NOVEL STRATEGIES FOR $\alpha$-HYDROXY C–H ARYLATION AND
OXIDATIVE C–N CROSS COUPLING VIA METALLAPHOTOREDOX CATALYSIS

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A DISSERTATION
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ABSTRACT

Transition metal catalyzed cross-coupling is an incredibly powerful platform for the construction of organic architectures, since the advent of these technologies their impact has been felt throughout the chemical sciences and society more broadly. Despite the advances that have been made in this field over the last half century, limitations with respect to the ability to construct C_{sp}^{3} rich frameworks, and carbon–heteroatom bonds with particularly electron deficient heteroatom coupling partners remains unsolved challenges. The moieties which would result from the realization of these transformations are of long-standing interest in the pharmaceutical industry, and academic medicinal chemistry discovery programs, due to unique biological properties they may possess.

Over the last decade photoredox catalysis has arisen as highly versatile platform for forging carbon–carbon and carbon–heteroatom bonds in a variety of molecular settings. In particular the merger of photoredox catalysis and transition metal catalysis has facilitated the development of a litany of new transformations which have the potential to vastly expedite the synthesis of organic frameworks of both academic and industrial interest, many of which have traditionally been difficult or impossible to access with prior art.

The design and development of a new paradigm for selective functionalization of C–H bonds adjacent to alcohols (an incredibly prevalent functional handle) is discussed. This strategy utilized a combination of three catalytic cycles in conjunction with a Lewis acid activation mode to access radical species from simple alcohols, which can then be cross coupled with aryl halides to deliver benzylic alcohol products in a highly modular fashion.
In addition, a novel cobalt photocatalyzed coupling of \(N\)-aryl amides and boronic acids is discussed. The development of a novel cobalt photoexcitation pathway facilitates the coupling of these partners via an open-shell homolytic substitution pathway. This methodology allows access to highly sterically encumbered diaryl amides in excellent yield, and also highlights the potential utility of base-metal chromophores in photocatalysis.
ACKNOWLEDGEMENTS

I would first like to thank my advisor, Professor David MacMillan, for his invaluable guidance, enthusiasm and patience during my time in his laboratory. Under his tutelage I have learnt how to critically think about what constitutes an important research problem and how to creatively approach and tackle challenges as they have arisen throughout my time here. I will always be grateful for his support both scientifically and personally, his openness toward new ideas and approaches has been fundamental to all the success the lab has experienced during my time here. Finally, I thank him for his support throughout the last year as I have been prepared to leave the department, and his assistance in acquiring the postdoctoral appointment I will be starting after I complete my PhD.

I thank the remainder of my thesis committee Professors Robert Knowles, Abigail Doyle and Todd Hyster. I fondly remember taking graduate classes from Rob and Abby in my first year, their excellent teaching really laid a foundation I have greatly benefitted from during my time in the MacMillan lab and will be sure to benefit me for the years to come as I begin my postgraduate career. In addition, I would like to thank Abby again for serving as my second reader and Robb for writing me a recommendation letter which helped me secure my position post-graduation. I have greatly enjoyed my interactions with all the faculty here at Princeton, of particular note, Marty Semmelhack who I had the great privilege of teaching with for two semesters. His approach towards the instruction of organic chemistry is something I always endeavored to emulate and will take forward with me in my career, he really is an excellent communicator of chemistry as was highlighted by his recent winning of the university presidents teaching award.
I would like to thank the entirety of the MacMillan lab both past and present, it has been an incredible privilege to work with and learn from the excellent group of scientists that have made up the lab throughout my time here. The opportunity to express, challenge and explore new ideas has been pivotal in the development of my own chemical understanding and my enjoyment of my time here. In particular I would like the express thanks to the senior graduate students and postdocs who mentored me during my time here, Andrew Capacci, Jen Alleva, Valarie Schurtleff, Jack Terrett, Jenna Jeffrey, Craig Johnson, and Megan Shaw come to mind in particular.

Thank you to the numerous coworkers who have worked with me on work described in this thesis, Jian Jin for his initial discovery and optimization of the Cobalt catalyzed process described in Chapter 3 and my Merck collaborators Melodie Christensen, Dan Di’Rocco, Rebecca Ruck, Dani Schultz and Ian Davies for their help in optimizing the alcohol arylation protocol in Chapter 2. Of those individuals I would like to particularly thanks Melodie and Dani for teaching, and learning with me the intricacies of metallophotoredox catalysis in a high throughput setting, It was a great pleasure to see them use what we learnt together to develop the incredible enabling technology that exists today for triple catalytic C–H functionalization within Merck. Also thank you Ian for writing me a recommendation letter and supporting me with the next stage in my career as a chemist. For the Cobalt project I would also like to thank Nick, Dani and Nadia for discussions, my incredibly rudimentary understanding of photo-physics was undoubtedly improved because of the time we spent together.

In addition to being an excellent mentor and co-worker in lab, I have also had the privilege of writing several reviews with Meg, we made a good team – I would type a lot
of stuff (garbage, but in a sensible order) really quickly and you would tidy it up very slowly. I recall the night we sent the JOC review to Dave with deep affection, we immediately decided to go to Ivy karaoke, before getting an email from Dave at 2 AM saying “looks good, please submit”. The following day was long and arduous for numerous reasons, least of all the fact both of us wanted to go lie down. Meg in particular was and is an incredible friend and I wish her all the best with her career in industry and with her upcoming wedding.

During my time in the MacMillan lab I have moved desk three times and have spent time in every bay on the 1st floor, each bay has had a unique atmosphere, it was great to get to work so closely with so many members of the lab. I apologize to the current and past denizens of bay 1 and 2, Yong, Yufan, Gabby and Moon Tao in particular, for my somewhat interesting taste in music, saying that who doesn’t love a playlist which alternates between Cher and K-pop. It has always been a great pleasure to hang and chat chemistry with you all in lab. I have been lucky enough to have a number of co-workers, I share fond memories of time outside the lab with, Meg, Patti and, Thom in particular, thank you for engaging frequently with me in my favorite pastime – anyone who knows me and is reading this knows what that is – I will miss interacting with you closely as I move on to Wisconsin. In addition, I would also like to thank Yong, Russell, Stefan and Jeff for their friendship, our “conference trip” to Asia was a blast, despite the fact I may or may not have been mugged in Japan. I also would like to thank Taehoon Kim (SIOC) for hosting us during our time in Korea, it was undoubtedly key to us really getting to experience so much of Seoul as we did in such a short time… as I am writing this I crave a meal from “chicken beer plate”.

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It’s be fun seeing the current third and second years, aka “the Pillars”, learn the ropes of graduate school and I hope I have been able to provide at least a modicum of useful advice and guidance as a senior graduate student. Patrick, it was a pleasure to sit next to you during your first year in the lab and you have really been an incredible addition to the lab – the successes you’ve had already honestly does make me a little jealous. Sitting next to you when I was in the pits of graduate school, utterly burnt out was a shock to my system and your enthusiasm for chemistry was a slap in the face and reminded me that I to actually like chemistry. I am genuinely excited to see what you can achieve in the time you have remaining. Gabby, I have and always will enjoy annoying you... not much to add there, other than I’ll remember our chats with Ian fondly – “nothing means anything” really is a key mantra in understanding the intricacies of chemistry. Thank you to Thom, Steve, Bobby, Kenneth and Jacob for keeping the lab fabulous, along these lines thanks again to Dave for making the lab such a welcoming environment where I have also felt comfortable being myself.

Outside of the lab, I would like to thank my friends Hope, Duy, Katie, Andy, Patsy and Laura. The time spent hanging out with you, away from the worries of grad school were key in keeping me at least partially sane. Along a similar note I thank Jacqui and Beth who I learnt so much from, notable about myself and how to focus of what really matters. Finally, I thank my whole family for supporting me throughout my time in grad school, Thanks to Angela, Tess, Char and my immediate family mum Karen, dad Jeff and Sophie. You always supported my choice to study abroad, the day you dropped me off at the airport to move here was not an easy day, I remember getting on that escalator and watching you get smaller and the temptation to turn around was so strong. I miss you and really am sorry
I won’t be coming home just yet. Sometimes you just need to get away from the tribulations of daily life and taking the time to talk to you guys and my friends back home, even though you’re on a different continent, has always made me smile.
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>acac</td>
<td>acetylacetonate</td>
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<td>ATRA</td>
<td>atom transfer radical addition</td>
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<td>Bn</td>
<td>benzyl</td>
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<td>ceric ammonium nitrate</td>
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<td>cat.</td>
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<td>compact fluorescent lamp</td>
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<td>dr</td>
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<td>HAT</td>
<td>hydrogen atom transfer</td>
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<td>highest occupied molecular orbital</td>
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<td>high throughput experimentation</td>
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<td>IR</td>
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<td>ligand to metal charge transfer</td>
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<tr>
<td>LUMO</td>
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<tr>
<td>s-Bu</td>
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Chapter 1

METALLAPHOTOREDOX CATALYSIS

I. Introduction

The primary focus of Chemistry is the study of the electronic and molecular structure of matter, and how these intrinsic features effect the properties and reactivity of the substance. The ultimate aim of these studies is to be able to predictably establish the reactivity of a given molecule based on its structure. As a result, chemistry is a highly interdisciplinary field, maintaining a central and important role in modern society and across the physical sciences. For example, novel chemical innovations have significant impact in the medical, materials and energy storage sciences. Continued advances in the understanding of electronic and molecular structure, offers a breadth of further opportunities for developments in these other fields of vital importance to modern society. As a corollary, deficiencies in chemical understanding reduces the propensity of novel discoveries in related fields, as a result continuing study of how the structure of molecular entities relates to their properties and reactivity is of vital importance in enabling ongoing discovery in the physical sciences more broadly.

Catalysis, the use of a chemical entity to accelerate a reaction or enable previously unobserved reactivity, is one particular area of chemistry of ever increasing significance in many areas of the physical sciences. Catalytic methods for the production of bulk commodity chemicals (such as ammonia) have drastically altered the growth and development of humanity,\(^1\) in addition catalysis plays a significant role in the development

and synthesis of fine chemicals of importance in the pharmaceutical, fragrances and agrarian sectors.

Advances in synthetic organic chemistry, a subdivision of chemistry, have facilitated the development of many modern medicinal agents and materials due to our ever-expanding ability to construct previously inaccessible molecular frameworks. In particular, the development of novel reaction methodologies, which tolerate a broad array of functional groups, has facilitated the production of compounds which were previously difficult to prepare efficiently – if they could be accessed at all. Over the last half century catalytic platforms in particular, have enabled the development of a litany of new bond forming transformations, which in turn have facilitated access to a range of new chemical architectures. Catalytic transformations are often characterized by their modularity and generality, this is often attributed to the ability of catalysts to access broadly applicable substrate activation modes, wherein one of the participants of a chemical reaction is activated towards subsequent steps which cannot proceed in the absence of the catalyst. The development of novel modes of activation often facilitates the development of a number of new transformations, as the activated intermediate can engage with a range of other substrates. Select examples of novel activation modes developed over the last half century include: (i) Lewis acid activation, (ii) enamine organocatalysis, (iii) iminium ion

organocatalysis,⁴ and (iv) oxidative addition into electrophiles,⁵ each of these platforms have enabled a multitude of new methodologies to be developed

II. Transition Metal Catalyzed Cross-Coupling

Transition metal catalysis has become a major force in coupling chemistry since the discoveries of the now synonymous reactions by Stille, Negishi and Suzuki (Scheme 1).⁵ These methodologies utilize an electrophilic organic coupling partner, typically an aryl halide or pseudohalide and a reactive organometallic nucleophile, in conjunction with a metal catalyst, to reliably construct a wide variety of carbon–carbon bonds. A significant challenge for traditional cross-coupling methodologies, such as these, can be accessing the required reactive organometallic nucleophile. Additionally, these organometallic nucleophiles can be highly reactive, requiring carefully controlled conditions (exclusion of oxygen and moisture, cryogenic temperatures) and showing low functional group tolerance. As an added caveat, the less-reactive tin reagents required for Stille couplings

Scheme 1. Commonly employed transition metal coupling protocols.

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can be highly toxic, necessitating special handling and waste disposal. In spite of these drawbacks, the power of these methodologies has led to an enormous field of active research, and these synthetic methodologies are today undoubtedly some of the most utilized reactions in the pharmaceutical industry and chemical sciences more broadly.\(^6\)

**Scheme 2.** Mechanism of transition metal catalyzed cross-coupling.

Carbon-carbon bonds are traditionally forged in this paradigm under the influence of nickel or palladium catalysis (Scheme 2), following oxidative addition of a low valent metal species to an aryl halide, an organometallic nucleophile can engage in transmetallation to deliver a species primed to undergo reductive elimination and furnish the C–C bond. For much of the early history of cross-coupling chemistry, palladium catalysis was dominant due the relative ease of access of stable low valent palladium catalysts and pre-catalysts,\(^7\) nickel catalysis was often avoided due to the increased

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propensity of nickel to engage in single electron transfer pathways (SET) and the instability of common Ni(0) pre-catalysts. In spite of these limitations, nickel-catalyzed cross-coupling has recently experienced a resurgence of interest due to a number of factors: (i) nickel is a more electropositive metal and can often engage substrates which are challenging for palladium catalysis under much milder conditions, (ii) nickel has a decreased propensity to undergo deleterious β-hydride elimination, which can often diminish the efficacy of palladium catalysis, and (iii) nickel’s tendency to engage in single-electron pathways has facilitated the development of a number of new bond forming technologies which have yet to be developed using palladium. These factors have facilitated the development of a number of C_sp^2–C_sp^3 and C_sp^3–C_sp^3 coupling technologies utilizing nickel catalysis, the continuing development of these methodologies remains of significant interest given the likely utility of highly C_sp^3 rich frameworks in medicinal chemistry.

In addition to the ability to forge C–C bonds, copper and palladium catalysis have also facilitated the development of a number of technologies for the formation of C–N, C–O and C–F bonds. The synonymous Buchwald-Hartwig coupling traditionally employs nitrogen nucleophiles and aryl halides to furnish aryl amines, an important pharmacophore. Since the initial reports of this methodology, further advances have rendered this transformation highly general and modular, and as a result have facilitated the implementation of this technology as one of the most utilized transformations in the

pharmaceutical industry (Scheme 3a,b). In addition to nitrogen nucleophiles, alkoxide and fluoride nucleophiles have also been employed in Buchwald-Hartwig like coupling protocols. The extension of this catalytic manifold to the formation of aryl fluorides is particularly notable given the utility of these motifs in medicinal chemistry, and the extreme challenge of C–F reductive elimination. This reductive elimination is particularly challenging due the high electronegativity of fluoride, and the fact that the elementary reductive elimination step required for bond formation, formally represents oxidation of the fluoride ligand by the metal center. Indeed more generally, reductive elimination with particularly electron-deficient coupling partners remains a significant problem due to this caveat, and often times requires the development and synthesis of highly specialized ancillary-ligand architectures.


In contrast to palladium, copper often engages in facile reductive elimination from the Cu(III) oxidation state, however the initial oxidative addition step can be kinetically and thermodynamically unfavorable. Often times copper systems necessitate highly activated electrophiles (such as aryl iodoniums and diazonium salts – which can have undesirable safety profiles), or extremely forcing reaction conditions to overcome the initially challenging oxidative addition step. A highly attractive alternate strategy is the oxidative coupling of two nucleophiles using a copper catalyst, generically referred to as Chan-Evans-Lam couplings, these transformations facilitate the coupling of a diverse array of nitrogen and oxygen nucleophiles with aryl boronic acids using molecular oxygen as the terminal oxidant. By circumventing the challenging oxidative addition step, replacing it with more kinetically facile transmetallation and SET oxidation steps, a highly enabling and general method for C–N and C–O bond formation has been developed (Scheme 3c).\(^{15}\) The technology has also been expanded to C–F bond formation, however these processes remain copper mediated due the difficulty in turning the copper catalyst over in these systems.\(^{16}\) The MacMillan laboratory has recently introduced an novel alternate strategy to this oxidation addition problem, which proceeds via the intermediacy of catalytically generated radical species.\(^{17}\)

Despite the many advances that have been realized in the field of cross-coupling, the necessity of organometallic nucleophile partners remains a significant limitation as these
can often be difficult to prepare in the presence of sensitive functionality found in molecules of significant interest in the pharmaceutical sciences (and others). Methods which utilize native function groups, functionality inherently present in naturally occurring and widely available compounds, would offer a significant advantage, and have the potential to greatly facilitate the expediated synthesis of a large number of biologically active organic molecules.

III. Photoredox Catalysis

Over the past several decades, photoredox catalysis has been extensively investigated as a powerful tool in a wide range of fields of interest to modern chemists, including: (i) water splitting,18 (ii) carbon dioxide reduction19 and (iii) the development of novel solar cell materials.20 Surprisingly, only recently has this powerful catalytic methodology attracted the attention of synthetic organic chemists. Towards the end of the last decade, the MacMillan, Yoon and Stephenson groups published seminal reports on the use of Ru(bpy)$_2^{2+}$ as a photocatalyst for a variety of synthetically relevant transformations: α-alkylation of aldehydes,21 [2+2] cycloaddition,22 and reductive dehalogenation of complex alkyl halides,23 respectively (Scheme 4). These reports demonstrated the potential power of this catalytic manifold in enabling previously undocumented synthetic transformations, using simple household light sources and readily available photosensitive catalysts, and

thus triggered a rapid growth of interest in this field. A large number of reports have subsequently been published and several extensive reviews on this field are available.\textsuperscript{24}

Scheme 4. Seminal reports in the field of modern organic photoredox catalysis.


\[
\begin{align*}
\text{dienone} & \quad 5 \text{ mol}\% \text{ [Ru(bpy)\textsubscript{3}]Cl\textsubscript{2}} \\
\text{LiBF\textsubscript{4} - Pr\textsubscript{2}NEt} & \quad \text{MeCN, 275 W CFL} \\
\text{58–98\% yield, 4:1 to 10:1 dr} & \quad \text{13 examples}
\end{align*}
\]

(b) MacMillan (2008) – Asymmetric catalytic \(\alpha\)-alkylation of aldehyde

\[
\begin{align*}
\text{aldehyde} & \quad 20 \text{ mol}\% \text{ [Ru(bpy)\textsubscript{3}]Cl\textsubscript{2}} \\
\text{N\textsubscript{2}H\textsubscript{Me}O\textsubscript{Me}} & \quad \text{DMF, 15 W CFL} \\
63–93\% yield, 88–96\% ee & \quad \text{12 examples}
\end{align*}
\]

(c) Stephenson (2009) – Reductive dehalogenation of activated alkyl halides

\[
\begin{align*}
\text{activated alkyl halide} & \quad 2.5 \text{ mol}\% \text{ [Ru(bpy)\textsubscript{3}]Cl\textsubscript{2}} \\
\text{HCO\textsubscript{2}H - Pr\textsubscript{2}NEt} & \quad \text{DMF, 14 W CFL} \\
79–99\% yield & \quad \text{10 examples}
\end{align*}
\]

Key to the rapid development of this catalytic platform has been the recognition that readily available metal–polypyridyl complexes and organic dyes have unique electronic properties when promoted to an excited state. More specifically, irradiation with low-energy visible light (at wavelengths at which common organic molecules do not absorb) allows targeted excitation of these catalytic chromophores. To understand the unique power of photoredox catalysis it is necessary to first understand the rudiments of their photophysical mechanism of operation. As seen in Figure 1, using the common catalyst

Ru(bpy)$_3^{2+}$ as a representative archetype, initial exposure to visible light induces a metal to ligand charge transfer (MLCT) event through which an electron is excited from a metal centered orbital to the $\pi^*$ system of the ligands. This event forms a high-energy singlet state that can undergo quantum mechanically forbidden intersystem system crossing (ISC) to give the lower-energy, long-lived triplet excited state with a quantum yield approaching unity. The triplet excited state then persists in solution until either phosphorescence (spin-forbidden photon emission) occurs or internal conversion, returning the molecule to the ground state, alternatively the excited can undergoes a single-electron transfer event (i.e. is quenched).

**Figure 1.** Photophysics and oxidation state potentials for [Ru(bpy)$_3$]$^{2+}$

The excited state of [Ru(bpy)$_3$]$^{2+}$ has a unique electronic structure, in which one electron occupies a high energy $\pi^*$ orbital and is primed for donation to a suitable oxidant, in what is termed an oxidative quench; the other unpaired electron resides in a singly occupied low-energy metal centered orbital which is predisposed to accept an electron from a suitable reductant, in what is known as a reductive quench. This unique situation allows the photocatalyst to act as either a strong reductant (yielding the Ru(III) complex) or a strong oxidant (yielding the Ru(I) complex). Both the Ru(I) and Ru(III) species have a
strong driving force to return to the thermodynamically most stable Ru(II) oxidation state, and this can be coupled to a second endothermic reduction or oxidation, respectively. The electronic structure of the photoredox catalyst allows both a strong oxidant and reductant to exist simultaneously in solution; leveraging of this catalytic manifold has allowed for the development of a wide range of new synthetic bond forming strategies, including net reductive, net oxidative and redox neutral transformations. Importantly, the well-defined relationship between the structural characteristics and redox properties of the photocatalyst allows for the rational design of these catalysts by modification of the ligand framework and the metal used.

The redox potentials of many common photocatalysts are in the same range as that of a number of common organic functionalities, as a corollary these catalysts can often engage in SET events with organic molecules providing access to open-shell species, commonly referred to as radicals. Radical intermediates typically have highly divergent modes of reactivity compared to their closed shell analogs, and as such photoredox catalysis provides a mild catalytic means by which to generate highly activated species from a range of highly abundant and naturally occurring functionalities. As a result of these features a number of novel substrate activation modes has been developed in the last decade utilizing this catalytic paradigm. As one such example, simple carboxylic acids can be engaged in a single electron oxidation event to provide access, after rapid decarboxylation, alkyl radical species, which have subsequently been shown to engage in a wide range of novel transformations including (i) Giese reactions, (ii) C–C bond forming radical

couplings,27 (iii) C–F bond formation,28 and (iv) radical substitution reactions with activated π-unsaturates (Figure 2).29 A number of other functionalities have been demonstrated to likewise provide access to activated intermediates via photoredox catalysis, which can subsequently be interfaced with a number of bond forming technologies.24

**Figure 2.** Carboxylic acids – lynchpin functionality enabled by photoredox catalysis.

![Chemical structures diagram](Image)

IV. **The Merger of Photoredox and Transition Metal Catalysis**

The merger of transition metal catalysis and photocatalysis, termed metallaphotocatalysis,30 has recently emerged as a versatile platform for the development of new, highly enabling synthetic methodologies. Photoredox catalysis provides access to reactive radical species under mild conditions from abundant, native functional groups, and, when combined with transition metal catalysis, this feature allows direct coupling of non-traditional nucleophile partners. This obviates the

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requirement for organometallic nucleophiles which has remained a long-standing drawback of traditional cross-coupling paradigms.

The first-row transition metals, in particular nickel, have a long established capacity to capture organic radical species. Photoredox-mediated radical generation has proved to be an effective strategy for activating non-traditional cross-coupling nucleophiles, wherein the subsequent radical can be captured by a nickel center and engaged in a cross-coupling manifold. In 2014 the MacMillan and Doyle laboratories reported the decarboxylicative cross coupling of carboxylic acids with aryl halides, a proposed mechanism for this transformation in shown in Scheme 5. Oxidative radical generation outlined previously, generates an alkyl radical which can be trapped by the oxidative addition product of nickel and an aryl halide to deliver a high-valent nickel species

**Scheme 5.** Mechanism and scope for dual nickel photoredox catalyzed decarboxylicative cross-coupling.

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primed for reductive elimination. The nickel and photoredox cycles can then simultaneously be closed via a SET event. In addition to engaging aryl electrophiles through this mechanistic paradigm, vinyl halides, acyl chlorides, and alkyl halides can also be utilized in related transformations. These results combined highlight the power of metallaphotocatalysis, wherein a single lynchpin functionality can be generically activated and employed in a litany of coupling protocols. In addition to dual photoredox-nickel catalysts, highly enabling novel dual photoredox-copper, photoredox-palladium, and photoredox-gold methodologies have reported. In each scenario, the photoredox catalyst facilitates radical generation from an organic precursor, which can then be interfaced with the transition metal catalysis manifold. By leveraging the unique reactivity of that metal, an ever-increasing number of previously elusive transformations have been developed.

In addition to facilitating radical generation, a photoredox catalyst can also be employed to directly modulate the oxidation state of a transition metal catalyst, the importance of the metal oxidation state in transition metal catalysis is well established. Indeed, it has long been noted that the acceleration of several elementary steps in coupling protocols can be observed on modulation of the oxidation state of the metal catalyst. For example, in a stoichiometric setting, Hillhouse and others have

demonstrated that oxidation of a metal center can vastly increase the rate of reductive elimination, thereby allowing the rapid formation of C–N and C–O bonds. More recently, these concepts have been exploited in catalytic variants: for example, the Chan–Evans–Lam reaction (*vide supra*), in which oxidation of a copper intermediate enables a rapid reductive elimination step to forge aryl–heteroatom bonds. Reductive elimination from Cu(II) is itself sluggish, but reductive elimination from a Cu(III) intermediate, which can be accessed using readily available and benign oxidants (such as atmospheric oxygen), is facile. Overall, these results are mechanistically consistent, given that reductive elimination steps formally represent an oxidation of the pendant substituent by the metal center. As such, a metal center that is in a higher oxidation state should have a greater thermodynamic driving force to participate in reductive elimination. Not surprisingly, these findings have inspired a renaissance in high-valent metal catalysis, which in turn has led to the development of valuable new bond-forming reactions.

The MacMillan laboratory and others have reported new nickel-catalyzed methods for C–O and C–N bond formation utilizing a photoredox catalyst to directly access a Ni(III) complex via SET, which is primed to undergo reductive elimination (Scheme 6). The non-photo-catalytic variants of these transformations either suffered from poor scope or remain entirely unknown. The proposed mechanism for C–O bond formation for aryl
halides and simple alcohols, as well as subsequently reported C–N bond forming protocols in shown in Scheme 6.

**Scheme 6.** Mechanism and select literature examples and scope for dual nickel photoredox catalyzed C–O and C–N bond formation.

![Scheme 6](image)

V. Summary of Thesis Work

Chapter 2 describe our efforts to develop a method for the direct α-arylation of alcohols via the merger of HAT, nickel and photoredox catalysis, wherein an alkyl radical species is generated directly from a C–H bond adjacent to an alcohol via the intermediacy of a catalytic electrophilic aminium radical cation. This radical can then be interfaced with a nickel manifold as outlined previously to deliver benzylic alcohol products of significant utility in drug discovery programs, as exemplified by the diverse array of substrates which can be employed and a concise 3-step synthesis of the SSRI Prozac, and a number of novel analogs. In order to confer selectivity in the HAT event, a novel Lewis acid mediated
HOMO raising strategy is discussed. The synthetic utility of this new method is also evaluated and elucidated. In the same chapter our efforts to develop a platform for the rapid optimization of these triple catalytic platforms is discussed. Chapter 3 discussed out efforts to develop novel base-metal photocatalyzed C–N coupling protocols via homolytic substitution using aryl boronic acid coupling partners. The scope of this novel method for oxidative C–N bond formation is discussed, as are several mechanistic aspects.
Chapter 2

The Arylation of α-Hydroxy C–H Bonds

I. Introduction

The functionalization of C–H bonds has long been termed the “Holy Grail” of organic synthesis, as the development of a suite of such transformations has the potential to revolution the construction of organic molecules.\textsuperscript{42} This is impart due to the fact C–H bonds represent the most ubiquitous “functionality” in organic frameworks and are as a result, are inherently a native functional group present in a wide array of commercially available compounds. In addition to the potential ability to functionalize an unprecedented number of molecules utilizing this strategy, C–H activation in theory proceeds in a highly atom economical fashion and represents the epitome of green chemistry ideals due to the possibility of minimal waste generation, and the utilization of readily accessible feedstock chemicals.\textsuperscript{43} To date a number of elegant catalytic strategies for the functionalization of an array of C–H bonds have been developed. The most widespread and commonly reported method for C–H functionalization utilize sp\textsuperscript{2} C–H bonds,\textsuperscript{44} strategies for the selective functionalization of sp\textsuperscript{3} C–H bonds which would facilitate access to a more diverse array of three dimensionally complex molecular architectures remain a field of considerable interest due to the limited success in applying existing technologies to the activation of these more challenging modalities. Arguably sp\textsuperscript{3} C–H bond functionalization remains


underdeveloped, and C–H bonds remain underutilized as cross-coupling handles for C–C bond formation.

With respect to selective C$_{sp}^3$–H functionalization, regioselectivity remains a preeminent problem, this is attributable to the array of electronically and sterically diverse C–H bonds present in the majority of organic molecules of interest. Existing technologies often rely on the installation of a direction group, wherein a pendant Lewis basic functionality directs a transition metal towards activation of specific bond in a molecule.\textsuperscript{45} Whilst many elegant and novel transformations have been developed utilizing this strategy, it necessitates the installation of a directing functionality, often this can be difficult to remove and their installation and removal inherently generates increased amounts of chemical waste. Others have capitalized on the inherent acidity of certain C–H bonds to enable functionalization at these positions providing one potentially attractive solution to the challenge of selective C$_{sp}^3$–H functionalization, however these methods often require strong base which can diminish the scope of the transformation with respect to functional group tolerance.\textsuperscript{46} Carbenoid intermediates generated from stabilized diazo compounds have also been demonstrated to selectively add across a variety of C–H bonds. Through the design and implementation of specialized ligand frameworks, the Davies laboratory and others have expanded the scope of this transformation to allow for the selective functionalization of a range of sterically differentiated C–H bonds. However diazo


compounds represent an undesirable substrate class due to their instability, toxicity and limited structural diversity. Arguably no general strategy for the functionalization of $C_{sp^3}-H$ has been developed to date, and this field remains a vibrant area of research in many laboratories.

II. Triple Catalytic C–H Arylation

The MacMillan laboratory maintains a long standing interest in the functionalization of C–H bonds via the intermediacy of alkyl radical species generated via hydrogen atom abstraction. HAT is an elementary chemical transformation wherein a proton and an electron are simultaneously transferred from one molecule to another, and has long served as an efficient method for the generation of organic radical species. Based on these ideals, a number of attractive strategies for C–C formation via cross-coupling, which utilize either stoichiometric oxidants or photocatalytic halogen atom generation have been developed. In these systems, an in-situ generated oxygen or halogen centered radical can abstract a hydrogen atom from C–H bonds in relatively simple substrates to furnish an alkyl radical, this species can subsequently be interfaced with a nickel catalysis manifold to deliver a


cross-coupled product after reductive elimination (Scheme 7). Despite these advances, a significant limitation remains as selectivity is typically governed by bond dissociation energies, and as a result the radical at the site which possess the weakest C–H bond, of the numerous perspective hydrogen atoms present in most organic molecules, is generated. As a result of these factors, selective generation of radicals via HAT at sites which do not possess the weakest C–H bonds in a given molecule, and subsequent cross-coupling remains a long-standing challenge.

**Scheme 7.** Nickel metallaphotoredox catalyzed C–H arylation.

As one potential solution to this problem, the MacMillan laboratory developed a triple catalytic method for the arylative functionalization of strong electron-rich C–H bonds adjacent to amines or ethers functionalities furnishing benzylic amines and ethers, an important class of pharmacophores, from simple abundant starting materials. Selectivity in this instance is achieved utilizing the principle of polarity-matching in elementary HAT steps (Scheme 8).

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Scheme 8. Polarity matching – kinetic vs. thermodynamic selectivity in HAT.

Polarity effects in HAT have long been documented, but remain poorly understood within the organic chemical community, and underutilized in the development of novel cross-coupling technologies. The surprising kinetic selectivity observed in these instances arises as during the transition state for a given HAT event, when the abstracting species is electron deficient (as is the case with the quinuclidinium radical cation), a stabilizing electrostatic interaction can develop if the hydrogen atom being abstracted resides on a center which can stabilize partial charge accumulation. This has the effect of significantly lowering the transition state energy for these “polarity matched” HAT events, to such an extent that thermodynamically less favorable HAT events at these “hydridic

sites can occur in the presence of weaker C–H bonds, which possess polarity mismatched, or unbiased C–H bonds, when using a highly electrophilic HAT agent.

The proposed mechanism of this triple catalytic transformation achieved via the merger of photoredox, nickel, and HAT catalysis is shown in Scheme 9. Oxidation of aceclidine (a quinuclidine derivative) (1) \( E_{1/2}^{\text{red}} = -1.10 \text{ V vs. SCE in MeCN} \) by the excited state of a photocatalyst \( E_{1/2}^{\text{red}} = +1.21 \text{ V vs. SCE in MeCN} \) generated via visible light excitation of an iridium complex generates a highly electrophilic radical species (2) which is polarity matched to abstract a hydrogen atom from an electron rich \( \alpha \)-amino position (N–H BDE ~ 100 kcal mol\(^{-1}\), C–H BDE ~ 90-94 kcal mol\(^{-1}\)), furnishing radical 3. This radical can then be trapped by the product (5) of oxidative addition of a nickel (0) species (4) and an aryl halide. The resultant Ni(III) species (6) is primed to undergo reductive elimination to generate the desired product. The Ni(I) species (7) and reduced photocatalyst can then undergo an SET event to regenerate Ni(0) complex 4 and the ground state photocatalyst. 

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This transformation proved to extremely general for the coupling of α-amino C–H bonds and aryl halides, this activation mode was subsequently extended by the MacMillan laboratory to the triple catalytic alkylation of similar C–H bonds with alkyl halides,\(^\text{56}\) and the highly selective functionalization of relatively weak but hydridic aldehydic C–H bonds.\(^\text{57}\) In the last case, the aldehydic C–H bond is both polarity matched and thermodynamically the weakest bond in these substrates facilitating its highly selective arylation, alkylation and vinylation in relatively complex molecular structures (Scheme 10).

Despite the many advances realized in the activation of C–H bonds via HAT cross-coupling, a number of unsolved challenges remain. Notably, all existing methods to date leverage an electrophilic radical to selectively activate hydridic C–H bonds often adjacent to heteroatoms. In molecules of significant interest where multiple hydridic C–H bonds are present achieving selective HAT remains non-trivial (Figure 3a). Prior to our efforts, no method for the arylation of C–H bond adjacent to alcohols had been reported via this HAT cross-coupling strategy. Addressing this challenge remains of significant interest as alcohols represent one of the most ubiquitous functional groups, found in nature in the form of sugars, steroids, and proteins, while synthetic variants are found across a broad range of pharmaceutical agents.\textsuperscript{58} The benzylic alcohol motifs which would be produced through the realization of this transformation are often present in biologically active compounds, and also common intermediates in their preparation (Figure 3b).

Figure 3. A. Potential substrates for site selectivity HAT arylation which possess multiple hydridic C–H bonds. B. benzzylic-, alcohols, ethers and ketones in commonly utilized medicinal agents.

As such we undertook an effort to develop a method for the highly selective cross-coupling of α-hydroxy C–H bonds via the merger of nickel, photoredox and HAT catalysis, in conjunction with a novel activation mode for the selective weakening and polarization of C–H bonds adjacent to alcohols. We envisaged the development of a strategy which predisposes α-hydroxy C–H bonds towards HAT, with highly electrophilic abstracting agents such as the quinuclidine radical cation, would be necessary in order to realize this goal (Scheme 11).
III. Lewis Acid Induced Selectivity in Hydrogen Atom Transfer

From the outset, we recognized that the successful development of an α-alcohol arylation reaction via HAT and nickel catalysis would require: (i) chemoselective formation and coupling of an α-C–OH, carbon-centered radical in the presence of α-CH–amines, and other electron rich C–H bonds, and (ii) comprehensive suppression of the more common C–O arylation mechanism – a pathway that readily operates under the influence of photoredox and nickel catalysis (Chapter 1.4 and Scheme 6).

The MacMillan lab has previously developed a strategy for the selective functionalization of α-hydroxy C–H bonds in the presence of weaker C–H bonds based on hydrogen bonding induced weakening of bonds adjacent to alcohols (Scheme 12A). By engaging a hydrogen bonding additive the electron density on the oxygen atom of an alcohol is increased, this in turn is conjugated with the C–H σ* orbital of the adjacent C–H bond, which both weakens it and increases its hydricity. These factors combined have the effect of drastically increasing the rate of abstraction of the α-hydroxy C–H bonds by an electrophilic abstraction agent. The resultant alkyl radicals where then demonstrated to undergo facile Giese reaction to deliver alkylated products, which lactonize spontaneously.

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upon work-up (Scheme 12B). The success of this strategy is strongly demonstrated in a competition study between a simple alcohol and THF a prototypical ether substrate (Scheme 12C). In the absence of the phosphate hydrogen bonding catalyst a mixture of alcohol and THF functionalization is observed, whereas in the presence of the additive the chemoselectivity of the reaction increases to 75:1 favoring alcohol functionalization. When this strategy is extended to substrates which possess multiple C–H bonds of similar electronic character and strength exclusive functionalization adjacent to the alcohol is observed (Scheme 12D).
Scheme 13. Proposed mechanism for metallaphotoredox HAT-catalyzed alcohol C–H arylation.

Given this prior work, we hypothesized that the same hydrogen bonding interaction could be used to effect selective arylation of an α-hydroxy C–H bond, via the intermediacy of a HAT generated carbon-centered radical in the presence of α-CH–amines, and other electron rich C–H bonds. The mechanism we envisaged for this transformation is shown in Scheme 13. Oxidation of quinuclidine (8) \( E_{1/2}^{\text{red}} \) [Quinuclidine+·/Quinuclidine = −1.10 V vs. SCE] in MeCN\(^{53} \) by the excited state of a photocatalyst (12) \( E_{1/2}^{\text{red}} \) [*Iridium\(^{\text{III}}\)/Iridium\(^{\text{II}}\) = +1.21 V vs. SCE in MeCN\(^{54} \) generated via visible light excitation of iridium complex 11 generates a highly electrophilic radical species (9). Simultaneously in solution a hydrogen bonding interaction between an alcohol and appropriate hydrogen bonding additive can activate an α-hydroxy C–H bond towards polarity matched hydrogen atom abstraction by the electrophilic quinuclidinium radical cation 9 (N–H BDE \( \approx 100 \) kcal mol\(^{-1} \), C–H BDE for methanol \( \approx 96\) kcal mol\(^{-1} \))\(^{55} \) furnishing radical 16. This radical can then be trapped by the product of oxidative addition (19) of a nickel (0) species (18) and an aryl
halide (17). The resultant Ni(III) species (20) is primed to undergo reductive elimination to generate the desired benzylic alcohol 23. Finally, Ni(I) species 21 and reduced photocatalyst 13 can then undergo an SET event to reconstitute Ni(0) complex 18 and the ground state photocatalyst 11. In order to achieve efficient C–H functionalization, we postulated that tuning of the ligand framework and reaction conditions could be utilized to suppress C–O bond formation via the intermediacy of a nickel aryl alkoxide species (22).

**Table 1.** Initial optimization studies for H-bonding induced bond polarization in triple catalytic cross coupling. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Ligand</th>
<th>Solvent</th>
<th>% Yield (23/26)</th>
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<td>None</td>
<td>dbbpy</td>
<td>MeCN</td>
<td>0/60</td>
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<tr>
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<td>None</td>
<td>dbbpy</td>
<td>DMSO</td>
<td>1/50</td>
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<tr>
<td>3</td>
<td>NaO2P(OPh)2</td>
<td>dbbpy</td>
<td>DMSO</td>
<td>8/24</td>
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<td>dOMephen</td>
<td>DMSO</td>
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<td>Me2phen</td>
<td>DMSO</td>
<td>13/21</td>
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<td>Me2phen</td>
<td>DMSO 10 equiv. H2O</td>
<td>23/12*</td>
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<tr>
<td>7</td>
<td>CsO2P(OPh)2</td>
<td>Me2phen</td>
<td>DMSO 10 equiv. H2O</td>
<td>20/23*</td>
</tr>
<tr>
<td>8</td>
<td>(NBu4)2O2P(OPh)2</td>
<td>Me2phen</td>
<td>DMSO 10 equiv. H2O</td>
<td>15/30*</td>
</tr>
</tbody>
</table>

*Performed on a 0.3 mmol scale with photocatalyst 1 (1 mol%), NiCl2•glyme (3 mol%), quinuclidine (100 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), additive (0.25 equiv.), in solvent (0.25 M). Yield determined by calibrated GC analysis. Formation of phenol was not observed, the remaining mass balanced is ArH, Ar2 and starting material.

Initial studies on this transformation involved subjecting 1-hexanol, and 4-bromobenzotrifluoride, as coupling partners, to a mixture of NiCl2•dtbbpy, [Ir(dF(CF3)ppy)2dtbbpy](PF6) and stoichiometric quinuclidine in MeCN. Unsurprisingly, in the absence of hydrogen-bonding additive a significant amount of ether product 26 was obtained (Table 1, entry 1). Sequentially changing the solvent to DMSO, the ligand to
Me₄phen (precomplex 24), and introduction of NBu₄(PhO)₂PO₂ flipped the selectivity of the reaction, furnishing C–C coupled product 23 as the major product albeit in low yield, to our concern C–O coupling still remained as a significant side reaction (entries 2–8). Moreover, when an analogous competition study, to that carried out for the Giese alkylation discussed previously (Scheme 12C), was conducted THF functionalization remained the major observed coupling product in the presence and absence of the hydrogen bonding additive with only a mild increase in arylation of the alcohol observed in the presence of the additive (Table 2).

Table 2. Competition study – ethereal vs. α-hydroxy C–H bonds in metallaphotoredox HAT catalyzed arylation with hydrogen bonding additives. a

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>% yield (23/27) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>without NaO₂P(OPh)₂</td>
<td>2/65</td>
</tr>
<tr>
<td>2</td>
<td>with NaO₂P(OPh)₂</td>
<td>7/35</td>
</tr>
</tbody>
</table>

aPerformed on a 0.3 mmol scale with photocatalyst 1 (1 mol%), NiCl₂•gylme (3 mol%), quinuclidine (100 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), additive (0.25 equiv.), in solvent (0.25 M). b Yield determined by calibrated GC analysis.

We attribute the diminished influence of the hydrogen-bonding additive in this transformation to the high polarity of DMSO (used in this method) when compared to MeCN (used for the alkylation), hydrogen bonding interactions are weakened in increasingly polar solvents. Efforts to obtain product in less polar solvents where

hindered by the tendency for C–O coupling to dominate in non-coordinating solvent, where the alcohol would function as a ligand for the Nickel-center in the place of solvato ligands, and thus facilitate ether formation via the intermediacy of a nickel-aryl-alkoxide complex. These results in hand led us to take a step-back in order to attempt to develop a strategy which could be used to overcome these significant challenges. We recognized that moving to a less polar solvent would be particularly problematic due the second of these factors, so instead choose to develop a strategy for selective bond weakening of α-hydroxy C–H bonds which is less sensitive to medium effects. We hypothesized that exposure of alcohol coupling partners to Lewis acids in the presence of base should lead to metal alkoxide systems that exhibit greatly enhanced hydridic character at the α-alkoxy C–H positions. As a consequence, we anticipated that any subsequent HAT events would be dramatically accelerated at these α-alkoxy carbons if we were to use polarity-matched ammonium radical cations to perform the hydrogen abstraction step. In contrast, the same Lewis acids are known to datively coordinate to electron rich amines (without deprotonation), which retards the rate of HAT at the resulting α–ammonium-metal C–H bond due to concomitant loss of hydridic character (Scheme 14). With respect to the question of C– versus O– arylation chemoselectivity, we felt that judicious selection of Lewis acid would lead to a metal alkoxide species that might not readily participate in transmetalation with the key Ni(II)aryl catalytic intermediate, a critical step towards suppressing the possibility of aryl ether formation (Scheme 14).
Scheme 14. Lewis acid induced bond polarization – a novel activation mode for selective metallaphotoredox HAT cross-coupling.

This hypothesis was supported by kinetic data previously reported in the literature (Scheme 15A).\(^61\) Cumyloxy radical (CumO\(^\cdot\)), a highly electrophilic oxygen centered radical, abstracts a hydrogen atom from the \(\alpha\)-amino position in a range of amine substrates at rates approaching diffusion control (\(\sim 10^8\) mol\(^{-1}\)s\(^{-1}\)), the analogous rate for simple secondary alcohols in two orders of magnitude lower (\(2.66 \pm 0.05 \times 10^6\) mol\(^{-1}\)s\(^{-1}\)) and of comparable rate to a number of common other functional groups – including ethers, amides and even simple alkane C–H bonds (All rates in MeCN at 25 °C). In this regime achieving selective HAT would represent a significant challenge for \(\alpha\)-hydroxy C–H positions. Of significant interest towards the goal of achieving the desired selective \(\alpha\)-hydroxy C–H arylation, Bietti and co-workers have demonstrated that these rates are highly influenced by the introduction of Lewis acids. In the presence of relatively mild Lewis acids such as

Ca\(^{2+}\) salts, complete chemoselective abstraction of alcohol C–H bonds is observed in the presence of amines and amides by CumO\(^{•}\). This observation is attributed to the decreased electron density on the amine or amide when engaging in a dative interaction with the Lewis acid, as a result of this interaction the adjacent \(\alpha\)-amino C–H bonds are strengthened and acidified by the loss of lone pair to \(\sigma^*\) donation. In a contemporaneous study, a primary amino alcohol was subjected to CumO\(^{•}\), in the absence of Lewis acids, complete selectivity for the abstraction of the C–H bond adjacent to the amine was observed (\(k_{\text{HAT}}\) C–HXNH2 = 1.58 x 10\(^7\) mol\(^{-1}\)s\(^{-1}\)). In the presence of a Lewis acid the rate for abstraction next to the primary amine decreases to below an upper limit of \~10^4\, mol\(^{-1}\)s\(^{-1}\) (\(\beta\)-scission of CumO\(^{•}\) is more facile), as such, in the amino alcohol substrate selective formation of the \(\alpha\)-hydroxy radical is observed at 5.6 x 10\(^5\) mol\(^{-1}\)s\(^{-1}\) (Scheme 15B).

**Scheme 15.** A. Rate of HAT between organic substrates and cumyloxy radical. B. Intramolecular competition study for rates of HAT in an amino alcohol with CumO\(^{•}\) in the presence and absence of a Lewis acid.

Ca\(^{2+}\) salts, complete chemoselective abstraction of alcohol C–H bonds is observed in the presence of amines and amides by CumO\(^{•}\). This observation is attributed to the decreased electron density on the amine or amide when engaging in a dative interaction with the Lewis acid, as a result of this interaction the adjacent \(\alpha\)-amino C–H bonds are strengthened and acidified by the loss of lone pair to \(\sigma^*\) donation. In a contemporaneous study, a primary amino alcohol was subjected to CumO\(^{•}\), in the absence of Lewis acids, complete selectivity for the abstraction of the C–H bond adjacent to the amine was observed (\(k_{\text{HAT}}\) C–HXNH2 = 1.58 x 10\(^7\) mol\(^{-1}\)s\(^{-1}\)). In the presence of a Lewis acid the rate for abstraction next to the primary amine decreases to below an upper limit of \~10^4\, mol\(^{-1}\)s\(^{-1}\) (\(\beta\)-scission of CumO\(^{•}\) is more facile), as such, in the amino alcohol substrate selective formation of the \(\alpha\)-hydroxy radical is observed at 5.6 x 10\(^5\) mol\(^{-1}\)s\(^{-1}\) (Scheme 15B).
Scheme 16. Acid induced selectivity in HAT oxidations – select examples.

Lewis acid induced deactivation of α-amino C–H bonds, has been utilized by Sanford\textsuperscript{62a} and White\textsuperscript{62b} to develop selective C–H oxidation protocols (Scheme 16 ). In the system developed by Sanford and co-workers, simple protons function as a Lewis acid and deactivate the C–H bonds in proximity to the amine, such that platinum mediated C–H oxidation occurs predominately at the most distal methylene or methine position. White and co-workers utilized a similar idea, this time employing HBF\textsubscript{4} or BF\textsubscript{3} as a protecting group for amines, the in situ generated zwitterionic structures are then susceptible to iron mediated C–H oxidation again at the site distal to the now highly electron deficient amine center. Inspired by these ideals, researchers at Merck in collaboration with academic partners have developed photo-HAT mediated methods for the C–H oxidation and flourination of amines, again distal to the amine utilizing acid both as an in-situ amine protecting groups, and to deactivate the α-amino C–H bonds.\textsuperscript{63}

We hypothesized that a similar strategy could be employed in a metallaphotoredox paradigm to achieve the highly selective arylation of α-hydroxy C–H bonds. Moreover,

we hypothesized that exposure of alcohols to Lewis acids in the presence of mild base, would facilitate formation of an alkoxide system where the relatively naked negative charge on the alkoxide center would drastically accelerate HAT at the desired site. Other heteroatom containing moieties may also co-ordinate to the Lewis acid, but in this instance, we envisage deactivation of the adjacent C–H bonds as a deprotonation event with the mild base used cannot take place. If such an activation mode could be realized, highly selective HAT adjacent to alcohols could be achieved though the synergistic effects of: (i) α-hydroxy C–H bond activation, and (ii) retardation of HAT at other hydric C–H motifs in a given molecule, due to induced bond polarization.

IV. Development of a Lewis Acid Mediated HAT Arylation with Alcohols

With the goal of developing a Lewis acid mediated HAT arylation of alcohols, via triple HAT, nickel, and photoredox catalysis, we entered into collaboration with scientists at the Process Research and Development arm of Merck, based in Rahway, NJ. This collaboration was established based on the mutual interest our laboratory and Merck scientists had in the development of this highly enabling transformation, and developing a general platform for the rapid optimization of complex multicatalytic photoredox reactions utilizing 96 well plates and high throughput experimentation (HTE). HTE offers a number of advantages vs. traditional methods for reaction optimization, first amongst these is the ability to evaluate multiple variables in concert. It is well established that the yield of a given reaction is a function of numerous factors which often have interdependent effects on the outcome of a reaction. As a secondary benefit, high throughput experimentation set-ups typically facilitate miniaturization, two main advantages arise from this: (i) reduced waste generation, and (ii) precious material can be conserved with the same amount of said
material being used to generate larger data set. In addition to optimizing the transformation
in question, a secondary end goal was the design and implementation of a “kit” which
would facilitate the rapid evaluation of range of conditions for metallaphotocatalytic HAT
arylation reactions, for previously not substrates previously evaluated when the need arose.
These “kits” are of significant interest in medicinal and process chemistry as they facilitate
rapid access to target drug-compounds, typically in better yield than is achieved using
literature reported conditions, which are invariable optimized for model systems.64

A work flow for the optimization of this triple catalytic HAT arylation protocol is
outlined below. HTE was carried out in 96-well Para-dox™ photoredox optimization
blocks with 1 mL glass vial inserts, under positive pressure nitrogen atmosphere (MBraun
Glovebox). Reaction scale was fixed at 10 μmol of aryl halide in about 50 μL of reaction
solvent to minimize path length for optimal photon flux (<2 mm). Dispense steps were
carried out via handheld pipets, following the general procedure outlined below, but minor
changes were made in each screen to minimize the number of unit operations:

1. A mixture of Ni precursor and ligand in acetonitrile was aged for at least 15 minutes
to generate the precatalyst complex and then dispensed to the block. The acetonitrile
was evaporated using a Genevac vacuum evaporator.

2. Parylene coated magnetic tumble stir bars (V&P Scientific, VP 711D-1) were
dispensed to the block using a stir bar dispensing tool (V&P Scientific, VP 711A-96-
AS-1).

3. A mixture of aryl halide, coupling partner, photocatalyst, quinuclidine, base and additive was prepared in each reaction solvent and dispensed to the block.

4. Two rubber mats and one PFA film were screwed down with a metal lid to prevent solvent evaporation.

5. Illumination was carried out with Lumidox™ 470 nm 96 LED-arrays set to 30 mA output, with tumble stirring (V&P Scientific, VP 710E5), under positive pressure nitrogen atmosphere, for 24 hours. Under these conditions, it was typical for the block temperature to reach 35 °C upon equilibration.

6. A mixture of internal standard in acetonitrile and DMSO was added to the block and the diluted mixtures were sampled into an analysis block containing acetonitrile and analyzed by UPLC-MS.

Our first forays into the development of a method for the arylation of α-hydroxy C–H bonds involved evaluating a large array of potential Lewis acid additives. n-Hexanol and 4-bromobenzotrifluoride where subjected to 10 mol% NiBr$_2$•Me$_4$phen, 1 mol% [Ir(dF(CF$_3$)ppy)$_2$dtbbpy](PF$_6$), stoichiometric quinuclidine (both base and HAT agent), and an equivalent of a Lewis acid additive in 4 solvents, which had been shown to be affect for triple catalytic HAT arylation for other substrate classes (data for DMSO shown in Table 3). A number of Lewis acids drastically affected the reaction profile, in all cases desired product was only observed in DMSO, with zinc halide salts proving to be uniquely effective in affecting the desired C–C coupling, with concomitant complete suppression of C–O bond formation. A number of other Lewis acid completely suppress C–O bond formation, but also shut down C–C bond formation, we attribute this to the fact that very strong Lewis acids will also attenuate the hydricity of the α-hydroxy C–H to such an extent.
that functionalization at this position also does not occur. A careful balance of sufficient C–H hydricity and oxophilicity to suppress nickel-alkoxide formation is required for efficient reactivity.

Table 3. Lewis Acid Additives in triple catalytic C–H arylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis Acid Additive</th>
<th>yield 23°</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeBr₂</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·OEt₂</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BiBr₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CaBr₂</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>CoCl₂</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>GaCl₃</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>InCl₃</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>In(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>La(OTf)₃</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>LaCl₃</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>LuCl₃</td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>MgCl₂</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>MgO</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>ScCl₃</td>
<td>16</td>
</tr>
<tr>
<td>16</td>
<td>SnCl₄</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>Sm(OTf)₃</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>Eu(OTf)₃</td>
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<td>19</td>
<td>Y(OTf)₃</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>Yb(OTf)₃</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>ZnBr₂</td>
<td>48</td>
</tr>
<tr>
<td>22</td>
<td>ZnCl₂</td>
<td>44</td>
</tr>
<tr>
<td>23</td>
<td>ZnO</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>None</td>
<td>3</td>
</tr>
</tbody>
</table>

°Performed with photocatalyst 1 (0.5 mol%), NiBr₂·Me₄phen (0.5 mol%), quinuclidine (100 mol%), ary1 halide (1.0 equiv.), alcohol (5.0 equiv.), additive (1.5 equiv.), on a 10 μmol scale in an 1ml vial in a sealed 96 well plate irradiated from below using DMSO as solvent (0.2 M). Yield determined by UPLC analysis of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

With an appropriate subset of Lewis acids defined, we next evaluated the effect of catalyst and quinuclidine loading on the outcome of the transformation. To our surprise, we rapidly noted that increased quinuclidine loading lead to formation of protodehalogenated and biaryl products, resulting from net reduction 2-electron reduction of the aryl halide coupling partner (Table 4). We rationalize these observations by suggesting high quinuclidine concentration leads to a build-up of the Ir(II) state of the photocatalyst which can facilitate either: (i) slow and direct reduction of the aryl halide coupling partner, or (ii) reduction of a aryl-nickel species. Reduction of the Ni(II)-aryl-halide complex pre-disposes it to protodemettallation, to give the
protodehalogenated product, or oxidative addition with a second equivalent of the aryl halide, and subsequent reductive elimination to deliver the dimer product. Based on these observations, we hypothesized that decreasing the quinuclidine loading and supplanting it as a base with a mild inorganic (and not oxidizable) base would increase the efficacy of these reactions. We also noted that increasing nickel concentrations lead to more formation of the undesirable ether product 26, we postulate that at higher nickel concentrations more of the alkoxide formed in situ resides on the nickel opposed to the Lewis acid additive, and as a result undesirable C–O coupling becomes increasingly competitive. By keeping the nickel concentration low, the equilibrium concentration of Ni-aryl-alkoxide species remains minimal and this undesired reaction does not take place.

With Zn(II) as the optimal Lewis acidic cation, we next evaluated ZnCl₂ and ZnBr₂ as additives with a range of inorganic bases in the presence and absence of water, while keeping the nickel concentration low (Table 5). We quickly identified ZnCl₂ with K₃PO₄ or NaOH as base under anhydrous conditions was the optimal combinations. Further studies demonstrated that ZnCl₂ in conjunction with K₃PO₄ was preferable, due to higher reproducibility and improved functional group tolerance. As a final point of optimization, a range of photoredox catalysts where evaluated (Table 6). The slightly more oxidizing [Ir(F,CF₃(CF₃)ppy)₂dtbbpy](PF₆) (25) proved to be optimal. (E_{1/2}^{red}[^{III}/^{II}] = +1.25 \text{ V vs. SCE in MeCN}), and led to a yield we deemed to be sufficient for our purposes (74% yield). Under these optimized reaction conditions a small amount of oxidized ketone

65. The ground state redox potentials for this catalyst as well as spectrochemical data are available data are detailed in the Supporting Information. Photocatalyst 25 has a similar excited state lifetime vs. photocatalyst 11 (2.0 µs vs. 2.3 µs, respectively).
product 28 is observed, in order to facilitate ease of isolation, this byproduct was reduced with NaBH₄ at the end of the reaction to return it to the alcohol product 23.
Table 4. Catalyst loading studies with ZnCl$_2$ as Lewis acid additive. Desirable results correspond to dark blue, undesirable with mustard yellow.$^a$

$^a$Performed with photocatalyst 1 (variable mol%), NiBr$_2$•Me$_4$phen (variable mol%), quinuclidine (variable mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), zinc chloride (1.0 equiv.), on a 10 μmol scale in an 1ml vial in a sealed 96 well plate irradiated from below using DMSO as solvent (0.2 M). Yield determined by UPLC analysis of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.
Table 5. Evaluation of inorganic bases with Zinc Lewis acid additives with and without water. Desirable results correspond to dark blue, undesirable with mustard yellow.\textsuperscript{a}

\textsuperscript{a}Performed with photocatalyst I (0.5 mol%), NiBr\textsubscript{2}•Me\textsubscript{4}phen (0.5 mol%), quinuclidine (30%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), zinc chloride (1.0 equiv.), with base (1.0 equiv.) on a 10 μmol scale in an 1ml vial in a sealed 96 well plate irradiated from below using DMSO as solvent (0.2 M). Yield determined by UPLC analysis of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.
Table 6. Evaluation of photoredox catalysts for triple catalytic C–H arylation.$^a$

![Photocatalyst diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photoredox Catalyst</th>
<th>% Yield (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td><a href="PF$_6$">Ru(bpy)$_3$</a>$_2$</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>[Ir(ppy)$_3$]$^+$</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Performed with photocatalyst (0.2 mol%), NiBr$_2$•Me$_4$phen (1.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), ZnCl$_2$ (1.5 equiv.), K$_3$PO$_4$ (1.0 equiv.) on a 0.3 mmol scale in an 8 mL vial using DMSO as solvent (0.25 M). Yield determined by UPLC analysis of the crude reaction using an internal standard.

Importantly control experiments demonstrated the importance of all components of the reaction (Table 7, entries 1-6). The reaction, whilst optimal with 5 equivalents of the alcohol coupling partner, can also be performed with lower equivalency of the C–H nucleophile without a significant decrease in efficacy (65% yield with 3 equivalents of hexanol). Finally, as an important control reaction, when an aldehyde equivalent of the alcohol coupling partner is subjected to the optimized reaction conditions, no desired alcohol or ketone coupled product are obtained, indicating the reaction does not likely proceed through the intermediacy of an aldehyde.  

66. An efficient oxidative coupling of alcohols and Aryl triflates proposed to proceed via the intermediacy of the corresponding aldehyde has been reported. Verheyen, T.; van Turnhout, L.;
Table 7. Control experiments for HAT metallaphotoredox cross-coupling.

\[
\begin{align*}
\text{entry} & & \text{control} & & \% \text{ yield (23-26, 28)} \\
1 & & \text{none} & & 74:50 (75\%) \\
2 & & \text{no nickel} & & 0:0:0 \\
3 & & \text{no quinuclidine} & & 0:0:25 \\
4 & & \text{no photocatalyst} & & 0:0:0 \\
5 & & \text{no light} & & 0:0:0 \\
6 & & \text{no ZnCl}_2 & & 0:0:54 \\
\end{align*}
\]

*Performed with photocatalyst 25 (0.2 mol%), NiBr\(2 \cdot \text{Me}_4\text{phen} \) (1.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), ZnCl\(2 \) (1.5 equiv.), K\(3\text{PO}_4 \) (1.0 equiv.) on a 0.3 mmol scale in an 8 mL vial using DMSO as solvent (0.25 M). Yield determined by UPLC analysis of the crude reaction using an internal standard.

To further demonstrate the importance of the Lewis acid additive, the reaction was conducted with varying amounts of the additive (Table 8). In the absence of the additive, exclusive C–O bond formation was observed (entry 1). As the amount of ZnCl\(2 \) was elevated, increasing amounts of the C–C coupled product was formed with diminishing amounts of the ether product (entry 2-7). At 1 equivalent of the additive no C–O bond formation is observed, when the zinc chloride loading is increased to 2 equivalents the efficiency of the reaction is diminished, we attribute this observation to formation of

insoluble zinc alkoxide clusters which do not form with lower loadings of the zinc additive. 67

Table 8. Effect of varying ZnCl₂ concentration on the chemoselectivity under otherwise optimized conditions.

![Chemistry reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>ZnCl₂ Equiv</th>
<th>% yield (23 ether)</th>
<th>C–O vs. C–C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.40</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>20:43</td>
<td>2.15</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>40:15</td>
<td>0.37</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>68:2</td>
<td>0.03</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>70:0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>73:0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>38:0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Performing with photocatalyst 25 (0.2 mol%), NiBr₂·Me₄phen (1.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), additive (1.5 equiv.), base (1.0 equiv.) on a 0.3 mmol scale in an 8 mL vial using DMSO as solvent (0.25 M). Yield determined by UPLC analysis of the crude reaction using an internal standard.

In addition to conditions for the formation of the alcohol product, an oxidative method for the coupling of alcohols and aryl halides to give ketones was also developed (Scheme 17). Herein, we proposed the initial benzylic alcohol product is subsequently engaged in a second round of HAT, wherein the resultant radical is oxidized by molecular oxygen or the photocatalyst to give the ketone product. Efforts to further optimize this transformation where abandoned following the publication of report documenting a similar transformation, 66 and the difficultly in incorporating molecular oxygen into a system which

in predicated on both photoredox and low-valent nickel catalysis, traditionally both of which are incompatible with O₂.

**Scheme 17.** Triple catalytic oxidative coupling of alcohols and aryl halides to give benzylic ketones.

---

V. **Scope of the Coupling of Alcohols and Aryl Halides**

With optimized conditions in hand we next sort to elucidate the scope of this triple catalytic method (Table 9). Aryl halides bearing electron-withdrawing substituents such as trifluoromethyl, carboxymethyl, and sulfonamide, delivered the corresponding benzylic alcohols in excellent yields (23, 32–38, 56–83% yield). Electron-neutral and electron-rich aryl bromides also performed well in this transformation (39–43, 56–70% yield). Importantly, *ortho* and *meta* substitution are tolerated (44 and 45, 44% and 61% yield, respectively). Moreover, 3- and 4-chloropyridines delivered the corresponding heteroarylated alcohols in good efficiency (46–50, 40–74% yield). Interestingly, these substrates required the use of magnesium chloride as the Lewis acid additive. We attribute the improved efficiency observed with heteroarene coupling partners, utilizing magnesium salts to the higher oxophilicity of magnesium compared to zinc.

We next examined the scope of this transformation with respect to the alcohol component. Remarkably, the simplest carbinol, methanol can be employed in this transformation, furnishing the corresponding benzylic alcohol (51, 51% yield). Simple aliphatic alcohols are generally competent substrates for this C–H arylation (23 and 52–54, 63–75% yield). Moreover, deuterated ethanol furnishes the corresponding deuterated-
phenethyl alcohol in good yield (53, 63% yield). Alcohols containing weak benzylic C–H bonds are exclusively functionalized at the α-hydroxy position (55 and 56, 66 and 59% yield, respectively) leaving the weaker benzylic C–H bonds untouched, highlighting the power of this hydricity driven HAT mediated method. In addition, a range of acyclic and cyclic β,β-disubstituted alcohols also perform well (57–60, 49–66% yield), demonstrating some tolerance for steric incumbrance around the forming C–C bond. Pleasingly, a variety of alcohols bearing γ-electron-withdrawing groups also couple efficiently despite the inductive deactivation of the α-hydroxy C–H bonds towards HAT in these substrates (61–62, 56–70% yield). Notably, protected and unprotected diols were competent coupling partners in this transformation furnishing monoarylated products exclusively (64–66, 58–68% yield). Finally, a variety of heteroatom-containing alcohols, which possess multiple hydric C–H bonds, furnished the products with exclusive functionalization at the α-hydroxy C–H position demonstrating the success of our Lewis acid activation mode (67–70, 46–71% yield). Unsurprisingly, subjecting the protected amino-alcohol substrates (deliver 69 and 70) to the optimized reaction conditions with omission of the zinc salt additive leads to formation of a mixture the C–O coupled ether, and α-amino arylated products.
Table 9. Scope of triple catalytic α-hydroxy C–H arylation via metallaphotoredox HAT catalysis in conjunction with Lewis acid induced bond polarization.

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<tr>
<th>Arenes</th>
<th>Native Functionality</th>
<th>Abundant Coupling Partners</th>
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<td><img src="image1.png" alt="Chemical Structures for Various Arenes" /></td>
<td><img src="image2.png" alt="Native Functionality" /></td>
<td><img src="image3.png" alt="Abundant Coupling Partners" /></td>
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<tr>
<th>Heteroarenes</th>
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<tr>
<th>Alcohols</th>
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<tr>
<td><img src="image5.png" alt="Chemical Structures for Various Alcohols" /></td>
<td><img src="image2.png" alt="Native Functionality" /></td>
<td><img src="image3.png" alt="Abundant Coupling Partners" /></td>
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α-hydroxy C–H arylation via metallaphotoredox HAT catalysis in conjunction with Lewis acid induced bond polarization.

- Performed with photocatalyst 25 (0.2 mol%), Ni catalyst 24 (1.5 mol%), quinuclidine (30 mol%), aryl halide (1.0 equiv.), alcohol (5.0 equiv.), ZnCl₂ (1.5 equiv.), potassium tribasic phosphate (1.0 equiv.) on a 1.0 mmol scale in an 8 mL vial using DMSO as solvent (0.25 M) for 24 hours, yield after isolation by column chromatography ². MgCl₂, 3 mol% quinuclidine. ³ 1 mol% photocatalyst 25. ⁴ 50 mol% quinuclidine-48 hours. ² 2 mol% photocatalyst 25. ⁵ 5 mol% quinuclidine. ⁶ 20 mol% quinuclidine. ¹ 1:1 mixture of diastereomers. ³ 3.0 equiv. of alcohol. ² 2 mol% Ni catalyst 24.
As further demonstration of the utility of this α-hydroxy C–H arylation protocol, we sought to rapidly prepare the medicinal agent Prozac (Scheme 18). Indeed, subjecting protected N-methyl propanolamine (71) to the optimized coupling conditions with bromobenzene delivered benzylic alcohol 72. The ethereal linkage present in the drug molecule was then constructed utilizing the metallaphotoredox etherification protocol previously developed in the MacMillan laboratory to deliver 73, which following deprotection furnished Prozac•HCl in 50% overall yield in only three steps from a simple, protected amino alcohol. Perhaps most notable is the chemo- and regioselectivity (>20:1) for the desired C–C coupling reaction at the α-alcohol C–H position without ether formation or arylation of the α-amino C–H bonds. This concise synthesis of Prozac highlights the utility of this method, in conjunction with metallaphotoredox catalyzed C–O coupling protocols, to rapidly deliver medicinal agents. Indeed, access to structurally complex ether products of this class can be achieved generally, and was further expanded to the syntheses of; (i) a protected derivative of the structurally related norepinephrine reuptake inhibitor Strattera (74), (ii) a structural isomer of Prozac (75) as well as, (iii) a derivative incorporating Lewis basicity nitrogen containing functionalities (76) (Scheme 18).
VI. HTE KITS for Triple Catalytic C–H Arylation via Metallaphotoredox Catalysis

In addition to the development of this methodology, a series of pre-dosed 24 well plates where developed for scientists in both medicinal and process chemistry at Merck (These pre-dosed plates allow scientists at Merck to rapidly optimize HAT coupling protocols for novel substrates pairs not evaluated in any prior report from our laboratory). For the HAT coupling of C–H nucleophiles, three common photocatalysts and the two most effective bases can be evaluated against two common nickel ligand systems, across two solvents. Two complementary plates for the functionalization of C–H bonds adjacent to alcohols (Figure 4) and amines (Figure 5) where developed based on the differing reaction conditions reported for these protocols. With these “kits” in hand, end users throughout the Merck chemistry division can then simple prepare mixture of starting material, base, and

additive in solvent, and dispense them to the photocatalysts plate. The prepared mixtures of nickel complex can then also be re-dissolved and subsequently added. Once all the components are present, the plates can be sealed, agitated and illuminated under inert atmosphere. Dilution, sampling, and UPLC analysis can then be rapidly performed to identify optimal catalysts and reagent combinations for a given coupling.

**Figure 4.** HTE kit for arylation of alcohol C–H bonds via metallaphotoredox HAT catalysis.

**Figure 5.** HTE kit for α-amino or α-oxy arylation.
VII. Conclusions

By using photoredox catalysis, nickel catalysis, and hydrogen atom transfer catalysis in conjunction with a novel Lewis acid activation mode, we have developed a general strategy for the direct arylation of \( \text{C}_{\text{sp}}^3 \)-H bonds adjacent to alcohols. This induced bond polarity paradigm represents a powerful method for the simultaneous activation of certain hydridic C–H bonds towards abstraction by electrophilic abstracting agents and the deactivation of others. As an added benefit to existing selective C–H functionalization protocols, which have leveraged deactivation of \( \alpha \)-amino C–H bonds by Lewis acid coordination, this strategy also facilitates activation of \( \alpha \)-hydroxy C–H bonds, thereby providing extremely high levels of selectivity. Furthermore, due to the use of an oxophilic Lewis acid additive, nickel-metallaphotoredox catalyzed C–O coupling is completely suppressed, an observation we attribute to inhibited formation of a nickel-aryl-alkoxide complex, required for C–O bond formation. This transformation represents a further testament to the unique reactivity afforded by merging photoredox catalysis with transition metal catalyzed reaction manifolds. As alcohols represent an incredibly versatile and useful function group we believe this transformation will be of significant utility to practitioners of synthetic organic chemistry, to demonstrate one potential application of the method, the psychoactive medical agents Prozac and Strattera, and well as a series of novel analogues were readily prepared in three steps from commercial materials.

In addition the scope of this transformation was found to be broad with respect to the aryl halides coupling partner, tolerating electron rich, electron deficient, and heterocyclic aromatic ring systems. A diverse array of alcohol C–H nucleophiles can also be employed in this transformation, including those baring potentially competitive reactive sites such as
benzylic, α-ethereal and α-amino C–H bonds. We have disclosed these findings in a recently published report,\textsuperscript{69} our report has subsequently been highlighted in a number of reviews in this area as a transformation of interest to both academic and pharmaceutical chemists.\textsuperscript{70} In addition to developing a novel method for C–H arylation of alcohol nucleophiles, a platform for the rapid evaluation of range of conditions for C–H coupling protocols for novel substrate pairings was developed and has recently been described in a separate publication and is currently in use at Merck.\textsuperscript{68}

VIII. Supporting Information

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I. General Information

Commercial reagents were purified prior to use following the guidelines of Perrine and Armarego.\textsuperscript{71} Ir[dF(CF\textsubscript{3})ppy\textsubscript{2}(dtbbpy)PF\textsubscript{6} and Ir[FCF\textsubscript{3}(CF\textsubscript{3})ppy\textsubscript{2}(dtbbpy)PF\textsubscript{6} were prepared using literature procedures.\textsuperscript{54} Regent grade dimethyl sulfoxide (99.7+%) was purchased from Acros Organics in AcroSeal\textsuperscript{®} containers over 4Å molecular sieves and was used as received. All other solvents were purified per the method of Grubbs.\textsuperscript{72} Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath set to 25 °C. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel per the method of Still.\textsuperscript{73} Thin-layer chromatography (TLC) was performed on Supelco 200 micron aluminium foil backed 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\textsuperscript{-1}). \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 126 MHz) instrument, and are internally referenced to residual protic solvent signals (note: CDCl\textsubscript{3} referenced at δ 7.26 and 77.16 ppm respectively, D\textsubscript{6}-Acetone references at δ 2.05 and ppm 29.84 ppm respectively, D\textsubscript{6}-DMSO reference at δ 2.50 and 39.52 ppm respectively). High temperature \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a Varian Inova 400 and are internally referenced to residual protic solvent signals. Data for \textsuperscript{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 \textsuperscript{13}C NMR are reported in terms of chemical

shift and no special nomenclature is used for equivalent carbons. In instances where
coupling to heteronuclei is observed $^{13}$C NMR are reported as follows: chemical shift
($\delta$ ppm), multiplicity ($s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet), and
coupling constant (Hz). $^{19}$F NMR spectra were redored on a Bruker NanoBay 300 (282
MHz) instrument, and are referenced to CF3Cl ($\delta 0.00$ ppm). 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). High-resolution mass
spectra were obtained at Princeton University mass spectrometry facilities. Gas
chromatography (GC) was performed on an Agilent 6890 Series chromatograph with split-
mode capillary injection and FID detection. Ultra-high performance liquid chromatography
(UPLC) was performed on a Waters ACQUITY UPLC H-Class System with an ACQUITY
QDa detector.

II. Preparation of Photocatalyst

![Chemical Structure]

2-(2-fluoro-4-(trifluoromethyl)phenyl)-5-(trifluoromethyl)pyridine Under air, a three-
neck round-bottom flask, equipped with a magnetic stir bar, was charged with (2-fluoro-
(4-trifluoromethyl)phenyl) boronic acid (15.59 g, 75.0 mmol, 1.5 equiv), THF (75 mL),
water (25 mL) and Na$_2$CO$_3$ (13.82 g, 100.0 mmol, 2.0 equiv). The flask was equipped with
a reflux condenser and placed under nitrogen before 2-bromo-5-(trifluoromethyl) pyridine
(11.30 g, 50.0 mmol, 1.0 equiv) and (2-Dicyclohexylphosphine-2’,4’,6’-triisopropyl-1,1’-
biphneyl)[2-(2’-amino-1,1’-biphenyl)]palladium(II) methanesulfonate (XPhos Pd G3) (212 mg, 0.250 mmol, 0.005 equiv) were added. Nitrogen was bubbled through the solution with stirring for 30 mins then the reaction flask was placed under nitrogen. The colorless mixture was heated to reflux for 12 hours then cooled to room temperature. Finally the mixture was diluted with Et₂O (100 mL) and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with ether (2 x 50 mL). The ethereal solution was washed with water then brine, followed by drying over MgSO₄. Filtration and removal of volatile solvent yielded a colorless solid. Column chromatography (silica gel, 0-2% EtOAc in hexanes) yielded the pure product as a white solid (12.68 g, 41.0 mmol, 82% yield).

**Synthesis of Ir[CF₃CF(CF₃)ppy]₂(dtbbpy)PF₆**

![Chemical Structure](image)

{Ir[FCF₃(CF₃)ppy]₂Cl}₂ Under air, a three-neck round-bottom flask, equipped with a Teflon coated magnetic stir bar, was charged with 2-(2-fluoro-4-(trifluoromethyl)phenyl)-5-(trifluoromethyl)pyridine (12.68 g, 41.0 mmol, 2.25 equiv) and IrCl₃•H₂O (5.77 g, 18.2 mmol, 1.0 equiv) and 2/1 mixture of 2-ethoxyethanol/water (180 mL). The flask was equipped with a reflux condenser and nitrogen was bubbled through the solution with stirring for an hour before the mixture was heated at 120 °C for 24 hours. Upon cooling to room temperature, water was added then the solid was isolated by filtration. Washing with
cold Et₂O yielded Ir[FCF₃(CF₃)ppy]₂Cl₂ as a bright yellow solid (12.49 g, 7.4 mmol, 81% yield). This complex was carried over to the next step without purification.

**Ir[FCF₃(CF₃)ppy]₂-(dtbbpy)PF₆ (25)** Under air, a round-bottom flask, equipped with a Teflon coated magnetic stir bar, and reflux condenser was charged with {Ir[FCF₃(CF₃)ppy]₂Cl₂ (12.59 g, 7.46 mmol, 1.0 equiv), 4,4’-di-tertbutyl-2,2’-bipyridine (4.40 g, 16.41 mmol, 2.2 equiv) and ethylene glycol (150 mL). Nitrogen was bubbled through the solution at 60 °C for 1h before the mixture was placed under nitrogen and heated to 200 °C in a sand bath for 24h. The mixture was allowed to cool to room temperature and then water (600 mL) was added. The resultant aqueous layer was washed with hexanes in order to remove unreacted bipyridine ligand (3x150ml). The aqueous layer was then transferred to a round-bottom flask and heated to 80 °C with stirring for 1 hours to remove residual hexanes. The mixture was then cooled to room temperature and then ammonium hexafluorophosphate (42.6g, 261 mmol, 35.0 equiv) dissolved in H₂O (120ml) was added. The resultant slurry was stirred for 12 hours. The yellow precipitate was isolated by vacuum filtrations, washed with copious quantities of water then sparingly with ethanol and ether which had been cooled to –20 °C in a freezer. The solid was then dried under high vacuum for 12 hours to remove water and residual ethanol. The solid was
dissolved in minimal dichloromethane and the purified by column chromatography (silica gel, 0 to 10% acetone in DCM). The yellow solid obtained was then recrystallized by slow mixing of the product dissolved in a minimal amount of acetone with a large layer of pentane, then left to sit for 24 hours. Filtration and drying in vacuo yielded the pure product as a yellow solid (10.62 g, 8.67 mmol, 58% yield). A second crop of spectroscopically inferior material which performs comparably in the arylation of α-hydroxy C–H bonds via triple metallaphotoredox HAT catalysis can be obtained by taking the resultant supernatant and concentrating in vacuo before repeating the recrystallization procedure.

\( ^1H \text{ NMR (500 MHz, Acetone-}d_6) \delta 8.95 (d, J = 2.0 \text{ Hz, 2H}), 8.79 (dd, J = 8.7, 2.7 \text{ Hz, 2H}), 8.53 (dd, J = 8.8, 2.0 \text{ Hz, 2H}), 8.17 (d, J = 5.9 \text{ Hz, 1H}), 7.98 (s, 2H), 7.79 (dd, J = 6.0, 1.9 \text{ Hz, 2H}), 7.29 (dd, J = 12.5, 1.5 \text{ Hz, 2H}), 1.42 (s, 18H). \)

\( ^{13}C \text{ NMR (126 MHz, Acetone-}d_6) \delta 168.34 (d, J = 6.9 \text{ Hz}), 166.48, 163.34, 161.26, 157.04, 155.42, 147.38 (q, J = 4.7 \text{ Hz}), 138.67 (d, J = 3.4 \text{ Hz}), 135.25 − 135.01 (m), 134.47 (qd, J = 32.0, 8.9 \text{ Hz}), 127.57 (q, J = 34.7 \text{ Hz}), 127.07, 126.57 (d, J = 21.3 \text{ Hz}), 124.66 − 124.40 (m), 123.68, 110.43 − 107.65 (m), 36.72, 30.45. \)

\( ^{19}F \text{ NMR (282 MHz, Acetone-}d_6) \delta -63.72, -63.78, -71.41, -73.92, -110.41 (dd, J = 12.4, 3.0 \text{ Hz}). \)
III. Spectrochemical Data of Photocatalyst 18

Electrochemical Data

Cyclic Voltammetry of photocatalyst 25 was conducted vs. SCE in MeCN utilizing a commercial CH instruments electrochemical workstation. A solution of photocatalyst 25 and tetrabutylammonium hexafluorophosphate (0.1M) as supporting electrolyte where scanned at 100 mVs⁻¹. Photocatalyst 25 was loaded at 1 mM. The experiment was conducted at 21 °C. The working electrode was glassy carbon and the counter electrode was platinum. The pH of the solution was uncorrected.

Figure 6. Cyclic voltammogram of photocatalyst 25 (0.001 M) vs. SCE in MeCN at 21 °C with 0.1 M NBu₄PF₆ as supporting electrolyte.

Redox Couples in MeCN vs. SCE

\[ E_{1/2}^{\text{red}}[\text{Ir(III)/Ir(II)}] = -1.27 \text{ V} \]

\[ E_{1/2}^{\text{red}}[\text{Ir(IV)/Ir(III)}] = +1.78 \text{ V} \]
UV-Vis and Excited State Lifetime Data

Electronic absorption spectra were acquired using a Cary 50 spectrophotometer. Steady-state emission spectra were acquired using a Horiba Fluorolog-3 fluorimeter and corrected for instrumental response using a NIST standard of spectral irradiance (Optronic Laboratories, Inc., OL220 M tungsten quartz lamp).

Absorbance Spectra

Absorption spectra where collected on a $10^{-5}$ M solution of photocatalyst 25 in spectrophotometric grade MeCN in a 1 cm quartz, and degassed before measurements where taken.

Absorption Maxima (nm) – 213, 254, 300, 389.

Emission Spectra

Emission spectra where collected on a $10^{-6}$ M solution of photocatalyst 25 in spectrophotometric grade MeCN, in a 1 cm quartz and where degassed before measurements were taken. The solution was excited utilizing 400 nm light.

Emission Maxima (nm) – 498.

Figure 7. Absorption and Emission Spectra for Photocatalyst 25.
**Calculated Excited State Redox Potentials**

Excited state potentials were estimated utilizing a thermodynamic square scheme.

\[ E_{1/2}^{\text{red}}[\text{Ir(III)/Ir(II)}] = +1.25 \text{ V} \]

\[ E_{1/2}^{\text{red}}[\text{Ir(IV)/Ir(III)*}] = -0.74 \text{ V} \]
Excited State Lifetime Measurement

The excited state lifetime of photocatalyst 25 was measured on a Horiba Scientific DeltaFlex™ Modular Fluorescence Lifetime System. The sample was prepared in a glovebox (10^{-5} M in MeCN) and was pulsed with light with a peak wavelength of 406 nm. Emission was measured at a peak of 498 nm with a pulse interval of 26000 ns. Data was then converted to the time axis and fitted (MATLAB) to the following equation.

\[
\log(\text{Photon Count}) = mt + c.
\]

In the linear portion of the curve.

\[
M = -0.000493 \quad \text{Lifetime} = 2028 \text{ ns}.
\]

**Figure 8.** Time resolved phosphorescence intensity spectra for photocatalyst 25.
IV. Procedure for Optimization Studies

To an oven-dried 8 mL vial equipped with a cross shaped stir bar was added: anhydrous zinc chloride – which was stored in a glovebox to preserve self-life (61 mg, 0.45 mmol, 1.5 equiv), anhydrous potassium phosphate tribasic – which was stored in a glovebox to preserve self-life (64 mg, 0.3 mmol, 1 equiv), 4-bromobenzotrifluoride (68 mg, 42 μL, 0.3 mmol, 1 equiv.), and n-hexanol (153 mg, 188 μL, 1.5 mmol, 5.0 equiv.). The vial was sealed and placed under nitrogen. To a separate vial was added NiBr$_2$•glyme (13.1 mg, 45 μmol, 0.15 equiv.), and 3,4,7,8-tetramethyl-1,10-phenanthroline (10.6 mg, 45 μmol, 0.15 equiv). The catalyst vial was sealed, purged with nitrogen then to it was added 6.0 mL of dimethyl sulfoxide. The pre-catalyst (24) solution was sonicated or stirred for 10 minutes, after which, 0.6 mL of the solution (1.5 mol% catalyst, 45 μmol, 0.015 equiv.) was syringed into the reaction vessel (The remainder can be stored to set up parallel reactions, if less stock solution is required the amount prepared can be appropriately reduced). To a separate vial was added Ir[FCF$_3$(CF$_3$)ppy]$_2$-(dtbbpy)PF$_6$ (7.3 mg, 6.0 μmol, 0.02 equiv.) (photocatalyst 25) and quinuclidine (100 mg, 0.9 mmol, 3.0 equiv). The catalyst vial was sealed, purged with nitrogen then to it was added 6 mL of dimethyl sulfoxide. The catalyst solution was sonicated or stirred for 10 minutes, after which, 0.6 mL of the solution (0.2 mol% catalyst, 0.6 μmol, 0.002 equiv.) was syringed into the reaction vessel (The remainder can be stored to set up parallel reactions, if less stock solution is required the amount prepared can be appropriately reduced). The reaction mixture was degassed by sparging with nitrogen while stirring for 15 min before sealing the vial with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (6 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 24 hours. The
reaction was quenched by addition of saturated ammonium chloride solution (4mL) and EtOAc (2mL). 1,3-Benzodioxole (internal standard, 20.00 μL, 0.19 mmol, 0.65 equiv.) was added then the reaction mixture was analyzed by GC and 1H NMR.

V. Procedure for Optimization Studies via HTE

Representative Procedure. To a 96-well photoredox optimization block (Analytical Sales and Services) with 1ml glass vial inserts (Analytical Sales and Services) in a nitrogen filled glove box, was dispensed solutions of NiBr$_2$glyme and tetramethylphenanthroline (0.05μmol, 0.002M, 25μl) in acetonitrile (0.05μmol, 0.002M, 25μl). The blocks were then aged for 15 minutes and the solvent was then evaporated under vacuum (Genevac), before addition of stirbars. Then, 50 μl of a solution of aryl bromide (10μmol, 0.20M), hexanol (50μmol, 1.00M), [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (0.05μmol, 0.001M), K$_3$PO$_4$ (10 mol, 0.20M), zinc chloride (15μmol, 0.30M) and quinuclidine (2.5μmol, 0.05M) in dimethyl sulfoxide was dispensed to the vials. The plate was then sealed with a screw driver and irradiated with a 96-LED array (Analytical Sales and Services) at 470nm for 24 hours at 37°C in a nitrogen filled glove box, efficient agitation was achieved utilizing a tumble stirrer (V&P Scientific). The block was then diluted with a solution of tetramethoxybenzene in acetonitrile (1μmol, 0.002M, 500μl) and sampled (25μl) into an HPLC collection block pre-filled with acetonitrile (700μl). The HPLC collection block was then analyzed utilizing UPLC-MS analysis and yields were determined with respect to tetramethoxybenzene utilizing calibration curves.

Changes where made to this procedure in order to minimize the number of operations for each variable that was evaluated.
VI. Representative procedures for the arylation of α-hydroxy C–H bonds via triple metallaphotoredox HAT catalysis

For non-heteroaryl bromides

To an 8 mL vial equipped with a stir bar was added photocatalyst Ir[FCF₃(CF₃)ppy]₂(dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv.), anhydrous zinc chloride – which was stored in a glovebox to preserve self-life (204 mg, 1.5 mmol, 1.5 equiv), anhydrous potassium phosphate tribasic – which was stored in a glovebox to preserve self-life (212 mg, 1.0 mmol, 1 equiv.) 4-bromobenzotrifluoride (225 mg, 140 μL, 1.0 mmol, 1 equiv.) and n-hexanol (630 μL, 5.0 mmol, 5.0 equiv.). The vial was sealed and placed under nitrogen before 3mL of dimethyl sulfoxide was added. To a separate vial was added NiBr₂•glyme (5.1 mg, 0.0165 mmol, 0.0165 equiv.) and 3,4,7,8-tetramethyl-1,10-phenanthroline (3.9 mg, 0.0165 mmol, 0.0165 equiv). The catalyst vial was sealed, purged with nitrogen then to it was added 1.1 mL of dimethyl sulfoxide. The pre-catalyst solution was sonicated or stirred for 10 minutes, after which, 1.0 mL of the solution (1.5 mol% catalyst, 0.015 mmol, 0.0015 equiv.) was syringed into the reaction vessel. The solution was degassed by sparging with nitrogen while stirring for 10 minutes before sealing with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (6 cm away, with cooling fan to keep the reaction temperature at 25 ºC) for 24 hours. The reaction mixture was then transferred to a 40 mL vial and diluted with methanol (5 mL) and dichloromethane (10 mL) and cooled to 0 ºC utilizing a water ice bath. NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) was added with stirring in order to reduce oxidized product to the desired benzylic alcohol. The mixture
was held at 0 °C and stirred for one hour before the slow addition of chilled saturated ammonium chloride solution (30 mL). The mixture was then transferred to a separatory funnel and the organic layer isolated. The aqueous layer was then further extracted with dichloromethane (3x20 mL). The combined organic layer was washed with saturated aqueous sodium chloride, dried over MgSO₄ and concentrated in vacuo. The residue was taken up in minimal dichloromethane and purified by column chromatography.

For heteroaryl chlorides

To an 8 mL vial equipped with a stir bar was added photocatalyst Ir[CF₃(CF₃)ppy]₂(dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), quinuclidine (3.4 mg, 0.03 mmol, 0.03 equiv.), anhydrous magnesium chloride – which was stored in a glovebox to preserve self-life (190 mg, 2.0 mmol, 2.0 equiv), anhydrous potassium phosphate tribasic – which was stored in a glovebox to preserve self-life (212 mg, 1.0 mmol, 1 equiv.) 4-chloro-2-fluoropyridine (132 mg, 100μL, 1.0 mmol, 1 equiv.) and n-hexanol (630 μL, 5.0 mmol, 5.0 equiv.). The vial was sealed and placed under nitrogen before 3mL of dimethyl sulfoxide was added. To a separate vial was added Ni(NO₃)₂•6H₂O (4.8 mg, 0.0165 mmol, 0.0165 equiv.) and 3,4,7,8-tetramethyl-1,10-phenanthroline (3.9 mg, 0.0165 mmol, 0.0165 equiv). The catalyst vial was sealed, purged with nitrogen then to it was added 1.1 mL of dimethyl sulfoxide. The pre-catalyst solution was sonicated or stirred for 10 minutes, after which, 1.0 mL of the solution (1.5 mol% catalyst, 0.015 mmol, 0.005 equiv.) was syringed into the reaction vessel. The solution was degassed by sparging with nitrogen while stirring for 10 minutes before sealing with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (6 cm away, with cooling fan to keep the
reaction temperature at 25 °C) for 24 hours. The reaction mixture was then transferred to a 40 mL vial and diluted with methanol (5 mL) and dichloromethane (10 mL) and cooled to 0 °C utilizing a water ice bath. NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) was added with stirring in order to reduce oxidized product to the desired benzylic alcohol. The mixture was held at 0 °C and stirred for one hour before the slow addition of 1M aqueous NaOH solution (10 mL). The mixture was then filtered through celite and subsequently transferred to a separatory funnel, and the organic layer isolated. The aqueous layer was then further extracted with dichloromethane (3x20 mL). The combined organic layer was washed with saturated aqueous sodium chloride, dried over MgSO₄ and concentrated *in vacuo*. The residue was taken up in minimal dichloromethane and purified by column chromatography.

**VII. Aryl Halide Scope**

![Image of 1-(4-(trifluoromethyl)phenyl)hexan-1-ol (23)](image_url)

**1-(4-(trifluoromethyl)phenyl)hexan-1-ol (23)**

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂(dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂-glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the
general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a clear oil (185 mg, 0.75 mmol, 75% yield).

**IR (film)** \( \nu_{\text{max}} \) 3340, 2959, 2933, 2861, 1621, 1417, 1380, 1323, 1163, 1121, 1066, 1016, 925, 839, 734, 678 cm\(^{-1}\).

**H NMR (500 MHz, CDCl\(_3\))** \( \delta \) 7.60 (d, \( J = 7.9 \) Hz, 2H), 7.46 (d, \( J = 7.8 \) Hz, 2H), 4.74 (t, \( J = 6.4 \) Hz, 1H), 1.74 (dtq, \( J = 29.0, 9.4, 4.9, 3.8 \) Hz, 2H), 1.52 – 1.34 (m, 1H), 1.30 (d, \( J = 4.1 \) Hz, 6H), 0.97 – 0.74 (m, 3H).

**C NMR (126 MHz, CDCl\(_3\))** \( \delta \) 148.98, 129.74 (q, \( J = 32.3 \) Hz), 126.27, 125.49 (q, \( J = 3.8 \) Hz), 124.31 (q, \( J = 271.9 \) Hz), 74.18, 39.38, 31.79, 25.45, 22.69, 14.16.

**F NMR (282 MHz, CDCl\(_3\))** \( \delta \) –62.44.

**HRMS (EI-GC-QTOF)** m/z calcd. for C\(_{13}\)H\(_{17}\)F\(_3\)O ([M]\(^{+}\)) 246.12315, found 246.12319.

**methyl 4-(1-hydroxyhexyl)benzoate (32)**

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \( \mu \)mol, 0.002 equiv.), NiBr\(_2\)•glyme (4.6 mg, 15 \( \mu \)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \( \mu \)mol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), \( n \)-hexanol (511 mg, 628 \( \mu \)L, 5.0 mmol, 5.0 equiv.), methyl 4-bromobenzoate (215 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in
hexanes) yielded the pure product as a white solid (174 mg, 0.74 mmol, 74% yield).

**IR (film)** $\nu_{\text{max}}$ 3468, 2954, 2930, 2858, 1722, 1611, 1575, 1504, 1436, 1408, 1278, 1193, 1177, 1101, 1018, 964, 859, 770, 708 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.3$ Hz, 2H), 4.67 (dd, $J = 7.6, 5.6$ Hz, 1H), 3.84 (s, 3H), 1.82 – 1.55 (m, 2H), 1.34 (dddd, $J = 12.8, 8.2, 6.5, 4.6$ Hz, 1H), 1.27 – 1.12 (m, 6H), 0.95 – 0.64 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.11, 150.19, 129.90, 129.36, 125.93, 74.35, 52.24, 39.30, 31.80, 25.46, 22.69, 14.16.

**HRMS (ESI-TOF)** m/z calcd. for C$_{14}$H$_{21}$O$_3$ ([M+H]$^+$) 237.14852, found 237.14644.

![5-((1-hydroxyhexyl)phthalide (33)](image)

5-((1-hydroxyhexyl)phthalide (33)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 5-bromophthalide (213 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (168 mg, 0.71 mmol, 71% yield).

**IR (film)** $\nu_{\text{max}}$ 3493, 3955, 2937, 2857, 1755, 1688, 1619, 1454, 1427, 1357, 1319, 1275,
1206, 1153, 1110, 1045, 1001, 894, 844, 776, 683 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.63 (d, J = 7.9 \text{ Hz}, 1\text{H}), 7.23 (d, J = 7.9 \text{ Hz}, 1\text{H}), 7.01 (s, 1\text{H}), 5.06 (s, 2\text{H}), 4.58 (dd, J = 7.6, 5.4 \text{ Hz}, 1\text{H}), 1.59 – 1.38 (m, 2\text{H}), 1.24 – 1.12 (m, 1\text{H}), 1.08 – 1.00 (m, 5\text{H}), 0.70 – 0.53 (m, 3\text{H}).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 171.09, 152.11, 147.18, 127.15, 125.89, 125.02, 119.36, 74.29, 69.78, 39.67, 31.76, 25.43, 22.68, 14.15.\)

HRMS (ESI-TOF) \(m/z\) calcd. for C\(_{14}\)H\(_{19}\)O\(_3\) ([M+H]\(^+\)) 235.13287, found 235.13270.

\begin{center}
\begin{tikzpicture}
\node {\includegraphics[width=0.1\textwidth]{5-hydroxyhexyl-benzenitrile.png}};
\end{tikzpicture}
\end{center}

\textbf{5-(1-hydroxyhexyl)benzonitrile (34)}

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \(\mu\)mol, 0.002 equiv.), NiBr\(_2\)·glyme (4.6 mg, 15 \(\mu\)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \(\mu\)mol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), \(n\)-hexanol (511 mg, 628 \(\mu\)L, 5.0 mmol, 5.0 equiv.), 4-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30\% EtOAc in hexanes) yielded the pure product as a clear oil (113 mg, 0.56 mmol, 56\% yield).

\textbf{IR (film)} \(\nu_{\max}\) 3434, 2956, 2930, 2859, 2229, 1609, 1504, 1465, 1407, 1378, 1251, 1202, 1112, 1054, 1018, 925, 834, 727 \(\text{cm}^{-1}\)
\[ ^1H \text{NMR (500 MHz, CDCl}_3 \] \delta 7.63 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 4.74 (p, \ J = 4.0 Hz, 1H), 1.94 (d, J = 3.5 Hz, 1H), 1.71 (dddt, J = 28.9, 14.2, 9.9, 4.9 Hz, 2H), 1.41 (t, J = 8.6 Hz, 1H), 1.29 (d, J = 4.7 Hz, 5H), 0.87 (t, 3H, J = 6.2).

\[ ^13C \text{NMR (126 MHz, CDCl}_3 \] \delta 150.35, 132.41, 126.66, 119.03, 111.25, 74.02, 39.37, 31.74, 25.35, 22.67, 14.14.

HRMS (ESI-TOF) m/z calcd. for C\textsubscript{13}H\textsubscript{18}NO ([M+H]\textsuperscript{+}) 204.13829, found 204.13797.

\[ \text{IR (film) } \nu_{\text{max}} 3476, 2928, 2857, 1694, 1599, 1465, 1407, 1298, 1182, 1149, 1088, 958, 835, 772, 727, 686 \text{ cm}^{-1}. \]

1-(4-(methylsulfonyl)phenyl)hexan-1-ol (35)

Prepared following the general procedure outlined above using Ir[CF\textsubscript{3}(CF\textsubscript{3})ppy]\textsubscript{2} (dtbbpy)PF\textsubscript{6} (2.4 mg, 2.0 \mu\text{mol}, 0.002 equiv.), NiBr\textsubscript{2}•glyme (4.6 mg, 15 \mu\text{mol}, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \mu\text{mol}, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 \mu\text{L}, 5.0 mmol, 5.0 equiv.), 1-bromo-4-(methylsulfonyl)benzene (235 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\textsubscript{4} (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–40% EtOAc in hexanes) yielded the pure product as a white solid (186 mg, 0.73 mmol, 73% yield).

IR (film) \( \nu_{\text{max}} \) 3476, 2928, 2857, 1694, 1599, 1465, 1407, 1298, 1182, 1149, 1088, 958, 835, 772, 727, 686 cm\textsuperscript{-1}.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 4.78 (t, $J = 6.5$ Hz, 1H), 3.05 (s, 3H), 1.83 – 1.61 (m, 2H), 1.48 – 1.35 (m, 1H), 1.36 – 1.17 (m, 6H), 1.02 – 0.67 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.40, 139.46, 127.67, 126.89, 73.94, 44.69, 39.46, 31.75, 25.38, 22.68, 14.15.

HRMS (ESI-TOF) m/z calcd. for C$_{13}$H$_{21}$O$_3$S ([M+H]$^+$) 256.11332, found 256.11445.

1-(4-(trifluoromethoxy)phenyl)hexan-1-ol (36)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), $n$-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 1-bromo-4-(trifluoromethoxy)benzene (241 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (217 mg, 0.83 mmol, 83% yield).

IR (film) $\nu_{\text{max}}$ 3347, 2958.6, 2932, 2860, 1683, 1597, 1510, 1465, 1421. 1380, 1255, 1213, 1158, 1057, 1018, 922, 850, 814, 726, 676 cm$^{-1}$.
**1H NMR (500 MHz, CDCl\textsubscript{3})** δ 7.37 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.81 – 4.55 (m, 1H), 1.96 – 1.59 (m, 3H), 1.41 (dq, J = 11.5, 4.0, 3.6 Hz, 1H), 1.29 (q, J = 5.0 Hz, 5H), 0.87 (t, J = 6.2 Hz, 3H).

**13C NMR (126 MHz, CDCl\textsubscript{3})** δ 148.54 (q, J = 2.2 Hz), 143.73, 127.39, 121.07, 120.61 (q, J = 256.9 Hz), 74.08, 39.35, 31.80, 25.55, 22.70, 14.16.

**19F NMR (282 MHz, CDCl\textsubscript{3})** δ –57.89.

**HRMS (EI-QTOF)** m/z calcd. for C\textsubscript{13}H\textsubscript{17}F\textsubscript{3}O\textsubscript{2} ([M\textsuperscript{+}]\textsuperscript{+}) 262.11806, found 262.11644.

![Image of a chemical structure](image-url)

**1-(4-chlorophenyl)hexan-1-ol (37)**

Prepared following the general procedure outlined above using Ir[FCF\textsubscript{3}(CF\textsubscript{3})ppy]\textsubscript{2} (dtbbpy)PF\textsubscript{6} (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr\textsubscript{2}•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 1-bromo-4-chlorobenzene (191 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\textsubscript{4} (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a white solid (156 mg, 0.74 mmol, 74% yield).

**1H NMR (500 MHz, CDCl\textsubscript{3})** δ 7.50 – 7.01 (m, 4H), 4.57 (dd, J = 7.5, 5.8 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.59 (ddt, J = 13.4, 10.1, 5.4 Hz, 1H), 1.42 – 1.25 (m, 1H), 1.21 (m, 6H), 0.86 – 0.74 (m, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 143.48, 133.18, 128.67, 127.41, 74.13, 39.26, 31.80, 25.51, 22.70, 14.16.

Spectroscopic data matched that previously reported.$^{74}$

4-(1-hydroxyhexyl)benzenesulfonamide (38)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzenesulfonamide (235 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–50% EtOAc in hexanes) yielded the pure product as a white solid (154 mg, 0.60 mmol, 60% yield).

IR (film) $\nu_{\text{max}}$ 3351, 3276, 3246, 2954, 2929, 2858, 1601, 1538, 1465, 1409, 1334, 1302, 1170, 1148, 1093, 1054, 1038, 1018, 991, 913, 900, 831, 755, 711 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 4.87 (s, 2H), 4.76 (dd, $J = 7.6$, 5.5 Hz, 1H), 1.92 – 1.62 (m, 2H), 1.49 – 1.35 (m, 1H), 1.34 – 1.19 (m, 6H), 0.99 – 0.81 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 150.34, 140.85, 126.74, 126.69, 73.99, 39.42, 31.76, 25.38, 22.69, 14.16.

HRMS (ESI-TOF) m/z calcd. for C$_{12}$H$_{20}$NO$_3$S ([M+H]$^+$) 257.10881, found 257.10854.

1-[(4-methylthio)phenyl]hexan-1-ol (39)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), (4-bromophenyl)(methyl)sulfane (202 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–50% EtOAc in hexanes) yielded the pure product as a white solid (143 mg, 0.64 mmol, 64% yield).

IR (film) $\nu_{\text{max}}$ 3372, 2954, 2925, 2857, 1599, 1493, 1463, 1436, 1405, 1318, 1182, 1114, 1091, 1032, 1013, 966, 924, 818, 726 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 – 7.14 (m, 4H), 4.55 (dd, $J = 7.4$, 5.9 Hz, 1H), 2.41 (s, 3H), 1.77 – 1.64 (m, 1H), 1.60 (dddd, $J = 13.6$, 10.5, 5.7, 4.2 Hz, 1H), 1.40 – 1.25 (m, 1H), 1.21 (m, 5H), 0.82 – 0.77 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 141.98, 137.51, 126.83, 126.61, 74.42, 39.12, 31.84, 25.61, 22.71, 16.10, 14.18.
HRMS (ESI-TOF) m/z calcd. for C\textsubscript{13}H\textsubscript{21}O\textsubscript{5} ([M+H]\textsuperscript{+}) 224.12349, found 224.12604.

1-(4-chlorophenyl)hexan-1-ol (40)

Prepared following the general procedure outlined above using Ir[FCF\textsubscript{3}(CF\textsubscript{3})ppy\textsubscript{2} (dtbbpy)PF\textsubscript{6} (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr\textsubscript{2}•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 1-bromo-4-methoxybenzene (187 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\textsubscript{4} (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (120 mg, 0.58 mmol, 58% yield).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.63 – 4.59 (m, 1H), 3.80 (s, 3H), 1.90 – 1.71 (m, 2H), 1.71 – 1.57 (m, 1H), 1.39 (dddd, J = 11.4, 10.1, 7.3, 5.3 Hz, 1H), 1.34 – 1.16 (m, 5H), 0.89 – 0.84 (m, 3H).

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 159.10, 137.21, 127.28, 113.91, 74.45, 55.41, 39.09, 31.87, 25.73, 22.73, 14.19.

Spectroscopic data matched that previously reported.\textsuperscript{75}

**1-phenylhexan-1-ol (41)**

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂ (dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂-glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), bromobenzene (157 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (118 mg, 0.66 mmol, 66% yield).

**1H NMR (500 MHz, CDCl₃)** δ 7.34–7.31 (m, 4H), 7.26–7.23 (m, 1H), 4.61 (t, J=7.0 Hz, 1H), 1.80–1.64(m, 2H), 1.42–1.28 (m, 6H), 0.86 (m, 3H).

**13C NMR (126 MHz, CDCl₃)** δ 145.06, 128.56, 127.61, 126.02, 74.86, 39.22, 31.87, 25.66, 22.72, 14.19.

Spectroscopic data matched that previously reported.⁷⁶⁵

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**1-(4-tert-butyl)phenyl)hexan-1-ol (42)**

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂

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(dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 1-bromo-4-(tert-butyl)benzene (213 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a white solid (163 mg, 0.70 mmol, 70% yield).

**IR (film)** ν max 3355, 2958, 2944, 2861, 1597, 1509, 1464, 1280, 1255, 1216, 1158, 1054, 1037, 1017, 922, 851, 814, 727, 676 cm⁻¹.

**¹H NMR (500 MHz, CDCl₃)** δ 7.39 – 7.35 (m, 2H), 7.30 – 7.26 (m, 2H), 4.64 (dd, J = 7.7, 5.7 Hz, 1H), 1.87 – 1.63 (m, 3H), 1.32 (m, 14H), 0.94 – 0.82 (m, 3H).

**¹³C NMR (126 MHz, CDCl₃)** δ 150.56, 142.11, 125.75, 125.47, 74.64, 39.08, 34.66, 31.91, 31.51, 25.80, 22.75, 14.21.

**HRMS (ESI-TOF)** m/z calcd. for C₁₆H₂₇O ([M+H]⁺) 235.39045, found 235.39039.

![1-(p-tolyl)hexan-1-ol](image)

**1-(p-tolyl)hexan-1-ol (43)**

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂ (dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a white solid (163 mg, 0.70 mmol, 70% yield).

**IR (film)** ν max 3355, 2958, 2944, 2861, 1597, 1509, 1464, 1280, 1255, 1216, 1158, 1054, 1037, 1017, 922, 851, 814, 727, 676 cm⁻¹.

**¹H NMR (500 MHz, CDCl₃)** δ 7.39 – 7.35 (m, 2H), 7.30 – 7.26 (m, 2H), 4.64 (dd, J = 7.7, 5.7 Hz, 1H), 1.87 – 1.63 (m, 3H), 1.32 (m, 14H), 0.94 – 0.82 (m, 3H).

**¹³C NMR (126 MHz, CDCl₃)** δ 150.56, 142.11, 125.75, 125.47, 74.64, 39.08, 34.66, 31.91, 31.51, 25.80, 22.75, 14.21.

**HRMS (ESI-TOF)** m/z calcd. for C₁₆H₂₇O ([M+H]⁺) 235.39045, found 235.39039.
equiv.), 1-bromo-4-methylbenzene (171 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (107 mg, 0.56 mmol, 56% yield).

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.23 (d, \( J = 8.0 \) Hz, 2H), 7.16 (d, \( J = 8.0 \) Hz, 2H), 4.63 (dd, \( J = 7.5, 5.9 \) Hz, 1H), 2.35 (s, 3H), 1.86 – 1.60 (m, 2H), 1.47 – 1.35 (m, 1H), 1.31 – 1.22 (m, 6H), 0.89 – 0.85 (m, 3H).

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3 \] \( \delta \) 142.10, 137.29, 129.24, 125.99, 77.16, 39.15, 31.89, 25.72, 22.73, 21.27, 14.20.

Spectroscopic data matched that previously reported.⁷⁶

1-(o-tolyl)hexan-1-ol (44)

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂ (dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂-glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.300 mmol, 0.3 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 1-bromo-2-methylbenzene (171 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined.
in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (84 mg, 0.44 mmol, 44% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.47 (dd, $J$ = 7.7, 1.4 Hz, 1H), 7.23 (td, $J$ = 7.5, 1.6 Hz, 1H), 7.17 (td, $J$ = 7.3, 1.5 Hz, 1H), 7.15 – 7.11 (m, 1H), 4.93 (dd, $J$ = 7.9, 4.9 Hz, 1H), 2.32 (s, 3H) 1.81 – 1.60 (m, 3H), 1.56 – 1.44 (m, 1H), 1.40 – 1.24 (m, 5H), 0.93 – 0.83 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 143.24, 134.57, 130.48, 127.23, 126.41, 125.22, 70.88, 38.28, 31.91, 25.91, 22.77, 19.23, 14.20.

Spectroscopic data matched that previously reported.77

![Chemical Structure](image)

1-(3-(trifluoromethyl)phenyl)hexan-1-ol (45)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33 mg, 0.30 mmol, 0.3 equiv), $n$-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 3-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a clear oil (151 mg, 0.61 mmol, 61% yield).

**IR (film)** $\nu_{\text{max}}$ 3340, 2957, 2931, 2861, 1702, 1616, 1451, 1326, 1163, 1071, 902, 803, 726, 703, 663 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 2.0$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 1H), 4.74 (dd, $J = 7.8$, 5.5 Hz, 1H), 1.85 – 1.60 (m, 2H), 1.48 – 1.37 (m, 1H), 1.35 – 1.23 (m, 6H), 0.94 – 0.76 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 146.03, 130.86 (q, $J = 32.1$ Hz), 129.37, 128.97, 124.37 (q, $J = 3.8$ Hz), 124.30 (q, $J = 272.3$ Hz), 122.79 (q, $J = 3.8$ Hz), 74.21, 39.39, 31.77, 25.50, 22.68, 14.14.

$^{19}$F NMR (282 MHz, CDCl$_3$) –62.58.

HRMS (EI-GC-QTOF) m/z calcd. for C$_{13}$H$_{17}$F$_3$O ([M]$^+$) 246.12315, found 246.12296.

1-(6-(trifluoromethyl)pyridin-3-yl)hexan-1-ol (46)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), Ni(NO$_3$)$_3$•6H$_2$O (4.4 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (3.3 mg, 30 μmol, 0.03 equiv), $n$-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 5-chloro-2-(trifluoromethyl)pyridine (181 mg, 1.0 equiv.), anhydrous magnesium chloride (210 mg, 2.0 mmol, 2.0 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (145 mg, 0.59 mmol, 59% yield).
IR (film) \( \nu_{\text{max}} \) 3364, 2958, 2932, 2861, 1583, 1464, 1398, 1249, 1176, 1135, 1085, 1027, 933, 850, 781, 742, 678 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.66 (d, \( J = 2.0 \) Hz, 1H), 7.88 (dd, \( J = 8.1, 2.0 \) Hz, 1H), 7.67 (d, \( J = 8.1 \) Hz, 1H), 4.84 – 4.81 (m, 1H), 2.25 (s, 1H), 1.84 – 1.65 (m, 2H), 1.42 (dq, \( J = 13.6, 5.3, 3.7 \) Hz, 1H), 1.36 – 1.24 (m, 5H), 0.90 – 0.85 (m, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 148.16, 147.31 (q, \( J = 34.6 \) Hz), 143.54 (d, \( J = 1.2 \) Hz), 134.92, 121.68 (q, \( J = 273.9 \) Hz), 120.39 (d, \( J = 5.5 \) Hz), 71.91, 39.40, 31.68, 25.26, 22.65, 14.12.

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) –67.77.

HRMS (ESI-TOF) m/z calcd. for C\(_{12}\)H\(_{17}\)F\(_3\)NO ([M+H]\(^+\)) 247.11840, found 247.11842.

1-(2-fluoropyridin-4-yl)hexan-1-ol (47)

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \( \mu \)mol, 0.002 equiv.), NiNO\(_3\)•6H\(_2\)O (4.4 mg, 15 \( \mu \)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \( \mu \)mol, 0.015 equiv.), quinuclidine (3.3 mg, 30 \( \mu \)mol, 0.03 equiv), \( n \)-hexanol (511 mg, 628 \( \mu \)L, 5.0 mmol, 5.0 equiv.), 4-chloro-2-fluoropyridine (131 mg, 1.0 mmol, 1.0 equiv.), anhydrous magnesium chloride (210 mg, 2.0 mmol, 2.0 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (144 mg, 0.74 mmol, 74% yield).
IR (film) $v_{\text{max}}$ 3353, 2956, 2931, 2866, 1613, 1569, 1480, 1467, 1408, 1276, 1230, 1149, 1112, 1062, 1002, 953, 915, 874, 839, 782, 726, 702, 660 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.13 (d, $J = 5.2$ Hz, 1H), 7.13 (d, $J = 5.2$ Hz, 1H), 6.93 (s, 1H), 4.75 – 4.71 (m, 1H), 2.42 (d, $J = 3.5$ Hz, 1H), 1.70 (ddt, $J = 13.7$, 10.5, 6.8 Hz, 2H), 1.51 – 1.18 (m, 6H), 0.87 (t, $J = 6.6$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 164.20 (d, $J = 238.9$ Hz), 160.32 (d, $J = 7.3$ Hz), 147.56 (d, $J = 14.8$ Hz), 118.74 (d, $J = 3.9$ Hz), 106.56 (d, $J = 37.5$ Hz), 72.75 (d, $J = 3.0$ Hz), 38.96, 31.69, 25.13, 22.64, 14.12.

$^{19}$F NMR (282 MHz, CDCl$_3$) $^{19}$F NMR (282 MHz, Chloroform- d) $\delta$ –68.20.

HRMS (ESI-TOF) m/z calcd. for C$_{11}$H$_{17}$FNO ([M+H]$^+$) 197.12159, found 197.12154.

1-(2-(trifluoromethyl)pyridin-4-yl)hexan-1-ol (48)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiNO$_3$•6H$_2$O (4.4 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (3.3 mg, 30 μmol, 0.03 equiv), n-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 4-chloro-2-(trifluoromethyl)pyridine (181 mg, 1.0 equiv.), anhydrous magnesium chloride (210 mg, 2.0 mmol, 2.0 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (182 mg, 0.74 mmol, 74% yield).
IR (film) $v_{\text{max}}$ 3356, 2952, 2933, 2862, 1610, 1567, 1429, 1326, 1278, 1245, 1179, 1083, 933, 903, 852, 760, 726, 712, 687, 671 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.62 (d, $J = 5.0$ Hz, 1H), 7.68 (d, $J = 1.5$ Hz, 1H), 7.45 (dd, $J = 5.1$, 1.5 Hz, 1H), 4.78 (t, $J = 6.4$ Hz, 1H), 2.60 (s, 1H), 1.77 – 1.65 (m, 2H), 1.51 – 1.20 (m, 6H), 0.90 – 0.84 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 156.29, 149.99, 148.40 (q, $J = 34.4$ Hz), 123.62 (q, $J = 1.2$ Hz), 121.68 (q, $J = 274.3$ Hz), 117.79 (q, $J = 2.8$ Hz), 72.77, 39.11, 31.64, 25.18, 22.62, 14.09.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ – 67.93.

HRMS (ESI-TOF) m/z calcd. for C$_{12}$H$_{17}$F$_3$NO ([M+H]$^+$) 247.11840, found 247.11855.

4-(1-hydroxyhexyl)picolinonitrile (49)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv NiNO$_3$•6H$_2$O (4.4 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (3.3 mg, 30 μmol, 0.03 equiv), $n$-hexanol (511 mg, 628 μL, 5.0 mmol, 5.0 equiv.), 4-chloropicolinonitrile (138 mg, 1.0 equiv.), anhydrous magnesium chloride (210 mg, 2.0 mmol, 2.0 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (82 mg, 0.40 mmol, 40% yield).
IR (film) $\nu_{\text{max}}$ 3374, 2955, 2930, 2859, 2237, 1738, 1378, 1229, 1217, 1116, 1056, 1024, 925, 848, 781, 761, 728 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.67 (d, $J = 2.1$ Hz, 1H), 7.85 (dd, $J = 8.0, 2.1$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 4.83 (dd, $J = 7.8, 5.3$ Hz, 1H), 2.21 (s, 1H), 1.82 – 1.67 (m, 2H), 1.48 – 1.37 (m, 1H), 1.36 – 1.29 (m, 5H), 0.91 – 0.86 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 149.35, 144.31, 134.42, 132.71, 128.42, 117.39, 71.82, 39.38, 31.64, 25.19, 22.64, 14.11.

HRMS (ESI-TOF) m/z calcd. for C$_{12}$H$_{17}$N$_2$O ([M+H]$^+$) 204.12626, found 204.12636.

1-(2-methylpyridin-4-yl)hexan-1-ol (50)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 µmol, 0.002 equiv.), Ni(NO$_3$)$_3$•6H$_2$O (4.4 mg, 15 µmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 µmol, 0.015 equiv.), quinuclidine (3.3 mg, 30 µmol, 0.03 equiv), $n$-hexanol (511 mg, 628 µL, 5.0 mmol, 5.0 equiv.), 4-chloro-2-methylpyridine (128 mg, 1.0 equiv.), anhydrous magnesium chloride (210 mg, 2.0 mmol, 2.0 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (81 mg, 0.42 mmol, 42% yield).

IR (film) $\nu_{\text{max}}$ 3460, 2955, 2929, 2859, 2353, 2268, 1631, 1562, 1490, 1456, 1381, 1298, 1184, 1129, 1062, 1038, 932, 836, 734, 693 cm$^{-1}$.
$^1$H NMR (500 MHz, CDCl$_3$) δ 8.63 (d, $J = 6.1$ Hz, 1H), 7.34 (d, $J = 1.8$ Hz, 1H), 7.23 (dd, $J = 6.2$, 1.8 Hz, 1H), 4.76 (t, $J = 6.3$ Hz, 1H), 2.73 (s, 3H), 2.20 (s, 1H), 1.70 (dt, $J = 11.9$, 6.8 Hz, 2H), 1.44 – 1.21 (m, 6H), 0.89 – 0.87 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.13, 157.65, 148.68, 123.67, 119.64, 72.43, 38.93, 31.64, 25.06, 22.81, 22.62, 14.12.

HRMS (ESI-TOF) m/z calcd. for C$_{12}$H$_{20}$NO ([M+H]$^+$) 193.14666, found 193.1469.

VIII. Alcohol Scope

![Image of alcohol structure]

(4-(trifluoromethyl)phenyl)methanol (51)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), methanol (160 mg, 202 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–40% EtOAc in hexanes) yielded the pure product as a clear oil (90 mg, 0.51 mmol, 51% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 7.9$ Hz, 2H), 4.79 (d, 1H), 1.99 (t, 1H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.83 (q, $J = 1.5$ Hz), 129.89 (q, $J = 32.3$ Hz), 126.96, 125.59 (q, $J = 3.8$ Hz), 124.28 (q, $J = 271.9$ Hz), 64.62.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ – 62.49.

Spectroscopic data matched that previously reported.  

![Chemical structure](image)

1-(4-(trifluoromethyl)phenyl)ethan-1-ol (52)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), ethanol (230 mg, 292 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (142 mg, 0.75 mmol, 75% yield).

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 7.9$ Hz, 2H), 7.48 (d, $J = 7.9$ Hz, 2H), 4.96 (q, $J = 6.6$ Hz, 1H), 2.03 (s, 1H), 1.50 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 149.81 (q, $J = 1.4$ Hz), 129.73 (q, $J = 32.4$ Hz), 125.77, 125.57 (q, $J = 3.8$ Hz), 124.28 (q, $J = 272.0$ Hz), 69.96, 25.54.

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$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ – 62.46.

Spectroscopic data matched that previously reported. 76

1-(4-(trifluoromethyl)phenyl)ethan-1,2,2,2-$d_4$-1-ol (53)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), $d_6$-ethanol (255 mg, 292 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotri fluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (123 mg, 0.63 mmol, 63% yield).

IR (film) $\nu_{max}$ 3340, 2941, 2267, 2233, 1621, 1410, 1323, 1162, 1110, 1066, 1047, 1014, 953, 932, 852, 816, 758, 704 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 149.74, 129.72 (q, $J = 32.3$ Hz), 125.78, 125.56 (q, $J = 3.8$ Hz), 124.28 (q, $J = 272.0$ Hz), 70.04 – 68.92 (m), 24.51 (dp, $J = 38.8$, 19.3 Hz).

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ – 62.46.

HRMS (GC-EI-QTOF) m/z calcd. for $C_9H_5D_4F_3O$ ([M]$^+$) 194.08566, found 194.08623.
1-(4-(trifluoromethyl)phenyl)decan-1-ol (54)

Prepared following the general procedure outlined above using Ir[FCF_3(CF_3)ppy]_2(dtbbpy)PF_6 (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr_2:glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), n-decanol (791 mg, 955 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH_4 (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–15% EtOAc in hexanes) yielded the pure product as a clear oil (221 mg, 0.73 mmol, 73% yield).

**IR (film)** ν_{max} 3342, 2925, 2855, 1689, 1620, 1466, 1416, 1324, 1164, 1125, 1067, 1016, 842, 722, 681, 658 cm⁻¹.

**¹H NMR (500 MHz, CDCl₃)** δ 7.60 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.74 (dd, J = 7.6, 5.6 Hz, 1H), 1.94 (s, 1H), 1.84 – 1.63 (m, 2H), 1.47 – 1.34 (m, 1H), 1.34 – 1.18 (m, 13H), 0.87 (t, J = 6.9 Hz, 3H).

**¹³C NMR (126 MHz, CDCl₃)** 148.98 (q, J = 1.3 Hz), 129.73 (q, J = 32.3 Hz), 126.27, 125.49 (q, J = 3.8 Hz), 124.41 (q, J = 271.9 Hz), 74.18, 39.41, 32.01, 29.67, 29.66, 29.60, 29.43, 25.77, 22.82, 14.26.

**¹⁹F NMR (282 MHz, CDCl₃)** δ – 62.44.

**HRMS (GC-EI-QTOF)** m/z calcd. for C₁₇H₂₄F₃O ([M⁺]⁺) 302.18575, found 302.18512.
3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (55)

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂ (dtbbpy)PF₆ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr₂•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), 3-phenylpropan-1-ol (681 mg, 680 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a clear oil (185 mg, 0.66 mmol, 66% yield).

$^1$H NMR (500 MHz, CDCl₃) δ 7.61 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.29 (dd, $J = 8.5$, 6.8 Hz, 2H), 7.24 – 7.16 (m, 3H), 4.77 (dd, $J = 8.0$, 5.1 Hz, 1H), 2.86 – 2.61 (m, 2H), 2.24 – 1.96 (m, 2H), 1.92 (s, 1H).

$^{13}$C NMR (126 MHz, CDCl₃) δ 148.65 (q, $J = 1.5$ Hz), 141.45, 129.91 (q, $J = 32.3$ Hz), 128.64, 128.55, 126.29, 126.19, 125.59 (q, $J = 3.8$ Hz), 124.26 (q, $J = 271.9$ Hz), 73.32, 40.73, 32.00.

$^{19}$F NMR (282 MHz, CDCl₃) δ – 62.47.

Spectroscopic data matched that previously reported. ⁷⁹

2-(4-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (56)

Prepared following the general procedure outlined above using \( \text{Ir}[\text{FCF}_3(\text{CF}_3)\text{ppy}]_2 \) (dtbbpy)PF_6 (12 mg, 10.0 \( \mu \)mol, 0.01 equiv.), NiBr_2•glyme (4.6 mg, 15 \( \mu \)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \( \mu \)mol, 0.015 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), 2-(4-chlorophenyl)ethan-1-ol (681 mg, 680 \( \mu \)L, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 48 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a white solid (176 mg, 0.59 mmol, 59% yield).

**IR (film)** \( \nu_{\text{max}} \) 3606, 3449, 2922, 3051, 1617, 1492, 1408, 1321, 1159, 1121, 1110, 1102, 1087, 1060, 1013, 881, 839, 803, 760, 738, 714, 674 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.60 (d, \( J = 8.1 \) Hz, 2H), 7.44 (d, \( J = 8.0 \) Hz, 2H), 7.27 (d, \( J = 8.4 \) Hz, 2H), 7.10 (d, \( J = 8.4 \) Hz, 2H), 4.94 (ddd, \( J = 8.0, 5.2, 2.8 \) Hz, 1H), 3.11 – 2.86 (m, 2H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 147.51 (q, \( J = 1.4 \) Hz), 135.86, 132.88, 131.01, 130.05 (q, \( J = 32.4 \) Hz), 128.83, 126.31, 125.55 (q, \( J = 3.8 \) Hz), 124.22 (q, \( J = 272.0 \) Hz), 74.71, 45.40.

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) – 62.45.

**HRMS (GC-EI-QTOF)** Molecular ion peak not observed. m/z calcd. for C\(_8\)H\(_6\)F\(_3\)O
([Fragment S1]) 175.03653, found 175.03849. m/z calcd. for C7H6Cl ([Fragment S2])
125.01525, found 125.01703.

2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (57)

Prepared following the general procedure outlined above using Ir[FCF3(CF3)ppy]2
dtbbpy)PF6 (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr2•glyme (4.6 mg, 15 μmol, 0.015
equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.),
quiniuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), isobutanol (371 mg, 462 μL, 5.0 mmol, 5.0
equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride
(204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0
equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture
was reduced with NaBH4 (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the
general procedure. Purification by column chromatography (0–30% EtOAc in hexanes)
yielded the pure product as a clear oil (120 mg, 0.55 mmol, 55% yield).

1H NMR (500 MHz, CDCl3) δ 7.60 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 4.47 (d,
J = 6.3 Hz, 1H), 2.08 – 1.81 (m, 2H), 0.97 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 147.62, 129.69 (q, $J$ = 32.3 Hz), 126.96, 125.23 (q, $J$ = 3.8 Hz), 124.33 (q, $J$ = 271.9 Hz), 79.31, 35.46, 19.03, 17.86.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ – 62.43.

Spectroscopic data matched that previously reported. 80

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\text{cyclopentyl(4-(trifluoromethyl)phenyl)methanol (58)}
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Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 $\mu$mol, 0.002 equiv.), NiBr$_2$glyme (4.6 mg, 15 $\mu$mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 $\mu$mol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), isobutanol (371 mg, 462 $\mu$L, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a clear oil (162 mg, 0.66 mmol, 66% yield).

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J$ = 8.0 Hz, 2H), 7.46 (d, $J$ = 8.0 Hz, 2H), 4.50 (d, $J$ = 8.1 Hz, 1H), 2.19 (h, $J$ = 8.2 Hz, 1H), 1.97 (s, 1H), 1.85 (dtd, $J$ = 11.8, 7.3, 4.2 Hz, 1H), 1.73 – 1.44 (m, 5H), 1.39 (dtd, $J$ = 11.7, 7.7, 4.0 Hz, 1H), 1.31 – 1.12 (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 148.29 (q, $J$ = 1.5 Hz), 129.64 (q, $J$ = 32.3 Hz), 126.73, 125.26 (q, $J$ = 3.8 Hz), 124.18 (q, $J$ = 271.9 Hz), 78.28, 47.75, 29.34, 29.12, 25.44, 25.41.

$^{19}$F NMR (282 MHz, CDCl$_3$) δ – 62.44.

Spectroscopic data matched that previously reported.  

\[\text{Cyclobutyl(4-(trifluoromethyl)phenyl)methanol (59)}\]

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (24 mg, 20.0 μmol, 0.02 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), cyclobutylmethanol (431 mg, 472 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 48 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a white solid (113 mg, 0.49 mmol, 49% yield).

**IR (film)** $\nu_{\text{max}}$ 3410, 2942, 2866, 1708, 1687, 1619, 1413, 1322, 1162, 1118, 1066, 1016, 986, 843, 787, 759, 731 cm$^{-1}$.

**$^1$H NMR (500 MHz, CDCl$_3$)** δ 7.58 (d, $J = 7.9$ Hz, 2H), 7.43 (d, $J = 7.9$ Hz, 2H), 4.64 (d, $J = 7.7$ Hz, 1H), 2.60 (m, 2H), 2.10 – 1.72 (m, 6H).

**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ 147.13 (d, $J = 1.5$ Hz), 129.76 (q, $J = 32.4$ Hz), 126.50, 125.39 (q, $J = 3.8$ Hz), 124.2 (q, $J = 272.0$ Hz), 77.74, 42.63, 24.63, 24.39, 17.83.

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\(^{19}\text{F NMR (282 MHz, CDCl}_3\) \(\delta = 62.47.\)

**HRMS (GC-EI-QTOF)** m/z calcd. for C\(_{12}\)H\(_{13}\)F\(_3\)O ([M]+) 230.09185, found 230.09214.

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\text{\(\text{OH}\)}
\]

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\begin{array}{c}
\text{F}_3\text{C} \\
\text{F}
\end{array}
\]

\((4,4\text{-difluorocyclohexyl})(4\text{-}(\text{trifluoromethyl})\text{phenyl})\text{methanol (60)}\)

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \(\mu\)mol, 0.002 equiv.), NiBr\(_2\)•glyme (4.6 mg, 15 \(\mu\)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \(\mu\)mol, 0.015 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), (4,4-difluorocyclohexyl)methanol (751 mg, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20\% EtOAc in hexanes) yielded the pure product as a white solid (171 mg, 0.58 mmol, 58\% yield).

**IR (film)** \(\nu_{\text{max}}\) 3353, 3275, 2965, 2933, 2874, 2856, 1621, 1452, 1416m 1381, 1361m 1320, 1275, 1261, 1241, 1213, 1203, 1169, 1130, 1115, 1105, 1064, 1041, 1017, 989, 961, 928, 878, 837, 854, 832, 810, 779, 764, 743, 699, 657 cm\(^{-1}\).

**\(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta \)** 7.62 (d, \(J = 8.0\) Hz, 2H), 7.43 (d, \(J = 8.0\) Hz, 2H), 4.51 (d, \(J = 7.0\) Hz, 1H), 2.14 (dddt, \(J = 13.6, 10.0, 6.7, 3.4\) Hz, 1H), 2.05 (dtq, \(J = 13.6, 6.4, 3.3\) Hz, 2H), 1.97 (s, 1H), 1.65 (dddt, \(J = 43.6, 22.1, 13.6, 8.2, 4.4\) Hz, 3H), 1.51 – 1.24 (m, 3H).
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta 147.02\) (q, \(J = 1.4\) Hz), \(130.06\) (q, \(J = 3.8\) Hz), \(124.05\) (q, \(J = 272.0\) Hz), \(123.35\) (dd, \(J = 242.2, 239.4\) Hz), \(77.46\) (d, \(J = 2.6\) Hz), \(43.09\) (d, \(J = 1.5\) Hz), \(33.21\) (ddd, \(J = 242.2, 239.4\) Hz), \(25.01\) (dd, \(J = 93.5, 9.9\) Hz).

\(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \(\delta -62.51\) (s, 3H), \(-91.84\) (d, \(J = 235.6\) Hz, 1H), \(-102.53\) (dt, \(J = 237.7, 35.1\) Hz, 1H).

HRMS (GC-EI-QTOF) m/z calcd. for \(\text{C}_{14}\text{H}_{15}\text{F}_5\text{O} ([M]^+)\) 294.10432, found 294.10439.

3-fluoro-1-(4-(trifluoromethyl)phenyl)propan-1-ol (61)

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy\]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \(\mu\)mol, 0.002 equiv.), NiBr\(_2\)glyme (4.6 mg, 15 \(\mu\)mol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 \(\mu\)mol, 0.015 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), 3-fluoropropan-1-ol (390 mg, 375 \(\mu\)L, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 48 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (125 mg, 0.56 mmol, 56% yield).

IR (film) \(\nu_{\text{max}}\) 3412, 2969, 2388, 2318, 2270, 1621, 1465, 1419, 1323, 1242, 1163, 1116, 1095, 1066, 1034, 1016, 983, 895, 837, 787 756, 732, 675, 658 cm\(^{-1}\).

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\(^1\text{H NMR (500 MHz, CDCl}_3)\) δ 7.63 (d, \(J = 7.9\) Hz, 2H), 7.50 (d, \(J = 7.9\) Hz, 2H), 5.08 – 4.92 (m, 1H), 4.71 (ddddd, \(J = 47.2, 9.5, 7.0, 4.6\) Hz, 1H), 4.53 (ddt, \(J = 46.9, 9.7, 5.2\) Hz, 1H), 2.18 (s, 1H), 2.16 – 1.96 (m, 2H).

\(^{13}\text{C NMR (126 MHz, CDCl}_3)\) δ 148.05 (q, \(J = 1.5\) Hz), 130.11 (q, \(J = 32.4\) Hz), 126.15, 125.72 (q, \(J = 3.8\) Hz), 124.21 (q, \(J = 272.0\) Hz), 81.35 (d, \(J = 163.6\) Hz), 70.54 (d, \(J = 4.1\) Hz), 39.77 (d, \(J = 19.0\) Hz).

\(^{19}\text{F NMR (282 MHz, CDCl}_3)\) –62.52, –221.03 – –221.87 (m).

HRMS (GC-EI-QTOF) m/z calcd. for C\(_{10}\)H\(_{10}\)F\(_4\)O ([M\(^+\)]\(^+\)) 222.06678, found 222.06653.

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\begin{align*}
\text{4,4,4-trifluoro-1-(4-(trifluoromethyl)phenyl)propan-1-ol (62)}
\end{align*}
\]

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr\(_2\)-glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), 4,4,4-trifluorobutan-1-ol (640 mg, 528 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (191 mg, 0.70 mmol, 70% yield).

IR (film) \(\nu_{max}\) 3373, 2946, 1621, 1453, 1418. 1391, 1326, 1254, 1223, 1166, 1123, 1068,
1H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 7.9$ Hz, 2H), 4.93 – 4.79 (m, 1H), 2.38 – 2.11 (m, 2H), 2.09 – 1.89 (m, 3H).

13C NMR (126 MHz, CDCl$_3$) $\delta$ 147.56 (d, $J = 1.5$ Hz), 130.39 (q, $J = 32.5$ Hz), 127.25 (q, $J = 276.0$ Hz), 126.12, 125.83 (q, $J = 3.8$ Hz), 124.13 (q, $J = 272.1$ Hz), 72.34, 31.39 (q, $J = 2.8$ Hz), 30.15 (q, $J = 29.2$ Hz).

19F NMR (282 MHz, CDCl$_3$) $\delta$ –62.58 (s, 3F), –66.18 (t, $J = 10.7$ Hz, 3F).

HRMS (GC-EI-QTOF) m/z calcd. for C$_{11}$H$_{10}$F$_6$O ([M]$^+$) 272.06358, found 272.06283.

2-cyclopropyl-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (63)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), 2-cyclopropylethan-1-ol (431 mg, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (165 mg, 0.72 mmol, 72% yield).

IR (film) $\nu_{\text{max}}$ 3371, 3079, 3003, 2923, 1620, 1464, 1418, 1323, 1162, 1118, 1066, 1016, 983, 966, 918, 843, 823, 754, 746, 705, 675, 656 cm$^{-1}$.  

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$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.1$ Hz, 2H), 4.86 (t, $J = 6.6$ Hz, 1H), 1.69 – 1.63 (m, 2H), 0.76 – 0.64 (m, 1H), 0.55 – 0.40 (m, 2H), 0.18 – 0.01 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 148.65 (q, $J = 1.4$ Hz), 129.72 (q, $J = 32.3$ Hz), 126.28, 125.43 (q, $J = 3.8$ Hz), 123.32 (q, $J = 272.0$ Hz), 74.58, 44.36, 7.59, 4.66, 4.03.

$^{19}$F NMR (282 MHz, CDCl$_3$) –62.43.

HRMS (GC-EI-QTOF) m/z calcd. for C$_{12}$H$_{13}$F$_3$O ([M]$^+$) 230.08997, found 230.09130.

1-(4-(trifluoromethyl)phenyl)propane-1,3-diol (64)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (5.6 mg, 0.05 mmol, 0.05 equiv.), propane-1,3-diol (380 mg, 359 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–40% EtOAc in hexanes) yielded the pure product as a colorless oil (127 mg, 0.58 mmol, 58% yield).

IR (film) $\nu_{\text{max}}$ 3333, 2930, 1621, 1417, 1323, 1162, 1114, 1065, 1016, 896, 837, 760, 732, 659 cm$^{-1}$. 
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J$ = 8.1 Hz, 2H), 7.49 (d, $J$ = 8.0 Hz, 2H), 5.04 (dd, $J$ = 8.2, 4.2 Hz, 1H), 3.89 (dd, $J$ = 6.3, 4.7 Hz, 2H), 2.06 – 1.88 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 148.39 (q, $J$ = 1.4 Hz), 129.81 (q, $J$ = 32.4 Hz), 126.05, 125.57 (q, $J$ = 3.8 Hz), 124.27 (q, $J$ = 271.9 Hz), 73.89, 61.58, 40.48.

$^{19}$F NMR (282 MHz, CDCl$_3$) –62.46.

HRMS (GC-EI-QTOF) m/z calcd. for C$_{10}$H$_{11}$F$_3$O$_2$ ([M]$^+$) 220.07057, found 220.07194.

Spectroscopic data matched that previously reported.

3-((tert-butyldimethylsilyl)oxy)-1-(4-(trifluoromethyl)phenyl)propan-1-ol (65)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), 3-((tert-butyldimethylsilyl)oxy)propan-1-ol$^{83}$ (952 mg, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–20% EtOAc in hexanes) yielded the pure product as a colorless oil (217 mg, 0.65 mmol, 65% yield).


IR (film) $\nu_{\text{max}}$ 3421, 2954, 2886, 1620, 1473, 1390, 1362, 1324, 1256, 1163, 1124, 1066, 1017, 973, 939, 871, 832, 811, 776, 725, 662 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 5.02 (t, $J = 5.8$ Hz, 1H), 3.89 – 3.85 (m, 2H), 2.04 – 1.85 (m, 2H), 0.93 (s, 9H), 0.10 (d, $J = 4.3$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 148.66 (q, $J = 1.3$ Hz), 129.44 (q, $J = 32.3$ Hz), 126.06, 125.35 (q, $J = 3.8$ Hz), 124.38 (q, $J = 271.9$ Hz), 73.98, 62.46, 40.45, 25.97, 18.25, -5.45.

$^{19}$F NMR (282 MHz, CDCl$_3$) –62.46.

HRMS (ESI-TOF) m/z calcd. for C$_{16}$H$_{25}$F$_3$NaO$_2$Si ([M+Na]$^+$) 334.15759, found 334.15940.

![Chemical structure](image)

3-methyl-1-(4-(trifluoromethyl)phenyl)butane-1,3-diol (66)

Prepared following the general procedure outlined above using Ir[FC$_3$(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$•glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (22.2 mg, 0.2 mmol, 0.2 equiv), 3-methylbutane-1,3-diol (521 mg, 534 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a white solid (169 mg, 0.68 mmol, 68%
yield).

**IR (film)** $v_{\text{max}}$ 3339, 2975, 2935, 1621, 1405, 1385, 1323, 1271, 1211, 1161, 1120, 1107, 1065, 1017, 909, 847, 828, 779, 739, 692, 671 cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 5.22 – 4.87 (m, 1H), 1.91 (dd, $J = 14.7$, 11.1 Hz, 1H), 1.67 (dd, $J = 14.7$, 2.1 Hz, 1H), 1.46 (s, 3H), 1.29 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $^{13}$C NMR $\delta$ 148.86 (q, $J = 1.5$ Hz), 129.65 (q, $J = 32.3$ Hz), 126.05, 125.50 (q, $J = 3.8$ Hz), 124.31 (q, $J = 271.9$ Hz), 72.30, 71.78, 50.55, 32.31, 27.72.

$^{19}$F NMR (470 MHz, CDCl$_3$) –62.41.

**HRMS (GC-EI-QTOF)** Molecular ion peak not observed. m/z calcd. for C$_3$H$_7$F$_3$O ([Fragment S1]$^+$) 175.03653, found 175.03773. m/z calcd. for C$_3$H$_7$O ([Fragment S3]$^+$) 59.04914, found 59.04994.
(S)-2,2-dimethyl-1,3-dioxolan-4-yl)(4-(trifluoromethyl)phenyl)methanol (67)

Prepared following the general procedure outlined above using Ir[FCF$_3$(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr$_2$·glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (661 mg, 643 μL, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH$_4$ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the product as a 1:1 mixture of diastereomers in the form of a colorless oil (165 mg, 0.60 mmol, 60% yield).

**IR (film)** $\nu_{\text{max}}$ 3438, 2988, 2941, 2878, 1620, 1456, 1417, 1372, 1324, 1245, 1216, 1160, 1119, 1064, 1016, 983, 881, 842, 790, 763, 737, 674 cm$^{-1}$.

**$^1$H NMR (500 MHz, CDCl$_3$)** $\delta$ 7.61 (dd, $J = 8.3$, 3.4 Hz, 2H), 7.49 (t, $J = 8.9$ Hz, 2H), 5.05 (dt, $J = 7.9$, 3.9 Hz, 0.5H), 5.01 (dd, $J = 8.0$, 4.8 Hz, 0.5H), 4.38 – 4.22 (m, 1H), 4.09 (m, 1H), 3.74 – 3.53 (m, 1H), 1.47 (d, $J = 5.5$ Hz, 3H), 1.38 (d, $J = 14.1$ Hz, 3H).

**$^{13}$C NMR (126 MHz, CDCl$_3$)** $\delta$ 148.40 (q, $J = 1.4$ Hz), 148.07 (q, $J = 1.5$ Hz), 129.78 (qd, $J = 32.4$, 11.0 Hz), 126.15, 125.97, 125.53 (p, $J = 3.8$ Hz), 125.51 (qd), 109.94, 109.46, 75.73, 73.27, 73.21, 71.18, 69.76, 69.40, 27.10, 27.06, 25.88, 25.74.

**$^{19}$F NMR (282 MHz, CDCl$_3$)** –62.45.
HRMS (GC-EI-QTOF) m/z calcd. for C_{13}H_{15}F_{3}O_{3} ([M]^{+}) 276.09678, found 276.09461.

![Chemical Structure]

2-(tetrahydro-2H-pyran-4-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (68)

Prepared following the general procedure outlined above using Ir[FCF_{3}(CF_{3})ppy]_{2} (dtbbpy)PF_{6} (2.4 mg, 2.0 μmol, 0.002 equiv.), NiBr_{2•}glyme (4.6 mg, 15 μmol, 0.015 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (3.5 mg, 15 μmol, 0.015 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol (661 mg, 5.0 mmol, 5.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH_{4} (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (0–30% EtOAc in hexanes) yielded the pure product as a colorless oil (195 mg, 0.71 mmol, 71% yield).

IR (film) \( \nu_{\text{max}} \) 3390, 2925, 2848, 1620, 1468, 1443, 1417, 1388, 1323, 1267, 1236, 1162, 1119, 1104, 1065, 1016, 983, 909, 882, 858, 839, 790, 758, 736, 703, 661 cm\(^{-1}\).

\(^{1}\text{H} \text{NMR} \ (500 \text{MHz, CDCl}_{3}) \ \delta \) 7.61 (d, \( J = 8.1 \text{ Hz, 2H} \)), 7.46 (d, \( J = 8.0 \text{ Hz, 2H} \)), 4.85 (dt, \( J = 8.0, 3.3 \text{ Hz, 1H} \)), 4.01 – 3.83 (m, 1H), 3.48 – 3.23 (m, 1H), 2.19 – 2.01 (m, 1H), 1.97 – 1.65 (m, 4H), 1.66 – 1.42 (m, 2H), 1.42 – 1.23 (m, 2H).

\(^{13}\text{C} \text{NMR} \ (126 \text{ MHz, CDCl}_{3}) \ \delta \) 149.07 (q, \( J = 1.4 \text{ Hz} \)), 129.78 (q, \( J = 32.4 \text{ Hz} \)), 126.02, 125.51 (q, \( J = 3.8 \text{ Hz} \)), 124.10 (q, \( J = 271.9 \text{ Hz} \)), 71.03, 67.93, 67.86, 46.46, 33.61, 32.58, 31.62.
\(^{19}\text{F NMR (470 MHz, CDCl}_3\) –62.46. \\
HRMS (GC-El-QTOF) \text{m/z calcd. for C}_{14}\text{H}_{17}\text{F}_3\text{O}_2 ([M]\text{\textsuperscript{+}}) 274.11752, \text{found 274.11855.}

(4-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)piperidin-1-yl)(phenyl)methanone (69)
Prepared following the general procedure outlined above using \text{Ir[FCF}_3\text{(CF}_3\text{)ppy]}\text{2 (dtbbpy)PF}_6\) (2.4 mg, 2.0 \text{\textmu}mol, 0.002 equiv.), \text{NiBr}_2\text{-glyme (6.1 mg, 20 \text{\textmu}mol, 0.02 equiv.),}
3,4,7,8-tetramethyl-1,10-phenanthroline (4.6 mg, 20 \text{\textmu}mol, 0.02 equiv.), quinuclidine (55.7 mg, 0.5 \text{mmol, 0.5 equiv}), (4-(2-hydroxyethyl)piperidin-1-yl)(phenyl)methanone (700 mg, 3.0 \text{mmol, 3.0 equiv.}), 4-bromobenzotri fluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 \text{mmol, 1.5 equiv.}), anhydrous potassium phosphate (212 mg, 1.0 \text{mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with \text{NaBH}_4\) (42 mg, 1.1 \text{mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (10–100% EtOAc in hexanes) yielded the pure product as a colorless oil (219 mg, 0.58 \text{mmol, 58% yield}).

\text{IR (film) } \nu_{\text{max}} 3380, 2924, 2860, 1608, 1576, 1498, 1467, 1443, 1372, 1323, 1281, 1160, 1113, 1065, 1016, 978, 966, 926, 892, 842, 787, 758, 732, 708, 698, 611 \text{ cm}^{-1}. \\
\text{\textsuperscript{1}H NMR (500 MHz, CD}_2\text{Cl}_2\) } \delta 7.60 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.43 – 7.29 (m, 5H), 4.81 (bs, 1H), 4.60 (bs, 1H), 3.82 – 3.52 (m, 1.3H), 3.11 – 2.84 (m, 1H), 2.71 (bs 1.7H), 2.01 – 1.42 (m, 6H), 1.23 (2H).
\(^{13}\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 170.42, 150.33, 137.12, 130.15, 129.58, 127.79, 127.29, 126.63, 125.82 (q, \(J = 3.8\) Hz), 124.87 (q, \(J = 271.8\) Hz). 71.37, 60.31, 48.42, 46.48, 42.76, 39.68, 33.32.

\(^{19}\)F NMR (470 MHz, CD\(_2\)Cl\(_2\)) –62.65.

HRMS (ESI-TOF) \(m/z\) calcd. for C\(_{21}\)H\(_{23}\)F\(_3\)NO\(_2\) ([M+H]+) 377.16026, found 377.15904.

\(N\)-(3-hydroxy-3-(4-(trifluoromethyl)phenyl)propyl)-\(N\)-methylbenzamide (70)

Prepared following the general procedure outlined above using Ir[FCF\(_3\)(CF\(_3\))ppy]\(_2\) (dtbbpy)PF\(_6\) (2.4 mg, 2.0 \(\mu\)mol, 0.002 equiv.), NiBr\(_2\)·glyme (6.1 mg, 20 \(\mu\)mol, 0.02 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (4.6 mg, 20 \(\mu\)mol, 0.02 equiv.), quinuclidine (55.7 mg, 0.5 mmol, 0.5 equiv), \(N\)-(3-hydroxylpropyl)-\(N\)-methylbenzamide (see below) (580 mg, 3.0 mmol, 3.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH\(_4\) (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (10–100% EtOAc in hexanes) yielded the pure product as a colorless oil (154 mg, 0.46 mmol, 46% yield).

IR (film) \(\nu_{\text{max}}\) 3369, 3063, 2936, 1737, 1610, 1577, 1504, 1481, 1446, 1406, 1374, 1323, 1253, 1203, 1160, 1114, 1065, 1016, 951, 925, 839, 788, 734, 713, 698, 656 cm\(^{-1}\).

\(^{1}H\) NMR (500 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.61 (d, \(J = 8.1\) Hz, 2H), 7.55 (d, \(J = 8.1\) Hz, 2H), 7.48 – 7.25 (m, 5H), 4.70 (dd, \(J = 10.7\), 3.0 Hz, 1H), 4.31 (ddd, \(J = 14.7\), 11.4, 3.9 Hz, 1H), 3.23
(dt, J = 14.1, 4.3 Hz, 1H), 2.99 (s, 3H), 2.09 (ddq, J = 14.3, 8.1, 2.5 Hz, 1H), 1.79 (ddt, J = 14.3, 10.5, 3.8 Hz, 1H), 1.56 (s, 1H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) δ 173.29, 149.23, 136.24, 130.43, 129.51, 128.93, 127.59, 126.52, 125.65 (d, J = 3.8 Hz), 69.62, 44.85, 37.96, 37.20. CF$_3$ bearing carbon was not observed.

$^{19}$F NMR (470 MHz, CD$_2$Cl$_2$) – 61.85.

HRMS (ESI-TOF) m/z calcd. for C$_{18}$H$_{19}$F$_3$NO$_2$ ([M+H]$^+$) 337.12896, found 337.12877.
IX. Procedure for the synthesis of Prozac\textbullet HCl

\[
\text{HO} \quad \overset{\text{N}}{\longrightarrow} \quad \overset{\text{N}}{\longrightarrow} \quad \text{Bz}
\]

\textit{N-(3-hydroxylpropyl)-N-methylbenzamide (71)}

To an oven dried two neck 250 mL round bottom flask fitted with a pressure equalizing dropping funnel was added 3-(methylamino)propan-1-ol (5.4 g, 60 mmol, 1.2 equiv.), trimethylamine (15.2 g, 150 mmol, 3.0 equiv.) and THF (100 mL). To the pressure equalizing dropping funnel was added a solution of benzoyl chloride (7.1 g, 50 mmol, 1.0 equiv.) in THF (50 mL). The reaction mixture was then stopped and placed under N\textsubscript{2} and subsequently cooled to 0ºC. The solution of benzoyl chloride was then added to the amine solution dropwise over 30 minutes. The mixture was then held at 0ºC for one hour before being allowed to warm to room temperature overnight, to the mixture was then added ice water (100 mL). The THF was subsequently removed under reduced pressure. The resulting mixture was again cooled to 0ºC before addition of sufficient concentrated HCl to adjust the pH to 5. The mixture was then extracted with EtOAc (5x100 mL). The combined organic layers where washed with saturated NaHCO\textsubscript{3} (150 mL), and then with brine (200 mL). The organic layer was then dried over MgSO\textsubscript{4} and concentrated under reduced pressure. The resulting oil was purified by passing it through a silica plug eluting with 5% methanol in DCM yielding the product as a viscous pale yellow oil (8.34g, 43.2 mmol, 86% yield).

\textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.38 (bs, 5H), 4.05 (bs, 1H), 3.67 (bs, 1.5H), 3.62 – 3.50 (m, 1.5H), 3.44 (bs, 0.3H), 3.31 (bs, 0.3H), 3.04 (bs, 0.4), 2.93 (s, 3H), 1.80 (bs, 2H).

\textit{\textsuperscript{13}C NMR} (126 MHz, CDCl\textsubscript{3}) \( \delta \) 172.71, 135.81, 129.87, 128.50, 126.98, 58.18, 43.80, 37.45, 29.25.
HRMS (ESI-TOF) m/z calcd. for C_{11}H_{16}NO₂ ([M+H]^+) 194.11756, found 194.11765.

\[
\text{N-}(3\text{-hydroxy-3-phenylpropyl)-N-methylbenzamide (72)}
\]

Prepared following the general procedure outlined above using Ir[FCF₃(CF₃)ppy]₂ (dtbbpy)PF₆ (12.2 mg, 10 μmol, 0.01 equiv.), NiBr₂•glyme (6.1 mg, 20 μmol, 0.02 equiv.), 3,4,7,8-tetramethyl-1,10-phenanthroline (4.6 mg, 20 μmol, 0.02 equiv.), quinuclidine (33.4 mg, 0.3 mmol, 0.3 equiv), N-(3-hydroxypropyl)-N-methylbenzamide (see below) (580 mg, 3.0 mmol, 3.0 equiv.), 4-bromobenzotrifluoride (225 mg, 1.0 mmol, 1.0 equiv.), anhydrous zinc chloride (204 mg, 1.5 mmol, 1.5 equiv.), anhydrous potassium phosphate (212 mg, 1.0 mmol, 1.0 equiv.) and DMSO (4.0 mL, 0.25 M). After irradiation for 24 hours, the reaction mixture was reduced with NaBH₄ (42 mg, 1.1 mmol, 1.1 equiv.) and worked up as outlined in the general procedure. Purification by column chromatography (10–100% EtOAc in hexanes) yielded the pure product as a colorless oil (146 mg, 0.54 mmol, 54% yield).

\[
\text{IR (film) } ν_{\text{max}} \quad 3378, 3061, 3029, 2931, 2868, 1611, 1601, 1576, 1502, 1480, 1447, 1402, 1374, 1301, 1286, 1256, 1201, 1179, 1154, 1065, 1029, 914, 844, 788, 729, 697 \text{ cm}^{-1}.
\]

\[
^1\text{H NMR (500 MHz, CD}_2\text{Cl}_2\text{)} \quad δ \quad 7.47 – 7.19 (m, 10H), 4.69 – 4.46 (m, 2H), 4.25 (ddd, J = 14.8, 10.9, 4.4 Hz, 1H), 3.37 – 3.18 (m, 1H), 2.97 (s, 3H), 2.16 – 1.47 (m, 3H).
\]

\[
^{13}\text{C NMR (126 MHz, CD}_2\text{Cl}_2\text{)} \quad δ \quad 173.01, 144.98, 136.51, 130.26, 128.88, 128.75, 127.56, 127.53, 126.17, 70.29, 44.95, 37.88, 37.21.
\]

HRMS (ESI-TOF) m/z calcd. for C_{17}H_{20}NO₂ ([M+H]^+) 270.14886, found 270.14795.
**N-methyl-N-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)benzamide (73)**

The ether linkage was forged utilizing a method previous developed in our laboratory.\(^\text{40}\)

To an 8 mL vial equipped with a stir bar was added photocatalyst Ir[dF(CF\(_3\)ppy)]\(_2\)(dtbbpy)PF\(_6\) (11.2 mg, 10.0 μmol, 0.01 equiv.), quinuclidine (11.1 mg, 0.1 mmol, 0.1 equiv.), potassium carbonate (138 mg, 1.00 mmol, 1.0 equiv.), 4-bromobenzotrifluoride (225 mg, 140μL, 1.0 mmol, 1 equiv.) and N-(3-hydroxy-3-phenylpropyl)-N-methylbenzamide (808 mg, 3.0 mmol, 3.0 equiv.). The vial was sealed and placed under nitrogen before 3mL of acetonitrile was added. To a separate vial was added NiBr\(_2\)•glyme (46.3 mg, 0.15 mmol, 0.15 equiv.) and 3 4,4'-di-\textit{ tert}-butyl-2,2'-dipyridyl (40.3 mg, 0.15 mmol, 0.15 equiv). The catalyst vial was sealed, purged with nitrogen then to it was added 1.5 mL of acetonitrile. The precatalyst solution was sonicated or stirred for 10 minutes, after which, 1.0 mL of the solution (10 mol% catalyst, 0.10 mmol, 0.1 equiv.) was syringed into the reaction vessel. The solution was then cooled to 0 °C in an ice bath, then degassed by sparging with nitrogen while stirring for 10 minutes before sealing with Parafilm. The reaction was stirred and irradiated with a 34 W blue LED lamp (6 cm away, with cooling fan to keep the reaction temperature at 25 °C) for 24 hours. The crude reaction mixture was then passed through a plug of celite eluting with dichloromethane. The reaction was then concentrated under reduced pressure, before the residue was taken up in minimal dichloromethane and purified by column chromatography.
(30:70 EtOAc:Hexanes) to yield the desired product as a colorless oil (393 mg, 0.95 mmol, 95% yield).

**IR (film)** $v_{\text{max}}$ 3063, 3030, 2930, 1628, 1614, 1579, 1516, 1497, 1480, 1449, 1426, 1401, 1323, 1246, 1177, 1158, 1108, 1066, 1051, 1027, 1008, 956, 835, 788, 757, 731, 698 cm$^{-1}$.

**$^1$H NMR (500 MHz, CD$_2$Cl$_2$)** $\delta$ (Mixture of Rotamers) 7.58 – 7.06 (m, 12H), 6.98 (bs, 1H), 6.73 (bs, 1H), 5.36 (bs, 0.5H), 5.03 (bs, 0.5H), 3.87 – 3.60 (m, 1H), 3.60 – 3.33 (m, 1H), 3.06 (bs, 1.5H), 2.93 (bs, 1.5H), 2.35 (bs, 1H), 2.29 – 2.03 (m, 2H).

**$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$)** $\delta$ (Mixture of Rotamers) 172.07, 171.58, 161.07, 160.65, 141.37, 140.73, 137.32, 137.15, 129.85, 129.75, 129.36, 128.79, 128.52, 127.37, 127.22, 126.45, 126.11, 123.95, 123.12 (q, $J = 32.5$ Hz), 121.79, 116.43, 116.20, 79.03, 77.64, 48.26, 45.28, 38.19, 37.82, 36.53, 33.17.

**$^{19}$F NMR (470 MHz, CD$_2$Cl$_2$)** $\delta$ – 61.82.

**HRMS (ESI-TOF)** m/z calcd. for C$_{24}$H$_{23}$F$_3$NO$_2$ ([M+H]$^+$) 414.16754, found 414.16742.

![](image.png)

$N$-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine•HCl - Prozac•HCl

To a plastic ependorf tube with screw cap fitted with a teflon stir bar was added $N$-methyl-$N$-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)benzamide (414mg, 1 mmol, 1.0 equiv), anisole (541 mg, 5 mmol, 5.0 equiv), and HF•pyridine (70% HF, 5.2 mL, 200 mmol, 200 equiv). The reaction mixture was then stirred at room temperature for 2 hours. The reaction mixture was then quenched by carefully and slowly adding the reaction mixture to a rapidly stirring suspension of methanol (100 mL) and sodium bicarbonate (25
g). The mixture was then passed through a plug of celite eluting with more methanol. The resulting methanolic solution was concentrated to dryness first on a rotary evaporator then under high vacuum for 48 hours (Note. At this stage it is important to ensure complete removal of pyridine). The crude solid was then taken up in methyl tert-butyl ether (10 mL) and a solution of HCl in dioxane (4M, 0.3 mL) was added. The resulting precipitate was collected onto a pre-tared fritted funnel and washed with copious quantities of methyl tert-butyl ether to yield N-methyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine•HCl as a white solid (329 mg, 0.95 mmol, 95% yield).

\[ ^1H \text{ NMR (500 MHz)} \delta 9.21 \text{ (s, 2H)}, 7.57 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 7.46 – 7.39 \text{ (m, 2H)}, 7.37 \text{ (t, } J = 7.6 \text{ Hz, 2H)}, 7.33 – 7.25 \text{ (m, 1H)}, 7.08 \text{ (d, } J = 8.6 \text{ Hz, 2H)}, 5.72 \text{ (dd, } J = 8.4, 4.5 \text{ Hz, 1H)}, 3.10 – 2.91 \text{ (m, 2H)}, 2.53 \text{ (s, 3H)}, 2.31 \text{ (dtd, } J = 14.3, 8.6, 6.1 \text{ Hz, 1H)}, 2.19 \text{ (ddddd, } J = 13.6, 8.9, 6.4, 4.6, 2.4 \text{ Hz, 1H)}.

\[ ^{13}C \text{ NMR (126 MHz, DMSO-}d_6\text{)} \delta 160.08, 139.96, 128.83, 128.09, 126.86 \text{ (d, } J = 3.8 \text{ Hz)}, 125.95, 124.42 \text{ (q, } J = 271.0 \text{ Hz)}, 121.39 \text{ (q, } J = 32.0 \text{ Hz)}, 116.29, 76.37, 45.07, 34.09, 32.39.

Spectroscopic data matched that previously reported. \(^{84}\)

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Chapter 3

Photoexcited Cobalt Catalyzed C–N Arylation of Amides

I. Introduction

As outlined in chapter 1 and exemplified in chapter 2, over the last decade photoredox catalysis has arisen as a powerful platform for the generation of organic radicals from simple abundant organic functionalities under exceptionally mild conditions. The majority of new radical generation modes enabled via this mechanistic paradigm rely on excited state iridium and ruthenium polypyridyl complexes, an inherent drawback in the use of this second and third row late transition metals it’s their terrestrial rarity and subsequent high cost. As a result of these factors, the scale up of photoredox reaction inherently incurs significant cost due to the expense involved in procurement of the necessary catalysts. A major drive within the field of photoredox catalyst design has been to replace these expensive chromophores with readily accessible and more economical alternatives. Significant advances have been made with respect to using organic chromophores in place of metal based systems, driven in advances in the fields of organic photovoltaic and photodevices, but a number of highly enabling transformations still necessitate the utilization of Ir and Ru based photosensitizers. Contrastingly, the use of earth abundant first row transition metal based chromophores remains an unexplored field, with only select reports of Cu(I) and Cr(III) based photosensitizers having been demonstrated to be broadly

85. At the time of writing, [Ir(dF(CF₃)ppy)dtbbpy](PF₆) retails at $915,000 per mol, Ru(bpy)₃(PF₆)₂ retails at $130,650 per mol. (Millipore Sigma accessed 05/14/19)
applicable in a range of photoredox transformations, due to the unique electronic configuration of these metals in the respective oxidation states indicated.

II. Photophysics of First Row Transition Metals

The majority of successfully employed metal based photoredox catalysts rely on the ability of these species to access long lived triplet MLCT excited states, which electronically consist of a reduced ligand and oxidized metal center (Figure 9A). The first-row transition metals typically have different excited state electronic structures due to the decreased ligand field splitting for the first row, a result of the primogenic effect. The 3d orbitals which dominate the bonding of the first row transition metals are particularly “core-like” when compared to the 4d and 5d orbitals of the 2nd and 3rd row metals due the absence of a radical node (Figure 9B). The node-less 3d orbitals overlaps less effectively with the orbitals of the metal ligand frameworks, which renders the ligand field splitting in these systems smaller. As a consequence, MLCT states, wherein an electron is promoted to the \( \pi^* \) of an appropriate ligand, tend to lie higher in energy than a metal based so called d-d excited state (Figure 9C). In these systems initial excitation to the MLCT states tend to remain dominant in the absorption spectra due to their fully allowed nature, but rapid relaxation to the ligand-field manifold occurs rendering these complexes no missive and do not possess long lived charge-transfer excited states. This can be represented in a number of ways, in the ruthenium series, potential energy surfaces corresponding to the MLCT states lie lower in energy than those which correspond to the d-d state, in the iron analogue the order of these surfaces is reversed, whilst direct excitation to the d-d state is

forbidden by the Laporte selection rule, MLCT excitation and subsequent relaxation is allowed and energetically favorable.\textsuperscript{88} The result of this is well demonstrated by comparing the emission spectra and excited state photophysics of Ru(bpy)\textsubscript{3}\textsuperscript{2+} again with its first row isoelectronic homolog Fe(bpy)\textsubscript{3}\textsuperscript{2+}, the ruthenium complex is phosphorescent with the lifetime of the MLCT state approaching \textasciitilde900 ns, whereas the Fe(bpy)\textsubscript{3}\textsuperscript{2+} MLCT state is non emissive and has been demonstrated to have a lifetime below 1 ps (\textasciitilde100 fs) before relaxing to a d-d excited state (\textsuperscript{5}T\textsubscript{2}) which persist in solution for 10s of nano seconds.\textsuperscript{89} The short lifetime of the MLCT state of Fe(bpy)\textsubscript{3}\textsuperscript{2+} mean they likely cannot be leveraged in solution phase SET events as relaxation is considerably more facile than encounter complex formation.

The select examples of Cr(III) and Cu(I) based photosensitizers avoid falling into regime, as relaxation from the d-d excited state back to the ground state is prohibited by the spin selection rule (\textsuperscript{2}E back to \textsuperscript{4}A\textsubscript{2}) or not present respectively (d\textsuperscript{10} metals inherent cannot possess a d-d excited state). In the chromium systems, upon irradiation Cr(III) initially accesses a MLCT state which relaxes to the quartet d-d excited state (\textsuperscript{4}T\textsubscript{2}) which then undergoes a quantum mechanically forbidden spin flip to furnish a doublet d-d excited state (\textsuperscript{2}E). Relaxation from this doublet state in a non-radiative fashion is spin forbidden and as such these complexes possess long-lived d-d excited states, as demonstrated by the long-lived phosphorescence observed in these systems. The doublet d-d excited state can

\textsuperscript{88} These potential energy surfaces can be summarized in a Tanabe-Sugano diagram, wherein the relative energy of the electronic states of a given d electron count are plotted as a function of the ligand field splitting parameter (see ref. 87e for an example for d\textsuperscript{6} electron configuration).

Figure 9. A Jablonski diagram for 2nd and 3rd row d\textsuperscript{6} transition metals. The 3\textit{MLCT} is the lowest lying excited state, and as such this can persist as a long-lived species in solution. Charge separation allows this species to function as both a strong oxidant and strong reductant (See chapter 1.III). B Radial distribution functions for n = 4 shell of Ru(II) and the n = 3 shell of Fe(II), and the corresponding ground state and lowest energy excited state electronic configurations for [Ru(bpy)\textsubscript{3}]\textsuperscript{2+} and [Fe(bpy)\textsubscript{3}]\textsuperscript{2+}. Part B is a modified variant of a figure from ref. 87c with permission of the author. C Jablonski diagram for 1st row d\textsuperscript{6} transition metals. Here the lowest energy excited state is a ligand field based excited state. The redox properties of these excited states are understood poorly.
function as both an oxidant or reductant in an analogous fashion to Ru and Ir based systems, albeit here the electron hole and high energy electron remain pre-dominantly localized on the metal center (Scheme 19). Here again the primogenic effect plays a secondary effect, the 3d orbitals of Cr(III) are particularly core like, and as such the excited state of the Cr(III) photocatalyst possess high oxidation potentials (+1.4 to 1.84 V vs. SCE) and have been employed in oxidative Diels-Alder cycloadditions. The Cu(I) systems have a closed 3d shell, and as such the MLCT state can not relax to an excited ligand-field state, as no d-d excited state exists (Scheme 20). As a result, the majority of transformations reported utilizing the Cu systems are reductive in nature, wherein the excited state functions as a strong single electron reductant (SET from the ligand radical anion).

Scheme 19. Chromium photoredox catalysts in oxidative radical Diels-Alder reactions.

The first-row homologues of Ru and Ir, Fe and Co, respectively have found limited application in organic photoredox catalysis as the majority of complexes of these metals lie solely in a regime where the d-d excited state manifold lies below the MLCT states. To date no emissive Fe(II) (isoelectronic to Ru(II)) complexes have been reported, with the best complexes possessing MLCT states with lifetimes of several hundred picoseconds. One blue emissive Co(III) complex (isoelectronic to Ir(III)) has been reported, which has been utilized in a photoredox catalyzed trifluoromethylation of pyrene (Scheme 20), albeit here the reaction is proposed to proceed via a two photon process requiring excitation of the cobalt catalyst to facilitate both rearomatization of pyrene and energy transfer to pyrene.
which can then function as an excited state photoreductant to generate CF$_3$ radical from trifyl chloride.$^{92}$ Here the ligand has high σ-donor capacity generating a large ligand field splitting, and the complex has relatively high energy ligand centered HOMO due to its electron-rich nature, as such excitation produces a long lived LMCT state. A high degree of symmetry and strong ligand field splitting pushes the metal-based d-d excited state up in energy such that the LMCT state does not thermally populate the d-d excited state and persists in solution functioning in a fashion analogous to Ir and Ru chromophores, albeit here the metal center is reduced and the ligand oxidized.

**Scheme 21.** [Co(dgpy)$_2$](BF$_4$)$_3$, a Co(III) complex with a long lived $^3$LMCT state. The trifluoromethylation of polycyclic arenes via dual Co(III)-ET photoredox catalysis.

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We recently questioned whether it would be possible to employ the d-d excited state of Co(III) complexes as photo-oxidants in organic photoredox catalysis directly, thereby obviating the need for highly specialized ligand frameworks. d-d Excited states have typically been assumed to be extremely short lived, with rapid non-radiative relaxation to the ground state accounting for the preponderance of the fate of these species, low spin

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Fe(II) complexes with a highly rigid octahedral ligand environment (i.e. Fe(bpy)$_2^{3+}$) can have relatively long lived d-d excited states ($^5T_2$). In these systems ($^1A$) irradiation initial proceeds to the $^1$MLCT manifold where subsequent relaxation through two ISC crossing event and vibrational relaxation results ultimately results in a high spin excited state, which can persist in solution for 10s of nanoseconds (Figure 9). This excited state has found limited applicability in photoredox catalysis, a report from Cozzi, Ceroni and co-workers, reports the enantioselective alkylation of aldehydes via dual photoredox-organocatalysis, first reported with ruthenium photocatalysts by the MacMillan laboratory in 2008 (Scheme 4). Albeit assessment here of the efficacy of the iron photosensitizer is complicated by the radical chain nature of this transformation. We hypothesize a similar system could be realized for isoelectronic Co(III), wherein the photoexcited low-spin Co(III) species could function as incredibly strong oxidants, thereby facilitating the discovery of new transformations. We believe this is a particularly attractive approach as cobalt is one of the most earth-abundant transition metals, if an inexpensive ligand system can be identified, a cobalt photocatalyst could greatly facilitate the inexpensive large-scale implementation of photoredox catalysis.

III. Identification of a Novel Cobalt Photo-oxidant for Homolytic Substitution

With the goal of identifying a suitable cobalt photocatalyst in mind, we identified a reaction recently discovered in our laboratory as an ideal model reaction for investigation (Scheme 22). $N$-Phenyl acetamide and 4-trifluoromethylphenyl boronic acid undergo oxidative coupling to give the $N$-arylated product upon exposure to

[Ir(dF(CF$_3$)ppy)dCF$_3$bpy](PF$_6$), molecular oxygen and visible light irradiation in low yield.

Cyclic-voltammetry indicates a likely mechanism involving oxidation of the amide coupling partner ($E_p$ AcNHP$^+$/AcNHP = + 1.68 V vs SCE loaded at 0.001M with 0.1M NBu$_4$PF$_6$ as supporting electrolyte in MeCN) by the Ir(IV) state of the photocatalyst (generated in situ via oxidative quench between the excited state and oxygen), and subsequent homolytic substitution at the ipso-carbon of the aryl boronic acid.$^{95}$

Scheme 22. Photoredox catalyzed C–N coupling of N-aryl amides and aryl boronic acids.

Homolytic substitution is a well-established mechanism for C–C and C–X bond formation between organic radicals and main-group element organometallics, with concomitant generation of a stanyl or silyl radical.$^{96}$ Allyl stananes react with a wide range of organic radicals via a $\text{S}_2\text{H}2$’ mechanism, in addition simple Si–alkyl and Sn–alkyl species can also undergo a range of $\text{S}_2\text{H}2$ reactions with organic radicals.$^{97}$ Alkyl boranes are also well known to undergo $\text{S}_2\text{H}2$ type reactions, and this is often utilized to initiate radical chain reactions,$^{98}$ however homolytic substitution reactions of aryl boronic acids are less well studied. A report from Goswami and co-workers in 2016 documents a method for the

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95. The excited state redox potential of [Ir(dF(CF$_3$)ppy)4,4’-dCF$_3$bpy]$^+$/[Ir(dF(CF$_3$)ppy)4,4’-dCF$_3$bpy]$^2^+$/[Ir(dF(CF$_3$)ppy)4,4’-dCF$_3$bpy]$^3^+$/[Ir(dF(CF$_3$)ppy)4,4’-dCF$_3$bpy]$^4^+$ is +1.43 V vs. SCE in MeCN. The redox potential of [Ir(dF(CF$_3$)ppy)4,4’-dCF$_3$bpy]$^+$ is + vs. SCE in MeCN, oxidation of the amide is outside the range expected for the Ir(III) excited state.
oxidative conversion of aryl boronic acids to primary anilines using cyanamide as the nitrogen source (Scheme 23A). DFT calculations in conjunction with experimental observations support a homolytic substitution type mechanism wherein aryl group transfer occurs via a radical -ate complex formation. We propose a similar pathway for bond formation in the system described herein. During our work in this area, a report similar method for the oxidative coupling of N-aryl amides and boronic acids appeared in the patent literature, here the oxidant is likely a photoexcited cerium(IV) LMCT state (Scheme 23B).

Scheme 23. A Oxidative amination of boronic acids, and proposed mechanism involving a homolytic ipso substitution of the aryl boronic acid. B Oxidative coupling of amides and boronic acids utilizing photoexcited CAN.

The yield of the reaction under the Ir photoredox catalyzed conditions (Scheme 22) is low, we hypothesize this is due to unproductive back electron transfer between the Ir(IV)

state and in situ generated superoxide. In order to improve the yield of this reaction we hoped to identify a photocatalyst which will engage in more facile SET with the amide. As a secondary goal, we aimed to move away from the use of oxygen as the terminal oxidant, incorporation of oxygen into reactions on large scale can prove challenging and oxygen, due to its ground state triplet configuration is known quencher of excited state species via SET and ET events.\textsuperscript{101} In order to rapidly identify an appropriate cobalt pre-catalyst and ligand architecture for this transformation, a range of diamine ligands and cobalt salts were evaluated in a HTE paradigm against a range of external oxidants. We rapidly identified a combination of Co(acac)\textsubscript{2}, bipyridine ligands and potassium persulfate in MeCN as optimal for the desired oxidative coupling of 4-trifluoromethyl boronic acid and N-phenyl acetamide (Table 10, entry 4). Interestingly, Co(acac)\textsubscript{3} was a vastly inferior cobalt pre-catalyst, which we attribute to the low spin configuration of this pre-catalysts rendering it inert to ligand substitution to generate the active diamine ligated complex (Table 10, entry 5),\textsuperscript{102} as where a number of simple binary cobalt halide salts (Table 10, entry 1-3). A number of bypyridine ligand where evaluated (Table 10, entry 4, entries 7-11), and 4,4'-dBrbpy was identifies as optimal, giving the desired product 77 in 85-90% yield reliably.


\textsuperscript{102} Evans method measures of Co(acac)\textsubscript{3} reveal no magnetic moment, and NMR spectra of Co(acac)\textsubscript{3} are well behaved.
Table 10. Cobalt pre-catalyst and ligand evaluation for oxidative C–N coupling.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cobalt Salt</th>
<th>Ligand</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CoCl₂</td>
<td>4,4'-dBrbpy</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>CoF₂</td>
<td>4,4'-dBrbpy</td>
<td>64%</td>
</tr>
<tr>
<td>3</td>
<td>CoBr₂</td>
<td>4,4'-dBrbpy</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>Co(acac)₂</td>
<td>4,4'-dBrbpy</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>Co(acac)₁</td>
<td>4,4'-dBrbpy</td>
<td>13%</td>
</tr>
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<td>6</td>
<td>Co(NO₃)₁</td>
<td>4,4'-dBrbpy</td>
<td>17%</td>
</tr>
<tr>
<td>7</td>
<td>Co(acac)₂</td>
<td>4,4'-dClbpy</td>
<td>81%</td>
</tr>
<tr>
<td>8</td>
<td>Co(acac)₂</td>
<td>4,4'-dCO₂Mebpy</td>
<td>62%</td>
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<td>9</td>
<td>Co(acac)₂</td>
<td>bpy</td>
<td>33%</td>
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<tr>
<td>10</td>
<td>Co(acac)₂</td>
<td>dbbpy</td>
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</tr>
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<td>11</td>
<td>Co(acac)₂</td>
<td>4,4'-dOMebpy</td>
<td>30%</td>
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<tr>
<td>12</td>
<td>Co(acac)₂</td>
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*Reactions where conducted with PhNHAc (0.5 mmol), 4-CF₃-C₆H₄-B(OH)₂ (1.5 equiv), K₂S₂O₈ (1.5 equiv), Co(acac)₂ (1 mol%), and 4,4'-diBr-bpy (2 mol%), and were irradiated with blue a 34 W LED lamp. Yields determined by UPLC-MS vs. an internal standard.

A proposed mechanism for the discovered reaction is shown in Scheme 24. Following excitation of the cobalt complex 78 by visible light, the highly oxidizing excited state can engage the amide partner 79 in an SET event, which following loss of a proton, forms amidyl radical 80. Homolytic substitution between the amidyl 80 and phenyl boronic acid 81 delivers the desired product 77. The concomitantly generated boryl radical 82 can then engage persulfate 83 to deliver sulfate radical 84, which can then reoxidized the Co(II) species 85 to the starting Co(III) complex 78. At this stage we cannot rule out a chain mechanism where sulfate radical 84 can directly engage the amide substrate 79 in a HAT event to generate amidyl radical 80. Another potential chain mechanism, analogous to that proposed by Goswami is also possible, involving HAT between the complex produced after arene migration and substrate 79 to also generate radical 80 and the product. Control
experiments demonstrate the necessity of all reaction components (Table 11), the reaction can also not be conducted thermally in the absence of light indicating the importance of accessing an electronically excited state (Table 11, entry 6).

Scheme 24. Initial working hypothesis for cobalt photocatalyzed oxidative coupling of amides and boronic acids.
Table 11. Control experiments for the cobalt-photocatalytic coupling of \(N\)-amides and aryl boronic acids.\(^a\)

\[
\begin{array}{c|c|c|c}
\text{Entry} & \text{Component omitted} & \text{Temperature (°C)} & \text{Yield} \\
\hline
1 & \text{none} & 35 ^\circ \text{C} & 86\% \\
2 & \text{K}_2\text{S}_2\text{O}_8 & 35 ^\circ \text{C} & 0\% \\
3 & \text{ligand} & 35 ^\circ \text{C} & 0\% \\
4 & \text{Co(acac)}_2 & 35 ^\circ \text{C} & 0\% \\
5 & \text{light} & 35 ^\circ \text{C} & 2\% \\
6 & \text{light} & 80 ^\circ \text{C} & 1\% \\
\end{array}
\]

\(^a\)Reactions where conducted with PhNHAc (0.5 mmol), 4-CF\(_3\)-C\(_6\)H\(_4\)-B(OH)\(_2\) (1.5 equiv), K\(_2\)S\(_2\)O\(_8\) (1.5 equiv), Co(acac)\(_2\) (1 mol%), and 4,4’-diBr-bpy (2 mol%), and were irradiated with blue a 34 W LED lamp. Yields determined by UPLC-MS vs. an internal standard.

IV. Scope of the Coupling of \(N\)-Aryl Amides and Boronic Acids

With optimized conditions in hand, we next sought to elucidate the scope of this new C–N coupling protocol (Table 12). A diverse array of electron-rich aryl-boronic acids smoothly react to afford the desired \(N,N\)-diaryl amides (86–88, 91–95% yield). As expected for a radical substitution reaction, which should proceed via a long transition state, sterically encumbered boronic acids where well tolerated (88, 89, 92, 86–92% yield). Boronic acids baring electron deficient functionalities, such as chloro, bromo, acetyl, and methoxy carbonyl groups, also perform well in the reaction affording the desired N–diaryl amides in excellent yield (89–97, 80–97% yield). Notably, an N–alkyl amide is untouched by the reaction (97, 80% yield), this is readily attributable to the higher oxidation potential of N–alkyl amides compared to N–aryl amides, as such the reaction occurs with high chemoselectivity at the N–aryl amide.
With respect to the amide component, electron deficient N–aryl amides, bearing trifluoromethyl, cyano, nitro, sulfonyl and free carboxylic acid groups, couple well under the optimized conditions, highlighting the highly oxidizing nature of the Co photocatalyst (77, 98–106, 80–95% yield). Included in this, are substrates baring a range of functionalities which can be engaged in subsequent coupling platforms, all of which are cleanly conserved under the optimized conditions (90, 91, 103–105, 90–98% yield). Electron rich acetonilides also perform admirably in this protocol delivering the corresponding coupled product without over oxidation (Ep AcNH2+/AcN2H = + 1.71 V vs SCE loaded at 0.001M with 0.1M NBu4PF6 as supporting electrolyte in MeCN) (107–109, 91–98% yield). With respect to substitution on the other side of the amide, benzocaprolactam, formanilide, and simple alkyl substituted amides all deliver the desired product in excellent yield (110–115, 75–92% yield). Notably, substrates containing saturated heterocyclic fragments also furnish the desired coupled product in good yield (116–117, 68–85% yield), important due the prevalence of this motifs in medicinal agents. In addition, phthalazine 1-one is also a competent coupling partner in the reported protocol (112, 89% yield), highlighting potential opportunities in the coupling of other oxidizable nitrogen nucleophiles.
Table 12. Scope of cobalt-photocatalytic oxidative coupling of amides and aryl boronic acids.\textsuperscript{a}

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<th>Amide</th>
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<td>105</td>
<td>90%</td>
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\textsuperscript{a} Amide (0.5 mmol), boronic acid (1.5 equiv.), K$_2$S$_2$O$_8$ (1.5 equiv), Co(acac)$_2$ (1 mol%), and 4,4'-dibromo-2,2'-bipyridine (2 mol%) were irradiated with blue a 34 W LED lamp. Isolated yields. See SI for full experimental details.
V. Kinetics and Mechanistic Investigation

With the scope of the reaction elucidated, we next sought to turn back and provide evidence to support our original mechanistic hypothesis. We identified that elucidation of the radical generated in situ and the cobalt species generated in situ to be of critical importance. Subjecting 117, a substrate with a pendant radical trap, known to provide a stable product 118 upon radical generation and cyclization,\textsuperscript{103} to the optimized reactions conditions led to a mixture of products (Scheme 25A), coupling with the boronic acid (119) and cyclization onto the pendant arene to give the product expected following radical generation (118). In the absence of the boronic acid coupling partner, this product is produced exclusively, albeit in moderate yield, lending significant credence to the hypothesis that the amidyl radical is an important operative pathway. An analogous boronic acid (119) which should cyclize following aryl radical generation led only to formation of a small amount of the coupled product (120) and no cyclization (Scheme 25B). As a second piece of evidence to support amidyl radical generation, when the reaction is conducted in the presence of pyridine (which is observed to co-ordinate to the boronic acid by NMR and as such attenuates it’s Lewis acidic nature), the amidyl radical reacts with a second equivalent of the substrate to give after oxidative rearomatization the dimer 121 (Scheme 25C). With these results in hand we were confident that amidyl radical production is a productive and necessary pathway in the reported transformation.

\textsuperscript{103} Natarajan, P.; Chuskit, P.; Chuskit, D. Green Chem., \textbf{2017}, 19, 5854.
Scheme 25. Evidence for amidyl radical generation and competence in the cobalt photocatalyzed oxidative coupling of amides and aryl boronic acids.

**A. Amidyl radical trapping**

\[ \text{aryl amide} \rightarrow 5\text{-exo trig} \rightarrow \text{carbazole} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Component omitted</th>
<th>Yield 109</th>
<th>Yield 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>boronic acid</td>
<td>0%</td>
<td>32%</td>
</tr>
</tbody>
</table>

**B. Aryl radical trapping - not observed**

**C. Amide oligimerization in the presence of pyridine**

pyridine co-ordinates to the boronic acid and induces boroxine formation
Figure 10. A. Job plot for Co(acac)$_2$ with 4,4'-dBrbpy. B. UV-vis spectra of the in situ formed 1:1 adduct.

A. Job Plot for Co(acac)$_2$ with 4,4'-dBrpy

B. UV-vis spectra for Co(acac)$_2$(4,4'-dBrbpy)

With evidence suggesting amidyl radical generation is the operative path, we next turned our attention to the identity of the cobalt catalyst. Bipyridyl ligands are known to form 1:1 adducts with Co(acac)$_2$ to confirm this is the case in our system, Job’s method of continuous variation was carried out. At a concentration relevant to the reaction conditions, a clean parabolic relationship between 4,4'-dBrbpy mol fraction and absorption at 420nm is observed (Figure 10A) establishing that a 1:1 adduct comparable to that observed in the solid state is present in solution. The Co(4,4'-dBrbpy)(acac)$_2$ complex observed in solution is a spin 3/2 species corresponding to a neutral monomeric high-spin Co(II) $d^7$ configuration, the spin state was accessed utilizing the Evan’s method and a magnetic moment of 3.6 $\mu_B$ was obtained and independently verified for the solid using a Gouy balance. The Co(4,4'-dBrbpy)(acac)$_2$ complex shows strong absorbance features in the visible region ($\lambda_{max} =$ 401 nm with a shoulder at 431nm) (Figure 10B), the

extinction co-efficient for this feature at 400nm is 660 M\(^{-1}\) cm\(^{-1}\) which is consistent with an MLCT event with weak interactions between the ligand \(\pi\) system and the metal based \(T_2\) orbitals, unsurprisingly as expected for first row transition metals no features are observed in the emission spectra.

**Figure 11.** A. UV-vis spectra of Cobalt precatalyst in the presence of the reaction components. B. UV-vis spectra of Co(III) species formed in situ. C. UV-vis data of each reaction component. D. Proposed in-situ pre-catalyst oxidation.

Our original hypothesis was that an excited state Co(III) species would be a powerful oxidant and could engage the amide to furnish the corresponding radical, as such we hypothesized a Co(III) species is formed at the beginning of the reaction by pre-catalyst oxidation. To our surprise exposing the Co(II) complex to \(K_2S_2O_8\) does not affect the UV-vis spectra of the complex or it’s spin state, addition of the amide to this mixture also has no effect on the UV-vis spectra, indicating this reagents have no effect on the oxidation.
state of the complex. However, in the presence of phenyl boronic acid and K$_2$S$_2$O$_8$ the UV-vis spectra undergoes a drastic change, with a complete bleach of the absorptive feature at 400 nm (Figure 11A). When a mixture of Co(4,4’-dBrbpy)(acac)$_2$, K$_2$S$_2$O$_8$ and phenyl boronic acid are subjected to the Evan’s method a magnetic susceptibility of 4.5 µB is observed corresponding to an s = 2 species. This indicates that in the presence of K$_2$S$_2$O$_8$ and phenyl boronic the Co(II) species 122 is likely oxidized to the high-spin Co(III) species we tentatively assigned as 123 (Figure 11D), which we believed to be the active cobalt catalyst.

We postulate that the Co(III) species is only seen upon addition of the boronic acid due to in-situ formation of an activated and more soluble persulfate species 124, which can be observed by $^{19}$F and $^{11}$B NMR. Dilution of a sample of the oxidized complex and UV-vis analysis reveals a new intense absorbance feature centered around 341 nm which tails in the near UV (Figure 11B). We again assign this feature as a MLCT event, where the blue shift is attributed to a stabilization of the $t_2$ orbitals following oxidation, which increases the energy gap between the metal-based orbitals and the $\pi$-system of the ligand. Further time resolved spectroscopy is on-going to assess the lifetime and ultimate fate of this MLCT state, it likely relaxes to a d-d excited state rapidly due to the weak ligand field in this system, as exemplified by the high-spin nature of the complex. We postulate that the result d-d state is long lived enough and sufficiently oxidizing to engage in a SET event with the amide substrate and further investigation to support this hypothesis in ongoing. Finally to demonstrate that this species is the catalyst resting state during the reaction, PhotoNMR was carried out in conjunction with measurement of the magnetic moment of
the reaction mixture by the Evans method.\textsuperscript{107} The total magnetic susceptibility of the reaction mixture was not found to change as a function of time and remained steady up-to 30\% yield of the product, any organic radicals generated in the reaction can assume to be fleeting in nature, as such we assign the observed magnetic moment to the in-situ formed high spin Co(III) species. A Curtin-Hammett scenarios where a small amount of low spin Co(III) species exists in solution and functions as the photocatalyst cannot yet be ruled out.

**Scheme 26.** Independent synthesis and characterization of 113.

\[
\text{[Co(4,4'-dBrbpy)(acac)](ClO}_4\text{)} (113) \text{ Synthesis}
\]

\[
\begin{align*}
\text{[Co(4,4'-dBrbpy)(acac)](ClO}_4\text{)} \\
S = 0
\end{align*}
\]

In order to confirm the identity of the in-situ formed Co(III) species, an independent synthesis of 113 was conducted by the method of Archer and Cotsoradis (Scheme 26).\textsuperscript{108} As reported in the literature this complex is actually only mildly paramagnetic and an NMR spectra is readily obtained. In order to explain why the in-situ formed Co(III) species in our system is high-spin, we exposed 113 to 4-trifluoromethyl phenyl boronic acid. The UV-vis spectra quickly morphed to match that observed for the in-situ generated species.

\begin{align*}
\text{[Co(4,4'-dBrbpy)(acac)](X)}_2 \\
S = 2
\end{align*}

and the observed magnetic moment increased to 4. \(\mu_B\) consistent with a \(s = 2\) system. Further efforts to elucidate the structural change responsible for these observations are ongoing, but our current working hypothesis involves boronic acid induced loss of an acac ligand (as free acac is observed in the \(^1\)H NMR), which will likely weaken the ligand field splitting in around the cobalt and lower the energy of the high-spin state. Once studies have been complete to further elucidate the structural features of this complex. Time resolved spectroscopy will be used to probe the electron transfer events responsible for bond formation.


![Scheme 27](image)

With our mechanistic hypothesis for the role of cobalt in this reaction evolving, we also sought to probe the mechanism of the amidyl radical generation and C–N bond forming event. A very small primary kinetic isotope effect (~1.07) is observed when the \(N\)–deuterated analog of the acetanilide is employed in the reaction (Scheme 27), a number of plausible explanation exist for this observation, (i) formation of the radical either via HAT or deprotonation after oxidation is turnover limiting, or (ii) this a secondary KIE and oxidation of the amide is rate limiting. An alternate explanation notes that sulfate radical is known to react at near diffusion rates with a range of organic functionalities. \(^{109}\) It is

---

possible that HAT is responsible for the formation of the amidyl but the reaction is essentially barrier-less and therefore insensitive to isotope effects – rate is limited by encounter complex formation. Initial-rates kinetic analysis of the reaction reveals a first order dependence on the concentration of the cobalt, the amide, and the intensity of photonic flux (Figure 12). At higher concentrations the reaction tends towards saturation kinetics, we attribute this to the fact that in these regimes photonic flux is rate limiting due to light penetration in this system being diminished due to the heterogenous nature of the reaction mixture. With respect to the boronic acid the reaction is insensitive to concentration in the initial rate regime suggesting that it is not involved in the any steps between the catalyst resting state or chain carrying radical and the turnover limiting step. These results are consistent with a turnover limiting oxidation of the amide by the cobalt
complex or outer sphere electron transfer between the amide, and subsequent rapid irreversible deprotonation of the amidinium to furnish the amidyl, which then undergoes subsequent homolytic substitution with the boronic acid to deliver the C–N coupled product. Turn-over of the Co(II) generated requires SET oxidation by the persulfate or in-situ generated sulfate radical to generate the Co(III) resting state. At this stage we are unable to rule out an inner-sphere oxidation of the amide by the photoexcited Co(III) center. This would require displacement of one of the ligands by the amide which could then be oxidized by the metal center. No features in the UV-vis appear upon addition of the amide to the Co(III) species, but we cannot rule out the possibility of an equilibrium.

**Scheme 28.** Potentially inner sphere mechanism for amidyl radical generation.

which provides undetectably amounts of amide-ligated cobalt which can undergo photoexcitation and inner sphere SET (Curtin-Hammett). Inner-sphere photooxidation of ligands by Co(III) has been observed previously and cannot be ruled out at this stage in this system (Scheme 28).

Scheme 29. Effect of substrate electronics on the cobalt photocatalyzed oxidative coupling of \(N\)-aryl amides and aryl boronic acids.

Finally to assess the effect of substrate electronics on the homolytic substitution step a range of competition studies and kinetics were conducted (Scheme 29). More electron rich amide couples preferentially in competition studies, consistent with a mechanism involving outer sphere SET of the amide substrate. Interestingly in side by side kinetic studies, the electronics of the amide have little to no effect on the rate of the reaction, Hammett analysis reveals a non-linear relationship between the amide electronics which could indicate a
change in mechanism for electronically differentiated pairs of substrates. With respect to the aryl boronic acid component, again no significant effect is observed on initial rates of reactions with various electronically differentiated boronic acids. In competition however, again it is observed that electron rich boronic acids couple preferentially. While the step involving the boronic acid is not turn-over limiting it can still affect the selectivity of the competition reaction, more electron rich boronic acids may react more rapidly with the relatively electron poor amidyl radical and this remains our working hypothesis. Further efforts to understand the mechanism of this transformation are on-going in the MacMillan laboratory.

VI. Conclusions

In conclusion we have developed a novel photoexcited cobalt system, which facilitates the oxidative coupling of aryl boronic acids and amides. Mechanistic studies suggest a mechanism involving turn over limiting amidyl radical generation by SET oxidation of isotope insensitive HAT. Photoexcited Co(III) here functions as a single electron oxidant which serves to either generate the amidyl directly or initiate a chain reaction. Loss of the chain carrying radical to deleterious side reactions can be remediated by continuous irradiation of the Co(III) species. The amidyl radical generated is postulated to undergo homolytic substitution with the boronic acid to deliver the C–N coupled product. The scope of the reaction is highly tolerant with respect to electronics and steric and facilitates access to molecules which are difficult to access using traditional C–N cross coupling platforms (Chapter 1). Work on elucidating the electronic nature of the excited state is ongoing in our laboratory through the use of ultrafast time resolved spectroscopy, and whether our original hypothesis invoking the d-d excited state as a potentially productive state is valid. We also
continue to explore the potential of utilizing this or similar cobalt systems in photoredox catalysis more broadly.
VII. Supporting Information

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I. General Information

Commercial reagents, Cobalt catalysts, bipyridine ligands, persulfates and acetonitrile were purchased from Sigma–Aldrich and Acros Organics, and used directly without purification. All amides and boronic acids were used directly from commercial suppliers. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an isopropyl alcohol-dry ice bath. Chromatographic purification of products was accomplished by flash chromatography on silica gel (Fluka, 230-400 mesh). Thin layer chromatography (TLC) was performed on Analtech Uniplate 0.25 mm silica gel plates. Visualization of the developed chromatogram was performed by fluorescence quenching, \( p \)-anisaldehyde, potassium permanganate, or ceric ammonium molybdate stain. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker UltraShield Plus 500 MHz (125 MHz) instrument,
and are internally referenced to residual protio solvent signals (note: CDCl$_3$ referenced at 7.26 and 77.0 ppm respectively; CD$_3$OD referenced at 3.31 and 49.0 ppm respectively). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad), coupling constant (Hz) and integration. Data for $^{13}$C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and are reported in wavenumbers (cm$^{-1}$). Electronic absorption spectra were acquired using a Cary 50 spectrophotometer. High resolution mass spectra were obtained at Princeton University mass spectrometry facilities on Agilent Technologies 6220 Time-Of-Flight LC/MS with electrospray ionization method. Ultra-highperformance liquid chromatography (UPLC) was performed on a Agilent Infinity II 1290 with an Infinity II 1290 diode array detector.

II. Substrate Synthesis

\[
\text{Me} - \overset{\text{O}}{\text{C}} - \overset{\text{N}}{\text{H}} - \overset{\text{O}}{\text{Me}}
\]

**N-phenylpropionamide:** To a 500 mL round bottom flask was added aniline (4.9 mL, 52.5 mmol), triethylamine (14.6 mL, 105 mmol, 2 equiv.), and dichloromethane (200 mL). The reaction was cooled to 0 °C and propionyl chloride (4.9 mL, 52.5 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the resultant white solid was recrystallized from EtOAc to give N-phenylpropionamide as a white solid. (8.4 g, 94% yield).
\[^1\text{H} \text{NMR}\] (500 MHz, \textit{d}_6-\text{DMSO}): \delta \approx 9.85 (s, 1H), 7.59 (d, \textit{J} = 8.0 \text{ Hz}, 2H), 7.28 (t, \textit{J} = 6.9 \text{ Hz}, 2H), 7.02 (t, \textit{J} = 7.1 \text{ Hz}, 1H), 2.32 (q, \textit{J} = 7.6 \text{ Hz} 2H), 1.08 (t, \textit{J} = 7.6 \text{ Hz}, 3H).

\[^{13}\text{C} \text{NMR}\] (125 MHz, \textit{d}_6-\text{DMSO}): \delta \approx 172.40, 129.11, 123.32, 119.43, 29.97, 10.16.

\textit{N-phenylisobutyramide}: To a 500 mL round bottom flask was added aniline (4.9 mL, 52.5 mmol), triethylamine (14.6 mL, 105 mmol, 2 equiv.), and dichloromethane (200 mL). The reaction was cooled to 0 °C and propionyl chloride (4.9 mL, 52.5 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the resultant white solid was recrystallized from EtOAc to given \textit{N}-phenylpropionamide as a white solid. (8.4 g, 94% yield).

\[^1\text{H} \text{NMR}\] (500 MHz, DMSO-\textit{d}_6): \delta \approx 9.81 (s, 1H), 7.60 (d, \textit{J} = 7.3 \text{ Hz}, 2H), 7.28 (t, \textit{J} = 7.8 \text{ Hz}, 2H), 7.02 (t, \textit{J} = 7.4 \text{ Hz}, 1H), 2.59 (p, \textit{J} = 6.8 \text{ Hz}, 1H), 1.10 (d, \textit{J} = 6.8 \text{ Hz}, 6H).

\[^{13}\text{C} \text{NMR}\] (125 MHz, DMSO- \textit{d}_6) \delta \approx 175.64, 175.64, 139.92, 129.09, 129.09, 123.37, 123.37, 119.54, 119.54, 35.37, 20.01. (mixture of rotamers).

\textit{N-phenylcyclopropanecarboxamide}: To a round bottom flask fitted with a teflon coated magnetic stir bar was added cyclopropane carboxylic acid (2.58g, 30 mmol, 1 equiv.), pyridine (6.1 mL, 75 mmol, 2.5 equiv.) and dichloromethane (30 mL, 1 M) under nitrogen. \textit{SOCl}_2 (2.6 mL, 36 mmol, 1.2 equiv.) was then added dropwise via syringe over 3 minutes. The resulting mixture was stirred at room temperature for 30 minutes, then a solution of aniline (3.1 mL, 34.5 mmol, 1.15 equiv.), triethylamine (14.7 mL, 105 mmol, 3.5 equiv.) and DMAP (0.36g, 3 mmol, 0.1 equiv.) in DCM (60 mL) was added. The resultant mixture
was stirred overnight at room temperature. The reaction was quenched by addition of 1M aqueous HCl (100 mL), the phases where separated and the aqueous layer extracted with DCM (2 x 50 mL). The combined organic phase was washed sequentially with saturated aqueous NaHCO₃ then saturated aqueous NaCl. The combined organic phase was dried over MgSO₄ and then concentrated to dryness on a rotary evaporator. The crude solid was recrystallized from EtOAc to yield N-phenylcyclopropanecarboxamide as a white solid (4.11 g, 25.5 mmol, 85% yield).

\(^1\)H NMR (500 MHz, Acetonitrile-d₃) \(\delta\) 8.54 (s, 1H), 7.58 (d, \(J = 7.8\) Hz, 3H), 7.32 (t, \(J = 7.9\) Hz, 2H), 7.08 (t, \(J = 7.4\) Hz, 1H), 1.67 (tt, \(J = 7.9, 4.5\) Hz, 1H), 0.95 – 0.87 (m, 2H), 0.86 – 0.77 (m, 2H).

\(^13\)C NMR (125 MHz, CD₃CN) \(\delta\) Carbonyl peak not observed due to solubility, 139.83, 129.32, 123.89, 119.79, 117.90, 15.12, 7.36.

\[\text{N-phenyltetrahydro-2H-pyran-4-carboxamide:}\] To a round bottom flask fitted with a teflon coated magnetic stir bar was added tetrahydro-2H-pyran-4-carbocyclic acid (1.952 g, 15 mmol, 1 equiv.), pyridine (3.0 mL, 37.5 mmol, 2.5 equiv.) and dichloromethane (15 mL, 1 M) under nitrogen. \(\text{SOCl}_2\) (1.3 mL, 18 mmol, 1.2 equiv.) was then added dropwise via syringe over 3 minutes. The resulting mixture was stirred at room temperature for 30 minutes, then a solution of aniline (1.6 mL, 17.3 mmol, 1.15 equiv.), triethylamine (7.3 mL, 52.5 mmol, 3.5 equiv.) and DMAP (0.18 g, 1.5 mmol, 0.1 equiv.) in DCM (30 mL) was added. The resultant mixture was stirred overnight at room temperature. The reaction was quenched by addition of aqueous 1M HCl (50 mL), the phases where separated and
the aqueous layer extracted with DCM (2 x 30 mL). The combined organic phase was washed sequentially with saturated aqueous NaHCO₃ then saturated aqueous NaCl. The combined organic phase was dried over MgSO₄ and then concentrated to dryness on a rotary evaporator. The crude solid was recrystallized from EtOAc to yield N-phenylcyclopropanecarboxamide as a white solid (2.40 g, 11.7 mmol, 78% yield).

**¹H NMR** (500 MHz, Acetonitrile-d₃) δ 8.27 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 3.97 (dt, J = 11.5, 3.4 Hz, 2H), 3.49 – 3.35 (m, 2H), 2.63 – 2.50 (m, 1H), 1.76 (dt, J = 8.3, 4.6 Hz, 4H).

**¹³C NMR** (125 MHz, CD₃CN) δ 173.76, 139.69, 129.33, 124.07, 120.00, 117.90, 67.23, 43.01, 29.60.

![TFAN](image)

**N-phenyl-1-(2,2,2-trifluoroacetyl)piperidine-4-carboxamide:**

To a round bottom flask fitted with a teflon coated magnetic stir bar was added piperidine-4-carboxylic acid (10 g, 77.4 mmol, 1 equiv.) and trifluoroacetic anhydride (31 mL, 98 mmol, 1.25 equiv.). The resultant slurry was vigorously stirred for reflux for 4 hours. The excess trifluoroacetic anhydride and trifluoroacetic acid byproduct where removed under reduced pressure, and the resultant residue was taken up in EtOAc (150 mL), and sequentially washed with aqueous 1M HCl, and saturated aqueous NaCl. The organic fraction was dried over MgSO₄ and concentrated to dryness to give crude **N-phenyl-1-(2,2,2-trifluoroacetyl)piperidine-4-carboxamide** which was used in the next step without purification.
To a round bottom flask fitted with a teflon coated magnetic stir bar was added crude 1-(2,2,2-trifluoroacetyl)piperidine-4-carboxyclic acid (5.3g, 23.5 mmol, 1 equiv.), pyridine (4.7 mL, 58.8 mmol, 2.5 equiv.) and dichloromethane (25 mL, 1 M) under nitrogen. SOCl$_2$ (2.1 mL, 28.2 mmol, 1.2 equiv.) was then added dropwise via syringe over 3 minutes. The resulting mixture was stirred at room temperature for 30 minutes, then a solution of aniline (2.5 mL, 27.1 mmol, 1.15 equiv.), triethylamine (8.34 mL, 82.0 mmol, 3.5 equiv.) and DMAP (0.288g, 2.4 mmol, 0.1 equiv.) in DCM (50 mL) was added. The resultant mixture was stirred overnight at room temperature. The reaction was quenched by addition of aqueous 1M HCl (100 mL), the phases where separated and the aqueous layer extracted with DCM (2 x 60 mL). The combined organic phase was washed sequentially with saturated aqueous NaHCO$_3$ then saturated aqueous NaCl. The combined organic phase was dried over MgSO$_4$ and then concentrated to dryness on a rotary evaporator. The crude solid was recrystallized from EtOAc to yield N-phenylcyclopropanecarboxamide as a white solid (3.48 g, 16.9 mmol, 72% yield over 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.43 (d, $J = 7.9$ Hz, 2H), 7.27 (t, $J = 7.7$ Hz, 1H), 7.10 (s, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 4.44 (d, $J = 13.3$ Hz, 1H), 4.03 (d, $J = 14.1$ Hz, 1H), 3.21 (ddd, $J = 14.3$, 11.3, 3.0 Hz, 1H), 3.03 – 2.85 (m, 1H), 2.49 (tt, $J = 10.8$, 4.1 Hz, 1H), 1.97 (dt, $J = 13.6$, 4.0 Hz, 3H), 1.84 (ddtd, $J = 17.9$, 14.8, 11.1, 4.1 Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.42, 155.52 (q, $J = 35.8$ Hz), 137.41, 129.16, 124.74, 119.91, 116.51 (q, $J = 288.0$ Hz), 44.96 (q, $J = 3.7$ Hz), 43.40, 42.75, 28.89, 28.24.
**N-((1,1'-biphenyl)-2-yl)acetamide (117):** To a 100 mL round bottom flask fitted with a magnetic stir bar was added 2-aminobiphenyl (5.0 g, 29.6 mmol, 1 equiv.) and Ac₂O (20 mL, 212 mmol, 7.2 equiv.). The resultant suspension was stirred vigorously for 10 minutes before further addition of Ac₂O (10 mL, 106 mmol, 3.6 equiv.). The mixture was stirred for 10 more minutes before being poured onto ice (~130 g). The ice was allowed to melt and the resultant solid was isolated by vacuum filtration, dried under high vacuum and recrystallized from EtOAc to afford N-((1,1'-biphenyl)-2-yl)acetamide as a white solid (5.25 g, 24.9 mmol, 87% yield).

**^1H NMR** (500 MHz, CDCl₃): δ 8.29 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.43 (dd, J = 25.1, 7.2 Hz, 4H), 7.30 – 7.25 (m, 1H), 7.19 (dd, J = 19.0, 11.4 Hz, 2H), 2.05 (s, 3H).

**^13C NMR** (125 MHz, CDCl₃): δ 168.28, 138.17, 134.69, 132.19, 130.08, 129.26, 129.12, 128.46, 128.00, 124.39, 121.67, 24.64.

**2-(naphthalen-1-yl)phenylboronic acid (120):** To a 500 mL round bottom flask with a teflon coated magnetic stir bar, was added K₂CO₃ (5.53 g, 40.0 mmol, 1 equiv.), 1,2-dibromobenzene (11.80 g, 50.0 mmol, 1.250 equiv.), naphthalen-1-ylboronic acid (6.88 g, 40.0 mmol, 1 equiv.), tetrakis triphenylphosphine palladium (0) (46 mg, 0.04 mmol, 0.001 equiv.) and PhMe (200 mL, 0.2M). A reflux condenser was attached, and the reaction
mixture was heated to 90 °C for 20h. After the reaction was quenched by addition of aqueous 1M HCl (150 mL), and extracted with Et₂O (3x150 mL). The combined organic layer was washed with saturated brine and dried over MgSO₄ before being filtered through silica and concentrated to dryness to yield crude 1-(2-bromophenyl)naphthalene, which after drying under high-vacuum for 24 h was used in the next step without further purification.

To a round bottom flask containing a magnetic stir bar was added the crude 1-(2-bromophenyl)naphthalene (8.5 g, 30 mmol, 1.0 equiv) and THF (30 mL, 1 M) under nitrogen. The mixture was cooled to –78 °C and then n-BuLi (2.5 M in hexane, 15.6 mL, 39.0 mmol, 1.3 equiv.) was added dropwise over 10 minutes. The mixture was stirred for 1 h at –78 °C before triethyl borate (25.5 mL, 150 mmol, 5 equiv.) was added. The reaction was stirred for another 90 minutes at –78 °C before being warmed to room temperature where it was stirred for a further 1 hour. The reaction was quenched by the addition of aqueous 2M HCl (200 mL) and diethyl ether (100 mL), the resultant slurry was stirred vigorously for 30 minutes before filtration. The resultant biphasic mixture was separated and the aqueous layer extracted with ether (2 x 100 mL). The combined organic fractions were washed with saturated aqueous NaCl (150 mL) and concentrated to dryness to yield the crude product. The crude was recrystallized from EtOAc twice to furnish (2-(naphthalen-1-yl)phenyl)boronic acid as a pale yellow solid (3.76 g, 14.9 mmol, 49% yield over 2 steps).

**¹H NMR** (500 MHz, Acetonitrile-\(d_3\)): \(\delta\) 7.98 (dd, \(J = 14.5, 8.2\) Hz, 2H), 7.81 (dd, \(J = 7.4, 1.5\) Hz, 1H), 7.63 (d, \(J = 8.5\) Hz, 1H), 7.60 – 7.52 (m, 3H), 7.51 – 7.41 (m, 3H), 7.35 (d, \(J = 7.5\) Hz, 1H), 5.34 (s, 2H).
\[^{13}\text{C} \text{NMR} \ \delta (125 \text{ MHz, CD}_3\text{CN}): \ \delta 134.13, 130.72, 129.89, 128.77, 128.28, 127.42, 127.30, 126.74, 126.58, 126.50, 125.91.\] Due to low solubility the carbons with no H-atom substituents were not observed.

III. Optimized Procedure

**General Procedure:** To an 8 mL vial equipped with a Teflon septum and a magnetic stir bar was charged K\(_2\)S\(_2\)O\(_8\) (202.7 mg, 0.75 mmol, 1.5 equiv.), amide (0.5 mmol, 1.0 equiv.), boronic acid (0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN. The reaction mixture was degassed by sparging with nitrogen for 10 min with an outlet needle, then irradiated with the blue LEDs (2×34 W for 4 vials, approximately 2 cm away from the light source) at room temperature under two mini fans. After 20 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL), washed with 0.5 M NaOH aqueous solution (20 mL) and brine (20 mL), dried over Na\(_2\)SO\(_4\), and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

III. UV-Vis measurements

Electronic absorption spectra were acquired using a Cary 50 spectrophotometer. Spectra work collected at 2.5 µM in Co, in a quartz cuvette of path length 1 cm, in MeCN. Amide and boronic acid spectra where collected at 250 µM. Studies where amide and boronic acid where added to the Co where measured at 2.5 µM in Co with 100 equivalents.
of PhNHAc or 4-CF$_3$C$_6$H$_4$B(OH)$_2$ to mimic the stoichiometry of the reaction mixture. Co(acac)$_2$ was pre-ligated with 4,4’-dBrbpy before addition to the cuvette. For the Job method, stock solutions of Co(acac)$_2$ and 4,4’-dBrbpy where prepared and mixed in appropriate ratio to give a fixed concentration of 0.625 µM. Measurements of the reaction mixture for quantum yield determination where taken at 450 nm at 2.5 µM, half the concentration of the reaction mixture.

V. Magnetic Moment determination and PhotoNMR Experiment

The magnetic moment of Co(4,4’-dBrbpy)(acac)$_2$ was conducted using the Evans method.$^{111}$ A pipette was fused with a blow torch at one end and a solution of DCM in d$_3$-MeCN was added (0.01M). The other end of the pipette was then exposed to mild vacuum and sealed with a blow torch to give a capillary tube fused a both ends containing a solution of DCM in d$_3$-MeCN. To a separate vial was added 20mg of Co(4,4’-dBrbpy)(acac)$_2$ (0.78 µmol), 6 ml of d$_3$-MeCN and DCM (3.8 µL, 0.1 M). To an NMR was added the capillary tube and 400 µL of the cobalt solution. NMR measurement was taken on a custom 400 MHz Bruker cryoprobe instrument, a peak shift of 0.29 ppm was observed for the DCM resonance in the $^1$H NMR. This corresponds to a magnetic moment per cobalt center of 3.58 µB which corresponds to $s = 3/2$ system (calculation shown below), consistent with a high-spin Co(II) configuration.

\[
\Delta f(\text{Hz}) = \frac{\Delta \text{ppm} F}{10^6} = \frac{(400 \times 10^6)(0.29)}{10^6} = 116 \text{ Hz}
\]

\[
X_M = \frac{3m}{4\pi Fc} = \frac{3(116)}{4\pi(500 \times 10^6)(1.30 \times 10^{-5})} = 0.00534 \text{ cm}^3 \text{ mol}^{-1}
\]

\[
\mu = (8(X_M T)^{1/2}) = (8(0.00534)(301.3)^{1/2}) = 3.59 \mu_B
\]

In a similar experiment, to a solution of 20 mg of Co(4,4'-dBrbpy)(acac)₂ (78 µmol), 6 ml of d₃-MeCN and DCM (3.8 µL, 0.1 M) prepared as above, was added 76 mg trifluoromethyl phenyl boronic acid (0.4 mmol) and 108 mg potassium persulfate, the mixture was then aged for ten minutes. 400 µL of it was added to an NMR tube containing a sealed capillary tube containing 0.01M DCM in d₃-MeCN. A similar NMR measurement as above was made, here the observed peak shift was 0.46 ppm, corresponding to magnetic moment per cobalt center of 4.56 µB (calculation shown below), suggestive of an s = 2 system, consistent with a high-spin Co(III) configuration.

\[ \Delta f(\text{Hz}) = \frac{\Delta \text{ppm} F}{10^6} = \frac{(400 \times 10^6) / (0.46)}{10^6} = 184.1 \text{ Hz} \]

\[ X_m = \frac{3 \Delta f}{4 \pi \mu c}\]

\[ \mu = (8(X_m T))^{1/2} = (8(0.00847)(301.3))^{1/2} = 4.52 \mu_B \]

In order to probe the spin-state of the catalyst resting state during the reaction, to an 8 mL vial equipped with a magnetic stir bar was charged K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), amide (0.5 mmol, 1.0 equiv.), boronic acid (0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.), methyl 4-fluorobenzoate (65 µL, 0.5 mmol, 1.0 equiv.), DCM (32 µL, 0.5 mmol, 1 equiv.) and 2.0 mL of d₃-MeCN. A 400 µL aliquot was removed and added to an NMR tube equipped with a capillary tube which contained a 0.05 M solution of DCM in d₃-MeCN. The sample was then subjected to continuous irradiation at 420 nm (1.4 W Blue LEDs through fiberoptic cable) inside an NMR machine.
\(^1\)H NMR and \(^{19}\)F NMR measurements where alternatively made for 24h at which point the reaction had reached 28\% yield of desired product, determined by \(^{19}\)F NMR against methyl 4-fluorobenzoate as internal standard, and independently verified by UPLC-MS analysis. The low levels of conversion can be attributed to low light intensity and no-agitation of the sample inside the magnet, which resulted in poor mass transfer of the \(\text{K}_2\text{S}_2\text{O}_8\) into solution. The peak shift for the DCM resonance in the \(^1\)H NMR was 0.08 ppm at the beginning of the experiment, which corresponds to a magnetic moment of 4.4 \(\mu_B\) per cobalt center (calculation shown below). The magnetic moment of the sample progressed as shown below, no noticeable change was observed suggesting the catalyst resting state is high-spin Co(III) throughout the reaction.

\[
\Delta f(\text{Hz}) = \frac{\Delta \text{ppm F}}{10^6} = \frac{(400 \times 10^6)(0.08)}{10^6} = 32 \text{ Hz}
\]

\[
X_m = \frac{3\mu}{4\pi F_0} = \frac{3(32)}{4\pi(500 \times 10^6)(1.30 \times 10^6)} = 0.007559 \text{ cm}^3 \text{ mol}^{-1}
\]

\[
\mu = \sqrt{(8X_m T)}^{1/2} = \sqrt{(8(0.007559)(301.3))^{1/2}} = 4.4 \mu_B
\]

VI. Quantum yield measurement

Quantum Yield Measurements Procedure: All quantum yield measurements were carried out in a prototype m1 photoreactor at 450 nm irradiation, 1000 rpm stirring, and 4700 rpm fan speed. Light output from the photoreactor was measured using the standard actinometer, potassium ferrioxalate(\(\text{K}_3\)[\(\text{Fe(C}_2\text{O}_4)\]3]). Photoinduced decomposition of the actinometer was monitored by UV/vis absorption spectroscopy, according to a published procedure to measure the reactor’s output at 10\% intensity. Since no literature value for the quantum yield of ferrioxalate decomposition at 450 nm irradiation exists, the value of
\( \Phi_{450} = 0.94 \) was obtained by interpolation of literature values for \( \Phi_{436} \) and \( \Phi_{458} \) (1.1 and 0.85, respectively).\textsuperscript{108A}
VII. Kinetics measurement procedure

**General Procedure for kinetics measurements:** To an 8 mL vial equipped with a Teflon septum and a magnetic stir bar was charged K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), amide (0.5 mmol, 1.0 equiv.), boronic acid (0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.), methyl 4-fluorobenzoate (65 µl, 0.5 mmol, 1.0 equiv) and 2.0 mL of MeCN. The reaction mixture was degassed by sparging with nitrogen for 10 min with an outlet needle, then irradiated in the M1 photoreactor. The LED intensity of the photoreactor was set to 100 %, the fans where set to 1500 RPM to maintain a reaction temperature of ~ 50 ºC with 1000 RPM magnetic stirring. Aliquots where removed via micro syringe through the septa at appropriate time points. The aliquot was diluted with MeCN and analyzed via UPLC-MS analysis. Time points where varied as a function of the experiment. For competition studies, 0.375 mmol and both amide (0.75 mmol total) or 0.5 mmol of both boronic acid (1.0 mmol total, 2.0 equiv.) where used in the procedure outlined above. All reported yields are an average of two measurements taken on separate days and where within 3% yield.
VII. Product Characterization

*N-Phenyl-4-isopropylacetanilide (86)*: According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-isopropylphenylboronic acid (126.8 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4′-dibromo-2,2′-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (120.3 mg, 95% yield).

^1^H NMR (500 MHz, CDCl₃): δ 7.50 - 7.08 (m, 9H), 2.90 (m, 1H), 2.06 (s, 3H), 1.24 (m, 6H).

^13^C NMR (125 MHz, CDCl₃): δ 170.5, 148.5, 142.7, 140.9, 129.6, 128.8, 128.4, 128.2, 127.6, 126.9, 126.3, 33.6, 23.8, 23.7.

HRMS (ESI-TOF) m/z calculated for C₁₇H₂₀N O [(M+H)+] 254.1539, found 154.1538.

IR (film) 3034, 2960, 1673, 1593, 1508, 1490, 1367, 1320, 1295, 1020, 831 cm⁻¹.

*N-Phenyl-3,5-(di-tert-butyl)acetanilide (87)*: According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.),
3,5-di-tert-butylphenylboronic acid (184.8 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4’-dibromo-2,2’-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (148.8 mg, 92% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.50 - 7.15 (m, 6H), 7.09 (s, 2H), 2.04 (s, 3H), 1.30 (s, 18H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.6, 152.5, 151.2, 142.7, 129.5, 128.8, 128.4, 127.5, 126.1, 125.8, 122.6, 121.5, 120.9, 120.5, 34.9, 31.3, 23.9.

HRMS (ESI-TOF) m/z calculated for C$_{22}$H$_{30}$NO [(M+H)$^+$] 324.2322, found 324.2321.

IR (film) 3063, 2959, 2905, 2867, 1674, 1593, 1495, 1428, 1366, 1306, 1247, 1032, 899 cm$^{-1}$.

$N$-Phenyl-2,4,6-trimethylacetanilide (88): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetonilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 2,4,6-trimethylphenylboronic acid (126.8 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4’-dibromo-2,2’-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (115.3 mg, 91% yield).
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31 - 7.23 (m, 4H), 7.11 - 7.05 (m, 1H), 6.98 (s, 2H), 2.33 (minor 2.29) (s, 3H), 2.16 (minor 2.16) (s, 6H), 1.90 (minor 2.27) (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.6, 140.7, 138.3, 137.9, 136.2, 129.9, 128.4, 124.5, 123.2, 23.8, 21.0, 17.9.

HRMS (ESI-TOF) m/z calculated for C$_{17}$H$_{20}$NO [(M+H)$^+$] 254.1539, found 254.1539.

IR (film) 2921, 1674, 1595, 1489, 1365, 1295, 1256, 1032, 1012, 853 cm$^{-1}$. Spectra data are consistent with those reported in the literature.\(^\text{112}\)

\[ \text{N-Phenyl-2-phenylacetanilide (89): According to the general procedure, K}_2\text{S}_2\text{O}_8 \text{ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 2-biphenylboronic acid (153.1 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (123.5 mg, 86% yield).} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.83 - 6.40 (m, 15H), 1.98 (minor 2.07) (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.9 (minor 170.3), 142.7 (minor 142.0), 140.6, 139.6 (minor 138.4), 131.1 (minor 131.7), 129.4 (minor 130.1), 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.5, 127.3 (minor 126.9), 125.4 (minor 125.0), 27.8 (minor 24.2).

HRMS (ESI-TOF) m/z calculated for C$_{20}$H$_{18}$NO [(M+H)$^+$] 288.1383, found 288.1383.

IR (film) 3059, 2926, 1667, 1593, 1490, 1478, 1434, 1367, 1332, 1292, 1032, 1009, 759 cm\(^{-1}\).

\[
\begin{align*}
\text{N-Phenyl-2’-bromoacetanilide (90): } & \text{ According to the general procedure, K}_2\text{S}_2\text{O}_8 (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 2-bromophenylboronic acid (158.5 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a colorless oil (135.0 mg, 93\% yield).
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.70 - 7.17 \) (m, 9H), 2.02 (minor 2.13) (s, 3H).

\(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 170.1, 142.0\) (minor 141.1), 134.2 (minor 133.6), 131.1 (minor 130.1), 129.8 (minor 129.5), 129.0 (minor 128.6), 127.6 (minor 127.8), 125.7 (minor 126.0), 124.3 (minor 123.1), 23.7 (minor 22.8).

HRMS (ESI-TOF) m/z calculated for C\(_{14}\)H\(_{13}\)BrNO [(M+H)\(^+\)] 290.0175, found 290.0175.

IR (film) 3061, 1676, 1594, 1491, 1472, 1368, 1325, 1299, 1029, 757 cm\(^{-1}\).

Spectra data are consistent with those reported in the literature.\(^ {112}\)

\[
\begin{align*}
\text{N-Phenyl-2’-chloroacetanilide (91): } & \text{ According to the general procedure, K}_2\text{S}_2\text{O}_8 (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 2-
\end{align*}
\]
chlorophenylboronic acid (123.5 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (119.1 mg, 97% yield).

\textbf{1H NMR} (500 MHz, CDCl$_3$): $\delta$ 7.67 - 7.01 (m, 9H), 2.02 (minor 2.12) (s, 3H).

\textbf{13C NMR} (125 MHz, CDCl$_3$): $\delta$ 170.2, 141.3 (minor 142.8), 140.6 (minor 140.3), 133.6 (minor 132.6), 130.9, 130.4, 130.0, 129.6, 129.5, 128.7, 128.3, 127.8, 127.6, 126.1, 125.9, 23.3 (minor 22.7).

\textbf{HRMS} (ESI-TOF) m/z calculated for C$_{14}$H$_{13}$ClNO [(M+H)$^+$] 246.0680, found 246.0681.

\textbf{IR} (film) 3063, 1676, 1594, 1492, 1476, 1369, 1327, 1299, 1065, 1033, 757 cm$^{-1}$.

\textbf{N-(1-Naphthalenyl)-acetanilide (92):} According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 1-naphthalenylboronic acid (135.8 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (120.2 mg, 92% yield).
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.10 - 8.01 (m, 1H), 7.99 - 7.77 (m, 2H), 7.63 - 7.43 (m, 4H), 7.43 - 7.38 (m, 2H), 7.37 - 7.23 (m, 2H), 7.23 - 7.06 (m, 1H), 1.95 (minor 2.28) (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.0, 142.4, 139.3, 134.7, 130.9, 128.9, 128.7, 128.5, 127.7, 127.2, 126.6, 125.8, 125.6, 125.0, 122.8, 23.7.

HRMS (ESI-TOF) m/z calculated for C$_{18}$H$_{16}$NO [(M+H)$^+$] 262.1226, found 262.1226.

IR (film) 3058, 2925, 1670, 1594, 1493, 1392, 1367, 1318, 1294, 1276, 1016, 801 cm$^{-1}$.

$N$-Phenyl-4-(trifluoromethoxy)acetanilide (93): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-(trifluoromethoxy)phenylboronic acid (157.6 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4'-dibromo-2,2'-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a colorless oil (137.3 mg, 93% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58 - 7.06 (m, 9H), 2.06 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 146.6, 142.9, 141.1, 129.9, 128.5, 128.1, 127.4, 126.5, 121.4, 120.3 (q, $J_{C-F}=257.4$ Hz, 1C), 23.8.

HRMS (ESI-TOF) m/z calculated for C$_{15}$H$_{13}$F$_3$NO$_2$ [(M+H)$^+$] 296.0893, found 296.0893.

IR (film) 3064, 1674, 1594, 1503, 1493, 1370, 1324, 1249, 1208, 1156, 1018, 922 cm$^{-1}$.
**N-Phenyl-4'-acetylacetanilide (94):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-acetylphenylboronic acid (125.5 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (117.8 mg, 93% yield).

**¹H NMR** (500 MHz, CDCl₃): δ 7.92 (d, J = 8.2 Hz, 2H), 7.43 (t, J = 7.0 Hz, 2H), 7.39 - 7.29 (m, 3H), 7.42 - 7.35 (m, 1H), 7.33 - 7.26 (m, 2H), 2.07 (s, 3H).

**¹³C NMR** (125 MHz, CDCl₃): δ 196.9, 170.4, 146.8, 142.4, 134.3, 129.8, 129.1, 128.2, 128.0, 125.9, 26.5, 24.1.

**HRMS** (ESI-TOF) m/z calculated for C₁₆H₁₆NO₂ [(M+H)⁺] 254.1176, found 254.1177.

**IR** (film) 3330, 3060, 3008, 1676, 1596, 1492, 1366, 1320, 1296, 1266, 1178, 1018, 958 cm⁻¹.

**N-Phenyl-4-formylacetanilide (95):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-
formylphenylboronic acid (118.3 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4’-dibromo-2,2’-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (110.0 mg, 92% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.93 (s, 1H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.50 - 7.39 (m, 4H), 7.36 (t, $J = 7.3$ Hz, 1H), 7.28 - 7.22 (m, 2H), 2.06 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.0, 170.4, 147.9, 142.3, 133.5, 130.3, 129.9, 128.4, 128.1, 126.2, 24.2.

HRMS (ESI-TOF) m/z calculated for C$_{15}$H$_{14}$NO$_2$ [(M+H)$^+$] 240.1019, found 240.1018.

IR (film) 3056, 2831, 2617, 1697, 1673, 1594, 1506, 1491, 1368, 1319, 1282, 1211, 1165, 1017, 828 cm$^{-1}$.

Methyl 4-(N-Phenylacetamido)benzoate (96): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-methoxycarbonylphenylboronic acid (139.2 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and
purified by flash chromatography (10% ethyl acetate/hexanes) to provide the title compound as a white solid (130.6 mg, 97% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.99 (d, $J = 8.1$ Hz, 2H), 7.41 (t, $J = 7.0$ Hz, 2H), 7.38 - 7.27 (m, 3H), 7.24 (d, $J = 7.8$ Hz, 2H), 3.88 (s, 3H), 2.06 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.5, 141.8, 135.8, 129.9, 127.4, 127.1, 127.0, 125.6, 119.2, 22.4.

HRMS (ESI-TOF) m/z calculated for C$_{16}$H$_{16}$NO$_3$ [(M+H)$^+$] 270.1125, found 270.1125.

IR (film) 3006, 2952, 1717, 1675, 1604, 1594, 1491, 1434, 1367, 1318, 1269, 1175, 1107, 1018, 854 cm$^{-1}$.

$N$-Methyl-4-($N$-phenylacetamido)benzamide (97): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.), 4-(methylaminocarbonyl)phenylboronic acid (137.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4'-dibromo-2,2'-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (50% - 100% ethyl acetate/hexanes) to provide the title compound as a white solid (107.3 mg, 80% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.81 - 7.61 (m, 2H), 7.48 - 7.36 (m, 2H), 7.35 - 7.28 (m, 1H), 7.28 - 7.20 (m, 4H), 6.61 (br s, 1H), 2.92 (s, 3H), 2.05 (s, 3H).
**$^{13}$C NMR** (125 MHz, CDCl$_3$): δ 158.5, 141.8, 135.8, 129.9, 127.4, 127.1, 127.0, 125.6, 119.2, 22.4.

**HRMS** (ESI-TOF) m/z calculated for C$_{16}$H$_{17}$N$_2$O$_2$ [(M+H)$^+$] 269.1285, found 269.1286.

**IR** (film) 3332, 3059, 2938, 1650, 1605, 1549, 1502, 1491, 1370, 1296, 1157, 1028, 852 cm$^{-1}$.

$N$-Phenyl-4’-(trifluoromethyl)acetanilide (77): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), 4’-(trifluoromethyl)acetanilide (103.7 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (127.0 mg, 91% yield).

**$^1$H NMR** (500 MHz, CDCl$_3$): δ 7.59 - 7.58 (m, 2H), 7.45 - 7.42 (m, 2H), 7.40 - 7.38 (m, 3H), 7.27 - 7.26 (m, 2H), 2.08 (s, 3H).

**$^{13}$C NMR** (125 MHz, CDCl$_3$): δ 170.4, 145.8, 142.5, 129.9, 128.2, 126.1, 123.8 (q, $J_{C-F} = 271.9$ Hz, 1C), 24.0.
HRMS (ESI-TOF) m/z calculated for C_{15}H_{13}F_{3}NO [(M+H)^+] 280.0944, found 280.0942.

IR (film) 3064, 1679, 1614, 1594, 1491, 1371, 1323, 1297, 1164, 1117, 1067, 1017, 839 cm\(^{-1}\). Spectra data are consistent with those reported in the literature.\(^{113}\)

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\textbf{N-Phenyl-4'-cyanooacetanilide (98):} According to the general procedure, K\(_2\)S\(_2\)O\(_8\) (202.7 mg, 0.75 mmol, 1.5 equiv.), 4'-cyanooacetanilide (81.7 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (95.6 mg, 81% yield).

\( ^1\text{H NMR} \text{ (500 MHz, CDCl}_3\text{):} \delta 7.58 \text{ (d, } J = 8.4 \text{ Hz, 2H), } 7.47 \text{ (t, } J = 7.5 \text{ Hz, 2H), } 7.41 \text{ (d, } J = 7.1 \text{ Hz, 1H), } 7.37 \text{ (d, } J = 8.5 \text{ Hz, 2 H), } 7.24 \text{ (d, } J = 7.8 \text{ Hz, 2H), } 2.05 \text{ (s, 3H).} \)

\( ^{13}\text{C NMR} \text{ (125 MHz, CDCl}_3\text{):} \delta 170.5, 146.5, 142.0, 132.7, 130.1, 128.5, 126.0, 118.5, 108.8, 24.3. \)

HRMS (ESI-TOF) m/z calculated for C_{15}H_{13}N_{2}O [(M+H)^+] 237.1022, found 237.1022.

IR (film) 3062, 2226, 1678, 1603, 1594, 1503, 1492, 1367, 1323, 1293, 1175, 1020, 838 cm\(^{-1}\). Spectra data are consistent with those reported in the literature.\(^{113}\)

**4-(N-Phenylacetamido)benzoic acid (99):** According to the general procedure, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (202.7 mg, 0.75 mmol, 1.5 equiv.), 4-acetamidobenzoic acid (91.5 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4’-dibromo-2,2’-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (50% ethyl acetate/hexanes) to provide the title compound as a white solid (109.7 mg, 86% yield).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 10.96 (br s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.40 - 7.32 (m, 3H), 7.27 (d, J = 7.9 Hz, 2H), 2.10 (s, 3H).

**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>): δ 170.8(2C), 147.3, 142.3, 131.1, 129.8, 128.2, 126.7, 125.9, 24.1.

**HRMS (ESI-TOF) m/z calculated for C<sub>15</sub>H<sub>14</sub>NNO<sub>3</sub> [(M+H)<sup>+</sup>] 256.0968, found 256.0969.**

**IR (film) 3070, 2923, 2852, 2533, 1671, 1595, 1491, 1420, 1364, 1272, 1171, 1019, 950 cm<sup>-1</sup>.**

**4-(N-Phenylacetamido)benzenesulfonyl azide (100):** According to the general procedure, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (202.7 mg, 0.75 mmol, 1.5 equiv.), 4-acetamidobenzenesulfonyl azide (123.8 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.),
Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (126.6 mg, 80% yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.91 - 7.82\) (m, 2H), 7.55 - 7.46 (m, 4H), 7.46 - 7.41 (m, 1H), 7.30 - 7.24 (m, 2H), 2.07 (s, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 170.7, 148.2, 141.8, 134.3, 130.3, 128.8, 128.7, 128.2, 125.9, 24.5\).

HRMS (ESI-TOF) m/z calculated for C\(_{14}\)H\(_{13}\)N\(_4\)O\(_3\)S [(M+H)\(^+\)] 317.0703, found 317.0702.

IR (film) 3066, 2363, 2126, 1681, 1584, 1491, 1367, 1293, 1164, 1089, 1019, 836 cm\(^{-1}\).

\(N\)-Phenyl-3’-nitroacetanilide (101): According to the general procedure, K\(_2\)S\(_2\)O\(_8\) (202.7 mg, 0.75 mmol, 1.5 equiv.), 3’-nitroacetanilide (92.9 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a colorless oil (110.2 mg, 86% yield).
**N-Phenyl-4'-iodoacetanilide (102):** According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), 4'-idoacetanilide (137.3 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (151.8 mg, 90% yield).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.75 - 7.55 (m, 2H), 7.46 - 7.27 (m, 3H), 7.26 - 7.20 (m, 2H), 7.05 - 7.00 (m, 2H), 2.05 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 170.2, 142.8, 138.7, 137.9, 129.8, 128.4, 128.0, 126.4, 90.5, 23.8.

HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{13}$O$_3$ [(M+H)$^+$] 338.0036, found 338.0036.

IR (film) 3059, 1671, 1594, 1483, 1367, 1319, 1294, 1007, 819 cm$^{-1}$.

Spectra data are consistent with those reported in the literature.\textsuperscript{112}
**N-Phenyl-4’-bromoacetanilide (103):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), 4’-bromoacetanilide (109.2 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a colorless oil (133.5 mg, 92% yield).

**1H NMR** (500 MHz, CDCl₃): δ 7.60 - 7.28 (m, 5H), 7.27 - 7.18 (m, 2H), 7.17 - 7.13 (m, 2H), 2.05 (s, 3H).

**13C NMR** (125 MHz, CDCl₃): δ 170.3, 142.7, 141.6, 132.8, 131.9, 129.8, 128.4, 127.8, 126.3, 119.3, 23.8.

**HRMS** (ESI-TOF) m/z calculated for C₁₄H₁₃BrNO [(M+H)⁺] 290.0175, found 290.0177.

**IR** (film) 3062, 1673, 1594, 1486, 1368, 1320, 1069, 1011, 984 cm⁻¹.

Spectra data are consistent with those reported in the literature.¹¹²

**N-Phenyl-4’-chloroacetanilide (104):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), 4’-chloroacetanilide (87.5 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg,
0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a colorless oil (114.3 mg, 93% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40 - 7.20 (m, 9H), 2.06 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.3, 142.9, 141.1, 131.4, 129.8, 128.9, 128.4, 128.0, 127.4, 126.4, 23.8.

HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{13}$ClNO [(M+H)$^+$] 246.0680, found 246.0681.

IR (film) 3061, 1673, 1594, 1489, 1369, 1321, 1298, 1090, 1014, 986 cm$^{-1}$.

Spectra data are consistent with those reported in the literature.$^{112}$

\[
\begin{align*}
\text{N-Phenyl-4'-fluoroacetanilide (105):} & \quad \text{According to the general procedure, K}_2\text{S}_2\text{O}_8 (202.7 mg, 0.75 mmol, 1.5 equiv.), 4'-fluoroacetanilide (78.2 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a colorless oil (108.8 mg, 95% yield).} \\
^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.50 - 6.93 (m, 9H), 2.05 (s, 3H).
\end{align*}
\]
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 160.5 (d, $J_{C-F} = 250.2$ Hz, 1C), 143.2, 138.5, 130.1, 129.8, 129.0, 128.3, 128.1, 126.2, 116.6, 115.8, 115.6, 23.7.

HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{13}$FNO [(M+H)$^+$] 230.0976, found 230.0976.

IR (film) 3064, 1670, 1595, 1504, 1376, 1326, 1304, 1220, 1154, 1094, 1015, 836 cm$^{-1}$.

$N$-Phenyl-$m$-acetanisidine (106): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), $m$-acetanisidine (86.9 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4'-dibromo-2,2'-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.), pyridine (8.0 µL, 0.1 mmol, 0.2 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (109.8 mg, 91% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 - 7.13 (m, 6H), 7.01 - 6.66 (m, 3H), 3.78 (s, 3H), 2.07 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 160.2, 144.3, 142.5, 130.2, 129.6, 128.9, 128.3, 127.8, 126.2, 120.7, 118.8, 114.4, 113.0, 112.5, 111.7, 55.3, 23.8.

HRMS (ESI-TOF) m/z calculated for C$_{15}$H$_{16}$NO$_2$ [(M+H)$^+$] 242.1176, found 242.1176.

IR (film) 3061, 2927, 1670, 1591, 1486, 1368, 1302, 1280, 1227, 1151, 1041, 1004, 864 cm$^{-1}$. 

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**N-Phenyl-p-acetotoluidide (107):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), p-acetotoluidide (76.1 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4'-dibromo-2,2'-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (110.3 mg, 98% yield). **¹H NMR** (500 MHz, CDCl₃): δ 7.32 - 7.15 (m, 9H), 2.35 (s, 3H), 2.06 (s, 3H).

**¹³C NMR** (125 MHz, CDCl₃): δ 170.5, 143.6, 140.8, 137.7, 130.3, 129.6, 128.8, 128.2, 127.6, 126.2, 125.9, 23.7, 21.0.

**HRMS** (ESI-TOF) m/z calculated for C₁₅H₁₆NO [(M+H)⁺] 226.1226, found 226.1226.

**IR** (film) 3032, 2923, 1668, 1594, 1508, 1492, 1367, 1326, 1295, 1031, 987 cm⁻¹.

Spectra data are consistent with those reported in the literature.¹¹²

**N-Phenyl-o-acetotoluidide (108):** According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), o-acetotoluidide (76.1 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4'-dibromo-2,2'-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup
procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (109.2 mg, 97% yield). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.29 - 9.13 (m, 9H), 2.22 (minor 2.32) (s, 3H), 1.96 (minor 2.15) (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 141.6, 141.3, 136.2, 131.8, 129.7, 128.5, 127.3, 125.3, 125.0, 23.9, 17.9.

HRMS (ESI-TOF) m/z calculated for C$_{15}$H$_{16}$NO [(M+H)$^+$] 226.1226, found 226.1227.

IR (film) 3048, 1672, 1595, 1489, 1368, 1332, 1301, 1032, 980 cm$^{-1}$.

Spectra data are consistent with those reported in the literature.$^{112}$

\[ \text{N,N-Diphenylacetamide: According to the general procedure, K}_2\text{S}_2\text{O}_8 \ (202.7 \text{ mg, 0.75 mmol, 1.5 equiv.}), \text{acetanilide (68.3 mg, 0.5 mmol, 1.0 equiv.)}, \text{phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.)}, \text{Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.)}, \text{4,4'-dibromo-2,2'-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (102.5 mg, 97% yield).} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36 - 7.20 (m, 10H), 2.07 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.4, 143.3, 142.6, 129.7, 128.9, 128.4, 127.8, 126.4, 126.1, 23.8.

HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{14}$NO [(M+H)$^+$] 212.1070, found 212.1069.

IR (film) 3038, 1668, 1592, 1488, 1368, 1332, 1295, 1030, 1002 cm$^{-1}$.

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Spectra data are consistent with those reported in the literature.\textsuperscript{112}

\begin{center}
\includegraphics[width=0.2\textwidth]{phényl.png}
\end{center}

1-Phenyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (109): According to the general procedure, K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (202.7 mg, 0.75 mmol, 1.5 equiv.), 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (82.2 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-dibromo-2,2’-bipyridine (3.2 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (109.1 mg, 92% yield).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.39 - 7.32 (m, 2H), 7.28 - 7.23 (m, 2H), 7.22 - 7.18 (m, 2H), 7.18 - 7.13 (m, 2H), 6.88 - 6.83 (m, 1H), 2.93 (t, \textit{J} = 7.2 Hz, 2H), 2.47 (t, \textit{J} = 7.1 Hz, 2H), 2.27 (p, \textit{J} = 7.2 Hz, 2H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 172.8, 143.3, 142.0, 135.7, 129.2, 128.9, 127.5, 127.4, 126.5, 126.3, 125.2, 33.8, 30.1, 29.0.

HRMS (ESI-TOF) m/z calculated for C\textsubscript{16}H\textsubscript{16}NO [(M+H)\textsuperscript{+}] 238.1226, found 238.1227.

IR (film) 3062, 2943, 2862, 1671, 1599, 1487, 1448, 1353, 11273, 1142, 1108, 959 cm\textsuperscript{-1}.

\begin{center}
\includegraphics[width=0.2\textwidth]{formamide.png}
\end{center}

\textit{N,N}-Diphenylformamide (111): According to the general procedure, K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (202.7 mg, 0.75 mmol, 1.5 equiv.), formanilide (61.2 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid
(95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (2.6 mg, 0.01 mmol, 0.02 equiv.), 4,4’-dibromo-2,2’-bipyridine (6.4 mg, 0.02 mmol, 0.04 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% ethyl acetate/hexanes) to provide the title compound as a white solid (83.8 mg, 85% yield).

\(^1\)HNMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.68 (s, 1H), 7.43 - 7.38 (m, 4H), 7.33 - 7.26 (m, 4H), 7.18 - 7.17 (m, 2H).

\(^13\)CNMR (125 MHz, CDCl\(_3\)): \(\delta\) 161.7, 141.7, 139.6, 129.7, 129.2, 127.0, 126.8, 126.1, 125.0.

HRMS (ESI-TOF) m/z calculated for C\(_{13}\)H\(_{12}\)NO \([\text{M+H}]^+\) 198.0913, found 198.0914.

IR (film) 3063, 2924, 1668, 1590, 1490, 1452, 1333, 1259, 1132, 950 cm\(^{-1}\).

Spectra data are consistent with those reported in the literature.\(^{114}\)

2-Phenylphthalazin-1(2H)-one (112): According to the general procedure, K\(_2\)S\(_2\)O\(_8\) (202.7 mg, 0.75 mmol, 1.5 equiv.), phthalalzone (73.9 mg, 0.5 mmol, 1.0 equiv.), phenylboronic acid (95.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (3.9 mg, 0.015 mmol, 0.03 equiv.), 4,4’-di-tert-butyl-2,2’-bipyridine (8.3 mg, 0.03 mmol, 0.06 equiv.) and 5.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (10% MeOH/CH\(_2\)Cl\(_2\)) to provide the title compound as a white solid (98.9 mg, 89% yield).

\(^{114}\) Fu, R.; Yang, Y.; Ma, Yunsheng, Yang, F.; Li, J.; Chai, W.; Wang, Q.; Yuan, R. Tetrahedron Lett. 2015, 56, 4527.
$^1$H NMR (500 MHz, CDCl$_3$): δ 8.51 (d, $J = 7.7$ Hz, 1H), 8.29 (s, 1H), 7.84 (t, $J = 7.4$ Hz, 1H), 7.80 (t, $J = 7.4$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.50 (t, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 7.5$ Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 159.1, 141.8, 138.4, 133.4, 129.4, 128.7, 128.5, 127.7, 127.2, 126.1, 125.7.

HRMS (ESI-TOF) m/z calculated for C$_{14}$H$_{11}$N$_2$O [(M+H)$^+$] 223.0866, found 223.0866.

IR (film) 3059, 2925, 2854, 1653, 1584, 1453, 1328, 1309, 1137, 1059, 904 cm$^{-1}$.

Spectra data are consistent with those reported in the literature.$^{115}$

$\text{N-phenyl-N-(4-(trifluoromethyl)phenyl)propionamide (113):}$ According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), N-phenylpropionamide (74.6 mg, 0.5 mmol, 1.0 equiv.), 4-trifluoromethyl phenylboronic acid (143.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-di-bromo -2,2’-bipyridine (2.8 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% EtOAc/hexane) to provide the title compound as a white solid (120 mg, 82% yield).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, $J = 8.2$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.38 (m, 3H), 7.28 – 7.23 (m, 2H), 2.27 (q, $J = 7.4$ Hz, 2H), 1.14 (t, $J = 7.4$ Hz, 3H).

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$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.10, 146.02, 142.31, 130.03, 128.64, 128.15 126.20, 124.04 (q, $J = 272.0$ Hz), 116.65, 29.25, 9.70.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -62.4.

HRMS (ESI-TOF) m/z calculated for C$_{16}$H$_{15}$F$_3$NO [(M+H)$^+$] 294.1100, found 294.1101.

IR (film) 2983, 2940, 1679, 1614, 1594, 1492, 1362, 1322M 1254, 1163, 1113, 1065, 1016, 837, 763, 699 cm$^{-1}$.

$N$-phenyl-$N$-(4-(trifluoromethyl)phenyl)isobutyramide (114): According to the general procedure, K$_2$S$_2$O$_8$ (202.7 mg, 0.75 mmol, 1.5 equiv.), $N$-phenylisobutyramide (81.6 mg, 0.5 mmol, 1.0 equiv.), 4-trifluoromethyl phenylboronic acid (143.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4′-di-bromo -2,2′-bipyridine (2.8 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% EtOAc/hexane) to provide the title compound as a white solid (112 mg, 73% yield).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58 (d, $J = 8.3$ Hz, 2H), 7.44 (t, $J = 7.7$ Hz, 2H), 7.38 – 7.30 (m, 3H), 7.28 – 7.21 (m, 2H), 2.70 (hept, $J = 6.7$ Hz, 1H), 1.15 (d, $J = 6.7$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 177.95, 146.17, 142.42, 130.00, 128.49, 128.08, 126.94 (q, $J = 3.9$ Hz), 126.20, 124.03 (q, $J = 272.1$ Hz), 115.56, 32.44, 19.69.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -62.4.

HRMS (ESI-TOF) m/z calculated for C$_{17}$H$_{17}$F$_3$NO [(M+H)$^+$] 308.1257, found 308.1253.
IR (film) 2977, 2937, 1675, 1614, 1593, 1492, 1322, 1250, 1164, 1114, 1065, 1017, 972, 831, 758, 699 cm⁻¹.

N-phenyl-N-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide (115): According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), N-phenylcyclopropanecarboxamide (81.6 mg, 0.5 mmol, 1.0 equiv.), 4-trifluoromethyl phenylboronic acid (143.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4'-di-bromo -2,2'-bipyridine (2.8 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% EtOAc/hexane) to provide the title compound as a white solid (130 mg, 85% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.58 (d, J = 8.2 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (dd, J = 30.0, 8.3 Hz, 4H), 1.52 (tt, J = 8.2, 4.6 Hz, 1H), 1.16 (p, J = 4.0 Hz, 2H), 0.78 (dq, J = 7.2, 3.7 Hz, 2H).

¹³C NMR (125 MHz, CDCl₃): ¹³C NMR (126 MHz, Chloroform-d) δ 174.07, 146.21, 142.46, 129.84, 128.58, 127.75, 126.87 (q, J = 3.8 Hz), 124.06 (q, J = 271.9 Hz), 115.49, 14.28, 9.88.

¹⁹F NMR (376 MHz, CDCl₃): δ -62.4.

HRMS (ESI-TOF) m/z calculated for C₁₇H₁₅F₃NO [(M+H)⁺] 306.1100, found 306.1104.

IR (film) 3014, 1669, 1614, 1594, 1515, 1491, 1449, 1392, 1322, 1292, 1254, 1161, 1114, 1065, 1016, 974, 913, 851, 833, 757, 697 cm⁻¹.

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**N-phenyl-N-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-4-carboxamide (116):**

According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), *N*-phenyltetrahydro-2H-pyran-4-carboxamide (102.6 mg, 0.5 mmol, 1.0 equiv.), 4-trifluoromethyl phenylboronic acid (143.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4′-di-bromo-2,2′-bipyridine (2.8 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% EtOAc/hexane) to provide the title compound as a white solid (136 mg, 78% yield).

**¹H NMR** (500 MHz, CDCl₃): δ 7.68 – 7.55 (m, 2H), 7.48 – 7.36 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 3H), 3.95 (dd, *J* = 11.6, 4.4, 2.0 Hz, 2H), 3.19 (td, *J* = 11.9, 2.1 Hz, 2H), 2.65 (tt, *J* = 11.4, 3.8 Hz, 1H), 1.99 (dtt, *J* = 13.5, 11.7, 4.5 Hz, 2H), 1.62 (ddd, *J* = 13.2, 4.1, 2.1 Hz, 2H).

**¹³C NMR** (125 MHz, CDCl₃): δ 175.04, 145.91, 142.07, 136.09, 134.66 (q, *J* = 32.3 Hz), 134.13, 130.16, 128.40, 126.30, 124.03 (q, *J* = 258.4 Hz), 67.06, 39.75, 29.11.

**¹⁹F NMR** (376 MHz, CDCl₃): δ -62.4.

**HRMS** (ESI-TOF) m/z calculated for C₁₉H₁₉F₃NO₂ [(M+H)+] 350.1362, found 350.1364.

**IR** (film) 2959, 2860, 1672, 1612, 1595, 1517, 1493, 1407, 1381, 1318, 1265, 1243, 1185, 1161, 1107, 1083, 1063, 1016, 981, 915, 844, 748, 703.9, 677 cm⁻¹.
N-phenyl-1-(2,2,2-trifluoroacetyl)-N-(4-(trifluoromethyl)phenyl)piperidine-4-carboxamide (117): According to the general procedure, K₂S₂O₈ (202.7 mg, 0.75 mmol, 1.5 equiv.), N-phenyl-1-(2,2,2-trifluoroacetyl)piperidine-4-carboxamide (150.1 mg, 0.5 mmol, 1.0 equiv.), 4-trifluoromethyl phenylboronic acid (143.0 mg, 0.75 mmol, 1.5 equiv.), Cobalt(II) acetylacetonate (1.3 mg, 0.005 mmol, 0.01 equiv.), 4,4’-di-bromo -2,2’-bipyridine (2.8 mg, 0.01 mmol, 0.02 equiv.) and 2.0 mL of MeCN were used. After 20 hours, the reaction mixture was subjected to the workup procedure outlined in the general procedure and purified by flash chromatography (20% EtOAc/hexane) to provide the title compound as a white solid (151 mg, 68% yield).

Mixture of rotamers

¹H NMR (500 MHz, CDCl₃): δ 7.59 (d, J = 8.1 Hz, 2H), 7.52 – 7.38 (m, 3H), 7.33 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2H), 4.43 (ddd, J = 14.5, 4.6, 3.0 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.02 (ddd, J = 14.4, 11.5, 3.0 Hz, 1H), 2.78 – 2.65 (m, 2H), 2.01 – 1.77 (m, 4H).

¹³C NMR (125 MHz, CDCl₃): δ 174.11, 155.52 (q, J = 35.7 Hz), 145.60, 141.83, 130.37, 128.72, 126.35, 123.91 (q, J = 272.0 Hz), 118.02, 116.58 (q, J = 288.0 Hz), 44.83 (q, J = 3.6 Hz), 42.63, 39.64, 28.83, 28.02.

¹⁹F NMR (376 MHz, CDCl₃): δ -62.5, -69.0.

HRMS (ESI-TOF) m/z calculated for C₂₁H₁₀F₆N₂O₂ [(M+H)+] 445.1345, found 445.1340.

IR (film) 2939, 1681, 1614, 1594, 1492, 1452, 1380, 1323, 1268, 1156, 1066, 1017, 973, 889, 844, 747, 700 658, 679 cm⁻¹.