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Development of Intermolecular Couplings of Aryl Radical Species with Olefins

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Development of Intermolecular Couplings of Aryl Radical Species with Olefins

By

Allyson J. Boyington

B.S., Dickinson College, 2015

Advisor: Nathan T. Jui, Ph.D.

An abstract of
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Abstract

Development of Intermolecular Couplings of Aryl Radical Species with Olefins

By: Allyson J. Boyington

The intermolecular hydroarylation of simple alkenes with pyridyl radicals has been achieved using a photoredox radical mechanism. The regiospecific single-electron reduction of halogenated pyridines with a commercially available iridium catalyst, followed by radical addition to unactivated alkene substrates, which occurs with exclusive anti-Markovnikov selectivity. This system was then expanded to include pyridyl radical addition to vinyl heteroatoms, as well as alkynes (giving the linear anti-Markovnikov product). Through mechanistic investigations, we hypothesize that this protocol is operating through a proton coupled electron transfer mechanism, uniquely enabled by slightly acidic 2,2,2-trifluoroethanol as the reaction solvent to give an electrophilic, protonated pyridyl radical intermediate which then engages electron-rich olefins. Additionally, an organocatalyzed photoredox protocol for the regioselective synthesis of arylethylamines via aryl radicals has been developed. While arylethylamine synthesis strategies have been previously reported utilizing styrene hydroamination, we offered a complementary approach, where photoinduced reduction of aryl halides and intermolecular coupling to vinylamine derivatives afforded a wide range of arylethylamine structures. Both hydroarylation systems are mild, scalable, tolerant of many functional groups, and effective for the preparation of a wide range of medicinally relevant scaffolds with complete regiocontrol.

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one of you has brought into my life and am better for having known all of you. In particular, you all encouraged me to take the job at Corteva that I was really excited about and provided support and affirmation when I really needed to hear that this was decision that I need to make for myself, and only for myself. I'm especially thankful to Kelly McDaniel for putting up with my mess in our hood bay, sitting next to me writing my dissertation and constantly needing to vent/ask if my figures look good, and just being an all-around gem of a person. I echo the words of Henry Zecca that "I'd be nothing without your support." Cecie's Angels have been the best officemates. Cecie has the most amazing sense of humor in the world and my day is always made brighter by her positive energy. Every time I talk to Henry, I learn something new. I will miss hearing Cam's singing and I hope that he continues to try to hit the last note in "Defying Gravity", knowing full well it's out of his range.

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List of Abbreviations

AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Bn	Benzyl
Boc	*Tert*-butyoxy carbonyl
Cbz	Carboxybenzyl
conPET	Consecutive photoinduced electron transfer
CySH	Cyclohexane thiol
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
FSIP	Face-sharing iodoplumbate
GCMS	Gas chromatography mass spectrometry
HAT	H-atom transfer
HDH	Hydrodehalogenation
HEH	Hantzsch Ester
Hex	Hexanes
HIOP	Hybrid inorganic organic perovskite
HOMO	Highest occupied molecular orbital
HP	Hantzsch pyridine
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectrometry
LEDs	Light-emitting diodes
LCMS	Liquid chromatography mass spectrometry
LUMO	Lowest occupied molecular orbital
MeCN	Acetonitrile
MOM	Methoxymethyl
NMR	Nuclear magnetic resonance
N-POX	*N*-napthylphenoxazine
N-PTH	*N*-napthylphenothiazine
PEA	Phenethylammonium
PCET	Proton coupled electron transfer
PDI	*N,N*-bis(2,6-diisopropylphenyl)perylene3,4,9,10-bis(dicarboximide)
Ph	Phenyl
PTH	*N*-phenylphenothizaine
RCA	Radical conjugate addition
Rt	Room Temperature
SCE	Standard calomel electrode
SET	Single electron transfer
SOMO	Singularly occupied molecular orbital
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
V	Volts

Chapter 1:

(Hetero)Aryl Radicals – Formation and Reactivity

1.1 Aryl radicals from diazoniums and aryl halides

Aryl radicals are highly reactive intermediates that can be generated from a wide variety of sources. From this intermediate, the radical can undergo many transformations including Sandmeyer reactions, halogen transfer, hydrogen atom abstraction, addition to iminium ions, as well as engaging unsaturated coupling partners (such as Meerwein arylation or biaryl coupling).[1] Two of the most common aryl radical precursors are arenediazonium salts and aryl halides. Arenediazonium salts are easily formed from the corresponding aniline but are highly reactive and typically unstable or even explosive. While the liberation of N_2 is typically innocuous, the scope of the olefin coupling partner in the Meerwein arylation remains limited in both photocatalytic and metal salt-mediated reaction conditions.[2] Additionally, access to the diazonium salt for more complex heteroaromatic substrates is limited.

Aryl halides are more stable, and often, are commercially available due to their prevalence in cross-coupling protocols. Historically, aryl halides were reacted under tributyltin hydride conditions to provide the aryl radical intermediate.[3] As organotin reagents are typically toxic, alternative methods utilizing silanes and samarium diiodide emerged.[4] While these are powerful advancements in the field of aryl radical methodology, the reagents are unstable, costly, and, occasionally less efficient.

1.2 Aryl radicals from photoredox catalysis

With a need for new methods of aryl radical formation, photocatalysis emerged as a promising alternative to toxic and unstable reagents as photo-mediated reactions are

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[1] Heinrich, M. R., Intermolecular olefin functionalisation involving aryl radicals generated from arenediazonium salts. *Chemistry - A European Journal* **2009,** *15* (4), 820-833, Kindt, S.; Heinrich, M. R., Recent Advances in Meerwein Arylation Chemistry. *Synthesis* **2016,** *48* (11), 1597-1606.

[2] Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; Burkhard, K., Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Accounts of Chemical Research* **2016,** *49*, 1566-1577.

[3] Neumann, W. P., Tri-n-butyltin hydride as reagent in organic synthesis. *Synthesis* **1987,** *8*, 665-683.

[4]Krief, A.; Laval, A.-M., Coupling of organic halides with carbonyl compounds promoted by SmI2, the Kagan reagent. *Chem. Rev.* **1999,** *99*, 745-777.

typically more mild and occur at room temperature. The past two decades in organic synthesis have seen a resurgence of the use of light as a reagent in organic transformations, often complementary to traditional two electron processes.[5] Photoredox catalysis is enabled by the selective excitation of a photoredox catalyst by a wavelength of light. The excited state of the catalyst then undergoes intersystem crossing to give a triple excited state which is relatively long lived. This triplet excited state can either donate an electron, thereby acting as a reductant, or accept an electron and act as an oxidant (Figure 1). By employing sacrificial reductants/oxidants (ideally those which form inert byproducts), the photoredox catalyst is regenerated to perform another transformation. Photocatalysts are extremely versatile and can be either organic molecules or metal based. Historically, the metal-based iridium and ruthenium complexes were thought to be the most tunable due to the ability to modify the ligands as well as exchanging the metal center, however, recent work has shown this type of tunability is possible in organocatalysts as well.[6]

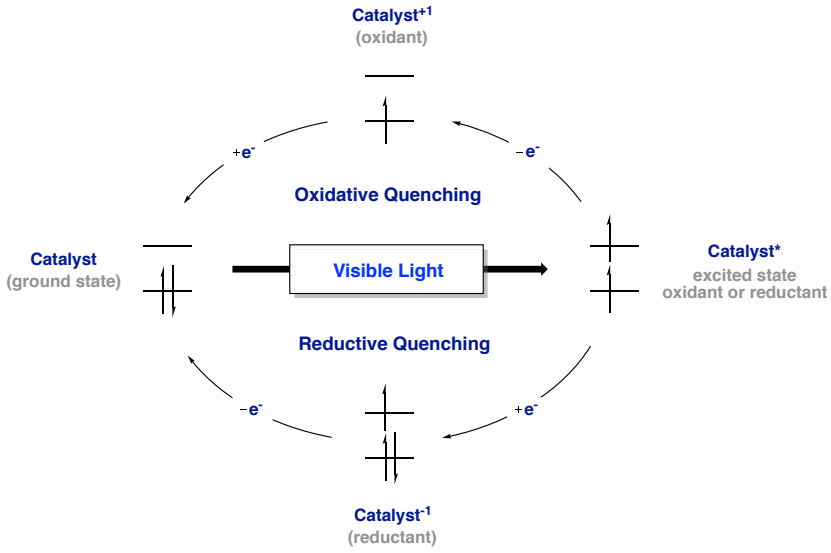

Figure 1: Ability of a photocatalyst to operate as a reductant or an oxidant

[5] Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chemical Reviews* **2013,** *113* (7), 5322-5363.
[6] Speckmeier, E.; Fischer, T. G.; Zeitler, K., A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor–Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018,** *140* (45), 15353-15365. Sartor, S. M.; Chrisman, C. H.; Pearson, R. M.; Miyake, G. M.; Damrauer, N. H., Designing High-Triplet-Yield Phenothiazine Donor–Acceptor Complexes for Photoredox Catalysis. *J. Phys. Chem. A* **2020,** *124* (5), 817-823.

Generation of an aryl radical intermediate from an aryl halide via photoredox catalysis was first reported in 2012 when the Stephenson lab reported the Ir-catalyzed reductive dehalogenation of alkyl, alkenyl, and aryl iodides.[7] In addition to hydrodehalogenation (HDH), intramolecular cyclization of the aryl radical with an alkyne or an alkene was reported in good to high yields. Expanding on the work by Stephenson, Weaver has reported numerous successful methods for reductive dehalogenation of bromoazoles and perfluoronated (het)arenes, and has demonstrated not only the HDH pathway, but also the ability to engage the aryl radical intermediate in a coupling reaction with an alkene or arene.[8] Building off this work, our lab achieved intermolecular coupling of a *N*-heterocyclic (pyridine or diazine) radical with an electron deficient olefin. Key to achieving intermolecular reactivity over the HDH pathway was limiting the amount of the sacrificial reductant in solution, as the reductant (Hantzsch ester) also acts as the H-atom source.

These protocols typically operate through reductive quenching pathways where the photoexcited Ir(III)* catalyst is reduced by a sacrificial reductant generating the reducing Ir(II) species which can, in turn, donate a radical to the (hetero)aryl halide radical precursor. The aryl radical anion then expels the halogen (mesolytic cleavage) to give the desired reactive aryl radical intermediate. In the majority of protocols, the sacrificial stoichiometric reductant (i.e. Hantzsch ester or a trialkylamine) also generates a stoichiometric hydrogen atom source after it is oxidized. This reductive quenching process is critical as the iridium catalysts are typically not strongly reducing enough in the excited state ($Ir(ppy)_3$ $E_{1/2}^* = -1.7$ V vs SCE) to achieve reduction of the aryl halide to give the aryl radical.[7]

[7] Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J., Engaging unactivated alkyl, alkenyl and aryl iodides in visible-light-mediated free radical reactions. *Nature Chemistry* **2012,** *4* (10), 854-859.
[8] Arora, A.; Weaver, J. D., Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates. *Accounts of Chemical Research* **2016,** *49* (10), 2273-2283.

Additional methods have been developed utilizing organophotoredox catalysts as an alternative to rare-earth metal catalysis. Importantly, in 2014 König was able to accomplish intermolecular coupling of an aryl radical with *N*-methylpyrrole in addition to demonstrating successful HDH of aryl iodides as well as activated aryl bromides and chlorides.[9] Crucial to achieving the reducing power required for aryl bromides and chlorides was utilizing a 2-photon consecutive photoinduced electron transfer (conPET) mechanism and organocatalyst *N,N*-bis(2,6-diisopropylphenyl)perylene3,4,9,10-bis(dicarboximide) (PDI) where, after reductive quenching, the PDI radical anion ($PDI^{\bullet-}$) can be photoexcited to give the highly reducing excited state radical anion ($PDI^{\bullet-*}$). More recently in 2015, Hawker and Read de Alaniz reported a highly reducing metal-free photocatalyst *N*-phenylphenothiazine, that is capable of reducing aryl iodides, bromides, and activated aryl chlorides.[10] Importantly, PTH is highly reducing in the excited state ($E_{1/2}^{*}$ = –2.1 V vs SCE) and therefore, can operate under an oxidative quenching mechanism where it directly donates an electron to the aryl halide after excitation under visible light.

Despite numerous ways to access aryl radical intermediates from aryl halides, utilizing these species in intermolecular reactions remains difficult. The previously described iridium- and PDI-catalyzed reactions to reduce an aryl halide typically use trialkyl amines as sacrificial reductants, and, upon oxidation, amines become facile H-atom donors which quickly quench the aryl radical by H-atom transfer. Because H-atom transfer is so rapid, it typically out-competes any other intermolecular pathway. This has been overcome by using super-stoichiometric amounts of the coupling partner, limiting the amount of H-atom source in solution, and/or by using an activated radical trap as the

[9] Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B., Reduction of aryl halides by consecutive visible light-induced electron transfer processes *Science* **2014,** *346* (6210), 725-728.
[10] Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; Read de Alaniz, J. R., A highly reducing metal-free photoredox catalyst: design and application in radical dehalogenations. *Chem. Commun.* **2015,** *51* (58), 11705-11708.

coupling partner. [9,11] While powerful, a generalizable system for intermolecular coupling of (hetero)aryl radicals (formed from stable aryl halides) with saturated systems has yet to materialize. Here, we describe progress towards this goal where successful conditions have been developed for the intermolecular coupling of pyridyl radicals (from commercial halopyridines) with unactivated alkenes and vinyl heteroatoms in exclusive anti-Markovnikov selectivity. Additionally, intermolecular coupling of aryl radicals with vinylamine derivatives was achieved by utilizing a catalytic H-atom transfer catalyst to form substituted arylethylamine derivatives.

[11] Aycock, R. A.; Wang, H.; Jui, N. T., A mild catalytic system for radical conjugate addition of nitrogen heterocycles. *Chem. Sci.* **2017,** *8*, 3121-3125. Aycock, R. A.; Vogt, D.; Jui, N., A Practical and Scalable System for Heteroaryl Amino Acid Synthesis. *Chemical Science* **2017,** *8*, 7998-8003.

Chapter 2:

Anti-Markovnikov hydroarylation of neutral olefins via pyridyl radical intermediates

2.1 Pyridine functionalization via radical intermediates

Heteroaromatic units are prevalent structural motifs in compounds that are biologically relevant.[12] Nitrogen containing heterocycles, specifically pyridines, are among the most highly represented heterocycles in pharmaceuticals. Therefore, new methods for the construction and substitution of complex pyridines is an important goal. In addition to *de novo* pyridine synthesis, there are a number of powerful methods for *N*-heterocycle substitution. However, a generalizable method for programmed regiospecific pyridine functionalization has yet to be realized. Substitution via S_NAr requires a good leaving group and is only effective at the electron-deficient 2- and 4-pyridyl positions. Cross-coupling is an extremely powerful method for arene functionalization, and methods have been developed for coupling with alkyl metals.[13] The Minisci radical addition is a highly chemoselective process where a radical adds to the 2- or 4-position of the pyridine, but functionalization of the electron-rich 3-position is difficult.[14] Our approach to pyridine functionalization takes inspiration from the inherent chemoselectivity of the Minisci reaction, but instead utilizes a heteroaryl radical which couples with an olefin to give an alkylated pyridine product. Us, and others, have utilized photoinduced electron transfer to form highly reactive (hetero)aryl radicals from stable aryl halide precursors.[7,8,9,11] This mode of radical formation involves the direct reduction of an aryl halide, which, after fragmentation of the Ar–X bond, regiospecifically furnishes the corresponding aryl radical.

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[12] Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *Journal of Medicinal Chemistry* **2014,** *57* (24), 10257-10274.

[13] Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011,** *111* (3), 1417-1492.

[14] Duncton, M. A. J., Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *Med. Chem. Commun.* **2011,** *2* (12), 1135-1161. Minisci, F.; Vismara, E.; Fontana, F., Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. *Heterocycles* **1989,** *28* (1), 489-519. O'Hara, F.; Blackmond, D. G.; Baran, P. S., Radical-Based Regioselective C–H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013,** *135* (32), 12122-12134.

2.2 Pyridyl radical conjugate addition, chain cyclization

In 2017, our group reported our conditions for the photoinitiated radical conjugate addition of nitrogen heterocyclic radicals to electron deficient alkenes.[11] Under iridium catalyzed conditions, it was found that a *N*-heterocyclic radial would successfully engage an electron deficient olefin to give the conjugate addition product (Figure 2). A key finding in this study was limiting the rate of H-atom transfer to the heteroaryl radical intermediate in order to get selectivity for the intermolecular coupling product. It was found that limiting the solubility of Hantzsch ester, the H-atom and electron source, by increasing the amount of water in the reaction (25% H_2O/DMSO) was effective for selecting for radical conjugate addition over HDH. These conditions are mild, tolerant of many functional groups, and broadly applicable to a range of halogenated pyridines and diazines as radical precursors.

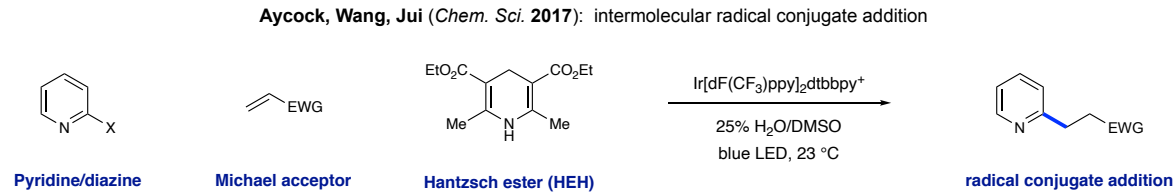


Figure 2: Previous work in the Jui Lab on *N*-heterocyclic radical addition to electron-deficient alkenes

Inspired by this reactivity, we sought to develop conditions for a radical conjugate addition cascade cyclization. From our studies on radical conjugate addition, we were confident that we would be able to form a pyridyl radical which would engage an electron-deficient alkene, and, in turn, undergo an intramolecular 5-exo-cyclization with a neutral olefin to give a cyclized product. Here, the challenge would be overcoming HAT to both the aryl radical and the α-acyl radical intermediates to get 1) intermolecular addition to the Michael acceptor and 2) cyclization, where the carbon-centered radical intermediate would undergo HAT to give the final product. In the initial attempt using conditions similar to those optimized for RCA, the cyclized product was formed in 10% yield. In addition to the expected byproducts of HDH and just RCA without cyclization, addition to the terminal, neutral olefin was observed, albeit in

low yields (5% yield) (Figure 3). A control experiment with 1-octene as the coupling partner with 2-iodopyridine provided the neutral olefin hydroarylation product in 17% yield. This was result was surprising as radical addition to electron deficient olefins is known to be a rapid process, with radical addition to neutral olefins occurring at much slower rate.[15]

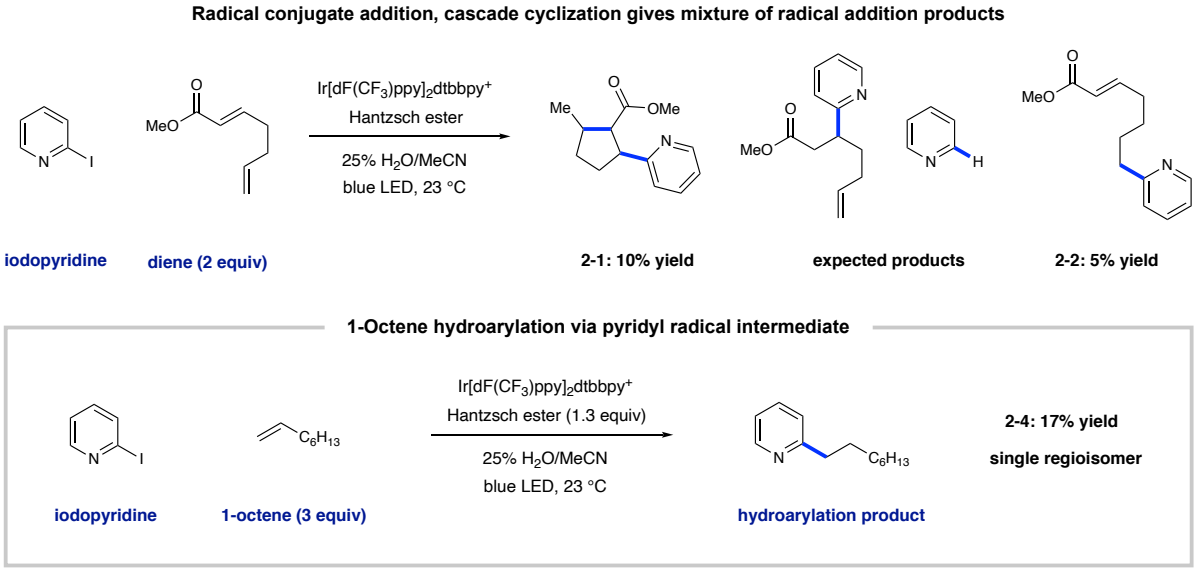


Figure 3: Designed radical conjugate addition, cascade cyclization and control reaction with 1-octene

2.3 Hydroarylation of neutral olefins with pyridine units

Building off of the control reaction, we focused our efforts on developing conditions for the photoinitiated hydroarylation of neutral olefins. We recognized hydroarylation, the addition of Ar–H across an alkene, as an attractive strategy for alkylarene synthesis, and much progress has been made to enable this type of process.[16] Simple alkenes are optimal starting materials because they are highly abundant and stable. While complementary radical-based simple olefin hydropyridylation methods have been developed for the Markovnikov (branched)

[15] Giese, B., Formation of CC Bonds by Addition of Free Radicals to Alkenes *Angewandte Chemie - International Edition* **1983,** *22* (10), 753-764.

[16] Kakiuchi, F.; Murai, S., Catalytic C-H olefin coupling. *Accounts of Chemical Research* **2002,** *35* (10), 826-834, Andreatta, J. R.; McKeown, B. A.; Gunnoe, T. B., Transition metal catalyzed hydroarylation of olefins using unactivated substrates: Recent developments and challenges. *Journal of Organometallic Chemistry* **2011,** *696* (1), 305-315, Foley, N. A.; Lee, J. P.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R., Ru(ll) catalysts supported by hydridotris(pyrazolyl)borate for the hydroarylation of olefins: Reaction scope, mechanistic studies, and guides for the development of improved catalysts. *Accounts of Chemical Research* **2009,** *42* (5), 585-597. Crisenza, G. E. M.; Bower, J. F., Branch Selective Murai-type Alkene Hydroarylation Reactions. *Chemistry Letters* **2016,** *45* (October 2012), 2-9.

product by the labs of Herzon[17] and Shenvi[18], selective formation of the linear, anti-Markovnikov product remains an important problem (Figure 4). To this end, two powerful methods exist for the anti-Markovnikov hydroarylation of pyridines that leverage metal insertion into a C–H bond and high temperatures. Lewis, Bergman, and Ellman utilized a Rh(I) catalyst to perform the addition of 2-substituted pyridines to a wide variety of olefins to provide the 2,6-disubstituted products with complete regiocontrol.[19] Additionally, the groups of Nakao and Hiyama[20] and Ong[21] separately reported a complementary strategy for regioselective functionalization of the 4-pyridyl position via a bimetallic Lewis acid/Ni(0) cooperative catalytic system. While these methods are powerful for 2- and 4-pyridyl alkylation, a system that allows for regiocontrolled functionalization at any pyridyl position would be advantageous, particularly without the use of directing groups and at ambient temperature with high functional group tolerance.

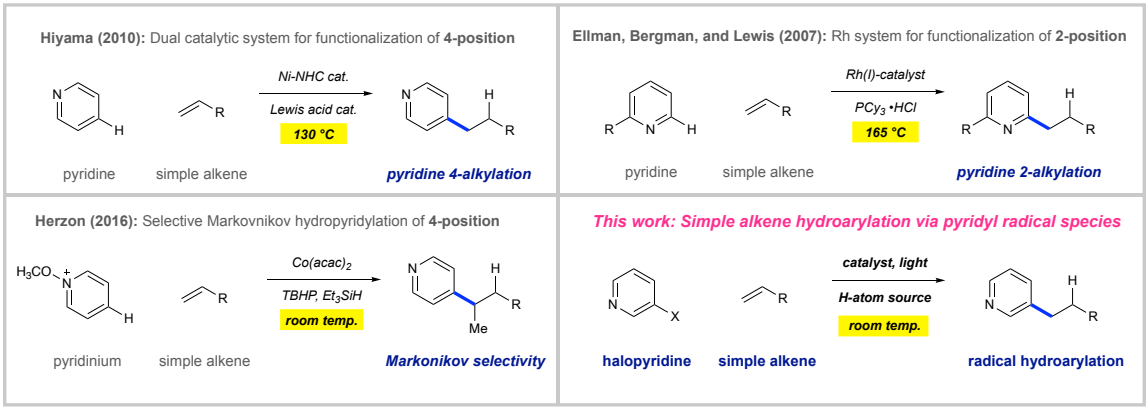


Figure 4: Previous efforts towards hydroarylation of neutral olefins with pyridine units

[17] Ma, X.; Herzon, S. B., Intermolecular Hydropyridylation of Unactivated Alkenes. *Journal of the American Chemical Society* **2016,** *138* (28), 8718-8721.
[18] Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A., Branch-Selective Hydroarylation: Iodoarene–Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016,** *138*, 12779-12782.
[19] Lewis, J. C.; Bergman, R. G.; Ellman, J. A., Rh(I)-catalyzed alkylation of quinolines and pyridines via C-H bond activation. *Journal of the American Chemical Society* **2007,** *129* (17), 5332-5333.
[20] Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T., Selective C-4 alkylation of pyridine by nickel Lewis acid catalysis. *J. Am. Chem. Soc.* **2010,** *132* (39), 13666-13668.
[21] Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A., Bimetallic nickel aluminum mediated para-selective alkenylation of pyridine: direct observation of 2,1-pyridine Ni(0)-Al(III) intermediates prior to C-H bond activation. *J. Am. Chem. Soc.* **2010,** *132* (34), 11887-11889.

Having recently developed conditions for the addition of a nucleophilic pyridyl radical to electron-poor alkenes to give conjugate addition products,[11] we questioned whether simple olefins could be engaged as coupling partners for pyridyl radicals under a similar mechanistic model. Specifically, reductive radical formation followed by regioselective intermolecular addition to neutral alkenes and radical termination via HAT would deliver linear alkylpyridines. This pathway has been similarly described by Weaver for the alkylation of 2-haloazoles and polyfluorinated arenes.[8] Importantly, because substituted pyridines containing a halogen at any position are commercially available and radical formation is regiospecific,[22] the outlined process could potentially grant access to programmed alkylation at any desired pyridyl position. Photoredox conditions are notably mild, and, ideally, this system would allow for substitution of a variety of functional groups on both the pyridyl radical precursor and the olefinic coupling partner.

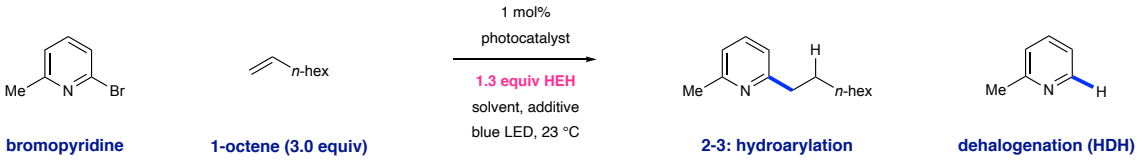
2.4 Optimization of the coupling of pyridyl radicals with 1-octene

We began our investigation by evaluating the intermolecular coupling of 1-octene (3 equiv) with 2-bromo-6-methylpyridine in the presence of a slight excess (1.3 equiv) of Hantzsch ester (HEH) and 1.0 mol % of the commercially available photocatalyst $Ir(ppy)_2dtbbpy•PF_6$ (Table 1). After irradiation with commercial blue LEDs for 16 h in a range of polar solvents, the desired hydroarylation product was formed, albeit in very low yields. The remainder of the mass balance was typically composed of 2-picoline, the HDH product. It was promising, however, that the ratio of the desired product to HDH seemed to be changing as a function of solvent. A broader solvent screen gave a promising result using 2,2,2-

[22] Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Savant, J. M., Heterogeneous and homogeneous electron transfers to aromatic halides. An electrochemical redox catalysis study in the halobenzene and halopyridine series. *Journal of the American Chemical Society* **1979,** *101* (13), 3431-3441, Enemærke, R. J.; Christensen, T. B.; Jensen, H.; Daasbjerg, K., Application of a new kinetic method in the investigation of cleavage reactions of haloaromatic radical anions. *Journal of the Chemical Society, Perkin Transactions 2* **2001,** (9), 1620-1630. Costentin, C.; Robert, M.; Savant, J.-m., Fragmentation of Aryl Halide pi Anion Radicals. Bending of the Cleaving Bond and Activation vs Driving Force Relationships. *Journal of the American Chemical Society* **2004,** *126*, 16051-16057.

trifluoroethanol (TFE) as the solvent where the hydroarylation product was observed in 74% yield with the remainder of the mass balance being unreacted starting material. When the progress of the reaction was observed over time, it was found that the progress was slowing significantly after 2 h and the starting material was no longer being consumed. Further experiments revealed that the reaction outcome is greatly impacted by the acidity/basicity of the reaction mixture. The addition of lutidine (1.0 equiv) had a strong inhibitory effect, with only 4% yield of the hydroarylation product forming. Conversely, the addition of 2 equivalents of acetic acid or ammonium chloride allowed for complete conversion of the starting material bromopyridine. Importantly, the branched isomer of the product was not detected by NMR or GCMS and the desired, linear product was formed with complete regiocontrol.

Table 1: Reaction optimization



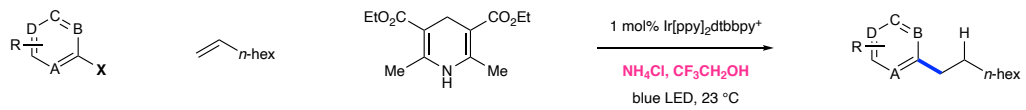
bromopyridine | 1-octene (3.0 equiv) | 2-3: hydroarylation | dehalogenation (HDH)

Entry	Photocatalyst	Solvent	Additive	Yield of 2-3	Yield of HDH
1	$[Ir(ppy)_2dtbbpy]PF_6$	25% H_2O/DMSO	—	4%	47%
2	$[Ir(ppy)_2dtbbpy]PF_6$	DMSO	—	19%	56%
3	$[Ir(ppy)_2dtbbpy]PF_6$	DMF	—	5%	55%
4	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3CN	—	17%	27%
5	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3OH	—	21%	18%
6	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	—	74%	0%
7	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	lutidine (1 equiv)	4%	0%
8	$[Ir(ppy)_2dtbbpy]PF_6$	$(CF_3)_2CHOH$	—	54%	49%
9	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	AcOH (2 equiv)	77%	15%
10	**$[Ir(ppy)_2dtbbpy]PF_6$**	**CF_3CH_2OH**	**NH_4Cl (2 equiv)**	**87%**	**9%**

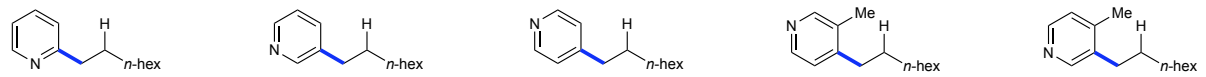
With effective conditions developed for the anti-Markovnikov hydroarylation of 1-octene, we evaluated the scope of the halogenated pyridine radical precursor. As expected, programmed radical formation gives selective alkylation at the 2-, 3-, or 4-pyridyl position in

great yields (80-86% yield). Generally, alkylation of the 2- and 4-positions is accomplished via reductive radical formation of the corresponding bromopyridines whereas alkylation of the 3-position is most efficient when the iodopyridine is utilized. There is no apparent substitution requirement and unsubstituted or alkyl-substituted halopyridines were successfully converted to the corresponding mono-, di-, or trialkylpyridines under the acidic TFE conditions. In addition to alkyl-substitution, electron-donating groups did not greatly inhibit product formation. Unprotected phenol (**2-9**, 40% yield), carbamate (**2-11**, 52% yield), and amide groups (**2-18**, 53% yield) all reacted smoothly and provide the ability to further functionalize the alkylpyridine product with via the acidic N–H or O–H bonds.

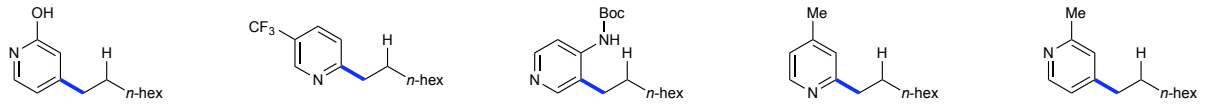
Table 2: Aryl halide scope



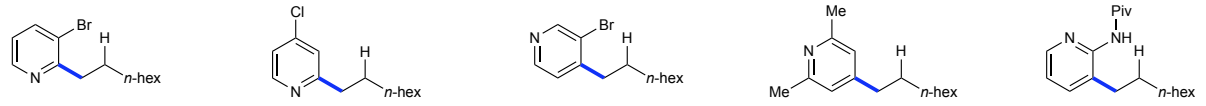
HetAr-X | octene (3 equiv) | Hantzsch ester (1.3 equiv) | hydroarylation product



2-4: X = Br, 86% yield | **2-5**: X = I, 80% yield | **2-6**: X = Br, 86% yield | **2-7**: X = Br, 84% yield | **2-8**: X = I, 70% yield



2-9: X = Br, 40% yield | **2-10**: X = I, 54% yield | **2-11**: X = I, 52% yield | **2-12**: X = Br, 66% yield | **2-13**: X = Br, 89% yield

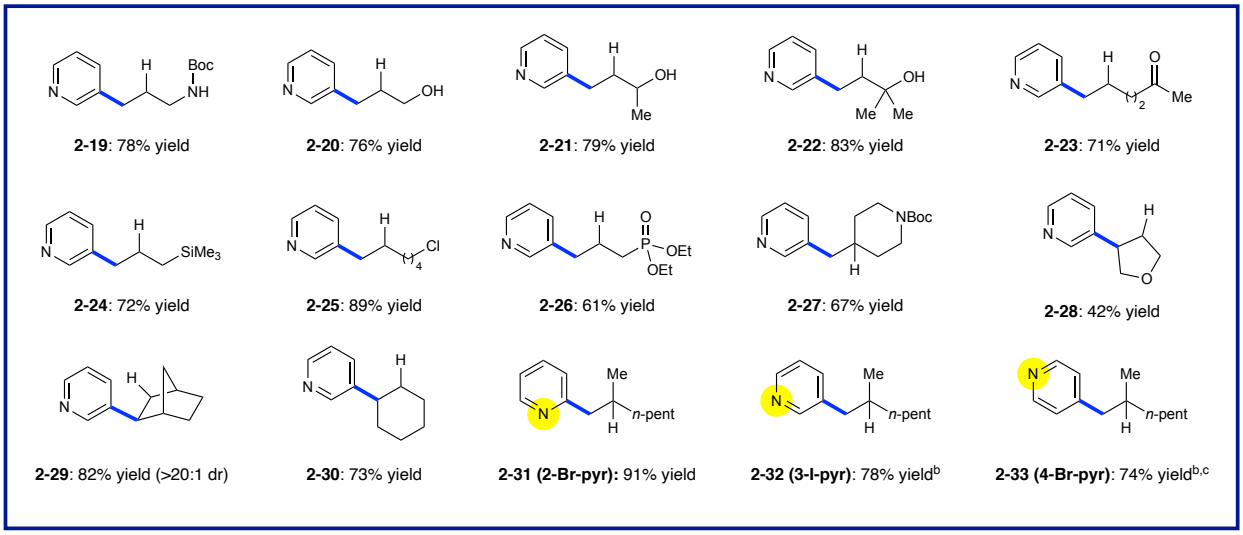


2-14: X = Br, 41% yield | **2-15**: X = Br, 43% yield | **2-16**: X = Br, 57% yield | **2-17**: X = Br, 82% yield | **2-18**: X = I, 53% yield

Electron-withdrawing substituents were tolerated; 2-iodo-5-trifluoromethylpyridine coupled to give the desired product **2-10** in 54% yield. Additionally, 2,3- and 3,4-dibromopyridiens underwent selective activation at the 2- or 4-pyridyl position to give products **2-14** and **2-16** in 41% and 57% yield respectively. This demonstrates the preferential radical

formation at the electrophilic 2- and 4-positions, which also parallels S_NAr reactivity.[23] Selectivity for the 2-position over the 4-position was achieved by employing the more readily fragmented aryl-bromide with complete retention of the chloride. The ability to retain an aryl halide under these conditions is particularly noteworthy as it provides an additional functional group for further synthetic elaboration.

Table 3: Scope of the olefin coupling partner



Using 3-iodopyridine as the radical precursor, the scope of the olefinic coupling partner was evaluated (Table 3). The acidic TFE photoredox conditions effectively enable the coupling to a wide range of simple, unactivated alkenes. Allylic carbamate (**2-19**, 78% yield), free alcohols (**2-20**–**22**, 76-83% yield), alkyl silane (**2-24**, 72% yield), primary alkyl chloride (**2-25**, 89% yield), and phosphonate (**2-26**, 61% yield) groups were all well tolerated to give exclusively the linear (anti-Markovnikov) product. In addition to terminal olefins, cyclic alkenes 2,5-dihydrofuran, norbornene, and cyclohexene reacted smoothly to give the desired products (**2-28**–**30**) in reasonable yields (42–82%). The 1,1-disubstituted alkenes

[23] Burnett, J. F.; Zahler, R. E., Aromatic Nucleophilic Substitution Reactions. *Chemical Reviews* **1951,** *49* (2), 273-412.

methylenepiperidine and 2-methylheptene were reacted to give the 3-alkylated products **2-27** and **2-32** in 67% and 78% yield respectively. To demonstrate the ability of this system to functionalize any position of the pyridine selectively the 2-bromo and 4-bromopyrdyl radical precursors were also reacted with 2-methylheptene and no decrease in yield was observed (2-position, **2-31** (91% yield); 4-position, **2-33** (74% yield)).

2.6 Application of the hydroarylation conditions to biaryl coupling

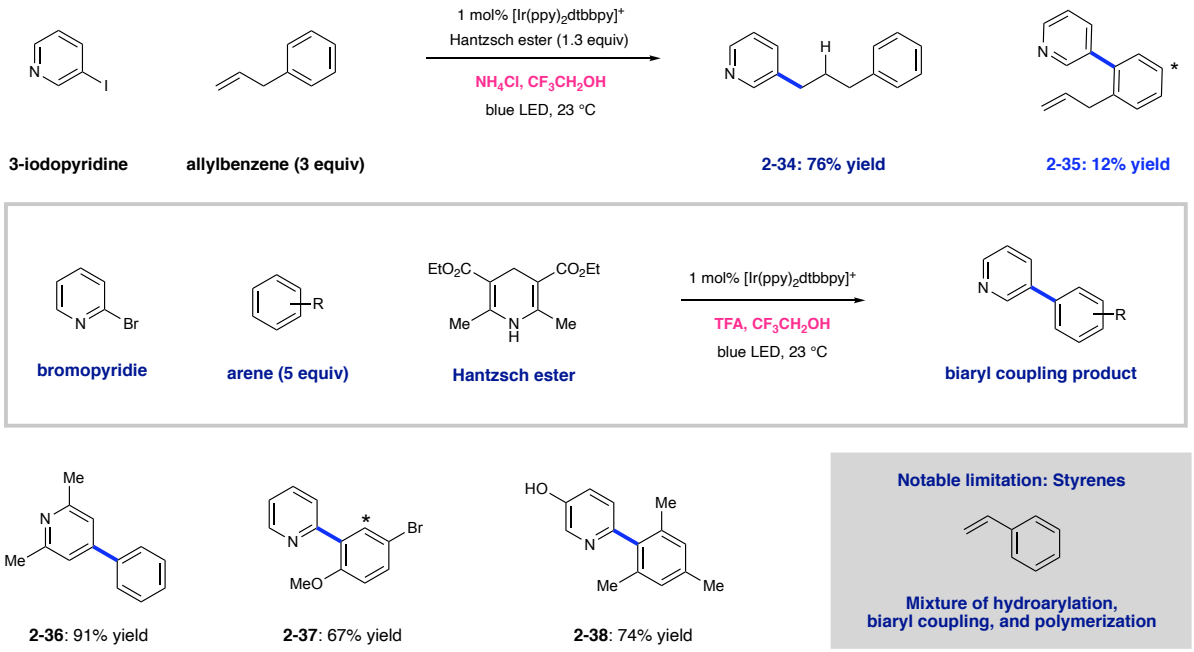


Figure 5: Optimization for bi-aryl coupling

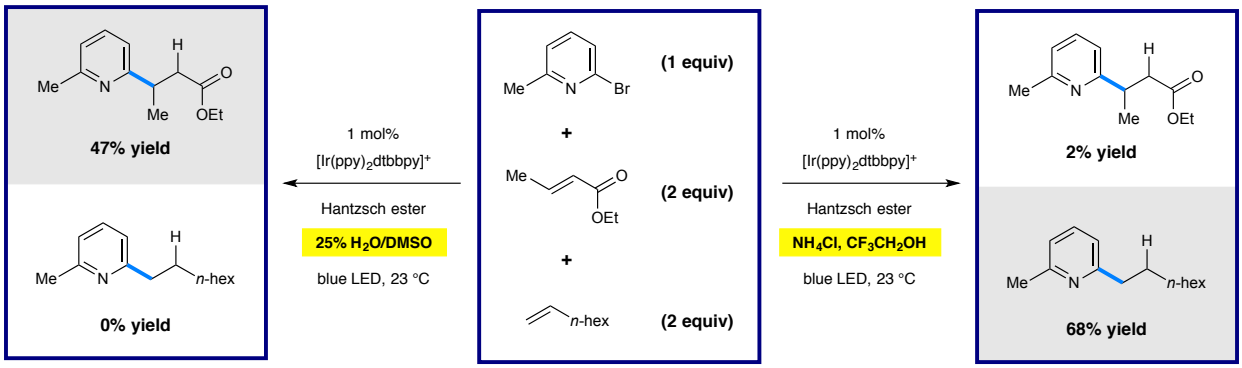
When applying the iridium catalyzed photoredox conditions to the coupling of 3-iodopyridine and allylbenzene, a mixture of products was observed. Not only was the expected hydroarylation product isolated in 76% yield, addition of the pyridyl radical to the benzene ring (with retention of the terminal alkene) was observed as a mixture of regioisomers in 12% yield (Figure 5). In an attempt to develop conditions that could select for the biaryl coupling product, it was found that simply substituting trifluoroacetic acid for ammonium chloride under otherwise identical reaction conditions allowed for the coupling of pyridyl radicals with benzene derivatives (5 equiv). Initial studies show that this reaction could be used to form a

variety of biaryl products with a regioisomeric mixture forming where expected (**2-36**–**38**, 67-91% yield).

2.7 Competition experiment

In contrast to our report on radical conjugate addition where the pyridyl radical intermediates displayed nucleophilic reactivity by successfully coupling with Michael acceptors in aqueous DMSO,[11] the pyridyl radicals generated in the slightly acidic TFE conditions preferentially react with neutral and electron-rich alkenes. To clearly illustrate this differential reactivity, competition experiments were carried out where 2-bromo-6-methylpyridine was activated in the presence of both 1-octene and ethyl crotonate (2 equiv of each) (Equation 1). In the aqueous DMSO conditions, exclusive formation of the RCA product (addition to ethyl crotonate) was observed whereas the hydroarylation product was not formed. Exchanging the solvent for TFE reversed the selectivity, providing the octene hydroarylation product in 68% yield with 2% yield of the RCA product.

Equation 1: Complementary radical reactivity determined by reaction solvent



2.8 Conclusion

In conclusion, we have developed a mild iridium-catalyzed system that enables the general hydroarylation of simple alkenes with pyridine units. Due to regiospecific pyridyl radical formation from the halopyridine, this method allows for the programmed installation of alkyl substituents at any position of the pyridine ring, and tolerates a wide range of functional groups.

Key to this development was the finding that the use of slightly acidic trifluoroethanol as the solvent imparts electrophilic character on the pyridyl radical intermediates thus favoring intermolecular addition to neutral and rich olefins.

2.9 Supporting information

2.9-I. General Information

2.9-I-A. General Reagent Information

All reactions were set up on the bench top and conducted under argon atomosphere while subjected to irradiation from a blue LED (PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.eaglelight.com). Silica gel chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalyst $Ir[ppy]_2dtbbpy•PF_6$ was prepared according to a literature procedure.[24] Halogenated heteroarenes were purchased from Combi-Blocks or Oakwood Products and were used as received, unless otherwise stated. Alkenes were purchased from Aldrich Chemical Co., Alfa Aesar, Oakwood Products, Combi-Blocks, Acros Organics, EMD Millipore and used as received. Trifluoroacetic acid was purchased from Oakwood Products and used as received. 2,2,2-trifluoroethanol was purchased from Oakwood Products and was degassed by sonication under vacuum and stored under Ar.

2.9-I-B. General Analytical Information

New compounds were characterized by NMR, IR spectroscopy, HRMS, and melting point. NMR data were recorded on one of four spectrometers: INOVA 600 MHz, INOVA 500 MHz, INONVA 400 MHz, or a Mercury 300 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR; or Benzene-d_6: δ 7.16 for ^1H NMR and 128.06 ppm for ^{13}C NMR). IR spectra were obtained with a Nicolet 380 Fourier transform infrared spectrophotometer. Mass spectrometry data were

[24] Lowry, M. S.; Hudson, W. R.; Pascal, R. A.; Bernhard, S., Accelerated Luminophore Discovery through Combinatorial Synthesis. *Journal of the American Chemical Society* **2004,** *126* (43), 14129-14135.

obtained from the Emory Mass Spectrometry Center. Melting point data was obtained with a Thomas Hoover Unimelt capillary melting point apparatus. Optimization data was obtained via gas chromatography with an Agilent Technologies 7890A Gas Chromatography system equipped with an Agilent Technologies 19091S-433UI column (30 m x 0.250 mm) with a 5977A MSD system and an Agilent Technologies G4513A autoinjector.

2.9-II. General Procedures for Hydropyridylation of Simple Olefins

2.9-II-A. General Procedure A

An oven-dried 30 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under Ar atmosphere. The tube was charged with $Ir[ppy]_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1.3 equiv), NH_4Cl (2 equiv), halopyridine (*if solid*, 1 equiv), and alkene (*if solid,* 3 or 5 equiv*)*. The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with alkene (*if liquid,* 3 or 5 equiv), halopyridine (*if liquid,* 1 equiv), and separately degassed 2,2,2-trifluoroethanol (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

2.9-II-B. General Procedure B

An oven-dried 30 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under Ar atmosphere. The tube was charged with $Ir[ppy]_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1.3 equiv), NH_4Cl (2 equiv), halopyridine (*if solid*, 1 equiv), and alkene (*if solid,* 3 or 5 equiv*)*. The atmosphere was

exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with alkene (*if liquid,* 3 or 5 equiv), halopyridine (*if liquid,* 1 equiv), and separately degassed 2,2,2-trifluoroethanol (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was transferred to a 50 mL round-bottom flask. The solvent was removed in vacuo and the residue was reconstituted in 15 mL of tetrahydrofuran and 3 mL of water. A stir bar was added and the flask was charged with LiOH (6.5 equiv). A reflux condenser was attached, and the flask was heated to 80 ºC in an oil bath with stirring for 2 hours to saponify Hantzsch pyridine. Upon cooling to room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (3 x 20 mL). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

2.9-II-C. General Procedure C

A 30-mL screw-top test tube equipped with a stir bar was charged with $Ir[ppy]_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1equiv), and halopyridine (1 equiv). The tube was sealed with a PTFE/silicon septa and the atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with biaryl coupling partner (5 equiv), degassed 2,2,2-trifluoroethanol (0.1 M), and trifluoroacetic acid (2 equiv) via syringe. The resulting mixture was stirred at 1200 RPM for 12 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

2.9-III. Optimization Details

2.9-III-A. Optimization Procedure

An oven-dried 15 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under Ar atmosphere. The tube was charged with photocatalyst (0.0025 mmol, 1 mol%), Hantzsch ester (0.082 g, 0.325 mmol, 1.3 equiv), and additive (*if solid*, 1 or 2 equiv). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, 1-octene (118 μL, 0.75 mmol, 3 equiv) and 2-bromo-6-methylpyridine (28 μL, 0.25 mmol, 1 equiv) were added via microsyringe. Separately degassed solvent (2.5 mL, 0.1 M) was added via syringe and the resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (8 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic extracts were filtered through a silica plug, with thorough acetone washing, into a 20 mL glass scintillation vial. An internal standard of dodecane (10 μL, 0.044 mmol) was delivered to the vial followed by thorough mixing. A sample was analyzed by gas chromatography and the integral values were used to calculate the data given in table 1.

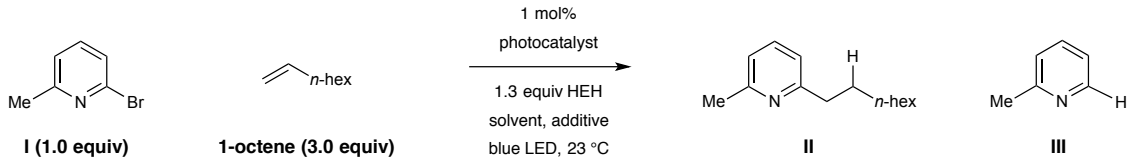
2.9-III-B. Gas Chromatography Method Conditions

The gas chromatography system hardware are reported in section I-B, General Analytical Information. The injection volume for each trial is 0.5 μL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Maximum temperature is held for one minute before concluding the run. Using this method, the retention time for 2-methyl-6-octylpyridine (**II**) was 10.25 min and the retention time for the starting material (**I,** 2-bromo-6-methylpyridine) was 5.90 min. The retention time for 2-picoline (**III**) was 2.90 min, and the retention time for the dodecane standard was 6.85 min

2.9-III-C. Optimization Tablea

The full optimization details are found in the following table:

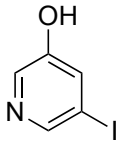
Table 4: Full optimization details



I (1.0 equiv) **1-octene (3.0 equiv)** **II** **III**

Entry	Photocatalyst	Solvent	Additive	Yield of **II**[b]	Yield of **III**[b]	Recovered **I**[b]
1	$[Ir(ppy)_2dtbbpy]PF_6$	25% H_2O/DMSO	—	4%	47%	0%
2	$[Ir(ppy)_2dtbbpy]PF_6$	DMSO	—	19%	56%	8%
3	$[Ir(ppy)_2dtbbpy]PF_6$	DMF	—	5%	55%	21%
4	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3CN	—	17%	27%	0%
5	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3OH	—	21%	18%	32%
6	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	—	74%	0%	18%
7	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	lutidine (1 equiv)	4%	0%	87%
8	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	AcOH (2 equiv)	77%	15%	8%
9	$[Ir(ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	NH_4Cl (2 equiv)	87%	9%	0%
10	$Ru(bpy)_2Cl_2$	CF_3CH_2OH	NH_4Cl (2 equiv)	9%	0%	76%
11	$[Ir(dF(CF_3)ppy)_2dtbbpy]PF_6$	CF_3CH_2OH	NH_4Cl (2 equiv)	79%	9%	0%
12	$[Ir(ppy)_2dtbbpy]PF_6$	25% H_2O/DMSO	NH_4Cl (2 equiv)	8%	90%	0%
13	$[Ir(ppy)_2dtbbpy]PF_6$	DMSO	NH_4Cl (2 equiv)	14%	71%	16%
14	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3CN	NH_4Cl (2 equiv)	20%	51%	25%
15	$[Ir(ppy)_2dtbbpy]PF_6$	DMF	NH_4Cl (2 equiv)	5%	0%	95%
16	$[Ir(ppy)_2dtbbpy]PF_6$	CH_3OH	NH_4Cl (2 equiv)	35%	53%	7%

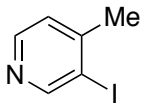
2.9-IV. Preparation of Starting Materials



5-iodopyridin-3-ol: According to the previously outlined procedure,[25] an oven dried 50 mL round bottom flask was charged with 5-bromopyrdin-3-ol (2.00 g, 11.5 mmol, 1 equiv), CuI (0.219 g, 1.15 mmol, 10 mol%), and NaI (3.45 g, 23.0 mmol, 2 equiv). A reflux condenser was attached and the atmosphere was exchanged by applying vacuum and backfilling with Ar (this

[25] Klapars, A.; Buchwald, S. L., Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2002,** *124*, 14844-14845.

process was conducted a total of three times). Under Ar atmosphere, the flask was charged with N,N-dimethylethylenediamine (0.250 mL, 2.30 mmol, 20 mol%) via syringe, followed by 1,4-dioxane (15 mL, 0.78 M). The flask was heated to 110 ºC in an oil bath with vigorous stirring for 24 h. Upon cooling to room temperature, the resulting suspension was poured onto 10 mL of 30% aqueous NH_4OH, diluted with 20 mL of H_2O, acidified to pH 6 with HCl, and extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered through a plug of silica, and concentrated to give the title compound (1.92 g, 96% yield) as an off white solid. The physical properties and spectral data match the reported values.[26]



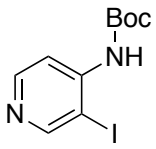
3-iodo-4-methylpyridine: According to the previously outlined procedure,[25] an oven dried 25 mL round bottom flask was charged with CuI (0.152 g, 0.80 mmol, 10 mol%), and NaI (2.40 g, 16.0 mmol, 2 equiv). A reflux condenser was attached and the atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the flask was charged with 3-bromo-4-methylpyridine (0.90 mL, 8.00 mmol, 1 equiv), N,N-dimethylethylenediamine (172 μL, 1.60 mmol, 20 mol%) via syringe, followed by 1,4-dioxane (10 mL, 0.80 M). The flask was heated to 110 ºC in an oil bath with vigorous stirring for 72 h. Upon cooling to room temperature, the resulting suspension was poured onto 10 mL of 30% aqueous NH_4OH, diluted with 20 mL of H_2O, and extracted with DCM (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered through a plug of silica, and concentrated to give the title compound (1.66 g, 95% yield) as a yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 8.44 – 8.29 (m, 1H), 7.19 (d, J = 4.8 Hz, 1H), 2.41 (s, 3H).

[26] Koren, A. O.; Horti, A. G.; Mukhin, A. G.; Gndisch, D.; Kimes, A. S.; Dannals, R. F.; London, E. D., 2-, 5-, and 6-Halo-3-(2(S)-azetidinylmethoxy)pyridines: Synthesis, Affinity for Nicotinic Acetylcholine Receptors, and Molecular Modeling. *Journal of Medicinal Chemistry* **1998,** *41* (19), 3690-3698.

^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.05, 151.51, 150.49, 148.88, 125.53, 27.42.

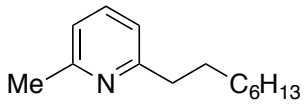
FTIR (neat) ν_{max}: 1578, 1470, 1439, 1394, 1286, 1120, 1083, 1008, 823, 810, 713, and 688 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for C_6H_7NI, 219.96177; found, 219.96163.



***tert*-butyl (3-iodopyridin-4-yl)carbamate:** According to the previously outlined procedure,[27] di-*tert*-butyl dicarbonate (2.182 g, 10.0 mmol) was added to a solution of 3-iodopyridin-4-ylamine (2.00 g, 9.09 mmol) in THF (10 mL, 0.1 M). The resulting solution was stirred for 3 hours at room temperature and then concentrated. The residue was reconstituted in ethyl acetate (20 mL), washed with saturated aqueous sodium bicarbonate solution (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (0:100 to 25:75 DCM:EtOAc) to give the title compound (2.30 g, 80% yield) as a white solid. The physical properties and spectral data match the reported values.[27]

2.9-V. Procedure and Characterization Data



2-methyl-6-octylpyridine (2-3)

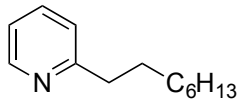
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 (m, 1H), 6.92 (m, 2H), 2.72 (m, 2H), 2.51 (s, 3H), 1.67 (m, 2H), 1.42 – 1.15 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H).

[27] Choi-Sledeski, Y. M.; Kearney, R.; Poli, G.; Pauls, H.; Gardner, C.; Gong, Y.; Becker, M.; Davis, R.; Spada, A.; Liang, G.; Chu, V.; Brown, K.; Collussi, D.; Leadley, R.; Rebello, S.; Moxey, P.; Morgan, S.; Bentley, R.; Kasiewski, C.; Maignan, S.; Guilloteau, J. P.; Mikol, V., Discovery of an orally efficacious inhibitor of coagulation factor Xa which incorporates a neutral P1 ligand. *J. Med. Chem.* **2003,** *46* (5), 681-684.

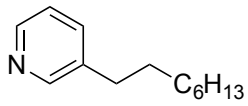
^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.08, 157.75, 136.53, 120.41, 119.53, 38.79, 31.99, 30.41, 29.64, 29.63, 29.38, 24.70, 22.80, 14.24.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{24}N$, 206.19033; found, 206.19022.

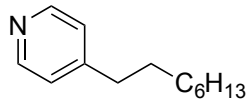
FTIR (neat) ν_{max}: 2922, 2853, 1591, 1578, 1455, 786, and 732 cm^{-1}.



2-octylpyridine (2-4): following general procedure B, the reaction of 2-bromopyridine (95 μL, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.164 g, 86% yield) as a pale, yellow oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[28]

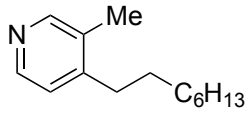


3-octylpyridine (2-5): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.152 g, 80% yield) as a pale, yellow oil after purification by silica gel chromatography (10:90 EtOAc:hexanes). The physical properties and spectral data match the reported values.[29]



[28] Everson, D. A.; Buonomo, J. A.; Weix, D. J., Nickel-catalyzed cross-electrophile coupling of 2-chloropyridines with alkyl bromides. *Synlett* **2014,** *25* (2), 233-238.
[29] Vechorkin, O.; Proust, V.; Hu, X., Functional group tolerant Kumada-Corriu-Tamao coupling of nonactivated alkyl halides with aryl and heteroaryl nucleophiles: Catalysis by a nickel pincer complex permits the coupling of functionalized Grignard reagents. *Journal of the American Chemical Society* **2009,** *131* (28), 9756-9766.

4-octylpyridine (2-6): following general procedure A, the reaction of 4-bromopyridine hydrochloride (0.195 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.164 g, 86% yield) as a pale, yellow oil after purification by silica gel chromatography (20:80 EtOAc:hexanes). The physical properties and spectral data match the reported values.[30]



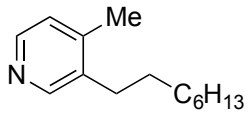
3-methyl-4-octylpyridine (2-7): following general procedure A, the reaction of 4-bromo-3-methylpyridine hydrochloride (0.209 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.172 g, 84% yield) as a clear oil after purification by silica gel chromatography (30:70 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 – 8.25 (m, 2H), 7.04 (d, *J* = 5.1 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.27 (s, 3H), 1.57 (p, *J* = 7.6 Hz, 2H), 1.43 – 1.21 (m, 10H), 0.92 – 0.84 (m, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 150.54, 149.85, 147.42, 131.49, 123.41, 32.51, 31.88, 29.56, 29.46, 29.25, 29.19, 22.68, 16.05, 14.12.

FTIR (neat) ν_{max}: 2923, 2853, 1730, 1593, 1409, 1404, 1379, 1194, 825, 722, and 576 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{24}N$, 206.19033; found, 206.19022.



[30] Bruce, D. W.; Metrangolo, P.; Meyer, F.; Pilati, T.; Prsang, C.; Resnati, G.; Terraneo, G.; Wainwright, S. G.; Whitwood, A. C., Structure-function relationships in liquid-crystalline halogen-bonded complexes. *Chemistry - A European Journal* **2010,** *16* (31), 9511-9524.

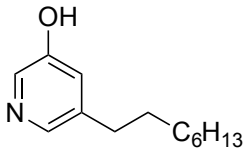
4-methyl-3-octylpyridine (2-8): following general procedure B, the reaction of 3-iodo-4-methylpyridine (0.219 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.143 g, 70% yield) as a pale, yellow oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 8.28 (d, *J* = 4.9 Hz, 1H), 7.02 (d, *J* = 4.9 Hz, 1H), 2.58 (m, 2H), 2.29 (s, 3H), 1.55 (m, 2H), 1.38 – 1.24 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.02, 147.28, 145.04, 136.70, 125.19, 31.99, 30.62, 30.21, 29.68, 29.56, 29.38, 22.80, 18.79, 14.24.

FTIR (neat) ν_{max}: 2942, 2868, 1729, 1573, 1477, 1453, 1420, 1023, 801, and 714 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{24}N$, 206.19033; found, 206.19006.



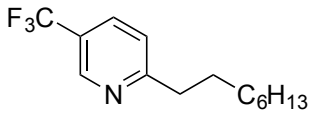
5-octylpyridin-3-ol (2-9): following general procedure A, the reaction of 5-iodo-pyridin-3-ol (0.221 g, 1.00 mmol, 1 equiv), 1-octene (0.785 mL, 5.00 mmol, 5 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.082 g, 40% yield) as a pale, yellow oil after purification by silica gel chromatography (10:90 to 70:30 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.90 (s, 1H), 7.14 (s, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.64 – 1.53 (m, 2H), 1.35 – 1.21 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.43, 140.58, 139.17, 133.63, 125.28, 32.95, 32.00, 31.03, 29.52, 29.35, 29.32, 22.81, 14.25.

FTIR (neat) ν_{max}: 2922, 2853, 2575, 1715, 1583, 1439, 1292, 1172, 1142, 865, 732, and 707 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{22}ON$, 208.16959; found, 208.16939.



2-octyl-5-(trifluoromethyl)pyridine (2-10): following general procedure B, the reaction of 2-iodo-5-trifluoromethylpyridine (0.273 g, 1.00 mmol, 1 equiv), 1-octene (0.785 mL, 5.00 mmol, 5 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.139 g, 54% yield) as a pale, yellow oil after purification by silica gel chromatography (3:97 to 30:70 EtOAc:hexanes).

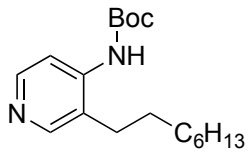
^{1}H NMR (600 MHz, Benzene-d_6) δ 8.79 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.2, 2.4 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 2.64 (t, J = 7.9 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.35 – 1.10 (m, 10H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.79, 146.28 (d, J = 4.3 Hz), 133.42 (d, J = 3.5 Hz), 122.54, 38.58, 31.98, 29.80, 29.54, 29.47, 29.33, 22.80, 14.24.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.22.

FTIR (neat) ν_{max}: 2925, 2856, 1607, 1573, 1325, 1161, 1127, 1079, 1016, 832, and 724 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{21}NF_3$, 260.16206; found, 260.16256.



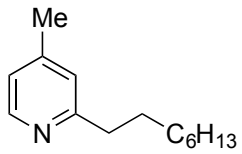
***tert*-butyl (3-octylpyridin-4-yl)carbamate (2-11):** following general procedure B, the reaction of *tert*-butyl (3-iodopyridin-4-yl)carbamate (0.320 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.158 g, 52% yield) as a pale, yellow oil after purification by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 5.6 Hz, 1H), 8.27 (s, 1H), 7.98 (d, *J* = 5.6 Hz, 1H), 6.56 (s, 1H), 2.52 (t, *J* = 7.5 Hz, 3H), 1.53 (s, 9H), 1.42 – 1.17 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.10, 150.46, 148.79, 143.48, 124.04, 112.67, 81.83, 31.94, 29.43, 29.30, 29.05, 28.49, 28.37, 22.78, 14.22.

FTIR (neat) ν_{max}: 2924, 2854, 1731, 1579, 1506, 1231, 1149, 839, and 733 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{31}O_2N_2$, 307.23800; found, 307.23778.



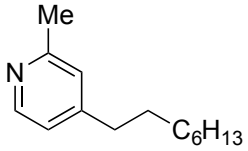
4-methyl-2-octylpyrinde (2-12): following general procedure A, the reaction of 2-bromo-4-methylpyridine (0.111 mL, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.135 g, 66% yield) as a pale, yellow oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 5.0 Hz, 1H), 6.96 (s, 1H), 6.92 (d, *J* = 5.1 Hz, 1H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 1.76-1.64 (m, 2H), 1.38 – 1.19 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.41, 149.03, 147.30, 123.68, 121.99, 38.47, 32.00, 30.12, 29.61, 29.37, 22.80, 21.13, 14.25.

FTIR (neat) ν_{max}: 2922, 2853, 1725, 1604, 1562, 1456, and 819 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{24}N$, 206.19033; found, 206.19036.



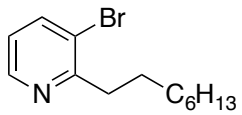
2-methyl-4-octylpyridine (2-13): following general procedure A, the reaction of 4-bromo-2-methylpyridine (119 μL, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.182 g, 89% yield) as a pale, yellow oil after purification by silica gel chromatography (20:80 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 – 8.32 (m, 1H), 6.95 (s, 1H), 6.89 (d, J = 4.9 Hz, 1H), 2.58 – 2.46 (m, 5H), 1.63 – 1.53 (m, 2H), 1.36 – 1.19 (m, 10H), 0.89 – 0.83 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.17, 152.11, 149.00, 123.49, 121.09, 35.32, 31.95, 30.47, 29.48, 29.34, 29.30, 24.45, 22.76, 14.20.

FTIR (neat) ν_{max}: 2923, 2853, 1730, 1603 1560, 1457, 1406, 827, and 732 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{24}N$, 206.19033; found, 206.19030.



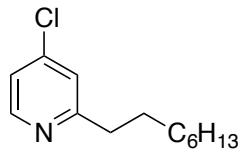
3-bromo-2-octylpyridine (2-14): following general procedure A, the reaction of 2,3-dibromopyridine (0.237 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.101 g, 49% yield) as a yellow oil after purification by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes). The connectivity was proven by reduction of the remaining aryl bromide function by treatment of an aliquot (25 mg, 0.09 mmol) with n-BuLi (0.25 mL of a 2.5 M solution in hexanes) in THF (2 mL, 0.045 M) at -78 °C. Methanol was added, the resulting mixture was warmed to room temperature, and directly concentrated using rotary evaporation. This procedure delivered 2-octylpyridine (2), as determined by ^{1}H NMR analysis.[28]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.99 (dd, *J* = 8.0, 4.7 Hz, 1H), 2.94 (t, *J* = 7.8 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.45 – 1.16 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.04, 147.90, 140.29, 122.41, 121.41, 37.86, 32.03, 29.67, 29.58, 29.39, 28.68, 22.84, 14.28.

FTIR (neat) ν_{max}: 2954, 2853, 1728, 1573, 1444, 1423, 1012, 789, and 723 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}NBr$, 270.08519; found, 270.08518.



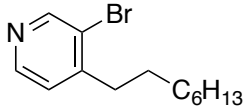
4-chloro-2-octylpyridine (2-15): following general procedure B, the reaction of 4-chloro-2-iodopyridine (0.192 g, 1.00 mmol, 1 equiv), 1-octene (0.470 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (97 mg, 43% yield) as a yellow oil after purification by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 5.4 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.11 (dd, *J* = 5.4, 2.0 Hz, 1H), 2.75 (t, *J* = 7.9 Hz, 2H), 1.76 – 1.65 (m, 2H), 1.41 – 1.17 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.26, 150.06, 144.08, 122.95, 121.28, 38.24, 31.83, 29.65, 29.40, 29.32, 29.18, 22.65, 14.10.

FTIR (neat) ν_{max}: 2924, 2854, 1727, 1557, 1546, 1447, 1358, 1136, 1100, 1070, 826, 796, 771, and 682 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}NCl$, 226.13570; found, 226.13558.



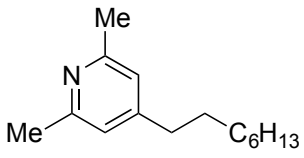
3-bromo-4-octylpyridine (2-16): following general procedure B, the reaction of 3,4-dibromopyridine (0.237 g, 1.00 mmol, 1 equiv), 1-octene (0.470 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.154 g, 57% yield) as a yellow oil after purification by silica gel chromatography (5:95 to 35:65 EtOAc:hexanes). The connectivity was proven by reduction of the remaining aryl bromide function by treatment of an aliquot (25 mg, .09 mmol) with 5% Pd/C (5 mg) in THF (2 mL, 0.045 M) under H_2 atmosphere. Upon completion by TLC, the resulting suspension was filtered through a plug of silica and concentrated by rotary evaporation. This procedure provided 4-octylpyridine (4) as determined by ^{1}HNMR analysis.[30]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 8.39 (d, *J* = 4.9 Hz, 1H), 7.14 (d, *J* = 4.9 Hz, 1H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.42 – 1.19 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 151.98, 151.03, 148.28, 125.21, 123.28, 35.54, 31.99, 29.47, 29.44, 29.33, 29.03, 22.81, 14.27.

FTIR (neat) ν_{max}: 2953, 2923, 2853, 1582, 1464, 1398, 1083, 1017, 823, 737, 696, and 597 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}NBr$, 270.08519; found, 270.08502.



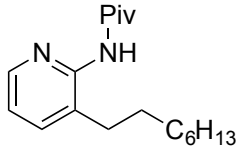
2,6-dimethyl-4-octylpyridine (2-17): following general procedure A, the reaction of 4-bromo-2,6-dimethylpyridine (0.186 g, 1.00 mmol, 1 equiv), 1-octene (0.47 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.179 g, 82% yield) as a pale, yellow oil after purification by silica gel chromatography (20:80 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.77 (d, *J* = 1.7 Hz, 2H), 2.48 (s, 6H), 1.62-1.53 (m, 2H), 1.33 – 1.25 (m, 10H), 0.90 – 0.85 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.50, 152.40, 120.56, 35.29, 31.98, 30.54, 29.52, 29.40, 29.32, 24.50, 22.78, 14.23.

FTIR (neat) ν_{max}: 2955, 2923, 2854, 1730, 1607, 1567, 1456, 1378, and 732 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{26}N$, 220.20707; found, 220.20607.



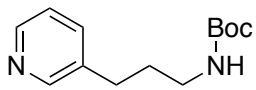
***N*-(3-octylpyridin-2-yl)pivalamide (2-18):** following general procedure A, the reaction of N-(3-Iodo-pyridin-2-yl)-2,2-dimethyl-propionamide (0.304 g, 1.00 mmol, 1 equiv), 1-octene (0.785 mL, 5.00 mmol, 5 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.153 g, 53% yield) as a pale, yellow oil after purification by silica gel chromatography (5:95 to 45:55 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.27 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.70 (s, 1H), 7.58 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.13 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 2H), 1.62 – 1.50 (m, 2H), 1.35 (s, 9H), 1.33 – 1.20 (m, 10H), 0.91 – 0.84 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.20, 149.19, 146.04, 138.72, 133.62, 122.19, 39.58, 31.99, 31.51, 29.72, 29.57, 29.50, 29.38, 27.74, 22.80, 14.26.

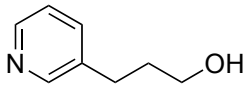
FTIR (neat) ν_{max}: 3179, 2955, 2923, 2854, 1679, 1581, 1498, 1434, 1284, 1161, and 775 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{31}ON_2$, 291.24309; found, 291.24278.



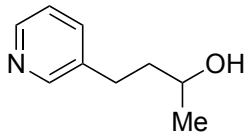
***tert*-butyl (3-(pyridin-3-yl)propyl)carbamate (2-19):** following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), Boc-allyl-amine (0.459 g, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.172 g, 78% yield) as a pale, yellow oil after purification by silica gel chromatography (15:85 Acetone:DCM).

The physical properties and spectral data match the reported values.[31]



3-(pyridin-3-yl)propan-1-ol (2-20): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), allyl alcohol (0.204 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.104 g, 76% yield) as a pale, yellow oil after purification by silica gel chromatography (40:60 Acetone:DCM).

The physical properties and spectral data match the reported values.[32]



4-(pyridin-3-yl)butan-2-ol (2-21): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), but-3-en-2-ol (0.260 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.119 g, 79% yield) as a pale, yellow oil after purification by silica gel chromatography (50:50 Acetone:DCM).

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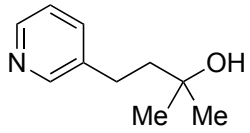
[31] Yano, J. K.; Denton, T. T.; Cerny, M. A.; Zhang, X.; Johnson, E. F.; Cashman, J. R., Synthetic inhibitors of cytochrome P-450 2A6: Inhibitory activity, difference spectra, mechanism of inhibition, and protein cocrystallization. *Journal of Medicinal Chemistry* **2006,** *49* (24), 6987-7001.

[32] Wypych, J. C.; Nguyen, T. M.; Bnchie, M.; Marazano, C., Reaction of aldimine anions with vinamidinium chloride: Three-component access to 3-alkylpyridines and 3-alkylpyridinium salts and access to 2-alkyl glutaconaldehyde derivatives. *Journal of Organic Chemistry* **2008,** *73* (3), 1169-1172.

The physical properties and spectral data match the reported values.[33]



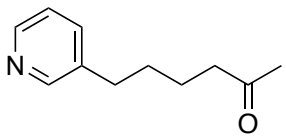
2-methyl-4-(pyridin-3-yl)butan-2-ol (2-22): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 2-methylbut-3-en-2-ol (0.314 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.133 g, 83% yield) as a dark, brown oil after purification by silica gel chromatography (50:50 Acetone:DCM).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 2.3 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.51 (m, 1H), 7.20 (m, 1H), 2.74 – 2.69 (m, 2H), 1.79 – 1.74 (m, 2H), 1.30 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.90, 147.32, 138.02, 135.94, 123.48, 70.72, 45.45, 29.53, 28.01.

FTIR (neat) ν_{max}: 3309, 2966, 1728, 1577, 1422, 1363, 1210, 930, and 712 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{10}H_{16}ON$, 166.12264; found, 166.12254.



6-(pyridin-3-yl)hexan-2-one (2-23): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 5-hexen-2-one (0.348 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.126 g, 71% yield) as a pale, yellow oil after purification by silica gel chromatography (40:60 EtOAc:hexanes).

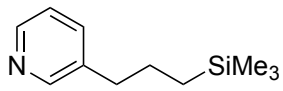
[33] Zhao, Q.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Goddard, J. P.; Lacte, E., N-heterocyclic carbene-catalyzed hydrosilylation of styryl and propargylic alcohols with dihydrosilanes. *Chemistry - A European Journal* **2011,** *17* (36), 9911-9914.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.44 – 8.40 (m, 2H), 7.50 – 7.46 (m, 1H), 7.19 (dd, J = 7.8, 4.8, 0.9 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.47 – 2.42 (m, 2H), 2.12 (s, J = 0.9 Hz, 3H), 1.65 – 1.57 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.76, 149.92, 147.41, 137.43, 135.94, 123.41, 43.45, 32.95, 30.67, 30.06, 23.33.

FTIR (neat) ν_{max}: 2934, 2859, 1710, 1421, 1359, 1165, 1026, 794, and 714cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{16}ON$, 178.12264; found, 178.12247.



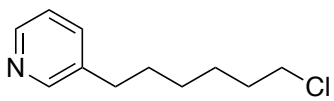
3-(3-(trimethylsilyl)propyl)pyridine (2-24): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), allyltrimethylsilane (0.480 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.138 g, 72% yield) as a pale, yellow oil after purification by silica gel chromatography (20:80 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.43 – 8.40 (m, 2H), 7.46 (m, 1H), 7.18 (dd, J = 7.8, 4.8 Hz, 1H), 2.60 (t, J = 7.6 Hz, 2H), 1.65 – 1.54 (m, 2H), 0.55 – 0.48 (m, 2H), -0.04 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 150.17, 147.32, 137.83, 135.93, 123.30, 36.94, 25.92, 16.48, -1.62.

FTIR (neat) ν_{max}: 2951, 1574, 1477, 1421, 1246, 833, 713, and 692 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{20}NSi$, 194.13595; found, 194.13592.



3-(6-chlorohexyl)pyridine (2-25): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 6-chloro-1-hexene (0.397 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2

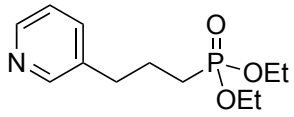
equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.176 g, 89% yield) as a pale, yellow oil after purification by silica gel chromatography (30:70 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.48 – 8.32 (m, 2H), 7.45 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.17 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.49 (t, *J* = 6.7 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.78-1.68 (m, 2H), 1.61 (p, *J* = 7.7 Hz, 2H), 1.49-1.39 (m, 2H), 1.37 – 1.29 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.96, 147.31, 137.70, 135.83, 123.33, 45.09, 32.92, 32.52, 31.00, 28.42, 26.68.

FTIR (neat) ν_{max}: 2931, 2856, 1574, 1478, 1422, 1026, 793, 713, and 649 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{17}NCl$, 198.10440; found, 198.10431.



diethyl (3-(pyridin-3-yl)propyl)phosphonate (2-26): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), diethyl allylphosphonate (0.523 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.157 g, 61% yield) as a pale, yellow oil after purification by silica gel chromatography (10:90 to 50:50 Acetone:DCM).

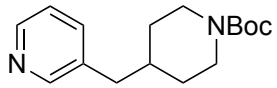
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 (m, 2H), 7.56 – 7.44 (m, 1H), 7.22 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.14 – 4.02 (m, 4H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.00 – 1.89 (m, 2H), 1.78 – 1.69 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.06, 147.80, 136.50, 136.10, 123.56, 61.70 (d, *J* = 6.6 Hz), 33.64 (d, *J* = 16.7 Hz), 25.78, 24.10 (d, *J* = 4.7 Hz), 16.63 (d, *J* = 5.9 Hz).

^{31}P NMR (121 MHz, Chloroform-*d*) δ 31.45.

FTIR (neat) ν_{max}: 2982, 2928, 1228, 1026, 963, 793, and 716 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}O_3NP$, 258.12536; found, 258.12534.



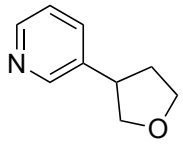
***tert*-butyl 4-(pyridin-3-ylmethyl)piperidine-1-carboxylate (2-27):** following general procedure B, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 1-N-Boc-4-methylenepiperidine (0.591 g, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.185 g, 67% yield) as a pale, yellow oil after purification by silica gel chromatography (30:70 to 80:20 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*, 50 ºC) δ 8.47-8.44 (m, 1H), 8.43-8.41 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.21 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.23-4.00 (m, 2H), 2.65 (t, *J* = 12.3 Hz, 2H), 2.55 (d, *J* = 7.0 Hz, 2H), 1.72-1.64 (m, 1H), 1.64 – 1.57 (m, 2H), 1.45 (s, 9H), 1.22 – 1.11 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*, 50 ºC) δ 178.51, 154.91, 150.49, 147.64, 136.63, 135.53, 123.37, 79.47, 40.24, 38.03, 31.92, 28.57.

FTIR (neat) ν_{max}: 2974, 2926, 2849, 1684, 1420, 1364, 1279, 1241, 1159, 769, and 715 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{25}O_2N_2$, 277.19215; found, 277.19101.



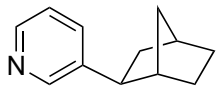
3-(tetrahydrofuran-3-yl)pyridine (2-28): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), 2,5-dihydrofuran (0.227 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (61 mg, 41% yield) as a pale, yellow oil after purification by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes).

^{1}H NMR (600 MHz, Benzene-d_6) δ 8.48 (d, *J* = 2.4 Hz, 1H), 8.46 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.01-6.97 (m, 1H), 6.69 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.76 – 3.70 (m, 2H), 3.58 – 3.52 (m, 1H), 3.44 (dd, *J* = 8.5, 6.7 Hz, 1H), 2.73 (p, *J* = 7.4 Hz, 1H), 1.75-1.67 (dtd, *J* = 12.6, 7.9, 4.7 Hz, 1H), 1.41 (dq, *J* = 12.2, 7.7 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.16, 148.11, 138.58, 134.62, 123.75, 74.50, 68.52, 42.55, 34.61.

FTIR (neat) ν_{max}: 2934, 2862, 1726, 1574, 1480, 1425, 1055, 1024, 902, 806, 714 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_9H_{12}ON$, 150.09134; found, 150.09130.



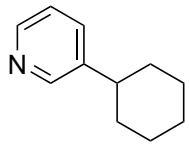
3-((1S,2S,4*R*)-bicyclo[2.2.1]heptan-2-yl)pyridine (2-29): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), norbornene (0.282 g, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.141 g, 82% yield) as a yellow oil after purification by silica gel chromatography (30:70 EtOAc, hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.49 – 8.48 (m, 1H), 8.40 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.21 – 7.18 (m, 1H), 2.75 (dd, *J* = 9.1, 5.6 Hz, 1H), 2.42 – 2.34 (m, 2H), 1.81 (ddd, *J* = 11.9, 9.1, 2.4 Hz, 1H), 1.71 – 1.53 (m, 2H), 1.51 (dt, *J* = 9.9, 2.1 Hz, 1H), 1.42 – 1.35 (m, 1H), 1.32 – 1.19 (m, 2H) 0.92-0.80 (m, 1H).

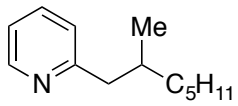
^{13}C NMR (151 MHz, Chloroform-*d*) δ 149.42, 146.98, 142.66, 134.25, 123.25, 45.07, 42.83, 38.99, 36.98, 36.19, 30.61, 28.87.

FTIR (neat) ν_{max}: 2949, 2868, 1729, 1573, 1477, 1453, 1420, 1023, 801, and 714 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{12}H_{16}N$, 174.12773; found, 174.12758.



3-cyclohexylpyridine (2-30): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), cyclohexene (0.303 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.117 g, 73% yield) as a yellow oil after purification by silica gel chromatography (20:80 to 30:70 EtOAc:hexanes). The physical properties and spectral data match the reported values.[34]



2-(2-methylheptyl)pyridine (2-31): following general procedure B, the reaction of 2-bromopyridine (95 μL, 1.00 mmol, 1 equiv), 2-methyl-1-heptene (0.470 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.175 g, 92% yield) as a pale, yellow oil after purification by silica gel chromatography (5:95-40:60 EtOAc:hexanes).

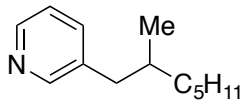
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 – 8.50 (m, 1H), 7.58 – 7.53 (m, 1H), 7.09 – 7.06 (m, 2H), 2.79 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.52 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.48 – 1.11 (m, 8H), 0.92-0.82 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.79, 149.28, 136.07, 123.68, 120.91, 46.19, 36.99, 34.11, 32.22, 26.83, 22.79, 19.51, 14.21.

FTIR (neat) ν_{max}: 2954, 2924, 2855, 1588, 1568, 1471, 1433, 1471, 1433, 1377, and 749 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{22}N$, 192.17468; found, 192.17456.

[34] Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A., Efficient cross-coupling of secondary alkyltrifluoroborates with aryl chlorides-reaction discovery using parallel microscale experimentation. *Journal of the American Chemical Society* **2008,** *130* (29), 9257-9259.



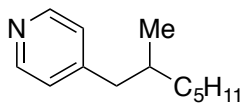
3-(2-methylheptyl)pyridine (2-32): following general procedure B, the reaction of 3-iodopyridine (0.205 g, 1 mmol, 1 equiv), 2-methyl-1-heptene (0.470 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product and an inseparable alkene by-product. The yield (78%) was determined by NMR and the byproduct was removed from and aliquot (25 mg, 0.13 mmol) of the mixture by hydrogenation with 5% Pd/C (5 mg) in EtOAc (2 mL) under H_2 atmosphere. The suspension was filtered through a plug of silica gel and thoroughly washed with EtOAc, and concentrated by rotary evaporation to afford the title compound.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 4.8 Hz, 1H), 8.40 (s, 1H), 7.47 – 7.43 (m, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 2.62 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.36 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.74-1.65 (m, 1H), 1.46 – 1.08 (m, 8H), 0.90 – 0.86 (m, 3H), 0.92-0.82 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.73, 147.34, 136.89, 136.62, 123.24, 40.77, 36.65, 34.95, 32.20, 26.86, 22.82, 19.40, 14.23.

FTIR (neat) ν_{max}: 2955, 2924, 2854, 1574, 1459, 1421, 1378, 1026, 909, 784, 732, 713, and 643 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}N$, 192.17468; found, 192.17454.



4-(2-methylheptyl)pyridine (2-33): following general procedure B, the reaction of 4-bromopyridine, HCl (0.195 g, 1 mmol, 1 equiv),), 2-methyl-1-heptene (0.470 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product and an

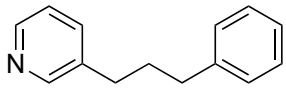
inseparable alkene by-product. The yield (74%) was determined by NMR and the byproduct was removed an aliquot (25 mg, 0.13 mmol) of the mixture by hydrogenation with 5% Pd/C (5 mg) in EtOAc (2 mL) under H_2 atmosphere. The resulting suspension was filtered through a plug of silica gel and thoroughly washed with EtOAc, and concentrated by rotary evaporation to afford the title compound.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 4.4 Hz, 2H), 7.07 (d, *J* = 4.4 Hz, 2H), 2.62 (dd, *J* = 13.3, 6.1 Hz, 1H), 2.34 (dd, *J* = 13.4, 8.3 Hz, 1H), 1.74 (dq, *J* = 13.3, 6.9 Hz, 1H), 1.41 – 1.11 (m, 8H), 0.90 – 0.86 (m, 3H), 0.85-0.82 (m, 3H).

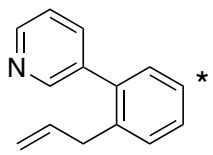
^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.79, 149.65, 124.79, 43.12, 36.75, 34.47, 32.17, 26.83, 22.81, 19.48, 14.23.

FTIR (neat) ν_{max}: 2955, 2923, 2854, 1729, 1601, 1557, 1458, 1414, 1378, 992, 789, 728, and 599 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}N$, 192.17468; found, 192.17453.

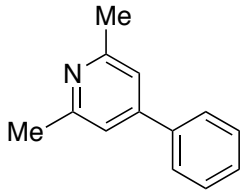


3-(3-phenylpropyl)pyridine (2-34): following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), allyl benzene (0.397 mL, 3.00 mmol, 3 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (0.149 g, 76% yield) as a pale, yellow oil after purification by silica gel chromatography (20:80 EtOAc:hexanes). The physical properties and spectral data match the reported values.[35]

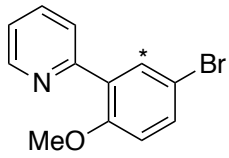


[35] Reimann, E.; Speckbacher, J., Synthese von 3,4-Dihydro-l'-rnethylspiro naphthalin-l(2H), 3'-piperidine. *Archiv der Pharmazie* **1990,** *323*, 13-15.

3-allylphenylpyridine (2-35): following general procedure A: following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), allyl benzene (0.40 mL, 3.00 mmol, 3 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.01 mmol, 1 mol %), NH_4Cl (0.107 g, 2.00 mmol, 2 equiv), and Hantzsch ester (0.329 g, 1.30 mmol, 1.3 equiv) provided the product (27 mg, 14% yield) as a mixture of regioisomers.



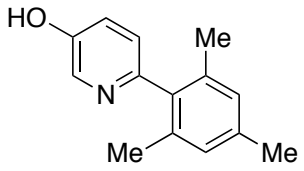
2,6-dimethyl-4-phenylpyridine (2-36): following general procedure C, the reaction of 4-bromo-2,6-dimethylpyridine (186 mg, 1.00 mmol, 1 equiv), benzene (445 uL, 5.00 mmol, 5 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.010 mmol, 1.0 mol%), trifluoroacetic acid (153 uL, 2.00 mmol, 2 equiv), and Hantzsch ester (253 mg, 1.00 mmol, 1 equiv), provided the product (0.167 g, 91% yield) as a white solid after purification by silica gel chromatography (15:85 THF:hexanes). The physical properties and spectral data match the reported values.[36]



2-(5-bromo-2-methoxyphenyl)pyridine/*2-(2-bromo-5-methoxyphenyl)pyridine (2-37): following general procedure C, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1 equiv), 4-bromoanisole (626 uL, 5.00 mmol, 5 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.010 mmol, 1.0 mol %), trifluoroacetic acid (153 uL, 2.00 mmol, 2 equiv), and Hantzsch ester (253 mg, 1.00 mmol, 1 equiv), provided the product (118 mg, *59 mg; 67% yield) as a white solid after

[36] Gupta, A.; Ila, H.; Junjappa, H., Cycloaromatization of alpha-oxoketene dithioacetals with lithioacetonitrile and lithiopropionitrile: a facile route to substituted and annelated pyridines. *Tetrahedron* **1990,** *46* (7), 2561-2572.

purification by silica gel chromatography (15:85 THF:hexanes). The physical properties and spectral data for each regioisomer matches the reported values.[37]



6-mesitylpyridin-3-ol (2-38): following general procedure C, the reaction of 2-bromo-5-hydroxypyridine (174 mg, 1.00 mmol, 1 equiv), mesitylene (696 uL, 5.00 mmol, 5 equiv), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.010 mmol, 1.0 mol %), trifluoroacetic acid (153 uL, 2.00 mmol, 2 equiv), and Hantzsch ester (253 mg, 1.00 mmol, 1 equiv), provided the product (0.158 g, 74% yield) as a white solid after purification by silica gel chromatography (40:60 EtOAc:hexanes).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.19 (d, J = 2.9, 0.8 Hz, 1H), 7.21 (dd, 1H), 7.05 (d, J = 8.4, 0.8 Hz, 1H), 6.89 (s, 2H), 2.25 (s, 3H), 1.92 (s, 6H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 152.37, 149.99, 138.20, 137.86, 136.50, 135.84, 128.29, 125.19, 122.80, 21.09, 20.38.

MP: 237-240 °C

FTIR (neat) ν_{max}: 2916.69, 2852.51, 1608.57, 1563.15, 1507.89, 1476.26, 1453.84, 1290.59, 1279.91, 1218.09

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{16}ON$, 214.12264; found, 214.12233.

2.9-VI. Equation 1

RCA Conditions

An oven-dried 15 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under Ar atmosphere. The tube was

[37] Yu, Q.; Hu, L. A.; Wang, Y.; Zheng, S.; Huang, J., Directed meta-Selective Bromination of Arenes with Ruthenium Catalysts. *Angewandte Chemie - International Edition* **2015,** *54* (50), 15284-15288. Serra, J.; Whiteoak, C. J.; Acua-Pars, F.; Font, M.; Luis, J. M.; Lloret-Fillol, J.; Ribas, X., Oxidant-Free Au(I)-Catalyzed Halide Exchange and Csp2-O Bond Forming Reactions. *Journal of the American Chemical Society* **2015,** *137* (41), 13389-13397.

charged with $[Ir(ppy)_2dtbbpy]PF_6$ (2.3 mg, 0.0025 mmol, 1 mol%) and Hantzsch ester (0.082 g, 0.325 mmol, 1.3 equiv). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, ethyl crotonate (62 μL, 0.50 mmol, 2 equiv) and 1-octene (78 μL, 0.50 mmol, 2 equiv) were added via microsyringe. 2-bromo-6-methylpyridine (28 μL, 0.25 mmol, 1 equiv) was added via microsyringe followed by the separately degassed mixture of 25% H_2O/DMSO. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (8 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic extracts were filtered through a silica plug, with thorough acetone washing, into a 20 mL glass scintillation vial. An internal standard of dodecane (10 μL, 0.044 mmol) was delivered to the vial followed by thorough mixing. A sample was analyzed by gas chromatography and the integral values were used to calculate the percent yield. The gas chromatography system hardware were reported in section I-B, General Analytical Information. The injection volume for each trial was 0.5 μL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Using this method, the retention times of **1**, **36**, and the dodecane standard were 10.25 min, 9.22 min, and 6.85 min, respectively. Maximum temperature was held for one minute before concluding the run. Analysis indicated 47% yield (**36**) and <1% yield (**1**).

Hydroarylation Conditions

An oven-dried 15 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under Ar atmosphere. The tube was charged with $[Ir(ppy)_2dtbbpy]PF_6$ (2.3 mg, 0.0025 mmol, 1 mol%), Hantzsch ester (0.082 g, 0.325 mmol, 1.3 equiv) and NH_4Cl (27 mg, 0.50 mmol, 2 equiv). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, ethyl crotonate (62 μL, 0.50 mmol, 2 equiv) and 1-octene

(78 μL, 0.50 mmol, 2 equiv) were added via microsyringe. 2-bromo-6-methylpyridine (28 μL, 0.25 mmol, 1 equiv) was added via microsyringe followed by separately degassed 2,2,2-trifluoroethanol. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (8 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic extracts were filtered through a silica plug, with thorough acetone washing, into a 20 mL glass scintillation vial. An internal standard of dodecane (10 μL, 0.044 mmol) was delivered to the vial followed by thorough mixing. A sample was analyzed by gas chromatography and the integral values were used to calculate the percent yield. The gas chromatography system hardware were reported in section I-B, General Analytical Information. The injection volume for each trial was 0.5 μL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Using this method, the retention times of **1**, **36**, and the dodecane standard were 10.25 min, 9.22 min, and 6.85 min, respectively. Maximum temperature was held for one minute before concluding the run. Analysis indicated 77% yield (**1**) and 2% yield (**36**).

Chapter 3:

Hydroarylation of functionalized olefins and mechanistic investigations of pyridyl radical intermediates

3.1 Pyridyl radical reactivity

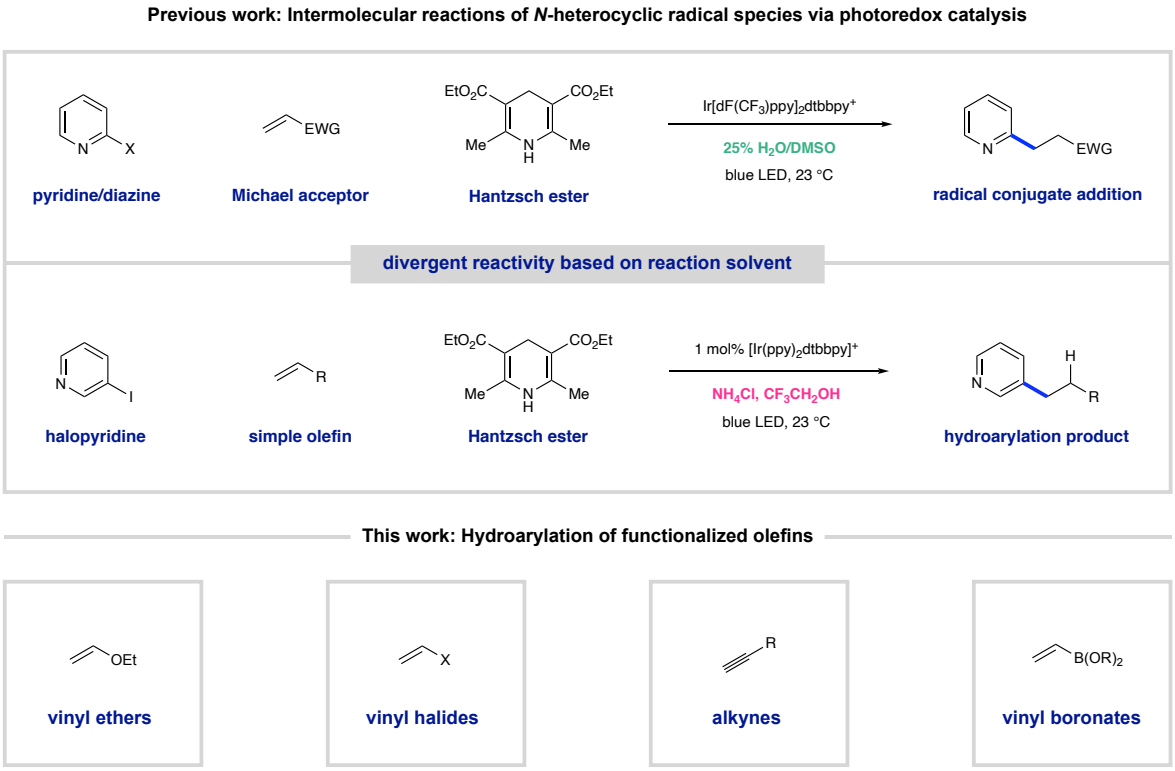


Figure 6: Previous work in the Jui Lab on heteroaryl radical addition to olefins

Functionalized pyridines and other nitrogen-containing heterocycles are ubiquitous structural motifs in compounds of biological relevance.[12] Us, and others, have developed conditions to leverage (hetero)aryl radical reactivity to functionalize pyridines under mild, photoredox conditions.[11,38,39] This system operates through single electron reduction of halogenated aryl units to give rise to aryl radicals in a regiospecific manner from stable, commercially available starting materials. Our studies in this area have been focused on controlling the propensity of the aryl radical to undergo rapid hydrogen atom transfer (HAT) to give the hydrodehalogenation (HDH) product and instead, selecting for intermolecular coupling with an olefin. To this end, we have developed conditions that

[38] Aycock, R. A.; Vogt, D.; Jui, N., A Practical and Scalable System for Heteroaryl Amino Acid Synthesis. *Chemical Science* **2017,** *8*, 7998-8003.
[39] Boyington, A. J.; Riu, M. L. Y.; Jui, N. T., Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *Journal of the American Chemical Society* **2017,** *139* (19), 6582-6585.

allow for divergent reactivity profiles of the typically ambiphilic pyridyl radical based exclusively on the reaction solvent (Figure 6).[11,39] In aqueous DMSO, the pyridyl radical selectively adds to electron-poor alkenes through a radical conjugate addition (RCA) mechanism. Conversely, in 2,2,2-trifluoroethanol (TFE), which is slightly acidic, the opposite reactivity is observed where highly selective hydroarylation of simple, electron-neutral olefins is observed. This protocol is complementary to recent radical hydroarylation reports by Shenvi[18] and Herzon[17] (Markovnikov addition), providing the linear, anti-Markovnikov product with complete regiocontrol.

3.2 Pyridyl radical addition to vinyl heteroatoms-development of polarity-matched HAT conditions

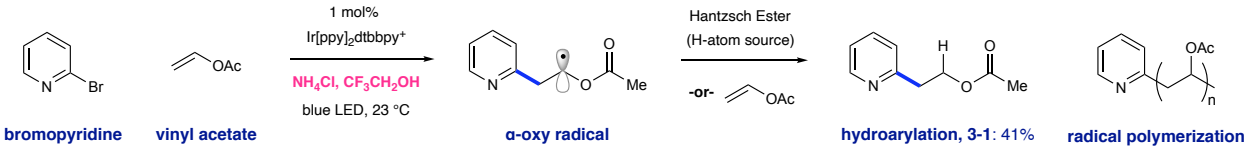


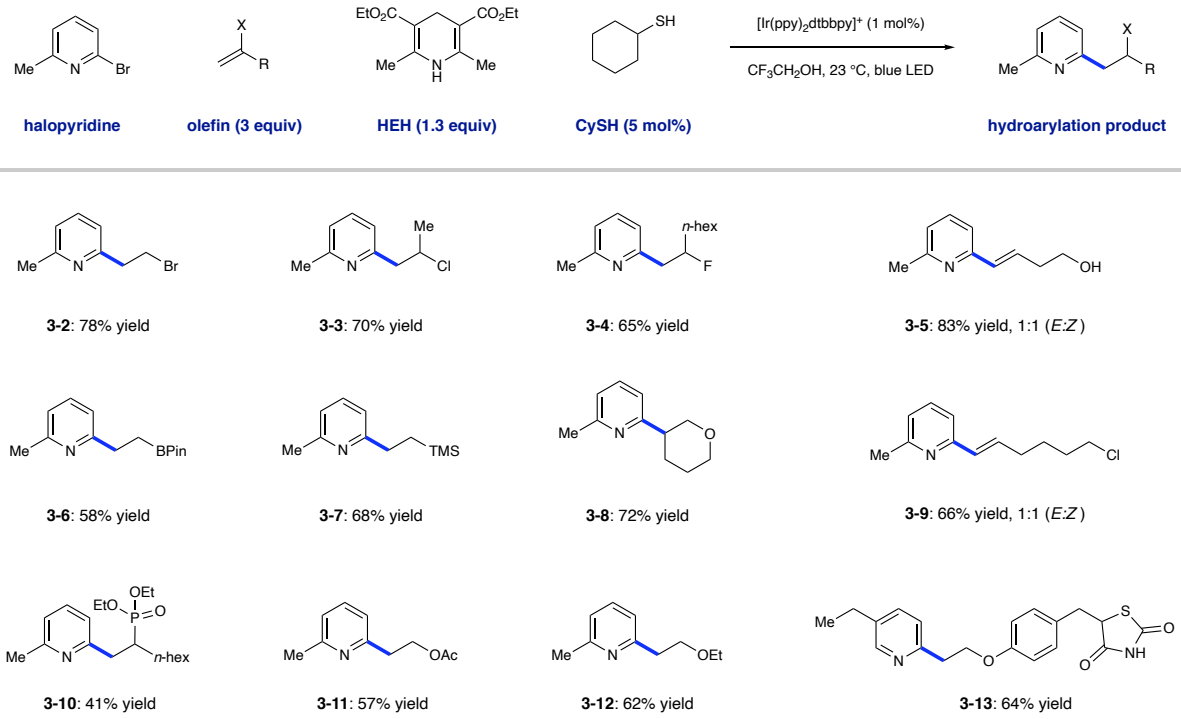
Figure 7: Polymerization observed when attempting hydroarylation of vinyl acetate

While powerful, when applied to electron rich olefins and vinyl heteroatoms, the acidic TFE conditions were low yielding and a variety of by products were observed. Specifically, when investigating the coupling of 2-bromopyridine with vinyl acetate, 41% yield of the hydroarylation product was isolated with the remainder of the mass balance consisting of HDH and oligomeric products (Figure 7). By LCMS analysis, the pyridyl radical was successfully adding to the vinyl acetate, however, instead of undergoing HAT from Hantzsch ester (HEH), the α-oxy radical intermediate was instead adding to another molecule of vinyl acetate. We questioned whether HEH, while an efficient electron source in the reaction, was the optimal hydrogen atom source to transfer a hydrogen atom to the α-oxy radical intermediate, thus leading to polymerization in addition to hydroarylation. The α-oxy radical intermediate is a nucleophilic radical, thus, a variety of electrophilic

polarity-reversal catalysts were surveyed, with cyclohexane thiol (CySH) significantly improving the selectivity for the hydroarylation pathway.[40] In this trial, a much cleaner reaction profile was observed with HDH being the major alternative pathway. A range of thiol HAT catalysts were surveyed, and no correlation was found between thiol structure and reaction efficiency.

3.3 Expanded pyridyl radical hydroarylation scope

Table 5: vinyl heteroatom and alkyne expanded hydroarylation scope



With the polarity matched HAT conditions in hand, the scope of functionalized alkenes was evaluated, specifically those that were absent from the hydroarylation literature and are common polymer feedstocks (Table 5). Of particular interest were halogenated alkenes as the products generated would allow for further functionalization. To this end, vinyl bromide was an effective coupling partner under the thiol-catalyzed photoredox conditions, giving the alkyl bromide **3-2** in 78% yield without any over-reduction products.

[40] Roberts, B. P., Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999,** (28), 25-35.

When the crude reaction mixture was exposed to silica gel, it rapidly converted to the vinylpyridine. This product is otherwise typically obtained through Stille cross-coupling with vinylstannane, thus providing an tin-free approach to the same product. Additionally, vinyl chlroides (**3-3**) and fluorides (**3-4**) were similarly effective giving the alkyl halides in 70% and 65% yield, respectively, under the optimized conditions and elimination during purification was not observed for these substrates.

Alkenylboronic esters reacted smoothly under the reaction conditions to furnish homobenzylic boronic ester **3-6** in 58% yield without protodeboronation or oxidation. Other vinyl heteroatoms were effective coupling partners despite a lack of knowledge on the reactivity of the resulting α-heteroatom intermediate. Alkenes substituted with Si and P functionalities were all well tolerated, delivering **3-7**, **3-10**, respectively, in moderate yields (41-68%). Polymer feedstocks ethyl vinyl ether and vinyl acetate reacted smoothly with bromopyridine in good yields (62% and 57%, respectively), where the remainder of the mass balance was HDH and not oligomeric side products. Alkyl enol ethers were successfully participated in the reaction to give **3-8** in 72% isolated yield. In addition to vinyl heteroatoms, alkynes were also successfully reacted under the photoredox conditions to give the exclusively the linear Mizoroki-Heck products **3-5** and **3-9** and 1:1 mixtures of geometrical isomers (66-83% yield). Notably, these transformations were tolerant of unprotected alcohols and primary alkyl chlorides, whereas classical Mizoroki–Heck conditions are intolerant of such sensitive functionalities.[41] To demonstrate the capacity of this reaction for the synthesis of biologically relevant small molecules, Pioglitazone[42] was

[41] Kim, B. H.; Lee, J. G.; Yim, T.; Kim, H.-J.; Lee, H. Y.; Kim, Y. G., Highly efficient two-step selective synthesis of 2,6-dimethylnaphthalene. *Tetrahedron Lett.* **2006,** *47*, 7727−7730.
[42] Sohda, T.; Ikeda, H.; Meguro, K., Studies on Antidiabetic Agents. XII. Synthesis and Activity of the Metabolites of (±)-5-[p-[2-(5-Ethyl2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (Pioglitazone). *Chem. Pharm. Bull.* **1995,** *43*, 2168−2172.

prepared in a short synthetic sequence (**3-13**, 64% yield) which utilized an aryl vinyl ether as the olefinic coupling partner.

3.4 Hydroarylation mechanistic analysis

With the scope of the hydroarylation of vinyl heteroatoms with pyridyl radicals established, we wanted to gain a deeper understanding of two mechanistic elements: (1) the successful reduction of halopyridine substrates that, as indicated by reported reduction potentials, is endergonic, and (2) the ability of reaction solvent to invoke remarkable chemoselectivity for different olefin coupling partners. We propose a dual catalytic cycle where an Ir-photoredox catalyst and CySH operate in concert to deliver the desired hydroarylation products (Figure 8). Specifically, the iridium catalyst is photoexcited under irradiation from commercially available blue LEDs to give the excited state of the catalyst ($*[Ir]^{III}$) which undergoes reductive quenching to give rise to the reducing $[Ir]^{II}$ species ($E^0_{1/2}$ = –1.51 V vs SCE). This mechanism is likely initiated by a sacrificial amount of HEH, which is supported by previous studies by Knowles[43] and Stern-Volmer quenching studies. Reduction of the bromopyridine via proton-coupled electron transfer (PCET) where TFE is the proton source, followed by rapid mesolytic cleavage would furnish the protonated pyridyl radical and an equivalent of bromide. Regioselective addition of the pyridyl radical to the terminal carbon of vinyl acetate would form the nucleophilic α-oxy radical intermediate which would undergo polarity-matched HAT from the thiol catalyst to deliver the hydroarylation product along with the thiyl intermediate. The HAT catalyst is regenerated via HAT with HEH which generates the corresponding dihydropyridine radical HEH•, this reductant then terminates the photoredox catalytic cycle by regenerating the $[Ir]^{II}$ reducing species and generating the stoichiometric byproduct, Hantzsch pyridinium.

[43] Gentry, E. C.; Knowles, R. R., Synthetic Applications of Proton-Coupled Electron Transfer. *Accounts of Chemical Research* **2016,** *49* (8), 1546-1556.

The HAT mechanism is supported by deuterium labeling studies which showed >80% incorporation of the label from HEH. Additionally, a quantum yield of $\Phi = 0.31$ indicates a predominantly photosensitized mechanism.[44]

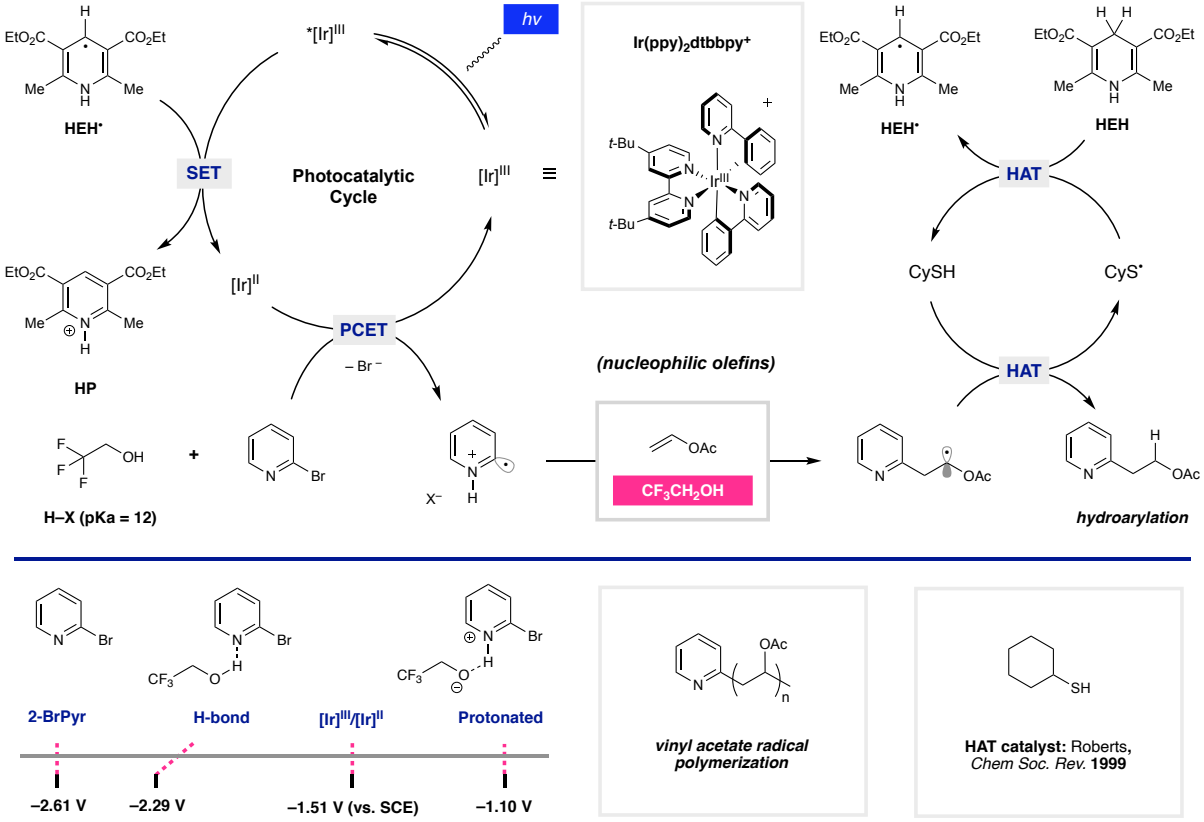


Figure 8: Proposed PCET mechanism

Essential to the observed radical reactivity is the slightly acidic, H-bond-donating (but poorly H-bond-accepting) reaction solvent, TFE.[45] When diene vinyl crotonate was reacted under the established TFE conditions, the pyridyl radical (from the reduction of bromopyridine) selectively added to the neutral olefin, giving rise to **3-15** as a single regioisomer (72% yield) (Figure 9). Conversely, when the solvent was exchanged for aqueous DMSO (the solvent for previously developed RCA reactivity), exclusive radical conjugate addition to the Michael acceptor was observed, giving **3-14** as a single

[44] Cismesia, M. A.; Yoon, T. P., Characterizing chain processes in visible light photoredox catalysis. *Chemical Science* **2015,** *6* (10), 5426-5434.
[45] Begué, J.-P.; Bonnet-Delpon, D.; Crousse, B., Fluorinated Alcohols: A New Medium for Selective and Clean Reaction. *Synlett 1*, 18-29.

regioisomer (56% yield). Regiochemical analysis was supported by GC, and, in both cases, <1% yield of the alternate regioisomer was observed and HDH was the major alternative pathway. These results are completely consistent with previous competition experiments in these two solvents, indicating that pyridyl radical addition to electron-deficient and electron-rich olefins operates through different reactive intermediates dictated by the reaction solvent.

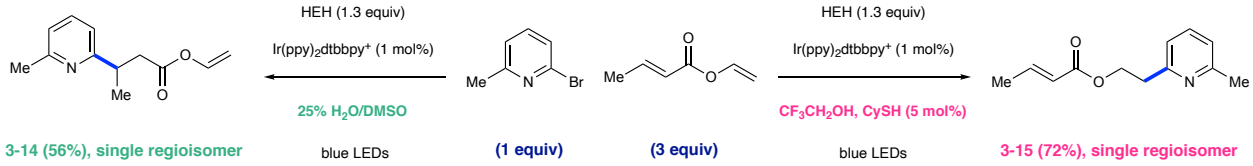


Figure 9: Divergent diene reactivity determined by reaction solvent

We propose that the hydroarylation of neutral olefins via pyridyl radicals occurs primarily through a reductive quenching pathway of the iridium photocatalyst which gives rise to the key pyridyl radical intermediate. However, the support of this mechanism with reduction potentials is complicated due to the rapid fragmentation halogenated pyridines to the pyridyl radical and the subsequent reduction of the pyridyl radical to the corresponding anion. The reduction potential of 2-bromopyridine has been reported between –1.80[46] and –2.29 V vs SCE[47] which is notably beyond the reducing ability of the Ir catalyst in our system ($E^0_{1/2}$ = –1.51 V vs SCE). Protonation of the 2-bromopyridine does significantly decrease the reduction potential ($E^0_{1/2}$ = –1.10 V vs SCE), analysis of the pK_a values of TFE (pK_a = 12 in DMSO) and 2-bromopyridinium (pK_a = 0.5 in DMSO) does not support the formation of the fully protonated pyridinium intermediate. Because of this, we hypothesize that the reductive activation of the halopyridine substrates in TFE occurs through a PCET

[46] Holubek, J.; Volke, J., Polarography of heterocyclic aromatic compounds. XIII. Polarographic fission of carbon-halogen bonds in monohalogenopyridines. . *Collect. Czech. Chem. Commun.* **1962,** *27*, 680-692.
[47] Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Savant, J. M., Heterogeneous and homogeneous electron transfers to aromatic halides. An electrochemical redox catalysis study in the halobenzene and halopyridine series. *Journal of the American Chemical Society* **1979,** *101* (13), 3431-3441.

mechanism.[48,49] This is further supported by our calculated reduction potentials. At the uB3LYP level of theory, the reduction potential of 2-bromopyridine was calculated to be −2.61 V vs SCE, and the potentials of H-bonded substrate ($E_{1/2}^0$ = −2.29 V vs SCE; N−H−O bond length = 2 Å) and fully protonated substrate ($E_{1/2}^0$ = −1.1 V vs SCE; bond length = 1.1 Å) were also computed.[50] These values are in agreement with the measured reduction potential of the $[Ir]^{II}$ catalytic species ($E_{1/2}^0$ = −1.51 V vs SCE) lying squarely between the calculated reduction potentials of the of the H-bonded and fully protonated substrate.

3.5 Conclusion

A general and efficient method for the hydroarylation of electron-rich olefins has been developed. Addition of a thiol polarity-reversal catalyst promotes a rapid intermolecular HAT step that prevents side reactions such as olefin polymerization and single-electron oxidation to provide the anti-Markovnikov products exclusively. Investigation of the reaction mechanism revealed a solvent-dependent mechanistic divergence. Use of the highly coordinating solvent TFE leads to a protonated, electrophilic pyridyl radical that is polarity-matched for alkene addition with electron-rich olefins. Use of a H-bond-accepting medium such as aqueous DMSO leads to a dissociated, neutral pyridyl radical that is polarity-matched for electron-poor olefins. We believe that these data will provide a greater rationale for chemistries utilizing heteroaryl radicals and expand the scope and understanding of related radical−olefin couplings.

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[48] Tarantino, K. T.; Liu, P.; Knowles, R. R., Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2013,** *135*, 10022-10025.
[49] Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J., Proton-Coupled Electron Transfer. *Chem. Rev.* **2012,** *112*, 4016-4093.
[50] Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T., Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *Journal of the American Chemical Society* **2018,** *140* (Scheme 1), 15525-15534.

3.6 Supporting information

3.6-I. General Information

3.6-I-A. General Reagent Information

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (LEDwholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or Hydrofarm® PPB1002 PowerPAR LED Bulb-Blue 15W/E27 (available from Amazon). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalyst, $[Ir(ppy)_2(dtbbpy)]PF_6$, was prepared according to a literature procedure.[24] Halogenated heteroarenes and heteroalkenes were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, Combi-Blocks, or Oakwood Chemicals and were used as received. Molecular sieves were activated in a commercial microwave oven then cooled under vacuum. 2,2,2-trifluoroethanol was purchased from Oakwood Chemicals and was degassed for 30 minutes prior to use by sonication under mild vacuum.

3.6-I-B. General Analytical Information:

Unless otherwise noted, all yields refer to isolated yields. New compounds were characterized by NMR, IR spectroscopy, and high-resolution mass spectrometry (HRMS). NMR data were recorded on one of six spectrometers: Bruker 600 MHz, INOVA 600 MHz, INOVA 500 MHz, VNMR 400 MHz, INOVA 400 MHz, or Mercury 300 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR; CD_3OD: δ 3.31 ppm for ^{1}H NMR and 49.1 ppm for ^{13}C NMR; THF–d_8: δ 3.58 ppm for ^{1}H NMR and 67.6 ppm for ^{13}C NMR). ^{11}B NMR were obtained on an INOVA 600 MHz spectrometer using $NaBH_4$ in D_2O as an external reference. IR spectra were obtained with a Thermo Scientific Nicolet iS10 Fourier transform infrared spectrophotometer. Mass spectrometry data were obtained from the

Emory Mass Spectrometry Center using a Thermo LTQ-FTMS high-resolution mass spectrometer. Adduct yields for optimization data were obtained via H^1 NMR with an Inova 500 MHz NMR using 1,1,2,2-tetrachloroethane as internal standard, with relaxation delay set to 5 seconds. Preparative HPLC was performed using an Agilent 1260 HPLC using an Eclipse XDB-C18 Prep HT column. Eluents used were unmodified unless otherwise stated.

3.6-II. General Procedures

General Procedure A: Hydropyridylation of Alkenes

An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with $Ir(ppy)_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1.3 equiv), NH_4Cl (2 equiv), halopyridine (if solid, 1 equiv), and alkene (if solid, 3 equiv). The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with alkene (if liquid, 3 equiv), halopyridine (if liquid, 1 equiv), cyclohexanethiol (5 mol%), and separately degassed 2,2,2-trifluoroethanol (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was quenched with saturated sodium bicarbonate and extracted with dichloromethane (3 x 20 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

General Procedure B: Hydropyridylation of Alkenes with Hydrolytic Work Up

An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with $Ir(ppy)_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1.3 equiv), NH_4Cl (2 equiv), halopyridine (if solid, 1 equiv), and alkene (if solid, 3 equiv). The atmosphere was

exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with alkene (if liquid, 3 equiv), halopyridine (if liquid, 1 equiv), cyclohexanethiol (5 mol%), and separately degassed 2,2,2-trifluoroethanol (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was transferred to a 50 mL round-bottom flask. The solvent was removed in vacuo and the residue was reconstituted in 15 mL of tetrahydrofuran and 3 mL of water. A stir bar was added and the flask was charged with LiOH (6.5 equiv). A reflux condenser was attached, and the flask was heated to 60 ºC in an oil bath with stirring for 2 hours to hydrolyze Hantzsch pyridine. Upon cooling to room temperature, the reaction was quenched water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

General Procedure C: Hydropyridylation of Complex Alkenes for Reaction Optimization

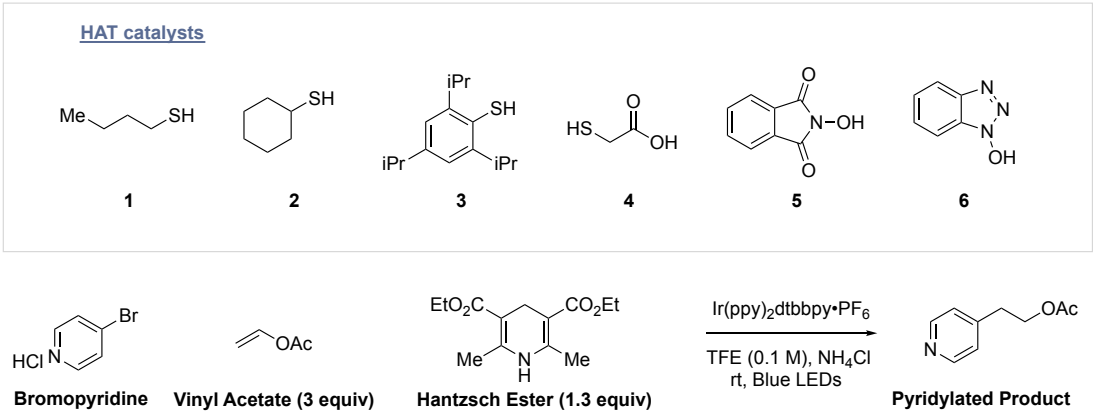
An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with $Ir(ppy)_2dtbbpy•PF_6$ (1 mol%), Hantzsch ester (1.3 equiv), NH_4Cl (2 equiv), 4-bromopyridine hydrochloride (1 equiv). The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with alkene (if liquid, 3 equiv), halopyridine (if liquid, 1 equiv) cyclohexanethiol (5 mol%), and separately degassed 2,2,2-trifluoroethanol (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was quenched with saturated sodium bicarbonate and extracted with dichloromethane (3 x 20 mL). The extracts were

combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. 1,1,2,2-Tetrachloroethane (1 equiv) was added as an internal standard to the crude residue. The sample was then dissolved in $CDCl_3$ for ^1H NMR analysis.

3.6-III. Optimization Table:

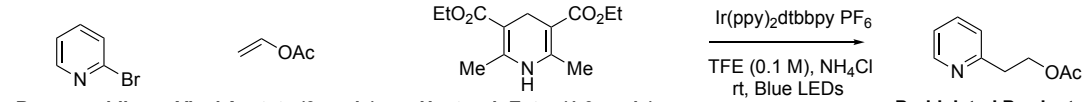
Initial optimization studies were performed on 6-bromopicoline with isopropenyl acetate as the reaction partner. This system was found to be relatively tolerant towards HAT catalyst and acidic modifier. The systems described below were chosen as more descriptive exemplars as they displayed significant variances in yield upon deviation of the reaction conditions. While thiol catalysts **3** and **4** showed a small improvement in yield for these substrates, we found that, overall, CySH performed better across a wide range of alkenes.

Table 6: Optimization with 4-bromopyridine



Entry	HAT Catalyst	Conditions	Yield (%)
1	none	as shown	17%
2	**1**	as shown	53%
3	**2**	as shown	63%
4	**3**	as shown	65%
5	**4**	as shown	62%
6	**5**	as shown	18%
7	**6**	as shown	22%
8	**2**	no photocatalyst	12%
9	**2**	no light	0%

Table 7: Optimization with 2-bromopyridine



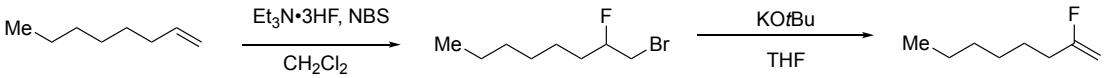
Bromopyridine **Vinyl Acetate (3 equiv)** **Hantzsch Ester (1.3 equiv)** **Pyridylated Product**

Entry	HAT Catalyst	Conditions	Yield (%)
1	none	as shown	35%
2	**1**	as shown	54%
3	**2**	as shown	65%
4	**3**	as shown	72%
5	**4**	as shown	67%
6	**5**	as shown	38%
7	**6**	as shown	52%

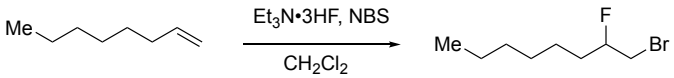
3.6-IV. Preparation of starting materials:

2-Fluorooct-1-ene, S1

Prepared according to the procedure.[51]

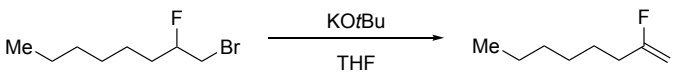


Step 1



To a round-bottomed flask charged with *N*-bromosuccinimide (2.1 g, 12 mmol) was added CH_2Cl_2 (5 mL) and 1-octene (1.56 mL, 1 equiv, 10 mmol). The suspension was cooled to 0 °C before the dropwise addition of triethylamine tris(hydrofluoride) (3.2 mL, 2 equiv, 20 mmol) in dichloromethane (5 mL) over the course of 15 min. After 2 h of additional stirring at 0 °C, the reaction mixture was absorbed directly onto silica gel (5 g) which was dried by evaporation before being loaded onto a column of silica gel. Elution with hexanes provided the desired product as a clear oil (1.8 g) that was taken directly into the next step.

Step 2



[51] Suga, H.; Hamatani, T.; Guggisberg, Y.; Schlosser, M., Regioselective formation of fluorohydrins and their stereoselective conversion to fluoroolefins. *Tetrahedron* **1990,** *46*, 4247-4254.

The 1-bromo-2-fluorooctane (1.8 g, 1 equiv, 8.6 mmol) was added to a solution of potassium *tert*-butoxide (1.34 g, 1.4 equiv, 12 mmol) in tetrahydrofuran (10 mL). After 5 h at 0 °C, the reaction mixture was passed through a thin plug of silica gel before being carefully concentrated at reduced pressure to provide the desired compound as a volatile colorless liquid (220 mg, 17 %)

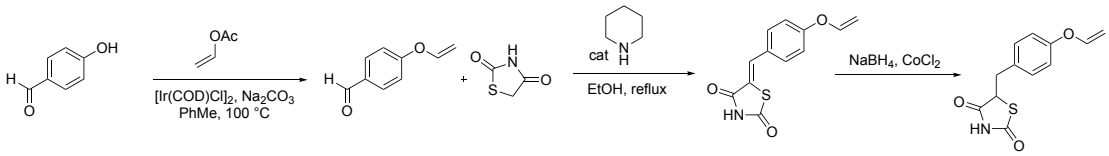
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 17.7, 2.6 Hz, 1H), 4.19 (dd, *J* = 50.5, 2.6 Hz, 1H), 2.25 – 2.08 (m, 2H), 1.55 – 1.45 (m, 2H), 1.31 (dddd, *J* = 20.4, 11.1, 7.2, 5.1 Hz, 6H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1 (d, $^{1}J_{C\text{-}F}$ = 256.6 Hz), 89.2 (d, $^{2}J_{C\text{-}F}$ = 20.5 Hz), 31.8 (d, $^{2}J_{C\text{-}F}$ = 27.1 Hz), 31.5, 28.6, 26.0 (d, $^{3}J_{C\text{-}F}$ = 2.1 Hz), 22.5, 14.0.

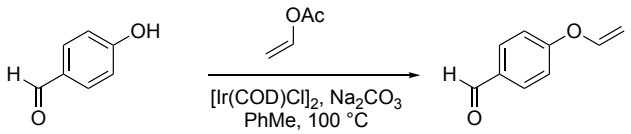
^{19}F NMR (565 MHz, $CDCl_3$) δ -94.65 (dq, *J* = 50.3, 16.5 Hz).

FTIR (neat) ν_{max}: 2928, 2858, 1468, 1239, 1099 cm^{-1}.

5-(4-(Vinyloxy)benzyl)thiazolidine-2,4-dione, S4



Synthesis of 4-(vinyloxy)benzaldehyde, S2



Synthesized according to literature procedure.[52]

To a toluene solution (15 mL) of $[IrCl(cod)]_2$ (100 mg, 1 mol%, 0.015 mmol) and Na_2CO_3 (945 mg, 0.6 equiv, 9 mmol) were added 4-hydroxybenzaldehyde (1830 mg, 1, equiv, 15 mmol) and vinyl acetate (2.8 mL, 2.6 g, 2 equiv, 30 mmol) under an atmosphere of Ar. The reaction mixture was stirred at 100 °C for 16 h. After quenching with wet ether, and

[52] Okimoto, Y.; Sakaguchi, S.; Ishii, Y., Development of a Highly Efficient Catalytic Method for Synthesis of Vinyl Ethers. *J. Am. Chem. Soc.* **2002,** *124*, 1590-1591.

concentration under reduced pressure, the residue was purified by column chromatography (silica gel, 0 – 5% hexane/EtOAc) to provide the desired compound as a clear oil (1.8 g, 81%).

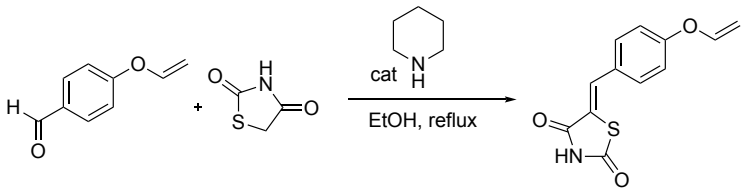
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.93 – 7.71 (m, 2H), 7.18 – 7.08 (m, 2H), 6.70 (ddd, *J* = 13.6, 6.0, 0.7 Hz, 1H), 4.95 (ddd, *J* = 13.6, 1.9, 0.8 Hz, 1H), 4.63 (ddd, *J* = 6.0, 1.9, 0.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 190.8, 161.7, 146.4, 132.0, 131.7, 116.8, 98.3.

FTIR (neat) ν_{max}: 2828, 2740, 1691, 1592, 1503, 1237, 1156 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_9H_9O_2$, 149.05971; found, 149.05961.

Synthesis of (Z)-5-(4-(vinyloxy)benzylidene)thiazolidine-2,4-dione, S3



To a round bottomed flask charged with 4-(vinyloxy)benzaldehyde (1.7 g, 1 equiv, 12 mmol) and 2,4-thiazolidinedione (2.2 g, 1.6 equiv, 19.2 mmol) was added piperidine (0.35 mL, 0.3 equiv, 3.6 mmol) and EtOH (48 mL). The reaction mixture was refluxed for 16 h. Upon cooling, the reaction mixture was poured onto ice water, leading to the precipitation of the desired product as a yellow solid. The yellow suspension was filtered and washed with cold methanol to provide the clean desired compound as an amorphous yellow solid (2.47g, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.83 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.17 – 7.03 (m, 2H), 6.68 (dd, *J* = 13.6, 6.0 Hz, 1H), 4.92 (dd, *J* = 13.6, 1.9 Hz, 1H), 4.60 (dd, *J* = 6.0, 1.9 Hz, 1H).

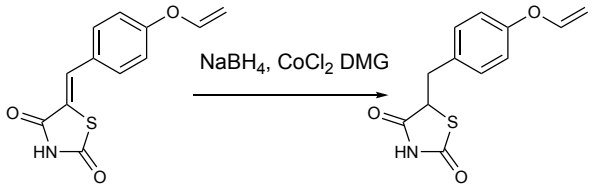
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 166.7, 158.8, 146.7, 134.0, 132.4, 127.8, 120.7, 117.4, 97.8.

FTIR (neat) ν_{max}: 2986 1691, 1678, 1590, 1426, 1343 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{10}O_3NS$, 248.03759; found, 248.03764.

Synthesis of 5-(4-(vinyloxy)benzyl)thiazolidine-2,4-dione, S4

Prepared according to literature procedure.[53]



To a round bottomed flask charged with (Z)-5-(4-(vinyloxy)benzylidene)thiazolidine-2,4-dione (520 mg, 1 equiv, 2.1 mmol) in 2:1 MeOH/H_2O (15 mL) and 1 M sodium hydroxide solution (1.6 mL, 1.6 mmol), and the resultant mixture was stirred for 15 min at ca. 23 °C. Then, 1 mL of a $CoCl_2$-DMG complex solution (2 mg of $CoCl_2$,$6H_2O$ and 13 mg of dimethylglyoxime in 5 mL of *N*,*N*-dimethylformamide) was added, and the stirring was continued. After 15 min, sodium borohydride (100 mg, 2.6 mmol) in water (2 mL) was added in a single portion. The blue-purple solution was warmed to 35 °C and stirred for 3 h. Then the reaction mixture was cooled to room temperature and brought to pH 6-7 with 1 M hydrochloric acid (70 mL), and the deposited precipitate of product was filtered off. The precipitate was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2 x 5 mL). The organics were passed though a plug of silica gel and concentrated under reduced pressure to provide the desired product as an amorphous off white solid (400 mg, 76%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.01 – 6.92 (m, 2H), 6.65 – 6.59 (m, 1H), 4.78 (dd, *J* = 13.6, 1.8 Hz, 1H), 4.52 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.46 (dd, *J* = 6.0, 1.7 Hz, 1H), 3.48 (dd, *J* = 14.2, 4.0 Hz, 1H), 3.14 (dd, *J* = 14.2, 9.4 Hz, 1H).

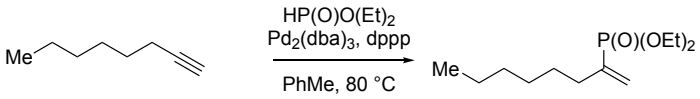
[53] Leś, A.; Pucko, W.; Szelejewski, W., Optimization of the Reduction of a 5-Benzylidenethiazolidine-2,4-dione Derivative Supported by the Reaction Response Surface Analysis: Synthesis of Pioglitazone Hydrochloride. *Org. Process Res. Dev.* **2004,** *8*, 157-162.

^{13}C NMR (151 MHz, $CDCl_3$) δ174.2, 170.4, 156.5, 148.0, 132.4, 130.7, 117.5, 95.8, 53.6, 37.9.

FTIR (neat) ν_{max}: 3039, 1665, 1658, 1641, 1591, 1333, 1247, 1168, 1144 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{12}O_3NS$, 250.05324; found, 250.05325.

Diethyl oct-1-en-2-ylphosphonate, S6



Synthesized according to the literature procedure.[54]

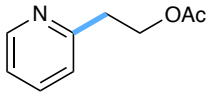
An oven-dried schlenck tube containing a stir bar was charged with $Pd_2(dba)_3$ (2.3 mg, 0.5 mol%, 0.5 mmol), 1,3-bis(diphenylphosphino)propane (2.0 mg, 1 mol%, 0.5 mmol) and 0.5 mL toluene under N_2 atmosphere and stirred at room temperature for 10 min, then diethylphosphite (64 µL, 1 equiv, 0.5 mmol) and 1-octyne (74 µL, 1 equiv, 0.5 mmol) were added and the mixture was stirred at 100 °C overnight. After removal of the solvent the crude residue was purified by column chromatography (silica gel, chloroform) to provide the desired compound as a pale yellow oil (61 mg, 49%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.36 – 7.31 (m, 3H), 6.55 (ddd, *J* = 16.6, 9.6, 2.1 Hz, 1H), 5.38 – 5.33 (m, 2H).

Spectral data consistent with previous reports.[54]

3.6-V. Preparation of Substrates

2-(Pyridin-2-yl)ethyl acetate (3-1)



Prepared according to the General Procedure A using 2-bromopyridine (103 µL, 156 mg, 1 mmol, 1 equiv), and vinyl acetate (276 µL, 258 mg, 3 mmol, 3 equiv), Hantzsch ester

[54] Chen, T.; Zhao, C.-Q.; Han, L.-B., Hydrophosphorylation of Alkynes Catalyzed by Palladium: Generality and Mechanism. *J. Am. Chem. Soc.* **2018,** *140*, 3139-3155.

(329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure B (silica gel, 40 – 100% EtOAc/hexanes) to provide the desired product as a yellow oil (107 mg, 65% yield).

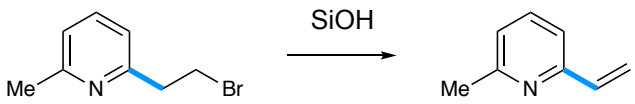
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.70 – 7.58 (m, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.5, 5.1 Hz, 1H), 4.48 (t, *J* = 6.8 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.04 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 158.1, 149.5, 136.7, 123.6, 121.8, 63.7, 37.5, 21.1.

FTIR (neat) ν_{max}: 2964, 1732, 1592, 1570, 1437, 1365 cm^{-1}.

HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{12}O_2N$, 166.08626; found, 166.08627.

2-Methyl-6-vinylpyridine (3-2)



An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with Ir(ppy)$_2$dtbbpy•PF$_6$ (9.1 mg, 1 mol%, 0.01 mmol), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv) and NH_4Cl (106 mg, 2 mmol, 2 equiv). The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). 2-Bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv) and cyclohexanethiol (6 µL, 5 mol%, 0.05 mmol) were added via syringe.

Separately, vinyl bromide (207 µL, 3 equiv, 3 mmol) was condensed into a sealed vial at -78 °C before the addition of separately degassed 2,2,2-trifluoroethanol (0.1 M) under a N_2 atmosphere via syringe. The vinyl bromide solution was transferred to the reaction vial and the resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was quenched with saturated sodium bicarbonate and

extracted with dichloromethane (3 x 20 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was treated with silica gel for 15 min in CH_2Cl_2 (10 mL) to afford the eliminated product. The resulting slurry was concentrated and purified by flash column chromatography (silica gel, 0 – 30% EtOAc/hexanes) then preparative HPLC (C_{18}, 30 – 99% MeCN/H_2O) to afford the title compound as a red-brown liquid (93 mg, 78 %).

Isolation of the alkyl bromide product was found to be extremely difficult, with rapid elimination occurring under all conditions attempted.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (t, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.71 (dd, *J* = 17.6, 11.2 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 17.6 Hz, 1H), 6.00 (d, *J* = 11.1 Hz, 1H), 3.03 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.0, 150.9, 145.0, 127.7, 127.5, 126.0, 120.0, 19.7.

FTIR (neat) ν_{max}: 1657, 1631, 1426, 1295, 1177 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_8H_{10}N$, 120.08078; found, 120.08029.

2-(2-Chloropropyl)-6-methylpyridine (3-3)

Prepared according to the General Procedure A using 2-Bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and 2-chloroprop-1-ene (254 µL, 228 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), Ir[ppy]$_2$dtbbpy•PF_6 (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 0 – 40% EtOAc/hexanes) to provide the desired product as a yellow oil (119 mg, 70% yield).

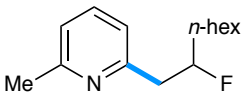
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.6 Hz, 1H), 7.00 (dd, *J* = 10.8, 7.7 Hz, 2H), 4.56 – 4.37 (m, 1H), 3.12 (dd, *J* = 7.0, 3.8 Hz, 2H), 2.52 (s, 3H), 1.57 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.2, 157.4, 136.7, 121.5, 121.2, 57.9, 48.9, 25.3, 24.6.

FTIR (neat) ν_{max}: 2975, 2927, 1590, 1577, 1456, 1377 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}NCl$, 170.07310; found, 170.07306.

2-(2-Fluorooctyl)-6-methylpyridine (3-4)



Prepared according to the General Procedure B using 2-bromo-6-methylpyridine (11.4 µL, 17.2 mg, 0.1 mmol, 1 equiv), and 2-fluorooct-1-ene (39 mg, 0.3 mmol, 3 equiv), Hantzsch ester (33 mg, 0.13 mmol, 1.3 equiv), cyclohexanethiol (0.6 µL, 0.005 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (0.9 mg, 0.001 mmol, 1 mol%), and NH_4Cl (10.6 mg, 0.2 mmol, 2 equiv) in 1 mL of 2,2,2-trifluoroethanol (0.1 M). After 18 h, the reaction was purified according to the General Procedure B (preparative thin layer chromatography, silica gel, 20% EtOAc/hexanes) to provide the desired product as a colorless oil (14.5 mg, 65% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 2H), 4.90 (dtt, *J* = 49.1, 8.2, 3.9 Hz, 1H), 3.11 – 2.94 (m, 1H), 2.53 (s, 3H), 1.77 – 1.56 (m, 2H), 1.56 – 1.47 (m, 1H), 1.45 – 1.21 (m, 9H), 0.88 (t, *J* = 6.9 Hz, 3H).

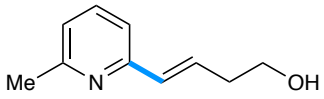
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 157.2 (d, $^3J_{C\text{-}F}$ = 4.2 Hz), 136.5, 121.1, 120.9, 93.9 (d, $^1J_{C\text{-}F}$ = 169.5 Hz), 44.2 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 35.1 (d, $^2J_{C\text{-}F}$ = 20.7 Hz), 31.7, 29.1, 25.0 (d, $^3J_{C\text{-}F}$ = 4.2 Hz), 24.5, 22.5, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$) δ -179.98 – -180.92 (m).

FTIR (neat) ν_{max}: 2924, 2854, 1495, 1453, 1361, 1226, 1097 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{23}NF$, 224.18090; found, 224.18091.

4-(6-Methylpyridin-2-yl)but-3-en-1-ol (3-5)



Prepared according to the General Procedure B using 2-bromo-6-methylpyridine (114 μL, 172 mg, 1 mmol, 1 equiv), and but-3-yn-1-ol (306 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure B (silica gel, 30 – 100% EtOAc/hexanes) to provide the cis alkene as a pale yellow oil (67 mg, 41% yield) and the trans alkene as a pale yellow oil (69 mg, 42%, 83% combined yield).

Cis alkene

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.7 Hz, 1H), 6.95 (dd, *J* = 12.1, 7.7 Hz, 2H), 6.46 (d, *J* = 11.8 Hz, 1H), 6.29 (s, 1H), 5.74 (dt, *J* = 12.0, 8.8 Hz, 1H), 3.68 (t, *J* = 5.5 Hz, 2H), 2.77 – 2.68 (m, 2H), 2.52 (s, 3H), 1.74 (dt, *J* = 11.0, 5.2 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.52, 155.56, 137.29, 136.16, 129.09, 121.82, 121.52, 59.71, 30.24, 24.42, 23.71.

FTIR (neat) ν_{max}: 3268, 2927, 2859, 1586, 1572, 1461, 1156 cm^{-1}.

Trans alkene

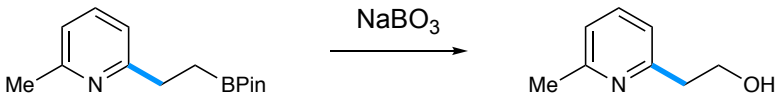
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.70 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.58 – 6.48 (m, 1H), 3.72 (t, *J* = 6.5 Hz, 2H), 2.53 (s, 3H), 2.42 – 2.30 (m, 2H), 1.79 (p, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 155.5, 136.7, 134.6, 130.9, 121.4, 118.0, 62.6, 32.0, 29.3, 24.7.

FTIR (neat) ν_{max}: 3349, 2925, 1587, 1461, 1451, 1060 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{16}ON$, 178.12264; found, 178.12261.

2-(6-Methylpyridin-2-yl)ethan-1-ol (3-6)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (28 µL, 43 mg, 0.25 mmol, 1 equiv), and vinylboronic acid, pinacol ester (187 mg, 127 µL, 0.75 mmol, 3 equiv), Hantzsch ester (82 mg, 0.325 mmol, 1.3 equiv), cyclohexanethiol (1.6 µL, 0.0125 mmol, 5 mol%), Ir[ppy]$_2$dtbbpy•PF_6 (2.25 mg, 0.0025 mmol, 1 mol%), and NH_4Cl (26 mg, 0.5 mmol, 2 equiv). After 18 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 10 mL). The combined extracts were concentrated under reduced pressure. Analysis of the crude residue showed a mixture of Hantzsch pyridine and the desired product (75% yield by NMR), which was confirmed by HRMS. The reaction mixture was then dissolved in 1:1 THF:H_2O before the addition of $NaBO_3$•$4H_2O$ (956 mg, 6.25 mmol, 25 equiv). The resulting slurry was stirred for 14 h before being quenched upon the addition of $Na_2S_2O_3$ (saturated solution, 5 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers dried over Na_2SO_4, filtered, and concentrated. Crude alcohol was purified by flash column chromatography (silica gel, 0 – 20% MeOH/CH_2Cl_2) to provide the desired product as a colorless oil (20 mg, 58% yield)

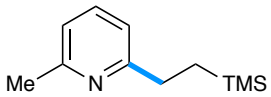
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 4.00 (t, *J* = 5.5 Hz, 2H), 2.97 (t, *J* = 5.5 Hz, 2H), 2.52 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.3, 157.6, 137.2, 121.2, 120.4, 62.1, 38.6, 24.5.

FTIR (neat) ν_{max}: 3349, 2925, 1596, 1578, 1459, 1235, 1046 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_8H_{12}ON$, 138.09134; found, 138.09128.

2-Methyl-6-(2-(trimethylsilyl)ethyl)pyridine (3-7)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and trimethyl(vinyl)silane (306 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 0 – 30% EtOAc/hexanes) to provide the desired product as a yellow oil (109 mg, 65% yield).

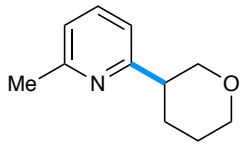
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 2.81 – 2.69 (m, 2H), 2.50 (s, 3H), 0.97 – 0.86 (m, 2H), 0.00 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 157.6, 136.6, 120.3, 118.7, 32.8, 24.7, 17.1, -1.6.

FTIR (neat) ν_{max}: 2951, 1591, 1578, 1454, 1246 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{20}NSi$, 194.13595; found, 194.13591.

2-Methyl-6-(tetrahydro-2*H*-pyran-3-yl)pyridine (3-8)



Prepared according to the General Procedure B using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and 3,4-dihydro-2*H*-pyran (254 µL, 252 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure B (silica gel, 20 – 50% EtOAc/hexanes) to provide the desired product as a yellow oil (125 mg, 72% yield).

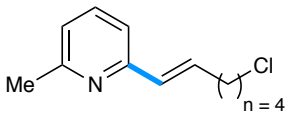
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.92 (m, 2H), 4.09 – 4.02 (m, 1H), 3.98 – 3.91 (m, 1H), 3.55 (t, *J* = 10.8 Hz, 1H), 3.47 (td, *J* = 11.2, 2.8 Hz, 1H), 2.97 (tt, *J* = 10.9, 4.0 Hz, 1H), 2.50 (s, 3H), 2.12 – 1.99 (m, 1H), 1.90 – 1.62 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 158.0, 136.6, 121.2, 118.6, 93.5, 72.5, 68.2, 44.8, 29.5, 25.9, 24.7.

FTIR (neat) ν_{max}: 2932, 2845, 1590, 1453, 1274, 1084 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{16}ON$, 178.12264; found, 315.12357.

2-(6-Chlorohex-1-en-1-yl)-6-methylpyridine (3-9)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and 5-chlorohex-1-yne (360 mg, 3 mmol, 3 equiv). Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 0 – 10% EtOAc/hexanes (cis isomer) then preparative reverse phase HPLC 30 – 99% $MeCN/H_2O$ with 1% TFA modifier (trans isomer)) to provide the cis alkene as a pale yellow oil (70 mg, 36% yield) and the trans alkene as a pale yellow oil (60 mg, 31%) 66% combined yield.

Trans alkene

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.67 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.49 (dd, *J* = 15.7, 1.6 Hz, 1H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.53 (s, 3H), 2.29 (qd, *J* = 7.2, 1.5 Hz, 2H), 1.85 (p, *J* = 6.7 Hz, 2H), 1.73 – 1.62 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.1, 155.5, 136.7, 134.6, 131.0, 121.4, 118.0, 45.1, 32.2, 32.1, 26.3, 24.7.

FTIR (neat) ν_{max}: 2928, 2860, 1581, 1571, 1453, 1157 cm^{-1}.

Cis alkene

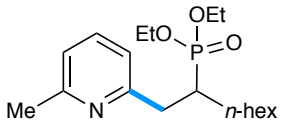
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 10.7 Hz, 1H), 5.83 (dtd, *J* = 11.7, 7.4, 0.9 Hz, 1H), 3.55 (td, *J* = 6.6, 0.8 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 3H), 1.88 – 1.78 (m, 2H), 1.67 – 1.60 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ158.0, 156.1, 136.3, 136.0, 129.5, 120.9, 120.9, 45.1, 32.3, 27.9, 26.9, 24.8.

FTIR (neat) ν_{max}: 2928, 2860, 1581, 1571, 1453, 1157 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{17}NCl$, 210.10440; found, 210.10445.

Diethyl (1-(6-methylpyridin-2-yl)octan-2-yl)phosphonate (3-10)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (11.4 µL, 17.2 mg, 0.1 mmol, 1 equiv), and diethyl oct-1-en-2-ylphosphonate (75 mg, 0.3 mmol, 3 equiv), Hantzsch ester (33 mg, 0.13 mmol, 1.3 equiv), cyclohexanethiol (0.6 µL, 0.005 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (0.9 mg, 0.001 mmol, 1 mol%), and NH_4Cl (10.6 mg, 0.2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 0 – 20% $MeOH/CH_2Cl_2$) to provide the desired product as a colorless oil (14 mg, 41% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.6 Hz, 1H), 6.97 (dd, *J* = 7.7, 2.0 Hz, 2H), 4.10 – 4.00 (m, 4H), 3.18 (ddd, *J* = 14.2, 11.9, 5.4 Hz, 1H), 2.81 (td, *J* = 14.3, 9.0 Hz, 1H), 2.51 (s, 3H), 2.50 – 2.44 (m, 1H), 1.70 – 1.66 (m, 2H), 1.52 – 1.40 (m, 2H), 1.31 – 1.22 (m, 11H), 0.83 (t, *J* = 7.1 Hz, 3H).

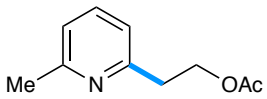
^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0 (d, J_{C-P} = 13.9 Hz), 156.8, 135.4, 119.8, 119.6, 60.6 – 60.3 (m), 36.2, 35.3, 34.4, 30.5, 28.2, 27.4 (d, J_{C-P} = 3.6 Hz), 26.4 (d, J_{C-P} = 7.7 Hz), 21.5, 15.4, 13.0.

^{31}P NMR (243 MHz, $CDCl_3$) δ 34.15.

FTIR (neat) ν_{max}: 2927, 2361, 2338, 1451, 1226, 1026 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{33}O_3NP$, 342.21926; found, 342.21991.

2-(6-Methylpyridin-2-yl)ethyl acetate (3-11)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), vinyl acetate (276 µL, 258 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 20 – 50% EtOAc/hexanes) to provide the desired product as a yellow oil (102 mg, 72% yield).

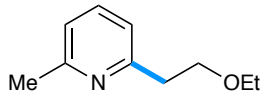
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.90 (m, 2H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.47 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 158.1, 157.2, 136.6, 121.2, 120.2, 63.8, 37.4, 24.4, 20.9.

FTIR (neat) ν_{max}: 2960, 1735, 1593, 1578, 1458, 1364, 1231 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{14}O_2N$, 180.10191; found, 180.10187.

2-(2-Ethoxyethyl)-6-methylpyridine (3-12)



Prepared according to the General Procedure B using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and ethoxyethene (287 µL , 216 mg, 1 mmol, 1 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv).

After 18 h, the reaction was purified according to the General Procedure B (silica gel, 20 – 50% EtOAc/hexanes) to provide the desired product as a yellow oil (103 mg, 62% yield).

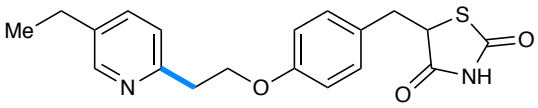
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 3.75 (t, *J* = 7.0 Hz, 2H), 3.48 (q, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.50 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 157.8, 136.5, 120.8, 120.3, 70.1, 66.2, 38.8, 24.5, 15.1.

FTIR (neat) ν_{max}: 2973, 2859, 2951, 1591, 1578, 1453, 1375 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{16}ON$, 166.12264; found, 166.12348.

Pioglitazone (3-13)



Prepared according to the General Procedure A using 2-bromo-5-ethylpyridine (93 mg, 0.5 mmol, 1 equiv), 5-(4-(vinyloxy)benzyl)thiazolidine-2,4-dione (375 mg, 1.5 mmol, 3 equiv), Hantzsch ester (164 mg, 0.65 mmol, 1.3 equiv), cyclohexanethiol (3 µL, 0.025 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (4.5 mg, 0.005 mmol, 1 mol%), NH_4Cl (53 mg, 2 mmol, 2 equiv) and 2,2,2-trifluoroethanol (10 mL, 0.05 M). After all reagents and solvents were added, the reaction misture was gently warmed until complete dissolution of all reagents. The reaction was then stirred at 1400 rpm at 30 °C for 18 h. After this time, the reaction was purified according to the General Procedure A (silica gel 30 – 80% EtOAc/hexanes) to provide the desired product as an amorphous white solid (114 mg, 64%).

^{1}H NMR (600 MHz, THF-d_8) δ 10.74 (br. s, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 4.60 (dd, *J* = 9.7, 4.0 Hz, 1H), 4.31 (t, *J* = 6.8 Hz, 2H), 3.39 (dd, *J* = 14.1, 4.0 Hz, 1H),

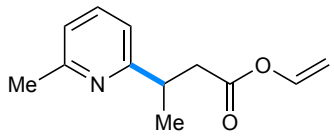
3.16 (t, J = 6.8 Hz, 2H), 3.01 (dd, J = 14.1, 9.7 Hz, 1H), 2.61 (d, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H).

^{13}C NMR (151 MHz, THF-d_8) δ 175.8, 171.3, 159.5, 157.0, 149.9, 137.8, 136.3, 131.2, 129.9, 123.9, 115.4, 68.1, 54.7, 38.6, 38.4, 26.6, 16.0.

FTIR (neat) ν_{max}: 2924, 1691, 1665, 1605, 1331, 1250, 1137 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{21}O_3N_2S$ 357.12674; found, 357.12680.

Vinyl 3-(6-methylpyridin-2-yl)butanoate (3-14)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (114 µL, 172 mg, 1 mmol, 1 equiv), and vinyl crotonate (364 µL, 336 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), Ir[ppy]$_2$dtbbpy•PF$_6$ (9.1 mg, 0.01 mmol, 1 mol%) in 10 mL DMSO:H_2O 3:1(0.1 M). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 10 – 50% EtOAc/hexanes) to provide the desired product as a pale yellow oil (115 mg, 56% yield).

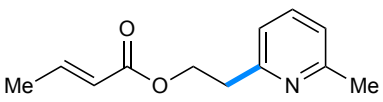
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (t, J = 7.7 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.97 (t, J = 8.6 Hz, 2H), 4.84 (d, J = 14.0 Hz, 1H), 4.53 (d, J = 6.2 Hz, 1H), 2.97 (dd, J = 16.0, 7.3 Hz, 1H), 2.66 (dd, J = 16.0, 7.3 Hz, 1H), 2.50 (s, 3H), 1.34 (d, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ170.0, 163.4, 158.0, 141.3, 136.7, 121.1, 118.4, 97.6, 40.6, 37.9, 24.7, 20.8.

FTIR (neat) ν_{max}: 2964, 2923, 1722, 1572, 1443, 1370 1177 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{16}O_2N$, 206.11756; found, 206.11753

2-(6-Methylpyridin-2-yl)ethyl (E)-but-2-enoate (3-15)



Prepared according to the General Procedure A using 2-bromo-6-methylpyridine (114 μL, 172 mg, 1 mmol, 1 equiv), and vinyl crotonate (364 μL, 336 mg, 3 mmol, 3 equiv), Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv), cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%), $Ir[ppy]_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 1 mol%), and NH_4Cl (106 mg, 2 mmol, 2 equiv). After 18 h, the reaction was purified according to the General Procedure A (silica gel, 10 – 50% EtOAc/hexanes) to provide the desired product as a pale yellow oil (147 mg, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 2H), 6.94 (dq, *J* = 15.6, 7.0 Hz, 1H), 5.81 (dd, *J* = 15.5, 1.8 Hz, 1H), 4.48 (t, *J* = 6.8 Hz, 2H), 3.10 (t, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 1.85 (dd, *J* = 6.9, 1.8 Hz, 3H).

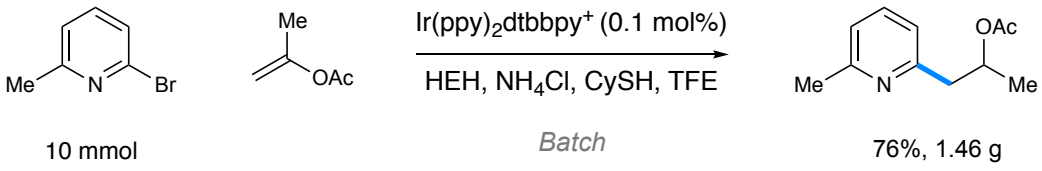
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 158.2, 157.6, 144.8, 136.8, 122.8, 121.3, 120.5, 63.7, 37.6, 24.6, 18.1.

FTIR (neat) ν_{max}: 2923, 2853, 1717, 1635, 1457, 1179 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{16}O_2N$, 206.11756; found, 206.11753

3.6-VII. Scale up

Batch scale up to 10 mmol



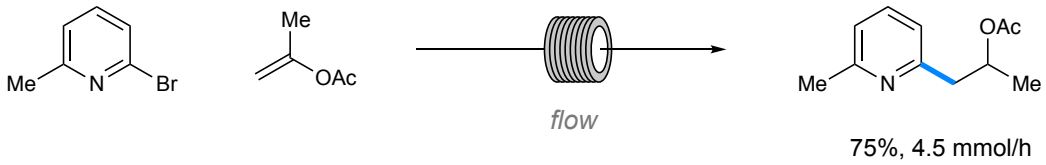
A flame dried 250 mL Schlenk tube equipped with a stir bar was charged with $Ir(ppy)_2dtbbpy•PF_6$ (9.1 mg, 0.01 mmol, 0.1 mol%), Hantzsch ester (3.3 g, 13 mmol, 1.3 equiv), NH_4Cl (1.1 g, 20 mmol, 2 equiv). The tube was sealed with a rubber septum and the atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with

prop-1-en-2-yl acetate (3.25 mL, 3 g, 30 mmol, 3 equiv), 2-bromo-6-methylpyridine (1.14 mL, 1.72 g, 1 mmol, 1 equiv), cyclohexanethiol (60 µL 0.5 mmol, 5 mol%), and separately degassed 2,2,2-trifluoroethanol (100 mL, 0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED array. The crude reaction mixture was quenched with saturated sodium bicarbonate (100 mL) and extracted with dichloromethane (3 x 100 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20 – 50% EtOAc/hexanes) to provide the desired product as a yellow oil (1.46 g, 76% yield).

3.6-VIII. Flow synthesis

3D printed flow reactor

A custom built, 3D printed, photo-flow reactor was used for this experiment. Vapourtec tubing was used, with 450 nm Blue LEDs. The residence volume of the reactor was 20 mL.



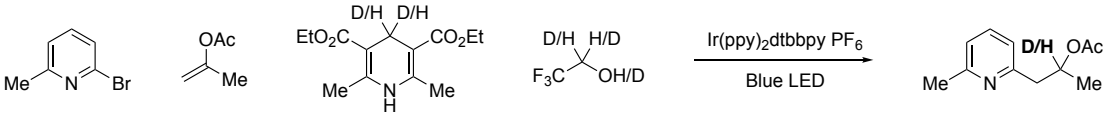
A 50 mL round bottomed flask was charged with $Ir(ppy)_2dtbbpy•PF_6$ (18.2 mg, 0.02 mmol, 1 mol%), Hantzsch ester (660 mg, 2.6 mmol, 1.3 equiv). The tube was sealed with a rubber septum and the atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with prop-1-en-2-yl acetate (650 µL, 600 mg, 6 mmol, 3 equiv), 2-bromo-6-methylpyridine (228 µL, 344 mg, 2 mmol, 1 equiv), and separately degassed 2,2,2-trifluoroethanol (20 mL, 0.1 M) via syringe. The solution was stirred until complete dissolution of the solids. The reaction solution was removed by syringe, placed into a syringe pump shielded from extraneous light, and attached to the inlet of the flow reactor.

The flow reactor, which had been pre-equilibrated with 20 mL of 2,2,2-trifluoroethanol, was switched on and the reaction solution was pumped through at 1 mL/min with the outlet draining into a 250 mL round bottomed flask. After complete addition of the reaction solution, a second syringe of 20 mL of 2,2,2-trifluoroethanol was pumped through the flow reactor at 1 mL/min.

The resulting solution was concentrated at reduced pressure and purified by flash column chromatography (silica gel, 20 – 50% EtOAc/hexanes) to provide the desired product as a yellow oil (288 mg, 75% yield).

3.6-IX. Mechanistic Investigation

1) Deuterium labeling study.



General procedur

An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with Ir(ppy)$_2$dtbbpy•PF_6 (0.9 mg, 1 mol%, 0.001 mmol) and Hantzsch ester (33 mg, 1.3 equiv, 0.13 mmol). The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with prop-1-en-2-yl acetate (33 µL, 30 mg, 3 equiv, 0.3 mmol), 2-bromo-6-methylpyridine (11 µL, 17 mg, 1 equiv, 0.1 mmol), and separately degassed 2,2,2-trifluoroethanol (1 mL, 0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was quenched with saturated sodium bicarbonate and extracted with dichloromethane (3 x 20 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR before purification. The

crude residue was then purified by preparatory TLC (silica gel, 40% EtOAc/Hexanes) to provide the desired product. ^{1}H NMR analysis was used to determine the % D incorporation.

Experiment 1 – HEH-D_2

Prepared according to the general procedure using Hantzsch ester-D_2 (33 mg, 1.3 equiv, 0.13 mmol). ^{1}H NMR analysis showed 83% deuterium incorporation.

Experiment 2 – HEH-D_2 + CySH

Prepared according to the general procedure using Hantzsch ester-D_2 (33 mg, 1.3 equiv, 0.13 mmol) and cyclohexane thiol (0.6 μL, 5 mol%, 0.005 mmol). ^{1}H NMR analysis showed 21% deuterium incorporation.

Experiment 3 – CF_3CH_2OD

Prepared according to the general procedure using CF_3CH_2OD (1 mL). ^{1}H NMR analysis showed <5% deuterium incorporation.

Experiment 4 – CF_3CD_2OH

Prepared according to the general procedure using CF_3CD_2OH (1 mL). ^{1}H NMR analysis showed 0% deuterium incorporation.

2) Stern – Volmer Quenching

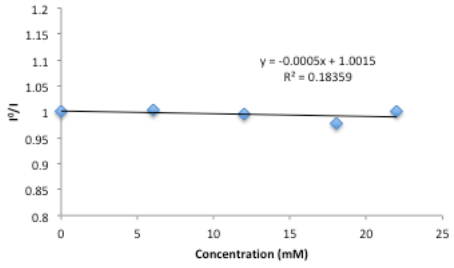
Quenching studies performed according to the procedure of MacMillan.[55]

Photocatalyst (1.2 μmol) was dissolved in 2,2,2-trifluoroethanol (or isopropanol) (5.0 mL) to prepare a 0.24 mM solution. This solution (0.95 mL) was then diluted to a volume of 46 mL by adding further 2,2,2-trifluoroethanol (or isopropanol). The resulting 5.0 μM solution (1.6 mL) was added to each of a set of 4 mL reaction vials fitted with PTFE-faced silicon septa. A stock solution of quencher (0.25 mmol) in 2,2,2-trifluoroethanol (or isopropanol) (5.0 mL, 50 mM in quencher) was added in increasing amounts (0, 0.40, 0.80, 1.20, and

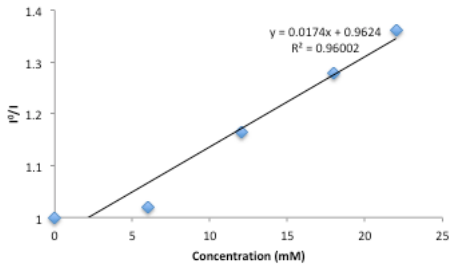
[55]Nacsa, E. D.; MacMillan, D. W. C., Spin-Center Shift-Enabled Direct Enantioselective α-Benzylation of Aldehydes with Alcohols. *Journal of the American Chemical Society* **2018,** *140*, 3322-3330.

1.6 mL) to the vials containing the photocatalyst solution, and the volume for each vessel was adjusted to 3.2 mL by adding the necessary amount of 2,2,2-trifluoroethanol (or isopropanol) (1.6, 1.2, 0.80, 0.40, and 0.0 mL). The resulting mixtures were sparged with nitrogen for 15 minutes, then irradiated at 450 nm. The fluorescence emission spectra (3 trials per sample) were recorded. The ratio of the maximum fluorescence emission intensities maximum between samples without and with quencher were plotted against the quencher concentration to generate the Stern-Volmer plots below.

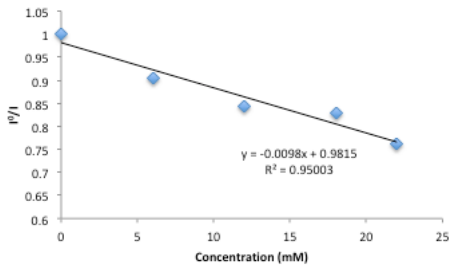
1) 2-Bromo-6-methylpyridine in isopropyl alcohol



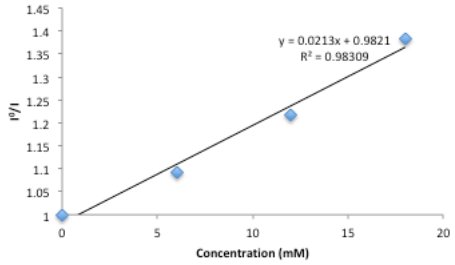
2) 2-bromo-6-methylpyridine in 2,2,2-trifluoroethanol



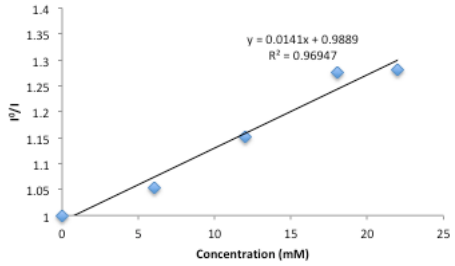
3) Prop-1-en-2-yl acetate in 2,2,2-trifluoroethanol



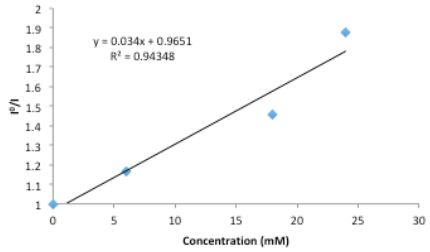
4) Hantzsch ester in 2,2,2-trifluoroethanol



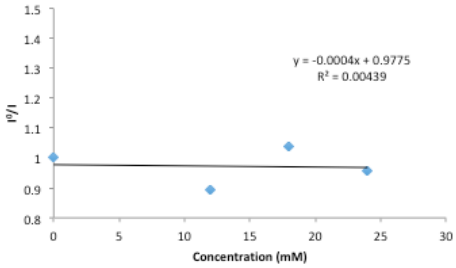
5) 4-Bromopyridine hydrochloride in 2,2,2-trifluoroethanol



6) 2-Bromo-6-methylpyridine in 2,2,2-trifluoroethanol with *fac*-Ir(ppy)$_3$



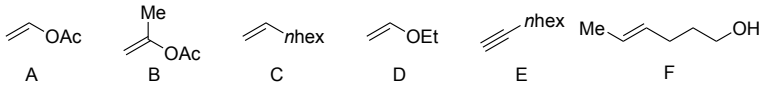
7) 2-Bromo-6-methylpyridine in DMSO:H_2O with *fac*-Ir(ppy)$_3$



3) Competition experiments

A wide range of electronically differentiated alkenes were effective in this reaction manifold, however, small steric contributions (1,2 trans alkenes) were not well tolerated, apart form in the most simple cases (see below). Since radical-olefin addition is often

highly tolerant of steric effects, based on an early transition state, we decided to investigate the effect that olefin stereo-electronics had on the reaction outcome. A small set of 1:1 competition reactions were undertaken to access the primary contributors to reaction success.



A B C D E F

Primary neutral alkene C, which has minimal steric contributions, was reacted in the presence of alkenes A, and D, which share a similar steric profile, yet differ electronically. Octene alkylation provided the major product in both cases, consistent with a more stable radical formed upon addition (alkyl vs. α-oxy). More electron rich ethoxyethene was more competitive than vinyl acetate, consistent with a greater stabilization of the resulting C-centred radical through the neighboring lone pair on oxygen. Comparison of vinyl acetate and isopropenyl acetate (1-, vs 1,1-di substitution) demonstrated the effect of increasing radical stability in otherwise similar systems, with the 1,1-disubstituted alkene providing low levels of chemoselectivity versus primary alkene A. Our scoping exercise in the alkene component showed that internal acyclic olefins were poorly tolerated. This was observed across a range of alkenes although the simplest example, Alkene F above did work effectively. Chemoselectivity experiments using this alkene showed it to be outcompeted by 1-octene but give a 50:50 mixture with isopropenyl acetate.

In line with these observations, a cyclic 1,2-disubstituted alkene was outcompeted by primary olefin D. These data suggest that both steric and electronic factors influence the reaction course. In systems where the steric barrier is low, alkene electronics play a significant, observable role; consistent with a mid to late transition state.

To determine information about which properties of the alkene-coupling partner (steric or electronic) most influence the fate of the reaction a number of competition experiments were performed.

Alkenes of similar steric properties, but different electronic properties (and *vice versa*) were compared to define the impact of alkene stereoelectronics on reaction efficiency. An excess of both alkenes was used to minimize any developing concentration gradient.

General procedure

An oven-dried screw-top test tube equipped with a stir bar was sealed with a PTFE-faced silicon septa and cooled to room temperature under N_2 atmosphere. The tube was charged with $Ir(ppy)_2dtbbpy•PF_6$ (0.9 mg, 1 mol%, 0.001 mmol) and Hantzsch ester (33 mg, 1.3 equiv, 0.13 mmol). The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with alkene 1 (3 equiv, 0.3 mmol), alkene 2 (3 equiv, 0.3 mmol), 2-bromo-6-methylpyridine (11 μL, 17 mg, 1 equiv, 0.1 mmol), and separately degassed 2,2,2-trifluoroethanol (1 mL, 0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The crude reaction mixture was quenched with saturated sodium bicarbonate and extracted with dichloromethane (3 x 20 mL). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR to determine the ratio of products.

Octene vs vinyl acetate

Prepared according to the general procedure using 1-octene (47 μL, 34 mg, 3 equiv, 0.3 mmol) and vinyl acetate (28 μL, 26 mg, 3 equiv, 0.3 mmol). ^1H NMR analysis showed a ratio of 75:25 in favor of the 1-octene addition product.

Octene vs ethoxyethene

Prepared according to the general procedure using 1-octene (47 μL, 34 mg, 3 equiv, 0.3 mmol) and ethoxyethene (29 μL, 22 mg, 3 equiv, 0.3 mmol). ^1H NMR analysis showed a ratio of 60:40 in favor of the 1-octene addition product.

Vinyl acetate vs prop-1-en-2-yl acetate

Prepared according to the general procedure using vinyl acetate (28 μL, 26 mg, 3 equiv, 0.3 mmol) and prop-1-en-2-yl acetate (33 μL, 30 mg, 3 equiv, 0.3 mmol). ^{1}H NMR analysis showed a ratio of 59:41 in favor of the prop-1-en-2-yl acetate addition product.

Ethoxyethene vs 3,4-dihydro-2*H*-pyran

Prepared according to the general procedure using ethoxyethene (29 μL, 22 mg, 3 equiv, 0.3 mmol) and 3,4-dihydro-2*H*-pyran (26 μL, 25 mg, 3 equiv, 0.3 mmol). ^{1}H NMR analysis showed a ratio of 63:37 in favor of the ethoxyethene addition product.

Octene vs octyne

Prepared according to the general procedure using 1-octene (47 μL, 34 mg, 3 equiv, 0.3 mmol) and 1-octyne (44 μL, 33 mg, 3 equiv, 0.3 mmol). ^{1}H NMR analysis showed a ratio of 71:29 in favor of the 1-octene addition product.

(*E*)-Hex-4-en-1-ol vs prop-1-en-2-yl acetate

Prepared according to the general procedure using prop-1-en-2-yl acetate (33 μL, 30 mg, 3 equiv, 0.3 mmol) and (*E*)-hex-4-en-1-ol (35 μL, 30 mg, 3 equiv, 0.3 mmol). ^{1}H NMR analysis showed a ratio of 50:50.

(*E*)-Hex-4-en-1-ol vs 1-octene

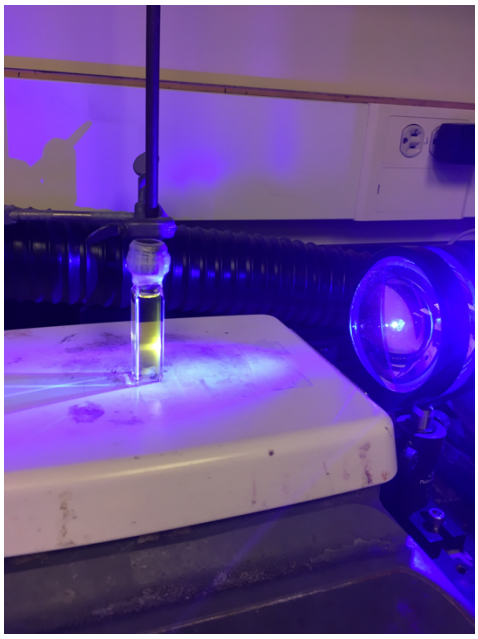
Prepared according to the general procedure using 1-octene (47 μL, 34 mg, 3 equiv, 0.3 mmol) and (*E*)-hex-4-en-1-ol (35 μL, 30 mg, 3 equiv, 0.3 mmol). ^{1}H NMR analysis showed a ratio of 86:14 in favor of the 1-octene addition product.

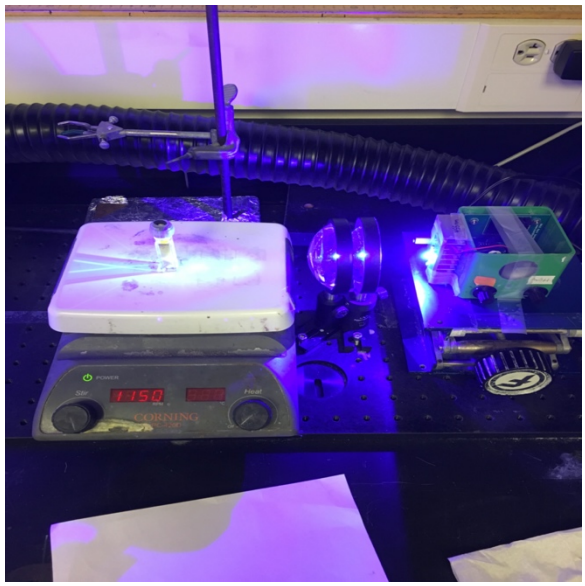
6) Quantum yield

In an Ar filled glovebox, a reaction vial was charged with $Ir(ppy)_2dtbbpy•PF_6$ (9.1 mg, 1 mol%, 0.01 mmol), Hantzsch ester (329 mg, 1.3 equiv, 1.3 mmol), prop-1-en-2-yl acetate (325 μL, 300 mg, 3 equiv, 3 mmol), 2-bromo-6-methylpyridine (114 μL, 172 mg, 1 equiv, 1 mmol), and separately degassed 2,2,2-trifluoroethanol (10 mL, 0.1 M). The mixture was

agitated until fully homogenized, and 3.5 mL of the solution was transferred to a 3.5 mL screw-top quartz cuvette fitted with a stir bar. The cuvette was sealed with a screw top fitted with a PTFE-faced silicon septa and removed from the glovebox.

Evaluation of the quantum yield was performed using a blue 455 nm LED that was focused on the quartz cuvette using Thorlabs optics (see picture below). 100 µL aliquots were removed via syringe every 5 minutes (0, 5, 10, 15, 20, 25, 30 mins). 10 µL of each aliquot was diluted with 2,2,2-trifluoroethanol (5 mL) and the UV/Vis spectra were recorded (Figure below). The consumption of Hantzsch ester was readily monitored with this method, and product formation could be monitored by ^{1}H NMR analysis of the same aliquots. After an initial burst phase, steady state, linear kinetics were observed. The quantum yield was determined from the steady state portion of the reaction.





The quantum yield (QY) was defined as the ratio between the amount of electrons consumed during the reaction and the total number of photons absorbed by the photosensitizer. QY can be determined through the following equations.

The photon flux was calculated based on the LED illumination power at the focal point of the LED right before the sample with a Ophir Starlite power meter with a 3A thermal sensor.

First, the number of photons, *n,* arrived onto the sample per second from the 455nm LED per second could be calculated as

$$n = E/hv$$

Where E = 90.9mW (455nm LED power before the sample)

h = Planck constant = 6.626 x 10^{-34} Js

v = frequency of the 455nm photon

$$v = c/\lambda$$

Where c = speed of light = 2.998 x 10^{8} ms^{-1}

λ = wavelength (455 nm = 455 x 10^{-9} m)

$$v = {}^{2.998 * 10\text{-}\wedge 8}/_{455 * 10\wedge - 9}$$

v = 6.589 x 10^{14}

So number of photons =

$$n = \frac{0.0909}{6.626 \text{ x } 10^{-34} * 6.589 \text{ x } 10\wedge 14}$$

n = 2.082 *10^{17} photons per sec

The amount of photons absorbed by the sample per minute n^* can be calculated based on the absorbance of the sample at 455nm A_{455} from Beer-Lambert law.

A_{455}=0.866 (taken from UV/Vis spectra–relative to Ir conc at t=0 should not change during the reaction, this tells us the amount of light Ir absorbs)

$$n^* = 60n(1 - 10^{-A_{455}})$$

n^* = 1.079*10^{19} photons absorbed per minute

The gradient of the slope derived from ^{1}H NMR analysis is equal to conc per min * vol = mol%min

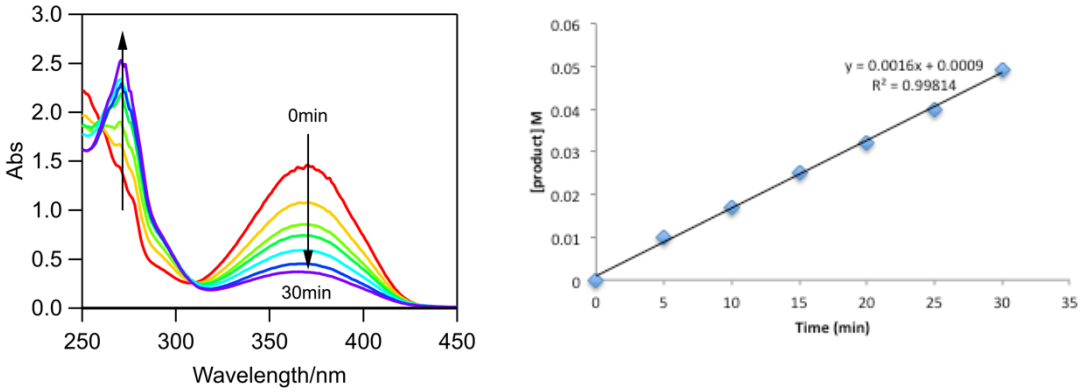
0.0016 mol/min = slope

(slope) * (3.5/1000) = 5.6 x10^{-6} M * Avogadro gives no. electrons

= 3.372*10^{17}

As defined, the QY can be calculated as

$$QY = \frac{ne}{n_*} \times 100\% = 31\%$$



Graph 1: Temporal profile by NMR (left) and UV/Vis (right

Aycock, R. A.; Wang, H.; Jui, N. T., A mild catalytic system for radical conjugate addition of nitrogen heterocycles. *Chem. Sci.* **2017,** *8*, 3121-3125.

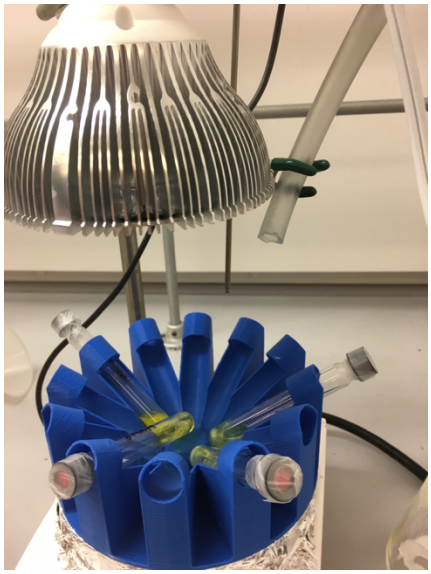
IX. General reaction set up

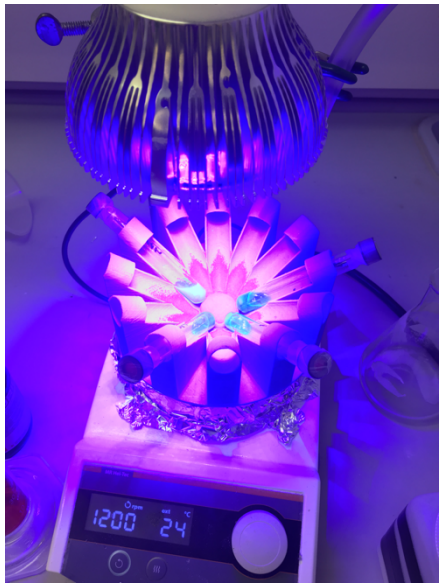
All reactions were performed in glass reaction vials as seen in picture 1. To run multiple reactions a 3D printed carousel was used, which exposed the reactions to the blue light evenly (picture 2).

A 15 W LED array lamp was used as a blue light source. We found these lamps to be extremely effective, particularly in comparison to standard LED strips. These lamps were routinely used for up to 12 reactions at a time (picture 3).

Our photoredox reactions were cooled with a line of compressed air (picture 4)

The blue LED was positioned approximately 6 inches above the reaction vials, to get good light coverage but without overheating the reactions.

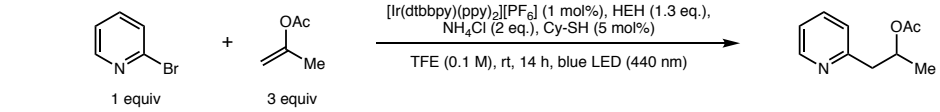




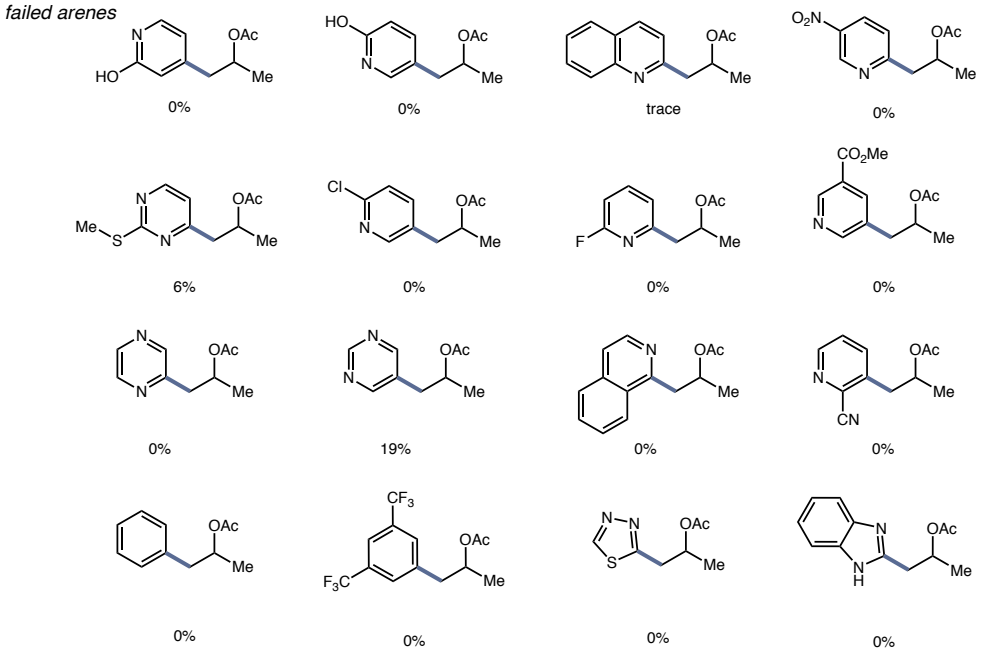
3.6-X. Reaction Limitations

The reaction scope, while broad, has many limitations. A representative portion of the (het)arenes and alkenes that were not tolerated under the reaction conditions are shown below.

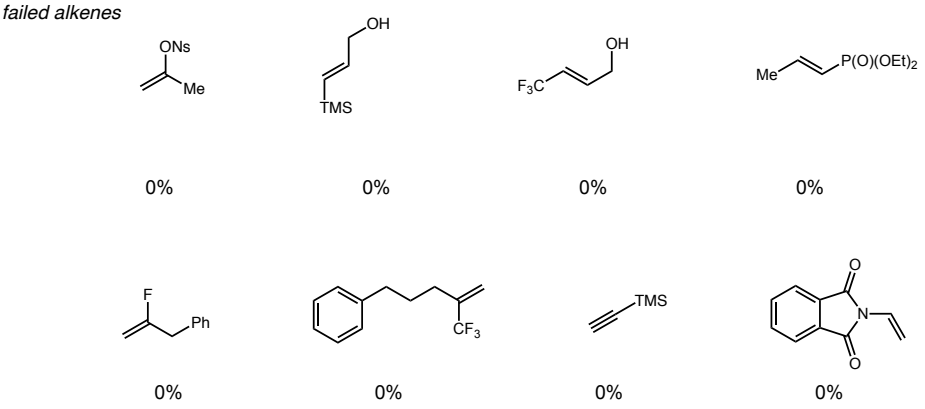
Table 8: Reaction limitations



failed arenes



failed alkenes



Chapter 4:

Photocatalytic strategy for complex arylethylamine synthesis via aryl radical intermediates

4.1 Arylethylamines: a highly privileged pharmacophore

Arylethylamines are a prominent building block in numerous compounds of biological importance such as native neurotransmitters, natural products, pharmaceuticals, and agrochemicals (Figure 10). Historically, the synthesis of this scaffold has been accomplished using classical methods such as amino acid decarboxylation and reductive amination. Modern techniques such as cross-coupling have been employed, however, these methods often require harsh reaction conditions, lack functional group compatibility, and require functionalized precursors and/or multiple steps. The ability to form the arylethylamine core with synthetic flexibility from readily available starting materials remains limited. Ideally, catalytic methods that allow for variation of the aryl unit (including heteroarenes), ethyl chain, and substitution on the nitrogen-atom would be synthetically useful for developing new arylethylamine derivatives and decreasing the number of synthetic steps required for established compounds.

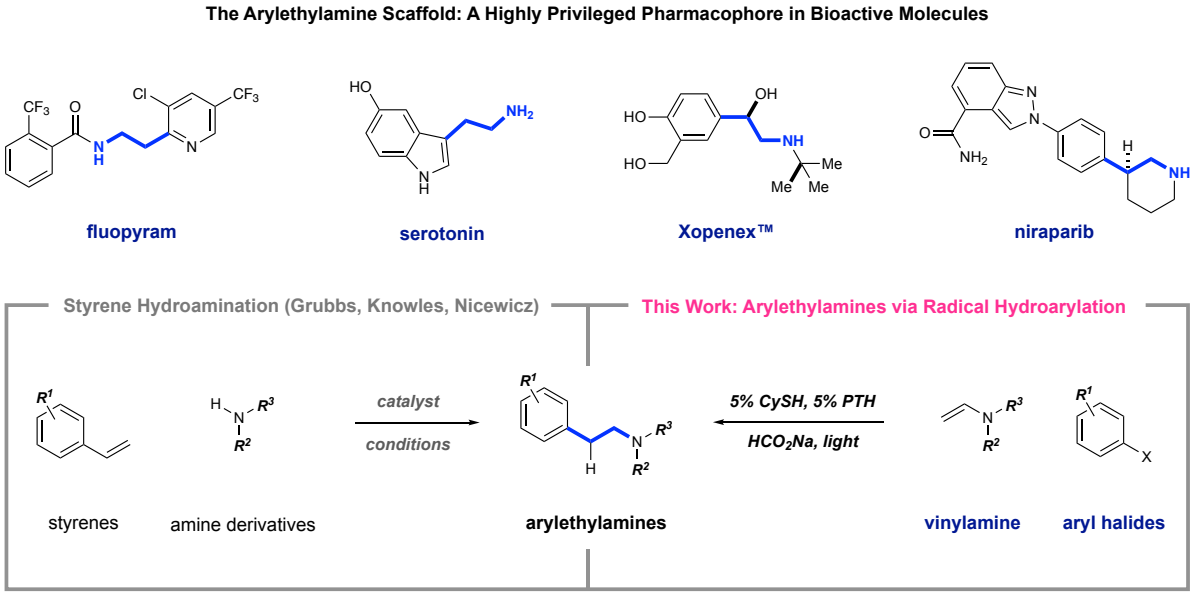


Figure 10: Complementary strategies to the arylethylamine scaffold

To achieve this goal, powerful methods for intermolecular anti-Markovnikov styrene hydroamination have recently been reported. Using this strategy, *N,N*-dialkylamines,[56,57,58,59] *N*-arylamines,[60] or sulfonamides[61,62] couple with styrene derivatives to give the arylethylamine product (Figure 10). We became interested in developing a complementary method for vinylamine hydroarylation. Specifically, an aryl radical would be able to add to an olefin for a wide variety of vinylamine derivatives in an anti-Markovnikov fashion, terminate the resulting alpha-amino radical with a hydrogen atom, to deliver the desired arylethylamine product. We identified aryl halides as optimal radical precursors as they are readily available, stable, and the reduction of an aryl halide to the corresponding aryl radical is well precedented.

4.2 Aryl radicals as synthetic intermediates

Aryl radicals are extremely reactive synthetic intermediates that have the ability to couple with a wide range of radical acceptors. Work from Stephenson[7], König[9,63], and Read de Alaniz and Hawker[10], and Weaver[64] has demonstrated the successful formation of an aryl radical from an aryl halide under photoredox conditions. The aryl radical then either rapidly gains an H-atom from the stoichiometric reductant (typically trialkyl amines), undergoes an intramolecular cyclization

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[56] Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F., Rhodium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *Journal of the American Chemical Society* **2003,** *125*, 5608-5609.
[57] Utsunomiya, M.; Hartwig, J. F., Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *Journal of the American Chemical Society* **2004,** *126* (9), 2702-2703.
[58] Basalov, I. V.; Roşca, S. C.; Lyubov, D. M.; Selikhov, A. N.; Fukin, G. K.; Sarazin, Y.; Carpentier, J. F.; Trifonov, A. A., Divalent heteroleptic ytterbium complexes - Effective catalysts for intermolecular styrene hydrophosphination and hydroamination. *Inorganic Chemistry* **2014,** *53* (3), 1654-1661.
[59] Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R., Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **2017,** *355* (6326), 727-730.
[60] Bronner, S. M.; Grubbs, R. H., Formal anti-Markovnikov hydroamination of terminal olefins. *Chemical Science* **2014,** *5* (1), 101-106.
[61] Nguyen, T. M.; Manohar, N.; Nicewicz, D. A., Anti-markovnikov hydroamination of alkenes catalyzed by a two-component organic photoredox system: Direct access to phenethylamine derivatives. *Angewandte Chemie - International Edition* **2014,** *53* (24), 6198-6201.
[62] Monos, T. M.; Mcatee, R. C.; Stephenson, C. R. J., Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylation. *Science* **2018,** *361*, 1369-1373.
[63] Bardagi, J. I.; Ghosh, I.; Schmalzbauer, M.; Ghosh, T.; König, B., Anthraquinones as Photoredox Catalysts for the Reductive Activation of Aryl Halides. *European Journal of Organic Chemistry* **2018,** *2018* (1), 34-40.
[64] Arora, A.; Weaver, J. D., Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates. *Accounts of Chemical Research* **2016,** *49* (10), 2273-2283.

with an olefin, or adds to an activated aromatic ring coupling partner to give a biaryl product (Figure 11). While much work has been done on the successful formation of aryl radicals from aryl halides, generalizable protocols for intermolecular reactions remain limited. Difficulty lies in the low (very negative) reduction potentials of the aryl halides, requiring a highly reducing photocatalyst, and the propensity of the aryl radical to rapidly undergo hydrogen atom transfer (HAT) to give the dehalogenated product.

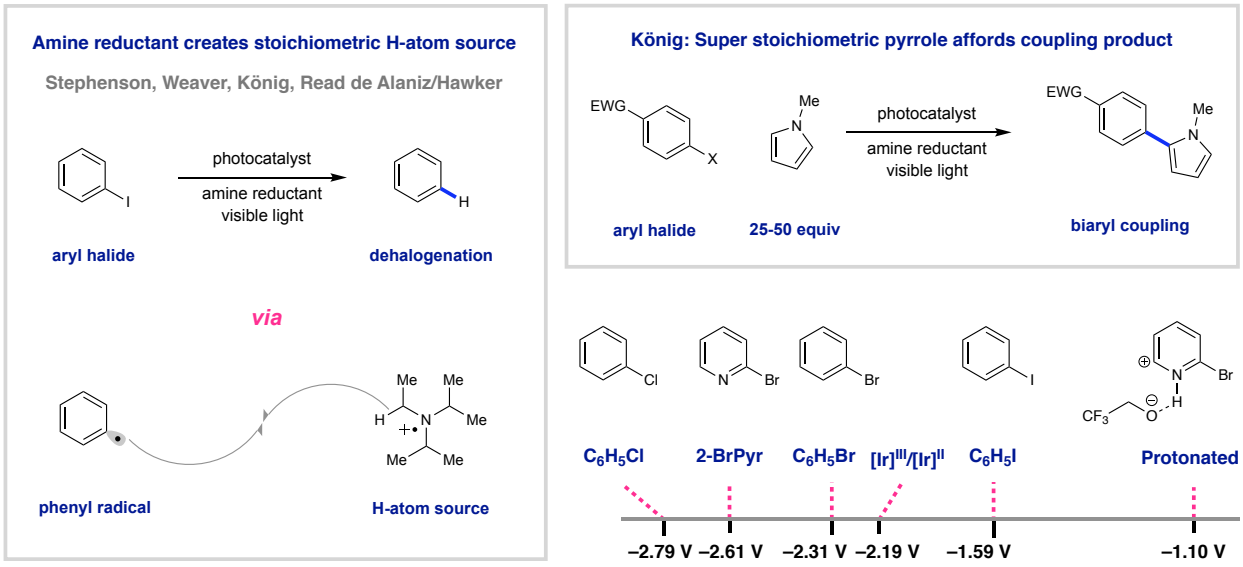


Figure 11: Strategies for overcoming very negative reduction potentials of aryl halides and rapid HAT to the aryl radical

Building on previous reports from our lab and others, we were inspired to develop a photoredox system for the coupling of aryl radicals with vinylamines. This system would require both a powerful catalytic reductant that is capable of reducing aryl halides (ideally Ar-I, -Br, and -Cl), and a catalytic hydrogen atom source such that intermolecular reactivity outcompetes the rate of HAT. Reports from Stephenson[7] and Weaver[8] successfully utilize iridium-based photocatalysts which, after reductive quenching, are reducing enough to form the aryl radical from an aryl halide radical precursor. While strongly reducing in the ground state, the reductive quenching mechanism also generates a stoichiometric H-atom source (typically from oxidation of the trialkylamine)

causing rapid HAT to the aryl halide. Because of this, we reasoned that a catalyst that is strongly reducing in the excited state that could directly undergo single electron transfer (SET) to reduce the aryl halide, and then be reduced to the ground state by a sacrificial reductant, would be ideal. Accordingly, we reasoned that *N*-phenylphenothiazine (PTH) with sodium formate (NaO_2CH) as the reductant and cyclohexane thiol (CySH) as the H-atom source could operate in concert to furnish the desired arylethylamine product.

In the excited state, PTH, developed by Hawker and Read de Alaniz, is strongly reducing ($E_{1/2}^* = -2.10$ V vs SCE) and has demonstrated the successful reduction of aryl iodides, bromides, and more activated aryl chlorides.[10] However, the resulting aryl radical rapidly abstracts an H-atom from the tributylamine additive to give HDH products. A singular example of an intramolecular radical cyclization with an olefin is reported, but intermolecular addition is a limitation. By using formate and thiol as electron and H-atom sources, respectively, we envisioned a dual catalytic cycle that would circumvent HAT to the aryl radical, allowing for intermolecular reactivity.[65]

4.3 Reaction development for arylethylamine synthesis via aryl radicals

When we began our studies, we selected an olefin that would allow for facile manipulation of the arylethylamine nitrogen. *t*-Butylvinylcarbamate was selected as an optimal substrate as it is easily boc-deprotected to give the free amine. While this olefin had historically been synthesized using a Curtius rearrangement, the reported yields were low and, on a large scale, this reaction poses an explosion hazard (Figure 12).[66] Although this chemical is commercially available, it requires a 4-week lead time and is costly ($240/1 g CombiBlocks). To circumvent the potential

[65] Wang, H.; Jui, N. T., Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *Journal of the American Chemical Society* **2018,** *140*, 163-166.
[66] Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S., Highly Enantioselective Synthesis of Cyclopropylamine Derivatives via Ru(II)-Pheox-Catalyzed Direct Asymmetric Cyclopropanation of Vinylcarbamates. *Org. Lett.* **2013,** *15* (4), 772-775.

scale-up issues with the Curtius rearrangement, we developed a gram-scale, one-pot synthesis from cheap precursors. The boc-protection of *N*-vinylformamide and then subsequent hydrolysis of the formamide under basic conditions (3 N LiOH) with heat provides the desired product in high yields (~80-90%) on large sale (15 g). This method requires no purification, no hazardous reagents, and gives the key substrate from cheap starting materials on a large scale.

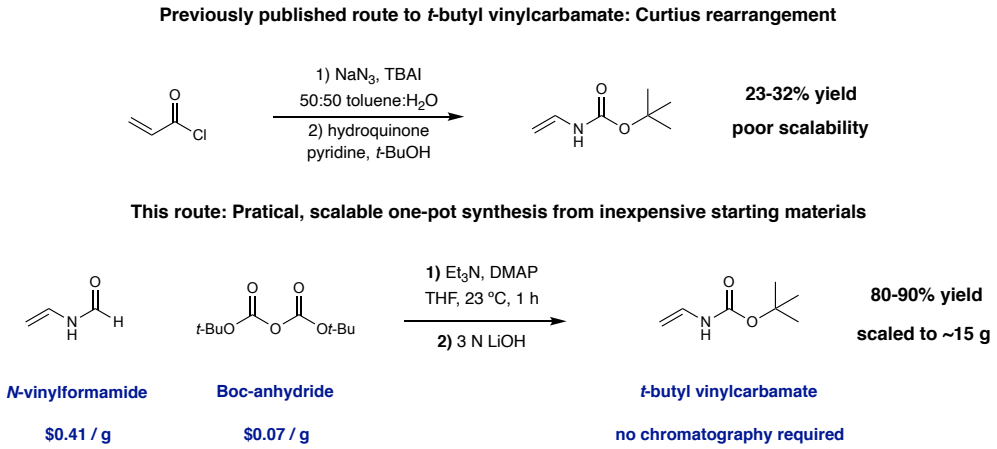


Figure 12: Facile synthesis of *t*-butyl vinylcarbamate

Initially, we found that iodobenzene effectively reacts with *t*-butylvinylcarbamate (2.5 equiv) in the presence of sodium formate (3 equiv) and 5 mol% of each catalyst under irradiation with commercial blue LEDs in aqueous DMSO. The desired arylethylamine product was formed as a single regioisomer (no branched, Markovnikov product) in 82% isolated yield. Our mechanistic proposal supports this initial result where photoexcited PTH ($E_{1/2}$* = –2.10 V vs SCE)[10] undergoes SET to activate iodobenzene ($E_{1/2}^0$ = –1.51 to –2.20 V vs SCE)**Error! Bookmark not defined.** which gives rise to the corresponding radical anion (Figure 13). Following mesolytic cleavage to expel iodide, the aryl radical then engages the olefin via regioselective intermolecular addition to the vinylcarbamate substrate which gives the α-carbamoyl radical. This nucleophilic radical, in turn, undergoes polarity-matched HAT from the

electrophilic thiol catalyst delivering the desired protected arylethylamine product.[67] Both catalysts are regenerated via HAT and SET to liberate inert byproducts CO_2 and NaI from sodium formate.

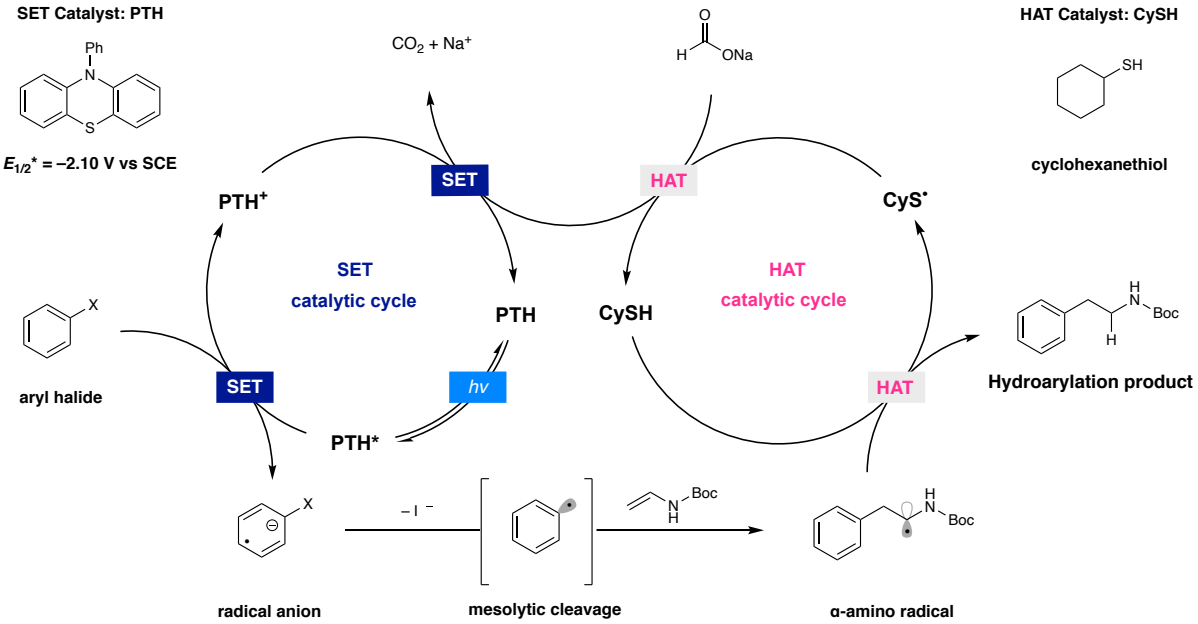


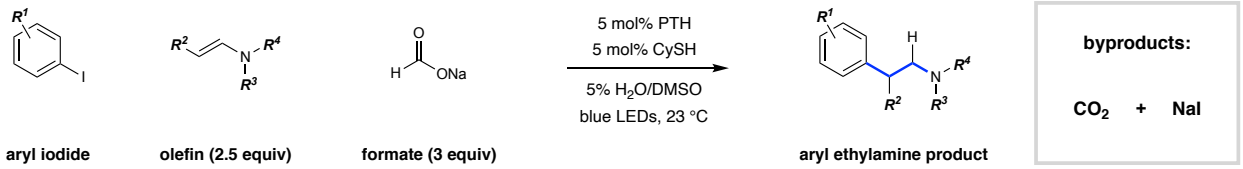
Figure 13: Proposed dual catalytic cycle

The mechanistic hypothesis was further supported by Stern-Volmer quenching experiments which demonstrated that the only reaction component that quenches the excited state of PTH is the aryl halide. In order to gain more insight into the potential for radical chains to contribute to the mechanism, we measured the quantum yield of the process. While $\Phi = 0.29$ is consistent with our hypothesized photosensitized mechanism ($\Phi < 1$), radical chains could still contribute to the formation of the arylethylamine product.[44] Not only are these conditions metal-free, but the inert byproducts of CO_2 and NaI allow for simple and rapid purification of the target molecule.

[67] Roberts, B. P., Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999,** (28), 25-35.

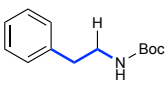
4.4 Reaction scope

Table 9: Hydroarylation scope to form arylethylamine derivatives

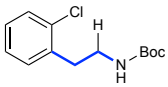


aryl iodide | olefin (2.5 equiv) | formate (3 equiv) | aryl ethylamine product

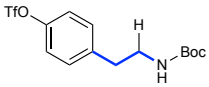
aryl iodide scope



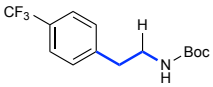
4-1: 82% yield



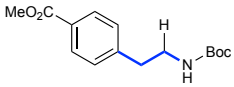
4-2: 70% yield



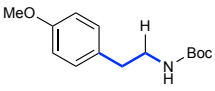
4-3: 88% yield



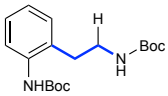
4-4: 85% yield



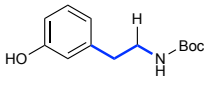
4-5: 73% yield



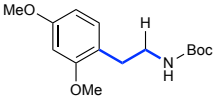
4-6: 61% yield



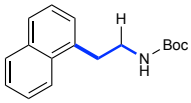
4-7: 61% yield



4-8: 72% yield

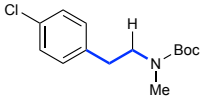


4-9: 60% yield

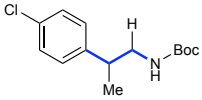


4-10: 74% yield

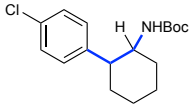
olefin scope



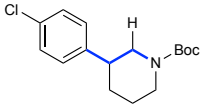
4-11: 62% yield



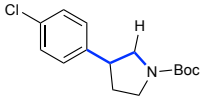
4-12: 60% yield



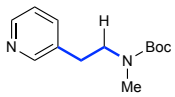
4-13: 42% yield (1:1 dr)



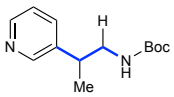
4-14: 42% yield[b]



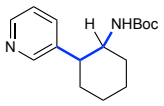
4-15: 53% yield[c]



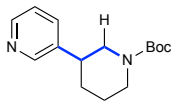
4-16: 70% yield



4-17: 66% yield



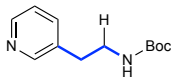
4-18: 43% yield (1:1 dr)



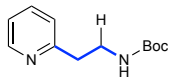
4-19: 47% yield

4-20: 67% yield[c,d]

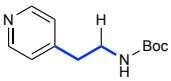
heteroaryl iodide/bromide scope



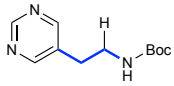
4-21: 91% yield



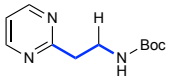
4-22: 69% yield[e]



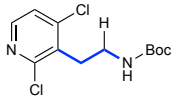
4-23: 89% yield[e]



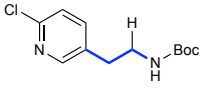
4-24: 70% yield[e]



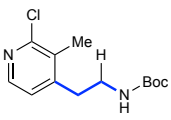
4-25: 64% yield[e]



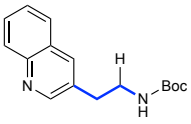
4-26: 66% yield



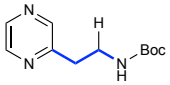
4-27: 78% yield



4-28: 75% yield



4-29: 72% yield[b]



4-30: 68% yield

The reduction of a wide range of other aryl iodides under the optimal PTH/CySH dual catalytic system provided a diverse scope of substituted arylethylamines (Table 9). Aryl iodide

derivatives containing chlorides (**4-2**) or triflate (**4-3**) substituents gave the product in high yields (70-88%) while maintaining the cross-coupling handles. Electron-donating groups on the aromatic ring did not substantially affect reactivity with yields only slightly lower for substrates containing methoxy (**4-6**, 61% yield and **4-9**, 60% yield), carbamate (**4-7**, 61% yield), and free-hydroxy groups (**4-8**, 72% yield). Electron-poor arenes reacted smoothly here and the trifluoromethyl (**4-4**, 85% yield) and methyl ester (**4-5**, 73% yield) groups were successfully retained. Our results uphold the assertion that the aryl radical SOMO lies within the plane of the arene and is thus reactivity is unaffected by electron-donating and electron-withdrawing groups.[68] Substitution was tolerated at every position of the aromatic ring and 2-iodonapthalene (**4-10**, 74% yield) reacted smoothly, leading to the potential alkylation of polyaromatics.

Additionally, substitution on the vinylamine coupling partner was tolerated on the nitrogen (**4-11**, 62% yield) and at the β-position (**4-12**, 60% yield). Cyclic substrates (**4-13**–**4-15**) operated in diminished, but useful yields (42–53% yield) as the synthesis of complex saturated N-heterocycles often requires multiple steps. For example, the 3-arylpiperidine motif formed through hydroarylation of the cyclic enecarbamate (**4-14**) was produced in 42% yield, a framework that required 3-arylpyridine reduction or lactam α-arylation and subsequent reduction in the development of PARP inhibitor Zejula to treat ovarian cancer.[69] Hydroarylation yields were slightly higher for 5-membered cyclic vinylamine derivatives with **4-15** and **4-20** operating in 53% and 67% yield, respectively.

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[68] Garden, S. J.; Avila, D. V.; Beckwit, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J., Absolute Rate Constant for the Reaction of Aryl Radicals with Tri-n-butyltin Hydride. *Journal of Organic Chemistry* **1996,** *61*, 805-809.

[69] Jones, P.; Wilcoxen, K.; Rowley, M.; Toniatti, C., Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. *Journal of Medicinal Chemistry* **2015,** *58*, 3302-3314. Chung, C. K.; Bulger, P. G.; Kosjek, B.; Belyk, K. M.; Rivera, N.; Scott, M. E.; Humphrey, G. R.; Limanto, J.; Bachert, D. C.; Emerson, K. M., Process Development of C − N Cross-Coupling and Enantioselective Biocatalytic Reactions for the Asymmetric Synthesis of Niraparib. *Organic Process Research \& Development* **2014,** *18*, 215-227.

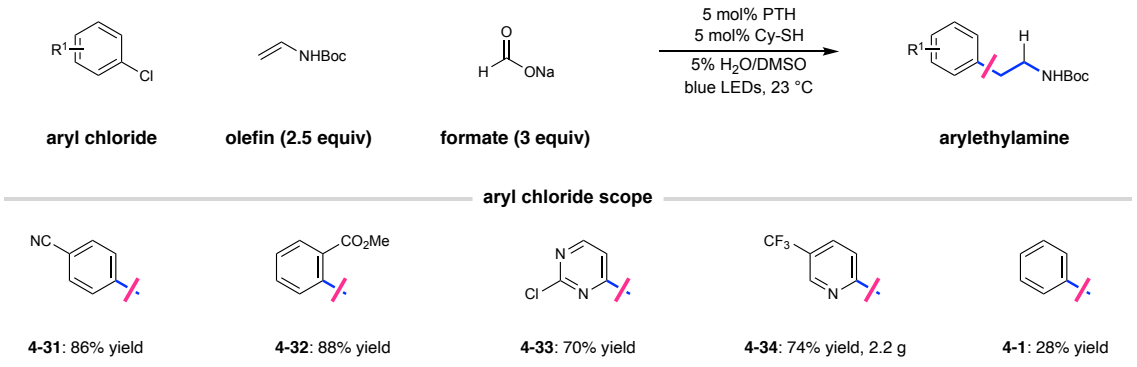
In order to synthesize more complex hetero-arylethylamines, we sought to apply this method to heteroaryl halides. Displaying similar reactivity to iodobenzene, 3-iodopyridine was successfully alkylated with the same vinylamine derivatives. The organocatalyzed conditions were operational for regiospecific alkylation at every position of the pyridine in good to excellent yields (**4-21**–**4-23**, 69–91% yield). As previously demonstrated, cleavage of the iodide occurs while retaining chloro-substitution (**4-26–4-28**, 66-78% yield). Despite steric hinderance from 2,4-dicholoro substitution, pyridylethylamine **4-26** was furnished in good yield, and, along with **4-27**, and 4-**28** where no overreduction products were observed. This is of particular importance as these substrates retain the ability to undergo cross-coupling or other nucleophilic aromatic substitutions. Additionally, because this system does not operate through a proton coupled electron transfer mechanism (PCET) as our previous protocol for the Ir-catalyzed hydropyridylation of neutral olefins[39,50], halogenated diazines and more complex N-heterocycles were able to be reduced to the corresponding radical and couple with *t*-butylvinylcarbamate. Halogenated pyrimidines (**4-24**, 70% yield and **4-25**, 64% yield), quinoline (**4-29**, 72% yield), and pyrazine (**4-30**, 68% yield) substrates all resulted in reasonable yields of the alkylated products.

4.5 Aryl chlorides as radical precursors

This metal-free process takes advantage of two inexpensive organocatalysts in a dual catalytic system. Additionally, the system provides complete regioselectivity for the linear arylethylamine product while generating inert byproducts, most of which are removed in the standard aqueous workup, allowing for more rapid purification and less waste generation. While all of these factors contribute to an affordable process, we recognized that the requirement for aryl iodide radical precursors is suboptimal as they can be significantly more expensive than the corresponding aryl bromides and aryl chlorides. Aryl bromides and chlorides, although cheaper,

are significantly more difficult to reduce. However, as demonstrated by Hawker and Read de Alaniz, PTH is capable of reducing aryl bromides and chlorides as long as they are sufficiently activated with an electron withdrawing group to give the HDH product.[10] In our hydroarylation conditions, we were able to effectively convert 4-chlorobenzonitrile (**4-31**, 86% yield) and ethyl-2-chlorobenzoate (**4-32**, 88% yield) ($E_{1/2}^0$ = –2.00 to –2.10 V v s SCE)[70] to the corresponding arylethylamines (Table 10). Alkylation of 2,4-dichloropyrimidine (**4-33**) was exclusively observed at the 4-position in 70% yield which mimics the selectivity observed in S_NAr and Pd-catalyzed cross-coupling reactions. Chloride retention under the hydroarylation conditions is possible presumably because the installation of the electron-donating alkyl group would increase the reduction potential outside of the range of PTH*, thus preventing a subsequent reduction of the chloride. Chlorobenzene reacted much slower under the optimal conditions, providing only 28% yield of the desired product after 16 h with the majority of the mass balance consisting of unreacted starting material. Importantly, the reaction was able to be scaled to 10 mmol without the use of any specialized equipment (two LED lamps were used as opposed to one). The coupling of 2-chloro-5-trifluoromethylpyridine occurred without alteration of the standard conditions to give 2.15 g of desired product **4-34** in 74% yield.

Table 10: Scope of aryl chlorides as radical precursors



[70] Enemærke, R. J.; Christensen, T. B.; Jensen, H.; Daasbjerg, K., Application of a new kinetic method in the investigation of cleavage reactions of haloaromatic radical anions. *Journal of the Chemical Society, Perkin Transactions 2* **2001,** (9), 1620-1630.

4.6 Catalytic thiol enables intermolecular reactivity

The design of this method enables intermolecular reactivity by limiting the availability of the H-atom source. As illustrated in the proposed catalytic cycle, there are two competing pathways for the aryl radical intermediate: intermolecular coupling with a vinylamine (desired) or reduction to the HDH product via HAT from the thiol (undesired). By using catalytic thiol as the H-atom transfer agent, we see remarkable selectivity for aryl radical hydroarylation over HDH which was previously unprecedented under photoredox conditions without the use of super-stoichiometric coupling partner. The rates of the HDH vs the hydroarylation pathways was conveniently manipulated by varying the loading, and the yields of the desired product were highest when using electrophilic aliphatic thiols. Increasing the thiol loading was seen with a corresponding increase in HDH. Under the optimized conditions (5 mol% thiol), iodobenzene coupled with *t*-butylvinylcarbamate in 78% yield (Figure 14). When a full equivalent (100 mol%) of thiol was utilized, the selectivity was completely reversed, giving benzene (the HDH product) in 81% yield.

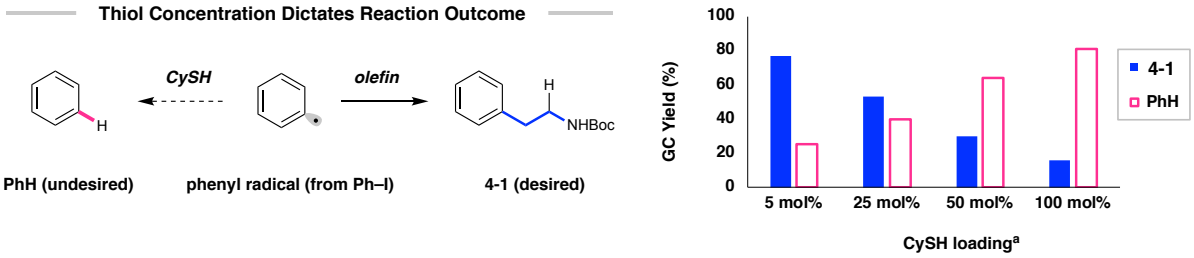


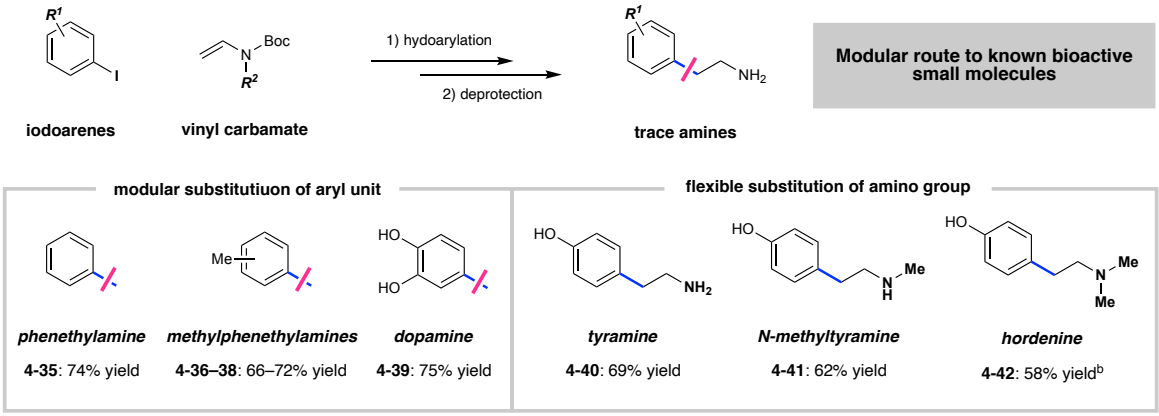
Figure 14: Catalytic thiol enables intermolecular reactivity

While it is accepted that radical anion fragmentation rate varies with respect to the aryl halide, we hypothesize that this system operated via neutral aryl radicals regardless of the Ar–X substrate used. To support this hypothesis, thiol loading experiments were carried out across a series of halobenzene substrates using methyl-4-iodo, -bromo, and -chlorobenzoate. These

substrates were selected as complete consumption of the chlorobenzoate was previously observed thus allowing for a reliable comparison across the substrate class. When the thiol loading was tested, the same thiol concentration-dependent product ratios were observed throughout the class. This confirms that, once the radical forms, the aryl radical behaves as a neutral radical and the halide, while influencing fragmentation, does not influence the reactivity of the aryl radical.

4.7 Native neurotransmitter synthesis via hydroarylation

Table 11: Synthesis of native neurotransmitters

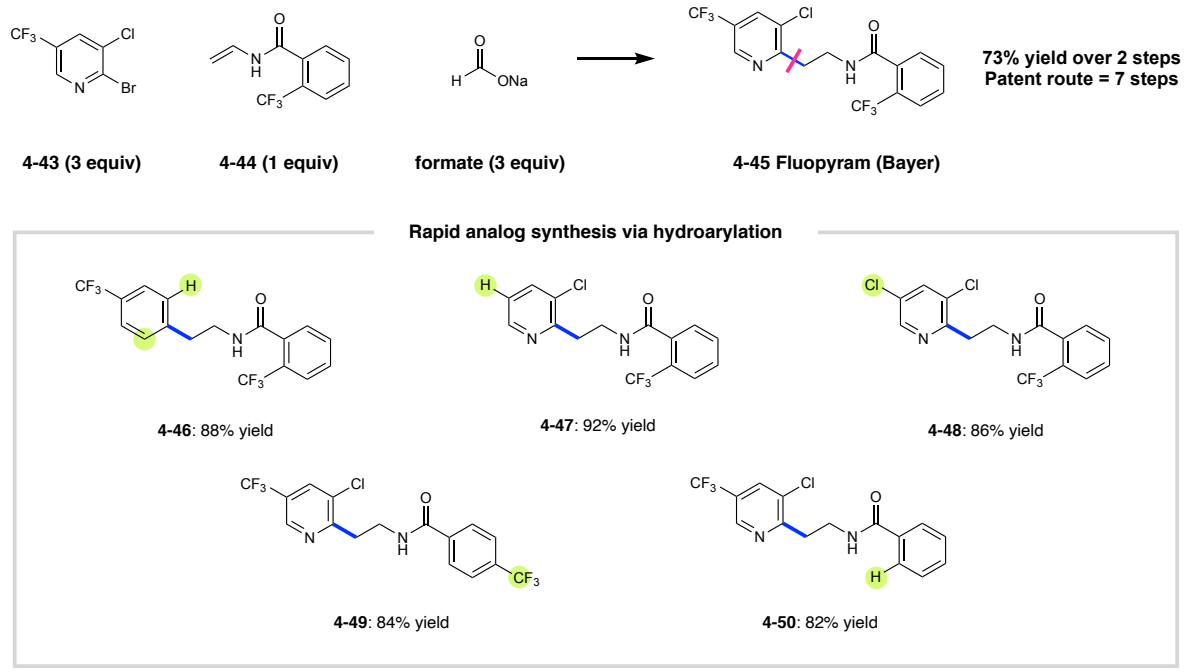


The arylethylamine scaffold is extremely prominent across endogenous and synthetic neuromodulators. To demonstrate the practical utility of our photoredox protocol, we sought to synthesize a variety of native neurotransmitters dopamine and other trace amine-associated receptor (TAAR) agonists (Table 11).[71] Because this system is highly tolerant of substitution on the aromatic ring, phenethylamine, all three methylphenethylamine isomers (**4-36–38**, 66–72% yield), and dopamine (**4-39**, 75% yield) were easily synthesized via a two-step hydroarylation/boc-deprotection sequence. Additionally, this system allows for substitution on the nitrogen atom which allowed for the synthesis of tyramine (**4-40**, 69% yield), *N*-methyltyramine (**4-41**, 62% yield), and hordenine (**4-42**, 58% yield) in two steps from *t*-butyl-(4-iodophenyl)-carbonate.

[71] Gainetdinov, R. R.; Hoener, M. C.; Berry, M. D., Trace Amines and Their Receptors. **2018,** *00069*.

4.8 Application to the synthesis of an agrochemical and derivatives

Table 12: Synthesis of Fluopyram and derivatives



To demonstrate the utility of this protocol for early-stage development of biologically relevant compounds, we synthesized the fungicide Fluopyram from the coupling of 2-bromopyridine with *N*-vinylbenzaminde (Table 12).[72] The optimal conditions for this transformation required inverting the stoichiometry to use 3 equivalents of the radical precursor, which is also the commercially available component. The olefin is easily synthesized in a single step, thus decreasing the overall synthesis to two steps from the seven-step patent route of the agrochemical. Not only is this route significantly faster, it also modular and, therefore, allows for

[72] Lhermitte, F.; Coqueron, P.-Y.; Desbordes, P.; Himmlet, T. WO2006/067103, June 29, 2006. Moradi, W. A.; Schnatterer, A.; Bielefeldt, D.; Gertzmann, R.; Havekest, D. WO2018/114484, June 28, 2018.

the rapid synthesis of a variety of analogs. Systematic substitution on either aromatic ring of Fluopyram was accomplished with excellent fidelity.

4.9 Perovskites

Hybrid inorganic organic perovskite (HIOP) structures have attracted significant attention due to their facile processability, defect tolerance, and optoelectronic properties that resemble that of traditional inorganic semiconductors. Particularly those consisting of lead(II) and iodide offer unique structural diversity and, ideally, tunability of the optoelectronic properties. These properties have led to the application of HIOP in highly efficient solar cells[73] as well as light emitting diodes.[74] The crystal structures of hybrid iodoplumbate perovskites and perovskitoids consist of an inorganic portion consisting of catenated PbI_6 octahedra bearing an overall negative charge and positively charged organic cations. The optical and electrical properties are primarily determined by the basic connectivity (2-dimensional vs. 1-dimensional etc, corner- vs. edge- vs. face-sharing octahedra) and subtle structural details (e.g., octahedral distortions) of the lead iodide part, which, in turn, is dictated by the properties of the organic cation. This includes the steric characteristics, geometry, charge, charge-bearing group(s), and the ability of the cation to engage in non-covalent interactions with other cations or with the inorganic portions. While many iodoplumbate HIOPs have been synthesized and structurally characterized (more than one hundred different organic

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[73] C. Smith, E. T. Hoke, D. Solis-Ibarra, M. D. McGehee and H. I. Karunadasa, *Angew. Chem. Int. Edit.*, 2014, **53**, 11232-11235. J. Yan, W. Qiu, G. Wu, P. Heremans and H. Chen, *J. Mater. Chem. A*, 2018, **6**, 11063-11077. Y. Chen, Y. Sun, J. Peng, W. Zhang, X. Su, K. Zheng, T. Pullerits and Z. Liang, *Adv. Energy Mater.*, 2017, **7**, 1700162. D. H. Cao, C. C. Stoumpos, O. K. Farha, J. T. Hupp and M. G. Kanatzidis, *J. Am. Chem. Soc.*, 2015, **137**, 7843-7850. C. Ma, D. Shen, T.-W. Ng, M.-F. Lo and C.-S. Lee, *Adv. Mater.*, 2018, **30**, 1800710. Lai, B. Kan, T. Liu, N. Zheng, Z. Xie, T. Zhou, X. Wan, X. Zhang, Y. Liu and Y. Chen, *J. Am Chem. Soc.*, 2018, **140**, 11639-11646. H. Tsai, W. Nie, J.-C. Blancon, C. C. Stoumpos, R. Asadpour, B. Harutyunyan, A. J. Neukirch, R. Verduzco, J. J. Crochet, S. Tretiak, L. Pedesseau, J. Even, M. A. Alam, G. Gupta, J. Lou, P. M. Ajayan, M. J. Bedzyk, M. G. Kanatzidis and A. D. Mohite, *Nature*, 2016, **536**, 312. L. Mao, W. Ke, L. Pedesseau, Y. Wu, C. Katan, J. Even, M. R. Wasielewski, C. C. Stoumpos and M. G. Kanatzidis, *J. Am. Chem. Soc.*, 2018, **140**, 3775-3783. C. C. Stoumpos, D. H. Cao, D. J. Clark, J. Young, J. M. Rondinelli, J. I. Jang, J. T. Hupp and M. G. Kanatzidis, *Chem. Mater.*, 2016, **28**, 2852-2867. S. Ahmad, P. Fu, S. Yu, Q. Yang, X. Liu, X. Wang, X. Wang, X. Guo and C. Li, *Joule*, 2019, **3**, 794-806.

[74] M. Yuan, L. N. Quan, R. Comin, G. Walters, R. Sabatini, O. Voznyy, S. Hoogland, Y. Zhao, E. M. Beauregard, P. Kanjanaboos, Z. Lu, D. H. Kim and E. H. Sargent, *Nat. Nanotechnol.*, 2016, **11**, 872.

cations have been successfully incorporated into 2D hybrid iodoplumbates) it is not well understood what structural features of the cation favor the formation of a 2D structure, and what features favor lower dimensional (1D or 0D) material. Development of reliable guidelines relating the cation's structure to the formation of different classes of low-dimensional hybrid perovskite and perovskitoid materials, would be highly beneficial to the field and would enable engineering materials with specific structures and properties.

1D perovskites, in the strict sense, consist of chains of corner-sharing octahedra, but haloplumbate examples, A_3PbHal_5 (A = organic cation, Hal = halogen), are relatively rare. Alternatively, reports of perovskitoid 1D face-sharing iodoplumbates (FSIPs), $APbI_3$, in which there are chains of face-sharing PbI_6 octahedra, are more common. While only a few small ions can be used in 3D lead-halide perovskites, such as methylammonium, and 2D structures usually incorporate bulkier ions, a much wider range of sterically bulky and complex cations can also be used in 1D FSIPs. To date there exists no reliable general strategy for ensuring formation of 1D FSIPs. Although it has been recognized that synthetic conditions affect the crystal structure obtained, no guidelines for using the cation to engineer the structure have been proposed.[75]

Here, we report the first example of how cation choice can be used to engineer 1D FSIP crystals. We can rationalize the formation of 1D FSIPs for a series of cations for which cation-cation hydrogen bonding interactions – either between neighboring cations or within a cation – are present. Specifically, we have obtained seven new crystals using hydrogen-bond acceptor (HBA) groups on the *ortho*- or *meta*-positions of a 2-(phenyl)ethylammonium (PEA) cation. On the other hand, the corresponding methyl-substituted PEA (which doesn't hydrogen bond) analogues afford

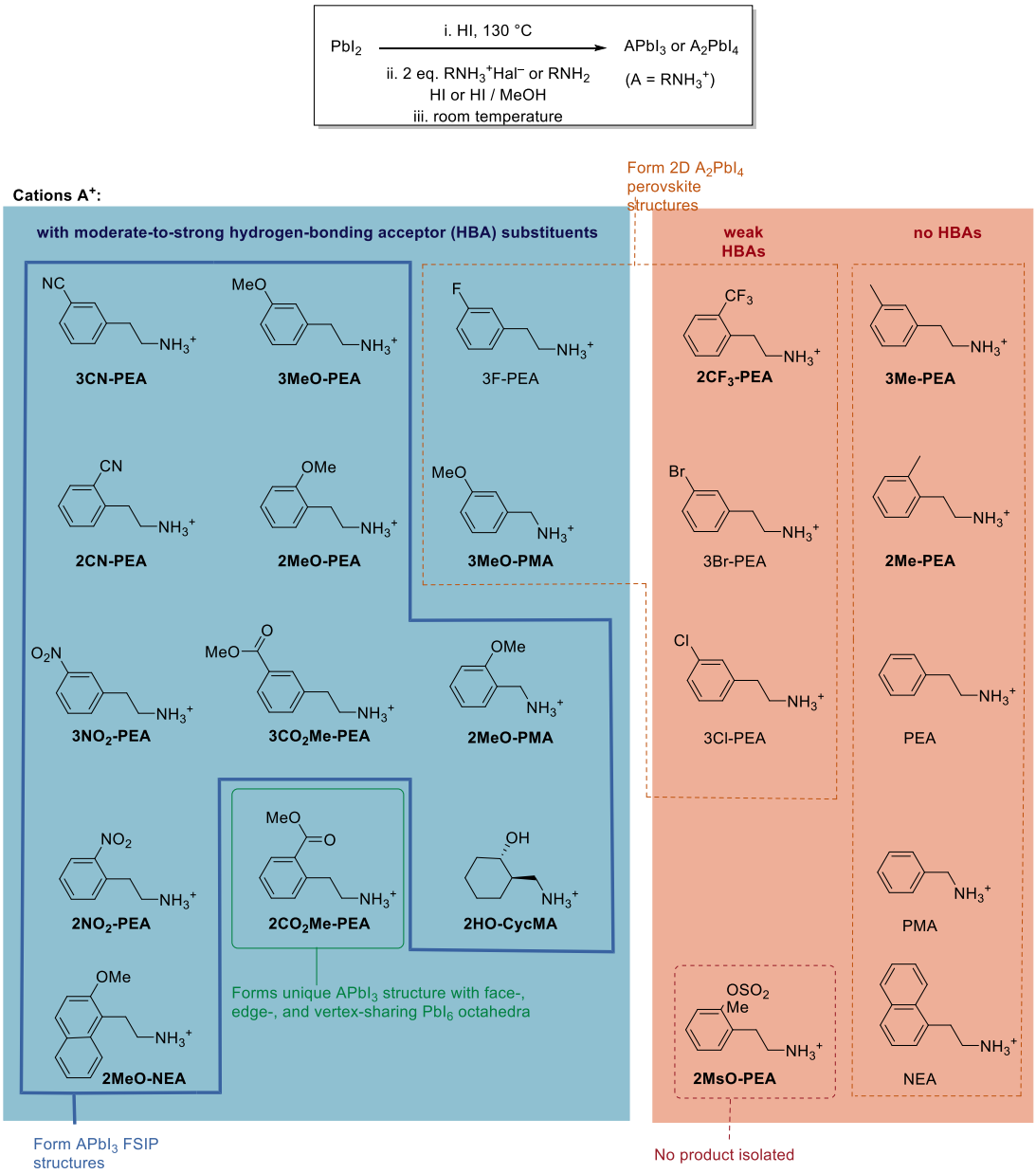
[75] V. Gómez, O. Fuhr and M. Ruben, *CrystEngComm*, 2016, **18**, 8207-8219. M. Safdari, D. Phuyal, B. Philippe, P. H. Svensson, S. M. Butorin, K. O. Kvashnina, H. Rensmo, L. Kloo and J. M. Gardner, *J. Mater. Chem. A*, 2017, **5**, 11730-11738. P. Gao, A. R. Bin Mohd Yusoff and M. K. Nazeeruddin, *Nat. Comm.*, 2018, **9**, 5028.

2D perovskites. In many cases, 1D FSIP structures are obtained rather than 2D HOIP structures because the atom(s) on which the cationic charge is formally located is sterically encumbered and, therefore, unable to interact with the inorganic part of the structure. To test this hypothesis, we set out to examine a wide variety of structures in which the ammonium cation is based on a six-membered ring (primarily benzene, but one example each of naphthalene and cyclohexane) is 1,2- or 1,3-functionalized with both a methylammonium ($CH_2NH_3^+$) or ethylammonium ($(CH_2)_2NH_3^+$) group and an HBA (CN, NO_2, OMe, CO_2Me). In addition, we examined several examples of cations containing substituents with similar steric bulk, but medium, weak, or no HBA character (F, CF_3, OSO_2Me, Me).

To expand the scope of this study, the described radical hydroarylation, deprotection protocol was followed to synthesize arylethylammonium salts.[76] In turn, these were utilized in collaboration with the Marder Group at Georgia Institute of Technology to obtain new HIOP structures. Of the twelve cations examined that bear moderate-to-strong HBA substituents, ten of the resulting hybrid organic-inorganic structures were found to be 1D $APbI_3$ FSIPs, i.e., linear PbI_3^- wires composed of face-sharing octahedra separated by layers of organic cations. When the substituents have little or no HBA character, but similar bulk as those described in the previous paragraph, we do not form 1D FSIPs under the same conditions. In the case of 2-(2-((methylsulfonyl)oxy)phenyl)ethan-1-ammonium (2MsO-PEA), no solid product was formed, while in the case of 3Me-PEA, 2Me-PEA, and $2CF_3$-PEA, 2D A_2PbI_4 structures were obtained.

[76] Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T., Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019,** *141*, 4147-4153.

Table 13: Cation blueprint for determining perovskite fine structure



4.10 Conclusion

In conclusion, we have developed a protocol for the intermolecular addition of aryl and heteroaryl radicals to enecarbamate substrates. This process operates at ambient temperature, mediated by the concerted action of two different catalytic species (PTH and CySH) that accomplish the transfer of electrons and hydrogen atoms, respectively. This system directly affords

valuable arylethylamine structures with complete regiocontrol with excellent functional group compatibility, and it utilizes stable halogenated arenes as radical precursors. The highly reducing character of the organic photoredox catalyst here allows for effective activation of a wide range of aryl halides, including electron-deficient aryl chlorides. This system was effective for the synthesis of known trace amine receptor agonists, native neurotransmitters, cation synthesis for hybrid inorganic-organic perovskites, as well as significantly decreasing the number of synthetic steps required for the synthesis of an agrochemical. We expect that this protocol, founded on the use of a thiol HAT catalyst in combination with a benign stoichiometric reductant, will enable a range of mild aryl radical-based transformations.

4.11 Supporting Information

4.11-I. General Information

4.11-I-A. General Reagent Information

All reactions were set up on the bench top and conducted under argon atmosphere while subjected to irradiation from a blue LED (PARsource PowerPAR LED Bulb-Blue 15 Watt available at www.1000bulbs.com). Silica gel chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalyst PTH was prepared according to a literature procedure.[10] Iodobenzene was purchased from MilliporeSigma and used as received. 1-Chloro-4-iodobenzene and 3-iodopyridine were purchased from Combi-Blocks and used as received. All other (het)aryl halides were purchased from Combi-Blocks, Oakwood Products, and Alfa Aesar and used as received unless otherwise noted. Olefins were purchased from MilliporeSigma and used as received unless otherwise noted. Sodium formate was purchased from MilliporeSigma. and used as received. DMSO was purchased from Fisher Scientific and was distilled over CaH_2

and degassed by sonication under vacuum after adding deionized water (Fisher Scientific) (20:1 DMSO/H_2O), stored under Ar, and used within 1 week of distilling.

4.11-I-B. General Analytical Information

New compounds were characterized by NMR, IR spectroscopy, HRMS, and melting point. NMR data were recorded on one of four spectrometers: INOVA 600 MHz, INOVA 500 MHz, INOVA 400 MHz, and Mercury 300 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR. C_6D_6: δ 7.16 ppm for ^1H NMR). IR spectra were obtained with a Nicolet 380 Fourier transform infrared spectrophotometer. Mass spectrometry data were obtained from the Emory Mass Spectrometry Center. Melting point data was obtained with a Thomas Hoover Unimelt capillary melting point apparatus. Thiol loading data was obtained via gas chromatography with an Agilent Technologies 7890B Gas Chromatography system equipped with an Agilent Technologies 19091J-413 column (30 m x 0.320 mm) with a 5977A MSD system and an Agilent Technologies G4513 autoinjector.

4.11-II. General Procedures

4.11-II-A. General Procedure A

An oven-dried 30 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under vacuum. The tube was charged with photocatalyst: *N*-phenylphenothiazine (PTH), *N*-napthylphenoxazine (N-POX), or *N*-napthylphenothiazine (N-PTH) (5-10 mol%), sodium formate (3 equiv), arene (*if solid*, 1 equiv), and alkene (*if solid,* 2.5 equiv*)*. The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with alkene (*if liquid,* 2.5 equiv), arene (*if liquid,* 1 equiv), cyclohexanethiol (5 mol%) and separately degassed 20:1 DMSO:H_2O (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours

under irradiation with a blue LED with cooling from compressed air. The reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

4.11-II-B. General Procedure B

An oven-dried 30 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under vacuum. The tube was charged with *N*-napthylphenothiazine (N-PTH) (5 mol%), sodium formate (3 equiv), arene (*if solid*, 5 equiv), and alkene (*if solid,* 1 equiv*)*. The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with alkene (*if liquid,* 1 equiv), arene (*if liquid,* 5 equiv), cyclohexanethiol (5 mol%) and separately degassed 20:1 DMSO, H_2O (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED with cooling from compressed air. The reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

4.11-II-C. General Procedure C

An oven-dried 30 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under vacuum. The tube was charged with *N*-phenylphenothiazine (PTH) (5 mol%), sodium formate (3 equiv), arene (*if solid*, 3 equiv), and alkene (*if solid,* 1 equiv*)*. The atmosphere was exchanged by applying vacuum and backfilling

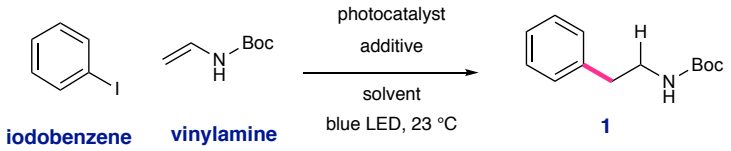
with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with alkene (*if liquid,* 1 equiv), arene (*if liquid,* 3 equiv), cyclohexanethiol (5 mol%) and separately degassed 20:1 DMSO, H_2O (0.1 M) via syringe. The resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED with cooling from compressed air. The reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

4.11-III. Optimization Procedure

An oven-dried 15 mL screw-top test tube equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under vacuum. The tube was charged with photocatalyst (*if iridium,* 0.0025 mmol, 1 mol%, *if PDI/PTH,* 0.0125 mmol, 5 mol%), *t*-butylvinyl carbamate (0.082 g, 0.625 mmol, 2.5 equiv) and additive (*if solid*, 1.3-3 equiv). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, iodobenzene (28 μL, 0.25 mmol, 1 equiv) and additive (*if liquid*, 5 mol% - 10 equiv) were added via microsyringe. Separately degassed solvent (2.5 mL, 0.1 M) was added via syringe and the resulting mixture was stirred at 1200 RPM for 16 hours under irradiation with a blue LED. The reaction was quenched with saturated aqueous sodium bicarbonate solution (8 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic extracts were filtered through a silica plug, and washed through with acetone, into a 20 mL glass scintillation vial. The crude mixture was concentrated under rotary evaporation, reconstituted in chloroform-*d*, and charged with CH_2Br_2 (17.5 μL, 0.25 mmol). Yields provided in table S1 were obtained by ^1H NMR using CH_2Br_2 as the internal standard. In table S2, the benzene yield, yield of **1**, and recovered

iodobenzene were quantified using gas chromatography with dodecane as an internal standard. The gas chromatography system hardware are reported in section **1A**, General Analytical Information. The injection volume for each trial is 0.5 µL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Maximum temperature is held for one minute before concluding the run. Using this method, the retention time for benzene was 1.48 min, the rentention time for boc-phenethylamine was 7.75 min, the retention time for iodobenzene was 3.70 min, and the retention time for the dodecane standard was 4.89 min.

Table 14: Reaction optimization



iodobenzene vinylamine 1

Entry	Solvent	Catalyst	Additive	Yield of **6**
1	CF_3CH_2OH	$Ir(ppy)_2dtbbpy^+$	HEH (1.3 equiv), NH_4Cl (2 equiv)	0%
2	20% H_2O/DMSO	$Ir(ppy)_2dtbbpy^+$	HEH (1.3 equiv)	0%
3	MeCN	*fac*-$Ir(ppy)_3$	Bu_3N (10 equiv), HCO_2H (10 equiv)	0%
4	DMSO	PDI	Et_3N (8 equiv)	0%
5	5% H_2O/DMSO	*fac*-$Ir(ppy)_3$	NaO_2CH (3 equiv), CySH (5 mol%)	37%
6	**5% H_2O/DMSO**	**PTH**	**NaO_2CH (3 equiv), CySH (5 mol%)**	**82%**
7	5% H_2O/DMSO	PTH	NaO_2CH (3 equiv)	11%
8	5% H_2O/DMSO	PTH	CySH (5 mol%)	0%
9	5% H_2O/DMSO	—	NaO_2CH (3 equiv), CySH (5 mol%)	5%

Table 15: Thiol screen

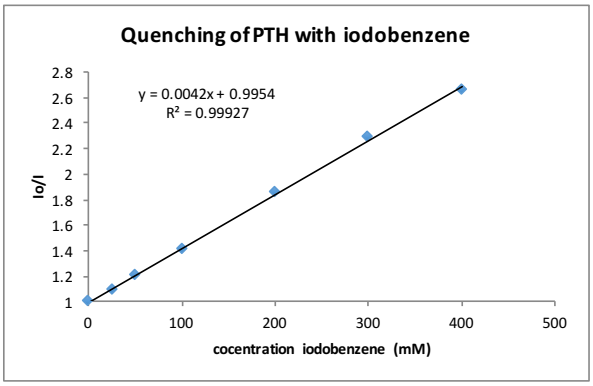
iodobenzene vinylamine 1 benzene

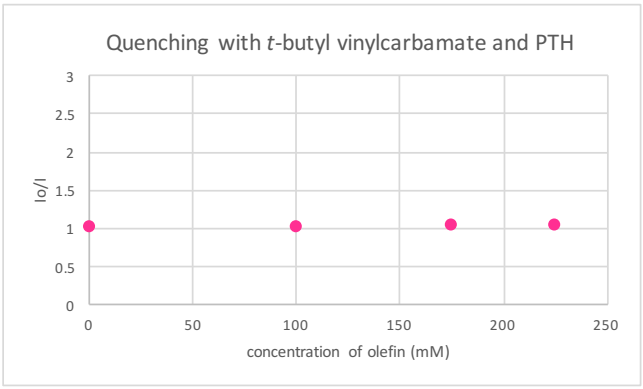
Entry	Thiol	Yield of **1**	Recovered Iodobenzene	Yield benzene
1	triphenylmethanethiol	11%	56%	13%
2	triisopropylsilanethiol	18%	49%	12%
3	butanethiol	68%	0%	30%
4	dodecanethiol	65%	3%	28%
5	2,4,6-triisopropylbenzenethiol	9%	61%	9%
6	methyl 2-mercaptoacetate	35%	22%	18%

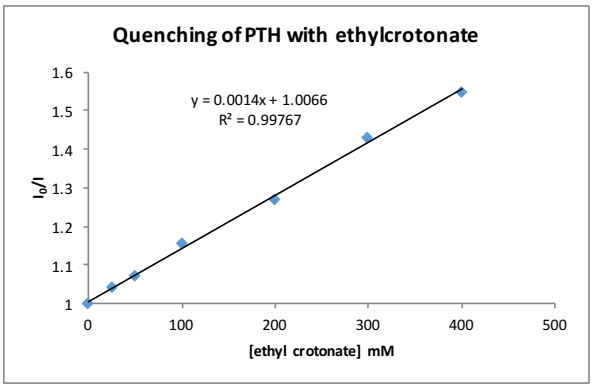
4.11-IV. Stern Volmer Fluorescence Quenching

For the quenching of PTH with iodobenzene, our results are consistent with those found by Hawker and Read de Alaniz.[10] The emission of a 0.17 mM solution of PTH in 5% H_2O/DMSO was measured with varying concentrations of iodobenzene and *t*-butyl vinylcarbamate at 20±0.5 ºC (Peltier temperature control). The solutions were excited at 350 nm and, with increasing concentrations of iodobenzene in solution, the intensity of the PTH peak linearly decreased. This demonstrates that iodobenzene is a quencher of PTH and is being reduced upon the excitation of the photocatalyst (PTH*). The emission spectra of PTH with varying concentrations of *t*-butyl vinylcarbamate was unchanged, thus showing no quenching from the olefin. Additionally, ethylcrotonate, an electron deficient olefin, was shown to be an effective quencher of PTH and is not an effective olefin in this system. Quenching was also not observed in similar experiments using cyclohexanethiol or sodium formate.

Figure 4-S1: Stern Volmer Quenching Studies







4.11-V Quantum Yield Calculations

Evaluation of the quantum yield was performed using a blue 455 nm LED that was focused on the quartz cuvette using a focal lens. The reaction was set up in a 3.5 mL quartz cuvette equipped with a stir bar and capped with a silicon septa. The cuvette was charged with PTH (4.8 mg, 0.0175 mmol, 5 mol%), *t*-butylvinyl carbamate (0.125 g, 0.875 mmol, 2.5 equiv), and sodium formate (0.071 g, 1.05 mmol, 3 equiv). The atmosphere was exchanged by pulling vacuum and backfilling with Ar (this process was completed a total of 3 times). Under Ar atmosphere, the cuvette was charged with iodobenzene (39 µL, 0.35 mmol, 1 equiv), cyclohexanethiol (2 µL, 0.0175 mmol, 5 mol%), and separately degassed 5% H_2O/DMSO. 80 µL aliquots were removed via syringe every hour (0h, 1h, 3h, 4h). 50 µL of each aliquot was diluted with 5 mL of 5% H_2O/DMSO and the UV/Vis spectra were recorded (Figure S3). The consumption of iodobenzene was readily monitored with this method. The quantum yield was determined from the steady state portion of

the reaction. The quantum yield (QY) was defined as the ratio between the amount of electron consumed during the reaction and the total number of photon absorbed by the photosensitizer. QY can be determined through the following equations.

First, the number of photon *n* arrived onto the sample per second from the 455nm LED per second could be calculated as

$$n = E/hv$$

Where E = 60mW (455nm LED power before the sample)

h = Planck constant = 6.626 x 10^{-34} Js

v = frequency of the 455 nm photon

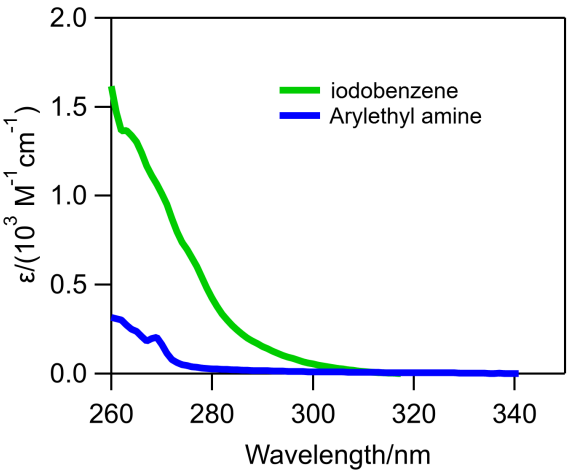
$$v = c/\lambda$$

Where c = speed of light = 2.998 x 10^{8} ms^{-1}

λ = wavelength (455 nm = 455 x 10^{-9} m

The amount of the photon absorbed by the sample per hour n^* can be calculated based on the absorbance of the sample at 455nm A_{455} from Beer-Lambert law

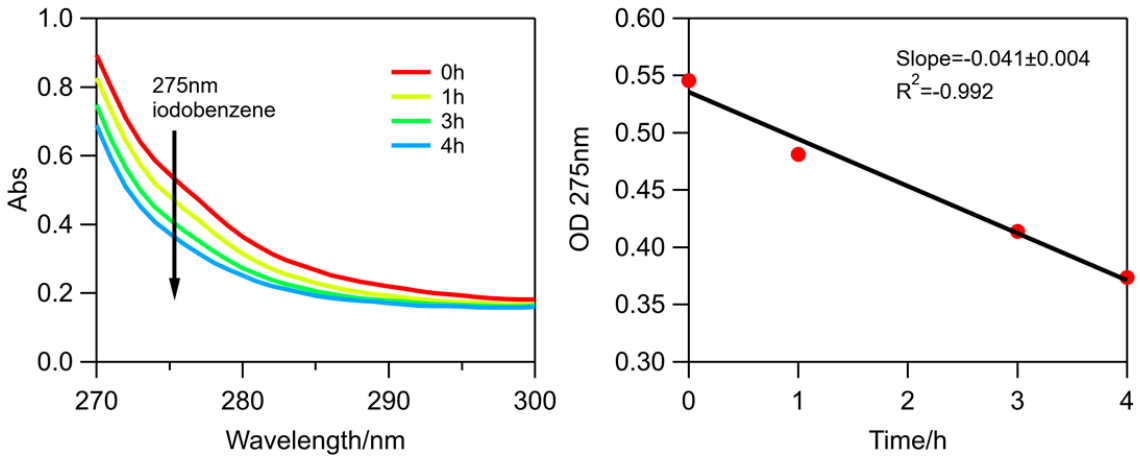
$$n^* = 3600n(1 - 10^{-A_{455}})$$



Graph 2: Absorbance Spectra of Iodobenzene and Arylethylamine

The amount of electrons per minute during the reaction can be obtained from the rate of consumption of iodobenzene on the UV-Vis spectrum. By the measurement of the extinction coefficient, (Fig. S2), we observed the decrease of the absorbance at 275nm is dominated by the consumption of iodobenze. The absorbance at 275nm was plotted against time and fitted with a linear fit. The result was shown in Fig. S3. The slope can be used to calculate the electron generated (and consumed) per hour n_e as

$$n_e = 100aV/\varepsilon$$



Graph 3: Absorbance of Iodobenzene Over Time

Here, a is the slope in Fig S3 from the linear fitting, V is the total volume of the cell as 3.5mL, ε is the extinction coefficient of iodobenzene at 275 nm.

As defined, the QY can be calculated as

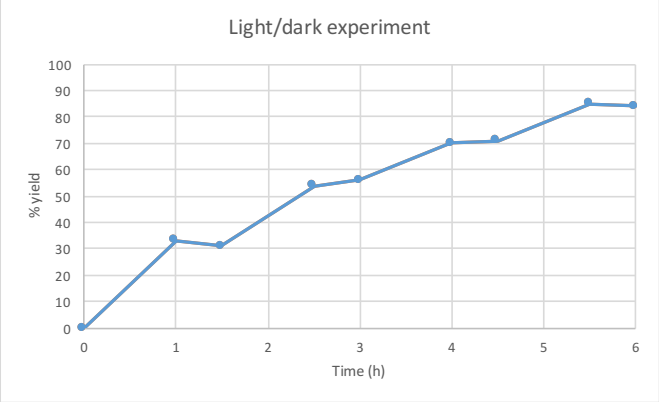
$$QY = \frac{n^*}{n_e} \times 100\% = 29.0 \pm 2.9\%$$

4.11-VI. Light/Dark Experiment

Following General Procedure A, an oven-dried 50 mL Schlenck flask equipped with a stir bar was sealed with a PTFE/silicon septa and cooled to room temperature under vacuum. The flask was charged with PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv),

t-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), and 1,3,5-trimethoxybenzene as an internal standard (0.168 g, 1 mmol). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Under Ar atmosphere, the tube was charged with iodobenzene (0.111 mL, 1.00 mmol, 1 equiv), cyclohexanethiol (6 µL, 0.05 mmol, 5 mol%), and separately degassed 20:1 DMSO, H_2O (10 mL, 0.1 M) via syringe. The reaction was stirred at 1200 RPM under irradiation by a blue LED and cooling with house air. The light was turned off every hour and the reaction was allowed to stir in the dark for 30 minutes before the LED was turned back on. 50 µL samples for analysis were removed via microsyringe immediately before the light was turned off/on. Yields were calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. An increase in yield was observed under irradiation (time points in blue) and no significant increase in product formation was observed when irradiation was stopped.

time (h)	% yield
0	0
1	33
1.5	31
2.5	54
3	56
4	70
4.5	71
5.5	85
6	84



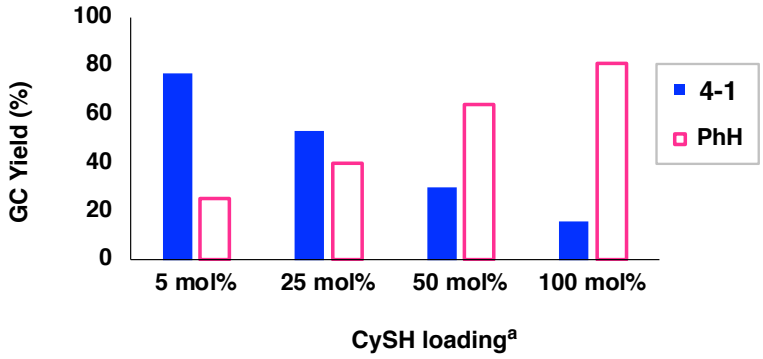
Graph 4: Light dark experiment

4.11-VII. Thiol Loading Experiment

All reactions were set up in accordance with General Procedure A using 0.25 mmol of iodobenzene, 0.625 mmol of t-butyl vinylcarbamate, 0.75 mmol of sodium formate, varying equivalents of thiol (5 mol%, 25 mol%, 50 mol%, 100 mol%), and 2.5 mL of 5% H_2O, DMSO. The product yields were calculated using ^{1}H NMR with dibromomethane as an internal standard.

The yield of hydrodehalogenation product (benzene) was quantified using gas chromatography with dodecanal as an internal standard. The gas chromatography system hardware are reported in section **1A**, General Analytical Information. The injection volume for each trial is 0.5 µL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Maximum temperature is held for one minute before concluding the run. Using this method, the retention time for benzene was 1.48 min and the retention time for the dodecane standard was 4.89 min.

Thiol loading (mol %)	% PhH	% 6	% rec. iodobenzene
5 mol%	25	77	0
25 mol%	40	53	0
50 mol%	64	30	0
100 mol%	81	16	0



Graph 5: Thiol loading experiment

4.11-VIII. Thiol Loading Experiment for Iodo/Bromo/Chloro-methylbenzoate

All reactions were set up in accordance with General Procedure A using 0.25 mmol of halobenzoate, 0.625 mmol of t-butyl vinylcarbamate, 0.75 mmol of sodium formate, varying equivalents of thiol (5 mol%, 50 mol%, 100 mol%, 200 mol%), and 2.5 mL of 5% H_2O, DMSO. The percent yield of **A** and **B** were quantified using gas chromatography with dodecane as an internal standard. The gas chromatography system hardware are reported in section **1A**, General Analytical Information. The injection volume for each trial is 0.5 µL. The initial oven

temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. Maximum temperature is held for one minute before concluding the run. Using this method, the retention time for **A** was 9.95 min, the retention time for methylbenzoate (**B**) was 4.19 min, and the retention time for the dodecane standard was 4.89 min.

Figure 4-S6. Thiol Loading Experiment for Iodo/Bromo/Chloro-methylbenzoate

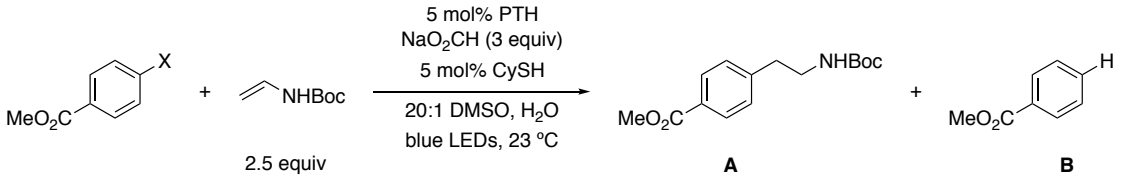
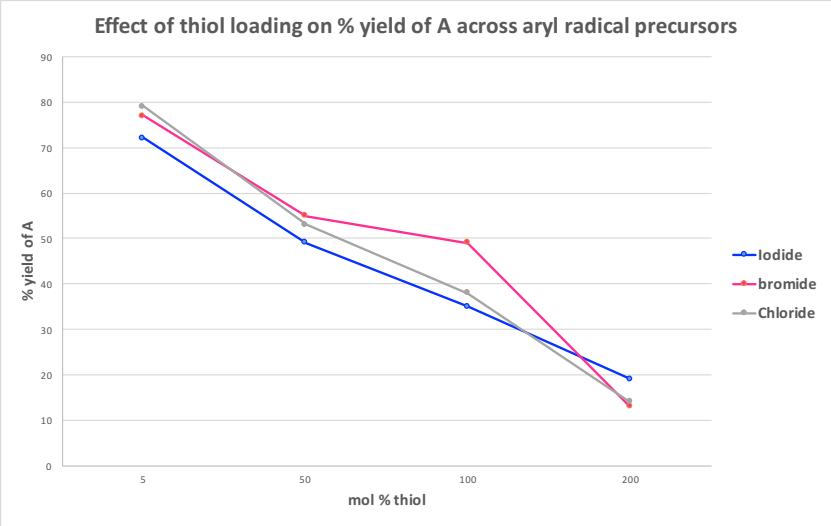


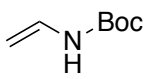
Table 16: Thiol loading data across Ar–I, –Br, –Cl

X = I			X = Br			X = Cl		
mol % thiol	% yield A	% yield B	mol % thiol	% yield A	% yield B	mol % thiol	% yield A	% yield B
5	72	25	5	77	24	5	79	22
50	49	45	50	55	37	50	53	39
100	35	63	100	49	47	100	38	53
200	19	76	200	13	79	200	14	79



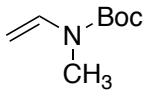
Graph 6: Thiol loading across aryl radical precursors

4.11-IX. Preparation of Starting Materials



***t*-Butyl vinylcarbamate**

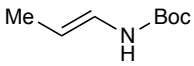
A 500 mL round bottom flask equipped with a stir bar was charged with freshly distilled n-vinyl formamide (7.00 mL, 100 mmol, 1 equiv) followed by dry THF (100 mL, 1 M) under Ar atmosphere. Triethylamine (19.5 mL, 140 mmol, 1.4 equiv) was added via syringe and the mixture was cooled to 0 ºC using an ice water bath. Di-*tert*-butyl dicarbonate (28.4 g, 130 mmol, 1.3 equiv) was added, followed by 4-dimethylaminopyridine (1.22 g, 10 mmol, 0.1 equiv). The reaction was warmed to room temperature and stirred until complete formation of the imide was observed by TLC and a vibrant yellow color change was observed (0.5 h, R_f =0.8, 30:70 EtOAc:hexanes, UV active). The flask was then charged with 5N LiOH (70 mL in deionized water), a reflux condenser was attached, and the reaction was warmed to 50 ºC. The biphasic mixture was stirred vigorously until complete by TLC (1.5 h, R_f=0.8, 20:80 EtOAc:hexanes, stains with $KMnO_4$). The reaction was cooled to room temperature and diluted with 100 mL of water. The aqueous layer was removed and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL) dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to an oil. The crude oil was taken up in a small amount of 20:80 EtOAc:hexanes and flushed through an eight-inch plug of silica eluting with 20:80 EtOAc:hexanes. The filtrate was concentrated to a white crystalline solid (12.67 g, 88% yield) and required no further purification. The physical properties and spectral data match the reported values.[77]



***t*-Butyl methyl(vinyl)carbamate**

[77] Kassir, A. F.; Ragab, S. S.; Nguyen, T. A. M.; Charnay-Pouget, F.; Guillot, R.; Scherrmann, M.-C.; Boddaert, T.; Aitken, D. J., Synthetic Access to All Four Stereoisomers of Oxetin. *Journal of Organic Chemistry* **2016,** *81* (20), 9983-9991.

A 250 mL round bottom flask with stir bar was charged with sodium hydride (60% dispersion in mineral oil, 0.575 g, 14.4 mmol, 1.2 equiv). The atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was conducted a total of three times). Dry THF (90 mL) was added via syringe and the solution was cooled to 0 ºC in an ice water bath. A solution of *t*-butyl vinylcarbamate dissolved in dry THF (30 mL) was added slowly via syringe and the reaction was allowed to stir for 20 minutes at 0 ºC. Iodomethane (1.12 mL, 18 mmol, 1.5 equiv) was added slowly dropwise via syringe. The reaction was warmed to room temperature and stirred for 16 h. Upon completion, the reaction was quenched with concentrated aqueous NH_4Cl (90 mL) and extracted with EtOAc (3 x 90 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude oil was purified by silica gel chromatography (0:100 to 25:75 EtOAc:hexanes) to give the title compound as a clear and colorless liquid (1.63 g, 87% yield). The physical properties and spectral data match the reported values.[78]

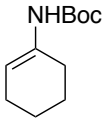


_t_-Butyl prop-1-en-1-ylcarbamate

An oven dried 50 mL round bottom flask with stir bar was charged with crotonoyl chloride (technical grade, 90%, 1.91 mL, 20 mmol, 1 equiv) and tetrabutylammonium iodide (TBAI) (0.370 g, 1 mmol, 5 mol%). Dry toluene (20 mL, 1 M) was added to the flask and the contents stirred until dissolved. In a separate 250 mL flask with stir bar under Ar was added sodium azide (1.56 g, 24 mmol, 1.2 equiv) and deionized water (20 mL, 1 M). The solution was cooled to 0 ºC in an ice water bath. The contents of the 50 mL flask were then transferred to the cooled solution in the 250

[78] Chu, S.; Niels, M.; Balan, T.; Smith, M. D., Total Synthesis A Cascade Strategy Enables a Total Synthesis of (+/-) -Morphine. *Angewandte Chemie - International Edition* **2016,** *55*, 14306-14309.

mL flask dropwise via cannula. The biphasic mixture was stirred vigorously at 0 ºC for 5 h. The organic layer was then separated, dried with Na_2SO_4, filtered, and kept on ice. The organic layer was added dropwise via a pressure equalizing addition funnel to a 100 ºC solution of hydroquinone (0.110 g, 1 mmol, 5 mol%) and pyridine (0.097 mL, 1.2 mmol, 6 mol%) and *t*-butanol (20 mL) in a 250 mL three-necked flask with a reflux condenser. The mixture was heated for 1 h, cooled to room temperature, and concentrated by rotary evaporation to a white solid. The crude product was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to give the title compound as a white crystalline solid (0.908 g, 29% yield). The physical properties and spectral data match the reported values.[79]



***tert*-butyl cyclohex-1-en-1-ylcarbamate**

K_2CO_3 (179 mg, 1.298 mmol) and *tert*-butylcarbamate (73 mg, 0.6230 mmol) were added to an oven-dried flask charged with $Pd_2(dba)_3$ (6 mg, 6.490 mmol) and tBuXphos (7.4 mg, 17.43 mmol) under N_2. The flask was flushed with N_2 and the reagents suspended in *t*-BuOH (1.04 mL). Cyclohexen-1-yl triflate (117 mg, 0.5192 mmol) was added and the reaction was heated at 80 °C for 5 h under N_2. After cooling, the reaction mixture was diluted with Et_2O (5 mL) and filtered through a celite pad and washed with Et_2O (30 mL). The filtrate was reduced in vacuo. The product was purified via flash column chromatography (1-5% Et_2O–hexanes) to yield the title compound as a white solid. (71 mg, 70%). The physical properties and spectral data match the reported values.[80]

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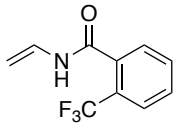
[79] Pansare, S. V.; Vederas, J. C., Synthesis and Reactivity of β-Lactones Derived from L-Threonine and Related Amino Acids. *Journal of Organic Chemistry* **1989,** *54* (10), 2311-2316.
[80] Willis, C.; Brace, G. N.; Holmes, P., Efficient Palladium-Catalysed Enamide Synthesis from Enol Triflates and. *Synthesis* **2005,** *19*, 3229-3224.



2-(trifluoromethyl)-*N*-vinylbenzamide (4-44)

An oven dried 250 mL round bottom flask with stir bar was charged with freshly distilled N-vinylformamide (2.24 mL, 30 mmol, 1 equiv) and dry THF (60 mL, 0.5 M) under Ar atmosphere. Triethylamine (5.85 mL, 42 mmol, 1.4 equiv) was added via syringe and the reaction was cooled to 0 ºC in an ice water bath. 2-(trifluoromethyl)benzoylchloride (5.30 mL, 36 mmol, 1.2 equiv) was added dropwise via syringe followed by the slow addition of 4-dimethylamino pyridine (0.366 g, 3 mmol, 0.1 equiv). The reaction was warmed to room temperature and let stir until the formation of the imide was complete by TLC (~ 0.5 h, R_f = 0.5, 30:70 EtOAc:hexanes). The reaction was then cooled to 0 ºC in an ice water bath and 5 N NaOH (60 mL in deionized water) was added. The biphasic reaction was stirred vigorously at room temperature until complete consumption of the imide was observed by TLC (~1 h, R_f = 0.3, 30:70 EtOAc:hexanes). The reaction mixture was diluted with water (60 mL) and extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with concentrated aqueous NH_4Cl (2 x 100 mL) and brine (2 x 100 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes) to give the title compound as a white solid (5.108 g, 79% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.53 (m, 3H), 7.44 (s, 1H), 7.11 (ddd, *J* = 15.9, 10.8, 8.8 Hz, 1H), 4.72 (d, *J* = 16.6 Hz, 1H), 4.56 (d, *J* = 8.8 Hz, 1H).

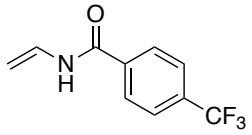
^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.06, 134.90, 132.21, 130.40, 128.65, 128.42, 127.56 (q, *J* = 32.5 Hz), 126.61 (q, *J* = 4.9 Hz), 123.56 (q, *J* = 273.6 Hz), 97.29.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.07.

FTIR (neat) ν_{max}: 3247, 1660, 1642, 1532, 1170, 1129, 1057, 1034, 879, 773 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{10}H_9F_3NO$, 216.0636. Found, 216.0650.

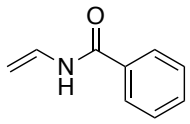
MP: 98-100 ºC



4-(trifluoromethyl)-*N*-vinylbenzamide

Following the same procedure described for **44**, an oven dried 100 mL round bottom flask with stir bar was charged with freshly distilled N-vinylformamide (0.700 mL, 10 mmol, 1 equiv) and dry THF (20 mL, 0.5 M) under Ar atmosphere. Triethylamine (1.95 mL, 14 mmol, 1.4 equiv) was added via syringe and the reaction was cooled to 0 ºC in an ice water bath. 4-(trifluoromethyl)benzoylchloride (1.78 mL, 12 mmol, 1.2 equiv) was added dropwise via syringe followed by the slow addition of 4-dimethylamino pyridine (0.147 g, 1.2 mmol, 0.12 equiv). The reaction was warmed to room temperature and let stir until the formation of the imide was complete by TLC (~ 0.5 h, R_f = 0.8, 30:70 EtOAc:hexanes). The reaction was then cooled to 0 ºC in an ice water bath and 5 N NaOH (20 mL in deionized water) was added. The biphasic reaction was stirred vigorously at room temperature until complete consumption of the imide was observed by TLC (~0.5 h, R_f = 0.6, 30:70 EtOAc:hexanes). The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with concentrated aqueous NH_4Cl (2 x 50 mL) and brine (2 x 50 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography

(10:90 to 30:70 EtOAc:hexanes) to give the title compound as a white solid (0.538 g, 25% yield). The physical properties and spectral data match the reported values.[81]

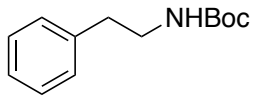


***N*-vinylbenzamide**

Following the same procedure described for **44**, an oven dried 100 mL round bottom flask with stir bar was charged with freshly distilled N-vinylformamide (0.560 mL, 8 mmol, 1 equiv) and dry THF (16 mL, 0.5 M) under Ar atmosphere. Triethylamine (1.56 mL, 11.2 mmol, 1.4 equiv) was added via syringe and the reaction was cooled to 0 ºC in an ice water bath. Benzoylchloride (1.11 mL, 9.6 mmol, 1.2 equiv) was added dropwise via syringe followed by the slow addition of 4-dimethylamino pyridine (0.098 g, 0.8 mmol, 0.1 equiv). The reaction was warmed to room temperature and let stir until the formation of the imide was complete by TLC. The reaction was then cooled to 0 ºC in an ice water bath and 5 N NaOH (20 mL in deionized water) was added. The biphasic reaction was stirred vigorously at room temperature until complete consumption of the imide was observed by TLC. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with concentrated aqueous NH_4Cl (2 x 50 mL) and brine (2 x 50 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes) to give the title compound as a white solid (0.824 g, 70% yield). The physical properties and spectral data match the reported values.[81]

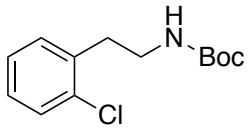
[81] Yuan, M.; Fu, H.; Li, R.; Chen, H., Rh(III)-Catalyzed 4 + 2 Self-Annulation of N-Vinylarylamides. *Organic Letters* **2018,** *20*, 6755-6759.

4.11-X. Characterization Data for Substrates



tert-Butyl phenethylcarbamate (4-1)

Following general procedure A, the reaction of iodobenzene (0.111 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.181 g, 82% yield) as a white solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[82]



tert-Butyl (2-chlorophenethyl)carbamate (4-2)

Following general procedure A, the reaction of 1-chloro-2-iodobenzene (0.122 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.179 g, 70% yield) as a clear, pale yellow oil after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The physical properties and spectral data match the reported values.[83]

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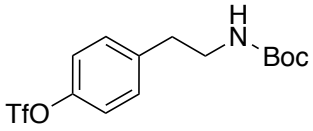
[82] Caddick, S.; Haynes, A. K. D. K.; Judd, B.; Williams, M. R. V., Convenient synthesis of protected primary amines from nitriles. *Tetrahedron Letters* **2000,** *41* (18), 3513-3516.
[83] Li, S.; Ji, H.; Cai, L.; Li, G., Pd(II)-catalyzed remote regiodivergent ortho- and meta-C–H functionalizations of phenylethylamines. *Chemical Science* **2015,** *6*, 5595-5600.



4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl trifluoromethanesulfonate (4-3)

Following general procedure A, the reaction of 4-iodophenyl trifluoromethanesulfonate (0.352 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.323 g, 88% yield) as a white crystalline solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes).

^{1}H NMR (400 MHz, Benzene-d_6) δ 6.73 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 8.6 Hz, 2H), 3.86 (s, 1H), 2.93 (q, J = 6.8 Hz, 2H), 2.24 (t, J = 7.1 Hz, 2H), 1.43 (s, 9H).

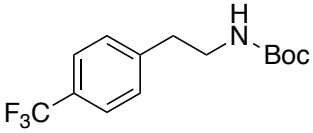
^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.8, 148.2, 139.7, 130.5, 121.3, 118.7 (q, J = 320.8 Hz), 79.4, 41.5, 35.6, 28.3.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.36.

FTIR (neat) ν_{max}: 3381, 2982, 1681, 1524, 1502, 1414, 1248, 1203, 1133, 889 cm^{-1}.

HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{14}H_{18}O_5NF_3NaS$, 392.07500; found, 392.0742.

Mp: 41-43 ºC



***tert*-Butyl (4-(trifluoromethyl)phenethyl)carbamate (4-4)**

Following general procedure A, the reaction of 1-iodo-4-(trifluoromethyl)benzene (0.095 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol,

5 mol%) provided the product (0.245 g, 85% yield) as a white crystalline solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.61 – 7.52 (m, 2H), 7.35 – 7.28 (m, 2H), 4.54 (s, 1H), 3.39 (q, J = 6.8 Hz, 2H), 2.86 (t, J = 7.1 Hz, 2H), 1.43 (s, 9H).

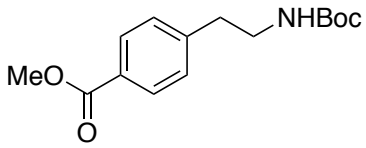
^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.8, 143.1, 129.1, 128.8 (d, $^{2}J_{C\text{-}F}$ = 31.7 Hz), 125.4 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 124.2 (d, $^{1}J_{C\text{-}F}$ = 271.8 Hz), 79.1, 41.5, 36.1, 28.4.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.44.

FTIR (neat) ν_{max}: 3359, 2979, 1704, 1671, 1525, 1325, 1287, 1250, 1156, 1111, 1067, 841, 825 cm^{-1}.

HRMS (NSI) m/z: $[M\text{-}H]^{+}$ calcd. for $C_{14}H_{17}O_2NF_3$, 288.12169; found, 288.12138.

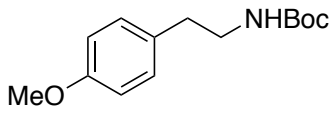
Mp: 74-76 ºC.



Methyl 4-(2-((*tert*-butoxycarbonyl)amino)ethyl)benzoate (4-5)

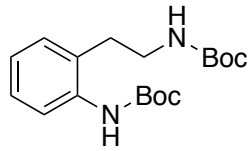
Following general procedure A, the reaction of methyl 4-iodobenzoate (0.234 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.204 g, 73% yield) as a white solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[84]

[84] Ward, R. A.; Brassington, C.; Breeze, A. L.; Caputo, A.; Critchlow, S.; Davies, G.; Goodwin, L.; Hassall, G.; Greenwood, R.; Holdgate, G. A.; Mrosek, M.; Norman, R. A.; Pearson, S.; Tart, J.; Tucker, J. A.; Vogtherr, M.; Whittaker, D.; Wingfield, J.; Winter, J.; Hudson, K., Design and Synthesis of Novel Lactate Dehydrogenase A Inhibitors by Fragment-Based Lead Generation. *Journal of Medicinal Chemistry* **2012,** *55*, 3285-3306.



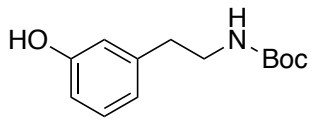
***tert*-Butyl (4-methoxyphenethyl)carbamate (4-6)**

Following general procedure A, the reaction of 4-iodoanisole (0.234 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.153 g, 61% yield) as a white solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[85]



***tert*-Butyl (2-((*tert*-butoxycarbonyl)amino)phenethyl)carbamate (4-7)**

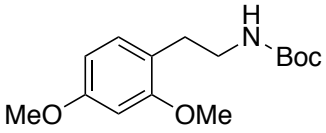
Following general procedure A, the reaction of *t*-butyl (2-iodophenyl)carbamate (0.319 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.204 g, 61% yield) as a clear oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[86]



[85] Jahani, F.; Tajbakhsh, M.; Golchoubian, H.; Khaksar, S., Guanidine hydrochloride as an organocatalyst for N -Boc protection of amino groups. *Tetrahedron Letters* **2011,** *52* (12), 1260--1264.
[86] Dengiz, C.; Zcan, S.; Şahin, E.; Balci, M., New Synthetic Methodology for Construction of the 1,3,4,5-Tetrahydro-2H-1,3-benzodiazepin-2-one Skeleton. *Synthesis* **2010,** *2010* (08), 1365-1370.

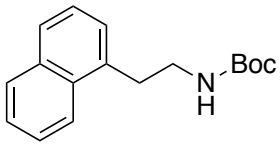
***tert*-Butyl (3-hydroxyphenethyl)carbamate (4-8)**

Following general procedure A, the reaction of 3-iodophenol (0.220 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.171 g, 72% yield) as a clear, thick oil after purification by silica gel chromatography (10:90 to 50:50 EtOAc:hexanes). The physical properties and spectral data match the reported values.[87]



***tert*-Butyl (2,4-dimethoxyphenethyl)carbamate (4-9)**

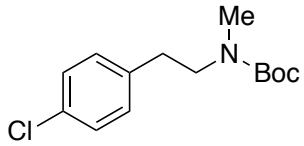
Following general procedure A, the reaction of 1-iodo-2,4-dimethoxybenzene (0.264 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.168 g, 60% yield) as a white solid after purification by silica gel chromatography (5:95 to 35:65 EtOAc:hexanes). The physical properties and spectral data match the reported values.[88]



***tert*-Butyl (2-(naphthalen-1-yl)ethyl)carbamate (4-10)**

[87] Santangelo Freel, R. M.; Ogden, K. K.; Strong, K. L.; Khatri, A.; Chepiga, K. M.; Jensen, H. S.; Traynelis, S. F.; Liotta, D. C., Synthesis and Structure Activity Relationship of Tetrahydroisoquinoline-Based Potentiators of GluN2C and GluN2D Containing N-Methyl-d-aspartate Receptors. *J. Med. Chem.* **2013,** *56* (13), 5351-5381.
[88] Molander, G. A.; Jean-Grard, L., Scope of the Suzuki - Miyaura Aminoethylation Reaction Using Organotrifluoroborates. *Journal of Organic Chemistry* **2007,** *72*, 8422-8426.

Following general procedure A, the reaction of 1-iodonaphthalene (0.149 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.201 g, 74% yield) as a clear oil after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The physical properties and spectral data match the reported values.[89]



***tert*-Butyl (4-chlorophenethyl)(methyl)carbamate (4-11)**

Following general procedure A, the reaction of 1-chloro-4-iodobenzene (0.238 g, 1.00 mmol, 1 equiv), *t*-butyl methyl(vinyl)carbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.167 g, 62% yield) as a clear oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). Isolated as a mixture of rotameric isomers.

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.01 (s, 2H), 6.79 – 6.42 (m, 2H), 3.31 – 2.86 (m, 2H), 2.77 – 2.09 (m, 5H), 1.58 – 1.07 (m, 9H).

^{13}C NMR (151 MHz, Chloroform-*d,* 50 ºC) δ 155.6, 137.9, 132.5, 130.3, 128.7, 79.5, 50.6, 34.6, 33.9, 28.5.

FTIR (neat) ν_{max}: 2975, 2930, 1689, 1491, 1391, 1365, 1164, 1134, 1091, 1016, 809, 770, 732 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{20}O_2NClNa$, 292.10748; found, 292.10761.

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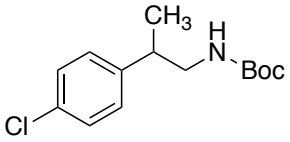
[89] Hunter, C.; Jackson, R. F. W.; Rami, H. K., Efficient synthesis of protected β-phenylethylamines, enantiomerically pure protected beta-phenyl-alpha-benzylethylamines and beta-phenyl-alpha-isopropylethylamines using organozinc chemistry. *Journal of the Chemical Society, Perkin Transactions 1* **2000,** (2), 219-223.



***tert*-Butyl (2-(4-chlorophenyl)propyl)carbamate (4-12)**

Following general procedure A, the reaction of 1-chloro-4-iodobenzene (0.238 g, 1.00 mmol, 1 equiv), *t*-butyl prop-1-en-1-ylcarbamate (0.393 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.161 g, 60% yield) as a white solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes).

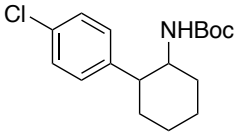
^{1}H NMR (400 MHz, Benzene-d_6) δ 7.04 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 3.99 (s, 1H), 3.15 (dt, J = 13.5, 6.7 Hz, 1H), 2.89 (ddd, J = 13.5, 8.0, 5.5 Hz, 1H), 2.53 (q, J = 7.1 Hz, 1H), 1.42 (s, 9H), 0.86 (d, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.0, 142.9, 132.4, 128.8, 128.7, 79.4, 47.4, 39.7, 28.5, 19.2.

FTIR (neat) ν_{max}: 3315, 2980, 2932, 1694, 1674, 1530, 1493, 1365, 1282, 1244, 1167, 1088, 1047, 1013, 930, 826, 771 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{20}O_2NClNa$, 292.10748; found, 292.10866.

Mp: 59–62 ºC



***tert*-butyl (2-(4-chlorophenyl)cyclohexyl)carbamate (4-13)**

Following general procedure A, the reaction of 1-chloro-4-iodobenzene (59 mg, 0.25 mmol, 1 equiv), *tert*-butyl cyclohex-1-en-1-ylcarbamate (123 mg, 0.625 mmol, 2.5 equiv), PTH (3.4 mg,

0.0125 mmol, 5 mol%), sodium formate (51 mg, 0.75 mmol, 3 equiv), and cyclohexanethiol (1.2 μL, 0.075 mmol, 5 mol%) provided the product (32 mg, 42% yield) as a colorless oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). This compound appears in the ^{1}H and ^{13}C spectrum as a pair of rotomers.

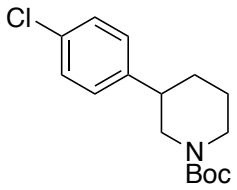
Diastereoselectivity was assigned as 1:1 following deprotection of the amine.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.18 (dd, *J* = 15.8, 8.2 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.00 (s, 1H), 2.77 (d, *J* = 13.4 Hz, 1H), 1.96 – 1.49 (m, 6H), 1.33 (q, *J* = 12.5, 12.0 Hz, 2H), 1.20 (d, *J* = 8.7 Hz, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.10, 141.9, 131.9, 129.0, 128.2, 79.0, 50.2, 45.3, 31.6, 28.2, 25.8, 25.6, 20.6.

FTIR (neat) ν_{max}: 3315, 2980, 2932, 1694, 1674, 1530, 1493, 1365, 1282, 1244, 1167, 1088, 1047, 1013, 930, 826, 771 cm^{-1}.

HRMS (TOF) m/z: $[M-C_4H_8]^+$ calcd. for $C_{13}H_{17}ClNO_2$, 254.09478; found, 254.09810.



***tert*-Butyl 3-(4-chlorophenyl)piperidine-1-carboxylate (4-14)**

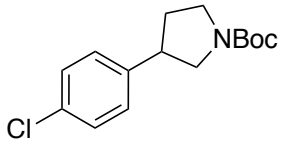
Following general procedure A, the reaction of 1-chloro-4-iodobenzene (0.119 g, 0.50 mmol, 1 equiv), *N*-Boc-3,4-dihydro-2*H*-pyridine (0.230 mL, 1.25 mmol, 2.5 equiv), N-POX (8 mg, 0.025 mmol, 5 mol%), sodium formate (0.102 g, 1.5 mmol, 3 equiv), and cyclohexanethiol (3 μL, 0.025 mmol, 5 mol%) provided the product (0.062 g, 42% yield) as a pale yellow oil after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). Isolated as a mixture of rotameric isomers.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.20 – 7.10 (m, 2H), 4.13 (s, 2H), 2.92 – 2.49 (m, 4H), 2.05 – 1.94 (m, 1H), 1.79 – 1.71 (m, 1H), 1.65 – 1.52 (m, 1H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*, 50 ºC) δ 155.0, 142.2, 132.5, 128.8, 128.6, 79.7, 50.7, 44.4, 42.1, 32.0, 28.7, 25.6.

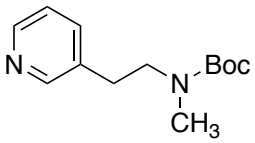
FTIR (neat) ν_{max}: 2976, 2933, 2856, 1687, 1418, 1365, f1253, 1170, 1148, 1136, 821 cm^{-1}.

HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{16}H_{22}O_2NClNa$, 318.12313; found, 318.12308.



***tert*-Butyl 3-(4-chlorophenyl)pyrrolidine-1-carboxylate (4-15)**

Following general procedure A, the reaction of 1-chloro-4-iodobenzene (0.238 g, 1.00 mmol, 1 equiv), *N*-Boc-2,3-dihydro-1*H*-pyrrole (0.431 mL, 2.5 mmol, 2.5 equiv), N-PTH (16 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.148 g, 53% yield) as a clear oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[90]



***tert*-Butyl methyl(2-(pyridin-3-yl)ethyl)carbamate (4-16)**

Following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), *t*-butyl methyl(vinyl)carbamate (0.393 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%),

[90] Greb, A.; Poh, J. S.; Greed, S.; Battilocchio, C.; Pasau, P.; Blakemore, D. C.; Ley, S. V., A Versatile Route to Unstable Diazo Compounds via Oxadiazolines and their Use in Aryl–Alkyl Cross-Coupling Reactions. *Angewandte Chemie - International Edition* **2017,** *56* (52), 16602-16605.

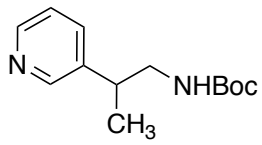
sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product as a mixture of rotameric isomers (0.155 g, 70% yield) as a clear and colorless oil after purification by silica gel chromatography (30:60 to 60:40 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d,* 50 ºC) δ 8.72 – 8.25 (m, 1H), 7.49 (s, 1H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.45 (t, *J* = 7.3 Hz, 2H), 3.08 – 2.62 (m, 5H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d,* 50 ºC) δ 150.4, 148.0, 136.4, 134.8, 123.7, 79.7, 50.1 (d, *J* = 59.1 Hz), 34.5 (d, *J* = 63.7 Hz), 31.5 (d, *J* = 64.2 Hz).28.5. Doublets arise from rotameric mixture.

FTIR (neat) ν_{max}: 2975, 2930, 1687, 1478, 1423, 1392, 1365, 1247, 1216, 1184, 1135, 1051, 1028, 882, 798, 770, 714 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}O_2N_2$, 237.15975; found, 237.15983.



***tert*-Butyl (2-(pyridin-3-yl)propyl)carbamate (4-17)**

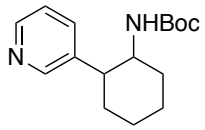
Following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), *t*-butyl prop-1-en-1-ylcarbamate (0.393 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.155 g, 66% yield) as a clear and colorless oil after purification by silica gel chromatography (35:65 to 80:20 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.29 (m, 2H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.58 (s, 1H), 3.38 (dt, *J* = 13.3, 6.5 Hz, 1H), 3.18 (ddd, *J* = 13.8, 8.3, 5.8 Hz, 1H), 3.04 – 2.90 (m, *J* = 7.4, 7.1, 6.0, 4.7 Hz, 1H), 1.38 (s, 9H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 149.4, 148.1, 139.6, 134.5, 123.6, 79.3, 47.2, 37.9, 28.4, 18.8.

FTIR (neat) ν_{max}: 3338, 2973, 2931, 1692, 1522, 1456, 1426, 1365, 1271, 1247, 1167, 1026, 986, 714 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{21}O_2N_2$, 237.15975; found, 237.15976.



***tert*-butyl (2-(pyridin-3-yl)cyclohexyl)carbamate (4-18)**

Following general procedure A, the reaction of 3-iodopyridine (51 mg, 0.25 mmol, 1 equiv), *tert*-butyl cyclohex-1-en-1-ylcarbamate (123 mg, 0.625 mmol, 2.5 equiv), PTH (3.4 mg, 0.0125 mmol, 5 mol%), sodium formate (51 mg, 0.75 mmol, 3 equiv), and cyclohexanethiol (1.2 μL, 0.075 mmol, 5 mol%) provided the product (30 mg, 43% yield) as a colorless oil after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). This compound appears in the ^{1}H and ^{13}C spectrum as a pair of rotomers.

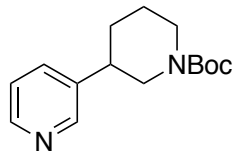
Diastereoselectivity was assigned as 1:1 following deprotection of the amine.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 2.3 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.53 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.19 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.66 (d, *J* = 9.7 Hz, 1H), 4.09 (s, 1H), 2.95 – 2.79 (m, 1H), 2.03 – 1.61 (m, 6H), 1.49 – 1.38 (m, 2H), 1.28 – 1.17 (m, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.0, 149.3, 147.6, 138.6, 135.2, 123.0, 79.2, 50.1, 44.1, 31.6, 29.6, 28.2, 25.5, 20.6.

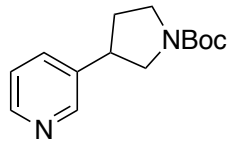
FTIR (neat) ν_{max}: 3270, 2926, 2852, 1694, 1526, 1424, 1389, 1364, 1248, 1168, 1075, 1049, 978, 777, 713 cm^{-1}.

HRMS (TOF) m/z: $[M+H]^+$ calcd. for $C_{16}H_{25}N_2O_2$, 277.19160; found, 277.19520.



***tert*-Butyl 3-(pyridin-3-yl)piperidine-1-carboxylate (4-19)**

Following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), *tert*-butyl 3,4-dihydropyridine-1(2*H*)-carboxylate (0.464 mL, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.120 g, 47% yield) as a clear and colorless oil after purification by silica gel chromatography (25:75 to 75:25 EtOAc:hexanes). The physical properties and spectral data match the reported values.[91]



***tert*-Butyl 3-(pyridin-3-yl)pyrrolidine-1-carboxylate (4-20)**

Following general procedure B, the reaction of 3-iodopyridine (0.1.025 g, 5.00 mmol, 5 equiv), *tert*-butyl pyrrolidine-1-carboxylate (0.181 mL, 1.0 mmol, 1 equiv), N-PTH (16 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.166 g, 67% yield) as a clear and colorless oil after purification by silica gel chromatography (45:55 to 100:0 EtOAc:hexanes). The physical properties and spectral data match the reported values.[92]

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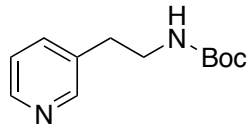
[91] Gonnard, L.; Gurinot, A.; Cossy, J., Cobalt-Catalyzed Cross-Coupling of 3- and 4-Iodopiperidines with Grignard Reagents. *Chemistry - A European Journal* **2015,** *21* (36), 12797-12803.

[92] Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J., Iron- and Cobalt-Catalyzed Arylation of Azetidines, Pyrrolidines, and Piperidines with Grignard Reagents. *Org. Lett.* **2014,** *16* (23), 6160-6163.



***tert*-Butyl (2-(pyridin-3-yl)ethyl)carbamate (4-21)**

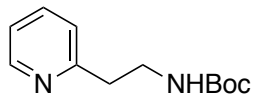
Following general procedure A, the reaction of 3-iodopyridine (0.205 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.202 g, 91% yield) as a clear and colorless oil after purification by silica gel chromatography (50:50 to 100:0 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 4.9 Hz, 1H), 8.42 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.71 (bs, 1H), 3.35 (q, *J* = 6.8 Hz, 2H), 2.78 (t, *J* = 7.1 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 150.3, 148.0, 136.4, 134.6, 123.6, 79.5, 41.6, 33.6, 28.5.

FTIR (neat) ν_{max}: 3353, 2977, 2932, 1737, 1695, 1518, 1424, 1365, 1243, 1166, 1045, 1027, 964, 783, 713 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{12}H_{19}O_2N_2$, 223.14410; found, 223.14396.



***tert*-Butyl (2-(pyridin-2-yl)ethyl)carbamate (4-22)**

Following general procedure A, the reaction of 2-bromopyridine (0.095 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%)

provided the product (0.153 g, 69% yield) as a white solid after purification by silica gel chromatography (40:60 to 80:20 EtOAc:hexanes).

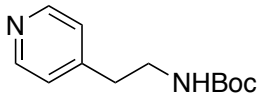
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.59 – 8.41 (m, 1H), 7.59 (td, *J* = 7.6, 1.9 Hz, 1H), 7.19 – 7.07 (m, 2H), 5.16 (s, 1H), 3.53 (q, *J* = 6.4 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.7, 156.1, 149.4, 136.6, 123.6, 121.6, 79.2, 40.1, 38.0, 28.6.

FTIR (neat) ν_{max}: 3215, 2976, 2931, 1702, 1647, 1544, 1366, 1277, 1250, 1164, 950, 871, 769 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{12}H_{19}O_2N_2$, 223.14410; found, 223.14385.

Mp: 69–71 ºC



***tert*-Butyl (2-(pyridin-4-yl)ethyl)carbamate (4-23)**

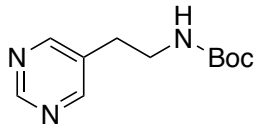
Following general procedure A, the reaction of 4-bromopyridine•HCl (0.195 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.197 g, 89% yield) as a clear and colorless oil after purification by silica gel chromatography (45:55 to 100:0 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 – 8.46 (m, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 4.73 (bs, 1H), 3.37 (q, *J* = 6.7 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 150.0, 148.2, 124.3, 79.6, 40.9, 35.7, 28.5.

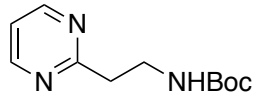
FTIR (neat) ν_{max}: 3336, 2976, 2932, 1689, 1604, 1522, 1455, 1365, 1273, 1250, 1165, 999, 808, 780 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{12}H_{19}O_2N_2$, 223.14410; found, 223.14387.



***tert*-Butyl (2-(pyrimidin-5-yl)ethyl)carbamate (4-24)**

Following general procedure A, the reaction of 5-bromopyrimidine (0.159 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.156 g, 70% yield) as a white solid after purification by silica gel chromatography (50:50 to 100:0 EtOAc:hexanes). The physical properties and spectral data match the reported values.[88]



***tert*-Butyl (2-(pyrimidin-2-yl)ethyl)carbamate (4-25)**

Following general procedure A, the reaction of 2-bromopyrimidine (0.158 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.143 g, 64% yield) as a white solid after purification by silica gel chromatography (40:60 to 80:20 EtOAc:hexanes).

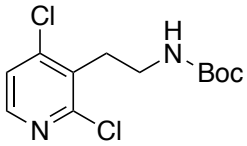
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 4.9 Hz, 2H), 7.15 (t, *J* = 4.9 Hz, 1H), 5.34 (s, 1H), 3.63 (q, *J* = 6.1 Hz, 2H), 3.15 (t, *J* = 6.1 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 169.5, 157.2, 156.0, 118.9, 79.2, 39.2, 38.6, 28.6.

FTIR (neat) ν_{max}: 3289, 2963, 1699, 1560, 1521, 1435, 1363, 1250, 1167, 1145, 1063, 1001, 980, 960, 866, 739 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{18}O_2N_3$, 224.13935; found, 224.13914.

Mp: 88–90 ºC



***tert*-Butyl (2-(2,4-dichloropyridin-3-yl)ethyl)carbamate (4-26)**

Following general procedure A, the reaction of 2,4-dichloro-3-iodopyridine (0.274 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.192 g, 66% yield) as a white crystalline solid after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes).

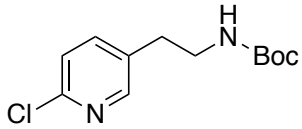
^{1}H NMR (400 MHz, Benzene-d_6) δ 7.59 (d, J = 5.2 Hz, 1H), 6.46 (d, J = 5.2 Hz, 1H), 3.91 (s, 1H), 3.10 (q, J = 6.7 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 153.0, 147.6, 146.3, 132.2, 124.2, 79.4, 38.6, 31.4, 28.4.

FTIR (neat) ν_{max}: 3361, 2966, 2930, 1679, 1542, 1180, 979, 766 cm^{-1}.

HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{12}H_{17}O_2N_2Cl_2$, 291.06616. Found, 291.06542.

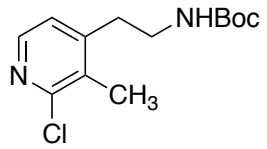
Mp: 62–64 ºC



***tert*-Butyl (2-(6-chloropyridin-3-yl)ethyl)carbamate (4-27)**

Following general procedure A, the reaction of 2-chloro-5-iodopyridine (0.239 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%),

sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.199 g, 78% yield) as a pale, light yellow oil after purification by silica gel chromatography (50:50 to 85:15 EtOAc:hexanes). The physical properties and spectral data match the reported values.[93]



***tert*-Butyl (2-(2-chloro-3-methylpyridin-4-yl)ethyl)carbamate (4-28)**

Following general procedure A, the reaction of 2-chloro-4-iodo-3-methylpyridine (0.095 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.202 g, 75% yield) as a white solid after purification by silica gel chromatography (10:90 to 60:40 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 4.9 Hz, 1H), 7.00 (d, *J* = 4.9 Hz, 1H), 4.65 (s, 1H), 3.34 (q, *J* = 6.9 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.43 (s, 9H).

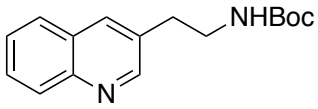
^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.9, 152.7, 149.4, 146.6, 131.3, 123.9, 79.8, 40.3, 34.2, 28.5, 15.8.

FTIR (neat) ν_{max}: 3243, 2968, 1713, 1548, 1437, 1363, 1274, 1249, 1223, 1054, 819 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{20}O_2N_2Cl$, 271.12078; found, 271.12068.

Mp: 96–98 ºC

[93] Phillips, D. P.; Gao, W.; Yang, Y.; Zhang, G.; Lerario, I. K.; Lau, T. L.; Jiang, J.; Wang, X.; Nguyen, D. G.; Bhat, B. G.; Trotter, C.; Sullivan, H.; Welzel, G.; Landry, J.; Chen, Y.; Joseph, S. B.; Li, C.; Gordon, W. P.; Richmond, W.; Johnson, K.; Bretz, A.; Bursulaya, B.; Pan, S.; Mcnamara, P.; Seidel, H. M., Discovery of Tri-fluoromethyl(pyrimidin-2-yl)azetidine-2-carboxamides as Potent, Orally Bioavailable TGR5 (GPBAR1) Agonists: Structure − Activity Relationships, Lead Optimization, and Chronic In Vivo Efficacy. *Journal of Medicinal Chemistry* **2014,** *57*, 3263-3282.



***tert*-Butyl (2-(quinolin-3-yl)ethyl)carbamate (4-29)**

Following general procedure A, the reaction of 3-bromoquinoline (0.136 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.195 g, 72% yield) as a yellow crystalline solid after purification by silica gel chromatography (35:65 to 80:20 EtOAc:hexanes).

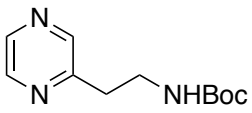
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.75 (d, *J* = 2.2 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 4.76 (s, 1H), 3.46 (q, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.0, 152.0, 147.2, 135.1, 131.9, 129.3, 129.0, 128.2, 127.5, 126.9, 79.6, 77.4, 77.2, 76.9, 41.7, 33.7, 28.5.

FTIR (neat) ν_{max}: 3241, 2973, 2930, 1703, 1530, 1500, 1364, 1280, 1248, 1167, 1140, 957, 789, 752 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{21}O_2N_2$, 273.15975; found, 273.15949.

Mp: 95–97 ºC



***tert*-Butyl (2-(pyrazin-2-yl)ethyl)carbamate (4-30)**

Following general procedure A, the reaction of 2-iodopyrazine (0.099 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%)

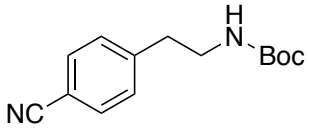
provided the product (0.151 g, 68% yield) as a yellow solid after purification by silica gel chromatography (40:60 to 80:20 EtOAc:hexanes).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.49 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.45 (d, *J* = 1.5 Hz, 1H), 8.41 (d, *J* = 2.6 Hz, 1H), 5.03 (s, 1H), 3.54 (q, *J* = 6.4 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.0, 155.3, 145.2, 144.2, 142.7, 79.5, 39.5, 35.3, 28.5.

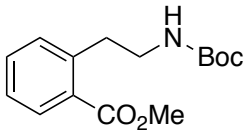
FTIR (neat) ν_{max}: 3326, 2930, 1707, 1524, 1446, 1366, 1251, 1230, 1059, 979, 962, 834, 782 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{11}H_{18}O_2N_3$, 224.13935; found, 224.13933.



***tert*-Butyl (4-cyanophenethyl)carbamate (4-31)**

Following general procedure A, the reaction of 4-chlorobenzonitrile (0.138 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.212 g, 86% yield) as a white solid after purification by silica gel chromatography (5:95 to 40:60 EtOAc:hexanes). The physical properties and spectral data match the reported values.[94]



Methyl 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)benzoate (4-32)

[94] Molander, G. A.; Vargas, F., B-Aminoethyltrifluoroborates : Efficient Aminoethylations via Suzuki − Miyaura. *Organic Letters* **2007,** *9* (2), 203-206.

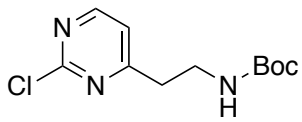
Following general procedure A, the reaction of methyl 2-chlorobenzoate (0.0853 g, 0.50 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.179 g, 1.25 mmol, 2.5 equiv), PTH (6.75 mg, 0.025 mmol, 5 mol%), sodium formate (0.102 g, 1.50 mmol, 3 equiv), and cyclohexanethiol (3 μL, 0.025 mmol, 5 mol%) provided the product (0.123 g, 88% yield) as a clear, light yellow oil after purification by silica gel chromatography (10:90 to 20:80 EtOAc:hexanes).

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.84 (d, J = 7.9 Hz, 1H), 7.07 – 6.76 (m, 3H), 4.56 (s, 1H), 3.59 – 3.34 (m, 5H), 3.06 (t, J = 7.0 Hz, 2H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.1, 156.1, 141.1, 132.3, 131.7, 130.9, 129.4, 126.5, 79.0, 52.1, 42.0, 34.6, 28.5.

FTIR (neat) ν_{max}: 3376, 2976, 1705, 1510, 1365, 1208, 1138, 1086, 960, 750 cm^{-1}.

HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{15}H_{22}O_4N$, 280.15433. Found, 280.15366.



***tert*-Butyl (2-(2-chloropyrimidin-4-yl)ethyl)carbamate (4-33)**

Following general procedure A, the reaction of 2,4-dichloropyrimidine (0.075 g, 0.50 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.179 g, 1.25 mmol, 2.5 equiv), PTH (6.75 mg, 0.025 mmol, 5 mol%), sodium formate (0.102 g, 1.50 mmol, 3 equiv), and cyclohexanethiol (3 μL, 0.025 mmol, 5 mol%) provided the product (0.090 g, 70% yield) as a white crystalline solid after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes).

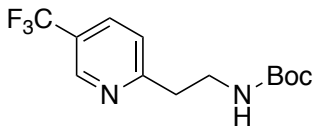
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, J = 5.0 Hz, 1H), 7.15 (d, J = 5.0 Hz, 1H), 4.85 (s, 1H), 3.54 (q, J = 6.4 Hz, 2H), 2.97 (t, J = 6.5 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.8, 161.4, 159.3, 155.9, 119.6, 79.7, 38.8, 37.7, 28.5.

FTIR (neat) ν_{max}: 3372, 2925, 1701, 1572, 1506, 1361, 1245, 1158, 1141, 972, 760 cm^{-1}.

HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{11}H_{17}O_2N_3Cl$, 258.10038. Found, 258.10005.

Mp: 63–66 ºC



***tert*-Butyl (2-(5-(trifluoromethyl)pyridin-2-yl)ethyl)carbamate (4-34)**

Performed on a 10 mmol scale in a Schlenk flask, following general procedure A, the reaction of 2-chloro-5-(trifluoromethyl)pyridine (0.1.82 g, 10.0 mmol, 1 equiv), *t*-butyl vinylcarbamate (3.58 g, 25 mmol, 2.5 equiv), PTH (0.135 g, 0.50 mmol, 5 mol%), sodium formate (2.04 g, 30.0 mmol, 3 equiv), and cyclohexanethiol (60 μL, 0.50 mmol, 5 mol%) provided the product (2.15 g, 74% yield) as an off-white crystalline solid after purification by silica gel chromatography (30:70 to 50:50 EtOAc:hexanes).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.85 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 5.04 (s, 1H), 3.57 (q, *J* = 6.4 Hz, 2H), 3.07 (t, *J* = 6.5 Hz, 2H), 1.42 (s, 9H).

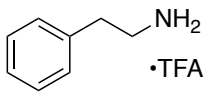
^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.7, 156.0, 146.4, 133.7, 133.6, 124.9, 123.4, 79.8, 79.5, 39.6, 38.1, 28.5.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.31.

FTIR (neat) ν_{max}: 3276, 2978, 2930, 1697, 1542, 1327, 1276, 1249, 1125, 1018, 948 cm^{-1}.

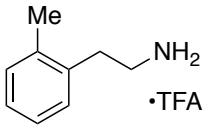
HRMS (NSI) m/z: $[M-H]^+$ calcd. for $C_{13}H_{18}O_2N_2F_3$, 291.13149. Found, 291.13079.

Mp: 106–108 ºC



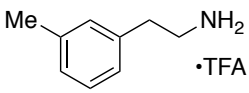
2-phenylethan-1-amine, TFA (4-35)

Following general procedure A, the reaction of iodobenzene (0.111 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (10:90 to 40:60 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added to provide a white crystalline solid which was collected by filtration (0.164 g, 75% yield). The physical properties and spectral data match the reported values.[95]



2-(*o*-tolyl)ethan-1-amine, TFA (4-36)

Following general procedure A, the reaction of 2-iodotoluene (0.127 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (5:95 to 20:80 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added to provide a white crystalline solid which was collected by filtration (0.165 g, 71% yield). The physical properties and spectral data match the reported values.[96]

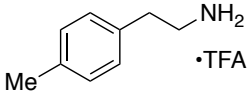


[95] Lui, E. K. J.; Brandt, J. W.; Schafer, L. L., Regio- and Stereoselective Hydroamination of Alkynes Using an Ammonia Surrogate: Synthesis of N - Silylenamines as Reactive Synthons. *Journal of the American Chemical Society* **2018,** *140*, 4973-4976.

[96] Liu, M.-c.; Lin, T.-s.; Penketh, P.; Sartorelli, A. C., Synthesis and Antitumor Activity of 4- and 5-Substituted Derivatives of Isoquinoline-l-carboxaldehyde Thiosemicarbazone. *Journal of Medicinal Chemistry* **1995,** *38*, 4234-4243.

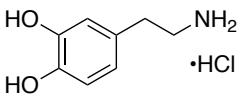
2-(*m*-tolyl)ethan-1-amine, TFA (4-37)

Following general procedure A, the reaction of 3-iodotoluene (0.128 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (5:95 to 20:80 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added to provide a white crystalline solid which was collected by filtration (0.154 g, 66% yield). The physical properties and spectral data match the reported values.[97]



2-(*p*-tolyl)ethan-1-amine, TFA (4-38)

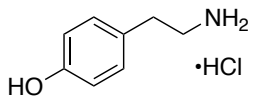
Following general procedure A, the reaction of 4-iodotoluene (0.111 mL, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (10:90 to 40:60 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Dietheyl ether was added to provide a white crystalline solid which was collected by filtration (0.168 g, 72% yield . The physical properties and spectral data match the reported values.[95]



[97] Mukherjee, A.; Srimani, D.; Chakraborty, S.; Ben-david, Y.; Milstein, D., Selective Hydrogenation of Nitriles to Primary Amines Catalyzed by a Cobalt Pincer Complex. *Journal of the American Chemical Society* **2015,** *137*, 8888-8891.

4-(2-aminoethyl)benzene-1,2-diol, HCl (4-39)

Following general procedure A, the reaction of 4-bromo-1,2-phenylene di-*tert*-butyl bis(carbonate) (0.389 g, 1.00 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the trisboc-protected product after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added but failed to produce a solid, methanolic HCl was added dropwise and the mixture was concentrated by rotary evaporation. The addition of diethyl ether provided the product as an off white crystalline solid (0.142 g, 75% yield). The physical properties and spectral data match the reported values.[98]

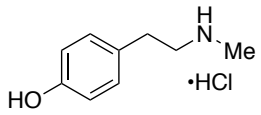


4-(2-aminoethyl)phenol, HCl (4-40)

Following general procedure A, the reaction of *tert*-butyl (4-iodophenyl) carbonate (0.320 g, 1.00 mmol, 1 equiv), *t*-butyl (vinyl)carbamate (0.358 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the bis-boc-protected product after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Dietheyl ether was added but failed to produce a solid, methanolic HCl was added dropwise and the mixture was concentrated by rotary evaporation. The addition of diethyl ether

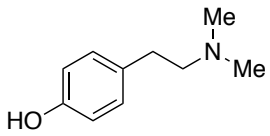
[98] Ding, P.; Wang, H.; Song, B.; Ji, X.; Su, Y.; He, Y., In Situ Live-Cell Nucleus Fluorescence Labeling with Bioinspired Fluorescent Probes. *Analytical Chemistry* **2017,** *89*, 7861-7868.

provided the product as an off white crystalline solid (0.119 g, 69% yield). The physical properties and spectral data match the reported values.[99]



4-(2-(methylamino)ethyl)phenol, HCl (4-41)

Following general procedure A, the reaction of *tert*-butyl (4-iodophenyl) carbonate (0.320 g, 1.00 mmol, 1 equiv), *t*-butyl methyl(vinyl)carbamate (0.393 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the bis-boc-protected product after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added but failed to produce a solid, methanolic HCl was added dropwise and the mixture was concentrated by rotary evaporation. The addition of diethyl ether provided the product as an off white crystalline solid (0.116 g, 62% yield). The physical properties and spectral data match the reported values.[100]

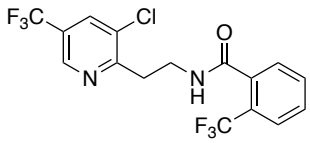


4-(2-(dimethylamino)ethyl)phenol (4-42)

Following general procedure A, the reaction of *tert*-butyl (4-iodophenyl) carbonate (0.320 g, 1.00 mmol, 1 equiv), *t*-butyl methyl(vinyl)carbamate (0.393 g, 2.5 mmol, 2.5 equiv), PTH (13.5 mg,

[99] Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T., Microwave-Assisted Deacylation of Unactivated Amides Using Using Ammonium-Salt-Accelerated Transamidation. *Angewandte Chemie - International Edition* **2012,** *51*, 8564-8567.
[100] Ruolto, A. E.; Hajipour, A. R.; Uyen, B.; Dominique, A. Sigma-1 Receptor Ligans and Methods of Use. US Patent 064970, May 27, 2010.

0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the bis-boc-protected product after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes). The purified product was transferred to a 100 mL round bottom flask with a stir bar equipped with a reflux condenser and the atmosphere was exchanged by applying vacuum and backfilling with Ar (this process was completed three times). Dry THF (10 mL) was added to the flask followed by $LiAlH_4$ (2.5 equiv). The reaction was heated to 65 ºC and let stir overnight. The reaction was quenched by the addition of concentrated aqueous Na_2SO_4, diluted with 20 mL of water, and then extracted with DCM (3 x 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated by rotary evaporation to give the dimethyl deprotected product as a white crystalline solid requiring no further purification (0.095 g, 58% yield). The physical properties and spectral data match the reported values.[101]



***N*-(2-(3-chloro-5-(trifluoromethyl)pyridine-2-yl)ethyl)-2-(trifluoromethyl)benzamide (4-45)**

Following general procedure C, the reaction of 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (0.781 g, 3 mmol, 3 equiv), 2-(trifluoromethyl)-N-vinylbenzamide (0.215 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.368 g, 93% yield) as a off white solid after purification by silica gel chromatography (10:90 to 50:50 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51 (s, 2H), 6.66 (s, 1H), 4.00 (q, *J* = 6.0 Hz, 2H), 3.30 (t, *J* = 5.9 Hz, 2H).

[101] Bahceevli, A.; Kurucu, S.; Kolak, U.; Topcu, F.; Adou, E.; Kingston, D. G. I., Alkaloids and Aromatics of Cyathobasis fruticulosa (Bunge) Aellen. *Journal of Natural Products* **2005,** *68*, 956-958.

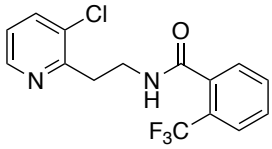
^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.67, 160.75, 143.58 (q, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 136.03 ($^{4}J_{C\text{-}F}$, *J* = 2.5 Hz), 133.80 ($^{4}J_{C\text{-}F}$, *J* = 3.7 Hz), 132.02, 131.93, 129.72, 128.63, 127.06 (q, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 126.27 (q, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 125.93 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz), 123.55 (q, $^{1}J_{C\text{-}F}$ = 273.7 Hz), 122.71 (q, $^{1}J_{C\text{-}F}$ = 272.7 Hz), 36.81, 34.07.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.05, -62.29.

FTIR (neat) ν_{max}: 3265, 1640, 1549, 1313, 1170, 1127, 1033, 768 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{12}ClF_6N_2O$, 397.0542. Found, 397.0350.

Mp: 107-109 ºC



***N*-(2-(3-chloropyridin-2-yl)ethyl)-2-(trifluoromethyl)benzamide (4-46)**

Following general procedure C, the reaction of 2-bromo-3-chloropyridine (0.579 g, 3 mmol, 3 equiv), 2-(trifluoromethyl)-N-vinylbenzamide (0.215 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.302 g, 92% yield) as a white crystalline solid after purification by silica gel chromatography (10:90 to 50:50 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (d, *J* = 4.6 Hz, 1H), 7.66 (dd, *J* = 10.9, 8.1 Hz, 2H), 7.58 – 7.46 (m, 3H), 7.13 (dd, *J* = 8.1, 4.6 Hz, 1H), 6.83 (s, 1H), 3.97 (q, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 5.9 Hz, 2H).

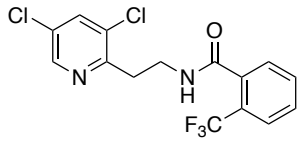
^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.72, 156.76, 146.99, 137.01, 136.44 (d, $^{4}J_{C\text{-}F}$ = 2.2 Hz), 132.09, 131.85, 129.71, 128.79, 127.28 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz), 126.36 (q, $^{3}J_{C\text{-}F}$ = 5.0 Hz), 123.70 (q, $^{1}J_{C\text{-}F}$ = 273.7 Hz) 122.75, 37.43, 33.84.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.07.

FTIR (neat) ν_{max}: 3270, 1640, 1548, 1448, 1431, 1316, 1270, 1174, 1126, 1110, 1061, 1035, 794, 710 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{13}ClF_3N_2O$, 329.0669. Found, 329.0680.

Mp: 95-98 ºC



***N*-(2-(3,5-dichloropyridin-2-yl)ethyl)-2-(trifluoromethyl)benzamide (4-47)**

Following general procedure C, the reaction of 2-bromo-3,5-dichloropyridine (0.681 g, 3 mmol, 3 equiv), 2-(trifluoromethyl)-N-vinylbenzamide (0.215 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.325 g, 86% yield) as an off white solid after purification by silica gel chromatography (10:90 to 50:50 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.35 (s, 1H), 7.71 (s, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51 (s, 2H), 6.64 (s, 1H), 3.95 (q, *J* = 6.1 Hz, 2H), 3.20 (t, *J* = 6.0 Hz, 2H).

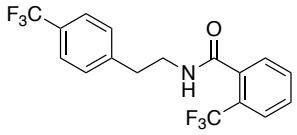
^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.63, 154.81, 145.79, 136.35, 136.12 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 131.99, 131.76, 130.11, 129.67, 128.63, 127.10 (q, $^2J_{C\text{-}F}$ = 31.8 Hz), 126.25 (q, $^3J_{C\text{-}F}$ = 5.0 Hz), 123.70 (q, $^1J_{C\text{-}F}$ = 273.7), 37.10, 33.37.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -59.04.

FTIR (neat) ν_{max}: 3273, 2160, 1642, 1313, 1170, 1127, 1033, 768 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{12}Cl_2F_3N_2O$, 397.0542. Found, 397.0350.

Mp: 106-108 ºC



2-(trifluoromethyl)-*N*-(4-(trifluoromethyl)phenethyl)benzamide (4-48)

Following general procedure C, the reaction of 4-iodobenzotrifluoride (0.816 g, 3 mmol, 3 equiv), 2-(trifluoromethyl)-N-vinylbenzamide (0.215 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.317 g, 88% yield) as a white solid after purification by silica gel chromatography (10:90 to 30:70 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.49 (m, 4H), 7.43 (d, *J* = 7.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 3.73 (q, *J* = 6.6 Hz, 2H), 3.00 (t, *J* = 6.8 Hz, 2H).

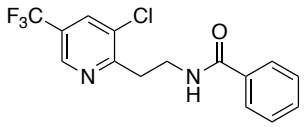
^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.87, 142.72, 135.71 (d, $^{4}J_{C\text{-}F}$ = 2.4 Hz), 132.05, 129.89, 129.10, 128.48 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 127.17 (q, $^{2}J_{C\text{-}F}$ = 31.8 Hz), 126.38 (q, $^{3}J_{C\text{-}F}$ = 5.0 Hz), 125.93, (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz), 125.59 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz), 124.19 (q, $^{1}J_{C\text{-}F}$ = 273.6 Hz), 123.59 (q, $^{1}J_{C\text{-}F}$ = 273.6 Hz), 40.95, 35.27.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -58.85, -62.49.

FTIR (neat) ν_{max}: 3278, 2362, 2337, 1646, 1531, 1329, 1312, 1177, 1127, 1068, 769 cm^{-1}.

HRMS (NSI) m/z: $[M\text{-}F]^-$ calcd. for $C_{17}H_{15}F_5NO$, 342.0917. Found, 342.0937.

Mp: 109-112 ºC



***N*-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)benzamide (4-49)**

Following general procedure C, the reaction of 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (0.781 g, 3 mmol, 3 equiv), N-vinylbenzamide (0.147 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05

mmol, 5 mol%) provided the product (0.268 g, 82% yield) as white solid after purification by silica gel chromatography (5:95 to 55:45 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.07 (s, 1H), 3.99 (q, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H).

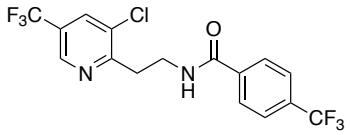
^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.42, 161.33, 143.81 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 134.74, 134.07 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 132.14, 131.56, 128.70, 127.00, 126.14 (q, $^2J_{C\text{-}F}$ = 33.7 Hz), 122.71 (q, $^1J_{C\text{-}F}$ = 272.7), 37.12, 34.64.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.23.

FTIR (neat) ν_{max}: 3274, 1666, 1593, 1494, 1405, 1144, 978, 779 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{15}H_{13}ClF_3N_2O$, 329.0669. Found, 329.0691.

Mp: 102-104 ºC



***N*-(2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)-4-(trifluoromethyl)benzamide (4-50)**

Following general procedure C, the reaction of 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (0.781 g, 3 mmol, 3 equiv), 4-(trifluoromethyl)-*N*-vinylbenzamide (0.147 g, 1 mmol, 1 equiv), PTH (13.5 mg, 0.05 mmol, 5 mol%), sodium formate (0.204 g, 3.00 mmol, 3 equiv), and cyclohexanethiol (6 μL, 0.05 mmol, 5 mol%) provided the product (0.268 g, 82% yield) as white solid after purification by silica gel chromatography (5:95 to 55:45 EtOAc:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 4.01 (q, *J* = 5.9 Hz, 2H), 3.33 (t, *J* = 5.8 Hz, 2H).

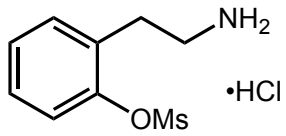
^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.96, 161.03, 143.66 (q, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 137.87, 134.03 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 133.18 (q, $^{2}J_{C\text{-}F}$ = 32.8 Hz), 132.03, 126.15 (q, $^{2}J_{C\text{-}F}$ = 34.0 Hz), 125.64 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.66 (q, $^{1}J_{C\text{-}F}$ = 272.5 Hz), 122.66 (q, $^{1}J_{C\text{-}F}$ = 273.0 Hz), 37.11, 34.26.

^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.25, -62.98.

FTIR (neat) ν_{max}: 3270, 1593, 1518, 1494, 1156, 1129, 857, 779 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{16}H_{12}ClF_6N_2O$, 397.0542. Found, 397.0350.

Mp: 144-146 ºC



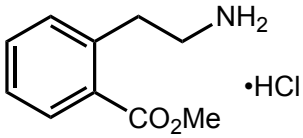
2-(2-aminoethyl)phenyl methanesulfonate, HCl

Following the general procedure, the reaction of 2-iodophenyl methanesulfonate (0.447 g, 1.5 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.536 g, 3.75 mmol, 2.5 equiv), PTH (20 mg, 0.075 mmol, 5 mol%), sodium formate (0.306 g, 4.5 mmol, 3 equiv), and cyclohexanethiol (9 μL, 0.075 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (12 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added followed by cold methanolic HCl. The mixture was concentrated by rotary evaporation and reconstituted in diethyl ether to yield a light orange crystalline solid which was collected by filtration (0.265 g, 70% yield).

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.52 – 7.26 (m, 4H), 3.43 – 3.18 (m, 2H), 3.11 (dd, *J* = 9.4, 6.0 Hz, 2H).

^{13}C NMR (126 MHz, Methanol-d_4) δ 147.63, 130.96, 130.07, 128.64, 127.48, 122.43, 48.11, 47.94, 47.77, 47.60, 47.43, 47.26, 47.09, 39.29, 37.26, 27.78.

HRMS (ESI) m/z: $[M-Cl]^-$ calcd. for $C_9H_{14}NO_3S$, 216.0689. Found, 216.0374.



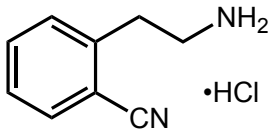
methyl 2-(2-aminoethyl)benzoate, HCl

Following the general procedure, the reaction of methyl 2-chlorobenzoate (0.215 g, 1.50 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.536 g, 3.75 mmol, 2.5 equiv), PTH (21.0 mg, 0.075 mmol, 5 mol%), sodium formate (0.306 g, 4.50 mmol, 3 equiv), and cyclohexanethiol (9 μL, 0.075 mmol, 5 mol%) provided the Boc-protected compound after purification by silica gel chromatography (10:90 to 20:80 EtOAc:hexanes). The purified compound was then stirred overnight in 25% TFA/DCM (12 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added followed by cold methanolic HCl. The mixture was concentrated by rotary evaporation and reconstituted in diethyl ether to yield a off-white crystalline solid which was collected by filtration (0.288 g, 89% yield). The physical properties and spectral data match the reported values.

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.99 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.46 – 7.36 (m, 2H), 3.92 (s, 3H), 3.43 – 3.15 (m, 4H).

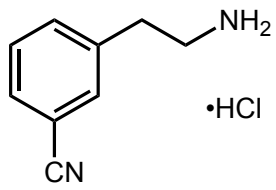
^{13}C NMR (126 MHz, Methanol-d_4) δ 167.58, 138.32, 132.56, 131.42, 130.82, 129.48, 127.24, 51.33, 48.09, 47.92, 47.75, 47.58, 47.41, 47.24, 47.07, 40.55, 32.02.

HRMS (ESI) m/z: $[M-Cl]^-$ calcd. for $C_{10}H_{14}NO_2$, 180.1025. Found, 180.0689.



2-(2-aminoethyl)benzonitrile, HCl

Following the general procedure, the reaction of 2-chlorobenzonitrile (1.1 g, 8 mmol, 1 equiv), *t*-butyl vinylcarbamate (2.86 g, 20 mmol, 2.5 equiv), PTH (110 mg, 0.40 mmol, 5 mol%), sodium formate (1.6 g, 24 mmol, 3 equiv), and cyclohexanethiol (49 μL, 0.4 mmol, 5 mol%) provided the Boc-protected compound after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (30 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added followed by cold methanolic HCl. The mixture was concentrated by rotary evaporation and reconstituted in diethyl ether to yield a white crystalline solid which was collected by filtration (0.834 g, 57% yield). The physical properties and spectral data match the reported values.[102]

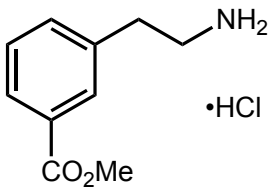


3-(2-aminoethyl)benzonitrile, HCl

Following the general procedure, the reaction of 3-iodobenzonitrile (0.343 g, 1.5 mmol, 1 equiv), *t*-butyl vinylcarbamate 0.536 g, 3.75 mmol, 2.5 equiv), PTH (21 mg, 0.075 mmol, 5 mol%), sodium formate (0.306 g, 4.5 mmol, 3 equiv), and cyclohexanethiol (9 μL, 0.075 mmol, 5 mol%) provided the Boc-protected after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (12 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added followed by cold methanolic HCl. The mixture was concentrated by rotary evaporation and reconstituted in diethyl ether to yield a white crystalline solid which was

[102] Li, S.; Cia, L.; Ji, H.; Yang, L.; Li, G. *Nature Commun.* **2016**, *7*, 10443

collected by filtration (0.202 g, 74% yield). The physical properties and spectral data match the reported values.[103]



methyl 3-(2-aminoethyl)benzoate, HCl

Following the general procedure, the reaction of methyl-3-iodobenzoate (0.393 g, 1.50 mmol, 1 equiv), *t*-butyl vinylcarbamate (0.536 g, 3.75 mmol, 2.5 equiv), PTH (21 mg, 0.075 mmol, 5 mol%), sodium formate (0.306 g, 4.50 mmol, 3 equiv), and cyclohexanethiol (9 μL, 0.075 mmol, 5 mol%) provided the boc-protected product after purification by silica gel chromatography (5:95 to 30:70 EtOAc:hexanes). The purified product was then stirred overnight in 25% TFA/DCM (8 mL). The reaction was concentrated by rotary evaporation and azeotroped with toluene. Diethyl ether was added followed by cold methanolic HCl. The mixture was concentrated by rotary evaporation and reconstituted in diethyl ether to yield a white crystalline solid which was collected by filtration (0.255 g, 79% yield). The physical properties and spectral data match the reported values.[104]

Reaction in Schlenk Flask on 10 mmol Scale:

[103] Pensa, A. V.; Cinelli, M. A.; Li, H.; Chreifi, G.; Mukherjee, P.; Roman, L. J.; Martásek, P.; Poulos, T. L.; Silverman, R. B. *J. Med. Chem.* **2017**, *60*, 7146.

[104] Fontán, N.; García-Domíngues, P.; Álvarez, R.; de Lera, A. R. *Bioorg. Med. Chem.* **2013**, *21*, 2056.