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Two Studies: Stereoselective C-C Bond Formations of N-Boc-Piperidines using Selected Organolithiums and Visible-Light-Mediated Synthesis of Fused Indolines using Tethered Styrenes

Scott Alan Morris

University of Arkansas, Fayetteville

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Two Studies: Stereoselective C–C Bond Formations of *N*-Boc–Piperidines using Selected Organolithiums and Visible–Light–Mediated Synthesis of Fused Indolines using Tethered Styrenes

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

By

Scott Alan Morris
Stephen F. Austin State University
Bachelor of Science in Biochemistry, 2010

August 2016
University of Arkansas

This dissertation is approved for recommendation to the Graduate Council.

Nan Zheng, Ph.D.
Committee Chair

Matthias McIntosh, Ph.D.
Committee Member

Neil Allison, Ph.D.
Committee Member

Bill Durham, Ph.D.
Committee Member

Abstract

Chemists worldwide have accepted the challenge of developing methods to access a variety of compounds as single enantiomers, including the use of enzymes, chiral auxiliaries, and resolutions. In particular, dynamic resolutions offer a unique way to access chiral compounds using a few controllable steps, including the variation of both time and temperature. Many groups have implemented this methodology to generate various polysubstituted pyrrolidines and piperidines, which are substructures ranking high on the list of nitrogen-containing pharmaceuticals.

The Gawley group revealed a catalytic dynamic resolution (CDR) of *N*-Boc-piperidine using a chiral ligand. Impressively, the chemistry was tolerant of a variety of electrophiles and generated the products with high enantioselectivity. However, due to unknown reasons, reproducibility emerged as an issue regarding this methodology. In this document, meticulous studies on factors that affect the CDR are discussed, including ligand purity, temperature studies, and impurity detection. Additionally, studies on the diastereoselective synthesis of α,α,α' -trisubstituted is presented, including 2D NMR data that aided in determining the relative configurations of select products.

Another focus was also pursued due to the unexpected passing of Dr. Bob Gawley. Visible light has recently emerged as a valuable reagent in the synthesis of organic molecules in the presence of a photoredox catalyst. This discovery has opened the doors for synthetic chemists to provide important molecules using sustainable methods.

Nan Zheng recently revealed an oxidative C–N bond-forming cascade of styrenyl anilines to yield a variety of substituted indoles using visible light photoredox catalysis. They proposed a benzylic cation intermediate that ultimately forms an indole by deprotonation in an

E1 fashion. In this document, the synthesis of C2,C3 fused indolines is presented using a similar approach. Using styryl anilines tethered with a nucleophile, the benzylic cation intermediate was effectively trapped in a S_N1 fashion to generate various fused indolines as single diastereomers. Additionally, detailed synthetic routes, including the challenges in substrate syntheses, as well as the limits of this photoredox cascade is presented.

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Acknowledgements

I thank my mom and dad for their support and love over the years. I would not be where I am today without your constant encouragement. I would also like to thank my church family for always being there for me during difficult trials in graduate school. I also thank all the believers I have come to know and love within our department. Thank you for your many prayers.

I thank my advisor, Dr. Nan Zheng, for openly accepting me into his group, paying attention to details, and helping me finish punctually. I also thank my deceased advisor, Professor Bob Gawley, for his support in my early years in graduate school and strongly motivating me to work hard. I also thank Drs. Neil Allison, Matt McIntosh, and Bill Durham for serving on my committee and always pushing me to be a better scientist.

I am also thankful for Dr. Jim Hinton and Kz Shein for their help running NMR experiments. I also thank my professors from Stephen F. Austin State University, namely Drs. Michele Harris, Michael Janusa, Russell Franks, and Alyx Frantzen for laying an incredible chemistry foundation prior to graduate school and for their ongoing communication with me about my progress as a scientist.

I thank Beng, Barry, Pooja, and Liz for their fruitful scientific conversations and their joyful attitudes during graduate school. I also thank the members of the Zheng group, especially Jiang and Theresa, for not only regarding me as a colleague but as a friend. I am grateful for all the help you have offered in the Zheng lab and wish the best for you in the future.

I thank my wonderful wife, Jacqueline, for her character and integrity. I love you very much and am blessed to be your husband.

Most of all, I thank Jesus Christ for saving me in my second year, opening my eyes to see meaning in life and giving me a future hope.

Dedication

I would like to dedicate this dissertation to my brother, David Morris. I am so grateful for the opportunity to get to go to college and achieve higher degrees, and you have served as my motivation to not waste what God has given me. Love ya bro!

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Chapter 4, published

Morris, S. A.; Nguyen, T. H.; Zheng, N., Diastereoselective Oxidative C-N/C-O and C-N/C-N Bond Formation Tandems Initiated by Visible Light: Synthesis of Fused N-Arylindolines. *Adv. Synth. Catal.* **2015**, 357 (10), 2311-2316.

Appendix C, published

Nguyen, T. H.; Morris, S. A.; Zheng, N., Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes, Enynes, and Diynes via Visible Light Photocatalysis. *Adv. Synth. Catal.* **2014**, 356 (13), 2831-2837.

Chapter 1

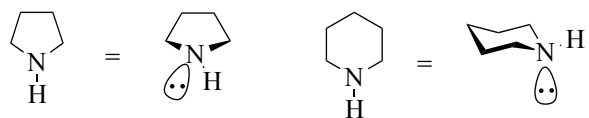
Synthesis of Chiral, Nonracemic Heterocycles using Organolithium Chemistry

One of the many pressing issues facing chemists today is the asymmetric synthesis of organic compounds. From pharmaceuticals¹ to pesticides,² fragrances³ to food flavorings,⁴ the synthesis of enantiopure compounds is seen as a worthy opponent facing numerous chemists.⁵ Since many drugs are chiral, it is essential to develop enantiopure pharmaceuticals in inexpensive, enantiopure form for FDA evaluation. Substituted piperidines and pyrrolidines are among the most common structural subunits in natural products and pharmaceuticals; therefore, enantioselective synthesis of these heterocycles has intrigued chemists over the past 20 years.^{6,7} Numerous approaches, ranging from the cyclization of chiral, nonracemic substrates^{8,9} to direct stereospecific attachment by way of asymmetric induction using some chiral component^{10,11} have been identified as viable routes to access these heterocycles asymmetrically.

1.1. Pyrrolidines and Piperidines

Pyrrolidine and piperidine rings are important scaffolds for drug discovery, an observation realized over a decade ago by Watson, who stated that there were [at that time] “over 12,000 discrete piperidine entities that have been mentioned in clinical or preclinical studies.”¹² Moreover, according to the Njardarson group at the University of Arizona, 14 of the top 100 drugs by retail sales in 2013 contained a pyrrolidine or piperidine ring.¹³ Pyrrolidine adopts an envelope conformation, while piperidine prefers a chair conformation with the lone-pair of electrons on the nitrogen conformed axially (Figure 1.1).

Figure 1.1. Conformations of Pyrrolidine and Piperidine

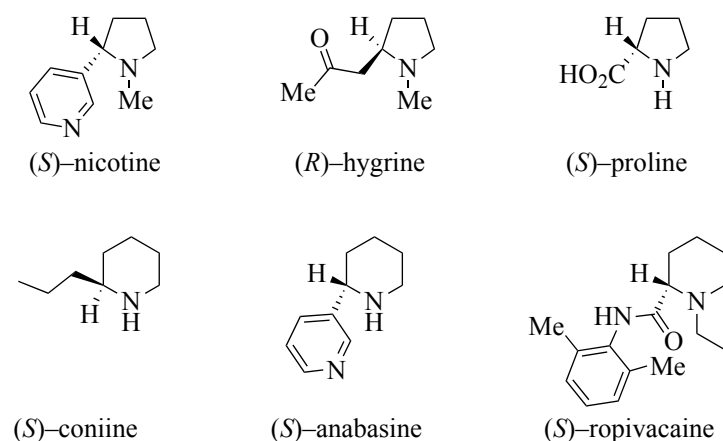


The asymmetric synthesis of substituted pyrrolidines and piperidines has been a hot topic among synthetic chemists, with much success coming from the groups of Beak,¹⁴ Charette,¹¹ Coldham,^{15,16} Comins,¹⁷ and Gawley.^{18,19} Due to the robust structure of these heterocycles and configurational stability at low temperatures, derivatization of simple pyrrolidines and piperidines utilizing functionalized organolithiums has been a successful method in accessing the substituted frameworks.

1.1.1. Pyrrolidine and Piperidine Natural Products

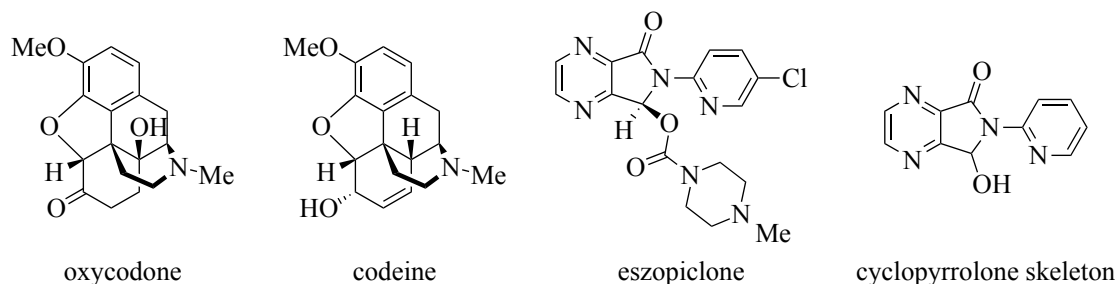
Pyrrolidines and piperidines are important substructures embedded in a variety of natural products. Select examples of well-known pyrrolidine alkaloids are nicotine,²⁰ hygrine,²¹ and the amino acid proline, while piperidine is a structural moiety in coniine,²² anabasine,²³ and ropivacaine (Figure 1.2).²⁴

Figure 1.2. Select Pyrrolidine and Piperidine Alkaloids



A number of pharmaceuticals also contain a pyrrolidine or piperidine ring (Figure 1.3). For instance, oxycodone, sold under the brand name OxyContin®, is a vitally important analgesic, ranking 18th overall in national retail sales and 45th overall in national prescriptions in 2013.¹³ Structurally, oxycodone is similar to codeine, possessing a pentacyclic core containing a piperidine ring. Oxycodone is synthesized semisynthetically from thebaine, found in both the opium poppy and Persian poppy. Another significant alkaloid is eszopiclone, sold as the brand name Lunesta®. Eszopiclone belongs to the class of drugs known as cyclopyrrolones, which contain a fused pyrrolidine ring possessing a lactam functional group. Being marketed for sleep aid, eszopiclone ranked 74th overall in retail sales and 79th overall in national prescriptions in 2013.¹³ Due to the importance of biologically active pyrrolidine and piperidine alkaloids, the need for synthetic methods that directly attach substitutions asymmetrically has become prevalent focus in the synthetic community.

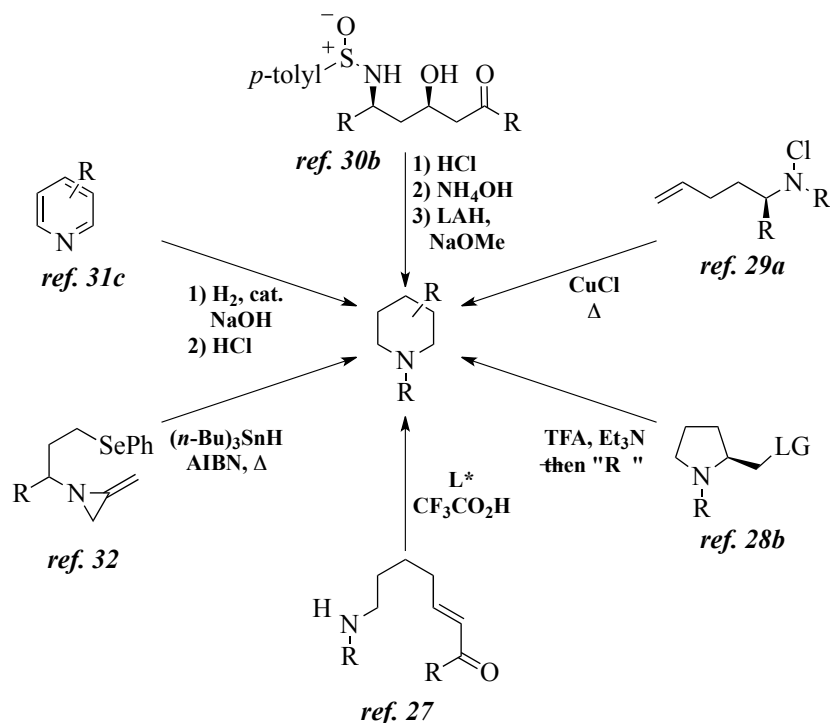
Figure 1.3. Select Pyrrolidine and Piperidine Pharmaceuticals



1.1.2. Non-Organolithium Methods of Asymmetric Heterocycle Synthesis

Recently, the number of protocols developed to provide enantioenriched substituted pyrrolidines and piperidines has increased.^{6,8,25,26} Select methods include asymmetric aza-Michael additions of acyclic amines,²⁷ ring contraction and expansion,²⁸ radical cyclizations,²⁹ reductive amination,³⁰ pyridine reduction,³¹ and rearrangements (Scheme 1.1).³² Many of these methods require multiple steps in the synthesis of the precursors, slightly diminishing the overall utility of the reaction. However, direct attachment of a substituent to a heterocyclic ring in a single step could be an invaluable tool to synthetic chemists. Indeed, asymmetric and regioselective nucleophilic addition has been showcased by both the Comins group and the Charette group using pyridinium salts possessing a chiral auxiliary, whereas asymmetric substitution using a variety of electrophiles on *N*-Boc-piperidine has been shown by a variety of groups, including the groups of Beak, Coldham, and Gawley. Such methods utilized functionalized organolithiums, either by way of asymmetric deprotonation/substitution or dynamic resolutions of racemic organolithiums.

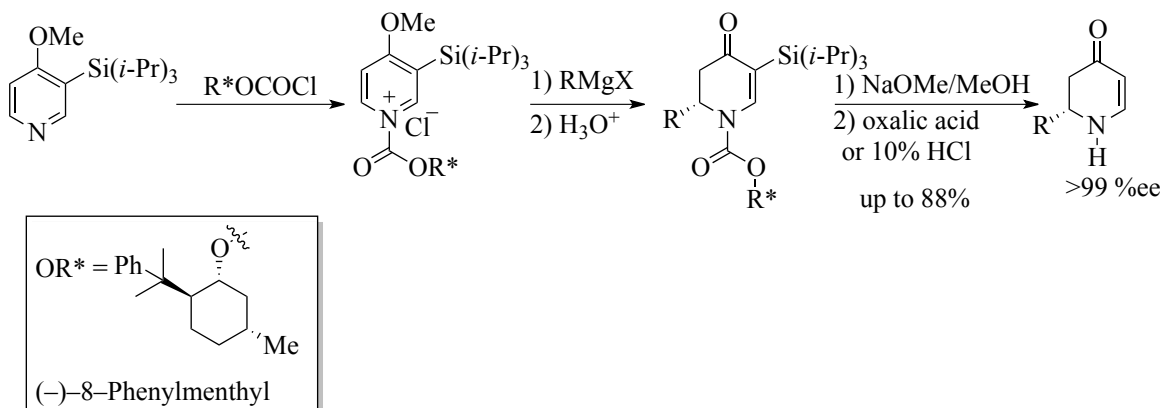
Scheme 1.1. Non–Organolithium Methods for Asymmetric Heterocycle Synthesis



Asymmetric Synthesis of Piperidines Using Chiral Pyridinium Salts

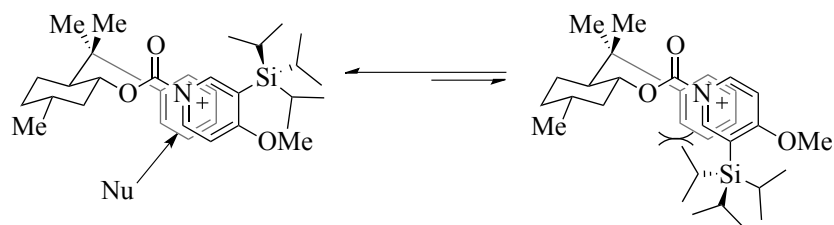
In the mid 1990's, Comins and coworkers revealed an enantioselective Grignard addition to a substituted pyridinium salt containing a menthol–derived chiral auxiliary (Scheme 1.2).¹⁷ The bulky C3 TIPS group of the pyridine blocked one of the α carbons, allowing nucleophilic addition regioselectively at the α' position. Acid hydrolysis of the enol ether moiety yielded the desired 2,3–dihydropyridone in high diastereoselectivity (up to 94% de). Fruitful results were obtained when attempting to remove both the bulky silyl group and the chiral auxiliary using a two–step protocol, resulting in the more synthetically useful 2,3–dihydropyridone in up to 88% yield and >99% ee. A follow–up report was published soon after, studying the effects on enantioselectivity using a variety of chiral auxiliaries.³³

Scheme 1.2. Asymmetric Synthesis of 6-Substituted 2,3-Dihydropyridones



The asymmetric induction was rationalized by π - π interactions of the pyridinium salt and the chiral auxiliary (Figure 1.4). Due to the π -stacking interactions, one face of the pyridinium salt was blocked. Additionally, the conformation of the π -stacking was locked as rotation about the N^+-CO_2 bond results in unfavorable π -stacking interactions from the bulky TIPS group.¹⁷

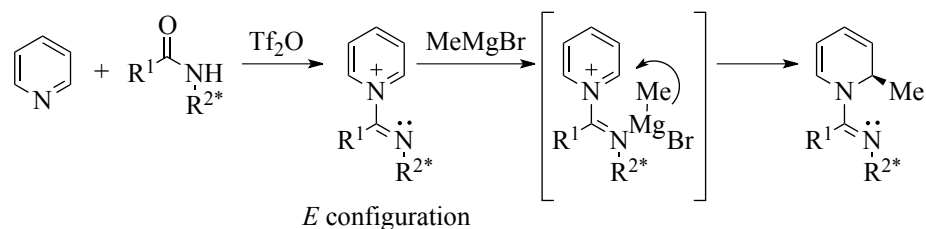
Figure 1.4. Asymmetric Induction Model using π -Stacking



Following Comins' reports, Charette and coworkers published similar work using both achiral and chiral *N*-imidoyl pyridinium salts, formed in situ from pyridine and amides activated by triflic anhydride (Scheme 1.3).^{11,34} Impressively, the imidate auxiliary addresses both regioselectivity and diastereoselectivity, avoiding the need of a bulky silyl group. It was proposed that the lone pair on the imidate nitrogen, fixed in an *E* configuration to avoid $A^{1,3}$ -

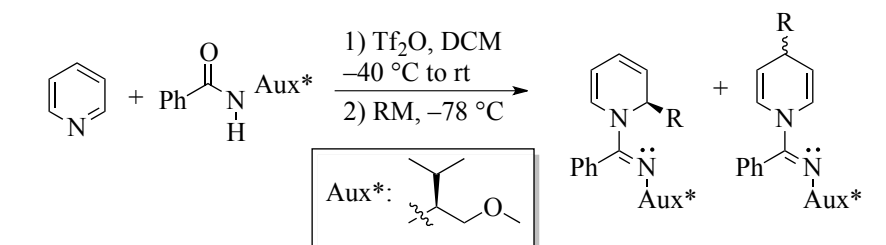
strain, directs the organometallic species to the 2 position, while the chiral auxiliary provided facial selectivity.

Scheme 1.3. Charette's Asymmetric Dehydropiperidine Synthesis



Grignard, organocuprate, and organozinc reagents were all amiable to the reaction conditions with moderate to high yields and diastereoselectivities. The authors chose the (*S*)-valinol-derived chiral auxiliary after extensive screening. The auxiliary provided bidentate coordination to the organometallic reagent while blocking 2' nucleophilic addition using the phenyl-substituted analogue (Table 1.1). This general methodology has been extended to a variety of systems, including 3-substituted pyridinium salts,³⁵ providing useful synthetic transformations, such as the conversion of activated 4-methoxypyridine to generate 2,3-dihydropyridones upon reaction with aqueous HCl³⁶ and intramolecular cyclization of auxiliary/diastereoselective substitution to provide dihydroindolizidines and dihydroquinolizidines.³⁷

Table 1.1. Summary of Charette's Asymmetric Dihydropiperidine Synthesis



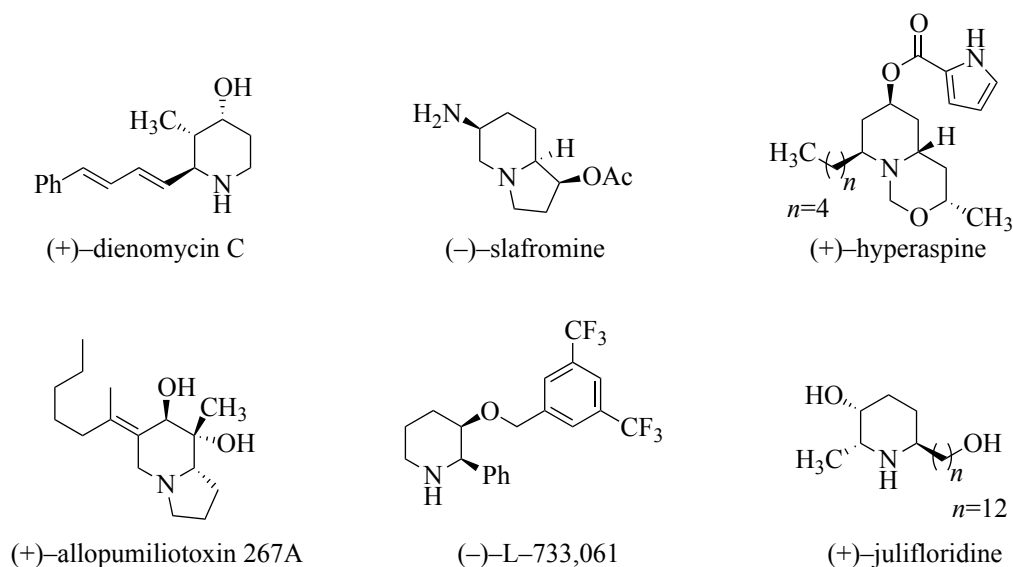
Entry	RM	Ratio C2/C4	dr	Yield (%)
1	MeMgBr	>95:5	>95:5	77
2	Et ₂ Zn	>95:5	>95:5	73
3	PhMgBr	90:10	>95:5	74
4	2-FurylmgBr	>95:5	>95:5	68
5	1-HexynylMgBr	>95:5	>95:5	65

The Charette group also demonstrated several methods to remove the chiral auxiliary. For instance, treatment with BBr₃ liberated a free alcohol from the methoxy ether moiety, which then cyclized in situ to yield the corresponding oxazolidine and free piperidine.³⁸ Reductive approaches include LiAlH₄/AlCl₃,³⁹ Li/NH₃ in EtOH/THF, or Pd(OH)₂ with H₂/cyclohexene in AcOH/EtOH.¹¹ Additionally, the amidine nitrogen has been removed by hydrolysis using HCl in MeOH and by methylation using MeI and K₂CO₃ followed by basic hydrolysis using aqueous NaOH.³⁹

Comins and Charette have both applied their methodologies to the synthesis of various alkaloids, showcasing the versatility of the functionalized piperidine motif (Figure 1.5). For instance, Comins and coworkers revealed the first asymmetric synthesis of (+)-dienomycin C,⁴⁰ which shows antibiotic activity against some strains of *Mycobacteria*,⁴¹ in just 7 steps and 46% yield. Additionally, in just 10 steps, Comins revealed an asymmetric synthesis of (+)-

allopumiliotoxin 267A,⁴² which contains an indolizidine substructure that has attracted the attention of many synthetic chemists due to its significant biological activity.⁴³ In 2004, Charette published the synthesis of (–)-L-733,061,³⁵ a 2,3-disubstituted piperidine showing biological activity as a potent Substance P antagonist.⁴⁴ (+)-Julifloridine,⁴⁵ a substituted 3-piperidinol derivative, was synthesized by Charette in just 4 steps and 33% overall yield.⁴⁶ Many other alkaloids have been synthesized using these methods, including, but not limited to, (–)-slafromine,⁴⁷ (+)-hyperaspine,⁴⁸ phlegmarine alkaloids,⁴⁹ and (+)-lepadine B.⁵⁰

Figure 1.5. Select Alkaloids Synthesized using Comins's and Charette's Methodologies



Although many clever methods exist to generate enantiopure piperidines, they are usually limited to a single enantiomer, require a chiral auxiliary, and often need multiple steps to synthesize the precursor. Therefore, it would benefit synthetic chemists to design methods that produce either enantiomer, utilize catalytic amounts of chiral component, and use chiral ligands rather than auxiliaries, thus avoiding tedious procedures involving the synthesis, connection, and

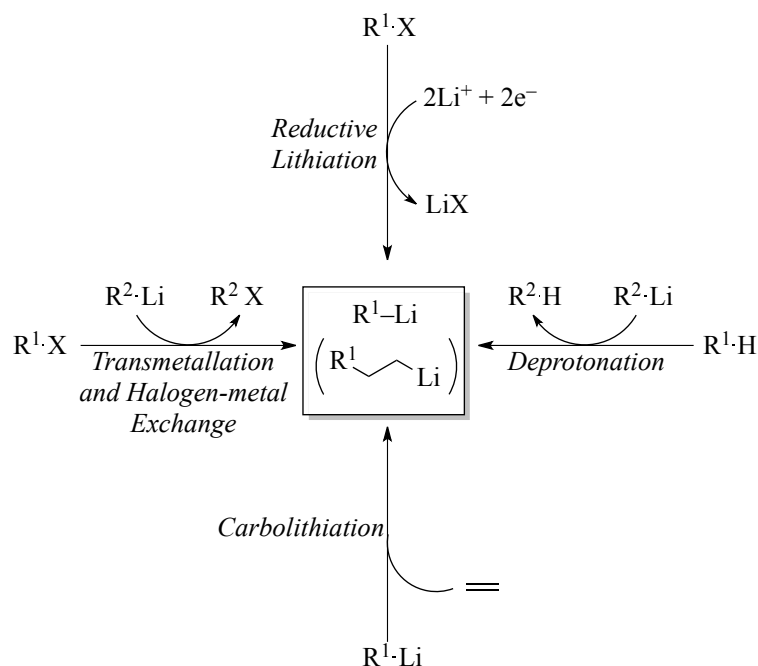
removal of the chirality element. Though there exists many strategies that chemists may examine, employing functionalized organolithiums derived from directed lithiation serves as a promising and viable route to address these issues.

1.2. Functionalized Organolithiums

Among the vast methods developed to overcome the challenges presented in asymmetric synthesis, utilization of functionalized organolithiums has been showcased as a valid option in both total syntheses⁵¹ and general methodologies^{19,52,53} due to its unique characteristics. Specifically, functionalized organolithiums have emerged as a powerful tool in tethering carbon–carbon bonds. One class of functionalized organolithiums is molecules containing a carbon–lithium bond α to a heteroatom, such as nitrogen or oxygen. Aggregation states,^{18,54–58} solvent/ligand effects,^{59,60} heteroatom coordination,^{61,62} and temperature^{15,16,19,63,64} are all common parameters that need to be addressed prior to implementing successful organolithium methodology. Organolithiums are best represented as ionic in nature, being considered as a close interaction rather than an actual bond.⁶⁵ Being the equivalent of a carbanion, these species have been shown to attack electrophiles with configurational stability at specific temperatures.^{19,66,67} Having configurational stability allows for a predictable asymmetric outcome when reacted with an electrophile, assuming the kinetic barrier for racemization is higher than that of an electrophilic quench at a given temperature. Although a variety of methods exist to prepare organolithium species, the forerunners used in literature include reductive lithiation,⁶⁸ carbolithiation,⁶⁹ halogen–lithium/tin–lithium exchange and transmetalation,⁷⁰ and direct deprotonation of a C–H bond (Scheme 1.4).^{71,72} With regards to asymmetric methods using

organolithiums, direct deprotonation of a C–H bond offers a couple of intriguing options: namely asymmetric deprotonations and dynamic resolutions.

Scheme 1.4. Common Methods used to Prepare Organolithiums



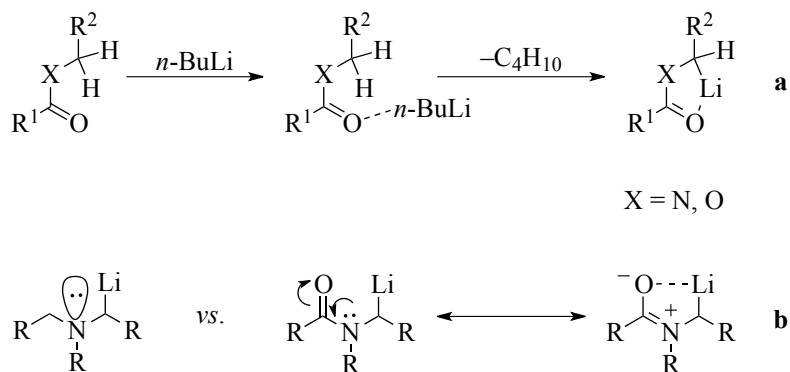
Preparation of Organolithiums via Deprotonation

Acidity plays a key role when predicting lithiation by deprotonation using commercially available alkyllithium reagents. For instance, deprotonating an sp -hybridized carbon atom is more feasible than that of an sp^2 or sp^3 hydrocarbon when considering the pK_a values alone. In addition, other factors can play a significant role in determining the outcome of deprotonation, such as deprotonation α to O or N and electronic effects. Specifically, by cleverly designing the substrate, a heteroatom directing group can aid in achieving the desired lithiation reaction. Based

on this reasoning, the rate of lithiation by deprotonation of a C–H bond can be increased by using amides and esters, which function in two separate ways. The first is that the electropositive lithium forms intramolecular coordination to a heteroatom (Scheme 1.5a, middle structure). This step allows for aggregates to form around the heteroatom, populating the region to aid in regioselectivity of the deprotonation. The second is that the electron–rich carbon–lithium bond, formed upon deprotonation, needs to be stabilized by a nearby electron–withdrawing group or an empty orbital (Scheme 1.5a, final structure). The carbonyl group can serve as this function, ultimately stabilizing the organolithium species. The use of a directing group, such as a carbonyl group, to aid in deprotonation has been well studied and termed the “Complex–Induced Proximity Effect (CIPE).”^{72,73}

The need for a directing group, especially a carbonyl group, is magnified when considering the heteroatom’s orbitals. An unfavorable interaction occurs when lithiating by deprotonation α to oxygen or nitrogen, as the lone–pair on the heteroatom causes electron repulsion with the C–Li bond. As a result, the electron–withdrawing benefit of the heteroatom is cancelled by this disruptive interaction. However, the repulsion is minimized when the electrons are delocalized to the carbonyl group, which also causes greater coordination to the electropositive lithium (Scheme 1.5b).

Scheme 1.5. Characteristics of Organolithiums

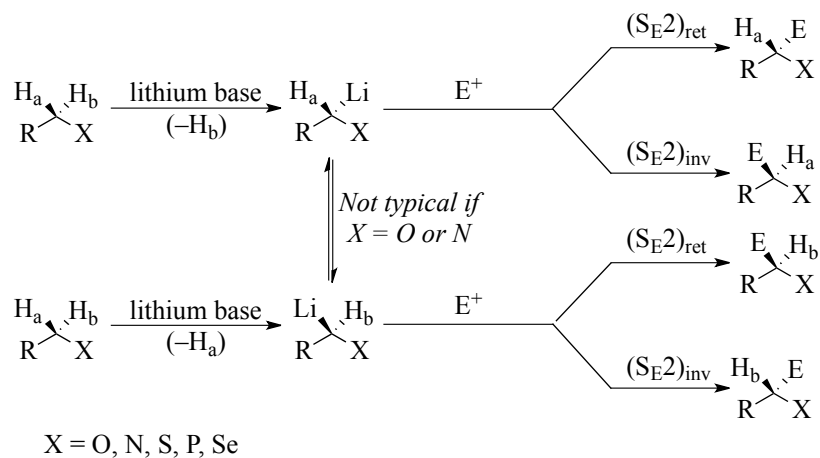


The utility of this method has been showcased in the last two decades on a variety of substrates,⁷² including Boc-protected pyrrolidines^{10,74,75} and piperidines.^{19,57,75} Specifically, asymmetric deprotonations and dynamic resolutions have offered direct access to enantiopure α and α' substitutions on these ubiquitous heterocycles.

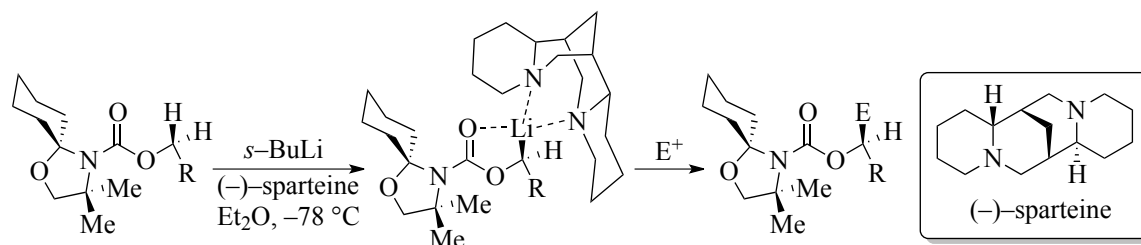
1.2.1. Preparation of Chiral Organolithiums by Asymmetric Deprotonation

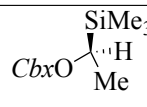
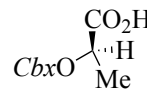
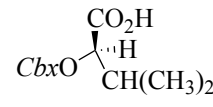
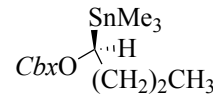
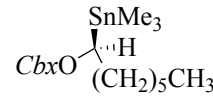
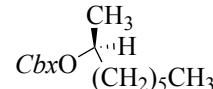
One strategy developed by chemists to generate chiral, nonracemic heterocycles is to use chiral bases that can stereospecifically deprotonate a stabilized species. A subsequent electrophilic quench results in an enantioenriched product, assuming the organolithium intermediate is configurationally stable at a given temperature within the chemical transformation's timescale. A general depiction of the various stereochemical outcomes is represented in Scheme 1.6.

Scheme 1.6. Stereochemical Fates of Organolithiums Prepared *via* Deprotonation



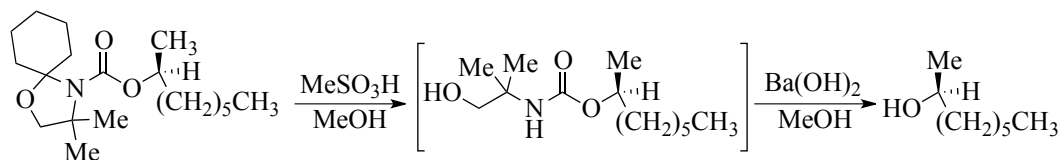
In 1990, Dieter Hoppe revealed an asymmetric deprotonative lithiation of hindered carbamates α to oxygen using (–)-sparteine and *s*-BuLi (Table 1.2).⁷⁶ This report marked the beginning of significant achievements in asymmetric deprotonation. The success of this procedure is in part due to the carbamate functionality, as it significantly increased the acidity of the α -proton and stabilized the organolithium species *via* chelation to the carbonyl group. In the report, a variety of electrophiles effectively quenched the enantioenriched organolithium, including Me₃SnCl, Me₃SiCl, MeI, and CO₂, to produce the corresponding substituted piperidine upon aqueous workup. Remarkably, the *s*-BuLi/(–)-sparteine system produced enantiopure products in >95% ee and yields up to 86%, proceeding *via* retention of configuration.

Table 1.2. Hoppe's Asymmetric Deprotonation of Carbamates


Entry	R	E ⁺	Product	Yield (%)	ee (%)
1	Me	Me ₃ SiCl		67	–
2	Me	CO ₂		75	>95
4	CH(CH ₃) ₂	CO ₂		52	>95
6	(CH ₂) ₂ CH ₃	Me ₃ SnCl		62	>95
7	(CH ₂) ₅ CH ₃	Me ₃ SnCl		86	>95
9	(CH ₂) ₅ CH ₃	CH ₃ I		81	96

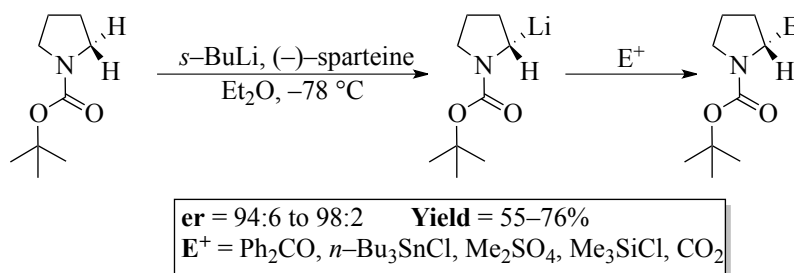
A computational paper was later published revealing a large kinetic preference for the pro-*S* proton abstraction using the *s*-BuLi/(–)-sparteine system with *N,N*-dialkylcarbamates.⁷⁷ Additionally, Hoppe et al. showed facile oxazolidine cleavage using a 2-step protocol consisting of methanolysis, yielding a urethane intermediate, and hydrolysis using Ba(OH)₂, which provided the desired alcohol (Scheme 1.7).⁷⁶ The Hoppe group later expanded these initial findings to a variety of alkyl carbamate derivatives, each giving enantioenriched products.⁷⁸

Scheme 1.7. Oxazolidine Cleavage *via* Methanolysis and Hydrolysis



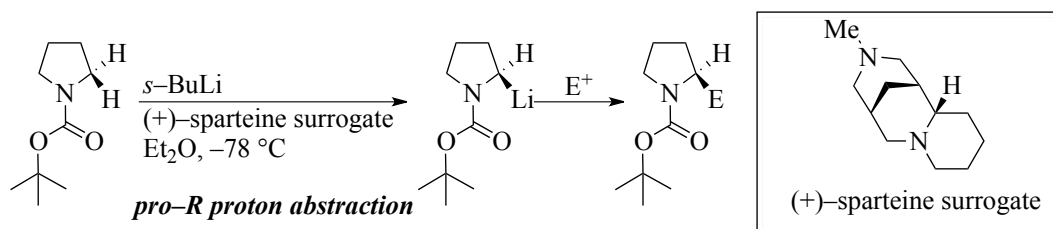
Around the same time, Beak and coworkers revealed a deprotonative lithiation/substitution sequence α to an amino group using substituted *N*-Boc-pyrrolidines and piperidines.⁶² Although the electrophilic substitution was rendered racemic when using TMEDA, these reports birthed a new method to directly substitute heterocycles by way of directed lithiation. By 1991, Beak applied Hoppe's asymmetric deprotonation methodology to *N*-Boc-pyrrolidines, achieving high enantioselectivity and yields using various electrophiles (Scheme 1.8).⁷⁹

Scheme 1.8. Beak's Asymmetric Deprotonation of *N*-Boc Pyrrolidine



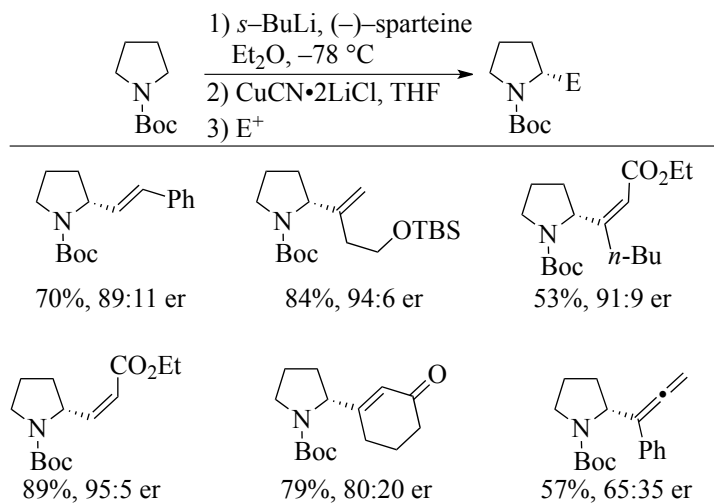
About 10 years later, O'Brien developed a (+)-sparteine surrogate, which, when reacted with *N*-Boc-pyrrolidine, provided the pro-*R* selective deprotonative lithiation (Scheme 1.9).⁸⁰ Although versatile, these approaches suffer the constraint on the scope of electrophiles, as alkyl halides do not react readily.^{14,81} Moreover, these methods are largely unsuccessful when applied to *N*-Boc-piperidine.^{55,82}

Scheme 1.9. O'Brien's Asymmetric Deprotonation of *N*-Boc-Pyrrolidine



It was also revealed that transmetalation reactions from lithium could occur with configurational stability. This discovery has led to many progressive developments in expanding the electrophile scope of enantiopure organolithiums. For instance, Dieter and coworkers showed that lithium could be transmetalated to copper using Beak's (*R*)-*N*-Boc-2-lithiopyrrolidine system with retention of configuration. Subsequent electrophilic quench using various alkenyl iodides provided the desired products in good yields and enantioselectivities in Et₂O, albeit slight loss in er depending on the electrophile used (Scheme 1.10).⁸³ It should be noted that when the selected conditions were subjected to a conjugate addition reaction with phenyl propargyl mesylate, the desired transformation occurred with the lowest er (65:35).

Scheme 1.10. Dieter's Lithium/Copper Transmetalation and Vinylation

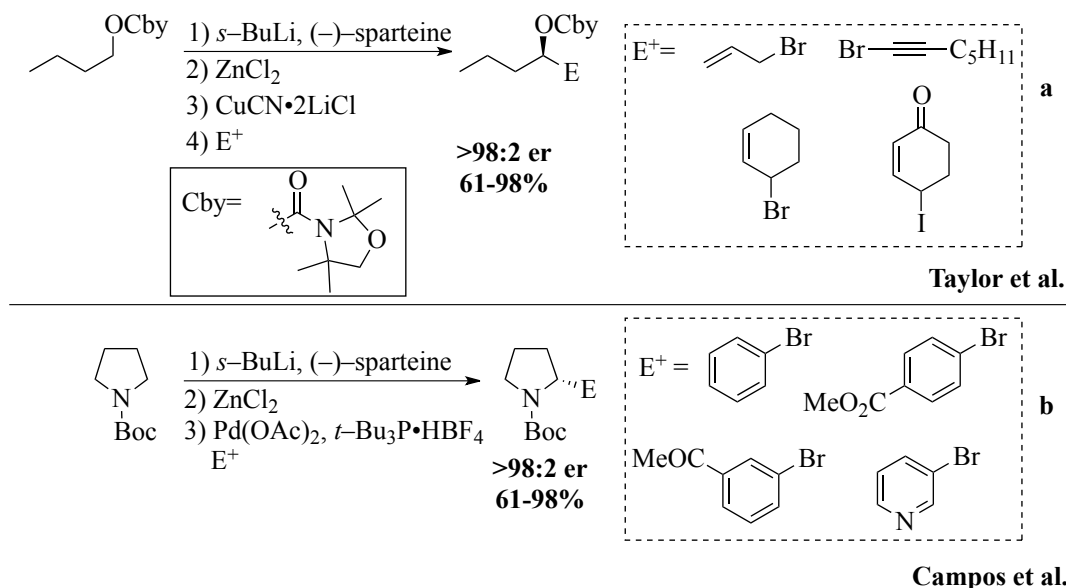


Richard Taylor was able to achieve asymmetric substitutions α to an oxygen, including allylations, vinylations, and alkynylations from acyclic carbamate precursors.⁸⁴ Essentially, the authors utilized Hoppe's methodology to generate enantiopure carbamates, which were transmetalated to the organozinc in situ. Transmetalation from lithium to zinc was necessary to achieve the final transformation, as direct transmetalation to copper was unsuccessful. However, once the organozinc reagent was formed, transmetalation to copper and electrophilic quench readily yielded a variety of enantiopure products (Scheme 1.11a).

In 2006, a general method for the arylation of Beak's (*S*)-*N*-Boc-2-lithiopyrrolidine system was revealed by Campos et al. utilizing a Negishi cross coupling (Scheme 1.11b).⁸⁵ Since the enantioenriched organolithium is configurationally labile at temperatures above -60°C ,⁸⁶ transmetalating to the organozinc served as a logical route for the arylation, as secondary organozinc reagents have been shown to possess configurational integrity at elevated temperatures.^{84,87} Once the organozinc reagent is formed, Pd-catalyzed arylation could deliver the enantioenriched product. After screening a variety of conditions, the authors proved their

hypothesis using ZnCl_2 followed by a Negishi cross coupling using $\text{Pd}(\text{OAc})_2$ and Fu's $t\text{-Bu}_3\text{P-HBF}_4$ ligand⁸⁸ with aryl bromides.

Scheme 1.11. Select Asymmetric Substitutions *via* Transmetalations with Zinc



Although successful in some specific systems, asymmetric deprotonations generally suffer from the inability to provide high enantiomeric ratios for *both* enantiomers on an achiral piperidine or pyrrolidine and it has only shown moderate success (whether er or yield) on the piperidine ring.

1.2.2. Preparation of Chiral Organolithiums by Dynamic Resolutions

In the asymmetric synthesis of pyrrolidine and piperidine alkaloids, dynamic resolutions have been shown to achieve impressive results using minimal steps.^{15,18,19,63} In a dynamic resolution, a racemic organolithium is treated with a chiral ligand, which resolves the complex dynamically. Such resolutions that afford the maximum yield of 100% are superior to classical

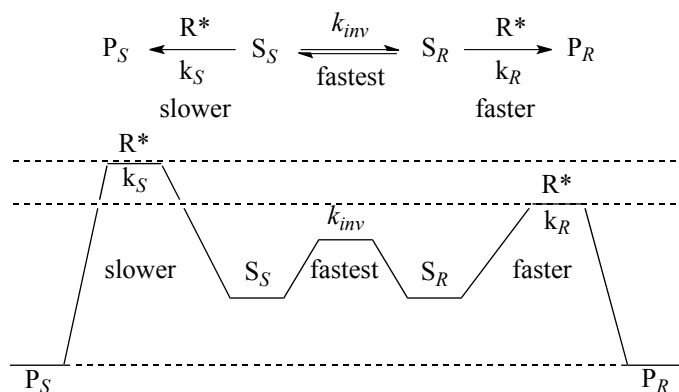
resolutions, where the maximum yield is 50% while discarding the undesired stereoisomer.^{5,89} In dynamic resolutions, time, temperature, and stoichiometry each play an independent role in generating optimal enantioselectivities.⁹⁰ Successful implementation of dynamic resolutions obviates the need for an asymmetric deprotonation, classical resolution, or an asymmetric synthesis of a stannane precursor in order to generate chiral, nonracemic organolithium compounds used in stereoselective synthesis. Similar to asymmetric substitution, subsequent electrophilic quench of the chiral organolithium leads to the asymmetric substitution product if the organolithium is configurationally stable below the equilibration temperature.⁹¹ Important dynamic resolutions reported throughout literature include dynamic kinetic resolutions (DKR), dynamic thermodynamic resolutions (DTR), catalytic dynamic resolutions (CDR), and crystallization-induced dynamic resolutions (CIDR).

Dynamic Kinetic Resolution

A kinetic resolution is defined as a process where two stereoisomers are transformed to products at different rates.⁹² Specifically, a dynamic kinetic resolution (DKR) applies when enantiomeric substrates, S_R and S_S , interconvert with a rate constant k_{inv} . When reacted with a chiral reagent, R^* , having a rate constant k_R and k_S for the perspective R and S enantiomers, the products P_R and P_S are formed. For convenience, one can assume the R enantiomer reacts faster than the S enantiomer upon addition of R^* . If $k_{inv} \gg k_R$, then k_S , being the product ratio P_R/P_S , depends on the difference in transition state energies, based on the Curtin–Hammett kinetics. Figure 1.6 illustrates the general DKR model. Essentially, in efficient DKR's, high er's and yields can be obtained assuming one of the rapidly equilibrating isomers reacts more rapidly with

the electrophile than the other. Literature is filled with examples of DKR's using either enzymes⁹³ or other chiral reagents (R^*) to generate the desired chiral, nonracemic product, as outlined in numerous reviews.^{92,94} The DKR is superior to the classical kinetic resolution, where high enantiomeric purity is achieved only if the reaction is stopped before 50% conversion, thus lowering the yield of the desired enantiomer to less than 50% of the moles of the initial carbon analogue.⁹⁵ Some researchers have addressed this problem by isolating and racemizing the undesired enantiomer and recycle using the resolution conditions.^{96,97} Although successful, the overall impact of such a process suffers, as it requires additional time and materials. These problems are negligible in a DKR scenario, as rapid interconversion of starting materials allows both high yields and enantiomeric ratios.

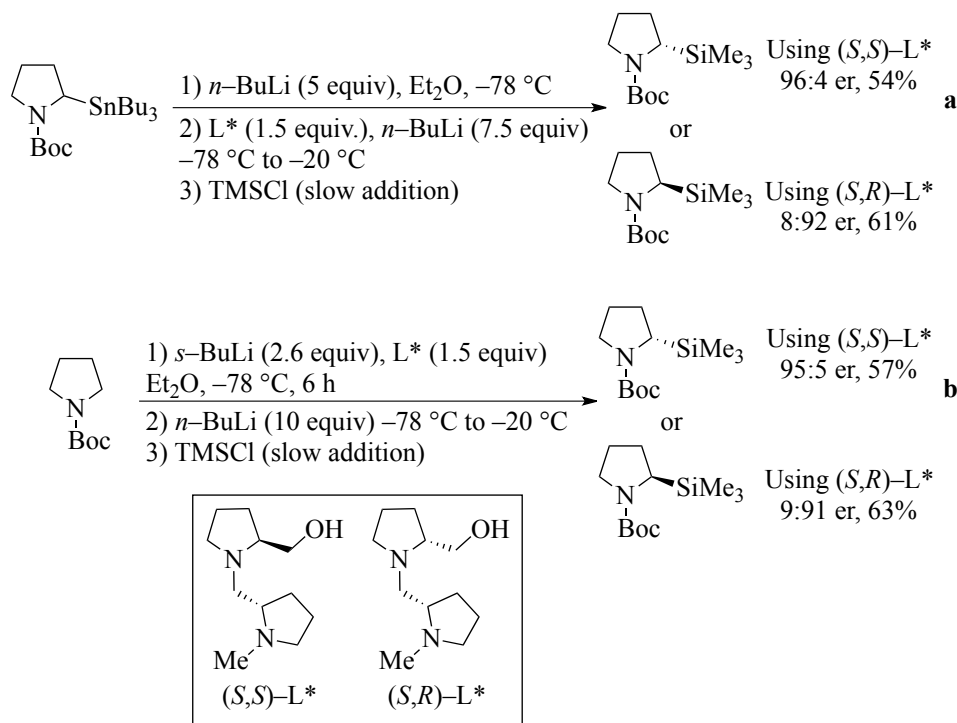
Figure 1.6. Dynamic Kinetic Resolution Model



An excellent example of a DKR was showcased by Coldham and coworkers on racemic *N*-Boc-2-lithiopyrrolidine using diastereomeric monolithiated diaminoalkoxide ligands (*S,S*)- L^* and (*S,R*)- L^* (Scheme 1.12a).¹⁰ Tin–lithium exchange of the stannane precursor gave racemic *N*-Boc-2-lithiopyrrolidine, which, when mixed with excess *n*-BuLi and ligand followed by an electrophilic quench with TMSCl, gave the corresponding product in high

enantiomeric ratios, albeit modest yields (up to 96:4 er and 61%). The authors were also able to achieve high enantioselectivities when performing a direct deprotonation of *N*-Boc-pyrrolidine to generate the racemic organolithium. Similarly, addition of chiral ligand and *n*-BuLi followed by an electrophilic quench yielded almost identical results (up to 95:5 er and 63%) (Scheme 1.12b). It is worth noting that the authors were able to obtain *either* enantiomer, depending on the chiral ligand used. Literature precedence suggests that the substitution occurs with retention of configuration.⁵⁶

Scheme 1.12. Coldham's Dynamic Kinetic Resolution of *N*-Boc-Pyrrolidines



The authors were able to distinguish this DKR from a dynamic thermodynamic resolution (DTR) by performing a tin–lithium exchange on *N*-Boc-2-tributylstannylpyrrolidine at -78 °C to generate the racemic organolithium. Chiral ligand ((-)-sparteine, (S,S)-L*, or (S,R)-L*) was

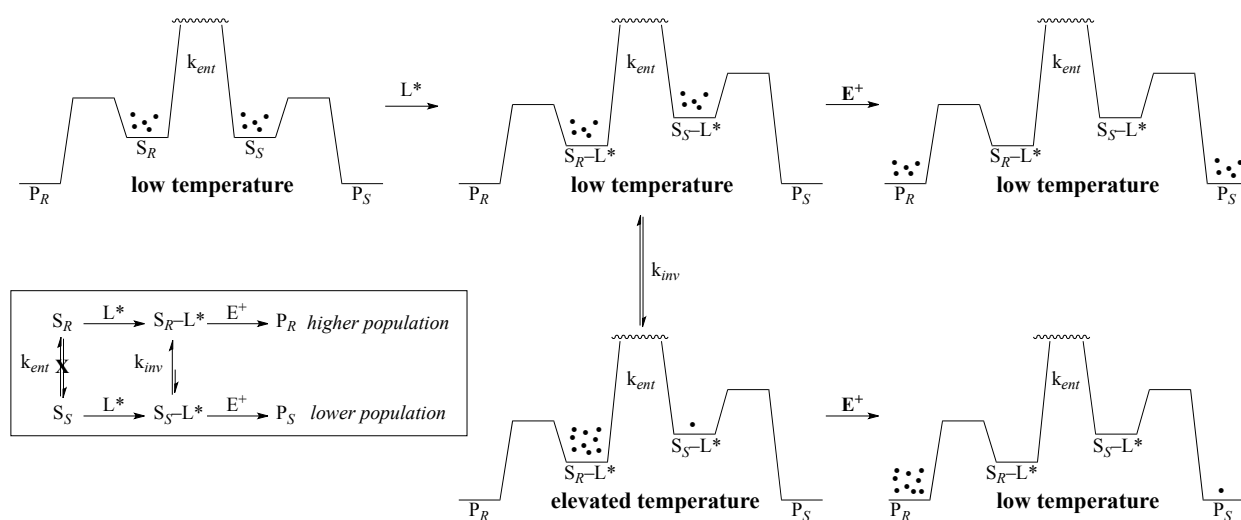
then added and the mixture was equilibrated at a variety of elevated temperatures favorable for a dynamic resolution. Upon electrophilic quench with TMSCl, the authors note that little to no selectivity was observed, suggesting no energetic preference for one diastereomeric organolithium species over another. However, high selectivities were observed when using substoichiometric amounts of TMSCl under identical reaction conditions, suggesting that TMSCl is a kinetic component to the reaction. The yield was then optimized by adding excess TMSCl slowly, noting that the diastereomeric organolithium complex was more reactive to the electrophile than *n*-BuLi.

Dynamic Thermodynamic Resolution

A dynamic thermodynamic resolution (DTR) may be employed when enantiomeric substrates exchange with a chiral ligand to afford a diastereomeric mixture that can be resolved thermodynamically (Figure 1.7). In order to successfully accomplish a thermodynamically controlled dynamic resolution, the diastereomeric complexes must favor one over the other at a given temperature, generally by having significantly different thermodynamic stabilities. In a DTR, the enantiomeric substrates, S_R and S_S , are not in rapid equilibrium with each other. Once a chiral ligand, L^* , is added, affording the diastereomeric species S_R-L^* and S_S-L^* , population of the more stable isomer occurs over a given time at a certain temperature.⁹⁰ The diastereomers can interconvert either by direct epimerization with rate constant k_{inv} or by L^* dissociation followed by enantiomerization with rate constant k_{ent} .⁹¹ The equilibrium, once established, is frozen at a lower temperature, allowing a final electrophilic quench to provide the desired enantioenriched product, reflecting the thermodynamic ratio of the two diastereomeric complexes, S_R-L^* and S_S-

L^* .⁹⁰ A major advantage of a DTR is that impressive enantioselectivities can be achieved *in situ* using a few separate, controllable steps. However, the need for stoichiometric amounts of chiral ligand potentially lowers the overall impact of such processes, depending on whether or not it can be easily recovered.

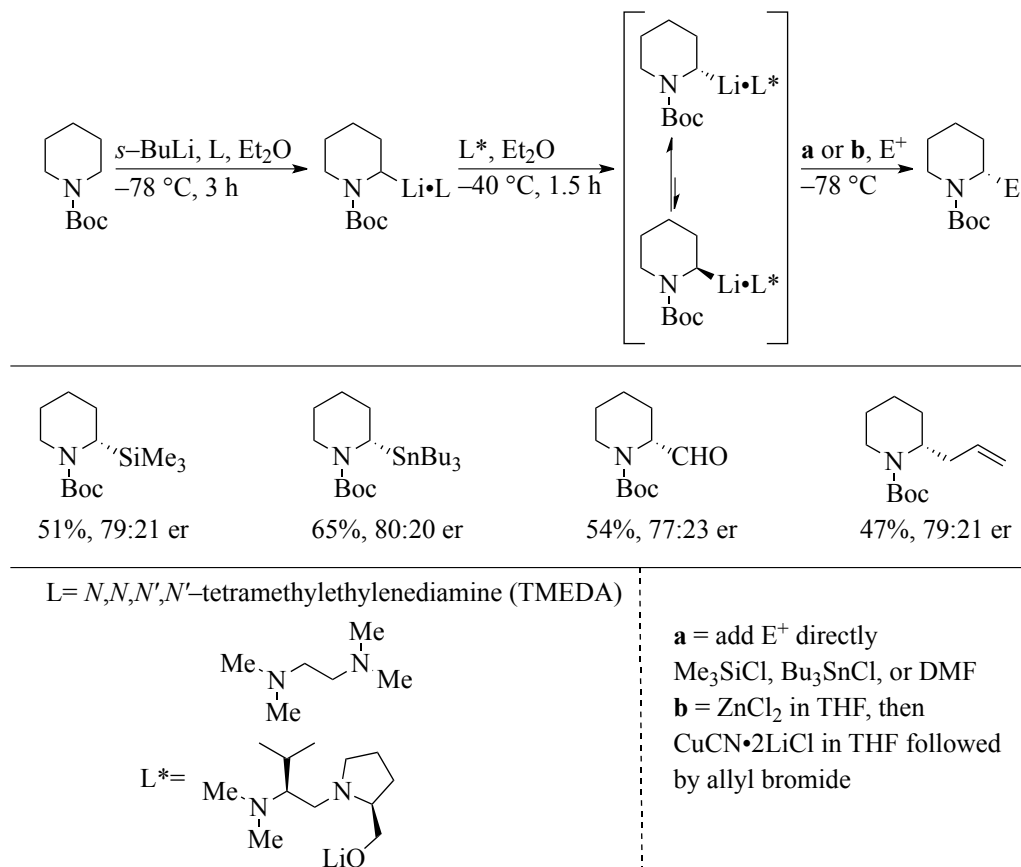
Figure 1.7. Dynamic Thermodynamic Resolution Model



The Coldham group revealed an important DTR on *N*-Boc-piperidine and a modified dipeptide ligand.¹⁵ Although asymmetry can be induced on substituted pyrrolidines,^{10,64} *N*-Boc-piperidine substrates were not as trivial.^{55,82} Despite the challenges associated with this class of substrates, the Coldham group discovered a DTR of racemic *N*-Boc-2-lithiopiperidine using peptide-based chiral ligands, providing up to 80:20 er and 65% yield. The procedure started with the deprotonative lithiation of *N*-Boc-piperidine with *s*-BuLi and the achiral ligand TMEDA in Et₂O at -78 °C, which generated the racemic organolithium. Addition of the chiral ligand in Et₂O followed by equilibration at 40 °C populated a single diastereomer. Subsequent electrophilic quench (or transmetalation followed by electrophilic quench) provided the desired enantioenriched product (Scheme 1.13). The authors also mentioned that aged bottles of *s*-BuLi

gave higher yields, possibly due to the presence of accumulated *s*-BuOLi. Additionally, although stoichiometric amounts of chiral ligand were needed for this chemistry, the authors mentioned that column chromatography and distillation are effective in its recovery.

Scheme 1.13. Coldham's Dynamic Thermodynamic Resolution of 2-Lithio-*N*-Boc-Piperidine



Catalytic Dynamic Resolution

When a dynamic resolution is operating under thermodynamic control using catalytic amounts of chiral ligand, a catalytic dynamic resolution (CDR) is observed. A CDR applies when a substoichiometric amount of chiral ligand, L*, dynamically resolves enantiomeric substrates, S_R and S_S, at a given temperature over a certain period of time. A requirement for a

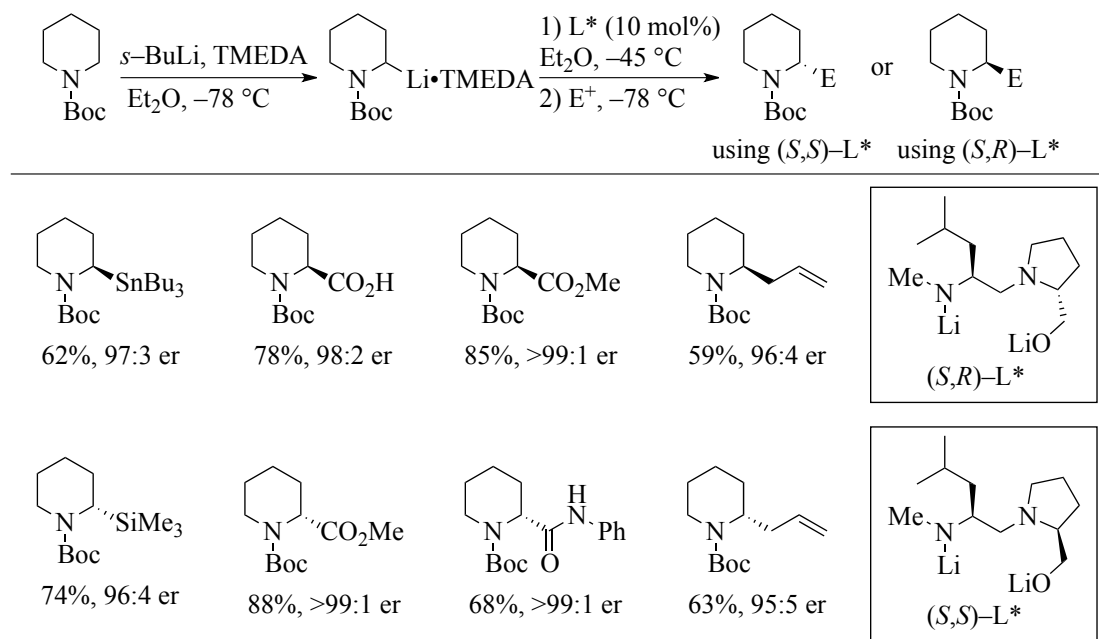
successful CDR is that the barrier for DTR is less than that for racemization at a given temperature.¹⁹

Previously, Beng and Gawley revealed a CDR of *N*-trimethylallyl-2-lithiopyrrolidine¹⁸ and *N*-Boc-2-lithiopiperidine.¹⁹ The novelty of this chemistry is illustrated by its ability to generate chiral, nonracemic products in high yields from resolving the racemic organolithium using substoichiometric amounts of chiral ligand (as low as 5 mol%) in a one-pot reaction. Variations in time, temperature, and stoichiometry eventually led the authors to achieve optimal enantioselectivity.⁹⁰

As an example, Beng and Gawley showcased a CDR on racemic 2-lithio-*N*-Boc-piperidine in the presence of the achiral ligand TMEDA, using either diastereotopic dilithiated diaminoalkoxide ligand (*S,S*)-L* and (*S,R*)-L* at -45 °C.¹⁹ After establishing the equilibrium, a broad range of electrophiles were used upon cooling to -78 °C, generating various substituted piperidines in high yields and enantioselectivities (Scheme 1.14).

In the allylation example, transmetalation with ZnCl₂ followed by another transmetalation to copper set up the Negishi-like cross coupling with allyl bromide, proceeding with retention of configuration.⁵⁸ Racemization occurred upon direct electrophilic quench with various allyl and benzyl halides, likely due to single electron transfer (SET) pathways.⁹⁸ The impact of this chemistry was magnified as the authors were able to generate *either enantiomer* of the 2-substituted piperidine (depending on L*) *in situ* using just 10 mol% of L*.

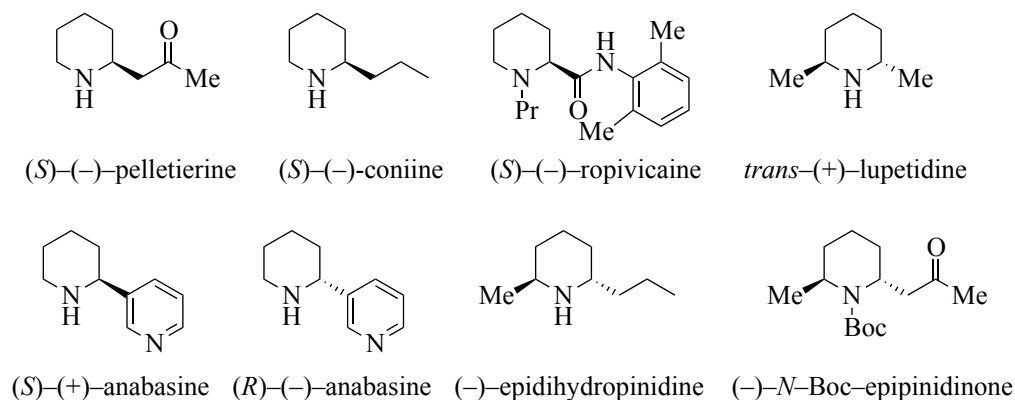
Scheme 1.14. Catalytic Dynamic Resolution of *N*-Boc-Piperidine



Additionally, the authors showcased this methodology in asymmetric syntheses of (*R*)-(+)-pipecolic acid, (*S*)-(-)-coniine, (*S*)-(-)-ropivacaine, and other simple alkaloids in less than 3 steps (Figure 1.8).¹⁹ Expansion of the CDR methodology to incorporate 2-aryl and 2-vinyl piperidines allowed the authors to synthesize (*R*)- and (*S*)-anabasine in only 2 steps.⁹⁹ Further expansion of the CDR accessing enantiomerically pure *trans*-2,6-disubstituted piperidines provided *trans*-(+)-lupetidine, (-)-epidihydropinidine, and (-)-*N*-Boc-epipinidinone in 2–4 steps.⁶⁶ Finally, in recently published work, the authors showed that benzylic lithiation/substitution from enantiopure 2-aryl-*N*-Boc-piperidines occur with retention of configuration, providing access to chiral, nonracemic 2,2-disubstituted aryl piperidines bearing a quaternary stereocenter.¹⁰⁰ The author's approach to asymmetric synthesis *via* CDR of chiral organolithiums is virtually unprecedented, as the closest model came from a Japanese group who performed a catalytic resolution *via* lithiation and resolution of benzyl trifluoromethyl sulfone

mediated by a bisoxazoline ligand, providing only a limited scope.^{101,102} However, recent attempts at reproducing this chemistry has been met with limited success, and factors leading to consistent CDR implementation need to be investigated.

Figure 1.8. Alkaloids Synthesized using the Catalytic Dynamic Resolution



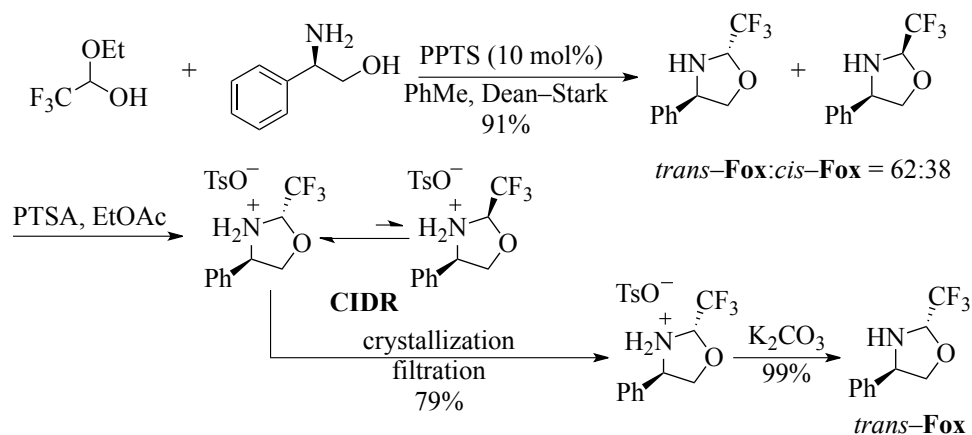
Crystallization–Induced Dynamic Resolution

Crystallization is a powerful means to develop highly stereoselective processes.¹⁰³ Indeed, if direct isolation of the crystals can occur, the overall economy of such processes stands superior as workup and purification are avoided.¹⁰⁴ It is possible to dynamically resolve racemic organolithiums using a crystallization–induced dynamic resolution (CIDR) when the organolithium has the ability to crystallize and there is a preferential crystallization of a homochiral aggregate. The generation of enantioenriched crystals occurs when diastereomeric organolithium complexes interconvert on the crystallization timescale. It is essential for the diastereoselective reaction leading to enantioenriched product to occur before loss of configuration.⁹¹ Optimization generally hinges on the critical control of temperature, solvent,

chiral ligand, and concentration. A recent review was published on CIDR's¹⁰⁵ in addition to interesting examples from Hoppe and Boche,^{59, 106} Strohmann,¹⁰⁷ Livinghouse,¹⁰⁸ Košmrlj,¹⁰⁹ and Shi.¹¹⁰

In 2013, the Brigaud group showcased a CIDR in an improved asymmetric synthesis of the *trans*-**Fox** (Fluorinated **ox**azolidine) chiral auxiliary.¹¹¹ Prior to their report, syntheses of these chiral auxiliaries were limited to 60:40 to 70:30 *trans*:*cis* mixtures that were not easily separated. Since the authors rationalized that the *trans*-**Fox** auxiliary was the useful isomer due to C₂ pseudosymmetry,¹¹² they aimed to design a synthesis where the *trans*-isomer was solely formed. The first step involved a simple condensation of (*R*)-phenylglycinol with the hemiacetal of fluoral, which provided both *trans*- and *cis*-**Fox** in 91% yield as a 62:38 *trans*:*cis* mixture (Scheme 1.15). The authors note that the separation of a single isomer was extremely difficult using a neutral medium. To circumvent this obstacle, they performed a CIDR by acidifying the mixture using *para*-toluenesulfonic acid (PTSA), generating an epimerization equilibrium in which the salt of the *trans*-diastereomer crystallized out of solution. The resulting crystals were collected by filtration (79%) and neutralized (99%) to give enantiopure *trans*-**Fox**. In addition, the authors performed a large-scale synthesis that successfully provided 27.75 grams of the enantiopure product.

Scheme 1.15. Brigaud's Crystallization-Induced Dynamic Resolution



1.3. Statement of the Problem

The overall aim is to utilize organolithium chemistry on *N*-Boc-piperidine to generate a variety of enantio- and diastereo-enriched products. The specific goals of this project are as follows:

1. Learn the CDR methodology and examine various factors that may play a role in the poor reproducibility of the results.
2. Investigate the potential of α' -lithiation/substitution of racemic α,α -disubstituted-*N*-Boc-piperidines and evaluate the observed diastereoselectivity using NOESY.

The importance of the first goal is that the CDR methodology has been shown to have an issue regarding reproducibility. A variety of factors could contribute to the low reproducibility, including improper organolithium aggregate formation, impurity incorporation, and synthesis of the chiral ligand that does not match the reported optical rotation values. By systematically examining various details of the CDR using careful experimentation, it is proposed that the key

factor in obtaining reproducible results will be made clear. The factors to be examined include the chiral ligand, resolution temperatures, addition of reagents, and impurity detection/addition.

The importance of the second goal is that polysubstituted piperidines can potentially be synthesized in just 3 steps from a Boc-substituted precursor by utilizing 3 separate lithiation/substitution sequences. Preliminary results show that the final α' -lithiation/substitution of both racemic α,α -disubstituted-*N*-Boc-pyrrolidines and *N*-Boc-piperidines occurs with high diastereoselectivity in some cases. In this goal, a variety of α,α,α' -trisubstituted-*N*-Boc-piperidines will be synthesized and NOESY analysis will be used to determine the relative configuration.

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Chapter 2

Examination of the Catalytic Dynamic Resolution of *N*-Boc-Piperidine and Stereoselective Synthesis of Trisubstituted Pyrrolidines and Piperidines

Organolithium chemistry has shown to be a useful tool in the synthesis of chiral, nonracemic heterocycles. Throughout a survey of literature, the catalytic dynamic resolution (CDR) stands out as one of the most powerful methods available to generate various substitutions on the piperidine and pyrrolidine ring.¹⁻⁷ By carefully monitoring time, temperature, and ligand stoichiometry, high enantiomeric ratios can be achieved upon electrophilic quench. The ability to directly generate chiral molecules in a single step from achiral precursors using catalytic amounts of chiral ligand seems to be the ideal situation for synthetic chemists aiming to improve preexisting methods or even designing new and innovative methods generating useful, yet synthetically challenging, chiral compounds. Additionally, the CDR has been shown to provide either enantiomer of the substituted heterocycle by simply using the same ligand with altered stereochemistry. The utility of the CDR was showcased in the synthesis of many small alkaloids, many of which were obtained in less than 3 steps.^{2,3,7} However, the benefits of the CDR are hindered by the low reproducibility of the reported results. Since this methodology presents considerable promise to the synthetic community, the issues regarding reproducibility need to be addressed.

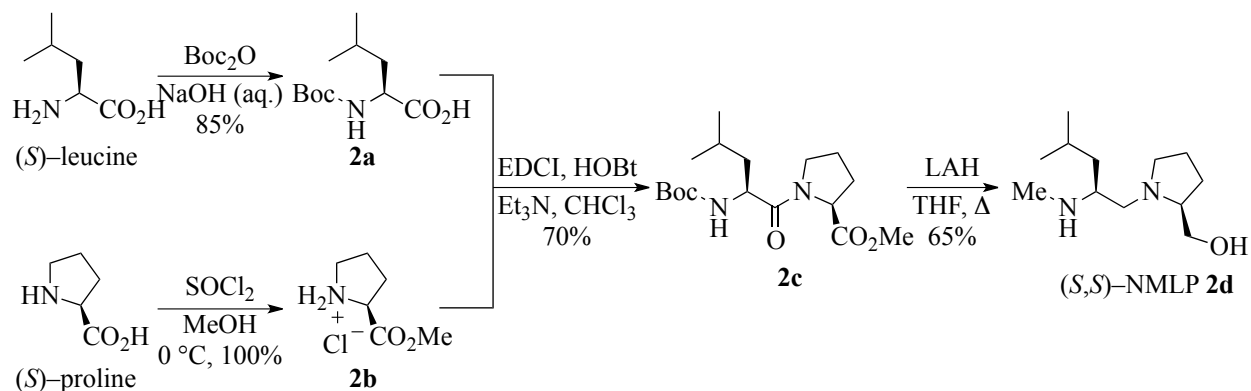
The next objective to be addressed is the synthesis of α,α,α' -trisubstituted piperidines and pyrrolidines using organolithium chemistry. The synthesis of polysubstituted heterocycles has been seldom reported in literature using organolithium chemistry.^{5, 7-9} For instance, α,α -disubstituted piperidines can be synthesized if an arylation occurs first followed by benzylic

lithiation/substitution, and α,α' -disubstituted piperidines can be synthesized *via* α -lithiation/substitution ($E^+ \neq \text{aryl}$) followed by α' -lithiation/substitution. However, if one were to perform an arylation, followed by benzylic lithiation/substitution, it would be reasonable to perform an additional α' -lithiation/substitution to generate trisubstituted products. If high diastereoselectivity exists on a racemic model, one can imagine achieving high enantioselectivities if the CDR is applied in the first step.

2.1. Investigation of the CDR on N-Boc-Piperidine: Aim for Reproducibility

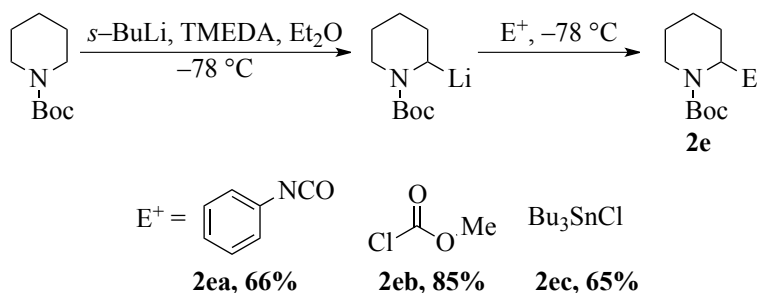
The first task was to synthesize the chiral ligand (*S,S*)-*N*-methyl-Leu-Pro **2d** ((*S,S*)-NMLP) from amino acid precursors (Scheme 2.1). (*S*)-Leucine was obtained from commercial retailers and Boc-protected using di-*tert*-butyl dicarbonate in aqueous NaOH. Upon workup, *N*-Boc-leucine **2a** was obtained in 85% yield as a thick oil. In a separate reaction, (*S*)-proline was stirred with SOCl₂ in MeOH, generating the hydrochloride salt of the corresponding methyl ester (**2b**) in quantitative yields. The two amino acid derivatives **2a** and **2b** were coupled together using EDCI and HOBt, which provided the anticipated dipeptide **2c** in 70% yield. LAH reduction of dipeptide **2c** provided the chiral ligand (*S,S*)-NMLP **2d** in 65% yield after Kugelrohr distillation. Starting from commercially available starting materials, the final chiral ligand was prepared in 39% overall yield in just 4 total steps. The ligand was stored in a -15 °C freezer for weeks at a time without losing purity by NMR, showing the stable nature of the dipeptide.

Scheme 2.1. Synthesis of Chiral Ligand (*S,S*)-NMLP **2d**



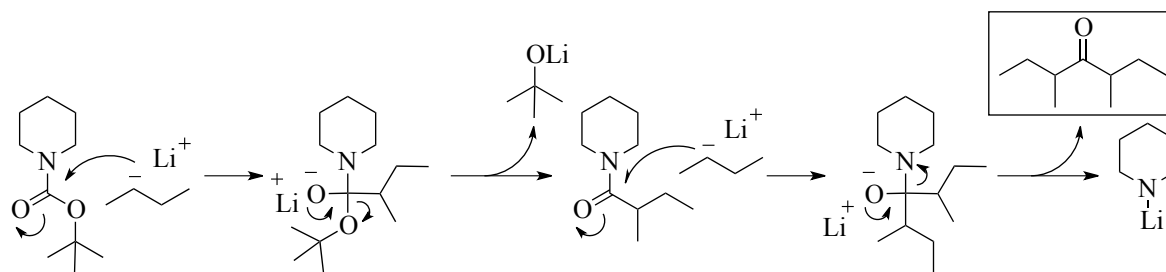
Next, the syntheses of racemic 2-substituted *N*-Boc-piperidines was attempted, which would ultimately serve as a standard for CSP-SFC analysis while also serving to gain organolithium chemistry experience. The procedure called for a 3 hour lithiation of freshly distilled *N*-Boc-Piperidine and TMEDA using *s*-BuLi in dry ether under argon atmosphere at -78°C . The progress of lithiation was monitored indirectly by taking an aliquot of the reaction and immediately quenching with MeOD, followed by GC-MS analysis to determine the percentage of deuterium incorporation. Once complete lithiation was observed, direct electrophilic quench was performed which, after subsequent workup and flash chromatography, provided the desired racemic product. All reactions proceeded uneventfully and provided the corresponding 2-substituted piperidines **2ea–2ec** in 65–85% yield (Scheme 2.2). The electrophiles used included phenyl isocyanate, methyl chloroformate, and tributyltin chloride.

Scheme 2.2. Racemic Lithiation/Electrophilic Quench using Select Electrophiles



Once all the precursors were synthesized, the catalytic dynamic resolution of *N*-Boc-piperidine was performed exactly as reported by Beng and Gawley.² Phenyl isocyanate (PhNCO) was selected as the electrophile due to facile analysis using diode array detection of the chromophore on CSP-SFC. Using 0.25 mmol (1 equiv) *N*-Boc-piperidine (freshly distilled *via* Kugelrohr distillation), 1.0 mmol (4 equiv) TMEDA (freshly distilled *via* short-path distillation), 0.30 mmol (1.2 equiv) *s*-BuLi (freshly titrated *via* No-D NMR with 1,4-cyclooctadiene) in 1.0 mL diethyl ether (freshly distilled *via* sodium benzophenone ketyl still), racemic 2-lithio-*N*-Boc-piperidine was formed in just 3 hours at $-78\text{ }^{\circ}\text{C}$ under argon atmosphere. In order to ensure maximum product formation, *s*-BuLi (1.2 M in cyclohexanes) was added to a pre-cooled solution of *N*-Boc-piperidine and TMEDA in diethyl ether dropwise down the side of the flask, resulting in a frozen mass inside the flask although not in solution. The flask was carefully agitated in order to slowly incorporate *s*-BuLi into solution with the hope of minimizing the 2,6-dimethylheptan-4-one byproduct, which is the result of a double nucleophilic attack on the Boc carbonyl group (Scheme 2.3).

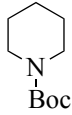
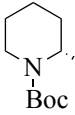
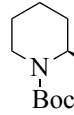
Scheme 2.3. Nonanone By-Product Formation from *s*-BuLi



After optimal lithiation was observed (>95% deuterated *via* GC-MS after quenching aliquot with MeOD), 0.025 mmol (10 mol%) (*S,S*)-NMLP **2d** in 1.0 mL diethyl ether (freshly distilled *via* sodium benzophenone ketyl still) was added to an argon-filled flask and treated with 0.050 mmol (20 mol%) *s*-BuLi. The dilithiated ligand solution was pre-cooled to $-45\text{ }^{\circ}\text{C}$ and dispensed into the 2-lithio-*N*-Boc-piperidine solution at $-78\text{ }^{\circ}\text{C}$ using a disposable syringe. The mixture was immediately transferred to a preset $-45\text{ }^{\circ}\text{C}$ bath to stir for 3 hours, moving quickly to avoid contact with room temperature atmosphere. Once equilibrated, the mixture was quickly transferred back to the $-78\text{ }^{\circ}\text{C}$ bath and stirred for 10 minutes to ensure a homogeneous temperature. 0.75 mmol (3 equiv) of neat phenyl isocyanate was added to the mixture and stirred for 2 hours at $-78\text{ }^{\circ}\text{C}$. MeOH was added prior to warming to room temperature, and CSP-SFC analysis was performed to determine the enantiomeric ratios. The results showed 2 peaks of equal areas matching the retention time of the racemate, indicating no resolution occurred (Table 2.1, entry 1). It is worth noting that all experiments were performed in triplicates to eliminate the possibility of failure due to glassware or stir bar impurities. Repeating the experiment using varying reaction scales resulted in racemic products (entries 2–4). Additionally, when the concentration was adjusted to both more concentrated conditions and more dilute conditions,

racemic products were observed (entries 2 and 5). After multiple failed CDR attempts, a more methodical approach was designed in hopes to identify the issues regarding reproducibility.

Table 2.1. Catalytic Dynamic Resolution Attempts using Varying Reaction Scales and Concentrations

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  1 equiv </div> <div style="text-align: center;"> <p>1) TMEDA (4 equiv) <i>s</i>-BuLi (1.2 equiv), Et₂O -78 °C, 3 h</p> <p>2) (<i>S,S</i>)-NMLP (10 mol%) <i>s</i>-BuLi (20 mol%), -45 °C, 3 h</p> <p>3) PhNCO, -78 °C, 2 h</p> </div> <div style="text-align: center;">  R-2ea </div> <div style="text-align: center;"> <p>+</p>  S-2ea </div> </div>			
Entry	Concentration (M) ^a	Scale ^a	er ^b
1 ^c	0.25	0.25 mmol	50:50
2 ^c	0.4	2.0 mmol	50:50
3	0.25	0.75 mmol	50:50
4	0.25	0.50 mmol	50:50
5	0.1	0.25 mmol	50:50

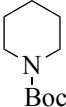
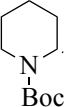
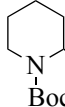
^aWith respect to *N*-Boc-piperidine. ^bDetermined using CSP-SFC.
^cRepeated 3 times

Ligand Addition Studies

Since facile syntheses of the racemates **2ea–2ec** was accomplished without the presence of (*S,S*)-NMLP **2d**, it seemed straightforward to study the ligand first, as the lithiation and electrophilic quench undoubtedly occurred in the CDR attempts. In order to examine the activity of the chiral ligand, control experiments were conducted using varying amounts of chiral ligand. Two reactions were performed, one of which a DTR was conducted (using 1 equivalent (*S,S*)-NMLP **2d** and 2 equivalents of *s*-BuLi with the ligand) and the other being a typical CDR, as described above. The results revealed racemic products for both, indicating that the resolution

failed to work even in the presence of stoichiometric amounts of chiral ligand (Table 2.2, entry 1). The same control reactions were conducted using chiral ligand prepared by a colleague, Dr. Barry Sharp, called BS-(*S,S*)-NMLP **2d** for ease of understanding, which gave identical results (entry 2). Repeating the control experiments once more using a different colleague's ligand, Timothy Beng, called TB-(*S,S*)-NMLP **2d** for ease of understanding, gave racemic products for both the CDR and DTR (entry 3). In all cases, the degree of lithiation was monitored and ligand was added only after >90% lithiation was confirmed. The next mode of action taken involved the addition of *s*-BuLi to (*S,S*)-NMLP **2d**, as the ligand is thought to be inactive unless properly lithiated to the dilithio dipeptide **Li-2d**. Trials conducted in which 20 mol% *s*-BuLi was added to the reaction tube followed by 10 mol% ligand addition resulted in racemic products (entry 4). Additional experiments using room temperature dilithiated ligand addition (entry 5), and cannula transfer of both pre-cooled and room temperature dilithiated ligands resulted in racemic products (entries 6 and 7). Upon data analysis, it was concluded that the failure to observe enantioenriched product was not a result of the physical methods of ligand addition, as Dr. Timothy Beng, the discoverer of the CDR methodology of *N*-Boc-piperidine, observed the techniques used and could not find any differences in the care taken during the course of the reaction.

Table 2.2. Ligand Examination for the Catalytic Dynamic Resolution

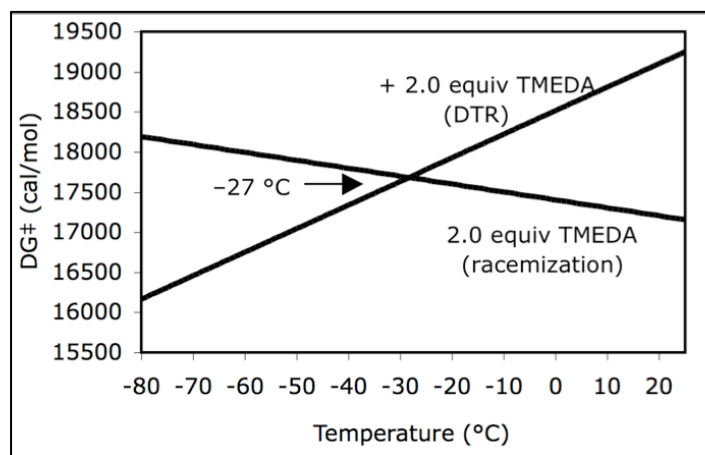
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  1 equiv </div> <div style="text-align: center;"> 1) TMEDA (4 equiv) <i>s</i>-BuLi (1.2 equiv), Et₂O -78 °C, 3 h 2) L* (10 mol%) <i>s</i>-BuLi (20 mol%), -45 °C, 3 h 3) PhNCO, -78 °C, 2 h </div> <div style="text-align: center;">  R-2ea </div> <div style="text-align: center;"> + </div> <div style="text-align: center;">  S-2ea </div> </div>				
Entry ^a	L* ^b	Ligand Addition ^c	DTR er ^d	CDR er ^d
1	(<i>S,S</i>)-NMLP 2d	A	50:50	50:50
2	BS-(<i>S,S</i>)-NMLP 2d	A	50:50	50:50
3	TB-(<i>S,S</i>)-NMLP 2d	A	50:50	50:50
4	(<i>S,S</i>)-NMLP 2d	B	50:50	50:50
5	(<i>S,S</i>)-NMLP 2d	C	50:50	50:50
6	(<i>S,S</i>)-NMLP 2d	D	50:50	50:50
7	(<i>S,S</i>)-NMLP 2d	E	50:50	50:50

^aUsing 0.25 mmol *N*-Boc-piperidine in 1 mL diethyl ether. ^b(*S,S*)-NMLP **2d** was freshly distilled; BS-(*S,S*)-NMLP **2d** was from Dr. Barry Sharp; TB-(*S,S*)-NMLP **2d** was from Dr. Timothy Beng. ^cA = Lithiated in a separate flask, pre-cooled to -45 °C, and added *via* syringe; B = Added directly to reaction flask to be lithiated *in situ*; C = Lithiated in a separate flask and added *via* syringe as a room temperature solution; D = Lithiated in a separate flask, pre-cooled to -45 °C, and added *via* cannula; E = Lithiated in a separate flask and added *via* cannula as a room temperature solution. ^dDetermined using CSP-SFC.

Equilibration Temperature Variations

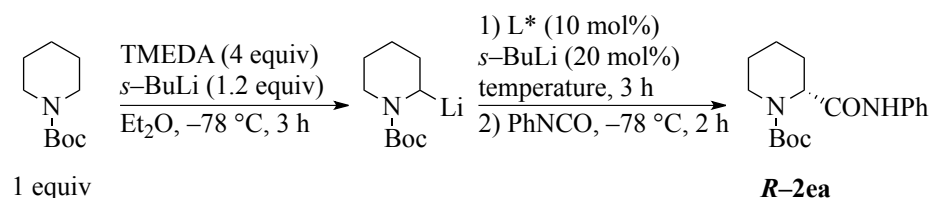
The authors of the CDR paper discovered that a DTR is realized at temperatures lower than -27 °C; therefore, the -45 °C thermostatted bath could be set to a higher temperature, although significant loss of enantioselectivity would be expected (Figure 2.1).

Figure 2.1. Racemization Plot for Dynamic Resolutions of *N*-Boc-Piperidine



Theoretically, the highest enantiomeric ratios could be achieved at the lowest possible temperatures given enough time, but slight enantiomeric ratios could be achieved in a reduced amount of time as temperatures approach $-27\text{ }^{\circ}\text{C}$. Increasing the temperature could potentially determine if the reproducibility issues involve thermodynamic parameters rather than ligand activity. Using freshly distilled *N*-Boc-piperidine, TMEDA, diethyl ether, and (*S,S*)-NMLP **2d**, a DTR and CDR were performed in parallel using a $-35\text{ }^{\circ}\text{C}$ thermostatted bath for the equilibration step (Table 2.3, entry 1). Upon CSP-SFC analysis, enantioenrichment was observed for both cases. The DTR was measured to be 73:27 er, while the CDR measured 90:10 er (Figure 2.2). Although the yield was substantially lower than the reported value (less than 20% for both), forward progress was achieved.

Table 2.3. Dynamic Resolutions of *N*-Boc-Piperidine using Various Ligands and Equilibration Temperatures

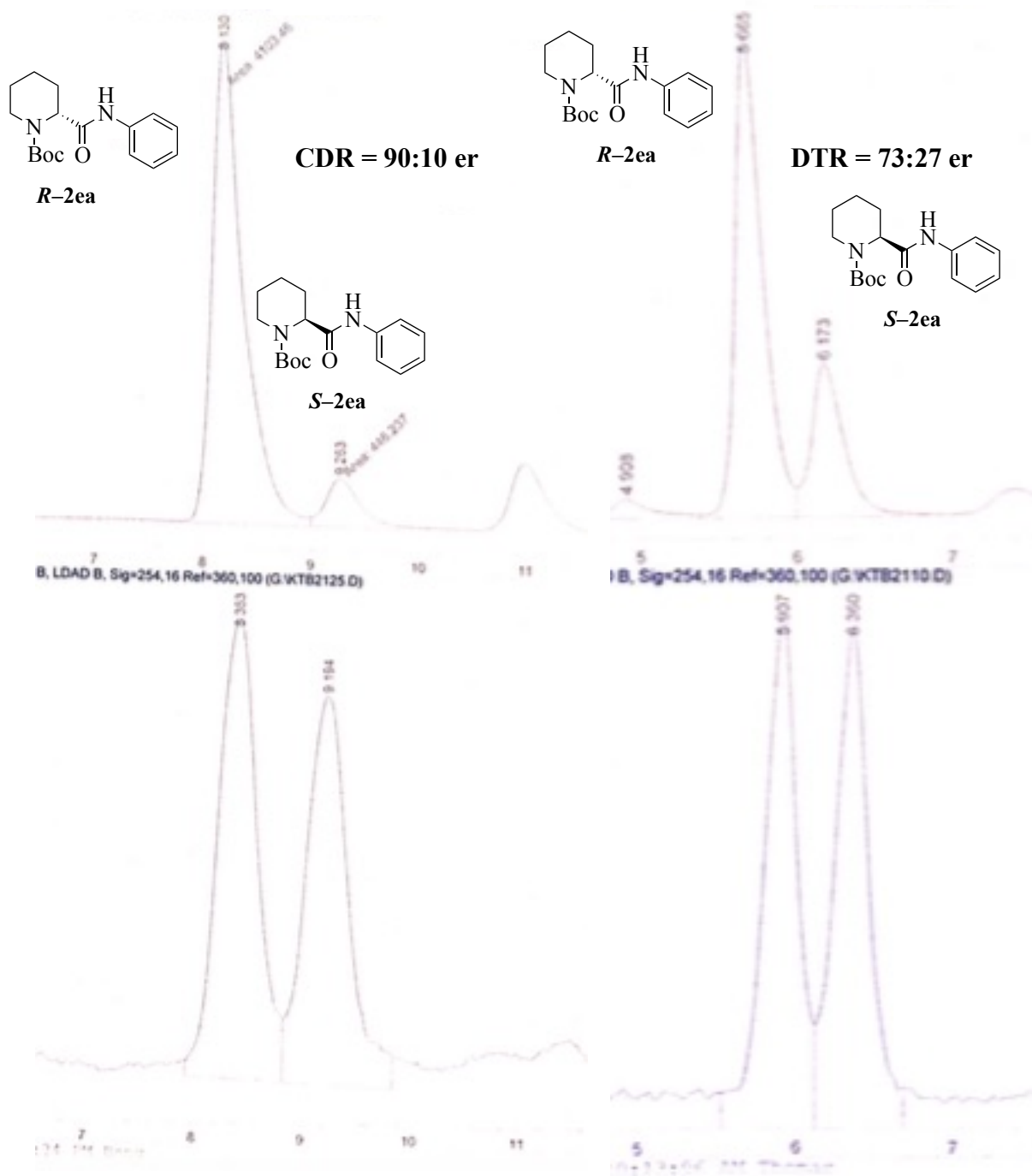


Entry ^a	L ^{*b}	Ligand Addition ^c	Temperature (°C)	DTR er ^d	CDR er ^d
1	(<i>S,S</i>)-NMLP 2d	A	-35	73:27	90:10
2 ^{e,f}	(<i>S,S</i>)-NMLP 2d	A	-35	50:50	50:50
3	BS-(<i>S,S</i>)-NMLP 2d	A	-35	50:50	50:50
4	TB-(<i>S,S</i>)-NMLP 2d	A	-35	50:50	50:50
5	BS-(<i>S,S</i>)-NMLP 2d	B	-40	N/A ^g	92:8
6 ^{e,f}	BS-(<i>S,S</i>)-NMLP 2d	B	-40	N/A ^g	50:50

^aUsing 0.25 mmol *N*-Boc-piperidine in 1.0 mL diethyl ether. ^b(*S,S*)-NMLP **2d** was freshly distilled; BS-(*S,S*)-NMLP **2d** was from Dr. Barry Sharp; TB-(*S,S*)-NMLP **2d** was from Dr. Timothy Beng. ^cA=Lithiated in a separate flask, pre-cooled to -45 °C and added *via* syringe; B = Lithiated in a separate flask, pre-cooled to -45 °C, and added *via* cannula. ^dDetermined using CSP-SFC. ^eRepeated within one week of the previous entry. ^fPerformed on 3 occasions with the same outcome in every case. ^gA DTR was not performed.

However, when repeated on multiple occasions, using either freshly prepared ligand or a colleague's ligand, racemic products were observed (entries 2–4). A CDR was observed on only one other isolated occasion in which BS-(*S,S*)-NMLP **2d** was added *via* cannulation after 3 minutes of ligand lithiation with *s*-BuLi. In this case, the equilibration temperature was set to -40 °C, resulting in a 92:8 er (entry 5). When attempted again using the same procedure and precursors, racemic products were observed (entry 6). It seemed best, at this point, to investigate the ligand purity and find alternate ways to ensure the absence of impurities.

Figure 2.2. Catalytic and Thermodynamic Resolution of *N*-Boc-Piperidine

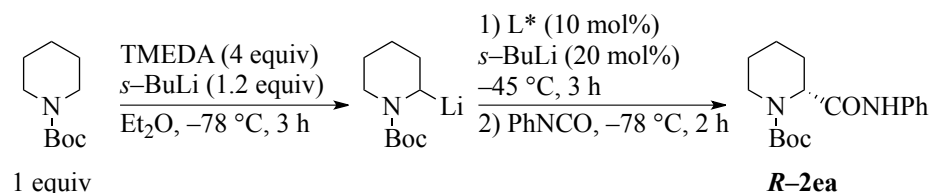


Ligand Purification

The ligand purity was investigated due to the simple rationale that if the ligand contained impurities, desired enantioselectivity might be hindered. This rationale stemmed from a comprehensive mechanistic analysis, which revealed that the aggregation states of the chiral ligand were different when a resolution occurred versus when a resolution did not occur.⁶ Since fractional kinetic orders were calculated with respect to the chiral ligand, a deaggregation event must occur in the transition state. Impurities, however small or seemingly insignificant, could perhaps play a vital role in whether a resolution occurs or not.

When following the published procedure for the synthesis of (*S,S*)-NMLP **2d**, simple extractions and distillations are the only means by which the ligand is purified. It seemed straightforward, then, to purify the final ligand using flash chromatography on silica gel prior to the Kugelrohr distillation in the final reduction step. However, after the ligand was purified using this method, no enantioenrichment was observed upon conducting a CDR (Table 2.4, entry 1).

Table 2.4. Catalytic Dynamic Resolution of *N*-Boc-Piperidine using Various Ligand Purification Methods

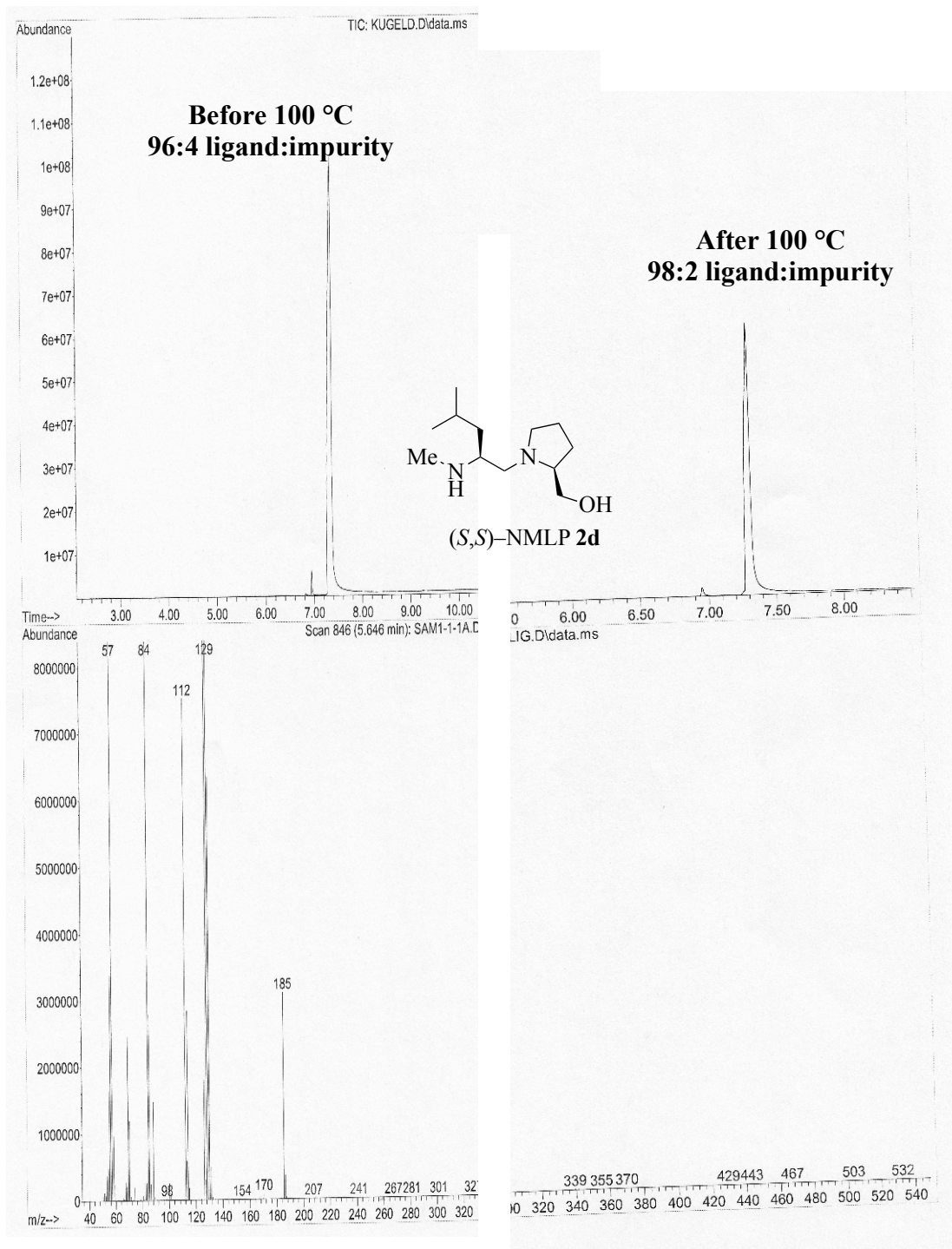


Entry ^a	L ^{*b}	Ligand Purification	er ^c
1	(<i>S,S</i>)-NMLP 2d	Flash chromatography	50:50
2	(<i>S,S</i>)-NMLP 2d	Kugelrohr distillation, <100 °C	50:50
3	(<i>S,S</i>)-NMLP 2d	Kugelrohr distillation, >100 °C	50:50
4	TB-(<i>S,S</i>)-NMLP Li-2d	Williard method ^d	93:7
	(<i>S,S</i>)-NMLP Li-2d		96:4
	(<i>S,S</i>)-NMLP Li-2d		97:3
5 ^{e,f}	(<i>S,S</i>)-NMLP 2d	Williard method	50:50
6 ^{e,f}	(<i>S,S</i>)-NMLP 2d	Williard method	50:50
7 ^f	(<i>S,S</i>)-NMLP 2d	SM method ^g	50:50

^aUsing 0.25 mmol *N*-Boc-piperidine in 1.0 mL diethyl ether. ^b(*S,S*)-NMLP **2d** was freshly synthesized by Scott Morris; TB-(*S,S*)-NMLP was from Dr. Timothy Beng. ^cDetermined using CSP-SFC. ^dUsing crystals formed using *n*-BuLi at -45 °C and washed with hexanes. ^eRepeated within one week of the previous entry. ^fPerformed on 3 occasions with the same outcome in every case. ^gUsing crystals formed using ethyl acetate and hexanes at -45 °C which were then washed with hexanes and further purified *via* Kugelrohr distillation.

Next, it was observed that when purifying the chiral ligand *via* Kugelrohr distillation, some distills at a lower temperature (<100 °C) while more distills at a higher temperature (>100°C). A GC-MS analysis revealed that the ligand distilling at a lower temperature contained slightly more of an unknown impurity (96:4 ligand:impurity) than the distillate from a higher temperature (98:2 ligand:impurity) (Figure 2.3). A CDR was conducted with each, both being met with no success, as racemic products were formed in both cases (Table 2.4, entry 2–3).

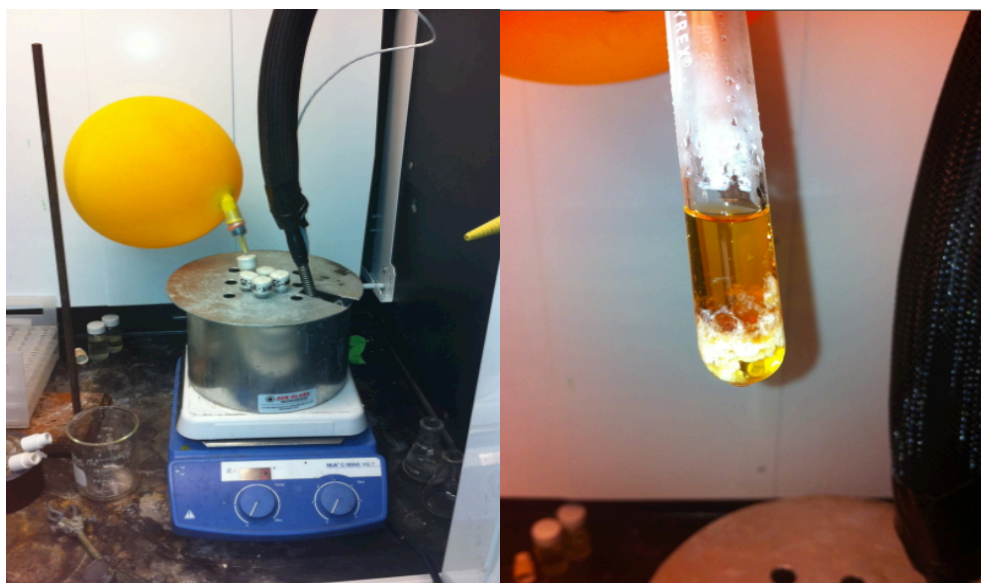
Figure 2.3. GC–MS Traces of Ligand **2d** and an Unknown Impurity



The ability to recrystallize the chiral ligand was then examined, hoping that absolute purity could be achieved. Dr. Paul Williard of Brown University suggested a crystallization

technique using *n*-BuLi. The procedure was to slowly add 2 equivalents of *n*-BuLi to the ligand in freshly distilled hexanes at $-45\text{ }^{\circ}\text{C}$ under argon atmosphere. The ligand solution was kept in the $-45\text{ }^{\circ}\text{C}$ thermostatted bath overnight for crystal growth. Once the crystals formed, the solution was decanted and the crystals were washed using hexanes. The resulting crystals were dried and stored in a freezer until needed. A photograph of the crystals and setup are shown in Figure 2.4. A CDR was then attempted using freshly prepared crystals of both TB-(*S,S*)-NMLP **Li-2d** and recently synthesized (*S,S*)-NMLP **Li-2d** (Table 2.4, entry 4). CSP-SFC analysis showed that a resolution occurred in each of the flasks, showing a 93:7, 96:4, and 97:3 er respectively. Excited by these results, the same procedure was conducted on the very next day. However, racemic product was observed using both TB-(*S,S*)-NMLP **Li-2d** and recently synthesized (*S,S*)-NMLP **Li-2d** (entry 5). Attempted resolutions were performed during the week, and identical results were obtained (entry 6). At this point, it is unclear why the CDR worked on the first attempt but failed upon further attempts.

Figure 2.4. Photograph of **Li-2d** Crystals using the Williard Method



A more facile approach was then developed to recrystallize the ligand in hopes that a CDR can be administered with reproducible and predictable results. In this approach, the ligand **2d** was dissolved in a minimal amount of hot ethyl acetate under argon atmosphere. The resulting mixture was brought to $-45\text{ }^{\circ}\text{C}$ and hexanes was carefully layered on top of the ethyl acetate solution. After allowing the mixture to sit at $-45\text{ }^{\circ}\text{C}$ overnight, crystals formed. Workup consisted of washing the crystals with hexanes and performing a Kugelrohr distillation for further purification. A CDR was performed on multiple occasions using (*S,S*)-NMLP **2d** purified using the described method; however, racemic product was observed (Table 2.4, entry 7).

As a final attempt to understand the activity of the chiral ligand, optical purity was measured using a polarimeter. In their paper, Beng and Gawley measured the specific rotation of (*S,S*)-NMLP to be $+18.15$ ($c = 2$ in MeOH).² With this in mind, the specific rotation was then measured using a freshly prepared sample of (*S,S*)-NMLP **2d**, which gave an $[\alpha]^{22}_{\text{D}}$ value of $+16.52$ ($c = 2$ in MeOH). Specific rotations of other samples were measured, including BS-(*S,S*)-NMLP **2d**, recrystallized (*S,S*)-NMLP **2d** (using ethyl acetate/hexanes method from Table 2.4), old (*S,S*)-NMLP **2d** stored as a refrigerated diethyl ether solution for 2 months, and various Kugelrohr distillates, all of which gave $[\alpha]^{22}_{\text{D}}$ values between $+16.21$ and $+17.62$ ($c = 2$ in MeOH). After subsequent discussions, it seems that the $[\alpha]^{22}_{\text{D}}$ value needs to be a minimum of $+18.00$ for a successful resolution, although some speculation may be involved in this conclusion. What is known, however, is that in all cases where the specific rotation was measured to be less than $+18.00$, racemic products were observed when attempting either a CDR or DTR. Although the $[\alpha]^{22}_{\text{D}}$ was not ideal, it was unclear how to proceed and attain a more optically pure sample. Therefore, (*S,S*)-NMLP **2d** was synthesized on 3 more occasions in hopes that the specific rotation matched the reported $+18.62$ values; however, the closest value

observed was +17.62, which gave racemic product when used in the CDR. Since no further experiments could be concocted regarding ligand purity, lithiation was the next area of focus in the investigation concerning the reproducibility of the CDR.

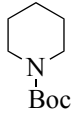
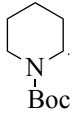
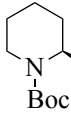
Lithiation Efficiency

Lithiation is an important event that is present in a successful CDR. If the initial *N*-Boc-piperidine is not properly lithiated, the ligand cannot coordinate, thus enantioselectivity will not be observed. Additionally, if little to no lithiation occurs, electrophilic substitution will not proceed and starting material will be recovered. Lastly, if improper lithiation occurs, the aggregation states of the organolithiums may be altered, resulting in aggregates that may be inactive in the CDR. Various factors influence lithiation, such as the concentration of *s*-BuLi, the reaction temperature, the reaction time, the *s*-BuLi supplier, the order of *s*-BuLi addition, the rate at which *s*-BuLi is added, and the age of the *s*-BuLi bottle, as lithium salts form over time. Since the reaction temperature and time are well understood, the concentration, supplier, order of addition, and age of *s*-BuLi were individually examined.

When examining the concentration of *s*-BuLi, a method of determining the concentration must be established. No-D NMR was the method of choice,¹⁰ which gave the concentration using NMR integrals after a simple calculation. When purchasing *s*-BuLi from Sigma-Aldrich, it is sold as a 1.4 M solution in cyclohexanes. Indeed, No-D NMR confirmed the 1.4 M concentration. However, the concentration of *s*-BuLi becomes lower over time, presumably due to the formation of lithium salts within the static volume of solution. In just 2 weeks, the concentration dropped to 1.3 M after initially opening the bottle, and 1.2 M within 1 month of

opening the bottle. Within 2 months, the concentration was measured to be 1.0 M. Visually, the solution of the *s*-BuLi over time became opaque rather than clear, indicating lithium salt formation. Each concentration of *s*-BuLi was used in a CDR. After measuring the initial lithiation of *N*-Boc-piperidine by taking an aliquot of the reaction mixture and submerging it quickly in MeOD, followed by GC-MS analysis to determine the percentage of deuterium incorporation, it was found that >90% lithiation occurred in every case (Table 2.5, entries 1–5). Therefore, it was determined that the concentration of *s*-BuLi did not play a significant role in the initial lithiation of *N*-Boc-piperidine. Additionally, freshly opened *s*-BuLi gave similar results to aged *s*-BuLi (2 months), revealing that the lithiation is efficient even when significant salt formation has occurred. It is of note, however, that *s*-BuLi that was opened for more than 2 months was not tested due to the authors of the paper obtaining their results using freshly opened bottles of *s*-BuLi rather than older bottles. Unfortunately, in every case performed, racemic products were observed when performing a catalytic dynamic resolution.

Table 2.5. Examination of *s*-BuLi in the Catalytic Dynamic Resolution of *N*-Boc-Piperidine

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  1 equiv </div> <div style="text-align: center;"> 1) TMEDA (4 equiv) <i>s</i>-BuLi (1.2 equiv), Et₂O -78 °C, 3 h <hr/> 2) (<i>S,S</i>)-NMLP (10 mol%) <i>s</i>-BuLi (20 mol%), -45 °C, 3 h 3) PhNCO, -78 °C, 2 h </div> <div style="text-align: center;">  <i>R</i>-2ea </div> <div style="text-align: center;"> + </div> <div style="text-align: center;">  <i>S</i>-2ea </div> </div>				
Entry ^a	<i>s</i> -BuLi Concentration (M) ^b	<i>s</i> -BuLi Supplier	% Lithiation ^c	er ^d
1	1.4	Sigma-Aldrich	94%	50:50
2	1.3	Sigma-Aldrich	94%	50:50
3	1.2	Sigma-Aldrich	92%	50:50
4	1.1	Sigma-Aldrich	90%	50:50
5	1.0	Sigma-Aldrich	90%	50:50
6	1.3	Acros Organics	93%	50:50
7	1.3	Alfa-Aesar	94%	50:50
8 ^e	1.4	Sigma-Aldrich	94%	50:50

^aUsing 0.25 mmol *N*-Boc-piperidine in 1.0 mL diethyl ether. All entries were performed in triplicates. ^bDetermined using No- D NMR. ^cDetermined by quenching an aliquot of 2-lithio-*N*-Boc-piperidine with MeOD and measuring deuterium incorporation *via* GC-MS. ^dDetermined using CSP-SFC.

^eUsing inverse lithiation procedure.

Next, lithiation using *s*-BuLi from various suppliers was examined. Although a comprehensive study was not administered during this time, it did not seem that the supplier made a large difference. Beng and Gawley used *s*-BuLi purchased from Sigma-Aldrich as a 1.4 M solution in cyclohexanes; however, when using *s*-BuLi purchased from Acros Organics (1.3 M in a 92:8 solution of cyclohexanes:hexanes) and Alfa-Aesar (1.3 M in cyclohexanes), >90 % lithiation was observed *via* GC-MS analysis of a MeOD quench of 2-lithio-*N*-Boc-piperidine for each trial, showing that the supplier of *s*-BuLi has little to no effect on the degree in which

N-Boc-piperidine is lithiated. However, racemic products were observed in every case (entries 1, 6–7).

Lastly, the order of *s*-BuLi addition was examined. In a typical procedure, *s*-BuLi is added to a pre-cooled solution of *N*-Boc-piperidine and TMEDA in freshly distilled diethyl ether. *s*-BuLi is either added slowly using a syringe pump or carefully added down the side of the tube in order to freeze the cyclohexane solution of *s*-BuLi. Subsequent agitation allows the *s*-BuLi to slowly become incorporated with the *N*-Boc-piperidine mixture, allowing both components to be chilled during the mixing process while also retarding the rate at which *s*-BuLi mixes with the substrate. Using this method, *s*-BuLi is in low concentration initially with respect to *N*-Boc-piperidine, allowing for careful control of α -lithiation over the undesired attack of the organolithium reagent with the Boc group (see Scheme 2.3). Although lithiation occurs well with this method, an inverse lithiation was attempted. Essentially, using this method, the *s*-BuLi and TMEDA would be dissolved in freshly distilled diethyl ether and pre-cooled to $-78\text{ }^{\circ}\text{C}$. *N*-Boc-piperidine would then be slowly added, allowing for lithiation. In this method, an excess of *s*-BuLi would come into contact with a substoichiometric of *N*-Boc-piperidine upon initial contact, which, hypothetically, would favor the undesired attack of the Boc group, generating more of the nonanone byproduct. However, when this method was attempted, efficient lithiation occurred with minimal nonanone byproduct and, racemic products were observed upon CSP-SFC analysis (94%, entry 8). After studying various lithiation conditions and factors that may hinder successful lithiations, it was concluded that the current conditions administered did not play a significant role in determining the outcome of the CDR. Since ligand purity was established along with proper lithiation conditions, attention was directed towards finding

impurities that might potentially be incorporated into the reaction flask that enhances the likelihood of a successful CDR.

Butylated Hydroxytoluene (BHT) Studies

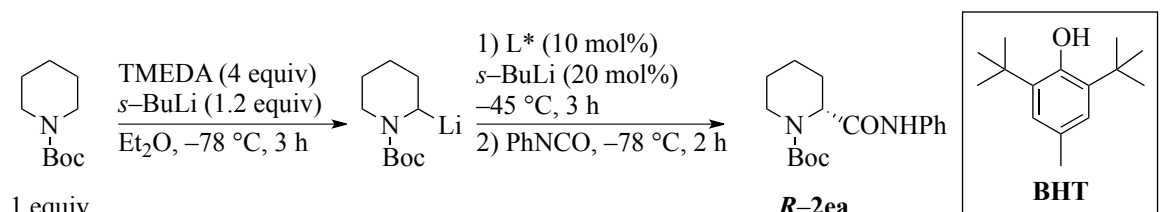
In the ongoing search for factors that either hinder or enhance the reproducibility of the catalytic dynamic resolution of *N*-Boc-piperidine, identifying potential impurities became the next area of focus. Since the aggregation state of the dilithio-(*S,S*)-NMLP **Li-2d** is important for proper activity in the CDR, minor impurities could potentially have a significant effect on the outcome of the reaction. Since purification of the ligand by flash chromatography, recrystallization, or Kugelrohr distillation did not solve the issues regarding reproducibility, it was thought that an impurity might be incorporated in the midst of reaction setup. Upon careful examination, it was speculated that diethyl ether may be the root of the problem, as all glassware was previously washed in both an acid and base baths followed by an acetone rinse, the ligand was freshly purified, the *N*-Boc-piperidine and TMEDA were freshly distilled, and *s*-BuLi was frequently titrated. However, each of these, with the exception of *s*-BuLi, were stored as a molar solution in diethyl ether; therefore, the impurity could be added inadvertently after purification.

Diethyl ether used was purchased from EMD Millipore as a 20-liter can, which was then added to a sodium benzophenone ketyl still. This particular still is used widely to remove water, peroxides, and oxygen for organic synthesis. The color of the solution in the still was always a deep blue color when used for a CDR, indicating the absence of water and oxygen. Another indication of absolute dryness is that >90% lithiation was always observed, which would not be the case with the presence of water. Additionally, the stills were kept under argon atmosphere to

prevent atmospheric oxygen from entering the chamber. However, upon close examination, it was noted that butylated hydroxytoluene (BHT) is added as a stabilizer to prevent peroxide formation in the diethyl ether (Table 2.6, reaction scheme). Although it is added in seemingly insignificant amounts (5–7 ppm), it could potentially affect the reaction due to the slightly acidic phenol group, which can be deprotonated in the presence of *s*-BuLi and coordinate to the other organolithium aggregates. With this concern in mind, efforts were made to identify the result of BHT in the CDR.

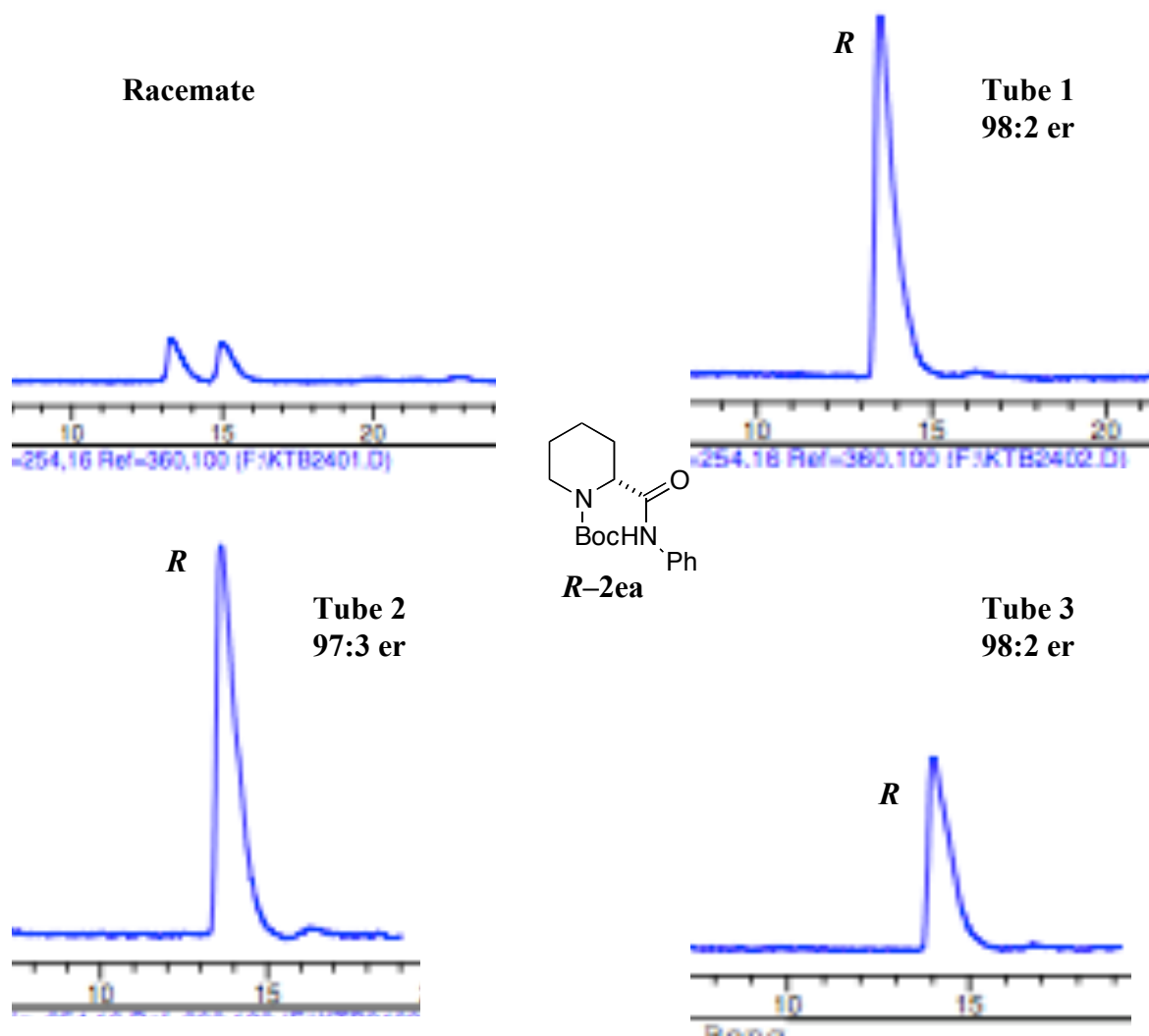
Pure BHT was purchased from Alfa-Aesar and made into a solution, which, upon multiple dilutions, was made into a 0.05 M solution in diethyl ether. A CDR was then attempted using freshly distilled chemicals with the addition of 0.1 mg of BHT. Interestingly, a resolution occurred in every tube as a 98:2, 97:3, and 98:2 er, as determined using CSP–SFC (Figure 2.5; Table 2.6, entry 1).

Table 2.6. Examination of the Effects of Butylated Hydroxytoluene on the Catalytic Dynamic Resolution of *N*-Boc–Piperidine

			
Entry ^a	L* ^b	Amount of BHT Added (mg)	er ^c
1	(<i>S,S</i>)-NMLP 2d	0.1; 0.1; 0.1	98:2; 97:3; 98:2
2 ^d	(<i>S,S</i>)-NMLP 2d	0; 0; 0.5; 1.0	96:4; 98:2; 70:30; 50:50
3 ^d	(<i>S,S</i>)-NMLP 2d	0; 0; 0; 0.03; 0.08	All 50:50
4 ^{d,e}	(<i>S,S</i>)-NMLP 2d	0; 0.1; 0.12	All 50:50
	TB-(<i>S,S</i>)-NMLP 2d	0; 0.1; 0.12	All 50:50

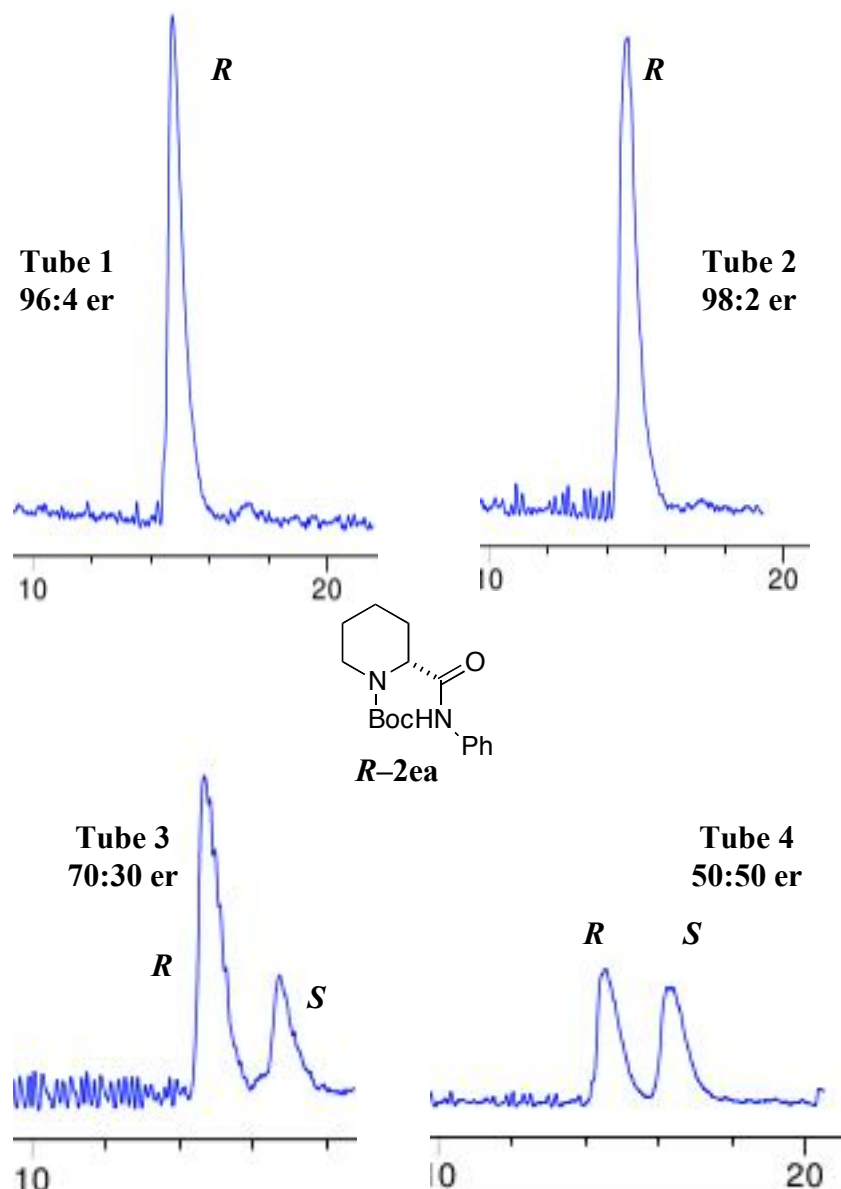
^aUsing 0.25 mmol *N*-Boc–piperidine in 1.0 mL diethyl ether. ^b(*S,S*)-NMLP **2d** was freshly synthesized by Scott Morris; TB-(*S,S*)-NMLP **2d** was from Dr. Timothy Beng. ^cDetermined using CSP–SFC. ^dRepeated within one day of the previous entry. ^ePerformed on 3 occasions with the same outcome in every case.

Figure 2.5. CSP–SFC Spectra of the Catalytic Dynamic Resolution of *N*-Boc–Piperidine using Static Amounts of Butylated Hydroxytoluene



With the positive results in hand, another resolution was attempted in which the amount of BHT added was varied. In tubes 1 and 2, a CDR was performed without the addition of any BHT. In tubes 3 and 4, 0.5 mg and 1 mg of BHT was added, respectively. The results showed a negative correlation between the CDR enantioselectivities and the amount of BHT added, as tubes 1 and 2 provided 96:4 and 98:2 er while the er dropped when more BHT was added, shown by a 70:30 er for tube 3 and a racemic mixture for tube 4 (Figure 2.6; Table 2.6, entry 2).

Figure 2.6. CSP–SFC Spectra of the Catalytic Dynamic Resolution of *N*-Boc–Piperidine using Varying Amounts of Butylated Hydroxytoluene



The next day, a similar experiment was conducted using 3 tubes with no modifications, 1 tube with 0.03 mg of BHT added, and 1 tube with 0.08 mg of BHT added. Upon CSP–SFC analysis, every tube yielded racemic products when a CDR was administered (entry 3). Again,

similar experiments were conducted using varying amounts of BHT, all of which yielded racemic products (entry 4).

Again, no definite conclusion could be made concerning the reproducibility of the CDR when adding BHT. Although some of the observed results seemed promising, the issues affecting a successful CDR appear to be more complex than initially thought.

Conclusion

It is unclear how and why the resolution worked on a particular day and not the others; however, it seems that when a resolution occurs, every tube shows enantiomeric excess, although the exact degree to which enantioenrichment occurs may vary. After a thorough investigation of the CDR, including ligand addition, studying the equilibration temperature, alternate modes of ligand purification, evaluating lithiation efficiency with various suppliers and concentrations, and monitoring the effects of adding BHT, it was concluded that the complications hindering consistent catalytic dynamic resolutions is highly complex and would require more experimentation to understand. However, occasional CDR's were observed with high enantioselectivities, showing that the methodology does, in fact, work. Further experimentation would be needed, however, to identify the phenomena associated successful CDR implementation.

2.2. Diastereoselective Synthesis of α,α,α' -Trisubstituted Piperidines and Pyrrolidines

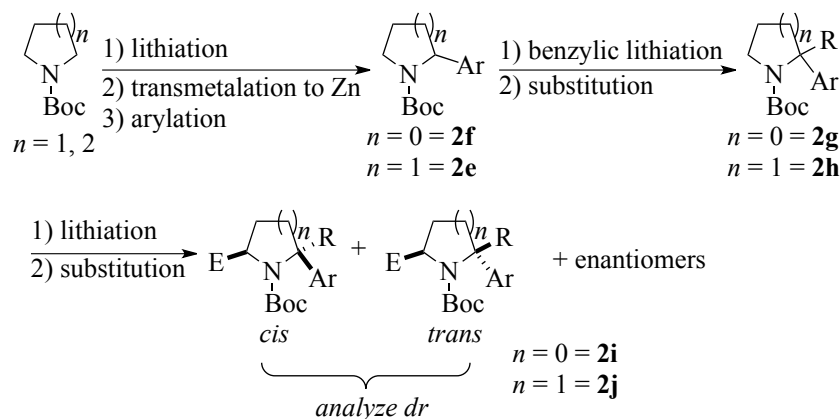
Pyrrolidines and piperidines are versatile heterocycles that are ubiquitous in natural products and pharmaceuticals.¹¹ As an ongoing investigation in the Gawley lab, polysubstituted azaheterocycle synthesis using organolithium chemistry was proposed using both *N*-Boc-pyrrolidine and *N*-Boc-piperidine. Various reports show that α,α' -disubstituted-*N*-Boc-pyrrolidines and α,α' -disubstituted-*N*-Boc-piperidines can be synthesized in both racemic and enantioenriched forms.¹²⁻¹⁴ It seemed plausible, then, to combine the reported methodologies and synthesize α,α,α' -trisubstituted-*N*-Boc-pyrrolidines and piperidines from the α,α' -disubstituted precursor. Herein, attempts to study the α' -lithiation/substitution of select 2,2-disubstituted Boc-protected pyrrolidines and piperidines are reported, including any conclusions that can be drawn concerning the diastereoselectivity of the transformation.

*Synthesis of α,α' -disubstituted-*N*-Boc-Pyrrolidines and Piperidines*

It has been previously shown that *N*-Boc-pyrrolidines and piperidines can be arylated at the 2-position using a combination of organolithium chemistry and palladium-catalyzed Negishi coupling.^{3, 13} The significance of this discovery not only lies in the expanded substrate scope, but also in the ability to lithiate at the more acidic benzylic position. Upon subsequent electrophilic quench, 2,2-disubstituted Boc-protected heterocycles can be formed in just 2 steps. In addition, it was found that the substitution of the benzylic organolithium occurs with retention of configuration (S_E2ret^{15}) from the enantioenriched precursor with little or no loss of enantioselectivity, allowing for predictable stereochemical outcomes using these specific

substitution patterns.^{5, 9, 16} Prompted by the facile synthesis of α,α -disubstituted Boc-protected heterocycles and intrigued by the notion of α' -lithiation/substitution, efforts were focused to test both the efficiency of the α' -lithiation/substitution sequence and the diastereomeric ratio of the final product (Scheme 2.4). For clarity in further discussion, the relative stereochemistry terms *cis* and *trans* will refer to the position of the α' -substituent with respect to the α -aryl group.

Scheme 2.4. Synthesis of α,α,α' -trisubstituted *N*-Boc-Pyrrolidines and Piperidines



Prior to joining the project, which was initiated by Dr. Timothy Beng, a variety of α,α -disubstituted *N*-Boc-pyrrolidines (**2ga** and **2gb**) and piperidines (**2ha** and **2hb**) were synthesized and successful α' -lithiation/substitutions were applied, some with high diastereoselectivity. The preliminary results are summarized in Table 2.7.

Table 2.7. Preliminary Triple Alkylation Results

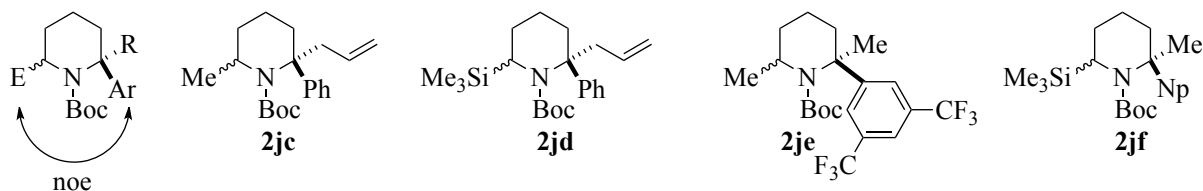
2ga, 2gb, 2ha, 2hb **2ia–2if; 2ja–2jd**
n = 1, 2

Entry	<i>n</i>	Ar ^a	R	E ⁺	Substrate	Product	Yield (%) ^b	dr (<i>cis:trans</i>) ^c
1	1	Ph	Me	Me ₂ SO ₄	2ga	2ia	94	14:86 ^d
2	1	Np	Me	Me ₂ SO ₄	2gb	2ib	89	>1:99 ^d
3	1	Np	Me	Me ₃ SiCl	2gb	2ic	84	2:98 ^d
4	1	Np	Me	Bu ₃ SnCl	2gb	2id	69	>1:99 ^d
5	1	Np	Me	EtCO ₂ Cl	2gb	2ie	77	2:98
6	1	Np	Me	allyl bromide	2gb	2if	54	24:76
7	1	Np	Me	allyl bromide ^e	2gb	2if	68	8:92
8	2	Ph	Me	Me ₂ SO ₄	2ha	2ja	85	>99:1 ^f
9	2	Ph	Me	EtCO ₂ Cl	2ha	2jb	70	60:40 ^f
10	2	Ph	allyl	Me ₂ SO ₄	2hb	2jc	81	>99:1 ^f
11	2	Ph	allyl	Me ₃ SiCl	2hb	2jd	77	>99:1 ^f

^aPh = phenyl; Np = naphthyl. ^bIsolated yield. ^cDetermined using GC–MS analysis of the crude product, filtered through silicagel. ^dRelative stereochemistry confirmed *via* NOESY or ROESY analysis. ^eUsing zinc– and copper–mediated coupling rather than direct quench. ^fRelative stereochemistry not determined at the time Scott Morris joined the project.

Since all of the pyrrolidine–based structures yielded *trans* stereochemistry, it was assumed that the piperidine–based structures also exhibited the same stereochemistry. However, conformation analysis of piperidines was needed; therefore, focused efforts were applied to synthesize piperidines that provided high diastereomeric ratios in order to obtain NOESY or ROESY spectra. The desired substrates are shown in Figure 2.7.

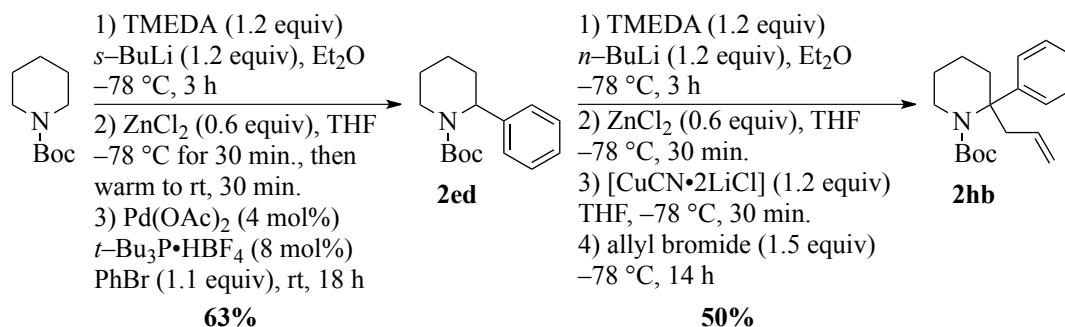
Figure 2.7. Target Substrates for NOESY Analysis



Piperidines **2je** and **2jf** were intriguing compounds, as preliminary results showed high diastereoselectivities *via* GC–MS (>99:1 dr). However, the difficulties in synthesis rendered both **2je** and **2jf** inappropriate for publication. Regardless, prior to publication, **2je** and **2jf** were thought to be plausible examples to showcase; therefore, syntheses and analyses of both compounds were pursued. Having a set goal in hand, synthesis of the α,α -disubstituted precursors was started.

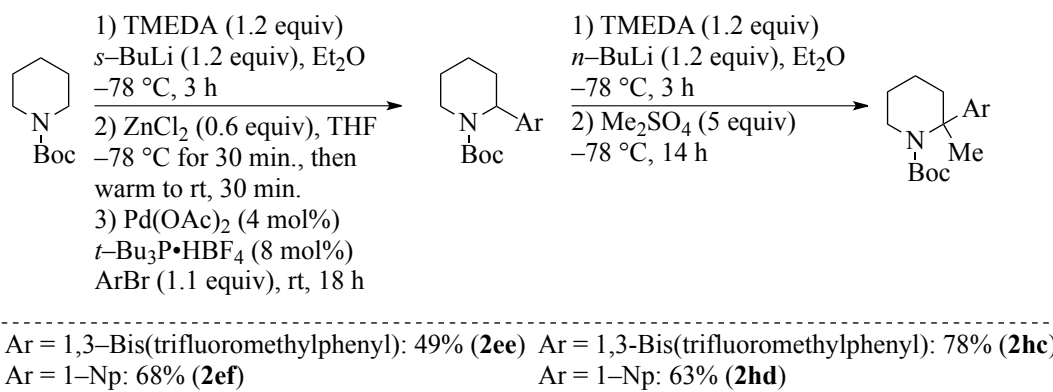
The first precursors synthesized were those leading to **2jc** and **2jd**, both bearing a phenyl group and an allyl group at the 2 position of the Boc-protected piperidine. Palladium-catalyzed Negishi coupling proceeded uneventfully, providing the arylated product **2ed** in 63% yield. This set up the benzylic lithiation/substitution using allyl bromide, mediated by both zinc- and copper-coupling. Indeed, benzylic lithiation/substitution provided the α,α -disubstituted product **2hb** smoothly, with slight problems concerning purification due to the matching R_f 's of the starting material and the product. However, the desired product was successfully obtained in 50% yield after multiple purification attempts (Scheme 2.5).

Scheme 2.5. Synthesis of α,α -disubstituted Piperidine **2hb**



Similarly, the precursors for substrates **2je** and **2jf** were synthesized using analogous procedures. Palladium-catalyzed Negishi coupling was administered using the respective aryl bromide to yield α -aryl piperidines **2ee** and **2ef**. Subsequent benzylic lithiation using n -BuLi followed by a direct quench using Me₂SO₄ provided the corresponding α,α -disubstituted piperidines **2hc** and **2hd** in good yields (Scheme 2.6). Once all the desired precursors were synthesized, α' -lithiation/substitution was the next focus in preparing for spectroscopic analysis and relative stereochemistry assignments.

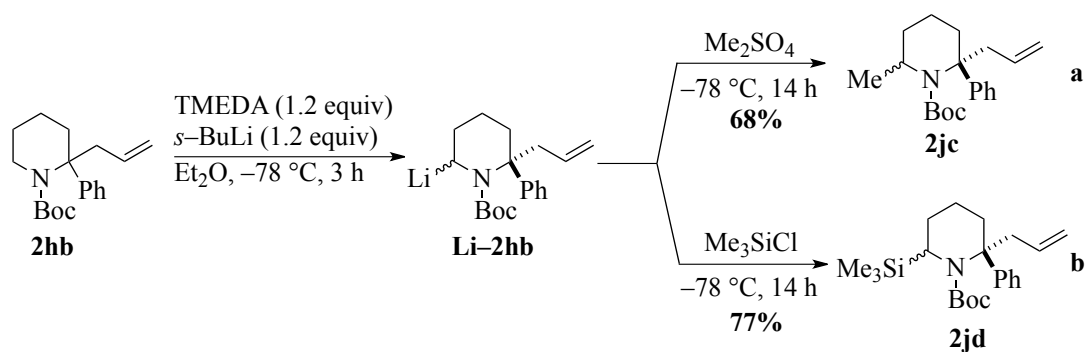
Scheme 2.6. Synthesis of α,α -disubstituted Piperidines **2hc** and **2hd**



α' -Lithiation/Substitution of Select Precursors

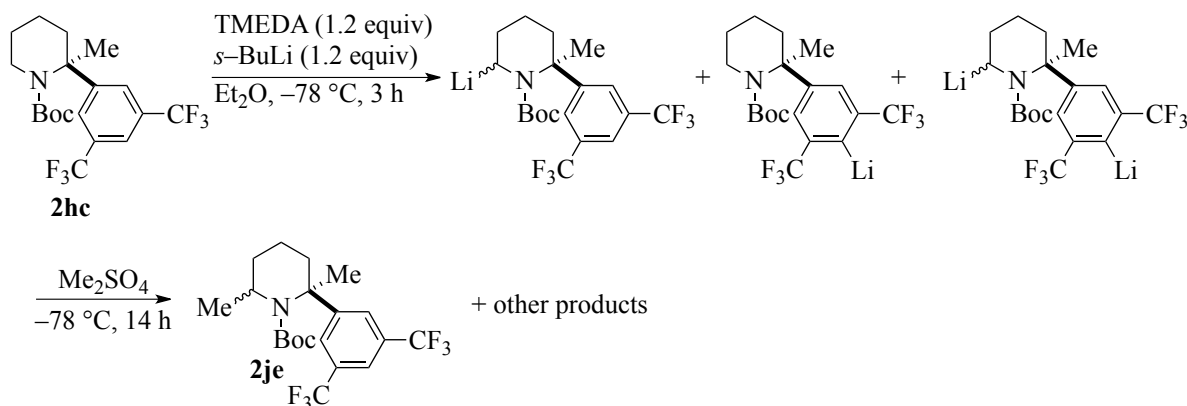
Having the precursors in hand, α' -lithiation was attempted followed by direct electrophilic quench. Product **2jc** was first attempted using the corresponding 2-allyl-2-phenyl-*N*-Boc-piperidine precursor **2hb**. When subjected to lithiation conditions using *s*-BuLi and TMEDA at $-78\text{ }^{\circ}\text{C}$ for 3 hours, 92% lithiation was observed by taking an aliquot from the reaction mixture and quenching with MeOD, followed by GC-MS analysis. Once adequate lithiation was observed, Me₂SO₄ was directly added to the mixture at $-78\text{ }^{\circ}\text{C}$, which was then stirred for an additional 14 hours at the same temperature. The isolated yields were slightly lower than that of Dr. Beng, likely due to purification difficulties (81% vs. 68%)¹⁷ but the diastereoselectivities matched and NOESY data could be obtained (>99:1 dr *via* GC-MS; Scheme 2.7a). Similarly, product **2jd** was formed through an identical lithiation/substitution sequence, changing the electrophile to Me₃SiCl rather than Me₂SO₄. The desired product was then detected *via* GC-MS, which also showed a diastereomeric ratio of >99:1. Purification by flash chromatography yielded the pure product in 77%, matching the published results (Scheme 2.7b).¹⁷

Scheme 2.7. Syntheses of Trisubstituted Piperidines **2jc** and **2jd** *via* α' -Lithiation/Substitution



Next, products **2je** and **2jf** were attempted to be made from the corresponding precursors. Product **2je** proved to be a challenging substrate to analyze, as lithiation was not trivial. Using *s*-BuLi/TMEDA and freshly distilled diethyl ether, the GC–MS showed both an *M*+1 peak, as expected, along with an *M*+2 peak. Intrigued by the results, electrophilic quench using Me₂SO₄ and workup yielded multiple products by GC–MS. NMR analysis showed methylation at the *para*-positions of the Bis(trifluoromethylphenyl) ring, indicating that lithiation occurred on the benzene ring as well as the α' position. Therefore, lithiation occurring in either of those positions in addition to double-lithiation contributed to the multiple products formed upon electrophilic quench (Scheme 2.8).

Scheme 2.8. Attempted Synthesis of Trisubstituted Piperidine **2je**

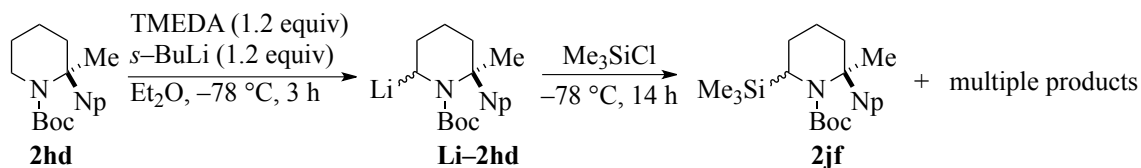


Furthermore, the reaction was performed again and then quenched with MeOD to provide the deuterated product. NMR analysis showed a depletion of an integral in the aromatic region, agreeing with the incorporation of a deuterium on the ring. After further discussion of these observations, **2je** was omitted from the substrate scope. However, when the paper was published, substrate **2je** was included in the Supplemental Information using improved conditions. According to the Supplemental Information, only 1 equivalent of *s*-BuLi was added to a solution

of pre-cooled diethyl ether and TMEDA. The author notes that it is important to control the amount of *s*-BuLi added in order to avoid undesirable aryl lithiation. The author was able to obtain pure product **2je** in 79% with >99:1 dr, showcasing the necessity of careful *s*-BuLi addition.

Lastly, **2jf** was attempted to be synthesized using the previously formed precursor. After multiple attempts, **2jf** could not be synthesized for unknown reasons. It was observed that lithiation occurred properly (>90%), but subsequent electrophilic quench and workup yielded multiple products using GC-MS analysis (Scheme 2.9). After further discussions with multiple colleagues and Dr. Gawley, the substrate was omitted from the substrate scope.

Scheme 2.9. Attempted Synthesis of Trisubstituted Piperidine **2jf**

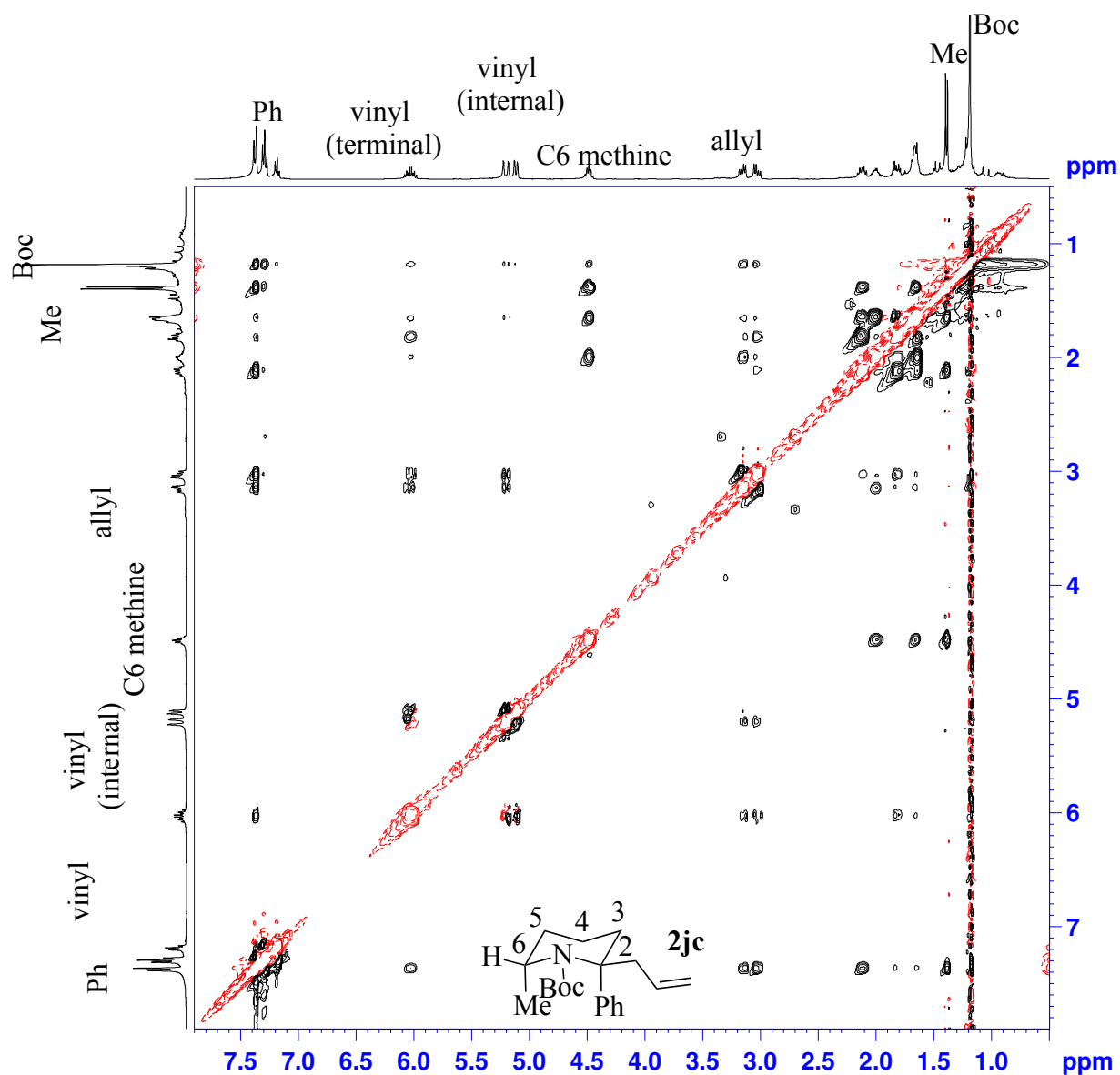


Relative Configuration using NOESY

Having successfully synthesized **2jc** and **2jd**, NOESY was performed in order to establish the relative configuration. Surprisingly, when the NOESY of **2jc** was carefully analyzed, a *cis* configuration was revealed (Figure 2.8). The spectrum clearly showed a crosspeak between the α -methyl and the aromatic protons while revealing the absence of a crosspeak between the α' -methyl and the allyl/vinyl protons. Additionally, a *cis*-diaxial arrangement was concluded, as the α' -methine proton did not crosspeak the allyl/vinyl protons,

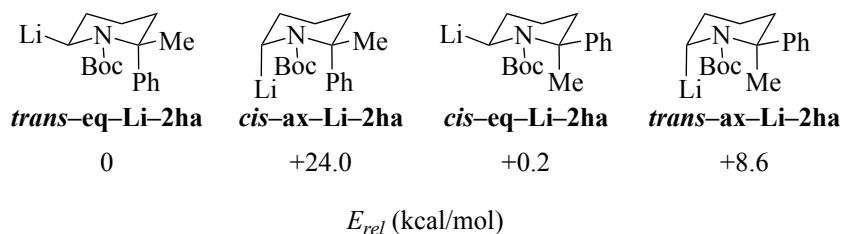
indicating an equatorial arrangement. It is of note that all protons were assigned using COSY and HMQC, which are shown in the Supplemental Information of the corresponding publication.¹⁷

Figure 2.8. NOESY Spectrum of Trisubstituted Piperidine **2jc**



In order to rationalize this observation, DFT calculations were reported in the paper, which are acknowledged to be performed by Dr. Timothy Beng and Nathan Fox (Figure 2.9).¹⁷

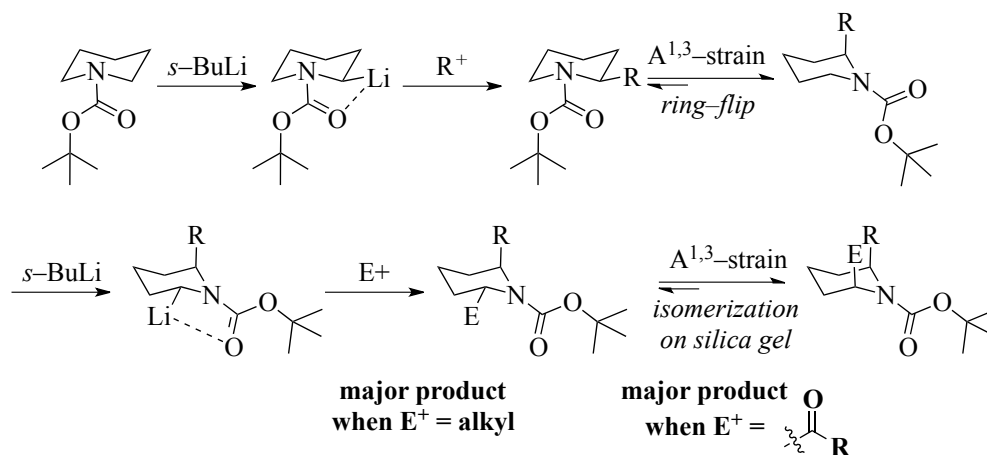
Figure 2.9. DFT Calculations of **Li-2ha** Conformers



Not surprisingly, equatorial lithiation is favored over axial lithiation, as shown by comparing organolithiums ***trans*-eq-Li-2ha** and ***cis*-eq-Li-2ha** with ***cis*-ax-Li-2ha** and ***trans*-ax-Li-2ha**. Interestingly, compound ***cis*-ax-Li-2ha** was calculated to be ~24 kcal/mol higher in energy than both the equatorial lithiation compounds, ***trans*-eq-Li-2ha** and ***cis*-eq-Li-2ha**, while also being ~15 kcal/mol higher in energy than its diastereomer ***trans*-ax-Li-2ha**. Since NOESY confirmed a *cis*-conformation between the methyl group and the aryl group for compound **2jc**, the intermediate arises from the allyl/phenyl analogue **2hb** of organolithium ***cis*-eq-Li-2ha**, having the phenyl group in the equatorial position. Due to the *cis*-diaxial conformation being the major isomer, a ring-flip was proposed. This was a plausible explanation, as the *cis*-diaxial conformer was calculated to be 4.7 kcal/mol more stable than the corresponding *cis*-diequatorial conformer. Indeed, the Beak group showed a ring-flip mechanism of substituted *N*-Boc-2-alkyl piperidines (Figure 2.10).⁸ In their report, A^{1,3}-strain of the alkyl group and the carbonyl of the Boc group drive the equilibrium to favor the alkyl group to occupy the axial conformation. Subsequent α' -lithiation, which occurs at the equatorial position, provides the *trans*-organolithium. Electrophilic quench with an alkyl electrophile, such

as Me₂SO₄, provided the corresponding 2,6-*trans*-disubstituted piperidine with retention of configuration. However, when using an electrophile that attaches a carbonyl group directly to the α'-position, A^{1,3}-strain drives the isomerization to favor the *cis*-2,6-disubstituted analogue upon equilibration on silica gel.

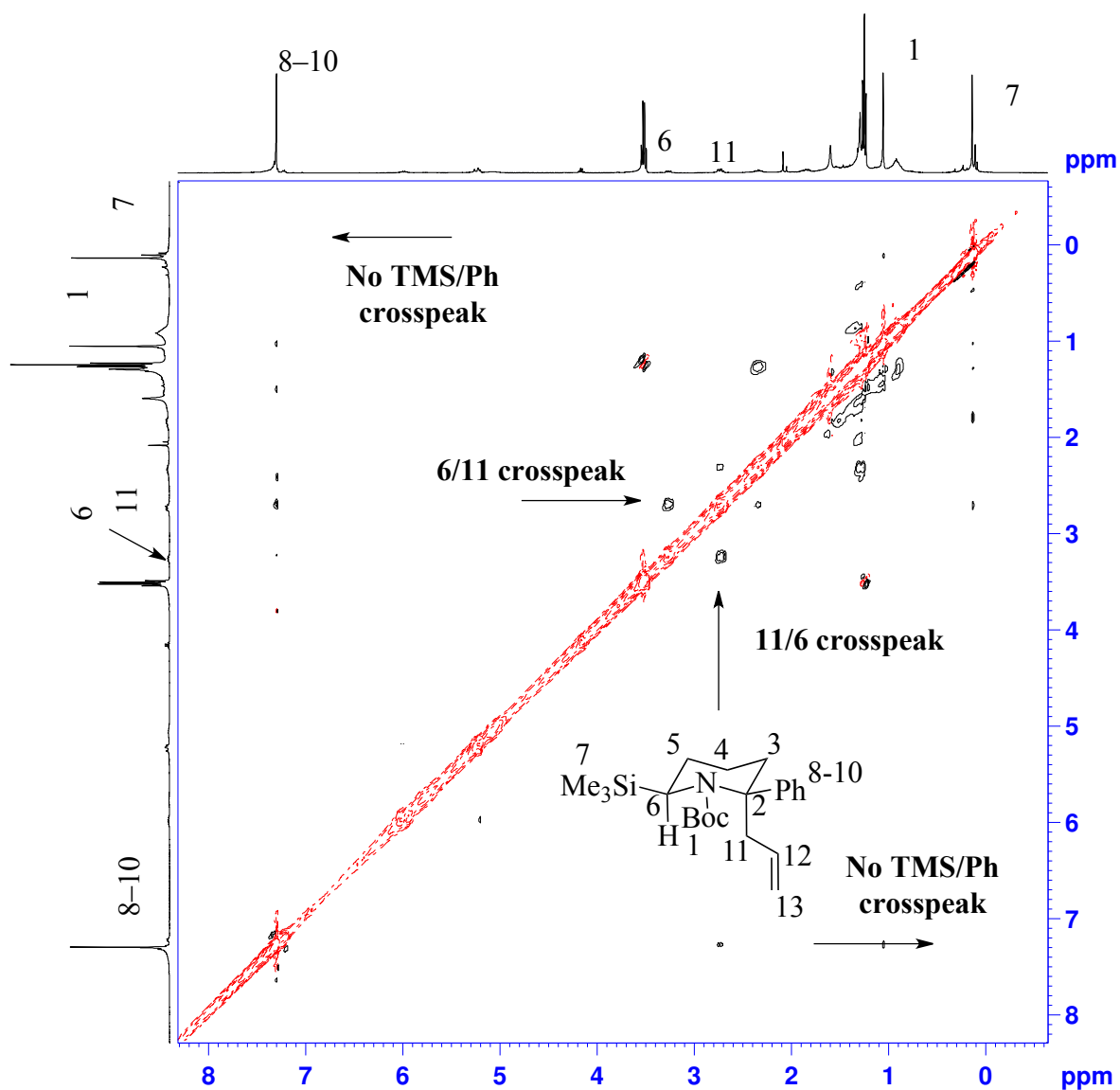
Figure 2.10. Beak's Synthesis of 2,6-disubstituted Piperidines utilizing a Ring-Flip



Although a conclusive explanation could not be identified to justify why **2jc** is formed as the sole isomer, the relative stereochemistry and conformation were solved using various techniques. Next, the relative configuration of **2jd** was examined using NOESY and other 2D NMR experiments. Interestingly, the NOESY showed a crosspeak between the α'-methine and the allylic protons (Figure 2.11). Additionally, no crosspeaks were observed between the α'-silyl group and the aromatic protons on the α-carbon. This result suggests another *cis* arrangement existing in the diequatorial conformation. Additional 2D experiments, namely COSY and HMQC, were used to assign the protons to the structure, as shown in the Supplemental Information of the corresponding publication.¹⁷ Additionally, a zoomed-in view of the expanded NOESY spectrum in Figure 2.11 reveals a distinct crosspeak between the C6 methine proton and

the allyl protons, which is also shown in the Supplemental Information of the corresponding publication. Although there is no conclusive rationale for the high diastereoselectivity, it appears that the organolithium intermediate is the same as that for **2jc**, which resembles the structure depicted in Figure 2.12 as **eq-Li-2ha**. The subsequent ring-flip, which was rationalized for **2jc**, does not occur in the formation of **2jd**, resulting in the *cis*-diequatorial conformation. The authors of the publication acknowledge the DFT calculations agree with this observation, giving a powerful argument for this conclusion.¹⁷

Figure 2.11. NOESY Spectrum of Trisubstituted Piperidine **2jd**



Conclusion

Throughout the study of using organolithium chemistry to generate α,α,α' -trisubstituted pyrrolidines and piperidines, it was found that facile α' -lithiation/substitution occurs on a variety

of α,α -disubstituted precursors. In addition, it was found that certain substrates undergo the α' -lithiation/substitution sequence to yield products in high diastereomeric ratios and yields. With regards to the pyrrolidines, it was confirmed that the *trans* isomer (as judged by the relationship of the α' substituent with the α aryl substituent) was the major product of the reactions using 2D NMR experiments. Interestingly, when evaluating the piperidine analogues with identical reaction conditions, it was found that the *cis* isomer was the major product of the lithiation/substitution sequence at the α' position. Using NOESY, it was confirmed that product **2jc** was arranged as a *cis*-diaxial conformation, which was concluded to form after a stereoelectronically favorable ring-flip to avoid A^{1,3}-strain with the carbonyl of the Boc group. NOESY analysis of compound **2jd** revealed a *cis*-diequatorial conformation, resulting from retentive substitution while omitting the ring-flip observed in **2jc**. Additional attempts to synthesize alternative trisubstituted piperidines exhibiting high diastereoselectivities failed at the α' -lithiation/substitution stage for unknown reasons, as crude reactions mixtures of inseparable products were obtained. This work was published in Tetrahedron Letters in 2015,¹⁷ albeit no authorship of Scott Morris was cited due the small body of work performed compared to the entire manuscript. However, acknowledgement for the NOESY spectra was noted at the end of the manuscript, signifying the work described within this subsection.

2.3. Experimental Procedures

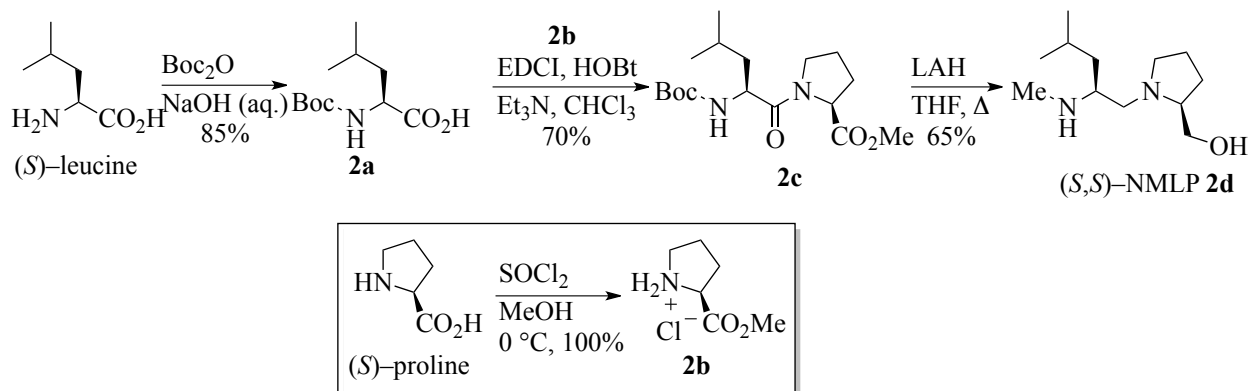
General Considerations

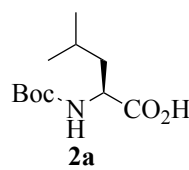
All experiments involving organolithium reagents were carried out under an inert atmosphere of argon and using freshly distilled solvents. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were

distilled from sodium benzophenone ketyl. *N,N,N,N'*-tetramethylethylene diamine (TMEDA) was purified by distillation from CaH₂. The chiral ligand (*S,S*)-NMLP **2d** was purified by Kugelrohr distillation. The concentrations of commercial *s*-BuLi (solution in cyclohexanes) and *n*-BuLi (solution in hexanes) were determined prior to use by No-D NMR spectroscopy with 1,5-cyclooctadiene.¹⁰ Column chromatography was performed on silica gel (230–400 mesh). Visualization of the TLC plates (silica plates) was performed by KMnO₄ staining. For all enantiomer ratio (er) analyses, authentic racemic compounds were used to establish the method of separation of the enantiomers. The enantiomer ratios were determined by CSP-SFC, monitoring at 210 and 254 nm. The diastereomer ratios were determined by GC-MS of the crude mixture using an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. The temperature was controlled by a thermostatted cooling coil and all reported temperatures were internal to a reaction vessel. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton or carbon signals in CDCl₃ (7.27 ppm, 77.23 ppm at room temperature. All ¹H, ¹³C, DEPT-135, HMQC NMR spectra were acquired using CDCl₃ as solvent at room temperature.

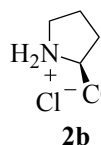
Procedures for the Synthesis of (*S,S*)-NMLP **2d**

Scheme 2.10. Synthetic Scheme for the Preparation of (*S,S*)-NMLP **2d**

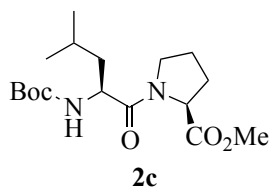



2a

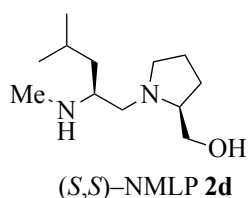
To a solution of (*S*)-leucine (1 equiv, 76.2 mmol, 10 g) in 2 M NaOH (aq.) (200 mL), di-*tert*-butyl dicarbonate (1.2 equiv, 91.5 mmol, 22.4 g) was added slowly. The mixture was stirred for 18 h at room temperature prior to addition of CH₂Cl₂ (50 mL). The layers were separated and the aqueous layer was acidified with citric acid (20 g) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated to give *N*-Boc-(*S*)-leucine **2a** as a clear oil (14.9 g, 85%). All spectroscopic data matched previously published reports.^{18, 19}



To a solution of (*S*)-proline (1 equiv, 25.0 mmol, 2.9 g) in anhydrous MeOH (1.4 M, 17.5 mL) at 0 °C, was added SOCl₂ (1.1 equiv, 27.5 mmol, 2.0 mL) dropwise over a five minute period. The mixture was stirred for 2 h and then concentrated under high vacuum to give (*S*)-proline methyl ester hydrochloride **2b** as a clear oil (4.17 g, 100%). All spectroscopic data matched previously published reports.^{18,19}



To a stirred solution of *N*-Boc-(*S*)-leucine (1.0 equiv, 50 mmol, 11.6 g) in CHCl₃ (0.5 M, 200 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, EDCI (1.0 equiv, 50 mmol, 9.8 g) and 1-hydroxybenzotriazole, HOBt (1.0 equiv, 50 mmol, 7.6 g). The suspension was stirred for 10 min and (*S*)-proline methyl ester hydrochloride (1.0 equiv, 50 mmol, 8.28 g) in a mixture of Et₃N (2.9 equiv, 144 mmol, 20 mL)/CHCl₃ (100 mL) was added. After 10 h at room temperature, the solvents were evaporated. Ethyl acetate (300 mL) was added and the mixture was stirred for 30 min. The solution was filtered and the filtrate was washed with 10% citric acid (aq.) (3 x 200 mL) and then with 10% NaHCO₃ (aq.) (3 x 100 mL). The organic layer was dried over Na₂SO₄ and evaporated to give (*S,S*)-*N*-Boc-Leu-Pro-OMe **2c** as a pale yellow oil (5.98 g, 70%). All spectroscopic data matched the previously published report.¹⁸



To a stirred suspension of LiAlH₄ (7.7 equiv, 15.4 mmol, 584 mg) in THF (5 mL), cooled to 0 °C, was added dropwise a solution of the (*S,S*)-*N*-Boc-Leu-Pro-OMe **2c** (1.0 equiv, 2 mmol, 70 mg) in THF (10 mL). The mixture was stirred for 10 min at room temperature prior to being heated under reflux for 16 h.

The mixture was cooled to 0 °C and Et₂O (10 mL) was added. The mixture was carefully quenched by slow addition of aqueous NaOH (2 M, 20 mL) upon stirring until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed with Et₂O. The Et₂O extracts were concentrated to 10 mL and extracted with 2 M HCl (aq.) (3 x 5 mL). The aqueous layer was then basified with 50% KOH (aq.) to pH 14 and extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to give the crude product. Purification by Kugelrohr distillation gave (*S,S*)-NMLP **2d** as a colorless oil (28.5 mg, 65%). All spectroscopic data matched the previously published report.¹⁸

Synthesis of 2-Substituted Piperidines

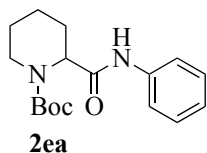
General Procedure 2A (GP2A): Synthesis of Racemic Precursors using Beak's

Methodology^{20,21}

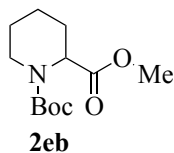
To an oven-dried, septum-capped 25-mL round bottom flask equipped with a stir bar was added *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (1.2 equiv) in freshly distilled Et₂O (0.25 M) under argon. The solution was cooled to -78 °C and *s*-BuLi (1.2 equiv) was slowly added slowly down the side of the flask using a syringe. The frozen mass was then carefully dissolved in the solution and the mixture was stirred for 3 h to effect deprotonation, affording the racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-*d*₁ (CH₃OD) and checking for deuterium incorporation by GC-MS. After complete deprotonation of *N*-Boc-piperidine as noted by GC-MS (>90%), subsequent electrophilic quench at the same temperature with excess electrophile (>1.5 equiv)

was administered. After 2–14 h, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to obtain the crude product. Purification by silica gel column chromatography provided the desired products in 65–85% yield.

Synthesis of Racemic Precursors

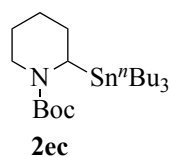


Following procedure **GP2A**, *N*-Boc-piperidine (1 equiv, 0.25 mmol, 46.25 mg), TMEDA (4.0 equiv, 1.0 mmol, 0.15 mL) in Et₂O (0.25 M, 1.0 mL), and phenyl isocyanate (3.0 equiv, 0.75 mmol, 0.082 mL) for 2 h prior to addition of MeOH (2 mL) gave the crude product as a yellowish solid. Purification by silica gel chromatography eluting with hexanes:EtOAc (90:10) afforded *rac*-*N*-Boc-piperidine-2-carboxylic acid phenyl amide **2ea** as a white crystalline solid (50.2 mg, 66%). All spectroscopic data matched that of literature values.¹⁸ ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.2 (1H, s), 7.44–6.91 (5H, m), 4.6 (1H, s), 4.13–4.02 (1H, br), 2.84–2.72 (1H, m), 2.32 (1H, d, *J* 14 Hz), 1.96–1.83 (1H, m), 1.66–1.51 (4H, m), 1.35 (9H, s,); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 170.5, 156.2, 137.7, 128.8, 123.9, 119.5, 80.7, 54.7, 42.2, 28.2, 25.1, 24.6 and 20.1.



Following procedure **GP2A**, *N*-Boc-piperidine (1 equiv, 0.25 mmol, 46.25 mg), TMEDA (4.0 equiv, 1.0 mmol, 0.15 mL) in Et₂O (0.25 M, 1.0 mL), and methyl chloroformate (3.0 equiv, 0.75 mmol, 19.3 μL) for 14 h prior to addition of

MeOH (2 mL) gave the crude product as a yellow oil. Purification by silica gel chromatography eluting with hexanes:EtOAc (95:5) afforded *rac*-*N*-Boc-piperidine-2-carboxylic acid methyl ester **2eb** as a colorless oil (73 mg, 85%). All spectroscopic data matched that of literature values.¹⁸ ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 4.4 (1H, s), 3.4 (3H, s), 2.84–2.72 (1H, m), 2.32 (1H, d, *J* 14 Hz), 1.96–1.83 (1H, m), 1.66–1.51 (4H, m), 1.35 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 170.5, 156.2, 80.7, 55.7, 54.7, 42.2, 28.2, 25.1, 24.6 and 20.1.



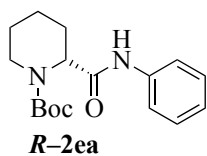
Following procedure **GP2A**, *N*-Boc-piperidine (1 equiv, 0.25 mmol, 46.25 mg), TMEDA (4.0 equiv, 1.0 mmol, 0.15 mL) in Et₂O (0.25 M, 1.0 mL), and tributyltin chloride (3.0 equiv, 0.75 mmol, 0.203 mL) for 4 h prior to addition of 2 mL of MeOH, gave the crude product as a yellow oil. Purification by silica gel chromatography eluting with hexanes:EtOAc (99:1) afforded *rac*-*N*-Boc-2-tributylstannyl piperidine **2ec** as a colorless oil (77 mg, 65%). All spectroscopic data matched that of literature values.²² ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 4.4 (1H, m), 2.85 (1H, dd), 1.71 (6H, m), 1.48 (12H, m), 1.35 (9H, s), 1.0 (18H, m); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 156.5, 79.0, 47.8, 37.6, 30.7, 30.4, 29.3, 28.1, 27.6, 21.2, 15.9, 14.0 and 12.1.

General Procedure 2B (GP2B): Catalytic Dynamic Resolution of *N*-Boc-Piperidine

To an oven-dried, septum-capped 10-mL test tube equipped with a stir bar was added *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (4.0 equiv) in freshly distilled Et₂O (0.25 M) under argon. The solution was cooled to –78 °C and *s*-BuLi (1.2 equiv) was slowly added slowly

down the side of the flask using a syringe. The frozen mass was then carefully dissolved in the solution and the mixture was stirred for 3 h to effect deprotonation, affording the racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol- d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. (*S,S*)-NMLP (10 mol%) in freshly distilled Et_2O (0.1 M) was treated with freshly titrated *s*-BuLi (20 mol%) at $-45\text{ }^\circ\text{C}$. After complete deprotonation of *N*-Boc-piperidine as noted by MS ($>90\%$), the preformed dilithiated analogue of (*S,S*)-NMLP was then added and the flask was quickly transferred to a second thermostatted bath at $-45\text{ }^\circ\text{C}$, and allowed to stir for 3 h. The mixture was then cooled to $-78\text{ }^\circ\text{C}$ and rapidly quenched with excess electrophile (>1.5 equiv). After 2–14 h, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et_2O . The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product. Purification by silica gel column chromatography was accompanied by er determination.

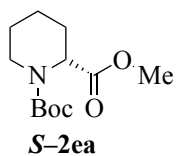
Successful CDR Attempts



Following procedure **GP2B**, *N*-Boc-piperidine (1 equiv, 0.25 mmol, 46.25 mg), TMEDA (4.0 equiv, 1.0 mmol, 0.15 mL) in Et_2O (0.25 M, 1.0 mL), (*S,S*)-NMLP (10 mol%, 0.025 mmol, 5.4 mg) with *s*-BuLi (20 mol%, 0.05 mmol, 42 μL) and phenyl isocyanate (3.0 equiv, 0.75 mmol, 0.082 mL) for 2 h prior to addition of MeOH (2 mL) gave the crude product as a yellowish solid. Purification by silica gel chromatography eluting with hexanes:EtOAc (90:10) afforded (*R*)-*N*-Boc-piperidine-2-

carboxylic acid phenyl amide **R-2ea** as a white crystalline solid (49.1 mg, 64%). All spectroscopic data matched that of literature values.¹⁸ $[\alpha]_D^{22} +40.7$ ($c = 2$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 8.2 (1H, s), 7.44–6.91 (5H, m), 4.6 (1H, s), 4.13–4.02 (1H, br), 2.84–2.72 (1H, m), 2.32 (1H, d, J 14 Hz), 1.96–1.83 (1H, m), 1.66–1.51 (4H, m), 1.35 (9H, s,); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 170.5, 156.2, 137.7, 128.8, 123.9, 119.5, 80.7, 54.7, 42.2, 28.2, 25.1, 24.6 and 20.1.

CSP-SFC was used to monitor the enantiomer ratio (er) at 210 or 254 nm by comparison with the previously prepared racemic sample, under the following column conditions: Column: Regis Technologies Pirkle Whelk-O-1, Chiral Stationary Phase: 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene, covalently bound to silica. Flow Rate = 2.0 mL/min, Polarity Modifier = 3.0% EtOH, Outlet Pressure = 150 psi, Oven Temperature = 35 °C, (*S*)-*N*-Boc-piperidine-2-carboxylic acid phenyl amide **S-2ea** elutes *ca* 13.1 minutes and (*R*)-*N*-Boc-piperidine-2-carboxylic acid phenyl amide elutes **R-2ea** *ca* 15.1 minutes.



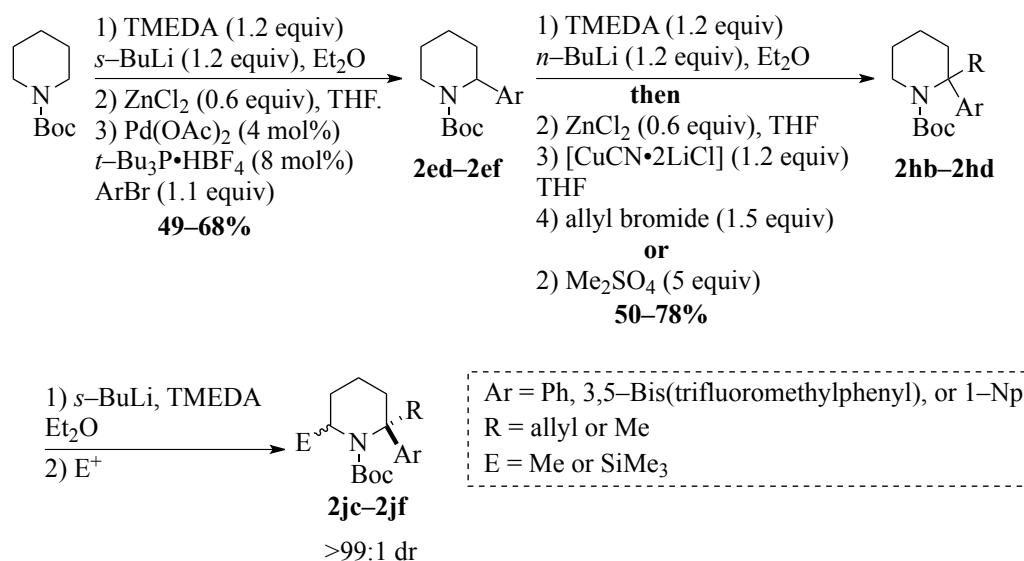
Following procedure **GP2B**, *N*-Boc-piperidine (1 equiv, 0.25 mmol, 46.25 mg), TMEDA (4.0 equiv, 1.0 mmol, 0.15 mL) in Et_2O (0.25 M, 1.0 mL), (*S,S*)-NMLP (10 mol%, 0.025 mmol, 5.4 mg) with *s*-BuLi (20 mol%, 0.05 mmol, 42 μL) and methyl chloroformate (3.0 equiv, 0.75 mmol, 19.3 μL) for 14 h prior to addition of MeOH (2 mL) gave the crude product as a yellow oil. Purification by silica gel chromatography eluting with hexanes:EtOAc (95:5) afforded *rac*-*N*-Boc-piperidine-2-carboxylic acid methyl ester **S-2eb** as a colorless oil (66 mg, 77%, 89:11 to 96:4 er). All spectroscopic data matched that of literature values.¹⁸ $[\alpha]_D^{22} +45.0$ ($c = 2$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 4.4 (1H,

s), 3.4 (3H, s), 2.84– 2.72 (1H, m), 2.32 (1H, d, *J* 14 Hz), 1.96–1.83 (1H, m), 1.66–1.51 (4H, m), 1.35 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 170.5, 156.2, 80.7, 55.7, 54.7, 42.2, 28.2, 25.1, 24.6 and 20.1.

The enantiomer ratio was determined using CSP GC {β-cyclodextrin–permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, Pressure = 15 psi, Initial temperature = 100 °C, Final temperature = 150 °C, Hold time = 5 min, Rate = 0.5 °C/min. (*S*)-*N*-Boc-piperidine-2-carboxylic acid methyl ester **S-2eb** elutes *ca* 49.8 min and (*R*)-*N*-Boc-piperidine-2-carboxylic acid methyl ester **R-2eb** elutes *ca* 51.3 minutes.

Synthesis of α,α,α' -trisubstituted *N*-Boc-piperidines **2jc–2jf**

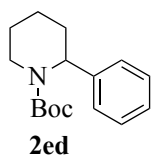
Scheme 2.11. Synthetic Scheme for the Preparation of Trisubstituted Piperidines **2jc–2jf**



General Procedure 2C (GP2C): Synthesis of *N*-Boc-2-arylpiperidines via α -lithiation/Transmetalation and Negishi Cross Coupling

To an oven-dried, septum-capped 25-mL round bottom flask equipped with a stir bar was added *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (1.2 equiv) in freshly distilled Et₂O (0.25 M) under argon. The solution was cooled to –78 °C and *s*-BuLi (1.2 equiv) was slowly added slowly down the side of the flask using a syringe. The frozen mass was then carefully dissolved in the solution and the mixture was stirred for 3 h to effect deprotonation, affording the

racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol- d_1 (CH_3OD) and checking for deuterium incorporation by GC-MS. After complete deprotonation of *N*-Boc-piperidine as noted by GC-MS (>90%), anhydrous, flame-dried $ZnCl_2$ (0.6 M in freshly distilled THF, 0.6 equiv) was slowly added over a 10 minute period at the same temperature and stirred for 30 minutes. The mixture was then warmed to room temperature and stirred for an additional 30 minutes prior to the addition of $Pd(OAc)_2$ (4 mol%), $t-Bu_3P \cdot HBF_4$ (8 mol%), and the aryl bromide (1.1 equiv). After stirring at room temperature for 18 hours, NH_4OH (10 mL, 10% aqueous solution) was added dropwise and the mixture was stirred for 30 minutes. The resulting slurry was filtered through Celite and rinsed with 10 mL Et_2O . The filtrate was washed with 1 M HCl (aqueous, 2 x 10 mL) then with water (2 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to yield crude product. Purification using flash chromatography on silica gel provided the desired *N*-Boc-2-arylpiperidine in 49–68% yield.

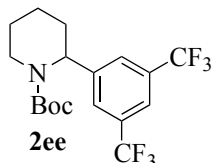


Following **GP2C**, *N*-Boc-piperidine (1 equiv, 2.0 mmol, 370 mg), TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL), Et_2O (0.5 M, 10 mL), *s*-BuLi (1.2 equiv, 1.0 M, 2.4 mmol, 2.4 mL), $ZnCl_2$ (0.6 equiv, 1.2 mmol, 164 mg) in THF (0.6 M, 2 mL), phenyl bromide (1.3 equiv, 2.6 mmol, 0.30 mL), $Pd(OAc)_2$ (4 mol%, 0.08 mmol, 20 mg) and $t-Bu_3P \cdot HBF_4$ (8 mol%, 0.16 mmol, 46 mg) gave the crude product as an oil. Purification by flash chromatography on silica gel eluting with hexanes/ $EtOAc$ (94:6) afforded *Rac-N*-Boc-2-phenylpiperidine **2ed** as an oil (329 mg, 63%). All spectroscopic data matches literature values.³

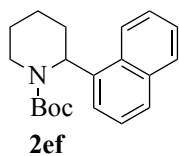
1H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.44–7.18 (5H, m), 5.45 (1H, s), 4.13–4.02 (1H, br),

2.84–2.72 (1H, m), 2.32 (1H, d, J 14 Hz), 1.96–1.83 (1H, m), 1.66–1.51 (4H, m), 1.48 (9H, s).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 155.6, 140.4, 128.5, 126.5, 126.3, 79.4, 53.2, 40.1, 28.4, 28.1, 25.5, 19.4.



Following **GP2C**, *N*-Boc-piperidine (1 equiv, 2.0 mmol, 370 mg), TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL), Et_2O (0.5 M, 10 mL), *s*-BuLi (1.2 equiv, 1.0 M, 2.4 mmol, 2.4 mL), ZnCl_2 (0.6 equiv, 1.2 mmol, 164 mg) in THF (0.6 M, 2 mL), 1,3-bis(trifluoromethyl)-5-bromobenzene (1.3 equiv, 2.6 mmol, 0.45 mL), $\text{Pd}(\text{OAc})_2$ (4 mol%, 0.08 mmol, 20 mg) and *t*-Bu₃P•HBF₄ (8 mol%, 0.16 mmol, 46 mg) gave the crude product as an oil. Purification by flash chromatography on silica gel eluting with hexanes/EtOAc (98:2) afforded *rac*-*N*-Boc-2-(3,5-bis(trifluoromethylphenyl))piperidine **2ee** as an oil (389 mg, 49%). All spectroscopic data matches literature values.¹⁷ ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 7.81 (1H, s), 7.68 (2H, s), 4.11 (1H, d, J 14 Hz), 2.75 (2H, m), 2.32 (2H, m), 2.02 (2H, m), 1.71 (2H, m), 1.48 (9H, s). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 155.5, 143.9, 131.8 (q, J = 32.2 Hz), 126.7, 125.1, 120.2 (q, J = 272.1 Hz), 80.6, 53.0, 40.2, 28.2, 28.0, 25.1, 19.1.



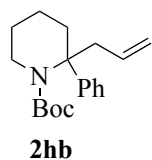
Following **GP2C**, *N*-Boc-piperidine (1 equiv, 2.0 mmol, 370 mg), TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL) Et_2O (0.5 M, 10 mL), *s*-BuLi (1.2 equiv, 1.0 M, 2.4 mmol, 2.4 mL), ZnCl_2 (0.6 equiv, 1.2 mmol, 164 mg) in THF (0.6 M, 2 mL), 1-bromonaphthalene (1.3 equiv, 2.6 mmol, 0.36 mL), $\text{Pd}(\text{OAc})_2$ (4 mol%, 0.08 mmol, 20 mg) and *t*-Bu₃P•HBF₄ (8 mol%, 0.16 mmol, 46 mg) gave the crude product as an oil. Purification by flash chromatography on silica gel eluting with hexanes/EtOAc (60:40) afforded *rac*-*N*-Boc-2-

(1-naphthyl)piperidine **2ef** as an amorphous solid (424 mg, 68%). All spectroscopic data matches literature values.³ ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 8.34–7.37 (m, 6H), 6.05–5.89 (1H, t), 4.22–4.07 (1H, m), 3.33–3.19 (1H, m), 2.24–2.09 (2H, m), 1.84–1.75 (1H, m), 1.71–1.54 (4H, m), 1.46 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 155.6, 139.1, 134.0, 128.9, 127.3, 125.8, 125.4, 124.9, 123.5, 123.2, 79.5, 52.1, 41.7, 29.5, 28.3, 24.7, 19.4.

General Procedure 2D (GP2D): Synthesis of *N*-Boc-2-aryl-2-allylpiperidines via Benzylic Lithiation/Copper Mediated Allylation

To an oven-dried, septum-capped 50-mL round bottom flask equipped with a stir bar was added *N*-Boc-2-arylpiperidine (1.0 equiv) and freshly distilled TMEDA (1.2 equiv) in freshly distilled Et₂O (0.1 M) under argon. The solution was cooled to –78 °C and *n*-BuLi (1.2 equiv) was slowly added slowly down the side of the flask using a syringe. The mixture was stirred for 3 h to effect deprotonation, affording the racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-*d*₁ (CH₃OD) and checking for deuterium incorporation by GC–MS. After complete deprotonation of *N*-Boc-piperidine as noted by GC–MS (>90%), a solution of ZnCl₂ (0.6 M in freshly distilled THF, 0.6 equiv) was slowly added over a 10 minute period at the same temperature. After 30 min, a solution of CuCN·2LiCl (prepared from CuCN (1.2 equiv) and LiCl (2.5 equiv)) in freshly distilled THF was added at the same temperature. After 30 min, allyl bromide (1.5 equiv) was added. The mixture was allowed to stir for 14 h at this temperature prior to addition of MeOH and warming to room temperature. A solution of NH₄Cl was added and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and evaporated to

give the crude product. Purification using flash chromatography on silica gel provided the desired product in 50% yield.

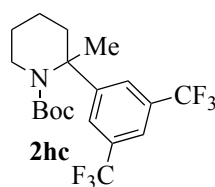


Following **GP2D**, *rac*-*N*-Boc-2-phenylpiperidine **2ed** (1 equiv, 2.0 mmol, 522 mg), TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL), Et₂O (0.1 M, 20 mL), *n*-BuLi (1.2 equiv, 2.4 mmol, 2.5 M, 0.96 mL), ZnCl₂ (0.6 equiv, 1.2 mmol, 164 mg) in THF (0.6 M, 2 mL), CuCN·2LiCl [prepared from CuCN (1.2 equiv, 2.4 mmol, 215 mg) and LiCl (2.5 equiv, 5.0 mmol, 214 mg)], allyl bromide (1.5 equiv, 3.0 mmol, 0.26 mL) for 14 h prior to addition of MeOH (2 mL) and warming to room temperature, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexanes:EtOAc (95:5) afforded *rac*-*N*-Boc-2-allyl-2-phenylpiperidine **2hb** as an oil (301.2 mg, 50%). All spectroscopic data matches literature values.²³ ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.72 (4H, s), 7.26-7.23 (1H, m), 5.95 (1H, m), 5.22 (2H, m), 3.95 (1H, m), 3.35 (2H, m), 2.75 (1H, m), 2.25 (1H, m), 1.85 (1H, m), 1.70 (1H, m), 1.62-1.52 (2H, m), 1.38 (1H, m), 1.14 (9H, s). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 156.1, 148.0, 134.5, 128.2, 126.3, 125.6, 118.5, 80.0, 63.0, 45.5, 41.3, 36.3, 28.5, 21.9, 16.5.

General Procedure 2E (GP2E): Synthesis of *N*-Boc-2-aryl-2-methylpiperidines *via* Benzylic Lithiation/Electrophilic Substitution

To an oven-dried, septum-capped 50-mL round bottom flask equipped with a stir bar was added *N*-Boc-2-arylpiperidine (1.0 equiv) and freshly distilled TMEDA (1.2 equiv) in freshly distilled

Et₂O (0.1 M) under argon. The solution was cooled to –78 °C and *n*-BuLi (1.2 equiv) was slowly added slowly down the side of the flask using a syringe. The mixture was stirred for 3 h to effect deprotonation, affording the racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-*d*₁ (CH₃OD) and checking for deuterium incorporation by GC–MS. After complete deprotonation of *N*-Boc–piperidine as noted by GC–MS (>90%), subsequent electrophilic quench at the same temperature with excess Me₂SO₄ (1.5 equiv) was administered. After 14 h, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl (aqueous) was added. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to obtain the crude product. Purification by silica gel column chromatography provided the desired products in 63–78% yield.



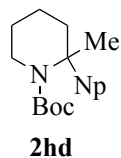
Following **GP2E**, *rac*-*N*-Boc-2-methyl-2-(3,5-

bis(trifluoromethylphenyl))piperidine **2ee** (1 equiv, 2.0 mmol, 795 mg),

TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL), Et₂O (0.1 M, 20 mL), *n*-BuLi (1.2

equiv, 2.4 mmol, 2.5 M, 0.96 mL), and Me₂SO₄ (1.5 equiv, 3.0 mmol, 0.28 mL) for 14 h prior to addition of MeOH (2 mL) and warming to room temperature, gave the crude product as an oil.

Purification by silica gel chromatography eluting with hexanes:EtOAc (97:3) afforded *rac*-*N*-Boc-2-methyl-2-(3,5-bis(trifluoromethylphenyl))piperidine **2hc** as an oil (642 mg, 78%). All spectroscopic data matches literature values.¹⁷ ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.72 (2H, s), 7.68 (1H, s), 3.94 (1H, m), 3.31 (1H, m), 1.82 (1H, m), 1.75 (3H, s), 1.68 (2H, m), 1.55 (2H, m), 1.47 (1H, m), 1.06 (9H, s). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 154.0, 152.1, 130.1 (q, *J* = 32.4 Hz), 124.0, 123.3, 118.0 (q, *J* = 32.1 Hz), 79.0, 58.5, 40.8, 40.1, 26.8, 22.0, 20.2, 17.0.

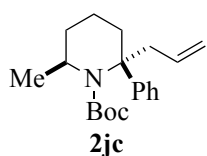


Following **GP2E**, *rac*-*N*-Boc-2-methyl-2-(1-naphthyl)piperidine **2ef** (1 equiv, 2.0 mmol, 623 mg), TMEDA (1.2 equiv, 2.4 mmol, 0.37 mL), Et₂O (0.1 M, 20 mL), *n*-BuLi (1.2 equiv, 2.4 mmol, 2.5 M, 0.96 mL), and Me₂SO₄ (1.5 equiv, 3.0 mmol, 0.28 mL) for 14 h prior to addition of MeOH (2 mL) and warming to room temperature, gave the crude product as an oil. Purification by silica gel chromatography eluting with hexanes:EtOAc (93:7) afforded *rac*-*N*-Boc-2-methyl-2-(1-naphthyl)piperidine **2hd** as an oil (410 mg, 63%). All spectroscopic data matches literature values.³ ¹H NMR (300 MHz, CDCl₃) = 8.34–7.37 (6H, m), 4.35 (1H, dd), 3.50 (1H, m), 2.22 (1H, m), 2.05–1.51 (17H, m), ¹³C NMR (75 MHz, CDCl₃) = 155.4, 139.1, 134.0, 131.5, 128.9, 127.3, 125.8, 125.4, 124.9, 123.5, 123.2, 79.5, 60.4, 41.6, 41.2, 28.3, 27.2, 25.1, 20.3.

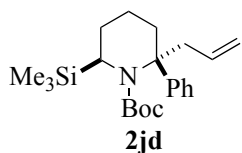
General Procedure 2F (GP2F): Synthesis of *N*-Boc-2-aryl-2-alkyl-6-alkylpiperidines via α' -Lithiation/Electrophilic Substitution

To an oven-dried, septum-capped 25-mL round bottom flask equipped with a stir bar was added *N*-Boc-piperidine (1.0 equiv) and freshly distilled TMEDA (1.2 equiv) in freshly distilled Et₂O (0.1 M) under argon. The solution was cooled to –78 °C and *s*-BuLi (1.2 equiv) was slowly added slowly down the side of the flask using a syringe. The frozen mass was then carefully dissolved in the solution and the mixture was stirred for 3 h to effect deprotonation, affording the racemic organolithium. The extent of deprotonation was monitored by quenching an aliquot of the reaction mixture with methanol-*d*₁ (CH₃OD) and checking for deuterium incorporation by GC–MS. After complete deprotonation of *N*-Boc-piperidine as noted by GC–MS (>90%), subsequent electrophilic quench at the same temperature with excess electrophile (>1.5 equiv)

was administered. After 2–14 h, MeOH was added and the mixture was stirred for 5 min. After warming to room temperature, 2 M HCl was added. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and evaporated to obtain the crude product. Purification by silica gel column chromatography provided the desired products in 68–77% yield.



Following **GP2F**, *rac*-*N*-Boc-2-allyl-2-phenylpiperidine **2hb** (1 equiv, 1 mmol, 301 mg), TMEDA (1.2 equiv, 1.2 mmol, 0.2 mL), Et₂O (0.1 M, 10 mL), *s*-BuLi (1.2 equiv, 1.2 mmol, 1.0 M, 1.2 mL), Me₂SO₄ (3 equiv, 3 mmol, 0.15 mL) gave the crude product as an oil in >99:1 dr by crude GC–MS analysis. Purification by flash chromatography on silica gel eluting with hexanes:EtOAc (98:2) afforded *cis*-*rac*-*N*-Boc-2-allyl-2-phenyl-6-methylpiperidine **2jc** (215 mg, 68%) ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.45 to 7.12 (5H, m), 6.05 (1H, m), 5.19 to 5.08 (2H, m), 4.45 (1H, m), 3.17 to 2.96 (2H, m), 2.14 to 0.85 (18H, m). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 155.5, 150.4, 136.2, 128.0, 125.8, 125.5, 117.3, 79.5, 62.4, 48.2, 45.3, 37.3, 28.3, 27.3, 22.5, 14.5.



Following **GP2F**, *rac*-*N*-Boc-2-allyl-2-phenylpiperidine **2hb** (1 equiv, 1 mmol, 301 mg), TMEDA (1.2 equiv, 1.2 mmol, 0.2 mL), Et₂O (0.1 M, 10 mL), *s*-BuLi (1.2 equiv, 1.2 mmol, 1.0 M, 1.2 mL), Me₃SiCl (3 equiv, 3 mmol, 360 mg) gave the crude product as an oil in >99:1 dr by crude GC–MS analysis. Purification by flash chromatography on silica gel eluting with hexanes:EtOAc (98:2) afforded *cis*-*rac*-*N*-Boc-2-allyl-2-phenyl-6-(trimethylsilyl)piperidine **2jd** (288 mg, 77%). ¹H NMR

(400 MHz, CDCl₃) δ (ppm) = 7.45 to 7.12 (5H, m), 6.05 (1H, m), 5.23 to 4.99 (2H, m), 3.25 (1H, m), 2.82 to 2.71 (2H, m), 2.14 to 0.85 (15H, m), 0.22 (9H, m). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 155.5, 150.4, 136.2, 128.0, 125.8, 125.5, 118.6, 78.8, 62.4, 45.8, 45.3, 35.3, 28.3, 23.7, 16.4, 0.1.

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Chapter 3

C–N Bond Formation using Visible Light: Synthesis of Indoles and Indolines

Society beckons scientists worldwide to provide sustainable solutions to enhance everyday life, which has sparked the research interest of synthetic chemists to provide more efficient reaction designs and generate small molecule scaffolds.¹ The overall goal of sustainable chemistry is to produce minimal waste, have high atom economy, form multiple bonds, and use abundant and renewable resources. For instance, an ideal reaction design would utilize visible light to initiate a cascade reaction, produce complex molecules, and generate minimal side products. The aim, from the standard point of pharmaceutical industry, is to provide drugs at a lower cost. Visible light offers many benefits from this perspective, as it is an abundant, clean, and renewable energy source. Combining the use of visible light in a cascade reaction would then be a highly desirable setup, since multiple bond formations could occur in a single pot using a renewable resource. Since most organic molecules do not absorb visible light well, a photoredox catalyst would be needed to achieve such transformations. Significant progress has been achieved in the realm of photoredox catalysis in both catalyst design and its application in bond formations. Recently, a surge of literature has been reported showing the utility of visible light photoredox catalysis, including the expedient work by Yoon,²⁻⁷ Stephenson,⁸⁻¹³ MacMillan,^{14,15} Zheng,¹⁶⁻¹⁹ Akita,²⁰ and others.²¹

3.1. Photochemistry

As early as 1908, Giacomo Luigi Ciamician revealed that light could serve as an abundant, renewable, and inexpensive reagent for chemical synthesis, as he was able to accomplish the transformation of carvone to carvone camphor after exposing the substrate to intense “Italian sunlight” for one year (Figure 3.1).²²

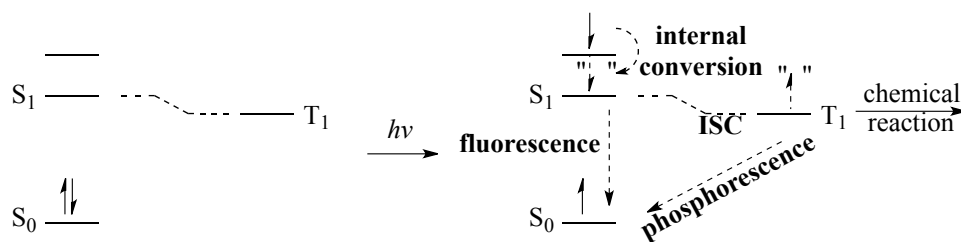
Figure 3.1. Ciamician’s Conversion of Carvone to Carvone Camphor using Sunlight



Since then, chemists have enjoyed the challenge of discovering numerous chemical reactions initiated using a variety of lights. At its simplest form, photochemistry is defined as a chemical reaction initiated by light. In a photochemical reaction, the energy from light is absorbed as a photon by a specific component of the reaction, promoting an electron to the singlet excited state S_1 (Figure 3.2). The energy absorbed can either be lost by radiative processes (fluorescence and phosphorescence), non-radiative processes (internal conversion or intersystem crossing), or by undergoing a chemical reaction. Radiative energy loss can occur directly from the short-lived singlet excited state or from the triplet excited state. The short-lived singlet excited state can either undergo direct vibrational relaxation to the ground state, defined as fluorescence, or can convert to the spin-forbidden triplet state T_1 *via* intersystem crossing, which has been shown to have a longer lifetime due to the spin-forbidden relaxation. When an electron relaxes

vibrationally from the triplet excited state back to the ground state, phosphorescence occurs. Non-radiative modes of energy loss include internal conversion and intersystem crossing. Internal conversion occurs when an electron drops an energy level within an energy state without spin change, such as an electron dropping from the highest energy level within S_1 to the lowest energy level of S_1 . Intersystem crossing (ISC) is the process in which an excited electron converts to a triplet state, effectively generating unpaired electrons.¹³ This process is only favored when little to no energy is being gained or lost in the transition.

Figure 3.2. Diagram of Various Energy Pathways *via* Absorbed Light

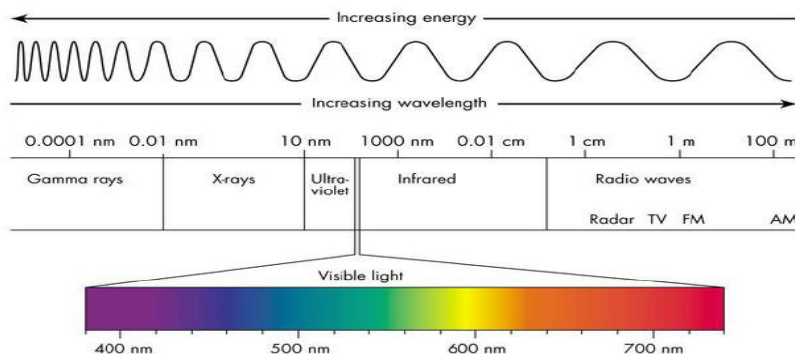


Jablonski diagrams also give a detailed outline of many electronic states of molecules and the transitions between them. These processes are of utmost importance to the synthetic chemist, as they aim to exploit the utility of the excited electrons by engaging them in chemical reactions.

3.1.1. Visible Light Photoredox Chemistry

Visible light is simply electromagnetic radiation that is visible to the human eye. As shown in Figure 3.3,²³ visible light comprises a small section within the realm of light, encompassing wavelengths from 400 nm (short wavelength, higher energy) to 700 nm (long wavelength, lower energy).

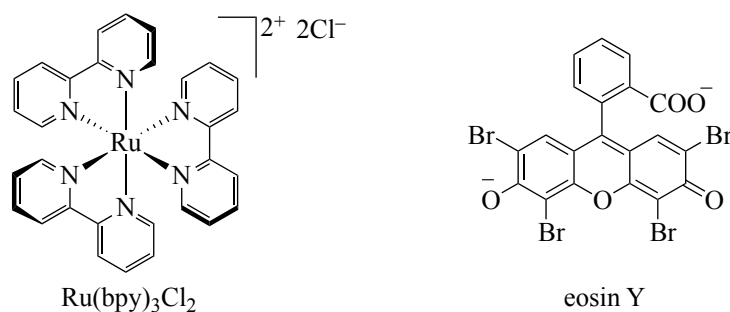
Figure 3.3. Energy and Wavelengths of Light



In recent years, a large portion of photochemistry has been revealed using UV light,²⁴ likely due to most organic molecules' inability to absorb visible-light efficiently. However, reactions utilizing UV light are typically performed in specialized reactors and require expensive high-intensity UV light source, compromising the benefits of harnessing solar radiation and limits scalability.² Therefore, a different approach designed to achieve chemical reactions of organic molecules while harnessing visible-light is using photoredox catalysts. To date, a variety of photoredox catalysts have been identified that successfully undergo electron transfer with organic substrates by direct excitation from visible light.^{7,13,15,16}

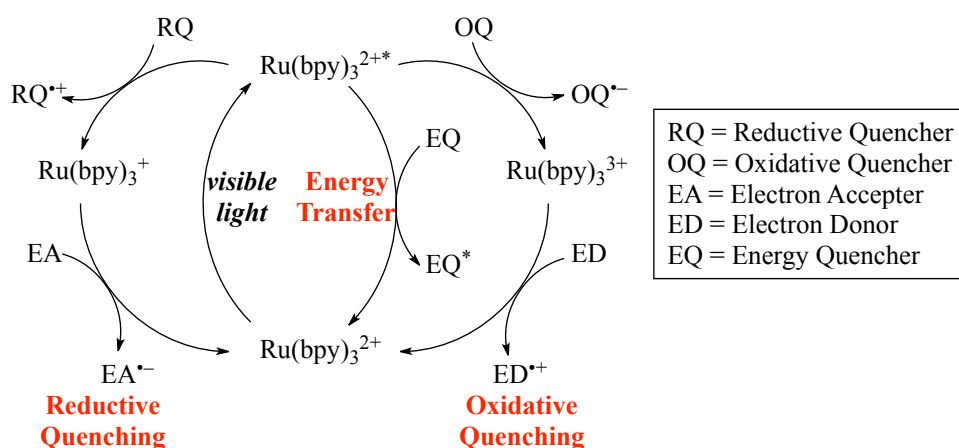
Ideally, the photocatalyst should absorb the higher energy spectrum of visible light (400–475 nm) in order to obtain maximum potential energy for photochemistry. For instance, $\text{Ru}(\text{bpy})_3\text{Cl}_2$ absorbs at 452 nm²⁵ while the organic dye eosin Y absorbs at 522 nm (red-shift),²⁶ allowing the excited-state of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ to be 0.37 eV more than eosin Y, resulting in a higher potential to apply to a chemical reaction (Figure 3.4).¹³

Figure 3.4. Structures of $\text{Ru}(\text{bpy})_3\text{Cl}_2$ and Eosin Y



The general process involves the absorption of a photon by the photoredox catalyst, resulting in a long-lived triplet excited-state complex (T_1 , Figure 3.2) capable of undergoing either oxidative, reductive, or energy transfer quenching cycles (Figure 3.5). It is within each of these cycles that formation of chemical bonds is possible using visible light. However, in order to understand the impact of photoredox processes on chemical reactions, an understanding of the photoredox catalyst, the oxidative quenching cycle, the reductive quenching cycle, and the energy transfer cycle need to be mastered.

Figure 3.5. Various Catalytic Cycles Involving Visible Light Photocatalysis

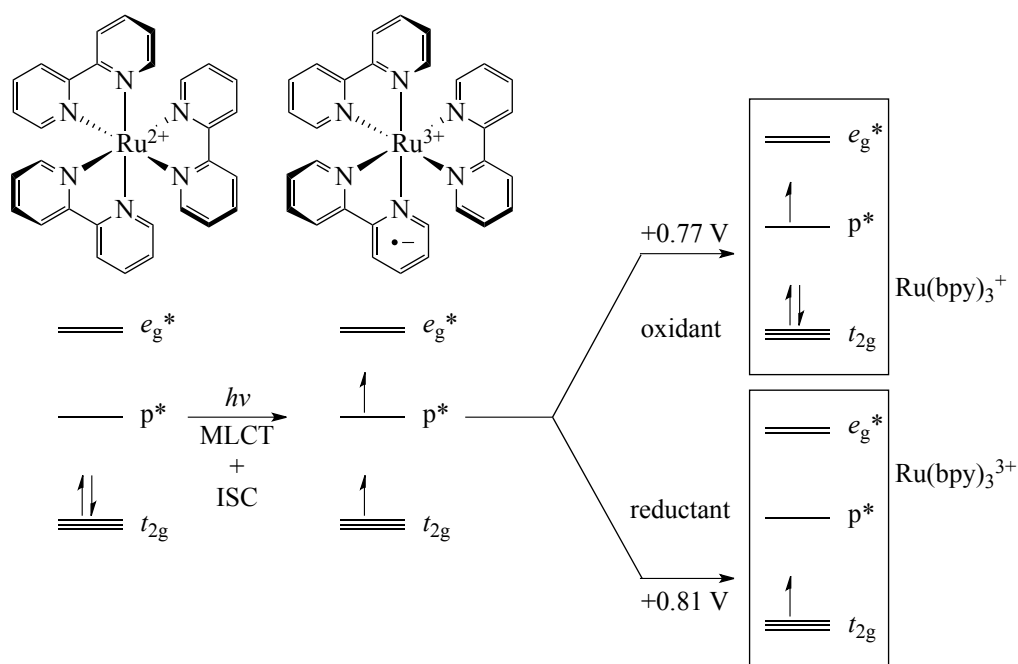


3.1.2. Photoredox Catalyst

An ideal photoredox catalyst has the ability to oxidize, reduce, or excite organic substrates, subsequently allowing the activated molecule to engage in radical processes to generate a final product. A variety of photoredox catalysts have been discovered, many of which are derived from polypyridyl complexes of ruthenium and iridium. Photoredox catalysis has been employed in a variety of applications, including splitting water into hydrogen and oxygen²⁷ and the reduction of carbon dioxide to methane.²⁸ Additionally, $\text{Ru}(\text{bpy})_3^{2+}$ and its analogues have been used as components of dye-sensitized solar cells,²⁹ initiators in polymerization reactions,³⁰ and have been applied in photodynamic therapy.³¹ Not surprisingly, interest in its applications in organic synthesis has recently been renewed, since catalysts of this kind have many benefits. For instance, $\text{Ru}(\text{bpy})_3^{2+}$ possesses a stable, long-lived excited state, has a maximum absorption at 452 nm (visible light), and has the ability to oxidize ($E_{1/2}^{\text{III/I}} = +0.77 \text{ V}$) and reduce ($E_{1/2}^{\text{III/*II}} = -0.81 \text{ V}$) organic substrates.¹⁵ Accepted mechanisms for the overall electron transfer photoredox process are described by an initial absorption of a photon from visible light, generating an excited singlet state. Rapid metal-to-ligand charge transfer occurs (MLCT), effectively transferring the excited electron from the metal center to the low-lying π^* -orbitals of the aromatic ligand, thus creating a reactive oxidized metal center and a reduced ligand. Intersystem crossing then provides the long-lived triplet excited state that is capable of activating organic substrates (Figure 3.6). A remarkable feature of these catalysts is their ability to be more oxidizing and more reducing in the excited state than the corresponding ground state. Due to this feature, chemists are able to design chemical reaction on a variety of substrates using the different oxidative, reductive, or energy transfer processes.

$\text{Ru}(\text{bpy})_3^{2+}$ has been extensively studied as a photoredox catalyst and, as a result, scientists know and understand how to tune the electronic properties of the polypyridyl ligands to ensure proper reactivity with organic substrates. Although Ir^{3+} and Ru^{2+} polypyridyl complexes have a broad absorption range, they generally relax initially to the lowest spin-allowed metal to ligand charge transfer excited state from various singlet excited states.³² From the lowest spin-allowed state, rapid intersystem crossing occurs to generate the triplet manifold, which undergoes internal conversion to form the lowest energy long-lived triplet excited state. As a result, fluorescence and internal conversion from the singlet excited state are minor deactivation pathways.¹³

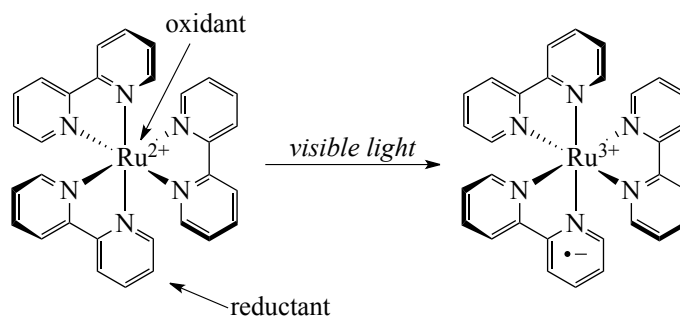
Figure 3.6. Depiction of Photoredox Catalysts' Ability to Oxidize or Reduce Substrates



As previously mentioned, the electronic properties of Ru^{2+} and Ir^{3+} polypyridyl complexes can be tuned to enhance certain reaction conditions. Generally, the redox behavior of

the complex can be illustrated by oxidations at the metal center and reductions of the ligands, as depicted in Figure 3.7.^{32,33}

Figure 3.7. Depiction of Photoredox Catalysts' Redox Behavior



Therefore, the ground state reduction potentials can be adjusted by designing a variety of metal and ligand combinations. For instance, $\text{Ru}^{3+}/\text{Ru}^{2+}$ can be designed for facile oxidations when π -accepting ligands are applied. Conversely, when more anionic ligands are employed, the reduction potentials are less positive. When examining $\text{Ru}^{2+}/\text{Ru}^{1+}$, the ligand becomes the distinguishing factor of the complexes ability to reduce substrates. Therefore, attaching electron-rich groups to the pyridyl complexes allows for a more negative reduction potential. Stephenson and coworkers have revealed the potential to fine-tune the ligands in order to serve in the reaction design, as outlined in numerous reports.^{11,12}

3.1.3. Photoredox Quenching Cycles

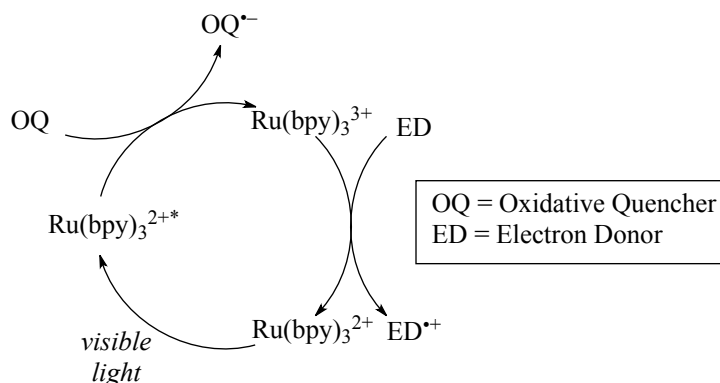
The mechanism of how the excited photocatalyst reacts with an organic molecule has been well studied and divided into three categories: oxidative quenching cycles, reductive

quenching cycle, and energy transfer processes. Essentially, the determining factor as to which mechanism occurs depends on the substrate's oxidation or reduction potential compared to that of the catalyst. If a photochemical reaction occurs when the substrate is out of the oxidation or reduction potential range designated for the catalyst of choice, an energy transfer process may be applicable, which depends on the excited state triplet energy (E_T) of the photoredox catalyst instead of efficient electron-transfer between the catalyst and the substrate. In order to further improve current methodologies and design new reactions, a deeper understanding of these catalytic cycles and their revealed applications is beneficial and worthy of discussion.

Oxidative Quenching Cycle

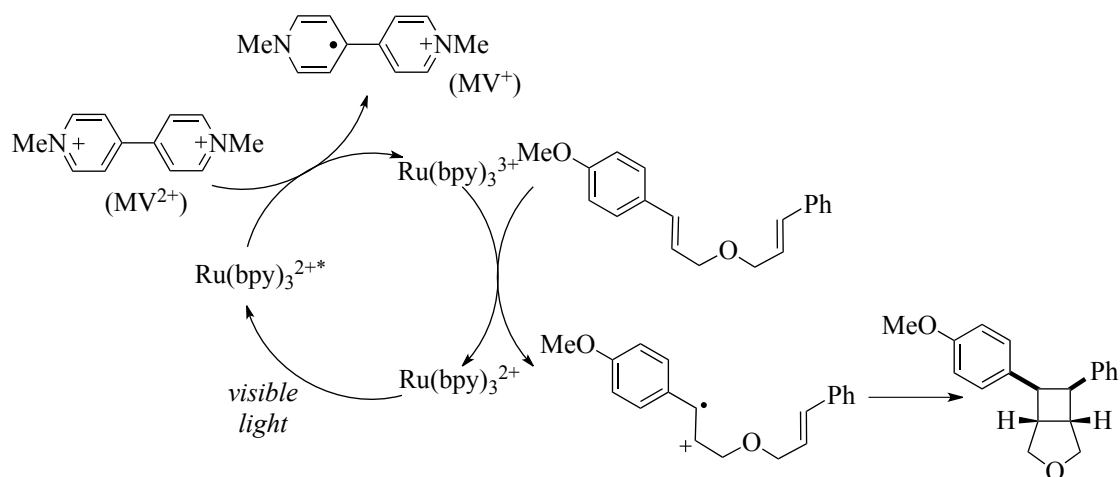
An oxidative quenching cycle applies when the excited state of the photoredox catalysts donates an electron to an oxidative quencher (OQ), resulting in an oxidized catalyst and a reduced oxidative quencher ($OQ^{\bullet-}$). An electron donor would then sacrifice an electron to the photoredox catalyst in order to regenerate the ground state, while the reduced oxidative quencher would participate in radical chemistry to achieve desired transformations. A general catalytic cycle is outlined in Scheme 3.1.

Scheme 3.1. Oxidative Quenching Cycle



Professor Tehshik Yoon has pioneered this model in various cycloaddition reactions.^{4,5,34} In a recent demonstration of this catalytic cycle, the Yoon lab revealed an intramolecular [2+2] cycloaddition reaction of various electron-rich styrenes.⁴ In their working mechanism, the excited state Ru^{2+*} is generated upon photon absorption. The resulting species then donates an electron to methyl viologen (MV^{2+}), a well-known electron acceptor (or oxidative quencher in this case). The oxidized Ru^{3+} then accepts an electron from the electron-rich styrene, regenerating the ground state catalyst and forming a reactive cation intermediate. The reactive intermediate rapidly constructs new C–C bonds *via* radical processes, ultimately forming the desired bicyclic products in high yields (54–92%) and diastereoselectivities (up to 7:1 dr) (Scheme 3.2). Although a variety of substrates were made, only electron-rich styrenes could be oxidized by $\text{Ru}(\text{bpy})_3^{3+}$ and the distal tethered alkene could only undergo the [2+2] cycloaddition with a terminal aryl group.

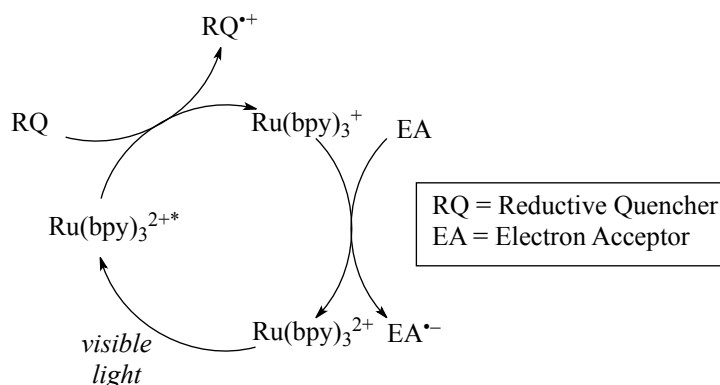
Scheme 3.2. Yoon's [2+2] Cycloaddition utilizing an Oxidative Quenching Cycle



Reductive Quenching Cycle

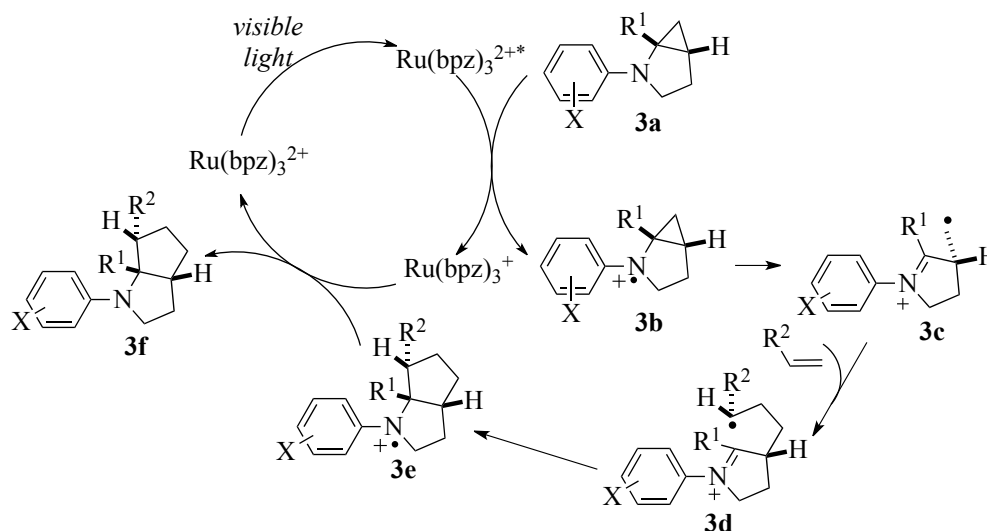
A reductive quenching cycle occurs when the excited state of the photoredox catalyst accepts an electron from a sacrificial reductive quencher (usually an amine, RQ), generating a reduced photoredox catalyst and an oxidized reductive quencher $\text{RQ}^{+•}$. An electron acceptor, EA, would then regenerate the ground state photoredox catalyst in order to finish the cycle. The general process is depicted in Scheme 3.3. Yoon,^{2,3} Stephenson,^{8,12} Zheng,^{16,19} and others³⁵ have employed this catalytic cycle to engage a variety of substrates to chemical transformations.

Scheme 3.3. Reductive Quenching Cycle



To highlight the reductive quenching cycle, Zheng and coworkers designed a substrate that would act as both a sacrificial electron donor and the substrate, cleverly avoiding the waste of reagents.¹⁶ In their work, a [3+2] annulation was revealed using various cyclopropyl amines. In their report, a variety of aryl anilines were tolerated, including electron deficient and electron rich systems. The reactions conditions were surprisingly mild, requiring a simple visible light source, 2 mol% $\text{Ru(bpz)}_3(\text{PF}_6)_2$, and degassed nitromethane. The proposed catalytic cycle, shown in Scheme 3.4, is initiated with the absorption of a photon from visible light, generating the excited state Ru^{2+*} . Cyclopropylamine (**3a**) then acts as a sacrificial electron donor, generating the nitrogen radical cation **3b** and the reduced photoredox catalyst. A series of single electron manipulations then occur, ultimately leading to the ring-opened iminium ion **3c** that undergoes a single-electron annulation process with an alkene to form the reactive intermediate **3d** that cyclizes to form the bicyclic nitrogen radical cation **3e**. The bicyclic intermediate then acts as an electron acceptor with the reduced photoredox catalyst, generating the annulated product **3f** and regenerating the ground-state catalyst.

Scheme 3.4. Zheng's [3+2] Annulation utilizing a Reductive Quenching Cycle

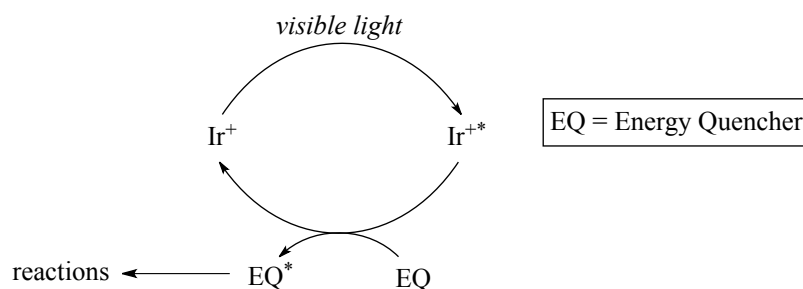


Energy Transfer Processes

In a photoredox system, the mechanism of electron transfer from the photoredox catalyst determines whether an oxidative quenching cycle or reductive quenching cycle applies, which relies upon efficient electron transfer between the substrate and catalyst. The efficiency of electron transfer between the photoredox catalyst and substrate is determined by their redox properties, which can limit the substrate scope of a variety of reactions. For instance, in the reductive quenching cycle using $\text{Ru}(\text{bpy})_3^{2+}$, the substrate's peak reduction potential has to be less positive than the reduction potential of $\text{Ru}(\text{bpy})_3^{2+*}/\text{Ru}(\text{bpy})_3^{+}$. Conversely, in the case of the oxidative quenching cycle, the substrate's peak reduction potential needs to be more positive than the reduction potential of $\text{Ru}(\text{bpy})_3^{3+}/\text{Ru}(\text{bpy})_3^{2+*}$. However, an additional reaction pathway, termed energy transfer, can achieve the desired chemical reaction using substrates that would not react using the oxidative or reductive photoredox catalysis. In energy transfer processes, the

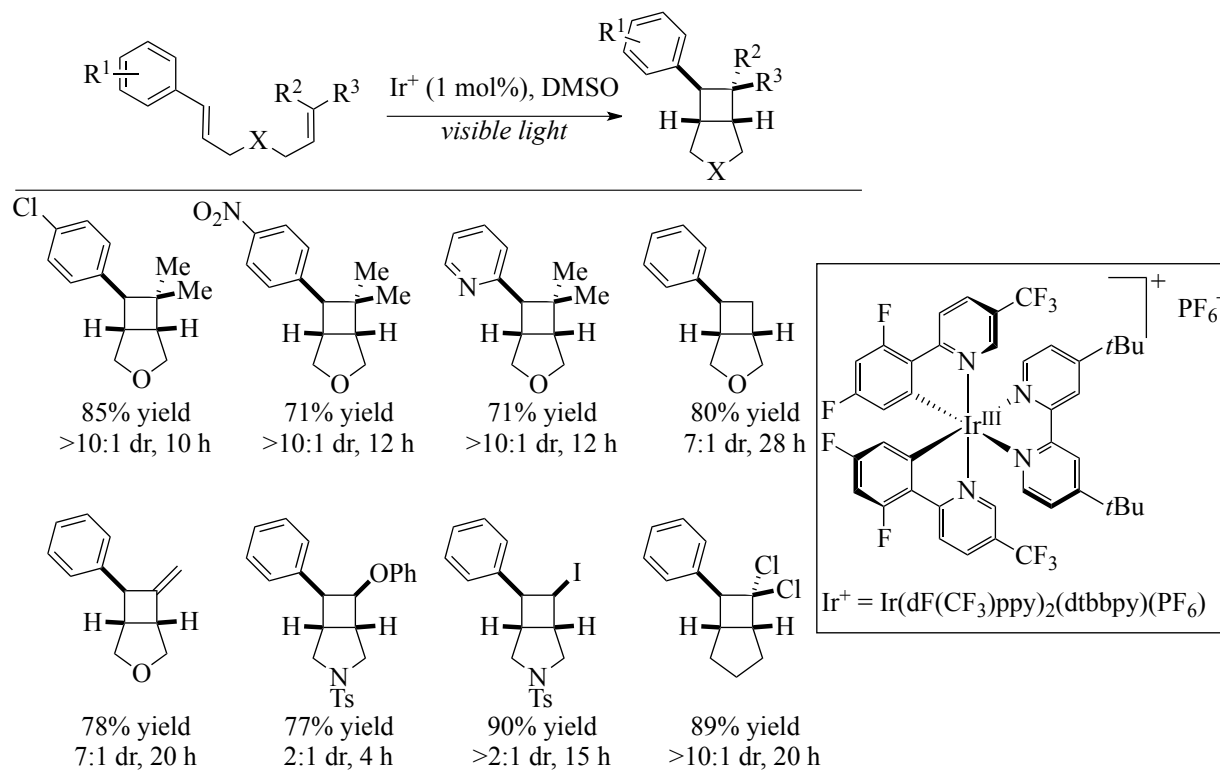
excited state triplet energies (E_T) of the substrate and photocatalyst determine the outcome of the reaction. Capitalizing on this quality allows chemists to generate substrate scopes that are unavailable when relying solely on electron–transfer processes. In these processes, the excited state of the photoredox catalyst directly transfers energy to an organic substrate, effectively avoiding the constraint on matching the potential of catalyst and substrate. A depiction of an energy transfer cycle is shown in Scheme 3.5.

Scheme 3.5. Energy Transfer Cycle



In 2012, the Yoon group published a [2+2] cycloaddition of various styrenes.⁶ In their previous cycloaddition reports using styrenes, a minimum requirement was that the styrene needed to be electron–rich in order to generate the corresponding radical cation.⁴ Additionally, the cycloaddition was unsuccessful when engaging substrates lacking an aryl group, meaning terminal and alkyl–substituted olefins were incompatible with the chemistry. However, the substrate scope of this chemistry was greatly expanded when using energy transfer rather than electron transfer, effectively displaying the utility of this method. As shown in Scheme 3.6, a variety of difficult transformations under the oxidative cycle were successful, affording the products in high yields and diastereoselectivities.

Scheme 3.6. Yoon's [2+2] Cycloaddition utilizing an Energy Transfer Process



The bottleneck of the previous chemistry relies on effective electron transfer, which results in many organic substrates being inadequate for electron–transfer–based photocatalysis. Many substrates used in the energy transfer system fit this model, as there is only a few photoredox catalysts capable of oxidizing non–electron–rich styrenes (~ 1.42 V vs. SCE⁶). However, since the excited state triplet energy (E_T) for these styrenes is ~ 60 kcal/mol³⁶ and the photocatalyst used in the study gives ~ 61 kcal/mol E_T at 470 nm,⁶ the intramolecular cycloaddition was shown to work effectively without the use of an external oxidant.

3.1.4. Summary of Photoredox Catalysts

As shown, photoredox catalysts provide the critical link needed to create reactions with certain organic molecules using visible light. Photoredox catalysts can either be organic dyes,³⁷ such as eosin Y and acridinium salts, or metal-based complexes, such as Ru and Ir polypyridyl complexes.^{15,38} Metal-based photoredox catalysts offer many advantages, such as tunable redox properties based on the complexed ligands, the ability to participate as either an oxidant or reductant upon irradiation with visible light, and, in some cases, the ability to be an energy donor to organic substrates. Having established the utility of photoredox catalysts, the next focus will be its application towards the formation of pharmaceutically relevant compounds *via* photogenerated amine radical cations.

3.2. Amine Radical Cations

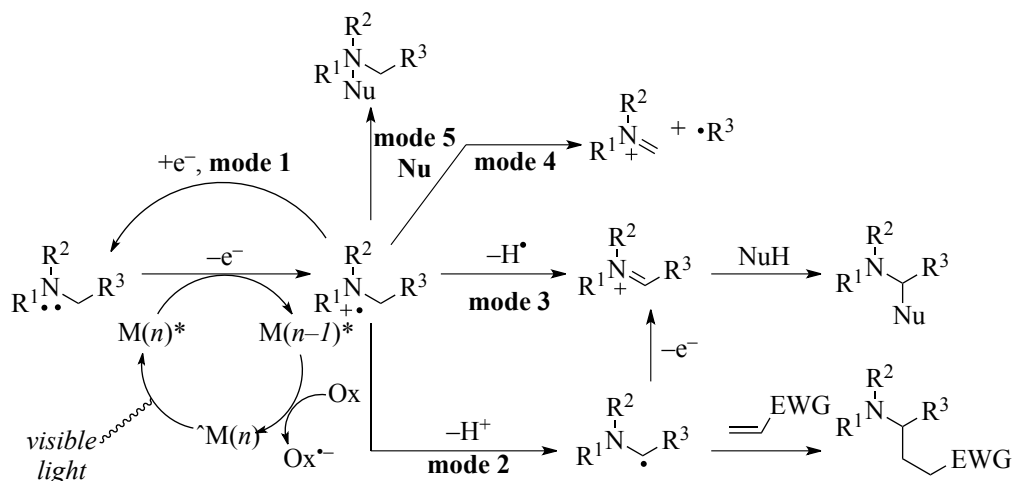
In a typical reductive quenching cycle, an amine serves as a sacrificial electron donor, resulting in an amine radical cation and a reduced photoredox catalyst. Recently, Zheng and coworkers opted to test the viability of using the photogenerated amine radical cation as an electrophilic source rather than a sacrificial reductant. Their results have been outlined in a number of reports, most of which include the formation of both carbocycles and heterocycles of varying complexity.^{16,17,19}

Amine radical cations are odd-electron electrophilic species that provide an electrophilic nitrogen source for chemical synthesis. Despite this umpolung reactivity (e.g. amine as electrophile instead of nucleophile), its use in amine synthesis remains limited.³⁹ A survey of the

challenges associated with the use of amine radical cations includes limited available precursors, the instability of the precursors, the requirement for Bu_3SnH , and the need for special conditions such as photolysis or strongly acidic conditions.⁴⁰ However, as previously stated and exemplified by the Zheng group, amine radical cations can readily be generated from bench-top-stable amines using visible light photoredox catalysis.

The synthesis of amine radical cations by one electron oxidation of amines using visible light was discovered in the late 1970's.^{41,42} However, it wasn't until recently that chemists started utilizing photogenerated amine radical cations in synthesis, primarily in the construction of C–C bonds.^{10,43} Amine radical cations have been shown to participate in five different reaction modes, as depicted in Scheme 3.7.⁴⁴ The first route is back electron transfer to regenerate the corresponding amine. In order to avoid this process, chemists often modify the ligand structure on the metal complex to retard back electron transfer or modify the reaction conditions to ensure fast/irreversible subsequent reactions.^{42,45} The second route is the loss of a proton to form α -aminoalkyl radicals, which can either be oxidized to the iminium ion or trapped with an electron-deficient alkene to generate a new α C–C bond. Radicals of this nature tend to be nucleophilic and strongly reducing. The third route is a hydrogen atom abstraction to form the corresponding iminium ion. This mode is typically employed when the reaction contains a good hydrogen atom acceptor, such as carbon radicals.^{8,12,46} The fourth route involves α C–C bond cleavage (with respect to the nitrogen) to an iminium ion and a neutral carbon radical. The resulting iminium ion is susceptible to a variety of reactions with nucleophiles due to its inherent electrophilicity. The final mode of reactivity is direct electrophilic addition to nucleophiles, creating a new C–N bond.

Scheme 3.7. Various Fates of Photogenerated Amine Radical Cations



It is within the realm of photogenerated amine radical cations that sustainable and medicinal chemistry can bridge together. Therefore, the aim of the remaining sections will be to demonstrate the importance of heterocycles in pharmaceuticals, survey published syntheses of target substructures, and examine recent avenues of heterocycle synthesis using visible light photoredox catalysis.

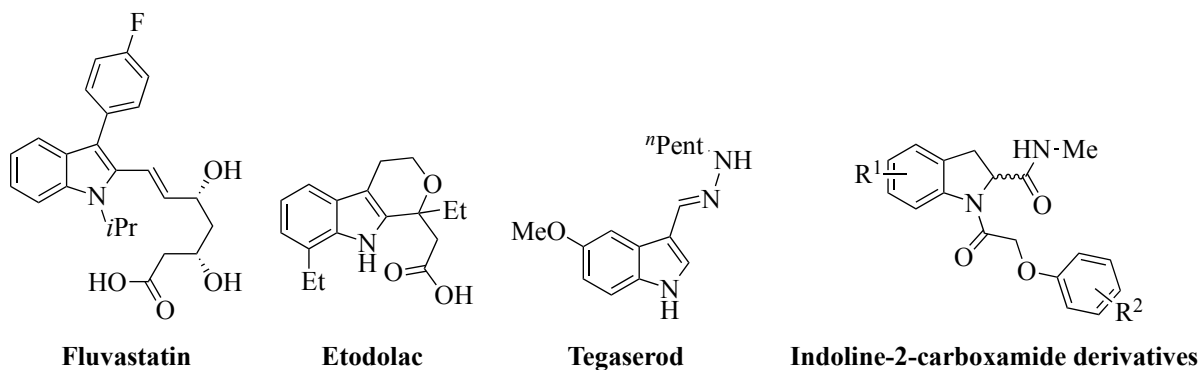
3.3. *Indoles and Indolines*

Recently, heterocycles have caught the attention of many scientists. In fact, when using a simple SciFinder search for the keyword “heterocycle” between the years of 2010 to 2016, over 5,500 references were found. Nitrogen heterocycles represent an important subclass, primarily due to their significance in pharmaceuticals, agrochemicals, and veterinary products.⁴⁷ In a recent review, the Njardarson group screened 1,035 unique small molecules drugs from their database and found that 59% of them contained at least one nitrogen heterocycle.⁴⁸ The drugs

identified encompassed a wide range of biological activity, including antiviral activity, skin cancer therapy, asthma treatment, and hypertension management.

An important subclass of nitrogen-containing heterocycles is the indole and indoline motif. Of the drugs screened from the Njardarson group, the indole substructure was ranked number 9 with regards to frequency, being the 3rd most frequent aromatic heterocycle containing a 5-membered nitrogen ring.⁴⁸ Indolines have also earned a place in substructure frequencies, being ranked number 5 of the nonaromatic nitrogen heterocycles containing a 5-membered nitrogen ring.⁴⁸ Indeed, compounds such as Fluvastatin, Etodolac, Tegaserod, indoline-2-carboxamide derivatives and many others contain indole and indoline substructures, many of which have improved the quality of life for many people (Figure 3.8).^{48,49}

Figure 3.8. Select Indole and Indoline Drugs that Exhibit Biological Activity



Another important subclass that exists is the fused indoline structure, especially those containing the fusion between C2 and C3.^{50,51} The next section will elaborate on the complexities involved in the syntheses of fused indolines along with strategies developed to overcome these obstacles.

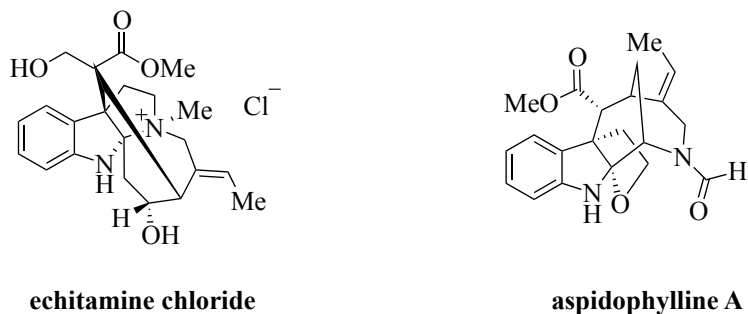
3.3.1. Fused Indolines

Fused indolines make up an important subclass of the indoline class. Compared to indoline, fused indolines possess greater structural complexity, as they incorporate polycyclic frameworks and often bear multiple stereocenters. For example, when examining a C2,C3 fused indoline, a minimum of two stereocenters is introduced when comparing to simple indoline, assuming the fused ring is asymmetric. Since fusion at the C2,C3 position is found in many important natural products, such as pyrroloindoline⁵² and furanoindoline^{53,54} alkaloids, synthetic chemists have enjoyed the challenge of developing rapid and facile access to these substructures.^{50,51,55-57} Typically, approaches to C2,C3 fused indolines involve an interrupted Fischer indolization,^{50,58,59} manipulation of indole precursors,^{57,60} functionalization of oxindoles,⁶¹⁻⁶³ and C–H amination of aromatics.⁶⁴ Although others methods exist, a deeper examination of the typical approaches will be the next focus.

Interrupted Fischer Indolization

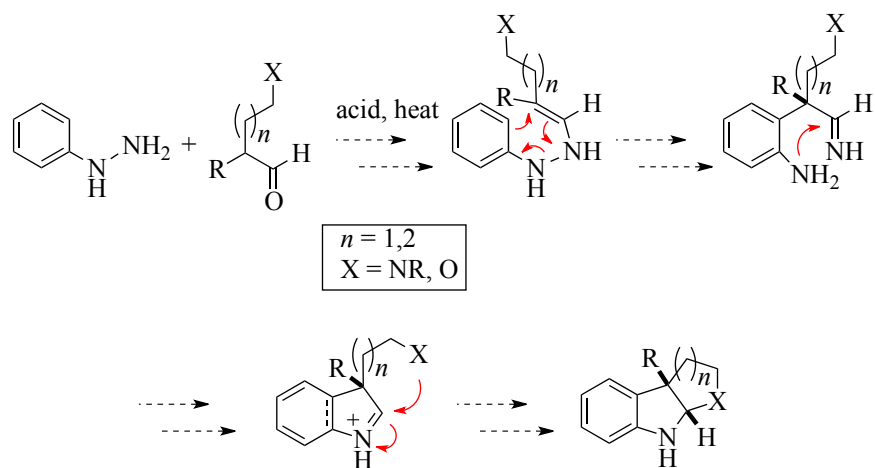
In 2009, Professor Neil Garg revealed an interrupted Fischer indolization leading to C2,C3 fused indolines.⁵⁹ The cascade reaction provides impressive frameworks that are found in a number of biologically active compounds, including echitamine chloride^{65,66} and aspidophylline A⁶⁷, using simple starting materials and mild aqueous conditions (Figure 3.9).

Figure 3.9. Select Natural Products Containing a C2,C3 Fused Indoline Substructure



Their hypothesis was inspired by the classic Fischer indole synthesis⁶⁸ using phenylhydrazine and an α -substituted aldehyde bearing a tethered nucleophile (Scheme 3.8).

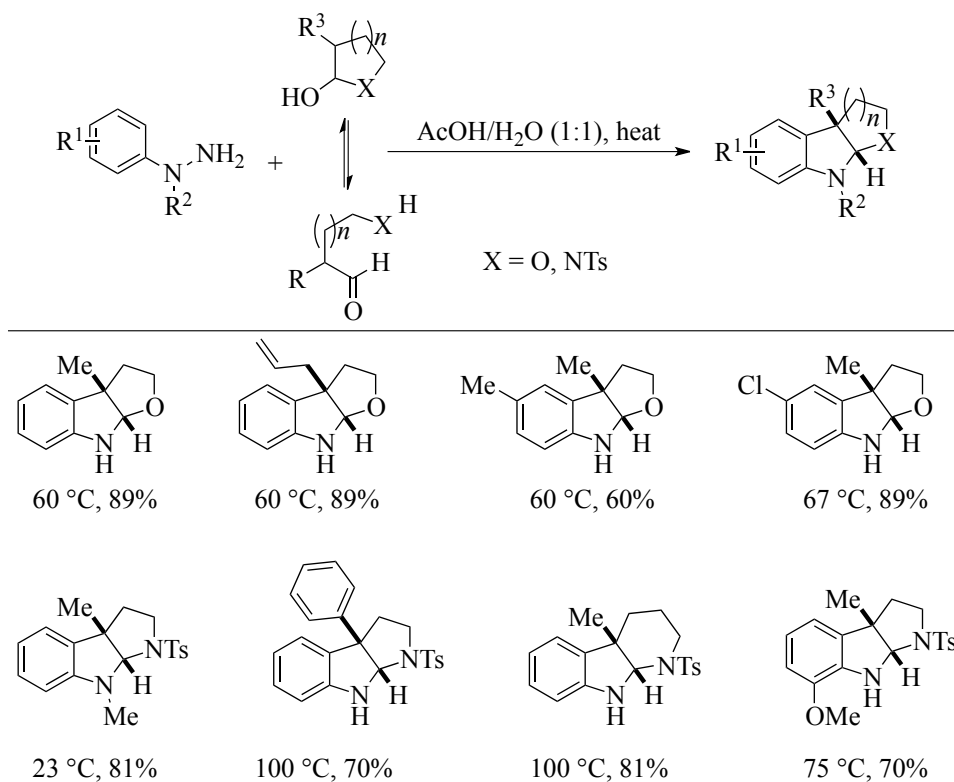
Scheme 3.8. Garg's Interrupted Fischer Indolization



In their model, the presence of acid would generate an enamine intermediate *via* condensation, which would setup the [3,3]-sigmatropic rearrangement and rearomatization to provide the corresponding aniline. Subsequent cyclization and loss of NH_3 would furnish the indolenine, which could then be intercepted by the benzylic nucleophilic tether (derived from the original aldehyde) to yield the desired fused indoline product. Garg and coworkers then tested

their hypothesis on a variety of substrates after identifying acetic acid as the choice acid in a heated aqueous system. Both oxygen and nitrogen intercepted the corresponding indolenine to generate the desired fused indoline product, providing both high yields and diastereoselectivities (Scheme 3.9).

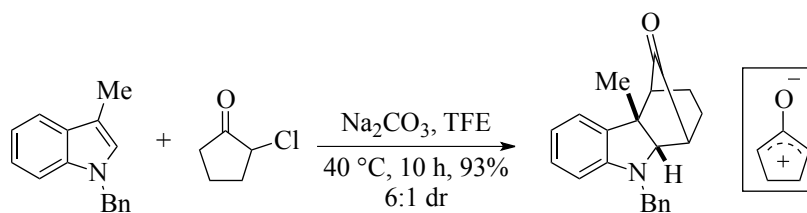
Scheme 3.9. Garg's Interrupted Fischer Indolization Summarized Substrate Scope



The interrupted Fischer indolization is a powerful and rapid way to generate both pyrrolo- and furanoindolines in a rapid fashion, forming multiple bonds in one step. Using aqueous reaction conditions and heat, important structural motifs were synthesized in high yields with diverse modifications.

Synthesis of fused indolines, namely pyrroloindolines, from indoles has been the aim of many groups worldwide, typically centering their strategy on the C3 alkylation of tryptophan, tryptamine, or their analogues, followed by nucleophilic attack of the iminium ion.⁶⁹ Although successful, an alternative route to generate C2,C3 fused indolines from indoles is by way of dearomative [3+2] annulation with oxyallyl cations or azaoxyallyl cations, establishing different bond disconnections than the tryptophan and tryptamine approach.^{57,70} It was discovered that 1,3-dipoles, such as oxyallyl cations,⁷¹ react particularly well in the [3+2] annulation reactions, which prompted the Wu group to test their amenability to participate in the corresponding dearomative annulation with indole.⁵⁷ Indeed, after optimizing reaction conditions, they were able to generate the desired cycloadduct in 93% yield and 6:1 dr in 10 hours (Scheme 3.10).

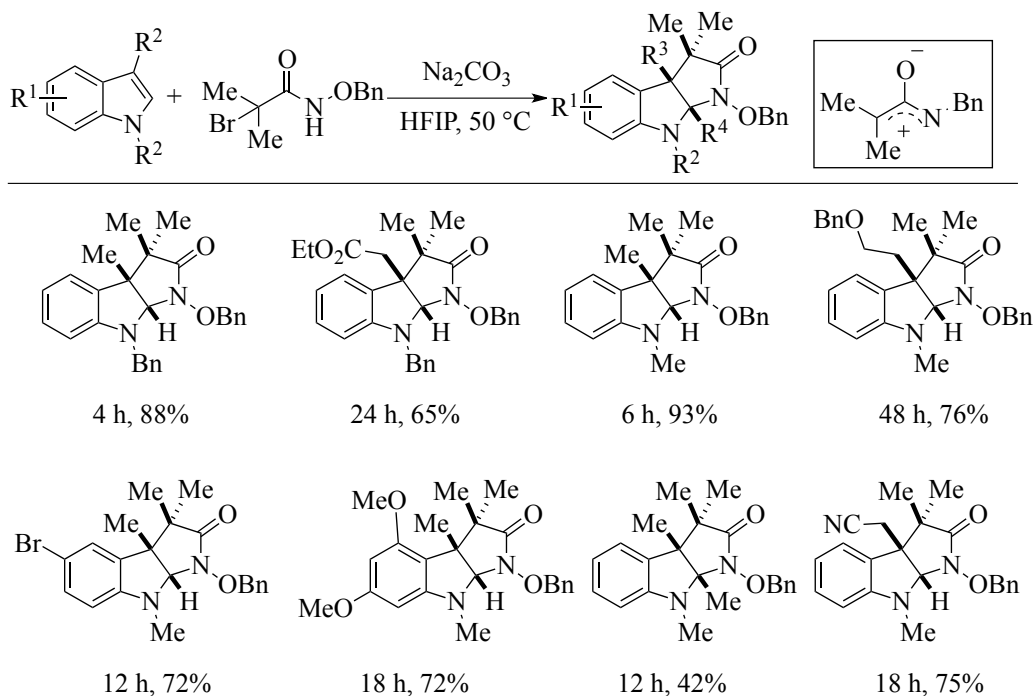
Scheme 3.10. Wu's C2,C3 Fused Indoline Formation *via* Dearomative [3+2] Annulation



The scope was then expanded to incorporate modifications around the structure, including electron-rich and electron-deficient substituents on the aromatic ring and altering the C3 methyl group to a variety of other groups. Additionally, they were able to also incorporate acyclic oxyallyl cations into their scope, which produced the analogous tricyclic framework. In a

following report just a year later, the group revealed the synthesis of a variety of pyrroloindolines using azaoxyallyl cations (generated *in situ*) and similar reactions conditions (Scheme 3.11).⁷⁰

Scheme 3.11. Wu's Pyrroloindoline Synthesis using Azaoxyallyl Cations



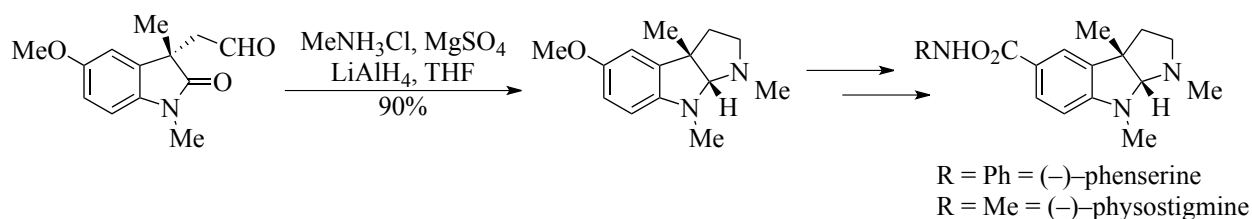
As shown, 1,3-dipoles are powerful species that can be used to generate molecular complexity in a single step. They are particularly useful in annulation reactions, which Wu and coworkers exploited to synthesize fused indolines from an indole precursor. Next, fused indoline synthesis from oxindoles will be explored and discussed.

Functionalization of Oxindoles

Fused indolines can also be synthesized from an oxindole precursor, usually occurring through a reductive cyclization with a C3 nucleophile. This approach was exploited in

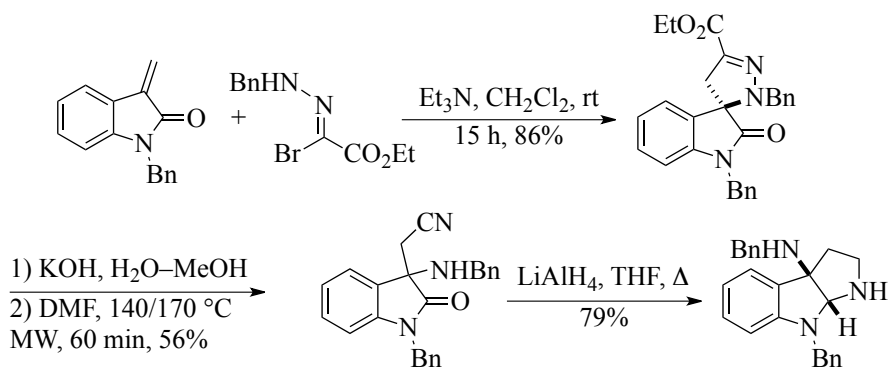
Overman's total synthesis of (–)-phenserine⁷² and Trost's adaption of the Overman methodology in a formal total synthesis of (–)-physostigmine (Scheme 3.12).⁶²

Scheme 3.12. Stepwise Synthesis of (–)-Phenserine and (–)-Physostigmine from an Oxindole Precursor



In 2012, Roth and coworkers illustrated a reductive cyclization of an oxindole with a nitrile.⁶³ Although the focus of their report was to reveal a [3+2] dipolar cycloaddition between a variety of nitrile imines and 3-alkylidene oxindoles, generating the corresponding spiro-pyrazolines (Scheme 3.13, top), the authors were able to perform a decarboxylative pyrazoline ring opening to yield 3-aminonitriles. Subsequent reductive cyclization using conditions similar to Overman's yielded the desired pyrroloindoline (Scheme 3.13, bottom).

Scheme 3.13. Roth's Stepwise Synthesis of an Oxindole to Form a Pyrroloindoline



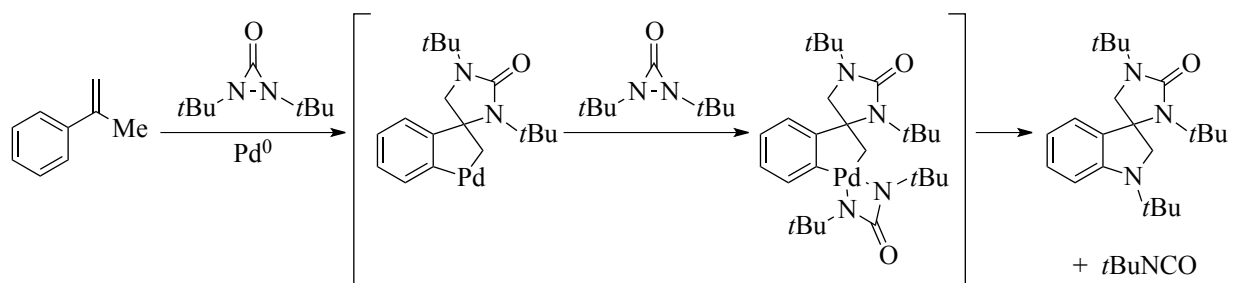
As shown, fused indolines can be constructed from oxindole precursors, usually derived from C3-substituted analogues. The examples discussed focused on reductive cyclization

methods, which required a stepwise synthesis of an amenable precursor. A final example used to illustrate the synthesis of fused indolines is the C–H amination of cleverly designed aromatics, establishing a bond connection not yet discussed in this report.

C–H Amination of Aromatics

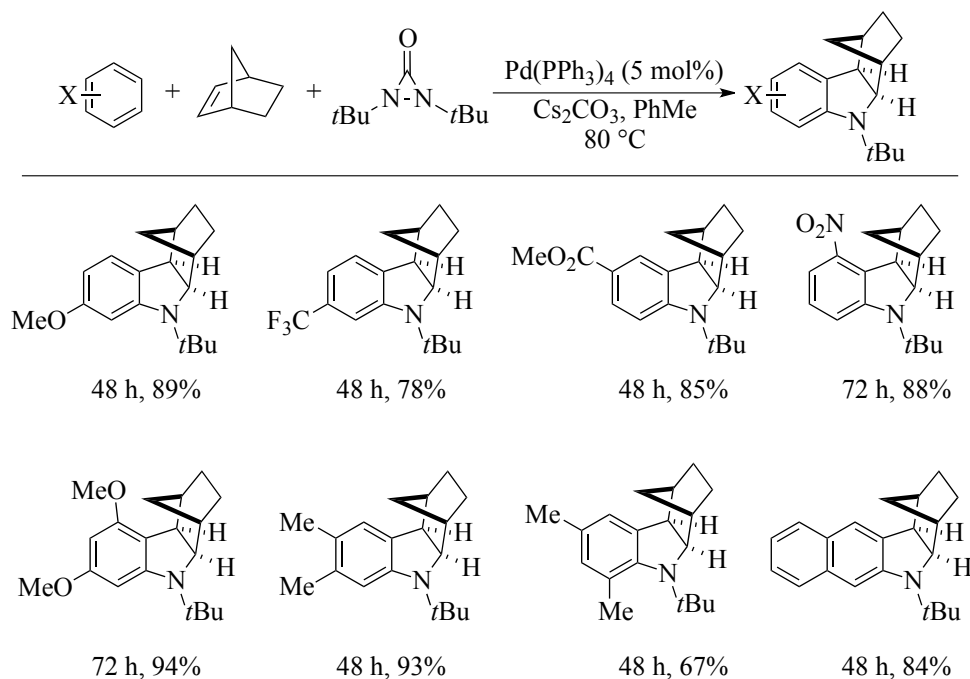
Formation of indolines *via* C–H amination has been an attractive synthetic route for many research groups.^{64,73} Yian Shi recently revealed a Pd–catalyzed C–H amination to produce C2,C3 fused indolines.⁷⁴ In previous studies, they found that di-*tert*-butyldiaziridinone can participate in a sequential C–N bond formation reaction with α -methylstyrene *via* aromatic and allyl C–H amination to produce C3 spirocyclic indolines (Scheme 3.14).⁷⁵

Scheme 3.14. Yian Shi’s Original C–H Amination to Generate Indolines



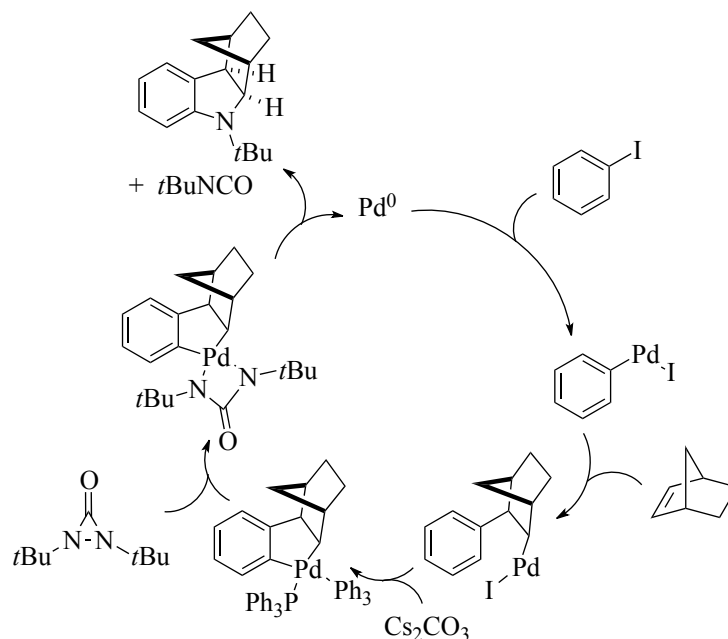
Using this knowledge, the Shi group decided to probe the possibility of synthesizing fused indolines using an aryl halide, norbornene, and di-*tert*-butyldiaziridinone. Indeed, upon optimization, the anticipated fused indoline was isolated in 89% yield using *p*-iodoanisole as the aromatic counterpart. A reaction scope was then developed encompassing a variety of electronic character and substitutions, which is summarized in Scheme 3.15.

Scheme 3.15. C–H Amination to Form C2,C3 Fused Indolines



The authors then proposed a catalytic cycle, which is outlined in Scheme 3.16. The first step involves a Heck reaction of aryl iodide and norbornene. The aryl iodide undergoes oxidative addition with Pd^0 to generate the corresponding Pd^{II} species. The Pd^{II} species then forms a π complex with norbornene, which then inserts itself into the Pd–C bond of the aryl group, forming the aryl–norbornene bond. Subsequent C–H activation, N–N bond insertion with di-*tert*-butyldiaziridinone and reductive elimination would then yield the corresponding fused indoline product and Pd^0 species.

Scheme 3.16. Proposed Catalytic Cycle

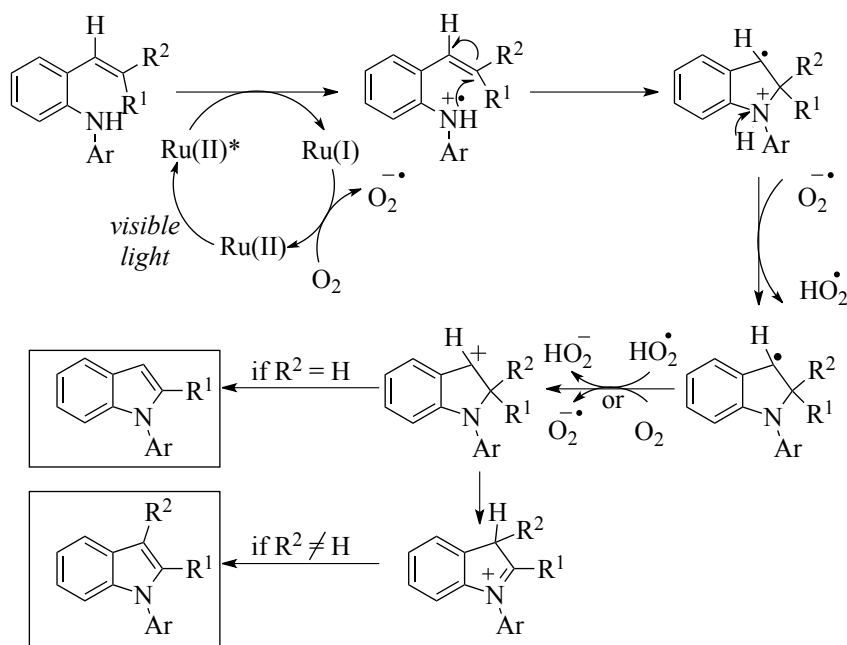


C–H amination offers an alternative route to access fused indolines, focusing on the use of transition metal catalysis. The bond connection differs from the previous methods discussed, as the aromatic C–N bond of the indoline is linked rather than C2,C3 cyclization. Although the methods discussed successfully generate C2,C3 fused indolines, many require properly designed substrates, heated reaction conditions, expensive reagents and multiple steps, which, from a sustainability chemistry standpoint, are not applicable for society’s needs. In the next section, the synthesis of indoles and indolines using visible light photoredox catalysis will be discussed, offering an improved method for the acquisition of these compounds.

3.3.2. Preparation of Indoles/Indolines using Visible Light Photoredox Catalysis

In 2012, Zheng and coworkers revealed an oxidative C–N bond forming cascade that generated a variety of C2 and C3 indoles by way of visible light photoredox catalysis of styrenyl anilines.¹⁷ In their report, an amine radical cation was proposed to be generated upon oxidation with a photoexcited photoredox catalyst, shown as “mode 5” in Scheme 3.7 (see section 3.2). By exploiting the inherent electrophilicity of the amine radical cation, they were able to create an intramolecular C–N bond with a styrene. Further redox manipulations, acid/base chemistry, and aromatization afforded both C2– and C2,C3–disubstituted indoles (Scheme 3.17).

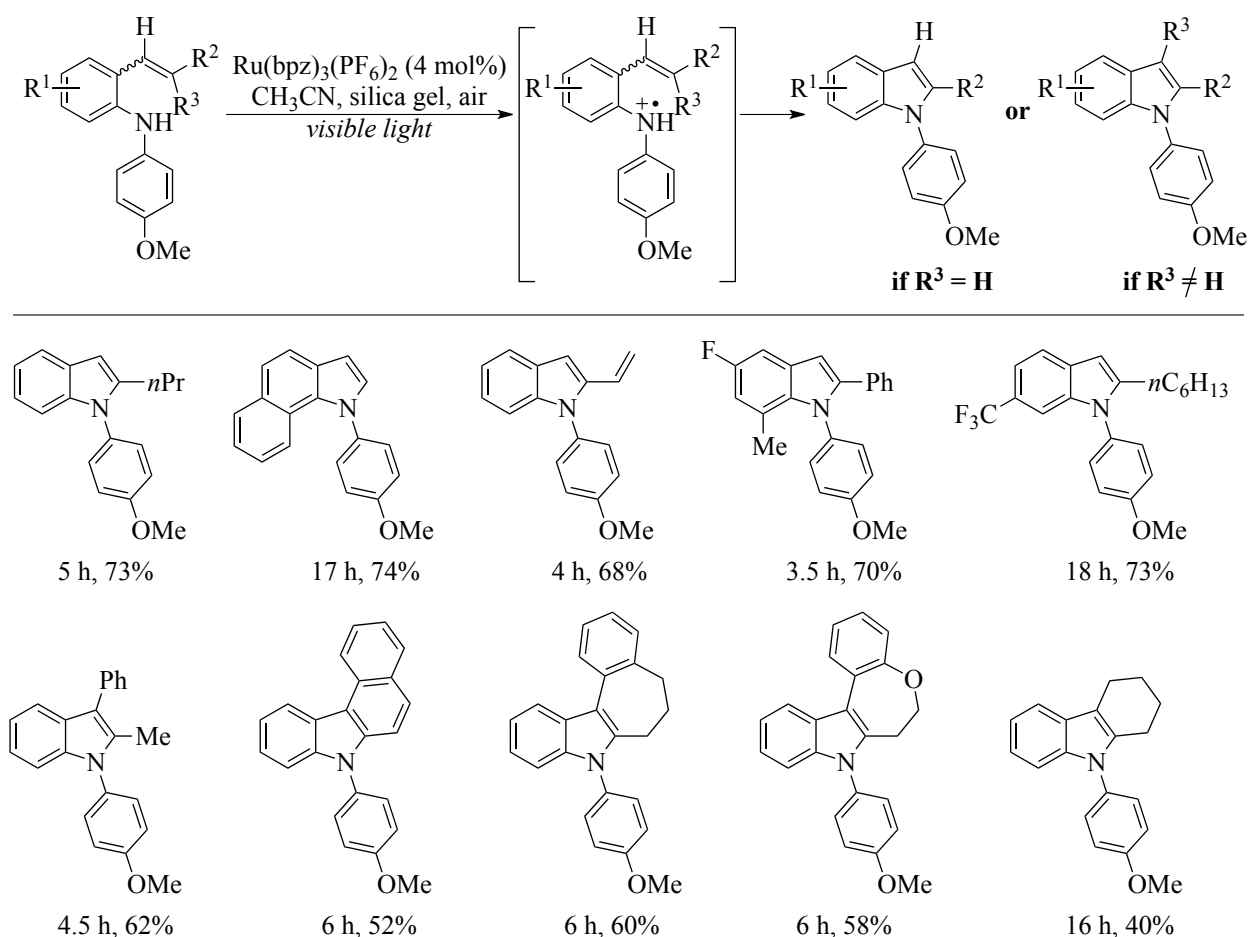
Scheme 3.17. Proposed Catalytic Cycle for Zheng’s Photoredox–Catalyzed Indole Synthesis



Using this methodology, the authors were able to develop a substrate scope, depicted in Scheme 3.18. Monosubstituted indoles were synthesized in yields ranging from 55% to 83%. Naphthalene–derived indoles succeeded facilely, providing the corresponding tricyclic structure.

Modified electronic character to the indole also generated the desired product, albeit substitution at C7 with CF₃ proceeded sluggishly. Lastly, C2,C3 disubstituted indoles were also synthesized using a 1,2-shift methodology from the substituted styryl aniline precursor, further improving the reaction scope. It is of note, however, that a *para*-alkoxyphenyl group on the nitrogen is a requirement for the cascade reaction to work properly.

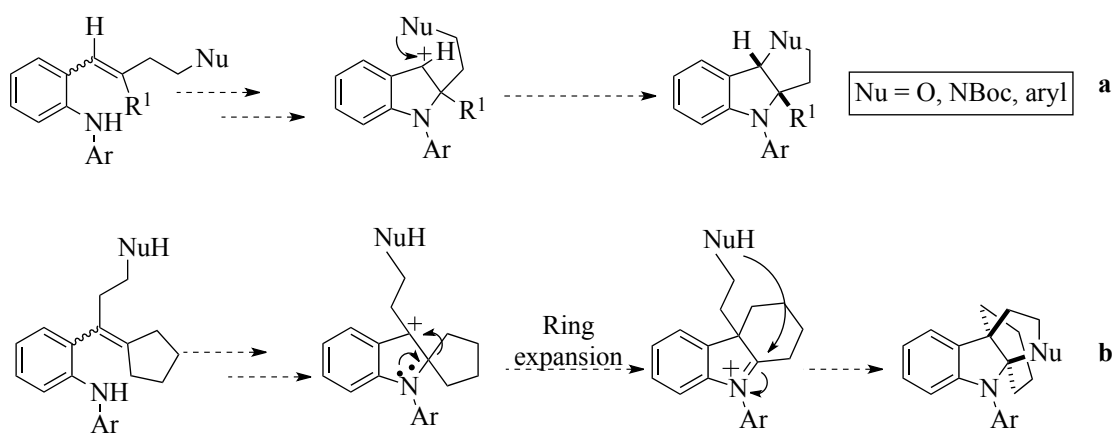
Scheme 3.18. Substrate Scope for Zheng's Photoredox Catalyzed Indole Synthesis



The reported chemistry is attractive from a sustainability standpoint because it is performed aerobically, creates multiple bonds in a single step, and uses a renewable resource (light) while only requiring a catalytic amount of $\text{Ru}(\text{bpz})_3(\text{PF}_6)_2$. In their proposed mechanism, a

C3 benzylic cation is the key intermediate that eventually leads to the indole product upon deprotonation *via* E1 pathway (monosubstituted cases) or 1,2-shift⁷⁶/deprotonation (disubstituted cases). Having established the case for an intermediate benzylic cation by their substrate scope, it should be considered if the benzylic cation could be potentially trapped using a nucleophile prior to deprotonation or 1,2-shift. Such a pathway would generate C2,C3 fused indolines when using intramolecular cases, and would meet many requirements that sustainability chemistry aims for. In one way, a tethered styryl aniline bearing a nucleophile could potentially trap the photogenerated benzylic cation via nucleophilic addition (Scheme 3.19a). Alternatively, by designing a styrene substrate possessing a tetrasubstituted olefin bearing a terminal cyclic moiety and an internal nucleophilic tether, a 1,2-ring expansion/nucleophilic attack could generate a tetracyclic C2,C3 fused indoline, which resembles the polycyclic core found in akuammiline alkaloids (Scheme 3.19b).^{53,55,66,77}

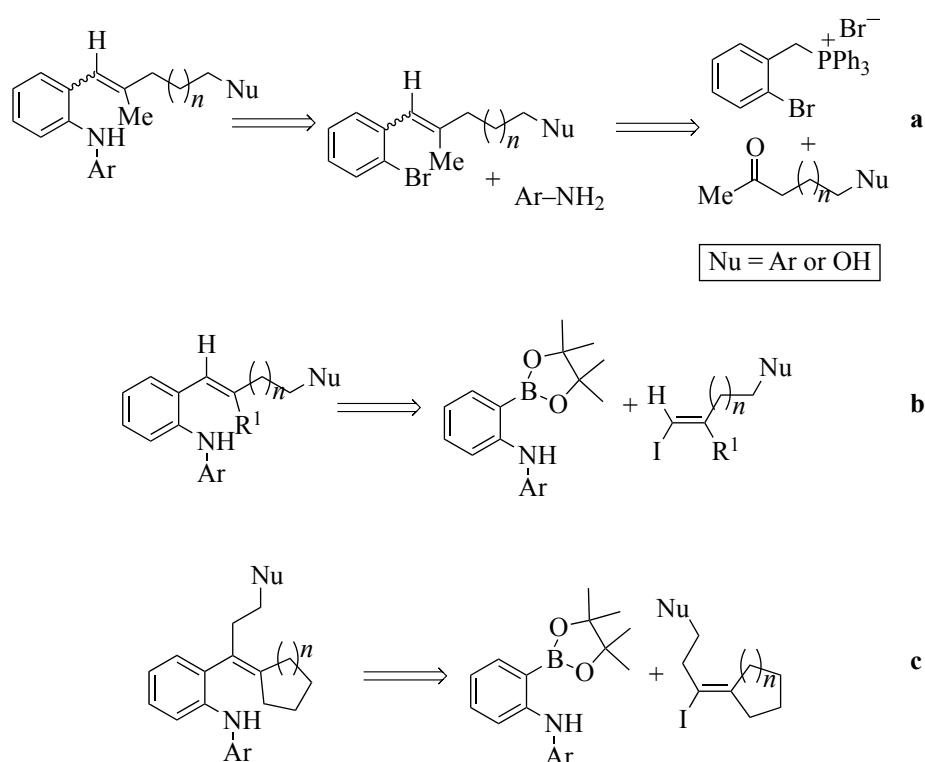
Scheme 3.19. Proposed Fused Indoline Synthesis using Visible Light



The synthesis of precursors would need to occur in a stepwise fashion. In Scheme 3.19a, Wittig reaction of a ketone with a properly designed ylide salt could yield the *ortho*-bromostyrene bearing a nucleophilic tether as a mixture of isomers, which could subsequently be transformed

into the aniline counterpart using a Buchwald–Hartwig amination (Scheme 3.20a). Alternatively, a Suzuki–Miyaura coupling using an *ortho*-substituted boronic ester and vinyl iodide could generate the starting material as a single isomer (Scheme 3.20b). In order to synthesize the precursor required for Scheme 3.19b, a Suzuki–Miyaura coupling using a tetrasubstituted vinyl iodide would establish the key bond connection (Scheme 3.20c).

Scheme 3.20. Proposed Syntheses of Tether Styrenyl Anilines



Since the depicted chemistry is a viable route to generate fused indolines with anticipated high diastereoselectivities using visible light photoredox catalysis, various hypotheses are stated below and the results of the studies are described in Chapter 4.

3.4. Statement of the Problem

The overall aim is to utilize visible light photoredox catalysis to generate a variety of C2,C3 fused indolines from styryl aniline precursors. The specific goals of this project are as follows:

1. Design and apply a viable forward synthesis for the substrates to be examined.
2. Examine the possibility of a photoredox cascade reaction using a model tethered styrenyl aniline substrate.
3. If successful, optimize reaction conditions and develop a substrate scope utilizing oxygen, nitrogen, and aryl nucleophiles as well as develop the 1,2-shift/nucleophilic trap system.
4. Explore various methods to cleave the *para*-alkoxyphenyl group from the nitrogen.

The importance of the first goal is to establish a straightforward synthesis for the non-trivial styrenyl aniline substrates. Once established, synthesis of various substrates can be tested and, if amenable, examined using visible light photoredox catalysis.

The importance of the second goal is to prove visible light photoredox catalysis is a viable option to synthesize the desired fused indolines. It will be important to choose a substrate that is easily synthesized and has a high chance for success.

The importance of the third goal is to obtain the highest yield possible by optimizing reaction conditions. The optimization will be performed by studying various photoredox catalysts, solvents, catalyst loadings, light sources, and additives and measuring yields using gas

chromatogram. Once optimized, substrate scopes can be developed in order to establish the utility of the reaction.

The importance of the fourth goal is to further improve the substrate scope by cleaving the *N*-aryl bond, which was a moiety required to establish the photoredox cascade. By cleaving the requisite aryl group, the fused indoline can be more useful for further modifications on the nitrogen and will better resemble the typical framework found in many bioactive natural products.

3.5. References

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Chapter 4

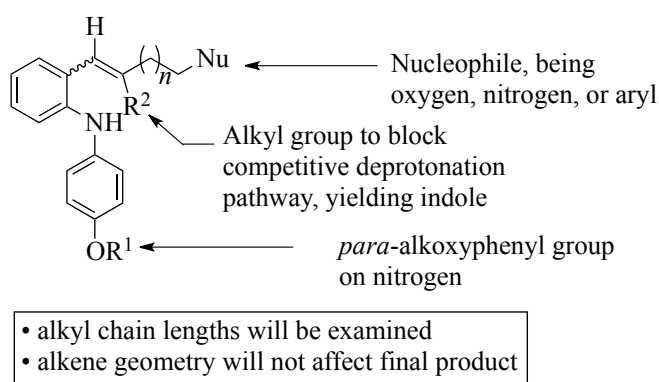
Synthesis of Fused Indolines using Visible Light Photoredox Catalysis

Visible light photoredox catalysis provides a way to generate unique chemical structures using a renewable resource.¹ Since indoles and indolines are common motifs found in a variety of biologically active compounds,² their syntheses should be streamlined in a sustainable manner. Visible light photoredox catalysis can offer the needed improvement of the synthesis of such frameworks, as many common methods require elevated temperatures,³ harsh reaction conditions,⁴ and lengthy preparation of precursors.⁵ Recently, Nan Zheng and coworkers developed an aerobic indole synthesis using visible light.⁶ The C–N bond forming cascade hinged on the formation of an amine radical cation, which, through umpoloung reactivity, electrophilically adds intramolecularly to a styrene. After various redox manipulations and deprotonations, various mono- and disubstituted indoles of varying electronic character were formed in moderate to high yields (40–83%). The authors proposed a mechanism which suggests an intermediate benzylic cation, which can either be satisfied by direct deprotonation to afford the corresponding C2-monosubstituted indole or participating in a 1,2-alkyl shift followed by deprotonation to yield the C2,C3-disubstituted indole. Since the authors demonstrated good evidence of an intermediate benzylic cation, it is hypothesized that alternate pathways could also trap this benzylic cation, thus generating a larger reaction scope. For instance, oxygen and nitrogen nucleophiles could participate in intramolecular S_N1 reactions with the benzylic cation to generate their corresponding structures. In a similar way, aryl nucleophiles could react with the benzylic cation in a Friedel–Crafts fashion, generating a fused indoline. The aim of this chapter is to document the scientific findings with regards to this hypothesis.

4.1. Design and Synthesis of Viable Starting Materials

The investigation commenced with the design and synthesis for the starting materials required for a proper photoredox-catalyzed reaction. A depiction of the required characteristics is shown in Figure 4.1.

Figure 4.1. Necessary Components of Styrenyl Anilines



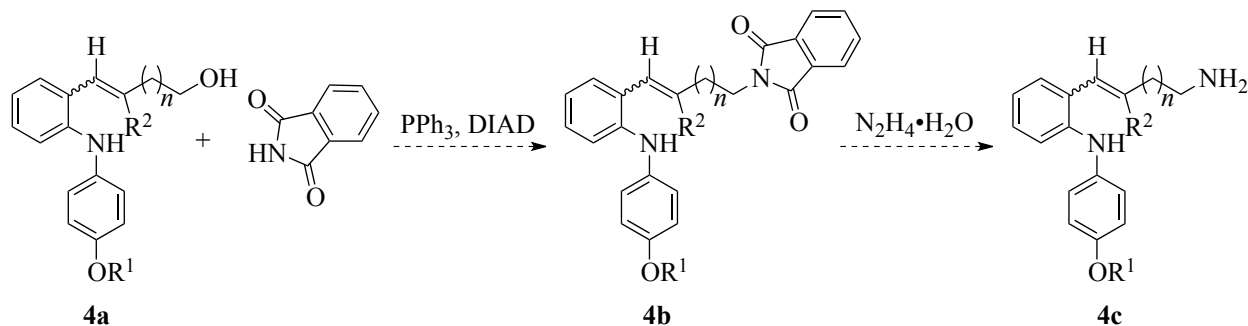
Since oxygen (such as hydroxyls) and nitrogen compounds (such as amines) are good nucleophiles, it is anticipated that both could successfully intercept the photogenerated benzylic cation or iminium ion. Additionally, it is expected that electron-rich aryl nucleophiles could participate in the desired reaction in a Friedel–Crafts fashion. With regards to R² in Figure 4.1, it seemed that by placing an alkyl group at this position, competitive indole formation by deprotonation is terminated, thus allowing the formation of fused indolines via a S_N1 pathway. Having an alkyl at R² would also form a quaternary carbon at C2 upon irradiation with visible light, further magnifying the significance of this chemistry. Lastly, as demonstrated in Zheng's previous report, a *para*-alkoxyphenyl group is required for these reactions to proceed.⁶ Having

the starting materials designed, the specific synthesis of each type of substrate will be further discussed.

Starting Material for Oxygen and Nitrogen Nucleophiles

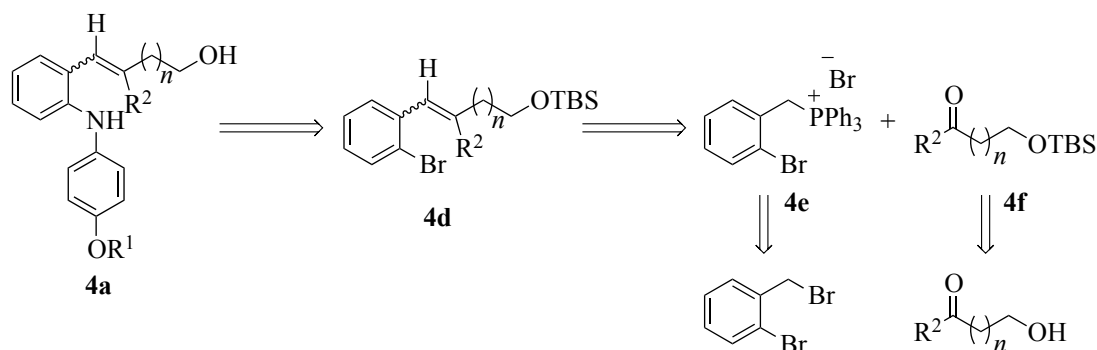
The synthesis of the starting materials for oxygen and nitrogen nucleophiles was conceived using two synthetic plans. Since hydroxyl groups such as **4a** can easily be converted into free amines (**4c**) *via* Gabriel synthesis, synthesis of precursors solely focused on the hydroxyl nucleophile (Scheme 4.1).⁷

Scheme 4.1. Proposed Synthesis of Free Amines from Alcohol Precursors



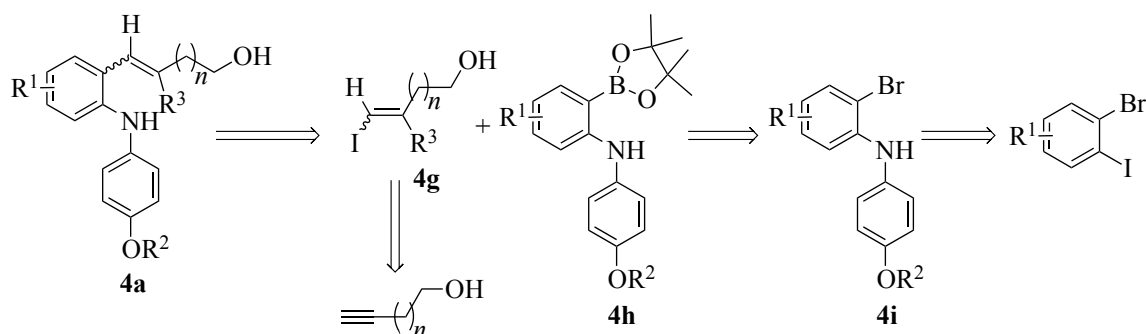
The first synthetic scheme would hinge on a Wittig reaction, which would establish the styrene moiety of substrate **4a**. In this route, the starting material would be derived from a Buchwald–Hartwig amination of *ortho*–bromo styrene **4d**. There was good precedence for this transformation, as it mimicked the synthetic plan using in the indole synthesis paper.⁶ The *ortho*–bromo styrene **4d** would be formed from a Wittig reaction of *ortho*–bromo ylide salt **4e** and ketone **4f**. Treatment of commercially available 2–bromobenzyl bromide with triphenylphosphine could form the requisite ylide salt **4e**. Ketone **4f** could be accessed by simple TBS protection of the commercially available alcohol (Scheme 4.2).

Scheme 4.2. Retrosynthesis of Styrenyl Anilines using the Wittig Approach



The second synthetic route would be dependent on a Suzuki–Miyaura coupling of vinyl iodide **4g** and *ortho*–aniline boronic ester **4h**, establishing the styrene moiety as a single isomer (Scheme 4.3). Boronic ester **4h** could be derived from a Miyaura borylation of *ortho*–*para*–alkoxyphenyl bromobenzene **4i** (prepared *via* Buchwald–Hartwig amination of 1–bromo–

Scheme 4.3. Retrosynthesis of Styrenyl Anilines using the Suzuki–Miyaura Approach

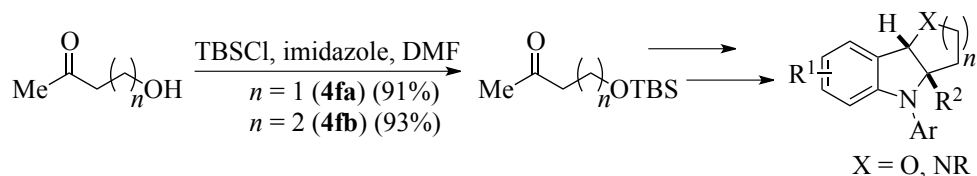


2–iodobenzene⁸) and bis(pinacolato)diboron ($B_2(\text{pin})_2$), whereas the vinyl iodide could be synthesized by carboalumination of the commercially available alkyne.^{9,10} It is worth noting that this route is modular and flexible. If the substrate syntheses become nontrivial, the Buchwald–Hartwig amination and Suzuki–Miyaura coupling reactions can be applied in an altered order in order to gain access to the desired substrates. With the two methods in hand, forward syntheses were attempted, which is discussed in the subsequent sections.

Hydroxyl-Based Styrenyl Aniline Synthesis using Wittig Approach

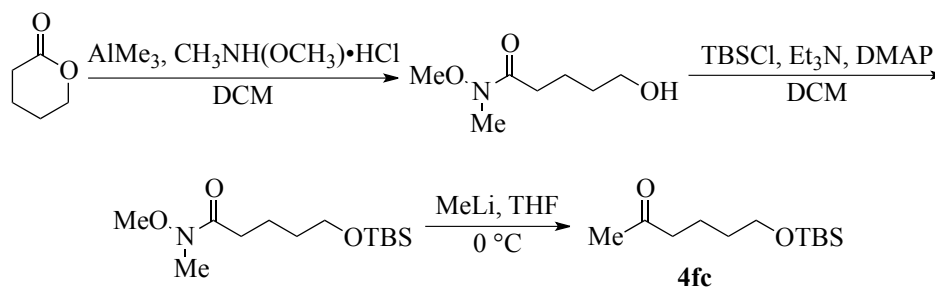
To commence the forward syntheses utilizing the Wittig approach, commercially available 4-hydroxybutan-2-one and 5-hydroxypentan-2-one were protected with a *tert*-butyldimethylsiloxy (TBS) group using a known procedure, yielding both **4fa** and **4fb** in high yields.¹¹ These substrates would correspond to the starting material that would generate a 5- and 6-membered fusion between C2 and C3 of the indoline product (Scheme 4.4).

Scheme 4.4. Alcohol Protection using *tert*-Butyldimethylsilyl Chloride



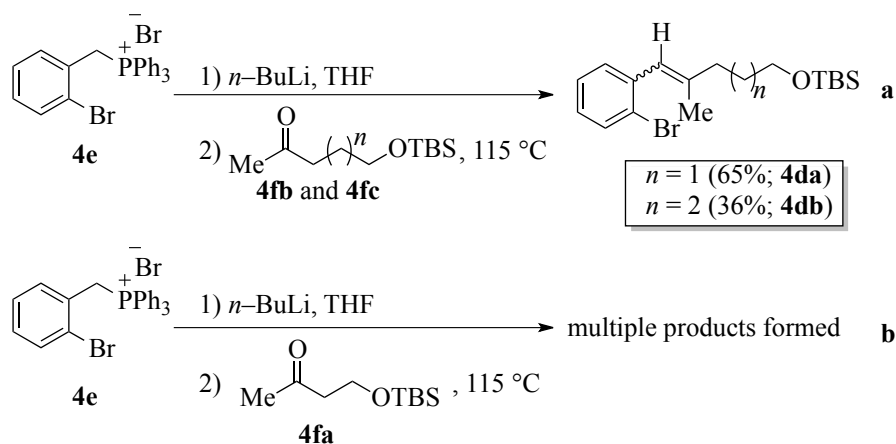
The formation of the counterpart bearing 4 methylenes ($n = 3$; 6-hydroxyhexan-2-one) in the tether was not as trivial, as its availability is limited and expensive. Therefore, the synthesis of **4fc** proceeded in a 3-step protocol starting with valerolactone. The first step was preparing the Weinreb amide using a Weinreb amidation procedure,¹² followed by alcohol protection using TBSCl¹³ and ketone synthesis with MeLi, successfully yielding **4fc** (Scheme 4.5).¹⁴

Scheme 4.5. Synthesis of 6-(*tert*-butyldimethylsiloxy)hexan-2-one from Valerolactone



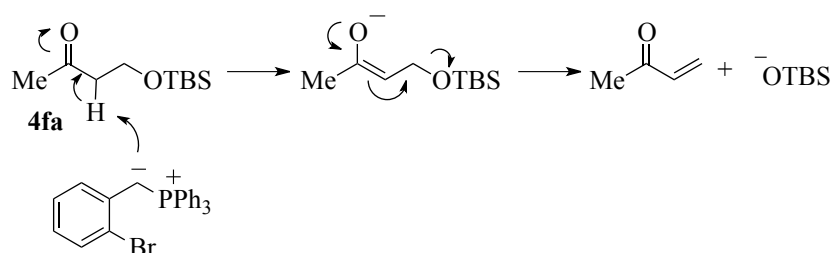
With the desired ketones in hand, a Wittig reaction⁶ was attempted using (2-bromobenzyl)triphenylphosphonium bromide (prepared *via* literature procedure¹⁵). The reaction proceeded uneventfully using both 5-(*tert*-butyldimethylsiloxy)pentan-2-one **4fb** and 6-(*tert*-butyldimethylsiloxy)hexan-2-one **4fc** (Scheme 4.6a), yielding the corresponding styrenes as a 1:1 inseparable mixture of isomers in 65% and 36% yield, respectively. However, the Wittig reaction using 4-(*tert*-butyldimethylsiloxy)butan-2-one **4fa** yielded multiple unidentified products (Scheme 4.6b).

Scheme 4.6. Wittig Reaction of Relevant Ketones



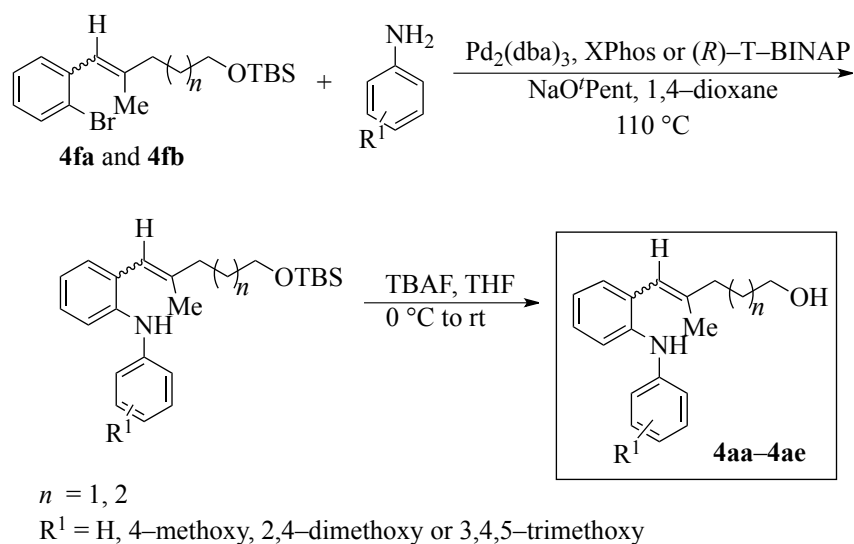
The formation of multiples products in Scheme 4.6b was likely caused by an enolate intermediate derived from deprotonation with the basic ylide, which could form the corresponding enone *via* a E1cB pathway (Scheme 4.7). Nonetheless, it was hypothesized that this substrate could be synthesized using the Suzuki–Miyaura approach; therefore, subsequent studies using the Wittig approach were performed using the styrenes formed in Scheme 4.6a.

Scheme 4.7. Hypothesis for the Fragmentation of 4-(*tert*-butyldimethylsiloxy)butan-2-one in the Wittig Reaction



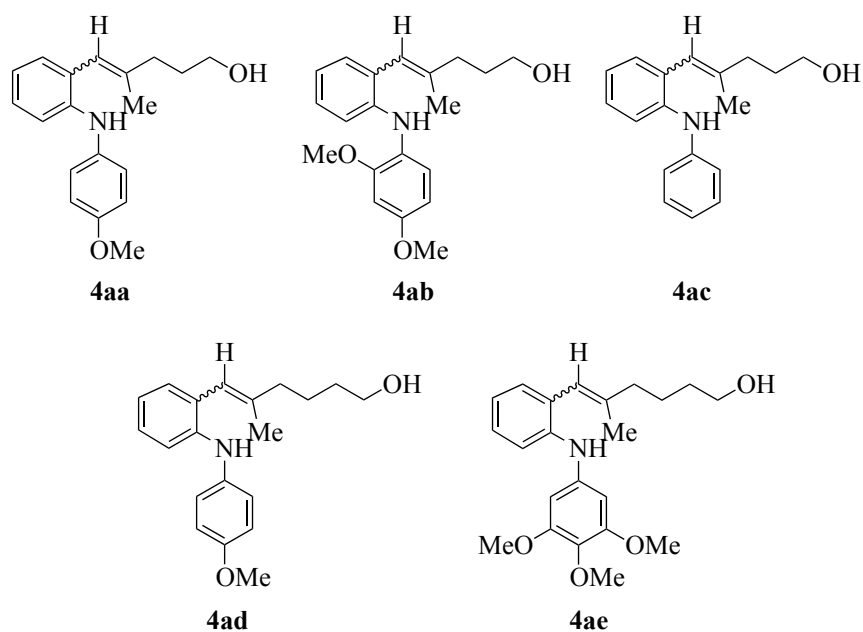
Subsequent Buchwald–Hartwig amination using XPhos or (*R*)-T-BINAP and $\text{Pd}_2(\text{dba})_3$ proceeded as expected using the previously synthesized styrenes **4da** and **4db**, yielding styrenyl aniline products bearing a variety of aryl groups in moderate to high yields (67–95%) as an inseparable 1:1 mixture of isomers (Scheme 4.8).⁶ Lastly, alcohol deprotection using TBAF yielded the corresponding alcohol-bearing styrenyl anilines **4aa–4ae** in high yields (64–89%) as a mixture of inseparable isomers as a 1:1 ratio.

Scheme 4.8. Synthesis of Final Styrenyl Aniline Adduct **4a** using Buchwald–Hartwig Amination and TBS Deprotection



The Wittig approach allows for a straightforward synthesis of the desired styrenyl aniline products. Using this approach, the products in Figure 4.2 were successfully obtained in 4 to 6 linear steps.

Figure 4.2. Hydroxyl–Based Substrates Synthesized using Wittig Approach

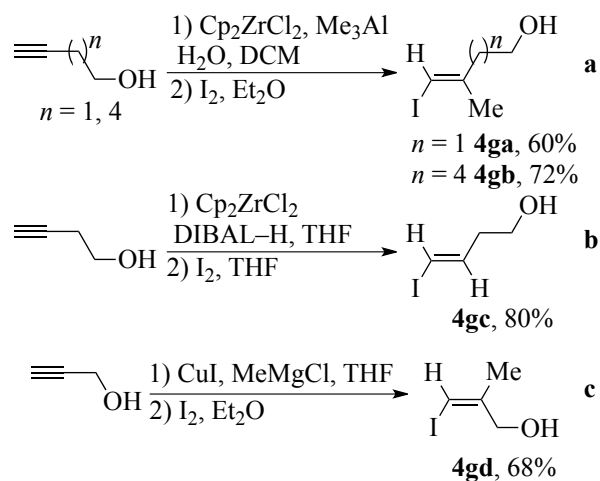


The strength of this synthesis is that many of the steps are reliable and give products in moderate to high yields. However, this synthesis lacks convergence, requires the non-atom economical Wittig reaction, and is not viable for many substrates due to being incompatible with the Wittig reaction or not being commercially available and inexpensive.

Hydroxyl-Based Styrenyl Aniline Synthesis using Suzuki–Miyaura Approach

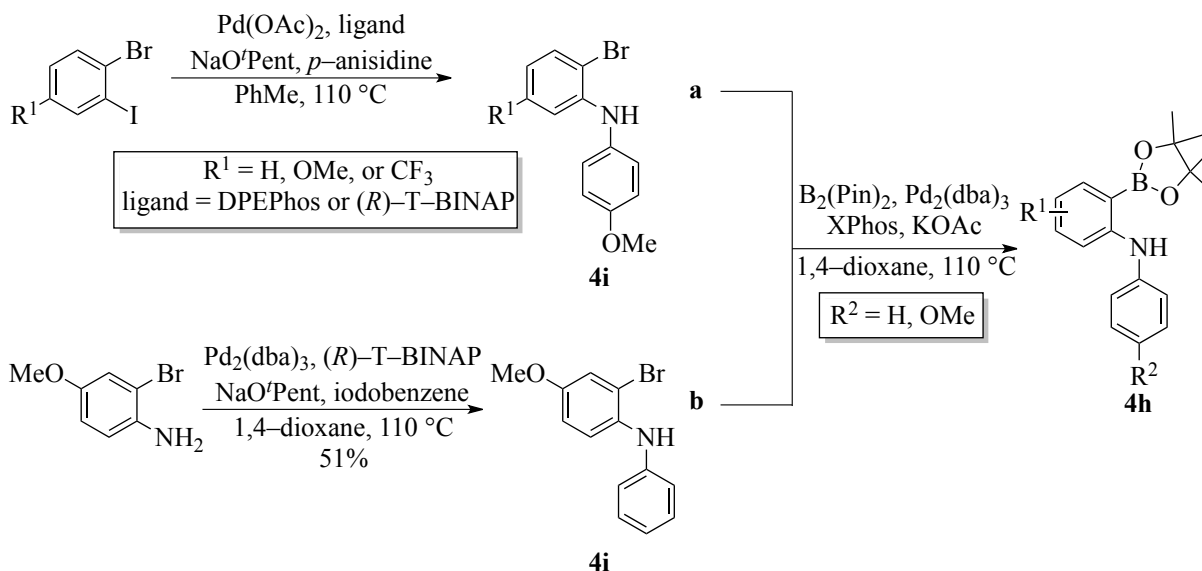
Substrate synthesis using the Suzuki–Miyaura approach began with a carboalumination/iodination of commercially available alkynes using Cp_2ZrCl_2 , AlMe_3 and I_2 (Scheme 4.9a).^{9,10} Utilizing 3-butyne-1-ol and 6-heptyne-1-ol allowed for substrates **4ga** and **4gb** that could potentially generate 5- and 8-membered ring fusions between C2 and C3 of the indoline product to be examined. Additionally, since the precursor for the furanoindoline could not be synthesized using the Wittig approach (see Scheme 4.6b), this offered an alternative route to access this substrate (**4ga**). A zirconium/DIBAL–H procedure¹⁶ was used to generate the disubstituted *trans* vinyl iodide **4gc** (Scheme 4.9b) whereas a copper-mediated addition procedure was used to generate (*Z*)-3-iodo-2-methylpropen-2-ol (**4gd**) from commercially available 2-propyne-1-ol (Scheme 4.9c).¹⁷

Scheme 4.9. Syntheses of Requisite Vinyl Iodides



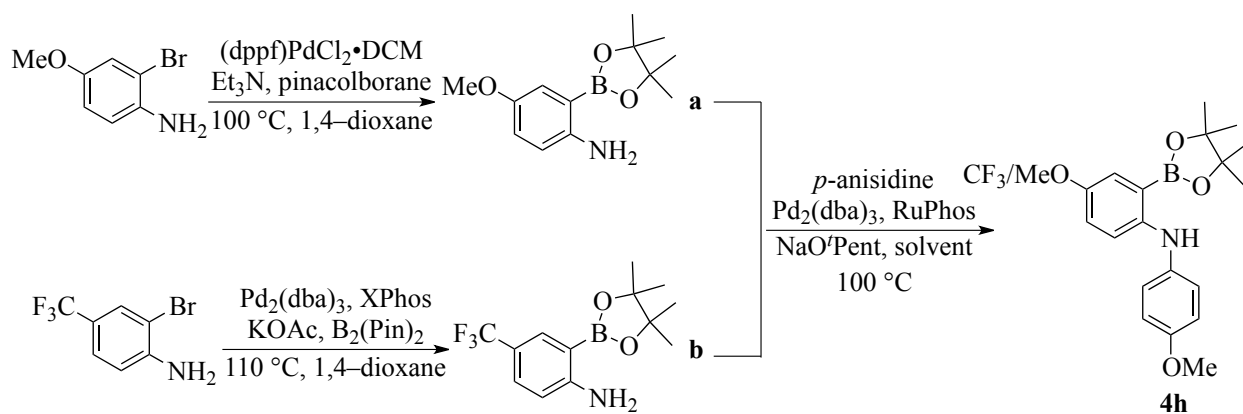
The next task was to synthesize the aryl boronic esters for the Suzuki–Miyaura coupling. Due to the varied reactivity of the precursors containing methoxy and trifluoromethyl groups, two different routes were needed in order to synthesize the desired boronic esters. The first route started with a Buchwald–Hartwig amination^{8,18} of various 1–bromo–2–iodobenzenes to yield the corresponding anilines (**4i**) followed by Miyaura borylation using $\text{B}_2(\text{pin})_2$, generating the desired boronic esters **4h** (Scheme 4.10a).¹⁹ This route had the most success using unsubstituted 1–bromo–2–iodobenzene as well as the corresponding 4–methoxy and 4–trifluoromethyl structures. In an isolated case, the Buchwald–Hartwig amination partners were reversed, utilizing iodobenzene and 2–bromo–4–methoxyaniline (Scheme 4.10b). The resulting *ortho*–haloaniline was then converted to the corresponding boronic esters (**4h**) *via* Miyaura borylation.¹⁹

Scheme 4.10. Forward Synthetic Routes utilized to Synthesize Boronic Esters



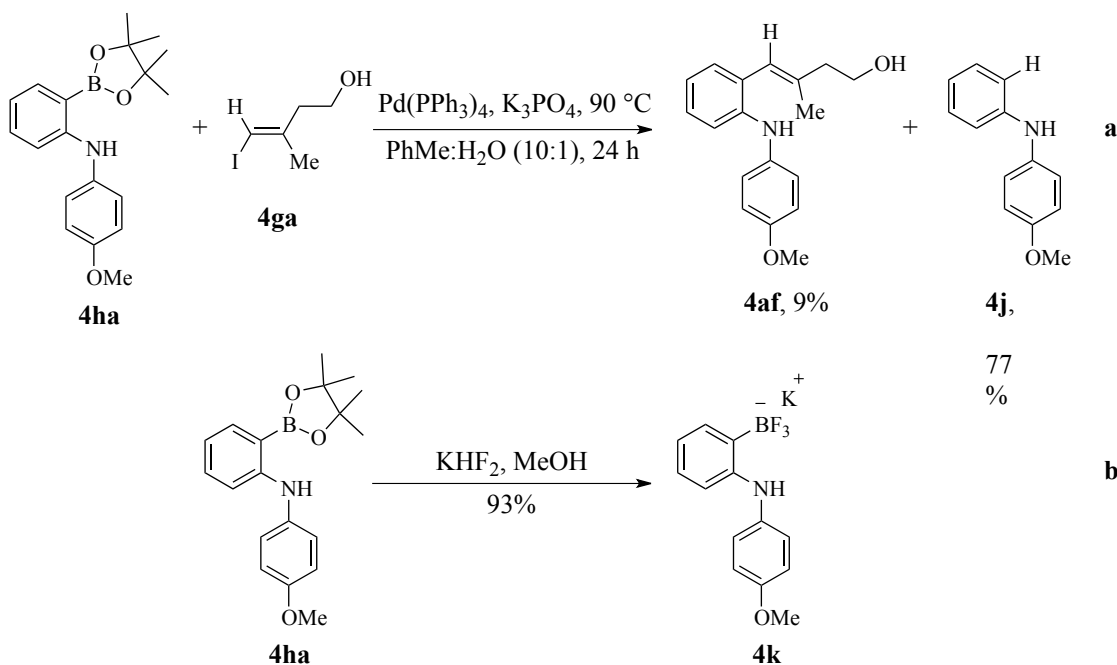
The second route involved a Miyaura borylation^{20,21} of substituted anilines followed by Buchwald–Hartwig amination⁶ of the synthesized aniline (containing an *ortho*-boronic ester) and an aryl halide (Scheme 4.11). Although both substrates participated in the Miyaura borylation, two different procedures were used depending on the substrate (eq. a and eq. b). The subsequent Buchwald–Hartwig amination proceeded as expected, yielding the desired boronic esters (**4h**).

Scheme 4.11. Alternative Route utilized to Synthesize Boronic Esters



The next step was to attempt the Suzuki–Miyaura coupling using arylboronic ester **4ha** and vinyl iodide **4ga**. Initial conditions using Pd(PPh₃)₄ in a degassed toluene/H₂O mixture (10:1) resulted in only 9% yield of the desired product **4af**, with the majority being the protodeboronation²² product **4j** (Scheme 4.12a). Since it quickly became obvious that the Suzuki–Miyaura coupling would not be trivial, some of boronic ester **4ha** was converted to the trifluoroborate salt **4k** using KHF₂,²³ since trifluoroborate salts often possess better reactivity (Scheme 4.12b).²⁴

Scheme 4.12. Initial Suzuki–Miyaura Cross Coupling Result and Conversion of Boronic Ester **4ha** to the Trifluoroborate Salt **4k**



Next, due to the poor results obtained from the initial examination, a colleague and coauthor, Theresa Nguyen, performed a Suzuki–Miyaura cross coupling reaction screen, shown in Table 4.1.

Table 4.1. Suzuki–Miyaura Cross Coupling Screen

<p> $\text{X} = \text{BF}_3\text{K}, \text{BPin}$ $\text{BPin} = \text{-(pinacolato)-B-}$ </p>						
Entry ^a	Pd catalyst	X	Ligand	Solvent	Yield 4af (%) ^b	Yield 4j (%) ^b
1	Pd(OAc) ₂	BF ₃ K	SPhos	PhMe:H ₂ O (10:1)	4	83
2	Pd(OAc) ₂	BF ₃ K	XPhos	PhMe:H ₂ O (10:1)	5	87
3	Pd(OAc) ₂	BF ₃ K	RuPhos	PhMe:H ₂ O (10:1)	5	79
4	Pd(PPh ₃) ₄	BF ₃ K	N/A	PhMe:H ₂ O (10:1)	8	51
5	(dppf)PdCl ₂ •DCM	BF ₃ K	N/A	PhMe:H ₂ O (10:1)	0	54
6	Pd(OAc) ₂	BPin	SPhos	PhMe:H ₂ O (10:1)	30	83
7	Pd(OAc) ₂	BPin	XPhos	PhMe:H ₂ O (10:1)	16	90
8	Pd(OAc) ₂	BPin	RuPhos	PhMe:H ₂ O (10:1)	55	58
9	Pd(PPh ₃) ₄	BPin	N/A	PhMe:H ₂ O (10:1)	9	77
10	(dppf)PdCl ₂ •DCM	BPin	N/A	PhMe:H ₂ O (10:1)	10	81
11	Pd(OAc) ₂	BPin	RuPhos	THF:H ₂ O (10:1)	83	9
12	Pd(OAc) ₂	BPin	RuPhos	THF:EtOH:H ₂ O (2:1:1)	95 (88) ^c	7
13	Pd(OAc) ₂	BPin	RuPhos	PhMe:EtOH:H ₂ O (2:1:1)	91	9
14	Pd(OAc) ₂	BPin	RuPhos	benzene:EtOH:H ₂ O (2:1:1)	87	8
15	Pd(OAc) ₂	BPin	RuPhos	EtOH:H ₂ O (1:1)	90	31

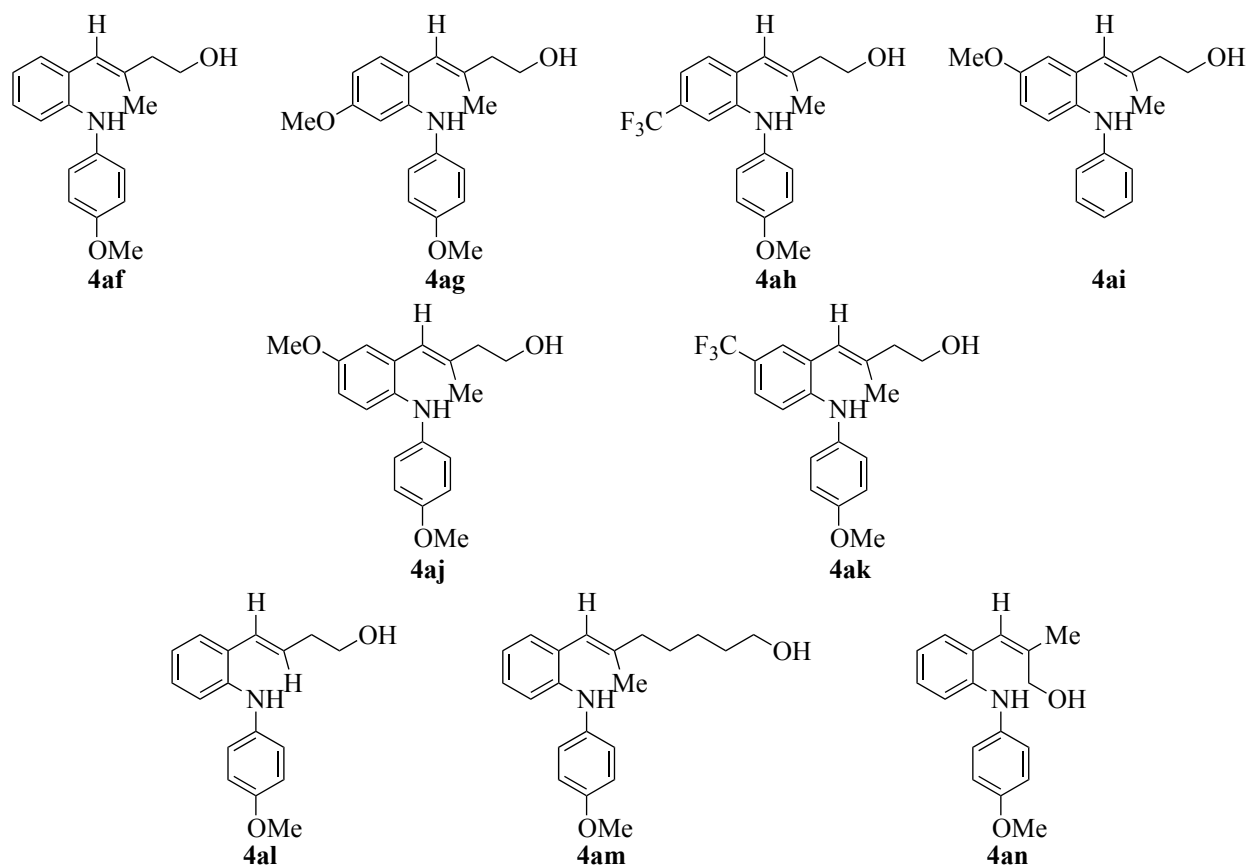
^aUsing 0.22 mmol vinyl iodide **4ga** (1 equiv), 0.33 mmol boronic ester **4ha** or trifluoroborate salt **4k** (1.5 equiv), 0.0044 mmol Pd catalyst (2 mol%), 0.0088 mmol ligand (4 mol%) and 0.66 mmol K₃PO₄ (3 equiv) in 0.44 mL solvent mixture. ^bGC yield using *n*-dodecane as an internal standard. ^cIsolated yield.

The reaction screen revealed that using Buchwald ligands with trifluoroborate salt **4k** yielded little to no product, as protodeboronation was the major reaction pathway (entries 1–3). Additionally, varying the palladium source did not improve the reaction using the trifluoroborate salt, although the amount of protodeboronation product **4j** was lessened (entries 4–5). Therefore,

further reaction screening utilized boronic ester **4ha** rather than the trifluoroborate salt. Using the Buchwald ligands in the 10:1 toluene:water mixture only yielded significant results using RuPhos, although protodeboronation existed as an equally competitive pathway (entries 6–8). As with the trifluoroborate salt, modifying the palladium source did not improve the reaction (entries 9–10). Next, a variety of solvent combinations were used in conjunction with RuPhos and Pd(OAc)₂, since moderate yields were obtained using this ligand in entry 8. Interestingly, the solvent combination played a significant role in suppressing the protodeboronation pathway, resulting in high Suzuki–Miyaura product **4af** yields (entries 11–15). The degassed triphasic THF:EtOH:H₂O (2:1:1) mixture presented the best results, yielding 95% GC yield and 88% isolated with only 7% protodeboronation product **4j** (entry 12). However, in all the solvent variation examples, higher yields were obtained than in the previous entries, revealing that the concentration of water plays a critical role in distinguishing the reaction pathway, as the latter examples have 25–50% water whereas the former examples contain ~10% water.

Having established optimal conditions for the Suzuki–Miyaura coupling, a variety of styrenyl anilines were synthesized using the vinyl iodides and boronic esters previously made. A summary of products generated is shown in Figure 4.3.

Figure 4.3. Hydroxyl-Based Substrates Synthesized using the Suzuki–Miyaura Approach

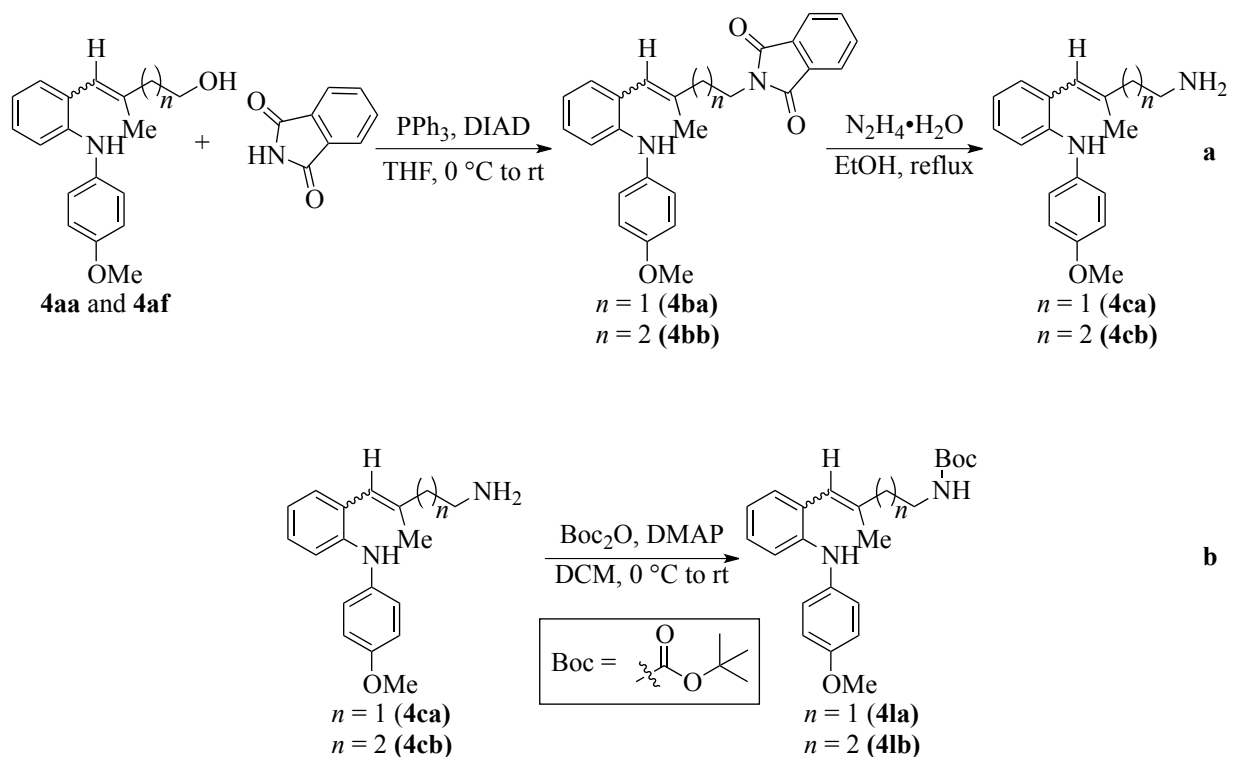


Gabriel Synthesis for Nitrogen-Based Styrenyl Anilines

In order to synthesize the starting materials needed to examine nitrogen-containing nucleophiles, a Gabriel synthesis⁷ was used to convert alcohols **4aa** and **4af** to the primary amine. The first step was to perform a Mitsunobu reaction using phthalimide as the nucleophile, generating the corresponding –NH₂ synthons **4ba** and **4bb**. The second step was phthalimide cleavage using the Ing–Manske hydrazinolysis,²⁵ generating the corresponding free amines **4ca** and **4cb** (Scheme 4.13, eq. 1). It is of note that, since it was hypothesized that the basic nature of

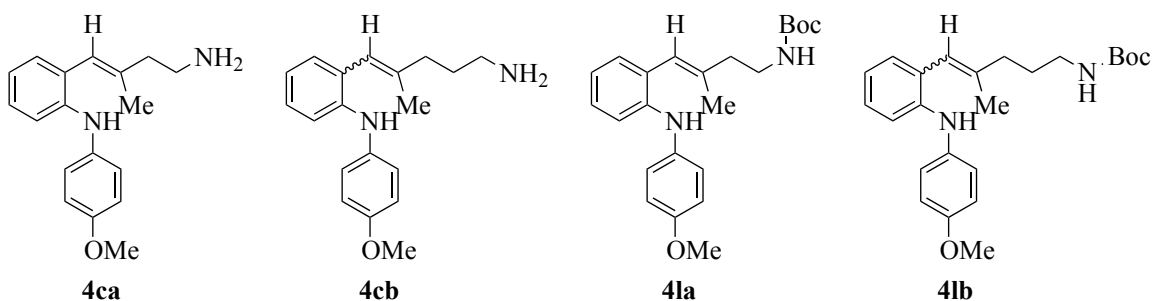
free amine nucleophile may interfere with the photochemistry, some of both **4ca** and **4cb** was converted to the Boc-protected carbamates **4la** and **4lb** for further studies (eq. 2).

Scheme 4.13. Gabriel Synthesis to Generate Primary Amines **4c** and Subsequent Boc Protection



The synthesis of both the primary amine and the Boc-protected amine proceeded as expected, generating various nitrogen-containing precursors to be tested in the photoredox-catalyzed synthesis of C2,C3 fused indolines. The substrates generated for potential use in the photochemical reaction are shown in Figure 4.4.

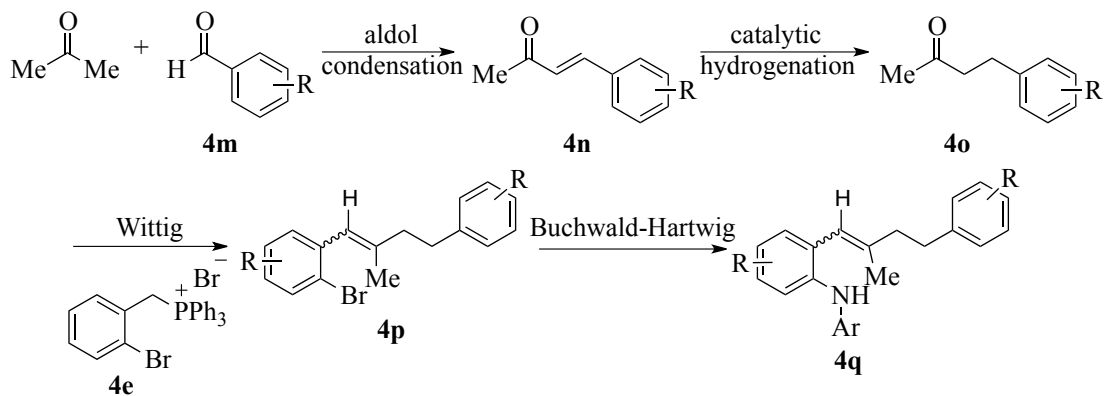
Figure 4.4. Nitrogen-Based Substrates Synthesized using the Gabriel Synthesis



Aryl-Based Styrenyl Aniline Synthesis

In order to investigate aryl nucleophiles in the photochemical reaction, a Wittig reaction approach seemed to be the most plausible, which is depicted in Scheme 4.14.

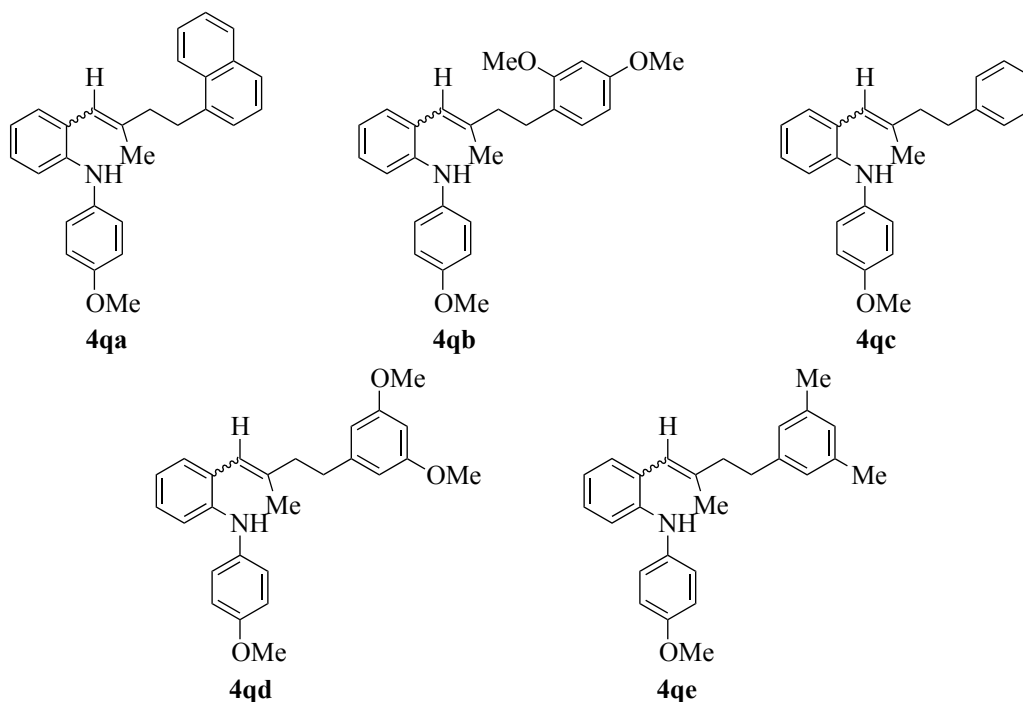
Scheme 4.14. Generation of Styrenyl Anilines Bearing Aryl-Containing Tethers



The sequence commenced with an aldol condensation of various substituted benzaldehydes (**4m**) with acetone to yield enones **4n** (90–96%).²⁶ Successive catalytic hydrogenation, yielding saturated ketones **4o** (60–92%), and Wittig reaction using ylide salt **4e** provided *ortho*-bromo styrenes **4p** as a mixture of *E:Z* isomers, albeit low to moderate yields (40–60%).⁶ The styrenes were then converted to styrenyl anilines **4q** using the Buchwald–Hartwig amination (76–94%),

which served as the starting material for the examination of fused indoline formation using aryl nucleophiles.⁶ The substrates generated using this forward synthesis are shown in Figure 4.5.

Figure 4.5. Aryl-Based Styrenyl Aniline Substrates Synthesized using the Wittig Approach

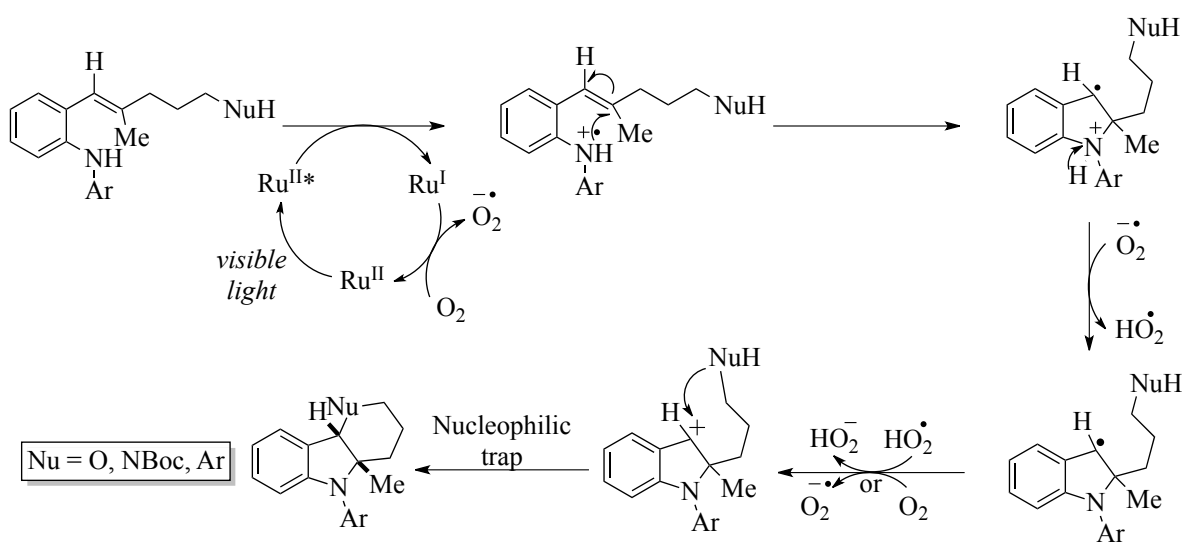


This method proved to be effective in generating a variety of styrenes tethered with oxygen and aryl nucleophiles for the examination of the proposed visible light photoredox cascade, albeit as a mixture of *E:Z* isomers, which ultimately proved to be inconsequential in undergoing the desired transformation. The synthesis of these substrates marked the conclusion of the substrate synthesis for the formation of C2, C3 fused indolines using visible light photoredox catalysis.

4.2. Visible Light Photoredox Catalysis of Tethered Styrenyl Anilines

As stated in Section 3.2.2. in Chapter 3, it was hypothesized that styrenyl anilines bearing a nucleophilic tether could effectively trap an intermediate benzylic cation formed in a C–N bond forming cascade initiated by visible light. The proposed mechanism is shown in Scheme 4.15.

Scheme 4.15. Proposed Mechanism for the Synthesis of C2,C3 Fused Indolines using Visible Light Photoredox Catalysis



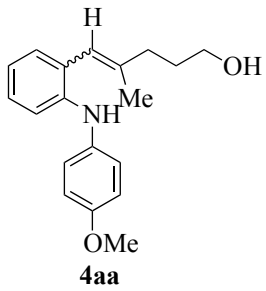
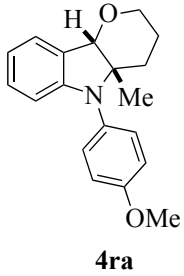
Using Zheng's previous proposed catalytic cycle,⁶ the tethered styrenyl aniline would be oxidized by the excited triplet state of the photoredox catalyst, generating the corresponding amine radical cation and the reduced photoredox catalyst. The photoredox catalyst would then be oxidized back to its ground state by oxygen, which in turn would be reduced to the superoxide anion. Meanwhile, the amine radical cation would electrophilically add to the styrene, forming the ammonium cation substrate containing a benzylic radical. Upon deprotonation with superoxide anion, the corresponding indoline containing a benzylic radical would form along with the hydroperoxide radical. Further oxidation by the hydroperoxide radical or molecular

oxygen would supply the intermediate benzylic cation, which could potentially be trapped by the tethered nucleophile to generate the C2, C3 fused indoline.

Visible Light Photochemistry Reaction Screen

Once the requisite substrates were synthesized, that is, those that were anticipated to participate in the C–N bond forming cascade initiated by visible light, substrate **4aa** was screened in order to discover the optimal reaction conditions, which is shown in Table 4.2. It is of note that the geometry of the alkene had no effect on the diastereoselectivity of the final product **4ra**, which exhibited >99:1 dr.

Table 4.2. Photochemistry Screen

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;">  <p>4aa</p> </div> <div style="text-align: center;"> $\xrightarrow[\text{18 W focused white LED, 8 hours}]{\text{catalyst, solvent (1.5 mL), HOAc (1 equiv)}}$ </div> <div style="text-align: center;">  <p>4ra</p> </div> </div>						
Entry	Catalyst	Solvent	Cat. Loading	Changes	Conversion ^b	GC Yield ^b
1	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	————	100%	78%
2	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	————	91%	43%
3	Ir(ppy) ₂ (dtb-bpy)(PF ₆)	CH ₃ CN	4 mol%	————	59%	35%
4	acridinium salt ^c	CH ₃ CN	4 mol%	————	6%	4%
5	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ NO ₂	4 mol%	————	100%	14%
6	Ru(bpy) ₃ (PF ₆) ₂	DMSO	4 mol%	————	96%	33%
7	Ru(bpy) ₃ (PF ₆) ₂	DMF	4 mol%	————	94%	11%
8	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	no light	0%	0%
9	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	no catalyst	0%	0%
10	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	no acid	70%	37%
11	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	TFA, not HOAc	96%	13%
12	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	degassed/N ₂	17%	11%
13	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	degassed/O ₂	100%	39%
14	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	4 mol%	1 equiv TEMPO added	100%	76%
15	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	2 mol%	————	100%	80% (73%) ^d
16	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	2 mol%	0.2 mmol scale	100%	78% (73%) ^d

^aUsing 0.1 mmol of styrenyl aniline **4aa** (1 equiv), photoredox catalyst, acetic acid (1 equiv), and 1.5 mL solvent in a test tube sealed by a screw cap with a Teflon septum pierced with a 16-gauge disposable needle. The contents were then stirred at a 6 cm distance from an 18W focused white LED for 8 hours.

^bDetermined using *n*-dodecane as an internal standard. ^c9-Mesityl-10-methylacridinium perchlorate.

^dIsolated yield.

Starting with conditions similar to those described in Zheng's previous report,⁶ various photoredox catalysts were examined, which revealed Ru(bpy)₃(PF₆)₂ as the best catalyst for this

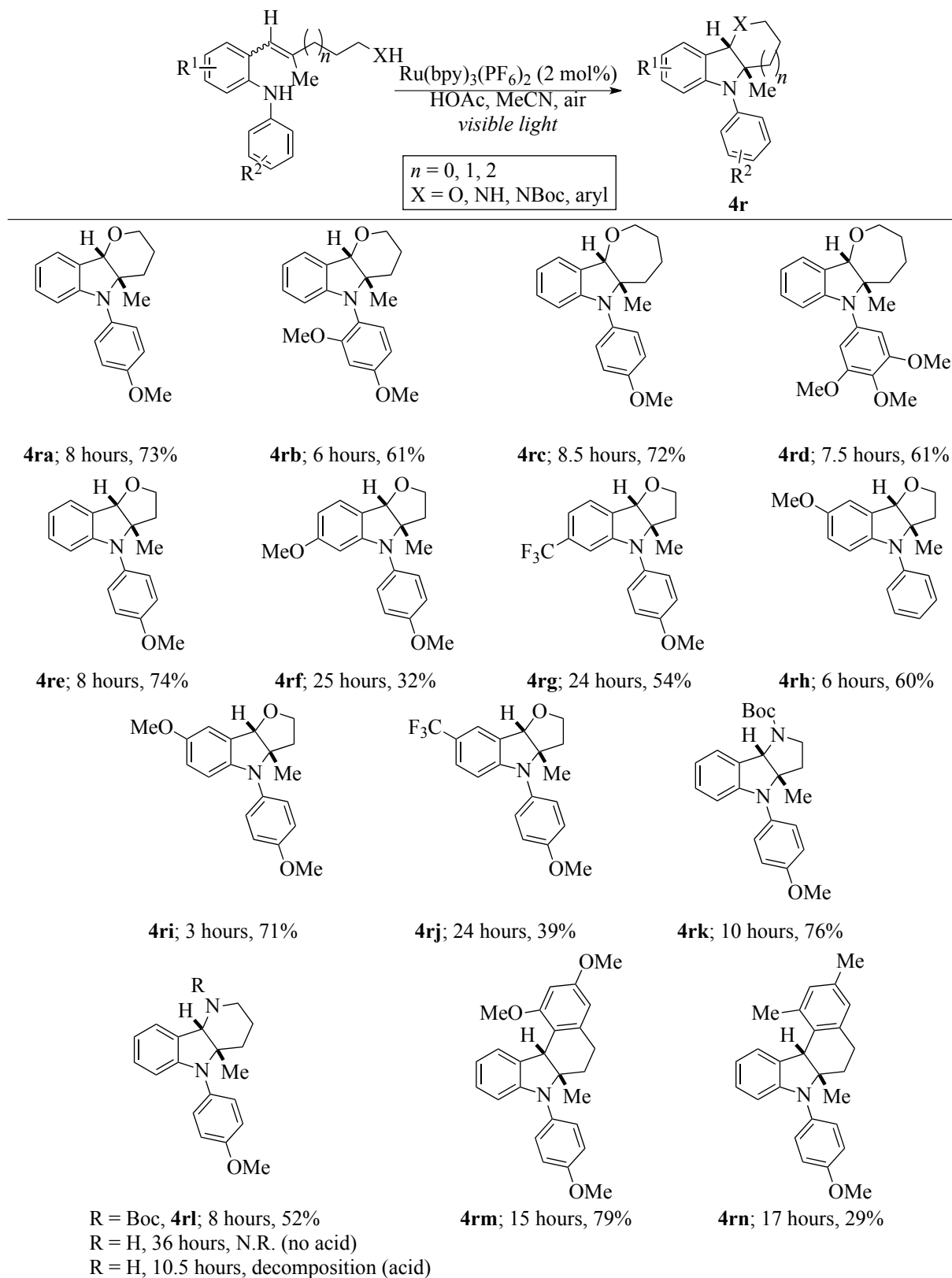
transformation (entries 1–4). Various solvents were then examined, all of which gave results inferior to acetonitrile (entries 5–7). Next, control experiments were performed to ensure that the transformation was governed by visible light photoredox catalysis. Indeed, in the absence of light or the photoredox catalyst, no reaction occurred (entries 8 and 9). In their previous report, Zheng discussed the need for an acid source for this type of cascade process to occur. In their report, silica gel functioned best for the indole synthesis, concluding its role was to act as a weak acid while also adsorbing oxygen.⁶ Interestingly, they revealed that acetic acid also achieved the desired transformation, albeit less efficient. It was hypothesized, however, that for the purposes of this chemistry, acetic acid could serve the role as a weak proton source. Additionally, utilizing acetic acid could circumvent the need to add one equivalent of silica gel, which complicates the reaction system by incorporating insoluble material. Applying this hypothesis, acetic acid proved to be effective in achieving the desired transformation (entries 1; 15–16). Surprisingly, the reaction proceeded in the absence of acetic acid, although with less efficiency (entry 10). Using a stronger acid, namely trifluoroacetic acid, resulted in decomposition, thus revealing the delicate range of pK_a values for a successful transformation (entry 11). Degassing the reaction mixture and backfilling with nitrogen resulted in both low conversion and yield, agreeing with the presumption that oxygen completes the photoredox catalyst's catalytic cycle (entry 12). When degassing the reaction mixture and backfilling with oxygen, complete conversion occurs, albeit in decreased yields (entry 13). This suggests that higher concentrations of O_2 result in greater decomposition. TEMPO was then added to the reaction mixture in an attempt to trap the radical intermediate; however, the TEMPO did not react with any intermediates, presumably due to the short-lived nature of the radicals formed in this cascade reaction (entry 14). Lastly, the reaction was performed using 2 mol% catalyst, which provided nearly identical results to the conditions

using 4 mol% catalyst (entry 1 vs. 15); therefore, the conditions using the lower catalyst loading was selected as the standard reaction conditions (entry 15). Having established optimal conditions, the reaction was ran using a 0.2 mmol scale, which provided the desired product **4ra** in 73% isolated yield (entry 16).

Substrate Scope

Attention was then directed towards generating a substrate scope for this transformation. A summary of the products successfully obtained using hydroxyl, nitrogen-based, and aryl nucleophiles are shown in Scheme 4.16.

Scheme 4.16. Substrate Scope

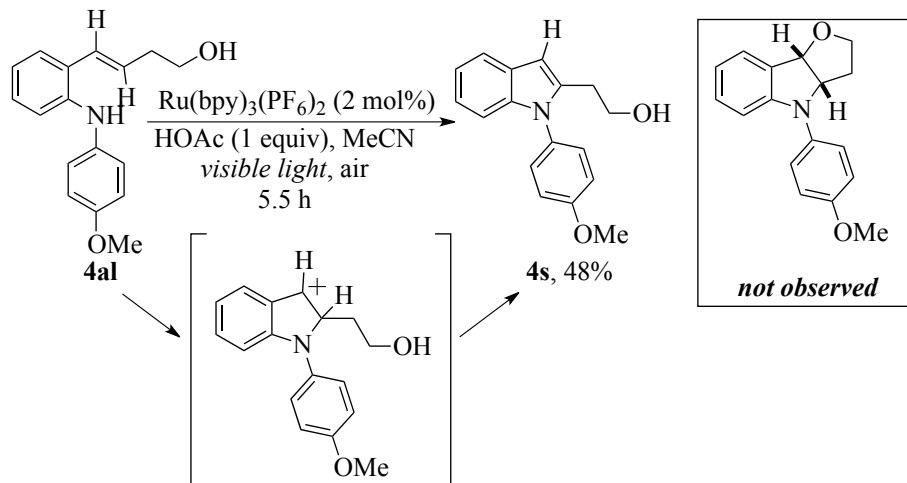


When modifying the alkyl tether length, the corresponding 5-, 6-, and 7-membered rings were generated as expected in good yields when using a *para*-methoxyphenyl group (72–74%; **4ra**, **4rc**, and **4re**). Additionally, modifying the *para*-methoxyphenyl group to the 2,4-dimethoxyphenyl (**4rb**) and the 3,4,5-trimethoxyphenyl (**4rd**) analogues proceeded in decreased yields and slightly higher rates (6–7.5 hours; 61% for both). This observation demonstrated the ability to modify the aryl ring in various substitution patterns so long as the *para*-alkoxy functionality remains present. Interestingly, using the 2,4-dimethoxyphenyl group yielded the product as a 1:1 mixture of rotamers while still yielding the product as a single diastereomer, which was confirmed using 2D NMR experiments. Changing the electronic character around the indoline ring yielded various results. For instance, when both the methoxy and trifluoromethyl groups are *meta* to the nitrogen, the reaction was both slow and low-yielding (~25 hours; 32% for **4rf** and 54% for **4rg**). When positioning a methoxy group on the indoline ring *para* to the nitrogen while changing the *para*-methoxyphenyl group to a simple phenyl group, the desired reaction proceeded in just 6 hours, yielding 60% of **4rh**. However, when comparing the substrates possessing a methoxy *para* to the nitrogen, the reaction rate and yield was increased (3 hours, 71%; **4ri**). When a trifluoromethyl group was positioned *para* to the nitrogen, the reaction was sluggish and the yield decreased (24 hours, 39%; **4rj**). This observation was expected, as it was previously known that the oxidation of styrenyl anilines using visible light photoredox catalysis is facile with electron-rich substrates. Next, nitrogen-based nucleophiles were examined. The reaction proceeded as expected with using the carbamate analogues (i.e. Boc-protected amines; **4rk** and **4rl**) but failed to proceed when using the free amine (**4cb**). It was hypothesized that this result could be due to pK_a issues regarding the free amine and acetic acid. Therefore, the reaction was also attempted in the absence of the proton source, which, for

unknown reasons, did not react after 36 hours. It is worth noting that facile cleavage of the Boc group was performed using trifluoroacetic acid, yielding the secondary amine in moderate yields (28–41%; see experimental section for more details). Lastly, electron-rich aryl nucleophiles were examined in hopes they would participate in a Friedel–Crafts manner. Indeed, when using a strong activator (3,5-dimethoxyphenyl; **4rm**) and a weak activator (3,5-dimethyl; **4rn**), the reaction proceeded with minimal complications. However, it was hypothesized that the low yield of the 3,5-dimethylphenyl substrate was likely due to a competing pathway, likely forming an indole by way of 1,2-alkyl shift that was unable to be characterized due to its innate instability.

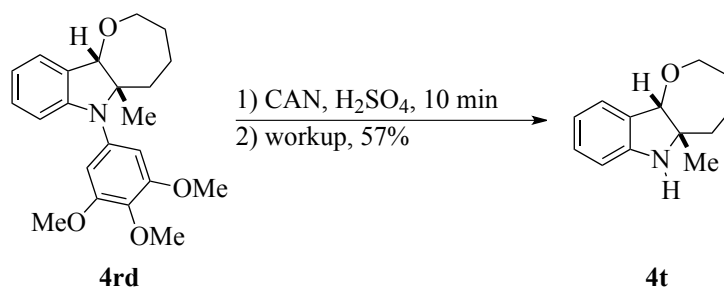
Next, it was wondered if the reaction would proceed if the methyl group on the styrene's olefin were replaced with a hydrogen atom. Essentially, this would probe the competition between the desired S_N1 pathway where the nucleophile traps the intermediate benzylic cation versus the undesired E1 pathway in which deprotonation would form the corresponding monosubstituted indole. When subjecting the substrate **4al** to the optimized reaction conditions, the monosubstituted indole **4s** was the sole product formed in the transformation (Scheme 4.17). Therefore, it is necessary to incorporate an alkyl group in the indole's C2 position in order to shut down the competing E1 pathway.

Scheme 4.17. E1 vs. S_N1 Examination



Lastly, in order to further increase the overall impact of this chemistry, the *para*-alkoxyphenyl group was removed (Scheme 4.18). This was achieved by subjecting photochemistry adduct **4rd** to CAN oxidative cleavage conditions for 10 minutes. Upon workup, the desired secondary amine **4t** was isolated in 57%.

Scheme 4.18. CAN Oxidative Cleavage of *para*-Alkoxyphenyl Group



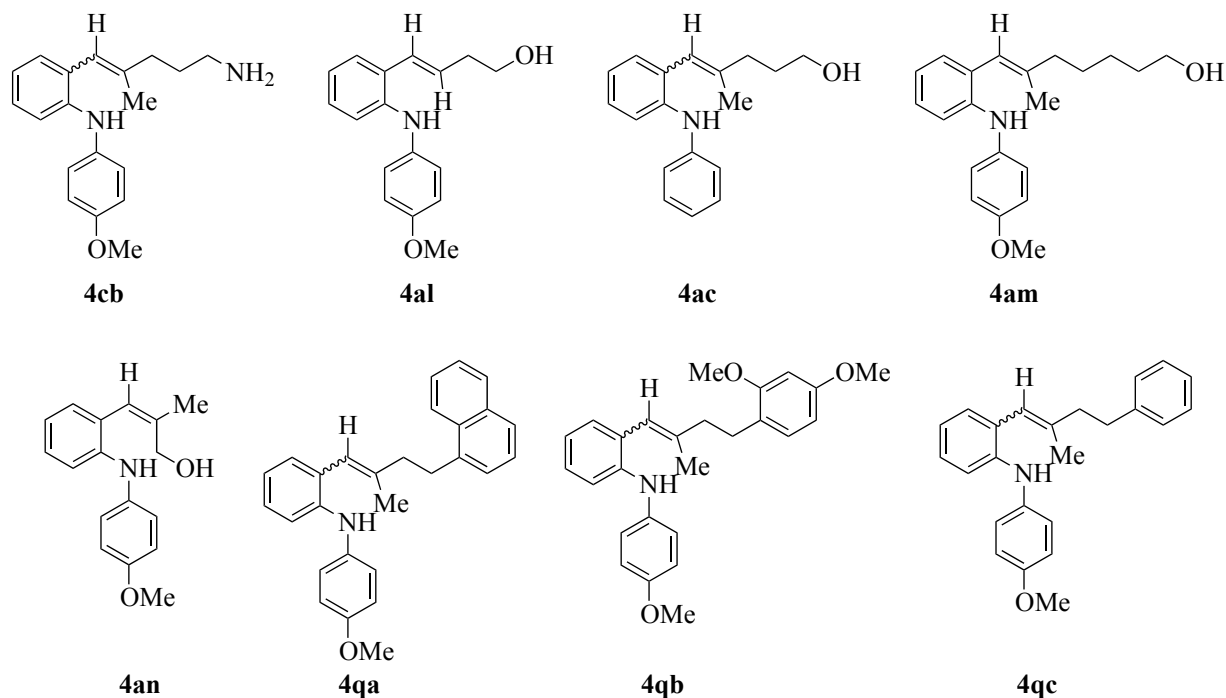
In summary, 14 substrates successfully underwent the proposed C–N bond forming cascade to provide the desired C2, C3 fused indolines in moderate to good yields as a single diastereomer. Modification of the alkyl chain length on the nucleophilic tether, *N*-aryl group,

nucleophile, and electronic character were all examined. The corresponding 5-, 6- and 7-membered ring fusions were all synthesized. Various electron-rich substitutions on the *N*-aryl component were incorporated as long as a *para*-alkoxy group was present. Hydroxyl, carbamate, and electron-rich aryl functionalities all accomplished the transformation ranging from 3 to 25 hours. The electronic character around the indoline ring played a distinct role in the reaction rate and the corresponding isolated yields. There is a need to form a quaternary carbon α to the nitrogen, as the reaction proceeds through a faster E1 pathway to generate the corresponding indole if a hydrogen atom is present. Lastly, the *N*-aryl group was successfully cleaved using CAN and sulfuric acid, effectively increasing the scope and impact of this transformation. The majority of this work was published in *Advanced Synthesis and Catalysis* in July 2015.²⁷

Unsuccessful Substrates

Throughout the course of this investigation, many substrates did not participate in the visible-light-mediated oxidative C–N bond forming cascade, including various hetero- and aryl nucleophiles. Those examples are depicted in Figure 4.6.

Figure 4.6. Unsuccessful Substrates



As previously discussed, free amine **4cb** and styrenyl anilines bearing a disubstituted olefin (**4al**) failed to give the desired fused indoline adduct. Additionally, the photochemical reaction did not proceed in the absence of a *para*-methoxyphenyl group,⁶ yielding only starting material after 36 hours (**4ac**). It was also discovered that alkyl chain lengths on the nucleophilic tether are limited to having 2–4 methylene groups, as both the 5-methylene group and the 1-methylene group counterparts (**4am** and **4an**, respectively) gave a complex mixture of unidentified products rather than the 8- and 4-member ring fusion adducts. Next, less electron-rich aryl groups were examined. Since the 3,5-dimethyl counterpart proceeded in poor yields (29%) with an unknown byproduct, it was assumed that any aryl groups without activating substituents would not undergo the desired transformation. Indeed, the naphthyl (**4qa**), 2,4-dimethoxyphenyl (**4qb**), and phenyl (**4qc**) nucleophiles were inadequate for this chemistry, each providing an unknown product that decomposed upon column chromatography. It is likely that,

since the aryl nucleophiles were not reactive enough to trap the benzylic cation, a 1,2-alkyl shift occurred, providing the corresponding 2,3-disubstituted indole.^{6,28,29}

To summarize, 8 substrates were synthesized and proved to be inadequate for the desired transformation. Additionally, 5 other substrates failed in this transformation, which are discussed briefly in Appendix A. Although there is compelling hypotheses and literature precedence as to why many of the substrates failed to react, further studies need to be performed to fully understand the reactivity of the photogenerated benzylic cation. Substrates that failed to participate in the photoredox cascade reaction included: free amine nucleophiles, *E* or *Z* disubstituted olefins on the styrene, substrates lacking a *para*-methoxyphenyl group on the nitrogen, precursors that would give rise to the 8- and 4-membered ring fusions (1 and 5 methylenes), and weakly activated or deactivated aryl groups.

4.3. Experimental Procedures

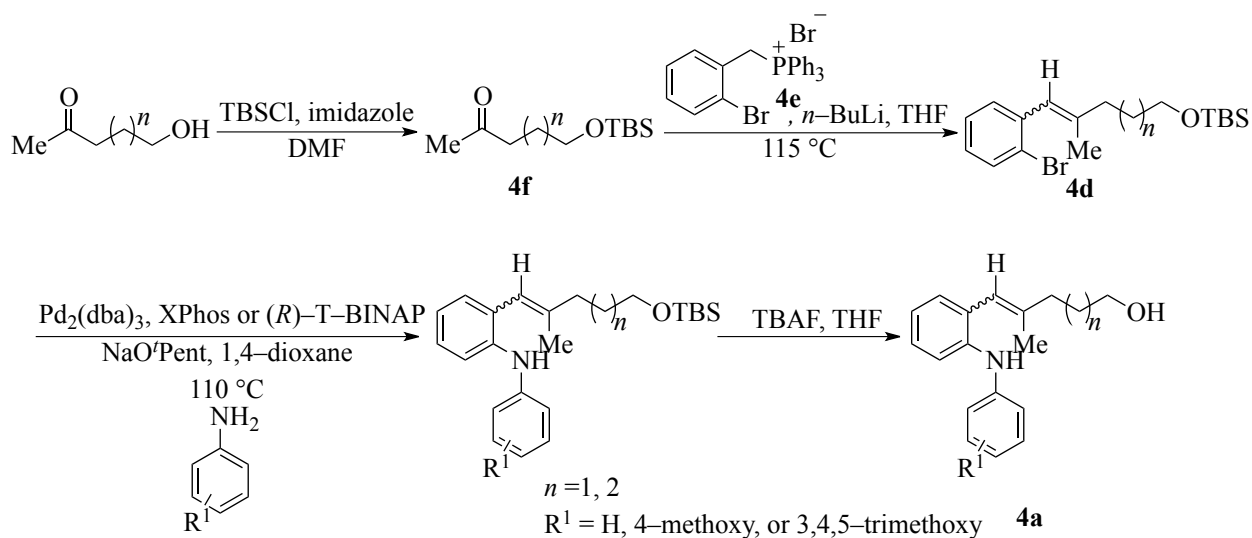
General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. Acetonitrile (CH₃CN) was pre-dried over molecular sieves. Toluene and THF were collected under argon from a solvent purification system. 1,4-Dioxane was dried over activated molecular sieves (8–12 mesh) prior to use. Column chromatography was performed using silica gel (230–400 mesh) or neutral alumina gel flash grade 32–63u. All new compounds were characterized by ¹H NMR, ¹³C NMR, high-resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), melting point (when applicable), and (in most cases) IR spectroscopy. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to

residual proton or carbon signals in CDCl_3 (7.27 ppm, 77.23 ppm), CD_2Cl_2 (5.32 ppm, 54.0 ppm), and $\text{DMSO}-d_6$ (2.50 ppm, 39.51 ppm) at room temperature. 2D NMR experiments were performed on some of the new compounds to establish their structure, including relative configuration. Diastereomeric ratios were determined using ^1H NMR of crude products. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on either a Bruker Ultraflex II TOF/TOF mass spectrometer or a Bruker Apex-Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas chromatography analyses were performed using a Shimadzu GC-2010 Plus instrument. When applicable, melting point ranges (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

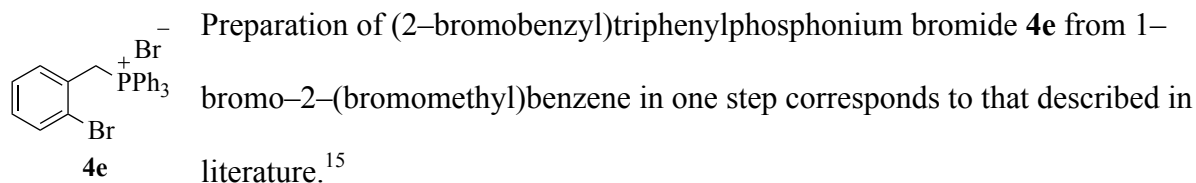
Procedures for the Synthesis of Styrenyl Aniline Precursors using the Wittig Reaction

Scheme 4.19. Forward Synthesis of Styrenyl Anilines using Wittig Approach

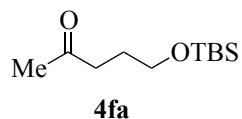


TBSCl = *tert*-Butyldimethylsilyl chloride
 XPhos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
 (R)-T-BINAP = (R)-(+)-2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
 TBAF = tetra-*n*-butylammonium fluoride

Preparation of (2-bromobenzyl)triphenylphosphonium Bromide 4e



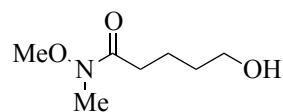
Preparation of 5-(*tert*-butyldimethylsilyloxy)pentan-2-one **4fa**



literature.¹¹

Preparation of 5-(*tert*-butyldimethylsilyloxy)pentan-2-one **4fa** from 5-hydroxypentan-2-one in one step corresponds to that described in

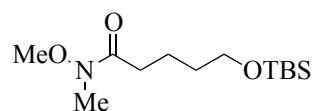
Preparation of 5-hydroxy-*N*-methoxy-*N*-methylpentanamide



described in literature.¹²

Preparation and characterization of 5-hydroxy-*N*-methoxy-*N*-methylpentanamide from valerolactone in one step corresponds to that

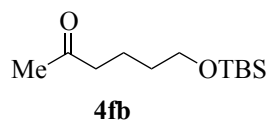
Preparation of 5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylpentanamide



methylpentanamide in one step corresponds to that described in literature.¹²

Preparation¹³ and characterization of 5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylpentanamide from 5-hydroxy-*N*-methoxy-*N*-

Preparation of 6-(*tert*-butyldimethylsilyloxy)hexan-2-one **4fb**

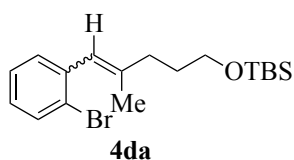


Synthesis of 6-(*tert*-butyldimethylsilyloxy)hexan-2-one **4fb** was achieved from 5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-

methylpentanamide using a method described literature.¹⁴ Characterization of 6-(*tert*-butyldimethylsilyloxy)hexan-2-one correspond to those described in literature.³⁰

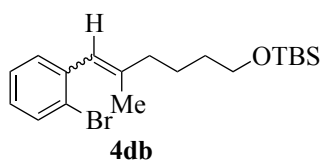
General Procedure 4A (GP4A): Preparation of (*E/Z*)-Styrenyl Compounds **4da** and **4db** using the Wittig Reaction

Preparation of **4da** and **4db** were accomplished using a literature procedure.⁶ To an oven-dried heavy wall pressure vessel equipped with a stir bar were added 1 equivalent of (2-bromobenzyl)triphenylphosphonium bromide **4e** and anhydrous THF (0.3 M) under N₂ atmosphere. The reaction vessel was brought to 0 °C and 1 equivalent of *n*-BuLi (1.5 M in hexanes) was added dropwise over 30 minutes. The contents were then stirred for 1 hour at 0 °C prior to the dropwise addition of silyl-protected ketone **4fa** or **4fb**. The contents were then stirred at 0 °C for 15 minutes, then warmed to room temperature to stir for an additional 10 minutes. The reaction vessel was then heated to 115 °C and stirred for 18 hours. Once complete, the mixture was cooled to room temperature prior to the addition of 1 equivalent of acetic acid. The resulting solution was then filtered through a pad of silica gel saturated with hexanes. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel to afford the corresponding isomeric styrenyl aniline compound as a 1:1 mixture of inseparable *E/Z* isomers.



Following procedure **GP4A** with 5-(*tert*-butyldimethylsilyloxy)pentan-2-one **4fa** (1 equiv, 4.5 mmol, 971.6 mg), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 4.5 mmol, 2.3

g), *n*-BuLi (1 equiv, 4.5 mmol, 3 mL) in 15 mL THF. Purification by flash chromatography on silica gel (99:1 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-(5-(2-bromophenyl)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane **4da** as a clear oil (1.66 g, 65%). IR ν_{\max} (cm⁻¹) 3069, 2958, 2858, 1650, 1467, 1432, 1259, 1104, 949, 845, 779. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.54 (m, 2H), 7.33 – 7.26 (m, 1H), 7.26 – 7.22 (m, 3H), 7.11 – 7.04 (m, 2H), 6.27 (pd, *J* = 1.3, 0.9 Hz, 1H), 6.25 (tt, *J* = 1.5, 0.8 Hz, 1H), 3.71 (t, *J* = 6.6 Hz, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.33 – 2.22 (m, 2H), 2.21 – 2.12 (m, 2H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.86 – 1.76 (m, 2H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.72 – 1.62 (m, 2H), 0.94 (s, 9H), 0.87 (s, 8H), 0.09 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 140.25, 140.16, 138.84, 138.76, 132.59, 131.14, 130.94, 127.91, 127.85, 127.06, 126.94, 125.60, 124.80, 124.48, 63.19, 62.99, 36.20, 31.41, 31.24, 29.20, 26.22, 26.15, 23.59, 18.60, 18.50, 17.93, -4.99, -5.09; GC/MS (CI) *m/z* [M+H]⁺ for C₁₈H₂₉BrOSi found 369.

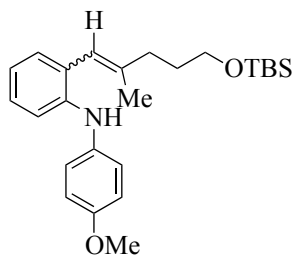


Following procedure **GP4A** with 6-(*tert*-butyldimethylsilyloxy)hexan-2-one **4fb** (1 equiv, 3.04 mmol, 701.5 mg), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 3.04 mmol, 1.55 g), *n*-BuLi (1 equiv, 3.04 mmol, 2.02 mL) in 10 mL THF. Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-(6-(2-bromophenyl)-5-methylhex-5-enyloxy)(*tert*-butyl)dimethylsilane **4db** as a clear liquid (423 mg, 36%). IR ν_{\max} (cm⁻¹) 2940, 2853, 1486, 1434, 1386, 1253, 1101, 838, 780, 665. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.57 (m, 1H), 7.56 (dt, *J* = 2.4, 0.6 Hz, 1H), 7.28 – 7.18 (m, 4H), 7.11 – 7.04 (m, 2H), 6.27 (q, *J* = 1.3 Hz, 1H), 6.25 – 6.21 (m, 1H),

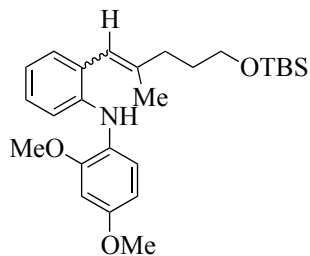
3.74 – 3.63 (m, 2H), 3.55 (t, J = 6.0 Hz, 2H), 2.24 (ddt, J = 7.0, 4.8, 2.1 Hz, 2H), 2.16 – 2.07 (m, 1H), 1.92 (d, J = 1.5 Hz, 2H), 1.88 (dd, J = 10.3, 1.4 Hz, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.64 – 1.56 (m, 4H), 1.56 – 1.41 (m, 3H), 0.93 (d, J = 0.6 Hz, 9H), 0.90 (d, J = 0.6 Hz, 8H), 0.08 (d, J = 0.6 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 140.60, 140.48, 138.92, 132.59, 131.17, 130.98, 128.26, 128.20, 127.91, 127.82, 127.01, 125.98, 125.55, 124.81, 124.53, 124.50, 63.28, 62.94, 39.74, 32.69, 32.58, 32.29, 26.22, 26.20, 24.23, 24.20, 23.39, 18.61, 18.55, 17.76, –5.05, –5.07; GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{19}\text{H}_{31}\text{BrOSi}$ found 385.

General Procedure 4B (GP4B): Preparation of *N*-Arylanilines using the Buchwald–Hartwig Amination

Preparation of *N*-arylanilines was accomplished using a literature procedure.⁶ To an oven-dried Schlenk flask equipped with a stir bar was added 0.5–8 mol% $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$ and 1.5–12 mol% ligand. Glove box was used to add 1.5–2 equivalents of NaO^tPent and the tube was sealed. 1 equivalent of aromatic halide **4da** or **4db**, 1.2–1.5 equivalents of aniline or aniline analogue, and anhydrous 1,4-dioxane or toluene (0.5–0.8 M) were then added to the reaction mixture and heated at 110 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel afforded the corresponding *N*-arylaniline.

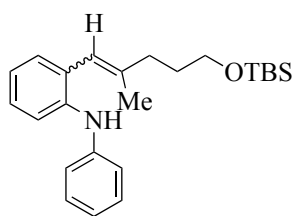


Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 4.22 mmol, 520 mg), (*E/Z*)-(5-(2-bromophenyl)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane **4da** (1 equiv, 3.52 mmol, 1.3 g), Pd₂(dba)₃ (0.75 mol%, 0.0264 mmol, 24 mg), XPhos (2.25 mol%, 0.08 mmol, 38 mg) and NaO^tPent (1.5 equiv, 5.3 mmol, 581 mg) in 1,4-dioxane (10 mL). Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-*N*-(4-methoxyphenyl)aniline as a yellow oil (1.22 g, 84%). IR ν_{max} (cm⁻¹) 3411, 2952, 1581, 1515, 1460, 1294, 1252, 1101, 838, 745. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.08 (m, 5H), 7.08 – 7.06 (m, 3H), 7.04 (td, *J* = 5.8, 2.4 Hz, 2H), 6.88 (dd, *J* = 2.3, 1.4 Hz, 2H), 6.87 (dd, *J* = 2.3, 1.3 Hz, 2H), 6.84 – 6.76 (m, 2H), 6.17 (s, 1H), 6.14 (s, 1H), 5.46 (s, 2H), 3.82 (s, 6H), 3.70 (t, *J* = 6.5 Hz, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.32 – 2.25 (m, 2H), 2.21 – 2.13 (m, 2H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.83 – 1.77 (m, 2H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.71 – 1.63 (m, 2H), 0.93 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 155.46, 143.05, 142.23, 141.86, 136.03, 130.49, 130.30, 127.51, 126.11, 126.00, 122.90, 122.83, 121.63, 120.87, 118.97, 118.91, 114.81, 113.84, 113.71, 63.35, 62.96, 55.78, 36.19, 31.65, 31.48, 29.48, 26.20, 26.15, 23.54, 18.59, 18.51, 17.98, -5.01, -5.08; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₅H₃₇NO₂Si 412.2666; found 412.2677.



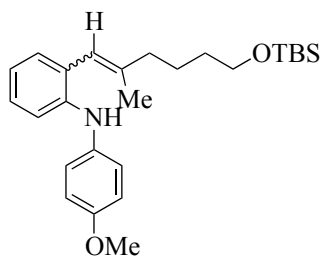
Following procedure **GP4B** with 2,4-dimethoxyaniline (1.2 equiv, 0.25 mmol, 38.3 mg), (*E/Z*)-(5-(2-bromophenyl)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane **4da** (1 equiv, 0.21 mmol, 77 mg), Pd₂(dba)₃ (0.75 mol%, 0.0016 mmol, 1.5 mg), (*R*)-T-BINAP (2.25

mol%, 0.0047 mmol, 3.2 mg) and NaO^tPent (1.5 equiv, 0.314 mmol, 35 mg) in 1,4-dioxane (1 mL). Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-*N*-(2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)phenyl)-2,4-dimethoxyaniline as a yellow oil (89 mg, 95%). IR ν_{max} (cm⁻¹) 3421, 2928, 2855, 1601, 1518, 1453, 1282, 1207, 835, 776. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.21 (dd, *J* = 8.6, 6.3 Hz, 2H), 7.15 (td, *J* = 8.4, 1.5 Hz, 2H), 7.12 – 7.05 (m, 4H), 6.87 – 6.77 (m, 2H), 6.53 (s, 1H), 6.53 (s, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 6.43 (d, *J* = 2.7 Hz, 1H), 6.18 (s, 1H), 6.16 (s, 1H), 3.83 (s, 3H), 3.82 (s, 2H), 3.81 (s, 5H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.54 (t, *J* = 6.7 Hz, 1H), 2.30 – 2.22 (m, 2H), 2.19 – 2.10 (m, 1H), 1.93 (d, *J* = 1.5 Hz, 2H), 1.83 – 1.75 (m, 2H), 1.75 – 1.72 (m, 3H), 0.91 (d, *J* = 0.4 Hz, 9H), 0.86 (d, *J* = 0.4 Hz, 6H), 0.07 (d, *J* = 0.4 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 155.25, 155.11, 151.53, 151.33, 142.53, 142.33, 141.77, 141.55, 130.41, 130.24, 127.36, 127.33, 127.12, 126.03, 121.80, 121.04, 119.79, 119.20, 119.14, 114.45, 114.26, 103.89, 103.84, 99.63, 99.60, 63.38, 63.03, 55.81, 36.19, 31.63, 29.41, 26.16, 26.13, 23.51, 18.54, 18.48, 17.96, -5.04, -5.11; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₆H₃₉NO₃Si 442.2772; found 442.2768.



Following procedure **GP4B** with aniline (1.2 equiv, 0.65 mmol, 60.5 mg), (*E/Z*)-(5-(2-bromophenyl)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane **4da** (1 equiv, 0.54 mmol, 200 mg), Pd₂(dba)₃ (0.75 mol%, 0.004 mmol, 3.7 mg), XPhos (2.25 mol%, 0.012 mmol, 5.7 mg) and NaO^tPent (1.5 equiv, 0.81 mmol, 89.2 mg) in 1,4-dioxane (1 mL). Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of

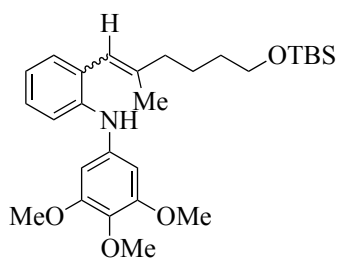
(*E/Z*)-2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-*N*-phenylaniline as a yellow oil (170 mg, 84%). IR ν_{\max} (cm⁻¹) 3404, 3045, 2928, 1594, 1505, 1309, 1254, 1103, 835, 746. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 4H), 7.26 – 7.21 (m, 2H), 7.19 – 7.11 (m, 3H), 7.09 (dq, *J* = 7.8, 1.3 Hz, 3H), 6.98 – 6.85 (m, 3H), 6.18 – 6.11 (m, 1H), 5.62 (s, 1H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.58 – 3.47 (m, 2H), 2.32 – 2.21 (m, 2H), 2.20 – 2.11 (m, 1H), 1.82 – 1.75 (m, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.73 – 1.62 (m, 2H), 0.94 – 0.91 (m, 9H), 0.87 (s, 7H), 0.08 (d, *J* = 0.5 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 143.34, 143.30, 142.25, 141.97, 141.06, 130.70, 130.51, 129.47, 129.00, 128.76, 127.94, 127.81, 127.42, 127.38, 121.63, 121.18, 121.16, 120.87, 120.43, 120.37, 118.56, 118.45, 116.25, 116.10, 63.30, 62.98, 36.25, 31.63, 31.51, 29.46, 26.20, 26.15, 23.59, 18.59, 18.51, 18.02, -5.00, -5.08; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₄H₃₅NOSi 382.2561; found 382.2565.



Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 0.78 mmol, 96.1 mg), (*E/Z*)-(6-(2-bromophenyl)-5-methylhex-5-enyloxy)(*tert*-butyl)dimethylsilane **4db** (1 equiv, 0.65 mmol, 250 mg), Pd₂(dba)₃ (0.75 mol%, 0.005 mmol, 4.6 mg), XPhos (2.25

mol%, 0.015 mmol, 7.15 mg) and NaO^tPent (1.5 equiv, 0.98 mmol, 108 mg) in 1,4-dioxane (1.5 mL). Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-1-enyl)-*N*-(4-methoxyphenyl)aniline as a yellow oil (197 mg, 71%). IR ν_{\max} (cm⁻¹) 3403, 2953, 2860, 1598, 1510, 1456, 1246, 1099, 1039, 775. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.11 (ddd, *J* = 3.8, 2.5, 0.6 Hz, 1H), 7.10 – 7.08 (m, 3H), 7.08 – 7.06 (m, 4H), 7.06 – 7.01 (m, 2H), 6.88 (d, *J* =

2.2 Hz, 2H), 6.86 (d, $J = 2.3$ Hz, 2H), 6.84 – 6.76 (m, 2H), 6.14 (dq, $J = 3.6, 1.2$ Hz, 2H), 5.47 (s, 2H), 3.82 (s, 6H), 3.70 – 3.64 (m, 2H), 3.58 – 3.52 (m, 2H), 2.29 – 2.19 (m, 2H), 2.14 (t, $J = 7.3$ Hz, 2H), 1.93 (d, $J = 1.5$ Hz, 2H), 1.74 (d, $J = 1.3$ Hz, 3H), 1.63 – 1.58 (m, 4H), 1.53 – 1.42 (m, 4H), 0.92 (s, 9H), 0.90 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.46, 155.39, 143.08, 142.94, 142.54, 142.21, 136.10, 135.98, 130.52, 130.35, 127.50, 127.45, 126.22, 126.04, 122.90, 122.60, 121.63, 120.85, 118.95, 118.87, 114.82, 113.88, 113.60, 63.25, 63.05, 55.79, 39.72, 32.77, 32.68, 32.58, 26.21, 26.19, 24.46, 24.32, 23.31, 18.60, 18.56, 17.80, –5.02, –5.07; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{26}\text{H}_{39}\text{NO}_2\text{Si}$ 426.2823; found 426.2824.

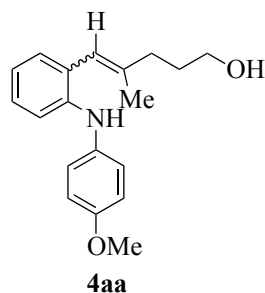


Following procedure **GP4B** with 3,4,5-trimethoxyaniline (1.2 equiv, 3.9 mmol, 711 mg), (*E/Z*)-(6-(2-bromophenyl)-5-methylhex-5-enyloxy)(*tert*-butyl)dimethylsilane **4db** (1 equiv, 3.23 mmol, 1.24 g), $\text{Pd}_2(\text{dba})_3$ (0.75 mol%, 0.024 mmol, 22 mg), (*R*)-*T*-BINAP (2.25 mol%, 0.073 mmol, 49.3 mg) and NaO^tPent (1.5 equiv, 4.85 mmol, 533.4 mg) in 1,4-dioxane (8 mL). Purification by flash chromatography on silica gel (87:13 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-*N*-(2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-1-enyl)phenyl)-3,4,5-trimethoxyaniline as a yellow oil (1.05 g, 67%). IR ν_{max} (cm^{-1}) 3405, 2956, 1601, 1507, 1460, 1254, 1113, 1009, 834, 777. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 (t, $J = 1.6$ Hz, 1H), 7.19 – 7.07 (m, 4H), 6.93 – 6.82 (m, 2H), 6.35 (s, 1H), 6.34 (s, 1H), 6.13 (s, 2H), 3.83 (s, 5H), 3.82 (s, 4H), 3.82 (s, 5H), 3.69 – 3.62 (m, 2H), 3.55 (t, $J = 6.0$ Hz, 2H), 2.28 – 2.18 (m, 2H), 2.13 (t, $J = 7.4$ Hz, 2H), 1.93 (d, $J = 1.5$ Hz, 2H), 1.74 (d, $J = 1.3$ Hz, 3H), 1.60 (h, $J = 2.8$ Hz, 4H), 1.54 – 1.36 (m, 4H), 0.91 (s, 9H), 0.89 (s, 7H), 0.07 (s, 6H); ^{13}C NMR (101 MHz,

CDCl₃) δ 153.98, 142.72, 142.34, 141.54, 141.50, 139.46, 139.35, 133.04, 132.99, 130.77, 130.56, 127.61, 127.48, 127.44, 127.39, 121.43, 120.71, 120.10, 120.02, 115.97, 115.67, 96.99, 96.84, 63.21, 62.99, 61.26, 56.26, 39.79, 32.83, 32.67, 32.63, 26.19, 26.16, 24.47, 24.43, 23.43, 18.58, 18.54, 17.87, -5.03, -5.08; HRMS (ESI) m/z [M+H]⁺, calc'd for C₂₈H₄₃NO₄Si 486.3034; found 486.3029.

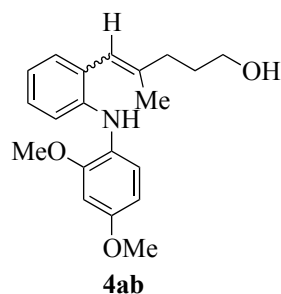
General Procedure 4C (GP4C): Deprotection of the TBS Group using TBAF: Preparation of (*E/Z*)–Styrenyl Anilines 4aa–4ae

To an oven-dried flask equipped with a stir bar was added 1 equivalent of siloxy aniline and anhydrous THF (0.5–0.7 M) under N₂ atmosphere. The reaction vessel was brought to 0 °C and 1.5 equivalents of TBAF (1 M in THF) was added dropwise over 10 minutes. The solution was then stirred for 10 minutes at 0 °C. The contents were then warmed to room temperature and stirred until completion as indicated by TLC. Once complete, the mixture was diluted with H₂O. The resulting mixture was then extracted with 3 portions of ethyl acetate and the combined organic layers were dried over Na₂SO₄. The solution was concentrated in vacuum and purified by flash chromatography on silica gel to afford the corresponding (*E/Z*)–styrenyl alcohol **4a** as a 1:1 mixture of inseparable *E/Z* isomers.



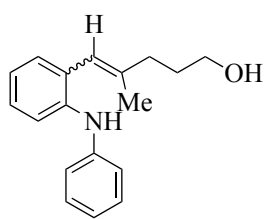
Following procedure **GP4C** with (*E/Z*)-2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-*N*-(4-methoxyphenyl)aniline (1 equiv, 2.3 mmol, 948 mg) and TBAF (1.5 equiv, 3.5 mmol, 3.5 mL) in THF (4.5 mL). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded an

inseparable isomeric mixture of (*E/Z*)-5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-en-1-ol **4aa** as a yellow oil (610 mg, 89%). IR ν_{max} (cm⁻¹) 3411, 2941, 1601, 1518, 1456, 1252, 1038, 821, 755, 620. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.10 (m, 3H), 7.09 – 7.08 (m, 3H), 7.08 – 7.05 (m, 3H), 7.05 – 7.03 (m, 1H), 7.02 (dd, *J* = 1.3, 0.5 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 2H), 6.88 – 6.85 (m, 2H), 6.85 – 6.78 (m, 2H), 6.22 – 6.19 (m, 1H), 6.19 – 6.16 (m, 1H), 5.54 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73 (t, *J* = 6.4 Hz, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 2.37 – 2.28 (m, 2H), 2.24 – 2.14 (m, 2H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.88 – 1.79 (m, 2H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.76 – 1.65 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 155.57, 155.33, 143.15, 142.98, 141.85, 141.42, 136.10, 135.80, 130.42, 130.19, 130.19, 127.69, 127.52, 126.04, 125.75, 123.11, 123.11, 123.11, 122.12, 121.25, 118.98, 118.97, 114.80, 114.77, 114.04, 113.72, 62.83, 62.62, 55.75, 36.39, 31.02, 30.92, 29.04, 23.31, 17.84; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₃NO₂ 298.1802; found 298.1799.



Following procedure **GP4C** with (*E/Z*)-*N*-(2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)phenyl)-2,4-dimethoxyaniline (1 equiv, 0.29 mmol, 130 mg) and TBAF (1.5 equiv, 0.44 mmol, 0.44 mL) in THF (0.5 mL). Purification by flash

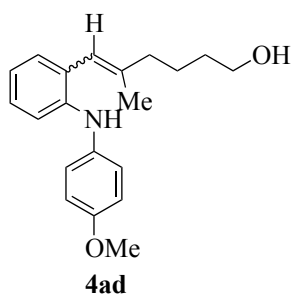
chromatography on silica gel (70:30 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-5-(2-(2,4-dimethoxyphenylamino)phenyl)-4-methylpent-4-en-1-ol **4ab** as a red oil (65 mg, 68%). IR ν_{max} (cm^{-1}) 3412, 2943, 1603, 1515, 1452, 1283, 1207, 1040, 834, 750. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.21 (dd, $J = 8.6, 4.4$ Hz, 2H), 7.18 (dd, $J = 2.4, 1.2$ Hz, 1H), 7.18 – 7.15 (m, 1H), 7.15 – 7.05 (m, 4H), 6.89 – 6.78 (m, 2H), 6.54 (d, $J = 2.7$ Hz, 2H), 6.49 – 6.40 (m, 2H), 6.21 (t, $J = 1.5$ Hz, 2H), 3.84 (d, $J = 1.5$ Hz, 3H), 3.83 (s, 2H), 3.82 (d, $J = 0.4$ Hz, 2H), 3.81 (d, $J = 0.4$ Hz, 3H), 3.73 (t, $J = 6.5$ Hz, 2H), 3.56 (t, $J = 6.4$ Hz, 1H), 2.37 – 2.28 (m, 2H), 2.26 – 2.17 (m, 1H), 1.95 (d, $J = 1.4$ Hz, 2H), 1.88 – 1.78 (m, 2H), 1.77 (d, $J = 1.3$ Hz, 3H), 1.73 – 1.65 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.63, 155.05, 151.88, 151.16, 142.74, 142.21, 141.51, 141.07, 130.41, 130.18, 127.60, 127.44, 127.10, 126.60, 126.07, 125.52, 122.40, 121.52, 120.63, 119.30, 119.16, 118.95, 114.71, 113.96, 103.97, 103.93, 99.67, 62.72, 62.46, 55.86, 36.22, 30.99, 30.75, 28.90, 23.25, 17.76; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{20}\text{H}_{25}\text{NO}_3$ 328.1907; found 328.1908.



4ac

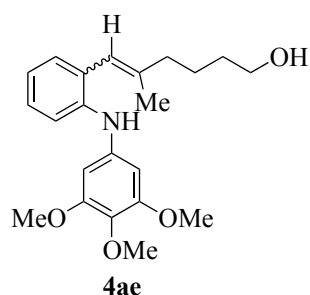
Following procedure **GP4C** with (*E/Z*)-2-(5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-enyl)-*N*-phenylaniline (1 equiv, 0.36 mmol, 130 mg) and TBAF (1.5 equiv, 0.54 mmol, 0.54 mL) in THF (0.5 mL). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-4-methyl-5-(2-(phenylamino)phenyl)pent-4-en-1-ol **4ac** as a yellow oil (75.7 mg, 83%). IR ν_{max} (cm^{-1}) 3407, 3045, 2941, 1594, 1511, 1456, 1308, 1066, 748, 700. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.35 – 7.20 (m, 7H), 7.20 – 7.01 (m, 6H), 6.98 – 6.83 (m, 3H), 6.19 (s, 1H),

6.18 – 6.15 (m, 1H), 3.77 – 3.64 (m, 2H), 3.54 (t, $J = 6.5$ Hz, 1H), 2.36 – 2.22 (m, 2H), 2.22 – 2.09 (m, 2H), 1.93 (d, $J = 1.5$ Hz, 2H), 1.84 – 1.77 (m, 2H), 1.77 – 1.70 (m, 3H), 1.72 – 1.60 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.45, 143.18, 141.89, 141.44, 141.13, 141.02, 130.63, 130.42, 129.50, 129.46, 128.99, 128.73, 128.39, 128.24, 127.98, 127.61, 127.56, 127.46, 122.10, 121.37, 121.34, 121.03, 120.51, 120.43, 118.65, 118.26, 116.60, 116.12, 62.85, 62.78, 36.45, 30.99, 29.13, 23.39, 17.85; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{18}\text{H}_{21}\text{NO}$ 268.1696; found 268.1697.



Following procedure **GP4C** with (*E/Z*)-2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-1-enyl)-*N*-(4-methoxyphenyl)aniline (1 equiv, 0.38 mmol, 160 mg) and TBAF (1.5 equiv, 0.57 mmol, 0.57 mL) in THF (0.6 mL). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-6-(2-(4-methoxyphenylamino)phenyl)-5-methylhex-5-en-1-ol **4ad** as a yellow oil (75 mg, 64%). IR ν_{max} (cm^{-1}) 3405, 2940, 1587, 1509, 1451, 1294, 1241, 1041, 825, 751. ^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 7.14 (ddt, $J = 7.7, 1.6, 0.7$ Hz, 3H), 7.12 – 7.04 (m, 5H), 6.93 – 6.88 (m, 3H), 6.88 – 6.79 (m, 2H), 6.19 (s, 2H), 3.82 (s, 5H), 3.70 (ddt, $J = 6.8, 4.7, 2.4$ Hz, 2H), 3.62 – 3.50 (m, 1H), 2.32 – 2.23 (m, 2H), 2.18 (t, $J = 7.2$ Hz, 1H), 1.96 (d, $J = 1.4$ Hz, 2H), 1.78 (d, $J = 1.3$ Hz, 3H), 1.68 – 1.61 (m, 4H), 1.56 – 1.47 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.35, 155.22, 142.96, 142.83, 142.22, 141.69, 136.06, 135.87, 130.42, 130.24, 127.47, 127.39, 126.17, 125.93, 122.75, 122.44, 121.69, 120.94, 118.96, 118.82,

114.72, 114.05, 113.65, 62.77, 62.63, 55.67, 39.57, 32.46, 32.42, 32.41, 24.26, 24.13, 23.22, 17.75; HRMS (ESI) m/z $[M+H]^+$, calc'd for $C_{20}H_{25}NO_2$ 312.1958; found 312.1959.

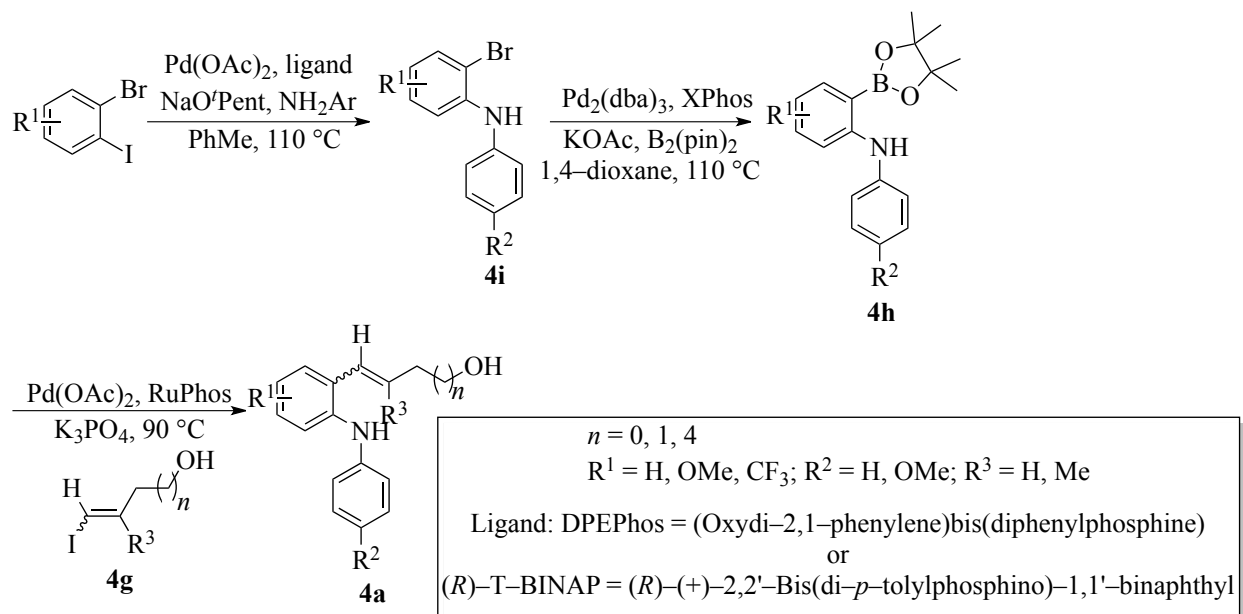


Following procedure **GP4C** with (*E/Z*)-*N*-(2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-1-enyl)phenyl)-3,4,5-trimethoxyaniline (1 equiv, 2.06 mmol, 1.0 g) and TBAF (1.5 equiv, 3.1 mmol, 3.1 mL) in THF (4 mL). Purification by flash chromatography on silica gel (50:50 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-en-1-ol **4ae** as an orange oil (675 mg, 88%). IR ν_{\max} (cm^{-1}) 3412, 2939, 1601, 1509, 1400, 1288, 1237, 1128, 1009, 753. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 1.3 Hz, 1H), 7.16 (tq, J = 7.8, 0.7 Hz, 3H), 7.10 (ddt, J = 7.5, 1.5, 0.6 Hz, 1H), 6.93 – 6.84 (m, 2H), 6.36 (s, 2H), 6.33 (s, 2H), 6.18 – 6.11 (m, 2H), 5.53 (s, 1H), 5.52 (s, 1H), 3.83 (s, 2H), 3.83 (s, 3H), 3.82 (s, 4H), 3.82 (s, 6H), 3.73 – 3.66 (m, 2H), 3.60 – 3.51 (m, 2H), 2.25 (ddq, J = 7.0, 5.5, 1.7 Hz, 2H), 2.15 (dd, J = 8.6, 5.9 Hz, 2H), 1.93 (d, J = 1.5 Hz, 2H), 1.75 (d, J = 1.3 Hz, 3H), 1.66 – 1.58 (m, 4H), 1.55 – 1.44 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.96, 142.48, 141.83, 141.54, 141.41, 139.57, 139.29, 133.06, 132.86, 130.73, 130.52, 127.76, 127.54, 127.47, 127.30, 121.62, 121.01, 120.25, 119.99, 116.31, 115.67, 97.01, 96.66, 77.55, 62.94, 62.80, 61.23, 56.24, 39.68, 32.62, 32.49, 24.27, 23.38, 17.86; HRMS (ESI) m/z $[M+H]^+$, calc'd for $C_{22}H_{29}NO_4$ 372.2169; found 372.2182.

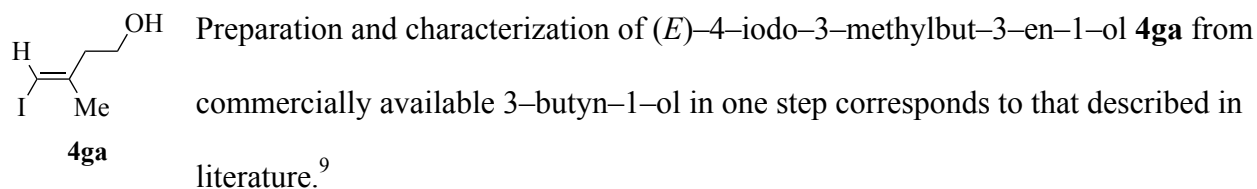
Procedures for the Synthesis of Styrenyl Aniline Precursors *via* Suzuki–Miyaura Cross

Coupling

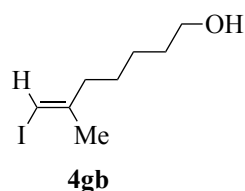
Scheme 4.20. Forward Synthesis of Styrenyl Anilines using Suzuki–Miyaura Approach



Preparation of (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga**

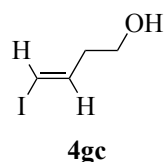


Preparation of (*E*)-7-iodo-6-methylhept-6-en-1-ol **4gb**



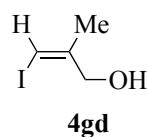
Preparation and characterization of (*E*)-7-iodo-6-methylhept-6-en-1-ol **4gb** from commercially available hept-6-yn-1-ol in one step corresponds to that described in literature.¹⁰

Preparation of (*E*)-4-iodobut-3-en-1-ol **4gc**



Preparation and characterization of (*E*)-4-iodobut-3-en-1-ol **4gc** from commercially available 3-butyn-1-ol in one step corresponds to that described in literature.¹⁶

Preparation of (*Z*)-3-iodo-2-methylprop-2-en-1-ol **4gd**



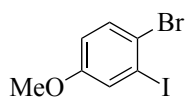
Preparation and characterization of (*Z*)-3-iodo-2-methylprop-2-en-1-ol **4gd** from commercially available prop-2-yn-1-ol in one step corresponds to that described in literature.¹⁷

General Procedure 4D (GP4D): Preparation of 1-bromo-2-iodoanilines using a

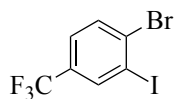
Sandmeyer Reaction

Preparation of 1-bromo-2-iodoanilines was performed using a literature procedure.³¹ To a cooled solution (0 °C) of the aniline (1 equiv, 5 mmol) and aq. HCl (3.6 M, 13 mL) in a round

bottom flask equipped with a stir bar was added slowly NaNO₂ (1.2 equiv, 6 mmol, 414 mg) in H₂O (10 mL, 0.6 M). Once the solid dissolved, a separate solution of KI (1.5 equiv, 7.5 mmol, 1.24 g) in H₂O (5 mL, 1.5 M) was added dropwise to the aniline-containing solution. The resulting solution was warmed to room temperature and stirred for 30 minutes prior to heating at 70 °C for 1 hour. The mixture was then cooled to room temperature and neutralized by slow addition of Na₂S₂O₃ (0.4 M). The neutralized solution was then extracted with DCM (3 x 20 mL), and the combined organic layers were washed with H₂O (3 x 20 mL). The organic layer was then dried over MgSO₄ and concentrated in vacuum to give crude product. Purification by flash chromatography on silica gel provided the desired product.

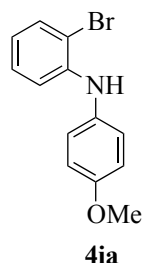


Following procedure **GP4D** with commercially available 2-bromo-5-iodo-4-methoxyaniline (1 equiv, 5 mmol, 1.01 g, 0.66 mL), 1-bromo-2-iodo-4-methoxybenzene was obtained after flash chromatography on silica gel (100% hexanes) as a clear yellow oil (1.28 g, 82%). Characterization of the pure compound matched literature values.³¹

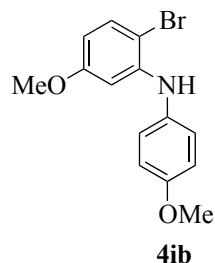


Following procedure **GP4D** with commercially available 2-bromo-5-iodo-4-(trifluoromethyl)aniline (1 equiv, 5 mmol, 1.2 g, 0.72 mL), 1-bromo-2-iodo-4-(trifluoromethyl)benzene was obtained after flash chromatography on silica gel (100% hexanes) as a clear yellow oil (1.45 g, 83%). Characterization of the pure compound matched literature values.³¹

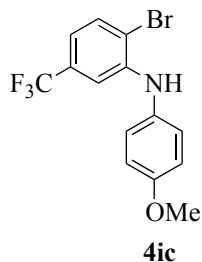
Preparation of 2-bromo-*N*-arylanilines **4i** from 1-bromo-2-iodobenzenes following GP4B



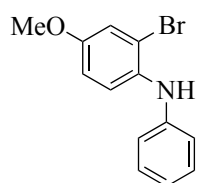
Following procedure **GP4B** with commercially available 1-bromo-2-iodobenzene (1 equiv, 7.79 mmol, 2.20 g), Pd(OAc)₂ (0.5 mol%, 0.039 mmol, 8.7 mg), DPEPhos (1.5 mol%, 0.117 mmol, 63 mg), *p*-anisidine (1.2 equiv, 9.35 mmol, 1.2 g) and NaO^tPent (1.5 equiv, 11.7 mmol, 1.3 g) in 15 mL of toluene. Purification by flash chromatography on silica gel (99:1 hexanes:EtOAc) afforded 2-bromo-*N*-(4-methoxyphenyl)aniline **4ia** as a white solid (2.17 g, 76%). Characterization of the pure compound matched described literature values.⁸



Following procedure **GP4B** with 1-bromo-2-iodo-4-methoxybenzene (1 equiv, 3.2 mmol, 1.0 g), Pd(OAc)₂ (8 mol%, 0.256 mmol, 57.5 mg), (*R*)-T-BINAP (12 mol%, 0.384 mmol, 261 mg), *p*-anisidine (1.5 equiv, 4.8 mmol, 591 mg), and NaO^tPent (2 equiv, 6.4 mmol, 705 mg) in 4 mL of toluene. Purification by flash chromatography on silica gel (95:5 hexanes:EtOAc) afforded 2-bromo-5-methoxy-*N*-(4-methoxyphenyl)aniline **4ib** as a pale cloudy oil (900 mg, 91%). IR ν_{max} (cm⁻¹) 3391, 3005, 2958, 2835, 1591, 1510, 1448, 1170, 832, 598. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.33 (m, 1H), 7.21 – 7.09 (m, 2H), 6.97 – 6.85 (m, 2H), 6.52 (t, *J* = 2.7 Hz, 1H), 6.27 (ddd, *J* = 8.8, 2.8, 1.2 Hz, 1H), 5.95 (s, 1H), 3.83 (d, *J* = 0.9 Hz, 3H), 3.70 (d, *J* = 0.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.11, 156.73, 144.30, 134.03, 133.12, 125.19, 114.97, 105.25, 101.69, 100.23, 55.75, 55.57; GC/MS (CI) *m/z* [M+H]⁺ for C₁₈H₂₀N₂O found 281.



Following procedure **GP4B** with 1-bromo-2-iodo-4-(trifluoromethyl)benzene (1 equiv, 2 mmol, 702 mg), Pd(OAc)₂ (8 mol%, 0.16 mmol, 36 mg), (*R*)-T-BINAP (12 mol%, 0.24 mmol, 163 mg), *p*-anisidine (1.5 equiv, 3 mmol, 369 mg), and NaO^tPent (2 equiv, 4 mmol, 440 mg) in 4 mL of toluene. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded 2-bromo-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)aniline **4ic** as a red-orange oil (406 mg, 59%). IR ν_{\max} (cm⁻¹) 3408, 2838, 1602, 1514, 1433, 1333, 1249, 1169, 1125, 1079. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (dd, *J* = 2.2, 0.7 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.90 – 6.82 (m, 1H), 6.16 – 6.06 (m, 1H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.37, 144.16, 133.34, 132.89, 130.94 (q, *J* = 32.3 Hz), 125.74, 124.06 (q, *J* = 272.5 Hz), 115.60, 115.24, 113.46, 1, 109.92, 55.75; GC/MS (CI) *m/z* [M+H]⁺ for C₁₄H₁₁BrNO₂ found 308.

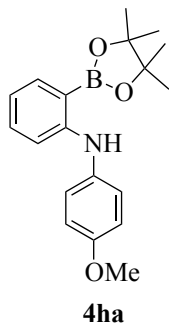


Following procedure **GP4B** with 2-bromo-4-methoxyaniline (1.2 equiv, 2.4 mmol, 485 mg), iodobenzene (1 equiv, 2 mmol, 408 mg), Pd₂(dba)₃ (0.75 mol%, 0.015 mmol, 14 mg), (*R*)-T-BINAP (2.25 mol%, 0.045 mmol, 30.5 mg) and NaO^tPent (1.5 equiv, 3 mmol, 330 mg) in 1,4-dioxane (5 mL). Purification by flash chromatography on silica gel (95:5 hexanes:EtOAc) afforded 2-bromo-4-methoxy-*N*-phenylaniline **4id** as a pale yellow solid, m.p. 63–66 °C (281 mg, 51%). IR ν_{\max} (cm⁻¹) 3400, 3047, 2955, 1599, 1507, 1279, 1209, 1035, 745. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.26 (dd, *J* = 6.5, 2.0 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.14 (d, *J* = 2.9 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.92 (ddt, *J* = 7.6, 7.1, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.9 Hz, 1H), 5.71 (s, 1H), 3.77 (s, 3H); ¹³C

NMR (101 MHz, CDCl₃) δ 154.87, 143.73, 134.58, 129.57, 121.18, 120.51, 118.25, 117.66, 115.45, 114.57, 56.03; GC/MS (CI) m/z [M+H]⁺ for C₁₃H₁₂BrNO found 278.

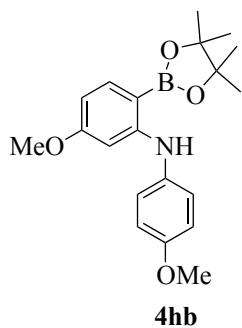
General Procedure 4E (GP4E): Preparation of *N*-aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilines 4ha–4hd from 2-bromo-*N*-arylanilines using Miyaura Borylation

Preparation of *N*-aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilines **4ha–4hd** was performed using a literature procedure.¹⁹ To an oven-dried Schlenk flask equipped with a stir bar was added 1.2–2 equiv of Bis(pinacolato)diboron (B₂(pin)₂), 4 mol% Pd₂(dba)₃ and 8 mol% XPhos. Glove box was used to add 3 equivalents of KOAc and the tube was sealed with a screw cap containing a Teflon septum. 1 equivalent of aromatic halide and 1,4-dioxane (0.33–0.5 M) were then added to the reaction mixture and heated at 110 °C for 24–48 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and filtered over a short pad of Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated in vacuum and purified by flash chromatography on silica gel to afford the corresponding *N*-aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline.



Following procedure **GP4E** with 2-bromo-*N*-(4-methoxyphenyl)aniline **4ia** (1 equiv, 14.4 mmol, 4.0 g), B₂(Pin)₂ (2 equiv, 28.8 mmol, 7.3 g), Pd₂(dba)₃ (4 mol%, 0.57 mmol, 527 mg), XPhos (8 mol%, 1.15 mmol, 548 mg), and KOAc (3 equiv, 43.1 mmol, 4.23 g) in 30 mL of anhydrous 1,4-dioxane. The reaction was

heated for 24 h. Purification by flash chromatography on silica gel (97:3 hexanes:EtOAc) afforded *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** as a brown solid, m.p. 89–91 °C (2.6 g, 55%). IR ν_{\max} (cm⁻¹) 3388, 2983, 2834, 1602, 1514, 1462, 1372, 1143, 1038, 753. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.71 (ddd, *J* = 7.4, 1.8, 0.5 Hz, 1H), 7.24 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.97 (ddd, *J* = 8.4, 1.0, 0.5 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.73 (td, *J* = 7.3, 1.0 Hz, 1H), 3.83 (s, 3H), 1.36 (s, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 153.92, 151.20, 138.66, 137.52, 132.81, 118.24, 113.42, 99.33, 84.09, 61.26, 56.33, 25.24, 25.14; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₄BNO₃ 326.1925; found 326.1926.

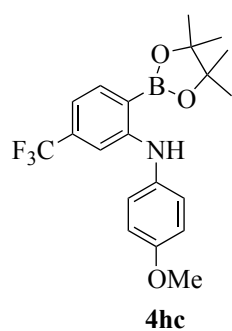


Following procedure **GP4E** with 2-bromo-5-methoxy-*N*-(4-methoxyphenyl)aniline **4ib** (1 equiv, 2.54 mmol, 783 mg), B₂(pin)₂ (1.2 equiv, 3.05 mmol, 774 mg), Pd₂(dba)₃ (4 mol%, 0.1 mmol, 93 mg), XPhos (8 mol%, 0.2 mmol, 97 mg), and KOAc (3 equiv, 7.62 mmol, 748 mg) in 5 mL of anhydrous 1,4-dioxane. The reaction was heated for 24 h.

Purification by flash chromatography on silica gel (85:15 hexanes:EtOAc) afforded 5-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4hb** as a yellow, m.p. 121–125 °C (292 mg, 32%). IR ν_{\max} (cm⁻¹) 3388, 2979, 2838, 1609, 1511, 1441, 1358, 1035, 861, 661. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.55 (d, *J* = 8.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.91 – 6.85 (m, 2H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.26 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 1.34 (s, 12H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 164.23, 156.53, 154.60,

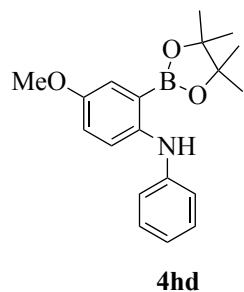
139.18, 135.37, 124.99, 115.04, 103.81, 97.59, 84.09, 56.01, 55.43, 25.23; FTMS (ESI) m/z

$[M+H]^+$, calc'd for $C_{20}H_{26}BNO_4$ 356.2031; found 356.2029.



Following procedure **GP4E** with 2-bromo-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)aniline **4ic** (1 equiv, 1.01 mmol, 350 mg), $B_2(\text{pin})_2$ (1.2 equiv, 1.21 mmol, 308 mg), $Pd_2(\text{dba})_3$ (4 mol%, 0.04 mmol, 37 mg), XPhos (8 mol%, 0.08 mmol, 38 mg), and KOAc (3 equiv, 3.03 mmol, 298 mg) in 2 mL of anhydrous 1,4-dioxane. The reaction was heated for 24 h. Purification

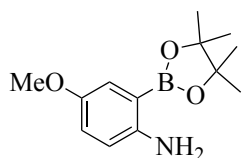
by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline **4hc** as a yellow solid, m.p. 86–90 °C. (220 mg, 55%) IR ν_{max} (cm^{-1}) 3390, 2986, 1576, 1511, 1435, 1333, 1248, 1167, 1126, 861. ^1H NMR (400 MHz, Chloroform- d) δ 7.78 (d, $J = 7.7$ Hz, 1H), 7.65 (s, 1H), 7.23 – 7.13 (m, 2H), 7.10 (d, $J = 1.6$ Hz, 1H), 6.99 – 6.87 (m, 3H), 3.85 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.71, 152.84, 137.97, 134.46 (q, $J = 31.7$ Hz), 134.14, 125.32, 124.34 (q, $J = 272.8$ Hz), 122.98, 115.03, 113.24, 108.05, 84.44, 55.78, 25.12; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{20}H_{23}BF_3NO_3$ 394.1799; found 394.1800.



Following procedure **GP4E** with 2-bromo-4-methoxy-*N*-phenylaniline **4id** (1 equiv, 1.52 mmol, 423 mg), $B_2(\text{pin})_2$ (1.2 equiv, 1.83 mmol, 465 mg), $Pd_2(\text{dba})_3$ (4 mol%, 0.061 mmol, 56 mg), XPhos (8 mol%, 0.122 mmol, 58 mg), and KOAc (3 equiv, 4.56 mmol, 448 mg) in 4.5 mL of anhydrous 1,4-

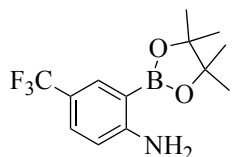
dioxane. The reaction was heated for 48 h. Because 4-methoxy-*N*-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4hd** was not stable to silica gel or neutral alumina column chromatograph, it was taken to the next step without purification.

Preparation of 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline from 2-bromoaniline Precursors



Preparation of 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline was performed using a literature procedure.²⁰ To an oven-dried Schlenk flask equipped with a stir bar was added (dppf)PdCl₂•CH₂Cl₂ (5 mol%, 0.25 mmol, 204 mg). The tube was then sealed with a screw cap containing a Teflon septum and filled with nitrogen prior to the addition of commercially available 2-bromo-4-methoxyaniline (1 equiv, 5 mmol, 1.01 g), pinacolborane (3 equiv, 15 mmol, 1.92 g), Et₃N (4 equiv, 20 mmol, 2.0 g), and 1,4-dioxane (25 mL). The solution was then heated and stirred at 100 °C for 24 h. After completion, the reaction mixture was cooled to room temperature, and diluted with saturated aqueous NH₄Cl solution. The layers were separated and the aqueous layer was extracted with 3 portions of CH₂Cl₂. The organic layers were then combined and washed with brine. The organic layers was then dried over Na₂SO₄, concentrated in vacuum, and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.25 g, 68%). Characterization of the pure compound matched described literature values.²⁹

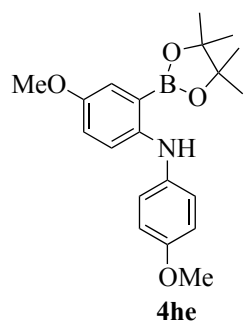
2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



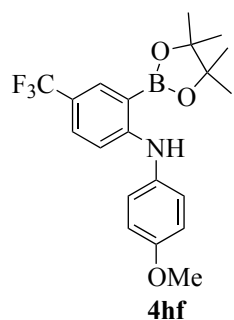
Preparation of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline was performed using a literature procedure.²¹ To an oven-dried Schlenk flask equipped with a stir bar was added

Bis(pinacolato)diboron (2 equiv, 2 mmol, 508 mg), Pd₂(dba)₃ (4 mol%, 0.04 mmol, 37 mg) and XPhos (8 mol%, 0.08 mmol, 38 mg). Glove box was used to add KOAc (3 equiv, 3 mmol, 294 mg) and the tube was sealed with a screw cap containing a Teflon septum. Commercially available 2-bromo-4-(trifluoromethyl)aniline (1 equiv, 1 mmol, 240 mg) and 1,4-dioxane (2 mL) were then added to the reaction mixture and heated at 110 °C for 24 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and filtered over a short pad of Celite. The Celite was then washed with ethyl acetate. The combined filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (90:10 hexanes:EtOAc) to afford the corresponding boronic ester (138 mg, 48%). Characterization of the pure compound matched described literature values.²¹

Preparation of *N*-aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilines **4he and **4hf** from the 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline Precursors using the Buchwald–Hartwig Amination (GP4B)**



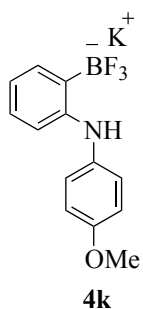
Following procedure **GP4B** with 4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.1 equiv, 1.1 mmol, 274 mg), Pd₂(dba)₃ (0.75 mol%, 0.0075 mmol, 6.9 mg), RuPhos (1.5 mol%, 0.015 mmol, 7 mg), bromoanisole (1.0 equiv, 1.0 mmol, 187.04 mg) and NaO^tPent (1.5 equiv, 1.5 mmol, 165 mg) in 2.5 mL of anhydrous 1,4-dioxane. Because 4-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4he** was not stable to silica gel or neutral alumina column chromatograph, it was taken to the next step without purification.



Following procedure **GP4B** with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (1.2 equiv, 0.48 mmol, 138 mg), Pd₂(dba)₃ (1 mol%, 0.004 mmol, 3.7 mg), RuPhos (3 mol%, 0.012 mmol, 5.6 mg), bromoanisole (1.0 equiv, 0.40 mmol, 75 mg) and NaO^tPent (1.5 equiv, 0.6 mmol, 66 mg) in 0.8 mL of anhydrous toluene. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline **4hf** as a white solid (36 mg, 23%). IR ν_{max} (cm⁻¹) 3387, 2983, 1618, 1512, 1368, 1316, 1268, 1142, 1109, 1077. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.92 (m, 1H), 7.78 (s, 1H), 7.43 – 7.37 (m, 1H),

7.21 – 7.15 (m, 2H), 6.97 – 6.91 (m, 2H), 6.90 – 6.85 (m, 1H), 3.84 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.99, 155.24, 134.72, 133.81, 129.72, 129.18, 125.98, 125.21 (q, J = 270.6 Hz), 118.72 (q, J = 32.5 Hz), 114.94, 111.15, 84.44, 55.78, 25.12; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{20}\text{H}_{23}\text{BF}_3\text{NO}_3$ 394.1799; found 394.1801.

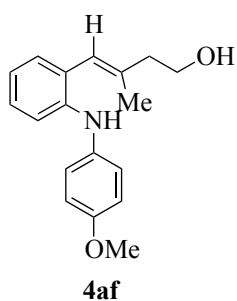
Preparation of potassium trifluoro(2-(4-methoxyphenylamino)phenyl)borate **4k**



Preparation of potassium trifluoro(2-(4-methoxyphenylamino)phenyl)borate **4k** was performed using a literature procedure.²³ To a flask equipped with a stir bar was added *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1 equiv, 9.22 mmol, 3.0 g) and MeOH (0.37 M, 25 mL). Potassium hydrogen difluoride (5.6 equiv, 51.63 mmol, 4.03 g) in H_2O (4.5 M, 11.25 mL) was then added to the boronic ester solution and the contents were stirred for 15 minutes. The solution was then concentrated in vacuum and the resulting solid was dissolved in hot acetone. The mixture was then filtered and the filtrate was concentrated in vacuum. Recrystallization with hot acetone and diethyl ether yielded the desired trifluoroborate salt **4k** as a white solid (2.02 g, 73%). IR ν_{max} (cm^{-1}) 1597, 1567, 1511, 1295, 1274, 1247, 1190, 1035, 935, 758. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.29 – 7.21 (m, 1H), 7.02 – 6.94 (m, 2H), 6.90 (td, J = 4.8, 4.2, 2.7 Hz, 3H), 6.85 – 6.76 (m, 2H), 6.57 (td, J = 6.3, 5.1, 2.7 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.08, 146.89, 137.65, 132.94, 132.91, 125.98, 119.38, 117.80, 114.47, 112.24, 55.23.

General Procedure 4F (GP4F): Preparation of 4-(2-(arylamino)phenyl)-3-methylbut-3-en-1-ols 4af-4an using Suzuki-Miyaura Cross Coupling

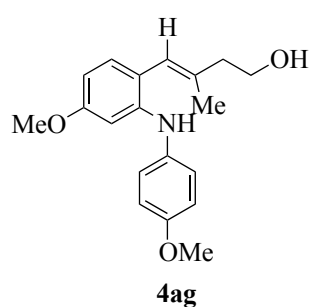
To an oven-dried Schlenk flask equipped with a stir bar was added 1.1–1.5 equivalents of the boronic ester **4h**, 2 mol% Pd(OAc)₂, 4 mol% RuPhos, and 3 equivalents of ground K₃PO₄. The tube was then sealed with a screw cap containing a Teflon septum and filled with nitrogen. Vinyl iodide **4g** (1 equiv) and THF:EtOH:H₂O (2:1:1, degassed *via* Freeze-Pump-Thaw or sparged with N₂ for 30 minutes, 0.15–0.5 M) were then added to the reaction mixture and the contents were heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over MgSO₄ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel to afford the corresponding 4-(2-(arylamino)phenyl)-3-methylbut-3-en-1-ol **4a**.



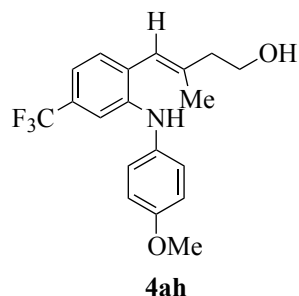
Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1.5 equiv, 0.33 mmol, 107 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.22 mmol, 47 mg), Pd(OAc)₂ (2 mol%, 0.0044 mmol, 1.0 mg), RuPhos (4 mol%, 0.0088 mmol, 4.1 mg), and ground K₃PO₄ (3 equiv, 0.66 mmol, 140 mg) in 0.44

mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4af** as a yellow oil (55 mg, 88%). IR ν_{max} (cm⁻¹) 3389, 2943, 1599, 1518, 1452, 1293, 1240,

1041, 825, 751. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.08 (m, 2H), 7.08 – 7.02 (m, 3H), 6.90 – 6.80 (m, 3H), 6.26 – 6.20 (m, 1H), 5.56 (s, 1H), 3.83 (d, J = 6.3 Hz, 2H), 3.81 (s, 3H), 2.48 (td, J = 6.3, 1.1 Hz, 2H), 1.78 (d, J = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.29, 142.88, 137.99, 136.17, 130.36, 127.74, 126.00, 123.75, 122.36, 119.12, 114.78, 114.42, 60.61, 55.78, 42.87, 17.66; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{18}\text{H}_{21}\text{NO}_2$ 284.1640; found 284.1641.

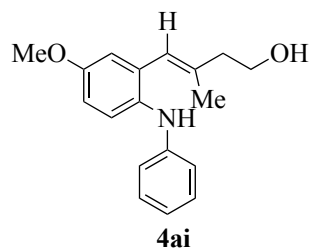


Following procedure **GP4F** with 5-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4hb** (1.1 equiv, 0.51 mmol, 180 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.46 mmol, 98 mg), $\text{Pd}(\text{OAc})_2$ (2 mol%, 0.0092 mmol, 2.1 mg), RuPhos (4 mol%, 0.0184 mmol, 8.6 mg), and ground K_3PO_4 (3 equiv, 1.38 mmol, 293 mg) in 2 mL of THF:EtOH: H_2O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-4-(4-methoxy-2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4ag** as an orange-brown oil (112 mg, 78%). IR ν_{max} (cm^{-1}) 3379, 2946, 2839, 1607, 1515, 1445, 1291, 1168, 1041, 828. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.05 (m, 2H), 7.02 (dt, J = 8.4, 0.7 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.62 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.3, 2.6 Hz, 1H), 6.17 (s, 1H), 3.83 – 3.78 (m, 5H), 3.74 (d, J = 0.7 Hz, 3H), 2.51 – 2.41 (m, 2H), 1.79 – 1.74 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 159.55, 155.53, 144.19, 137.48, 135.66, 131.03, 123.27, 122.96, 118.53, 114.80, 104.06, 100.14, 60.61, 55.74, 55.33, 42.88, 17.63; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{19}\text{H}_{23}\text{NO}_3$ 314.1751; found 314.1752.



Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline **4hc** (1.2 equiv, 0.51 mmol, 200 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.42 mmol, 89 mg), Pd(OAc)₂ (2 mol%, 0.008 mmol, 2 mg), RuPhos (4 mol%, 0.017 mmol, 8 mg), and ground K₃PO₄ (3 equiv,

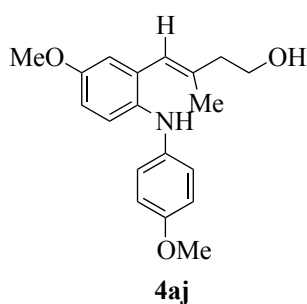
1.27 mmol, 270 mg) in 2 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-4-(2-(4-methoxyphenylamino)-4-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol **4ah** as an orange-brown oil (122 mg, 83%). IR ν_{\max} (cm⁻¹) 3388, 2939, 2840, 1575, 1513, 1434, 1338, 1245, 1121, 830. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.22 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.17 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.13 – 7.04 (m, 2H), 7.04 – 6.98 (m, 1H), 6.95 – 6.85 (m, 2H), 6.20 (d, *J* = 1.8 Hz, 1H), 5.77 (s, 1H), 3.85 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 2.50 (td, *J* = 6.3, 1.1 Hz, 2H), 1.77 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.16, 143.72, 139.93, 134.71, 130.54, 129.92 (q, *J* = 31.9 Hz), 128.53, 124.53 (q, *J* = 272.2 Hz), 123.59, 122.53, 115.04, 115.00, 114.93, 109.59, 60.50, 55.76, 42.71, 17.69; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₀F₃NO₂ 352.1519; found 352.1521.



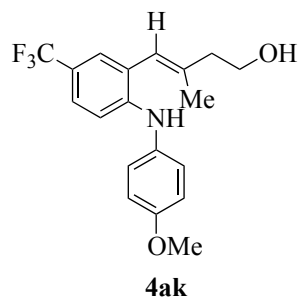
Following procedure **GP4F** with crude 4-methoxy-*N*-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4hd** (1.5 equiv, 1.1 mmol, 356 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.72 mmol, 155 mg), Pd(OAc)₂ (2 mol%, 0.014 mmol, 3.2 mg),

RuPhos (4 mol%, 0.029 mmol, 13.1 mg), and ground K₃PO₄ (3 equiv, 2.16 mmol, 459 mg) in 4 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30

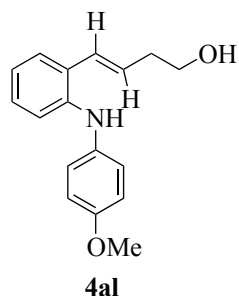
hexanes:EtOAc) afforded (*E*)-4-(5-methoxy-2-(phenylamino)phenyl)-3-methylbut-3-en-1-ol **4ai** as a brown oil (328 mg, 76% over 2 steps). IR ν_{\max} (cm⁻¹) 3388, 2946, 1599, 1501, 1286, 1212, 1162, 1039, 749, 697. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.16 (m, 3H), 6.84 – 6.77 (m, 5H), 6.23 (s, 1H), 3.82 (s, 3H), 3.70 (t, *J* = 6.1 Hz, 2H), 2.39 (td, *J* = 6.1, 1.0 Hz, 2H), 1.78 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 155.25, 145.51, 137.36, 133.57, 132.55, 129.39, 124.41, 122.83, 119.53, 115.94, 115.61, 113.09, 60.44, 55.79, 42.94, 17.69; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₈H₂₁NO₂ 284.1645; found 284.1647.



Following procedure **GP4F** with crude 4-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4he** (1.5 equiv, 0.35 mmol, 124 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.23 mmol, 49 mg), Pd(OAc)₂ (2 mol%, 0.0046 mmol, 1.0 mg), RuPhos (4 mol%, 0.0092 mmol, 4.3 mg), and ground K₃PO₄ (3 equiv, 0.69 mmol, 146 mg) in 1.3 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-4-(5-methoxy-2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4aj** as a brown oil (182 mg, 58% over 2 steps). IR ν_{\max} (cm⁻¹) 3379, 2940, 2832, 1513, 1280, 1244, 1179, 1113, 1041, 820. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.00 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.85 – 6.78 (m, 2H), 6.75 (d, *J* = 7.0 Hz, 2H), 6.22 (s, 1H), 3.79 (s, 3H), 3.79 – 3.67 (m, 5H), 2.42 (t, *J* = 6.2 Hz, 2H), 1.78 (d, *J* = 1.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 154.22, 153.95, 138.28, 137.65, 135.70, 129.92, 124.01, 119.43, 115.92, 114.81, 113.11, 60.52, 55.84, 55.83, 42.89, 17.71; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₃NO₃ 314.1751; found 314.1751.

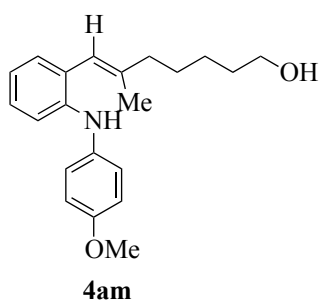


Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline **4hf** (1.2 equiv, 0.41 mmol, 163 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4ga** (1 equiv, 0.34 mmol, 73 mg), Pd(OAc)₂ (2 mol%, 0.0069 mmol, 1.5 mg), RuPhos (4 mol%, 0.014 mmol, 6.4 mg), and ground K₃PO₄ (3 equiv, 1.04 mmol, 220 mg) in 2 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-4-(2-(4-methoxyphenylamino)-5-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol **4ak** as a brown oil (115 mg, 96%). IR ν_{\max} (cm⁻¹) 3373, 2940, 1612, 1516, 1330, 1111, 1075, 1038, 912, 826. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 2H), 7.17 – 7.06 (m, 2H), 6.98 (dd, *J* = 9.3, 0.8 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.19 (s, 1H), 5.91 (s, 1H), 3.86 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.50 (td, *J* = 6.3, 1.1 Hz, 2H), 1.77 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.51, 146.36, 140.12, 134.24, 127.23, 125.12 (q, *J* = 270.7 Hz), 124.96, 124.52, 124.46, 122.32, 119.95, 119.83 (q, *J* = 32.5 Hz), 119.63, 114.95, 111.92, 60.52, 55.76, 42.64, 17.64; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₀F₃NO₂ 352.1519; found 352.1521.



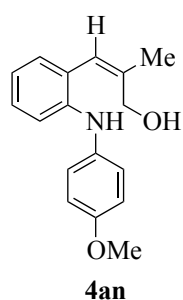
Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1.5 equiv, 1.5 mmol, 488 mg), (*E*)-4-iodobut-3-en-1-ol **4gc** (1 equiv, 1.0 mmol, 198 mg), Pd(OAc)₂ (2 mol%, 0.02 mmol, 4.5 mg), RuPhos (4 mol%, 0.04 mmol, 18.7 mg), and ground K₃PO₄ (3 equiv, 3.0 mmol, 637 mg) in 5 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-

4-(2-(4-methoxyphenylamino)phenyl)but-3-en-1-ol **4al** as a yellow oil (173 mg, 64%). IR ν_{\max} (cm⁻¹) 3388, 2937, 1601, 1577, 1518, 1247, 1044, 973, 825, 749. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.34 (m, 1H), 7.13 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.07 – 7.02 (m, 1H), 7.01 – 6.92 (m, 2H), 6.92 – 6.81 (m, 3H), 6.68 – 6.59 (m, 1H), 6.13 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.79 – 3.71 (m, 2H), 2.50 (dtd, *J* = 7.6, 6.3, 1.5 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 155.07, 142.00, 136.81, 129.08, 128.73, 128.35, 127.62, 127.57, 121.56, 120.96, 117.18, 114.87, 62.20, 55.81, 36.90; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₇H₁₉NO₂ 270.1489; found 270.1490.



Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1.5 equiv, 1.04 mmol, 338 mg), (*E*)-4-iodobut-3-en-1-ol **4gb** (1 equiv, 0.7 mmol, 178 mg), Pd(OAc)₂ (2 mol%, 0.014 mmol, 3.1 mg), RuPhos (4 mol%, 0.028 mmol, 13.1 mg), and ground K₃PO₄ (3 equiv, 2.1 mmol, 446 mg) in 3 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*E*)-7-(2-(4-methoxyphenylamino)phenyl)-6-methylhept-6-en-1-ol **4am** as a brown oil (209 mg, 92%). IR ν_{\max} (cm⁻¹) 3406, 2931, 2856, 1576, 1510, 1452, 1293, 1241, 1038, 748. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.03 (m, 5H), 6.90 – 6.85 (m, 2H), 6.85 – 6.78 (m, 1H), 6.17 – 6.08 (m, 1H), 5.46 (s, 1H), 3.81 (d, *J* = 0.5 Hz, 3H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.27 – 2.16 (m, 2H), 1.74 (t, *J* = 1.0 Hz, 3H), 1.67 – 1.54 (m, 4H), 1.48 – 1.38 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 155.38, 142.95, 142.01, 136.13, 130.51, 127.46, 126.25,

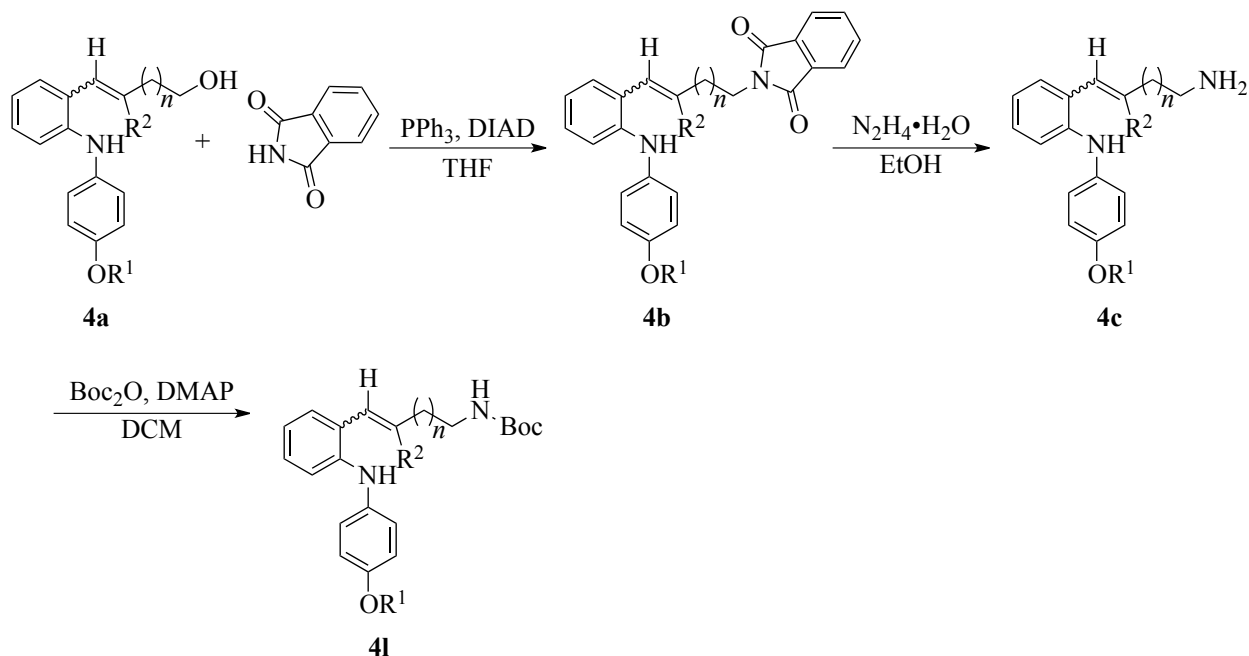
122.61, 120.91, 118.99, 114.82, 113.99, 63.15, 55.80, 39.86, 32.81, 27.90, 25.60, 17.84; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{21}H_{27}NO_2$ 326.2115; found 326.2116.



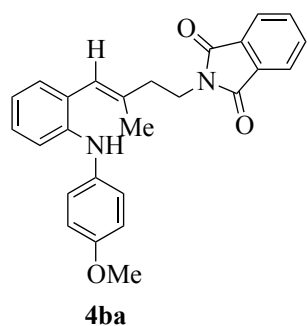
Following procedure **GP4F** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1.5 equiv, 1.5 mmol, 300 mg), (*Z*)-3-iodo-2-methylpropen-2-ol **4gd** (1 equiv, 0.6 mmol, 122 mg), $Pd(OAc)_2$ (2 mol%, 0.012 mmol, 2.7 mg), RuPhos (4 mol%, 0.024 mmol, 11.2 mg), and ground K_3PO_4 (3 equiv, 1.8 mmol, 382 mg) in 3 mL of THF:EtOH:H₂O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded (*Z*)-3-(2-(4-methoxyphenylamino)phenyl)-2-methylprop-2-en-1-ol **4an** as a brown solid, m.p. 109–113 °C (129 mg, 80%). IR ν_{max} (cm⁻¹) 3375, 2953, 2839, 1598, 1514, 1453, 1246, 1035, 1006, 753. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.07 (m, 2H), 7.07 – 7.00 (m, 3H), 6.90 – 6.85 (m, 2H), 6.84 – 6.78 (m, 1H), 6.32 (dq, J = 1.6, 0.8 Hz, 1H), 5.49 (s, 1H), 4.18 (d, J = 0.7 Hz, 2H), 3.82 (s, 3H), 2.04 (d, J = 1.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 155.62, 143.20, 140.51, 135.71, 130.36, 128.14, 125.08, 124.06, 123.01, 119.24, 114.86, 114.25, 62.88, 55.76, 21.44; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{17}H_{19}NO_2$ 270.1489; found 270.1491.

Synthesis of Nitrogen-Based Tethers *via* Gabriel Synthesis

Scheme 4.21. Gabriel Synthesis of Primary Alcohols



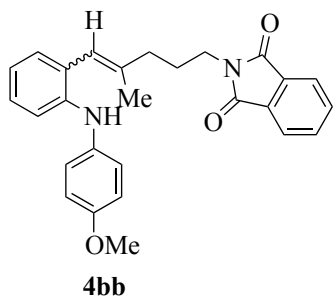
Preparation of (*E*)-2-(4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enyl)isoindoline-1,3-dione **4ba** *via* Mitsunobu Reaction of Alcohol Precursor



Preparation of (*E*)-2-(4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enyl)isoindoline-1,3-dione **4ba** was accomplished using a literature procedure.³² To an oven-dried flask equipped with a stir bar was added triphenylphosphine (2.4 equiv, 2.19 mmol, 573 mg) and anhydrous THF (2.0 mL) under N₂ atmosphere. The contents were stirred at 0 °C for 10 minutes prior to the dropwise addition of diisopropyl azodicarboxylate

(DIAD) (2 equiv, 1.82 mmol, 0.353 mL). After stirring for 1 hour at the same temperature, a separate solution containing (*E*)-4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4af** (1 equiv, 0.91 mmol, 258 mg) and phthalimide (1.5 equiv, 1.4 mmol, 201 mg) in THF (2 mL) was added dropwise over 10 minutes. After stirring at 0 °C for 1 hour, the ice bath was removed and the solution was stirred at room temperature for 7 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford the corresponding (*E*)-styrylisoindoline-1,3-dione **4ba** as a yellow oil (320 mg, 85%). IR ν_{max} (cm⁻¹) 3386, 2942, 1769, 1709, 1511, 1447, 1395, 1240, 1031, 719. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.83 – 7.72 (m, 2H), 7.71 – 7.62 (m, 2H), 7.00 (dd, *J* = 20.3, 8.6 Hz, 6H), 6.90 – 6.67 (m, 3H), 6.09 (d, *J* = 2.2 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.82 (s, 3H), 2.59 (t, *J* = 6.3 Hz, 2H), 1.90 – 1.77 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.70, 155.44, 143.14, 138.15, 135.85, 134.14, 132.08, 130.39, 127.68, 125.24, 124.02, 123.44, 123.11, 118.75, 114.67, 113.74, 55.77, 38.85, 36.81, 17.99; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₆H₂₄N₂O₃ 413.1860; found 413.1866.

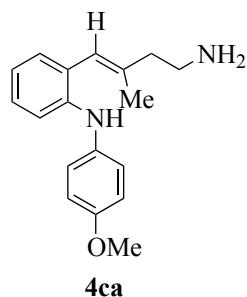
Preparation of (*E/Z*)-2-(5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enyl)isoindoline-1,3-dione **4bb via Mitsunobu Reaction of Alcohol Precursor**



Preparation of (*E/Z*)-2-(5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enyl)isoindoline-1,3-dione **4bb** was accomplished using a literature procedure.³² To an oven-dried flask equipped with a stir bar was added triphenylphosphine (2.4 equiv, 1.61 mmol, 422

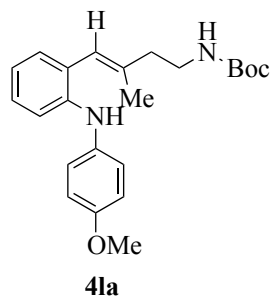
mg) and anhydrous THF (1.6 mL) under N₂ atmosphere. The contents were stirred at 0 °C for 10 minutes prior to the dropwise addition of diisopropyl azodicarboxylate (DIAD) (2 equiv, 1.34 mmol, 0.26 mL). After stirring for 1 hour at the same temperature, a separate solution containing (*E/Z*)-5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-en-1-ol **4aa** (1 equiv, 0.67 mmol, 200 mg) and phthalimide (1.5 equiv, 1.0 mmol, 149 mg) in THF (1.5 mL) was added dropwise over 10 minutes. After stirring at 0 °C for 1 hour, the ice bath was removed and the solution was stirred at room temperature for 7 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford the corresponding (*E/Z*)-styrylisoindoline-1,3-dione **4bb** as a yellow oil (235 mg, 82%) as a 1:1 mixture of isomers. IR ν_{max} (cm⁻¹) 3373, 2981, 2943, 1719, 1574, 1515, 1238, 1112, 1044, 719. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.83 (m, 4H), 7.83 – 7.78 (m, 2H), 7.76 – 7.66 (m, 4H), 7.15 – 7.10 (m, 3H), 7.10 – 7.04 (m, 4H), 7.01 – 6.92 (m, 3H), 6.91 – 6.83 (m, 4H), 6.80 (ddd, *J* = 7.6, 5.3, 2.8 Hz, 1H), 6.18 (d, *J* = 9.4 Hz, 2H), 5.64 (s, 1H), 3.81 – 3.80 (m, 3H), 3.76 (t, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 7.3 Hz, 2H), 2.28 (t, *J* = 7.7 Hz, 2H), 2.24 – 2.13 (m, 2H), 1.98 (d, *J* = 7.3 Hz, 2H), 1.94 (t, *J* = 2.2 Hz, 3H), 1.84 (tt, *J* = 6.9, 1.8 Hz, 2H), 1.76 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.65, 168.48, 155.38, 155.17, 143.06, 142.99, 140.91, 139.86, 136.22, 135.91, 134.42, 134.10, 133.95, 132.26, 130.46, 130.06, 127.52, 125.91, 125.63, 123.70, 123.39, 123.30, 122.88, 122.52, 122.50, 121.98, 118.86, 114.74, 114.69, 114.02, 113.73, 76.91, 60.56, 55.71, 37.85, 37.51, 36.70, 30.02, 27.00, 26.45, 23.23, 17.63; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₇H₂₆N₂O₃ 427.2016; found 427.2020.

Preparation of Boc-Protected Amines 4la and 4lb from the Precursor Isoindoline-1,3-Dione



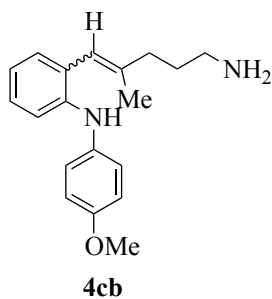
Preparation of (*E*)-*tert*-butyl 4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enylcarbamate **4ca** was achieved using a literature procedure.³² To an oven-dried flask equipped with a stir bar were added (*E*)-2-(4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enyl)isoindoline-1,3-dione **4ba** (1 equiv, 0.78 mmol, 320 mg) and EtOH

(14 mL). Hydrazine hydrate (1.4 equiv, 1.1 mmol, 54 μ L) was then added and the reaction was refluxed for 24 hours. Once complete, the solution was cooled to room temperature and the mixture was filtered. The remaining white solid was washed with EtOH (3 x 10 mL) and concentrated HCl (10 equiv, 7.8 mmol, 0.7 mL) was added to the filtrate. The acidic solution was then stirred and heated at 60 $^{\circ}$ C for 30 minutes. The resulting solution was concentrated in vacuum, cooled to 0 $^{\circ}$ C, diluted with H₂O (5 mL), and basified to pH 13 using 10 M NaOH. The aqueous solution was then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuum to give the intermediate primary amine **4ca** as a brown oil, which was taken to the next step without purification.



The resulting amine **4ca** (1 equiv, 0.53 mmol, 150 mg), 4-dimethylaminopyridine (DMAP) (10 mol%, 0.053 mmol, 6.5 mg) and anhydrous DCM (0.60 mL) was added to an oven-dried flask equipped

with a stir bar. The resulting solution was stirred at 0 °C prior to the dropwise addition of di-*tert*-butyl dicarbonate (Boc₂O) (1.1 equiv, 0.58 mmol, 128 mg) in anhydrous DCM (0.5 mL) over 10 minutes. The mixture was then warmed to room temperature and stirred for 15 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford carbamate **4la** as a clear oil (137 mg, 46% over 2 steps). IR ν_{max} (cm⁻¹) 3389, 2985, 1705, 1602, 1511, 1450, 1265, 1174, 1037, 755. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.02 (m, 5H), 6.90 – 6.84 (m, 2H), 6.84 – 6.77 (m, 1H), 6.20 (s, 1H), 5.53 (s, 1H), 4.60 (s, 1H), 3.81 (s, 3H), 3.36 (q, *J* = 6.6 Hz, 2H), 2.39 (t, *J* = 6.6 Hz, 2H), 1.78 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.21, 155.38, 143.02, 138.68, 136.07, 130.49, 127.73, 125.69, 123.20, 122.69, 118.99, 114.80, 114.24, 79.50, 55.79, 40.29, 39.01, 28.60, 17.88; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₃H₃₀N₂O₃ 383.2329; found 383.2328.

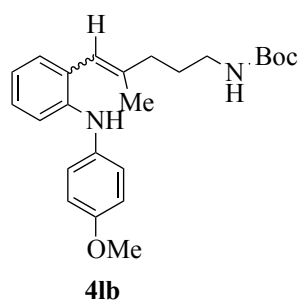


Preparation of (*E/Z*)-2-(5-amino-2-methylpent-1-enyl)-*N*-(4-methoxyphenyl)aniline **4cb** was achieved using a literature procedure.³²

To an oven-dried flask equipped with a stir bar was added (*E/Z*)-2-(5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enyl)isoindoline-1,3-dione **4bb** (1 equiv, 0.94 mmol, 400 mg) and EtOH (14 mL).

Hydrazine hydrate (1.4 equiv, 1.3 mmol, 64 μ L) was then added and the reaction was refluxed for 24 hours. Once complete, the solution was cooled to room temperature and the mixture was filtered. The remaining white solid was washed with EtOH (3 x 10 mL) and concentrated HCl (10 equiv, 7.8 mmol, 0.7 mL) was added to the filtrate. The acidic solution was then stirred and heated at 60 °C for 30 minutes. The resulting solution was concentrated in vacuum, cooled to 0

°C, diluted with H₂O (5 mL), and basified to pH 13 using 10 M NaOH. The aqueous solution was then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na₂SO₄, concentrated in vacuum and purified by flash chromatography on silica gel (98:2:4 hexanes:MeOH:Et₃N) to afford **4cb** as a brown oil (200 mg, 72%) as a 1:1 mixture of *E*:*Z* isomers. IR ν_{max} (cm⁻¹) 3292, 2937, 2865, 1651, 1600, 1510, 1460, 1244, 1041, 751. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.01 (m, 11H), 6.92 – 6.84 (m, 4H), 6.84 – 6.74 (m, 2H), 6.22 – 6.12 (m, 2H), 5.55 – 5.42 (m, 2H), 3.80 (s, 6H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.26 (td, *J* = 7.5, 1.2 Hz, 2H), 2.19 – 2.11 (m, 2H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.73 – 1.67 (m, 2H), 1.62 – 1.54 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 155.30, 155.19, 142.89, 142.81, 141.89, 141.52, 135.90, 135.72, 130.29, 130.10, 127.42, 127.32, 125.92, 125.67, 122.70, 122.44, 121.67, 120.82, 118.78, 118.71, 114.62, 113.82, 113.48, 55.58, 41.99, 37.21, 32.06, 30.02, 29.72, 23.20, 17.72; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₄N₂O 297.1961; found 297.1962.

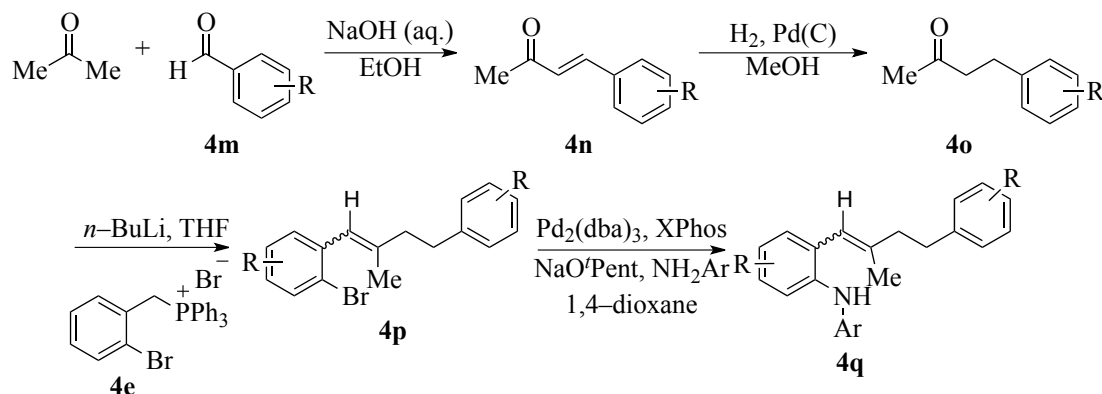


To an oven-dried flask equipped with a stir bar was added (*E/Z*)-2-(5-amino-2-methylpent-1-enyl)-*N*-(4-methoxyphenyl)aniline **4cb** (1 equiv, 0.47 mmol, 140 mg), 4-dimethylaminopyridine (DMAP) (10 mol%, 0.047 mmol, 5.8 mg) and anhydrous DCM (0.5 mL). The resulting solution was stirred at 0 °C prior to the dropwise addition of di-*tert*-butyl dicarbonate (Boc₂O) (1.1 equiv, 0.52 mmol, 113 mg) in anhydrous DCM (0.4 mL) over 10 minutes. The mixture was then warmed to room temperature and stirred for 15 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography

on silica gel (80:20 hexanes:EtOAc) to afford carbamate **4lb** as a yellow oil (80 mg, 43%). IR ν_{\max} (cm⁻¹) 3364, 2976, 2937, 1701, 1512, 1244, 1170, 1037, 751. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.17 – 6.99 (m, 10H), 6.88 (t, *J* = 2.5 Hz, 2H), 6.86 (t, *J* = 2.5 Hz, 2H), 6.80 (td, *J* = 7.2, 1.7 Hz, 2H), 6.17 (s, 2H), 5.74 (s, 1H), 5.47 (s, 1H), 4.58 (t, *J* = 6.0 Hz, 1H), 4.42 (s, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.21 (q, *J* = 6.6 Hz, 2H), 3.03 (q, *J* = 6.7 Hz, 2H), 2.31 – 2.20 (m, 2H), 2.15 (dd, *J* = 8.9, 6.5 Hz, 2H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.72 (d, *J* = 7.2 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 156.17, 156.05, 155.57, 155.30, 143.20, 143.10, 141.54, 140.47, 136.17, 135.81, 130.50, 130.21, 127.71, 127.52, 125.93, 125.66, 123.09, 122.82, 122.28, 121.85, 118.99, 118.76, 114.80, 114.70, 113.95, 113.77, 79.34, 79.13, 53.63, 40.23, 39.94, 36.80, 29.91, 28.60, 28.32, 28.17, 23.31, 17.69; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₄H₃₂N₂O₃ 397.2486; found 397.2488.

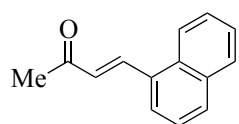
Preparation of Styrenyl Aniline Substrates Containing Aryl Nucleophiles

Scheme 4.22. Synthesis of Styrenyl Anilines **4qa–4qe**



General Procedure 4G (GP4G): Preparation of (*E*)-4-(aryl)but-3-en-2-ones **4na–4nd** via Aldol Condensation

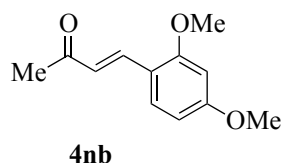
Preparation of enones **4na–4nd** were accomplished using a literature procedure.³³ To an oven-dried round bottom flask equipped with a stir bar containing 1.25 equivalents of NaOH (2.75 M in H₂O) was added 1 equivalent of substituted benzaldehyde **4m**. Slow addition of 1 equivalent of acetone (3.6 M in EtOH) followed at 0 °C prior to stirring at room temperature until completion. Once the reaction was complete, as indicated by TLC analysis, saturated NH₄Cl (aq.) was added and the mixture was extracted using Et₂O. The resulting solution organic layer was dried over Na₂SO₄ and concentrated in vacuum. The crude product was then subjected to liquid/liquid diffusion crystallization using DCM and hexanes to yield the corresponding pure enone in 90–96% yield.



4na

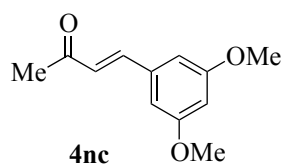
Following procedure **GP4G** with 1-naphthaldehyde **4ma** (1.0 equiv, 15 mmol, 2.35 g, 2.0 mL), acetone (1 equiv, 15 mmol, 871 mg, 1.1 mL in 4.2 mL EtOH), and NaOH (1.25 equiv, 18.8 mmol, 750 mg in 6.8 mL H₂O).

Crystallization using liquid/liquid diffusion (DCM/hexanes) afforded (*E*)-4-(naphthalen-1-yl)but-3-en-2-one **4na** as an orange oil (2.83 g, 95%). Characterization of the pure compound matched literature values.³⁴



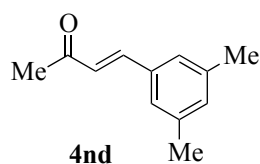
Following procedure **GP4G** with 2,4-dimethoxybenzaldehyde **4ma** (1.0 equiv, 40 mmol, 6.65 g), acetone (1 equiv, 40 mmol, 2.32 g, 2.94 mL in 11 mL EtOH), and NaOH (1.25 equiv, 50 mmol, 2.0 g in 18 mL H₂O).

Crystallization using liquid/liquid diffusion (DCM/hexanes) afforded (*E*)-4-(2,4-dimethoxyphenyl)but-3-en-2-one **4nb** as a yellow solid (7.4 g, 90%). Characterization of the pure compound matched literature values.³⁵



Following procedure **GP4G** with 3,5-dimethoxybenzaldehyde **4mc** (1.0 equiv, 43.2 mmol, 7.18 g), acetone (1 equiv, 43.2 mmol, 2.51 g, 3.71 mL in 12 mL EtOH), and NaOH (1.25 equiv, 54 mmol, 2.16 g in 20 mL

H₂O). Crystallization using liquid/liquid diffusion (DCM/hexanes) afforded (*E*)-4-(3,5-dimethoxyphenyl)but-3-en-2-one **4nc** as a yellow oil (8.4 g, 94%). Characterization of the pure compound matched literature values.³⁶

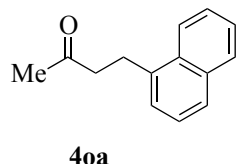


Following procedure **GP4G** with 3,5-dimethylbenzaldehyde **4md** (1.0 equiv, 17.6 mmol, 7.18 g), acetone (1 equiv, 17.6 mmol, 1.02 g, 1.3 mL in 4.9 mL EtOH), and NaOH (1.25 equiv, 22 mmol, 880 mg in 8 mL H₂O).

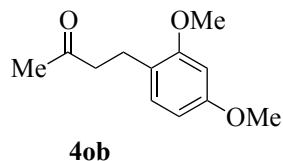
Crystallization using liquid/liquid diffusion (DCM/hexanes) afforded (*E*)-4-(3,5-dimethylphenyl)but-3-en-2-one **4nd** as a yellow oil (2.95 g, 96%). Characterization of the pure compound matched literature values.³⁶

General Procedure 4H (GP4H): Preparation of 4-(aryl)butan-2-ones **4oa**–**4od** via Catalytic Hydrogenation

To an oven-dried heavy wall pressure vessel was added enone **4n** (1 equiv) in anhydrous methanol (0.3 M). 10 wt% Pd(C) (10 mol%) was then carefully added under nitrogen atmosphere and the flask was secured in a Parr hydrogenator. After 3 cycles of flushing and refilling with hydrogen, the reaction vessel was filled with hydrogen (40 psi) and shaken until the reaction was complete. The mixture was then filtered through Celite and concentrated in vacuum to yield the crude ketone. Purification by flash chromatography on silica gel to afford the corresponding ketone **4o** in 60–92% yield.

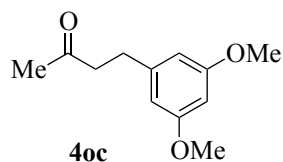


Following procedure **GP4H** with (*E*)-4-(naphthalen-1-yl)but-3-en-2-one **4na** (1.0 equiv, 14.4 mmol, 2.83 g), Pd(C) (10 wt%, 10 mol% 1.44 mmol, 153 mg) and MeOH (47 mL) for 5 hours. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded 4-(naphthalen-1-yl)butan-2-one **4oa** as a yellow oil (2.64 g, 92%). Characterization of the pure compound matched described literature values.³⁷

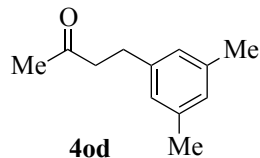


Following procedure **GP4H** with (*E*)-4-(2,4-dimethoxyphenyl)but-3-en-2-one **4nb** (1.0 equiv, 9.7 mmol, 2.06 g), Pd(C) (10 wt%, 10 mol% 0.97 mmol, 103 mg) and MeOH (35 mL) for 3 hours. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded 4-(2,4-

dimethoxyphenyl)butan-2-one **4ob** as a clear oil (1.91 g, 92%). Characterization of the pure compound matched described literature values.³⁸

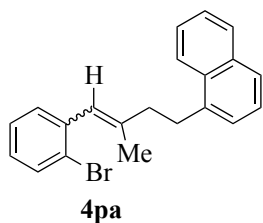


Following procedure **GP4H** with (*E*)-4-(3,5-dimethoxyphenyl)but-3-en-2-one **4nc** (1.0 equiv, 12.1 mmol, 2.49 g), Pd(C) (10 wt%, 10 mol% 1.21 mmol, 128 mg) and MeOH (40 mL) for 2 hours. Purification by flash chromatography on silica gel (85:15 hexanes:EtOAc) afforded 4-(3,5-dimethoxyphenyl)butan-2-one **4oc** as a clear oil (2.34 g, 93%). Characterization of the pure compound matched described literature values.³⁹



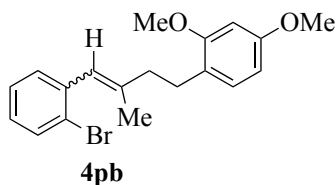
Following procedure **GP4H** with (*E*)-4-(3,5-dimethylphenyl)but-3-en-2-one **4nd** (1.0 equiv, 17.4 mmol, 3.03 g), Pd(C) (10 wt%, 10 mol% 1.74 mmol, 185 mg) and MeOH (60 mL) for 5 hours. Purification by flash chromatography on silica gel (95:5 hexanes:EtOAc) afforded 4-(3,5-dimethylphenyl)butan-2-one **4od** as a clear oil (1.84 g, 60%). Characterization of the pure compound matched described literature values.⁴⁰

Preparation of *ortho*-bromostyrenes 4pa–4pe via Wittig Reaction (GP4A)



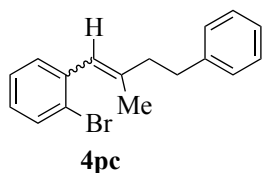
Following procedure **GP4A** with 4-(naphthalen-1-yl)butan-2-one **4oa** (1 equiv, 6.1 mmol, 1.21 g), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 6.1 mmol, 3.11 g), *n*-BuLi (1 equiv, 6.1 mmol, 4.1 mL) in 10 mL THF. Purification by flash chromatography on silica gel (97:3

hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-en-1-yn-1-yl)naphthalene **4pa** as a clear oil (1.11 g, 50%). IR ν_{max} (cm^{-1}) 3055, 2935, 1651, 1595, 1510, 1464, 1433, 1396, 1166, 1024, 946, 795, 777, 750, 670. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, $J = 8.4$ Hz, 1H), 7.89 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.82 (t, $J = 8.3$ Hz, 1H), 7.80 – 7.66 (m, 2H), 7.65 – 7.48 (m, 4H), 7.44 (dt, $J = 8.3, 6.0$ Hz, 2H), 7.37 (dd, $J = 8.4, 6.7$ Hz, 1H), 7.35 – 7.17 (m, 3H), 7.17 – 7.03 (m, 2H), 7.03 – 6.97 (m, 1H), 6.36 (s, 1H), 6.32 (s, 1H), 3.47 – 3.28 (m, 2H), 3.25 – 3.12 (m, 1H), 2.76 – 2.59 (m, 2H), 2.58 – 2.46 (m, 1H), 2.17 – 2.01 (m, 1H), 1.86 (d, $J = 1.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.99, 142.96, 141.52, 141.42, 140.85, 140.75, 140.71, 140.19, 130.27, 130.24, 129.13, 129.05, 128.43, 128.27, 128.20, 128.18, 127.66, 127.33, 127.20, 127.10, 125.88, 125.77, 122.48, 121.77, 120.90, 120.64, 120.18, 119.99, 118.48, 117.87, 116.07, 116.00, 41.16, 34.10, 33.95, 33.89, 23.14, 17.48; GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{21}\text{H}_{19}\text{Br}$ found 351/353.



Following procedure **GP4A** with 4-(2,4-dimethoxyphenyl)butan-2-one **4ob** (1 equiv, 2.64 mmol, 549 mg), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 2.64

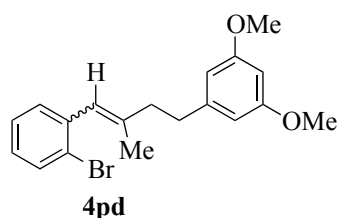
mmol, 1.35 g), *n*-BuLi (1 equiv, 2.64 mmol, 1.65 mL) in 7.5 mL THF. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-2,4-dimethoxybenzene **4pb** as a clear oil (953 mg, 42%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.54 (m, 1H), 7.31 – 7.20 (m, 4H), 7.16 – 7.12 (m, 1H), 7.11 – 7.03 (m, 3H), 6.49 – 6.40 (m, 4H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 2H), 3.71 (s, 2H), 2.87 – 2.80 (t, *J* = 1.7 Hz, 2H), 2.76 – 2.71 (t, *J* = 1.8 Hz, 1H), 2.50 – 2.49 (t, *J* = 1.6 Hz, 2H), 2.48 – 2.44 (t, *J* = 1.7 Hz, 1H), 2.01 (s, 2H), 1.80 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 159.40, 159.35, 158.51, 158.45, 140.52, 140.42, 138.39, 138.78, 132.56, 132.42, 131.17, 131.06, 130.14, 129.99, 127.77, 126.89, 126.86, 125.74, 124.86, 124.50, 122.91, 122.83, 103.97, 103.89, 98.68, 98.60, 55.54, 55.47, 55.28, 40.43, 34.87, 33.27, 31.80, 28.59, 28.37, 23.64, 22.87, 18.04, 14.34; GC/MS (CI) *m/z* [M+H]⁺ for C₁₉H₂₁BrO₂ found 361/363.



Following procedure **GP4A** with commercially available 4-phenylbutan-2-one (1 equiv, 8 mmol, 1.19 g, 1.2 mL), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 8.0 mmol, 4.1

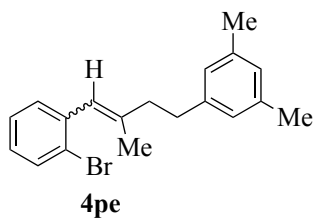
g), *n*-BuLi (1 equiv, 8.0 mmol, 5.0 mL) in 12 mL THF. Purification by flash chromatography on silica gel (93:7 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-1-bromo-2-(2-methyl-4-phenylbut-1-enyl)benzene **4pc** as a clear oil (1.35 g, 56%). IR ν_{max} (cm⁻¹) 3108, 3056, 2912, 2884, 1633, 1621, 1618, 1511, 1492, 1481, 1472, 1447, 1192, 1021, 648. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.78 (m, 1H), 7.68 – 7.62 (m, 1H), 7.55 – 7.51 (m, 1H), 7.42 – 7.39 (m, 2H), 7.38 – 7.23 (m, 6H), 7.22 – 7.19 (m, 1H), 7.18 – 7.13 (m, 2H), 6.48 (s, 1H), 3.01 – 2.94 (t, *J* = 1.7 Hz, 2H), 2.88 – 2.84 (t, *J* = 1.6 Hz, 1H), 2.66 – 2.61 (t, *J* = 1.8 Hz, 2H), 2.54 – 2.49 (t, *J* = 1.9 Hz, 1H), 2.09 (s, 2H), 1.88 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 139.56,

138.62, 132.55, 132.52, 131.07, 130.80, 138.59, 128.50, 128.49, 128.43, 127.99, 127.87, 126.96, 126.89, 126.16, 126.03, 126.00, 125.28, 124.46, 124.40, 41.72, 34.67, 34.24, 23.54, 18.02; GC/MS (CI) m/z $[M+H]^+$ for $C_{17}H_{17}Br$ found 301/303.



Following procedure **GP4A** with 4-(3,5-dimethoxyphenyl)butan-2-one **4oc** (1 equiv, 0.946 mmol, 197 mg), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 0.946 mmol, 483 mg), *n*-BuLi (1 equiv, 0.946 mmol, 0.63 mL) in 5.0 mL

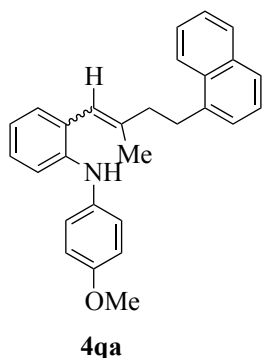
THF. Purification by flash chromatography on silica gel (95:5 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-3,5-dimethoxybenzene **4pd** as a clear yellow oil (205 mg, 60%). IR ν_{\max} (cm^{-1}) 2949, 2841, 1616, 1560, 1464, 1436, 1319, 1212, 1163, 1073, 1025, 921, 839, 756, 700. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.53 (m, 2H), 7.36 – 7.14 (m, 5H), 7.11 – 7.03 (m, 2H), 6.46 – 6.41 (m, 2H), 6.35 (t, J = 2.3 Hz, 1H), 6.31 (q, J = 1.9, 1.4 Hz, 2H), 6.28 (d, J = 2.3 Hz, 2H), 3.80 (s, 6H), 3.75 (s, 4H), 2.88 – 2.81 (m, 2H), 2.74 – 2.67 (m, 1H), 2.57 – 2.50 (m, 2H), 2.45 – 2.39 (m, 1H), 1.99 (d, J = 1.5 Hz, 2H), 1.80 (d, J = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 160.69, 160.63, 144.25, 144.09, 139.42, 139.32, 138.41, 138.37, 132.33, 130.85, 130.63, 128.73, 128.00, 127.77, 127.67, 126.73, 126.68, 125.92, 124.98, 124.20, 124.16, 106.43, 106.25, 97.77, 55.18, 55.12, 41.29, 34.81, 34.38, 34.24, 23.33, 17.84; GC/MS (CI) m/z $[M+H]^+$ for $C_{19}H_{21}BrO_2$ found 361/363.



Following procedure **GP4A** with 4-(3,5-dimethylphenyl)butan-2-one **4od** (1 equiv, 4.36 mmol, 764 mg), (2-bromobenzyl)triphenylphosphonium bromide **4e** (1 equiv, 4.36 mmol, 2.23 g), *n*-BuLi (1 equiv, 4.36 mmol, 2.9 mL) in 20 mL THF.

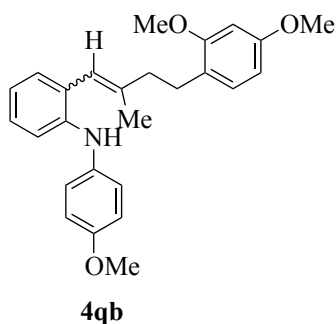
Purification by flash chromatography on silica gel (100% hexanes) afforded an inseparable *E/Z* mixture of (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-3,5-dimethylbenzene **4pe** as a clear oil (60 mg, 40%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.56 (m, 2H), 7.33 – 7.22 (m, 4H), 7.14 – 7.06 (m, 3H), 6.94 – 6.83 (m, 4H), 6.78 – 6.73 (m, 2H), 6.34 – 6.27 (m, 2H), 2.84 (dd, *J* = 6.3, 4.5 Hz, 2H), 2.74 – 2.69 (m, 2H), 2.54 – 2.50 (m, 2H), 2.43 (t, *J* = 2.2 Hz, 2H), 2.35 (t, *J* = 0.8 Hz, 6H), 2.29 (t, *J* = 0.8 Hz, 5H), 2.01 (d, *J* = 1.5 Hz, 3H), 1.82 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 141.75, 141.54, 139.64, 139.47, 138.47, 138.42, 137.63, 137.61, 132.33, 132.27, 130.85, 130.65, 127.70, 127.61, 127.42, 126.69, 126.64, 126.22, 126.04, 126.04, 125.80, 124.85, 124.26, 124.19, 41.69, 34.36, 33.83, 23.32, 21.27, 21.22, 17.82; GC/MS (CI) *m/z* [M+H]⁺ for C₁₉H₂₁Br found 329/331.

Preparation of Styrenyl Anilines **4qa–4qe** via Buchwald–Hartwig Amination (GP4B)



Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 0.528 mmol, 65 mg), (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)naphthalene **4pa** (1 equiv, 0.44 mmol, 173 mg), Pd₂(dba)₃ (0.75 mol%, 0.0033 mmol, 3 mg), XPhos (2.25 mol%, 0.0099 mmol, 5 mg) and NaO^tPent (1.5 equiv, 0.66 mmol, 73 mg) in 1,4-dioxane (1.5 mL). Purification by flash

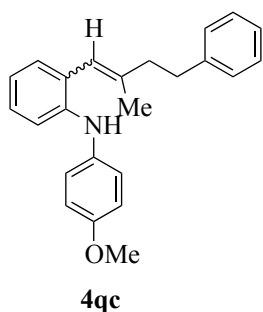
chromatography on silica gel (97:3 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-4-(naphthalen-1-yl)but-1-enyl)aniline **4qa** as a yellow oil (182 mg, 94%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.96 (m, 1H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.66 – 7.57 (m, 2H), 7.48 – 7.36 (m, 2H), 7.35 – 7.20 (m, 3H), 7.20 – 7.11 (m, 1H), 6.98 (dddd, *J* = 13.0, 10.2, 4.9, 3.2 Hz, 3H), 6.94 – 6.84 (m, 4H), 6.83 – 6.59 (m, 4H), 6.13 (s, 1H), 5.94 (s, 1H), 5.34 (s, 1H), 5.15 – 4.96 (m, 1H), 3.71 (d, *J* = 1.8 Hz, 3H), 3.69 (d, *J* = 3.3 Hz, 1H), 3.24 (t, *J* = 7.6 Hz, 2H), 3.15 – 3.01 (m, 1H), 2.74 – 2.52 (m, 2H), 2.52 – 2.37 (m, 1H), 1.99 (t, *J* = 1.7 Hz, 1H), 1.88 – 1.73 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 190.74, 155.27, 145.69, 142.87, 140.66, 140.57, 137.89, 137.78, 135.70, 135.64, 133.85, 131.74, 130.18, 130.07, 128.84, 128.57, 127.28, 126.76, 126.06, 125.85, 125.59, 125.42, 123.66, 122.89, 122.66, 122.66, 121.66, 118.76, 118.62, 118.50, 114.47, 113.72, 99.89, 55.51, 40.64, 31.83, 31.52, 23.50, 17.77; GC/MS (CI) *m/z* [M+H]⁺ for C₂₈H₂₇NO found 394.



Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 0.4 mmol, 49 mg), (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-2,4-dimethoxybenzene **4pb** (1 equiv, 0.332 mmol, 120 mg), Pd₂(dba)₃ (0.75 mol%, 0.0025 mmol, 2.3 mg), XPhos (2.25 mol%, 0.0075 mmol, 3.6 mg) and NaO^tPent (1.5 equiv, 0.5 mmol, 55 mg)

in 1,4-dioxane (1.5 mL). Purification by flash chromatography on silica gel (91:9 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-2-(4-(2,4-dimethoxyphenyl)-2-methylbut-1-enyl)-*N*-(4-methoxyphenyl)aniline **4qb** as a brown oil (123 mg, 92%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.12 – 6.92 (m, 9H), 6.92 – 6.82 (m, 3H), 6.77 (tt, *J* = 6.9, 1.4 Hz, 2H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.38 (ddt, *J* = 6.7, 4.3, 2.5 Hz, 2H), 6.10 (s, 1H), 5.98 (s, 1H), 5.19

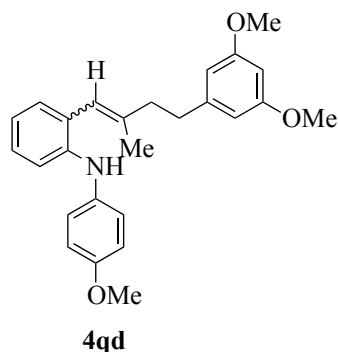
(s, 1H), 3.82 (s, 3H), 3.81 (s, 2H), 3.80 (s, 3H), 3.78 (s, 2H), 3.73 (s, 3H), 3.63 (s, 2H), 2.82 (t, J = 7.3 Hz, 2H), 2.70 (dd, J = 9.0, 6.5 Hz, 1H), 2.55 – 2.46 (m, 2H), 2.42 (dd, J = 9.0, 6.4 Hz, 1H), 1.98 (d, J = 1.4 Hz, 2H), 1.78 (d, J = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.14, 159.06, 158.35, 155.30, 154.96, 142.96, 142.71, 141.70, 141.12, 135.99, 135.83, 130.30, 130.14, 130.05, 129.79, 127.08, 126.29, 125.76, 123.10, 122.42, 122.30, 122.07, 121.97, 121.27, 118.74, 118.42, 114.54, 114.50, 113.62, 113.40, 103.75, 103.64, 98.51, 98.34, 55.54, 55.25, 55.15, 54.96, 39.74, 32.73, 28.18, 27.89, 23.20, 17.52; GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{26}\text{H}_{29}\text{NO}_3$ found 404.



Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 3.4 mmol, 416 mg), (*E/Z*)-1-bromo-2-(2-methyl-4-phenylbut-1-enyl)benzene **4pc** (1 equiv, 2.8 mmol, 849 mg), $\text{Pd}_2(\text{dba})_3$ (0.75 mol%, 0.021 mmol, 19.2 mg), XPhos (2.25 mol%, 0.063 mmol, 30 mg) and NaO^tPent (1.5 equiv, 4.2 mmol, 462.4 mg) in 1,4-dioxane (5.5 mL). Purification by flash

chromatography on silica gel (95:5 hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-4-phenylbut-1-enyl)aniline **4qc** as a clear oil (875 mg, 91%). IR ν_{max} (cm^{-1}) 3397, 3026, 2900, 2833, 1532, 1512, 1454, 1294, 1242, 1180, 1037, 823, 747, 699, 458. ^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 7.39 – 7.21 (m, 8H), 7.19 – 7.10 (m, 6H), 7.09 – 7.07 (m, 1H), 7.06 (m, 1H), 7.05 – 7.04 (m, 2H), 7.03 – 7.01 (m, 1H), 6.95 – 6.91 (m, 3H), 6.81 – 6.83 (m, 2H), 6.94 – 6.84 (m, 4H), 6.24 (s, 1H), 6.08 (s, 1H), 5.40 – 5.02 (s, 2H), 3.86 (s, 3H), 2.99 – 2.95 (t, J = 1.7 Hz, 2H), 2.92 – 2.81 (t, J = 1.8 Hz, 1H), 2.65 – 2.60 (t, J = 1.7 Hz, 2H), 2.58 – 2.51 (t, J = 1.9 Hz, 1H), 2.08 (s, 2H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.28, 143.15, 142.91, 141.84, 141.81, 141.26, 140.38, 136.00, 135.88, 130.31, 130.29, 128.70, 128.52, 128.48, 128.44, 127.56, 127.44, 126.13, 126.05, 126.01, 125.74, 123.25,

122.58, 122.46, 122.11, 118.98, 118.71, 114.76, 114.65, 113.87, 113.75, 55.71, 55.69, 41.35, 34.54, 34.29, 34.20, 23.44, 17.68; GC/MS (CI) m/z $[M+H]^+$ for $C_{24}H_{25}NO$ found 344.



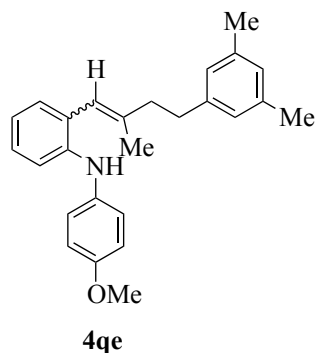
Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 1.96 mmol, 241.4 mg), (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-3,5-dimethoxybenzene **4pd** (1 equiv, 1.63 mmol, 589 mg), $Pd_2(dba)_3$ (0.75 mol%, 0.0122 mmol, 11.2 mg), XPhos (2.25 mol%, 0.0367 mmol, 17.5 mg) and NaO^tPent (1.5 equiv, 2.45 mmol, 270

mg) in 1,4-dioxane (3 mL). Purification by flash chromatography on silica gel (90:10

hexanes:EtOAc) afforded an inseparable *E/Z* mixture of (*E/Z*)-2-(4-(3,5-dimethoxyphenyl)-2-methylbut-1-enyl)-*N*-(4-methoxyphenyl)aniline **4qd** as a brown oil (500 mg, 76%). IR ν_{max}

(cm^{-1}) 3391, 2949, 2841, 1602, 1515, 1457, 1294, 1246, 1208, 1160, 1073, 1039, 828, 752, 697.

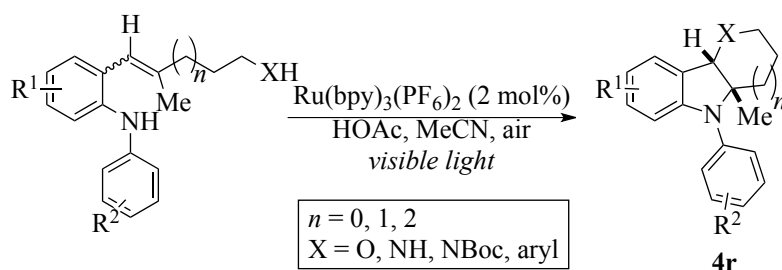
1H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 6.99 (m, 8H), 6.91 – 6.86 (m, 4H), 6.83 – 6.86 (m, 1H), 6.43 (s, 2H), 6.33 – 6.31 (m, 1H), 6.27 (m, 1H), 6.18 (s, 1H), 6.10 (s, 1H), 5.41 – 5.12 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 2.90 – 2.85 (t, J = 2.1 Hz, 2H), 2.78 – 2.23 (t, J = 2.2 Hz, 1H), 2.62 – 2.58 (t, J = 2.1 Hz, 2H), 2.55 – 2.48 (t, J = 2.2 Hz, 2H), 2.12 (d, J = 1.4 Hz, 2H), 1.82 (d, J = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.74, 160.66, 155.40, 155.11, 144.10, 143.11, 141.00, 140.31, 135.87, 135.77, 130.18, 127.41, 127.33, 126.04, 125.56, 123.19, 122.54, 122.25, 121.90, 118.82, 118.55, 114.62, 114.52, 113.76, 113.53, 106.63, 106.28, 98.04, 97.84, 55.60, 40.83, 34.47, 34.41, 34.11, 23.29, 17.62; GC/MS (CI) m/z $[M+H]^+$ for $C_{26}H_{29}NO_3$ found 404.



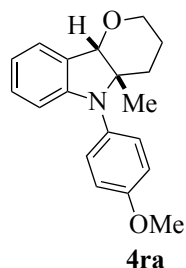
Following procedure **GP4B** with *para*-anisidine (1.2 equiv, 3.42 mmol, 421 mg), (*E/Z*)-1-(4-(2-bromophenyl)-3-methylbut-3-enyl)-3,5-dimethylbenzene **4pe** (1 equiv, 2.85 mmol, 940 mg), Pd₂(dba)₃ (0.75 mol%, 0.021 mmol, 20.0 mg), XPhos (2.25 mol%, 0.063 mmol, 30.6 mg) and NaO^tPent (1.5 equiv, 4.28 mmol, 471 mg) in 1,4-dioxane (10 mL). Purification by flash chromatography on silica gel (98:2 hexanes:EtOAc) afforded an inseparable isomeric mixture of (*E/Z*)-2-(4-(3,5-dimethylphenyl)-2-methylbut-1-enyl)-*N*-(4-methoxyphenyl)aniline **4qe** as a yellow oil (889 g, 84%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.18 – 7.05 (m, 6H), 7.05 – 6.96 (m, 4H), 6.89 (dq, *J* = 8.7, 2.1 Hz, 5H), 6.87 – 6.78 (m, 3H), 6.75 – 6.68 (m, 1H), 6.16 (s, 1H), 6.12 – 6.04 (m, 1H), 5.16 (s, 1H), 3.85 (d, *J* = 1.4 Hz, 3H), 3.84 (s, 1H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.77 – 2.68 (m, 1H), 2.61 – 2.53 (m, 2H), 2.49 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.30 – 2.27 (m, 6H), 2.04 – 1.97 (m, 2H), 1.82 (d, *J* = 1.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 142.96, 141.43, 141.43, 141.08, 140.46, 137.64, 137.58, 135.97, 135.67, 135.65, 130.12, 130.06, 130.04, 127.60, 127.39, 127.18, 126.27, 126.07, 123.07, 123.06, 122.22, 121.89, 121.59, 118.80, 118.42, 118.41, 114.49, 114.38, 113.38, 55.44, 41.02, 34.12, 33.90, 33.78, 23.17, 21.22, 21.19, 17.51; GC/MS (CI) *m/z* [M+H]⁺ for C₂₆H₂₉NO found 372.

General Procedure 4I (GP4I): Preparation of Fused *N*-Arylindolines using Visible Light Photoredox Catalysis

Scheme 4.23. Fused Indoline Synthesis using Visible Light Photoredox Catalysis



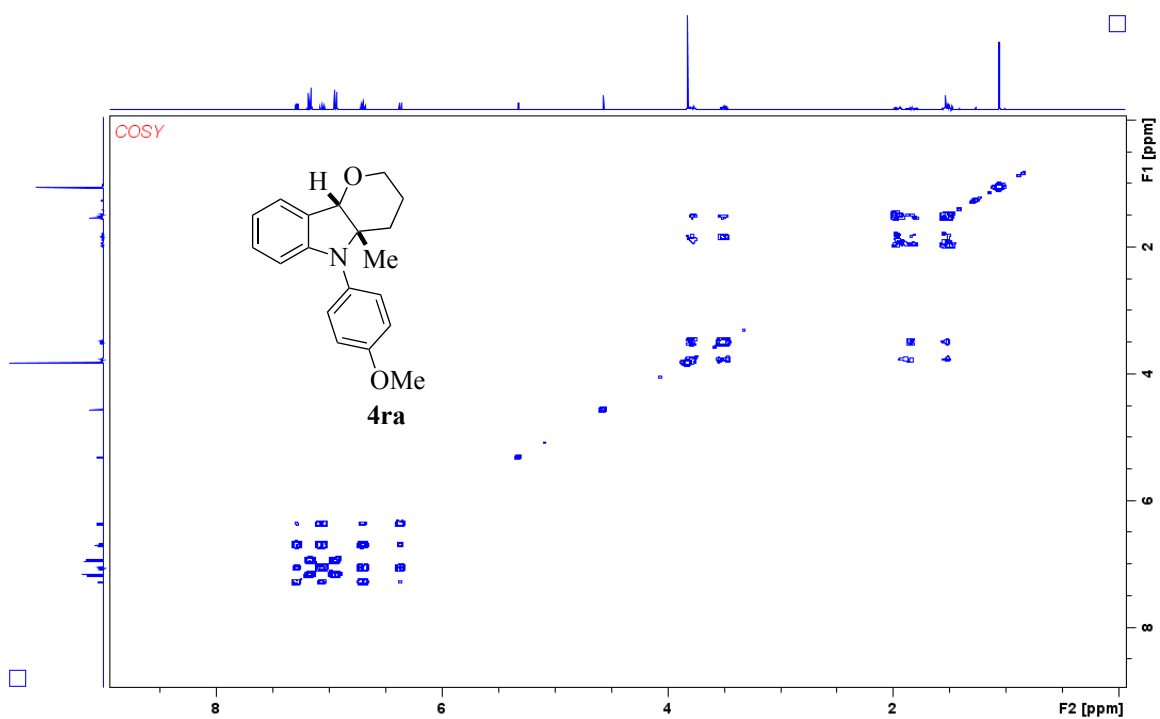
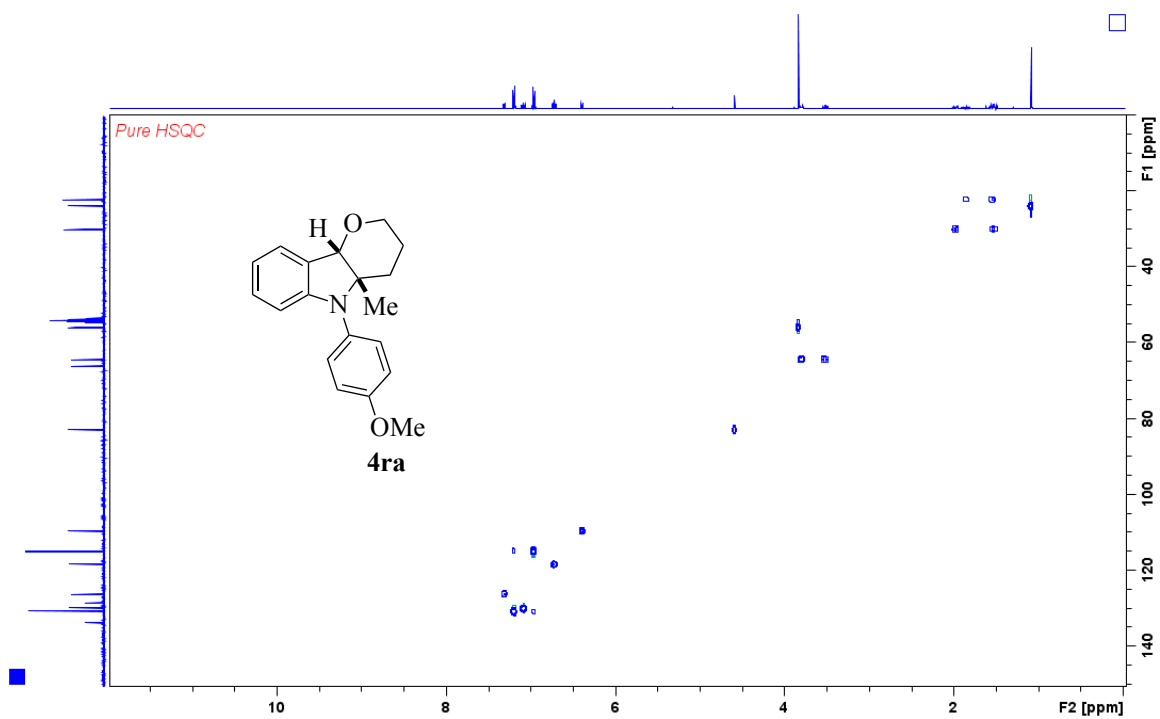
To a test tube equipped with a stir bar was added the styrenyl aniline (1 equiv, 0.2 mmol), tris(2,2t tube equipped with a sti hexafluorophosphate (2 mol%, 0.004 mmol, 3.5 mg), acetic acid (1 equiv, 0.2 mmol, 11.4 μ L) and MeCN (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16-gauge needle. The test tube was then clamped at a 6 cm distance from an 18W focused white LED and stirred until completion by TLC. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on neutral alumina gel to afford the pure fused *N*-arylindoline **4r**.

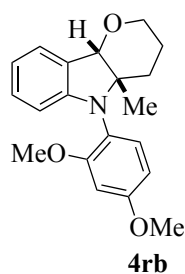
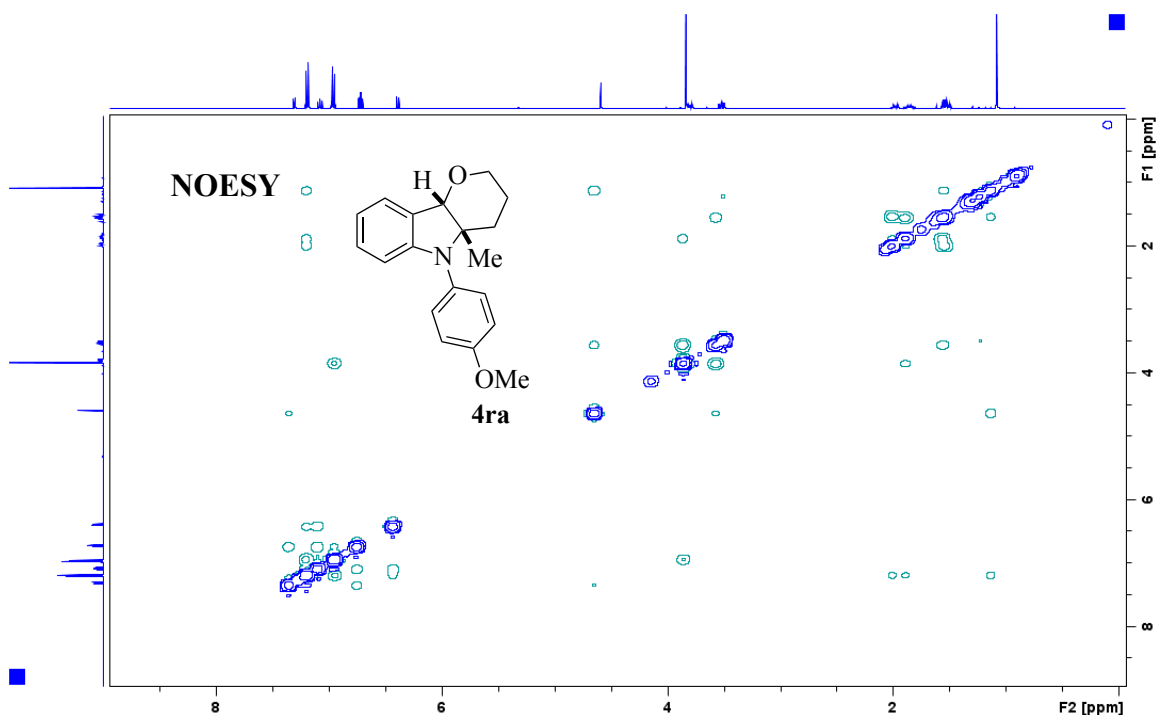


Following procedure **GP4I** with (*E/Z*)-5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-en-1-ol **4aa** (1 equiv, 0.2 mmol, 59.5 mg) for 8 hours.

Purification by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) afforded (4*aS*,9*bS*)-5-(4-methoxyphenyl)-4*a*-methyl-

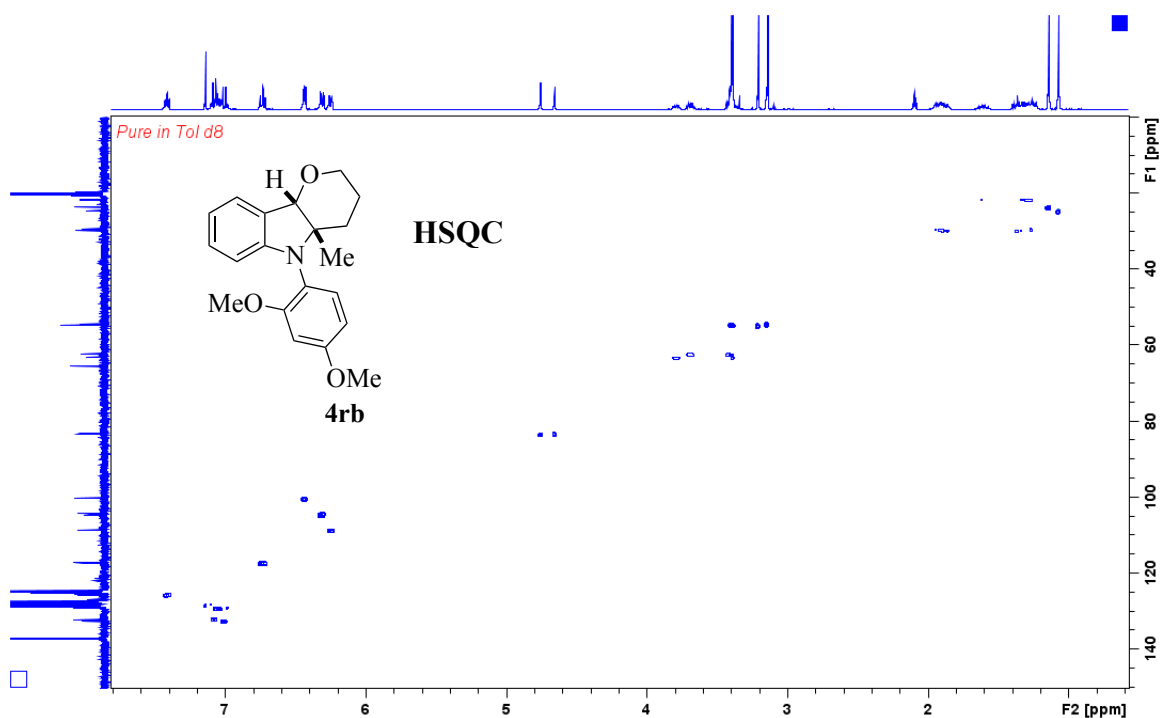
2,3,4,4*a*,5,9*b*-hexahydropyrano[3,2-*b*]indole **4ra** as a yellow solid, m.p. 96–99 °C (43 mg, 73%). IR ν_{max} (cm⁻¹) 3456, 2965, 1619, 1511, 1463, 1370, 1246, 1035, 752, 565. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.31 (ddt, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.08 (dddd, *J* = 7.5, 1.4, 0.3 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.72 (td, *J* = 7.3, 1.0 Hz, 1H), 6.39 (ddt, *J* = 8.0, 1.0, 0.5 Hz, 1H), 4.59 (d, *J* = 0.7 Hz, 1H), 3.84 (s, 3H), 3.80 (dtdd, *J* = 9.0, 4.2, 1.6, 0.5 Hz, 1H), 3.56 – 3.45 (m, 1H), 2.03 – 1.94 (m, 1H), 1.91 – 1.78 (m, 1H), 1.59 – 1.54 (m, 1H), 1.52 (tt, *J* = 3.7, 1.4 Hz, 1H), 1.08 (s, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 158.63, 151.68, 133.58, 130.62, 129.79, 128.53, 126.23, 118.22, 114.94, 109.53, 82.82, 66.13, 64.39, 55.93, 30.07, 23.82, 22.24; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₁NO₂ 296.1645; found 296.1635.

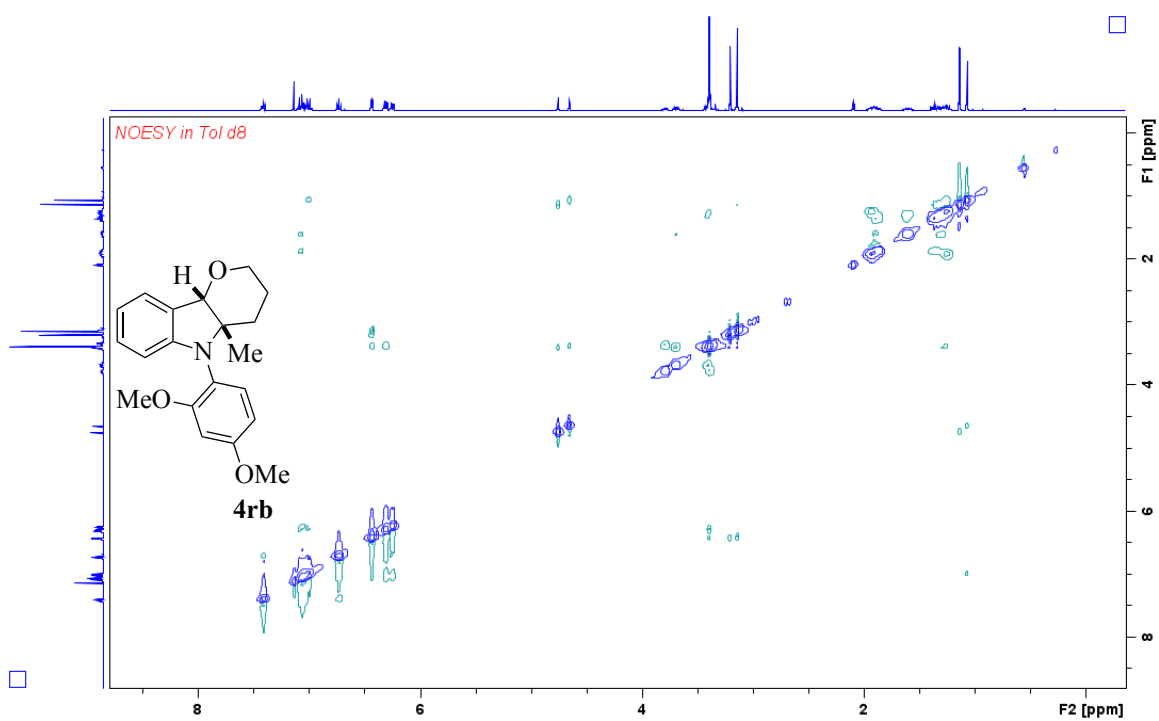
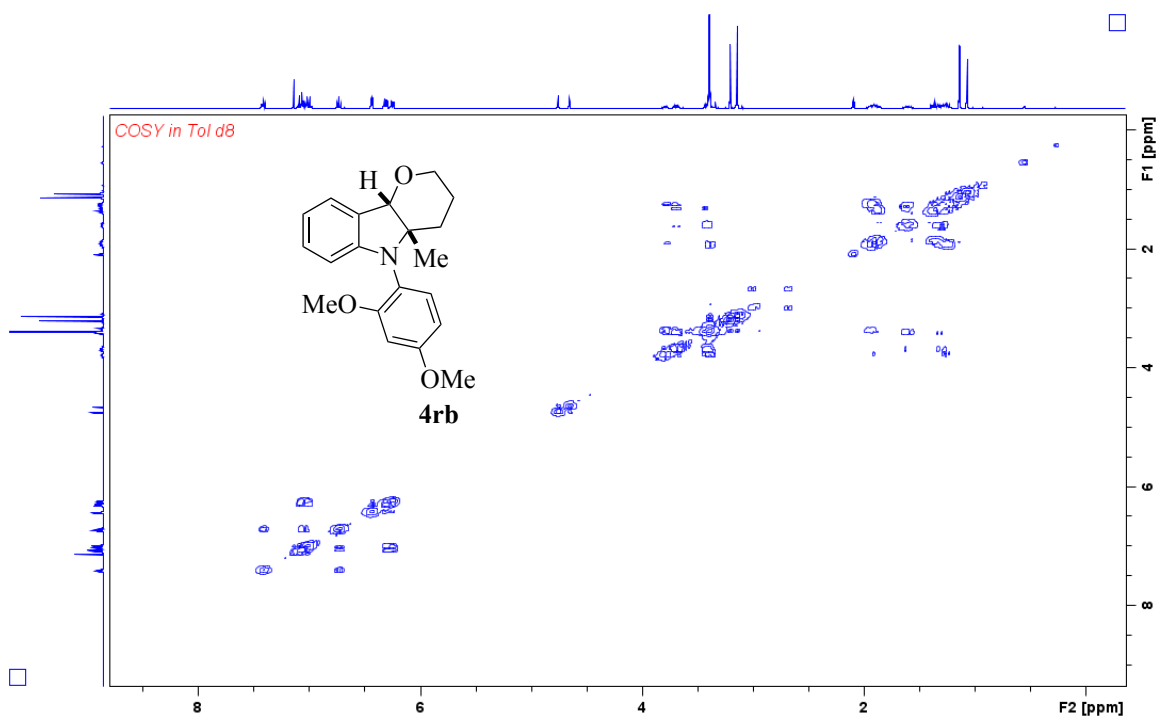


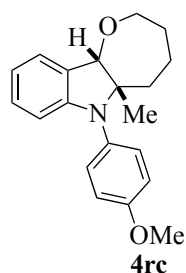


Following procedure **GP4I** with (*E/Z*)-5-(2-(2,4-dimethoxyphenylamino)phenyl)-4-methylpent-4-en-1-ol **4ab** (1 equiv, 0.2 mmol, 65.5 mg) for 6 hours. Purification by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) afforded (4*aS*,9*bS*)-5-(2,4-dimethoxyphenyl)-4a-methyl-2,3,4,4a,5,9b-hexahydropyrano[3,2-*b*]indole **4rb** as a yellow oil (39.7 mg, 61%). NMR showed a doubling of peaks. In order to confirm *cis* selectivity, NOESY was performed. IR ν_{max} (cm⁻¹) 2950, 2838, 1611, 1208, 1034, 834, 744. ¹H NMR (400 MHz, Toluene-*d*₈) δ 7.41 (dddt, *J* = 7.1, 5.7, 1.3, 0.7 Hz, 2H), 7.14 (s, 1H), 7.12 – 7.06 (m, 2H), 7.05 – 7.02 (m, 1H), 6.73 (tdd, *J* = 7.4, 1.0, 0.5 Hz, 2H), 6.44 (dt, *J* = 4.3, 2.2 Hz, 2H), 6.35 – 6.28 (m, 2H), 6.28 – 6.17 (m, 2H), 4.75 (s, 1H), 3.84 – 3.74 (m, 1H), 3.73 – 3.62 (m, 1H), 3.44 – 3.41 (m, 1H), 3.39 (d, *J* = 1.6 Hz, 3H), 3.38 (s, 2H), 3.20 (s, 2H), 3.14 (s, 3H), 1.91 (dddt, *J* = 19.0, 14.0, 6.3, 3.8 Hz, 3H), 1.67 – 1.52 (m, 1H), 1.42 – 1.19 (m, 5H), 1.13 (s, 3H), 1.06 (s, 2H); ¹³C NMR

(101 MHz, Tol) δ 160.06, 159.99, 159.49, 159.42, 151.82, 151.46, 132.89, 132.41, 129.44, 129.37, 128.50, 127.18, 125.95, 125.79, 117.49, 117.44, 108.92, 108.86, 104.85, 104.55, 100.61, 100.48, 83.55, 83.38, 65.75, 65.74, 63.43, 62.52, 54.98, 54.84, 54.63, 29.97, 29.72, 24.89, 23.83, 21.98, 21.93; HRMS (ESI) m/z $[M+H]^+$, calc'd for $C_{20}H_{23}NO_3$ 326.1748; found 326.1750.





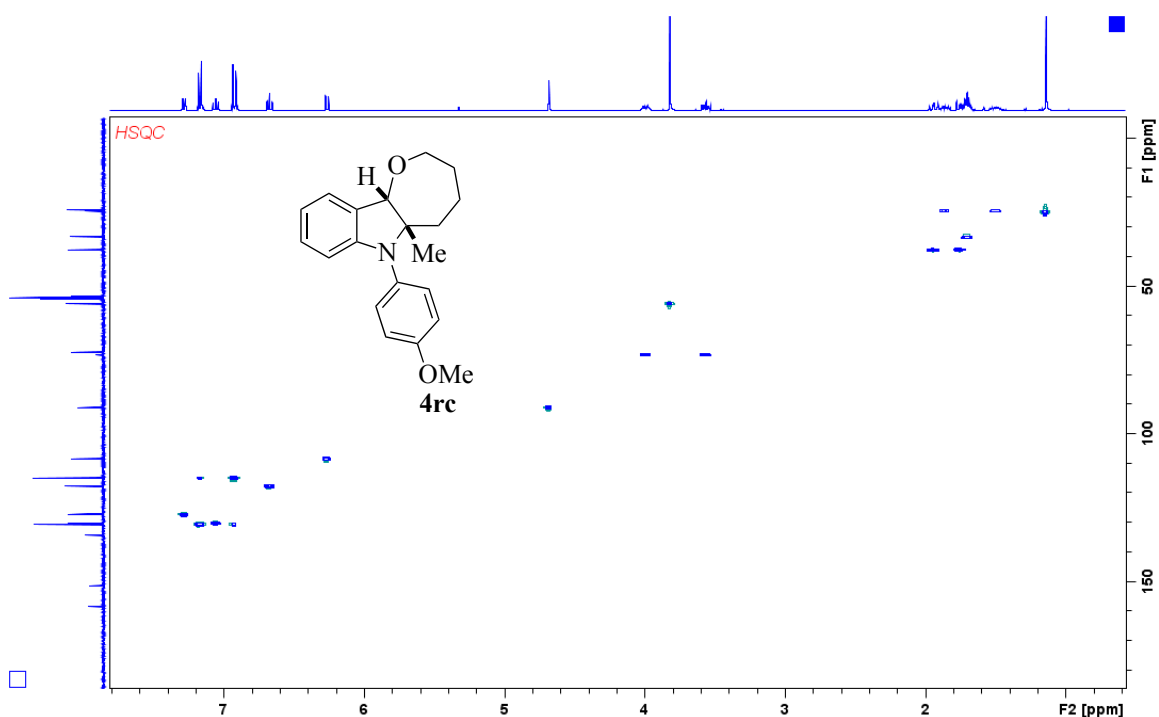


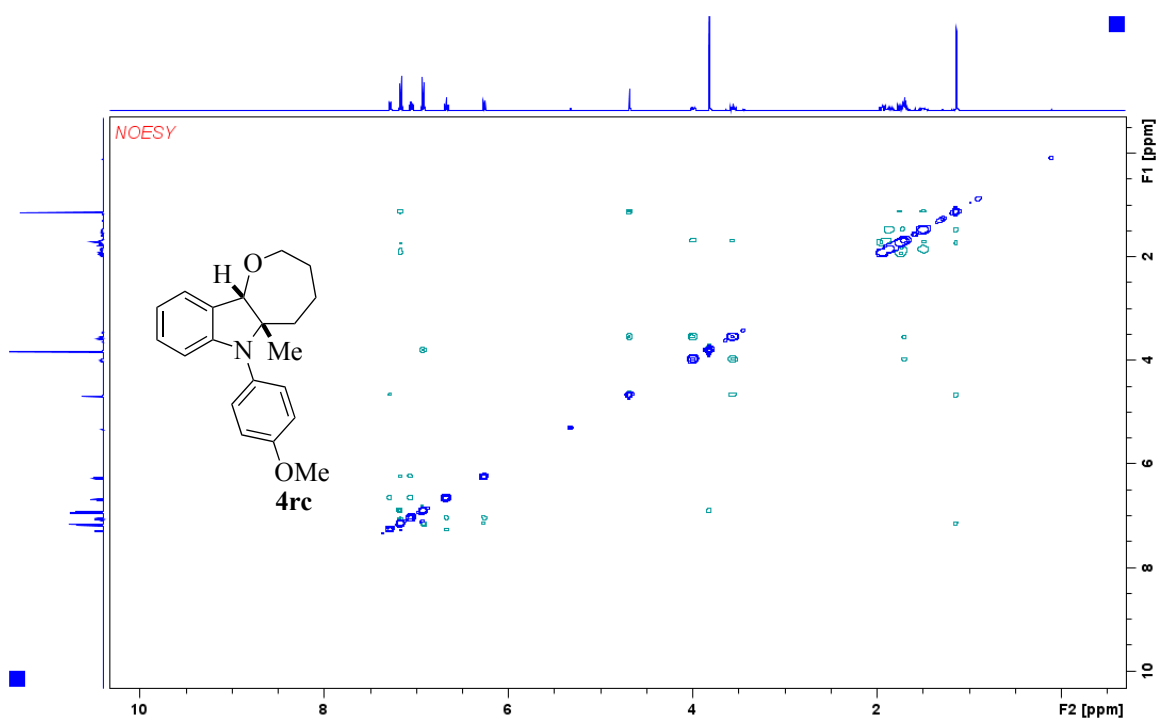
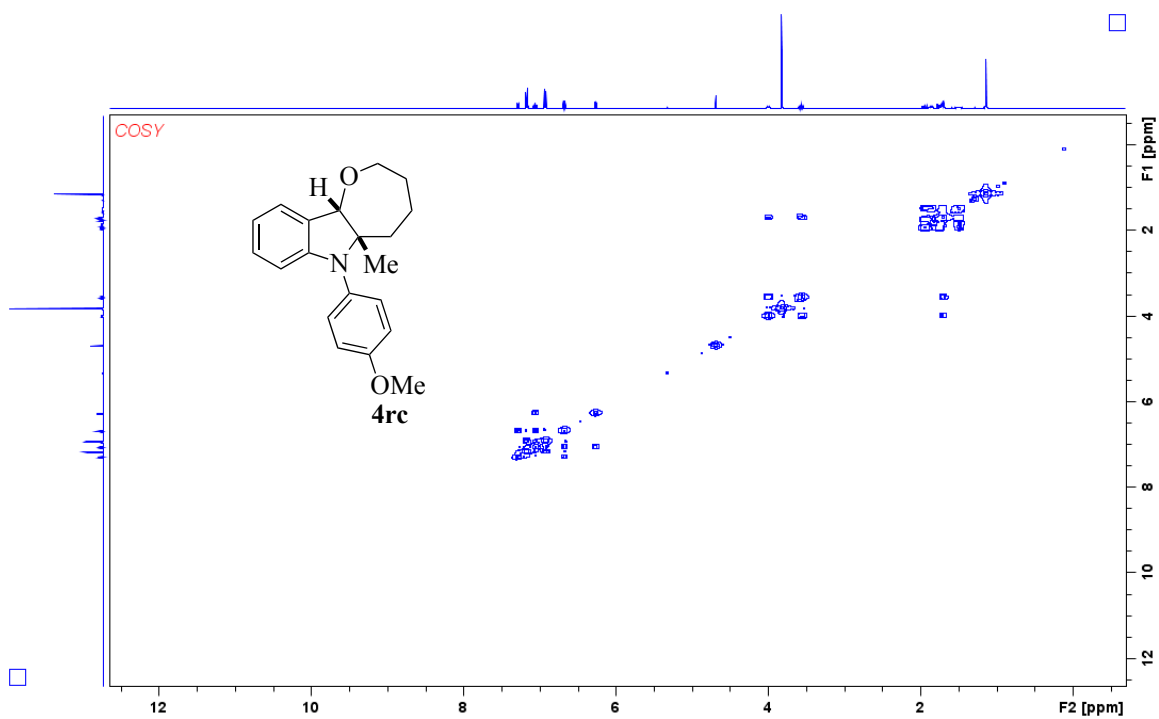
Following procedure **GP4I** with (*E/Z*)-6-(2-(4-methoxyphenylamino)phenyl)-5-methylhex-5-en-1-ol **4ad** (1 equiv, 0.2 mmol, 62.3 mg) for 8.5 hours.

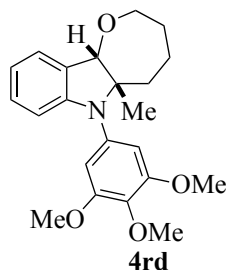
Purification by flash chromatography on neutral alumina gel (98:2

hexanes:EtOAc) afforded (5a*S*,10b*S*)-6-(4-methoxyphenyl)-5a-methyl-

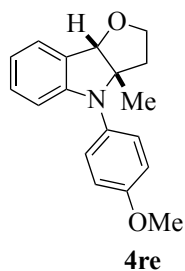
3,4,5,5a,6,10b-hexahydro-2*H*-oxepino[3,2-*b*]indole **4rc** as a yellow oil (44.6 mg, 72%). IR ν_{max} (cm^{-1}) 3468, 3047, 2935, 1612, 1514, 1366, 1250, 1103, 833, 745. ^1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.28 (ddq, $J = 7.3, 1.2, 0.6$ Hz, 1H), 7.20 – 7.13 (m, 2H), 7.10 – 7.02 (m, 1H), 6.96 – 6.88 (m, 2H), 6.67 (tdd, $J = 7.3, 1.0, 0.5$ Hz, 1H), 6.26 (ddt, $J = 8.0, 1.1, 0.5$ Hz, 1H), 4.68 (s, 1H), 4.05 – 3.94 (m, 1H), 3.82 (s, 3H), 3.62 – 3.50 (m, 1H), 1.98 – 1.90 (m, 1H), 1.90 – 1.80 (m, 1H), 1.79 – 1.73 (m, 1H), 1.70 (tt, $J = 8.0, 4.2$ Hz, 2H), 1.56 – 1.41 (m, 1H), 1.14 (d, $J = 0.6$ Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.46, 151.43, 134.30, 130.59, 130.26, 127.28, 127.12, 117.72, 114.88, 108.57, 91.04, 73.24, 72.38, 55.91, 37.67, 33.26, 24.60, 24.16; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for 310.1797; found 310.1798.





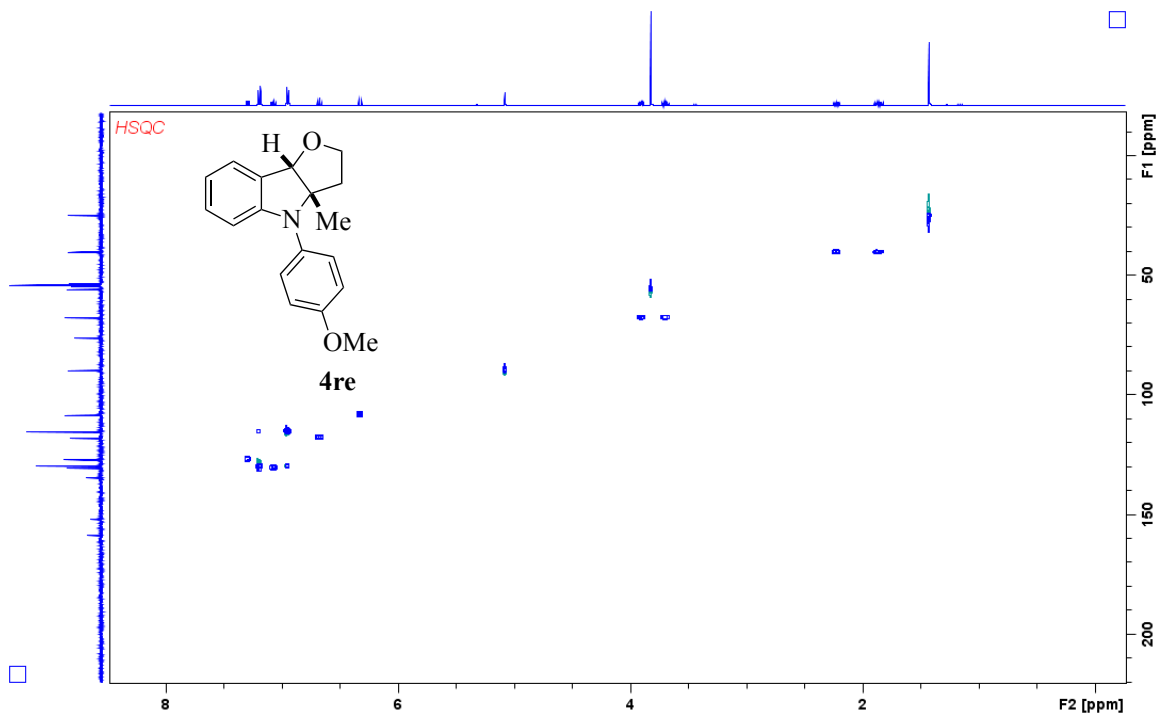


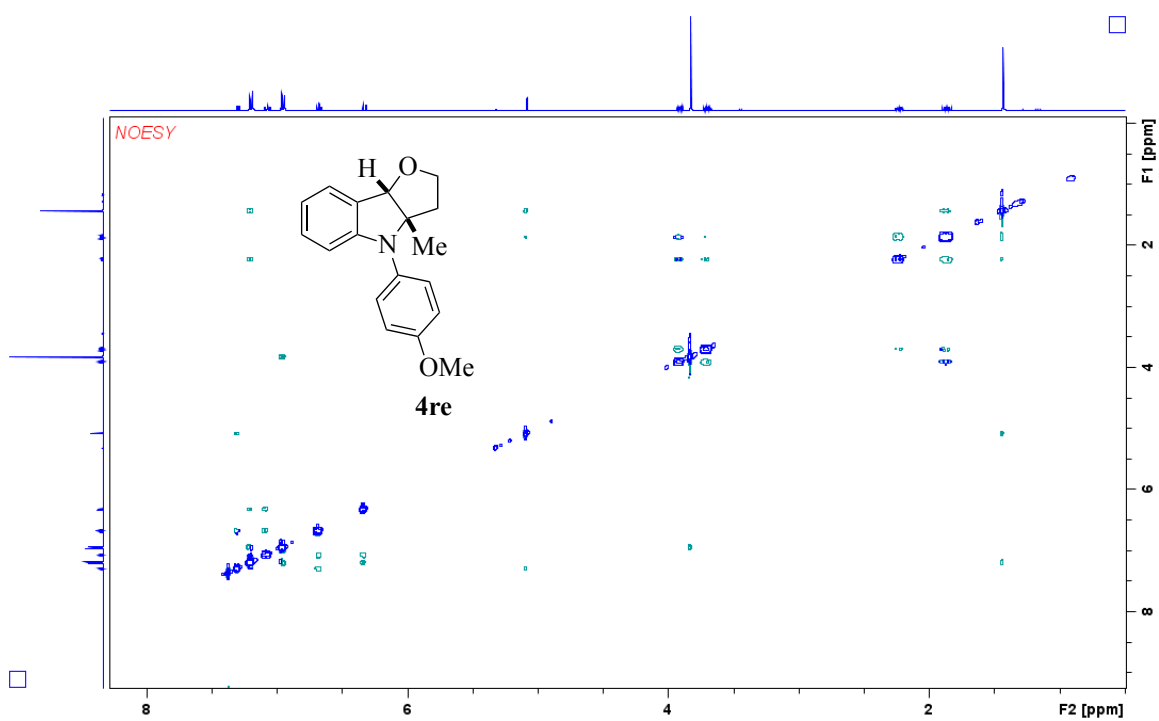
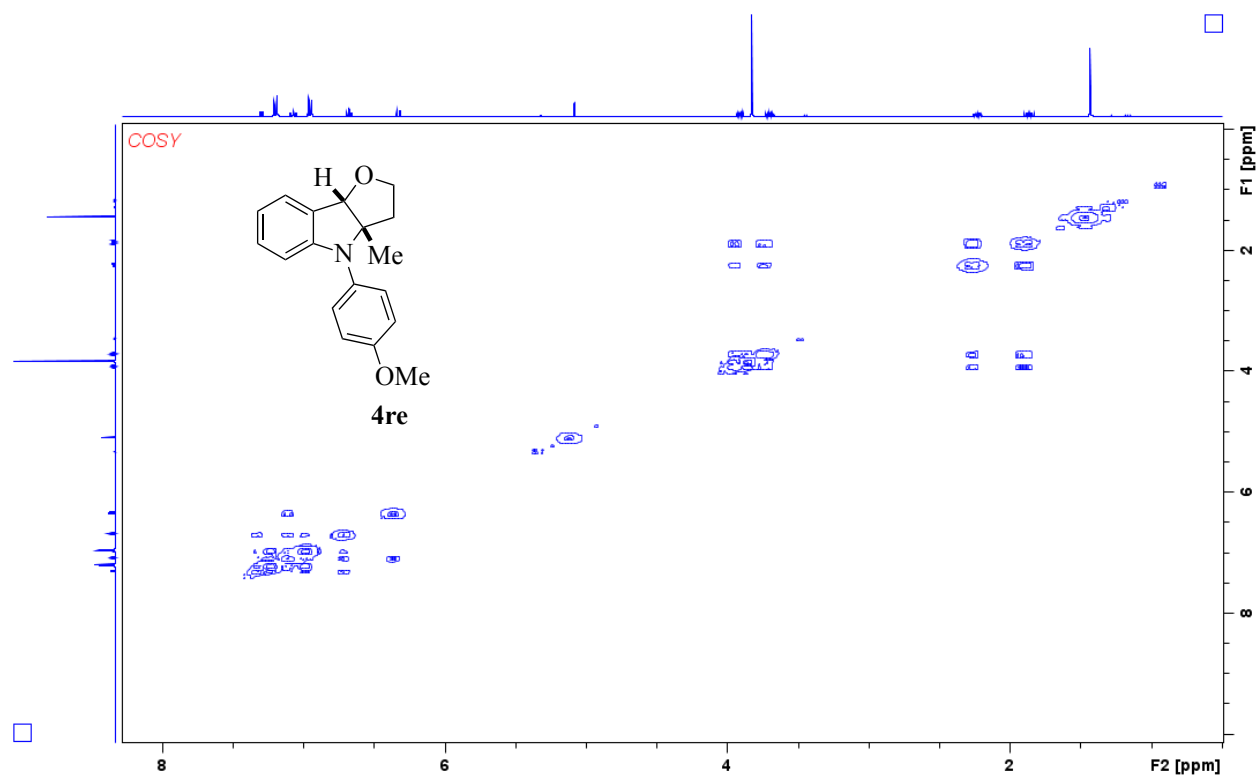
Following procedure **GP4I** with (*E/Z*)-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-en-1-ol **4ae** (1 equiv, 0.2 mmol, 74.3 mg) for 7.5 hours. Purification by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) afforded (5*aS*,10*bS*)-5*a*-methyl-6-(3,4,5-trimethoxyphenyl)-3,4,5,5*a*,6,10*b*-hexahydro-2*H*-oxepino[3,2-*b*]indole **4rd** as a clear oil (45 mg, 61%). IR ν_{\max} (cm⁻¹) 3436, 2935, 1587, 1507, 1415, 1328, 1229, 1124, 1100, 752. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.31 – 7.24 (m, 1H), 7.13 – 7.05 (m, 1H), 6.74 – 6.65 (m, 1H), 6.49 – 6.40 (m, 3H), 4.65 (d, *J* = 4.4 Hz, 1H), 4.05 – 3.93 (m, 1H), 3.80 – 3.78 (m, 3H), 3.79 – 3.77 (m, 6H), 3.56 (ddd, *J* = 12.6, 8.2, 4.7 Hz, 1H), 1.97 (dq, *J* = 15.3, 5.2 Hz, 1H), 1.91 – 1.79 (m, 2H), 1.69 (ddq, *J* = 18.7, 10.1, 4.3 Hz, 2H), 1.51 (dtd, *J* = 18.6, 9.7, 8.1, 4.7 Hz, 1H), 1.18 (d, *J* = 5.1 Hz, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 154.07, 150.73, 137.61, 136.91, 130.33, 127.38, 127.37, 118.08, 109.23, 106.21, 91.14, 73.41, 72.77, 61.02, 56.59, 37.60, 33.23, 24.79, 24.20; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₂H₂₇NO₄ 370.2013; found 370.2015.

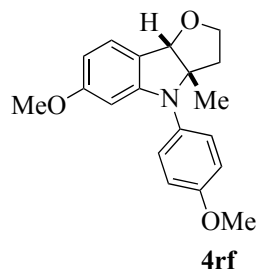


Following procedure **GP4I** with (*E*)-4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4af** (1 equiv, 0.2 mmol, 57 mg) for 8 hours. Purification by flash chromatography on neutral alumina gel (98:2 hexanes:EtOAc) afforded (3*aS*,8*bS*)-4-(4-methoxyphenyl)-3*a*-methyl-3,3*a*,4,8*b*-tetrahydro-2*H*-furo[3,2-*b*]indole **4re** as a yellow oil (41.4 mg, 74%). IR ν_{\max} (cm⁻¹) 3043, 2970, 2862, 1606, 1509, 1474, 1244, 1036, 826, 744. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.30 (ddt, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.11 – 7.03 (m, 1H), 6.98 – 6.91 (m, 2H), 6.71 – 6.64 (m, 1H), 6.33 (ddq, *J* = 8.0, 1.0, 0.5 Hz, 1H), 5.08 (s, 1H), 3.91 (ddd, *J* = 8.6, 6.9, 3.3 Hz, 1H),

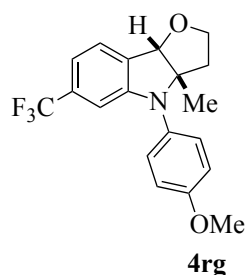
3.83 (s, 3H), 3.74 – 3.65 (m, 1H), 2.23 (dddd, $J = 12.7, 5.5, 3.4, 0.6$ Hz, 1H), 1.94 – 1.80 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.34, 151.75, 134.40, 130.27, 129.43, 127.01, 126.81, 117.97, 115.24, 108.35, 89.84, 76.14, 67.51, 55.95, 40.12, 24.70; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$ 282.1483; found 282.1485.





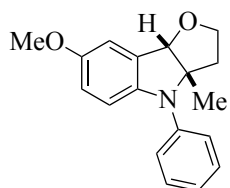


Following procedure **GP4I** with (*E*)-4-(4-methoxy-2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4ag** (1 equiv, 0.2 mmol, 63 mg) for 25 hours. Purification by flash chromatography on neutral alumina gel (85:15 hexanes:EtOAc) afforded (3a*S*,8b*S*)-6-methoxy-4-(4-methoxyphenyl)-3a-methyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4rf** as a clear oil (20 mg, 32%). IR ν_{\max} (cm⁻¹) 2930, 2866, 1622, 1510, 1455, 1377, 1245, 1164, 1033, 828. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.21 – 7.11 (m, 3H), 6.95 (d, *J* = 2.2 Hz, 1H), 6.94 – 6.91 (m, 1H), 6.21 (dt, *J* = 8.0, 1.9 Hz, 1H), 5.83 (t, *J* = 3.6 Hz, 1H), 3.87 (tdd, *J* = 6.0, 4.5, 3.0 Hz, 1H), 3.83 – 3.80 (m, 3H), 3.73 – 3.66 (m, 1H), 3.66 – 3.61 (m, 3H), 2.24 – 2.13 (m, 1H), 1.87 – 1.76 (m, 1H), 1.43 – 1.37 (m, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 162.50, 158.46, 153.34, 134.11, 129.71, 127.31, 119.62, 115.27, 103.44, 94.40, 89.37, 77.06, 67.30, 55.97, 55.73, 40.12, 24.66; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₁NO₃ 312.1594; found 312.1597.

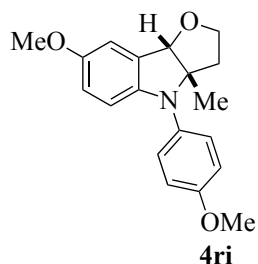


Following procedure **GP4I** with (*E*)-4-(2-(4-methoxyphenylamino)-4-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol **4ah** (1 equiv, 0.2 mmol, 71 mg) for 24 hours. Purification by flash chromatography on neutral alumina gel (95:5 hexanes:EtOAc) afforded (3a*S*,8b*S*)-4-(4-methoxyphenyl)-3a-methyl-6-(trifluoromethyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4rg** as a yellow oil (38 mg, 54%). IR ν_{\max} (cm⁻¹) 2936, 2866, 1620, 1513, 1445, 1378, 1327, 1126, 1042, 832. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.39 (dq, *J* = 7.6, 0.7 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.01 – 6.95 (m, 2H), 6.91 (ddt, *J* = 7.6, 1.6, 0.7 Hz, 1H), 6.44 (dp, *J* = 1.7,

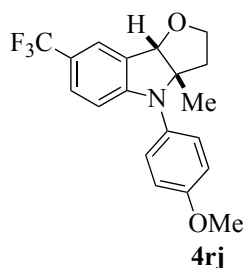
0.5 Hz, 1H), 5.11 (t, $J = 0.7$ Hz, 1H), 3.95 (ddd, $J = 8.7, 7.0, 3.0$ Hz, 1H), 3.84 (s, 3H), 3.71 (ddd, $J = 9.8, 8.7, 5.4$ Hz, 1H), 2.24 (dddd, $J = 12.8, 5.4, 3.1, 0.5$ Hz, 1H), 1.88 (ddd, $J = 12.8, 9.8, 7.0$ Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.06, 152.29, 132.99, 130.68, 130.66, 130.11, 129.15, 127.11, 125.16 (q, $J = 272.33$ Hz), 115.62, 132.43 (q, $J = 31.3$ Hz), 88.90, 76.87, 67.78, 56.01, 39.88, 24.48; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}_2$ 350.1362; found 350.1364.



Following procedure **GP4I** with (*E*)-4-(5-methoxy-2-(phenylamino)phenyl)-3-methylbut-3-en-1-ol **4ai** (1 equiv, 0.2 mmol, 56.7 mg) for 6 hours. Purification by flash chromatography on neutral alumina gel (92:8 hexanes:EtOAc) afforded (3a*S*,8b*S*)-7-methoxy-3a-methyl-4-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4rh** as a yellow oil (34 mg, 60%). IR ν_{max} (cm^{-1}) 2950, 2869, 1595, 1490, 1356, 1261, 1198, 1148, 1039, 697. ^1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.39 – 7.31 (m, 2H), 7.31 – 7.25 (m, 2H), 7.16 – 7.08 (m, 1H), 6.94 (dt, $J = 2.7, 0.5$ Hz, 1H), 6.73 (ddd, $J = 8.7, 2.7, 0.4$ Hz, 1H), 6.62 (dt, $J = 8.7, 0.5$ Hz, 1H), 5.02 (d, $J = 0.7$ Hz, 1H), 3.88 (ddd, $J = 8.7, 6.9, 4.1$ Hz, 1H), 3.76 (s, 3H), 3.67 (tdd, $J = 8.7, 5.8, 0.3$ Hz, 1H), 2.30 (dddd, $J = 12.7, 5.8, 4.1, 0.5$ Hz, 1H), 1.94 (ddd, $J = 12.7, 8.7, 6.9$ Hz, 1H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 153.67, 144.03, 143.08, 129.82, 128.79, 124.80, 124.49, 116.26, 112.29, 110.50, 90.42, 76.36, 67.71, 56.43, 40.38, 25.23; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{18}\text{H}_{19}\text{NO}_2$ 282.1489; found 282.1490.

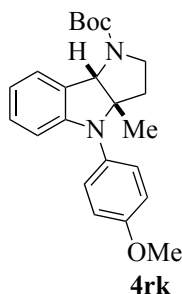


Following procedure **GP4I** with (*E*)-4-(5-methoxy-2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4aj** (1 equiv, 0.2 mmol, 63 mg) for 3 hours. Purification by flash chromatography on neutral alumina gel (95:5 hexanes:EtOAc) afforded (3a*S*,8b*S*)-7-methoxy-4-(4-methoxyphenyl)-3a-methyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4ri** as a yellow oil (45 mg, 71%). IR ν_{\max} (cm⁻¹) 2934, 2865, 2832, 1510, 1489, 1245, 1147, 1037, 817, 775. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.21 – 7.15 (m, 2H), 6.96 – 6.87 (m, 3H), 6.69 (ddt, *J* = 8.6, 2.7, 0.5 Hz, 1H), 6.34 (dt, *J* = 8.6, 0.5 Hz, 1H), 5.03 (s, 1H), 3.89 (dddd, *J* = 8.6, 7.0, 3.5, 0.5 Hz, 1H), 3.81 (s, 3H), 3.74 (d, *J* = 0.4 Hz, 3H), 3.72 – 3.63 (m, 1H), 2.27 – 2.14 (m, 1H), 1.84 (dddd, *J* = 12.7, 9.4, 7.0, 0.4 Hz, 1H), 1.41 (d, *J* = 0.5 Hz, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 157.82, 153.20, 145.72, 135.56, 128.43, 128.08, 116.34, 115.12, 112.39, 109.39, 90.08, 76.45, 67.66, 56.48, 55.94, 40.21, 24.90; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₉H₂₁NO₃ 312.1594; found 312.1596.



Following procedure **GP4I** with (*E*)-4-(2-(4-methoxyphenylamino)-5-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol **4ak** (1 equiv, 0.2 mmol, 70.4 mg) for 24 hours. Purification by flash chromatography on neutral alumina gel (95:5 hexanes:EtOAc) afforded (3a*S*,8b*S*)-4-(4-methoxyphenyl)-3a-methyl-7-(trifluoromethyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4rj** as a clear oil (27 mg, 39%). IR ν_{\max} (cm⁻¹) 2936, 2871, 1623, 1509, 1452, 1377, 1326, 1248, 1109, 821. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.53 (dp, *J* = 1.9, 0.6 Hz, 1H), 7.31 (dddd, *J* = 8.5, 2.3, 1.1, 0.5 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.02 – 6.94 (m, 2H), 6.26 (dq, *J* = 8.4,

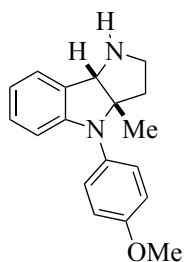
0.6 Hz, 1H), 5.11 (s, 1H), 3.95 (ddd, $J = 8.7, 7.0, 3.0$ Hz, 1H), 3.83 (s, 3H), 3.70 (ddd, $J = 9.8, 8.7, 5.3$ Hz, 1H), 2.23 (dddd, $J = 12.9, 5.4, 3.0, 0.6$ Hz, 1H), 1.94 – 1.81 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.15, 154.55, 132.70, 130.16, 128.11, 127.09, 124.11, 123.07 (q, $J = 270.2$ Hz), 119.12 (q, $J = 32.3$ Hz), 115.55, 107.34, 88.80, 77.08, 67.65, 56.02, 39.81, 24.45; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}_2$ 350.1362; found 350.1365.



Following procedure **GP4I** with (*E*)-*tert*-butyl 4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enylcarbamate **4la** (1 equiv, 0.2 mmol, 76.1 mg) for 10 hours. Purification by flash chromatography on neutral alumina gel (95:5 hexanes:THF) afforded (3*aS*,8*bS*)-*tert*-butyl 4-(4-methoxyphenyl)-3*a*-methyl-2,3,3*a*,4-tetrahydropyrrolo[3,2-*b*]indole-1(8*bH*)-carboxylate **4rk** as a clear oil (57.6 mg, 76%). IR ν_{max} (cm^{-1}) 2980, 1700, 1604, 1512, 1404, 1250, 1175, 1101, 1036, 750. ^1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.62 – 7.53 (m, 1H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.18 (d, $J = 2.2$ Hz, 2H), 7.16 (d, $J = 2.2$ Hz, 2H), 7.06 – 6.98 (m, 2H), 6.96 (d, $J = 2.3$ Hz, 2H), 6.94 (d, $J = 2.2$ Hz, 2H), 6.65 (q, $J = 7.3$ Hz, 2H), 6.28 (dt, $J = 1.0, 0.5$ Hz, 1H), 6.26 (dt, $J = 1.0, 0.5$ Hz, 1H), 5.03 – 4.94 (m, 1H), 4.94 – 4.86 (m, 1H), 3.82 (s, 6H), 3.74 (ddd, $J = 10.9, 7.6, 3.3$ Hz, 1H), 3.64 (td, $J = 10.0, 8.3, 5.7$ Hz, 1H), 3.47 – 3.28 (m, 2H), 2.16 (ddt, $J = 13.1, 6.4, 3.4$ Hz, 2H), 1.86 – 1.69 (m, 2H), 1.57 (s, 9H), 1.48 (d, $J = 11.6$ Hz, 8H), 1.37 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.62, 158.58, 154.63, 154.26, 151.42, 151.22, 133.90, 133.75, 130.17, 130.11, 129.63, 129.48, 128.72, 128.30, 128.03, 127.23, 118.07, 117.91, 115.19, 108.47, 108.30, 80.14, 79.60, 77.02, 75.87, 69.24, 55.96, 46.21, 45.89, 36.75,

35.92, 29.02, 28.78, 23.72; HRMS (ESI) m/z $[M+H]^+$, calc'd for $C_{23}H_{28}N_2O_3$ 381.2173; found 381.2171.

Rotamers were observed due to the Boc group, complicating the spectra. In order to justify the *cis* selectivity, the Boc was removed and 2D experiments were performed.



(3a*S*,8b*S*)-*tert*-butyl 4-(4-methoxyphenyl)-3a-methyl-2,3,3a,4-

tetrahydropyrrolo[3,2-*b*]indole-1(8b*H*)-carboxylate **4rk** (1 equiv, 0.184 mmol,

70 mg) was transferred to a flask and neat trifluoroacetic acid (5 equiv, 0.92

mmol, 70 μ L) was added. The mixture was swirled vigorously for 5 minutes then

completely concentrated in vacuum. Purification by flash chromatography on neutral alumina gel

(96:4 DCM:MeOH) yielded (3a*S*,8b*S*)-4-(4-methoxyphenyl)-3a-methyl-1,2,3,3a,4,8b-

hexahydropyrrolo[3,2-*b*]indole as a clear oil (21 mg, 41%). IR ν_{\max} (cm^{-1}) 2967, 2929, 2867,

1605, 1510, 1485, 1244, 1183, 884, 750. ^1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.22 –

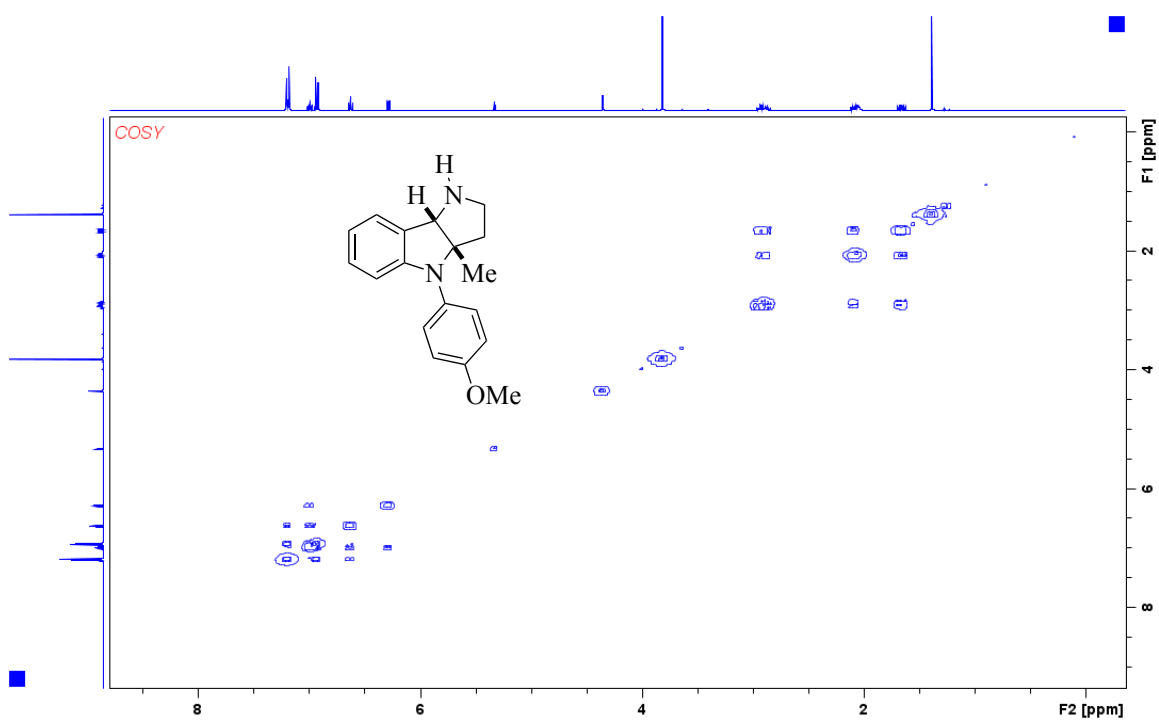
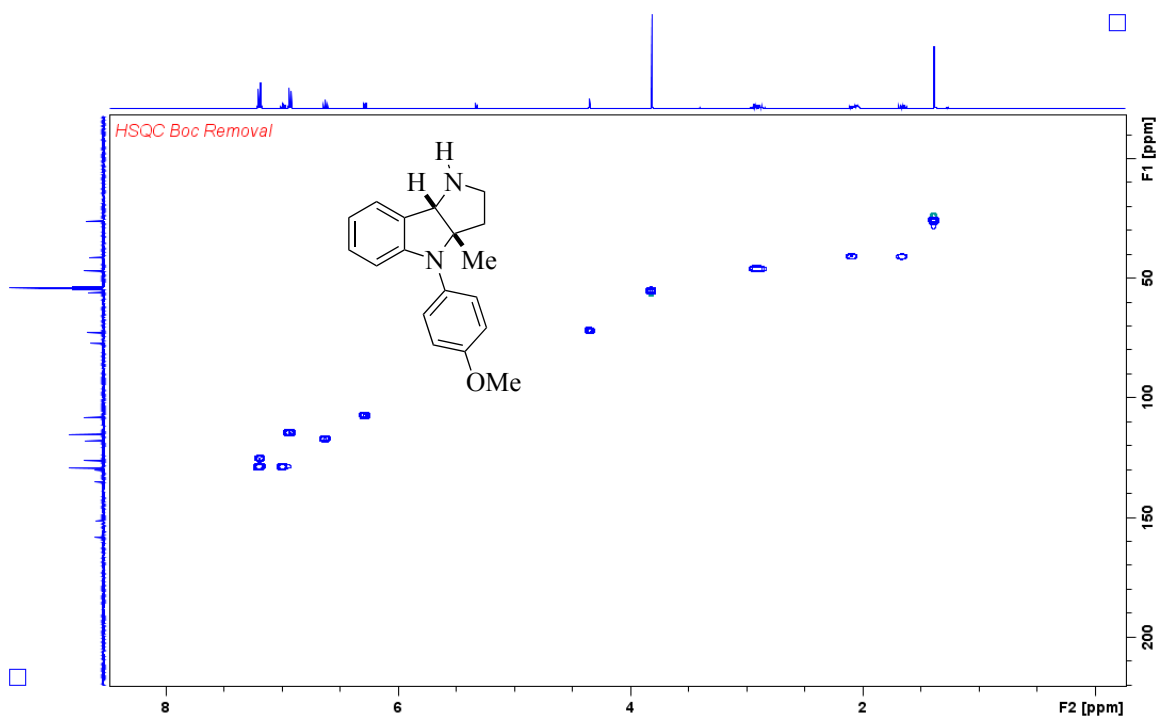
7.16 (m, 3H), 7.03 – 6.95 (m, 1H), 6.95 – 6.90 (m, 2H), 6.63 (td, J = 7.3, 1.0 Hz, 1H), 6.29 (ddt,

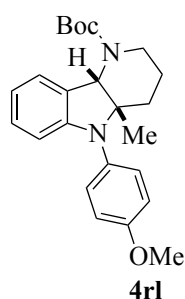
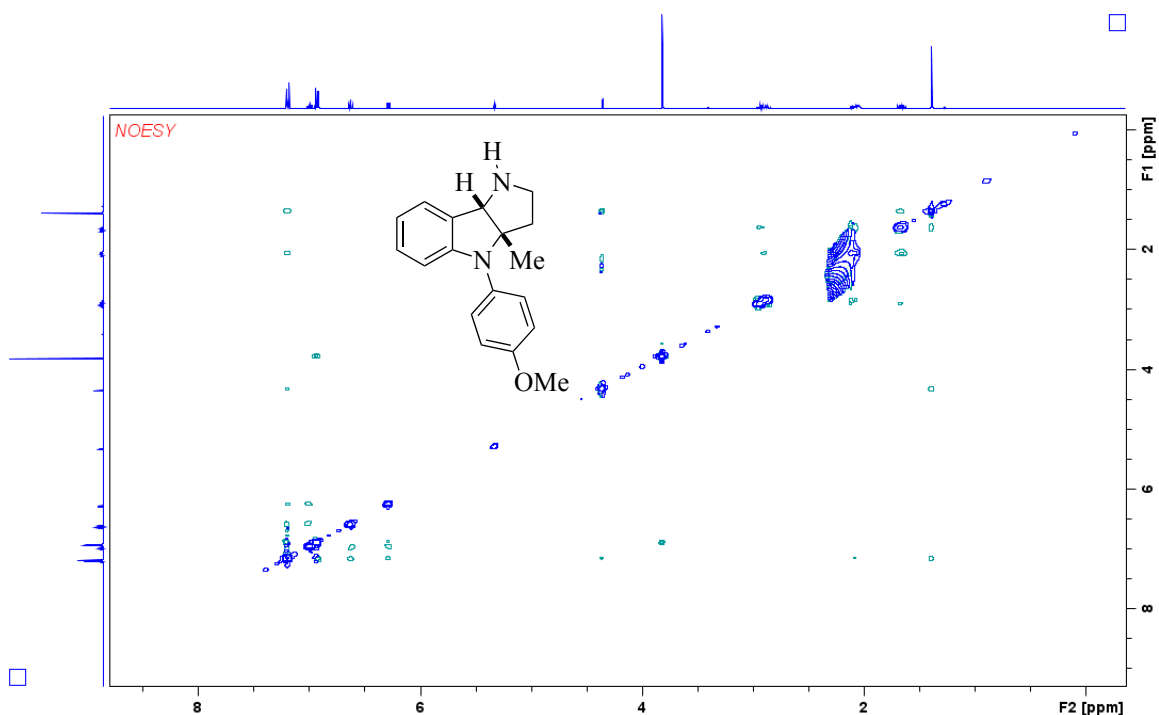
J = 8.0, 1.0, 0.5 Hz, 1H), 4.35 (s, 1H), 3.82 (s, 3H), 2.98 – 2.82 (m, 2H), 2.13 – 2.00 (m, 2H),

1.66 (ddd, J = 12.7, 8.4, 6.6 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.05,

151.14, 134.95, 130.08, 129.18, 129.13, 125.82, 117.74, 115.11, 107.92, 76.96, 72.54, 55.94,

46.87, 41.33, 26.01; GC/MS (CI) m/z $[M+H]^+$ for $C_{18}H_{20}N_2O$ found 281.

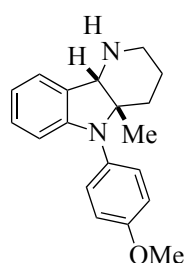




Following procedure **GP4I** with (*E/Z*)-*tert*-butyl 5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enylcarbamate **4Ib** (1 equiv, 0.2 mmol, 73 mg) for 8 hours. Purification by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) afforded (*4aS,9bS*)-*tert*-butyl 5-(4-methoxyphenyl)-4a-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[3,2-*b*]indole-1-carboxylate **4rI** as a yellow oil (38 mg, 52%). IR ν_{max} (cm⁻¹) 2970, 2934, 1691, 1613, 1510, 1414, 1247, 1153, 1035, 743. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.25 – 7.16 (m, 4H), 7.07 – 6.96 (m, 4H), 6.97 – 6.89 (m, 4H), 6.69 (t, *J* = 7.4 Hz, 2H), 6.37 – 6.29 (m, 2H), 5.51 (s, 1H), 5.40 (s, 1H), 4.15 – 4.00 (m, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 6H), 2.88 – 2.64 (m, 2H), 1.70 (ddd, *J* = 13.0, 10.9, 4.4 Hz, 2H), 1.53 – 1.47 (m, 18H), 1.39 (s, 6H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 158.63, 156.08, 150.48, 133.62, 130.35, 128.83, 127.61, 123.89,

118.36, 114.86, 108.90, 80.18, 68.07, 64.20, 63.06, 55.94, 40.74, 39.67, 31.18, 28.71, 24.58, 24.19, 21.55; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{24}H_{30}N_2O_3$ 395.2329; found 395.2332.

Rotamers were observed due to the Boc group, complicating the spectra. In order to justify the *cis* selectivity, the Boc was removed and 2D experiments were performed.



(4a*S*,9b*S*)-*tert*-butyl 5-(4-methoxyphenyl)-4a-methyl-2,3,4,4a,5,9b-

hexahydro-1*H*-pyrido[3,2-*b*]indole-1-carboxylate **4rI** (1 equiv, 0.084 mmol,

33 mg) was transferred to a flask and neat trifluoroacetic acid (5 equiv, 0.42

mmol, 32 μ L) was added. The mixture was swirled vigorously for 5 minutes

then completely concentrated in vacuum. Purification by flash chromatography on neutral

alumina gel (98:2 DCM:MeOH) yielded (4a*S*,9b*S*)-5-(4-methoxyphenyl)-4a-methyl-

2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[3,2-*b*]indole as a clear oil (24.7 mg, 28%). IR ν_{\max} (cm^{-1})

2930, 2853, 1701, 1607, 1509, 1477, 1460, 1244, 1034, 747. ^1H NMR (400 MHz, Methylene

Chloride- d_2) δ 7.28 – 7.21 (m, 1H), 7.21 – 7.15 (m, 2H), 7.01 (dddd, J = 7.9, 7.4, 1.4, 0.5 Hz,

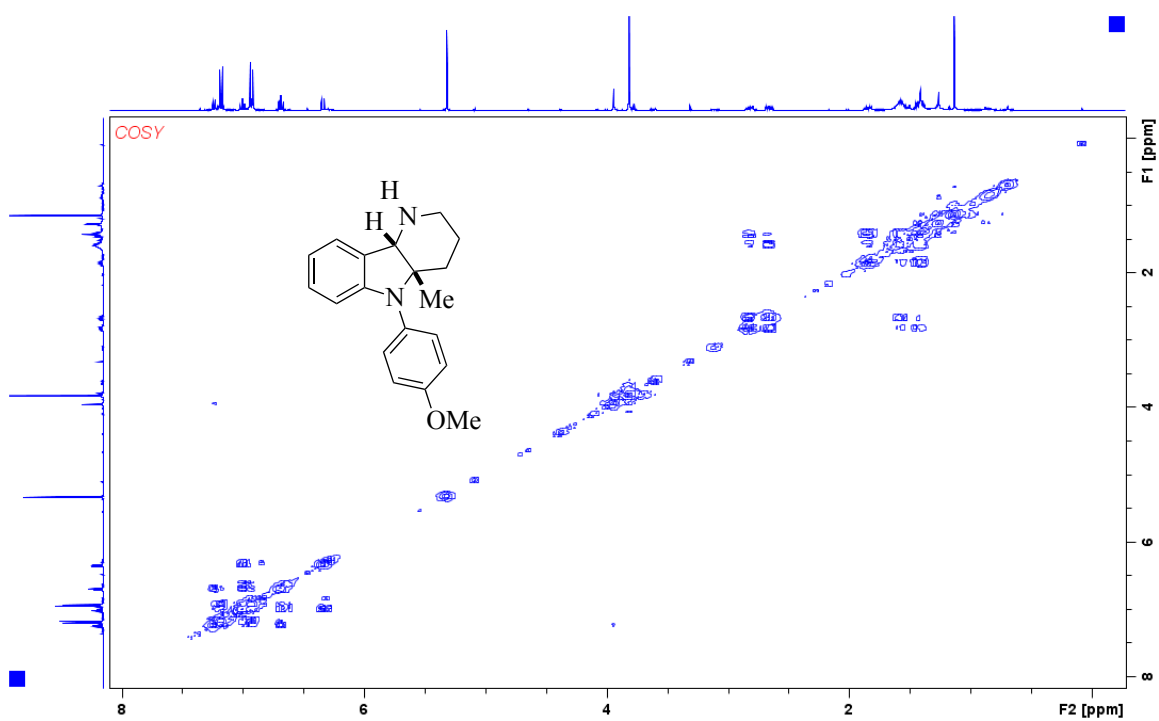
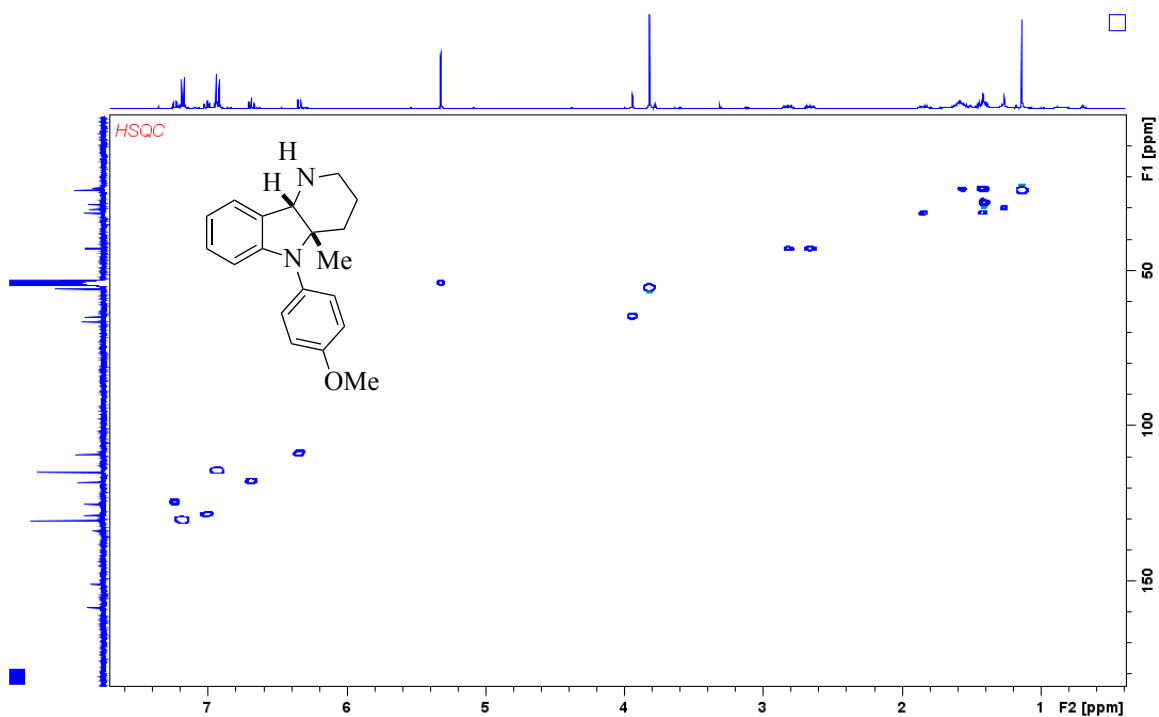
1H), 6.96 – 6.91 (m, 2H), 6.69 (td, J = 7.3, 1.0 Hz, 1H), 6.36 – 6.31 (m, 1H), 3.94 (d, J = 0.8 Hz,

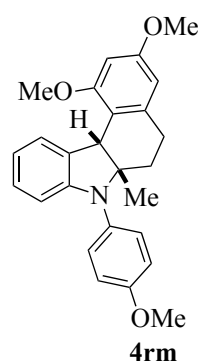
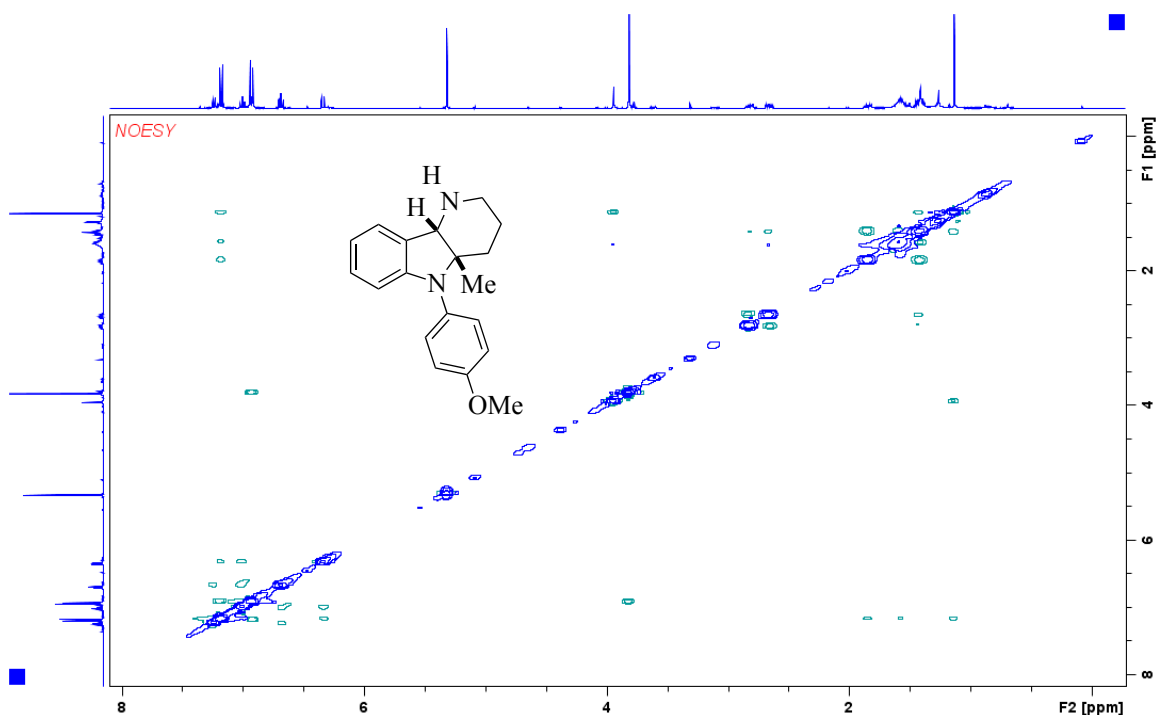
1H), 3.82 (s, 3H), 2.89 – 2.77 (m, 1H), 2.74 – 2.59 (m, 1H), 1.91 – 1.80 (m, 1H), 1.60 – 1.55 (m,

2H), 1.41 (td, J = 5.9, 2.7 Hz, 2H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.53, 150.92,

133.82, 130.54, 128.82, 125.23, 118.27, 114.80, 109.37, 66.53, 64.98, 55.93, 42.89, 31.46, 24.07,

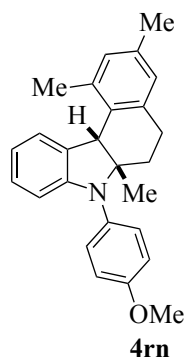
23.43; GC/MS (CI) m/z $[M+H]^+$, calc'd for $C_{19}H_{22}N_2O$ 294.17; found 295.



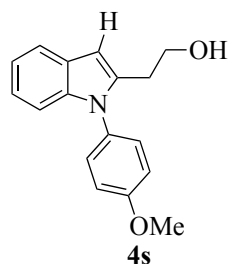


Following procedure **GP4I** with (*E/Z*)-2-(4-(3,5-dimethoxyphenyl)-2-methylbut-1-enyl)-*N*-(4-methoxyphenyl)aniline **4qd** (1 equiv, 0.2 mmol, 81 mg) for 16 hours. Purification by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) afforded (6*aS*,11*bR*)-1,3-dimethoxy-7-(4-methoxyphenyl)-6*a*-methyl-6,6*a*,7,11*b*-tetrahydro-5*H*-benzo[*c*]carbazole **4rm** as a brown oil (63 mg, 79%). IR ν_{max} (cm⁻¹) 2966, 2931, 2841, 1605, 1508, 1484, 1464, 1363, 1287, 1246, 1204, 1153, 1039, 832, 749. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.28 – 7.22 (m, 2H), 7.12 (dtd, *J* = 7.4, 1.3, 0.5 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.88 (dddd, *J* = 7.8, 7.4, 1.4, 0.8 Hz, 1H), 6.52 (td, *J* = 7.4, 1.1 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.30 – 6.25 (m, 1H), 6.21 (ddd, *J* = 7.9, 1.1, 0.5 Hz, 1H), 4.51 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 2.87 (ddd, *J* = 16.1, 8.3, 4.4 Hz, 1H), 2.62 – 2.42 (m, 1H), 2.05 – 1.89 (m, 1H), 1.41 (dddd, *J* = 13.3, 8.3, 4.3, 0.6 Hz, 1H), 1.35 (s, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 159.31, 159.04, 158.55,

151.10, 139.74, 134.18, 132.61, 130.99, 127.60, 125.77, 119.03, 117.72, 114.89, 107.89, 104.79, 96.97, 68.68, 55.94, 55.79, 55.70, 47.51, 31.26, 27.87, 26.45; GC/MS (CI) m/z $[M+H]^+$ for $C_{26}H_{27}NO_3$ found 402.



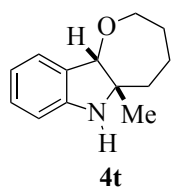
Following procedure **GP4I** with (*E/Z*)-2-(4-(3,5-dimethylphenyl)-2-methylbut-1-enyl)-*N*-(4-methoxyphenyl)aniline **4qe** (1 equiv, 0.2 mmol, 74 mg) for 15 hours. Purification by flash chromatography on neutral alumina gel (97:3 hexanes:EtOAc) afforded (6*S*,11*bS*)-7-(4-methoxyphenyl)-1,3,6a-trimethyl-6,6a,7,11*b*-tetrahydro-5*H*-benzo[*c*]carbazole **4rn** as a brown oil (21 mg, 29%). 1H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, J = 2.3 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.04 – 6.89 (m, 4H), 6.83 – 6.74 (m, 2H), 6.54 (td, J = 7.4, 1.1 Hz, 1H), 6.32 – 6.26 (m, 1H), 4.45 (s, 1H), 3.87 (d, J = 1.4 Hz, 3H), 2.71 (dt, J = 16.1, 5.8 Hz, 1H), 2.55 (dd, J = 8.9, 4.7 Hz, 1H), 2.51 (s, 3H), 2.34 – 2.27 (m, 3H), 2.02 (ddd, J = 13.3, 8.0, 4.7 Hz, 1H), 1.43 (s, 3H), 1.35 – 1.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.98, 150.92, 137.58, 136.31, 135.43, 133.51, 132.09, 130.86, 130.65, 129.21, 127.23, 126.91, 124.12, 117.10, 114.44, 107.19, 69.81, 55.43, 50.10, 30.48, 27.40, 26.39, 20.93, 19.66; GC/MS (CI) m/z $[M+H]^+$ for $C_{26}H_{27}NO$ found 370.



Following procedure **GP4I** with (*E*)-4-(2-(4-methoxyphenylamino)phenyl)but-3-en-1-ol **4al** (1 equiv, 0.2 mmol, 54 mg) for 6 hours. Purification by flash chromatography on neutral alumina gel (70:30 hexanes:EtOAc) afforded 2-(1-(4-methoxyphenyl)-1*H*-indol-2-

yl)ethanol **4s** as a yellow oil (26 mg, 48%). IR ν_{max} (cm^{-1}) 3377, 2932, 1613, 1513, 1458, 1295, 1248, 1035, 831, 746. ^1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.60 – 7.50 (m, 1H), 7.30 – 7.19 (m, 2H), 7.11 – 6.93 (m, 5H), 6.50 – 6.42 (m, 1H), 3.91 – 3.83 (m, 3H), 3.73 (q, J = 6.9 Hz, 2H), 2.91 – 2.79 (m, 2H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.87, 139.39, 138.66, 130.75, 129.99, 128.48, 121.76, 120.42, 120.16, 115.21, 110.60, 101.27, 61.76, 56.10, 31.01; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{17}\text{H}_{17}\text{NO}_2$ 268.1332; found 268.1334.

Oxidative Cleavage of the 3,4,5-trimethoxyphenyl Group of **4rd** using Ceric Ammonium Nitrate



Formation of **4t** was achieved using a literature procedure.⁴¹ To a flask equipped with a stir bar was added (5a*S*,10b*S*)-5a-methyl-6-(3,4,5-trimethoxyphenyl)-3,4,5,5a,6,10b-hexahydro-2*H*-oxepino[3,2-*b*]indole **4rd** (1 equiv, 0.05 mmol, 19.5 mg) and a mixture of MeCN/ H_2O (2.7:1, 0.4 mL total). The mixture was cooled to 0 °C and H_2SO_4 (2.02 equiv, 0.1 mmol, 5.3 μL) was added along with immediate addition of ceric ammonium nitrate (2.15 equiv, 0.114 mmol, 62 mg) in one portion. The mixture was stirred at 0 °C for 10 minutes prior to dilution with H_2O (3 mL). The solution was separated and the aqueous layer was washed with diethyl ether (3 x 5 mL). The organic layer was saved and stored for a later time in the workup. The combined aqueous layer was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 20 mL) and combined. The saved organic layer from the initial wash was then extracted with 0.1 M HCl (3 x 15 mL). The combined aqueous phase was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 20 mL) and added to the previous organic extract from the

basified extract. The organic layer was then dried of MgSO₄, concentrated in vacuum, and purified by flash chromatography on neutral alumina gel (90:10 hexanes:EtOAc) to afford (5a*S*,10b*S*)-5a-methyl-3,4,5,5a,6,10b-hexahydro-2*H*-oxepino[3,2-*b*]indole **4t** as a clear oil (6.13 mg, 57%). IR ν_{max} (cm⁻¹) 3349, 2928, 1612, 1485, 1471, 1319, 1098, 1077, 1003, 746. ¹H NMR (400 MHz, Methylene Chloride-*d*₂) δ 7.23 (ddt, *J* = 7.4, 1.4, 0.7 Hz, 1H), 7.10 (dddd, *J* = 7.9, 7.4, 1.4, 0.5 Hz, 1H), 6.70 (td, *J* = 7.4, 1.0 Hz, 1H), 6.58 (ddt, *J* = 7.9, 1.0, 0.5 Hz, 1H), 4.53 (d, *J* = 0.7 Hz, 1H), 3.84 – 3.69 (m, 2H), 3.52 – 3.39 (m, 1H), 1.88 – 1.79 (m, 3H), 1.69 – 1.59 (m, 2H), 1.54 – 1.45 (m, 1H), 1.21 (d, *J* = 0.3 Hz, 3H); ¹³C NMR (101 MHz, CD₂Cl₂) δ 150.68, 130.32, 127.86, 127.37, 118.61, 110.08, 90.58, 72.11, 66.98, 38.73, 33.13, 28.06, 24.33; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₃H₁₇NO 204.1383; found 204.1380.

4.4. References

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Chapter 5

Conclusions for Organolithium Chemistry

As discussed, organolithium chemistry has shown to be a powerful tool to access enantioenriched pyrrolidines and piperidines. As early as 1989, chemists discovered that *N*-Boc heterocycles can be lithiated at the 2 position and subsequently quenched with an electrophile to produce the racemic 2-substituted heterocycle. Furthermore, it was found that racemic organolithiums derived from deprotonation is amenable to a dynamic thermodynamic resolution in the presence of peptide-based ligands. Subsequent reports from Coldham and Gawley revealed various enantioselective substitutions of *N*-Boc-piperidine and *N*-Boc-pyrrolidine using dynamic thermodynamic resolutions, with Gawley's chemistry yielding either enantiomer in high yields and selectivities using a catalytic amount of ligand. Gawley and coworkers expanded their scope from simple electrophilic quenches using highly active electrophiles to vinylations, allylations, and arylations using various transmetalation chemistry, all of which proceeded with retention of configuration and delivered the desired products in high yields and selectivities. Later, the Gawley group expanded this methodology to synthesize *trans* 2,6-disubstituted piperidines and 2,2-disubstituted piperidines in high yields and enantioselectivities. Importantly, Gawley and coworkers were able to use this methodology to synthesize a variety of alkaloids in minimal steps, including *S*-($-$)-ropivacaine, *S*-($+$)-anabasine, and *S*-($-$)-coniine. Unfortunately, this methodology's impact suffers as the high enantioselectivities reported have been seldom reproduced.

Initial lab work described in chapter 2 focused on examining the reproducibility issues related to Gawley's thermodynamic resolution methodology on *N*-Boc-piperidine. Meticulous

studies were carried out in which ligand purity, ligand addition, *s*-BuLi concentration and supplier, reaction concentration, impurity addition, electrophile addition, lithiation conditions, and equilibration time and temperature were studied. Although high enantioselectivities were observed a few of times out of many attempts, there was no pattern or consistency in the results that could eliminate the reproducibility issues.

A second project was pursued in which α,α,α' -trisubstituted piperidines and pyrrolidines were synthesized, some of which possessed high diastereoselectivities. In order to generate the trisubstituted products, the *N*-Boc heterocycle was α -lithiated and arylated, followed by benzylic lithiation/substitution to provide the corresponding 2-aryl-2-alkyl *N*-Boc heterocycle. Subsequent α' -lithiation/substitution provided the corresponding trisubstituted heterocycle in high yields. Since some of adducts showed high diastereoselectivities, NOESY analysis was conducted to determine the absolute stereochemistry. Although some were problematic to synthesize in a reproducible manner when compared to initial results, NOESY analysis was successfully performed on 2 substrates. Relative stereochemistry was then proposed for these structures, indicating a *cis* relationship with respect to the α -aryl group to the α' -alkyl group. These results may not be conclusive, however, as further studies need to be carried out to determine if the heterocyclic ring exists in a perfect chair conformation or a twist boat conformation. Then with that information, reexamination of the obtained NOESY spectra will be performed to verify the original assignment..

Chapter 6

Conclusions for Visible Light Photochemistry

In summary, it has previously been shown that visible light photoredox catalysis offers a unique strategy to form chemical bonds using benign reaction conditions. The photoredox catalyst is the key to achieve chemical transformations, as they have the ability to oxidize or reduce organic substrates upon photoexcitation with visible light. Typical metal-based photoredox catalysts possess an iridium or ruthenium center complexed to polypyridyl ligands. These photoredox catalysts have been shown to undergo both reductive and oxidative quenching cycles. Zheng and coworkers wondered if interesting reactivity could be derived from the amine radical cation generated in the reductive quenching cycle, as this quenching cycle requires a stoichiometric amount of reductive quencher, which have typically been amines. Indeed, Zheng revealed an overall redox-neutral [3+2] annulation of cyclopropylanilines with alkenes using $\text{Ru}(\text{bpz})_3(\text{PF}_6)_2$ in degassed nitromethane. This work was later expanded to alkynes, dienes, diynes, and enynes. Additionally, the Zheng group revealed a [4+2] annulation of cyclobutylanilines with alkynes, generating the corresponding cyclohexene adducts. Since such success was achieved using the photogenerated amine radical cation, the Zheng group tested a different reactivity using styryl anilines. In this model, the photogenerated amine radical cation adds electrophilically to an alkene intramolecularly, ultimately generating a mono- or disubstituted indole in good to high yields. The authors proposed an intermediate benzylic cation, which ultimately forms an indole upon deprotonation or 1,2-shift/deprotonation. It was proposed that C2,C3 fused indolines could be formed by trapping this benzylic cation

intermediate intramolecularly using a styryl aniline tether with an aliphatic chain bearing a nucleophile.

Since the starting materials were nontrivial, various syntheses were developed to provide the desired styryl aniline substrates. A linear approach was first implemented in which a key Wittig reaction generated the styrene component whereas a Buchwald–Hartwig amination provided the aniline component. This approach, although reproducible and scalable, generates a mixture of alkene isomers and consists of a non–atom–economical, low–yielding Wittig reaction. Therefore, a convergent approach was developed hinging on a successful Suzuki–Miyaura cross coupling reaction. This method allowed for ample modifications, as varying chain lengths could be incorporated as well as various electronic characters around the styrene ring. When subjected to visible light photoredox catalysis, numerous fused indolines were successfully formed. Oxygen and nitrogen nucleophiles worked well, whereas only electron–rich aryl nucleophiles provided the desired product. Additionally, the requisite para–alkoxyphenyl group was successfully removed using oxidative conditions, thus expanding the substrate scope and enhancing the impact of this methodology.

Lastly, a variety of substrates were tested and determined to be unsuccessful for this chemistry. For instance, it was not possible to form a 4–membered ring or an 8–membered ring. Additionally, sulfur nucleophiles did not provide the desired product. Furthermore, when using aryl nucleophiles in a Friedel–Crafts manner, phenyl, naphthyl, pyrrole, and phenoxide nucleophiles were unproductive in generating the anticipated product.

The bulk of this work was subsequently published in *Advanced Synthesis and Catalysis* in 2015 (Morris, S. A.; Nguyen, T. H.; Zheng, N., Diastereoselective Oxidative C–N/C–O and C–

N/C-N Bond Formation Tandems Initiated by Visible Light: Synthesis of Fused N-Arylindolines.

Adv. Synth. Catal. **2015**, 357 (10), 2311-2316).

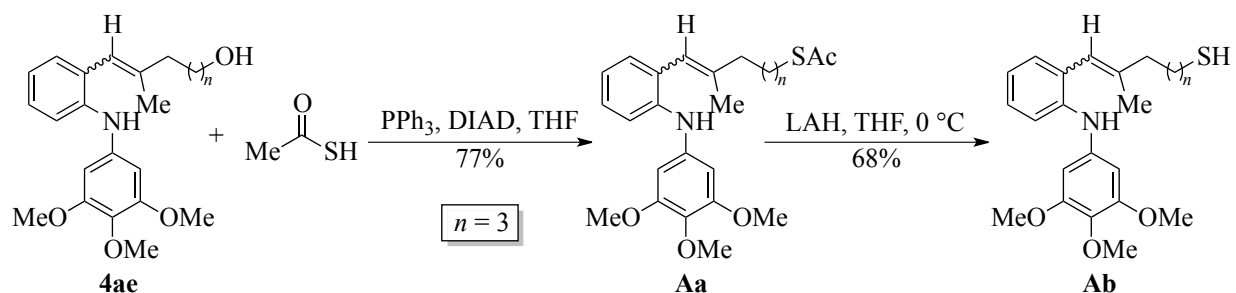
Appendix A

Additional Unsuccessful Substrates in the Fused Indoline Synthesis using Visible Light

A.1. Substrate Synthesis

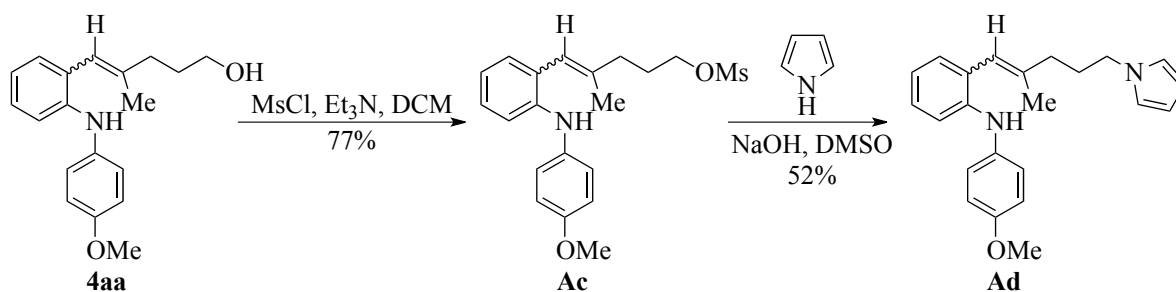
In addition to the styrenyl anilines described in Chapter 4, a variety of substrates requiring alternate synthetic routes were synthesized. In an attempt to examine sulfur-based nucleophiles, a Mitsunobu reaction of **4ae** with thioacetic acid and subsequent acetyl cleavage using lithium aluminum hydride provided both the thioester **Aa** and free thiol **Ab**, as shown in Scheme A.1.

Scheme A.1. Mitsunobu Reaction/Reduction to Generate Sulfur-Based Nucleophiles



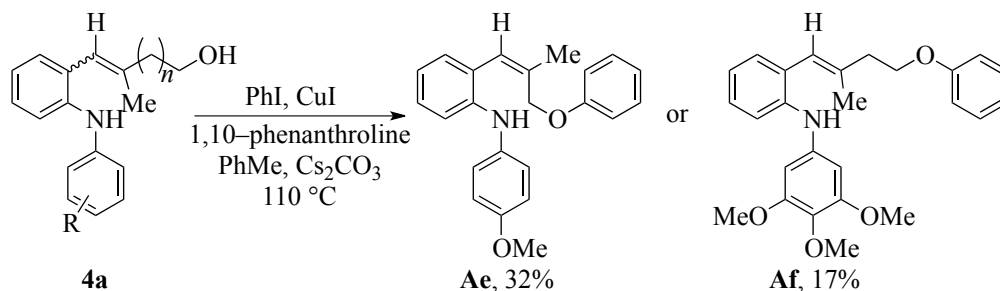
Moreover, Daylan Sheppard, an undergraduate summer researcher, synthesized three new molecules incorporating aryl nucleophiles. The first substrate, **Ad**, contained a pyrrole tether, which was synthesized using a two-step procedure of alcohol mesylation,¹ yielding **Ac**, followed by $\text{S}_\text{N}2$ reaction of the mesylate with pyrrole in sodium hydroxide² (Scheme A.2).

Scheme A.2. Synthesis of Pyrrole Nucleophile from the Alcohol Precursor



The next two substrates synthesized by Daylan Sheppard contained a phenyl ether tether with 2 different chain lengths and anilines (**Ae** and **Af**), which were formed using a known cross-coupling procedure catalyzed by copper iodide, albeit low yields (Scheme A.3).³

Scheme A.3. Synthesis of Phenyl Ether Substrates from the Alcohol Precursor

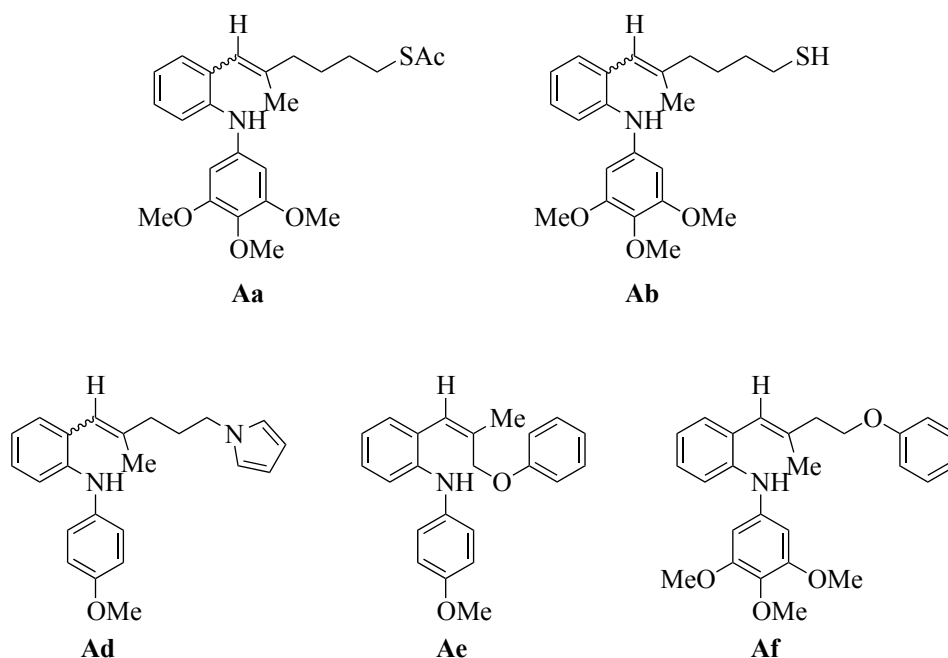


A.2. Photochemistry Results

When attempting the photochemistry using sulfur-based nucleophiles, the reaction formed an unidentified compound that did not match what would be expected in a proper cyclization when testing thioester **Aa**. When using the free thiol **Ab**, complete decomposition was observed. It was thought that the thioester was unable to trap the benzylic cation, resulting in a 1,2-alkyl shift similar to that described above with the unreactive aryl nucleophiles. In the case

of the free thiol, it was hypothesized that the photoredox catalyst oxidized the sulfur, which in turn could promote other reaction pathways, such as disulfide bond formation or a decomposition pathway. Next, pyrrole **Ad** was analyzed using the optimized photochemical conditions. Since pyrrole is known to undergo Friedel–Crafts reactions α to the nitrogen, it was highly anticipated that cyclization would occur.⁴ However, after just 8 hours, complete decomposition was observed. The reaction was then performed a second time in the absence of acetic acid, and complete decomposition was again observed in 8 hours. A likely hypothesis for the decomposition pathway is that the pyrrole was oxidized by the photoredox catalyst, thus participating in other reaction pathways,⁵ or a complex was formed involving the pyrrole and the photogenerated superoxide anion, which proceeded to decompose the pyrrole ring.⁶ Since this methodology requires aerobic atmosphere, no remedy could be drawn up to circumvent this issue. Lastly, phenyl ether nucleophiles **Ae** and **Af** were examined using the optimized photochemistry conditions. Interestingly, both substrates yielded multiple fragmented products. Although it is unknown why the homoallyl ether substrate **Af** fragments, it is likely that allyl ether substrate **Ae** underwent a Photo–Claisen rearrangement to yield various products.⁷ A summary of the substrates synthesized using these procedures are shown in Figure A.1.

Figure A.1. Summary of Synthesized Substrates



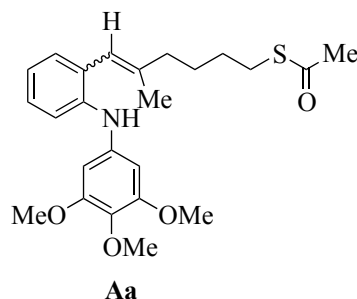
A.3. Experimental Procedures

General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. Toluene and THF were collected under argon from a solvent purification system. Dimethylsulfoxide (DMSO) and triethylamine (Et_3N) were pre-dried over molecular sieves. Triethylamine was further purified prior to use *via* short path distillation. Column chromatography was performed using silica gel (230–400 mesh). All new compounds were (at minimum) characterized using 2 of the following: ^1H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), and melting point (when applicable). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to

residual proton or carbon signals in CDCl₃ (7.27 ppm, 77.23 ppm). IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on either a Bruker Ultraflex II TOF/TOF mass spectrometer or a Bruker Apex-Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas chromatography analyses were performed using a Shimadzu GC-2010 Plus instrument. When applicable, melting point ranges (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

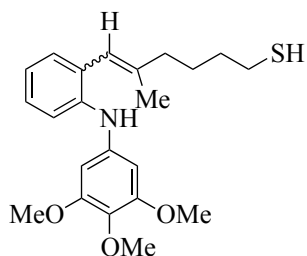
Preparation of Sulfur-Based Nucleophilic Tethers



Preparation of (*E/Z*)-*S*-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-enyl ethanethioate **Aa** was accomplished using a literature procedure.⁸ To an oven-dried flask equipped with a magnetic stir bar was added triphenylphosphine

(2.4 equiv, 1.7 mmol, 437.2 mg) and anhydrous THF (0.17 M, 4.0 mL) under N₂ atmosphere. The contents were stirred at 0 °C for 10 minutes prior to the dropwise addition of diisopropyl azodicarboxylate (DIAD) (2 equiv, 1.38 mmol, 0.268 mL). After stirring for 1 hour at the same temperature, a separate solution containing (*E/Z*)-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-en-1-ol **4ae** (1 equiv, 0.69 mmol, 258 mg) and thioacetic acid (1.5 equiv, 1.04 mmol, 0.074 mL) in THF (0.35 M, 2 mL) was added dropwise over 10 minutes. After stirring at 0 °C for 1 hour, the ice bath was removed and the solution was stirred at room temperature for 7 hours. Once complete, the solution was concentrated in vacuum and

purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford (*E/Z*)-*S*-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-enyl ethanethioate **Aa** as an orange oil (228 mg, 77%). IR ν_{max} (cm⁻¹) 3387, 2936, 2853, 1688, 1596, 1576, 1507, 1354, 1286, 1123, 1008. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.82 – 7.67 (m, 1H), 7.60 – 7.40 (m, 1H), 7.35 – 7.23 (m, 2H), 7.22 – 7.12 (m, 3H), 7.12 – 7.05 (m, 1H), 6.90 (qd, *J* = 7.2, 1.3 Hz, 2H), 6.38 (s, 2H), 6.36 (s, 2H), 6.17 (s, 2H), 5.66 – 5.44 (m, 2H), 3.84 (s, 7H), 3.84 (s, 3H), 3.84 (s, 5H), 3.02 – 2.88 (m, 2H), 2.88 – 2.73 (m, 2H), 2.34 (s, 3H), 2.32 (s, 2H), 2.29 – 2.21 (m, 2H), 2.15 (tq, *J* = 8.3, 4.8, 3.7 Hz, 2H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.66 (tp, *J* = 6.1, 3.4, 2.5 Hz, 4H), 1.53 (p, *J* = 3.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.72, 153.60, 141.67, 141.18, 141.15, 141.13, 139.16, 138.94, 132.62, 132.51, 132.14, 132.00, 130.38, 130.16, 128.43, 128.27, 127.23, 127.14, 126.85, 121.52, 120.84, 119.84, 119.67, 115.85, 115.34, 96.57, 96.35, 60.87, 55.90, 55.88, 39.00, 31.91, 30.48, 30.46, 29.11, 29.00, 28.77, 28.69, 26.79, 26.77, 23.04, 17.47.

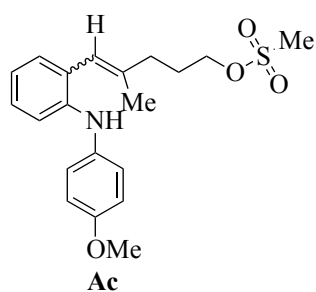


Preparation of (*E/Z*)-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-ene-1-thiol **Ab** was accomplished using a literature procedure.⁹ To a clean, dry 10-mL round bottom flask equipped with a magnetic stir bar was added

thioester **Aa** (1 equiv, 0.24 mmol, 103.3 mg) in 6 mL of freshly distilled THF (0.04 M). Lithium aluminum hydride (LAH; 1 equiv, 0.24 mmol, 9.0 mg) in THF (0.6 M, 0.4 mL) was then added dropwise to the stirred thioester solution at 0 °C. After stirring for 30 minutes at the same temperature, the reaction was carefully quenched with 10 mL of water. The flask was then transferred to a rotary evaporator and the THF was evacuated. The remaining aqueous phases

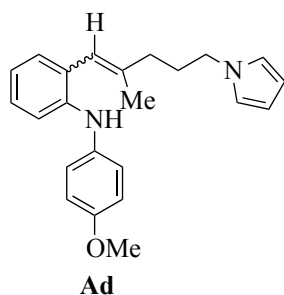
was extracted with DCM (3 x 10 mL) prior to drying over MgSO₄. The mixture was then concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford (*E/Z*)-5-methyl-6-(2-(3,4,5-trimethoxyphenylamino)phenyl)hex-5-ene-1-thiol **Ab** as a dark brown oil (63 mg, 68%). ¹H NMR (300 MHz, Chloroform-*d*) δ 7.30 – 7.22 (m, 2H), 7.20 – 7.12 (m, 3H), 7.12 – 7.03 (m, 1H), 6.89 (qd, *J* = 7.6, 1.3 Hz, 2H), 6.36 (s, 2H), 6.34 (s, 2H), 6.14 (s, 2H), 5.50 (d, *J* = 7.0 Hz, 2H), 3.83 (d, *J* = 0.9 Hz, 9H), 3.82 (s, 8H), 3.79 – 3.69 (m, 3H), 2.64 – 2.52 (m, 2H), 2.50 – 2.35 (m, 1H), 2.29 – 2.18 (m, 2H), 2.18 – 2.06 (m, 2H), 1.90 – 1.82 (m, 2H), 1.58 – 1.49 (m, 4H), 1.28 (d, *J* = 2.0 Hz, 4H), 1.26 (s, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 153.78, 142.03, 141.46, 141.24, 139.25, 139.01, 132.89, 132.74, 130.52, 130.31, 127.39, 127.31, 126.94, 121.59, 120.92, 120.00, 119.77, 115.97, 115.38, 96.86, 96.51, 94.43, 61.04, 56.08, 56.06, 39.16, 33.63, 33.55, 31.95, 26.52, 26.48, 24.47, 24.30, 23.17, 17.63.

Preparation of Pyrrole-Based Nucleophilic Tethers



Preparation of (*E/Z*)-5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enyl methanesulfonate **Ac** was accomplished using a literature procedure.¹ To a clean, dry 10-mL round bottom flask equipped with a magnetic stir bar was added styrenyl aniline **4aa** (1 equiv, 0.25 mmol, 74.4 mg) and freshly distilled triethylamine (1 equiv, 0.25 mmol, 35 μL) in anhydrous DCM (0.25 M, 1 mL). The reaction mixture was then stirred and brought to 0 °C prior to the dropwise addition of methanesulfonyl chloride (MsCl; 1 equiv, 0.25 mmol, 19.3 μL) over 10 minutes. The reaction was then stirred at 0 °C for 30 minutes

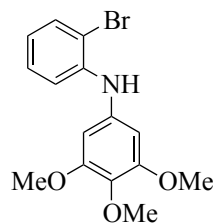
before warming the contents to room temperature. After stirring for an additional 30 minutes at room temperature, the DCM was evaporated using a rotary evaporator. 20 mL of ethyl acetate (EtOAc) and 20 mL of H₂O were then added and the layers were separated. The remaining aqueous layer was extracted with EtOAc (2 x 20 mL) and then the combined organic layers were then washed with brine (2 x 40 mL). The resulting organic layer was then dried over MgSO₄, concentrated in vacuum, and filtered through a pad of silica gel eluting with EtOAc to afford pure (*E/Z*)-5-(2-(4-methoxyphenylamino)phenyl)-4-methylpent-4-enyl methanesulfonate **Ac** as a yellow oil (72.4 mg, 77%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.05 (m, 8H), 7.05 – 7.00 (m, 2H), 6.90 – 6.85 (m, 4H), 6.81 (dtd, *J* = 8.8, 7.3, 1.4 Hz, 2H), 6.22 (s, 2H), 5.50 (d, *J* = 25.2 Hz, 1H), 4.30 (t, *J* = 6.2 Hz, 2H), 4.14 (t, *J* = 6.5 Hz, 2H), 3.81 (d, *J* = 1.0 Hz, 6H), 3.02 (s, 3H), 2.86 (s, 3H), 2.42 – 2.31 (m, 2H), 2.32 – 2.22 (m, 2H), 2.10 – 1.97 (m, 2H), 1.95 (d, *J* = 1.5 Hz, 3H), 1.89 (ddt, *J* = 9.8, 7.5, 6.4 Hz, 2H), 1.78 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 155.35, 155.15, 142.93, 142.85, 139.95, 139.13, 135.84, 135.53, 130.25, 130.01, 127.61, 127.50, 125.56, 125.28, 122.94, 122.72, 122.42, 122.26, 118.86, 118.78, 114.63, 114.56, 114.16, 113.66, 69.19, 69.04, 55.55, 37.39, 37.27, 35.34, 28.49, 27.28, 27.06, 23.00, 17.46; GC/MS (CI) *m/z* [M+H]⁺ for C₂₀H₂₅NO₄S found 376.



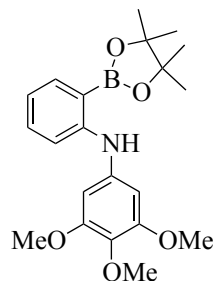
Preparation of (*E/Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-5-(1*H*-pyrrol-1-yl)pent-1-enyl)aniline **Ad** was accomplished using a literature procedure.² To a clean, dry 10-mL round bottom flask equipped with a magnetic stir bar was added pyrrole (1 equiv, 0.20 mmol, 13.8 μL) and NaOH (2 equiv, 0.4 mmol, 16.0 mg) in DMSO (1 M, 0.4 mL) at room

temperature under N₂ atmosphere. After stirring the suspension for 30 minutes at room temperature, the contents were brought to 0 °C and mesylate **Ac** (1 equiv, 72.4 mg, 0.20 mmol) was slowly added over a 10 minute period. Once added, the solution was slowly brought to room temperature by keeping the reaction stirring in the ice bath until all the ice melted. Once the ice melted, the mixture was stirred at room temperature for 14 hours prior to pouring the solution into 5 mL of ice water. The resulting mixture was extracted with Et₂O (3 x 5 mL) and the combined organic layer was then washed with brine (2 x 15 mL). The organic layer was then dried over MgSO₄, concentrated in vacuum, and The resulting organic layer was then dried over MgSO₄, concentrated in vacuum, and purified by flash chromatography on silica gel (96:4 hexanes:EtOAc) to afford (*E/Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-5-(1*H*-pyrrol-1-yl)pent-1-enyl)aniline **Ad** as a brown oil (34.7 mg, 52%). ¹H NMR (300 MHz, Chloroform-*d*) δ 7.20 – 6.99 (m, 9H), 6.95 – 6.77 (m, 5H), 6.72 (t, *J* = 2.1 Hz, 2H), 6.58 (t, *J* = 2.1 Hz, 1H), 6.20 (dq, *J* = 3.5, 1.8 Hz, 3H), 6.14 (t, *J* = 2.1 Hz, 1H), 5.42 (d, *J* = 6.2 Hz, 2H), 3.97 (t, *J* = 7.0 Hz, 2H), 3.83 (d, *J* = 1.3 Hz, 5H), 3.79 (t, *J* = 7.3 Hz, 2H), 2.29 – 2.20 (m, 2H), 2.17 (dd, *J* = 9.7, 6.1 Hz, 2H), 2.12 – 2.01 (m, 2H), 2.01 – 1.87 (m, 4H), 1.78 (d, *J* = 1.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.32, 155.22, 142.76, 140.88, 140.31, 135.72, 135.55, 130.24, 129.95, 127.48, 127.42, 125.66, 125.34, 122.65, 122.47, 122.17, 121.43, 120.47, 120.32, 118.84, 118.78, 114.61, 114.57, 113.97, 113.59, 107.96, 107.85, 55.53, 49.28, 49.02, 36.66, 29.99, 29.95, 29.68, 23.09, 17.68; GC/MS (CI) *m/z* [M+H]⁺ for C₂₃H₂₆N₂O found 347.

Preparation of Phenyl Ether–Based Nucleophilic Tethers

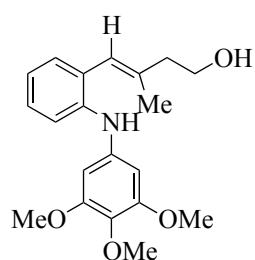


Preparation of *N*-(2-bromophenyl)-3,4,5-trimethoxyaniline was accomplished using a literature procedure.¹⁰ To an oven-dried Schlenk flask equipped with a magnetic stir bar was added 3,4,5-trimethoxyaniline (1.2 equiv, 9.35 mmol, 1.7 g), Pd(OAc)₂ (0.5 mol%, 0.039 mmol, 8.8 mg) and DPEPhos (1.5 mol%, 0.117 mmol, 63 mg). Glove box was used to add 1 NaO^tPent (1.5 equiv, 11.7 mmol, 1.3 g,) and the tube was sealed with a screw cap containing a Teflon septum. 1-bromo-2-iodobenzene (1 equiv, 7.79 mmol, 1 mL) and anhydrous toluene (0.5 M, 15 mL) were then added and the reaction mixture was heated at 110 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel (82:18 hexanes:EtOAc) afforded *N*-(2-bromophenyl)-3,4,5-trimethoxyaniline as a white solid, m.p. 97–100 °C (2.4 g, 76%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.44 (m, 1H), 7.24 – 7.11 (m, 2H), 6.72 (ddd, *J* = 7.9, 6.5, 2.3 Hz, 1H), 6.42 (s, 2H), 6.01 (s, 1H), 3.85 (s, 3H), 3.83 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 153.73, 141.84, 137.38, 133.98, 132.84, 128.06, 120.46, 115.43, 111.54, 98.79, 60.91, 55.99; GC/MS (CI) *m/z* [M+H]⁺ for C₁₅H₁₆BrNO₃ found 338/340.



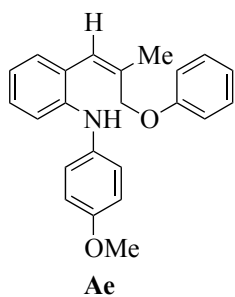
Preparation of 3,4,5-trimethoxy-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aniline was accomplished using a literature procedure.¹¹ To an oven-dried Schlenk flask equipped with a magnetic stir bar was added *N*-(2-bromophenyl)-3,4,5-trimethoxyaniline (1 equiv, 1.0 mmol,

338 mg), Bis(pinacolato)diboron ($B_2(\text{pin})_2$; 1.1 equiv, 1.1 mmol, 279.3 mg), and $Pd(PPh_3)_2Cl_2$ (3 mol%, 0.03 mmol, 21 mg). Glove box was used to add KOAc (2 equiv, 2 mmol, 196.3 mg) and the tube was sealed with a screw cap contained a Teflon septum. Anhydrous 1,4-dioxane (0.25 M, 4.0 mL) was then added and the reaction mixture was heated at 80 °C for 16 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and filtered over a short pad of Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 3,4,5-trimethoxy-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aniline as a yellow solid, m.p. 125–134 °C (304 mg, 79%). 1H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dt, J = 7.4, 1.5 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.29 – 7.19 (m, 1H), 6.92 – 6.84 (m, 1H), 6.59 – 6.50 (m, 2H), 3.99 – 3.85 (m, 9H), 1.50 – 1.39 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.67, 150.94, 138.41, 137.26, 133.64, 132.54, 117.98, 113.18, 99.09, 83.82, 60.98, 56.07, 24.88; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{21}H_{28}BNO_5$ 386.2137; found 386.2137.



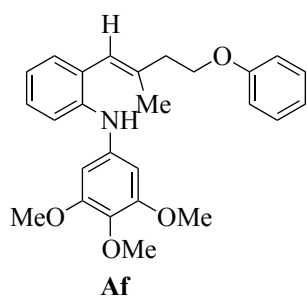
Preparation of (*E*)-3-methyl-4-(2-(3,4,5-trimethoxyphenylamino)phenyl)but-3-en-1-ol was accomplished using **General Procedure 4F (GP4F)** from Chapter 4. To an oven-dried Schlenk flask equipped with a magnetic stir bar was added 3,4,5-trimethoxy-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aniline (1.5 equiv, 0.3 mmol, 76 mg), $Pd(OAc)_2$ (2 mol%, 0.006 mmol, 1.3 mg), RuPhos (4 mol%, 0.012 mmol, 5.6 mg), and ground K_3PO_4 (3 equiv, 0.45 mmol, 191 mg). The tube was then sealed with a screw cap containing a

Teflon septum and filled with nitrogen. Vinyl iodide **4ga** (1 equiv, 0.3 mmol, 76 mg) and THF:EtOH:H₂O (2:1:1, degassed *via* Freeze–Pump–Thaw or sparged with N₂ for 30 minutes (0.2 M, 1.5 total mL) were then added to the reaction mixture and the contents were heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over MgSO₄ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (50:50 hexanes:EtOAc) to afford (*E*)-3-methyl-4-(2-(3,4,5-trimethoxyphenylamino)phenyl)but-3-en-1-ol as a clear oil (84 mg, 82%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.22 (m, 1H), 7.20 – 7.11 (m, 2H), 6.91 (ddd, *J* = 7.5, 5.9, 1.3 Hz, 1H), 6.31 (s, 2H), 6.24 – 6.18 (m, 1H), 5.65 (s, 1H), 3.84 – 3.75 (m, 11H), 2.47 (dt, *J* = 7.5, 3.7 Hz, 2H), 1.80 – 1.71 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 153.72, 141.21, 139.38, 137.92, 132.63, 130.32, 127.51, 127.27, 123.41, 120.09, 116.30, 96.31, 61.01, 60.38, 56.01, 42.69, 17.49; GC/MS (CI) *m/z* [M+H]⁺ for C₂₀H₂₅NO₄ found 344.



Preparation of (*Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-3-phenoxyprop-1-enyl)aniline **Ae** was accomplished using a literature procedure.³ To a clean, dry 10-mL round bottom flask equipped with a magnetic stir bar was added CuI (10 mol%, 0.02 mmol, 3.8 mg), 1,10-phenanthroline (20 mol%, 0.04 mmol, 7.2 mg), Cs₂CO₃ (2 equiv, 0.4 mmol, 130.3 mg), iodobenzene (1 equiv, 0.2 mmol, 22.4 μL), and (*Z*)-3-(2-(4-methoxyphenylamino)phenyl)-2-methylprop-2-en-1-ol **4an** (2 equiv, 0.4 mmol, 107.7 mg) in anhydrous toluene (1 M, 0.2 mL). The tube was then sealed with a screw cap containing a Teflon septum and flushed with N₂. The contents were

then heated to 110 °C and stirred for 24 hours. Once complete, the mixture was cooled to room temperature and filtered through a short pad of silica gel, eluting with Et₂O. The resulting mixture was concentrated in vacuum and purified by flash chromatography on silica gel (92:8 hexanes:EtOAc) to afford (*Z*)-*N*-(4-methoxyphenyl)-2-(2-methyl-3-phenoxyprop-1-enyl)aniline **Ae** as a brown oil (22.1 mg, 32%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.19 (m, 2H), 7.16 – 7.10 (m, 1H), 7.08 – 7.02 (m, 4H), 6.96 – 6.90 (m, 1H), 6.88 – 6.83 (m, 2H), 6.83 – 6.75 (m, 3H), 6.46 (s, 1H), 5.44 (s, 1H), 4.62 – 4.49 (m, 2H), 3.81 (d, *J* = 0.4 Hz, 3H), 2.07 (d, *J* = 1.5 Hz, 3H); GC/MS (CI) *m/z* [M+H]⁺ for C₂₃H₂₃NO₂ found 346.



Preparation of (*E*)-3,4,5-trimethoxy-*N*-(2-(2-methyl-4-phenoxybut-1-enyl)phenyl)aniline **Af** was accomplished using a literature procedure.³ To a clean, dry 10-mL round bottom flask equipped with a magnetic stir bar was added CuI (10 mol%, 0.04 mmol, 7.6 mg), 1,10-phenanthroline (20 mol%, 0.08 mmol, 14.4 mg), Cs₂CO₃ (2 equiv, 0.8 mmol, 260.6 mg), iodobenzene (1 equiv, 0.4 mmol, 44.8 μL), and (*E*)-3-methyl-4-(2-(3,4,5-trimethoxyphenylamino)phenyl)but-3-en-1-ol (2 equiv, 0.8 mmol, 226.7 mg) in anhydrous toluene (1 M, 0.4 mL). The tube was then sealed with a screw cap containing a Teflon septum and flushed with N₂. The contents were then heated to 110 °C and stirred for 24 hours. Once complete, the mixture was cooled to room temperature and filtered through a short pad of silica gel, eluting with Et₂O. The resulting mixture was concentrated in vacuum and purified by flash chromatography on silica gel (90:10 hexanes:EtOAc) to afford (*E*)-3,4,5-trimethoxy-*N*-(2-(2-methyl-4-phenoxybut-1-enyl)phenyl)aniline **Af** as a brown oil (24.4 mg, 17%). ¹H NMR (400

MHz, Chloroform-*d*) δ 7.22 – 7.12 (m, 2H), 7.00 – 6.85 (m, 4H), 5.65 (s, 1H), 4.17 (t, J = 6.3 Hz, 2H), 3.82 (d, J = 0.3 Hz, 3H), 3.73 (s, 6H), 2.69 (td, J = 6.3, 1.1 Hz, 2H), 1.80 (d, J = 1.3 Hz, 3H); GC/MS (CI) m/z $[M+H]^+$ for C₂₆H₂₉NO₄ found 421.

A.4. References

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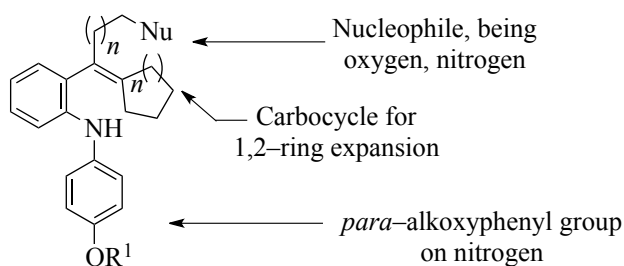
Appendix B

Synthesis of Tetracyclic Fused Indolines using Visible Light Photoredox Catalysis

B.1. Introduction

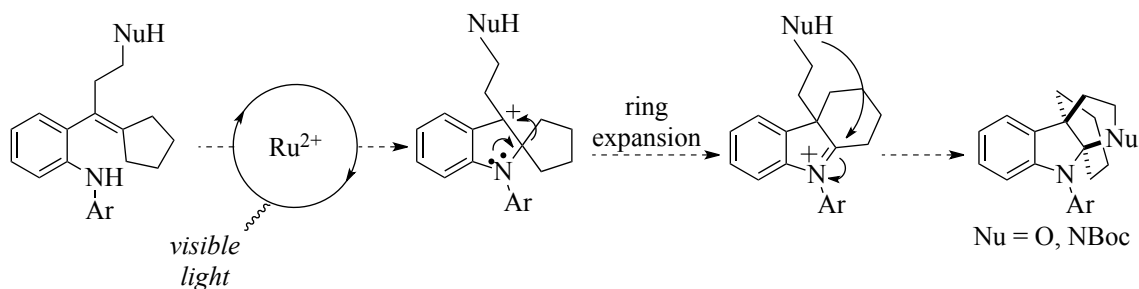
In addition to the work presented in this document, it was hypothesized that the photogenerated benzylic cation could be intercepted *via* 1,2–ring expansion using styrenyl anilines resembling that in Figure B.1.

Figure B.1. Substrate Design



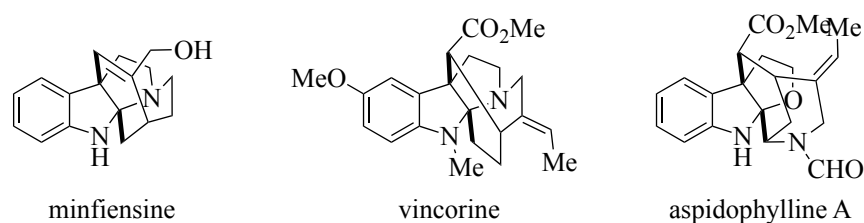
By intentionally designing a substrate that could subsequently attack the resulting iminium intramolecularly, various complex tetracyclic C2,C3 fused indolines could be generated (Scheme B.1).

Scheme B.1. Proposed Mechanism for Tetracyclic C2,C3 Fused Indoline Formation



The fused indolines that would be formed using this methodology resemble the substructure of akuammiline alkaloids. Indeed, akuammiline alkaloids have received much attention recently in literature, as they have been shown to possess synthetically challenging chemical architectures while also displaying a broad range of biological activity.¹ To date, a variety of total syntheses have been accomplished, which have been detailed in a many recent reviews.^{1,2} In order to showcase their molecular complexity, examples of well-known akuammiline alkaloids are shown in Figure B.2.

Figure B.2. Select Akuammiline Alkaloids



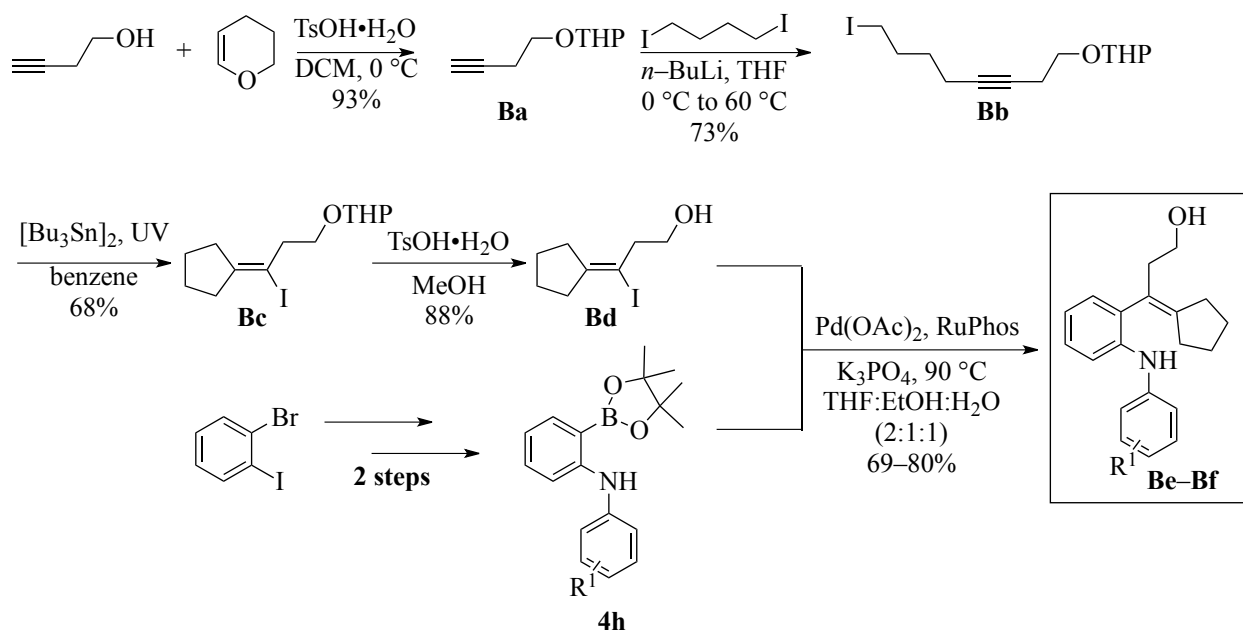
Noting that many of these syntheses use multiple steps to generate a single target, the photoinduced 1,2-shift/cyclization route not only seemed feasible from a sustainability viewpoint but also from a medicinal chemistry viewpoint, as this method could potentially give rise to numerous analogues and generate a wide range of structural diversity. In fact, in a single

step, 4 of the 5 rings in the polycyclic framework could be constructed and further elaborated to generate products that contain structural features that have otherwise been prevented from studies due to synthetic limitations. Encouraged by this hypothesis, substrate synthesis was then carried out in order to determine the feasibility of this method.

B.2. Substrate Syntheses

The original synthesis of the styrenyl aniline substrates capable of undergoing a 1,2-shift/nucleophilic attack to generate the corresponding tetracyclic fused indolines was planned and verified by a former post-doc, Jie Hu. Dr. Hu noted that the forward synthesis was not trivial, as the synthesis of the tetrasubstituted vinyl iodide proved to be challenging. After numerous attempts to synthesize the styrenyl aniline, the synthesis depicted in Scheme B.2 was found to be the best option, providing the desired substrate in 7 total steps with a longest linear sequence of 5 steps. The sequence below and all subsequent data, unless otherwise noted, are the results of Scott Morris, who successfully completed and verified the below synthesis.

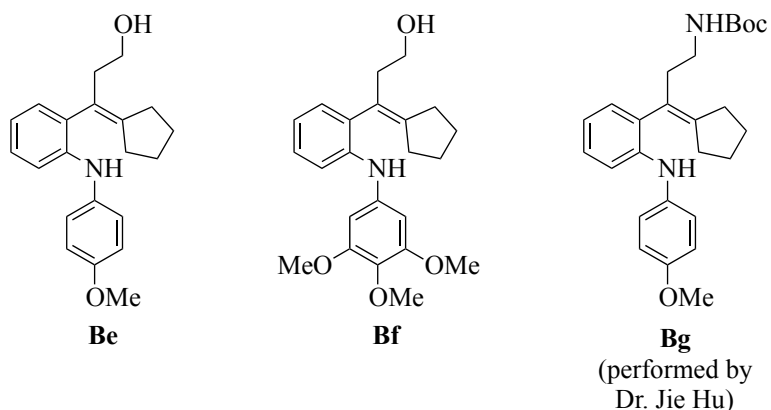
Scheme B.2. Forward Synthesis of Styrenyl Aniline Substrates



The synthesis began with THP protection of 3-butyne-1-ol catalyzed by *para*-toluenesulfonic acid monohydrate.³ Alkylation of the terminal alkyne in the presence of *n*-BuLi and 1,4-diiodobutane yielded the corresponding internal alkyne in 73% yield.³ Subsequent atom transfer radical cyclization (ATRC) initiated by UV-mediated homolysis of hexabutylditin yielded the anticipated vinyl iodide in 68% yield.⁴ Upon THP deprotection of the protected alcohol,⁵ the desired vinyl iodide was obtained in 88% (81% over 4 steps). Suzuki-Miyaura coupling of the previously formed 2-bromo-*N*-(4-methoxyphenyl)aniline **4ia** or 3,4,5-trimethoxy-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aniline (synthesis depicted in Appendix A) completed the substrate synthesis, yielding the styrenyl aniline in 69–80%. The substrates generated using this synthetic route are shown in Figure B.3. It is of note that Dr. Jie Hu synthesized the NBoc analogue by submitting the alcohol substrate to a Gabriel synthesis using the Mitsunobu reaction with phthalimide⁶ and Ing-Manske hydrazinolysis⁷

followed by a Boc protection of the primary amine in a manner identical to that described in Chapter 4.

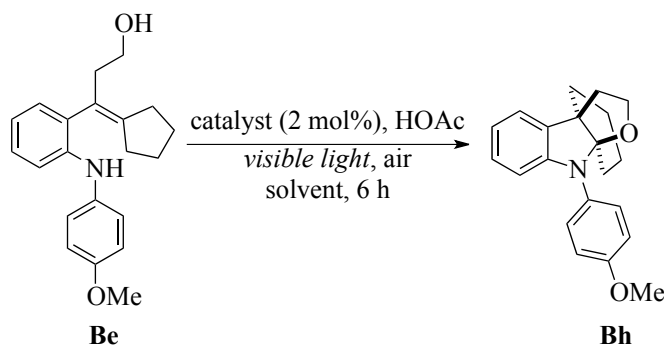
Figure B.3. Substrates Synthesized



This synthesis, although comprising multiple steps, allows for a variety of analogues to be obtained, including the modification of the carbocycle ring size, the nucleophilic alkyl chain size, modification of the nucleophile to either a hydroxyl group or a carbamate, modification of the *para*-alkoxyphenyl group, and, based on previous precedence, modification of the electronic character around the styrene's aryl group.⁸ Additionally, this method provides a single alkene isomer, resulting in less convoluted spectra. It is anticipated that a variety of analogues can be synthesized and examined using this forward synthesis in future studies.

B.3. Visible Light Photochemistry

The synthesized substrates were then subjected to photochemistry conditions. After obtaining positive results using substrate **Be**, a brief reaction screen was conducted, which is shown in Table B.1.

Table B.1. Reaction Screen

Entry ^a	Catalyst	Solvent	Scale ^b	GC Yield ^c
1	Ru(bpy) ₃ (PF ₆) ₂	CH ₃ CN	0.1 mmol	57%
2	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ CN	0.1 mmol	71%
3	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ NO ₂	0.1 mmol	71%
4	Ir(dF(CF ₃)ppy) ₂ (dtb-bpy)(PF ₆)	DMSO	0.1 mmol	22% (28%) ^d
5 ^e	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ NO ₂	0.1 mmol	68%
6	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ NO ₂	0.2 mmol	73%
7	Ru(bpz) ₃ (PF ₆) ₂	CH ₃ NO ₂	0.2 mmol	72% ^f

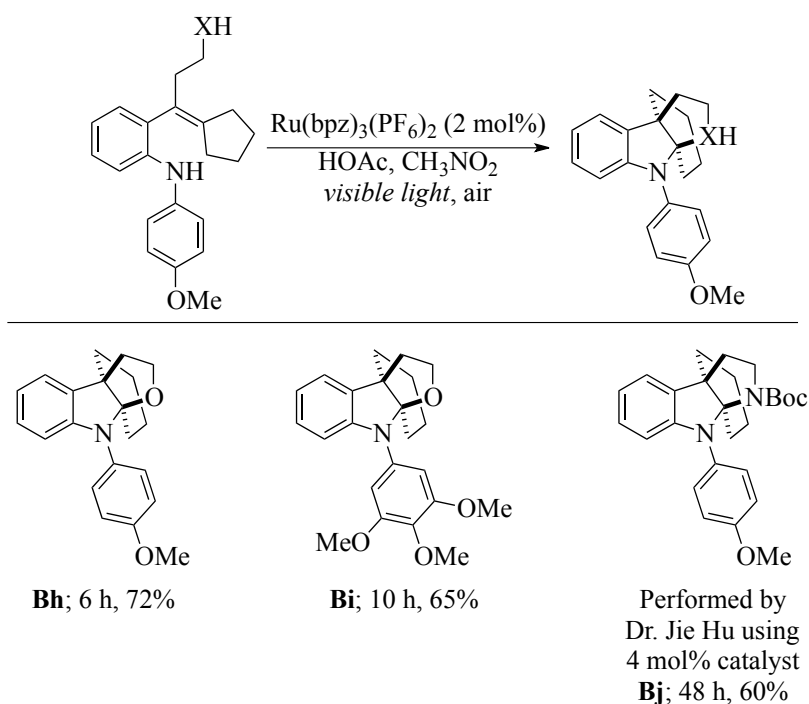
^aUsing styrenyl aniline **Be**, photoredox catalyst, 1 equiv HOAc, and 0.07 M solvent (1.5 mL or 3.0 mL depending on the scale) in a test tube sealed with a screw cap containing a Teflon septum pierced with a 16-gauge disposable needle. The contents were then stirred at a 6 cm distance from an 18W focused white LED for 6 hours. ^bWith respect to styrenyl aniline **Be**. ^cDetermined using *n*-dodecane as an internal standard. ^dAfter 22 hours of reaction time. ^eAdding 1 mol% catalyst every 3 hours. ^fIsolated yield.

Using conditions identical to that described for the synthesis of C2,C3 fused indolines (Chapter 4), only 57% yield was obtained (entry 1). However, switching to the stronger-oxidizing Ru(bpz)₃(PF₆)₂ in the same solvent increased the yield to 71% (entry 2). Interestingly, an identical yield was obtained when using nitromethane rather than acetonitrile (71%, entry 3). Using an iridium-based catalyst in DMSO gave low yields, even after extended reaction times (entry 4). It was hypothesized that the yield could be increased by adding the photocatalyst in 2 portions since Ru(bpz)₃(PF₆)₂ is known to have decreased efficiency than Ru(bpy)₃(PF₆)₂ after a

certain amount of time. However, when adding the photoredox catalyst in 2 portions, no increase in yield was observed (entry 5). Lastly, doubling the scale to 0.2 mmol had no effect on the yield, giving 73% GC yield and 72% isolated yield (entries 6 and 7).

With optimized reaction conditions in hand, a substrate scope was initiated that will be further extended in future studies. A list of successful adducts is shown in Scheme B.3.

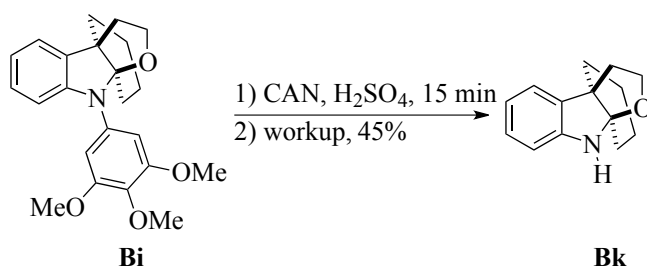
Scheme B.3. Present Substrate Scope



Although only a small substrate scope has been developed at the present, it has been found that both the aryl group on the nitrogen and the nucleophile can be modified. For instance, both **Bh** and **Bi** can be synthesized using this methodology, with the latter containing extra methoxy groups on the aniline. Additionally, Dr. Jie Hu revealed that NBoc nucleophiles are amenable to this transformation, as pyrroloindoline **Bj** was successfully formed, albeit a longer reaction time and decreased yield (48 hours; 60%).

Lastly, removal of the *para*-alkoxyphenyl group was attempted using ceric ammonium nitrate (CAN) in sulfuric acid (Scheme B.4). Indeed, the corresponding secondary amine **Bk** was formed in 45% in just 15 minutes. The ability to remove the necessary *para*-alkoxyphenyl group from the nitrogen further increased the substrate scope and opens the possibility to generate various targets upon further chemical synthesis.

Scheme B.4. Oxidative Cleavage of *para*-Alkoxyphenyl Group



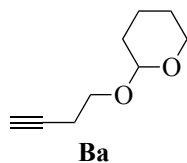
Although this project is still in its early stages, the results obtained thus far have demonstrated the effectiveness to generate complicated and interesting structures that are present in many biologically relevant natural products. In future studies, modification of the fused indoline's ring size will be studied as well as change in electronic character of the indoline ring. Additionally, it would be necessary in future analyses to understand the 1,2-ring expansion in detail. Such studies would include: 1) modification of ring size, 2) establishing asymmetry in the carbocycle and documenting what increases or decrease the rate or ring expansion, and 3) intentionally installing group on the carbocycle to mimic natural products. Lastly, it is anticipated that formal syntheses of some akuammiline alkaloids can be achieved using this methodology once the 1,2-ring expansion is better understood.

B.4. Experimental Procedures

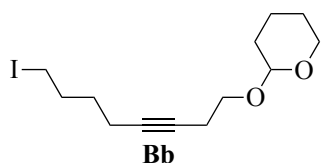
General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. THF was collected under argon from a solvent purification system. Acetonitrile and nitromethane were pre-dried over molecular sieves. Column chromatography was performed using silica gel (230–400 mesh). All new compounds were (at minimum) characterized using 2 of the following: ^1H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), and melting point (when applicable). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton or carbon signals in CDCl_3 (7.27 ppm, 77.23 ppm), CD_2Cl_2 (5.32 ppm, 54.0 ppm), and benzene- d_6 (7.16 ppm, 128.39 ppm) at room temperature. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on a Bruker Apex-Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas chromatography analyses were performed using a Shimadzu GC-2010 Plus instrument. When applicable, melting point ranges (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected. The data obtained by Dr. Jie Hu will not be presented in this document.

Synthesis of Styrenyl Anilines Be and Bf



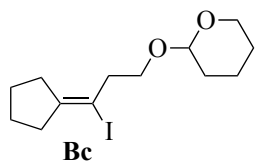
Preparation and characterization of 2-(but-3-yn-1-yloxy)tetrahydro-2*H*-pyran **Ba** from commercially available 3-butyn-1-ol in one step corresponds to that described in literature.³



Preparation of 2-(8-iodooct-3-yn-1-yloxy)tetrahydro-2*H*-pyran **Bb** was accomplished using a literature procedure.³ To an oven-dried heavy wall pressure vessel equipped with a stir bar was added 2-(but-

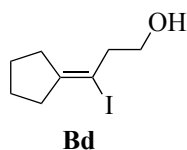
3-yn-1-yloxy)tetrahydro-2*H*-pyran **Ba** (1 equiv, 13 mmol, 2.0 g) in anhydrous THF (0.25 M, 52 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to -78°C and *n*-BuLi (1.6 M in hexanes, 1.1 equiv, 14.3 mmol, 8.9 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior to the addition of 1,4-diiodobutane (1.5 equiv, 19.5 mmol, 2.6 mL). The mixture was then stirred for 30 minutes at -78°C prior to warming to room temperature. The septum was then replaced with a screw cap and stirred at 60°C for 14 hours. Once complete, the contents were cooled to room temperature and poured into 50 mL of saturated aq. NH_4Cl . The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then dried over MgSO_4 , concentrated in vacuum, and purified by flash chromatography on silica gel (97:3 hexanes:EtOAc) to afford 2-(8-iodooct-3-yn-1-yloxy)tetrahydro-2*H*-pyran **Bb** as a clear oil (3.2 g, 73%). IR ν_{max} (cm^{-1}) 2938, 2868, 1452, 1439, 1352, 1285, 1200, 1159, 1121, 1030. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.70 – 4.57

(m, 1H), 3.94 – 3.83 (m, 1H), 3.83 – 3.72 (m, 1H), 3.57 – 3.44 (m, 2H), 3.20 (td, $J = 7.0, 0.6$ Hz, 2H), 2.45 (tttd, $J = 7.2, 2.4, 0.7$ Hz, 2H), 2.23 – 2.12 (m, 2H), 1.98 – 1.87 (m, 2H), 1.87 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H), 1.64 – 1.45 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 98.67, 80.20, 77.56, 66.08, 62.15, 32.35, 30.54, 29.53, 25.40, 20.16, 19.40, 17.68, 6.33; FTMS (ESI) m/z $[\text{M}+\text{H}]^+$, calc'd for $\text{C}_{13}\text{H}_{21}\text{IO}_2$ 338.0386/340.0366; found 338.0384/340.0364.

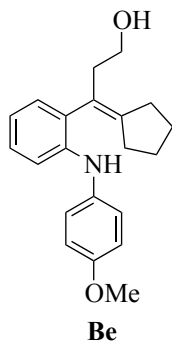


Preparation of 2-(3-cyclopentylidene-3-iodopropoxy)tetrahydro-2H-pyran **Bc** was accomplished using a literature procedure.⁴ To a clean, dry test tube equipped with a stir bar was added 2-(8-iodooct-3-

ynyloxy)tetrahydro-2H-pyran **Bb** (1 equiv, 0.8 mmol, 269 mg), hexabutyliditin (10 mol%, 0.08 mmol, 40 μL), and anhydrous benzene (degassed *via* Freeze-Pump-Thaw; 0.67 M, 1.2 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 24 hours (internal reaction temperature = 40 $^{\circ}\text{C}$). Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (97:3 hexanes:EtOAc) to afford 2-(3-cyclopentylidene-3-iodopropoxy)tetrahydro-2H-pyran **Bc** as a yellow liquid (752 mg, 68%). IR ν_{max} (cm^{-1}) 2938, 2866, 1652, 1452, 1427, 1352, 1200, 1119, 1030, 986 968, 870. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.62 (dd, $J = 4.2, 2.8$ Hz, 1H), 3.94 – 3.76 (m, 2H), 3.58 – 3.44 (m, 2H), 2.84 – 2.68 (m, 2H), 2.45 – 2.33 (m, 2H), 2.28 (ddq, $J = 7.2, 5.9, 1.4$ Hz, 2H), 1.89 – 1.74 (m, 3H), 1.74 – 1.63 (m, 3H), 1.62 – 1.49 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 151.24, 98.66, 90.82, 66.02, 62.11, 42.34, 41.34, 31.82, 30.63, 28.30, 25.81, 25.45, 19.42; GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{13}\text{H}_{21}\text{IO}_2$ found 338/340.

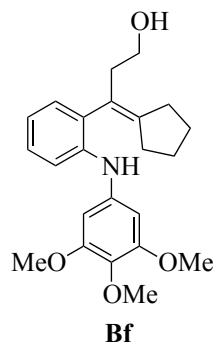


Preparation of 3-cyclopentylidene-3-iodopropan-1-ol **Bd** was accomplished using a literature procedure.⁵ To a clean, dry 25-mL round bottom flask was added 2-(3-cyclopentylidene-3-iodopropoxy)tetrahydro-2*H*-pyran **Bc** (1 equiv, 2.23 mmol, 752 mg) and *para*-toluenesulfonic acid monohydrate (PTSA•H₂O; 10 mol%, 0.224 mmol, 42.5 mg) in anhydrous MeOH (0.34 M, 6.6 mL). The contents were then stirred for 4 hours at room temperature. Upon completion, the solution was transferred to a separatory funnel and diluted with DCM (13 mL). The resulting mixture was washed with saturated aq. NaHCO₃ (3 x 5 mL). The aqueous layer was then extracted with DCM (3 x 5 mL). The organic layers were then combined and dried over MgSO₄. Subsequent concentration in vacuum and purification by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 3-cyclopentylidene-3-iodopropan-1-ol **Bd** as a clear oil (495 mg, 88%). IR ν_{max} (cm⁻¹) 3308, 2947, 2864, 1647, 1423, 1304, 1233, 1188, 1036, 953, 860. ¹H NMR (300 MHz, Chloroform-*d*) δ 3.77 (dt, *J* = 8.8, 6.1 Hz, 2H), 2.71 (dd, *J* = 7.1, 5.1 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.31 (td, *J* = 7.5, 7.0, 1.9 Hz, 2H), 1.84 (p, *J* = 6.8 Hz, 2H), 1.71 (dd, *J* = 7.5, 5.2 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 152.49, 91.01, 61.54, 44.48, 41.47, 32.13, 28.24, 25.68; GC/MS (CI) *m/z* [M+H]⁺ for C₈H₁₃IO found 254/256.



Preparation of 3-cyclopentylidene-3-(2-(4-methoxyphenylamino)phenyl)propan-1-ol **Be** was accomplished using **General Procedure 4F (GP4F)** from Chapter 4. To an oven-dried Schlenk flask equipped with a stir bar was added *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4ha** (1.5 equiv, 3 mmol, 976 mg), Pd(OAc)₂ (2 mol%,

0.04 mmol, 9 mg), RuPhos (4 mol%, 0.08 mmol, 37 mg), ground K₃PO₄ (3 equiv, 6 mmol, 1.3 g). The tube was then sealed with a screw cap containing a Teflon septum and filled with nitrogen. 3-Cyclopentylidene-3-iodopropan-1-ol **Bd** (1 equiv, 2 mmol, 504.2 mg) and THF:EtOH:H₂O (2:1:1, degassed *via* Freeze-Pump-Thaw or sparged with N₂ for 30 minutes; 0.2 M, 10 mL total) were then added to the reaction mixture and the contents were heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over MgSO₄ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 3-cyclopentylidene-3-(2-(4-methoxyphenylamino)phenyl)propan-1-ol **Be** as a brown oil (446 mg, 69%). IR ν_{max} (cm⁻¹) 3343, 2949, 2866, 1597, 1574, 1508, 1449, 1292, 1233, 1179, 1034, 816, 746. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.06 (m, 3H), 7.03 (ddt, *J* = 8.2, 1.1, 0.6 Hz, 1H), 6.98 (ddq, *J* = 7.5, 1.6, 0.5 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.85 – 6.76 (m, 1H), 3.81 (dd, *J* = 1.3, 0.8 Hz, 3H), 3.70 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.59 (ddd, *J* = 10.4, 8.0, 5.2 Hz, 1H), 2.81 – 2.65 (m, 1H), 2.49 (td, *J* = 14.8, 12.0, 5.7 Hz, 3H), 2.13 – 2.01 (m, 2H), 1.81 – 1.70 (m, 2H), 1.68 – 1.55 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 155.51, 145.85, 142.72, 136.08, 130.56, 129.22, 127.46, 124.98, 123.12, 119.39, 114.79, 113.92, 60.96, 55.72, 38.40, 32.15, 30.71, 26.79, 26.77; FTMS (ESI) *m/z* [M+H]⁺, calc'd for C₂₁H₂₅NO₂ 324.1958; found 324.1953.



Preparation of 3-cyclopentylidene-3-(2-(3,4,5-

trimethoxyphenylamino)phenyl)propan-1-ol **Bf** was accomplished using

General Procedure 4F (GP4F) from Chapter 4. To an oven-dried Schlenk

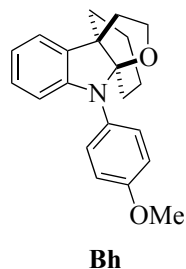
flask equipped with a stir bar was added 3,4,5-trimethoxy-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)aniline (see Appendix A for

synthesis; 1.5 equiv, 1.7 mmol, 656 mg), Pd(OAc)₂ (2 mol%, 0.023 mmol, 5.1 mg), RuPhos (4 mol%, 0.046 mmol, 21.1 mg), ground K₃PO₄ (3 equiv, 3.39 mmol, 720 mg). The tube was then sealed with a screw cap containing a Teflon septum and filled with nitrogen. 3-

Cyclopentylidene-3-iodopropan-1-ol **Bd** (1 equiv, 2 mmol, 504.2 mg) and THF:EtOH:H₂O (2:1:1, degassed *via* Freeze-Pump-Thaw or sparged with N₂ for 30 minutes; 0.23 M, 5 mL total) were then added to the reaction mixture and the contents were heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over MgSO₄ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (65:35 hexanes:EtOAc) to afford 3-cyclopentylidene-3-(2-(3,4,5-trimethoxyphenylamino)phenyl)propan-1-ol **Bf** as a brown solid, m.p. 115–119 °C (346 mg, 80%). IR ν_{max} (cm⁻¹) 3335, 2938, 1593, 1504, 1474, 1447, 1402, 1288, 1229, 1123, 1038, 1005, 748. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.24 (m, 1H), 7.15 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1H), 7.06 – 6.96 (m, 1H), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H), 6.33 (s, 2H), 6.03 (s, 1H), 3.82 (d, *J* = 0.6 Hz, 9H), 3.73 – 3.52 (m, 2H), 2.71 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.49 (dq, *J* = 13.2, 6.7, 6.2 Hz, 3H), 2.05 (ddt, *J* = 8.5, 7.2, 1.4 Hz, 2H), 1.81 – 1.69 (m, 2H), 1.66 – 1.55 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 153.65, 145.74, 141.07, 139.35, 132.67, 131.47, 129.28, 127.15, 124.51,

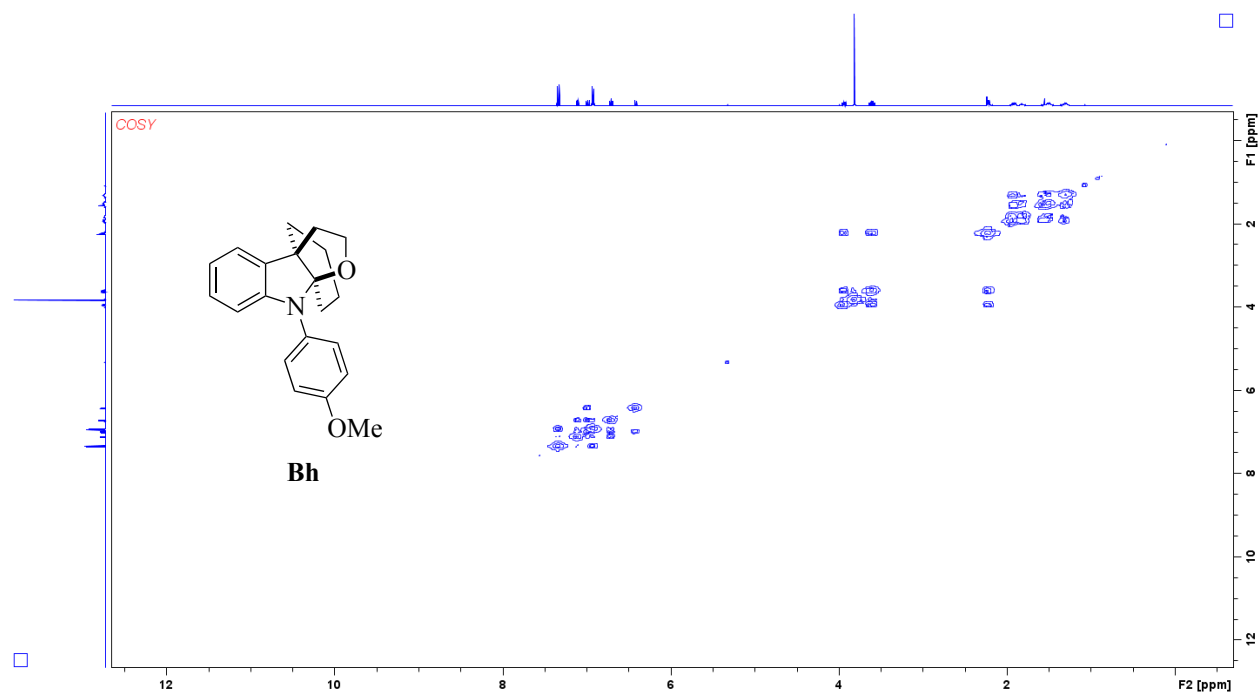
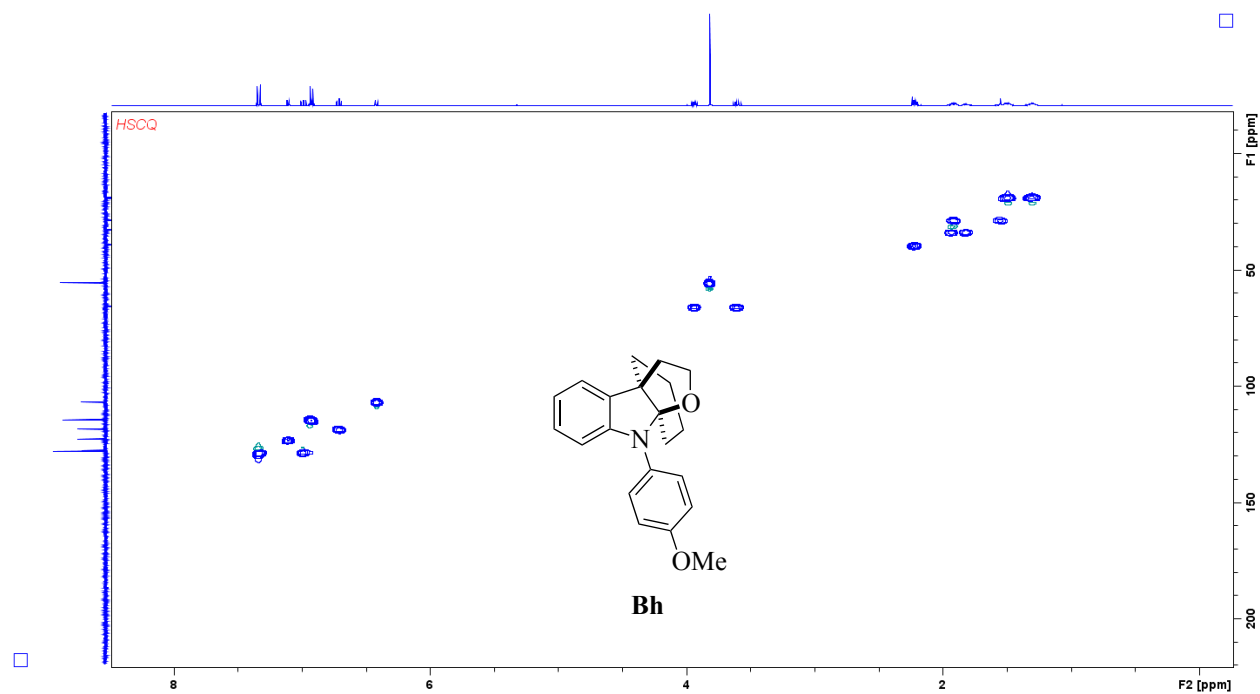
120.00, 115.34, 96.72, 60.92, 60.61, 55.97, 38.03, 31.88, 30.48, 26.51, 26.47; FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{23}H_{29}NO_4$ 384.2169; found 384.2172.

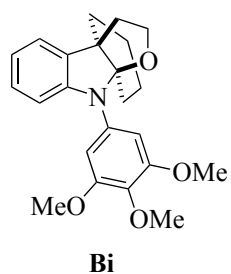
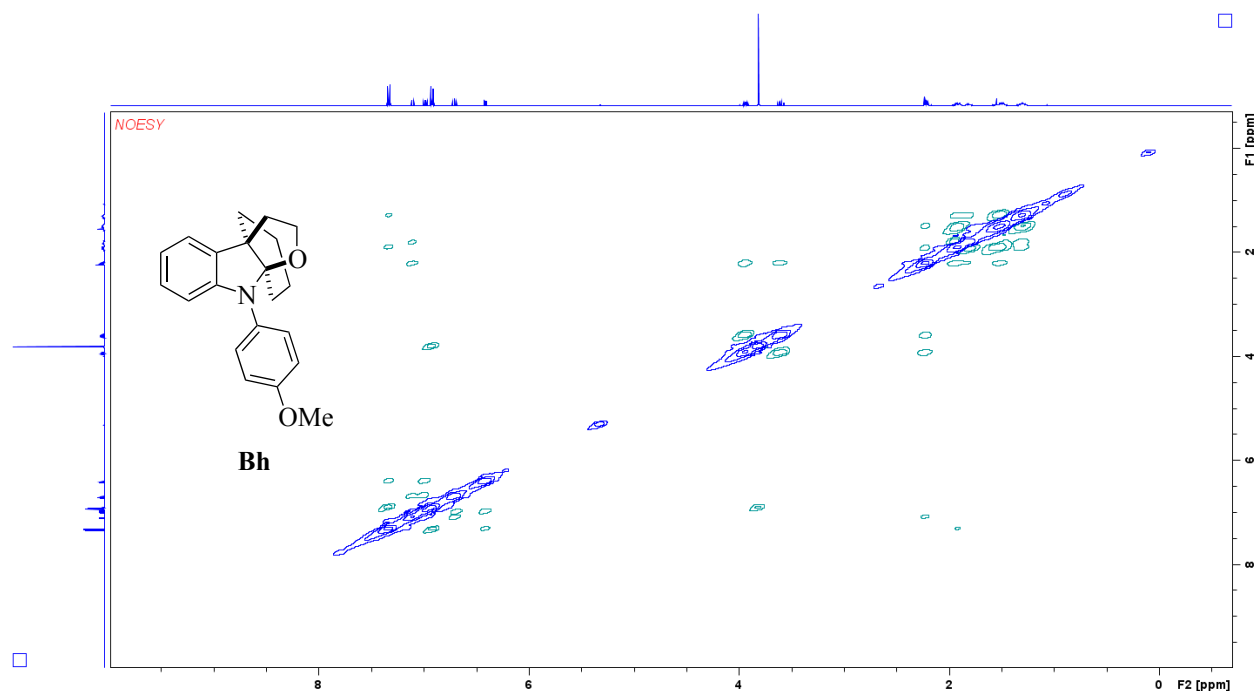
Visible Light Photochemistry of Styrenyl Anilines **Be** and **Bf**



Preparation of fused *N*-arylindoline **Bh** was accomplished using **General Procedure 4I (GP4I)** from Chapter 4 with $Ru(bpz)_3(PF_6)_2$ in anhydrous CH_3NO_2 . To a test tube equipped with a stir bar was added 3-cyclopentylidene-3-(2-(4-methoxyphenylamino)phenyl)propan-1-ol **Be** (1 equiv, 0.2 mmol, 64.9 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), HOAc (1 equiv, 0.2 mmol, 11.4 μ L) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16-gauge needle. The test tube was then clamped at a 6 cm distance from an 18W focused white LED and stirred for 6 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (95:5 hexanes:EtOAc) to afford the pure fused *N*-arylindoline **Bh** as a white solid, m.p. 105–108 °C (42.6 mg, 72%). IR ν_{max} (cm^{-1}) 2940, 2860, 1593, 1506, 1481, 1454, 1443, 1373, 1288, 1236, 1167, 1030, 833, 808, 746, 757. 1H NMR (400 MHz, Methylene Chloride- d_2) δ 7.36 – 7.31 (m, 2H), 7.11 (ddd, J = 7.3, 1.3, 0.6 Hz, 1H), 6.99 (ddd, J = 7.9, 7.4, 1.3 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.71 (td, J = 7.4, 1.0 Hz, 1H), 6.42 (ddd, J = 7.9, 1.0, 0.5 Hz, 1H), 3.94 (ddd, J = 8.4, 6.1, 3.6 Hz, 1H), 3.82 (s, 3H), 3.66 – 3.55 (m, 1H), 2.27 – 2.16 (m, 2H), 1.98 – 1.87 (m, 2H), 1.86 – 1.75 (m, 1H), 1.61 – 1.43 (m, 3H), 1.37 – 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.90,

149.89, 134.99, 133.59, 128.38, 128.11, 123.26, 118.63, 114.76, 107.06, 105.47, 65.97, 55.92, 54.40, 39.53, 33.40, 29.15, 19.49, 19.16; GC/MS (CI) m/z $[M+H]^+$ for $C_{21}H_{23}NO_2$ found 322.

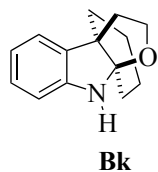




Preparation of fused *N*-arylindoline **Bi** was accomplished using **General Procedure 4I (GP4I)** from Chapter 4 with Ru(bpz)₃(PF₆)₂ in anhydrous CH₃NO₂. To a test tube equipped with a stir bar was added 3-cyclopentylidene-3-(2-(3,4,5-trimethoxyphenylamino)phenyl)propan-1-ol **Bf** (1 equiv, 0.2 mmol, 76.7 mg), Ru(bpz)₃(PF₆)₂ (2 mol%, 0.004 mmol, 3.6 mg), HOAc (1 equiv, 0.2 mmol, 11.4 μL) and CH₃NO₂ (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16-gauge needle. The test tube was then clamped at a 6 cm distance from an 18W focused white LED and stirred for 10 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford the pure fused *N*-arylindoline **Bi** as a yellow oil (49.6 mg, 65%). IR ν_{max} (cm⁻¹) 2934, 2864, 1582, 1504, 1460, 1287, 1229, 1123,

1018, 741, 712, 656, 501. ^1H NMR (400 MHz, Benzene- d_6) δ 7.09 (ddt, $J = 8.8, 6.2, 1.3$ Hz, 1H), 7.00 (ddd, $J = 7.4, 1.7, 0.9$ Hz, 1H), 6.97 – 6.92 (m, 2H), 6.89 – 6.77 (m, 2H), 3.88 (tt, $J = 3.1, 1.2$ Hz, 3H), 3.81 – 3.74 (m, 1H), 3.64 – 3.53 (m, 1H), 3.42 (t, $J = 0.9$ Hz, 6H), 2.28 – 2.17 (m, 1H), 1.99 – 1.80 (m, 2H), 1.79 – 1.58 (m, 3H), 1.37 – 1.23 (m, 4H); ^{13}C NMR (101 MHz, C_6D_6) δ 154.90, 149.52, 137.44, 136.90, 135.01, 128.77, 123.56, 119.39, 108.04, 105.78, 104.27, 65.94, 60.96, 56.19, 54.71, 39.85, 33.37, 29.24, 19.50, 19.00; GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{23}\text{H}_{27}\text{NO}_4$ found 382.

Oxidative Cleavage of 3,4,5-trimethoxyphenyl Group using Ceric Ammonium Nitrate



Formation of (9CI)-1,2,3,4-tetrahydro-9a,4a-(epoxyethano)-*H*-carbazole **Bk**

was achieved using a literature procedure.⁹ To a flask equipped with a stir bar was added fused *N*-arylindoline **Bi** (1 equiv, 0.1 mmol, 38 mg) and a mixture of

$\text{MeCN}/\text{H}_2\text{O}$ (2.7:1, 0.12 M, 0.82 mL total). The mixture was cooled to 0 °C and H_2SO_4 (2.02 equiv, 0.202 mmol, 10.6 μL) was added along with immediate addition of ceric ammonium nitrate (2.15 equiv, 0.215 mmol, 118 mg) in one portion. The mixture was stirred at 0 °C for 10 minutes prior to dilution with H_2O (3 mL). The solution was separated and the aqueous layer was washed with diethyl ether (3 x 10 mL). The organic layer was saved and stored for a later time in the workup. The combined aqueous layer was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 25 mL) and combined. The saved organic layer from the initial wash was then extracted with 0.1 M HCl (3 x 15 mL). The combined aqueous phase was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 25 mL) and added to the previous organic extract from the

basified extract. The organic layer was then dried of MgSO_4 , concentrated in vacuum, and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford (9CI)-1,2,3,4-tetrahydro-9a,4a-(epoxyethano)-*H*-carbazole **Bk** as a white solid, m.p. 82–85 °C (10 mg, 45%). This compound was documented by Zu et al. in 2015, having NMR's obtained in CDCl_3 and lacking melting point and IR characterizations.¹⁰ IR ν_{max} (cm^{-1}) 3285, 2922, 2857, 1611, 1466, 1258, 1200, 1063, 1016, 976, 858, 743, 588. ^1H NMR (400 MHz, Benzene- d_6) δ 7.06 (td, J = 7.6, 1.3 Hz, 1H), 6.91 (ddd, J = 7.3, 1.4, 0.6 Hz, 1H), 6.80 (td, J = 7.4, 1.0 Hz, 1H), 6.42 (ddd, J = 7.8, 1.1, 0.6 Hz, 1H), 3.73 (ddt, J = 6.9, 5.1, 3.4 Hz, 2H), 3.57 (ddd, J = 9.1, 8.2, 7.0 Hz, 1H), 1.89 – 1.82 (m, 2H), 1.78 (dt, J = 13.8, 4.8 Hz, 1H), 1.70 – 1.61 (m, 2H), 1.50 (dt, J = 13.8, 6.9 Hz, 1H), 1.46 – 1.39 (m, 1H), 1.38 – 1.23 (m, 2H), 1.20 – 1.13 (m, 2H); GC/MS (CI) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{14}\text{H}_{17}\text{NO}$ found 216.

B.5. References

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9. Nguyen, T. H.; Morris, S. A.; Zheng, N., Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes, Enynes, and Diynes via Visible Light Photocatalysis. *Adv. Synth. Catal.* **2014**, 356 (13), 2831-2837.
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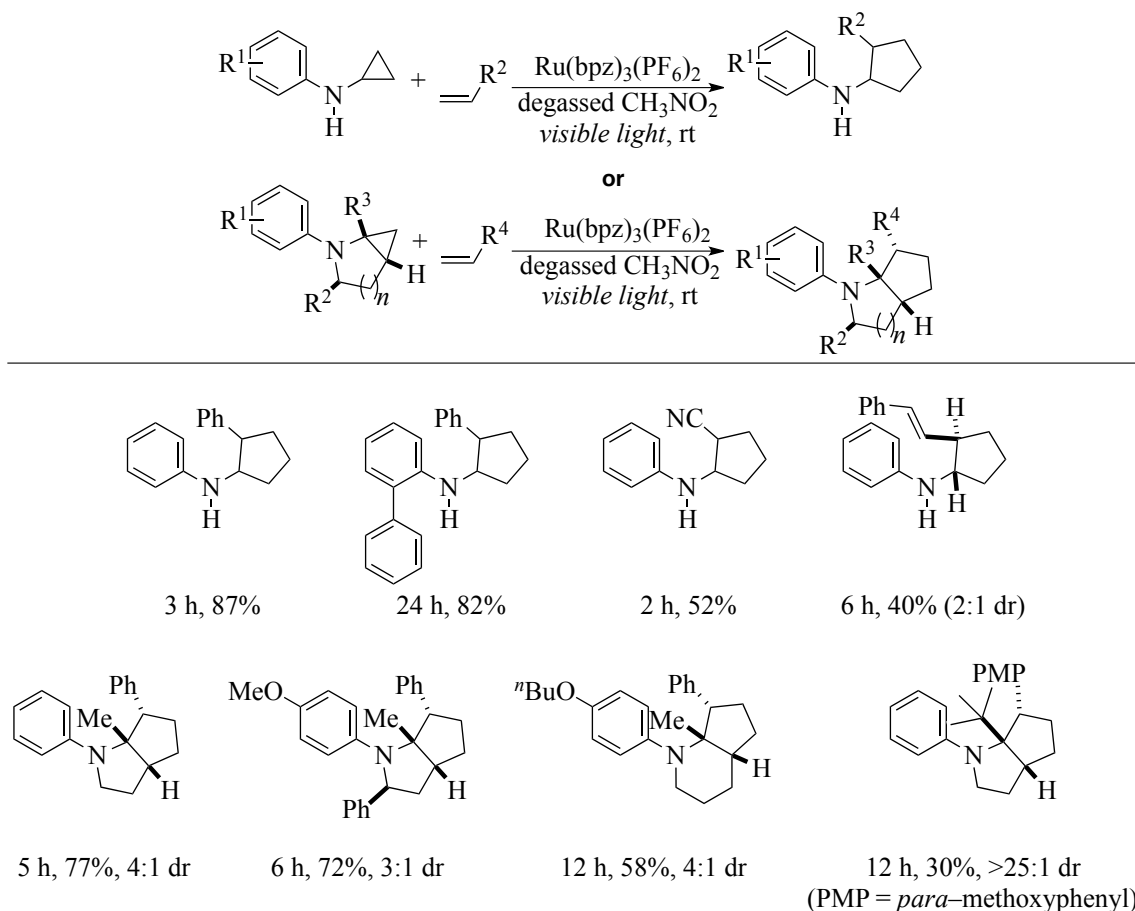
Appendix C

Miscellaneous Experiments for the [3+2] Annulation of Cyclopropylanilines with Alkynes using Visible Light

C.1. Introduction

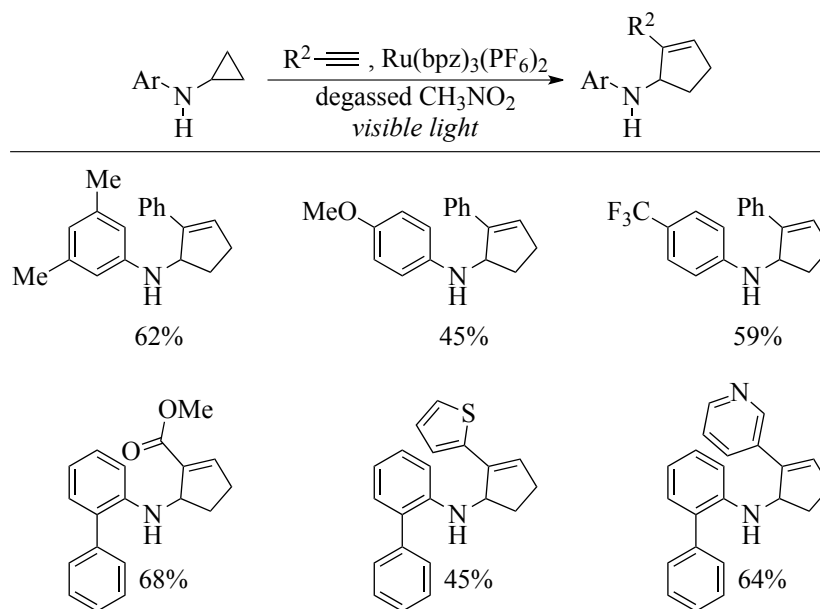
In 2012, the Zheng group revealed a photoredox-catalyzed [3+2] annulation of monocyclic and bicyclic cyclopropylanilines with alkenes, producing a variety of carbocycles in 30–87%, albeit no diastereoselectivity in the monocyclic case and moderate diastereoselectivity in the bicyclic case (Scheme C.1).¹

Scheme C.1. [3+2] Annulation of Cyclopropylanilines with Alkenes using Visible Light



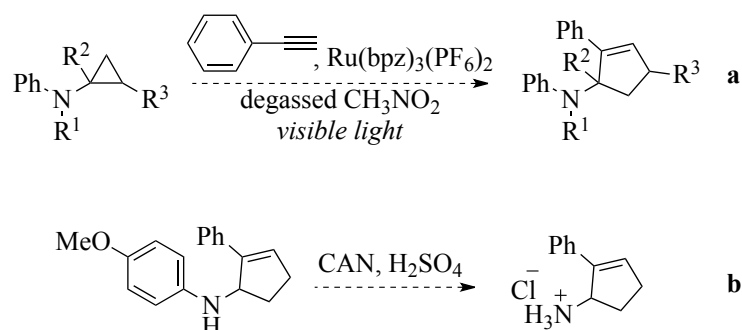
Subsequently, in 2014, Zheng et al. published a similar report revealing a [3+2] annulation of cyclopropylanilines with terminal alkynes using visible light, generating various cyclopentenes in 41–72% (Scheme C.2).²

Scheme C.2. [3+2] Annulation of Cyclopropylanilines and Terminal Alkynes using Visible Light



It was hypothesized that additional π -containing partners could undergo a [3+2] annulation with cyclopropylanilines using visible light, such as dienes, diynes, an enynes. Indeed, Theresa Nguyen was able to accomplish this transformation and generated a broad substrate scope while also rationalizing the regioselectivity when applicable. However, additional help was needed and Scott Morris temporarily joined the project in order to 1) examine the possibility of using cyclopropylanilines bearing substituents on the cyclopropane ring (Scheme C.3a) and 2) oxidatively cleave the requisite aryl group from the nitrogen (Scheme C.3b).

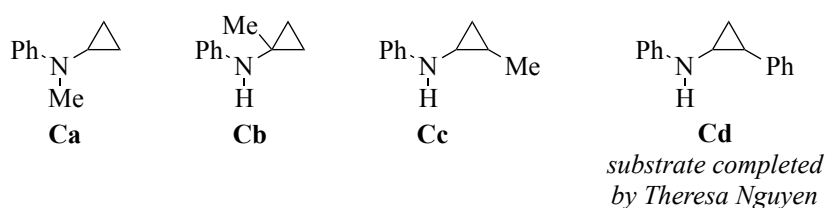
Scheme C.3. Proposed Project Goals



C.2. Results and Discussion

Studies commenced with the synthesis of starting materials **Ca**, **Cb**, **Cc**, and **Cd** (Figure C.1). It is of note that substrate **Cd** was completed by Theresa Nguyen and data for this compound will not be presented in this document.

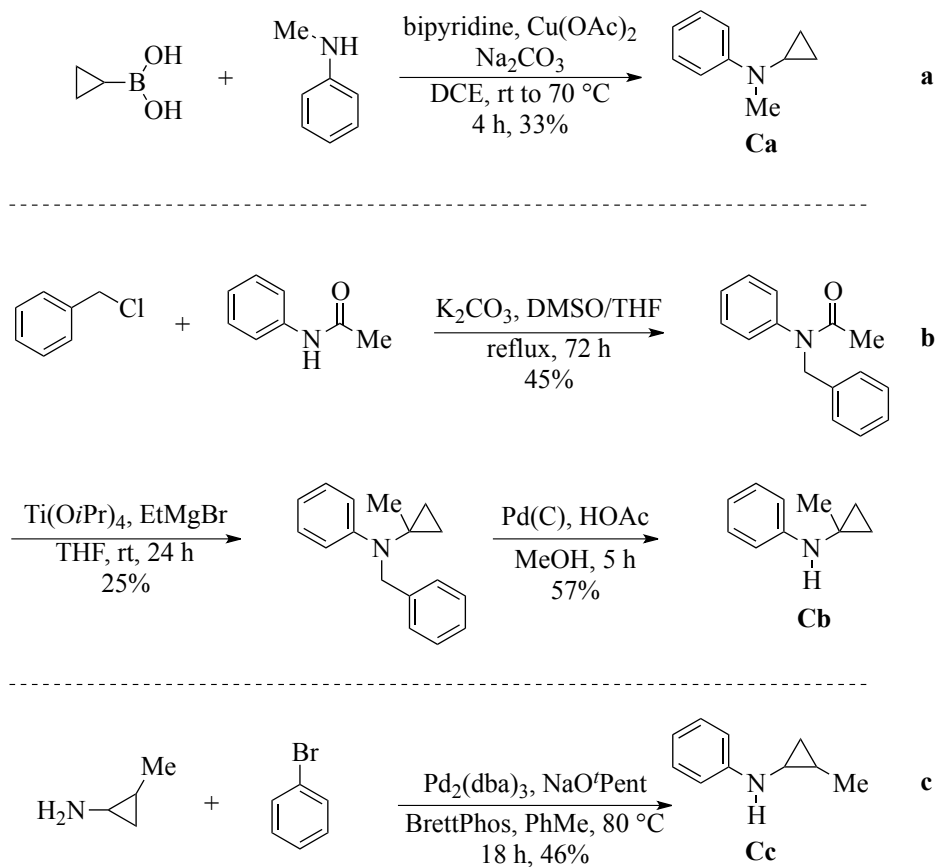
Figure C.1. Substituted Cyclopropylaniline Starting Materials



The synthesis of **Ca** was accomplished using a Cu(II)-mediated coupling of cyclopropylboronic acid with *N*-methylaniline, albeit low yields were obtained (Scheme C.4a).³ Substituted cyclopropylaniline **Cb** was synthesized using a 3-step protocol of substitution/Kulinkovich-de Meijere cyclopropanation/debenzylation, as shown in Scheme C.4b.⁴ Lastly, cyclopropylaniline

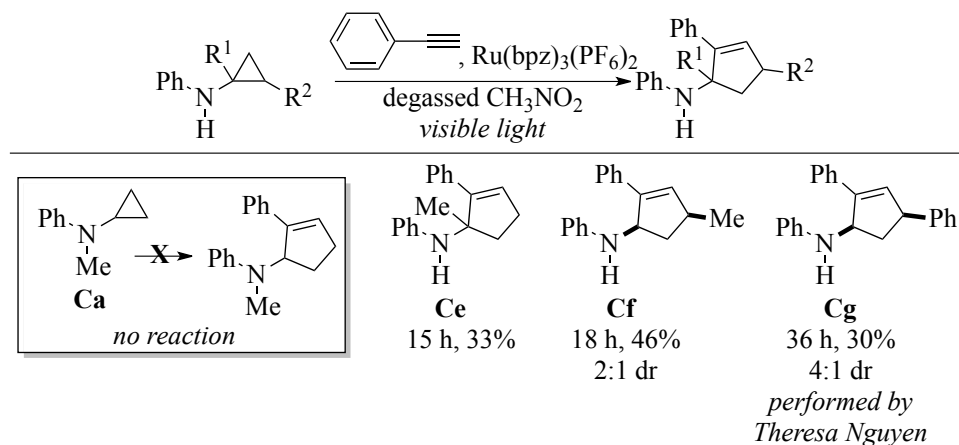
Cc was synthesized upon Buchwald–Hartwig amination of commercially available 2-methylcyclopropylamine and bromobenzene.^{1,2}

Scheme C.4. Synthesis of Starting Materials



Having the desired substrates in hand, [3+2] annulation reactions were attempted using visible light (Scheme C.5).

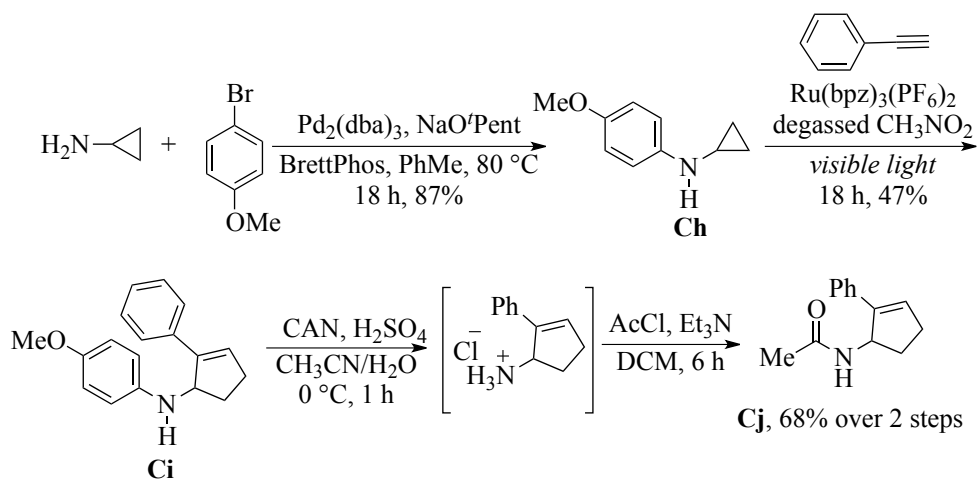
Scheme C.5. Photochemistry Results



As expected, the [3+2] annulation of **Ca** did not react, which is consistent with the observation made by Tanko and coworkers that the ring opening of cyclopropylamines of type **Ca** is extremely sluggish.⁵ However, the desired annulation adducts **Ce**, **Cf**, and **Cg** (performed by Theresa Nguyen) were obtained upon irradiation with visible light and $\text{Ru}(\text{bpz})_3(\text{PF}_6)_2$ in 30–46%, showcasing the ability for this chemistry to yield a vast array of carbocycles in a single step.

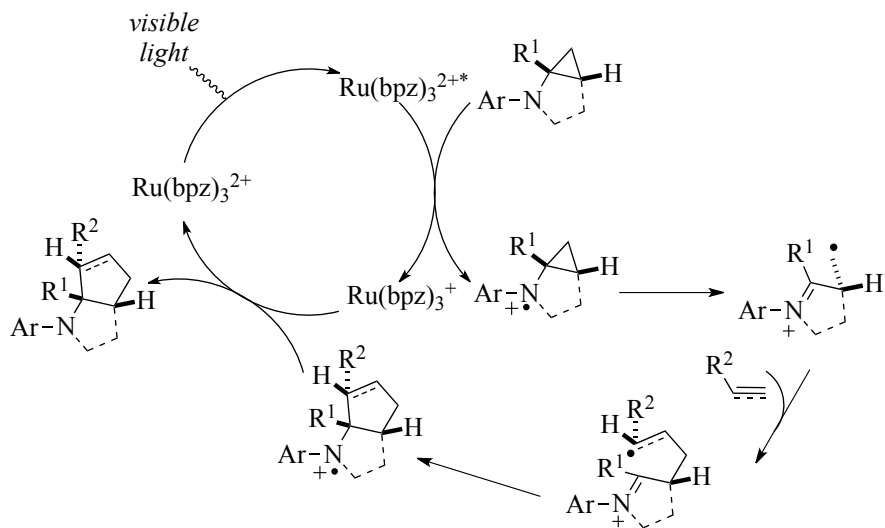
Next, cleavage of the requisite *N*-aryl group using ceric ammonium nitrate was attempted and the results are shown in Scheme C.6. To begin, cyclopropylaniline **Ch** was synthesized *via* Buchwald–Hartwig amination of cyclopropylamine and 4-bromoanisole.^{1,6} Cyclopropylaniline **Ch** was then subjected to visible light photoredox catalysis to generate carbocycle **Ci**. Substrate **Ci** was chosen as an ideal test substrate to due the facile cleavage of *para*-methoxyphenyl groups under oxidative conditions.⁷ Indeed, when using ceric ammonium nitrate, successful oxidative cleavage occurred, generating an intermediate ammonium salt that was subsequently acylated⁸ for ease of analysis to amide **Cj** (68% over 2 steps). The work described in this section was published in 2014 in *Advanced Synthesis and Catalysis* as a full article.⁹

Scheme C.6. Oxidative Cleavage of *para*-Methoxyphenyl Group



A proposed mechanism for the [3+2] annulation transformations is shown in Scheme C.7.

Scheme C.7. Proposed Mechanism



Upon visible light irradiation, $\text{Ru}(\text{bpz})_3^{2+}$ gets excited to its triplet excited state, which subsequently oxidizes the cyclopropylamine to the corresponding amine radical cation and generates the reduced $\text{Ru}(\text{bpz})_3^+$. The amine radical cation then undergoes C-C bond cleavage¹⁰

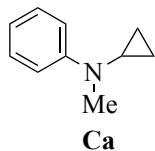
to yield the distonic ion that adds with the π -containing partner. Ring close with the iminium generates the amine radical cation which, upon reduction from $\text{Ru}(\text{bpz})_3^+$, yields the desired carbocycle in a redox-neutral fashion.

C.3. Experimental Procedures

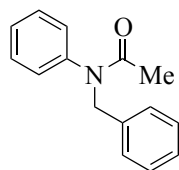
General Considerations

All reactions were carried out under a nitrogen atmosphere. Nitromethane (CH_3NO_2) was pre-dried over molecular sieves. Toluene was collected under argon from a solvent purification system. Column chromatography was performed using silica gel (230–400 mesh). All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS), and melting point (when applicable). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton signals in CDCl_3 (7.27 ppm, 77.23 ppm) at room temperature. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High resolution mass spectra were recorded on a Bruker Ultraflex II TOF/TOF mass spectrometer. Gas chromatography/mass spectroscopy (GC/MS) analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Melting points (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

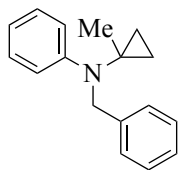
Synthesis of Cyclopropylanilines **Ca**, **Cb**, **Cc**, and **Ch**



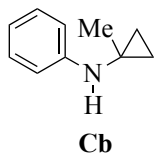
Preparation of *N*-cyclopropyl-*N*-methylaniline **Ca** was accomplished using a literature procedure.³ To a clean, dry 50-mL round bottom flask was added cyclopropyl boronic acid (2 equiv, 4.11 mmol, 353 mg), *N*-methylaniline (1 equiv, 2.05 mmol, 220 mg), and Na₂CO₃ (2 equiv, 4.11 mmol, 435 mg) in dichloroethane (0.25 M, 8.2 mL) was added Cu(OAc)₂ (1 equiv, 2.05 mmol, 373 mg) and bipyridine (1 equiv, 2.05 mmol, 321 mg). The contents were then warmed to 70 °C and stirred for 4 h. The resulting mixture was cooled to room temperature and a 25% aqueous NH₄OH solution was added (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over Na₂SO₄, concentrated in vacuum, and purified by flash chromatography on silica gel (99:1 hexanes:EtOAc) to afford *N*-cyclopropyl-*N*-methylaniline **Ca** as a clear oil (101 mg, 33%). Characterization of the pure compound matched that described in literature.¹¹



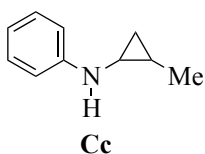
Preparation and characterization of *N*-benzylacetanilide from acetanilide and benzyl chloride in one step corresponded to that described in literature (45%).⁴



Preparation and characterization of *N*-benzyl-*N*-(1-methylcyclopropyl)-*N*-phenylamine from *N*-benzylacetanilide and ethyl magnesium bromide in one step corresponded to that described in literature (25%).⁴

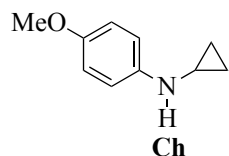


Preparation and characterization of *N*-(1-methylcyclopropyl)-*N*-phenylamine **Cb** from *N*-benzyl-*N*-(1-methylcyclopropyl)-*N*-phenylamine in one step corresponded to that described in literature (57%).⁴



Preparation of *N*-(2-methylcyclopropyl)aniline **Cc** was accomplished using a literature procedure.^{1, 2} To an oven-dried Schlenk flask equipped with a magnetic stir bar was added commercially available 2-

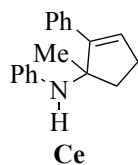
methylcyclopropylamine (1.6 equiv, 1 mmol, 71.12 mg), Pd₂(dba)₃ (1 mol%, 0.0063 mmol, 5.8 mg), and BrettPhos (3 mol%, 0.019 mmol, 10.1 mg). Glove box was used to add NaO^tPent (1.5 equiv, 0.94 mmol, 103 mg) and the tube was sealed with a screw cap containing a Teflon septum. Bromobenzene (1 equiv, 0.625 mmol, 67 μL anhydrous and anhydrous toluene (0.2 M, 3 mL) were then added to the reaction mixture and heated at 80 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel afforded the corresponding *N*-(2-methylcyclopropyl)aniline **Cc** as a clear oil (48 mg, 46%). Characterization of the pure compound matched that described in literature.⁴



Preparation and characterization of 4-methoxy-*N*-cyclopropylaniline **Ch**

from cyclopropylamine and 4-bromoanisole in one step corresponded to that described in literature (87%).²

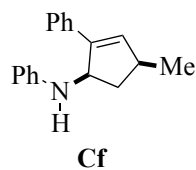
Photoredox-Catalyzed [3+2] Annulation



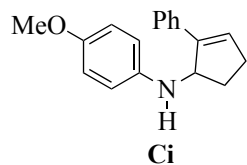
Preparation of *N*-(1-methyl-2-phenylcyclopent-2-enyl)aniline **Cb** was

accomplished by adding to an oven-dried test tube equipped with a magnetic stir

bar Ru(bpz)₃(PF₆)₂ (2 mol%, 0.004 mmol, 3.6 mg), *N*-(1-methylcyclopropyl)-*N*-phenylamine **Cb** (1 equiv, 0.2 mmol, 29.4 mg), phenylacetylene (5 equiv, 1 mmol, 110 μ L), dry CH₃NO₂ (0.1 M, 2 mL). The test tube was then sealed with a screw cap containing a Teflon septum. The contents were subsequently degassed by Freeze-Pump-Thaw cycles and then irradiated at room temperature with a sing 18W focused white LED positioned 8 cm from the test tube. After 15 hours, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (98:2 hexanes:EtOAc) to afford *N*-(1-methyl-2-phenylcyclopent-2-enyl)aniline **Cb** as a clear oil (16.4 mg, 33%). IR ν_{max} (cm⁻¹) 3411, 3052, 2962, 2927, 2844, 1605, 1501, 1322, 1194, 762, 693. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.47 (m, 2H), 7.20 – 7.13 (m, 3H), 7.07 – 6.98 (m, 2H), 6.68 – 6.55 (m, 3H), 6.00 (t, *J* = 2.6 Hz, 1H), 3.84 (s, 1H), 2.58 – 2.31 (m, 3H), 1.88 – 1.75 (m, 1H), 1.38 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 148.42, 146.83, 136.11, 129.46, 129.20, 129.05, 128.31, 127.35, 117.47, 115.30, 67.43, 35.84, 29.31, 29.26; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₈H₁₉N 250.1590; found 250.1591.

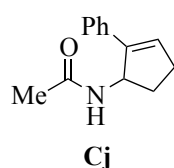


Preparation of *N*-(4-methyl-2-phenylcyclopent-2-enyl)aniline **Cf** was accomplished by adding to an oven-dried test tube equipped with a magnetic stir bar Ru(bpz)₃(PF₆)₂ (2 mol%, 0.004 mmol, 3.6 mg), *N*-(2-methylcyclopropyl)aniline **Cc** (1 equiv, 0.2 mmol, 29.4 mg), phenylacetylene (5 equiv, 1 mmol, 110 μL), dry CH₃NO₂ (0.1 M, 2 mL). The test tube was then sealed with a screw cap containing a Teflon septum. The contents were subsequently degassed by Freeze–Pump–Thaw cycles and then irradiated at room temperature with a sing 18W focused white LED positioned 8 cm from the test tube. After 18 hours, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (98:2 hexanes:EtOAc) to afford and inseparable isomeric mixture (2:1 *cis:trans*) of *N*-(4-methyl-2-phenylcyclopent-2-enyl)aniline **Cf** as a clear oil (23 mg, 46%). IR ν_{max} (cm^{−1}) 3411, 3052, 2955, 2927, 2869, 1600, 1501, 1311, 765, 748. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.48 (m, 3H), 7.36 – 7.30 (m, 3H), 7.29 – 7.20 (m, 4.4H), 6.74 (tq, *J* = 7.3, 1.0 Hz, 1.4H), 6.69 – 6.62 (m, 3H), 6.34 (d, *J* = 2.1 Hz, 0.4H), 6.33 (dd, *J* = 2.7, 1.3 Hz, 1H), 4.96 – 4.91 (m, 0.4H), 4.91 – 4.86 (m, 1H), 3.83 (s, 1H), 3.11 (qt, *J* = 7.1, 2.1 Hz, 0.4H), 2.99 – 2.87 (m, 1H), 2.75 (ddd, *J* = 13.2, 8.4, 7.5 Hz, 1H), 2.32 (ddd, *J* = 13.2, 7.3, 1.6 Hz, 0.4H), 1.82 (dt, *J* = 12.9, 7.1 Hz, 0.4H), 1.59 (dt, *J* = 13.2, 4.1 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 4H); ¹³C NMR (101 MHz, CDCl₃, mixture of diastereomers) δ 147.72, 141.86, 136.45, 135.91, 134.80, 134.65, 129.54, 129.49, 128.76, 128.70, 127.64, 127.58, 126.60, 126.35, 121.20, 118.00, 117.24, 117.17, 113.27, 113.14, 59.47, 59.15, 40.87, 40.51, 38.80, 38.62, 22.60, 20.95; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₈H₁₉N 250.1590; found 250.1589.



Preparation and characterization of *N*-(2-phenylcyclopent-2-en-1-yl)amine **Ci** from 4-methoxy-*N*-cyclopropylaniline **Ch** and phenyl acetylene in one step corresponded to that described in literature (47%).²

Oxidative Cleavage of *para*-Methoxyphenyl Group



Preparation of *N*-(2-phenylcyclopent-2-en-1-yl)acetamide **Cj** was accomplished by adding to an oven-dried test tube equipped with a magnetic stir bar a pre-cooled solution of *N*-(2-phenylcyclopent-2-en-1-yl)amine **Ci** (1 equiv, 0.2 mmol, 51 mg) in CH₃CN:H₂O (2.7:1, 0.1 M, 2 mL). Concentrated H₂SO₄ (1.9 equiv, 0.385 mmol, 22 μL) was slowly added at 0 °C over a 2 minute period. Ceric ammonium nitrate (2 equiv, 0.4 mmol, 220 mg) was then immediately added in one portion and the mixture was stirred for one hour at 0 °C. The resulting mixture was then diluted with water (2 mL) and separated. The aqueous phase was then washed with Et₂O (3 x 5 mL). The combined organic phase was then extracted with 0.1 N HCl (1 x 15 mL), and the resulting aqueous phase was added to the previous aqueous mixture, which was immediately basified to pH 14 using 5 N KOH. The basic aqueous layer was then extracted with Et₂O (2 x 30 mL). The combined organic layer was then acidified to pH 1 using hydrogen chloride (2 M in Et₂O). The resulting solution was then dried over MgSO₄ and concentrated to give the HCl salt as a dark brown oil. The crude HCl salt was used in the next step without further purification.

Acylation of the HCl salt was accomplished using a literature procedure.⁸ To a solution of the HCl salt (1 equiv, 0.18 mmol, 35 mg) in dry DCM (5 mL) was added Et₃N (2.2 mmol, 0.4 mmol, 56 μL) dropwise at room temperature. Acetyl chloride (1.2 equiv, 0.22 mmol, 16 μL) was slowly

added and the reaction was stirred for 6 hours at room temperature. The reaction was quenched with H₂O (10 mL) and the layers were separated. The aqueous phase was then extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated to give the crude product. Purification by flash chromatography on silica gel (50:50 hexanes:EtOAc) provided *N*-(2-phenylcyclopent-2-enyl)acetamide **Cj** as a red-brown oil (26.5 mg, 68% over 2 steps). IR ν_{max} (cm⁻¹) 3421, 2934, 2855, 1774, 1646, 1556, 1449, 1377, 1204, 759, 696. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.23 (m, 2H), 7.20 – 7.12 (m, 2H), 7.10 – 7.04 (m, 1H), 6.18 (t, *J* = 2.5 Hz, 1H), 5.40 – 5.20 (m, 2H), 2.44 – 2.26 (m, 3H), 1.74 (s, 3H), 1.70 – 1.59 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 169.91, 142.57, 134.29, 130.62, 128.83, 127.73, 126.23, 55.16, 32.78, 30.88, 23.67; HRMS (ESI) *m/z* [M+H]⁺, calc'd for C₁₃H₁₅NO 202.1226; found 202.1232.

C.4. References

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