adduct is only 26 kcal/mol. However, these adducts can be purified by column chromatography and stored for months at room temperature without decomposition. Furthermore, these substrates are oxidized at relatively mild potentials (+0.7 V vs. Fc/Fc⁺) which will not limit nucleophile compatibility.

Figure 3: Using TEMPO-derived alkoxyamines as substrates in mesolytic bond cleavage.

Expanding upon the work described in Chapter 2, our ultimate goal was to derivatize enantioenriched TEMPO-functionalized products into a variety of valuable pyrroloindoline architectures including bioactive natural products (Figure 4). Specifically, we imagined that oxidation of the enantioenriched TEMPO-functionalized pyrroloindolines by an excited state oxidant would yield a transient radical cation intermediate with a C–O bond weak enough to undergo spontaneous scission. Cleavage of this bond would release TEMPO• and reveal a configurationally-biased tertiary pyrroloindoline carbocation able to react with a wide range of nucleophiles to give a variety of enantioenriched C3a-substituted pyrroloindoline products.

---

Using the thermochemical cycle for bond weakening, we calculated the bond strength of the scissile C–O bond for several alkoxyamine radical cations, including the TEMPO-functionalized pyrroloindoline 2. To our delight, the C–O bond strength for 2 was predicted to be weakened by about 20 kcal/mol upon single electron oxidation while styryl-derived alkoxyamine 16 displayed a similar weakening effect of 17 kcal/mol (Figure 5). We imagined that this was sufficient to induce spontaneous C–O bond scission and reveal a transient carbocation species.

**Figure 4:** TEMPO-functionalized pyrroloindolines as a synthetic intermediate for pyrroloindoline natural products.
Figure 5: Bond weakening of C–O bond in alkoxyamine radical cations.

We first opted to evaluate the practicality of C–O bond cleavage in TEMPO-substituted pyrroloindoline radical cations using cyclic voltammetry. In this experiment, we anticipated that anodic oxidation would trigger cleavage of the scissile bond and result in the generation of TEMPO• in situ. We reasoned that this would generate a new reversible peak in the voltammogram corresponding to the redox signature of TEMPO• ($E_{1/2} = + 0.29$ V vs Fc/Fc$^+$ in THF). Indeed, following oxidation of 2 on the initial sweep, a new redox feature appeared which exactly matched that of TEMPO•, confirming scission of the C–O bond in the radical cation (Figure 6).

Figure 6: Cyclic voltammetry of TEMPO-functionalized pyrroloindoline 2.
To assess the feasibility of our hypothesis, we chose to implement our mesolytic cleavage strategy using TEMPO-substituted pyrroloindoline 2 and photoexcited oxidant [Ir(dCF$_3$(Me)ppy)$_2$(dtbbpy)]PF$_6$ (*$E_{1/2}$ = +0.84 V vs Fc/Fc$^+$) with a potassium trans-styrenyl trifluoroborate nucleophile. We imagined that this reaction would proceed via a catalytic cycle initiated with excitation of an iridium photocatalyst by visible light (Figure 7).

**Figure 7:** Proposed catalytic cycle for mesolytic bond cleavage reaction.

This excited state would then remove an electron from the lone pair of the indoline in 2 ($E_{1/2}$ = +0.54 V vs Fc/Fc$^+$) to produce a transient radical cation intermediate. Weakening of the C–O bond in the radical cation will lead to mesolytic bond cleavage to yield a benzylic tertiary pyrroloindoline carbocation intermediate and TEMPO$^*$. Subsequent trapping of the carbocation with the styrenyl trifluoroborate salt would result in C–C bond formation. Coordination of TEMPO$^*$ to BF$_3$ and subsequent reduction of this adduct would produce the desired pyrroloindoline derivative and regenerate the active form of the
Based on prior work, we anticipated that this mesolytic bond cleavage protocol would proceed with complete stereoretention due to the preference for cis configuration about the [5,5] ring system.

Preliminary experiments revealed that subjecting C3a-substituted pyrroloindoline alkoxyamine 2 to [Ir(dCF₃(Me)ppy)₂(dtbbpy)]PF₆ in the presence of potassium trans-styrenyl trifluoroborate provided the desired vinylated product with no loss in optical purity albeit with low efficiency (Table 1). Evaluating different solvents, temperatures, and photocatalysts failed to improve the yields of the reaction. We postulated that the poor mass balance might be due to interaction of the unprotected indoline with Lewis acidic BF₃ generated in situ. Indeed, we found that N-Boc-protected TEMPO-functionalized pyrroloindoline 17 ($E_{1/2} = +0.90 \text{ V vs Fc/Fc}^+$) was a much more competent substrate for the reaction in the presence of a more oxidizing photocatalyst [Ir(dF(CF₃)ppy)₂(4,4′-dCF₃bpy)]PF₆ (*$E_{1/2} = +1.26 \text{ V vs Fc/Fc}^+$), providing 71% yield when performed in MeNO₂ at room temperature.

III. Scope of Mesolytic Bond Cleavage Reaction

With optimized conditions in hand, we explored the scope of our method with respect to the nucleophilic coupling partner, and found that the reaction tolerated a variety of C-, N-, and O- substituted nucleophilic coupling partners (Table 2). In addition to the model styrenyl trifluoroborate nucleophile, naphthyl, phenyl, and 5-indolyl BF₃K salts performed well in the reaction to obtain the corresponding arylated pyrroloindoline products (18–22). Furthermore, silyl nucleophiles such as allyl silanes, silyl enol ethers, and TMS azide were successful in the protocol to construct 23–25. Alcohols, including sterically encumbered tert-butanol, could also be utilized to obtain ethers 26 and 27. Finally, nitrogen-based nucleophiles ortho-iodoaniline and sulfamide functioned in the reaction to produce 28 and 29. Notably, sulfamide pyrroloindoline derivatives are key intermediates in recent work from the Movassaghi group for...
the photochemical coupling of diazene-linked pyrroloindoline dimers. Overall, our mesolytic bond cleavage approach provides a concise route to a variety of enantioenriched C3a-functionalized pyrroloindolines from a common synthetic intermediate.

![Diagram of the reaction](image)

**Table 2**: Substrate scope of mesolytic bond cleavage with pyrroloindoline alkoxyamines.

The utility of this mesolytic bond cleavage protocol has been further demonstrated by Qilei Zhu in the generation of simple secondary and tertiary alkyl carbocations from TEMPO-derived alkoxyamines (Table 3). Similar to the previously described protocol, [Ir(dF(CF3)ppy)2(dCF3-bpy)]PF6 performs one-electron oxidation on a number of alkoxyamines to prompt scission of the central C–O bond and nucleophilic capture by silyl enol ether 30. In acyclic scaffolds, both secondary and tertiary carbocations could be

---

formed to construct a variety of substituted phenyl derivatives 32–42. Allylic carbocations and oxocarbenium ions were also competent in the protocol to provide 43 and 44 in good yields. Even tertiary alkyl carbocations were successfully generated in the reaction as demonstrated by the formation of alkylation products 45 and 46.

![Reaction scheme]

Electrophile scope

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>92%</td>
</tr>
<tr>
<td>32 (R = Me)</td>
<td>89%</td>
</tr>
<tr>
<td>33 (R = i-Pr)</td>
<td>71%</td>
</tr>
<tr>
<td>34 (R = Ph)</td>
<td>84%</td>
</tr>
<tr>
<td>35</td>
<td>92%</td>
</tr>
<tr>
<td>36 (R = Me)</td>
<td>90%</td>
</tr>
<tr>
<td>37 (R = t-Bu)</td>
<td>91%</td>
</tr>
<tr>
<td>38 (R = OMe)</td>
<td>90%</td>
</tr>
<tr>
<td>39 (R = F)</td>
<td>93%</td>
</tr>
<tr>
<td>40 (R = Cl)</td>
<td>75%</td>
</tr>
<tr>
<td>41 (R = Br)</td>
<td>67%</td>
</tr>
<tr>
<td>42</td>
<td>88%</td>
</tr>
<tr>
<td>43</td>
<td>83%</td>
</tr>
<tr>
<td>44</td>
<td>55%</td>
</tr>
<tr>
<td>45</td>
<td>85%</td>
</tr>
<tr>
<td>46</td>
<td>21%a</td>
</tr>
</tbody>
</table>

*GC yield with Ph2O as internal standard.

**Table 3:** Scope of TEMPO-derived alkoxyamine electrophiles.

To evaluate the scope in terms of the nucleophilic component, we used TEMPO-derived alkoxyamine 47 as our model substrate. Upon C–O mesolytic bond cleavage, the resulting benzylic carbocation intermediate could be intercepted with a number of competent carbon nucleophiles including silyl enol ethers, allyl silanes, vinyl trifluoroborate salts to construct structures 48–53 (Table 4). Additionally, 5-fluoroindole was successful in a Friedel-Crafts alkylation to produce 54 with complete regioselectivity.
Nitrogen-centered nucleophiles such as TMS azide, methyl carbamate, tosyl amine, and aniline were also tolerated in the protocol to provide 55–59 in good yields. Secondary and tertiary alcohols were also effective nucleophiles in the reaction to generate hindered ether products 60–61 which are difficult to synthesize by traditional methods. Finally, this method could be extended to intramolecular variants 62 and 63 to construct the corresponding etherification and arylation products.

Table 4: Nucleophile scope in C–O cleavage of secondary benzylic alkoxyamine.

Nitrogen-centered nucleophiles such as TMS azide, methyl carbamate, tosyl amine, and aniline were also tolerated in the protocol to provide 55–59 in good yields. Secondary and tertiary alcohols were also effective nucleophiles in the reaction to generate hindered ether products 60–61 which are difficult to synthesize by traditional methods. Finally, this method could be extended to intramolecular variants 62 and 63 to construct the corresponding etherification and arylation products.
IV. Conclusion

In conclusion, we have developed a new protocol for the catalytic generation of carbocation intermediates that proceeds via one-electron oxidation and subsequent C–O bond cleavage of TEMPO-derived alkoxyamines. This method has been employed in the asymmetric synthesis of a variety of C3a-substituted pyrroloindolines and has also been extended to the formation of secondary and tertiary carbocations. Notably, our mesolytic cleavage strategy differs from prior work in cation generation in that it occurs under Brønsted neutral conditions, enabling the use of a range of acid-sensitive or Lewis basic nucleophiles that might prove incompatible with traditional methods involving acidic or electrophilic activators.
Chapter 4: Asymmetric Total Synthesis of Pyrroloindoline Natural Products

I. Introduction to Pyrroloindoline Natural Products

The pyrroloindoline alkaloids are a large family of natural products that display a myriad of biological activities and molecular architectures. These compounds are found to occur naturally in a variety of different organisms, from bacteria to amphibians. These alkaloids are classical synthetic targets due to their potential as therapeutic agents and the complexity of their structures. The defining feature of this class of natural products is the presence of a hexahydropyrrolo[2,3-b]indole or pyrroloindoline motif, either in monomeric form or as repeating units in polymeric structures. In polymeric compounds, the pyrroloindoline monomers are primarily joined in one of two ways: either through a C3a–C3a’ or a C3a–C7’ linkage (Figure 1). While both types of linkages contain sterically-congested quaternary stereocenters, the C3a-C3a’ type of bond consists of two vicinal quaternary carbon stereocenters, posing a particular challenge for synthesis. Thus, efforts to construct this C3a–C3a’ bond stereoselectively have spanned decades and have utilized a number of different strategies.

In nature, it is proposed that this C3a–C3a’ linkage is constructed via an oxidative dimerization of two tryptamine units (Figure 2a). However, this biosynthetic conclusion arose from a single study performed over 50 years ago, and the enzyme(s) required to perform this stereoselective dimerization remain(s) unknown. In this biosynthetic study, Kirby synthesized tryptamine derivatives radiolabeled with $^{14}$C and $^{3}$H and separately fed these compounds to Chimonanthus fragrans plants (Figure 2b).

---

The dimeric alkaloid chimonanthine was then extracted from the leaves after seven days, and the incorporation of radioactivity was measured. An 11.1% incorporation of radiolabeled tryptamine was observed while radiolabeled tryptophan and N'-Me tryptamine showed 3.6% and 0.1% incorporation, respectively. The low incorporation of the latter compound was postulated to result from its poor solubility in aqueous feeding solutions. The main finding in this study was that the tritium label was retained at the C2 position, confirming that tryptamines rather than oxindoles are the biosynthetic precursors of chimonanthine. Therefore, the biosynthetic pathway for chimonanthine was proposed to begin with...
decarboxylation of tryptophan by tryptophan decarboxylase (TDC) followed by methylation of the primary amine by \(N\)-methyltransferase (NMT) and the key dimerization step. Recent preliminary studies from the Britton lab suggest that the enzyme responsible for this challenging transformation is a dirigent protein within the cell walls of *Chimonanthus praecox*, but they were unable to isolate it.\(^{67}\)

---

\(^{67}\) Hur, S. Studies Toward the Biosynthesis of Chimonanthine in *Chimonanthus praecox*. MSc. Thesis, Simon Fraser University, Burnaby, BC, Canada, 2016.
Further support for this biosynthetic hypothesis comes from synthetic work by Scott in 1964 which relies on an oxidative radical-radical coupling mechanism (Figure 2c). In this one step procedure, exposure of N’-Me-tryptamine to methyl magnesium iodide forms the magnesium salt which is then oxidized with iron (III) chloride to generate the radical intermediate. Subsequent radical-mediated dimerization provides racemic chimonanthine, albeit with low yields and diastereoselectivity. Since this initial synthetic report, there have been many efforts to form pyrroloindoline products in a much more concise and selective manner. Notably, the first asymmetric synthesis of (–)-chimonanthine was accomplished by Overman and coworkers, wherein a diastereoselective intramolecular Heck cascade enabled the rapid construction of vicinal quaternary stereocenters (Figure 3).

Figure 3: Overman’s asymmetric synthesis of (–)-chimonanthine.

An alternative approach was later demonstrated by Movassaghi in which a radical-mediated reductive coupling furnished the central C3a–C3a’ bond of dimeric pyrroloindoline products (Figure 4a). Specifically, the key step in this route was reduction of C3a-brominated monomers by Co(PPh3)3Cl to provide enantioenriched pyrroloindoline radicals and subsequent radical-radical coupling to afford the

---

chimonanthine skeleton. This approach relies on a chiral pool strategy in which the chirality of tryptophand-derived starting materials furnishes stereoselectivity in the subsequent steps. Stephenson used an analogous photoredox-mediated strategy to unite an indole fragment with a C3a-brominated pyrroloindoline monomer in the synthesis of (+)-gliocladin C. In this mechanism, the excited state of Ru(bpy)_3Cl_2 was first quenched by a sacrificial amount of Et_3N to furnish the more reducing RuI state which served as the reductant for the tertiary benzylic bromide (Figure 4b).^{71}

![Figure 4: Radical-mediated pathways to pyrroloindoline natural products.](image)

While the aforementioned reductive radical-radical coupling protocol provides a concise route to homodimeric and arylated scaffolds, it is insufficient for the selective synthesis of heterodimeric variants such as (–)-calycanthidine. As such, Movassaghi and coworkers have developed a second-generation radical-mediated strategy that is amenable to heterodimeric couplings (Figure 5).^{72} Specifically, they designed a photolabile intermediate that possesses two non-identical pyrroloindoline units linked by a diazene fragment. Irradiation with UV light expels dinitrogen and leads to selective heterocoupling of the resulting enantioenriched monomeric radicals. The selectivity for heterodimerization is proposed to arise from the reaction taking place within a solvent cage. While this critical step enabled the first reported

---

asymmetric synthesis of (–)-calycanthidine, the overall synthetic sequence still requires 18 total chemical steps (13 steps longest linear sequence).\(^{73}\)

![Chemical structure and reaction scheme]

**Figure 5:** Movassaghi’s synthesis of heterodimeric pyrroloindoline architectures.

Seeking a more modular approach to the synthesis of these classical dimeric products, we hypothesized that the use of our mesolytic bond cleavage protocol could generate a pyrroloindoline carbocation which could then be intercepted by a tryptamine nucleophile to forge the central C3α–C3α’ bond (Figure 6). We imagined that this strategy would be advantageous for the formation of unsymmetrical dimers in which the substitution patterns on the four peripheral nitrogens differ. To put this approach in context, Movassaghi and co-workers have elegantly utilized an Ag-mediated ionization of related bromo-substituted pyrroloindolines to trap aryl boron nucleophiles in the synthesis of (+)-naseseazines A and B.\(^ {74,75}\) However, this key step did not have any diastereoselectivity requirements since the carbocation was reacting with an aryl nucleophile. Therefore, the key question in our proposal was whether we could set the relative configuration about the vicinal quaternary carbon stereocenters in C–C bond formation using a prochiral nucleophile.


III. Asymmetric Synthesis of (–)-calycanthidine

With this proposal in mind, we first aimed to use our method in the construction of heterodimeric alkaloid (–)-calycanthidine. This natural product exhibits local $C_2$ symmetry at the bisquaternary centers, but possesses a methyl group on one of the two indoline nitrogens which breaks the overall symmetry of the structure. As mentioned previously, enantioselective syntheses of calycanthidine are arduous compared to its homodimeric counterpart (–)-chimonanthine. However, our proposed synthetic route using oxidative PCET and trapping of TEMPO• followed by mesolytic bond cleavage would access (–)-calycanthidine in just four chemical steps from $N'$-Cbz-tryptamine.

Specifically, similar to our previous mesolytic bond cleavage studies, we imagined that our model TEMPO-functionalized pyrroloindoline 2 ($E_{\text{ep}} = + 0.92$ V vs SCE) would undergo one-electron oxidation by the excited state of $[\text{Ir(}d\text{CF}_3\text{(Me)}\text{ppy})_2(dtbbpy)]PF_6$ ($E_{\text{i/2}} = + 1.22$ V vs SCE). The resulting radical cation would undergo spontaneous C–O scission to form a transient carbocation that could be trapped by $N$-Me-$N'$-Cbz-tryptamine to afford the heterodimeric framework. When we initially performed this reaction in THF, we obtained moderate yield of the desired product; however, the reaction proceeded with no diastereoselectivity (Table 1). Subsequent evaluation of solvent and temperature provided little improvement in the stereoselectivity, prompting us to evaluate an alternative approach: $N$-methylolation of

---

the electrophilic component which could be accomplished in excellent yields using methyl iodide and NaHMDS in THF. Using this methylated version of the TEMPO-trapped pyrroloindoline (64) \(E_{1/2} = +0.81\) V vs SCE) with \(N^\prime\text{-Cbz}\) tryptamine and \([\text{Ir}(\text{dCF}_3\text{(Me)}\text{ppy})_2(\text{dtbbpy})]\text{PF}_6\), we were able to accomplish higher diastereoselectivities albeit with low yield. After further exploration, we found that lowering the reaction temperature and adding 1 equivalent of trifluoroacetic acid achieved high diastereoselectivity and good yield. Notably, a time course of this reaction was performed monitoring both yield and diastereomeric ratio by \(^1\text{H}\) NMR which indicated that high dr is maintained over the course of the reaction but yield begins to erode after full consumption of the starting material, presumably due to oxidative decomposition of the product (Figure 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>solvent</th>
<th>additive</th>
<th>temp</th>
<th>% yield</th>
<th>dr ((C_2) meso)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>THF</td>
<td>—</td>
<td>rt</td>
<td>21</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>THF</td>
<td>—</td>
<td>-40°C</td>
<td>10</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>H</td>
<td>CH(_2)Cl(_2)</td>
<td>—</td>
<td>rt</td>
<td>48</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>H</td>
<td>CH(_2)Cl(_2)</td>
<td>—</td>
<td>-40°C</td>
<td>30</td>
<td>14:1</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>H</td>
<td>CH(_2)Cl(_2)</td>
<td>TFA (1 equiv)</td>
<td>-40°C</td>
<td>71</td>
<td>14:1</td>
</tr>
</tbody>
</table>

**Table 1:** Optimization of heterodimerization reaction.
Figure 7: Time course of heterodimerization reaction in cryocool (blue) or dewar (red).

With optimal conditions in hands, we performed the heterodimerization on a 2 mmol scale to provide 71% isolated yield of the desired product as a 13:1 mixture of diastereomers. Subsequent reduction of Cbz-protected intermediate 65 with Red-Al afforded the desired heterodimeric natural product (–)-calycanthidine (66) in 43% overall yield over 4 steps from N’-Cbz tryptamine (Figure 8).

Figure 8: Asymmetric synthesis of (–)-calycanthidine.
IV. Asymmetric Synthesis of (−)-chimonanthine

Next, we sought to adapt the aforementioned protocol to the synthesis of the homodimeric (−)-chimonanthine. Analogous to the calycanthidine system, oxidation of pyrroloindoline-derived alkoxyamine 2 ($E_{1/2} = +0.92$ V vs SCE) by the excited state of an iridium photocatalyst would provide a pyrroloindoline carbocation that could be trapped by $N'$-protected tryptamine to form symmetrical dimer 67. Upon evaluation of a variety of protecting groups on the tryptamine nucleophile, we found that Cbz provided the best diastereoselectivity albeit with just 2:1 dr favoring the desired $C_2$ isomer (Table 2, Entries 1–4). The diastereoselectivity and efficiency did not improve in other solvents, and the selectivity actually reversed when the reaction was performed in toluene (Table 2, Entries 5–6). Lowering the temperature of the reaction led to a slight improvement in diastereoselectivity albeit with a decrease in efficiency (Table 2, Entries 7–8). As in the previous heterodimerization reaction, addition of 3 equivalents of trifluoroacetic acid boosted the efficiency of the reaction (Table 2, Entry 9). However, the diastereoselectivity of the homodimerization was incredibly variable, ranging from 3:1 to >20:1, sometimes even within a group of reactions that were set up under seemingly identical conditions!
In an effort to better understand the underlying reason for this inconsistency in diastereoselectivity, we performed a variety of different experimental and computational studies. The most important discovery in this foray was that the dr of the reaction increased over time, and the enrichment process required both a photocatalyst and an air atmosphere (Figure 9).

Table 2: Optimization of homodimerization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>solvent</th>
<th>additive</th>
<th>temp</th>
<th>% yield</th>
<th>dr (C$_2$:meso)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO$_2$Me</td>
<td>THF</td>
<td>—</td>
<td>rt</td>
<td>52</td>
<td>1.6:1</td>
</tr>
<tr>
<td>2</td>
<td>Boc</td>
<td>THF</td>
<td>—</td>
<td>rt</td>
<td>31</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>Ts</td>
<td>THF</td>
<td>—</td>
<td>rt</td>
<td>48</td>
<td>1:2</td>
</tr>
<tr>
<td>4</td>
<td>Cbz</td>
<td>THF</td>
<td>—</td>
<td>rt</td>
<td>45</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>Cbz</td>
<td>toluene</td>
<td>—</td>
<td>rt</td>
<td>13</td>
<td>1:2.2</td>
</tr>
<tr>
<td>6</td>
<td>Cbz</td>
<td>CH$_2$Cl$_2$</td>
<td>—</td>
<td>rt</td>
<td>51</td>
<td>1:1</td>
</tr>
<tr>
<td>7</td>
<td>Cbz</td>
<td>THF</td>
<td>—</td>
<td>-40 °C</td>
<td>28</td>
<td>2.8:1</td>
</tr>
<tr>
<td>8</td>
<td>Cbz</td>
<td>THF</td>
<td>—</td>
<td>-40 °C</td>
<td>26</td>
<td>3:1</td>
</tr>
<tr>
<td>9</td>
<td>Cbz</td>
<td>THF</td>
<td>TFA (3 equiv)</td>
<td>-40 °C</td>
<td>40–60</td>
<td>3:1 to &gt;20:1</td>
</tr>
</tbody>
</table>

Table 2: Optimization of homodimerization.
Figure 9: $^1$H NMR analysis of homodimer diastereoenrichment.

Initially, we hypothesized that a dynamic resolution might be responsible for the enrichment, wherein oxidation of the product could lead to mesolytic cleavage of the sterically encumbered central C–C bond to afford a carbocation and radical intermediate. The carbocation could then be trapped by exogenous tryptamine nucleophile to reform the homodimeric product with preference for the C$_2$ isomer. However, this possibility was ruled out due to several computational and experimental findings. First, the quaternary-quaternary bond of the C$_2$ and meso radical cations exhibit bond strengths of 21 kcal/mol and 22 kcal/mol (UB3LYP/6-31G+, CPCM = THF), respectively, which is rather high for spontaneous scission. Furthermore, the yield and optical purity of the major diastereomer remains constant throughout the enrichment process. Also, when this enrichment reaction was carried out in the presence of an exogenous $N^\alpha$-CO$_2$Me tryptamine nucleophile, no crossover products were observed. Therefore, we proposed a simple resolution process in which the meso isomer is selectively destroyed via an oxidative decomposition.
pathway to provide high diastereoenrichment favoring the $C_2$-symmetric product. Unfortunately, despite extensive efforts, none of the complex mixture of meso degradation byproducts could be identified.

In this proposal, we questioned the origin of selectivity for decomposition of the meso diastereomer. Although non-intuitive, we wondered whether the two diastereomeric isomers exhibited different redox properties and, therefore, varying rates of one-electron oxidation by the photocatalyst. However, cyclic voltammetry experiments revealed that the potential for oxidation of the $C_2$ isomer is only 20 mV higher than that of the meso (Figure 10).

![Cyclic voltammograms of meso and $C_2$ diastereomers of homodimer.](image)

**Figure 10:** Cyclic voltammograms of meso and $C_2$ diastereomers of homodimer.

Furthermore, Stern-Volmer quenching studies showed that there is no significant difference in the quenching slope between the two isomers (Figure 11). Therefore, while the selectivity for meso degradation is likely not due to the oxidation step in the decomposition pathway, the exact origin of selectivity remains unknown.
Figure 11: Stern-Volmer quenching of meso vs. C2 diastereomers of homodimer.

Using this diastereoenrichment step in our synthesis, we were able to obtain (–)-chimonanthine selectively from N’-Cbz tryptamine in 4 chemical steps. The synthetic sequence proceeded via initial homodimerization using our mesolytic cleavage protocol to generate the desired product in 54% yield as a 3:1 mixture of diastereomers (C2:meso). The aforesaid diastereocorrection procedure was then utilized to obtain the natural product precursor as a single diastereomer. The intermediate was then subjected to excess Red-Al to deliver (–)-chimonanthine in 24% overall yield (Figure 12).
V. Formal Synthesis of (–)-psychotriasine

Finally, we recognized our method could provide concise access to the C3a-N’ linkage found in psychotriasine, psychotrimine, and psychopentamine. Therefore, we adapted our method to the synthesis of the dimeric natural product (–)-psychotriasine. Using the unprotected TEMPO-functionalized pyrroloindoline 2 with [Ir(dCF$_3$(Me)ppy)$_2$(dtbbpy)]PF$_6$ in MeNO$_2$, we were able to efficiently trap ortho-iodoaniline to produce N-aryl pyrroloindoline 69. As developed by Baran in the synthesis of psychotrimine, this iodoaniline intermediate was then subjected to a Larock annulation with alkyne 70 to furnish the desired natural product scaffold.

Finally, reduction of the carbamate protecting groups with Red-Al delivers (–)-psychotriasine (71) in four chemical steps from N’-Cbz tryptamine in 38% overall yield (Figure 13).

---

**VI. Conclusion and Future Directions**

In brief, we have developed a new protocol for the asymmetric synthesis of pyrroloindoline natural products that proceeds via sequential reactions of catalytically generated radical cation intermediates. Specifically, we were able to accomplish the stereoselective syntheses of (–)-calycanthidine, (–)-chimonanthine, and (–)-psychotriasine in only four chemical steps. Notably, our route provides remarkably concise access to challenging heterodimeric structures with the synthesis of (–)-calycanthidine being the shortest reported to date. We anticipate that this synthetic method will greatly advance the synthesis of more complex higher-order pyrroloindoline alkaloids.
Appendix A

Supporting Information

for

Chapter 2

Development of an Asymmetric Proton-Coupled Electron Transfer Reaction to Form Enantioenriched TEMPO-Functionalized Pyrroloindolines

Table of Contents

I. Synthesis and characterization of starting materials
II. Synthesis and characterization of products
III. Photochemical reaction setup
IV. Stern-Volmer Luminescence Quenching Studies
V. Cyclic Voltammetry Studies
VI. DFT Calculations
VII. $^1$H and $^{13}$C NMR Spectra
VIII. HPLC traces
Synthesis of H8-TRIP BINOL Phosphate Base

H8-TRIP BINOL phosphoric acid was synthesized according to a previously reported method.\textsuperscript{78}

To a solution of (S)-H8-TRIP BINOL phosphoric acid (1 g, 1.328 mmol, 1 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (0.5 M) was added 1 M tetrabutylammonium hydroxide solution in MeOH (1.328 mL, 1.328 mmol, 1 equiv).\textsuperscript{79} The resulting solution was allowed to stir at rt for 30 min then concentrated \textit{in vacuo} to yield (S)-H8-TRIP BINOL phosphate (1.29 g, 1.297 mmol, 98% yield) as a slightly off-white solid.

General procedure for the synthesis of tryptamine derivatives (GP1):

4-Br, 5-Br, and 6-Br tryptamines were synthesized according to literature procedure and characterization data is consistent with reported data.\textsuperscript{80}

5-Cl, 5-OMe, and 5-Me tryptamine hydrochloride salts are commercially available and were used as the free base.

A 25-mL round bottom flask was charged with N,N-dimethyl-2-nitroethenamine (1.458 g, 12.56 mmol, 1.1 equiv) and methyl 1H-indole 5-carboxylate (2 g, 11.42 mmol, 1 equiv). To the resulting slurry was added trifluoroacetic acid (11.42 mL, 1 equiv) at room temperature. The reaction was allowed to stir at rt for 2 h then the reaction was slowly quenched with sat. aqueous NaHCO₃ solution. The aqueous mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to yield the crude product as a bright yellow solid which was used without further purification.

To a stirred slurry of NaBH₄ (3 equiv) in THF/MeOH (4:1) was slowly added the nitroalkene. The mixture was stirred overnight at room temperature then neutralized with 1 M HCl and extracted with ethyl acetate (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using 5-15% EtOAc in hexanes to afford methyl 3-(2-nitroethyl)-1H-indole-5-carboxylate as a light yellow solid.

**Methyl 3-(2-nitroethyl)-1H-indole-5-carboxylate**: IR (thin film): 3335, 1693, 1677, 1551, 1430, 1284, 1247, 1113, 766, 747 cm⁻¹; °H NMR (500 MHz, CDCl₃) δ 8.34 (s, 1H), 8.30 (s, 1H), 7.94 (dd, J = 8.6, 1.6 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 4.69 (t, J = 7.0 Hz, 2H), 3.95 (s, 3H), 3.52 (t, J = 7.1 Hz, 2H); °C NMR (126 MHz, CDCl₃) δ 168.10, 138.92, 126.45, 124.11, 124.05, 122.16, 121.24,
111.67, 111.28, 75.73, 52.14, 23.45. HRMS (ESI) exact mass calculated for [M+Na]$^+$ \((\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_4)\) requires \(m/z\) 271.06948, found 271.06901 with a difference of 0.31 ppm.

**General procedure for the Cbz protection of tryptamines (GP2):**

![General procedure for the Cbz protection of tryptamines (GP2)](image)

To a solution of tryptamine (1 equiv) in dichloromethane (0.1 M) was added a saturated aqueous solution of \(\text{NaHCO}_3\) (5 equiv). The suspension was vigorously stirred and freshly distilled benzyl chloroformate (1.1 equiv) was added. The mixture was allowed to stir at rt for 2 h then the phases were separated and the aqueous phase extracted with dichloromethane (3x). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The crude product was purified by flash column chromatography on silica gel using ethyl acetate and hexanes.

**Benzyl (2-(1H-indol-3-yl)ethyl)carbamate**

The title compound was synthesized according to general procedure \textbf{GP2} and purified on silica gel using a gradient of 10\% ethyl acetate/hexanes to 30\% ethyl acetate/hexanes to yield product as a white solid (92\% by column chromatography, 79\% by recrystallization). IR (neat): 3409, 3328, 3059, 2939, 1696, 1619, 1517, 1455, 1436, 1338, 1245, 1227, 1135, 1081, 1045, 1008, 741, 697 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.60 (d, $J = 7.9$ Hz, 1H), 7.39 – 7.29 (m, 6H), 7.21 (t, $J = 7.3$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.01 (s, 1H), 5.10 (s, 2H), 4.82 (s, 1H), 3.55 (q, $J = 6.5$ Hz, 2H), 2.99 (t, $J = 6.8$ Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.37, 136.62, 136.36, 128.52, 128.14, 128.10, 127.26, 122.23, 122.06, 119.51,

---

118.77, 112.90, 111.20, 66.60, 41.25, 25.74.; HRMS (ESI) exact mass calculated for [M+H]+ (C18H19N2O2) requires m/z 295.14411, found m/z 295.14388 with a difference of 0.75 ppm. Spectral data is in agreement with the reported literature values. 81

Benzyl (2-(4-bromo-1H-indol-3-yl)ethyl)carbamate

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as an off-white solid (72% yield). IR (thin film): 3419, 3309, 3063, 3034, 2940, 1694, 1517, 1424, 1334, 1243, 1184, 1137, 1041, 911, 773, 737, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.35 (s, 1H), 7.38 – 7.29 (m, 5H), 7.26 (t, J = 8.0 Hz, 2H), 7.04 – 6.87 (m, 2H), 5.10 (s, 2H), 4.98 – 4.56 (m, 0.85 H, major rotamer), 4.65 (s, 0.15 H, minor rotamer) 3.57 (q, J = 6.7 Hz, 2H), 3.20 (t, J = 7.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 156.61, 137.84, 136.72, 128.63, 128.21, 128.20, 125.38, 124.30, 124.05, 122.97, 114.25, 113.60, 110.79, 66.73, 42.61, 26.57; HRMS (ESI) exact mass calculated for [M+H]+ (C18H18BrN2O2) requires m/z 373.05462, found m/z 373.05496 with a difference of 0.92 ppm.

Benzyl (2-(5-bromo-1H-indol-3-yl)ethyl)carbamate

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as a white solid (84%). IR (thin film): 3422, 3319, 3033, 2940, 1698, 1519, 1456, 1250, 1137, 1094, 1043, 884, 795, 776,
746, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (s, 1H), 7.71 (s, 1H), 7.39 – 7.29 (m, 5H), 7.28 (dd, J = 8.6, 1.9 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 5.10 (s, 2H), 4.81 (br s, 0.88 H, major rotamer), 4.58 (br s, 0.12 H, minor rotamer), 3.51 (q, J = 6.6 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 156.48, 136.66, 135.06, 129.23, 128.67, 128.29, 128.27, 125.18, 123.41, 121.50, 112.92, 112.79, 66.83, 41.33, 25.70. HRMS (ESI) exact mass calculated for [M+H]⁺ (C₁₈H₁₇BrN₂O₂) requires m/z 373.05462, found m/z 373.05436 with a difference of 0.69 ppm.

Benzyl (2-(6-bromo-1H-indol-3-yl)ethyl)carbamate

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as a light tan solid (92% yield). IR (thin film): 3420, 3319, 3033, 2940, 1696, 1518, 1455, 1333, 1244, 1136, 1048, 895, 802, 775, 741, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (s, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.20 (d, J = 8.3 Hz, 1H), 6.95 (s, 1H), 5.10 (s, 2H), 4.84 (s, 1H), 3.51 (q, J = 6.6 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 156.52, 137.22, 136.63, 128.67, 128.28, 128.25, 126.35, 122.87, 122.75, 120.10, 115.83, 114.26, 113.19, 66.80, 41.40, 25.72. HRMS (ESI) exact mass calculated for [M+H]⁺ (C₁₈H₁₈BrN₂O₂) requires m/z 373.05462, found m/z 373.05441 with a difference of 0.55 ppm.

Benzyl (2-(5-chloro-1H-indol-3-yl)ethyl)carbamate
The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as an off-white solid (91% yield). IR (thin film): 3422, 3319, 2939, 1696, 1517, 1458, 1243, 796, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H), 7.41 – 7.29 (m, 5H), 7.26 (d, J = 8.6 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 6.99 (s, 1H), 5.11 (s, 2H), 4.85 (br s, 0.88 H, major rotamer), 4.63 (br s, 0.12 H, minor rotamer), 3.51 (q, J = 6.6 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 156.51, 136.62, 134.78, 128.66, 128.53, 128.26, 128.24, 125.32, 123.60, 122.57, 118.34, 112.74, 112.36, 66.82, 41.33, 25.68; HRMS (ESI) exact mass calculated for [M+H]+ (C₁₈H₁₈ClN₂O₂) requires m/z 329.10541, found m/z 329.10514 with a difference of 0.86 ppm.

**Benzyl (2-(5-methoxy-1H-indol-3-yl)ethyl)carbamate**

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as a light brown oil (84% yield). IR (thin film): 3338, 2941, 1697, 1516, 1485, 1454, 1214, 1173, 1027, 796, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.33 (s, 1H), 7.46 – 7.32 (m, 5H), 7.26 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.98 – 6.85 (m, 2H), 5.17 (s, 2H), 5.11 – 5.02 (m, 0.85H, major rotamer), 4.85 (s, 0.15H, minor rotamer), 3.89 (s, 3H), 3.57 (q, J = 6.6 Hz, 2H), 2.97 (q, J = 13.5, 10.2 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 156.53, 153.97, 136.62, 131.60, 128.56, 128.14, 128.12, 127.67, 123.02, 112.38, 112.33, 112.09, 100.49, 66.66, 55.92, 41.32, 25.75; HRMS (ESI) exact mass calculated for [M+H]+ (C₉H₂₁N₂O₃) requires m/z 325.15517, found m/z 325.15467 with a difference of 1.55 ppm.
Methyl 3-((benzyloxy)carbonyl)amino)ethyl)-1H-indole-5-carboxylate

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 20% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as a white solid (89% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.50 (s, 1H), 7.90 (dd, \(J = 8.6, 1.6\) Hz, 1H), 7.39 – 7.27 (m, 6H), 5.10 (s, 2H), 4.89 (br s, 0.88 H, major rotamer), 4.65 (br s, 0.12 H, minor rotamer), 3.92 (s, 3H), 3.54 (q, \(J = 6.6\) Hz, 2H), 2.99 (t, \(J = 6.9\) Hz, 2H). \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.30, 156.53, 139.07, 136.63, 128.63, 128.23, 128.19, 127.05, 123.65, 123.53, 121.79, 121.57, 114.39, 111.07, 66.79, 52.03, 41.36, 25.66. HRMS (ESI) exact mass calculated for [M+Na\(^+\)] (C\(_{20}\)H\(_{20}\)N\(_2\)O\(_4\)) requires \(m/z\) 375.13208, found \(m/z\) 375.13181 with a difference of 0.79 ppm.

Benzyl (2-(5-methyl-1H-indol-3-yl)ethyl)carbamate

The title compound was synthesized according to general procedure GP2 and purified on silica gel using a gradient of 10% ethyl acetate/hexanes to 30% ethyl acetate/hexanes to yield product as an off-white solid (93% yield). IR (thin film): 3405, 3329, 2925, 1695, 1514, 1454, 1243, 1226, 1133, 793, 735, 696 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.88 (s, 1H), 7.31 – 7.19 (m, 6H), 7.15 (d, \(J = 7.8\) Hz, 1H), 6.94 (dd, \(J = 8.3, 1.6\) Hz, 1H), 6.85 (s, 1H), 5.02 (s, 2H), 4.76 (s, 0.85 H, major rotamer), 4.54 (s, 0.15 H, minor rotamer), 3.45 (q, \(J = 6.6\) Hz, 2H), 2.86 (t, \(J = 6.8\) Hz, 2H), 2.36 (s, 3H); \(^1\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 156.50, 136.73, 134.82, 128.81, 128.63, 128.22, 128.20, 127.57, 123.89, 122.39, 118.50, 112.36, 111.01, 66.71, 41.36, 25.82, 21.63; HRMS (ESI) exact mass calculated for [M+H\(^+\)] (C\(_{20}\)H\(_{21}\)N\(_2\)O\(_2\)) requires \(m/z\) 309.15976, found \(m/z\) 309.15974 with a difference of 0.04 ppm.
Benzyl (2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1\textit{H}-indol-3-yl)ethyl)carbamate

Preparation of the title compound was adapted from the synthesis of a similar compound. A 50-mL round bottom flask was charged with benzyl (2-(5-bromo-1\textit{H}-indol-3-yl)ethyl)carbamate (650 mg, 1.74 mmol, 1 equiv), XPhos Pd G3 (73.7 mg, 0.087 mmol, 0.05 equiv), XPhos (125 mg, 0.261 mmol, 0.15 equiv), bis(pinacolato)diboron (1.33 g, 5.22 mmol, 3 equiv), and tribasic potassium phosphate (1.11 g, 5.22 mmol, 3 equiv). The vessel was then evacuated and backfilled with argon three times. Degassed anhydrous DMSO (17.4 mL) was then added to the flask and the resulting mixture was stirred at 60 °C for 2 h. The resulting black solution was then allowed to cool to rt, diluted with ethyl acetate, and washed with sat. aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The resulting crude residue was purified on silica gel using a gradient of 10% ethyl acetate/hexanes to 20% ethyl acetate/hexanes to yield product as a pale yellow solid (590 mg, 81% yield). IR (thin film): 3329, 2978, 1702 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.45 (s, 1H), 7.66 (dd, J = 8.2, 1.1 Hz, 1H), 7.38 – 7.27 (m, 6H), 6.95 (s, 1H), 5.09 (s, 2H), 4.88 (t, J = 6.1 Hz, 0.85H), 4.72 (s, 0.15H), 3.52 (q, J = 6.5 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H), 1.37 (s, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.50, 138.59, 136.76, 128.61, 128.52, 128.22, 128.17, 127.07, 126.53, 122.29, 120.38, 113.51, 110.79, 83.62, 75.17, 66.71, 41.29, 25.02, 24.99; HRMS (ESI) exact mass calculated for [M+H]$^+$ (C$_{24}$H$_{30}$BN$_2$O$_4$) requires m/z 421.22931, found m/z 421.22912 with a difference of 0.46 ppm.

---

Benzyl (2-(1-methyl-1H-indol-3-yl)ethyl)carbamate

An acetone solution (0.33M) of N’-Cbz tryptamine was cooled to 0 ºC and powdered potassium hydroxide (5 equiv) was added to the solution. After 10 min, MeI (1.1 mmol) was added with vigorous stirring and the reaction was allowed to stir at room temperature for 30 min. After this time, the same amount of KOH and MeI were added again and the reaction was allowed to stir at room temperature overnight. Benzene was added and the mixture was filtered through Celite to remove all insoluble salts. The solution was concentrated in vacuo and purified on silica gel using 10-20% EtOAc/hexanes to yield the product as a clear oil in 89% yield.\textsuperscript{83} IR (thin film): 3338, 3054, 2937, 1702, 1513, 1238, 1213, 1131, 733, 696 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.59 (d, J = 7.9 Hz, 1H), 7.41 – 7.29 (m, 6H), 7.25 – 7.21 (m, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.87 (s, 1H), 5.11 (s, 2H), 4.92 – 4.56 (m, 1H), 3.74 (s, 3H), 3.54 (q, J = 6.5 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 156.46, 137.23, 136.76, 128.64, 128.27, 128.21, 127.79, 121.86, 119.04, 118.98, 111.36, 109.41, 66.70, 41.52, 32.77, 25.74; HRMS (ESI) exact mass calculated for [M+H]\textsuperscript{+} (C\textsubscript{19}H\textsubscript{21}N\textsubscript{2}O\textsubscript{3}) requires m/z 309.15976, found m/z 309.15935 with a difference of 1.3 ppm.

General procedure for the synthesis of TEMPO-functionalized pyrroloindoline products:

0.5 mmol batch reaction (GP3): N'-Cbz tryptamine (147 mg, 0.5 mmol, 1.0 equiv), Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol, 0.5 mol%), H-8 TRIP BINOL phosphate (15 mg, 0.015 mmol, 3 mol%), TEMPO (156 mg, 1 mmol, 2 equiv), TIPS-EBX iodonium (321 mg, 0.75 mmol, 1.5 equiv) were added to a 20-mL vial equipped with a magnetic stirbar. Anhydrous THF (10 mL) was then added and the reaction mixture was irradiated in a blue LED dish setup (see Figure S2) for 12h. After completion, the solvent was removed by rotary evaporation to give a crude residue that was further purified on silica gel in 2-5% EtOAc/hexanes with 1% added Et$_3$N.

10mmol flow reaction (GP4): To a 250-mL round bottom flask was added N-Cbz tryptamine (2.94 g, 10 mmol, 1.0 equiv), Ir(ppy)$_3$ (33 mg, 0.05 mmol, 0.5 mol%), H-8 TRIP BINOL phosphate (301 mg, 0.3 mmol, 3 mol%), TEMPO (3.12 g, 20 mmol, 2 equiv) and TIPS-EBX iodonium (6.43 g, 15 mmol, 1.5 equiv) followed by addition of anhydrous THF (200 mL). The reaction was pumped through the irradiated reactor (see Figure S1) at room temperature ($t_r = 7$ min, 0.5 mmol/h). The solvent was then removed by rotary evaporation to give a crude residue that was further purified on silica gel in 2-5% EtOAc/hexanes with 1% added Et$_3$N.
Benzyl (3aS,8aR)-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy) 3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using GP4, the title compound was obtained as a white solid (3.63 g, 81% yield). The material was determined to be 93% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, t<sub>r</sub> (minor) = 9.1 min, t<sub>r</sub> (major) = 10.2 min]. IR (thin film): 3356, 2932, 1700, 1611, 1469, 1417, 1355, 1300, 1257, 1195, 1109, 743, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 7.47 – 7.28 (m, 5H), 7.10 (tdd, <i>J</i> = 6.4, 5.0, 1.2 Hz, 1H), 6.77 (td, <i>J</i> = 7.4, 3.4 Hz, 1H), 6.51 (dd, <i>J</i> = 24.5, 7.9 Hz, 1H), 6.00 (d, <i>J</i> = 38.8 Hz, 1H), 5.26 – 5.06 (m, 2H), 4.92 (s, 0.5H), 4.53 (s, 0.5H), 3.94 – 3.79 (m, 1H), 3.11 (dt, <i>J</i> = 17.7, 11.3, 6.5 Hz, 1H), 2.67 (dt, <i>J</i> = 26.7, 12.0, 8.7 Hz, 1H), 2.41 (dd, <i>J</i> = 12.5, 6.4 Hz, 1H), 1.55 – 1.14 (m, 6H), 1.08 (d, <i>J</i> = 3.2 Hz, 2H), 1.04 (s, 2H), 0.88 – 0.70 (m, 5H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 154.97, 154.24, 150.56, 150.35, 136.79, 136.79, 130.25, 130.14, 129.78, 129.73, 128.62, 128.48, 128.15, 128.10, 127.98, 127.79, 126.00, 125.90, 118.83, 118.59, 109.34, 109.26, 97.97, 96.87, 78.44, 77.74, 76.02, 66.83, 59.99, 59.27, 45.60, 45.36, 40.81, 40.42, 40.35, 40.12, 39.74, 33.01, 32.94, 32.62, 32.48, 20.59, 20.45, 20.41, 17.08; HRMS (ESI) exact mass calculated for [M+H]<sup>+</sup> (C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>) requires <i>m/z</i> 450.27512, found <i>m/z</i> 450.27455 with a difference of 1.27 ppm; <i>[α]<sub>D</sub></i> <sup>21</sup> = -139 (c = 1.00, CHCl<sub>3</sub>). 
Benzyl \((3aR,8aS)-4\text{-bromo-3a-((2,2,6,6-tetramethylpiperidin}-1\text{-yl})oxy})\)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using GP3, the title compound was obtained as a white foamy solid (208 mg, 79% yield). The desired product was found to be 90% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, \(t\) (minor) = 8.8 min, \(t\) (major) = 10.8 min]. IR (thin film): 3346, 2932, 1694, 1601, 1452, 1415, 1352, 1297, 1255, 1215, 1181, 1115, 905, 754, 742, 696 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\), ca. 55:45 mixture of rotamers) \(\delta\) 7.44 – 7.28 (m, 5H), 6.96 – 6.85 (m, 2H), 6.54 (dd, \(J = 31.2, 3.2\) Hz, 1H), 6.42 (dd, \(J = 19.2, 7.6\) Hz, 1H), 5.31 – 5.08 (m, 2H), 4.76 (dd, \(J = 179.8, 3.2\) Hz, 1H), 3.98 – 3.81 (m, 1H), 3.30 – 3.15 (m, 1H), 2.84 – 2.59 (m, 2H), 1.54 – 1.23 (m, 6H), 1.16 (d, \(J = 5.4\) Hz, 3H), 1.06 (d, \(J = 37.6\) Hz, 6H), 0.39 (d, \(J = 11.9\) Hz, 3H); \(^13\)C NMR (126 MHz, CDCl\(_3\), ca. 55:45 mixture of rotamers) \(\delta\) 155.23, 154.35, 151.31, 151.20, 136.92, 136.71, 131.10, 131.06, 130.18, 130.01, 128.71, 128.60, 128.26, 128.15, 128.11, 127.83, 123.15, 122.91, 119.62, 119.48, 107.98, 107.91, 98.92, 97.78, 76.20, 75.37, 67.13, 67.02, 60.19, 60.16, 59.54, 59.53, 45.18, 44.96, 40.67, 40.63, 40.56, 40.39, 39.07, 38.47, 33.65, 33.33, 32.30, 32.18, 21.26, 21.23, 20.77, 20.69, 17.14; HRMS (ESI) exact mass calculated for [M+H]\(^{+}\) (\(C_{27}H_{35}BrN_{3}O_{3}\)) requires \(m/z\) 528.18563, found \(m/z\) 528.18592 with a difference of 0.55 ppm; \([\alpha]_{D}^{21} = -239\) (\(c = 0.5\), CHCl\(_3\)).
Benzyl (3aR,8aS)-5-bromo-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using GP3, the title compound was obtained as a white foamy solid (211 mg, 80% yield). The product was found to be 92% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, t<sub>1</sub> (minor) = 7.6 min, t<sub>1</sub> (major) = 12.0 min]. IR (thin film): 3352, 2972, 2932, 1697, 1605, 1475, 1415, 1355, 1299, 1261, 1194, 1112, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 7.44 – 7.29 (m, 6H), 7.19 (ddd, J = 8.4, 3.5, 2.1 Hz, 1H), 6.39 (dd, J = 23.8, 8.4 Hz, 1H), 6.01 (dd, J = 36.0, 2.3 Hz, 1H), 5.24 – 5.08 (m, 2H), 4.74 (dd, J = 201.3, 2.3 Hz, 1H), 3.94 – 3.78 (m, 1H), 3.18 – 3.05 (m, 1H), 2.74 – 2.57 (m, 1H), 2.42 – 2.32 (m, 1H), 1.55 – 1.22 (m, 6H), 1.12 – 0.99 (m, 6H), 0.86 – 0.71 (m, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 155.06, 154.23, 149.57, 149.36, 136.79, 136.62, 132.63, 132.57, 132.49, 129.02, 128.92, 128.78, 128.64, 128.37, 128.27, 128.19, 127.95, 110.79, 110.71, 110.38, 110.09, 97.71, 96.59, 78.81, 78.10, 67.25, 67.08, 60.23, 59.51, 45.64, 45.41, 40.89, 40.54, 40.47, 40.31, 39.94, 33.25, 33.18, 32.79, 32.65, 20.73, 20.64, 20.61, 17.17; HRMS (ESI) exact mass calculated for [M+H]<sup>+</sup> (C<sub>27</sub>H<sub>35</sub>BrN<sub>3</sub>O<sub>3</sub>) requires m/z 528.18563, m/z found 528.18494 with a difference of 1.31 ppm; [α]<sub>D</sub><sup>21</sup> = -119 (c = 0.50, CHCl<sub>3</sub>).
Benzyl (3aR,8aS)-6-bromo-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using GP3, the title compound was obtained as a white foamy solid (171 mg, 65% yield). The desired product was found to be 87% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, t (major) = 10.9 min, t (minor) = 12.3 min]. IR (thin film): 3354, 2973, 2932, 2873, 1697, 1604, 1481, 1449, 1415, 1353, 1311, 1298, 1240, 1195, 1110, 1044, 897, 697 cm⁻¹. ¹H NMR (500 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 7.45 – 7.29 (m, 5H), 7.16 (d, J = 8.0 Hz, 1H), 6.88 (ddd, J = 7.8, 5.3, 1.7 Hz, 1H), 6.64 (dd, J = 23.2, 1.7 Hz, 1H), 5.95 (dd, J = 33.1, 1.9 Hz, 1H), 5.25 – 5.07 (m, 2H), 4.82 (dd, J = 212.4, 1.9 Hz, 1H), 3.86 (dddd, J = 40.0, 10.5, 8.7, 1.3 Hz, 1H), 3.10 (dtd, J = 15.1, 11.3, 6.4 Hz, 1H), 2.64 (dtd, J = 26.4, 12.0, 8.7 Hz, 1H), 2.36 (dd, J = 12.4, 6.4 Hz, 1H), 1.55 – 1.22 (m, 7H), 1.09 – 1.00 (m, 6H), 0.83 – 0.73 (m, 6H); ¹³C NMR (126 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 155.04, 154.18, 151.90, 151.65, 136.76, 136.60, 129.14, 129.09, 128.78, 128.62, 128.38, 128.27, 128.18, 127.95, 127.41, 127.34, 123.72, 123.70, 121.68, 121.40, 112.19, 112.14, 97.33, 96.17, 78.91, 78.19, 67.25, 67.07, 60.18, 60.17, 59.47, 45.68, 45.46, 40.88, 40.50, 40.44, 40.23, 39.87, 33.33, 33.28, 32.70, 32.56, 20.71, 20.59, 20.56, 17.16. HRMS (ESI) exact mass calculated for [M+H]⁺ (C₂₇H₃₅BrN₃O₃) requires m/z 528.18563, found m/z 528.18581 with a difference of 0.34 ppm; [α]D²¹ = -234 (c = 0.50, CHCl₃).
Benzyl (3aR,8aS)-5-chloro-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-
tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using **GP3**, the title compound was obtained as a white foamy solid (178 mg, 77\% yield). The desired product was found to be 92\% ee by chiral HPLC analysis [ChiralPak AD-H, 10\% IPA in hexanes, 1 mL/min, 250 nm, \( t_c \) (minor) = 7.5 min, \( t_c \) (major) = 10.9 min]. IR (thin film): 3353, 2932, 1695, 1479, 1415, 1354, 1260, 1194, 755, 697 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\), ca. 55:45 mixture of rotamers) δ 7.44 – 7.29 (m, 5H), 7.28 (d, \( J = 2.1 \) Hz, 1H), 7.06 (ddd, \( J = 8.4, 3.7, 2.2 \) Hz, 1H), 6.43 (dd, \( J = 23.4, 8.4 \) Hz, 1H), 6.02 (dd, \( J = 36.8, 2.2 \) Hz, 1H), 5.24 – 5.07 (m, 2H), 4.74 (dd, \( J = 199.2, 2.3 \) Hz, 1H), 3.95 – 3.78 (m, 1H), 3.17 – 3.05 (m, 1H), 2.74 – 2.59 (m, 1H), 2.38 (dd, \( J = 12.6, 6.6 \) Hz, 1H), 1.57 – 1.23 (m, 7H), 1.10 – 1.01 (m, 6H), 0.85 – 0.70 (m, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\), ca. 55:45 mixture of rotamers) δ 154.99, 154.18, 149.11, 148.90, 136.75, 136.58, 132.04, 131.95, 129.78, 129.71, 128.72, 128.58, 128.31, 128.21, 128.13, 127.90, 126.09, 125.99, 123.43, 123.16, 110.22, 110.14, 97.70, 96.58, 78.88, 78.18, 67.19, 67.02, 60.17, 60.16, 59.45, 45.60, 45.36, 40.83, 40.49, 40.42, 40.25, 39.87, 33.19, 33.13, 32.73, 32.59, 20.68, 20.68, 20.59, 20.55, 17.12; HRMS (ESI) exact mass calculated for [M+H]\(^+\) (C\(_{27}\)H\(_{35}\)ClN\(_3\)O\(_3\)) requires m/z 464.29077, found m/z 464.29163 with a difference of 1.87 ppm; [\( \alpha \)]\(_D\)\(^{21} \) = -127 (c = 1.00, CHCl\(_3\)).
Benzyl (3aR,8aS)-5-methoxy-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using **GP3**, the title compound was obtained as a white foamy solid (149 mg, 62% yield). The desired product was found to be 88% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, t (minor) = 12.1 min, t (major) = 17.2 min]. IR (thin film): 3357, 2933, 1698, 1493, 1415, 1353, 1191, 1033, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 7.46 – 7.27 (m, 5H), 6.93 (t, J = 3.0 Hz, 1H), 6.75 – 6.69 (m, 1H), 6.48 (dd, J = 23.5, 8.5 Hz, 1H), 6.06 (d, J = 43.9 Hz, 1H), 5.28 – 5.05 (m, 2H), 4.49 (d, J = 168.3 Hz, 1H), 3.94 – 3.80 (m, 1H), 3.78 (s, 3H), 3.20 – 3.07 (m, 1H), 2.72 – 2.57 (m, 1H), 2.39 (dd, J = 12.2, 6.2 Hz, 1H), 1.55 – 1.23 (m, 7H), 1.09 (d, J = 3.9 Hz, 3H), 1.04 (s, 3H), 0.90 – 0.64 (m, 6H); ¹³C NMR (126 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 154.98, 154.34, 153.81, 153.70, 144.59, 144.38, 136.92, 136.74, 132.07, 131.89, 128.67, 128.55, 128.19, 128.15, 128.05, 127.89, 116.01, 115.91, 111.48, 111.44, 110.63, 110.52, 98.35, 97.27, 79.05, 78.35, 67.08, 66.91, 60.12, 60.11, 59.37, 56.19, 56.17, 45.57, 45.32, 40.96, 40.54, 40.46, 40.24, 39.82, 33.11, 33.03, 32.83, 32.66, 20.71, 20.69, 20.51, 20.48, 17.15; HRMS (ESI) exact mass calculated for [M+H]⁺ (C₃₂H₃₈N₃O₄) requires m/z 480.28569, found m/z 480.28513 with a difference of 1.15 ppm; [α] D²¹ = -104 (c = 1.00, CHCl₃).
Benzyl (3aR,8aS)-5-methyl-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydroprrolo[2,3-b]indole-1(2H)-carboxylate

Using GP3, the title compound was obtained as a white foamy solid (182 mg, 79% yield). The desired product was found to be 91% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, t<sub>(minor)</sub> = 7.4 min, t<sub>(major)</sub> = 10.2 min]. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 7.44 – 7.27 (m, 5H), 7.12 (s, 1H), 6.95 – 6.88 (m, 1H), 6.43 (dd, J = 23.8, 7.9 Hz, 1H), 6.05 (dd, J = 38.7, 2.7 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.59 (dd, J = 182.9, 2.8 Hz, 1H), 3.94 – 3.77 (m, 1H), 3.18 – 3.05 (m, 1H), 2.73 – 2.58 (m, 1H), 2.43 – 2.33 (m, 1H), 2.29 (s, 3H), 1.63 – 1.19 (m, 7H), 1.09 (d, J = 3.7 Hz, 3H), 1.03 (s, 3H), 0.84 (d, J = 31.5 Hz, 3H), 0.70 (d, J = 8.5 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>, ca. 55:45 mixture of rotamers) δ 155.05, 154.38, 148.34, 148.14, 136.96, 136.80, 130.98, 130.84, 130.43, 130.37, 128.70, 128.57, 128.42, 128.21, 128.19, 128.17, 128.06, 127.89, 126.28, 126.18, 109.54, 109.43, 98.13, 97.03, 78.58, 77.87, 67.08, 66.90, 60.09, 60.08, 59.34, 45.63, 45.39, 40.94, 40.57, 40.50, 40.16, 39.79, 33.07, 33.00, 32.93, 32.76, 21.10, 20.72, 20.70, 20.54, 20.51, 17.20; HRMS (ESI) exact mass calculated for [M+H]<sup>+</sup> (C<sub>28</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub>) requires m/z 464.29077, found m/z 464.29084 with a difference of 0.16 ppm; [α]<sup>D</sup> = -121 (c = 1.00, CHCl<sub>3</sub>).
1-benzyl 5-methyl (3aR,8aS)-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,5(2H)-dicarboxylate

Using GP3, the title compound was obtained as a white foamy solid (162 mg, 64% yield). The desired product was found to be 92% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 280 nm, t (minor) = 11.6 min, t (major) = 20.6 min]. H NMR (500 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 8.03 (t, J = 2.2 Hz, 1H), 7.87 (ddd, J = 8.4, 4.2, 1.7 Hz, 1H), 7.49 – 7.31 (m, 5H), 6.48 (dd, J = 23.1, 8.4 Hz, 1H), 6.09 (dd, J = 33.0, 1.6 Hz, 1H), 5.38 (s, 0.6H), 5.27 – 5.09 (m, 2H), 4.94 (s, 0.4H), 3.97 – 3.84 (m, 1H), 3.89 (s, 3H), 3.19 – 3.06 (m, 1H), 2.80 – 2.64 (m, 1H), 2.53 – 2.41 (m, 1H), 1.59 – 1.23 (m, 7H), 1.11 (d, J = 2.6 Hz, 3H), 1.06 (s, 3H), 0.88 – 0.74 (m, 6H); C NMR (126 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 167.45, 167.38, 155.11, 154.46, 154.23, 154.16, 136.72, 136.54, 132.80, 132.77, 129.92, 129.86, 128.81, 128.64, 128.43, 128.29, 128.22, 128.20, 128.15, 127.95, 120.32, 120.01, 107.72, 107.70, 97.18, 96.04, 78.64, 77.92, 67.31, 67.14, 60.20, 59.53, 51.84, 51.81, 45.65, 45.44, 40.83, 40.52, 40.45, 40.31, 39.91, 33.14, 33.07, 32.82, 32.67, 20.74, 20.73, 20.65, 20.62, 17.15; HRMS (ESI) exact mass calculated for [M+H]+ (C₂₉H₃₈N₃O₅) requires m/z 508.27926, found m/z 508.28090 with a difference of 0.59 ppm; [α]D₂¹ = -142 (c = 1.00, CHCl₃).
Benzyl (3aR,8aS)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Using GP3, the title compound was obtained as a white foamy solid (169 mg, 59% yield). The desired product was found to be 88% ee by chiral HPLC analysis [ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250 nm, tₘ (major) = 9.7 min, tₘ (minor) = 11.0 min]. IR (thin film): 3358, 2977, 2932, 1697, 1611, 1350, 1194, 1145, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 7.78 (s, 1H), 7.60 (dd, J = 7.9, 5.1 Hz, 1H), 7.48 – 7.30 (m, 5H), 6.49 (dd, J = 22.4, 7.9 Hz, 1H), 6.17 (d, J = 29.0 Hz, 1H), 5.34 – 5.08 (m, 2.6H), 4.73 (s, 0.4H), 3.87 (dt, J = 38.5, 9.9 Hz, 1H), 3.22 – 3.06 (m, 1H), 2.80 – 2.63 (m, 1H), 2.55 – 2.44 (m, 1H), 1.50 – 1.25 (m, 21H), 1.09 (d, 7H), 0.90 (d, J = 30.4 Hz, 4H), 0.67 (d, J = 13.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 153.15, 152.91, 137.28, 136.74, 132.41, 132.34, 130.11, 130.06, 128.73, 128.59, 128.27, 128.15, 128.09, 127.86, 108.20, 108.14, 96.52, 83.41, 83.38, 77.68, 67.12, 66.96, 60.07, 59.39, 45.57, 45.36, 40.88, 40.60, 40.52, 40.16, 39.80, 33.12, 32.94, 32.89, 32.82, 25.21, 24.81, 20.71, 20.68, 20.56, 20.53, 17.20; HRMS (ESI) exact mass calculated for [M+H]+ (C₉₃H₄₇BN₃NaO₅) requires m/z 576.36053, found m/z 576.36016 with a difference of 0.64 ppm; [α]₀ⁿ²¹ = -98 (c = 1.00, CHCl₃).
Photochemical Flow Reactor Design:
The flow reactor was built using a glass condenser wrapped with 1/16” i.d. PFA tubing (IDEX Health and Science 1514L). Inside of the condenser were placed two LED strips and outside of the condenser was wrapped a blue LED “jacket” with four LED strips (470nm, SuperBrightLEDs, NFLS-X3-blue, 3.3W per 3.28 ft LED strip). Total light output was 20W. The apparatus was cooled by water flowing through the condenser and a small fan blowing over the system.

Figure S1: Flow photoreactor photos. Upper left/center: Blue LED “jacket”. Upper right: PFA tubing around condenser. Lower right: Overall flow set up.
**Photoredox Batch Reaction Design:**

Photoredox reactions at room temperature were run in a blue LED dish setup with two blue LED strips (470nm, SuperBrightLEDs, NFLS-X3-blue, 3.3W per 3.28 ft LED strip) wrapped inside of a crystallizing dish. The set up was cooled by a small fan (Holmes HCF0611A-BM).

**Figure S2:** Blue LED dish set up.
**Stern-Volmer Experiments**

Stern-Volmer experiments were conducted on an Agilent Technologies Cary Eclipse Fluorescence Spectrophotometer using the Cary Eclipse Scan Application. Stern-Volmer luminescence quenching experiments were run with freshly prepared solutions of $1.0 \times 10^{-4}$ M $[\text{Ir}(ppy)_{2}(4,4^{'-}\text{dtbbpy})](\text{PF}_6)$ in anhydrous THF at room temperature under an inert atmosphere. The solutions were irradiated at 360nm and luminescence was measured at 580 nm. The data summarized in the tables is the phosphorescence intensity measure three times for each sample. The data illustrated in the graphs is the average of three experiments.

**Table S1:** Luminescence quenching data for Ir(ppy)$_2$(dtbbpy)PF$_6$ and tryptamine.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Vial</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Average</th>
<th>$I_0/I$</th>
<th>Tryptamine [M]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run 1</strong></td>
<td>0</td>
<td>897</td>
<td>892</td>
<td>908</td>
<td>899.0</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>901</td>
<td>903</td>
<td>904</td>
<td>902.7</td>
<td>0.96</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>891</td>
<td>889</td>
<td>890</td>
<td>890.0</td>
<td>0.97</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>894</td>
<td>892</td>
<td>893</td>
<td>893.0</td>
<td>0.97</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>880</td>
<td>880</td>
<td>891</td>
<td>883.7</td>
<td>0.98</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Table S2:** Luminescence quenching data for Ir(ppy)$_2$(dtbbpy)PF$_6$ and variable NBu$_4$(OPh)$_2$PO$_2$.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Vial</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Average</th>
<th>$I_0/I$</th>
<th>base [M]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run 1</strong></td>
<td>0</td>
<td>865</td>
<td>867</td>
<td>882</td>
<td>871.3</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>621</td>
<td>617</td>
<td>621</td>
<td>619.7</td>
<td>1.41</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>560</td>
<td>565</td>
<td>571</td>
<td>565.3</td>
<td>1.54</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>551</td>
<td>534</td>
<td>544</td>
<td>543</td>
<td>1.60</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>518</td>
<td>520</td>
<td>519</td>
<td>519</td>
<td>1.68</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table S3: Luminescence quenching data for Ir(ppy)$_2$(dtbbpy)PF$_6$, 0.002M NBu$_4$(OPh)$_2$PO$_2$, and variable protiated tryptamine.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Vial</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Average</th>
<th>$I_0/I$</th>
<th>tryptamine [M]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Run 1</strong></td>
<td>0</td>
<td>523</td>
<td>515</td>
<td>514</td>
<td>517.3</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>200</td>
<td>203</td>
<td>201</td>
<td>201.3</td>
<td>2.57</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>136</td>
<td>138</td>
<td>137</td>
<td>137.0</td>
<td>3.78</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>108</td>
<td>108</td>
<td>109</td>
<td>108.3</td>
<td>4.78</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>91</td>
<td>90</td>
<td>90</td>
<td>90.3</td>
<td>5.73</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Run 2</strong></td>
<td>0</td>
<td>522</td>
<td>524</td>
<td>520</td>
<td>522.0</td>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>223</td>
<td>225</td>
<td>226</td>
<td>224.7</td>
<td>2.32</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>144</td>
<td>146</td>
<td>144</td>
<td>144.7</td>
<td>3.61</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>112</td>
<td>115</td>
<td>114</td>
<td>113.7</td>
<td>4.59</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>97</td>
<td>96</td>
<td>95</td>
<td>96.0</td>
<td>5.44</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Table S4: Luminescence quenching data for Ir(ppy)$_2$(dtbbpy)PF$_6$, 0.01M tryptamine, and variable NBu$_4$(OPh)$_2$PO$_2$.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Vial</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Average</th>
<th>I$_0$/I</th>
<th>Base [M]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run 1</td>
<td>0</td>
<td>855</td>
<td>869</td>
<td>868</td>
<td>864</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>207</td>
<td>206</td>
<td>208</td>
<td>207</td>
<td>4.17</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>131</td>
<td>131</td>
<td>130</td>
<td>130.7</td>
<td>6.61</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>8.64</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>82</td>
<td>82</td>
<td>81</td>
<td>81.7</td>
<td>10.58</td>
<td>0.0020</td>
</tr>
<tr>
<td>Run 2</td>
<td>0</td>
<td>860</td>
<td>861</td>
<td>853</td>
<td>899.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>203</td>
<td>202</td>
<td>201</td>
<td>902.7</td>
<td>4.25</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>130</td>
<td>129</td>
<td>130</td>
<td>890.0</td>
<td>6.62</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>100</td>
<td>101</td>
<td>100</td>
<td>100</td>
<td>8.55</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>81</td>
<td>81</td>
<td>82</td>
<td>81</td>
<td>10.55</td>
<td>0.0020</td>
</tr>
<tr>
<td>Run 3</td>
<td>0</td>
<td>876</td>
<td>873</td>
<td>872</td>
<td>873.7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>201</td>
<td>203</td>
<td>203</td>
<td>202.3</td>
<td>4.32</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>132</td>
<td>131</td>
<td>132</td>
<td>131.7</td>
<td>6.64</td>
<td>0.0010</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>104</td>
<td>105</td>
<td>104</td>
<td>104.3</td>
<td>8.37</td>
<td>0.0015</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>87</td>
<td>85</td>
<td>86</td>
<td>86</td>
<td>10.16</td>
<td>0.0020</td>
</tr>
</tbody>
</table>
Cyclic Voltammetry Experiments

Reduction potential of TIPS EBX iodonium in acetonitrile

**Figure S3:** The cyclic voltammogram of TIPS-EBX iodonium and FeCp$_2^+$ vs Ag/Ag$^+$ in acetonitrile at 0.1V/s.

Conditions: 1mM of TIPS-EBX iodonium, 1mM FeCp$_2^+$ and 0.1M tetrabutylammonium hexafluorophosphate.

A glassy working electrode and, Ag/Ag$^+$ reference electrode and platinum mesh counter electrode was used. The experiment was conducted in acetonitrile at 23 °C.
Reduction potential of $N'$-Cbz tryptamine (1) in THF

Figure S4: The cyclic voltammogram of $N'$-Cbz tryptamine (1) vs SCE in THF at 0.1V/s.

Conditions: 1mM of $N'$-Cbz tryptamine (1) and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Reduction potential of $N$-Me-$N'$-Cbz tryptamine (25) in THF

**Figure S5**: The cyclic voltammogram of $N$-Me-$N'$-Cbz tryptamine (25) and vs SCE in THF at 0.1V/s.

Conditions: 1mM of $N$-Me-$N'$-Cbz tryptamine (25) and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Cyclic voltammogram of Ir(ppy)$_3$:

**Figure S6**: The cyclic voltammogram of Ir(ppy)$_3$ vs SCE in THF at 0.1V/s.

Conditions: 1mM of Ir(ppy)$_3$, and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode and, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Cyclic voltammogram of Ir(ppy)$_3$ does not change upon addition of tryptamine 1:

**Figure S7:** The cyclic voltammogram of a solution of 1 and Ir(ppy)$_3$ vs SCE in THF at 0.1V/s.

Conditions: 1mM of Ir(ppy)$_3$, 3mM of 1 and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode and, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Cyclic voltammogram of Ir(ppy)$_3$ does not change upon addition of diphenyl phosphate base:

**Figure S8:** The cyclic voltammogram of a solution of NBu$_4$(PhO)$_2$PO$_2$ and Ir(ppy)$_3$ vs SCE in THF at 0.1V/s.

Conditions: 1mM of Ir(ppy)$_3$, 3mM of NBu$_4$(PhO)$_2$PO$_2$ and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode and, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Addition of both 1 and diphenyl phosphate produces an irreversible catalytic peak:

In the presence of all the three components: 1, diphenyl phosphate base, and Ir(ppy)$_3$, the return wave diminishes hence the Ir$^{III/IV}$ redox couple becomes irreversible and generates a catalytic peak. In this regime, the electrode initially oxidizes the Ir(ppy)$_3$ to its Ir$^{IV}$ state. The tryptamine can then undergo oxidation by the ground state Ir$^{IV}$ in the presence of base to generate the indole radical cation. The resulting Ir$^{III}$ species will continue to cycle on the electrode in this process producing a catalytic current. This observation supports a PCET mechanism in which the base is necessary for one-electron oxidation of the tryptamine substrate.

**Figure S9:** The cyclic voltammogram of a solution of N-Cbz tryptamine, NBu$_4$(PhO)$_2$PO$_2$ and Ir(ppy)$_3$ vs SCE in THF at 0.1V/s.

Conditions: 1mM of Ir(ppy)$_3$, 3mM of NBu$_4$(PhO)$_2$PO$_2$, 3mM of N-Cbz tryptamine and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode and, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Mechanistic support for PCET oxidation of tryptamine:

![Figure S10](image)

**Figure S10:** A superimposed cyclic voltammogram a solution of N-Cbz tryptamine, NBu₄(PhO)₂PO₂ and Ir(ppy)₃ vs SCE in THF at 0.1V/s. Each voltammogram obtained independently.

*Conditions:* 1mM of Ir(ppy)₃, 3mM of NBu₄(PhO)₂PO₂, 3mM of N-Cbz tryptamine and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Investigating the change in onset potential of tryptamine-phosphate complex:

**Figure S11:** Cyclic voltammetry experiment to demonstrate early onset of tryptamine oxidation in the presence of phosphate base.

Conditions: 1mM of N-Cbz tryptamine, xmM of NBu₄(PhO)₂PO₂, and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode, SCE reference electrode and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C with a scan rate of 0.1 V/s.
DFT Computations

All calculations used DFT methodology as implemented in the Gaussian 16 series of computer programs. We employed the unrestricted B3LYP functional and 6-31+G(d,p) basis set. Calculations were performed with the CPCM polarizable conductor calculation model for THF.

We first evaluated the optimized geometry of the H-bonded indole radical cation complex with biphenyl phosphate. The input structure of the complex featured the proton bound to the phosphoric acid in a covalent O-H bond of 1.08 Å in length and an N-H distance of 2.19 Å. This structure then underwent

---

geometry optimization and stationary points were subjected to normal mode analysis. Below are the Cartesian coordinates (Å) for both the input and output structures and the energies (Hartree) of the stationary point.

**Input structure:**

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>C</td>
<td>-5.88474468</td>
<td>0.20723575</td>
<td>-0.70840261</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-3.72083059</td>
<td>0.25363794</td>
<td>-0.29153393</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-2.87473338</td>
<td>1.29242370</td>
<td>-0.68321858</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-3.42522248</td>
<td>2.35959463</td>
<td>-1.37981189</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-4.75662119</td>
<td>2.33606239</td>
<td>-1.80398159</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-5.60612819</td>
<td>1.26774323</td>
<td>-1.47573851</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-5.63065118</td>
<td>-1.00013057</td>
<td>-0.20116789</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>-4.57987015</td>
<td>-1.66028230</td>
<td>0.51289849</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-1.84360836</td>
<td>1.30485394</td>
<td>-0.27365956</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-2.79035666</td>
<td>3.18377585</td>
<td>-1.64402493</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-5.13741654</td>
<td>3.15784084</td>
<td>-2.39186612</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-6.63554927</td>
<td>1.25899739</td>
<td>-1.80432125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-6.34432031</td>
<td>-1.36952948</td>
<td>-0.31667225</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-4.61097849</td>
<td>-2.59992833</td>
<td>1.03425787</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>-3.46779281</td>
<td>-0.92408230</td>
<td>0.45615730</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>-1.50621506</td>
<td>-1.36983094</td>
<td>1.33009521</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>-8.52134693</td>
<td>-1.55877229</td>
<td>1.74068484</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>0.80683953</td>
<td>-0.74011821</td>
<td>2.04237288</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>1.22248070</td>
<td>-0.32297134</td>
<td>3.50282183</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>0.70595685</td>
<td>0.62155976</td>
<td>0.91695791</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>2.19702666</td>
<td>-1.52128751</td>
<td>1.38619587</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>1.86140618</td>
<td>1.33233821</td>
<td>0.52656887</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.82590010</td>
<td>2.63086313</td>
<td>1.00879222</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.75979424</td>
<td>0.76407811</td>
<td>-0.39632350</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>3.10102911</td>
<td>3.40239914</td>
<td>0.58888873</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>1.30718219</td>
<td>3.81723566</td>
<td>1.71641785</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>3.83615296</td>
<td>1.56497488</td>
<td>-0.82453416</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>4.00755040</td>
<td>2.86659226</td>
<td>-0.35322840</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>3.23018174</td>
<td>4.40898285</td>
<td>0.94077287</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>4.55167479</td>
<td>1.14903666</td>
<td>-1.52054484</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>4.84803732</td>
<td>3.45493240</td>
<td>-0.69448661</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.27735333</td>
<td>-1.78154736</td>
<td>-0.88774688</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.12585666</td>
<td>-2.99338687</td>
<td>-0.59293331</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.58332546</td>
<td>-0.61187218</td>
<td>-0.92471802</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.29293029</td>
<td>-3.23116735</td>
<td>-1.95470934</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>1.89357190</td>
<td>-3.79298789</td>
<td>0.09777981</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.74639940</td>
<td>-0.87933264</td>
<td>-2.29795217</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>2.60595111</td>
<td>-2.16894988</td>
<td>-2.81032199</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>2.17982197</td>
<td>-4.23313781</td>
<td>-2.34827995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>2.96976939</td>
<td>-0.85934241</td>
<td>-2.96617795</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>2.73021680</td>
<td>-2.34265585</td>
<td>-3.87018229</td>
</tr>
</tbody>
</table>
Output information:

\[ E(UB3LYP) = -1468.31454034 \]

Zero-point correction = 0.307356 (Hartree/Particle)
Thermal correction to Energy = 0.320186
Thermal correction to Enthalpy = 0.329130
Thermal correction to Gibbs Free Energy = 0.252003

Sum of electronic and zero-point Energies = -1468.007185
Sum of electronic and thermal Energies = -1467.986355
Sum of electronic and thermal Enthalpies = -1467.985411
Sum of electronic and thermal Free Energies = -1468.061737

Symbolic Z-matrix:
Charge = 0 Multiplicity = 2

\[
\begin{align*}
C & : & -5.08474 & 0.20724 & -0.7074 \\
C & : & -3.72083 & 0.25364 & -0.29153 \\
C & : & -2.87473 & 1.29242 & -0.60322 \\
C & : & -3.42522 & 2.35059 & -1.37981 \\
C & : & -4.75662 & 2.33686 & -1.80398 \\
C & : & -5.60613 & 1.26774 & -1.47574 \\
C & : & -5.63865 & -1.00013 & -0.20117 \\
C & : & -4.57987 & -1.6602 & 0.51289 \\
H & : & -1.8436 & 1.30405 & -0.27337 \\
H & : & -2.79036 & 3.18378 & -1.64482 \\
H & : & -5.13742 & 3.15784 & -2.39187 \\
H & : & -6.63555 & 1.259 & -1.80433 \\
H & : & -6.63443 & -1.36953 & -0.31667 \\
H & : & -4.51987 & -2.59933 & 1.83426 \\
N & : & -3.46779 & -0.92408 & 0.45616 \\
H & : & -1.50622 & -1.36983 & 1.3307 \\
O & : & -0.52135 & -1.55877 & 1.74068 \\
P & : & 0.80684 & -0.74012 & 2.04237 \\
O & : & 1.22246 & -0.32297 & 3.50282 \\
O & : & 0.7896 & 0.62156 & 0.91696 \\
O & : & 2.19703 & -1.52121 & 1.3062 \\
C & : & 1.86141 & 1.33234 & 0.52657 \\
C & : & 2.0259 & 2.63039 & 1.00879 \\
C & : & 2.75979 & 0.76488 & -0.39632 \\
C & : & 3.10183 & 3.4824 & 0.56881 \\
C & : & 1.30718 & 3.01726 & 1.71642 \\
C & : & 3.83615 & 1.56497 & -0.82453 \\
C & : & 4.00755 & 2.86659 & -0.35323 \\
H & : & 3.23018 & 4.40898 & 0.94077 \\
H & : & 4.55167 & 1.14984 & -1.52054 \\
H & : & 4.84004 & 3.45493 & -2.69941 \\
C & : & 2.27735 & -1.70155 & -0.88775 \\
C & : & 2.12586 & -2.99339 & -0.59029 \\
C & : & 2.58333 & -0.61187 & -0.92472 \\
H & : & 2.29293 & -3.23117 & -1.9547 \\
H & : & 1.89357 & -3.79299 & 0.89778 \\
C & : & 2.74654 & -0.87933 & -2.29795 \\
C & : & 2.6051 & -2.16895 & -2.81032 \\
H & : & 2.17982 & -4.23314 & -2.34483 \\
H & : & 2.96977 & -0.05893 & -2.96618 \\
H & : & 2.73022 & -2.34266 & -3.87012
\end{align*}
\]
Figure S12: Optimized geometry of oxidized indole-biphenyl phosphate complex using UB3LYP/6-31G+(d,p). Bond distance (N-H) = 1.075 Å; bond distance (O-H) = 1.527 Å.
Supporting Information

for

Chapter 3

Mesolytic Bond Cleavage of Alkoxyamine Radical Cations

Table of Contents

I. Synthesis and characterization of starting materials
II. Synthesis and characterization of products
III. Cyclic Voltammetry Studies
IV. DFT Calculations
V. $^1$H and $^{13}$C NMR Spectra
VI. HPLC traces
Boc Protection of TEMPO-functionalized pyrroloindolines:

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

To a solution of Boc₂O (2 equiv) and 2 (1 equiv) in THF (0.1M) was added NaHMDS (5 equiv) dropwise. Once addition is complete, the reaction was allowed to stir for 30 min then sat. NaHCO₃ solution was added and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using 2-5% EtOAc in hexanes to afford the desired product in 88% yield.

IR (thin film): 2975, 2932, 1705, 1604, 1480, 1407, 1364, 1341, 1312, 1290, 1253, 1236, 1193, 1151, 1092, 1079, 1022, 947, 735, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 1H), 7.45 – 7.31 (m, 5H), 7.31 – 7.27 (m, 2H), 7.07 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 5.17 (d, J = 10.8 Hz, 2H), 3.98 (dd, J = 11.5, 7.9 Hz, 1H), 2.84 (td, J = 13.0, 12.3, 5.1 Hz, 1H), 2.55 (dt, J = 12.2, 8.0 Hz, 1H), 2.30 (dd, J = 12.3, 5.2 Hz, 1H), 1.57 – 1.19 (m, 15H), 1.09 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.53 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 152.74, 144.19, 137.13, 133.36, 129.79, 128.51, 127.93, 127.88, 125.03, 123.43, 95.33, 81.50, 78.32, 66.95, 60.39, 59.53, 45.99, 40.91, 40.51, 33.07, 28.47, 20.73, 20.46, 17.15; HRMS (ESI) exact mass calculated for [M+H]+ (C₃₂H₄₄N₃O₅) requires m/z 550.32755, m/z found 550.32818 with a difference of 1.14 ppm. [α]D¹⁹ = -128 (c = 0.5, CHCl₃).

General procedure for mesolytic bond cleavage reaction (GP5):
To a flame dried 2-dram vial equipped with stir bar was added 11 (0.25 mmol), nucleophile (0.375 mmol, 1.5 equiv), and [Ir(dF, CF₃-ppy)₂(dCF₃-bpy)]PF₆ (0.005 mmol, 0.02 equiv). The vial was evacuated and backfilled with argon three times then anhydrous degassed MeNO₂ (5 mL) was added. The reaction was sealed with parafilm and irradiated at room temperature with 7 W blue LEDs for 12 h or until full conversion of starting material by TLC analysis (See Figure S2). The mixture was then concentrated in vacuo and the resulting residue was purified on silica gel by flash column chromatography.

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-((E)-styryl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 5% ethyl acetate in hexanes to give the desired product as a white solid (81mg, 65% yield) that was determined to be 94% ee by HPLC analysis (ChiralPak AS-H, 5% IPA in hexanes, 1 mL/min, 250nm, tᵣ (major) = 7.6 min, tᵣ (minor) = 10.5 min). IR (thin film): 1703, 1479, 1405, 1366, 1320, 1196, 1149, 1099, 747, 695 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.64 (d, J = 8.1 Hz, 1H), 7.40 – 7.18 (m, 12H), 7.13 (t, J = 7.5 Hz, 1H), 6.52 (d, J = 16.1 Hz, 1H), 6.21 (d, J = 16.1 Hz, 1H), 6.16 (s, 1H), 5.13 (s, 2H), 3.88 – 3.72 (m, 1H), 2.96 – 2.79 (m, 1H), 2.40 – 2.24 (m, 2H), 1.47 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.17, 153.30, 143.56, 138.30, 137.53, 134.86, 132.20, 130.78, 129.60, 129.52, 129.37, 128.77, 128.68, 128.48, 127.24, 125.20, 124.73, 82.14, 82.14, 67.31, 59.50,
47.14, 36.13, 28.41; HRMS (ESI) exact mass calculated for [M+H]+ (C_{31}H_{33}N_{2}O_{4}) requires m/z 497.24349, found m/z 497.24319 with a difference of 0.59 ppm; [α]_D^{21} = -100 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(naphthalen-2-yl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 2-5% ethyl acetate in hexanes to give the desired product as a white solid (64mg, 49% yield) that was determined to be 94% ee by HPLC analysis (ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250nm, tₘ (minor) = 10.4 min, tₘ (major) = 11.6 min). IR (thin film): 1705, 1479, 1408, 1367, 1341, 1318, 1196, 1154, 751 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.86 – 7.76 (m, 3H), 7.73 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 – 7.24 (m, 8H), 7.07 (t, J = 7.6 Hz, 1H), 6.47 (s, 1H), 5.14 (s, 2H), 3.93 (dd, J = 11.1, 6.9 Hz, 1H), 2.97 (td, J = 10.9, 6.1 Hz, 1H), 2.76 – 2.59 (m, 2H), 1.50 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.17, 153.18, 143.05, 141.35, 138.26, 136.68, 134.12, 133.22, 129.68, 129.54, 129.36, 128.82, 128.78, 128.49, 128.37, 127.51, 127.16, 125.03, 124.92, 83.38, 82.39, 67.38, 61.09, 47.23, 36.43, 28.44; HRMS (ESI) exact mass calculated for [M+H]+ (C_{33}H_{33}N_{2}O_{4}) requires m/z 521.24349, found m/z 521.24348 with a difference of 0.01 ppm; [α]_D^{21} = -196 (c = 1.00, CHCl₃).
1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(1-(tert-butoxycarbonyl)-1H-indol-5-yl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a white solid (79 mg, 52% yield) that determined to be 94% ee by HPLC analysis (ChiralPak AD-H, 20% IPA in hexanes, 1 mL/min, λ, (minor) = 13.1 min, λ, (major) = 15.8 min). IR (thin film): 1706, 1407, 1368, 1338, 1254, 1196, 1162, 1144, 751 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 8.03 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 3.7 Hz, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.38 – 7.16 (m, 8H), 7.05 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 3.7 Hz, 1H), 6.38 (s, 1H), 5.13 (s, 2H), 3.95 – 3.85 (m, 1H), 2.93 (td, J = 10.8, 6.3 Hz, 1H), 2.68 – 2.56 (m, 2H), 1.61 (s, 9H), 1.48 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.13, 153.16, 150.39, 142.92, 138.42, 138.25, 137.20, 134.93, 131.69, 129.34, 129.33, 128.74, 128.46, 127.79, 124.91, 124.81, 122.84, 118.75, 116.23, 107.91, 84.77, 83.78, 82.29, 67.32, 60.83, 47.25, 36.59, 28.42, 28.22; HRMS (ESI) exact mass calculated for [M+H]⁺ (C₃₆H₄₀N₃O₆) requires m/z 610.29117, found m/z 610.29063 with a difference of 0.88 ppm; [α]D²¹ = -151 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(4-methoxyphenyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a white solid (90 mg, 72% yield) that was determined to be 93% ee by HPLC analysis (ChiralPak...
**AD-H, 5% IPA in hexanes, 1 mL/min, 250nm, t_r (minor) = 13.7 min, t_r (major) = 21.9 min). IR (thin film): 1704, 1407, 1367, 1316, 1252, 1182, 1148, 749, 697 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.63 (d, J = 7.8 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.26 (td, J = 7.7, 1.4 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 – 7.10 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.90 – 6.76 (m, 2H), 6.29 (s, 1H), 5.13 (s, 2H), 3.90 – 3.81 (m, 1H), 3.73 (s, 3H), 2.90 (td, J = 11.2, 5.5 Hz, 1H), 2.64 – 2.45 (m, 2H), 1.49 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 159.63, 155.13, 153.15, 142.86, 138.28, 137.13, 135.96, 129.36, 129.35, 128.77, 128.50, 127.68, 124.84, 124.79, 115.02, 83.53, 82.29, 67.32, 60.26, 55.85, 47.24, 36.48, 28.43; HRMS (ESI) exact mass calculated for [M+H]^+ (C₃₀H₃₃N₂O₅) requires m/z 501.23840, found m/z 501.23827 with a difference of 0.26 ppm; [α]_D^{21} = -159 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(4-((benzyloxycarbonyl)amino)phenyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 10-30% ethyl acetate in hexanes to give the desired product as a white solid (90 mg, 72% yield) that was determined to be 94% ee by HPLC analysis (ChiralPak AS-H, 5% IPA in hexanes, 1 mL/min, 250nm, t_r (major) = 7.6 min, t_r (minor) = 10.5 min). IR (thin film): 3314, 2976, 1704, 1531, 1479, 1409, 1368, 1322, 1217, 1150, 745 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.84 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.42 – 7.29 (m, 12H), 7.26 (td, J = 7.9, 1.4 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.30 (s, 1H), 5.14 (s, 4H), 3.87 (dd, J = 10.9, 7.4 Hz, 1H), 2.90 (td, J = 11.3, 5.6 Hz, 1H), 2.63 – 2.46 (m, 2H), 1.48 (s, 9H). ¹³C NMR (126 MHz, CD₃CN) δ 155.15, 154.48, 153.13, 142.91, 138.78, 138.47, 138.25, 137.83, 136.85, 129.47, 129.41, 129.36, 128.99, 128.79, 128.77, 128.48, 127.12, 124.86, 119.77, 83.49, 82.33, 67.35, 67.17, 60.41, 47.22, 36.54,
28.42. HRMS (ESI) exact mass calculated for [M+H]^+ (C_{37}H_{38}N_{3}O_{6}) requires m/z 620.27552, found m/z 620.27526 with a difference of 0.40 ppm; [α]_D^{21} = -77 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(2-oxo-2-phenylethyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 20-30% ethyl acetate in hexanes to give the desired product as a colorless oil (102 mg, 80% yield) that was determined to be 93% ee by HPLC analysis (ChiralPak AD-H, 20% IPA in hexanes, 1 mL/min, 250nm, tᵣ (minor) = 8.0 min, tᵣ (major) = 9.2 min). IR (thin film): 2977, 1693, 1407, 1366, 1321, 1198, 749, 692 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.92 – 7.82 (m, 2H), 7.64 – 7.53 (m, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.41 – 7.25 (m, 6H), 7.19 (td, J = 7.8, 1.3 Hz, 1H), 7.00 (td, J = 7.5, 1.1 Hz, 1H), 6.34 (s, 1H), 5.23 – 5.04 (m, 2H), 3.88 – 3.76 (m, 1H), 2.85 – 2.72 (m, 1H), 2.28 – 2.19 (m, 2H), 1.49 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 198.72, 153.45, 143.97, 138.35, 138.07, 135.96, 134.21, 129.56, 129.34, 129.15, 128.92, 128.74, 128.52, 124.36, 124.18, 81.89, 81.41, 67.34, 54.75, 46.11, 45.85, 37.67, 28.50; HRMS (ESI) exact mass calculated for [M+H]^+ (C_{31}H_{33}N_{2}O_{5}) requires m/z 513.23706, found m/z 513.23752 with a difference of 1.72 ppm; [α]_D^{21} = -146 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aS,8aR)-3a-(2-phenylallyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

1-benzyl 8-(tert-butyl) (3aS,8aR)-3a-(2-oxo-2-phenylethyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

134
The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a white solid (89 mg, 70% yield) that was determined to be 94% ee by HPLC analysis (ChiralPak AD-H, 5% IPA in hexanes, 1 mL/min, 280nm, tₘ (minor) = 7.3 min, tₘ (major) = 7.8 min). IR (thin film): 1704, 1480, 1407, 1367, 1316, 1162, 1149, 749, 699 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.48 (d, J = 8.1 Hz, 1H), 7.41 – 7.27 (m, 5H), 7.18 (s, 5H), 7.12 – 7.05 (m, 2H), 6.87 (t, J = 7.5 Hz, 1H), 6.00 (s, 1H), 5.21 – 4.94 (m, 4H), 3.64 (dd, J = 10.4, 7.4 Hz, 1H), 3.07 (d, J = 13.8 Hz, 1H), 2.89 (d, J = 13.9 Hz, 1H), 2.67 (td, J = 11.0, 6.4 Hz, 1H), 2.03 – 1.95 (m, 2H), 1.48 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.08, 153.01, 146.40, 143.53, 142.66, 138.34, 135.57, 129.34, 129.05, 128.95, 128.72, 128.41, 128.19, 127.23, 124.74, 123.92, 118.08, 81.71, 80.62, 67.15, 57.76, 46.78, 43.22, 36.44, 28.44; HRMS (ESI) exact mass calculated for [M+H]^+ (C₃₂H₃₅N₂O₄) requires m/z 511.25914, found m/z 511.25864 with a difference of 0.97 ppm; [α]D²¹ = -76 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-azido-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a colorless oil (105 mg, 92% yield) that was determined to be 94% ee by HPLC analysis (ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250nm, tₘ (minor) = 6.5 min, tₘ (major) = 8.3 min). IR (thin film): 2978, 2100, 1709, 1479, 1407, 1368, 1313, 1152, 753 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.70 (d, J = 8.2 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.40 – 7.33 (m, 4H), 7.33 – 7.27 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 5.13 (s, 2H), 3.82 (dd, J = 11.2, 8.3 Hz, 1H), 2.87 (td, J = 11.6, 5.5 Hz, 1H), 2.49 (dd, J = 12.4, 5.5 Hz, 1H), 2.31 (td, J = 12.2, 8.3 Hz, 1H), 1.50 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.01, 152.89, 144.13, 138.06, 131.90, 129.44, 129.38, 128.84, 128.52, 125.00, 124.91, 82.82, 81.73, 75.88, 67.53, 46.82, 35.04, 28.37; HRMS (ESI) exact mass calculated for [M+Na]^+ (C₂₃H₂₅N₅NaO₄) requires m/z 458.18045, found m/z 458.17930 with a difference of 1.32 ppm; [α]D²¹ = -84 (c = 1.00, CHCl₃).
Benzyl 8-(tert-butyl) (3aR,8aR)-3a-methoxy-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a white solid (95 mg, 90% yield) that was determined to be 93% ee by HPLC analysis (ChiralPak AD-H, 10% IPA in hexanes, 1 mL/min, 250nm, tᵣ (minor) = 6.3 min, tᵣ (major) = 8.1 min). IR (thin film): 1705, 1479, 1406, 1367, 1342, 1310, 1192, 1148, 1091, 1076, 753 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.69 (d, J = 8.2 Hz, 1H), 7.42 – 7.28 (m, 7H), 7.15 (t, J = 7.5 Hz, 1H), 6.12 (s, 1H), 5.14 (s, 2H), 3.83 (dd, J = 11.3, 8.0 Hz, 1H), 2.81 (td, J = 11.7, 5.7 Hz, 1H), 2.41 – 2.23 (m, 2H), 1.49 (s, 9H); ¹³C NMR (126 MHz, CD₃CN) δ 155.33, 153.06, 145.09, 138.18, 131.35, 129.88, 129.37, 128.80, 128.49, 125.52, 124.57, 91.79, 82.45, 79.44, 67.45, 52.91, 46.42, 36.57, 28.42; HRMS (ESI) exact mass calculated for [M+Na]⁺ (C₂₄H₂₈N₂NaO₅) requires m/z 447.18959, found m/z 447.18866 with a difference of 0.90 ppm; [α]D²¹ = -68 (c = 1.00, CHCl₃).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(tert-butoxy)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate (21)

The crude material was purified on silica gel using 2-5% ethyl acetate in hexanes to give the desired product as a white solid (54 mg, 46% yield) that was determined to be 91% ee by HPLC analysis (ChiralPak AD-H, 1% IPA in hexanes, 1 mL/min, 280nm, tᵣ (minor) = 10.3 min, tᵣ (major) = 13.9 min). IR (thin film):
Benzyl (3aR,8aS)-3a-((2-iodophenyl)amino)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

The crude material was purified on silica gel using 5-10% ethyl acetate in hexanes to give the desired product as a white solid (82 mg, 64% yield) that was determined to be 93% ee by HPLC analysis (ChiralPak AS-H, 10% IPA in hexanes, 1 mL/min, 250nm, t, (major) = 16.6 min, t, (minor) = 28.4 min). IR (thin film): 3384, 2955, 1696, 1415, 1351, 1318, 1198, 749, 697 cm\(^{-1}\); \(^1\)H NMR (ca. 1:1 mixture of rotamers, 500 MHz, CDCl\(_3\)) \(\delta\) 7.69 – 7.61 (m, 1H), 7.42 – 7.29 (m, 5H), 7.20 – 7.11 (m, 2H), 6.99 (q, \(J = 7.7\) Hz, 1H), 6.77 (td, \(J = 7.4, 3.4\) Hz, 1H), 6.63 (dd, \(J = 27.5, 7.9\) Hz, 1H), 6.45 – 6.32 (m, 2H), 5.71 (dd, \(J = 35.9, 2.3\) Hz, 1H), 5.28 – 5.11 (m, 2.5H), 4.74 (s, 0.5H), 4.65 (d, \(J = 14.6\) Hz, 1H), 3.95 – 3.77 (m, 1H), 3.41 – 3.29 (m, 1H), 2.66 – 2.56 (m, 1H), 2.44 – 2.34 (m, 1H); \(^{13}\)C NMR (ca. 1:1 mixture of rotamers, 126 MHz, CDCl\(_3\)) \(\delta\) 155.42, 154.57, 148.99, 148.82, 144.49, 144.45, 139.49, 139.38, 136.50, 136.45, 130.01, 129.95, 129.30, 129.27, 128.99, 128.82, 128.68, 128.43, 128.29, 128.11, 123.50, 123.40, 119.91, 119.81, 119.58, 113.68, 113.38, 109.78, 109.65, 87.79, 87.67, 78.34, 77.60, 73.82, 72.64, 67.47, 67.28, 44.72, 44.51, 39.31, 38.77; HRMS
(ESI) exact mass calculated for \([M+H]^+\) \((C_{24}H_{23}IN_3O_2)\) requires \(m/z\) 512.08295, found \(m/z\) 512.08206 with a difference of 1.73 ppm; \([\alpha]_D^{21} = -207\) (c = 0.50, CHCl$_3$).

1-benzyl 8-(tert-butyl) (3aR,8aR)-3a-(sulfamoylamino)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate

The reaction was performed according to GP5 with 6 equivalents of sulfamide (144 mg, 1.5 mmol). The crude material was purified on silica gel using 30-50% ethyl acetate in hexanes to give the desired product as a white solid (87 mg, 71% yield) that was determined to be 93% ee by HPLC analysis (ChiralPak OD-H, 25% IPA in hexanes, 1 mL/min, 250 nm, \(t_r\) (minor) = 9.9 min, \(t_r\) (major) = 16.8 min). IR (thin film): 3259, 2979, 1698, 1481, 1412, 1367, 1332, 1152, 1096, 750, 697 cm$^{-1}$; \(^1\)H NMR (500 MHz, CD$_3$CN) \(\delta\) 7.65 (d, \(J = 8.2\) Hz, 1H), 7.42 (d, \(J = 7.5\) Hz, 1H), 7.40 – 7.29 (m, 6H), 7.13 (t, \(J = 7.5\) Hz, 1H), 6.48 (s, 1H), 5.98 (s, 1H), 5.11 (d, \(J = 34.1\) Hz, 4H), 3.83 (dd, \(J = 11.3, 7.8\) Hz, 1H), 2.72 (td, \(J = 11.7, 5.2\) Hz, 1H), 2.52 (td, \(J = 12.2, 7.9\) Hz, 1H), 2.34 (dd, \(J = 12.3, 5.2\) Hz, 1H), 1.49 (s, 9H); \(^{13}\)C NMR (126 MHz, CD$_3$CN) \(\delta\) 155.23, 153.42, 144.48, 138.14, 131.09, 130.96, 129.37, 128.81, 128.49, 124.49, 124.49, 124.49, 123.45, 82.34, 80.77, 71.55, 67.52, 45.52, 37.28, 28.45; HRMS (ESI) exact mass calculated for \([M+Na]^+\) \((C_{23}H_{28}N_4NaO_5S)\) requires \(m/z\) 511.16273, found \(m/z\) 511.16293 with a difference of 1.54 ppm; \([\alpha]_D^{21} = -55\) (c = 1.00, CHCl$_3$).
Cyclic Voltammetry Experiments

Cyclic voltammograms were taken on a CH Instruments 600E potentiostat using a glassy carbon working electrode, a saturated calomel (SCE) reference electrode, and a Pt mesh counter electrode. The pH was not adjusted and voltammograms were taken at RT in a 100 mM MeCN solution of tetrabutylammonium hexafluorophosphate containing 1 mM of the designated substance unless otherwise specified. The scan rate was 100 mV/s. For conversion to the Fc/Fc\(^+\) couple, it is known that Fc/Fc\(^+\) is 380 mV more positive than SCE in MeCN \(^{89}\) (and 350 mV more positive in MeNO\(_2\)) this value may be subtracted from obtained potentials in SCE to determine potentials against Fc/Fc\(^+\).

Upon oxidation, mesolytic cleavage of the TEMPO-substituted pyrroloindoline is apparent by liberation of TEMPO into solution:

**Figure S1**: The cyclic voltammogram of 2 overlayed with TEMPO vs. SCE in THF at 0.1V/s.

*Conditions*: 1mM of TEMPO-functionalized pyrroloindoline 2 or 0.1mM TEMPO in 0.1M tetrabutylammonium hexafluorophosphate solution. A glassy working electrode, SCE reference electrode, and platinum mesh counter electrode were used. The experiments were conducted at 23 °C.
Mesolytic cleavage of the *N*-Boc TEMPO-functionalized pyrroloindoline:

![Diagram showing one-electron oxidation](image)

\[ E_{1/2} = +1.28 \text{ V vs SCE (in THF)} \]

\[ E_{1/2} = +0.67 \text{ V vs SCE (in THF)} \]

**Figure S2:** The cyclic voltammogram of *N*-Boc TEMPO-functionalized pyrroloindoline 11 vs SCE in THF at 0.1V/s.

*Conditions:* 1mM of *N*-Boc TEMPO derivative and 0.1M tetrabutylammonium hexafluorophosphate. A glassy working electrode, SCE reference electrode, and platinum mesh counter electrode was used. The experiment was conducted in THF at 23 °C.
Determining the excited-state redox potential of [Ir(dF(CF₃)ppy)₂(dCF₃-bpy)]PF₆:

Ground state potentials were measured by cyclic voltammetry in MeCN with 0.1 M tetrabutylammonium hexafluorophosphate at room temperature using a 0.1 V/s scan rate with a negative initial direction. Excited state reduction potential was calculated using the Rehm-Weller equation: $E^{*\text{red}} = E^{\text{red}} + E_{0-0}$ where $E^{*\text{red}}$ denotes the excited state reduction potential, $E^{\text{red}}$ the ground state reduction potential, and $E_{0-0}$ the energy difference between the 0th vibration level of the ground state and that of the excited state. Due to the poor overlap between the absorption and emission spectra, $E_{0-0}$ is approximated as the high-energy onset of phosphorescence where the emission intensity is 10% of the obtained at the maximum emission wavelength, using the “10% rule.” These estimations were corroborated by approximating the HOMO-LUMO gap as the difference between the onset of oxidation and the onset of reduction.

![Structural diagram of [Ir(dF(CF₃)ppy)₂(dCF₃-bpy)]⁺]

Ir(II)/Ir(III): $E_{1/2} = -0.69$ V vs SCE
Ir(III)/Ir(IV): $E_{1/2} = +1.94$ V vs SCE
Ir(II)/Ir(II)*: $E_{1/2} = +1.68$ V vs SCE
Ir(III)*/Ir(IV): $E_{1/2} = -0.43$ V vs SCE

---

Figure S3: A cyclic voltammogram of \([\text{Ir}\{\text{dFCF}_3\text{ppy}\}_2(\text{5,5'}\text{dCF}_3\text{bpy})]\text{PF}_6\) with data tabulated. In cases where peaks are reversible, \(E_{1/2}\) is provided. Otherwise \(E_p\) is reported instead. The emission maxima of this complex was found to be 606 nm in acetonitrile at room temperature; the emission intensity was found to be 10% of the maxima at 524 nm. All potentials are provided against SCE.

Figure S4: Emission spectra for of \([\text{Ir}(\text{dF(CF}_3)\text{ppy})_2(\text{5,5'}\text{d(CF}_3\text{bpy})]\text{PF}_6\). The maximum was obtained at 606 nm; the intensity is 10% of the emission maxima at 524 nm.
DFT Calculations

All calculations in this chapter used DFT methodology as implemented in the Gaussian 16 series of computer programs. We employed the unrestricted B3LYP functional and 6-311G+ basis set. Calculations were performed with the CPCM polarizable conductor calculation model for MeCN. The absolute values were benchmarked with the experimental bond strength of styryl-TEMPO ether (30.8 kcal/mol). All complexes underwent geometry optimization, and stationary points were subjected to normal mode analysis.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Entry</th>
<th>E + ZPE (Hartrees)</th>
<th>G (Hartrees)</th>
<th>H (Hartrees)</th>
<th>S (cal K⁻¹ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-793.568782</td>
<td>-793.615977</td>
<td>-793.549559</td>
<td>139.858923</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-310.089772</td>
<td>-310.122024</td>
<td>-310.082486</td>
<td>83.256679</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-1439.223520</td>
<td>-1439.286075</td>
<td>-1439.193166</td>
<td>195.642036</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-955.742510 (-955.756564)</td>
<td>-955.792308 (-955.806851)</td>
<td>-955.724659 (-955.738599)</td>
<td>142.451087 (143.720847)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-955.517429 (-955.590778)</td>
<td>-955.566302 (-955.641290)</td>
<td>-955.499668 (-955.573046)</td>
<td>140.313763 (143.704001)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Thermodynamic stationary points. Values in parentheses are energies in MeCN.

---

**Figure S5**: Isodesmic reaction used for ground state BDFE calculation.

\[
\text{BDFE (C–O)} = (30.8 - 0.1) = 30.7 \text{ kcal/mol}
\]

**Figure S6**: Thermodynamic scheme for calculation of benzylic radical oxidation potential.$^9$ 

\[
E^0_{\text{vs NHE}} = 0.32 \text{ V} \\
E^0_{\text{vs Fc/Fc}^+} = -0.31 \text{ V}
\]

The BDFE of radical cation can be calculated using the thermodynamic cycle shown in Chapter 3:

<table>
<thead>
<tr>
<th>Compound</th>
<th>BDFE of neutral species (kcal/mol)</th>
<th>Oxidation potential of substrate (V vs. Fc/Fc$^+$)</th>
<th>Oxidation potential of radical (V vs. Fc/Fc$^+$)</th>
<th>BDFE of radical cation (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30.7</td>
<td>0.54</td>
<td>-0.31</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Appendix C

Supporting Information

for

Chapter 4

Asymmetric Total Synthesis of Pyrroloindoline Natural Products

Table of Contents

I. Synthesis and characterization of starting materials
II. Synthesis and characterization of products
III. Photochemical reaction setup
VII. $^1$H and $^{13}$C NMR Spectra
VIII. HPLC traces
**Benzyl (3αR,8αS)-8-methyl-3α-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-3,3α,8,8α-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate**

To a solution of MeI (2 equiv) and 2 (1 equiv) in THF (0.1M) was added NaHMDS (5 equiv) dropwise. Once addition is complete, the reaction was allowed to stir for 30 min then sat. NaHCO₃ solution was added and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using 2-5% EtOAc in hexanes to afford the desired product in 93% yield.

IR (thin film): 2931, 1702, 1609, 1411, 1360, 1195, 1094, 992, 939, 742, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 7.47 – 7.28 (m, 5H), 7.26 – 7.22 (m, 1H), 7.14 (tdd, J = 7.7, 6.2, 1.3 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.32 (dd, J = 21.3, 7.9 Hz, 1H), 6.16 (d, J = 37.2 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.11 – 3.91 (m, 1H), 3.15 – 2.80 (m, 4H), 2.62 (dt, J = 22.7, 12.1, 8.7 Hz, 1H), 2.36 – 2.25 (m, 1H), 1.55 – 1.18 (m, 6H), 1.09 (d, J = 3.8 Hz, 3H), 1.01 (d, J = 5.8 Hz, 3H), 0.84 (d, J = 14.8 Hz, 3H), 0.53 (d, J = 26.3 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃, ca. 55:45 mixture of rotamers) δ 155.21, 154.50, 152.15, 151.95, 136.97, 136.69, 131.22, 131.15, 129.85, 129.82, 128.65, 128.65, 128.59, 128.46, 128.25, 128.07, 127.92, 124.99, 124.92, 117.41, 117.24, 106.03, 105.94, 97.68, 96.59, 83.89, 82.97, 67.29, 66.98, 60.03, 59.98, 59.40, 45.27, 45.19, 41.50, 40.97, 40.94, 40.92, 40.54, 40.54, 33.64, 33.32, 33.29, 33.04, 33.02, 32.64, 20.79, 20.73, 20.50, 20.49, 17.17; HRMS (ESI) exact mass calculated for [M+H]⁺ (C₂₈H₃₈N₃O₃) requires m/z 464.29077, m/z found 464.29044 with a difference of 0.70 ppm. [α]D²¹ = -110 (c = 1.0, CHCl₃).
Synthesis of pyrroloindoline natural products:

Dibenzyl (3aS,3’aS,8aS,8’aS)-8-methyl-2,2’,3,3’,8,8a,8’,8’a-octahydro-1H,1’H-[3a,3’a-
bipyrrrolo[2,3-b]indole]-1,1’-dicarboxylate

To a flame dried 100-mL round bottom flask equipped with stir bar was added 24 (927 mg, 2 mmol, 1 equiv), N’-Cbz tryptamine 1 (882 mg, 3 mmol, 1.5 equiv), and [Ir(dCF3, Me-ppy)2(dtbbpy)]PF6 (48.6 mg, 0.04 mmol, 0.02 equiv). The reaction vessel was evacuated and backfilled with argon three times then anhydrous degassed CH2Cl2 (40 mL) was added. The reaction mixture was then cooled to -40 °C in an acetonitrile/dry ice bath and degassed trifluoroacetic acid (0.153 mL, 2 mmol, 1 equiv) was added at low temperature. After addition, the reaction was irradiated in one of two possible set ups (see Figures SX & SX): (1) in a cryocool bath with 7 W blue LEDs at -40 °C or (2) in an acetonitrile/dry ice bath with three 34W Kessil H150 blue lamps for 18 h or until complete conversion of starting material by TLC analysis at which point the reaction is deep magenta in color. Be careful to stop the reaction as soon as it reaches full conversion as product decomposition can occur under the reaction conditions. Upon completion, the reaction was immediately quenched with sat. aqueous NaHCO3 and the mixture was extracted with CH2Cl2 three times. The combined organic layer was dried over Na2SO4, filtered and concentrated in vacuo to yield a bright red-orange residue. This crude material was purified by column chromatography on silica gel using 5-15% ethyl acetate in hexanes with 1% added Et3N to yield the desired product as a 13:1 mixture of diastereomers (849 mg, 1.41 mmol, 71% yield, white solid) which were carried through to the next step without separation. The diastereomeric ratio was determined by 1H NMR analysis of the crude reaction mixture. The dr is retained following the above purification protocol. If desired, the diastereomers can be separated by preparative TLC on silica gel using 2% ethyl acetate in chloroform.
The desired product was determined to be 97% ee by HPLC analysis (ChiralPak AD-H, 25% IPA in hexanes, 1 mL/min, 250 nm, t (minor) = 12.6 min, t (major) = 14.0 min). IR (thin film): 3377, 2954, 2884, 1694, 1411, 1352, 1200, 1100, 746, 697 cm⁻¹. ¹H NMR (500 MHz, CD₃CN) δ 7.51 – 7.19 (m, 11H), 7.19 – 7.04 (m, 3H), 6.72 (p, J = 14.7, 7.4 Hz, 1H), 6.69 – 6.56 (m, 2H), 6.39 (d, J = 7.8 Hz, 1H), 5.51 – 5.25 (m, 1H), 5.18 – 4.92 (m, 5H), 4.79 (dd, J = 57.7, 44.7 Hz, 1H), 3.90 – 3.71 (m, 1H), 3.68 – 3.52 (m, 1H), 2.96 – 2.73 (m, 4H), 2.72 – 2.43 (m, 3H), 2.28 – 2.03 (m, 2H); ¹³C NMR (126 MHz, CD₃CN) δ 155.75, 155.71, 155.04, 154.80, 154.18, 152.91, 151.78, 151.66, 138.14, 138.06, 137.90, 130.23, 130.09, 130.05, 130.03, 129.98, 129.74, 129.59, 129.57, 129.47, 129.40, 129.37, 128.86, 128.78, 128.77, 128.65, 128.40, 128.25, 125.84, 125.75, 125.67, 125.59, 125.54, 125.44, 125.37, 125.10, 124.84, 119.34, 118.11, 118.02, 110.26, 110.10, 106.75, 84.71, 84.27, 84.25, 79.70, 79.63, 79.02, 67.32, 67.24, 67.16, 63.10, 63.04, 62.53, 62.34, 61.83, 61.43, 61.27, 60.86, 46.17, 46.14, 46.05, 45.91, 34.56, 34.22, 34.18, 32.89, 32.76, 32.53; HRMS (ESI) exact mass calculated for [M+H]^+ (C₃₇H₃₇N₄O₄) requires m/z 601.28094, found m/z 601.28211 with a difference of 1.96 ppm; [α]D²¹ = -198 (c = 1.00, CHCl₃).
(-)-calycanthidine

To a 250 mL flame dried two-neck round bottomed flask was added heterodimer 26 (849 mg, 1.41 mmol, 1 equiv). The compound was then azeotropically dried from anhydrous benzene (200mL) and the resulting residue was dissolved in anhydrous toluene (144mL). The reaction was equipped with a stir bar and reflux condenser then Red Al ® (70 wt% solution in toluene, 6.13 mL, 21.2 mmol, 15 equiv) was slowly added at room temperature. Following addition, the reaction was heated to reflux for 1 h. After completion, the solution was allowed to cool to rt then it was slowly quenched by sat. aqueous Na₂SO₄ solution until effervescence subsided and the resulting mixture was allowed to stir for 10 min. Solid Na₂SO₄ was then added and the mixture was stirred for another 10 min. The mixture was then poured through a plug of Celite washing thoroughly with CH₂Cl₂. The resulting solution was concentrated in vacuo to yield a light pink residue. Purification by flash column chromatography on silica gel using 1-4% aq. NH₄OH solution in acetonitrile yielded (-)-calycanthidine (27) as a white solid (404 mg, 1.12 mmol, 80% yield).

IR (thin film): 3315, 2932, 2791, 1603, 1488, 1251, 1155, 1024 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.08 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.99 (app-t, J = 7.8 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 6.53 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.47 (s, 1H), 4.38 (s, 1H), 3.00 (s, 3H), 2.68 – 2.42 (m, 8H), 2.40 (s, 3H), 2.35 (s, 3H), 2.04 – 1.91 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 153.14, 151.11, 133.64, 133.06, 128.28, 128.03, 124.58, 123.82, 118.42, 116.90, 109.17, 106.05, 92.25, 85.34, 63.66, 63.12, 52.83, 52.79, 38.11, 37.20, 35.94, 35.65, 35.54; HRMS (ESI)
exact mass calculated for [M+H]+ (C_{23}H_{29}N_{4}) requires m/z 361.23868, found m/z 361.23907 with a difference of 1.11 ppm; \([\alpha]_D^{21} = -115 \text{ (c = 1.00, CHCl}_3\).\(^95\)

**Table S1:** Comparison of \(^1\)H NMR data for (–)-calycanthidine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Overman’s Report(^96) (–)-calycanthidine (500 MHz, CDCl(_3), 50 °C)</th>
<th>Takayama’s Report(^97) (–)-calycanthidine (500 MHz, CDCl(_3), 50 °C)</th>
<th>Movassaghi’s Report(^98) (–)-calycanthidine (500 MHz, CDCl(_3), 50 °C)</th>
<th>This Work (–)-calycanthidine (500 MHz, CDCl(_3), 50 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1'-CH(_3)</td>
<td>2.41 (s, 3H)</td>
<td>2.38 (s, 3H)</td>
<td>2.38 (s, 3H)</td>
<td>2.40 (s, 3H)</td>
</tr>
<tr>
<td>N1-CH(_3)</td>
<td>2.36 (s, 3H)</td>
<td>2.33 (s, 3H)</td>
<td>2.33 (s, 3H)</td>
<td>2.35 (s, 3H)</td>
</tr>
<tr>
<td>C2'</td>
<td>2.68–2.42 (m, 2H)</td>
<td>2.65–2.40 (m, 2H)</td>
<td>2.65–2.40 (m, 2H)</td>
<td>2.68–2.42 (m, 2H)</td>
</tr>
<tr>
<td>C2</td>
<td>2.68–2.42 (m, 2H)</td>
<td>2.65–2.40 (m, 2H)</td>
<td>2.65–2.40 (m, 2H)</td>
<td>2.68–2.42 (m, 2H)</td>
</tr>
<tr>
<td>C3'</td>
<td>2.68–2.42 (m, 1H), 2.00–1.86 (m, 1H)</td>
<td>2.65–2.40 (m, 1H), 2.05–1.95 (m, 1H)</td>
<td>2.65–2.40 (m, 1H), 2.01–1.93 (m, 1H)</td>
<td>2.68–2.42 (m, 1H), 2.04–1.91 (m, 1H)</td>
</tr>
<tr>
<td>C3</td>
<td>2.68–2.42 (m, 1H), 2.00–1.86 (m, 1H)</td>
<td>2.65–2.40 (m, 1H), 2.05–1.95 (m, 1H)</td>
<td>2.65–2.40 (m, 1H), 2.01–1.93 (m, 1H)</td>
<td>2.68–2.42 (m, 1H), 2.04–1.91 (m, 1H)</td>
</tr>
<tr>
<td>C3a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C3a'</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C4'</td>
<td>7.10 (d, J = 7.3 Hz, 1H)</td>
<td>7.07 (d, J = 7.3 Hz, 1H)</td>
<td>7.06 (d, J = 7.4 Hz, 1H)</td>
<td>7.08 (d, J = 7.5 Hz, 1H)</td>
</tr>
<tr>
<td>C4</td>
<td>7.05 (d, J = 7.2 Hz, 1H)</td>
<td>7.02 (d, J = 7.3 Hz, 1H)</td>
<td>7.00 (d, J = 5.8 Hz, 1H)</td>
<td>7.03 (d, J = 7.2 Hz, 1H)</td>
</tr>
<tr>
<td>C4a'</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C4a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C5'</td>
<td>6.55 (t, J = 7.4 Hz, 1H)</td>
<td>6.52 (dd, J = 7.3, 7.3 Hz, 1H)</td>
<td>6.51 (app-t, J = 7.2 Hz, 1H)</td>
<td>6.53 (t, J = 7.3 Hz, 1H)</td>
</tr>
<tr>
<td>C5</td>
<td>6.58 (t, J = 7.4 Hz, 1H)</td>
<td>6.59 (dd, J = 7.3, 7.3 Hz, 1H)</td>
<td>6.58 (app-t, J = 7.5 Hz, 1H)</td>
<td>6.60 (t, J = 6.9 Hz, 1H)</td>
</tr>
</tbody>
</table>


### Table S2: Comparison of $^{13}$C NMR data for (−)-calycanthidine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Overman’s Report</th>
<th>Takayama’s Report</th>
<th>Movassaghi’s Report</th>
<th>This Work</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(−)-calycanthidine (500 MHz, CDCl$_3$, 50 °C)</td>
<td>(−)-calycanthidine (500 MHz, CDCl$_3$, 50 °C)</td>
<td>(−)-calycanthidine (500 MHz, CDCl$_3$, 50 °C)</td>
<td>(−)-calycanthidine (500 MHz, CDCl$_3$, 50 °C)</td>
</tr>
<tr>
<td>N1'-CH$_3$</td>
<td>37.9</td>
<td>37.9</td>
<td>38.2</td>
<td>38.1</td>
</tr>
<tr>
<td>N1'-C</td>
<td>37.0</td>
<td>37.0</td>
<td>37.3</td>
<td>37.2</td>
</tr>
<tr>
<td>C2'</td>
<td>52.6</td>
<td>52.6</td>
<td>52.9</td>
<td>52.8</td>
</tr>
<tr>
<td>C2</td>
<td>52.6</td>
<td>52.6</td>
<td>52.9</td>
<td>52.8</td>
</tr>
<tr>
<td>C3'</td>
<td>35.7</td>
<td>35.7</td>
<td>35.7</td>
<td>35.9</td>
</tr>
<tr>
<td>C3</td>
<td>35.7</td>
<td>35.7</td>
<td>35.6</td>
<td>35.7</td>
</tr>
<tr>
<td>C3a</td>
<td>62.9</td>
<td>62.8</td>
<td>63.2</td>
<td>63.1</td>
</tr>
<tr>
<td>C3a'</td>
<td>63.5</td>
<td>63.2</td>
<td>63.8</td>
<td>63.7</td>
</tr>
<tr>
<td>C4'</td>
<td>123.6</td>
<td>123.6</td>
<td>124.0</td>
<td>123.8</td>
</tr>
<tr>
<td>C4</td>
<td>124.4</td>
<td>124.4</td>
<td>124.7</td>
<td>124.6</td>
</tr>
<tr>
<td>C4a'</td>
<td>132.9</td>
<td>132.7</td>
<td>133.1</td>
<td>133.1</td>
</tr>
<tr>
<td>C4a</td>
<td>133.4</td>
<td>133.3</td>
<td>133.6</td>
<td>133.6</td>
</tr>
<tr>
<td>C5'</td>
<td>116.7</td>
<td>116.7</td>
<td>117.1</td>
<td>116.9</td>
</tr>
<tr>
<td>C5</td>
<td>118.2</td>
<td>118.2</td>
<td>118.6</td>
<td>118.4</td>
</tr>
<tr>
<td>C6'</td>
<td>128.1</td>
<td>128.1</td>
<td>128.4</td>
<td>128.3</td>
</tr>
<tr>
<td>C6</td>
<td>127.8</td>
<td>127.9</td>
<td>128.2</td>
<td>128.0</td>
</tr>
<tr>
<td>C7'</td>
<td>105.8</td>
<td>105.9</td>
<td>106.2</td>
<td>106.1</td>
</tr>
<tr>
<td>C7</td>
<td>108.9</td>
<td>109.0</td>
<td>109.3</td>
<td>109.1</td>
</tr>
<tr>
<td>C7a'</td>
<td>152.9</td>
<td>152.8</td>
<td>153.2</td>
<td>153.1</td>
</tr>
<tr>
<td>C7a</td>
<td>151.0</td>
<td>150.8</td>
<td>151.2</td>
<td>151.1</td>
</tr>
<tr>
<td>N8'-CH$_3$</td>
<td>35.4</td>
<td>35.4</td>
<td>35.6</td>
<td>35.5</td>
</tr>
<tr>
<td>N8'-H</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C8a'</td>
<td>92.1</td>
<td>91.8</td>
<td>92.4</td>
<td>92.3</td>
</tr>
<tr>
<td>C8a</td>
<td>85.1</td>
<td>85.0</td>
<td>85.5</td>
<td>85.3</td>
</tr>
</tbody>
</table>
To a flame dried vial equipped with stir bar was added 2 (112 mg, 0.25 mmol, 1 equiv), N'-Cbz tryptamine 1 (88 mg, 0.3 mmol, 1.2 equiv), and [Ir(dCF3, Me-ppy)2(dtbbpy)]PF6 (6.1 mg, 0.005 mmol, 0.02 equiv). The reaction vessel was evacuated and backfilled with argon three times then anhydrous degassed THF (2.5 mL) was added. The reaction mixture was then cooled to -40 °C in an acetonitrile/dry ice bath and degassed trifluoroacetic acid (0.057 mL, 0.75 mmol, 3 equiv) was added at low temperature. After addition, the reaction was irradiated with 7 W blue LEDs in a -40 °C cryocool bath (see Figure S3) for 36 h or until complete conversion of starting material by TLC analysis. Upon completion, the reaction was quenched with sat. aqueous NaHCO3 and the mixture was extracted with CH2Cl2 three times. The combined organic layer was dried over Na2SO4, filtered and concentrated in vacuo. This residue was purified by column chromatography on silica gel using 5-20% ethyl acetate in hexanes with 1% added Et3N to yield the desired product as a 3:1 mixture of diastereomers as determined by 1H NMR analysis (79 mg, 0.135 mmol, 54% yield).

To a vial containing this purified 3:1 mixture of diastereomers was added [Ir(dCF3, Me-ppy)2(dtbbpy)]PF6 (3.3 mg, 0.0027 mmol, 0.02 equiv) and THF (1.35 mL). The reaction vial was equipped with a septa and cap and a large-gauged needle was pierced into the septa to expose the reaction to air. The reaction mixture was then irradiated with 7 W blue LEDs at -40 °C for 24 h or until the product composition reached >20:1 dr by 1H NMR analysis. Upon completion, the reaction mixture was concentrated in vacuo and the
Residue was purified by column chromatography using 5-20% ethyl acetate in hexanes with 1% added Et3N to yield the product as a single diastereomer in 69% yield.

IR (thin film): 3369, 2955, 1687, 1414, 1352, 1199, 1105, 746, 696 cm⁻¹; ¹H NMR (500 MHz, CD3CN) δ 7.41 – 7.20 (m, 13H), 7.11 (q, J = 8.4 Hz, 2H), 6.74 (td, J = 7.4, 3.7 Hz, 2H), 6.66 – 6.58 (m, 2H), 5.36 (dd, J = 83.4, 15.5 Hz, 2H), 5.17 – 4.89 (m, 4H), 4.80 (dd, J = 39.7, 15.6 Hz, 2H), 3.59 (ddd, J = 10.4, 7.9, 5.4 Hz, 2H), 2.83 – 2.69 (m, 2H), 2.66 – 2.53 (m, 2H), 2.26 – 2.18 (m, 2H); ¹³C NMR (126 MHz, CD3CN) δ 155.06, 154.19, 151.89, 151.85, 151.77, 151.73, 138.16, 138.13, 137.94, 130.09, 129.49, 129.41, 129.38, 128.87, 128.82, 128.66, 128.40, 126.19, 126.08, 125.98, 119.30, 118.30, 110.19, 110.16, 110.05, 110.01, 79.54, 78.85, 67.24, 62.89, 62.73, 61.64, 61.47, 46.12, 45.97, 32.74, 32.70, 32.65, 32.60; HRMS (ESI) exact mass calculated for [M+H]⁺ (C₃₆H₃₅N₄O₄) requires m/z 587.26529, found m/z 587.26451 with a difference of 1.32 ppm; [α]₂₁ = -168 (c = 1.00, CHCl₃).

(-)-chimonanthine

To a flame dried round bottomed flask was added homodimer 28 (55 mg, 0.094 mmol, 1 equiv). The compound was then azeotropically dried from anhydrous benzene (15 mL) and the resulting residue was dissolved in anhydrous toluene (10 mL). The reaction was equipped with a stir bar and reflux condenser then Red Al ® (70 wt% solution in toluene, 0.271 mL, 0.94 mmol, 10 equiv) was slowly added at room temperature. Following addition, the reaction was heated to reflux for 30 min. After completion, the solution was allowed to cool to rt then it was slowly quenched by sat. aqueous Na₂SO₄ solution until effervescence subsided and the resulting mixture was allowed to stir for 10 min. Solid Na₂SO₄ was then added and the mixture was stirred for another 10 min. The mixture was then poured through a plug of
Celite washing thoroughly with CH$_2$Cl$_2$. The resulting solution was concentrated in vacuo. Purification by flash column chromatography on silica gel using 2-5% aq. NH$_4$OH solution in acetonitrile yielded (−)-chimonanthine (29) as a white solid (25.7 mg, 0.074 mmol, 79% yield).

IR (thin film): 3308, 2932, 1605, 1485, 1246, 734; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.18 (d, J = 7.4 Hz, 2H), 6.97 (t, 2H), 6.65 (t, 2H), 6.52 (d, J = 7.8 Hz, 2H), 4.38 (s, 3H), 4.18 (s, 2H), 2.74 – 2.44 (m, 6H), 2.32 (s, 6H), 2.18 – 1.95 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.94, 133.55, 128.15, 124.54, 118.67, 109.30, 85.40, 63.66, 52.82, 37.26, 35.87; HRMS (ESI) exact mass calculated for [M+H]$^+$ (C$_{22}$H$_{27}$N$_4$) requires m/z 347.22303, found m/z 347.22318 with a difference of 0.45 ppm; $[\alpha]_D^{21} = -139$ (c = 1.00, CHCl$_3$).  

### Table S3: Comparison of our $^1$H NMR data for (–)-chimonanthine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Verotta’s Report$^{100}$ (+)-chimonanthine (200 MHz, CDCl$_3$)</th>
<th>Movassaghi’s Report$^{101}$ (+)-chimonanthine (500 MHz, CDCl$_3$, 50 °C)</th>
<th>This Work (–)-chimonanthine (500 MHz, CDCl$_3$, 50 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>2.50 (m, 4H)</td>
<td>2.57 (m, 2H)</td>
<td>2.63-2.44 (m, 4H)</td>
</tr>
<tr>
<td>C3</td>
<td>2.50 (m, 2H), 2.07 (dt, $J = 12.0$, 6.4 Hz, 2H)</td>
<td>2.57 (m, 2H), 2.05 (app dd, $J = 10.5$, 5.0 Hz, 2H)</td>
<td>2.63-2.44 (m, 2H), 2.13-1.99 (m, 2H)</td>
</tr>
<tr>
<td>C3a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C4</td>
<td>7.20, (d, $J = 7.4$ Hz, 2H)</td>
<td>7.19 (d, $J = 7.5$ Hz, 2H)</td>
<td>6.52 (d, $J = 7.3$ Hz, 2H)</td>
</tr>
<tr>
<td>C4a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C5</td>
<td>6.67 (t, $J = 7.3$ Hz, 2H)</td>
<td>6.66 (t, $J = 7.3$, 2H)</td>
<td>6.65 (t, $J = 7.3$ Hz, 2H)</td>
</tr>
<tr>
<td>C6</td>
<td>7.00 (t, $J = 7.6$ Hz, 2H)</td>
<td>6.98 (t, $J = 7.3$ Hz, 2H)</td>
<td>6.99 (t, $J = 7.3$ Hz, 2H)</td>
</tr>
<tr>
<td>C7</td>
<td>6.55, (d, $J = 7.7$ Hz, 2H)</td>
<td>6.53 (d, $J = 7.5$ Hz, 2H)</td>
<td>6.52 (d, $J = 7.3$ Hz, 2H)</td>
</tr>
<tr>
<td>C7a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>N8-H</td>
<td>–</td>
<td>4.23 (s, 2H)</td>
<td>4.18 (br s, 2H)</td>
</tr>
<tr>
<td>C8a</td>
<td>4.35 (br s, 2H)</td>
<td>4.40 (br s, 2H)</td>
<td>4.38 (br s, 2H)</td>
</tr>
<tr>
<td>N1-CH$_3$</td>
<td>2.31 (s, 6H)</td>
<td>2.33 (s, 6H)</td>
<td>2.32 (s, 6H)</td>
</tr>
</tbody>
</table>


Table S4: Comparison of our $^{13}$C NMR data for (–)-chimonanthine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Tokuyama’s Report $^{100}$ (+)-chimonanthine (25.05 MHz, CDCl₃)</th>
<th>Movassaghi’s Report $^{101}$ (+)-chimonanthine (125.8 MHz, CDCl₃, 50 ºC)</th>
<th>This Work (–)-chimonanthine (125.8 MHz, CDCl₃, 50 ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>52.7</td>
<td>52.9</td>
<td>52.8</td>
</tr>
<tr>
<td>C3</td>
<td>36.5</td>
<td>36.1</td>
<td>35.9</td>
</tr>
<tr>
<td>C3a</td>
<td>63.2</td>
<td>63.8</td>
<td>63.7</td>
</tr>
<tr>
<td>C4</td>
<td>124.4</td>
<td>124.6</td>
<td>124.5</td>
</tr>
<tr>
<td>C4a</td>
<td>133.1</td>
<td>133.8</td>
<td>133.6</td>
</tr>
<tr>
<td>C5</td>
<td>118.7</td>
<td>118.8</td>
<td>118.7</td>
</tr>
<tr>
<td>C6</td>
<td>128.1</td>
<td>128.2</td>
<td>128.2</td>
</tr>
<tr>
<td>C7</td>
<td>109.4</td>
<td>109.4</td>
<td>109.3</td>
</tr>
<tr>
<td>C7a</td>
<td>150.6</td>
<td>151.1</td>
<td>150.9</td>
</tr>
<tr>
<td>N8-H</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C8a</td>
<td>85.2</td>
<td>85.5</td>
<td>85.4</td>
</tr>
<tr>
<td>N1-CH₃</td>
<td>37.2</td>
<td>37.4</td>
<td>37.3</td>
</tr>
</tbody>
</table>

Benzyl (3aR,8aS)-3a-(3-(2-((methoxycarbonyl)amino)ethyl)-1H-indol-1-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate

Preparation of the title compound was adapted from the synthesis of a related compound.$^{1}$ To a flask was added aniline 22 (82 mg, 0.16 mmol, 1 equiv), alkyne 30 (73 mg, 0.392 mmol, 2.5 equiv), Na₂CO₃ (42 mg, 0.392 mmol, 2.5 equiv), LiCl (6.0 mg, 0.141 mmol, 0.9 equiv) and Pd(OAc)₂ (7.1 mg, 0.031 mmol, 0.2 equiv). The vessel was evacuated and backfilled with argon three times before degassed anhydrous DMF (3.14 mL) was added and the resulting suspension was sparged with argon for 15 minutes. The reaction was heated to 100 ºC for 30 min then allowed to cool, diluted with CH₂Cl₂ and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate and washed with 2M HCl. The layers were separated and...
the aqueous layer was extracted with EtOAc (5x). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give a residue that was purified by column chromatography on silica gel with 2-10% EtOAc/CH₂Cl₂ to yield the desired product as a white foam in 83% yield.

IR (thin film): 3347, 1697, 1456, 1352, 1256, 1196, 745 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.59 (t, J = 8.0 Hz, 1H), 7.41 – 7.31 (m, 6H), 7.25 – 7.19 (m, 2H), 7.19 – 7.09 (m, 2H), 6.95 (d, J = 5.6 Hz, 1H), 6.84 (q, J = 7.8 Hz, 1H), 6.71 (dd, J = 33.6, 7.9 Hz, 1H), 5.94 (d, J = 30.0 Hz, 1H), 5.28 – 5.11 (m, 2H), 4.75 (d, J = 38.4 Hz, 1H), 4.16 – 3.93 (m, 1H), 3.65 (s, 3H), 3.53 – 3.22 (m, 4H), 2.88 (t, J = 6.9 Hz, 2H), 2.71 – 2.56 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 157.16, 154.99, 154.16, 149.40, 149.18, 136.31, 135.39, 135.29, 130.88, 130.80, 129.90, 129.85, 128.87, 128.71, 128.51, 128.37, 128.20, 128.15, 126.90, 126.66, 125.09, 124.90, 124.33, 124.30, 122.15, 121.50, 119.86, 119.73, 119.60, 119.57, 119.45, 112.20, 112.06, 110.67, 110.50, 79.55, 78.94, 77.41, 77.16, 76.91, 75.86, 74.66, 67.60, 67.38, 52.16, 45.77, 45.58, 41.45, 35.83, 35.65, 25.87; HRMS (ESI) exact mass calculated for [M+H]+ (C₃₀H₃₁N₄O₄) requires m/z 511.23399, found m/z 511.23416 with a difference of 0.35 ppm; [α]D²¹ = -165 (c = 1.00, CHCl₃).
To a 25 mL flame dried round bottomed flask was added benzyl (3aR,8aS)-3a-(3-(2-((methoxycarbonyl)amino)ethyl)-1H-indol-1-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (66.5 mg, 0.13 mmol, 1 equiv). The compound was then azeotropically dried from anhydrous benzene (20 mL) and the resulting residue was dissolved in anhydrous toluene (13.5 mL). The reaction was equipped with a stir bar and reflux condenser then Red Al ® (70 wt% solution in toluene, 0.375 mL, 1.3 mmol, 10 equiv) was slowly added at room temperature. Following addition, the reaction was heated to reflux for 30 min. After completion, the solution was allowed to cool to rt then it was slowly quenched by sat. aqueous Na₂SO₄ solution until effervescence subsided and the resulting mixture was allowed to stir for 10 min. Solid Na₂SO₄ was then added and the mixture was stirred for another 10 min. The mixture was then poured through a plug of Celite washing thoroughly with CH₂Cl₂. The resulting solution was concentrated in vacuo. Purification by flash column chromatography on silica gel using 1% aq. NH₄OH solution in acetonitrile yielded (−)-psychotriasine (31) as a white solid (38.2 mg, 0.111 mmol, 85% yield).

IR (thin film): 3382, 2928, 1608, 1486, 1459, 742 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 7.53 (dt, J = 8.0, 0.9 Hz, 1H), 7.41 (s, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.07 (td, J = 7.7, 1.2 Hz, 1H), 7.01 – 6.90 (m, 2H), 6.86 (dd, J = 7.5, 0.7 Hz), 6.70 (d, J = 7.8 Hz, 1H), 6.58 (td, J = 7.4, 1.0 Hz, 1H), 5.23 (s, 1H), 3.27 – 3.18 (m, 1H), 3.02 – 2.93 (m, 3H), 2.92 – 2.85 (m, 2H), 2.66 – 2.57 (m, 1H), 2.52 – 2.45 (m, 4H), 2.42 (s, 3H); ¹³C NMR (126 MHz, CD₃OD) δ 152.56, 137.76, 131.46, 130.84, 130.65, 125.08, 124.71, 122.44, 120.16, 119.69, 119.54, 113.00, 112.93, 110.11, 87.08, 77.48, 52.86, 52.15, 39.99, 36.34, 35.85, 25.75. HRMS
(ESI) exact mass calculated for \([M+H]^+\) (C\(_{22}\)H\(_{27}\)N\(_4\)) requires \(m/z\) 347.22303, found \(m/z\) 347.22250 with a difference of 1.50 ppm. \(\alpha\)D\(_{21}\) = -97 \((c = 0.33, \text{MeOH})\).\(^{102}\)

Table S5: Comparison of \(^1\)H NMR data for (–)-psychotriasine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Hao’s Report(^{103}) (+)-psychotriasine (500 MHz, CD(_3)OD)</th>
<th>This Work (–)-psychotriasine (500 MHz, CD(_3)OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N’-CH(_3)</td>
<td>2.39 (s, 3H)</td>
<td>2.42 (s, 3H)</td>
</tr>
<tr>
<td>N-CH(_3)</td>
<td>2.44 (s, 3H)</td>
<td>2.47 (s, 3H)</td>
</tr>
<tr>
<td>C2’</td>
<td>2.96-2.93 (m, 1H), 2.57-2.54 (m, 1H)</td>
<td>3.01-2.97 (m, 1H), 2.64-2.58 (m, 1H)</td>
</tr>
<tr>
<td>C2</td>
<td>7.38 (s, 1H)</td>
<td>7.41 (s, 1H)</td>
</tr>
<tr>
<td>C3’</td>
<td>3.30-3.28 (m, 1H), 2.49-2.46 (m, 1H)</td>
<td>3.26-3.19 (m, 1H), 2.51-2.48 (m, 1H)</td>
</tr>
<tr>
<td>C3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C3a</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C3a’</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C4’</td>
<td>7.12 (dd, (J = 7.8, 1.0) Hz)</td>
<td>7.13 (d, (J = 8.1) Hz, 1H)</td>
</tr>
<tr>
<td>C4</td>
<td>6.85 (dd, (J = 7.8, 1.0) Hz)</td>
<td>6.86 (dd, (J = 7.5, 0.7) Hz)</td>
</tr>
<tr>
<td>C4a’</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C5’</td>
<td>6.94 (dt, (J = 7.8, 1.0) Hz)</td>
<td>6.96-6.91 (m, 1H)</td>
</tr>
<tr>
<td>C5</td>
<td>6.97 (dt, (J = 7.8, 1.0) Hz)</td>
<td>6.98 (td, (J = 7.8, 1.2) Hz)</td>
</tr>
<tr>
<td>C6’</td>
<td>6.56 (dt, (J = 7.8, 1.0) Hz)</td>
<td>6.58 (td, (J = 7.4, 1.0) Hz, 1H)</td>
</tr>
<tr>
<td>C6</td>
<td>7.04 (dt, (J = 7.8, 1.0) Hz)</td>
<td>7.07 (td, (J = 7.7, 1.2) Hz, 1H)</td>
</tr>
<tr>
<td>C7’</td>
<td>6.68 (dd, (J = 7.8, 1.0) Hz)</td>
<td>6.70 (d, (J = 7.8) Hz, 1H)</td>
</tr>
<tr>
<td>C7</td>
<td>7.52 (dd, (J = 7.8, 1.0) Hz)</td>
<td>7.53 (dt, (J = 8.1, 1.0) Hz)</td>
</tr>
<tr>
<td>C7a’</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C7a</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>N8’-H</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C8</td>
<td>2.94-2.91 (m, 2H)</td>
<td>2.98-2.94 (m, 2H)</td>
</tr>
<tr>
<td>C8a’</td>
<td>5.20 (s)</td>
<td>5.23 (s, 1H)</td>
</tr>
<tr>
<td>C9</td>
<td>2.88-2.85 (m, 2H)</td>
<td>2.91-2.85 (m, 1H)</td>
</tr>
</tbody>
</table>


**Table S6:** Comparison of $^{13}$C NMR data for (−)-psychotriasine:

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Hao’s Report (+)-psychotriasine (500 MHz, CD$_3$OD)</th>
<th>This Work (−)-psychotriasine (500 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N’-CH$_3$</td>
<td>35.7</td>
<td>35.9</td>
</tr>
<tr>
<td>N-CH$_3$</td>
<td>36.3</td>
<td>36.3</td>
</tr>
<tr>
<td>C2’</td>
<td>52.0</td>
<td>52.2</td>
</tr>
<tr>
<td>C2</td>
<td>125.0</td>
<td>125.1</td>
</tr>
<tr>
<td>C3’</td>
<td>39.9</td>
<td>40.0</td>
</tr>
<tr>
<td>C3</td>
<td>112.7</td>
<td>112.9</td>
</tr>
<tr>
<td>C3a</td>
<td>130.4</td>
<td>130.8</td>
</tr>
<tr>
<td>C3a’</td>
<td>79.4</td>
<td>77.5</td>
</tr>
<tr>
<td>C4’</td>
<td>112.2</td>
<td>113.0</td>
</tr>
<tr>
<td>C4</td>
<td>124.7</td>
<td>124.7</td>
</tr>
<tr>
<td>C4a’</td>
<td>131.3</td>
<td>131.5</td>
</tr>
<tr>
<td>C5’</td>
<td>122.4</td>
<td>122.5</td>
</tr>
<tr>
<td>C5</td>
<td>120.1</td>
<td>120.2</td>
</tr>
<tr>
<td>C6’</td>
<td>119.6</td>
<td>119.5</td>
</tr>
<tr>
<td>C6</td>
<td>130.7</td>
<td>130.7</td>
</tr>
<tr>
<td>C7’</td>
<td>110.0</td>
<td>110.1</td>
</tr>
<tr>
<td>C7</td>
<td>120.1</td>
<td>119.7</td>
</tr>
<tr>
<td>C7a’</td>
<td>152.5</td>
<td>152.6</td>
</tr>
<tr>
<td>C7a</td>
<td>137.7</td>
<td>137.8</td>
</tr>
<tr>
<td>N8’-H</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C8</td>
<td>25.6</td>
<td>25.8</td>
</tr>
<tr>
<td>C8a’</td>
<td>87.0</td>
<td>87.1</td>
</tr>
<tr>
<td>C9</td>
<td>52.0</td>
<td>52.9</td>
</tr>
</tbody>
</table>
The photoredox reactions run at low temperature can be set up in one of two ways:

(1) In a -40 °C Cryocool bath for optimum temperature control:

For this protocol, a submersible blue LED apparatus was made from a 2L beaker fused to a 300mL tall form beaker with an open bottom allowing the reaction to be effectively cooled. Two blue LED strips were wrapped around the outside of the inner beaker. The reaction was placed in the center of the inner beaker, approximately 2 cm from the light source.

Figure S1: Low temperature cryocool set up.
(2) In an acetonitrile/dry ice bath irradiated with three 34W Kessil lamps:

A large dewar was filled with an acetonitrile/dry ice mixture to maintain a temperature of -40 °C or lower.

**Figure S2:** Acetonitrile/dry ice bath set up for low temperature reactions. Picture on the right is filtered by blue-blocking lenses.