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Cecilia M. Hendy Date

Radical Reactivity via Transient Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$)

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Doctor of Philosophy

Chemistry

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Radical Reactivity via Transient Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$)

By

Cecilia M. Hendy

B.S., College of Charleston, 2018

Advisor: Simon B. Blakey, Ph.D.

An abstract of
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Abstract

Radical Reactivity via Transient Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$)

By: Cecilia M. Hendy

Single electron reduction is a straightforward pathway towards the formation of valuable radical intermediates from electron poor substrates. Visible-light photoredox catalysis has transpired at the forefront of single electron chemistry over the past decade owing to its exceedingly mild energetic requirements and its ability to promote unprecedented carbon-carbon and carbon-heteroatom bond formations. However, a variety of valuable radical precursors extend beyond the energetic limits of traditional photoredox catalysts. We have developed an alternative method towards single electron reduction that relies on the carbon dioxide radical anion ($CO_2^{\bullet-}$) as a powerful single electron reductant ($E^{\circ}_{1/2}$= -2.21 V vs SCE). We generate $CO_2^{\bullet-}$ through a hydrogen atom transfer (HAT) between formate and a thiol HAT catalyst. In addition to reduction, we found $CO_2^{\bullet-}$ undergoes radical conjugate addition with electron deficient olefins that have more negative reductions potentials to form the corresponding carboxylated products. Following these initial discoveries detailed in chapter 2, we exploit the highly reducing nature of $CO_2^{\bullet-}$ towards a variety of reductive transformations that enable unique carbon-carbon bond formations. The $CO_2^{\bullet-}$ system enabled highly selective 5-*exo* radical cyclizations from bromopyridines which was demonstrated in conjunction with a method to selectively form the 6-*endo* product. The selectivity was controlled through the choice of HAT catalyst. Last, we report a method developed for the coupling of difluorobenzylic radicals with N,N-dialkylhydrazones to form unique β-difluorobenzylic hydrazines.

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Reflecting on my journey through graduate school, I am filled with gratitude for the people who have supported me along the way. I have grown and learned so much not only as a chemist but as a person. No matter how many challenges and unexpected twists and turns that I've experienced in the past five years, I am so thankful to have had the opportunity to pursue what I love and meet so many amazing and inspirational people who have shared this passion for chemistry with me.

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List of Abbreviations

3DPAFIPN	2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
4CzTPN	2,3,5,6-tetrakis(carbazol-9-yl)-1,4-dicyanobenzene
AcOH	acetic acid
AIBN	azobisisobutyronitrile
APCI	atmospheric-pressure chemical ionization
CySH	cyclohexanethiol
CV	cyclic voltammetry
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	density functional theory
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
Et_2O	diethyl ether
EtOAc	ethyl acetate
GCMS	gas chromatography mass spectrometry
HAT	hydrogen atom transfer
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
LCMS	liquid chromatography mass spectrometry

MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
PC	photocatalyst
PCET	proton-coupled electron transfer
PhSH	thiophenol
PTFE	polytetrafluoroethylene
PTH	10-phenylphenothiazine
SCE	saturated calomel electrode
SET	single electron transfer
TAS	transient absorption spectroscopy
TBDPS	*tert*-Butyldiphenylsilyl
TEA	triethylamine
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1:

Introduction to Single Electron Reduction and Photoredox Catalysis

1.1 Single Electron Reduction in Organic Synthesis

The overarching goal of synthetic chemistry is the intentional manipulation of organic molecules through the formation of new carbon-carbon or carbon-heteroatom bonds that are important to many scientific areas such as drug discovery, chemical biology, and materials science. Consequently, there is a constant demand for new technologies that expand and improve upon the possible chemical transformations that can be performed synthetically, particularly, reactions that are sustainable, economical, and safe. While the earliest synthetic transformations operated through closed-shell two electron pathways, reactions involving open-shell radical intermediates have become increasingly prevalent due to their unique reactivity. Single electron reactions usually display umpolung reactivity and complimentary selectivities to their two electron counterparts opening unexplored territories of chemical reactivity.

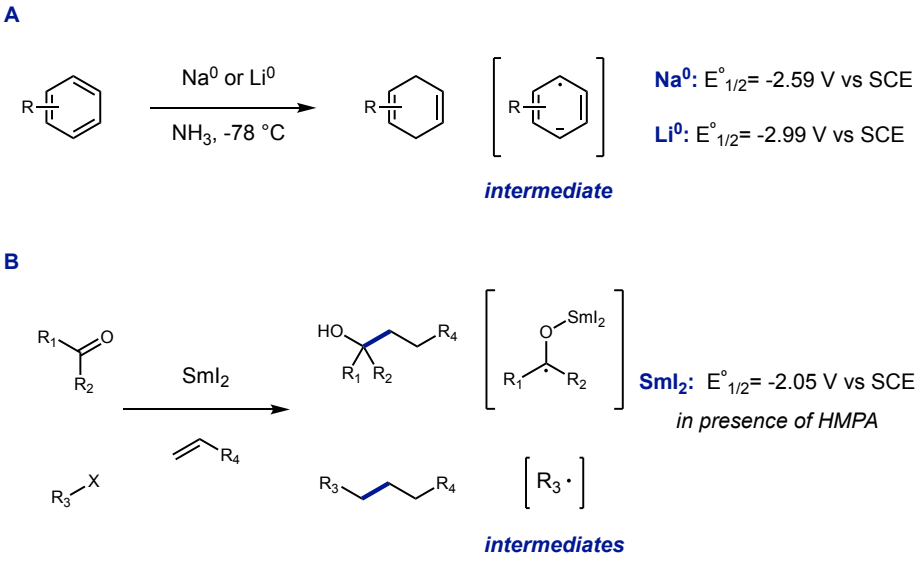
1.1.1 Single Electron Reduction

Regarding radical generation, single electron reduction is, perhaps, one of the most routinely employed strategies.[1] This can be accredited to the diverse range of electron-poor substrate classes that can undergo single electron transfer (SET). The Birch reduction is one of the oldest examples of single electron reduction dating back to the 1940s.[2] It involves dissolving alkali metals (e.g. sodium or lithium) in liquid ammonia to generate solvated electrons that can perform powerful single electron reductions. The Birch reduction specifically describes a reaction involving the dearomatization of aromatic compounds to form 1,4-cyclohexyldienes (Scheme 1.1A), however, dissolving alkali metal techniques have been utilized for many other types of reductive transformations.[3] Electrochemical techniques can also perform powerful single electron reductions reaching highly negative potentials.[4] However, these approaches are limited in their

ability to promote free radical reactivity because the transient radical intermediates undergo a rapid sequential single-electron reduction to the corresponding anions.[5]

Samarium diiodide (SmI_2), introduced a few decades later, is a powerful single electron reductant that was commonly utilized for the reduction of alkyl halides and carbonyls (Scheme 1.1B).[6] SmI_2 was particularly useful for C–C bond formations and was commonly employed in total synthesis endeavors.[7] Despite the significant advances SmI_2 brought to single-electron reduction chemistry, there are major drawbacks in its utility including the high air sensitivity of the reagent and the requirement for a highly toxic HMPA additive which is crucial for reactivity in most SmI_2 promoted reactions.[8]

Scheme 1.1: Traditional approaches towards single electron reduction.

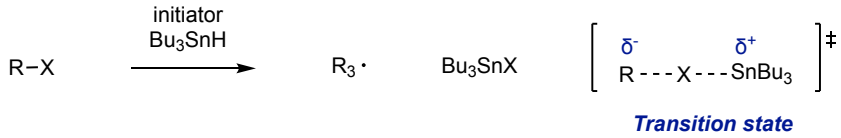


1.1.2 Halogen Atom Abstraction (XAT)

Beyond single electron reduction, the most notable approach towards radical generation is halogen atom abstraction (XAT) of alkyl and aryl halides.[9] While there have been a multitude of halogen atom abstracting agents reported in the literature,[10] by far the most abundant are alkyl tin hydrides (R_3SnH).[11] Tin is an exceptional reagent for XAT chemistry because of the high thermodynamic favorability involving the formation of a strong tin-halogen bond compared to the

weaker carbon-halogen bonds of alkyl or aryl halides (Scheme 1.2). Radical tin reactions are most famous for their elegant ring closures constructing valuable C–C bonds. However, the toxicity associated with tin reagents has severely declined the utilization of this chemistry over recent years.

Scheme 1.2: Generic scheme of halogen abstraction with butyl tin hydride.



These early developments in radical chemistry over the 20th century laid the groundwork for the many possibilities of unique reactivity that radicals can offer the synthetic chemistry community. However, radical chemistry has arguably seen its greatest resurgence in the past decade with the ascent of photoredox catalysis.

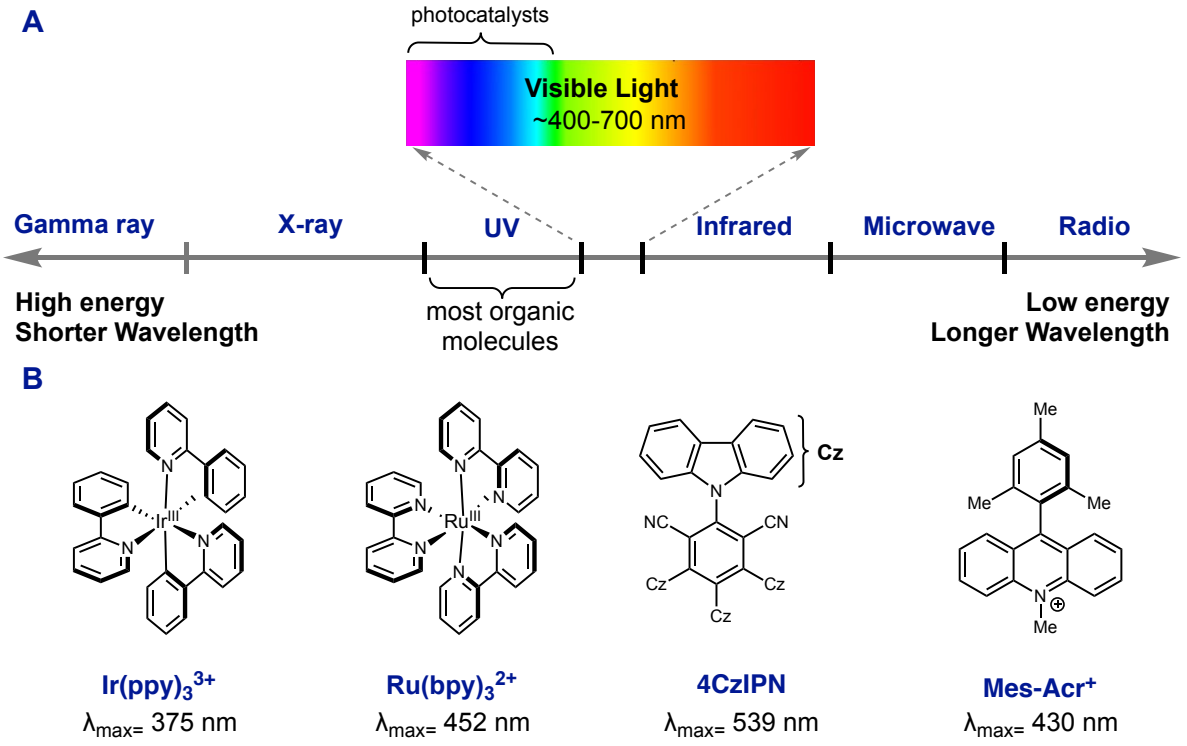
1.2 Photoredox Catalysis

Modern day photoredox catalysis was first introduced in 2008 by Yoon and coworkers where they described a photoredox-catalyzed [2+2] enone cycloaddition reaction.[12] Around the same time MacMillan and coworkers presented a dual photoredox organocatalytic method for the enantioselective α-alkylation of aldehydes.[13] In the years ensuing these seminal reports there has been a profusion of new photoredox-mediated reactions that have offered a significant advance in the types of possible synthetic chemical transformations driven by radical intermediates.

1.2.1 General Principles of Photoredox Catalysis

Photoredox catalysis harnesses the energy of visible light to drive its reactions. This offers a significant advantage over traditional light catalyzed reactions that required UV-light which suffered from a general lack of selectivity. The use of visible light avoids deleterious side reactions

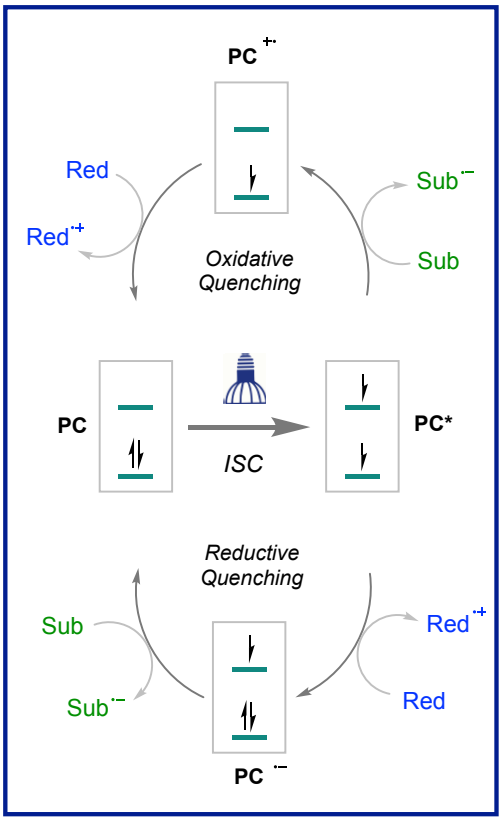
Figure 1.1 Electromagnetic spectrum and select examples of photocatalysts.



that arise from direct excitation of the substrates themselves. The ability to harness longer wavelength light to catalyze these reactions hinges on the use of specially designed photosensitizers that are capable of absorbing light in the visible region (Figure 1.1A). Polypyridyl complexes of ruthenium and iridium were the first types of photocatalysts (PCs) described.[14] However, now a plethora of organic dye based catalysts have been developed (Figure 1.1B).[15]

Upon absorption of a photon, an electron in the ground state of the PC is promoted to a higher energy orbital. This is considered the singlet excited state. The electron undergoes intersystem crossing (ISC) where it spin-flips to the triplet excited state (PC*). The triplet state is a long-lived excited state because it is spin forbidden to decay back to the singlet ground state. The triplet excited state of the PC is both a better oxidant and reductant than the ground state and can

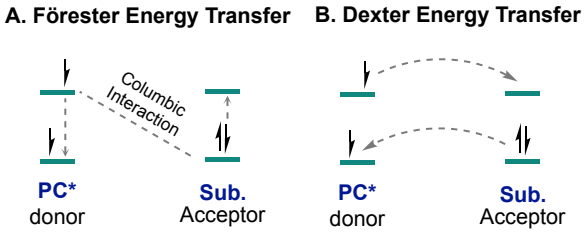
Figure 1.2 Oxidative and reductive quenching cycles.



undergo biomolecular electron transfers. The catalyst can either operate through an oxidative or reductive quenching cycle (Figure 1.2). In an oxidative quenching cycle, the PC* reduces the substrate which generates the PC radical cation. A stoichiometric reductant reduces the PC radical cation back to the ground state. In a reductive quenching cycle, the PC* functions as an oxidant. The stoichiometric reductant reduces the PC* to its ground state radical anion which in turn reduces the substrate regenerating the ground state of the PC.

The redox activity of excited state photocatalysts is not the only mode of small molecule activation that can be performed by PC*. Energy transfer (EnT) is another mode of activation involving transfer of the triplet excited energy from the PC* to the substrate.[16] There are two distinct mechanisms of EnT derived from fundamental columbic and exchange interactions. The first is referred to as Förster resonance energy transfer (FRET) where the PC* (donor) transfers its energy to the substrate (acceptor) through non-radiative dipole-dipole coupling (Figure 1.3A).[17] The electronic oscillation in the PC* generates a dipole that can interact with the electronic oscillation in the ground state. This resonant interaction eventually leads to electronic transfer. The

Figure 1.3: Types of energy transfer.



second is known as Dexter energy transfer and is the presumed mode of small molecule activation from PC*. Dexter energy transfer involves the concurrent intermolecular exchange of ground state and excited state electrons (Figure 1.3B).[18] Energy transfer processes have found numerous applications in organic reactions involving visible light and PC. However, this dissertation will

focus on single electron transfer (SET) mechanisms as the primary mode of small molecule activation.

1.2.2 Single Electron Reduction via Photoredox Catalysis

As previously mentioned, PCs can induce single electron reduction from the excited state of a photocatalyst in an oxidative quenching cycling or from the ground state radical anion of the photocatalyst in a reductive quenching cycle. Various methods have been developed for the reductive activation of a diverse range of substrate classes including the reduction of aryl halides,[19] enones,[12] aryl aldehydes/ketones,[20] and more.

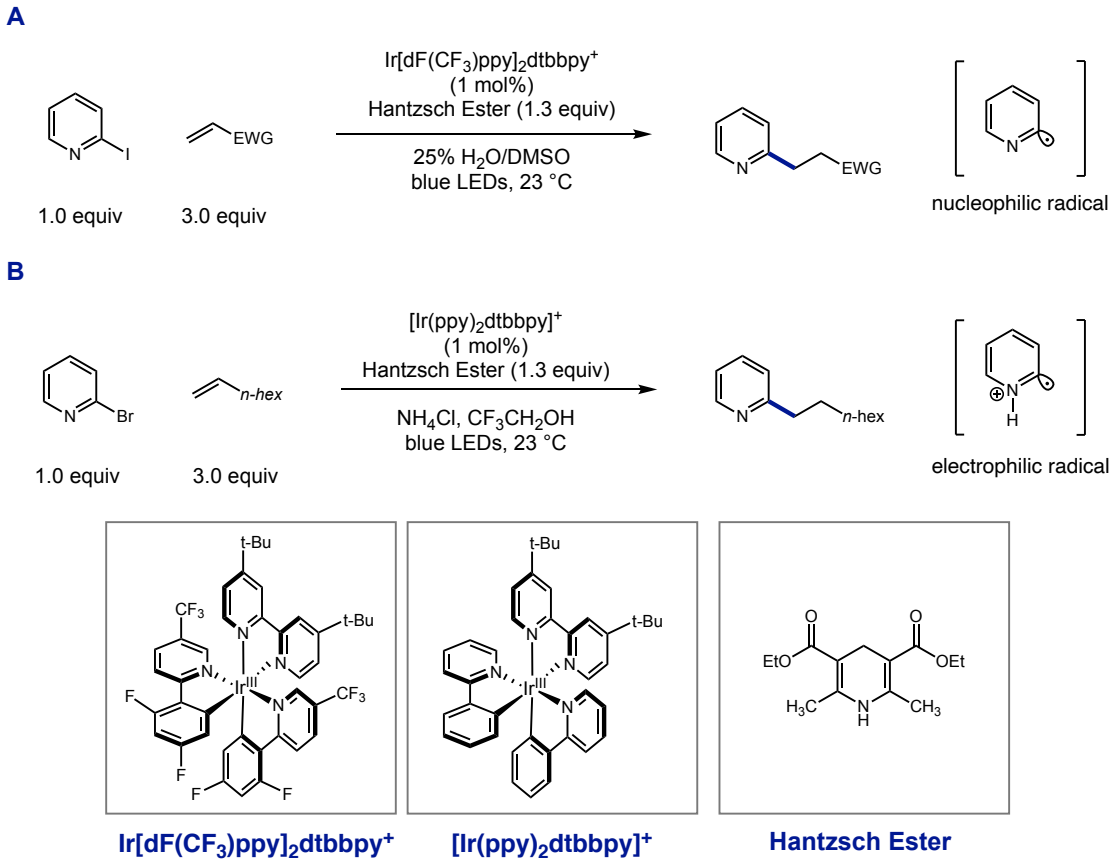
1.2.3 Photoredox Catalysis in the Jui Lab

A large focus in the Jui lab has been the development of new methodologies for the construction of carbon-carbon bonds particularly reactions that are practical for the pharmaceutical and agrochemical industries. Many of the methods developed in our lab have used single electron reduction as a key mechanistic step for carbon radical formation. Because of the relatively mild and catalytic conditions used for radical generation by photoredox catalysis, it is possible to engage the radicals with olefins in a highly selective fashion.

In 2017, our group demonstrated the regioselective coupling of pyridine and diazene iodides with electron-poor alkenes (Scheme 1.3A) through a radical conjugate addition reaction (Giese Reactivity).[21] The reaction utilized an iridium photocatalyst and Hantzsch ester as the stoichiometric reductant in DMSO. This work was further expanded in a later report from our group demonstrating the coupling of pyridyl radicals with unactivated olefins (Scheme 1.3B).[22] A key discovery from this report was the use of trifluoroethanol (TFE) as the solvent with a mild acid additive (NH_4Cl). The reduction occurred from the photocatalyst through a proton-coupled electron transfer (PCET) mechanism from the TFE solvent generating an electrophilic pyridyl

radical which preferentially reacts with electron-rich alkenes (unactivated olefins). The high control of chemoselectivity that is imparted by these radicals was elegantly shown in a competition experiment when bromopyridine was exposed to 2 equivalents of unactivated olefin and 2 equivalents of electron-deficient olefin. When DMSO was used as the solvent the reaction gave complete selectivity for addition to the electron deficient olefin which stood in stark contrast to when TFE was used as the solvent which gave almost exclusive addition to the unactivated olefin.

Scheme 1.3: Coupling of pyridyl halides with olefins.

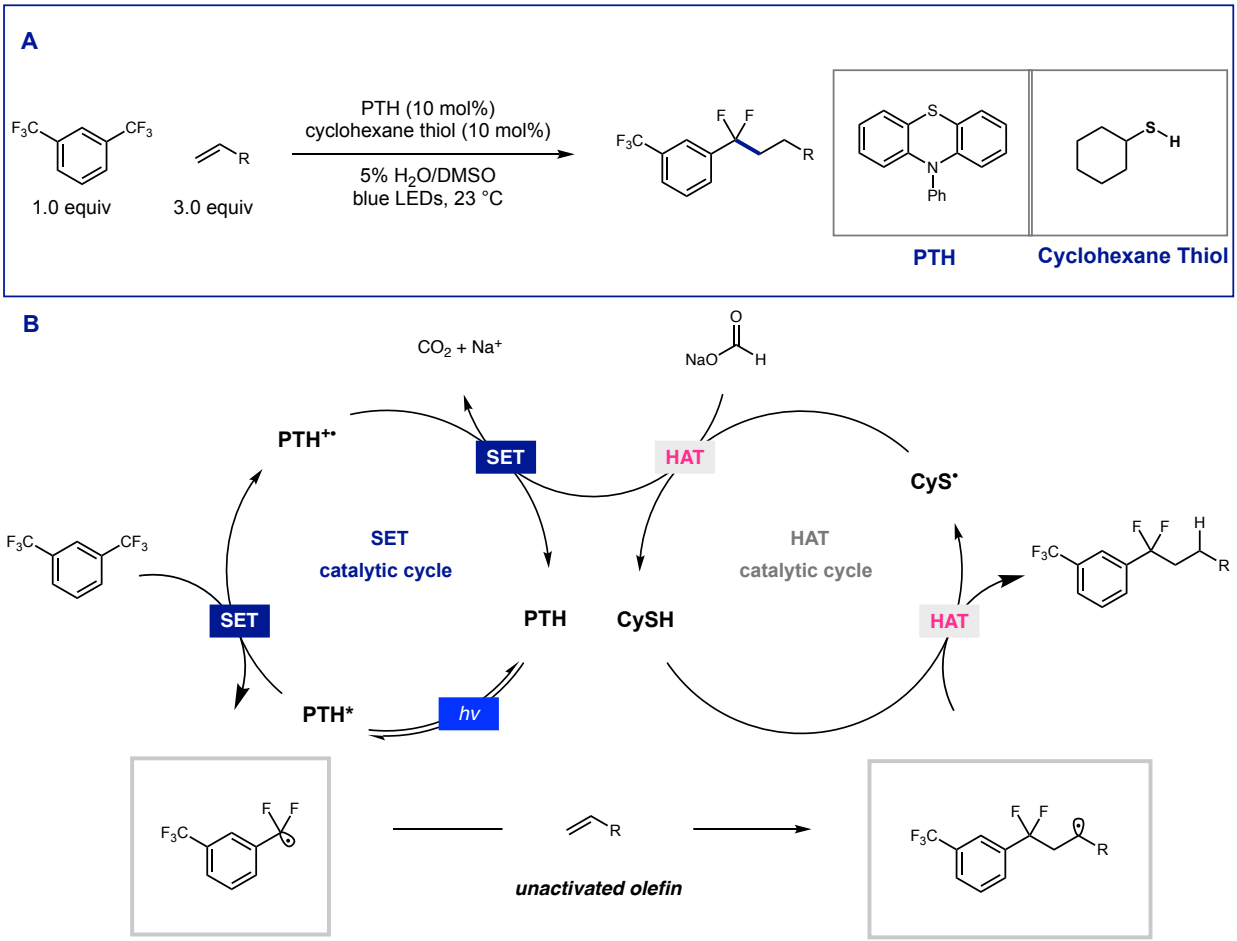


A later report in our lab demonstrated the coupling of aryl iodides with vinyl amines to form phenethylamines which go through an unactivated benzene-derived radical intermediate.[23] In 2020, it was demonstrated that photocatalytically generated aryl radicals can undergo 5-*exo* cyclization onto a pendant arene delivering dearomatized spirocyclic cyclohexadienes.[24] These

reports established the diverse reactivity that can be achieved with aryl radical intermediates through mild photocatalytic reduction to rapidly access molecular complexity from feedstock building blocks such as aryl halides and simple olefins.

Another area of reductive chemistry in our lab has focused on the selective manipulation of trifluoromethylarenes (CF_3-arene) triggered through a reductive C–F cleavage. In 2018, our group developed an elegant strategy for the defluoroalkylation of electron-deficient CF_3-arenes with unactivated olefins (Figure 1.4A).[25] This method relied on the use of a highly reducing organic dye catalyst, PTH (PTH*; $E^{\circ}_{1/2} = -2.10$ V vs SCE),[26] to achieve the high reduction potential

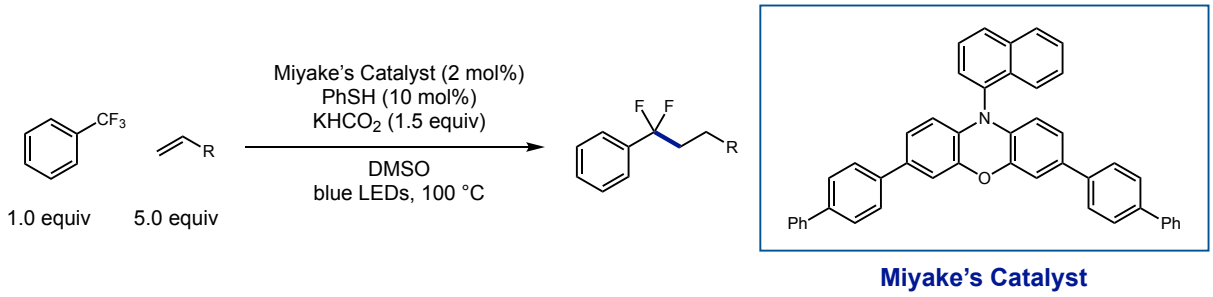
Figure 1.4 (A) Defluoroalkylation of CF_3-arenes with olefins and (B) proposed mechanism.



required for the activation of the CF_3-arenes (–2.07 V vs SCE).[25] The reaction used a novel terminal reductant, formate, in combination with a thiol HAT catalyst. The proposed mechanism

shows a dual catalytic cycle where the PC and HAT catalyst operate in concert (Figure 1.4B). The CF_3-arene is reduced by PC* to give the radical anion of the CF_3-arene which triggers a rapid mesolytic cleavage of one of the benzylic fluoride bonds to deliver a difluorobenzylic radical. The difluorobenzylic radical undergoes addition to the olefin delivering a nucleophilic carbon-centered radical which can undergo a polarity-matched HAT with the electrophilic thiol catalyst. Formate was proposed to regenerate both the PC and thiol catalyst through a concerted HAT and SET. However, the exact mechanistic role of formate was not fully understood. In a subsequent report, the reduction of non-activated CF_3-arenes towards defluoroalkylation was developed.[27] It relied on a similar dual photocatalyst and HAT catalyst system (Scheme 1.4). However, key to activating these more challenging reductions was the choice of a different organic dye catalyst, Miyake's Catalyst. While this catalyst has a lower reduction potential (Miyake's catalyst*; $E^{\circ}_{1/2} = -1.70$ V vs SCE),[28] it has a uniquely long-lived triplet excited state ($\tau = 480$ μs) which was proposed to enable an endergonic electron transfer to the CF_3-arene which is rapidly followed by an irreversible C–F cleavage.

Scheme 1.4: Defluoroalkylation of unactivated CF_3-arenes with olefins.



The following chapters focus on developments in reductive transformations built off the work that has been described above. The second chapter details the discovery of the carbon dioxide radical anion ($CO_2^{\bullet-}$), a transient intermediate formed in the photoredox systems that contain

formate and thiol. The $CO_2^{\bullet-}$ was found to serve as a powerful single electron reductant and a nucleophilic carboxylating agent. The third and fourth chapters describe novel reactivity that has been enabled through $CO_2^{\bullet-}$ reduction pathways. Importantly, this chemistry relies on inexpensive reagents under mild light-driven conditions making its use highly practical in the pharmaceutical and agrochemical industries.

1.3 References

(1) Ashby, E. C. Single-Electron Transfer, a Major Reaction Pathway in Organic Chemistry. An Answer to Recent Criticisms. *Acc. Chem. Res.* **1988**, *21*, 414- 421.

(2) Birch, A. J. Reduction by Dissolving Metals. Part I. *J. Chem. Soc.* **1944**, *430*, 430-436.

(3) Pradhan, S. K. Mechanism and Sterochemistry of Alkali Metal Reductions of Cyclic Saturated and Unsaturated Ketones in Protic Solvents. *Tetrahedron* **1986**, *42*, 6351- 6388.

(4) Mohle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew, Chem. Int. Ed.* **2018**, *57*, 6018-6041.

(5) Nelleborg, P.; Lund, H.; Eriksen, J. Photochemical Vs. Electrochemical Electron Transfer Reactions. One-Electron Reduction of Aryl Halides by Photoexcited Anion Radicals. *Tetrahedron Lett.* **1985**, *26*, 1773- 1776.

(6) Girard, P.; Namy, J. L.; Kagan, H. B. Divalent lanthanide derivatives in organic synthesis. 1. Mild Preparation of Samarium Iodide and Ytterbium Iodide and their use as Reducing or Coupling Agents. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

(7) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. Samarium Diiodide Mediated Reactions in Total Synthesis. *Angew. Chemie. Int. Ed.* **2009**, *48*, 7140-7165.

(8) Junji, I.; Mitsuhiro, I.; Masaru, Y. A Mild and Convenient Method for the Reduction of Organic Halides by Using a SmI2-THF Solution in the Presence of Hexamethylphosphoric Triamide (HMPA). *Chem. Lett.* **1987**, *1485-1486*.

(9) Julia, F.; Constantin, T.; Leonori, D. Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis. *Chem. Rev.* **2022**, *122*, 2292-2352.

(10) Baguley, P. A.; Walton, J. C. Flight from the Tyranny of Tin: The Quest for Practical Radical Sources Free from Metal Encumbrances. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082. Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. Indium(III) Chloride-Sodium Borohydride System: a Convenient Radical Reagent for an Alternative to Tributyltin Hydride System. *J. Am. Chem. Soc.* **2002**, *124*, 906- 907. Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. Triethylborane-Induced Radical Reactions with Gallium Hydride Reagent HGaCl2. *Org Lett* **2001**, *3*, 1853-1855.

(11) Kuivila, H. Organotin Hydrides and Organic Free Radicals. *Acc. Chem. Res.* **1968**, *1*, 299-305.

(12) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008**, *130*, 12886-12887.

(13) Nicewicz, D. A.; MacMillan, D. W. Merging Photoredox Catalysis with Organocatalysis: the Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**, *322*, 77-80.

(14) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322-5363.

(15) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075-10166.

(16) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy Transfer Catalysis Mediated by Visible Light: Principles, Applications, Directions. *Chem. Soc. Rev.* **2018**, *47*, 7190-7202.

(17) Sahoo, H. Forster Resoncance Energy Transfer- A Spectroscopic nanoruler: Principle and Applications. *J. Photochem. Photobiol.* **2011**, *12*, 20-30.

(18) Dexter, D. L. A Theory of Sensitized Luminescence in Solids. *J. Chem. Phys.* **1953**, *21*, 836- 850.

(19) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M.; Stephenson, C. R. Engaging Unactivated Alkyl, Alkenyl and Aryl Iodides in Visible-Light-mediated Free Radical Reactions. *Nat. Chem.* **2012**, *4*, 854- 859.

(20) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. *Angew. Chem. Int. Ed.* **2015**, *54*, 8828-8832.

(21) 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.

(22) Boyington, A. J.; Riu, M. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J Am Chem Soc* **2017**, *139* (19), 6582-6585. DOI: 10.1021/jacs.7b03262.

(23) 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* (9), 4147-4153. DOI: 10.1021/jacs.9b01077.

(24) Flynn, A. R.; McDaniel, K. A.; Hughes, M. E.; Vogt, D. B.; Jui, N. T. Hydroarylation of Arenes via Reductive Radical-Polar Crossover. *J Am Chem Soc* **2020**, *142* (20), 9163-9168.

(25) Wang, H.; Jui, N. T. Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 163-166.

(26) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; Read de Alaniz, J. A Highly Reducing Metal-free Photoredox Catalyst: Design and Application in Radical Dehalogenations. *Chem. Comm.* **2015**, *51*, 11705- 11708.

(27) Vogt, D. B.; Seath, C. P.; Wang, H.; Jui, N. T. Selective C-F Functionalization of Unactivated Trifluoromethylarenes. *J. Am. Chem. Soc.* **2019**, *141*, 13203-13211.

(28) Du, Y.; Pearson, R. M.; Lim, C. H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; D'amrauer, N.; Miyake, G. M. Strongly Reducing Visible-Light Organic Photoredox Catalysts as Sustainable Alternatives to Precious Metals. *Chem. Eur. J.* **2017**, *23*, 10962- 10968.

Chapter 2:

Discovery of the Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$) as a Potent Single Electron Reductant and Carboxylating Agent

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G.C. Smith contributed to both carboxylation and reduction scope and performed alternative initiator experiments. Z. Xu performed transient absorption spectroscopy and Stern-Volmer quenching experiments.

Abstract: A variety of reductive photoredox catalyzed processes in our lab rely on the use of stoichiometric formate, which was believed to serve as the photocatalyst's terminal reductant. During attempts to develop a photoredox catalyzed method for the dearomatization of electron-deficient arenes utilizing our formate-based conditions, we observed an interesting side product containing a carboxylic acid adduct. We hypothesized that the carbon dioxide radical anion ($CO_2^{\bullet-}$) was being generated from formate through the course of the reaction and was behaving as a carboxylating reagent to an alkene-containing intermediate produced during the dearomatization reaction. Investigation of this hypothesis revealed that $CO_2^{\bullet-}$ is being generated via a polarity-matched hydrogen atom transfer (HAT) between formate and a thiol-based HAT catalyst. We developed this reactivity into an efficient method for the preparation of carboxylic acids from formate and electron-deficient olefins. Additionally, this research led us to discover the $CO_2^{\bullet-}$ intermediate could serve as a powerful single electron reductant ($E^{\circ}_{1/2}$= – 2.21 V vs SCE) that can engage a diverse class of electron-poor substates. The reaction operates through a radical chain mechanism and could be used with a variety of radical initiators. This chemistry establishes two novel modes of divergent reactivity by $CO_2^{\bullet-}$, where substrate reduction potentials can be utilized to predict reaction outcome (e.g. carboxylation or reduction).

2.1 Introduction

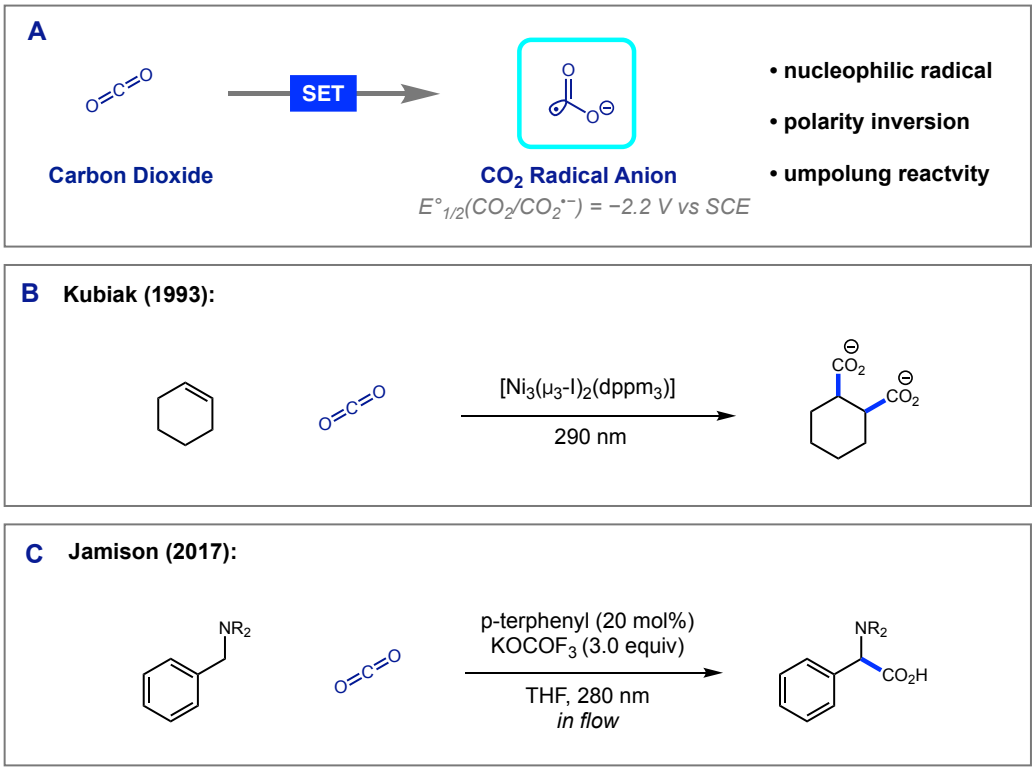
2.1.1 Single Electron Reduction

As introduced in chapter 1, single electron reduction is an important pathway towards the formation of radical species from diverse classes of electron poor substrates. Traditional approaches relied on dissolving alkali metals[1] and electrochemical techniques[2] that could reach extremely high reducing potentials. However, these strategies were limited in their ability to promote free radical reactivity. This is because typically two sequential single electron transfers

occur rapidly on the metal surface preventing any radical reactivity.[3] Photoredox catalysis has offered many advantages in the arena of single electron reduction compared to these traditional approaches.[4] The mild visible-light catalyzed conditions allow for precise tuning of kinetic factors (e.g. reduction potential, effective reductant concentration) and enable interception of the transient radicals produced. Visible-light catalyzed systems have been used to promote a plethora of single electron reductive transformations over the past decade. Despite the advantages, the reducing power is inherently limited by the energy contained in a blue photon (up to 2.8 eV).[5] Strategies to overcome this have been developed recently involving photoexcitation of radical anions to yield super-reductants that are capable of engaging species that require highly challenging reductions.[6,7]

2.1.2 Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$)

Figure 2.1: Traditional approaches to $CO_2^{\bullet-}$ formation and its reactivity.

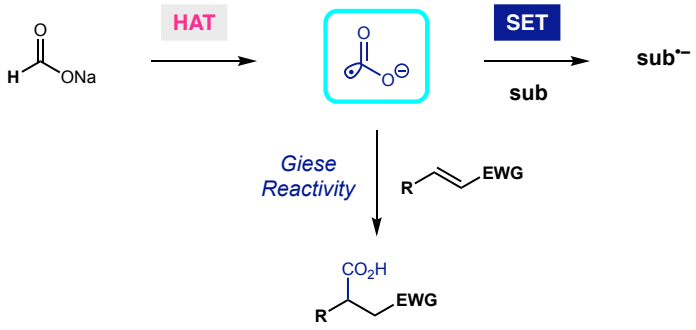


The carbon dioxide radical anion ($CO_2^{\bullet-}$) has been an elusive and underutilized intermediate in organic synthesis. However, it is routinely accessed through the electrochemical reduction of carbon dioxide gas with applications towards energy storage (Figure 2.1A).[8] Its reduction potential is more reducing than some of the most potent photoredox catalysts ($E^{\circ}_{1/2}$= – 2.21 V vs SCE for $CO_2^{\bullet-}$).[9] Additionally, this radical can serve as a nucleophilic carboxylating reagent (umpolung reactivity compared to CO_2). Despite the interesting properties of this transient intermediate, its use in organic synthesis is scarce. In 1993, Kubiak et al. demonstrated $CO_2^{\bullet-}$ formation could be achieved through a photochemical reduction of CO_2 using UV-light and a nickel catalyst. They demonstrated this intermediate could engage cyclohexene in a carboxylation reaction (Figure 2.1B).[10] Later in 2006, Barba demonstrated generation of $CO_2^{\bullet-}$ through a cathodic reduction to make phenylacetic acid from toluene.[11] The most recent reports of $CO_2^{\bullet-}$ in synthetic chemistry come from the Jamison lab. They demonstrate that through the photochemical reduction of CO_2 using UV-light in continuous flow, they can engage $CO_2^{\bullet-}$with α-amino radicals to form valuable α-amino acid products (Figure 2.1C).[12] Unfortunately, these methods suffer from their requirement for harsh conditions that require high cathodic potentials or UV-light. Beyond these small scatterings of reports, $CO_2^{\bullet-}$ has been underexplored likely due to the harsh conditions required for its generation limiting its synthetic practicality.

In this chapter, we describe a method for generation of $CO_2^{\bullet-}$ that relies on an HAT event from formate rather than reduction of CO_2 gas. This approach enables its generation under much milder conditions than traditional methods. We first demonstrate that $CO_2^{\bullet-}$ can undergo a Giese type conjugate addition with electron deficient olefins to afford a variety of valuable carboxylated products (Figure 2.2) including 1,4-dicarbonyls. We later report this intermediate can serve as a potent reducing agent to activate a diverse range of substrate classes via SET (Figure 2.2) that are

typically inert under classic photoredox systems. These discoveries together demonstrate the value of this transient intermediate in organic synthesis and the novel modes of reactivity that it enables.

Figure 2.2: This work: Accessing radical reactivity via transient $CO_2^{\bullet-}$.

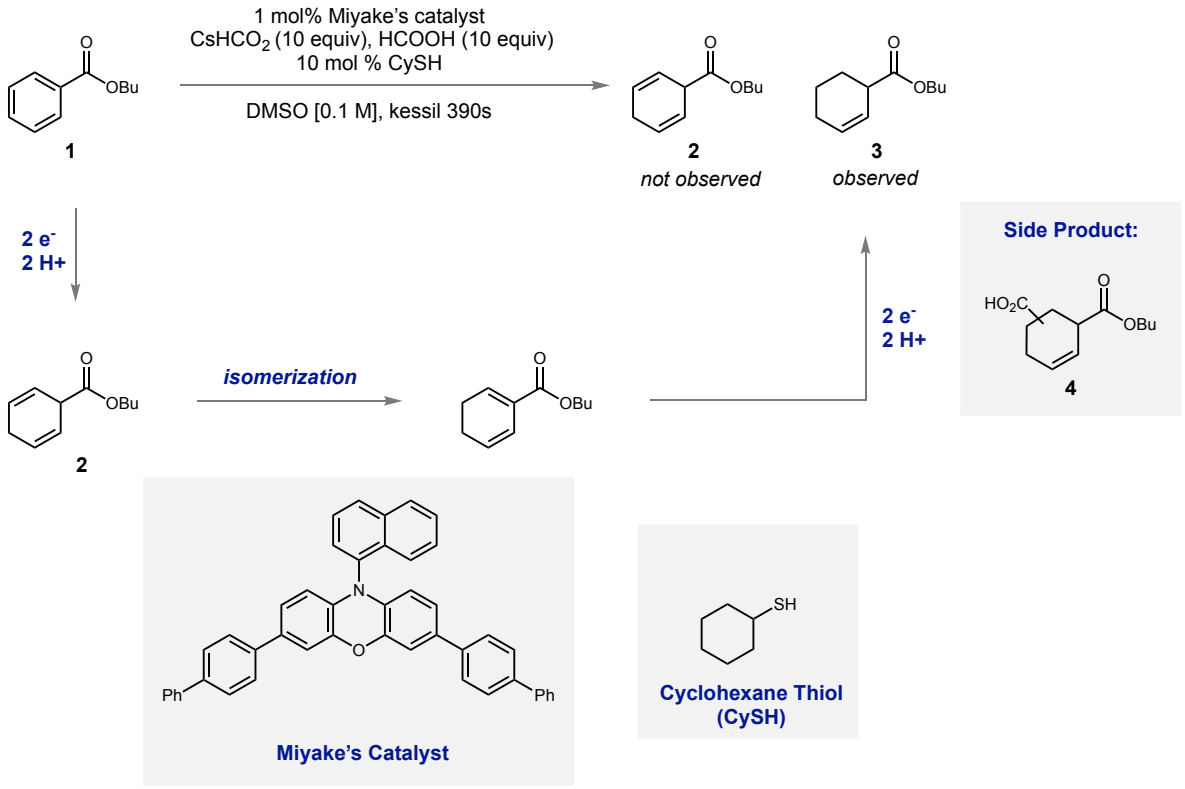


2.2 Results and Discussion

2.2.1 Discovery of $CO_2^{\bullet-}$ as a Nucleophilic Carboxylating Reagent

As previously mentioned, our lab has a longstanding goal of developing novel visible-light catalyzed systems capable of engaging new substrate classes. One class of reductions we became interested in exploring was dearomatization of aromatic systems. The largest challenge presented with this goal was the highly negative reduction potential required to activate aromatic rings.[13] We sought to probe the feasibility of a photocatalytic dearomatization using butyl benzoate (**1**) as the model substrate. We quickly found this was possible using reductive conditions previously developed in our lab including the use of Miyake's catalyst[14] as the photocatalyst and cesium formate as the stoichiometric reductant (Figure 2.3).[15] Upon analysis of the ^{1}H NMR spectrum and GCMS trace, we observed formation of the cyclohexene product **3** as the major product instead of

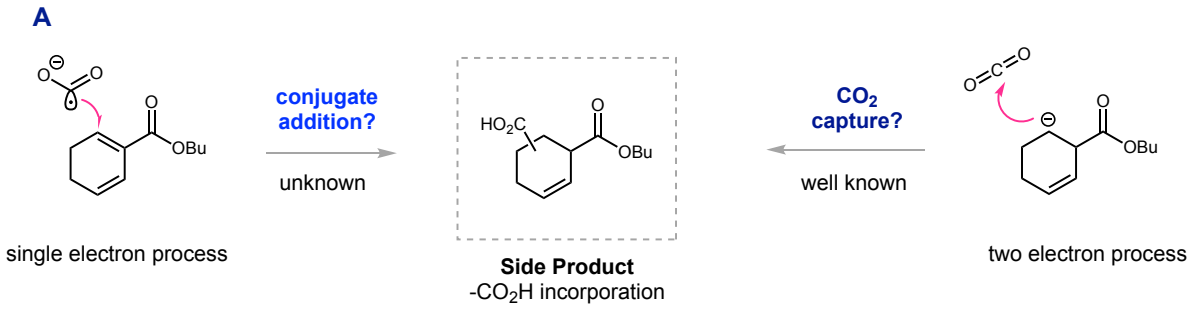
Figure 2.3: Photochemical dearomatization and proposed mechanism.



the traditional Birch 1,4-diene **2**. We hypothesized this was occurring through two sequential single electron reductions to first form the 1,4-diene intermediate (this intermediate was observed at early time points in the reaction via NMR), followed by an isomerization to the conjugated Michael acceptor intermediate which could subsequently undergo reduction to give the observed cyclohexene product (Figure 2.3).

During this study a minor side product was observed that contained a carboxylic acid (**4**) incorporated into the dearomatized ring system (as observed by ^{1}H NMR and GCMS). We imagined two possible pathways that could lead to this product: (1) if CO_2 is being expelled through the course of the reduction, a carbanion intermediate could capture electrophilic CO_2 or, (2) if we are generating a $CO_2^{\bullet-}$ intermediate from formate, it could engage a Michael acceptor intermediate in a Giese conjugate addition fashion (Figure 2.4A). To further understand this side product, we ran an experiment subjecting Michael acceptor **5** to the same reaction conditions used

Figure 2.4: (A) Plausible mechanisms for carboxylic acid incorporation and (B) Reaction of Michael acceptor[a]



[a]Conditions: **5** (1.0 equiv), Miyake's Catalyst (1 mol%), sodium formate (10 equiv), formic acid (10 equiv), cyclohexane thiol (10 mol%), DMSO [0.1 M], 390 nm, N_2, 16 hrs, 0.2 mmol scale. [b]Yield determined by ^{1}H NMR with dibromomethane as standard.

for dearomatization and observed a 30% yield of carboxylation product **6**. This result was highly suggestive of a radical conjugate addition pathway with $CO_2^{\bullet-}$.

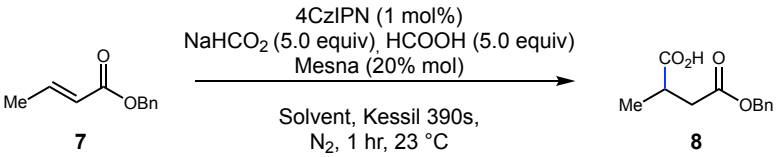
During this time several other labs published similar photoredox catalyzed dearomatization reactions.[16] For this reason, we became interested in focusing our attention on the carboxylation reaction. We were intrigued by this result due to the lack of $CO_2^{\bullet-}$ chemistry found in the literature. We sought to develop a method for the carboxylation of Michael acceptors with $CO_2^{\bullet-}$ as a nucleophilic carboxylating reagent. This method would offer umpolung reactivity compared to traditional carboxylation protocols using CO_2. Furthermore, we wanted to learn more about the mechanism behind generation of $CO_2^{\bullet-}$ and how it was operating under photoredox systems that use formate.

2.2.2 Optimization of the Carboxylation of Michael Acceptors

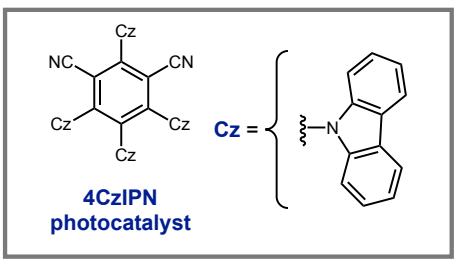
We optimized the reaction for the carboxylation of Michael acceptors with $CO_2^{\bullet-}$ using unsaturated ester **7** (Table 2.1). We found we could use the more cost-effective sodium formate in place of cesium formate and 4CzIPN in place of Miyake's catalyst. Additionally, we exchanged cyclohexane thiol for the solid odorless thiol, mesna. The reaction of **7** in the presence of 4CzIPN (1mol%), sodium formate (5.0 equiv), formic acid (5.0 equiv), mesna (20 mol%) in DMSO [0.1 M] under irradiation by blue lights for 1 hour yielded 31% of **8** (Table 2.1, entry 1). The addition of water increased the yield to 47% of **8** with a 10% H_2O/DMSO solvent system (Table 2.1, entry 2) and 95% of **8** with a 20% H_2O/DMSO solution (Table 2.1, entry 3). The enhanced yields with water can be attributed to better solubility of sodium formate in aqueous DMSO. However, the use of a 50% H_2O/DMSO solvent decreased the yield of **8** (73%, Table 2.1, entry 4). For the remainder of this work, we used the optimized reaction conditions found in entry 3 of Table 2.1. Control experiments indicated both light and thiol were necessary for desired reactivity (Table 2.1, entries

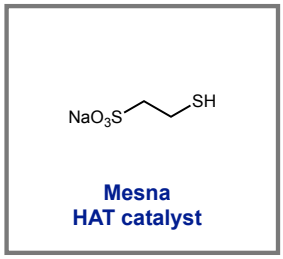
5 and 7). In the absence of formic acid, the reaction proceeds well but with a slightly diminished yield (77%, Table 2.1, entry 6).

Table 2.1: Optimization table of carboxylation of Michael acceptors.[a]



Entry	Solvent	Deviation	Yield[b]
1	DMSO	-	31%
2	10% H_2O/DMSO	-	47%
3	20% H_2O/DMSO	-	95%
4	50% H_2O/DMSO	-	73%
5	20% H_2O/DMSO	no mesna	15%
6	20% H_2O/DMSO	no HCOOH	77%
7	20% H_2O/DMSO	no light	0%[c]

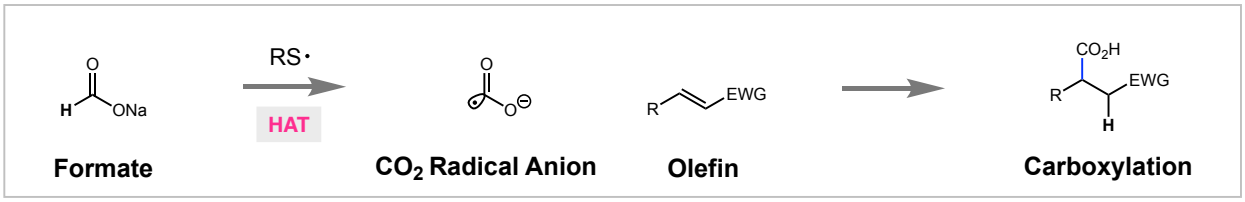




[a]Conditions: **7** (1.0 equiv), 4CzIPN (1 mol%), sodium formate (5.0 equiv), formic acid (5.0 equiv), mesna (20 mol%), Solvent [0.1 M], 390 nm light, N_2, 1 hr, 0.1 mmol scale. [b]Yield determined by ^1H NMR with dibromomethane as standard. [c] Reaction ran for 16 hrs.

2.2.3 Mechanistic Investigations of Carboxylation Reaction

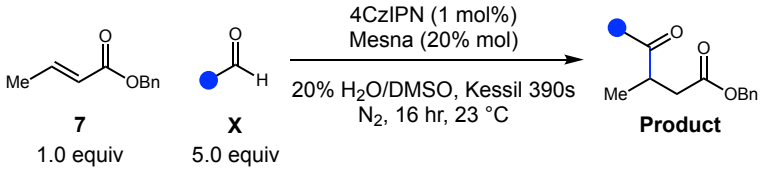
Figure 2.5: Proposed mechanism for the carboxylation of Michael acceptors.



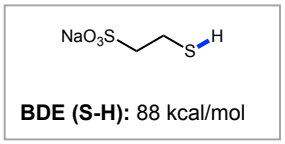
The proposed mechanism of this transformation can be seen in Figure 2.5. The $CO_2^{\bullet-}$ is formed through a polarity-matched HAT event between the thiol catalyst and formate. The nucleophilic $CO_2^{\bullet-}$ undergoes addition to the Michael acceptor where the resulting alkyl radical could either be terminated through reduction/protonation or HAT to deliver the carboxylation product.

We hypothesized that if $CO_2^{\bullet-}$ is being generated via HAT from formate, a variety of other types of formyl reagents should also feed into this mechanism. We conducted a series of experiments where we replaced formate with various types of formyl reagents to see if we observed their incorporation into unsaturated ester **7** (Table 2.2). Surprisingly, when subjecting formic acid, ethyl formate, and DMF to the reaction conditions we observed no incorporation into **7** (Table 2.2,

Table 2.2: Radical addition using other types of formyl C–H bonds.[a]



Entry	Reagent (X)	C-H BDE[b]	Product Yield[c]
1	Sodium Formate	90	**86%**
2	Formic Acid	101	**0%**
3	Ethyl Formate	100	**0%**
4	DMF	99	**0%**
5	Octanal	86	**64%**



BDE (S-H): 88 kcal/mol

BDE (C-H): shown in table

[a]Conditions: **7** (1.0 equiv), **X** (5.0 equiv) 4CzIPN (1 mol%), mesna (20 mol%), Solvent [0.1 M], 390 nm light, N_2, 16 hrs, 0.1 mmol scale. [b]BDEs reported in kcal/mol. [c]Yield determined by ^{1}H NMR with dibromomethane as standard.

entries 2-4). To better understand this, the bond dissociation energies (BDEs) of the corresponding

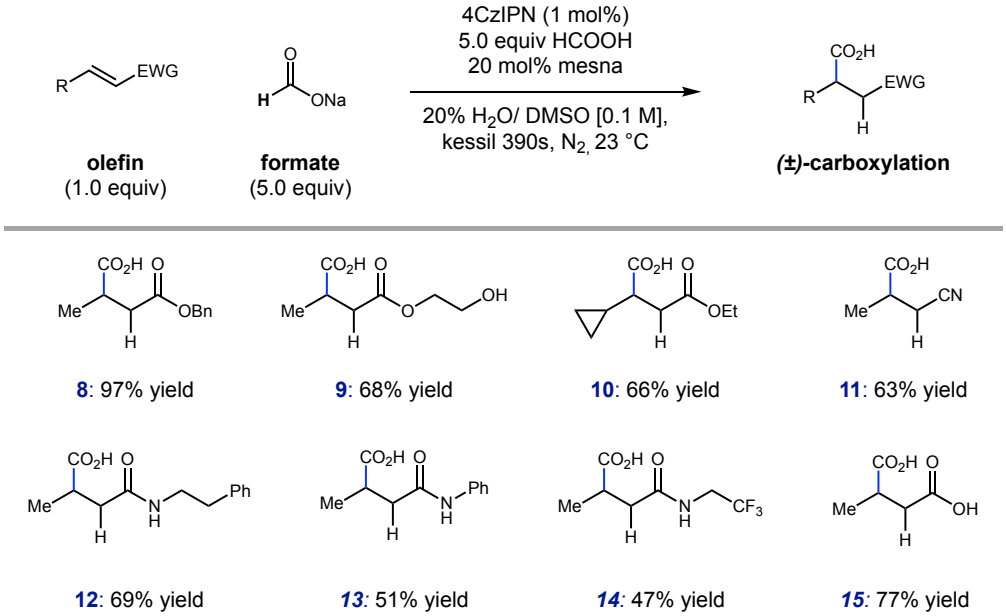
formyl C-H bonds were calculated using computational techniques (see *supporting information*). This revealed that formic acid, ethyl formate and DMF have relatively high BDEs (99-101 kcal/mol) leading to a large thermodynamic barrier for HAT with the thiol catalyst (88 kcal/mol BDE for S–H, see *supporting information*). However, formate has a significantly lower BDE (90 kcal/mol) producing an essentially thermal neutral HAT event which is consistent with the observed reactivity. With this knowledge, we reasoned that an aldehyde would be a successful reacting partner because of its relatively low BDE (86 kcal/mol, see *supporting information*). Indeed, when subjecting octanal to the reaction conditions (Table 2.2, entry 5) we observe 64% yield of acyl radical addition into the Michael acceptor. These data are consistent with our proposed mechanism for HAT generation of $CO_2^{\bullet-}$ and highlights the BDE dependence of this reaction in predicting the reactivity of other formyl reagents.

2.2.4 Carboxylation of Michael Acceptors Scope

We turned our attention to the scope of this transformation (Table 2.3). The reaction tolerated a variety of unsaturated esters (**8-10**) in good yields (66- 97% yield). The cyclopropyl substrate **10** additionally served as a mechanistic probe and further validated this reaction is proceeding through $CO_2^{\bullet-}$ conjugate addition pathway. If the reaction is proceeding through a reduction of the Michael acceptor, radical formation occurs at the β-position resulting in opening of the adjacent cyclopropyl ring.[17] Conversely, if the reaction is proceeding through a conjugate addition pathway, radical formation would occur at the α-position and the cyclopropyl ring would remain intact. Because we solely observe carboxylation product **10** with the cyclopropyl ring intact, we can rule out any product formation occurring through a reductive pathway. An unsaturated nitrile reacted well to give **11** in a 63% yield. Additionally, a series of unsaturated secondary amides transformed smoothly to the carboxylated products **12-14** (47-69% yields).

However, tertiary amides were not compatible under these conditions. Lastly, we were please to find unsaturated carboxylic acid reacted in excellent yield to afford the diacid **15** in a 77% yield.

Table 2.3: Scope of carboxylation of Michael acceptors.[a]



[a]Conditions: Olefin (1.0 equiv), 4CzIPN (1 mol%), sodium formate (5.0 equiv), formic acid (5.0 equiv), mesna (20 mol%), Solvent [0.1 M], 390 nm light, N_2, 16 hrs, 1.0 mmol scale, isolated yields shown.

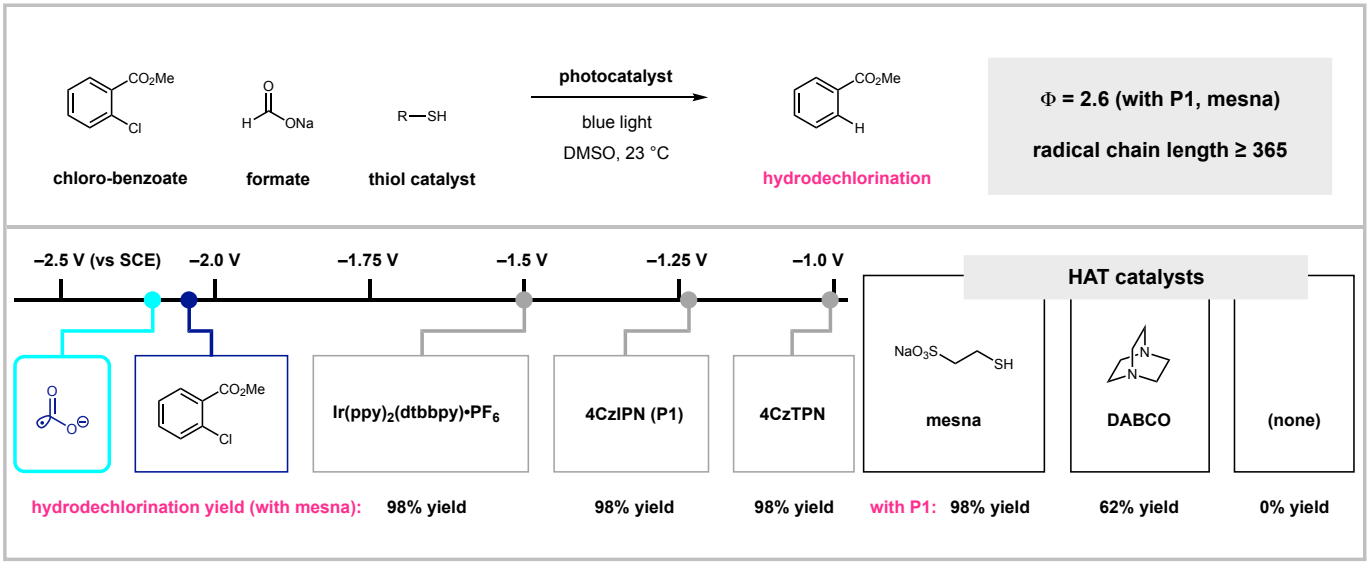
An unanticipated limitation in the scope of this chemistry was that enones did not undergo carboxylation. Instead, when enones were subjected to the reaction, we observed products consistent with reduction of the unsaturated bond (e.g. hydrogenation and dimerization). This result was surprising because enones present a highly negative reduction potentials ($E^{\circ}_{1/2} \cong -2.10$ V vs SCE, see *supporting information*) and 4CzIPN ($E^{\circ}_{1/2} = -1.24$ V vs SCE for $4CzIPN^{\bullet-}$)[18] has a significant underpotential with respect to this class of substrates. This result introduced the idea that reduction was potentially occurring from the $CO_2^{\bullet-}$ ($E^{\circ}_{1/2} = -2.21$ V vs SCE) intermediate as its reduction potential is significantly higher than the photocatalyst's.

We were excited to further explore reduction by $CO_2^{\bullet-}$ to assess if it could serve as a competent single electron reductant to activate a diverse range of substrates that require challenging reductions. Because $CO_2^{\bullet-}$ is more reducing than traditional photocatalysts, it has potential to engage substrates that are typically inert under classic photoredox catalyzed systems while maintaining the same mild conditions and simple set-up.

2.2.5 Mechanistic Investigations of $CO_2^{\bullet-}$ Reduction

To probe the feasibility of reduction by $CO_2^{\bullet-}$, we evaluated the reductive dechlorination of methyl-2-chloro benzoate (Figure 2.6). The exposure of aryl chloride to sodium formate (5.0 equiv) in the presence of various combinations of photoredox catalysts and HAT catalysts resulted in hydrodechlorination. A diverse range of photoredox catalysts promoted this reactivity in nearly quantitative yields with the HAT catalyst, mesna. This data suggests it is highly likely reduction is occurring from $CO_2^{\bullet-}$, as SET from the PCs would be exceedingly unfavored (based off reduction potential). As shown in Figure 2.6, the reducing states of the PCs are at least 600 mV more positive than that of the aryl chloride ($E^{\circ}_{1/2}$= – 2.10 V vs SCE).[19] In terms of HAT catalysts, a variety of thiols were found to catalyze this transformation. Additionally, amine-based HAT

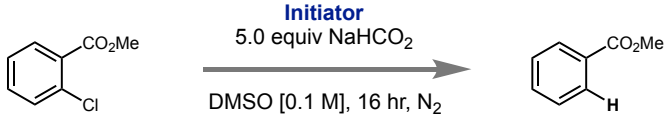
Figure 2.6: Experimental data in support of reduction by $CO_2^{\bullet-}$.



catalyst, DABCO, delivered hydrodechlorination albeit in a lower yield. No conversion was observed in the absence of an HAT catalyst. Light, formate and photocatalyst were also critical for substrate conversion (see *supporting information*). To gain a better understanding of the mechanism, we found the quantum yield (Φ) of the reaction under our standard conditions (with 4CzIPN and mesna) to be 2.63. This revealed the presence of a radical chain as the quantum yield cannot be greater than one for a closed photocatalytic cycle. Using transient absorption spectroscopy (see *supporting information* for details), we determined the rate of thiyl radical formation under the standard conditions (4.0×10^3 M^{-1} s^{-1}) which occurs from photocatalytic oxidation of thiol from 4CzIPN. Additionally, the quantum yield of thiyl radical production was calculated (Φ = 0.0072). This data indicates the average radical chain length to be greater than or equal to 365 (standard conditions).

With the understanding that this reaction is operating through a radical chain mechanism, we reasoned a variety of alternative initiators should feed into this mechanism in the absence of PC. We were pleased to find nearly quantitative reduction of aryl chloride was observed when thiyl radical generation was performed via photolysis of dimethyl disulfide (20 mol%) in the

Table 2.4: Alternative initiators.[a]



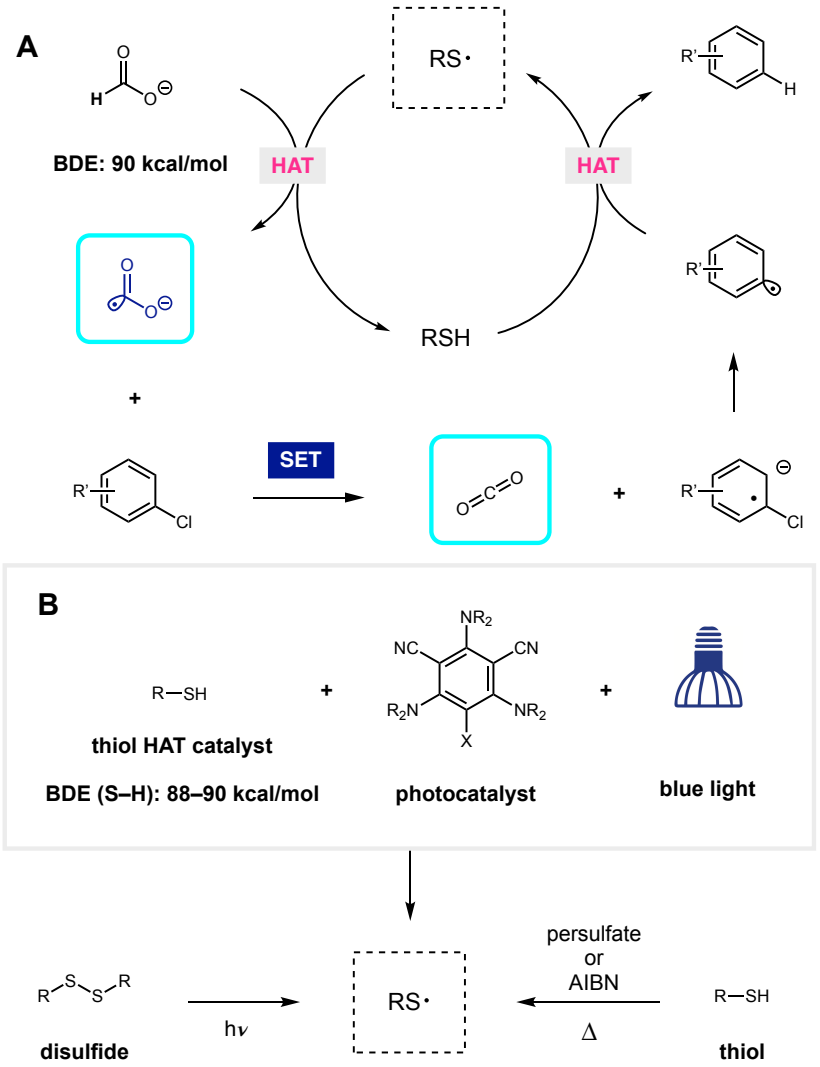
Entry	Initiator	Yield[b]
1	1 mol% 4CzIPN, 20 mol% mesna, blue LEDs, 23 °C	98%
2	20 mol% methyldisulfide, blue LEDs, 23 °C	99%
3	20 mol% ammonium persulfate, 20 mol% mesna, 100 °C	96%
4	20 mol% AIBN, 20 mol% mesna, 100 °C	48%

[a]Conditions: Aryl chloride (1.0 equiv), sodium formate (5.0 equiv), initiator (details found in table), DMSO [0.1 M], N_2, 16 hrs, 0.1 mmol scale. [b]Yield determined by ^1H NMR with dibromomethane as standard.

presence of sodium formate (5.0 equiv, Table 2.4 entry 2). Additionally, the thermal homolysis of both persulfate (20 mol%) or AIBN (20 mol%) in presence of thiol promoted the desired reactivity (Table 2.4, entries 3-4).

The proposed radical chain reduction mechanism using $CO_2^{\bullet-}$ can be seen in Figure 2.7A. Thiyl radical undergoes HAT with formate to deliver the $CO_2^{\bullet-}$, an essentially thermoneutral process. The $CO_2^{\bullet-}$ undergoes SET with aryl chloride expelling CO_2 gas (thermodynamic driving force). The aryl chloride radical anion undergoes mesolytic cleavage resulting in fragmentation of the C–Cl bond to produce regioselective formation of aryl radical. Thiol supplies a hydrogen atom

Figure 2.7: (A) Proposed radical chain mechanism and (B) Initiation pathways.



to the aryl radical via HAT delivering the hydrodechlorination product as well as propagating the chain mechanism. Key to this reactivity is formation of thiyl radical in the presence of formate. A variety of initiation events can induce this reactivity (Figure 2.7B).

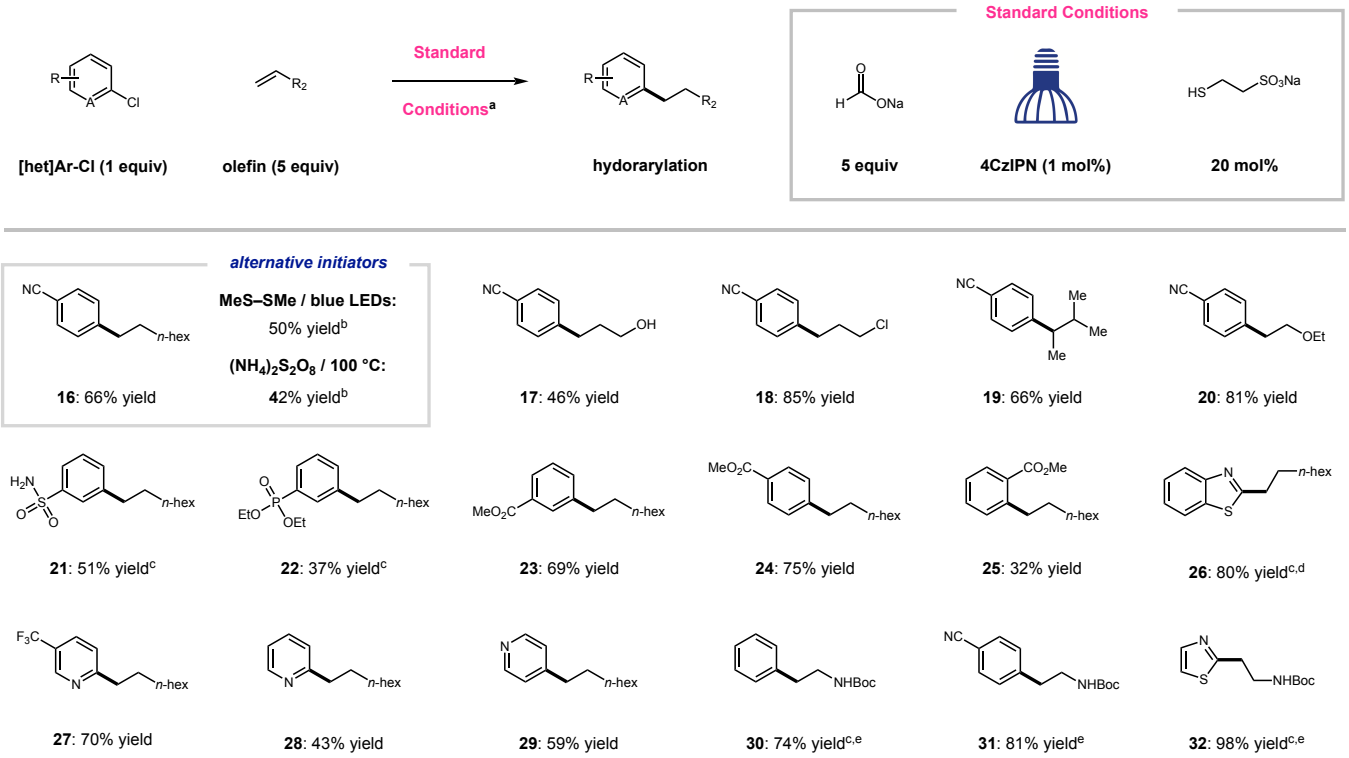
2.2.6 Scope of Reactivity Enabled by $CO_2^{\bullet-}$ Reduction

With the understanding that $CO_2^{\bullet-}$ can be generated and utilized under mild conditions for challenging reductions, we sought to utilize the radical chain process in other valuable synthetic processes. Specifically, we considered the intermolecular coupling of aryl radicals with unactivated olefins. We found radical chain reduction by $CO_2^{\bullet-}$ could successfully be employed for the coupling of aryl radicals with unactivated olefins. Here, propagation would occur between thiol and the alkyl radical produced upon aryl radical addition to olefin. While our lab has demonstrated a variety radical hydroarylation systems,[20] the coupling of benzene derived radicals with unactivated olefins has remained a challenge. This radical chain approach demonstrates the first system capable of achieving this reactivity without the need for directing groups on either reaction component.

As shown in Table 2.5, the reaction of 4-chlorobenzonitrile ($E_{p/2} = -2.10$ V vs SCE)[42] with 1-octene afforded the desired hydroarylation product **16** in 66% yield under the photoredox initiation conditions in a 50% MeCN/DMSO solution. This transformation can be performed under disulfide (50% yield **16**) and persulfate (42% yield **16**) initiation, however, resulted in a lower yield of the hydroarylation and produced more hydrodehalogenation side product compared to photoredox initiation. Monosubstituted olefins bearing an alcohol and alkyl chloride reacted to produce **17** and **18** in 46% and 85% yield, respectively. Additionally, internal olefins could be engaged under this system such as a trialkyl substituted olefin to afford **19** in a 66% yield. Vinyl ether reacted to give **20** in excellent yield (81%).

We next evaluated the aryl chloride scope with 1-octene. Aryl sulfonamides and phosphate esters were tolerated under this system to afford **21** and **22** in moderate yields (51% and 37%, respectively). We examined a series of methylbenzoates with varying substitution with respect to the chloride (**23-25**). All positions were tolerated; however, 2-chloro-methyl benzoate gave slightly lower yield (32% of **25**). A variety of heteroaryl chlorides were successful in this reaction such as thiazole **26** (80% yield) and pyridines **27**-**28** (43-70% yield). In addition, aryl radical coupling reactions could engage *tert*-butylvinyl carbamate (3 equiv) and was demonstrated with

Table 2.5: Coupling of aryl radicals with unactivated olefins



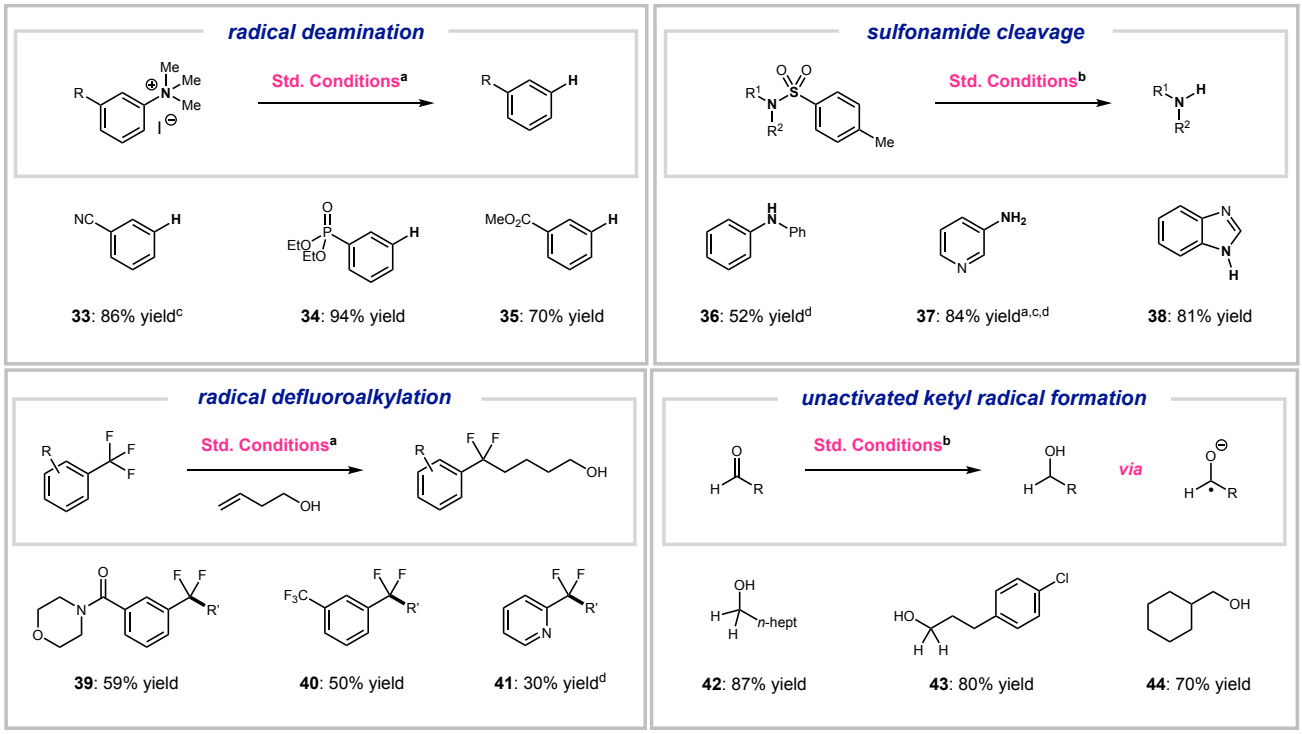
[a]Reaction conditions: substrate (1 equiv), olefin (5 equiv), P1 (1 mol %), mesna (20 mol %), sodium formate (5 equiv), MeCN/DMSO (1:1, v/ v), blue light, 16 h. [b]Yield determined by H NMR with internal standard. [c]Reaction conducted with aryl bromide. [d]Reaction conducted at 100 °C. [e]DMSO used as solvent.

bromo- benzene, 4-chlorobenzonitrile, and 2-bromothiazole as the reacting partners to afford the corresponding phenethylamines (**30**–**32**, 74–98% yield). The reductive activation of the aryl halide

substrates can be reliably predicted based upon reduction potential; substrates whose reduction potentials lie within the range of $CO_2^{\bullet-}$ (less negative than – 2.2 V vs SCE) smoothly undergo reduction. Substrates with more highly negative potentials do not react (e.g. chlorobenzene and electron-rich aryl chlorides).

To further illustrate the value of this radical chain approach, we applied it towards other classes of substrates that require a challenging reduction (Table 2.6). Phenyl ammonium salts have been demonstrated to engage in SET reactivity under Birch conditions.[21] Under our standard conditions, we found that electron-poor arylammonium salts undergo efficient deamination (**33**-

Table 2.6: Other reductive transformations utilizing $CO_2^{\bullet-}$



[a]Reaction conditions: substrate (1 equiv), olefin (5 equiv), P1 (1 mol %), mesna (20 mol %), sodium formate (5 equiv), DMSO, blue light, 16 h. [b]20% H_2O/DMSO (v/v) used as solvent. [c]Yield determined by H NMR with internal standard. [d]Reaction conducted at 100 °C.

36, 70-94% yield). This process is currently limited to substrates that contain electron-withdrawing groups in the *meta*-position. This limitation can be attributed to a competitive nucleophilic

demethylation process with *para*- and *ortho*-activated substrates. Nicewicz and coworkers have demonstrated SET-induced N–S cleavage of arylsulfonamides using a radical anion excitation of acridinium based photocatalysts approach.[6] We found $CO_2^{\bullet-}$ reduction can also achieve this for the deprotection of a variety of N-aryl tosylates (**36-38**, 52-84% yield). We also demonstrate this system can accomplish defluoroalkylation of trifluoromethyl arenes, a strategy that has previously been developed by our group,[15,22] to give difluoroalkyl products **39**- **41** (30- 59% yield). Finally, we found this system can accomplish reduction of aliphatic aldehydes which operates through a valuable ketyl radical intermediate. Presumably, chain propagation occurs through the ketyl radical intermediate to deliver the corresponding alcohols (**42**-**44**, 70- 87% yield).

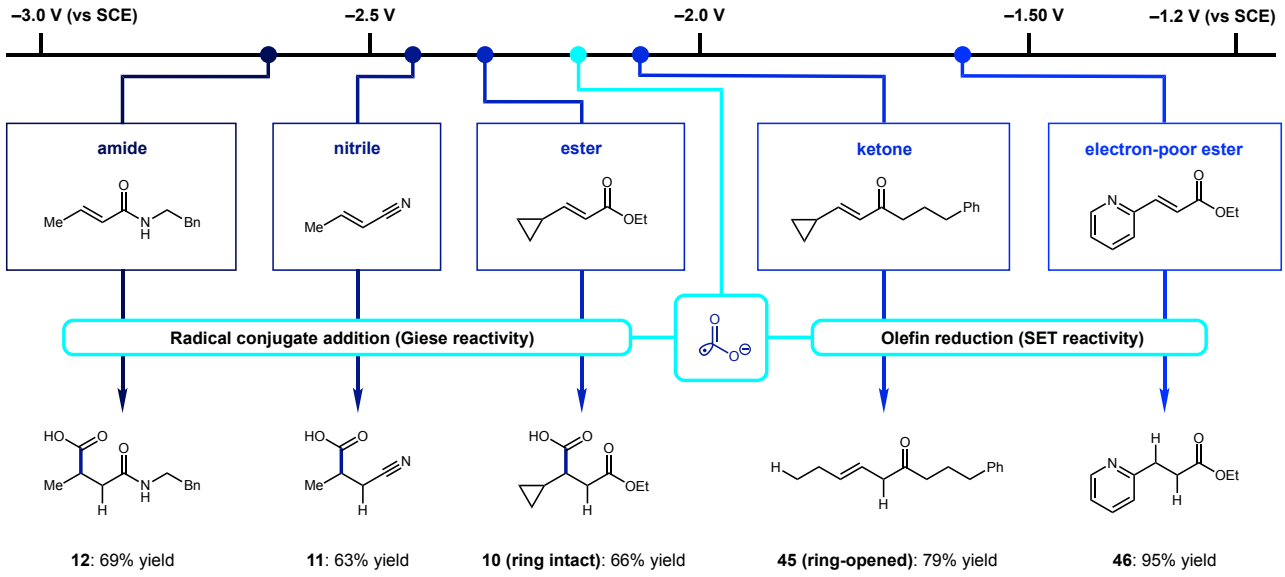
2.2.7 Divergent Reactivity of $CO_2^{\bullet-}$

The reaction of electron-deficient olefins highlights the two-modes of divergent and predictable reactivity that can be accomplished by $CO_2^{\bullet-}$. Bringing the project full circle from its initial discovery of carboxylation, Michael acceptors can either undergo carboxylation or SET which can be predicted solely based on the reduction potential of the substrate. This concept is shown in Figure 2.8. Pyridyl cinnamate ester ($E_{p/2} = -1.60$ V vs SCE, see *supporting information*) gave solely hydrogenated product **46** in excellent yield (95%). To confirm this is indeed operating through a SET pathway β-cyclopropyl enone was subjected to conditions and yielded a 79% yield of the ring opened product **45**. This result is in strong support of SET process as radical formation is known to occur in the β-position of enones.

As previously mentioned, the β-cyclopropyl unsaturated ester delivers solely carboxylation in a 66% yield of **10** with the ring intact. This result in conjunction with the enone, emphasizes the mechanistic divergencies of $CO_2^{\bullet-}$ controlled solely by substrate reduction potential. In line with this assertion, unsaturated nitrile and amide are outside the reduction potential range of $CO_2^{\bullet-}$ and

deliver selective formation of carboxylation products (**11-12**, 63- 69%). To summarize, more electron-poor olefins ($E^{\circ}_{1/2} \geq -2.1$ V vs SCE) undergo SET and less electron-poor olefins ($E^{\circ}_{1/2} \leq -2.1$ V vs SCE) undergo radical hydrocarboxylation.

Figure 2.8: Reaction of $CO_2^{\bullet-}$ with electron-deficient alkenes: Divergent reactivity based on reduction potential.



2.3 Conclusions

In summary, we have developed a unique method for $CO_2^{\bullet-}$ generation under simple and mild conditions. The relatively weak C–H bond of formate readily undergoes abstraction by thiyl radical to produce $CO_2^{\bullet-}$. We first demonstrate the ability of $CO_2^{\bullet-}$ to successfully engage a variety of Michael acceptors in a hydrocarboxylation reaction. During the development of this reaction, it was observed that certain substrates would undergo a SET pathway leading to the corresponding hydrogenation product instead of carboxylation. This led us to the discovery of $CO_2^{\bullet-}$ as a powerful single electron reducing reagent. We demonstrate it's ability to engage a diverse array of substrates via SET that required challenging reductions (e.g. aryl chlorides). Reduction by $CO_2^{\bullet-}$ operates in an efficient radical chain process and a variety of initiators can successfully induce this process without the need for a photocatalyst. Michael acceptors display divergent reactivity (e.g. reduction or carboxylation) in the presence of $CO_2^{\bullet-}$, where reaction outcome can be predicted by reduction potential of the substrate. These discoveries inspired later work that can be found in subsequent chapters of this dissertation.

2.4 References

(1) Birch, A. J. Reduction by Dissolving Metals. Part I. *J. Chem. Soc.* **1944**, 430, 430-436.

(2) (a) Mohle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew, Chem. Int. Ed.* **2018**, 57, 6018-6041. (b) Peters, B. K.; Rodriguez, K. X.; Reisberg, S. H.; Beil, S. B.; Hickey, D. P.; Kawamata, Y.; Collins, M.; Starr, J.; Chen, L.; Udyavara, S.; et al. *Scalable and Safe Synthetic Organic Electroreduction Inspired by Li-Ion Battery Chemistry*. Science. **2019**, 363, 838-845.

(3) Nelleborg, P.; Lund, H.; Eriksen, J. Photochemical Vs. Electrochemical Electron Transfer Reactions. One-Electron Reduction of Aryl Halides by Photoexcited Anion Radicals. *Tetrahedron Lett.* **1985**, 26, 1773- 1776.

(4) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, 113, 5322-5363. (b) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, 116, 10075-10166.

(5) Arias-Rotondo, D. M.; McCusker, J. K. The Photophysics of Photoredox Catalysis: a Roadmap for Catalyst Design. *Chem. Soc. Rev*. **2016**, 45, 5803-5820.

(6) MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. Discovery and Characterization of an Acridine Radical Photoreductant. *Nature.* **2020**, 580, 76-80.

(7) (a) Cowper, N. G. W.; Chernowsky, C. P.; Williams, O. P.; Wickens, Z. K. Potent Reductants via Electron-Primed Photoredox Catalysis: Unlocking Aryl Chlorides for Radical Coupling. *J. Am. Chem. Soc.* **2020**, 142, 2093-2099. (b) Kim, H.; Kim, H.; Lambert, T. H.; Lin, S. Reductive

Electrophotocatalysis: Merging Electricity and Light to Achieve Extreme Reduction Potentials. *J. Am. Chem. Soc*. **2020**, 142, 2087-2092.

(8) (a) Stevens, G. B.; Reda, T.; Raguse, B. Energy Storage by the Electrochemical Reduction of CO2 to CO at Porous Au Film. *J. Electroanal. Chem.* **2002**, 526, 125-133. (b) Franco, F.; Rettenmaier, C.; Jeon, H. S.; Roldan Cuenya, B. Transition Metal-Based Catalysts for the Electrochemical CO_2 Reduction: from Atoms and Molecules to Nanostructured Materials. *Chem. Soc. Rev.* **2020**, 49, 6884-6946.

(9) Koppenol, W. H.; Rush, J. D. Reduction Potential of the Carbon Dioxide/Carbon Dioxide Radical Anion: A Comparison with Other C_1 Radicals. *J. Phys. Chem.* **1987**, 91, 4429-4430.

(10) Morgenstern, D. A.; Wittrig, R. E.; Fanwick, P. E.; Kubiak, C. P. Photoreduction of Carbon Dioxide to Its Radical Anion by $[Ni_3(\mu^3\text{-}I)_2(dppm)_3]$: Formation of Two Carbon-Carbon Bonds via Addition of $CO_2^{\bullet-}$ to Cyclohexene. *J. Am. Chem. Soc.* **1993**, 115, 6470-6471.

(11) Otereo, M. D.; Batanero, B.; Barba, F. CO_2 Anion-Radical in Organic Carboxylations. *Tetrahedron Lett*. **2006**, 47, 2171-2173.

(12) Seo, H.; Katcher, M. H.; Jamison, T. F. Photoredox Activation of Carbon Dioxide for Amino Acid Synthesis in Continuous Flow. *Nat. Chem.* **2017**, 9, 453-456.

(13) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett.* **2016**, 27, A-J.

(14) Du, Y.; Pearson, R. M.; Lim, C. H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; Damrauer, N. H.; Miyake, G. M. Strongly Reducing, Visible-Light Organic Photoredox Catalysts as Sustainable Alternatives to Precious Metals. *Chem. Eur. J.* **2017**, 23, 10962-10968.

(15) Vogt, D. B.; Seath, C. P.; Wang, H.; Jui, N. T. Selective C-F Functionalization of Unactivated Trifluoromethylarenes. J. Am. Chem. Soc. 2019, 141, 13203-13211.

(16) (a) Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. Organocatalyzed Birch Reduction Driven by Visible Light. *J. Am. Chem. Soc.* **2020**, 142, 13573-13581.(b) Chatterjee, A.; Konig, B. Birch-Type Photoreduction of Arenes and Heteroarenes by Sensitized Electron Transfer. *Angew. Chem. Int., Ed. Engl.* **2019**, 58, 14289-14294.

(17) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions. *J. Am. Chem. Soc.* **2008**, 130, 12886-12887.

(18) 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, 15353-15365.

(19) 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. *J. Chem. Soc., Perkin Trans.* 2. **2001**, 1620-1630.

(20) (a) 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. (b) 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. (c) Boyington, A. J.; Riu, M. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, 139, 6582-6585.

(21) Paras, N. A.; Simmons, B.; MacMillan, D. W. A Process for the Rapid Removal of Dialkylamino-Substituents from Aromatic Rings. Application to the Expedient Synthesis of (R)-

Tolterodine. *Tetrahedron.* **2009**, 65, 3232-3238.

(22) Wang, H.; Jui, N. T. Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, 140, 163-166.

2.5 Supporting Information

2.5.1. General Information

A. General Reagent Information

Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. 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); or a Kessil® PR160L- 390 nm. Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using $KMnO_4$, p- anisaldehyde, or ninhydrin stains. DMSO was purchased from Fisher Scientific and was distilled over CaH2 and degassed by sonication under vacuum and stored under nitrogen. Photoredox catalyst 4CzIPN was prepared according to literature procedures.[1]

B. General Analytical Information.

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. New compounds were characterized by NMR and HRMS. ^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), Bruker 400 (400 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz), and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows:

chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. High Resolution mass spectra were obtained from the Emory University Mass Spectral facility.

D. General Photoredox Reaction Setup

To run multiple reactions, an appropriately sized 3D printed carousel was used, which exposed the reactions to the blue light evenly (photo 1). A 15 W LED array lamp was used as a blue light source (photo 2,3). These lamps were routinely used for up to 12 reactions at a time (photo 2,3). The blue LEDs were positioned approximately 6 inches above the reaction vials to get good light coverage without overheating the reactions (photo 2,3). Reactions run at elevated temperatures were irradiated in a shallow oil bath (photo 4,5).

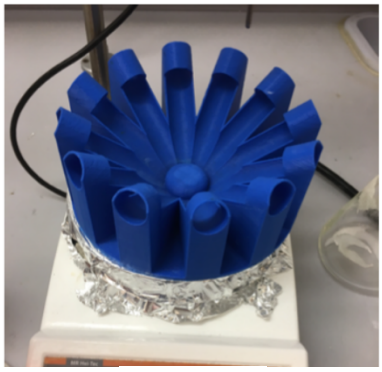


Photo 1

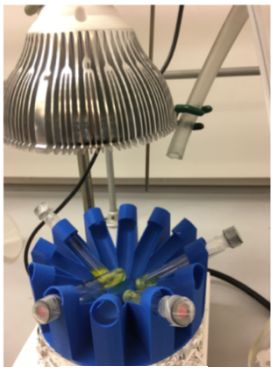


Photo 2

Photo 3

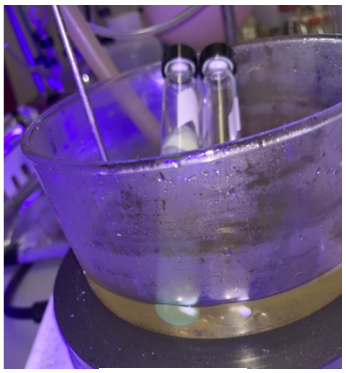


Photo 4

Photo 5

2.5.2 Optimization of Carboxylation of Michael Acceptors

Procedure:

An 8 mL screw-top test tube was charged with benzyl (*E*)-but-2-enoate **S1** (1.0 equiv, 0.1 mmol), 4CzIPN (1 mol%, 0.001 mol), sodium formate (5.0 equiv, 0.5 mmol), formic acid (5.0 equiv, 0.5 mmol) and mesna (20 mol%, 0.02 mol). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed solvent (1 mL) was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by a kessil 390s lamp. Saturated aqueous potassium carbonate was added and reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 µL, 0.1 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data given in Table 2.1.

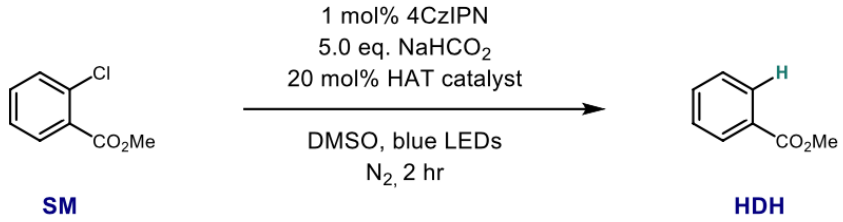
2.5.3 Optimization of Hydrodechlorination with $CO_2^{\bullet-}$

Procedure:

An 8 mL screw-top test tube was charged with 4CzIPN (1 mol%, 0.001 mol), sodium formate (5.0 equiv, 0.5 mmol) and mesna (20 mol%, 0.02 mol). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO (1

mL) was added via syringe, followed by 2-chloromethylbenzoate (1 equiv, 0.1 mmol). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs. The reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 µL, 0.1 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data given in Table S1- S3.

HAT catalysts:



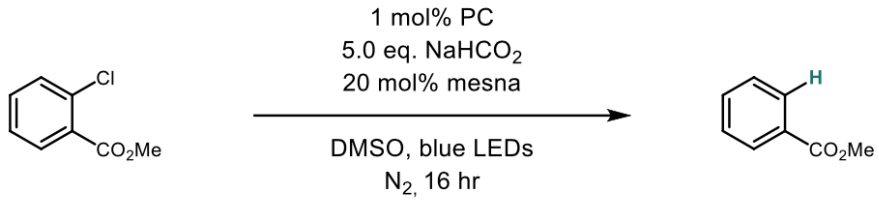
SM **HDH**

Entry	HAT catalyst	SM	HDH
1	none	97	0
2	mesna	0	100
3	cyclohexane thiol	0	91
4	dodecane thiol	0	93
5	thiophenol	0	92
6	thiobenzoic acid	0	92
7	DABCO	39	62

yields determined by ^{1}H NMR with dibromomethane as internal standard

Table S2.1: HAT catalysts screen.

Varying Photocatalysts:



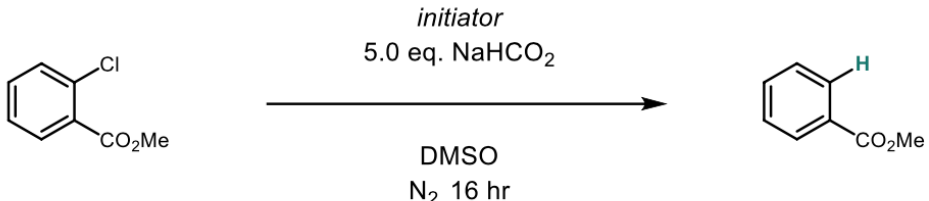
SM **HDH**

Entry	PC	$E_{1/2}$ ($PC^*/PC^{\cdot+}$)	$E_{1/2}$ ($PC^{\cdot-}/PC$)	SM	HDH
1	4CzIPN	-1.18 V	-1.24 V	0	100
2	4CzTPN	-0.99 V	-1.02 V	0	92
3	$Ir(df\text{-}CF_3\text{-}ppy)_2(dtbbpy)PF_6$	-0.89 V	-1.37 V	0	98
4	$Ir(ppy)_2(dtbbpy)PF_6$	-0.96 V	-1.51 V	0	93

yields determined by ^{1}H NMR with dibromomethane as internal standard
(Reductions potentials reported vs. SCE)

Table S2.2: Photocatalyst screen.

Controls:



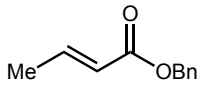
SM **HDH**

Entry	deviations	SM	HDH
1	no 4CzIPN	100	0
2	no formate	99	0
3	no light	102	0
4	in presence of air	3	94

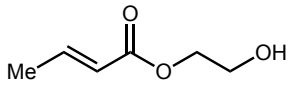
yields determined by ^{1}H NMR with dibromomethane as internal standard

Table S2.3: Control experiments

2.5.4 Preparation of Starting Materials



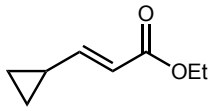
Benzyl (*E*)-but-2-enoate (S1): To a round bottom flask was added crotonic acid (22 mmol, 1.89 g, 1.2 equiv), K_2CO_3 (12 mmol, 1.65 g, 0.6 equiv.), and DMF (20 mL). The reaction mixture was then cooled to 0 ^oC and benzyl bromide (20 mmol, 2.4 mL, 1 equiv.) was added dropwise. The reaction mixture was then stirred overnight and quenched with saturated aqueous $NaHCO_2$ and extracted with EtOAc (3x). The combined organic extracts were washed with brine and water (20 mL), dried over Na_2SO_4, pushed through a silica plug (100% EtOAc as the eluent), and concentrated *in vacuo* to afford the title compound as a clear oil (2.93 g, 82% yield). The physical and spectral properties match the reported values.[2] **^{1}H NMR (400 MHz, $CDCl_3$)** 7.38-7.29 (m, 5H), 7.03 (m, 1H), 5.90 (m, 1H), 5.17 (s, 2H), 1.88 (dd, J = 6.9 Hz, 1.7 Hz, 3H).



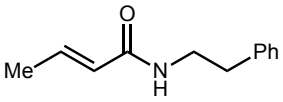
2-hydroxyethyl (*E*)-but-2-enoate (S2): To a round bottom flask was added crotonic acid (10 mmol, 0.86 g, 1 equiv), DBU (10 mmol, 0.70 mL, 1 equiv.), 2-bromoethanol (10 mmol, 1.5 mL, 1 equiv) and CH_3CN (20 mL). The reaction mixture was then equipped with a reflux condenser and refluxed at 80 ^oC overnight. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and transferred to a separatory funnel. The combined organic extracts were washed with 1M HCl (2x) followed by saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was then purified by silica chromatography to afford the

title compound as a light yellow oil (0.64 g, 50% yield.) The physical and spectral properties match the reported values.[3]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06-6.97 (m, 1H), 5.90-5.85 (m, 1H), 4.28-4.24 (m, 2H). 3.86-3.82 (m, 2H), 1.89 (d, J = 6.9 HZ, 3H).

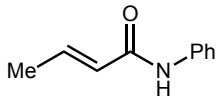


Ethyl (*E*)-3-cyclopropylacrylate (S3): The title compound was prepared according to literature procedure. The physical and spectral properties were consistent with the reported values.[4] **^{1}H NMR (600 MHz, Chloroform-d)** δ 6.41 (dd, J = 15.4 Hz, 10.1 Hz, 1H), 5.89 (d, J = 15.4 Hz, 1H), 4.17 (q, J = 10.7 Hz, 2H), 1.58-1.53 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 0.95-0.91 (m, 2H), 0.65-0.61 (m, 2H).



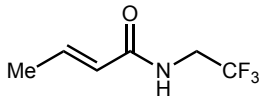
(*E*)-N-phenethylbut-2-enamide (S4): To a flame dried round bottom flask was added crotonic acid (5 mmol, 0.43 g, 1 equiv) after which the atmosphere was exchanged three times with N_2. CH_2Cl_2 (20 mL) was then added followed by oxalyl chloride (5.5 mmol, 0.46 mL, 1.5 equiv) and DMF (2 drops), the reaction mixture was then allowed to stir for 1 hour. Phenethylamine (6 mmol, 0.76 mL, 1.2 equiv) was then added in one portion followed by triethylamine (5.5 mmol, 0.77 mL, 1.1 equiv.). The reaction mixture was allowed to stir overnight, diluted with CH_2Cl_2 (20 mL) and 1M HCl (10 mL). The organic phase was separated from the aqueous phase and washed with 1M HCl (10 ml), brine (2x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was pushed through a silica plug (50% EtOAc/hexanes as the eluent) to afford the title compound as white solid (0.96 g, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.9 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 6.83 (dq, J = 15.2, 6.9 Hz, 1H), 5.72 (dd, J = 15.2 Hz, 1.6 Hz, 1H), 5.39 (bs, 1H), 3.59 (td, J = 6.9 Hz, 5.9 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H), 1.83 (dd, J = 6.9, 1.6 Hz, 3H). **^{13}C NMR (600 MHz, $CDCl_3$)** δ165.9, 140.5, 138.5, 128.8, 128.7, 125.9, 124.9, 40.53, 35.7, 17.2. **GCMS:** m/z: $[M]^+$ calc'd for $C_{15}H_{18}O$, 214.1; found 214.2.



(*E*)-N-phenylbut-2-enamide (S5): To a flame dried round bottom flask was added crotonic acid (5.0 mmol, 0.43 g, 1.0 equiv.) after which the atmosphere was exchanged three times with nitrogen. CH_2Cl_2 (20 mL) was then added followed by oxalyl chloride (5.5 mmol, 0.46 mL, 1.5 equiv) and DMF (2 drops). The reaction mixture was then allowed to stir for 1 hour. Aniline (6.0 mmol, 0.55 mL, 1.2 equiv) was then added in one portion followed by triethylamine (5.5 mmol, 0.77 mL, 1.1 equiv.). The reaction mixture was allowed to stir overnight, diluted with CH_2Cl_2 (20 mL) and 1M HCl (10 mL). The organic phase was separated from the aqueous phase and washed with 1 M HCl (1x), brine (2x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was pushed through a silica plug (30% EtOAc/hexanes as the eluent) to afford the title compound as brown solid (0.72 g, 90% yield). The physical and spectral properties match the reported values.[5]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.20 (bs, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.03-6.03 (m, 1H), 5.95 (d, J = 15.1 Hz, 1H), 1.91 (dd, J = 6.9 Hz, 1.7 Hz, 3H).



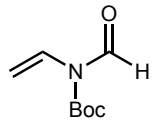
(E)-N-(2,2,2-trifluoroethyl)but-2-enamide (S6): To a flame dried round bottom three neck flask was added crotonic acid (5 mmol, 0.43 g, 1 equiv) after which the atmosphere was exchanged three times with nitrogen. CH_2Cl_2 (20 mL) was then added followed by oxalyl chloride (5.5 mmol, 0.46 mL, 1.5 equiv) and DMF (2 drops). The reaction mixture was then allowed to stir for one hour. 2,2,2-trifluoroethylamine (6 mmol, 0.47 mL, 1.2 equiv) was added in one portion followed by triethylamine (5.5 mmol, 0.77 mL, 1.1 equiv). The reaction mixture was allowed to stir overnight, diluted with CH_2Cl_2 (20 mL) and 1M HCl (10 mL). The organic phase was separated from the aqueous phase and washed with 1M HCl (10 ml), brine (2x), dried over Na_2SO_4, and concentrated in vacuo. The crude product was pushed through a silica plug (50% EtOAc/hexanes as eluent) to afford the title compound as a white solid (0.43 g, 52% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98-6.90 (m, 1H), 5.84 (d, J = 15.6 Hz, 1H), 5.72 (bs, 1H), 4.01-3.94 (m, 2H), 1.89-1.86 (m, 3H), 1.96-1.88 (m, 2H), 1.55-1.48 (m, 1H), 0.98-0.91 (m, 2H), 0.64-0.59 (m, 2H).

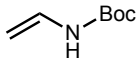
^{13}C NMR (600 MHz, $CDCl_3$) δ 165.8, 140.5, 125.6, 123.4, 40.9, 16.9.

^{19}F NMR (600 MHz, $CDCl_3$) δ -72.48 (t, J = 9.1 Hz, 3F).

GCMS: m/z: $[M]^+$ calcd. for $C_6H_8F_3NO$, 167.1; found 167.1.

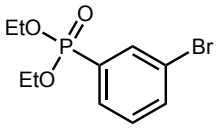


***tert*-butyl formyl(vinyl)carbamate (S7):** The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[6]



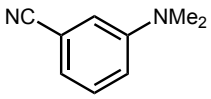
***tert*-butyl vinylcarbamate (S8):** The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[6]

^{1}H NMR (600 MHz, DMSO-d$_6$) δ (9.20, s, 1H), 6.51 (ddd, J = 15.9, 10.4, 8.9 Hz, 1H), 4.45 (d, J = 15.9 Hz, 1H), 4.09 (d, J = 8.9 Hz, 1H), 1.41 (s, 9H).



Diethyl (3-bromophenyl)phosphonate (S9): The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[7]

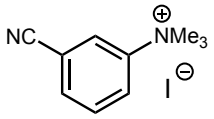
^{1}H NMR (500 MHz, Chloroform-d) δ 7.94 (ddd, *J* = 13.6, 1.9, 1.4 Hz, 1H), 7.73 (ddt, *J* = 12.9, 7.6, 1.2 Hz, 1H), 7.67 (ddt, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.34 (td, *J* = 7.8, 4.7 Hz, 1H), 4.11 (m, 4H), 1.32 (t, J = 7.1 Hz, 6H).



3-(dimethylamino)benzonitrile (S10): A round bottom flask equipped with a stirbar was added 3-aminobenzonitrile (10 mmol, 1.2 g, 1.0 equiv), Na_2CO_3 (20 mmol, 2.1 g, 2.0 equiv) and DMF (10 mL). Methyl iodide (25 mmol, 1.6 mL, 2.5 equiv) was added dropwise to the solution a few minutes later. The reaction was heated to 80 °C and stirred overnight. The reaction was allowed to cool to room temp. and it was diluted in EtOAc. The solution was washed with a solution of 1 M LiCl, extracted with EtOAc (3 x), dried over Na_2SO_4 and concentrated *in vacuo.* The crude reaction

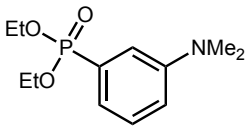
mixture was pushed through a silica plug (10% EtOAc/hexanes) to afford the title compound as an orange oil (1.0 g, 69% yield). The spectral properties were consistent with the reported values.[8]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 1H), 6.95 (dt, *J* = 7.5, 1.1 Hz, 2H), 6.91 – 6.82 (m, 1H), 2.98 (s, 6H).



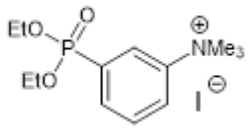
3-cyano-N,N,N-trimethylbenzenaminium iodide (S11): The procedure used was adapted from Wang.[9] A round bottom flask equipped with a stir bar was added methyl 3-(dimethylamino)benzonitrile **S4** (6.0 mmol, 0.88 g, 1.0 equiv) and DMF (4 mL). Methyl iodide (12 mmol, 0.74 mL, 2.0 equiv) was added dropwise. The reaction was heated to 50 °C and stirred overnight. The reaction was allowed to cool to room temp. and it was diluted with Et_2O. The solid precipitate was collected by vacuum filtration to afford the title compound as a white solid (1.26 g, 73% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (dd, *J* = 2.4, 1.3 Hz, 1H), 8.34 (ddd, *J* = 8.7, 2.8, 0.9 Hz, 1H), 8.15 – 8.06 (m, 1H), 7.90 – 7.85 (m, 1H), 3.64 (s, 9H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 147.43, 133.94, 131.33, 125.86, 125.13, 117.47, 112.81, 56.47. **HRMS** (APCI) *m/z*: [M+] calcd. for $C_{10}H_{13}N_2$, 161.0709; found, 161.0711. [M-] calcd. for I, 126.9050; found, 126.9057.



diethyl (3-(dimethylamino)phenyl)phosphonate (S12): The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[10]

^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.26 (m, 1H), 7.20 – 7.05 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 4.20 – 3.99 (m, 4H), 2.98 (s, 6H), 1.32 (t, J = 7.1 Hz, 6H).



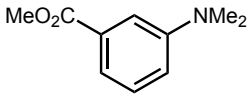
3-(diethoxyphosphoryl)-N,N,N-trimethylbenzenaminium iodide (S13): The procedure used was adapted from Wang.[9] A round bottom flask equipped with a stir bar was added diethyl (3-(dimethylamino)phenyl)phosphonate **S6** (2.0 mmol, 0.51 g, 1.0 equiv) and DMF (1.5 mL). Methyl iodide (4 mmol, 0.25 mL, 2.0 equiv) was added dropwise. The reaction was heated to 50 °C and stirred overnight. The reaction was allowed to cool to room temp. and it was diluted with Et2O. The solid precipitate was collected by vacuum filtration to give the title compound as a white solid (0.65 g, 81% yield).

^{1}H NMR (400 MHz, Methanol-d4) δ 8.26 (dd, J = 14.8, 3.3 Hz, 2H), 8.02 (ddt, J = 12.7, 7.5, 1.0 Hz, 1H), 7.94 – 7.83 (m, 1H), 4.31 – 4.12 (m, 4H), 3.77 (s, 9H), 1.38 (t, J = 7.1 Hz, 6H).

^{13}C NMR (151 MHz, Methanol-d4) δ 148.80 (d, J = 18.9 Hz), 134.72 (d, J = 8.9 Hz), 132.56 (d, J = 15.7 Hz), 132.52 (d, J = 192.1 Hz), 124.15 (d, J = 12.7 Hz), 64.56 (d, J = 6.0 Hz), 57.84, 16.64 (d, J = 6.1 Hz).

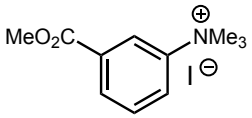
^{31}P NMR (162 MHz, Methanol-d4) δ 15.49.

HRMS (APCI) *m/z*: [M+] calcd. for $C_{13}H_{23}NO_3P$, 272.1410; found, 272.1410. [M-] calcd. for I, 126.9050; found, 126.9056.



methyl 3-(dimethylamino)benzoate (S14): To a round bottom flask equipped with a stirbar was added 3-(dimethylamino)benzoic acid (20 mmol, 3.3 g, 1.0 equiv) and MeOH (20 mL). A few drops of concentrated HCl was added and the reaction was refluxed overnight and then concentrated *in vacuo*. The crude product was diluted in EtOAc and washed with sat. $NaHCO_3$ (3 x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was pushed through a silica plug (5% EtOAc) to give the title compound as a clear oil (1.7 g, 47% yield). The physical and spectral properties were consistent with the reported values.[11]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.90 (s, 3H), 3.00 (s, 6H).

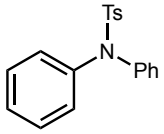


3-(methoxycarbonyl)-N,N,N-trimethylbenzenaminium iodide (S15): The procedure used was adapted from Wang.[9] A round bottom flask equipped with a stir bar was added methyl 3-(dimethylamino)benzoate **S8** (9.0 mmol, 1.6 g, 1.0 equiv) and DMF (7 mL). Methyl iodide (15 mmol, 0.93 mL, 1.5 equiv) was added dropwise. The reaction was heated to 50 °C and stirred overnight. The reaction was allowed to cool to room temp. and it was diluted with Et_2O. The solid precipitate was collected by vacuum filtration to give the title compound as a white solid (2.4 g, 84% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (dd, *J* = 2.8, 1.4 Hz, 1H), 8.30 (ddd, *J* = 8.6, 2.9, 0.9 Hz, 1H), 8.14 (ddd, *J* = 7.8, 1.4, 0.9 Hz, 1H), 7.82 (t, 1H), 3.92 (s, 3H), 3.66 (s, 9H).

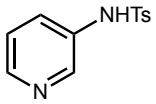
^{13}C NMR (101 MHz, DMSO-d_6) δ 165.03, 147.48, 131.29, 130.83, 130.60, 125.55, 121.14, 56.40, 52.81.

HRMS (APCI) *m/z*: [M+] calcd. for $C_{11}H_{16}NO_2$, 194.0812; found, 194.0813. [M-] calcd. for I, 126.9050; found, 126.9056.



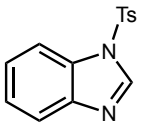
4-methyl-N,N-diphenylbenzenesulfonamide (S16): The title compound was prepared according to literature procedure.[12] The physical and spectral properties were consistent with the reported values.[13]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 6.7 Hz, 2H), 7.35 – 7.22 (m, 12H), 2.43 (s, 3H).



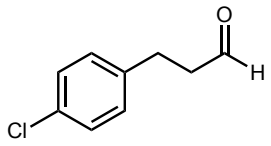
4-methyl-*N*-(pyridine-3-yl)benzenesulfonamide (S17): The title compound was prepared according to literature procedure.[12] The physical and spectral properties were consistent with the reported values.[14]

^{1}H NMR (400 MHz, DMSO-d6): δ 10.49 (bs, 1H), 8.26 (d, J = 2.6 Hz, 1H), 8.23 (dd, J = 4.7, J = 1.5 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.48 (ddd, J = 8.3, 2.7, 1.5 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.27 (dd, J = 8.3, 4.7 Hz, 1H), 2.33 (s, 3H).



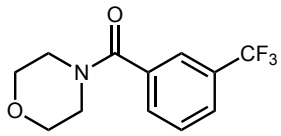
1-tosyl-1*H*-benzo[*d*]imidazole (S18): The title compound was prepared according to literature procedure.[12] The physical and spectral properties were consistent with the reported values.[15]

^{1}H NMR (600 MHz, Chloroform-d) δ 8.39 (s, 1H), 7.86 (m, 3H), 7.76 (m, 1H), 7.37 (m, 2H), 7.30 (m, 2H), 2.38 (s, 3H).



3-(4-chlorophenyl)propanal (S19): To a round bottom flask was added 3-(4-chlorophenyl)propan-1-ol (10 mmol, 1.5 mL, 1 equiv), $[Cu(CH_3CN)_4]PF_6$ (0.5 mmol, 0.19 g, 0.05 equiv.), TEMPO (0.5 mmol, 0.078 g, 0.05 equiv.), 2,2-bipyridine (0.5 mmol, 0.078 g, 0.05 equiv), NMI (1 mmol, 80 μL, 0.1 equiv) and CH_3CN (50 mL). The reaction was then sparged with air overnight then pushed through a silica plug using EtOAc and concentrated *in vacuo*. The crude product was then purified by silica chromatography (0-30% EtOAc/Hexanes as the eluent) to give the title compound as a light yellow oil (0.519 g, 31% yield.) The physical and spectral properties were consistent with the reported values.[16]

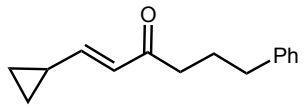
^{1}H NMR (400 MHz, Chloroform-d) δ 9.80 (t, J = 1.3 Hz, 1H), 7.27-7.21 (m, 2H), 7.15-7.08 (m, 2H), 2.96-2.87 (m, 2H), 2.80-2.73 (m, 2H).



morpholino(3-(trifluoromethyl)phenyl)methanone (S20): A round bottom flask equipped with a stir bar was added morpholine (11 mmol, 0.95 mL, 1.1 equiv), triethylamine (12.5 mmol, 1.7 g, 1.25 equiv) and CH_2Cl_2 (20 mL) and stirred for 10 minutes. 3-(trifluoromethyl)benzoyl chloride (10 mmol, 1.5 mL, 1.0 equiv) was added dropwise and the solution was allowed to stir for 1 hour. The reaction mixture was quenched with 1 M HCl, extracted with CH_2Cl_2 (3 x), and concentrated

in vacuo. The crude reaction mixture was pushed through a silica plug (50% EtOAc/hexanes as the eluent) and concentrated *in vacuo* to afford the title compound as a white solid (2.3 g, 90% yield). The spectral properties were consistent with the reported values.[17]

^{1}H NMR (600 MHz, Chloroform-d) δ 7.70 (d, J = 11.7 Hz, 2H), 7.62 – 7.53 (m, 2H), 3.99 – 3.30 (m, 8H).



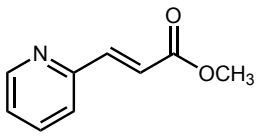
(E)-1-cyclopropyl-6-phenylhex-1-en-3-one (S21): To a flame dried round bottom flask was added 1-(triphenylphosphoraneylidene)-2-propanone (4 mmol, 1.27 g, 1 equiv) after which the atmosphere was exchanged three times with nitrogen followed. THF was added (30 mL), the reaction mixture was cooled to -78 °C and n-butyllithium (5.2 mmol, 2.5 mL, 1.3 equiv.) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hour followed by the dropwise addition of (2-bromoethyl)benzene (5.2 mmol, 0.71 mL, 1.3 equiv). The reaction mixture was warmed to room temperature, stirred for 7 hours, and concentrated in vacuo. The crude mixture was then dissolved in CH_2Cl_2 (40 mL), washed with water (3x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was then dissolved in $CHCl_3$ followed by the addition of cyclopropane carboxaldehyde (6 mmol, 0.45 mL, 1.5 equiv). The reaction mixture was refluxed overnight at 60 °C, concentrated in vacuo, and purified by silica chromatography (0-5% EtOAc/hexanes as the eluent) to afford the title compound as a colorless oil (0.35 g, 41% yield).

R_f: 0.48 (10% EtOAc/Hexanes)

^{1}H NMR (600 MHz, Chloroform-d) δ 7.28-7.22 (m, 2H), 7.19-7.13 (m, 3H), 6.27-6.14 (m, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.47 (t, J = 6.8 Hz, 2H), 1.96-1.88 (m, 2H), 1.55-1.48 (m, 1H), 0.98-0.91 (m, 2H), 0.64-0.59 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 199.65, 152.58, 141.92, 128.65, 128.49, 127.34, 126.03, 77.37, 77.16, 76.95, 39.59, 35.33, 25.95, 14.78, 9.08.

HRMS (APCI) m/z: [M+H] calcd. for $C_{15}H_{19}O$, 215.1430; found, 215.1233.



Methyl (*E*)-3-(pyridine-2-yl)acrylate (S22): A round bottom flask was equipped with 2-pyridinecarboxaldehyde (5 mmol, 0.48 mL, 1 equiv), methyl (triphenylphosphoranylidene)acetate (7.5 mmol, 2.50 g, 1.5 equiv) and benzene (10 mL) under nitrogen. The reaction was then heated to 80 ^{0}C for three hours, cooled to room temperature, and concentrated *in vacuo*. The crude product was purified by silica chromatography (30- 40% EtOAc/hexanes as the eluent) to afford the title compound as a light brown solid (0.59 g, 73% yield). The physical properties and spectral data were consistent with the reported values. [18]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (d, J = 4.8 Hz, 1H), 7.73-7.64 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.29-7.24 (m, 1H), 6.93 (d, J = 15.7 Hz, 1H), 3.81 (s, 3H).

2.5.5 Preparation of Products from Substrate Tables

2.5.5A General Procedures

General Procedure A

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (5.0 equiv), mesna (20 mol%), Michael Acceptor (*if solid*, 1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separately the indicated degassed solvent [0.1 M] was added via syringe followed by the substrate (*if liquid*, 1.0 equiv) and formic acid (5.0 equiv). The resulting mixture was stirred at

1400 RPM for 16 h under irradiation by Kessil 390s lamp. Water was added and then the reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. The residue was purified by silica chromatography using the indicated solvent mixture as the eluent to afford the title compound.

General Procedure B

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (5.0 equiv), mesna (20 mol%), (hetero)aryl halide (*if solid*, 1.0 equiv) and alkene (*if solid*, 5.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separately degassed solvents were added via syringe in a 1:1 ratio (50% MeCN/ 50% DMSO, 0.1 M) followed by the (hetero)aryl halide (*if liquid*, 1.0 equiv) and the alkene (*if liquid*, 1.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs. Water was added and then the reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

General Procedure C

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (5.0 equiv), mesna (20 mol%), and the phenyl ammonium salt (1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, degassed DMSO (0.1 M) was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs. Water was added and then the

reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated to afford the title compound.

General Procedure D

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (10.0 equiv), mesna (20 mol%), and the N-tosyl (hetero)arene (1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, a degassed solution of 20% H_2O/DMSO (0.1 M) was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs, unless noted otherwise. Water was added and then the reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

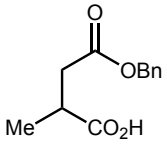
General Procedure E

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (10.0 equiv), mesna (20 mol%), and the trifluoromethyl- arene (*if solid*, 1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, degassed DMSO (0.1 M) was added via syringe followed by trifluoromethyl arene (*if liquid*, 1.0 equiv) and buten-1-ol (3.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs, unless noted otherwise. Water was added and then the reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

General Procedure F

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (10.0 equiv), and mesna (20 mol). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, a degassed solution of 20% H_2O/DMSO (0.1 M) was added via syringe followed by the aldehyde (1.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs. Water was added and then the reaction mixture was extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. The residue was purified on silica using the indicated solvent mixture as eluent to afford the title compound.

2.5.5B Preparation of Substrates in Carboxylation Scope Table

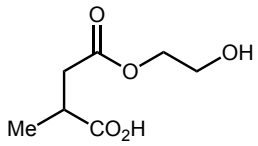


4(benzyloxy)-2-methyl-4-oxobutanoic acid (8): Prepared according to general procedure A using benzyl (*E)*-but-2-enoate (1 mmol, 0.176 g, 1 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (50% EtOAc/hexanes + 1% AcOH as the eluent) to afford the title compound as a yellow oil (0.216 g, 97% yield).

^{1}H NMR (600 MHz, CDCl3): δ 7.39-2.28 (m, 5H), 5.12 (s, 2H), 3.04-2.93 (m, 1H), 2.80 (dd, J = 16.8, 8.1 Hz, 1H), 2.49 (dd, J = 16.8, 5.9 Hz, 1H), 1.27 (d, J = 7.3 Hz, 3H).

^{13}C NMR (600 MHz, CDCl3): δ 180.7, 171.5, 134.9, 128.6, 128.3, 128.2, 66.6, 37.3, 35.6, 16.3**.**

GCMS: m/z: $[M]^+$ calcd. for $C_{12}H_{14}O_4$, 222.1; found 222.0.

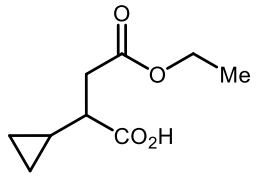


4-(2-hydroxyethoxy)-2-methyl-4-oxobutanoic acid (9): Prepared according to general procedure A using 2-hydroxyethyl (*E)*-but-2-enoate (1.00 mmol, 0.130 g, 1.0 equiv), sodium formate (5.00 mmol, 0.34 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.010 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (50% EtOAc/hexanes + 1% AcOH as the eluent) to afford the title compound as a yellow oil (0.119 g, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.25-4.20 (m, 2H), 3.82 (t, J = 4.8 Hz, 1H), 3.01-2.94 (m, 1H), 2.74 (dd, J = 16.6, 7.5 Hz, 1H), 2.52 (dd, J = 16.5, 5.2 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H).

^{13}C NMR (600 MHz, $CDCl_3$): δ 180.2, 171.9, 66.1, 60.9, 37.6, 35.7, 16.8.

FTMS (ESI) *m/z*: [M-H] calcd. for $C_7H_{11}O_5$, 175.07; found, 175.06.



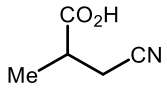
2-cyclopropyl-4-ethoxy-4-oxobutanoic acid (10): Prepared according to general procedure A using ethyl (*E*)-3-cyclopropylacrylate **S16** (1.00 mmol, 0.140 g, 1.0 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 0.1 M 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (10-70% EtOAc/Hexanes + 1% AcOH as eluent) to afford the title compound as a yellow oil (0.122 g, 66% yield).

Rf: 0.52 (50% EtOAc/Hexanes)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.24 – 3.95 (m, 2H), 2.82 (dd, *J* = 16.1, 10.2 Hz, 1H), 2.59 (dd, *J* = 16.1, 5.5 Hz, 1H), 2.06 (td, *J* = 9.7, 4.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.97 – 0.80 (m, 1H), 0.63 – 0.52 (m, 2H), 0.52 – 0.43 (m, 1H), 0.25 – 0.16 (m, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 180.30, 171.96, 60.88, 46.27, 36.53, 14.23, 13.59, 4.44.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_9H_{15}O_4$, 187.0965; found, 187.0968.



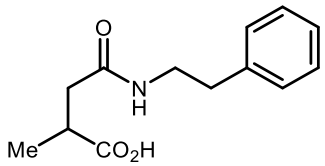
3-cyano-2-methylpropanoic acid (11): Prepared according to general procedure A using crotonitrile (1.00 mmol, 0.076 g, 1.0 equiv), sodium formate (5.00 mmol, 0.34 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 0.1 M 20% H_2O/ DMSO (10 mL). After 16 hours the crude reaction mixture was diluted with EtOAc and washed with saturated aqueous potassium carbonate. The organic phase was collected in a flask and the aqueous phase was acidified with concentrated HCl to pH 1-2. The aqueous phase was then extracted with EtOAc (3x) and the combined organic extracts were pushed through a silica plug (100% EtOAc as eluent) and concentrated *in vacuo* to afford the title compound as a yellow oil (0.071 g, 63% yield).

Rf: 0.35 (50% EtOAc/Hexanes)

^{1}H NMR (600 MHz, Chloroform-*d*): δ 2.94-2.84 (m, 1H), 2.70 (dd, J = 16.7, 5.91 H, 1H), 2.57 (dd, J = 16.8, 7.4 Hz, 1H), 1.43 (d, J = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.31, 117.59, 77.37, 77.16, 76.95, 36.09, 20.93, 16.60.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_5H_8NO_2$, 114.0550; found, 114.0553.



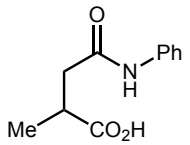
2-methyl-4-oxo-4-(phenethylamino)butanoic acid (12): Prepared according to general procedure A using (*E*)-N-phenethylbut-2-enamide **S4** (1.0 mmol, 0.189 g, 1.0 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (10- 100% EtOAc/Hexanes + 1% AcOH as eluent) to afford the title compound as a white solid (0.162 g, 69% yield).

Rf: 0.14 (85% EtOAc/Hexanes)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (m, 2H), 7.23 (m, 3H), 5.72 (br s, 1H), 3.64 – 3.47 (m, 2H), 3.01 – 2.87 (m, 1H), 2.83 (t, *J* = 6.9 Hz, 2H), 2.54 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.30 (dd, *J* = 15.5, 4.3 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 176.72, 170.30, 139.48, 128.61, 128.27, 126.02, 40.15, 38.66, 35.45, 35.17, 16.65.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{18}NO_3$, 236.1281; found, 236.1285.

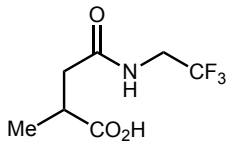


2-methyl-4-oxo-4-(phenylamino)butanoic acid (13): Prepared according to general procedure A using (E)-N-phenylbut-2-enamide **S5** (1.00 mmol, 0.161 g, 1.0 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL).

After 16 hours the crude reaction mixture was diluted with EtOAc and washed with saturated aqueous potassium carbonate. The organic phase was collected in a flask and the aqueous phase was acidified with concentrated HCl to pH 1-2. The aqueous phase was then extracted with EtOAc (3 x 20 mL) and the combined organic extracts were pushed through a silica plug with EtOAc and concentrated *in vacuo* to afford the title compound as a white solid (0.106 g, 51% yield). **^{1}H NMR (600 MHz, DMSO-d$_6$)**: δ 9.93 (s, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 7.8 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 2.84-2.74 (m, 1H), 2.65 (dd, J = 15.4, 7.8 Hz, 1H), 2.39 (dd, J = 15.4, 6.5 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H).

^{13}C NMR (600 MHz, CDCl$_3$): δ 177.1, 168.8, 139.7, 129.1, 124.1, 119.4, 35.8, 16.0.

LCMS: m/z: $[M+H]^+$ calcd. for $C_{11}H_{13}NO_3$, 208.1; found 208.2.



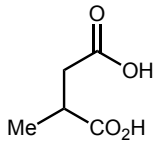
2-methyl-4-oxo-4-((2,2,2-trifluoroethyl)amino)butanoic acid (14): Prepared according to general procedure A using (E)-N-(2,2,2-trifluoroethyl)but-2-enamide **S6** (1.00 mmol, 0.167 g, 1.0 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude reaction mixture was diluted with EtOAc and washed with saturated aqueous potassium carbonate. The organic phase was collected in a flask and the aqueous phase was acidified with concentrated HCl to pH 1-2. The aqueous phase was then extracted with EtOAc (3 x 20 mL) and the combined organic extracts were pushed through a silica plug with EtOAc and concentrated *in vacuo* to afford the title compound as a white solid (0.101 g, 47% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.90-3.71 (m, 2H), 2.85-2.77 (m, 1H), 2.56 (dd, J = 14.9, 7.6 Hz 1H), 2.26 (dd, J = 14.9, 7.9 Hz, 1H), 1.12 (d, J = 7.2 Hz, 3H).

^{13}C NMR (600 MHz, $CDCl_3$): δ 179.0, 173.1, 124.6, 39.7, 38.5, 35.8, 14.1.

^{19}F NMR (400 MHz, $CDCl_3$): -74.01 (t, J = 9.4 Hz, 3F).

LCMS: m/z: $[M+H]^+$ calcd. for $C_7H_{11}F_3NO_3$, 214.1; found 214.2.



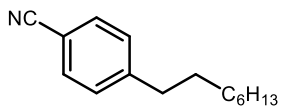
2-methylsuccinic acid (15): Prepared according to general procedure A using crotonic acid (1.00 mmol, 0.086 g, 1.0 equiv), sodium formate (5.00 mmol, 0.340 g, 5.0 equiv), formic acid (5.00 mmol, 0.190 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (70% EtOAc/Hexanes + 1% AcOH as eluent) to afford the title compound as a yellow solid (0.101 g, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.86-2.79 (m, 1H), 2.64 (dd, J = 16.8, 8.4 Hz, 1H), 2.39 (dd, J = 16.8, 5.8 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H).

^{13}C NMR (600 MHz, $CDCl_3$): δ 179.3, 176.3, 38.9, 36.6, 17.31.

LCMS: m/z: $[M+H]^+$ calcd. for $C_5H_9O_4$, 133.1; found 133.2.

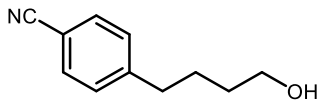
2.5.4C Preparation of Substrates in Reduction Scope Table



4-octylbenzonitrile (16): Prepared according to general procedure B using 4-chlorobenzonitrile (0.500 mmol, 0.069 g, 1 equiv.), 1-octene (2.50 mmol, 390 µL, 5.0 equiv), sodium formate (2.50

mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (5% EtOAC/Hexanes as the eluent) to afford the title compound as a clear oil (0.071 g, 66% yield). The physical and spectral properties were consistent with the reported values.[19]

^{1}H NMR (500 MHz, Chloroform-d) δ 7.55 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.60 (m, 2H), 1.35-1.16 (m, 10H), 0.87 (t, J = 6.8 Hz , 3H).



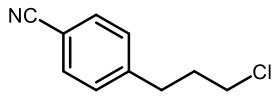
4-(4-hydroxybutyl)benzonitrile (17): Prepared according to general procedure B using 4-chlorobenzonitrile (0.500 mmol, 0.069 g, 1.0 equiv.), 3-buten-1-ol (2.50 mmol, 215 µl, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (30% EtOAc/Hexanes to 50% EtOAc:/Hexanes as the eluent) to afford the title compound as a colorless solid (0.040 g, 46% yield).

Rf: 0.23 (30% EtOAc/Hexanes)

^{1}H NMR (500 MHz, Benzene-*d6*) δ 7.01 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8. Hz, 2H), 3.22 (t, J = 6.3 Hz, 2H), 2.13 (t, J = 7.6 Hz, 2H), 1.32-1.24 (m, 2H), 1.20-1.13 (m, 2H).

^{13}C NMR (100 MHz, Chloroform-d) δ 148.17, 132.27, 129.31, 119.23, 109.71, 62.57, 35.88, 32.18, 27.23.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{11}H_{14}NO$, 176.1069; found, 176.1071.



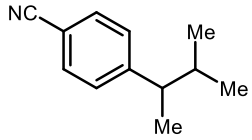
4-(6-chlorohexyl)benzonitrile (18): Prepared according to general procedure B using 4-chlorobenzonitrile (0.500 mmol, 0.069 g, 1.0 equiv), 6-chlorohex-1-ene (2.50 mmol, 0.33 mL, 5.0 equiv), sodium formate (2.50 mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (0%- 20% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (0.094 g, 85% yield).

Rf: 0.40 (10% EtOAc/ Hexanes)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 6.9 Hz, 2H), 3.53 (t, J = 6.6 Hz, 2H), 2.71 – 2.58 (m, 2H), 1.82 – 1.70 (m, 2H), 1.64 (p, J = 7.6 Hz, 2H), 1.54 – 1.41 (m, 2H), 1.40 – 1.31 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-d) δ 148.35, 132.44, 132.29, 129.31, 119.29, 109.73, 45.14, 36.07, 32.55, 30.89, 28.51, 26.74.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{17}NCl$, 222.1044; found, 222.1043.



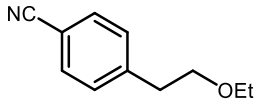
4-(3-methylbutan-2-yl)benzonitrile (19): Prepared according to general procedure B using 4-chlorobenzonitrile (0.500 mmol, 0.069 g, 1.0 equiv), 2-methyl-2-butene (2.50 mmol, 265 µl, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (5% EtOAc/Hexanes as the eluent) to afford the title compound as a light yellow oil (0.057 g, 66% yield).

R_f: 0.66 (5% EtOAc/Hexanes)

^{1}H NMR (500 MHz, Benzene-*d6*) δ 7.01 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 1.99 (q, J = 7.2 Hz, 1H), 1.43-1.31 (m, 1H), 0.88 (d, J = 7.1 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H), 0.53 (d, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-d) δ 152.95, 132.11, 128.56, 119.35, 109.69, 47.24, 34.41, 36.62, 21.17, 20.16, 18.60.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{12}H_{16}N$, 174.1277; found, 174.1277.



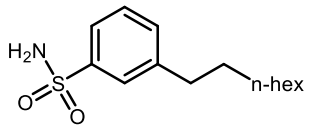
4-(2-ethoxyethyl)benzonitrile (20): Prepared according to general procedure B using 4-chloro-benzontrile (0.500 mmol, 0.07 g, 1.0 equiv), ethyl vinyl ether (2.50 mmol, 0.24 mL, 5.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (0%- 50% EtOAc/hexanes as eluent) to provide the title compound as a clear oil (0.070 g, 81% yield).

R_f: 0.25 (10% EtOc/ Hexanes)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.64 (t, *J* = 6.7 Hz, 2H), 3.48 (q, *J* = 7.0 Hz, 2H), 2.93 (t, *J* = 6.7 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 145.24, 132.25, 129.85, 119.22, 110.23, 70.57, 66.53, 36.62, 15.24.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{11}H_{14}NO$, 176.1069; found, 176.1070.



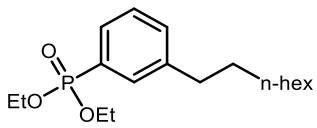
3-octylbenzenesulfonamide (21): Prepared according to general procedure B using 3-bromobenzenesulfonamide (0.500 mmol, 0.118 g, 1.0 equiv), 1-octene (2.50 mmol, 390 µl, 5 equiv), sodium formate (2.50 mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (30-50% EtOAc/Hexanes as the eluent) to afford the title compound as a clear amorphous solid (0.068 g, 51% yield).

Rf: 0.75 (40% EtOAc/Hexanes)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.76-7.72 (m, 2H), 7.44-7.37 (m, 2H), 4.75 (s, 2H), 2.67 (t, J = 7.8 Hz, 2H), 1.66-1.58 (m, 2H), 1.36-1.21 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 144.60, 141.91, 133.03, 129.15, 126.24, 123.80, 35.89, 31.97, 31.34, 29.51, 29.37, 29.33, 22.78, 14.23.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{14}H_{24}NO_3S$, 270.1522; found, 270.1515.



Diethyl (4-octlyphenyl)phosphonate (22): Prepared according to general procedure B using diethyl (3-bromophenyl)phosphonate **S9** (0.500 mmol, 0.147 g, 1 equiv), 1-octene (2.50 mmol, 390 µl, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (15- 50% EtOAc/Hexanes as the eluent) to afford the title compound as a colorless oil (0.060 g, 37% yield).

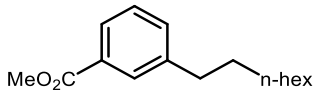
Rf: 0.62 (50% EtOAc/Hexanes)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.65-7.57 (m, 2H), 7.38-7.34 (m, 2H), 4.19-4.02 (m, z2H), 2.64 (t, J = 7.7 Hz, 2H), 1.65-1.58 (m, 2H), 1.35-1.22 (m, 16H), 0.87 (t, J = 12.9 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 143.46 (d, *J* = 14.5 Hz), 132.67 (d, *J* = 3.2 Hz), 131.89 (d, *J* = 10.2 Hz), 129.13 (d, *J* = 9.8 Hz), 128.51 (d, *J* = 15.6 Hz), 128.21 (d, *J* = 186.5 Hz), 62.16 (d, *J* = 5.4 Hz), 35.92, 31.98, 31.46, 29.53, 29.39, 29.36, 22.78, 16.46 (d, *J* = 6.5 Hz), 14.21.

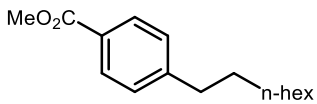
^{31}P NMR (243 MHz, Chloroform-d) δ 19.42

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{18}H_{32}O_3P$, 327.2084; found, 327.2078.



Methyl 3-octylbenzoate (23): Prepared according to general procedure B using methyl 3-chlorobenzoate (0.500 mmol, 70 µL, 1.0 equiv), 1-octene (2.5 mmol, 390 µL, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was pushed through a silica plug using EtOAc, concentrated *in vacuo*, and left under vacuum overnight to afford the title compound as a colorless oil (0.086 g, 69% yield). The physical and spectral properties were consistent with the reported values.[20]

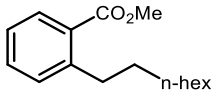
^{1}H NMR (500 MHz, Chloroform-d) δ 7.88-7.82 (m, 2H), 7.39-7.31 (m, 2H), 3.91 (s, 3H), 2.65 (t, J = 7.9 Hz 2H), 1.61 (m, 2H), 1.36-1.21 (m, 10H), 0.88 (t, J = 6.9 Hz , 3H).



Methyl-4-octylbenzoate (24): Prepared according to general procedure B using methyl 4-chlorobenzoate (0.500 mmol, 0.085 g, 1.0 equiv), 1-octene (2.50 mmol, 390 µL, 5.0 equiv), sodium

formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was pushed through a silica plug using EtOAc, concentrated *in vacuo*, and left under vacuum overnight to afford the title compound as a light yellow oil (0.093 g, 75% yield). The physical and spectral properties were consistent with the reported values.[21]

^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 3.90 (s, 3H), 2.65 (t, J = 7.8 Hz 2H), 1.64-1.59 (m, 2H), 1.32-1.22 (m, 10H), 0.89 (t, J = 7.0 Hz , 3H).



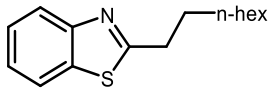
Methyl-2-octylbenzoate (25): Prepared according to general procedure B using methyl 2-chlorobenzoate (0.500 mmol, 72 μL , 1 equiv), 1-octene (2.50 mmol, 390 μL, 5 equiv), sodium formate (2.5 mmol, 0.170 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (5% EtOAc/Hexanes as the eluent) to afford the title compound as a colorless oil (0.040 g, 32% yield).

Rf: 0.59 (5% EtOAc/Hexanes).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.84 (dd, J = 7.8, 1.5 Hz, 2H), 7.41 (td, J = 7.5, 1.3 Hz, 2H), 3.89 (s, 3H), 2.93 (t, J = 7.8 Hz, 2H), 1.62-1.54 (m, 2H), 1.36-1.21 (m, 10H), 0.87 (t, J = 7.04 Hz, 3H).

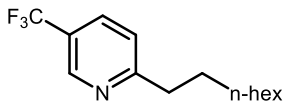
^{13}C NMR (151 MHz, Chloroform-d) δ 168.41, 144.87, 131.91, 131.03, 130.66, 129.66, 125.77, 52.00, 34.61, 32.04, 31.98, 29.91, 29.63, 29.43, 22.82, 14.25.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{16}H_{25}O_2$, 249.1849; found, 249.1851.



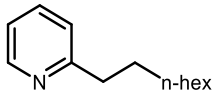
2-octylbenzo[*d*]thioazole (26): Prepared according to general procedure B at 100 °C using 2-bromobenzothiazole (0.500 mmol, 0.107 g, 1.0 equiv),1-octene (2.50 mmol, 390 µL, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (5% EtOAc/Hexanes as the eluent) to afford the title compound as a yellow oil (0.099 g, 80% yield). The physical and spectral properties were consistent with the reported values.[22]

^{1}H NMR (500 MHz, Chloroform-d) δ 7.97 (dd, J = 8.2, 1.2 Hz, 1H), 7.83 (d, J = 8.0, 1.3 Hz, 1H), 7.44 (dt, J = 8.3, 1.3 Hz 1H), 7.33 (dt, J = 7.4, 1.2 Hz 1H), 3.11 (t, J = 7.4 Hz, 2H), 1.46-1.24 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H).



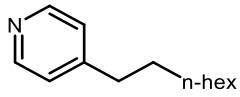
2-octyl-5-(trifluoromethyl)pyridine (27): Prepared according to general procedure B using 2-chloro-5-(trifluoromethyl)pyridine (0.500 mmol, 0.091 g, 1.0 equiv), 1-octene (2.50 mmol, 0.39 mL, 5.0 equiv), sodium formate (2.50 mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 0.1 M 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (0%- 50% EtOAc/hexanes as eluent) to provide the title compound as a clear oil (0.09 g, 70% yield). The spectral properties were consistent with the reported values.[23]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 2.92 – 2.78 (m, 2H), 1.76 (p, *J* = 7.8 Hz, 2H), 1.41 – 1.18 (m, 10H), 0.96 – 0.84 (m, 3H).



2-octylpyridine (28): Prepared according to general procedure B using 2-chloro-pyridine (0.250 mmol, 24 µL, 1.0 equiv), 1-octene (1.25 mmol, 0.20 mL, 5.0 equiv), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), formic acid (1.25 mmol, 47 µL, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in 50% MeCN/ DMSO (2.5 mL). After 16 hours the reaction was purified quenched with $NaHCO_3$ and extracted with EtOAc (3x). It was purifed by silica chromatography (0%- 50% EtOAc/hexanes as eluent) to provide the title compound as a pale yellow oil (0.020 g, 43% yield). The spectral properties were consistent with the reported values.[24]

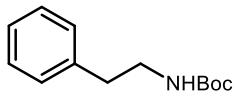
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.70 – 8.26 (m, 1H), 7.58 (td, *J* = 7.6, 1.9 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.09 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 2.81 – 2.75 (m, 2H), 1.76 – 1.68 (m, 2H), 1.41 – 1.19 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H).



4-octylpyridine (29): Prepared according to general procedure B using 4-chloropyridin-1-ium chloride (0.500 mmol, 0.075 g, 1.0 equiv), 1-octene (2.50 mmol, 0.39 mL, 5.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was

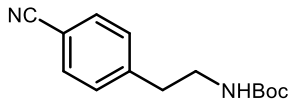
purified quenched with $NaHCO_3$ and extracted with EtOAc (3x). It was purifed by silica chromatography (10- 50% EtOAc/hexanes as eluent) to provide the title compound as a yellow oil (0.056 g, 70% yield). The spectral properties were consistent with the reported values.[25]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.48 (d, *J* = 5.2 Hz, 2H), 7.10 (d, *J* = 4.4 Hz, 2H), 2.63 – 2.56 (m, 2H), 1.62 (p, *J* = 7.3 Hz, 2H), 1.48 – 1.12 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H).



***Tert*-butyl phenethylcarbamate (30)**: Prepared according to general procedure B using bromobenzene (0.500 mmol, 53 μL, 1.0 equiv), *tert*-butyl vinylcarbamate **S8** (1.50 mmol, 0.214 g, 3.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (10- 15% EtOAc/Hexanes as the eluent) to afford the title compound as a white solid (0.082 g, 74% yield). The spectral properties were consistent with the reported values.[26]

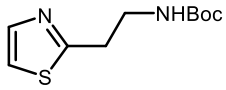
^{1}H NMR (500 MHz, Chloroform-d) δ 7.32-7.28 (m, J = 8.2, 1.2 Hz, 1H), 7.24-7.17 (m, 3H), 3.42-2.32 (m, 2H), 2.80 (t, J = 7.0 Hz, 2H), 1.43 (s, 9H).



***Tert*-butyl (4-cyanophenethyl)carbamate (31)**: Prepared according to general procedure B using 4-chlorobenzonitrile (0.500 mmol, 0.069 g, 1.0 equiv), *tert*-butyl vinylcarbamate **S8** (1.5 mmol, 0.214 g, 3.0 equiv),), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After

16 hours the reaction was purified by silica chromatography (20-30% EtOAc/Hexanes as the eluent) to afford the title compound as a white solid (0.100 g, 81% yield). The physical and spectral properties were consistent with the reported values.[26]

^{1}H NMR (500 MHz, Chloroform-d): δ 7.59 (d, J = 7.8 Hz 1H), 7.65-7.57 (m, 2H), 7.53 (t, J = 7.6 Hz), 3.65 (t, J = 5.8 Hz, 2H), 2.17 (tt, J = 17.1, 7.6 Hz, 2H), 1.68-1.57 (m, 4H), 1.42 (bs, 1H).



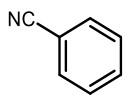
***Tert*-butyl (2-(thiazol-2-yl)ethyl) carbamate (32):** Prepared according to general procedure B using 2-bromothiazole (0.500 mmol, 45 μL, 1.0 equiv.), *tert*-butyl vinylcarbamate **S8** (1.5 mmol, 0.214 g, 1.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 50% MeCN/ DMSO (5 mL). After 16 hours, the crude product was purified by silica gel chromatography (20- 50% EtOAc/Hexanes as the eluent) to afford the title compound as a yellow solid (0.112 g, 98% yield).

Rf: 0.50 (40% EtOAc/Hexanes)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.70 (d, *J* = 3.4 Hz, 1H), 7.23 (d, *J* = 3.3 Hz, 1H), 5.12 (s, 1H), 3.62-3.53 (m, 2H), 3.22 (t, J = 6.4 Hz, 2H), 1.44 (s, 9H).

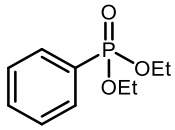
^{13}C NMR (100 MHz, Chloroform-d) δ 168.11, 155.93, 142.56, 118.71, 79.43, 39.92, 33.41, 28.49.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{10}H_{17}N_2O_2$, 229.1005; found, 229.1007.



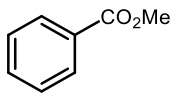
Benzonitrile (33): Prepared according to general procedure C 3-cyano-N,N,N-trimethylbenzenaminium iodide **S11** (0.250 mmol, 0.072 g, 1.0 equiv), sodium formate (1.25

mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in d_6-DMSO (2.5 mL). After 16 hours the reaction was stopped and dibromomethane was added (0.25 mmol, 17.5 µL, 1.0 equiv) as internal standard. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the product yield (86% yield by NMR).



diethyl phenylphosphonate (34): Prepared according to general procedure C 3-(diethoxyphosphoryl)-N,N,N-trimethylbenzenaminium iodide **S13** (0.25 mmol, 0.099 g, 1.0 equiv), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in 20% H_2O/ DMSO (2.5 mL). After 16 hours the reaction was washed with water and extracted with EtOAc (3x) to provide the title compound with no extra purification needed as a tan oil (0.050 g, 94% yield). The spectral properties were consistent with the reported values.[27]

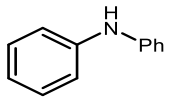
^{1}H NMR (600 MHz, Chloroform-d) δ 7.81 (ddd, J = 13.3, 8.3, 1.4 Hz, 2H), 7.61 – 7.51 (m, 1H), 7.46 (td, J = 7.5, 4.3 Hz, 2H), 4.19 – 4.02 (m, 4H), 1.32 (t, J = 6.8 Hz, 6H).



Methylbenzoate (35): Prepared according to general procedure C using 3-(methoxycarbonyl)-N,N,N-trimethylbenzenaminium iodide **S15** (0.500 mmol, 0.160 g, 1.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in in DMSO (5 mL). After 16 hours the reaction was washed with

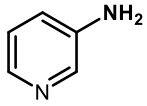
water and extracted with EtOAc (3x) to provide the title compound with no extra purification needed as a yellow oil (0.047 g, 70% yield). The spectral properties were consistent with the reported values.[28]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.42 (m, 2H), 3.92 (s, 3H).



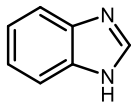
diphenyl amine (36): Prepared according to general procedure D at 100 °C 4-methyl-N,N-diphenylbenzenesulfonamide **S16** (0.500 mmol, 0.162 g, 1.0 equiv), sodium formate (5.00 mmol, 0.34 g, 10.0 equiv), mesna (0.100 mmol, 0.0164 g, 20 mol%) and 4CzIPN (0.0039 mmol, 0.0039 g, 1 mol%) in 0.1 M 20% H_2O/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (30- 100% EtOAc/hexanes as the eluent) to provide the title compound as an off white solid (0.044 g, 52% yield). The spectral properties were consistent with the reported values.[29]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.3 Hz, 4H), 7.08 (d, *J* = 7.4 Hz, 4H), 6.93 (t, *J* = 7.4 Hz, 2H), 5.71 (br s, 1H).



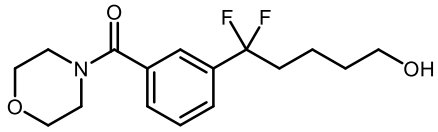
3-aminopyridine (37): Prepared according to general procedure D at 100 °C 4-methyl-*N*-(pyridine-3-yl)benzenesulfonamide **S17** (0.250 mmol, 0.062 g, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 10.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in d_6-DMSO (2.5 mL). After 16 hours the reaction was stopped and dibromomethane was added (0.25 mmol, 17.5 µL, 1.0 equiv) as internal standard. The sample was

analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the product yield (84% yield by NMR).



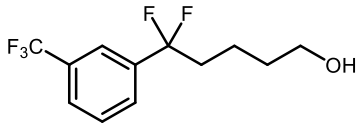
1H-benzo[d]imidazole (38): Prepared according to general procedure D 1-tosyl-1*H*-benzo[*d*]imidazole **S18** (0.250 mmol, 0.068 g, 1.0 equiv), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in 20% H_2O/ DMSO (2.5 mL). After 16 hours the reaction was purified by silica chromatography (30%- 100% EtOAc/hexanes as eluent) to provide the title compound as an off white solid (0.024 g, 81% yield). The spectral properties were consistent with the reported values.[30]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.69 (br s, 2H), 7.31 (dd, *J* = 6.1, 3.0 Hz, 2H).



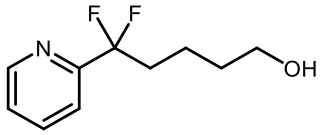
(3-(1,1-difluoro-5-hydroxypentyl)phenyl)(morpholino)methanone (39): Prepared according to general procedure E using morpholino(3-(trifluoromethyl)phenyl)methanone **S20** (0.500 mmol, 0.129 g, 1.0 equiv), 3-buten-1-ol (1.5 mmol, 130 µL, 3.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in in DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (20-30% EtOAc/hexanes as the eluent) to afford the title compound as a clear oil (0.078 g, 56% yield). The physical and spectral properties were consistent with the reported values.[17]

^{1}H NMR (600 MHz, Chloroform-d): δ 7.55-7.43 (m, 4H), 3.78 (bs, 4H), 3.66-3.54 (m, 4H), 3.42 (bs, 2H), 2.23-2.04 (m, 2H), 1.73 (bs, 1H), 1.61-1.47 (m, 4H).



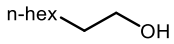
5,5-difluoro-5-(3-(trifluoromethyl)phenyl)pentan-1-ol (40): Prepared according to general procedure E using 1,3-bis(trifluoromethyl)benzene (0.500 mmol, 78 μL, 1.0 equiv), 3-buten-1-ol (1.50 mmol, 130 μL, 3.0 equiv), sodium formate (2.50 mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in in DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (20-40% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (0.073 g, 56% yield). The physical and spectral properties were consistent with the reported values.[17]

^{1}H NMR (600 MHz, Chloroform-d): δ 7.78 (d, J = 7.9 Hz 2H), 7.30 (d, J = 7.9 Hz, 2H), 4.54 (br s, 1H), 3.42-3.33 (m, 2H), 2.89-2.82 (m, 2H), 1.42 (s, 9H).



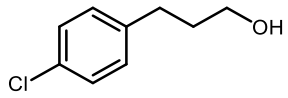
4,4-difluoro-4-(pyridine-2-yl)butan-1-ol (41): Prepared according to general procedure E at 100 ^{o}C using 2-(trifluoromethyl)pyridine (0.500 mmol, 58 μL, 1.0 equiv), 3-buten-1-ol (1.50 mmol, 130 μL, 3.0 equiv), sodium formate (2.50 mmol, 0.17 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in in DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (20-70% EtOAc/hexanes as the eluent) to afford the title compound as a clear oil (0.031 g, 30% yield). The physical and spectral properties were consistent with the reported values.[17]

^{1}H NMR (600 MHz, Chloroform-d): δ 8.66 (d, J 4.8 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 3.66 (t, J = 6.3 Hz, 2H), 2.37 (dp, J = 16.5 Hz, J = 8.0 Hz, 2H), 1.66-1.50 (m, 4H).



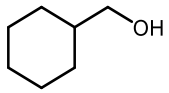
Octanol (42): Prepared according to general procedure F using octanal (0.500 mmol, 78 μL, 1.0 equiv), sodium formate (2.50 mmol, 0.170 g, 5.0 equiv), mesna (0.100 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 20% H_2O/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (5- 30% EtOAc/hexanes as the eluent) to provide the title compound as a yellow oil (0.057 g, 87% yield). The spectral properties were consistent with the reported values.[31]

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.64 (t, *J* = 6.5 Hz, 2H), 1.56 (p, *J* = 6.7 Hz, 2H), 1.39 – 1.22 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H).



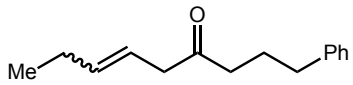
3-(4-chlorophenyl)propanol (43): Prepared according to general procedure F using 3-(4-chlorophenyl)propanal **S19** (0.250 mmol, 0.042 g, 1.0 equiv), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%) and 4CzIPN (0.0025 mmol, 0.0020 g, 1 mol%) in 20% H_2O/ DMSO (2.5 mL). After 16 hours the reaction was purified by silica chromatography (0- 30% EtOAc/hexanes as eluent) to provide the title compound as a pale yellow oil (0.033 g, 80% yield). The spectral properties were consistent with the reported values.[32]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.65 (m, 2H), 1.92 – 1.82 (m, 2H).



Cyclohexylmethanol (44): Prepared according to general procedure F using cyclohexanecarbaldehyde (0.500 mmol, 60 µL, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in 20% H_2O/ DMSO (5 mL). After 16 hours the reaction was purified by silica chromatography (0- 20% EtOAc/hexanes as eluent) to provide the title compound as a pale-yellow oil (0.033 g, 80% yield). The spectral properties were consistent with the reported values.[33]

^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.44 (d, *J* = 6.4 Hz, 2H), 1.86 – 1.60 (m, 5H), 1.52 – 1.42 (m, 1H), 1.31 – 1.12 (m, 4H), 0.99 – 0.88 (m, 2H).



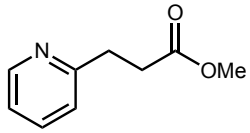
1-phenylnon-6-en-4-one (45): Prepared according to general procedure A using (*E*)-1-cyclopropyl-6-phenylhex-1-en-3-one **S21** (1 mmol, 0.214 g, 1 equiv), sodium formate (5 mmol, 0.34 g, 5.0 equiv), formic acid (5 mmol, 0.19 mL, 5 equiv), mesna (0.2 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was purified by silica chromatography (5- 20% EtOAc/hexanes as the eluent) to afford the title compound as a mixture of E/Z isomers as a clear oil (0.168 g, 77% yield).

Rf: 0.60 (10% EtOAc/hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.28 (t, J = 7.4 Hz, 2H), 7.21-7.15 (m, 3H), 5.61—5.53 (m, 1H), 5.51-5.46 (m, 1H), 3.14-3.12 (d, J = 7.1 Hz, 0.37 H, Z isomer), 3.07 (d, J = 6.7 Hz, 1.70 H, E isomer), 2.61 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.1 Hz, 2H), 2.08-1.99 (m, 2H), 1.94-1.87 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 209.50, 208.89, 141.78, 136.84, 135.46, 128.61, 128.51, 126.07, 121.01, 120.38, 46.97, 41.78, 41.53, 41.38, 35.20, 25.75, 25.33, 25.26, 20.95, 14.06, 13.66.

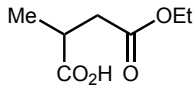
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{21}O$, 217.1587; found, 217.1590.



Methyl 3-(pyridin-2-yl)propanoate (46): Prepared according to general procedure A using methyl (*E*)-3-(pyridine-2-yl)acrylate **S22** (1.00 mmol, 0.163 g, 1.0 equiv), sodium formate (5.00 mmol, 0.34 g, 5.0 equiv), formic acid (5.00 mmol, 0.19 mL, 5.0 equiv), mesna (0.200 mmol, 0.032 g, 20 mol%) and 4CzIPN (0.01 mmol, 0.0078 g, 1 mol%) in 20% H_2O/ DMSO (10 mL). After 16 hours the crude product was by silica chromatography (30- 50% EtOAc/hexanes as the eluent) to afford the title compound as a colorless oil (0.157 g, 95% yield). The physical and spectral properties are consistent with the reported values.[34]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (d, J = 3.2 Hz, 1H), 7.59 (td, J = 7.7, 2.0 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.14-7.07 (m, 1H), 3.66 (s, 3H), 3.11 (t, J = 7.5 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H).

2.5.6 Initial Discovery of Carboxylation of Michael Acceptors



4-ethoxy-2-methyl-4-oxobutanoic acid (6): An 8 mL screw-top test tube was charged with miyake's catalyst (0.002 mmol, 1.2 mg, 1 mol%) and cesium formate (2.00 mmol, 0.356 g, 10 equiv). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO (2 mL) was added via syringe followed by ethyl

crotonate (0.200 mmol, 25.0 μL, 1.0 equiv), formic acid (2.00 mmol, 7.50 μL, 10 equiv), and cyclohexane thiol (0.020 mmol, 2.40 μL, 10 mol%). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by a kessil 390s lamp. Brine was added, and reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. Deutro-chloroform with an internal standard of dibromomethane (14 μL, 0.200 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the yield (30% by NMR). The spectral properties were consistent with the reported values.[35]

2.5.7 Investigation into other Formyl C–H Reagents

2.5.7 A Procedure

An 8 mL screw-top test tube was charged with benzyl (*E*)-but-2-enoate **S1** (1.0 equiv, 0.1 mmol), 4CzIPN (1 mol%, 0.001 mol), formyl reagent (5.0 equiv, 0.5 mmol), and mesna (20 mol%, 0.02 mol). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed solvent (1 mL) was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by a kessil 390s lamp. Saturated aqueous potassium carbonate was added, and reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 μL, 0.1 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data given in Table 2.2.

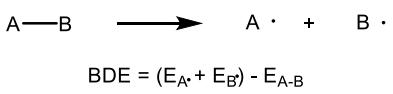
2.5.7 B Calculated Bond Dissociation Energies (BDEs)

General

All DFT calculations were carried out using the Gaussian 9 software package[36] at the (U)B3LYP[37] or R(B3LYP)[37] level of theory with the 6-311+G(d,p)[38] basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in DMSO, and the default parameters as implemented in Gaussian were used.

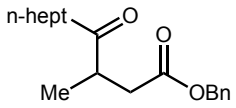
BDEs

Calculations were carried out at the (U)B3LYP[36] level of theory with the 6-311+G(d,p)[38] basis set Bond dissociation energies (BDEs) were calculated according to the following equation:



The calculated BDEs are found in Table 2.2

2.5.7 C Acyl Radical Addition into Michael Acceptor



benzyl 3-methyl-4-oxoundecanoate: A 20 mL screw-top test tube was charged with 4CzIPN (0.01 mol, 7.88 mg, 1 mol%) and mesna (0.200 mmol, 32.8 mg, 20 mol%). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed 20% H_2O/DMSO (10 mL) was added via syringe followed by benzyl (*E*)- but-2-enoate **S1** (1.00 mmol, 0.170 mL, 1.0 equiv l) and octanal (10.0 mmol, 1.50 mL, 10.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by a kessil 390s lamp. Brine was added, and reaction was then extracted with ethyl acetate (3 x), dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was purified by silica chromatography (0-6% EtOAc/hexanes as the eluent) to give the desired product as a yellow oil (174 mg, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.24 – 4.84 (dd, J= 12.51, 18.51 Hz, 2H), 3.01 (dqd, *J* = 8.9, 7.2, 5.2 Hz, 1H), 2.84 (dd, *J* = 16.7, 8.9 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.34 (dd, *J* = 16.8, 5.2 Hz, 1H), 1.61 – 1.49 (m, 2H), 1.35 – 1.18 (m, 8H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.93 – 0.83 (t, J=6.80 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.12, 172.33, 135.95, 128.70, 128.39, 128.36, 66.54, 42.13, 41.37, 37.11, 31.84, 29.34, 29.25, 23.70, 22.76, 16.93, 14.23.

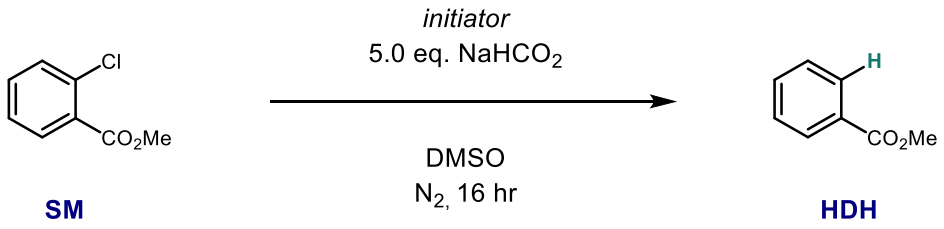
FTMS (ESI) *m/z*: [M+H] calcd. for $C_{19}H_{29}O_3$, 305.20; found, 305.21.

2.5.8 Alterative Initiators

Procedure

An 8 mL screw-top test tube was charged with appropriate initiator (20 mol%, 0.02 mol), sodium formate (5.0 equiv, 0.5 mmol) and mesna (20 mol%, 0.02 mol, *if needed- refer to table below*). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separately degassed DMSO (0.1 M, 1 mL) was added via syringe, followed by 2-chloromethylbenzoate (1 equiv, 0.1 mmol). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs or heated to 100 °C (*refer to table below*). The reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc to remove any excess DMSO and concentrated. Deutro-chloroform with an internal standard of dibromomethane (7 µL, 0.1 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data given in Table S4.

Initiators:



Entry	initiator	SM	HDH
1	20 mol% methyl disulfide, blue LEDs	0	99
2	20 mol% ammonium persulfate, 20 mol% mesna, 100 °C	0	96
3	20 mol% AIBN, 20 mol% mesna, 100 °C	50	48

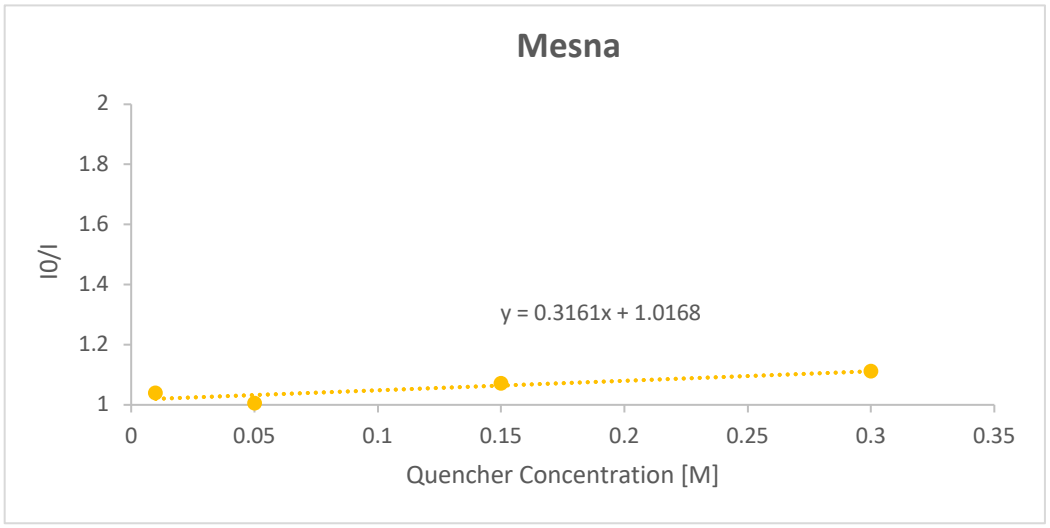
yields determined by ^{1}H NMR with dibromomethane as internal standard

Table S2.4: Alternative Initiators.

2.5.9 Fluorescence Quenching Experiments

Fluorescence spectra is measured on a Horiba Fluoromax_Plus C. The sample is placed in a 1 cm pathlength cell. Quenching studies were conducted in DMSO with a photocatalyst (4CzIPN) concentration of 70 μM with varying concentrations of quenchers (*refer to Table S5*). All samples were prepared and stored under a nitrogen atmosphere. The sample is placed in a 1 cm pathlength cell. The sample is excited at 435 nm and the PL spectra is detected with 1 nm resolution at a 90 degree angle. Data is analyzed by Igor Pro and the points were fitted with a linear trend.

(A)



(B)

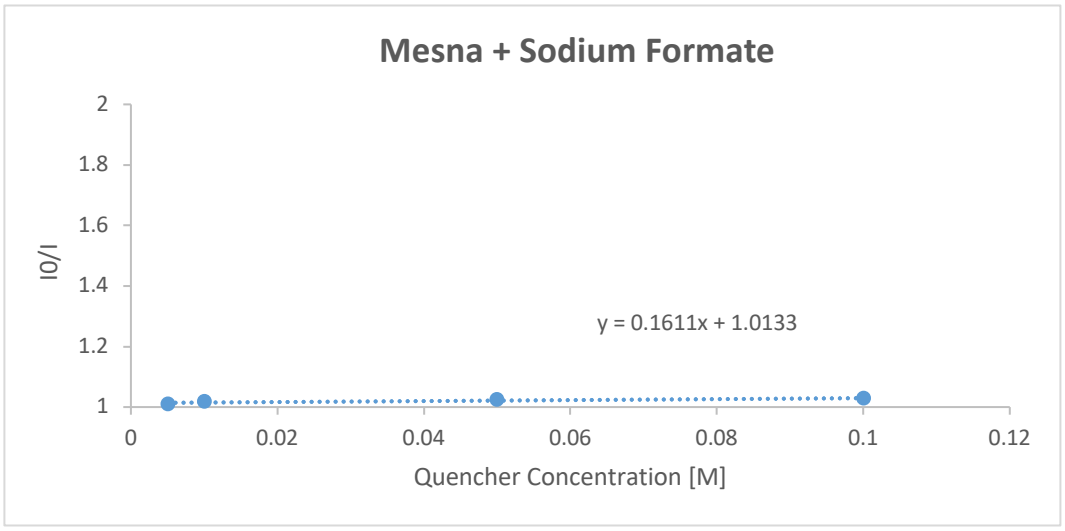


Figure S2.1: Stern-Volmer plots (a) with mesna (b) with mesna and sodium formate

2.5.10 Transient Absorption Spectroscopy

Methods

Transient spectroscopy is performed on Ultrafast Systems Helios and EOS system. The laser system is based on a Coherent Legend regenerative amplifier system, with 150 fs pulse width, 1 kHz repetition rate, and 2 mJ pulse energy. For the measurement within 1 ns, the fundamental 800 nm light is split to generate the 400 nm excitation light via a BBO crystal (pump) and a broadband whitelight extended into UV region by focusing on a rotating CaF_2 window (probe). The pump

and probe are focused on the sample cell (1 mm) and the probe light is collected via a fiber. For longer delay time the whitelight is generated by a supercontinuum laser. The detection scheme is similar. The data is analyzed by Surface Xplorer and Igor Pro.

Analysis

Transient spectroscopy is employed to investigate the single electron transfer (SET) from the photosensitizer to the thiol at the initialization of the reaction. First, we studied the photosensitizer by exciting at 400 nm, at the ground state absorption. The transient absorption spectrum shows an intersystem crossing process of PS from singlet to triplet excited state at delay time ranging from 10 ns to 10 μs as shown in Figure S2.3a, 1b, and 1c. The singlet and triplet excited state shows similar ground state bleach (GSB, ~390-400 nm) and broad excited state absorption (ESA, ~450-900 nm) position, but different amplitude. The SET is observed by comparing the kinetics at one of the ESA signal at 473 nm, where the triplet state of PS decays faster with more thiol added as shown in Figure S2.2c. The SET occurs on a relatively slow time scale where the singlet state decay away as both systems show no difference within 1 ns as shown in Figure S2.3. Since the excited PS concentration is significant lower (more than 1000 times) than the thiol concentration, the bimolecular reaction rate can be simplified to a pseudo-first order reaction.

Fitting functions and quantum yield calculation

The singlet and triplet lifetime of photosensitizer can be fitted with a bi-exponential function to the kinetics shown in Figure 1c:

$$\Delta A = \Delta A_0(a_1 e^{k_1 t} + a_2 e^{k_2 t})$$

where k_1 and k_2 are the decay rate of the singlet and triplet state. From the fitting shown in Figure S2.3c, k_1=13.8±0.1 ns^{-1}, k_2=1.80±0.06 μs^{-1}.

With the thiol in the system, since the SET occurs in the triplet state, the additional decay rate k leads to faster reaction, which is:

$$\Delta A = \Delta A_0(a_1 e^{k_1 t} + a_2 e^{(k_2+k)t})$$

Fitting result at different concentrations in Figure 1c gives the k value at different concentration and the pseudo-first order reaction rate k_0 can be obtained by:

$$k_0 = k[thiol] = 0.402\ \mu s^{-1} M^{-1}$$

Although the absolute quantum yield of triplet state of the photosensitizer cannot be determined by the transient study, we can estimate the upper limit of the quantum yield of the SET from triplet state by assuming a unity intersystem crossing efficiency.

The upper limit of SET quantum yield in real experimental condition (0.01M thiol) can be calculated by:

$$QY_{SET} = \frac{k_{ET}[thiol]}{k_{ET}[thiol] + k_{triplet}} = \frac{0.402 * 0.01}{0.402 * 0.01 + 1/1.80} = 0.72\%$$

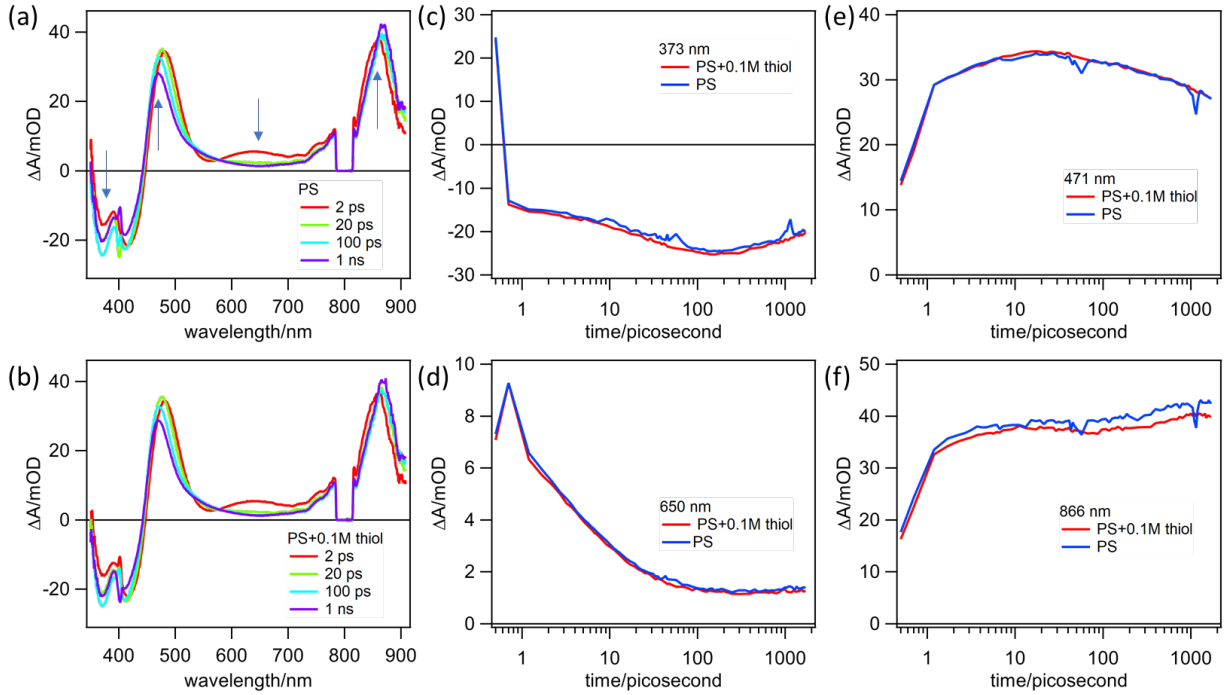


Figure S2.2: TAS of photosensitizer and with 0.1M thiol within 1 ns time window**.** (a)-(b) TA spectra of PS and PS+0.1M thiol. (c)-(f) Kinetics comparison at various indicated wavelength. The spectra and kinetics show no difference at this time range.

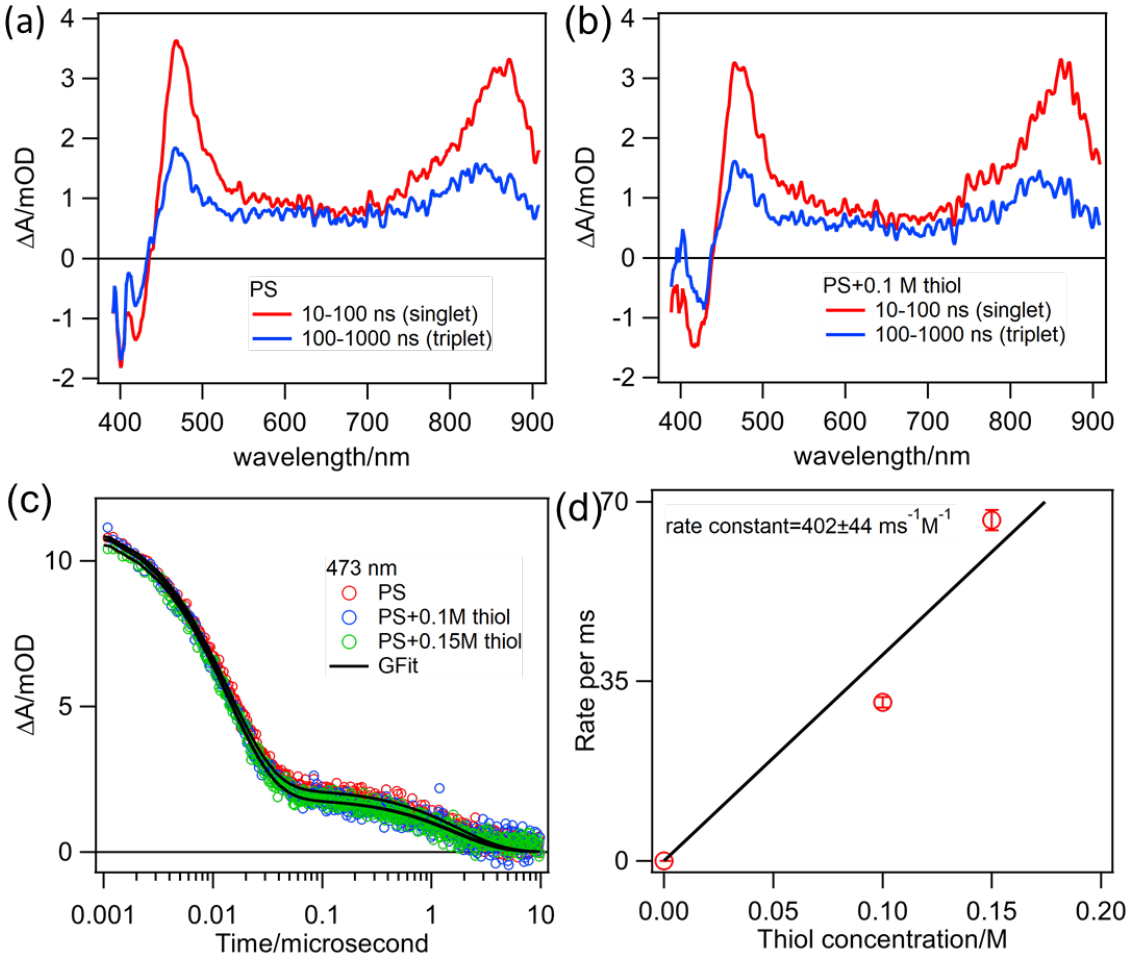


Figure S2.3: Transient absorption spectroscopy (TAS) of the photosensitizer with thiol. (a) TA spectra of photosensitizer and (b) photosensitizer with 0.1M thiol after 400 nm excitation with delay time at 10-100 ns and 100-1000 ns, which corresponds to the singlet and triplet excited state, respectively. (c) Kinetics probed at 473 ns of photosensitizer, photosensitizer with 0.1M and 0.15M thiol. The higher concentration of thiol leads to faster decay of triplet state. (d) The thiol induced quenching rate of the triplet state is plotted against the thiol concentration, the fitting gives the pseudo-first order rate constant of thiol quenching to be 402 $ms^{-1}M^{-1}$.

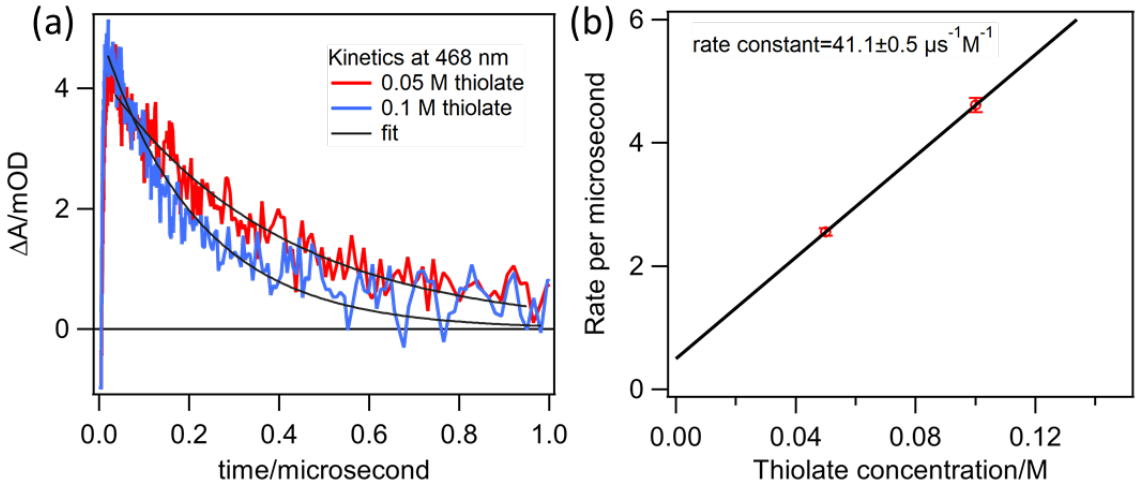


Figure S2.4: TAS of the photosensitizer with thiolate (a) Quenching kinetics of thiolate with photosensitizer at 0.05M and 0.1M concentration. (b) Pseudo-first order rate constant of thiolate.

2.5.11 Quantum Yield Experiment

Quantum Yield Experiments were performed according to the procedure of Yoon.[39]

Determination of the light intensity at 436 nm:

The photon flux of the spectrophotometer was determined by standard ferrioxalate actinometry.[40] A 0.15 M solution of ferrioxalate was prepared by dissolving 2.21 g of potassium ferrioxalate hydrate in 30 mL of 0.05 M H_2SO_4. A buffered solution of phenanthroline was prepared by dissolving 50 mg of phenanthroline and 11.25 g of sodium acetate in 50 mL of 0.5 M H_2SO4. Both solutions were covered in foil and stored in the dark. To determine the photon flux of our lamp source, 2.0 mL of the ferrioxalate solution was placed in an 8 mL screw-top test tube and irradiated for 10.0s with a blue LED lamp (λ= 435 nm, LED wholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue) at a distance of exactly 7.0 cm. After irradiation, 0.35 mL of the phenanthroline solution was added to the test tube. The solution was then allowed to rest for 1 h in the dark to allow the ferrous ions to completely coordinate to the phenanthroline. The absorbance of the solution was measured at 510 nm. Conversion was calculated using eq. 1.

$$(1)\ \text{mol } Fe^{2+} = \frac{V \bullet \Delta A}{l \bullet \varepsilon}$$

Where V is the total volume (0.00235 L) of the solution after addition of phenanthroline, ΔA is the difference in absorbance at 510 nm between the irradiated and non-irradiated solutions, l is the path length (1.000 cm), and ε is the molar absorptivity at 510 nm (11,100 L mol^{-1} cm^{-1}).[40] The photon flux can be calculated using eq 2.

$$(2)\ \text{Photon flux} = \frac{\text{mol Fe2+}}{\Phi \bullet t \bullet f}$$

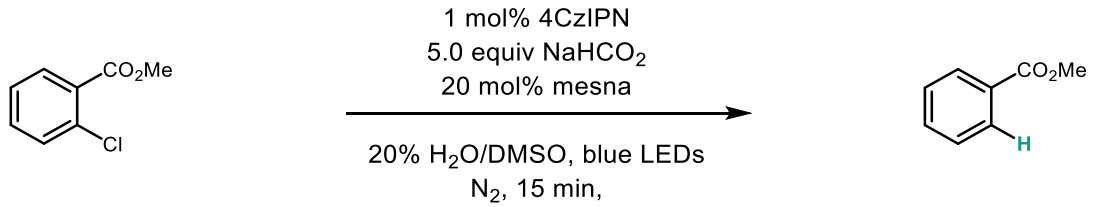
Where Φ is the quantum yield for the ferrioxalate actinometer (1.01 for a 0.15 M solution at λ = 436 nm)[40], t is the time (10.0 s), and f is the fraction of light absorbed at λ = 436 nm (0.99833, vide infra). The photon flux was calculated (average of three experiments) to be 4.02 × 10^{-8} einstein s^{-1}.

Sample Calculation:

$$\text{Mol } Fe^{2+} = \frac{0.0235\ L \bullet 1.91328}{1.00\ cm \bullet 11{,}100\ L\ mol^{-1}cm^{-1}} = 4.05 \times 10^{-7}\ \text{mol}$$

$$\text{Photon flux} = \frac{4.05 \times 10^{-7}\ \text{mol}}{1.01 \bullet 10\ \text{s} \bullet 0.99833} = 4.02 \times 10^{-8}\ \text{einsteins s}^{-}$$

Determination of quantum yield



An 8 mL screw-top test tube was charged with 4CzIPN (0.002, 29 μL, 1 mol%), sodium formate (1.0 mmol, 0.068 g, 5.0 equiv) and mesna (0.04, 20 mol%, 0.02 mol). The tube was equipped with

a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO (2 mL) was added via syringe, followed by 2-chloromethylbenzoate (0.2 mmol, 29 µL, 1.0 equiv). The resulting mixture was stirred at 1400 RPM for 15 min. under irradiation by blue LEDs at a distance of exactly 7.0 cm, unless noted otherwise. The reaction was then extracted with ethyl acetate (3 x). The organic layer was passed through a small silica plug with 100% EtOAc and concentrated. Deutro-chloroform with an internal standard of dibromomethane (14 µL, 0.2 mmol) was added. The sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values were used to calculate the data. Essentially all incident light (f > 0.999, *vide infra*) is absorbed by the 4CzIPN at the reaction conditions described above. The quantum yield was calculated using eq. 3 the average yield of three experiments to be **2.63**.

$$(3)\ \Phi = \frac{\text{mol product}}{\text{flux} \bullet \text{t} \bullet \text{f}}$$

Average yield of 3 experiments: 47% yield (avg. mmol= 0.095)

Sample quantum yield calculation:

$$\Phi = \frac{9.5\ x\ 10^{-5}\ mol}{4.02\ x\ 10^{-8} \bullet 900\ \text{s} \bullet 1.00} = 2.63$$

2.5.12 Chain Length Approximation

Chain length

Chain length values calculated in this paper are a lower limit approximation of the actual chain lengths and were calculated using eq. 4, where QY (initial SET) was calculated through transient absorption spectroscopy experimentation.

$$(4)\ \text{Chain length} = \frac{\Phi\ (\text{overall reation})}{\Phi(\text{inital SET})}$$

Sample Calculation:

$$\text{Chain length} = \frac{2.63}{0.0072} = 365$$

The lower limit of the chain length was determined to be **365**.

2.5.13 Calculated Reduction Potentials

General.

All DFT calculations were carried out using the Gaussian 9 software package[36] at the (U)B3LYP[367]or R(B3LYP)[37] level of theory with the 6-311+G(d,p)[38] basis set. The CPCM formalism for the Self Consistent Reaction Field (SCRF) model of solvation was employed in calculations to account for solvation in DMSO, and the default parameters as implemented in Gaussian were used.

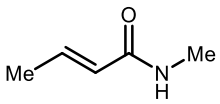
Reduction Potentials

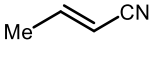
Reduction potentials were calculated using a modified procedure as described by Nicewicz and coworkers.[41] Geometry optimizations were carried out for the reduced and neutral forms of each molecule, and frequency calculations were performed on the minimized structures to ensure no imaginary frequencies existed. Geometry optimizations that did not converge to an energy minimum upon the initial calculation were sequentially optimized using a tight convergence criteria. Gibbs free energies (G_{298}) were obtained from the calculation and employed in the following equation:

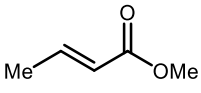
$$E_{1/2}^{0,calc} = -\frac{(G_{298}[reduced] - G_{298}[oxidized])}{n_e\mathcal{F}} - E_{1/2}^{0,SHE} + E_{1/2}^{0,SCE}$$

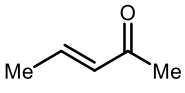
Where n_e is the number of electrons transferred (n_e= 1 for all calculations here), $\mathcal{F}$ is the Faraday constant (value 23.061 kcal mol^{-1} V^{-1}), $E_{1/2}^{0,SHE}$ is the absolute value for the standard hydrogen

electrode (SHE, value = 4.281 V) and $E_{1/2}^{0,SCE}$ is the potential of the saturated calomel electrode (SCE) relative to the SHE in DMSO (value = –0.279), and G_{298}[oxidized] and G_{298}[reduced] are the Gibbs free energies in DMSO obtained from DFT calculations.









$E_{1/2}^{red}$ vs SCE =	-2.67 V	-2.44 V	-2.35 V	-2.11 V

2.5.14 Electrochemical Measurements

Electrochemical potentials were obtained with a standard set of conditions according to literature procedure.[42] Cyclic voltammograms (CVs) were collected with a VersaSTAT 4Potentiostat. Samples were prepared with 0.1 mmol of substrate in 10 mL of 0.1 M tetra-n-butylammonium hexafluorophosphate in dry, degassed DMSO. Measurements employed a glassy carbon working electrode, platinum wire counter electrode, 3M NaCl silver-silver chloride reference electrode, and a scan rate of 100 mV/s. Reductions were measured by scanning potentials in the negative direction and oxidations in the positive direction; the glassy carbon electrode was polished between each scan. Data was analyzed using Microsoft Excel by subtracting a background current prior to identifying the maximum current (Cp) and determining the potential (Ep/2) at half this value (Cp/2). The obtained value was referenced to Ag|AgCl and converted to SCE by subtracting 0.035 V.

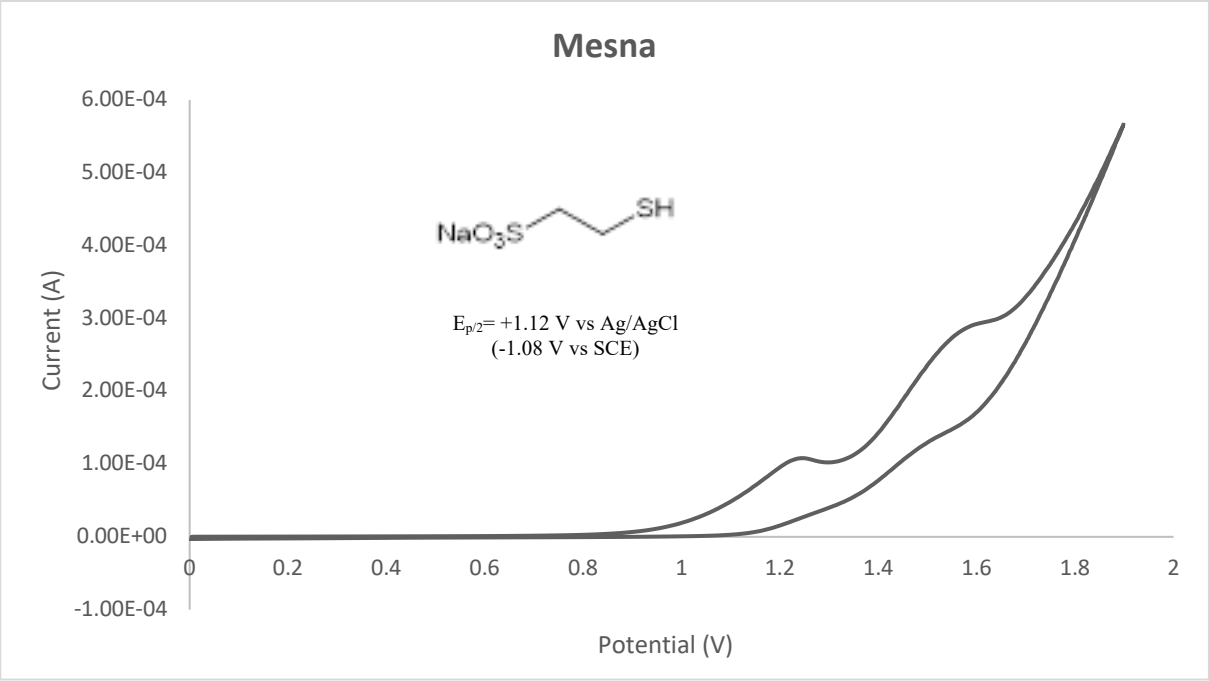


Figure S2.5: CV of mesna.

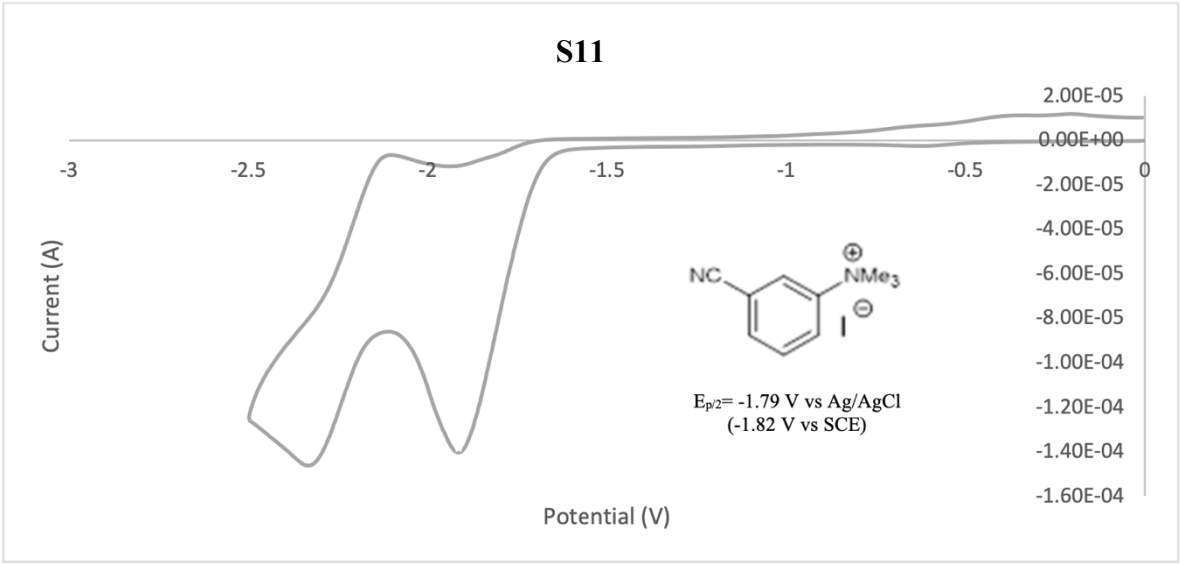


Figure S2.6: CV of 3-(methoxycarbonyl)-N,N,Ntrimethylbenzenaminium iodide (S11).

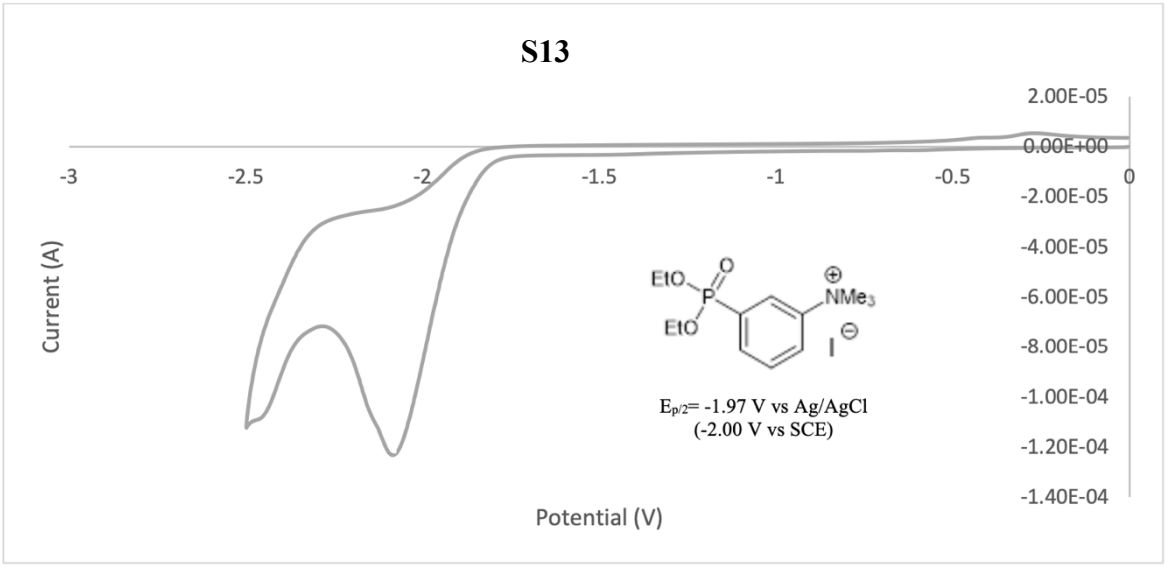


Figure S2.7: CV of 3-(diethoxyphosphoryl)-N,N,N-trimethylbenzenaminium iodide (S13).

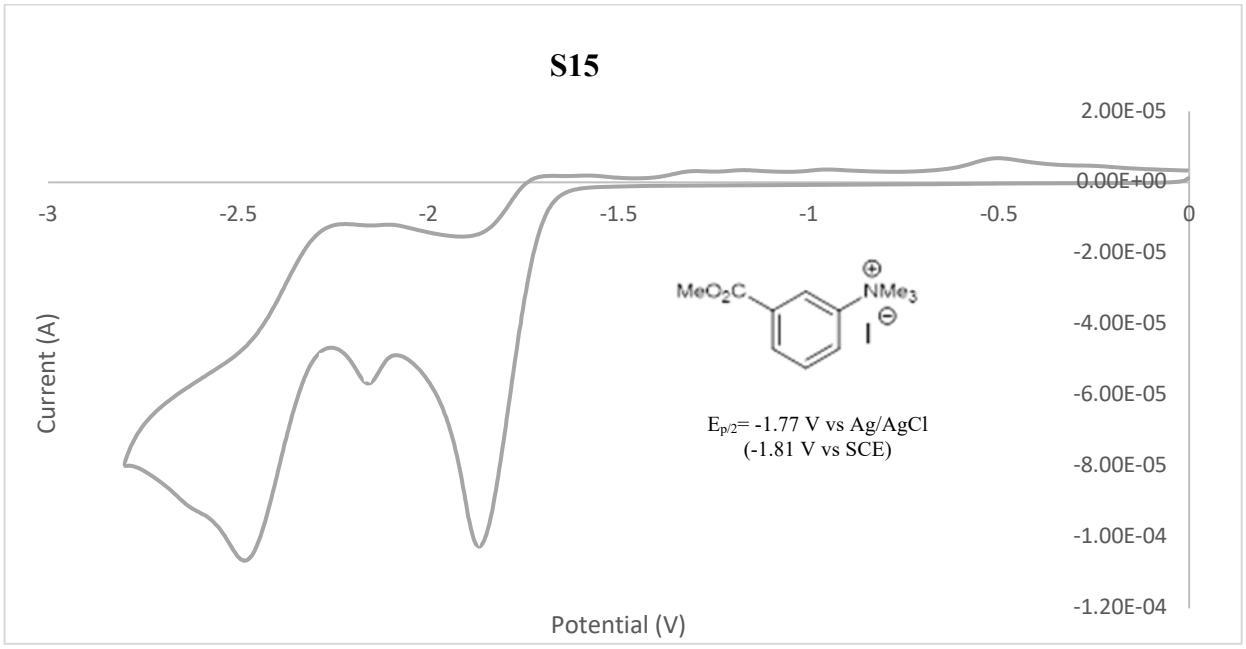


Figure S2.8: CV of 3-(methoxycarbonyl)-N,N,Ntrimethylbenzenaminium iodide (S15).

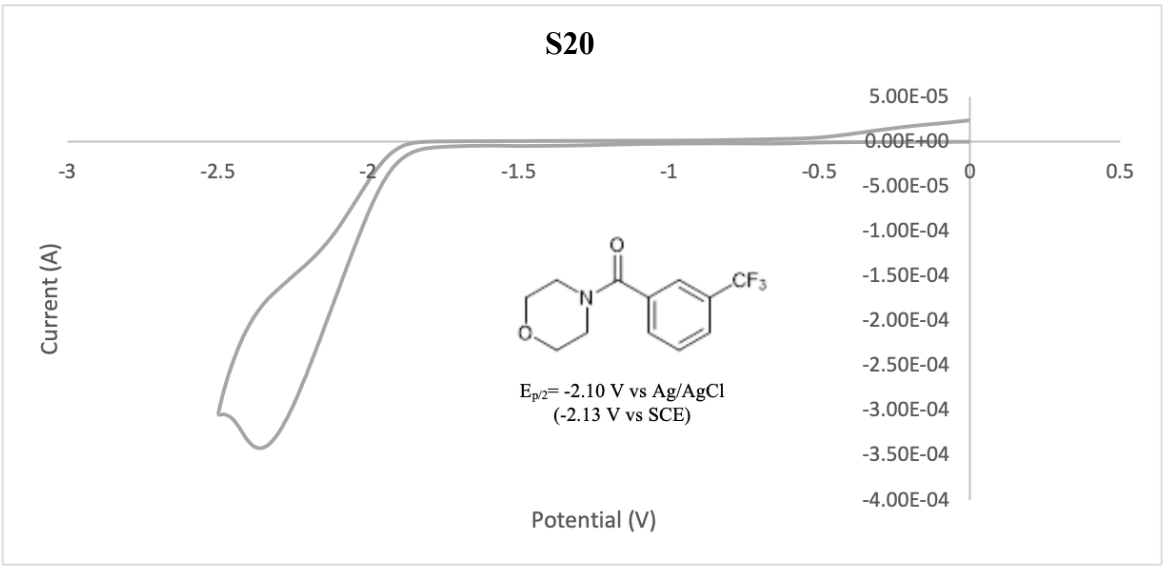


Figure S2.9: CV of morpholino(3-(trifluoromethyl)phenyl)methanone (S20).

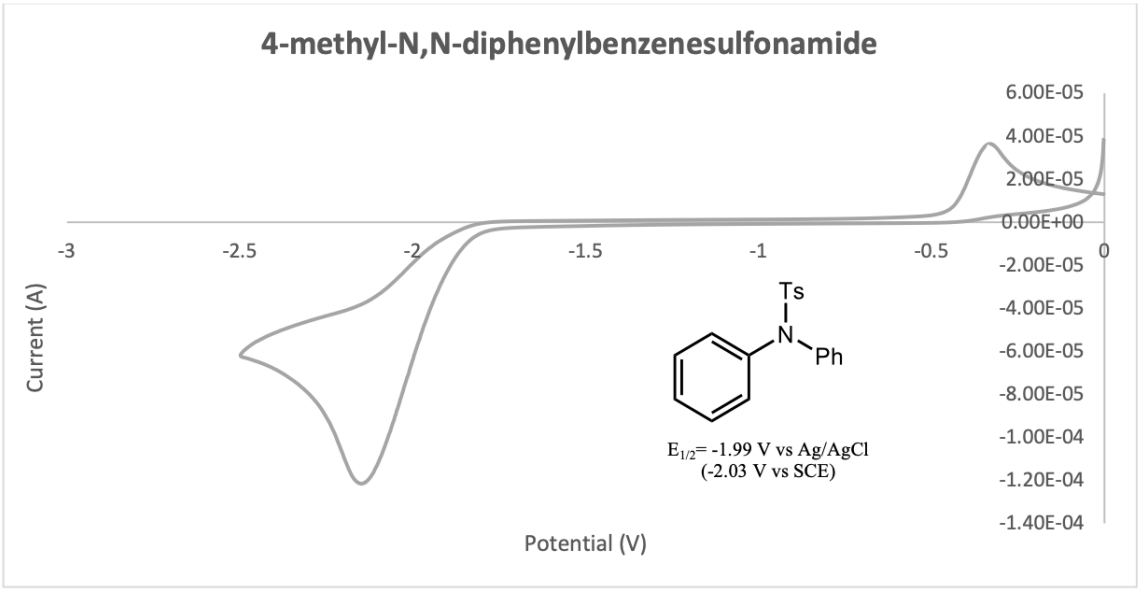


Figure S2.10: CV of 4-methyl-N,N-diphenylbenzenesulfonamide.

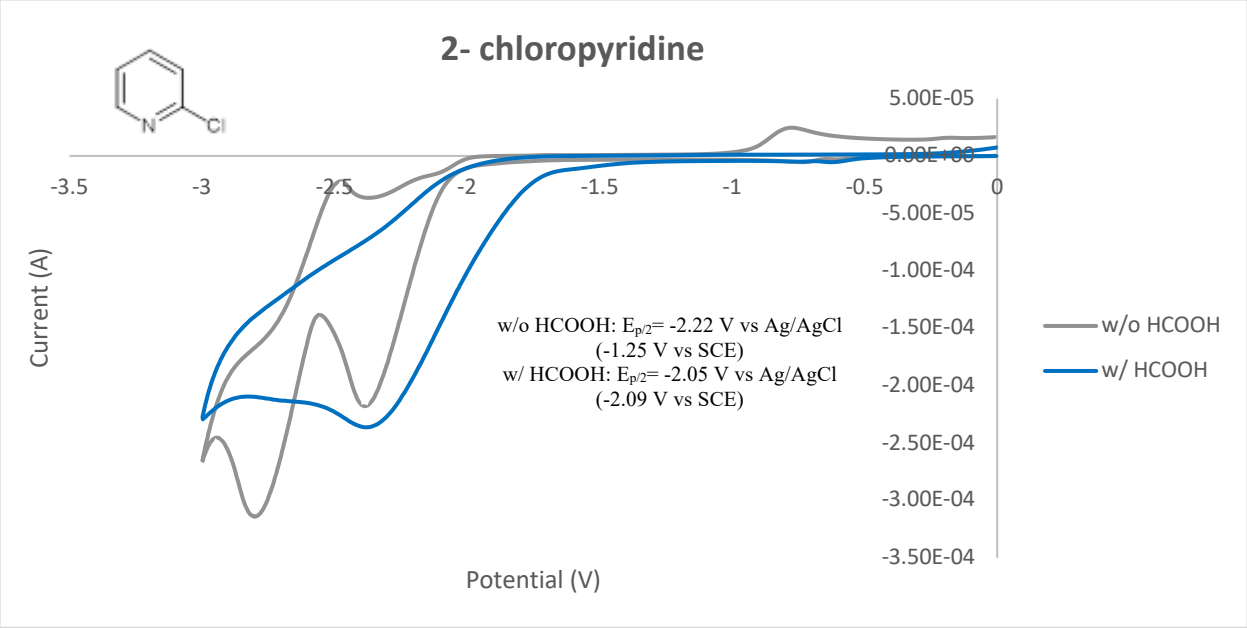


Figure S2.11: CV of 2-chloropyridine [in the absence of formic acid (gray line) and in the presence of 5.0 eq. of formic acid (blue)]

2.5.15 Supporting Information References

(1) Luo, J.; Zhang, J. "Donor-Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/ Ni Dual Catalytic C(sp^3)-C(sp^2) Cross- Coupling." *ACS. Catal.* **2016**, 6, 873–877.

(2) Xie, H.; Wang, J.; Wang, K.; Guo, P.; Su, P.; Wang, X.; Shu, X. "Radical Dehydroxylative Alkylation of Tertiary Alcohols by Ti Catalysis." *J. Am. Chem. Soc.*, **2020**, *142*, 16787-16794.

(3) Aycock, A.; Wang, H.; Jui, N. "A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles." *Chem. Sci*., **2017**, *8*, 3121.

(4) Cheng, R.; Shi, Z.; Ding, W.; Liu, Z.; Jin, H.; Yu, X.; Wang, S. "Facile Synthesis of alpha-beta unsaturated esters through a one-pot copper catalyzed aerobic oxidation-Wittig reaction." *Tett. Lett.*, **2018**, 59, 14-17.

(5) Tang, X.; Dolbier, W. "Efficient Cu-catalyzed Atom Transfer Radical Addition Reactions of Fluoroalkylsulfonyl Chlorides with Electron-deficient Alkenes Induced by Visible Light." *Angew. Chem. Int. Ed*., **2015**, *54*, 4246-4249.

(6) Kassir, A.; Ragab, S.; Nguyen, T.; Pouget, F.; Guillot, R.; Scherrmann, M.; Boddaert, T.; Aitken, D. "Synthetic Access to All Four Stereoisomers of Oxetin." *J. Org. Chem*., **2016**, 81, 9983-9991.

(7) Andaloussi, M.; Lindh, J.; Savmarker, J.; Sjoberg, P.; Larhed, M. Microwave-Promoted Palladium (II)-Catalyzed C-P Bond Formation by Using Arylboronic Acids or Aryltrifluoroborates. *Chem. Eur. J*., **2009**, *15*, 13069-13074.

(8) Takise, R.; Itami, K,; Yamaguchi, J. "Cyanation of Phenol Derivatives with Aminoacetonitriles by Nickel Catalysis." *Org. Lett.* **2016**, 18, 4428–4431.

(9) Xie, M.; Wang, Z. "Nickel-Catalyzed Cross-Coupling of Aryltrimethylammonium Iodides with Organozinc Reagents." *Angew. Chem. Int. Ed.* **2011**, 50, 4901 –490.

(10) Liu, C.; Ji, C.; Zhou, T.; Hong, X.; Szostak, M. "Decarbonylative Phosphorylation of Carboxylic Acids via Redox- Neutral Palladium Catalysis." *Org. Lett.* **2019**, 21, 9256– 9261.

(11) Peng, Z.; Wong, J.; Hansen, E.; Dermenci, A.; Clarke, H. "Development of a Concise, Asymmetric Synthesis of a Smoothened Receptor (SMO) Inhibitor: Enzymatic Transamination of a 4-Piperidinone with Dynamic Kinetic Resolution." *Org. Lett.*, **2014**, 16, 860-863.

(12) MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. "Discovery and Characterization of an Acridine Radical Photoreductant." *Nature.* **2020**, 580, 76–80.

(13) Takise, R.; Itami, K,; Yamaguchi, J. "Cyanation of Phenol Derivatives with Aminoacetonitriles by Nickel Catalysis." *Org. Lett.* **2016**, 18, 4428–4431.

(14) Bordi, S.; Starr, J. "Hydropyridylation of Olefins by Intramolecular Minisci Reaction." *Org. Lett.*, **2017**, 19, 2290-2293.

(15) Peng, Z.; Wong, J.; Hansen, E.; Dermenci, A.; Clarke, H. "Development of a Concise, Asymmetric Synthesis of a Smoothened Receptor (SMO) Inhibitor: Enzymatic Transamination of a 4-Piperidinone with Dynamic Kinetic Resolution." *Org. Lett.*, **2014**, 16, 860-863.

(16) Huang, H.; Belloti, P.; Pfluger, P.; Schwarz, L.; Heidrich, B.; Glorius, F. "Three- Component, Interrupted Radical Heck/Allylic Substitution Cascade Involving Unactivated Alkyl Bromides." *J. Am. Chem. Soc.*, **2020**, 142, 10173-10183.

(17) Wang, H.; Jui, N. "Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes." *J. Am. Chem. Soc.* **2018**, 140, 1, 163–166.

(18) Li, W.; Tang, J.; Li, S.; Zheng, X.; Yuan, M.; Xu, B.; Jiang, W.; Fu, H.; Li, R.; Chen, H. "Stereodivergent Synthesis of Alkenylpyridines via Pd/Cu Catalyzed C–H Alkenylation of Pyridinium Salts with Alkynes." *Org. Lett*., **2020**, 22, 7814-7819.

(19) Liu, Z.; Dong, N.; Xu, M.; Sum, Z.; Tu, T. "Mild Negishi Cross-Coupling Reactions Catalyzed by Acenaphtoimidazolyidene Palladium Complexes at Low Catalyst Loadings." *J. Org. Chem*., **2013**, *78*, 7436-7444.

(20) Mader, P.; Bartholomaus, R.; Nicolussi, S.; Baumann, A.; Weis, M.; Chicca, A.; Rau, M.; Simao, A.; Gertsch, J.; Altmann, K. "Synthesis and Biological Evaluation of Endocannabinoid Uptake Inhibitors Derived from WOBE437." *ChemMedChem*., **2021**, *16*, 145-154.

(21) Kim, S.; Goldfogel, M.; Gilbert, M.; Weix, D. "Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Chlorides with Primary Alkyl Chlorides." *J. Am. Chem. Soc*., **2020**, *142*, 9902-9907.

(22) Ackermann, L.; Punji, B.; Song, W. "User-Friendly [(Diglyme)$NiBr_2$]-Catalyzed Direct Alkylations of Heteroarenes with Unactivated Alkyl Halides through C-H Bond Cleavages*." Adv. Synth. Catal*., **2011**, *353*, 3325-3329.

(23) Boyington, A.; Riu, M.; Jui, N. "Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates." *J. Am. Chem. Soc.* **2017**, 139, 19, 6582–6585.

(24) Hara, N.; Saito, T.; Semba, K.; Kuriakose, N.; Zheng, H.; Sakaki, S.; Nako, Y. "Rhodium Complexes Bearing PAIP Pincer Ligands." *J. Am. Chem. Soc.* **2018**, 140, 23, 7070–7073.

(25) Kondolff, I.; Doucet, H.; Santelli, M. "Tetraphosphine/palladium catalysed Suzuki cross-coupling reactions of aryl halides with alkylboronic acids." *Tetrahedon Lett.* **2004**, 60, 3813-3818.

(26) Cassani, C.; Bergonzini, G.; Wallentin, C. "Photocatalytic Decarboxylative Reduction of Carboxylic Acids and Its Application in Asymmetric Synthesis." *Org. Lett.,* **2014**, *16*, 4228-4231.

(27) Wang, T.; Sang, S.; Liu, L.; Qiao, H.; Gao, Y.; Zhao, Y. "Experimental and Theoretical Study on Palladium- Catalyzed C-P Bond Formation via Direct Coupling of Triarylbismuths with P(O)-H Compounds." *J. Org. Chem.* **2014**, 79, 2, 608–617.

(28) Xia, Q.; Liu, X.; Zhang, Y.; Chen, C.; Chen, W. "Copper- Catalyzed N-Methylation of Amides and O-Methylation of Carboxylic Acids by Using Peroxides as the Methylating Reagents." *Org. Lett.* **2013**, 15, 13, 3326–3329.

(29) Suarez-Pantiga, S.; Hernandez-Ruiz, R.; Virumbrales, C.; Pedrosa, M.; Sanz, R. "Reductive Molybdenum-Catalyzed Direct Amination of Boronic Acids with Nitro Compounds." *Angew. Chem. Int. Ed.* **2019**, 58, 2129 –2133.

(30) Z.; Sun, Q.; Xia, C.; Sun, W. "CO_2 as a C1 Source: $B(C_6F_5)_3$-Catalyzed Cyclization of *o*-Phenylene-diamines To Construct Benzimidazoles in the Presence of Hydrosilane." *Org. Lett.* **2016**, 18, 24, 6316–6319.

(31) Bonfio, C.; Caumes, C.; Duffy, C.; Patel, B.; Percivalle, C.; Tsnakopoulou, M.; Sutherland, J. "Length-Selective Synthesis of Acylglycerol-Phosphates through Energy-Dissipative Cycling." *J. Am. Chem. Soc.* **2019**, 141, 9, 3934–3939.

(32) Houjeiry, T.; Poe, S.; McQuade, T. "Synthesis of Optically Active 4-Substituted 2-Cyclohexenones." *Org. Lett.* **2012**, 14, 17, 4394–4397.

(33) Tamang, S.; Bedi, D.; Shafiei-Haghighi, S.; Smith, C Crawford, C.; Findlater, M. "Cobalt-Catalyzed Hydroboration of Alkenes, Aldehydes, and Ketones." *Org. Lett.* **2018**, 20, 6695–6700.

(34) Li, W.; Tang, J.; Li, S.; Zheng, X.; Yuan, M.; Xu, B.; Jiang, W.; Fu, H.; Li, R.; Chen, H. "Stereodivergent Synthesis of Akenylpyridines via Pd/Cu Catalyzed C-H Alkenylation of Pyridinium Salts with Alkynes." *Org. Lett*., **2020**, *22*, 7814-7819.

(35) Alektair, S.; Wickens, Z. "Photoinduced Hydrocarboxylation via Thiol-Catalyzed Delivery of Formate Across Activated Alkenes." *J. Am. Chem. Soc.* **2021**, 143, 13022- 13028.

(36) Zhang, Z.; Sun, Q.; Xia, C.; Sun, W. "CO_2 as a C1 Source: B(C6F5)3-Catalyzed Cyclization of o-Phenylene-diamines to Construct Benzimidazoles in the Presence of Hydrosilane." *Org. Lett*., **2016**, *18*, 6316-6319.

(37) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K.

Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2016**.

(38) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B,* **1988**, *37* (2), 785–789. (b) Becke, A. D. *J. Chem. Phys*. **1993**, *98* (7), 5648–5652.

(39) Cismesia, M.; Yoon, T. "Characterizing chain processes in visible light photoredox catalysis." *Chem. Sci*., **2015**, 6, 5426–5434.

(40) Hatchard, C. G.; Parker, C. A. *Proc. Roy. Soc*. (London) **1956**, A235, 518–536

(41) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single Electron Redox Chemistry. *Synlett* **2016**, *27* (05), 714–723.

(42) Isse, A. A.; Gennaro, A. "Absolute Potential of the Standard Hydrogen Electrode and the Problem of Interconversion of Potentials in Different Solvents." *J. Phys. Chem. B* **2010**, 114, 7894–7899.

Chapter 3:

Reagent Controlled Regioselective Formation of 6-*endo* or 5-*exo* Reductive Radical Cyclizations

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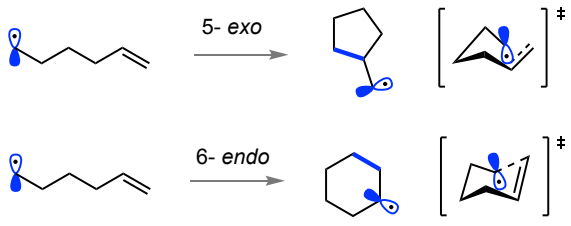
M. C. Maust optimized conditions for the 6-*endo* cyclization reaction, contributed to product isolations in the scope and performed the Hantzsch Ester Solubility Experiment

Abstract: Radical cyclizations of aryl and vinyl halides have historically resulted in a mixture of 5-exo and 6-endo regioisomers. Typically, they display higher selectively for the kinetically favored 5-exo regioisimer. To address this challenge, we have developed a switchable method for the 5-exo and 6-endo regioselective radical cyclization of N-heterocyclic bromides onto pendant olefins where selectivity is reagent controlled. Radical generation occurs through single electron reduction of the heteroaryl bromide under mild, visible-light driven conditions. The selectivity is governed through the appropriate selection of hydrogen atom transfer (HAT) reagent. We found $CO_2^{\bullet-}$ chemistry described in chapter 2 was excellent for the formation of the 5-exo product. This can be attributed to the utilization of a thiol-based HAT catalyst. The use of Hantzsch ester (HEH) as the HAT reagent led to formation of the 6-endo product. This is attributed to a longer lifetime of the cyclized radical intermediate when using HEH allowing thermodynamic equilibration to the 6-membered ring via neophyl rearrangement before HAT termination. This discovery allows for two modes of divergent reactivity to form either 6-membered or 5-membered fused N-heteroaromatic/saturated ring systems.

Introduction 3.1

Free radical cyclizations are arguably one of the most exploited forms of radical reactivity. It has been seen as a key step in many total synthesis endeavors of complex molecules forging imperative C-C bonds.[1] It is well established that radical cyclizations typically occur in the 5-*exo* mode. This can be attributed to better orbital overlap in the transition state of 5-*exo* radical cyclizations which grants a lower kinetic barrier compared to its 6-*endo* counterpart (Figure 3.1).[2] Achieving 6-*endo* product formation has

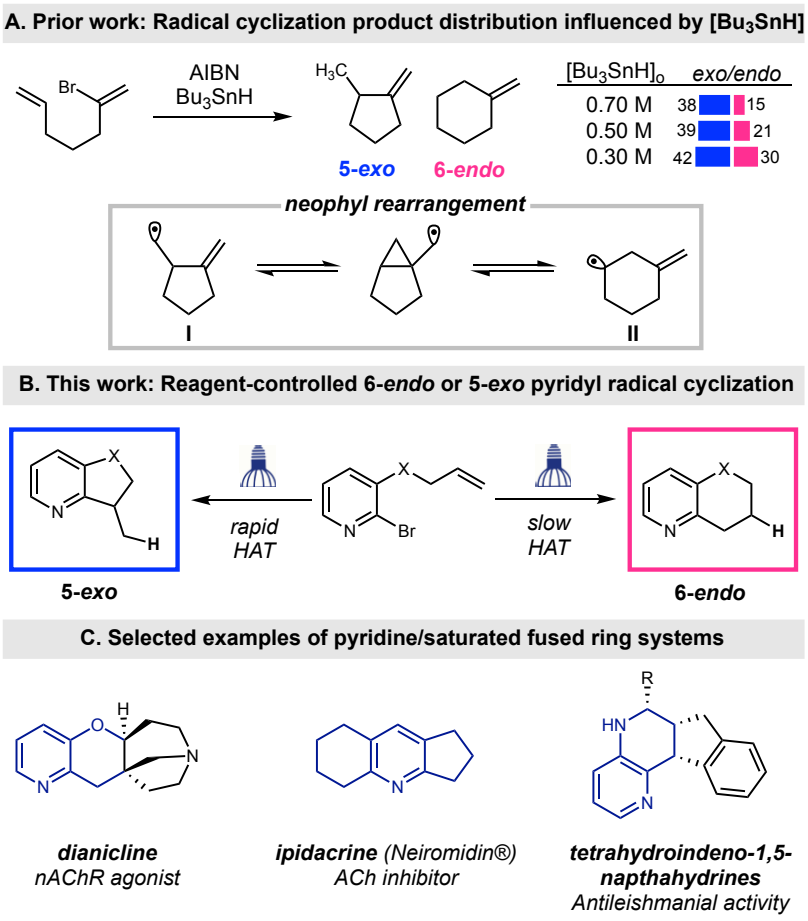
Figure 3.1: 5-*exo* and 6-*endo* radical cyclization transition states



traditionally required either substrate manipulation to sterically inhibit 5-*exo* cyclization[3] or the introduction of ring strain to encourage formation of the more thermodynamically stable 6-membered ring.[4] However, in the absence of *regio*-directing features no reliable method exists for selective 6-*endo* radical formation.

In this chapter, we describe the development of switchable catalytic methods that utilize reagent control to determine either 5-*exo* or 6-*endo* product formation. This methodology utilizes principles of single electron reduction and hydrogen atom transfer that have been established in previous chapters of this dissertation to enable the reactivity and selectivity seen in this chemistry. The ability to select for either 5-*exo* or 6-*endo* product for a given substrate represents a significant

Figure 3.2: Approach to 6-*endo* and 5-*exo* radical cyclization product.



advance and provides new opportunities to exploit radical cyclizations for the synthesis of pharmaceutically relevant molecules.

Our reaction design was inspired by Beckwith[5] and Stork's[6] seminal studies using Bu_3SnH/AIBN initiated vinyl radical ring closures. They found that the concentration of Bu_3SnH had influence over product distribution. While high initial concentrations of Bu_3SnH favored the 5-*exo* product, slow addition and lower concentrations of Bu_3SnH gave a moderate decrease in the *exo*/*endo* ratio (Figure 3.2A). This observation can be attributed to the neophyl rearrangement. The neophyl rearrangement can be defined as a reversible cyclopropanation with the adjacent *π-system* (i.e. alkene or aromatic ring) from the radical resulting in a 1,2-carbon migration to deliver the thermodynamically favored 6-membered ring.[7,8] This reversible migration allows for interconversion of the kinetic (5- *exo*) and themodynamic (6-*endo*) radical intermediates. However, despite these early findings, a general and practical method to access both 5- and 6-membered cyclization products from the same starting material with high selectivity has yet to be established.

We envisioned developing a switchable catalysis method to access the 5-*exo* or 6-*endo* products using the mild conditions photoredox catalysis offers (Figure 3.2B).[9] Key to the success of this methodology hinges on controlling the lifetime of intermediate **I** resulting from 5-*exo* cyclization. The rapid interception of this radical would result in selective formation of the 5-*exo* product. In contrast, slow hydrogen atom delivery would result in prolonged lifetime of the radical and favor the 6-*endo* radical intermediate **II**. Accordingly, we hypothesized we can regulate regioselectivity through the rate of the hydrogen atom delivery to the alkyl radical intermediate.

We demonstrate this strategy using pyridyl bromides with pendant olefins as our radical precursors which can be activated using a single electron reduction approach. This reaction will

result in fused N-heteroaromatic/saturated ring systems. This motif can be found in a variety of natural products and medicinally relevant compounds (Figure 3.2C)[10,11] and the methods outlined in this chapter present a particularly attractive way to access them.[12]

3.2 Results and Discussions

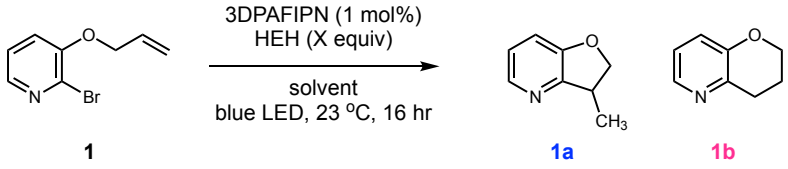
3.2.1 Optimization of 5-*exo* and 6-*endo* Radical Cyclizations

Our studies began through testing the feasibility of our reagent-controlled regioselective radical cyclization hypothesis with 2-bromo-3-allyloxy pyridine (**1**). We reasoned that selection of an HAT reagent that has a faster rate of hydrogen atom delivery to alkyl radicals than the rate for pyridyl-neophyl rearrangement would lead to selective formation of the 5-*exo* cyclization product. The rate constant for *t*-BuSH to primary alkyl radicals ($k \cong 8 \times 10^6\ M^{-1}\ s^{-1}$) [13] exceeds pyridyl-neophyl rearrangement ($k \cong 8 \times 10^2\ s^{-1}$)[8] by 4-orders of magnitude (Figure 3.3A). This exceedingly fast rate of HAT can be attributed to the relatively low BDE of thiol S–H bonds and polarity matching of the electrophilic thiol H-atom with a nucleophilic alkyl radical. Thus, we recognized that $CO_2^{\bullet-}$ chemistry discussed in chapter 2 would be an excellent choice of conditions for 5-*exo* formation, as it relies on a thiol-based HAT catalyst and the highly reducing $CO_2^{\bullet-}$ would be capable of activating **1** for pyridyl radical formation through a single electron transfer.[14] Indeed, subjecting allyloxy bromopyridine **1** to irradiation under blue light for 16 h with photocatalyst 4CzIPN (1 mol %), HAT catalyst mesna (20 mol %), and 5 equiv of sodium formate/ formic acid in DMSO selectively delivered 5-exo product **1a** in 97% yield, with no 6-endo product **1b** observed (Table 3.1, entry 1).

To select for the 6-*endo* product, we sought to exploit the tunability of Hanztsch ester (HEH) H-atom transfer reagents. An initial experiment using 1 mol% 3DPAFIPN as the photocatalyst and HEH (5 equiv) gave a 26% yield of the 6-*endo* product **1b** (2.7: 1 *exo/endo*, entry 2). Subsequently, lowering the concentration of HEH to 3 equivalents increased the yield of **1b** (39%, entry 3) but **1a** was still the major product (55%, entry 3). It has previously been demonstrated by our group that solvent choice can significantly change the solubility of HEH.[15]

The change in solubility would alter the effective concentration of HEH and ultimately should have a substantial impact on the reaction outcome. With this in mind, we moved away from DMSO to MeCN as the solvent choice. We were pleased to find this change in solvent resulted in mixture of products now favoring 6-*endo* isomer **1b** (58%) over the 5-*exo* (28%, 1.0:2.1 *exo*/*endo*, entry 4). We could further limit the solubility of HEH by adding water as a cosolvent which improved the yield of **1b** (80%) and *exo/endo* ratio to 1.0:4.4 (entry 5). Finally, lowering the equivalents of HEH to 1.5 gave full starting material consumption, increased the yield of **1b** to 84%, and limited production of **1a to** just 15% (1.0:5.6 *exo/endo*, entry 6).

Table 3.1: Optimization of switchable catalysis to access either the 5-*exo* or 6-*endo* cyclization Products[a,c]



Entry	Reductant	Solvent	% exo	% endo
1[b]	thiol/formate	DMSO	97	
2	HEH (5 equiv)	DMSO	70	26
3	HEH (3 equiv)	DMSO	55	39
4	HEH (3 equiv)	MeCN	28	58
5	HEH (3 equiv)	50% H_2O/ MeCN	18	80
6	HEH (1.5 equiv)	50% H_2O/ MeCN	15	84

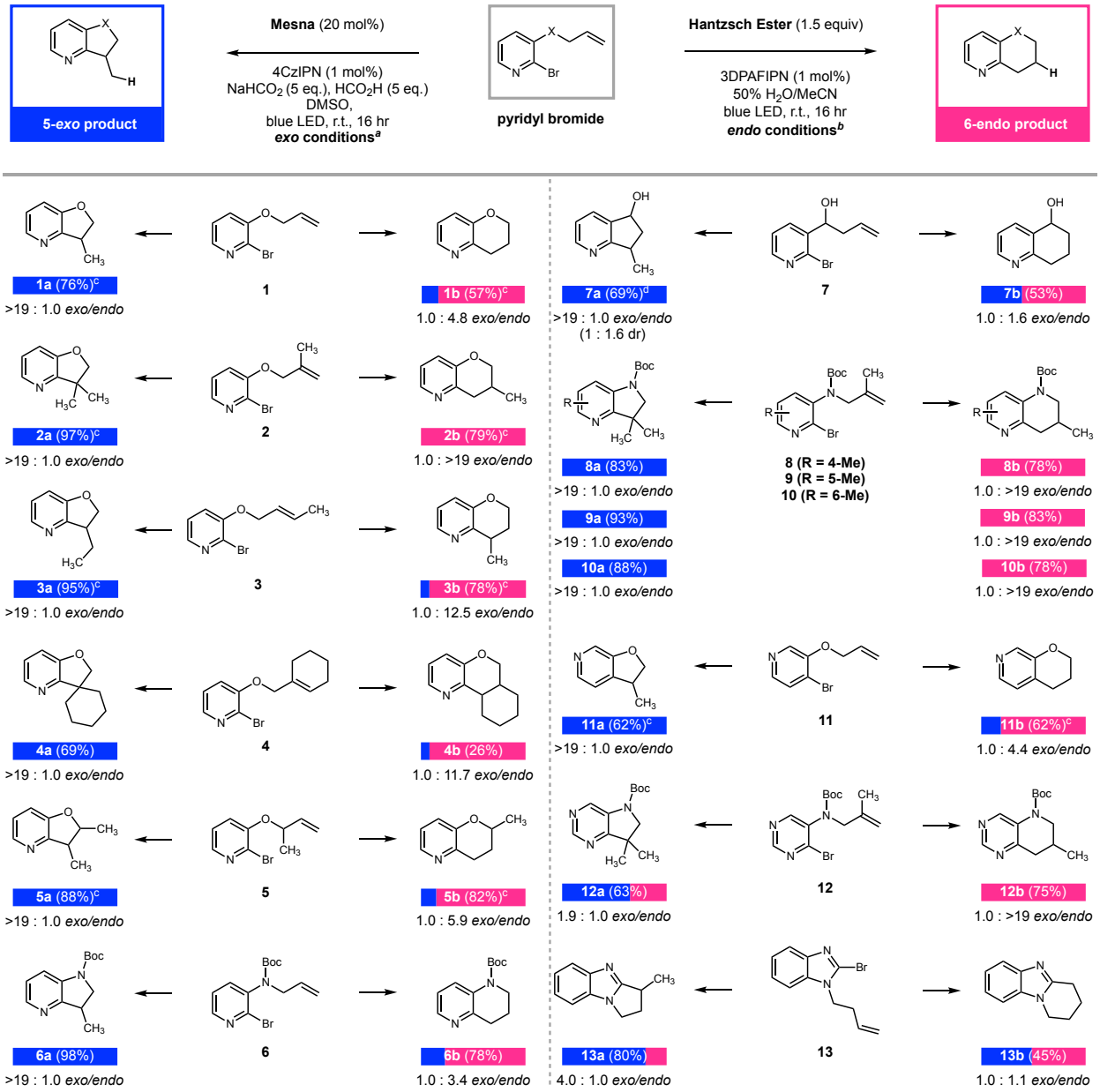
[a]Conditions: 2-bromo-3-allyloxypyridine (0.1 mmol), 3DPAFIPN (1 mol %), HEH (0.15 mmol), solvent (3 mL), blue LED, 23 °C, 16 h. [b]Conditions: 2-bromo-3-allyloxypyridine (0.1 mmol), 4CzIPN as photocatalyst (1 mol %), mesna (20 mol %), formic acid (2.5 mmol), sodium formate (2.5 mmol), solvent (2 mL), blue LED, 23 °C, 16 h. [c]Yields determined by ^{1}H NMR with internal standard.

3.2.2 Scope of 5-*exo* and 6-*endo* Radical Cyclization

With optimized *exo* and *endo* conditions in hand, we evaluated the ability of these methods to discriminate between the *exo* and *endo* products by designing a series of substrates that assess the impact on selectivity through the variation of the olefin and pyridine substitution (Table 3.2). We first looked at a variety of substrates that had varying substitution around the olefin. Substrate **2** with internal substitution of the olefin should increase the thermodynamic favorability of neophyl rearrangement as it would result in a tertiary alkyl radical intermediate over a secondary radical intermediate with the non-substituted olefin. We were pleased when subjecting substrate **2** to *exo* conditions we observed **2a** in a 97% yield. When substrate **2** was subjected to *endo* conditions, selectivity was completely switched giving **2b** in good yield (79%), with no detection of **2a** in the crude NMR, highlighting the power of reagent control for switchable catalysis. Terminal olefin substitution at the 6-position (**3**), gave good yields under (95% and 78% *exo* and *endo*, respectively) and excellent selectivity (>19:1.0 and 1.0:12.5 *exo/endo*). Finally, trisubstituted olefin **4** gave similar selectivity (>19:1.0 and 1.0:11.7 *exo/endo*) albeit with reduced yields (69% and 26%, respectively).

We next turned our attention to investigating the nature of the linker and its effect on product distribution. Alpha-substitution in substrate 5 had little impact on product distribution with *exo* (**5a**, 88%, >19:1.0 *exo/endo*) and *endo* (**5b**, 82%, 1.0:5.9 *exo/endo*) conditions giving good yields and selectivity. N-boc linked olefin (**6**) delivered *endo* product **6b** in a 78% yield and 1.0:3.4 *exo/endo* ratio. This slightly lower *endo* selectivity can be attributed to decreased stabilization of the radical in the cyclopropyl intermediate from the N-boc lone pair compared to the oxygen lone pair in the previous substrates.[16] The selectivity is further decreased when carbon linked olefin **7** is used giving a 53% yield of **7b** in a 1.0:1.6 *exo/endo* ratio. The carbon linker does not offer any

Table 3.2: Scope of 5-*exo* and 6-*endo* Radical Cyclizations.



[a]Conditions: 4CzIPN (1 mol %), substrate (1 equiv), mesna (20 mol %), sodium formate (5 equiv), formic acid (5 equiv), DMSO, blue LED, 23 °C, 16 h, isolated yields shown. [b]Conditions: 3DPAFIPN (1 mol %), substrate (1 equiv), Hanztsch ester (1.5 equiv), H_2O:MeCN (1:1 v/v), blue LED, 23 °C, 16 h, isolated yields shown. [c]Isolated as a HCl salt. [d]Yields determined by ^1H NMR with an internal standard.

lone pair stabilization of the radical intermediate and explains why we observe the lowest *endo* ratio for this substrate. However, both **6** and **7** remained highly selective under *exo* conditions

(>19:1.0 *exo/endo* in both cases).

We next examined substitution around the pyridine ring. Unsurprisingly, substitution at the 4-,5-, and 6-positions of the pyridine (**8**, **9**, **10**) all reacted in good yield with exquisite selectivity (>19:1.0 for *exo* and 1.0:>19 *exo/endo* for *endo*). Additionally, bromination at the 4-position of pyridine (**11**) exhibits similar selectivity for both *exo* (>19:1.0 *exo/endo*) and *endo* (1.0:4.4 *exo/endo*) albeit in lower yields (62% for **11a** and 26% for **11b**). The lower yield with substrate **11** likely arise from the instability of 4-brominated pyridines[17]. Expanding the scope to other N-heterocycles, pyrimidine **12** gave lower *exo* selectivity (1.9:1.0 *exo/endo*) but gave excellent selectivity under *endo* conditions (1.0:>19 *exo/endo*). This pattern in explained by the lower aromatic stabilization energy of pyrimidine relative to pyridine, accelerating dearomatization to from the cyclopropyl intermediate thus increasing rate of neophyl rearrangement.[18] Benzimidazole **13** was also reactive under both conditions, with the stability of the cyclopropyl intermediate again impacting selectivity.

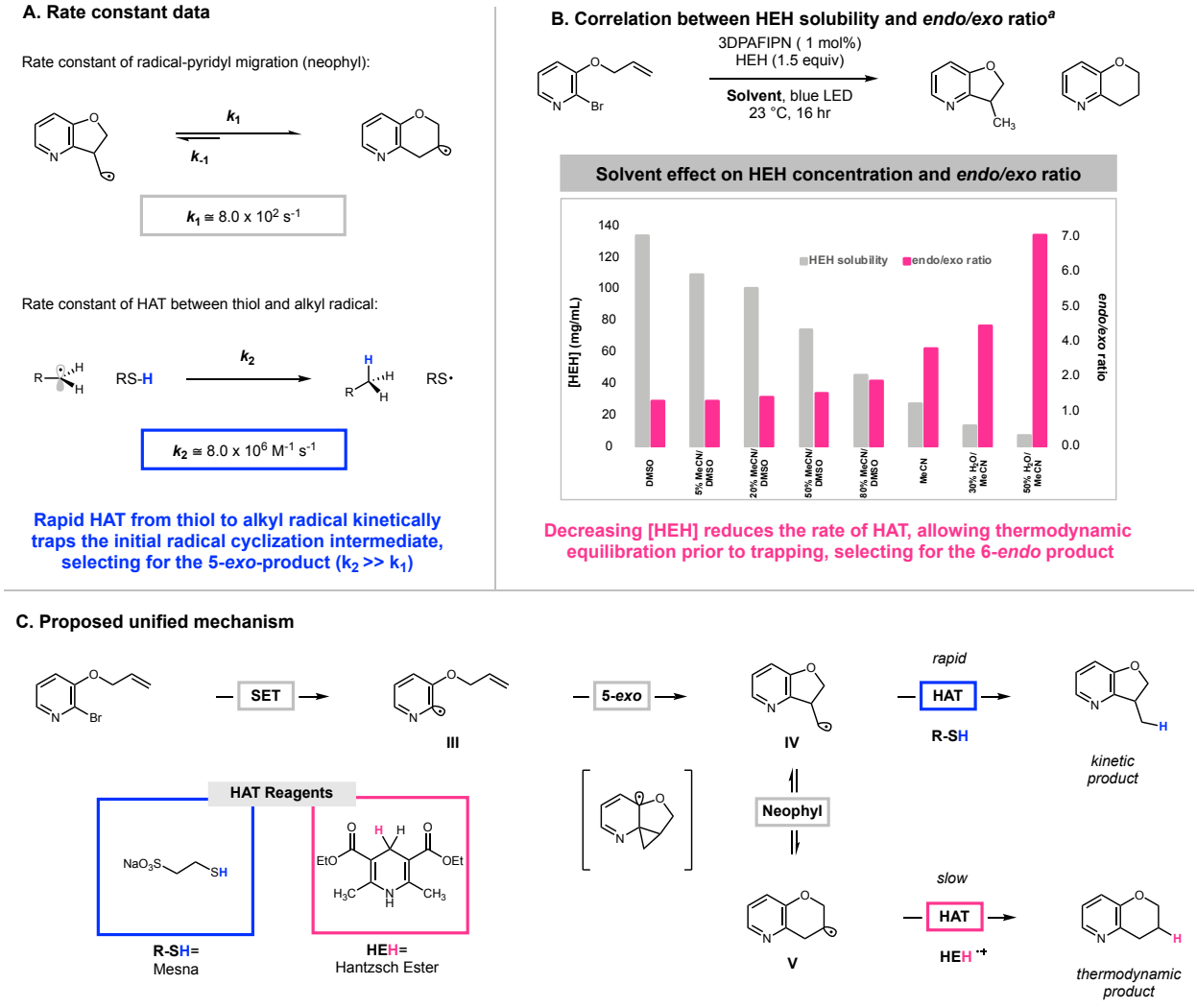
3.2.3 Mechanistic Investigations

We next sought to probe our mechanistic hypothesis through a series of experiments where we assessed the solubility of HEH across a range of solvent systems from DMSO/MeCN to H_2O/MeCN. We then subjected substrate **1** to each of the solvent systems to observe a trend between HEH solubility and *endo* selectivity. Indeed, we observed a strong correlation between HEH solubility and *endo* selectivity (Figure 3.3B). HEH was most soluble in DMSO and gave the lowest *endo* ratio. Conversely, HEH was least soluble in the 50% H_2O/MeCN mixture and gave the highest selectivity.

Our proposed unified mechanism can be seen in Figure 3.3C. Under *exo* conditions, single electron reduction of **1** by $CO_2^{\bullet-}$ ($E_{1/2}^{\circ}$= -2.21 V vs SCE), generated through an HAT with thiyl

radical (as previously discussed in chapter 2), induces homolytic cleavage of the bromopyridine delivering pyridyl radical **III**.[14] Under *endo* conditions, reduction occurs through single electron reduction of **1** by 3DPAFIPN$^{\bullet-}$, which is generated upon quenching reductive quenching of 3DPAFIPN* ($E_{1/2}^{\circ}$= +1.09 V vs SCE)[19] with HEH ($E_{1/2}^{\circ}$= +0.97 V vs SCE),[20] to deliver the pyridyl

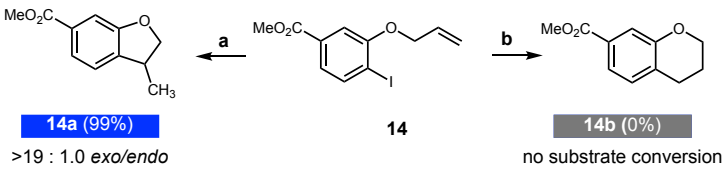
Figure 3.3: Mechanistic proposal explaining the origins of the reagent controlled switchable selectivity. [a]Ratio determined by ^{1}H NMR with an internal standard.



radical **III**.[21] Given 3DPAFIPN$^{\bullet-}$ ($E_{1/2}^{\circ}$= -1.59 V vs SCE)[19] has an underpotential for reducing 2-bromopyridines ($E_{1/2}^{\circ}$= -2.26 V vs SCE for 2-bromopyridine)[22] it is highly likely the substrate is

undergoing a proton-assisted reduction from the Hantzsch pyridinium produced in each catalytic turnover.[23,24] In both cases following reduction, the resulting radical undergoes the kinetically favored 5-*exo* cyclization to produce the alkyl radical **IV** intermediate. Under *exo* conditions, alkyl radical **IV** is rapidly trapped by the highly polarity-matched thiol HAT catalyst. Under the *endo* conditions, with the low concentration of the less efficient HAT reagent HEH, alkyl radical **IV** has a sufficient lifetime to undergo thermodynamically driven neophyl rearrangement to the more stable secondary alkyl radical **V**. Hydrogen atom delivery to **V** from $HEH^{\bullet+}$ furnishes the 6-*endo* product.

Scheme 3.1: Investigation of non-heteroaryl substrate.



[a]Conditions: 4CzIPN (1 mol %), substrate (1 equiv), mesna (20 mol %), sodium formate (5 equiv), formic acid (5 equiv), DMSO, blue LED, 23 °C, 16 h, isolated yields shown. [b]Conditions: 3DPAFIPN (1 mol %), substrate (1 equiv), Hanztsch ester (1.5 equiv), H_2O :MeCN (1:1 v/v).

` To further investigate the reduction mechanism of each pathway, aryl iodide **14** was subjected to both sets of reactions conditions (Scheme 3.1) As expected under the *exo*-selective conditions, the stronger $CO_2^{\bullet-}$ could initiate the reaction, and near quantitative yield (99%) of **14a** with complete *exo* selectivity (>19:1.0 *exo/endo*) was observed. However, substrate **14,** which cannot undergo proton-assisted reduction, did not react under *endo* conditions and quantitative starting material return was observed by ^{1}H NMR. This is consistent with hypothesis that $3DPAFIPN^{\bullet-}$ is the reductant in the *endo*-selective conditions and that it is not sufficiently reducing to engage aryl iodide **14**.

3.3 Conclusions

In this chapter, we have described the development of a mild photoredox reaction conditions to allow the switchable formation of either the 5-*exo* or 6-*endo* cyclization products. The two reactivity modes are controlled by the choice of HAT reagent, rather than substrate manipulation. The use of $CO_2^{\bullet-}$ chemistry with a thiol HAT catalyst promoted rapid capture of the radical intermediate before any thermodynamic equilibration could occur delivering the 5-*exo* product. Conversely, decreasing the rate of HAT by limiting the solubility of a less efficient HAT reagent preferentially generates the 6-*endo* product. We demonstrated these switchable catalysis modes across a range of substrates that provide a blueprint for the prediction of the selectivity for other substrates.

3.4 References

(1) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. Radicals in natural product synthesis. *Chem. Soc. Rev.* **2018**, 47, 7851− 7866.

(2) (a) Beckwith, A. L. J. Regio- and stereo-selectivity in radical reactions. *Tetrahedron*. **1981**, 37, 3073−3100. (b) Beckwith, A. L. J.; Schiesser, C. H. Regio- and stereo-selectivity of alkenyl radical ring closure: A theoretical study. *Tetrahedron*. **1985**, 41, 3925−3941.

(3) (a) Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. Subsituent effects on the cyclization of hex-5-enyl radical. *Tetrahedron Lett.* **1974**, 15, 2251−2254. (b) Beckwith, A. L. J.; Lawrence, T. The effect of non- bonded interactions on the regioselectivity of cyclization of the hex-5- enyl radical. *J. Chem. Soc., Perkin Trans.* **1979**, 1535−1539.

(4) (a) Ishibashi, H. Controlling the regiochemistry of radical cyclizations. *Chem. Rec.* **2006**, 6, 23−31. (b) Gómez, A. M.; Company, M. D.; Uriel, C.; Valverde, S.; López, J. C. 6-endo versus 5-exo radical cyclization: streamlined syntheses of carbohexopyra- noses and derivatives by 6-endo-trig radical cyclization. *Tetrahedron Lett.* **2007**, 48, 1645−1649.

(5) Beckwith, A. L. J.; O'Shea, D. M. Kinetics and mechanism of some vinyl radical cyclisations. *Tetrahedron Lett.* **1986**, 27, 4525− 4528.

(6) Stork, G.; Baine, N. H. Cyclization of vinyl radicals: A versatile method for the construction of five-and six-membered rings. *J. Am. Chem. Soc.* **1982**, 104, 2321−2323.

(7) Stork, G.; Mook, R. Five vs six membered rings formation in the vinyl radical cyclization. *Tetrahedron Lett.* **1986**, 27, 4529−4532.

(8) Chen, Z.-M.; Zhang, X.-M.; Tu, Y.-Q. Radical aryl migration reactions and synthetic applications. *Chem. Soc. Rev.* **2015**, 44, 5220− 5245.

(9) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible light photoredox catalysis with transition metal complexes: Applications in organic synthesis. *Chem. Rev.* **2013**, 113, 5322−5363. (b) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, 116, 10075−10166.

(10) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocyclse among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, 57, 10257−10274.

(11) (a) Wall, T. R.; Henderson, B. J.; Voren, G.; Wageman, C. R.; Deshpande, P.; Cohen, B. N.; Grady, S. R.; Marks, M. J.; Yohannes, D.; Kenny, P. J.; Bencherif, M.; Lester, H. A. TC299423, a novel agonist for nicotinic acetylcholine receptors. *Front. Pharmacol*. **2017**, 8, 641. (b) Dejos, C.; Voisin, P.; Bernard, M.; Régnacq, M.; Bergés, T. Canthin-6-one displays antiproliferative activity and causes accumu- lation of cancer cells in the G2/M phase. *J. Nat. Prod*. **2014**, 77, 2481−2487. (c) Tejería, A.; Pérez-Pertejo, Y.; Reguera, R. M.; Balaña-Fouce, R.; Alonso, C.; Fuertes, M.; González, M.; Rubiales, G.; Palacios, F. Antileishmanial effect of new indeno-1,5-naphthyridines, selective inhibitors of Leishmania infantum type IB DNA topoisomer- ase. *Eur. J. Med. Chem*. **2016**, 124, 740−749.

(12) (a) Maiti, S.; Achari, B.; Mukhopadhyay, R.; Banjerjee, A. K. Heteroaryl radicals. Part 1. Synthesis of linear pyridine-fused ring systems by endo-selective 2-pyridyl radical cyclizations. *J. Chem. Soc., Perkin Trans. I.* **2002**, 1769−1773. (b) Ward, J.; Caprio, V. A radical mediated approach to the core structure of huperzine A. *Tetrahedron Lett.* **2006**, 47, 553−556. (c) Jones, K.; Fiumana, A.; Escudero- Hernandex, M. L. Pyridine radicals in synthesis. Part 3: Cyclo-pentannulation of pyridine via the 3-pyridyl radical and a formal synthesis of (±)-oxerine.

Tetrahedron. **2000**, 56, 397−406. (d) Harrowven, D. C.; Browne, R. Dichotomy in the addition of carbon-centred radicals to ketenedithioacetals. *Tetrahedron Lett.* **1994**, 35, 5301−5302.

(13) Newcomb, M.; Glenn, A. G.; Manek, M. B. Rate constants and arrhenius functions for hydrogen atom transfer from tert-butyl thiol to primary alkyl radicals. *J. Org. Chem.* **1989**, 54, 4603−4606.

(14) Hendy, C. M.; Smith, G. C.; Xu, Z.; Lian, T.; Jui, N. T. Radical Chain Reduction via Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$). *J. Am. Chem. Soc.* **2021**, 143, 8987−8992.

(15) 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.

(16) Coote, M. L.; Lin, C. Y.; Beckwith, A. L. J.; Zavitsas, A. A. A comparison of methods for measuring relative radical stabilities of carbon-centred radicals. *Phys. Chem. Chem. Phys.* **2010**, 12, 9597− 9610.

(17) Feast, W. J.; Tsibouklis, J. The self-condensation of 4- bromopyridine. *Polym. Int.* **1994**, 35, 67−74.

(18) Tjebbes, J.; Mollberg, R.; Lindberg, B.; McKay, J.; Theander, O.; Flood, H. The heats of combustion and formation of the three diazines and their resonance energies. *Acta Chem. Scand.* **1962**, 16, 916−921.

(19) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A toolbox approach to contruct 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, 15353−15365.

(20) Maitland, J. A. P.; Leitch, J. A.; Yamazaki, K.; Christensen, K. E.; Cassar, D. J.; Hamlin, T. A.; Dixon, D. J. Switchable, reagent- controlled diastereodivergent photocatalytic

carbocyclisation of imine-derived α-amino radicals. *Angew. Chemie. Int. Ed.* **2021**, 60, 24116−24123.

(21) Wang, P.-Z.; Chen, J.-R.; Xiao, W.-J. Hantzsch esters: an emerging versatile class of reagents in photoredox catalyzed organic synthesis. *Org. Biomol. Chem.* **2019**, 17, 6936−6951.

(22) Enemaerke, 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. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1620−1630.

(23) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* **2017**, 8, 7998− 8003.

(24) Experiments adding base to *endo* conditions result in hindered reduction of the substrate, suggesting a proton-assisted reduction mechanism (see *Supporting Information*).

3.5 Supporting Information

3.5.1 General Information

A. General Reagent Information

Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Astatech, and TCI America and used as received, unless stated otherwise. 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. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using $KMnO_4$, p-anisaldehyde, or ninhydrin stains. DMSO was purchased from Fisher Scientific and was distilled over CaH_2 and degassed by sonication under vacuum and stored under nitrogen. Photoredox catalysts 4CzIPN and 3DPAFIPN were prepared according to literature procedures.[1]

B. General Analytical Information.

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. New compounds were characterized by NMR and HRMS. ^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), Bruker 400 (400 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz), and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet,

dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. High Resolution mass spectra were obtained from the Emory University Mass Spectral facility.

C. General Photoredox Reaction Setup

To run multiple reactions, an appropriately sized 3D printed carousel was used (photo 1), which exposed the reactions evenly to blue light (photo 2). A 15 W LED array lamp was used as a blue light source. The blue LEDs were positioned approximately 6 inches above the reaction vials. Reactions were place in a solvent cabinet renovated for constant airflow to prevent heating from the light source (photos 3, 4, and 5).

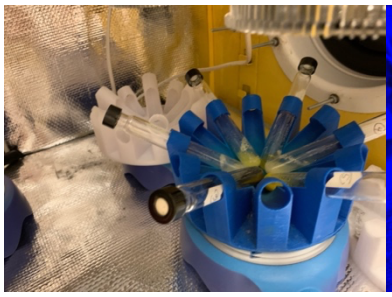


Photo 1

Photo 2

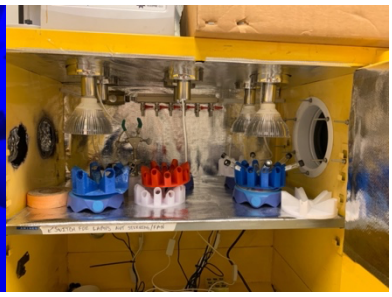


Photo 3

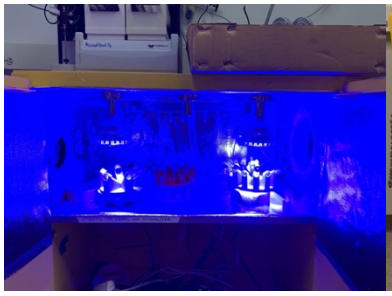


Photo 4

Photo 5

3.5.2 General Procedures

General Procedure A

A 20 mL screw-top test tube was charged with 3DPAFIPN (1 mol%), Hantzsch Ester (1.5 equiv), and pyridyl halide (1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent (1:1 MeCN/H_2O, 0.033 M) was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs at room temperature. The reaction was quenched with sat. K_2CO_3 (aq) and extracted with EtOAc (3x). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude sample was analyzed by ^1H NMR (d = 5 s), and the integral values gave the *exo*/*endo* ratio. The residue was then purified by silica chromatography using the indicated solvent mixture as the eluent to afford the title compound.

General Procedure B

A 20 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (5.0 equiv), mesna (20 mol%) and pyridyl halide (1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent (DMSO, 0.05 M) was added via syringe followed by formic acid (5.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs at room temperature. The reaction was quenched with sat. K_2CO_3 (aq) and extracted with EtOAc (3x). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude sample was analyzed by ^1H NMR (d = 5 s), and the integral values gave the

exo/*endo* ratio. The residue was then purified by silica chromatography using the indicated solvent mixture as the eluent to afford the title compound.

3.5.3 Optimization Details

Optimization Procedure A

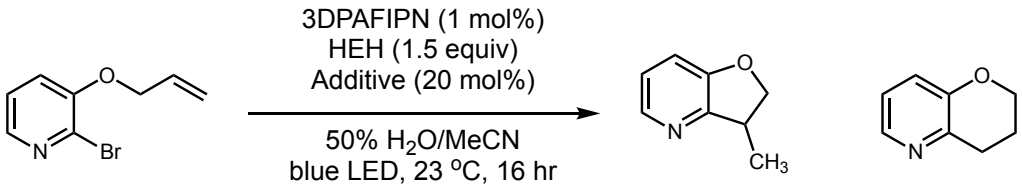
An 8 mL screw-top test tube was charged with photocatalyst (1 mol%), Hantzsch Ester, and 3-(allyloxy)-2-bromopyridine (0.1 mmol, 0.021 g, 1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent was added via syringe. The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs at room temperature. The reaction was quenched with sat. K_2CO_3 (aq) and extracted with diethyl ether (3x). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. Dibromomethane (0.1 mmol, 7 μL) as internal standard was added and the crude sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values gave the *exo*/*endo* ratio and yield.

Optimization Procedure B

A 8 mL screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (5.0 equiv), mesna (20 mol%) and pyridyl halide (1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent (DMSO, 0.05 M) was added via syringe followed by formic acid (5.0 equiv). The resulting mixture was stirred at 1400 RPM for 16 h under irradiation by blue LEDs at room temperature. The reaction was quenched with sat. K_2CO_3 (aq) and extracted with diethyl ether (3x). The combined organic layers were pushed through small silica plug to remove

excess DMSO and concentrated *in vacuo*. Dibromomethane (0.1 mmol, 7 μL) as internal standard was added and the crude sample was analyzed by ^{1}H NMR (d = 5 s), and the integral values gave the *exo*/*endo* ratio and yield.

Control Experiment for *endo* conditions[a]



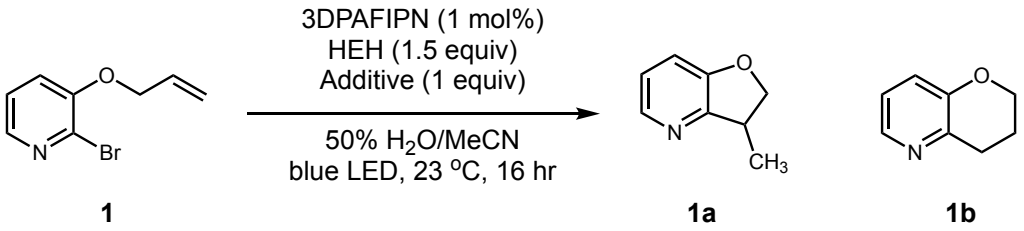
1 **1a** **1b**

Entry	Condition	**1 (%)**	**1a (%)**	**1b (%)**	*exo/endo*
1	no light	99	0	0	ND
2	no 3DPAFIPN	100	0	0	ND
3	no HEH	103	0	0	ND
4	4CzIPN as photocatalyst	0	20	62	1.0 : 3.1
5	mesna additive	0	69	30	2.3 : 1.0

[a]Following optimization procedure A

Table S3.1: Control experiments for *endo* conditions

Base additive experiment in *endo* conditions[a]



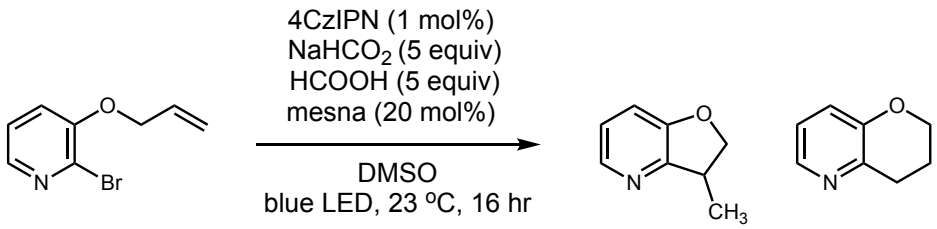
1 **1a** **1b**

Entry	Additive	**1 (%)**	**1a (%)**	**1b (%)**	*exo/endo*
1	pyridine	22	47	18	2.6 : 1.0
2	K_2CO_3	94	0	0	ND
3	$NaHCO_3$	95	0	0	ND

[a]Following optimization procedure A

Table S3.2: Base additive screens

Control Experiments for *exo* conditions[b]



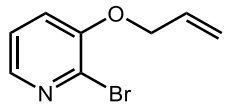
1 **1a** **1b**

Entry	Condition	**1** (%)	**1a** (%)	**1b** (%)	*exo/endo*
1	no light	80	0	0	ND
2	no photocatalyst	92	0	0	ND
3	no $NaHCO_2$/HCOOH	81	0	0	ND
4	3DPAFIPN as photocatalyst	0	76	0	> 19: 1.0

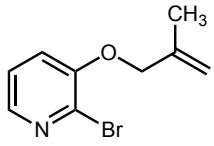
[b]Following optimization procedure B

Table S3.3: Control experiments for *exo* conditions

3.5.4 Preparation of Starting Materials



3-(allyloxy)-2-bromopyridine (1): A 50 mL round bottom flask equipped with a stirbar was added 2-bromopyridin-3-ol (5 mmol, 0.87 g, 1.0 equiv) and potassium carbonate (10 mmol, 1.4 g, 2.0 equiv) followed by DMF (10 mL). The mixture was allowed to stir at room temperature for 15 minutes before allyl bromide (7.5 mmol, 0.65 mL, 1.5 equiv) was added. The reaction was heated to 40 °C and allowed to stir overnight. The reaction was cooled to room temperature and diluted in EtOAc. The crude mixture was washed with a solution of 1 M LiCl (2x), followed by a wash with brine (1x). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo.* The crude reaction was purified by silica chromatography (0- 30% EtOAc/ hexanes as the eluent) to afford the title compound as a yellow oil (0.89 g, 85% yield). The physical properties and spectral data were consistent with the reported values.[2]



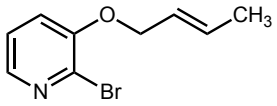
2-bromo-3-((2-methylallyl)oxy)pyridine (2): A 50 mL round bottom flask equipped with a stirbar was added 2-bromopyridin-3-ol (5 mmol, 0.87 g, 1.0 equiv) and potassium carbonate (10 mmol, 1.4 g, 2.0 equiv) followed by DMF (10 mL). The mixture was allowed to stir at room temperature for 15 minutes before 3-bromo-2-methylprop-1-ene (7.5 mmol, 0.725 mL, 1.5 equiv) was added. The reaction was heated to 40 °C and allowed to stir overnight. The reaction was cooled to room temperature and diluted in EtOAc. The crude mixture was washed with a solution of 1 M LiCl (2x), followed by a wash with brine (1x). The organic layer was dried over Na_2SO_4 and

concentrated *in vacuo.* The crude reaction was purified by silica chromatography (0- 20% EtOAc/ hexanes as the eluent) to afford the title compound as a colorless oil (1.048 g, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 4.6, 1.6, Hz, 1H), 7.19 (dd, *J* = 8.1, 4.6 Hz, 1H), 7.12 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.15 (m, 1H), 5.05 (m, 1H), 4.53 (s, 2H), 1.86 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.03, 141.39, 139.42, 133.19, 123.25, 119.99, 113.66, 72.63, 19.25.

HRMS (APCI) m/z: [M+H] calcd. for $C_9H_{11}ONBr$, 228.00185; found 228.00198.

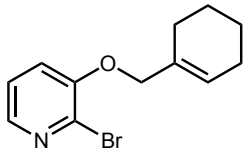


2-bromo-3-(but-2-en-1-yloxy)pyridine (3): A 50 mL round bottom flask equipped with a stirbar was added 2-bromopyridin-3-ol (5 mmol, 0.87 g, 1.0 equiv) and potassium carbonate (10 mmol, 1.4 g, 2.0 equiv) followed by DMF (10 mL). The mixture was allowed to stir at room temperature for 15 minutes before 1-bromobut-2-ene (6 mmol, 0.610 mL, 1.2 equiv) was added. The reaction was heated to 40 °C and allowed to stir 4 hours. The reaction was cooled to room temperature and diluted in EtOAc. The crude mixture was washed with a solution of 1 M LiCl (2x), followed by a wash with brine (1x). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo.* The crude reaction was purified by silica chromatography (0- 20% EtOAc/ hexanes as the eluent) to afford the title compound as a colorless oil and a mixture of diastereomers (0.639 g, 56% yield). Mixture of diastereomers (*denotes major diastereomer, # denotes minor diastereomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 4.6, 1.7, Hz, 1H), 7.19 (m, 1H), 7.13 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.96 – 5.85 (m, 1H*), 5.85 – 5.76 (m, 1H#), 5.76 – 5.65 (m, 1H), 4.72 – 4.64 (d, *J* = 6.5, Hz, 1H#), 4.55 (d, *J* = 5.9, 2H*), 1.83 – 1.69 (d, *J* = 6.4, Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.16, 141.29, 141.24, 133.25, 133.21, 131.37, 129.82, 124.73, 124.34, 123.30, 120.20, 120.10, 69.87, 65.11, 17.89, 13.52.

HRMS (APCI) m/z: [M+H] calcd. for $C_9H_{11}ONBr$, 228.00185, found 228.00197.

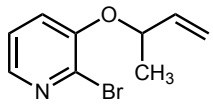


2-bromo-3-(cyclohex-1-en-1-ylmethoxy)pyridine (4): To a flame-dried round bottom flask equipped with a stir bar cyclohex-1-en-1-ylmethanol (785 mg, 7 mmol 1.2 equiv), NEt_3 (1.17 mL, 8.4 mmol, 1.4 equiv) and dry Et_2O (15 mL) was added. The solution was cooled to -78 ºC and methanesulfonyl chloride (650 µL, 8.4 mmol, 1.4 equiv) was added dropwise. The solution was warmed to 0 ºC and stirred for 15 minutes. The reaction was diluted with Et_2O (20 mL) and washed with water (2x) and brine (1x). The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo*. The crude reaction product was reconstituted in THF (5 mL) and added to a stirring solution of 2-bromopyridin-3-ol (1.015 g, 5.8 mmol, 1 equiv) and potassium carbonate (1.603 g, 11.6 mmol, 2 equiv) in THF (10 mL). The resulting mixture was stirred for 16 h then quenched with sat. K_2CO_3 and extracted 3x with EtOAc. The organic layers were combined and washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5-20% MTBE/Hexanes as the eluent) to give the title compound as a colorless oil (778 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, J = 4.6, 1.7 Hz, 1H), 7.18 (dd, J = 8.1, 4.6 Hz, 1H), 7.13 (dd, J = 8.1, 1.7 Hz, 1H), 5.85 (m, 1H), 4.46 (s, 2H), 2.07 (m, 4H), 2.13 – 2.02 (m, 3H), 1.72 – 1.64 (m, 2H), 1.63 – 1.57 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.26, 141.18, 133.28, 132.52, 126.44, 123.25, 120.22, 73.74, 25.56, 24.99, 22.30, 22.19.

HRMS (APCI) m/z: [M+H] calcd. for $C_{12}H_{15}ONBr$**,** 268.03315; found 268.03323.

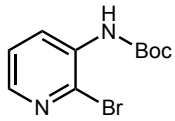


2-bromo-3-(but-3-en-2-yloxy)pyridine (5): A flame-dried 50 mL round bottom flask equipped with a stir bar was added 2-bromopyridin-3-ol (4 mmol, 0.700 g, 1 equiv), triphenylphosphine (4 mmol, 1.05 g, 1 equiv), NEt_3 (4 mmol, 0.56 mL, 1 equiv), and but-3-en-2-ol (4 mmol, 0.70 mL, 1 equiv) followed by THF (10 mL). Stirred for 15 minutes until all solids dissolved then added DIAD (4 mmol, 0.80 mL, 1 equiv) The reaction was stirred at room temperature overnight then concentrated *in vacuo*. The crude reaction was purified using silica gel chromatography (30% EtOAc/hexanes as the eluent) to afford the title compound as a pale-yellow oil (0.681 g, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 4.0, 2.2 Hz, 1H), 7.16 – 7.14 (m, 2H), 5.95 – 5.87 (td, *J* = 17.4, 6.2, 0.6 Hz, 1H), 5.29 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.22 (dt, *J* = 10.5, 1.1 Hz, 1H), 4.80 (m, 1H), 1.53 (d, *J* = 6.4 Hz, 3H).

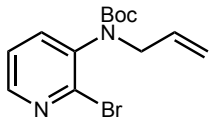
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.58, 141.52, 137.79, 134.12, 123.11, 122.41, 116.82, 77.00, 21.30.

HRMS (APCI) m/z: [M+H] calcd. for $C_9H_{11}ONBr$, 228.00185; found 228.00198.



***tert*-butyl (2-bromopyridin-3-yl)carbamate (S1):** A 3-neck round bottom flask was equipped with a stirbar and 2-bromopyridin-3-amine (10 mmol, 1.73 g, 1.0 equiv). The atmosphere was exchanged for nitrogen (3x) and 60 mL of dry THF was added. The reaction was cooled to 0 °C and 1.0 M LiHMDS was added (20 mmol, 20 mL, 2.0 equiv) dropwise. The solution stirred for 30 minutes followed by addition of di-*tert*-butyl dicarbonate (10.5 mmol, 2.29 g, 1.05 equiv). The

reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 0.1 M HCl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatography (0- 30% EtOAc/ hexanes as eluent) to afford the title compound as a white solid (2.03 g, 75% yield). The physical properties and spectral data were consistent with the reported values.[3]

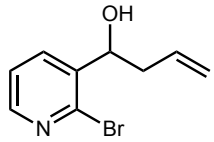


***tert*-butyl allyl(2-bromopyridin-3-yl)carbamate (6):** An oven dried 3-neck round bottom flask equipped with a stir bar was added 60% NaH in mineral oil (9 mmol, 0.360 g, 1.2 equiv), had its atmosphere exchanged for N_2 (3x), and added dry THF (20 mL). The reaction was cooled to 0 °C and *tert*-butyl (2-bromopyridin-3-yl)carbamate **S2** (7.5 mmol, 2.04 g, 1.0 equiv) in a solution of dry TFF was added and allowed to stir at room temperature for 15 minutes. Allyl bromide (9 mmol, 0.78 mL, 1.2 equiv) was added dropwise and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with sat. NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatography (0-20% EtOAc/hexanes as the eluent) to afford the title compound as a white solid (1.92 g, 82% yield). Mixture of rotamers (*denotes major rotamer, #denotes minor rotamer).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.56 (broad s, 1H#), 7.50 – 7.44 (d, *J* = 7.0 Hz, 1H*), 7.29 – 7.23 (m, 1H), 5.95 – 5.83 (m, 1H), 5.22 – 4.99 (m, 2H), 4.50 (dd, *J* = 15.2, 5.7 Hz, 1H*), 4.40-4.48 (broad s, 1H#) 3.83 (dd, *J* = 15.2, 7.3 Hz, 1H*), 3.73-3.80, (broad s, 1H#), 1.52 (s, 9H#), 1.35 (s, 9H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.49, 148.18, 144.09, 139.25, 138.54, 138.38, 133.16, 122.91, 118.51, 117.87, 81.47, 81.14, 52.80, 51.57, 28.31, 28.12.

HRMS (APCI) m/z: [M+H] calcd. for $C_{13}H_{18}O_2N_2Br$, 313.05462; found 313.05458.

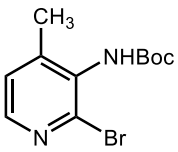


1-(2-bromopyridin-3-yl)but-3-en-1-ol (7): A flame dried 3-neck round bottom flask equipped with a stirbar had its atmosphere exchanged for nitrogen (3x) and dry THF (50 mL) was added to the flask. 2-bromonicotinaldehyde (5 mmol, 0.93 g, 1.0 equiv) dissolved in dry THF (10 mL) was added to the flask. The reaction was cooled to – 78 °C and a 1.0 M solution of allylmagnesium bromide in diethyl ether (10 mmol, 10 mL, 2.0 equiv) was added dropwise. The reaction was stirred overnight and quenched with aq. NH_4Cl and extracted with EtOAc (3x), dried over Na_2SO_4 and concentrated *in vacuo.* The crude reaction mixture was purified by silica chromatography (0-50% EtOAc/ hexanes as the eluent) to afford the title compound as a brown oil (0.445 g, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 4.7, 2.0 Hz, 1H), 7.88 (ddd, *J* = 7.7, 2.0, 0.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.94 – 5.79 (m, 1H), 5.20 (br s, 1H), 5.17 (dq, *J* = 6.7, 1.3 Hz, 1H), 5.04 (dd, *J* = 8.3, 3.7 Hz, 1H), 2.68 (dddt, *J* = 14.2, 6.4, 3.7, 1.4 Hz, 1H), 2.31 (dtt, *J* = 14.2, 7.9, 1.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.90, 141.37, 140.32, 136.28, 133.70, 123.27, 119.46, 70.87, 41.96.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_9H_{11}ONBr$, 228.00185; found 228.00204.



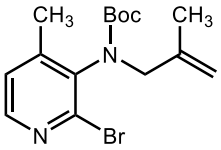
***tert*-butyl (2-bromo-4-methylpyridin-3-yl)carbamate (S2):** A 3-neck round bottom flask was equipped with a stirbar and 2-bromo-4-methylpyridin-3-amine (4 mmol, 0.75 g, 1.0 equiv). The

atmosphere was exchanged for nitrogen (3x) and dry THF (40 mL) was added. The reaction was cooled to 0 °C and 1.0 M LiHMDS was added (12 mmol, 12 mL, 3.0 equiv) dropwise. The solution stirred for 30 minutes followed by addition of di-*tert*-butyl dicarbonate (4.2 mmol, 0.92 g, 1.05 equiv). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 0.1 M HCl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatography (5- 30% EtOAc/ hexanes as eluent) to afford the title compound as a beige solid. (1.01 g, 89%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, J = 4.9 Hz, 1H), 7.13 (d, J = 4.8 Hz, 1H), 2.36 (s, 3H), 1.51 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.05, 147.85, 147.21, 138.95, 132.41, 125.59, 81.47, 28.36, 19.07.

HRMS (APCI) m/z: [M+H] calcd. for $C_{11}H_{16}O_2N_2Br$, 287.03897; found 287.03937.



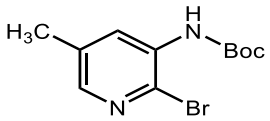
***tert*-butyl (2-bromo-4-methylpyridin-3-yl)(2-methylallyl)carbamate (8):** An oven dried 3-neck round bottom flask equipped with a stir bar was added 60% NaH in mineral oil (3.6 mmol, 0.144 g, 1.2 equiv), had its atmosphere exchanged for N_2 (3x), and added dry THF (30 mL). The reaction was cooled to 0 °C and *tert*-butyl (2-bromo-4-methylpyridin-3-yl)carbamate **S3** (3 mmol, 0.57 g, 1.2 equiv) in a solution of dry TFF was added and allowed to stir at room temperature for 15 minutes. 3-bromo-2-methylprop-1-ene (3.6 mmol, 0.36 mL, 1.2 equiv) was added dropwise and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with sat. NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was pushed through a silica plug (20% EtOAc/Hexanes as eluent) to afford the

title compound as a white solid (0.633 g, 93% yield). Mixture of rotamers (*denotes major rotamer, #denotes minor rotamer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 1H*,#), 7.14 – 7.08 (m, 1H*,#), 4.83 – 4.75 (m, 1H*,#), 4.64 (dq, *J* = 1.9, 1.0 Hz, 1H#), 4.62 (dq, *J* = 1.9, 0.9 Hz, 1H*), 4.43 (d, *J* = 14.4 Hz, 1H*), 4.38 (d, *J* = 14.9 Hz, 1H#), 3.71 – 3.65 (m, 1H*,#), 2.28 (s, 3H#), 2.27 (s, 3H*), 1.87 (s, 3H*,#), 1.54 (s, 9H#), 1.34 (s, 9H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.10, 153.86, 150.57, 149.68, 147.88, 147.69, 144.32, 141.52, 141.35, 138.12, 125.37, 125.12, 115.57, 81.55, 80.90, 56.32, 55.06, 28.45, 28.21, 21.54, 21.50, 18.91, 18.78.

HRMS (APCI) m/z: [M+H] calcd. for $C_{15}H_{22}O_2N_2Br$ 341.08592; found 341.08643.

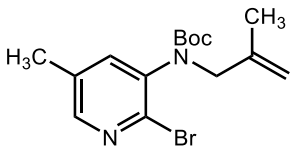


***tert*-butyl (2-bromo-5-methylpyridin-3-yl)carbamate (S3):** A 3-neck round bottom flask was equipped with a stirbar and 2-bromo-5-methylpyridin-3-amine (6 mmol, 1.1 g, 1.0 equiv). The atmosphere was exchanged for nitrogen (3x) and dry THF (60 mL) was added. The reaction was cooled to 0 °C and 1.0 M LiHMDS was added (12 mmol, 12 mL, 2.0 equiv) dropwise. The solution stirred for 30 minutes followed by addition of di-*tert*-butyl dicarbonate (6.3 mmol, 1.4 g, 1.05 equiv). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 0.1 M HCl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatography (0- 20% EtOAc/ hexanes as eluent) to afford the title compound as a white solid. (0.681 g, 40%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.85 (s, 1H), 6.98 (s, 1H), 2.29 (s, 3H), 1.53 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.33, 143.73, 133.93, 133.63, 129.31, 127.65, 81.94, 28.38, 18.04.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{11}H_{16}O_2N_2Br$, 287.03897; found 287.03911.

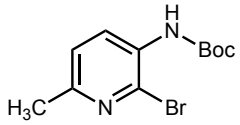


***tert*-butyl (2-bromo-5-methylpyridin-3-yl)(2-methylallyl)carbamate (9):** An oven dried 3-neck round bottom flask equipped with a stir bar was added 60% NaH in mineral oil (2.4 mmol, 0.096 g, 1.2 equiv), had its atmosphere exchanged for N_2 (3x), and added dry THF (20 mL). The reaction was cooled to 0 °C and *tert*-butyl (2-bromo-5-methylpyridin-3-yl)carbamate **S4** (2 mmol, 0.57 g, 1.2 equiv) in a solution of dry TFF was added and allowed to stir at room temperature for 15 minutes. 3-bromo-2-methylprop-1-ene (2.4 mmol, 0.24 mL, 1.2 equiv) was added dropwise and the reaction was allowed to stir overnight at room temperature. The reaction was quenched with sat. NH_4Cl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was pushed through a silica plug (20% EtOAc/Hexanes as eluent) to afford the title compound as a white solid (0.633 g, 93% yield). Mixture of rotamers (*denotes major rotamer, #denotes minor rotamer).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H*,#), 7.36 (s, 1H#), 7.26 (s, 1H*), 4.86 (s, H*,#), 4.75 (s, 1H*,#), 4.54 (d, J = 15.3 Hz, 1H*,#), 3.58 (d, J = 15.6 Hz, 1H*,#), 2.30 (s, 3H*,#), 1.80 (s, 3H*,#), 1.52 (s, 9H#), 1.36 (s, 9H*).

^{13}C NMR (151 MHz, CDCl3) δ 154.51, 154.08, 148.80, 148.48, 141.19, 140.59, 139.84, 138.81, 138.18, 133.18, 113.63, 113.22, 81.53, 81.15, 56.01, 55.00, 28.40, 28.26, 20.50, 17.64.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{22}O_2N_2Br$, 341.08592; found 341.0862.

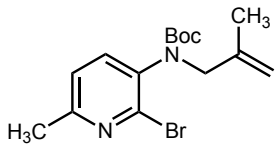


***tert*-butyl (2-bromo-6-methylpyridin-3-yl)carbamate (S4):** A 3-neck round bottom flask was equipped with a stirbar and 2-bromo-5-methylpyridin-3-amine (800 mg, 4.25 mmol, 1 equiv). The atmosphere was exchanged for nitrogen (3x) and dry THF (60 mL) was added. The reaction was cooled to 0 °C and 1.0 M LiHMDS was added (8.5 mL, 8.5 mmol, 2 equiv) dropwise. The solution stirred for 30 minutes followed by addition of di-*tert*-butyl dicarbonate (1.025 g, 4.7 mmol, 1.1 equiv). The reaction was warmed to room temperature and stirred overnight. The reaction was quenched with 0.1 M HCl, extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatography (0- 20% EtOAc/ hexanes as eluent) to afford the title compound as a white solid. (0.649 g, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 1H), 7.13 (dd, *J* = 7.9, 0.6 Hz, 1H), 2.57 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.66, 150.04, 142.07, 137.74, 133.57, 122.64, 83.50, 27.84, 23.87.

HRMS (APCI) m/z: [M+H] calcd. for $C_{11}H_{16}O_2N_2Br$, 287.03897; found, 287.03925.



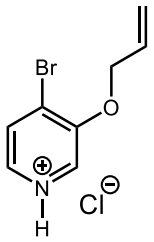
***tert*-butyl (2-bromo-6-methylpyridin-3-yl)(2-methylallyl)carbamate (10):** To a flame-dried round bottom flask equipped with a stir bar *tert*-butyl (2-bromo-6-methylpyridin-3-yl)carbamate **S5** (600 mg, 2.1 mmol, 1 equiv) and dry THF (10 mL) was added. The solution was cooled to 0 °C and NaH in 60% mineral oil dispersion (100 mg, 2.5 mmol, 1.2 equiv) was quickly added and stirred for 30 minutes at 0 °C. After 30 minutes, 3-bromo-2-methylprop-1-ene (260 µL, 2.5 mmol,

1.2 equiv) was added dropwise and stirred overnight. After full starting material consumption, the reaction was slowly quenched with 1 M NH_4Cl, extracted 3x with EtOAc, washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5-30% EtOAc/Hexanes as the eluent) to give the title compound as a thick yellow oil (298 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (broad s, 1H#), 7.33 (d, *J* = 7.8 Hz, 1H*), 7.08 (d, *J* = 7.8 Hz, 1H), 4.83 (s, 1H), 4.72 (s, 1H), 4.56 (d, *J* = 15.3 Hz, 1H*), 4.47 (d, *J* = 14.7 Hz, 1H#), 3.57 (d, *J* = 15.3 Hz, 1H), 2.54 (s, 3H), 1.79 (s, 3H), 1.53 (s, 9H#), 1.36 (s, 9H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.25, 157.96, 154.35, 154.07, 142.45, 140.99, 139.13, 138.26, 135.74, 122.44, 113.69, 113.29, 81.26, 80.88, 55.85, 54.74, 28.25, 28.12, 23.78, 20.32.

HRMS (APCI) m/z: [M+H] calcd. for $C_{15}H_{22}O_2N_2Br$, 341.08592; found, 341.08643.



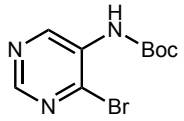
3-(allyloxy)-4-bromopyridin-1-ium chloride (11): A 50 mL round bottom flask equipped with a stirbar was added 4-bromopyridin-3-ol (4 mmol, 0.69 g, 1.0 equiv) and potassium carbonate (8 mmol, 1.1 g, 2.0 equiv) followed by DMF (15 mL). The mixture was allowed to stir at room temperature for 10 minutes before allyl bromide (4.8 mmol, 0.41 mL, 1.2 equiv) was added. The reaction was heated to 60 °C and allowed to stir for 3 hours. The reaction was cooled to room temperature and diluted in EtOAc. The crude mixture was washed with a solution of 1 M LiCl (2x), followed by a wash with brine (1x). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo.* The crude reaction was pushed through a silica plug (50% EtOAc/ hexanes

as the eluent) followed by protonation with 4 M HCl/dioxane (1 mL) to afford the title compound as a tan solid (0.58 g, 59% yield).

^{1}H NMR (500 MHz, D_2O) δ 8.40 (m, 1H), 8.23 (q, *J* = 0.7 Hz, 2H), 6.09 (ddt, *J* = 17.3, 10.6, 5.2 Hz, 1H), 5.53 – 5.45 (m, 1H), 5.40 (dq, *J* = 10.7, 1.3 Hz, 1H), 4.87 (dt, *J* = 5.3, 1.5 Hz, 2H).

^{13}C NMR (151 MHz, D_2O) δ 154.56, 134.64, 133.36, 131.46, 130.59, 126.85, 119.53, 71.44.

HRMS (APCI) *m/z*: [M+] calcd. for C_8H_9ONBr, 213.9862; found, 213.98644.

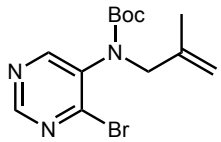


***tert*-butyl (4-bromopyrimidin-5-yl)carbamate (S5):** To a flame-dried round bottom flask equipped with a stir bar 4-bromopyrimidin-5-amine (398 mg, 2.3 mmol, 1 equiv) and dry THF (15 mL) was added. The solution was cooled to 0 °C and a 1 M solution of LiHMDS (6.9 mL, 6.9 mmol, 3 equiv) in hexanes was added slowly. The solution was stirred for 30 minutes at 0 °C and then a solution of di-*tert*-butyl dicarbonate (550 mg, 2.5 mmol, 1.1 equiv) in dry THF (8 mL) was added dropwise at 0 °C. Following di-*tert*-butyl dicarbonate addition, the temperature was elevated to room temperature and stirred overnight. After full starting material consumption, the reaction was slowly quenched with 1 M NH_4Cl, extracted with EtOAc (3x), washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica chromatography (10% EtOAc/Hexanes as the eluent) to give the title compound as a yellow oil (626 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (broad s, 1H), 8.60 (s, 1H), 6.89 (broad s, 1H), 1.55 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.83, 151.45, 146.68, 141.75, 133.60, 82.81, 28.16.

HRMS (APCI) m/z: [M+H] calcd. for $C_9H_{13}O_2N_3Br$, 274.01857; found 274.01856.

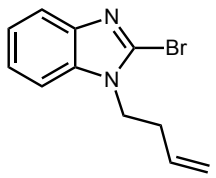


***tert*-butyl (4-bromopyrimidin-5-yl)(2-methylallyl)carbamate (12):** To a flame-dried round bottom flask equipped with a stir bar *tert*-butyl (2-bromo-6-methylpyridin-3-yl)carbamate **S7** (505 mg, 1.8 mmol, 1 equiv) and dry THF (20 mL) was added. The solution was cooled to 0 ºC and NaH in 60% mineral oil dispersion (90 mg, 2.2 mmol, 1.2 equiv) was quickly added and stirred for 30 minutes at 0 ºC. After 30 minutes, 3-bromo-2-methylprop-1-ene (240 µL, 2.2 mmol, 1.2 equiv) was added dropwise, stirred at room temperature, and monitored by TLC. After 6 hours, starting material consumption was low, so the reaction was heated to 50 ºC and stirred overnight. After full starting material consumption, the reaction was slowly quenched with 1 M NH_4Cl, extracted with EtOAc (3x), washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (10% EtOAc/Hexanes as the eluent) to give the title compound as a thick yellow oil (433 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.49 (broad s, 1H#), 8.41 (s, 1H*), 4.89 (s, 1H), 4.75 (s, 1H), 4.59 (d, *J* = 15.3 Hz, 1H), 3.66 (d, *J* = 15.2 Hz, 1H), 1.83 (s, 3H), 1.60 – 1.48 (broad s, 9H#), 1.38 (s, 9H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.04, 156.40, 153.85, 153.26, 140.30, 137.54, 114.87, 114.25, 81.95, 55.72, 54.55, 29.71, 28.04, 20.22.

HRMS (APCI) m/z: [M+H] calcd. for $C_{13}H_{19}O_2N_3Br$, 328.06552; found, 328.06595.



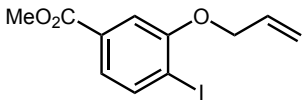
2-bromo-1-(but-3-en-1-yl)-1*H*-benzo[*d*]imidazole (13): To a flame-dried round bottom flask equipped with a stir bar 2-bromo-1*H*-benzo[*d*]imidazole (985 mg, 5 mmol, 1 equiv) and dry DMF (10 mL) was added. The solution was cooled to 0 ºC and NaH in 60% mineral oil dispersion (240

mg, 6 mmol, 1.2 equiv) was quickly added and stirred for 30 minutes at 0 ºC. After 30 minutes, 4-bromobut-1-ene (560 µL, 5.5 mmol, 1.2 equiv) was added dropwise, stirred at room temperature, and monitored by TLC. After 4 hours, the reaction was slowly quenched with water, extracted with EtOAc (3x), washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes as the eluent) to give the title compound as a yellow tinted oil (808 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 1H), 7.37 – 7.33 (m, 1H), 7.32 – 7.24 (m, 2H), 5.90 – 5.70 (m, 1H), 5.17 – 4.99 (m, 2H), 4.33 – 4.20 (t, *J* = 7.3 Hz, 2H), 2.59 (q, *J* = 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.21, 135.38, 133.29, 129.90, 123.10, 122.53, 119.48, 118.46, 109.53, 44.92, 33.68.

HRMS (APCI) m/z: [M+H] calcd. for $C_{11}H_{12}N_2Br$, 251.01784; found, 251.01795.



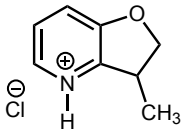
Methyl 4-iodo-3-(2-propen-1-yloxy)benzoate (14): A 100 mL round bottom flask equipped with a stirbar was added methyl 3-hydroxy-4-iodobenzoate (10 mmol, 2.78 g, 1.0 equiv) and potassium carbonate (20 mmol, 2.76 g, 2.0 equiv) followed by DMF (10 mL). The mixture was stirred at room temperature for 15 minutes before allyl bromide (5.5 mmol, 0.470 mL, 1.1 equiv) was added. The reaction was heated to 40 ºC and stirred for 3 hours. The reaction was cooled to room temperature and diluted in EtOAc. The crude mixture was washed with a solution of LiCl (2x), followed by a wash with brine (1x). The organic layer was dried over sodium sulfate and concentrated *in vacuous*. The crude reaction was recrystallized from hot hexanes (~10 mL) to afford the title compound as a white, crystalline solid (2.307 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) d 7.87 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.40-7.35 (m, 1H), 6.08 (m, 1H), 5.55 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.34 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.67 (dt, *J* = 4.9, 1.7 Hz, 2H), 3.92 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) d 166.59, 157.18, 139.58, 132.08, 131.50, 123.45, 118.00, 112.54, 93.30, 69.79, 52.40.

HRMS (APCI) m/z: [M+H] calcd. for $C_{11}H_{11}O_3I$, 318.98256; found 318.98246.

3.5.5 Preparation of Products from Substrate Table

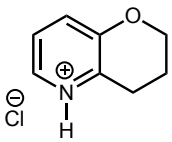


3-methyl-2,3-dihydrofuro[3,2-b]pyridin-4-ium chloride (1a): Prepared according to general procedure B using 3-(allyloxy)-2-bromopyridine **1** (0.5 mmol, 0.107 g, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19 : 1.0 *exo*/*endo*). The reaction was purified by silica chromatography (0- 30% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a yellow amorphous solid (0.0647 g, 76% yield).

^{1}H NMR (600 MHz, D_2O) δ 8.11 (dd, *J* = 5.8, 1.0 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.68 – 7.62 (m, 1H), 4.99 (t, *J* = 9.3 Hz, 1H), 4.46 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.99 (h, *J* = 8.0, 7.6 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, D_2O) δ 157.46, 150.31, 132.71, 126.21, 124.74, 79.61, 35.23, 16.59.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_8H_{10}ON$, 136.07569; found 136.07579.

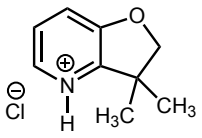


3,4-dihydro-2H-pyrano[3,2-b]pyridin-5-ium chloride (**1b**): Prepared according to general procedure A using 3-(allyloxy)-2-bromopyridine **1** (0.5 mmol, 0.107 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1 : 4.8 *exo*/*endo*). The reaction was purified by silica chromatography (0- 30% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a white amorphous solid (0.0486 g, 57% yield).

^{1}H NMR (600 MHz, D_2O) δ 8.17 (dt, *J* = 5.7, 1.3 Hz, 1H), 7.86 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.67 (dd, *J* = 8.7, 5.7 Hz, 1H), 4.37 – 4.32 (m, 2H), 3.12 (t, *J* = 6.5 Hz, 2H), 2.19 – 2.12 (m, 2H).

^{13}C NMR (101 MHz, D_2O) δ 153.75, 139.86, 132.95, 132.86, 125.27, 67.33, 22.88, 19.29.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_8H_{10}ON$, 136.07569; found 136.07581.



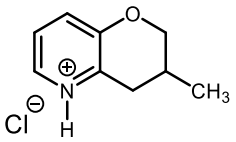
3,3-dimethyl-2,3-dihydrofuro[3,2-b]pyridin-4-ium chloride (2a): Prepared according to general procedure B using 2-bromo-3-((2-methylallyl)oxy)pyridine **2** (0.5 mmol, 0.114 g, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19 :1 *exo*/*endo*).

The reaction was purified by silica chromatography (10- 30% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a yellow amorphous solid (0.0893 g, 97% yield).

^{1}H NMR (500 MHz, D_2O) δ 8.14 (d, *J* = 5.8 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.65 (m, 1H), 4.60 (s, 2H), 1.51 (s, 6H).

^{13}C NMR (151 MHz, D_2O) δ 156.81, 152.76, 132.96, 126.32, 125.47, 85.22, 41.63, 24.53.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_9H_{12}ON$, 150.09134; found 150.09144.



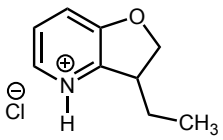
3-methyl-3,4-dihydro-2H-pyrano[3,2-b]pyridin-5-ium chloride (2b): Prepared according to general procedure A using 2-bromo-3-((2-methylallyl)oxy)pyridine **2** (0.5 mmol, 0.114 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1 : >19 *exo*/*endo*). The reaction was purified by silica chromatography (10- 50% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a yellow amorphous solid (0.0728 g, 79% yield).

^{1}H NMR (500 MHz, D_2O) δ 8.18 (dd, *J* = 5.6, 1.3 Hz, 1H), 7.84 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.66 (dd, *J* = 8.7, 5.6 Hz, 1H), 4.37 (ddd, *J* = 11.0, 3.5, 1.8 Hz, 1H), 3.93 (dd, *J* = 11.1, 9.1 Hz, 1H),

3.20 (ddd, *J* = 17.8, 5.4, 1.8 Hz, 1H), 2.78 (dd, *J* = 17.7, 9.2 Hz, 1H), 2.45 – 2.22 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, D_2O) δ 153.19, 139.89, 133.72, 132.18, 125.22, 72.20, 30.71, 24.95, 15.33.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_9H_{12}ON$, 150.09134; found 150.09142.

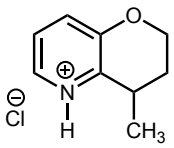


3-ethyl-2,3-dihydrofuro[3,2-b]pyridin-4-ium chloride (3a): Prepared according to general procedure B using (E)-2-bromo-3-(but-2-en-1-yloxy)pyridine **3** (0.5 mmol, 0.113 g, 1.0 equiv.), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19 :1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 30% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 , 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a tan wax (0.0878 g, 95% yield).

^{1}H NMR (500 MHz, D_2O) δ 8.13 (dp, *J* = 5.5, 1.2 Hz, 1H), 7.81 – 7.71 (m, 1H), 7.69 (dd, *J* = 8.5, 5.7 Hz, 1H), 4.95 (t, *J* = 9.3 Hz, 1H), 4.65 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.91 (tt, *J* = 10.5, 5.3 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.87 – 1.75 (m, 1H), 0.96 – 0.84 (m, 3H).

^{13}C NMR (151 MHz, D_2O) δ 157.96, 148.95, 132.45, 126.43, 125.04, 77.75, 41.43, 25.30, 9.62.

HRMS (APCI) *m/z*: [M+] calcd. for $C_9H_{12}ON$, 150.09134; found 150.09143.

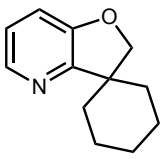


4-methyl-3,4-dihydro-2H-pyrano[3,2-b]pyridin-5-ium chloride (3b): Prepared according to general procedure A using (E)-2-bromo-3-(but-2-en-1-yloxy)pyridine **3** (0.5 mmol, 0.113 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^1H NMR to give the ratio (1 : 12.5 *exo*/*endo*). The reaction was purified by silica chromatography (0- 30% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a yellow amorphous solid (0.0721 g, 78% yield).

^{1}H NMR (500 MHz, D_2O) δ 8.20 (d, *J* = 5.6 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.70 (dd, *J* = 8.6, 5.7 Hz, 1H), 4.38 (m, 2H), 3.37 (h, *J* = 6.7 Hz, 1H), 2.32 – 2.20 (m, 1H), 1.94 (dtd, *J* = 14.1, 5.2, 3.1 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, D_2O) δ 153.38, 143.45, 133.41, 133.35, 125.39, 64.60, 27.69, 26.84, 19.07.

HRMS (APCI) *m/z*: [M+] calcd. for $C_9H_{12}ON$, 150.09134; found 150.09146.



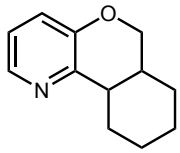
2'*H*-spiro[cyclohexane-1,3'-furo[3,2-*b*]pyridine] (4a): Prepared according to general procedure B using 2-bromo-3-(cyclohex-1-en-1-ylmethoxy)pyridine **4** (0.5 mmol, 0.134 g, 1.0 equiv.), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL).

After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19 : 1 *exo*/*endo*). The reaction was purified by silica gel chromatography (5-20% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (0.065 g, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 4.3, 1.9 Hz, 1H), 7.10 – 6.92 (m, 2H), 4.45 (s, 3H), 1.91 – 1.78 (m, 4H), 1.69 (ddd, *J* = 10.4, 3.1, 1.5 Hz, 3H), 1.44 – 1.23 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.22, 153.04, 141.58, 122.30, 115.85, 81.26, 45.62, 34.95, 25.24, 23.02.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{12}H_{16}ON$, 190.12264; found 190.12278.

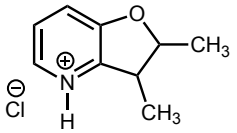


6a,7,8,9,10,10a-hexahydro-6*H*-isochromeno[4,3-*b*]pyridine (4b): Prepared with an adaptation to general procedure A using 2-bromo-3-(cyclohex-1-en-1-ylmethoxy)pyridine **4** (0.5 mmol, 0.134 g, 1.0 equiv.), Hantzsch Ester (0.75 mmol , 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.004 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours MeCN was removed *in vacuo* and the crude sample was reconstituted in 1:1 THF:H_2O (12 mL). LiOH (110 mg, 4.5 mmol, 9 equiv.) was added and the solution was heated to reflux at 80 ^{o}C. After 6 hours the reaction was worked up as outlined in general procedure A and the crude sample was analyzed by ^{1}H NMR to give the ratio (1 :1 1.7 *exo*/*endo)*. The reaction was purified by silica gel chromatography (0-5% EtOAc/benzene as the eluent) to afford the title compound as a yellow oil (0.025 g, 26%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 4.5, 1.6 Hz, 1H), 7.08 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.04 (dd, *J* = 8.2, 4.5 Hz, 1H), 4.22 (dd, *J* = 10.7, 7.5 Hz, 1H), 4.12 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.06 (dt, *J* = 7.9, 4.9 Hz, 1H), 2.26 (m, 1H), 1.90 (m, 1H), 1.79 – 1.69 (m, 1H), 1.68 – 1.54 (m, 1H), 1.55 – 1.34 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.80, 146.74, 141.38, 123.40, 122.28, 68.54, 38.20, 32.61, 28.73, 25.99, 23.60, 23.44.

HRMS (APCI) *m/z*: [M+H] calcd. For $C_{12}H_{16}ON$, 190.12264; found 190.12282

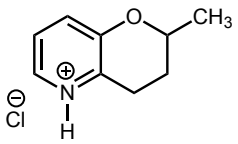


2,3-dimethyl-2,3-dihydrofuro[3,2-b]pyridin-4-ium chloride (5a): Prepared according to general procedure B using 2-bromo-3-(but-3-en-2-yloxy)pyridine **5** (0.5 mmol, 0.16 g, 1.0 equiv.), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 30% EtOAC/hexanes as the eluent) to afford the title compound as an off white amorphous solid (0.115 g, 88% yield). Mixture of diastereomers (4.0: 1.0 dr, *denotes major diastereomer, # denotes minor diastereomer).

^{1}H NMR (600 MHz, MeOD) δ 8.25 (dp, *J* = 5.8, 1.2 Hz, 1H*,#), 7.86 (ddd, *J* = 8.4, 3.0, 1.1 Hz, 1H*,#), 7.79 (ddt, *J* = 8.1, 6.7, 5.1 Hz, 1H*,#), 5.31 (dqd, *J* = 8.4, 6.6, 1.6 Hz, 1H#), 4.83 (dqd, *J* = 7.9, 6.3, 1.6 Hz, 1H*), 3.97 (ddt, *J* = 11.6, 7.8, 4.1 Hz, 1H#), 3.67 – 3.58 (m, 1H*), 1.59 (d, *J* = 6.4 Hz, 3H*), 1.54 (d, *J* = 8.6 Hz, 1H*), 1.51 (d, *J* = 6.6 Hz, 1H#), 1.40 (dd, *J* = 7.4, 1.3 Hz, 1H#).

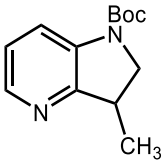
^{13}C NMR (151 MHz, MeOD) δ 159.10, 158.76, 151.34, 133.47, 128.03, 128.00, 126.35, 126.33, 91.04, 86.72, 43.87, 39.60, 20.17, 16.42, 15.34, 13.13.

HRMS (APCI) *m/z*: [M+] calcd. for $C_9H_{12}ON$ 150.09134; found 150.09137.



2-methyl-3,4-dihydro-2H-pyrano[3,2-b]pyridin-5-ium chloride (5b): Prepared according to general procedure A using 2-bromo-3-(but-3-en-2-yloxy)pyridine **5** (0.5 mmol, 0.113 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: 5.9 *exo*/*endo*). The reaction was purified by silica chromatography (10- 50% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a yellow amorphous solid (0.0756 g, 82% yield). **^{1}H NMR (600 MHz, D_2O)** δ 8.14 (d, *J* = 5.7 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, *J* = 8.7, 5.4 Hz, 1H), 4.39 (m, 1H), 3.26 – 2.94 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.41 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, D_2O) δ 153.39, 140.31, 133.94, 131.86, 125.05, 74.53, 26.17, 23.22, 19.60. **HRMS** (APCI) *m/z*: [M+H] calcd. for $C_9H_{12}ON$, 150.09134; found 150.09146.

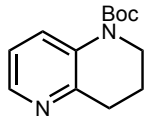


***tert*-butyl 3-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (6a)**: Prepared according to general procedure B using *tert*-butyl allyl(2-bromopyridin-3-yl)carbamate **6** (0.5 mmol, 0.16 g, 1.0 equiv.), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1

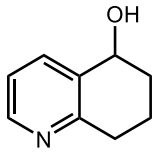
mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (0- 30% EtOAC/hexanes as the eluent) to afford the title compound as an off white amorphous solid (0.115 g, 98% yield). Mixture of rotamers (*denotes major rotamer # denotes minor isomer). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 5.0, 1.4 Hz, 1H*,#), 8.00 (br s, 1H*), 7.59 (br s, 1H#), 7.07 – 7.02 (m, 1H*,#), 4.17 (br s, 1H*,#), 3.53 (br s, 1H*,#), 3.43 (dt, *J* = 9.5, 6.8 Hz, 1H*,#), 1.67 (br s, 9H#), 1.55 (br s, 9H#), 1.41 (d, *J* = 7.0 Hz, 3H*,#).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.98, 152.79, 142.99, 136.83, 122.11, 121.01, 82.18, 81.24, 54.37, 53.95, 35.74, 35.23, 28.54, 18.99.

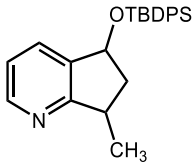
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{19}O_2N_2$, 235.1441; found, 235.14433.



***tert*-butyl 3,4-dihydro-1,5-naphthyridine-1(2*H*)-carboxylate (6b):** Prepared according to general procedure A using *tert*-butyl (4-bromopyrimidin-5-yl)(2-methylallyl)carbamate **6** (0.5 mmol, 0.156 g, 1.0 equiv.), Hantzsch Ester (0.75 mmol , 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.004 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours crude sample was analyzed by ^{1}H NMR to give the ratio (1.0: 3.4 *exo*/*endo)*. The reaction was purified by silica gel chromatography (20% EtOAc/hexanes as the eluent) to afford the title compound as a white solid (0.093 g, 78%). The physical properties and spectral data were consistent with previously reported data.[4]



5,6,7,8-tetrahydroquinolin-5-ol (7b): Prepared according to general procedure A using 1-(2-bromopyridin-3-yl)but-3-en-1-ol **7** (0.25 mmol, 0.055 g, 1.0 equiv), Hantzsch Ester (0.38 mmol, 0.095 g, 1.5 equiv), 3DPAFIPN (0.0025 mmol, 0.0016 g, 1 mol%) in 50% H_2O/MeCN (7.5 mL). After 16 hours the crude sample was analyzed by ^1H NMR to give the ratio (1: 1.7 *exo*/*endo*). The reaction was purified by silica chromatography (10- 100% EtOAC/hexanes as the eluent) to afford the title compound as a yellow oil (0.020 g, 53% yield). The physical properties and spectral data were consistent with the reported values.[5]



5-((*tert*-butyldiphenylsilyl)oxy)-7-methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (S6):

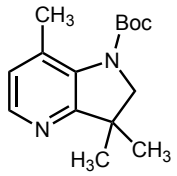
Prepared according to general procedure B using 1-(2-bromopyridin-3-yl)but-3-en-1-ol **7** (0.25 mmol, 0.055 g, 1.0 equiv.), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.0082 g, 20 mol%), formic acid (1.25 mmol, 49 µL, 5.0 equiv) and 4CzIPN (0.0025 mmol, 0.0019 g, 1 mol%) in DMSO (5 mL). After 16 hours the crude sample was analyzed by ^1H NMR to give the ratio and yield of **7a** (69%, >19: 1 *exo*/*endo*). The crude reaction mixture was dissolved in CH_2Cl_2 (2 mL) in a 10 mL RBF. *tert*-Butyl(chloro)diphenylsilane (0.375 mmol, 98 uL, 1.5 equiv) and imidazole (0.50 mmol, 0.039 g, 2.0 equiv) was added to the flask. After 16 hours, the reaction was quenched with H_2O (5 mL), extracted with CH_2Cl_2 (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was purified by silica chromatography (5- 20% EtOAC/hexanes as the

eluent) to afford the title compound as a clear oil (0.020 g, 21% yield). Mixture of diastereomers (1.0: 1.5 dr, *denotes major diastereomer, # denotes minor diastereomer).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (ddd, J = 5.1, 2.7, 1.3 Hz, 1H*,#), 7.79 – 7.64 (m, 4H*,#), 7.50 – 7.35 (m, 7H*,#), 7.22 (ddd, J = 7.6, 1.6, 0.7 Hz, 1H#), 7.08 (ddd, J = 7.6, 5.0, 0.9 Hz, 1H*), 7.02 (ddd, J = 7.6, 5.0, 0.7 Hz, 1H#), 5.32 (dd, J = 6.5, 4.0 Hz, 1H#), 5.20 (t, *J* = 7.3 Hz, 1H*), 3.49 (td, J = 7.5, 5.9 Hz, 1H*), 3.00 – 2.93 (m, 1H#), 2.48 (dt, J = 12.4, 7.2 Hz, 1H#), 2.36 (ddd, J = 13.2, 7.9, 4.0 Hz, 1H*), 1.83 (ddd, J = 13.2, 6.6, 5.8 Hz, 1H#), 1.73 – 1.65 (m, 1H*), 1.42 (d, J = 6.9 Hz, 1H*), 1.26 (d, J = 7.1 Hz, 1H#), 1.12 (s, 9H*), 1.07 (s, 9H#).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.78, 166.09, 148.95, 148.75, 138.93, 138.07, 136.07 – 135.93 (m), 134.05 (dd, *J* = 8.7, 5.9 Hz), 133.52, 132.68, 130.01 (d, *J* = 2.9 Hz), 129.96 (d, *J* = 4.1 Hz), 127.93, 127.85 (d, *J* = 3.1 Hz), 74.06, 44.40, 43.51, 37.97, 37.76, 27.12, 27.06, 19.35, 19.11.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{25}H_{30}ONSi$, 388.20912; found 388.20958.



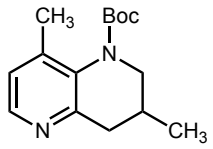
***tert*-butyl 3,3,7-trimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (8a):**

Prepared according to general procedure B using *tert*-butyl (2-bromo-4-methylpyridin-3-yl)(2-methylallyl)carbamate **8** (0.5 mmol, 0.171 g, 1.0 equiv.), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 30% EtOAC/hexanes as the eluent) to afford the title compound as a white amorphous solid (0.115 g, 98% yield). Mixture of rotamers (*denotes major rotamer # denotes minor isomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.1 Hz, 1H), 6.91 (d, *J* = 5.1 Hz, 1H), 3.82 (s, 2H), 2.33 (s, 3H), 1.53 (s, 9H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.24, 154.10, 144.85, 136.20, 135.54, 124.46, 81.21, 63.68, 41.44, 28.29, 25.12, 19.71.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; found 263.17574.

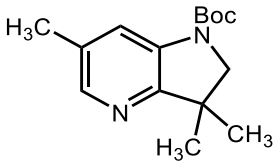


***tert*-butyl 3,8-dimethyl-3,4-dihydro-1,5-naphthyridine-1(2*H*)-carboxylate (8b):** Prepared according to general procedure A *tert*-butyl (2-bromo-4-methylpyridin-3-yl)(2-methylallyl)carbamate **8** (0.5 mmol, 0.171 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: >19 *exo*/*endo*). The reaction was purified by silica chromatography (10-30% EtOAC/hexanes as the eluent) to afford the title compound as a yellow solid (0.096 g, 78% yield). Mixture of rotamers (*denotes major rotamer # denotes minor isomer). *^{1}H NMR was taken at 100 ^{o}C to coalesce rotational isomers.*

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.11 (d, *J* = 4.9 Hz, 1H), 7.01 (d, *J* = 4.9, 1H), 3.79 (broad s, 1H), 3.11 (broad s, 1H), 2.98 (dd, *J* = 17.0, 6.6 Hz, 1H), 2.43 (dd, *J* = 17.0, 8.6 Hz, 1H), 2.15 (s, 3H), 2.13 (m, 1H), 1.42 (s, 9H), 1.02 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.83, 164.23, 153.87, 151.37, 145.22, 143.28, 135.10, 123.44, 81.02, 51.39, 38.45, 29.70, 29.44, 28.21, 28.08, 21.25, 19.38, 18.41.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; 263.17567.



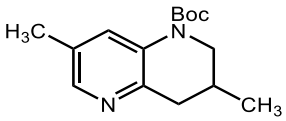
***tert*-butyl 3,3,6-trimethyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (9a):**

Prepared according to general procedure B using *tert*-butyl (2-bromo-5-methylpyridin-3-yl)(2-methylallyl)carbamate **9** (0.5 mmol, 0.171 g, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (0- 30% EtOAC/hexanes as the eluent) to afford the title compound as a yellow oil (0.121 g, 93% yield). Mixture of rotamers (*denotes major rotamer # denotes minor rotamer).

^{1}H NMR (500 MHz, CDCl3) δ 7.95 (s, 1H*,#), 7.88 (s, 1H*), 7.43 (s, 1H#), 3.72 (s, 2H*,#), 2.29 (s, 3H*,#), 1.67 (s, 9H*,#), 1.36 (s, 6H*,#).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.54, 152.96, 143.37, 136.02, 131.98, 122.14, 81.24, 61.67, 40.00, 28.54, 27.33, 18.69.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; found 263.17552.



***tert*-butyl 3,7-dimethyl-3,4-dihydro-1,5-naphthyridine-1(2H)-carboxylate (9b):**

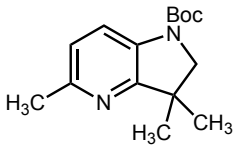
Prepared according to general procedure A using *tert*-butyl (2-bromo-5-methylpyridin-3-yl)(2-methylallyl)carbamate **9** (0.5 mmol, 0.171 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: >19 *exo*/*endo*). The reaction was

purified by silica chromatography (5- 30% EtOAC/hexanes as the eluent) to afford the title compound as a yellow solid (0.096 g, 83% yield).

^{1}H NMR (500 MHz, CDCl3) δ 8.04 (s, 1H), 7.92 (s, 1H), 3.94 (ddt, J = 12.6, 4.0, 1.3 Hz, 1H), 3.13 (dd, J = 12.7, 9.7 Hz, 1H), 3.03 (dd, J = 17.0, 5.6 Hz, 1H), 2.54 (dd, J = 17.0, 9.4 Hz, 1H), 2.29 (s, 3H), 2.10 (m, 1H), 1.53 (s, 9H), 1.08 (d, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, CDCl3) δ 153.87, 146.03, 144.46, 134.49, 131.15, 130.51, 81.43, 50.88, 38.83, 28.47, 18.80, 18.30.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; found 263.17556.



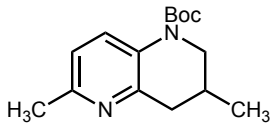
***tert*-butyl 3,3,5-trimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (10a):**

Prepared according to general procedure B using *tert*-butyl (2-bromo-6-methylpyridin-3-yl)(2-methylallyl)carbamate **10** (0.25 mmol, 0.085 g, 1.0 equiv), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.008 g, 20 mol%), formic acid (1.25 mmol, 47 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (5 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (5% EtOAC/hexanes as the eluent) to afford the title compound as an off-white solid (0.058 g, 88% yield). Mixture of rotamers (*denotes major rotamer # denotes minor rotamer). *^{1}H NMR was taken at -10 °C to partially resolve rotamers*.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 1H*), 7.49 (d, *J* = 8.2 Hz, 1H#), 6.92 (d, *J* = 8.2 Hz, 1H*), 6.89 (d, *J* = 8.3 Hz, 1H#), 3.73 (s, 1H#), 3.69 (s, 1H*), 2.49 (s, 3H), 1.59 (s, 9H#), 1.53 (s, 9H*), 1.36 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.08, 152.73, 151.58, 133.33, 121.51, 121.09, 81.12, 61.30, 40.11, 28.42, 27.05, 23.49.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; found, 263.17575.



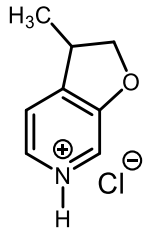
***tert*-butyl 3,6-dimethyl-3,4-dihydro-1,5-naphthyridine-1(2*H*)-carboxylate (10b):**

Prepared according to general procedure A using *tert*-butyl (2-bromo-6-methylpyridin-3-yl)(2-methylallyl)carbamate **10** (0.25 mmol, 0.085g, 1.0 equiv.), Hantzsch Ester (0.38 mmol , 0.095 g, 1.5 equiv), 3DPAFIPN (0.003 mmol, 0.002 g, 1 mol%) in 50% H_2O/MeCN (7.5 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: >19 *exo*/*endo)*. The reaction was purified by silica gel chromatography (20% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (0.045 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 6.92 (dd, *J* = 8.5, 0.8 Hz, 1H), 3.94 (dd, *J* = 12.6, 3.9, 1H), 3.12 (dd, *J* = 12.7, 9.6 Hz, 1H), 3.03 (dd, *J* = 17.1, 5.7, 1H), 2.56 (dd, *J* = 17.1, 9.4 Hz, 1H), 2.46 (s, 3H), 2.17 – 2.04 (m, 1H), 1.51 (s, 9H), 1.07 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.76, 152.39, 147.96, 132.26, 131.14, 120.42, 81.20, 50.56, 39.12, 28.42, 28.35, 23.74, 18.67.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{15}H_{23}O_2N_2$, 263.1754; found, 263.1758.



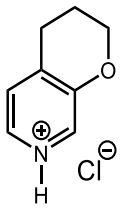
3-methyl-2,3-dihydrofuro[2,3-c]pyridin-6-ium chloride (11a): Prepared according to general procedure B using 3-(allyloxy)-4-bromopyridin-1-ium chloride **11** (0.15 mmol, 0.037 g, 1.0

equiv), sodium formate (0.75 mmol, 0.051 g, 5.0 equiv), mesna (0.03 mmol, 0.0049 g, 20 mol%), formic acid (0.75 mmol, 28 μL, 5.0 equiv) and 4CzIPN (0.0015 mmol, 0.0012 g, 1 mol%) in DMSO (3 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (>19: 1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 60% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M HCl/ dioxane (0.15 mmol, 0.04 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a white solid (0.0158 g, 62% yield).

^{1}H NMR (600 MHz, MeOD) δ 8.39 (dd, *J* = 5.7, 2.7 Hz, 1H), 8.35 (d, *J* = 2.6 Hz, 1H), 7.96 (dd, *J* = 5.9, 2.6 Hz, 1H), 5.04 (t, *J* = 9.2 Hz, 1H), 4.46 (ddd, *J* = 8.9, 7.3, 2.8 Hz, 1H), 3.94 (dq, *J* = 9.6, 7.2 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, MeOD) δ 160.83, 155.69, 136.63, 124.04, 123.91, 82.07, 38.15, 18.39.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_8H_{10}ON$, 136.07569; found 136.07584.



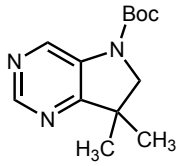
3,4-dihydro-2H-pyrano[2,3-c]pyridin-7-ium chloride (11b): Prepared according to general procedure A using 3-(allyloxy)-4-bromopyridin-1-ium chloride **11** (0.5 mmol, 0.124 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.039 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: 4.4 *exo*/*endo*). The reaction was purified by silica chromatography (0- 50% EtOAC/hexanes as the eluent, note: *the column was loaded directly with combined hexane layers from workup because the compound is volatile*), the combined fractions were protonated with 4 M

HCl/ dioxane (0.5 mmol, 0.138 mL, 1.0 equiv) and concentrated *in vacuo* to afford the title compound as a white amorphous solid (0.0217 g, 28% yield).

^{1}H NMR (600 MHz, D_2O) δ 8.19 (s, 1H), 8.11 (d, *J* = 5.8 Hz, 1H), 7.68 (d, *J* = 5.8 Hz, 1H), 4.38 – 4.35 (m, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 2.09 – 2.05 (m, 2H).

^{13}C NMR (151 MHz, D_2O) δ 154.20, 144.44, 131.94, 129.81, 127.65, 67.80, 24.64, 19.69.

HRMS (APCI) *m/z*: [M+] calcd. for $C_8H_{10}ON$, 136.07569; found 136.07588.



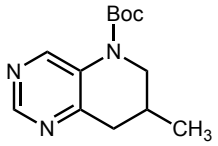
***tert*-butyl 7,7-dimethyl-6,7-dihydro-5*H*-pyrrolo[3,2-*d*]pyrimidine-5-carboxylate (12a):**

Prepared according to general procedure B using *tert*-butyl (4-bromopyrimidin-5-yl)(2-methylallyl)carbamate **12** (0.25 mmol, 82 mg, 1.0 equiv.), sodium formate (1.25 mmol, 0.085 g, 5.0 equiv), mesna (0.05 mmol, 0.008 g, 20 mol%), formic acid (1.25 mmol, 47 µL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (5 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1.9: 1 *exo*/*endo*). The reaction was purified by silica chromatography (20% EtOAC/hexanes as the eluent) to afford the title compound as a yellow oil (0.039 g, 63% yield). Mixture of rotamers (*denotes major rotamer # denotes minor rotamer).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (broad s, 1H*), 8.77 (s, 1H), 8.60 (broad s, 1H#), 3.74 (broad s, 3H), 1.59 (s, 9H*), 1.56 (s, 9H#), 1.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.69, 167.97, 152.83, 152.20, 140.65, 134.88, 133.91, 83.05, 81.94, 60.47, 59.81, 40.92, 40.21, 29.70, 28.33, 26.59.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{20}O_2N_3$; 250.15500; found, 250.15522.



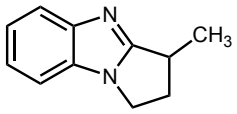
***tert*-butyl 7-methyl-7,8-dihydropyrido[3,2-*d*]pyrimidine-5(6*H*)-carboxylate (12b):**

Prepared according to general procedure A using *tert*-butyl (4-bromopyrimidin-5-yl)(2-methylallyl)carbamate) **12** (0.25 mmol, 0.082g, 1.0 equiv.), Hantzsch Ester (0.38 mmol , 0.095 g, 1.5 equiv), 3DPAFIPN (0.003 mmol, 0.002 g, 1 mol%) in 50% H_2O/MeCN (7.5 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (1: >19 *exo*/*endo)*. The reaction was purified by silica gel chromatography (30-50% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (0.047 g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (broad s, 1H), 8.76 (s, 1H), 4.02 (dd, *J* = 12.9, 3.8 Hz, 1H), 3.15 (dd, *J* = 12.9, 9.8 Hz, 1H), 3.03 (dd, *J* = 17.9, 5.5 Hz, 1H), 2.55 (dd, *J* = 17.9, 9.6 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.54 (s, 9H), 1.11 (d, *J* = 6.7 Hz, 3H).

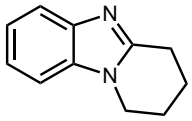
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.89, 152.95, 152.31, 150.58, 133.85, 82.43, 77.25, 50.23, 38.43, 28.28, 27.41, 18.51.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{20}O_2N_3$, 250.15500; found, 250.15529.



3-methyl-2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole (13a): Prepared according to general procedure B using 2-bromo-1-(but-3-en-1-yl)-1H-benzo[d]imidazole **13** (0.5 mmol, 0.126 g, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 μL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (5.5 : 1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 50% EtOAC/hexanes with 5%

TEA as the eluent) to afford the title compound as a clear oil (0.067 g, 78% yield). The physical properties and spectral data were consistent with the reported values.[6]

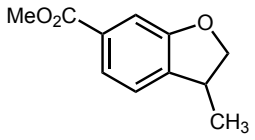


1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (13b): Prepared according to general procedure A using 2-bromo-1-(but-3-en-1-yl)-1H-benzo[d]imidazole **13** (0.5 mmol, 0.126 g, 1.0 equiv), Hantzsch Ester (0.75 mmol, 0.189 g, 1.5 equiv), 3DPAFIPN (0.005 mmol, 0.032 g, 1 mol%) in 50% H_2O/MeCN (15 mL). After 16 hours the crude sample was analyzed by ^1H NMR to give the ratio (1 :1.1 *exo*/*endo*). The reaction was purified by silica chromatography (10- 100% EtOAC/hexanes with 5% TEA as the eluent) to afford the title compound as a yellow solid (0.038 g, 45% yield). The physical properties and spectral data were consistent with the reported values.[7]

3.5.6 Hantzsch ester solubility experiment

Adapted from previously reported procedure from Aycock et al.[8] A 1,000 μL aliquot of % MeCN in DMSO (0%, 5%, 20%, 50%, 80%) or % H_2O in MeCN (0%, 30%, 50%) was delivered to a 4 mL screw-top dram vial. The solution was saturated with excess Hantzsch ester (200 mg, 0.79 mmol). The solution was drawn into a syringe through a syringe filter. The filter was removed and the solution was delivered to a fresh vial. The Hantzsch ester was oxidized to the pyridine by sparging with air for 2 hours. Following sparging, the sample was concentrated *in vacuo*. Dibromomethane (7 μL, 0.1 mmol) was added to the concentrated and the sample was analyzed by ^1H NMR where the integral values were used to calculate the concentration of Hantzsch ester dissolved in solution.

3.5.7 Investigation of Non-Heteroaryl Substrates

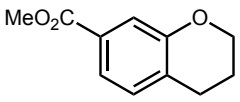


Methyl 2,3-dihydro-3-methyl-6-benzofurancarboxylate (14a): Prepared according to general procedure B using methyl 4-iodo-3-(2-propen-1-yloxy)benzoate (**14**) (0.159 g, 0.5 mmol, 1.0 equiv), sodium formate (2.5 mmol, 0.17 g, 5.0 equiv), mesna (0.1 mmol, 0.016 g, 20 mol%), formic acid (2.5 mmol, 94 μL, 5.0 equiv) and 4CzIPN (0.005 mmol, 0.0039 g, 1 mol%) in DMSO (10 mL). After 16 hours the crude sample was analyzed by ^{1}H NMR to give the ratio (16.7 : 1 *exo*/*endo*). The reaction was purified by silica chromatography (0-20% EtOAC/hexanes as the eluent) to afford the title compound as a clear oil (0.095 g, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.40 (s, 1H), 7.19 (ddd, *J* = 7.7, 1.2, 0.5 Hz, 1H), 5.01 – 4.46 (m, 1H), 4.12 (dd, *J* = 8.7, 7.5 Hz, 1H), 3.89 (s, 3H), 3.62 – 3.50 (m, 1H), 1.34 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.14, 160.02, 138.01, 130.47, 123.64, 122.71, 110.42, 78.94, 52.24, 36.63, 19.21.

HRMS (APCI) m/z: [M+H] calcd. for C11H13O3, 193.08592; found, 193.08604.



Methyl 3,4-dihydro-2*H*-1-benzopyran-7-carboxylate (14b): Subjecting methyl 4-iodo-3-(2-propen-1-yloxy)benzoate (**S6**) (0.032 g, 0.1 mmol, 1.0 equiv) to optimization procedure A with 3DPAFIPN (0.001 g, 0.01 mmol, 1 mol%) Hantzsch ester (0.038 g, 0.15 mmol, 1.5 equiv) in 50%

MeCN/H_2O (3 mL). After 16 hours the crude sample was analyzed by NMR. Analysis of the ^1H NMR revealed 103% return of starting material with no cyclization products **S7** or **S8** observed.

3.5.8 Supporting Information References

1. Luo, J.; Zhang, J. "Donor-Acceptor Fluorophores for Visible-Light Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic C(sp^3)-C(sp^2) Cross-Coupling." *ACS Cat.* **2016**, 6, 873-877.

2. Fantasia, S.; Windisch, J.; Scalone, "Ligandless Copper-Catalyzed Coupling of Heteroaryl Bromides with Gaseous Ammonia." *M. Adv. Synth.* **2013**, 355, 627-631.

3. Plamthottam, S.; Sun, D.; Van Valkenburgh, J.; Valenzuela, J.; Ruehle, B.; Steele, D.; Poddar, S.; Marshalik, M.; Hernandez, S.; Radu, C. G.; Zink, J. I., J. "Activity and Electrochemical Properties: Iron Complexes of the Anticancer Drug Triapine and its Analogs." *Biol. Inorg. Chem.* **2019**, 24, 621-632.

4. Sotnik, S. O.; Subota, A. I.; Kliuchynskyi, A. Y.; Yehorov, D. V.; Lytvynenko, A. S.; Rozhenko, A. B.; Kolotilov, S. V.; Ryabukhin, S. V.; Volochnyuk, D. M. "Cu-Catalyzed Pyridine Synthesis via Oxidative Annulation of Cyclic Ketones with Propargylamine." *J. Org. Chem.* **2021**, 86, 7315-7325.

5. Rodriguez, S.; Qu, B.; Fandrick, K. R.; Buono, F.; Haddad, N.; Xu, Y.; Herbage, M. A.; Zeng, X.; Ma, S.; Grinberg, N.; Lee, H.; Han, Z. S.; Yee, N. K.; Senanayake C. H. "Amine-Tunable Ruthenium Catalysts for Aysymmetric Reduction of Ketones." *Adv. Synth. Catal.* 2014, 356, 301-307.

6. Lou, S.-J.; Mo, Z.; Nishiura, M.; Hou, Z. "Construction of All-Carbon Quaternary Stereocenters by Scandium-Catalyzed Intramolecular C-H Alkylation of Imidazoles with 1,1-Disubstituted Alkenes." *J. Am. Chem. Soc.* **2020**, 142, 1200-1205.

7. Li, A.; Li, C.; Yang, T.; Yang, Z.; Liu, Y.; Li, L.; Tang, K.; Zhou, C. "Electrochemical Synthesis of Benzo[d]imidazole via Intramolecular C(sp3)-H Amination." *J. Org. Chem.* **2021** DOI: 10.1021/acs.joc.1c01842.

8. 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.

Chapter 4:

Defluoroalkylation of Trifluoromethylarenes with N,N-dialkylhydrazones: Rapid Access to Benzylic Difluoroarylethylamines

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Hendy, C. M.; Pratt, C. J.; Jui, N. T.; Blakey, S. B. *Org. Lett.* **2023**, *25*, 1397-1402.

https://pubs.acs.org/doi/10.1021/acs.orglett.3c00126

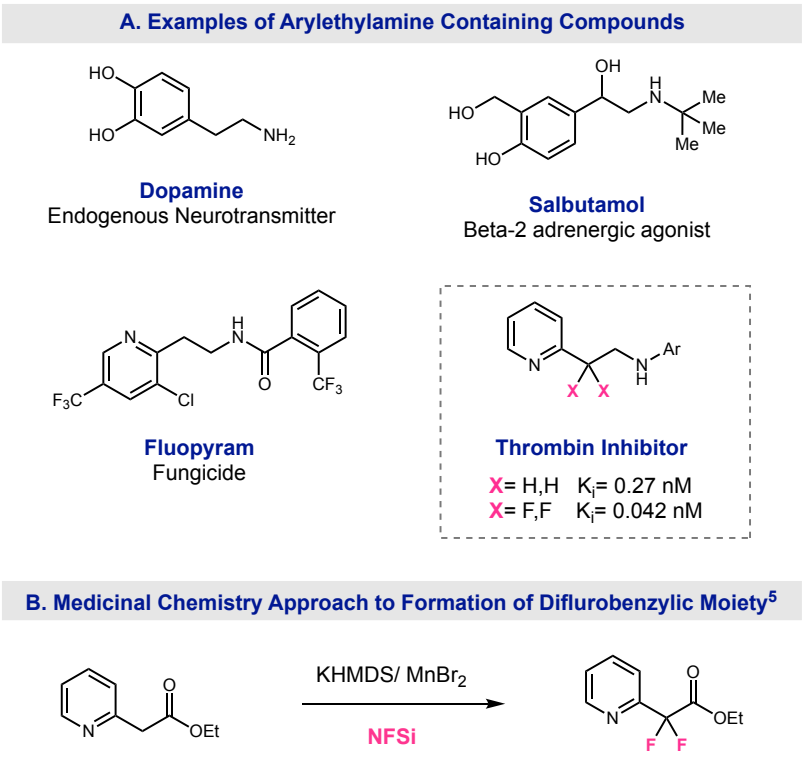
Abstract: *Fluorine has been extensively exploited in the development of new pharmaceuticals owing to the profound impact fluorine can impart on the pharmacological and structural properties of organic molecules. Unsurprisingly, there is a demand for the development of new technologies to selectively form novel fluorinated motifs. Herein, we describe a method for the formation of novel difluorinated arylethylamines from simple aldehyde derived N,N-dialkylhydrazones and trifluoromethylarenes (CF_3-arenes). This method relies on single electron reduction by $CO_2^{\bullet-}$ for activation of the CF_3-arene to form a difluorobenzylic radical intermediate. We show this radical can effectively engage with N,N-dialkylhdyrazones to deliver unique β-difluorobenzylic hydrazines. The corresponding hydrazine bond of the product can be selectively cleaved in the presence of the benzylic difluoro group to deliver the pharmaceutically relevant benzylic difluoroarylethylamines. Intriguingly, we found that more electron-deficient N-acylhydrazones react with the nucleophilic $CO_2^{\bullet-}$ to form the corresponding carboxylated hydrazines.*

Introduction 4.1

Arylethylamines are a highly privileged scaffold that have been seen across a wide variety of biologically active molecules such as endogenous neurotransmitters (e.g. dopamine), natural products, pharmaceuticals and agrochemicals (Figure 4.1A).[1] The incorporation of fluorinated motifs into small molecule frameworks is a routinely employed strategy to generate analogs for the optimization of pharmaceuticals. The prevalence of fluorine in pharmaceuticals and agrochemicals can be attributed to the impacts fluorine can impart on the drug-like properties of a compound such as potency, bioavailability and metabolic stability.[2] In particular, the α,α-difluorobenzylic motif has been recognized as an excellent bioisostere for aryl ethers and ketones,[3] and its introduction into arylethylamines would provide significant opportunity to tune biological

activity. In fact, this has been demonstrated by Merck with the develop of a series of thrombin inhibitors that contain an arylethylamine core.[4] They found that replacement of the benzylic hydrogen atoms on the 2-aminopyridyl portion of the molecule with fluorine atoms significantly enhanced the potency of the inhibitor (Figure 4.1A). However, the medicinal chemistry route for the fluorinated arylethylamine moiety required a five- step sequence that involved the use of a fluorinating reagent, N-Fluorobenzenesulfonimide (NFSi), to incorporate the benzylic fluorines (Figure 4.1B) and hazardous sodium azide for installation of the amine (upon Pd/C reduction). The route towards the benzylic difluorinated 2-aminopyridine was further improved by the process team but still required three steps and metal catalysts.[5] Beyond this example, the evaluation of benzylic difluorinated arylethylamine motifs in other bioactive small molecules is underexplored, likely due to the current lack of convenient synthetic methods to access these compounds. In this chapter, we describe a modular reaction for the formation of benzylic difluoroarylethylamines

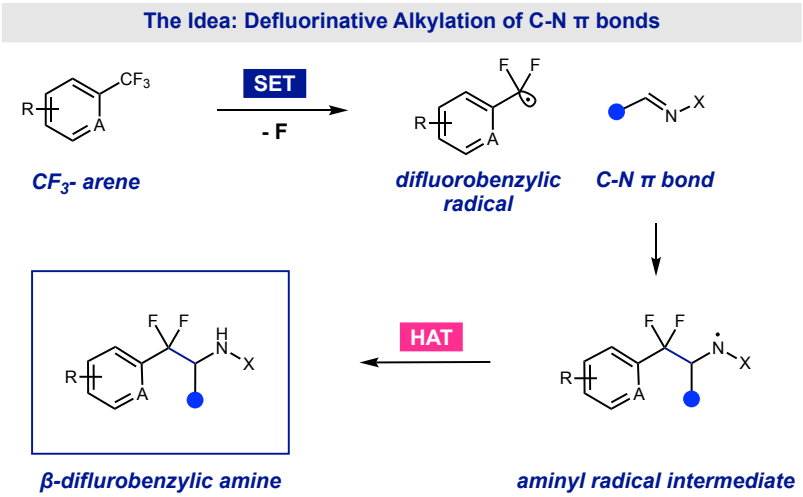
Figure 4.1: Arylethylamines and fluorinated arylethylamine examples.



using $CO_2^{\bullet-}$ reduction to activate trifluoromethylarenes (CF_3-arenes) which is key to enabling this reactivity.

As mentioned in previous chapters, our lab[6] as well as others[7] have developed excellent chemistry to selectively activate CF_3-arenes through a reductive C-F cleavage that is induced through single electron transfer to afford the difluorobenzylic radical (*see chapters 1 and 2 for more background*). We envisioned using this chemistry to generate the difluorobenzylic radical followed by engagement with a C–N π-bond and capture of the resulting aminyl radical by hydrogen atom transfer (HAT) to deliver the desired difluorobenzylic arylethylamine scaffold (Figure 4.2).

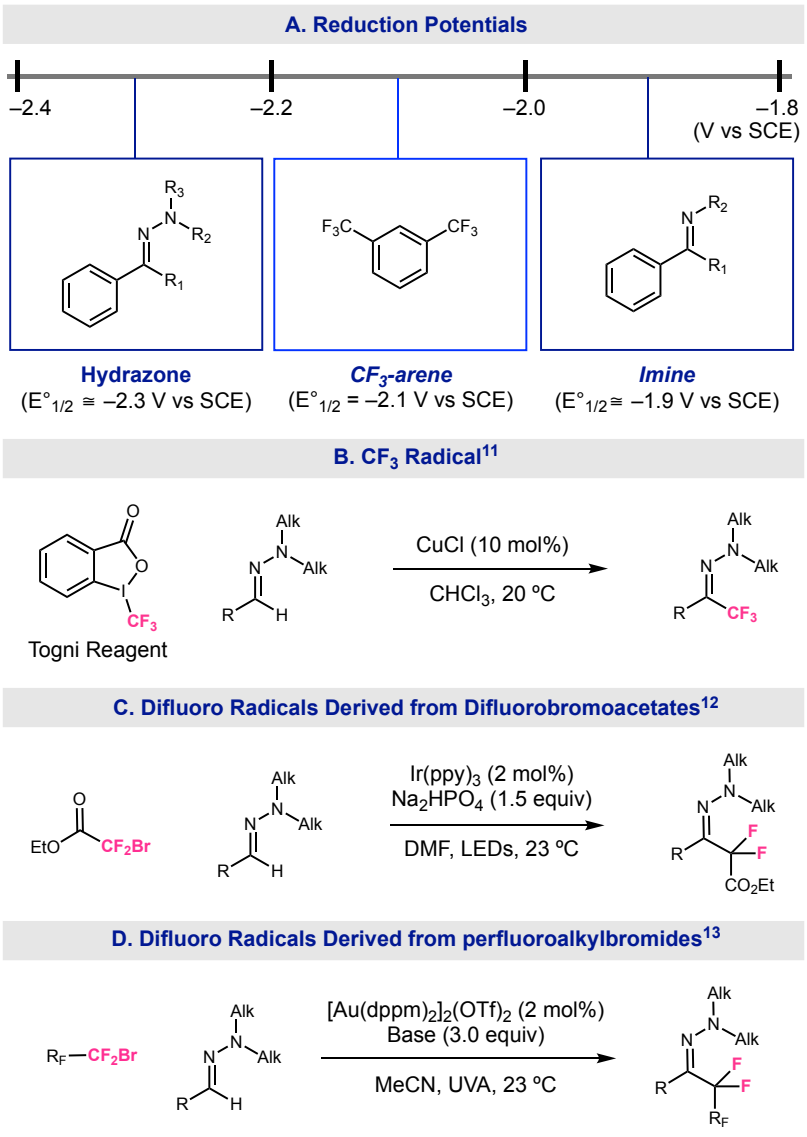
Figure 4.2: Strategy for defluorinative alkylation of C–N π-bonds.



However, the key to unlocking this methodology would lie in selection of the appropriate C–N π bond type (Figure 4.3A). Although imines would serve as a straightforward building block for direct access to the desired product, two significant problems impede their use. The reaction of an electrophilic difluorobenzylic radical with an electron-poor imine would result in a high energy transition state due to unfavorable polar interactions.[8] Additionally, the CF_3-arene ($E^{\circ}_{1/2} = -2.07$ V

vs SCE for bis(1,3-trifluoromethyl)benzene) requires a more challenging reduction than typical imines ($E^{\circ}_{1/2}$ = –1.91 V vs SCE for *N*-benzylideneaniline)[9] which would lead to issues arising from competitive reduction of the two species. Conversely, N,N-dialkylhydrazones have been demonstrated to display umpolung reactivity compared to their imine counterparts. This can be attributed to the nucleophilic aza-enamine character of N,N-dialkylhydrazones owing to the conjugation of the terminal nitrogen lone pair with the with the C–N π-bond.[10] In fact, it has been

Figure 4.3: Selection of appropriate hydrazone as C–N π bond and precedence for difluoro radical addition to hydrazones.



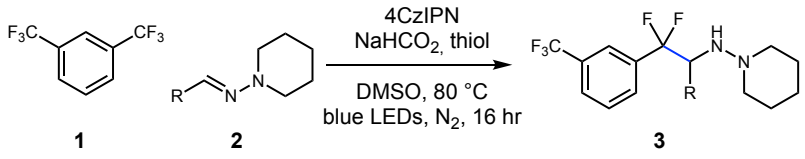
demonstrated that trifluoromethyl radicals (Figure 4.3B)[11] and difluoro radicals derived from difluorobromoacetate (Figure 4.3C)[12] and perfluoroalkylbromides (Figure 4.3D)[13] can efficiently undergo addition to aldehyde-derived N,N-dialkylhydrazones. However, in all these cases the resulting aminyl radical undergoes oxidation and deprotonation to deliver the corresponding fluorinated hydrazone as shown in Figure 4.3(B-D). Furthermore, hydrazones ($E^{\circ}_{1/2}$ = –2.30 V vs SCE for benzophenone phenylhydrazone)[14] are more challenging to reduce than CF_3-arenes, preventing complications from competitive reduction. For these reasons we have chosen N,N-dialkylhydrazones as our reacting partner for the development of this method.

4.2 Results and Discussion

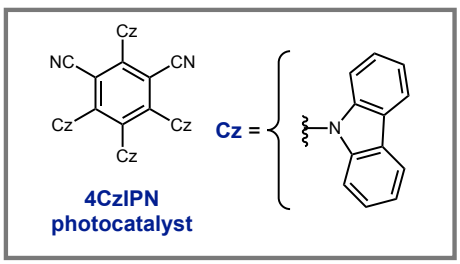
4.2.1 Optimization of Defluoroalkylation of Hydrazones with CF_3-arenes

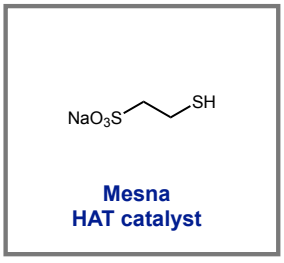
We commenced our studies by using conditions previously developed for generation of $CO_2^{\bullet-}$ as the reductant.[15] We have already demonstrated that $CO_2^{\bullet-}$ can successfully engage CF_3-arenes by single electron transfer (SET) in chapter 2 where we demonstrated its use on the defluoroalkylatioin of unactivated alkenes. We believed this would serve as a good starting point for developing a method for the defluoroalkylation with hydrazones. We used CF_3-arene **1** and hydrazone **2** for optimization of this reaction. Upon treating 1.0 equivalent of **1** and 3.0 equivalents

Table 4.1: Optimization of defluoroalkylation of CF_3-arenes with hydrazones.[a,]



Entry	1a (equiv)	2a (equiv)	Deviation	Yield[b]
1	1.0	3.0	23 °C	**39%**
2	3.0	1.0	23 °C	**54%**
3	3.0	1.0	-	**99% (82%)[c]**
4	3.0	1.0	No 4CzIPN	**3%**
5	3.0	1.0	no $NaHCO_2$	**3%**
6	3.0	1.0	no light	**0%**
7	3.0	1.0	no thiol	**13%**





[a]Conditions: **1** (0.3 mmol), **2** (0.1 mmol) 4CzIPN (1 mol%), $NaHCO_2$ (0.4 mmol), mesna (20 mol%), DMSO (1 mL), blue LEDs, N_2, 80 °C, 16 hr. [b]Yields determined by ^{19}F NMR with 2-(trifluoromethyl)pyridine as internal standard. [c] Isolated yield shown.

of **2** in the presence of 4CzIPN (1 mol%), sodium formate (4 equiv), and mesna (20 mol%) in DMSO, we observed the desired product **3** in a 39% yield (Table 4.1, entry 1). When reversing the stoichiometry to 3.0 equivalents of **1** and 1.0 equivalent of **2** we observed an increased yield of **3** (54%, Table 4.1, entry 2). We were pleased to find when heating the reaction to 80 °C we observed a 99% yield of **3** (Table 4.1, entry 3). We next ran a series of control experiments (Table 4.1, entries 4-7). by performing the reaction in the absence of photocatalyst, sodium formate, light and mesa (HAT catalyst). These experiments revealed all components of the reaction are crucial for observed reactivity and are in good agreement with experimental data in chapter 2.

4.2.2 Scope of Defluoroalkylation of Hydrazones with CF_3-arenes

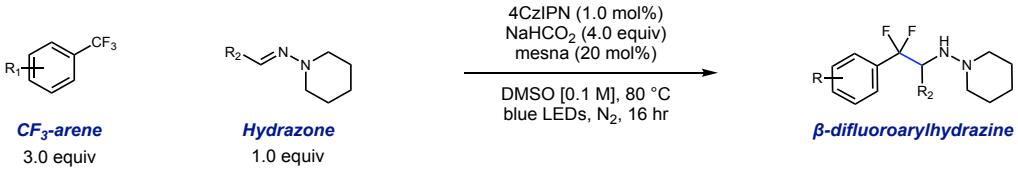
Examination of the scope of this transformation revealed this chemistry tolerated a wide variety of CF_3-arenes and -heteroarenes as well as aryl and alkyl hydrazones (Table 4.2). However, during this evaluation we found that certain substrates gave higher yields in the presence of 3.0 equivalents formic acid (noted in Table 4.2 accordingly). The enhanced yield with formic acid is likely due to protonation of the hydrazine product which prevents undesired oxidation of the nitrogen lone pair by the photocatalyst which can lead to degradation products.[16]

We first looked at the scope in terms of the CF_3-arene using hydrazone **2**. The 1,3- and 1,4-bis(trifluoromethyl)benzenes (**3**-**4**) gave excellent yields (82% for **3** and 77% for **4**). Only slightly diminished reactivity was observed when using 1,2-bis(trifluoromethyl)benzene **5** (54% yield). In addition, 5-substituted 1,3-bis(trifluoromethyl)benzene substrates (**6**-**7**) gave good yields (72%-75% yield). Other activating groups could be tolerated on the arene such as amide **8** (34% yield). Importantly, we were pleased to find this reactivity extended to a variety of nitrogen containing heterocycles. We examined a series of (trifluoromethyl)pyridines with variation of the position of the trifluoromethyl group around the pyridine. 2-(trifluoromethyl)pyridine (**9)** gave the highest

yield (48%), while both the 4- and 3-trifluoromethyl substituted pyridine (**10** and **11**) gave lower yields (36% and 26%, respectively). In addition to pyridines, benzimidazole **12** (72% yield) and thiazole **13** (51% yield) reacted in good yields. Unfortunately, this chemistry could not be extended to CF_3-arenes that are not activated with electron-withdrawing group because they lie outside the reduction potentials of the $CO_2^{\bullet-}$ reductant. Additionally, CF_3-arenes that bear even stronger electron-withdrawing group (e.g. cyano) were unsuccessful as they led to a complex mixture of products likely due to over-reduction (*see supporting information*).

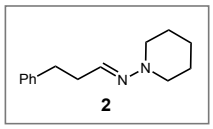
The N,N-dialkylhydrazone scope was evaluated using CF_3-arene **1**. We first examined the steric tolerance around the hydrazone. When an isopropyl group was placed two carbons from the hydrazone (**14),** we observed a 62% yield of the product. However, when the isopropyl group was one carbon from the hydrazone (**15)** we observed slightly diminished reactivity (41% yield) and when a *tert*-butyl group was adjacent to hydrazone we observed no desired product. Additionally, ketone-derived hydrazones were unreactive. Formaldehyde derived hydrazone **16** reacted to give a moderate yield (51%) under slightly modified conditions (1.0 equiv CF_3-arene and 3.0 equiv hydrazone). Different functional groups could be tolerated on the hydrazone such as a Boc-protected amine (**17**, 59% yield) and a benzyl-protected alcohol (**18**, 61% yield). Arylaldehyde derived hydrazones were also suitable reaction partners. Benzaldehyde derived hydrazone **19** reacted in good yield (67%). A series of ortho-, meta- and para-anisaldehyde derived hydrazones were examined (**20**-**22**) and we found substitution of the benzene ring was tolerated in all positions (43-62%). While electron-rich benzaldehyde hydrazones reacted well, electron-deficient hydrazones (e.g. cyano) gave no desired product and led to a complex mixture of unidentified products. However, halogenation on the hydrazone could be tolerated such as aryl fluoride (**23**) and chloride (**24**) which reacted well (77% and 53% yield, respectively) with no detectable

Table 4.2: Scope of defluoroalkylation of CF_3-arenes with hydrazones.[a]



CF_3-arene Scope:

using



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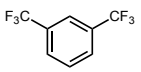
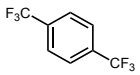
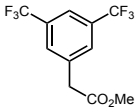


3: 82% yield

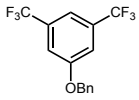


4: 73% yield[b]

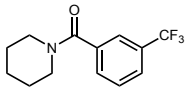
5: 54% yield[b]



6: 72% yield[b]



7: 75% yield[b]

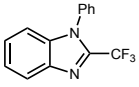


8: 34% yield[d]

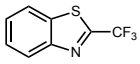
9: 48% yield

10: 36% yield[c]

11: 26% yield[c]



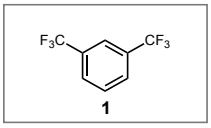
12: 72% yield[b,c]



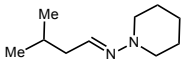
13: 51% yield[b,c]

Hydrazone Scope:

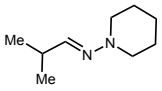
using



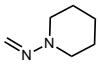
1



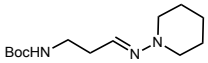
14: 62% yield



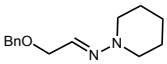
15: 41% yield



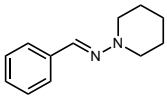
16: 51% yield[b,d,e]



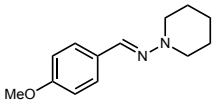
17: 59% yield



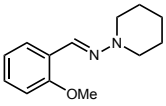
18: 61% yield



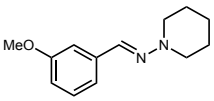
19: 67% yield



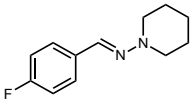
20: 54% yield



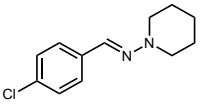
21: 62% yield[b]



22: 43% yield[b]



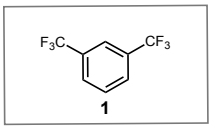
23: 77% yield[b]



24: 53% yield[b]

Variation of Hydrazone Nitrogen Substituent:

using



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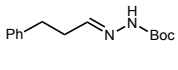
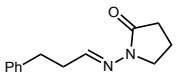
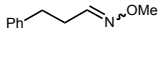


25: 43% yield

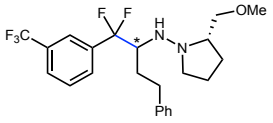


26: 24% yield



27: 12% yield

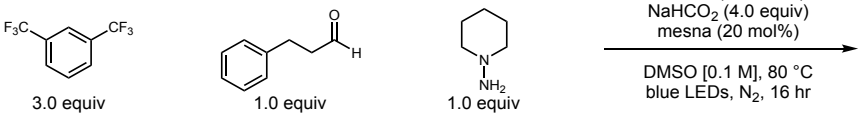
SAMP-Hydrazone:



28: 65% yield

1.0 : 1.9 d.r.

Telescoped Sequence:



3.0 equiv
1

1.0 equiv
29

1.0 equiv
30

3: 52% yield[f]

[a]Conditions: CF_3-arene (3 equiv), hydrazone (1 equiv), 4CzIPN (1 mol%), $NaHCO_2$ (4 equiv), mesna (20 mol%), DMSO [0.1 M], blue LEDs, N_2, 80 °C, 16 hr, isolated yields shown, performed on 0.1- 0.5 mmol scale (see *supporting information*). [b]3.0 equiv HCOOH added to reaction. [c] Yields determined by ^1H NMR with dibromomethane as internal standard. [d] Yields determind by ^{19}F NMR using 2-(trifluoromethyl) as internal standard. [e]CF_3-arene (1 equiv), hydrazone (3 equiv), $NaHCO_2$(8 equiv). [f]Conditions: CF_3-arene (3 equiv), aldehyde (1 equiv), hydrazine (1 equiv) 4CzIPN (1 mol%), $NaHCO_2$ (4 equiv), mesna (20 mol%), DMSO [0.1 M], blue LEDs, N_2, 80 °C, 16 hr, isolated yields shown, performed on 0.5 mmol scale.

hydrodehalogenation side products. Unfortunately, the corresponding aryl bromide gave a good yield of addition to the hydrazone but contained a mixture of hydrodehalogenation of the aryl bromide.

We next evaluated a small series of hydrazones with varying substitution on the hydrazone nitrogen. We found that the more electron-deficient the hydrazone, the lower yield of product we observed. This trend is consistent with the favorable polar effects between the electron deficient difluorobenzylic radical and the electron rich N,N-dialkylhydrazone. The NHBoc hydrazone **25** gave a moderate yield (43%). The N-acyl hydrazone **26**, the most electron-deficient hydrazone, gave the lowest yield (24%). We additionally tried an oxime in place of a hydrazone C–N π bond and, intriguingly, found it reacted but in low yield (12% of **27**). We evaluated a SAMP-hydrazone to see if we could induce stereoselectivity in the radical addition. This reaction proceeded in good yield (65% yield of **28**), but unfortunately gave relatively low diastereoselectivity (1.0 : 1.9).

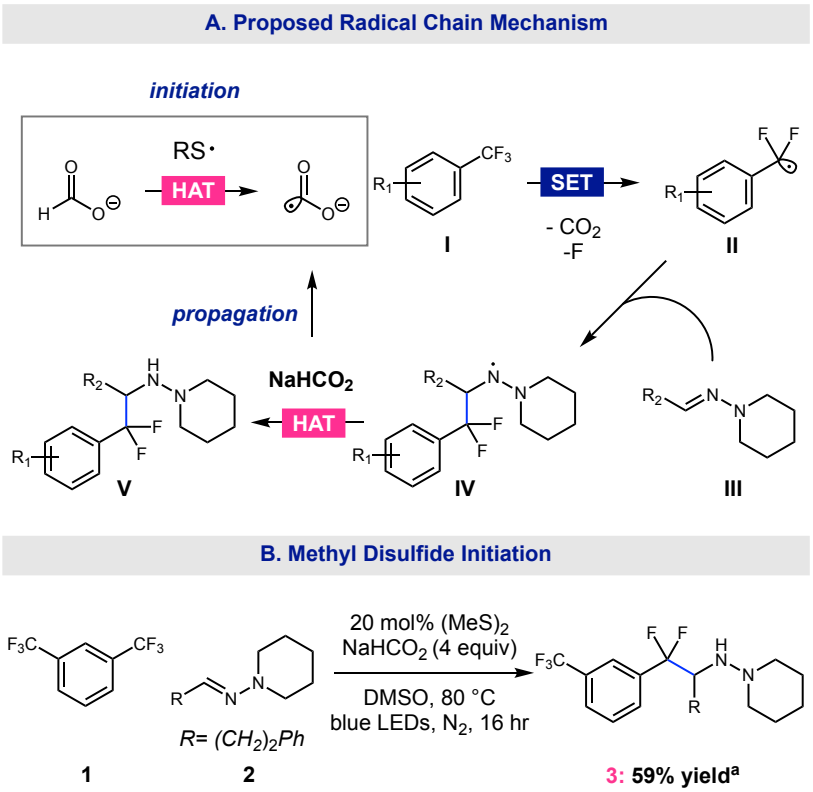
Lastly, we wanted to probe if we could run this reaction in a one-pot sequence bypassing the need for isolation of the hydrazone. We were pleased to find this reaction worked in a telescoped sequence where the hydrazone is formed *in situ* with aldehyde **29** and hydrazine **30** giving the expected product **3** in a 52% yield.

4.2.3 Proposed mechanism

The proposed mechanism of this transformation can be seen in Figure 4.4A. The reaction operates in a similar radical chain mechanism that was described in chapter 2. The reaction begins with a photocatalytic oxidation of mesna ($E^{\circ}_{1/2}$ = +1.18 V vs SCE) by the excited state of the photocatalyst 4CzIPN* ($E^{\circ}_{1/2}$ = +1.43 V vs SCE)[17] to produce thiyl radical. Thiyl radical undergoes a polarity matched HAT with formate to deliver the $CO_2^{\bullet-}$ ($E^{\circ}_{1/2}$= -2.21 V vs SCE).[18] This undergoes single electron transfer with CF_3-arene **I** to deliver the radical anion of **I**. This undergoes

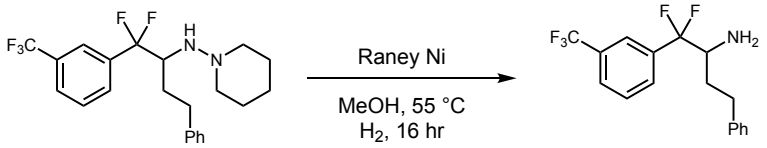
a rapid mesolytic cleavage of the benzylic fluoride to generate the difluorobenzylic radical **II**. The coupling of radical **II** with hydrazone **III** results in aminyl radical **IV**. Due to the electrophilicity of nitrogen centered radicals, we propose HAT is occurring with nucleophilic formate to deliver the desired product **V** as well as propagate the chain mechanism. However, despite thiol being an electrophilic H-atom donor, we cannot rule out HAT from mesna. Traditional deuteration experiments typically reveal which species in the reaction is responsible for H-atom delivery, however, these experiments cannot be performed due to the exchangeable nature of the hydrogen atoms under this system. The reaction was ran in absence of photocatalyst with methyl disulfide as an alternative initiator to validate the presence of a radical chain mechanism (Figure 4.4B). We observed a 59% yield of **3** which is consistent with findings in chapter 2 of radical chain reduction via $CO_2^{\bullet-}$.

Figure 4.4: (A) Proposed radical chain mechanism and (B) alternative initiation using methyl disulfide. [a]Yield determined by ^{19}F NMR using 2-(trifluoromethyl)pyridine as internal standard.



4.2.4 N-N Bond Cleavage

To demonstrate the synthetic utility of this method towards the formation of *β*-difluorobenzylic arylethylamines we wanted to show the N–N bond could be selectivity cleaved to deliver the pharmaceutically relevant amine. While the reductive cleavage of N–N σ-bonds has been well established in the literature by a variety of methods,[19] it was important to show that this could be achieved selectively in the presence of the relatively weak benzylic fluorine bonds. We first attempted a hydrogenolysis reaction using palladium on carbon as the catalyst; this gave no desired cleavage even when high pressures were applied. However, we were pleased to find that the use of Raney nickel under a balloon of hydrogen resulted in efficient cleavage of the hydrazine bond to the amine **31** in excellent yield (79%, Scheme 4.1). A trace amount of benzylic defluorination was observed by ^{1}H NMR and LCMS, however, this could easily be separated from the desired product.



3 **31: 79% yield**

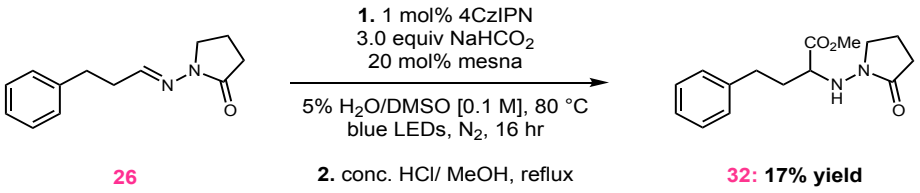
Scheme 4.1: Hydrazine bond cleavage using Raney nickel[a]
[a]Conditions: **3** (0.1 mmol), Raney nickel (0.310 g), MeOH (2.5 mL), H_2 (balloon), 55 °C, 16 hr, isolated yield shown.

4.2.5 Carboxylation of N-acyl Hydrazone with $CO_2^{\bullet-}$

During the development of this chemistry, we questioned whether we could engage the $CO_2^{\bullet-}$ itself with hydrazones to form the corresponding carboxylated hydrazines. We found the key to unlocking the coupling of electron deficient difluorobenzylic radicals with hydrazones hinges on the use of an electron rich N,N-dialkylhydrazone to allow for favorable polar effects in the transition state of radical addition. Additionally, in chapter 2 we describe that the nucleophilic

$CO_2^{\bullet-}$ intermediate can undergo addition to electron deficient olefins that lie outside of the reduction potential window of $CO_2^{\bullet-}$. With this knowledge, we hypothesized that the use of a more electron deficient hydrazone, such as N-acyl hydrazone, could enable the desired reactivity with nucleophilic $CO_2^{\bullet-}$.

To test this hypothesis, we subjected N-acyl hydrazone **26** to slightly modified conditions (Scheme 4.2) in the absence of a CF_3-arene to see if we observed carboxylation of the hydrazone. We found no desired product after ^{1}H NMR analysis of the organic layer upon workout of the reaction. However, we did observe the mass of the carboxylation product by an LCMS trace of an aliquot of the aqueous layer. Upon subjecting this to esterification, we were able to isolate the desired carboxylated product as the methyl ester **32** in a 17% yield. While the yield was low, this result demonstrates a proof of principle reaction for the carboxylation of hydrazones with $CO_2^{\bullet-}$, expanding upon the types of reactivity possible with this transient intermediate. Additionally, it highlights the power of polarity matching in radical additions for dictating reaction outcome and selectivity.



Scheme 4.2: Carboxylation of N-acyl hydrazone[a]

[a]Conditions: **26** (1.0 equiv), 4CzIPN (1 mol%), $NaHCO_2$ (3.0 equiv), mesna (20 mol%), 5% H_2O/DMSO [0.1 M], blue blue LEDs, N_2, 80 °C, 16 hr, isolated yield of methyl ester shown, performed on 0.1 mmol scale.

Conclusion 4.3

In summary we have developed a streamlined method for the formation of pharmaceutically relevant benzylic difluorinated arylethylamines that relies on reductive activation of CF_3-arenes by the powerful reductant, $CO_2^{\bullet-}$, and it was found to operate in a similar radical chain mechanism as initially discovered from work described in chapter 2. This method demonstrates a novel radical addition of an electrophilic difluorobenzylic radical with a C–N π-bond. The key to enabling this reactivity is the use of a relatively electron rich C–N π-bond type, N,N-dialkylhydrazones, which allow for favorable polar effects in the transition state of radical addition. A variety of both CF_3-arene and hydrazone coupling partners can be engaged under this system to deliver a diverse array of *β*-difluorobenzylic hydrazines. Importantly, the hydrazine product can be selectively cleaved to form the difluorinated arylethylamines. This approach offers a direct and modular approach towards the formation of this motif which can be used as a valuable tool in the evaluation of bioactive fluorinated arylethylamine analogs for both the medicinal and agrochemical industries. Additionally, during this study we discovered the nucleophilic $CO_2^{\bullet-}$ intermediate could effectively undergo carboxylation with an electron deficient N-acyl hydrazone to deliver the corresponding carboxylated hydrazine product. This result expands upon the possible carboxylation-type reactivity of $CO_2^{\bullet-}$ and highlights it versatility as an intermediate in organic synthesis.

4.4 References

(1) (a) Claudi, F.; Cardellini, M.; Cingolani, G. M.; Piergentili, A.; Peruzzi, G.; Balduini, W. Synthesis and Dopamine Receptor Affinities of 2-(4-fluoro-3- hydroxyphenyl)ethylamine and N-Substituted Derivatives. *J. Med. Chem.* **1990**, 33, 2408-2412. (b) Bentley, K. W. β-Phenylethylamines and Isoquinoline Alkaloids. *Nat. Prod. Rep.* **1999**, 16, 367-388.

(2) (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, 58, 8315-8359. (b) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, 51, 4359-4369.

(3) Muller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science*. **2007**, 317, 1881-1886.

(4) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Sanderson, P. E.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; et al. Metabolism-Directed Optimization of 3-Aminopyrazinone Acetamide Thrombin Inhibitors. Development of an Orally Bioavailable Series Containing P1 and P3 Pyridines. *J. Med. Chem.* **2003**, 46, 461-473.

(5) Ashwood, M. S.; Alabaster, R. J.; Cottrell, I. F.; Cowden, C. J.; Davies, A. J.; Dolling, U. H.; Emerson, K. M.; Gibb, A. D.; Hands, D.; Wallace, D. J.; et al. Development of a Scaleable Synthesis of a 3-Aminopyrazinone Acetamide Thrombin Inhibitor. *Org. Process Res. Dev.* **2004**, 8, 192-200.

(6) (a) Vogt, D. B.; Seath, C. P.; Wang, H.; Jui, N. T. Selective C-F Functionalization of Unactivated Trifluoromethylarenes. J. Am. Chem. Soc. 2019, 141, 13203-13211. (b) Wang, H.; Jui, N. T. Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, 140, 163-166.

(7) (a) Xu, P.; Wang, X. Y.; Wang, Z.; Zhao, J.; Cao, X. D.; Xiong, X. C.; Yuan, Y. C.; Zhu, S.; Guo, D.; Zhu, X. Defluorinative Alkylation of Trifluoromethylbenzimidazoles Enabled by Spin-Center Shift: A Synergistic Photocatalysis/Thiol Catalysis Process with $CO2^{\bullet-}$. *Org. Lett.* **2022**, 24, 4075-4080. (b) Liu, C.; Shen, N.; Shang, R. Photocatalytic Defluoroalkylation and Hydrodefluorination of Trifluoromethyls using o-Phosphinophenolate. *Nat. Commun.* **2022**, 13, 354. (c) Liu, C.; Li, K.; Shang, R. Arenethiolate as a Dual Function Catalyst for Photocatalytic Defluoroalkylation and Hydrodefkuorination of Trifluoromethyls. *ACS Catal.*. **2022**, 12, 4103-4109.

(8) Ruffoni, A.; Mykura, R. C.; Bietti, M.; Leonori, D. The Interplay of Polar Effects in Controlling the Selectivity of Radical Reactions. *Nat. Synth*. **2022**, 1, 682- 695.

(9) Leitch, J.; Rossolini, T.; Rogova, T.; Maitland, J. A. P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal*. **2020**, 10, 2009-2025.

(10) Xu, P.; Li, W.; Xie, J.; Zhu, C. Exploration of C-H Transformations of Aldehyde Hydrazones: Radical Strategies and Beyond. *Acc. Chem. Res.* **2018**, 51, 484-495.

(11) Pair, E.; Monteiro, N.; Bouyssi, D.; Baudoin, O. Copper-Catalyzed Trifluoromethylation of N,N-Dialkylhydrazones. *Angew. Chemie. Int. Ed.* **2013**, 52, 5346-5349.

(12) Xu, P.; Wang, G.; Zhu, Y.; Li, W.; Cheng, Y.; Li, S.; Zhu, C. Visible-Light Photoredox-Catalyzed C-H Difluoroalkylation of Hydrazones through an Aminyl Radical/Polar Mechanism. *Angew. Chemie. Int. Ed.* **2016**, 55, 2939-2943.

(13) Xie, J.; Zhang, T.; Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. Gold-catalyzed Highly Selective Photoredox C(sp^2)-H Difluoroalkylation and Perfluoroalkylation of Hydrazones. *Angew. Chemie. Int. Ed.* **2016**, 55, 2934-2938.

(14) Soucaze-Guillous, R.; Lund, H. Reduction of Hydrazones of Aromatic Carbonyl Compounds in Aprotic Media. J. *Electroanal. Chem.* **1997**, 423, 109- 114.

(15) Hendy, C. M.; Smith, G. C.; Xu, Z.; Lian, T.; Jui, N. T. Radical Chain Reduction via Carbon Dioxide Radical Anion ($CO_2^{\bullet-}$). *J. Am. Chem. Soc.* **2021**, 143, 8987-8992.

(16) (a) Zhu, M.; Zheng, N. Photoinduced Cleavage of N-N Bonds of Aromatic Hydrazines and Hydrazides by Visible Light. *Synthesis*. **2011**, 2223-2236. (b) Vega, J. A.; Alonso, J. M.; Mendez, G.; Ciordia, M.; Delgado, F.; Trabanco, A. A. Continuous Flow α-Arylation of N,N-Dialkylhydrazones under Visible-Light Photoredox Catalysis. *Org. Lett.* **2017**, 19, 938-941.

(17) 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, 15353-15365.

(18) Koppenol, W. H.; Rush, J. D. Reduction Potential of the Carbon Dioxide/Carbon Dioxide Radical Anion: A Comparison with Other C1 Radicals. *J. Phys. Chem.* **1987**, 91, 4429-4430.

(19) (a) Hinman, R. L. Hydrogenolysis of the Nitrogen-Nitrogen Bond of Acylhydrazines with Raney Nickel. *J. Org. Chem.* **1957**, 22, 148-150. (b) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. Organolithium Addition to Aldehyde Dimethylhydrazones: a Highly Diastereocontrolled Synthesis of Threo 2-amino Alcohols, and (1R,2R)-(-)-Norpseudoephedrine. *J. Am. Chem. Soc.* **1986**, 26, 8265- 8266. (c) Takahashi, H.; Noguchi, H.; Tomita, K.; Otomasu, H. Asymmetric Synthesis by using the Chirality of I-Ephedrine. II. Synthesis of (R)- α-Phenylethylamine. *Chem. Pharm. Bull.* **1981**, 29, 3387- 3391.

4.5 Supporting Information

4.5.1 General Information

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. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or staining using KMnO4 or ninhydrin stains. Anhydrous sodium formate was purchased from Sigma Aldrich and stored in a desiccator. Raney Nickel (W.R. Grace and Co. Raney® 2400, slurry, in H2O, active catalyst) was purchased from Sigma Aldrich. Drisolv® DMSO was purchased from VWR and dried over 4Å molecular sieves. Photoredox catalyst 4CzIPN was prepared according to literature procedures.[1] All other reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Oakwood Chemicals, Ambeed, and TCI America and used as received.

B. General Analytical Information

Unless otherwise noted, all yields refer to chromatographically and spectroscopically (1H NMR) homogenous materials. New compounds were characterized by NMR and HRMS. 1H and 13C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker 400 (400 MHz), Bruker 600 (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), or VNMR 400 (400 MHz), and are internally referenced to residual protio solvent signals. Data for 1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t =

triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled 13C NMR are reported in terms of chemical shift and multiplicity when applicable. High Resolution mass spectra were obtained from the Emory University Mass Spectral facility.

C. General Photoredox Reaction Setup

The reactions were ran in a shallow oil bath at elevated temperatures (Photo 1). A 15 W LED array lamp was used as the light source. It was positioned approximately 6 inches above the reaction vials (Photo 2).

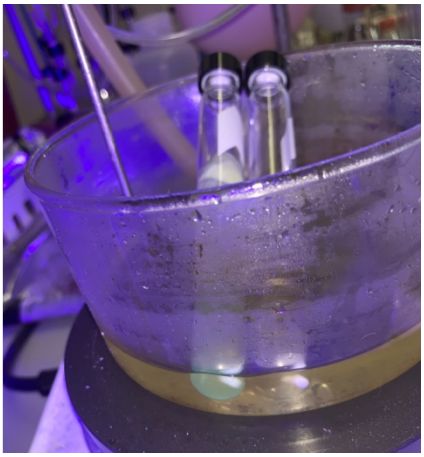


Photo 1.

Photo 2.

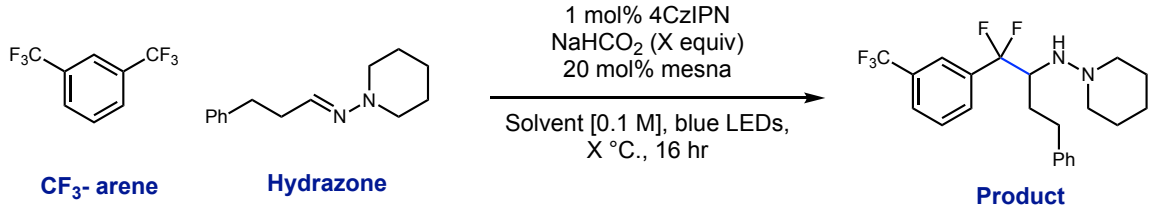
4.5.2 Optimization Details

Optimization Procedure

An 8 mL oven-dried screw-top test tube was charged with 4CzIPN (1 mol%, 0.001 mol), sodium formate (4.0 equiv, 0.4 mmol), mesna (20 mol%, 0.02 mol), and (*E*)-3-phenyl-*N*-(piperidin-1-yl)propan-1-imine **S6** (1.0 equiv, 0.1 mmol). The tube was equipped with an oven-dried stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO

(1 mL) was added via syringe, followed by 1,3-bis(trifluoromethyl)benzene (3.0 equiv, 0.3 mmol). The resulting mixture was heated to 80 °C and stirred at 700 RPM for 16 h under irradiation by blue LEDs. The reaction was cooled to room temperature and 2-(trifluoromethyl)pyridine (0.1 mmol) was added as the internal standard. A small aliquot of the reaction mixture was diluted in d_6-DMSO and the sample was analyzed by ^{19}F NMR and the integral values were used to calculate the data given in Table S4.1.

Table S4.1: Full optimization of defluoroalkylation of CF_3-arenes with hydrazones



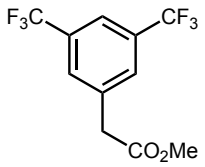
CF_3- arene **Hydrazone** **Product**

Entry	CF_3 arene	Hydrazone	Formate	Solvent	Temp.	Other	Product*
1	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	80 °C	-	**99%**
2	1.0 equiv	3.0 equiv	4.0 equiv	DMSO	80 °C	-	**74%**
3	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	23 °C	-	**54%**
4	1.0 equiv	3.0 equiv	4.0 equiv	DMSO	23 °C	-	**39%**
5	3.0 equiv	1.0 equiv	4.0 equiv	20% H_2O/DMSO	80 °C	-	**38%**
6	3.0 equiv	1.0 equiv	3.0 equiv	DMSO	80 °C	-	**55%**
7	3.0 equiv	1.0 equiv	5.0 equiv	DMSO	80 °C	-	**97%**
8	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	80 °C	-	**89%**
9	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	80 °C	open to air	**3%**
10	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	80 °C	no 4CzIPN	**0%**
11	3.0 equiv	1.0 equiv	none	DMSO	80 °C	no light	**3%**
12	3.0 equiv	1.0 equiv	4.0 equiv	DMSO	80 °C	no formate	**13%**
13	3.0 equiv	1.0 equiv	4.0 equiv	DMF	80 °C	no mesna	**93%**
14	3.0 equiv	1.0 equiv	4.0 equiv	DMA	80 °C	-	**91%**
15	3.0 equiv	1.0 equiv	4.0 equiv	MeCN	80 °C	-	**0%**

*Yields determined by ^{19}F NMR using 2-(trifluoromethyl)pyridine as internal standard

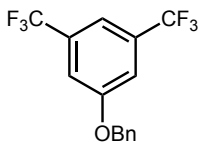
4.5.3 Preparation of Starting Materials

4.5.3A. Preparation of CF_3-Arenes



methyl 2-(3,5-bis(trifluoromethyl)phenyl)acetate (**S1**): To a solution of 2-(3,5-bis(trifluoromethyl)phenyl)acetic acid (5.00 mmol, 1.36 g, 1.0 equiv) dissolved in MeOH (12 mL) was added a few drops of conc. HCl. The reaction was stirred overnight under reflux. The reaction was allowed to cool to temperature. The reaction was concentrated *in vacuo*, washed with sat. $NaHCO_3$ (3x) and extracted with EtOAc (2x), dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was passed with through a plug of silica gel (20-30% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (1.22 g, 85% yield). The physical properties and spectral data were consistent with reported values.[2]

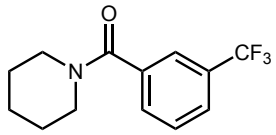
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (s, 2H), 3.77 (s, 2H), 3.74 (s, 3H).



1-(benzyloxy)-3,5-bis(trifluoromethyl)benzene (S2): An oven-dried round bottom flask was charged with 3,5-bis(trifluoromethyl)phenol (7.14 mmol. 1.64 g, 1.02 equiv), benzyl bromide (7.00 mmol, 0.831 mL, 1.0 equiv) and potassium carbonate (21.0 mmol, 2.90 g, 3.0 equiv) and dissolved in acetone (30 mL). The reaction was stirred overnight under reflux. The reaction was allowed to cool to room temperature. The reaction was filtered and concentrated *in vacuo*. The reaction was purified via silica chromatography (5-10% EtOAc/hexanes) to afford the title

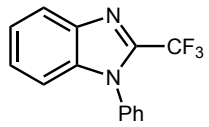
compound as a clear oil (1.92 g, 86% yield). The physical properties and spectral data were consistent with reported values.[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.46 – 7.35 (m, 7H), 5.14 (s, 2H).



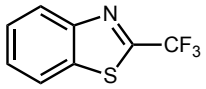
piperidin-1-yl(3-(trifluoromethyl)phenyl)methanone (S3): To a solution of piperidine (5.50 mmol, 0.543 mL, 1.1 equiv) and triethylamine (5.00 mmol, 0.697 mL, 1.0 equiv) in an RBF was added 3-(trifluoromethyl)benzoyl chloride (5.00 mmol, 0.834 mL, 1.0 equiv) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was washed with 1 M HCl (3x), dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was pushed through a plug of silica gel (30% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (1.30 g, quantitative). The physical properties and spectral data were consistent with reported values.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.62 – 7.49 (m, 2H), 3.72 (br s, 2H), 3.32 (br s, 2H), 1.76 – 1.44 (m, 6H).



1-phenyl-2-(trifluoromethyl)-1H-benzo[d]imidazole (S4): The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[5]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 8.1 Hz, 1H), 7.67 – 7.57 (m, 3H), 7.52 – 7.40 (m, 4H), 7.19 (d, J = 8.1 Hz, 1H).



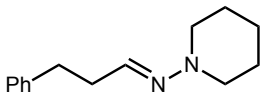
2-(trifluoromethyl)benzo[*d*]thiazole (S5): The title compound was prepared according to literature procedure. The physical properties and spectral data were consistent with reported values.[5]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.64- 7.61 (m, 1H), 7.61 – 7.48 (m, 1H).

4.5.3B Preparation of Hydrazones

General Procedure SA

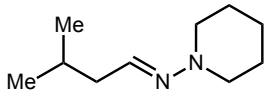
In a screw-top test tube equipped with a stirbar was added a solution of aldehyde (1 equiv) dissolved in DCM. The hydrazine (1.1 equiv) was added to the reaction dropwise followed by the addition of sodium sulfate. The reaction was warmed to room temperature and stirred overnight. The reaction was filtered and concentrated *in vacuo.* The crude reaction mixture was purified by silica chromatography.



(*E*)-3-phenyl-*N*-(piperidin-1-yl)propan-1-imine (S6): Prepared according to general procedure SA using 3-phenylpropanal (25.0 mmol, 3.32 mL, 1.0 equiv), N-aminopiperidine (30.0 mmol, 3.24 mL, 1.1 equiv) and DCM (20 mL). The crude reaction was purified by silica chromatography (5-30% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil. (3.36 g, 62% yield). The physical properties and spectral data were consistent with the reported values.[6]

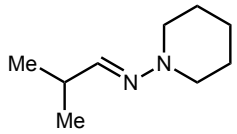
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.14 (m, 3H), 6.95 (t, *J* = 5.4 Hz, 1H), 2.91 (t, J= 5.7 Hz, 4H), 2.84- 2.78 (m, 2H), 2.61 – 2.51 (m, 2H), 1.69 (p, *J* = 5.8 Hz, 4H),

1.52 – 1.42 (m, 2H).



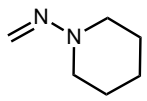
(*E*)-3-methyl-*N*-(piperidin-1-yl)butan-1-imine (S7): Prepared according to general procedure SA using 3-methylbutanal (4.00 mmol, 0.439 mL, 1.0 equiv), N-aminopiperidine (4.40 mmol, 0.475 mL, 1.1 equiv) and DCM (3 mL). The crude reaction was purified by silica chromatography (10-30% EtOAc/hexanes as eluent) to afford the title compound as a clear oil. (507 mg, 75% yield).The physical properties and spectral data were consistent with the reported values.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (t, *J* = 5.9 Hz, 1H), 2.91 (t, J=5.5Hz, 4H), 2.13-2.11 (m, 2H) 1.83-1.75 (m1H), 1.69 (p, *J* = 5.8 Hz, 4H), 1.51 – 1.42 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 6H).



(*E*)-2-methyl-*N*-(piperidin-1-yl)propan-1-imine (**S8**): Prepared according to general procedure SA using isobutyraldehyde (5.00 mmol, 0.460 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.1 equiv) and DCM (5 mL). The crude reaction was purified by silica chromatography (10-20% EtOAc/hexanes as eluent) to afford the title compound as a clear oil. (370 mg, 48% yield).The physical properties and spectral data were consistent with the reported values.[6]

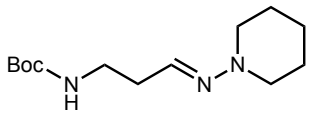
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (s, 1H), 2.89 (t, *J* = 5.6 Hz, 4H), 2.53 – 2.42 (m, 1H), 1.69 (p, *J* = 5.9 Hz, 4H), 1.52 – 1.42 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 6H).



***N*-(piperidin-1-yl)methanimine (S9):** Prepared according to a slightly modified version of general procedure SA using paraformaldehyde (15.0 mmol, 450 mg, 1.5 equiv), N-

aminopiperidine (10..0 mmol, 1.08 mL, 1.0 equiv) and Et_2O (10 mL). The crude reaction was purified by silica chromatography (70% Et_2O/hexanes as eluent) to afford the title compound as a clear oil (599 mg, 53% yield). The physical properties and spectral data were consistent with the reported values.[7]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 11.1 Hz, 1H), 6.28 (d, *J* = 11.1 Hz, 1H), 2.99 (t, *J* = 5.7 Hz, 3H), 1.70 (p, *J* = 5.8 Hz, 2H), 1.54 – 1.46 (m, 1H).



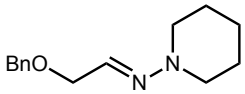
***tert*-butyl (*E*)-(3-(piperidin-1-ylimino)propyl)carbamate (S10):** Prepared according to general procedure SA using *tert*-butyl (3-oxopropyl)carbamate (4.00 mmol, 0.690 g, 1.0 equiv), N-aminopiperidine (4.40 mmol, 0.470 mL, 1.1 equiv) and DCM (4 mL). The crude reaction was purified via silica chromatography (20-50% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (0.629 g, 62% yield).

R_f= 0.34 (60% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (t, *J* = 4.8 Hz, 1H), 3.34 (q, *J* = 6.3 Hz, 2H), 2.95 – 2.87 (t, J= 5.7 Hz, 4H), 2.40 (td, *J* = 6.3, 4.6 Hz, 2H), 1.73 – 1.65 (p, J= 5.7 Hz, 4H), 1.51 – 1.44 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.09, 136.99, 79.17, 52.68, 38.10, 33.68, 28.57, 25.37, 24.26.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{26}O_2N_3$, 256.20195; found 256.20176.



(*E*)-2-(benzyloxy)-*N*-(piperidin-1-yl)ethan-1-imine (S11): Prepared according to general procedure SA using 2-(benzyloxy)acetaldehyde (5.00 mmol, 0.702 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.1 equiv) and DCM (5 mL). The crude reaction was

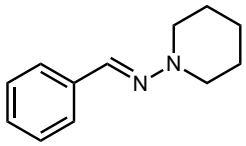
purified by silica chromatography (10-20% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil. (767 mg, 66% yield).

R_f= 0.48 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 6.90 (t, *J* = 5.2 Hz, 1H), 4.54 (s, 2H), 4.17 (d, *J* = 5.3 Hz, 2H), 3.02 – 2.96 (ap. t, J=5.6 Hz, 4H), 1.69 (p, *J* = 5.9 Hz, 4H), 1.53 – 1.45 (m, 2H).

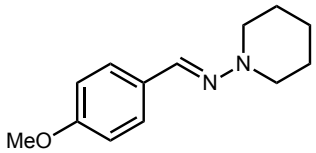
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.31, 134.00, 128.53, 128.06, 127.79, 72.46, 71.06, 52.07, 25.26, 24.19.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{14}H_{21}ON_2$, 233.16484; found 233.16529.



(*E*)-1-phenyl-*N*-(piperidin-1-yl)methanimine (S12): Prepared according to general procedure SA using benzaldehyde (10.0 mmol, 1.00 mL, 1.0 equiv), N-aminopiperidine (12.0 mmol, 1.30 mL, 1.2 equiv) and DCM (6 mL). The reaction was concentrated *in vacuo* without further purification to afford the title compound as a white solid. (1.76 g, 93% yield). The physical properties and spectral data were consistent with the reported values.[8]

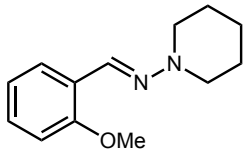
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.55 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 1H), 3.18 (t, J= 5.6 Hz, 4H), 1.75 (p, J= 5.7 Hz, 4H), 1.64 – 0.88 (m, 2H).



(*E*)-1-(4-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine (S13): Prepared according to general procedure SA using 4-methoxybenzaldehyde (4.00 mmol, 0.486 mL, 1.0 equiv), N-

aminopiperidine (4.80 mmol, 0.518 mL, 1.2 equiv) and DCM (2.5 mL). The crude reaction was purified by silica chromatography (5-20% EtOAc/hexanes as eluent) to afford the title compound as a clear oil. (672 mg, 78% yield).The physical properties and spectral data were consistent with the reported values.[9]

^{1}H NMR (500 MHz, $CDCl_3$) δ ,7.55 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.12 (t, J=5.6 Hz, 4H), 1.75 (p, *J* = 5.8 Hz, 4H), 1.57 – 1.49 (m, 2H).



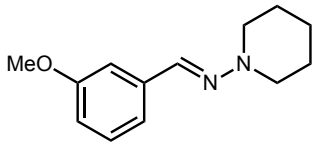
(*E*)-1-(2-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine (S14): Prepared according to general procedure SA using 2-methoxybenzaldehyde (5.00 mmol, 0.602 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.2 equiv) and DCM (5 mL). The crude reaction was purified by silica chromatography (0-20% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (1.05 g, 96% yield).

R_f= 0.62 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.87 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.24 (t, J= 7.7 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.16 (t, *J* = 5.7 Hz, 4H), 1.76 (p, *J* = 5.5 Hz, 4H), 1.54 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.00, 130.84, 128.93, 125.42, 125.39, 121.00, 110.90, 55.61, 52.40, 25.41, 24.35.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{19}ON_2$, 219.14919; found 219.14965.



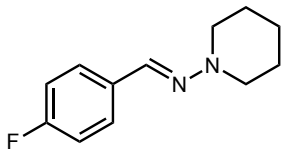
(*E*)-1-(3-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine (S15): Prepared according to general procedure SA using 3-methoxybenzaldehyde (5.00 mmol, 0.582 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.2 equiv) and DCM (5 mL). The crude reaction was pushed through a silica plug (20% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (1.01 g, 93% yield).

R_f= 0.58 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.22 – 7.20 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.83 (s, 3H), 3.19 – 3.13 (m, 4H), 1.76 (p, *J* = 5.7 Hz, 4H), 1.60 – 1.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.97, 138.34, 134.46, 129.54, 119.27, 114.36, 110.05, 76.84, 55.38, 52.20, 25.34, 24.27.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{19}ON_2$, 219.14919; found 219.1495.



(*E*)-1-(4-fluorophenyl)-*N*-(piperidin-1-yl)methanimine (S16): Prepared according to general procedure SA using 4-fluorobenzaldehyde (5.00 mmol, 0.535 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.1 equiv) and DCM (5 mL). The crude reaction was purified by silica chromatography (0-20% EtOAc/hexanes as eluent) to afford the title compound as a white solid (937 mg, 91% yield).

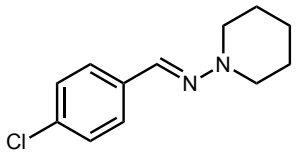
R_f= 0.78 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.51 (s, 1H), 7.06 – 6.97 (m, 2H), 3.14 (t, J=5.6 Hz, 4H), 1.75 (p, *J* = 5.8 Hz, 4H), 1.60 – 1.50 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.68 (d, *J* = 246.8 Hz), 133.55 (d, *J* = 1.0 Hz), 133.09 (d, *J* = 3.2 Hz), 127.57 (d, *J* = 8.0 Hz), 115.55 (d, *J* = 21.7 Hz), 52.25, 25.35, 24.46.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.19 (tt, *J* = 8.7, 5.5 Hz).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{12}H_{16}N_2F$, 207.1292; found 207.12967.



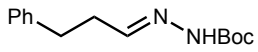
(*E*)-1-(4-chlorophenyl)-*N*-(piperidin-1-yl)methanimine (S17): Prepared according to general procedure SA using 4-chlorobenzaldehyde (5.00 mmol, 0.582 mL, 1.0 equiv), N-aminopiperidine (5.50 mmol, 0.594 mL, 1.1 equiv) and DCM (5 mL). The crude reaction was purified via silica chromatography (10-20% EtOAc/hexanes as eluent) to afford the title compound as a white solid (1.03 g, 92% yield).

R_f= 0.73 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.47 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 2H), 3.20 – 3.09 (t, J= 5.6 Hz, 4H), 1.81 – 1.71 (p, J= 5.8 Hz, 4H), 1.61 – 1.40 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.46, 133.32, 132.95, 128.77, 127.15, 52.11, 25.31, 24.23.

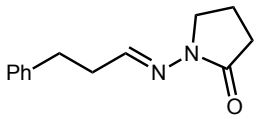
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{12}H_{16}N_2Cl$, 223.09965; found 223.0994.



***tert*-butyl (*E*)-2-(3-phenylpropylidene)hydrazine-1-carboxylate (S18):** Prepared according to general procedure SA using 3-phenylpropanal (3.00 mmol, 0.395 mL, 1.0 equiv), tert-butyl hydrazinecarboxylate (3.0 mmol, 396 mg, 1.0 equiv) and DCM (3 mL). The crude reaction was purified via silica chromatography (10-50% EtOAc/hexanes as eluent) to afford the title compound

as a white solid (739 mg, 99% yield). The physical properties and spectral data were consistent with the reported values.[10]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 7.15 (br s, 1H), 2.88 – 2.81 (m, 2H), 2.67 – 2.59 (m, 2H), 1.50 (s, 9H).



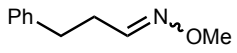
(*E*)-1-((3-phenylpropylidene)amino)pyrrolidin-2-one (S19): Prepared according to general procedure SA using 3-phenylpropanal (3.00 mmol, 0.395 mL, 1.0 equiv), 1-Aminopyrrolidin-2-one hydrochloride (3.30 mmol, 450 mg, 1.1 equiv) and DCM (3 mL). The crude reaction was purified via silica chromatography (50-100% EtOAc/hexanes as eluent) to afford the title compound as an off white solid (383 mg, 59% yield).

R_f= 0.07 (100% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 6.5 Hz, 2H), 7.24 – 7.18 (m, 3H), 7.18- 7.13 (m, 1H), 3.60 – 3.49 (m, 2H), 2.87 (t, J= 7.6 Hz, 2H), 2.78 – 2.69 (m, 2H), 2.58 – 2.50 (m, 2H), 2.20 – 2.08 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.52, 148.51, 140.77, 128.70, 128.54, 126.38, 44.73, 34.60, 33.37, 30.20, 16.21.

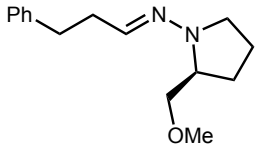
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{13}H_{17}ON_2$, 217.13354; found 217.13352.



3-phenylpropanal *O*-methyl oxime (S20): An RBF was charged with sodium acetate (7.50 mmol, 615 mg, 1.5 equiv) and methoxyamine hydrochloride (7.50 mmol, 627 mg, 1.5 equiv) and dissolved in MeOH/H_2O (10 mL, 9:1). 3-phenylpropanal (5.00 mmol, 0.658 mL, 1.0 equiv) was

added dropwise to the mixture. The reaction was stirred overnight at room temperature. The reaction was concentrated, diluted in H_2O and extracted with EtOAc (3x). The combined organic phase was washed with H_2O (2x) and brine (1x), dried over Na_2SO_4 and concentrated *in vacuo*. The reaction was purified by silica chromatography (5-20% EtOAc/hexanes) to afford the title compound as a clear oil (572 mg, 70% yield, 1.0 : 1.4 dr). The physical properties and spectral data were consistent with the reported values.[5] (#denotes major diastereomer, *denotes minor diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 6.0 Hz, 1H, #), 7.34 – 7.27 (m, 2H, #*), 7.23 – 7.13 (m, 3H, #*), 6.72 – 6.63 (t, J=5.36 Hz, 1 H, *), 3.87 (s, 3H, *), 3.82 (s, 3H, #), 2.85 – 2.77 (m, 2H, *,#), 2.69 – 2.61 (m, 2H, *), 2.55 – 2.47 (m, 2H, #).



(*S*,*E*)-*N*-(2-(methoxymethyl)pyrrolidin-1-yl)-3-phenylpropan-1-imine (S21): Prepared according to general procedure SA using 3-phenylpropanal (3.00 mmol, 0.395 mL, 1.0 equiv), (*S*)-2-(methoxymethyl)pyrrolidin-1-amine (3.30 mmol, 0.440 mL, 1.1 equiv) and DCM (5 mL). The crude reaction was purified via silica chromatography (20-30% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (680 mg, 92% yield). The physical properties and spectral data were consistent with the reported values.[11]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.14 (m, 3H), 6.66 (t, J= 5.4 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.44 – 3.39 (m, 2H), 3.38 (s, 3H), 3.36 – 3.31 (m, 1H), 2.80 (dd, *J* = 9.2, 6.7 Hz, 2H), 2.71 (q, *J* = 8.4 Hz, 1H), 2.54 (dd, *J* = 13.1, 7.8 Hz, 2H), 2.00 – 1.84 (m, 3H), 1.84 – 1.73 (m, 1H).

4.5.4 Preparation of Products from Substrate Table

4.5.4A General Procedures

General Procedure A

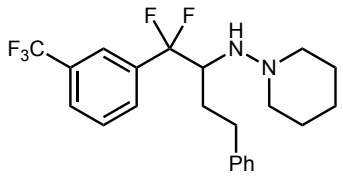
A 15 mL oven-dried screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (4.0 equiv), mesna (20 mol%) hydrazone (1.0 equiv, *if solid or oil*) and CF_3-arene (3.0 equiv, *if solid or oil*). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent (DMSO, 0.1 M) was added via syringe followed by hydrazone (1.0 equiv, *if liquid*) and CF_3-arene (3.0 equiv, *if lqiuid*) The resulting mixture was stirred for 16 h under irradiation by blue LEDs at 80 °C. Upon completion, the reaction was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were passed through silica to remove excess DMSO and concentrated *in vacuo*. The residue was then purified by silica chromatography using the indicated solvent mixture as the eluent to afford the title compound.

General Procedure B

A 15 mL oven-dried screw-top test tube was charged with 4CzIPN (1 mol%), sodium formate (4.0 equiv), mesna (20 mol%) hydrazone (1.0 equiv, *if solid or oil*) and CF_3-arene (3.0 equiv, *if solid or oil*). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, the degassed solvent (DMSO, 0.1 M) was added via syringe followed by hydrazone (1.0 equiv, *if liquid*), CF_3-arene (3.0 equiv, *if lqiuid*) and formic acid (3.0 equiv). The resulting mixture was stirred for 16 h under irradiation by blue LEDs at 80 °C. Upon completion, the reaction was diluted with H_2O and extracted with EtOAc

(3x). The combined organic layers were passed through silica to remove excess DMSO and concentrated *in vacuo*. The residue was then purified by silica chromatography using the indicated solvent mixture as the eluent to afford the title compound.

4.5.5B Isolated Products from Substrate Table



***N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (3):** Prepared according to general procedure A using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 108 mg, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (10% EtOAc/hexanes as eluent) to afford the title compound as yellow oil (169 mg, 82% yield).

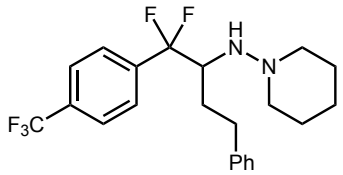
R_f= 0.70 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.67 (t, *J* = 8.9 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 6.9 Hz, 2H), 3.39 – 3.29 (m, 1H), 2.84 – 2.76 (m, 1H), 2.76 – 2.67 (m, 1H), 2.59 – 2.02 (m, 5H), 1.68 – 1.57 (m, 1H), 1.29 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.26, 137.75- 137.39 (m), 130.36 (q, *J* = 32.6 Hz), 129.57 (t, *J* = 6.5 Hz), 128.66, 128.48, 128.39, 126.31, 126.25 (m), 124.09 (q, *J* = 272.0 Hz), 123.63 (dt, *J* = 8.8, 4.1 Hz), 122.08 (dd, *J* = 249.1, 245.2 Hz), 62.71 (dd, *J* = 29.3, 26.0 Hz), 57.24, 32.72, 29.66, 26.07, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.69 (s, 3F), -97.89 (dd, *J* = 246.9, 7.6 Hz, 1F), -111.71 (dd, *J* = 247.3, 16.3 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{22}H_{26}N_2F_5$, 413.20107; found 413.20116.



***N*-(1,1-difluoro-4-phenyl-1-(4-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (4):** Prepared according to general procedure B using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.250 mmol, 54.1 mg, 1.0 equiv), 1,4-Bis(trifluoromethyl)benzene (0.750 mmol, 0.116 mL, 3.0 equiv), 4CzIPN (2.50 μmol, 2.0 mg, 1 mol%), sodium formate (1.00 mmol, 68.0 mg, 4.0 equiv), mesna (0.05 mmol, 8.20 mg, 20 mol%), formic acid (0.750 mmol, 28.0 μL, 3.0 equiv) in DMSO (2.5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-10% EtOAc/hexanes as eluent with 5% triethylamine) to afford the title compound as yellow oil (75.2 mg, 73% yield).

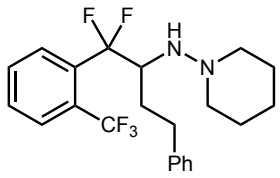
R_f= 0.61 (10% EtOAc/ hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.50 (m, 4H), 7.28 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.14 (m, 2H), 3.39 – 3.29 (m, 1H), 2.80 (m, 1H), 2.75 – 2.65 (m, 1H), 2.58 – 2.12 (m, 4H), 2.11 – 1.99 (m, 1H), 1.66 – 1.55 (m, 1H), 1.44 – 1.19 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.30, 140.08 (t, *J* = 26.4 Hz), 131.66 (q, *J* = 32.5 Hz), 128.63, 128.48, 126.87 (dd, *J* = 7.6, 5.4 Hz), 126.27, 124.82 (q, *J* = 3.8 Hz), 124.04 (q, *J* = 272.6 Hz), 122.15 (dd, *J* = 248.8, 245.5 Hz), 62.75 (t, *J* = 27.4 Hz), 57.34, 32.71, 29.82, 26.07, 23.79.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72 (s, 3F), -99.27 (dd, *J* = 247.3, 8.7 Hz, 1F), -110.34 (dd, *J* = 247.3, 14.9 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{22}H_{26}N_2F_5$, 413.20107; found 413.20126.



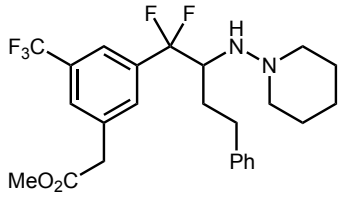
***N*-(1,1-difluoro-4-phenyl-1-(2-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (5):** Prepared according to general procedure B using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 54.1 mg, 1.0 equiv), 1,2-bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.90 mg, 1 mol%), sodium formate (2.00 mmol, 0.140 g, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%), formic acid (1.50 mmol, 56.0 μL, 3.0 equiv) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-10% EtOAc/hexanes as eluent). This was further purified by a second column (0-10% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (110.3 mg, 54% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (t, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 3.58 – 3.49 (m, 1H), 2.84 – 2.76 (m, 1H), 2.75 – 2.67 (m, 1H), 2.57 – 1.84 (m, 5H), 1.80 – 1.71 (m, 1H), 1.41 – 0.85 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.41, 135.36 (t, *J* = 27.1 Hz), 130.98, 129.47 (m), 129.45, 128.60, 128.47, 127.95 (qd, *J* = 32.1, 4.1 Hz), 127.07 (q, *J* = 6.6 Hz), 126.23, 123.97 (q, *J* = 273.4 Hz), 122.13 (dd, *J* = 250.4, 246.6 Hz), 62.09 (td, *J* = 27.9, 3.0 Hz), 56.68, 32.86, 29.32 (d, *J* = 5.5 Hz), 26.02, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -57.30 (dd, *J* = 21.8, 7.3 Hz, 3F), -98.56 (dqd, *J* = 251.8, 21.2, 5.9 Hz, 1F), -105.05 (ddq, *J* = 251.8, 20.8, 7.3 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{22}H_{26}N_2F_5$, 413.20107; found 413.20115.



Methyl 2-(3-(1,1-difluoro-4-phenyl-2-(piperidin-1-ylamino)butyl)-5 (trifluoromethyl)phenyl)acetate (**6**): Prepared according to general procedure B using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.100 mmol, 21.8 mg, 1.0 equiv), methyl 2-(3,5-bis(trifluoromethyl)phenyl)acetate **S1** (0.300 mmol, 85.9 mg, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0 equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%), formic acid (0.300 mmol, 11.0 μL, 3.0 equiv) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica prep plate (10% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (35.0 mg, 72% yield).

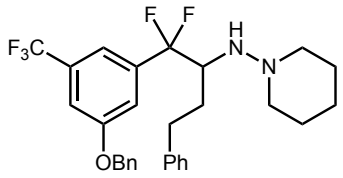
$\mathbf{R_f}$= 0.48 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.59 (s, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (dd, *J* = 19.4, 7.5 Hz, 3H), 3.71 (s, 2H), 3.69 (s, 3H), 3.39 – 3.25 (m, 1H), 2.85 – 2.67 (m, 2H), 2.62 – 2.04 (m, 5H), 1.68 – 1.56 (m, 1H), 1.37 – 1.16 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.94, 141.22, 137.98 (t, *J* = 26.8 Hz), 134.65, 130.65 (q, *J* = 32.6 Hz), 130.63 – 130.43 (m), 128.66, 128.47, 127.16 (m), 126.31, 123.8 (q, J= 272.5 Hz), 126.70 – 120.91 (m), 121.93 (dd, J=244.71, 248.93 Hz), 62.73 (dd, *J* = 29.3, 26.0 Hz), 57.28, 52.37, 40.90, 32.69, 29.53, 26.04, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.61 (s, 3F), -97.79 (dd, *J* = 247.1, 7.5 Hz, 1F), -112.08 (dd, *J* = 246.7, 16.5 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{25}H_{30}O_2N_2F_5$, 485.22220; found 485.22221.



***N*-(1-(3-(benzyloxy)-5-(trifluoromethyl)phenyl)-1,1-difluoro-4-phenylbutan-2-yl)piperidin-1-amine (7):** Prepared according to general procedure B using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 108 mg, 1.0 equiv), 1-(benzyloxy)-3,5-bis(trifluoromethyl)benzene **S2** (1.50 mmol, 0.480 g, 3.0 equiv), 4CzIPN (5.00 μmol, 3.90 mg, 1 mol%), sodium formate (2.00 mmol, 0.136 g, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%), formic acid (1.50 mmol, 56 μL, 3.0 equiv) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (195 mg, 75% yield).

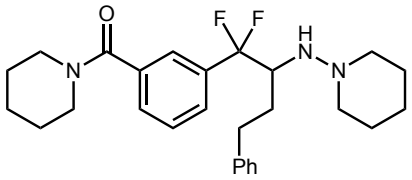
R_f=0.41 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 6H), 7.31 – 7.27 (m, 3H), 7.25 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.10 (s, 2H), 3.40 – 3.20 (m, 1H), 2.81 – 2.65 (m, 2H), 2.59 – 2.12 (m, 4H), 2.10 – 2.01 (m, 1H), 1.67 – 1.57 (m, 1H), 1.41 – 1.16 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.62, 141.28, 139.05 (t, *J* = 26.9 Hz), 136.08, 131.61 (q, *J* = 32.6 Hz), 128.86, 128.64, 128.49, 127.72, 126.28, 123.84 (q, J= 272.9 Hz), 121.87 (dd, J= 246.0, 246.1 Hz), 116.20 (t, J=6.4 Hz), 116.11-115.84 (m), 112.86, 112.84, 70.64, 62.63 (dd, J= 28.37, 26.2 Hz), 57.30, 32.69, 29.70, 26.12, 23.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72 (s, 3F), -98.65 (dd, *J* = 245.9, 9.0 Hz, 1F), -110.46 (dd, *J* = 246.2, 16.0 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{29}H_{32}ON_2F_5$, 519.24293; found 519.24316.



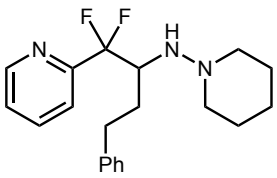
(3-(1,1-difluoro-4-phenyl-2-(piperidin-1-ylamino)butyl)phenyl)(piperidin-1-yl)methanone (8): Prepared according to general procedure A using ((E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.100 mmol, 216 mg, 1.0 equiv), piperidin-1-yl(3-(trifluoromethyl)phenyl)methanone **S3** (0.300 mmol, 771 mg, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0 equiv), and mesna (20.0 μmol, 3.28 mg, 20 mol%) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica chromatography (2-30% EtOAc/DCM as eluent) followed by further purification by silica prep plate (5% EtOAc/DCM as eluent) to afford the title compound as clear oil (8.40 mg, 18% yield).

R_f= 0.41 (20% EtOAc/DCM)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.47 – 7.39 (m, 2H), 7.32 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 3.86 – 3.59 (m, 2H), 3.49 – 3.14 (m, 3H), 2.84 – 2.74 (m, 1H), 2.74 – 2.64 (m, 1H), 2.58 – 2.18 (m, 5H), 2.06 – 1.92 (m, 1H), 1.74 – 1.56 (m, 6H), 1.50 – 1.37 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.74, 141.68, 136.55 (t, J= 26.5 Hz), 136.39, 128.97, 128.56, 128.53, 128.26, 128.21, 126.13, 124.81 (t, J= 6.7 Hz), 122.49 (dd, J= 246.01, 247.49 Hz), 62.81 (t, J= 27.0 Hz), 57.58, 32.75, 30.37, 30.13, 29.84, 26.19, 24.73, 23.89.

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{27}H_{36}ON_3F_2$, 456.28210; found 456.28198.



***N*-(1,1-difluoro-4-phenyl-1-(pyridin-2-yl)butan-2-yl)piperidin-1-amine (9):** Prepared according to general procedure A using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 108 mg, 1.0 equiv), 2-(trifluoromethyl)pyridine (1.50 mmol, 0.173 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% acetone/hexanes as eluent) to afford the title compound as yellow oil (82.2 mg, 48% yield).

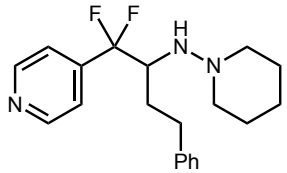
R_f= 0.12 (20% Acetone/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.2 Hz, 1H), 7.75 (td, *J* = 7.8, 2.0 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.19 (d, *J* = 7.2 Hz, 3H), 3.78 – 3.67 (m, 1H), 2.86 – 2.69 (m, 2H), 2.56 – 2.09 (m, 5H), 1.81 – 1.71 (m, 1H), 1.24 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.05 (dd, *J* = 30.4, 26.0 Hz), 149.04, 141.81, 136.49, 128.48 128.47, 126.02, 124.20, 120.59 (t, *J* = 5.3 Hz), 120.50 (dd, *J* = 248.8, 244.9 Hz), 60.91 (dd, *J* = 27.6, 23.2 Hz), 57.00, 32.82, 29.60, 26.01, 23.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -103.68 (dd, *J* = 249.0, 8.3 Hz, 1F), -116.18 (dd, *J* = 249.0, 17.3 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{26}N_3F_2$, 346.20893; found 346.20886.



***N*-(1,1-difluoro-4-phenyl-1-(pyridin-4-yl)butan-2-yl)piperidin-1-amine (10):** Prepared according to general procedure A using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 108 mg, 1.0 equiv), 4-(trifluoromethyl)pyridine (1.50 mmol, 0.173 mL, 3.0 equiv), 4CzIPN

(5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-30% EtOAc/hexanes as eluent). This was further purified by silica prep plate (60% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (19.0 mg, 11% yield).

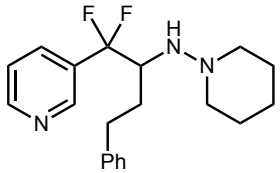
R_f= 0.67 (60% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.8 Hz, 2H), 7.41 (d, *J* = 5.1 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 3.35 (m, 1H), 2.88 – 2.64 (m, 2H), 2.35 (m, 4H), 2.12 – 2.02 (m, 1H), 1.66 – 1.55 (m, 1H), 1.45 – 1.13 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.61, 144.73 (t, *J* = 27.6 Hz), 141.09, 128.67, 128.45, 126.34, 121.38 (dd, *J* = 248.8, 245.1 Hz), 120.96 (dd, *J* = 7.1, 5.1 Hz), 62.42 (dd, *J* = 27.9, 25.9 Hz), 57.27, 32.66, 29.60, 25.96, 23.86.

^{19}F NMR (376 MHz, $CDCl_3$) δ -100.54 (d, *J* = 245.5 Hz, 1F), -113.28 (d, *J* = 246.9 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{26}N_3F_2$, 346.2089; found 346.2097



***N*-(1,1-difluoro-4-phenyl-1-(pyridin-3-yl)butan-2-yl)piperidin-1-amine (11):** Prepared according to general procedure A using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.500 mmol, 108 mg, 1.0 equiv), 3-(trifluoromethyl)pyridine (1.50 mmol, 0.173 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100

mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (5-25% acetone/hexanes as eluent) to afford the title compound as a yellow oil (30.0 mg, 17% yield).

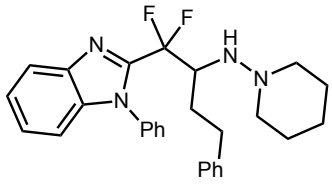
R_f= 0.29 (50% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.64 (d, *J* = 4.9 Hz, 1H), 7.79 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.26 – 7.10 (m, 3H), 3.47 – 3.24 (m, 1H), 2.92 – 2.63 (m, 2H), 2.57 – 2.00 (m, 5H), 1.66 – 1.54 (m, 1H), 1.43 – 1.14 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.51, 147.98 (dd, *J* = 8.3, 5.5 Hz), 141.17, 133.95 (dd, *J* = 7.7, 5.0 Hz), 132.21 (t, *J* = 26.5 Hz), 128.66, 128.45, 126.31, 122.56, 121.90 (dd, *J* = 249.1, 245.2 Hz), 62.76 (dd, *J* = 29.3, 26.5 Hz), 57.25, 32.71, 29.67, 26.09, 23.77.

^{19}F NMR (376 MHz, $CDCl_3$) δ -97.72 (dd, *J* = 251.3, 7.5 Hz), -112.34 (dd, *J* = 251.1, 16.0 Hz).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{26}N_3F_2$, 346.20893; found 346.20942.



***N*-(1,1-difluoro-4-phenyl-1-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)butan-2-yl)piperidin-1-amine (12):** Prepared according to general procedure A using (E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.250 mmol, 54.1 mg, 1.0 equiv), 1-phenyl-2-(trifluoromethyl)-1H-benzo[d]imidazole **S4** (0.750 mmol, 0.197 g, 3.0 equiv), 4CzIPN (2.50 μmol, 2.0 mg, 1 mol%),

sodium formate (1.00 mmol, 68.0 mg, 4.0 equiv), mesna (0.05 mmol, 8.20 mg, 20 mol%), formic acid (0.750 mmol, 28.0 μL, 3.0 equiv) in DMSO (2.5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-20% EtOAc/hexanes as eluent) followed by further purification by silica prep plate (20% EtOAc/hexanes as eluent) to afford the title compound as clear oil (44.0 mg, 38% yield).

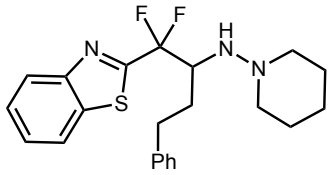
R_f= 0.29 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.53- 7.46 (m, 3H), 7.44 – 7.26 (m, 4H), 7.22 – 7.08 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 3.51 – 3.39 (m, 1H), 2.83-2.61 (m, 3H), 2.38 (br s, 3H), 2.16- 2.08 (m, 1H), 1.89 – 1.77 (m, 1H), 1.40 – 1.10 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 146.93 (t, *J* = 30.5 Hz), 141.58, 141.31, 137.72, 135.98, 129.55-129.04 (m), 129.34, 128.60- 127.92 (m), 128.53, 128.50, 126.04, 124.50, 123.19, 120.76, 118.55 (dd, *J* = 249.6, 244.1 Hz), 110.90, 61.44 (dd, *J* = 26.4, 22.1 Hz), 57.52, 32.52, 29.11, 26.00, 23.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -97.86 (dd, *J* = 269.1, 8.7 Hz, 1F), -106.91 (dd, *J* = 269.6, 17.2 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{28}H_{31}N_4F_2$, 461.25113; found 461.25103.



***N*-(1-(benzo[*d*]thiazol-2-yl)-1,1-difluoro-4-phenylbutan-2-yl)piperidin-1-amine (13):**

Prepared according to general procedure B using ((E)-3-phenyl-N-(piperidin-1-yl)propan-1-imine **S6** (0.100 mmol, 216 mg, 1.0 equiv), 2-(trifluoromethyl)benzo[d]thiazole **S5** (0.300 mmol, 0.0609, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0

equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%), formic acid (0.300 mmol, 11 μL, 3.0 equiv) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) followed by further purification by silica prep plate (10% Acetone/hexanes as eluent) to afford the title compound as clear oil (15.0 mg, 37% yield).

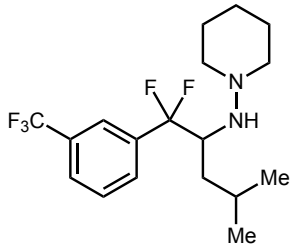
R_f= 0.63 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.49 – 7.41 (m, 1H), 7.31 – 7.26 (m, 2H), 7.20 (m, 3H), 3.83 – 3.72 (m, 1H), 2.92 – 2.72 (m, 2H) 2.64 – 2.14 (m, 5H), 1.87 – 1.75 (m, 1H), 1.34 – 1.01 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.95 (dd, *J* = 34.0, 31.1 Hz), 152.79, 141.32, 135.31, 128.64, 128.55, 126.57, 26.28, 126.15, 124.18, 121.86, 119.46 (dd, *J* = 249.3, 246.0 Hz), 61.69 (dd, *J* = 26.6, 23.5 Hz), 57.18, 32.78, 29.39 (t, *J* = 2.5 Hz), 25.93, 23.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -95.08 (dd, *J* = 259.7, 7.6 Hz, 1F), -107.07 (dd, *J* = 259.7, 16.0 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{22}H_{26}N_3F_2S$, 402.18100; found 402.18121.



***N*-(1,1-difluoro-4-methyl-1-(3-(trifluoromethyl)phenyl)pentan-2-yl)piperidin-1-amine (14):** Prepared according to general procedure A using (*E*)-3-methyl-*N*-(piperidin-1-yl)butan-1-imine **S7** (0.500 mmol, 97 μL, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked

up and purified by silica chromatography (0-20% EtOAc/hexanes as eluent) to afford the title compound as yellow oil (112 mg, 62% yield).

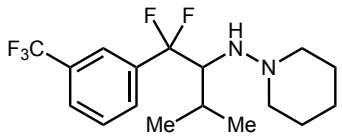
R_f= 0.71 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 3.39 – 3.27 (m, 1H), 2.59 – 1.89 (m, 4H), 1.67 (m, 1H), 1.50 (m, 1H), 1.35 – 1.14 (m, 7H), 0.96 (t, *J* = 6.9 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.88 (t, *J* = 26.8 Hz), 130.19 (q, *J* = 32.6 Hz), 129.66 (t, *J* = 6.4 Hz), 128.21, 126.03, 124.17 (q, *J* = 272.2 Hz), 127.05 – 121.36 (m), 122.13 (dd, J= 248.2, 244.2 Hz), 61.16 (dd, *J* = 29.8, 26.6 Hz), 57.14, 37.09, 26.05, 24.72, 24.02, 23.80, 21.97.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.69 (s, 3F), -96.89 (dd, *J* = 246.0, 6.8 Hz, 1F), -113.69 (dd, *J* = 245.5, 16.3 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{18}H_{26}N_2F_5$, 365.20107; found 365.20107.



***N*-(1,1-difluoro-3-methyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (15):**

Prepared according to general procedure A using (E)-2-methyl-N-(piperidin-1-yl)propan-1-imine **S8** (0.500 mmol, 88 μL, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 140 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-10% EtOAc/hexanes as eluent) to afford the title compound as clear oil (72.3 mg, 41% yield).

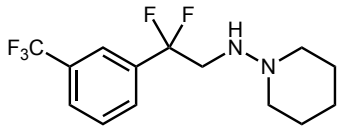
R_f= 0.52 (10% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 3.19 – 3.10 (m, 1H), 2.68 – 1.85 (m, 5H), 1.37 – 1.13 (m, 6H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.60 (qt, *J* = 26.7, 7.3 Hz), 130.27 (q, *J* = 32.5 Hz), 129.50 (t, *J* = 6.6 Hz), 128.30, 126.02, 124.15 (q, *J* = 272.3 Hz), 127.25 – 120.91 (m), 122.79 (dd, *J* = 252.1, 244.9 Hz), 68.03 – 66.70 (m), 56.94, 27.06, 26.07, 23.81, 21.70, 17.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.68 (s, 3F), -96.27 (dd, *J* = 245.5, 8.3 Hz, 1F), -110.95 (dd, *J* = 245.5, 20.8 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{17}H_{24}N_2F_5$, 351.18542; found 351.18622.



***N*-(2,2-difluoro-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (16):** Prepared according to a slighty modified version of general procedure B using *N*-(piperidin-1-yl)methanimine **S9** (0.300 mmol, 34.7 μL, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (0.100 mmol, 16.0 μL, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.800 mmol, 54.4 mg, 4.0 equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%), formic acid (0.300 mmol, 11.0 μL, 3.0 equiv) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica chromatography (5-50% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (8.2 mg, 27% yield).

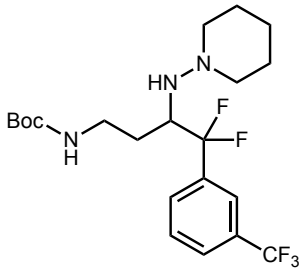
R_f=0.56 (40% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 3.45 (t, *J* = 13.5 Hz, 2H), 2.75 – 2.10 (m, 4H), 1.47 (p, *J* = 5.6 Hz, 4H), 1.37 – 1.11 (m, 2H).

^{13}C NMR (101 MHz, MeOD) δ 137.4 (t, J= 26.17), 132.1 (q, J= 32.86 Hz), 130.9, 130.7 (t, J=6.26 Hz), 128.6- 128.4 (m), 125.3 (q, J= 272.82), 123.9-123.2 (m), 120.8 (t, J=243.80 Hz), 56.7, 52.1 (t, J=31.4), 24.0, 22.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.78(s, 3F), -99.69 (t, *J* = 13.5 Hz, 2F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{14}H_{18}N_2F_5$, 309.1385; found 309.1391



Tert-butyl (4,4-difluoro-3-(piperidin-1-ylamino)-4-(3-(trifluoromethyl)phenyl)butyl carbamate (17): Prepared according to general procedure A *tert*-butyl (*E*)-(3-(piperidin-1-ylimino)propyl)carbamate **S10** (0.500 mmol, 128 mg, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 140 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (3-20% EtOAc/hexanes as eluent) to afford the title compound as clear oil (134 mg, 59% yield).

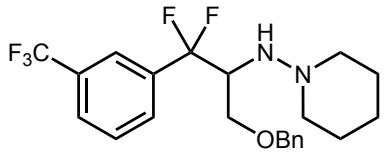
R_f=0.59 (30% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.9 Hz, 1H), 5.66 (br s, 1H), 3.43 – 3.30 (m, 1H), 3.21 (m, 2H), 2.42 (br s, 4H), 1.92 (m, 1H), 1.74 – 1.39 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.13 136.79 (t, J= 25.61 Hz), 130.79 (q, J=32.88 Hz), 129.45 (t, J= 6.22 Hz), 128.84, 126.76, 123.96 (q, J= 273.06 Hz), 123.29 (m), 121.82 (dd, J= 246.03, 247.48 Hz), 79.19, 61.26 (t, J= 27.64 Hz), 57.22, 38.26, 29.53, 28.55, 25.96, 23.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.73 (s, 3F), -100.50 (dd, *J* = 249.0, 8.0 Hz, 1F), -108.28 (dd, *J* = 249.5, 14.0 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{21}H_{31}O_2N_3F_5$, 452.23309; found 452.23278



***N*-(3-(benzyloxy)-1,1-difluoro-1-(3-(trifluoromethyl)phenyl)propan-2-yl)piperidin-1-amine (18):** Prepared according to general procedure A (*E*)-2-(benzyloxy)-*N*-(piperidin-1-yl)ethan-1-imine **S11** (0.500 mmol, 116 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) to afford the title compound as clear oil (130 mg, 61% yield).

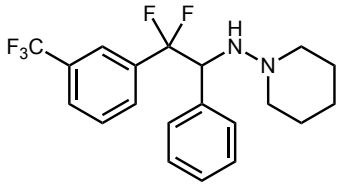
R_f= 0.64 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.68 (dd, *J* = 13.9, 7.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.32 – 7.26 (m, 3H), 4.58 – 4.47 (dd, J= 15.24, 11.87 Hz, 2H), 3.86 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.68 – 3.57 (m, 1H), 3.45 (t, *J* = 9.4 Hz, 1H), 2.73 – 1.80 (m, 4H), 1.37 – 1.07 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.83, 137.71 – 137.16 (m), 130.28 (q, *J* = 32.6 Hz), 129.53 (t, *J* = 6.7 Hz), 128.60, 128.32, 127.94, 127.68, 129.53 (m), 124.0 (q, J= 271.92 Hz), 137.71 – 137.16 (m), 121.38 (dd, *J* = 249.9, 244.4 Hz), 73.49, 66.66 (dd, *J* = 5.3, 3.0 Hz), 63.56 (dd, *J* = 30.3, 24.8 Hz), 56.94, 26.03, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.71, -96.86 (dd, *J* = 247.2, 5.9 Hz), -113.28 (dd, *J* = 247.2, 18.6 Hz).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{22}H_{26}ON_2F_5$, 429.19598; found 429.19718.



***N*-(2,2-difluoro-1-phenyl-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (19):**

Prepared according to general procedure A using (*E*)-1-phenyl-*N*-(piperidin-1-yl)methanimine **S12** (0.500 mmol, 94.1 mg, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-10% EtOAc/hexanes as eluent) to afford the title compound as yellow oil (128 mg, 67% yield).

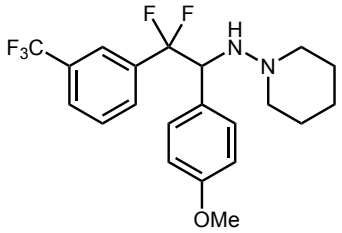
R_f= 0.44 (10% EtOAc/ hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.59 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.25 – 7.19 (m, 2H), 4.43 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.73 – 2.16 (m, 4H), 1.55 – 1.01 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.16-136.78 (m), 136.80, 130.17 (q, 32.71 Hz), 129.86-129.78 (m), 129.04, 128.44, 128.24, 128.19, 124.03 (q, *J* = 272.3 Hz), 126.32-126.24 (m), 123.84 (tq, *J* = 7.7, 3.9 Hz), 121.23 (dd, *J* = 249.9, 247.7 Hz), 68.38 (dd, *J* = 28.7, 26.0 Hz), 57.59, 25.96, 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75(s, 3F), -98.66 (dd, *J* = 247.3, 8.7 Hz, 1F), -106.76 (dd, *J* = 247.3, 14.2 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{22}N_2F_5$, 385.16977; found 385.16918.



***N*-(2,2-difluoro-1-(4-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (20):** Prepared according to general procedure A using (*E*)-1-(4-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine **S13** (0.500 mmol, 94.1 mg, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 140 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-10% EtOAc/hexanes as eluent). Some of the product co-eluted with a byproduct, this was further purified by a silica gel prep plate (20% EtOAc/hexanes) to afford the title compound as yellow oil (111 mg, 54% yield).

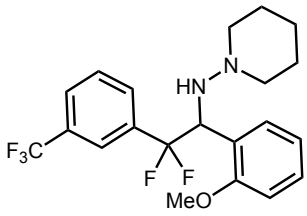
R_f= 0.60 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.60 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.78 (m, 2H), 4.38 (dd, *J* = 14.3, 8.7 Hz, 1H), 3.79 (s, 3H), 2.63 – 2.17 (m, 4H), 1.45 – 1.16 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.70, 137.09 (t, *J* = 26.9 Hz), 130.14 (q, 32.6 Hz), 130.11, 129.83 (t, *J* = 6.4 Hz), 128.82, 128.23, 128.17, 126.22 (q, *J* = 4.0 Hz), 124.06 (q, *J* = 272.6 Hz), 121.30 (dd, J=247.69, 249.24 Hz), 113.66, 67.64 (dd, *J* = 28.7, 26.0 Hz), 57.57, 55.34, 26.06, 23.91.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72 (s, 3F), -98.57 (dd, *J* = 246.6, 9.4 Hz, 1F), -107.00 (dd, *J* = 246.6, 14.2 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{21}H_{24}ON_2F_5$, 415.18033; found 415.18064.



***N*-(2,2-difluoro-1-(2-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (21):** Prepared according to general procedure B using (*E*)-1-(2-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine **S14** (0.100 mmol, 21.8 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (0.300 mmol, 47 μL, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0 equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%), formic acid (0.300 mmol, 11.0 μL, 3.0 equiv) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (25.8 mg, 62% yield).

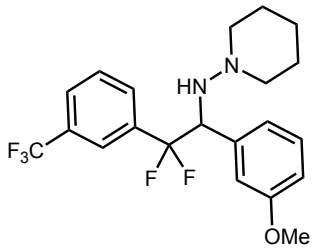
R_f= 0.54 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CCCl_3$) δ 7.64 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.28 – 7.21 (m, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.02 (t, *J* = 12.9 Hz, 1H), 2.83 – 2.10 (m, 4H), 1.40 (m, 4H), 1.29 – 1.18 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.08, 137.67 (t, *J* = 26.8 Hz), 129.99 (q, *J* = 32.6 Hz), 137.67 (t, *J* = 26.8 Hz), 129.38, 129.33, 127.97, 126.02 (m), 125.60 (m), 124.11 (q, *J* = 272.1 Hz), 123.63 (td, *J* = 6.5, 3.3 Hz), 121.31 (dd, 248.13, 250.20), 120.50, 110.46, 60.11 (t, *J* = 26.0 Hz), 57.60, 55.29, 25.97, 23.70.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.67 (s, 3F), -102.47 (d, *J* = 244.5 Hz, 1F), -106.44 (dd, *J* = 242.6, 13.4 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{21}H_{24}ON_2F_5$, 415.18033; found 415.18128.



***N*-(2,2-difluoro-1-(3-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (22):** Prepared according to general procedure B using (*E*)-1-(4-methoxyphenyl)-*N*-(piperidin-1-yl)methanimine **S15** (0.500 mmol, 94.1 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%), formic acid (1.50 mmol, 56.0 μL, 3.0 equiv) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) to afford the title compound as yellow oil (88.2 mg, 43% yield).

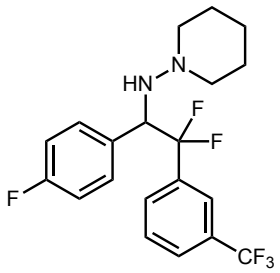
R_f= 0.60 (20% EtOAc/hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.60 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.88 – 6.74 (m, 3H), 4.40 (dd, *J* = 14.3, 8.8 Hz, 1H), 2.42 (m, 4H), 1.57 – 1.00 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.45, 138.33 (t, *J* = 2.0 Hz), 136.95 (t, *J* = 26.8 Hz), 130.17 (q, *J* = 32.8 Hz), 129.84 (t, *J* = 6.2 Hz), 129.20, 128.20, 128.09, 126.30 (m), 124.03 (q, J= 273.1 Hz), 123.87 (m), 121.19 (dd, J= 247.8, 250.2), 114.52, 114.05, 68.40 (dd, *J* = 28.4, 26.3 Hz), 57.64, 55.33, 25.98, 23.81.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.74 (s, 3F), -98.81 (dd, *J* = 247.2, 8.8 Hz, 1F), -106.56 (dd, *J* = 247.2, 14.4 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{21}H_{24}ON_2F_5$, 415.18033; found 415.18036.



***N*-(2,2-difluoro-1-(4-fluorophenyl)-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (23):** Prepared according to general procedure B using (*E*)-1-(4-fluorophenyl)-*N*-(piperidin-1-yl)methanimine **S16** (0.100 mmol, 206 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (0.300 mmol, 47 μL, 3.0 equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0 equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%), formic acid (0.300 mmol, 11.0 μL, 3.0 equiv) in DMSO (1 mL). After 16 hours the reaction was worked up and purified by silica chromatography (0-12% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (31.1 mg, 77% yield).

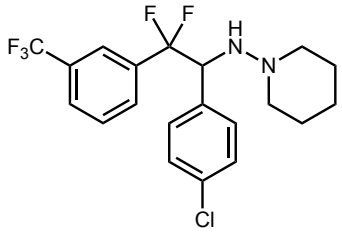
R_f= 0.72 (20% EtOAc/hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (m, 1H), 7.57 (s, 1H), 7.46 (m, 2H), 7.22 – 7.16 (m, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 4.43 (dd, *J* = 13.8, 9.1 Hz, 1H), 2.51 (m, 4H), 1.49 – 1.19 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.82 (d, *J* = 247.1 Hz), 136.66 (t, *J* = 26.8 Hz), 132.45, 130.73 (d, *J* = 7.7 Hz), 130.33 (q, *J* = 32.6 Hz), 129.74 (t, *J* = 6.1 Hz), 128.33, 126.46 (m), 123.97 (q, *J* = 272.0 Hz), 123.72 (tq, *J* = 7.6, 4.1 Hz), 121.07 (dd, *J* = 248.77 Hz, 248.53), 115.13 (d, *J* = 21.6 Hz), 67.51 (t, *J* = 27.4 Hz), 57.52, 25.92. 23.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.77 (s, 3F), -99.35 (dd, *J* = 247.8, 8.8 Hz, 1F), -106.41 (dd, *J* = 247.8, 14.0 Hz, 1F), -113.89 (td, *J* = 8.7, 4.2 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{21}N_2F_6$, 403.16034; found 403.16135.



***N*-(1-(4-chlorophenyl)-2,2-difluoro-2-(3-(trifluoromethyl)phenyl)ethyl)piperidin-1-amine (24):** Prepared according to general procedure B using (*E*)-1-(4-chlorophenyl)-*N*-(piperidin-1-yl)methanimine **S17** (0.500 mmol, 111 mg, 1.0 equiv), 1,3- bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.90 mg, 1 mol%), sodium formate (2.00 mmol, 0.136 g, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%), formic acid (1.50 mmol, 56.0 μL, 3.0 equiv) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (3-10% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (111 mg, 53% yield).

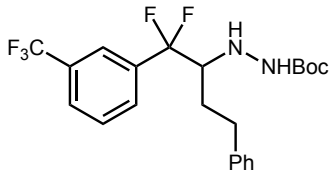
R_f=0.46 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 1H), 7.59 (s, 1H), 7.45 (dt, *J* = 4.6, 1.3 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.43 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.60 (br s, 1H), 2.41 (br s, 3H), 1.36 (m, 4H), 1.28 – 1.17 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.80 (t, J= 26.75 Hz), 135.21 (t, *J* = 2.0 Hz), 134.29, 130.46, 130.37 (q, J= 32.72 Hz), 129.72 (t, J= 5.96 Hz), 128.39, 128.38, 126.54, 123.95 (q, J= 271.09 Hz), 123.68 (m), 120.94 (dd, J= 248.52, 249.18 Hz), 67.64 (dd, *J* = 28.2, 26.4 Hz), 57.52, 25.92, 23.78.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.78 (s, 3F), -99.24 (dd, *J* = 248.5, 9.2 Hz, 1F), -106.25 (dd, *J* = 248.3, 13.9 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{20}H_{21}N_2ClF_5$, 419.13079; found 419.1305.



***tert*-butyl 2-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)hydrazine-1-carboxylate (25):** Prepared according to general procedure A using *tert*-butyl (*E*)-2-(3-phenylpropylidene)hydrazine-1-carboxylate **S18** (0.500 mmol, 124 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (5-12% EtOAc/hexanes as eluent) to afford the title compound as yellow oil (95.5 mg, 43% yield).

R_f= 0.52 (20% EtOAc/hexanes)

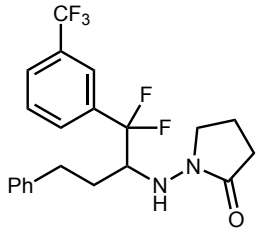
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.22 - 7.13 (m, 3H), 6.09 (s, 1H), 4.11 (s, 1H), 3.39 (tdt, *J* = 11.6, 9.2, 2.7 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.89 – 2.76 (m, 1H), 1.86 – 1.75 (m, 1H), 1.65 – 1.55 (m, 1H), 1.51 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.47, 141.18, 136.21 (t, *J* = 26.7 Hz), 130.99 (q, *J* = 32.8 Hz), 129.46 (t, *J* = 6.1 Hz), 129.03, 128.60, 128.53, 127.31 – 126.60 (m), 126.20, 123.83 (q, J= 272.80),

123.26 – 123.02 (m), 122.58 (t, J= 246.80 Hz), 80.93, 65.24 (t, *J* = 25.8 Hz), 32.09, 29.39, 28.43.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.65 (s, 3F), -99.65 – -108.98 (m, 2F).

HRMS (APCI) *m/z*: [M+Na] calcd. for $C_{22}H_{25}O_2N_2F_5{}^{23}Na$, 467.17284; found 467.17266.



1-((1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)amino)pyrrolidin-2-one (26): Prepared according to general procedure A using (*E*)-1-((3-phenylpropylidene)amino)pyrrolidin-2-one **S19** (0.500 mmol, 108 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (30-100% EtOAc/hexanes as eluent) to afford the title compound as a clear oil (50.0 mg, 24% yield).

R_f= 0.48 (75% EtOAc/hexanes)

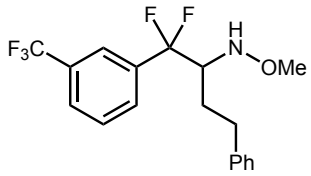
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.73 – 7.66 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 4.6 Hz, 1H), 3.48 – 3.37 (m, 1H), 3.36 – 3.27 (m, 1H), 3.26 – 3.19 (m, 1H), 3.00 – 2.90 (m, 1H), 2.90 – 2.80 (m, 1H), 2.40 – 2.31 (m, 1H), 2.30 – 2.21 (m, 1H), 2.04 – 1.94 (m, 1H), 1.93 – 1.79 (m, 2H), 1.66 – 1.56 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.62, 141.12, 136.28 (t, *J* = 26.9 Hz), 130.88 (q, *J* = 32.8 Hz), 129.64 (t, *J* = 6.3 Hz), 128.90, 128.62, 128.60, 127.14 – 126.62 (m), 126.29, 123.89 (q, J= 272.69

Hz), 123.51 – 123.15 (m), 121.64 (t, J=247.47 Hz), 63.23 (dd, *J* = 28.1, 26.9 Hz), 48.42 (t, *J* = 1.7 Hz), 32.10, 30.29 (t, *J* = 2.7 Hz), 29.12, 16.29.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.73 (s, 3F), -99.54 (dd, *J* = 253.9, 9.7 Hz, 1F), -106.46 (dd, *J* = 253.7, 12.7 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{21}H_{22}ON_2F_5$, 413.16468; found 413.16495.



***N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)-*O*-methylhydroxylamine (27):** Prepared according to general procedure A 3-phenylpropanal *O*-methyl oxime **S20** (0.500 mmol, 81.6 mg, 1.0 equiv), 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.232 mL, 3.0 equiv), 4CzIPN (5.00 μmol, 3.93 mg, 1 mol%), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 16.4 mg, 20 mol%) in DMSO (5 mL). After 16 hours the reaction was worked up and purified by silica chromatography (2-12% EtOAc/hexanes as eluent) to afford the title compound as clear oil (22 mg, 12% yield).

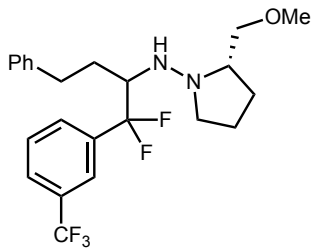
R_f=0.68 (20% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 6.8 Hz, 2H), 5.62 (s, 1H), 3.39 (s, 3H), 3.37 – 3.28 (m, 1H), 2.93 – 2.83 (m, 1H), 2.78 – 2.68 (m, 1H), 2.03 – 1.92 (m, 1H), 1.86 – 1.73 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.06, 136.82 (t, *J* = 26.9 Hz), 130.89 (q, *J* = 32.8 Hz), 129.41 (t, *J* = 6.2 Hz), 128.93, 128.68, 128.54, 126.90 – 126.70 (m), 126.35, 123.91 (q, J= 271.5 Hz), 123.33 – 123.01 (m), 121.87 (dd, J= 248.50, 249.3 Hz), 65.19 (dd, *J* = 27.7, 26.4 Hz), 62.20, 32.47, 27.79 (t, *J* = 2.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72 (s, 3F), -100.81 (dd, *J* = 252.1, 11.1 Hz, 1F), -104.63 (dd, *J* = 252.3, 13.7 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{18}H_{19}ONF_5$, 360.13813; found 360.13658.



(2*S*)-*N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)-2-(methoxymethyl)pyrrolidin-1-amine (28): Prepared according to general procedure A using (*S*,*E*)-*N*-(2-(methoxymethyl)pyrrolidin-1-yl)-3-phenylpropan-1-imine **S21** (0.100 mmol, 246 mg, 1.0 equiv), 1,3-Bis(trifluoromethyl)benzene (1.50 mmol, 47.0 μL, 3.0 equiv), 4CzIPN (1.00 μmol, 0.788 mg, 1 mol%), sodium formate (0.400 mmol, 27.2 mg, 4.0 equiv), mesna (0.020 mmol, 3.28 mg, 20 mol%) in DMSO (1 mL). Crude ^{19}F NMR analysis shows a 1.0 : 1.9 d.r. After 16 hours the reaction was worked up and purified by silica chromatography (3-20% EtOAc/hexanes as eluent) to afford the title compound as a yellow oil (10.0 mg, 23% yield, diastereomer 1and 18.6 mg, 42% yield, diastereomer 2).

Diastereomer 1:

R_f= 0.56 (30% EtOAc/hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.70 (t, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 3.52 – 3.41 (m, 2H), 3.35 – 3.30 (m, 1H), 3.30 (s, 3H), 3.18 – 3.01 (m, 1H), 2.83 – 2.66 (m, 2H), 2.64 – 2.58 (m, 1H), 2.18 (q, *J* = 8.5 Hz, 1H), 1.92 – 1.47 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.92, 136.97 (t, *J* = 27.1 Hz), 130.74 (q, *J* = 32.6 Hz), 129.50 (t, J= 5.5 Hz), 128.79, 128.65, 128.51, 126.74- 126.60 (m), 126.06, 123.97 (q, J= 272.4 Hz),

123.53- 123.34 (m), 122.37 (t, J=247.1), 75.30, 66.09, 63.62 (t, *J* = 25.7 Hz), 59.17, 56.95, 32.71, 30.94, 26.46, 21.12.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75 (s, 3F), -100.87 (dd, *J* = 251.3, 12.0 Hz, 1F), -103.94 (dd, *J* = 251.8, 12.8 Hz, 1F).

HRMS (APCI) *m/z*: [M+H] calcd. for $C_{23}H_{28}ON_2F_5$, 443.21163; found 443.21172.

Diastereomer 2:

R_f= 0.52 (30% EtOAc/hexanes)

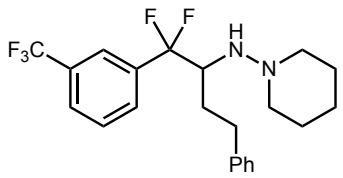
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.74 – 7.64 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.23 – 7.16 (m, 1H), 7.15 – 7.11 (m, 2H), 3.49 – 3.27 (m, 2H), 3.26 – 3.23 (m, 1H), 3.23 (s, 3H), 3.09 – 2.92 (m, 1H), 2.87 – 2.78 (m, 1H), 2.77 – 2.64 (m, 1H), 2.58- 2.52 (m, 1H), 2.24 – 2.12 (q, J= 8.7 Hz, 1H), 2.06 – 1.92 (m, 1H), 1.91 – 1.78 (m, 1H), 1.78 – 1.59 (m, 3H), 1.58 – 1.45 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.40, 137.56 (t, *J* = 27.0 Hz), 130.68 (q, J= 32.2 Hz), 129.70 (t, J= 6.0 Hz), 128.65, 128.52, 128.46, 126.57- 126.34 (m), 126.28, 124.06 (q, J= 273.02 Hz), 123.71-123.37 (m), 122.18 (t, J= 247.1 Hz), 74.78, 66.11, 64.15 (t, *J* = 26.4 Hz), 59.05, 58.21, 32.55, 30.93, 26.24, 21.06.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.67, -98.78 (dd, *J* = 251.3, 9.5 Hz), -107.15 (dd, *J* = 251.1, 14.9 Hz).

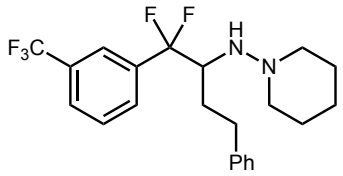
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{23}H_{28}ON_2F_5$, 443.21163; found 443.21180.

4.5.4B 1.0 mmol Scale Reaction



***N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (3):** A 25 mL screw-top test tube was charged with 4CzIPN (10.0 μmol, 7.87 mg, 1 mol%), sodium formate (4.00 mmol, 0.270 g, 4.0 equiv), mesna (0.200 mmol, 32.8 mg, 20 mol%), and (*E*)-3-phenyl-*N*-(piperidin-1-yl)propan-1-imine **S6** (1.00 mmol, 216 mg, 1.0 equiv). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, degassed DMSO (10 mL) was added via syringe followed by 1,3-bis(trifluoromethyl)benzene (3.00 mmol, 0.465 mL, 3.0 equiv) The resulting mixture was stirred for 16 h under irradiation by blue LEDs at 80 °C. Upon completion, the reaction was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were passed through silica to remove excess DMSO and concentrated *in vacuo*. The residue was then purified by silica chromatography (5-20% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (316 mg, 77% yield).

4.5.4C Telescoped Reaction Procedure

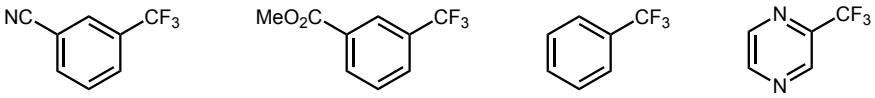


***N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine (3):** A 15 mL screw-top test tube was charged with 4CzIPN (5.00 μmol, 3.93 mg, *1* mol%,), sodium formate (2.00 mmol, 136 mg, 4.0 equiv), mesna (0.100 mmol, 0.0164 g, 20 mol%). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total

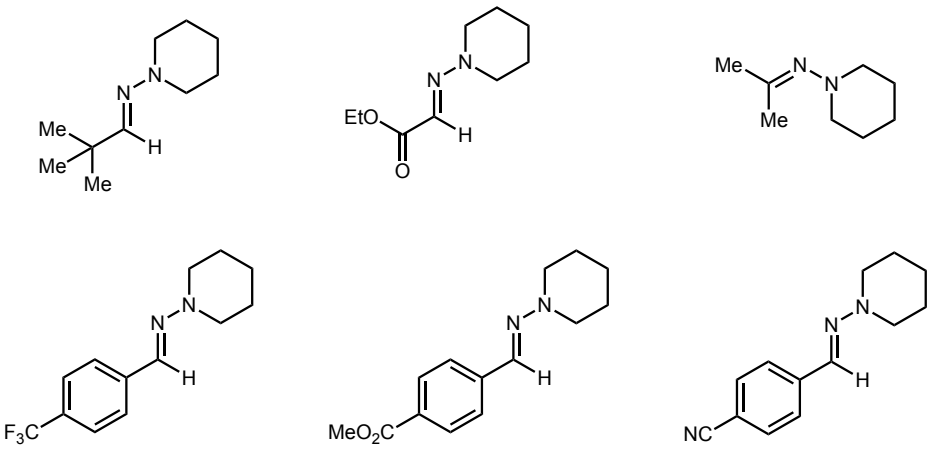
of three times). Under nitrogen atmosphere, the degassed solvent (DMSO, 5 mL) was added via syringe followed by 3-phenylpropanal (0.500 mmol, 65.8 µL, 1 equiv), N-aminopiperidine (0.500 mmol, 54.0 µL, 1.0 equiv) and 1,3-bis(trifluoromethyl)benzene (1.50 mmol, 0.233 mL, 3.0 equiv). The reaction was allowed to stir for 5 minutes before placing under lamps. The resulting mixture was stirred for 16 h under irradiation by blue LEDs at 80 °C. Upon completion, the reaction was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were passed through silica to remove excess DMSO and concentrated *in vacuo*. The residue was purified by silica chromatography (3-12% EtOAc/hexanes as the eluent) to afford the title compound as a yellow oil (107 mg, 52% yield).

4.5.4D Unsuccessful Substrates

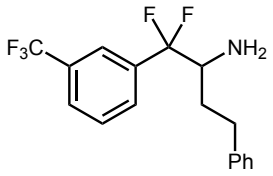
CF_3- Arenes:



Hydrazones:



4.5.5 Nitrogen-Nitrogen Bond Cleavage



1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-amine (31): A 7-mL screw top vial equipped with a stir bar was charged with *N*-(1,1-difluoro-4-phenyl-1-(3-(trifluoromethyl)phenyl)butan-2-yl)piperidin-1-amine **3** (0.100 mmol, 412 mg, 1.0 equiv) and Raney nickel (0.310 g). The atmosphere was exchanged for N_2 (3x) and freshly degassed MeOH (2.5 mL) was added via syringe. The reactions atmosphere was sparged with H_2 gas. The reaction was heated to 55 °C and stirred under a H_2 balloon for 16 hours. The reaction was cooled to room temperature, filtered through celite and concentrated. The crude material was purified via silica chromatography (5- 30% EtOAc/hexanes as the eluent) to afford the title compound as a clear oil (25.9 mg, 79% yield).

R_f=0.36 (50% EtOAc/hexanes)

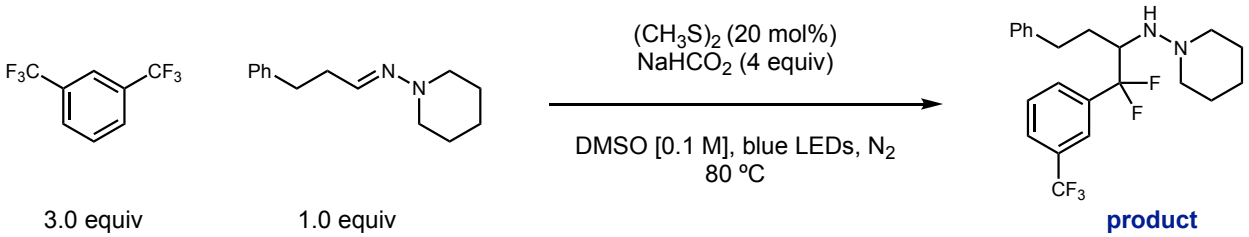
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 1H), 7.70 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.20 (t, J= 7.4 Hz, 1H), 7.12 (d, J= 7.4 Hz, 2H), 3.21 – 3.12 (m, 1H), 2.93 – 2.85 (m, 1H), 2.69 – 2.61 (m, 1H), 1.90– 1.84 (m, 1H), 1.54 – 1.45 (m, 1fH), 1.29 (br s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.32, 136.51 (t, *J* = 27.4 Hz), 131.16 (q, *J* = 32.8 Hz), 129.36 (t, *J* = 6.4 Hz), 129.13, 128.62, 128.51, 126.98- 126.76 (m), 126.24, 123.86 (q, J= 272.49), 123.13 – 122.75 (m), 122.50 (dd, J= 246.48, 247.16), 56.81 (t, *J* = 27.6 Hz), 32.30, 31.98 (t, *J* = 2.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75 (s, 3F), -104.68 (dd, *J* = 246.2, 10.8 Hz, 1F), -109.63 (dd, *J* = 246.6, 13.5 Hz, 1F).

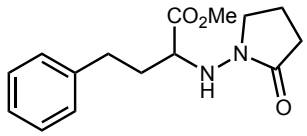
HRMS (APCI) *m/z*: [M+H] calcd. for $C_{17}H_{17}NF_5$, 330.12757; found 330.12763.

4.5.6 Alternative Initiators



Procedure: An 8 mL screw-top test tube was charged with sodium formate (0.400 mmol, 27.2 mg),and (*E*)-3-phenyl-*N*-(piperidin-1-yl)propan-1-imine **S6** (0.100 mmol, 21.6 mg, 0.1 mmol). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO (1 mL) was added via syringe, followed by 1,3-bis(trifluoromethyl)benzene (0.300 mmol, 47.0 μL, 3.0 equiv) and dimethyl disulfide (0.020 mmol, 1.80 μL, 20 mol%). The resulting mixture was heated to 80 °C and stirred at 700 RPM for 16 h under irradiation by blue LEDs. The reaction was cooled to room temperature and 2-(trifluoromethyl)pyridine (0.1 mmol) was added as the internal standard. A small aliquot of the reaction mixture was diluted in d_6-DMSO and the sample was analyzed by ^{19}F NMR and the integral values were used to calculate the yield of the product (59% yield).

4.5.7 Carboxylation of N-Acyl Hydrazone



methyl 2-((2-oxopyrrolidin-1-yl)amino)-4-phenylbutanoate (32): An 8 mL screw-top test tube was charged with (E)-1-((3-phenylpropylidene)amino)pyrrolidin-2-one (0.100 mmol, 21.6 mg, 1.0

equiv), 4CzIPN (1.00 μmol, 0.787 mg, 1 mol%), sodium formate (0.300 mmol, 0.020 g, 3.0 equiv), mesna (20.0 μmol, 3.28 mg, 20 mol%). The tube was equipped with a stir bar and sealed with a PTFE/silicon septum. Under nitrogen atmosphere, separately degassed DMSO (1 mL) was added via syringe. The resulting mixture heated to 80 °C and stirred at 700 RPM for 16 h under irradiation by blue LEDs. The reaction was allowed to cool to room temperature and was diluted with water. The reaction was extracted with EtOAc (3x) to remove starting material. The aqueous layer was concentrated on a Smart Evaporator at 70 °C. The crude material was then dissolved in MeOH, a few drops of conc. HCl were added and the reaction was ran at reflux overnight. The reaction was allowed to cool to room temperature and was concentrated *in vacuo*. The crude reaction was purified via silica gel prep plate (75% EtOAc/Hexanes) and was isolated as a yellow oil (4.7 mg, 17% yield).

R_f= 0.60 (75% EtOAc/Hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.23 – 7.16 (m, 3H), 5.05 (d, *J* = 6.2 Hz, 1H (N–H)), 3.72 (s, 3H), 3.70 – 3.62 (m, 1H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.82 – 2.65 (m, 2H), 2.35 (t, 1H, J= 8.0 Hz), 2.10 – 1.92 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.70, 173.18, 141.02, 128.62, 128.60, 126.30, 61.39, 52.31, 48.64, 32.57, 31.76, 29.17, 16.52.

LCMS: *m/z*: [M+H] calcd. for $C_{15}H_{20}N_2O_3$, 277.2; found 277.2

4.5.8 Supporting Information References

(1) Luo, J.; Zhang, J. "Donor-Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/ Ni Dual Catalytic C(sp^3)-C(sp^2) Cross- Coupling." *ACS. Catal.* **2016**, 6, 873–877.

(2) Hutchyby, M.; Houlden, C.; Haddow, M.; Tyler, S.; Lllyod-Jones, G.; Booker-Milburn, K. "Switching Pathways: Room-Termperature Neutral Solvolysis and Substitution of Amides." *Angew. Chem. Int. Ed.* 51, 548- 551.

(3) Wright, S.; Bandar, J. "A Base-Promoted Reductive Coupling Platform for the Divergent Defluorofunctionalization of Trifluoromethylarenes." *J. Am. Chem. Soc.* **2022**, 144, 13032-13038.

(4) Leow, D. "Phenazinium Salt-Catalyzed Aerobic Oxidative Amidation of Aromatic Aldehydes." *Org. Lett.* **2014**, 16, 5812-5815.

(5) Rene, O.; Souverneva, A.; Magnusion, S.; Fauber, B. "Efficient syntheses of 2-fluoroalkylbenzimidazoles and -benzothiazoles." *Tetrahedron Lett.* **2013**, 54, 201-204.

(6) Marqués-López, E.; Herrera, R.; Fernández, R.; Lassaletta, J. "Uncatalyzed Strecker-Type Reaction of N,N-Dialkylhydrazones in Pure Water." *Eur. J. Chem.* **2008**, 3457-3460.

(7) Monge, D.; Martín-Zamora, E.; Vázquez, H,; Alcarazo, M.; Álvarez, E.; Fernández, R.; Lassaletta, J. "Enantioselective Conjugate addition of N,N-Dialkylhydrazones to α- Hydroxy Enones." *Org. Lett.* **2007**, 9, 2867- 2870.

(8) Panda, A.; Das, U.; Dimmock, J. "Synthesis of Bicyclic N-Methylpyrazoline and Pyrazole Derivatives from α, β-Unsaturated Ketones and N,N-Dimethylhydrazine: An Illustration of Reductive Cyclization." J. *Heterocycl. Chem.* **2014**, 5, 219- 223.

(9) Vega, J.; Alonso, J.; Méndez, G.; Ciordia, M.; Delgado, F.; Trabanco, A. "Continuous Flow α -Arylation of N,N-Dialkylhydrazones under Visible Light Photoredox Catalysis." *Org. Lett.* **2017**, 19, 938–941.

(10) Zhang, W.; Mo, J.; He, W.; Kennepohl, P.; Sammis, G. "Regiocontrolled and Stereoselective Synthesis of Tetrahydrophthalazine Derivatives using Radical Cyclizations." Chem. Eur. J. **2019**, 25, 976-980.

(11) Demark, S.E.; Edwards, J.P.; Weber, T.; Piotrowski, D.W. "Organocerium Additions to Proline-Derived Hydrazones: Synthesis of Enantiomerically Enriched Amines." *Tetrahedron Asymmetry.* **2010**, 21, 1278-1302.