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Amber Lucille Harris Date

Radical Spirocyclization via Organic Photoredox Catalysis

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Master of Science

Chemistry

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Radical Spirocyclization via Organic Photoredox Catalysis

By

Amber Lucille Harris
B.S., James Madison University, 2018

Advisor: Nathan T. Jui, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Chemistry
2019

Abstract

Radical Spirocyclization via Organic Photoredox Catalysis

By Amber Lucille Harris

Spirocyclic compounds are prevalent in drugs and natural products due to their unique three-dimensional scaffold that allows for tighter binding within structurally complex proteins, but these compounds are not easily synthesized by current methods. The use of expensive and hazardous materials, such as organotin and transition metal catalysts, makes up the majority of the literature precedent for synthesizing spirocyclic compounds. As an alternative, a mild method has been developed utilizing an organic photoredox catalyst, amine reductant, and irradiation from blue LEDs to form an array of diverse spirocyclic compounds. This new methodology allows for intramolecular radical 5-*exo*-trig cyclization of (hetero)aryl halide starting materials producing tricyclic ring systems that contain inherent three-dimensional properties.

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List of Abbreviations:

Ac: acetic acid

AIBN: azobisisobutyronitrile

Bn: benzyl

Boc: *tert*-butyloxycarbonyl

Bu: butyl

CBz: benzyloxycarrbonyl

DCM: dichloromethane

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

equiv: equivalents

Et: ethyl

Et_2O: diethyl ether

EtOAc: ethyl acetate

FDA: Food and Drug Administration

GCMS: gas chromatography mass spectrometry

HAT: hydrogen atom transfer

hr: hour

Hünig's base: *N*-ethyl-*N*-isopropylpropan-2-amine

***i*-Pr:** iso-propyl

ICS: intersystem-crossing

LCMS: liquid chromatography mass spectrometry

LED: light emitting diode

LRMS: low resolution mass spectrometry

Me: methyl

MeCN: acetonitrile

MeOH: methanol

mg: milligram

mmol: millimole

NMR: nuclear magnetic resonance

PC: photocatalyst

$PC^{\bullet -}$: photocatalyst (radical anion)

$PC^{\bullet +}$: photocatalyst (radical cation)

Ph: phenyl

Pr: propyl

PTH: 10-phenyl-10*H*-phenothiazine

RT: room temperature

SET: single electron transfer

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TFE: 2,2,2-trifluoroethanol

3DPA2FBN: 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile

3DPAFIPN: 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile

4-CzIPN: (2*s*,4*r*,5*r*,6*s*)-2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile

5CzBN: (2*r*,3*r*,4*s*,5*s*)-2,3,4,5,6-penta(9*H*-carbazol-9-yl)benzonitrile

Introduction:

Common scaffolds, such as indoles, quinolines, and aromatic rings are prevalent among small molecule drugs.[1] Included in these common scaffolds are nitrogen-containing heterocycles, which are present in over 50% of U.S. FDA approved drugs.[2] Of these nitrogen-containing heterocycles, piperidines are the most prevalent.[2] Piperidines are predominant in current drugs , in part, because their scaffold allows for control over functional group stereo-diversity, allowing for tighter binding when in contact with target proteins.[1] Three common drugs that require piperidine rings are Livostin, Paxil, and Claritin (Figure 1). Piperidine scaffolds are typically synthesized through a variety of methods, including reduction of pyridines, reductive amination, and alkylation.[3]

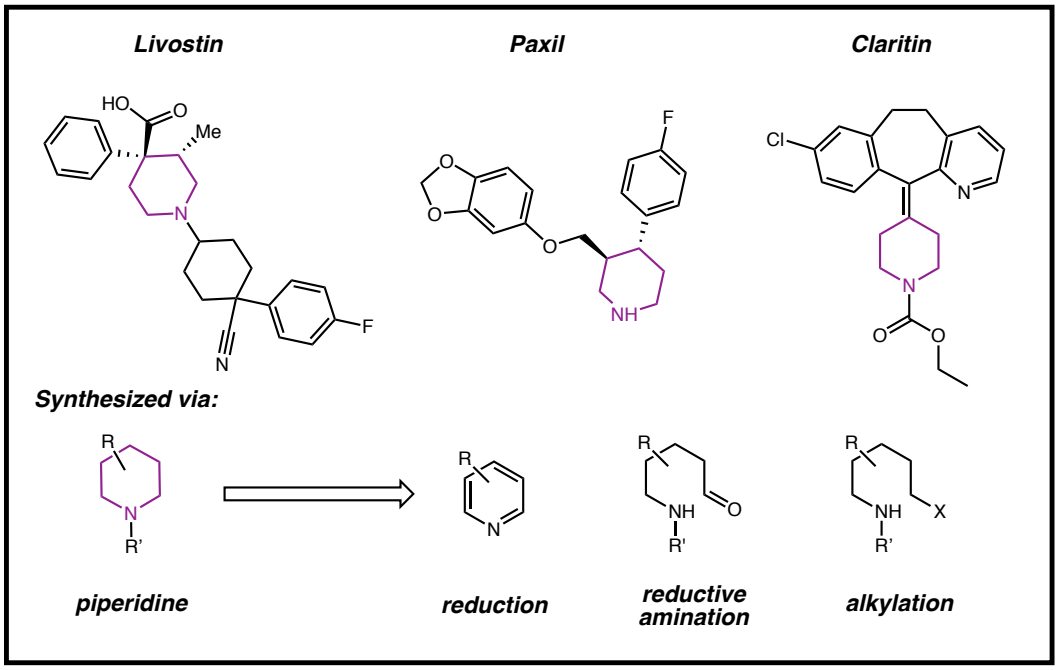


Figure 1. Three common piperidine containing pharmaceuticals and three common methods of piperidine synthesis.

Despite their great biological promise, traditional methods (*vide supra)* are incapable of forming the quaternary spirocyclic center. Piperidines that contain a spirocyclic center, where two rings share one common atom, are termed spiropiperidines. These compounds have increasingly appeared in pharmaceuticals because of their unique three-dimensional complexity stemming from their sp^3 unsaturated character which also allows for additional points of contact within unique three-dimensional binding pockets.[4] In many contexts, spiropiperidines and other spirocylic compounds have been associated with increased solubility and decreased lipophilicity— critical factors for a small molecule to become an effective drug.[5] Due to their inherent complexity and biological properties, over 86,600 compounds containing this spiropiperidine core have been logged in the Scifinder database, and of those, over 26,300 compounds have been screened for biological activity. Three selected examples, MK-0677 (Ibutamoren), AT-121, and a potent β-tryptase inhibitor, have demonstrated their efficacy as biological modulators and the viability of spiropiperidine based therapeutics (Figure 2).

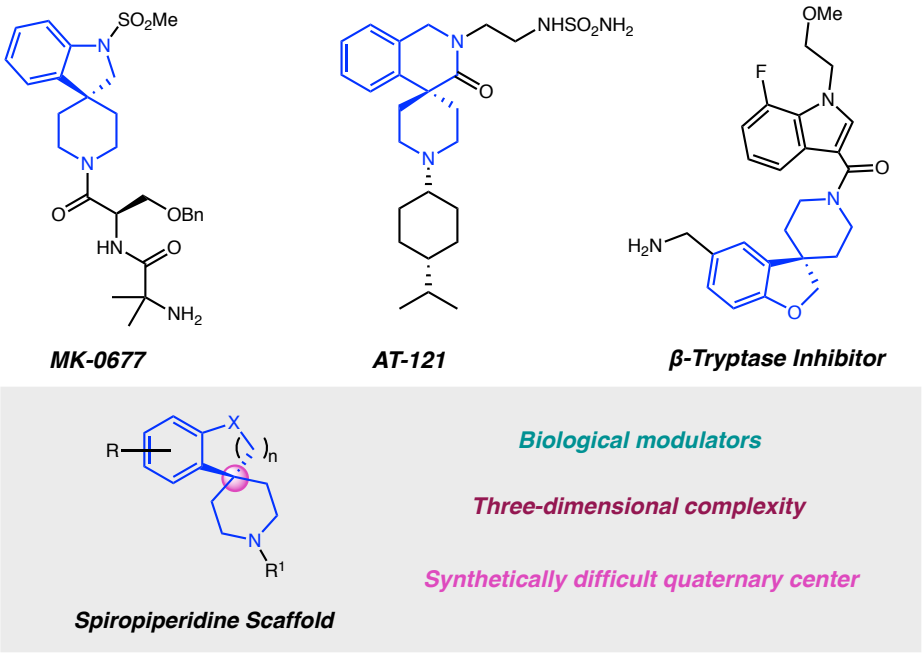


Figure 2. Three selected examples of biologically active compounds containing the spiropiperidine core.

MK-0677 (Ibutamoren) was first synthesized by Merck in 1997.[6] While this drug is currently in the investigational stage, it has already shown to be a very potent growth hormone secretagogue.[7] Ibutamoren is already used by the bodybuilding community as a growth hormone supplement, with an example being MK ULTRA sold by Blackstone Labs. Ibutamoren has also shown to be beneficial to children with growth hormone deficiencies.[8] To prepare the desired spirocycle, phenyl hydrazine was condensed onto protected 4-formylpiperidine, giving an unstable hydrazone, which subsequently underwent a reduction to give the observed spirocycle (Figure 3).[6] After which, six additional synthetic steps were completed to produce ibutamoren.[6]

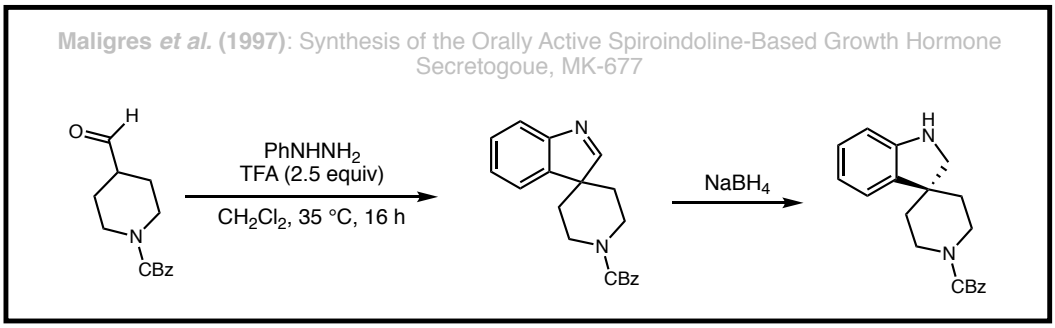


Figure 3. Synthesis of ibutamoren's spirocyclic core.

One of the most commonly prescribed narcotics is the opiate morphine, which also contains a spiropiperidine core.[9] Morphine binds directly to the μ-opioid peptide (MOP) receptor, blocking pain messages.[10] Because of morphine's strong affinity for this receptor, structural analogues have been widely sought after in order to mitigate many of the sometimes-fatal side effects associated with the drug, including respiratory depression and addictiveness.[10] Studies focused on novel morphine analogues have been very successful with the discovery of a new agonist that targets the MOP receptor, as well as the nociception/orphanin FQ (N/OFQ) peptide (NOP) receptor, which has been shown to modulate the addictive properties of MOP agonists.[11] In 2018, a dual agonist, AT-121, was designed, which contained a spiropiperidine core, but instead of a furan connecting the spiropiperidine to the aromatic ring, it was a six-membered lactam[11] (Figure 4). The lactam based structure allowed for increased binding affinities while decreasing the addictive qualities of the drug in monkeys, suggesting that this compound holds high promise as an opioid alternative with a lower addiction profile compared to morphine.[11] The spiropiperidine core of AT-121 was prepared in 4 steps from commercially available 4-cyano-4-phenylpiperidine hydrochloride with the key step consisting of a Pictet-Spengler reaction (Figure 4).[12] This reaction resulted in a modest 38% yield of the spirocyclic center.

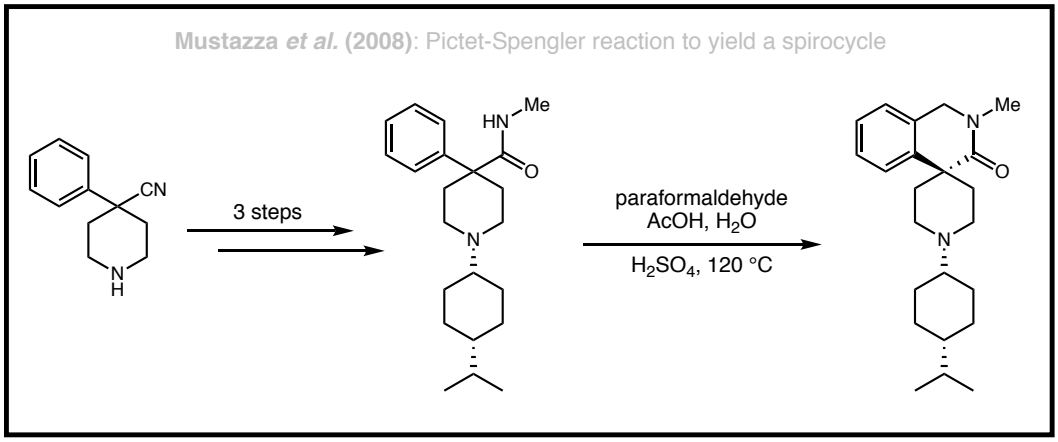


Figure 4. Mustazza's approach to the spirocyclic compound, AT-121, via a Pictet-Spengler reaction to form the spirocycle.

Researchers from Sanofi-Aventis successfully synthesized a spiropiperidineamide-based human β-tryptase inhibitor that is a potent anti-inflammatory agent used for the treatment of allergic disorders such as asthma and chronic obstructive pulmonary disease (COPD).[13] Other β-tryptase inhibitors have been investigated, but they lack the three-dimensional structure of a spirocyclic center, directly decreasing their metabolic stability in the human liver microsome.[13] In order to synthesize this spirocyclic center, the researchers at Sanofi-Aventis used one-electron chemistry by means of tributyltin hydride and a radical initiator, azobisisobutyronitrile (AIBN), in order to generate an aryl radical which engages in a 5-*exo*-trig cyclization with the tethered olefin.[13] This resulted in a 96% yield of the spirocycle, leaving only three more steps to synthesize the desired inhibitor (Figure 5). This synthetic strategy demonstrated the unique ability of radical chemistry to form spirocyclic scaffolds.

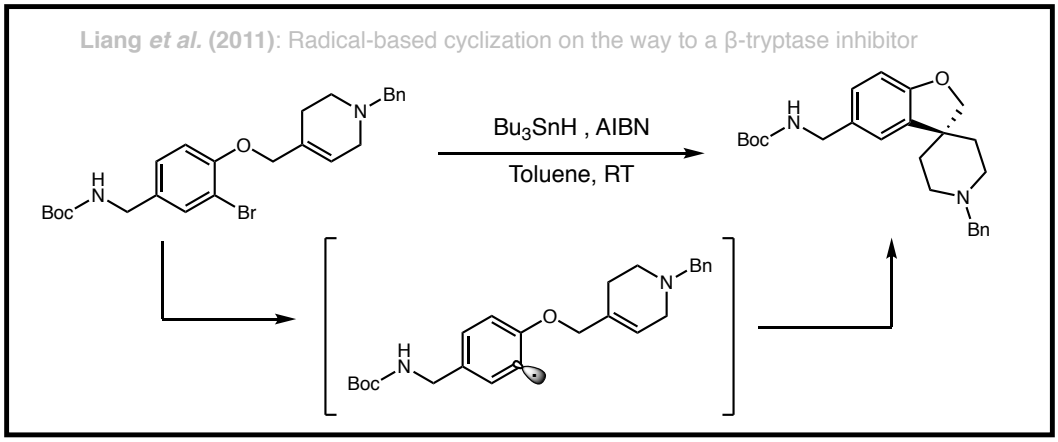


Figure 5. Synthesis of the spirocyclic core on the way to the total synthesis of Sanofi-Aventis' potent β-tryptase inhibitor with the radical intermediate shown.

Spirocyclic compounds with a core similar to spiropiperidine have also been synthesized via transition metal catalysis with rhodium[14] and palladium.[15] Palladium-catalyzed Heck-like cyclizations have been successful but are contingent on harsh conditions and temperatures up to 140 °C.[15] Using precious metal catalysts in Heck-like reactions also requires one more synthetic step, a hydrogenation, to achieve the same core.[15] Although the conventional methods to produce spirocycles are effective, they rely on multiple steps to create the quaternary center[12], precious metal catalysts[14-15], or hazardous reagents to generate aryl radicals.[13] Because of this, a unique approach is required for each novel spirocycle depending upon the ring size and functionality present. Therefore, a unified approach that is mild, safe, flexible, and regioselective was sought after.

Photoredox catalysis offers a mild strategy for the reduction of aryl halides by harnessing energy from light to generate strong reductants. As displayed in Figure 6, photoredox catalysts (PC) absorb visible (blue) light to promote an electron from its ground state to a high-energy singlet state.[16] Intersystem crossing to the corresponding, long-lived triplet excited state gives the redox active species, PC*. These species have the ability to act as both an oxidant and a reductant based on their environment, allowing photoredox catalysts to be operational in multiple mechanisms.[16] More specifically, the triplet-excited state catalyst would oxidize a sacrificial reductant through reductive quenching to become a ground state radical anion, $PC^{\bullet-}$, which acts as a potent reductant. Reduction of a substrate of interest from $PC^{\bullet-}$ would return the catalyst to its ground state, closing the catalytic cycle.[16] Alternatively, the triplet excited state catalyst could directly reduce the substrate of interest, becoming a potent oxidant, $PC^{\bullet+}$, in the process. Subsequent oxidation of a stoichiometric reductant would return the catalyst to the neutral ground state.[16] The associated redox potentials are controlled through tuning the catalyst structure, allowing for modularity.[16] In this way, photoredox systems allow for tight control of the radicals produced in a system. We envisioned that reductive quenching and subsequent reduction of aryl halides would give useful aryl radicals in a safe, green, and efficient way.

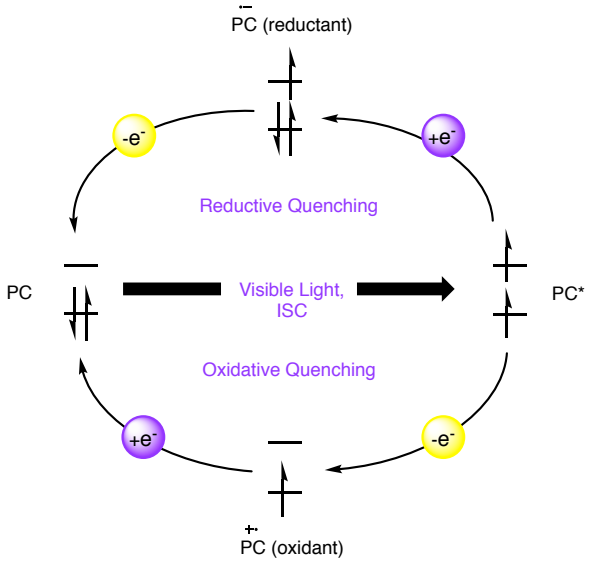


Figure 6. Photoredox catalyst cycle.

Photoredox first showed potential as an effective replacement for organotin and AIBN in 2012 when Stephenson and his coworkers developed an efficient reductive radical deiodination

method that was able to utilize a metal photoredox catalyst and an inexpensive hydrogen atom donor/stoichiometric reductant.[17] After demonstrating that aryl radicals could be produced from aryl iodides, Stephenson expanded the method by demonstrating that the radicals produced could undergo cyclization to produce bicyclic structures in high yields (86% yield) (Figure 7).[17] This cyclization occurred in the 5-*exo*-trig mode, which is in accordance with Beckwith's rules.[18]

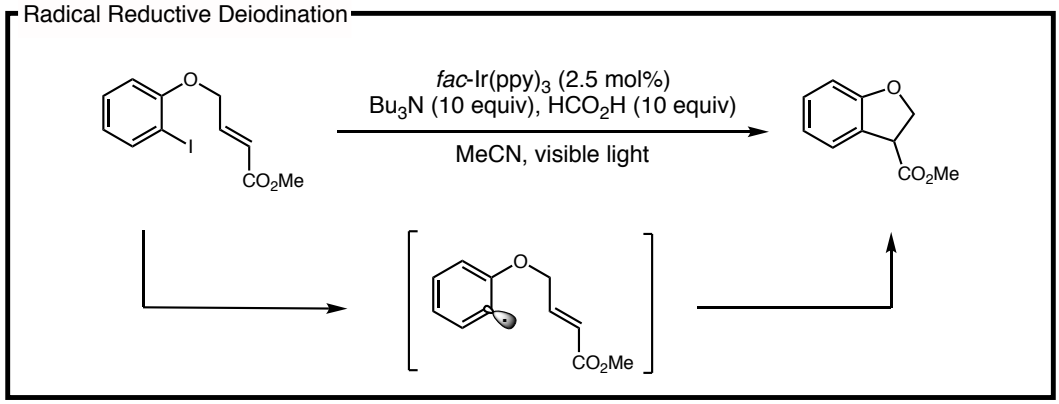


Figure 7. Stephenson's proposed radical reductive deiodination and subsequent cyclization.

Building upon Stephenson's work[17], our lab was interested in utilizing photoredox catalysis to access and utilize aryl and heteroaryl radicals. We have developed a series of intermolecular reactions that have selectively engaged electron-poor, -neutral, and -rich olefins. The first hydrorarylation system was developed by Aycock *et al*. using intermolecular radical conjugate addition.[19] In this work, a photoredox catalyst, Ir[dF(CF_3)ppy]dtbbpy$^+$, reduced 2-iodopyridine, which undergoes mesolytic cleavage to give a pyridyl radical.[19] This pyridyl radical subsequently engages in radical conjugate addition with a Michael acceptor, forming a new carbon-carbon bond (Figure 8). Because this system utilized photoredox chemistry, it became a safer, more stable, and cost-effective process for the formation of alkylpyridines. In this paper, we also showed an example of aryl radicals intramolecularly forming a bicyclic, fused-ring structure, a reaction that

would inspire further work from other members of our group. The second major hydroarylation system developed in the Jui lab was published by Boyington *et al*. (Figure 8).[20] In this work, pyridyl radicals engaged simple alkenes, forming new carbon-carbon bonds.[20] Isotopic labeling studies from each of these papers showed that the final mechanistic step is a hydrogen atom transfer from Hantzsch ester to the radical intermediate adduct.[18, 19]

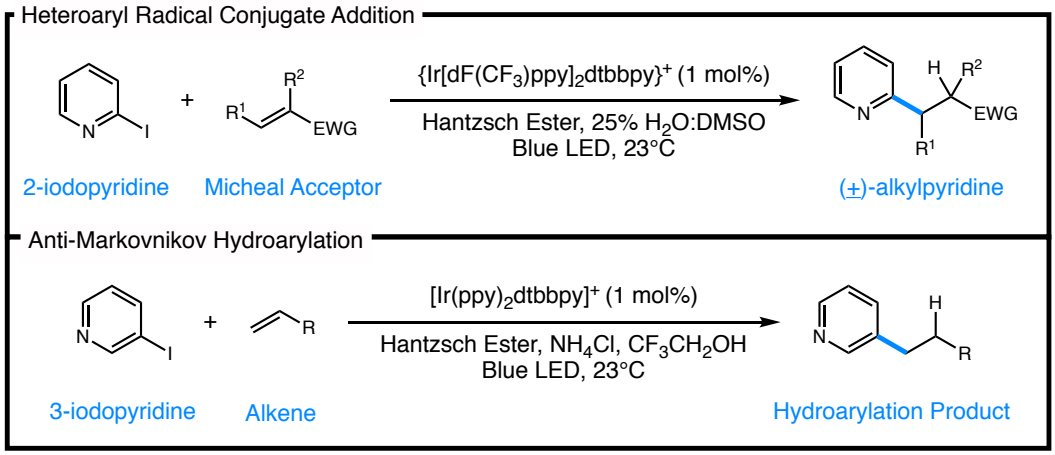


Figure 8. Previous inspirational work from the Jui lab by Aycock *et al*. and Boyington *et al*., respectively.[19, 20]

Based on this work from our lab and others, we envisioned a mild, safe, and flexible approach to yield spiropiperidine scaffolds and other spirocyclic motifs through photoredox catalysis. These spirocyclic compounds show great promise as biological modulators. Their aromatic rings allow for easy modularity[21], and their saturated ring systems allow for conformational complexity and derivatization[1] (Figure 9).

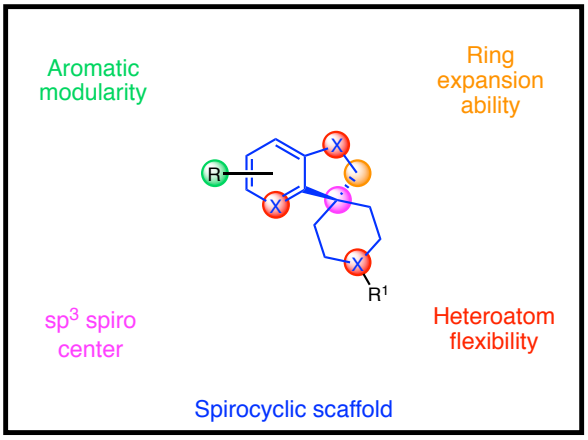


Figure 9. Our envisioned approach would offer flexibility in the spirocyclic scaffolds produced.

Results and Discussion

To accomplish the synthesis of spirocyclic compounds, our efforts were focused on a 5-*exo*-trig radical cyclization (Figure 10). The envisioned pathway involves reduction of an aryl halide **(1)** by an organic photocatalyst, followed by mesolytic cleavage to form an aryl radical (**2**). In accordance with Beckwith's rules, the aryl radical subsequently undergoes 5-*exo*-trig cyclization to produce an alkyl radical (**3**). This alkyl radical can be terminated through hydrogen atom transfer (HAT) (from Hünig's base) or reduction followed by protonation to afford the desired spirocyclic compound (**4**).

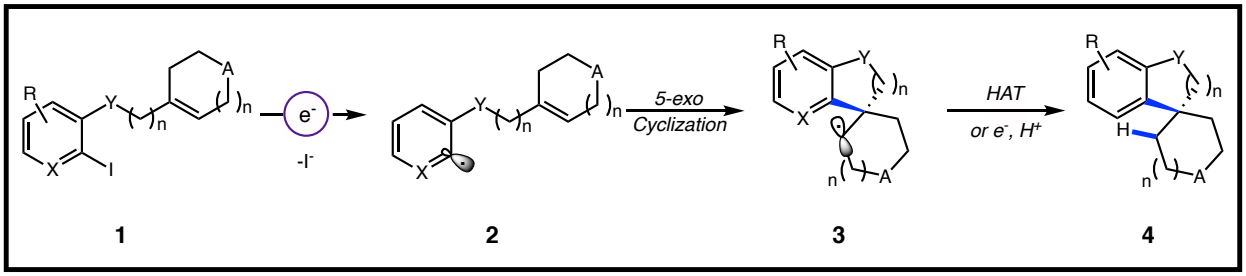
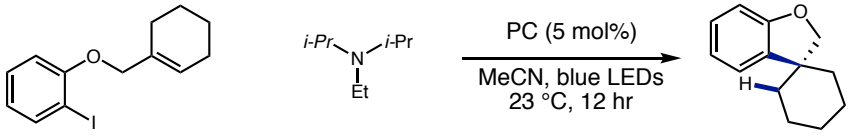


Figure 10. Proposed mechanism for the 5-*exo*-trig radical cyclization.

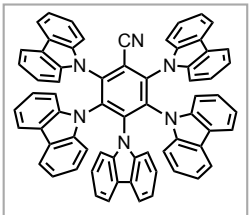
To test this, a simple starting material, 1-(cyclohex-1-en-1-ylmethoxy)-2-iodobenzene (**5**), was synthesized to gain proof-of-principle that the 5-*exo* radical cyclization would work using this approach. The first attempt at the radical cyclization utilized simple reductive conditions: 5CzBN (5 mol%), Hünig's base (1 equiv.) and acetonitrile (0.05 M) (Table 1, Entry 1). This reaction yielded 56% of the desired product, 2H-spiro[benzofuran-3,1'-cyclohexane] (**6**), but 43% of **5**. Further optimization of this system was completed, which found that the organic photocatalyst 3DPAFIPN produced higher yields of the desired product **6** (Table 1, Entry 2) than 5CzBN or 3DPAFBN (Entry 1 and 3, respectively). It was also found that increasing the amount of reductant increased conversion of the reaction but resulted in a lower product yield (Table 1, Entry 4).

Table 1. Model system catalyst and stoichiometric reductant equivalent screen. Yields determined by ^{1}H NMR with an internal standard of 1,1,2,2-tetrachloroethane.

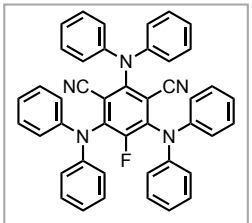


5 **Reductant** **6**

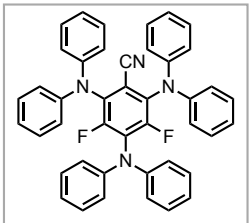
Entry	PC	*i*-Pr$_2$NEt	Solvent (rxn conc)	5	6
1	5CzBN	1 equiv	MeCN (0.05 M)	43%	56%
2	3DPAFIPN	1 equiv	MeCN (0.05 M)	31%	72%
3	3DPA2FBN	1 equiv	MeCN (0.05 M)	90%	29%
4	5CzBN	3 equiv	MeCN (0.05 M)	0%	65%



5CzBN
$E_{1/2}(PC/PC^{\bullet-})$ = -1.52 V
$E_{1/2}(^*PC/PC^{\bullet-})$ = +1.41 V



3DPAFIPN
$E_{1/2}(PC/PC^{\bullet-})$ = -1.59 V
$E_{1/2}(^*PC/PC^{\bullet-})$ = +1.30 V

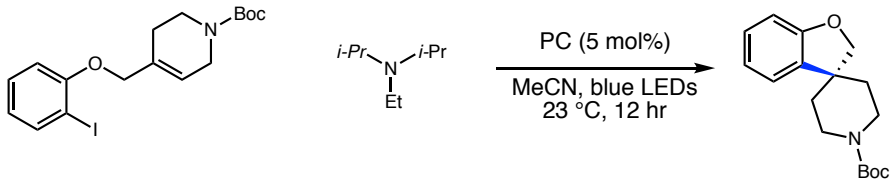


3DPA2FBN
$E_{1/2}(PC/PC^{\bullet-})$ = -1.92 V
$E_{1/2}(^*PC/PC^{\bullet-})$ = +1.24 V

With an optimized system for 5-*exo* radical cyclization in hand, more pharmaceutically relevant spirocyclic compounds were synthesized, starting with *tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**7**), which was synthesized in accordance with a patented procedure from Costanzo *et al*.[22] The 5-*exo* radical cyclization conditions as previously described were used to determine if the cyclization of **7** would proceed similarly. The first attempt with this new compound resulted in an NMR yield of 58% (Table 2, Entry 1).

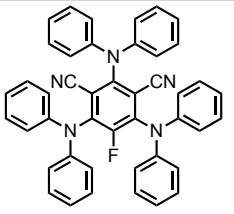
The system was further optimized for substrate **7** in collaboration with Racheal Spurlin (Table 2). First, control experiments running the reaction with no irradiation from blue LEDs, no base, and no catalysts were run in acetonitrile, which demonstrated the expected results of no reaction, returning only starting material **7**. Then, catalysts differing in quenching mechanisms were screened for. PTH, which operates through oxidative quenching, failed to reduce any of the starting material (Table 2, Entry 2). All of the donor-acceptor cyano-arene organic photocatalysts, which operate under a mechanism of reductive quenching, worked similarly (Table 2, Entries 1, 3-4), with the 3DPAFIPN catalyst yielding the best results. Stoichiometric loading of Hünig's base was also screened (Table 2, Entries 5-7). Five molar equivalents yielded the best results, resulting in a 60% yield of the desired product *tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**8**) (Table 2, Entry 6).

Table 2. Catalyst and Hünig's base equivalents screens. Yields determined by ^{1}H NMR with an internal standard of 1,1,2,2-tetrachloroethane.

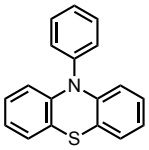


7 **Reductant** **8**

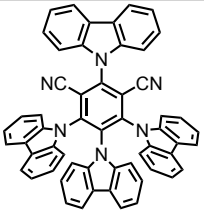
Entry	PC	*i*-Pr$_2$NEt	Solvent (rxn conc)	7	8
1	3DPAFIPN	3 equiv	MeCN (0.05 M)	0%	58%
2	PTH	3 equiv	MeCN (0.05 M)	102%	0%
3	3DPA2FBN	3 equiv	MeCN (0.05 M)	0%	55%
4	4CzIPN	3 equiv	MeCN (0.05 M)	0%	48%
5	3DPAFIPN	1 equiv	MeCN (0.05 M)	24%	29%
6	3DPAFIPN	5 equiv	MeCN (0.05 M)	0%	60%
7	3DPAFIPN	10 equiv	MeCN (0.05 M)	0%	49%



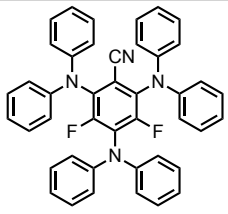
3DPAFIPN
$E_{1/2}(PC/PC^{\bullet-}) = -1.59$ V
$E_{1/2}(^*PC/PC^{\bullet-}) = +1.30$ V



PTH
$E_{1/2}(PC^{\bullet+}/PC) = -2.1$
$E_{1/2}(PC^{\bullet+}/PC^*) = +0.68$ V



4-CzIPN:
$E_{1/2}(PC/PC^{\bullet-}) = -1.21$ V
$E_{1/2}(^*PC/PC^{\bullet-}) = +1.35$ V

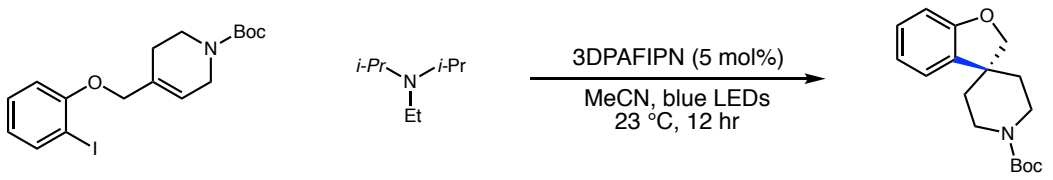


3DPA2FBN
$E_{1/2}(PC/PC^{\bullet-}) = -1.92$ V
$E_{1/2}(^*PC/PC^{\bullet-}) = +1.24$ V

Photocatalyst 3DPAFIPN and the use of five equivalents of Hünig's base was found to be sufficient for reduction of substrate **7** in acetonitrile. A solvent screen was conducted to further optimize the system. We first screened multiple solvents differing in their polarity (Table 3, Entries 1-7). From this, we observed that polar solvents were the most successful, so we next sought to increase the polarity of our solvent system by the addition of water (Table 3, Entries 8-13). To our surprise, a drastic difference occurred when water was included as cosolvent with THF (Table 3,

Entries 10), resulting in high yield (83%) and complete conversion of starting material. Following these results, the percent of water in THF was varied (Table 3, Entries 14-18), demonstrating that 20% water in THF is optimal for production of spirocycle **8** (Table 3, Entry 10).

Table 3. Solvent optimization screen. All NMR yields were determined with an internal standard of dibromomethane.



7 **Reductant (5 equiv)** **8**

Entry	% Water	Solvent (rxn conc)	7	8
1	0%	MeCN (0.05)	0%	51%
2	0%	DCM (0.05)	22%	39%
3	0%	THF (0.05)	69%	0%
4	0%	DMSO (0.05)	0%	41%
5	0%	DMF (0.05)	22%	47%
6	0%	MeOH (0.05)	0%	53%
7	0%	Et_2O (0.05)	66%	18%
8	20%	MeCN (0.05)	0%	47%
9	20%	DCM (0.05)	0%	47%
10	**20%**	**THF (0.05)**	**0%**	**84%**
11	20%	DMSO (0.05)	0%	41%
12	20%	DMF (0.05)	0%	47%
13	20%	MeOH (0.05)	0%	53%
14	10%	THF (0.05)	0%	68%
15	30%	THF (0.05)	0%	56%
16	40%	THF (0.05)	0%	69%
17	50%	THF (0.05)	0%	50%
18	75%	THF (0.05)	0%	55%

With an optimized system, mechanistic experiments were run in order to investigate the 5-*exo*-trig radical spirocyclization. We believe that the first step of the reaction occurs through a

single electron transfer (SET) from the reduced photocatalyst ($PC^{\bullet-}$) since control experiments showed that reduction of **7** did not occur in the absence of Hünig's base. This SET event produces an aryl radical, which operates through a 5-*exo*-trig radical cyclization. The final mechanistic step is the termination of the alkyl radical. This termination step could be achieved through two different mechanisms: HAT (a one electron process), or reduction and subsequent protonation (a two-electron process). The mechanism of this last step was tested through the use of 20% deuterated water (D_2O) in tetrahydrofuran to see if deuterium would be incorporated into the final product. Results from this experiment showed no deuterium incorporation, suggesting that the mechanism does not terminate via pronation. *N*,*N*-diisopropyloctan-1-amine-1,1-d_2 (to mimic deuterated Hünig's base) was synthesized in order to probe if the last step in the mechanism occurred through HAT. This experiment also showed no deuterium incorporation. Although this experiment does not definitively prove that the termination step is HAT, it is hypothesized that termination of the alkyl radical results from HAT from the isopropyl group of Hünig's base rather than the ethyl group (Figure 11).

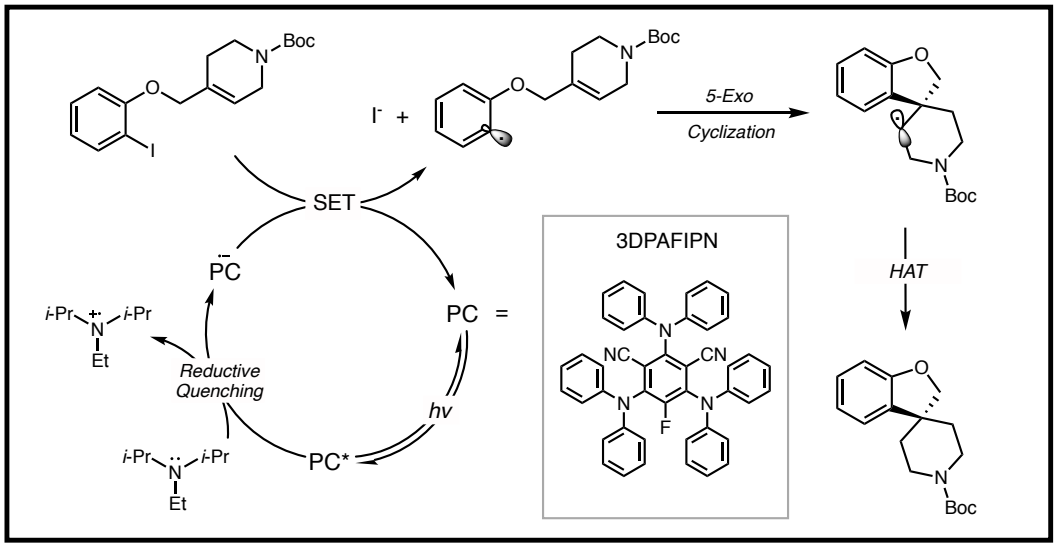


Figure 11. Proposed mechanism for radical 5-*exo*-trig cyclization.

A time study was also conducted on **7** to determine how quickly the reaction occurred (Figure 12). Time points were obtained every hour to monitor the progression of the reaction. After four hours, all starting material was consumed. From this time study, it was also determined that no unwanted side products were formed, and no decomposition was occurring in this solvent system.

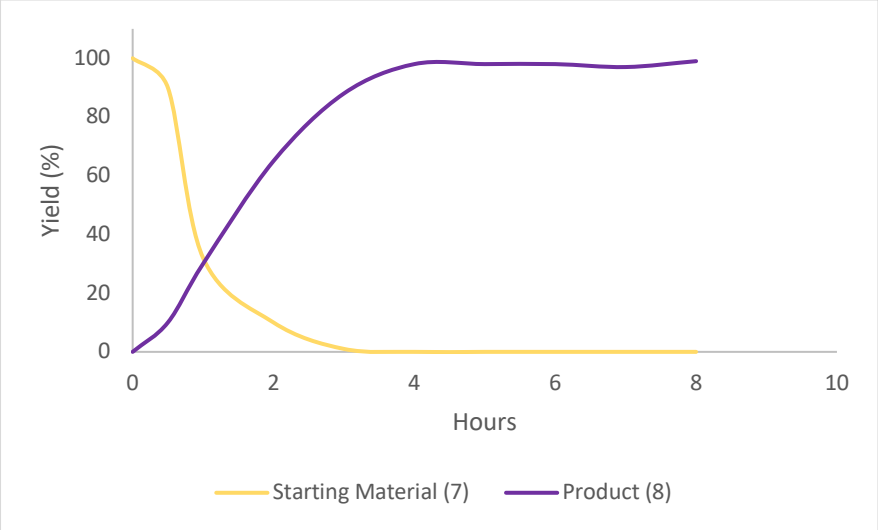


Figure 12. Time study on starting material **7** that demonstrated that all starting material was consumed after four hours.

Tert-butyl 4-(((2-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**10**) was synthesized and subsequently treated to the optimized radical 5-*exo* cyclization conditions. This reaction resulted in a 72% isolated yield of the desired product, *tert*-butyl 2*H*-spiro[furo[3,2-*b*]pyridine-3,4'-piperidine]-1'-carboxylate (**11**). As illustrated in Figure 13, this blue light driven reaction can successfully transform electron-rich (**12**) and electron-deficient (**13**) arenes (70% and 51% yield, respectively). In addition, halogenation (chloride) is tolerated on the aromatic ring, leaving a handle for further elaboration (**14**). The best yield on any substrate has occurred with a 5-membered alkene ring, giving **15** in an 80% yield. Extended tethers which yield

a six membered spirocycle (**16**) also operate in this system, though the system is not yet optimized for **16**. Spirocyclic compounds can now be obtained in high yields with complex functionality by means of a unified, hazard-free, and green method that before required the use of transition metal catalysis or harsh conditions.

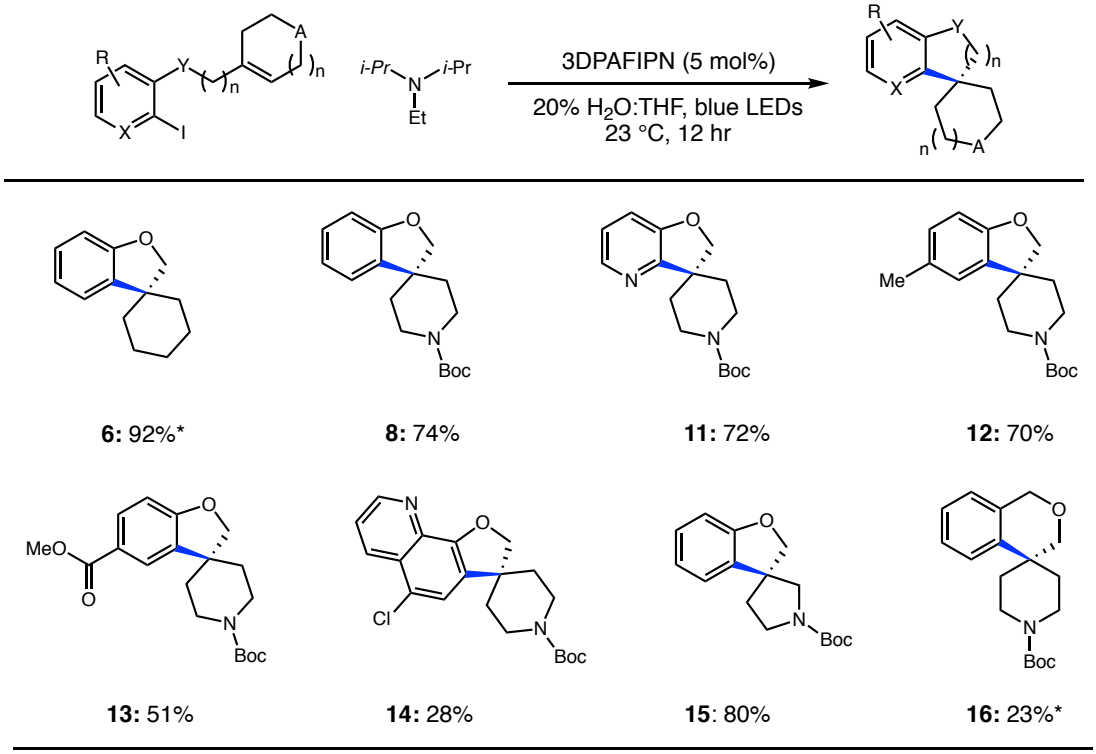


Figure 13. Current scope of synthesized spirocyclic products. **15** and **16** synthesized by Racheal Spurlin.

Conclusions and Future Work

We have developed a new method for radical 5-*exo*-trig cyclization that removes the need for toxic reagents and expensive catalysts to provide an economical and sustainable alternative to previous radical- and transition metal-catalyzed cyclization reactions via photoredox catalysis. Currently, eight spirocyclic substrates have been successfully synthesized through this new

method, with most resulting in high yields. For the two compounds with low yields (**14** and **16**), further optimization of the reaction conditions will be completed. New starting materials are currently in preparation to provide the desired substrate scope shown in Figure 14. This scope will demonstrate the utility of this new method to yield products with diverse substitution on the aromatic left ring, multiple different tethered linkers that will yield five- or six-membered connecting rings, and different hetero-saturated right rings.

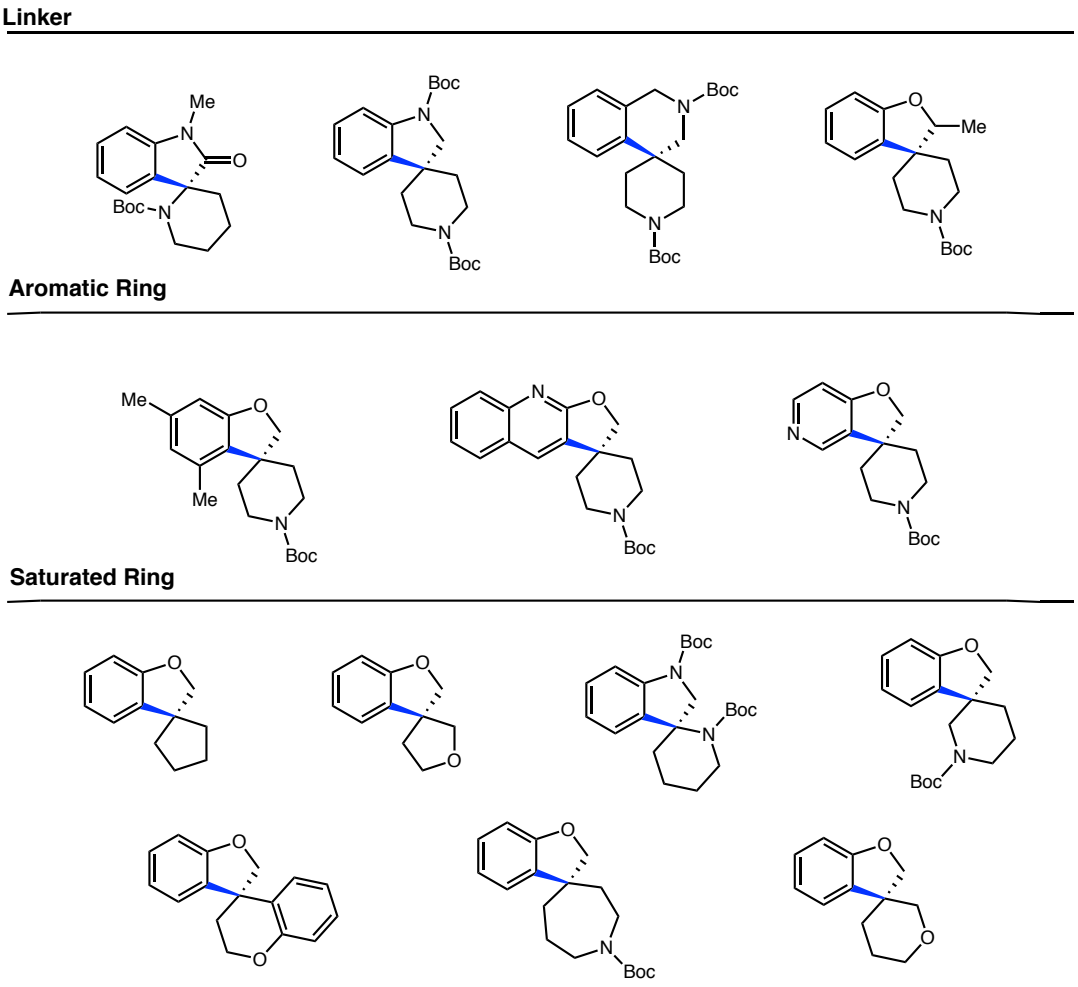


Figure 14. Future substrate scope.

Although the mechanism for radical 5-*exo*-trig cyclization has nearly been elucidated, future experiments will focus on determining how the alkyl radical is terminated. To this end, deuterated Hünig's base will be synthesized with all hydrogens alpha to the nitrogen replaced with deuterium so that the termination step of the reaction can be conclusively determined.

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Experimental:

General Reagent Information:

All solvents used were purified by passing over activated alumnia and storing under argon. All degassed solvents were subjected to ~15-30 minutes of sonication and vacuum. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Silica gel chromatography was carried out using Siliaflash® P60 silica gel purchased from Silicycle. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using KMnO4. All photoredox reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs, unless stated otherwise (LED wholesalers PAR38 Indoor Outdoor 16- Watt LED Flood Light Bulb, Blue; or Hydrofarm® PPB1002 PowerPAR LED Bulb-Blue 15W/E27 (available from Amazon). Photoredox catalysts 3DPAFIPN, 3DPA2FBN, 4CzIPN, 5CzBN, PTH were prepared according to literature procedures.[23, 24]

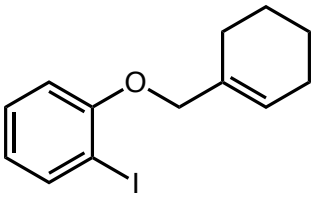
General Analytical Information:

^{1}H and ^{13}C NMR spectra of new compounds were obtained from the Emory University NMR facility and run on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz) and are internally referenced to residual protio solvent signals. NMR spectra were run in solutions of deuterated chloroform ($CDCl_3$) or deuterated methanol and were reported in parts per million

(ppm). Abbreviations for signal multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets, b = broad, etc. Coupling constants (J values) were calculated directly from the spectra. Data for decoupled ^{13}C NMR are reported in terms of chemical shift. Gas Chromatography Mass Spectrometry (GC-MS) was performed on an Agilent 5977A mass spectrometer with an Agilent 7890A gas chromatography inlet. Liquid Chromatography Mass Spectrometry (LC-MS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet.

Preparation of starting materials from the substrate scope

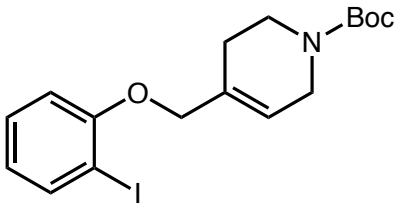
1-(cyclohex-1-en-1-ylmethoxy)-2-iodobenzene (5)



A round bottom flask was charged with 2-iodophenol (101 mg, 0.46 mmol, 1.0 equiv) and K_2CO_3 (70 mg, 0.51 mmol, 1.1 equiv). Acetonitrile (0.1 M) was added, followed by 1-(chloromethyl)cyclohex-1-ene (40 mg, 0.46 mmol, 1.0 equiv). The reaction was heated to 80°C and left to proceed for 12 hours. The reaction mixture was cooled to room temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude oil was purified by column chromatography (10% EtOAc in Hexanes) to yield the desired product as a colorless oil (49 mg, 51% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.19 – 7.14 (m, 1H), 6.71 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.60 (td, *J* = 7.5, 1.4 Hz, 1H), 5.78 (tt, *J* = 3.7, 1.8 Hz, 1H), 4.35 – 4.30 (m, 2H), 2.04 (td, *J* = 6.2, 3.4 Hz, 2H), 1.98 (m, *J*

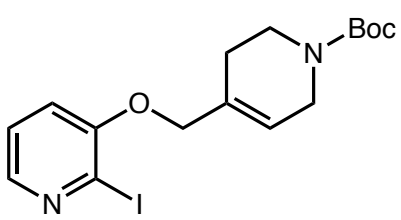
= 6.3, 4.2, 2.2 Hz, 2H), 1.60 (m, *J* = 9.3, 5.5, 3.2 Hz, 2H), 1.57 – 1.48 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.44, 139.41, 133.26, 129.35, 125.42, 122.43, 112.55, 86.82, 73.64, 25.82, 25.06, 22.48, 22.38. **LRMS (GCMS):** m/z: calc'd. for $C_{13}H_{15}IO$: 314.0, found 314.0.

***Tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (7)**



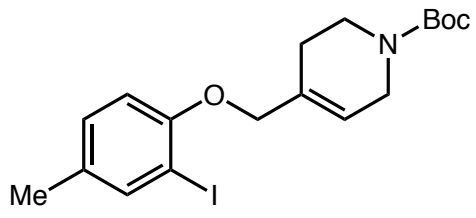
A round bottom flask was charged with 2-iodophenol (209 mg, 0.95 mmol, 1.1 equiv) and K_2CO_3 (357 mg, 2.6 mmol, 3.0 equiv). DMF (0.1 M) was added, followed by *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate dissolved in DMF (200 mg, 0.86 mmol, 1.0 equiv). The reaction was heated to 70°C and left to proceed for 12 hours. The reaction mixture was cooled to room temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude oil was purified via column chromatography (10-20% EtOAc:Hexanes) to yield an off white solid (270 mg, 76% yield). **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.72 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.27 (ddd, *J* = 8.7, 7.5, 1.6 Hz, 1H), 6.90 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.68 (td, *J* = 7.6, 1.4 Hz, 1H), 5.86 (s, 1H), 4.48 (d, *J* = 2.4 Hz, 2H), 3.90 (s, 2H), 3.52 (t, *J* = 5.5 Hz, 2H), 2.23 (dq, *J* = 6.0, 3.2 Hz, 2H), 1.44 (s, 10H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.06, 154.91, 139.51, 132.09, 129.42, 128.34, 122.92, 122.76, 122.37, 121.80 – 120.81 (m), 112.41, 86.66, 79.67, 72.04, 43.08 (d, *J* = 83.7 Hz), 40.76, 39.43, 28.49, 25.84. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{17}H_{23}INO_3$: 416.1, found 315.7 (-$CO_2C(CH_3)_3$)

***tert*-butyl 4-(((2-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (10)**



A round bottom flask was charged with 2-iodopyridin-3-ol (243 mg, 1.1 mmol, 1.0 equiv) and K_2CO_3 (304 g, 2.2 mmol, 2.2 equiv). DMF (0.1 M) was added, followed by *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate dissolved in DMF (10 mL, 1.0 mmol, 1.0 equiv). The reaction was heated to 70°C and left to proceed for 12 hours. The reaction mixture was cooled to room temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude oil was dissolved in EtOAc and washed with sodium hydroxide (1 M) to remove excess 2-iodopyridin-3-ol to yield an off white solid (348 mg, 84% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.1, 4.6 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.84 (s, 1H), 4.48 (s, 2H), 3.94 (s, 2H), 3.55 (s, 2H), 2.22 (s, 2H), 1.45 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.93, 152.28, 140.93, 129.46, 121.54, 121.33 (d, *J* = 2.4 Hz), 120.29, 116.39, 110.31, 77.84, 70.26, 41.15 (d, *J* = 80.9 Hz), 38.12 (d, *J* = 198.7 Hz), 26.58, 23.87. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{16}H_{22}IN_2O_3$: 417.1, found 416.7.

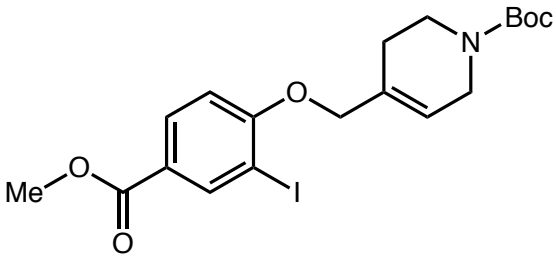
***tert*-butyl 4-((2-iodo-4-methylphenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate**



A round bottom flask was charged with 2-iodo-4-methylphenol (257 mg, 1.1 mmol, 1.1 equiv) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv). DMF (0.1 M) was added, followed by *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate dissolved in DMF (10 mL, 1.0 mmol, 1.0 equiv). The reaction was heated to 70°C and left to proceed for 12 hours. The reaction mixture was cooled to room

temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude oil was dissolved in EtOAc and washed with sodium hydroxide (1 M) to remove excess 2-iodo-4-methylphenol to yield the desired product (359 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.2 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.84 (s, 1H), 4.44 (s, 2H), 3.95 (s, 2H), 3.56 (t, *J* = 5.7 Hz, 2H), 2.25 (s, 3H), 1.47 (s, 9H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.04, 154.89, 139.80, 132.34, 132.24, 129.87, 121.74 (d, *J* = 147.8 Hz), 112.32, 86.53, 79.62, 72.21, 43.37, 40.11 (d, *J* = 200.6 Hz), 28.50, 25.85, 19.99. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{18}H_{25}INO_3$: 430.1, found: 329.7 ($-CO_2C(CH_3)_3$).

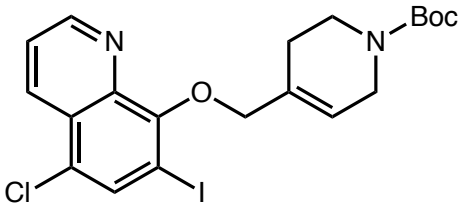
***tert*-butyl 4-((2-iodo-4-(methoxycarbonyl)phenoxy)methyl)-3,6-dihydropyridine-1(2*H*) carboxylate**



A round bottom flask was charged with methyl 4-hydroxy-3-iodobenzoate (306 mg, 1.1 mmol, 1.1 equiv) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv). DMF (0.1 M) was added, followed by *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate dissolved in DMF (10 mL, 1.0 mmol, 1.0 equiv). The reaction was heated to 70°C and left to proceed for 12 hours. The reaction mixture was cooled to room temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The desired product was obtained after one wash with NaOH (1 M) (391 mg, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.1 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 5.85 (s, 1H), 4.52 (s, 2H), 3.95 (s, 2H), 3.87 (s, 3H),

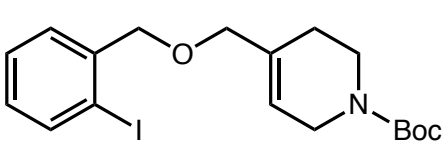
3.55 (s, 2H), 2.23 (s, 2H), 1.46 (s, 9H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.49, 165.40, 160.47, 154.79, 140.92, 131.45, 124.40, 116.36, 111.09, 85.81, 79.67, 72.12, 52.08, 42.97 (d, *J* = 89.9 Hz), 39.96 (d, *J* = 199.1 Hz), 28.41, 25.69. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{19}H_{24}INO_5$: 474.1, found: 373.7 ($-CO_2C(CH_3)_3$).

***tert*-butyl 4-(((5-chloro-7-iodoquinolin-8-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate**



A round bottom flask was charged with 5-chloro-7-iodoquinolin-8-ol (336 mg, 1.1 mmol, 1.1 equiv) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv). DMF (0.1 M) was added, followed by *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate dissolved in DMF (10 mL, 1.0 mmol, 1.0 equiv). The reaction was heated to 70°C and left to proceed for 12 hours. The reaction mixture was cooled to room temperature and subsequently quenched with water, followed by extraction with EtOAc. The organic layer was then washed with brine (x3), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The desired product was obtained after column chromatography (30% EtOAc:Hexanes) as a green oil (378 mg, 76% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.49 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.94 (s, 1H), 7.52 (dd, *J* = 8.6, 4.1 Hz, 1H), 5.87 (d, *J* = 4.1 Hz, 1H), 4.77 (s, 2H), 3.94 (s, 2H), 3.58 (s, 2H), 2.46 (dq, *J* = 5.9, 3.1 Hz, 2H), 1.45 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.86, 150.36, 142.42, 135.09, 133.46, 133.17, 127.46, 126.50, 123.48, 122.58, 122.29, 90.25, 79.52, 77.79, 43.45, 40.28 (d, *J* = 200.4 Hz), 28.52, 26.58. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{20}H_{23}ClIN_2O_3$: 501.0, found 500.5.

***tert*-butyl 4-(((2-iodobenzyl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate**



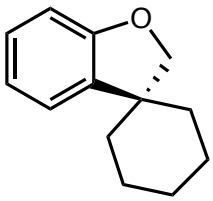
To a flame dried round bottom flask equipped with a stir bar and a condenser, sodium hydride (60% in mineral oil, 60 mg, 1.5 mmol, 1.5 equiv) was added and degassed, followed by the addition of DMF (0.1 M). This solution was cooled to 0°C and (2-iodophenyl)methanol (257 mg, 1.1 mmol, 1.1 equiv) was added. This solution stirred at 0°C for approximately 30 minutes. *Tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (10 mL, 1.0 mmol, 1.0 equiv) dissolved in DMF (0.1 M) was then added dropwise and then temperature was slowly raised to room temperature over 12 hours. The reaction was then quenched by the slow addition of water and extracted with ethyl acetate (EtOAc) two times. The combined organic layers were then washed with brine (x3), dried over magnesium sulfate ($MgSO_4$), and concentrated via rotatory evaporation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (td, *J* = 7.5, 1.8 Hz, 1H), 5.67 (s, 1H), 4.41 (s, 2H), 3.96 (s, 2H), 3.88 (s, 2H), 3.48 (t, *J* = 5.8 Hz, 2H), 2.14 (d, *J* = 6.4 Hz, 2H), 1.42 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 153.01, 138.60, 137.30, 127.34, 126.99, 126.36, 96.03, 77.68, 73.94, 72.12, 41.48, 40.90, 38.94, 37.66, 26.62, 24.16. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{18}H_{23}INO_3$: 430.3, found 329.7 (-$CO_2C(CH_3)_3$).

Preparation of Products from the Substrate Scope:

General Procedure A: A 16 mL screw top test tube equipped with a stir bar was charged with substrate (0.3 mmol, 1.0 equiv) and photocatalyst (0.015 mmol, 5 mol%). The test tube was then sealed with a PTFE/silicon septa and the atmosphere was exchanged by applying vacuum and backfilling with nitrogen three times. Under a nitrogen atmosphere, Hünig's base (5.0 equiv) was

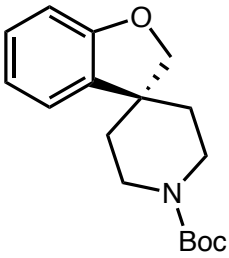
added, followed by the addition degassed THF (4.8 mL) and degassed DI H_2O (1.2 mL) to yield an 0.05 M solution. The resulting mixture was stirred at 800 RPM for 12 hours under irradiation by blue LEDs. Nitrogen atmosphere was kept by applying Parafilm test tube screw caps. After removal from LEDs, the reaction mixtures were concentrated by rotary evaporation and water was azeotroped off by the addition of acetonitrile. The residues were purified on silica using the indicated solvent mixture as eluent to afford the title compound.

2*H*-spiro[benzofuran-3,1'-cyclohexane] (6)



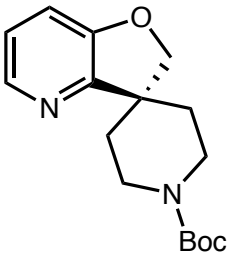
General Procedure A was followed using 1-(cyclohex-1-en-1-ylmethoxy)-2-iodobenzene (5) (94.5 mg, 0.3 mmol, 1 equiv), Hünig's Base (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%). After 12 hours, the reaction mixture was concentrated via rotary evaporation with acetonitrile added to azeotrope water from the solvent. The reaction was purified on silica (0-20% EtOAc:Hexanes) to yield the desired product. Product is volatile on rotary vacuum, so crude NMR yield with an internal standard of dibromomethane was used (92% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.07 – 7.00 (m, 2H), 6.79 (td, *J* = 7.4, 1.0 Hz, 1H), 6.74 – 6.68 (m, 1H), 4.28 (s, 2H), 1.73 – 1.59 (m, 5H), 1.62 – 1.51 (m, 2H), 1.35 – 1.21 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.32, 136.30, 128.03, 122.91, 120.35, 109.62, 81.00, 46.13, 36.75, 25.46, 23.32. **LRMS (GCMS)** m/z: calc'd. for $C_{13}H_{16}O$: 188.1, found 188.2.

***tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (8)**



General Procedure A was followed using *tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (124.5 mg, 0.3 mmol, 1 equiv), Hünig's Base (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%). After 12 hours, the reaction was concentrated via rotary evaporation. The crude oil was purified on silica (10%-50 EtOAc/Hexanes) to yield the desired product as an off-white solid (64 mg, 74% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 2H), 6.89 (td, *J* = 7.5, 2.4 Hz, 1H), 6.81 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.40 (s, 2H), 4.07 (s, 2H), 2.90 (t, *J* = 13.0 Hz, 2H), 1.84 (d, *J* = 12.7 Hz, 2H), 1.72 (d, *J* = 13.5 Hz, 2H), 1.49 (d, *J* = 2.6 Hz, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.38, 154.86, 134.38, 128.59, 122.98, 120.70, 109.92, 79.85, 79.79, 44.62, 41.09, 35.95, 28.47. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{17}H_{22}N_2O_3$: 289.2, found 233.9 ($-C(CH_3)_3$).

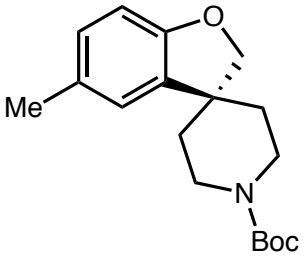
***tert*-butyl 2*H*-spiro[furo[3,2-*b*]pyridine-3,4'-piperidine]-1'-carboxylate (11)**



General procedure A was followed using *tert*-butyl 4-(((2-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (125 mg, 0.3 mmol, 1 equiv), Hünig's Base (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%). After 12 hours, the reaction was concentrated via rotary evaporation using acetonitrile to azeotrope water. The crude oil was purified on silica (50% EtOAc:Hexanes) yielding the desired product (63 mg, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 3.7, 2.5 Hz, 1H), 7.07 – 7.00 (m, 2H), 4.46 (s, 2H), 4.09 (s, 2H), 3.05 (t, *J* = 12.3 Hz, 2H), 2.02 (ddd, *J* = 13.6, 10.7, 4.4 Hz, 2H), 1.66 (d, *J* = 13.6 Hz, 2H), 1.46 (s, 10H). **^{13}C NMR** (151 MHz, $CDCl_3$)

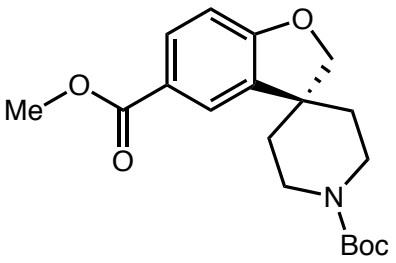
δ 155.55, 154.68, 153.17, 141.80, 122.73, 116.19, 80.73, 79.60, 43.78, 40.58 (d, J = 138.5 Hz), 34.49, 28.45. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{16}H_{22}N_2O_3$: 290.2, found 290.9.

***tert*-butyl 5-methyl-2*H*-spiro[benzofuran-3,4'-piperidine]-1'-carboxylate (12)**



General procedure A was followed using *tert*-butyl 4-((2-iodo-4-methylphenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (129 mg, 0.3 mmol, 1 equiv), Hünig's Base (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%). After 12 hours, the reaction was concentrated via rotary evaporation using acetonitrile to azeotrope water. The crude oil was purified on silica by column chromatography (10% EtOAc:Hexanes) yielding the desired product as a yellow oil (64 mg, 70% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.94 (ddd, J = 8.0, 1.9, 0.8 Hz, 1H), 6.91 (dt, J = 1.9, 0.7 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 4.37 (s, 2H), 4.07 (s, 2H), 2.96 – 2.83 (m, 2H), 2.29 (s, 3H), 1.83 (dq, J = 12.7, 4.3 Hz, 2H), 1.74 – 1.66 (m, 2H), 1.49 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.28, 154.82, 134.40, 129.98, 128.96, 123.54, 109.44, 79.96, 79.73, 44.66, 41.12, 35.90, 28.48, 20.88. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{16}H_{25}NO_3$: 304.2, found 248.0 (-$C(CH_3)_3$).

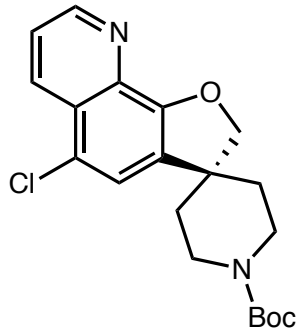
1'-(*tert*-butyl) 5-methyl 2*H*-spiro[benzofuran-3,4'-piperidine]-1',5-dicarboxylate (13)



General procedure A was followed *tert*-butyl 4-((2-iodo-4-(methoxycarbonyl)phenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (192 mg, 0.4 mmol, 1 equiv), Hünig's Base (0.36 mL, 2.0 mmol, 5 equiv), and 3DPAFIPN (13 mg, 5 mol%). After 12 hours, the reaction was concentrated via rotary evaporation using acetonitrile to azeotrope water.

Purification by column chromatography (20% EtOAc:Hexanes) yielded the desired product as an off-yellow solid (72 mg, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 4.47 (s, 2H), 4.08 (s, 2H), 3.85 (s, 4H), 2.86 (t, *J* = 13.1 Hz, 2H), 1.87 (td, *J* = 12.8, 12.4, 4.5 Hz, 3H), 1.70 (d, *J* = 13.6 Hz, 3H), 1.47 (s, 10H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.77, 163.54, 154.70, 134.87, 131.57, 124.99, 123.05, 109.65, 80.92, 79.88, 51.87, 44.28, 40.78, 28.44. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{16}H_{25}NO_3$: 348.2, found 291.0 ($-C(CH_3)_3$).

***tert*-butyl 5-chloro-2*H*-spiro[furo[3,2-*h*]quinoline-3,4'-piperidine]-1'-carboxylate (14)**



General Procedure A was followed using *tert*-butyl 4-(((5-chloro-7-iodoquinolin-8-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (150 mg, 0.3 mmol, 1 equiv), Hünig's Base (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%). After 12 hours, the reaction was purified on silica (10%-50 EtOAc/Hexanes) to yield the desired product as a brown oil (31 mg, 28% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.49 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.48 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 4.72 (s, 2H), 4.16 (s, 2H), 2.89 (s, 2H), 1.92 (dd, *J* = 12.9, 4.4 Hz, 2H), 1.84 – 1.77 (m, 2H), 1.49 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.83, 151.92, 148.49, 134.43, 131.40, 129.96, 124.74, 120.47, 120.09, 119.79, 114.46, 79.28, 78.08, 44.25, 39.05, 26.57. **LRMS (LCMS):** m/z: $[M+H]^+$ calc'd. for $C_{20}H_{23}ClN_2O_3$: 375.2, found 374.8.