Remote C–H Functionalization of Aliphatic Amines

By

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ABSTRACT

This thesis summarizes our efforts in the development of methodologies aimed at remote C(sp^3)–H functionalization of aliphatic amines. Amines are an important functional group present in a variety of biologically relevant molecules; however, examples of remote C–H functionalization of unprotected amines remain scarce. Many of the challenges associated with the remote functionalization of amines are related to the susceptibility of C–H functionalization proximal to the nitrogen center. Chapter 1 provides a perspective and summary of the field and Chapters 2-5 cover strategies we have developed to perform selective, remote C(sp^3)–H functionalization of aliphatic amines.

We have employed protonation as a strategy in combination with platinum-catalysis to achieve terminal-selective functionalization of aliphatic amines (Chapter 2). This strategy is based on the *in situ* formation of an ammonium salt to deactivate the C–H bonds proximal to nitrogen. Similarly, Chapter 3 describes the remote oxidation of 2º and 3º C–H bonds of protonated aliphatic amines mediated by potassium persulfate.

In contrast to Chapters 2 and 3, Chapters 4 and 5 describe our efforts on the palladium-catalyzed, directed method that takes advantage of the basic nitrogen atom to enable transannular C–H functionalization of biologically relevant cyclic amine scaffolds. In Chapter 4, we optimized conditions to accelerate functionalization and directing group removal steps to enable the rapid generation of fragments. Chapter 5 describes the ligand-effects that led to our second-generation conditions for transannular C–H arylation that allowed for the functionalization of pharmaceutically relevant bicyclic amines. Mechanistic studies are presented along with preliminary studies on the incorporation of additional functional groups.

CHAPTER 1

Introduction

1.1. C(sp^3)–H Functionalization of Aliphatic Amines

The area of C–H functionalization is a rapidly expanding field that utilizes the ubiquitous C–H bonds found in small molecules to install new functionality, increasing their complexity and, often, their value.[1] Many examples from this field involve the use of a transition metal (*e.g.*, Pd, Ir, Rh) to catalyze this process (**Scheme 1.1a**). In these cases, the transition metal inserts into a specific C–H bond (C–H activation) with selectivity that is controlled by sterics, electronics or an intramolecular directing group. This C–H activated intermediate undergoes further functionalization in the catalytic cycle, often in the presence of an oxidant and/or nucleophile, to form a carbon-carbon or carbon-heteroatom bond (*e.g.*, C–X, where X = C, N, O, halide) as shown in **Scheme 1.1b**. A variety of other mechanisms that enable selective C–H functionalization are referenced.[2]

Scheme 1.1. (a) Metal Mediated C–H Bond Functionalization (b) Concise Catalytic Cycle
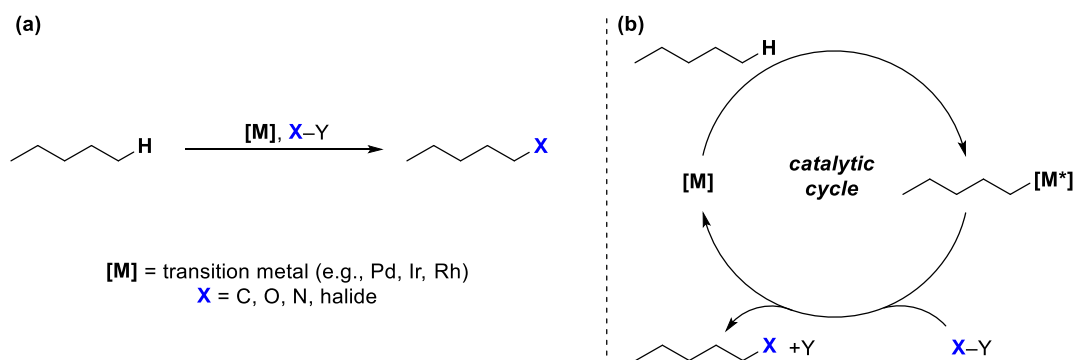
This thesis summarizes our work on of remote C(sp^3)–H functionalization reactions of aliphatic amines, predominantly focusing on transition metal catalyzed processes. Our developments in this area are outlined in chapters 2 through 5. The central theme of chapters 2

and 3 is the use of protonated amines to access remote C–H oxidation products through Pt-catalysis (Chapter 2) and a persulfate-mediated oxidation (Chapter 3) (**Scheme 1.2**). Chapter 4 highlights research completed in collaboration with AbbVie, during which we focused on applying a $C(sp^3)$–H arylation methodology for the synthesis of cyclic amine fragments (**Scheme 1.2**). Lastly, Chapter 5 outlines our work to further develop the Pd-catalyzed transannular C–H functionalization of cyclic amines through the study of ligand effects (**Scheme 1.2**).[3]

Scheme 1.2. Overview of Work on Remote $C(sp^3)$–H Functionalization of Aliphatic Amines
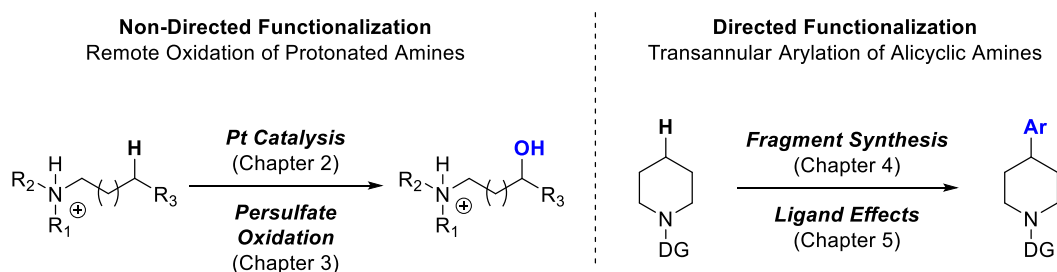
The first section of Chapter 1 will focus on $C(sp^3)$–H bond functionalization and the general strategies researchers have employed to enable this transformation with high efficiency and site-selectivity. The second half of the introduction will outline the relevant properties of amines that have led to exhaustive studies of $C(\alpha)$–H functionalization. Additionally, chemists have been able to harness the amine functional group and access site-selective functionalization at remote C–H sites through a variety of directed and non-directed pathways. These advances provided the groundwork for the developments that we report in chapters 2 through 5.

1.2. $C(sp^3)$–H Functionalization

C–H bonds are typically thought of as inert sites that rarely undergo functional group transformations. However, over the past decade, the field of C–H functionalization has expanded such that the synthetic toolbox includes a multitude of catalysts, directing groups, oxidants, and reagents that enable the cleavage of a C–H bond and installation of new functional group.[2] Within this field, researchers have examined the activation of both $C(sp^2)$–

H and C(sp^3)–H bonds. The following discussion will focus on developments in the area of C(sp^3)–H bond functionalization as it pertains to the work described in this thesis.

Table 1.1. Bond Dissociation Energies and pKa of C–H Bonds[4,5,6]

Entry	Compound	BDE(C–H)[a]	pKa
1	CH_4	105.0 ± 0.1	56[b]
2	CH_3CH_3	100.5 ± 0.3	50[c]
3	$(CH_3)_2CH_2$	98.1 ± 0.7	-
4	$(CH_3)_3CH$	95.7 ± 0.7	-
5	$(C_6H_5)CH_3$	90.9 ± 1.2	-
6	$CH=CHCH_3$	88.2 ± 0.7	-
7	C_6H_6	112.9 ± 0.5	40[c]

[a] kcal/mol [b] ref 5 in DMSO [c] ref 6

The activation of C(sp^3)–H bonds is challenging and often best characterized by bond dissociation energies that are between 85–100 kcal/mol (BDE, homolytic cleavage) and pKa values in excess of 50 (heterolytic cleavage).[4,5,6] For example, the BDE of the C–H bond in methane is around 105 kcal/mol, and this molecule has a pKa of approximately 56 (**Table 1.1**, entry 1).[4,5] The BDE of the primary (1º) C–H bonds of ethane and extended alkyl chains is closer to 100 kcal/mol (**Table 1.1**, entry 2).[4] Secondary (2º) C–H bonds and tertiary (3º) C–H bonds have lower BDEs of approximately 98.1 kcal/mol and 95.7 kcal/mol respectively (**Table 1.1**, entries 3,4).[4] As such, these undergo more facile homolytic cleavage relative to 1º C–H bonds. An aromatic or π-system adjacent to a C(sp^3)–H bond often leads to a decrease in the BDE as seen in the case of toluene and propene (**Table 1.1**, entries 5,6).[4] Compared to C(sp^3)–H bonds, C(sp^2)–H bonds have significantly higher BDEs, but are considerably more acidic than a typical C(sp^3)–H bond (pKa benzene ~43).[4,5]

Figure 1.1. Highlighting C–H Bonds in Valsartan (antihypertensive)
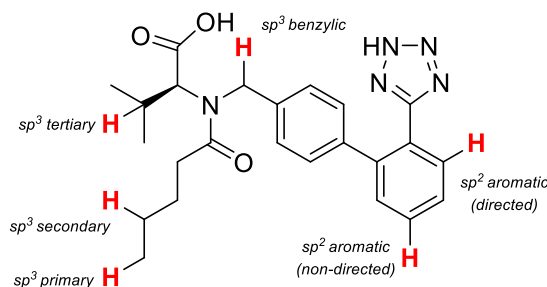
In addition to the relative inertness of C–H bonds[4], another major challenge in C–H functionalization is site-selectivity. As exemplified in **Figure 1.1** with Valsartan, there are often many different types of $C(sp^3)$–H and $C(sp^2)$–H bonds in a given organic molecule. Developing methods to selectively target the activation of a specific C–H bond has been achieved by the use of directing groups and/or catalyst/reagent-controlled selectivity, occurring through a variety of mechanisms.[2] In Chapter 2, we describe the development of a Pt-catalyzed 1º-selective $C(sp^3)$–H oxidation. Chapter 3 summarizes our efforts to activate weaker 2º and 3º $C(sp^3)$–H bonds mediated by potassium persulfate. Lastly, a directing group approach is utilized in Chapters 4 and 5 to selectively functionalize remote 2º-$C(sp^3)$–H bonds on alicyclic amine scaffolds.

Scheme 1.3. Directed C–H Bond Activation
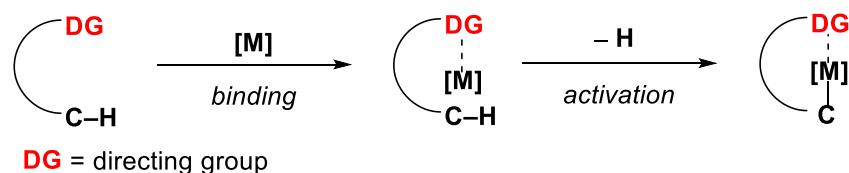
DG = directing group

To overcome the relative inertness of C–H bonds and enable site-selective functionalization, one key strategy that researchers have employed is the use of transition metals in combination with a tethered directing group (**Scheme 1.3**).[2e,f] This process involves reversible binding between the transition metal and the directing group, placing the catalyst in close proximity to the C–H bond of interest, and thus allowing for site-selective C–H activation. An early example by Murai and co-workers demonstrated this concept in the context of the Ru-catalyzed C–H alkylation of aromatic ketones (**Scheme 1.4**). The carbonyl oxygen functions as a directing group for Ru, facilitating *ortho* activation and subsequent addition into the olefin to forge a new C–C bond.[7] Subsequently, numerous other groups have contributed important discoveries to further develop the field of directed $C(sp^2)$–H functionalization.[2e,f,j,l,n]

Scheme 1.4. Ru-catalyzed C(sp^2)–H Functionalization Enabled by Ketone Directing Group[7]
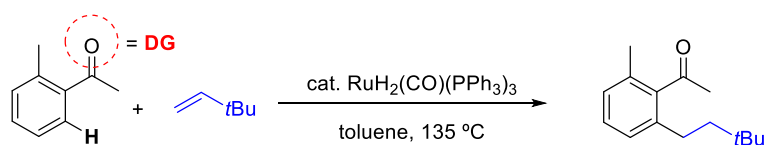
In the late 1990s, the stoichiometric and, subsequently, catalytic C–H borylation of alkanes was demonstrated with transition metal catalysts.[2g,h,8] **Scheme 1.5** describes the conditions for a Re-catalyzed C(sp^3)–H borylation of *n*-pentane.[9] High selectivity for 1° C–H borylation is dictated by the steric properties of the substrate/catalyst. Subsequently, the use of Ir and Rh for the non-directed C(sp^3)–H borylation of aliphatic small molecules was reported.[2g,h,10] While these catalyst systems enable the selective formation of terminal C(sp^3)–H borylation products, the transformations are largely limited to the use of simple alkanes under neat conditions.

Scheme 1.5. Re-catalyzed C(sp^3)–H Borylation of Alkanes [9]
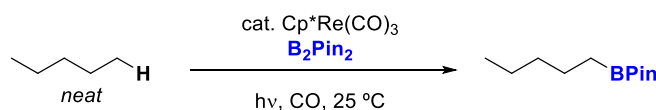
An alternative approach involves the introduction of directing groups to enable C(sp^3)–H functionalization (analogous to C(sp^2)–H functionalization). The reports of Pd-catalyzed, directed C(sp^3)–H functionalization by Yu, Daugulis, as well as our group, expanded the field to include diverse transformations of more complex molecules.[11] In 2004, our group demonstrated a Pd-catalyzed, oxime-ether directed acetoxylation of C(sp^3)–H bonds in the presence of PhI(OAc)$_2$ as the stoichiometric oxidant (**Scheme 1.6**).[12] This reaction proceeds through a concerted metalation-deprotonation (CMD) mechanism,[13] leading to formation of a five-membered palladacycle, which plays a key role in site selectivity (**Scheme 1.6**). Following these early reports, many others have built upon and expanded the area of directed C(sp^3)–H functionalization.[2e,j,l]

Scheme 1.6. Pd$^{II/IV}$-catalyzed, Heteroatom Directed C(sp^3)–H Acetoxylation[12]
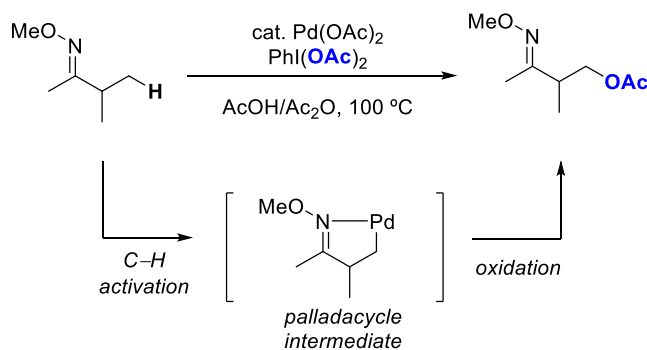
While this area of research has expanded to encompass synthetically relevant scaffolds and transformations, many limitations and challenges remain. First, within the area of directed functionalization, there is major room for further exploration of substrate scaffolds and site-selectivity. Second, a directed method is inherently limited to substrates containing an existing directing group (or one that can be easily appended) in proximity to the C–H bond of interest. With these limitations in mind, we sought to develop new strategies for the functionalization of aliphatic amines, which represent a challenging class of substrates for remote C(sp^3)–H functionalization (*vide infra*). In particular, we were interested in accessing site-selectivity patterns that were inaccessible with modern methods. This next section will outline the chemistry of aliphatic amines and their common reactivity patterns.

1.3. Chemistry of Aliphatic Amines

Properties of Aliphatic Amines Relevant to C–H Bond Functionalization

Figure 1.2. Aliphatic Amines in Commodity Chemicals and Bioactive Molecules

| triethanolamine | trans-1,2 diaminocyclohexane | glyphosate | cocaine | Lyrica® |
| (bulk chemical) | (chiral ligand scaffold) | (herbicide) | (stimulant) | (antiepileptic) |
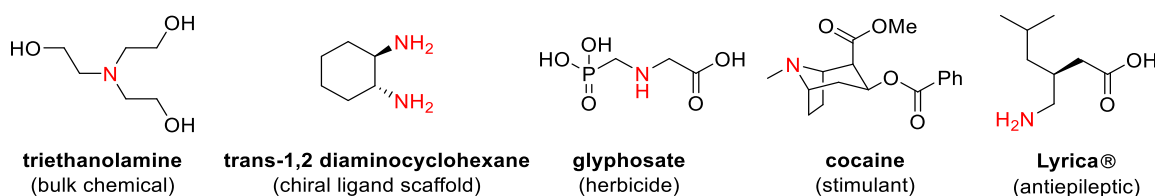
Aliphatic amines are present in a variety of bioactive molecules, materials, and commodity chemicals (**Figure 1.2**). They represent an important and versatile functional group that can undergo a variety of transformations.[14] We were especially intrigued by their

prevalence in bioactive molecules and sought to develop new methodologies that could facilitate their rapid derivatization. For example, C–H functionalized products could potentially be utilized for the study of metabolites (Chapters 2 and 3).[15] Additionally, C–H functionalization could also facilitate the synthesis and exploration of small molecules for early stage discovery efforts as well as find applications in the late-stage modification of drug-like molecules (Chapters 4 and 5).

Challenges of Aliphatic Amine Functionalization in C(sp³)–H Bond Functionalization

Figure 1.3. C–H BDE of Piperidine and Cyclohexane [4]

BDE(C–H) = 92.2 kcal/mol   BDE(C–H) = 97.7 kcal/mol
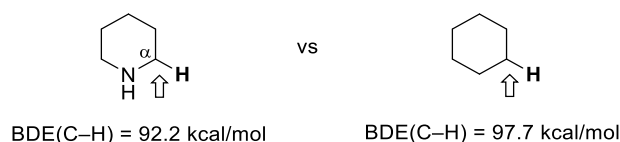
Aliphatic amines contain an electron-rich, Lewis basic nitrogen atom with weak C(α)–H bonds. In the case of piperidine, the BDE of the 2º C(α)–H is approximately 92.2 kcal/mol, while the analogous 2º C–H in cyclohexane is >5 kcal/mol stronger (**Figure 1.3**).[4] Binding of the amine to a metal can lead to catalyst deactivation and/or β–H elimination (**Scheme 1.7a, b**). Additionally, C–H functionalization reactions often require the use of strong oxidants, which are often incompatible with electron-rich amines as they can promote oxidative functionalization and dealkylation (**Scheme 1.7c, d**). Due to these properties, functionalization at the C(α)–H has been well-studied; however, transition metal-mediated, remote C–H functionalization has proven to be significantly more challenging (**Scheme 1.7e**).

Scheme 1.7. Reactions of Aliphatic Amines with Metals and Oxidants
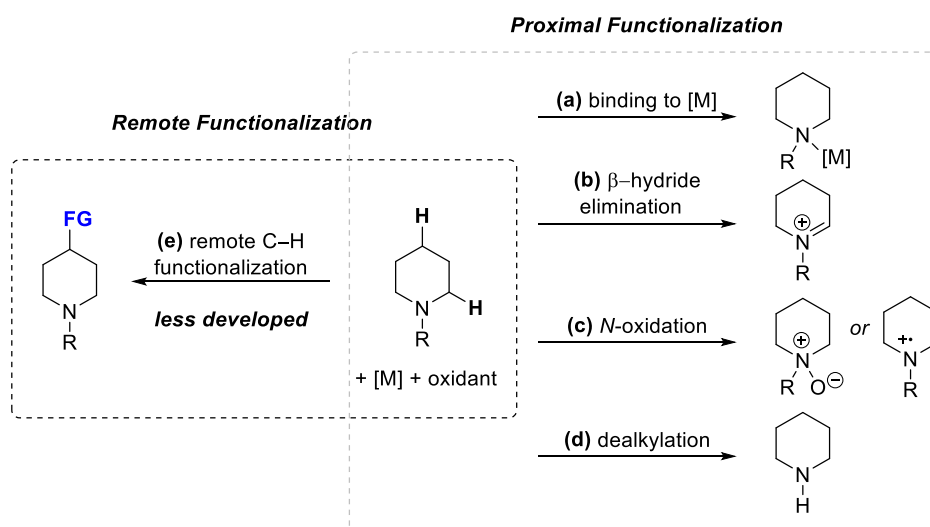
C(α)–H Functionalization of Aliphatic Amines

Leveraging these properties, the C–H functionalization of aliphatic amines has traditionally been limited to the exploration of C(α)–H bond reactivity. For instance, a well-established method for C(α)–H bond functionalization involves lithiation of *N*–Boc-protected cyclic amines such as piperidine and pyrrolidine and subsequent addition of an electrophile. This transformation can be rendered enantioselective by chiral reagents.[16] In addition to deprotonation, the activation of C(α)–H bonds has been functionalized in reactions such as oxidation, oxidative dealkylation, and cross-coupling.[17]

As stated above, amines can bind to metals and undergo β–H elimination to form iminium species, which react readily with nucleophiles such as water. The hemiaminal intermediate can be further oxidized to an amide (**Scheme 1.8a**).[18] The iminium can also undergo hydrolysis to furnish a secondary amine and aliphatic aldehyde (**Scheme 1.8b**).[19] This type of reactivity has also been demonstrated for more complex molecules such as oxycodone in the presence of catalytic Pd and oxygen as the terminal oxidant (**Scheme 1.8c**).[20]

Scheme 1.8. Oxidative Functionalization of C(α)–H Bonds in Aliphatic Amines [18,19,20]
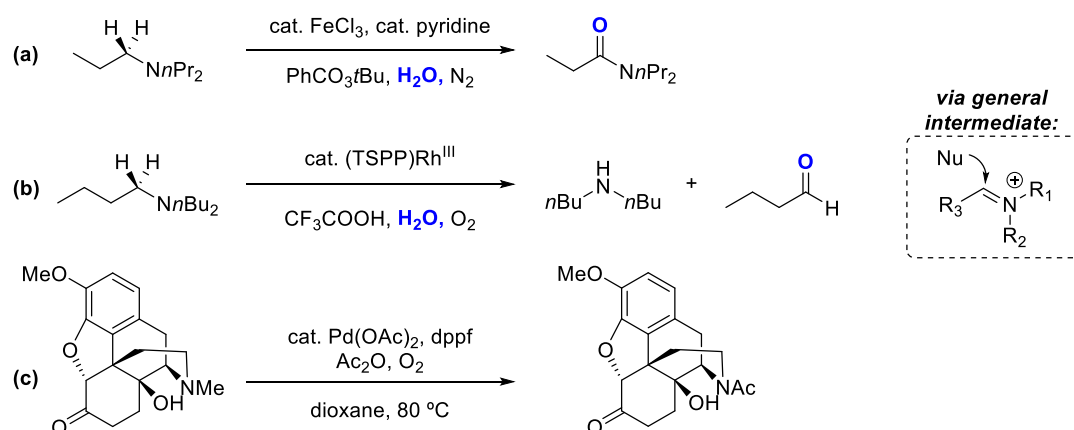
Many groups have also utilized amines as coupling partners in photoredox catalysis by intercepting the stabilized C(α) radical. **Scheme 1.9a** depicts the coupling of pyrrolidine to electron-poor arenes reported by MacMillan and co-workers. In this example, the photoexcicted Ir(ppy)$_3$ oxidizes the tertiary amine, which undergoes deprotonation to generate a C(α) radical.[21] Work by Hashmi and co-workers demonstrated similar reactivity in the context of cyclic and linear amines, where they used alkynes as the radical coupling partner to generate a net C–H alkynylation product (**Scheme 1.9b**).[22]

Scheme 1.9. Single Electron Functionalization of C(α)–H Bonds in Aliphatic Amines [21,22]
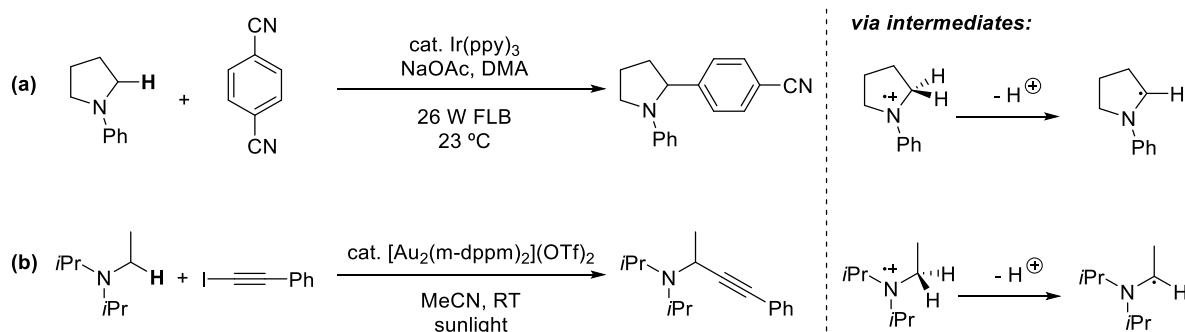
Davies and co-workers reported a carbene insertion into the C(α)–H bond of protected cyclic amines.[23] Their methodology was recently further applied in the context of unprotected aliphatic amines, demonstrating similar reactivity at the *N*-Me C(α)–H bond of complex, bioactive amines (**Scheme 1.10**).[24]

Scheme 1.10. Rh-catalyzed Functionalization of C(α)–H Bonds in Aliphatic Amines [24]
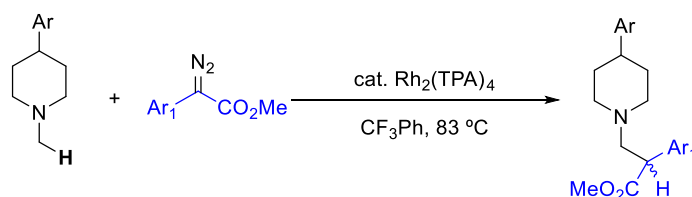
Additionally, the attachment of a directing group such as pyridine, has enabled Ru-catalyzed C–C bond formation (**Scheme 1.11**).[25] Reports by Sames[26], Maes[27], Yu[28], Shibata[29], and Ackermann[30] have developed this type of reaction through introduction of various directing groups, catalysts, and coupling partners. As summarized here, much research has been devoted to the study of C(α)–H functionalization reactions of amines. However, in recent years, our group and others have sought to develop strategies to override the inherent reactivity of these C(α)–H sites in order to access remote C–H bonds. These endeavors are outlined in the following section.

Scheme 1.11. Ru-catalyzed, Directed C(α)–H Bond Functionalization [25]
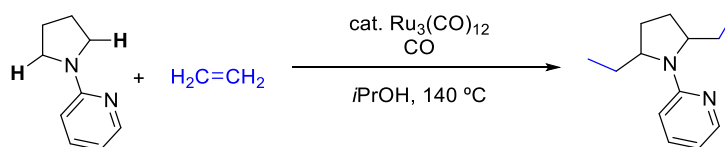
1.4. Strategies for Remote C–H Functionalization of Amines

Directed Functionalization

The directing group strategy has also been employed extensively in the context of remote functionalization of aliphatic amines. First introduced by the Daugulis group, the picolinamide motif has found many applications in the functionalization of primary amines.[31] These reactions occur through bidentate chelation with the amide and pyridine nitrogen atoms and subsequent directed C–H activation, leading to the intermediate in **Scheme 1.12a**. This strategy has since been applied to cyclic and bicyclic primary amines, including privileged scaffolds such as 3-pinanamine[32] and 3-amino piperidine (**Scheme 1.12b**).[33] Furthermore, a

variety of functionalizations can be accomplished with this directing group including alkenylation,[34] etherification,[35] acetoxylation,[36] and alkylation.[37] In all cases, the requirement for a primary amine remains a limiting factor.

Scheme 1.12. Pd-catalyzed, Directed Functionalization of Primary Amines [31,32,33]
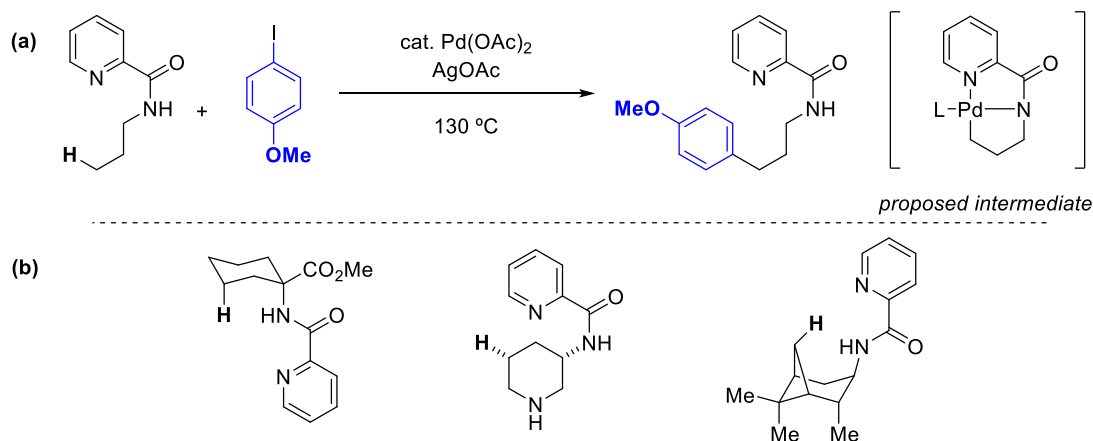
Another drawback of this directed functionalization is the need to install and cleave the directing group while preserving the integrity of the functionalized product. Cleavage of the directing group is integral to accessing the desired molecule, and we address this in the context of our work in Chapter 4. To circumvent this step, chemists have also explored the use of transient directing groups that can be generated *in situ*.[38] A report by Ge and co-workers takes advantage of the facile condensation between a primary amine and glyoxic acid to generate a bis-chelating directing group for γ-C–H arylation of amines (**Scheme 1.13**).[39] Although an elegant approach, a major limitation is the need for primary amines bearing a dimethyl group at C(α), which the authors attribute to both the Thorpe-Ingold effect and the need to avoid C(α)–H oxidation.

Scheme 1.13. Pd-catalyzed Arylation with Transient Directing Group [39]
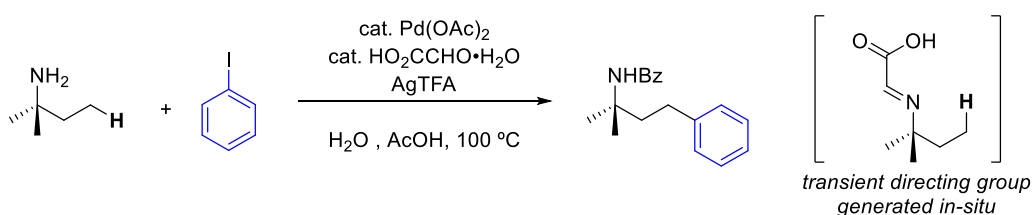
While the area of directed functionalization has been widely explored in the context of protected amines, far fewer examples demonstrate free amine-directed C–H bond functionalization. An early example from 2001 applied Pt-catalysis for the functionalization of amino acids.[40] The Sames group utilized free amino acids as chelating functional groups to direct C–H bond activation (**Scheme 1.14**). Although low isolated yields and moderate selectivities were achieved, this work was a seminal demonstration of amine-directed C–H functionalization.

Scheme 1.14. Amino Acid Directed, Pt-catalyzed C–H Oxidation [40]
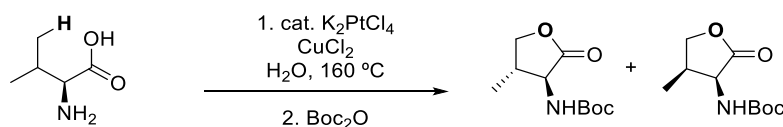
More than a decade later, pioneering work from the Gaunt group explored secondary amine-directed C–H bond functionalization. Their first report in this area described amine-directed β-C–H bond activation to access an unusual 4-membered palladacycle intermediate (**Scheme 1.15**).[41] Reductive elimination from this strained palladacycle provided aziridine products. This model was further explored for the C–H arylation, acetoxylation, carbonylation, and alkenylation of amines.[42]

Scheme 1.15. Secondary Amine Directed β C–H Functionalization [41]

proposed intermediate
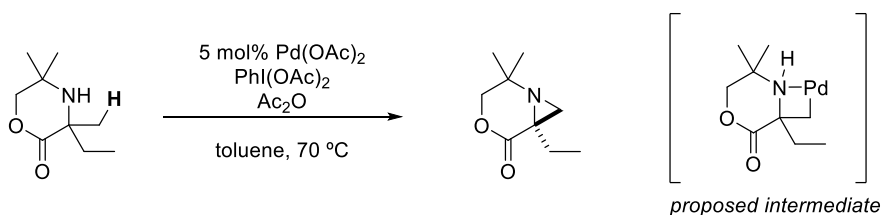
In these examples of protected and free amine-directed methodologies, functionalization occurs at 1° or 2° C–H bonds in linear systems. In Chapters 4 and 5, we sought to leverage the directing group ability of amines to access C–H bonds in biologically relevant, cyclic amine scaffolds. At that time, the functionalization of remote 2° C–H bonds in cyclic amines was an unsolved challenge. Our contribution was in the use of cyclic tertiary amines to

access remote C–H bonds through an amine-directed, transannular pathway (**Figure 1.4**).[43] This work laid the foundation for its application in the synthesis of fragments (Chapter 4) and for our studies of ligand effects (Chapter 5).

Figure 1.4. Directed C–H of Aliphatic Amines [31,41,43]

DG and N directed
(Daugulis)

Free amine directed
(Gaunt)

Free Amine and DG Enabled Transannular Functionalization
(Chapter 4 and 5)
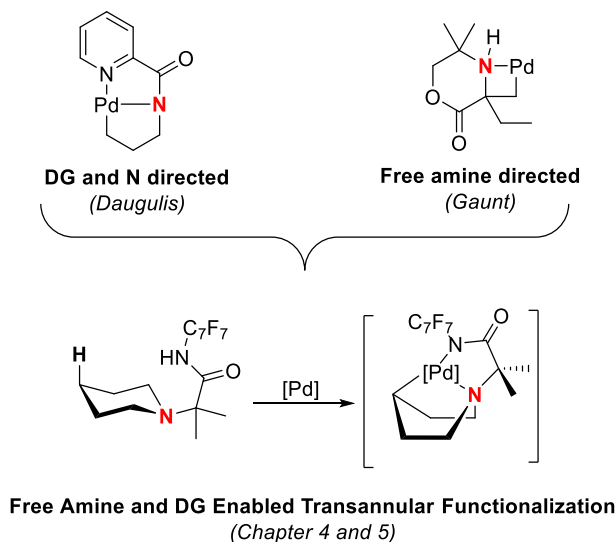
Non-Directed Functionalization

All of the above examples of remote amine functionalization utilized a directing group consisting of either a protected or free amine. This necessitates the correct positioning between the directing group and C–H bond of interest. Due to steric hindrance, reactivity is typically limited to 1º and 2º C–H bonds. In contrast, non-directed functionalization, in which the nitrogen atom does not participate through a binding event, can enable complementary reactivity. This strategy requires deactivation of the amine, which is often achieved through the formation of an amide bond. Additionally, many non-directed methods target hindered, homolytically weak 3º C–H bonds.

Scheme 1.16. Remote Functionalization of Peptides with DMDO [45]
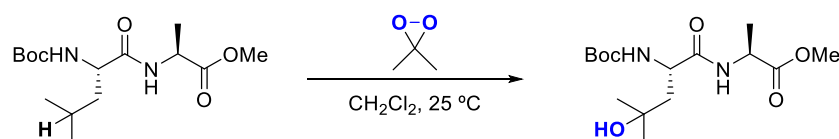
Dioxiranes, which operate through C–H insertion pathways and single electron radical processes, are known to selectively target 3º C–H bonds in the presence of stronger 1º and 2º C–H sites.[44] With the use of *N*-Boc protected peptides, selective 3º oxidation is possible with dimethyldioxiirane (DMDO) (**Scheme 1.16**).[45] The use of stronger oxidants such as TFDO leads to additional side-products such as *N*-oxidation.[46] Other types of protecting groups such as phthalimide[47] and trifluoroacetamide[48] function similarly to deactivate the amine and thus enable remote functionalization (**Scheme 1.17**).

Scheme 1.17. Examples of Remote Functionalization at Tertiary C–H Bonds [47,48]
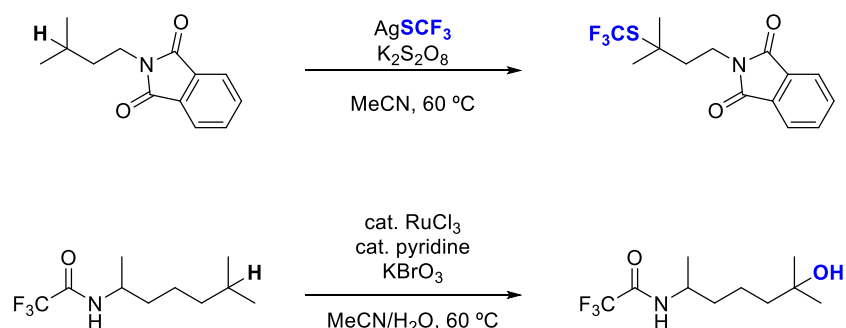
Asensio and co-workers were the first to explore amine protonation as an alternate strategy to deactivate C–H sites proximal to nitrogen.[49] They showed that protonation with HBF$_4$ to form an ammonium species deactivates the C(α)–H bonds and thus allows for selective oxidation at remote sites. In this study, the oxidation of linear and cyclic amines at remote 2º and 3º C–H bonds was achieved using TFDO (**Scheme 1.18**).

Scheme 1.18. TFDO Remote Oxidation of Protonated Amines [49]
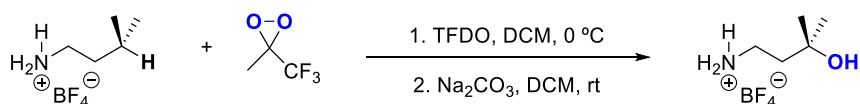
We applied the protonation strategy in the context of Pt-catalysis (Chapter 2) and in the persulfate-mediated oxidation (Chapter 3) to achieve complementary reactivity patterns. Recently, Bietti and co-workers quantified the deactivation of protonated amines through rate studies of C–H abstraction with cumyloxy radicals.[50] The rate of hydrogen atom abstraction

was found to be nearly three orders of magnitude higher with the free amine (**Scheme 1.19**). In the case of the protonated pentylamine, the observed rate corresponds to C–H abstraction at the remote methylene.

Scheme 1.19. Hydrogen Atom Abstraction from Free and Protonated Amines [50]
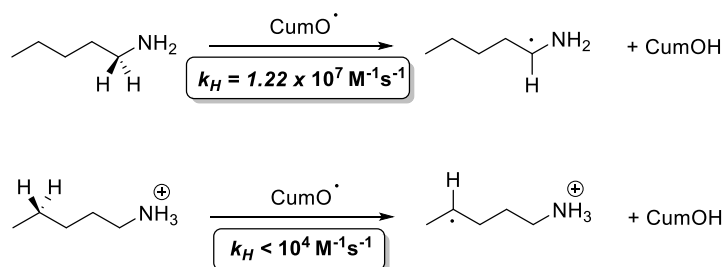
Another example of non-directed, remote C–H bond functionalization of free amines is in the Rh[51] and Ir-catalyzed borylation[52] of terminal aliphatic amines pioneered by the Hartwig group (**Scheme 1.20**). Here, the terminal selectivity is sterically-controlled, and activation occurs at the most sterically accessible C–H bond with a strong preference for β-C–H borylation (compared to α and C–H bonds further removed). While this reaction is tolerant of free amines, it is limited to the use of tertiary amines and is biased towards activation at the C(β)–H bond.

Scheme 1.20. Rh-catalyzed C–H Borylation of Tertiary Amines [51]
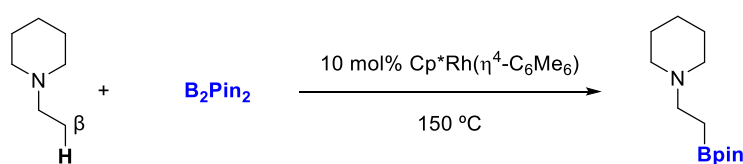
Based on our assessment of the field at the onset of these studies, we saw many opportunities for methods development in the area of amine functionalization. As described above, the traditional reactivity of aliphatic amines was largely limited to functionalization at C(α)–H sites. Very few studies effectively addressed the inherent challenges associated with the remote C–H functionalization of primary, secondary, and tertiary aliphatic amines. To this end, we took two approaches: (1) non-directed functionalization of protonated primary,

secondary, and tertiary amines (Chapters 2 and 3) and (2) amine-directed functionalization of alicyclic amines through a novel transannular approach (Chapters 4 and 5).

1.5. References

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CHAPTER 2

Platinum Catalyzed, Remote C(sp^3)–H Oxidation of Protonated Aliphatic Amines[1]

2.1. Introduction

Chapter 2 focuses on the Pt-catalyzed terminal C(sp^3)–H oxidation of protonated amines. We were interested in developing a method for the selective functionalization of strong 1º C(sp^3)–H bonds in the presence of weaker 3º and 2º C(sp^3)–H bonds.[2,3,4] The Pt-catalyzed oxidation of alkanes offers a promising approach to this challenge.[5] Shilov and others have demonstrated that aqueous solutions of Pt^{II} (catalyst) and Pt^{IV} (oxidant) salts can be used to promote the C–H hydroxylation of alkanes (**Scheme 2.1**).[6] Furthermore, these reactions have been shown to proceed with moderate selectivity for stronger (but less hindered) 1º C–H bonds over weaker (but more hindered) 2º C–H bonds.[6,7] Pt-catalyzed H/D exchange studies have also demonstrated higher deuterium incorporation at less hindered 1º C–H sites versus more hindered 2º C–H bonds.[8]

Scheme 2.1. Platinum Catalyzed C–H Chlorination of Pentane [6c]

56 : 44 selectivity
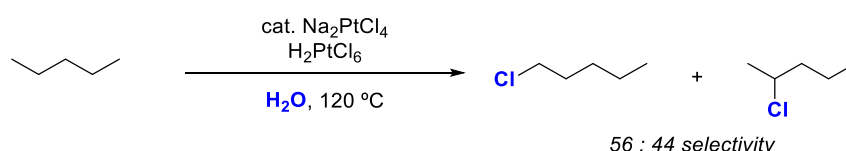
Despite the great promise of Pt catalysis in the functionalization of C(sp^3)–H bonds, Pt-catalyzed C–H oxidation has found minimal application in organic synthesis over the past 40 years.[9] This is due to three significant limitations: (1) the substrate scope was historically limited to simple water soluble organic molecules, (2) the selectivity is generally modest (1º

vs $2°$ $C(sp^3)$–H bond selectivity generally ranges from 1.5:1 to 3:1), and (3) expensive Pt^{IV} salts are typically used as the terminal oxidant, rendering the reactions impractical on even small scale.

We hypothesized that these challenges could be addressed in the context of the Pt-catalyzed $C(sp^3)$–H oxidation of aliphatic amines. Aliphatic amines functional groups appear in diverse organic materials, natural products, and bioactive molecules.[10] Most existing methods for the $C(sp^3)$–H functionalization of aliphatic amines involve either (1) functionalization at the highly activated C–H bond α-to nitrogen[11] or (2) the use of the amine nitrogen as the directing group.[9c,12,13]

Scheme 2.2. Protonation Strategy to Achieve Remote Functionalization

in situ protonation
- renders amine substrate water soluble
- electronically deactivates C–H sites proximal to nitrogen atom

non-directed, terminal selective
C–H hydroxylation
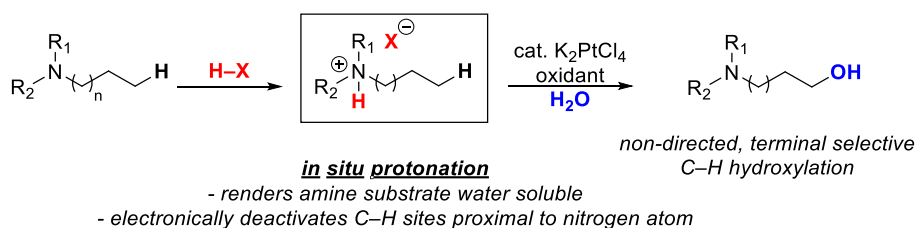
We sought to achieve terminal-selective C–H functionalization at sites remote to nitrogen, providing access to complementary reactivity without the use of a directing group.[14] We hypothesized that protonation of the amine substrates could lead to terminal-selective C–H oxidation, by addressing two of the underlying challenges associated with Pt catalysis (**Scheme 2.2**). First, quaternization of the amine substrates should increase their aqueous solubility. Second, the inductive electron-withdrawing effect of the ammonium cation[15] is expected to electronically deactivate C–H sites proximal to the nitrogen atom, increasing selectivity for $1°$ $C(sp^3)$–H activation.[16] We also noted that previous work by Sames[9c] and Sen[9d] had shown that Cu^{II} salts and O_2 can serve as the terminal oxidants for Shilov-type reactions in place of the costly Pt^{IV} salts (**Scheme 2.3**).[17] Our protonation strategy is also crucial in this context because free amines are known to undergo undesired reactions with Cu^{II} salts.[18]

Scheme 2.3. C–H Functionalization of Water Soluble Substrates with Cu^{II} Oxidant [8d]

cat. K_2PtCl_4
$CuCl_2$, H_2SO_4

O_2 (1300 psi)
H_2O, 150 ºC

5 : 1 selectivity
28 TON Pt
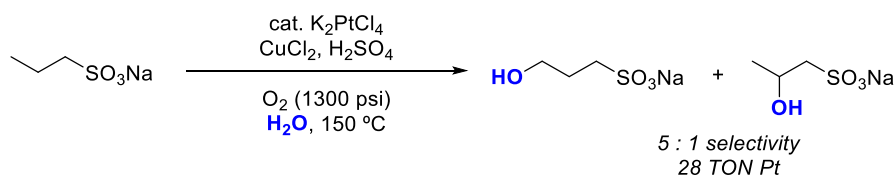
2.2.   Results and Discussion

Protonation Strategy and Reaction Optimization

Our initial investigations focused on the Pt^{II}-catalyzed C–H hydroxylation of dipropylamine, which contains three types of $C(sp^3)$–H bonds, allowing us to probe selectivity and reactivity. We began with traditional Shilov conditions, using 10 mol % of K_2PtCl_4, 1 equiv of K_2PtCl_6 as the terminal oxidant (and limiting reagent), and 2 equiv of the amine H_2SO_4 salt (protonated *in situ* with 2.2 equiv of H_2SO_4) at 120 ºC. These conditions afforded the $C(sp^3)$– H hydroxylation product with high terminal selectivity (>10:1 ratio of **1** to **1a**) but only modest yield (36%) over 48 h (**Table 2.1**, entry 1). Notably, early on in our investigations, we also explored the use of HCl, triflic acid, and trifluoroacetic acid to protonate the amine *in situ*, and observed products corresponding to terminal C–H functionalization. However, we chose to proceed with H_2SO_4 for the remainder of the studies shown here due to high solubility and good reactivity.

Changing the terminal oxidant to $CuCl_2$ under otherwise analogous conditions provided an increased yield (66%) while maintaining high selectivity for **1** (>10:1; entry 2). Increasing the temperature to 150 ºC afforded a similar yield (63%) over 30 h (entry 3). At this temperature, the catalyst loading could be dropped to 1 mol % with minimal impact on the yield or selectivity, although this required a longer reaction time (48 h; entry 5). Upon moving to 5 equiv of the amine H_2SO_4 salt relative to Cu, the hydroxylated product was obtained in 97% yield (97 turnovers of Pt) as determined by ^1H NMR spectroscopic analysis, with 8:1 selectivity for **1** over **1a** (entry 6). Control reactions demonstrate that no product is formed in the absence of Cu or Pt (entries 7 and 8). Furthermore, in the absence of H_2SO_4, <1% of the

C–H hydroxylation product was observed (entry 9). The results from these control reactions are consistent with our hypothesis that protonation of the amine is essential for this transformation.

Table 2.1. Optimization of Pt-Catalyzed C–H Hydroxylation of Protonated Dipropylamine
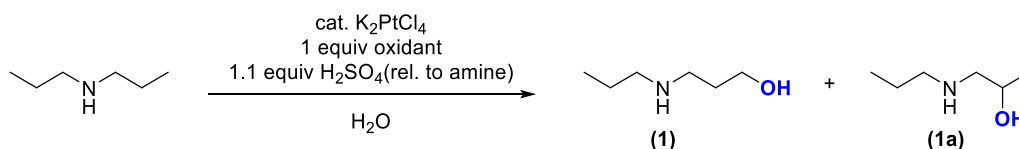
entry	equiv of amine	oxidant	temp (°C)	K_2PtCl_4 loading (mol%)	yield of 1 + 1a (%)[a]	1 :1a[a]
1[b]	2	K_2PtCl_6	120	10	36	>10:1
2[b]	2	$CuCl_2$	120	10	66	>10:1
3[c]	2	$CuCl_2$	150	10	63	>10:1
4[c]	2	$CuCl_2$	150	1	40	>10:1
5[b]	2	$CuCl_2$	150	1	70	8:1
6[c]	5	$CuCl_2$	150	1	97	8:1
7[c]	5	--	150	1	nd[e]	--
8[c]	5	$CuCl_2$	150	--	nd[e]	--
9[c,d]	5	$CuCl_2$	150	1	<1	--

[a] Yield and ratio of products determined by ^{1}H NMR. Reactions were conducted in sealed vials under an atmosphere of ambient air. Yields are calculated based on the oxidant (K_2PtCl_4 or $CuCl_2$) as the limiting reagent. [b] 48 h [c] 30 h [d] No H_2SO_4 added. [e] Products **1** and **1a** were not detected.

Probing Site-Selectivity of Platinum Oxidation

We next examined the Pt-catalyzed C–H hydroxylation of a series of *N*-alkyl pyrrolidine substrates to probe the impact of chain length on site selectivity (**Table 2**.**2**). In all cases, the major product was derived from C–H hydroxylation at the terminal position. As the terminal methyl group is moved closer to the nitrogen atom, selectivity for the 1° C–H bond increases sequentially from 2:1 in **5** to >20:1 in **2**.[19] In all cases, the selectivity was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (see the supporting information in reference 1 for crude ^{1}H NMR spectra). The amino alcohol products were then derivatized with pivaloyl chloride (PivCl) to facilitate product isolation and characterization. Using these conditions, the oxygenated amino ester products **3-5** could be isolated in high yields.[20]

Table 2.2. Pt-Catalyzed C–H Functionalization of *N*-Alkylpyrrolidines

substrate	major product	crude selectivity[a]	isolated yield (isolated selectivity)
	(2-OH)	$\beta : \alpha$ = >20 : 1	25%[b] $\beta : \alpha$ = >20 : 1
	(3)	$\gamma : \beta$ = 10 : 1	85% $\gamma : \beta$ = 10 : 1
	(4)	$\delta : \gamma$ = 4 : 1	126% $\delta : \gamma$ = 4 : 1
	(5)	$\varepsilon : \delta$ = 2 : 1	73% $\varepsilon : \delta$ = 2 : 1

[a] Crude selectivity determined by ^{1}H NMR spectroscopic analysis prior to treatment with PivCl.
[b] Yield determined by spectroscopic analysis

The observed increase in selectivity with shorter chain length correlates with a decreased reactivity towards C–H functionalization at sites that are closer to the ammonium cation. For example, the C–H hydroxylation of *N*-ethyl pyrrolidine to form **2** proceeded in modest 25% yield under conditions used to obtain products **3**–**5**. This is consistent with β-C(sp^3)–H bonds being significantly less reactive than more remote C–H sites. In addition, a competition between *N*-propyl and *N*-butyl pyrrolidine afforded a 10 : 7 : 1 : <1 ratio of products **4-OH** : **3-OH** : **4a-OH** : **3a-OH** (**Scheme 2.4**). Again, the selectivity for **4-OH** over **3-OH** as well as for **4a-OH** over **3a-OH** is consistent with higher reactivity of C–H sites that are further from the protonated nitrogen atom. Overall, these results support our hypothesis that quaternization of the amine electronically deactivates the C(sp^3)–H sites proximal to nitrogen via an inductive electron-withdrawing effect.

Scheme 2.4. Competition between *N*-Propyl- and *N*-Butylpyrrolidine

4-OH : 3-OH : 4a-OH : 3a-OH = 10 : 7 : 1 : <1
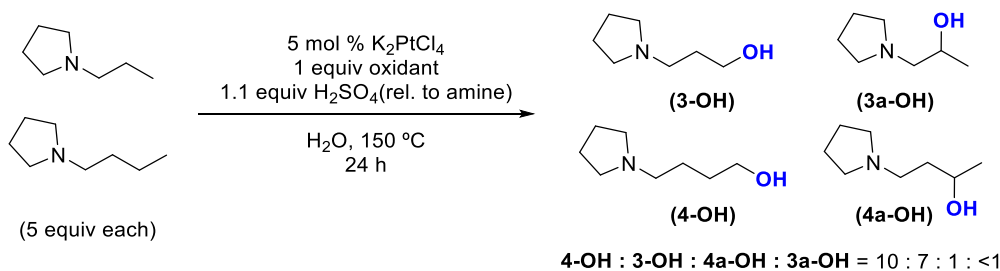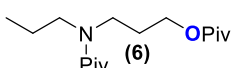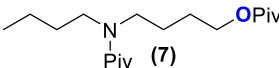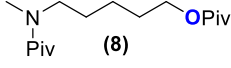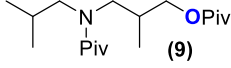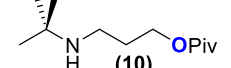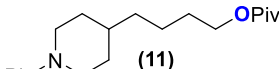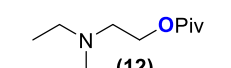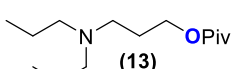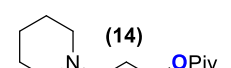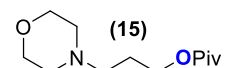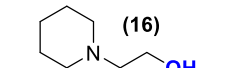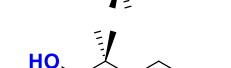
Substrate Scope of Remote Oxidation

Our standard conditions were effective for the C–H hydroxylation of a variety of 2º and

3º aliphatic amine substrates (**Table 2.3**). In all cases, the site selectivity was determined by [1]H

NMR spectroscopic analysis of the crude reaction mixtures (see supporting information in

reference 1 for crude ^{1}H NMR spectra).[19] Following C–H hydroxylation, the amino alcohol

products were derivatized with pivaloyl chloride to facilitate isolation and characterization.

Notably, the $CuCl_2$ oxidant is the limiting reagent in these transformations. As such, yields

greater than 100% reflect regeneration of the Cu[II] oxidant, presumably by O_2.[21]

All the examples in **Table 2.3** display modest to excellent selectivity for terminal C–H

functionalization.[19] Notably, the derivatization and purification sequence results in an upgrade

of selectivity for the terminal product in many cases. This is likely attributed to an inefficient

protection of the secondary alcohol with PivCl and subsequent recovery during purification.

The terminal selectivity partially reflects the inherent steric preference of Pt for the activation

of 1º over 2º or 3º C–H bonds.[5,7] However, selectivity is highest in the formation of the products

in entries **1**, **4**, **5**, and **7**-**10** where the competing 2º C(sp^3)–H sites are β or α to the quaternized

nitrogen atom. Again, these results implicate a significant inductive deactivation by the

ammonium cation. In addition to linear aliphatic amines, nitrogen heterocycles including

pyrrolidine, piperidine, and morpholine are compatible with the reaction conditions. Minimal

C–H oxidation of the 2º C–H bonds of the ring (<5%) is observed in these systems. Although

terminal β-C(sp^3)–H sites are electronically deactivated, triethylamine does provide the β-C–

H oxygenation product in high yields under slightly modified reaction conditions with 15 equivalents of amine over 48 hours (entry 7). Minimal oxidation of *tert*-butyl groups is observed (entry 10) even in the absence of competing 1º C–H bonds (*e.g.*, entries **11**, **12**). Similar observations have been made by Hartwig in Ir-catalyzed alkane borylation[3] and can be rationalized based on steric deactivation of the *tert*-butyl C–H bonds.

Table 2.3. Pt-Catalyzed C–H Hydroxylation of Secondary and Tertiary Amines

entry	major product	crude selectivity	isolated yield (isolated selectivity)
1	(6)	8 : 1	87% >20 : 1
2	(7)	5 : 1	78% 7 : 1
3	(8)	3 : 1	47% >10 : 1
4	(9)	8 : 1	54% >20 : 1
5	(10)	>20 : 1	46% >20 : 1
6[b]	(11)	5 : 1	65% >10 : 1
7[c]	(12)	>20 : 1	88% >20 : 1
8[d]	(13)	7 : 1	102% >20 : 1
9[e]	(14)	14 : 1	90% >20 : 1
10[e]	(15)	10 : 1	122% >20 : 1
11[f]	(16)	---	<5%[g]
12	(17)	---	<5%[g]

[a] General conditions: 1 mol % K_2PtCl_4, 1 equiv $CuCl_2$, 5 equiv of amine, 5.5 equiv H_2SO_4 (1.1 equiv relative to amine), 150 ºC, 24 h. [b] Entry 6: Amine used as HCl salt, 10 mol % K_2PtCl_4. [c] Entry 7: 15 equiv amine, 16.5 equiv H_2SO_4, 48 h. [d] Entry 8: 0.5 mol % K_2PtCl_4, 15 equiv amine, 16.5 equiv H_2SO_4. [e] Entries 9-11: 5 mol % K_2PtCl_4. [f] Entries 11-12: Amine used as HCl salt, 10 mol % K_2PtCl_4; [g] Yields estimated by ^1H NMR analysis of crude reaction mixtures; <5% of C(sp³)–H hydroxylation or C(sp³)–H chlorination products were observed.

Comparison to Other State of the Art Methodologies

We next compared this terminal-selective C–H hydroxylation reaction to Ir-catalyzed C–H borylation, which represents the current state-of-the-art method for terminal-selective alkane C–H functionalization.[3] The Hartwig group published a report on the C(sp^3)–H borylation of tertiary aliphatic amines in which diethylbutylamine undergoes Ir-catalyzed C–H borylation to afford the terminal β-C(sp^3)–H borylation product **18-BPin** with 6 : 1 selectivity relative to the terminal δ-C(sp^3)–H borylation product **19-BPin** (**Scheme 2.5a**).[14] Formation of the 2º C(sp^3)–H borylation product **19a-BPin** was not observed. In contrast, our Pt-catalyzed hydroxylation conditions with diethylbutylamine provide a complete switch in site selectivity, affording a >20:1 preference for **19-OH** over **18-OH** and a 3:1 ratio of **19-OH** to **19a-OH** (**Scheme 2.5b**). These results highlight the complementarity of the two methods. Notably, Pt catalysis has the additional advantages of compatibility with ambient air and moisture as well as applicability to 1º, 2º and 3º amine substrates.

Scheme 2.5. Comparison of Selectivity of Ir-Catalyzed C–H Borylation Versus Pt-Catalyzed C–H Hydroylation of Diethylbutylamine [14]

(a) Ir-Catalyzed C–H Borylation (results from *JACS* **2015**, *136*, 8755)

cat. [Ir]
B$_2$Pin$_2$

120 ºC, 24 h

(9 equiv)

(18-BPin)   +   (19-BPin)   +   (19a-BPin)

92% yield
18-BPin : 19-BPin : 19a-BPin = 6 : 1 : not reported

(b) Pt-Catalyzed C–H Hydroxylation

cat. [Pt]
1 equiv CuCl$_2$
1.1 equiv H$_2$SO$_4$(rel. to amine)

H$_2$O, 150 ºC
24 h

(5 equiv)

(18-OH)   +   (19-OH)   +   (19a-OH)

56% isolated yield
18-OH : 19-OH : 19a-OH = not detected : 3 : 1 (crude)
18-OPiv : 19-OPiv : 19a-OPiv = not detected : 6 : 1 (isolated)
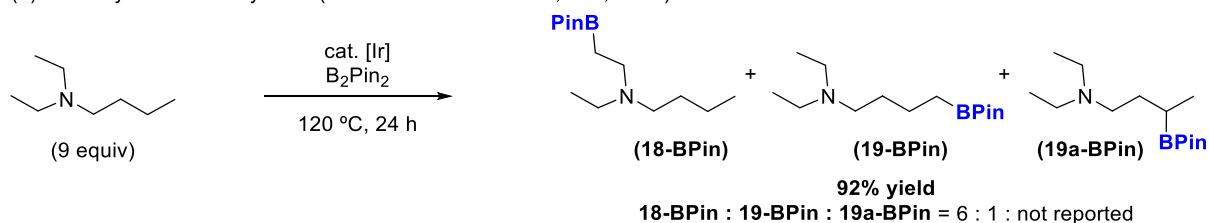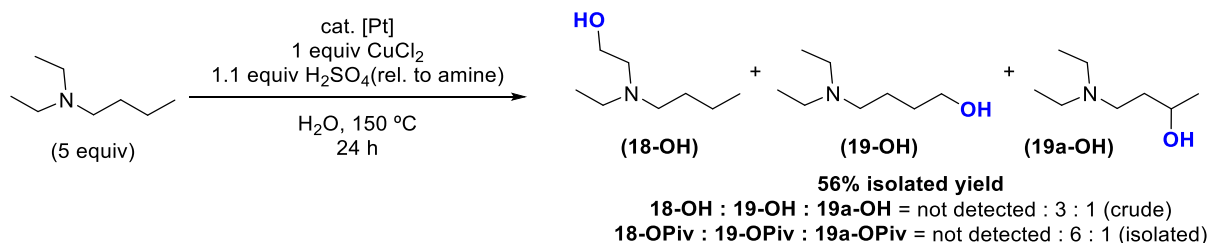
Mechanistic Insights

A final set of investigations focused on probing the mechanism of this transformation. In particular, we noted that C–H hydroxylation products are formed exclusively at the end of 24–48 hours under our reaction conditions, despite the presence of a high concentration of chloride. In other studies of Shilov-type alkane C–H oxidation, mixtures of C–H chlorination and C–H hydroxylation products are often observed under related conditions.[6,7,22]

Figure 2.1. Formation and Decay of Intermediate A in the Pt-catalyzed C–H Oxidation of Dipropylamine
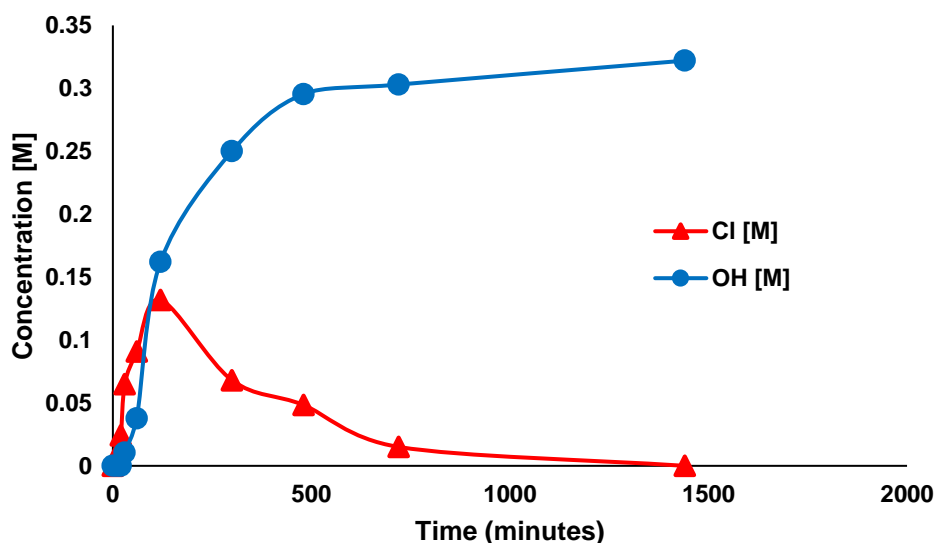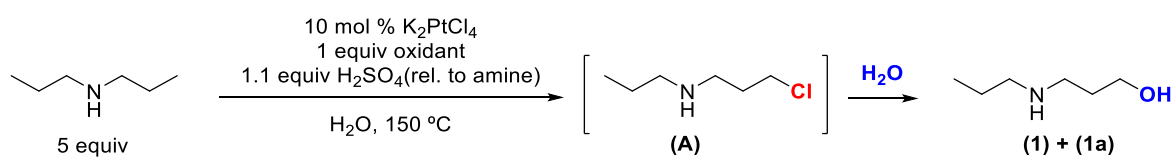
When the Pt-catalyzed C–H oxidation of dipropylamine was monitored by ^{1}H NMR spectroscopy, we observed rapid initial formation of an intermediate (**A**), which then fully converted to the C–H hydroxylation product over a 24 h period (**Figure 2.1**). Intermediate **A** was identified as the terminal C–H chlorination product based on *in situ* characterization by ^{1}H NMR spectroscopy and by the independent synthesis (see experimental section for more details and the supporting information of reference 1 for ^{1}H NMR spectra). We also confirmed that an

authentic sample of **A** undergoes quantitative conversion to **1** over 24 h at 150 ºC in H_2O, both in the presence and in the absence of the Pt catalyst. This suggests that a significant quantity of the hydroxylated product **1** is formed from the chlorinated intermediate **A** via a nucleophilic substitution reaction.

Further Reactivity of Chlorinated Products

The time study profile in **Figure 2.1** suggests the feasibility of selectively accessing $C(sp^3)$–H chlorination products. As proof-of-principle, we subjected substrates **20** and **24** to our Pt-catalyzed C–H oxidation conditions for short reaction times (2 h). We hypothesized that the presence of branching in **20** and **24** could slow the nucleophilic attack of possible chlorinated intermediates by H_2O. Analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy showed exclusive formation of the C–H chlorination products **21** and **25** (**Scheme 2.7**). While **21** and **25** proved challenging to isolate due to their high volatility, work up of these reactions with $KHCO_3$ resulted in the formation of the corresponding oxazinones **23** and **26**, which were isolated in 65% and 55% isolated yield, respectively (**Scheme 2.6**). In addition, the treatment of **21** with phenyl isothiocyanate afforded **22** in 73% yield (**Scheme 2.6**).

Scheme 2.6. Pt-Catalyzed $C(sp^3)$–H Functionalization of 20 and 24

29
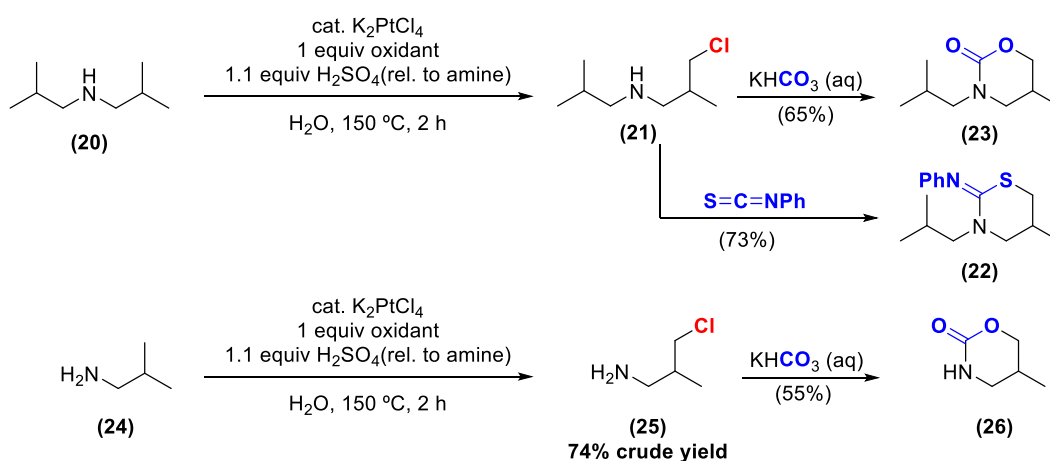
2.3. Conclusion and Outlook

In conclusion, Chapter 2 describes the Pt[II] catalyzed, primary selective C(sp^3)–H oxidation of protonated aliphatic amines utilizing Cu[II] as the terminal oxidant. These reactions proceed with low catalyst loadings, high TONs, and high selectivities. Protonation of the amine plays three critical roles in this transformation. First, protonation renders the substrates water-soluble. Second, protonation prevents deactivation of the Pt[II] and Cu[II] via amine binding. Finally, the inductive electron-withdrawing ammonium cation electronically deactivates proximal C–H bonds, resulting in high selectivity for terminal C(sp^3)–H sites remote from the nitrogen atom. Preliminary H/D exchange experiments demonstrate higher selectivity compared to hydroxylation, suggesting modifications to reaction conditions (oxidant, solvent, nucleophile) can potentially impact the site selectivity of the functionalized product (**Scheme 2.8**). Current efforts in our laboratory are focused on designing second-generation Pt catalysts with water-soluble ligands to enhance selectivity and catalyst longevity, as well as investigating the use of organic co-solvents to expand the current substrate scope.

Scheme 2.8. Deuterium Incorporation Studies with Dipropylamine and Dibutylamine
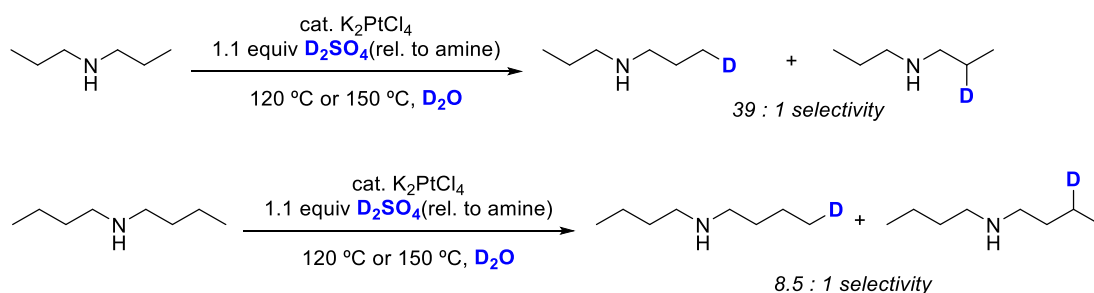
2.4. Updates Since Publication

Since our publication on the remote functionalization of protonated aliphatic amines, several groups have utilized a similar strategy for transition metal mediated, remote C–H oxidation. Both the White group and our group have utilized protonated aliphatic amines as substrates for Fe-catalyzed oxidation of remote secondary, tertiary, and benzylic C(sp^3)–H bonds.[23] The Sigman group jointly with the DuBois group recently published a Ru-catalyzed

remote tertiary and benzylic C–H oxidation.[24] Schulz and co-workers achieved the remote C–H oxidation of protonated cyclic and linear aliphatic amines via decatungstate photocatalysis.[25] This ongoing work demonstrates the promise of this approach for the selective C–H oxidation of important amine scaffolds.

2.5. Experimental Procedures and Characterization of Compounds

2.5.1 General Procedures and Materials and Methods

General Procedures

NMR spectra were recorded on a Varian vnmrs 700 (700 MHz for ^{1}H; 176 MHz for ^{13}C), Varian vnmrs 500 (500 MHz for ^{1}H; 126 MHz for ^{13}C), Varian Inova 500 (500 MHz for ^{1}H), or Varian MR400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) with the residual solvent peak ($CDCl_3$; ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), qd (quartet of doublets). Coupling constants (J) are reported in Hz. Infrared (IR) spectroscopy was performed on a Perkin-Elmer Spectrum BX Ft-IR spectrometer and peaks are reported in cm^{-1}. Melting points were determined with a Thomas Hoover Uni-Melt 6427-H10 Capillary Melting-Point Apparatus and are uncorrected. High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Stock solutions were made using volumetric glassware. Liquid reagents were dispensed by difference from syringes. All reagents were weighed out under ambient conditions.

Materials and Methods

HPLC grade water, ethyl acetate (EtOAc), hexanes, methanol, and dichloromethane for column chromatography were purchased from VWR. Silica gel for flash column chromatography was purchased from Dynamic Adsorbents. $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc. K_2PtCl_4, K_2PtCl_6 (Acros), and copper(II) chloride dihydrate (J.T. Baker Chemicals) were used as purchased without further purification. Amine substrates were purchased from commercial sources (Alfa Aeser, Sigma Aldrich, TCI, and ACROS, Astatech) and used without further purification, unless otherwise noted. Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silica gel 60 F_{254}.

2.5.2 Synthesis and Characterization of Substrates

N-(tert-butyl)propan-1-amine:
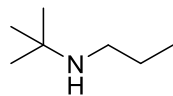
N-(tert-butyl)propan-1-amine was synthesized from *tert*-butylamine and 1-iodopropane using a literature procedure[26] and was purified via distillation.

<u>HRMS:</u> ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_7H_{18}N$: 116.1434; found: 116.1434

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 2.50 (t, *J* = 7.5 Hz, 2H), 1.46 (sex, *J* = 7.5 Hz, 2H), 1.08 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.61 (s, 1H, N–H)

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 50.2, 44.7, 29.2, 24.4, 12.1

1-propylpyrrolidine:
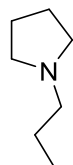
1-propylpyrrolidine was synthesized from pyrrolidine and 1-iodopropane using a literature procedure[26] and was purified via distillation.

<u>HRMS:</u> ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_7H_{16}N$: 114.1277; found: 114.1279

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 2.47 (m, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.76 (m, 4H), 1.52 (sex, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H)

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 58.8, 54.4, 23.5, 22.5, 12.3

1-butylpyrrolidine:
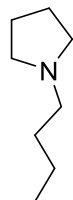
1-butylpyrrolidine was synthesized from pyrrolidine and 1-iodobutane using a literature procedure[26] and was purified via distillation.

<u>HRMS:</u> ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_8H_{18}N$: 128.1434; found: 128.1433

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 2.48 (m, 4H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.77 (m, 4H), 1.50 (sex, *J* = 7.5 Hz, 2H), 1.34 (sex, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3H)

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 56.6, 54.4, 31.4, 23.6, 21.1, 14.2

1-pentylpyrrolidine:

1-pentylpyrrolidine was synthesized from pyrrolidine and 1-iodopentane using a literature procedure[26] and was purified via distillation.

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_8H_{20}N$: 143.1590; found: 143.1590

^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.48 (m, 4H), 2.40 (t, J = 7.5 Hz, 2H), 1.77 (m, 4H), 1.51 (quin, J = 7.5 Hz, 2H), 1.36-1.28 (multiple peaks, 4H), 0.91 (t, J = 7.5 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 56.9, 54.4, 30.1, 29.0, 23.6, 22.8, 14.2

1-propylpiperidine:
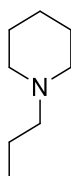
1-Propylpiperidine was synthesized from piperidine and 1-iodopropane using a literature procedure[26] and was purified via distillation.

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_8H_{18}N$: 128.1434; found: 128.1435

^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.35 (br s, 4H), 2.23 (t, J = 7.5 Hz, 2H), 1.57 (m, 4H), 1.52 (m, 2H), 1.42 (sex, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 61.8, 54.8, 26.2, 24.7, 20.3, 12.3

4-propylmorpholine:
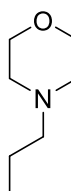
4-Propylmorpholine was synthesized from morpholine and 1-iodopropane using a literature procedure[26] and was purified via distillation.

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_7H_{16}N$: 130.1226; found: 130.1227

^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.71 (t, J = 4.5 Hz, 4H), 2.42 (m, 4H), 2.29 (t, J = 7.5 Hz, 2H), 1.50 (sex, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 67.2, 61.3, 53.9, 19.9, 12.0

2.5.3 Synthesis and Characterization of Minor Isomers

1-(pyrrolidin-1-yl)propan-2-ol:
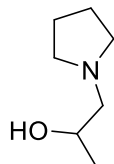
An authentic sample of 1-(pyrrolidin-1-yl)propan-2-ol (for comparison with samples produced from Pt catalysis) was synthesized from pyrrolidine and propylene oxide using a literature procedure.[27]

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_7$H$_{16}$NO: 130.1226; found: 130.1226

^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.78 (m, 1H), 3.50 (br s, 1H, O-H) 2.66 (m, 2H), 2.52 (app t, J = 12.0 Hz, 1H), 2.43 (m, 2H), 2.23 (dd, J = 12.0 Hz, J = 2.5 Hz, 1H), 1.75 (m, 4H), 1.12 (d, J = 6.0 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 64.5, 63.7, 54.1, 23.7, 20.4

1-(piperidin-1-yl)propan-2-ol:
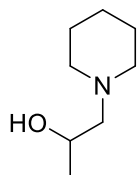
An authentic sample of 1-(piperidin-1-yl)propan-2-ol (for comparison with samples produced from Pt catalysis) was synthesized from piperidine and propylene oxide using a literature procedure.[27]

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_8$H$_{18}$NO: 144.1383; found: 144.1383

^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.79 (m, 1H), 3.69 (br s, 1H, O-H), 2.57 (m, 2H), 2.27 (m, 2H), 2.24 (dd, J = 12.5 Hz, J = 3.0 Hz, 1H), 2.13 (t, J = 10.5 Hz, 1H), 1.55 (m, 4H), 1.42 (m, 2H), 1.10 (d, J = 6.0 Hz, 3H)

^{13}C NMR (CDCl$_3$, 175.95 MHz): δ 66.5, 62.3, 54.8, 26.3, 24.5, 20.2

1-morpholinopropan-2-ol:
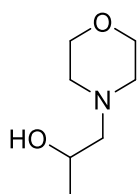
An authentic sample of 1-morpholinopropan-2-ol (for comparison with samples produced from Pt catalysis) was synthesized from morpholine and propylene oxide using a literature procedure.[27]

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_7H_{16}NO_2$: 146.1175; found: 146.1176

^{1}H NMR (CDCl$_3$, 700 MHz): δ 3.84 (m, 1H), 3.70 (m, 4H), 3.40 (br s, 1H, O-H), 2.64 (m, 2H), 2.38 (m, 2H), 2.31 (dd, J = 12.5 Hz, J = 3.0 Hz, 1H), 2.21 (dd, J = 12.5 Hz, J = 10.5 Hz, 1H), 1.12 (d, J = 6.0 Hz)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 67.2, 66.3, 62.2, 53.8, 20.1

1-(propylamino)propan-2-ol:
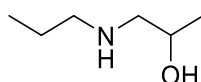
An authentic sample of 1-(propylamino)propan-2-ol (for comparison with samples produced from Pt catalysis) was synthesized from *n*-propylamine and propylene oxide using a literature procedure.[27]

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_6H_{16}NO$: 118.1226; found: 118.1228

^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.76 (m, 1H), 2.70 (dd, J = 12.0 Hz, J = 3.5 Hz, 1H), 2.61 (m, 1H), 2.56 (m, 1H), 2.39 (dd, J = 12.0 Hz, J = 9.0 Hz, 1H), 2.16 (br s, 2H, O-H and N-H), 1.50 (sex, J = 7.5 Hz, 2H), 1.14 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 65.6, 56.9, 51.6, 23.4, 20.6, 11.8

1-(dipropylamino)propan-2-ol:
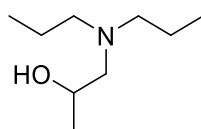
An authentic sample of 1-(dipropylamino)propan-2-ol (for comparison with samples produced from Pt catalysis) was synthesized from dipropylamine and propylene oxide using a literature procedure.[27]

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_9H_{22}NO$: 160.1696; found: 160.1693

^{1}H NMR (CDCl$_3$, 500 MHz): δ 3.70 (multiple peaks, 2H, where 1H from O-H), 2.47 (m, 2H), 2.38-2.33 (multiple peaks, 3H), 2.21 (dd, J = 10.5 Hz, J = 12.5 Hz, 1H), 1.45 (m, 4H), 1.11 (d, J = 6.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 6H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 63.1, 62.6, 56.4, 20.5, 19.9, 11.9

5-(N-methylpivalamido)pentan-2-yl pivalate:
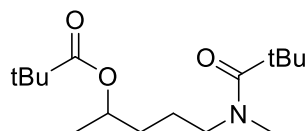
An authentic sample of 5-(N-methylpivalamido)pentan-2-yl pivalate (for comparison with samples produced from Pt catalysis) was synthesized from 5-chloro-2-pentanone using a literature procedure.[28]

HRMS: ESI[+] (m/z): [M+H][+] calcd for C$_{16}$H$_{32}$NO$_3$: 286.2377; found: 286.2376

^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.88 (sex, J = 6.8 Hz, 1H), 3.36 (m, 2H), 3.01 (s, 3H), 1.65-1.45 (multiple peaks, 4H), 1.27 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H), 1.18 (s, 9H)

^{13}C NMR (CDCl$_3$, 126 MHz): 178.3, 177.4, 70.2, 49.9, 38.9, 38.9, 33.2, 28.5, 27.3, 27.2, 23.5, 20.0

2.5.4 General Procedures for Reaction Optimization

General Procedure A:

120 °C Conditions: To a 4 mL scintillation vial containing K$_2$PtCl$_4$ (10 mol %, 2.1 mg), CuCl$_2$•2H$_2$O (1 equiv, 0.1 mmol, 17 mg) were added aqueous H$_2$SO$_4$ (2.2 equiv, 0.11 mmol) from a stock solution and dipropylamine (2.0 equiv, 0.1 mmol, 14 µL). The reaction vial was equipped with a micro stir bar, sealed with a Teflon-lined cap, and placed in an aluminum block preheated to 120 °C. The reaction mixture was stirred for 48 h at 120 ºC. The reaction mixture was then quenched with NH$_4$OH (28% aqueous solution, 0.5 mL) and saturated NaCl. The product was extracted into CDCl$_3$ (2.0 mL) containing mesitylene as an internal standard (0.025 mmol). The organic extracts were filtered through a Celite plug and the yield was determined via ^{1}H NMR spectroscopic analysis.

150 °C Conditions: To a 10 mL scintillation vial (10 cm tall) containing K$_2$PtCl$_4$ (10 mol %, 2.1 mg), CuCl$_2$•2H$_2$O (1 equiv, 0.1 mmol, 17 mg) were added aqueous H$_2$SO$_4$ (2.2 or 5.5 equiv, 0.11 mmol or 0.55 mmol) from a stock solution, and dipropylamine (2.0 or 5.0 equiv, 0.1 mmol

or 0.25 mmol, 14 μL or 34 μL). The reaction vial was equipped with a micro stir bar, sealed with a Teflon-lined cap and placed in an aluminum block preheated to 150 °C. The reaction mixture was stirred for 30–48 h at 120 ºC. The reaction mixture was then cooled to room temperature and quenched with NH$_4$OH (28% aqueous solution, 0.5 mL) and saturated NaCl. The product was extracted into CDCl$_3$ (2.0 mL) containing mesitylene as an internal standard (0.025 mmol). The organic extracts were filtered through a Celite plug and the yield was determined via ^{1}H NMR spectroscopic analysis. Notably, when 1 mol % of Pt was used, the K$_2$PtCl$_4$ was added from a stock solution (0.0124 M aqueous stock solution) and was the last reagent added.

2.5.5 General Procedures for Isolation of Products and Characterization

General Procedure B:

To a 10 mL scintillation vial (10 cm tall) containing CuCl$_2$•2H$_2$O (1 equiv) were added aqueous H$_2$SO$_4$ (5.5 equiv) from a stock solution, the appropriate amine substrate (5 equiv), and K$_2$PtCl$_4$ (0.5-1 mol % from a 0.0124 M aqueous stock solution and 5-10 mol % as a solid). The reaction vial was equipped with a micro stir bar, sealed with a Teflon-lined cap, and placed in an aluminum block preheated to 150 °C. The reaction mixture was stirred for 24 to 48 h at 150 ºC. Unless otherwise noted, all reactions were run until all C–H chlorination products transformed into C–H hydroxylation products for accurate determination of selectivity and for ease of isolation. The reaction was cooled to room temperature and quenched with NH$_4$OH (28% aqueous solution, 0.5 mL) and saturated NaCl. The product was extracted into CHCl$_3$ (3 x 3 mL), the organic extracts were filtered through a Celite plug, and the resulting mixture was concentrated by rotary evaporation.

General Procedure C:

Two reactions conducted and worked on the scale of procedure B were combined. To the crude reaction mixture from part B was added dichloromethane (3 mL), and then triethylamine (0.7 mL) and pivaloyl chloride (1 equiv, 61 μL for products **3-5, 11, 14, 15, 19** or 3 equiv, 184 μL for products **6-10, 12, 13**) were added. The resulting mixture was stirred at room temperature for 3 h. The reaction was diluted with dichloromethane (50 mL), and the organic layer was washed three times with NaOH (1M aqueous solution, 50 mL). The organic extracts were collected and the volatiles were removed by rotary evaporation. The resulting residue was

purified by column chromatography. In all cases, the yield is calculated based on $CuCl_2 \cdot 2H_2O$ as the limiting reagent. Since the copper acts as a 1-electron oxidant, 100% yield = 0.5*(mmol $CuCl_2 \cdot 2H_2O$ added to the reaction).

2-(pyrrolidin-1-yl)ethan-1-ol (2-OH):

2-OH
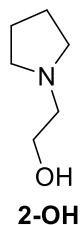
General procedure A was followed using 1-ethylpyrrolidine (0.25 mmol, 30.6 μL, 5 equiv), $CuCl_2 \cdot 2H_2O$ (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H_2SO_4 (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K_2PtCl_4 (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 48 h. The reaction was performed side-by-side in duplicate and the reaction was quenched and analyzed by ^{1}H NMR as outlined in **general procedure A**. The identity of the product was confirmed by a commerically available authentic sample of 2-(pyrrolidin-1-yl)ethan-1-ol.

^{1}H NMR Yield: 25%

3-(pyrrolidin-1-yl)propyl pivalate (3):

3   **3a**
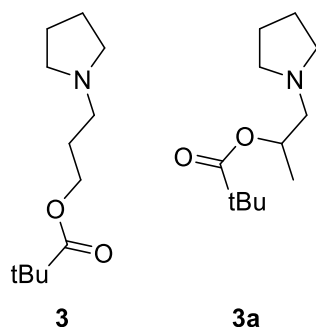
General procedure B was followed using 1-propylpyrrolidine (0.25 mmol, 28.3 mg, 5 equiv), $CuCl_2 \cdot 2H_2O$ (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H_2SO_4 (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K_2PtCl_4 (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

Isolated Yield: 85% (18.2 mg, crude ratio of **3-OH** : **3a-OH** = 10 : 1; isolated ratio of **3** : **3a** = >20:1; light yellow oil)

IR (ν, cm^{-1}): 2958, 2791, 1727, 1480, 1459, 1284, 1151, 732

HRMS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{24}NO_2$: 214.1807; found: 214.1802

^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.11 (t, J = 6.3 Hz, 2H), 2.50 (overlapping m, 6H), 1.85 (quin, J = 7.0 Hz, 2H), 1.78 (m, 4H), 1.19 (s, 9H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.7, 63.0, 54.4, 53.2, 38.9, 28.5, 27.3, 23.6

4-(pyrrolidin-1-yl)butyl pivalate (4):
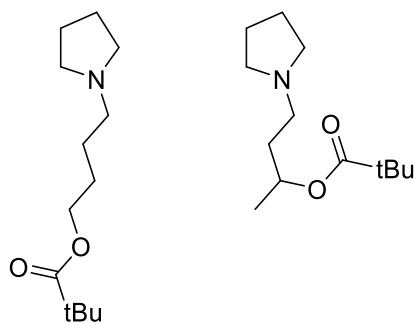
4   **4a**

General procedure B was followed using 1-butylpyrrolidine (0.25 mmol, 31.8 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

Isolated Yield: 126% (28.7 mg as a mixture of isomers; crude ratio of **4-OH : 4a-OH** = 4 : 1; isolated ratio of **4 : 4a** = 4 : 1; yellow oil)

R_f: 0.48 (**4**), 0.55 (**4a**) (10% MeOH/90% DCM)

IR (ν, cm^{-1}) (mixture of isomers): 2966, 1719, 1479, 1459, 1284, 1161, 908, 724

HRMS:

4: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{26}NO_2$: 228.1958; found: 228.1959

4a: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{26}NO_2$: 228.1958; found: 228.1959

4: ^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.07 (t, J = 6.3 Hz, 2H), 2.50 (br s, 4H), 2.47 (t, J = 7.0 Hz, 2H), 1.78 (br s, 4H), 1.67 (sex, J = 7.0 Hz, 2H), 1.59 (br s, 2H, overlaps with water peak), 1.92 (s, 9H)

4: ^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.8, 64.4, 56.3, 54.3, 38.9, 27.4, 27.0, 25.6, 23.6

4a: <u>^{1}H NMR</u> (CDCl$_3$, 700 MHz): δ 4.92 (sex, J = 6.3 Hz, 1H), 2.50 (overlapping peaks, 6H), 1.78 (overlapping peaks, 6H), 1.22 (d, J = 5.6 Hz, 3H), 1.18 (s, 9H)

4a: <u>^{13}C NMR</u> (CDCl$_3$, 176 MHz): δ 178.2, 69.4, 54.4, 52.7, 38.9, 35.5, 27.3, 23.6, 20.2

5-(pyrrolidin-1-yl)pentyl pivalate (5):

5   **5a**
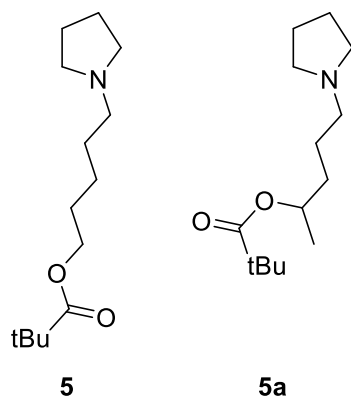
General procedure B was followed using 1-pentylpyrrolidine (0.25 mmol, 35.3 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

<u>Isolated Yield</u>: 73% (17.7 mg, crude ratio of **5-OH : 5a-OH** = 2:1; isolated ratio of **5 : 5a** = 3:1; light yellow oil)

<u>Major R$_f$ (**5**)</u>: 0.52 (10% MeOH/90% DCM)

<u>IR (ν, cm^{-1}) (mixture of **5** and **5a**)</u>: 2958, 2934, 2872, 2783, 1727, 1480, 1459, 1396, 1284, 1159

<u>HRMS (mixture of **5** and **5a**)</u>: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{14}$H$_{28}$NO$_2$: 242.2115; found: 242.2116

5: <u>^{1}H NMR</u> (CDCl$_3$, 700 MHz): δ 4.04 (t, J = 6.3 Hz, 2H), 3.16 (br s, 4H), 2.94 (t, J = 7.7 Hz, 2H), 2.11 (br s, 4H), 1.90 (quin, J = 7.7 Hz, 2H), 1.67 (quin, J = 7.7 Hz, 2H), 1.41 (quin, J = 7.7 Hz, 2H), 1.18 (s, 9H)

5: <u>^{13}C NMR</u> (CDCl$_3$, 176 MHz): δ 178.7, 63.8, 55.6, 53.7, 38.9, 28.3, 27.3, 23.6, 23.5, 20.1

3-(N-propylpivalamido)propyl pivalate (6):

6   **6a**
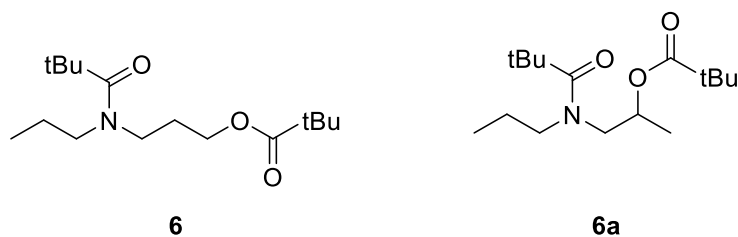
General procedure B was followed using dipropylamine (0.50 mmol, 68.5 μL, 5 equiv), CuCl$_2$·2H$_2$O (0.2 mmol, 34.1 mg, 1 equiv), 0.50 mL of aqueous H$_2$SO$_4$ (0.55 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.001 mmol, 80 μL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in triplicate, the three triplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 0 to 20%, EtOAc in Hex).

Isolated Yield: 87% (74.4 mg, crude ratio of **6-OH** : **6a-OH** = 10:1; isolated ratio of **6** : **6a** = >20:1; light yellow oil)

R$_f$: 0.41 (20% EtOAc/ 80% Hex)

IR (v, cm^{-1}): 2964, 1728, 1625, 1481, 1413, 1365, 1283, 1150, 1124

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{16}$H$_{32}$NO$_3$: 286.2377; found: 286.2377

^{1}H NMR (CDCl$_3$, 400 MHz): 4.07 (t, J = 6.0 Hz, 2H), 3.39 (poorly resolved triplet, 2H), 3.29 (t, J = 8.0 Hz, 2H), 1.90 (quin, J = 6.4 Hz, 2H), 1.58 (sex, J = 7.6 Hz, 2H), 1.26 (s, 9H), 1.20 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H)

^{13}C NMR (CDCl$_3$, 176 MHz, 50 °C): δ 178.4, 177.3, 62.3, 49.9, 44.9, 41.7, 39.2, 38.9, 28.7, 27.3. 21.7, 11.2

Scale-up: The same reaction was carried out on a larger scale using dipropylamine (1.0 mmol, 137 μL, 5 equiv), CuCl$_2$·2H$_2$O (0.4 mmol, 68.2 mg, 1 equiv), 1.0 mL of aqueous H$_2$SO$_4$ (1.1 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.002 mmol, 160 μL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via general procedure **C**. The product was then purified as above and a 70% yield was obtained (79.9 mg).

4-(N-butylpivalamido)butyl pivalate (7):

7   **7a**
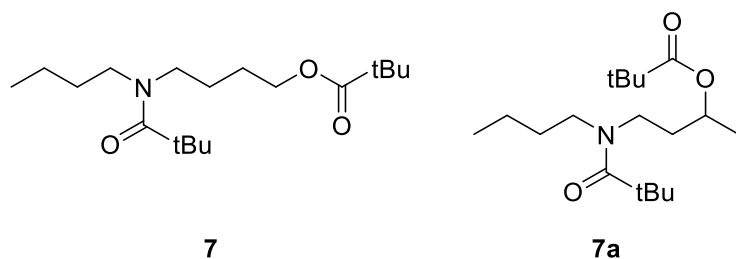
General procedure B was followed using dibutylamine (0.25 mmol, 42 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0005 mmol, 40 μL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 0 to 30%, EtOAc in Hex).

Isolated Yield: 76% (23.9 mg, crude ratio of **7-OH : 7a-OH** = 5:1; isolated ratio of **7 : 7a** = 7:1; light yellow oil)

R$_f$: 0.42 (**7**), 0.52 (**7a**) (20% EtOAc/80% Hex)

IR (ν, cm^{-1}) (mixture of **7** and **7a**): 2958, 1726, 1625, 1480, 1458, 1414, 1364, 1283, 1155, 1126

HRMS:

7: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{36}$NO$_3$: 314.2690; found: 314.2690

7a: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{36}$NO$_3$: 314.2690; found: 314.2690

7: ^{1}H NMR (CDCl$_3$, 700 MHz, 50 °C): δ 4.08 (t, J = 5.6 Hz, 2H), 3.33 (m, 4H), 1.63 (m, 4H), 1.55 (quin, J = 7.0 Hz, 2H), 1.32 (sex, J = 7.7 Hz, 2H), 1.27 (s, 9H), 1.20 (s, 9H), 0.95 (t, J = 7.7 Hz, 3H)

7: ^{13}C NMR (CDCl$_3$, 176 MHz, 50 °C): δ 178.8, 177.4, 64.2, 48.0, 47.6, 39.4, 39.1, 30.9, 29.0, 27.6, 26.7, 25.1, 20.6, 14.2

7a: ^{1}H NMR (CDCl$_3$, 700 MHz, 50 °C): δ 4.90 (sex, J = 6.3 Hz, 1H), 3.35 (m, 4H), 1.83 (m, 2H), 1.54 (m, 2H), 1.32 (sex, J = 7.7 Hz, 2H), 1.27 (s, 9H), 1.24 (d, J = 6.3 Hz, 3H), 1.21 (s, 9H), 0.95 (t, J = 7.7 Hz, 3H)

7a: ^{13}C NMR (CDCl$_3$, 176 MHz, 50 °C): δ 178.1, 177.3, 69.1, 48.1, 44.5, 39.2, 39.0, 34.5, 30.7, 28.8, 27.4, 20.4, 20.2, 14.0

5-(N-methylpivalamido)pentyl pivalate (8):

8   **8a**
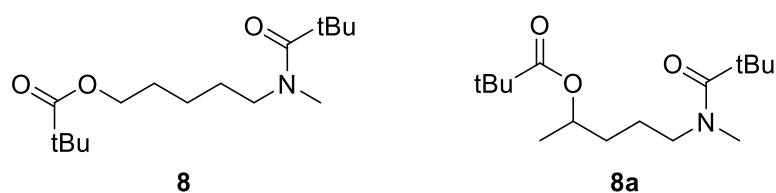
General procedure B was followed using *N*-methylpentylamine (0.25 mmol, 34 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0025 mmol, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The 2° C–H chlorination product (~14%) was observed at the end of the reaction (24 h). This compound still remained after 48 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 0 to 30%, EtOAc in Hex).

Isolated Yield: 47% (13.5 mg, crude ratio of **8-OH : 8a-OH** = 3:1; isolated ratio **8 : 8a** = 17:1; light yellow oil)

R$_f$ (**8**): 0.50 (30% EtOAc/70% Hex)

IR (v, cm^{-1}) (isolated mixture of **8** and **8a**): 2936, 2871, 1725, 1626, 1480, 1401, 1364, 1283, 1152, 1077, 1030

HRMS (isolated mixture of **8** and **8a**): EI$^+$ (m/z): M$^+$ calcd for C$_{16}$H$_{31}$NO$_3$: 285.2304; found: 285.2308

8: ^{1}H NMR (CDCl$_3$, 401 MHz): δ 4.04 (t, *J* = 6.8 Hz, 2H), 3.35 (dd, *J* = 7.6 Hz, 2H), 3.03 (s, 3H), 1.66 (m, 2H), 1.57 (m, 2H), 1.34 (m, 2H), 1.27 (s, 9H), 1.19 (s, 9H)

8: ^{13}C NMR (CDCl$_3$, 176 MHz, 50 °C): δ 178.7, 177.4, 64.3, 50.2, 39.0, 38.9, 36.4, 28.8, 28.6, 27.4, 27.3, 23.6

3-(N-isobutylpivalamido)-2-methylpropyl pivalate (9):
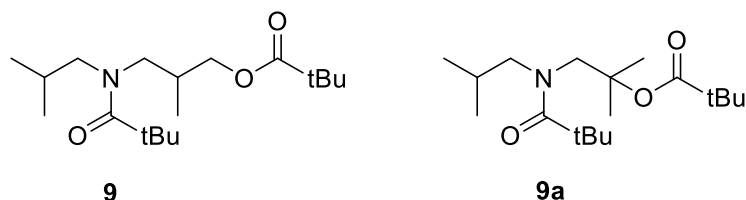
9   **9a**

General procedure B was followed using diisobutylamine (0.25 mmol, 43 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0005 mmol, 40 μL of a 0.0124 M aqueous stock solution,

1 mol %). The reaction was stirred at 150 °C for 48 h. Trace amounts of the aldehyde product were observed at the end of the reaction (see spectra for more detail). The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 0 to 30%, EtOAc in Hex).

Isolated Yield: 54% (16.8 mg, crude ratio of **9-OH** : **9a-OH** = 8:1; isolated ratio of **9** : **9a** = >20:1, light orange oil)

R_f: 0.54 (20% EtOAc/80% Hex)

IR (v, cm^{-1}): 2963, 2872, 1729, 1628, 1479, 1411, 1364, 1283, 1200, 1152, 1126

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{19}H_{36}NO_3$: 314.2690; found: 314.2689

^{1}H NMR (CDCl$_3$, 700 MHz, 50 °C): δ 3.99 (dd, J = 11.2 Hz, 4.9 Hz, 1H), 3.89 (dd, J = 10.5 Hz, 5.6 Hz, 1H), 3.40 (multiplet, 2H), 3.29 (dd, J = 14.0 Hz, 7.7 Hz, 1H), 3.10 (m, 1H), 2.23 (m, 1H), 1.98 (m, 1H), 1.28 (s, 9H), 1.20 (s, 9H), 0.90 (m, 9H)

^{13}C NMR (CDCl$_3$, 175.95 MHz, 50 °C): δ 178.4, 178.4, 67.0, 54.2, 48.9, 39.8, 39.1, 31.4, 29.3, 27.4, 26.8, 20.2, 19.9, 14.9

3-(tert-butylamino)propyl pivalate (10):

10
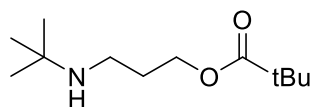
General procedure B was followed using *N*-(tert-butyl)propan-1-amine (0.25 mmol, 28.6 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0005 mmol, 40 µL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 24 h. Trace amounts of the terminal C(sp^3)–H chlorination product were present at the end of the reaction. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1 to 8%, MeOH in DCM).

Isolated Yield: 46% (9.9 mg, >20:1 selectivity, yellow oil)

R_f: 0.40 (10% MeOH/90% DCM)

IR (v, cm^{-1}): 2958, 2924, 2871, 1725, 1480, 1459, 1395, 1363, 1283, 1157

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{26}NO_2$: 216.1958; found: 216.1956

^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.14 (t, J = 6.5 Hz, 2H), 2.63 (t, J = 7.0 Hz, 2H), 1.80 (quin, J = 7.0 Hz, 2H), 1.19 (s, 9H), 1.10 (s, 9H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 178.7, 62.8, 39.3, 38.9, 30.3, 29.9, 29.1, 27.4

4-(1-pivaloylpiperidin-4-yl)butyl pivalate (11):

11   **11a**
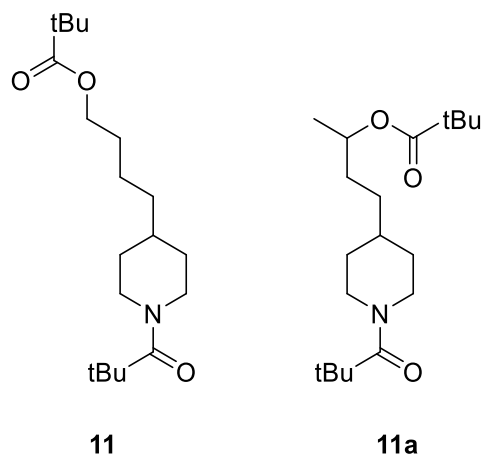
General procedure B was followed, using commerically available 4-butylpiperidine hydrochloride as the substrate (0.25 mmol, 44.4 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), H$_2$O (0.25 mL), and K$_2$PtCl$_4$ (0.005 mmol, 2.1 mg, 10 mol %). The reaction stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 0 to 30%, EtOAc in DCM).

Isolated Yield: 65% (21.1 mg, crude ratio of **11-OH : 11a-OH** = 5:1; isolated ratio of **11:11a** = 17:1; yellow oil)

R$_f$ (**11**): 0.24 (20% EtOAc/80% Hex)

IR (v, cm^{-1}) (isolated mixture of **11** and **11a**): 2924, 2864, 1725, 1695, 1627, 1480, 1419, 1364, 1283, 1152

HRMS (isolated mixture of **11** and **11a**): ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{36}$NO$_3$: 326.2690; found: 326.2693

11: ^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.40 (m, 2H), 4.05 (t, J = 6.3 Hz, 2H), 2.73 (m, 2H), 1.70 (m, 2H), 1.61 (quin, J = 7.0 Hz, 2H), 1.48 (m, 1H), 1.37 (quin, J = 7.0 Hz, 2H), 1.26 (overlapping s and m, 11 H), 1.89 (s, 9H), 1.08 (qd, J = 3.5 Hz, J = 12.6 Hz, 2H)

11: ^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.8, 176.2, 64.4, 45.7, 38.9, 38.8, 36.3, 36.2, 32.7, 28.9, 28.6, 27.4, 23.1

2-(diethylamino)ethyl pivalate (12):

12
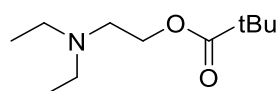
General procedure B was followed using triethylamine (0.75 mmol, 104 μL, 15 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.83 mmol, 16.5 equiv, 3.3 M stock solution), and K$_2$PtCl$_4$ (0.0005 mmol, 40 μL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 48 h. The reaction stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

Isolated Yield: 88% (17.8 mg, single isomer, orange oil)

R$_f$: 0.31 (10% MeOH/ 90% DCM)

IR (v, cm^{-1}): 2970, 2818, 1727, 1480, 1460, 1396, 1364, 1282, 1151, 1066, 1036

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{11}$H$_{24}$NO$_2$: 202.1802; found: 202.1801

^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.13 (t, J = 6.3 Hz, 2H), 2.70 (t, J = 6.3 Hz, 2H), 2.57 (q, J = 7.0 Hz, 4H), 1.19 (s, 9H), 1.03 (t, J = 7.0 Hz, 6H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.7, 63.1, 51.1, 47.9, 38.8, 27.4, 12.3

3-(dipropylamino)propyl pivalate (13):
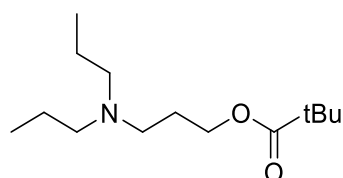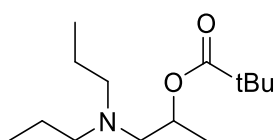
13 **13a**

General procedure B was followed using tripropylamine (0.75 mmol, 142 μL, 15 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.83 mmol, 16.5 equiv, 3.3 M stock solution), and K$_2$PtCl$_4$ (0.00025 mmol, 20 μL of a 0.0124 M aqueous stock solution, 0.5 mol %). The reaction was stirred at 150 °C for 24 h. Trace amounts of the dihydroxylated product were observed at the end of the reaction. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

Isolated Yield: 102% (24.9 mg, crude ratio of **13-OH** to **13a-OH** = 7:1; isolated ratio of **13:13a** = >20:1; yellow oil)

R_f: 0.50 (10% MeOH/90% DCM)

IR (v, cm^{-1}): 2958, 2803, 1728, 1480, 1459, 1283, 1079

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{14}H_{30}NO_2$: 244.2272; found: 244.2271

^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.09 (t, J = 6.4 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.34 (t, J = 7.2 Hz, 4H), 1.73 (quin, J = 6.4 Hz, 2H), 1.42 (sex, J = 7.2 Hz, 4H), 1.19 (s, 9H), 0.86 (t, J = 7.2 Hz, 6H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.7, 62.9, 56.3, 50.5, 38.8, 27.3, 26.6, 20.5, 12.1

3-(piperidin-1-yl)propyl pivalate (14):

| 14 | 14a |
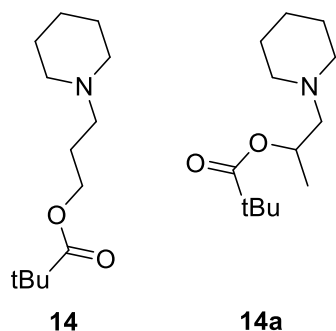
General procedure B was followed using 1-propylpiperidine (0.25 mmol, 31.8 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient 1% to 10%, MeOH in DCM).

Isolated Yield: 90% (20.5 mg, crude ratio of **14-OH**:**14a-OH** = 14:1; isolated ratio of **14:14a** = >20:1; light yellow oil)

R_f: 0.33 (10% MeOH/90% DCM)

IR (v, cm^{-1}): 2935, 2769, 1728, 1672, 1480, 1283, 1152, 1126, 1037

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{26}NO_2$: 228.1958; found: 228.1956

^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.09 (t, J = 6.3 Hz, 2H), 2.36 (t, J = 7.7 Hz, 6H), 1.82 (quin, J = 6.3 Hz, 2H), 1.58 (quin, J = 5.6 Hz, 4H), 1.43 (br m, 2H), 1.19 (s, 9H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.5, 62.2, 55.4, 54.1, 39.0, 27.4, 24.9, 24.2, 23.3

3-morpholinopropyl pivalate (15):

15   **15a**
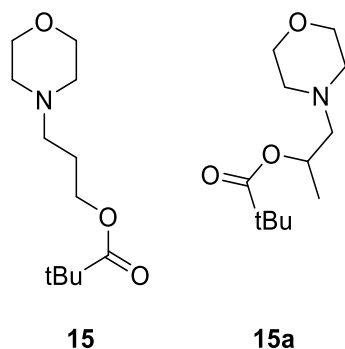
General procedure B was followed using 1-propylmorpholine (0.25 mmol, 32.3 mg, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.0025, 1.0 mg, 5 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

Isolated Yield: 122% (27.9 mg, crude ratio of **15-OH**:**15a-OH** = 10:1; isolated ratio of **15**:**15a** = >20:1; light yellow oil)

R$_f$: 0.61 (10% MeOH/90% DCM)

IR (ν, cm^{-1}): 2964, 2906, 1725, 1485, 1284, 1152, 1117, 1036, 862

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{12}$H$_{24}$NO$_3$: 230.1752; found: 230.1751

^{1}H NMR (CDCl$_3$, 400 MHz): δ 4.11 (t, J = 6.4 Hz, 2H), 3.71 (t, J = 4.4 Hz, 4H), 2.43 (multiple peaks, 6H), 1.82 (quin, J = 6.4 Hz, 2H), 1.19 (s, 9H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.7, 67.1, 62.8, 55.6, 53.9, 38.9, 27.3, 26.0

4-(diethylamino)butyl pivalate (19):

19-OPiv   **19a-OPiv**
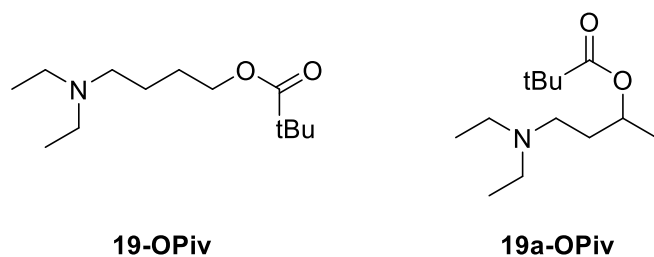
General procedure B was followed using diethylbutylamine (0.25 mmol, 43 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution) and K$_2$PtCl$_4$ (0.0005 mmol, 40 μL of a 0.0124 M aqueous stock solution, 1 mol %). The reaction was stirred at 150 °C for 24 h. The reaction was performed side-by-side in duplicate, the two duplicate runs were combined, and the hydroxylated product was

protected via **general procedure C**. The product was then purified by silica column chromatography (gradient of 1% to 10%, MeOH in DCM).

<u>Isolated Yield</u>: 52% (11.9 mg, crude ratio of **19-OH:19a-OH** = 3:1; isolated ratio **19-OPiv:19a-OPiv** = 6:1; yellow oil)

<u>R_f (mixture of isomers)</u>: 0.39 (10% MeOH/90% DCM)

<u>IR (v, cm^{-1}) (mixture of isomers)</u>: 2970, 2804, 1728, 1480, 1368, 1284, 1154, 1072, 910, 731

19-OPiv: <u>HRMS: ESI$^+$</u> (m/z): [M+H]$^+$ calcd for $C_{13}H_{28}NO_2$: 230.2115; found: 230.2112

19a-OPiv: <u>HRMS: ESI$^+$</u> (m/z): [M+H]$^+$ calcd for $C_{13}H_{28}NO_2$: 230.2115; found: 230.2114

19-OPiv: <u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 4.07 (t, J = 6.5 Hz, 2H), 2.52 (q, J = 7.5 Hz, 4H), 2.44 (t, J = 7.5 Hz, 2H), 1.64 (quin, J = 7.0 Hz, 2H), 1.51 (quin, J = 7.5 Hz, 2H), 1.19 (s, 9H), 1.01 (t, J = 7.0 Hz, 6H)

19-OPiv: <u>^{13}C NMR</u> (CDCl$_3$, 100 MHz): δ 178.8, 64.5, 52.6, 47.0, 38.9, 27.4, 27.0, 23.7, 11.8

19a-OPiv: <u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 4.90 (sex, J = 6.5 Hz, 1H), 2.50 (m, 6H), 1.74 (m, 1H), 1.67 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H), 1.19 (s, 9H), 1.02 (t, J = 7.0 Hz, 6H)

19a-OPiv: <u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 178.2, 69.5, 48.9, 47.1, 38.9, 29.9, 27.3, 20.3, 11.9

1-isobutyl-5-methyl-3-phenyltetrahydropyrimidine-2(1H)-thione (22)
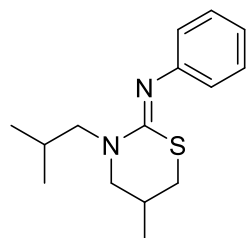
22

General procedure B was followed using diisobutylamine (0.25 mmol, 43 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.005 mmol, 2.1 mg, 10 mol %), and the reaction was stirred at 150 °C for 2 h. The reaction was allowed to cool to room temperature, and the water layer was saturated with NaCl. The reaction mixture was then cooled to room temperature and quenched with NH$_4$OH (28% aqueous solution, 0.5 mL) and saturated NaCl. The product was extracted into CHCl$_3$ and filtered through a plug of celite. To the CHCl$_3$ extract were added triethylamine (0.7 mL) and phenyl isothiocyanate (1.25 mmol, 150 μL, 2.5 equiv). The reaction was allowed to stir overnight at room temperature. The reaction was washed with 1 M NaOH (50 mL) and extracted into DCM (2 x 50 mL) and purified by silica column chromatography

(gradient 1 to 6% MeOH in DCM) and repurified via preparative TLC (5% MeOH in DCM). The product assignment was based on the ^{13}C shift of the imine carbon.

Isolated Yield: 73% (19.3 mg, yellow oil)

R$_f$: 0.53 (10% MeOH/ 90% DCM)

IR (v, cm^{-1}): 2959, 1575, 1492, 1463, 1358, 1221, 1154

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{15}$H$_{23}$N$_2$S: 263.1576; found: 263.1578

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.24 (t, J = 7.6 Hz, 2 H), 6.98 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.6 Hz, 2H), 3.43 (dd, J = 7.6 Hz, J = 2.4 Hz, 2H), 3.28 (ddd, J = 6.0 Hz, J = 4.0 Hz, J = 1.2 Hz, 1H), 3.11 (dd, J = 12.8 Hz, J = 9.6 Hz, 1H), 2.86 (ddd, J = 11.6 Hz, J = 4.4 Hz, J = 1.2 Hz, 1H), 2.62 (dd, J = 12.0 Hz, J = 9.6 Hz, 1H), 2.30 (m, 1H), 2.13 (sep, J = 6.8 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), .98 (d, J = 1.2 Hz, 3H), .08 (d, J = 1.6 Hz, 3H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 151.5, 150.8, 128.8, 122.7, 122.4, 58.7, 56.2, 34.7, 30.2, 27.2, 20.4, 20.3, 18.8

3-isobutyl-5-methyl-1,3-oxazinan-2-one (23):
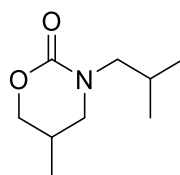
23

General procedure B was followed using diisobutylamine (0.25 mmol, 43 μL, 5 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.28 mmol, 5.5 equiv, 1.1 M stock solution), and K$_2$PtCl$_4$ (0.005 mmol, 2.1 mg, 10 mol %), and the reaction was stirred at 150 °C for 2 h. The reaction was allowed to cool to room temperature, and then KHCO$_3$ (1 mL of a saturated aqueous solution) was added. The resulting mixture was stirred for 4 h at 50 °C. The reaction was allowed to cool to room temperature, and NH$_4$OH (0.5 mL of a 28% aqueous solution) was added. The product was extracted into CHCl$_3$ and purified by silica column chromatography (gradient of 1 to 6%, MeOH in DCM).

Isolated Yield: 65% (11.2 mg, single isomer, yellow oil)

R$_f$: 0.77 (10% MeOH/ 90% DCM)

IR (v, cm^{-1}): 2959, 2925, 2871, 1681, 1488, 1431, 1251, 1204, 1158, 1112, 1073, 758

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_9$H$_{18}$NO$_2$: 172.1332; found: 172.1330

^{1}H NMR (CDCl$_3$, 700 MHz): δ 4.18 (d, J = 10.5 Hz, 1H), 3.85 (t, J = 10.5 Hz, 1H), 3.25 (ddd, J = 11.9 Hz, J = 5.6 Hz, J = 1.4 Hz, 1H), 3.21 (dd, J = 13.3 Hz, J = 7.7 Hz, 1H), 3.06 (dd, J =

13.3 Hz, $J = 7.0$ Hz, 1H), 2.97 (dd, $J = 11.2$ Hz, $J = 9.1$ Hz, 1H), 2.25 (m, 1H), 2.00 (sep, $J = 6.3$ Hz, 1H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 3.5$ Hz, 3H), 0.90 (d, $J = 3.5$ Hz, 3H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 57.0, 52.9, 27.2, 26.5, 20.1, 19.9, 14.1

Cl - product (**21**) before derivitization to form **22** and **23**; GC-MS: EI$^+$ (m/z): [M]$^+$ found: 165.10
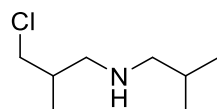
21
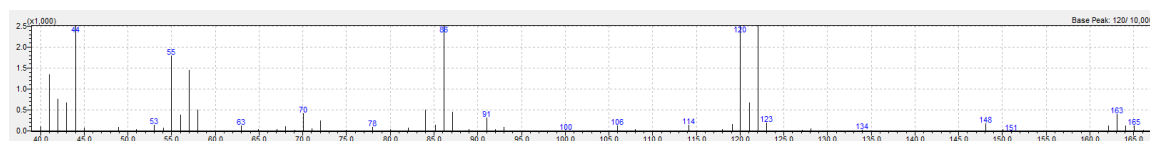
5-methyl-1,3-oxazinan-2-one (26)

26
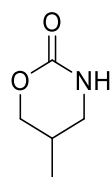
General procedure B was followed using isobutylamine (0.75 mmol, 74 μL, 15 equiv), CuCl$_2$•2H$_2$O (0.1 mmol, 17 mg, 1 equiv), 0.25 mL of aqueous H$_2$SO$_4$ (0.83 mmol, 16.5 equiv, 3.3 M stock solution), and K$_2$PtCl$_4$ (0.005 mmol, 2.1 mg, 10 mol %). The reaction was heated at 150 °C for 2 h. The resulting mixture was allowed to cool to room temperature, after which a solution of saturated aqueous KHCO$_3$ (1 mL) was added. The resulting mixture was stirred at for 1 h at 100 °C, and then allowed to cool to room temperature. NH$_4$OH (28% aqueous solution, 1 mL) was added. The product was extracted into CHCl$_3$ and purified by silica column chromatography (gradient of 1 to 5%, MeOH in DCM).

Isolated Yield: 59% (6.8 mg, singel isomer, white solid)

R$_f$: 0.61 (10% MeOH/ 90% DCM)

IR (v, cm^{-1}): 1688, 1488, 1272, 1112

MP: 47-48 °C

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_5$H$_{10}$NO$_2$: 116.0706; found: 116.0707

^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.32 (br s, 1H), 4.24 (ddd, J = 11.0 Hz, 3.5 Hz, 2.0 Hz, 1H), 3.92 (dd, J = 11.0 Hz, J = 10.0 Hz, 1H), 3.39 (m, 1H), 3.01 (t, J = 10.0 Hz, 1H), 2.22 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): δ 153.9, 72.2, 47.0, 26.3, 13.9

Cl - product **(25)** before derivatization to form **26**; GC-MS: EI$^+$ (m/z): [M]$^+$ found: 107.00
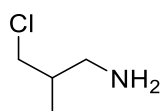
25
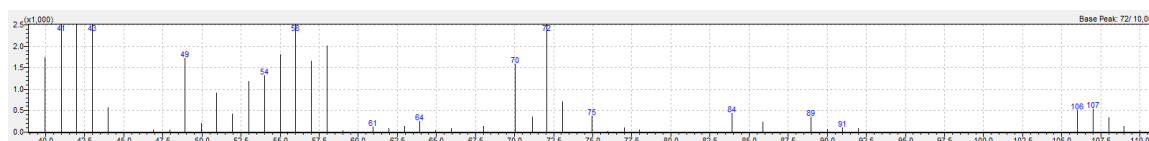
3-chloro-N-propylpropan-1-amine (A):
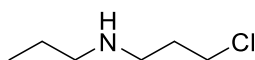
A

3-(propylamino)propan-1-ol was formed from dipropylamine (**General procedure B**). The volatiles were removed via rotary evaporation. The HCl salt of 3-(propylamino)propan-1-ol was generated using 4M HCl in THF and dried to obtain a yellow solid. The salt was redissolved in DCM, subjected to excess SOCl$_2$, and allowed to stir at room temperature overnight. The volatiles were removed via rotary evaporation. The HCl salt of the chlorinated amine was dissolved in CDCl$_3$ and free-based with 1M aqueous NaOH. The ^{1}H and ^{13}C NMR spectra of the authentic product match the ^{1}H and ^{13}C NMR shifts of the intermediate formed in the time study, thereby further confirming the identity of terminal chlorinated product as an intermediate en route to the hydroxylated product (see NMR spectra for more detail).

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_6$H$_{15}$ClN: 136.0888; found: 136.0888

^{1}H NMR (CDCl$_3$, 700 MHz): δ 3.59 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H), 2.54 (t, J = 7.0 Hz, 2H), 1.92 (quin, J = 7.0 Hz, 2H), 1.47 (sex, J = 7.0 Hz, 2H), 0.89 (t, J = 7.0 Hz, 3H)

^{13}C NMR (CDCl$_3$, 176 MHz): δ 51.9, 46.9, 43.3, 33.0, 23.3, 11.8

2.5.6 General Procedure for Time Study Reaction Profile

General Procedure D:

Reactions were set up using general procedure A at 150 °C and were individually quenched at the appropriate time points. The reactions were worked up using general procedure A and the product yields and ratios were determined via ^{1}H NMR spectroscopic analysis.
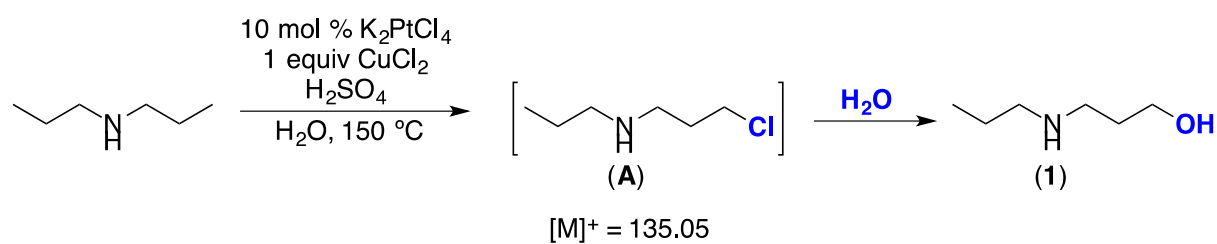
$[M]^+ = 135.05$

GC-MS of **A**: EI$^+$ (m/z): [M]$^+$ found: 135.05
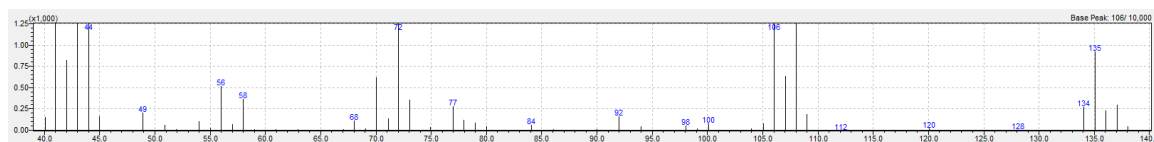
2.6.   References

(1) Adapted with permission from (a) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796. © American Chemical Society

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(19) The only internal chain oxidation products detected in more than trace quantities were at the site that is one carbon away from the terminal position. Additionally, only small amounts of products derived from C–H functionalization on the pyrrolidine ring were observed, except with *N*-ethylpyrrolidine. In the latter case, we estimate that ~15% of ring oxidation products are formed.

(20) The yields are calculated based on CuCl$_2$•2H$_2$O as the limiting reagent. Since Cu is a 1*e*– oxidant, 100% yield = 0.5 x mmol CuCl$_2$•2H$_2$O added to the reaction). Yields above 100% reflect regeneration of Cu by ambient air.

(21) The NMR yield of the C–H hydroxylation to form **4** under our standard conditions was 142%. When this same reaction was conducted under an atmosphere of N$_2$ (rather than air), a significantly lower yield of 41% was obtained. Furthermore, when the reaction under air was conducted in a small vessel (4 mL vs 10 mL sealed vial), the yield decreased to 47%. All of these pieces of data are consistent with the proposal that the O$_2$ (in air) is turning over the Cu.

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CHAPTER 3

Potassium Persulfate Mediated Remote C(sp^3)–H Oxidation of Protonated Aliphatic Amines[1]

3.1. Introduction

Chapter 3 focuses on the remote secondary and tertiary C(sp^3)–H oxygenation of protonated aliphatic amines. Aliphatic amines appear in a wide variety of pharmaceuticals and agrochemicals.[2] As such, methods for the selective C–H functionalization of aliphatic amines would be valuable for the synthesis and late-stage modification of biologically active molecules.[3] A variety of methods have been developed for the functionalization of the weak C(sp^3)–H bonds α to a nitrogen atom .[3b,4]

In contrast, at the time of our investigation, very few protocols addressed the challenge of selectively functionalizing less activated C(sp^3)–H bonds remote from nitrogen.[3a,c,d,5,6] The incorporation of various nitrogen protecting groups including carbamates,[7] amides,[7b,8] imides,[3a,9] and sulfonamides[4f,10] is one of the main strategies organic chemists have utilized to deactivate the α-C–H bonds and enable C(sp^3)–H functionalization at alternate sites (**Scheme 3.1a**). Similarly, directing groups can be installed on the nitrogen to enforce selective C(sp^3)–H functionalization at remote sites (**Scheme 3.1b**).[3c,11] However, both strategies require additional steps of protecting group installation and subsequent removal. Furthermore, these strategies are generally only applicable to 1º and 2º amine substrates.

Scheme 3.1. Remote C(sp³)–H Functionalization of Protected Aliphatic Amines [9b,11a]

(a) Remote Oxidation with Aromatic Ketones and Hydrogen Peroxide
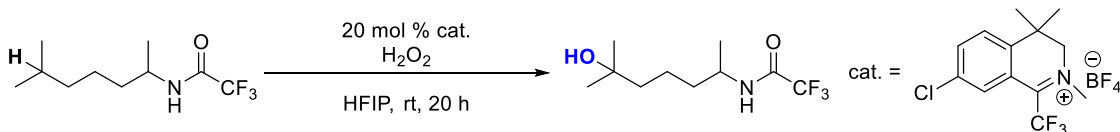
(b) Pd-catalyzed arylation of aliphtic amine scaffolds with picolinamde directing group

proposed intermediate
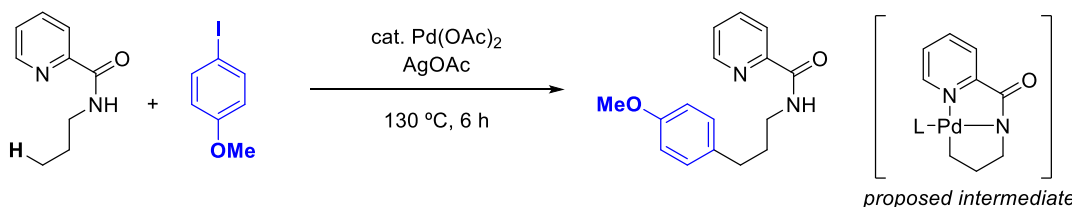
An alternative approach involves the strategy we introduced in Chapter 2 – the *in situ* protonation of unprotected aliphatic amines.[3a,3d,12] Protonation of the nitrogen reversibly converts it into a strong electron-withdrawing group,[13] thereby deactivating the α-C–H bonds.[14] Our lab[3d,12b] and others[3a,12a] have utilized this strategy to achieve several different types of amine C(sp³)–H functionalization reactions. However, the existing methods have some limitations. For example, the earliest reported example of this approach examined a narrow substrate scope and required the use of an impractical oxidant, methyl(trifluoromethyl)dioxirane (TFDO) (**Scheme 3.2**).[12a,15] More recent approaches have utilized transition metal catalysts such as Pd and Fe,[3a,d,12b] which can be expensive and/or difficult to separate from the functionalized amine products. Finally, in most reported examples, the scope is largely restricted to the oxygenation of remote primary (Chapter 2),[12b] tertiary,[3a] or benzylic[3d] C(sp³)–H bonds.

Scheme 3.2. TFDO Mediated Oxidation of Protonated Aliphatic Amines
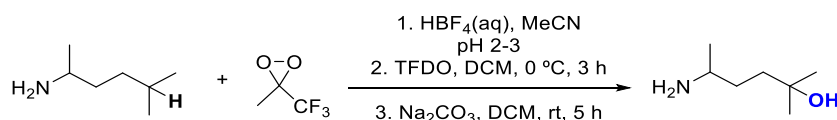
This chapter addresses these limitations via the development of an operationally simple, remote C(sp³)–H hydroxylation of protonated amines that is applicable to a broad range of aliphatic amine substrates. This method uses aqueous solutions of the inexpensive oxidant

$K_2S_2O_8$ to achieve this transformation. The method is effective for the oxygenation of tertiary and benzylic $C(sp^3)$–H bonds as well as secondary $C(sp^3)$–H sites. Additionally, by controlling the amount of oxidant in the reaction, both alcohol and ketone products can be accessed from the latter. We further demonstrate that this method can be applied to the C–H oxidation of unprotected amino acids and to the amine-containing drug memantine (Alzheimer's).

3.2. Results and Discussion

Protonation Strategy and Reaction Optimization

Our initial studies focused on the hydroxylation of the remote, tertiary C–H bond in 4-methyl piperidine (**1**) using commercially available and inexpensive $K_2S_2O_8$ as the oxidant, which has been demonstrated to facilitate C–H functionalization of 2º and 3º C–H bonds (Table 1).[9d,16] Water was selected as the ideal solvent for two main reasons. First, unlike most organic solvents, water lacks C–H bonds that could undergo competitive oxidation. Second, both $K_2S_2O_8$ and most protonated amine substrates are soluble in water, while the free amine is less soluble. As such, these conditions were expected to enable selective oxidation at the remote C–H.[17]

The combination of 1 equiv of **1** and 1.1 equiv of D_2SO_4 at room temperature, followed by the addition of 1 equiv of $K_2S_2O_8$ and heating at 80 ºC for 2 h afforded the 3º alcohol product **2** in 47% yield as determined by ^{1}H NMR spectroscopy. A significant quantity of starting material (25%) remained under these conditions. Increasing the reaction time to 4 h did not lead to further conversion of **1** (entry 2), implying that potassium persulfate is fully consumed within 2 h and additional oxidant is necessary to increase the conversion/yield. Indeed, the use of 2 equiv of $K_2S_2O_8$ in conjunction with 2.2 equiv of D_2SO_4 under otherwise identical conditions resulted in complete consumption of the starting material **1** and the formation of the product **2** in 75% yield (entry 4). Increasing to 3.3 equiv of D_2SO_4 did not lead to further improvement in the yield of **2** (entry 5). Most importantly, the protonation of **1** is crucial for

accessing product **2**. As shown in entry 6, in the absence of added D_2SO_4, <5% of the 3º

hydroxylation product **2** was detected.

Table 3.1. Remote Hydroxylation of Protonated 4-Methylpiperidine with $K_2S_2O_8$
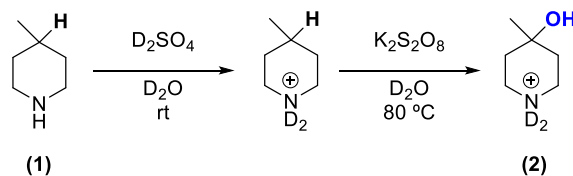
entry	$K_2S_2O_8$ (equiv)	D_2SO_4 (equiv)	time (h)	conv **1** (%)	yield **2** (%)[a]
1	1	1.1	2	75	47
2	1	1.1	4	76	51
3	2	1.1	2	>99	53
4	2	2.2	2	>99	75
5	2	3.3	2	>99	75
6	2	none	2	50	<5

[a]Yields and conversions determined by ^1H NMR spectroscopy

Comparison to Platinum Catalyzed Remote Oxidation

This method represents an inexpensive and operationally simple approach for the

selective C–H hydroxylation of **1**. Furthermore, the observed site selectivity is highly

complementary to that of the method described in Chapter 2 for the Pt-catalyzed oxidation of

protonated amines.[12b] For example, as shown in **Scheme 3.3**, the Pt-catalyzed reaction of **1**

leads to selective functionalization at the least hindered primary $C(sp^3)$–H bond to form the

chlorinated product **3**, while the method described in this chapter affords tertiary $C(sp^3)$–H

hydroxylation with high selectivity. The observed oxidation of the weaker tertiary C–H bond

and the published reactivity of persulfate salts, suggests oxygenation occurs through a radical

pathway.[18]

Scheme 3.3. Complementary Reactivity of Protonated Aliphatic Amines
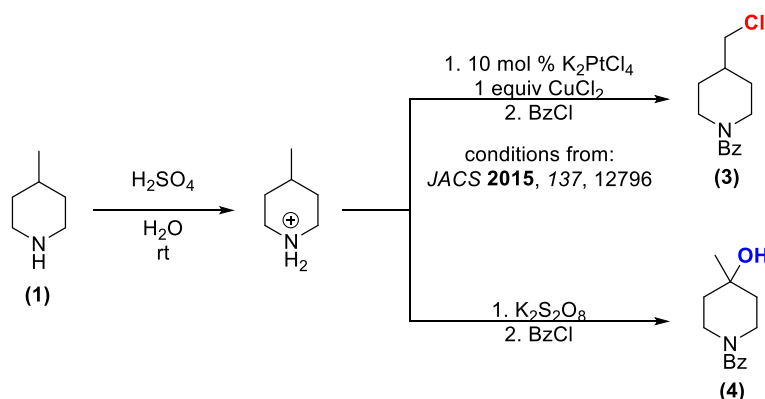
Substrate Scope of Remote Oxidation for Remote Tertiary Oxidation

We next applied this method to the hydroxylation of tertiary C–H bonds in a variety of secondary and primary amine substrates to form products **4-12**. The amino alcohol products derived from primary and secondary amine substrates were subsequently converted to amides to facilitate isolation (**Scheme 3.4**). In all cases, we observed selective hydroxylation at a remote tertiary C–H site. However, the yield and selectivity vary as a function of substrate. In general, the highest yields and selectivities are obtained when the tertiary C–H bond is two or three carbons from the protonated nitrogen (*e.g.*, forming products **4**, **5**, **8–10**). The modest yields of **6** and **7** were due to incomplete conversion of starting material, and conducting the reaction of **6** under more forcing conditions (i.e., at 100 ºC) led to the formation of side products.[19] In systems with longer alkyl chains between the protonated nitrogen and the tertiary C–H site (*e.g.*, **11**, **12**), side products most likely derived from oxidation of secondary C–H bonds were detected by crude ^{1}H NMR spectroscopy. Conducting these reactions at a 65 ºC led to more selective functionalization, albeit in modest isolated yields (**11**, **12**).

Scheme 3.4. C(sp^3)–H Hydroxylation of Secondary and Primary Aliphatic Amines

(4)	**(5)**	**(6)**	**(7)**
64%^{a}	44%^{a}	31%^{a}	32%^{a}

(8)	**(9)**	**(10)**	**(11)**	**(12)**
51%^{a}	60%^{a}	50%^{a}	39%^{b}	32%^{b}
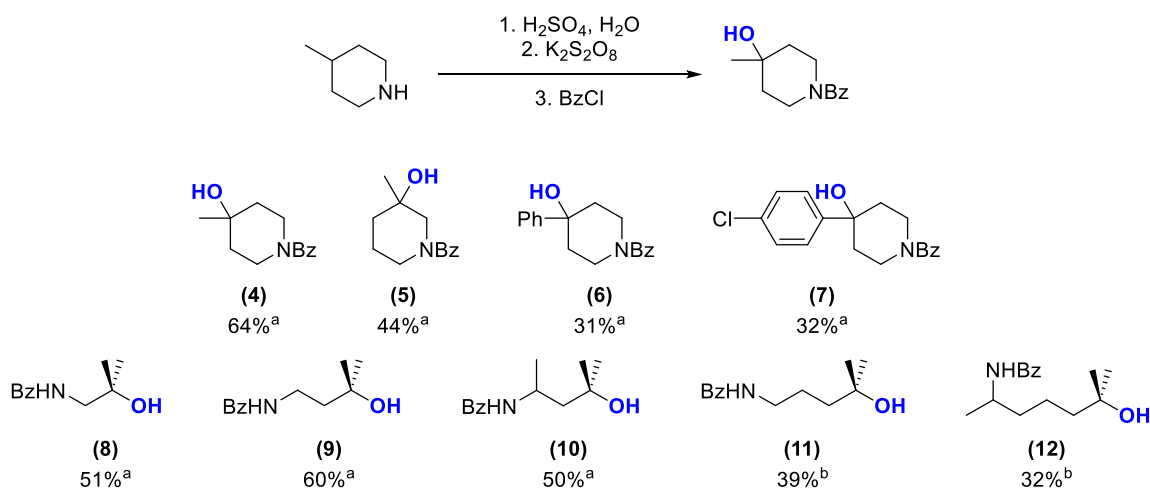
^{a}2.2 equiv H_2SO_4, 2 equiv $K_2S_2O_8$, 80 °C, followed by protection with BzCl. ^{b}1.1 equiv H_2SO_4, 2 equiv $K_2S_2O_8$, 65 °C, followed by protection with BzCl.

These conditions were also applied in the context of cyclic tertiary amine substrates to form products **13–17** (**Scheme 3.5**). Similar to the results in **Scheme 3.4**, good yields and selectivities were obtained when the tertiary C–H bond is three carbons from the protonated nitrogen atom (*e.g.*, forming products **14–16**). In ring systems where the tertiary C–H bond is located two carbons from the protonated nitrogen, lower reactivity is observed, and side products derived ring oxidation become more prominent. Similar side products were problematic in larger ring systems such as **17**. Thus, the reactions were conducted at 65 ºC to minimize ring oxidation. Small quantities of related ring oxidation side products were also observed in **13–16**.

Scheme 3.5. C(sp^3)–H Hydroxylation of Tertiary Aliphatic Amines

(13)	**(14)**	**(15)**	**(16)**	**(17)**
24%^{a}	67%^{a}	51%^{a}	43%^{a}	26%^{b}
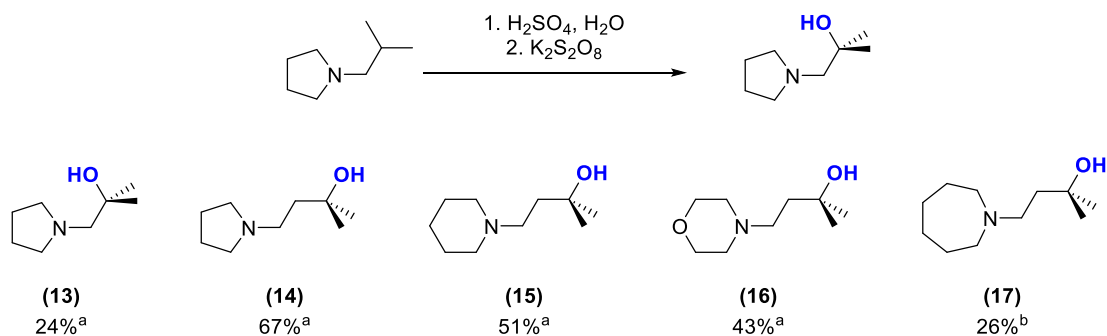
^{a} 2.2 equiv H_2SO_4, 2 equiv $K_2S_2O_8$, 80 °C. ^{b} 1.1 equiv H_2SO_4, 2 equiv $K_2S_2O_8$, 65 °C.

The yields and selectivities in **Scheme 3.3** and **Scheme 3.4** are consistent with protonation of the nitrogen deactivating proximal C–H bonds. As the alkyl chain length increases, a decrease in selectivity is observed due to a decrease in electronic differentiation between the remote C–H bonds. This effect is best demonstrated in a competition study between isobutylamine and isopentylamine, wherein a 1 : 5 ratio of **8-OH** : **9-OH** was observed by ^{1}H NMR spectroscopy, favoring hydroxylation at the more remote 3º C–H bond (**Scheme 3.6**).

Scheme 3.6. Competition between Isobutylamine and Isopentylamine
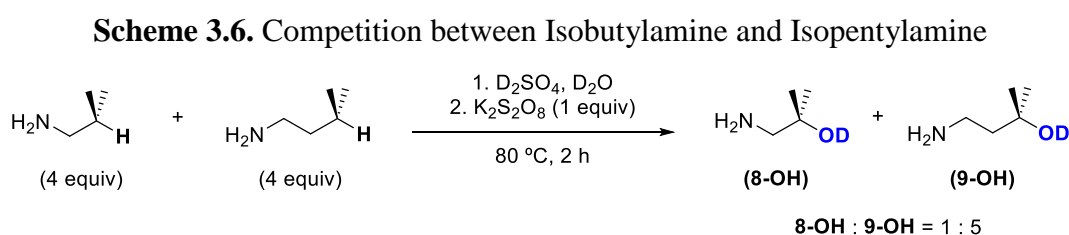
Substrate Scope of Remote Oxidation for Remote Secondary Oxidation

We next probed secondary $C(sp^3)$–H oxidation in the absence of competing tertiary C–H bonds. Initial studies investigated the use of aliphatic amines containing secondary benzylic C–H bonds (**Scheme 3.7**). Under our standard reaction conditions these substrates afforded mixtures of alcohol and ketone products. For example, 4-ethyl benzylamine reacted to form a 0.94 : 1 mixture of alcohol **18-OH** to ketone **18-O** (61% overall yield of C–H oxygenated products). By using 1 equiv of $K_2S_2O_8$ under otherwise identical conditions, the ratio could be shifted to favor the alcohol affording a 1 : 0.48 ratio of **18-OH** : **18-O** (55% yield). The alcohol product was also favored when the benzylic C–H bonds were closer to the protonated amine. This is demonstrated for phenethylamine, which afforded benzylic alcohol **19-OH** as the major product (**19-OH** : **19-O** = 1 : 0.28) under our standard conditions with 2 equiv of $K_2S_2O_8$. Unactivated secondary C–H sites in butylamine also afforded secondary alcohol products. Under the standard conditions with excess amine, butylamine reacted to form a 1 : 0.29 ratio of the γ : β-hydroxylated products (**23-OH-a** : **23-OH-b**) in moderate 32% isolated yield.

Scheme 3.7. Substrate Scope Containing Amines with Remote Secondary $C(sp^3)$–H Bonds
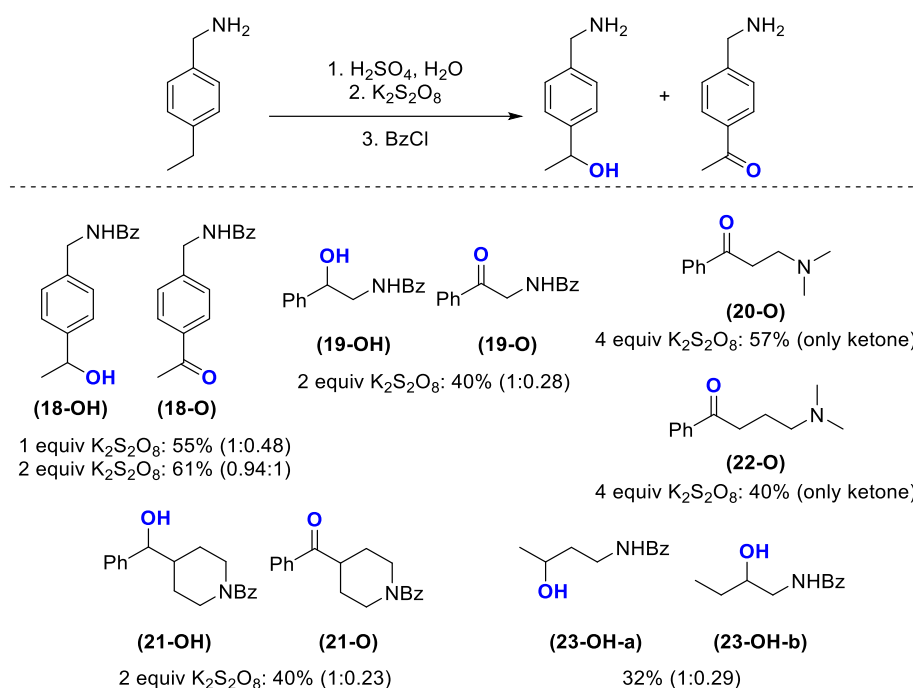
The product selectivity in **Scheme 3.7** shows several differences compared to reported systems for the remote $C(sp^3)$–H oxygenation of protonated amines. For example, the Pt/Cu system described in Chapter 2 affords primary $C(sp^3)$–H hydroxylation products with dibutylamine (analogous to butylamine in **Scheme 3.7**).[12b] The White group's Fe(PDP)/H_2O_2 system provided ketone products selectively, and was only effective for oxygenation of $C(sp^3)$–H bonds that were ≥ 3 carbons from the protonated nitrogen.[3a] Meanwhile, our group's FeCl$_3$/TBHP system only oxidizes benzylic C–H bonds to form ketone products selectively.[3d] Furthermore, no reactivity was observed when the benzylic C–H sites were < 3 carbons from the amine. Overall, these comparisons highlight the complementarity of the method described here to those reported in the literature at the time of our investigations.

Oxidation of Bioactive Molecules

A final set of studies focused on applying this transformation to amine-containing biologically active molecules. As shown in **Scheme 3.8**, under our standard conditions the Alzheimer's drug memantine was converted to the corresponding 3° alcohol **24** in moderate yield. Similarly, the amino acid leucine underwent $C(sp^3)$–H oxygenation to afford lactone **25**

in 47% isolated yield and 90% ee, after protection of the product and isolation. Pregabalin (epilepsy drug) underwent selective oxygenation at the remote, tertiary $C(sp^3)$–H site to afford lactone **26** in 40% yield after protection and isolation.[20]

Scheme 3.8. Substrate Scope Containing Bioactive Amines
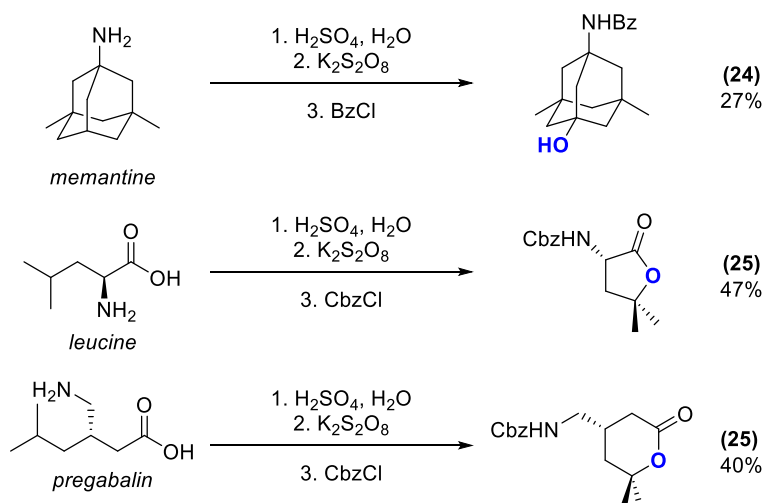
3.3. Conclusion and Outlook

In summary, the work in Chapter 3 demonstrates an operationally straightforward method for the remote $C(sp^3)$–H oxygenation of protonated amines. This method uses an inexpensive and bench stable oxidant (potassium persulfate) and proceeds in water under mild conditions. We demonstrate that this transformation is complementary to several recently reported C–H oxidation reactions of protonated amines and that it is applicable to bioactive substrates, including unprotected amino acids. We anticipate that this method will prove useful in early stage discovery chemistry efforts, for the elaboration of small molecules, and for the late-stage derivatization of amine-containing bioactive targets.

Current work in our laboratory is focused on expanding the breadth $C(sp^3)$–H functionalization, and investigations into the feasibility of accessing C–F and C–N bond forming reactions are underway. Additionally, we are interested in developing and applying complementary C–H functionalization methods in the context of complex, bioactive molecules and scaffolds to rapidly access multiple products.

3.4. Experimental Procedures and Characterization of Compounds

3.4.1 General Procedures and Materials and Methods

General Procedures

NMR spectra were recorded on a Varian vnmrs 700 (700 MHz for ^{1}H; 176 MHz for ^{13}C), Varian vnmrs 500 (500 MHz for ^{1}H; 126 MHz for ^{13}C), or Varian MR400 (400 MHz for ^{1}H; 100 MHz for ^{13}C) with the residual solvent peak (CDCl$_3$; ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm; C$_6$D$_5$CD$_3$; ^{1}H: δ = 2.09 ppm, ^{13}C: δ = 20.40 ppm; CD$_3$OD; ^{1}H: δ = 3.30 ppm, ^{13}C: δ = 49.00 ppm; D$_2$O; ^{1}H: δ = 4.79 ppm) as the internal reference unless otherwise noted. NMR spectra were recorded at room temperature unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), sep (septet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), td (triplet of doublets). Coupling constants (*J*) are reported in Hz. Infrared (IR) spectroscopy was performed on a Perkin-Elmer Spectrum BX Ft-IR spectrometer and peaks are reported in cm^{-1}. Melting points were determined with a OptiMelt (Stanford Research Systems) and are uncorrected. High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Stock solutions were made using volumetric glassware. The enatiomeric excess for compound **23** was determined using chiral HPLC analysis with a Daicel Chiralpak OD-H chiral stationary phase column. Liquid reagents were dispensed by difference from syringes. All reagents were weighed out under ambient conditions.

Materials and Methods

HPLC grade water, ethyl acetate (EtOAc), hexanes (Hex), methanol (MeOH), and dichloromethane (DCM) for column chromatography were purchased from VWR. Basic aluminum oxide (Brockmann 1) for flash column chromatography was purchased from Acros. Biotage® SNAP Ultra column cartridges were used for flash column chromatography. CDCl$_3$, C$_6$D$_5$CD$_3$, CD$_3$OD, and D$_2$O were purchased from Cambridge Isotope Laboratories, Inc. K$_2$S$_2$O$_8$ was purchased from Acros and used without further purification. Amine substrates were purchased from commercial sources (Alfa Aeser, Sigma Aldrich, TCI, Acros, Astatech, Ark Pharm, Enamine, and Matrix Scientific) and used without further purification. Thin layer chromatography (TLC) was performed on Macherey-Nagel SIL G-25 TLC plates pre-coated with silica gel UV$_{254}$ or Merck TLC plates pre-coated with basic aluminum oxide 60 F$_{254}$.

3.4.2 Synthesis and Characterization of Substrates

1-isobutylpyrrolidine:
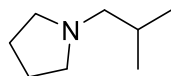
1-isobutylpyrrolidine was synthesized from pyrrolidine and 1-iodo-2-methylpropane using a literature procedure[21] and was purified via distillation.

<u>HRMS:</u> ESI[+] (m/z): [M+H^{+}] calcd for $C_8H_{18}N$: 128.1434; found: 128.1434.

<u>^{1}H NMR</u> (CDCl$_3$, 700 MHz): δ 2.47 (m, 4H), 2.23 (d, *J* = 7.0 Hz, 2H), 1.77 (multiple peaks, 5H), 0.93 (t, *J* = 6.3 Hz, 6H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 65.4, 54.6, 27.7, 23.6, 21.3.

1-isopentylpyrrolidine:
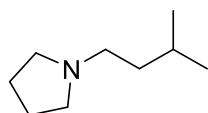
1-isopentylpyrrolidine was synthesized from pyrrolidine and 1-bromo-3-methylbutane using a literature procedure[21] and was purified via distillation.

<u>HRMS:</u> ESI[+] (m/z): [M+H^{+}] calcd for $C_9H_{20}N$: 142.1590; found: 142.1589.

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 2.45 (m, 4H), 2.40 (dd, *J* = 8.0 Hz, 6.0 Hz, 2H), 1.75 (m, 4H), 1.57 (app sep, *J* = 6.5 Hz, 1H), 1.39 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 6H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 55.0, 54.4, 38.3, 26.9, 23.5, 22.9.

1-isopentylpiperidine:
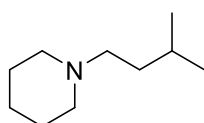
1-isopentylpyrrolidine was synthesized from piperidine and 1-bromo-3-methylbutane using a literature procedure[21] and was purified via distillation.

<u>HRMS:</u> ESI[+] (m/z): [M+H^{+}] calcd for $C_{10}H_{22}N$: 156.1747; found: 156.1754.

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 2.35 (br s, 4H), 2.28 (dd, *J* = 7.5 Hz, 5.0 Hz, 2H), 1.57 (quin, *J* = 5.5 Hz, 4H), 1.54 (app sep, *J* = 6.5 Hz, 1H), 1.40 (multiple peaks, 4H), 0.88 (d, *J* = 6.5 Hz, 6H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 58.1, 54.9, 36.2, 27.1, 26.2, 24.7, 22.9.

4-isopentylmorpholine:
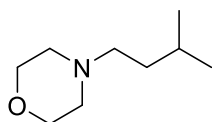
1-isopentylmorpholine was synthesized from morpholine and 1-bromo-3-methylbutane using a literature procedure[21] and was purified via distillation.

<u>HRMS</u>: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_9H_{20}NO$: 158.1539; found: 158.1539.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 3.72 (br s, 4H), 2.44 (br s, 4H), 2.34 (t, J = 7.0 Hz, 2H), 1.58 (overlapping with water peak, 1H), 1.38 (q, J = 7.0 Hz, 2H), 0.90 (d, J = 3.2 Hz, 6H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 67.2, 57.6, 54.0, 35.7, 26.8, 22.9.

1-isopentylazepane:
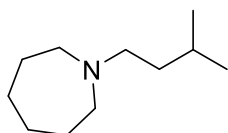
1-isopentylazepane was synthesized from azepane and 1-bromo-3-methylbutane using a literature procedure[21] and was purified via distillation.

<u>HRMS</u>: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{11}H_{24}N$: 170.1903; found: 170.1901.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 2.61 (dd, J = 5.0 Hz, 4.0 Hz, 4H), 2.46 (dd, J = 7.5 Hz, 5.5 Hz, 2H), 1.61 (multiple peaks, 8H), 1.55 (app sep, J = 7.0 Hz, 1H), 1.35 (m, 2H), 0.89 (d, J = 7.0 Hz, 6H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 56.81, 55.8, 36.7, 28.2, 27.1, 26.9, 23.0.

3.4.3 General Procedures for Reaction Optimization and Crude ^{1}H NMR Analysis

General Procedure A:

To a 4 mL scintillation vial containing $K_2S_2O_8$, D_2SO_4 (1.1 M aqueous solution), and D_2O (combined volume 1 mL) was added 4-methylpiperidine (1.0 equiv, 0.25 mmol, 24.8 mg). The reaction vial was equipped with a micro stir bar, sealed with a Teflon-lined cap, and placed in an aluminum block preheated to 80 ºC and stirred for 2 h at 80 ºC. To the crude reaction, nitromethane (10 μL, 0.186 mmol) was added and the crude yield was determined via ^{1}H NMR spectroscopic analysis.

3.4.4 General Procedures for Isolation of Products and Characterization

General Procedure B:

To a 4 mL (0.25 mmol substrate) or 20 mL (0.75 mmol substrate) scintillation vial containing $K_2S_2O_8$, H_2SO_4 (aqueous) and H_2O was added the amine substrate. The reaction vial was equipped with a micro magnetic stir bar, sealed with a Teflon-lined cap, placed in an aluminum block preheated to 65 or 80 ℃, and stirred for 2–4 h at 65 or 80 ℃.

General Procedure C:

The crude reaction mixture was quenched with Na_2SO_3 and was then stirred at room temperature until a peroxide test strip was negative. The aqueous solution was acidified with concentrated H_2SO_4 to pH ~2 before the water was removed as an azeotrope with toluene via rotary evaporation at ~65 ℃. To the resulting solid was added Na_2CO_3 (159 mg for 0.25 mmol reactions and 954 mg for 1.5 mmol reactions), and then the product was purified via chromatography on basic alumina.

General Procedure D:

The crude reaction mixture was quenched with Na_2SO_3 and was then stirred at room temperature until a peroxide test strip was negative. The aqueous solution was acidified with concentrated H_2SO_4 to a pH ~2 before the water was removed as an azeotrope with toluene via rotary evaporation at 65–70 ℃. To the resulting solid was added MeCN, triethylamine, and benzoyl chloride. The mixture was allowed to stir at room temperature for 1–12 h. The acetonitrile was removed by rotary evaporation, the product was dissolved in dichloromethane (150 mL), and the organic layer was washed with NaOH (1M, 1x100 mL). The aqueous layer was extracted a second time with dichloromethane (150 mL). The organic extracts were combined, washed with brine (100 mL), and dried over sodium sulfate. The volatiles were removed via rotary evaporation and purified via flash column chromatography on silica.

General Procedure E:

The crude reaction mixture was quenched with Na_2SO_3 and was then stirred at room temperature until a peroxide test strip was negative. To the crude reaction was added THF (20 mL), NaOH (6.0 mL of a 2 M aqueous solution), and CbzCl (0.32 mL) at 0 ℃.[4] The reaction was allowed to warm to room temperature and was then stirred at room temperature for 36 h. The aqueous layer was extracted with diethyl ether and the organic layer was set aside. The

aqueous layer was acidified with 1 M HCl to a pH ~2 and extracted with ethyl acetate (3x150 mL). The organic extracts were combined and dried over sodium sulfate after which the volatiles were removed via rotary evaporation and the product was purified via flash column chromatography on basic alumina.

(4-(chloromethyl)piperidin-1-yl)(phenyl)methanone (3):
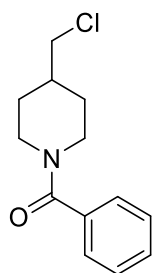
3

To a solution of $CuCl_2 \cdot 2H_2O$ (0.10 mmol, 17 mg, 1 equiv) and K_2PtCl_4 (0.005 mmol, 2.1 mg, 10 mol %) in aqueous H_2SO_4 (0.55 mmol, 0.25 mL 11 equiv, 2.2 M stock solution) was added 4-methylpiperidine (0.50 mmol, 50 mg, 10 equiv) in a 10 mL scintillation vial. The reaction was stirred at 150 ºC for 12 h. The reaction was performed side-by-side in duplicate. The two duplicate runs were combined and the product was protected via a reported procedure.[12b] The product was then purified by flash column chromatography on silica (gradient of 12% to 100%, EtOAc in hexanes) and isolated as a colorless oil.

Isolated Yield: 84% (20.0 mg)

R$_f$: 0.42 (1:1 EtOAc : Hex)

IR (v, cm^{-1}): 2940, 2856, 1716, 1624, 1576, 1432, 1322, 1279, 1108, 966, 786, 708.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{13}H_{17}ClNO$: 238.0993; found: 238.0990.

^{1}H NMR ($C_6D_5CD_3$, 700 MHz, 90 ºC): δ 7.27 (m, 2H), 7.08 (multiple peaks, 3H), 4.03 (br s, 2H), 2.91 (m, 2H), 2.41 (t, $J = 12.6$ Hz, 2H), 1.31 (multiple peaks, 3H), 0.87 (m, 2H).

^{13}C NMR ($C_6D_5CD_3$, 176 MHz, 90 ºC): δ 169.8, 129.4, 128.4, 127.6, 49.2, 44.7, 39.2, 30.3 (1 aromatic peak overlaps with $C_6D_5CD_3$).

^{13}C NMR (CDCl$_3$, 176 MHz, room temperature): δ 170.5, 136.4, 128.6, 127.0, 49.4, 47.6, 42.0, 38.9, 30.6, 29.7. Rotamers present at room temperature

(4-hydroxy-4-methylpiperidin-1-yl)(phenyl)methanone (4):

4
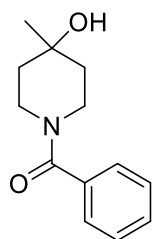
General procedure B was followed using 4-methylpiperidine (1.50 mmol, 149 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure D**, using MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a light yellow solid.

Isolated Yield: 64% (208.9 mg)

R_f: 0.65 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3382, 2926, 1607, 1443, 1373, 1256, 1178, 1117, 969, 708.

mp: 91–93 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{13}H_{18}NO_2$: 220.1332; found: 220.1330.

^{1}H NMR ($C_6D_5CD_3$, 700 MHz, 90 ºC): δ 7.29 (m, 2H), 7.07 (multiple peaks, 3H), 3.71 (br s, 2H), 3.19 (m, 2H), 1.23 (m, 2H), 1.17 (m, 2H), 0.89 (s, 3H), 0.78 (br s, 1H).

^{13}C NMR ($C_6D_5CD_3$, 176 MHz, 90 ºC): δ 169.9, 137.9, 129.3, 128.4, 127.6, 67.6, 41.7, 39.3, 30.1.

^{13}C NMR (CDCl$_3$, 176 MHz, room temperature): δ 170.5, 136.4, 129.6, 127.0, 68.3, 44.2, 39.3, 38.5, 30.5. Rotamers present at room temperature

(3-hydroxy-3-methylpiperidin-1-yl)(phenyl)methanone (5):

5
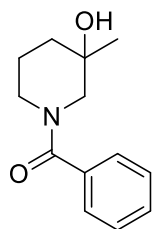
General procedure B was followed using 3-methylpiperidine (1.50 mmol, 149 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ℃ for 4 h. The product was protected via **general procedure D** with MeCN (100 mL), ethyldiisopropylamine (3.37 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a light brown oil.

Isolated Yield: 44% (143.5 mg)

R$_f$: 0.66 (1:9 MeOH : dichloromethane)

IR (ν, cm^{-1}): 3393, 2928, 1608, 1439, 1280, 1131, 930, 788, 700.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{13}H_{18}O_2$: 220.1332; found: 220.1329.

^{1}H NMR ($C_6D_5CD_3$, 700 MHz, 80 ℃): δ 7.38 (m, 2H), 7.09 (m, 3H), 3.73 (br s, 1H), 3.63 (br s, 1H), 2.79 (m, 2H), 2.54 (br s, 1H), 1.67 (m, 1H), 1.49 (m, 1H), 1.18 (m, 1H), 1.13 (m, 1H), 0.98 (s, 3H).

^{13}C NMR ($C_6D_5CD_3$, 176 MHz, 80 ℃): δ 171.2, 137.5, 129.4, 128.4, 127.9 (overlaps with peak from $C_6D_5CD_3$), 69.1, 55.8, 45.8, 38.0, 27.2, 22.4.

(4-hydroxy-4-phenylpiperidin-1-yl)(phenyl)methanone (6):
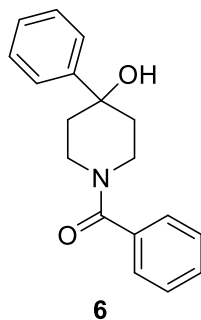
General procedure B was followed using 4-phenlylpiperidine (0.25 mmol, 40 mg, 1 equiv), $K_2S_2O_8$ (0.50 mmol, 135 mg, 2 equiv), aqueous H_2SO_4 (0.55 mmol, 2.2 equiv, 0.5 mL of a 1.1 M stock solution), and water (0.5 mL). The reaction was stirred at 80 ℃ for 2 h. The product was protected via **general procedure D** with MeCN (10 mL), triethylamine (348 μL, 2.5 mmol), and benzoyl chloride (89 μL, 0.75 mmol). The product was then purified by flash column chromatography on silica (gradient of 12% to 100%, EtOAc in hexanes) and isolated as a light yellow oil.

Isolated Yield: 31% (21.9 mg)

R$_f$: 0.27 (1:1 EtOAc : hexanes)

IR (v, cm⁻¹): 3363, 3059, 2923, 1598, 1444, 1283, 1254, 1111, 1004, 697.

HRMS: ESI⁺ (m/z): [M+H⁺] calcd for $C_{18}H_{20}NO_2$: 282.1489; found: 282.1488.

¹H NMR ($C_6D_5CD_3$, 700 MHz, 100 °C): δ 7.32 (m, 2H), 7.21 (m, 2H), 7.13 (m, 2H), 7.07 (multiple peaks, 4H), 4.02 (br s, 2H), 3.22 (t, J = 12.6 Hz, 2H), 1.74 (m, 2H), 1.39 (d, J = 12.6 Hz, 2H), 1.31 (br s, 1H).

¹³C NMR ($C_6D_5CD_3$, 176 MHz, 100 °C): δ 170.0, 148.2, (some aromatic peaks overlap with $C_6D_5CD_3$), 71.6, 41.4, 39.0.

¹³C NMR (CD_3OD, 176 MHz, room temperature): δ 172.5, 149.5, 137.2, 131.0, 129.7, 129.3, 127.9, 127.8, 125.7, 72.0, 45.4, 39.7, 38.8. Rotamers present at room temperature

(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)(phenyl)methanone (7):
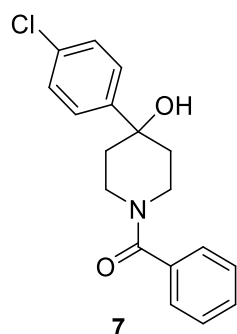
General procedure B was followed using 4-(4-chlorophenyl)piperidine (0.25 mmol, 49 mg, 1 equiv), $K_2S_2O_8$ (0.50 mmol, 135 mg, 2 equiv), aqueous H_2SO_4 (0.55 mmol, 2.2 equiv, 0.5 mL of a 1.1 M stock solution), and water (0.5 mL). The reaction was stirred at 80 °C for 2 h. The product was protected via **general procedure D** with MeCN (10 mL), triethylamine (348 μL, 2.5 mmol), and benzoyl chloride (89 μL, 0.75 mmol). The product was then purified by flash column chromatography on silica (gradient of 12% to 100%, EtOAc in hexanes) and isolated as an off-white solid.

Isolated Yield: 32% (25.2 mg)

R_f: 0.24 (1:1 EtOAc : hexanes)

IR (v, cm⁻¹): 3370, 2924, 1600, 1444, 1281, 1094, 1002, 826, 709.

mp: 154–156 °C

HRMS: ESI⁺ (m/z): [M+H⁺] calcd for $C_{18}H_{19}ClNO_2$: 316.1099; found: 316.1097.

¹H NMR ($C_6D_5CD_3$, 700 MHz, 100 °C): δ 7.32 (m, 2H), 7.10 (m, 4H), 7.06 (br s, 1H), 7.00 (m, 2H), 3.99 (br s, 2H), 3.14 (t, J = 12.6 Hz, 2H), 1.63 (t, J = 12.6 Hz, 2H), 1.28 (d, J = 12.6 Hz, 2H), 1.16 (s, 1H).

^{13}C NMR ($\text{C}_6\text{D}_5\text{CD}_3$, 176 MHz, 100 ºC): δ 170.1, 147.2, 133.6, 129.6, 128.5, 126.5 (some aromatic peaks overlap with $\text{C}_6\text{D}_5\text{CD}_3$), 71.4, 41.3, 38.8.

^{13}C NMR (CD_3OD, 176 MHz, room temperature): δ 172.5, 148.5, 137.2, 133.7, 131.0, 129.3, 127.6, 71.8, 45.3, 39.6, 39.6, 38.6. Rotamers present at room temperature

N-(2-hydroxy-2-methylpropyl)benzamide (8):

8
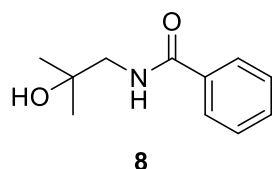
General procedure B was followed using isobutylamine (1.50 mmol, 110 mg, 1 equiv), $\text{K}_2\text{S}_2\text{O}_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a white solid.

Isolated Yield: 51% (147.8 mg)

R_f: 0.40 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3326, 2974, 1636, 1540, 1489, 1385, 1306, 1177, 925, 709.

mp: 101–103 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $\text{C}_{11}\text{H}_{16}\text{NO}_2$: 194.1176; found: 194.1170.

^1H NMR (CDCl$_3$, 401 MHz): δ 7.79 (d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.2, 2H), 6.69 (br s, 1H), 3.47 (d, J = 6.0 Hz, 2H), 2.56 (s, 1H), 1.28 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 168.6, 134.5, 131.7, 128.7, 127.1, 71.2, 50.8, 27.6.

N-(3-hydroxy-3-methylbutyl)benzamide (9):

9
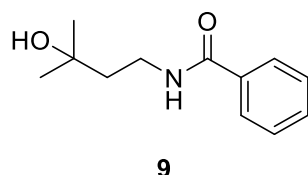
General procedure B was followed using isoamylamine (1.50 mmol, 131 mg, 1 equiv), $\text{K}_2\text{S}_2\text{O}_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product

was protected via **general procedure D** with MeCN (100 mL), ethyldiisopropylamine (3.37 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a light yellow solid.

Isolated Yield: 60% (187.8 mg)

R$_f$: 0.62 (1:9 MeOH : dichloromethane)

IR (ν, cm^{-1}): 3258, 2969, 1631, 1540, 1492, 1378, 1312, 1159, 912, 688.

mp: 101–102 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{12}H_{18}NO_2$: 208.1332; found: 208.1329.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.76 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 7.31 (br s, 1H), 3.62 (q, J = 5.6 Hz, 2H), 1.98 (br s, 1H), 1.79 (t, J = 5.6 Hz, 2H), 1.32 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 167.4, 134.8, 131.4, 128.6, 127.0, 71.8, 41.0, 36.7, 30.0.

N-(4-hydroxy-4-methylpentan-2-yl)benzamide (10):

10
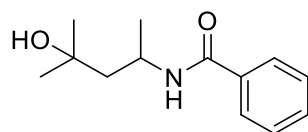
General procedure B was followed using 4-methylpentan-2-amine (1.50 mmol, 152 mg, 1 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H$_2$SO$_4$ (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a light brown oil.

Isolated Yield: 50% (166.0 mg)

R$_f$: 0.62 (1:9 MeOH : dichloromethane)

IR (ν, cm^{-1}): 3322, 2970,1635, 1539, 1489, 1354, 1311, 1169, 908, 729.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{13}H_{20}NO_2$: 222.1489; found: 222.1488.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.76 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.23 (br s, 1H), 4.23 (m, 1H), 3.06 (br s, 1H), 1.76 (dd, J = 15.0, 10.0 Hz, 1H), 1.65 (dd, J = 15.0, 4.0 Hz, 1H), 1.29 (d, J = 6.5 Hz, 3H), 1.25 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 167.4, 134.8, 131.4, 128.5, 127.0, 70.8, 48.9, 44.0, 31.7, 28.4, 22.5.

N-(4-hydroxy-4-methylpentyl)benzamide (11):

11
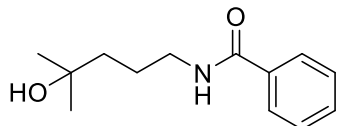
General procedure B was followed using 3-methylbutan-1-amine (0.25 mmol, 25 mg, 1 equiv), K$_2$S$_2$O$_8$ (0.50 mmol, 135 mg, 2 equiv), aqueous H$_2$SO$_4$ (0.28 mmol, 1.1 equiv, 0.25 mL of a 1.1 M stock solution), and water (0.75 mL). The reaction was stirred at 65 ºC for 2 h. The product was protected via **general procedure D** with MeCN (10 mL), triethylamine (348 µL, 2.5 mmol), and benzoyl chloride (89 µL, 0.75 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane) and isolated as a white solid.

Isolated Yield: 39% (21.8 mg)

R$_f$: 0.46 (1:9 MeOH : dichloromethane)

IR (ν, cm^{-1}): 3326, 2968, 1636, 1540, 1374, 1308, 1157, 1075, 905, 694.

mp: 84–87 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{13}$H$_{20}$NO$_2$: 222.1489; found: 222.1485.

^1H NMR (CDCl$_3$, 401 MHz): δ 7.76 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 6.62 (br s, 1H), 3.47 (q, J = 7.0 Hz, 2H), 1.88 (br s, 1H), 1.72 (quin, J = 7.0 Hz, 2H), 1.55 (m, 2H), 1.23 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 167.7, 134.9, 131.5, 128.7, 127.0, 71.0, 40.7, 40.5, 29.7, 24.7.

N-(6-hydroxy-6-methylheptan-2-yl)benzamide (12):

12
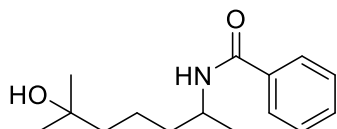
General procedure B was followed using 2-amino-6-methylheptane (1.50 mmol, 194 mg, 1 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H$_2$SO$_4$ (1.65 mmol, 1.1 equiv, 1.5 mL of a 1.1 M stock solution), and water (4.5 mL). The reaction was stirred at 65 ºC for 4 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09

mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 10% to 100%, EtOAc in hexanes) and isolated as a light yellow solid.

Isolated Yield: 32% (119.2 mg)

R_f: 0.50 (1: 9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3326, 2968, 2936, 1635, 1540, 1490, 1457, 1351, 1300, 1166, 934, 801, 695.

mp: 101–103 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{15}H_{24}NO_2$: 250.1802; found: 250.1799.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.74 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 5.97 (d, J = 7.0 Hz, 1H), 4.23 (app sep, J = 7.0 Hz, 1H), 1.66 (br s, 1H), 1.54 (multiple peaks, 3H), 1.46 (multiple peaks, 3H), 1.24 (d, J = 7.0 Hz, 3H), 1.20 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 167.1, 135.1, 131.4, 128.7, 127.0, 70.9, 45.6, 43.5, 37.6, 29.7, 29.2, 21.3, 20.8.

2-methyl-1-(pyrrolidin-1-yl)propan-2-ol (13):

13
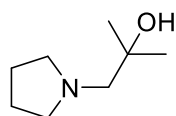
General procedure B was followed using 1-isobutylpyrrolidine (0.25 mmol, 32 mg, 1 equiv), K$_2$S$_2$O$_8$ (0.50 mmol, 135 mg, 2 equiv), aqueous H$_2$SO$_4$ (0.55 mmol, 2.2 equiv, 0.5 mL of a 1.1 M stock solution), and water (0.5 mL). The reaction was stirred at 80 ºC for 2 h. The reaction was quenched following **general procedure C** and the product was purified by column chromatography on basic alumina (gradient of 1% to 10%, MeOH in dichloromethane) and isolated as a colorless oil.

Isolated Yield: 24% (8.5 mg)

R_f: 0.83 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3392, 2966, 2807, 1658, 1460, 1293, 1382, 1137, 909.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_8H_{18}NO$: 144.1383; found: 144.1381.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 2.69 (m, 4H), 2.48 (s, 2H), 1.76 (s, 4H), 1.18 (s, 6H). OH peak not observed

^{13}C NMR (CDCl$_3$, 176 MHz): δ 69.4, 67.3, 56.8, 28.5, 24.3.

2-methyl-4-(pyrrolidin-1-yl)butan-2-ol (14):

14
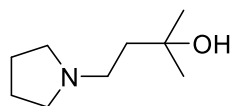
General procedure B was followed using 1-isopentylpyrrolidine (1.50 mmol, 212 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The reaction was quenched following **general procedure C**, and the product was purified by column chromatography on basic alumina (gradient of 1% to 10%, MeOH in dichloromethane) and isolated as a light yellow oil.

Isolated Yield: 67% (158.2 mg)

R_f: 0.80 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3360, 2967, 2925, 2803, 1700, 1652, 1558, 1457, 1376, 1203, 1162.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_9H_{20}NO$: 158.1539; found: 158.1538.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.26 (br s, 1H), 2.75 (m, 2H), 2.55 (br s, 4H), 1.74 (br s, 4H), 1.60 (m, 2H), 1.21 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 71.1, 54.1, 52.7, 38.8, 29.8, 23.5.

2-methyl-4-(piperidin-1-yl)butan-2-ol (15):

15
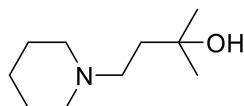
General procedure B was followed using 1-isopentylpiperidine (1.50 mmol, 233 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The reaction was quenched following **general procedure C** and the product was purified by column chromatography on basic alumina (gradient of 1% to 10%, MeOH in dichloromethane) and isolated as a light yellow oil.

Isolated Yield: 51% (132.2 mg)

R_f: 0.89 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3371, 2931, 2803, 1717, 1652, 1456, 1374, 1156, 1113, 890, 758.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{10}H_{22}NO$: 172.1696; found: 172.1695.

^{1}H NMR (D$_2$O/D$_2$SO$_4$, 700 MHz): δ 3.30 (d, J = 12.6 Hz, 2H), 2.95 (m, 2H), 2.69 (td, J = 12.6, 2.1 Hz, 2H), 1.69 (m, 4H), 1.57 (d, J = 12.6 Hz, 1H), 1.46 (qt, J = 12.6, 3.5 Hz, 2H), 1.23 (qt, J = 12.6, 3.5 Hz, 1H), 1.01 (s, 6H). OH peak not observed

^{13}C NMR (D$_2$O/D$_2$SO$_4$, 176 MHz, not referenced): δ 69.8, 53.2, 53.1, 35.9, 27.6, 22.7, 21.0.

2-methyl-4-(piperidin-1-yl)butan-2-ol (16):

16
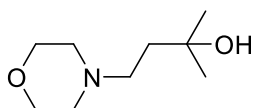
General procedure B was followed using 1-isopentylpiperidine (1.50 mmol, 236 mg, 1 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H$_2$SO$_4$ (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The reaction was quenched following **general procedure C** and the product was purified by column chromatography on basic alumina (gradient of 1% to 10%, MeOH in dichloromethane) and isolated as a light yellow oil.

Isolated Yield: 43% (111.6 mg)

R$_f$: 0.78 (1:9 MeOH : dichloromethane)

IR (v, cm^{-1}): 3377, 2965, 2852, 1654, 1458, 1362, 1164, 1114, 1008, 866.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_9$H$_{20}$NO$_2$: 174.1489; found: 174.1489.

^{1}H NMR: (CDCl$_3$, 500 MHz): δ 5.90 (br s, 1H), 3.69 (t, J = 4.5 Hz, 4H), 2.63 (dd, J = 6.0, 4.5 Hz, 2H), 2.52 (br s, 4H), 1.62 (dd, J = 6.0, 4.5 Hz, 2H), 1.22 (s, 6H).

^{13}C NMR: (CDCl$_3$, 126 MHz): δ 71.1, 67.1, 55.5, 53.7, 36.5, 29.7.

4-(azepan-1-yl)-2-methylbutan-2-ol (17):

17
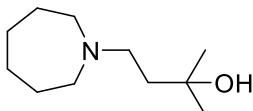
General procedure B was followed using 1-isopentylazepane (1.50, 254 mg, 1 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H$_2$SO$_4$ (1.65 mmol, 1.1 equiv, 1.5 mL of a 1.1 M stock solution), and water (4.5 mL). The reaction was stirred at 65 ºC for 4 h. The reaction was quenched following **general procedure C** and the product was purified by column chromatography on basic alumina (gradient of 1% to 10% MeOH in dichloromethane) and isolated as a light yellow oil.

Isolated Yield: 26% (72.4 mg)

R_f: 0.52 (1:4 EtOAc : hexanes)

IR (v, cm^{-1}): 3383, 2924, 2851, 1456, 1361, 1266, 1185, 1156, 1083, 943, 884.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{11}H_{24}NO$: 186.1852; found: 186.1852.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 6.86 (br s, 1H), 2.70 (dd, J = 6.0, 4.8 Hz, 2H), 2.62 (dd, J = 5.2, 3.6 Hz, 4H), 1.63 (m, 4H), 1.54 (multiple peaks, 6H), 1.19 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 71.0, 56.2, 55.8, 37.6, 30.0, 28.2, 26.8.

N-(4-(1-hydroxyethyl)benzyl)benzamide (18-OH and 18-O):
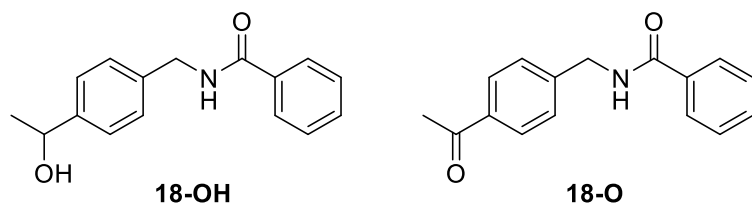
General procedure B was followed using (4-ethylphenyl)methanamine (0.25 mmol, 34 mg, 1 equiv), $K_2S_2O_8$ (0.25 or 0.50 mmol, 68 or 135 mg, 1 or 2 equiv), aqueous H_2SO_4 (0.28 mmol, 1.1 equiv, 0.25 mL of a 1.1 M stock solution), and water (0.75 mL). The reaction was stirred at 80 ºC for 2 h. The products were protected via **general procedure D** with MeCN (10 mL), triethylamine (348 µL, 2.5 mmol), and benzoyl chloride (89 µL, 0.75 mmol). The products were then then purified by flash column chromatography on silica (gradient of 10% to 100%, EtOAc in hexanes). Compound **18-OH** was isolated as a light yellow viscous oil and compound **18-O** was isolated as a white solid. For the purposes of obtaining an accurate isolated yield and ratio, products **18-OH** and **18-O** were isolated as a mixture and the isolated ratio was determined by ^{1}H NMR spectroscopy. For the purposes of characterizing each compound, fractions that only contained **18-OH** or **18-O** were collected and analyzed.

Isolated Yield: 1 equiv $K_2S_2O_8$: 55% (34.8 mg, **18-OH : 18-O** = 1:0.48; crude ratio = 1:0.42)

  2 equiv $K_2S_2O_8$: 61% (38.6 mg, **18-OH : 18-O** = 0.93:1; crude ratio = 0.94:1)

18-OH R_f: 0.55 (1:1 EtOAc:hexanes)

18-O R_f: 0.63 (1:1 EtOAc:hexanes)

18-OH IR (v, cm^{-1}): 3316, 2692, 1635, 1539, 1292, 1073, 801, 693.

18-O IR (v, cm^{-1}): 3312, 1670, 1636, 1532, 1269, 792, 693.

18-O mp: 106–108 ºC

18-OH HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{16}H_{18}NO_2$: 256.1332; found: 256.1335

18-O HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{16}H_{16}NO_2$: 254.1176; found: 254.1175

18-OH [sup]1[/sup]H NMR (CDCl$_3$, 700 MHz): δ 7.78 (d, J = 7.7 Hz, 2H), 7.50 (t, J = 7.7 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.36 (d, J = 7.0 Hz, 2H), 7.34 (d, J = 7.0 Hz, 2H), 6.42 (br s, 1H), 4.90 (q, J = 7.0 Hz, 1H), 4.63 (d, J = 5.6 Hz, 2H), 1.84 (br s, 1H), 1.49 (d, J = 7.0 Hz, 3H).

18-OH [sup]13[/sup]C NMR (CDCl$_3$, 176 MHz): δ 167.5, 145.5, 137.5, 134.5, 131.7, 128.8, 128.4, 127.1, 126.0, 70.2, 44.0, 25.4.

18-O [sup]1[/sup]H NMR (CDCl$_3$, 700 MHz): δ 7.93 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.52 (t, J = 8.4 Hz, 1H), 7.45 (multiple peaks, 4H), 6.55 (br s, 1H), 4.71 (d, J = 5.6 Hz, 2H), 2.59 (s, 3H).

18-O [sup]13[/sup]C NMR (CDCl$_3$, 176 MHz): δ 197.8, 167.6, 143.8, 136.6, 134.2, 131.9, 129.0, 128.8, 127.9, 127.1, 43.8, 26.8.

N-(2-hydroxy-2-phenylethyl)benzamide (19-OH and 19-O):
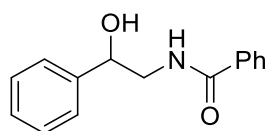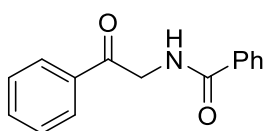
19-OH   **19-O**

General procedure B was followed using 2-phenylethan-1-amine (1.50 mmol, 182 mg, 1 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H$_2$SO$_4$ (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The products were then purified by flash column chromatography on silica (gradient 10% to 100% EtOAc/hexanes). Compound **19-OH** was isolated as a white solid, and compound **19-O** was isolated as a light yellow solid.

Isolated Yield: 2 equiv K$_2$S$_2$O$_8$: 40% total yield (**19-OH** + **19-O**) (116.8 mg **19-OH**; 32.6 mg **19-O**; Ratio of **19-OH : 19-O** (isolated) = 1:0.28; Ratio of **C-OH:C=O** (crude) = 1:0.18)

19-OH R$_f$: 0.39 (1:1 EtOAc:hexanes)

19-O R$_f$: 0.58 (1:1 EtOAc:hexanes)

19-OH IR (ν, cm^{-1}) 3402, 3298, 1617, 1541, 1315, 1230, 1062, 923, 817, 692.

19-O IR (ν, cm^{-1}) 3356, 1691, 1634, 1520, 1484, 1442, 1362, 1222, 999, 756, 686.

19-OH mp: 144–146 ºC

19-O mp: 117–119 ºC

19-OH HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{15}$H$_{16}$NO$_2$: 242.1176; found: 242.1176.

19-O HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{15}$H$_{14}$NO$_2$: 240.1019; found: 240.1017.

19-OH ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.76 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.43 (multiple peaks, 4H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 6.59 (br s, 1H), 4.97 (dd, J = 7.5, 3.5 Hz, 1H), 3.93 (ddd, J = 14.0, 7.0, 3.5 Hz, 1H), 3.54 (ddd, J = 14.0, 7.5, 4.5 Hz, 1H). OH peak not observed

19-OH ^{13}C NMR (CDCl$_3$, 126 MHz): δ 168.8, 141.9, 134.2, 131.9, 128.8, 128.8, 128.1, 127.1, 126.0, 74.0, 48.0.

19-O ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.04 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.53 (multiple peaks, 3H), 7.47 (t, J = 7.5 Hz, 2H), 7.31 (br s, 1H), 4.97 (d, J = 4.0 Hz, 2H).

19-O ^{13}C NMR (CDCl$_3$, 126 MHz): δ 194.4, 167.5, 134.5, 134.4, 134.1, 131.9. 129.1, 128.8, 128.1, 127.3, 47.0.

3-(dimethylamino)-1-phenylpropan-1-one (20-O):
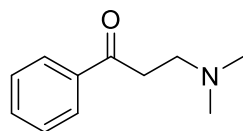
20-O

General procedure B was followed using N,N-dimethyl-3-phenylpropan-1-amine (0.25 mmol, 41 mg, 1 equiv), K$_2$S$_2$O$_8$ (1.00 mmol, 270 mg, 4 equiv), aqueous H$_2$SO$_4$ (0.28 mmol, 1.1 equiv, 0.25 mL of a 1.1 M stock solution), and water (0.75 mL). The reaction was stirred at 80 ºC for 2 h. The reaction was quenched following **general procedure C**, evaporated to dryness, and purified by column chromatography on basic alumina (0.5–5% MeOH/DCM). The product was isolated as a light yellow oil. The ^{1}H and ^{13}C NMR spectra matched literature values.[4]

Isolated Yield: 57% (25.1 mg)

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{11}$H$_{16}$NO: 178.1226; found: 178.1225.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.97 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 3.17 (t, J = 7.0 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.30 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 199.2, 137.0, 133.2, 128.8, 128.2, 54.5, 45.6, 37.0.

(4-(hydroxy(phenyl)methyl)piperidin-1-yl)(phenyl)methanone (21-OH and 21-O):

21-OH   **21-O**
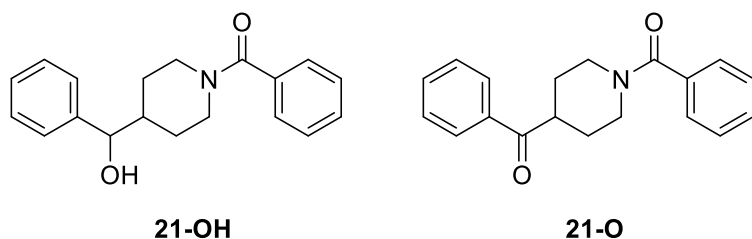
General procedure B was followed using (4-ethylphenyl)methanamine (1.50 mmol, 263 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 1 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The reaction was quenched with sodium sulfite, evaporated to dryness, and protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 µL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 10% to 100%, EtOAc in hexanes). Compound **21-OH** was isolated as a light yellow, viscous oil, and compound **21-O** was isolated as a light yellow solid.

Isolated Yield: 2 equiv oxidant: 40% total (32.6 mg of **21-OH**,144.0 mg of **21-O**; Ratio of **21-OH:21-O** (isolated) = 1:0.23)

21-OH R_f: 0.34 (1:1 EtOAc:hexanes)

21-O R_f: 0.56 (1:1 EtOAc:hexanes)

21-OH IR (v, cm^{-1}): 3401, 2859, 1610, 1447, 1282, 1026, 909, 728, 700.

21-O IR (v, cm^{-1}): 2947, 1681, 1624, 1446, 1285, 1212, 970, 700.

21-O mp: 100–102 ºC

21-OH HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1648.

21-O HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{19}H_{20}NO_2$: 294.1489; found: 294.1494.

21-OH ^{1}H NMR ($C_6D_5CD_3$, 700 MHz, 90 ºC): δ 7.25 (m, 2H), 7.12 (multiple peaks, 4H), 7.06 (multiple peaks, 4H), 4.09 (br s, 2H), 4.07 (d, J = 7.0 Hz, 1H), 2.48 (td, J = 12.6, 2.8 Hz, 1H), 2.41 (m, 1H), 1.99 (br s, 1H), 1.68 (d, J = 12.6 Hz, 1H), 1.55 (m, 1H), 1.19 (qd, J = 12.6, 4.2 Hz, 1H), 1.10 (multiple peaks, 2H).

21-OH ^{13}C NMR ($C_6D_5CD_3$, 176 MHz, 90 ºC): δ 169.9, 144.3, 129.3, 128.4, 127.6, 126.9 (some aromatic peaks overlap with $C_6D_5CD_3$), 45.4, 44.4, 29.4, 20.7.

21-OH ^{13}C NMR (CDCl$_3$, 176 MHz, room temperature): 170.4, 143.0, 137.6, 136.3, 129.5, 128.5, 127.8, 126.9, 126.6, 78.2, 47.9, 43.7, 42.3, 29.2, 29.0, 28.4, 28.1. Rotamers present at room temperature.

21-O ^{1}H NMR (C$_6$D$_5$CD$_3$, 700 MHz, 90 ºC): δ 7.71 (d, J = 7.7 Hz, 2H), 7.29 (m, 2H), 7.17 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 7.7 Hz, 2H), 7.08 (m, 3H), 4.03 (br s, 2H), 2.99 (m, 1H), 2.75 (t, J = 12.6 Hz, 2H), 1.60 (q, J = 12.6 Hz, 2H), 1.48 (d, J = 12.6 Hz, 2H).

21-O ^{13}C NMR (C$_6$D$_5$CD$_3$, 176 MHz, 90 ºC): δ 200.5, 169.9, 137.0, 132.7, 129.4, 128.5, 127.6, (some aromatic peaks overlap with C$_6$D$_5$CD$_3$), 44.5, 43.7, 29.0.

21-O ^{13}C NMR (CDCl$_3$, 176 MHz, room temperature): 201.8, 170.6, 136.1, 135.8, 133.4, 129.8, 128.9, 128.6, 128.4, 127.0, 47.3, 43.5, 41.9, 28.8. Rotamers present at room temperature

4-(dimethylamino)-1-phenylbutan-1-one (22-O):
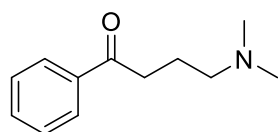
22-O

General procedure B was followed using N,N-dimethyl-4-phenylbutan-1-amine (0.25 mmol, 44 mg, 1 equiv), K$_2$S$_2$O$_8$ (1.00 mmol, 270 mg, 4 equiv), aqueous H$_2$SO$_4$ (0.28 mmol, 1.1 equiv, 0.25 mL of a 1.1 M stock solution), and water (0.75 mL). The reaction was stirred at 80 ºC for 2 h. The reaction was quenched following **general procedure C**, evaporated to dryness, and purified by column chromatography on basic alumina (0.5–5% MeOH/dichloromethane). The product was isolated as a light yellow oil. The ^{1}H and ^{13}C NMR spectra matched literature values.[4]

Isolated Yield: 40% (19.0 mg)

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{12}$H$_{18}$NO: 192.1383; found: 192.1381.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.97 (d, J = 7.7 Hz, 2H), 7.54 (t, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.23 (s, 6H), 1.92 (quin, J = 7.0 Hz, 2H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 200.2, 137.2, 133.0, 128.7, 128.2, 59.1, 45.5. 36.4, 22.2.

N-(3-hydroxybutyl)benzamide (23-OH-a and 23-OH-b):
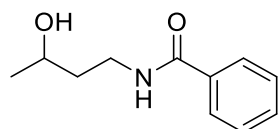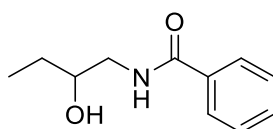
23-OH-a   **23-OH-b**

General procedure B was followed using 1-butylamine (6.00 mmol, 439 mg, 2 equiv), K$_2$S$_2$O$_8$ (3.00 mmol, 811 mg, 1 equiv), and aqueous H$_2$SO$_4$ (13.2 mmol, 2.2 equiv, 6.0 mL of a 2.2 M

stock solution). The reaction was stirred at 80 ºC for 2 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (8.36 mL, 60.0 mmol), and benzoyl chloride (2.09 mL, 18.0 mmol). The product was then purified by flash column chromatography on silica (gradient of 2% to 10%, MeOH in dichloromethane). Compound **23-OH-a** was isolated as a light yellow oil, and compound **23-OH-b** was isolated as a white solid.

Isolated Yield: 32% total (143.6 mg of **23-OH-a**, 41.6 mg of **23-OH-b**; Ratio of **23-OH-a:23-OH-b** (isolated) = 1:0.29; Ratio of **23-OH-a:23-OH-b** (crude) = 1:0.39)

23-OH-a R$_f$: 0.38 (1:9 MeOH:dichloromethane)

23-OH-b R$_f$: 0.38 (1:9 MeOH:dichloromethane); this compound elutes after **23-OH-a** with the gradient used for purification

23-OH-a IR (v, cm^{-1}): 3312, 2967, 1635, 1540, 1489, 1449, 1310, 1134, 1002, 909, 694.

23-OH-b IR (v, cm^{-1}): 3356, 3310, 2932, 1631, 1540, 1373, 1257, 1128, 909, 696.

23-OH-b mp: 93-96 ºC

23-OH-a HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{11}$H$_{16}$NO$_2$: 194.1176; found: 194.1176.

23-OH-b HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{11}$H$_{16}$NO$_2$: 194.1176; found: 194.1175.

23-OH-a ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.77 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 6.83 (br s, 1H), 3.91 (m, 2H), 3.35 (dq, J = 14.0 Hz, 5.2 Hz, 1H), 3.14 (br s, 1H), 1.69 (multiple peaks, 2H), 1.34 (d, J = 6.4 Hz, 3H).

23-OH-a ^{13}C NMR (CDCl$_3$, 101 MHz): δ 168.4, 134.4, 131.7, 128.7, 127.0, 65.9, 38.7, 37.5, 23.5.

23-OH-b ^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.78 (d, J = 7.7 Hz, 2H), 7.49 (t, J = 7.7 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 6.71 (br s, 1H), 3.75 (m, 1H), 3.70 (ddd, J = 14.0, 6.3, 2.8 Hz, 1H), 3.32 (ddd, J = 14.0, 7.7, 4.9 Hz, 1H), 2.32 (br s, 1H), 1.55 (multiple peaks, 2H), 0.99 (t, J = 7.0 Hz, 3H).

23-OH-b ^{13}C NMR (CDCl$_3$, 176 MHz): δ 168.5, 134.4, 131.7, 128.7, 127.1, 73.0, 45.9, 28.2, 10.0.

N-((1r,3s,5R,7S)-3-hydroxy-5,7-dimethyladamantan-1-yl)benzamide (24):

24
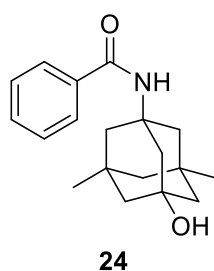
General procedure B was followed using (1r,3R,5S,7r)-3,5-dimethyladamantan-1-amine (0.75 mmol, 134 mg, 1 equiv), $K_2S_2O_8$ (0.75 mmol, 202 mg, 1 equiv), aqueous H_2SO_4 (1.65 mmol, 2.2 equiv, 1.5 mL of a 1.1 M stock solution), and water (1.5 mL). The reaction was stirred at 80 ºC for 2 h. The product was protected via **general procedure D** with MeCN (100 mL), triethylamine (2.09 mL, 15.0 mmol), and benzoyl chloride (552 μL, 4.5 mmol). The product was then purified by flash column chromatography on silica (gradient of 12% to 100%, EtOAc/hexanes) and isolated as a white solid.

Isolated Yield: 27% (61.4 mg)

R_f: 0.30 (1:1 EtOAc:hexanes)

IR (v, cm^{-1}): 3326, 2946, 2851, 1641, 1531, 1335, 1201, 1063, 910, 731.

mp: 163–164 ºC

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for $C_{19}H_{26}NO_2$: 300.1958; found: 300.1967.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.69 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 5.92 (br s, 1H), 2.01 (s, 2H), 1.77 (d, J = 11.9 Hz, 2H), 1.71 (d, J = 11.9 Hz, 2H), 1.46 (d, J = 11.9 Hz, 2H), 1.38 (d, J = 11.9 Hz, 2H), 1.18 (d, J = 12.6 Hz, 1H), 1.13 (d, J = 12.6 Hz, 1H), 0.96 (s, 6H). OH peak not observed

^{13}C NMR (CDCl$_3$, 176 MHz): δ 167.0, 135.7, 131.4, 128.6, 126.8, 70.5, 55.6. 50.5, 49.6, 47.8, 46.7, 34.4, 29.3.

benzyl (S)-(5,5-dimethyl-2-oxotetrahydrofuran-3-yl)carbamate (25):
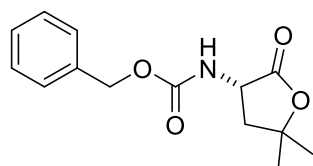
25
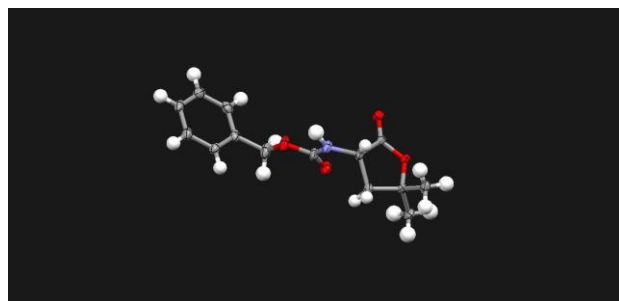
General procedure B was followed using *L*-leucine (1.50 mmol, 197 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure E**, purified by flash column chromatography on silica

(gradient of 20% to 75%, EtOAc in hexanes), and isolated as a white solid. The product was recrystallized from hot hexanes with a few drops of dichloromethane to obtain an X-ray crystal structure, which shows retention of stereochemistry (see supporting information from reference 1).[1]

Isolated Yield: 47% (187.1 mg)

R$_f$: 0.52 (1:1 EtOAc:hexanes)

IR (v, cm^{-1}): 3325, 3058, 2979, 1753, 1708, 1534, 1242, 1179, 1109, 925, 739, 702.

mp: 103–104 ºC

HRMS: ESI$^+$ (m/z): [M+Na$^+$] calcd for NaC$_{14}$H$_{17}$NO$_4$: 287.1101; found: 287.1109.

^{1}H NMR (CD$_3$OD, 700 MHz): δ 7.32 (multiple peaks, 5H), 5.10 (s, 2H), 4.84 (s, 1H), 4.62 (t, J = 10. 5 Hz, 1H), 2.46 (t, J = 10.5 Hz, 1H), 2.12 (t, J = 11.9 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (CD$_3$OD, 176 MHz): δ 176.7, 158.2, 138.0, 129.5, 129.0, 128.9, 83.3, 67.8, 52.6, 41.4, 29.1, 27.1.

HPLC trace of racemic mixture of **25**: OD-H column 30% isopropanol/ 70% hexanes, 210.2 nm

Auto-Scaled Chromatogram

Peak Results

	Name	RT	Area	Height	% Area
1		7.540	14147215	895657	43.54
2		9.571	18343855	910636	56.46
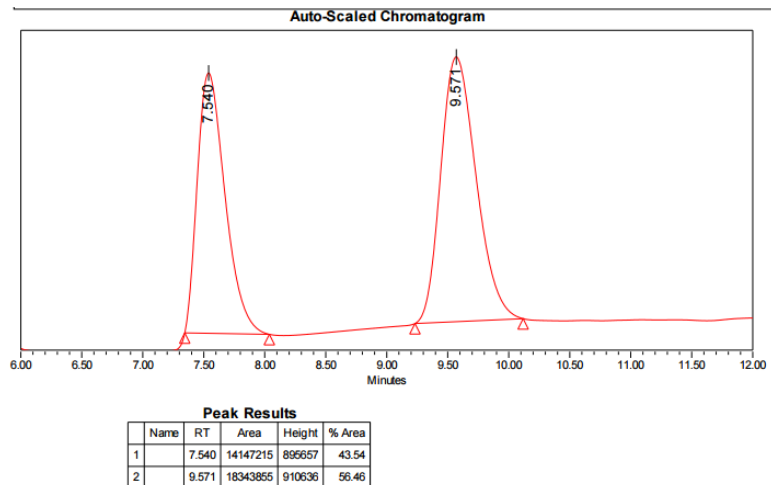
HPLC trace of isolated compound **25**: OD-H column 30% isopropanol/ 70% hexanes, 210.2 nm, 90% ee

Auto-Scaled Chromatogram

Peak Results

	Name	RT	Area	Height	% Area
1		7.295	28449440	1716329	94.88
2		9.200	1534091	90194	5.12
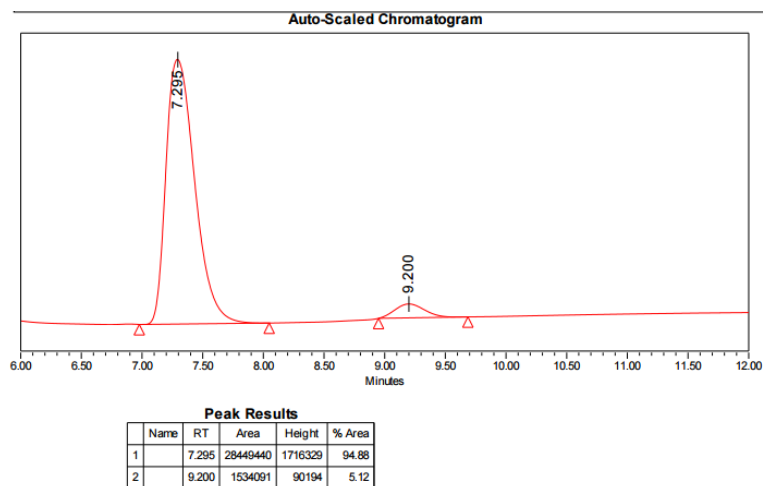
3-[(benzyloxy)carbonyl(aminomethyl)]-5-hydroxy-5-methylhexanoic acid (26):

26
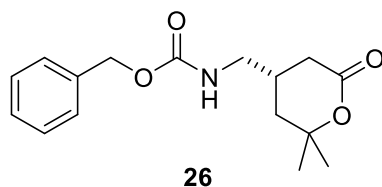
General procedure B was followed using (*S*)-3-(ammoniomethyl)-5-methylhexanoate (1.50 mmol, 239 mg, 1 equiv), $K_2S_2O_8$ (3.00 mmol, 811 mg, 2 equiv), aqueous H_2SO_4 (3.3 mmol, 2.2 equiv, 3.0 mL of a 1.1 M stock solution), and water (3.0 mL). The reaction was stirred at 80 ºC for 4 h. The product was protected via **general procedure E**, purified by flash column chromatography on silica (gradient 2% to 10%, MeOH/dichloromethane), and isolated as a light pink oil.

Isolated Yield: 40% (175.6 mg)

R$_f$: 0.63 (1:9 MeOH:dichloromethane)

IR (v, cm^{-1}): 3325, 2978, 1699, 1522, 1456, 1374, 1242, 1108, 981, 734, 697.

HRMS: ESI$^+$ (m/z): [M+Na$^+$] calcd for $NaC_{16}H_{21}NO_4$: 314.1363; found: 314.1463.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.35 (multiple peaks, 5H), 5.09 (s, 2H), 5.01 (s, 1H), 3.15 (m, 2H), 2.64 (dd, *J* = 18.2, 4.9 Hz, 1H), 2.26 (m, 1H), 2.02 (dd, *J* = 18.2, 11.9 Hz, 1H), 1.84 (d, *J* = 13.3 Hz, 1H), 1.43 (s, 3H), 1.40 (t, *J* = 13.3 Hz, 1H), 1.35 (s, 3H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 170.6, 156.7, 136.3, 128.7, 128.4, 128.3, 82.0, 67.1, 45.8, 38.3, 33.5, 30.8, 30.2, 27.6.

3.5. References

(1) Adapted with permission from (a) Lee, M.; Sanford, M. S. *Org. Lett.* **2017**, *19*, 572. © American Chemical Society

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(6) Example of remote C–H borylation of an unprotected amine: Li, Q.; Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 8755.

(7) For examples using carbamate protected amino acids and peptides, see: (a) Detomaso, A.; Curci, R. *Tetrahedron Lett.* **2001**, *42*, 755. (b) Rella, M. R.; Williard, P. G. *J. Org. Chem.* **2007**, *72*, 525. (c) Annese, C.; D'Accolti, L.; De Zotti, M.; Fusco, C.; Toniolo, C.; Williard, P. G.; Curci, R. *J. Org. Chem.* **2010**, *75*, 4812.

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(14) Salamone, M.; Carboni, G.; Bietti, M. *J. Org. Chem.* **2016**, *81*, 9269.

(15) Methyl(trifluoro-methyl)dioxirane. *e-EROS Encyclopedia of Reagents for Organic Synthesis* [Online]; John Wiley & Sons, Posted March 31, 2016. http://onlinelibrary.wiley.com/doi/10.1002/047084289X.rm267.pub3/abstract (accessed Nov 16, 2016).

(16) Cat. no. 216224 ($41.09/mol) from Sigma Aldrich Online Catalogue (accessed Dec 4, 2016).

(17) A control reaction (Table 3.1, entry 6) confirmed that **2** is not formed in appreciable quantities in the absence of acid; instead, mostly starting material was recovered. Notably, 1.1 equiv of H_2SO_4 was added at the end of this reaction to ensure solubility of starting material and products during the NMR analysis of the crude reaction mixture.

(18) Under the optimized conditions for the oxidation of substrate **1**, the addition of TEMPO or dinitrobenzene led to significantly diminished conversion of **1** and yield of **2**. For example, with 1 equiv of TEMPO, the yield of **2** was just 13%, along with 74% of substrate **1** remaining. With 20 mol % of 1,4-dinitrobenzene, the yield of **2** was 44%, along with 49% of substrate **1** remaining. These preliminary results point to a radical pathway, which is fully consistent with the known chemistry of persulfate oxidations. For example, see: House, D. A. *Chem. Rev.* **1962**, *62*, 185.

(19) The crude NMR spectrum is provided in the Supporting Information in reference 1.

(20) Initial attempts to oxidize higher molecular weight amines under our standard conditions were hampered by the modest solubility of many of these substrates in water (even when protonated). Current efforts are focusing on identifying suitable co-solvents and re-optimizing the reaction for such systems.

(21) Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V.; Zaidlewicz, M. *J. Org. Chem.* **1999**, 64, 6263.

CHAPTER 4

Palladium-Catalyzed, Transannular C(sp^3)–H Arylation of Cyclic Amines: Application to Fragment Based Drug Discovery[1]

4.1.   Introduction

This Chapter focuses on the work that was completed in collaboration with AbbVie Pharmaceuticals in the Fragment Based Drug Discovery Group in North Chicago. Recently, our group demonstrated a Pd-catalyzed remote C–H arylation of a variety of alicyclic amines (**Scheme 4.1**).[2] This proved effective for the selective functionalization of complex molecules and could thus be used in late-stage modification of drug candidates. Another potential application of this work is in the synthesis of small molecules for fragment based drug discovery (FBDD). In recent years, FBDD has become an increasingly important approach for the identification of lead compounds in the pharmaceutical industry.[3] However, one key limitation of current fragment libraries is that they predominantly consist of sp^2-rich, planar compounds.[4] To cover a wider chemical space, there is increasing demand for fragments containing three-dimensional character, and alicyclic amine-based fragments could be particularly desirable in this context.[5]

Scheme 4.1. Pd-Catalyzed C(sp^3)–H Arylation of Alicyclic Amines [2]
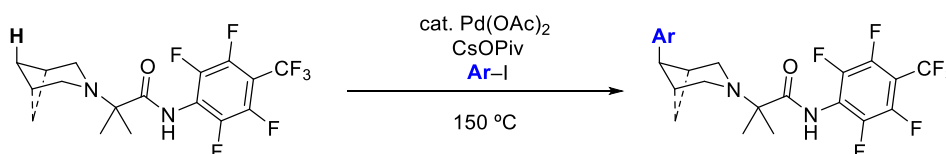
As such, we sought to leverage recent work from our group on the Pd-catalyzed remote C(sp^3)–H arylation of alicyclic amines to assemble 3D fragments for FBDD.[2] In order to

rapidly access the amine-containing fragments, we needed to address several key challenges

associated with the existing method. First, the reaction times must be as short as possible to

accelerate drug discovery efforts. To assemble a diverse fragment library, the conditions should

must be compatible with a variety of coupling partners, particularly those containing

heteroatoms and halogenated functional groups. Finally, the directing group required for the

functionalization step must be easily removed to access the desired fragments.

Figure 4.1. 3-azabicylco[3.1.0]hexane Containing Bioactive Molecules [6]
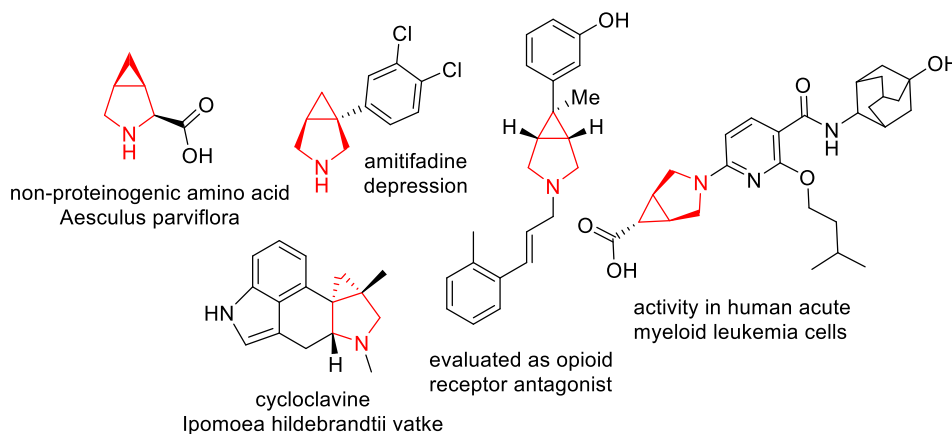
Our efforts in this area focused on the $C(sp^3)$–H functionalization of the 3-

azabicylco[3.1.0]hexane core to generate C-4-arylated derivatives. Under the originally

reported conditions, arylation of 3-azabicylco[3.1.0]hexane occurred with excellent yield and

good functional group compatibility. As such, this reaction provided a good starting point for

fragment generation.[2] Notably, 3-azabicylco[3.1.0]hexane serves as the core structure of a

variety of bioactive molecules (**Figure 4.1**).[6] C-4-arylated derivatives of this core possess

three-dimensional character and are rule-of-three compliant (MW < 300; ClogP < 3; hydrogen

bond donors/acceptors < 3; rotatable bonds < 3).[7] Traditionally, the assembly of 3-

azabicylco[3.1.0]hexane derivatives with functionalization at the C-4 position has required

long synthetic sequences.[6a-c] However our Pd-catalyzed transannular C–H arylation method

enables selective functionalization of this core in just three steps: (1) directing group

installation, (2) transannular C(sp^3)–H arylation, and (3) directing group removal (**Scheme 4.2**).

Scheme 4.2. Pd-Catalyzed C(sp^3)–H Arylation for Fragment Generation
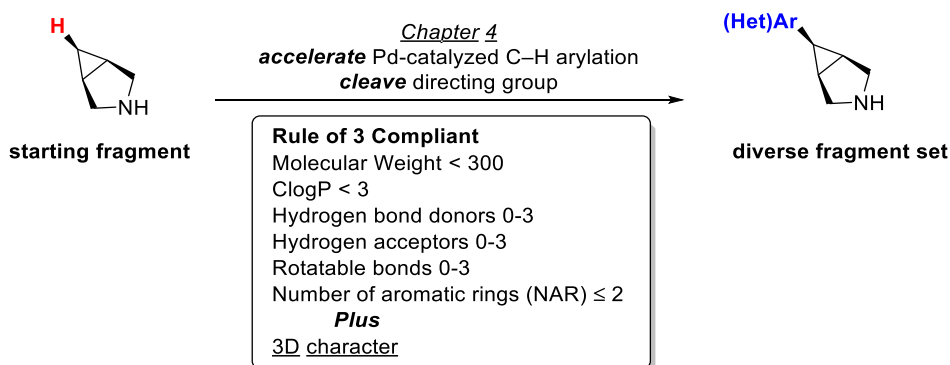
We focused on assembling 3-azabicylco[3.1.0]hexane fragments for FBDD, while addressing the challenges of shortening the reaction times to increase reaction throughput, optimizing and developing new conditions for directing group removal, and preparing derivatives relevant to FBDD. The resulting structures are then analyzed and compared to ideal fragment properties.

4.2. Results and Discussion

Results from Microwave Conditions

Our original conditions for the C–H arylation of 3-azabicyclo[3.1.0]hexanes required a glovebox set up and reaction times of 18 h at 130 °C to achieve high yields.[2] We first sought to develop conditions to accelerate these reactions as well as to eliminate the need for a glovebox. Microwave technology is often used to accelerate the reaction rates and thus reduce reaction times.[8] As shown in **Scheme 4.3**, we found that Pd-catalyzed C–H arylation to afford **1** proceeds in under 1 h at 180 °C under microwave heating, without the use of a glovebox. These reactions were set up in a microwave tube on the bench-top and purged with N$_2$. At 0.52 mmol scale, the arylated product **1** was obtained in 68% yield, which is comparable to the previously reported 74% yield from the 18 h reactions.[2] Furthermore, when the new conditions were scaled to 1.04 mmol, a comparable 83% yield of **1** was obtained (**Scheme 4.3**).

Scheme 4.3. Revised Microwave Conditions for Pd-Catalyzed C–H Arylation

S-1

new conditions
10% Pd(OAc)$_2$
CsOPiv (3 equiv)
Ph–I (3 equiv)
t-AmylOH
180 ºC (microwave), 30-50 min

previous conditions required
130 ºC (hot plate), 18 h

1
83% yield (1.08 mmol scale)
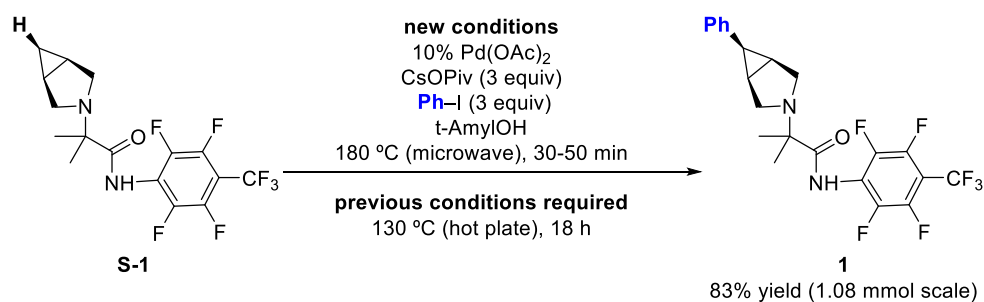
With these microwave conditions in hand, we next explored the scope of aryl and heteroaryl iodide coupling partners for this reaction (**Figure 4.2**). A wide variety of aryl iodides were compatible with the modified conditions, affording 4-aryl-3-azabicyclo[3.1.0]hexanes products **2**-**9** in moderate to good yields. Aryl iodides containing halogen, ether, and unprotected phenol functional groups were generally well-tolerated without any modification of the standard microwave conditions. Notably, a low yield of 12% was obtained for product **8.** As a result, this reaction was not carried forward to the next step of directing group removal. A variety of substituted pyridyl and quinolinyl iodides also reacted under the standard conditions to afford modest to good yields of the transannular C(sp^3)–H arylation products **10**-**16**. We did observe that *para*-substituted phenol and pyridyl groups resulted in low yields of functionalized product (**8**, **10**), possibly because they bind to Pd and deactivate the catalyst.

Figure 4.2. Synthesis of Arylated Products with Microwave Conditions

1 68%[a], 83%[b]	**2** 42%[b]	**3** 60%[b]	**4** 34%[b]	**5** 79%[b]	**6** 71%[b]
7 72%[b]	**8** 12%[b]	**9** 56%[b]	**10** 16%[a]	**11** 49%[b]	**12** 45%[b]
13 42%[b]	**14** 40%[b]	**15** 24%[b]	**16** 65%[a]		
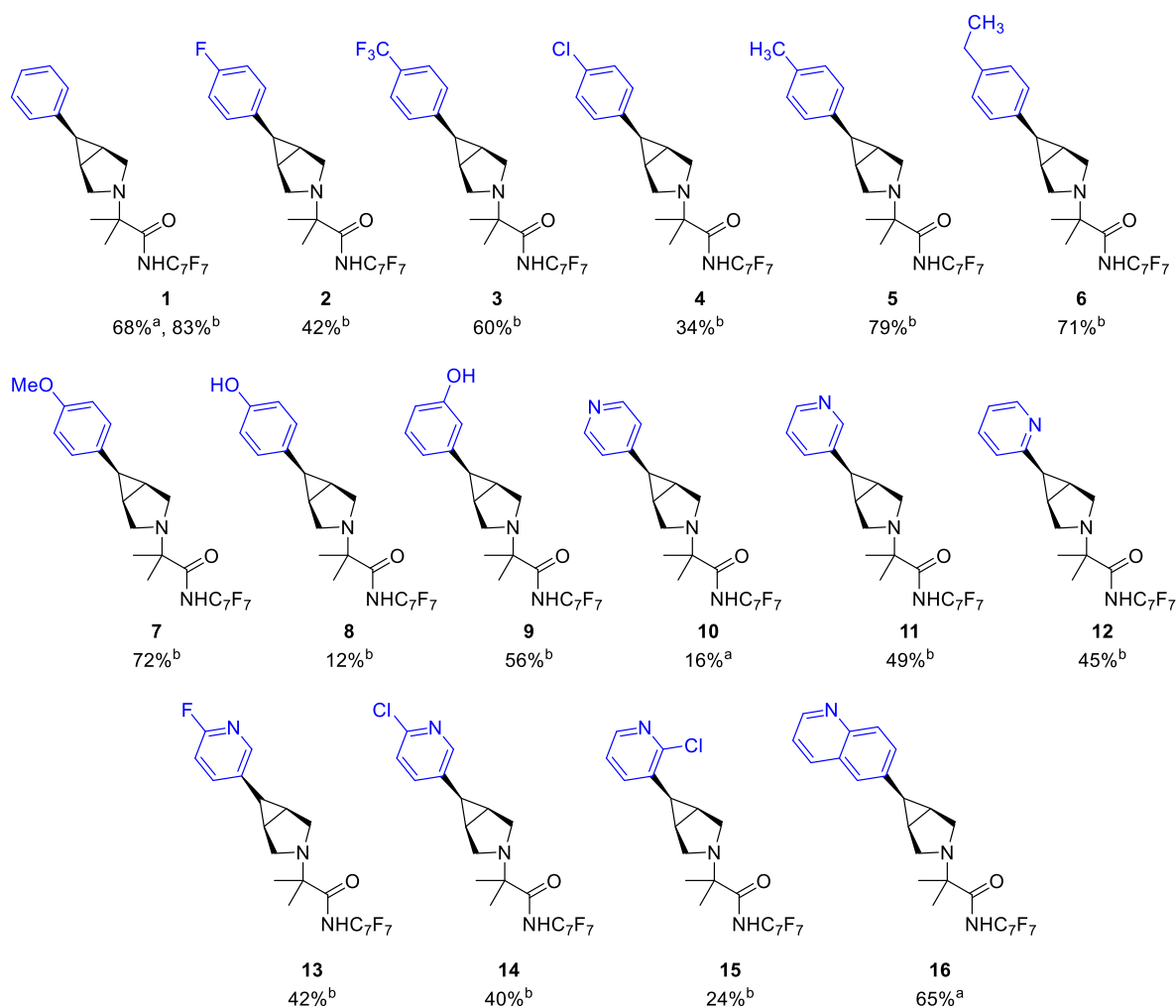
[a] Reaction conditions with 0.52 mmol of **S-1** [b] Reaction conditions with 1.04 mmol **S-1**. Isolated yields. See details in experimental section.

Strategies for Directing Group Cleavage

A key remaining challenge for the application of this directed C–H arylation in FBDD is the development of practical methods for removing the directing group from the product. Our previously reported conditions involved reduction of the fluoroimide directing group with SmI$_2$, protection of the resulting 2° amine product with pivaloyl chloride, and finally isolation of the amide.[2] One concern with these conditions in the context of FBDD is the use of hexamethylphosphoramide (HMPA) activator, which has been shown to be toxic.[9] In addition, the original process yielded higher molecular weight amide products rather than the free 2° amines, which are lower molecular weight and can be further derivatized.

Scheme 4.4. Removal of Directing Group with Model Substrate **S-2**

new conditions
1. SmI$_2$, TPPA
MeOH, NEt$_3$
THF, RT, 3 h
2. aqueous extraction

previous conditions required
1. HMPA, overnight
2. PivCl protection of amine

17
(93% yield, TFA salt)
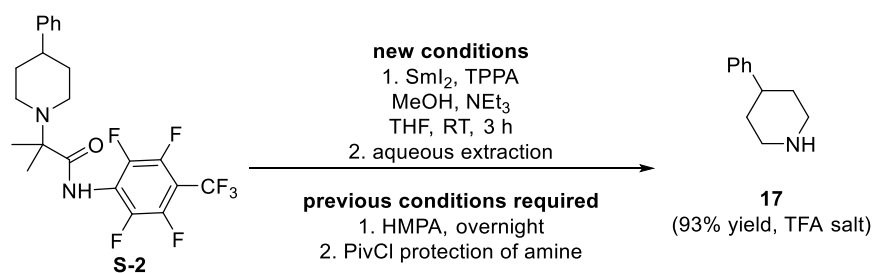
We first explored alternative activators for SmI$_2$ and identified tripyrrolidinophosphoric acid triamide (TPPA) as a viable replacement.[10] **S-2** was selected as an ideal substrate for optimization because the starting material, 4-phenyl piperidine, was commercially available. Upon replacing HMPA with TPPA, the complete cleavage of the directing group was observed within 3 h (**Scheme 4.4**). Under these revised conditions, the directing group cleavage proceeded within 3 h at room temperature, compared to 24 h under previous conditions. Further studies revealed that the 2° amine product could be isolated directly by changing the work-up procedure. Rather than protection with pivaloyl chloride at the end of the SmI$_2$ reaction, we subjected the crude reaction mixture to an aqueous work-up and then purified the resulting product by reverse phase HPLC. This procedure enabled direct isolation a variety of 2° amine fragments in yields ranging from 34-51% (**Table 4.1**). Notably, a slightly modified procedure involving a Boc-protection step was required for efficient isolation of the polar secondary amine **9-A**.

A key limitation of the SmI$_2$-mediated directing group cleavage process is that it is incompatible with substrates containing aryl halide functional groups (Cl, Br, and I) that are easily reduced.[11] In addition, pyridine derivatives such as **11-A** undergo competing heteroarene reduction in the presence of SmI$_2$ (entry 9, **Table 4.1**).[12] These limitations highlight the need to develop a complementary procedure to remove the directing group from these substrates. Literature precedent suggested that acylation of the tertiary amine could enable subsequent

Table 4.1. Reductive Cleavage of Directing Group with SmI_2
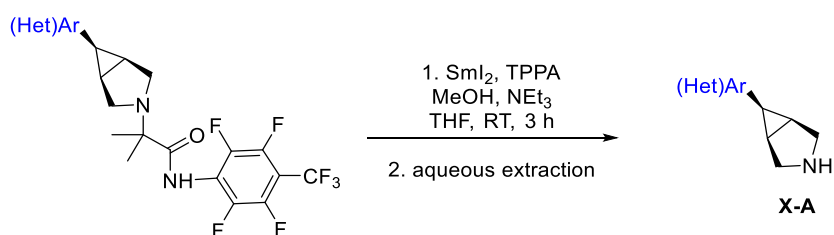
entry	product	yield[a]
1	4-Ph (**1-A**)	34%
2	4-F-Ph (**2-A**)	48%
3	4-CF$_3$-Ph (**3-A**)	44%
5	4-Me-Ph (**5-A**)	49%
6	4-Et-Ph (**6-A**)	39%
7	4-MeO-Ph (**7-A**)	51%
8	3-OH-Ph (**9-A**)	38%[b]
9	3-Pyr (**11-A**)	0%

[a] Isolated yields. [b] Boc protection of intermediate followed by deprotection. See details in experimental section.

dealkylation of the fluoroamide directing group.[13] However, one challenge for this process is that the nitrogen atom is highly sterically hindered, and, as such, acylation might require more forcing reaction conditions. Temperature, reaction time, and the use of Lewis acids was investigated. However, the use of Lewis acid additives was inconclusive, leading to NMR spectra that were difficult to interpret due to peak broadening and shifting. We found that the treatment of **1** with neat acetyl chloride with microwave heating at 150 °C for 3 h led to reproducible formation of amide product **1-B** in 35% yield as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Furthermore, the product was isolated in 25% yield from this procedure (**Table 4.2**, entry 6 and **Table 4.3**, entry 1). Similar optimization studies were carried out with **11** resulting in a 23% yield of **11-B** as determined by ^{1}H NMR spectroscopy.

These conditions proved effective to cleave the directing group from products **1** and **4** as well as most of the pyridine-containing derivatives, although the isolated yields were relatively low (12-25%, **Table 4.3**). In the case of **10**, complete consumption of starting material and minimal formation of **10-B** was observed. This is most likely due to the

Table 4.2. Optimization Conditions for Acylative Dealkylation
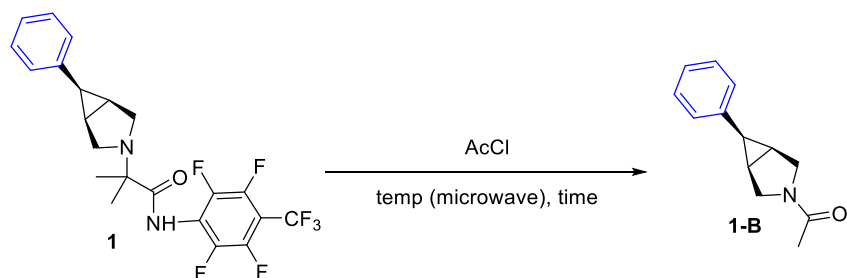
entry	temp (°C)	time (h)	yield[a]
1	100	5	trace
2	100[b]	5	trace
3	125	5	32%
4	150	1.5	12%
5	150	2.5	29%
6	150	3	35%

[a] NMR Yields. See details in experimental section. [b] hot plate

decomposition of the starting material under these conditions, as the neat acetyl chloride solution turned dark even prior to heating. Notably, the aryl-Cl bonds of **4-B**, **14-B**, and **15-B** were compatible with these conditions (**Table 4.3**). In contrast, product **13-B** was not isolable due to competing nucleophilic aromatic substitution at the C–F bond to generate the 2-chloro product **13-B**.

Table 4.3. Acylative Dealkylation of Directing Group with Acetyl Chloride
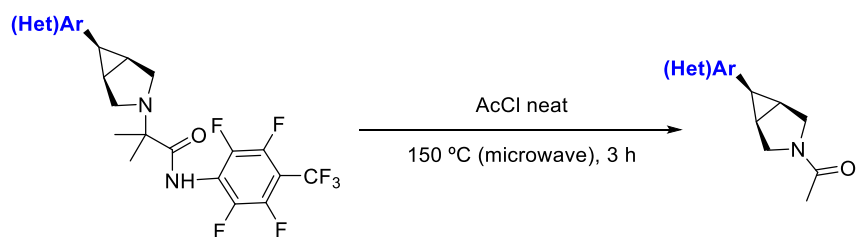
entry	product	yield[a]
1	4-Ph (**1-B**)	25%
2	4-Cl-Ph (**4-B**)	25%
3	4-Pyr (**10-B**)	0%
4	3-Pyr (**11-B**)	19%
5	2-Pyr (**12-B**)	19%
6	2-F-5-Pyr (**13-B**)	0%
7	2-Cl-5-Pyr (**14-B**)	19%
8	2-Cl-3-Pyr (**15-B**)	12%
9	6-quinoline (**16-B**)	23%

[a] Isolated yields. See details in experimental section.

Relating Products to Fragment Properties

Finally, the physicochemical properties of the fragments synthesized via C–H functionalization were assessed.[14] The calculated values show that nearly all of the prepared arylated amines and amides fall within the ideal range as defined by the restrictions set by the Rule of 3 and guidelines by Astex Pharmaceuticals (**Table 4.4**).[7] The fragments in this study have a low mean molecular weight (204), while maintaining high levels of Fsp^3 (Fraction aromatic = 0.48). The Principal Moments of Inertia (PMI), which describes whether a molecule is rod-, disk-, or sphere-like, demonstrate that most of the fragments possess rod- and sphere-like characteristics.[15] The Plane of Best Fit (PBF) is another topographic descriptor that describes the average distance (Å) from the plane, and is a measure of molecular complexity. The average PBF score for the 14 fragments is 0.69.[16]

Table 4.4. Physicochemical Properties of Synthesized Fragments

Property[a]	Ideal[7]	This Work
ClogP	0-2	0.92
MW	140-230	204
PSA	≤60	22.8
HBA	≤3	1.5
HBD	≤3	0.57
RBC	--	1.2
Fraction Aromatic	--	0.48

[a] cLogP = partition coefficient, MW = molecular weight, PSA = polar surface area, HBA = hydrogen bond acceptor, HBD = hydrogen bond donor, RBC = rotatable bond count

Preliminary Efforts in Expanding Fragment Synthesis

To further explore the utility of C–H functionalization in the synthesis of fragments, the C(α)–H arylation of the 3-azabicyclo[3.1.0]hexane core was conducted using modified conditions developed by the Yu laboratory.[17] Preliminary results indicate that C(α)–H arylation can be achieved, albeit in low yields. The isolated mixture of diastereomers were analyzed by ^{1}H NMR spectroscopy via integration of the newly formed benzylic proton. With the use of either phenyl or *p*-tolylboronic acid, a slight excess of the *trans* diastereomer is observed. To provide useful quantities of the final amine fragment, further optimization and subsequent

removal of the thioamide directing group will be necessary. Accessing these regio- and stereoisomeric products would be attractive, as they would further broaden current fragment libraries.

Scheme 4.5. Preliminary Results on C(α)–H Arylation Reactions

10% Pd(TFA)$_2$
KHCO$_3$, BQ
Ph-B(OH)$_2$

t-amylOH
200 ºC (microwave), 1 h

S-3

18-a   **18-b**

19% isolated yield, 1.2:1 **18-a : 18-b**
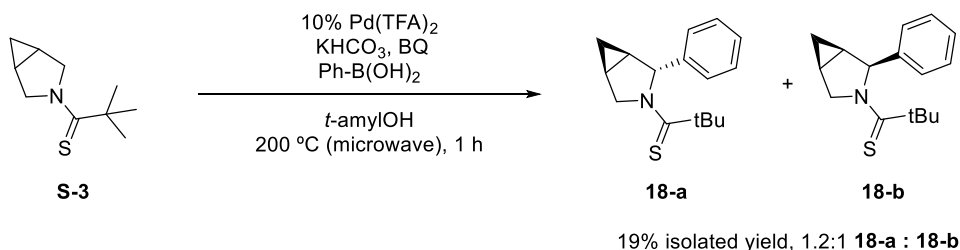
4.3. Conclusion and Outlook

In conclusion, we have shown that C–H functionalization is a viable method for the generation of amine fragments from the 3-azabicylco[3.1.0]hexane core. With the use of microwave technology, we rapidly generated a library of molecules bearing aryl substituents at remote C–H bonds. In the process, we addressed several key challenges associated with removal of the directing group. Cleavage of the directing group was accomplished while maintaining the integrity of the newly installed functional groups. Analysis of the final amines demonstrate that they possess desirable physicochemical properties, and that they can be added to current FBDD libraries and serve as possible scaffolds for early stage drug discovery efforts.

4.4. **Experimental Procedures and Characterization of Compounds**

4.4.1 Materials and Methods

Materials and Methods

HPLC grade water, ethyl acetate (EtOAc), heptanes (Hep), methanol (MeOH), dichloromethane (DCM), and acetonitrile (MeCN) for column chromatography were purchased from Aldrich. Deuterated solvents for NMR spectroscopy were purchased from Sigma Aldrich. Reagents were purchased from commercial sources (Sigma Aldrich, Alfa Aeser, Ark Pharm, and ACROS) and used without further purification, unless otherwise noted. Microwave reactions were carried out with Biotage® Initiator+. Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silica gel 60 F$_{254}$. NMR spectra were recorded on Bruker Avance 500 NMR Spectrometer (500 MHz for ^{1}H; 126 MHz for ^{13}C) and a Varian 400-MR NMR Spectrometer (400 MHz for ^{1}H; 101 MHz for ^{13}C; 376 MHz for ^{19}F) with the residual solvent peak (CDCl$_3$; ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm), (CDCN; ^{1}H: δ = 1.94 ppm, ^{13}C: δ = 1.32 ppm), and (DMSO-d_6; ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.52 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in parts per million (ppm) (δ) relative to tetramethylsilane. Multiplicities are reported as follows: br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), qd (quartet of doublets). Coupling constants (*J*) are reported in Hz. Liquid chromatography mass spectra were recorded on a high performance liquid chromatography with mass spectrometer (LC: Agilent 1200 Series, MS: Thermo Electron Corporation Finnigan Surveyor MSQ Plus). Liquid reagents were dispensed by difference from syringes. All reagents were weighed out under ambient conditions.

4.4.2 Synthesis and Characterization of Substrates

Compound (S-1):
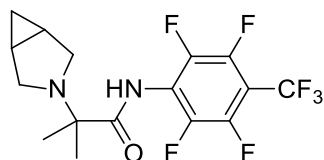
Compound **S-1** was synthesized based on a modified literature procedure[1] with the addition of 0.5 equiv NaI. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[2]

Compound (S-2):
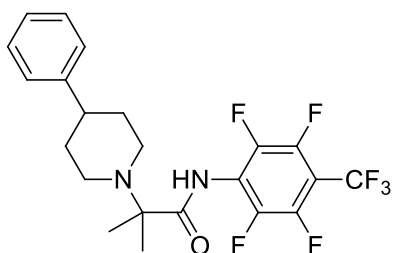
An authentic sample of compound **S-2** was synthesized using 4-phenyl piperidine based on a modified literature procedure[1] with the addition of 0.5 equiv NaI. ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[2]

Compound (S-3):
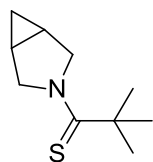
Compound **S-3** was synthesized based on literature a procedure in 75% yield after two purifications.[2]

<u>LC-MS:</u> APCI^{+} (m/z): [M+H]$^{+}$ calcd for $C_{10}H_{18}NS$: 184.116 ; found: 184.229.

<u>^{1}H NMR</u> (CDCl$_3$, 400 MHz): δ 4.50 (d, J = 12.8 Hz, 1H), 4.27 (J = 10.0 Hz, 1H), (m, 2H), 1.71 (br s, 1H), 1.5 (br s, 1H), 1.38 (s, 9H), 0.74 (m, 1H), 0.14 (q, J = 10.0 Hz, 1H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 211.4, 59.7, 54.2, 43.9, 30.5, 16.8, 13.0, 9.2.

4.4.3 General Procedures for the Isolation of C–H Arylation Products and Characterization

General Procedure A for Small Scale Microwave Reactions:

To a medium biotage microwave tube (biotage, 2-5 mL) equipped with a stir bar was added Pd(OAc)$_2$ (11.7 mg, 0.052 mmol, 10 mol %), **S-1** (200 mg, 0.52 mmol, 1 equiv), cesium pivalate (365 mg, 1.56 mmol, 3 equiv), aryl iodide (2-3 equiv) and 4.8 mL anhydrous *tert*-amyl alcohol. The cap was crimped and the vessel was flushed with nitrogen. The microwave tube was heated with following parameters: 1 min pre-stirring, followed by a ramp (Normal) to 180 °C and held at temperature for 40 min. To the reaction was added 250 μL hydrazine (35% aqueous) and allowed to stir at 60°C for 1 hr. The *tert*-amyl alcohol was removed and the remaining residue was dissolved with EtOAc and filtered through a plug of celite and concentrated en vacuo. The crude reaction was purified via flash column chromatography with EtOAc/Heptanes.

General Procedure B for Large Scale Microwave Reactions:

To a large biotage microwave tube (biotage, 10-20 mL) equipped with a stir bar was added Pd(OAc)$_2$ (23.4 mg, 0.10 mmol, 10 mol %), **S-1** (400 mg, 1.04 mmol, 1 equiv), cesium pivalate (731 mg, 3.12 mmol, 3 equiv), aryl iodide (2-3 equiv) and 9.6 mL anhydrous *tert*-amyl alcohol. The cap was crimped and the vessel was flushed with nitrogen. The microwave tube was heated with following parameters: 1 min pre-stirring, followed by a ramp (Normal) to 180 °C and held at temperature for 40 to 50 min. To the reaction was added 500 μL hydrazine (35% aqueous) and allowed to stir at 60°C for 1 hr or at room temperature overnight. The *tert*-amyl alcohol was removed en vacuo and the remaining residue dissolved with EtOAc and filtered through a plug of celite and concentrated en vacuo. The crude reaction was purified via flash column chromatography with EtOAc/Heptanes.

Compound (1):
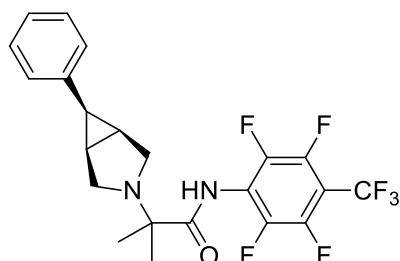
General procedures **A** and **B** were followed using 3 equiv iodobenzene for 40 min (small scale) and 3 equiv iodobenzene for 30 min (large scale). ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[2]

Isolated Yield (small scale 0.13 mmol): 68% (40.7 mg)

Isolated Yield (large scale 1.04 mmol): 83% (average of two runs 412.0 mg, 377.0 mg)

Compound (2):
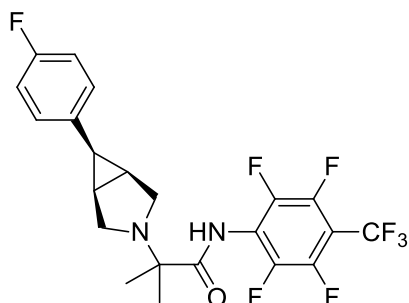
General procedures **A** and **B** were followed using 3 equiv 4-fluoroiodobenzene for 40 min (small and large scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 50% (125.0 mg)

Isolated Yield (large scale 1.04 mmol): 42% (210.2 mg)

<u>R$_f$</u>: 0.38 (20% EtOAc/80% Hex)

<u>LC-MS</u>: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{22}$H$_{19}$F$_8$N$_2$O: 479.129; found: 479.119.

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 7.27 (m, 2H), 6.78 (t, J = 8.5 Hz, 2H), 6.48 (br s, 1H), 2.94 (d, J = 9.0 Hz, 2H), 2.89 (ddd, J = 9.0 Hz, J = 2.0 Hz, J = 1.0 Hz, 2H), 2.04 (t, J = 8.0 Hz, 1H), 1.87 (m, 2H), 1.14 (s, 6 H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 175.7, 161.1 (d, J_{C-F} = 246 Hz), 133.7, 129.6 (d, J_{C-F} = 7.6 Hz) Hz), 61.1, 45.1, 22.2, 20.9. 20.1. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

<u>^{19}F NMR</u> (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -116.4 (m, 1F), -141.4 (m, 2F), -143.1 (m, 2F).

Compound (3):
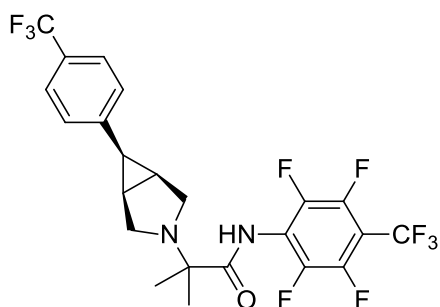
General procedures A and **B** were followed using 3 equiv 4-iodobenzotrifluoride for 40 min (small scale) and 3 equiv 4-iodobenzotrifluoride for 30 min (large scale) and isolated as a light yellow solid.

<u>Isolated Yield (small scale 0.52 mmol)</u>: 64% (175.3 mg)

<u>Isolated Yield (large scale 1.04 mmol)</u>: 59% (254 mg)

<u>R$_f$</u>: 0.26 (20% EtOAc/80% Hex)

<u>LC-MS</u>: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{23}$H$_{19}$F$_{10}$N$_2$O: 529.134; found: 529.071.

<u>^{1}H NMR</u> (CDCl$_3$, 500 MHz): δ 7.46 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 6.31 (br s, 1H), 3.98 (d, J = 9.0 Hz, 2H), 2.90 (d, J = 9.0 Hz, 2H), 2.11 (t, J = 8.0 Hz, 1H), 1.94 (d, J = 8.0 Hz, 2H), 1.14 (s, 6 H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): 175.7, 142.4, 128.6, 128.3 (q, J_{C-F} = 32.8 Hz), 125.1 (q, J_{C-F} = 3.0 Hz), 123.8 (q, J_{C-F} = 272 Hz), 61.2, 46.1, 22.8, 21.0, 20.2. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

<superscript>19</superscript>F NMR (CDCl$_3$, 376 MHz): δ -56.3 (t, J = 22.2 Hz, 3F), -63.3 (s, 3F), -141.3 (m, 2F), -143.5 (m, 2F).

Compound (4):

General procedure B was followed using 3 equiv 1-chloro-4-iodobenzene for 40 min (large scale) and isolated as a light yellow solid.

Isolated Yield (large scale 1.04 mmol): 34% (183.1 mg)

R$_f$: 0.44 (20% EtOAc/80% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{22}$H$_{19}$ClF$_7$N$_2$O: 495.107; found: 495.167.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.25 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.41 (br s, 1H), 2.90 (multiple peaks, 4H), 2.03 (t, J = 8.0 Hz, 1H), 1.87 (m, 2H), 1.15 (s, 6 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 175.9, 136.5, 132.0, 129.5, 128.3, 61.1, 45.1, 22.3, 21.0.   The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.2 (t, J = 21.8 Hz, 3F), -141.2 (m, 2F), -143.1 (m, 2F).

Compound (5):
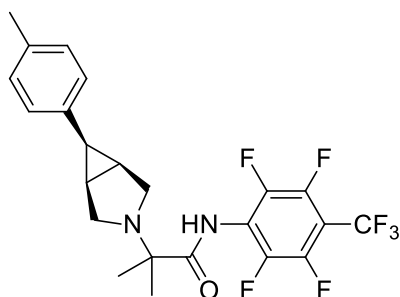
General procedures A and **B** were followed using 3 equiv 4-iodotoluene for 40 min (small scale) and 3 equiv 4-iodotoluene for 30 min (large scale) and isolated as a light yellow solid.

Isolated Yield (small scale 0.52 mmol): 53% (130.0 mg)

Isolated Yield (large scale 1.04 mmol): 79% (388.0 mg)
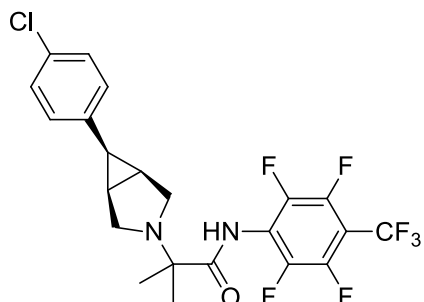
R$_f$: 0.50 (20% EtOAc/80% Hex)

LC-MS: APCI[+] (m/z): [M+H][+] calcd for $C_{23}H_{22}F_7N_2O$: 475.162; found: 475.131.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.18 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 6.44 (br s, 1H), 2.97 (d, J = 9.2 Hz, 2H), 2.86 (dd, J = 9.2 Hz, J = 2.0 Hz, J = 1.2 Hz, 2H), 2.02 (t, J = 8.0 Hz, 1H), 1.99 (s, 3H), 1.83 (m, 2H), 1.13 (s, 6 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 176.2, 135.5, 134.9, 128.8, 128.0, 61.0, 45.1, 22.4, 20.9, 20.5, 20.0. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.2 (t, J = 21.8 Hz, 3F), -141.8 (m, 2F), -142.7 (m, 2F).

Compound (6):
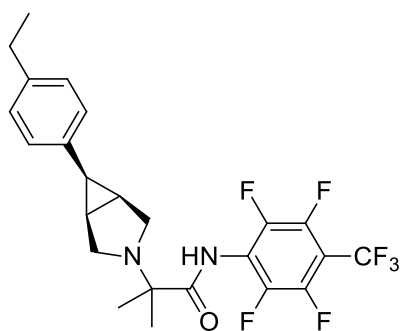
General procedure B was followed using 3 equiv 4-ethyliodobenzene for 30 min (large scale) and isolated as a light brown oil.

Isolated Yield (large scale 1.04 mmol): 71% (360.0 mg)

R$_f$: 0.52 (20% EtOAc/80% Hex)

LC-MS: APCI[+] (m/z): [M+H][+] calcd for $C_{24}H_{24}F_7N_2O_2$: 489.178 ; found: 489.113.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.22 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 6.51 (br s, 1H), 2.98 (d, J = 9.2 Hz, 2H), 2.85 (m, 2H), 2.27 (q, J = 7.6 Hz, 2H), 2.02 (t, J = 8.0 Hz, 1H), 1.83 (m, 2H), 1.12 (s, 6H), 0.95 (t, J = 7.6 Hz, 3H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 176.3, 141.9, 135.3, 128.2, 127.6, 61.0, 45.2, 28.0, 22.5, 20.9, 20.0, 14.9. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.2 (t, J = 21.8 Hz, 3F), -141.9 (m, 2F), -142.6 (m, 2F).

Compound (7):
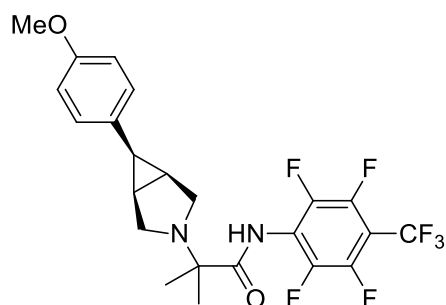
General procedures A and **B** were followed using 3 equiv 4-iodoanisole for 40 min (small scale) and and 3 equiv 4-iodoanisole for 30 min (large scale). ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[2]

Isolated Yield (small scale 0.52 mmol): 60% (32.7 mg)

Isolated Yield (large scale 1.04 mmol): 72% (365.4 mg)

Compound (8):
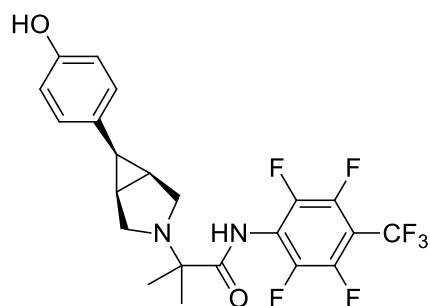
General procedure A was followed using 3 equiv 4-iodophenol for 40 min (small scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 12% (30.5 mg)

R_f: 0.66 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{22}H_{20}F_7N_2O_2$: 477.141; found: 477.141.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.97 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.56 (br s, 1H), 6.44 (d, J = 8.4 Hz, 2H), 2.84 (m, 4H), 1.92 (t, J = 7.6 Hz, 1H), 1.79 (d, J = 7.6 Hz, 2H), 1.04 (s, 6H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 175.4, 155.5, 128.8, 127.5, 114.7, 60.3, 44.6, 21.5, 20.8, 19.6. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -55.3 (t, J = 21.4 Hz, 3F), -142.7 (m, 2F), -143.6 (m, 2F).

Compound (9):
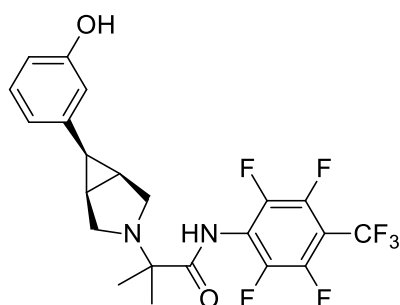
General procedures A and **B** were followed using 3 equiv 3-iodophenol for 40 min (small scale) and 2 equiv 3-iodophenol for 30 min (large scale). ^{1}H and ^{19}F NMR of the isolated product was consistent with literature values.[2]

Isolated Yield (small scale 0.52 mmol): 62% (153.1 mg)

Isolated Yield (large scale 1.04 mmol): 56% (278.0 mg)

Compound (10):
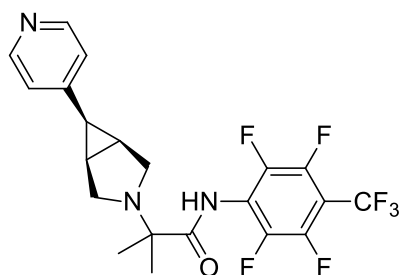
General procedures A and **B** were followed using 3 equiv 4-iodopyridine for 40 min (small scale) and 2 equiv 4-iodopyridine for 1 h 40 min (1 equiv at 0 min, then 1 equiv at 50 min, large scale) and isolated as a white solid.

Isolated Yield (small scale 0.52 mmol): 18% (43.5 mg)

Isolated Yield (large scale 1.04 mmol): 16% (76.9 mg), recovered 37% SM (144.7 mg)

R$_f$: 0.40 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{19}$F$_7$N$_3$O: 462.142; found: 462.123.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.36 (d, J = 5.2 Hz, 2H), 7.28 (d, J = 5.2 Hz, 2H), 6.34 (br s, 1H), 2.98 (d, J = 9.2 Hz, 2H), 2.88 (d, J = 9.2 Hz, 2H), 2.07 (t, J = 4.4 Hz, 1H), 1.96 (m, 2H), 1.14 (s, 6 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 175.3, 149.6, 147.2, 123.6, 61.2, 45.1, 22.2, 20.9, 20.0. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -141.0 (m, 2F), -142.9 (m, 2F).

Compound (11):
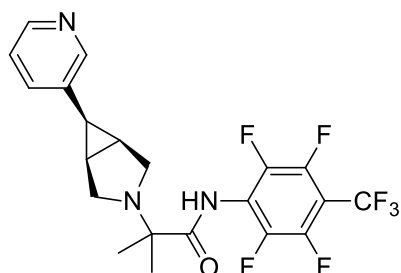
General procedures A and **B** were followed using 3 equiv 3-iodopyridine for small scale (40 min) and 2 equiv 3-iodopyridine for 50 min (large scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 58% (139.0 mg)

Isolated Yield (large scale 1.04 mmol): 49% (234.8 mg)

R$_f$: 0.39 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{19}$F$_7$N$_3$O: 462.142; found: 462.130.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.58 (m, 1H), 8.28 (d, J = 4.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 6.31 (br s, 1H), 2.95 (d, J = 9.2 Hz, 2H), 2.90 (m, 2H), 2.06 (t, J = 8.0 Hz, 1H), 1.95 (m, 2H), 1.12 (s, 6 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 175.1, 149.5, 147.5, 135.7, 133.7, 123.1, 61.2, 45.1, 20.8, 20.4, 19.9. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -141.2 (m, 2F), -142.8 (m, 2F).


Compound (12):
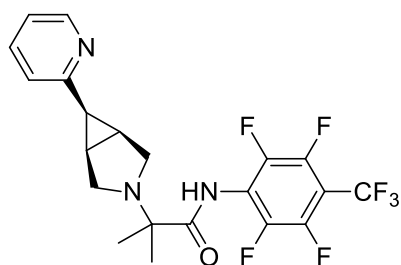
General procedures A and **B** were was followed using 2 equiv 2-iodopyridine for 40 min (small scale) and 2 equiv 2-iodopyridine for 1 h 40 min (1 equiv at 0 min, then 1 equiv at 50 min, large scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 28% (66.6 mg)

Isolated Yield (large scale 1.04 mmol): 45% (217.4 mg)

R$_f$: 0.16 (50% EtOAc/50% Hex)

<u>LC-MS:</u> APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{21}H_{19}F_7N_3O$: 462.142; found: 462.124.

<u>^{1}H NMR</u> (CDCl$_3$, 400 MHz): δ 8.36 (dd, J = 4.8 Hz, J = 0.8 Hz, 1), 7.47 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.31 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H), 6.98 (dd, J = 7.6 Hz, J = 4.8 Hz, 1H), 6.76 (br s, 1H), 3.11 (d, J = 9.2 Hz, 2H), 2.87 (dd, J = 8.8 Hz, J = 1.6 Hz, 2H), 2.20 (t, J = 8.0 Hz, 1H), 1.98 (m, 2H), 1.12 (s, 6 H).

<u>^{13}C NMR</u> (CDCl$_3$, 126 MHz): δ 175.4, 158.6, 149.1, 135.9, 123.3, 121.2, 61.3, 45.3, 24.5, 20.8, 20.5. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

<u>^{19}F NMR</u> (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -141.1 (m, 2F), -142.3 (m, 2F).

<u>Compound (13):</u>
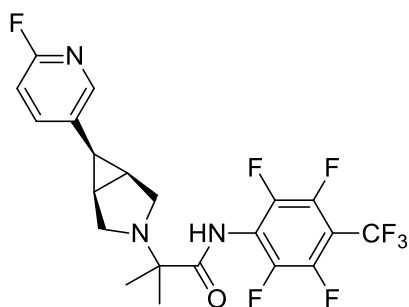
General procedures A and **B** were followed using 2 equiv 2-fluoro-5-iodopyridine for 40 min (small scale) and 2 equiv 2-fluoro-5-iodopyridine for 50 min (large scale) and isolated as an off-white solid.

<u>Isolated Yield (small scale 0.52 mmol):</u> 49% (123.0 mg)

<u>Isolated Yield (large scale 1.04 mmol):</u> 42% (211.8 mg)

<u>R$_f$:</u> 0.51 (50% EtOAc/50% Hex)

<u>LC-MS:</u> APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{21}H_{18}F_8N_3O$: 480.132; found: 480.069.

<u>^{1}H NMR</u> (CDCl$_3$, 400 MHz): δ 8.14 (m, 1H), 7.76 (td, J = 8.0 Hz, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.4 Hz, J = 2.8 Hz, 1H), 6.49 (br s, 1H), 2.93 (s, 4H), 1.99 (multiple peaks, 3H), 1.15 (s, 6 H).

<u>^{13}C NMR</u> (CDCl$_3$, 101 MHz): δ 174.9, 162.3 (d, J_{C-F} = 240 Hz), 146.7 (d, J_{C-F} = 13.9 Hz), 140.9 (d, J_{C-F} = 7.4 Hz), 131.2 (d, J_{C-F} = 4.6 Hz), 109.1 (d, J_{C-F} = 37.3 Hz), 61.3, 45.2, 20.9, 20.2, 19.6. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -70.6 (d, J = 7.5 Hz, 1F), -141.1 (m, 2F), -143.5 (m, 2F).

Compound (14):
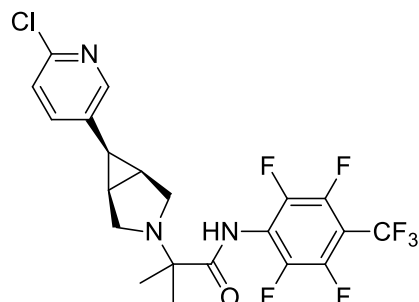
General procedure B was followed using 2 equiv 2-chloro-5-iodopyridine for 50 min (large scale) and isolated as a yellow solid.

Isolated Yield (large scale 1.04 mmol): 40% (206.6 mg)

R$_f$: 0.46 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{18}$Cl$_1$F$_7$N$_3$O: 496.103 ; found: 496.160.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.33 (m, 1H), 7.63 (ddd, J = 8.5 Hz, J = 2.5 Hz, J = 1.0 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.41 (br s, 1H), 2.93 (m, 4H), 1.97 (multiple peaks, 3H), 1.16 (s, 6 H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 175.1, 149.5, 149.2, 138.5, 132.5, 123.8, 61.3, 45.1, 20.9, 20.0, 19.7. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.2 (t, J = 21.8 Hz, 3F), -141.0 (m, 2F), -143.2 (m, 2F).

Compound (15):
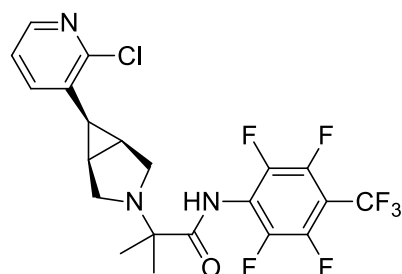
General procedures A and **B** were followed using 2 equiv 2-chloro-3-iodopyridine for 40 min (small scale) and 2 equiv 2-chloro-3-iodopyridine for 50 min (large scale) and isolated as a white solid.

Isolated Yield (small scale 0.52 mmol): 25% (63.6 mg)

Isolated Yield (large scale 1.04 mmol): 24% (124.0 mg)

R$_f$: 0.59 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{18}$Cl$_1$F$_7$N$_3$O: 496.103 ; found: 496.081.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.11 (dd, J = 4.5 Hz, J = 1.5 Hz, 1H), 7.76 (ddd, J = 7.5 Hz, J = 2.0 Hz, J = 1.0 Hz, 1H), 7.13 (dd, J = 7.5 Hz, J = 4.5 Hz, 1H), 6.46 (br s, 1H), 3.05 (d, J = 9.5 Hz, 2H), 2.88 (m, 2H), 2.06 (multiple peaks, 3H), 1.14 (s, 6 H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 175.0, 152.4, 147.6, 138.4, 133.4, 121.8, 61.3, 45.8, 21.6, 21.3, 20.7. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 376 MHz): δ -56.1 (t, J = 21.8 Hz, 3F), -141.0 (m, 2F), -143.0 (m, 2F).

Compound (16):
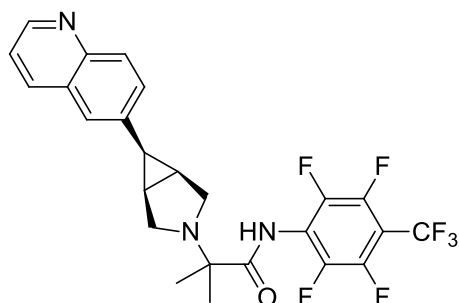
General procedures A and **B** were followed using 2 equiv 6-iodoquinoline for 40 min (small and large scale) and isolated as an off-white solid.

Isolated Yield (small scale 0.52 mmol): 65% (174.0 mg)

Isolated Yield (large scale 1.04 mmol): 31% (164.9 mg)

R$_f$: 0.54 (50% EtOAc/50% Hex)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{21}$F$_7$N$_3$O: 512.157 ; found: 512.098.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.66 (dd, J = 4.0 Hz, J = 1.6 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.4 Hz, J = 0.8 Hz, 1H), 7.74 (dd, J = 8.8 Hz, J = 1.6 Hz, 1H), 7.68 (m, 1H), 7.09 (dd, J = 8.0 Hz, J = 4.0 Hz, 1H), 5.98 (br s, 1H), 3.05 (d, J = 9.2 Hz, 2H), 2.93 (dd, J = 9.6 Hz, J = 1.2 Hz, 2H), 2.26 (t, J = 8.0 Hz, 1H), 1.99 (m, 2H), 1.12 (s, 6 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 175.7, 149.8, 146.7, 136.6, 134.7, 129.5, 127.7, 125.8, 120.8, 60.9, 45.2, 22.7, 21.0, 20.3. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

<u>19F NMR</u> (CDCl$_3$, 376 MHz): δ -56.3 (t, *J* = 21.8 Hz, 3F), -141.5 (m, 2F), -143.3 (m, 2F).

4.4.4 General Procedure for Isolation of Amine and Amide Products after Directing Group Removal and Characterization

General Procedure C for Removal of Directing Group:

To a round bottom flask under a flow of nitrogen equipped with a stir bar was added the arylated product (1 equiv), 0.1 M SmI$_2$ (12 equiv), anhydrous triethylamine (80 equiv), anhydrous methanol (40 equiv), and tris(*N,N*-tetramethylene)phosphoricacid triamide (5.5 equiv) and allowed to stir at room temperature for 3 h. The reaction vessel was then exposed to atmosphere and formation of a white precipitate is observed within 30 minutes. The reaction was quenched with 1 N HCl. To the mixture was added ethyl acetate and the product was extracted into the aqueous acidic layer. The organic layer was set aside and the aqueous layer was basified with solid NaOH until a pH of 11-12. The aqueous layer was extracted with ethyl acetate (3x 100 mL) and dried over sodium sulfate. After volatiles were removed a viscous yellow oil remained that was purified by reverse-phase HPLC [Waters XBridge™ C-18 column, 5 μm, 30×100 mm, flow rate 40 mL/minute, 5-100% gradient of acetonitrile in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide) (or 0.1% TFA)].

General Procedure D for Removal of Directing Group via Boc Protection:

To a round bottom flask under a flow of nitrogen equipped with a stir bar was added the arylated product (1 equiv), 0.1 M SmI$_2$ (12 equiv), anhydrous triethylamine (80 equiv), anhydrous methanol (40 equiv), and tris(*N,N*-tetramethylene)phosphoricacid triamide (5.5 equiv) and allowed to stir at room temperature for 3 h. The reaction vessel was then exposed to atmosphere and formation of a white precipitate is observed within 30 minutes. To the reaction at 0 ºC was added additional trimethylamine (140 equiv) and Boc$_2$O (81 equiv) and allowed to stir overnight. To the reaction solution was added 1 M citric acid until pH 3-4. The reaction is extracted with DCM (3x, 50 mL). The organic layers were combined, washed with brine and dried over sodium sulfate. The volatiles were removed and the product was purified via flash column chromatography with EtOAc/Heptanes. To the isolated Boc protected amine was added HCl (dioxane, 4 M, 20 equiv) and allowed to stir overnight at room temperature. The product was purified by reverse-phase HPLC.

General Procedure E for Optimization of Removal of Directing Group via Acetylation:

To a microwave tube (biotage, 0.2-0.5 mL vial) equipped with a stir bar was added the **1** (10 mg, 0.022 mmol) and acetyl chloride (neat, 0.3 mL). The reaction was heated to 110 to 150 ℃ for 1.5 to 10 hours in the microwave. The acetyl chloride was removed under reduced pressure and diluted with 0.5 mL of chloroform containing 0.011 mmol of trimethoxybenzene (from a stock solution of 18.5 mg in 5 mL chloroform) was added. The crude yield was obtained by quantitative ^{1}H NMR spectroscopy in CDCl$_3$.

General Procedure F for Removal of Directing Group via Acetylation:

To a microwave tube (biotage, 2-5 mL vial) equipped with a stir bar was added the arylated product (0.217 mmol, 1 equiv) and acetyl chloride (neat, 3.0 mL). The reaction was heated to 150 ℃ for 3 hours. The acetyl chloride was removed under reduced pressure and the product, diluted in DCM (10 mL) and added 1 M NaOH (10 mL). The product was extracted with DCM (2 x 10 mL). The volatiles were removed en vacuo and the product was purified by reverse-phase HPLC.

Compound (17):
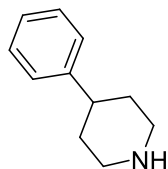
General procedure C was followed using **17** (0.216 mmol, 100 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 93% yield (55.3 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{11}$H$_{15}$N: 162.120; found: 162.108.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.55 (br s, 1H), 9.11 (br s, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 (m, 1H), 7.21 (d, J = 7.5 Hz, 2H), 3.53 (d, J = 12.5 Hz, 2H), 3.02 (d, J = 11.0 Hz, 2H), 2.76 (m, 1H), 2.04 (m, 4H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 143.5, 128.8, 127.1, 126.6, 44.5, 40.6, 29.9.

Compound (1-A):
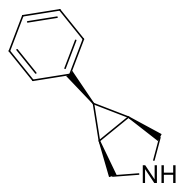
General procedure C was followed using **1** (0.272 mmol, 125 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 34% yield (25.4 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{11}H_{14}N$: 160.113 ; found: 160.069.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.48 (br s, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 4.73 (br s, 1H), 3.64 (d, J = 12.4 Hz, 2H), 3.32 (d, J = 12.4 Hz, 2H), 2.46 (t, J = 8.0 Hz, 1H), 2.22 (m, 2H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 132.0, 130.0, 129.3, 128.5, 45.3, 23.3, 21.4.

Compound (2-A):
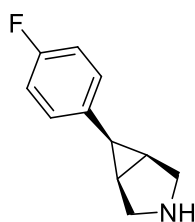
General procedure C was followed using **2** (0.408 mmol, 195 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 49% yield (57.9 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{11}H_{13}FN$: 178.103 ; found: 178.069.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 10.85 (br s, 1H), 7.19 (t, J = 8.4 Hz, 2H), 7.08 (t, J = 8.4 Hz, 2H), 5.94 (br s, 1H), 3.58 (d, J = 11.2 Hz, 2H), 3.30 (d, J = 11.2 Hz, 2H), 2.39 (t, J = 8.0 Hz, 1H), 2.22 (m, 2H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 162.6 (d, J_{C-F} = 249 Hz), 131.2 (d, J_{C-F} = 8.1 Hz), 127.2 (d, J_{C-F} = 3.0 Hz), 116.9 (d, J_{C-F} = 22.2 Hz), 45.0, 23.3. 22.0.

^{19}F NMR (CDCl$_3$, 376 MHz): -75.8 (s, 3F), -113.2 (s, 1F).

Compound (3-A):
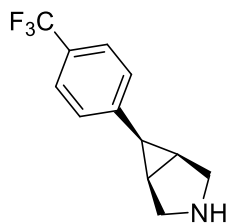
General procedure C was followed using **3** (0.848 mmol, 448 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 44% (128.4 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{13}F_3N$: 228.100 ; found: 227.994

^{1}H NMR (CDCl$_3$, 500 MHz): δ 11.07 (br s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.26 (br s, 1H), 3.58 (d, J = 12.5 Hz, 2H), 3.29 (d, J = 12.5 Hz, 2H), 2.48 (t, J = 8.5 Hz, 1H), 2.28 (m, 2H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 135.8, 130.6 (d, J_{C-F} = 32.8 Hz), 130.1, 126.7 (d, J_{C-F} = 3.7 Hz) Hz), 123.9 (d, J_{C-F} = 273 Hz), 44.8, 24.2, 22.2.

^{19}F NMR (CDCl$_3$, 376 MHz): -63.0 (s, 3F), -75.9 (s, 3F).

Compound (5-A):
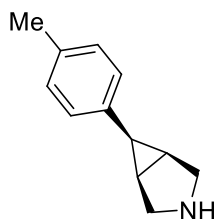
General procedure C was followed using **5** (0.769 mmol, 365 mg) and isolated by reverse-phase HPLC as the TFA amine salt (light brown solid).

Isolated Yield: 49% (109.0 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{16}N$: 174.128 ; found: 174.194.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 12.35 (br s, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.52 (br s, 1H), 3.63 (m, 2H), 3.32 (dd, J = 12.0 Hz, J = 3.2 Hz, 2H), 2.41 (t, J = 8.4 Hz, 1H), 2.35 (s, 3H), 2.20 (m, 2H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 138.5, 130.7, 128.9, 128.7, 45.4, 22.7, 21.3, 21.1.

Compound (6-A):
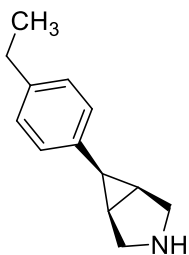
General procedure C was followed using **6** (0.588 mmol, 287 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 39% (69.0 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{18}N$: 188.144 ; found: 188.312.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 11.47 (br s, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.02 (br s, 1H), 3.60 (m, 2H), 3.32 (dd, J = 12.0 Hz, J = 4.4 Hz, 2H), 2.64 (q, J = 7.6 Hz, 2H), 2.41 (t, J = 8.4 Hz, 1H), 2.20 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 144.7, 129.4, 129.2, 128.8, 45.4, 28.4, 23.1, 21.5, 15.2.

Compound (7-A):
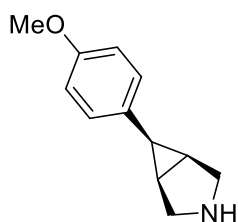
General procedure C was followed using **7** (0.367 mmol, 180 mg) and isolated by reverse-phase HPLC as the TFA amine salt (off-white solid).

Isolated Yield: 51% yield (56.7 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{16}NO$: 190.123 ; found: 190.153.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 10.85 (br s, 1H), 7.13 (d, J = 8.4 H, 2H), 6.91 (d, J = 8.4 Hz, 2H), 5.38 (br s, 1H), 3.78 (s, 3H), 3.56 (m, 2H), 3.32 (dd, J = 11.6 Hz, J = 3.6 Hz, 2H), 2.36 (t, J = 8.4 Hz, 1H), 2.17 (m, 2H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ 159.6, 130.4, 123.4, 115.3, 55.2, 45.4, 22.8, 21.6.

Compound (9-A):
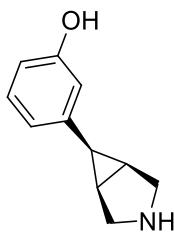
General procedure D was followed using **9** (0.301 mmol, 143 mg) and isolated by reverse-phase HPLC as the free amine (light brown solid).

<u>Isolated Yield</u>: 38% over two steps (20.1 mg)

<u>LC-MS</u>: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{11}$H$_{14}$NO: 176.108 ; found: 176.304.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.12 (t, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.56 (multiple peaks, 2H), 2.99 (s, 4H), 2.05 (t, J = 8.5 Hz, 1H), 1.82 (d, J = 8.5 Hz, 2H). NH and OH peak not present

^{13}C NMR (CDCl$_3$, 126 MHz): δ 157.6, 137.6, 130.0, 119.5, 115.6, 114.3, 46.7, 22.6, 22.0.

Compound (1-B):
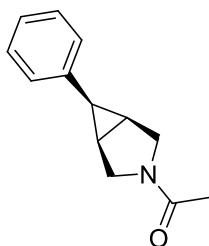
General procedure F was followed using **1** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as a light brown oil.

<u>Isolated Yield</u>: 25% yield (11 mg)

<u>LC-MS</u>: APCI$^+$ (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{16}$NO: 202.123 ; found: 202.153.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.30 (t, J = 7.6 Hz, 2H), 7.21 (multiple peaks, 3H), 4.92 (d, J = 12.4 Hz, 1H), 3.59 (dd, J = 11.0, 4.0 Hz, 1H), 3.32 (d, J = 11.0 Hz, 1H), 3.39 (dd, J = 12.4, 4.0 Hz Hz, 1H), 2.23 (t, J = 8.0 Hz, 1H), 1.97 (m, 2H), 1.47 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 101 MHz): δ 168.9, 133.8, 128.8, 128.5, 126.9, 46.8, 44.6, 22.5, 21.6, 20.6, 20.1.

Compound (4-B):

General procedure F was followed using **4** (0.217 mmol, 107 mg) and isolated by reverse-phase HPLC as a light yellow oil.

Isolated Yield: 26% yield (13.2 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{13}H_{15}ClNO$: 236.084 ; found: 236.162.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.28 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 3.89 (d, J = 12.4 Hz, 1H), 3.62 (dd, J = 11.0, 4.0 Hz, 1H), 3.45 (d, J = 11.0 Hz, 1H), 3.42 (dd, J = 12.4, 4.0 Hz Hz, 1H), 2.17 (t, J = 8.0 Hz, 1H), 1.99 (m, 2H), 1.55 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 101 MHz): δ 169.3, 132.8, 132.2, 130.1, 128.7, 46.7, 44.7, 21.9, 21.6, 20.7, 20.1.

Compound (10-B):

General procedure F was followed using **10** (0.217 mmol, 100 mg) and yield was below threshhold for collection.

Compound (11-B):
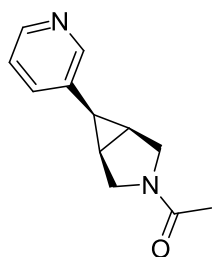
General procedure F was followed using **11** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as the free pyridine (yellow oil).

Isolated Yield: 19% yield (8.4 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{15}N_2O$: 203.118 ; found: 203.334.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.51 (s, 1H), 8.46 (d, J = 4.8 Hz, 1H), 7.54 (d, J = 7.6, 1H), 7.24 (dd, J = 7.6, 4.8 Hz, 1H), 3.84 (d, J = 12.4 Hz, 1H), 3.63 (dd, J = 11.2, 4.0 Hz, 1H), 3.47 (d, J = 11.2 Hz, 1H), 3.41 (dd, J = 12.4, 4.0 Hz, 1H), 2.18 (t, J = 8.0 Hz, 1H), 2.03 (multiple peaks, 2H), 1.50 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 101 MHz): δ 168.3, 150.1, 148.1, 136.4, 129.9, 123.5, 46.6, 44.3, 22.0, 20.7, 19.9, 19.7.

Compound (12-B):
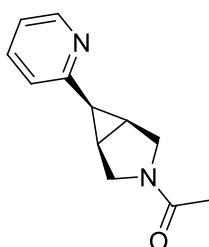
General procedure F was followed using **12** (0.217 mmol, 100 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

Isolated Yield: 22% yield (15.1 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{15}N_2O$: 203.118 ; found: 203.219.

^{1}H NMR (CD$_3$CN, 500 MHz): δ 8.75 (dd, J = 5.5, 0.5 Hz, 1H), 8.32 (td, J = 8.0, 1.5 Hz, 1H), 7.75 (multiple peaks, 2H), 3.81 (d, J = 12.5 Hz, 1H), 3.64 (multiple peaks, 2H), 3.27 (dd, J = 12.5, 4.0 Hz, 1H), 2.48 (t, J = 8.0 Hz, 1H), 2.20 (m, 1H), 2.15 (m, 1H), 1.44 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CD$_3$CN, 126 MHz): δ 169.2, 152.5, 145.8, 143.5, 128.1, 125.7, 46.9, 44.6, 22.9, 22.1, 21.5, 20.8.

Compound (13-B):
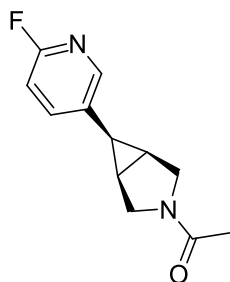
General procedure F was followed using **13** (0.217 mmol, 104 mg) and SNAr was observed on the pyridine. Unable to isolate each product cleanly.

Compound (14-B):
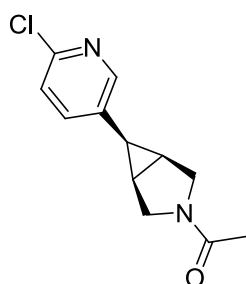
General procedure F was followed using **14** (0.217 mmol, 108 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (light yellow oil).

Isolated Yield: 16% yield (11.8 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{14}ClN_2O$: 237.079 ; found: 237.103.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.29 (d, J = 1.0 Hz, 1H), 7.52 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 3.81 (d, J = 12.5 Hz, 1H), 3.67 (dd, J = 11.0, 4.5 Hz, 1H), 3.46 (d, J = 11.0 Hz, 1H), 3.45 (dd, J = 12.5, 4.5 Hz, 1H), 2.15 (t, J = 8.0, 1H), 2.09 (m, 1H), 2.05 (m, 1H), 1.59 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 126 MHz): δ 169.0, 149.9, 149.7, 139.3, 128.9, 124.4, 46.6, 44.4, 21.9, 20.8, 19.8, 19.3.

Compound (15-B):
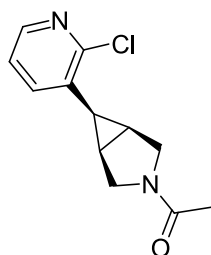
General procedure F was followed using **15** (0.217 mmol, 108 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

Isolated Yield: 12% yield (9.0 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{12}H_{14}ClN_2O$: 237.079 ; found: 236.918.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.29 (d, J = 4.8 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.19 (dd, J = 7.6, 4.8 Hz, 2H), 4.05 (d, J = 13.2 Hz, 1H), 3.61 (dd, J = 11.2, 4.4 Hz, 1H), 3.44 (m, 2H) 2.15 (multiple peaks, 3H), 1.52 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 101 MHz): δ 168.8, 152.3, 148.1, 138.9, 129.8, 122.5, 47.0, 44.8, 22.4, 21.9, 21.2, 20.7.

Compound (16-B):

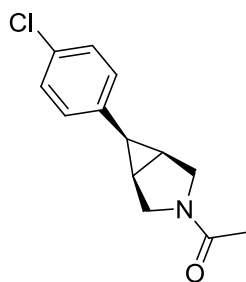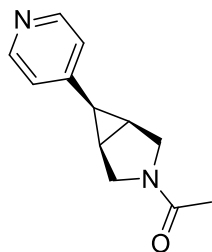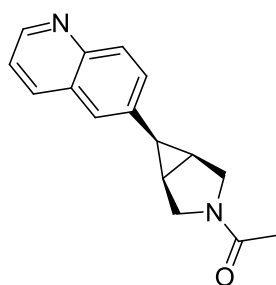**General procedure F** was followed using **16** (0.217 mmol, 111 mg) and isolated by reverse-phase HPLC as the pyridine TFA salt (colorless oil).

Isolated Yield: 23% yield (18.1 mg)

LC-MS: APCI$^+$ (m/z): [M+H]$^+$ calcd for $C_{16}H_{17}N_2O$: 253.134 ; found: 253.137.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.18 (d, J = 5.0 Hz, 1H), 8.73 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 9.0 Hz, 1H), 7.93 (m, 1H), 7.91 (d, J = 9.0 Hz, 1H), 8.83 (dd, J = 8.0, 5.0 Hz 1H), 4.03 (d, J = 12.4 Hz, 1H), 3.71 (dd, J = 11.5, 4.5 Hz, 1H), 3.50 (multiple peaks, 2H), 2.46 (m, 1H), 2.20 (m, 1H), 1.40 (s, 3H). Hindered rotation of acetyl group breaks symmetry of molecule

^{13}C NMR (CDCl$_3$, 126 MHz): δ 169.2, 144.5, 144.1, 138.7, 136.9, 135.6, 129.0, 127.6, 122.8, 121.6, 46.7, 44.5, 22.5, 21.7, 21.3, 20.4.

4.4.5 Synthesis and Characterization of Products of C(α)–H Arylation

General Procedure C for Microwave Reactions for C(α)-H Arylation[17]:

Using modified conditions from reference 17, to a large biotage microwave tube (biotage, 10-20 mL) equipped with a stir bar was added Pd(TFA)$_2$ (43.5 mg, 0.13 mmol, 10 mol %), potassium bicarbonate (262 mg, 2.62 mmol, 2 equiv), aryl boronic acid (2.62 mmol, 2 equiv),

benzoquinone (283 mg, 2.62 mmol, 2 equiv), **S-3** (240 mg, 1.31 mmol, 1 equiv), and 9.0 mL of wet *tert*-amyl alcohol. The microwave tube was heated with following parameters: 1 min pre-stirring, followed by a ramp (Normal) to 200 °C and held at temperature for 60 min. The *tert*-amyl alcohol was removed en vacuo and the remaining residue dissolved with EtOAc and filtered through a plug of celite and concentrated en vacuo. The crude reaction was product was purified by reverse-phase HPLC. The ratio of diastereomers was obtained from the isolated mixture.

4.5. References

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CHAPTER 5

Ligand Effects on Palladium-Catalyzed, Remote C(sp^3)–H Arylation of Cyclic Amines[1]

5.1. Introduction

Cyclic and bicyclic amines appear in a variety of natural products and bioactive molecules. Over 59% of FDA approved pharmaceuticals contain a nitrogen heterocycle.[2] More importantly, over 20% of the top 200 pharmaceuticals contain an alicyclic amine.[3] These drugs include those utilized for the treatment of depression, pain, nicotine addiction, and Parkinson's disease, as well as many other illnesses (**Figure 5.1**). As such, methods for the C–H functionalization of such heterocyclic cores are highly desired in order to facilitate SAR studies. While many strategies exist for C(α)–H functionalization[4], far fewer methods exist for the remote C–H functionalization of aliphatic amines (see Chapter 1 for more detail).[5,6,7,8,9] We viewed this as an opportunity to develop methods to access the distal C–H bonds in cyclic amine scaffolds.

Figure 5.1. Cyclic Amines in Natural Products and Bioactive Molecules

paroxetine
(anti-depressant)

cycloclavine
(ergot alkaloid)

granisertron
(antiemetic)

cytisine
(nicotine addiction)

euphococcinine
(*coccinellid* alkaloid)

benzatropine
(Parkinson's disease)

amitifadine
(anti-depressant)

epiboxidine
(analgesic properties)

varenicline
(smoking cessation)
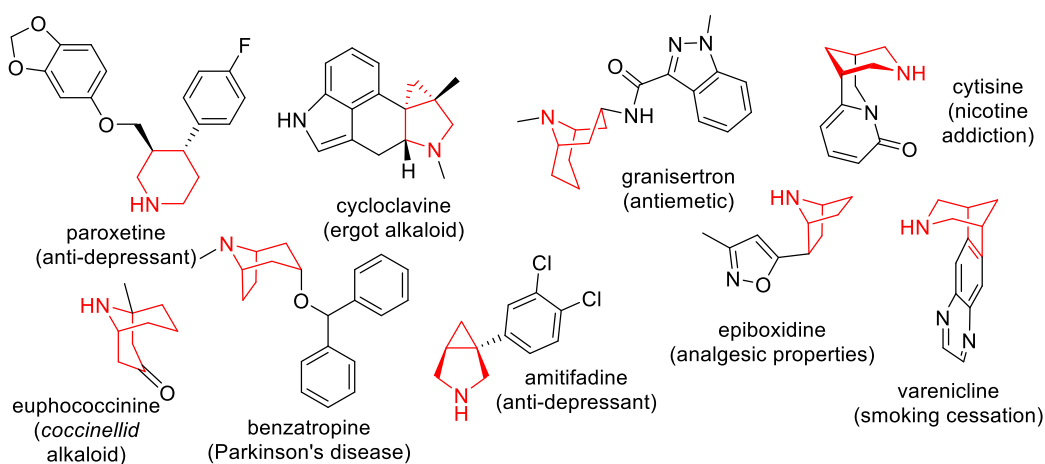
Recent work from our laboratory demonstrated the Pd-catalyzed remote C–H arylation of a variety of alicyclic amines (**Scheme 5.1**).[10] In this system, coordination of Pd to the amine nitrogen and the perfluoroamide directing group enables transannular C–H arylation. Reactivity was first demonstrated on a model system containing the conformationally rigid 3-azabicylco[3.1.0]hexane (explored for fragment synthesis in Chapter 4). High yields of remote C–H arylation products were achieved with catalytic Pd(OAc)$_2$, aryl iodide, and cesium pivalate. Under analogous conditions with excess aryl iodide (neat conditions), the arylation of piperidine and variety of bicyclic amine cores was achieved (**Scheme 5.1**).

Scheme 5.1. First Generation Pd-Catalyzed C(sp^3)–H Arylation of Alicyclic Amines
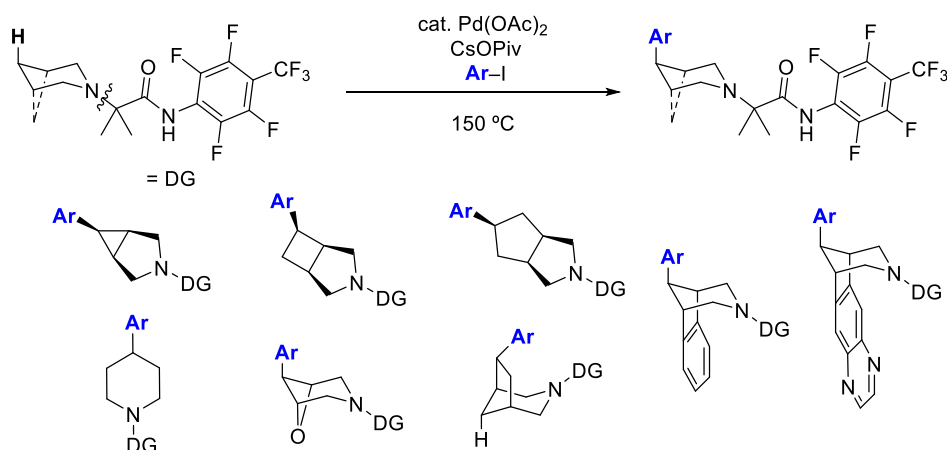
In addition to demonstrating practical applications of the C–H arylation methodology (Chapter 4), we also sought to address key limitations of the first-generation protocol by increasing yields (many of the bicyclic substrates provided arylated products in <50% yield) and expanding the substrate scope to include less reactive classes of bioactive azabicycloalkanes such as the tropane, 7-azanorbornane, and homotropane cores (**Figure 5.1**). Furthermore, we were also interested in incorporating additional functional groups at remote C–H sites by varying nucleophiles and/or oxidants.

At the onset of our studies in Chapter 5, we hypothesized that the low to modest yields with the first-generation system might be due to one or more of the following: (1) high

activation barriers for C–H activation, (2) formation of inactive Pd species via reversible (e.g., product inhibition) and/or (3) irreversible off-cycle pathways (e.g., palladium black). Thus, we hypothesized that the addition of ligands could be used to increase reaction yields and expand the substrate scope. Previous work from our group demonstrated that the addition of ligands can have dramatic impacts on reaction rates and modulate selectivity in other C–H functionalization reactions.[11] Additionally, other groups have successfully utilized ligands in the context of Pd(II)-catalyzed C–H functionalization to (1) enable or improve selectivity (stereoselectivity, **Scheme 5.2a**)[12] (2) enhance reaction rates (**Scheme 5.2b**)[13] and (3) prevent catalyst decomposition (**Scheme 5.2c**)[14] and/or inhibition.[15,16]

Scheme 5.2. Examples of Ligand Enabled Reactivity in Pd(II)-Catalysis[12b,13a,14b]

(a) Enantioselective C(sp^3)-H Arylation
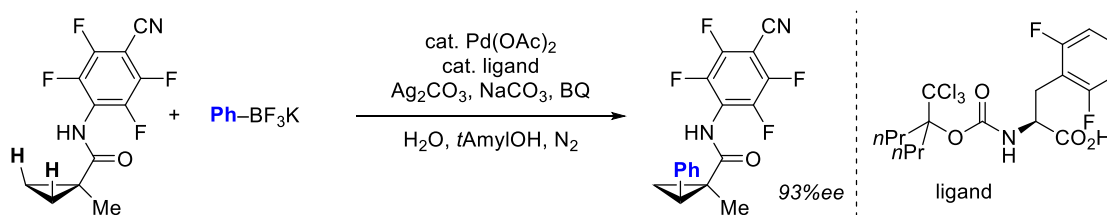
(b) Accelerated C(sp^3)-H Olefination
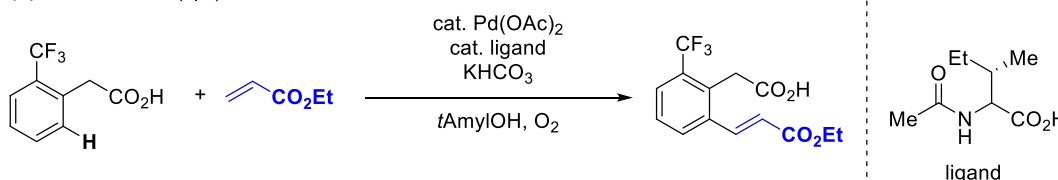
(c) Stabilization of Pd(0) with Pyridine Ligands for C-H Arylation
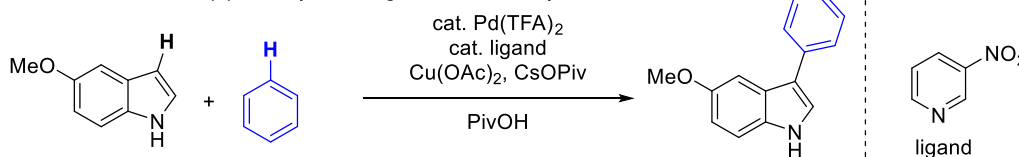
This chapter outlines our use of ligands to address shortcomings associated with our first-generation method for the transannular C–H arylation of alicyclic amines. These efforts led to the discovery of important ligand effects with pyridine-carboxylate and quinoline-

carboxylate ligands that lead to improved yields and substrate scope. To probe the role of the ligand, a series of mechanistic experiments were employed to elucidate the role of ligand potential involvement in C–H activation, product inhibition and/or catalyst decomposition. Together these investigations strongly suggest the ligand serves to enhance catalyst longevity and to restore the activity of deactivated Pd species. Portions of Chapter 5 were completed in collaboration with Dr. Pablo Cabrera and Michael Bellas.[1,17]

5.2. Results and Discussion

Ligand Effects and Reaction Optimization

Our initial studies focused on the benzo-fused 3-azabicyclo[3.2.1.]octane scaffold (**S1**), which is an important bicyclic core present in Pfizer's smoking cessation drug vareniciline and in isotropane alkaloids (explored for cocaine addiction).[18] The first generation conditions required temperatures of 150 ºC and neat phenyl iodide to achieve product **1a** in 46% yield (**Table 5.1**, entry 1). We started by utilizing pyridine-based ligands **L1**-**L5**, which have been shown previously by our group and others to accelerate the C–H acetoxylation of arenes (by altering catalyst resting state) and to enhance site selectivity in Pd-catalyzed arene C–H functionalization.[11] While these ligands did not lead to improved yields, we were encouraged that their presence did not shut down reactivity (**Table 5.1**, entries 2-6).

We next hypothesized that if product inhibition was leading to low yields, the use of bidentate ligands could facilitate product dissociation more readily. Gratifyingly, the use of **L6** led to an ~10% increase in yield, and the use of **L7**-**L9** further improved the yield of **1a**. The pyridine-carboxylate and quinoline-carboxylates **L8** and **L9** provided the most promising improvements (**Table 5.1**). With 5-10 mol% ligand loading, they provided comparable yields of **1a**, with **L9** tolerating a wider range of ligand loadings.

Table 5.1. Evaluation of Ligands for the C–H Arylation of Compound **S1**
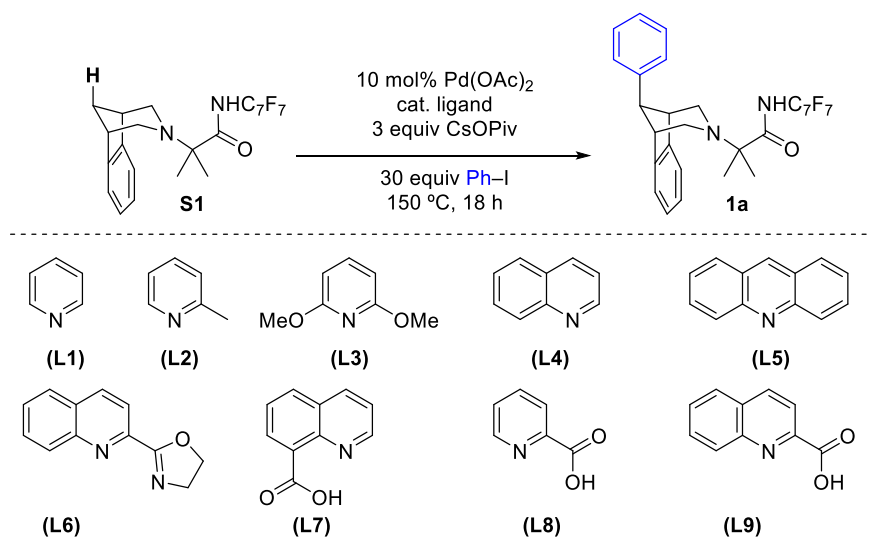
entry	ligand	L (mol %)	conversion **S-1**	yield **1a**
1	--	--	68%	46%
2	**L1**	5	68%	44%
3	**L2**	5	73%	47%
4	**L3**	5	68%	43%
5	**L4**	5	68%	40%
6	**L5**	5	75%	46%
7	**L6**	5	80%	56%
8	**L7**	5	96%	68%
9	**L8**	5	>99%	80%
10	**L8**	10	>99%	78%
11	**L8**	20	26%	24%
12	**L9**	5	>99%	77%
13	**L9**	10	>99%	77%
14	**L9**	20	>99%	85% (82%)[b]

[a] Conditions: **S1** (0.03 mmol, 1 equiv), Pd(OAc)$_2$ (10 mol %), ligand (5-20 mol%), CsOPiv (3 equiv), PhI (30 equiv), 150 ℃. Calibrated GC yields for **1a**. [b] Isolated yield of **1a**

We conducted further optimization with **L9** and found that both temperature and equivalents of phenyl iodide could be significantly lowered in the presence of *t*-amylOH as solvent, while still providing high yields of **1a** and good mass balance (**Table 5.2**). This led to the optimized conditions shown in entry 8, which were conducted at 100 ℃ and with 3 equiv of phenyl iodide (**Table 5.2**). A high yield of **1a** was maintained with 5 mol % **L8**, while a control reaction with no ligand under these conditions afforded a significantly lower yield of 29% (**Table 5.2,** entry 9 and 10 respectively).

Table 5.2. Optimization Table for Compound **S1** with **L9**
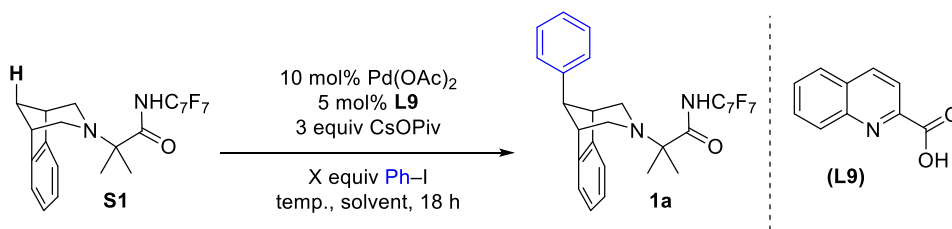
entry	temp.	solvent	Ph–I (equiv)	yield **2a**	conv.
1	150 ℃	neat	30	77%	> 99%
2	120 ℃	neat	30	60%	74%
3	120 ℃	*t*AmylOH	30	87%	> 99%
4	120 ℃	*t*AmylOH	15	85%	> 99%
5	120 ℃	*t*AmylOH	3	87%	> 99%
6	120 ℃	*t*AmylOH	1	79%	95%
7	110 ℃	*t*AmylOH	3	86%	> 98%
8	100 ℃	*t*AmylOH	3	84%	95%
9[b]	100 ℃	*t*AmylOH	3	85%	96%
10[c]	100 ℃	*t*AmylOH	3	29%	42%

[a] Conditions: **S1** (0.03 mmol, 1 equiv), Pd(OAc)$_2$ (10 mol %), quinaldic acid (5 mol %) CsOPiv (3 equiv), PhI (1-30 equiv), 100-150 ℃. Calibrated GC yields for **1a**. [b] Ligand: picolinic acid (5 mol%). [c] No ligand additive.

Application of Ligand Conditions to the Arylation of Alicyclic Amines

Encouraged by the ligand-effects observed for the C–H arylation **S1**, we examined the application of ligands to previously reported substrates, including alicyclic amines that provided both good and low yields (**Figure 5.2**).[10] In many cases, we observed that the addition of **L8** greatly improved the yields of poorly performing substrates such as **S2-S6**. In the case of **2** and **5** an approximate two-fold increase in the yield was observed. While **S7** and **S8** performed similarly to ligand-free conditions, it is important to note that the addition of **L8** was not detrimental to the final yield after 18 h. The C–H arylation of the anti-depressant drug, amitifidine, led to a 10% increase in the yield of product **9**. We were pleased that a simple adjustment to our previous protocol could lead to dramatically increased yields. Next, we explored the functionalization of additional bicyclic amine cores of high relevance to medicinal chemistry.

Figure 5.2. Demonstrating Ligand Effects on Previously Reported Substrates[10]

2
76%[a] (33%[b])

3
86%[a] (62%[b])

4
72%[a] (35%[b])

5
64%[a] (34%[b])

6
81%[a] (45%[b])

7
60%[a] (55%[b])

8
75%[a] (74%[b])

9
51%[a] (40%[b])
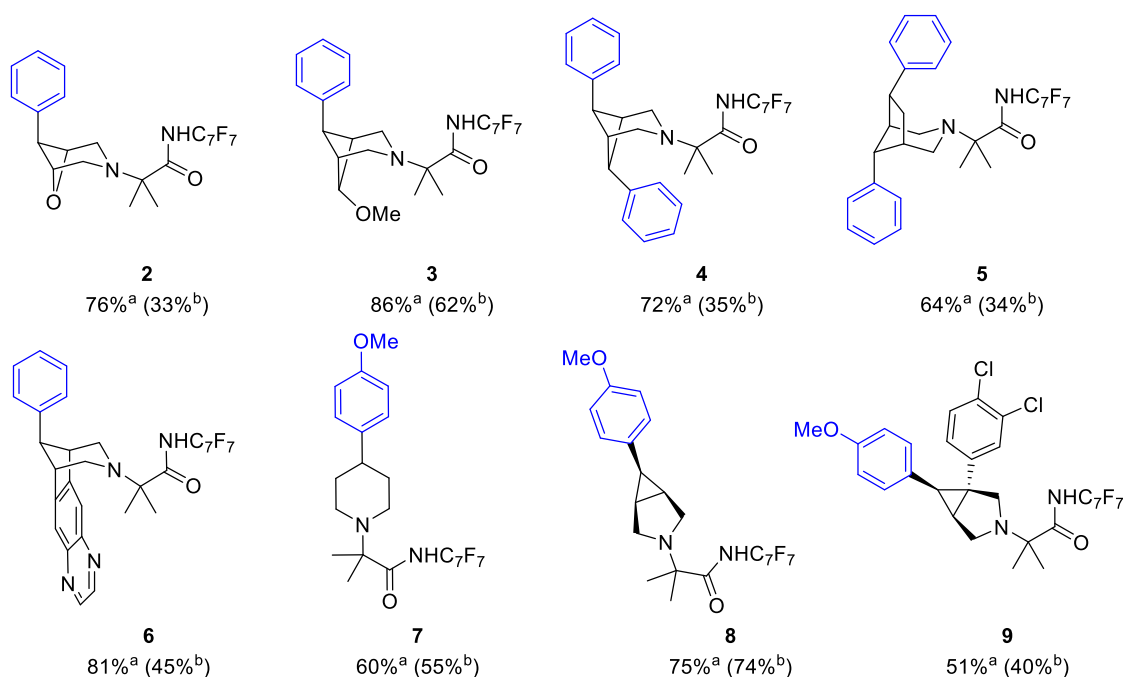
[a] Reaction conditions in ref. 10 with **L8** (5 mol%) [b] Reported yield in ref. 10

More specifically, we were interested in tropane and other azabicycloalkaloids containing substitution at the carbon adjacent to the nitrogen atom. These scaffolds have shown promise as treatments for cocaine addiction, pain, and Parkinson's disease.[19] Under our first-generation conditions with neat aryl iodide, a significant amount of **S10** (>50%) remained after 18 h, and only trace amounts of arylated product **10a** was observed by GC (<5% yield, uncalibrated, **Scheme 5.3**).

Scheme 5.3. Arylation of Tropane under First Generation Conditions

10 mol% Pd(OAc)$_2$
3 equiv CsOPiv
45 equiv Ph–I

tAmylOH, 150 °C, 18 h

S10

10a
<5% desired product observed
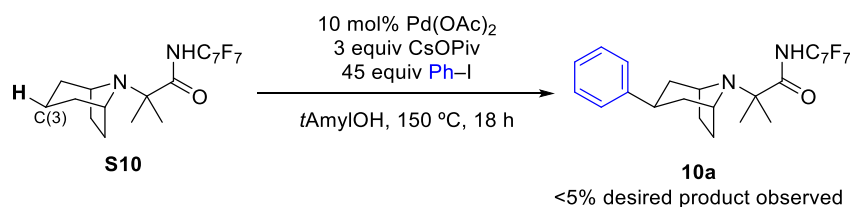
As such, we conducted optimization studies with **S10** and found that the addition of ligand **L8** led to high conversions of **S10** and greatly improved yields of the C-3 arylated

product **10a** (**Table 5.5** in experimental). Attempts to run the reaction with lower equivalents of phenyl iodide and solvent led to lower conversion and decreased formation of **10**. With these conditions in hand, a variety of aryl iodides with heteroatom functionality could be coupled in moderate to good yields (**Figure 5.3**, **10b-10k**).

Figure 5.3. Scope of Aryl Iodide Functionalization of the Tropane Core with Picolinic Acid

10b
49%

10c
60%

10d
40%

10e
47%

10f
46%

10g
47%

10h
44%

10i
34%

10j
42%

10k
54%
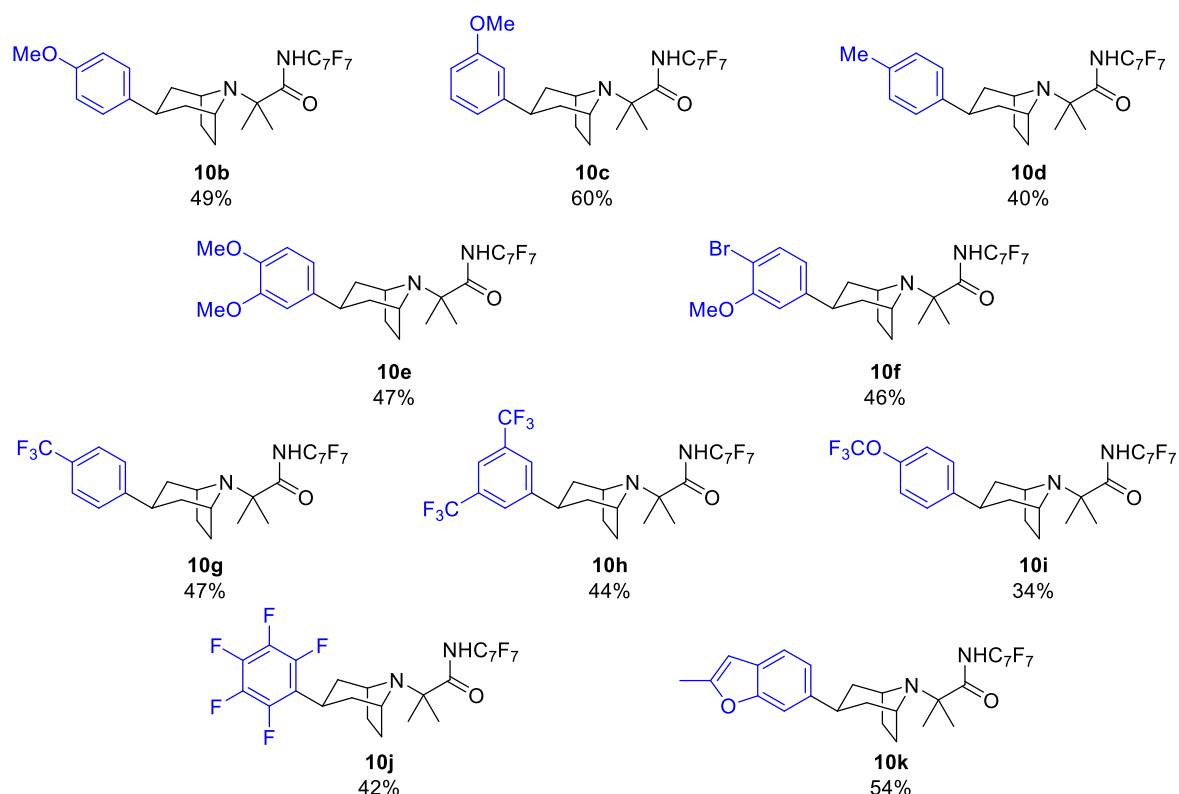
Reaction conditions: substrate **S10** (0.1 mmol, 1 equiv), Pd(OAc)$_2$ (0.01 mmol, 10 mol %), CsOPiv (0.3 mmol, 3 equiv), **L8** (0.005 mmol, 5 mol%), neat Ar–I, 140 °C, 18 h. Isolated yields. See details in experimental section.

We did observe that the use of neat aryl iodide led to incompatibilities with the Pd catalyst and difficulties with product isolation in some cases. For example, 4-iodobenzonitrile afforded poor results, presumably due to competing coordination of the cyano functional group present in solvent quantities to Pd. Similarly, poor reactivity was observed with 3-hydroxy iodobenzene, as well as 2-iodothiophene, 3-iodopyridine and 2-fluoro-3-iodopyridine. In contrast, 4-iodoacetophenone did afford the desired C-3 arylation product, as observed by GC-MS. However, all attempts to purify this product away from other minor side-products as well

as from the aryl iodide by silica gel chromatography were unsuccessful, and thus the product was not pursued further. Future studies should focus on efforts to lower the equivalents of aryl iodide, which should enable the incorporation of more coordinating functional groups and should also facilitate isolation of functionalized products.

We also synthesized two tropane derivatives, **S11** and **S12**, which underwent arylation smoothly, demonstrating tolerance for functionality (desaturation and substitution) (**Figure 5.4**). The protected azabicyclo[3.3.1]nonane, led to good yields of **13**, while preserving the ketal protecting group. In the case of the azabicyclo[2.2.1]heptane, the core of epibatidine, monoarylated product **14** was isolated in 42% yield.[20]

Figure 5.4. Scope of Azabicycloalkanes with **L8**

| **11** | **12** | **13** | **14** |
| 50% | 40% | 54% | 42% |
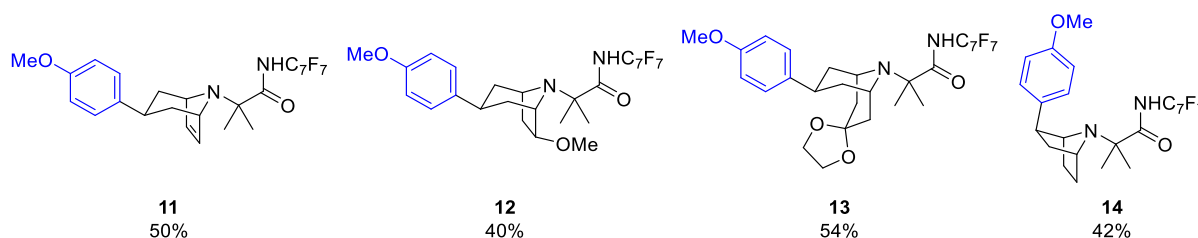
Reaction conditions: substrate **S11-S14** (0.1 mmol, 1 equiv), Pd(OAc)$_2$ (0.01 mmol, 10 mol %), CsOPiv (0.3 mmol, 3 equiv), **L8** (0.005 mmol, 5 mol%), neat 4-iodoanisole, 140 ºC, 18 h.

Mechanistic Studies to Probe Ligand Effects

Following our studies on reaction scope with **L8** and **L9**, we sought to understand the role of ligand in improving these reactions. Based on the enhanced yields of arylated product, we hypothesized that the ligand could be serving multiple roles within the catalytic cycle. These could be divided into two general roles: (1) the ligand could be bound to the Pd catalyst during key steps of the catalytic cycle and thus enhance the rate and/or selectivity and/or (2) the ligand could bind to the Pd catalyst at points outside of the catalytic cycle to prevent reversible or irreversible catalyst deactivation, including pathways such as product inhibition, formation of other off-cycle Pd-intermediates, or formation of Pd black. To probe which role(s) the ligand

was playing in the reaction, we carried out a series of mechanistic studies to study the C–H activation step, possible product inhibition, and possible catalyst decomposition.

We began by quantifying the initial rate associated with product formation from **S1** with and without the presence of **L9**. Based on the two-fold increase in rate with 5 mol% **L9** ($k_{obs,ligand-free} = 6.2 \times 10^{-4}\, M \cdot s^{-1}$ and $k_{obs,\mathbf{L9}} = 1.3 \times 10^{-3}\, M \cdot s^{-1}$), we hypothesized that the ligand could be lowering the barrier for the rate determining step (RDS) in the reaction (**Figure 5.5**). Unpublished preliminary KIE studies from our laboratory with **S7** indicated that C–H activation is likely the RDS. Furthermore, recent DFT calculations from the Zimmerman group concluded that C–H activation is turnover limiting and has the highest relative barrier of all the computed steps for the activation and functionalization of **S7**.[21]

Figure 5.5. Initial Rates of **S1** with and without **L9**
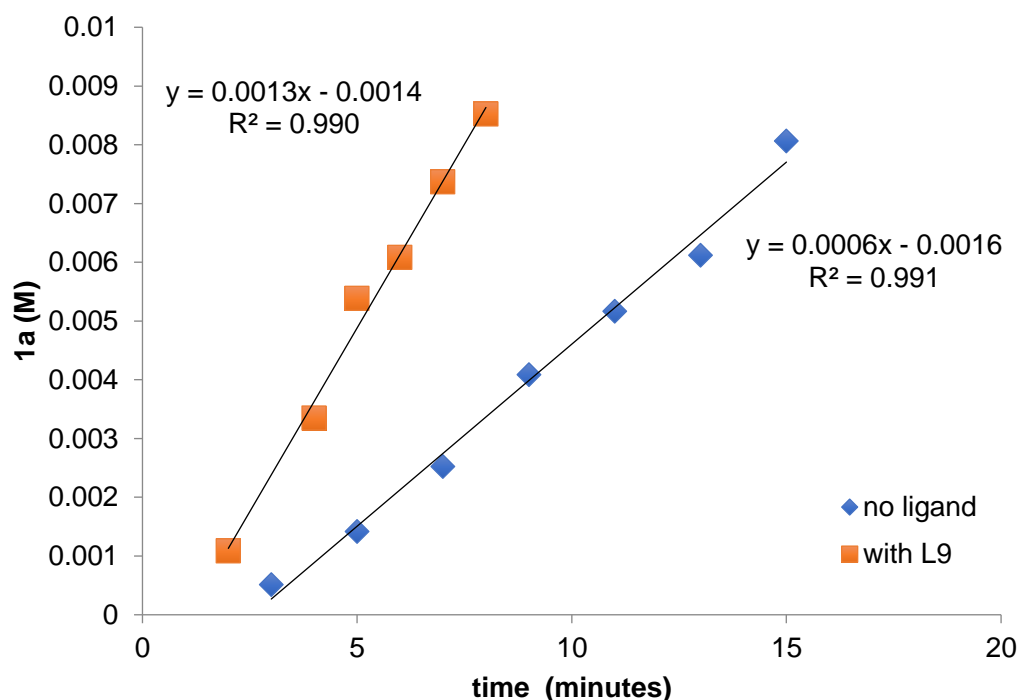
Conditions red curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), **L9** (0.006 M), 0.25 mL *t*AmylOH, 100 ºC. Conditions blue curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), 0.25 mL *t*AmylOH, 100 ºC.

This led us to question whether the ligand was intimately involved in the C–H activation step of **S1** under our second-generation conditions. To probe this possibility, we synthesized *d₅*-**S1** by following a published route by Pfizer Global Research and Development in Groton, CT.[22] The procedure was modified to include deuteration steps early in the synthesis to arrive at the final product *d₅*-**S1** (see experimental for more detail). According to Simmons and Hartwig, independent rate studies with proteo- and deutero- substrates can provide conclusive data on whether C–H bond cleavage is turnover limiting.[23,24] First, we obtained the initial rates for the formation of **1a** and *d₅*-**1a** from **S1** and *d₅*-**S1** under standard conditions *without ligand* and observed a primary KIE of 3.3. With the addition of 5 mol % **L9**, we observed an extremely similar primary KIE value of 3.2 (**Scheme 5.4**). Together, these experiments demonstrate that C–H bond activation is rate limiting both with and without ligand. Furthermore, because the value of the primary KIE is essentially the same under both conditions, it also suggests that **L9** does not significantly alter the transition state of the C–H bond activation step.[25]

Scheme 5.4. Kinetic Isotope Effect for **S1** and *d₅*-**S1** with and without **L9**

Next, we were interested in examining possible catalyst deactivation pathways. To this end, we conducted an extended reaction profile of **S1** without ligand and observed that the reaction stalls after 480 min, reaching a maximum 29% yield of **1a** (0.035 M). In contrast, the

reaction with 5 mol % **L9** displays a higher rate of arylation over the course of the time study and does not stall, providing a final yield of 84% (**Figure 5.6**). Based on these results, we hypothesized that the formation of product could be leading to reaction inhibition and that the strongly coordinating **L9** could be facilitating the exchange of **1a** for **S1** on the Pd catalyst.
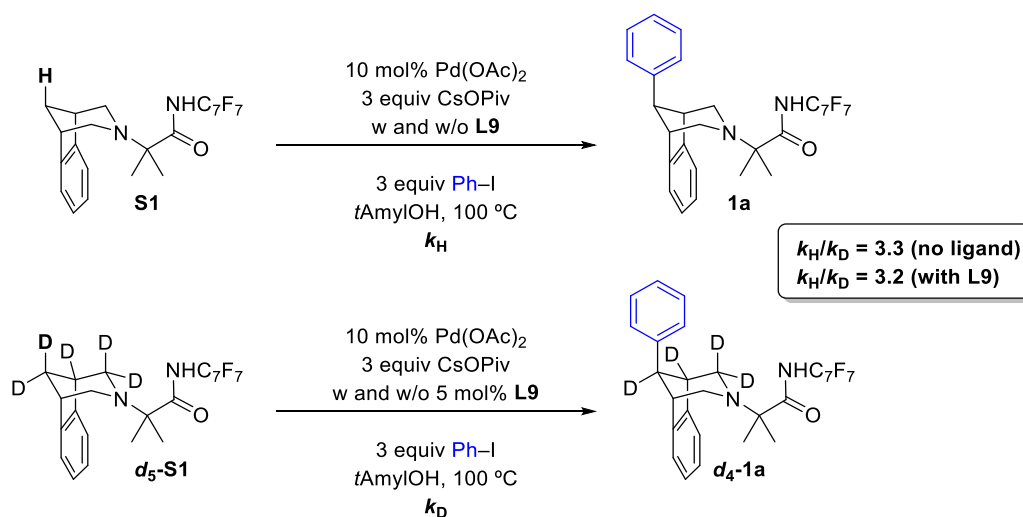
Figure 5.6. Reaction Profile of **S1** with and without **L9**
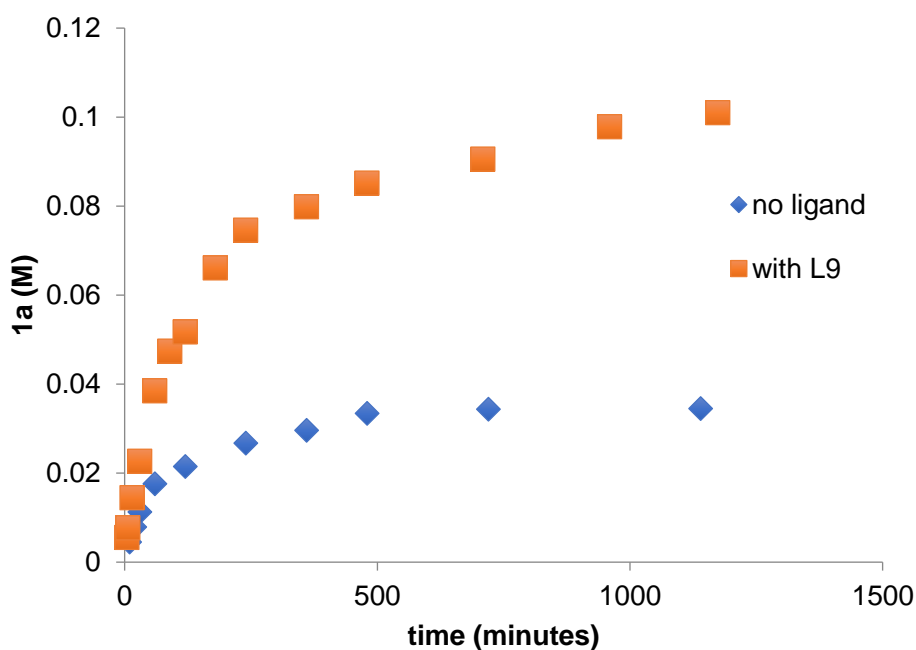
Conditions red curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), **L9** (0.006 M), 0.25 mL tAmylOH, 100 ℃. Conditions blue curve: **S1** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), 0.25 mL tAmylOH, 100 ℃.

To probe the possibility of product inhibition, we conducted two sets of experiments that involved addition of **1b** at the onset of the reaction. This allowed us to differentiate between the product **1b** added initially and product **1a** formed during the reaction. By conducting the reaction to low conversions, we could determine whether the presence of **1b** impacts the formation of **1a**.[15] As shown in **Table 5.3**, the addition of **1b** (0.1 – 0.75 equiv relative to **S1**) did not impact the yield of **1a** at this early time point (45 min). Similarly, with the addition of 5 mol % **L9**, the yield of **1a** remained unaffected by the presence of **1b**. Initial rates studies of the reaction of **S1** in the presence and absence of added **1b** corroborated the data in **Table 5.3** (see experimental section for more detail). Together, these experiments imply that product

inhibition is most likely not occurring during the C–H arylation of **S1**. However, we still lacked

a good explanation for the difference in initial rates upon the addition of **L9** (**Figure 5.5**) as

well as for the higher yields of **1a** at early time points (**Table 5.3**). This warranted further

investigation into additional catalyst deactivation pathways.

Table 5.3. Testing for Product Inhibition by Addition of **1b** to the Arylation of **S1**
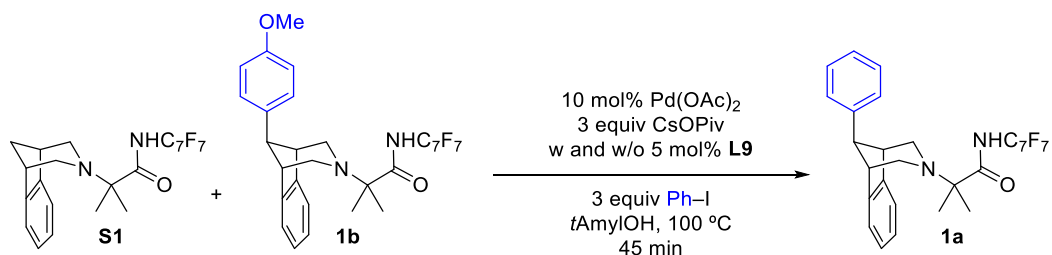
entry	[1b] (M)	1b (equiv)	yield 1a (no ligand)	yield 1a (5 mol % L9)[b]
1	0	0	13%	28%
2	0.012	0.1	13%	29%
3	0.03	0.25	13%	30%
4	0.06	0.50	13%	28%
5	0.09	0.75	11%	28%

[a] Conditions**: 1** (0.03 mmol, 1 equiv, 0.12 M), **2b** (0, 0.012, 0.03, 0.06 or 0.09 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), 0.25 mL tAmylOH, 100 ºC.[b] Reaction with **L9** (0.006 M).

If catalyst deactivation were reversible, the addition of **L9** at the time when the

formation of **1a** begins to stall should lead to a change in the reaction profile. To test this

hypothesis, we conducted our standard ligand-free reaction and added **L9** after 240 minutes.

The addition of **L9** led to a reaction profile that diverged drastically from the ligand-free profile

(**Figure 5.7**). We observed an increase in the yield of **1a** leading to a final yield of 58%. While

this yield is not as high as that in the reaction conducted with **L9** at the onset (**Figure 5.6**), the

experiment provides preliminary evidence that the ligand plays an important role in "re-

activating" off-cycle Pd catalyst species. This a possible explanation for the increased yields

of **1a** with **L9** in the above studies.

Figure 5.7. Catalyst Recovery Experiment with **L9**[a]
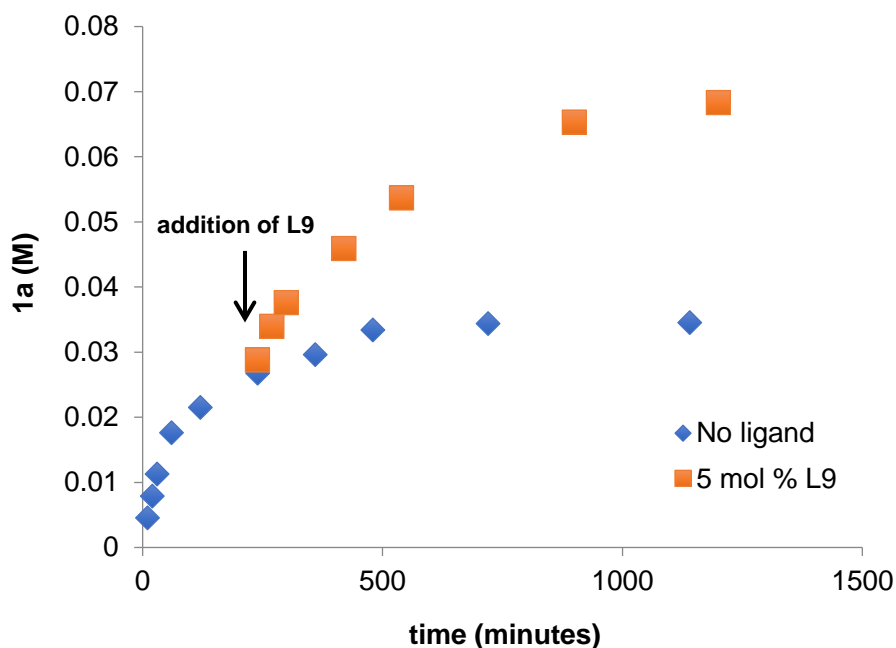
^{a} Conditions blue curve**: S1** (0.03 mmol, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), PhI (0.36 M), 0.25 mL tAmylOH, 100 ºC, 4 hours. ^{b} Conditions red curve: At 240 minutes, add **L9** (0.006 M) and heat to 100 ºC.

To further confirm the formation of deactivated Pd species, visual inspection of the reactions with **S1** in the absence of ligand revealed the formation of a dark precipitate within 90 minutes (**Scheme 5.5**, step 1). ICP-OES analysis of the precipitate showed the presence of both Pd and Cs. While ^{1}H NMR and ESI+ mass spectrometry indicated the presence of **1a**, the exact structure of the Pd-species remained inconclusive. Nevertheless, this observation led us to question whether the precipitate contained off-cycle palladium species. To test for this possibility, the dark precipitate was resubjected to the reaction conditions with 4-iodoanisole in the presence and absence of **L9**. In the presence of ligand a 47% yield of product **1b** was obtained, while a significantly lower yield of 10% was observed in the absence of ligand (**Scheme 5.5**, step 2). This suggests that a small amount of active Pd is present in the precipitate, and that the addition of **L9** plays a role in "re-activating" off-cycle Pd-species from the insoluble precipitate.

Scheme 5.5. Precipitate Formation and Catalyst Recovery with Ligand
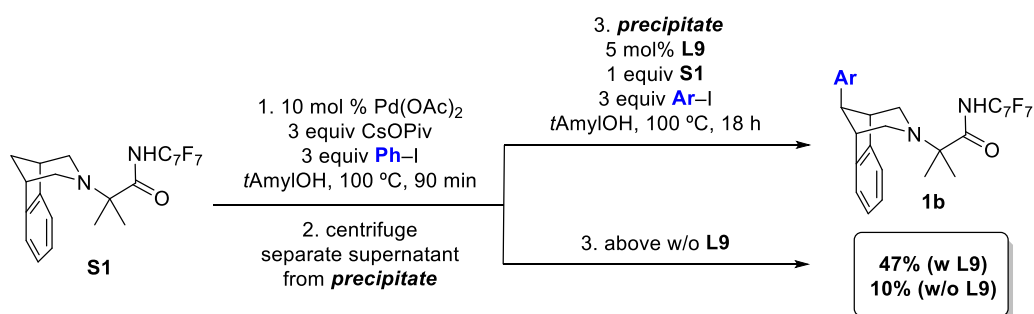
Conditions**:** **S1** (0.03 mmol), precipitate, CsOPiv (0.09 mmol), with or without **L9** (0.0015 mmol), Ar–I = 4-OMe(C$_6$H$_4$)I (0.09 mmol), 0.25 mL *t*AmylOH, 100 ºC, 18 hours

Incorporating Additional Functional Groups

Another important advancement would be the development of conditions to incorporate different functional groups in these transformations. During our above studies on ligand effects with **S10**, trace amounts of byproducts were observed by GC-MS. Although we were unable to cleanly isolate the small of amounts of side-products being formed during reactions, we were aware that the product distribution could differ depending on the nature of the aliphatic amine. Additionally, we hypothesized the pivalate anion from the base could potentially act as a nucleophile to provide C–O bond forming products.

Scheme 5.6. Incorporation of Multiple Functional Groups
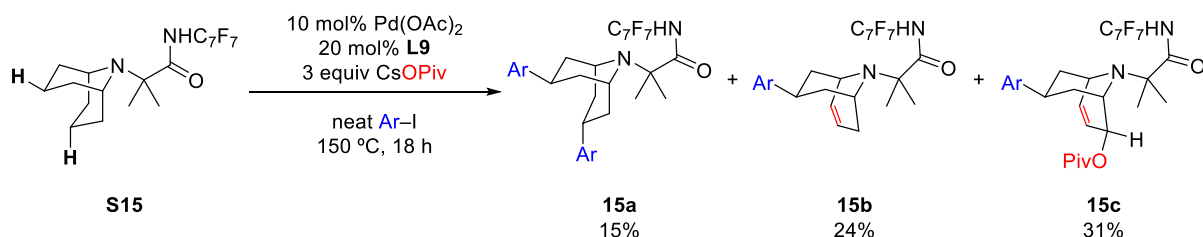
When **S15** was subjected to our reaction conditions, we expected to observe diarylation and possible formation of similar side-products observed with **S10**. In addition to the diarylated product **15a** (formed in 11% yield), we also observed the formation of **15b** and **15c** (**Scheme 5.6**). The product **15b** represents a single C–H arylation, along with a second C–H functionalization event and likely β–H elimination to yield an alkene on the second ring.

Control experiments demonstrate that subjecting **15b** to the reaction conditions leads to allylic oxidation to form **15c**. Follow-up studies should be conducted to probe whether additional cyclic amines scaffolds can undergo multiple C–H bond functionalization transformations.

Scheme 5.7. Exclusive Formation of a C–O bond or a C–C bond in **S16**
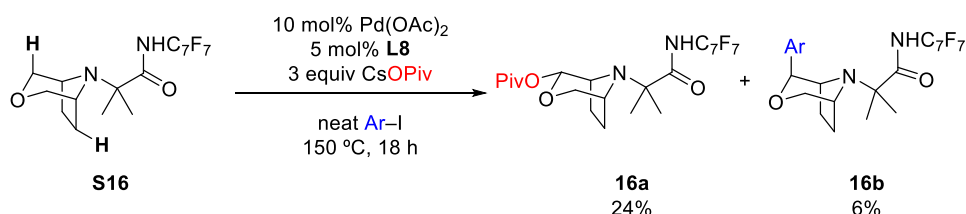
Based on the reactivity of **S14**, there are two possible C–H sites that could be functionalized on **S16**. Under our second-generation conditions, functionalization occurred exclusively at the remote C–H adjacent to the oxygen atom to provide **16a** and **16b**, which were isolated in 24% and 6% yield, respectively. In contrast to **S15** wherein arylation occurred at least once in all the products, **S16** led to the selective formation of either a C–O bond product **16a** or a C–C bond product **16b** (**Scheme 5.7**). Conditions that lead to **16a** should be further investigated in the context of additional oxidants and heteroatom nucleophiles (e.g. nitrogen, sulfur, and halogen containing nucleophiles). NMR spectroscopy and X-ray crystallography were used to determine the identity and conformation of the products from **S15** and **S16**.

Scheme 5.8. Selective Incorporation of Remote Alkene
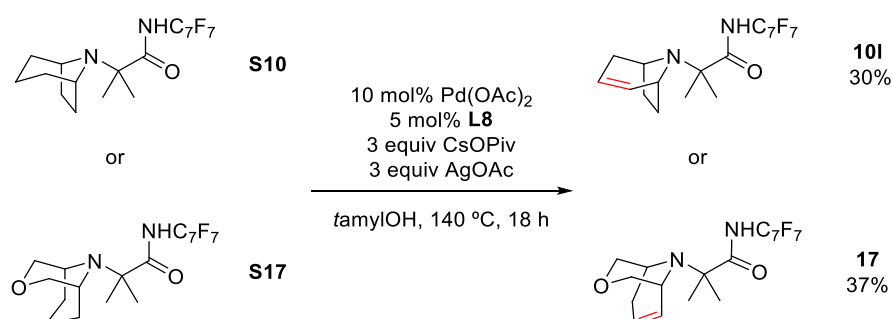
Reaction conditions: substrate (0.1 mmol, 1 equiv), Pd(OAc)$_2$ (0.01 mmol, 10 mol %), CsOPiv (0.3 mmol, 3 equiv), **L8** (0.005 mmol, 5 mol%), AgOAc (0.3 mmol, 3 equiv), 0.25 mL *t*AmylOH, 140 ºC, 18 h. Isolated yields. See details in experimental section.

In addition to the discovery of this C–O bond forming reaction, we were also interested in selective C–H functionalization that leads to a net desaturation of the azabicycloalkane scaffold.[26] We hypothesized that the formation of the alkene was occurring through a Pd(II/0) catalytic cycle, and that the aryl iodide could be replaced with a different 1 or 2 electron oxidant utilized in Pd catalyzed C–H functionalization reactions.[27] Initial studies with **S10** and **S17** and 3 equivalents of AgOAc led to the selective formation of **10l** and **17**, albeit in moderate isolated yields (**Scheme 5.8**). Further investigation showed that other bases (e.g., CsOAc, KOPiv, KOAc, and NaOPiv) provided **10l** in diminished yields compared to CsOPiv. Replacing *t*-amylOH with nitrile solvents, DMSO, and THF also led to a decrease in yield. A range of quinone oxidants were investigated, with 2,6-dichloro-1,4-benzoquinone providing a 44% GC yield of **10l** (**Table 5.4**, entry 8).[17] Further studies are necessary to optimize and probe the generality of this protocol in the context of mono- and bicyclic aliphatic amines.

Table 5.4. Oxidant Screen for Remote Alkene Formation from **S10**[a, 17]
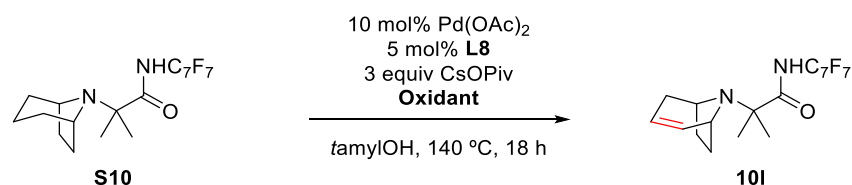
entry	oxidant	(equiv)	yield **10l**[c]	conv (%)
1	AgOAc	3	18%	85%
2	CuCl$_2$	3	6%	87%
3	Oxone	3	20%	45%
4	1,4 benzoquinone	3	8%	41%
5	2,6-Di-*tert*-butyl-1,4 benzoquinone	1.5	11%	69%
6	Tetrachloro-1,4 benzoquinone	1.5	4%	15%
7	2,6-Dichloro-1,4 benzoquinone	1.5	35%	47%
8[b]	2,6-Dichloro-1,4 benzoquinone	1.5	44%	51%

[a] Conditions**: S10** (0.03 mmol, 1 equiv, 0.12 M), Pd(OAc)$_2$ (0.012 M), CsOPiv (0.36 M), **Oxidant** (0.045 or 0.09 M), **L8** (0.006 M), 0.25 mL *t*AmylOH, 100 ºC. [b] Reaction with **L9** (0.012 M) [c] Yields and conversions based on calibrated GC-FID curve of **S10** and **10l**

5.3. Conclusion and Future Outlook

This chapter describes ligand effects on the Pd-catalyzed transannular C–H arylation of alicyclic amines, with a focus on extending the scope of azabicylcoalkane cores to tropanes, homotropanes, and 7-azanorbornanes. The addition of catalytic 2-picolinic acid (**L8**) or 2-quinalidic acid (**L9**) led to significant improvements in yields of the arylated products. The beneficial role of ligand in these reactions was studied through a series of mechanistic investigations. The data suggest that the ligand is most likely not involved in the rate determining C–H activation step; furthermore, it does not appear to be preventing product inhibition. Instead, catalyst recovery experiments suggest the ligand serves to regenerate active catalyst from insoluble, off-cycle Pd species, thereby improving the overall efficiency of arylation. Preliminary studies on the formation of minor side products led us to discover new types of bond-forming reactions that generate C–O bonds and alkenes. Future investigations should further pursue these transformations in order to increase the repertoire of remote functionalization.

Additionally, our group and others have a longstanding interest in understanding the fundamental mechanistic steps of catalytic cycles in order to inform further developments in transition metal catalysis. Ongoing work in our laboratory is focused on understanding the mechanism of transannular C–H functionalization through the synthesis of catalytically relevant Pd complexes. Information regarding the different steps within the catalytic cycle is expected to lead to the development of milder reactions as well as to new methods for the incorporation of additional functional groups. The development of second-generation directing groups should focus on scaffolds that are easily installed, enable C–H functionalization with high efficiency, and can be easily cleaved under mild conditions.

5.4. Experimental Procedures and Characterization of Compounds

5.4.1 Materials and Methods

Materials and Methods

All reagents were obtained from a commercial vendor (Aldrich, CombiBlocks, Oakwood, AstaTech, Synthonix, Enamine, Manchester Organics, Carbosynth, Pressure Chemicals, Matrix, SantaCruz Biotech, PharmaBlock, Ark Pharm, or Ontario Chemicals) and were used without further purification unless otherwise stated. Reagents were stored under ambient conditions unless otherwise stated. The solvent *tert*-amyl alcohol was stored over activated molecular sieves. The manipulation of solid reagents was conducted on the benchtop unless otherwise stated. Reactions were conducted under an ambient atmosphere unless otherwise stated. Reaction vessels were sealed with either a septum (flask) or a Teflon lined cap (4-mL or 20-mL vial). Reactions conducted at elevated temperatures were heated on a hot plate using an aluminum block. Temperatures were regulated using an external thermocouple. For reactions that were heated in excess of the ambient boiling point of the solvent (*i.e. tert*-amyl alcohol heated to 140 ℃), the cap of the sealed vial was re-tightened after 5 minutes of heating. For TLC analysis, R_f values are reported based on normal phase silica plates with fluorescent indicator and sample detection was conducted based on quenched fluorescence at 254 nm or $KMNO_4$ stain.

Instrumental Information

NMR spectra were obtained on Varian 400 MHz, Varian 500 MHz, or Varian 700 MHz NMR spectrometers. ^{1}H, ^{2}H and ^{13}C NMR chemical shifts are reported in parts per million relative to TMS with the residual solvent peak (most commonly $CDCl_3$) used as an internal reference (δ 7.26 for ^{1}H, ^{2}H NMR and δ 77.16 for ^{13}C NMR for $CDCl_3$). ^{19}F NMR spectra were referenced to the solvent lock. ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt) and multiplet (m). High resolution mass spectra were obtained at the University of Michigan core facility. Flash chromatography was conducted on a Biotage Isolera One auto chromatography system using preloaded high performance silica gel columns (10 g, 25 g, 50 g, or 100 g as appropriate). GC-FID was conducted on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl/95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 µm df) column. All stock solutions were made using volumetric glassware. Melting points were obtained on an OptiMelt

automated melting point system. Ligand additives were weighed on a Sartorius ME36S microgram analytical balance unless otherwise stated.

5.4.2 Synthesis and Characterization of Substrates for Ligand Promoted Functionalization
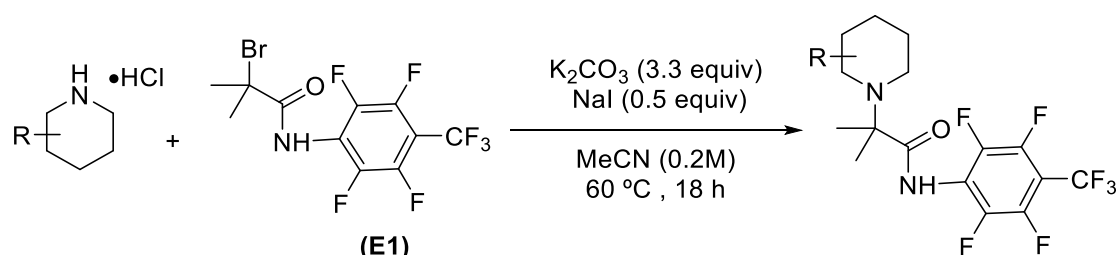
General Procedure A: A 20 mL scintillation vial was charged with the corresponding hydrochloride salt of the azabicycloalkane (2.5 mmol, 1 equiv), α-bromo methylpropanamide **E1** (955 mg, 2.50 mmol, 1 equiv), K$_2$CO$_3$ (1.1 g, 8.25 mmol, 3.3 equiv), and NaI (188 mg, 1.25 mmol, 0.5 equiv). Anhydrous acetonitrile (12 mL, 0.2 M) was added. The vial was equipped with a stirbar, sealed with a Teflon-lined screw cap, and heated to 60 ºC for 18 h. The reaction was cooled to room temperature, diluted with EtOAc (~5 mL), and filtered through a pad of silica gel using 100% EtOAc (~50 mL). The filtrate was concentrated under reduced pressure. Final purification via silica gel column chromatography (gradient elution from 0% to 20% EtOAc in hexanes) afforded product. See each substrate for specific details.

Compound (E1):
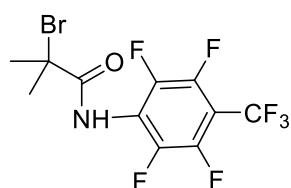
Compound **E1** was synthesized using 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline and 2-bromoisobutyryl bromide following a literature procedure.[10]

Compound (S1):
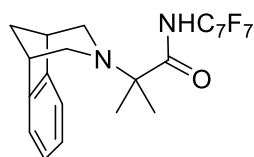
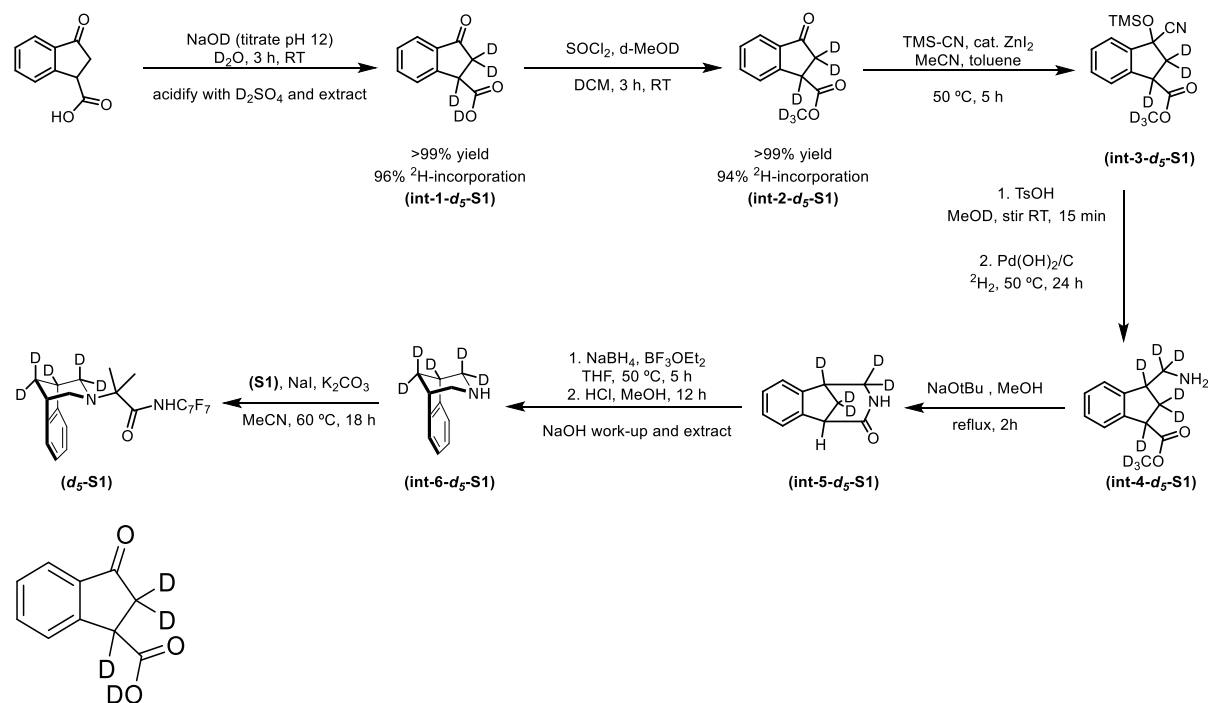Compound **S1** was isolated in 85% yield as a white solid following **general procedure A**. Product characterization matches with previous literature report. [10]

Compound (*d₅*-S1):

int-1-*d₅*-S1

A 20-mL scintillation vial was charged with solid 3-oxo-2,3-dihydro-1*H*-indene-1-carboxylic acid (500 mg, 2.83 mmol) and D_2O (10 mL). To this solution, dropwise NaOD (30% in D_2O) was added at 0 °C to a pH 12-13. The reaction was warmed to room temperature and allowed to stir for 3 hours. The reaction was quenched with dropwise addition of D_2SO_4 at 0 °C to a pH 2–3. The reaction mixture was extracted with DCM (3 x 75 mL), dried over Na_2SO_4, decanted, and the volatiles were removed by rotary evaporation, affording compound **int-1-*d₅*-S1** in >99% yield as an off-white solid that was used without further purification (96% deuterium incorporation by ^{1}H NMR).

Isolated Yield: >99%
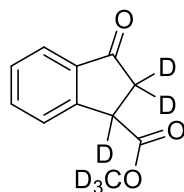
HRMS: ESI⁻ (m/z): [M-H]⁻ calcd for $C_{10}H_4D_3O_3$: 178.0589; found: 178.0588.

^{1}H NMR (CDCl₃, 700 MHz): δ 7.79 (d, *J* = 7.7, 1H), 7.76 (d, *J* = 7.7, 1H), 7.66 (t, *J* = 7.7, 1H), 7.48 (t, *J* = 7.7, 1H).

^{2}H NMR (CDCl₃, 700 MHz): δ 4.34 (br s, 1D), 3.13 (br s, 1D), 2.90 (br s, 1D).

^{13}C NMR (CDCl₃, 176 MHz): δ 204.1, 177.5, 150.5, 136.5, 135.3, 129.2, 126.8, 124.2, 43.1, 38.7.

Note: J_{C-D} were not assigned, the incorporation of deuterium was confirmed by ^{2}H NMR and HRMS.

int-2-*d₅*-S1

A 20-mL scintillation vial was charged with solid **int-1-*d₅*-S1** (485 mg, 2.69 mmol) and DCM (27 mL). Thionyl chloride (0.39 mL, 5.38 mmol) was added dropwise at 0 °C, followed by *d₄*-MeOD (1.09 mL, 26.9 mmol), and warmed to room temperature. The reaction was stirred for 3 hours at room temperature. The volatiles were removed, leading to quantitative conversion to compound **int-2-*d₅*-S1** as a yellow oil. The intermediate was used without further purification (94% deuterium incorporation by ^{1}H NMR).

<u>HRMS</u>: ESI[+] (m/z): [M+H][+] calcd for $C_{11}H_5D_6O_3$: 197.1079; found: 197.1076.

^{1}H NMR (CDCl₃, 700 MHz): δ 7.78 (d, J = 7.7, 1H), 7.70 (d, J = 7.7, 1H), 7.64 (t, J = 7.7, 1H), 7.46 (t, J = 7.7, 1H).

^{2}H NMR (CDCl₃, 700 MHz): δ 4.30 (br s, 1D), 3.77 (br s, 3D), 3.13 (br s, 1D), 2.87 (br s, 1D).

^{13}C NMR (CDCl₃, 176 MHz): δ 204.3, 172.4, 151.2, 136.6, 135.1, 129.0, 126.6, 124.1, 52.1, 43.3, 39.1.

Note: J_{C-D} were not assigned, the incorporation of deuterium was confirmed by ^{2}H NMR and HRMS.

Compounds int-3-*d₅*-S1 through int-6-*d₅*-S1: Intermediates **int-3-*d₅*-1** through **int-6-*d₅*-1** were prepared following a reported literature procedure.[22] Note: For the synthesis of **int-4-*d₅*-1** (hydrogenation step), D₂ gas (3.6 bar) was employed instead of H₂.
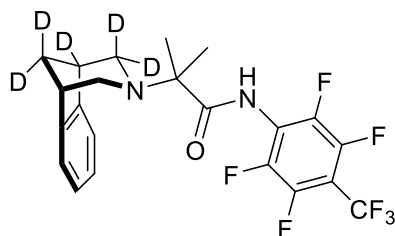
***d₅*-S1**

Compound ***d₅*-S1** was isolated as a white solid using **general procedure A** (90% deuterium incorporation by ^{1}H NMR) and purified by column chromatography (silica gel; 0% EtOAc to

20% EtOAc in hexanes). Collection of fractions containing product showed minor impurities by NMR and the product was further purified by subsequent column chromatography (0% to 5% THF in hexanes).

Isolated Yield: 54% yield (over seven steps)

R$_f$: 0.24 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{22}H_{15}D_5F_7N_2O$: 466.1772; found: 466.1758.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.49 (br s, 1H), 7.16 (multiple peaks, 2H), 7.07 (multiple peaks, 2H), 3.21 (m, 1H), 2.79 (m, 1H), 2.69 (m, 1H), 1.21 (s, 6H).

^{2}H NMR (CDCl$_3$, 700 MHz): δ 3.21 (br s, 1D), 2.79 (br s, 1D), 2.69 (br s, 1D), 2.30 (br s, 1D), 1.73 (br s, 1D).

^{13}C NMR chemical shifts were not assigned due to complex J_{C-D} and J_{C-F} splitting. The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 377 MHz): δ –56.02 (t, J = 21.7 Hz, 3F), –141.46 (m, 2F), –143.58 (m, 2F).

Compound (S2):
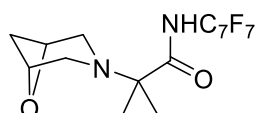
Compound **S2** was isolated in 59% yield following a previous literature report.[10]

Compound (S3):
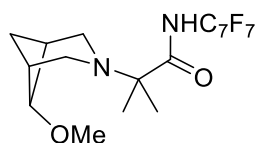
Compound **S3** was isolated in 33% yield following a previous literature report.[10]

Compound (S4):
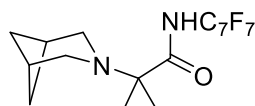
Note: Reaction was heated to 75 ºC for 6 hours. Compound **S4** was isolated in 31% yield as a white solid following **general procedure A**. Product characterization matches with previous literature report.[10]

Compound (S5):
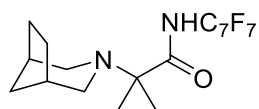
Compound **S5** was isolated in 93% yield following a previous literature report.[10]

Compound (S6):
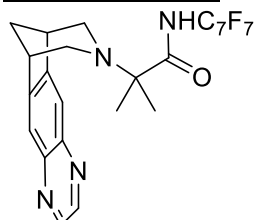
Compound **S6** was isolated in 81% yield following a previous literature report.[10]

Compound (S7):
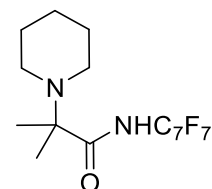
Compound **S7** was isolated in 84% yield following a previous literature report.[10]

Compound (S8):
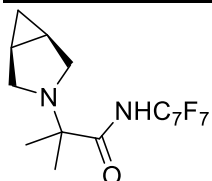
Compound **S8** was isolated in 81% yield following a previous literature report.[10]

Compound (S9):
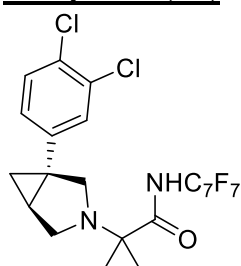
Compound **S9** was isolated in 87% yield following a previous literature report.[10]

Compound (S10):
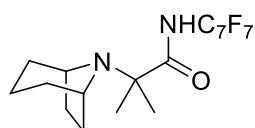
Compound **S10** was isolated as a white solid following **general procedure A**.

R<u>f</u>: 0.23 (10% EtOAc in hexanes)

<u>Isolated Yield</u>: 69%

<u>HRMS</u>: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{18}H_{20}F_7N_2O$: 413.1458; Found: 413.1461.

<u>^{1}H NMR</u> (CDCl$_3$, 401 MHz): δ 9.86 (s, 1H), 3.45 (m, 2H), 1.89–1.51 (multiple peaks, 10H), 1.33 (s, 6H).

<u>^{13}C NMR</u> (CDCl$_3$, 176 MHz): δ 176.40, 63.97, 57.20, 34.87, 29.81, 23.75, 17.27.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

<u>^{19}F NMR</u> (CDCl$_3$, 377 MHz): δ –56.03 (t, $J = 21.7$ Hz, 3F), –141.36 (m, 2F), –143.57 (m, 2F).

Compound (E2):
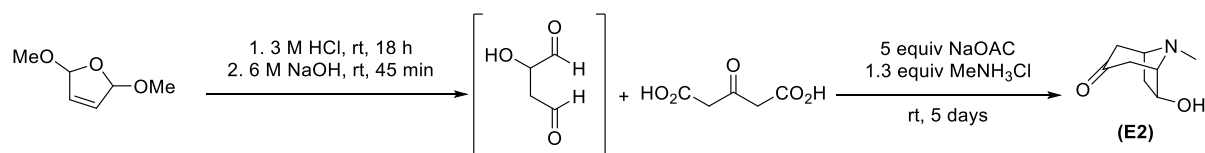
E2 was prepared by a modified literature procedure.[28] In a 100-mL round-bottom flask 2,5-dimethoxy-2,5-dihydrofuran (mixture of *cis* and *trans*) (2.6 g, 2.5 mL, 20 mmol, 1 equiv) was added to a 3 M aqueous HCl solution (36 mL). The mixture was stirred overnight (~12 h). The solution was neutralized (pH 7–8) with 6 M aqueous NaOH (~18 mL) and stirred for 45 minutes. During this time, the pH dropped to 5 so dropwise addition of 6 M aq. NaOH was used to bring the pH back to 7. This solution was added to a 500-mL round-bottom flask containing a solution of NaOAc•3H$_2$O (13.6 g, 100 mmol, 5 equiv), methylamine hydrochloride (1.75 g, 26 mmol, 1.3 equiv) and 1,3 acetonedicarboxylic acid (3.8 g, 26 mmol, 1.3 equiv) in H$_2$O (150 mL). The reaction mixture was stirred at room temperature for 5 days. Solid K$_2$CO$_3$ (15 g) and NaCl (15 g) were added to the brown solution and stirred for 30 minutes. The solution was extracted with CHCl$_3$ (15 × 75 mL) and EtOAc:Acetone (9:1; 4 × 75 mL). The combined organics were dried over Na$_2$SO$_4$, decanted, and volatiles removed via rotary evaporation. The crude product was purified via column chromatography (silica gel; 0% to 10% MeOH in DCM) using a Biotage column (50-g column) affording a 36% yield of **E2** as a brown solid. NMR characterization of product matches the literature report.[28]

Compound (E3):
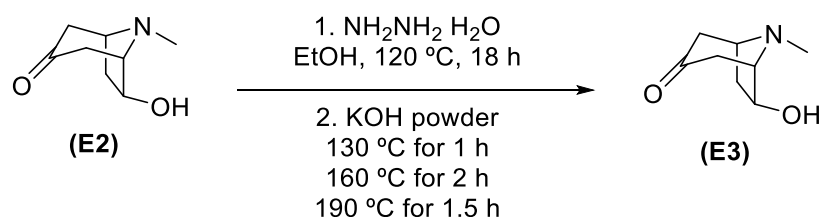
E3 was prepared following a modified literature procedure.[29] In a 50-mL round bottom flask, **E2** (0.6 g, 3.87 mmol, 1 equiv) was dissolved in absolute ethanol (8 mL, 0.5 M), followed by addition of hydrazine monohydrate (1.9 mL, 38.7 mmol, 10 equiv). The reaction mixture was refluxed to 120 °C for 2 hours. The reflux condenser was replaced with a short-path distillation apparatus and the temperature increased to 130 °C allowing the solvent to gradually distill over 1 hour. After the solvent was distilled, KOH powder (2 g, 34.8 mmol, 9 equiv) was added to the oily residue in one portion. The reflux condenser (no water flowing) was fitted to the flask and the mixture was heated to 130 °C for 1 hour, then at 160 °C for 2 hours and finally to 190 °C for 1.5 hours (Caution: Fumes evolve). After cooling to room temperature, the residue was dissolved in water (20 mL) and extracted with Et$_2$O (5 × 30 mL), DCM (5 × 30 mL) and EtOAc:Acetone (9:1; 1 × 30 mL). The combined organic extracts were dried over Na$_2$SO$_4$, decanted, and volatiles removed via rotary evaporation. The product was obtained in 56% yield as a brown semi-solid and it was utilized without further purification. NMR characterization matches the literature report.[29]

Compound (E4):
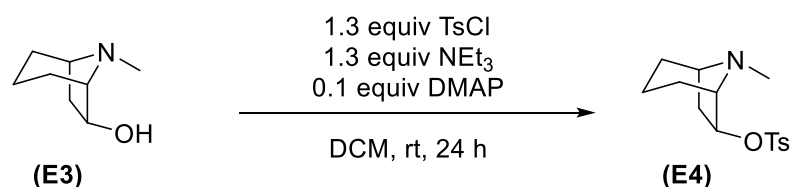
Synthesis of E4. A 50-mL round bottom flask was charged with **E3** (298 mg, 2.11 mmol, 1 equiv), Et$_3$N (0.4 mL, 2.87 mmol, 1.3 equiv), 4-dimethylaminopyridine (27 mg, 0.21 mmol, 0.1 equiv), *p*-toluenesulfonyl chloride (0.55 g, 2.87 mmol, 1.3 equiv), and DCM (9.6 mL, 0.23 M). The mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water (10 mL) and the product was extracted with DCM (5 × 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, decanted, and volatiles removed via rotary evaporation. The crude product was purified via column chromatography (silica gel, hexanes:EtOAc:Et$_3$N 3:2:0.5), affording **E4** as a yellow oil.

Isolated Yield: 61%

R_f: 0.2 (Hex:EtOAc:Et$_3$N ratio of 3:2:0.5)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{15}$H$_{22}$NO$_3$S: 296.1315; Found: 296.1316.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.96 (app. dd, J = 7.8, 3.0 Hz, 1H), 3.29 (m, 1H), 3.16 (app. br s, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 2.21 (m, 1H), 1.98 (m, 1H), 1.77–1.68 (multiple peaks, 2H), 1.50 (m, 1H), 1.37 (m, 1H), 1.26–1.11 (multiple peaks, 2H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 144.80, 134.38, 129.99, 127.89, 86.45, 67.23, 61.99, 40.32, 36.11, 28.64, 27.30, 21.82, 16.96.

Compound (E5):
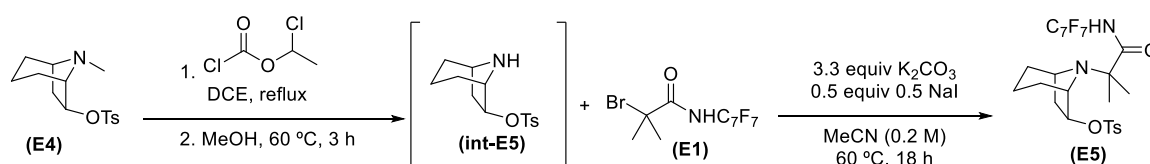
A Schlenk flask was charged with compound **E4** (0.379 g, 1.28 mmol, 1 equiv) and anhydrous 1,2-dichloroethane (4.7 mL, 0.4 M) under a N$_2$ atmosphere. To this mixture, 1-chloroethyl chloroformate (0.28 mL, 2.57 mmol, 2 equiv) was added dropwise via syringe. The mixture was heated to reflux for 5 hours. After cooling to room temperature, the reaction was concentrated via rotary evaporation and placed under high vacuum for 1 hour. The remaining brown oil was dissolved in methanol (5 mL) and heated to 60 ºC for 3 hours under a N$_2$ atmosphere. The reaction mixture was transferred to a 20-mL scintillation vial and solvent was removed via rotary evaporation. The crude hydrochloride salt of the amine intermediate **int-E5** was dried under high vacuum for 2 hours. **Int-E5** was mixed with α-bromo 2-methylpropanamide **E1** (0.489 g, 1.28 mmol, 1 equiv), K$_2$CO$_3$ (0.584 g, 4.22 mmol, 3.3 equiv) and NaI (96 mg, 0.64 mmol, 0.5 equiv) in MeCN (6.4 mL, 0.2 M) and heated to 60 ºC. After 18 h, the reaction was cooled to room temperature, diluted with EtOAc (~5 mL), and filtered through a pad of silica gel using 100% EtOAc (~50 mL). The filtrate was concentrated under reduced pressure. Final purification via column chromatography (gradient elution from 0% to 10% EtOAc in hexanes) afforded product **E5** as a white solid.

Isolated Yield: 60%

R_f: 0.1 (10% EtOAc in Hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{26}$F$_7$N$_2$O$_4$S: 583.1496 ; Found: 583.1503.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 9.56 (s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 5.03 (t, J = 5.6 Hz, 1H), 3.75 (app. s, 1H), 3.51 (app. s, 1H), 2.46 (s, 3H), 2.04 (m, 2H), 1.77–1.61 (multiple peaks, 4H), 1.47–1.35 (multiple peaks, 8H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.05, 145.23, 133.98, 130.12, 127.79, 85.81, 63.60, 61.35, 58.26, 38.33, 31.73, 31.49, 26.73, 21.81, 21.61, 17.53.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 377 MHz): δ –56.03 (t, J = 21.7 Hz, 3F), –140.36 (m, 2F), –143.57 (m, 2F).

Compound (S11):
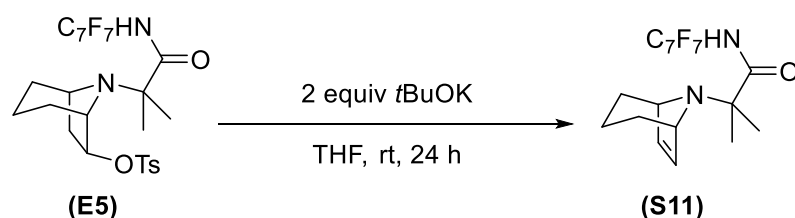
In a N$_2$-filled glove box a 20-mL vial was charged with **E5** (0.414 g, 0.71 mmol, 1 equiv), tBuOK (0.16 g, 1.4 mmol, 2 equiv) and THF (7 mL, 0.1 M). The reaction mixture was stirred at room temperature for 24 hours (Caution: excess tBuOK leads to S$_N$Ar in the perfluorinated ring). The reaction was mixed with water (1 mL) and stirred for 10 minutes. The solution was filtered through a silica gel plug with 100% EtOAc (~10 mL). The volatiles were removed via rotary evaporation and the crude product was purified by column chromatography (silica gel, 0% to 10% EtOAc in Hexanes) affording **S11** as a white solid.

Isolated Yield: 45% (90% yield based on recovered starting material)

R$_f$: 0.3 (10% EtOAc in Hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{18}$H$_{18}$F$_7$N$_2$O: 411.1302 ; Found: 411.1304.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 5.94 (s, 2H), 3.73 (s, 2H), 1.76–1.69 (multiple peaks, 2H), 1.61 (m, 1H), 1.53–1.43 (multiple peaks, 3H), 1.24 (s, 6H). The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.84, 130.23, 64.13, 61.57, 27.35, 24.03, 16.98.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 377 MHz): δ –56.04 (t, J = 21.7 Hz, 3F), –141.3 (m, 2F), –143.49 (m, 2F).

Compound (S12):
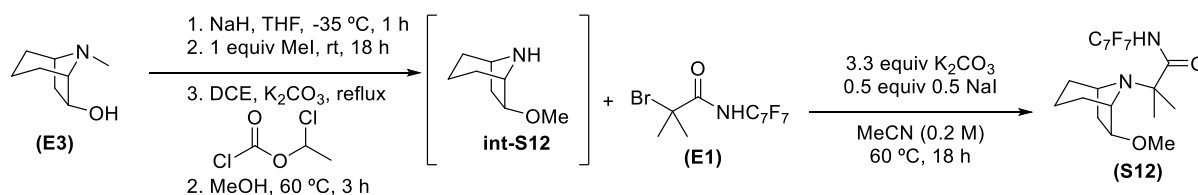
Steps i and ii: In a N$_2$-filled glovebox, a dry 50-mL round-bottom flask was charged with **E3** (0.6 g, 4.25 mmol, 1 equiv) and THF (15 mL, 0.2 M). The mixture was cooled inside a freezer (–35 ℃) for 10 minutes and then NaH (0.11g, 4.5 mmol, 1.05 equiv) was added to the mixture. The suspension was brought out of the glovebox and placed under a N$_2$ atmosphere in the fume hood. After 30 minutes, methyl iodide (0.28 mL, 4.5 mmol, 1.05 equiv) was added via syringe at room temperature. The mixture was stirred vigorously overnight. The white suspension was filtered through a pad of celite and washed with DCM. The volatiles were removed by rotary evaporation. **Steps iii and iv:** The concentrated crude mixture was transferred to a Schlenk flask using anhydrous DCE (10 mL, 0.4 M). To this solution K$_2$CO$_3$ (587 mg, 4.25 mmol, 1 equiv) was added followed by dropwise addition of 1-chloro ethylchloroformate (1.38 mL, 12.75 mmol, 3 equiv). The reaction mixture was refluxed for 5 hours under N$_2$ atmosphere. After cooling to room temperature, the solution was concentrated via rotary evaporation and placed under vacuum for 1 hour. The residue was dissolved in methanol (10 mL) and heated to 60 ℃ overnight under a N$_2$ atmosphere. The reaction mixture was transferred to a 20-mL scintillation vial and the solvent was removed via rotary evaporation to afford crude **int-S12**. **Step v**: The crude **int-S12** was mixed with α-bromo 2-methylpropanamide **S1** (1.6 g, 4.25 mmol, 1 equiv), K$_2$CO$_3$ (1.9 g, 14 mmol, 3.3 equiv) and NaI (0.32 g, 2.12 mmol, 0.5 equiv) in MeCN (18 mL) and heated to 60 ℃ for 18 hours. The reaction was cooled to room temperature, diluted with EtOAc (~5 mL), and filtered through a pad of silica gel using 100% EtOAc (~80 mL). The filtrate was concentrated under reduced pressure. Purification via column chromatography (gradient elution from 0% to 10% THF in hexanes). Collection of fractions containing product showed minor impurities by NMR and the product was further purified by a subsequent column chromatography (0% to 80% THF in DCM) to afford product **6b** as a white solid.

Isolated Yield: 5%

R$_f$: 0.3 (10% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{22}$F$_7$N$_2$O$_2$: 443.1564; Found: 443.1564.

<u>^{1}H NMR</u> (CDCl$_3$, 700 MHz): δ 9.97 (s, 1H), 3.86 (dd, J = 7.1, 2.8 Hz, 1H), 3.59 (app. s, 1H), 3.55 (m, 1H), 3.27 (s, 3H), 2.02–1.86 (multiple peaks, 2H), 1.76–1.58 (multiple peaks, 4H) 1.53–1.40 (multiple peaks, 8H).

<u>^{13}C NMR</u> (CDCl$_3$, 176 MHz): δ 177.13, 86.03, 63.32, 59.77, 57.59, 56.44, 37.62, 31.69, 31.05, 27.03, 22.47, 17.72.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

<u>^{19}F NMR</u> (CDCl$_3$, 377 MHz): δ –56.02 (t, J = 21.7 Hz, 3F), –141.46 (m, 2F), –143.58 (m, 2F).

<u>Compound (S13)</u>:
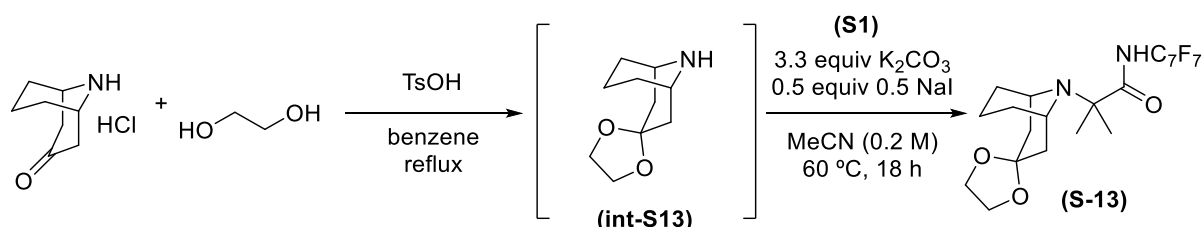
Step 1: A round-bottom flask was charged with 9-azabicyclo[3.3.1]nonan-3-one hydrochloride (500 mg, 2.84 mmol, 1 equiv), toluene sulfonic acid (594 mg, 3.12 mmol, 1.1 equiv), ethylene glycol (1.7 mL, 28.4 mmol, 10 equiv) and benzene (14 mL, 0.2 M). The flask was equipped with a Dean-Stark trap and heated to 110 ℃ overnight. The reaction was cooled to room temperature, followed by addition of Na$_2$CO$_3$ (1.18 g) and brine (26 mL). The aqueous layer was extracted with chloroform (3 x 75 mL). The organic layer was dried over Na$_2$SO$_4$, decanted, and concentrated via rotary evaporation. Intermediate **int-S13** was carried forward without analysis or purification.

Step 2: **Int-S13** was used as starting amine reagent following **general procedure A** to isolate compound S**13** as a white solid.

<u>Isolated Yield</u>: 19% (over the two steps)

<u>R$_f$:</u> 0.13 (5% EtOAc in hexanes)

<u>HRMS:</u> ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{24}$F$_7$N$_2$O$_3$: 485.1670; Found: 485.1671.

<u>^{1}H NMR</u> (CDCl$_3$, 700 MHz): δ 10.87 (s, 1H), 3.89 (m, 4H), 3.46 (d, J = 10.5 Hz, 2H), 2.34 (t, J = 12.6 Hz, 2H), 2.07 (m, 1H), 1.85–1.77 (multiple peaks, 4H), 1.66 (app. d, J = 14.7 Hz, 1H), 1.49 (s, 6H), 1.30 (d, J = 13.3 Hz, 2H).

<u>^{13}C NMR</u> (CDCl$_3$, 176 MHz): δ 178.1, 108.9, 64.7, 64.0, 45.8, 38.4, 29.5, 26.7, 14.3.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 377 MHz): δ –56.03 (t, J = 21.8 Hz, 3F), –141.69 (m, 2F), –143.87 (m, 2F).

Compound (S14):
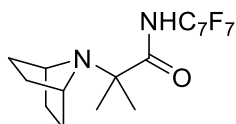
Compound **S14** was isolated as a pale yellow solid following **general procedure A**.

Isolated Yield: 50%

R$_f$: 0.29 (10% EtOAc in Hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{17}H_{18}F_7N_2O$: 399.1302; Found: 399.1304.

^1H NMR (CDCl$_3$, 700 MHz): δ 10.21 (s, 1H), 3.61 (m, 2H), 1.74 (m, 4H), 1.45–1.39 (multiple peaks, 10H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.58, 61.23, 56.78, 30.94, 24.43.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –141.35 (m, 2F), –144.17 (m, 2F).

Compound (S15):
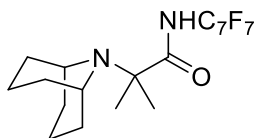
Compound **S15** was isolated in 75% yield as a white solid following **general procedure A**.

Isolated Yield: 75%

R$_f$: 0.42 (10% EtOAc in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{19}H_{22}F_7N_2O$: 427.1615; Found: 427.1619.

^1H NMR (CDCl$_3$, 700 MHz): δ 9.73 (s, 1H), 3.15 (m, 2H), 2.14 (m, 2H), 1.96 (m, 4H), 1.71 (m, 2H), 1.64 (dd, J = 14.0, 6.3 Hz, 4H), 1.47 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 177.26, 65.21, 48.13, 30.09, 25.62, 20.54.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.25 (t, J = 21.7 Hz, 3F), –141.76 (m, 2F), –143.73 (m, 2F).

Compound (S16):
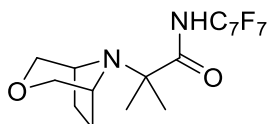
Compound **S16** was isolated as a white solid following **general procedure A**.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{17}$H$_{18}$F$_7$N$_2$O$_2$: 415.1251; found: 415.1255.

^1H NMR (CDCl$_3$, 700 MHz): δ 9.76 (s, 1H), 3.76 (dd, J = 9.8 Hz, J = 2.1 Hz, 2H), 3.68 (d, J = 9.8 Hz, 2H), 2.03 (m, 1H), 1.87 (m, 1H), 1.35 (s, 6 H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.6, 75.6, 63.8, 58.3, 28.6, 23.4. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 377 MHz): δ -56.0 (t, J = 21.8 Hz, 3F), -140.9 (m, 2F), -143.7 (m, 2F).

Compound (S17):
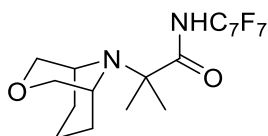
Compound **S17** was isolated as a white solid following **general procedure A**.

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{18}$H$_{20}$F$_7$N$_2$O$_2$: 429.1408; found: 429.1413.

^1H NMR (CDCl$_3$, 700 MHz): δ 9.54 (s, 1H), 3.97 (d, J = 11.2 Hz, 2H), 3.88 (d, J = 11.2 Hz, 2H), 2.60 (m, 1H), 2.01 (m, 1H), 1.77 (m, 1H), 1.53 (s, 6 H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 1756.2, 72.4, 65.1, 50.0, 29.1, 25.8, 20.2. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 377 MHz): δ -56.0 (t, J = 21.9 Hz, 3F), -141.0 (m, 2F), -143.6 (m, 2F).

5.4.3 Ligand Evaluation and Optimization of Arylation Conditions for S1

General Procedure B: Ligand evaluation reaction conditions in Table 5.1. Under ambient conditions, a 0.02 M stock solution of Pd(OAc)$_2$ (23 mg Pd(OAc)$_2$ in 5 mL of DCM) was prepared. An aliquot of this solution was transferred to a vial (4 mL capacity, 150 μL, 0.003 mmol Pd, 10 mol %). DCM was removed by heating the open vial to 45 ºC for 5 minutes. To the concentrated Pd(OAc)$_2$, the appropriate ligand (0.0015 mmol, 5 mol%), substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv) and CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) were added. To this mixture, PhI (0.1 mL, 0.9 mmol, 30 equiv) was added via plastic syringe. The vial was equipped with a stirbar, sealed with a Telfon-lined screw cap, and heated to an external temperature of 150 ºC in a preheated aluminum block. After 18 hours, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yield of **1a** was determined based on a 10-point calibration curve. Variations of this procedure were used in all optimization reactions (Tables 5.1) where the yield was determined by GC-FID.

General Procedure C: Reaction optimization in Table 5.2. Under ambient conditions, a 0.02 M stock solution of Pd(OAc)$_2$ (23 mg Pd(OAc)$_2$ in 5 mL of DCM) and a 0.02 M stock solution of quinaldic acid (17.3 mg of quinaldic acid (**L9**) in 5 mL of DCM) were prepared. An aliquot of the Pd(OAc)$_2$ solution was transferred to a vial (4 mL capacity, 150 μL, 0.003 mmol Pd, 10 mol %) followed by an aliquot of the quinaldic acid (**L9**) solution (75 μL, 0.0015 mmol, 5 mol %). DCM was removed by heating the open vial to 45 ºC for 5 minutes. To the concentrated reaction mixture, solid substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv), CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) and PhI (1–30 equiv) were added. The reaction mixture was then diluted with *t*AmylOH (0.25 mL, if indicated in Table 5.2). The vial was equipped with a stirbar, sealed with a Telfon-lined screw cap and heated to the indicated temperature in Table 2 in a preheated aluminum block. After 18 hours, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was

added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yield of **1a** was determined based on a 10-point calibration curve.

5.4.4 Optimization of Arylation Conditions for S10

General procedure D: Reaction optimization of S10 Under ambient conditions, a 0.02 M stock solution of picolinic acid (12.3 mg picolinic acid (**L8**) dissolved in 5 mL of MeOH) and a 0.02 M stock solution of Pd(OAc)$_2$ (23 mg of Pd(OAc)$_2$ dissolved in 5 mL of DCM) were prepared. An aliquot of the picolinic acid stock solution was transferred to a vial (4 mL capacity, 75 µL, 0.0015 mmol ligand, 5 mol %). MeOH was removed by heating the open vial to 68 ºC for 10 minutes. To the concentrated picolinic acid (**L8**), an aliquot of the Pd(OAc)$_2$ stock solution (150 µL, 0.003 mmol Pd, 10 mol %) was added. DCM was removed by gently heating the open vial to 45 ºC for 5 minutes. To the concentrated reaction mixture, solid substrate **S10** (12.4 mg, 0.03 mmol, 1 equiv), CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) and PhI (3–45 equiv) were added. The reaction mixture was then diluted with *t*AmylOH (0.25 mL, if indicated in **Table 5.5**). The vial was equipped with a stirbar, sealed with a Telfon-lined screw cap, and heated to the indicated temperature in **Table 5.5** in a preheated aluminum block. After 18 hours, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 µL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 µL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yield of **10a** is uncalibrated.

In the cases where quinaldic acid (**L9**) was used, a 0.02 M stock solution of quinaldic acid (17.3 mg of quinalidic acid (**L9**) in 5 mL of DCM) was prepared and an aliquot (75 µL, 0.0015 mmol, 5 mol %) was added to the 4-mL vial. Different volumes of ligand stock solution were used depending on the amount of ligand indicated in each entry of **Table 5.5**.

Table 5.5. Optimization of C–H Arylation for **S10**

10 mol% Pd(OAc)$_2$
X mol % ligand
3 equiv CsOPiv

X equiv Ph–I
solvent, temp, 18 h

S10 → **10a**
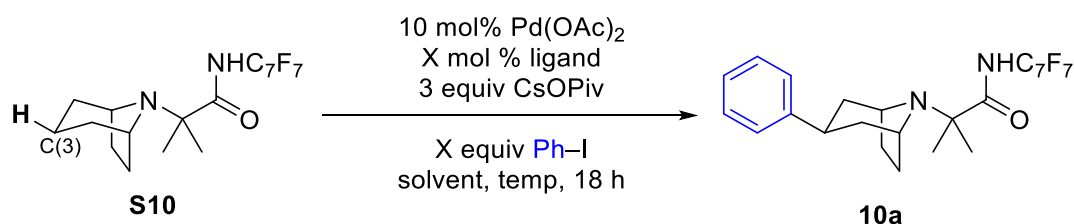
entry	ligand (mol %)[a]	temp	solvent	PhI (equiv)	conv.	yield **10a**[b]
1	L8 (5)	150 °C	neat	45	> 99%	41
2	L8 (10)	150 °C	neat	45	87%	47
3	L9 (5)	150 °C	neat	45	97%	31
4	L9 (20)	150 °C	neat	45	94%	33
5	**L8 (5)**	**140 °C**	**neat**	**45**	**91%**	**51**
6	L8 (10)	140 °C	neat	45	51%	21
7	L8 (5)	130 °C	neat	45	74%	38
8	L8 (10)	130 °C	neat	45	53%	28
9	L8 (5)	140 °C	*t*AmylOH	45	72%	26
10	L8 (5)	140 °C	*t*AmylOH	15	96%	24
11	L8 (5)	140 °C	*t*AmylOH	3	94%	18
12	-----	140 °C	neat	45	47%	4

Conditions from **general procedure D**. [a] L8 = picolinic acid; L9 = quinaldic acid. [b] Uncalibrated GC yields.

5.4.5 Synthesis and Characterization of Products of Ligand Promoted Functionalization

General Procedure E: **Isolation of 1a and 1b**. A 4-mL vial was charged with solid substrate **S1** (115.1 mg, 0.25 mmol, 1 equiv), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 10 mol %), CsOPiv (176 mg, 0.75 mmol, 3 equiv), quinaldic acid (**L9**, 2.2 mg, 0.013 mmol, 5 mol %), iodoarene (0.075 mmol, 3 equiv) and *t*AmylOH (2.1 mL, 0.12 M). The vial was equipped with a magnetic stirbar, sealed with a Teflon-lined screw cap, and heated to an external temperature of 100 ºC in an aluminum heating block. After 18 h, the reaction was cooled to room temperature and diluted with DCM (1 mL). Hydrazine hydrate (0.7 mL) was added to the solution. The mixture was allowed to stir for 30 min at room temperature to remove Pd from the product. The mixture was filtered through Celite and washed with DCM (10 mL). The volatiles were removed by rotary evaporation and the residue was purified via column chromatography (0% to 10% EtOAc in hexanes) affording the desired product. See each substrate for specific notes.

General Procedure F: Under ambient conditions, a 0.1 M stock solution of picolinic acid (24.6 mg picolinic acid (**L8**) dissolved in 2 mL of methanol) was prepared. An aliquot of this solution was transferred to a vial (4 mL capacity, 50 µL, 0.005 mmol picolinic acid **L8**, 5 mol

%). Methanol was removed by heating the open vial to 68 ºC for approximately 15 minutes (Note: leftover methanol can lead to Pd-catalyst decomposition). To the concentrated picolinic acid (**L8**), solid substrate **S10** (41.2 mg, 0.1 mmol, 1 equiv), Pd(OAc)$_2$ (2.3 mg, 0.01 mmol, 10 mol %), CsOPiv (70.2 mg, 0.3 mmol, 3 equiv), and iodoarene (45 equiv) were added. The vial was equipped with a magnetic stirbar, sealed with a Teflon-lined screw cap, and heated to an external temperature of 140 ºC. After 18 h, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine hydrate (0.4 mL) was added to the solution. The mixture was allowed to stir for 30 min at room temperature to remove Pd from the product. The mixture was filtered through Celite and washed with DCM (10 mL). The volatiles were removed by rotary evaporation, and the residue was purified via column chromatography (commonly mixtures of EtOAc:Hex or THF:Hex) affording the desired product. See each product for specific notes.

Compound (1a):
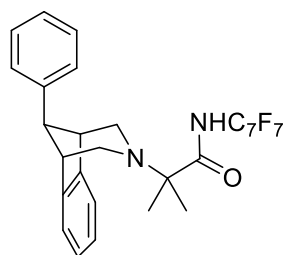
Compound **1a** was isolated as a white solid following **general procedure E** at 100 ºC or 120 ºC.

Isolated Yield: 67% (100 ºC), 77% (at 120 ºC)

R$_f$: 0.31 (10% EtOAc in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{28}$H$_{24}$F$_7$N$_2$O: 537.1771; Found: 537.1772.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50–7.37 (multiple peaks, 3H), 7.34 (m, 2H), 7.30–7.23 (multiple peaks, 3H), 7.14 (m, 2H), 3.75 (t, J = 4.1 Hz, 2H), 3.67 (t, J = 4.4 Hz, 1H), 3.02 (d, J = 10.7 Hz, 2H), 2.58 (dd, J = 10.9, 4.0 Hz, 2H), 1.01 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.20, 146.22, 139.08, 129.06, 128.45, 126.93, 126.26, 121.88, 63.74, 51.96, 43.88, 42.59, 21.57.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.08 (t, J = 21.7 Hz, 3F), –141.52 (m, 2F), –142.99 (m, 2F).

Compound (1b):
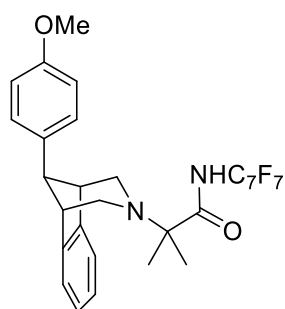
Compound **1b** was isolated as a white solid following **general procedure E** at 100 ºC or 120 ºC. NMR characterization matched the literature report.[X]

Isolated Yield: 68% (100 ºC), 81% (at 120 ºC)
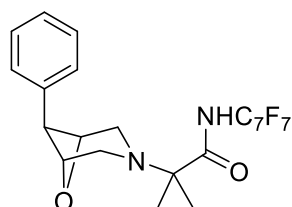
Compound (2):

Compound **2** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 76%

Compound (3):

Compound **3** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 86%

Compound (4):

Compound **4** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 72%

Compound (5):

Compound **5** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 64%

Compound (6):

Compound **6** was isolated following previously reported conditions with addition of 5 mol % **L8** and 20 mol % **L9**.[10]

Isolated Yield: 68% (**L8**), 81% (**L9**)

Compound (7):

Compound **7** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 60%

Compound (8):

Compound **8** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]
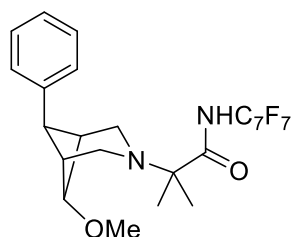
Isolated Yield: 75%

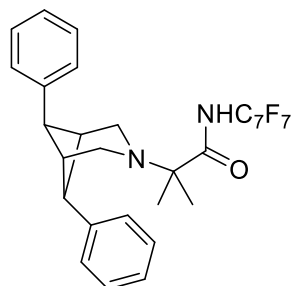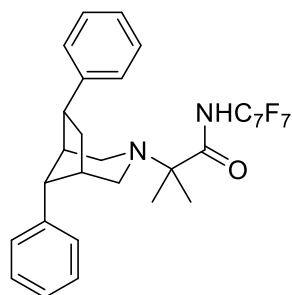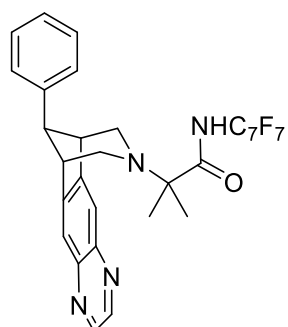## Compound (9):

Compound **9** was isolated following previously reported conditions with addition of 5 mol % **L8**.[10]

Isolated Yield: 51%

Compound (10b):
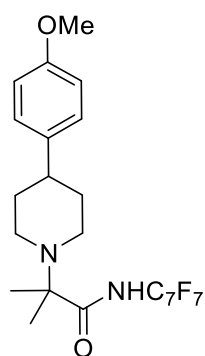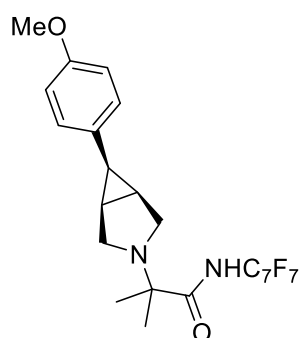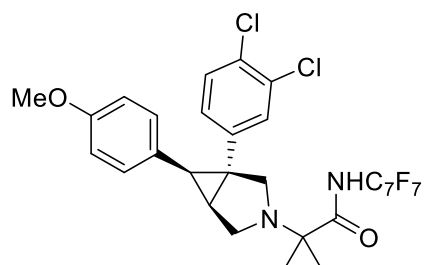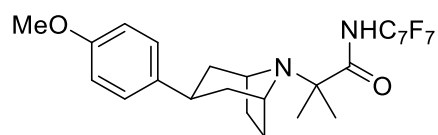

Compound **10b** was isolated as a yellow semi-solid following **general procedure F**.

Isolated Yield: 49%

R_f: 0.10 (5% EtOAc in Hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{25}H_{26}F_7N_2O_2$: 519.1877; Found: 519.1875.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 9.81 (br s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.59 (m, 2H), 2.97 (tt, J = 10.8, 4.0 Hz, 1H), 2.00–1.81 (multiple peaks, 8H), 1.39 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.07, 158.20, 137.35, 128.04, 114.07, 63.96, 57.11, 55.43, 42.92, 34.72, 30.09, 23.90.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.00 (t, J = 21.6 Hz, 3F), –141.08 (m, 2F), –143.59 (m, 2F).

Compound (10c):
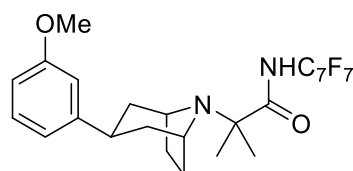
Compound **10c** was isolated as a colorless oil following **general procedure F**.

Isolated Yield: 60%

R_f: 0.10 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{25}H_{26}F_7N_2O_2$: 519.1877; Found: 519.1881.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.24 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.82–6.75 (multiple peaks, 2H), 3.81 (s, 3H), 3.61 (m, 2H), 3.01 (p, J = 8.7 Hz, 1H), 2.04–1.82 (multiple peaks, 8H), 1.39 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.66, 159.53, 146.62, 129.27, 119.21, 113.01, 110.98, 63.59, 56.70, 54.91, 42.17, 35.25, 29.71, 23.50.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.6 Hz, 3F), –141.10 (m, 2F), –143.60 (m, 2F).

Compound (10d):
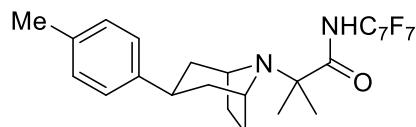
Compound **10d** was isolated as a colorless oil following **general procedure F**.

Isolated Yield: 40%

R$_f$: 0.37 (100% DCM)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{26}$F$_7$N$_2$O: 503.1928; Found: 503.1926.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.13 (app. s, 4H), 3.59 (m, 2H), 2.99 (m, 1H), 2.32 (s, 3H), 1.99–1.92 (multiple peaks, 2H), 1.90–1.82 (multiple peaks, 6H), 1.39 (s, 6H).

The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.09, 142.24, 136.03, 129.36, 127.05, 63.94, 57.10, 42.76, 35.15, 30.08, 23.88, 21.12.

The carbon resonances corresponding to the perfluoroarene (C_7F_7) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.00 (t, J = 21.6 Hz, 3F), –141.14 (m, 2F), –143.57 (m, 2F).

Compound (10e):
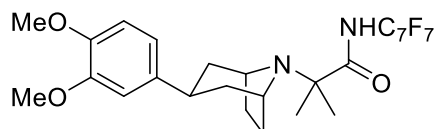
Compound **10e** was isolated as a light yellow oil following **general procedure F**.

Isolated Yield: 47%

R$_f$: 0.07 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{26}$H$_{28}$F$_7$N$_2$O$_3$: 549.1983; found 549.1990.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.86–6.72 (multiple peaks, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60 (m, 2H), 2.96 (m, 1H), 2.03–1.78 (multiple peaks, 8H), 1.39 (s, 6H).

The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.90, 149.07, 147.66, 137.94, 118.84, 111.46, 110.70, 63.97, 57.07, 56.08, 55.95, 42.85, 35.20, 30.07, 23.86.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –55.97 (t, J = 21.6 Hz, 3F), –141.11 (m, 2F), –143.73 (m, 2F).

Compound (10f):
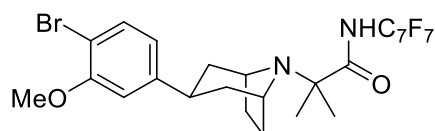
Compound **10f** was isolated as a colorless oil following **general procedure F**.

Isolated Yield: 46%

R$_f$: 0.71 (20% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{25}$BrF$_7$N$_2$O$_2$: 597.0982; Found: 597.0977.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 7.45 (d, J = 8.1 Hz, 1H), 6.77 (m, 1H), 6.72 (dd, J = 8.1, 2.0 Hz, 1H), 3.90 (s, 3H), 3.61 (m, 2H), 2.99 (tt, J = 11.8, 6.2 Hz, 1H), 2.02–1.94 (multiple peaks, 2H), 1.91–1.80 (multiple peaks, 6H), 1.39 (s, 6H).

The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.75, 156.01, 146.29, 133.35, 120.49, 111.19, 109.39, 63.99, 56.99, 56.23, 42.54, 35.67, 30.06, 23.85.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –55.99 (t, J = 21.7 Hz, 3F), –141.02 (m, 2F), –143.80 (m, 2F).

Compound (10g):
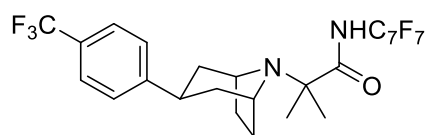
Compound **10g** was isolated as a white solid following **general procedure F**.

Isolated Yield: 47%

R$_f$: 0.29 (100% CHCl$_3$)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{23}$F$_{10}$N$_2$O: 557.1645; Found: 557.1644.

^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.75 (br s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 3.63 (m, 2H), 3.08 (m, 1H), 2.06–1.78 (m, 8H), 1.40 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.81, 149.28, 128.85 (q, J_{C-F} = 32.4 Hz), 127.54, 125.64 (q, J_{C-F} = 3.7 Hz), 124.36 (q, J_{C-F} = 271.8 Hz), 64.00, 56.99, 42.36, 35.59, 30.08, 23.88.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.02 (t, J = 21.7 Hz, 3F), –62.44 (s, 3F), –140.96 (m, 2F), –143.75 (m, 2F).

Compound (10h):
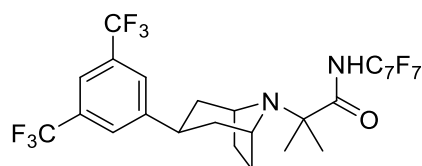
Compound **10h** was isolated as a colorless semi-solid following **general procedure F**.

Isolated Yield: 44%

R$_f$: 0.19 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{26}$H$_{22}$F$_{13}$N$_2$O: 625.1519; found 625.1524.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.72 (s, 1H), 7.74 (s, 1H), 7.68 (s, 2H), 3.66 (m, 2H), 3.17 (tt, J = 11.9, 5.9 Hz, 1H), 2.09–1.78 (multiple peaks, 8H), 1.41 (s, 6H).

^{13}C NMR (CDCl$_3$, 126 MHz): δ 175.53, 147.69, 131.94 (q, J = 32.9 Hz), 127.47 (m), 123.51 (q, J = 272.6 Hz), 120.63 (m), 64.02, 56.84, 42.28, 35.61, 30.05, 23.84.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling.

Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.5 Hz, 3F), –62.88 (s, 6F), –140.97 (m, 2F), –143.97 (m, 2F).

Compound (10i):
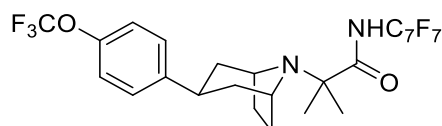
Compound **10i** was isolated as a light yellow oil following **general procedure F** with 20 mol % Pd(OAc)$_2$ and 10 mol% **L8**.

Isolated Yield: 34%

R$_f$: 0.77 (100% DCM)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{25}$H$_{23}$F$_{10}$N$_2$O$_2$: 573.1594; found 573.1592.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 7.22 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 3.62 (app. s, 2H), 3.04 (tt, J = 11.9, 6.2 Hz, 1H), 2.02–1.76 (multiple peaks, 8H), 1.39 (s, 6H). The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.88, 147.76 (m), 143.91, 128.40, 121.23, 63.99, 57.01, 42.62, 35.05, 30.09, 23.90.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) and CF$_3$O are not listed due to complexities in the region between 105 ppm and 150 ppm. ^{19}F NMR and HRMS were used to confirm the presence of these groups.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –57.96 (s, 3F), –140.95 (m, 2F), –143.70 (m, 2F).

Compound (10j):
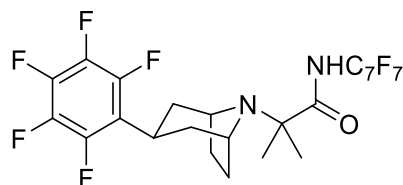
Compound **10j** was isolated as a colorless semi-solid following **general procedure F**.

Isolated Yield: 42%

R$_f$: 0.46 (100% CHCl$_3$)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{24}$H$_{19}$F$_{12}$N$_2$O: 579.1300; found: 579.1305.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 9.73 (s, 1H), 3.62 (m, 2H), 3.50 (tt, J = 12.2, 6.0 Hz, 1H), 2.23 (app. t, J = 7.2 Hz, 2H), 2.00 (m, 2H), 1.86 (m, 2H), 1.75 (m, 2H), 1.39 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.86, 63.89, 56.82, 39.16, 29.82, 25.82, 23.79.

The carbon resonances corresponding to the perfluoroarenes (C$_7$F$_7$ and C$_6$F$_5$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of these groups, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of both ring systems.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.04 (t, J = 21.7 Hz, 3F), –141.07 (m, 2F), –143.55 (app. d, J = 18.4 Hz, 2F), –143.85 (m, 2F), –157.06 (t, J = 21.0 Hz, 1F), –162.07 (m, 2F).

Compound (10k):
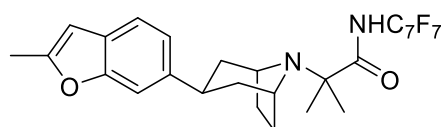
Compound **10k** was isolated as a colorless oil following **general procedure F**.

Isolated Yield: 54%

R$_f$: 0.10 (5% EtOAc in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{27}$H$_{26}$F$_7$N$_2$O$_2$: 543.1877; found 543.1879.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 9.88 (br s, 1H), 7.33–7.30 (multiple peaks, 2H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.32 (s, 1H), 3.61 (m, 2H), 3.09 (p, J = 9.1 Hz, 1H), 2.44 (s, 3H), 2.02–1.83 (multiple peaks, 8H), 1.40 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.11, 156.02, 153.62, 139.47, 129.51, 122.43, 118.21, 110.57, 102.58, 63.95, 57.17, 43.26, 35.57, 30.10, 23.89, 14.24.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –141.15 (m, 2F), –143.59 (m, 2F).

Compound (11):
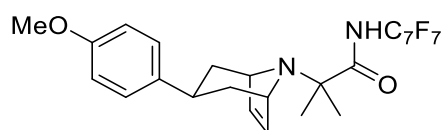
Compound **11** was isolated as a colorless semi-solid following **general procedure F**.

Isolated Yield: 50%

R$_f$: 0.19 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{25}H_{24}F_7N_2O_2$: 517.1721; found: 517.1718.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 7.15 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 6.05 (s, 2H), 3.88 (app. s, 2H), 3.79 (s, 3H), 2.89 (m, 1H), 1.87–1.76 (multiple peaks, 4H), 1.29 (s, 6H). The N–H proton in the amide is not observed.

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.49, 158.16, 137.40, 130.64, 128.64, 113.99, 64.14, 61.44, 55.40, 35.86, 35.24, 24.20.

The carbon resonances corresponding to the perfluoroarenes (C$_7$F$_7$ and C$_6$F$_5$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of these groups, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of both ring systems.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.02 (t, J = 21.7 Hz, 3F), –141.07 (m, 2F), –143.55 (m, 2F).

Compound (12):
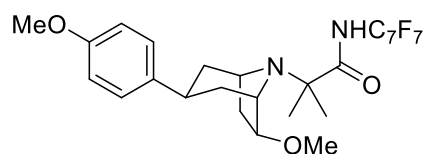
Compound **12** was isolated as a colorless oil following **general procedure F**.

Isolated Yield: 40%

R$_f$: 0.42 (2% EtOAc in DCM)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for $C_{26}H_{28}F_7N_2O_3$: 549.1983; found: 549.1978.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 10.00 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.97 (dd, J = 7.2, 2.6 Hz, 1H), 3.79 (s, 3H), 3.76–3.68 (multiple peaks, 2H), 3.31 (s, 3H), 2.75 (m, 1H), 2.12 (m, 1H), 2.00 (m, 1H), 1.91–1.67 (multiple peaks, 4H), 1.54 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.91, 158.32, 137.19, 127.92, 114.16, 85.79, 63.11, 59.76, 56.89, 56.52, 55.44, 39.20, 38.44, 37.96, 35.30, 27.18, 23.33.

The carbon resonances corresponding to the perfluoroarenes (C$_7$F$_7$ and C$_6$F$_5$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of these groups, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of both ring systems.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –141.29 (m, 2F), –143.61 (m, 2F).

Compound (13):
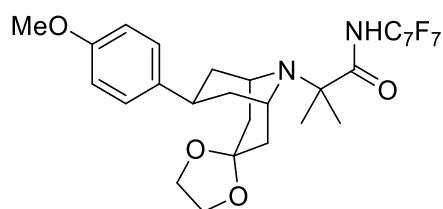
Compound **13** was isolated as a yellow oil following **general procedure F** with 20 mol % Pd(OAc)$_2$ and 10 mol % **L8**.

Isolated Yield: 54%

R$_f$: 0.31 (20% EtOAc in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{28}$H$_{30}$F$_7$N$_2$O$_4$: 591.2088; found: 591.2087.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 10.90 (s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 3.93 (app. s, 4H), 3.80 (s, 3H), 3.63 (app. d, J = 10.5 Hz, 2H), 3.27 (m, 1H), 2.44 (t, J = 12.6 Hz, 2H), 1.94 (d, J = 14.7 Hz, 2H), 1.88 (m, 2H), 1.60–1.52 (multiple peaks, 8H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 177.8, 158.3, 138.1, 128.1, 114.2, 108.7, 64.8, 64.1, 55.4, 46.5, 38.9, 37.6, 31.4, 26.8.

The carbon resonances corresponding to the perfluoroarenes (C$_7$F$_7$ and C$_6$F$_5$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of these groups, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of both ring systems.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 18.0 Hz, 3F), –141.57 (m, 2F), –143.82 (m, 2F).

Compound (14):
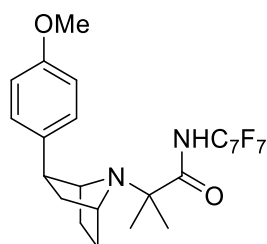
Compound **14** was isolated as a colorless oil following **general procedure F** with 5 mol % **L9**.

Isolated Yield: 42%

R$_f$: 0.26 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{24}$H$_{24}$F$_7$N$_2$O$_2$: 505.1721; found: 505.1720.

^{1}H NMR (CDCl$_3$, 401 MHz): δ 9.18 (s, 1H), 7.21 (d, J = 8.3 Hz, 2H), 6.70 (d, J = 8.3 Hz, 2H), 3.80 (m, 1H), 3.65–3.53 (multiple peaks, 4H), 2.91 (dd, J = 9.0, 4.4 Hz, 1H), 2.13 (m, 1H), 1.95–1.55 (multiple peaks, 5H), 1.40 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.35, 157.89, 136.57, 128.03, 113.78, 64.81, 61.14, 56.99, 55.06, 47.83, 37.03, 30.72, 30.13, 25.42, 23.91.

The carbon resonances corresponding to the perfluoroarenes (C$_7$F$_7$ and C$_6$F$_5$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of these groups, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of both ring systems.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.14 (t, J = 21.7 Hz, 3F), –141.93 (m, 2F), –143.61 (m, 2F).

Compound (15a):
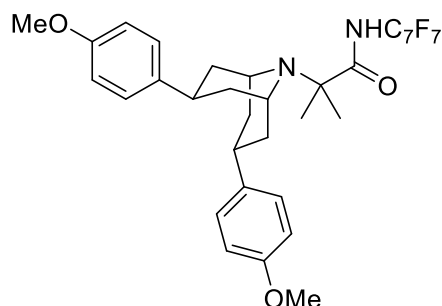
Compound **15a** was isolated as a white solid following **general procedure F** with 20 mol % **L9**.

Isolated Yield: 15%

R$_f$: 0.10 (5% THF in hexanes)

HRMS: ESI$^+$ (m/z): [M+H]$^+$ calcd for C$_{24}$H$_{24}$F$_7$N$_2$O$_2$: 505.1721; found: 505.1720.

^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.70 (br s, 1H), 7.21 (d, J = 8.5 Hz, 4H), 6.89 (d, J = 8.5 Hz, 4H), 3.81 (s, 6H), 3.69 (tt, J = 12.7, 6.4 Hz, 2H), 3.51 (m, 2H), 2.15–1.96 (multiple peaks, 8H), 1.62 (s, 6H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 176.63, 158.24, 138.93, 127.78, 114.16, 65.27, 55.44, 49.36, 38.38, 37.55, 26.11.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR, X-ray, and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –140.95 (m, 2F), –143.56 (m, 2F).

Compound (15b):
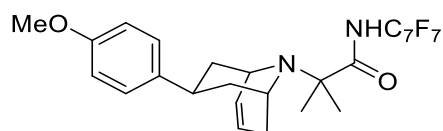
Compound **15b** was isolated as a colorless oil following **general procedure F** with 20 mol % **L9**.

Isolated Yield: 24%

Rf: 0.16 (5% THF in hexanes)

HRMS: ESI⁺ (m/z): [M+H]⁺ calcd for $C_{26}H_{26}F_7N_2O_2$: 531.1877; found: 531.1872.

^{1}H NMR (CDCl₃, 700 MHz): δ 9.77 (br s, 1H), 7.15 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.3 Hz, 2H), 6.06 (dt, J = 9.9, 3.0 Hz, 1H), 5.92 (m, 1H), 3.79 (s, 3H), 3.61 (m, 1H), 3.42 (app. s, 1H), 3.21 (tt, J = 12.4, 6.2 Hz, 1H), 2.47 (dd, J = 18.9, 7.0 Hz, 1H), 2.03–1.96 (multiple peaks, 2H), 1.93–1.78 (multiple peaks, 3H), 1.49 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (CDCl₃, 126 MHz): δ 176.52, 158.17, 137.72, 130.41, 128.51, 128.04, 114.04, 65.12, 55.42, 50.53, 47.29, 43.76, 37.82, 33.61, 28.91, 24.83, 23.28.

The carbon resonances corresponding to the perfluoroarene (C₇F₇) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl₃, 376 MHz): δ –56.01 (t, J = 21.7 Hz, 3F), –141.09 (m, 2F), –143.74 (m, 2F).

Compound (15c):
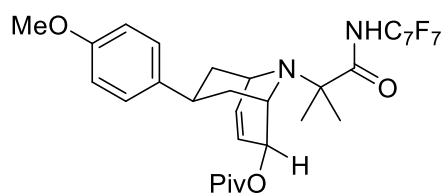
Compound **X** was isolated as a white solid following **general procedure F** with 20 mol % **L9**.

Isolated Yield: 31%

Rf: 0.13 (5% THF in hexanes)

HRMS: ESI⁺ (m/z): [M+H]⁺ calcd for $C_{31}H_{34}F_7N_2O_4$: 631.2401; found: 631.2397.

^{1}H NMR (CDCl₃, 700 MHz): δ 9.47 (s, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.05 (ddd, J = 10.3, 4.6, 1.8 Hz, 1H), 5.95 (dd, J = 10.3, 2.3 Hz, 1H), 5.49 (d, J = 6.8 Hz, 1H), 3.86 (m, 1H), 3.80 (s, 3H), 3.37 (app. s, 1H), 3.29 (tt, J = 12.5, 4.5 Hz, 1H), 2.16 (m, 1H), 1.99

(td, J = 12.8, 4.2 Hz, 1H), 1.80 (m, 1H), 1.76 (td, J = 13.3, 4.6 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 178.37, 175.69, 158.29, 137.27, 133.79, 128.04, 127.95, 114.16, 68.00, 65.15, 55.41, 51.20, 48.78, 39.02, 36.23, 36.06, 33.39, 27.38, 25.78, 23.59.

The carbon resonances corresponding to the perfluoroarene (C$_7$F$_7$) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of ^{13}C/^{19}F coupling. Due to the complexities of the system, the peaks are not listed. ^{19}F NMR, X-ray, and HRMS were used to confirm the presence of this ring system.

^{19}F NMR (CDCl$_3$, 376 MHz): δ –56.03 (t, J = 21.7 Hz, 3F), –140.86 (m, 2F), –143.63 (m, 2F).

Compound (16a):
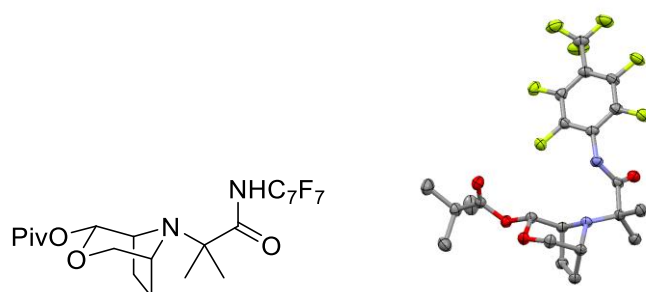
Compound **16a** was isolated as a white solid following **general procedure F**. The compound was recyrstallized from methanol for X-ray crystallography.

Isolated Yield: 24% (12.3 mg)

HRMS: ESI$^+$ (m/z): [M+H$^+$] calcd for C$_{22}$H$_{26}$F$_7$N$_2$O$_4$: 515.1775; found: 515.1778.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 9.30 (s, 1H), 4.71 (s, 1H), 3.88 (d, J = 10.5 Hz, 1H), 3.74 (d, J = 10.5 Hz, 1H), 3.41 (d, J = 6.3 Hz, 1H), 3.33 (d, J = 6.3 Hz, 1H), 2.19 (m, 1H), 2.12 (m, 1H), 1.95 (m, 1H), 1.90 (m, 1H), 1.75 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.8, 174.9, 95.0, 74.4, 63.8, 59.6, 57.4, 39.0, 28.1, 27.1, 24.8, 24.5, 22.9. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

Compound (16b):
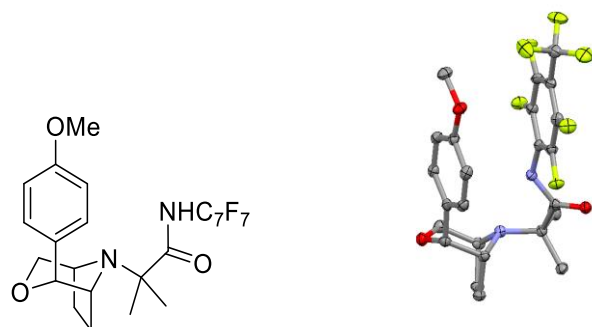
Compound **16a** was isolated as a yellow solid following **general procedure F**. The compound was recyrstallized from hexanes for X-ray crystallography.

Isolated Yield: 6% (3.0 mg)

HRMS: ESI⁺ (m/z): [M+H⁺] calcd for $C_{24}H_{24}F_7N_2O_3$: 521.1670; found: 532.1675.

^{1}H NMR (CDCl₃, 700 MHz): δ 8.67 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.77 (s, 1H), 4.27 (d, J = 10.5 Hz, 1H), 3.82 (d, J = 7.0 Hz, 1H), 3.70 (d, J = 10.5 Hz, 1H), 3.62 (s, 3H), 3.37 (d, J = 7.0 Hz, 1H), 2.25 (m, 1H), 2.12 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (CDCl₃, 176 MHz): δ 175.3, 158.3, 133.1, 126.6, 113.9, 81.6, 72.1, 63.4, 61.7, 58.3, 55.1, 29.7, 28.1, 23.6, 23.2. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

Compound (10l):
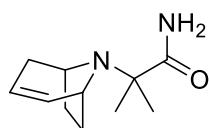
Compound **10l** was isolated as a light yellow oil following **general procedure F**, replacing the iodoarene with 3 equiv AgOAc.

Isolated Yield: 30% (3.7 mg)

HRMS: ESI⁺ (m/z): [M+H⁺] calcd for $C_{18}H_{18}F_7N_2O$: 411.1302; found: 411.1307.

^{1}H NMR (CDCl₃, 700 MHz): δ 9.84 (s, 1H), 6.03 (m, 1H), 5.51 (m, 1H), 3.64 (m, 2H), 3.55 (t, J = 5.6 Hz, 1H), 2.64 (dd, J = 17.5 Hz, J = 1.4 Hz, 1H), 2.06 (m, 1H), 1.98 (m, 1H), 1.90 (m, 2H), 1.70 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (CDCl₃, 176 MHz): δ 176.3, 134.5, 123.3, 62.9, 55.1, 35.7, 31.0, 27.5, 24.4, 22.7. The carbon resonances of the directing group (perfluoroarene, C_7F_7) appear as complex

multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 377 MHz): δ -56.0 (t, J = 21.5 Hz, 3F), -141.3 (m, 2F), -143.8 (m, 2F).

Compound (17):
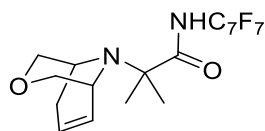
Compound **10l** was isolated as a light yellow solid following **general procedure F**, replacing the iodoarene with 3 equiv AgOAc.

Isolated Yield: % (4.7 mg)

HRMS: ESI[+] (m/z): [M+H^{+}] calcd for C$_{18}$H$_{18}$F$_7$N$_2$O$_2$: 427.1251; found: 427.1255.

^{1}H NMR (CDCl$_3$, 700 MHz): δ 9.84 (s, 1H), 6.03 (m, 1H), 5.51 (m, 1H), 3.64 (m, 2H), 3.55 (t, J = 5.6 Hz, 1H), 2.64 (dd, J = 17.5 Hz, J = 1.4 Hz, 1H), 2.06 (m, 1H), 1.98 (m, 1H), 1.90 (m, 2H), 1.70 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ 175.8, 129.4, 127.4, 76.4, 76.4, 69.8, 64.9, 51.3, 48.9, 28.1, 24.1, 22.9. The carbon resonances of the directing group (perfluoroarene, C$_7$F$_7$) appear as complex multiplets and are not listed. ^{19}F NMR and LC-MS were used to confirm characterization of structure.

^{19}F NMR (CDCl$_3$, 377 MHz): δ -56.0 (t, J = 21.5 Hz, 3F), -140.9 (m, 2F), -143.9 (m, 2F).

5.4.6 Initial Rates and Reaction Profile with S1

General Procedure G: Reaction conditions for kinetic studies. Under ambient conditions, if ligand was used, a 0.02 M stock solution of **L9** (quinaldic acid, 17.3 mg dissolved in 5 mL of DCM) was prepared. An aliquot of this solution was transferred to a vial (4 mL capacity, 75 µL, 0.0015 mmol ligand, 5 mol %). MeOH was removed by heating the open vial to 68 ºC for 10 minutes or DCM was removed by heating the open vial to 45 ºC for 5 minutes. To the concentrated carboxylate ligand, a Pd(OAc)$_2$ aliquot (150 µL, 0.003 mmol Pd, 10 mol %) of a 0.02 M stock solution (23 mg Pd(OAc)$_2$ in 5 mL of DCM) was added. DCM was removed by heating the open vial to 45 ºC for 5 minutes.

To the vial containing the resulting solids, substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv) and CsOPiv (21.1 mg, 0.09mmol, 3 equiv) were added, followed by PhI (10 µL, 0.09 mmol, 3

equiv) and *t*AmylOH (0.25 mL). The vial was equipped with a stirbar, tightly sealed with a Teflon-lined screw cap and heated to 100 ºC in a preheated aluminum block. At the desired reaction time (measured by a stopwatch), the reaction was flash-cooled in a liquid nitrogen bath until frozen solid (35 seconds). The reaction was then allowed to warm up to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yields and concentrations of **1a** were used to obtain reaction rate profiles and initial rates in **Figure 5.5** and **5.6**.

5.4.7 Kinetic Isotope Experiment Studies

KIE without ligand: Intermolecular KIE was performed following **General Procedure G** with addition of **S1** (13.8 mg, 0.03 mmol, 1 equiv, 0.12 M) or d_5-**S1** (14 mg, 0.03 mmol, 1 equiv, 0.12 M).

Figure 5.8. KIE of **S1** versus d_5-**1** Without Ligand
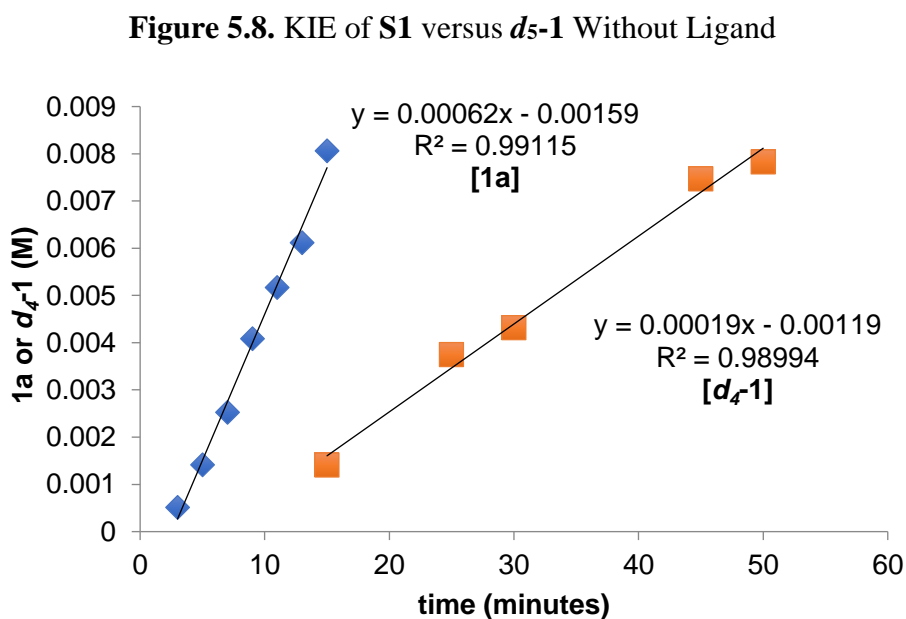
$$KIE = \frac{k_H}{k_D} = \frac{0.00062}{0.00019} = 3.3$$

KIE with 5 mol % quinaldic acid (L9): Intermolecular KIE was performed following **General Procedure G** using **L9** and with addition of **S1** (13.8 mg, 0.03 mmol, 1 equiv, 0.12 M) or d_5-**S1** (14 mg, 0.03 mmol, 1 equiv, 0.12 M).

Figure 5.9. KIE of **S1** versus *d₅*-**1** with 5 mol % **L9**
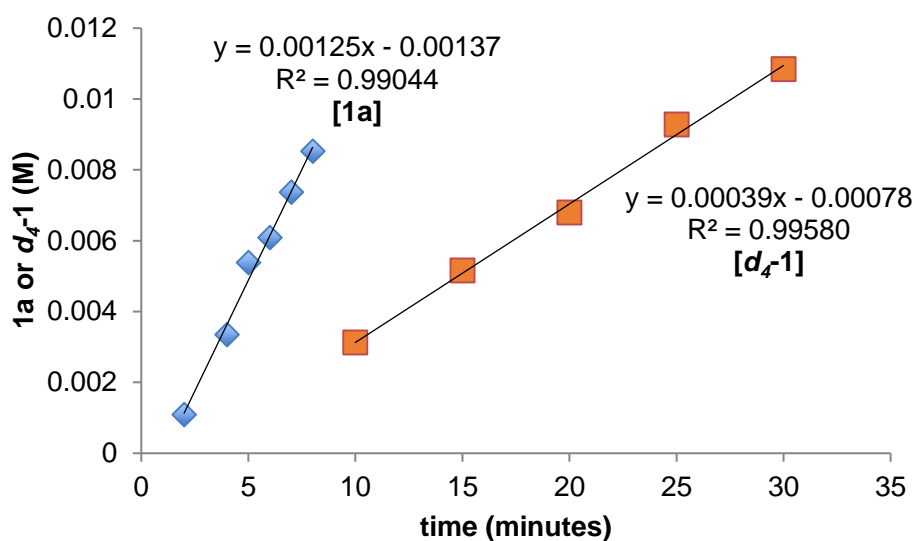
$$KIE = \frac{k_H}{k_D} = \frac{0.00125}{0.00039} = 3.2$$

5.4.8 Product Inhibition Experiments with S1

General Procedure G was used for **Table 5.3** with the following modifications/details: To each vial, a varying amount of **1b** was added (1.7 mg–12.8 mg, 0.003–0.0225 mmol, 0.1–0.75 equiv, 0.012–0.09 M). The amount of **1b** is indicated in each entry of Table5. 3. Reactions were stopped after 45 minutes and immediately flash-cooled in a liquid nitrogen bath until frozen solid (35 seconds).

General procedure G was used for **Figure 5.101** without ligand additive. Product **1b** (8.5 mg, 0.015 mmol, 0.5 equiv, 0.06 M) was added to the reaction mixture to obtain the data shown in the red line

Figure 5.10. Overlay of Initial Rate of **1a** versus Time in the Absence (blue) and Presence of **1b** (red)

$y = 0.00064x - 0.00197$
$R^2 = 0.99682$

$y = 0.00062x - 0.00159$
$R^2 = 0.99115$

■ 0.06 M **1b**

◆ No product added
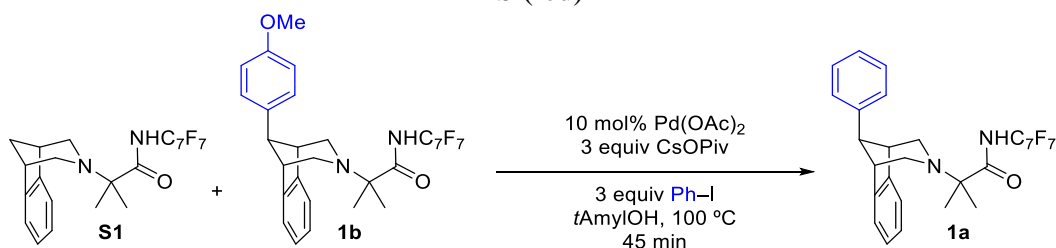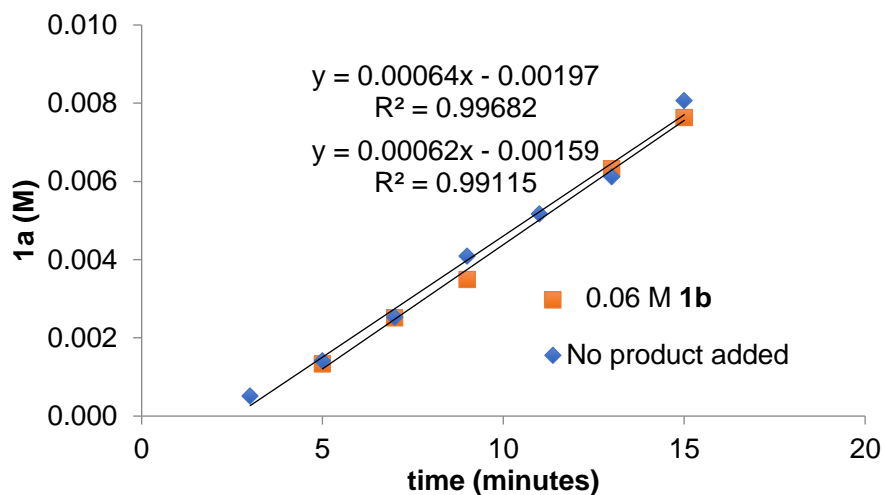
General procedure G was used for **Figure 5.11** with 5 mol% **L9** (0.006 M). Product **1b** (8.5 mg, 0.015 mmol, 0.5 equiv, 0.06 M) was added to the reaction mixture to obtain the data shown in the red line.

Figure 5.11. Overlay of Initial Rate of **1a** versus Time in Absence (blue) and Presence of **1b** (red) with 5 mol % **L9**

$y = 0.00129x - 0.00151$
$R^2 = 0.98880$

$y = 0.00125x - 0.00137$
$R^2 = 0.99044$

■ 0.06 M **1b**

◆ No product added
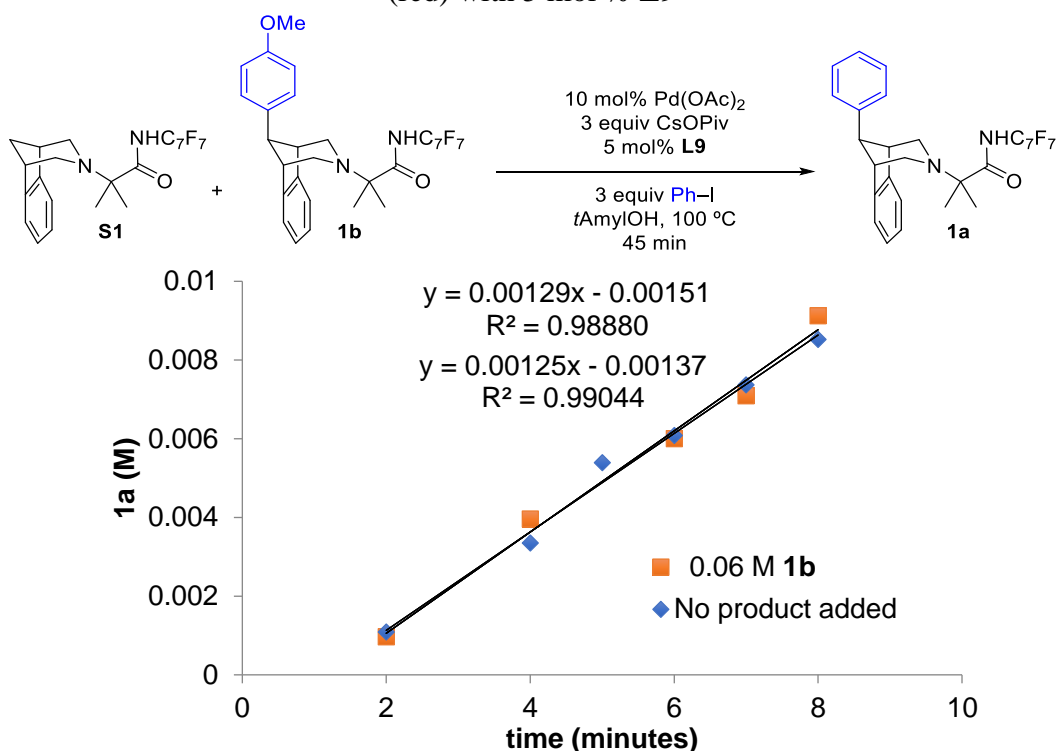
5.4.9 Catalyst Recovery Experiment with S1

General Procedure E: Under ambient conditions, an aliquot of Pd(OAc)$_2$ aliquot (150 μL, 0.003 mmol Pd, 10 mol %) from a 0.02 M stock solution (23 mg Pd(OAc)$_2$ in 5 mL of DCM) was added to a vial (4 mL capacity). DCM was removed by heating the open vial to 45 ℃ for

5 minutes. To the vial containing the resulting solid, substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv) and CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) were added, followed by PhI (10 μL, 0.09 mmol, 3 equiv) and *t*AmylOH (0.25 mL). The vial was equipped with a stirbar, sealed with a Teflon-lined screw cap and heated to 100 ℃ in a preheated aluminum block. After four hours (240 minutes), the reaction was removed from the heating source and cooled to room temperature. The reaction mixture was opened to air and solid quinaldic acid (**L9**, 0.260 mg, 0.0015 mmol, 5 mol %) was added. The reaction was then reheated to 100 ℃. At the desired reaction time (measured by a stopwatch), the reaction was flash cooled in a liquid nitrogen bath and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. The concentration of **1a** over time was used to plot the reaction profiles of **Figure 5.7**.

5.4.10 Precipitate Experiments

Isolation procedure for precipitate: Under ambient conditions, a 0.02 M stock solution of Pd(OAc)$_2$ (23 mg, 0.1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution was transferred to a vial (4 mL capacity, 150 μL, 0.003 mmol Pd, 10 mol %). DCM was removed by heating the open vial to 45 ℃ for 5 minutes. To the concentrated Pd(OAc)$_2$, substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv) and CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) were added, followed by PhI (10 μL, 0.09 mmol, 3 equiv) and *t*AmylOH (0.25 mL). The vial was equipped with a stirbar, sealed with a Teflon-lined screw cap and heated to 100 ℃ in a preheated aluminum block. During the course of 90 minutes the reaction color changed from bright yellow to black. At this point, the reaction was removed from the heating source and cooled to room temperature. The stirbar was removed from the vial with a magnetic retriever. The vial was resealed and centrifuged (5000 rpm, 5 minutes). The dark precipitate settled to the bottom of the vial and the supernatant was carefully removed with a pipette. The dark precipitate was washed with *t*AmylOH (0.1 mL), re-centrifuged, and solvent was removed with a syringe. The remaining precipitate was used for subsequent reactions. The supernatant was first passed through a pipette packed with a small piece of glass fiber filter paper before use the subsequent reactions.

Reaction with isolated dark precipitate: To the vial containing precipitate, if indicated in **Table 5.6**, quinalidic acid (**L9**, 0.260 mg, 0.0015 mmol, 5 mol%) or picolinc acid (**L8**, 0.190 mg, 0.0015 mmol, 5 mol%) were added. Solid substrate **S1** (13.8 mg, 0.03 mmol, 1 equiv), CsOPiv (21.1 mg, 0.09 mmol, 3 equiv) and 4-iodoanisole (21 mg, 0.09 mmol, 3 equiv) were added. To this mixture, *t*AmylOH (0.25 mL) was added. The vial was equipped with a stirbar, sealed with a Teflon-lined screw cap and heated to 100 ºC in a preheated aluminum block. After 18 hours, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yields of **1b** are shown in **Table 5.6** along with reaction details.

Reaction with supernatant after removal of precipitate: The supernatant was further reacted as follows: To the vial containing the supernatant, if indicated in **Table 5.6**, solid quinaldic acid (**L9**, 0.260 mg, 0.0015 mmol, 5 mol %) or picolinic acid (**L8**, 0.190 mg, 0.0015 mmol, 5 mol %) were added. Additional CsOPiv (14 mg, 0.06 mmol, 2 equiv) and PhI (3.5 μL, 0.03 mmol, 1 equiv) were added. The vial was equipped with a stirbar, sealed with a Teflon-lined screw cap, and heated to 100 ºC in a preheated aluminum block. After 18 hours, the reaction was cooled to room temperature and diluted with DCM (2.5 mL). Hydrazine monohydrate (50 μL) was added and the solution was vigorously stirred for 15 minutes. A 0.2 M stock solution of 1,3,5-trimethoxybenzene (168 mg, 1 mmol) dissolved in DCM (5 mL) was prepared. An aliquot of this solution (150 μL, 0.03 mmol) was added to the reaction as the GC internal standard. The reaction solution was then filtered through a pipette packed with Celite and was analyzed by GC-FID. Yield of **1a** is shown in **Table 5.6** along with reaction details.

Table 5.6. Experiments with Precipitate and Supernatant

entry	ligand	catalyst source	conversion	yield **1a**	yield **1b**
1	----	precipitate	20%	---	10%
2	**L9**	precipitate	81%	---	47%
3	**L8**	precipitate	71%	---	60%
4	----	supernatant	61%	39%	---
5	**L9**	supernatant	96%	73%	---
6	**L8**	supernatant	77%	56%	---

5.5.   Data for X-Ray Crystallography[30]

Structure Determination for 16a

Colorless plates of **ml6052** were grown from a methanol solution of the compound at 70 deg. C. A crystal of dimensions 0.14 x 0.12 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 6 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The crystal was determined to be a two-component non-merohedral twin. Components from both domains as well as overlaps were used as the basis for a HKLF5 reflection file for refinement. The integration of the data yielded a total of 85620 reflections to a maximum 2θ value of 139.52° of which 19462 were independent and 14820 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids of 28433 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1)/c with Z = 8 for the formula $C_{22}H_{25}N_2O_4F_7$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0887 and wR2 = 0.2366 [based on I > 2sigma(I)], R1 = 0.1043 and wR2 = 0.2458 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Structure Determination for 16b

Colorless plates of **ml6052ar** were grown from a hexanes solution of the compound at 68 deg. C. A crystal of dimensions 0.22 x 0.22 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 5 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 33581 reflections to a maximum 2θ value of 138.52° of which 4127 were independent and 4079 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids 26893 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1)/n with Z = 4 for the formula $C_{24}H_{23}N_2O_3F_7$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0389 and wR2 = 0.1004 [based on I > 2sigma(I)], R1 = 0.0392 and wR2 = 0.1007 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

5.6. References

(1) This work was largely completed in collaboration with Dr. Pablo Cabrera at the University of Michigan. The identification of ligand effects and reaction optimization of **S1** and **S10** arylation were conducted by Dr. Pablo Cabrera. Our collaborative work involved the studies on substrate scope and mechanistic investigations.

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