Innovations in Photochemical C–C and C–N Bond Forming Reactions

by

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DEDICATION

For my grandmothers -
who showed me the value of hard work and the importance of family.
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My time at the University of Michigan has been filled with valuable learning opportunities that have been facilitated by so many supportive people. I am especially grateful for the mentorship my advisor, Corey, has provided me during my graduate studies. Even before I embarked on my graduate studies, Corey was an invaluable mentor. In the summer of 2014, he accepted me into his lab as an REU student—that experience solidified my ambitions to pursue graduate studies in organic chemistry. Since then, I have seen the group change, grow, and evolve into the amazing and productive research program that it is today. But I always believed that as new lab members came onboard and old members moved on, that there was value in being a part of the group when a few of the original lab members (who built the lab from the bottom up) were still here. I learned from them perseverance, discipline, and how to challenge myself to be the best chemist I could be. I set high standards and lofty goals for myself before entering graduate school; Corey helped me achieve these goals and even challenged me to make new and more ambitious objectives. His high standards and expectations of me certainly enabled me to have a successful, productive, and worthwhile graduate school experience. Thank you, Corey, for the exciting opportunities you provided for me in your lab, the intellectual freedom to pursue my own curiosities, encouraging me to attend national and international conferences, and setting me up for success in the next steps of my scientific career.
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LIST OF ABBREVIATIONS

[O] oxidant
°C degree Celsius
Ac acetyl
AIBN azobisisobutyronitrile
aq aqueous
Ar aryl
ATRA atom transfer radical addition
BF4 tetrafluoroborate anion
Bn benzyl
Boc tert-butoxycarbonyl
bpy 2,2'-bipyridine
bpz 2,2'-bipyrazine
BrCF3 bromotrichloromethane
Cbz carboxybenzyl
CF3 trifluoromethyl
CF3I trifluoromethyliodide
CFL compact fluorescent lightbulb
cm centimeter
Cu copper
CV cyclic voltammetry
d doublet
DABCO 1,4-diazabicyclo[2.2.2]octane
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM dichloromethane
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dF(CF3)ppy 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine
DIPEA N,N-diisopropylethylamine
DMF dimethylformamide
DMSO dimethylsulfoxide
d.r. diastereomeric ratio
dtbbppy 4,4'-di-tert-butyl-2,2'-bipyridine
equiv equivalents
e.r. enantiomeric ratio
Ered reduction potential
ESI electrospray ionization
Et ethyl
Fac facial
Fc ferrocene
g       grams
h       hours
Het     heteroarene
HCF₃    fluoroform
HRMS    high resolution mass spectroscopy
Hz       hertz
IR      infrared
Ir       iridium
J       coupling constant
K       Kelvin
L       liters
LED     light emitting diode
Li      lithium
M       molar concentration
m       multiplet
MCFDA   methyl chlorodifluoroacetate
Me      methyl
Mes     mesityl
mg      milligrams
MHz     megahertz
min     minutes
mL      milliliters
MLCT    metal to ligand charge transfer
mm      millimeters
mmol    millimoles
mol     moles
mol%    mole percent
MW      molecular weight
nm      nanometers
NMR     nuclear magnetic resonance
ns      nanosecond
PC      photocatalyst
PF₆     hexafluorophosphate anion
Ph      phenyl
phen    1,10-phenanthroline
PMP     paramethoxyphenyl
PNO     pyridine N-oxide
ppm     parts per million
PPNO    4-phenylpyridine N-oxide
ppy     2-phenylpyridine
ps      picoseconds
py or pyr pyridine
q       quartet
rt or RT room temperature
Ru      ruthenium
s       singlet
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SCE</td>
<td>saturated calomel electrode</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>Tf</td>
<td>triflyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THIQ</td>
<td>tetrahydroisoquinoline</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethlenediamine</td>
</tr>
<tr>
<td>TMSCF₃</td>
<td>trfluoromethyltrimethylsilane</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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<td>volts</td>
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</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million</td>
</tr>
<tr>
<td>λₘₚₓ</td>
<td>maximum wavelength</td>
</tr>
<tr>
<td>μL</td>
<td>microliters</td>
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ABSTRACT

Over the past decade, photoredox catalysis has risen to the forefront of synthetic organic chemistry as an indispensable tool for selective small-molecule activation and chemical-bond formation. New bond forming strategies have the potential to impact a variety of synthetic endeavors including, pharmaceuticals, natural product synthesis, and material sciences. This cutting-edge platform allows photosensitizers to convert visible light into chemical energy, prompting generation of reactive radical intermediates. In particular, the formation of new C–C and C–N bonds is fundamental to organic synthesis. This thesis describes some of our contributions to the design, optimization, implementation, and mechanistic underpinnings of novel C–C and C–N bond forming reactions mediated by photoredox catalysis.

Chapter 1 provides a detailed summary of the importance of photoredox catalysis in organic synthesis and its appeal as an enabling technology for free radical generation. The history, key contributions in the field, the impact of light arrays on reactivity, aliphatic amine functionalization, designing complementary mechanistic paradigms, and applications of photoredox catalysis in industry is reviewed.

Chapter 2 focuses on a method for the radical chlorodifluoromethylation of (hetero)arenes using chlorodifluoroacetic anhydride. A historical perspective on (hetero)arene functionalization via the classic Minisci reaction, along with strategies for radical (perfluoro)alkylation, are
presented. Optimization studies, elucidation of scope, and product diversification of chlorodifluoromethylated (hetero)arenes is described.

Chapter 3 describes our efforts in the area of alkene aminoarylation using simple bifunctional arylsulfonylacetamide reagents to synthesize 2,2-diarylethylamines. In this process, single-electron alkene oxidation enables C–N bond formation to provide a key benzylic radical poised for a Smiles-Truce 1,5-aryl shift. This reaction is redox-neutral, exhibits broad functional group compatibility, and occurs at room temperature with loss of sulfur dioxide. The ability of photoredox catalysis to mediate the formation C–C and C–N bonds in a single operation is established in this Chapter.

Chapter 4 continues to explore the utility of bifunctional arylsulfonylacetamide reagents; now in the context of arene dearomatization. Arene dearomatization reactions are an important class of synthetic technologies for the rapid assembly of unique chemical architectures. Here, we describe a catalytic protocol to initiate a carboamination/dearomatization cascade that proceeds through transient sulfonamidyl radical intermediates formed from strong N–H bonds leading to 1,4-cyclohexadiene-fused sultams. Reaction optimization, substrate scope, and mechanistic features of this transformation are presented. Additionally, several new substrate classes are identified which undergo N-radical aryl transfer reactivity with electron-neutral olefins leading to functionalized arylethylamine products in good yields.
Chapter 1

General Principles, Recent Trends, and Applications of Photoredox Catalysis

*Portions of this chapter have been published in R. C. McAtee, E. J. McClain, C. R. J. Stephenson. Illuminating photoredox catalysis. Trends in Chemistry 2019, 1, 111–125.

1.1. Introduction

Over the past decade, photoredox catalysis has risen to the forefront of synthetic organic chemistry as an indispensable tool for selective small-molecule activation and chemical-bond formation. This cutting-edge platform allows photosensitizers to convert visible light into chemical energy (400-600 nm, 40-70 kcal/mol) prompting generation of reactive radical intermediates. The use of light for promoting chemical reactivity has far-reaching implications in minimizing the environmental impact of the chemical industry. While traditional photochemistry has generally utilized ultraviolet light for initiating chemical transformations, visible light is a more desirable energy source due to an increased level of selectivity and control of reactivity. Visible light is absorbed by relatively few organic molecules, and therefore it can be used to selectively activate specific molecules or even transient species in solution. In addition to the promise of reduced waste streams, the use of a more sustainable energy source (e.g. sunlight), and the avoidance of the hazardous and/or toxic reagents classically-employed for carbon-centered radical formation (e.g., AIBN, Bu₃SnH, BEt₃/O₂), photoredox catalysis has gained meaningful traction due to its ability to integrate with continuous flow technology.¹⁻⁴ The enhanced light penetration available in flow
can lead to order(s) of magnitude improvements in material throughput, and the applicability of these combined strategies will only increase as methods for in-line manipulation of materials continue to improve. Importantly, photoredox catalysis is already exerting a significant influence on industrial chemistry by enabling otherwise infeasible bond disconnections and aiding sustainability efforts.

Given the ever-increasing industrial investment (e.g., Merck\textsuperscript{1,2} Eli Lilly\textsuperscript{1,5-8} AbbVie\textsuperscript{9}), photoredox catalysis promises to be the most enabling synthetic technology since Pd-based cross-coupling, which happens to be the only methodology invented in the last few decades to dramatically impact industrial synthesis.\textsuperscript{10}

### 1.2. Photoredox Catalysis as a Modern Approach to Generate Radicals

Radical intermediates are molecules that are transiently generated during a reaction and contain an unpaired electron (Figure 1.1A). Classic chemical approaches to generate these intermediates rely on hazardous radical initiators (e.g., AIBN and BEt\textsubscript{3}), toxic reagents (e.g., Bu\textsubscript{3}SnH), and in many cases, high temperature or high energy UV irradiation.\textsuperscript{11-13} These modes of traditional radical generation have partly led to radical intermediates being both underexploited and underappreciated in chemical synthesis.
Figure 1.1. Photoredox catalysis as a modern approach to radical intermediate generation. (A) The classic (left) and modern (right; photoredox catalysis) approach to radical intermediates. (B) Commonly employed metal-centered and organic photocatalysts. (C) A general representation of the oxidative and reductive quenching cycle of Ru(bpy)$_3^{2+}$. MLCT and ISC are metal-to-ligand charge transfer and intersystem coupling, respectively.

For nearly fifty years, photoredox catalysis has found widespread utility in the areas of carbon dioxide reduction,$^{14}$ water splitting,$^{15}$ and solar-cell materials.$^{16}$ Only recently, have these fundamental principles been translated to radical generation for chemical synthesis by recognizing that visible light can be converted to chemical energy for synthetic applicability in a controlled and mild fashion.$^{17-23}$ Common photocatalysts include Ru(II) (1.1) and Ir(III) (1.2, 1.3) complexes, as well as organic dyes (1.4) (Figure 1.1B). Upon irradiation with visible light, metal-centered catalysts undergo a metal-to-ligand charge transfer (MLCT) followed by intersystem crossing (ISC) revealing a relatively long-lived triplet excited-state species (e.g., for Ru(bpy)$_3^{2+}$, $\tau = 1100$...
ns) (Figure 1.1C). From the excited state, these catalysts can engage in single-electron transfer (SET) events with organic substrates providing access to reactive open-shell intermediates. Notably, excited-state species may act as both a strong oxidant and strong reductant simultaneously (generating Ru(bpy)$_3^{3+}$ or Ru(bpy)$_3^{+}$, respectively) allowing for exceptional operator flexibility. Additional catalyst tuning (e.g., metal center and ligand sphere) allows one to predictively modify the catalyst’s redox potential and thus the inherent catalyst properties. In contrast to classic chemical approaches to radical intermediate generation, methods in photoredox catalysis are exceptionally mild relying on easily accessible and bench-stable materials with ambient-temperature operation. Despite remarkable advances in classical UV radical photochemistry, the need for specialized equipment and lack of predictable product outcomes have ultimately skewed the perception and industrial adaptation of such methods. Fortunately, a modern era of radical chemistry dawns with photoredox catalysis (and electrocatalysis), which promises to be a steadfast and translatable tool for years to come.

1.3. Light Mediated-Excitation of Polypyridyl Photocatalysts

Visible light irradiation of the polypyridyl photocatalysts leads to an excitation event that ultimately furnishes a triplet excited state which is sufficiently long-lived (i.e., rate of relaxation is slower than the rate of diffusion) to allow for single electron transfer events to occur (Figure 1.2). To access the triplet excited state, the photocatalyst first undergoes a metal-to-ligand charge-transfer (MLCT) event upon visible light irradiation. This photophysical process is characterized by the promotion of an electron from a metal-centered t$_{2g}$ orbital to a ligand-centered π* orbital, resulting in a singlet excited state ($S_1$) of the photocatalyst. Following MLCT, the singlet excited state undergoes intersystem crossing (ISC), which is characterized as a configurational spin flip of the electron in the ligand-centered π* orbital, to give the lowest energy triplet excited
state \((T_i)\). The resultant triplet excited state is a long-lived excited state, capable of undergoing single-electron transfer events with organic substrates. Importantly, these processes result in the oxidation of the metal center, reduction of the ligand, and a configurational spin flip of the promoted electron; but the overall charge of the complex remains unchanged.

![Diagram of light mediated-excitation of polypyridyl photocatalysts](image.png)

**Figure 1.2. Light mediated-excitation of polypyridyl photocatalysts.** Metal-to-ligand charge-transfer (MLCT) and intersystem crossing (ISC) events from the ground state to the triplet excited state for the prototypical transition-metal photocatalyst, Ru(bpy)\(_3\)\(^{2+}\), upon visible light irradiation.

### 1.4. Evolution of Light Sources for Enhanced Reactivity and Scalability

The diverse reaction profiles accessible via photochemical approaches have reinvigorated researchers in both academia and industry to solve a host of synthetic challenges.\(^{27,31}\) Significant effort has been expended on novel reaction invention; however, there has also been significant interest in decreasing reaction times, developing standardized operating protocols to improve reproducibility, and scaling photochemical reactions for industrial applications. As revealed by the Beer-Lambert-Bouguer law, photon flux decreases exponentially with increasing path length and concentration. Thus, in large batch reactors, incomplete irradiation of reaction solutions causes the photoexcited catalyst to exist only at the reactor surface.\(^{32}\) This phenomenon leads to both long reaction times and poor reaction efficiencies for larger reaction volumes. It is clear that an increase in light intensity will proportionally lead to an increase in photon capture by the photocatalyst affording a higher concentration of the excited-state species.\(^{33}\)
Figure 1.3. Evolution of light array designs for enhanced reaction efficiency and scalability. (A) Small library of commonly employed light array designs over the past decade. (B) The demonstration of enhanced reaction efficiency with the use of an integrated photoreactor. (C) The comparison of batch and flow processing for the trifluoromethylation of N-Boc pyrrole.

The synthetic photoredox community has witnessed a rapid evolution of light sources employed to improve established photochemical transformations and aid in the discovery of novel bond-forming reactions (Figure 1.3A). Importantly, a suite of light setups of varying intensities and wavelengths allows for modular reaction tailoring to best fit the selected photocatalyst. For example, common household compact fluorescent lightbulbs (CFL, broadband emission) can be easily converted to light-emitting diode (LED) arrays of both specific wavelengths and varying intensities. One unique development toward improving reaction efficiencies and rates has been the design of a small-scale integrated photoreactor by MacMillan and co-workers (Figure 1.3B). The photoreactor was optimized for maximum power output from the chosen LED array, electronic interface for operating simplicity, and outcome reproducibility. Of note, calorimeter measurements
revealed a 10× increase in total incident radiant power with their chosen high power 450 nm LED array (>1.1 W output per LED) system relative to a standard LED lamp apparatus. This reactor was shown to provide significantly shorter reaction times in eight photoredox transformations commonly employed in medicinal chemistry, thereby supporting its further utility.

There is an increasing drive from industry to employ photoredox catalysis because it is well-suited to operate in continuous flow, allowing for more uniform light penetration, and therefore, efficient catalyst excitation relative to batch processes. Further, continuous flow processing enhances scalability while simultaneously reducing occupational hazards and industrial waste streams. A successful demonstration of photoredox continuous flow processing was exemplified by Beatty and co-workers radical trifluoromethylation method seeking to address the limited number of scalable trifluoromethylation protocols (Figure 1.3C). In collaboration with Eli Lilly, the authors identified trifluoroacetic anhydride (TFAA) as a trifluoromethyl radical source, in conjunction with pyridine N-oxide (PNO) as a sacrificial redox auxiliary. This low cost and operationally simple procedure uses 0.1 mol% Ru(bpy)_3Cl_2 as the photocatalyst and is proposed to proceed via single-electron reduction of acylated pyridine N-oxide, followed by fragmentation to give the reactive trifluoromethyl radical, CO_2, and pyridine. Comparison of the trifluoromethylation of N-Boc pyrrole revealed that the reaction efficiency was significantly superior with flow processing compared with that of batch processing, generating 3.33 g (71% yield, \( R_t = 10 \text{ min} \)) of product per hour (compared with 17.8 g, 57% yield over 15 hours in batch). Later, this method was efficiently performed on kilogram scale (0.95 kg isolated, 20 g h\(^{-1}\), 50% yield). Very recently, Harper and co-workers reported on the design of a continuous flow stirred-tank reactor equipped with a high intensity laser to achieve kg/day throughput for several commonly encountered photochemical coupling reactions. Using this 100 mL reactor, the authors
reported tremendous reaction-time acceleration and catalysts-loading optimization. Continued advancements in light array designs will ensure optimal photocatalyst loadings, reduced waste streams, and decreased reaction times ultimately leading to a more sustainable approach to chemical synthesis.

1.5. Selective Oxidation of Aliphatic Amines

Aliphatic amines represent a ubiquitous functionality in biologically active compounds and pharmaceuticals. As such, selective and efficient functionalization of aliphatic amines has represented a major point of emphasis for organic chemists.\textsuperscript{38-39} The direct oxidation of trisubstituted aliphatic amines has an astounding impact on the bond dissociation energy of $\alpha$-C–R bonds (\textbf{Figure 1.4A}).\textsuperscript{40} Initial efforts in this area focused on \textit{in situ} generation and subsequent functionalization of imines from $N$-aryl tetrahydroquinoline core structures (\textbf{Figure 1.4B}).\textsuperscript{41-42} This work served as an important proof-of-concept, as the reductive quenching of the photocatalyst excited state (PC*) can give rise to radical cations of tri-substituted amines; subsequent hydrogen-atom transfer led to the formation of imines that could be efficiently trapped upon the addition of a nucleophile.
Figure 1.4. Selective oxidation of aliphatic amines enabled by photoredox catalysis and subsequent synthetic applications.
(A) The resultant impact on the oxidation of aliphatic amines. (B) Initial efforts aimed at the direct oxidation of \( N \)-aryl tetrahydroquinoline and subsequent functionalization. (C) Amine oxidation to mimic the proposed biosynthesis of several catharanthine derived alkaloids. (D) The utility of photoredox catalysis in providing new tools for the synthesis of saturated building blocks of interest to the pharmaceutical sector.

As the breadth of reactivity enabled by photoredox catalysis expanded, Stephenson and co-workers applied these methods to novel bond disconnections in organic synthesis. Based on the proposed biosynthesis of several catharanthine derived alkaloids, it was hypothesized that (+)-catharanthine would be an ideal entry point to the selective modification of complex molecular scaffolds through amine oxidation. Following amine oxidation to intermediate 1.5, subsequent strain driven cleavage of the C16-C21 bond (\( \alpha \) to the amine) led to the facile production of an imine (not shown). Trapping of the imine with an equivalent of cyanide followed by single-electron reduction and protonation of intermediate 1.6 led to \( \alpha \)-amino nitrile 1.7; a common intermediate in the synthesis of several structurally related alkaloids (Figure 1.4C). The synthetic utility of \( \alpha \)-amino nitrile 1.7 was demonstrated as it was readily converted to (−)-pseudotabersonine, (+)-coronaridine, and (−)-pseudovincadifformine in 90%, 48%, and 55% yields, respectively.

New and mild tools enabled by photoredox catalysis have afforded the preparation of new saturated compounds of interest to the pharmaceutical sector because they are less prone to adverse metabolic processing. Anilines represent a common structural alert motif known to predispose a potential drug candidate to metabolism-driven toxicities. However, this functionality is commonly found in modern drug discovery screening libraries due to the cornucopia of methods for its preparation.10 1-Aminonorbornanes represent a class of molecules that are well suited to serve as bioisosteres for anilines, providing a core saturated structure likely less prone to adverse metabolic processing events (Figure 1.4D). Although historical examples of 1-aminonorbornanes
applications exist, their application to drug discovery has been precluded by limited synthetic accessibility. Recently, Stephenson and co-workers provided a solution to this need by reporting the application of photoredox catalysis to access a formal (3+2) cycloaddition of aminocyclopropanes with tethered olefins to provide the corresponding 1-aminonorbornane products.\textsuperscript{45} In this work, the oxidation of aminocyclopropanes allows for the strain-driven homolysis of the $\alpha$-amino C–C bond, and subsequent serial 6-exo-trig and 5-exo-trig radical cyclizations furnishes the desired 1-aminonorbornane core. This methodology proved general as it allowed access to a variety of C2-, C3-, C4-, and C7- substituted 1-aminonorbornanes. Metabolic stability studies supported the initial hypothesis that the saturated 1-aminonorbornanes is less prone to metabolic processing than their aniline counterparts. In all cases, the 1-aminonorbornanes were found to outperform, or were \textit{on par}, with the stability of the most robust aniline compounds.

1.6. \textbf{Complementary Reaction Paradigms for Anti-Markovnikov Additions to Alkenes}

Photoredox catalysis offers unique opportunities for developing complementary mechanistic profiles depending on how a given substrate is initially activated. For example, photocatalytic \textit{anti}-Markovnikov selective hydrofunctionalization of alkenes was recently demonstrated by both Nicewicz\textsuperscript{46} and Knowles\textsuperscript{47} through contrasting C–nucleophile bond forming strategies while using a common photoredox catalysis cycle (\textbf{Figure 1.5}). Despite the pervasiveness of Markovnikov-selective additions (H–nucleophiles to alkenes) in organic chemistry, methods to access the opposite selectivity with the same substrates remains challenging and is limited to forcing transition metal catalysis and monosubstituted activated alkenes.\textsuperscript{48-49}
Figure 1.5. Complementary mechanistic paradigms for anti-Markovnikov additions to alkenes.
(A) Anti-Markovnikov selective hydrofunctionalization of alkenes via alkene radical cations. (B) Anti-Markovnikov selective hydrofunctionalization of alkenes via concerted proton-coupled electron transfer approach.

Over the past several years, Nicewicz and colleagues have developed powerful strategies that reverse selectivity of traditional hydrofunctionalization reactions of alkenes by taking advantage of the known reactivity of transiently generated radical cations (Figure 1.5A). In these cases, polar nucleophiles selectively add to the least hindered site of radical cations generating a stabilized radical adduct. Key to the success of this single-electron alkene oxidation strategy is the judicious choice of a potent oxidizing photocatalyst. Notably, many terminal styrenes, as well as mono-, di-, and trisubstituted alkenes, have oxidation potentials outside the range of commonly employed transition-metal-based polypyridyl catalysts. Consequently, the group has spent tremendous effort on designing acridinium photocatalysts with potent redox
behaviors.\textsuperscript{55} Following mechanistic studies, the authors propose the following steps for their reported \textit{anti}-Markovnikov hydrofunctionalization reactions of alkenes.\textsuperscript{50,56} Initial single-electron transfer from the alkene to an excited-state acridinium photocatalyst provides the reactive radical cation intermediate \textbf{1.8}. Inter- or intramolecular nucleophilic addition to the radical cation followed by a hydrogen atom transfer (HAT) event between a suitable donor, such as 2-phenylmalonitrile, furnishes the functionalized \textit{anti}-Markovnikov product. The authors have successfully extended this photoredox HAT strategy to accomplish \textit{anti}-Markovnikov hydroetherifications,\textsuperscript{46} hydroaminations,\textsuperscript{51,57} hydroacetoxylations,\textsuperscript{58} and hydrohalogentaions\textsuperscript{59-60} of alkenes. These reports illustrate the power of alkenes radical cations to provide access to valuable chemical motifs in a succinct manner.

Instead of alkene oxidation, nucleophile activation via non-covalent catalysis in conjunction with photoredox catalysis has enabled a wide breadth of fundamentally distinct transformations. Knowles and colleagues have pioneered the use of concerted proton-coupled electron transfer (PCET) in organic synthesis.\textsuperscript{61-62} PCETs are unconventional elementary redox processes resulting in the concomitant transfer of a proton and an electron to or from two independent donor/acceptor species. This strategy for homolytic activation of strong bonds, often in the presence of weaker ones, allows access to radical species that would be kinetically challenging to form via sequential proton and electron transfer steps. To showcase the synthetic utility of photoredox PCET, the group has developed \textit{anti}-Markovnikov alkene functionalization methods through the oxidative generation of amidyl radicals (\textbf{1.9}) from the corresponding amides (Figure 1.5B).\textsuperscript{47,63-65} Following homolytic cleavage of a redox activated amide N–H bond (BDFE = 110 kcal mol\textsuperscript{−1}), the generated amidyl radical is poised to cyclize onto pendent alkenes to provide a nucleophilic carbon-centered radical. Depending on the nature of the reaction conditions, the
radical intermediate can (i) be trapped with a suitable Michael acceptor for a C−C bond forming event or (ii) abstract an H-atom from a HAT catalyst (such as thiophenol) to provide hydroamination products. Overall, given the exceptionally mild nature of both photoredox alkene oxidation and PCET methods, a wide range of functional groups are tolerated and will aid in accelerating the synthetic utility of these complementary approaches for substrate activation.

1.7. Recent Applications of Photoredox Catalysis

Since 2008, the field of photoredox catalysis has experienced exponential growth, providing synthetic chemists with novel bond-disconnection strategies and direct approaches to targeting native functionalities (including C−H bonds\textsuperscript{66-67}) under exceptionally mild conditions. Photoredox catalysis has also proven useful in the synthesis of congested quaternary centers through either oxidative\textsuperscript{68} or reductive generation\textsuperscript{69-73} of radical intermediates. Given these qualities, it is unsurprising that photoredox catalysis has served as a key bond-forming strategy in the total synthesis of complex natural products (including (+)-gliocladin C,\textsuperscript{74} heitziamide A,\textsuperscript{75} and (−)-aplyviolene\textsuperscript{76-77}), as well as medicinally relevant compounds (Figure 1.6A).\textsuperscript{31}
Figure 1.6. Recent applications of photoredox catalysis in total synthesis and the industrial sector.

(A) The use of photoredox catalysis as a key step in the synthesis of natural products. (B) The use of photoredox catalysis in the direct late-stage C–H methylation, ethylation, and cyclopropanation of pharmaceutical and agrochemical agents. (C) Photocatalytic indoline dehydrogenation as a key step in the sustainable synthesis of elbasvir. (D) A practical photoredox-mediated hydrogen atom transfer protocol to selectively deuterate and tritiate α-amino sp³ C–H bonds of 18 pharmaceutical compounds.
The feasibility of translating small-scale photoredox reactions to large-scale flow-platforms has attracted industrial chemists for applications in late-stage drug modifications and large-scale production of key synthetic intermediates. For example, DiRocco and co-workers have reported a direct late-stage C–H methylation, ethylation, and cyclopropanation of pharmaceutical and agrochemical agents (Figure 1.6B). From high-throughput experimentation, it was found that photoredox catalysis can activate organic peroxides to be suitable radical alkylating agents. Given that the method exhibits exceptional functional group tolerance, it is ideally suited for drug discovery. In a subsequent report, the Merck team in collaboration with Knowles and colleagues, reported on a photocatalytic indoline dehydrogenation as a key step in the sustainable synthesis of elbasvir, a clinically investigated inhibitor of the hepatitis C virus (Figure 1.6C). The photocatalyst 1.2 could be used in combination with tert-butyl perbenzoate to provide good yield and excellent ee (85% yield, >99% ee) of the dehydrogenative product. Notably, the reaction could be scaled to 100 g and processed over 5 h with a residence time of 60 min using Merck’s in-house flow reactor. More recently, MacMillan and colleagues reported a practical photoredox-mediated hydrogen atom transfer protocol to selectively deuterate and tritiate α-amino sp³ C–H bonds of 18 pharmaceutical compounds (Figure 1.6D). Isotopically labeled molecules are essential diagnostic tools in drug discovery as they provide information about compound metabolism and biological uptake. This single-step operation, which uses isotopically labeled water as the heavy atom source, is anticipated to be broadly enabling for interrogating the biological activity of novel drug candidates in the future.

1.8. Conclusions and Future Outlook

Modern advances in visible-light photoredox catalysis have led to a myriad of novel synthetic methodologies. The ability of excited state photocatalysts to simultaneously act as both
an oxidant and reductant and their ability to convert visible light into useful chemical energy have led to unprecedented reactivity, holding significant promise for enabling the continued discovery of valuable organic transformations. As the pharmaceutical sector continues to embrace photoredox catalysis, there is an ever-increasing opportunity for academic discoveries to be immediately translated to future technologies. Moreover, in an era when sustainable chemical practices are of crucial importance, further development of novel visible light-mediated methodologies and easily adaptable platforms for scaling reactions are needed for this field to continue to grow and thrive.
1.9. References


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Chapter 2

Photochemical Chlorodifluoromethylation of Arenes and Heteroarenes


2.1. Introduction

Fluorine has the unique ability to alter the physiochemical properties of small molecules, meaning that the introduction of fluorine into molecular scaffolds can dramatically affect their behavior in biological systems, often increasing metabolic stability. Consequently, the fluorine atom is widely acknowledged to be a valuable heteroatomic surrogate. Moreover, organofluorine chemistry has recently found many diverse applications in the development of new pharmaceuticals, agrochemicals, and materials.

Since the late 1950s, fluorinated drugs have consisted of roughly 5–15% of newly launched pharmaceuticals on a yearly basis, and about 200 fluorine-containing drugs have been approved to
Commodity trifluoromethylated arenes are produced industrially through direct halogen-fluoride exchange of benzotrichlorides; however, this process is limited to methylated arenes of significant oxidative and thermal stability (Figure 2.1B). Alternative strategies are required to produce electron-rich and acid-sensitive benzotrifluorides. Because of the challenges and limited substrate scope associated with direct C–F bond formation, many reagents for the direct incorporation of organofluorinated groups have found widespread synthetic utility. This is particularly true for the trifluoromethyl group which may be incorporated through nucleophilic, electrophilic, or radical addition chemistry.

**Figure 2.1. The importance of the trifluoromethyl group and synthesis on industrial scale.** (A) Selected examples of trifluoromethylated arenes and heteroarenes in pharmaceuticals. (B) The Swarts reaction for industrial preparation of the trifluoromethyl group.
While a great deal of effort has been directed toward developing new methodologies for introducing the trifluoromethyl (CF$_3$) moiety into organic molecules,$^{17-21}$ procedures for incorporating the corresponding, yet chemically distinct,$^{22}$ difluoromethylene functionality (CF$_2$X) are less established. In particular, the difluoromethyl group (CF$_2$H) has garnered recent interest in medicinal chemistry as a lipophilic hydrogen-bond donor and is considered a competent bioisostere for thiols and alcohols (Figure 2.2, left).$^{23-24}$ As a consequence, there is a growing demand to develop efficient and practical methods for the introduction of the difluoromethylene motif, in particular, the difluoromethyl group,$^{25-28}$ into organic and medicinally relevant compounds. Within the past decade, numerous radical based difluoromethylation reaction platforms have been reported.$^{15, 29-34}$ Many of these methods demonstrate excellent functional group tolerance and have potential to be adopted for applications beyond discovery scale. A notable limitation though of direct radical difluoromethylation may be partly attributed to the limited substrate scope, arising from the difluoromethyl radical preferentially functionalizing electron-deficient π-systems. Therefore, the development of a simple and complementary protocol capable of overcoming the inherent electronic paradigm of existing radical difluoromethylation methods would be a valuable addition to the organic practitioner’s repertoire (Figure 2.2, right).
2.1.1. Minisci Type Functionalization of Arenes with Photoredox Catalysis

Nitrogen-containing heterocycles constitute the backbone of natural products, medicinally valuable small molecules, and agrochemicals (Figure 2.3A). Methodologies for the direct C–H alkylation and perfluoroalkylation of N-heteroarenes enable both the late-stage modification of clinical leads and rapid diversification of drug-like libraries. These strategies allow for expedient access to unexplored chemical space and circumvent conventional de novo chemical syntheses. Notably, the medicinal chemistry community has placed growing interest on late-stage functionalization technologies, as they allow for rapid modulation of drug metabolism and pharmacokinetic profiles of lead compounds. Thus, synthetic approaches that are not dependent on strong oxidants/reductants, high reaction temperatures, or pre-functionalized substrates are of high-value to both academic and industrial sectors.
Figure 2.3. The Minisci alkylation of N-heteroarenes.

(A) Nitrogen containing heterocycles in selected pharmaceuticals. (B) The classic Minisci reaction. (C) A general representation of the mechanism for the Minisci reaction.

The addition of open-shell alkyl and perfluoroalkyl radical intermediates to heteroarenes is referred to as the Minisci reaction (Figure 2.3B).\textsuperscript{39-41} Minisci’s original protocol relied on free radical formation from carboxylic acids via formation of their corresponding silver salts, followed by oxidative decarboxylation upon treatment with a persulfate oxidizing agent. Addition of an alkyl radical intermediate onto a protonated heteroarene, followed by rearomatization, yields the desired alkylated heterocyclic product (Figure 2.3C). Based on Studer and Curran’s mechanistic studies, rearomatization is proposed to occur via deprotonation and sequential single electron oxidation of the functionalized heteroarene upon radical addition.\textsuperscript{42} Since Minisci’s seminal contributions, this reactive paradigm for the alkylation of (hetero)arenes has been a stalwart
foundation for modern drug discovery and development.\textsuperscript{43} Furthermore, renewed interest in the mild and operationally simple generation of radical intermediates has spurred rapid evolution in the area of (hetero)arene alkylation.\textsuperscript{15} In part, the driving inertia for this interest has been the emergence of visible-light-mediated photoredox catalysis, which facilitates exceptionally mild single-electron-transfer (SET) events with organic substrates.\textsuperscript{44-46} Given that state-of-the-art photochemical methods are already employed in drug development (see Chapter 1), we anticipate that the photoredox radical (perfluoro)alkylation of (hetero)arenes will be an invaluable synthetic technology for years to come.

\textit{Alkyl Carboxylic Acids and Carboxylic Acid Derivatives}

Alkyl carboxylic acids are versatile feedstock chemicals that are ubiquitous throughout nature and have been widely used as chemical building blocks.\textsuperscript{47-48} Owing to their low cost, stability, minimal toxicity, and commercial availability, alkyl carboxylic acids have been widely utilized across a variety of synthetic transformations and represent preeminent building blocks for combinatorial chemistry (e.g. amide bond formation). In recent years, the radical decarboxylation of aliphatic carboxylic acids and their activated derivatives has emerged as a powerful strategy for the Minisci functionalization of bioactive organic molecules.

A broad selection of methods have been developed to promote the decarboxylation of alkyl carboxylic acid derivatives through a reductive pathway. In the context of photoredox catalysis, the formation of alkyl radicals via a reductive pathway would enable a net redox neutral catalytic cycle, thereby eliminating the need for a terminal oxidant. At the same time, a reductive alkylation strategy has the potential to expand upon the scope of alkylation reagents, allowing access to compounds with significantly higher oxidation potentials.\textsuperscript{49} Pioneering studies on the reductive decarboxylative generation of alkyl radicals were conducted by Barton and co-workers in the
1960s (Figure 2.4A), Barton et al. utilized N-hydroxypridin-2-thione in the reductive activation of carboxylic acids for applications such as carbonyl reduction and reductive halogenation. In 1991, Oda and Okada disclosed the use of N-(acyloxy)phthalimides (NAP) as redox auxiliaries to enable the decarboxylative generation of alkyl radicals upon single electron reductive fragmentation ($E_{1/2} = -1.26$ to $-1.39$ V vs. SCE (saturated calomel electrode)), using visible light-mediated photoredox catalysis (Figure 2.4B).

Figure 2.4. Seminal studies for the radical decarboxylation of aliphatic carboxylic acids and their activated derivatives for the Minisci functionalization (hetero)arenes.

(A) Barton’s decarboxylative reduction of thiohydroxamate esters. (B) Oda’s and Okada’s N-(acyloxy)phthalimide reductive decarboxylation

Since 2017, NAP esters have been employed in several visible light-driven Minisci alkylation protocols to promote reductive alkyl radical generation. Notably, Phipps and co-workers have reported an enantioselective variant of the Minisci reaction (Figure 2.5) which utilizes a combination of asymmetric Brønsted acid catalysis and photoredox catalysis. The use of a chiral phosphoric acid catalyst provides both stereo- and regiocontrol in the direct addition of prochiral $\alpha$-amino alkyl radicals to the 2-position of a variety of pyridine and quinoline-based substrates. This strategy elegantly facilitates the synthesis of enantioenriched $\alpha$-heterocyclic amines through an efficient late-stage functionalization approach. In 2018, Sherwood and co-workers at Bristol-Meyers Squibb developed an operationally simple, one-pot protocol for the in
situ generation of NAP esters, which obviates the need for isolating the pre-functionalized alkyl partner and facilitates the rapid generation of analog libraries.$^57$

![Figure 2.5. Enantioselective synthesis of α-heterocyclic amines using a Brønsted acid/photoredox catalytic platform](image)

**Alkylboronic Acids**

In 2016, Chen and coworkers disclosed the Minisci C–H alkylation of N-heteroarenes with primary and secondary alkyl boronic acids using the photocatalyst Ru(bpy)$_3$Cl$_2$ and acetoxybenziodoxole as a sacrificial oxidant (Figure 2.6).$^{58}$ Diversely substituted primary and secondary boronic acids (e.g., alkyl bromide, aryl iodide, ester, amide, carbamate, terminal alkyne, and benzyl chloride) were well tolerated. Pyridines, pyrimidines, and a purine riboside substrate were all efficiently functionalized. It should be noted that more electron-rich heteroarenes, including benzothiazole and benzoimidazole, could also be successfully alkylated. The authors propose that the reaction is initiated by a single-electron reduction from the photoexcited Ru(II)* to acetoxybenziodoxole, providing an oxygen-centered radical intermediate. This radical species is then proposed to react with the alkyl boronic acid reagent to form the desired alkyl radical via a
radical “ate” transition state. DFT calculations support that this is a facile and highly exothermic process at room temperature.

Figure 2.6. Photoredox Minisci alkylation using boronic acid alkylating reagents.

Potassium Alkyl- and Alkoxymethyltrifluoroborates

Potassium organotrifluoroborates are considerably more attractive radical precursors than their corresponding boronic acids, given their lack of an empty $p$-orbital, which increases their overall stability and robustness toward harsh reaction conditions. In 2011, Molander and coworkers reported the first use of potassium alkyl- and alkoxymethyltrifluoroborates as radical precursors in the direct C–H alkylation of (hetero)arenes employing manganese(III) acetate as an oxidant in the presence of trifluoroacetic acid. Under the optimized reaction conditions, the
authors were able to functionalize several nitrogen-containing heterocycles all in good to excellent yields.

Figure 2.7. Organophotocatalytic Minisci alkylation using alkyltrifluoroborate radical precursors.

In 2017, the Molander group reported an impressive advance from their earlier manganese(III) acetate-mediated Minisci chemistry by showcasing that alkyltrifluoroborates (many of which are commercially available) can be activated by an inexpensive, sustainable organophotocatalyst (Figure 2.7). Following reaction optimization, the authors found the utility of a mesityl acridinium photocatalyst, potassium persulfate (as a sacrificial oxidant), and trifluoroacetic acid to be the optimal reagent combination for the C–H functionalization of heteroarenes. Under the title reaction conditions, medicinally important cores including quinolines, isoquinolines, indazoles, pyridines, and quinazolinones, could all be functionalized
with an impressive scope of primary, secondary, and tertiary alkyltrifluoroborates in good to excellent yields. As expected, electron-rich cores such as benzimidazole, were unreactive toward these Minisci alkylation conditions. These conditions proved tolerant of a diverse array of functional groups including aryl halides, unprotected amines, thioethers, and amides. Notably, quinine, which features a free alcohol, terminal alkene, and a tertiary amine (which has a known propensity for competitive photocatalytic oxidation) was efficiently (54% yield) and selectively (C2-) functionalized. To showcase the late-stage functionalization utility of their developed protocol, the authors successfully functionalized camptothecin, an anti-cancer drug candidate, at the C7-position. Mechanistically, the authors propose single electron oxidation of the alkyltrifluoroborate reagent, which leads to generation of the desired alkyl radical intermediate and BF₃.

2.1.2. Radical Trifluoromethylation of (Hetero)arenes with Photoredox Catalysis

In 2011, the MacMillan group developed the first reported method for the visible light-driven radical trifluoromethylation of (hetero)arenes (Figure 2.8). In this report, reduction of trifluoromethanesulfonyl chloride by a ruthenium photocatalyst induced the loss of sulfur dioxide, affording the reactive trifluoromethyl radical species. This trifluoromethyl radical could be effectively trapped by several (hetero)arenes, resulting in C–H trifluoromethylation. This method demonstrated the applicability of photoredox catalysis in medicinal chemistry, as several trifluoromethylated pharmacophores could be easily accessed.
Trifluoromethyl iodide has been extensively utilized as a source for generating the trifluoromethyl radical and subsequently participating in π-bond functionalization, including atom transfer radical additions across aliphatic olefins. In 2012, Ye and Sanford reported an impressive advance wherein the generated trifluoromethyl radical can be intercepted with a Cu(III) catalyst to trifluoromethylate a diverse array of aryl boronic acids (Figure 2.9) with complete positional selectivity. In this example, the photoredox catalyst cycle of [Ru(bpy)₃]Cl₂ directly interacts with the copper-catalyzed cross-coupling reaction. The key intermediate of this method is the generation of a Cu₃⁺-CF₃, which may participate in base-promoted transmetallation with an aryl boronic acid. The resultant intermediate can then undergo bond forming aryl-CF₃ reductive elimination while regenerating the Cu¹ catalyst.

Figure 2.8. Photoredox catalysis for the radical trifluoromethylation of arenes and heteroarenes.
2.1.3. Trifluoromethylation with TFAA and Pyridine N-Oxides

The impressive number of reagents that have been developed for the synthesis of trifluoromethylated compounds speaks volumes to the importance of the CF₃ group (Figure 2.10). Despite the undeniable value and utility of a wide library of trifluoromethylating reagents for discovery research, the use of many of these reagents in large-scale applications becomes less appealing when logistics such as reagent cost, environmental impact, and material sourcing are considered. Trifluoroacetic acid (TFA) and fluoroform (HCF₃) are the most attractive CF₃ source materials in these respects because they are inexpensive and available in large quantities. In fact, many reagents for trifluoromethylation are prepared from these materials, and the environmental impact of the direct use of TFA or HCF₃ is consequently minimal in comparison. For a scalable trifluoromethylation methodology, trifluoroacetic acid and its anhydride are most attractive in terms of cost and availability.
A particular challenge preventing the widespread use of TFA for trifluoromethylation chemistry is the large enthalpic barrier for decarboxylation, which can be accomplished thermally in a 2 e– pathway in the presence of copper salts at or above 140 °C (Figure 2.11). The decarboxylation of the reagent results in the chlorodifluoromethly anion, which is very short lived and undergoes ipso elimination to provide the dilfluorocarbene. Fluoride anion is essential to this process and adds to the carbene to form the trifluoromethyl anion, which is stabilized by coordination to copper.

Figure 2.10. Library of commonly employed trifluoromethylating reagents.
Figure 2.11. Trifluoromethylation of aryl halides with methyl chlorodifluoroacetate.

Decarboxylation of trifluoroacetate has thus far been shown to be incompatible with electron-rich and electron-neutral substrates, as the potentials required for this reactivity will oxidize many common organic solvents ($\text{F}_3\text{CO}_2\text{Na}$, $E_{1/2}^{\text{ox}} = >2.4$ V vs. SCE in MeCN) (Figure 2.12). The convergence of these factors has resulted in the use of TFA as a trifluoromethyl source only in very limited contexts of thermallystable or oxidativelystable substrates, such as benzonitriles, often in the presence of stoichiometric or superstoichiometric metal promoters.

![Mechanistic Proposal](image)

*Figure 2.11. Trifluoromethylation of aryl halides with methyl chlorodifluoroacetate.*

(A) Electrochemical characteristics of TFA and its sodium salt

(B) Electrochemical trifluoromethylation with TFA/pyridine salt

Figure 2.12. Electrochemical trifluoromethylation through oxidation of TFA salts. (A) Electrochemical characteristics of TFA which makes it such as challenging reagent for trifluoromethylation. (B) An example of electrochemical activation of TFA/pyridine complex for trifluoromethylation of oxidatively stable substrates.
To address this challenge, our group envisioned that a mild decarboxylation of trifluoroacetic anhydride (TFAA) could be accomplished through appending a sacrificial redox auxiliary to alter the requisite electrochemical potentials.\(^{49,74}\) The use of an electron-rich auxiliary would enable the oxidation of the TFAA adduct at less-forcing potentials; however, because of electronic matching effects, the resultant electrophilic CF\(_3\) radical would be highly likely to recombine with the cleaved auxiliary. The alternative reduction of an electron-deficient auxiliary presents a solution to this problem, as the use of an electron-deficient reagent would fail to out-compete more electron-rich substrates for CF\(_3\) radical addition.

Pyrdine N-oxide (PNO) was identified as the reagent of choice for the formation of a reducible TFAA adduct.\(^{49,74}\) The strategic use of PNO: (1) nucleophilically activates the acid through acylation; (2) presents a weak N–O bond and low-lying LUMO for facile single-electron reduction; (3) produces pyridine as an endogenous base necessary to avoid acid buildup; and (4) avoids trifluoromethylation of the pyridine itself due to poor electronic matching with the electron-poor CF\(_3\) radical (Figure 4C). Mixing TFAA with one equivalent of PNO results in the formation of a putative adduct which undergoes reduction at mild potentials (\(E_{\text{red}}^{1/2} = -1.10\) V vs SCE in MeCN), forming the CF\(_3\) radical within the redox-window of Ru(bpy)\(_3\)^{2+}. A proposed mechanism for this process is represented in Figure 2.14.
Figure 2.13. Our design strategy for trifluoromethylation with TFAA and pyridine N-oxide as a redox auxiliary.
(A) Employing a redox auxiliary to TFAA to enable a mild decarboxylation within the redox window of Ru(bpy)$_3^{2+}$. (B) Identifying pyridine N-oxide as a suitable redox auxiliary for TFAA and the generated pyridine is inert to CF$_3$ radical functionalization.

Figure 2.14. Proposed mechanism for the use of TFAA and pyridine N-oxide for the radical trifluoromethylation of (hetero)arenes.
The reagent combination is effective in equal stoichiometry with respect to the substrate and is sufficiently inexpensive for large-scale implementation (pyridine N-oxide $40–$70 per kg at 1,000 kg). Trifluoromethylation reactions may be performed in acetonitrile, with 1–2 equivalents of pyridine N-oxide providing generally optimal results (Figure 2.15, yields in black font). Arenes containing both electron-donating and mildly electron-withdrawing groups were trifluoromethylated in moderate yields. A variety of functionalized heterocycles can also be functionalized; many of which would not be tolerant to highly forcing electrochemical conditions. In addition, trifluoromethylated pyrrolidines can be generated in excellent yield and diastereoselectivity by first trifluoromethylating substituted pyrroles followed by standard hydrogenation conditions.

**Figure 2.15. Scope of radical trifluoromethylation with TFAA and pyridine N-oxide.**
Among the issues encountered in the activation of TFAA with PNO, we identified the reduction potential of the TFAA adduct \( E_{1/2}^{\text{red}} = -1.10 \text{ V vs SCE} \) as potentially problematic, as the reducing power of photoexcited Ru(bpy)_3Cl_2 \( E_{1/2}^{\text{red}} = -0.81 \text{ V vs SCE} \) is too positive for efficient reduction of this species. Of the wide array of pyridines available for investigation, 4-phenylpyridine N-oxide (4-Ph-PNO) was expected to both stabilize the immediate product of reduction through additional conjugation, as well as present a lower LUMO due to the electron-withdrawing nature of the phenyl substituent. Indeed, reduction of the 4-Ph-PNO/TFAA adduct is shifted 200 mV in the positive direction \( E_{1/2}^{\text{red}} = -0.91 \text{ V vs SCE} \) as compared to the reduction of PNO/TFAA, suggesting that this alteration of N-oxide electronics can promote the decarboxylation of TFAA under even more mild conditions. Electron transfer from photoexcited Ru(bpy)_3Cl_2 (as indicated by fluorescence quenching) is accomplished roughly 7 times faster with the 4-Ph-PNO adduct. Significantly improved yields of trifluoromethylation products are obtained for an array of electron-rich substrates, many of which display significant further utility in the context of cross-coupling and unnatural amino acid synthesis (Figure 2.15, yields in blue font).

2.1.4. Radical Approaches to Chlorodifluoromethylation of Arenes and Alkenes

While the difluoromethyl radical exhibits nucleophilic behavior,\(^{75}\) the chlorodifluoromethyl radical may be characterized as an electrophilic radical (Figure 2.16A). We targeted the chlorodifluoromethyl radical as an attractive surrogate to the difluoromethyl radical to efficiently prepare electron-rich difluoromethyated (hetero)arenes and other high-value, fluorinated heterocycles. Herein, we report the direct chlorodifluoromethylation of (hetero)arenes with commercially available chlorodifluoroacetic anhydride (Figure 2.16B). The chlorodifluoromethyl group acts as a difluorinated linchpin, which readily participates in
postfunctionalization reactions, enabling the rapid generation of aryl esters, gem-difluoroenones, and β-keto-esters. Notably, the chlorodifluoromethyl group is shown to be a critical entryway to electron-rich difluoromethylated (hetero)arenes, which previous methods have been found challenging to prepare.

**Figure 2.16. The electronic advantage of employing chlorodifluoromethyl radicals.**
(A) The electronic paradigm of fluorinated radicals. (B) This work: utilizing chlorodifluoromethyl radicals for (hetero)arene functionalization.

Only a few precursors to the chlorodifluoromethyl radical have been reported (Figure 2.17), including bromochlorodifluoromethane (Figure 2.17A),\textsuperscript{76-77} bis-(chlorodifluoroacetyl)peroxide in the presence of Freon-113 (Figure 2.17B),\textsuperscript{78} and O-octadecyl-S-chlorodifluoromethyl xanthate (Figure 2.17C), which requires an AIBN/(Me_3Si)_3SiH combination to reductively remove the xanthate group.\textsuperscript{79} We realized that these methods would not be suitable for practical or large-scale implementation.
Reported conditions to generate the chlorodifluoromethyl radical

A. 1955

\[
\begin{align*}
\text{Benzoyl peroxide} & \quad \xrightarrow{100 \, ^\circ C, \, 4 \, h} \quad \text{ClF}_2\text{C} = \text{CF}_2\text{Cl} \\
\text{ClF}_2\text{C} & \quad \xrightarrow{\text{R}} \quad \text{ClF}_2\text{C} \cdot \\
\text{ClF}_2\text{C} & \quad \xrightarrow{\text{Br}} \quad \text{ClF}_2\text{C} \text{Br} \\
\text{ClF}_2\text{C} & \quad \xrightarrow{\text{Me}} \quad \text{ClF}_2\text{C} \text{Me} \\
\end{align*}
\]

B. 1992

\[
\begin{align*}
\text{5-10 equiv} & \quad \text{electro-rich arenens} \\
\text{Me} & \quad \xrightarrow{\text{ClF}_2\text{C} = \text{CF}_2\text{Cl}} \quad \text{Ar} \\
\text{Cl} & \quad \xrightarrow{\text{Bu}_3\text{SnH}, \text{AIBN}} \quad \text{Ar} \\
\end{align*}
\]

C. 2014

\[
\begin{align*}
\text{Lauryl peroxide} & \quad \xrightarrow{\text{EtOAc, reflux}} \quad \text{RCF}_2\text{Cl} \\
\text{DBU} & \quad \xrightarrow{\text{Me, PhMe/C}_2\text{H}_2 \text{reflux}} \quad \text{RCF}_2\text{Cl} \\
\end{align*}
\]

Figure 2.17. Reported methods for the generation of chlorodifluoromethyl radicals. (A) Chlorodifluoromethyl radicals from bromochlorodifluoromethane, (B) bis-(chlorodifluoroacetyl)peroxide, and (C) O-octadeyl-S-chlorodifluoromethyl xanthate.

2.2. Results and Discussion

Recently, our group identified pyridine N-oxide as a suitable redox trigger for the reductive decarboxylation of trifluoroacetic anhydride for the intermolecular coupling of a range of vinyl, aryl, and heteroaryl substrates. This inexpensive reagent combination enables the direct generation of the CF\textsubscript{3} radical. In addition, our group reported a complementary mode of reactivity
by altering the electronics of this redox-active system for the direct coupling of electron-deficient heterocyclic N-oxides with electron-rich alkyl radicals. This fragment coupling paradigm uses the heterocyclic N-oxide reagent as both a transient redox auxiliary as well as the (hetero)aryl coupling partner. Inspired by these reports, we envisioned the development of a mild reagent combination (chlorodifluoroacetic anhydride/pyridine N-oxide adduct $E_{1/2}^{\text{red}} = -1.57$ V vs SCE) for the generation of the chlorodifluoromethyl radical ($\bullet$CF$_2$Cl) (Figure 2.18).

Figure 2.18. Radical chlorodifluoromethylation for (hetero)arene functionalization.

Benzene (2.1a) was the substrate of choice for our initial exploration of reaction conditions (Table 2.1). We were pleased to find that the combination of chlorodifluoroacetic anhydride, pyridine N-oxide, and 1 mol% Ru(bpy)$_3$Cl$_2$ furnished the desired chlorodifluoromethylated benzene (2.2a) in 78% yield (entry 1). Changing solvent from acetonitrile to dichloromethane or nitromethane gave comparable reaction efficiencies with only slight decreases in yield (entries 2-3). Altering the identity of the N-oxide proved to have a dramatic effect on the yield. For example, changing the redox trigger from pyridine N-oxide to 4-Ph-pyridine N-oxide resulted in a minimal
decrease in product yield for this substrate (entry 4), whereas electron-poor N-oxides consistently led to reduced reaction efficiency (entries 5-8). Phenyl substitution at the 2-position of the N-oxide gave modest yield of 2.2a (entry 9). We were pleased to observe that the reaction proceeded just as smoothly with a reduced catalyst loading of 0.1 mol% Ru(bpy)₃Cl₂ (entry 10). Importantly, exclusion of light (entry 11) or photocatalyst (entry 12) from the reaction failed to give product.

Table 2.1. Optimization of the radical chlorodifluoromethylation with benzene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>x mol%</th>
<th>N-Oxide</th>
<th>Solvent</th>
<th>Yield [%] [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>pyridine N-oxide</td>
<td>MeCN</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>pyridine N-oxide</td>
<td>CH₂Cl₂</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>pyridine N-oxide</td>
<td>MeNO₂</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>4-Ph-pyridine N-oxide</td>
<td>MeCN</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>4-Cl-pyridine N-oxide</td>
<td>MeCN</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>4-CO₂Et-pyridine N-oxide</td>
<td>MeCN</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>4-CN-pyridine N-oxide</td>
<td>MeCN</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>4-′Bu-pyridine N-oxide</td>
<td>MeCN</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>2-Ph-pyridine N-oxide</td>
<td>MeCN</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>pyridine N-oxide</td>
<td>MeCN</td>
<td>74</td>
</tr>
<tr>
<td>11[c]</td>
<td>1</td>
<td>pyridine N-oxide</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>pyridine N-oxide</td>
<td>MeCN</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reactions run on a 0.8 mmol scale and with 5 equiv of benzene, and 2 mL of the indicated solvent. [b] Determined by ¹⁹F NMR spectroscopy with trifluorotoluene as the internal standard. [c] Reaction performed without blue LED irradiation.

The scope of chlorodifluoromethylation was evaluated for a wide array of electron-rich and pharmaceutically relevant (hetero)aromatics (Figure 2.19). Several substrates exhibited good reactivity toward the radical fluoroalkylation protocol under the optimized reaction conditions,
while modest conversions for select substrates could be overcome by simply increasing the equivalents of pyridine N-oxide and anhydride or changing the redox trigger to 4-phenylpyridine N-oxide. The increase in yield can be rationalized by the in situ formation of an electron donor–acceptor complex, providing an additional productive mechanistic pathway. Mesitylene (2.2b), pyrroles (2.2i, 2.2l, 2.2m, 2.2o), pyridones (2.2f, 2.2g, 2.2h, 2.2n), benzofuran (2.2d), furan (2.2k), xanthines (2.2p, 2.2q), aza-indoles (2.2e), anisole (2.2c), thiophene (2.2j), and quinoline (2.2s) all proved to be competent substrates. Subjection of 4-methylstyrene to the established conditions afforded the bis-substituted product (2.2r). This method was further shown to be tolerant of several sensitive functional groups, including esters, aryl halides, Boc-protected heterocycles, aryl methyl ethers, and MIDA boronates. In particular, the MIDA boronate products are appealing as potential fluorinated cross-coupling reagents and are frequently encountered in drug discovery efforts.

Moreover, in all reported examples, we observed a high preferential functionalization of the substrate over the concomitantly generated pyridine. Many products shown in Figure 2.19 are compounds with unreported synthetic preparations. While the title reaction is amenable to gram scale-up in batch (2.2p), successful implementation of a flow reactor manifold (1 mL internal reactor volume, 0.04 in. internal diameter PFA tubing, 0.2 mL/min flow rate, and residence time of 10 min) suggests that this chemistry can translate beyond discovery scale (2.2i).
With several classes of chlorodifluoromethylated (hetero)aromatic products prepared, we turned our attention toward exploring the reactivity of the chlorodifluoromethyl group and in particular to accessing the difluoromethyl group (CF₂H). Notably, subjecting electron-rich 4-tBu-anisole to the standard conditions with difluoroacetic anhydride or the known difluoromethylation reagent, zinc difluoromethanesulfinate (DFMS),¹⁵ failed to give radical CF₂H addition (Figure 2.20). Satisfyingly, under basic hydrogenolysis conditions, the electron-rich difluoromethylanisole
product (2.3c) was generated in excellent yield. These observations align with a literature precedent\textsuperscript{82-84} detailing the preferential addition of electron-rich difluoromethyl radicals to electron-deficient (hetero)aromatics. Sodium carbonate proved crucial for the success of this transformation and only trace amount of product was isolated in its absence, presumably due to deactivation of the palladium catalyst by in situ generated HCl.

Figure 2.20. Electronic effects of fluoroalkyl radicals to functionalize 4-tBu-anisole.\textsuperscript{[a]} no reaction as determined by TLC, GCMS, \textsuperscript{1}H NMR, and \textsuperscript{19}F NMR; DFMS = zinc difluoromethanesulfinate.

A diverse set of (hetero)arene–CF\textsubscript{2}H products could be garnered in high yields (Figure 2.21, 2.3a–e) and, in the case of 2.3e, excellent diastereoselectivity. Our two-step protocol stands as a robust synthetic equivalent to direct radical difluoromethylation and is an efficient solution to overcome the radical’s electronic limitations (Figure 2.21B). Chlorodifluoromethylation followed by hydrogenolysis of 2.3f provides the electronically mis-matched 5-difluomethylquinoline (2.3g). Notably, direct radical difluoromethylation of dihydroquinine is selective for the electrophilic 2-position of the quinoline core, further supporting the synthetic value and the complementary nature of the CF\textsubscript{2}Cl motif. Additionally, exposing pyridone-CF\textsubscript{2}Cl products to methanolysis conditions
in either a one or two-pot sequence readily afforded the corresponding methyl esters in moderate to good yields (Figure 2.21C, 2.3h–2.3j).

Figure 2.21. Synthetic utility of the chlorodifluoromethyl group.  
[1] reagents and conditions: 4-phenylpyridine N-oxide (1 equiv), Ru(bpy)₃Cl₂ (1 mol%), and chlorodifluoroacetic anhydride (1.1 equiv) [unless otherwise noted], MeCN, rt, 16 h, blue LEDs; yield in parenthesis is of direct methanolysis from the isolated chlorodifluoromethylated product.

Subjection of internal aryl acetylenes to our standard conditions provided exclusive formation of gem-difluoroenones in excellent yields (Figure 2.22A, 2.4a, 2.4b). These difluorinated products are especially attractive synthetic building blocks.85-90 A plausible
mechanism for this transformation (Figure 2.22B) may involve vinylic radical oxidation and subsequent chloride elimination, which may lead to the observed gem-difluoroenone upon hydrolysis.91-93 Terminal and alkyl-substituted alkynes decomposed or failed to react under the same conditions. In an analogous reaction setup, as shown in Figure 2.22C, quenching the reaction with triethylamine and a primary alcohol furnished the corresponding β-keto esters in one reaction pot starting from simple aryl alkyne building blocks (2.4c–2.4e).

Figure 2.22. Chlorodifluoromethylation and diversification of internal aryl alkynes.

[a] reagents and conditions: 4-phenylpyridine N-oxide (1 equiv), Ru(bpy)$_2$Cl$_2$ (1 mol%), and chlorodifluoroacetic anhydride (1.1 equiv) [unless otherwise noted], MeCN, rt, 16 h, blue LEDs.

2.3. Conclusions

In conclusion, we report a robust and efficient method for the decarboxylative radical chlorodifluoromethylation of medicinally valuable (hetero)arenes. Chlorodifluoromethylation with the corresponding acetic anhydride under visible light irradiation, in both batch and flow processing, proceeds with broad substrate scope compatibility, high regioselectivity, and
operational simplicity. The work herein demonstrates that the electrophilic chlorodifluoromethyl radical is a valuable synthetic precursor to prepare electron-rich difluoromethylated (hetero)arenes. Furthermore, the chlorodifluoromethyl group is shown to participate in a wide array of postfunctionalization reactions to provide new and rapid avenues to important molecular complexity.
2.4. Experimental Procedures and Characterization of Compounds

2.4.1. General Information, Procedures, and Mechanistic Studies

General Information

All chemicals were used as received and stored as recommended by the supplier. Reactions were monitored by thin layer chromatography (TLC) using glass-backed plates pre-coated with 230–400 mesh silica gel (250 mm thickness) with fluorescent indicator F254, available from EMD Millipore (cat. #: 1.05715.0001). Plates were visualized with a dual short wave/long wave UV lamp. Column flash chromatography was performed using 230-400 mesh silica (SiliCycle cat. #: R12030B). gel or via automated column chromatography. Preparative TLC purifications were run on silica plates of 1000 µm thickness. NMR spectra were recorded on Varian MR400, Varian Inova 500, Varian Vnmrs 500, or Varian Vnmrs 700 spectrometers. Chemical shifts for \(^1\)H NMR were reported as \(\delta\), parts per million, relative to the signal of CHCl\(_3\) at 7.26 ppm. Chemical shifts for \(^13\)C NMR were reported as \(\delta\), parts per million, relative to the center line signal of the CDCl\(_3\) triplet at 77.0 ppm. Chemical shifts for \(^19\)F NMR were reported as \(\delta\), parts per million, relative to the signal of a trifluorotoluene internal standard at -63.72 ppm. N-oxide screening experiments were quantitatively analyzed by \(^19\)F NMR with a relaxation delay of 1s, and all other internal standard yields were quantified by \(^19\)F NMR with a 1s relaxation delay. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer fitted with an ATR accessory. Mass Spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPCL-MS with ESI high resolution mass
spectrometer using electrospray ionization (ESI), positive ion mode, or electron impact ionization (EI). We thank Dr. James Windak and Dr. Paul Lennon at the University of Michigan Department of Chemistry instrumentation facility for conducting these experiments. UV-Vis measurements were obtained on a Shimadzu UV-1601 UV-Vis Spectrometer. LED lights and the requisite power box and cables were purchased from Creative Lighting Solutions (http://www.creativelightings.com) with the following item codes: CL-FRS5050-12WP-12V (4.4W blue LED light strip), CL-PS94670-25W (25 W power supply), CL-PC6FT-PCW (power cord), CL-TERMBL-5P (terminal block).

Unless stated otherwise, all title reactions were run on a 0.8 mmol scale in a 2-dram vial equipped with stir bar and cap. The light apparatuses used to irradiate the reactions were constructed from test tube racks and wrapped with three 4.4 W LED strips. Reactions were run only in slots marked by a black dot (right) in the picture below to keep a moderate distance from the light source (~2.5 cm). At this distance the temperature of the reactions did not exceed 35 °C.
General Chlorodifluoromethylation Procedures

**General Procedure 1:**

To a 2-dram vial equipped with a stir bar was added pyridine N-oxide (76 mg, 0.80 mmol, 1.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (6.0 mg, 1.0 mol%), and substrate (0.80 mmol).\textsuperscript{1} The combined materials were then dissolved in MeCN (2.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (154 μl, 214 mg, 0.88 mmol, 1.1 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 12-16 hours before the light source was removed. Trifluorotoluene (98 μl, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl$_3$ for NMR analysis. The trifluorotoluene signal was referenced to -63.72 ppm. Workup was performed by diluting the reaction with CH$_2$Cl$_2$ and washing with 1N HCl, followed by saturated NaHCO$_3$ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. Yields are reported as duplicates of at least two runs.

**General Procedure 2**

General Procedure 2 is identical to Procedure 1 except 137 mg of 4-phenylpyridine N-oxide (0.8 mmol, 1.0 equiv) was used instead of pyridine N-oxide.
Voltammetry Measurements

Cyclic voltammetry measurements of the pyridine N-oxide/chlorodifluoroacetic anhydride adduct were performed with a model 1000 series multi-potentiostat from CH Instruments. Measurements were performed with a glassy carbon working electrode, Pt auxiliary electrode, Ag/AgCl reference electrode, Bu₄NPF₆ electrolyte (0.1 M in MeCN), and analyte (pyridine N-oxide:chlorodifluoroacetic anhydride, 1:1, 0.01 M) with a sweep rate of 10 mV s⁻¹. A reproducible signal was obtained for an irreversible reduction ($E_{1/2}^{red} = -1.57$ vs SCE). Onset reduction is observable near −0.6 V vs SCE.

Attempted Substrates

The substrates listed below failed to provide chlorodifluoromethylated products in sufficient quantities for purification and isolation under the described conditions.
General Procedure for Chlorodifluoromethylation in Flow

Set-up of the flow reactor for chlorodifluoromethylation: 0.04 inch diameter PFA tubing, with a total internal volume exposed to visible light irradiation of 1 mL, was coiled around 2 x 25 mL test tubes (Figure 2.23A). 2 x Luxeon Rebel high power LEDs- Royal Blue 447.5 nm (Item # SP-02-V4) where placed surrounding the tubing approximately 5 cm away from it in order to avoid overheating (Figure 2.23B). A syringe pump (Harvard Apparatus PHD 2000) was used in order to control the flow of the reactor (Figure 2.23C).

![Flow Reactor](A.png)

**Figure 2.23.** Set-up of the flow reactor for radical chlorodifluoromethylation in flow.
To a 4-dram vial was added 4-phenylpyridine N-oxide (137 mg, 0.80 mmol, 1.0 equiv), Ru(bpy)$_3$Cl$_2$$\cdot$H$_2$O (6.0 mg, 1.0 mol%), and substrate (180 mg, 0.80 mmol). The combined materials were then dissolved in MeCN (4.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (154 μl, 214 mg, 0.88 mmol, 1.1 equiv). The solution was added to a 10 mL syringe which was connected to the flow reactor tubing and syringe pump. At this point the LEDs were turned on. A 0.2 mL/min flow (residence time of 10 min) was selected and the reaction was flowed. The temperature of the flow reactor system was measured by introducing a thermometer into one of the test tubes that supported the coiled tubing (see A). This temperature was measured and never exceeded 35 °C during the 10 min residence time. The collected mixture was diluted with CH$_2$Cl$_2$ and washed with 1N HCl, followed by saturated NaHCO$_3$ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. The crude was purified by flash column chromatography to provide the title compound as a clear oil (163 mg, 66% yield). See below for purification and characterization details.
2.4.2. Preparation and Characterization of Substrates and Products

Preparation and Data for Chlorodifluoromethylated (Hetero)Arenes

(chlorodifluoromethyl)benzene (2.2a)

General Procedure 1 (357 μL, 4.0 mmol, 5.0 equiv benzene): 78% $^{19}$F NMR yield

The $^1$H and $^{19}$F NMR spectral data of the crude reaction mixture were identical to those of an authentic sample (Sigma-Aldrich item # 759309).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.63 (m, 2H), 7.48 (br. m, 3H) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta$ = -48.67 ppm
Modification of **General Procedure 2** was followed. To a 2-dram vial equipped with a stir bar was added 4-Ph-pyridine N-oxide (136 mg, 0.8 mmol, 1.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (6.0 mg, 1.0 mol%), and mesitylene (96 mg, 0.8 mmol). The combined materials were then dissolved in MeCN (2.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with N$_2$ for 30 sec. Chlorodifluoroacetic anhydride (294 µl, 408 mg, 1.68 mmol, 2.1 equiv) was then added to the resulting solution. The vial was equipped with a screw-on cap for the duration of the reaction. Three 3 x 4.4 W LED light strips were turned on and the reaction was allowed to run for 14 h before the light source was removed. The crude reaction was filtered through silica, and the resulting filtrate was concentrated to yield a mixture of starting material (mesitylene) and product which proved challenging to separate. Partial separation of the two can be accomplished with preparative TLC (100% hexanes).

$^{19}$F NMR yield = 72%.

The $^1$H and $^{19}$F NMR spectral data of the isolated material (with trace mesitylene) are consistent with that reported for the corresponding trifluoromethylated mesitylene.$^{49}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.93$ (s, 2H), 2.45 (d, $J = 3.5$ Hz, 3H), 2.32 (s, 3H) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta = -40.58$ ppm

HRMS (EI+) $m/z$ calculated for C$_{10}$H$_{11}$ClF$_2$ (M+) 204.0517, found 204.0520.

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2-(chlorodifluoromethyl)-1,3,5-trimethylbenzene (2.2b)
4-(tert-butyl)-2-(chlorodifluoromethyl)-1-methoxybenzene (2.2c)

General Procedure 2 was followed (131 mg, 0.8 mmol 4'-Bu-anisole) and purification by flash column chromatography (SiO₂, 100:0→98:2 Hex:EtOAc) furnished the title anisole compound as a clear oil (82 mg, 42%). ¹⁹F NMR yield = 59%.

¹H NMR (400 MHz, CDCl₃): δ = 7.53 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 8.7, 2.4 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 1.31 (s, 9H) ppm

¹³C NMR (176 MHz, CDCl₃): δ = 154.4, 142.9, 129.6, 125.3, 122.5 (t, J = 286.8 Hz), 123.6 (t, J = 22.1 Hz), 122.4, 122.4, 112.0, 56.0, 34.2, 31.3 ppm

¹⁹F NMR (CDCl₃, 377 MHz): δ = -48.92 ppm

IR (neat): 2963, 1616, 1505, 1274, 1048, 939, 897, 706 cm⁻¹

HRMS (EI⁺) m/z calculated for C₁₂H₁₅ClF₂O (M⁺) 248.0779, found 248.0788.
2-(chlorodifluoromethyl)-3-methylbenzofuran (2.2d)

A modification of General Procedure 2 was followed (0.4 mmol scale). To a 2-dram vial equipped with a stir bar was added 4-phenylpyridine N-oxide (69 mg, 0.40 mmol, 1.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (3.0 mg, 1.0 mol%), and 3-methylbenzofuran (53 mg, 0.40 mmol). The combined materials were then dissolved in MeCN (2.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (140 μl, 194 mg, 0.80 mmol, 2.0 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (49 μl, 0.40 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl$_3$ for NMR analysis. Workup was performed by diluting the reaction with CH$_2$Cl$_2$ and washing with 1N HCl, followed by saturated NaHCO$_3$ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. Purification by flash column chromatography (SiO$_2$, 100:0→97:3 Hex:EtOAc) furnished the title compound as a clear oil (62 mg, 71%). $^{19}$F NMR yield = 68%.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.59 (d, $J =$ 7.8 Hz, 1H), 7.52 (d, $J =$ 7.9 Hz, 1H), 7.43 (t, $J =$ 7.8 Hz, 1H), 7.32 (t, $J =$ 7.5 Hz, 1H), 2.41 (t, $J =$ 1.9 Hz, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta =$ 153.8 (s), 142.3 (t, $J =$ 34.3 Hz), 128.6 (s), 126.9 (s), 123.4 (s), 120.7 (s), 122.0 (t, $J =$ 302.9 Hz) 116.3 (s), 111.8 (s), 7.9 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta =$ -49.29 ppm

IR (neat): 1615, 1454, 1372, 1392, 1263, 1129, 909, 788, 743 cm$^{-1}$

HRMS (EI+) $m/z$ calculated for C$_{10}$H$_7$ClF$_2$O (M+) 216.0153, found 216.0152.
General Procedure 1 was followed (238 mg, 0.8 mmol N-Boc-5-bromo-7-azaindole) and purification by flash column chromatography (SiO₂, 100:0→95:5 Hex:EtOAc) furnished the title azaindole compound as a clear oil (121 mg, 40%). 19F NMR yield = 50%.

1H NMR (400 MHz, CDCl₃): δ = 8.64 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 6.97 (s, 1H), 1.69 (s, 9H) ppm

13C NMR (176 MHz, CDCl₃): δ = 148.5 (s), 146.7 (s), 133.1 (t, J = 34.1 Hz), 132.6 (s), 121.2 (t, J = 286.2 Hz), 120.3 (s), 115.2 (s), 107.0 (t, J = 5.9 Hz), 86.9 (s), 27.7 (s) ppm

19F NMR (CDCl₃, 377 MHz): δ = -45.47 ppm

IR (neat): 2987, 1775, 1759, 1541, 1366, 1134, 1102, 766 cm⁻¹

HRMS (ESI+) m/z calculated for C₁₃H₁₂BrClF₂N₂O₂ ([M+H]+, -[Boc]) 280.9287, found 280.9285.
3-(chlorodifluoromethyl)-1-methylpyridin-2(1H)-one (2.2f)

**General Procedure 2** was followed (87 mg, 0.8 mmol N-methylpyridone) and purification by flash column chromatography (SiO$_2$, 100:0→90:10 DCM:MeOH) furnished the title pyridone as a tan solid (72 mg, 45%). $^{19}$F NMR yield = 48%.

$^1$H NMR (CDCl$_3$, 400 MHz): δ = 7.71 (dd, $J = 7.2$, 2.0 Hz, 1H), 7.50 (dd, $J = 6.7$, 1.8 Hz, 1H), 6.23 (t, $J = 7.0$ Hz, 1H), 3.62 (s, 3H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): δ = 158.4 (s), 141.8 (s), 136.8 (t, $J = 6.7$ Hz), 125.4 (t, $J = 25.1$ Hz), 124.1 (t, $J = 288.5$ Hz), 103.9 (s), 37.9 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): δ = -53.38 ppm

**IR (neat):** 3070, 1729, 1627, 1582, 1560, 1484, 1455, 1410, 1301, 1282, 1068 cm$^{-1}$

**HRMS (ESI+) m/z** calculated for C$_7$H$_6$ClF$_2$NO ([M+H]$^+$) 194.0179, found 194.0177.
**5-bromo-3-(chlorodifluoromethyl)-1-methylpyridin-2(1H)-one (2.2g)**

**General Procedure 1** was followed (5-bromo-1-methyl-pyridin-2-one, 150 mg, 0.8 mmol) and purification by flash column chromatography (SiO₂, 95:5→70:30 Hex:EtOAc) furnished the title pyridone as a yellow/tan solid (86 mg, 40%). ¹⁹F NMR yield = 42%.

**¹H NMR** (CDCl₃, 400 MHz): δ = 7.75 (d, J = 2.6 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 3.61 (s, 1H) ppm

**¹³C NMR** (CDCl₃, 126 MHz): δ = 156.9 (s), 141.9 (s), 139.9 (t, J = 7.0 Hz), 126.1 (t, J = 25.8 Hz), 123.2 (t, J = 289.2 Hz), 95.5 (s), 38.1 (s) ppm

**¹⁹F NMR** (CDCl₃, 377 MHz): δ = -54.09 ppm

**IR (neat):** 2964, 1705, 1665, 1608, 1546, 1461, 1446, 1339, 1287, 1228, 1072, 984, 912 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₇H₅BrClF₂NO ([M+H]+) 271.9284, found 271.9284.
**4-bromo-3-(chlorodifluoromethyl)-1-methylpyridin-2(1H)-one (2.2h)**

General Procedure 1 was followed (4-bromo-1-methyl-pyridin-2-one, 150 mg, 0.8 mmol) and purification by flash column chromatography (SiO₂, 100:0→95:5 DCM:MeOH) furnished the title pyridone as an off white/tan solid (112 mg, 51%). ¹⁹F NMR yield = 68%.

¹H NMR (CDCl₃, 400 MHz): δ = 7.24 (d, J = 7.2 Hz, 1H), 6.47 (d, J = 7.2 Hz, 1H), 3.55 (s, 3H) ppm

¹³C NMR (CDCl₃, 176 MHz): δ = 157.7 (s), 139.3 (s), 133.8 (s), 124.6 (t, J = 22.5 Hz), 124.0 (t, J = 293.1 Hz), 111.6 (s), 37.9 (s) ppm

¹⁹F NMR (CDCl₃, 377 MHz): δ = -48.50 ppm

IR (neat): 3075, 1633, 1597, 1525, 1462, 1435, 1414, 1348, 1277, 1242, 1072 cm⁻¹

HRMS (ESI+) m/z calculated for C₇H₅BrClF₂NO ([M+H]+) 271.9284, found 271.9280.
**1-(tert-butyl) 2-methyl 5-(chlorodifluoromethyl)-1H-pyrrole-1,2-dicarboxylate (2.2i)**

General Procedure 2 was followed (1-tert-butyl 2-methyl pyrrole-1,2-dicarboxylate, 180 mg, 0.8 mmol) and purification by flash column chromatography (SiO$_2$, 95:5→85:15 Hex:EtOAc) furnished the title pyrrole as a clear oil (170 mg, 70%). $^{19}$F NMR yield = 72%.

$^1$H NMR (CDCl$_3$, 400 MHz): δ = 6.80 (d, $J$ = 3.9 Hz, 2H), 6.58 (d, $J$ = 3.9 Hz, 2H), 3.87 (s, 3H), 1.62 (s, 9H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): δ = 160.0 (s), 147.4 (s), 130.3 (t, $J$ = 33.8 Hz), 127.4 (s), 120.9 (t, $J$ = 285.6 Hz), 115.9 (s), 111.8 (t, $J$ = 4.3 Hz), 86.9 (s), 52.1 (s), 27.1 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): δ = -44.69 ppm

**IR (neat):** 2986, 1777, 1725, 1372, 1267, 1141, 991, 837 cm$^{-1}$

**HRMS (ESI+) m/z** calculated for C$_{12}$H$_{14}$ClF$_2$NNaO$_4$ ([M+Na]+) 332.0472, found 332.0475.
(5-(chlorodifluoromethyl)thiophen-2-yl)boronic acid MIDA ester (2.2j)

A modification of General Procedure 2 was followed to ensure full consumption of starting material as it is challenging to isolate it away from the chlorodifluoromethylated product. To a 2-dram vial equipped with a stir bar was added 4-phenylpyridine N-oxide (548 mg, 3.2 mmol, 4.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (6.0 mg, 1.0 mol%), and 2-thiopheneboronic acid MIDA ester (191 mg, 0.80 mmol). The combined materials were then dissolved in MeCN (3.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (573 μL, 797 mg, 3.28 mmol, 4.1 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (98 μL, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl$_3$ for NMR analysis. Workup was performed by diluting the reaction with CH$_2$Cl$_2$ and washing with 1N HCl, followed by brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. The residue was purified with flash column chromatography. Pyridine derivatives were flushed off the column with ~750 mL of 2% methanol in Et$_2$O before the product was eluted with 10% MeCN in CH$_2$Cl$_2$ to provide the title thiophene as an amorphous, off-white solid (182 mg, 70%). $^{19}$F NMR yield = 87%.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.48$ (d, $J = 3.6$ Hz, 1H), 7.23 (d, $J = 3.6$ Hz, 1H), 3.94 (d, $J = 16.4$ Hz, 2H), 3.83 (d, $J = 16.3$ Hz, 2H), 2.73 (s, 3H) ppm

$^{13}$C NMR (CD$_3$CN, 176 MHz): $\delta = 169.2$ (s), 142.0 (t, $J = 31.0$ Hz), 134.7 (s), 131.4 (s), 125.5 (t, $J = 284.0$ Hz), 63.1 (s), 49.0 (s) ppm
$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta = -38.17$ ppm

IR (neat): 3006, 1765, 1245, 1142, 1008, 818, 660 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{10}$H$_9$BCIF$_2$NO$_4$S [M+H]$^+$ 324.0075, found 324.0064.
(5-(chlorodifluoromethyl)furan-2-yl)boronic acid MIDA ester (2.2k)

A modification of General Procedure 2 was followed to ensure full consumption of starting material as it is challenging to isolate it away from the chlorodifluoromethylated product. To a 2-dram vial equipped with a stir bar was added 4-phenylpyridine N-oxide (274 mg, 1.6 mmol, 2.0 equiv), Ru(bpy)_3Cl_2•6H_2O (6.0 mg, 1.0 mol%), and 2-furanylboronic acid MIDA ester (178 mg, 0.80 mmol). The combined materials were then dissolved in MeCN (3.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (294 μL, 408 mg, 1.68 mmol, 2.1 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (98 μL, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl_3 for NMR analysis. Workup was performed by filtering the reaction through a small pad of silica and concentrating in vacuo. The residue was purified with flash column chromatography. Pyridine derivatives were flushed off the column with ~750 mL of 2% methanol in Et_2O before the product was eluted with 10% MeCN in CH_2Cl_2 to provide the title furan as an amorphous, off-white solid (151 mg, 62%).

^{19}F NMR yield = 56%.

^{1}H NMR (CDCl_3, 400 MHz): δ = 6.83 (d, J = 3.4 Hz, 1H), 6.75 (d, J = 3.4 Hz, 1H), 3.93 (d, J = 16.1 Hz, 2H), 3.86 (d, J = 16.2 Hz, 2H), 2.78 (s, 3H) ppm

^{13}C NMR (CD_3CN, 176 MHz): δ = 169.3 (s), 149.6 (t, J = 35.1 Hz), 136.6 (s), 122.0 (t, J = 282.0 Hz), 120.6 (s), 112.9 (s), 63.1 (s), 48.7 (s) ppm

^{19}F NMR (CDCl_3, 377 MHz): δ = -49.95 ppm
**IR (neat):** 3015, 2968, 1764, 1468, 1286, 1070, 1009, 812 cm$^{-1}$

**HRMS (ESI$^+$) m/z calculated for C$_{10}$H$_9$BClF$_2$NO$_5$Na [M+Na]$^+$ 330.0123, found 330.0131.
(tert-butyl 5-(chlorodifluoromethyl)-1H-pyrrole-1-carboxylate)boronic acid MIDA ester

![Chemical structure]

A modification of General Procedure 2 was followed to ensure full consumption of starting material as it is challenging to isolate it away from the chlorodifluoromethylated product. To a 2-dram vial equipped with a stir bar was added 4-phenylpyridine N-oxide (411 mg, 2.4 mmol, 3.0 equiv), Ru(bpy)_3Cl_2•6H_2O (6.0 mg, 1.0 mol%), and N-Boc-pyrroleboronic acid MIDA ester (258 mg, 0.80 mmol). The combined materials were then dissolved in MeCN (3.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (433 μL, 602 mg, 2.48 mmol, 3.1 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (98 μL, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl_3 for NMR analysis. Workup was performed by filtering the reaction through a small pad of silica and concentrating in vacuo. The residue was purified with flash column chromatography. Pyridine derivatives were flushed off the column with ~750 mL of 2% methanol in Et_2O before the product was eluted with 10% MeCN in CH_2Cl_2 to provide the title pyrrole as an amorphous, off-white solid (185 mg, 57%, trace inseparable starting material observed in ^1H and ^13C NMR spectra). ^19F NMR yield = 53%.

^1H NMR (CDCl_3, 400 MHz): δ = 6.70 (d, J = 3.5 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 4.18 (d, J = 16.8 Hz, 2H), 3.89 (d, J = 16.8 Hz, 2H), 3.01 (s, 3H), 1.59 (s, 9H) ppm

^13C NMR (CDCl_3, 176 MHz): δ = 168.4 (s), 150.4 (s), 130.0 (t, J = 33.0 Hz), 121.6 (t, J = 285.2 Hz), 120.7 (s), 115.8 (s), 87.4 (s), 65.1 (s), 49.8 (s), 27.4 (s) ppm
$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta = -41.89$ (broad) ppm

IR (neat): 2988, 1772, 1736, 1316, 1210, 1027, 806 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{15}$H$_{18}$BClF$_2$N$_2$O$_6$ [M+NH$_4$]$^+$ 424.1253, found 424.1254.
**tert-butyl 2-acetyl-5-(chlorodifluoromethyl)-1H-pyrrole-1-carboxylate (2.2m)**

**General Procedure 1** was followed (tert-butyl 2-acetylpyrrole-1-carboxylate, 167 mg, 0.8 mmol) and purification by flash column chromatography (SiO₂, 100:0→97:3 Hex:EtOAc) furnished the title pyrrole as a pale yellow oil (163 mg, 69%). ¹⁹F NMR yield = 74%.

**¹H NMR (CDCl₃, 400 MHz):** δ = 6.79 (d, J = 4.0 Hz, 1H), 6.58 (d, J = 4.0 Hz, 1H), 2.47 (s, 3H), 1.62 (s, 9H) ppm

**¹³C NMR (CDCl₃, 176 MHz):** δ = 187.7 (s), 147.9 (s), 134.8 (s), 131.2 (t, J = 33.6 Hz), 120.9 (t, J = 286.0 Hz), 116.0 (s), 111.4 (t, J = 4.1 Hz), 86.9 (s), 27.1 (s), 26.5 (s) ppm

**¹⁹F NMR (CDCl₃, 377 MHz):** δ = -45.07 ppm

**IR (neat):** 2984, 1775, 1676, 1540, 1370, 1273, 1235, 1149, 982 cm⁻¹

**HRMS (ESI+) m/z calculated for C₇H₆ClF₂NO ([M+]⁻[-Boc]) 193.0106, found 193.0111.**
**methyl 5-(chlorodifluoromethyl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (2.2n)**

**General Procedure 1** was followed (methyl 1-methyl-6-oxo-pyridine-3-carboxylate, 134 mg, 0.8 mmol) and purification by flash column chromatography (SiO₂, 90:10→60:40 Hex:EtOAc) furnished the title pyridone as a white solid (49 mg, 25%), ¹⁹F-NMR yield = 31%.

**¹H NMR** (CDCl₃, 400 MHz): δ = 8.38 (d, J = 2.3 Hz, 1H), 8.25 (d, J = 2.2 Hz, 1H), 3.90 (s, 3H), 3.68 (s, 3H) ppm

**¹³C NMR** (CDCl₃, 126 MHz): δ = 163.7 (s), 158.1 (s), 146.1 (s), 136.1 (s), 124.1 (t, J = 26.0 Hz), 123.5 (t, J = 289.7 Hz), 107.7 (s), 52.4 (s), 38.5 (s) ppm

**¹⁹F NMR** (CDCl₃, 377 MHz): δ = -53.87 ppm

**IR** (*neat*): 3071, 1723, 1661, 1620, 1559, 1446, 1325, 1279, 1108, 957, 813, 711 cm⁻¹

**HRMS** (ESI⁺) m/z calculated for C₉H₆ClF₂NO₃ ([M+H]⁺) 252.0234, found 252.0236.
Modification of General Procedure 1 was followed. To a 2-dram vial equipped with a stir bar was added pyridine N-oxide (76 mg, 0.80 mmol, 3.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (6.0 mg, 1.0 mol%), and N-Boc-pyrrole (0.80 mmol). The combined materials were then dissolved in MeCN (2.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (154 μl, 214 mg, 0.88 mmol, 3 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (98 μl, 0.80 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl$_3$ for NMR analysis. The trifluorotoluene signal was referenced to -63.72 ppm. Workup was performed by diluting the reaction with CH$_2$Cl$_2$ and washing with 1N HCl, followed by saturated NaHCO$_3$ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure to give the title bis-substituted pyrrole as a pale yellow oil (226 mg, 84%). $^{19}$F NMR yield = 78%.

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 6.64 (s, 1H), 1.64 (s, 6H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): δ = 146.5 (s), 130.5 (t, $J = 34.5$ Hz), 120.9 (t, $J = 285.5$ Hz), 112.7 (t, $J = 4.6$ Hz), 88.1 (s), 27.2 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): δ = -43.94 ppm

IR (neat): 2987, 1778, 1398, 1284, 1261, 1003, 972, 797 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_6$H$_3$Cl$_2$F$_4$N ([M-Boc+H]+) 234.9579, found 234.9578.
8-(chlorodifluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (2.2p)

1-Gram Scale: To a flame dried 50 mL round bottom flask equipped with a stir bar was added pyridine N-oxide (490 mg, 5.2 mmol, 1.0 equiv), Ru(bpy)₃Cl₂•6H₂O (3.3 mg, 0.1 mol%), and caffeine (1.0 g, 5.2 mmol). The combined materials were then dissolved in MeCN (26 mL) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (986 μL, 1.37 g, 5.66 mmol, 1.1 equiv). The flask was equipped with a septa then placed in a jacketed chilling beaker containing isopropanol, wrapped in three 4.4 W LED light strips and connected to a recirculating chiller set to 20 °C. The LED strips were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Trifluorotoluene (63.2 μL, 0.52 mmol) was added as a stoichiometric internal standard. A sample of the reaction was removed and diluted with CDCl₃ for NMR analysis. Workup was performed by diluting the reaction with CH₂Cl₂ and washing with 1N HCl, followed by saturated NaHCO₃ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. Purification by flash column chromatography (SiO₂, 100:0→90:10 CH₂Cl₂:EtOAc) furnished the title compound as a white solid (539 mg, 38%). ¹⁹F NMR yield = 42%.

¹H NMR (CDCl₃, 400 MHz): δ = 4.17 (s, 3H), 3.59 (s, 3H), 3.42 (s, 3H) ppm

¹³C NMR (CDCl₃, 176 MHz): δ = 155.4 (s), 151.2 (s), 146.2 (s), 142.4 (t, J = 33.0 Hz), 119.6 (t, J = 288.2 Hz), 109.5 (s), 33.4 (s), 29.8 (s), 28.1 (s) ppm

¹⁹F NMR (CDCl₃, 377 MHz): δ = -51.02 ppm

IR (neat): 2960, 1974, 1705, 1694, 1608, 1541, 1446, 1423, 1339, 1227, 1671, 984 cm⁻¹

HRMS (ESI+) m/z calculated for C₉H₇ClF₂N₄O₂ ([M+H]⁺) 279.0455, found 279.0457.
8-[(chlorodifluoromethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione (2.2q)

General Procedure 2 was followed (223 mg, 0.8 mmol pentoxifylline) and purification by flash column chromatography (SiO$_2$, 70:30→30:70 Hex:EtOAc) furnished the title compound as a white solid (120 mg, 42%). $^{19}$F NMR yield = 44%.

$^1$H NMR (CDCl$_3$, 400 MHz): δ = 4.16 (s, 3H), 4.02 (t, $J$ = 6.7 Hz, 2H), 3.58 (s, 3H), 2.50 (t, $J$ = 6.7 Hz, 2H), 2.14 (s, 3H), 1.73 – 1.57 (m, 4H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): δ = 208.6 (s), 155.3 (s), 151.0 (s), 146.3 (s), 142.5 (t, $J$ = 33.1 Hz), 119.6 (t, $J$ = 288.2 Hz), 109.6 (s), 43.1 (s), 41.1 (s), 33.4 (s), 29.9 (s), 29.8 (s), 27.3 (s), 20.9 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): δ = -51.06 ppm

IR (neat): 2956, 1705, 1662, 1544, 1319, 1129, 1089, 913, 738 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{14}$H$_{17}$ClF$_2$N$_4$O$_3$ ([M+H]+) 363.1030, found 363.1032.
3-chloro-3,3-difluoro-1-(p-tolyl)propyl 2-chloro-2,2-difluoroacetate (2.2r)

General Procedure 2 was followed (95 mg, 0.8 mmol 4-methyl styrene) and workup by filtering through a pad of celite and concentrating to a light yellow oil. Purification by flash column chromatography (SiO₂, 100:0→90:10 Hex:EtOAc) furnished the title compound as a clear oil (164 mg, 62%). ¹⁹F NMR yield = 68%.

¹H NMR (CDCl₃, 400 MHz): δ = 7.28 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.22 (dd, J = 9.3, 2.5 Hz, 1H), 3.18 (ddt, J = 22.6, 13.0, 9.4 Hz, 1H), 2.80 (qd, J = 13.7, 2.8 Hz, 1H), 2.36 (s, 3H) ppm

¹³C NMR (CDCl₃, 176 MHz): δ = 157.8 (t, J = 35.0 Hz), 139.7 (s), 133.3 (s), 129.8 (s), 127.0 (t, J = 292.9 Hz), 126.3 (s), 116.7 (t, J = 300.7 Hz), 74.6 (t, J = 2.9 Hz), 47.5 (t, J = 24.5 Hz), 21.2 (s) ppm

¹⁹F NMR (CDCl₃, 377 MHz): δ = -49.45 – -51.07 (m), -64.31 (d, J = 3.6 Hz) ppm

IR (neat): 2927, 1781, 1299, 1169, 1103, 973, 815 cm⁻¹

HRMS (EI⁺) m/z calculated for C₁₂H₁₀Cl₂F₄O₂ ([M⁺]) 331.9994, found 331.9980.
Modification of **General Procedure 1** was followed. To a 2-dram vial equipped with a stir bar was added pyridine N-oxide (231 mg, 2.40 mmol, 3.0 equiv), Ru(bpy)$_3$Cl$_2$•6H$_2$O (6.0 mg, 1.0 mol%), and 6-methoxyquinoline (127 mg, 0.80 mmol). The combined materials were then dissolved in MeCN (2.0 ml) and stirred to form a homogeneous solution. The reaction was sparged with nitrogen gas for 30 seconds with a glass pipette, followed by the addition of chlorodifluoroacetic anhydride (416 μl, 2.40 mmol, 3 equiv). The vial was equipped with a rubber-lined screw-on cap. Three 4.4 W LED light strips (positioned ~2.5 cm away) were turned on and the reaction was allowed to run for 14 hours before the light source was removed. Workup was performed by diluting the reaction with CH$_2$Cl$_2$ and washing with 1N HCl, followed by saturated NaHCO$_3$ and then brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure. Purification by flash column chromatography (SiO$_2$, 95:5→85:15 Hex:EtOAc) furnished a 3:1 separable mixture of the title compound as an off white solid (60 mg, 33%) and the 7-(chlorodifluoromethyl)-6-methoxyquinoline regioisomer as an off white solid (20 mg, 11%).

$^1$H NMR (CDCl$_3$, 700 MHz): δ = 8.84 (dd, $J = 4.0$, 1.1 Hz, 1H), 8.65 (d, $J = 8.9$ Hz, 1H), 8.25 (d, $J = 9.3$ Hz, 1H), 7.55 (d, $J = 9.4$ Hz, 1H), 7.48 (dd, $J = 8.9$, 4.1 Hz, 1H), 4.07 (s, 3H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): δ = 155.6 (s), 148.4 (s), 143.5 (s), 135.5 (s), 132.4 (s), 126.3 (t, $J = 293.7$ Hz), 125.4 (s), 122.3 (s), 117.2 (s), 116.3 (t, $J = 23.4$ Hz), 57.2 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): δ = -40.88 ppm

**IR (neat):** 2959, 2927, 2838, 1629, 1597, 1497, 1455, 1347, 1277, 1198, 1034, 935, 875 cm$^{-1}$

**HRMS (EI+) m/z** calculated for C$_{11}$H$_8$ClF$_2$NO ([M+H$^+$]) 244.0335, found 244.0334.
7-(chlorodifluoromethyl)-6-methoxyquinoline (2.2s*)

**¹H NMR** (CDCl₃, 700 MHz): δ = 8.82 (d, J = 3.9 Hz, 1H), 8.30 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.42 (dd, J = 8.2, 4.1 Hz, 1H), 7.16 (s, 1H), 4.02 (s, 3H) ppm

**¹³C NMR** (CDCl₃, 176 MHz): δ = 154.0 (s), 149.2 (s), 142.5 (s), 134.4 (s), 130.7 (s), 128.3 (t, J = 25.4 Hz), 128.0 (t, J = 7.1 Hz), 124.3 (t, J = 290.2 Hz), 123.0 (s), 106.8 (s), 56.2 (s) ppm

**¹⁹F NMR** (CDCl₃, 377 MHz): δ = -50.56 (s) ppm

**IR** (neat): 2959, 2928, 2838, 1629, 1597, 1497, 1331, 1277, 1165, 1034, 976, 798 cm⁻¹

**HRMS** (EI⁺) m/z calculated for C₁₁H₈ClF₂NO ([M+H⁺]) 244.0335, found 244.0335.
Preparation and Data for Difluoromethylated (Hetero)Arenes

\[
\text{Cl} \quad \text{F} \quad \stackrel{\text{Pd/C, 1 atm H}_2}{\longrightarrow} \quad \text{CF}_2\text{H}
\]

\[
\text{Ar} \quad \text{F} \quad \text{Na}_2\text{CO}_3 \text{ (1 equiv)} \quad \text{MeOH, rt, <1 h}
\]

To a 10 mL RBF equipped with a stir bar was added palladium on activated carbon (10 wt%, 0.10 equiv). The flask was evacuated and backfilled with N\textsubscript{2} three times. Methanol (3 mL) was then added to the flask followed by the chlorodifluoromethylated (hetero)arene substrate (1 equiv) and sodium carbonate (1 equiv). The heterogeneous mixture was stirred under a H\textsubscript{2} atmosphere (gas balloon) and monitored by TLC analysis. Once the reaction was complete (under 1 h), the mixture was filtered over a pad of silica and concentrated under reduced pressure.
8-(difluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (2.3a)

The reaction was performed using 8-[chloro(difluoro)methyl]-1,3,7-trimethyl-purine-2,6-dione (20 mg, 0.07 mmol, 1 equiv). Purification by flash column chromatography (SiO₂, 100:0→50:50 Hex:EtOAc) furnished the title compound as a white solid (17.5 mg, 99%).

**^1H NMR** (CDCl₃, 700 MHz): δ = 6.75 (t, J = 52.3 Hz, 1H), 4.16 (s, 3H), 3.57 (s, 3H), 3.42 (s, 2H) ppm

**^13C NMR** (CDCl₃, 176 MHz): δ = 155.5 (s), 151.4 (s), 146.9 (s), 142.8 (s), 109.7 (t, J = 237.6 Hz), 109.5 (s), 32.9 (s), 29.8 (s), 28.1 (s) ppm

**^19F NMR** (CDCl₃, 377 MHz): δ = -115.0 (d, J = 52.3 Hz) ppm

**IR (neat):** 2925, 1706, 1665, 1604, 1549, 1459, 1090, 1036, 801 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₉H₁₀F₂N₄O₂ ([M+H]+) 245.0845, found 245.0838.
3-(difluoromethyl)-1-methylpyridin-2(1H)-one (2.3b)

The reaction was performed using 3-(chlorodifluoromethyl)-1-methylpyridin-2(1H)-one (38.7 mg, 0.20 mmol, 1 equiv). Purification by flash column chromatography (SiO$_2$, 100:0→40:60 Hex:EtOAc) furnished the title compound as a tan solid (14.5 mg, 46%).

$^{1}H$ NMR (CDCl$_3$, 700 MHz): δ = 7.69 (d, $J = 6.8$ Hz, 1H), 7.42 (d, $J = 6.6$ Hz, 1H), 6.84 (t, $J = 55.3$ Hz, 1H), 6.26 (t, $J = 6.8$ Hz, 1H), 3.59 (s, 3H) ppm

$^{13}C$ NMR (CDCl$_3$, 176 MHz): δ = 160.7 (s), 140.4 (s), 137.1 (t, $J = 5.9$ Hz), 124.7 (s), 111.2 (t, $J = 236.5$ Hz), 105.0 (s), 37.6 (s) ppm

$^{19}F$ NMR (CDCl$_3$, 377 MHz): δ = -118.8 (d, $J = 55.3$ Hz) ppm

IR (neat): 3090, 2927, 1656, 1587, 1562, 1406, 1305, 1116, 1083, 999, 758 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_7$H$_7$F$_2$NO ([M+H]$^+$) 160.0568, found 160.0567.
4-(tert-butyl)-2-(difluoromethyl)-1-methoxybenzene (2.3c)

The reaction was performed using 4-tert-butyl-2-
[chloro(difluoro)methyl]-1-methoxy-benzene (50 mg, 0.2 mmol, 1 equiv). Purification by flash column chromatography (SiO₂, 100:0→95:5 Hex:EtOAc) furnished the title compound as a clear oil (40 mg, 93%).

¹H NMR (CDCl₃, 400 MHz): δ = 7.58 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 6.95 (t, J = 55.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 1.31 (s, 9H) ppm

¹³C NMR (CDCl₃, 176 MHz): δ = 155.0 (s), 143.5 (s), 128.6 (s), 123.0 (t, J = 5.7 Hz), 121.9 (s), 111.8 (t, J = 235.5 Hz), 110.5 (s), 55.7 (s), 34.2 (s), 31.4 (s) ppm

¹⁹F NMR (CDCl₃, 377 MHz): δ = -114.94 (d, J = 55.8 Hz) ppm

IR (neat): 2962, 1618, 1505, 1384, 1264, 1057, 1021, 817 cm⁻¹

HRMS (EI⁺) m/z calculated for C₁₂H₁₆F₂O ([M⁺]) 214.1169, found 214.1176.
**8-(difluoromethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione (2.3d)**

The reaction was performed using 8-chloro(difluoro)methyl]-3,7-dimethyl-1-(5-oxohexyl)purine-2,6-dione (50 mg, 0.14 mmol, 1 equiv). Purification by flash column chromatography (SiO$_2$, 100:0→80:20 Hex:EtOAc) furnished the title compound as a clear white solid (41 mg, 91% along with an inseparable trace impurity observed in the $^1$H and $^{13}$C NMR spectra).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 6.74 (t, $J$ = 52.3 Hz, 1H), 4.15 (s, 3H), 4.02 (t, $J$ = 6.9 Hz, 2H), 3.55 (s, 3H), 2.50 (t, $J$ = 6.9 Hz, 2H), 2.14 (s, 3H), 1.68 – 1.62 (m, 4H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta$ = 208.6 (s), 155.4 (s), 151.1 (s), 146.9 (s), 142.7 (s), 109.7 (t, $J$ = 237.9 Hz), 109.5 (s), 43.1 (s), 40.9 (s), 32.9 (s), 29.9 (s), 29.7 (s), 27.3 (s), 20.9 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta$ = -115.0 (d, $J$ = 52.2 Hz) ppm

IR (neat): 2952, 1700, 1658, 1545, 1331, 1041, 750 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{14}$H$_{18}$F$_2$N$_4$O$_3$ ([M+H]$^+$) 329.1420, found 329.1428.
1-(tert-butyl) 2-methyl (2S,5R)-5-(difluoromethyl)pyrrolidine-1,2-dicarboxylate (2.3e)

The reaction was performed using 1-(tert-butyl) 2-methyl 5-(chlorodifluoromethyl)-1H-pyrrole-1,2-dicarboxylate (53 mg, 0.17 mmol, 1 equiv). Purification by flash column chromatography (SiO$_2$, 100% CH$_2$Cl$_2$) furnished the title cis-substituted compound as a clear oil (45 mg, 94%).

The analogous cis-trifluoromethylated substituted pyridine has been previously reported.$^{49}$

$^1$H NMR (d$_6$-DMSO @ 60 °C, 400 MHz): $\delta = 6.05$ (t, $J = 56.4$ Hz, 1H), 4.26 (t, $J = 8.0$ Hz, 1H), 4.15 – 3.96 (m, 1H), 3.65 (s, 3H), 2.33 – 2.14 (m, 1H), 2.13 – 1.73 (m, 3H), 1.39 (s, 9H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta = 172.6$ (s), 153.9 (s), 115.0 (t, $J = 245.6$ Hz), 114.4 ((t, $J = 244.6$ Hz), 81.1 (s), 60.1 (s), 52.0 (s), 46.3 (s), 29.6 (d, $J = 22.7$ Hz), 28.2 (d, $J = 24.5$ Hz), 23.3 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta = -118.4$ (dt, $J = 104.1$, 54.5 Hz), -124.5 (ddd, $J = 77.4$, 60.6, 21.5 Hz), -126.0 (ddd, $J = 79.5$, 57.0, 21.2 Hz) ppm

IR (neat): 2978, 1746, 1698, 1438, 1391, 1365, 1160, 1035 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{12}$H$_{19}$F$_2$NO$_4$ ([M+H]$^+$) 280.1355, found 280.1351.
5-(difluoromethyl)-6-methoxyquinoline (2.3g)

The reaction was performed using 5-[chloro(difluoro)methyl]-6-methoxyquinoline (30 mg, 0.12 mmol, 1 equiv), sodium carbonate (13 mg, 0.12 mmol), and ethyl acetate (3 mL) instead of methanol as an inseparable by-product was formed when methanol was used. Purification by flash column chromatography (SiO\textsubscript{2}, 90:10→60:40, Hex:EtOAc) furnished the title compound as a white solid (20 mg, 78%).

\textbf{\textsuperscript{1}H NMR} (CD\textsubscript{3}CN, 700 MHz): \(\delta = 8.83\) (d, \(J = 3.0\) Hz, 1H), 8.64 (d, \(J = 8.4\) Hz, 1H), 8.21 (d, \(J = 9.3\) Hz, 1H), 7.66 (d, \(J = 9.3\) Hz, 1H), 7.56 (t, \(J = 54.3\) Hz, 1H), 7.51 (dd, \(J = 8.7, 4.0\) Hz, 1H), 4.03 (s, 3H) ppm

\textbf{\textsuperscript{13}C NMR} (CD\textsubscript{3}CN, 176 MHz): \(\delta = 157.9\) (s), 150.3 (s), 145.3 (s), 136.3 (s), 133.4 (t, \(J = 3.8\) Hz), 127.3 (s), 123.8 (s), 118.0 (s), 114.9 (t, \(J = 22.2\) Hz), 114.5 (t, \(J = 231.8\) Hz), 58.1 (s) ppm

\textbf{\textsuperscript{19}F NMR} (CDCl\textsubscript{3}, 377 MHz): \(\delta = -111.65\) (d, \(J = 54.4\) Hz) ppm

\textbf{IR} (\textit{neat}): 2959, 2927, 2837, 1629, 1597, 1497, 1470, 1347, 1276, 1198, 1103, 1034, 935, 848, 798, 704 cm\textsuperscript{-1}

\textbf{HRMS} (ESI+) \textit{m/z} calculated for C\textsubscript{11}H\textsubscript{9}F\textsubscript{2}NO ([M+H]\textsuperscript{+}) 210.0725, found 210.0722.
Attempted Difluoromethylation with Difluoroacetic Anhydride and Zinc Difluoromethane-sulfinate

A. Difluoromethylation Attempt with Difluoroacetic Anhydride

To a 2-dram vial equipped with a stir bar was added 4-Ph-pyridine N-oxide (136 mg, 0.8 mmol, 1 equiv), Ru(bpy)_3Cl_2•6H_2O (6 mg, 1 mol%), and 4-tBu-anisole (140 μL, 0.8 mmol, 1 equiv). The combined materials were then dissolved in MeCN (2.5 mL) and stirred to form a homogeneous solution. The reaction solution was then sparged with N_2 for 30 sec. Difluoroacetic anhydride (109 μL, 0.88 mmol, 1.1 equiv) was then added to the resulting solution. The vial was equipped with a screw-on cap for the duration of the reaction. Three 4.4 W blue LED light strips were turned on and the reaction was allowed to run overnight (16 h) before the light source was removed. Workup was performed by diluting the reaction with CH_2Cl_2 and washing with 1N HCl, followed by saturated NaHCO_3 and then brine. The organic layer was dried over sodium sulfate, filtered, concentrated, and analyzed by ^1H NMR, ^19F NMR, TLC, and GCMS to reveal recovered starting 4-tBu-anisole.

n.r. = no detectable trace of difluoromethylated product (TLC, GCMS, ^1H NMR, ^19F NMR) was observed during the course of the reaction or upon reaction workup.
To a 2 dram vial equipped with a stir bar was prepared a solution of 4-\textsuperscript{t}Bu-anisole (41 mg, 0.25 mmol, 1 equiv) and zinc difluoromethanesulfinate (DFMS) (200 mg, 0.66 mmol, 2.7 equiv) in dichloromethane (1 mL) and water (0.4 mL). At rt, trifluoroacetic acid (20 µL, 0.25 mmol, 1 equiv) was added to the solution followed by slow addition of \textsuperscript{t}Bu-hydroperoxide (70% solution in water, 0.17 mL, 1.25 mmol, 5 equiv). The reaction was capped, stirred, and monitored by thin layer chromatography (5% EtOAc in Hex). After 22 h, the reaction was partitioned between CH\textsubscript{2}Cl\textsubscript{2} (2mL) and saturated NaHCO\textsubscript{3} (2 mL). The organic layer was separated, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 X 2 mL). The organic layers were dried over sodium sulfate, concentrated, and analyzed by \textsuperscript{1}H NMR, \textsuperscript{19}F NMR, TLC, and GCMS to reveal recovered starting 4-\textsuperscript{t}Bu-anisole.

n.r. = no detectable trace of difluoromethylated product (TLC, GCMS, \textsuperscript{1}H NMR, \textsuperscript{19}F NMR) was observed during the course of the reaction or upon reaction workup.
Preparation and Data for Methylester Pyridones

One-Pot Sequence: General Procedure 1 was followed running the reaction with pyridone (0.8 mmol, 1 equiv). After 14-24 h of stir time, the light source was turned off and 2 mL of dried MeOH and (1-2 equiv) of sodium acetate was added to the dark reaction mixture. The whole was heated to 50 °C and allowed to stir for 4-6 h. Workup was performed by diluting the reaction with 4 mL CH₂Cl₂ and 3 mL of dH₂O. The aqueous layer was washed with CH₂Cl₂ (3 x 5 mL), and the organic layers combined, washed with brine, dried over sodium sulfate, filtered and concentrated at 40 °C under reduced pressure.

From CF₂Cl-pyridone: To a 2-dram vial was added CF₂Cl-pyridone (1 equiv), sodium acetate (1 equiv) and methanol (2 mL). The whole was heated to 50 °C and allowed to stir for 4-6 hours. Workup was performed by diluting the reaction mixture with CH₂Cl₂ and extracting with de-ionized water followed by washing with brine. The organic layer was dried over sodium sulfate before filtering and concentrating at 40 °C under reduced pressure.
**methyl 1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (2.3h)**

*One-Pot Sequence: General Procedure 1* was followed running the reaction with 1-methyl-pyridin-2-one (87 mg, 0.8 mmol, 1 equiv). After 24 h of stir time, the light source was turned off and 2 mL of dried MeOH and 66 mg (0.80 mmol, 1 equiv) of sodium acetate was added to the dark reaction mixture. The whole was heated to 50 °C and allowed to stir for 6 h. Workup was performed by diluting the reaction with 4 mL CH$_2$Cl$_2$ and 3 mL of dH$_2$O. The aqueous layer was washed with CH$_2$Cl$_2$ (3 x 5 mL), and the organic layers combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude dark brown oil. Purification by flash column chromatography (SiO$_2$, 100:0→90:10 CH$_2$Cl$_2$:MeOH) furnished the title pyridone as a tan solid (76 mg, 57%).

**From 3-[chloro(difluoro)methyl]-1-methyl-pyridin-2-one:** To a 2-dram vial was added 3-[chloro(difluoro)methyl]-1-methyl-pyridin-2-one (19 mg, 0.1 mmol, 1 equiv), 1 mL dried MeOH, and sodium acetate (8 mg, 0.1 mmol, 1 equiv). The whole was allowed to stir for 6 h at 50 °C. Workup was performed by diluting the reaction with 4 mL CH$_2$Cl$_2$ and 3 mL of dH$_2$O. The aqueous layer was washed with CH$_2$Cl$_2$ (3 x 5 mL), and the organic layers combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude dark brown oil. Purification by flash column chromatography (SiO$_2$, 100:0→90:10 CH$_2$Cl$_2$:MeOH) furnished the title pyridone as a tan solid (15 mg, 91%).

$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.16 (d, $J$ = 7.2 Hz, 1H), 7.54 (d, $J$ = 6.5 Hz, 1H), 6.23 (t, $J$ = 6.8 Hz, 1H), 3.91 (s, 3H), 3.60 (s, 3H) ppm

$^{13}$C NMR (CDCl$_3$, 126 MHz): δ 165.8 (s), 159.8 (s), 144.8 (s), 143.1 (s), 120.5 (s), 104.5 (s), 52.3 (s), 38.3 (s) ppm

IR (neat): 2936, 1717, 1648, 1590, 1435, 1376, 1272, 1102, 772 cm$^{-1}$
HRMS (ESI+) $m/z$ calculated for $C_8H_9NO_3$ ([M+Na]+) 190.0475, found 190.0475.
**methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (2.3i)**

*One-Pot Sequence: General Procedure 1* was followed running the reaction with 5-bromo-1-methyl-pyridin-2-one (150 mg, 0.8 mmol, 1 equiv). After 16 h of stir time, the light source was turned off and 2 mL of dried MeOH and 131 mg (1.6 mmol, 2 equiv) of sodium acetate was added to the dark reaction mixture. The whole was heated to 50 °C and allowed to stir for 6 h. Workup was performed by diluting the reaction with 4 mL of CH₂Cl₂ and 3 mL of dH₂O. The aqueous layer was washed with CH₂Cl₂ (3 x 5 mL), and the organic layers combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude dark brown oil. Purification by flash column chromatography (SiO₂, 100:0→90:10 CH₂Cl₂:MeOH) furnished the title pyridone as a light yellow solid (85 mg, 44% along with trace inseparable starting material observed in the ¹H NMR spectra).

**¹H NMR** (CDCl₃, 400 MHz): δ 8.18 (d, J = 2.8 Hz, 1H), 7.66 (d, J = 2.8 Hz, 1H), 3.91 (s, 3H), 3.58 (s, 3H) ppm

**¹³C NMR** (CDCl₃, 175 MHz): δ 164.5 (s), 158.2 (s), 147.2 (s), 142.9 (s), 121.4 (s), 95.9 (s), 52.6 (s), 38.5 (s) ppm

**IR (neat):** 2960, 2362, 1734, 1700, 1634, 1540, 1457, 1430, 1297, 1101 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₈H₈BrNO₃ ([M+Na]+) 267.9580, found 267.9582.
**methyl 4-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (2.3j)**

**One-Pot Sequence: General Procedure 1** was followed running the reaction with 4-bromo-1-methyl-pyridin-2-one (150 mg, 0.8 mmol, 1 equiv).

After 16 h of stir time, the light source was turned off and 2 mL of dried MeOH and 66 mg (0.80 mmol, 1 equiv) of sodium acetate was added to the dark reaction mixture. The whole was heated to 50 °C and allowed to stir for 4 h. Workup was performed by diluting the reaction with 4 mL CH2Cl2 and 3 mL of dH2O. The aqueous layer was washed with CH2Cl2 (3 x 5 mL), and the organic layers combined, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a crude dark brown oil. Purification by flash column chromatography (SiO2, 100:0–90:10 CH2Cl2:MeOH) furnished the title pyridone as an off white solid (107 mg, 54%).

**1H NMR** (CDCl3, 400 MHz): δ 7.19 (d, J = 7.2 Hz, 1H), 6.39 (d, J = 7.2 Hz, 1H), 3.94 (s, 3H), 3.52 (s, 3H) ppm

**13C NMR** (CDCl3, 126 MHz): δ 165.1 (s), 158.7 (s), 138.5 (s), 133.1 (s), 127.4 (s), 110.1 (s), 52.9 (s), 37.7 (s) ppm

**IR (neat):** 2955, 1705, 1660, 1608, 1545, 1445, 1425, 1339, 1228, 1072, 912, 741 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₈H₈BrNO₃ ([M+Na]+) 267.9580, found 267.9582.
**Attempted Substrates**

The substrates listed below failed to provide methyl carboxylate products in sufficient quantities for purification and isolation under the described conditions.
Preparation and Data for gem-Difluoroenones

General Procedure 2 was followed then after 16 h the mixture was filtered through a silica plug and concentrated under reduced pressure. The crude was purified via flash column chromatography using a 0 to 3% ethyl acetate in hexanes elution gradient.

3,3-difluoro-2-methyl-1-phenylprop-2-en-1-one (2.4a)

The reaction was performed using 1-phenyl-1-propyne (0.10 mL, 0.8 mmol, 1 equiv). The title compound was furnished as a light yellow oil (132 mg, 91%). $^{19}$F NMR yield = 95%.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.49 - 7.34$ (m, 5H), 2.02 (s, 3H) ppm

$^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta = 155.9$ (t, $J = 35.8$ Hz), 131.8 (s), 130.3 (s), 129.1 (s), 128.2 (s), 125.2 (t, $J = 291.9$ Hz), 116.4 (t, $J = 300.8$ Hz), 12.4 (s) ppm

$^{19}$F NMR (CDCl$_3$, 377 MHz): $\delta = -48.88, -64.18$ ppm

IR (neat): 2362, 1751, 1696, 1469, 1490, 1277, 1102 cm$^{-1}$

HRMS (EI, ESI, APCI) was attempted, but no molecular ion peak was observed under various conditions.
2-(difluoromethylene)-1-phenylbutan-1-one (2.4b)

The reaction was performed using 1-phenyl-1-butyne (0.11 mL, 0.8 mmol, 1 equiv). The title compound was furnished as a clear oil (140 mg, 89%). 19F NMR yield = 95%.

1H NMR (CDCl3, 400 MHz): δ = 7.51 – 7.36 (m, 5H), 2.40 (q, J = 7.15 Hz, 2H), 1.24 (td, J = 7.5, 3.5 Hz, 1H) ppm

13C NMR (CDCl3, 176 MHz): δ =156.2 (t, J = 35.6 Hz), 131.9 (s), 130.2 (s), 129.2 (s), 128.1 (s), 125.4 (t, J = 292.6 Hz), 116.3 (t, J = 300.8 Hz), 20.9 (s), 13.0 (s) ppm

19F NMR (CDCl3, 377 MHz): δ = -47.69, -64.38 ppm

IR (neat): 2980, 1795, 1491, 1286, 1172, 1105, 958, 829 cm⁻¹

HRMS (EI, ESI, APCI) was attempted, but no molecular ion peak was observed under various conditions.
Attempted Substrates

The substrates listed below failed to provide gem-difluoroenone products in sufficient quantities for purification and isolation under the described conditions.
Preparation and Data for $\beta$-keto esters

General Procedure 2 was followed then after 16 h, the reaction was diluted with $R^1$OH (1 mL) and triethylamine (0.12 mL, 1 equiv) then the whole was let stir for 1 h. The mixture was filtered through a silica plug and concentrated under reduced pressure. The crude was purified via flash column chromatography using a 0 to 5% ethyl acetate in hexanes elution gradient.

**methyl 2-methyl-3-oxo-3-phenylpropanoate (2.4c)**

General Procedure 2 was followed using 1-phenyl-1-propyne (93 mg, 0.8 mmol, 1 equiv) then the reaction was quenched with 1 mL of methanol. The title compound was isolated as a clear oil (65 mg, 42%).

The $^1$H NMR data and HRMS is identical to that reported in the literature.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.98 (d, $J$ = 7.3 Hz, 2H), 7.59 (t, $J$ = 7.4 Hz, 1H), 7.48 (t, $J$ = 7.7 Hz, 2H), 4.41 (q, $J$ = 7.1 Hz, 1H), 3.69 (s, 3H), 1.50 (d, $J$ = 7.1 Hz, 3H) ppm

HRMS (EI+) $m/z$ calculated for C$_{11}$H$_{12}$O$_3$ (M+) 192.0786, found 192.0795.
methyl 2-benzoylbutanoate (2.4d)

General Procedure 2 was followed using 1-phenyl-1-ethyne (104 mg, 0.8 mmol, 1 equiv) then the reaction was quenched with 1 mL of methanol. The title compound was isolated as a clear oil (60 mg, 36%).

The $^1$H-NMR data and HRMS is identical to that reported in the literature.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.99 (d, $J = 7.4$ Hz, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 4.25 (t, $J = 7.2$ Hz, 1H), 3.69 (s, 3H), 2.05 (pd, $J = 7.29$, 2.04 Hz, 2H), 0.99 (t, $J = 7.4$ Hz, 3H) ppm

HRMS (EI+) m/z calculated for C$_{12}$H$_{14}$O$_3$ (M+) 207.1016, found 207.1016.
ethyl 2-benzoylbutanoate (2.4e)

General Procedure 2 was followed using 1-phenyl-1-ethyne (104 mg, 0.8 mmol, 1 equiv) then the reaction was quenched with 1 mL of ethanol. The title compound was isolated as a clear oil (34 mg, 20%).

The $^1$H-NMR data and HRMS is identical to that reported in the literature.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.99 (dd, $J = 5.3$, 3.2 Hz, 2H), 7.58 (t, $J = 7.3$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 4.21 (t, $J = 7.2$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.04 (p, $J = 7.31$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.00 (t, $J = 7.4$ Hz, 3H) ppm

HRMS (EI+) m/z calculated for C$_{13}$H$_{16}$O$_3$ (M+H$^+$) 221.1172, found 221.1172.
2.5. References


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Chapter 3

Arylsulfonylacetamides as Bifunctional Reagents for Alkene Aminoarylation

*Portions of this chapter have been published in T. M. Monos*, R. C. McAtee*, C. R. J. Stephenson. Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylation. Science 2018, 361, 1369–1373. *contributed equally

3.1. Introduction

3.1.1. Significance of Alkene Difunctionalization Reactions and Arylethylamine Scaffolds

Alkenes are fundamental building blocks in organic chemistry and are essential in natural product synthesis, pharmaceutical development, and material sciences. Alkene difunctionalization reactions offer unique advantages by allowing for the formation of two chemical bonds in a single operation, potentially simplifying synthetic plans and leading directly to biologically desirable pharmacophores (Figure 3.1A). Pharmaceutical synthesis often requires the formation of adjacent carbon-carbon and carbon-nitrogen bonds and thus methods to forge these new bonds in a single operation are particularly desirable.

Alkene aminoarylation (a subclass of alkene difunctionalization reactions) allows direct access to the biologically active arylethylamine pharmacaphore. The arylethylamine motif is conserved in dopamine, serotonin, and many opioid receptor drugs responsible for modulating pain sensation and treating neurobehavioral disorders (Figure 3.1B). In light of the opioid
epidemic, it is also noteworthy that frontline medications treating opioid addiction also contain such arylethylamine substructures (Figure 3.1C). With this rationale, continued drug development in the arylethylamine chemical space is necessary for general hit-to-lead exploration and the discovery of new and safer pain-management medicines. Conventional methods to synthesize arylethylamines use multistep homologation and reductive amination sequences (Figure 3.1D). Alternatively, alkene aminoarylation, particularly of anethole and other biomass-derived alkenes, allows for direct access to this medicinally desirable functionality. The development of methodologies to rapidly construct two new bonds (C–C and C–N) in a single operation from feedstock chemicals can improve and expedite the discovery of new arylethylamine-based small-molecule therapeutics.
Figure 3.1. The importance of alkene difunctionalization reactions and the arylethylamine pharmacaphore.
(A) A general representation of alkene difunctionalization reactions. (B) The importance of the arylethylamine motifs in medicines. (C) The arylethylamine motif at the center of the opioid epidemic. (D) Conventional methods to synthesize arylethylamines.

3.1.2. Transition-Metal Catalyzed Aminoarylation Reactions

Alkene aminoarylation has been demonstrated with palladium,\textsuperscript{5-6} copper,\textsuperscript{7-9} nickel,\textsuperscript{10-11} and gold,\textsuperscript{12} in which alkenes are activated by the transition metal to facilitate a stereoselective amine cyclization, followed by a two-electron metal-mediated arylation event (Figure 3.2). The metals used in these aminoarylation platforms control stereoselectivity and activate the alkene for reactivity while suppressing protodemetalation or β-hydride elimination pathways that hinder desired C–C bond formation. Amides and amines are more nucleophilic than the alkene coupling.
partner; thus, elevated temperatures are often necessary to facilitate ligand substitution to unite the reactants in the initial amination event. Despite robust investigation, these methods are generally limited by the need for directing groups and intramolecular reaction designs that restrict the products to pyrrolidine and piperidine products.

![Figure 3.2. General representation of transition-metal mediated alkene aminoarylation reactions.](image)

Recently, transformations effecting intermolecular aminoarylation and carboamination have been accomplished in which the alkene is decoupled from the arylation and amination reagents. In one case, Lin and Liu demonstrated an enantioselective copper(I)-catalyzed aminoarylation of vinyl arenes relying upon preoxidized sulfonamide reactants (N-fluoro-N-methylbenzenesulfonamide) as both the copper oxidant and nitrogen nucleophile (Figure 3.3). Only vinyl arenes are presented in their substrate scope, potentially suggesting the allylic functionality is not compatible with the developed conditions.
Separately, Rovis and Piou demonstrated an intermolecular carboamination using $N$-enoxypthalimides and Rh(I-III) catalysis in a diastereoselective fashion (Figure 3.4). This approach allows for both nitrogen and carbon containing functionalities to be delivered from the same, easily prepared reagent. While this approach allows for the incorporation of a wide array of arenes, it is limited to fumarate and maleate esters as the reactive alkene component.

**Figure 3.4. Intermolecular carboamination reaction using a bifunctional reagent.**

### 3.1.3. Visible Light-Mediated Carboamination Reactions

Photocatalysis and radical-based chemistry have proven similarly influential in alkene difunctionalization. The simplest strategy is Meerwein aminoarylation, a Markovnikov-selective
reaction that begins with the reductive generation of a radical from a suitable precursor (arene diazonium salt or diaryliodonium salt) followed by radical-polar crossover and Ritter trapping with acetonitrile solvent and hydrolysis (Figure 3.5). These reactions are regioselective but are devoid of stereoselectivity.

![Figure 3.5](image_url)

**Figure 3.5.** Markovnikov-selective Meerwein aminoarylation enabled by phoptoredox catalysis.

Photocatalytic anti-Markovnikov–selective alkene hydro- and carboamination reactions were recently demonstrated by Knowles and Nicewicz. These approaches represent contrasting C–N bond formation strategies while using a common catalytic cycle (see also Chapter 1). Knowles and co-workers have demonstrated both aminium radical cation (Figure 3.6A) and amidyl radical (Figure 3.6B) generation for the addition to olefins. In both cases, nitrogen-centered radicals couple with π-systems to generate β-amino radicals that are rapidly trapped with an H-atom transfer reagent or an appropriate acceptor for a C–C bond forming event. Successful H-atom transfer reagents are minimally nucleophilic to prevent thiol-ene reactivity. Nitrogen radical–based chemistry is particularly challenging because both alkene addition and allylic H-atom abstraction are kinetically competitive processes; thus, success often requires excesses of the alkene component or intramolecular amino-cyclization. Importantly, this proton-coupled electron transfer strategy allows for native functionalities (N–H bonds of amines and amides) to become directly activated without the need for N-pre-functionalization (such as N-chloroamines...
or elaborate fragmentable redox-auxiliaries). This system operates with a highly oxidizing photocatalyst in combination with a weak base to initiate a homolytic N–H bond fragmentation. The resultant N-centered radicals then chemoselectively react with alkenes in both intra- and intermolecular fashions. It should be noted that amine and amide oxidation generate a more reactive, but not a more nucleophilic, nitrogen atom.

Figure 3.6. Activation of native N–H bonds (amines and amides) for hydro- and carboamination of alkenes.

(A) Amine activation to aminium radical cation for alkene hydroamination. (B) PCET activation of aryl amides for alkene carboamination.

In contrast to the developed PCET activation of nitrogenous nucleophiles for hydro- and carboamination methods, Nicewicz and co-workers have targeted alkene single-electron oxidation, a process approximately as rapid as amide or amine oxidation. This approach benefits from converting the alkene to a more electrophilic species in solution, necessitating lower equivalents
of the nitrogen nucleophile to conduct alkene difunctionalization. Mechanistically, these reactions operate via oxidation of the aliphatic olefin with a potent photoexcited acridinium catalyst (Figure 3.7A). The resultant radical cation is poised for nucleophilic trapping from either a nitrogen or oxygen-based nucleophile. The resultant carbon-centered radical can be trapped by a suitable H-atom transfer agent (Figure 3.7B) or a radical acceptor reagent (Figure 3.7C) for C–C bond formation.

**Figure 3.7. Alkene oxidation for hydro- and carboamination of alkenes.**
(A) Potent acridinium photocatalysts from the excited state. (B) Alkene oxidation for alkene hydroamination. (C) Alkene oxidation for alkene carboamination.
3.1.4. Photochemical Smiles Rearrangements – The Potential for Alkene Aminoarylation

To contrast the widely investigated field of transition metal–mediated aminoarylation and build on the successes of photocatalytic alkene difunctionalization chemistry, we were inspired by the possibility of a radical Smiles rearrangement to provide alkene aminoarylation products in a diastereoselective fashion. The classic Smiles rearrangement is an intramolecular nucleophilic aromatic substitution reaction that interchanges one biaryl-heteroatom linker for another (Figure 3.8A). This process is largely controlled by the relative acidities of the two interchangeable heteroatomic nucleophiles. Traditionally, the Truce variant of the Smiles rearrangement is a nucleophilic aromatic substitution effected by benzylic lithiation of o-tolyl-arylsulfones (Figure 3.8B).25 The rearrangement is more broadly applicable to ipso-substitution reactions with aryl sulfides, sulfoxides, sulfones, and amides. Pennell and Motherwell furthered the utility of this transformation by demonstrating that aryl radicals are also capable of the same arene transposition (Figure 3.8C).26
Figure 3.8. Classic aryl transfer strategies.  
(A) The classic anionic Smiles rearrangement.  (B) The Truce modification of the Smiles rearrangement extending the reaction to C-nucleophiles.  (C) The Motherwell and Pennel modification of the Smiles rearrangement extending to C-centered radicals.

In the past, our group, in collaboration with Eli Lilly developed a method toward preparing gem-difluorobenzyl motifs via a radical Smiles-Truce rearrangement.\textsuperscript{27-28} Prior to this collaboration, Lilly had been using a non-sustainable sequence to produce a thiophene-based intermediate (Figure 3.9A) that required excess of AIBN, Deoxo-Fluor, and several chromatographic purifications. Our solution instead allowed for the simple coupling of the corresponding sulfonyl chloride and a readily-available alcohol (one step from commercial) followed by single-electron reduction to initiate a radical Smiles-Truce rearrangement sequence, generating the difluorinated alcohol substrate after loss of SO\textsubscript{2} (Figure 3.9B). Multiple (hetero)aryl substrates were amenable to this chemistry (Figure 3.9C), with the energy of dearomatization during the ipso attack providing the major enthalpic barrier (elevated temperatures generally recovered any loss in efficiency due to this factor).
Figure 3.9. Employing a photochemical Smiles rearrangement for the synthesis of gem-difluoroaryl ethanol motifs.
(A) The inspiration for the developed photochemical Smiles rearrangement. (B) The design strategy and proposed key intermediate for the photochemical Smiles rearrangement. (C) Select substrate scope for the developed method.

Although there are numerous intramolecular examples of radical Smiles-Truce reactions,^27,^29^–^32^ many of these reactions use net reductive conditions, generate a stoichiometric amount of waste, and rely on a substrate design that tethers the radical precursor to the aryl-sulfonyl derivative. Realizing that this intramolecular tether can be formed via in situ oxidation of an alkene and subsequent nucleophilic trapping with an arylsulfonylacetamide,^33^ we sought to design a photocatalyzed radical Smiles-Truce reaction that showcases the utility of arylsulfonylacetamides as capable reagents for both C–N and C–C bond formation in aminoarylation (Figure 3.10).
Figure 3.10. General design strategy for the reported alkene aminoarylation employing arylsulfonylacetamides as bifunctional reagents.
3.2. Results and Discussion

A general catalytic cycle was postulated to begin with an oxidation event between a photoexcited catalyst (*IrIII) and an alkene (I) (Figure 3.11A).\textsuperscript{22-23} Single-electron oxidation of the alkene would enable nucleophilic addition of an arylsulfonylacetamide (II) to afford the desired β-aminoalkyl radical intermediate (III).\textsuperscript{34-36} This radical is poised for regioselective cyclization onto the ipso-position of the appended arene to generate IV.\textsuperscript{37} Lastly, an entropically favored desulfonylation can proceed via two plausible pathways to generate the aminoarylation product, VII: (i) rapid radical desulfonylation from IV to generate nitrogen-centered radical V followed by catalyst turnover, or (ii) homolytic fragmentation of the C\textsubscript{Ar}–S bond to furnish VI, which can turn over the catalyst and undergo desulfonylation to VII. Exploiting both the electronic activation of the sulfonylated arene unit and the tunable nucleophilicity of the nitrogen motif allows for this photoredox catalysis platform to promote both the C–N and C–C bond-forming events with arylsulfonylacetamides.
To realize the proposed aminoarylation reactivity, we first conducted reaction optimization with vinyl anisole (3.1) \( E_{p/2} = 1.6 \text{ V versus saturated calomel electrode (SCE)} \)\(^{38} \) and 1-naphthylsulfonylacetamide (3.2). A potent photooxidant, \([\text{Ir}(dF(CF_3)ppy)_2](5,5′-CF_3-bpy))\( \text{PF}_6 \) (3.3) \( (\text{Ir}^{III/II} = 1.68 \text{ V versus SCE in MeCN}) \)\(^{39} \) was initially selected for alkene radical cation formation (Figure 3.11B). Early optimization experiments lent evidence to the chemoselectivity of this reaction; excess loading of arylsulfonylacetamide and base were unnecessary. Nearly equivalent stoichiometry between 3.1 and 3.2 afforded the highest yield for the optimization product 3.4. A base screen revealed potassium acetate, benzoate, and tribasic phosphate as superior bases to the less basic potassium trifluoroacetate and potassium phosphate (mono- or dibasic). The reaction was incompatible with pyridine or with stronger alkoxide bases, as photocatalyst decomposition was observed. Reaction dilution past 0.1 M slowed the rate of product formation, whereas reaction concentrations greater than 0.1 M inhibited product formation. Further
optimization proved that less oxidizing photocatalysts such as [Ru(bpy)$_3$]Cl$_2$ (Ru$^{II/III} = 0.77$ V versus SCE in MeCN), [Ir(dF(CF$_3$ppy)$_2$(dtbbpy))]PF$_6$ (Ir$^{III/II} = 0.89$ V versus SCE in MeCN), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (Ir$^{III/II} = 0.31$ V versus SCE in MeCN),$^{40}$ were unable to catalyze this transformation. Use of Fukuzumi’s catalyst (PC$^\bullet$/PC$^\ast$ = 1.88 V versus SCE in MeCN)$^{41}$ did produce $3.4$ in 13% yield. Finally, H-atom donor additives such as 1,4-cyclohexadiene and isopropanol did not improve on the established conditions for the optimization product $3.4$. Exclusion of either light or photocatalyst failed to promote aminoarylation. With the proof of concept established, we identified the acyl group, among a range of amides and carbamates, as the optimal activating group for the sulfonamide reagent in this transformation (Figure 3.12A, 3.4–3.7). We reasoned that the acidity and the steric encumbrance of the sulfonamide activating group control the nucleophilicity of the arylsulfonylacetamide.

A substantial increase in aminoarylation was observed when using 1,2-disubstituted $p$-methoxyphenyl alkenes in comparison to $3.1$ (Figure 3.12A). This substitution allowed us to realize the aryl transfer of several groups including 1-naphthyl ($3.4$–$3.6$, $3.8$–$3.10$, $3.21$, $3.22$), 2-napthyl ($3.11$), 3-thiophenyl ($3.12$, $3.13$), 2-thiophenyl ($3.14$, $3.15$, $3.18$), 2-furanyl ($3.16$), 8-quinolino ($3.17$), 2-benzothiazole ($3.19$), and $\beta$-styrene ($3.20$) all in greater than 20:1 diastereoselectivity. X-ray crystallographic analysis of $3.15$ was found to show a syn-configuration between the 5-bromothiophene and the acetamide groups supporting the stereochemical assignment. Use of cyclic ($E$)-alkenes allowed for the synthesis of cyclic arylethylamines ($3.23$–$3.26$) containing two contiguous stereocenters, one of which is quaternary (Figure 3.12B). Furthermore, the cis-diastereomer $3.27$ can be formed when a cyclic ($Z$)-alkene is used as the oxidizable alkene substrate partner (Figure 3.13C). Preparation of arylethylamine $3.21$ containing an $N$-tosyl amide showcases the chemoselective nature of this aminoarylation, and the successful
isolation of 3.22 suggests that nucleophiles tethered to the alkene are well tolerated under the reaction conditions.

Figure 3.12. Exploration of substrate scope.
All yields are isolated yields. Relative configurations of products were assigned by analogy to 3.15 and 3.23. (A) Evaluation of scope of aryl group. (B) Scope of cyclic trans-PMP alkenes. (C) Scope of a compatible cyclic cis-PMP alkene. *2:1 mixture of E/Z alkene diastereomers.

To provide mechanistic insight, we carried out several studies to understand the efficiency and high diastereoselectivity of this transformation. We hypothesized that both acyclic (Z)- and (E)-alkenes would convert to the same trans-aminoarylation diastereomer as a result of bond rotation outcompeting cyclization of intermediate III. Notably, performing the title aminoarylation...
with (Z)-anethole afforded a nearly identical yield of 3.9 (72%), in comparison to (E)-anethole (82%), whereas diastereomer 3.9′ was not observed (Figure 3.13A). Reaction progress analysis by 1H-nuclear magnetic resonance spectroscopy of (Z)-anethole aminoarylation revealed that (E)-anethole is generated during the reaction (Figure 3.13B). On the basis of this observation, we examined the rates of isomerization for each anethole isomer to the photostationary state (Figure 3.13C). This revealed a photostationary state of 1.4:1 (Z:E), with the initial rate of (Z)-anethole isomerization being much faster than (E)-anethole isomerization. Furthermore, initial rate analysis of aminoarylation shows alkene consumption to be slower than (Z)-anethole isomerization. These data suggest that the diastereoselectivity arises from either (i) a kinetically favored generation of (E)-anethole radical cation and subsequent aminoarylation, or (ii) a thermodynamic preference of radical intermediate III to adopt an anti-periplanar conformation between the paramethoxyphenyl (PMP) and methyl substituents prior to cyclization (Figure 3.13D). One other competing possibility is that the (E)-anethole radical cation reacts with 3.2 faster than does the (Z)-anethole radical cation. Overall, these mechanistic details describe how the combination of a Smiles-Truce aryl transfer and radical cation chemistry can be combined into a highly diastereoeconvergent alkene aminoarylation reaction platform.
Figure 3.13. Experiments to probe reaction mechanism.
(A) Aminoarylation with (Z)-anethole (3.28). (B) Tracking reaction progress for aminoarylation with (Z)-anethole (3.28) (▲ = 2, ■ = (Z)-anethole, ♦ = 3.9, ■ = (E)-anethole). (C) Determination of the photostationary state for anethole isomers catalyzed by 3.3. (D) Favored and disfavored conformations for intermediate III.

3.3. Conclusions

In conclusion, given the current availability of sulfonamide building blocks along with the ubiquity of alkenes as feedstock substrates, we view the method to be a highly enabling platform for research efforts synthesizing the arylethylamine pharmacophore diastereoselectively in a single operation. We believe that because this process is driven by visible light and uses readily available chemical reagents it is well suited to immediately impact a variety of chemical disciplines, including simplifying the synthesis of drug-like molecules we encounter in our everyday lives.
3.4. Experimental Procedures and Characterization of Compounds

3.4.1. General Procedures, Reaction Optimization, Materials and Methods

General Information

All chemicals were used as received and stored as recommended by the supplier. Reactions were monitored by thin layer chromatography (TLC) using glass-backed plates pre-coated with 230–400 mesh silica gel (250 mm thickness) with fluorescent indicator F254, available from EMD Millipore (cat. #: 1.05715.0001). Plates were visualized with a dual short wave/long wave UV lamp. Column flash chromatography was performed using 230-400 mesh silica (SiliCycle cat. #: R12030B) gel or via automated column chromatography. NMR spectra were recorded on Varian MR400, Varian Inova 500, Varian Vnmrs 500, or Varian Vnmrs 700 spectrometers. Chemical shifts for \( ^1H \) NMR were reported as \( \delta \), parts per million, relative to the signal of CHCl\(_3\) at 7.26 ppm and for DMSO 2.50. Chemical shifts for \( ^{13}C \) NMR were reported as \( \delta \), parts per million, relative to the center line signal of the CDCl\(_3\) triplet at 77.0 ppm and for DMSO 39.52 for center of septet. \( ^{19}F \) NMR chemical shifts were reported as \( \delta \), parts per million, relative to CFCl\(_3\) at 0.0 ppm. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublets of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer fitted with an ATR accessory. Melting points were obtained using a Mel-Temp 3.0 (model no. 1401). Mass Spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPCL-MS with ESI high resolution mass spectrometer using electrospray ionization (ESI), positive ion mode, or electron impact ionization.
Fluorescence quenching was recorded using a Horiba Scientific Fluoromax 2 using DataMax software. We thank Dr. James Windak and Dr. Paul Lennon at the University of Michigan Department of Chemistry instrumentation facility for conducting these experiments. X-Ray Crystallography work was done by Dr. Jeff. W. Kampf. UV-Vis measurements were obtained on a Shimadzu UV-1601 UV-Vis Spectrometer. Electrochemical data was collected on a CHI600E potentiostat with the accompanying CH Instruments software. H150 Blue grow lights from Kessil were used as the visible light irradiation source.

**General Reaction Set-up**

Unless stated otherwise, all reactions were run on a 0.3 mmol scale in a 2 dram vial equipped with an oval shaped stir bar. 1 x H150 Blue Kessil lamp sufficiently irradiated 1-3 reaction vials at one time, about 5 cm away (A, side view). At this distance, with a fan dissipating the standing atmosphere (B, top view), the air temperature surrounding the reactions did not exceed 25 °C.
General Procedure A: Radical Aminoarylation of Alkenes (0.3 mmol scale)

Unless otherwise noted, to a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added (aryl-sulfonyl)acetamide (1 equiv, 0.3 mmol), potassium benzoate (14.4 mg, 30 mol%), and Ir(dF(CF$_3$)ppy)$_2$(5,5'-d(CF$_3$)bpy)PF$_6$ (3 mg, 1 mol%). The vial contents were then dissolved in anhydrous DMF (3 mL, 0.1 M). Finally, the alkene (1.2 equiv) was added to the reaction vial. The reaction was sparged under argon for 15 min, quickly capped and sealed with parafilm. Reactions were irradiated with 1 x blue H150 Kessil LED light and stirred (500 to 550 rpm) for 12 to 16 h at room temperature.

Reaction workup was performed by diluting the reaction with 15 mL dH$_2$O and extracting the aqueous layer with EtOAc (3 x 10 mL). The organic layers were combined, washed with 5 wt% LiCl (3 x 10 mL), brine (15 mL), dried over sodium sulfate, filtered and concentrated to provide the crude residue, which was purified by flash column chromatography.

Step-by-step Reaction Set-up Pictures

Step 1: Flame dried 2-dram vial and stir bar

Step 2: Solid reagents loaded
Step 3: Solid reagents diluted in DMF (0.1 M)

Step 4: Sparge degassing technique with argon balloon and 4” hypodermic needle

Step 5: Vial-cap juncture wrapped in parafilm immediately after argon sparging

Step 6: Blue light irradiation with 1 x H150 blue Kessil grow lamp, 500 rpm, and fan for cooling
### Reaction Optimization Studies

![Chemical Reaction Diagram]

Table 3.1. Reaction optimization for the alkene aminoarylation with arylsulfonylacetamides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>B equiv</th>
<th>Base</th>
<th>Base equiv.</th>
<th>Catalyst</th>
<th>Solvent [M]</th>
<th>C (%) yield</th>
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<td>3</td>
<td>KOAc</td>
<td>3</td>
<td>None</td>
<td>DMF [0.1 M]</td>
<td>0</td>
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<tr>
<td>2</td>
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<td>KOAc</td>
<td>3</td>
<td>[Ir-1] (no light)</td>
<td>DMF [0.1 M]</td>
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<tr>
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<td>3</td>
<td>[Ir-1]</td>
<td>DMF [0.1 M]</td>
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<tr>
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<td>[Ir-1]</td>
<td>DMF [0.1 M]</td>
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<tr>
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<td>K2CO3</td>
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<tr>
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<td>3</td>
<td>K3PO4</td>
<td>3</td>
<td>[Ir-1]</td>
<td>DMF [0.1 M]</td>
<td>41</td>
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<tr>
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<td>[Ir-1]</td>
<td>DMF [0.1 M]</td>
<td>41</td>
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<td>11</td>
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<td>DMF [0.1 M]</td>
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</tr>
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**Photocatalyst Redox Potentials**

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<th>$M^*/M^-$</th>
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<th>$M/M^-$</th>
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Electrochemical potentials reported vs. SCE reference electrode in MeCN Solvent.

Table 3.2. Chemical structures of screened photocatalysts and their associated redox potentials.
**Unreactive Substrates in the Aminoarylation Reaction**

\[ R_1\text{--}R_2 + \text{ArSO}_2\text{N--R}_3 \xrightarrow{\text{General Procedure A}} \text{ArH--N--R}_1\text{--}R_2 \]

**0.3 mmol scale**

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<td>phen</td>
<td>benz</td>
<td>benz</td>
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**\( E_{\text{p/2}} \)**

\( E_{\text{p/2}} \) (vs SCE in MeCN)

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<td>Attempted Sulfonamides:</td>
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Table 3.3. Unreactive alkenes and sulfonamides screened for the aminoarylation reaction.
### 3.4.2. Reaction Profiling and Mechanism Elucidation Experiments

**Stern-Volmer Luminescent Quenching Experiment**

Fluorescence quenching of [Ir]-1 was recorded with a Horiba Scientific Fluoromax 2 using DataMax software. Samples consisting of the noted concentrations were prepared and degassed by sparging with argon for 3 minutes prior to each measurement. The solutions were irradiated at 420 nm and luminescence was measured at 593 nm. $I_0/I$ values were generated from the average of three scans taken per quencher concentration. The quenching studies were repeated three times. Potassium benzoate was not sufficiently soluble in DMF in order to run this analysis.

**Conclusion:** This quenching study supports the hypothesis of alkene activation over sulfonamide activation as the sulfonamide is not shown to quench the photocatalyst.

**Constant [Ir]-1, variable $E$-anethole**

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### Constant [Ir]-1, variable Z-anethole

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The linear regression equation is:

$$y = 80.771x + 0.9968$$

with $R^2 = 0.9952$. 

$[trans-anethol]$ (mM) vs. $I_0/I$
Constant [Ir]-1, variable sulfonylacetamide

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$y = -4.4206x + 1.011$

$R^2 = 0.0811$
Reaction Profile and Initial Rates for Aminoarylation with vinyl-Anisole

To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added vinyl-anisole (20.1 mg, 0.15 mmol), \( N \)-(1-naphthylsulfonyl)acetamide (37.4 mg, 0.15 mmol), potassium benzoate (7.21 mg, 30 mol%), and \( \text{Ir(dF(CF}_3\text{)ppy)}_2(5,5'\text{d(CF}_3\text{)bpy})\text{PF}_6 \) (1.5 mg, 1 mol%). The vial contents were then dissolved in anhydrous \( d_7\)-DMF (1.5 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (8.52 μL, 0.05 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 1.5 mL solution volume was equally separated between 3 argon sparged NMR tubes (0.5 mL each). The tubes were quickly capped and sealed with parafilm. Time zero (\( t_0 \)) \(^1\)H-NMR measurements were taken of all three samples prior to irradiation. Then, the 3 NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the alloted time (i.e. 5, 10, 15, 20... min), the light was turned off and reaction solution analyzed by \(^1\)H-NMR.

**Analysis:** The concentrations and yields for the aminoarylation substrates and product were plotted against time in minutes. The slope through five points for the first ~20% reaction conversion was utilized to calculate the initial rates of reaction. The procedure was repeated in triplicate (3 \(^1\)H-NMR measurements) and the average of these three trials was determined. Calculated values are tabulated below.
### Aminoarylation Reaction Profile with vinyl-anisole

**([M] vs. time)**

<table>
<thead>
<tr>
<th>min</th>
<th>Product Formation</th>
<th>Alkene Consumption</th>
<th>Sulfonamide Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0000</td>
<td>0.12633</td>
<td>0.10133</td>
</tr>
<tr>
<td>5</td>
<td>0.0020</td>
<td>0.12433</td>
<td>0.09967</td>
</tr>
<tr>
<td>10</td>
<td>0.0027</td>
<td>0.12267</td>
<td>0.09933</td>
</tr>
<tr>
<td>15</td>
<td>0.0030</td>
<td>0.12133</td>
<td>0.09867</td>
</tr>
<tr>
<td>30</td>
<td>0.0087</td>
<td>0.11733</td>
<td>0.09433</td>
</tr>
<tr>
<td>45</td>
<td>0.0144</td>
<td>0.10567</td>
<td>0.08467</td>
</tr>
<tr>
<td>60</td>
<td>0.0214</td>
<td>0.09767</td>
<td>0.07800</td>
</tr>
<tr>
<td>90</td>
<td>0.0328</td>
<td>0.08833</td>
<td>0.06567</td>
</tr>
<tr>
<td>180</td>
<td>0.0455</td>
<td>0.02500</td>
<td>0.05233</td>
</tr>
<tr>
<td>240</td>
<td>0.0488</td>
<td>0.01733</td>
<td>0.04933</td>
</tr>
<tr>
<td>300</td>
<td>0.0501</td>
<td>0.01200</td>
<td>0.04667</td>
</tr>
<tr>
<td>360</td>
<td>0.0495</td>
<td>0.00500</td>
<td>0.04700</td>
</tr>
</tbody>
</table>

### Plotted Aminoarylation Reaction Profile with vinyl-anisole

**([M] vs. time)**

- **Product Formation**
- **Alkene Consumption**
- **Sulfonamide Consumption**
Plotted Aminoarylation Reaction Profile with vinyl-anisole
(yield vs. time)

Product formation stalls ~45%
Alkene continues to be consumed
Plotted Initial Rates for Aminoarylation with vinyl-anisole
([M] vs. time)

Average of 3 trials

<table>
<thead>
<tr>
<th>Initial rate ([M] • min⁻¹)</th>
<th>Product Formation</th>
<th>Vinyl-Anisole Consumption</th>
<th>Sulfonamide Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0003</td>
<td>-0.0003</td>
<td>-0.0002</td>
<td></td>
</tr>
<tr>
<td>0.9563</td>
<td>0.9920</td>
<td>0.9666</td>
<td></td>
</tr>
</tbody>
</table>
Reaction Profile and Initial Rates for Aminoarylation with trans-Anethole

![Reaction Profile Diagram]

To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added trans-anethole (54 μL, 0.36 mmol), N-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol), potassium benzoate (14.4 mg, 30 mol%), and Ir(dF(CF\(_3\))ppy)\(_2\)(5,5’d(CF\(_3\))bpy)PF\(_6\) (3 mg, 1 mol%). The vial contents were then dissolved in anhydrous DMF (3 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (17 μL, 0.1 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 3 mL solution volume was equally separated between 3 argon sparged NMR tubes (1 mL each). The tubes were quickly capped and sealed with parafilm. Time zero (\(t_0\)) \(^1\)H-NMR measurements were taken of all three samples prior to irradiation. Then, the 3 NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the allotted time (i.e. 5, 10, 15, 20... min), the light was turned off and reaction solution analyzed by \(^1\)H-NMR.

**Analysis:** The concentrations and yields for the aminoarylation substrates and product were plotted against time in minutes. The slope through five points for the first ~20% reaction conversion was utilized to calculate the initial rates of reaction. The procedure was repeated in triplicate (3 \(^1\)H-NMR measurements) and the average of these three trials was determined. Calculated values are tabulated below.
### Aminoarylation Reaction Profile with trans-Anethole

([M] vs. time)

<table>
<thead>
<tr>
<th>min</th>
<th>Avg. of 3 trials [M] (mmol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Product Formation</strong></td>
</tr>
<tr>
<td>0</td>
<td>0.0000</td>
</tr>
<tr>
<td>5</td>
<td>0.0060</td>
</tr>
<tr>
<td>10</td>
<td>0.0151</td>
</tr>
<tr>
<td>15</td>
<td>0.0205</td>
</tr>
<tr>
<td>30</td>
<td>0.0373</td>
</tr>
<tr>
<td>45</td>
<td>0.0497</td>
</tr>
<tr>
<td>60</td>
<td>0.0571</td>
</tr>
<tr>
<td>120</td>
<td>0.0644</td>
</tr>
<tr>
<td>180</td>
<td>0.0725</td>
</tr>
<tr>
<td>240</td>
<td>0.0745</td>
</tr>
<tr>
<td>300</td>
<td>0.0795</td>
</tr>
<tr>
<td>360</td>
<td>0.0812</td>
</tr>
</tbody>
</table>

### Plotted Aminoarylation Reaction Profile with trans-Anethole

([M] vs. time)

- **Product Formation**
- **Alkene Consumption**
- **Sulfonamide Consumption**
Plotted Aminoarylation Reaction Profile with trans-Anethole
(yield vs. time)

Plotted Initial Rates for Aminoarylation with trans-Anethole
([M] vs. time)

<table>
<thead>
<tr>
<th></th>
<th>Average of 3 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Formation</strong></td>
<td><strong>trans-Anethole Consumption</strong></td>
</tr>
<tr>
<td>Initial rate ([M] • min⁻¹)</td>
<td>0.0012</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.9917</td>
</tr>
</tbody>
</table>
Reaction Profile and Initial Rates for Aminoarylation with \textit{cis}-Anethole

To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added \textit{cis}-anethole (35.6 mg, 0.24 mmol), \textit{N}-(1-naphthylsulfonyl)acetamide (49.9 mg, 0.2 mmol), potassium benzoate (9.61 mg, 30 mol%), and Ir(dF(CF$_3$)ppy)$_2$(5,5’d(CF$_3$)bpy)PF$_6$ (2 mg, 1 mol%). The vial contents were then dissolved in anhydrous d$_7$-DMF (2 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (11.4 μL, 0.066 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 2 mL solution volume was equally separated between 3 argon sparged NMR tubes (0.67 mL each). The tubes were quickly capped and sealed with parafilm. Time zero ($t_0$) $^1$H-NMR measurements were taken of all three samples prior to irradiation. Then, the 3 NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the allotted time (i.e. 5, 10, 15, 20... min), the light was turned off and reaction solution analyzed by $^1$H-NMR.

**Analysis:** The concentrations and yields for the aminoarylation substrates and product were plotted against time in minutes. The slope through five points for the first ~20% reaction conversion was utilized to calculate the initial rates of reaction. The procedure was repeated in triplicate (3 $^1$H-NMR measurements) and the average of these three trials was determined. Calculated values are tabulated below.
Aminoarylation Reaction Profile with *cis*-Anethole

([M] vs. time)

<table>
<thead>
<tr>
<th>min</th>
<th>Product Formation</th>
<th><em>cis</em>-Anethole Consumption</th>
<th>Sulfonamide Consumption</th>
<th>trans-Anethole Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0000</td>
<td>0.0617</td>
<td>0.0743</td>
<td>0.0000</td>
</tr>
<tr>
<td>5</td>
<td>0.0070</td>
<td>0.0527</td>
<td>0.0703</td>
<td>0.0113</td>
</tr>
<tr>
<td>10</td>
<td>0.0123</td>
<td>0.0463</td>
<td>0.0633</td>
<td>0.0170</td>
</tr>
<tr>
<td>15</td>
<td>0.0160</td>
<td>0.0400</td>
<td>0.0590</td>
<td>0.0193</td>
</tr>
<tr>
<td>20</td>
<td>0.0200</td>
<td>0.0360</td>
<td>0.0533</td>
<td>0.0220</td>
</tr>
<tr>
<td>30</td>
<td>0.0260</td>
<td>0.0290</td>
<td>0.0477</td>
<td>0.0240</td>
</tr>
<tr>
<td>45</td>
<td>0.0333</td>
<td>0.0220</td>
<td>0.0383</td>
<td>0.0247</td>
</tr>
<tr>
<td>60</td>
<td>0.0377</td>
<td>0.0173</td>
<td>0.0337</td>
<td>0.0247</td>
</tr>
<tr>
<td>120</td>
<td>0.0460</td>
<td>0.0103</td>
<td>0.0233</td>
<td>0.0220</td>
</tr>
<tr>
<td>180</td>
<td>0.0484</td>
<td>0.0077</td>
<td>0.0207</td>
<td>0.0197</td>
</tr>
<tr>
<td>240</td>
<td>0.0510</td>
<td>0.0060</td>
<td>0.0120</td>
<td>0.0153</td>
</tr>
<tr>
<td>300</td>
<td>0.0540</td>
<td>0.0000</td>
<td>0.0067</td>
<td>0.0137</td>
</tr>
</tbody>
</table>

Plotted Aminoarylation Reaction Profile with *cis*-Anethole

([M] vs. time)
Plotted Aminoarylation Reaction Profile with *cis*-Anethole
(yield vs. time)

- % Yield of Product
- % cis-Alkene
- % Sulfonamide
- % trans-Alkene

Plotted Initial Rates for Aminoarylation with *cis*-Anethole
([M] vs. time)

- Product Formation
- cis-Alkene Consumption
- Sulfonamide Consumption
- trans-Alkene Formation

Equations and R² values:

- y = 0.001x + 0.0013
  R² = 0.981

- y = -0.0013x + 0.0601
  R² = 0.982

- y = 0.001x + 0.0035
  R² = 0.8879

- y = 0.001x + 0.0013
  R² = 0.981
<table>
<thead>
<tr>
<th></th>
<th>Product Formation</th>
<th><em>cis</em>-Anethole Consumption</th>
<th>Sulfonamide Consumption</th>
<th><em>trans</em>-Anethole Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial rate ([M] • min⁻¹)</td>
<td>0.0010</td>
<td>-0.0013</td>
<td>-0.0011</td>
<td>-0.0010</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.9810</td>
<td>0.9820</td>
<td>0.9943</td>
<td>0.8879</td>
</tr>
</tbody>
</table>
To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added trans-anethole (14.8 mg, 0.1 mmol) and Ir(dF(CF₃)ppy)₂(5,5'd(CF₃)bpy)PF₆ (1 mg, 1 mol%). The vial contents were then dissolved in anhydrous d₇-DMF (1 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (5.68 μL, 0.033 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 1 mL solution volume was equally separated between 2 argon sparged NMR tubes (0.5 mL each). The tubes were quickly capped and sealed with parafilm. Time zero ($t_0$) $^1$H-NMR measurements were taken of both samples prior to irradiation. Then, the 2 NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the allotted time (i.e.10, 15, 20... min), the light was turned off and reaction solution analyzed by $^1$H-NMR.

**Analysis:** The alkene yields for the isomerization were plotted against time in minutes. The slope through five points for the first ~20% reaction conversion was utilized to calculate the initial rate of isomerization. The procedure was repeated and the average of these two trials was determined. Calculated values are tabulated below.
<table>
<thead>
<tr>
<th>min</th>
<th>% trans-anethole</th>
<th>% cis-anethole</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>96.86</td>
<td>6.73</td>
</tr>
<tr>
<td>15</td>
<td>89.69</td>
<td>12.56</td>
</tr>
<tr>
<td>20</td>
<td>82.96</td>
<td>16.14</td>
</tr>
<tr>
<td>30</td>
<td>76.68</td>
<td>30.04</td>
</tr>
<tr>
<td>45</td>
<td>63.23</td>
<td>38.12</td>
</tr>
<tr>
<td>60</td>
<td>53.81</td>
<td>44.39</td>
</tr>
<tr>
<td>120</td>
<td>40.36</td>
<td>51.12</td>
</tr>
<tr>
<td>180</td>
<td>40.81</td>
<td>50.67</td>
</tr>
</tbody>
</table>

Plotted Isomerization Reaction Profile with cis-Anethole
(yield vs. time)
Plotted Initial Rates for Isomerization with cis-Anethole

$([M] \text{ vs. time})$

<table>
<thead>
<tr>
<th></th>
<th>Avg. of 2 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cis-Anethole Formation</strong></td>
<td><strong>trans-Anethole Consumption</strong></td>
</tr>
<tr>
<td>Initial rate $([M] \cdot \text{min}^{-1})$</td>
<td>0.0009</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.9883</td>
</tr>
</tbody>
</table>
Reaction Profile for Alkene Isomerization with *cis*-Anethole

![Reaction Profile Diagram]

To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added *cis*-anethole (14.8 mg, 0.1 mmol) and Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(5,5'd(CF<sub>3</sub>)bpy)PF<sub>6</sub> (1 mg, 1 mol%). The vial contents were then dissolved in anhydrous d<sub>7</sub>-DMF (1 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (5.68 μL, 0.033 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 1 mL solution volume was equally separated between 2 argon sparged NMR tubes (0.5 mL each). The tubes were quickly capped and sealed with parafilm. Time zero (t<sub>0</sub>) <sup>1</sup>H-NMR measurements were taken of both samples prior to irradiation. Then, the 2 NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the allotted time (i.e. 10, 15, 20... min), the light was turned off and reaction solution analyzed by <sup>1</sup>H-NMR.

**Analysis:** The alkene yields for the isomerization were plotted against time in minutes. Because the isomerization of *cis*-trans anethole is so rapid, initial rates could not be determined. Qualitatively, these isomerization studies suggest the following:
Plotted Isomerization Reaction Profile with *trans*-Anethole
(yield vs. time)

<table>
<thead>
<tr>
<th>min</th>
<th>% cis</th>
<th>% trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10</td>
<td>45.11</td>
<td>64.67</td>
</tr>
<tr>
<td>15</td>
<td>44.02</td>
<td>66.30</td>
</tr>
<tr>
<td>20</td>
<td>45.65</td>
<td>60.87</td>
</tr>
<tr>
<td>30</td>
<td>47.83</td>
<td>59.24</td>
</tr>
<tr>
<td>45</td>
<td>52.72</td>
<td>51.09</td>
</tr>
<tr>
<td>60</td>
<td>54.89</td>
<td>47.28</td>
</tr>
<tr>
<td>120</td>
<td>58.70</td>
<td>39.13</td>
</tr>
<tr>
<td>180</td>
<td>59.24</td>
<td>38.04</td>
</tr>
</tbody>
</table>
Plotted Isomerization Reaction Profile for 10 min with *trans*-Anethole
(yield vs. time)

<table>
<thead>
<tr>
<th>min</th>
<th>% cis</th>
<th>% trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>67.86</td>
<td>41.67</td>
</tr>
<tr>
<td>2</td>
<td>59.52</td>
<td>49.40</td>
</tr>
<tr>
<td>3</td>
<td>56.55</td>
<td>56.55</td>
</tr>
<tr>
<td>4</td>
<td>50.60</td>
<td>58.93</td>
</tr>
<tr>
<td>5</td>
<td>47.02</td>
<td>62.50</td>
</tr>
<tr>
<td>10</td>
<td>40.48</td>
<td>75.60</td>
</tr>
</tbody>
</table>

Average of 2 trials
Determination of Photostationary State Between cis-Anethole and trans-Anethole

The following isomeric ratios were extrapolated from the above alkene isomerization experiments. The cis:trans ratios were taken from $t_{\text{final}}$ (180 min) once the equilibrium state between the two isomers had been observed.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>From trans to cis</th>
<th>From cis to trans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% cis</td>
<td>% trans</td>
</tr>
<tr>
<td>180</td>
<td>50.67</td>
<td>40.81</td>
</tr>
<tr>
<td>Normalized yields</td>
<td>55.39</td>
<td>44.61</td>
</tr>
</tbody>
</table>

Photostationary State between cis-Anethole and trans-Anethole

<table>
<thead>
<tr>
<th>min</th>
<th>% cis</th>
<th>% trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>58.15</td>
<td>41.86</td>
</tr>
<tr>
<td></td>
<td>(1.4)</td>
<td>(1)</td>
</tr>
</tbody>
</table>
Aminoarylation Product Stability Assay

In order to validate the stability of the aminoarylation product and to be sure that it is not decomposing under the title reaction conditions over time, a stability assay analysis was performed.

To a flame dried 2-dram vial, equipped with a teflon coated oval shaped stir bar, was added the aminoarylation product (33.3 mg, 0.1 mmol), potassium benzoate (4.81 mg, 30 mol%), Ir(dF(CF₃)ppy)₂(5,5'd(CF₃)bpy)PF₆ (1 mg, 1 mol%), and in the case of trial B trans-anethole (2.97 μL, 0.02 mmol, 20 mol%). No trans-anethole was added for trial A. The vial contents were then dissolved in anhydrous DMF (1 mL, 0.1 M) followed by addition of trimethyl(phenyl)silane (5.7 μL, 0.033 mmol) as an internal standard. The reaction was sparged under argon for 15 min before the 1 mL solution volume was added to an argon sparged NMR tube. The tube was quickly capped and sealed with parafilm. Time zero \( t_0 \) \(^1\)H-NMR measurements were taken prior to irradiation. Then, the NMR tubes were irradiated with 1 x blue H150 Kessil LED light (~2 cm) and cooled by one overhead fan. After the alloted time (i.e. 5, 10, 15, 20... min), the light was turned off and reaction solution analyzed by \(^1\)H-NMR.

**Analysis:** The concentration of the aminoarylation product was plotted against time in minutes. As the plots below suggest, no noticable degradation of the aminoarylation product occurs either
in the presence or absence of *trans*-anethole. These results suggest the aminoarylation product is stable and does not readily undergo decomposition.
3.4.3. Synthesis and Characterization of Reagents, Starting Materials, and Aminoarylation Products

Preparation of \( \text{Ir(dF(CF}_3\text{)ppy)}_2\text{(5,5'd(CF}_3\text{)bpy)PF}_6\text{(3)}/[\text{Ir}]\cdot1 \)

The following procedure has been adopted from a two-step, one-pot literature procedure from our laboratory disclosing the synthesis of heteroleptic-Ir(I) complexes through microwave irradiation.\(^{43}\)

To an oven dried 20 mL microwave vial was charged a magnetic stirring bar, \( \text{IrCl}_3\cdot6\text{H}_2\text{O} \) (507 mg, 1.6 mmol, 1 equiv), and 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine (1.04 g, 4.0 mmol, 2.5 equiv). The vial contents were dissolved in ethylene glycol (15 mL) and then the microwave vial capped. Then the reaction was sonicated for 3 minutes to increase homogeneity (picture A). The reaction was heated in a microwave reactor at 200 °C for 50 min with a 5 min pre-stir period. After the reaction had cooled to room temperature (picture B), 5-(trifluoromethyl)-2-[5-(trifluoromethyl)-2-pyridyl]pyridine (617 mg, 2.1 mmol, 2 equiv) was added, the vial re-capped, and the reaction was heated to 200 °C for 30 min with a 5 min pre-stir period.

After the reaction had cooled to room temperature (picture C), the solution was dissolved in \( \text{dH}_2\text{O} \) (50 mL) and extracted with \( \text{CH}_2\text{Cl}_2 \) (3 x 20 mL). The organic layers were combined and concentrated down, followed by the addition of \( \text{NH}_4\text{PF}_6 \) (10 g in ~50 mL \( \text{dH}_2\text{O} \)). The whole was placed in the freezer overnight to allow for maximum crystal formation. The yellow/orange
crystals were filtered and washed with cold Et₂O. Re-crystallization was performed with pentane and acetone (insoluble in pentane) to provide the title complex as a free-flowing yellow powder (1.08 g, 59%).

¹H and ¹⁹F NMR characterization data is identical to that reported in the literature.³⁹

¹H NMR (500 MHz, d₆-Acetone) δ = 9.32 (d, J = 8.6 Hz, 1H), 8.83 (d, J = 8.5 Hz, 1H), 8.61 (d, J = 8.7 Hz, 1H), 8.56 (s, 1H), 8.40 (d, J = 8.9 Hz, 1H), 8.19 (s, 1H), 6.91 (t, J = 11.7 Hz, 1H), 5.98 (dd, J = 8.4, 2.2 Hz, 1H) ppm

¹⁹F NMR (471 MHz, d₆-Acetone) δ = -62.66 (d, J = 107.9 Hz), -71.75(d, Jₚₑ = 707.4 Hz), -103.14(dd, J = 20.1, 9.3 Hz), -106.81(t, J = 12.2 Hz) ppm

<table>
<thead>
<tr>
<th>A: After sonication</th>
<th>B: After step 1</th>
<th>C: After step 2</th>
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<tr>
<td>![Image A]</td>
<td>![Image B]</td>
<td>![Image C]</td>
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**N-(naphthalen-1-ylsulfonyl)acetamide (3.2)**

(Step 1): To a dry 250 mL round bottom flask equipped with a sizable oval shaped stir bar, a 3:1 mixture of Ether:Acetone was prepared (100 mL total). To this the solid naphthalene-1-sulfonyl chloride (10.0 g, 44.1 mmol), added into the flask. The solution is homogeneous at this point. Then by dropwise addition, saturated NH₄OH ((5809 µl) 44.1 mmol, 1 equiv) was added at 0 °C. The reaction was checked by TLC (4:6 EtOAc:Hexanes). If the reaction was not complete in 1 hour, an additional 1 equiv of NH₄OH was added to ensure full conversion. The reaction was then neutralized to a pH of 6-7. Caution should be taken to not inhale the off gassing excess ammonia from the solution, and this will process faster if the reaction is under a continuous flush of nitrogen gas. Dilute the reaction in an equal volume of water and extract 2x with an equal amount of ethyl acetate. Combine the organic portions and dry over sodium sulfate, with a final concentration in vacuo to reveal a white powder.

(Step 2A): To a dry 250 mL round bottom flask equipped with a sizeable oval shaped stir bar, KOH (4426 mg, 78.9 mmol – crushed fine powder) and naphthalene-1-sulfonamide (5.45 g, 26.3 mmol) were added. The flask was evacuated and backfilled with nitrogen 3 times, after which the contents were diluted in dichloromethane solvent (50 mL). After stirring for a few minutes, acetyl chloride (2244 µL, 31.6 mmol) was added dropwise at room temperature. During this addition, the reaction very noticeably goes heterogeneous, then homogeneous and then back to
heterogeneous. After 2 hours this reaction is complete but is stable if left under nitrogen for up to 24 hours. At this point the reaction was diluted with 100 mL of water and acidified past neutrality. These contents were then transferred to a 500 mL separatory funnel and the aqueous layer was extracted 2x times with 75 mL of CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extracts were combined, and concentrated, and the product was recrystallized in methanol to yield dense white crystals.

Alternatively, the product can be separated from the starting material by first combining the CH$_2$Cl$_2$ extraction and concentrating \textit{in vacuo} to take back up in a minimal amount of EtOAc (60 mL). This was then extracted 5x times with 60 mL of 5 % NaHCO$_3$ aq solution. These combined aqueous extracts were then acidified using 4 M HCl beyond neutrality (product becomes insoluble in solution. Finally, the desired product can be extracted from the acidic aqueous layer using EtOAc or CH$_2$Cl$_2$. Combination and drying over Na$_2$SO$_4$ and concentration \textit{in vacuo} yields the desired product. The product can be further purified by recrystallization in MeOH. Non-recrystallized material is lighter in density, and more difficult to handle.

\textbf{(Step 2B):} To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added naphthalene-1-sulfonamide (1 g, 4.83 mmol), DMAP (6 mg, 1 mol%), CH$_2$Cl$_2$ (35 mL), and THF (6 mL). The reaction mixture at this point appears mostly heterogeneous. Then the reaction was cooled to 0 °C and via syringe was added pyridine (777 µL, 9.65 mmol, 2 equiv) followed by acetic anhydride (1.82 mL, 19.3 mmol, 4 equiv). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring overnight (12 h). Upon completion of the reaction as judged by TLC analysis (40% EtOAc in Hex), the reaction was diluted in 20 mL dH$_2$O, layers separated, and the aqueous layer washed with 20 mL CH$_2$Cl$_2$. The organic layers were combined and rinsed with 1 N HCl (2 x 20 mL), brine, dried over sodium sulfate, filtered and concentrated \textit{in vacuo} to provide white, compact
crystals. The product may be further purified via flash column chromatography (0-40% EtOAc in Hex elution gradient).

**$^1$H NMR** (700 MHz, CDCl$_3$): $\delta = 8.68$ (bs, 1H), 8.59 (d, $J = 8.5$ Hz, 1H), 8.51 (d, $J = 7.2$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.63 (dd, $J = 12.5$, 7.3 Hz, 2H), 2.03 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$): $\delta = 168.1$, 135.8, 134.2, 133.0, 132.1, 129.4, 128.9, 128.0, 127.1, 124.2, 123.6, 23.4 ppm

$R_f$ (4:6 – EtOAc:Hex) = 0.3

**IR** (neat): 3246, 1730, 1441, 1410, 1372, 1328, 1215, 1127, 760, 734 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{12}$H$_{11}$NO$_3$S [M+H]$^+$ 250.0532, found 250.0529

**MP:** 184–187 °C
**ethyl (naphthalen-1-ylsulfonyl)carbamate (3.S1)**

![Chemical Structure](image)

To a 100 mL round bottom flask charged with a magnetic stir bar was added naphthalene-1-sulfonamide (1 g, 4.83 mmol), DMAP (29.5 mg, 0.24 mmol), CH₂Cl₂ (30 mL), and ethyl chloroformate (0.59 mL, 6.27 mmol). The whole was cooled to 0 °C then triethylamine (0.74 mL, 5.31 mmol) was added dropwise via syringe. The reaction slowly went from a white, heterogeneous mixture to a clear colorless, homogenous solution. The reaction was gradually warmed to rt and monitored by TLC (50% EtOAc in Hex). After 2 h, the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (30 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 40% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (782 mg, 59%).

**¹H NMR** (700 MHz, CDCl₃): \( \delta = 8.60 \ (d, J = 8.6 \ Hz, 1H) \), 8.49 \( (d, J = 7.4 \ Hz, 1H) \), 8.15 \( (d, J = 8.2 \ Hz, 1H) \), 7.98 \( (d, J = 8.1 \ Hz, 1H) \), 7.80 \( (s, 1H) \), 7.70 \( (t, J = 7.7 \ Hz, 1H) \), 7.62 \( (dt, J = 12.1 \ Hz, 1H) \), 7.04 \( (q, J = 7.1 \ Hz, 2H) \), 1.11 \( (t, J = 7.1 \ Hz, 3H) \) ppm

**¹³C NMR** (176 MHz, CDCl₃): \( \delta = 150.2, 135.7, 134.1, 132.8, 132.4, 129.3, 128.3, 128.0, 127.0, 124.1, 123.9, 63.1, 13.9 \) ppm

**Rᵣ** (5:5 – EtOAc:Hex) = 0.5

**IR** (neat): 3081, 1712, 1507, 1476, 1352, 1309, 1167, 1139, 917, 802, 766 cm⁻¹

**HRMS** (ESI⁺) \( m/z \) calculated for C₁₃H₁₃NO₄S [M+H]+ 280.00638, found 280.0634.

**MP:** 137–140 °C

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**tert-butyl (naphthalen-1-ylsulfonyl)carbamate (3.52)**

![Chemical Structure](image)

To a 50 mL round bottom flask charged with a magnetic stir bar was added naphthalene-1-sulfonamide (1 g, 4.83 mmol), DMAP (58.9 mg, 0.483 mmol), CH₂Cl₂ (30 mL), and Boc anhydride (1.22 mL, 5.31 mmol). The whole was cooled to 0 °C then triethylamine (0.74 mL, 5.31 mmol) was added dropwise via syringe. The reaction slowly went from a cloudy white color to clear. The whole was slowly warmed to rt and monitored by TLC (50% EtOAc in Hex). After 2 h, the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (30 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 40% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (1.02 g, 69%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.58 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.63 – 7.59 (m, 3H), 1.27 (s, 9H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 149.0, 135.4, 134.1, 133.2, 132.1, 129.2, 128.7, 128.0, 126.9, 124.0, 123.9, 84.3, 27.7 ppm

Rᵣ (5:5 – EtOAc:Hex) = 0.5

**IR** (neat): 3073, 2982, 1701, 1354, 1332, 1134, 804, 777 cm⁻¹

**HRMS** (ESI⁺) m/z calculated for C₁₅H₁₇NO₄S [M+H]⁺ 308.0951, found 308.0947.

**MP:** 134–138 °C
**2,2,2-trifluoro-N-(naphthalen-1-ylsulfonyl)acetamide (3.S3)**

![Structural formula](image)

To a 100 mL round bottom flask charged with a magnetic stir bar was added naphthalene-1-sulfonamide (1 g, 4.83 mmol), DMAP (58.9 mg, 0.483 mmol), CH₂Cl₂ (40 mL), and TFAA (0.783 mL, 5.31 mmol). The whole was cooled to 0 °C then triethylamine (0.74 mL, 5.31 mmol) was added dropwise via syringe. The reaction slowly went from a cloudy white color to clear. The whole was slowly warmed to rt and monitored by TLC (50% EtOAc in Hex). After 4 h, the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (30 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 40% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (1.28 g, 88%).

**¹H NMR** (400 MHz, DMSO-d₆): δ = 11.06 (bs, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.14 – 8.01 (m, 2H), 7.98 (d, J = 7.4 Hz, 1H), 7.72 – 7.40 (m, 3H) ppm

**¹³C NMR** (176 MHz, DMSO-d₆): δ = 159.9 (q, J = 32.9 Hz), 139.9, 133.6, 131.7, 128.3, 128.3, 127.4, 126.6, 126.1, 124.3, 117.6 (q, J = 291.4 Hz)

**¹⁹F NMR** (377 MHz, DMSO-d₆) = δ -74.1 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.3

**IR (neat):** 3209, 1762, 1508, 1452, 1362, 1201, 1108, 988, 765 cm⁻¹

**HRMS (ESI⁺) m/z** calculated for C₁₂H₈F₃NO₃S [M+H]+ 326.0069, found 326.0066.

**MP:** 165-168 °C
To a flame dried 250 mL round bottom flask charged with a magnetic stir bar was added thiophene-2-sulfonamide (3 g, 18.4 mmol), DMAP (22.5 mg, 0.184 mmol), CH₂Cl₂ (50 mL), and THF (10 mL). The reaction appears mostly heterogeneous. Then the reaction was cooled to 0 °C then via syringe was added pyridine (4.44 mL, 55.1 mmol) followed by acetic anhydride (6.95 mL, 73.5 mmol). The reaction was allowed to warm to rt and monitored by TLC (50% EtOAc in Hex). After 3 h, the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (30 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (2.57 g, 68%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.71 (s, 1H), 7.90 (dd, J = 3.8, 1.2 Hz, 1H), 7.71 (dd, J = 5.0, 1.2 Hz, 1H), 7.14 (dd, J = 4.9, 3.9 Hz, 1H), 2.13 (s, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 168.1, 138.6, 135.2, 134.2, 127.5, 23.6 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.4

**IR** (neat): 3105, 1688, 1446, 1421, 1368, 1351, 1017, 999, 728 cm⁻¹

**HRMS** (EI) m/z calculated for C₆H₇NO₃S₂ [M⁺] 204.9867, found 204.9871.

**MP:** 84–87 °C
methyl 3-(N-acetyl sulfamoyl)thiophene-2-carboxylate (3.55)

To a flame dried 100 mL round bottom flask charged with a magnetic stir bar was added methyl 3-sulfamoylthiophene-2-carboxylate (500 mg, 2.26 mmol), DMAP (2.76 mg, 0.0226 mmol), CH$_2$Cl$_2$ (35.0 mL), and THF (5.00 mL). The reaction appears mostly heterogeneous. The whole was cooled to 0 °C then via syringe was added pyridine (0.546 mL, 6.78 mmol) and acetic anhydride (0.854 mL, 9.04 mmol). The reaction was allowed to warm to rt and monitored by TLC (50% EtOAc in Hex). After 12 h, the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (30 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (512 mg, 86%).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta$ = 8.92 (s, 1H), 7.72 (d, $J = 5.2$ Hz, 1H), 7.58 (d, $J = 5.2$ Hz, 1H), 3.95 (s, 3H), 2.15 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ = 168.5, 160.3, 142.9, 132.6, 131.5, 130.4, 53.3, 23.6 ppm

$R_f$ (5:5 – EtOAc:Hex) = 0.2

IR (neat): 3131, 1719, 1701, 1435, 1358, 1265, 1173, 1144, 898, 772 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_8$H$_9$NO$_5$S$_2$Na [M+Na]$^+$ 285.9814, found 285.9818.

MP: 178–181 °C
To a flame dried 250 mL round bottom flask charged with a magnetic stir bar was added quinoline-8-sulfonamide (1000 mg, 4.80 mmol), DMAP (5.87 mg, 0.0480 mmol), CH₂Cl₂ (35.0 mL), and THF (5.00 mL). The reaction appears mostly heterogeneous. The whole was cooled to 0 °C then via syringe was added pyridine (0.387 mL, 4.80 mmol) followed by acetic anhydride (1.82 mL, 19.2 mmol). The reaction was allowed to warm to rt and monitored by TLC (50% EtOAc in Hex). After 12 h, the reaction was diluted in 100 mL dH₂O. The white crystalline solid were filtered off and washed with cold acetone to provide the title substrate as a compact white solid (1.03 g, 86%).

\[^1\text{H} \text{NMR}\] (700 MHz, DMSO-d₃): \(\delta = 12.32\) (s, 1H), 9.10 (m, 1H), 8.57 (d, \(J = 8.1\) Hz, 1H), 8.46 (d, \(J = 8.1\) Hz, 1H), 8.35 (d, \(J = 8.1\) Hz, 1H), 7.80 (t, \(J = 7.7\) Hz, 1H), 7.72 (dd, \(J = 8.2, 4.1\) Hz, 1H), 1.88 (s, 3H) ppm

\[^{13}\text{C} \text{NMR}\] (176 MHz, DMSO-d₃): \(\delta = 169.0, 151.5, 142.8, 137.1, 135.2, 134.7, 133.1, 128.5, 125.6, 122.6, 23.1\) ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.3

\(\text{IR (neat)}\): 3003, 2818, 1713, 1499, 1457, 1330, 1166, 1139, 995, 973 cm\(^{-1}\)

\(\text{HRMS (ESI+)}\) \(m/z\) calculated for \(\text{C}_{11}\text{H}_{10}\text{N}_{2}\text{O}_{3}\text{S} [\text{M+H}]^+ 251.0485\), found 251.0484.

\(\text{MP}\): 240–245 °C
**N-(naphthalen-2-ylsulfonyl)acetamide (3.87)**

![Chemical Structure](image)

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added naphthalene-1-sulfonamide (1 g, 4.83 mmol), DMAP (6 mg, 1 mol%), CH₂Cl₂ (35 mL), and THF (6 mL). The reaction mixture at this point appears mostly heterogeneous. Then the reaction was cooled to 0 °C and via syringe was added pyridine (777 uL, 9.65 mmol, 2 equiv) followed by acetic anhydride (1.82 mL, 19.3 mmol, 4 equiv). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring overnight (12 h). Upon completion of the reaction as judged by TLC analysis (40% EtOAc in Hex), the reaction was diluted in 20 mL dH₂O, layers separated, and the aqueous layer was extracted with 20 mL CH₂Cl₂. The organic layers were combined and rinsed with 1 N HCl (2 x 20 mL), brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide a white powder. The material may be further purified via flash column chromatography (0 to 40% EtOAc in Hex elution gradient) to provide the title substrate as a compact white solid (848 mg, 78%).

**¹H NMR (700 MHz, CDCl₃):** δ = 8.67 (bm, 2H), 8.02 (d, J = 8.2 Hz, 1H), 7.99 (s, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 2.09 (s, 3H) ppm

**¹³C NMR (176 MHz, CDCl₃):** δ = 168.0, 135.5, 135.1, 131.9, 130.5, 129.6, 129.5, 129.4, 127.9, 127.8, 122.5, 23.5 ppm

**Rf (5:5 – EtOAc:Hex) = 0.3**

**IR (neat):** 3274, 1719, 1436, 1412, 1328, 1150, 1126, 994, 877, 747 cm⁻¹

**HRMS (ESI⁺) m/z** calculated for C₁₂H₁₁NO₃S [M+H]⁺ 272.0352, found 272.0353.

**MP:** 137–139 °C
methyl 5-\(N\text{-acetylsulfamoyl}\)furan-2-carboxylate (3.S8)

![Chemical structure](image)

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added methyl 5-sulfamoylfuran-2-carboxylate (184 mg, 0.897 mmol), DMAP (1.10 mg, 0.00897 mmol), CH\(_2\)Cl\(_2\) (20.0 mL), and THF (5.00 mL). The reaction mixture at this point appears mostly heterogeneous. Then the reaction was cooled to 0 °C and via syringe was added pyridine (0.217 mL, 2.69 mmol) followed by acetic anhydride (0.339 mL, 3.59 mmol). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring for 3 h. Upon completion of the reaction as judged by TLC analysis (50% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with CH\(_2\)Cl\(_2\) (15 mL) then washed 3 x with 1 N HCl (10 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (172 mg, 78%).

\(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta = 8.89\) (s, 1H), 7.38 (d, \(J = 3.6\) Hz, 1H), 7.24 (d, \(J = 3.6\) Hz, 1H), 3.93 (s, 3H), 2.17 (s, 3H) ppm

\(^13\)C NMR (176 MHz, CDCl\(_3\)): \(\delta = 168.0, 158.0, 148.9, 147.3, 120.3, 118.0, 52.8, 23.6\) ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.2

IR (neat): 3303, 3159, 1732, 1574, 1431, 1355, 1040, 917 cm\(^{-1}\)

HRMS (ESI+) \(m/z\) calculated for C\(_8\)H\(_9\)NO\(_6\)S [M+H]\(^+\) 265.0489, found 265.0488.

MP: 133–137 °C
To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added thiophene-3-sulfonylamide (1000 mg, 6.13 mmol), DMAP (7.48 mg, 0.0613 mmol), CH₂Cl₂ (35.0 mL), and THF (5.0 mL). The reaction mixture at this point appears mostly heterogeneous. Then the reaction was cooled to 0 °C and via syringe was added pyridine (1.48 mL, 18.4 mmol) followed by acetic anhydride (2.32 mL, 24.5 mmol). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring for 12 h. Upon completion of the reaction as judged by TLC analysis (50% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with CH₂Cl₂ (25 mL) then washed 3 x with 1 N HCl (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (1.12 g, 89%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.78 (s, 1H), 8.32 – 8.20 (m, 1H), 7.60 – 7.48 (m, 1H), 7.44 (dd, J = 5.1, 3.1 Hz, 1H), 2.11 (s, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 168.3, 138.0, 133.7, 127.8, 126.1, 23.6 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.3

**IR (neat):** 3070, 2867, 1691, 1460, 1417, 1346, 1235, 1157, 788 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₆H₇NO₃S₂Na [M+Na]⁺ 227.9760, found 227.9757.

**MP:** 98–101 °C
N-((5-chlorothiophen-2-yl)sulfonyl)acetamide (3S10)

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added 5-chlorothiophene-2-sulfonamide (500 mg, 2.53 mmol), DMAP (3.09 mg, 0.0253 mmol), CH₂Cl₂ (35.0 mL), and THF (5.00 mL). Then the reaction was cooled to 0 °C and via syringe was added pyridine (0.611 mL, 7.59 mmol) followed by acetic anhydride (0.956 mL, 10.1 mmol). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring for 12 h. Upon completion of the reaction as judged by TLC analysis (50% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with CH₂Cl₂ (25 mL) then washed 3x with 1 N HCl (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white powder (486 mg, 77%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.69 (s, 1H), 7.69 (d, J = 4.1 Hz, 1H), 6.97 (d, J = 4.1 Hz, 1H), 2.14 (s, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 168.1, 140.0, 136.0, 134.7, 126.8, 23.6 ppm

Rₕ (5:5 – EtOAc:Hex) = 0.4

**IR (neat):** 3076, 2874, 1689, 1463, 1409, 1357, 1235, 1162, 1004, 990 cm⁻¹

**HRMS (ESI⁺) m/z** calculated for C₆H₆ClNO₅S₂ [M+H]⁺ 239.9550, found 239.9548.

**MP:** 106–109 °C
**N-((5-bromothiophen-2-yl)sulfonyl)acetamide (3.51)**

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added 5-bromothiophene-2-sulfonamide (1000 mg, 4.13 mmol), DMAP (5.05 mg, 0.0413 mmol), CH₂Cl₂ (35.0 mL), and THF (5.0 mL). Then the reaction was cooled to 0 °C and via syringe was added pyridine (1.0 mL, 12.4 mmol) followed by acetic anhydride (1.56 mL, 16.5 mmol). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring for 12 h. Upon completion of the reaction as judged by TLC analysis (50% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with CH₂Cl₂ (25 mL) then washed 3 x with 1 N HCl (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white powder (1.07 g, 91%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.62 (s, 1H), 7.64 (d, J = 4.1 Hz, 1H), 7.11 (d, J = 4.1 Hz, 1H), 2.13 (s, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 168.0, 138.9, 135.4, 130.4, 122.7, 23.6 ppm

**Rₖ (5:5 – EtOAc:Hex) = 0.3**

**IR (neat):** 3301, 1713, 1412, 1395, 1209, 1155, 1025, 799, 678 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₆H₆BrNO₅S₂ [M+Na]⁺ 305.8865, found 305.8869.

**MP:** 110–113 °C

![Chemical Structure](image)

To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added 1,3-benzothiazole-2-sulfonamide (294 mg, 1.37 mmol), DMAP (1.68 mg, 0.0137 mmol), CH$_2$Cl$_2$ (35.0 mL), and THF (5.0 mL). Then the reaction was cooled to 0 °C and via syringe was added pyridine (0.322 mL, 4.12 mmol) followed by acetic anhydride (0.519 mL, 5.49 mmol). The whole slowly became more homogeneous over a few minutes. The reaction was slowly allowed to warm to rt while stirring for 12 h. Upon completion of the reaction as judged by TLC analysis (50% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with CH$_2$Cl$_2$ (25 mL) then washed 3 x with 1 N HCl (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a white solid. Purification by flash column chromatography (10 to 50% EtOAc in Hex elution gradient) provided the title substrate as a compact white solid (443 mg, 99%).

**1H NMR** (700 MHz, DMSO-$_d$6): $\delta = 13.06$ (s, 1H), 8.31 (d, $J = 7.8$ Hz, 1H), 8.23 (d, $J = 7.9$ Hz, 1H), 7.75 – 7.61 (m, 2H), 2.04 (s, 3H) ppm

**13C NMR** (176 MHz, DMSO-$_d$6): $\delta = 169.7, 165.4, 151.4, 136.3, 128.1, 127.9, 124.7, 123.3, 23.4$ ppm

**R$_f$** (5:5 – EtOAc:Hex) = 0.1

**IR (neat):** 3022, 2855, 1726, 1484, 1358, 1162, 1132, 1094, 994 cm$^{-1}$

**HRMS (ESI+) m/z** calculated for C$_9$H$_8$N$_2$O$_3$S$_2$ [M+H]$^+$ 257.0049, found 257.0052.

**MP:** 194–197 °C
(E)-N-(styrlysulfonyl)acetamide (3.S13)

A 25 mL flame dried round bottom flask charged with a magnetic stir bar was added KOH (91.9 mg, 1.64 mmol) and (E)-2-phenylethenesulfonamide (100 mg, 0.546 mmol). The flask was septa capped and put under nitrogen, before diluting in CH₂Cl₂ [0.2 M]. This reaction was then cooled to 0 °C followed by dropwise addition of AcCl (58.2 μL, 1.5 equiv) to the reaction. Over 2.5 hours, the reaction was allowed to warm to room temperature. The reaction was quenched by adding 4 M HCl at 0 °C to equal the mmol of KOH added. This was then diluted in water and extracted 3x with CH₂Cl₂. The CH₂Cl₂ layers were combined dried over sodium sulfate, filtered and concentrated to provide the crude residue which was purified by column chromatography (4:6 EtOAc to Hexanes) to afford the desired acetamide (52 mg, 42%).

^1H NMR (400 MHz, DMSO-d6) δ = 11.84 (s, 1H), 7.75 (d, J = 6.3 Hz, 2H), 7.60 – 7.35 (m, 5H), 1.97 (s, 3H) ppm

^13C NMR (126 MHz, DMSO-d6) δ = 169.1, 142.6, 132.3, 131.1, 129.1, 128.9, 125.9, 23.4 ppm

Rf (1:1 – EtOAc:Hex) = 0.4

IR (neat): 3243, 3049, 1714, 1615, 1417, 1369, 1326, 1213, 1199, 1142, 1039, 991, 968, 944, 869, 824, 805, 744, 687, 651, 631, 609 cm⁻¹

HRMS (ESI+) m/z calculated for [M+H]⁺ 226.0532, found 226.0532.

MP: 108–111 °C
**N-(naphthalen-1-ylsulfonyl)hexanamide (3.S14)**

![Chemical Structure](image)

To a dry round bottom flask hexanoic acid (420 mg, 3.62 mmol) was added and diluted into 6 mL of DCM and 100 μL of DMF. This solution was cooled to 0°C and oxyalyl chloride was added neat and dropwise over the course of 3 minutes. The reaction was stirred at 0°C for 30 minutes. Then the reaction was warmed to room temperature and concentrated *in vacuo* to a thick yellow oil. The reaction was then taken back up into a fresh supply of 6 mL of DCM, followed by naphthalene-1-sulfonamide (500 mg, 2.41 mmol) in one portion. Slow addition of pyridine (389 μL, 2 equiv) and DMAP (14.7 mg, 0.05 eq), occurred with considerable exotherm. The reaction was then stirred for 15 hours and stopped by the addition of 10 mL of water. The whole was transferred to a separatory funnel and extracted three times with 15 mL of ethyl acetate. The combine organic layer was then washed with saturated sodium bicarbonate followed by saturated sodium chloride solutions. Drying over magnesium sulfate and concentration *in vacuo* afforded an orange oil that was purified on column (0-50% EtOAc in Hexanes) to afford N-(1-naphthylsulfonyl) hexanamide (382 mg, 1.25 mmol, yield: 52%)

$^1$H NMR (700 MHz, DMSO-d6) δ 12.40 (s, 1H), 8.61 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 7.4 Hz, 2H), 8.16 (m, 1H), 7.79 (t, J = 7.0 Hz, 1H), 7.76 – 7.69 (m, 2H), 1.36 – 1.28 (m, 2H), 1.04 (m, 2H), 0.90 (m, 2H), 0.66 (dt, J = 7.2, 5.3 Hz, 3H) ppm

$^{13}$C NMR (176 MHz, DMSO-d6) δ = 172.4, 135.9, 134.8, 134.5, 132.1, 130.1, 129.2, 128.2, 127.8, 125.3, 124.5, 36.3, 31.1, 24.7, 22.5, 14.5 ppm

Rf = 0.5 in 1:1 Hexanes:EtOAc

IR (neat): 3301, 2958, 2926, 2869, 1713, 1506, 1472, 1442, 1411, 1364, 1324, 1271, 1221, 1204, 1177, 1160, 1144, 1131, 1085, 1057, 1035, 975, 945, 864, 807.3, 797.5, 776.3, 741, cm⁻¹

HRMS (ESI+) m/z calculated for [M+H]⁺ 306.1164, found 306.1158.
Vinyl-anisole was purchased from Sigma Aldrich (97%, item # 141003) and was distilled under hi-vac (~ 13 mbar), at 60 °C. It was then stored in the dark, under argon in a 4 dram vial for the remainder of the work.
(E)-1-methoxy-4-(prop-1-en-1-yl)benzene (3.S15)

trans-Anethole was purchased from AK Scientific (98%, item # X8716) and was used as received. The material was stored in the dark and under argon when not in use.
(Z)-1-methoxy-4-(prop-1-en-1-y1)benzene (3.28)

Z-anethole preparation was repeated based on the procedure detailed by Yoon and co-workers.44-45 *(Step 1)*: To a dry round bottom flask, 1-ethynyl-4-methoxy-benzene (1000 mg, 7.57 mmol) was added as a clear liquid and diluted into solution with 20 mL of THF. The solution was cooled to -78°C for 30 minutes and then the starting material was deprotonated with the dropwise addition of LiHMDS (8.323 μL, 1.1 equiv) over the course of 10 minutes. The solution was allowed to stir and deprotonate for 30 minutes. Following this time, MeI (565 μL, 1.2 equiv) was added dropwise, and the reaction was allowed to stir another 30 minutes before warming to room temperature. The reaction was quenched with 4 mL of saturated aqueous ammonium chloride solution, and diluted in 30 mL of water. The whole was transferred to a separatory funnel where 20 mL of diethyl ether was added and the layers were separated. The aqueous layer was then extracted twice more with 30 mL of diethylether each time. The combined organic layer was then washed with saturated sodium chloride solution and dried over magnesium sulfate. Concentration *in vacuo* produced an orange oil that was then purified by a short column (0-5% EtOAc in Hexanes) to afford 1-methoxy-4-prop-1-ynyl-benzene which was taken directly onto the next step.

*(Step 2)*: To a flame dried flask, a solution of cyclohexene (15.2 mmol, 2.11 equiv, 1601 μL) was diluted in 8 mL of THF. The solution was cooled to 0°C and then a 2.0 M solution of BH₃•DMS complex in toluene was added (749 μm 1.1 equiv). After 10 minutes the reaction becomes heterogeneous, and this was allowed to stir for another twenty minutes. After this time, 1-methoxy-4-prop-1-ynyl-benzene was added as a 1 M solution in THF, to the reaction at 0°C. This was allowed to stir for 45 minutes, followed by quenching with 1 mL of glacial acetic acid. The acid quench was allowed to stir for 45 minutes and warm up to room temperature. The reaction
solution was transferred to a separatory funnel and diluted in 30 mL of water. The layers were separated and the aqueous layer was extracted twice more with 30 mL of diethyl ether each time. The combined organic layer was washed with saturated sodium bicarbonate followed by saturated aqueous sodium chloride solution. Drying over magnesium sulfate followed by concentration in vacuo afforded an oil that was purified by silica chromatography (0-5% EtOAc in Hexanes). The spectral data of 1-methoxy-4-[(Z)-prop-1-enyl]benzene (512 mg, 49% yield) was consistent with the literature.\textsuperscript{45}
The following procedure was followed according to that reported in the literature for the preparation of the title substrate.\textsuperscript{46}

CeCl$_3$·7H$_2$O (2218 mg, 9.00 mmol) was quickly ground to a fine powder in a mortar, placed in a three-neck 250 mL round bottom flask and dried at 140 °C for 2 h. At rt, nitrogen gas was introduced, and anhydrous THF (25 mL) was added with vigorous stirring. The suspension was stirred for 1.5 h at rt. To a cold (-78 °C) and stirred solution of 4-bromoanisole (0.828 mL, 6.60 mmol) in anhydrous THF (25 mL) was added 1.6 M nBuLi in hexanes (4.50 mL, 7.20 mmol). This solution was stirred at -78 °C for 1.5 h then added to the cold (-78 °C) suspension of CeCl$_3$ in THF. The resulting solution was stirred at -78 °C for 1 h. Cyclopentanone (0.531 mL) 6.00 mmol) dissolved in anhydrous THF (5 mL) was added to the corresponding organocerium reagent. The resulting mixture was stirred at -78 °C for 1 h then at rt for 1 h. At -30 °C, after dilution with anhydrous THF (20 mL), DBU (2.32 mL, 10.5 mmol, 3 equiv) then MsCl (1.39 mL, 10.5 mmol, 3 equiv) were added dropwise. The reaction mixture was then allowed to warm to rt and stirred overnight. At 0 °C, aqueous HCl 1 M (15 mL) was added and the solution was stirred for 1 h. The aqueous layer was extracted with Et$_2$O (3 x 30 mL). The resulting organic layers were washed with aqueous NaOH 2 M (10 mL), water (10 mL), brine (10 mL), dried over sodium sulfate and the solvent evaporated to provide a light yellow oil. The residue was purified by flash column chromatography on silica gel using a 0 to 1% EtOAc in Hex elution gradient to provide the desired olefin as a white fluffy powder (616 mg, 59%).
All analytical data matches that reported in the literature.\textsuperscript{46}

\textbf{\textsuperscript{1}H NMR} (700 MHz, CDCl\textsubscript{3}): \(\delta = 7.38\) (d, \(J = 8.7\) Hz, 2H), 6.86 (d, \(J = 8.7\) Hz, 2H), 6.08 – 5.99 (m, 1H), 3.81 (s, 3H), 2.68 (td, \(J = 7.8, 2.1\) Hz, 2H), 2.52 (td, \(J = 7.7, 2.3\) Hz, 2H), 2.08 – 1.95 (m, 2H) ppm

\textbf{\textsuperscript{13}C NMR} (176 MHz, CDCl\textsubscript{3}): \(\delta = 158.5, 141.8, 129.7, 126.7, 123.9, 113.6, 55.3, 33.3, 33.2, 23.4\) ppm

\(R_r\) (1:9 – EtOAc:Hex) = 0.6

\textbf{IR} (\textit{neat}): 2951, 2894, 2841, 1601, 1510, 1309, 1252, 1180, 1030 cm\textsuperscript{-1}

\textbf{HRMS (EI)} \(m/z\) calculated for C\textsubscript{12}H\textsubscript{14}O [M+] 174.1045, found 174.1042.
1-(4-methoxyphenyl)cyclohept-1-ene (3.517)

The following procedure was followed according to that reported in the literature for the preparation of the title substrate.46

![Chemical Structure](image)

CeCl₃·7H₂O (2218 mg, 9.00 mmol) was quickly ground to a fine powder in a mortar, placed in a three-neck 250 mL round bottom flask and dried at 140 °C for 2 h. At rt, nitrogen gas was introduced, and anhydrous THF (25 mL) was added with vigorous stirring. The suspension was stirred for 1.5 h at rt. To a cold (-78 °C) and stirred solution of 4-bromoanisole (0.828 mL, 6.60 mmol) in anhydrous THF (25 mL) was added 1.6 M nBuLi in hexanes (4.50 mL, 7.20 mmol). This solution was stirred at -78 °C for 1.5 h then added to the cold (-78 °C) suspension of CeCl₃ in THF. The resulting solution was stirred at -78 °C for 1 h. Cycloheptanone (0.709 mL, 6.00 mmol) dissolved in anhydrous THF (5 mL) was added to the corresponding organocerium reagent. The resulting mixture was stirred at -78 °C for 1 h then at rt for 1 h. At -30 °C, after dilution with anhydrous THF (20 mL), DBU (2.32 mL, 10.5 mmol, 3 equiv) then MsCl (1.39 mL, 10.5 mmol, 3 equiv) were added dropwise. The reaction mixture was then allowed to warm to rt and stirred overnight. At 0 °C, aqueous HCl 1 M (15 mL) was added and the solution was stirred for 1 h. The aqueous layer was extracted with Et₂O (3 x 30 mL). The resulting organic layers were washed with aqueous NaOH 2 M (10 mL), water (10 mL), brine (10 mL), dried over sodium sulfate and the solvent evaporated to provide a light yellow oil. The residue was purified by flash column
chromatography on silica gel using a 0 to 1% EtOAc in Hex elution gradient to provide the desired olefin as a colorless oil (655 mg, 54%).

All analytical data matches that reported in the literature.46

\(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta = 7.27\) (d, \(J = 8.7\) Hz, 2H), \(6.85\) (d, \(J = 8.6\) Hz, 2H), \(6.03\) (t, \(J = 6.7\) Hz, 1H), \(3.81\) (s, 3H), \(2.64 - 2.54\) (m, 2H), \(2.28\) (dd, \(J = 11.0, 6.5\) Hz, 2H), \(1.84\) (dt, \(J = 11.8, 6.0\) Hz, 2H), \(1.64\) (dt, \(J = 11.3, 5.8\) Hz, 2H), \(1.56\) (dt, \(J = 11.3, 5.9\) Hz, 2H) ppm

\(^1^3\)C NMR (176 MHz, CDCl\(_3\)): \(\delta = 158.2, 144.3, 137.5, 128.8, 126.7, 113.4, 55.3, 32.8, 32.7, 28.8, 26.9, 26.8\) ppm

\(R_f\) (1:9 – EtOAc:Hex) = 0.8

\textbf{IR (neat)}: 2916, 2834, 1609, 1509, 1489, 1286, 1242, 1177, 1032 cm\(^{-1}\)

\textbf{HRMS (ESI+)} \(m/z\) calculated for \(C_{14}H_{18}O\) [M+H]+ 203.1430, found 203.1424.
To a flame dried 50 mL round bottom flask charged with a magnetic stir bar was added 5 mL of DMF. To this, NaH (60%, 86.6 mg, 2.26 mmol, 0.9 equiv) was added portion-wise to the flask and the sulfonamide was allowed to react at 0 °C for 30 minutes. After this time, 2-bromo-1-phenyl-ethanone (500 mg, 2.51 mmol, 1 equiv), was diluted separately in 6 mL of DMF and transferred to the reaction via syringe at 0 °C. The reaction was slowly allowed to warm to room temperature over 1 h, and then quenched with 7 mL of aqueous 5% citric acid and 7 mL of 10% sodium thiosulfate at 0 °C. The mixture was then transferred to a separatory funnel and extracted 3 times with 50 mL of diethyl ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, followed by 5% LiCl wash (equal volume). The combined organic fractions were dried over sodium sulfate and then concentrated in vacuo to provide a crude dark oil which was purified by silica gel chromatography (30% EtOAc in Hexanes). N-allyl-4-methyl-N-phenacyl-benzenesulfonamide isolated in 47% yield (396 mg) and corresponded to literature characterization.47

To a flame dried 25 mL round bottom flask charged with a magnetic stir bar was added 6 mL of dry CH₂Cl₂, followed by 1-methoxy-4-vinyl-benzene (202 µL, 1.52 mmol, 5 equiv). The reaction was sparged by an argon line for 5 minutes. Then Hoveyda-Grubbs II (CAS No. 301224-40-8) (4.76 mg, 0.00759 mmol, 2.5 mol %) was added, the flask was flushed with argon and then the reaction was
capped and allowed to stir for 12 hours. Following this time, the crude mixture was pushed through a celite plug and concentrated to provide the crude residue. The material was purified by silica gel chromatography (3:7 ethyl acetate/Hexanes), and the stilbene impurity was triturated out with cold ether, after concentrating to yield 29 mg of the title substrate (22% yield).

**1H NMR** (700 MHz, CDCl₃) δ = 7.89 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.33 (d, J = 15.8 Hz, 1H), 6.33 (d, J = 15.8 Hz, 1H), 5.88 (dt, J = 14.6, 7.0 Hz, 1H), 5.88 (dt, J = 14.6, 7.0 Hz, 1H), 4.76 (s, 2H), 4.05 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 2.45 (s, 3H) ppm

**13C NMR** (176 MHz, CDCl₃) δ = 194.2, 159.5, 143.4, 136.9, 134.9, 134.4, 133.7, 129.6, 128.7, 128.0, 127.7, 127.5, 121.0, 113.9, 55.3, 51.9, 50.5, 21.6 ppm

Rf (3:7 – EtOAc:Hex) = 0.3

**IR** (neat): 2932, 2836, 2254, 1699, 1606, 1579, 1510, 1448, 1420, 1334, 1304, 1249, 1224, 1174, 1154, 1092, 1059, 1032, 1001, 971, 906, 856, 839, 812, 729, 689, 668, 607 cm⁻¹

To a solution of (E)-3-(4-methoxyphenyl)prop-2-en-1-ol (200 mg, 1.22 mmol) in CH$_2$Cl$_2$ (15 mL) and THF (5 mL) was added DMAP (14.9 mg, 0.122 mmol). Then the reaction was cooled to 0 °C and via syringe was added pyridine (0.294 mL, 3.65 mmol) followed by acetic anhydride (0.345 mL, 3.65 mmol). The reaction was slowly allowed to warm to rt while stirring for 12 h. Upon completion of the reaction as judged by TLC analysis (10% EtOAc in Hex), the reaction was concentrated under reduced pressure to give a light yellow oil. This crude mixture was diluted with EtOAc (25 mL) then washed 3 x with 1 N HCl (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered to give a crude, colorless oil. Purification by flash column chromatography (0 to 5% EtOAc in Hex elution gradient) provided the title substrate as a clear, colorless oil (219 mg 87%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.33$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.60 (d, $J = 15.9$ Hz, 1H), 6.15 (dt, $J = 15.8$, 6.6 Hz, 1H), 4.70 (d, $J = 6.6$ Hz, 2H), 3.81 (s, 3H), 2.09 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta =$ 170.9, 159.5, 134.0, 128.9, 127.8, 120.8, 113.9, 65.3, 55.3, 21.0 ppm

R$_r$ (1:10 – EtOAc:Hex) = 0.7

IR (neat): 2938, 1733, 1607, 1362, 1222, 1174, 1023, 958, 842 cm$^{-1}$

HRMS (EI) $m/z$ calculated for C$_{12}$H$_{14}$O$_3$ [M]$^+$ 206.0943, found 206.0951.
7-methoxy-1,2-dihydronaphthalene (3.S20)

A solution of 6-methoxytetralin-1-one (1000 mg, 5.67 mmol) in diethyl ether (17 mL) was added to a suspension of LiAlH₄ (108 mg, 2.84 mmol) in diethyl ether (8.5 mL). The temperature of the reaction was kept below 5 °C during this addition. The addition process took, 30 minutes, and the reaction was allowed to stir for 30 more minutes to reach completion. The reaction was quenched by the addition of 220 μL of a 3M NaOH solution at 0 °C, followed by 600 μL of water. The solution was then gravity filtered to remove the aluminum salts, and then washed with 30 mL of water, followed by 30 mL of saturated sodium chloride solution. Drying over magnesium sulfate and concentration yielded a clear liquid.

The crude alcohol was dissolved in toluene (30 mL, 0.2 M), and 4-methylbenzenesulfonic acid;hydrate (6.75 mg, 0.0355 mmol) was added. The reaction was heated to reflux for no longer than 30 minutes, and then cooled to room temperature. The mixture was washed with 30 mL of water followed by 30 mL of saturated sodium chloride solution, followed by drying over magnesium sulfate. Vacuum filtration with additional washing with ethyl acetate removed the desiccant, while azeotropic distillation of the toluene with ethyl acetate afforded a brown oil free of toluene. The brown oil was distilled to yield under vacuum at 0.2 mbar/80 °C afforded 7-methoxy-1,2-dihydronaphthalene (275 mg, 1.72 mmol, yield: 30%). Spectral data of the product corresponded with previous reports.
**Aminoarylation Products**

\[ N-(2-(4-methoxyphenyl)-2-(naphthalen-1-yl)ethyl)acetamide (3.4) \]

The General Procedure A was followed performing the reaction with \( N-(1\text{-naphthylsulfonyl})acetamide \) (75 mg, 0.3 mmol) and 1-methoxy-4-vinyl-benzene (48 \( \mu \)L, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10 → 30:70 Hex:EtOAc) to furnish the title compound as a white foam (39 mg, 41%).

\textbf{\( ^1\)H NMR} (700 MHz, CDCl\(_3\)): \( \delta = 8.13 \) (d, \( J = 8.1 \text{ Hz, 1H} \)), 7.88 – 7.81 (m, 1H), 7.77 (d, \( J = 8.1 \text{ Hz, 1H} \)), 7.51 – 7.43 (m, 3H), 7.39 (d, \( J = 7.1 \text{ Hz, 1H} \)), 7.19 (d, \( J = 8.6 \text{ Hz, 2H} \)), 6.83 (d, \( J = 8.6 \text{ Hz, 2H} \)), 5.53 (bs, 1H), 4.96 (t, \( J = 7.7 \text{ Hz, 2H} \)), 4.03 (ddd, \( J = 13.6, 7.5, 6.0 \text{ Hz, 1H} \)), 3.97 – 3.86 (m, 1H), 3.76 (s, 3H), 1.88 (s, 3H) ppm

\textbf{\( ^{13}\)C NMR} (176 MHz, CDCl\(_3\)): \( \delta = 170.1, 158.3, 137.5, 134.1, 133.9, 131.9, 129.1, 128.8, 127.6, 126.3, 125.7, 125.3, 124.2, 123.7, 114.1, 55.2, 45.1, 44.1, 23.3 \text{ ppm} \)

\( R_f \) (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 2929, 1648, 1547, 1510, 1260, 1240, 1140, 1025, 781 cm\(^{-1}\)

**HRMS** (ESI) \( m/z \) calculated for \( C_{21}H_{21}NO_2 \) [M+H]\(^+\) 320.1645, found 320.1645.
ethyl-(2-(4-methoxyphenyl)-2-(naphthalen-1-yl)ethyl)carbamate (3.5)

The General Procedure A was followed performing the reaction with ethyl-N-(1-naphthylsulfonyl)carbamate (251 mg, 0.9 mmol) and 1-methoxy-4-vinyl-benzene (40 μL, 0.3 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (38 mg, 36%).

**¹H NMR** (500 MHz, CDCl₃): δ = 8.12 (d, J = 6.9 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.46 (m, 3H), 7.38 (d, J = 7.0 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.95 (bs, 1H), 4.73 (bs, 1H), 4.09 (m, 2H), 3.96 (dd, J = 13.4, 6.3 Hz, 1H), 3.90 – 3.79 (m, 1H), 1.19 (t, J = 6.5 Hz, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 158.3, 156.5, 137.5, 134.1, 133.9, 131.9, 129.2, 128.8, 127.6, 126.3, 125.6, 125.3, 124.1, 123.7, 114.1, 60.8, 55.2, 45.7, 45.5, 14.6 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 2931, 1693, 1609, 1509, 1244, 1177, 1032, 799, 729 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₂₂H₂₃NO₃ [M+H]⁺ 350.1751, found 350.1747.
*tert*-butyl-(2-(4-methoxyphenyl)-2-(naphthalen-1-yl)ethyl)carbamate (3.6)

The General Procedure A was followed performing the reaction with *t*-butyl-N-(1-naphthylsulfonyl)carbamate (277 mg, 0.9 mmol) and 1-methoxy-4-vinyl-benzene (40 μL, 0.3 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a white foam (30 mg, 27%).

**¹H NMR** (700 MHz, CDCl₃): δ = 8.10 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.42 (d, J = 6.6 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 4.93 (t, J = 7.0 Hz, 1H), 4.62 (s, 1H), 3.89 (dd, J = 13.3, 6.3 Hz, 1H), 3.84 (dd, J = 12.9, 6.2 Hz, 1H), 3.76 (s, 3H), 1.41 (s, 9H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 158.2, 155.8, 137.6, 134.1, 132.1, 129.2, 128.8, 127.5, 126.2, 125.6, 125.3, 124.1, 123.7, 114.0, 79.3, 55.2, 45.7, 45.2, 29.7, 28.4 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 2975, 1696, 1508, 1365, 1245, 1161, 1035, 799, 780 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₂₄H₂₇NO₃ [M+H]+ 378.2064, found 378.2049.
**tert-butyl-1-(4-methoxyphenyl)-1-(naphthalen-1-yl)propan-2-yl)carbamate (3.8)**

The **General Procedure A** was followed performing the reaction with tert-butyl- N-(1-naphthylsulfonyl)carbamate (277 mg, 0.9 mmol) and *trans*-anethole (45 μL, 0.3 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a white foam (43 mg, 37%).

**\( ^1\)H NMR** (700 MHz, CDCl\(_3\)): \( \delta = 8.13 \) (d, \( J = 8.3 \) Hz, 1H), 7.82 (d, \( J = 7.9 \) Hz, 1H), 7.72 (d, \( J = 7.8 \) Hz, 2H), 7.50 (t, \( J = 7.6 \) Hz, 1H), 7.46 (t, \( J = 7.4 \) Hz, 1H), 7.42 (t, \( J = 7.3 \) Hz, 1H), 7.26 (d, \( J = 7.6 \) Hz, 2H), 6.78 (d, \( J = 8.2 \) Hz, 2H), 4.61 (s, 1H), 4.56 (d, \( J = 9.9 \) Hz, 1H), 4.33 (s, 1H), 3.72 (s, 3H), 1.33 (s, 9H), 1.18 (d, \( J = 5.7 \) Hz, 3H) ppm

**\( ^{13}\)C NMR** (176 MHz, CDCl\(_3\)): \( \delta = 158.1, 155.3, 137.5, 134.1, 132.0, 129.4, 128.9, 127.1, 125.9, 125.5, 125.2, 124.4, 123.3, 114.3, 113.9, 79.1, 55.1, 52.2, 49.3, 28.3, 21.1 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 2974, 2831, 1689, 1609 1509, 1452, 1365, 1247, 1162, 929, 782 cm\(^{-1}\)

**HRMS (ESI+) m/z** calculated for C\(_{25}\)H\(_{29}\)NO\(_3\) [M+H]\(^+\) 392.2220, found 392.2230.
N-1-(4-methoxyphenyl)-1-(naphthalen-1-yl)propan-2-ylacetamide (3.9)

**With trans-Anethole:** The General Procedure A was followed performing the reaction with N-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol) and *trans*-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (82 mg, 82%).

**With cis-Anethole:** The General Procedure A was followed performing the reaction with N-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol) and *cis*-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (72 mg, 72%).

**1H NMR** (700 MHz, CDCl₃): δ = 8.14 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.47 (td, J = 8.1, 7.1 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.22 (d, J = 7.8 Hz, 1H), 5.01 – 4.87 (m, 1H), 4.58 (d, J = 10.4 Hz, 1H), 3.72 (s, 3H), 1.74 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H) ppm

**13C NMR** (176 MHz, CDCl₃): δ = 169.4, 158.2, 137.1, 134.1, 133.7, 131.9, 129.5, 129.1, 127.3, 126.0, 125.6, 125.3, 124.2, 123.2, 113.9, 55.1, 51.9, 48.1, 23.4, 20.7 ppm

**Rf** (5:5 – EtOAc:Hex) = 0.1

**IR (neat):** 3089, 2929, 1637, 1509, 1370, 1302, 1249, 1177, 1031 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₂₂H₂₃NO₂ [M+H]⁺ 334.1802, found 334.1802.
**N-1-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-2-yl)-n-pentamide (3.10)**

The **General Procedure A** was followed performing the reaction on 0.2 mmol scale with N-(1-naphthylsulfonyl)hexanamide and *trans*-anethole (59.3 mg, 0.400 mmol). Purification by flash column chromatography (SiO₂, 90:10 to 60:40 Hex:EtOAc) to furnish the title compound as a light yellow foam (45%). Further removal of residual N-(1-naphthylsulfonyl)hexanamide (~10%) was done by washing with 1 N NaOH and extracting into Et₂O. Reconcentration of the purified product provided a light yellow foam (20.7 mg, 25%).

**¹H NMR (400 mHz, CDCl₃)** = δ 8.16 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.46 – 7.38 (t, 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.20 (d, J = 8.6 Hz, 1H), 4.95 (m, 1H), 4.60 (d, J = 10.5 Hz, 1H), 3.73 (s, 3H), 1.90 (dtd, J = 29.3, 14.5, 7.5 Hz, 2H), 1.47 – 0.86 (m, 9H), 0.78 (t, J = 7.2 Hz, 2H) ppm

**¹³C NMR (100 mHz, CDCl₃)** = 172.4, 158.2, 137.3, 134.1, 133.8, 131.9, 129.5, 129.1, 127.3, 126.0, 125.6, 125.2, 124.5, 123.1, 113.9, 55.1, 51.9, 48.0, 36.9, 31.2, 25.3, 22.3, 20.8, 13.8 ppm

**Rᵣ (4:6 – EtOAc:Hex) = 0.5**

**IR (neat)** = 2996, 2932, 2253, 1641, 1510, 1252, 905, 784, 729, 649 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₂₆H₃₁NO₂ [M+H⁺] 390.2428, found 390.2431.
**N-1-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-2-yl)acetamide (3.11)**

The **General Procedure A** was followed performing the reaction with **N-(2-naphthylsulfonyl)acetamide** (75 mg, 0.3 mmol) and **trans-anethole** (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (78 mg, 78%).

**¹H NMR** (700 MHz, CDCl₃): δ = 7.79 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.73 (m, 1H), 7.45 (td, J = 11.0, 3.9 Hz, 1H), 7.42 (t, J = 6.9 Hz, 1H), 7.38 (dd, J = 8.5, 1.2 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.22 (d, J = 8.4 Hz, 1H), 5.01–4.87 (m, 1H), 3.97 (d, J = 9.7 Hz, 1H), 3.76 (s, 3H), 1.77 (s, 3H), 1.17 (d, J = 6.4 Hz, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 169.3, 158.3, 139.6, 134.2, 133.4, 132.2, 129.3, 128.3, 127.8, 127.5, 126.5, 126.4, 126.1, 125.6, 114.1, 57.2, 55.2, 47.5, 23.5, 20.3 ppm

**Rₜ** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 3268, 2971, 1636, 1509, 1371, 1247, 1178, 1032, 915 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₂₂H₂₃NO² [M+H]⁺ 334.1802, found 334.1805.
The General Procedure A was followed performing the reaction with \( N-(3\text{-thienylsulfonyl}) \text{acetamide (62 mg, 0.3 mmol)} \) and \( \text{trans-anethole (54 \( \mu \)L, 0.36 mmol)} \) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (26 mg, 30%).

\(^1\text{H NMR (700 MHz, CDCl}_3\): } \delta = 7.24 – 7.21 (m, 1H), 7.14 (d, \( J = 8.4 \) Hz, 2H), 7.09 (s, 1H), 6.93 (d, \( J = 4.8 \) Hz, 1H), 6.83 (d, \( J = 8.4 \) Hz, 2H), 5.20 (d, \( J = 8.1 \) Hz, 1H), 4.83 – 4.66 (m, 1H), 3.94 (d, \( J = 8.7 \) Hz, 1H), 3.78 (s, 3H), 1.87 (s, 3H), 1.07 (d, \( J = 6.5 \) Hz, 3H) ppm

\(^{13}\text{C NMR (176 MHz, CDCl}_3\): } \delta = 169.2, 158.4, 142.8, 133.4, 129.5, 127.8, 125.6, 120.9, 113.9, 55.2, 52.2, 48.2, 23.6, 19.6 ppm

\( \text{Rf (5:5 – EtOAc:Hex) = 0.1} \)

\( \text{IR (neat): } 3325, 3000, 1628, 1511, 1373, 1251, 1032, 849, 796, 708 \text{ cm}^{-1} \)

\( \text{HRMS (ESI+) } m/z \) calculated for \( \text{C}_{16}\text{H}_{19}\text{NO}_{2}\text{S [M+H]⁺ } 290.1209, \text{ found } 290.1211. \)
methyl-2-acetamido-1-(4-methoxyphenyl)propylthiophene-2-carboxylate (3.13)

The **General Procedure A** was followed performing the reaction with methyl 3-(acetylsulfamoyl)thiophene-2-carboxylate (79 mg, 0.3 mmol) and *trans*-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (92 mg, 89%).

**¹H NMR** (700 MHz, CDCl₃): δ = 7.36 (d, *J* = 5.2 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 5.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.86 (d, *J* = 9.0 Hz, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.86 – 4.65 (m, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 1.75 (s, 3H), 1.12 (d, *J* = 6.4 Hz, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃): δ = 169.1, 163.9, 158.4, 151.8, 133.1, 130.9, 129.5, 129.0, 126.2, 114.0, 55.2, 52.0, 49.6, 49.1, 23.3, 20.7 ppm

**Rᵣ** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 3289, 2941, 1718, 1639, 1585, 1512, 1445, 1226, 1104, 1075, 829 cm⁻¹

**HRMS** (ESI⁺) *m/z* calculated for C₁₈H₂₁NO₄S [M+H]⁺ 348.1264, found 348.1265.
**N-1-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-2-yl)acetamide (3.14)**

The **General Procedure A** was followed performing the reaction with $N$-(2-thienylsulfonyl)acetamide (62 mg, 0.3 mmol) and *trans*-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO$_2$, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (69 mg, 69%).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta = 7.21$ (d, $J = 8.6$ Hz, 2H), 7.15 (d, $J = 4.9$ Hz, 1H), 6.93 – 6.91 (m, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.31 (d, $J = 8.3$ Hz, 1H), 4.73 – 4.67 (m, 1H), 4.15 (d, $J = 8.1$ Hz, 1H), 3.79 (s, 3H), 1.89 (s, 3H), 1.11 (d, $J = 6.6$ Hz, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta = 169.3, 158.6, 145.6, 133.2, 129.5, 126.7, 124.9, 124.1, 113.9, 55.2, 51.6, 49.1, 23.5, 19.5$ ppm

$R_f$ (5:5 – EtOAc:Hex) = 0.1

IR (neat): 2987, 2983, 1638, 1538, 1512, 1373, 1282, 1030 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{16}$H$_{19}$NO$_2$S [M+H]$^+$ 290.1209, found 290.1209.
The **General Procedure A** was followed performing the reaction with \(N\)-[(5-bromo-2-thienyl)sulfonyl]acetamide (85 mg, 0.3 mmol) and \textit{trans}-anethole (54 \(\mu\)L, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (49 mg, 45%).

\(^1\text{H NMR}\) (700 MHz, CDCl\(_3\)): \(\delta = 7.17\) (d, \(J = 8.5\) Hz, 2H), 6.86 – 6.85 (m, 3H), 6.67 (d, \(J = 3.6\) Hz, 1H), 5.27 (d, \(J = 7.4\) Hz, 1H), 4.77 – 4.55 (m, 1H), 4.06 (d, \(J = 8.1\) Hz, 1H), 3.79 (s, 3H), 1.92 (s, 3H), 1.09 (d, \(J = 6.6\) Hz, 3H) ppm

\(^{13}\text{C NMR}\) (176 MHz, CDCl\(_3\)): \(\delta = 169.3, 158.8, 147.5, 132.4, 129.5, 129.4, 125.2, 114.1, 110.5, 55.3, 51.9, 48.7, 23.6, 19.3\) ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.1

**IR** (\textit{neat}): 3313, 2930, 1627, 1511, 1446, 1372, 1281, 1222, 1175, 801 cm\(^{-1}\)

**HRMS** (ESI+) \(m/z\) calculated for C\(_{16}\)H\(_{18}\)BrNO\(_2\)S [M+H]\(^+\) 368.0314, found 368.0315.
The General Procedure A was followed performing the reaction with methyl 5-(acetylsulfamoyl)furan-2-carboxylate (74 mg, 0.3 mmol) and trans-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO$_2$, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a white foam (79 mg, 80%).

$^1$H NMR (700 MHz, CDCl$_3$): δ = 7.19 (d, $J$ = 8.7 Hz, 2H), 7.09 (d, $J$ = 3.5 Hz, 1H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.29 (d, $J$ = 3.4 Hz, 1H), 5.53 (d, $J$ = 9.3 Hz, 1H), 4.77 – 4.60 (m, 1H), 4.05 (d, $J$ = 8.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 1.89 (s, 3H), 1.07 (d, $J$ = 6.7 Hz, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): δ = 169.3, 160.4, 159.1, 158.9, 143.5, 130.1, 129.5, 119.1, 114.1, 109.3, 55.2, 51.8, 50.4, 48.2, 23.5, 19.5 ppm

R$_r$ (5:5 – EtOAc:Hex) = 0.1

IR (neat): 3294, 2989, 1721, 1634, 1628, 1515, 1308, 1251, 1126, 1031, 826 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{18}$H$_{21}$NO$_5$ [M+H]$^+$ 332.1492, found 332.1491.
**N-1-(4-methoxyphenyl)-1-(quinolin-8-yl)propan-2-yl)acetamide (3.17)**

![Chemical Structure](image)

The **General Procedure A** was followed performing the reaction with methyl *N-(8-quinolylsulfonyl)acetamide* (62 mg, 0.25 mmol) and *trans*-anethole (44 μL, 0.3 mmol) and purification by flash column chromatography (SiO$_2$, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (47 mg, 58%).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta = 8.95$ (d, $J = 2.7$ Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 7.3$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 1H), 7.42 (dd, $J = 8.2$, $J = 4.1$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 6.44 (s, 1H), 5.45 (d, $J = 11.1$ Hz, 1H), 4.89 – 4.76 (m, 1H), 3.76 (s, 3H), 1.48 (s, 3H), 1.25 (d, $J = 6.3$ Hz, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta = 169.1$, 158.1, 149.2, 146.6, 141.1, 136.9, 134.2, 129.8, 128.8, 128.4, 126.8, 126.5, 120.8, 113.8, 55.2, 49.6, 48.9, 23.1, 21.0 ppm

$R_f$ (5:5 – EtOAc:Hex) = 0.1

**IR (neat):** 3259, 2965, 1664, 1638, 1495, 1369, 1302, 1230, 1031, 930 cm$^{-1}$

**HRMS (ESI+)** $m/z$ calculated for $C_{21}H_{22}N_2O_2$ $[M+H]^+$ 335.1754, found 335.1752.
**N-1-(5-chlorothiophen-2-yl)-1-(4-methoxyphenyl)propan-2-yl)acetamide (3.18)**

The **General Procedure A** was followed performing the reaction with **N-[(5-chloro-2-thienyl)sulfonyl]acetamide** (72 mg, 0.3 mmol) and **trans-anethole** (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (67 mg, 79%).

\textbf{\(^1\)H NMR} (700 MHz, CDCl\(_3\)): \(\delta = 7.17\) (d, \(J = 8.6\) Hz, 2H), 6.86 (d, \(J = 8.6\) Hz, 2H), 6.71 (d, \(J = 3.8\) Hz, 1H), 6.68 (d, \(J = 3.6\) Hz, 1H), 5.30 (d, \(J = 8.5\) Hz, 1H), 4.71 – 4.58 (m, 1H), 4.03 (d, \(J = 8.2\) Hz, 1H), 3.79 (s, 3H), 1.92 (s, 3H), 1.09 (d, \(J = 6.6\) Hz, 3H) ppm

\textbf{\(^{13}\)C NMR} (176 MHz, CDCl\(_3\)): \(\delta = 169.3, 158.8, 144.6, 132.4, 129.5, 128.3, 125.6, 124.2, 114.1, 55.2, 51.9, 48.7, 23.6, 19.3\) ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.1

\textbf{IR (neat)}: 3275, 2985, 1652, 1585, 1511, 1484, 1249, 1034 cm\(^{-1}\)

\textbf{HRMS} (ESI+) \(m/z\) calculated for C\(_{16}\)H\(_{18}\)ClNO\(_2\)S [M+H]\(^{+}\) 324.0820, found 324.0819.
The **General Procedure A** was followed performing the reaction with \(N\)-(1,3-benzothiazol-2-ylsulfonyl)acetamide (77 mg, 0.3 mmol) and *trans*-anethole (54 μL, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (43 mg, 42%).

\(^{1}\text{H NMR}\) (700 MHz, CDCl\(_3\)): \(\delta = 8.03\) (d, \(J = 8.2\) Hz, 1H), 7.83 (d, \(J = 8.0\) Hz, 1H), 7.49 (t, \(J = 7.7\) Hz, 1H), 7.38 (t, \(J = 7.6\) Hz, 1H), 7.27 (d, \(J = 8.7\) Hz, 2H), 6.90 (d, \(J = 8.3\) Hz, 1H), 6.85 (d, \(J = 8.6\) Hz, 2H), 4.76 (dq, \(J = 13.0, 6.4\) Hz, 1H), 4.48 (d, \(J = 5.9\) Hz, 1H), 3.78 (s, 3H), 1.91 (s, 3H), 1.27 (d, \(J = 6.7\) Hz, 3H) ppm

\(^{13}\text{C NMR}\) (176 MHz, CDCl\(_3\)): \(\delta = 171.9, 169.4, 159.0, 152.9, 134.9, 130.9, 129.4, 126.1, 125.1, 122.9, 121.6, 114.1, 55.2, 53.8, 49.7, 23.6, 20.1\) ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.1

\(\text{IR (neat): } 3309, 2924, 1639, 1531, 1515, 1247, 1183, 1038, 832, 757\) cm\(^{-1}\)

\(\text{HRMS (ESI+)} m/z\) calculated for \(\text{C}_{19}\text{H}_{20}\text{N}_{2}\text{O}_{2}\text{S [M+H]}^+\) 341.1318, found 341.1320.
N-(3-(4-methoxyphenyl)-5-phenylpent-4-en-2-yl)acetamide (3.20)

The General Procedure A was followed performing the reaction with N-[(E)-styryl]sulfonylacetamide (20.1 mg, 0.0894 mmol) and trans-anethole (13.3 mg, 0.0894 mmol) and purification by flash column chromatography (SiO₂, 30:70 Hex:EtOAc) to furnish the title compound (23 mg, 83%).

Major Diastereomer:

^1^H NMR (700 MHz, CDCl₃) δ 1.94 (s, 3H), 1.06 (d, J=6.6 Hz, 3H), 3.39 (t, J= 8.2 Hz, 3H), 3.80 (s, 3H), 4.43-4.36 (m, 1H), 5.39 (d, J=6.2 Hz, 1H), 6.39 (dd, J = 15.8, 8.1 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 7.18-7.37 (m, 9H) ppm

Minor diastereomer:

^1^H NMR (700 MHz, CDCl₃) δ = 0.94 (d, J = 6.6 Hz, 3H), 1.92 (s, 3H), 3.66 (t, J = 9.83, 1H), 3.80 (s, 3H), 4.27 (m, 1H), 5.16 (d, J=8.45, 1H), 5.99 (t, J=11.2 Hz, 1H), 6.59 (d, J=11.6 Hz, 1H), 7.18-7.37 (m, 9H) ppm

^1^3^C NMR (mixture): (176 mHz, CDCl₃) δ = 169.4, 158.5, 158.4, 137.1, 137.0, 133.5, 133.0, 131.3, 131.0, 129.6, 129.1, 128.7, 128.5, 128.3, 127.3, 127.0, 126.2, 114.2, 114.1, 55.3, 54.9, 50.0, 49.5, 49.1, 23.6, 23.5, 18.8, 18.6 ppm

R<sub>f</sub> (7:3 – EtOAc:Hex) = 0.5

IR (neat): 3283.5, 2969.8, 2836.8 2244.7, 1651.1, 1610.5, 1550.3, 1511.6, 1449.9, 1372.4, 1301.8, 1250.8, 1178.4, 1147.5, 1034.9, 964.9, 908.9, 829.3, 732.1, 696.7, 650.4, 624.6, 607.5 cm⁻¹

HRMS (ESI+) m/z calculated for C₂₀H₂₃NO₂ [M+H]+ 310.1807, found 310.1805.
The **General Procedure A** was followed performing the reaction with N-(1-naphthylsulfonyl)acetamide (18.9 mg, 0.0758 mmol) and N-[(E)-3-(4-methoxyphenyl)allyl]-4-methyl-N-phenacyl-benzenesulfonamide (33.0 mg, 0.0758 mmol) and purification by flash column chromatography (SiO₂, 30:70 Hex:EtOAc) to furnish the title compound (10 mg, 28%).

**1H NMR** (700 MHz, CDCl₃) δ = 8.16 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.62 – 7.55 (m, 4H), 7.45 (m, 5H), 7.22 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.71 (d, J = 9.2 Hz, 1H, N-H), 5.13 (ddd, J = 20.1, 9.8, 3.8 Hz, 1H), 4.96, 4.81 (ABq, 2H, Jₐₖ = 18.9) 4.87 (d, J = 9.9 Hz, 1H), 3.64 (dd, J = 15.1, 10.1 Hz, 1H), 3.31 (dd, J = 15.1, 3.7 Hz, 1H) ppm

**13C NMR** (mixture): (176 MHz, CDCl₃) δ = 193.7, 171.1, 158.3, 143.4, 137.2, 137.0, 134.8, 134.1, 133.9, 132.8, 131.7, 129.5, 129.1, 128.8, 127.9, 127.4, 127.3, 126.2, 125.5, 125.3, 124.6, 123.1, 114.2, 55.1, 52.4, 50.7, 49.3, 48.2, 23.3, 21.5 ppm

**Rₑ** (7:3 – EtOAc:Hex) = 0.5

**IR** *(neat)*: 2833, 2790, 2752, 2730, 2709, 1699, 1658, 1597, 1511, 1449, 1333, 1304, 1253, 1226, 1157, 1033, 980, 812, 785 cm⁻¹

**HRMS** (ESI+) *m/z* calculated for C₃₇H₅₆N₂O₅S [M+H]⁺ 621.2423, found 621.2418.
The General Procedure A was followed performing the reaction with \(N\)-(1-naphthylsulfonyl)acetamide (74.8 mg, 0.300 mmol) and [(E)-3-(4-methoxyphenyl)allyl] acetate (74.2 mg, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→50:50 Hex:EtOAc) to furnish the title compound as a white foam (70 mg, 60%).

\(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta = 8.13\) (d, \(J = 8.5\) Hz, 1H), 7.83 (d, \(J = 8.0\) Hz, 1H), 7.74 (d, \(J = 8.2\) Hz, 1H), 7.67 (d, \(J = 7.2\) Hz, 1H), 7.54 – 7.46 (m, 2H), 7.43 (t, \(J = 7.4\) Hz, 1H), 7.25 (d, \(J = 9.8\) Hz, 2H), 6.77 (d, \(J = 8.6\) Hz, 2H), 5.40 (d, \(J = 9.1\) Hz, 1H), 5.21 – 5.08 (m, 1H), 4.93 (d, \(J = 11.2\) Hz, 1H), 4.18 (dd, \(J = 11.3, 2.9\) Hz, 1H), 3.96 (dd, \(J = 11.3, 4.0\) Hz, 1H), 3.71 (s, 3H), 2.15 (s, 3H), 1.76 (s, 3H). ppm

\(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \(\delta = 169.8, 158.5, 136.2, 134.2, 132.4, 131.8, 129.3, 129.1, 127.5, 126.1, 125.6, 125.4, 124.1, 123.0, 114.2, 65.1, 55.2, 50.8, 46.5, 23.2, 20.9\). ppm

R\(_f\) (5:5 – EtOAc:Hex) = 0.1

IR (neat): 2929, 2752, 1737, 1648, 1510, 1369, 1243, 1177, 1032, 783, 728 cm\(^{-1}\)

HRMS (ESI+) \(m/z\) calculated for \(C_{24}H_{25}NO_4\) [M+H]\(^+\) 392.1856, found 392.1856.
N-(2-(4-methoxyphenyl)-2-(naphthalen-1-yl)cyclopentyl)acetamide (3.23)

The General Procedure A was followed performing the reaction with N-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol) and 1-(cyclopenten-1-yl)-4-methoxy-benzene (63 mg, 0.36 mmol) and purification by flash column chromatography (SiO$_2$, 90:10→30:70 Hex:EtoAc) to furnish the title compound as a light yellow foam (40 mg, 37%).

$^1$H NMR (700 MHz, CDCl$_3$): δ = 7.80 (d, $J$ = 8.2 Hz, 1H), 7.77 (t, $J$ = 7.3 Hz, 2H), 7.66 (d, $J$ = 8.7 Hz, 1H), 7.51 (t, $J$ = 7.7 Hz, 1H), 7.31 (t, $J$ = 7.4 Hz, 1H), 7.19 (d, $J$ = 8.8 Hz, 2H), 7.16 (t, $J$ = 7.7 Hz, 1H), 6.75 (d, $J$ = 8.8 Hz, 2H), 5.47 (dd, $J$ = 13.3, 7.3 Hz, 1H), 4.88 (d, $J$ = 7.4 Hz, 1H), 3.73 (s, 3H), 2.67 – 2.59 (m, 1H), 2.59 – 2.50 (m, 1H), 2.17 (s, 1H), 1.84 (dd, $J$ = 19.9, 10.0 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.60 (dd, $J$ = 20.6, 9.5 Hz, 1H), 1.40 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): δ = 168.8, 157.6, 139.9, 139.1, 134.7, 131.9, 128.7, 128.6, 127.4, 126.8, 126.0, 125.4, 125.3, 124.7, 113.7, 58.9, 55.1, 54.9, 41.6, 34.0, 23.1, 20.7 ppm

$R_f$ (5:5 – EtoAc:Hex) = 0.1

IR (neat): 2954, 1642, 1609, 1508, 1372, 1249, 1183, 1034, 827, 776 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{24}$H$_{25}$NO$_2$ [M+H]$^+$ 360.1958, found 360.1962.
**N-(2-(4-methoxyphenyl)-2-(thiophen-2-yl)cyclopentyl)acetamide (3.24)**

The **General Procedure A** was followed performing the reaction with \(N\)-(2-thienylsulfonyl)acetamide (62 mg, 0.3 mmol) and 1-(cyclopenten-1-yl)-4-methoxy-benzene (63 mg, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foamy oil (55 mg, 58%).

**\(^1\)H NMR** (700 MHz, CDCl\(_3\)): \(\delta\) 7.25 – 7.17 (m, 3H), 6.98 (dd, \(J = 4.8\), 3.7 Hz, 1H), 6.81 (d, \(J = 8.7\) Hz, 2H), 6.75 (d, \(J = 3.0\) Hz, 1H), 5.36 (d, \(J = 9.4\) Hz, 1H), 5.01 (dd, \(J = 17.3\), 9.9 Hz, 1H), 3.78 (s, 3H), 2.63 (ddd, \(J = 13.9\), 9.5, 4.4 Hz, 1H), 2.25 – 2.13 (m, 2H), 2.03 – 1.94 (m, 1H), 1.92 (s, 3H), 1.81 (ddd, \(J = 17.8\), 11.3, 4.5 Hz, 1H), 1.60 – 1.51 (m, 1H) ppm

**\(^{13}\)C NMR** (176 MHz, CDCl\(_3\)): \(\delta\) = 169.3, 158.0, 149.8, 139.4, 128.0, 126.7, 126.1, 124.7, 113.5, 55.1, 54.7, 54.6, 41.3, 30.4, 23.7, 19.5 ppm

**\(R_f\)** (5:5 – EtOAc:Hex) = 0.1

**IR** (neat): 3292, 2927, 1651, 1607, 1510, 1372, 1248, 1181, 1032, 827 cm\(^{-1}\)

**HRMS (ESI+)** \(m/z\) calculated for C\(_{18}\)H\(_{21}\)NO\(_2\)S [M+H]\(^+\) 316.1366, found 316.1364.
Methyl-2-acetamido-1-(4-methoxyphenyl)cyclopentylthiophene-2-carboxylate (3.25)

The General Procedure A was followed performing the reaction with methyl 3-(acetylsulfamoyl)thiophene-2-carboxylate (79 mg, 0.3 mmol) and 1-(cyclopenten-1-yl)-4-methoxy-benzene (63 mg, 0.36 mmol) and purification by flash column chromatography (SiO₂, 90:10→30:70 Hex:EtOAc) to furnish the title compound as an off white foam (62 mg, 55%).

\(^1\text{H NMR}\) (700 MHz, CDCl₃):  δ = 7.43 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.39 (d, J = 6.3 Hz, 1H), 5.03 (q, J = 6.6 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 2.44 – 2.40 (bm, 1H), 2.39 – 2.33 (bm, 2H), 1.89 – 1.80 (bm, 4H), 1.77 – 1.67 (bm, 1H), 1.67 – 1.55 (bm, 2H) ppm

\(^{13}\text{C NMR}\) (176 MHz, CDCl₃):  δ = 169.8, 163.3, 157.6, 150.4, 137.5, 131.2, 129.0, 128.4, 127.8, 113.2, 56.5, 56.3, 55.2, 52.4, 39.9, 31.0, 23.4, 20.6 ppm

\(R_f\) (5:5 – EtOAc:Hex) = 0.2

IR (neat): 3290, 2949, 1719, 1649, 1510, 1434, 1371, 1246, 1182, 1031, 780 cm\(^{-1}\)

HRMS (ESI+) \(m/z\) calculated for C\(_{20}\)H\(_{23}\)NO\(_4\)S [M+H]\(^+\) 374.1421, found 374.1428.
The General Procedure A was followed performing the reaction with \(N\)-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol) and 1-(4-methoxyphenyl)cycloheptene (73 mg, 0.36 mmol) and purification by flash column chromatography (SiO\(_2\), 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (36 mg, 31%).

\(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta = 7.80 – 7.72 (m, 2H), 7.50 (d, J = 8.8 \text{ Hz}, 1H), 7.48 (t, J = 7.8 \text{ Hz}, 1H), 7.31 (t, J = 7.4 \text{ Hz}, 1H), 7.20 – 7.04 (m, 3H), 6.73 (d, J = 8.4 \text{ Hz}, 2H), 5.22 (bs, 1H), 5.15 (bs, 1H), 3.74 (s, 3H), 2.61 (dd, J = 15.0, 9.2 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.36 (d, J = 22.7 Hz, 1H), 2.21 – 2.12 (m, 1H), 1.90 (s, 1H), 1.75 (dd, J = 14.2, 6.6 Hz, 1H), 1.71 – 1.61 (m, 1H), 1.56 (bs, 2H), 1.49 (dd, J = 12.7, 8.6 Hz, 1H), 1.35 (s, 3H) ppm

\(^{13}\)C NMR (176 MHz, CDCl\(_3\)): \(\delta = 168.5, 157.4, 142.1, 140.9, 135.0, 132.3, 128.8, 128.5, 127.4, 125.6, 125.2, 125.1, 124.2, 113.6, 56.9, 55.1, 55.0, 42.1, 32.0, 29.7, 24.8, 24.6, 22.8 \text{ ppm}

\(R_f\) (5:5 – EtOAc:Hex) = 0.1

IR (neat): 2928, 2859, 1650, 1608, 1508, 1462, 1247, 1183, 726 cm\(^{-1}\)

HRMS (ESI+) \(m/z\) calculated for C\(_{26}\)H\(_{29}\)NO\(_2\) [M+H]\(^+\) 388.2271, found 388.2268.
N-6-methoxy-1,2,3,4-tetrahydro-[1,1'-binaphthalen]-2-yl)acetamide (3.27)

The General Procedure A was followed performing the reaction with N-(1-naphthylsulfonyl)acetamide (75 mg, 0.3 mmol) and 7-methoxy-1,2-dihydronaphthalene (57.7 mg, 0.36 mmol) and purification by flash column chromatography (SiO$_2$, 90:10→30:70 Hex:EtOAc) to furnish the title compound as a light yellow foam (29 mg, 28%).

$^1$H NMR (700 MHz, CDCl$_3$): $\delta = 8.33$ (d, $J = 7.9$ Hz, 1H), 7.87 (d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 8.1$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 6.84 (d, $J = 6.9$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.73 (d, $J = 1.8$ Hz, 1H), 6.63 (dd, $J = 8.5$, 2.2 Hz, 1H), 5.38 (d, $J = 2.5$ Hz, 1H), 4.77 (bs, 2H), 3.80 (s, 3H), 3.17 – 2.98 (m, 2H), 1.99 (ddd, $J = 24.0$, 12.0, 5.9 Hz, 1H), 1.74 (ddd, $J = 12.3$, 5.9 Hz, 1H), 1.54 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$): $\delta = 169.5$ (s), 158.1 (s), 138.6 (s), 137.1 (s), 133.5 (s), 133.3 (s), 131.9 (s), 130.6 (s), 129.7 (s), 128.7 (s), 127.2 (s), 126.1 (s), 125.6 (s), 125.1 (s), 123.7 (s), 113.1 (s), 112.6 (s), 55.2 (s), 48.4 (s), 29.7 (s), 28.8 (s), 24.0 (s), 23.4 (s) ppm

$R_f$ (5:5 – EtOAc:Hex) = 0.1

IR (neat): 2923, 2851, 1651, 1609, 1499, 1268, 1229, 1038, 907, 726, 647 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{23}$H$_{23}$NO$_2$ [M+H]$^+$ 346.1802, found 346.1803.
3.4.4. X-Ray Crystallography Data

\[ \text{N-1-(5-bromothiophen-2-yl)-1-(4-methoxyphenyl)propan-2-yl)acetamide (3.15)} \]

![Structural figure of compound 3.15, with 50% probability ellipsoids.](image)

Accession Number

The structure of 3.15 has been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1572215.

Structure Determination

Colorless plates of 3.15 were grown from diethyl ether/pentane vapor diffusion at 22 °C. A crystal of dimensions 0.04 x 0.02 x 0.01 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (\( \lambda = 1.54187 \) A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in \( \omega \). The exposure times were 15 sec. for the low angle images, 80 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 24869 reflections to a maximum 2θ value of 138.84° of which 3075 were independent and 2171 were greater than 2σ(I). The final cell constants (Table 3.4) were based on the xyz centroids of 3709 reflections above 10σ(I). Analysis of the data showed
negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1)/c with Z = 4 for the formula C16H18NO2SBr. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. Full matrix least-squares refinement based on F2 converged at R1 = 0.0599 and wR2 = 0.1512 [based on I > 2sigma(I)], R1 = 0.0894 and wR2 = 0.1732 for all data. Additional details are presented in Table 3.4.

**Table 3.4.** Crystal data and structure refinement for 3.15.

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<th><strong>Empirical formula</strong></th>
<th>C16 H18 Br N O2 S</th>
</tr>
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<td><strong>Formula weight</strong></td>
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<tr>
<td><strong>Temperature</strong></td>
<td>85(2) K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>1.54184 A</td>
</tr>
<tr>
<td><strong>Crystal system, space group</strong></td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>a = 16.2401(10) A, alpha = 90 deg.</td>
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<tr>
<td></td>
<td>c = 9.5079(6) A, gamma = 90 deg.</td>
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<td><strong>Volume</strong></td>
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<td><strong>Z, Calculated density</strong></td>
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<tr>
<td><strong>Absorption coefficient</strong></td>
<td>4.607 mm^-1</td>
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<tr>
<td><strong>F(000)</strong></td>
<td>752</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.040 x 0.020 x 0.010 mm</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
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<td>-19&lt;=h&lt;=19, -13&lt;=k&lt;=13, -11&lt;=l&lt;=11</td>
</tr>
<tr>
<td><strong>Reflections collected / unique</strong></td>
<td>24869 / 3075</td>
</tr>
<tr>
<td><strong>Completeness to theta</strong></td>
<td>= 67.684 99.9 %</td>
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<tr>
<td><strong>Absorption correction</strong></td>
<td>Semi-empirical from equivalents</td>
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<tr>
<td><strong>Max. and min. transmission</strong></td>
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<td><strong>Refinement method</strong></td>
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<td><strong>Data / restraints / parameters</strong></td>
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<tr>
<td><strong>Goodness-of-fit on F^2</strong></td>
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<tr>
<td><strong>Final R indices [I&gt;2sigma(I)]</strong></td>
<td>R1 = 0.0599, wR2 = 0.1512</td>
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<tr>
<td><strong>R indices (all data)</strong></td>
<td>R1 = 0.0894, wR2 = 0.1732</td>
</tr>
<tr>
<td><strong>Extinction coefficient</strong></td>
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</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>1.452 and -0.856 e.A^-3</td>
</tr>
</tbody>
</table>
**N-(2-(4-methoxyphenyl)-2-(naphthalen-1-yl)cyclopentyl)acetamide (3.23)**

![Structural figure of compound 3.23, with 50% probability ellipsoids](image)

**Accession Number**

The structure of 3.23 has been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1572214.

**Structure Determination**

Colorless blocks of 3.23 were grown by vapor diffusion of diethyl ether into a pentane solution of the compound at 22 °C. A crystal of dimensions 0.10 x 0.10 x 0.09 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 Å) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 4 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 28115 reflections to a maximum 2θ value of 138.62° of which 6933 were independent and 5766 were greater than 2σ(I). The final cell constants (Table 3.5) were based on the xyz centroids of 8542 reflections above
Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P1bar with Z = 4 for the formula C24H25NO2. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. Full matrix least-squares refinement based on F2 converged at R1 = 0.0537 and wR2 = 0.1504 [based on I > 2sigma(I)], R1 = 0.0634 and wR2 = 0.1646 for all data. Additional details are presented in Table 3.5.

**Table 3.5.** Crystal data and structure refinement for 3.23.

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<th>Property</th>
<th>Value</th>
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<td>Temperature</td>
<td>85(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 A</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 12.6453(6) Å  beta = 76.578(4) deg.</td>
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<tr>
<td></td>
<td>c = 16.9508(5) Å  gamma = 83.003(5) deg.</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Absorption coefficient</td>
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<tr>
<td>F(000)</td>
<td>768</td>
</tr>
<tr>
<td>Crystal size</td>
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</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.680 to 69.309 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-11&lt;=h&lt;=11, -15&lt;=k&lt;=15, -20&lt;=l&lt;=20</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>28115 / 6933 [R(int) = 0.0461]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>= 67.684  97.5 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.00000 and 0.76714</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<td>R indices (all data)</td>
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<td>Extinction coefficient</td>
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<td>Largest diff. peak and hole</td>
<td>0.273 and -0.248 e.A⁻³</td>
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</tbody>
</table>
3.5. References


Chapter 4

Arene Dearomatization via a Catalytic N-Centered Radical Cascade Reaction

* Portions of this chapter have been published on the chemistry preprint server in R. C. McAtee, E. A. Noten, C. R. J. Stephenson. Arene dearomatization via a catalytic N-centered radical cascade reaction. ChemRxiv 2019, DOI: org/10.26434/chemrxiv.9864071.v1

4.1. Introduction

Arenes obtained from inexpensive petrochemical feedstocks are incorporated on industrial scale into pharmaceuticals, agrochemicals, and organic materials. Selective dearomatization reactions\(^1\)\(^-\)\(^2\) of these flat, two-dimensional aromatic compounds are modular strategies to access substituted, three-dimensional chemical space,\(^3\) including fused, complex heterocyclic skeletons (Figure 4.1A).\(^4\)\(^-\)\(^5\) In addition, the potential to form stereogenic centers through substituent addition concomitant with the dearomatization process is particularly appealing. Of the selective dearomatization methods reported (including, UV-promoted photochemical cycloadditions,\(^6\)\(^-\)\(^7\) oxidative,\(^8\) enzymatic,\(^9\)\(^-\)\(^11\) transition metal-mediated,\(^12\)\(^-\)\(^13\) and nucleophilic dearomatizations\(^14\)\(^), the Birch reduction of arenes to 1,4-cyclohexadienes (1,4-CHD) is most well-known relying on liquid ammonia as solvent and pyrophoric alkali metals at cryogenic temperatures (Figure 4.1B).\(^15\)\(^-\)\(^16\) Modifications of the canonical Birch reduction conditions have expanded the scope and synthetic utility of the reaction.\(^17\)\(^-\)\(^21\) While both electrochemical\(^22\) and visible light-mediated\(^23\)\(^-\)\(^27\) arene
Dearomatization reactions have been reported with proven utility, they have not been integrated with other reaction pathways via reactive intermediates.

**Figure 4.1. Arene dearomatization reactions to rapidly build molecular complexity.**

(A) Arene dearomatization reactions from petrochemicals allows for rapid assembly of complex, three-dimensional molecules. (B) The classic Birch reduction; benefits and limitations.

An alternative strategy addressing the inherent drawbacks of the classic Birch reduction is to promote an arene dearomatization via a radical cascade sequence. Radical cascades, processes in which multiple chemical bonds are formed in a single operation, are step and atom-economical means to rapidly build complex organic molecules (Figure 4.2). Moreover, initiating cascade sequences from strong N–H bonds leading to dearomatized molecular frameworks has the potential to impact a variety of synthetic endeavors.
Figure 4.2. Cascade approach to deliver complex, three dimensional frameworks.

Concerted proton-coupled electron transfer (PCET) has emerged as a powerful strategy for homolytic activation of strong N–H bonds, often in the presence of weaker ones, avoiding the need for N-pre-functionalization.\textsuperscript{31-33} The Knowles group recently reported the activation of both amide\textsuperscript{34} and sulfonamide\textsuperscript{35} N–H bonds for intramolecular and intermolecular hydroamination reactions, respectively, of electron neutral olefins. The authors propose an excited-state redox catalyst and a weakly coordinating phosphate base jointly mediate the concerted homolytic activation of the strong N–H bonds under visible light irradiation to afford transient N-centered amidyl and sulfonamidyl radicals capable of adding to olefins with \textit{anti}-Markovnikov regioselectivity. Separately, Rovis and co-workers described the generation of amidyl radicals from trifluoroacetamide derivatives for sequential 1,5-HAT and δ-C–H functionalization.\textsuperscript{36} By using superstoichiometric quantities of K\textsubscript{3}PO\textsubscript{4} as base, trifluoroacetamides are deprotonated to the amide anions then oxidized to the amidyl radical by the excited state of an iridium(III) photocatalyst.
With respect to sulfonamide-based $N$-radical alkene carboamination platforms, Chemler and co-workers have developed racemic and enantioselective intramolecular Cu(II)-mediated oxidative $N$-radical cyclizations of alkenyl arylsulfonamides at elevated temperatures (120 °C) to garner benzosultams in good yields.\textsuperscript{37-39} In the enantioselective example, MnO$_2$ is used as a super-stoichiometric (3 equiv) oxidant. Later, Kanai and co-workers reported an intermolecular alkene carboamination reaction of aliphatic alkenes under Cu(I) catalysis and $N$-fluorobenzenesulfonylimide (NFSI) as both a bifunctional reagent, for C−C and C−N bond formation, and an oxidant for the concise synthesis of six-membered sultams.\textsuperscript{40} Very recently, Chen and Xiao described a process for a radical 5-\textit{exo} cyclization/addition/aromatization cascade of $\beta,\gamma$-unsaturated $N$-tosyl hydrazones under cooperative photocatalysis and cobalt catalysis enabling the synthesis of dihydropyrazole-fused benzosultams.\textsuperscript{41}
**Previous work: sulfonamide-based alkene carboaminations**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CuI ligand* MnO₂ K₂CO₃ 120 °C</td>
<td>RuI ligand* PhN₂ (1 equiv) K₂CO₃ 120 °C</td>
<td>CuI ligand* NBS 60 °C</td>
</tr>
</tbody>
</table>

Enantioselective Cu(II)-catalyzed carboamination

\[
\text{Me–} \overset{\text{Cu(II)I, ligand*}}{\text{N–}} \overset{\text{MnO₂ (3 equiv)}}{\text{MeO–}} \overset{\text{K₂CO₃ (1 equiv)}}{\text{Me}} \overset{\text{PHCF₃, 120 °C}}{\text{68%, 80% ee}} \overset{\text{Me–}}{\text{Me}} \overset{\text{N–}}{\text{Me}} \overset{\text{Me}}{\text{Me}} \overset{\text{Me}}{\text{Ph}} \overset{\text{ligand*} = \text{Ph}}{\text{(R,R)-Ph-Box}}
\]

**Selected Products**

- 73%, 92% ee
- 45%, 92% ee
- 75%, 94% ee
- 30%, 86% ee

**Proposed Mechanism**

![Proposed Mechanism Diagram]

**Figure 4.4. Sulfonamide-based N-radical alkene carboamination platforms.**

We reasoned that the work outlined above, along with our ongoing interests in alkene carboamination reactions with bifunctional arylsulfonamide reagents, would serve as a basis for developing a catalytic protocol to initiate a carboamination/dearomatization cascade starting from γ,δ-unsaturated N-arylsulfonyl enamides 4.1 (Figure 4.5). Ideally, this process would proceed through transient sulfonamidyl radical intermediates formed via a visible light-mediated proton-coupled electron transfer or stepwise deprotonation/oxidation sequence. This strategy obviates the need for N-pre-functionalization, elevated reaction temperatures, and stoichiometric oxidants. The reaction would lead to the synthesis of 1,4-cyclohexadiene-fused sultams.
Sultams are important heterocyclic motifs that are frequently encountered in numerous biologically active natural products and medicinally relevant compounds (Figure 4.6). Of note, fused sultams have been shown to exhibit a broad range of biological activities including calpain I and nuclear factor kappaB inhibition activities, as well as an efficient treatment for glaucoma. In addition, Oppolzer’s sultam has been used extensively as a chiral auxiliary for chemical synthesis. Herein, we describe the combination of the aforementioned reaction classes, whereby visible light-mediated photoredox catalysis is used to promote and control a sulfonamidyl radical cyclization/dearomatization cascade reaction.
4.2. Results and Discussion

At the outset, we recognized two major challenges in implementing this design strategy. The first was the potential for competitive hydroamination, wherein the vicinal carbon-centered radical that is formed following $N$-radical cyclization would undergo direct hydrogen atom transfer (terminating the radical process) resulting in the hydroamination product.\textsuperscript{32, 34-35, 49-56} The second challenge was rearomatization of the cyclohexadienyl radical intermediate. Identifying an efficient photocatalytic system, to convert the cyclohexadienyl radical to the cyclohexadienyl anion and returning the ground state of the photocatalyst, would be imperative to circumvent this obstacle. With judicious choice of reaction additives and modifying reaction parameters we believed such challenges could be surmounted.

Initially, we choose arylsulfonamide 4.1a as the model substrate to test the feasibility of the visible light-induced sulfonamidyl carboamination/dearomatization cascade reaction and representative results are summarized in Table 4.1. The expected reaction did occur with 1 mol\% Ir photocatalyst A ([Ir(dF(CF$_3$ppy)$_2$)(5,5'-CF$_3$-bpy)]PF$_6$, $\text{Ir}^{\text{III}}$/II = 1.68 V versus SCE in MeCN)\textsuperscript{34} and 65 mol\% of tetrabutylammonium dibutylphosphate base providing the desired 1,4-cyclohexadiene-fused sultam 4.2a in 48\% \textsuperscript{19}F-NMR yield and excellent diastereoselectivity (>20:1) following irradiation with blue LEDs in trifluorotoluene (0.2 M) at room temperature (entry 1). Dearomatized product 4.2a was unambiguously characterized by single-crystal X-ray analysis (CCDC: 1952459). Other iridium photocatalysts structurally similar to A (B = [Ir(dF(CF$_3$ppy)$_2$)(dtbbpy)]PF$_6$, $\text{Ir}^{\text{III}}$/II = 1.21 V versus SCE in MeCN; C = Ir(dF(Meppy)$_2$)(dtbbpy)]PF$_6$, $\text{Ir}^{\text{III}}$/II = 0.97 V versus SCE in MeCN)\textsuperscript{57-58} were also effective in these reactions (entries 2, 3), but the reaction yields diminished as the oxidation potential of the excited-state species decreased. Importantly, decreasing the reaction concentration (0.05 M)
delivered the desired product in 67% yield (entry 4). Also, the reaction is moderately to equally successful in other solvents (entry 5-7) with tert-butanol providing a noticeable increase in yield (entry 8). A 1:1 mixed solvent system of trifluorotoluene/tert-butanol (0.05 M) was finally identified as the optimal solvent combination (entry 9). When the reactions were run using conditions developed by Rovis, relying on step-wise deprotonation/oxidation,\textsuperscript{36} no product was isolated. Control reactions of \textbf{4.1a} lacking photocatalyst, base, or light were uniformly unsuccessful, and the starting material was recovered unchanged (entries 10-12).
Table 4.1 Reaction optimization and control experiments.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>photocatalyst</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>PhCF$_3$ (0.2 M)</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>PhCF$_3$ (0.2 M)</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>PhCF$_3$ (0.2 M)</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>PhCF$_3$ (0.05 M)</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>DMF (0.05 M)</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>C$_2$H$_2$Cl$_2$ (0.05 M)</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>1,2-DCE (0.05 M)</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>t-BuOH (0.05 M)</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>PhCF$_3$/t-BuOH (0.05 M)</td>
<td>83 (75)[$b$]</td>
</tr>
</tbody>
</table>

variation from best conditions (entry 9)

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>yield (%)</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>no blue LEDs</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>no photocatalyst</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>no NBu$_4$OP(O)(OBu)$_2$</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reactions were run on 0.1 mmol scale, and yields are determined by $^{19}$F-NMR analysis relative to 1,3,5-trifluorobenzene (1 equiv) as an internal standard. [b] Isolated yield of 4.2a on 0.2 mmol scale. Photocatalysts and single-crystal X-ray of 4.2a:

![Photocatalyst and solvent](image)

With optimized conditions established, we investigated the generality of this carboamination/dearomatization cascade reaction with a series of diversely substituted arylsulfonamides (Figure 4.7). For example, arenes bearing various electron-withdrawing (4.2a, 4.2b, 4.2f-4.2i), electron-neutral (4.2c-4.2e), and electron-donating (4.2j) groups delivered the
desired dearomatized products in moderate to good yields (12-80%) and excellent diastereoselectivity (>20:1). Unsurprisingly, the latter electron-rich product $4.2j$ was prone to rapid oxidative decomposition leading to diminished yields. Of note, dearomatized product $4.2h$ was isolated as an inseparable mixture of the aromatized benzosultam product. Next, we investigated modifications to the alkene tether which allowed for the synthesis of an all-carbon spirocycle ($4.2k$), fused tetracycle ($4.2l$), and cyclic carbamate ($4.2m$) in moderate to good yields (21-77%). Interestingly, 3-fluoro and 3,4-difluoro substituted arylsulfonamide substrates generated single dearomatized regioisomers in good yields ($4.2n$, $4.2o$) highlighting the regio- and chemoselective nature of the C–C bond forming cyclization step. Furthermore, this methodology proved tolerant of diverse functionality including, electron-rich heterocycles ($4.2p$), olefins ($4.2q$), amino acids ($4.2r$), aliphatic carbocycles ($4.2s$), and benzyl groups ($4.2t$) selectively furnishing the corresponding dearomatized products in good yields. Lastly, a tetrasubstituted-olefin substrate ($4.1u$) allowed direct access to dearomatized tertiary-amine$^{59}$ product $4.2u$, suggesting the initial 5-exo, N-radical cyclization is tolerant to steric encumbrance. Terminal olefin $4.3$ failed to convert to the desired dearomatized product (Figure 4.7C) likely due to the instability of the resultant vicinal primary radical following C–N bond formation. To probe the importance of the carbonyl moiety and to determine whether it is a necessary functionality on the substrate, we prepared and subjected o-prenyl aniline derivative $4.4$ (pK$_a$ ≈ 13)$^{60}$ and alkyl sulfonamide $4.5$ (pK$_a$ ≈ 12)$^{61}$ to the optimized reaction conditions and found they were unreactive returning starting material unchanged. These experiments highlight the importance of the carbonyl moiety for this process to occur by lowering the pK$_a$ of the substrate (pK$_a$ for $4.2$ ≈ 5)$^{61}$ Importantly, many of the richly functionalized 1,4-cyclohexadiene products are envisaged to be valuable building blocks for post-
functionalization transformations. Studies to explore their synthetic utility are ongoing in our laboratory.

Figure 4.7. Reaction scope.
All yields are isolated yields. Relative configurations of products were assigned by analogy to 2a. (a) General reaction scheme; all reactions were run on 0.2 mmol scale and degassed by sparging with argon for 15 min prior to exposure to optimized conditions. (b) Arylsulfonamide modifications. (c) Control experiments with differentially substituted alkene side-chains. *Product isolated as an inseparable mixture of diene and arene products (3:1, diene:arene).

To gain insight into the reaction mechanism, we initially performed Stern-Volmer luminescence quenching studies with the model substrate 4.1a. it was revealed that there is no
luminescence quenching of the photoexcited state of catalyst A when 4.1a is used alone suggesting direct oxidation, followed by deprotonation, of the substrate is unlikely. This conclusion was further supported by cyclic voltammetry analysis (CH$_2$Cl$_2$ containing 0.1 M NBu$_4$PF$_6$) indicating that direct oxidation of substrate 1a occurs at potentials $>$1.6 V (vs SCE). Comparatively, when tetrabutylammonium dibutylphosphate base is used alone in the Stern-Volmer analysis, significant nonlinear photoluminescence quenching of the photoexcited state of catalyst A is observed. This observation aligns with Knowles,$^{62}$ and others,$^{63}$ suggesting the formation of a less emissive iridium-phosphate complex and may be the active ground-state catalytic species in solution. Importantly, no additional photoluminescence quenching is observed upon addition of substrate 4.1a as one would expect for a proton coupled-electron transfer process. Performing cyclic voltammetry studies of 4.1a in the presence of varying concentrations of monobasic dibutyl phosphate base, revealed that current response increased for increasing concentrations of phosphate base but did not show a shifted, less positive potential for the oxidation of substrate 4.1a. Additionally, we have found that the reaction fails to yield product when stronger bases are employed. This result suggests the formation of sulfonamidyl anion is not necessary for the reaction to proceed. Qualitatively, these results are consistent with a phosphate radical being generated under the reaction conditions and serving as a hydrogen-atom abstracting species and is at least partly responsible for the generation of the nitrogen radical.$^{64,65}$ Moreover, a deuterium labeling experiment was conducted to probe the role of tert-BuOH in this reaction. By performing the reaction in the presence of tert-BuOD, the desired product (4.2a-D) was produced in 51% yield with complete deuterium incorporation (Figure 4.8A). This result suggests that the tert-BuOH is serving as a reaction terminating proton source of a 1,4-cyclohexadienyl intermediate in accord with previous mechanistic studies of the classic Birch reduction reaction.$^{66,67}$
A prospective catalytic cycle accounting for these observations, and those made during reaction optimization, is shown in Figure 4.8. We suspect that the Ir-photocatalyst A and phosphate base first form a ground-state iridium-phosphate complex (i). Upon excitation, the Ir-photocatalyst can undergo single-electron transfer from the phosphate salt, generating an oxygen-centered radical (ii). Abstraction of the most activated N–H bond of the substrate (iii) generates a transient sulfonamidyl radical intermediate (iv). Next, the N-radical can undergo 5-exo cyclization onto the tethered alkene to furnish a new C–N bond and a vicinal carbon-centered radical (v). This alkyl radical is poised to undergo cyclization with the appended arene to generate a stabilized cyclohexadienyl radical (vi) that can undergo single-electron reduction by the reduced Ir(II) state of the photocatalyst \( E_{1/2}[\text{Ir}^{III}/\text{Ir}^{II}] = -1.07 \text{ V vs Fc}^+/\text{Fc} \).34,35 Favorable proton transfer between the cyclohexadienyl anion and tert-BuOH (tert-butoxide can then return phosphoric acid\(^{68}\) back to the phosphate salt) should follow delivering the dearomatized product, regenerating the active forms of both catalysts.
Following the completion of this work, we questioned whether a similar reaction design could allow for the rapid assembly of arylethylamine products (see Chapter 3) via an intermediate $N$-centered radical (Figure 4.9A). Unlike with the first-generation aryl transfer chemistry, which relied on electron-rich olefins (Figure 4.9B), this chemistry would rely on the N-nucleophile activation. If successful, the scope with respect to alkene identity would be greatly expanded, including to electron-neutral olefins, allowing for the synthetic utility of this chemistry to be greatly expanded. By modifying the identity of the heteroaromatic group, alkene substitution, and tether length we believed that we could identify various substrate classes which undergo radical aryl transfer (instead of arene dearomatization) providing rapid access to diversely functionalized arylethylamine products in a single-pot operation. It is important to point out that this reaction
design is possible because photoredox catalysis allows complementary reaction mechanism to be developed (see Chapter 1).

Figure 4.9. Proposed approach for the synthesis of arylethlamines via the intermediary of N-centered radicals.

(A) Previous work showing that arylsulfonylacetamides are viable functional reagents for alkene aminoarylation via the intermediary of alkene radical cations from electron-rich olefins. (B) This proposed work: engaging native N–H bonds for the formation of N-centered radicals which can under alkene aminoarylation.

To test the viability of aryl transfer enabled by N-centered radicals to generate arylethlamine products, following extrusion of SO₂, several structurally distinct substrates were prepared and subjected to the arene dearomatization conditions as described above (Figure 4.10). We were delighted to see that by extending the alkene tether length by one carbon and taking advantage of Thorpe-Ingold effect (4.6) led to exclusive formation of the arylethlamine product 4.7 in 35% yield while the dearomatized product 4.8 was not observed (Figure 4.10A). Additionally, five-membered ring heterocycles such as thiophene substrate 4.9 led to the anticipated arylethlamine product 4.10 in good isolated yields (Figure 4.10B). Lastly, preparing
substrate 4.12 allowed us to probe the influence of double ortho-substitution on the aromatic backbone (Figure 4.10C). Interestingly, the sole product isolated from this reaction is arylethylamine 4.13 in 46% isolated yield. The dearomatized, tertiary fluoride product 4.14 was never detected. These experiments highlight several substrate classes which will be amenable for our N-radical aryl transfer methodology to form a wide variety of structurally distinct arylethylamine products which were not accessible under our first-generation approach (Chapter 3). The substrate classes which should be amenable include, (1) those with extended alkene tethers, (2) five-membered ring heteroaromatics, and (3) doubly ortho-substituted aromatics. With these guiding principles established, a full set of optimization studies, substrate scope evaluation, and mechanism elucidation are currently underway in our laboratory and will be reported in due course.

Figure 4.10. Proof-of-concept established for radical aryl transfer. (A) Modification of alkene tether length and taking advantage of Thorpe-Ingold effect. (B) Five-membered ring heterocycles are amenable to this methodology. (C) Doubly ortho-substituted six-membered ring aromatics are viable substrates.
4.3. Conclusions

In summary, in this Chapter we have reported the discovery and development of a photoredox mediated $N$-centered radical strategy to facilitate a carboamination/dearomatization cascade reaction. Simple $\gamma,\delta$-unsaturated $N$-arylsulfonyl enamides were converted into complex and stereodefined 1,4-cyclohexadiene-fused sultams in satisfactory yields and excellent diastereoselectivity. This mild and efficient catalytic system demonstrates a broad substrate scope and high functional group tolerance while avoiding premature hydroamination or undesired rearomatization reactivity. Lastly, we presented several new substrate classes which undergo radical aryl transfer chemistry and not arene dearomatization. Overall, we believe the photochemical strategies outlined here will inspire future synthetic endeavors aimed at employing simple arene building blocks for the rapid synthesis of complex, three-dimensional molecular frameworks in a single operation.
4.4. Experimental Procedures and Characterization of Compounds

4.4.1. General Procedures, Materials, and Methods

General Considerations

All chemicals were used as received and stored as recommended by the supplier. Reactions were monitored by thin layer chromatography (TLC) using glass-backed plates pre-coated with 230–400 mesh silica gel (250 mm thickness) with fluorescent indicator F254, available from EMD Millipore (cat. #: 1.05715.0001). Plates were visualized with a dual short wave/long wave UV lamp. Column flash chromatography was performed using 230-400 mesh silica (SiliCycle cat. #: R12030B) gel or via automated column chromatography. NMR spectra were recorded on Varian MR400, Varian Inova 500, Varian Vnmrs 500, or Varian Vnmrs 700 spectrometers. Chemical shifts for $^1$H NMR were reported as δ, parts per million, relative to the signal of CHCl$_3$ at 7.26 ppm and for DMSO 2.50 ppm. Chemical shifts for $^{13}$C NMR were reported as δ, parts per million, relative to the center line signal of the CDCl$_3$ triplet at 77.0 ppm and for DMSO 39.52 ppm for center of septet. $^{19}$F NMR chemical shifts were reported as δ, parts per million, relative to CFCl$_3$ at 0.0 ppm. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiple, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer fitted with an ATR accessory. Melting points were obtained using a Mel-Temp 3.0 (model no. 1401). Mass Spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPCL-MS with ESI high resolution mass spectrometer using electrospray ionization (ESI), positive ion mode, or electron impact ionization (EI). Fluorescence quenching was recorded using a PTI Horiba Quanta Master.
using Felix GX software. We thank Dr. James Windak and Dr. Paul Lennon at the University of Michigan Department of Chemistry instrumentation facility for conducting these experiments. X-Ray crystallography work was done by Dr. Jeff. W. Kampf. UV-Vis measurements were obtained on a Shimadzu UV-1601 UV-Vis Spectrometer. Electrochemical data was collected on a CHI600E potentiostat with the accompanying CH Instruments software. H150 Blue grow lights from Kessil were used as the visible light irradiation source.
General Reaction Set-up

Unless stated otherwise, all reactions were run on a 0.2 mmol scale in a 2-dram vial equipped with an oval shaped stir bar. 2 x H150 Blue Kessil lamp sufficiently irradiated 1-3 reaction vials at one time, at ~5 cm away (A). At this distance, with an overhead fan dissipating the standing atmosphere, the air temperature surrounding the reactions did not exceed 25 °C. The reactions were stirred at a rate of ~550 rpms on an IKA magnetic stir plate. The photochemical dearomatization reactions were covered with ~0.5 m x 0.5 m dimension Blue Light Filter Amber Reaction Boxes (B) purchased from PLAS Labs, Inc (Lansing, MI). In addition, each experimentalist who may have been exposed to blue light wore UVEX Skyper Orange Safety Glasses which were purchased through Amazon.
Reaction Discovery, Optimization Studies, and Control Reactions

To an oven-dried 1-dram vial was added 1a (33.5 mg, 0.1 mmol), base, and photocatalyst. The vial contents were then dissolved in the indicated solvent or solvent mixture. The reaction solution was degassed by sparging with argon for 15 min. Then, the vial was quickly capped and sealed with parafilm. The reaction was irradiated with two, H150 blue Kessil lamps positioned ~5 cm away and cooled with an overhead fan. After 14 h, 1,3,5-trifluorobenzene was added to the reaction as a stoichiometric internal standard (10.3 μL, 0.1 mmol, 1 equiv). An aliquot was removed from the reaction vial and analyzed by $^{19}$F NMR spectroscopy to determine the internal standard yield of 2a.
Table 4.2. Structure of screened photocatalysts.\textsuperscript{57-58, 62-64}
Table 4.3. Reaction optimization.

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<tr>
<th>entry</th>
<th>PC</th>
<th>base</th>
<th>base equiv</th>
<th>solvent</th>
<th>% yield (^a)</th>
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<td>PhCF₃</td>
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<td>PhCF₃</td>
<td>16</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃</td>
<td>0</td>
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<td>14</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>PhCF₃</td>
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<td>PhCF₃</td>
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<td>PhCF₃</td>
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<td>Cs₂CO₃</td>
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<td>PhCF₃</td>
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<td>PhCO₂K</td>
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<td>PhCF₃</td>
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<td>PhCF₃</td>
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<td>PhCF₃</td>
<td>7</td>
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<td>PhCF₃</td>
<td>18</td>
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<tr>
<td>29</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃</td>
<td>59</td>
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<td>30</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>PhCF₃ (0.1 M)</td>
<td>67</td>
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<tr>
<td>31</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>PhCF₃ (0.05 M)</td>
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<tr>
<td>32</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃ (0.02 M)</td>
<td>56</td>
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<td>33</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃ (0.01 M)</td>
<td>56</td>
</tr>
<tr>
<td>34</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>PhCF₃ (0.07 M)</td>
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<tr>
<td>35</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>THF (0.05 M)</td>
<td>19</td>
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<tr>
<td>36</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>Ether (0.05 M)</td>
<td>39</td>
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<tr>
<td>37</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>CH₂Cl₂ (0.05 M)</td>
<td>47</td>
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<tr>
<td>38</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>DMF (0.05 M)</td>
<td>50</td>
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<tr>
<td>39</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>DMSO (0.05 M)</td>
<td>34</td>
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<tr>
<td>40</td>
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<td>0.65</td>
<td>Methanol (0.05 M)</td>
<td>0</td>
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<tr>
<td>41</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>Toluene (0.05 M)</td>
<td>14</td>
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<tr>
<td>42</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>MeCN (0.05 M)</td>
<td>55</td>
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<tr>
<td>43</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>Acetone (0.05 M)</td>
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<tr>
<td>44</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>1,2-DCE (0.05 M)</td>
<td>65</td>
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<tr>
<td>45</td>
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<td>0.65</td>
<td>DMA (0.05 M)</td>
<td>28</td>
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<tr>
<td>46</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>NMP (0.05 M)</td>
<td>30</td>
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<tr>
<td>47</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>EtOAc (0.05 M)</td>
<td>46</td>
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<tr>
<td>48</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>CHCl₃ (0.05 M)</td>
<td>6</td>
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<td>49</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>NO₂Ph (0.05 M)</td>
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<tr>
<td>50</td>
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<td>Bu₄N[OP(O)(OBu)₂]</td>
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<td>HFIP (0.05 M)</td>
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<tr>
<td>51</td>
<td>A</td>
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<td>0.65</td>
<td>C₅H₅N (0.05 M)</td>
<td>27</td>
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<tr>
<td>52</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>NO₂Me (0.05 M)</td>
<td>0</td>
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<tr>
<td>53</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>t-BuOH (0.05 M)</td>
<td>73</td>
</tr>
<tr>
<td>54</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>t-BuOH/PhCF₃ (1:1, 0.05 M)</td>
<td>83</td>
</tr>
<tr>
<td>55</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>t-BuOH/PhCF₃ (2:1, 0.05 M)</td>
<td>78</td>
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<tr>
<td>56</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>t-BuOH/PhCF₃ (1:2, 0.05 M)</td>
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<td>57</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>PhCF₃ (0.05 M) @ 60 °C</td>
<td>45</td>
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<tr>
<td>58</td>
<td>A</td>
<td>Bu₄N[OP(O)(OBu)₂]</td>
<td>0.65</td>
<td>1,2-DCE (0.05 M) @ 60 °C</td>
<td>62</td>
</tr>
</tbody>
</table>

\(^a\)Yield determined by \(^19\)F NMR spectroscopy using 1,3,5-trifluorobenzene as the internal standard.
4.4.2. Substrate and Reagent Synthesis and Characterization

**Photoredox Catalysts**

[\text{Ir(dF(CF}_3\text{ppy})_2(5,5'\text{d(CF}_3\text{bpy})])PF}_6\text{ (A)} was prepared according to a procedure previously reported in the literature. Spectral data matched values reported in the literature.  

[\text{Ir(dF(CF}_3\text{ppy})_2(dtbbpy)])PF}_6\text{ (B)} was prepared as previously reported in the literature. Spectral data matched values reported in the literature.

[\text{Ir(dF(Me)ppy})_2(dtbbpy)])PF}_6\text{ (C)} was prepared according to a procedure reported in the literature. Spectral data matched values reported in the literature.

**Tetrabutylammonium dibutylphosphate**

Tetrabutylammonium dibutylphosphate was prepared as previously reported in the literature. Spectral data matched values reported in the literature.
**Substrate Synthesis**

**General Procedure A for sulfonamide coupling with carboxylic acids**

In a flame-dried round bottom flask under inert atmosphere, carboxylic acid (1.1 equiv) was dissolved in dry CH$_2$Cl$_2$ (0.1 M with respect to aryl sulfonamide). Aryl sulfonamide (1 equiv) and DMAP (0.1 equiv) were sequentially added in one portion each and the mixture was stirred for approximately 1 min at RT. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 equiv) was added in one portion and the reaction was stirred at room temperature under an argon atmosphere for 14-16 hours. The reaction was concentrated *in vacuo* to provide a viscous oil and the residue was purified with flash chromatography on silica gel (0 to 10% acetone in CH$_2$Cl$_2$ gradient). To obtain the products as solids, the concentrated chromatography fractions were triturated with pentane and dried under a vigorous nitrogen stream.

**General Procedure B for Steglich esterification**

In a flame-dried round bottom flask under inert atmosphere, carboxylic acid (1 equiv.) was dissolved in dry CH$_2$Cl$_2$ (0.1 M with respect to carboxylic acid). 4-hydroxybenzenesulfonamide (1.1 equiv.) and DMAP (0.1 equiv.) were sequentially added in one portion each and the mixture was stirred for approximately 1 min at RT. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 equiv) was added in one portion and the reaction was stirred at room
temperature under an argon balloon for 14-16 hours. The reaction was concentrated in vacuo and the residue was purified with flash chromatography on silica gel (CH$_2$Cl$_2$/acetone gradient).
**5-methylhex-4-enoic acid**

![Chemical structure of 5-methylhex-4-enoic acid]

Prepared according to a previous literature report.\(^1\) Spectral data matched values reported in the literature.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) = δ 11.46 (br s, 1H), 5.13 – 5.07 (m, 1H), 2.40 – 2.35 (m, 2H), 2.35-2.28 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H) ppm

**4-cyclobutylidenebutanoic acid**

![Chemical structure of 4-cyclobutylidenebutanoic acid]

Prepared via a Wittig olefination from modified literature procedure.\(^1\) To a suspension of (3-carboxypropyl)triphenylphosphonium bromide (4.29 g, 10 mmol, 2 equiv.) in THF (20 mL, anhydrous) in a 100 mL RBF with 2 stir bars (for better agitation of resulting suspension) was added sodium bis(trimethylsilyl)amide (20 mL, 20 mmol, 4 equiv., 1 M in THF) dropwise at room temperature. The bright orange mixture was stirred at this temperature for 30 minutes. A solution of cyclobutanone (5 mmol, 0.37 mL, 1 equiv.) in THF (5 mL, anhydrous) was added dropwise. The reaction was refluxed (80 °C) for 7.5 hours. After cooling to room temperature, the reaction contents were transferred to a separatory funnel with 100 mL Et\(_2\)O and 100 mL 1 M NaOH solution. The aqueous layer was washed with Et\(_2\)O (2 x 50 mL), acidified with conc. HCl to pH = 1, and washed with Et\(_2\)O (3 x 50 mL). The organic washes of the acidic aqueous phase were dried with Na\(_2\)SO\(_4\), filtered, and concentrated. The resulting crude was purified by silica gel chromatography (5-35% EtOAc in hexanes) to deliver the title product as a clear colorless oil. 201 mg, 29% yield. Spectral data matched values reported in the literature.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) = δ 11.43 (br s, 1H), 5.04 (tp, \(J = 7.2, 2.6\) Hz, 1H), 2.69 – 2.58 (m, 4H), 2.37 (t, \(J = 7.4\) Hz, 2H), 2.20 (q, \(J = 7.2\) Hz, 2H), 1.93 (p, \(J = 7.9\) Hz, 2H) ppm
$^{13}$C NMR (100 MHz, CDCl$_3$) = δ 179.8, 142.2, 117.9, 34.3, 31.0, 29.3, 23.4, 17.1 ppm
**2-(2-methylprop-1-en-1-yl)benzoic acid**

[Chemical structure image]

Prepared *via* a Wittig olefination according to a previous literature report.\textsuperscript{10} Spectral data matched values reported in the literature.

\textbf{\textsuperscript{1}H NMR}: (500 MHz, CDCl\textsubscript{3}) = δ 10.74 (br s, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.33 – 7.26 (m, 2H), 6.70 (s, 1H), 1.95 (s, 3H), 1.73 (s, 3H) ppm

**4,5-dimethylhex-4-enoic acid**

[Chemical structure image]

Prepared according to a previous literature report.\textsuperscript{11} Spectral data matched values reported in the literature.

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) = δ 11.04 (br s, 1H), 2.38 (app s, 4H), 1.67 (s, 3H), 1.64 (app s, 6H) ppm
5-methyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)hex-4-enamide (4.1a)

Prepared according to General Procedure A. 414 mg, 82%. White solid.

\[ \delta 8.53 \text{ (br s, 1H)}, 8.21 \text{ (d, } J = 8.3 \text{ Hz, 2H)}, 7.82 \text{ (d, } J = 8.4 \text{ Hz, 2H)}, 5.02-4.95 \text{ (m, 1H)}, 2.33-2.22 \text{ (m, 4H)}, 1.64 \text{ (s, 3H)}, 1.54 \text{ (s, 3H)} \text{ ppm} \]

\[ \delta 171.1, 142.1, 136.0, 135.7 \text{ (q, } J = 33.2 \text{ Hz)}, 135.4, 134.7, 129.1, 126.3 \text{ (q, } J = 3.6 \text{ Hz)}, 125.5, 123.2 \text{ (q, } J = 273 \text{ Hz)}, 121.4, 120.9, 36.6, 25.7, 23.2, 17.7 \text{ ppm} \]

\[ \delta -63.33 \text{ ppm} \]

IR (neat): 3125, 2901, 1698, 1459, 1404, 1354, 1221, 1133, 1090, 1061, 1038 cm\(^{-1}\)

HRMS (ESI+) \(m/z\) calculated for \(C_{14}H_{17}F_3NO_3S^+ [M+H]^+\): 335.0803, found 335.0813.

\( R_f = 0.5 \) (1:1, Hex:EtOAc), one streaky yellow spot, KMnO\(_4\), UV
N-((4-fluorophenyl)sulfonyl)-5-methylhex-4-enamide (4.1b)

Prepared according to General Procedure A. 403 mg, 71%. White solid.

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 8.76 – 8.62 (m, 1H), 8.12 – 8.07 (m, 2H), 7.24 – 7.19 (m, 2H), 4.98 (t, $J$ = 6.9 Hz, 1H), 2.31 – 2.22 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H ppm)

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 170.7, 166.1 (d, $J$ = 257 Hz), 134.7, 134.6 (d, $J$ = 3.1 Hz), 131.5 (d, $J$ = 9.8 Hz), 121.5, 116.4 (d, $J$ = 22.8 Hz), 35.7, 25.8, 23.2, 17.8 ppm

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -102.64 – -102.74 (m) ppm

IR (neat) 3190, 2914, 1696, 1594, 1495, 1455, 1356, 1223, 1180, 1135 cm$^{-1}$

HRMS (EI+) m/z calculated for C$_{13}$H$_{16}$FNO$_3$S [M]$^+$: 285.0835, found 285.0834.

$R_f$ = 0.4 (1:1, Hex:EtAOc), one streaky yellow spot, KMnO$_4$, UV
N-((4-chlorophenyl)sulfonyl)-5-methylhex-4-enamide (4.1c)

Prepared according to General Procedure A. 401 mg, 63%. White solid.

$^1$H NMR (700 MHz, CDCl$_3$) = $\delta$ 8.85 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 4.97 (t, $J = 6.4$ Hz, 1H), 2.33 – 2.21 (m, 4H), 1.63 (s, 3H), 1.53 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 171.0, 140.9, 137.0, 134.6, 130.0, 129.4, 121.5, 36.6, 25.7, 23.2, 17.8 ppm

IR (neat) 3244, 2971, 1727, 1577, 1433, 1411, 1331, 1282, 1181, 1081 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{13}$H$_{17}$ClNO$_3$S [M+H]$^+$: 302.0612, found 302.0617.

Rf: (1:19 – Acetone:DCM) = 0.49
N-((4-bromophenyl)sulfonyl)-5-methylhex-4-enamide (4.1d)

Prepared according to General Procedure A. 664 mg, 48%. White solid.

$^1$H NMR (700 MHz, CDCl$_3$) = δ 8.81 (s, 1H), 7.92 (d, $J = 8.6$ Hz, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 5.00 – 4.95 (m, 1H), 2.31 – 2.22 (m, 4H), 1.64 (s, 3H), 1.53 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = δ 170.9, 137.6, 134.6, 132.4, 130.0, 129.5, 121.5, 36.6, 25.8, 23.2, 17.8 ppm

IR (neat) 3246, 2970, 1728, 1573, 1433, 1411, 1388, 1331, 1123, 1084 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{13}$H$_{17}$BrNO$_3$S [M+H]$^+$: 346.0107, found 346.0117.

$R_f$ = 0.5 (1:1, Hex:EtOAc), one streaky yellow spot, KMnO$_4$, UV
N-((4-iodophenyl)sulfonyl)-5-methylhex-4-enamide (4.1e)

Prepared according to General Procedure A. 301 mg, 77%. White solid.

$^1$H NMR (400 MHz, CDCl$_3$) = $\delta$ 8.11 (br s, 1H), 7.91 (d, $J = 8.7$ Hz, 2H), 7.76 (d, $J = 8.6$ Hz, 2H), 5.04 – 4.95 (m, 1H), 2.29 – 2.23 (m, 4H), 1.67 (s, 3H), 1.56 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 170.3, 138.4, 138.3, 135.1, 129.9, 121.5, 102.2, 36.7, 25.8, 23.22, 17.8 ppm

IR (neat) 3248, 2908, 1728, 1567, 1434, 1410, 1384, 1330, 1170, 1084 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{13}$H$_{17}$INO$_3$S [M+H]$^+$: 393.9968, found 393.9978.

Rf: (1:19 – Acetone:DCM) = 0.63.
N-((4-cyanophenyl)sulfonyl)-5-methylhex-4-enamide (4.1f)

Prepared according to **General Procedure A**. 213 mg, 33%. White solid.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 8.75 (br s, 1H), 8.19 (d, $J$ = 8.3 Hz, 2H), 7.85 (d, $J$ = 8.3 Hz, 2H), 5.01 – 4.93 (m, 1H), 2.33 – 2.20 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = $\delta$ 170.9, 142.7, 134.4, 132.9, 129.3, 121.4, 117.7, 117.7, 117.2, 36.6, 25.8, 23.1, 17.8 ppm

**IR** (neat) 3203, 2916, 2235, 1699, 1444, 1402, 1355, 1288, 1187, 1170, 1084 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{14}$H$_{17}$N$_2$O$_3$S $[M+H]^+$: 293.0954, found 293.0968.

**$R_f$**: (1:19 – Acetone:DCM) = 0.52.
5-methyl-N-((4-(trifluoromethoxy)phenyl)sulfonyl)hex-4-enamide (4.1g)

Prepared according to **General Procedure A.** 244 mg, 58%. White solid.

**$^1$H NMR** (400 MHz, CDCl$_3$) = \( \delta \) 8.21 (br s, 1H), 8.13 (d, \( J = 8.9 \) Hz, 2H), 7.37 (d, \( J = 8.8 \) Hz, 2H), 5.03 – 4.96 (m, 1H), 2.32 – 2.22 (m, 4H), 1.66 (s, 3H), 1.55 (s, 3H) ppm

**$^{13}$C NMR** (175 MHz, CDCl$_3$) = \( \delta \) 170.6, 153.3, 136.8, 134.9, 131.0, 121.5, 120.8, 120.3 (q, \( J = 260 \) Hz) 36.7, 25.8, 23.2, 17.9 ppm

**$^{19}$F NMR** (377 MHz, CDCl$_3$) = \( \delta \) -57.68 ppm

**IR** (neat): 3142, 2902, 1698, 1592, 1457, 1408, 1381, 1354, 1300, 1241 cm$^{-1}$

**HRMS (ESI+)** $m/z$ calculated for C$_{14}$H$_{17}$F$_3$NO$_4$S$^+ \ [M+H]^+$: 352.0825, found 352.0834.

$R_f$ (1:9 – Acetone:DCM) = 0.81.
Methyl 4-(N-(5-methylhex-4-enoyl)sulfamoyl)benzoate (4.1h)

Prepared according to **General Procedure A**. 456 mg, 70%. White solid.

**1H NMR** (500 MHz, CDCl$_3$) = δ 9.02 (br s, 1H), 8.19 (d, $J$ = 8.6 Hz, 2H), 8.12 (d, $J$ = 8.6 Hz, 2H), 4.99 – 4.93 (m, 1H), 3.96 (s, 3H), 2.33 – 2.27 (m, 2H), 2.27 – 2.20 (m, 2H), 1.61 (s, 3H), 1.51 (s, 3H) ppm

**13C NMR** (176 MHz, CDCl$_3$) = δ 171.1, 165.7, 142.5, 135.0, 134.5, 130.2, 128.5, 121.5, 52.9, 36.6, 25.7, 23.1, 17.7 ppm

**IR** (neat) 3236, 2962, 1719, 1435, 1400, 1349, 1279, 1175, 1116, 1084 cm$^{-1}$

**HRMS (ESI+) m/z** calculated for C$_{15}$H$_{20}$NO$_5$S$^+$ [M+H]$^+$: 326.1057, found 326.1060.

**R$_f$** (2:3 – EtOAc:Hex) = 0.48.
**N-([1,1'-biphenyl]-4-ylsulfonyl)-5-methylhex-4-enamide (4.1i)**

Prepared according to **General Procedure A**. 531 mg, 70%. Colorless foam.

**$^1$H NMR** (500 MHz, CDCl$_3$) = δ 9.16 (br s, 1H), 8.15 (d, $J = 8.5$ Hz, 2H), 7.75 (d, $J = 8.5$ Hz, 2H), 7.63 – 7.56 (m, 2H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.46 – 7.39 (m, 1H), 5.06 – 4.96 (m, 1H), 2.39 – 2.32 (m, 2H), 2.32 – 2.24 (m, 2H), 1.63 (s, 3H), 1.53 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = δ 171.2, 147.0, 139.2, 137.1, 134.2, 129.2, 129.0, 128.8, 127.7, 127.5, 121.6, 36.6, 25.7, 23.2, 17.7 ppm

**IR** (neat) 3234, 2912, 1693, 1594, 1481, 1433, 1338, 1165, 1124, 1086 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{19}$H$_{22}$NO$_3$S$^+ [M+H]$^+$: 344.1315, found 344.1318

$R_f$: (1:9 – Acetone:DCM) = 0.89.
**N-((4-methoxyphenyl)sulfonyl)-5-methylhex-4-enamide (4.1j)**

Prepared according to General Procedure A. 743 mg, 64%. White solid.

**$^1$H NMR** (700 MHz, CDCl$_3$) = $\delta$ 8.95 (br s, 1H), 7.99 (d, $J$ = 9.0 Hz, 2H), 6.99 (d, $J$ = 9.0 Hz, 2H), 4.99 – 4.95 (m, 1H), 3.87 (s, 3H), 2.29 – 2.21 (m, 4H), 1.62 (s, 3H), 1.52 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = $\delta$ 171.0, 164.1, 134.2, 130.8, 130.0, 121.7, 114.2, 55.8, 36.5, 25.7, 23.2, 17.7 ppm

**IR** (neat) 3231, 2914, 1696, 1595, 1579, 1498, 1437, 1339, 1261, 1158 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{14}$H$_{20}$NO$_4$S$^+$ [M+H]$^+$: 298.1108, found 298.1117.

**Rr** = 0.7 (1:1, Hex:EtOAc), one streaky yellow spot, KMnO$_4$, UV.
4-cyclobutylidene-N-((4-(trifluoromethyl)phenyl)sulfonyl)butanamide (4.1k)

Prepared according to **General Procedure A**. 175 mg, 41%. White solid.

**$^1$H NMR** (700 MHz, CDCl$_3$) = $\delta$ 8.67 (br s, 1H), 8.22 (d, $J$ = 8.3 Hz, 2H), 7.83 (d, $J$ = 8.4 Hz, 2H), 4.94 (tp, $J$ = 7.2, 2.4 Hz, 1H), 2.58 (t, $J$ = 7.9 Hz, 2H), 2.54 (t, $J$ = 7.9 Hz, 2H), 2.30 (t, $J$ = 7.2 Hz, 2H), 2.15 (q, $J$ = 7.2 Hz, 2H), 1.89 (p, $J$ = 7.9 Hz, 2H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = $\delta$ 170.8, 143.8, 142.1, 135.8 (q, $J$ = 33.3 Hz), 129.2, 126.3 (q, $J$ = 3.7 Hz), 123.2 (q, $J$ = 273 Hz), 117.2, 36.5, 31.0, 29.3, 23.2, 17.0 ppm

**$^{19}$F NMR** (377 MHz, CDCl$_3$) = $\delta$ -63.3 ppm

**IR** (neat) 3134, 2920, 1699, 1458, 1404, 1357, 1319, 1165, 1132, 1089 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{15}$H$_{17}$F$_3$NO$_3$S$^+$ [M+H]$^+$: 348.0876, found 348.0887.

**Rf**: (1:9 – Acetone:DCM) = 0.79
2-(2-methylprop-1-en-1-yl)-N-((4-(trifluoromethyl)phenyl)sulfonyl)benzamide (4.11)

Prepared according to General Procedure A. 194 mg, 81%. Colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) = $\delta$ 9.13 (s, 1H), 8.28 (d, $J$ = 8.3 Hz, 2H), 7.84 (d, $J$ = 8.4 Hz, 3H), 7.49 (t, $J$ = 7.5 Hz, 1H), 7.33 (t, $J$ = 7.7 Hz, 1H), 7.17 (d, $J$ = 7.7 Hz, 1H), 6.40 (s, 1H), 2.02 (s, 3H), 1.67 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 165.2, 142.2, 142.2, 137.1, 135.7 (q, $J$ = 33.2 Hz), 132.7, 131.1, 130.4, 130.2, 129.4, 127.5, 126.2 (q, $J$ = 3.5 Hz), 123.2 (q, $J$ = 273 Hz), 122.9, 26.0, 19.5 ppm

$^{19}$F NMR (377 MHz, CDCl$_3$) = $\delta$ -63.30 ppm

IR (neat) 3106, 2912, 1679, 1596, 1428, 1404, 1361, 1321, 1164, 1122 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{18}$H$_{17}$F$_3$NO$_3$S [M+H]+$^+$: 384.0876, found 384.0881.

$R_f$: (1:19 – Acetone:DCM, 1 drop HOAc) = 0.65.

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methyl ((4-(trifluoromethyl)phenyl)sulfonyl)carbamate

In a 100 mL flame-dried flask, 4-(trifluoromethyl)benzenesulfonamide (901 mg, 4.0 mmol, 1 equiv.) was suspended in 40 mL dry dichloromethane. The reaction was cooled to 0 °C, then triethylamine (1.56 mL, 11.2 mmol, 2.8 equiv.) was added dropwise. Methyl chloroformate (0.37 mL, 4.8 mmol, 1.2 equiv.) was added dropwise and the reaction was stirred at 0 °C for 30 minutes. At this point, all starting material was consumed (TLC). The reaction was allowed to warm to room temperature, then transferred to a separatory funnel with 10 mL additional dichloromethane. The organic phase was washed with 50 mL 1 M HCl, 50 mL water, dried over MgSO₄, and concentrated under reduced pressure to afford the product as a white solid (863 mg, 76%).

Partial characterization is provided below.

¹H NMR (400 MHz, CDCl₃) = δ 8.20 (d, J = 8.2 Hz, 2H), 8.08 – 7.50 (br s, 1H), 7.83 (d, J = 8.3 Hz, 2H), 3.73 (s, 3H) ppm

¹⁹F NMR (377 MHz, CDCl₃) = δ -63.33 ppm
3-methylbut-2-en-1-yl ((4-(trifluoromethyl)phenyl)sulfonyl)carbamate (4.1m)

Prepared according to a modified literature procedure.\textsuperscript{12} To a 20 mL microwave vial with a stir bar was added methyl ((4-(trifluoromethyl)phenyl)sulfonyl)carbamate (350 mg, 1.24 mmol, 1 equiv.) and 3-methylbut-2-en-1-ol (10 mL, 98.5 mmol, 80 equiv.). The vial was sealed and heated with microwave irradiation at 100 °C for 30 minutes. Upon cooling to room temperature, the alcohol was distilled off under reduced pressure at 50 °C using a BioChromato Smart Evaporator. The residue was purified using flash chromatography on silica gel (0 – 10% acetone in DCM gradient) to give the product as a white solid. (254 mg, 61%).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) = δ 8.19 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.40 (br s, 1H), 5.28 – 5.20 (m, 1H), 4.58 (d, J = 7.2 Hz, 2H), 1.74 (s, 3H), 1.66 (s, 3H) ppm

\textsuperscript{13}C NMR (176 MHz, CDCl\textsubscript{3}) = δ 150.4, 142.0, 141.5, 135.7 (q, J = 33.3 Hz), 129.2, 126.3 (q, J = 3.7 Hz), 123.2 (q, J = 273 Hz), 117.1, 64.3, 25.8, 18.1 ppm

\textsuperscript{19}F NMR (377 MHz, CDCl\textsubscript{3}) = δ -63.30 ppm

IR (neat) 3257, 1769, 1443, 1407, 1354, 1322, 1213, 1157, 1121, 1112 cm\textsuperscript{-1}

HRMS (ESI+) \textit{m/z} calculated for C\textsubscript{13}H\textsubscript{19}F\textsubscript{3}N\textsubscript{2}O\textsubscript{4}S\textsuperscript{+} [M+NH\textsubscript{4}\textsuperscript{+}]: 355.0934, found 355.0947.

\textit{Rf}: (1:19 – Acetone:DCM) = 0.17.
**N-((3-fluorophenyl)sulfonyl)-5-methylhex-4-enamide (4.1n)**

Prepared according to **General Procedure A.** 260 mg, 46%. Colorless oil.

**1H NMR** (700 MHz, CDCl₃) = δ 8.85 (s, 1H), 7.89 – 7.85 (m, 1H), 7.76 (dt, J = 8.0, 2.0 Hz, 1H), 7.54 (td, J = 8.1, 5.2 Hz, 1H), 7.35 (tdd, J = 8.3, 2.5, 0.6 Hz, 1H), 5.00-4.96 (m, 1H), 2.33 – 2.23 (m, 4H), 1.63 (s, 3H), 1.53 (s, 3H) ppm

**13C NMR** (176 MHz, CDCl₃) = δ 170.9, 162.3 (d, J = 252 Hz), 140.6 (d, J = 7.2 Hz), 134.6, 130.9 (d, J = 7.7 Hz), 124.3 (d, J = 3.3 Hz), 121.5, 121.4 (d, J = 21 Hz), 115.8 (d, J = 25 Hz), 36.6, 25.7, 23.2, 17.7 ppm

**19F NMR** (376 MHz, CDCl₃) = δ -109.30 ppm

**IR** (neat) 3241, 3068, 2915, 1724, 1594, 1478, 1429, 1406, 1335, 1229, 1118 cm⁻¹

**HRMS** (ESI⁺) m/z calculated for C₁₃H₁₇FNO₃S [M+H]⁺: 286.0908, found 286.0907.

**Rf:** (1:9 – Acetone:DCM) = 0.65.
N-((3,4-difluorophenyl)sulfonyl)-5-methylhex-4-enamide (4.1o)

Prepared according to **General Procedure A**. 387 mg, 58%. White solid.

**$^1$H NMR** (700 MHz, CDCl$_3$) = $\delta$ 8.78 (s, 1H), 7.95 – 7.90 (m, 1H), 7.90 – 7.86 (m, 1H), 7.34 (q, $J = 8.9$ Hz, 1H), 4.99 (t, $J = 7.0$ Hz, 1H), 2.33 – 2.23 (m, 4H), 1.64 (s, 3H), 1.55 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = $\delta$ 170.9, 151.5 (dd, $J = 259.5$, 12.7 Hz), 150.1 (dd, $J = 255$, 13.4 Hz), 135.2 (dd, $J = 5.6$, 4.1 Hz), 134.8, 126.0 (dd, $J = 4.0$, 7.8 Hz), 121.4, 118.6 (dd, $J = 20.5$, 1.4 Hz), 118.2 (d, $J = 18.7$ Hz), 36.6, 25.7, 23.2, 17.8 ppm

**$^{19}$F NMR** (376 MHz, CDCl$_3$) = $\delta$ -126.95 (m), -133.25 (dt, $J = 20.6$, 8.5 Hz) ppm

**IR** (neat) 3196, 2919, 1702, 1606, 1511, 1441, 1348, 1277, 1174, 1123, 1075 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{13}$H$_{16}$F$_2$NO$_3$S [M+H]$^+$: 304.0813, found 304.0817.

**Rf**: (1:19 – Acetone:DCM, 1 drop HOAc) = 0.71.
4-sulfamoylphenyl thiophene-2-carboxylate

Prepared according to General Procedure B. 318 mg, 51%. Tan solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.13 (dd, $J$ = 5.0, 1.3 Hz, 1H), 8.06 (dd, $J$ = 3.8, 1.3 Hz, 1H), 7.91 (d, $J$ = 8.8 Hz, 2H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.44 (s, 2H), 7.33 (dd, $J$ = 5.0, 3.8 Hz, 1H) ppm

4-sulfamoylphenyl cyclohexanecarboxylate

Prepared according to General Procedure B. 430 mg, 69%. White solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 (d, $J$ = 8.7 Hz, 2H), 7.23 (d, $J$ = 8.7 Hz, 2H), 4.79 (br s, 2H), 2.58 (tt, $J$ = 11.2, 3.5 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.88 – 1.78 (m, 2H), 1.74 – 1.66 (m, 1H), 1.65 – 1.56 (m, 2H), 1.46 – 1.26 (m, 3H) ppm

1-(tert-butyl) 2-(4-sulfamoylphenyl) (S)-pyrrolidine-1,2-dicarboxylate

Prepared according to General Procedure B. 606 mg, 77%. Pale yellow solid. At room temperature, N-Boc rotamers of this compound are well-resolved by $^1$H NMR.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (app dd, $J$ = 20.0, 8.7 Hz, 2H), 7.24 (d, $J$ = 8.7 Hz, 2H), 5.08 (br s, 2H), 4.48 (ddd, $J$ = 19.4, 8.5, 4.4 Hz, 1H), 3.67 – 3.40 (m, 2H), 2.48 – 2.29 (m, 1H), 2.23 – 2.11 (m, 1H), 2.11 – 1.88 (m, 2H), 1.45 (app d, $J$ = 13.1 Hz, 9H) ppm
**4-sulfamoylphenyl 2-phenylacetate**

![Structure](image)

Prepared according to general procedure B. 446 mg, 70%. White solid.

**1H NMR** (700 MHz, CDCl$_3$) $\delta$ 7.92 (d, $J = 8.5$ Hz, 2H), 7.40 – 7.30 (m, 5H), 7.22 (d, $J = 8.5$ Hz, 2H), 4.84 (br s, 2H), 3.89 (s, 2H) ppm

**4-(N-(5-methylhex-4-enoyl)sulfamoyl)phenyl thiophene-2-carboxylate (4.1p)**

![Structure](image)

Prepared according to General Procedure A. 195 mg, 50%. White solid.

**1H NMR** (700 MHz, CDCl$_3$) = $\delta$ 8.60 (br s, 1H), 8.14 (d, $J = 8.7$ Hz, 2H), 8.00 (dd, $J = 3.8$, 0.9 Hz, 1H), 7.72 (dd, $J = 5.0$, 0.9 Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.21 – 7.19 (m, 1H), 5.01 (t, $J = 6.9$ Hz, 1H), 2.33 – 2.23 (m, 4H), 1.66 (s, 3H), 1.56 (s, 3H) ppm

**13C NMR** (176 MHz, CDCl$_3$) = $\delta$ 170.5, 159.7, 154.8, 135.8, 135.4, 134.5, 134.4, 131.8, 130.3, 128.3, 122.3, 121.5, 36.5, 25.6, 23.1, 17.7 ppm

**IR** (neat): 3244, 2254, 1718, 1434, 1339, 1252, 1203, 1179, 1157, 1060 cm$^{-1}$

**HRMS (ESI+)** $m/z$ calculated for C$_{18}$H$_{20}$NO$_5$S$_2^+$ [M+H]$^+$: 394.0777, found 394.0782.

**Rf**: (1:6 – Acetone:DCM) = 0.81.
4-(N-(5-methylhex-4-enoxy)sulfamoyl)phenyl 5-methylhex-4-enoate (4.1q)

Prepared according to **General Procedure A** from 4-hydroxybenzenesulfonamide using 2.1 equiv. of 5-methylhex-4-enoic acid, 2.6 equiv. EDC-HCl, and 0.2 equiv DMAP. 113 mg, 57%. Viscous, colorless oil.

**$^1$H NMR** (700 MHz, CDCl$_3$) $\delta$ 8.35 (br s, 1H), 8.09 (d, $J$ = 8.8 Hz, 2H), 7.27 (d, $J$ = 8.5 Hz, 2H), 5.16 (t, $J$ = 7.2 Hz, 1H), 5.02 – 4.98 (m, 1H), 2.61 (t, $J$ = 7.4 Hz, 2H), 2.44 (q, $J$ = 7.3 Hz, 2H), 2.30 – 2.23 (m, 4H), 1.72 (s, 3H), 1.66 (s, 6H), 1.56 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) $\delta$ 171.2, 170.4, 155.2, 135.7, 134.8, 134.1, 130.3, 122.4, 121.8, 121.6, 36.6, 34.7, 25.9, 25.8, 23.6, 23.2, 17.9, 17.8 ppm

**IR** (neat) 3242, 2915, 2915, 1763, 1723, 1696, 1590, 1435, 1204, 1177, 1159 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{20}$H$_{28}$NO$_5$S$^+$ [M+H]$^+$: 394.1683, found 394.1688.

**Rf**: (1:19 – Acetone:DCM) = 0.68.
1-(tert-butyl) 2-(4-(N-(5-methylhex-4-enyl)sulfamoyl)phenyl) (S)-pyrrolidine-1,2-dicarboxylate (4.1r)

Prepared according to General Procedure A. 458 mg, 58%. Clear, glassy solid. At room temperature, N-Boc rotamers of this compound are well-resolved by $^1$H and $^{13}$C NMR.

$^1$H NMR (500 MHz, CDCl$_3$) = $\delta$ 8.64 (br s, 1H), 8.09 (app dd, $J = 19.8, 8.5$ Hz, 2H), 7.29 (app t, $J = 8.1$ Hz, 2H), 5.03 – 4.96 (m, 1H), 4.50 (app ddd, $J = 31.8, 8.5, 4.4$ Hz, 1H), 3.67 – 3.42 (m, 2H), 2.47 – 2.31 (m, 1H), 2.31 – 2.21 (m, 4H), 2.21 – 2.10 (m, 1H), 2.10 – 1.91 (m, 2H), 1.64 (s, 3H), 1.54 (s, 3H), 1.46 (app d, $J = 13.6$ Hz, 9H).

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 171.1, 170.9, 170.6, 170.6, 155.1, 154.8, 154.7, 153.8, 136.1, 136.0, 134.6, 134.6, 130.5, 130.3, 122.3, 121.9, 121.6, 121.6, 80.7, 80.5, 59.3, 59.2, 46.8, 46.6, 45.2, 36.6, 31.1, 30.1, 28.8, 28.6, 25.8, 25.5, 25.3, 23.9, 23.2, 17.8 ppm

IR (neat) 3202, 2976, 2931, 1772, 1670, 1403, 1366, 1347, 1204, 1124 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for $C_{23}H_{33}N_2O_7S^+$ [M+H]$^+$: 481.2003, found 481.2013

Rf: (1:6 – Acetone:DCM) = 0.62
4-(N-(5-methylhex-4-enoyl)sulfamoyl)phenyl cyclohexanecarboxylate (4.1s)

Prepared according to General Procedure A. 345 mg, 69%. White solid.

$^1$H NMR (700 MHz, CDCl$_3$) = δ 8.38 (br s, 1H), 8.08 (d, $J$ = 8.8 Hz, 2H), 7.26 (d, $J$ = 8.8 Hz, 2H), 5.03 – 4.98 (m, 1H), 2.58 (tt, $J$ = 11.2, 3.4 Hz, 1H), 2.29 – 2.23 (m, 4H), 2.09 – 2.03 (m, 2H), 1.85 – 1.79 (m, 2H), 1.72 – 1.67 (m, 1H), 1.66 (s, 3H), 1.63 – 1.57 (m, 2H) 1.56 (s, 3H), 1.41 – 1.27 (m, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = δ 173.8, 170.4, 155.4, 135.6, 134.8, 130.3, 122.3, 121.6, 43.3, 36.6, 29.0, 25.8, 25.8, 25.4, 23.2, 17.8 ppm

IR (neat) 3255, 2932, 2854, 1755, 1721, 1685, 1585, 1448, 1406, 1147 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{20}$H$_{28}$NO$_5$S$^+$ [M+H]$^+$: 394.1683, found 394.1684.

Rf: (2:3 – EtOAc:Hex) = 0.52.
4-(N-(5-methylhex-4-enyl)sulfamoyl)phenyl 2-phenylacetate (4.1t)

Prepared according to General Procedure A. 131 mg, 55%. White solid. Isolated with a small amount of an inseparable impurity (<10%).

$^1$H NMR (700 MHz, CDCl$_3$) = $\delta$ 8.80 (s, 1H), 8.07 (d, $J = 8.8$ Hz, 2H), 7.46 – 7.30 (m, 5H), 7.27 (d, $J = 8.8$ Hz, 2H), 5.01 – 4.94 (m, 1H), 3.90 (s, 2H), 2.27 – 2.21 (m, 4H), 1.63 (s, 3H), 1.53 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 170.8, 169.3, 154.9, 135.8, 134.3, 132.8, 130.2, 129.3, 128.9, 127.6, 122.1, 121.5, 41.3, 36.4, 25.6, 23.0, 17.6 ppm

IR (neat) 3122, 2930, 1751, 1686, 1587, 1445, 1406, 1354, 1209, 1188 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{21}$H$_{24}$NO$_5$S$^+$ [M+H]$^+$: 402.1370, found 402.1377

Rf: (2:3 – EtOAc:Hex) = 0.47.
4,5-dimethyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)hex-4-enamide (4.1u)

Prepared according to General Procedure A. 238 mg, 68%. White solid. Isolated with a small amount of an inseparable impurity (<10%).

¹H NMR (400 MHz, CDCl₃) = δ 8.21 (d, J = 8.2 Hz, 2H), 8.05 (br s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 2.32 (app s, 4H), 1.63 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H) ppm

¹³C NMR (176 MHz, CDCl₃) = δ 170.8, 142.0, 135.8, 129.2, 127.6, 126.3, 124.8, 123.2, 35.1, 29.2, 20.8, 20.3, 17.9 ppm

¹⁹F NMR (376 MHz, CDCl₃) = δ -63.33 ppm

IR (neat) 3266, 2931, 2862, 1730, 1421, 1404, 1344, 1320, 1172, 1138 cm⁻¹

HRMS (ESI+) m/z calculated for C₁₅H₁₉F₃NO₃S⁺ [M+H]⁺: 350.1032, found 350.1034

Rf: (1:19 – Acetone:DCM) = 0.74.
**N-((4-(trifluoromethyl)phenyl)sulfonyl)pent-4-enamide (4.3)**

Prepared according to General Procedure A using commercially available 4-pentenoic acid.

247 mg, 40%. White solid.

$^1$H NMR (700 MHz, CDCl$_3$) = $\delta$ 8.69 (br s, 1H), 8.21 (d, $J = 8.2$ Hz, 2H), 7.83 (d, $J = 8.2$ Hz, 2H), 5.71 (ddt, $J = 16.9$, 10.5, 6.5 Hz, 1H), 5.01 – 4.95 (m, 2H), 2.39 (t, $J = 7.3$ Hz, 2H), 2.32 (q, $J = 6.9$ Hz, 2H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 170.3, 141.9, 135.8 (q, $J = 33.2$ Hz), 135.7, 129.2, 126.3 (q, $J = 3.6$ Hz), 123.2 (q, $J = 273$ Hz), 116.7, 35.7, 28.2 ppm

$^{19}$F NMR (376 MHz, CDCl$_3$) = $\delta$ -63.34 ppm

IR (neat) 3108, 2985, 1696, 1460, 1406, 1357, 1325, 1158, 1126, 1090 cm$^{-1}$

HRMS (ESI$^+$) $m/z$ calculated for C$_{12}$H$_{13}$F$_3$NO$_3$S$^+$ [M+H]$^+$: 308.0563, found 308.0563

Rf: (2:3 – EtOAc:Hex, 1 drop HOAc) = 0.54.
**Procedure for the preparation of aniline S4b** was adapted from a procedure previously reported.\textsuperscript{13} A solution of aniline (730 μL, 8.00 mmol) and tert-butyl-(2-methylbut-3-en-2-yl) carbonate\textsuperscript{14} S4a (2.00 g, 10.8 mmol) in THF (20 mL) and DMF (1 mL) was treated with Pd(PPh\textsubscript{3})\textsubscript{4} (186 mg, 2 mol%) and stirred at room temperature for 20 h. The mixture was diluted with ethyl acetate (20 mL) and washed with brine (15 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (95:5 Hex:EtOAc) to give aniline S4b as a light-yellow oil (947 mg, 73%). All spectra and characterization data matches that previously reported in the literature.\textsuperscript{13,15}

Partial characterization of aniline S4b is provided below.

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) = δ 7.19 – 7.04 (m, 2H), 6.76 – 6.62 (m, 3H), 6.01 (dd, J = 17.5, 10.7 Hz, 1H), 5.26 – 5.01 (m, 2H), 3.70 (s, 1H), 1.39 (s, 7H) ppm

\textbf{HRMS} (ESI+) m/z calculated for C\textsubscript{11}H\textsubscript{15}N (M+H)+ 162.1277, found 162.1275.

Procedure for the preparation of arylsulfonamide 4.4 was adapted from a procedure previously reported.\textsuperscript{15}

\textit{Step 1}: To a solution of aniline S4b (574 mg, 3.56 mmol) in MeCN:H\textsubscript{2}O (10 mL:1.0 mL) under inert atmosphere was added pTsOH-H\textsubscript{2}O (68 mg, 0.36 mmol, 0.1 equiv), and it was heated at 80
°C overnight. After cooling back to room temperature, it was washed with water (20 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was directly used in next step without further purification.

**Step 2:** To a solution of the above crude material in pyridine (5 mL) at room temperature under inert atmosphere was added 4-(trifluoromethyl)benzenesulfonyl chloride (1045 mg, 4.27 mmol, 1.2 equiv). After one hour, EtOAc (20 mL) was added, and it was washed with 10% aq HCl (100 mL). The aqueous layer was extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated. Flash column chromatography (Hex:EtOAc, 10:1) afforded 435 mg (33% over two steps) of compound 4.4 as a white solid.

**1H NMR** (700 MHz, CDCl₃) = δ 7.83 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.44 (dd, J = 8.1, 1.3 Hz, 1H), 7.21 (td, J = 7.7, 1.7 Hz, 1H), 7.13 (td, J = 7.5, 1.3 Hz, 1H), 7.09 (dd, J = 7.6, 1.6 Hz, 1H), 6.63 (s, 1H), 4.95 (ddt, J = 7.0, 5.5, 1.5 Hz, 1H), 2.95 (d, J = 7.1 Hz, 2H), 1.74 (s, 3H), 1.69 (s, 3H) ppm

**13C NMR** (176 MHz, CDCl₃) = δ 143.2, 135.1, 134.6 (q, J = 33.2 Hz), 134.3, 133.7, 130.2, 127.6, 127.5, 126.5, 126.1 (q, J = 3.7 Hz), 123.8, 123.1 (q, J = 272.9 Hz), 121.0, 31.1, 25.6, 17.8 ppm

**19F NMR** (377 MHz, CDCl₃) = δ -63.17 ppm

**IR (neat)** = 3230, 1452, 1405, 1317, 1154, 1128, 1106, 1060, 907, 840, 755, 716, 674 cm⁻¹

**HRMS (ESI+) m/z** calculated for C₁₈H₁₈F₃NO₂S (M+H)+ 370.1083, found 370.1081.
**N-(5-methylhex-4-en-1-yl)-4-(trifluoromethyl)benzenesulfonamide (4.5)**

In a flame-dried flask with a stir bar, lithium aluminum hydride (24 mg, 0.6 mmol, 1.05 equiv) was suspended in 3 mL THF and cooled to -78 °C. A solution of 5-methyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)hex-4-enamide (200 mg, 0.596 mmol, 1 equiv) in 3 mL THF was slowly added to the LAH solution down the side of the flask over ~2 minutes. The reaction was stirred at -78 °C for 3 hours, removed from the dry ice/acetone bath and allowed to warm to RT for 30 minutes. Quenched with 0.5 mL sat. aq. potassium sodium tartrate, added dropwise slowly at RT. The reaction was transferred to a separatory funnel with 50 mL EtOAc and 50 mL sat. aq. potassium sodium tartrate. The organic phase was isolated and the aqueous phase was washed with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified with flash chromatography on silica gel (0 to 25% EtOAc in hexanes gradient) to give the product as a white solid (137 mg, 72%).

**H NMR** (700 MHz, CDCl₃) = δ 8.00 (d, J = 8.1 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 5.01 – 4.96 (m, 1H), 4.76 – 4.49 (m, 1H), 3.01 – 2.96 (m, 2H), 1.96 (q, J = 7.0 Hz, 2H), 1.65 (s, 3H), 1.55 – 1.48 (m, 5H) ppm

**C NMR** (176 MHz, CDCl₃) = δ 143.9, 134.5 (q, J = 33.1 Hz), 133.2, 127.7, 126.4 (q, J = 3.6 Hz), 123.4 (q, J = 273 Hz), 122.8, 43.2, 29.8, 25.8, 25.1, 17.8 ppm

**F NMR** (377 MHz, CDCl₃) = δ -63.15 ppm

**IR** (neat) 3256, 2913, 1431, 1404, 1318, 1294, 1196, 1153, 1122, 1060 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₁₄H₁₉F₃NO₂S⁺ [M+H]⁺: 322.1083, found 322.1088.

**Rf** (1:3 – EtOAc:Hex) = 0.75.
4.4.3. Dearomatized Product Synthesis and Characterization

**Procedure C**

To an oven dried 2-dram vial was added substrate 4.1 (0.2 mmol), NBu₄OP(O)(OBu)₂ (58 mg, 0.13 mmol, 0.65 equiv), and photocatalyst A (2 mg, 1 mol%). The vial contents were then dissolved in a 1:1 mixture of t-BuOH:PhCF₃ (2 mL each, 0.05 M). The reaction solution was degassed by sparging with argon for 15 min. Then the vial was quickly capped and sealed with parafilm. The reaction was irradiated with two, H150 blue Kessil lamps positioned ~5 cm away and cooled with an overhead fan. After 14 h, the reaction was directly concentrated *in vacuo*. The resultant residue was subjected to flash column chromatography over silica providing the pure diene 4.2.
**C8-trifluoromethyl cyclohexadiene-fused sultam (4.2a)**

Prepared according to Procedure C with 67.1 mg, 0.2 mmol of 4.1a. White powder (50.5 mg, 75% yield). R_f = 0.5 (1:1, Hex:EtOAc), one yellow spot, KMnO_4, UV.

![Chemical Structure]

**^1H NMR** (700 MHz, CDCl_3) = δ 7.02 (t, J = 3.2 Hz, 1H), 6.38 (s, 1H), 4.16 (dd, J = 8.4, 5.8 Hz, 1H), 3.49 (s, 1H), 3.19 − 2.99 (m, 2H), 2.58 − 2.42 (m, 2H), 2.20 (dddd, J = 13.3, 10.0, 8.5, 6.6 Hz, 1H), 1.92 (ddddd, J = 13.1, 9.8, 7.1, 5.8 Hz, 1H), 1.14 (s, 3H), 0.79 (s, 3H) ppm

**^13C NMR** (176 MHz, CDCl_3) = δ 172.7, 134.3, 131.3, 127.9 (q, J = 31.4 Hz), 125.8 (q, J = 5.6 Hz), 122.8 (q, J = 272.3 Hz), 67.0, 45.3, 41.4, 30.9, 23.9, 22.0, 19.0, 13.8 ppm

**^19F NMR** (377 MHz, CDCl_3) = δ -69.85 ppm

**IR** (neat) = 2983, 1738, 1392, 1344, 1312, 1297, 1169, 1123, 986, 896, 706 cm⁻¹

**HRMS** (ESI+) m/z calculated for C_{14}H_{16}F_{3}NO_{3}S (M+H)^+ 336.0876, found 336.0874.
C8-fluoro cyclohexadiene-fused sultam (4.2b)

Prepared according to Procedure C with 57.1 mg, 0.2 mmol of 4.1b. Off-white, tan powder (34.1 mg, 60% yield). R_f = 0.5 (1:1, Hex:EtOAc), one yellow spot, KMnO_4, UV.

\[
\text{F} \quad \text{S} \quad \text{N} \\
\text{H} \quad \text{H} \\
\text{H} \quad \text{H} \\
\text{H} \quad \text{H}
\]

^1H NMR (700 MHz, CDCl_3) = \( \delta \) 6.95 – 6.85 (m, 1H), 5.33 (d, \( J = 14.8 \) Hz, 1H), 4.23 – 4.00 (m, 1H), 3.60 – 3.41 (m, 1H), 3.24 – 2.94 (m, 2H), 2.57 – 2.40 (m, 2H), 2.25 – 2.10 (m, 1H), 1.99 – 1.84 (m, 1H), 1.04 (s, 3H), 0.80 (s, 3H) ppm

^13C NMR (176 MHz, CDCl_3) = \( \delta \) 172.8, 157.7 (d, \( J = 257.0 \) Hz), 135.2 (d, \( J = 2.5 \) Hz), 131.3 (d, \( J = 11.5 \) Hz), 99.2 (d, \( J = 18.1 \) Hz), 67.1, 46.5 (d, \( J = 7.5 \) Hz), 41.5 (d, \( J = 1.7 \) Hz), 31.0, 27.0 (d, \( J = 29.8 \) Hz), 22.0, 19.1, 13.4 ppm

^19F NMR (377 MHz, CDCl_3) = \( \delta \) -102.48 (d, \( J = 17.0 \) Hz) ppm

IR (neat) = 2975, 1734, 1719, 1339, 1208, 1180, 1148, 1105, 1006, 954, 847 cm\(^{-1}\)

HRMS (ESI+) \( m/z \) calculated for C_{13}H_{16}FNO_3S (M+H)+ 286.0908, found 286.0910.
**C8-chloro cyclohexadiene-fused sultam (4.2c)**

Prepared according to **Procedure C** with 60.4 mg, 0.2 mmol of 4.1c. Off-white, tan powder (31.5 mg, 52% yield). R_f = 0.3 (7:3, Hex:EtOAc), one yellow spot, KMnO_4, UV.

![Chemical structure](image)

**^1H NMR** (500 MHz, CDCl_3) = δ 6.91 (t, J = 3.4 Hz, 1H), 5.97 – 5.83 (m, 1H), 4.11 (dd, J = 8.5, 5.7 Hz, 1H), 3.46 (q, J = 6.9 Hz, 1H), 3.34 – 3.05 (m, 2H), 2.59 – 2.42 (m, 2H), 2.30 – 2.07 (m, 1H), 2.01 – 1.81 (m, 1H), 1.09 (s, 3H), 0.81 (s, 3H) ppm

**^13C NMR** (176 MHz, CDCl_3) = δ 172.7, 134.4, 132.0, 130.9, 120.3, 66.9, 47.6, 41.6, 33.3, 30.9, 22.0, 19.1, 13.7 ppm

**IR (neat)** = 2971, 2935, 1736, 1676, 1339, 1205, 1175, 983, 953, 839, 643 cm\(^{-1}\)

**HRMS (ESI+) m/z** calculated for C_{13}H_{16}ClNO_3S (M+H)+ 302.0612, found 302.0611.
**C8-bromo cyclohexadiene-fused sultam (4.2d)**

Prepared according to **Procedure C** with 69.2 mg, 0.2 mmol of 4.1d. Off-white, tan powder (45.2 mg, 65% yield). R$_f$ = 0.5 (1:1, Hex:EtOAc), one yellow spot, KMnO$_4$, UV.

\[
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{image}
\end{center}}
\]

$^1$H NMR (400 MHz, CDCl$_3$) = δ 6.85 (t, J = 3.2 Hz, 1H), 6.13 (s, 1H), 4.10 (dd, J = 8.5, 5.7 Hz, 1H), 3.54 – 3.12 (m, 3H), 2.50 (ddd, J = 9.6, 7.4, 2.7 Hz, 2H), 2.18 (dq, J = 16.6, 8.4 Hz, 1H), 1.91 (dq, J = 14.9, 7.9 Hz, 1H), 1.09 (s, 3H), 0.82 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = δ 172.8, 134.2, 132.3, 124.4, 120.2, 66.8, 48.2, 41.4, 35.4, 30.9, 21.9, 19.0, 13.7 ppm

IR (neat) = 2969, 1737, 1471, 1344, 1169, 1124, 1103, 982, 954, 701, 655 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{13}$H$_{16}$BrNO$_3$S (M+H)$^+$ 346.0107, found 346.0105.
**C8-iodo cyclohexadiene-fused sultam (4.2e)**

Prepared according to Procedure C with 78.6 mg, 0.2 mmol of 4.1e. Off-white, tan powder (52.2 mg, 66% yield). R$_f$ = 0.4 (1:1, Hex:EtOAc), one yellow spot, KMnO$_4$, UV.

![Chemical Structure](image)

**$^1$H NMR** (700 MHz, CDCl$_3$) = δ 6.71 (q, $J$ = 3.0 Hz, 1H), 6.41 (d, $J$ = 2.8 Hz, 1H), 4.08 (dt, $J$ = 8.5, 4.0 Hz, 1H), 3.46 – 3.19 (m, 3H), 2.48 (ddd, $J$ = 15.8, 7.7, 4.8 Hz, 2H), 2.26 – 2.09 (m, 1H), 1.90 (ddt, $J$ = 13.8, 10.7, 6.6 Hz, 1H), 1.08 (s, 3H), 0.81 (s, 3H) ppm

**$^{13}$C NMR** (176 MHz, CDCl$_3$) = δ 172.8, 134.0, 132.9, 132.7, 93.4, 66.8, 48.9, 41.4, 39.3, 30.9, 21.9, 19.0, 13.8 ppm

**IR** (neat) = 2970, 2928, 1729, 1330, 1219, 1163, 1134, 951, 822, 716 cm$^{-1}$

**HRMS** (ESI+) $m/z$ calculated for C$_{13}$H$_{16}$INO$_3$S (M+H)$^+$ 393.9968, found 393.9975.
C8-cyano cyclohexadiene-fused sultam (4.2f)

Prepared according to Procedure C with 58.5 mg, 0.2 mmol of 4.1f. Off-white, tan powder (22.7 mg, 39% yield). R<sub>f</sub> = 0.5 (1:9, Acetone:CH<sub>2</sub>Cl<sub>2</sub>), one yellow spot, KMnO<sub>4</sub>, UV.

![Chemical structure](image)

**<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) = δ 6.94 (t, J = 3.0 Hz, 1H), 6.62 (s, 1H), 4.13 (dd, J = 8.6, 5.6 Hz, 1H), 3.49 (td, J = 7.5, 4.1 Hz, 1H), 3.27 – 3.04 (m, 2H), 2.58 – 2.39 (m, 2H), 2.19 (dddd, J = 19.9, 15.0, 10.7, 6.4 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.13 (s, 3H), 0.80 (s, 3H) ppm

**<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) = δ 172.5, 139.3, 133.9, 130.5, 117.3, 112.0, 66.8, 46.0, 41.7, 30.8, 27.7, 22.0, 19.0, 14.2 ppm

**IR (neat)** = 2967, 2938, 2220, 1739, 1338, 1203, 1178, 1138, 1090, 996, 955, 845 cm<sup>-1</sup>

**HRMS (ESI+) m/z** calculated for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S (M+H)<sup>+</sup> 293.0954, found 293.0961.
C8-trifluoromethoxy cyclohexadiene-fused sultam (4.2g)

Prepared according to Procedure C with 70.3 mg, 0.2 mmol of 4.1g. Off-white, tan powder (56.5 mg, 80% yield). Rf = 0.5 (1:1, Hex:EtOAc), one yellow spot, KMnO4, UV.

\[\text{\textsuperscript{1}H NMR} (700 \text{ MHz, CDCl}_3) = \delta 6.91 (t, J = 3.2 \text{ Hz, 1H}), 5.64 (s, 1H), 4.13 (dd, J = 8.5, 5.8 \text{ Hz, 1H}), 3.54 (q, J = 7.0 \text{ Hz, 1H}), 3.21 – 2.99 (m, 2H), 2.60 – 2.41 (m, 2H), 2.19 (dddd, J = 13.5, 10.1, 8.5, 6.7 \text{ Hz, 1H}), 1.92 (ddddd, J = 13.1, 9.8, 7.2, 5.8 \text{ Hz, 1H}), 1.07 (s, 3H), 0.80 (s, 3H) \text{ ppm}\]

\[\text{\textsuperscript{13}C NMR} (176 \text{ MHz, CDCl}_3) = \delta 172.7, 145.3, 134.6, 131.2, 120.2 (q, J = 258.5 \text{ Hz}), 109.9, 67.0, 46.5, 41.6, 30.9, 28.3, 22.0, 19.1, 13.5 \text{ ppm}\]

\[\text{\textsuperscript{19}F NMR} (377 \text{ MHz, CDCl}_3) = \delta -57.44 \text{ ppm}\]

\[\text{IR (neat)} = 2980, 1739, 1701, 1341, 1256, 1175, 1132, 1097, 1009, 955, 828, 673 \text{ cm}^{-1}\]

\[\text{HRMS (ESI+)} \text{ m/z calculated for } C_{14}H_{16}F_3NO_4S (M+H)^+ 352.0825, \text{ found 352.0837}.\]
**C8-methyl carboxylate cyclohexadiene-fused sultam (4.2h)**

Prepared according to Procedure C with 65.1 mg, 0.2 mmol of 4.1h. White powder (20.2 mg, 31% yield isolated as an inseparable 3:1 mixture of diene:arene products). R_f = 0.3 (1:1, Hex:EtoAc), one yellow spot, KMnO_4, UV.

![Diagram](attachment:diagram.png)

**Diene**

\[
\text{H NMR (700 MHz, CDCl}_3\text{) } \delta \text{ 7.03 (s, 1H), 6.97 (s, 1H), 4.16 (dd, } J = 8.5, 5.7 \text{ Hz, 1H), 3.80 (s, 3H), 3.52 (td, } J = 7.4, 4.0 \text{ Hz, 1H), 3.26 – 3.11 (m, 2H), 2.56 – 2.41 (m, 2H), 2.25 – 2.12 (m, 2H), 1.97 – 1.86 (m, 1H), 1.16 (s, 3H), 0.78 (s, 3H) ppm}
\]

**Arene**

\[
\text{H NMR (700 MHz, CDCl}_3\text{) } \delta \text{ 8.15 (d, } J = 1.6 \text{ Hz, 1H), 8.09 (dd, } J = 8.3, 1.6 \text{ Hz, 1H), 8.01 (d, } J = 8.3 \text{ Hz, 1H), 4.40 (dd, } J = 8.2, 6.1 \text{ Hz, 1H), 3.97 (s, 3H), 2.63 (dd, } J = 9.3, 7.5 \text{ Hz, 2H), 2.37 (dq, } J = 12.7, 7.9 \text{ Hz, 1H), 2.26 – 2.10 (m, 2H), 1.49 (s, 3H), 1.33 (s, 3H) ppm}
\]

**Mixture of Diene and Arene**

\[
\text{C NMR (176 MHz, CDCl}_3\text{) } \delta 173.3, 172.7, 165.8, 165.3, 144.1, 139.8, 134.4, 133.6, 133.6, 132.2, 128.8, 127.7, 125.0, 67.1, 64.7, 52.8, 52.2, 46.3, 41.4, 39.4, 30.9, 30.5, 26.1, 23.3, 22.0, 20.4, 19.0, 14.1 \text{ ppm}
\]

**Mixture of Diene and Arene**

\[\text{IR (neat)} = 2971, 2948, 2246, 1737, 1700, 1441, 1341, 1263, 1203, 1175, 1088, 922, 724 \text{ cm}^{-1}\]

**Diene**

\[\text{HRMS (ESI+) } m/z \text{ calculated for C}_{15}\text{H}_{19}\text{NO}_5\text{S (M+H)+ 326.1057, found 326.1055.} \]

**Arene**

\[\text{HRMS (ESI+) } m/z \text{ calculated for C}_{15}\text{H}_{17}\text{NO}_5\text{S (M+H)+ 324.0900, found 324.0909.} \]
**C8-phenyl cyclohexadiene-fused sultam (4.2i)**

Prepared according to Procedure C with 68.7 mg, 0.2 mmol of 4.1i. Clear, colorless oil which solidifies to a white solid over time (22.8 mg, 33% yield). $R_f = 0.3$ (1:1, Hex:EtOAc), one yellow spot, KMnO$_4$, UV.

\[
\text{\includegraphics[width=0.3\textwidth]{image.png}}
\]

$^1$H NMR (700 MHz, CDCl$_3$) = $\delta$ 7.42 – 7.35 (m, 4H), 7.35 – 7.31 (m, 1H), 7.13 – 7.09 (m, 1H), 6.15 – 6.07 (m, 1H), 4.17 (dd, $J = 8.4$, 5.9 Hz, 1H), 3.52 (td, $J = 7.1$, 4.1 Hz, 1H), 3.42 – 3.22 (m, 2H), 2.56 – 2.45 (m, 2H), 2.19 (dddd, $J = 13.4$, 9.8, 8.5, 6.7 Hz, 1H), 1.93 (dddd, $J = 13.3$, 9.7, 7.5, 6.0 Hz, 1H), 1.16 (s, 3H), 0.82 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 173.0, 139.6, 136.0, 134.4, 133.5, 128.6, 128.2, 125.3, 119.5, 67.3, 46.4, 41.8, 31.0, 28.8, 22.1, 19.1, 13.7 ppm

IR (neat) = 2974, 2919, 2234, 1734, 1714, 1340, 1218, 1163, 1090, 956, 772 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{19}$H$_{21}$NO$_3$S (M+H)$^+$ 344.1315, found 344.1310.
**C8-methoxy cyclohexadiene-fused sultam (4.2j)**

Prepared according to a modification of **Procedure C** with 89.2 mg, 0.3 mmol of 4.1j, NBu₄OP(O)(OBu)₂ (58 mg, 0.13 mmol, 0.43 equiv), and photocatalyst A (3 mg, 1 mol%). in 1.5 mL of PhCF₃ (0.2 M). Off-white, tan powder (10.4 mg, 12% yield). Rf = 0.3 (1:1, Hex:EtOAc), one yellow spot (multiple spots are observed on TLC following decomposition), KMnO₄, UV.

The title diene product is unstable and readily undergoes decomposition. Partial characterization is provided below.

\[
\begin{align*}
\text{IR (neat)} &= 2941, 1736, 1680, 1580, 1146, 1163, 1023, 977, 731, 649 \text{ cm}^{-1} \\
\text{HRMS (ESI+)} &\text{ m/z calculated for C}_{14}\text{H}_{19}\text{NO}_{4}\text{S (M+H)}^+ 298.1108, \text{ found } 298.1112.
\end{align*}
\]

\[\text{^1H NMR (500 MHz, CDCl}_3) = \delta 6.92 (t, J = 3.2 \text{ Hz}, 1H), 4.65 (d, J = 3.1 \text{ Hz}, 1H), 4.10 (dd, J = 8.4, 5.9 \text{ Hz}, 1H), 3.61 (s, 3H), 3.46 (q, J = 5.9 \text{ Hz}, 1H), 3.09 – 2.81 (m, 2H), 2.49 (ddd, J = 9.2, 7.5, 1.8 \text{ Hz}, 2H), 2.28 – 2.09 (m, 1H), 2.00 – 1.83 (m, 1H), 1.06 (s, 3H), 0.75 (s, 3H) \text{ ppm} \]
**C8-trifluoromethyl C10-cyclobutyl cyclohexadiene-fused sultam (4.2k)**

Prepared according to **Procedure C** with 69.5 mg, 0.2 mmol of 4.1k. Off-white, tan powder (14.8 mg, 21% yield). R<sub>f</sub> = 0.3 (1:1, Hex:EtOAc), one yellow spot, KMnO<sub>4</sub>, UV.

![Chemical Structure](image)

**<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) = δ 7.02 (s, 1H), 6.73 – 6.62 (m, 1H), 4.17 (t, J = 7.5 Hz, 1H), 3.55 (q, J = 7.8, 6.2 Hz, 1H), 3.24 – 3.04 (m, 2H), 2.59 (dd, J = 9.0, 7.8, 3.2 Hz, 2H), 2.37 (ddt, J = 14.7, 8.7, 6.4 Hz, 1H), 2.25 (dq, J = 15.9, 8.3 Hz, 1H), 2.09 (dq, J = 12.8, 5.3 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.92 – 1.72 (m, 3H), 1.62 (q, J = 8.5, 7.5 Hz, 1H) ppm

**<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) = δ 172.8, 133.9, 131.6, 128.2 (q, J = 31.2 Hz), 126.4 (q, J = 5.6 Hz), 122.9 (q, J = 272.3 Hz), 64.7, 47.1, 42.7, 30.8, 24.1, 23.3, 19.9, 19.7, 14.1 ppm

**<sup>19</sup>F NMR** (377 MHz, CDCl<sub>3</sub>) = δ -69.80 ppm

**IR (neat)** = 2943, 1730, 1653, 1341, 1299, 1205, 1159, 1108, 1101, 958, 696 cm<sup>-1</sup>

**HRMS (ESI+) m/z** calculated for C<sub>15</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub>S (M+H)+ = 348.0876, found 348.0884.
C8-trifluoromethyl benzo-fused cyclohexadiene-fused sultam (4.21)

Prepared according to Procedure C with 76.7 mg, 0.2 mmol of 4.11. White powder (59.0 mg, 77% yield). 

\[ R_f = 0.3 \text{ (1:1, Hex:EtOAc), one yellow spot, KMnO}_4, \text{ UV.} \]

\[ \text{IR (neat) = 2973, 1729, 1467, 1350, 1315, 1168, 1109, 1011 cm}^{-1} \]

\[ \text{HRMS (ESI+) } m/z \text{ calculated for C}_{18}\text{H}_{16}\text{F}_3\text{NO}_3\text{S (M+H)+ 384.0876, found 384.0884.} \]

\[ \begin{align*}
\text{H NMR (700 MHz, CDCl}_3) &= \delta 7.95 (d, J = 7.6 \text{ Hz, 1H}), 7.67 (\text{td, } J = 7.6, 1.3 \text{ Hz, 1H}), 7.62 - 7.52 (m, 2H), 7.10 (t, J = 3.7 \text{ Hz, 1H}), 6.49 (\text{dt, } J = 4.0, 1.8 \text{ Hz, 1H}), 5.10 (s, 1H), 3.76 (s, 1H), 3.10 (s, 2H), 1.52 (s, 3H), 0.35 (s, 3H) \text{ ppm} \\
\text{C NMR (176 MHz, CDCl}_3) &= \delta 163.8, 141.5, 134.5, 133.5, 130.7, 130.7, 129.5, 128.2 (q, J = 31.3 \text{ Hz}), 125.9, 125.6 (q, J = 5.7 \text{ Hz}), 124.2, 122.8 (q, J = 272.4 \text{ Hz}), 69.1, 44.9, 43.2, 23.9, 22.4, 14.0 \text{ ppm} \\
\text{F NMR (377 MHz, CDCl}_3) &= \delta -69.77 \text{ ppm} \\
\end{align*} \]
**C8-trifluoromethyl carbamate cyclohexadiene-fused sultam (4.2m)**

Prepared according to Procedure C with 67.5 mg, 0.2 mmol of 4.1m. Off-white, tan powder (49.0 mg, 73% yield). R<sub>f</sub> = 0.3 (1:1, Hex:EtOAc), one yellow spot, KMnO<sub>4</sub>, UV.

![Chemical Structure](image)

1<sup>H</sup> NMR (700 MHz, CDCl<sub>3</sub>) = δ 7.06 (s, 1H), 6.36 (s, 1H), 4.42 (t, <i>J</i> = 8.8 Hz, 1H), 4.36 (dd, <i>J</i> = 8.4, 4.2 Hz, 1H), 4.21 (dd, <i>J</i> = 9.2, 4.2 Hz, 1H), 3.55 (d, <i>J</i> = 8.5 Hz, 1H), 3.12 (q, <i>J</i> = 6.2, 5.6 Hz, 2H), 1.11 (s, 3H), 0.87 (s, 3H) ppm

13<sup>C</sup> NMR (176 MHz, CDCl<sub>3</sub>) = δ 149.8, 133.8, 131.9, 128.3 (q, <i>J</i> = 31.9, 31.3 Hz), 125.0 (q, <i>J</i> = 5.7 Hz), 122.6 (q, <i>J</i> = 272.4 Hz), 64.2, 63.2, 45.1, 40.5, 23.9, 21.6, 13.7 ppm

19<sup>F</sup> NMR (377 MHz, CDCl<sub>3</sub>) = δ -69.90 ppm

IR (neat) = 2924, 1779, 1365, 1301, 1159, 1114, 1048, 967, 708, 648 cm<sup>-1</sup>

HRMS (ESI+) <i>m/z</i> calculated for C<sub>13</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>4</sub>S (M+H)<sup>+</sup> 338.0668, found 338.0679.
C9-fluoro cyclohexadiene-fused sultam (4.2n)

Prepared according to Procedure C with 57.1 mg, 0.2 mmol of 4.1n. Light-yellow powder (23.4 mg, 41% yield). $R_f = 0.3$ (1:1, Hex:EtOAc), one yellow spot, KMnO$_4$, UV.

$^{1}$H NMR (700 MHz, CDCl$_3$) = δ 6.98 (s, 1H), 5.48 (ddt, $J = 17.7, 4.0, 2.3$ Hz, 1H), 4.09 (dd, $J = 8.3, 6.2$ Hz, 1H), 3.59 (q, $J = 5.9$ Hz, 1H), 3.15 – 2.93 (m, 2H), 2.55 – 2.42 (m, 2H), 2.25 – 2.11 (m, 1H), 1.91 (dddd, $J = 13.5, 9.7, 7.6, 6.2$ Hz, 1H), 1.17 (d, $J = 3.8$ Hz, 3H), 0.89 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = δ 172.8, 155.9 (d, $J = 258.4$ Hz), 134.1 (d, $J = 10.6$ Hz), 133.9 (d, $J = 2.1$ Hz), 102.7 (d, $J = 19.4$ Hz), 66.8, 46.9 (d, $J = 26.4$ Hz), 41.6 (d, $J = 4.3$ Hz), 30.8, 25.8 (d, $J = 7.5$ Hz), 23.4 (d, $J = 7.6$ Hz), 19.1, 13.5 ppm

$^{19}$F NMR (377 MHz, CDCl$_3$) = δ -100.54 (d, $J = 17.6$ Hz) ppm

IR (neat) = 2976, 2936, 1738, 1703, 1343, 1170, 1132, 977, 855, 673, 634 cm$^{-1}$

HRMS (ESI+) m/z calculated for C$_{13}$H$_{16}$FNO$_3$S (M+H)$^+$ 286.0908, found 286.0908.
**C8, C9-difluoro cyclohexadiene-fused sultam (4.2o)**

Prepared according to **Procedure C** with 60.7 mg, 0.2 mmol of **4.1o**. Off-white, tan powder (27.9 mg, 46% yield). \( R_f = 0.4 \) (1:1, Hex:EtOAc), one yellow spot, KMnO\(_4\), UV.

![Structure](image_url)

\(^1\text{H NMR}\) (700 MHz, CDCl\(_3\)) = \( \delta \) 6.85 (s, 1H), 4.10 (t, \( J = 7.0 \) Hz, 1H), 3.76 (s, 1H), 3.39 – 3.15 (m, 2H), 2.59 – 2.42 (m, 2H), 2.20 (dddd, \( J = 18.6, 10.3, 6.3, 1.9 \) Hz, 1H), 2.00 – 1.84 (m, 1H), 1.18 (s, 3H), 0.90 (s, 3H) ppm

\(^{13}\text{C NMR}\) (176 MHz, CDCl\(_3\)) = \( \delta \) 172.6, 141.7 (dd, \( J = 256.1, 12.6 \) Hz), 139.5 (dd, \( J = 257.5, 12.7 \) Hz), 134.1 (d, \( J = 9.2 \) Hz), 130.8 (d, \( J = 10.2 \) Hz), 66.6, 48.1 (d, \( J = 21.9 \) Hz), 42.11 (dd, \( J = 4.1, 2.0 \) Hz), 30.8, 27.4 (d, \( J = 25.2 \) Hz), 23.1 (d, \( J = 7.2 \) Hz), 19.0, 13.5 ppm

\(^{19}\text{F NMR}\) (377 MHz, CDCl\(_3\)) = \( \delta \) -137.19, -137.33 ppm

**IR** (neat) = 2976, 1735, 1345, 1200, 1178, 1120, 1010, 962, 879, 826 cm\(^{-1}\)

**HRMS** (ESI+) \( m/z \) calculated for C\(_{13}\)H\(_{15}\)F\(_2\)NO\(_3\)S (M+H)+ 304.0813, found 304.0816.
**C8-thiophene-2-carboxylate cyclohexadiene-fused sultam (4.2p)**

Prepared according to Procedure C with 78.7 mg, 0.2 mmol of 4.1p. Off-white, tan powder (35.9 mg, 46% yield). R<sub>f</sub> = 0.3 (1:1, Hex:EtOAc), one yellow spot, KMnO<sub>4</sub>, UV.

![Chemical Structure](image)

\[\text{R}
\]

**<sup>1</sup>H NMR** (700 MHz, CDCl<sub>3</sub>) = δ 7.88 (dd, \(J = 3.7, 1.3 \text{ Hz}, 1\text{H}\)), 7.66 (dd, \(J = 4.9, 1.3 \text{ Hz}, 1\text{H}\)), 7.16 (dd, \(J = 5.0, 3.7 \text{ Hz}, 1\text{H}\)), 6.96 (t, \(J = 3.6 \text{ Hz}, 1\text{H}\)), 5.65 (dd, \(J = 4.3, 2.0 \text{ Hz}, 1\text{H}\)), 4.21 – 4.06 (m, 1H), 3.58 (td, \(J = 7.1, 4.1 \text{ Hz}, 1\text{H}\)), 3.35 – 3.02 (m, 2H), 2.51 (ddd, \(J = 9.2, 7.4, 2.0 \text{ Hz}, 2\text{H}\)), 2.27 – 2.12 (m, 1H), 2.01 – 1.86 (m, 1H), 1.07 (s, 3H), 0.92 (s, 3H) ppm

**<sup>13</sup>C NMR** (176 MHz, CDCl<sub>3</sub>) = δ 172.8, 160.1, 146.5, 134.8, 134.6, 133.8, 132.2, 132.0, 128.1, 111.2, 67.2, 46.6, 41.6, 31.0, 28.3, 22.0, 19.1, 13.5 ppm

**IR** (neat) = 2975, 2916, 1736, 1701, 1520, 1469, 1342, 1272, 1204, 1175, 1131, 875, 743 cm<sup>-1</sup>

**HRMS** (ESI+) \(m/z\) calculated for C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub>S<sub>2</sub> (M+H)<sup>+</sup> 394.0777, found 394.0780.
**C8-homoprenyl carboxylate cyclohexadiene-fused sultam (4.2q)**

Prepared according to Procedure C with 78.7 mg, 0.2 mmol of 4.1q. Light-yellow powder (33.3 mg, 42% yield). $R_f = 0.2$ (1:1, Hex:EtOAc), one yellow spot, KMnO$_4$, UV.

![Chemical Structure](image)

$^1$H NMR (700 MHz, CDCl$_3$) = $\delta$ 6.91 (t, $J = 3.1$ Hz, 1H), 5.46 (dd, $J = 4.4$, 1.9 Hz, 1H), 5.10 (ddt, $J = 8.6$, 7.2, 1.4 Hz, 1H), 4.11 (dd, $J = 8.4$, 5.8 Hz, 1H), 3.51 (td, $J = 7.1$, 4.2 Hz, 1H), 3.18 – 2.87 (m, 2H), 2.49 (ddd, $J = 9.1$, 7.3, 3.5 Hz, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 2.34 (q, $J = 7.5$ Hz, 2H), 2.21 – 2.11 (m, 1H), 1.92 (dddd, $J = 13.3$, 9.5, 7.6, 5.8 Hz, 2H), 1.70 (d, $J = 1.8$ Hz, 3H), 1.63 (s, 3H), 1.04 (s, 3H), 0.86 (s, 3H) ppm

$^{13}$C NMR (176 MHz, CDCl$_3$) = $\delta$ 172.8, 171.5, 146.6, 134.5, 133.6, 132.1, 121.8, 110.5, 67.2, 46.5, 41.6, 34.3, 31.0, 28.2, 25.7, 23.5, 22.0, 19.1, 17.7, 13.4 ppm

IR (neat) = 2972, 2932, 2257, 1742, 1452, 1343, 1168, 1129, 908, 726 cm$^{-1}$

HRMS (ESI+) $m/z$ calculated for C$_{20}$H$_{27}$NO$_5$S (M+H)+ 394.1683, found 394.1690.
C8-N-Boc-proline cyclohexadiene-fused sultam (4.2r)

Prepared according to Procedure C with 75.0 mg, 0.16 mmol of 4.1r. Light-yellow foam (33.6 mg, 45% yield). R_f = 0.2 (1:1, Hex:EtOAc), one yellow spot, KMnO_4, UV.

\[
\text{IR (neat) = 2975, 2249, 1745, 1702, 1405, 1361, 1339, 1163, 1143, 906, 729 cm}^{-1}
\]

\[
\text{HRMS (ESI+) } m/z \text{ calculated for C}_{23}\text{H}_{32}\text{N}_{2}\text{O}_{7}\text{S (M+H)+ 481.2003, found 481.2000.}
\]
C8-cyclohexyl carboxylate cyclohexadiene-fused sultam (4.2s)

Prepared according to Procedure C with 78.7 mg, 0.2 mmol of 4.1s. Off-white, tan powder (41.7 mg, 53% yield). R_f = 0.4 (1:1, Hex:EtOAc), one yellow spot, KMnO_4, UV.

\[
\text{\textit{1H NMR} (700 MHz, CDCl}_3) = \delta 6.91 (t, J = 3.7 Hz, 1H), 5.44 (dd, J = 4.3, 1.9 Hz, 1H), 4.11 (dd, J = 8.4, 5.7 Hz, 1H), 3.51 (td, J = 7.1, 4.1 Hz, 1H), 3.18 – 2.86 (m, 2H), 2.49 (ddd, J = 10.0, 7.2, 3.3 Hz, 2H), 2.40 (tt, J = 11.3, 3.7 Hz, 1H), 2.23 – 2.11 (m, 1H), 2.01 – 1.85 (m, 3H), 1.77 (dq, J = 7.8, 3.9 Hz, 2H), 1.72 – 1.60 (m, 1H), 1.54 – 1.43 (m, 2H), 1.38 – 1.15 (m, 3H), 1.04 (s, 3H), 0.86 (s, 3H) ppm}
\]

\[
\text{\textit{13C NMR} (176 MHz, CDCl}_3) = \delta 174.1, 172.8, 146.6, 134.5, 132.1, 110.4, 67.2, 46.6, 42.9, 41.6, 31.0, 28.8, 28.8, 28.1, 25.6, 25.2, 25.2, 22.0, 19.1, 13.4 ppm}
\]

\[
\text{IR (neat) = 2937, 2857, 1742, 1704, 1450, 1344, 1132, 1001, 894, 668 cm}^{-1}
\]

\[
\text{HRMS (ESI+)} \text{ m/z calculated for } C_{20}H_{27}NO_5S (M+H)+ 394.1683, \text{ found } 394.1690.
\]
C8-benzyl carboxylate cyclohexadiene-fused sultam (4.2t)

Prepared according to Procedure C with 74.5 mg, 0.19 mmol of 4.1t. Light-yellow oil (20.3 mg, 27% yield). R_f = 0.3 (1:1, Hex:EtOAc), one yellow spot, KMnO_4, UV.

1H NMR (700 MHz, CDCl_3) = δ 7.41 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 6.89 (t, J = 3.7 Hz, 1H), 5.49 (dd, J = 4.4, 1.9 Hz, 1H), 4.10 (dd, J = 8.5, 5.7 Hz, 1H), 3.73 (s, 2H), 3.50 (td, J = 7.1, 4.2 Hz, 1H), 3.19 – 2.85 (m, 3H), 2.57 – 2.42 (m, 2H), 2.24 – 2.07 (m, 2H), 1.99 – 1.84 (m, 1H), 1.03 (s, 3H), 0.84 (s, 3H) ppm

13C NMR (176 MHz, CDCl_3) = δ 172.8, 169.7, 146.6, 134.5, 133.0, 132.0, 129.2, 128.8, 127.5, 110.8, 67.2, 46.5, 41.6, 41.1, 31.0, 28.1, 22.0, 19.1, 13.4 ppm

IR (neat) = 2971, 1740, 1340, 1164, 1125, 1006, 952, 698 cm⁻¹

HRMS (ESI⁺) m/z calculated for C_{21}H_{23}NO_{5}S (M+H)+ 402.1370, found 402.1371.
**C8-trifluoromethyl-C11-methyl cyclohexadiene-fused sultam (4.2u)**

 Prepared according to Procedure C with 69.9 mg, 0.2 mmol of 4.1u. Light-yellow powder (23.6 mg, 34% yield). \( R_f = 0.3 \) (1:1, Hex:EtOAc), one yellow spot, KMnO₄, UV.

![Chemical Structure](image)

\(^1\)H NMR (700 MHz, CDCl₃) = \( \delta \) 7.02 (d, \( J = 3.8 \) Hz, 1H), 6.36 (dq, \( J = 3.5, 1.8 \) Hz, 1H), 3.81 (t, \( J = 3.9 \) Hz, 1H), 3.08 (q, \( J = 6.6, 6.2 \) Hz, 2H), 2.57 (ddd, \( J = 18.1, 10.2, 7.8 \) Hz, 1H), 2.47 (ddd, \( J = 18.1, 10.3, 5.0 \) Hz, 1H), 2.23 (ddd, \( J = 13.2, 10.3, 7.9 \) Hz, 1H), 1.80 (ddd, \( J = 13.1, 10.2, 5.0 \) Hz, 1H), 1.67 (s, 3H), 1.10 (s, 3H), 0.88 (s, 3H) ppm

\(^13\)C NMR (176 MHz, CDCl₃) = \( \delta \) 172.8, 134.5, 131.1, 128.1 (q, \( J = 31.4 \) Hz). 126.5 (q, \( J = 5.5 \) Hz), 122.8 (q, \( J = 272.5 \) Hz), 72.1, 43.7, 40.7, 29.9, 28.2, 23.8, 23.0, 21.4, 17.9 ppm

\(^19\)F NMR (377 MHz, CDCl₃) = \( \delta \) -69.85 ppm

IR (neat) = 2962, 1754, 1654, 1337, 1300, 1253, 1163, 1116, 977, 896, 707 cm\(^{-1}\)

HRMS (ESI+) \( m/z \) calculated for C\(_{15}\)H\(_{18}\)F\(_3\)NO\(_3\)S (M+H)+ 350.1032, found 350.1041.
4.4.4. Mechanistic Investigations

Stern – Volmer Fluorescence Quenching

Fluorescence quenching experiments were conducted on a Horiba PTI QuantaMaster 8000 using FelixGX software. Samples were prepared in dichloromethane (CH$_2$Cl$_2$ is a successful solvent for this reaction) due to the poor solubility of the photocatalyst in 1:1 trifluorotoluene:BuOH. Each sample was degassed in the sealed septum screw-capped cuvette by sparging with argon for 30 seconds immediately prior to each measurement. The solutions were irradiated at 420 nm and luminescence was measured at 593 nm. I$_0$/I values were generated from the average of three scans taken per quencher concentration. Solutions of a given concentration were produced and measured in triplicate (triplicate of triplicates).

**Conclusion:** The sulfonyl enamide substrate does not quench the excited state of the photocatalyst. Additionally, when the substrate is present in solution with tetrabutylammonium dibutyl phosphate, there is no additional quenching of the excited state of the photocatalyst beyond the contribution from the phosphate base by itself. This data suggests that neither direct oxidation of the substrate by the photocatalyst nor oxidative proton-coupled electron transfer (PCET) of a sulfonyl amide-phosphate complex is primarily responsible for N-radical formation and initiation of the cyclization cascade. Comparatively, when tetrabutylammonium dibutylphosphate base is used alone, significant nonlinear photoluminescence quenching of the photoexcited state of catalyst **A** is observed. This observation aligns with Knowles, and others, suggesting the formation of a less emissive iridium-phosphate complex and may be the active catalytic species in solution.
Substrate / sulfonyl enamide used in fluorescence quenching and cyclic voltammetry studies:

\[
\text{[Photocatalyst]} = 0.2 \text{ mM}
\]

<table>
<thead>
<tr>
<th>[substrate] (mM)</th>
<th>Average ( \frac{I_o}{I} )</th>
<th>[substrate] (mM)</th>
<th>Average ( \frac{I_o}{I} )</th>
</tr>
</thead>
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<tr>
<td>0.3</td>
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<tr>
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<td>0.6</td>
<td>1.859189</td>
</tr>
<tr>
<td>1.2</td>
<td>1.074968438</td>
<td>1.2</td>
<td>1.899883</td>
</tr>
</tbody>
</table>
Experiment A: Constant [Ir], fixed substrate:phosphate ratio, variable [substrate:phosphate]

[Photocatalyst] = 0.05 mM, [phosphate] = 0.65*[substrate]

<table>
<thead>
<tr>
<th>[substrate] mM</th>
<th>Avg I₀/I</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
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<tr>
<td>0.2</td>
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</tr>
<tr>
<td>0.25</td>
<td>1.501165</td>
</tr>
</tbody>
</table>

[Graph showing the relationship between [Sulfonyl enamide] (mM) and I₀/I]
Experiment B: Constant [Ir], variable [phosphate], no substrate

[Photocatalyst] = 0.05 mM, [phosphate] = 0.65*(theoretical [substrate])

<table>
<thead>
<tr>
<th>Theoretical [substrate] (mM)</th>
<th>Average $I_0/I$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
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</tr>
<tr>
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<td>1.523735</td>
</tr>
<tr>
<td>0.25</td>
<td>1.618825</td>
</tr>
</tbody>
</table>

We wish to make a direct comparison of the fluorescence quenching between experiment A, where the base is present in a fixed ratio to the sulfonamide; and experiment B, where the sulfonamide is absent, but the concentrations of the base are the same as those in experiment A. For this reason, experiment B is plotted such that the $x$-axis will remain the same when the two experiments are plotted in the same graph.
Superimposed Experiment A and Experiment B

- **Experiment A** (0.65 equiv base with substrate)
- **Experiment B** (0.65 equiv base only)

[Graph showing the relationship between $I_0/I$ and [Sulfonyl enamide] (mM).]
Cyclic Voltammetry

Cyclic voltammetry was performed using a CHI620E electrochemical analyzer (from CH Instruments) and was performed with a three-electrode set-up, using a glassy carbon working electrode (3 mm diameter), a graphite counter electrode and a silver/silver ion nonaqueous reference electrode. All experiments were conducted in dichloromethane with 0.1 M NBu₄PF₆.

In all experiments containing the substrate, the concentration of the substrate was 10 mM. In the control containing no substrate, the tetrabutylammonium dibutylphosphate base concentration is 10 mM.

**Conclusions:** The oxidation of the substrate occurs at a potential >1.6 V vs Ag/Ag⁺. This result suggests that direct oxidation and subsequent deprotonation of the substrate (1a) is an unlikely process. A solution of the tetrabutylammonium dibutylphosphate base alone exhibits an oxidation wave at ~1 V vs Ag/Ag⁺. As the concentration of tetrabutylammonium dibutylphosphate base increases relative to substrate 1a, the current response increases for the oxidation wave ~1 V vs Ag/Ag⁺. These data seem to suggest that as the tetrabutylammonium dibutylphosphate base is oxidatively active at oxidation potentials attainable by photocatalyst A and that the base may be the species being oxidized (to phosphate radical) in solution and thus initiating the N-radical cascade process. Importantly, there is no obvious oxidation potential shift (to less positive potential) for the substrate 1a as one would expect for a PCET process.
Deuterium Labeling Studies

*D*-C8-trifluoromethyl cyclohexadiene-fused sultam (4.2a-D)

To an oven dried 2-dram vial was added substrate 4.1a (67.1 mg, 0.2 mmol), NBu₄OP(O)(OBu)₂ (58 mg, 0.13 mmol, 0.65 equiv), and photocatalyst A (2 mg, 1 mol%). The vial contents were then dissolved in a 1:1 mixture of t-BuOD:PhCF₃ (2 mL each, 0.05 M). The reaction solution was degassed by sparging with argon for 15 min. Then the vial was quickly capped and sealed with parafilm. The reaction was irradiated with two, H150 blue Kessil lamps positioned ~5 cm away and cooled with an overhead fan. After 14 h, the reaction was directly concentrated *in vacuo*. The resultant residue was subjected to flash column chromatography over silica providing the pure diene 4.2a-D. Off-white, tan powder (33.4 mg, 51% yield). Rᵣ = 0.3 (1:1, Hex:EtOAc), one yellow spot, KMnO₄, UV.

**¹H NMR** (700 MHz, CDCl₃) = δ 7.02 (d, J = 2.9 Hz, 1H), 6.38 (s, 1H), 4.16 (dd, J = 8.5, 5.8 Hz, 1H), 3.48 (s, 1H), 3.17 – 2.99 (m, 1H), 2.60 – 2.43 (m, 2H), 2.20 (dddd, J = 13.7, 10.3, 8.6, 6.6 Hz, 1H), 1.99 – 1.83 (m, 1H), 1.14 (s, 3H), 0.78 (s, 3H) ppm

**¹³C NMR** (176 MHz, CDCl₃) = δ 172.7, 134.3, 131.3, 127.8 (q, J = 31.2 Hz), 125.9 (q, J = 5.6 Hz), 122.8 (q, J = 272.0 Hz), 67.0, 45.3, 41.4, 30.9, 24.3 – 22.8 (m), 22.0, 19.0, 13.8 ppm

**¹⁹F NMR** (377 MHz, CDCl₃) = δ -69.85 ppm

**IR** (neat) = 2982, 1738, 1473, 1344, 1299, 1168, 1122, 986, 897, 700 cm⁻¹

**HRMS** (ESI+) m/z calculated for C₁₄H₁₃DF₃NO₃S (M+H)+ 337.0939, found 337.0943.
4.4.5. X-Ray Crystallographic Data

Crystallographic data for C8-trifluoromethyl cyclohexadiene-fused sultam 4.2a

Structural figure of compound 4.2a, with 50% probability ellipsoids.

Accession Number The structure of 4.2a has been deposited in the Cambridge Crystallographic Data Center under accession number CCDC: 1952459.

Structure Determination:71

Colorless needles of 4.2a were grown from a dichloromethane/pentane solution of the compound at 23 °C. A crystal of dimensions 0.18 x 0.15 x 0.12 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 Å) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 3 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 20775 reflections to a maximum 2θ value of 138.66° of which 2593 were independent and 2538 were greater than 2σ(I). The final cell constants (Table 4.4) were based on the xyz centroids of 10883 reflections above 10σ(I). Analysis of the data
showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group P2(1)/n with Z = 4 for the formula C_{14}H_{16}NO_{3}F_{3}S. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0371 and wR2 = 0.0952 [based on I > 2\sigma(I)], R1 = 0.0377 and wR2 = 0.0958 for all data. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Table 4.4. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
<td>C_{14}H_{16}F_{3}N_{3}O_{3}S</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>335.34</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>85(2) K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>1.54184 Å</td>
</tr>
<tr>
<td><strong>Crystal system, space group</strong></td>
<td>Monoclinic, P2(1)/n</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>a = 11.0713(2) Å, α = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>b = 6.16810(10) Å, β = 99.5210(10) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 21.0140(3) Å, γ = 90 deg.</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>1415.26(4) Å^3</td>
</tr>
<tr>
<td><strong>Z, Calculated density</strong></td>
<td>4, 1.574 Mg/m^3</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>2.492 mm^-1</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>696</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.180 x 0.150 x 0.120 mm</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
<td>4.253 to 69.332 deg.</td>
</tr>
<tr>
<td><strong>Limiting indices</strong></td>
<td>-13&lt;=h&lt;=12, -7&lt;=k&lt;=7, -25&lt;=l&lt;=25</td>
</tr>
<tr>
<td><strong>Reflections collected / unique</strong></td>
<td>20775 / 2593 [R(int) = 0.0488]</td>
</tr>
<tr>
<td><strong>Completeness to theta</strong></td>
<td>67.684 98.5 %</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td><strong>Max. and min. transmission</strong></td>
<td>1.00000 and 0.66699</td>
</tr>
</tbody>
</table>
Refinement method: Full-matrix least-squares on $F^2$

Data / restraints / parameters: 2593 / 0 / 201

Goodness-of-fit on $F^2$: 1.069

Final R indices [$I > 2\sigma(I)$]: $R1 = 0.0371$, $wR2 = 0.0952$

R indices (all data): $R1 = 0.0377$, $wR2 = 0.0958$

Extinction coefficient: n/a

Largest diff. peak and hole: 0.314 and -0.436 e.A$^{-3}$
4.5. References


