Novel Coupling Reactions Utilizing Base Metal and Photoredox Catalysis

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ABSTRACT

Novel coupling reactions have an inherent interest amongst the practitioners of molecular construction. This strategy allows for a convergent strategy towards synthetic routes, resulting in faster syntheses. This is especially true if novel couplings can be developed utilizing catalysis. As such, an important goal in organic synthesis is the development of these reactions.

The α-amino carbonyl is a valuable motif in the pharmaceutical industry. However, the direct construction of this motif to construct has remained challenging. As a result, numerous methods have used electrophilic sources of nitrogen atoms to install the C–N bond, and elaborated substituents on the nitrogen atom. In Chapter 2, a method detailing the direct construction of this motif with elaborated nitrogen fragments is discussed. This functions via copper catalysis, and this studied culminated in the one step synthesis of the drug Plavix.

Photoredox catalysis has emerged as a mild platform towards activating common functionalities towards coupling reactions. Recently, a method detailing a decarboxylative arylation emerged from our group in collaboration with the Doyle group. This methodology relied on both photoredox and nickel catalysis to forge the desired motif. In chapter 3, this methodology is reexamined to address several shortcomings of the seminal initial report. A more general protocol for carboxylic acids was developed. Furthermore, the scope of heteroaryl halides was also expanded and a more radical resistant photocatalyst was designed. The combination of nickel, photoredox, and hydrogen-atom-transfer catalysis is discussed in Chapter 4, as applied to a C–H
alkylation. This method allows for a site-selective alkylation of a sp$^3$ C–H bond to form a sp$^3$-sp$^3$ C–C bond.

Another valuable motif is the trifluoromethyl group. While there have been many elegant advances in the last decade for the installation of this challenging motif, the formation of sp$^3$ C–CF$_3$ bonds has remained difficult. In Chapter 5, a decarboxylative trifluoromethylation is discussed, that furnishes the desired sp$^3$ C–CF$_3$ bond. This is still under the initial stages of investigation, but promising results are disclosed.
AKNOWLEDGEMENTS

Hopefully this is the only section of this that anyone will ever read, so I will attempt to do a good job on this part, at least. I’m not particularly verbose or sentimental, so these should be fairly short. The first person I need to thank is David W. C. MacMillan, for being a great advisor over the years. I know that I would not have gotten to where I am today, both professionally as well as scientifically, without your help. Thank you for everything you have done for me, and for helping me get the job I wanted. You have put together a fantastic group of people to spend far too much time with everyday. I would also like to thank my second reader, Todd Hyster. Thank you for reading the rest of the document, and I am sorry I accused you of stealing my fidy. I am also sorry for the music selection of bay 4 that you had to suffer through. In addition, thank you Rob for the advice over the years. Thanks for taking the time to give me second opinions on when I needed them. In addition, thank you Brad for serving on my committee, and for writing a recommendation letter for me.

I’ve had the opportunity to work with many fantastic coworkers, and I’ll start with the ones that I worked on projects with. I need to start with Jason Zbieg. As a first year, I cannot thank you enough for helping me through the process of working in a lab, and knowing what the expectations were. Although you were very intense, it was a fantastic experience working with you, and I am positive I am a much better scientist because of it. Next I should mention Eric Welin. You were one of this first people I came to advice for during the early years, and for the brief time we worked together on the decarboxylative arylation project, I really enjoyed it. I know the direction of project sometimes consisted of a directive to make every type of heteroarenes compatible, but I enjoyed that project.
Also it was great to work with him in the bay, as he always found a way to keep a fun atmosphere in the bay. Mike was also a great coworker. Again, we did not overlap much on that project, as we were both had other preoccupations at the time, but thanks for being such a fun and lively person. It was also great being able to discuss the intricacies of the job application process with you. Finally, for that project, Simon Allmendiger has been what that project needed to push it to the end. He has had to deal with the worst that project has to offer, and has been doing a great job.

Next comes the alkylation project. I did not enjoy this project, but I did enjoy working with Chip and Yufan. While we tried to finish that project as fast as possible, it was great to be working with you so that we could all vent our frustrations when the chemistry was not quite working out. Chip is the most dedicated person I have ever met, and is a great and knowledgeable chemist, as well as someone who always stays grounded. Yufan is similarly dedicated, and no matter what he says about the likelihood of success, tries his hardest to make things work. Finally, Jacob Kautzky has done a great job with the trifluoromethylation. During the early stages of that project, when I was preoccupied with job applications and the HAT alkylation, you did a great job moving the project forward and answering a lot of the fundamental questions about the project. It was great seeing you advance the project, and I’m sure you have a successful time in graduate school.

As for numerous great coworkers I have not had a chance to directly work with, I will start with my classmates, Tracy Liu and Patti Zhang. It has been great progressing through this program with you, and I wouldn't wish for any other classmates. With our graduation, the chicks will no longer be chirping. I would also like to thank Jeff Garber
for being a good mentor when I first arrived. He always took the time to talk to me about my project, giving me advice for where to go next, and also helped brainstorm new ideas for projects, and displayed a curiosity for all fields of chemistry. Continuing on with those who have either had the fortune or misfortune of inhabited Bay 4 with me, Schultzy always brought a certain energy to the bay. This lead to fun, if combative times. The current group of Vlad, Jens, Steve, and Rusty have lead to a heightened state of weirdness. From the punishment playlist, JPop, Let It Go, Watermelons, the SnackmasterPro, and We Built This City, we have had a very fun and weird time. I still do not like dehydrated watermelon, but the kiwis were delicious. Hopefully, some semblance of the current Bay 4 will survive during the next lab reorganization, as I’m not sure the rest of the group could handle the weirdness of our normal day. In addition Chris Nawrat was a great coworker in the lab. He was always a great resource, and showed me a world of dark beers that I didn’t know existed. I cannot count the amount of times he brought in a delicious beer for us to try.

I would also like to thank my William and Stitch, our stater-dogs, also known as cats. I had never had a pet before, and it was nice having you two around for the first three years. I would like to thank our three dogs: Minerva, Elsa, and Major Tom. The rest of my family deserves some acknowledgment as well, for supporting my decision to continue school to the 21st grade. Finally, I would like to acknowledge the sacrifices Alex had to put up with during graduate school. Grad school isn’t easy, and she has put with a lot of things during the last 5 years, from the hours to having to live in New Jersey. Soon, our schedule will go back to being more normal, and I’m looking forward to our life together in Boston.
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LIST OF ABBREVIATIONS

Ac  acetyl
Ad  adamantyl
Alk  generic alkyl group
Ar  generic aryl group
BDE  bond dissociation energy
Bn  benzyl
Boc  tert-butoxycarbonyl
Boc-Pro-OH  (tert-butoxycarbonyl)-L-proline
Bpy  2,2'-bipyridine
BTMG  2-(tert-butyl)-1,1,3,3-tetramethylguanidine
Bz  benzoic
Cbz  carboxyl benzyl
CFL  compact fluorescent lamp
CMD  concerted metalation deprotonation
CN  cyano
Cy  cyclohexyl
DABCO  1,4-diazabicyclo[2.2.2]octane
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DFT  density functional theory
DMA  N,N-dimethylacetamide
DMF  N,N-dimethylformamide
DMSO  dimethylsulfoxide
dOMebpy  4,4’-dimethoxy-2,2’-dipyridyl
dr  diastereomeric ratio
dtbbpy  4,4’-di-tert-butyl-2,2’-dipyridyl
E  generic electrophile
ESI-TOF  electrospray ionization-time of flight
Et  ethyl
EtOAc  ethyl acetate
EWG  generic electron withdrawing group
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>GC</td>
<td>gas chromotography</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HAT</td>
<td>hydrogen atom transfer</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>hi resolution mass spectrometry</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>ISC</td>
<td>intersystem crossing</td>
</tr>
<tr>
<td>L</td>
<td>generic ligand</td>
</tr>
<tr>
<td>LED</td>
<td>light emitting diode</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>generic metal</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Me₄Phen</td>
<td>3,4,7,8-tetramethyl-1,10-phenanthroline</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MHz</td>
<td>mega hertz</td>
</tr>
<tr>
<td>MLCT</td>
<td>metal to ligand charge transfer</td>
</tr>
<tr>
<td>mol</td>
<td>mol</td>
</tr>
<tr>
<td>nm</td>
<td>nanometer</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nuc</td>
<td>generic nucleophile</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxy</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>ppy</td>
<td>2-phenylpyridine</td>
</tr>
<tr>
<td>R</td>
<td>generic group</td>
</tr>
<tr>
<td>rr</td>
<td>regiomeric ratio</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SCE</td>
<td>saturated calomel electrode</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMG</td>
<td>1,1,3,3-tetramethylguanidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>tR</td>
<td>rentention time</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>X</td>
<td>generic atom or substituent</td>
</tr>
</tbody>
</table>
To my family
and friends
Chapter 1

Catalysis in Modern Organic Synthesis

1. Organic synthesis.

In a very general sense, organic chemistry consists of the study of molecules that have a carbon backbone. This can take many forms, from the study of their physical properties so that more and more accurate predictions about the properties of future compounds can be made, to the field of organic synthesis, which aims to take advantage of those predictive properties to reliably assemble complex molecules. It is this latter area that consumes the large amount of attention from the pharmaceutical and agrochemical industries, as large portions of their products are small molecules that must be assembled in a concise and predictable manner. These industries have an inherent interest in what motifs are accessible, as well as the ease at which they can be assembled. As the field has grown, the complexity of molecules that were accessible has vastly increased. In modern times, it is safe to say that given enough money and man-hours, any given molecule can be synthesized in a laboratory. As a result, an emerging focus of the field has become the ease and efficiency of the synthesis, rather than the feasibility. What used to take five steps to accomplish, we now aim to accomplish in one. Such

\[ \text{Scheme 1. The decreasing yield over a synthetic sequence} \]

advancements not only save time for the chemist performing them, but also can increase the overall yield of a sequence and reduce the amount of waste generated. If every step of a 5-step sequence proceeds in 80% yield, the overall yield is 33%. Therefore, methods
that allow for excision of even only four of these steps will drastically increase the overall yield to 64%. This simple math has lead to the developing of more efficient steps, where large amounts of molecular complexity are added, to become the major focus of modern synthetic organic chemistry.

II. The role of catalysis in organic synthesis.

Over the past 30 years, the field of catalysis has emerged as one of the most attractive avenues for decreasing the costs associated with synthesis. This can be through enabling novel reactions, allowing for milder, higher yielding conditions for a specific transformation, or by shortening of synthetic routes. Fundamentally, catalysis allows for reactions to occur by lowering the energy of activation necessary, while not being consumed itself. This can be accomplished among a number of discrete modes, but fundamentally either the HOMO of the nucleophile is raised, or the LUMO of the electrophile is lowered. This allows for the decrease in the size of the HOMO–LUMO gap, allowing for a more facile reaction. The nature of how much this gap is reduced determines how much milder the reaction conditions can be. This can allow for more efficient reactions, as harsher conditions can lead to deleterious side reactions.

Within the field of catalysis, there are many different modes of activation of substrates, as well as many different classes of catalysts. So much so that it would be futile exercise to attempt to name them all. However, in a very broad sense, transition metal catalysis has remained one of the most popular classes of catalysis. This can be attributed to the number of transition metals on the periodic table, the differing reactivity depending on row and column on that table, and the ease of fine-tuning that reactivity by
ligand modification. Indeed, the most widely used processes in both the pharmaceutical and agrochemical industries rely on transition metal catalysis. Typically these rely on so-called “noble metals”, 2\textsuperscript{nd} and 3\textsuperscript{rd} row transition metals. While numerous methodologies utilize these metals, concerns of cost due to the rarity of some of these elements has lead to a desire to utilize base metals; those derived from the 1\textsuperscript{st} row of the transition metals. This is due to their abundance in the earth’s crust, which results in inexpensive catalysts in most cases. Most recently, 1\textsuperscript{st} row transition metals have gained attention due to their ability to catalyze reactions that noble metals cannot. This can partly be attributed to their ability to readily undergo one-electron changes in oxidation state, whereas noble metals typically undergo two-electron changes in oxidation state. This allows for a completely different set of transformations to be developed. Chapter 2 will discuss one such method in the synthesis of \(\alpha\)-amino carbonyls via copper catalysis (Figure 1).

\[\text{III. The combination of 1}^{\text{st}}\text{ row transition metals and photoredox catalysis.}\]

Transformations incorporating more than one catalyst can greatly increase complexity of a molecule in a single step. Towards this end, the MacMillan group has become interested in combining 1\textsuperscript{st} row transition metal catalysis with photoredox catalysis. Photoredox catalysis functions via the addition of a photosensitizer to the reaction mixture, followed by shining light on the flask. The light activates the photosensitizer, allowing it to catalyze transformations. There are a number of factors that interest in this area, but there are several factors are that it allows for a selective delivery of energy to only the photosensitizer. Furthermore, this can create an environment that is simultaneously oxidizing and reducing at the same time. This is
typically thought of as a difficult state to achieve, but can be routinely achieved via a literal flip of the switch. Another factor is that since the photosensitizer typically interacts with the other components of the reaction mixture via outer-sphere electron transfer, there is very little chance for inhibition of the catalyst via interactions with the reaction mixture, as no covalent or even transient bonding occurs to the photosensitizer.

Using the paradigm of photoredox catalysis and 1st row transition metals, we aim to tackle challenging problems in the pharmaceutical industry. Typically, we aim to develop transformations that would not be possible otherwise via conventional catalysis, which can allow for shorter synthetic routes. Ideally, we aim to activate common functional groups towards coupling reactions. This is appealing to us, as it allows for not only a decreased amount of steps to achieve the desired structure, the molecules can also be constructed in a convergent manner. Two methods detailing this strategy will be discussed in chapters 3 and 4. These methods are accomplished via combining photoredox catalysis with nickel catalysis. In chapter 3, a decarboxylative arylation is discussed, with a focus on continuing to develop a previously published methodology from our group. This was further developed to expand the generality of the transformation to better match the needs of the pharmaceutical industry. In chapter 4, the combination of photoredox, nickel, and hydrogen-atom-transfer catalysis towards a C–H alkylation is discussed.

Another goal of our group is to combine photoredox catalysis with transition metals that are not nickel. This hope is that this will allow for novel reactions that nickel cannot catalyze. Towards this end, we have become interested in the utilization of copper, as copper is an abundant first row transition metal that engages in a variety of one
electron chemistry without the assistance of photoredox catalysis. In chapter 5, the combination of photoredox catalysis and copper catalysis will be discussed. Indeed, we found that this can catalyze a sp$^3$ C–CF$_3$ bond formation, which is traditionally a challenging bond to form due to the nature of the trifluoromethyl group.

**Figure 1. The combinations of different modes of catalysis discussed.**
Chapter 2

The Direct $\alpha$-Amination of Carbonyls via Copper Catalysis Utilizing Simple Amines and Carbonyls

I. A Challenging Bond to Form

Of all the functional groups, the carbonyl has remained the most versatile and one of the most widely utilized in both traditional and modern organic synthesis. Many classic reactions of organic synthesis exploit the diverse reactivity of the carbonyl group, and the development of novel methodologies based upon the group continues to be an area of intense research. Many powerful concepts of catalysis were first developed utilizing reactions of the carbonyl group (Scheme 1). The Evans oxazolidinone auxiliary both demonstrated the utility of chiral auxiliaries, and later the power of Lewis acid catalysis.\(^1\) Later the ability of small organic molecules to catalyze organic transformations, a field termed organocatalysis, was shown and developed into an entire field, that is still an active area of research today.\(^2\) Unsurprisingly, given the extensive

![Scheme 1. Common platforms for carbonyl functionalization](image)


history of methodologies based upon the reactivity of the carbonyl motif, a diverse range of functionalities can be installed, both racemically and asymmetrically, at the α-position of the carbonyl group.

Surprisingly, given this history, the direct α-amination of a carbonyl remained an unmet need in synthetic organic chemistry. This motif, the α-amino carbonyl, is prevalent across a wide variety of compounds, including the blockbuster pharmaceutical agent Plavix. Furthermore, numerous compounds with medicinal properties contain this simple motif (Figure 1), including those for appetite suppression, treatment of cocaine addiction, and monoamine uptake inhibition. In addition, the building blocks of cells, amino acids, contain this valuable motif. Given the importance of the α-amino carbonyl in medicinal chemistry, we sought to establish a simple and convenient method to directly construct this pharmacophore.

Figure 1. Examples of α-amino carbonyls

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When the reactivity of the group is examined, it is easy to see why this transformation has remained elusive. Upon enolization of the carbonyl unit, the α position of the carbonyl is rendered nucleophilic. Amines, possessing a lone pair, are also inherently nucleophilic. Unsurprisingly, given the electronics of the reactants, the direct reaction between the two is kinetically slow. To facilitate forging of the desired C–N bond, one of the reaction partners must be rendered electrophilic. This strategy allows for the direct installation of a nitrogen atom at the alpha position of the carbonyl. Most commonly, the amine component is rendered electrophilic via the inclusion of a suitably electron-withdrawing group on the nitrogen. As shown in Figure 2, sulfonyl azides, oxazirides, and Chloramine-T have all been utilized as electrophilic sources of nitrogen atoms to facilitate the amination of a diverse range of nucleophiles. However, of all the sources of electrophilic nitrogen, the most utilized towards the α-amination of carbonyls have been diazodicarboxylates. Specifically, after the desired reaction occurs, a hydrazine is adorned at the α-position of the carbonyl. Notably, in 2002 Jørgensen and List independently demonstrated that these hydrazine motifs could be installed

![Figure 2. Electrophilic sources of nitrogen](image)

---

asymmetrically at the $\alpha$-position of aldehydes.\(^5\) While these reports represent a seminal contribution towards this area, these methods often suffer from needing to elaborate the hydrazine motif into the desired compound; a process that can be rather laborious. Ideally, this desired amine could be installed directly, with no further elaboration required of the amine component to reach the desired compound. A number of research groups have contributed towards this goal, developing new sources of electrophilic nitrogen that allow for the coupling of entire fragments. Of the sources developed, N–OBz compounds have emerged as the most attractive. These were first demonstrated as useful sources of electrophilic nitrogen fragments by Miura in the $\alpha$-amination of esters, and have since been applied by Lalic and Buchwald in a diverse range of copper catalyzed hydroaminations\(^6\). However, ideally the simple, unfunctionalized, free amine could be utilized, allowing for the direct coupling of two nucleophilic fragments.

II. Copper Catalysis to Forge the Requisite Bond

Given this fact, we wondered if an oxidative approach could directly furnish the desired compound from a simple amine and the silyl enol ether of a carbonyl. Towards this end, we hypothesized that copper catalysis under atmospheric conditions, could directly furnish this valuable motif. Specifically, we envisioned that this transformation could proceed via a catalytic $\alpha$-bromination of the carbonyl, rendering this component


electrophilic. Ultimately, we hoped this strategy could be extended to unfunctionalized carbonyls via an in-situ enolization.

The first reported example of copper mediating the $\alpha$-halogenation of a carbonyl dates back to 1904, when Veazey and Kohlschütter observed that the electrical conductivity of a solution of CuCl$_2$ in acetone increased over time.$^7$ However, it was not until 1955 that this result could be explained. Copper(II) chloride salts were found to form chloroacetone, as well as Copper(I) chloride and HCl, thereby increasing the concentration of electrolytes present in solution.$^8$ Furthermore, in 1964 King and Ostrum disclosed the first reports of a copper mediated bromination (Scheme 2).$^9$ In their report, they described this method as “the cleanest and most direct for selective bromination reported to date.” In the 50 years since this initial report, copper mediated halogenations have remained as one of the most mild and selective halogenation methods, and have been applied in complex systems in the pursuit of natural product synthesis. Notably, in Garg’s synthesis of $N$-methylwelwitindolinone D isonitrile, treatment of the advanced

Scheme 2. Copper mediated $\alpha$-bromination

have remained as one of the most mild and selective halogenation methods, and have been applied in complex systems in the pursuit of natural product synthesis. Notably, in Garg’s synthesis of $N$-methylwelwitindolinone D isonitrile, treatment of the advanced

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intermediate provided the desired compound in 71% yield while tolerating a diverse range of functionalities.\textsuperscript{10}

While the exact mechanism of this transformation has never been fully elucidated, mechanistic studies have illuminated some aspects of the transformation. Kochi found that the halogenation is first order in halide and half order in copper.\textsuperscript{8} While the latter order seems smaller than expected, it can be rationalized by the dimeric structures copper (II) halide salts form in solution. This pre-equilibrium likely obscures the true order of copper in the transition state. Nevertheless, Kosower and Wu elucidated key aspects of the mechanism.\textsuperscript{11} As shown in Scheme 3, when an enone was compared to the corresponding β-γ unsaturated compound, similar distributions of the product were observed, suggesting the intermediacy of a common enolate. The authors propose that once this enolate is generated, a second equivalent of copper can associate to the enolate, and the resulting 2e\textsuperscript{−} oxidation to form the α-halo carbonyl can be accomplished with two simultaneous 2e\textsuperscript{−} reductions of the two copper centers. However, an alternative mechanism of a single copper center carrying out the oxidation to form copper(0),

\textbf{Scheme 3. The results of Kowower and Wu’s studies}

Both starting materials give the same products


followed by comproportionation with an equivalent of Cu(II) to yield two equivalents of Cu(I) cannot be ruled out.

Surprisingly, despite the history of this simple process, it has never been applied in a catalytic sense. This was surprising to us, given the large field of oxidative copper catalysis. It is well known that oxygen, either under atmospheric conditions or at increased pressures, can readily oxidize copper (I) to copper (II). Many venerable reactions utilize this feature, like the Chan-Lam coupling, or more recently, Stahl’s copper catalyzed oxidation of alcohols to aldehydes. Furthermore, copper mediated halogenations operating via other mechanisms have also recently been rendered catalytic. Given this area of research, we thought the desired bromination could easily be rendered catalytic via simple exposure of the reaction mixture to the atmosphere, and an S$_N$2 displacement of the bromide by the amine would recycle the bromide anion.

A detailed catalytic mechanism is shown in Scheme 4. First the copper (II) bromide can act as a Lewis acid, and affect the enolization of the carbonyl group. This process also produces an equivalent of HBr, which is likely quenched by the amine component present in solution. A second equivalent of copper (II) bromide can coordinate the enol, and the requisite oxidation can occur to generate two equivalents of copper (I) bromide and the α-bromo carbonyl. This species we believe to be rather short lived in solution, as the bromide should rapidly be displaced by the secondary amine in an S$_N$2 fashion to furnish both the desired product as well as a second equivalent of acid.

---


At this stage, all that remains is to regenerate the catalyst. This can be accomplished by oxidation of the copper via molecular oxygen present in the atmosphere. For this process, $\frac{1}{2}$ equivalent of O$_2$ in the presence of two equivalents of acid, which have been generated in the preceding steps, can oxidize the two equivalents of copper (I) to copper (II), while generating water as the only stoichiometric byproduct of this transformation. Given the physical impossibility of the existence of half a molecule of O$_2$, under the reaction conditions, the molecular oxygen is likely converted to hydrogen peroxide during the reoxidation of the copper catalyst, and the hydrogen peroxide produced likely allows a second turnover of the copper catalyst, producing two equivalents of water at that time.$^{14}$

**Scheme 4. Proposed catalytic cycle of the $\alpha$-amination**

III. The $\alpha$-Amination of Carbonyls$^{15}$

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$^{15}$ This work has been published online and in print, see: Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* 2013, *135*, 16074.
To start this project, silyl enol ethers derived from oxazolidinones were synthesized. When this was subjected to 10 mol% CuBr$_2$ and 3 eq. of morpholine in acetonitrile we were delighted to find that the desired product was formed in ~35% yield, depending upon the exact oxazolidinone utilized (Scheme 5). While this was a good proof of principle experiment, ultimately we wished to demonstrate that this process could be feasible with an unfunctionalized carbonyl. Towards this end, propiophenone was selected as a model substrate. Again, when subjected to the reaction conditions, a promising 68% yield of the desired product was observed. While we were delighted with

![Scheme 5: Initial results](image)

this result, we recognized that an alternative mechanism could be operating. It is known that copper (II) amino complexes, in the presence of oxygen, can be oxidized to copper (III) complexes, which readily undergo reductive elimination to furnish the desired C–N bond (Scheme 6). Toward distinguishing between these mechanisms, a few simple experiments were performed (Table 1). When CuCl$_2$ was utilized instead, only 2% yield was observed, which is consistent with a slower displacement of the intermediate.

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Scheme 6. Alternative mechanism towards the α-amination

chloride. When CuBr was utilized, the amount of desired product was significantly decreased to 31%, which is consistent with Kochi’s observation that halogenation is first order with respect to the halide. What is more significant though is that when a copper salt lacking a halide was utilized, none of the desired product was observed. However, if 30 mol% of an exogenous bromide source was added, the reactivity could be restored to 50% yield. These experiments suggest that halide salts are in fact necessary for the reaction, and therefore the desired transformation is likely operating through an α-bromination rather than a copper (III) reductive elimination. However, we wished to

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>additive</th>
<th>yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CuBr₂</td>
<td>MeCN</td>
<td>none</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>CuCl₂</td>
<td>MeCN</td>
<td>none</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>CuBr</td>
<td>MeCN</td>
<td>none</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(TFA)₂</td>
<td>MeCN</td>
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<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Cu(TFA)₂</td>
<td>MeCN</td>
<td>LiBr</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>CuBr₂</td>
<td>CHCl₃/EtOAc</td>
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<td>45%</td>
</tr>
<tr>
<td>8</td>
<td>CuBr₂</td>
<td>THF</td>
<td>none</td>
<td>67%</td>
</tr>
<tr>
<td>9</td>
<td>CuBr₂</td>
<td>DMF</td>
<td>none</td>
<td>71%</td>
</tr>
<tr>
<td>10</td>
<td>CuBr₂</td>
<td>DMSO</td>
<td>none</td>
<td>93%</td>
</tr>
</tbody>
</table>

Table 1. Optimization of the reaction
directly observe our putative intermediate. Towards this end, if the amine was simply omitted, and the reaction was run under an inert atmosphere, α-bromo propiophenone could be observed. Given this data, we believe that the proposed mechanism of α-bromination of the carbonyl is likely to be correct. However, at this stage the enamine catalyzed α-bromination of the carbonyl cannot be discounted. However, when the enamine of propiophenone and morpholine was independently synthesized and subjected to the reaction conditions, only minimal product was observed, indicating that this pathway is also inoperative.

IV. Substrate Scope

With a more complete mechanistic understanding, the desired transformation was optimized. Given that the mechanism is dependent upon a copper mediated soft enolization, we hypothesized that a more polar solvent would help facilitate this. Indeed, DMSO was found to the optimal solvent, furnishing the desired product 1 in 93% isolated yield. We next examined the scope of this reaction, which is summarized in Table 2. When various cyclic amines were tested, the scope was quite broad. A variety of ring sizes could be tolerated, from piperdine, azepane, and even an aziridine in good yield (2 to 7, 71 – 93% yield). Furthermore, thioethers and tertiary amines could be tolerated with no sign of poisoning of the copper catalyst (3 and 4). Tetrahydroisoquinoline could be utilized to afford 7 with no sign of oxidation to the corresponding isoquinoline as well.

However, when acyclic amines were tested, low conversions were observed. We hypothesized that this could be a result of the lower nucleophilicity of acyclic secondary amines relative to their cyclic counterparts. This leads to a slower displacement of the
Table 2. Scope of the amine component

intermediate bromide. To overcome this inherent diminished reactivity, two measures were taken: raising the temperature to promote the displacement and including substoichiometric amounts of sodium iodide. This latter was included to allow a Finkelstein reaction of the intermediate α-bromo carbonyl to furnish the more reactive α-iodo analogue. When both of these modifications to the reaction conditions are employed, acyclic secondary amines can be employed in good efficiencies (8 to 10, 70 – 74% yield). Furthermore, sensitive functional groups, like acetals and allyl amines, are tolerated under these reaction conditions. Unfortunately, primary amines were never coupled successfully under this protocol, as in addition to the further decreased nucleophilicity of primary amines compared to their secondary amine counterparts, the reaction conditions promoted imine formation, which is a catalytically inactive species. However, as
demonstrated, a variety of protecting groups could be utilized, allowing for an easy workaround.

![Chemical reaction diagram](image_url)

**Table 3. The scope of the carbonyl component**

<table>
<thead>
<tr>
<th>Benzylic ketones</th>
<th>Aliphatic ketones</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Structure 11" /></td>
<td><img src="image_url" alt="Structure 16" /></td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 12" /></td>
<td><img src="image_url" alt="Structure 17" /></td>
</tr>
<tr>
<td>11, 92% Yield</td>
<td>16, 71% Yield</td>
</tr>
<tr>
<td>12, 78% Yield</td>
<td>17, 61% Yield</td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 13" /></td>
<td><img src="image_url" alt="Structure 18" /></td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 14" /></td>
<td><img src="image_url" alt="Structure 19" /></td>
</tr>
<tr>
<td>13, 85% Yield</td>
<td>18, 63% Yield</td>
</tr>
<tr>
<td>14, 82% Yield</td>
<td>19, 41% Yield</td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 15" /></td>
<td><img src="image_url" alt="Structure 20" /></td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 15" /></td>
<td><img src="image_url" alt="Structure 21" /></td>
</tr>
<tr>
<td>15, 73% Yield</td>
<td>20, 75% Yield</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>α-Aryl esters</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Structure 22" /></td>
<td><img src="image_url" alt="Structure 24" /></td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 23" /></td>
<td><img src="image_url" alt="Structure 25" /></td>
</tr>
<tr>
<td>22, 71% Yield</td>
<td>24, 71% Yield</td>
</tr>
<tr>
<td>23, 63% Yield</td>
<td>25, 61% Yield</td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 24" /></td>
<td><img src="image_url" alt="Structure 26" /></td>
</tr>
<tr>
<td><img src="image_url" alt="Structure 26" /></td>
<td><img src="image_url" alt="Structure 27" /></td>
</tr>
<tr>
<td>24, 71% Yield</td>
<td>26, 63% Yield</td>
</tr>
<tr>
<td>25, 61% Yield</td>
<td>27, 70% Yield</td>
</tr>
</tbody>
</table>
As shown in Table 3, we found that in addition to propiophenone, a wide range of aromatic ketones could be coupled in good yield (11 to 14, 78 – 92% yield). When electron-donating groups were incorporated onto the aromatic ring, the reaction turned sluggish, and the temperature had to be elevated and the reaction concentrated to 6M. Conversely, with electron withdrawing groups, the reaction mixture needed to be cooled to 5 °C to prevent over oxidation of the substrate. Additionally, both electron-rich and electron-poor heteroarenes could be utilized, with both pyridine (14) and furan (13) providing the desired α-amino carbonyl is good yields. Furthermore, when isovalerophenone, a ketone with β-branching, was utilized, 15 could be isolated in 73% yield with additional heating.

Nevertheless, so far only a small subset of the carbonyl group had been shown to be compatible under the reaction conditions. When butanone was employed, 16 could be observed, however the efficiency of the transformation was lower than desired. While this was certainly a promising result, we hypothesized that the difference of reactivity between the two substrates was due to the difference of the pK\textsubscript{a} between the two classes of substrates (Figure 3). While benzylic ketones typically have a pK\textsubscript{a} of 24.4, aliphatic ketones are harder to enolize, as demonstrated by their pK\textsubscript{a} of 27.1.\footnote{Evans, D. A. pK\textsubscript{a} table, http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf (accessed 4/4/17).} To overcome

![Figure 3. pK\textsubscript{a} of common carbonyls](image)
this inherent decrease in reactivity, we hypothesized that the addition of a catalytic amount of Lewis acid would accelerate the enolization and allow for a more efficient transformation. Indeed, when 25 mol% Sc(OTf)$_3$ was added to the reaction mixture, an 14% increase in yield was observed, affording 61% yield of the desired amine (Table 4). When other Lewis acids were tested, a few trends emerged. Titanium and boron Lewis acids failed to be beneficial to the reaction mixture, and in some cases inhibited the desired transformation. However, the inclusion of additional metal halide salts (NiBr$_2$, MgBr$_2$, MgI$_2$, and ZnBr$_2$) proved to be beneficial.$^{18}$

![Chemical structure](image)

**Table 4. Effect of Lewis acid additives**

<table>
<thead>
<tr>
<th>additive</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>47%</td>
</tr>
<tr>
<td>BBr$_3$</td>
<td>23%</td>
</tr>
<tr>
<td>BF$_3$$\cdot$OEt$_2$</td>
<td>51%</td>
</tr>
<tr>
<td>Bu$_2$BOTf</td>
<td>45%</td>
</tr>
<tr>
<td>SnCl$_2$</td>
<td>6%</td>
</tr>
<tr>
<td>Sc(OTf)$_3$</td>
<td>61%</td>
</tr>
<tr>
<td>NiCl$_2$</td>
<td>33%</td>
</tr>
<tr>
<td>NiBr$_2$</td>
<td>86%</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>0%</td>
</tr>
<tr>
<td>ZnBr$_2$</td>
<td>83%</td>
</tr>
</tbody>
</table>

A range of ketones could be utilized, provided Lewis acidic additives were included. In the case of unsymmetrical ketones, methylene positions were preferentially substituted over both methyl and methine positions (16 to 19). Copper mediated halogenations have long been known to be selective for methylene positions over other types, and the selectivity has never been fully elucidated. The selectivity over the methyl

position can be explained by the increased nucleophilicity of the internal enol\(^{19}\), while the same argument cannot be made for the selectivity over the methine position. It is possible that in this case a steric argument can explain this selectivity, however no theories have been put forth that comprehensively explain the observed reactivity. Mechanistic concerns aside, this transformation is tolerant of steric bulk, as ketones attached to \(^1\)Bu groups can still undergo the desired transformation in good yield (20, 75% yield). When pentanone, a symmetrical ketone, was utilized, selective mono-amination could be achieved under slightly modified reaction conditions (21, 50% yield). These consist of a lower temperature to limit difunctionalization, utilization of THF instead of DMSO to allow for lower temperature, and inclusion of sodium iodide to promote the requisite S\(_\text{N}\)2 displacement.

Satisfied with the scope of ketones, we turned our attention towards other types of carbonyls. Given the pK\(_a\)’s of ketones, it appeared that the \(\alpha\)-amination of aldehydes should be possible. Indeed this was found to be the case. However, the product of the desired transformation was unstable, as after enolization of the product, the resulting enamine could hydrolyze, removing the newly installed amine. For isolation purposes, the crude reaction was subjected to a Wittig workup, where it was treated with 6.75 equivalents of a preformed phosphorous ylide. With this workup procedure, we found that lowering the equivalents to 1.5 eq. of the amine component was beneficial, presumably to decrease the amount of condensation between the two starting materials, which forms a catalytically inactive species. Both octanal and isovaleraldehyde, an

aldehyde with β-branching, could be utilized in good efficiencies (22 and 23, 71 and 63% yields, respectively).

Still, we wished to further expand the scope of carbonyls in this transformation, specifically to also include esters. Attempts to utilize simple esters were unsuccessful, even under our most forcing conditions, due to the higher pKₐ of 30.3 for the carbonyl. In fact, the only observed transformation was direct attack on the carbonyl by the amine to form an amide side product. However, the pKₐ of α-aryl esters is 23.6, which is significantly lower, and we hypothesized that in this case the desired transformation could outcompete the undesired amidation pathway. Indeed, this was the case, even under elevated temperatures, as a variety of α-aryl esters could be utilized with only 1–2% of the amidation product observed. Aryl bromides had no effect upon the reaction, and electron-rich and electron-withdrawing groups could be incorporated on the aromatic ring (24 to 26, 61 – 71% yield). Unsurprisingly, chemoselectively for the amination could be achieved between morpholine and a tosylamine, as 27 is formed in 70% yield when a tosylamine is incorporated on the aromatic ring.

Satisfied with the scope of the developed transformation at this time, the utility of this transformation was demonstrated by synthesizing pharmaceutical agents. First, this methodology was applied towards the synthesis of amfepramone. This can readily be achieved from subjecting propiophenone and diethyl amine to the reaction conditions. This directly affords the pharmaceutical in 80% yield (Scheme 7). Additionally, the blockbuster drug Plavix could also be directly synthesized using this method. When the requisite starting materials, both commercially available, were subjected to the reaction

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conditions, Plavix could be isolated in 87% isolated yield, allowing for a one step racemic synthesis of the pharmaceutical agent.

Scheme 7. The direct synthesis of amfepramone and (±)-Plavix

V. Conclusion

In conclusion, we have shown that this important motif can be directly synthesized via the use of copper catalysis under mildly oxidizing conditions. This protocol allows for the selective coupling of two nucleophiles by rendering one component transiently electrophilic. This has been applied to a number of classes of substrates, culminating in the synthesis of two pharmaceutical agents, including the blockbuster drug Plavix. While initial attempts to render this transformation asymmetric showed promising results, ultimately this effort proved unsuccessful due to \textit{in-situ} Finkelstein reaction of the bromide that eroded the stereoselectivity of the initial bromination.
VI. Supporting Information

General Information

Commercial reagents were purchased from Sigma Aldrich and purified prior to use following the guidelines of Perrin and Armarego. All solvents were purified according to the method of Grubbs. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography according to the method of Still on ICN 60 32-64 mesh silica gel 63. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or by KMnO₄ and iodine stain.

¹H NMR spectra was recorded on a Bruker 500 (500 MHz) or a Bruker 300 (300 MHz) and are internally referenced to residual protio solvent signals (CDCl₃) at δ 7.27 ppm (¹H). Data for ¹H NMR are reported as follows: chemical shift (δ ppm) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad), integration, coupling constant (Hz) and assignment. ¹³C spectra were recorded on a Bruker 500 (126 MHz) and are referenced relative to CDCl₃ at δ 77.16 ppm. Data for ¹³C NMR are reported in terms of chemical shift and multiplicity where appropriate. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of wavenumber of absorption (cm⁻¹). High Resolution Mass spectra were obtained from the Princeton University Mass Spectral Facility.
2-Morpholino-1-phenylpropan-1-one (1)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (152 mg, 93% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.07 (d, J = 6.9 Hz, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 4.05 (q, J = 6.8 Hz, 1H), 3.66 (m, 4H), 2.60 (m, 2H), 2.53 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H).

Data are consistent with those reported in the literature: Stas, S.; Abbaspour Tehrani, K. Synthesis, 2007, 433.

2-Morpholino-1-phenylpropan-1-one (1)

CuBr$_2$ (800 mg, 3.72 mmol, 0.1 equiv) was dissolved in DMSO (37.25 mL, 1.0 M with respect to the carbonyl component), and propiophenone (5.0 g, 37.25 mmol, 1.0 equiv)
was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (10 mL, 111.50 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was diluted with brine (200 mL), and extracted with EtOAc until TLC analysis showed no product in the aqueous phase (7X200 mL). The organic layers were dried with MgSO₄, filtered, concentrated and purified by column chromatography to give the tertiary amine (7.1 g, 87% Yield).

![Image](image_url)

1-Phenyl-2-(piperidin-1-yl)propan-1-one (2)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of piperidine (148 µL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (142 mg, 88% Yield). £H NMR (500 MHz, CDCl₃) δ 8.12 (m, 2H), 7.52 (m, 1H), 7.44 (m, 2H), 4.06 (q, J = 6.8 Hz, 1H), 2.55 (m, 4H), 1.54 (m, 4H), 1.42 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H);

**1-Phenyl-2-thiomorpholinopropan-1-one (3)**

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.37 mL, 2.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of thiomorpholine (149 µL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at 50 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (153 mg, 87% Yield). \(^1\)H NMR (500 MHz, CDCl₃) δ 8.07 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.15 (q, J = 6.8 Hz, 1H), 2.92 (m, 4H), 2.67 (m, 4H), 1.25 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (100 MHz) δ 200.1, 136.2, 133.0, 128.9, 128.4, 65.2, 51.6, 28.4, 9.9; HRMS (ESI-TOF) m/z calculated for C\(_{13}\)H\(_{18}\)NOS [M+H]\(^+\) 235.10305, found 235.10266, Δ 1.79 ppm; IR (film) 2909, 2819, 1683, 1596, 1447, 1231, 1209, 1183, 1122, 980, 958, 907, 741, 693.

**2-(4-Methylpiperazin-1-yl)-1-phenylpropan-1-one (4)**

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv)
was added. This was stirred for 10 minutes at room temperature before the addition of 1-methylpiperazine (165 µL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (130 mg, 75% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.11 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.07 (q, J = 6.8 Hz, 1H), 2.70 (m, 4H), 2.49 (m, 2H), 2.26 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz) δ 200.5, 136.2, 133.0, 128.9, 128.4, 64.5, 55.3, 46.0, 11.7; HRMS (ESI-TOF) m/z calculated for C14H20N2O [M+H]$^+$ 232.15756, found 245.15727, Δ 1.28 ppm; IR (film) 2935, 2794, 1682, 1597, 1448, 1373, 1284, 1231, 1170, 1146, 1013, 922, 812, 746, 702, 687.

![Chemical Structure](image)

2-(Azepan-1-yl)-1-phenylpropan-1-one (5)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of azepane (269 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (141 mg, 82% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.13 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 4.27 (q, J = 6.6 Hz, 1H), 2.72 (t, J = 5.6 Hz), 1.71 (m, 2H), 1.54 (m, 6H), 1.25 (d, J = 6.6
Hz, 3H); \textsuperscript{13}C NMR (100 MHz) \( \delta \) 201.0, 136.6, 132.7, 129.0, 128.2, 64.6, 51.5, 29.4, 27.1, 10.0; HRMS (ESI-TOF) m/z calculated for \( \text{C}_{15}\text{H}_{22}\text{NO} \) \([\text{M+H}]^+\) 231.16231, found 231.16197, \( \Delta \) 1.49 ppm; IR (film) 2925, 2852, 1684, 1597, 1580, 1448, 1393, 1368, 1330, 1262, 1220, 1175, 1138, 1110, 1007, 969, 899, 728, 691.

![Chemical structure](image)

1-Phenyl-2-(2,2,3,3-tetramethylaziridin-1-yl)propan-1-one (6)

\( \text{CuBr}_2 \) (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 2,2,3,3-tetramethylaziridine (148 mg, 1.49 mmol, 2.0 equiv). The reaction was stirred for 8 hours at 40 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (122 mg, 71% Yield). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.94, (m, 2H) 7.48 (m, 1H), 7.38 (m, 2H), 3.82 (q, \( J = 7.0 \) Hz, 1H), 1.34 (d, \( J = 7.0 \) Hz, 3H), 1.21 (s, 3H), 1.16 (m, 6H), 0.90 (s, 3H); \textsuperscript{13}C NMR (100 MHz) \( \delta \) 201.8, 135.6, 132.8, 128.7, 128.5, 57.9, 41.9, 41.0, 24.5, 23.2, 20.53, 15.2, 14.7; HRMS (ESI-TOF) m/z calculated for \( \text{C}_{15}\text{H}_{22}\text{NO} \) \([\text{M+H}]^+\) 231.16231, found 232.16260, \( \Delta \) 1.25 ppm; IR (film) 3065, 2998, 2942, 1693, 1673, 1448, 1377, 1274, 1206, 1156, 970, 697.
2-(3,4-Dihydroisoquinolin-2(1H)-yl)-1-phenylpropan-1-one (7)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 1,2,3,4-tetrahydroisoquinoline (189 µL, 1.49 mmol, 2.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (178 mg, 90% Yield). ¹H NMR (500 MHz, CDCl₃) δ 8.17 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.15 (m, 4H), 4.32 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 14.8 Hz, 1H), 3.81 (d, J = 14.8 Hz, 1H), 2.91 (m, 4H), 1.39 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz) δ 200.6, 136.2, 134.9, 134.5, 133.0, 128.9, 128.8, 128.5, 126.6, 126.0, 125.6, 65.3, 52.1, 47.2, 29.7, 11.3; HRMS (ESI-TOF) m/z calculated for C₁₈H₁₉NO [M+H]⁺ 265.14666, found 245.14704, Δ 1.42 ppm; IR (film) 3063, 2977, 2920, 2805, 1681, 1596, 1447, 1388, 1222, 1153, 1107, 971, 922, 710, 699.
2-(Butyl(4-methoxybenzyl)amino)-1-phenylpropan-1-one (8)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of $N$-(4-methoxybenzyl)butan-1-amine (360 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (179 mg, 74% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (m, 2H), 7.53 (m, 1H), 7.39 (m, 2H), 7.10 (d, $J = 8.6$ Hz, 2H), 6.81 (d, $J = 8.6$ Hz, 2H), 4.34 (q, $J = 6.6$ Hz, 1H), 3.80 (s, 3H), 3.65 (d, $J = 13.5$ Hz, 1H) 3.45 (d, $J = 13.5$ Hz, 1H), 2.52 (m, 2H), 1.45 (m, 2H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.24 (m, 2H), 0.77 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (100 MHz) δ 202.0, 158.7, 136.9, 132.5, 131.7, 130.4, 128.9, 128.0, 113.5, 58.6, 55.3, 54.4, 49.7, 30.5, 20.2, 14.0, 8.3; HRMS (ESI-TOF) m/z calculated for C$_{21}$H$_{27}$NO$_2$ [M+H]$^+$ 326.20418, found 326.20456, Δ 1.17 ppm; IR (film) 2959, 2934, 2873, 2836, 2175, 2085, 1990, 1913, 1680, 1601, 1543, 1513, 1450, 1377, 1304, 1248, 1177, 1112, 1069, 1025, 832, 790, 716, 672, 656.
2-(Allyl(4-methoxybenzyl)amino)-1-phenylpropan-1-one (9)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of $N$-(4-methoxybenzyl)prop-2-en-1-amine (330 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (161 mg, 70% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.40 (t, 7.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 5.79 (m, 1H), 5.16 (dd, J = 23.5 Hz, 10.0 Hz, 2H), 4.42 (q, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.65 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.19 (dd, J = 14.0, 5.5 Hz, 1H), 3.06 (dd, J = 14.0, 8.0 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz) δ 202.0, 158.7, 136.9, 136.6, 132.6, 131.4, 130.2, 129.0, 128.1, 117.6, 113.5, 58.1, 55.3, 53.6, 53.3, 8.7; HRMS (ESI-TOF) m/z calculated for C$_{20}$H$_{21}$NO$_2$ [M+H]$^+$ 309.17288, found 309.16637, Δ 21.05 ppm; IR (film) 2937, 2837, 2048, 1960, 1901, 1680, 1601, 1512, 1448, 1378, 1303, 1246, 1178, 1111, 1069, 1026, 991, 932, 831, 759, 718.
2-(Benzyl(2,2-dimethoxyethyl)amino)-1-phenylpropan-1-one (10)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) and NaI (56 mg, 0.37 mmol, 0.5 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of N-benzyl-2,2-dimethoxyethan-1-amine (330 mg, 1.86 mmol, 2.5 equiv). The reaction was stirred for 12 hours at 60 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (181 mg, 74% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.99 (m, 2H), 7.60 (m, 1H), 7.46 (m, 2H), 7.31 (m, 3H), 7.19 (m, 2H), 4.53 (q, J = 6.7 Hz, 1H), 4.19 (t, J = 5.3 Hz, 1H), 3.80 (d, J = 13.6 Hz, 1H), 3.67 (d, J = 13.6 Hz, 1H), 3.32 (s, 3H), 3.14 (s, 3H), 2.81 (m, 2H), 1.34 (d, J = 6.7 Hz, 3H);

$^{13}$C NMR (100 MHz) δ 202.0, 139.6, 136.7, 132.7, 129.2, 128.2, 128.1, 127.2, 104.7, 59.9, 56.0, 54.5, 53.2, 52.6, 9.7; HRMS (ESI-TOF) m/z calculated for C$_{20}$H$_{25}$NO$_3$ [M+H]$^+$ 327.18344, found 327.18299, Δ 1.38 ppm; IR (film) 3066, 3027, 2934, 2832, 2201, 2178, 2052, 2008, 1961, 1682, 1597, 1581, 1494, 1448, 1374, 1227, 1124, 1075, 1027, 971, 927, 829, 739, 696.
2-Morpholino-1-(4-(trifluoromethyl)phenyl)propan-1-one (11)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(4-(trifluoromethyl)phenyl)propan-1-one (151 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was then stirred at 5 °C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give tertiary amine (197 mg, 92% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.20 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 4.03 (q, J = 6.8 Hz, 1H), 3.64 (m, 4H), 2.56 (m, 4H), 1.27 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz) δ 199.1, 138.7, 134.1 (q, J = 32.7 Hz) 129.2, 125.4, 67.0, 65.3, 49.8, 10.4; HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{17}$F$_3$NO$_2$ [M+H]$^+$ 287.11331, found 245.11311, Δ 0.71 ppm; IR (film) 2961, 2855, 2824, 1691, 1453, 1409, 1320, 1254, 1220, 1166, 1110, 1065, 1016, 925, 853, 786, 696.

1-(4-Methoxyphenyl)-2-morpholinopropan-1-one (12)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 1-(4-methoxyphenyl)propan-1-one (122 mg,
0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was then heated to 60 °C and stirred for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (145 mg, 78% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.95 (q, J = 7.0 Hz, 1H), 3.82 (s, 3H), 3.63 (m, 4H), 2.57 (m, 2H), 2.48 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz) δ 198.8, 163.4, 131.2, 129.8, 113.6, 67.2, 64.8, 55.4, 50.2, 12.1; HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{19}$NO$_3$ [M+H]$^+$ 249.13649, found 249.13665, Δ 0.62 ppm; IR (film) 2959, 1851, 1673, 1598, 1508, 1454, 1306, 1254, 1228, 1168, 1115, 1028, 926, 844, 785.

1-(Furan-2-yl)-2-morpholinopropan-1-one (13)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(furan-2-yl)propan-1-one (92 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred for 12 hours at room temperature, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (133 mg, 85% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (d, J = 1.8 Hz, 1H), 7.36
(d, J = 3.6 Hz, 1H), 6.49 (dd, J = 3.6, 1.8 Hz, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.64 (m, 4H), 2.57 (m, 2H), 2.47 (m, 2H), 1.24 (d, J = 6.9 Hz, 3H).


![Structural formula](image)

**2-Morpholino-1-(pyridin-4-yl)propan-1-one (14)**

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 1-(pyridin-4-yl)propan-1-one (101 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 5 °C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (164 mg, 82% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.77 (d, J = 6.1 Hz, 2H), 7.84 (d, J = 6.1 Hz, 2H), 3.99 (q, J = 6.8 Hz, 1H), 3.64 (m, 4H), 2.55 (m, 4H), 1.26 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz) δ 199.5, 150.8, 142.0, 121.8, 67.0, 65.2, 49.7, 10.0; HRMS (ESI-TOF) m/z calculated for C$_{12}$H$_{16}$N$_2$O$_2$ [M+H]$^+$ 220.12118, found 245.12044, Δ 3.35 ppm; IR (film) 2952, 2853, 1697, 1554, 1454, 1408, 1255, 1226, 1116, 930, 855, 771.
3-Methyl-2-morpholino-1-phenylbutan-1-one (15)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and 3-methyl-1-phenylbutan-1-one (121 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was then heated to 50 ºC and stirred for 12 hours, at which point morpholine was added (200 µL, 2.23 mmol, 3.0 equiv) and stirred at 50 ºC for 12 hours. The crude reaction mixture was then loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (135 mg, 73% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (m, 2H), 7.51 (m, 1H), 7.47 (m, 2H) 3.80 (d, J = 10.0 Hz, 1H), 3.64 (m, 2H), 3.57 (m, 2H), 2.56 (m, 4H), 2.26 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz) δ 200.6, 139.4, 128.8, 127.9, 72.2, 67.7, 50.1, 26.6, 19.9, 19.8; HRMS (ESI-TOF) m/z calculated for C$_{15}$H$_{22}$NO$_2$ [M+H]$^+$ 247.15723, found 247.15673, Δ 2.01 ppm; IR (film) 2958, 2852, 1669, 1596, 1579, 1447, 1292, 1252, 1217, 1114, 1011, 916, 867, 843, 730, 712, 687.
3-Morpholinobutan-2-one (16)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) and ZnBr₂ (40 mg, 0.18 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and butanone (54 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (83 mg, 71% Yield). ¹H NMR (500 MHz, CDCl₃) δ 3.66 (m, 2H), 3.00 (q, J = 6.9 Hz, 1H), 2.44 (m, 2H), 2.36 (m, 2H), 2.15 (s, 3H), 1.09 (d, J = 6.9 Hz; ¹³C NMR (100 MHz) δ 210.9, 69.9, 67.1, 50.4, 26.5, 11.2; HRMS (ESI-TOF) m/z calculated for C₈H₁₆NO₂ [M+H]⁺ 157.11028, found 157.11035, Δ 0.45 ppm; IR (film) 2960, 2853, 2818, 1713, 1453, 1353, 1264, 1252, 1232, 1147, 1114, 1068, 930, 917, 856, 731.

3-Morpholino-4-phenylbutan-2-one (17)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) and NiBr₂ (24 mg, 0.11 mmol, 0.15 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 4-
phenylbutan-2-one (110 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 18 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (106 mg, 61% Yield). \[^1^H\text{NMR}\] (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.30 (m, 2H), 7.22 (m, 3H), 3.76 (m, 4H), 3.40 (dd, \(J = 9.5, 4.5\) Hz, 1H), 2.99 (dd, \(J = 13.3, 9.5\) Hz, 2H), 2.87 (dd, \(J = 13.3, 4.5\) Hz, 1H), 2.69 (m, 4H), 2.08 (s, 3H); \[^{13}\text{C}\text{NMR}\] (100 MHz) \(\delta\) 208.5, 138.8, 129.3, 128.8, 126.3, 75.6, 67.3, 50.3, 31.3, 29.5; HRMS (ESI-TOF) m/z calculated for C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} [M+H]\textsuperscript{+} 233.14158, found 245.14195, \(\Delta\) 1.59 ppm; IR (film) 3028, 2957, 2852, 1713, 1602, 1494, 1453, 1351, 1290, 1248, 1134, 1120, 1009, 861, 736, 698.

3-Morpholino-5-en-2-one (18)

CuBr\textsubscript{2} (16 mg, 0.07 mmol, 0.1 equiv) and NiBr\textsubscript{2} (24 mg, 0.11 mmol, 0.15 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and hex-5-en-2-one (73 mg, .75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 18 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (86 mg, 63% Yield).
Yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.72 (ddr, $J = 17.1, 10.1, 7.0$ Hz, 1H), 5.12 (m, 2H), 3.75 (m, 4H), 3.08 (dd, $J = 8.5, 5.5$ Hz, 1H), 2.64 (m, 2H), 2.52 (m, 4H), 2.19 (s, 3H); $^{13}$C NMR (100 MHz) $\delta$ 209.1, 134.5, 117.5, 74.2, 67.2, 50.6, 30.5, 28.4; HRMS (ESI-TOF) m/z calculated for C$_{10}$H$_{17}$NO$_2$ [M+H]$^+$ 184.13375, found 184.13380, $\Delta$ 0.26 ppm; IR (film) 2959, 2853, 1714, 1640, 1452, 1353, 1291, 1248, 1141, 1170, 1117, 977, 911, 875, 862.

![2-Methyl-4-morpholinopentan-3-one (19)](image)

2-Methyl-4-morpholinopentan-3-one (19)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) and MgI$_2$ (51 mg, 0.19 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 2-methylpentan-3-one (75 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 $\mu$L, 2.23 mmol, 3.0 equiv) and placed under an atmosphere of oxygen. The reaction was stirred at room temperature for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (58 mg, 41% Yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.70 (m, 4H), 3.31 (q, $J = 7.0$ Hz, 1H), 2.0 (hept, $J = 7.0$ Hz, 1H), 2.55 (m, 2H), 2.47(m, 2H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.06 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (100 MHz) $\delta$ 215.5, 67.1, 50.2, 37.6, 29.7, 18.9, 18.5, 10.6; HRMS (ESI-TOF) m/z calculated for C$_{10}$H$_{20}$NO$_2$ [M+H]$^+$
185.14171, found 185.14171, \( \Delta \) 0.73 ppm; IR (film) 2965, 2933, 2853, 1711, 1453, 1379, 1326, 1290, 1251, 1147, 1116, 1001, 939, 854.

\[
\text{2,2-Dimethyl-4-morpholinopentan-3-one (20)}
\]

CuBr\(_2\) (16 mg, 0.07 mmol, 0.1 equiv) and NiBr\(_2\) (40 mg, 0.19 mmol, 0.25 equiv) were dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and 2,2-dimethylpentan-3-one (85 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 \( \mu \text{L}, 2.23 \text{ mmol, 3.0 equiv}) and placed under an atmosphere of oxygen. The reaction was stirred at 60 °C for 12 hours, at which point morpholine (200 \( \mu \text{L}, 2.23 \text{ mmol, 3.0 equiv}) was added again. The reaction was stirred at 60 °C for another 12 hours, before another addition of morpholine (200 \( \mu \text{L}, 2.23 \text{ mmol, 3.0 equiv}). This was stirred at 60 °C for another 12 hours, before the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (111 mg, 75% Yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.74 (m, 5H), 2.63 (m, 2H), 2.49 (m, 2H), 1.19 (s, 9H); \(^{13}\)C NMR (100 MHz) \( \delta \) 214.8, 67.1, 61.9, 49.7, 44.0, 26.7, 11.0; HRMS (ESI-TOF) m/z calculated for C\(_{11}\)H\(_{21}\)NO\(_2\) [M+H]\(^+\) 200.16505, found 245.16447, \( \Delta \) 2.89 ppm; IR (film) 2958, 2853, 1702, 1479, 1453, 1363, 1326, 1289, 1254, 1200, 1143, 1117, 1046, 990, 933, 857, 793.
2-Morpholinopentan-3-one (21)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) and ZnBr₂ (16 mg, 0.07 mmol, 0.10 equiv) were dissolved in THF (0.12 mL, 6.0 M with respect to the carbonyl component), and pentan-3-one (64 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv) and sodium iodide (112 mg, 0.75 mmol, 1.0 equiv). The reaction was then placed under an atmosphere of oxygen and stirred at 10 °C for 12 hours. The crude reaction mixture was then loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (64 mg, 50% Yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.65 (m, 4H), 3.06 (q, J = 6.9 Hz, 1H), 2.52 (t, J = 7.3 Hz, 2H), 2.45 (m, 2H), 2.37 (m, 2H), 1.08 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.3 H, 3H).


\((E)-4-(1-\text{Phenynon-1-en-3-yl})\text{morpholine (22)}\)
CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in MeCN (1.5 mL, 0.5 M with respect to the carbonyl component), and octanal (96 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (100 µL, 1.12 mmol, 1.5 equiv). The reaction was stirred at room temperature for 6 hours. The reaction mixture was then added to a 0.3 M solution of the wittig reagent (16.75 mL, 5.03 mmol, 6.75 equiv) under a atmosphere of nitrogen. The reaction was stirred for 16 hours, and then quenched with a saturated solution of ammonium chloride. The organics were extracted three times with DCM, dried with MgSO$_4$, and filtered. The solution was concentrated and purified by column chromatography to give the tertiary amine (161 mg, 75% Yield, 3:1 d.r.). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (m, 2H), 7.33 (m, 2H), 7.24 (m, 1H), 6.43 (d, $J = 15.9$ Hz, 1H), 6.09 (dd, $J = 15.9$, 9.1 Hz, 1H), 3.68 (m, 4H), 2.83 (td, $J = 9.1$, 4.2 Hz, 1H), 2.58 (m, 4H), 1.74 (m, 1H), 1.49 (m, 1H), 1.28 (m, 8H), 0.86 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz) $\delta$ 136.9, 132.8, 129.9, 128.6, 127.4, 126.3, 68.5, 67.3, 50.7, 31.9, 31.8, 29.5, 26.3, 22.7, 14.2; HRMS (ESI-TOF) m/z calculated for C$_{19}$H$_{29}$NO [M+H]$^+$ 287.22491, found 287.22491, $\Delta$ 1.15 ppm; IR (film) 2954, 2926, 2853, 2811, 1494, 1456, 1267, 1117, 968, 865, 747, 692.
(E)-4-(4-Methyl-1-phenylpent-1-en-3-yl)morpholine (23)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in MeCN (1.5 mL, 0.5 M with respect to the carbonyl component), and isovaleraldehyde (64 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (100 µL, 1.12 mmol, 1.5 equiv). The reaction was stirred at room temperature for 5 hours. The reaction mixture was then added to a then added a 0.3 M solution of the Wittig reagent (16.75 mL, 5.03 mmol, 4.5 equiv). The reaction was stirred for 16 hours, and then quenched with a saturated solution of ammonium chloride. The organics were extracted three times with DCM, dried with MgSO₄, and filtered. The solution was concentrated and purified by column chromatography to give the tertiary amine (122 mg, 67% Yield, 6:1 d.r.). ¹H NMR (500 MHz, CDCl₃) δ 7.42 (m, 2H), 7.35 (m, 2H), 7.25 (m, 1H), 6.41 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 9.5 Hz), 3.77 (m, 4H), 2.63 (m, 2H), 2.51 (dd, J = 9.5, 7.2 Hz, 1H), 2.48 (m, 2H), 2.1 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz) δ 137.2, 133.8, 128.6, 128.1, 127.5, 126.4, 74.5, 67.5, 50.8, 28.2, 20.5, 18.4; HRMS (ESI-TOF) m/z calculated for C₁₆H₂₃NO [M+H]⁺ 245.17796, found 245.17785, Δ 0.48 ppm; IR (film) 3026, 2955, 2851, 2807, 1599, 1494, 1449, 1384, 1365, 1285, 1268, 1253, 1139, 1116, 1070, 1030, 1008, 971, 877, 747, 692.
Methyl 2-morpholino-2-phenylacetate (24)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-phenylacetate (112 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 °C for 12 hours, at which point morpholine (200 µL, 2.23 mmol, 3.0 equiv) was added again. The reaction was stirred at 50 °C for another 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (142 mg, 81% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42 (m, 2H), 7.33 (m, 3H), 3.96 (s, 3H), 3.72 (t, J = 4.7 Hz, 4H), 3.67 (s, 3H), 2.43 (t, J = 4.7 Hz, 4H).


Methyl 2-(3-methoxyphenyl)-2-morpholinoacetate (25)
CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-(3-methoxyphenyl)acetate (134 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 °C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (140 mg, 71% Yield). \( ^1H \) NMR (500 MHz, CDCl₃) δ 7.52 (d, \( J = 8.1 \) Hz, 1H), 7.27 (m, 2H), 7.12 (m, 1H), 4.19 (s, 1H), 4.07 (s, 3H), 3.99 (m, 4H), 3.94 (s, 3H), 2.71 (m, 4H); \( ^13C \) NMR (100 MHz) δ 171.6, 159.8, 136.7, 129.6, 121.3, 114.2, 114.0, 74.5, 66.8, 55.4, 55.2, 51.7; HRMS (ESI-TOF) m/z calculated for C₁₄H₂₀NO₄ [M+H]^+ 265.13141, found 265.13155, Δ 0.53 ppm; IR (film) 2954, 2838, 1742, 1599, 1585, 1489, 1450, 1435, 1259, 1197, 1149, 1114, 1022, 876, 781, 745, 693.

Methyl 2-(4-bromophenyl)-2-morpholinoacetate (26)

CuBr₂ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.12 mL, 6.0 M with respect to the carbonyl component), and methyl 2-(4-bromophenyl)acetate (171 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv). The reaction was stirred at 50 °C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (213 mg,
91% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 3.91 (s, 1H), 3.68 (t, J = 5.0 Hz, 4H), 3.63 (s, 3H), 2.40 (t, J = 5.0 Hz, 4H).


Methyl 2-(4-((4-methylphenyl)sulfonamido)phenyl)-2-morpholinoacetate (27)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.24 mL, 3.0 M with respect to the carbonyl component), and methyl 2-(4-((4-methylphenyl)sulfonamido)phenyl)acetate (238 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of morpholine (200 µL, 2.23 mmol, 3.0 equiv), and placed under an atmosphere of oxygen. The reaction was stirred at 70 °C for 12 hours, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (211 mg, 70% Yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 6.61 (br, 1H), 3.89 (s, 1H), 3.69 (t, J = 4.6 Hz, 4H), 3.66 (s, 3H), 2.38 (s, 3H), 2.36 (m, 4H); $^{13}$C NMR (100 MHz) δ 169.0, 141.6, 134.3, 133.6, 129.5, 127.3, 127.2, 124.7, 118.3, 71.1, 64.2, 49.7, 49.0, 19.1; HRMS (ESI-TOF) m/z calculated for C$_{20}$H$_{24}$N$_2$O$_5$S [M+H]$^+$
404.14059, found 404.13996, Δ 1.56 ppm; IR (film) 3257, 2954, 2856, 1737, 1611, 1598, 1510, 1452, 1329, 1157, 1115, 1091, 1020, 910, 879, 814, 728, 662.

2-(Benzy|l(2,2-dimethoxyethyl)amino)-1-phenylpropan-1-one (amfepramone)

CuBr₂ (32 mg, 0.14 mmol, 0.2 equiv) and phenanthroline (30 mg, 0.16 mmol, 0.22 equiv) were dissolved in DMSO (0.75 mL, 1.0 M with respect to the carbonyl component), and propiophenone (100 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of diethylamine (154 µL, 1.49 mmol, 2.0 equiv). The reaction was placed under an atmosphere of oxygen, and the reaction flask was sealed. The reaction was stirred for 90 minutes at 35 °C, after which the crude reaction mixture was loaded directly onto a column of silica gel and purified by column chromatography to give the tertiary amine (122 mg, 80% Yield). ¹H NMR (500 MHz, CDCl₃) δ 8.16 (m, 2H), 7.57 (m, 3H), 4.38 (q, J = 7.0 Hz, 1H), 2.72 (m, 4H), 1.25 (d, J = 7.0 Hz, 3H), 1.03 (t, J = 7.0 Hz, 6H);

Methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate (Plavix)

CuBr$_2$ (16 mg, 0.07 mmol, 0.1 equiv) was dissolved in DMSO (0.37 mL, 2.0 M with respect to the carbonyl component), and methyl 2-(2-chlorophenyl)acetate (148 mg, 0.75 mmol, 1.0 equiv) was added. This was stirred for 10 minutes at room temperature before the addition of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (311 mg, 2.23 mmol, 3.0 equiv). The reaction was placed under an atmosphere of oxygen and stirred at room temperature for 24 hours, after which the crude reaction mixture was loaded directly onto a Biotage KP-NH snap column and purified by column chromatography to give the tertiary amine (209 mg, 87% Yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.41 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.25 (m, 2H), 7.00 (d, $J = 4.0$ Hz, 1H), 6.61 (d, $J = 4.0$ Hz, 1H), 4.85 (s, 1H), 3.70 (d, $J = 12.0$ Hz, 1H), 3.64 (s, 3H), 3.57 (d, $J = 12.0$ Hz, 1H), 2.82 (s, 4H);

Data are consistent with those reported in the literature: Aillaud, I.; Haurena, C.; Le Gall, E.; Martens, T.; Ricci, G. *Molecules*, **2010**, 8144.
Chapter 3

A Dual Catalytic Decarboxylative Coupling of sp\(^3\) Hybridized Carboxylic Acids and Aryl Halides

I. A Brief Introduction to Photoredox Catalysis

In recent years, one of the most exciting areas of catalysis to emerge has been photoredox catalysis. Although there were initial reports in the late 1970s and early 1980s, it wasn’t until seminal reports by Yoon,\(^1\) MacMillan,\(^2\) and Stephenson\(^3\) in the late 2000s that the field gained mainstream attention and saw a near exponential increase in growth (Figure 1).\(^4\) This area of research has become a prominent focus in our group, and

Figure 1. Number of photoredox publications by year

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we aim to leverage this class of catalysis to develop new methods for organic synthesis.

One reason for our interest in this area is that it allows for the conversion of visible light of visible light into 55 kcal mol\(^{-1}\) of chemical energy.\(^5\) This can be accomplished by utilizing a catalyst that absorbs in the visible region of the spectra. Since the majority of organic compounds only absorb higher energy light (i.e. UV light), this allows for the targeted delivery of energy to the catalyst over everything else in the reaction mixture.

Typically photoredox catalysts are metal polypyridyl complexes (Figure 2); most commonly iridium and ruthenium complexes. However, photocatalysts based upon gold\(^6\), platinum,\(^7\) molybdenum,\(^8\) chromium,\(^9\) tungsten,\(^10\) osmium,\(^11\) and copper\(^12\) have been

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\(^5\) This number can be calculated from emission of the triplet state of Ir(ppy)\(_3\). See: Hofbeck, T.; Yersin, H.; Inorg. Chem. 2010, 49, 9290.


developed, and in recent years fully organic photocatalysts have become an increasing area of research.\textsuperscript{13}

To explain the reactivity of these classes of compounds, we shall examine an Iridium catalyst, Ir(dF(CF\textsubscript{3})ppy)\textsubscript{2}(dtbbpy)PF\textsubscript{6} (Figure 3).\textsuperscript{14} Upon absorption of visible light, an electron is promoted from a metal centered d orbital to generate a high-

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Photochemical behavior of Ir(dF(CF\textsubscript{3})ppy)\textsubscript{2}(dtbbpy)PF\textsubscript{6}}
\end{figure}
\end{center}


\textsuperscript{13} For a recent review, see: Romero, N. A.; Nicewiz, D. A. \textit{Chem. Rev.} 2016, 116, 10075.

energy singlet. This species rapidly undergoes metal to ligand charge transfer (MLCT) and inter-system-crossing (ISC) to generate a long-lived triplet state, completing the process of harvesting light and transforming it into chemical energy to reach the Ir*(III) state. This species contains both a hole in the d orbital, as well as an electron in a high energy π* orbital. As a result, it can react in seemingly disparate manifolds. It can act as an oxidant, and accept an electron into the low energy unfilled d orbital to generate an Ir(II) species (Figure 3, lower pathway). Alternatively, the electron in the higher energy orbital can be donated to an appropriate acceptor, acting as a reductant to generate an Ir(IV) species (Figure 3, upper pathway). Effectively, the high-energy triplet can act as both a reductant and an oxidant. Generically, photoredox catalysis allows for accessing this unique paradigm, a typically challenging regime to access via more conventional methods.

With this ability to be both oxidizing and reducing at the same time, our group has become interested in the concept of transforming common functionalities into carbon centered radicals under mild conditions. Ideally, functionalities present in either biomass or pharmaceutical compounds could readily be activated without the need for any prefuctionalization. From these reactive intermediates, we aim to develop generic strategies to incorporate various motifs that are prevalent molecules with biological activity. The combination of multiple methods of radical generation with multiple motifs

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that can be installed allows for numerous novel couplings, and numerous unconventional
disconnections when planning molecular synthesis. Towards this goal, our group had
previously demonstrated that carboxylic acids could be transformed into a carbon-
centered radical under mild photoredox conditions.\textsuperscript{17} This is accomplished by
deprotonating the acid to form the corresponding carboxylate, which have oxidation
potentials between 0.95 V and 1.2 V, depending on the exact nature of the acid.\textsuperscript{17,18} This
potential is within the capabilities of fluorinated iridium photocatalysts, and after
oxidation the resulting carboxy radical rapidly decomposes to release CO\textsubscript{2} while
generating a carbon centered radical (Scheme 1). This allows for the transformation of a

\textit{Scheme 1. Photoredox-mediated decarboxylation}

carboxylic acid into an open shelled nucleophile, with can subsequently be trapped by an
appropriate electrophile. Previously in our laboratory, we had demonstrated that
cyanoarylations and Michael additions, amongst others, could be accomplished utilizing
this concept, but we wondered if we could combine this platform of reactivity with
traditional transition metal catalysis to enable a general strategy towards sp\textsuperscript{3}-sp\textsuperscript{2} cross
coupling.


II. The Challenge of \( sp^3-sp^2 \) C–C Coupling

Cross coupling has emerged as one of the most preeminent methods in which compounds of pharmaceutical relevance are constructed.\(^\text{19}\) Specifically, palladium cross couplings have enabled facile construction of a variety of valuable motifs in the pharmaceutical industry (Figure 4). Beginning in the 1970s and continuing through the present day, this has been a heavily researched and highly impactful area of research. In particular, the field of \( sp^2-sp^2 \) C–C bond formations has been revolutionized to the point that the biaryl bond is trivial to construct via the development of palladium catalysis. In present times, this motif is incredibly common in screening libraries of pharmaceutical compounds due to robustness of the catalytic systems developed in the last 40 years. In fact, there have been calls to limit this motif in screening libraries, and to increase the topological diversity by incorporation of less flat, stereocenterless molecules.\(^\text{20}\)

Utilizing the same sets of organometallic electrophiles, there are numerous named reactions which differ in the nature of the organometallic nucleophile. Utilization of Organomagnesium nucleophile is named the Kumada coupling, organozincs the

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\(^{19}\) For a review that follows the historical development of the field, see: Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* 2012, 51, 5062

Negishi coupling, Boronic acids the Suzuki coupling, and organosilicates the Hiyama coupling. Palladium couplings have become so ubiquitous in organic synthesis that when a new variety was developed of C–N bond formation, the Buchwald-Hartwig coupling, it quickly became one of the most common reactions performed at pharmaceutical companies.\textsuperscript{21} For this remarkable achievement the fathers of this field, Negishi, Suzuki, and Heck, were rewarded the Nobel Prize in 2010.

While the accomplishments of palladium-catalyzed couplings are certainly impressive, one area in which traditional cross couplings have struggled is in the field of $\text{sp}^3$-$\text{sp}^2$ cross couplings.\textsuperscript{22} In his 2012 review,\textsuperscript{19} Snieckus highlighted this struggle: “Thus, only partial success in $\text{C}_{\text{sp}^3}$–$\text{C}_{\text{sp}^3}$ and $\text{C}_{\text{sp}^2}$–$\text{C}_{\text{sp}^3}$ cross-coupling reactions involving alkyl halides have been achieved.” To better understand why this is the case, it is useful to examine the basic mechanism of cross couplings. On a basic overview, there are three fundamental steps: oxidative addition into a weak bond via a low valent metal center, transmetallation with an organometallic nucleophile (or coordination and deprotonation of an amine for the Buchwald-Hartwig coupling), and finally reductive elimination to form both the desired bond as well as the original low valent metal complex (Scheme 2, left). One of the most notorious offcycle pathways when utilizing $\text{sp}^3$-hybridized nucleophiles is β-hydride elimination. At best, this process for isomerization of the alkyl fragment via hydride elimination followed by migratory insertion, and at worst generates a palladium

\textsuperscript{22} For reviews of such efforts, see: (a) O’Neill, B. T. Synthetic Methods in Drug Discovery, Volume 2, 2016, 2, 371. (b) Molander, G. A.; Canturk, B. Angew. Chem. Int. Ed. 2009, 48, 9240.
Scheme 2. Mechanism of cross-couplings and the mechanism of isomerization that arises from β-hydride elimination

hydride that can undergo deleterious side reactions while also consuming an equivalent of the nucleophilic component in the reaction (Scheme 2, right). To further exasperate the situation, the reductive elimination of alkyl groups is slower compared to vinyl or aryl groups,\textsuperscript{23} resulting in an increased residence time of the alkyl group on the metal center.

Nevertheless, there have been several elegant methods that minimize this pathway. As early as 1989, Suzuki reported that primary alkyl boranes could be coupled with aryl halides to yields the desired products in good yields.\textsuperscript{24} Furthermore, Fu expanded on this finding, and developed a system that allowed for the direct coupling of primary alkyl halides with aryl boronic acids in 2002.\textsuperscript{25} One of the key factors in Fu’s conditions was the use of sterically bulky, electron-rich ligands that allow for both facile oxidative addition as well as reductive elimination. Another mitigating factor in these


systems is that even if β-hydride elimination occurs, typically migratory insertion of the resulting metal hydride species occurs in a manner that regenerates the original species, as this places the bulky metal center on the least sterically encumbered position.

However, the coupling of secondary alkyl groups has been considerably more challenging. In this case, β-hydride elimination leads to facile isomerization of the alkyl group, and can lead to placing the metal center at the terminus of alkyl chains. One solution to this isomerization is to have reductive elimination completely outcompete β-hydride elimination, and therefore isomerization of the alkyl group. In 2002, Hartwig reported a single example utilizing a secondary boronic acid, and did not observe any isomerization while using a bulky phosphine ligand and palladium catalysis (Figure 5). However, the authors noted that the reaction was slower, and for better yields a more active organozinc nucleophile was utilized instead. In 2008, it was shown that when a simpler, less sterically bulky ligand RuPHos is utilized, isomerization can be minimized. However, the authors postulated that this is not due to the lack of β-hydride elimination, but instead due to the lack of migratory insertion onto the generated olefin. In 2008, Molander, in collaboration with Merck, attempted to achieve both high efficiencies of the reaction and low isomerization of the alkyl group by utilizing parallel microscale experimentation to rapidly evaluate many ligands under several reaction conditions. After this approach was undertaken, a few effective catalyst systems emerged that could mitigate the undesired side products while still maintaining the desired efficiencies in the

coupling of aryl halides and alkyl boronic acids. In general, bulky electron-rich phosphine ligands proved to be the most effective, as was found by Hartwig and Fu, matching the trends observed in sp²-sp² cross couplings. Generally levels of isomerization were quite low, but isomerization did occur. In some cases the ratio of regioselectivity of the coupling was as low as 1.4 : 1, depending on the nature of aromatic halide and boronic acid. Nevertheless, this was an influential study, as

![Diagram of palladium catalyzed alkyl couplings](image)

Figure 5. Summary of ligands that enable palladium catalyzed alkyl couplings.

Molander and coworkers were the first to attempt to look at secondary alkyl coupling in a systematic way. However, utilizing more active nucleophiles has led to higher levels of success. Isomerizationless coupling of secondary groups utilizing Grignard reagents was disclosed in 1984,²⁹ and Buchwald reported a method towards the coupling of secondary

alkyl groups with aromatic halides. Using a newly developed ligand, CPhos, and a more active organozinc nucleophile, the authors were able to demonstrate that very high levels of efficiencies with minimal amounts of isomerization of the alkyl group, typically above 20:1, could be achieved.

It was not until 2013 that isomerizationless sp\(^3\)-sp\(^2\) coupling could be achieved while utilizing bench stable nucleophiles. Biscoe disclosed a report utilizing alkyl azastannatranes with palladium catalysis to allow for isomerizationless cross coupling of secondary alkyl fragments. Additionally, when the azastannatranne was prepared in an enantioenriched fashion, the coupling was found to proceed with retention of stereochemistry. Biscoe further expanded this system, showing that secondary alkyl boronic acids could also be coupled without isomerization. Utilizing 5 mol\% of a palladium precatalyst that delivers Pd(P(tBu)\(_3\)), the authors showed that >50:1 ratios of retention to isomerization could routinely be achieved under this protocol. Furthermore, when the boronate was prepared in an enantioenriched fashion, the authors observed net inversion during the reaction, with high stereofidelity. Finally, the Carrow group disclosed a method using P(ad)\(_3\) as a ligand for palladium catalysis that also allows for the isomerizationless coupling of secondary alkyl boronic acids.

Another strategy towards this challenging bond has been to utilize a transition metal that engages in β-hydride elimination at a slower rate. In recent years, Nickel has

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emerged as the metal of choice for these transformations. This can be attributed to lower cost of nickel compared to palladium, ease at which low valent nickel species undergo oxidative addition, in addition to its decreased propensity towards β-hydride elimination. The energetics which d⁸ metals undergo this pathway has been quantified via DFT calculation. While the elimination pathway for palladium is calculated to be endothermic by 4.8 kcal mol⁻¹, it is considerably more endothermic for nickel at 11.4 kcal mol⁻¹. Furthermore, continuing down the periodic table to platinum reveals that this metal is even more likely to undergo β-elimination, as this process is exothermic by 6.9 kcal mol⁻¹. This trend can be rationalized, as the first interaction during hydride elimination is the agostic interaction between the C–H bond and an empty orbital on the metal center. As transition metals are more electronegative further down the periodic table, so it stands to reason that nickel, the least electronegative metal in this series, would be the least likely to agostically coordinate to the C–H bond, and therefore the least likely to engage in β-hydride elimination.

Given this information, it is not surprising nickel-catalyzed sp³-sp² cross couplings have become more common in recent years. Notably, regioisomers are very

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rarely observed under nickel catalysis, as opposed to the frequency they appear when utilizing palladium. While the exact mechanism of nickel-catalyzed couplings are not nearly as well studied as their palladium counterparts, it was generally assumed to undergo the same elementary steps as palladium catalysis. What was unique to nickel though was when a sp\(^3\)-hybridized electrophile was utilized, the reaction could be rendered enantioconvergent, indicating that a radical intermediate was possible.\(^{38}\)

However, it wasn't until recently that radical intermediates were conclusively shown to be involved. In recent reports\(^ {39}\) by Weix, Fu, and Hu, the mechanism of the couplings (alkyl halides with aryl halides, arylzincs, and Grignard reagents, respectively) they were studying was elucidated (Scheme 3). As a common feature, once a nickel aryl complex was generated, it was found that a radical generated from the alkyl halide added to the metal center, generating a nickel (III) complex, which undergoes reductive elimination to generate the desired bond. Given this mechanistic insight, we wondered if nickel catalysis, with its inherently lower aptitude at ß-hydride elimination, could be combined with photoredox catalysis to allow for a mild and simple method to enable a general sp\(^3\)-sp\(^2\) cross coupling. This would allow for a general solution to a traditionally

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challenging transformation using an orthogonal class of nucleophiles that could be generated in-situ from common functionalities.

### III. Our Laboratories’ Initial Forays into Metallaphotoredox

We envisioned a nickel and photoredox catalyzed decarboxylative arylation could operate where the photocatalyst would activate the carboxylic acid component, while a nickel catalyst could activate the aryl halide. Specifically, after absorption of visible light, the excited Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)$^+$ species could act as an oxidant ($E_{1/2}^{\text{red}}[\ast \text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = +1.21$ V vs SCE in MeCN),$^{14}$ and oxidize a carboxylate ($E_{1/2}^{\text{red}} = +0.95$ V vs SCE in MeCN for Boc-Pro-OH)$^{17a}$ to generate Ir(II), and the carboxy radical could rapidly extrude CO$_2$ to generate a carbon centered radical (Scheme 4). Simultaneously, a nickel (0) complex could undergo oxidative addition into an aryl halide, to generate an aryl nickel (II) complex. The radical can then add to this species to generate a Ni(III) complex. This can rapidly undergo reductive elimination, to furnish the desired product containing the sp$^3$-sp$^2$ bond. This process also generates Ni(I), which can be reduced ($E_{1/2}^{\text{red}}[\text{Ni}^{\text{II}}/\text{Ni}^0] = -1.2$ V vs SCE in DMF)$^{41}$ by the previously generated Ir(II) ($E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37$ V vs SCE in MeCN) complex to simultaneously complete both catalytic cycles. This step is important to the catalytic system, as it provides a useful checkpoint that stops one catalytic cycle from operating faster than the other, ensuring consumption of the starting materials at the same rate.

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This concept of combining photoredox and nickel catalysis was first demonstrated by our group in collaboration with the Doyle group. The successful merger of these disparate modes of catalysis was disclosed at the same time as a report by the Molander group, who developed a similar system utilizing trifluoroborates as the radical precursor. Under the disclosed conditions, amino acids could be coupled with aryl halides with good efficiencies under mild conditions utilizing an iridium photocatalyst and an air-stable nickel complex. The substrate scope of this protocol is shown in Table

Scheme 4. Proposed catalytic cycle of the decarboxylative arylation

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1. The scope of the aryl halide component was broad, with both electron rich and electron deficient aromatic rings affording the desired product (1 to 9, 65 – 90% yield). When electron rich aromatic systems were employed, it was found that a more active halide such as iodide was necessary for good efficiencies, indicating that oxidative addition was challenging in these systems. In addition, heteroaromatic systems were found to be well tolerated in this protocol as well (10 to 16, 60 – 85% yield). Both cyclic and acyclic amino acids could be utilized in good yields (17 to 24, 61 – 93% yield). In this initial
report, there is one example of a cyclic oxy acid (25, 82% yield) and the only examples of an acid non-adjacent to a heteroatom were phenylacetic acids (26 and 27, 85% and 81% yields, respectively). In the time since this original publication, our group, as well as others, have shown that a diverse range of functionalities can be converted into radicals, allowing for a diverse range of functional groups to serve as generic precursors for an aromatic ring.

IV. Acknowledging the Remaining Challenges

While this study was certainly impactful, both in our research program as well as across the pharmaceutical industry, we wished to revisit this methodology to address several limitations of the initial publication. First, the high dilution (0.02 M) of the original report rendered this protocol impractical on larger scales. Second, since heteroarenes have such a large role in the pharmaceutical industry, we wished to demonstrate an increased scope of these valuable pharmacophores, especially five-


45 This work was performed in collaboration with Eric Welin, Dominik Hager, Michael VanHeyst, and Simon Allmendinger. A manuscript detailing these findings is under preparation, and the this work has been presented at The International Chemical Congress of Pacific Basin Societies 2015, Honolulu, Hawaii, December 2015.

membered heteroarenes. Finally, the original protocol was not general with respect to the carboxylic acid, as simple carboxylic acids such as cyclohexane carboxylic acid failed to yield any of the desired product.

V. Alkyl Carboxylic Acids

Initially, it was puzzling as to why non-α-hetetrotatom carboxylic acids failed to furnish the desired cross-coupled product. When a variety of carboxylic acids were utilized, not even any consumption of the aryl halide was observed. While alkyl carboxylic acids do have higher oxidation potentials when compared to amino acids,\textsuperscript{18} the oxidizing power of the photocatalyst utilized in the original protocol, \textit{Ir(dF(CF\textsubscript{3})ppy\textsubscript{2})(dtbbpy)PF\textsubscript{6}}, appeared to be sufficient. In fact, our group had previously utilized this photocatalyst in the decarboxylative Michael addition, where cyclohexane carboxylic furnished good yields of the desired product.\textsuperscript{17b} Given this fact, radical generation is unlikely to be the cause of the intractable nature of these acids towards the desired coupling. Similarly, the mechanistic analysis of Weix\textsuperscript{39a} indicated that alkyl radicals lacking an adjacent heteroatom could add to a near identical nickel complex, indicating that the different electronic nature of the radical does not preclude the desired nickel coupling.

Faced with no single mechanistic step that is infeasible with cyclohexane carboxylic acid, we began studying this reaction via thorough evaluation of the reaction conditions. Uniquely, when DMSO was utilized as a solvent in place of DMF, to our delight the desired product was observed in low yield. Having a catalytic system that provided minimal amount of yields, the various components of the reaction mixture were
carefully reisolated. This process revealed that the photocatalyst was functionalized with
cyclohexyl fragments, as revealed by HRMS analysis (Figure 6). We believe

Figure 6. Observed decomposition of the photocatalyst

that this process deactivates the catalyst, causing the desired coupling to only achieve low
yields under these reaction conditions. At this time, the exact position of the
photocatalyst undergoing functionalization could not be determined. However, we
viewed it likely that this was occurring on the ligand framework, rather than the iridium
center, as iridium photocatalysts are saturated 18e⁻ compounds that are known to be
configurationally stable.

The functionalization of iridium photocatalysts with organic radicals had not been
described in the literature at that time. Studies of the decomposition of photocatalysts had
been limited to photodegradation of homoleptic iridium complexes.⁴⁷ However, while
we were studying this deleterious side-reaction, the Stephenson group published a related
study⁴⁸ of photocatalyst decomposition with electrophilic radicals. In this system, which
generates nucleophilic radicals, we believe the pathway which alkyl groups are

Scheme 5. The traditional Minisci reaction and the observed alkylation incorporated onto the ligand framework is analogous to that of the Minisci reaction.\textsuperscript{49}

The Minisci reaction proceeds via a radical adding to the $\pi$ system of an aromatic ring, followed by oxidation and deprotonating of the resulting intermediate to regenerate the aromatic system (Scheme 5). Although similar reactions\textsuperscript{50} had been described as early as the 1890s, it wasn’t until 1971 when such transformations became synthetically useful.\textsuperscript{51} This was due to the poor reactivity of the systems, as well as poor regioselectivity of the transformation. Minisci reported that protonation of the heteroarene renders the arene more electrophilic and therefore more reactive towards the desired reaction. Protonation also changes the LUMO coefficients of the arene, rendering the transformation more regioselective as well. Since this advance, the Minisci reaction has emerged as a useful way for late stage modification of arenes, typically installing alkyl groups to a wide array of electron-deficient arenes.

Given the wealth of knowledge about the Minisci reaction, it was surprising to us that a strategy for Lewis acid activation of the heteroarene had not been reported. Such a system would be more analogous to our iridium photocatalyst, and would have been


helpful in diagnosing the site of reactivity in our system. Nevertheless, we hypothesized
that the lessons learned from Minisci could be utilized in reverse to design a more robust
photocatalyst. Specifically, since electron-deficient aromatic rings are known to be more
reactive in Minisci reactions, a less electron-deficient phenyl pyridine ligand should
result in a more radical resistant photocatalyst.

![Chemical structures](image)

**Figure 7. Simple variations of the photocatalyst and the outcome**

However, the oxidizing power of the photocatalyst results from the energy level
of the HOMO, which is located on the very same ligand.\(^\text{14}\) Therefore, if all the electron
withdrawing groups were removed, the photocatalyst would doubtless be more radical
resistant, but no longer posses the necessary oxidizing ability to catalyze the
decarboxylation. As such, small, conservative, modifications to the phenyl pyridine
ligand were undertaken initially. When the trifluoromethyl group was replaced with a
fluourine atom, a small increase in yield of the desired cross-coupled product was
observed. However, when the catalyst was made even less oxidizing,\(^\text{52}\) with the inclusion
of a methyl group instead, the yield of the desired product was increased (Figure 7).
Unfortunately, further increases of the electron density of this ligand did not lead to better

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\(^{52}\) Cline, E. D.; Bernard, S. *Chimia* **2009**, *63*, 709.
results, as the oxidation of aliphatic carboxylic acids is already endothermic for the methyl catalyst.

While \( \text{Ir(dF(Me)ppy)}_2(\text{dtbbpy})\text{PF}_6 \) still degrades due to Minisci-type functionalizations, it is considerably more stable during the reaction. In fact, after reisolation from the reaction mixture, we were able to determine the site of functionalization. As revealed by \(^1\text{H NMR}\), the signals corresponding to the protons at the 3, and 3’ positions of the bypridine ligand are no longer visible in the spectra, suggesting that this position is substituted with cyclohexyl units (Figure 8). Initially, this seemed counterintuitive to traditional Minisci regioselectivity, where ortho and para positions are typically alkylated. These positions of the aromatic ring typically have the

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**Figure 8.** NMR spectra of the pure photocatalyst and photocatalyst recovered from the reaction mixture
highest LUMO coefficients, but back-bonding from the iridium catalyst donates electron density to these very same positions. The meta position is simply rendered more electron poor due to the metal center coordinating the lewis basic nitrogen. DFT calculations conducted by Bernhard support this, as the 3 and 5 positions of the bypridine ligand have the highest LUMO coefficients of all the positions on the photocatalyst.\(^\text{14}\) While we were satisfied with the results that Ir(dF(Me)ppy)\(_2\)(dtbbpy)PF\(_6\) gave, we did attempt to design a photocatalyst that did not degrade under the reaction conditions. This effort was a laborious failure, with all photocatalysts faring poorer under the reaction conditions.

Having discovered the cause to the intractable nature of alkyl acids in the desired coupling, we continued to optimize the reaction conditions. While K\(_2\)CO\(_3\) was found to be a superior base, providing satisfactory efficiencies, its use necessitated high dilutions (0.02 M), as well as 3 equivalents of the carboxylic acid partner. When the reaction

![Chemical structure and reaction scheme](image)

**Scheme 6. Optimization of the decarboxylative coupling of cyclohexane carboxylic acid**
mixture was concentrated to 0.1 M, there were large amounts of insoluble base particles that blocked light from entering the reaction vessel. Sadly, simply lowering the equivalents of potassium carbonate did not lead to a more homogenous solution that would allow for a higher yielding reaction. To solve this, fully soluble organic bases were investigated, as these permit the maximum amount of photon flux. After an extensive evaluation of organic bases, it was found that a majority of them led to diminished yields and an increase in the amount of the reductive dehalogation of the arene, even at 0.02 M. However, Barton’s base (BTMG), as well as phosphazene bases, was found to be effective in this transformation. Due to the expense of phosphazene bases, conditions with the comparatively cheaper BTMG were advanced. With this base, the concentration could be increased to 0.1 M, and furthermore that the amount of the carboxylic acid partner could be reduced to 1.5 eq. The final conditions are summarized in Scheme 6.

With these conditions in hand we explored the scope of the reaction. Cyclic systems of a variety of rings sizes could be coupled in good yield (28 to 38, 54 – 77% yield). Notably, a cyclobutane carboxylic acid afforded the desired product 38, and when a chiral β-amino acid was utilized 37 was observed with a 10:1 d.r. Although heteroatoms could be incorporated in the alkyl fragment, typically the utilization of these acids required a slightly more oxidizing photocatalyst. Due to the inductively withdrawing nature of heteroatoms, the oxidation potential of the carboxylate is raised in comparison to the fully carbocyclic analogue. Due to this, it is unfavorable for Ir(dF(Me)ppy)₂(dtbbpy)PF₆ to oxidize the carboxylate, and instead it engages in energy transfer with the nickel
This process catalyzes the formation of an aryl ester side product. While the fluoro and trifluoromethyl analogues of the iridium catalyst are more susceptible to degradation by the generated radical, the inclusion of the heteroatom also decreases the nucleophilicity of the radical, decreasing the propensity at which the radical engages in Minisci reactions. Generally, these two factors compensate for each other.

Table 2. Scope of aliphatic carboxylic acids

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Acyclic systems could be coupled in good yield (39 and 40, 67% and 72% yield, respectively). Notably, when an oxygen atom was incorporated at the β position, 40 was still produced in good yields. Furthermore, fully substituted carbon centers can be generated with this protocol, as α-fluoro carboxylic acids could be coupled in good yields (42 and 43, 57% and 71% yield, respectively). In all cases, no regioisomers of the alkyl group were observed.

![Diagram](image)

### Table 3. Scope of α-amino and oxy acids

The scope of α-amino and α-oxy acids was also reinvestigated in this protocol (Table 3). With these classes of carboxylic acids, the significantly less costly Cs$_2$CO$_3$
could be utilized as a base, even at 0.1 M. Under this protocol, a wide variety of acids could be coupled efficiently. Again, constrained four-membered rings could be coupled efficiently, with both azetidine and oxetane providing useful to excellent yields (46 and 56). Radicals generated β to a carbonyl still provided the desired product (50), and when serine was utilized the unnatural phenylglycinol 47 could be directly generated. The only time any significant amounts of β-hydride elimination was observed was when that would lead to a fully aromatic system, however useful yields could still be achieved (45). Primary radicals could undergo the desired coupling in moderate yield (53, 58% yield). Additionally, both tetrahydropyran and azaoxepane carboxylic acids underwent the desired coupling in good yields (54 and 55, 90 and 73% yield, respectively).

Furthermore, excellent diastereoselectivities could be achieved on cyclic systems. A stereogenic fluorine atom leads to a 4:1 d.r. in 44, while more architecturally complex systems can lead to single diastereomers (51, and 58). However, acyclic systems containing stereocenters failed to impart any significant amount of diastereoselectivity, as demonstrated by 57. Finally, when a nucleoside was utilized in the desired coupling reaction, a synthetically useful yield of 59 was achieved.

VI. Heteroaromatic Halides

We next examined the scope of heteroarenes in the decarboxylative coupling. While promising levels of activity were observed, a major side product was dehalogenated arene. This results from protonation of the aryl nickel complex outcompeting radical capture. Ultimately, this arises from a mismatched rate of the two catalytic cycles. Even though a built in checkpoint is present in the mechanism that keeps
the rates from being too disparate, we hypothesized it would be beneficial if the residence
time of the aryl on the nickel center could be minimized. In other words, the rate of radical
generation needed to be increased while also decreasing the nickel concentration.

The latter is quite simple, and in a generic sense, as decreasing the nickel loading
to 5 mol% from 10 mol% to be beneficial (Scheme 7). To increase the rate of radical
generation, several changes were made. First, 34 W blue LEDs were used, as this is both
more powerful than the original light source, and emits fully in the region where iridium
photocatalysts absorb. Furthermore, DBU was utilized as a fully organic base, decreasing
the amount of light reflected away from the reaction vessel. These conditions limit the
amount of byproducts formed, and we were pleased to find that these reaction conditions
could be increased to 0.1 M as well.

We demonstrated that a wide range of heteroarenes could be utilized in this
transformation (Table 4). 2-, 3-, and 4-halo pyridines all lead to acceptable levels of the
desired sp^3-sp^2 coupled product (60 to 71, 57 – 83% yield). Useful functional handles,
like 2-fluoropyrdines and acetamides, were well tolerated (61 and 62). Most surprising to
to us was that boronic esters could also be tolerated, with 2-bromopyridine-5-boronic acid
pinacol ester providing 70 in 57% yield. When 2,6-dichloropyridine was employed, selective mono-functionalization could easily be achieved to afford 71 in 61% yield. Furthermore, bicyclic aromatic systems could be tolerated, with both azaindole and azaindazole systems providing good yield of the desired products (63 and 67, 60% and 73% yield, respectively). Furthermore steric bulk near the reaction center was well tolerated (69, 80% yield).

We were happy to find that pyrazines, pyrimidines, and pyridazines could all be coupled effectively (72 to 77, 52 – 79% yield). This was especially pleasing given that traditionally these aromatic systems are challenging in cross-couplings due to their Lewis basicity.\(^{54}\) Both the unadorned pyrazine as well as one substituted with a pyrazole ring provided the desired products (76 and 77). Pyrimidines can be coupled at the 4 and 5 positions (72 and 73), however to date the 2-position has remained out of our grasp. Given this information, it was not surprising to find that when 2,4-dichloro pyrimidine was utilized, coupling occurred exclusively at the 4 position to afford 74 in 57% yield. This is consistent with known reactivity observed in palladium couplings.\(^{55}\) Finally, a chloro-pyrdazine could also be utilized to afford 75.

While these were results were encouraging, we viewed the final challenge to be five membered heteroarenes. These are traditionally a challenging class of substrates in cross-couplings, and therefore the ability to utilize this class of substrates would demonstrate the robustness of this protocol. After extensive evaluation, these substrates were determined to be exceptionally prone towards were prone to large levels of


Table 4. Scope of the aryl halide component
dehalogenation Minimization of this byproduct necessitated lowering the reaction conditions back to 0.02 M. With this insight, a range of different classes of heteroarenes were found to be compatible with this coupling (78 to 83, 53 – 74% yield). 3-Iodopyrazoles with disparate functional groups at N-1 could be utilized to afford 78 and 79. Both thiazoles and isothiazoles could be employed in acceptable yields to afford 80 and 81, respectively. Finally, with more electron rich aromatic systems, like benzothiophenes and furans, the desired product could be achieved to afford 82 and 83.

**VII. Increasing the Photon Flux**

Having explored the scope, we wished to further increase the attractiveness of this technology in industry; both in medicinal and process chemistry departments. One potential reason for a possible lack of uptake in a medicinal chemistry setting is the setup required for the lights. Although commercial LEDs that simply plug into an outlet were utilized, there is some variability in the setup with respect to distance from the lights, and the temperature the LEDs raise the reaction due to heat generation. Furthermore, in a process setting, the scale at which these reactions can be run is limited to too small of an amount. This is due to the photon limitation of the reactions\(^5^6\), which is a byproduct of the power of the light source. Even with bright LEDs, the majority of photons are absorbed at the surface of the reaction vessel, so by increasing the reaction vessel the surface area to volume ratio gets worse, and therefore the overall rate of the reaction slows and there is an increase of nickel-mediated byproducts.

To address the former, we partnered with Merck to design a benchtop photoreactor. This not only standardizes the setup so that any medicinal chemist can add a vial to the reactor, turn it on, and run the reaction as well as the original researchers, but also allows for increased rates of reaction. To ensure this later effect, more powerful LEDs were utilized in the construction. When several substrates were tested in the reactor, we typically observed completion in 4 hours, instead of 12 to 24 hours in the original setup (Table 5). For some substrates, they reached completion in as little as 75 minutes, as demonstrated by 30. Additionally, in all cases the observed yields were similar or improved compared to the original setup.

Table 5. Evaluation of substrates in the Merck Photoreactor

While this was an improvement, this did not solve the challenges with regard to the scales necessary for process chemistry. For this, we turned to flow technology. In recent years, flow has emerged as a promising technique for manufacturing,57 and can enable chemistry that is otherwise difficult on scale. Flow functions by using pumps to allow continuous processing of material, mixing solution containing the relevant reagents in small tubes. In our case, we envisioned that the small diameter of the clear plastic

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tubes utilized in flow technology would allow for the reaction to occur in a photon-excess regime. This was indeed the case, and it in our test reaction it was necessary to increase the nickel concentration to 10 mol% to match the pace of the photocatalyst (Table 6). Due to this, we were able to further modify the conditions to decrease solvent waste. In the flow reactor, the reaction could be concentrated more than six-fold to 0.67 M while still maintaining similar yields compared to batch. Utilizing a reactor which has an internal volume of only 10 mL, and using a 45 minute retention time, we can produce 33 grams of the desired product in a single 24 hour period. The downside to carrying out such an experiment would be the cost of the iridium photocatalyst. However, 4CzIPN is

![Photocatalyst diagram](image)

**Table 6. Optimized condition in flow**

<table>
<thead>
<tr>
<th>Photocatalyst</th>
<th>Yield: mmol/day</th>
<th>Yield: grams/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ir(dF(CF&lt;sub&gt;3&lt;/sub&gt;)ppy)&lt;sub&gt;2&lt;/sub&gt;(dtbbpy)PF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>121 mmol/d</td>
<td>33 g/d</td>
</tr>
<tr>
<td>4CzIPN</td>
<td>117 mmol/d</td>
<td>31 g/d</td>
</tr>
</tbody>
</table>

an organic photocatalyst<sup>58</sup> developed by Adachi that possesses similar potentials to Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)PF<sub>6</sub>. When this fully organic photocatalyst was utilized under the same conditions, near identical yields were observed. This significantly decreases the total cost of the system, as this catalyst is one fiftieth of the price as the precious metal containing iridium catalyst.

VIII. Conclusion

In conclusion, we have developed a general strategy towards the challenging \( \text{sp}^3 \)-\( \text{sp}^2 \) C–C bond formation utilizing a dual catalytic platform. We expanded upon the initial publication, and investigated several of its shortcomings. We determined that the radicals derived from alkyl radicals deactivate the photocatalyst, and designed several more radical resistant catalysts. This allowed for a greater scope of carboxylic acids to be utilized, rendering the transformation considerably more general. Furthermore, we investigated the scope of heteroarenes, and found that a variety of both five and six membered heteroarenes provided satisfactory efficiencies. Finally, we demonstrated that two alternative setups relevant to industry can not only match the standards of the typical photoredox setup, but can provide advantages as well.
VIII. Supporting Information

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. All solvents were purified according to the method of Grubbs. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still. Thin-layer chromatography (TLC) was performed on Analtech 250 micron silica gel plates. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm$^{-1}$). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 125 MHz) instrument, and are internally referenced to residual protic solvent signals (note: CDCl$_3$ referenced at δ 7.26 and 77.16 ppm respectively). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for $^{13}$C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. Gas chromatography (GC) was performed on an Agilent 6850 Series chromatograph with splitless capillary injection and FID detection.

General procedure

To a 8 mL or 40 mL vial equipped with a magnetic stir bar, the photocatalyst, nickel, and bipyridine ligand were added. The aryl halide (if solid) followed by the solvent. This
solution was allowed to stir for 5 minutes, and then the aryl halide (if liquid), carboxylic acid, and base were added, in that order. The solution was then degassed for 15 mins by sparging with nitrogen. The vial was then sealed and the cap was wrapped in parafilm. Unless otherwise noted, the vial was placed approximately 8 cm away from a 34 W Blue LED and a fan was turned on to cool the vial. The reaction was stirred for 12 hours, and then the LED was turned off. The vial was poured into a mixture of water and ethyl acetate. The water layer was extracted 3 times with ethyl acetate, and then the organic layer was washed with water, dried with Na₂SO₄, and concentrated. The product was then purified by column chromatography.

**Standard reaction setup**

In a typical reaction, the reaction mixture is irradiated with 34W Kessil KSH150B from 5 cm away. Regular fans are employed to maintain the temperature at room temperature.
**tert-butyl 2-(4-(methoxycarbonyl)phenyl)pyrrolidine-1-carboxylate (6)**

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (161 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The vial was then placed in the Merck Photoreactor for 2 hours. The product was isolated by flash chromatography (134 mg, 88%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.08 – 4.69 (m, 1H), 3.93 (s, 3H), 3.74 – 3.45 (m, 2H), 2.45 – 2.21 (m, 1H), 1.98 – 1.75 (m, 3H), 1.48 (s, 3H), 1.19 (s, 6H)


**Methyl 4-cyclohexylbenzoate (28)**

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.61 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (161 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The vial was then placed in the Merck Photoreactor for 2 hours. The product was isolated by flash chromatography (134 mg, 88%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.08 – 4.69 (m, 1H), 3.93 (s, 3H), 3.74 – 3.45 (m, 2H), 2.45 – 2.21 (m, 1H), 1.98 – 1.75 (m, 3H), 1.48 (s, 3H), 1.19 (s, 6H)
mmol, 1.0 equiv), cyclohexane carboxylic acid (96 mg, 0.75 mmol, 1.5 equiv), BTMG (150 µL, 0.75 mmol, 1.5 equiv) and 5 mL of DMSO were used. The product was isolated by flash chromatography as a clear oil (73 mg, 67%). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.95 (d, \(J = 8.3\) Hz, 2H), 7.27 (d, \(J = 8.4\) Hz, 2H), 3.90 (s, 3H), 2.56 (m, 1H), 1.86 (m, 4H), 1.76 (d, \(J = 12.8\) Hz, 1H), 1.50 – 1.34 (m, 4H), 1.27 (m, 1H).

Spectral data was consistent with that previously reported: Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. J. Am. Chem. Soc. 2015, 137, 2195.

Methyl 4-(tetrahydro-2H-pyran-3-yl)benzoate (29)

According to the general procedure, Ir\([\text{dF(ppy)}]_2(\text{dtbbpy})\text{PF}_6\) (5.1 mg, 5.00 µmol, 0.01 equiv), NiCl\(_2\)•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), tetrahydro-2H-pyran-3-carboxylic acid (130 mg, 0.75 mmol, 2.0 equiv), BTMG (200 µL, 1.0 mmol, 2.0 equiv) and 15 mL of DMSO were used. This reaction mixture was placed in 3 8mL vials. The product was isolated by flash chromatography (85 mg, 77%). \(^1H\) NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 8.00 (d, \(J = 8.3\) Hz, 2H), 7.31 (d, \(J = 6.6\) Hz, 2H), 4.02 (dddd, \(J = 15.9, 11.4, 4.2, 2.1\) Hz, 2H), 3.93 (s, 3H), 3.54 – 3.39 (m, 2H), 2.99 – 2.90 (m, 1H), 2.11 – 2.03 (m, 1H), 1.87 – 1.71 (m, 3H). \(^{13}C\) NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 167.0, 148.0, 129.81, 128.5, 127.4, 77.3, 77.0, 76.8, 73.3, 68.2, 52.1,
43.0, 30.5, 30.2, 25.9. IR (film): $\nu_{\max}$ 2947, 2845, 1720, 1610, 1435, 1278, 1183, 1101, 1085. HRMS (ESI-TOF): m/z calcd. for C$_{12}$H$_{17}$O$_3$ ([M+H]$^+$) 220.1099, found 211.1105.

![Methyl 4-(tetrahydro-2H-pyran-4-yl)benzoate (30)](image)

According to the general procedure, Ir[dF(F)ppy]$_2$(dtbbpy)PF$_6$ (5.1 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4'-di-tert-butyl-2,2'-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), tetrahydro-2H-pyran-4-carboxylic acid (130 mg, 0.75 mmol, 2.0 equiv), BTMG (200 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMSO were used. The product was isolated by flash chromatography (71 mg, 65%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.09 (dd, J = 11.5, 3.0 Hz, 2H), 3.91 (s, 3H), 3.54 (td, J = 11.6, 2.4 Hz, 2H), 2.82 (m, 1H), 1.89-1.73 (m, 4H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 167.0, 151.1, 129.9, 128.3, 126.8, 68.2, 52.0, 41.7. 33.6; IR (film) 2963, 2932, 2907, 2857, 1719, 1440, 1278, 1110, 1097, 764. HRMS (ESI-TOF): m/z calcd. for C$_{13}$H$_{17}$O$_3$ ([M + H]$^+$) 220.1099, found 220.1107.

According to the general procedure, Ir[dF(F)ppy]$_2$(dtbbpy)PF$_6$ (5.1 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4'-di-tert-butyl-2,2'-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), tetrahydro-2H-pyran-4-carboxylic acid (130 mg, 0.75 mmol, 2.0 equiv), BTMG (200 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMSO were used. The vial was then placed
in the Merck Photoreactor for 75 minutes. The product was isolated by flash chromatography (79 mg, 72%).

**Methyl 4-(1-benzoylpiperidin-4-yl)benzoate (31)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.61 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-benzoylpiperidine-4-carboxylic acid (175 mg, 0.75 mmol, 1.5 equiv), BTMG (150 µL, 0.75 mmol, 1.5 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (30% EtOAc/hexanes) as a colorless solid (116 mg, 72%). ¹H-NMR (500 MHz, CDCl₃): δ 8.01 – 7.97 (m, 2H), 7.47 – 7.39 (m, 5H), 7.31 – 7.27 (m, 2H), 4.91 (br s, 1H), 3.91 (s, 3H), 3.13 (br s, 1H), 2.86 (tt, J = 12.1, J = 3.7 Hz, 2H), 2.03 – 1.54 (m, 4H). ¹³C-NMR (126 MHz, CDCl₃): δ 170.6, 167.1, 150.5, 136.3, 130.1, 129.8, 128.7, 128.6, 127.0, 126.9, 52.2, 48.4, 43.0, 42.8, 33.8, 32.8. IR (film): ν max 3063, 3007, 2945, 2917, 2861, 1714, 1611, 1574, 1497, 1467, 1444, 1435, 1365, 1330, 1311, 1289, 1265, 1242, 1176, 1144, 1106, 1088, 1074, 1018, 995, 968, 939, 930, 852, 828, 794, 770, 732, 712, 705, 681. HRMS (ESI-TOF): m/z calcd. for C₂₀H₂₂NO₃ ([M+H⁺]⁺) 324.15942, found 324.15914.
**Tert-butyl 3-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (32)**

According to the general procedure, Ir[dF(CF\(_3\))ppy\(_2\)](dtbbpy)PF\(_6\) (5.61 mg, 5.00 µmol, 0.01 equiv), NiCl\(_2\)•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (172 mg, 0.75 mmol, 1.5 equiv), BTMG (150 µL, 0.75 mmol, 1.5 equiv) and 10 mL of DMSO were used. The product was isolated by flash chromatography (10% EtOAc/hexanes) as a colorless solid (116 mg, 72%). \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.01 – 7.94 (m, 2H), 7.34 – 7.28 (m, 2H), 4.28 – 4.08 (m, 2H), 3.91 (s, 3H), 2.83 – 2.68 (m, 3H), 2.03 (d, \(J = 12.3\) Hz, 1H), 1.82 – 1.73 (m, 1H), 1.71 – 1.55 (m, 2H), 1.47 (s, 9H). \(^13\)C-NMR (126 MHz, CDCl\(_3\)): \(\delta\) 167.1, 154.9, 149.0, 130.0, 128.7, 127.3, 79.8, 52.2, 50.3, 44.3, 42.7, 31.7, 28.6, 25.5. IR (film): \(\nu_{\text{max}}\) 2975, 2934, 2857, 1721, 1687, 1611, 1574, 1465, 1415, 1365, 1340, 1275, 1238, 1169, 1136, 1147, 1105, 1019, 982, 966, 945, 906, 891, 854, 838, 821, 792, 766, 707. HRMS (ESI-TOF): m/z calcd. for C\(_{18}\)H\(_{25}\)NNaO\(_4\) ([M+Na]\(^+\)) 342.16758, found 342.16741.

**Methyl 4-(4,4-difluorocyclohexyl)benzoate (33)**

According to the general procedure, Ir[dF(CF\(_3\))ppy\(_2\)](dtbbpy)PF\(_6\) (5.61 mg, 5.00 µmol, 0.01 equiv), NiCl\(_2\)•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-
bipyridyl (6.71 mg, 25.0 μmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 4,4-difluorocyclohexane-1-carboxylic acid (123 mg, 0.75 mmol, 1.5 equiv), BTMG (150 μL, 0.75 mmol, 1.5 equiv) and 5 mL of DMSO were used. The product was isolated by flash chromatography (10% EtOAc/hexanes) as a colorless solid (95 mg, 75%). $^1$H-NMR (500 MHz, CDCl$_3$): δ 8.02 – 7.94 (m, 2H), 7.31 – 7.27 (m, 2H), 3.91 (s, 3H), 2.72 – 2.61 (m, 1H), 2.28 – 2.18 (m, 2H), 1.99 – 1.76 (m, 6H). $^{13}$C-NMR (126 MHz, CDCl$_3$): δ 167.1, 150.6 (d, $J = 2.4$ Hz), 130.0, 128.6, 127.0, 123.1 (dd, $J = 242.7, 239.4$ Hz), 52.2, 42.7 (d, $J = 1.7$ Hz), 34.1 (dd, $J = 25.7, 22.8$ Hz), 30.2 (d, $J = 10.1$ Hz) $^{19}$F-NMR (282 MHz, CDCl$_3$): δ −91.8 (d, $J = 236.2$ Hz), -102.4 (d, $J = 236.3$ Hz). IR (film): $\nu_{\text{max}}$ 2960, 2871, 1713, 1674, 1609, 1574, 1510, 1444, 1434, 1416, 1375, 1359, 1332, 1311, 1278, 1266, 1249, 1183, 1128, 1099, 1019, 972, 951, 931, 873, 852, 826, 782, 763, 741, 704, 680. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{17}$F$_2$O$_2$ ([M+H]$^+$) 255.11911, found 255.11946.

![Methyl 4-cyclopentylbenzoate (34)](image)

**Methyl 4-cyclopentylbenzoate (34)**

According to the general procedure, Ir[dF(F)ppy]$_2$(dtbbpy)PF$_6$ (5.1 mg, 5.00 μmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 μmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 μmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), cyclopentane carboxylic (86 mg, 0.75 mmol, 1.5 equiv), BTMG (150 μL, 0.75 mmol, 1.5 equiv) and 5 mL of DMSO were used. The product was isolated by flash chromatography (56 mg, 55%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, $J = 8.3$ Hz, 2H),
7.32 (d, J = 8.3 Hz, 2H), 3.92 (s, 3H), 3.07 (tt, J = 9.6, 7.6 Hz, 1H), 1.84 (m, 2H), 1.74 (m, 2H), 1.64 (m, 2H).


![Methyl 4-(tetrahydrofuran-3-yl)benzoate (35)](image)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), tetrahydrofuran-3-carboxylic acid (174 mg, 1.5 mmol, 3.0 equiv), BTMG (300 µL, 1.5 mmol, 3.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (56 mg, 55%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.20 – 4.12 (m, 1H), 4.10 (td, J = 8.3, 4.6 Hz, 1H), 3.99 – 3.90 (m, 4H), 3.78 (dd, J = 8.6, 7.0 Hz, 1H), 3.48 (p, J = 7.6 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.05 – 1.98 (m, 1H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ 167.0, 148.4, 129.9, 128.4, 127.3, 77.3, 77.0, 76.8, 74.5, 68.5, 52.1, 45.0, 34.6, 30.6, 29.7. IR (film): $\nu_{\text{max}}$ 2951, 2863, 1718, 1610, 1435, 1276, 1181, 1109, 1056, 1019, 967, 904, 855. HRMS (ESI-TOF): m/z calcd. for C$_{12}$H$_{15}$O$_3$ ([M+H]$^+$) 206.0941, found 206.0943.
**Tert-Butyl 3-(4-(methoxycarbonyl)phenyl)pyrrolidine-1-carboxylate (36)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (11.2 mg, 10.0 µmol, 0.02 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (161 mg, 0.75 mmol, 1.5 equiv), BTMG (153 µL, 0.75 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (15% EtOAc/hexanes) as a yellow oil (97 mg, 64%). 

**¹H-NMR** (500 MHz, CDCl₃): δ 8.06 – 7.95 (m, 2H), 7.33 – 7.27 (m, 2H), 3.91 (s, 3H), 3.83 (dd, J = 10.4, 7.4 Hz, 1H), 3.61 (t, J = 9.0 Hz, 1H), 3.46 – 3.36 (m, 2H), 3.33 (t, J = 9.8 Hz, 1H), 2.29 (ddt, J = 12.8, 6.5, 2.9 Hz, 1H), 1.99 (ddt, J = 12.4, 9.8, 8.3 Hz, 1H), 1.48 (s, 9H). 

**¹³C-NMR** (126 MHz, CDCl₃): δ 167.0, 154.6, 147.0, 130.1, 128.9, 127.3, 79.5, 52.2, 52.1, 45.8, 44.0, 32.9, 28.7. IR (film): νmax 2975, 2952, 3878, 1721, 1690, 1612, 1478, 1434, 1397, 1365, 1339, 1312, 1276, 1165, 1106, 1019, 967, 880, 856, 829, 808, 767, 727, 705. HRMS (ESI-TOF): m/z calcd. for C₁₇H₂₃NNaO₄ ([M+Na]⁺) 328.15193, found 328.15160.

**Methyl 4-(((1R,2R)-2-((tert-butoxycarbonyl)amino)cyclopentyl)benzoate (37)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-
bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (1S,2S)-2-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylic acid (229 mg, 1.0 mmol, 2.0 equiv), BTMG (200 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (86 mg, 54%).

Major diastereomer: $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.99 (d, $J$ = 7.9 Hz, 2H), 7.34 (d, $J$ = 8.0 Hz, 2H), 4.50 (s, 1H), 4.03 (s, 1H), 3.92 (d, $J$ = 1.1 Hz, 3H), 2.87 (s, 1H), 2.30 – 2.24 (m, 1H), 2.22 – 2.12 (m, 1H), 1.90 – 1.72 (m, 2H), 1.63 – 1.49 (m, 2H), 1.38 (m, 9H), $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 167.09, 155.39, 148.41, 129.79, 128.32, 127.46, 77.28, 77.02, 76.77, 58.37, 52.02, 32.78, 32.57, 28.46, 28.29, 22.20. IR (film): $\nu_{\text{max}}$ 3363, 2962, 2874, 1713, 1610, 1514, 1434, 1365, 1275, 1242, 1165, 1108, 1020, 771, 706. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{18}$NO$_4$ ([M–tBu+H]$^+$) 263.1158, found 263.1167. $\alpha_d^{20} = +51.01$ (CHCl$_3$, c = 0.10)

Minor diastereomer: $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.99 (d, $J$ = 8.4 Hz, 2H), 7.29 (d, $J$ = 8.3 Hz, 2H), 4.30 (s, 1H), 4.12 (s, 1H), 3.93 (d, $J$ = 4.2 Hz, 3H), 3.40 (d, $J$ = 7.9 Hz, 1H), 2.20 – 2.05 (m, 1H), 2.03 – 1.87 (m, 2H), 1.88 – 1.71 (m, 1H), 1.67 – 1.53 (m, 1H), 1.45 (d, $J$ = 10.1 Hz, 1H), 1.31 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 167.1, 155.2, 146.8, 129.4, 128.6, 128.2, 127.5, 79.1, 55.0, 52.1, 47.9, 31.9, 30.5, 29.1, 28.3, 22.0. IR (film): $\nu_{\text{max}}$ 3369, 2961, 2875, 1702, 1610, 1511, 1364, 1277, 1246, 1165, 1108. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{18}$NO$_4$ ([M–tBu+H]$^+$) 263.1158, found 263.1162. $\alpha_d^{20} = -32.90$ (CHCl$_3$, c = 0.20)
Methyl 4-(bicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)benzoate (38)

According to the general procedure, Ir[dF(Me)ppy]2(dtbbpy)PF6 (10.1 mg, 10.0 µmol, 0.02 equiv), NiCl2•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-Benzocyclobutenecarboxylic acid (111 mg, 0.75 mmol, 1.5 equiv), BTMG (153 µL, 0.75 mmol, 2.0 equiv) and 10 mL of DMSO were used. The product was isolated by flash chromatography (5% EtOAc/hexanes) as a colorless solid (72 mg, 60%). 1H-NMR (500 MHz, CDCl3): δ 7.99 – 7.95 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 2H), 7.19 – 7.12 (m, 2H), 4.74 (dd, J = 5.8, 2.7 Hz, 1H), 3.90 (s, 3H), 3.76 (dd, J = 14.0, 5.7 Hz, 1H), 3.09 (dd, J = 13.9, 2.8 Hz, 1H). 13C-NMR (126 MHz, CDCl3): δ 167.2, 148.3, 147.0, 144.0, 129.9, 128.5, 128.1, 127.5, 127.1, 123.5, 122.9, 52.2, 47.5, 40.0. IR (film): νmax 3068, 2951, 2925, 2844, 1718, 1611, 1574, 1509, 1457, 1434, 1412, 1310, 1274, 1191, 1178, 1104, 1019, 1000, 978, 965, 933, 887, 851, 826, 770, 758, 734, 711, 700. HRMS (ESI-TOF): m/z calcd. for C17H15O2 ([M+H]+) 239.10666, found 239.10645.

Methyl 4-(sec-butyl)benzoate (39)

According to the general procedure, Ir[dF(Me)ppy]2(dtbbpy)PF6 (5.1 mg, 5.00 µmol, 0.01 equiv), NiCl2•glyme (1.1 mg, 5.0 µmol, 0.02 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (1.3
mg, 5.0 µmol, 0.02 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 2-methylbutanoic acid (82 µL, 0.75 mmol, 1.5 equiv), BTMG (150 µL, 0.75 mmol, 1.5 equiv) and 15 mL of DMSO were used. This reaction was then divided amongst 3 8mL vials. The product was isolated by flash chromatography (64 mg, 67%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 3.90 (s, 3H), 2.66 (h, J = 7.3 Hz, 1H), 1.61 (p, J = 7.3 Hz), 1.25 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 7.4 Hz, 3H).

Spectral data was consistent with that previously reported: Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. J. Am. Chem. Soc. 2015, 137, 2195.

Methyl 4-(1-(tert-butyldimethylsilyloxy)propan-2-yl)benzoate (40)

According to the general procedure, Ir[dF(F)ppy]$_2$(dtbbpy)PF$_6$ (5.11 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoic acid (218 mg, 1.00 mmol, 2.0 equiv), BTMG (204 µL, 1.00 mmol, 2.0 equiv) and 10 mL of DMSO were used. The product was isolated by flash chromatography (5% EtOAc/hexanes) as a yellow oil (114 mg, 73%). $^1$H-NMR (500 MHz, CDCl$_3$): δ 7.99 – 7.92 (m, 2H), 7.31 – 7.27 (m, 2H), 3.90 (s, 3H), 3.65 (qd, J = 9.8, 6.5 Hz, 2H), 2.96 (h, J = 6.8 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.83 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H). $^{13}$C-NMR (126 MHz, CDCl$_3$): δ 167.3, 150.3, 129.6, 128.2, 127.8, 68.9, 52.1, 42.7, 26.0, 18.4, 17.4, -5.4, -5.4.
IR (film): ν_max 2954, 2929, 2888, 2857, 1723, 1611, 1471, 1463, 1418, 1388, 1311, 1276, 1255, 1180, 1100, 1055, 1017, 969, 939, 834, 815, 772, 706, 669. HRMS (ESI-TOF): m/z calcd. for C_{17}H_{29}O_{3}Si ([M+H]^+) 308.18077, found 308.18101.

Methyl 4-pentylbenzoate (41)

According to the general procedure, Ir[dF(H)ppy]_2(dtbbpy)PF_6 (25.0 mg, 25.0 μmol, 0.05 equiv), NiCl_2·glyme (5.49 mg, 25.0 μmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 μmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), hexanoic acid (94 μL, 0.75 mmol, 1.5 equiv), BTMG (153 μL, 0.75 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (5% EtOAc/hexanes) as a yellow oil (55 mg, 53%). ^1H-NMR (500 MHz, CDCl_3): δ 8.00 – 7.90 (m, 2H), 7.26 – 7.22 (m, 3H), 3.90 (s, 3H), 2.70 – 2.60 (m, 2H), 1.67 – 1.59 (m, 2H), 1.38 – 1.26 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H). ^13C-NMR (126 MHz, CDCl_3): δ 167.4, 148.7, 129.8, 128.6, 127.7, 77.2, 52.1, 36.1, 31.6, 31.0, 22.6, 14.2. IR (film): ν_max 2954, 2929, 2858, 1720, 1610, 1574, 1512, 1458, 1435, 1415, 1379, 1310, 1274, 1192, 1178, 1107, 1020, 968, 857, 832, 796, 761, 729, 703. HRMS (ESI-TOF): m/z calcd. for C_{13}H_{19}O_2 ([M+H]^+) 207.13796, found 207.13796.
Methyl 4-(1-fluorocyclohexyl)benzoate (42)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (11.2 mg, 10.0 µmol, 0.02 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 2,2’-bipyridyl (3.90 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-fluorocyclohexane-1-carboxylic acid (115 mg, 0.75 mmol, 1.5 equiv), BTMG (153 µL, 0.75 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (5% EtOAc/hexanes) as a colorless solid (67 mg, 57%). ¹H-NMR (500 MHz, CDCl₃): δ 8.05 – 7.98 (m, 2H), 7.48 – 7.41 (m, 2H), 3.91 (s, 3H), 2.04 – 1.94 (m, 2H), 1.87 – 1.64 (m, 7H), 1.39 – 1.20 (m, 1H). ¹³C-NMR (126 MHz, CDCl₃): δ 167.0, 151.0 (d, J = 21.7 Hz), 129.8 (d, J = 1.4 Hz), 129.2 (d, J = 1.3 Hz), 124.1 (d, J = 9.7 Hz), 96.1 (d, J = 175.3 Hz), 52.3, 37.1 (d, J = 23.7 Hz), 25.0, 21.9 (d, J = 1.6 Hz). ¹⁹F-NMR (282 MHz, CDCl₃): δ −160.1 (s). IR (film): ν max 2945, 2863, 2849, 1721, 1611, 1577, 1436, 1409, 1362, 1338, 1316, 1274, 1187, 1141, 1114, 1104, 1066, 1035, 1013, 970, 946, 928, 910, 863, 845, 922, 767, 719, 703, 671. HRMS (ESI-TOF): m/z calcd. for C₁₄H₁₇FO₂ ([M+H]⁺) 237.12853, found 237.12874.

Tert-butyl 4-fluoro-4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (43)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (371 mg,
1.5 mmol, 3.0 equiv), BTMG (300 µL, 1.5 mmol, 3.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (119 mg, 71%). \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.07 – 7.99 (m, 2H), 7.48 – 7.37 (m, 2H), 4.09 (d, \( J = 38.2 \) Hz, 2H), 3.91 (s, 3H), 3.17 (s, 2H), 2.08 – 1.88 (m, 4H), 1.48 (s, 9H). \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 166.62, 154.67, 148.79 (d, \( J = 21.4 \) Hz), 129.76 (dd, \( J = 30.5, 3.8 \) Hz), 129.53 (d, \( J = 11.0 \) Hz), 123.89 (d, \( J = 9.6 \) Hz), 94.23 (d, \( J = 176.1 \) Hz), 79.81, 52.14, 39.58 (dd, \( J = 73.7, 10.6 \) Hz), 36.35 (d, \( J = 24.8 \) Hz), 28.42. IR (film) 2971, 2913, 2873, 1722, 1683, 1424, 1365, 1265, 1165. HRMS (ESI-TOF): m/z calcd. for C\(_{13}\)H\(_{17}\)NO\(_3\) ([M + Na]\(^+\)) 360.15816, found 360.15843.

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\text{Tert-butyl (2S,4S)-4-fluoro-2-(4-(methoxycarbonyl)phenyl)-pyrrolidine-1-carboxylate (44)}
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According to the general procedure, Ir[dF(CF\(_3\))ppy]\(_2\)(dtbbpy)PF\(_6\) (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl\(_2\)•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (275 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography in a 4:1 mixture of diastereomers (144 mg, 89%). \( ^1H \) NMR (500 MHz, D\(_6\)-Acetone) Mixture of diastereomers and rotomers: \( \delta \) 8.00 (m, 2H), 7.46 (m, 2H), 5.35 (d, \( J = 52.8 \) Hz, 1 H), 4.97 (m, 1H), 3.99 (m, 1H), 3.89 (s, 3H), 3.82 (m, 1H), 2.72 (m, 1H), 2.1 (m, 1H), 1.44
(s, 3H), 1.13 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) Major diastereomer is reported:s 
166.9, 154.4, 129.9, 128.9, 125.6, 111.8, 91.18 (d, J = 177 Hz), 80.16, 60.0, 54.0 (d, J = 25 Hz), 52.1, 43.4 (d, J = 23 Hz), 28.0; IR (film) 2977, 1720, 1693, 1612, 1392, 1276, 1159, 1111, 769. HRMS (ESI-TOF): m/z calcd. for C$_{13}$H$_{15}$FNO$_4$ ([M – tBu + H]$^+$) 267.0907, found 267.0907. $\Delta$$^{20}$D = +47.75 (CHCl$_3$, c = 1.00)

**Tert-butyl 2-(4-(methoxycarbonyl)phenyl)indoline-1-carboxylate (45)**

According to the general procedure, Ir[dlF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (S)-1-(tert-butoxycarbonyl)indoline-2-carboxylic acid (197 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (130 mg, 74%). $^1$H NMR (500 MHz, D$_6$-Acetone) δ 7.99 (d, J = 8.3 Hz, 2H), 7.91 (br, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.25 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1 H), 7.00 (td, J = 7.4, 1.0 Hz, 1H), 5.55 (dd, J = 10.7, 3.5 Hz, 1H), 3.88 (s, 3H), 3.79 (dd, J = 16.5, 10.8 Hz, 1H), 2.93 (dd, J = 16.4 Hz, 3.5 Hz, 1H), 1.47-1.16 (br, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 166.9, 152.2, 149.8, 130.0, 129.1, 127.8, 125.5; 125.3, 124.8, 122.8, 114.7, 81.1, 62.4, 52.1, 37.6, 28.2; IR (film) 2977, 1721, 1703, 1608, 1483, 1385, 1277, 1167, 1139, 1107, 1017, 752. HRMS (ESI-TOF): m/z calcd. for C$_{17}$H$_{16}$NO$_4$ ([M – tBu + H]$^+$) 297.1003, found 297.1001.
**Tert-butyl 2-(4-(methoxycarbonyl)phenyl)azetidine-1-carboxylate (46)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (151 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (131 mg, 90%). ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 5.26 (dd, J = 8.8, 6.3 Hz, 1H), 4.12-3.97 (m, 2H), 3.94 (s, 3H), 2.67 (m, 1H), 2.13 (m, 1H), 1.35 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.0, 156.4, 129.8, 129.1, 125.8, 79.8, 64.1, 52.1, 28.4, 28.2, 25.3 IR (film) 2974, 2891, 1721, 1701, 1365, 1277, 1177, 1133, 1112, 770. HRMS (ESI-TOF): m/z calcd. for C₁₂H₁₄NO₄ ([M – tBu + H⁺]⁺) 235.0844, found 235.0841.

**Methyl 4-((tert-butoxycarbonyl)amino)-2-hydroxyethyl-benzoate (47)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)serine (154 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product
was isolated by flash chromatography (74 mg, 50%). $^1$H NMR (500 MHz, D$_6$-Acetone) \(\delta\) 7.96 (d, \(J = 8.0\) Hz, 2H), 7.51 (d, \(J = 8.0\) Hz, 2H), 6.45 (br, 1H), 4.78 (br, 1H), 4.05 (m, 1H), 8.87 (s, 3H), 3.77 (m, 2H), 1.38 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) \(\delta\) 166.8, 155.8, 144.9, 130.1, 129.5, 126.6, 80.2, 66.4, 56.3, 52.2, 28.3; IR (film) 3363, 2977, 1702, 1698, 1515, 1366, 1279, 1166, 1019. HRMS (ESI-TOF): m/z calcd. for C$_{11}$H$_{14}$NO$_5$ ([M – tBu + H]$^+$) 239.0793, found 239.0805.

Methyl 4-((tert-butoxycarbonyl)amino)-2-phenylethylbenzoate (48)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)phenylalanine (199 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (141 mg, 79%). $^1$H NMR (500 MHz, CDCl$_3$) \(\delta\) 7.99 (d, \(J = 8.3\) Hz, 2H), 7.28 - 7.20 (m, 5H), 7.03 (d, \(J = 7.5\) Hz, 2H), 5.01 (s, 1H), 4.94 (s, 1H), 3.93 (s, 3H), 3.06 (s, 2H), 1.39 (br, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) \(\delta\) 166.9, 155.0, 136.7, 129.8, 129.4, 129.2, 128.6, 126.8, 126.4, 79.9, 55.7, 52.1, 43.1, 28.3; IR (film) 3363, 2977, 1702, 1611, 1503, 1278, 1166, 1100, 1018, 700. HRMS (ESI-TOF): m/z calcd. for C$_{17}$H$_{18}$NO$_4$ ([M – tBu + H]$^+$) 299.1157, found 299.1155.
4-benzyl 1-(tert-butyl) 2-(4-(methoxycarbonyl)phenyl)piperazine-1,4-dicarboxylate (49)

According to the general procedure Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.61 mg, 5.00 µmol, 1 mol%), NiCl₂·glyme (5.49 mg, 25.0 µmol, 5 mol%), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 5 mol%), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1 eq), 4-[(benzyloxy)carbonyl]-1-[(tert-butoxy)carbonyl]piperazine-2-carboxylic acid (273 mg, 0.75 mmol, 1.5 eq), cesium carbonate (244 mg, 0.75 mmol, 1.5 eq) in dimethylacetamide (5 mL, 0.1 M) was utilized. The product was isolated by flash chromatography as a white solid (162 mg, 71%). ¹H-NMR (500 MHz, CDCl₃): δ 8.08 – 7.84 (m, 2H), 7.43 – 7.23 (m, 7H), 5.39 – 4.96 (m, 3H), 4.57 – 4.38 (m, 1H), 4.07 – 3.80 (m, 2H), 3.92 (s, 3H), 3.53 – 3.38 (m, 1H), 3.23 – 2.93 (m, 2H), 1.43 (s, 9H) ppm. ¹³C-NMR (125 MHz, CDCl₃) rotameric mixture, resonances for second rotamer enclosed in parenthesis: δ 166.9, 155.5 (155.2), 155.0, 144.3, 136.5, 130.1, 129.3, 128.7 (128.4), 128.3, 128.0, 126.8, 80.9, 67.6, 54.6 (54.0), 52.3, 45.7 (45.0), 43.8 (43.6), 39.5 (39.1), 28.4 ppm. IR (film): 2971, 1689, 1413, 1276, 1099, 859, 751.
**Tert-butyl 2-(4-(methoxycarbonyl)phenyl)-4-oxopiperidine-1-carboxylate (50)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 1-(tert-butoxycarbonyl)-4-oxopiperidine-2-carboxylic acid (182 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (130 mg, 78%).

**¹H NMR (500 MHz, Chloroform-d)** \(\delta\) 7.94 (d, \(J = 8.4\) Hz, 2H), 7.26 (d, \(J = 8.2\) Hz, 2H), 5.62 (s, 1H), 4.28 – 4.01 (m, 1H), 3.84 (s, 3H), 3.16 (s, 1H), 2.94 – 2.68 (m, 2H), 2.53 – 2.37 (m, 1H), 2.32 (dt, \(J = 16.5\), 3.7 Hz, 1H), 1.38 (s, 9H).

**¹³C NMR (126 MHz, Chloroform-d)** \(\delta\) 207.3, 166.6, 154.7, 145.7, 130.1, 129.5, 126.4, 81.1, 54.5, 52.2, 44.4, 40.5, 39.0, 28.3. IR (film): \(ν_{max}\) 2976, 1721, 1692, 1612, 1393, 1366, 1279, 1247, 1160, 1110, 1017.

**HRMS (ESI-TOF):** m/z calcd. For C₁₄H₁₆N₃O₅ ([M–tBu+H]+) 277.0950, found 277.0947.

**IR (film):** \(ν_{max}\) 3032, 2950, 1719, 1697, 1612, 1417, 1351, 1277, 1226, 1108. HRMS (ESI-TOF): m/z calcd. For C₂₁H₂₄N₅O₅ ([M+H]+) 369.1576, found 369.1576.
**Tert-butyl (1R,3S,4S)-3-(4-(methoxycarbonyl)phenyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (51)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (1R,3S,4S)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (181 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (141 mg, 85%). ¹H NMR (500 MHz, CDCl₃) Mixture of rotemers δ 7.99 (apparent dd, J = 8.3, 3.0 Hz, 2H), 7.28 (apparent dd, J = 8.2, 6.2 Hz, 2H), 4.43 (apparent d, J = 65.7 Hz, 1H), 4.35 (apparent d, J = 69.3 Hz, 1H), 3.91 (apparent d, J = 10.5 Hz, 3H), 2.45 (s, 1H), 1.9 - 1.6 (m, 5H), 1.49 (s, 4H), 1.22 (s, 5H), 1.18 (d, J = 9.7 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) Rotomeric peaks are listed in parenthesis: δ 167.1, 155.1 (154.3), 148.0 (147.3), 129.6 (129.3), 128.5 (128.4), 126.0 (125.9), 79.6 (79.5), 67.0 (66.7), 57.9, 56.8, 52.1 (51.0), 45.9 (45.3), 33.9 (33.8), 30.8 (30.7), 28.5 (28.2, 27.9); IR (film) 2973, 1723, 1696, 1388, 1277, 1160, 1105 cm⁻¹. HRMS (ESI-TOF): m/z calcd. for C₁₅H₁₈NO₄ ([M – tBu + H]⁺) 275.1157, found 275.1155. a₀ = - 124.77 (CHCl₃, c = 1.00)
Methyl 4-(1-(benzyloxy)ethyl)benzoate (52)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 2-(benzyloxy)propanoic acid (135 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (115 mg, 85%). ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.35 - 7.25 (m, 5H), 4.56 (q, J = 6.5 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.32 (d, J = 11.8 Hz, 1H), 3.93 (s, 3H), 1.48 (d, J = 6.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 167.0, 149.1, 138.2, 129.9, 129.3, 129.0, 128.4, 127.7, 126.2, 76.8, 70.6, 52.1, 24.1; IR (film) 3030, 2977, 2951, 2864, 1719, 1611, 1435, 1274, 1109, 1092, 1018, 706, 697. HRMS (ESI-TOF): m/z calcd. for C₁₇H₁₉O₃ ([M + H]⁺) 270.1256, found 270.1251.

Methyl 4-(phenoxyethyl)benzoate (53)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl₂•glyme (11.00 mg, 50.0 µmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), methyl 4-bromobenzoate (108 mg, 0.50
mmol, 1.0 equiv), 2-phenoxyacetic acid (152 mg, 1.0 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (70 mg, 58%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.3$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.30 (t, $J = 8.0$ Hz, 2H), 7.02 - 6.93 (m, 3H), 5.13 (s, 2H), 3.92 (s, 3H).

Spectral data was consistent with that previously reported: Manos-Turvey, A.; Watson, E. E.; Sykes, M. L.; Jones, A. J.; Baell, J. B.; Kaiser, M.; Avery, V. M.; Payne, R. J. MedChemComm. 2015, 6, 403.

**Methyl 4-(tetrahydro-2H-pyran-2-yl)benzoate (54)**

According to the general procedure, Ir[dF(aw)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), tetrahydro-2H-pyran-2-carboxylic acid (98 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 25 mL of DMF were used. The product was isolated by flash chromatography (60 mg, 55%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.2$ Hz, 2H), 4.39 (dd, $J = 11.2$, 2.3 Hz, 1H), 3.91 (s, 3H), 3.63 (td, $J = 11.6$, 2.6 Hz, 1H), 1.96 (m, 1H), 1.86 (m, 1H), 1.78 - 1.49 (m, 4H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 167.0, 148.5, 129.6, 129.0, 79.5, 68.9, 52.0, 34.1, 25.8, 23.9;
IR (film) 2939, 2846, 1719, 1611, 1434, 1273, 1085, 763. HRMS (ESI-TOF): m/z calcd. for C_{13}H_{17}O_{3} ([M + H]^+) 220.1099, found 220.1098.

**Benzyl 2-(4-(methoxycarbonyl)phenyl)-1,4-oxazepane-4-carboxylate (55)**

According to the general procedure, Ir[dF(CF_{3})ppy]_{2}(dtbbpy)PF_{6} (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl_{2}•glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 4-((benzyloxy)carbonyl)-1,4-oxazepane-2-carboxylic acid (209 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The reaction was placed in front of the light for 48 hours. The product was isolated by flash chromatography (134 mg, 73%). \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 8.00 (dd, \(J = 19.3, 8.3\) Hz, 2H), 7.63 – 7.26 (m, 7H), 5.36 – 4.94 (m, 2H), 4.58 (ddd, \(J = 43.2, 10.0, 2.6\) Hz, 1H), 4.33 – 3.96 (m, 2H), 3.91 (s, 3H), 3.78 – 3.54 (m, 2H), 3.31 (ddt, \(J = 18.7, 7.9, 6.4\) Hz, 1H), 3.04 (ddd, \(J = 56.8, 14.6, 10.0\) Hz, 1H), 2.19 – 1.96 (m, 2H). \(^13\)C NMR (126 MHz, Chloroform-d) \(\delta\) 166.9, 156.2, 145.0, 136.6, 129.7, 128.6, 128.1, 127.9, 125.9, 115.2, 82.7, 69.0, 67.3, 56.4, 52.1, 45.5, 29.9. IR (film) 3032, 2950, 1719, 1697, 1612, 1455, 1434, 1417, 1277, 1226, 1108. HRMS (ESI-TOF): m/z calcd. for C_{21}H_{24}NO_{5} ([M + H]^+) 369.1576, found 369.1568.
Methyl 4-(oxetan-2-yl)benzoate (56)

According to the general procedure, Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ (5.1 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), oxetane-2-carboxylic acid (77 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv), 1.25 mL of DMSO and 23.75 mL of DMF were used. The product was isolated by flash chromatography (50 mg, 50%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 5.86 (dd, $J = 7.6, 7.6$ Hz, 1H), 4.85 (ddd, $J = 7.9, 5.9, 5.9$ Hz, 1H), 4.68 (ddd, $J = 9.2, 5.8, 5.8$ Hz, 1H), 3.92 (s, 3H), 3.07 (m, 1H), 2.62 (m, 1H).

Spectral data was consistent with that previously reported: Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. Science. 2016, 352, 1304.

Methyl 4-((benzyloxy)((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)benzoate (57)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), 2-(benzyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid (200
mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 5 mL of DMA were used. The product was isolated in 1:1.5 diastereomeric ratio by flash chromatography (151 mg, 85%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) Peaks listed for Major diastereomer \(\delta\) 8.06 (m, 2H), 7.45 (m, 2H), 7.32 (m, 5H), 4.50-4.30 (4H), 4.07 (m, 2H), 3.93 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) Major diastereomer: \(\delta\) 166.9, 144.3, 137.6, 130.2, 129.8, 128.5, 127.9, 127.7, 109.7, 81.8, 78.8, 71.0, 67.0, 52.1, 26.9, 26.8, 25.2; Minor diastereomer: \(\delta\) 166.8, 143.0, 137.7, 130.3, 129.7, 128.4, 128.0, 127.8, 110.0, 81.5, 78.5, 70.7, 65.7, 52.2, 26.4, 26.2, 25.3; IR (film) 2987, 2950, 2878, 1721, 1611, 1277, 1106, 1072, 851. HRMS (ESI-TOF): m/z calcd. for C\(_{21}\)H\(_{24}\)NaO\(_5\) ([M + Na]\(^{+}\)) 356.1626, found 356.1623. \(\text{a}_{D}^{21} = +3.97\) (CHCl\(_3\), \(c = 1.00\))

Methyl 4-((3a\(R\),4\(R\),6\(R\),6\(a\)\(R\))-6-methoxy-2,2-dimethyltetrahydrofuro\([3,4-d][1,3]\)dioxol-4-yl)benzoate (58)

According to the general procedure, Ir[dF(Me)ppy]\(_2\) (dtbbpy)PF\(_6\) (10.1 mg, 10.0 \(\mu\)mol, 0.02 equiv), NiCl\(_2\) • glyme (5.49 mg, 25.0 \(\mu\)mol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 \(\mu\)mol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (3a\(S\),4\(S\),6\(R\),6\(a\)\(R\))-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (164 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 25 mL of DMA were used. The product was isolated in >20:1 diastereomeric ratio by flash chromatography (121 mg, 78%). \(^1\)H NMR (500 MHz,
CDCl$_3$ δ 8.02 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 5.37 (d, J = 2.1 Hz, 1H), 5.15 (s, 1H), 4.86 (dd, J = 5.9, 2.0 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 3.91 (s, 3H), 3.38 (s, 3H), 1.58 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 166.8, 145.7, 129.7, 129.4, 126.1, 113.1, 110.1, 88.6, 85.7, 55.6, 52.1, 28.8, 25.2; IR (film) 2990, 2945, 1723, 1612, 1436, 1376, 1278, 1107, 1089 cm$^{-1}$.

HRMS (ESI-TOF): m/z calcd. for C$_{16}$H$_{21}$O$_6$ ([M + H]$^+$) 308.1256, found 308.1258. $\Delta$$\delta^{21}$ = -16.27 (CHCl$_3$, c = 1.00)

According to the general procedure, Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ (10.1 mg, 10.0 µmol, 0.02 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (3aS,4S,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-carboxylic acid (164 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 25 mL of DMA were used. The vial was then placed in the Merck Photoreactor for 2.5 hours. The product was isolated in >20:1 diastereomeric ratio by flash chromatography (107 mg, 69%).

![Chemical structure](image)

**Methyl 4-((3aR,4R,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)benzoate (59)**

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.00 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-
bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), methyl 4-bromobenzoate (108 mg, 0.50 mmol, 1.0 equiv), (3aS,4S,6R,6aR)-6-(6-amino-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (241 mg, 0.75 mmol, 1.5 equiv), cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv) and 25 mL of DMA were used. The product was isolated by reverse phase chromatography (72 mg, 35%). $^1$H NMR (300 MHz, Acetone-$d_6$) δ 8.28 – 8.09 (m, 2H), 7.96 (dd, $J = 15.2, 8.3$ Hz, 2H), 7.53 (m, 2H), 6.60 (s, 2H), 6.42 – 6.29 (m, 1H), 5.69 (d, $J = 5.0$ Hz, 1H), 5.64 – 5.37 (m, 1H), 5.21 (d, $J = 4.3$ Hz, 1H), 3.87 (d, $J = 4.1$ Hz, 3H), 1.39 (m, 3H), 1.20 (s, 3H). IR (Film) 3327, 3166, 2986, 1716, 1642, 1597, 1476, 1432, 1420, 1374, 1329, 1277, 1205, 1157, 1077, 1018, 864, 838. HRMS (ESI-TOF): m/z calcd. for $C_{20}H_{22}N_5O_5$ ([M + H]$^+$) 441.1543, found 441.15461

![Tert-butyl 2-(pyridin-4-yl)pyrrolidine-1-carboxylate (60)]

According to the general procedure, Ir[dtbbpy]$_2$PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 4-bromopyridine hydrobromide (119 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 mL, 1.15 mmol, 2.3 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (95 mg, 77%). $^1$H-NMR (500 MHz, CDCl$_3$), rotameric mixture: δ 8.52 (d, $J = 5.7$ Hz, 2H), 7.11 (d, $J = 5.1$ Hz, 2H), 7.18 – 7.12 (m, 8H), 4.97 – 4.66 (m, 1H), 3.69 – 3.48 (m, 2H), 2.40 – 2.26 (m, 1H), 1.93 – 1.72 (m, 3H), 1.45 and 1.19 (2s,
9H, rotamers); $^{13}$C-NMR (125 MHz, CDCl$_3$), rotameric mixture, resonances for minor rotamer enclosed in parenthesis: $\delta$ (154.6), 154.5, 154.4 (153.7), 149.7 (149.6), 120.9, 80.0, 60.6 (60.1), 47.5 (47.3), 35.7 (34.5), (28.6) 28.3, (23.8) 23.4 ppm. IR (Film) 2975, 2879, 1690, 1599, 1388, 1250, 1158, 773. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{21}$N$_2$O$_2$ ([M + H]$^+$) 249.1598, found 249.1594

**Tert-butyl 2-(2-fluoropyridin-4-yl)pyrrolidine-1-carboxylate (61)**

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 4-bromo-2-fluoropyridine (88 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (111 mg, 83%). $^1$H-NMR (500 MHz, CDCl$_3$), rotameric mixture: $\delta$ = 8.16 – 8.07 (m, 1H), 7.03 – 6.96 (m, 1H), 6.75 – 6.68 (m, 1H), 4.98 – 4.66 (m, 1H), 3.67 – 3.46 (m, 2H), 2.43 – 2.28 (m, 1H), 1.93 – 1.75 (m, 3H), 1.45 and 1.21 (2s, 9H, rotamers); $^{13}$C-NMR (125 MHz, CDCl$_3$), rotameric mixture, resonances for minor rotamer enclosed in parenthesis: $\delta$ = 164.3 (d, J = 240.7 Hz), 160.6 (d, J = 7.4 Hz) (159.6), (154.6) 154.2, 147.7 (d, J = 14.9 Hz), (118.7) 118.6, 106.3 (d, J = 37.9 Hz), 80.15, 60.4 (60.0), (47.5) 47.2, 35.5 (34.4), (28.6) 28.3, (23.8) 23.4 ppm. IR (film) 2976, 2880, 1690, 1609, 1479, 1387, 1278, 1161, 866, 772. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{20}$FN$_2$O$_2$ ([M + H]$^+$) 267.1503, found 267.1501.
According to the general procedure, \( \text{Ir[dF(CF}_3\text{)ppy}]_2(dtbppy)PF_6 \) (525 mg, 468 µmol, 0.01 equiv), NiCl$_2$•glyme (1.027 g, 4.68 mmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (1.255 g, 4.68 mmol, 0.10 equiv), 4-bromo-2-fluoropyridine (8.48 g, 46.76 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (15.10 g, 70.1 mmol, 1.5 equiv), DBU (10.49 mL, 70.1 mmol, 1.5 equiv) and 70.5 mL of DMA were used. This solution was then passed through a Vapourtech flow reactor at 0.22222 mL/min so that the retention time was 45 minutes, and after a constant concentration of reaction mixture was reached in the flow reactor, the light was turned on, and 100 mL of the solution was collected. The product was isolated by flash chromatography (10.1 g, 81%).

According to the general procedure, 4CzIPN (538 mg, 682 µmol, 0.01 equiv), NiCl$_2$•glyme (1.498 g, 6.82 mmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (1.830 g, 6.82 mmol, 0.10 equiv), 4-bromo-2-fluoropyridine (12.0 g, 68.2 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (22.02 g, 102 mmol, 1.5 equiv), DBU (15.30 mL, 102 mmol, 1.5 equiv) and 90 mL of DMA were used. This solution was then passed through a Vapourtech flow reactor at 0.22222 mL/min so that the retention time was 45 minutes, and after a constant concentration of reaction mixture was reached in the flow reactor, the light was turned on, and 120 mL of the solution was collected. The product was isolated by flash chromatography (14.16 g, 78%).
**Tert-butyl 2-(2-acetamidopyridin-4-yl)pyrrolidine-1-carboxylate (62)**

According to the general procedure, \( \text{Ir}[dF(CF_3)ppy]_2(\text{dtbbpy})\text{PF}_6 \) (5.6 mg, 5.0 µmol, 0.01 equiv), \( \text{NiCl}_2\text{•glyme} \) (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), \( N-(4\text{-bromopyridin-2-yl})\text{acetamide} \) (108 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (92 mg, 60%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) mixture of rotamers \( \delta 8.76 - 8.62 \) (m, 1H), 8.20 – 8.12 (m, 1H), 8.07 (br s, 1H), 6.88 – 6.82 (m, 1H), 4.95 – 4.70 (m, 1H), 3.67 – 3.45 (m, 2H), 2.41 – 2.25 (m, 1H), 2.18 and 2.17 (2s, 3H, rotamers), 1.92 – 1.77 (m, 3H), 1.45 and 1.21 (2s, 9H, rotamers); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta 168.9, 157.3 \) (156.2), (154.7) 154.4, (152.0) 151.8, (147.6) 147.6, (117.2) 116.8, 111.5 (111.1), (79.9) 79.8, 60.9 (60.4), (47.5) 47.2, 35.6 (34.5), (28.6) 28.3, 24.9, (23.8) 23.4 ppm; IR (film) 3266, 2976, 2881, 1683, 1567, 1532, 1390, 1257, 1113, 966, 750. HRMS (ESI-TOF): m/z calcd. for \( \text{C}_{16}\text{H}_{24}\text{N}_3\text{O}_3 \) ([M + H\(^+\)]\(^{\text{a}}\)) 306.1812, found 306.1811.

**Tert-butyl 2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)pyrrolidine-1-carboxylate (63)**

According to the general procedure, \( \text{Ir}[dF(CF_3)ppy]_2(\text{dtbbpy})\text{PF}_6 \) (5.6 mg, 5.0 µmol, 0.01 equiv), \( \text{NiCl}_2\text{•glyme} \) (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl
(13.4 mg, 50.0 µmol, 0.10 equiv), 4-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (176 mg, 0.50 mmol, 1.0 equiv), \((\text{tert-butoxycarbonyl})\)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMF were used. The product was isolated by flash chromatography (109 mg, 65%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) mixture of rotamers \(\delta\) 8.37 (d, \(J = 5.0\) Hz, 1H), 8.07 (d, \(J = 8.4\) Hz, 2H), 7.72 (d, \(J = 4.0\) Hz, 1H), 7.28 (d, \(J = 7.7\) Hz, 2H), 6.96 (dd, \(J = 20.1, 5.0\) Hz, 1H), 6.61 (d, \(J = 4.1\) Hz, 1H), 5.12 (apparent ddd, \(J = 112.1, 8.6, 4.0\) Hz, 1H), 3.71 - 3.52 (m, 2H), 2.38 (apparent s, 4H), 1.89 (m, 3H), 1.45 (s, 4H), 0.97 (s, 5H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 154.5, 154.1, 147.5, 145.1, 135.4, 129.6, 128.0, 126.1, 119.9, 115.5, 114.8, 103.5, 79.6, 59.1, 47.0, 34.9, 27.9, 23.7, 21.6. IR (film) 2978, 2923, 1691, 1393, 1165, 680. HRMS (ESI-TOF): m/z calcd. for C\(_{23}\)H\(_{28}\)N\(_3\)O\(_4\)S ([M + H]\(^{+}\)) 441.1722, found 441.1717.

\(N\)-Boc-2-pyrid-3-ylpyrrolidine (64)

According to the general procedure, Ir[dF(CF\(_3\))ppy\(_2\)(dtbbpy)]PF\(_6\) (2.8 mg, 2.5 µmol, 0.005 equiv), NiCl\(_2\)•glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4′-di-\(\text{tert}\)-butyl-2,2′-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), 3-bromopyridine (79 mg, 0.50 mmol, 1.0 equiv), \((\text{tert-butoxycarbonyl})\)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 25 mL of DMF were used. The product was isolated by flash chromatography (87 mg, 70%). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.48 (br s, 1H), 7.49 (dt, \(J = 7.9, 2.0\) Hz, 1H), 7.24 (dd, \(J = 7.8, 4.9\) Hz, 1H), 4.97 (s, 0.31 H), 4.78 (t, \(J = 6.4\) Hz, 0.60 H), 3.69 – 3.46 (m, 2H), 2.38 (dt, \(J = 20.2, 10.0\) Hz, 1H), 1.92 (dq, \(J = 11.9, 6.4\)) Hz, 1H).
7.1, 5.6 Hz, 2H), 1.84 (dt, J = 9.5, 4.7 Hz, 1H), 1.46 (s, 3.17H), 1.20 (s, 5.89H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 154.3, 148.1, 147.4, 140.4, 133.0, 123.2, 79.7, 59.2 47.1, 35.9 28.2, 23.3.

Spectral data was consistent with that previously reported: Campos, K. R.; Klapars, A.; Waldman, P. G.; Chen, C.-y. J. Am. Chem. Soc. 2006, 128, 3538

![N-Boc-2-(5-trifluoromethylpyrrole-3-yl)pyrrolidine (65)](image)

$\text{N-Boc-2-(5-trifluoromethylpyrrole-3-yl)pyrrolidine (65)}$

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.8 mg, 2.5 µmol, 0.005 equiv), NiCl$_2$•glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4'-di-tert-butyl-2,2'-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), 3-bromo-5-(trifluoromethyl)pyridine (113 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 25 mL of DMF were used. The product was isolated by flash chromatography (112 mg, 77%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.77 (s, 1H), 8.67 (d, J = 2.0 Hz, 1H), 7.72 (s, 1H), 5.02 (s, 0.33H), 4.87 – 4.80 (m, 0.57H), 3.74 – 3.52 (m, 2H), 2.45 (d, J = 13.1 Hz, 1H), 1.95 (q, J = 7.3 Hz, 2H), 1.85 (d, J = 16.8 Hz, 1H), 1.46 (s, 4H), 1.20 (s, 5H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 154.1, 151.1, 144.9, 140.8, 130.1 (q, J = 3.6 Hz), 126.4 (q, J = 32.8 Hz), 123.5 (q, J = 272.4 Hz), 80.1, 59.0, 47.2, 34.6, 28.1, 23.5. IR (Film): 2976.8, 2880.4, 1692.1, 1388.3, 1365.6, 1334.8, 1158.7, 1126.8, 1085.1, 1025.8, 902.7, 716.2, 672.0. HRMS (ESI-TOF) m/z calcd. for C$_{15}$H$_{19}$F$_3$N$_2$O$_2$ ([M+H]$^+$) 316.1399, found 316.1403.
**Tert-butyl 2-(5-methoxypyridin-3-yl)pyrrolidine-1-carboxylate (66)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), 3-bromo-5-methoxypyridine (94 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 25 mL of DMA were used. The product was isolated by flash chromatography (92 mg, 66%). ¹H NMR (500 MHz, CDCl₃) δ 8.18 (s, 1H), 8.10 (s, 1H), 7.00 (s, 1H), 5.06 – 4.71 (m, 1H), 3.85 (s, 3H), 3.77 – 3.45 (m, 2H), 2.36 (m, 1H), 1.92 (m, 3H), 1.92 (s, 3H), 1.47 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 155.6, 154.3, 141.2, 140.2, 135.6, 117.6, 79.6, 59.0, 55.6, 47.1, 35.8, 28.2, 23.3; IR (film) 2973, 2878, 1690, 1743, 1589, 1390, 1365, 1286, 1162, 1112, 866, 714. HRMS (ESI-TOF): m/z calcd. for C₁₅H₂₂N₂O₃ ([M + H]⁺) 278.1630, found 278.1624.

**Tert-butyl 5-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (67)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), tert-butyl 5-bromo-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (149 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg,
1.0 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (141 mg, 73%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.61 (m, 1H), 8.10 (m, 1H), 7.03 (m, 1H), 5.14 (m, 1H), 3.78 – 3.48 (m, 2H), 2.40 (m, 1H), 1.85 (m, 2H), 1.65 (s, 9H), 1.38 (s, 4H), 1.02 (s, 5H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 153.0, 149.7, 146.9, 134.5, 114.6, 114.3, 84.5, 79.1, 57.9, 46.0, 34.5, 27.4, 27.1, 22.7; IR (film) 2977, 1754, 1743, 1692, 1388, 1367, 1297, 1250, 1151, 730. HRMS (ESI-TOF): m/z calcd. for C$_{20}$H$_{29}$N$_4$O$_4$ ([M + H]$^+$) 388.2111, found 338.2101.

Tert-butyl 2-(pyridin-2-yl)pyrrolidine-1-carboxylate (68)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (8.23 mg, 37.5 µmol, 0.075 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (10.06 mg, 37.5 µmol, 0.075 equiv), 2-bromopyridine (79 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (77 mg, 62%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.56 – 8.50 (m, 1H), 7.65 – 7.57 (m, 1H), 7.21 – 7.06 (m, 2H), 5.05 – 4.79 (m, 1H), 3.71 – 3.44 (m, 2H), 2.43 – 2.22 (m, 1H), 2.10 – 1.80 (m, 3H), 1.45 and 1.19 (2s, 9H, rotamers).

Spectral data was consistent with that previously reported: Beng, T. K.; Woo, J. S.; Gawley, R. E.; J. Am. Chem. Soc. 2012, 134, 14764
Tert-butyl 2-(6-(tert-butyl)pyridin-2-yl)pyrrolidine-1-carboxylate (69)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 2-(tert-butyl)-6-chloropyridine (85 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (122 mg, 80%). ¹H NMR (500 MHz, CDCl₃) δ 7.53 (r, J = 7.7 Hz, 1H), 7.14 (m, 1H), 6.96 (m, 1H), 5.03 – 4.72 (m, 1H), 3.74 – 3.46 (m, 2H), 2.37 – 2.16 (m, 1H), 2.13 – 1.94 (m, 2H), 1.94 – 1.78 (m, 2H), 1.47 (s, 4H), 1.34 (s, 9H), 1.19 (s, 5H); ¹³C NMR (CDCl₃, 125 MHz): δ 168.4, 162.2, 154.6, 136.0, 116.9, 116.4, 78.9, 62.7, 47.0, 37.3, 34.0, 30.2, 28.2, 23.2; IR (film) 2965, 2874, 1743, 1694, 1576, 1389, 1364, 1250, 1161, 1113. HRMS (ESI-TOF): m/z calcd. for C₁₈H₂₈N₂O₂ ([M + H]⁺) 304.2151, found 304.2133.

Tert-butyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)pyrrolidine-1-carboxylate (70)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (11.0 mg, 50.0 µmol, 0.10 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), 2-bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-
yl)pyridine (142 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMF were used. A NMR yield of 57% was observed using 0.2 eq of benzodioxazole as standard. For isolation purposes, after removal of the DMF, the resulting oil was redissolved in 5 mL of THF, and sodium perborate tetrahydrate (3 eq, 231 mg) was added and the solution was stirred for 24 hours. Then water was added, and the aqueous layer was extracted with DCM. The combined organic layers were dried with sodium sulfate, and concentrated. The corresponding phenol was isolated by column chromatography, giving 60 mg, corresponding to 45% yield. The following characterization data is for the phenol. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.26 – 7.80 (m, 1H), 7.27 – 7.00 (m, 1H), 6.91 (m, 1H), 4.92 (m, 1H), 3.72 – 3.44 (m, 2H), 2.32 (m, 1H), 2.02 – 1.81 (m, 3H), 1.28 (s, 4H), 1.22 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 155.13, 154.5, 152.4, 123.5, 120.3, 80.2, 61.6, 47.6, 33.5, 28.6, 24.9; IR (film) 3300 (br), 2976, 2879, 1665, 1398, 1272, 1161, 1117. HRMS (ESI-TOF): $m/z$ calcd. for C$_{14}$H$_{21}$N$_2$O$_3$ ([M + H]$^+$) 264.1474, found 264.1470.

![Tert-butyl 2-(6-chloropyridin-2-yl)pyrrolidine-1-carboxylate (71)](image)

*Tert-butyl 2-(6-chloropyridin-2-yl)pyrrolidine-1-carboxylate (71)*

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 2,6-dichloropyridine (74 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (129 mg, 0.6 mmol, 1.2 equiv), DBU (104 µL, 0.6 mmol, 1.2 equiv) and 5 mL of DMA were used. The product was isolated by flash
chromatography (86 mg, 61%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 – 7.53 (m, 1H), 7.19 (app. dd, J = 15.7, 7.8 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 5.03 – 4.81 (m, 1H), 3.72 – 3.42 (m, 2H), 2.39 (m, 1H), 2.16 – 1.96 (m, 2H), 1.95 – 1.80 (m, 2H), 1.47 (s, 3H), 1.26 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 169.0, 154.4, 150.6, 138.8, 122.0, 118.0, 79.6, 62.4, 47.0, 28.2, 23.1; IR (film) 2975, 2878, 1693, 1576, 1390, 1365, 1158, 1115. HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{20}$N$_2$ClO$_2$ ([M + H]$^+$) 282.1135, found 282.1130.

![Tert-buty 2-(pyrimidin-5-yl)pyrrolidine-1-carboxylate (72)](image)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 5-bromopyrimidine (79 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), Cesium Carbonate (326 mg, 1.0 mmol, 2.0 equiv) and 25 mL of MeCN were used. This reaction mixture was then divided amongst 5 8mL vials. The product was isolated by flash chromatography (88 mg, 71%). $^1$H NMR (500 MHz, CDCl$_3$) δ 9.26 – 9.06 (m, 1H), 8.61 (m, 1H), 5.02 – 4.72 (m, 1H), 3.64 (m, 2H), 2.49 – 2.33 (m, 1H), 2.05 – 1.80 (m, 3H), 1.95 – 1.08 (m, 2H), 1.47 (s, 3H), 1.25 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 157.44, 154.7, 137.8, 117.3, 80.2, 57.3, 47.1, 35.7, 28.2, 23.4; IR (film) 2975, 2879, 1690, 1565, 1388, 1365, 1161, 1117. HRMS (ESI-TOF): m/z calcd. for C$_{13}$H$_{20}$N$_2$O$_2$ ([M + H]$^+$) 249.1477, found 249.1471.
**Tert-butyl 2-(pyrimidin-4-yl)pyrrolidine-1-carboxylate (73)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 4-chloropyrimidine (57 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of MeCN were used. The product was isolated by flash chromatography (78 mg, 63%). $^1$H NMR (500 MHz, CDCl₃) δ 9.16 (s, 1H), 8.68 (dd, J = 10.4, 5.2 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 4.97 – 4.76 (m, 1H), 3.72 – 3.53 (m, 2H), 2.47 – 2.26 (m, 1H), 2.04 – 1.80 (m, 3H), 1.48 (s, 3H), 1.24 (s, 6H); $^{13}$C NMR (CDCl₃, 125 MHz): δ 172.4, 158.5, 156.9, 154.2, 117.3, 80.0, 62.3, 47.1, 43.0, 28.2, 23.3; IR (film) 2975, 2879, 1691, 1580, 1387, 1365, 1159, 1116. HRMS (ESI-TOF): m/z calcd. for C₁₃H₂₀N₃O₂ ([M + H]⁺) 249.1477, found 249.1474.

**Tert-butyl 2-(2-chloropyrimidin-4-yl)pyrrolidine-1-carboxylate (74)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 2,4-dichloropyrimidine (74 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of MeCN were used. The product was isolated by flash
chromatography (81 mg, 57%). Arylation at the 4-position, rather than the 2-position, was confirmed by HMBC correlation of the 2-pyrrolidyl carbon (13C δ = 61.9) with the hydrogen on C5 of the pyrimidine ring (1H δ = 7.15). ¹H NMR (500 MHz, CDCl₃) δ 8.54 (br d, J = 5.1 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 4.88 (dd, J = 8.8, 3.5 Hz, 0.46H), 4.77 (dd, J = 8.4, 4.4 Hz, 0.61H), 3.67 – 3.46 (m, 2H), 2.48 – 2.30 (m, 1H), 2.09 – 1.80 (m, 3H), 1.45 (s, 4H), 1.25 (s, 5H); ¹³C NMR (CDCl₃, 125 MHz): δ 176.4, 161.2, 159.4, 154.0, 115.6, 80.3, 62.1, 47.1, 33.9, 28.2, 23.3; IR (film) 2977, 2881, 2246, 1795, 2688, 1572, 1543, 1390, 1366, 1339, 1254, 1158, 1118, 1085, 1027, 973, 910, 843, 774, 727, 667. HRMS (ESI-TOF): m/z calcd. for C₁₃H₁₈ClN₃O₂ ([M + H⁺]⁺) 283.1088, found 283.1085.

Tert-butyl 2-(6-methylpyridazin-3-yl)pyrrolidine-1-carboxylate (75)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (11.00 mg, 50.0 µmol, 0.10 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (13.4 mg, 50.0 µmol, 0.10 equiv), 3-chloro-6-methylpyridazine (64 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (69 mg, 52%). ¹H NMR (500 MHz, CD₂Cl₂) δ 7.34 – 7.14 (m, 2H), 5.13 – 4.96 (m, 1H), 3.64 – 3.47 (m, 2H), 2.65 (s, 3H), 2.47 – 2.28 (m, 1H), 2.04 – 1.82 (m, 3H), 1.42 (s, 4H), 1.17 (s, 5H). ¹³C NMR (126 MHz, CD₂Cl₂) δ 163.64, 162.82, 158.82, 154.42, 127.20, 124.35, 123.77, 79.59, 61.62, 61.11, 47.79, 47.52, 34.88, 33.42, 28.54,
28.26, 24.39, 23.74, 22.09; IR (film) 2974, 2930, 2878, 1688, 1388, 1365, 1159, 1117.

HRMS (ESI-TOF): m/z calcd. for C₉H₁₄N₃ ([M – Boc + H]+) 164.11822, found 164.11825.

Tert-butyl 2-(pyrazin-2-yl)pyrrolidine-1-carboxylate (76)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 2-bromopyrazine (79 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMA were used. The product was isolated by flash chromatography (80 mg, 64%). ¹H NMR (500 MHz, CDCl₃) δ 8.52 (m, 2H), 8.46 (m, 1H), 7.23 (d, J = 5.0 Hz, 1H), 4.97 (m, 1H), 3.74 – 3.49 (m, 2H), 2.51 – 2.27 (m, 1H), 2.17 – 1.86 (m, 3H), 1.47 (s, 3H), 1.23 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.0, 158.0, 154.1, 143.8, 142.8, 79.8, 60.7, 47.1, 34.1, 28.2, 23.5; IR (film) 2975, 2878, 1692, 1390, 1365, 1161, 1115. HRMS (ESI-TOF): m/z calcd. for C₁₃H₂₀N₃O₂ ([M + H]+) 249.1477, found 249.1476.

Tert-butyl 2-(6-(1H-pyrazol-1-yl)pyrazin-2-yl)pyrrolidine-1-carboxylate (77)

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂·glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl
(6.71 mg, 25.0 μmol, 0.05 equiv), 2-chloro-6-(1H-pyrazol-1-yl)pyrazine (90 mg, 0.50 mmol, 1.0 equiv), \((\text{tert-butoxycarbonyl})\)L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 μL, 1.0 mmol, 2.0 equiv) and 25 mL of DMA were used. The product was isolated by flash chromatography (125 mg, 79%). \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 9.11 (d, \(J = 11.1\) Hz, 1H), 8.52 – 8.36 (m, 1H), 8.40 – 8.22 (m, 1H), 7.72 (d, \(J = 7.6\) Hz, 1H), 6.52 – 6.21 (m, 1H), 5.01 – 4.65 (m, 1H), 3.73 – 3.41 (m, 2H), 2.40 – 2.19 (m, 1H), 2.11 – 1.79 (m, 3H), 1.39 (s, 4H), 1.16 (s, 5H). \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 156.3, 154.1, 146.6, 143.1, 139.4, 133.2, 127.4, 108.5, 79.9, 60.0, 47.1, 33.9, 28.3, 23.5. IR (film) 2972, 2926, 2875, 1689, 1585, 1537, 1453, 1385, 1362, 1246, 1158, 1112, 1038, 1011, 952, 875, 758, 694. HRMS (ESI-TOF): m/z calcd. for \(\text{C}_{16}\text{H}_{21}\text{N}_{5}\text{O}_{2}\) ([M + H]+) 315.1695, found 315.1689.

\[
\text{tert-buty}l\ 3-\(\text{(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-pyrazole-1-carboxylate (78)}\)
\]

According to the general procedure, Ir[dF(CF\(_3\))ppy\(]_2\)dtbbpyPF\(_6\) (5.6 mg, 5.0 μmol, 0.01 equiv), NiCl\(_2\)•glyme (8.23 mg, 37.5 μmol, 0.075 equiv), 2,2'-bipyridine (5.86 mg, 37.5 μmol, 0.075 equiv), \(\text{tert-buty}l\ 3\)-iodo-1\(H\)-pyrazole-1-carboxylate (147 mg, 0.50 mmol, 1.0 equiv), \((\text{tert-butoxycarbonyl})\)L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 μL, 1.0 mmol, 2.0 equiv) and 25 mL of DMF were used. The product was isolated by flash chromatography (109 mg, 66%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.96 (d, \(J = 2.7\) Hz, 1H), 6.25 (s, 1H), 4.99 (s, 1H), 3.61 – 3.44 (m, 2H), 2.30 – 2.10 (m, 2H), 1.65 (s, 9H), 1.50 – 1.20 (m, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 160.3, 154.5, 147.6, 131.0, 106.6,
According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂•glyme (8.23 mg, 37.5 µmol, 0.075 equiv), 2,2'-bipyridine (5.86 mg, 37.5 µmol, 0.075 equiv), tert-butyl 3-iodo-1H-pyrazole-1-carboxylate (147 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMF were used. The vial was then placed in the Merck Photoreactor for 4 hours. The product was isolated by flash chromatography (129 mg, 76%).

![Tert-butyl 2-(1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate](image)

**Tert-butyl 2-(1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)pyrrolidine-1-carboxylate (79)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂•glyme (11.00 mg, 50.0 µmol, 0.10 equiv), 2,2'-bipyridine (7.81 mg, 50.0 µmol, 0.10 equiv), 5-fluoro-2-(3-iodo-1H-pyrazol-1-yl)pyridine (145 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (122 mg, 73%). $^1$H NMR (500 MHz, CDCl₃) δ 8.37 (d, J = 2.6 Hz, 1H), 8.24 (s, 1H), 7.95 (dd, J = 9.0, 3.9 Hz, 1H), 7.52 (t, J = 6.8 Hz, 1 H), 6.31 (s, 1H), 5.02 (s,
1H), 3.55 (m, 2H), 2.37 - 2.09 (m, 2H), 2.08 - 1.88 (m, 2H), 1.47 (s, 3H), 1.33 (s, 6H); \n\n$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 158.7 (d, J = 252.6 Hz), 154.6, 147.9, 135.4 (d, J = 22.7 Hz), 127.3, 125.7 (d, J = 22.9 Hz), 113.3, 106.3, 105.7, 79.3, 55.7, 46.4, 33.8, 28.4, 23.4; IR (film) 2974, 2878, 1690, 1479, 1529, 1479, 1386, 1365, 1233, 1161, 1114, 1042, 953, 836, 768. HRMS (ESI-TOF): m/z calcd. for C$_{12}$H$_{14}$FN$_4$ ([M – Boc + H]$^+$) 232.1123, found 232.1126.

Tert-butyl 2-(thiazol-2-yl)pyrrolidine-1-carboxylate (80)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4’-di-tert-butyl-2,2’-bipyridyl (6.71 mg, 25.0 µmol, 0.05 equiv), 2-bromothiazole (82 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMA were used. The product was isolated by flash chromatography (67 mg, 53%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68 (d, J = 3.3 Hz, 1H), 7.20 (apparent s, 1H), 5.31 - 5.08 (m, 1H), 3.67 - 3.38 (m, 2H), 2.37 - 2.11 (m, 2H), 1.93 (m, 2H), 1.47 and 1.31 (2s, 9H, rotomers); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 175.5, 154.2, 142.4, 118.2, 80.1, 59.6, 46.5, 34.0, 28.2, 23.2; IR (film) 2975, 2880, 1690, 1382, 1365, 1158, 1109, 872, 769. HRMS (ESI-TOF): m/z calcd. for C$_{12}$H$_{18}$N$_2$O$_2$S ([M + H]$^+$) 254.1089, found 254.1079
**Tert-butyl 2-(3-methylisothiazol-5-yl)pyrrolidine-1-carboxylate (81)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂•glyme (5.49 mg, 25.0 µmol, 0.05 equiv), 4,4′-dimethoxy-2,2′-bipyridine (5.41 mg, 25.0 µmol, 0.05 equiv), 5-bromo-3-methylisothiazole (89 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMSO were used. The product was isolated by flash chromatography (90 mg, 67%). ¹H NMR (500 MHz, CDCl₃) δ 6.81 (m, 1H), 5.32 – 5.07 (m, 1H), 3.64 – 3.17 (m, 2H), 3.46 (s, 3H), 2.29 (m, 1H), 2.06 – 1.78 (m, 3H), 1.41 (s, 3H), 1.37 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 173.4, 167.0, 154.1, 120.6, 80.2, 55.5, 46.2, 35.1, 28.5, 23.2 19.1; IR (film) 2974, 2930, 2880, 1691, 1383, 1363, 1162, 1107. HRMS (ESI-TOF): m/z calcd. for C₁₅H₂₁N₂SO₂ ([M + H]⁺) 268.1246, found 268.1239.

**Tert-butyl 2-(benzo[b]thiophen-2-yl)pyrrolidine-1-carboxylate (82)**

According to the general procedure, Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl₂•glyme (8.23 mg, 37.5 µmol, 0.075 equiv), 4,4′-di-tert-butyl-2,2′-bipyridyl (10.06 mg, 37.5 µmol, 0.075 equiv), 2-bromobenzo[b]thiophene (107 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 25 mL of DMA were used. The product was isolated by flash chromatography (99 mg, 66%). ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 9.1 Hz, 1H),
7.69 (d, J = 7.8 Hz, 1H), 7.37 (m, 2H), 7.10 (s, 1H), 5.31 - 5.05 (m, 1H), 3.75 - 3.43 (m, 2H), 2.34 (m, 1H), 2.09 (m, 2H), 1.96 (m, 1H), 1.93 (m, 2H), 1.49 and 1.33 (2s, 9H, rotomers); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 153.3, 148.7, 138.6, 137.9, 123.1, 122.6, 122.0, 121.2, 118.3, 78.7, 56.4, 45.2, 34.2, 27.5, 22.1; IR (film) 2973, 2876, 1690, 1384, 1364, 1249, 1160, 1102, 1042, 744. HRMS (ESI-TOF): m/z calcd. for C$_{13}$H$_{14}$NO$_2$S ([M – tBu + H]$^+$) 247.0667, found 247.0665.

Tert-butyl 2-(5-(methoxycarbonyl)furan-2-yl)pyrrolidine-1-carboxylate (83)

According to the general procedure, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv), NiCl$_2$•glyme (2.25 mg, 12.5 µmol, 0.025 equiv), 4,4’-dimethoxy-2,2’-bipyridine (2.70 mg, 12.5 µmol, 0.025 equiv), methyl 5-bromofuran-2-carboxylate (89 mg, 0.50 mmol, 1.0 equiv), (tert-butoxycarbonyl)-L-proline (215 mg, 1.0 mmol, 2.0 equiv), DBU (173 µL, 1.0 mmol, 2.0 equiv) and 5 mL of DMSO were used. The product was isolated by flash chromatography (109 mg, 54%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.10 (s, 1H), 6.22 (m, 1H), 5.09 – 4.81 (m, 1H), 3.88 (s, 3H), 3.62 –3.35 (m, 2H), 2.32 – 2.05 (m, 2H), 2.05 – 1.85 (m, 2H) 1.47 (s, 3H), 1.34 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 161.5, 159.2, 154.2, 143.1, 118.9, 107.4, 79.8, 55.1, 51.8, 46.2, 32.3, 28.3, 23.2; IR (film) 2975, 2881, 1730, 1692, 1386, 1365, 1302, 1159, 1134, 1113, 761. HRMS (ESI-TOF): m/z calcd. for C$_{11}$H$_{13}$NO$_5$ ([M – tBu + H]$^+$) 239.0794, found 239.0790.
Chapter 4

A Triple Catalytic C–H Alkylation

I. C–H Bonds: The Most Native Functionality

The MacMillan group has long been interested in utilizing native functionalities in cross coupling methodology (Figure 1). While numerous functional groups have proved amenable towards this strategy, we wished to develop methodologies that utilize C–H bonds, due the ubiquity of C–H bonds in organic molecules, as it is difficult design an organic compound that does not contain at least one C–H bond. However, given the ubiquity of this simple motif, the major challenge towards their activation is achieving selectivity amongst the multitude of C–H bonds present in any complex molecules. While in the last decades there have become a number of elegant strategies towards the selective activation of sp\(^2\) C–H bonds, the selective activation of sp\(^3\) C–H bonds has remained challenging. Typically, methods rely of deprotonation of the most acidic hydrogen via strong base, followed by transmetallation for coupling reactions (Figure 2). In a landmark

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Figure 1. Native Functionalities

study, Campos and coworkers\(^2\) demonstrated that this entire process could be rendered enantioselective via an enantioselective deprotonation with chiral lithium complexes derived from sparteine. Furthermore, the Fu group demonstrated that using a racemic organozinc, generated \textit{in-situ} via deprotonation and transmetallation, the enantioenriched product could still be achieved via utilization of a chiral nickel catalyst. Alternatively, if a suitable directing group is present on the carbon architecture, a Concerted-Metalation-Deprotonation (CMD) mechanism can be utilized to activate the desired bond. Typically, this proceeds via generating a five-membered palladacylc, which can then react with an appropriate electrophile to furnish a coupled product. Finally, metal carbene complexes

![Diagram of sp3 C–H functionalization]

\textbf{Figure 2. Common methods for sp}^3 \textbf{C–H functionalization}

have been shown to insert into the most electron-rich, sterically accessible C–H bond in the complex in a concerted fashion.\(^3\) While these methods provide access to a great number of architectures, we recently wondered if hydrogen atom transfer would provide a complimentary method towards sp\(^3\) C–H activation.


II. HAT Catalysis

The MacMillan group has become interested in Hydrogen Atom Transfer (HAT) as a catalytic manifold. This is an effective method for the conversion of typically inert sp\(^3\) hybridized C–H bonds into a carbon-centered radical.\(^4\) This strategy allows for facile interfacing with metallaphotoredox catalyzed cross-couplings, allowing for a broad array of couplings of typically inert substrates. HAT functions when an open shelled species abstracts a hydrogen atom from a second molecule, creating a new bond to hydrogen on the original radical, and a new radical on the substrate. This process is governed via established and predictable selectivity for site-selective cleavage of C–H bonds.\(^5\) This selectivity results from both the Bond Dissociation Energy (BDE) of the C–H bond as well as the electronic nature of the hydrogen atom (Figure 3). How these two factors compete is analogous to the classic thermodynamics vs kinetics argument for selectivity in classic, closed shell processes. In this system, unsurprisingly the BDE component represents the thermodynamics component, and rarely is important when considering the regioselectivity of an abstraction. It is typically the electronics of the system that determine the selectivity of the HAT event. For selective abstraction of a hydrogen atom, the abstractor should be of the opposite polarity of the hydrogen atom. For example, to selectively abstract an electron-rich, or hydridic, hydrogen atom in the presence of a weaker, protic C–H bond, the ideal abstractor should be electrophilic. This effect is shown Figure 3, where an electrophilic HAT species abstracts the higher energy, hydridic


Figure 3. Thermodynamic vs kinetic control in HAT events

position of 1-methylazepan-2-one while the weaker, protic α–carbonyl position is untouched. It should be noted that amongst this class of abstractions, BDE does play a role after the electronics of the system have been accounted for. HAT events follows Marcus theory, and therefore faced between a strong hydric bond or a weak hydridic bond, the weaker bond will be selectively abstracted.

During the end of the 20th century, the pioneering work of Roberts demonstrated that HAT events could be applied to organic synthesis. The Roberts group developed hydroacylation of olefins, epimerization of tertiary C–H bonds, deoxygenation, and even activation of neutral C–H bonds in cyclohexane. This was accomplished using in situ generated thiy radicals as the HAT species, which generates the necessary carbon-

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centered radical for the desired transformation. While Roberts demonstrated the feasibility of this HAT catalysis in organic synthesis, this area of research remained limited until recently. A few notable exceptions are Lei’s nickel catalyzed cross coupling of C–H bonds with aryl boronic acids\(^\text{10}\), as well as Leckta’s protocols for C–H fluorination.\(^\text{11}\)

**III. A C–H Alkylation via a Triple Catalytic Manifold\(^\text{12}\)**

Our group has had a growing interest in combining HAT catalysis with photoredox catalysis. Previously, we have demonstrated a number of transformations using a catalytic amount of thiol as the active C–H abstractor,\(^\text{1a}\) but the finding that quinuclidine\(^\text{1f}\) could also act as an efficient HAT catalyst expanded the classes of C–H bonds that could be activated. This is both due to the highly electrophilic nature of the quinuclidine radical cation, as well as the stronger N–H BDE of the protonated catalyst compared to S–H bonds. This has allowed the activation of strong, hydridic bonds, such as \(\alpha\)-hydroxyl C–H bonds. Furthermore, this catalyst was found to be compatible with nickel and photoredox catalysis, allowing for the direct arylation of C–H bonds (Scheme 1).\(^\text{1g}\) Given the importance of installation of alkyl groups in medicinal chemistry


\(^{12}\)This work was done in collaboration with Chi “Chip Le, Yufan Liang, and Ximing Li. It was recently accepted into *Nature.*
programs, we hypothesized that this triple catalytic manifold could be applied towards a sp\(^3\)-sp\(^3\) C–H alkylation.

**Scheme 1. Our group’s triple catalytic C–H arylation**

Traditionally this has been a challenging coupling to achieve.\(^{13}\) \(\beta\)-hydride elimination can occur on either alkyl group, allowing for a facile isomerization of the alkyl groups or removal of the metal from from the catalytic cycle. Our group, however, had previously developed a methodology that accomplishes a sp\(^3\)-sp\(^3\) coupling between carboxylic acids and alkyl halides,\(^{14}\) demonstrating that the desired bond formation was possible with nickel and photoredox catalysis. Given the impact that a selective alkylation adjacent to an amine would have in the pharmaceutical industry, we chose to pursue this HAT alkylation protocol.

We envisioned that this transformation could be achieved via a triple catalytic manifold, utilizing photoredox, nickel, and HAT catalysis (Scheme 2). For how these catalysts would work in concert to achieve this transformation, we hypothesized that the catalytic cycle would begin via excitation of iridium photocatalyst 1 to generate the excited state 2. This can act as an oxidant (\(E_{1/2}^{\text{red}}[^{\text{III}\text{Ir}}/\text{Ir}^{\text{II}}] = +1.21\) V vs SCE in

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Scheme 2. Proposed mechanism for the C–H alkylation

MeCN),\textsuperscript{15} to generate the active HAT catalyst from 3 (E_{1/2}^{\text{red}}[{+}^{\bullet}\text{NR}_3/\text{NR}_3] = +1.10 \text{ V vs SCE in MeCN})\textsuperscript{16}, the radical cation of quinuclidine 4, as well as Ir(II) species 5. Then 4 would selectively abstract a hydrogen atom from 6 to generate the requisite carbon-centered radical 7, as well as a protonated quinuclidine species 8. The latter can be deprotonated to regenerate 3, to close the organocatalytic cycle. Alkyl radical 7 can add to Ni(0) species 9 to generate the corresponding alkyl Ni(I) complex 10. This then undergoes oxidative addition with an alkyl halide, to generate Ni(III) complex 11. From here reductive elimination generates the desired product 13, as well as Ni(I) species 12. Finally, To complete both catalytic cycles, Ni(I) can be reduced to Ni(0) (E_{1/2}^{\text{red}}[\text{Ni(II)/Ni(0)}] = −1.20 \text{ V vs SCE in DMF})\textsuperscript{16} by the previously generated Ir(II) complex 5 (E_{1/2}^{\text{red}}[\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = −1.37 \text{ V vs SCE in MeCN}).

\textbf{IV. Optimization of the Reaction Conditions}


To test this reaction, N-Boc pyrrolidine and cyclohexylmethyl bromide were chosen as model substrates. To prevent difunctionalization of the amine, this component was utilized in excess at 2.0 eq. When subjected to the reaction conditions outlined in Scheme 3, we were delighted to find that the alkylated product could be observed. However, we were disappointed to find that the HAT catalyst undergoing alkylation

![Scheme 3](image)

**Scheme 3. Optimization of the reaction conditions**

via a direct SN2 reaction with the alkyl halide, consuming both the HAT catalyst as well as the limiting reagent. In some regards, this was not surprising given the nucleophilicity of quinuclidine. To overcome deleterious side reaction that consumed both our catalyst as well as the limiting reagent, two strategies were explored.

The first, and least successful, was modification of the structure of the HAT catalyst to minimize the amount of alkylation. Initial attempts with a thiol catalyst were unsuccessful, as the thiol-based abstractors typically have lower BDEs, limiting the types of hydrogen bonds they can abstract. Additionally, the tendency for sulfur to coordinate to transition metals frequently causes inhibition of transition metal catalysts. Therefore, we continued with the quinuclidine framework. When DABCO was utilized, this also was unsuccessful due to the lower N–H BDE, rendering it a less efficient HAT
catalyst. Given these results, we next turned our attention to fine tuning the electronics of the original quinuclidine system in hopes of modulating the nucleophilicity of the nitrogen atom. To accomplish this, for reasons of synthetic accessibility, we turned our attention towards modifications of quinuclidol or quinuclidone, as these possess useful functional handles at the 3-position. In terms of efficiency, none surpassed that of the commercially available, unadorned quinuclidine. In addition, when analyzed, no derivative appeared to form less of the quaternized ammonium salt.

Decreasing the concentration of quinuclidine was examined next. Lowering the quinuclidine loading to a catalytic 10 mol%, while incorporating an inorganic base for catalyst turnover, lead to an improvement in both the overall efficiency as well as a decrease in the quantity of alkylated catalyst. To further improve the system, we found that the addition of large equivalencies of water was beneficial. We rationalize this result by recognizing that the system consists of two competing pathways: a background reaction of catalyst consumption, and the desired photoredox cross-coupling. If the desired transformation can be accelerated, this would allow for more turnovers of the catalysts, and therefore a higher yield, before the HAT catalyst was consumed. We believe water accomplishes this via creating a more polar solvent, which allows for a more efficient separation of charge transfer complexes. This helps to minimize back electron transfer from the photocatalyst, allowing for a faster photoredox cycle. However, we cannot rule out other effects, such as hydrogen bonding from the water to the quinuclidine to decrease its nucleophilicity. Nevertheless, under these conditions we only observe minimal amounts of catalyst alkylation and high levels of efficiency.

V. Reaction Scope
We first examined the scope of the amine “nucleophile” partner, as shown in Table 1. To our delight, a variety of amines could be efficiently coupled using this protocol. It should be noted that although the amine component is used in excess, typically at 2.0 eq, the remainder of the mass balance is unreacted starting material that can be recovered. Cyclic amines, from 4 to 7 membered rings, all provided the desired compounds in satisfactory yield (14 to 19, 42 – 83% yield). Furthermore, when 3-fluorouropyrrrolidine was utilized, functionalization was exclusively observed distal to the fluorine atom to afford 17. This results from the inductive effects of the electronegative fluorine atom decreasing the hydricity of the proximal hydrogen atoms. Furthermore, a variety of protecting groups for nitrogen could be utilized. In addition to Boc, we found that Cbz and acetate groups allowed for the desired coupling to occur (15 and 16, 56 and 74% yield, respectively). When a lactam was subjected to the reaction conditions, the polarity-matching model for HAT correctly predicted the production of 20. Although the α-carbonyl hydrogen atoms possess a lower BDE, abstraction occurs selectively at the kinetically favored α-amino position. Surprisingly, complete regioselectivity for the exocyclic methyl position over the internal methylene was observed. Acyclic amines were also amenable to this transformation (21, 22, 24 to 27, 52 – 75% yield). Dimethylamine with both Boc and Ac protecting groups both gave the desired product in good yield (21 and 22, 64% and 52% yield, respectively). When there was a choice between reactivity on an ethyl or methyl group, we observed a 5:1 regiomeric ratio favoring functionalization on the methyl group (25). When the ethyl group was replaced
with an isopropyl group, the observed regioselectivity was 20:1 for the methyl group to afford 26. Adjacent steric bulk is well tolerated in the transformation, as 27 was formed in 75% yield. Additionally, this protocol is not limited to dialkyl amines, as boc protected butylamine afforded 24 in 62% yield.
Given this success, we wished to expand this protocol C–H bonds adjacent to other motifs. We were gratified to find that ureas are also compatible with this coupling protocol (23, 59% yield). Furthermore, ethers and thioethers could also be incorporated into this protocol. When cyclic ethers were utilized good yields could be achieved (28 and 29, 70% and 60% yield, respectively). However, ethers do require higher equivalents of the nucleophile component that compared to the amine case, typically in the region of 50 eqs, due to the reduced hydricity of the α-oxy C–H bonds as compared to α-amino C–H bonds. Furthermore, thioethers are readily amenable to this protocol, and do not require the levels of excess nucleophile as ethers. Both cyclic and acyclic thioethers could be coupled in good yield (30 to 33, 61–71% yield). Again, given a choice between an isopropyl group and a methyl group, the same regioselectivity as the corresponding amine (>20:1 r.r.) was observed to afford 32.

This HAT alkylation protocol was then applied towards more complex molecules. When a protected lysine was subjected to the reaction conditions, the desired product 34 was generated in 41% yield, with exclusive functionalization occurring on the side chain of the amino acid. This is consistent for selective abstraction of the most hydridic hydrogen, even in the presence of weaker, protic C–H bonds. Given the success of thioethers in the coupling, methionine was next targeted as a possible handle for alkylation. Indeed, when a dipeptide containing this amino acid was utilized, 35 was observed in 52% yield and 5:1 r.r. The regioisomers observed were between the internal and terminal α-mercapto positions, and consistent with all previously observed patterns of reactivity, where functionalization on the methyl group was the major product.
Similarly, when a tripeptide containing methionine was utilized, a similar efficiency and regioselectivity was observed (39, 58% yield, 8:1 r.r).

The scope of the alkyl halide component was examined next (Table 2). In addition to the β-branched cyclohexylmethyl bromide, a variety of alkyl bromides containing functional groups are well tolerated in this transformation (37, 38, 44 to 49, 43 – 82% yield). Esters, nitriles, acetals, phosphonates, ethers, protected alcohols, and heteroaromatic systems provided the desired products in useful to good yields.

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Product</th>
<th>Yield</th>
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<tbody>
<tr>
<td>Br–Cl</td>
<td>(±)-37</td>
<td>64%</td>
</tr>
<tr>
<td>Br–OBn</td>
<td>(±)-38</td>
<td>63%</td>
</tr>
<tr>
<td>Br–Me</td>
<td>(±)-39</td>
<td>46%</td>
</tr>
<tr>
<td>Br–Me</td>
<td>(±)-40</td>
<td>55%</td>
</tr>
<tr>
<td>Br–Me</td>
<td>(±)-41</td>
<td>53%</td>
</tr>
<tr>
<td>Br–OMe</td>
<td>(±)-42</td>
<td>61%</td>
</tr>
<tr>
<td>R = Ac</td>
<td>(±)-43</td>
<td>41%</td>
</tr>
<tr>
<td>R = Boc</td>
<td>(±)-44</td>
<td>82%</td>
</tr>
<tr>
<td>R = Boc</td>
<td>(±)-45</td>
<td>43%</td>
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<tr>
<td>R = Boc</td>
<td>(±)-46</td>
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<td>R = Boc</td>
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</tr>
<tr>
<td>R = Boc</td>
<td>(±)-55</td>
<td>43%</td>
</tr>
</tbody>
</table>

Table 2. Scope of the alkyl halide component
Furthermore, secondary alkyl halides proved to be amenable to this transformation (41, 50 to 55, 42 – 71% yield). In all cases, no isomerization of the alkyl group was observed. Both fully carbocyclic rings as well as those incorporating heteroatoms could be efficiently utilized in this sp$^3$-sp$^3$ coupling protocol (50 to 52, 51 – 70% yield). Notably, constrained ring systems, such as oxetanes, cyclobutanes, and cyclopropanes could be coupled in useful to good yields (53 to 55, 42 – 71% yield).

One potential application of this technology is the coupling of small alkyl groups for the purpose of elucidating structure-activity relationships. With this in mind, we wished to demonstrate that methyl, ethyl, and isopropyl groups could be incorporated using this technology. To our delight, both ethyl and isopropyl groups could easily be incorporated into the desired product (40, 41, 55% and 53% yield, respectively). However, when we attempted to incorporate a methyl group, the desired product was not observed. Given the reactivity of methyl sources compared to ethyl, we believe that the HAT catalyst was deactivated via the direct alkylation of the nitrogen atom with the methyl electrophile. However, methyl is one of the most desirable groups to incorporate due to the “Magic Methyl” effect, where a methyl group can drastically improves the potency of a medicinal compound. Due to the demand for methods of direct methyl installation, we wished to find an alternative method for methyl installation.

From the beginning of the project we were cognizant of the possibility of

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halogen atoms acting as hydrogen atom abstractors, although quinuclidine was ultimately chosen as our HAT catalyst. However, given the reactivity of quinuclidine with electrophilic methyl sources, we wondered if alternative conditions could be developed using bromide as a HAT catalyst for the direct methylation of compounds.

Scheme 4. Optimization of the bromide abstraction for methylation

When quinuclidine and water were emitted from the reaction conditions, and using methylbromide as the methyl source, we were delighted to find that the desired methylated product could be observed. For ease of operation, the methyl source was changed from gaseous methyl bromide to the liquid methyl tosylate. This species generates methylbromide in-situ via $S_N2$ reaction with a bromide anion. Indeed, inclusion of 1.2 equivalents of CsBr gives near identical yields as compared to that of methylbromide. Ultimately, acetone was found to be a superior solvent, and the desired methylated product of N-Boc pyrolidine 44 could be generated in 41% yield. However,

\[ \textbf{Scheme 4. Optimization of the bromide abstraction for methylation} \]

\[ \begin{align*}
\text{Ni}(\text{BF}_4)_2\cdot6\text{H}_2\text{O} \\
10 \text{ mol\% quinuclidine} \\
\text{MeCN} \\
70 \text{ eq water} \\
X = \text{Br} \\
0 \text{ eq CsBr}
\end{align*} \]  

\[ \begin{align*}
\text{NiBr}_2\cdot\text{diglyme} \\
\text{no quinuclidine} \\
\text{Acetone} \\
0 \text{ eq water} \\
X = \text{OTs} \\
1.2 \text{ eq CsBr}
\end{align*} \]

\[ \text{via:} \]

\[ \begin{align*}
\text{MeCN} \\
70 \text{ eq water} \\
X = \text{Br}
\end{align*} \]

when that N-acetyl pyrolidine was utilized instead, 43 could be generated in 61% yield. This effect is likely due to a slower C–H abstraction, allowing for better matching of the catalytic rates.

As mentioned previously, one potential application of this technology is late stage functionalization. To demonstrate this, the pharmaceutical agent Prozac was chosen as a model substrate. When boc-protected Prozac was subjected to the HAT alkylation protocol, we were delighted to observe the desired compound. Prozac was regioselectively alkylated on the methyl group, and both primary and secondary alkyl halides could be utilized in this late-stage modification (56 to 58, 45 – 52% yield). We believe this strategy could be beneficial as it removes the need for de-novo synthesis to reach these advanced pharmacophores.

**VI. Conclusion**

In conclusion, we have demonstrated that a triple catalytic manifold can be applied towards the direct C–H alkylation. Selectivity is achieved in a predictable manner via a selective HAT event that is determined by the electronics of the bond itself. This
protocol demonstrated tolerance for a wide range of functional groups, and successfully functionalized a wide variety of frameworks. To demonstrate the utility of this protocol, several small peptides were functionalized, and Prozac was diversified via installation of several alkyl groups.
VII. Supporting Information

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. All solvents were purified according to the method of Grubbs. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still. Thin-layer chromatography (TLC) was performed on Analtech 250 micron silica gel plates. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm$^{-1}$). $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 125 MHz) instrument, and are internally referenced to residual protic solvent signals (note: CDCl$_3$ referenced at $\delta$ 7.26 and 77.16 ppm respectively). Data for $^1$H NMR are reported as follows: chemical shift (\(\delta\) ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for $^{13}$C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. Gas chromatography (GC) was performed on an Agilent 6850 Series chromatograph with splitless capillary injection and FID detection.
Standard reaction setup

In a typical reaction, the reaction mixture is irradiated with 34W Kessil KSH150B from 5 cm away. Regular fans are employed to maintain the temperature at room temperature. For reactions that require elevated temperature, fans are turned off to allow the reaction to reach 50 °C.

General procedure for HAT-Alkylation protocol

To an oven-dried 8-mL vial equipped with a stir bar was added Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(II) salt and bipyridyl ligand. MeCN was added and the solution was stirred under nitrogen for 15 minutes to allow for complete complexation. Quinuclidine (as a MeCN solution), inorganic base, amine (1.00 mmol, 2.0 equiv.) and alkyl halide (0.50 mmol, 1.0 equiv) were added, followed by addition of water. The reaction was sparged with nitrogen for 15 minutes at 0 °C (ice water bath) before being parafilmed and placed 5 cm away from 34W blue LEDs without fan. The
temperature of the reaction is approximately 50 °C. After 24 hours, the reaction was quenched via exposure to air. The organic layer was diluted with EtOAc then washed with NaHCO$_3$ (saturated, aq) and brine. The organic layer was then separated, dried with MgSO$_4$ and concentrated to give the crude product. Purification by column chromatography yields the pure product.

(±)-**tert-butyl 2-(cyclohexylmethyl)azetidine-1-carboxylate (14)**

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), N-Boc azetidine (157 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 17 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc) yielded the pure product as a clear oil (70 mg, 0.276 mmol, 55% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.24 – 4.18 (m, 1H), 3.81 – 3.72 (m, 2H), 2.26 – 2.19 (m, 1H), 1.90 – 1.72 (m, 2H), 1.68 – 1.56 (m, 5H), 1.45 – 1.35 (m, 10H), 1.32 – 1.07 (m, 4H), 0.97 – 0.83 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 156.78, 79.06, 60.77, 46.46, 43.65, 34.38, 33.86, 33.35, 28.55, 26.57, 26.37, 26.28, 23.21. IR (film) $\nu_{\text{max}}$ 2922, 2852, 1700, 1449, 1364, 1254, 1182, 1134 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{13}$H$_{27}$NNaO$_2$ ([M+Na]$^+$) 276.1934, found 276.1932.
(±)-**tert**-butyl 2-(cyclohexylmethyl)pyrrolidine-1-carboxylate (13)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub> (dtbbpy)PF<sub>6</sub> (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF<sub>4</sub>)<sub>2</sub>•6H<sub>2</sub>O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), **tert**-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 µL, 0.50 mmol, 1.0 equiv.), K<sub>2</sub>CO<sub>3</sub> (104 mg, 0.75 mmol, 1.5 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (78 mg, 0.29 mmol, 58% yield).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.93 – 3.76 (m, 1H), 3.43 – 3.24 (m, 2H), 1.96 – 1.76 (m, 4H), 1.76 – 1.56 (m, 6H), 1.56 – 1.39 (s, 9H), 1.34 – 1.09 (m, 5H), 1.05 – 0.80 (m, 2H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 154.69, 78.98, 55.25, 46.07, 42.31, 35.46, 34.60, 32.83, 30.70, 28.76, 26.75, 26.61, 26.41, 23.33.


(±)-**benzyl** 2-(cyclohexylmethyl)pyrrolidine-1-carboxylate (15)
Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂·6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4'-di-tert-butyl-2,2'-bipyridine (2.7 mg, 10.0 µmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), benzyl pyrrolidine-1-carboxylate (205.3 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc) yielded the pure product as a clear oil (85 mg, 0.28 mmol, 56% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.27 (m, 5H), 5.17 – 5.07 (m, 2H), 4.03 – 3.84 (m, 1H), 3.50 – 3.33 (m, 2H), 1.97 – 1.43 (m, 10H), 1.36 – 1.06 (m, 5H), 1.04 – 0.66 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 154.71, 154.46, 137.08, 136.79, 128.18, 127.82, 127.64, 127.57, 127.54, 66.51, 66.11, 55.63, 55.04, 46.10, 45.82, 42.24, 41.43, 35.11, 34.97, 34.16, 32.38, 30.79, 29.99, 26.45, 26.40, 26.26, 26.04, 25.93, 23.57, 22.72. IR (film) νmax 2921, 2850, 1698, 1447, 1408,1357,1100 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₉H₂₇NNaO₂ ([M+Na]+) 324.1934, found 324.1936.

(±)-1-(2-(cyclohexylmethyl)pyrrolidin-1-yl)ethan-1-one (16)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂·6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 µmol, 0.10equiv.)
equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), 1-acetylpipyrrolidine (113 mg, 110 µL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 12 h. Purification by column chromatography (silica gel, 1:2 hexane:EtOAc) yielded the pure product as a clear oil (77 mg, 0.37 mmol, 74% yield). H NMR (500 MHz, CDCl₃) δ 4.16 – 4.12 and 3.84 – 3.79 (m, 1H, rotamer), 3.48 – 3.28 (m, 2H), 2.03 and 1.97 (s, 3H, rotamer), 1.95 – 1.73 (m, 4H), 1.71 – 1.55 (m, 5H), 1.33 – 1.29 (m, 1H), 1.26 – 0.84 (m, 7H). C NMR (125 MHz, CDCl₃) δ 168.84, 168.81, 56.44, 54.98, 47.43, 45.25, 42.49, 40.89, 35.46, 35.29, 34.53, 34.37, 32.44, 32.42, 30.50, 29.63, 26.63, 26.47, 26.44, 26.34, 26.21, 26.13, 23.96, 23.08, 22.17, 22.09. IR (film) νmax 2922, 2851, 1637, 1447, 1415 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₃H₂₄NO ([M+H]+) 210.1852, found 210.1853.

***tert*-butyl (4S)-2-(cyclohexylmethyl)-4-fluoropyrrolidine-1-carboxylate (17)***

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4'-dimethyl-2,2'-bipyridine (1.8 mg, 10.0 µmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), (S)-*tert*-butyl 3-fluoropyrrolidine-1-carboxylate (189.2 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg,
0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc) yielded the pure product as a clear oil (105 mg, 0.37 mmol, 74% yield, 1.5:1 d.r. by $^{19}$F NMR and GC).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.25 – 5.00 (m, 1H), 4.14 – 3.20 (m, 3H), 2.45 – 1.55 (m, 8H), 1.44 (s, 9H), 1.26 – 1.05 (m, 5H), 1.00 – 0.82 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.84, 154.30, 94.44, 93.61, 93.04, 92.71, 92.41, 92.21, 91.30, 91.00, 79.63, 54.76, 53.93, 53.12, 52.96, 52.77, 52.51, 52.34, 43.68, 42.40, 41.65, 39.76, 39.61, 38.87, 37.21, 37.06, 36.18, 36.04, 35.16, 35.00, 34.58, 34.20, 32.75, 32.61, 28.58, 26.65, 26.59, 26.46, 26.31, 26.25. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -168.4 – -170.0 (m, 0.4F), -176.7 – -178.0 (m, 0.6F). IR (film) $\nu_{\text{max}}$ 2975, 2923, 2852, 1694, 1449, 1395, 1365, 1275, 1258, 1163,
1113 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{28}$FNNaO$_2$ ([M+Na]$^+$) 308.1996, found 308.1996.

(±)-*tert*-butyl 2-(cyclohexylmethyl)piperidine-1-carboxylate (18)

Prepared following the general procedure outlined above (*without* fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.8 mg, 2.5 µmol, 0.005 equiv.), Ni(BF$_4$)$_2$$\cdot$6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50 µmol, 0.10 equiv.), N-Boc piperidine (463 mg, 0.48 mL, 2.50 mmol, 5.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 18 h. Purification by column chromatography (silica gel, 30:1 hexane:EtOAc) yielded the pure product as a clear oil (59 mg, 0.21 mmol, 42% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.30 (br s, 1H), 3.96 (br s, 1H), 2.80 – 2.66 (m, 1H), 1.91 – 1.83 (m, 1H), 1.71 – 1.50 (m, 10H), 1.44 (s, 9H), 1.40 – 1.30 (m, 1H), 1.23 – 1.08 (m, 5H), 0.98 – 0.78 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.16, 79.09, 47.98, 38.42, 37.55, 34.39, 33.95, 33.51, 29.07, 28.64, 26.77, 26.58, 26.45, 25.88, 19.15. IR (film) $\nu_{max}$ 2922, 2852, 1689, 1448, 1415, 1364, 1269, 1252, 1182, 1161, 1150 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for $C_{17}$H$_{31}$NNaO$_2$ ([M+Na]$^+$) 304.2247, found 304.2249.
(±)-tert-butyl 2-(cyclohexylmethyl)azepane-1-carboxylate (19)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$·6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), N-Boc azepane (199 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 20:1 hexane:EtOAc) yielded the pure product as a clear oil (123 mg, 0.42 mmol, 83% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.16 – 4.09 and 3.97 – 3.90 (m, 1H, rotamer), 3.65 – 3.59 and 3.52 – 3.46 (m, 1H, rotamer), 2.61 – 2.54 (m, 1H), 2.00 – 1.88 (m, 1H), 1.84 – 1.48 (m, 9H), 1.40 and 1.39 (s, 9H, rotamer), 1.25 – 0.97 (m, 9H), 0.92 – 0.70 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.80, 155.74, 78.92, 78.49, 52.40, 51.57, 46.94, 46.54, 43.12, 42.72, 41.39, 41.05, 35.26, 34.66, 34.54, 34.17, 33.85, 33.74, 33.56, 33.37, 30.04, 29.99, 28.88, 28.57, 28.53, 28.17, 26.69, 26.65, 26.45, 26.36, 25.04, 24.78. IR (film) $\nu_{max}$ 2920, 2852, 1687, 1411, 1364, 1172, 1157, 982 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{18}$H$_{33}$NNaO$_2$ ([M+Na]$^+$) 318.2404, found 318.2401.
1-(2-cyclohexylethyl)azepan-2-one (20)

Prepared following the general procedure outlined above (with fan) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4'-dimethyl-2,2'-bipyridine (9.2 mg, 50.0 µmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50 µmol, 0.10 equiv.), N-methylcaprolactam (191 mg, 192 µL, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (0.4 mL). After stirring for 12 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs with a fan. Continue stirring for another 24 h. Purification by column chromatography (silica gel, 1:1 hexane:EtOAc) yielded the pure product as a clear oil (56 mg, 0.25 mmol, 50% yield).

¹H NMR (500 MHz, CDCl₃) δ 3.34 – 3.29 (m, 2H), 3.28 – 3.23 (m, 2H), 2.46 – 2.40 (m, 2H), 1.73 – 1.54 (m, 11H), 1.35 – 1.30 (m, 2H), 1.25 – 1.02 (m, 4H), 0.90 – 0.81 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) δ 175.40, 49.44, 46.24, 37.38, 35.61, 35.51, 33.29, 30.05, 28.76, 26.58, 26.27, 23.50. IR (film) νₓmax 2920, 2850, 1638, 1484, 1446, 1423, 1198, 975 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₄H₂₅NNaO ([M+Na]+) 246.1828, found 246.1829.
tert-butyl (2-cyclohexylethyl)(methyl)carbamate (21)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (5.1 mg, 15.0 µmol, 0.03 equiv.), 4,4′-di(tert-butyl)-2,2′-bipyridine (4.0 mg, 15.0 µmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl dimethylcarbamate (145.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), Li₂CO₃ (37 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (77 mg, 0.32 mmol, 64% yield).

¹H NMR (500 MHz, CDCl₃) δ 3.26 – 3.16 (m, 2H), 2.81 (s, 3H), 1.77 – 1.60 (m, 5H), 1.45 (s, 9H), 1.37 (q, J = 7.1 Hz, 2H), 1.27 – 1.08 (m, 4H), 0.91 (qd, J = 13.9, 13.0, 3.8 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 155.79, 79.05, 46.55, 35.18, 33.86, 33.30, 28.49, 26.58, 26.32. IR (film) νₘₚₓₚ 2975, 2921, 2851, 1693, 1393, 1364, 1155 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₄H₂₇NNaO₂ ([M+Na]⁺) 264.1934, found 264.1938.

N-(2-cyclohexylethyl)-N-methylacetamide (22)

Prepared following the general procedure outlined above (with fan cooling) using
Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethyl-2,2’-bipyridine (9.2 mg, 50.0 µmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50 µmol, 0.10 equiv.), DMA (131 mg, 139 µL, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (0.4 mL). After stirring for 16 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs with a fan. Continue stirring for another 22 h. Purification by column chromatography (silica gel, 1:3 hexane:EtOAc) yielded the pure product as a light yellow oil (48 mg, 0.26 mmol, 52% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.28 – 3.22 and 3.18 – 3.12 (m, 2H, rotamer), 2.85 and 2.78 (s, 3H, rotamer), 1.96 and 1.94 (s, 3H, rotamer), 1.63 – 1.50 (m, 5H), 1.38 – 1.24 (m, 2H), 1.19 – 1.02 (m, 4H), 0.89 – 0.74 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 170.07, 170.03, 48.72, 45.28, 35.80, 35.68, 35.39, 35.23, 34.48, 33.12, 33.04, 26.42, 26.28, 26.11, 26.02, 21.84, 21.02. IR (film) νmax 2921, 2851, 1638, 1487, 1448, 1405, 1034, 1010 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₁H₂₂NO ([M+H]⁺) 184.1696, found 184.1694.

1-(2-cyclohexylethyl)-1,3,3-trimethylurea (23)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (5.1 mg,
15.0 µmol, 0.03 equiv.), 4,4’-di(tert-butyl)-2,2'-bipyridine (4.0 mg, 15.0 µmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tetramethylurea (174.0 mg, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 5% to 20% EtOAc in hexanes) yielded the pure product as a clear oil (62 mg, 0.29 mmol, 59% yield). \(^1\)H NMR (500 MHz, CDCl₃) δ 3.20 – 3.11 (m, 2H), 2.79 (s, 6H), 2.77 (s, 3H), 1.74 – 1.58 (m, 5H), 1.47 – 1.38 (m, 2H), 1.27 – 1.08 (m, 4H), 0.91 (qd, J = 13.4, 12.6, 3.6 Hz, 2H). \(^{13}\)C NMR (125 MHz, CDCl₃) δ 165.51, 48.47, 38.76, 36.37, 35.58, 34.99, 33.31, 26.57, 26.28. IR (film) \(\nu_{\text{max}}\) 2919, 2850, 1642, 1493, 1379, 1143, 1110 cm\(^{-1}\). HRMS (ESI-TOF) m/z calcd. for \(C_{12}H_{25}N_2O\) ([M+H]⁺) 213.1961, found 213.1962.

\begin{center}
\includegraphics[width=0.5\textwidth]{chemical_structure.png}
\end{center}

(±)-tert-butyl (1-cyclohexylpentan-2-yl)carbamate (24)

Prepared following the general procedure outlined above (without fan) using \(\text{Ir[dF(CF}_3\text{)ppy]}_2\) (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), \(\text{Ni(BF}_4\text{)}_2\)•6H₂O (5.1 mg, 15.0 µmol, 0.03 equiv.), 1,10-phenanthroline (2.7 mg, 15.0 µmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), Di-tert-butyl dicarbonate (21.8 mg, 0.10 mmol, 0.2 equiv.), tert-butyl butylcarbamate (173.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), Li₂CO₃ (37 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica
gel, gradient 2\% to 10\% EtOAc in hexanes) yielded the pure product as a white solid (83 mg, 0.31 mmol, 62\% yield). $^1$H NMR (500 MHz, CDCl$_3$) \( \delta \) 4.15 (d, \( J = 7.1 \) Hz, 0.7H), 3.90 (s, 0.15H), 3.90 (s, 0.8H), 3.56 (s, 0.2H), 1.83 (d, \( J = 12.9 \) Hz, 1H), 1.74 – 1.61 (m, 4H), 1.44 (s, 9H), 1.41 – 1.08 (m, 5H), 0.99 – 0.88 (m, 1H), 0.9 (t, \( J = 6.7 \) Hz, 3H), 0.86 – 0.75 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) \( \delta \) 155.62, 78.73, 47.90, 43.68, 38.51, 34.43, 33.91, 33.01, 28.44, 26.61, 26.42, 26.27, 19.02, 14.08. IR (film) \( \nu_{\max} \) 3341, 2957, 1921, 1851, 1689, 1523, 1364, 1172 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{16}$H$_{31}$NNaO$_2$ ([M+Na]$^+$) 292.2247, found 292.2252.

$t$-butyl (2-cyclohexylethyl)(ethyl)carbamate (major isomer) and ($\pm$)-$t$-butyl (1-cyclohexylpropan-2-yl)(methyl)carbamate (minor isomer) (25)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 \( \mu \)mol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (5.1 mg, 15.0 \( \mu \)mol, 0.03 equiv.), 4,4’-di($t$-butyl)-2,2’-bipyridine (4.0 mg, 15.0 \( \mu \)mol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 \( \mu \)mol, 0.10 equiv.), Di-$t$-butyl dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), $t$-butyl ethyl(methyl)carbamate (159.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 \( \mu \)L, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1\% to 8\% EtOAc in hexanes) yielded a mixture of regioisomers as a clear oil (82 mg, 0.32 mmol, 64\% yield, 5:1 r.r by NMR). $^1$H NMR (500 MHz, CDCl$_3$) \( \delta \) 3.25 – 3.14 (m, 3.25H), 2.64 (s, 0.5H, minor isomer), 1.76 – 1.56
(m, 5H), 1.45 (s, 9H), 1.42 – 1.34 (m, 2H), 1.26 – 1.13 (m, 4H), 1.08 (t, J = 7.1 Hz, 2.82H, major isomer), 1.04 (d, J = 6.8 Hz, 0.55H, minor isomer), 0.99 – 0.85 (m, 2H). 

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.42, 78.89, 44.52, 41.49, 36.08, 35.48, 33.32, 28.53, 26.62, 26.60, 26.48, 26.33, 13.69.

IR (film) $\nu_{\text{max}}$ 2974, 2922, 2851, 1691, 1416, 1159 cm$^{-1}$. 

HRMS (ESI-TOF) m/z calcd. for C$_{15}$H$_{29}$NNaO$_2$ ([M+Na]$^+$) 278.2091, found 278.2097.

**tert-butyl (2-cyclohexylethyl)(isopropyl)carbamate (26)**

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$$\cdot$6H$_2$O (5.1 mg, 15.0 µmol, 0.03 equiv.), 4,4’-di(tert-butyl)-2,2’-bipyridine (4.0 mg, 15.0 µmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), Di-tert-butyl dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), tert-butyl isopropyl(methyl)carbamate (173.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 8% EtOAc in hexanes) yielded the pure product as a clear oil (76 mg, 0.28 mmol, 56% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.17 (bs, 1H), 3.08 – 3.00 (m, 2H), 1.80 – 1.57 (m, 5H), 1.45 (s, 9H), 1.42 – 1.37 (m, 2H), 1.26 – 1.14 (m, 4H), 1.11 (d, J = 6.8 Hz, 6H), 0.97 – 0.89 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.39, 78.87, 36.19, 33.35, 28.59, 26.60, 26.34, 20.89. IR (film) $\nu_{\text{max}}$ 2973, 2923, 2851, 1689, 1449, 1364, 1163, 1142 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{16}$H$_{31}$NNaO$_2$ ([M+Na]$^+$) 292.2247, found 292.2253.
tert-butyl tert-butyl(2-cyclohexylethyl)carbamate (27)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (5.1 mg, 15.0 µmol, 0.03 equiv.), 4,4’-di(tert-butyl)-2,2'-bipyridine (4.0 mg, 15.0 µmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), Di-tert-butyl dicarbonate (32.7 mg, 0.15 mmol, 0.3 equiv.), tert-butyl tert-butyl(methyl)carbamate (187.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (105 mg, 0.37 mmol, 75% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.27 – 3.24 (m, 2H), 1.75 – 1.56 (m, 6H), 1.46 (s, 9H), 1.42 – 1.32 (m, 2H), 1.38 (s, 9H), 1.25 – 1.12 (m, 5H), 0.96 – 0.88 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 155.43, 78.78, 55.19, 43.26, 38.63, 36.22, 33.35, 29.65, 28.63, 26.60, 26.33. IR (film) ν max 2974, 2922, 2852, 1694, 1477, 1449, 1388, 1362, 1167, 1138 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₇H₃₃NNaO₂ ([M+Na]⁺) 306.2403, found 306.2404.

(±)-2-(cyclohexylmethyl)oxetane (28)

Prepared following the general procedure outlined above (with fan cooling) using
Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-di(tert-butyl)-2,2’-bipyridine (13.4 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), oxetane (1.45 g, 1.63 mL, 25.0 mmol, 50.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 17 h. Purification by column chromatography (silica gel, 1:3 pentane:DCM) yielded the pure product as a clear oil (54 mg, 0.35 mmol, 70% yield). ^1H NMR (500 MHz, CDCl₃) δ 4.97 – 4.90 (m, 1H), 4.68 – 4.61 (m, 1H), 4.50 – 4.45 (m, 1H), 2.68 – 2.59 (m, 1H), 2.35 – 2.27 (m, 1H), 1.80 – 1.73 (m, 1H), 1.70 – 1.62 (m, 4H), 1.53 – 1.47 (m, 1H), 1.40 – 1.29 (m, 1H), 1.27 – 1.09 (m, 4H), 0.98 – 0.85 (m, 2H). ^13C NMR (125 MHz, CDCl₃) δ 81.43, 68.18, 46.12, 34.07, 33.94, 33.24, 28.66, 26.61, 26.39, 26.33. IR (film) νmax 2920, 2851, 1448, 973 cm⁻¹. HRMS (EI-TOF) m/z calcd. for C₁₉H₁₈O (M⁺) 154.1352, found 154.1351.

![Image of tetrahydrofuran](image)

(±)-2-(cyclohexylmethyl)tetrahydrofuran (29)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethyl-2,2’-bipyridine (9.2 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), THF (1.80 g, 2.02 mL, 25.0 mmol, 50.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 20 h.
Purification by column chromatography (silica gel, 1:2 hexane:DCM) yielded the pure product as a clear oil (51 mg, 0.30 mmol, 60% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.90 – 3.80 (m, 2H), 3.70 – 3.64 (m, 1H), 1.97 – 1.91 (m, 1H), 1.89 – 1.75 (m, 3H), 1.71 – 1.58 (m, 4H), 1.51 – 1.32 (m, 3H), 1.30 – 1.06 (m, 4H), 0.94 – 0.81 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 77.17, 67.60, 43.71, 35.27, 34.13, 33.32, 32.05, 26.72, 26.44, 26.36, 25.77. IR (film) $\nu_{\text{max}}$ 2919, 2850, 1448, 1068, 1057 cm$^{-1}$. HRMS (EI-TOF) m/z calcd. for C$_{11}$H$_{20}$O (M$^+$) 168.1509, found 168.1507.

![Chemical Structure](image)

(±)-2-(cyclohexylmethyl)tetrahydrothiophene (30)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), tetrahydrothiophene (88 mg, 88 µL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 12:1 hexane:DCM) yielded the pure product as a clear oil (58 mg, 0.315 mmol, 63% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.44 (ddd, $J$ = 14.1, 8.5, 5.5 Hz, 1H), 2.90 – 2.77 (m, 2H), 2.10 – 2.02 (m, 2H), 1.90 – 1.79 (m, 1H), 1.77 – 1.58 (m, 5H) 1.55 – 1.38 (m, 3H), 1.35 – 1.06 (m, 4H), 0.92 – 0.78 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 46.74, 45.60, 37.92, 37.37, 33.93, 32.95, 32.19, 30.36, 26.72, 26.36, 26.31. IR (film) $\nu_{\text{max}}$ 2920,
2851, 1446 cm\(^{-1}\). HRMS (EI-TOF) m/z calcd. for C\(_{11}\)H\(_{20}\)S (M\(^+\)) 184.1280, found 184.1282.

(±)-2-(cyclohexylmethyl)tetrahydro-2\(H\)-thiopyran (31)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF\(_4\))\(_2\) • 6H\(_2\)O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (22.2 mg, 200 µmol, 0.40 equiv.), tetrahydrothiopyran (102 mg, 103 µL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K\(_2\)CO\(_3\) (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 10:1 hexane:DCM) yielded the pure product as a clear oil (61 mg, 0.307 mmol, 61% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 2.79 – 2.73 (m, 1H), 2.64 (td, \(J = 12.7, 11.8, 2.8\) Hz, 1H), 2.57 – 2.53 (m, 1H), 1.95 – 1.87 (m, 2H), 1.86 – 1.80 (m, 1H), 1.78 – 1.74 (m, 1H), 1.68 – 1.59 (m, 4H), 1.58 – 1.51 (m, 1H), 1.49 – 1.39 (m, 1H), 1.38 – 1.07 (m, 7H), 0.91 – 0.77 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 44.19, 39.95, 35.36, 34.39, 33.87, 33.10, 29.29, 27.61, 26.74, 26.44, 26.38, 26.34. IR (film) \(\nu_{\text{max}}\) 2919, 2848, 1447 cm\(^{-1}\). HRMS (EI-TOF) m/z calcd. for C\(_{12}\)H\(_{22}\)S (M\(^+\)) 198.1437, found 198.1442.
(2-cyclohexylethyl)(isopropyl)sulfane (32)

Prepared following the general procedure outlined above (with fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethyl-2,2’-bipyridine (9.2 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), isopropyl methyl sulfide (0.45 g, 0.54 mL, 5.00 mmol, 10.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL).

Reaction time: 21 h. Purification by column chromatography (silica gel, 8:1 hexane:DCM) yielded the pure product as a clear oil (66 mg, 0.354 mmol, 71% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 2.93 – 2.84 (m, 1H), 2.54 – 2.50 (m, 2H), 1.73 – 1.60 (m, 5H), 1.48 – 1.42 (m, 2H), 1.36 – 1.29 (m, 1H), 1.24 (d, $J$ = 6.8 Hz, 6H), 1.21 – 1.07 (m, 3H), 0.92 – 0.83 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 37.49, 37.20, 34.82, 33.19, 28.21, 26.70, 26.35, 23.52. IR (film) $\nu_{\text{max}}$ 2921, 2851, 1448, 1241 cm$^{-1}$. HRMS (EI-TOF) m/z calcd. for C$_{11}$H$_{22}$S (M$^+$) 186.1437, found 186.1440.

$\text{tert-buty1(2-cyclohexylethyl)sulfane (33)}$

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-di(tert-buty1)-2,2’-bipyridine (13.4 mg, 50.0 µmol, 0.10
equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), tert-butyl methyl sulfide (0.52 g, 0.63 mL, 5.00 mmol, 10.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 10:1 hexane:DCM) yielded the pure product as a clear oil (66 mg, 0.33 mmol, 66% yield). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 2.55 – 2.49 (m, 2H), 1.74 – 1.59 (m, 5H), 1.46 – 1.41 (m, 2H), 1.37 – 1.31 (m, 1H), 1.30 (s, 9H), 1.26 – 1.09 (m, 3H), 0.92 – 0.84 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl₃) \(\delta\) 41.86, 37.43, 37.35, 33.20, 31.10, 26.72, 26.36, 25.93. IR (film) \(\nu_{max}\) 2922, 2852, 1449, 1363, 1165 cm\(^{-1}\). HRMS (EI-TOF) m/z calcld. for C₁₂H₂₄S (M\(^+\)) 200.1593, found 200.1597.

![Chemical structure](attachment:image.png)

methyl (2S)-2-(((benzyloxy)carbonyl)amino)-6-((tert-butoxycarbonyl)amino)-9-cyanononanoate (34)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 1,10-phenanthroline (9.0 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.2 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), di-tert-butyl dicarbonate (22 mg, 0.10 mmol, 0.20 equiv.), methyl \(\text{N}^2\)-((benzyloxy)carbonyl)-\(\text{N}^6\)-(tert-butoxycarbonyl)-\(\text{L}\)-lysinate (592 mg, 1.50 mmol, 3.0 equiv.), 4-bromobutyronitrile (74 mg, 50.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 33 h. Purification by column chromatography (silica gel, 2:1 hexane:EtOAc)
yielded the pure product as a clear oil (95 mg, 0.205 mmol, 41% yield, 1:1 d.r.). $^1$H NMR (500 MHz, C$_6$D$_6$) δ 7.26 – 7.21 (m, 2H), 7.14 – 7.04 (m, 3H), 5.35 (d, J = 8.1 Hz, 0.42H), 5.28 (d, J = 8.1 Hz, 0.49H), 5.16 – 5.04 (m, 2H), 4.51 – 4.40 (m, 1H), 3.85 (d, J = 9.2 Hz, 0.37H), 3.66 (d, J = 9.5 Hz, 0.43H), 3.38 – 3.26 (m, 4H), 1.69 – 1.54 (m, 1H), 1.49 – 1.39 (m, 11H), 1.38 – 1.28 (m, 1H), 1.21 – 0.72 (m, 8H). $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 172.93, 172.80, 156.43, 156.27, 155.98, 155.82, 137.18, 137.11, 128.68, 128.55, 128.46, 128.35, 119.32, 119.31, 78.79, 67.14, 67.04, 54.01, 53.94, 51.84, 51.77, 49.22, 48.97, 35.11, 34.79, 34.72, 34.36, 32.25, 28.53, 28.51, 22.14, 22.11, 21.84, 21.75, 16.43, 16.41. IR (film) $\nu_{\text{max}}$ 3342, 2947, 1696, 1521, 1455, 1366, 1248, 1214, 1169, 1054, 1029, 741, 699 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{24}$H$_{35}$N$_3$NaO$_6$ ([M+Na]$^+$) 484.2418, found 484.2419.

methyl (tert-butoxycarbonyl)-L-methionyl-D-phenylalaninate (S1)

To a 250 mL round bottom flask containing (tert-butoxycarbonyl)-L-methionine (5.0 g, 20 mmol, 1 equiv.) and methyl D-phenylalaninate hydrochloride (4.3 g, 20 mmol, 1 equiv.) in 60 mL CH$_2$Cl$_2$ at 0 ºC was added Et$_3$N (2.8 mL, 20 mmol, 1 equiv.). After stirring at 0 ºC for 5 min, N,N’-dicyclohexylcarbodiimide (4.1 g, 20 mmol, 1 equiv.) was added. The reaction mixture was warmed to room temperature and stirred for 12 hours. Next, 100 mL deionized water was added to the same flask. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 70 mL), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography.
(silica gel, 4:1 hexane:EtOAc). The title compound was isolated as a white solid (4.8 g, 11.7 mmol, 59% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.14 (d, \(J = 7.0\) Hz, 2H), 6.99 (d, \(J = 7.5\) Hz, 1H), 5.44 (d, \(J = 7.9\) Hz, 1H), 4.88 (q, \(J = 7.4\) Hz, 1H), 4.39 – 4.24 (m, 1H), 3.71 (s, 3H), 3.17 (dd, \(J = 13.9, 5.5\) Hz, 1H), 3.04 (dd, \(J = 13.8, 7.2\) Hz, 1H), 2.48 – 2.29 (m, 2H), 2.05 (s, 3H), 2.03 – 1.97 (m, 1H), 1.87 – 1.77 (m, 1H), 1.43 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.80, 171.34, 155.52, 135.81, 129.15, 128.57, 127.09, 79.92, 53.30, 53.13, 52.34, 37.84, 31.79, 29.84, 28.27, 15.17. IR (film) \(\nu_{\text{max}}\) 3306, 2977, 2920, 1739, 1656, 1507, 1437, 1366, 1282, 1246, 1215, 1164, 1048, 1024, 744, 700 cm\(^{-1}\). HRMS (ESI-TOF) m/z calcd. for C\(_{20}\)H\(_{30}\)N\(_2\)NaO\(_5\) ([M+Na]\(^{+}\)) 433.1768, found 433.1764.

\[
\begin{align*}
\text{methyl} &\quad N-(\text{tert-butoxycarbonyl})-S-(4-cyanobutyl)-L-homocysteinyl-D-phenylalaninate (major isomer) (35) \\
\text{Prepared following the general procedure outlined above (with fan) using} \\
\text{Ir[dF(CF}_3\text{)ppy}_2 (dtbbpy)PF}_6 (5.6\ \text{mg, 5.0 \mu mol, 0.01 equiv.}), \text{Ni(BF}_4)_2\cdot6\text{H}_2\text{O (17.0 mg,}}
\end{align*}
\]
50.0 µmol, 0.10 equiv.), 4,4’-di(tert-butyl)-2,2’-bipyridine (13.4 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), methyl (tert-butoxycarbonyl)-L-methionyl-D-phenylalaninate (411 mg, 1.00 mmol, 2.0 equiv.), 4-bromobutyronitrile (74 mg, 50.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 23 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilled and placed 4 cm away from 34W blue LEDs with a fan. Continue stirring for another 21 h. Purification by column chromatography (silica gel, 2:1 to 1:1 hexane:EtOAc) yielded the product as a clear oil (124 mg, 0.26 mmol, 52% yield, mixture of regioisomers, rr = 5:1). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.31 – 7.20 (m, 3H), 7.15 – 7.08 (m, 2H), 6.85 (d, J = 6.9 Hz, 0.12H, minor isomer), 6.65 (d, J = 6.7 Hz, 0.71H, major isomer), 5.40 (d, J = 7.7 Hz, 0.13H, minor isomer), 5.14 (d, J = 6.9 Hz, 0.72H, major isomer), 4.85 (q, J = 6.6 Hz, 1H), 4.31 – 4.19 (m, 1H), 3.72 (s, 2.58H, major isomer), 3.70 (s, 0.46H, minor isomer), 3.16 (dd, J = 14.0, 5.5 Hz, 1H), 3.06 (dd, J = 13.8, 6.8 Hz, 1H), 2.64 – 2.39 (m, 4H), 2.36 (t, J = 6.8 Hz, 2H), 2.06 – 1.67 (m, 6H), 1.42 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl₃) δ 171.78, 171.38, 171.21, 155.54, 135.86, 135.80, 129.20, 128.66, 127.18, 119.49, 119.22, 80.16, 53.32, 53.18, 52.44, 37.85, 37.76, 32.24, 30.78, 30.32, 28.32, 28.11, 27.85, 27.72, 24.95, 24.27, 16.80, 15.97. IR (film) \(v_{\text{max}}\) 3317, 2936, 1741, 1710, 1661, 1510, 1455, 1441, 1366, 1247, 1217, 1167, 1047, 1024, 756, 702 cm\(^{-1}\). HRMS (ESI-TOF) m/z calcd. for C₂₃H₃₅N₃NaO₅S ([M+Na]⁺) 500.2190, found 500.2191.
methyl (tert-butoxycarbonyl)-L-methionyl-L-phenylalanyl-L-alaninate (S2)

To a 250 mL round bottom flask containing (tert-butoxycarbonyl)-L-methionine (2.8 g, 11.2 mmol, 1 equiv.) and methyl D-phenylalanyl-L-alaninate (2.8 g, 11.2 mmol, 1 equiv., prepared based on a published procedure) in 50 mL DMF at 0 ºC was added N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.6 g, 13.4 mmol, 1.2 equiv.), 1-hydroxybenzotriazole hydrate (2.1 g, 13.4 mmol, 1.2 equiv.) and Et₃N (3.4 mL, 24.6 mmol, 1 equiv.). After stirring at 0 ºC for 1 hour, the reaction mixture was warmed to room temperature and stirred for 24 hours. Next, the solution was extracted with ethyl acetate (150 mL) and washed with deionized water (4 × 50 mL). The organic layer was collected and the aqueous layer was combined and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by column chromatography (silica gel, 1:1 hexane:EtOAc). The title compound was isolated as a white solid (1.7 g, 3.53 mmol, 32% yield).

1H NMR (500 MHz, CDCl₃) δ 7.31 – 7.25 (m, 2H), 7.24 – 7.18 (m, 3H), 7.09 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 6.1 Hz, 1H), 5.50 (d, J = 7.1 Hz, 1H), 4.80 (q, J = 6.9 Hz, 1H), 4.51 (p, J = 7.2 Hz, 1H), 4.41 – 4.23 (m, 1H), 3.72 (s, 3H), 3.09 (d, J = 6.6 Hz, 2H), 2.54 – 2.46 (m, 2H), 2.07 (s, 3H), 2.05 – 1.97 (m, 1H), 1.94 – 1.84 (m, 1H), 1.43 (s, 9H), 1.35 (d, J = 7.2 Hz, 3H).

13C NMR (125 MHz, CDCl₃) δ 172.81, 171.59, 170.35, 155.63, 136.34, 129.42, 128.59, 127.00, 80.18, 54.16, 53.87, 52.46, 48.18, 38.33, 31.76, 30.14, 28.36, 18.09, 15.32. IR (film) νmax 3280, 2979, 2921, 1748, 1694, 1641, 1548, 1520, 1360, 1234, 1161, 1052, 740, 699 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₂₃H₃₃N₃NaO₆ ([M+Na]⁺)
methyl \(N\text{-}(\text{tert}-\text{butoxycarbonyl})\text{-}S\text{-}(4\text{-cyanobutyl})\text{-}L\text{-}\text{homocysteiny}l\text{-}L\text{-}\text{phenylalanyl}\text{-}L\text{-}\text{alaninate\ (36)} \) and methyl \((2S)\text{-}2\text{-}((\text{tert}-\text{butoxycarbonyl})\text{amino})\text{-}7\text{-cyano}4\text{-}(\text{methylthio})\text{heptanoyl})\text{-}D\text{-}\text{phenylalanyl}\text{-}L\text{-}\text{alaninate (minor isomer)}\)

Prepared following the general procedure outlined above (with fan cooling) using \(\text{Ir}\[dF(\text{CF}_3)\text{ppy}]_2\text{-}(\text{dtbbpy})\text{PF}_6\) (5.6 mg, 5.0 \(\mu\text{mol}, 0.01\) equiv.), \(\text{Ni}(\text{BF}_4)_2\cdot6\text{H}_2\text{O}\) (17.0 mg, 50.0 \(\mu\text{mol}, 0.10\) equiv.), \(4,4'\text{-}\text{di(tert}-\text{butyl)}\text{-}2,2'\text{-bipyridine}\) (13.4 mg, 50.0 \(\mu\text{mol}, 0.10\) equiv.), \(\text{MeCN}\) (2.0 mL), quinuclidine (11.1 mg, 100 \(\mu\text{mol}, 0.20\) equiv.), methyl \((\text{tert}-\text{butoxycarbonyl})\text{-}L\text{-}\text{methionyl}\text{-}D\text{-}\text{phenylalanyl}\text{-}L\text{-}\text{alaninate\ (482 mg, 1.00 mmol, 2.0 equiv.)\), 4-bromobutyronitrile\ (74 mg, 50.0 \(\mu\text{L}, 0.50\) mmol, 1.0 equiv.), \(\text{K}_2\text{CO}_3\) (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). Reaction time: 40 h. Purification by column chromatography (silica gel, 1:1 to 1:2 hexane:EtOAc) yielded the product as a yellow oil (163 mg, 0.297 mmol, 59% yield, mixture of regioisomers, \(rr = 8:1\)). \(^1\text{H NMR\ (500 MHz, CDCl}_3\) \(\delta\) 7.32 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.80 – 6.70 (m, 1H), 6.50 – 6.35 (m, 1H), 5.46 – 5.05 (m, 1H), 4.76 (q, \(J = 7.2\) Hz, 0.09H, minor isomer), 4.66 (q, \(J = 6.9\) Hz, minor isomer).
0.88H, major isomer), 4.47 (p, J = 7.2 Hz, 1H), 4.41 – 4.15 (m, 1H), 3.71 (s, 2.61H, major isomer), 3.70 (s, 0.33H, minor isomer), 3.14 – 3.03 (m, 2H), 2.71 – 2.41 (m, 4H), 2.38 (t, J = 6.7 Hz, 2H), 2.08 – 1.67 (m, 6H), 1.41 (s, 9H), 1.33 (d, J = 7.2 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 172.79, 171.87, 171.45, 170.24, 155.64, 155.57, 136.36, 136.31, 129.40, 129.15, 128.65, 128.54, 127.07, 119.57, 119.30, 80.33, 54.18, 53.84, 52.50, 48.23, 38.20, 32.24, 32.19, 30.84, 30.37, 30.17, 29.74, 28.34, 28.14, 28.00, 27.91, 24.97, 24.29, 22.73, 18.08, 16.83, 16.01. IR (film) νmax 3295, 2932, 1744, 1646, 1526, 1454, 1367, 1246, 1212, 1163, 1052, 700 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C27H40N4NaO6S ([M+Na]+) 571.2561, found 576.2560.

(±)-tert-butyl 2-(3-chloropropyl)pyrrolidine-1-carboxylate (37)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF3)ppy]2 (dtbbpy)PF6 (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF4)2•6H2O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 1-bromo-3-chloropropane (79 mg, 0.50 mmol, 1.0 equiv.), K2CO3 (105 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 3% to 5% Ether in Toluene) yielded the pure product as a clear oil (81 mg, 0.33 mmol, 64% yield). 1H NMR (500 MHz, CDCl3) δ 3.88 – 3.64 (m, 1H), 3.55 (m, 2H), 3.36 (m, 2H), 2.02 – 1.70 (m, 6H), 1.63 (m, 1H), 1.46 (m, 10H). 13C NMR (125 MHz, CDCl3) δ 154.66, 153.75, 79.27,
57.04, 56.62, 46.50, 46.07, 45.01, 32.18, 31.79, 31.49, 30.87, 30.40, 30.11, 29.97, 29.69, 29.56, 27.78, 26.81, 23.77, 23.05.


(±)-*tert*-butyl 2-(2-(1,3-dioxolan-2-yl)ethyl)pyrrolidine-1-carboxylate (38)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), 2-(2-bromoethyl)-1,3-dioxolane (90.5 mg, 58.7 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 3:1 hexane:EtOAc) yielded the pure product as a clear oil (85 mg, 0.31 mmol, 63% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.83 – 4.78 (m, 1H), 3.95 – 3.65 (m, 5H), 3.40 – 3.20 (m, 2H), 1.94 – 1.67 (m, 4H), 1.65 – 1.52 (m, 3H), 1.45 – 1.36 (m, 10H). ¹³C NMR (125 MHz, CDCl₃) δ 154.67, 104.49, 104.40, 79.11, 78.83, 64.91, 64.86, 57.03, 46.55, 46.12, 30.79, 29.94, 29.06, 28.56, 23.82, 23.09. IR (film) ν max 2971, 2878, 1690, 1394, 1366, 1167 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₄H₂₅NNaO₄ ([M+Na]⁺) 294.1676, found 294.1676.
(±)-*tert*-butyl 2-neopentylpyrrolidine-1-carboxylate (39)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (11.0 mg, 50.0 µmol, 0.10 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), 1-bromo-2,2-dimethylpropane (75.5 mg, 63.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (54 mg, 0.23 mmol, 46% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.90 – 3.74 (m, 1H), 3.38 – 3.22 (m, 2H), 2.00 – 1.89 (m, 1H), 1.89 – 1.73 (m, 2H), 1.73 – 1.65 (m, 1H), 1.65 – 1.59 (m, 1H), 1.52 – 1.41 (s, 9H), 1.30 – 1.17 (m, 1H), 1.03 – 0.90 (s, 9H) ¹³C NMR (125 MHz, CDCl₃) δ 154.51, 79.16, 54.60, 48.64, 45.91, 32.92, 30.37, 28.87, 23.43. IR (film) νₘₐₓ 2957, 2872, 1694, 1477, 1392, 1364, 1247, 1171, 1114, 1096 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₄H₂₇NNaO₂ ([M+Na]⁺) 264.1934, found 264.1932.

(±)-*tert*-butyl 2-ethylpyrrolidine-1-carboxylate (40)

Prepared following the general procedure outlined above (with fan cooling) using
Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-dimethoxy-2,2′-bipyridine (11.0 mg, 50.0 µmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), bromoethane (54.0 mg, 36.7 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.4 mL). Purification by column chromatography (silica gel, gradient 3% to 10% ether in hexanes) yielded the pure product as a clear oil (55 mg, 0.28 mmol, 55% yield).

¹H NMR (500 MHz, CDCl₃) δ 3.95 – 3.56 (m, 1H), 3.55 – 3.12 (m, 2H), 2.15 – 1.74 (m, 4H), 1.74 – 1.9 (m, 2H), 1.59 – 1.40 (s, 9H), 0.80 (t, J = 7.7 Hz, 3H) ¹³C NMR (125 MHz, CDCl₃) δ 154.77, 78.81, 58.67, 46.61, 46.16, 30.21, 29.32, 28.57, 27.50, 26.77, 23.82, 23.13, 10.55. IR (film) νmax 2968, 2932, 2876, 1694, 1478, 1456, 1392, 1364, 1255, 1171, 1139, 1107 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₁H₂₁NNaO₂ ([M+Na]⁺) 222.1465, found 222.1459.

(±)-tert-butyl 2-isopropylpyrrolidine-1-carboxylate (41)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (6.8 mg, 20.0 µmol, 0.04 equiv.), 4,4’-dimethoxy-2,2′-bipyridine (4.32 mg, 20.0 µmol, 0.04 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 2-bromopropane (61.5 mg, 47.0 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (95 eq,
0.86 mL). Purification by column chromatography (silica gel, gradient 5% to 20% ether in hexanes) yielded the pure product as a clear oil (56 mg, 0.26 mmol, 53% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.69 (m, 1H), 3.57 – 3.46 (m, 1H), 3.23 (m, 1H), 2.12 (m, 1H), 1.91 – 1.65 (m, 4H), 1.47 (s, 9H), 0.88 (d, $J$ = 6.9 Hz, 1H), 0.81 (d, $J$ = 6.8 Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.08, 78.86, 62.35, 46.90, 30.50, 26.19, 23.95, 19.57, 16.91. IR (film) $\nu_{\text{max}}$ 2965, 2874, 1689, 1455, 1383, 1164, 1102 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_8$H$_{16}$NO$_2$ ([M–tBu+H]$^+$) 157.1103, found 157.1106.

![Image](image_url)

(±)-1-(2-methylpyrrolidin-1-yl)ethan-1-one (42)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), NiBr$_2$•diglyme (3.25 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), Acetone (4.0 mL), methyl tosylate (93 mg, 0.50 mmol, 1.00 equiv.), 1-(pyrrolidin-1-yl)ethan-1-one (113.0 mg, 1.00 mmol, 2.0 equiv.), CsBr (128 mg, 0.60 mmol, 1.2 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (silica gel, gradient 5% to 30% ether in pentanes) yielded the pure product as a clear oil (39 mg, 0.31 mmol, 61% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.18, 3.95 (m, 1H), 3.95, 3.52 – 3.30 (m, 2H), 2.08, 2.01 (s, 3H) 2.10 – 1.82 (m, 3H), 1.71 – 1.53 (m, 1H), 1.18 (m, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.05, 53.94, 52.62, 47.65, 45.48, 33.19, 32.01, 23.83, 22.93, 22.07, 21.96, 20.97, 19.51. IR (film) $\nu_{\text{max}}$ 2968, 2876, 1615, 1455, 1383, 1164, 1102 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_7$H$_{13}$NO ([M+H]$^+$) 127.0997, found
Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), NiBr$_2$·diglyme (3.25 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), Acetonitrile (4.0 mL), methyl tosylate (93 mg, 0.50 mmol, 1.00 equiv.), 1-(pyrrolidin-1-yl)ethan-1-one (113.0 mg, 1.00 mmol, 2.0 equiv.), CsBr (128 mg, 0.60 mmol, 1.2 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.). This yielded an inseperable mixture of product and starting material, and 41% yield (average of three reactions: 42% yield, 39% yield, and 41% yield) was calculated from a calibrated GC assay after the addition of a standard (biphenyl). (average of three reactions: 42% yield, 39% yield, and 41% yield) (Authentic product was synthesized following the procedure from C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, Nature. **536**, 322–325 (2016)).

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$·6H$_2$O (3.4 mg,
10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), 4-bromobutanenitrile (74.0 mg, 49.7 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 10% to 30% EtOAc in hexanes) yielded the pure product as a clear oil (98 mg, 0.41 mmol, 82% yield). 

\[ \text{[M+Na]} \] 

HRMS (ESI-TOF) m/z calcd. for C₁₃H₂₂N₂NaO₂ 

\( \text{C₁₃H₂₂N₂NaO₂} \) 261.1574, found 261.1573.

(±)-*tert*-butyl 2-(2-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (45)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 2-(2-bromoethyl)pyridine hydrobromide (133 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (105 mg, 0.75 mmol, 1.5 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 10% to 30%
EtOAc in hexanes) yielded the pure product as a clear oil (62 mg, 0.22 mmol, 43% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.44 (s, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.19 – 6.96 (m, 2H), 3.79 (m, 1H), 3.45 – 3.12 (m, 2H), 2.84 – 2.56 (m, 2H), 2.19 – 1.96 (m, 1H), 1.94 – 1.78 (m, 2H), 1.71 (m, 3H), 1.37 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.77, 154.68, 149.25, 136.38, 122.60, 121.01, 79.07, 56.90, 46.10, 35.37, 34.83, 30.65, 28.56, 23.81. IR (film) $\nu_{\text{max}}$ 2970, 2873, 1688, 1392, 1363, 1168, 1119, 1103 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{16}$H$_{25}$N$_2$O$_2$ ([M+H]$^+$) 276.1838, found 276.1833.

(±)-t-Butyl 2-(4-ethoxy-4-oxobutyl)pyrrolidine-1-carboxylate (46)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$•6H$_2$O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), t-Butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), ethyl 4-bromobutanoate (97.5 mg, 71.5 µL, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (81 mg, 0.28 mmol, 58% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.20 – 4.08 (q, $J = 7.0$ Hz, 2H), 3.82 – 3.70 (m, 1H), 3.44 – 3.35 (m, 1H), 3.35 – 3.26 (m, 1H), 2.42 – 2.24 (m, 2H), 2.00 – 1.71 (m, 4H), 1.71 – 1.54 (m, 4H), 1.54 – 1.42 (s, 9H), 1.31 – 1.18 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.63, 173.44, 154.61, 79.07, 78.84, 60.21, 56.88, 46.49, 46.00, 34.24, 33.56,

(±)-tert-butyl 2-(3-((tert-butyldimethylsilyl)oxy)propyl)pyrrolidine-1-carboxylate (47)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), (3-bromopropoxy)(tert-butyl)dimethylsilane (89 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (105 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 10% to 30% EtOAc in hexanes) yielded the pure product as a clear oil (116 mg, 0.34 mmol, 68% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.81 – 3.64 (m, 1H), 3.64 – 3.48 (m, 2H), 3.43 – 3.18 (m, 2H), 1.96 – 1.55 (m, 5H), 1.42 (m, 11H), 1.36 – 1.26 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 154.62, 78.73, 63.24, 57.15, 46.02, 31.21, 29.76, 28.52, 25.94, 23.04, 18.31, -5.29. IR (film) νmax 2954, 2929, 2858, 1693, 1389, 1364, 1251, 1168, 1096, cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₈H₃₈NΟ₃Si ([M-+H]⁺) 343.2543, found 343.2541.
(±)-
tert-
butyl 2-(3-phenoxypropyl)pyrrolidine-1-carboxylate (48)

Prepared following the general procedure outlined above (with fan cooling) using
Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), (3-bromopropoxy)benzene (107.5 mg, 78.8 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (110 mg, 0.36 mmol, 72% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.19 (m, 2H), 7.00 – 6.83 (m, 3H), 4.05 – 3.89 (m, 2H), 3.89 – 3.69 (m, 1H), 3.48 – 3.35 (m, 1H), 3.35 – 3.21 (m, 1H), 2.10 – 1.72 (m, 6H), 1.72 – 1.56 (m, 2H), 1.55 – 1.39 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 159.10, 154.84, 129.55, 120.66, 114.58, 79.16, 67.85, 57.63, 57.20, 46.47, 45.94, 31.15, 30.60, 28.88, 28.71, 26.37. IR (film) νmax 2969, 2872, 1689, 1600, 1497, 1391, 1365, 1244, 1169, 1107 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₈H₂₇NNaO₃ ([M+Na]⁺) 328.1883, found 328.1884.

(±)-
tert-
butyl 2-(3-(diethoxyphosphoryl)propyl)pyrrolidine-1-carboxylate (49)
Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 µmol, 0.10 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 µL, 1.00 mmol, 2.0 equiv.), diethyl (3-bromopropyl)phosphonate (129.5 mg, 96.1 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 50% to 100% EtOAc in hexanes) yielded the pure product as a clear oil (99 mg, 0.28 mmol, 56% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.45 – 3.85 (m, 4H), 3.84 – 3.54 (m, 1H), 3.54 – 3.04 (m, 2H), 1.96 – 1.67 (m, 6H), 1.67 – 1.51 (m, 4H), 1.49 – 1.41 (s, 9H), 1.34 – 1.25 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 153.99, 78.48, 78.21, 60.82, 56.21, 45.93, 45.47, 35.43, 34.44, 30.31, 29.32, 27.97, 25.81, 24.52, 23.27, 22.50, 18.98, 15.98. IR (film) νmax 2974, 2934, 1689, 1392, 1365, 1241, 1167, 1055, 1028 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₆H₃₂NNaO₅P ([M+Na⁺]⁺) 372.1910, found 372.1909.

(±)-tert-butyl 2-cyclohexylpyrrolidine-1-carboxylate (50)

Prepared following the general procedure outlined above (with fan cooling) using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-
carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclohexane (82 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (60 eq, 0.54 mL). Purification by column chromatography (silica gel, gradient 2% to 5% EtOAc in hexanes) yielded the pure product as a clear oil (66 mg, 0.26 mmol, 52% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.66 (m, 1H), 3.52 – 3.37 (m, 1H), 3.27 – 3.14 (m, 1H), 1.84 – 1.53 (m, 10H), 1.46 (s, 9H), 1.27 – 0.85 (m, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 155.07, 78.80, 61.82, 46.66, 41.15, 30.14, 28.55, 27.95, 26.64, 26.55, 26.33. IR (film) ν max 2972, 2924, 2852, 1689, 1388, 1363, 1376, 1164, 1105 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₁H₂₀NO₂ ([M–tBu+H⁺]⁺) 197.1416, found 197.1412.

(±)-tert-butyl 2-(tetrahydro-2H-pyran-4-yl)pyrrolidine-1-carboxylate (51)

Prepared following the general procedure outlined above using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), tert-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 4-bromotetrahydro-2H-pyran (83 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 5% to 15% EtOAc in hexanes) yielded the pure product as a clear oil (89 mg, 0.35 mmol, 70% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.08 – 3.94 (m, 2H), 3.74 (s, 1H), 3.48 (s, 1H), 3.35 (m, 2H), 3.23 (m, 1H), 1.89 – 1.73 (m, 5H), 1.47 (s, 12H), 1.42 – 1.29 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ

![](image)

(±)-**tert**-butyl 2-cyclopentylpyrrolidine-1-carboxylate (52)

Prepared following the general procedure outlined above using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), **tert**-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclopentane (62 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 2% to 5% EtOAc in hexanes) yielded the pure product as a clear oil (66 mg, 0.26 mmol, 52% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.88 – 3.77 (m, 1H), 3.46 (m, 1H), 3.33 – 3.16 (m, 1H), 2.05 (m, 1H), 1.92 – 1.75 (m, 3H), 1.73 – 1.57 (m, 5H), 1.56 – 1.48 (m, 2H), 1.46 (s, 9H), 1.42 – 1.33 (m, 1H), 1.23 – 1.12 (m, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 155.18, 78.84, 60.70, 46.26, 44.34, 30.00, 28.81, 28.54, 25.33, 25.06. IR (film) νmax 2953, 2869, 1689, 1385, 1363, 1167, 1103 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₄H₂₅NNaO₂ ([M+Na]⁺) 239.1885, found 239.1881.
(±)-*tert*-butyl 2-(oxetan-3-yl)pyrrolidine-1-carboxylate (53)

Prepared following the general procedure outlined above using Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂·6H₂O (3.4 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 3-bromooxetane (68.5 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (60 eq, 0.54 mL). Purification by column chromatography (silica gel, gradient 5% to 15% EtOAc in hexanes) yielded the pure product as a clear oil (81 mg, 0.36 mmol, 71% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.81 (m, 1H), 4.68 (dd, J = 8.1, 6.2 Hz, 1H), 4.64 (dd, J = 8.4, 6.1 Hz, 1H), 4.50 (t, J = 6.7 Hz, 1H), 4.14 (tt, J = 7.3, 3.7 Hz, 1H), 3.56 – 3.34 (m, 1H), 3.36 – 3.13 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.59 (m, 1H), 1.47 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 154.78, 79.99, 76.23, 73.87, 58.80, 46.57, 40.12, 28.52, 22.94. IR (film) ν max 2971, 2874, 1688, 1386, 1342, 1250, 1164, 1104, cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₁₂H₂₁NO₃Na ([M+Na]⁺) 227.1521, found 227.1518.

(±)-*tert*-butyl 2-(3,3-difluorocyclobutyl)pyrrolidine-1-carboxylate (54)

Prepared following the general procedure outlined above using Ir[dF(CF₃)ppy]₂
(±)-**tert**-butyl 2-cyclopropylpyrrolidine-1-carboxylate (55)

Prepared following the general procedure outlined above using Ir[dF(CF₃)ppy]₂ (dtbbpy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), NiBr₂•diglyme (3.5 mg, 10.0 µmol, 0.02 equiv.), 4,4’-dimethoxy-2,2’-bipyridine (2.2 mg, 10.0 µmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 µmol, 0.05 equiv.), **tert**-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 3-bromo-1,1-difluorocyclobutane (85 mg, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 5% to 10% ether in hexanes) yielded the pure product as a clear oil (85.5 mg, 0.33 mmol, 65% yield). ¹H NMR (500 MHz, CDCl₃) δ 3.99 – 3.83 (m, 1H), 3.42 (s, 1H), 3.36 – 3.25 (m, 2H), 2.70 – 2.45 (m, 3H), 2.36 – 2.14 (m, 2H), 1.98 – 1.77 (m, 4H), 1.62 – 1.54 (m, 1H), 1.46 (d, J = 1.9 Hz, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 155.21, 119.61 (dd, J = 286.0, 270.1 Hz), 79.58, 60.43, 46.74, 38.83 (dd, J = 23.7, 21.6 Hz), 38.02 (dd, J = 23.7, 21.6 Hz), 28.45, 28.19, 25.36. ¹⁹F NMR (282 MHz, CDCl₃) δ -81.48 – -82.87 (m, 1F), -98.68 – -99.90 (m, 0.78F), -102.16 (dp, J = 191.9, 17.1 Hz, 0.13F). IR (film) νmax 2973, 2882, 1689, 1384, 1365, 1293, 1163, 1105 cm⁻¹. HRMS (ESI-TOF) m/z calcd. for C₉H₁₄NO₂F₂ ([M–tBu+H]⁺) 205.0914, found 205.0913.
(171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclopropane (61 mg, 0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (70 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.67 mL). Purification by column chromatography (silica gel, gradient 5% to 20% ether in hexanes) yielded the pure product as a clear oil (48 mg, 0.23 mmol, 43% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.40 – 3.26 (m, 3H), 2.00 – 1.67 (m, 4H), 1.46 (s, 9H), 0.86 (m, 1H), 0.53 (m, 1H), 0.47 (m, 1H), 0.35 (m, 1H), 0.12 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.24, 79.09, 60.90, 46.67, 31.48, 28.72, 23.55, 15.98, 4.50, 1.80.


(-)- tert-butyl Methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (S3)

To a 250 mL round bottom flask containing Fluoxetine hydrochloride (6.9 g, 20 mmol, 1.0 equiv.) in 100 mL CH$_2$Cl$_2$ at 0 ºC was added Et$_3$N (5.9 mL, 42 mmol, 2.1 equiv.). The solution was stirred for 5 min at 0 ºC, then a solution of Boc$_2$O (4.8 g, 22 mmol, 1.1 equiv.) in 20 mL CH$_2$Cl$_2$ was added in one portion. The reaction mixture was warmed to room temperature and stirred for 2 hours. Next, 100 mL deionized water was added to quench the reaction. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 70 mL), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude
product was purified by column chromatography (silica gel, 10:1 hexane:EtOAc). The title compound was isolated as a viscous clear oil (8.0 g, 19.5 mmol, 98% yield). $^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 7.49 (d, $J$ = 8.6 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.00 (d, $J$ = 8.5 Hz, 2H), 5.33 (dd, $J$ = 8.7, 4.1 Hz, 1H), 3.55 – 3.23 (m, 2H), 2.81 (s, 3H), 2.19 – 1.99 (m, 2H), 1.45 – 1.23 (m, 9H). $^{13}$C NMR (125 MHz, CD$_3$CN) $\delta$ 161.70, 151.29, 142.03, 129.67, 128.83, 127.67 (q, $J$ = 3.7 Hz), 126.98, 125.61 (q, $J$ = 268.4 Hz), 122.97 (q, $J$ = 32.4 Hz), 117.09, 79.60, 78.71, 78.19, 46.22, 45.99, 37.50, 37.12, 34.70, 34.43, 28.51. $^{19}$F NMR (282 MHz, CD$_3$CN) $\delta$ –62.0 (s, 3F). IR (film) $\nu_{max}$ 2977, 2931, 1691, 1614, 1517, 1454, 1393, 1366, 1323, 1246, 1154, 1109, 1067, 1049, 1009, 835, 762, 701 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{22}$H$_{26}$F$_3$NaO ([M+Na]$^+$) 432.1757, found 432.175

(±)-tert-butyl (2-cyclohexylethyl)(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (56)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF$_4$)$_2$$\cdot$6H$_2$O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4'-di(tert-butyl)-2,2'-bipyridine (13.4 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), N-Boc fluoxetine (614 mg, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 µL,
0.50 mmol, 1.0 equiv.), K$_2$CO$_3$ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 23 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs. Continue stirring for another 27 h. Purification by column chromatography (silica gel, 25:1 hexane:EtOAc) yielded the product as a clear oil (131 mg, 0.26 mmol, 52% yield, rr >20:1). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, $J$ = 8.5 Hz, 2H), 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 6.90 (d, $J$ = 8.5 Hz, 2H), 5.22 – 5.12 (m, 1H), 3.50 – 3.06 (m, 4H), 2.34 – 2.06 (m, 2H), 1.70 – 1.60 (m, 5H), 1.50 – 1.35 (m, 11H), 1.24 – 1.09 (m, 4H), 0.93 – 0.83 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.54, 155.63, 140.96, 128.94, 127.97, 126.85 (q, $J$ = 3.5 Hz), 125.75, 124.47 (q, $J$ = 269.3 Hz), 123.93 (q, $J$ = 33.7 Hz), 115.79, 79.38, 78.51, 77.85, 45.53, 44.09, 43.82, 38.01, 37.48, 36.27, 35.67, 35.34, 33.36, 33.30, 28.51, 26.64, 26.37, 26.36. $^{19}$F NMR (282 MHz, CDCl$_3$) δ –61.6 (s, 3F). IR (film) $\nu_{\text{max}}$ 2925, 2853, 1691, 1518, 1452, 1417, 1366, 1327, 1250, 1162, 1117, 1069, 835, 756, 701 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{29}$H$_{38}$F$_3$NNaO$_3$ ([M+Na]$^+$) 528.2696, found 528.2692.

(±)-tert-butyl (3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)(4-phenylbutyl)carba-
Prepared following the general procedure outlined above (*without* fan) using \( \text{Ir}[(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6 \) (5.6 mg, 5.0 µmol, 0.01 equiv.), \( \text{Ni(BF}_4)_2 \cdot 6\text{H}_2\text{O} \) (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4’-di(tert-butyl)-2,2’-bipyridine (13.4 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.2 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), di-tert-butyl dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), \( N\)-Boc fluoxetine (1.02 g, 2.50 mmol, 5.0 equiv.), 1-bromo-3-phenylpropane (100 mg, 76 µL, 0.50 mmol, 1.0 equiv.), \( \text{K}_2\text{CO}_3 \) (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 19 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv.) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilled and placed 4 cm away from 34W blue LEDs. Continue stirring for another 21 h. Purification by column chromatography (silica gel, 25:1 hexane:EtOAc) yielded the product as a clear oil (119 mg, 0.225 mmol, 45% yield, \( \text{rr} > 20:1 \)). \(^1\text{H} \) NMR (500 MHz, CD\(_3\)CN) \( \delta \) 7.49 (d, \( J = 8.4 \text{ Hz, } 2\text{H} \)), 7.40 – 7.32 (m, 4H), 7.29 – 7.23 (m, 3H), 7.18 – 7.14 (m, 3H), 6.99 (d, \( J = 8.5 \text{ Hz, } 2\text{H} \)), 5.31 (dd, \( J = 8.3, 4.2 \text{ Hz, } 1\text{H} \)), 3.40 – 3.28 (m, 2H), 3.26 – 3.08 (m, 2H), 2.58 (t, \( J = 7.2 \text{ Hz, } 2\text{H} \)), 2.17 – 2.00 (m, 2H), 1.58 – 1.45 (m, 4H), 1.34 (s, 9H). \(^{13}\text{C} \) NMR (125 MHz, CD\(_3\)CN) \( \delta \) 161.67, 156.16, 143.53, 141.97, 129.67, 129.31, 129.23, 128.82, 127.68 (q, \( J = 3.6 \text{ Hz} \)), 126.96, 126.63, 125.60 (q, \( J = 268.8 \text{ Hz} \)), 122.97 (q, \( J = 32.4 \text{ Hz} \)), 117.09, 79.56, 78.72, 78.46, 47.92, 47.40, 44.50, 38.19, 37.85, 36.01, 29.43, 28.56. \(^{19}\text{F} \) NMR (282 MHz, CD\(_3\)CN) \( \delta \) –61.9 (s, 3F). IR (film) \( \nu_{\text{max}} \) 2931, 1690, 1615, 1517, 1454, 1416, 1366, 1326, 1249, 1160, 1115, 1068, 836, 700 cm\(^{-1}\). HRMS (ESI-TOF) m/z calcd. for \( C_{31}H_{56}F_3NNaO_3 ([\text{M+Na}]^+) \) 550.2540, found 55.2535.
(±)-tert-butyl (oxetan-3-ylmethyl)(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (major isomer) and tert-butyl methyl(1-(oxetan-3-yl)-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (minor isomer) (58)

Prepared following the general procedure outlined above (without fan) using Ir[dF(CF₃)ppy]₂(dtbppy)PF₆ (5.6 mg, 5.0 µmol, 0.01 equiv.), Ni(BF₄)₂•6H₂O (17.0 mg, 50.0 µmol, 0.10 equiv.), 4,4′-dimethoxy-2,2′-bipyridine (10.8 mg, 50.0 µmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 µmol, 0.20 equiv.), N-Boc fluoxetine (614 mg, 1.50 mmol, 3.0 equiv.), 3-bromooxetane (68 mg, 41 µL, 0.50 mmol, 1.0 equiv.), K₂CO₃ (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 21 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 µmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs. Continue stirring for another 23 h. Purification by column chromatography (silica gel, 3:1 hexane:EtOAc) yielded the product as a clear oil (105 mg, 0.225 mmol, 45% yield, mixture of regioisomers, rr = 5:1). ¹H NMR (500 MHz, CD₃CN) δ 7.50 (d, J = 8.7 Hz, 2H), 7.41 – 7.32 (m, 4H), 7.30 – 7.25 (m, 1H), 7.00 (d, J = 8.6 Hz, 2H), 5.42 – 5.28 (m, 1H), 5.00 – 4.56 (m, 2H), 4.38 – 4.17 (m, 2H), 3.56 – 3.13 (m, 4.36H, major isomer + minor isomer), 2.81 (s, 0.48H, minor isomer), 2.19 – 1.99 (m, 2H), 1.36 (s, 9H). ¹³C NMR (125 MHz, CD₃CN) δ
161.65, 156.31, 143.68, 142.76, 142.52, 141.90, 135.22, 134.84, 130.03, 129.69, 128.86, 128.12, 127.69 (q, J = 3.7 Hz), 127.36, 127.28, 126.97, 125.54, 125.44, 125.60 (q, J = 268.4 Hz), 123.00 (q, J = 32.4 Hz), 117.11, 80.04, 79.61, 79.02, 79.00, 78.97, 78.59, 75.79, 75.77, 50.39, 44.97, 40.83, 40.63, 37.81, 35.59, 28.51, 28.44. $^{19}$F NMR (282 MHz, CD$_3$CN) $\delta$ –62.0 (s, 3F). IR (film) $\nu_{\text{max}}$ 2972, 2931, 2874, 1691, 1614, 1517, 1416, 1367, 1326, 1249, 1160, 1112, 1068, 836, 702 cm$^{-1}$. HRMS (ESI-TOF) m/z calcd. for C$_{25}$H$_{30}$F$_3$NNaO$_4$ ([M+Na]$^+$) 488.2019, found 488.2020.
Chapter 5

Decarboxylative Trifluoromethylation

I. Combining Copper and Photoredox Catalysis

The combination of nickel and photoredox catalysis leads to a powerful new platform for cross-couplings. This technology enables the use of carboxylic acids, oxalates, alkyl bromides, and C–H bonds as nucleophilic components in cross couplings, and aryl, vinyl, and alkyl halides as the electrophilic component (Figure 1).\(^1\) In previous chapters, the combination of carboxylic acids with aryl halides, as well as the combination of C–H bonds with alkyl halides were discussed.

![Figure 1. Methods of radical generation and subsequent couplings](image)

However, one goal of the MacMillan group is to utilize transition metals that are not nickel, to enable novel transformations. As first row transition metals are known to readily engage in one electron chemistry, as opposed to the two-electron chemistry that second and third row metals typically engage in,\(^2\) the majority of base metals should

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\(^1\) For a review that covers the majority of this work, see: Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. J. Org. Chem. 2016, 81, 6898.

\(^2\) Chririk, P. J.; Wieghardt, K. Science 2010, 327, 794.
engage organic radicals and allow for novel couplings. Toward this end, the reactivity of copper with photoredox catalysis was investigated. In particular, we wished to incorporate copper catalysis with our established modes of radical generation towards the sp³ trifluoromethylation of organic compounds (Scheme 1). This would immediately allow for a number of new trifluoromethylation reactions, based upon the numerous methods of mild radical generation.

![Scheme 1. Proposed transformation](image)

### II. CF₃: A Valuable, Challenging Motif in Medicinal Chemistry

The trifluoromethyl group is an important motif in medicinal chemistry.³ Incorporation of fluorine atoms onto medicinal frameworks can lead to improvements in pharmokinetics, pharmodynamics, and metabolic stability, amongst others. As a general strategy, incorporation of a fluourine atom at a site of metabolic instability blocks metabolism this site towards degradation, allowing for a longer half-life of the drug. Today, 20–25% of FDA approved drugs contain a fluorine atom.⁴ The incorporation of

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fluorine into these drugs can come in several forms, one of which is the alkyl CF$_3$ group. Several examples are shown in Figure 2. As an example of the importance of the development of new methods to incorporate fluorinated motifs, ~20 years after the development of the first deoxygenating fluorination reagents, there was a noticeable increase in the number of drugs that contained a fluorine atom.$^{3a}$ While new strategies towards fluorination have emerged in recent years that allow for the direct introduction of fluoride atoms onto sp$^3$ hybridized carbons, the incorporation of trifluoromethyl groups has remained a challenging transformation. This has limited the development of pharmaceutical agents that contain this valuable and simple motif.

![Diagram of approved drugs containing trifluoromethyl groups](image)

**Figure 2. Approved drugs containing trifluoromethyl groups**

There are a couple factors to explain why this is, which relate to the reactivity of the trifluoromethyl group. First, the trifluoromethyl group does not readily act as an electrophile, and specialized reagents have needed to facilitate formation of bonds to heteroatoms and enolates.$^5$ Nor does CF$_3$ generically act as a nucleophile, as most anion equivalents undergo elimination to form difluorocarbene.$^6$ One of the few nucleophilic sources of CF$_3$, the Ruppert-Prakash reagent delivers an anion equivalent sufficiently

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nucleophilic to add to activated $\pi$ systems. Given the inherent limitations of the reactivity of this functional group in both nucleophilic and electrophilic settings, metal based coupling is the next logical strategy to consider. However, metal CF$_3$ complexes rarely undergo reductive elimination to form the desired C–CF$_3$ bond. In fact, reductive elimination of trifluoromethyl groups are amongst the most difficult.\textsuperscript{7} Upon ligation of a metal, the trifluoromethyl groups act to stabilize the HOMO of the metal center, leading to a slower reductive elimination. This effect of this HOMO stabilization is dramatic enough that CF$_3$ groups are commonly used to stabilize high valent metal complexes. In a recent publication, trifluoromethyl groups were used to stabilize Ni(IV) species to the extent that column chromatography is possible as a purification technique (Figure 3).\textsuperscript{8} To date, only four metals have been shown to mediate reductive elimination of trifluoromethyl groups. In an elegant example, Buchwald demonstrated that Palladium complexes can catalyze the trifluoromethylation of aryl chlorides at elevated temperatures.


temperatures.\textsuperscript{9} To investigate the mechanism of the coupling, the authors isolated the intermediate trifluoromethyl palladium complex. This complex was stable at room temperature, and only underwent reductive elimination at elevated temperatures. Recently, nickel was shown to be capable of reductive elimination to form aryl CF\textsubscript{3} products.\textsuperscript{10} However, this necessitates the formation of nickel (IV) species in order for reductive elimination to occur, and this process has yet to be demonstrated in a catalytic sense. Similarly, Toste demonstrated that gold (IV) species also furnish the desired bond.\textsuperscript{11}

Furthermore, upon ligation of a CF\textsubscript{3} group, many metals rapidly undergo $\alpha$-elimination to form difluorocarbene complexes\textsuperscript{12} though in some cases this process has been observed to be reversible.\textsuperscript{13} Difluorocarbene complexes can then decompose further via addition of nucleophiles to the difluorocarbene, and in the presence of water this process forms the corresponding carbonyl complex. This process limits the metals that are capable of acting as catalysts for trifluoromethylation.

Copper, however, has been shown to catalyze a whole host of trifluoromethylation.\textsuperscript{14} Notably, copper has been shown to catalyze the

\begin{enumerate}
\item[(12)] Tomashenko, O. A.; Grushin, V. V. \textit{Chem. Rev.} \textbf{2011}, \textit{111}, 4475.
\item[(14)] For an excellent set of reviews, see (a) ref. 11, and (b) Alonso, C.; de Marigorta, E. M.; Rubiales, G. Palacios, \textit{F. Chem. Rev.} \textbf{2015}, \textit{115}, 1847.
\end{enumerate}
trifluoromethylation of aryl boronic acids, as well as aryl iodides. However, the trifluoromethylation of sp³ hybridized centers has remained a challenging problem. This has limited the development of medicinal agents containing this simple motif, and any general solution would immediately have an impact in medicinal chemistry programs. Current methods towards this motif typically involve stoichiometrically forming a Cu–CF₃ complex and displacing primary, benzylic, allylic, or α-carbonyl halides (Scheme 2).¹⁵ This strategy dates back to 1979, and in the ensuing years milder conditions with catalytic copper have been developed. In 2012, Fu disclosed a method where alkyl boronic acids could be converted to trifluoromethyl groups under oxidative conditions with copper catalysis (Scheme 2).¹⁶ With the development of photoredox catalysis, the addition of trifluoromethyl radicals across a double bond has also emerged as an


attractive method, as this allows for both a difunctionalization of an olefin\textsuperscript{17} as well as the simple hydrotrifluoromethylation\textsuperscript{18}. Given the developed strategies towards this motif, we thought a decarboxylative trifluoromethylation would be complimentary method. In this transformation, we would take a carboxylic acid, a one carbon unit in a $+3$ oxidation state, remove it from the molecule, and then install a trifluoromethyl group, another one carbon unit in a $+3$ oxidation state.

### III. Copper as a Radical Trap

Although radical additions to nickel are relatively well known in the literature, examples of radical addition to copper species are considerably sparser. In recent years, Fu and Peters have demonstrated that copper readily traps electrophilic radicals, such as $\alpha$-acyl radicals (Scheme 3).\textsuperscript{19} Additionally, in one of the first examples of photoredox catalysis combined with transition metal catalysis, Sanford demonstrated that aryl copper complexes can trap CF$_3$ radicals, ultimately generating trifluoromethylated arenes.\textsuperscript{20} However, it was not until recently that nucleophilic radicals adding to copper was


conclusively demonstrated. Mechanistically this has been unclear, as it was posited that copper instead engages in atom transfer or direct oxiditation of the radical to the corresponding carbocation instead of an inner-sphere ligation.\(^{21}\) However, in 2012 Buchwald demonstrated that copper catalyzes the oxytrifluoromethylation of alkenes.\(^{22}\)

At the time, Buchwald posited that the copper catalyst generates a trifluoromethyl radical from Togni’s reagent, which adds across the olefin to form an alkyl radical. However, Buchwald was unable to determine how the C–O bond was formed. The two most likely pathways consist of the copper catalyst oxidizing the radical to the carbocation followed by a fast intramolecular trapping by the pendant heteroatom, or radical addition to a copper species followed by reductive elimination. In 2013, Xu demonstrated a hydroxyltrifluoromethylation of dienes, where the source of oxygen was from the

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**Scheme 3. Bond forming reactions of radicals with copper catalysts**

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reduced Togni’s reagent.\textsuperscript{23} When methanol was used as a cosolvent, C–O bond formation was selective for the reduced Togni’s reagent, indicating that a carbocation was not likely in the mechanism. Furthermore, Buchwald later demonstrated that the C–O bond formation could be rendered enantioselective via a chiral copper catalyst, proving that copper is involved in the critical bond formation.\textsuperscript{24} Furthermore, Stahl and Liu have recently disclosed a copper catalyzed benzylic cyanation that proceeds via a benzylic radical addition to copper.\textsuperscript{25} Finally, the asymmetric arylation of a benzylic radical via copper catalysis has been reported.\textsuperscript{26}

\section*{IV. Optimization of the Desired Transformation\textsuperscript{27}}

Initially, we chose to utilize phenyl acetic acid as a model system, as this would form a stabilized benzylic radical and would likely not decompose the photocatalyst. Using commercially available Togni’s II as the trifluoromethyl source as well as the

\begin{center}
\begin{tabular}{c}
\textbf{carboxylic acid} & \textbf{trifluoromethyl source} & \textbf{Scheme 4. Initial results} \\

\end{tabular}
\end{center}


\textsuperscript{27} This work has been conducted in collaboration with Jacob Kautzky and Tao Wang.
oxidant, cesium carbonate as the base, 10 mol% copper (II) chloride, and Ir(dF(CF\(_3\))ppy)\(_2\)(dtbbpy)PF\(_6\) as the photocatalyst in DMA, we were delighted to observe the desired product in 16% yield (Scheme 4). Further optimization revealed that dioxane was a better solvent, TMG provided better efficiencies, 20 mol% CuBr\(_2\) was superior to CuCl\(_2\), and that Togni’s I was our optimal CF\(_3\) source. While these results were exciting, several byproducts were observed, namely benzyl bromide and an ester pseudo dimer of the starting acid (Scheme 5). The benzyl bromide is presumably formed via an atom transfer reaction with the copper source,\(^{28}\) while the ester presumably arose from the reaction of benzyl bromide and the carboxylate. The obvious path to removing these side products would be to remove the source of halide. However, attempts to change copper sources to those that do not contain a halogen proved to be unsuccessful, and at this time it was unclear if the presence of halide anions was necessary by mechanism. Since an

![Scheme 5. Initial optimization of phenylacetic acid](image)

equivalent of base was produced during the reaction, as reduced Togni’s reagent provides an alkoxide, the loading of TMG to catalytic amounts should be feasible. This should

decrease the amount of ester side product by lowering the concentration of carboxylate throughout the course of the reaction. Utilizing 50 mol% of TMG lead to an increased efficiency of 53%, however the amount of the ester byproduct increased as well. At this time we turned our attention towards more challenging carboxylic acids in hopes of finding more general reaction conditions.

As a model substrate for primary carboxylic acids, 3-phenylpropionic acid was utilized. Disappointingly, the yield was significantly diminished compared to our model benzylic system. In addition, large amounts of the analogous ester byproduct were observed. Further optimization revealed that CuCl₂ was a superior source of copper, and that an addition of 25 mol% of tetramethylphenanthroline improved the yield (Scheme 6). At this time, an evaluation of copper sources revealed two important pieces of information. First, Cu(OTFA)₂ could catalyze the desired trifluoromethylation in inferior, but significant yield, indicating that halogen anions are not necessary in the mechanism for the desired transformation. Second, with almost all sources of copper, the undesired ester was observed, indicating that copper mediates the C–O bond formation, and it does
not arise from the direct reaction of an alkyl halide with a carboxylate. To minimize the formation of this side product, solvent was reevaluated. It was found that EtOAc both removed ester formation, as well improved the efficiency of the desired reaction. Further optimization revealed that Barton’s Base was superior to TMG, and that water improved the efficiency of this process to 77%.

Simultaneously, the reactivity of secondary carboxylic acids was also being investigated in the desired transformation. Unlike primary carboxylic acids, ester formation was never observed. However, large amounts of the proto-decarboxylation was formed (Scheme 7). Presumably this arises from protonation of an intermediate alkyl copper species. Also, while unligated copper can give satisfactory yields with primary carboxylic acids, it is essential that the copper is ligated when utilizing secondary carboxylic acids. Indeed, even when a 1:1 ratio of copper to ligand was utilized,

![Scheme 7. Optimization of secondary carboxylic acids](image)

irreproducible results were obtained. We believe that the reaction with unligated copper species is considerably faster than with ligated copper, which necessitates that no unligated copper species are present in solution. To ensure that the copper remained ligated throughout the course of the reaction, the ligand loading was increased to 30
mol%. While inclusion of water with primary carboxylic acids lead to increased yield, with secondary acids the addition of water leads to increased amounts of protonation. To minimize this byproduct, we reevaluated the copper source. Remarkably, when CuCN was utilized as our copper source, clean conversion to the desired product was observed, with only 1-2% of the unwanted protodecarboxylated product formed. With this catalyst system, the addition of water is beneficial, and the inclusion of 30 equivalents of water leading to an increased yield of 71%.

The last class of carboxylic acids we have investigated are α-amino and α-oxy acids. To date, these carboxylic acids have been recalcitrant towards the desired coupling. For example, when Boc-Proline is utilized, the only observed product is the cyclic enamine (Scheme 8). This species results from the intermediate α-amino radical undergoing further oxidation. This phenomenon is well known in copper catalyzed decarboxylations with peroxide oxidants. In these reactions, after iminium formation the resulting iminium ions are trapped by *in-situ* nucleophiles.²⁹ We hypothesized that more electron-withdrawing groups on the heteroatom would help disfavor this process. Indeed, when phthalimide-protected glycine was utilized, in combination with bpy as a ligand, a 28% yield could be achieved. Additionally, this system also can be extended to phenoxy acetic acid, as overoxidation on this substrate should also be challenging.

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V. Scope

To date, the scope is still being investigated (Table 1). However, our initial results have been promising. Benzylic carboxylic acids typically give good of the trifluoromethylated products. Conjugated electron poor (1, 2, and 6, 32 – 70% yield) aromatic rings, electron neutral (4 and 5, 66% and 55% yield, respectively) aromatic rings, as well as electron rich (3, 7, and 8, 60 – 72% yield) aromatic rings did not substantially alter the reactivity of the resulting radical. In the case of the utilization of electron rich aromatic systems, no trifluoromethylation of the aromatic ring was observed. This potential byproduct would indicate that trifluoromethyl radical is produced during the reaction.

A broad variety of primary acids are afford the desired products (9 to 15, 38 – 84% yield). Again, acids containing functionalities that typically react with trifluoromethyl radicals, such as olefins provided the desired trifluoromethyl product in good yield (10, 51% yield). Furthermore, steric bulk has minimal effects on the efficiency (9, 50% yield). Heteroatoms such as nitrogen and oxygen can readily be incorporated into the substrate (11 and 13, 84% and 60% yield, respectively), and although the inclusion coordinating heteroaromatic rings does decrease the yield, 14 was still produced in synthetically useful yields. When a carboxylic acid β to a ketone was utilized, 15 was observed in low yield.

At the present time, secondary carboxylic acids have also been shown to give the desired products. Both cyclic systems (16 to 21, 40 – 90% yield) as well as acyclic systems (22 and 23, 63% and 41% yield, respectively) give satisfactory yields. Notably,
both protected and unprotected alcohols were tolerated, affording 19 and 23.

Additionally, when a β-amino acid was utilized, 20 was generated in 60% yield. Finally, we have initial results with two α-heteroatom acids, and 24 and 25 can be generated in 28% and 14% yield, respectively.

### Table 1. Scope of the decarboxylative trifluoromethylation

<table>
<thead>
<tr>
<th>Benzylic</th>
<th>Secondary</th>
<th>Primary</th>
<th>α-heteroatom</th>
</tr>
</thead>
<tbody>
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<td><img src="image2.png" alt="Chemical Structures" /></td>
<td><img src="image3.png" alt="Chemical Structures" /></td>
<td><img src="image4.png" alt="Chemical Structures" /></td>
</tr>
<tr>
<td>1. 70% yield</td>
<td>16. 71% yield</td>
<td>9. 50% yield</td>
<td>24. 28% yield</td>
</tr>
<tr>
<td>2. 48% yield</td>
<td>17. 64% yield</td>
<td>10. 51% yield</td>
<td>25. 14% yield</td>
</tr>
<tr>
<td>3. 60% yield</td>
<td>18. 90% yield</td>
<td>11. 84% yield</td>
<td>22. 63% yield</td>
</tr>
<tr>
<td>4. 66% yield</td>
<td>19. 40% yield</td>
<td>12. 77% yield</td>
<td>23. 41% yield</td>
</tr>
<tr>
<td>5. 53% yield</td>
<td>20. 60% yield</td>
<td>13. 60% yield</td>
<td>21. 41% yield</td>
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<tr>
<td>6. 32% yield</td>
<td>21. 41% yield</td>
<td>14. 49% yield</td>
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<tr>
<td>7. 72% yield</td>
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<tr>
<td>8. 63% yield</td>
<td></td>
<td>15. 38% yield</td>
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</tbody>
</table>

**VI. Mechanistic Discussion**

While there are still several unanswered questions as to the exact mechanism of the transformation, several details have been determined. First, the excited state of the photocatalyst oxidizes the carboxylate, as when a range of photocatalysts were evaluated, only those that are capable of oxidizing the carboxylate from the excited state yielded any appreciable amounts of product, suggesting that the photocatalyst first undergoes a
Figure 4. Relevant electrochemical potentials for the discussion of the mechanism of the decarboxylative trifluoromethylation

reduction to form Ir(II), and this reduces a species later in the catalytic cycle. Further Stern-Volmer analysis is necessary, however, to probe this mechanism. The nature of the species that is reduced is either a Cu(II) complex to form a Cu(I) species ($E_{\text{p red}}^{\text{Cu(II)/Cu(I)}} = -0.11$ V vs SCE for Cu(bpy)Cl$_2$ in MeCN$^{30}$), or the Togni’s reagent ($E_{\text{p red}}^{\text{Cu(bpy)Cl}_2} = -1.11$ V vs SCE in MeCN$^{31}$) to form trifluoromethyl radical. To date, no direct evidence for the formation of the trifluoromethyl radical has been observed, lending credence to the reduction of the copper species. However, the Ir(II) species is a strong enough reducing agent ($E_{1/2}^{\text{Ir(II)/Ir(III*)}} = -1.37$ V vs SCE in MeCN$^{32}$) for this process to be exothermic (Figure 4). As such, this pathway cannot be discounted completely. However, based on electrochemical potentials, it is unlikely that the Ir(II) species would reduce Togni’s reagent in the presence of Cu(II), but it is theoretically possible. When Ir(dF(CF$_3$)ppy)$_2$(d(CF$_3$)bpy)PF$_6$, a photocatalyst that is not as reducing ($E_{1/2}^{\text{Ir(III)/Ir(IV)}} = 1.21$ V vs SCE in MeCN$^{32}$) for this process to be exothermic (Figure 4). As such, this pathway cannot be discounted completely.

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−0.69 V vs SCE in MeCN$^{33}$), was utilized product was observed in a slightly diminished yield. This catalyst should not be able to reduce Togni’s reagent, indicating that direct reduction of the Togni’s is unlikely under the reaction conditions.

While these results suggest the nature of the photocatalytic cycle, they do not illuminate the copper catalytic cycle. We assume that this transformation operates via a Cu(I)/Cu(II)/Cu(III) cycle, with reductive elimination occurring from Cu(III). From here, of particular interest is the order the two groups, the alkyl group and the CF$_3$, become ligands for the copper catalyst. Based upon the known reactivity of copper salts with Togni’s reagent, we propose that two copper (I) species first react with Togni’s reagent to form a copper (II) CF$_3$ complex, as well as a second equivalent of a copper (II) salt. (Scheme 9). This second species can then be reduced by the photocatalyst to regenerate

copper (I). The Cu–CF₃ complex could then trap an alkyl radical to yield a copper (III) complex, which can then undergo reductive elimination to complete the catalytic cycle.

To investigate the addition of nucleophilic alkyl radicals to Cu–CF₃ species, trifluoromethylator,³⁴ was subjected to the reaction conditions (Scheme 10). When a primary acid was utilized, 15% yield with respect to the equivalents of copper added was observed, indicating that our proposed mechanism is feasible. As a final note, during optimization it was observed that the nature of the ligand for the copper species was dependent upon the nature of the alkyl radical generated. We believe this results from a narrow tolerance of the electronics of the copper for radical addition, and as such the electronic nature of the copper needs to be tailored for the radical generated.

Another possible mechanism is a formal radical-radical coupling mediated by the copper catalyst. This would operate where both the trifluoromethyl radical as well as the alkyl radical are generated via the photocatalyst. These two species can then sequentially react with the copper center, to generate a copper (III) complex. This can then undergo reductive elimination to generate the desired compound as well as the starting state for the copper catalyst. This mechanism has been proposed for similar transformations in the literature.³⁵ While at the present time, this mechanism cannot be discounted, given the

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lack of any evidence for the production of trifluoromethyl radical under the reaction conditions, we view it as the less likely mechanism.

**VII. Conclusion**

In conclusion, we have developed a novel decarboxylative trifluoromethylation that relies upon copper catalysis to furnish the desired bond. This protocol has been shown to be applicable towards a number of classes of carboxylic acids, allowing for facile construction of sp³ trifluoromethyl groups. While these results are promising, further optimization is necessary so that tertiary carboxylic acids, amino and oxy acids, as well as benzoic acids can be incorporated into this protocol.
VIII. Supporting Information

General Information

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. All solvents were purified according to the method of Grubbs. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still. Thin-layer chromatography (TLC) was performed on Analtech 250 micron silica gel plates. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm\(^{-1}\)). \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 125 MHz) instrument, and are internally referenced to residual protic solvent signals (note: CDCl\(_3\) referenced at \(\delta\) 7.26 and 77.16 ppm respectively). Data for \(^1\)H NMR are reported as follows: chemical shift (\(\delta\) ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for \(^{13}\)C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. Gas chromatography (GC) was performed on an Agilent 6850 Series chromatograph with splitless capillary injection and FID detection.

General procedure

In a 20 mL vial, the copper catalyst was added, and dissolved in enough MeCN so that the concentration of the copper is 0.01 M. In a separate reaction vial, the ligand (if any) was dissolved in enough CHCl\(_3\) so that the concentration of the ligand is 0.01 M. Once
both species are fully dissolved, 1 mL of each solution is added to a separate 8 mL vial equipped with a magnetic stir bar. This solution is then stirred for 1 hour, before the solvent is removed via Genevac. Then, the Togni’s reagent is added to this reaction vial. In a separate vial, the photocatalyst and carboxylic acid are added. Then enough EtOAc is added so that the concentration of the carboxylic acid is 0.025 M. Then the base is added to this solution. 2 mL of this solution is then added to vial containing the copper catalyst, ligand, and Togni’s reagent. This solution is then degassed for 10 minutes via sparging with nitrogen gas. The vial was then sealed and the cap was wrapped in parafilm. Unless otherwise noted, the vial was placed approximately 8 cm away from a 34 W Blue LED and a fan was turned on to cool the vial. The reaction was stirred for 5 hours, and then the LED was turned off. A known amount of standard was then added to the reaction mixture, and the yield is determined via GC or $^{19}$F NMR analysis.

**Standard reaction setup** In a typical reaction, the reaction mixture is irradiated with 34W Kessil KSH150B from 5 cm away. Regular fans are employed to maintain the temperature at room temperature.