The Discovery, Development, and Mechanistic Investigations of Transition Metal-Catalyzed Organic Reactions

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Abstract

The Discovery, Development, and Mechanistic Investigations of Transition Metal-Catalyzed Organic Reactions

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Organic reactions have wide spread applications in drug development, chemical biology, and materials science. However, traditional chemical techniques can be inefficient *i.e.*, low yields and/or poor selectivity, for constructing structurally complex motifs and for selectively activating strong bonds. To address these problems, there has been an increasing focus on developing new organic reactions catalyzed by transition metals.

This document describes my contributions to transition metal catalysis and includes the following works: 1) Catalytic activation of a single C-F bond in trifluoromethyl arenes for the synthesis of difluoromethyl arenes, 2) Mild copper-catalyzed fluorination of alkyl triflates using potassium fluoride, 3) Copper-catalyzed reduction of alkyl triflates and iodides: an efficient

method for the deoxygenation of primary and secondary alcohols, 4) Synthesis of hindered anilines, and 5) Synthesis of tertiary alkyl amines from terminal alkenes: copper-catalyzed amination of alkyl boranes. For each work, I will describe its significance to organic synthesis, its discovery and development, and the investigation of its mechanism.

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ACKNOWLEDGEMENTS

The university requires this document to be written in English, and given that my writing skills are pretty poor (I am sure Gojko, without hesitation, will attest to this fact.), I'm not certain I can properly fulfill that requirement. I realized this limitation early on when my mentor flat out said: "I just want to scratch my eyes out and roll on the floor when I read your writing." I laughed, and I said that I'd work on it. Over the last few years, I practiced writing. I also did a lot of praying during that time. I guess this thesis is an opportunity for you all to assess the power of prayer. Gojko, if at any time you feel a compelling urge to scratch your eyes out, you can stop reading, I completely understand.

To my mentor Gojko-nator: It took a while for you to develop trust in me and my abilities to science, but it happened. It wasn't a spontaneous process like I'd hoped, but eventually I figured out the magic ingredients needed: diligence and hard work on my part. The road to earning your trust was long and rocky as hell, but it was worth it because I've become a better person and a better scientist. None of that would have happened if you hadn't given me the second (and possibly third) chance that I very much needed. Gojko, thank you for investing in me; it was truly a privilege to be your student.

To my former colleagues Nick Cox, Richard Rucker, Mycah Uehling, and Aaron Whittaker: Working in lab side by side with you all was one of the best experiences of my life. Thank you all for giving me tough skin; it was one of the most valuable gifts I'd ever received.

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To Melrose T. Mailig: My friend, always.

To Holly Dang: Dear sister, thank you for providing me love and support from a far.

To my committee: Thank you for being a part of this process. I appreciate your time.

To Antonio: My love, you are the cornerstone to my (in)sanity.

DEDICATION

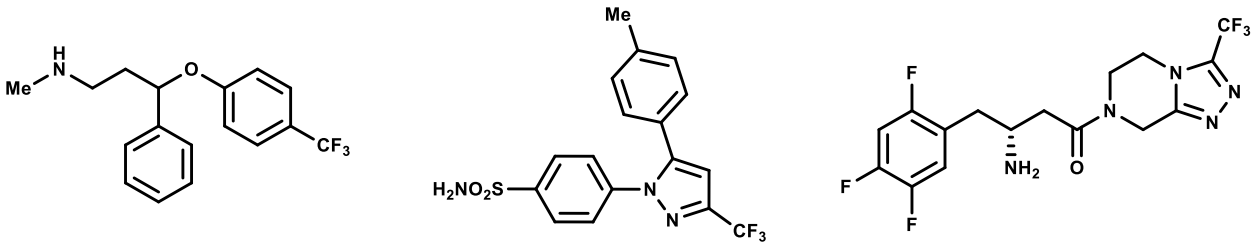
I dedicate this work to my parents. I will never fully realize the sacrifices made by you both to give me a chance to do well in life. Thank you for the unconditional love.

You both mean the world to me.

Chapter 1. CATALYIC ACTIVATION OF A SINGLE C-F BOND IN TRIFLUOROMETHYL ARENES FOR THE SYNTHESIS OF DIFLUOROMETHYL ARENES[1]

1.1 INTRODUCTION

Arene trifluoromethylation is a powerful method for fluorinating organic compounds within the context of drug discovery and development.[2,3] Fluorination of aromatic compounds enhances the therapeutic properties of an organic molecule through changes in bioavailability, binding selectivity, and metabolic stability. Accordingly, a number of reliable techniques for synthesizing trifluoromethyl arenes, ($ArCF_3$), have been developed over the last twenty years and has enabled arene trifluoromethylation to become a standard practice in medicinal chemistry. As a result of the extensive application of trifluoromethyl arenes in medicinal chemistry, a number of successful prescription drugs such as Prozac, Celebrex, and Januvia were developed (Fig. 1.1).



Prozac Celebrex Januvia

Figure 1.1. Prozac, Celebrex, and Januvia are examples of successful pharmaceuticals containing $ArCF_3$.

The success observed with drugs containing $ArCF_3$ groups has garnered interest in difluoroalkyl arenes, $ArCF_2R$. Due to the similarities in structure, the difluoroalkyl, (CF_2R), and trifluoromethyl, (CF_3), groups produce analogous effects on the therapeutic properties of a drug-like molecule. However, the CF_2R substituent can offer greater potential in terms of structural and functional diversity, which is often critical for optimizing bio-lead compounds *i.e.*,

molecules identified for favorable therapeutic properties. In order to efficiently explore $ArCF_2R$ in medicinal chemistry, synthetic techniques that allow the direct access of $ArCF_2R$ groups from $ArCF_3$ precursors are needed. This strategy would enable the CF_3 group to function as a starting point for structural diversification and fundamentally change the process of optimizing $ArCF_3$ bio-lead molecules. Finally, it would also effectively leverage the reliable techniques developed in the last two decades for synthesizing $ArCF_3$.

Unfortunately, selective functionalization of a single C-F bond in $ArCF_3$ remains one of the great unmet challenges in organic chemistry (Fig. 1.2 A). The problems associated with the selective C-F functionalization become evident when we consider the fundamental properties of C-F bonds in $ArCF_3$. The C-F bond is the strongest single bond to carbon, with a bond dissociation energy (BDE) of 109 kcal/mol in CH_3-F [4].

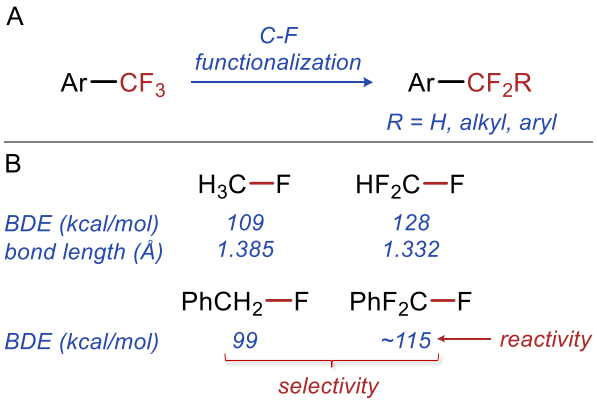


Figure 1.2. Functionalization of C-F bond. (A) Application in synthesis of $ArCF_2R$. (B) Problems associated with selective C-F activation in $ArCF_3$.

Even a relatively weak C-F bond in benzyl fluoride has a BDE of 99 kcal/mol (Fig. 1.2 B) [5]. Not surprisingly, any transformation involving the activation of such strong bonds is difficult to accomplish, despite the significant progress made in the field of C-F bond activation.[6,7] Furthermore, with increased fluorination of a carbon atom, C-F bonds become stronger and

shorter, and thus less reactive (Fig. 1.2 B).[8-10] As a result, selective functionalization of a single C-F bond in $ArCF_3$ poses an additional selectivity challenge: the product of the C-F functionalization ($ArCF_2R$) is inherently more reactive than the starting material ($ArCF_3$). Overcoming this selectivity problem has proven to be particularly difficult, and so far no examples of a catalytic functionalization of a single C-F bond in a trifluoromethyl group have been reported in the literature.

In this report, we describe the discovery of a method for the catalytic activation of a single C-F bond in $ArCF_3$ that results in the selective formation of $ArCF_2H$. We present the results of mechanistic studies that provide insight into the source of the unusual selectivity and the results of our exploration of the substrate scope.

1.2 Catalytic Activation of a Single C-F bond in Trifluoromethyl Arenes

1.2.1 *Initial Discovery and Reaction Optimization*

We recently discovered that the reduction of 4-(4-MePh)$C_6H_4CF_3$ (**1**) to 4-(4-MePh)$C_6H_4CH_3$ (**2**) can be accomplished at room temperature using just 1 mol % of palladium(II) acetate as a catalyst, in the presence of triphenylsilane and potassium *tert*-butoxide (Table 1.1, entry 1). We also found that replacing potassium *tert*-butoxide with sodium *tert*-butoxide abolishes the reactivity. Even at a higher temperature reduction products ($ArCH_3$ and $ArCF_2H$) are obtained in low yields (Table 1.1, entry 2). However, the addition of a copper co-catalyst restores the reactivity, and leads to the formation of 4-(4-MePh)$C_6H_4CF_2H$ as the major product of the reaction (Table 1.1, entry 3). Considering that all known methods for catalytic reduction of $ArCF_3$ produce only the fully reduced $ArCH_3$ products, [11-17] we were intrigued by

the unusual selectivity of our reduction reaction and decided to pursue the development of a synthetic method for the selective mono-reduction of $ArCF_3$.

Table 1.1. The discovery and initial optimization of monodefluorination reaction.

1 **2** **3**

Entry[a]	catalyst	base	Ar—CH_3	Ar—CF_2H	conversion
1.	$Pd(OAc)_2$ 1 mol %	KO*t*-Bu	94%	0%	100%
2.[b]	$Pd(OAC)_2$ 1 mol %	NaO*t*-Bu	8%	7%	-
3.[b]	$Pd(OAc)_2$ 1 mol % & SIPrCuCl 1 mol%	NaO*t*-Bu	12%	52%	90%
4.[c]	$Pd(OAc)_2$ 3 mol % & SIPrCuCl 20 mol%	NaO*t*-Bu	15%	51%	100%
5.[c]	$Pd(OAc)_2$ 3 mol % & SIPrCuCl 20 mol% & 2-pyridone 5 mol %	NaO*t*-Bu	3%	56%	100%

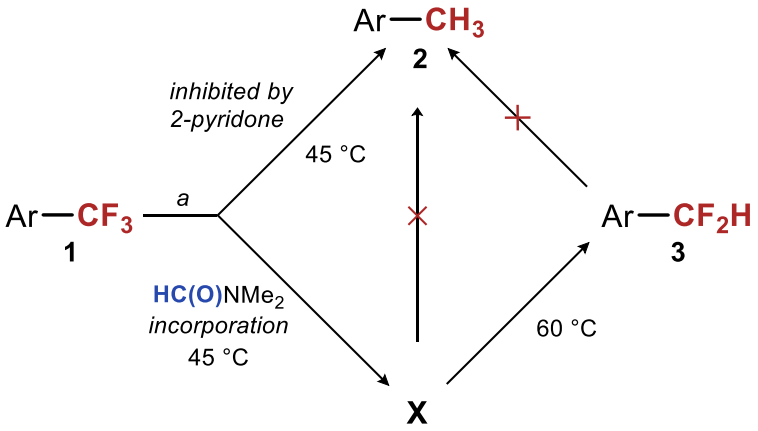
a) Reaction conditions: Ph_3SiH (4 equiv), base (5 equiv), DMF, 25 °C, 1 h. b) Reaction performed at 45 °C for 11 h then 60 °C for 17 h. c) Reaction performed at 45 °C for 2 h, followed by 60 °C for 17 h. Ar = 4-(4-CH_3Ph)C_6H_4; SIPr = N,N'-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; DMF = N,N-dimethylformamide. All yields were determined by GC using an internal standard.

In the initial experiments we confirmed that both copper and palladium catalysts were necessary for the observed selectivity. Furthermore, we found that in the absence of both catalysts, starting material is fully recovered. Our initial attempts to optimize the reaction focused on improving the conversion of the starting material. We achieved complete conversion of 4-(4-MePh)$C_6H_4CF_3$ by increasing the catalyst loading and modifying the ratio of the two catalysts (Table 1.1, entry 4). However, these changes did not improve the yield and instead decreased the selectivity. We also explored modifying the palladium catalyst with various classes of ligands and found that phosphine and *N*-heterocyclic carbene (NHC) ligands completely inhibited the reaction. The presence of amines, diamines, amides, and amino alcohols had a small, but consistently positive effect on selectivity. The greatest improvement was observed in the presence of 5 mol % of 2-pyridone (Table 1.1, entry 5). To facilitate further reaction

optimization, we decided to focus on gaining a better understanding of the reaction mechanism and the source of the observed selectivity.

1.2.2 *Reaction Mechanism*

Our first hypothesis was that $ArCF_2H$ is an intermediate in the formation of $ArCH_3$ and that high selectivity can be achieved only at a low conversion or with a low mass balance. However, the results of experiments in which we closely monitored the progress of the reaction shown in entry 3 of Table 1.1 contradicted this hypothesis. We found that the conversion of the starting material reached 90% and stopped after 11 hours at 45 °C. At this point, most of the fully reduced $ArCH_3$ **2** had already been formed (11%), while almost no $ArCF_2H$ **3** (4%) was present in the reaction mixture (see Fig. 1.7). At the same time point, the major component of the reaction mixture was intermediate **X**, which over the next 18 hours was converted into $ArCF_2H$ **3** (Fig. 1.3).



Scheme 1.1 The reaction mechanism. [a] Reactions conditions shown in Table 1, entries 3 or 5.

Over the same period, essentially no more **2** was formed (12% vs 11%). The same observations were made when the reaction was performed in the presence of 2-pyridone (Table 1, entry 5) (Fig. 1.8). The only difference is that 2-pyridone inhibits the formation of **2**. Overall, the results

of these experiments suggest that the formation of $ArCH_3$ and $ArCF_2H$ occurs through two independent reaction pathways, and that $ArCF_2H$ and intermediate **X** are not intermediates in the formation of $ArCF_3$ (Scheme 1.1). Encouragingly, this finding suggested that, at least in principle, high yields of $ArCF_2H$ can be obtained with high selectivity.

1.2.2.1 *Intermediate X*

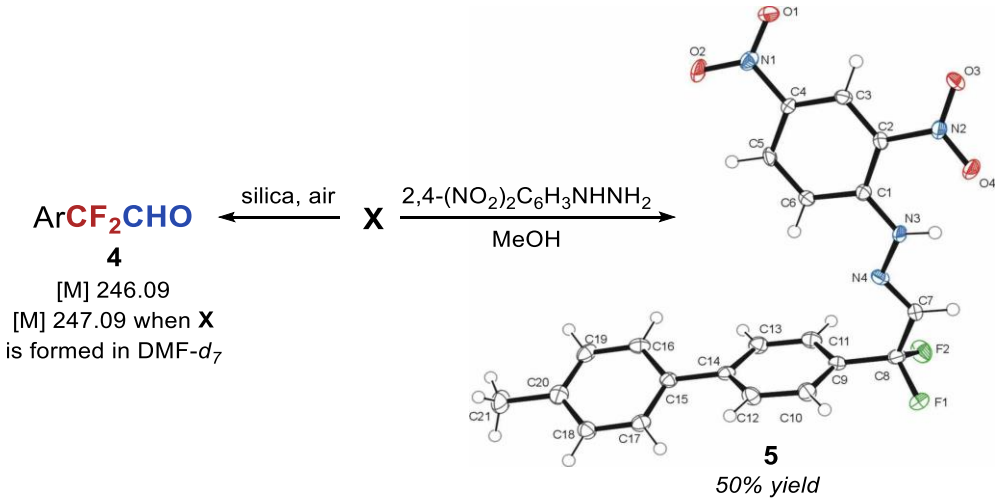


Figure 1.3. Identity of intermediate X. Structure of the intermediate **X**. Ar = 4-(4-CH_3Ph)C_6H_4.

Our next goal was to determine the structure of intermediate **X**. The analysis of the reaction mixture by mass spectrometry suggested $ArCF_2CHO$ **4** as the intermediate (Fig. 1.3). Furthermore, a reaction performed in DMF-*d7* solvent resulted in the formation of the mono-deuterated intermediate (mass increased by 1 amu), indicating that the formyl group of $ArCF_2CHO$ is likely derived from DMF. We were also able to isolate the 2, 4-dinitrophenyl hydrazone of 4-(4-MePh)$C_6H_4CF_2CHO$ (**5**) in 50% yield from the reaction mixture containing intermediate **X** as the major species. The structure of **5** was confirmed by x-ray crystallography (Fig. 1.3). On the other hand, attempts to establish the presence of the aldehyde in the reaction mixture by in situ methods were not successful. For example, in situ analysis of the reaction mixture by ^{1}H and ^{13}C NMR indicated no presence of $ArCF_2CHO$. Furthermore, a significant

amount of the aldehyde could be identified in the mass spectrum only if the sample was exposed to air and silica gel. Overall, these results are consistent with the idea that intermediate **X** is a hemiacetal or a hemiaminal of $ArCF_2CHO$ **4**, or a silylated version of the two, and that the aldehyde is revealed only in the presence of a protic acid (MeOH or moisture).

1.2.2.2 *Role of a Mild Brønsted Acid*

Based on the hypothesis that intermediate **X** is a silylated hemiacetal or a hemiaminal, we speculated that the relatively slow conversion of intermediate **X** to the aldehyde before decarbonylation to the difluoromethyl arene may be responsible for the low yield of the desired product. We reasoned that decomposition of the intermediate could be facilitated by the presence of a mild Brønsted acid. Indeed, we found that if 1 equivalent of *tert*-butanol was added to the reaction mixture after full conversion of the 4-(4-MePh)$C_6H_4CF_3$ is achieved, there was a dramatic increase in both the rate of the reaction and in the yield of $ArCF_2H$. The complete conversion of intermediate **X** was achieved in 2 hours at 60 °C, and $ArCF_2H$ **3** was obtained in 95% yield (Fig. 1.4 A). Similar results can be accomplished using phenol as an acid. Addition of an acid at the beginning of the reaction resulted in significantly lower yields.

To gain more information about the mechanism of decarbonylation and the role of the acid we performed isotope labeling experiments. We found that the hydrogen atom in $ArCF_2H$ **3** is derived from *tert*-butanol, and not from the silane or from DMF (via intermediate **X**) (Fig. 1.4 B). Based on these results, we favor the mechanism of decarbonylation that involves a difluorobenzyl anion intermediate, akin to the haloform reaction. It is interesting to note that the presence of the two intermediates (intermediate X and difluorobenzyl anion) in this transformation provides a great opportunity for the development of other transformations of $ArCF_3$.

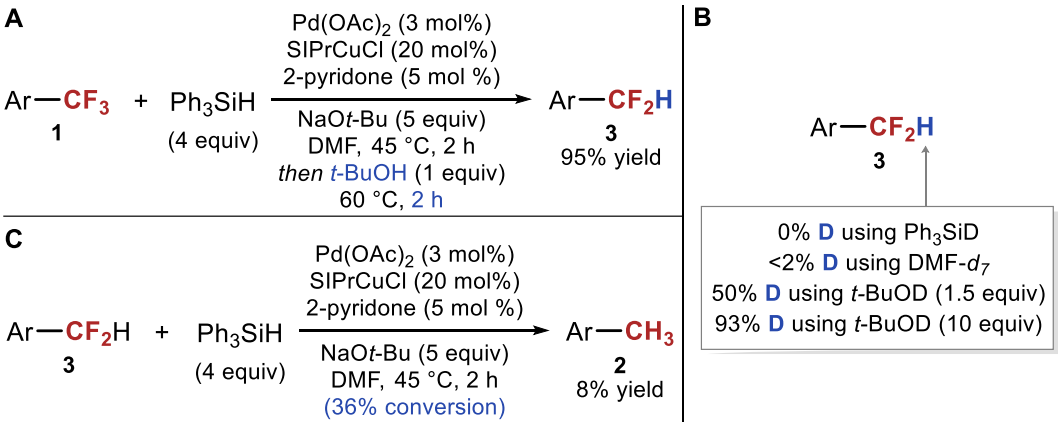


Figure 1.4. Studies of the mono-defluorination reaction. (A) The effect of *t*-BuOH on the rate of the formation of $ArCF_2H$. (**B**) Results of deuterium labeling studies. (**C**) Reactivity of $ArCF_2H$. Ar = 4-(4-CH_3Ph)C_6H_4; SIPr = *N*,*N*'-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; DMF = *N*,*N*-dimethylformamide.

Finally, we were interested in the mechanism of C-F activation. The general understanding of the catalytic C-F activation by transition metals suggest that $ArCF_2H$ would be more reactive than $ArCF_3$. However, we found that the opposite is true. With 4-(4-MePh)$C_6H_4CF_2H$ as the substrate, only ~36% conversion is achieved at the time necessary for the full conversion of $ArCF_3$ **1** (2 h at 45 °C) (Figure 1.4 C). One mechanistic hypothesis that accounts for this order of reactivity ($ArCF_3$ > $ArCF_2H$) is C-F activation by a single electron transfer: $ArCF_3$ are better electron acceptors than $ArCF_2H$ [18], although the difference in energy of σ* orbitals is often too small to allow good selectivity [19,20]. This mechanism would also explain why intermediate **X** is resistant to further reduction. Furthermore, mixtures of silanes and alkoxides have previously been implicated in single electron chemistry [21,22]. However, it is important to note that the presence of transition metal catalysts is essential for C-F activation. In the absence of transition metals, we can fully recover the starting material, in agreement with the observations made by Grubbs and Stoltz [22].

1.2.3 *Scope*

After exploring the mechanism of the mono-defluorination reaction, we turned our attention to further the reaction optimization and the exploration of the substrate scope. In the process, we found that SIPrCuCl could be replaced by significantly less expensive and commercially available CuF_2, and that consistently better selectivity could be obtained using $KOSiMe_3$ instead of NaO*t*-Bu. The optimized reaction conditions shown in Table 1.2, were used in mono-reduction of several trifluoromethyl arenes. We found that the reaction can be accomplished in the presence of amines, ethers, and acetals with several biphenyl and aryl substrates. Reducible groups, such as aryl halides, nitro arenes, or nitriles are reduced under the reaction conditions. ortho-substituted trifluoromethyl arenes provided low yields of the desired products.

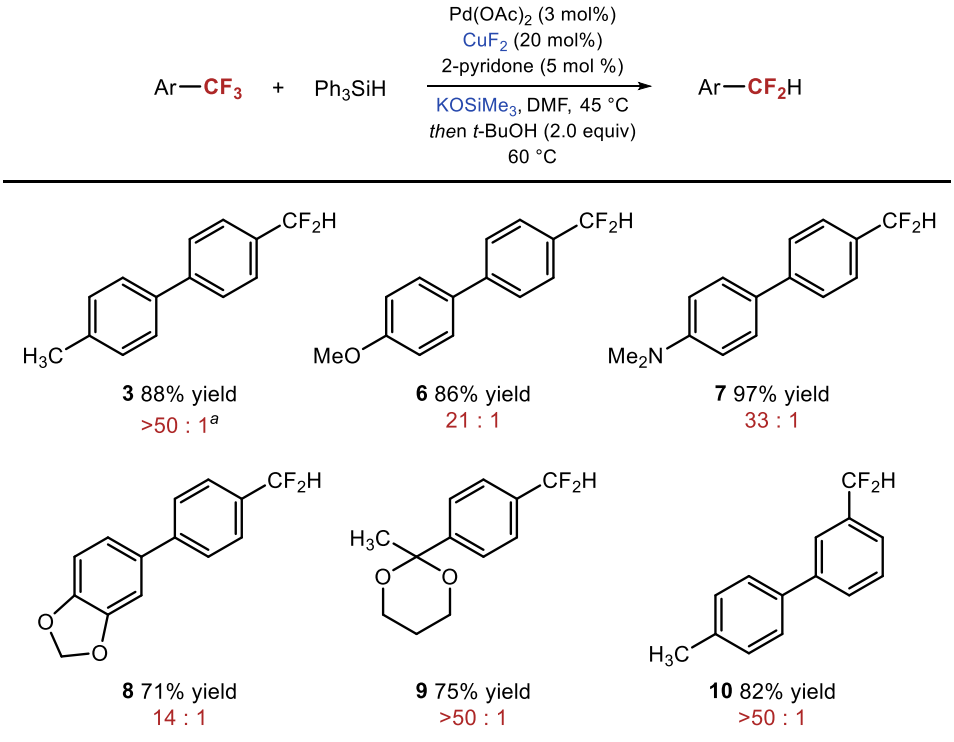


Table 1.2. Optimized reaction conditions and reaction scope.

1.2.4 *Conclusion*

We have discovered a combination of palladium and copper catalysts that allows selective activation of a single C–F bond in trifluoromethyl arenes under relatively mild conditions. This discovery allowed the development of a method for selective reduction of $ArCF_3$ to $ArCF_2H$. More importantly, the unique mechanism of the reaction and the unusual source of the selectivity provide new opportunities for the development of useful transformations based on selective C–F activation.

1.3 EXPERIMENTAL

1.3.1 *General Information*

All reactions were performed in a nitrogen-filled glovebox (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh) or activated alumina purchased from Sigma Aldrich (CAS# 344-28-1). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to the residual solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 Mass Spectrometer, a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer, or a Hewlett Packard

5971A gas chromatograph Mass Spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 µm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad.

Materials: DriSolv™ DMF (EMD Millipore) was stored over activated 3Å molecular sieves in the glovebox and used without any further purification. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Common commercial reagents such as triphenylsilane, sodium *tert*-butoxide, potassium trimethylsilanoate, palladium(II) acetate, and copper (II) fluoride were purchased from Sigma-Aldrich Co., VWR International, LLC., TCI America, Gelest, or STREM Chemicals, Inc and was used without further purification.

1.3.2 *Reaction Development*

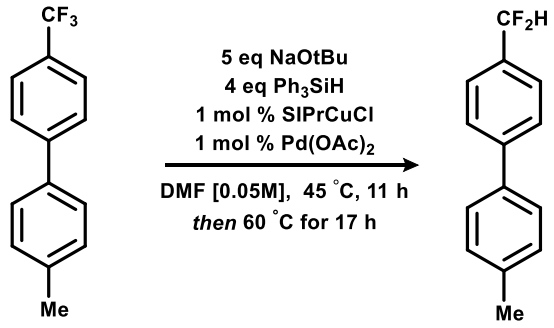


Figure 1.5. Standard reaction conditions without *t*-BuOH

Procedure A (General procedure used in experiments shown in Table 1.1, entries 2 and 3): In a glovebox, a dram vial was charged with a stir bar, sodium *t*-butoxide (24.0 mg, 0.25 mmol, 5.0 equiv), triphenylsilane (52.1 mg, 0.20 mmol, 4.0 equiv), trifluoromethyl arene **1** (11.8 mg,

0.05 mmol, 1.0 equiv), and internal standard (dodecane, 4.3 mg, 0.025 mmol, 0.05 equiv). 500 µL of DMF was added and reaction was allowed to stir at 25°C for 5 minutes. SIPrCuCl (when applicable, 0.2 mg, 0.001 mmol, 0.01 equiv from a 0.1 M stock solution) and palladium (II) acetate (when applicable, 0.1 mg, 0.001 mmol, 0.01 equiv. from a 0.1 M stock solution) was then deposited into a separate vial and diluted to a total volume of 500 µL with DMF and transferred into the reaction vessel. The reaction vessel was then sealed and temperature was elevated and maintained at 45 °C until full conversion of substrate was observed by GC analysis. When conversion of starting substrate was observed to have stopped or was completed, the temperature was increased to 60 °C and the progress of the reaction was monitored using GC analysis.

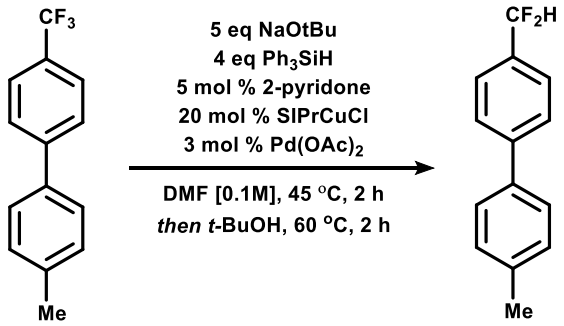


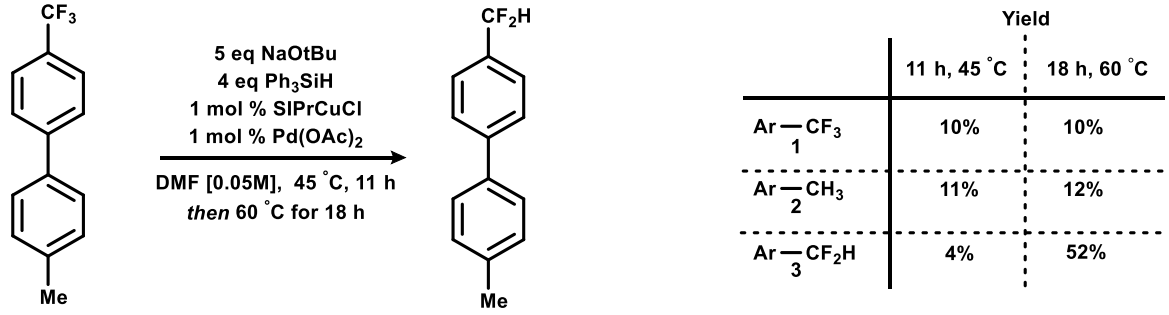
Figure 1.6. Standard reaction conditions with *t*-BuOH

Procedure B (General procedure used in experiments shown in Table 1.1 (entries 4 and 5), Table 1.2, and Fig. 1.6): In a glovebox, a dram vial was charged with a stir bar, sodium *t*-butoxide (24.0 mg, 0.25 mmol, 5.0 equiv), trifluoromethyl arene **1** (11.8 mg, 0.05 mmol, 1.0 equiv), internal standard (dodecane, 4.3 mg, 0.025 mmol, 0.05 equiv), 2-pyridone (where applicable, 0.2 mg, 0.003 mmol, 0.05 equiv from a 0.15 M stock solution), SIPrCuCl (4.9 mg, 0.010 mmol, 0.20 equiv) and palladium(II) acetate (0.3 mg, 0.002 mmol, 0.03 equiv. from a 0.17 M stock solution), and 168 µL DMF. After allowing the mixture to stir vigorously at 45 °C for 2 minutes, triphenylsilane (52.1 mg diluted up to 300 µL of solvent, 0.200 mmol, 4.0 equiv.) was

added slowly (due to evolution of gas) to the stirring reaction mixture. The reaction vessel was then sealed and temperature was maintained at 45 °C until full conversion of substrate was observed with ^{19}F NMR analysis. *t*-BuOH (when applicable, 3.7 mg, 1.0 mmol, 1.0 equiv) was then added and the reaction temperature was increased to 60 °C. GC analysis was used to monitor reaction until completion. **Note* Pressure build up from gas production occurs as the starting substrate gets consumed in the reaction.*

1.3.3 *Reaction Time Course*

Procedure A (as described previously) was used to set up the experiment shown in **Figure 1.7**. Reaction progress was monitored by taking aliquots for GC analysis every hour.



	Yield	
	11 h, 45 °C	18 h, 60 °C
Ar—CF_3 (1)	10%	10%
Ar—CH_3 (2)	11%	12%
Ar—CF_2H (3)	4%	52%

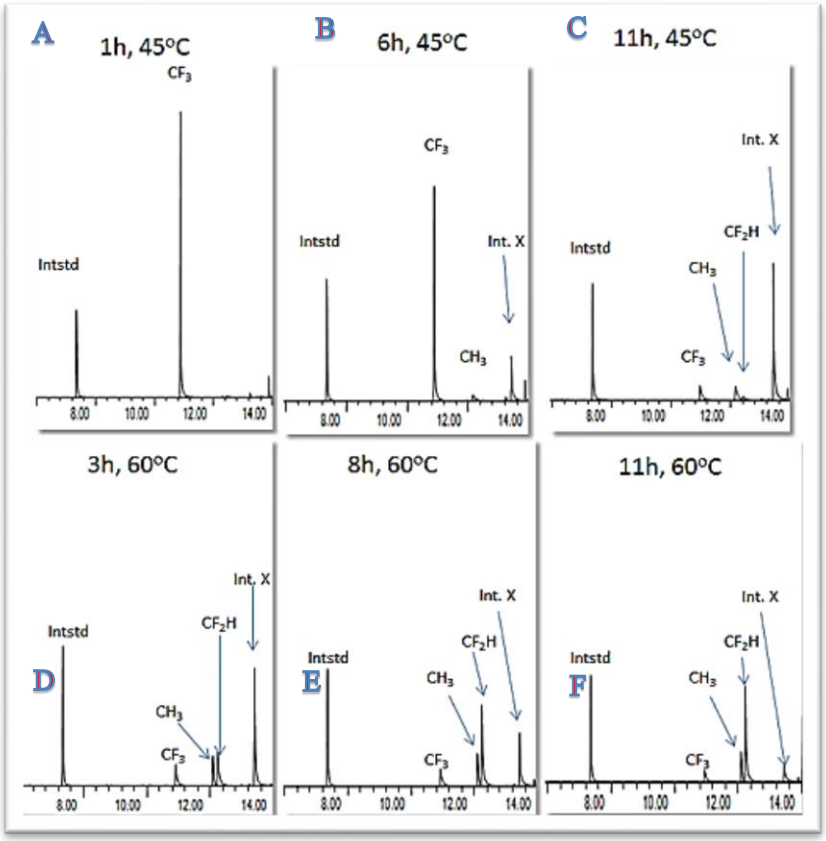


Figure 1.7. Time course of reaction with *t*-BuOH Shown are results and GC traces of the reaction progress at selected time points. Abbreviations: Instd (Internal Standard), Int.X (Intermediate X.)

Procedure B (as described previously) was used to set up the experiment shown in **Figure 1.8**. Reaction progress was monitored by taking aliquots for GC analysis.

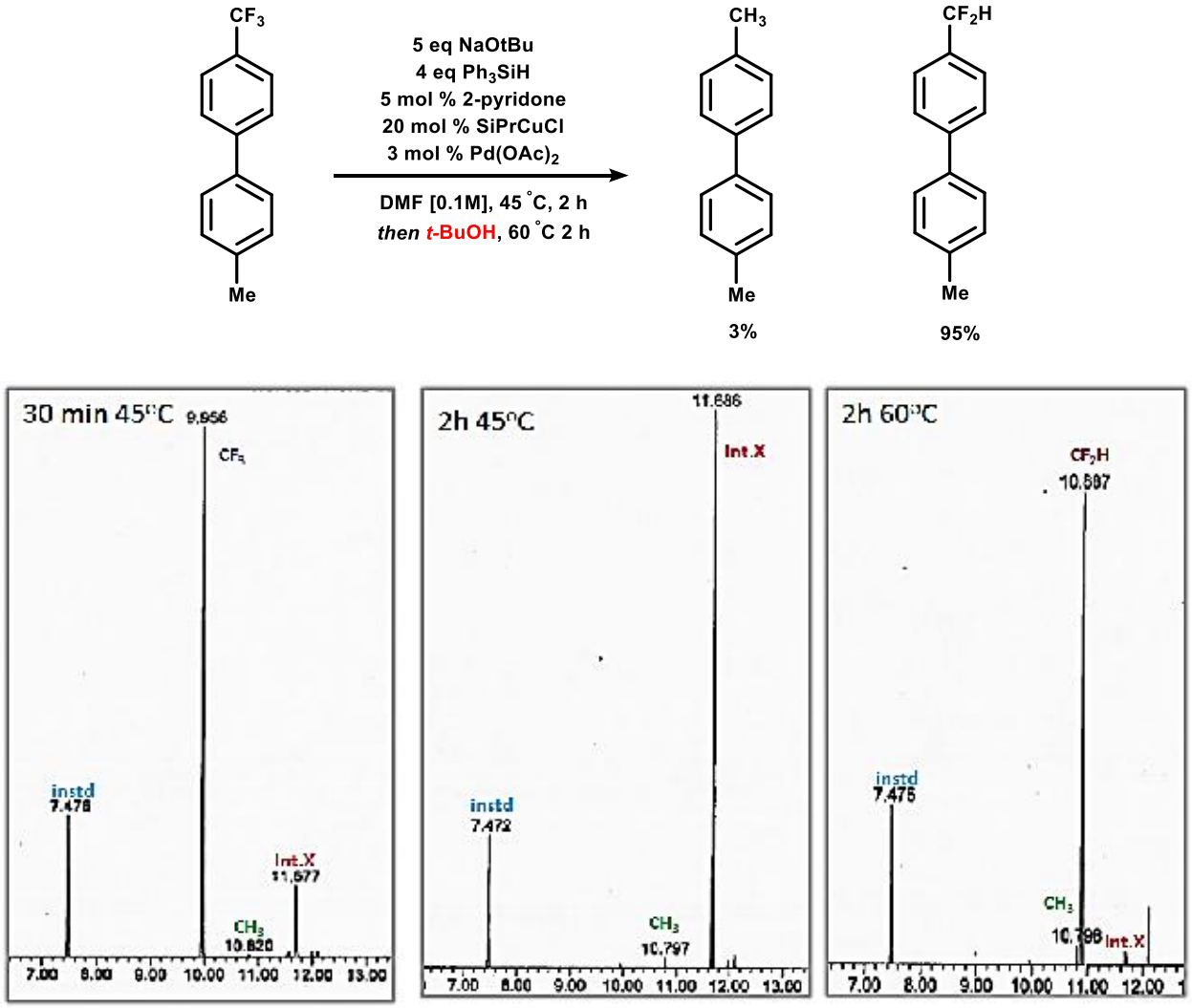


Figure 1.8. Optimized reaction profile with addition of *t*-BuOH. Shown are the GC results of the reaction progress at selected time points.

1.3.4 *Intermediate X: Isolation and Characterization*

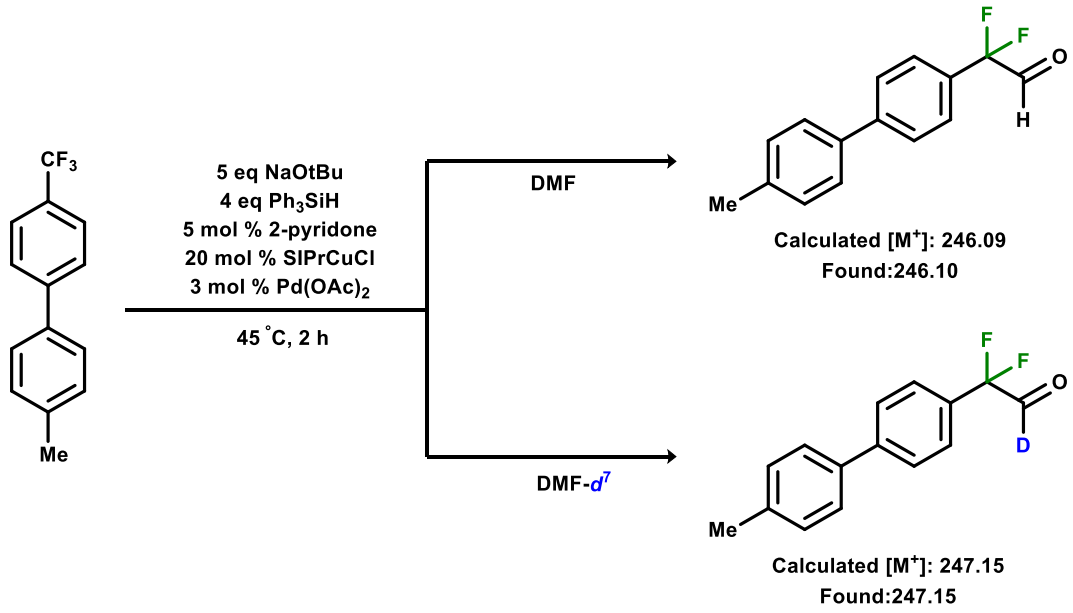


Figure 1.9. GC-MS observations on Intermediate X.

1.3.4.1 *Isolation of Intermediate X.*

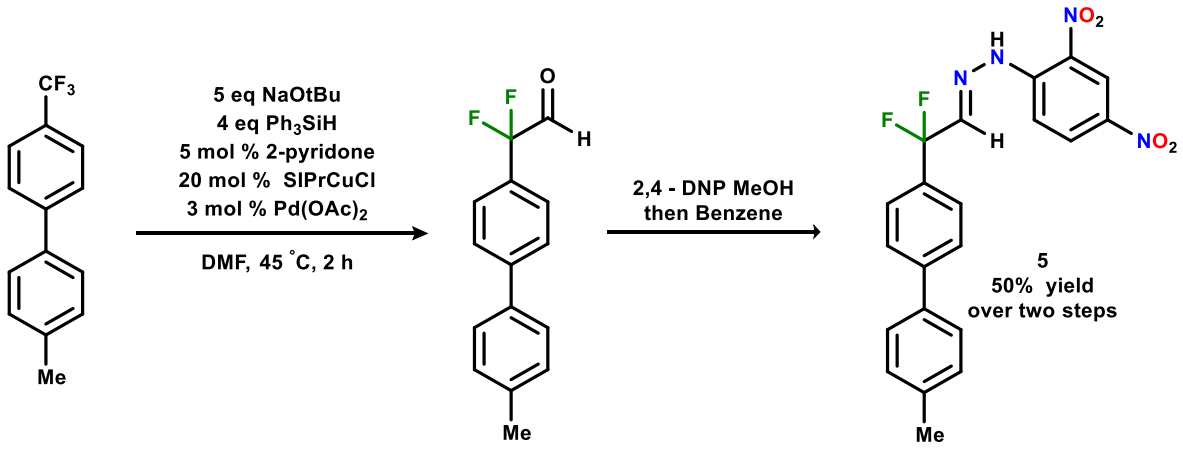


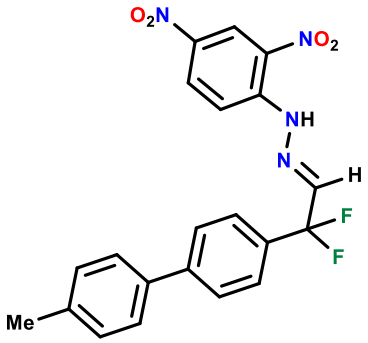
Figure 1.10. Isolation and 2, 4 – DNP derivative of Intermediate X (0.50 mmol scale).

In a glovebox, a scintillation vial was charged with a stir bar, sodium *t*-butoxide (240.0 mg, 0.25 mmol, 5.0 equiv), trifluoromethyl arene **1** (118 mg, 0.50 mmol, 1.0 equiv), internal standard (dodecane, 43 mg, 0.25 mmol, 0.05 equiv), 2-pyridone (2.4 mg, 0.025 mmol, 0.05 equiv from a

0.1 M stock solution), SiPrCuCl (49.1 mg, 0.10 mmol, 0.20 equiv from a 0.1 M stock solution), palladium(II) acetate (3.0 mg, 0.015 mmol, 0.03 equiv from a 0.1 M stock solution), and 1680 µL DMF. After allowing the mixture to stir vigorously at 45 °C for 2 minutes, triphenylsilane (520.8 mg dissolved in 3000 µL of solvent, 0.20 mmol, 4.0 equiv) was added slowly (due to evolution of gas) to the stirring reaction mixture. The reaction vessel was then sealed and temperature was maintained at 45 °C until full conversion of substrate was observed by ^{19}F NMR analysis. Pressure builds up over time in the reaction vessel, and it was necessary to vent the vessel intermittently during the substrate conversion phase. Temperature was maintained at 45 °C until full conversion of substrate was observed. At this point, the reaction mixture was loaded directly onto a 100 g silica column and flushed with 0-35% diethyl ether in hexanes. GC analysis was used to determine the fractions that contained Intermediate X. Concentrated combined fractions down until 2 mL of solvent remained.

1.3.4.2 *Synthesis of 2, 4-Dinitrophenylhydrazine (2, 4- DNP) derivative of Intermediate X.*

To the 2 mL solution of intermediate X obtained after the column chromatography (see above) in a scintillation vial, was added 3 mL of freshly prepared 2, 4- DNP solution. 5 mL of benzene was then layered over the reaction mixture and allowed to sit overnight. The resulting orange crystals were collected via Buchner funnel filtration and washed with small portions of cold benzene. The final product was then dried under reduced pressure. *(Preparation of 2, 4-DNP solution: Suspend 2.0 g of 2, 4-dinitrophenylhydrazine in 100 mL of methanol. Cool mixture to 0 °C, and cautiously add 4.0 mL of concentrated sulphuric acid).*



(E)-1-{2,2-difluoro-2-[4-(4-methylphenyl)phenyl]ethylidene}-2-(2,4-dinitrophenyl)hydrazine (5): Compound **5** was isolated as an orange crystal, 107 mg, 50% overall yield from two steps shown in figure S4. ^{1}H NMR (300 MHz, C_6D_6) δ 10.29 (s, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 7.98 – 7.20 (m, 7H), 7.07 (t, *J* = 8.6 Hz, 3H), 6.32 (td, *J* = 5.0, 1.1 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 145.1, 144.0, 140.1, 138.7, 137.4, 131.1, 130.7, 130.2, 127.5, 127.5, 126.8, 126.8, 126.7, 123.5, 118.2 (t, *J* = 37.7 Hz), 117.5, 108.9 (t, *J* = 26.6 Hz), 93.9 (t, *J* = 239.8 Hz), 21.4. ^{19}F NMR (282 MHz, C_6D_6) δ -94.9 (d, *J* = 5.0 Hz).

1.3.4.3 *X-Ray Crystallography Data*

A yellow prism, measuring 0.32 x 0.03 x 0.03 mm^3 was mounted on a glass capillary with oil. Data was collected at -173^{o}C on a Bruker APEX II single crystal X-ray diffractometer, Mo-radiation.

Crystal-to-detector distance was 40 mm and exposure time was 240 seconds per degree for all sets. The scan width was 1.0^{o}. Data collection was 99.8% complete to 24.76^{o}. A total of 37,909 (merged) reflections were collected covering the indices, h = -28 to 28, k = -7 to 7, l = -29 to 29. 3,300 reflections were symmetry independent and the R_{int} = 0.141 indicated that the data was less than average quality (average quality 0.07). Indexing and unit cell refinement indicated an orthorhombic lattice. The space group was found to be P b c a (No.61).

The data was integrated and scaled using SAINT, SADABS within the APEX2 software package by Bruker.[1]

Solution by direct methods (SHELXS[2], SIR97[3]) produced a complete heavy atom phasing model consistent with the proposed structure. The structure was completed by difference Fourier synthesis with SHELXL97.[4,5] Scattering factors are from Waasmair and Kirfel.[6] Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C---H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters U_{eq} were fixed such that they were $1.2U_{eq}$ of their parent atom Ueq for CH's and $1.5U_{eq}$ of their parent atom U_{eq} in case of methyl groups. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares.

A close bond distance between O4 and itself related through symmetry of 2.60 Å is noticed. This is due to hydrogen bond interactions with the hydrogen of N3.

---

1. Bruker (2007) APEX2 (Version 2.1-4), SAINT (version 7.34A), SADABS (version 2007/4), BrukerAXS Inc, Madison, Wisconsin, USA.

2. A. Altomare, *et al.*, *J. Appl. Crystallogr.* **32**, 115-119 (1999).

3. A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **26**, 343-350 (1993).

4. Sheldrick, G. M. SHELXL-97: Program for the Refinement of Crystal Structures 1997 University of Gottingen, Germany.

5. S. Mackay *et al.*, *MaXus: a computer program for the solution and refinement of crystal structures from diffraction data*. University of Glasgow, Scotland, 1997.

6. D. Waasmaier, A. Kirfel, *Acta Crystallogr.* A. **51**, 416 (1995).

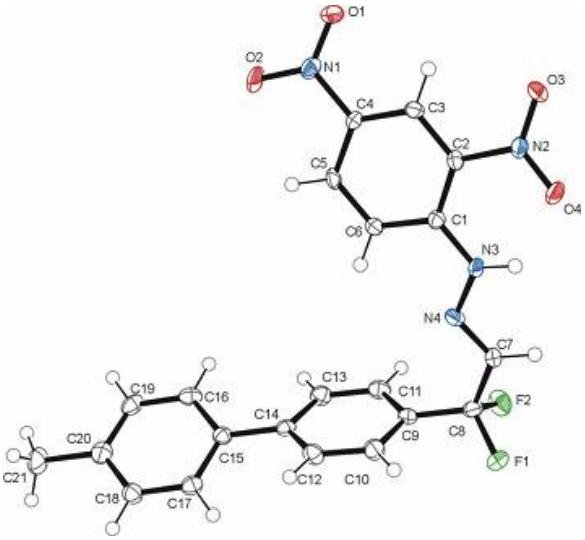


Figure 1.11. ORTEP of the structure with thermal ellipsoids at the 50% probability level.[7]

Crystal data and structure refinement for Intermediate X.

Identification code	hd_bam_0ma	
Empirical formula	C21 H16 F2 N4 O4	
Formula weight	426.38	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 24.4634(19) Å	□= 90°.
	b = 6.1982(4) Å	□= 90°.
	c = 25.443(2) Å	□ = 90°.
Volume	3857.8(5) Å^3	
Z	8	

[7]. L. Farrugia, *J. Appl. Crystallogr.* **30**, 565 (1997).

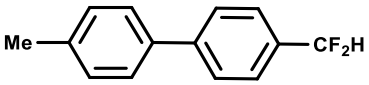
Density (calculated)	1.468 Mg/m^3
Absorption coefficient	0.117 mm^{-1}
F(000)	1760
Crystal size	0.32 x 0.03 x 0.03 mm^3
Theta range for data collection	1.80 to 24.76°.
Index ranges	-28<=h<=28, -7<=k<=7, -29<=l<=29
Reflections collected	37909
Independent reflections	3300 [R(int) = 0.1414]
Completeness to theta = 24.76°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9965 and 0.9636
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3300 / 0 / 281
Goodness-of-fit on F^2	1.003
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.0925
R indices (all data)	R1 = 0.1047, wR2 = 0.1112
Largest diff. peak and hole	0.283 and -0.254 $e.Å^{-3}$

1.3.5 *Representative Procedure for Catalytic Mono-Defluorination (0.5 mmol scale)*

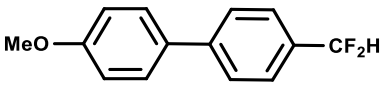
In a nitrogen filled glovebox, a scintillation vial was charged with a stir bar, potassium trimethyl siloxide (449.0 mg, 7.0 equiv 4.0 mmol), trifluoromethyl arene substrate **1** (118.2 mg, 0.5 mmol, 1.0 equiv), 2-pyridone (2.4 mg, 0.025 mmol 0.05 equiv), copper(II) fluoride (10.2 mg, 0.1 mmol, 0.2 equiv) and DMF was added to obtain a reaction volume of 2 mL. The resulting mixture was

stirred at 45 °C until homogenized, and palladium acetate (3.4 mg, 0.015 mmol, 0.03 equiv) was added. After allowing the resulting mixture to stir vigorously at 45 °C for an additional 10 minutes, triphenylsilane (651 mg, 2.5 mmol, 5.0 equiv) dissolved in 3 mL of DMF was added slowly (evolution of a gas). Pressure builds over time in the reaction vessel, and it was necessary to vent the vessel intermittently during the substrate conversion phase. Temperature was maintained at 45 °C until full conversion of substrate was observed by ^{19}F NMR. When conversion of starting substrate was completed, *t*-BuOH (74.1mg, 2.0 equiv 1.0 mmol) was added. Reaction mixture was placed at 60 °C and progress of the reaction was monitored using GC analysis. When full conversion of the intermediate was observed, the reaction mixture was passed through a pad of silica gel using EtOAc as an eluent. The crude mixture was concentrated under reduced pressure and purified by column chromatography using silica gel.

1.3.6 *Characterization Data for Difluoromethylarene Products*

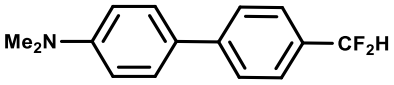


1-[4-(difluoromethyl)phenyl]-4-methylbenzene (3): Isolated as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.26 (m, 8H), 6.69 (t, *J* = 56.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 137.9, 137.4, 133.04 (t, *J* = 22.3 Hz), 129.8, 127.3, 127.2, 126.12 (t, *J* = 5.6 Hz), 114.94 (t, *J* = 238.5 Hz), 21.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.11 (d, *J* = 56.5 Hz). GC/MS calculated for $[M]^+$ 218.09, found 218.10. FTIR (neat, cm^{-1}): 3047 (m), 2906 (m), 1609 (w), 1495 (w), 1372 (m), 1264 (s), 1023 (s).

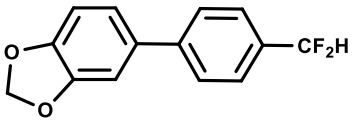


1-[4-(difluoromethyl)phenyl]-4-methoxybenzene (6): Isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.47 (m, 6H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.69 (t, *J* = 56.6 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 143.3, 132.6 (t, *J* = 22.4

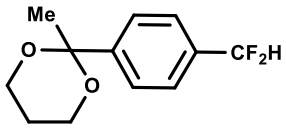
Hz), 132.6, 128.3, 126.9, 126.0 (t, J = 6.0 Hz), 114.8 (t, J = 238.3 Hz), 114.4, 55.4. ^{19}F NMR (282 MHz, C_6D6) δ -110.08 (d, J = 56.4 Hz). GC/MS calculated for $[M]^+$ 234.09, found 234.10. FTIR (neat, cm^{-1}): 3000 (w), 2972 (s), 2883 (m), 1661 (w), 1467 (m), 1379 (s), 1309 (m), 1161 (s), 1130 (s).



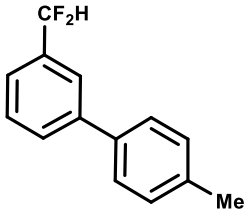
N,N-dimethyl-4-[4-(difluoromethyl)phenyl]aniline (7): Isolated as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.40 (m, 6H), 6.97 – 6.26 (m, 3H), 3.02 (s, 6H). ^{13}C NMR (126 MHz, THF) δ 151.6, 144.8 (t, J = 2.1 Hz), 133.2 (t, J = 22.4 Hz), 128.6, 128.4, 126.9 (t, J = 6.0 Hz), 126.9, 116.4 (t, J = 236.7 Hz), 113.6, 40.6. ^{19}F NMR (282 MHz, CD_3CN) δ -111.24 (d, J = 56.4 Hz). GC/MS calculated for $[M]^+$ 247.12, found 247.10. FTIR (neat, cm^{-1}): 3028 (w), 2972 (s), 2931 (m), 2884 (m), 1658 (w), 1465 (m), 1380 (s), 1162 (s), 1129 (s).



5-[4-(difluoromethyl)phenyl]-2H-1,3-benzodioxole (8): Isolated as a white solid. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.7 – 7.4 (m, 4H), 7.2 – 7.0 (m, 2H), 6.9 – 6.9 (m, 1H), 6.7 (t, J = 56.5 Hz, 1H), 6.0 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.6, 143.4, 134.5, 132.9 (t, J = 22.8 Hz), 127.1, 126.0 (t, J = 6.1 Hz), 120.9, 114.8 (t, J = 238.6 Hz), 108.7, 107.7, 101.3. ^{19}F NMR (282 MHz, C_6D6) δ -110.24 (d, J = 56.4 Hz). GC/MS calculated for $[M]^+$ 248.06, found 248.10. FTIR (neat, cm^{-1}): 3000 (w), 2971 (s), 2884 (m), 1656 (w), 1465 (m), 1379 (m), 1162 (s), 1129 (s).



2-[4-(difluoromethyl)phenyl]-2-methyl-1,3-dioxane (9): Isolated as a colorless oil. ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.48 – 7.23 (m, 4H), 6.19 (t, J = 56.4 Hz, 1H), 3.78 – 3.05 (m, 4H), 1.98 – 1.73 (m, 1H), 1.58 (s, 3H), 0.72 – 0.48 (m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 145.1, 134.0 (t, J = 22.4 Hz), 127.7, 126.3 (t, J = 6.0 Hz), 115.3 (t, J = 237.8 Hz), 100.4, 61.7, 32.4, 25.8. ^{19}F NMR (282 MHz, C_6D_6) δ -110.24 (d, J = 56.4 Hz). GC/MS calculated for $[M]^+$ 228.10, found 228.10. FTIR (neat, cm^{-1}): 3056 (w), 2963 (m), 2870 (m), 1617 (w), 1419(w), 1371 (s), 1240 (s), 1193 (s), 1146 (s), 1075 (s).



1-(difluoromethyl)-3-(4-methylphenyl)benzene (10): Isolated as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 7.93 – 6.70 (m, 8H), 6.21 (t, J = 56.4, 56.4 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 142.40, 138.90, 137.87, 135.97 (t, J = 22.1 Hz), 130.6, 130.4, 130.2, 127.8, 125.1 (t, J = 6.0 Hz), 124.9 (t, J = 6.3 Hz), (peak which completes triplet with peaks 116.2 and 114.3 is hidden under solvent signal) 116.2, 114.3, 21.1. ^{19}F NMR (282 MHz, C_6D6) δ -110.58 (d, J = 56.1 Hz). GC/MS calculated for $[M]^+$ 218.19, found 218.10. FTIR (neat, cm^{-1}): 3028 (m), 2960 (m), 2923 (m), 1612 (w), 1518 (m), 1485 (s), 1369 (s), 1197 (s), 1030 (s).

1.3.7 *Synthesis of Trifluoromethyl Arenes*

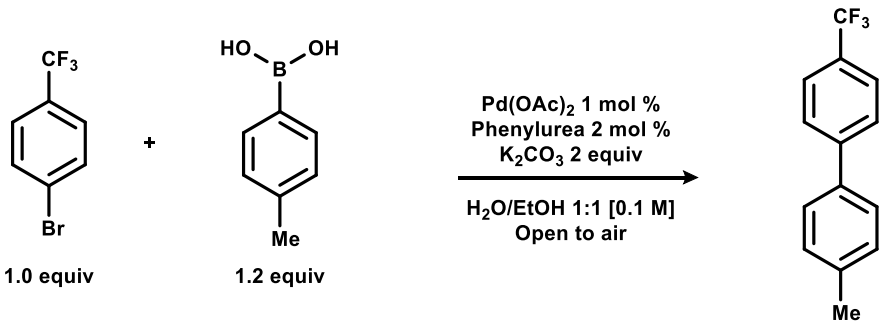
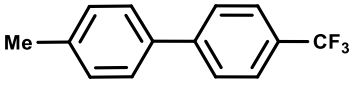
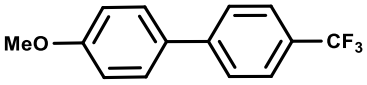


Figure 1.12. Suzuki coupling for the synthesis of trifluoromethyl arene substrates

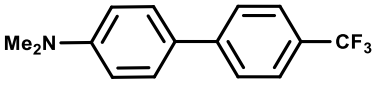
Syntheses of the following compounds were done according to a known literature procedure.[8]



1-methyl-4-[4-(trifluoromethyl)phenyl]benzene (1): is a known compound and spectral data match the reported literature values.[9]



1-methoxy-4-[4-(trifluoromethyl)phenyl]benzene (S1): is a known compound and spectral data match the reported literature values.[45]



N,N-dimethyl-4-[4-(trifluoromethyl)phenyl]aniline (S2): is a known compound and spectral data match the reported literature values.[10]

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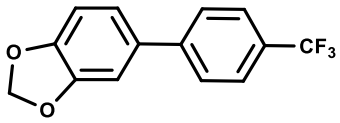
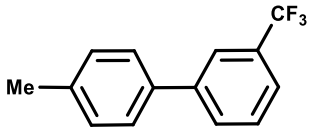
8. X. Cui, Y. Zhou, N. Wang, L. Liu, Q. X. Guo, *Tetrahedron Lett.* **48**, 163-167 (2007).

9. L. Ackermann, A. Althammer, *Org. Lett.* **8**, 3457-3460 (2006).

10. S. E. Denmark, R. C. Smith, W. T. T. Chang, J. M. Muhuhi, *J. Am. Chem. Soc.* **131**, 3104-3118 (2009).



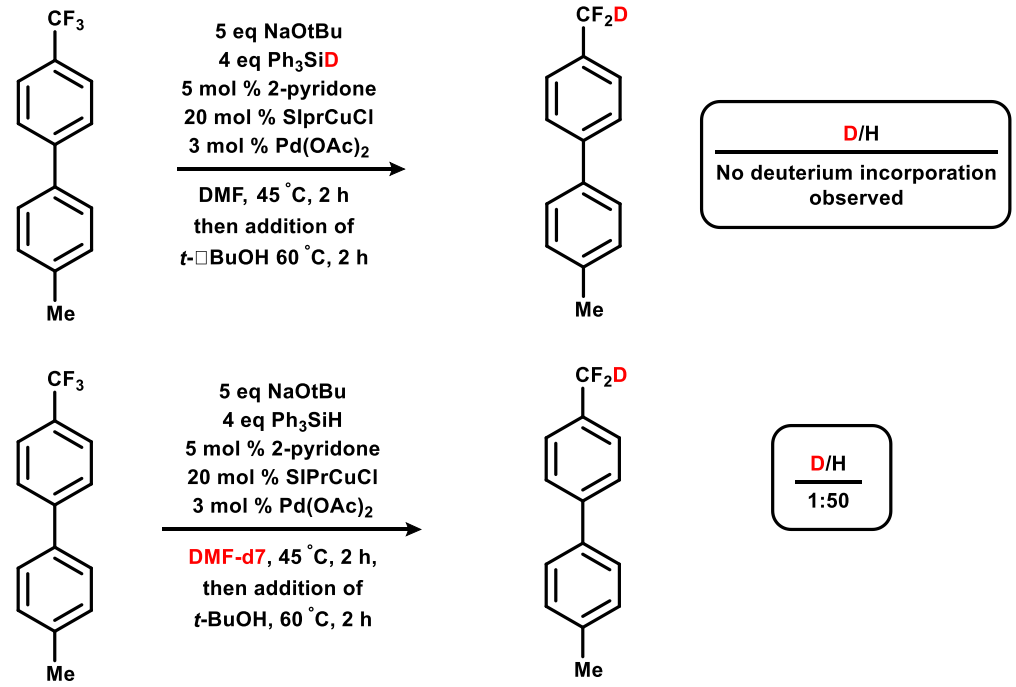
5-[4-(trifluoromethyl)phenyl]-2H-1,3-benzodioxole (S3): is a known compound and spectral data match the reported literature values.[11]



1-(4-methylphenyl)-3-(trifluoromethyl)benzene (S4): spectral data match the reported literature values.[12]

1.3.8 *Deuterium Incorporation Experiments, 0.05 mmol scale, 0.1 M.*

Procedure B (as a described in the reaction development section) was used to set up deuterium labeling experiments shown in Figure 1.14.



[11]. C. M. So, H. W. Lee, C. P. Lau, F. Y. Kwong, *Org. Lett.* **11**, 317-320 (2009).

[12]. J. Albaneze-Walker et al., *Org. Lett.* **11**, 1463-1466 (2009).

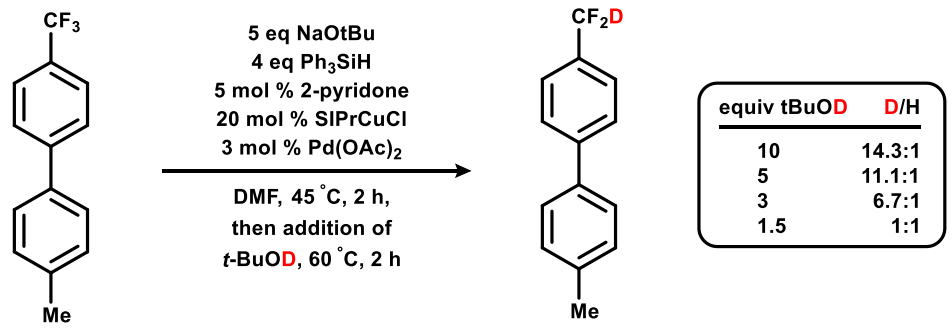


Figure 1.13. Deuterium incorporation using various deuterated reagents

A control experiment, figure 1.15, was performed to eliminate the possibility that the deuterium incorporation was a result of the base induced H/D exchange after the formation of the product. The following procedure was used: In a glovebox, a dram vial was charged with a stir bar, sodium *t*-butoxide (24.0 mg, 0.25 mmol, 5.0 equiv.), difluoromethyl arene (10.9 mg, 0.05 mmol, 1.0 equiv.), *t*-BuOD (5.6 mg, 0.75 mmol, 1.5 equiv), and 500 µL of DMF. The reaction temperature was maintained at 60 °C for 2 hours. At 2 hours, a 100 µL aliquot was diluted with 400 µL dry C_6D_6 and transferred into a J. Young tube for ^{19}F NMR analysis.

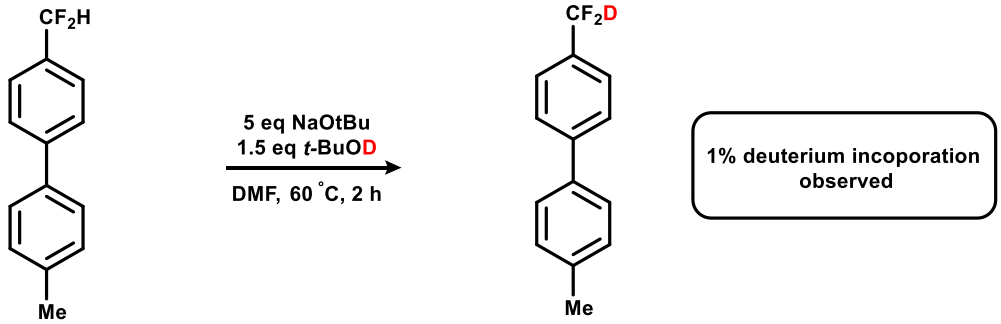


Figure 1.14. Control reaction for deuterium exchange

1.3.9 *Synthesis of 2-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-dioxane and SIPrCuCl*

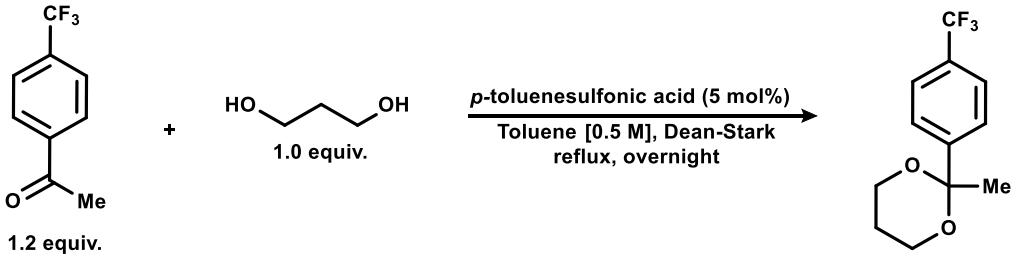
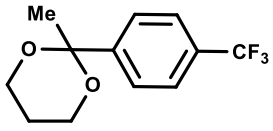


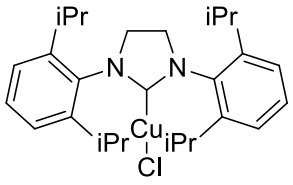
Figure 1.15. Synthesis of 2-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-dioxane.

To a one neck 100 mL round bottom flask was added the ketone substrate (3.7 g, 1.2 equiv, 20 mmol) and diluted with 40 mL of toluene (0.50 M). After cooling to 0 °C, 1,3-propanediol (1.9 mL, 1.0 equiv, 16.7 mmol) and *p*-toluenesulfonic acid (0.16 g, 0.05 equiv, 0.83 mmol) was added and the reaction vessel was fitted with a dean-stark apparatus. Reaction mixture was heated to a reflux overnight. After completion of the reaction, the reaction mixture was filtered through a plug of deactivated silica gel (doped with triethylamine). Silica plug was eluted with 10% ethyl acetate in hexanes solvent mixture. The solvent was then removed under reduced pressure. Product purification by flash chromatography affords (3.6 g, 74%) pale yellow oil, which solidifies overtime into a translucent pale yellow solid.



2-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-dioxane **(S5)**: Isolated as a translucent pale yellow solid. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.22 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 3.67 – 2.97 (m, 4H), 1.81 – 1.46 (m, 1H), 0.85 – 0.77 (m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 146.9,130.4 (q, *J* = 32.2 Hz), 128.2, 126.4 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 271.8 Hz), 100.7, 62.0, 32.6, 26.2. ^{19}F NMR (471 MHz, CD_2Cl_2) δ -62.86. GC/MS calculated for $[M]^+$ 246.09, found 246.20. FTIR (neat, cm^{-1}): 3059 (w), 2967 (m), 2870 (m), 1618 (m), 1409 (m), 1327 (s), 1239 (s). 1125 (s).

1.3.10 *Synthesis of SIPrCuCl*



SIPrCuCl (S6): In a nitrogen-filled glovebox, a 100-mL round bottom flask was charged with 1,3-bis(2,6-di-iso-propylphenyl)imidazolinium chloride (3.0g, 1.00 equiv, 7.0 mmol), sodium *t*-butoxide (682 mg, 1.01 equiv, 7.1 mmol), and 30 mL THF. The mixture was allowed to stir at 23 °C for 15 minutes then CuCl (696 mg, 1.00 equiv, 7.0 mmol) was added. After 16 hours, the reaction mixture was removed from the glovebox and concentrated under reduced pressure. The white-green solid was purified by silica plug filtration using dry DCM as an eluent. Upon removal of the solvent under reduced pressure, 2.8 g of SIPrCuCl was obtained as a white solid, 80% yield. This compound has been previously characterized.[13]

H. Dang, A. M. Whittaker and G. Lalic, *Chem. Sci.*, 2016, **7**, 505.
DOI: 10.1039/C5SC03415A
- Published by The Royal Society of Chemistry.

[13]. J. E. Thomson et al., *J. Org. Chem.* **73**, 2784-2791 (2008).

Chapter 2. MILD COPPER-CATALYZED FLUORINATION OF ALKYL TRIFLATES USING POTASSIUM FLUORIDE[23]

2.1 INTRODUCTION

Fluorination is a powerful tool used in medicinal chemistry to manipulate the physical, chemical, and biological properties of organic molecules without making significant changes to the overall structure.[24,25] As a result, fluorine is found in nearly 20% of pharmaceuticals.[24] Furthermore, ^{18}F-labeled organic molecules are used as contrast reagents in positron emission tomography (PET).[26,27] Not surprisingly, the importance of organofluorine compounds has made the development of new fluorination reactions a major focus of research in the field of transition metal catalysis.[28-30] Since 2006, a number of catalytic methods for synthesis of fluoroarenes[31-36] have been reported, including several procedures suitable for the synthesis of radiolabeled probes.[37,38] Similarly, several catalytic methods for the synthesis of allylic fluorides have been developed[39-44] following an initial report from the Doyle group in 2010.[45]

In contrast, catalytic methods for the synthesis of aliphatic fluorides are relatively underdeveloped.[46,47-54] In fact, the most general method for the synthesis of this class of compounds remains the nucleophilic substitution of alkyl electrophiles. Because of the low solubility of fluorides in aprotic solvents and poor nucleophilicity in protic ones, this reaction is usually performed in the presence of additives that increase the solubility and/or the nucleophilicity of the fluoride source. While numerous additives, including *t*BuOH[55] and ionic liquids[56] have been used, by far the most common is the use of phase transfer catalysts.[57] The most commonly used phase transfer catalyst, crown ether Kryptofix-222,[58] allows the fluorination of alkyl electrophiles within minutes in the presence of KF. It is important to note that this method is one of the very few methods for fluorination of organic molecules that meets

the two key requirements for application in the synthesis of radiolabeled PET probes:[58-60] 1) The fluorination is fast relative to the rate of ^{18}F decay (half-life of 110 minutes) and 2) [^{18}F]-KF, the most common and the most enriched source of ^{18}F, can be used. Unfortunately, the nucleophilic fluorination promoted by crown ethers also has several drawbacks. High reactivity is observed only at high temperatures (often >110 °C). High temperatures along with the basicity of the fluoride anion[61] lead to unwanted side reactions, such as elimination, even with simple primary alkyl electrophiles.[62]

Here, we describe a new approach to phase transfer catalysis in fluorination reactions featuring transition metal complexes as surprisingly effective catalysts (eq 1). Using the general approach described in equation 1, we developed copper-catalyzed fluorination of alkyl triflates with potassium fluoride as a fluoride source. The fluorination proceeds under mild reaction conditions, without any evidence of side reactions, and can be accomplished within minutes.

$$R{-}X + KF_{(s)} \xrightarrow[\text{aprotic solvent}]{\text{LCuX, phase transfer catalyst}} R{-}F + KX_{(s)} \qquad (1)$$

2.2 Copper-Catalyzed Fluorination of Alkyl Triflates with Potassium Fluoride

2.2.1 *Reaction Development*

We decided to explore the use of copper complexes as phase transfer catalysts in fluorination of alkyl electrophiles (eq 1) based on our recent observation[63] that IPrCuF[64] (see table 2.3 for structure of IPr ligand) can be efficiently generated from IPrCuOTf and potassium fluoride in dioxane. Furthermore, IPrCuF is soluble in organic solvents and has been established as a catalytic intermediate in few reactions performed in organic solvents.[63,64] These observations

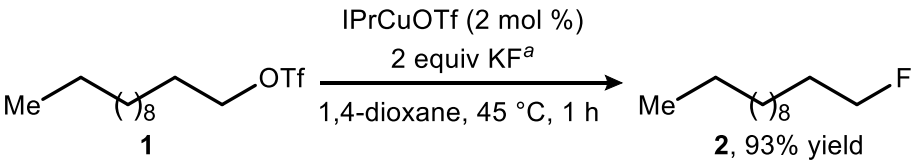
suggest the ability of IPr copper complexes to function as phase transfer catalysts for fluoride anion. Our major concern was that the copper fluoride complex will not be sufficiently nucleophilic to accomplish the fluorination of alkyl electrophiles. Indeed, stoichiometric reactions of diamine-supported copper fluoride with a range of electrophiles were recently explored,[65] and poor nucleophilicity of the copper fluoride complex resulted in the high reaction temperature, the formation of the alkene byproducts, and relatively low yield of the alkyl fluorides. However, we speculated that by using strong sigma donor ligands we could improve the nucleophilicity of the copper fluoride complex and achieve the desired reactivity. We were also encouraged by several reports in which high nucleophilicity of other transition-metal fluorides has been demonstrated in stoichiometric reactions with electrophiles.[66-68]

Based on the general approach outlined in eq 1 and our initial observations about the reactivity of IPrCuF, we were able to develop a catalytic fluorination of alkyl triflates shown in Table 2.3. Under the standard reaction conditions, in the presence of just 2 mol % of IPrCuOTf catalyst alkyl fluoride **2** is formed in excellent yield, after less than an hour at 45 °C. Importantly, we did not observe the formation of even a trace amount of the elimination product.

Table 2.3 summarizes the observations we made during the development of the reaction. A simple control experiment confirms that the copper catalyst is necessary for the formation of the alkyl fluoride (Table 2.3, entry 1). Similarly, the use of alkyl triflates as electrophiles was necessary, and other common electrophiles could not be used in the reaction. Several NHC copper complexes also catalyzed the reaction, albeit at a lower rate than IPrCuOTf (entries 4 and 5). During the optimization of the reaction conditions, we found that the reaction solvent has a profound effect on the rate of fluorination. A number of common organic solvents were tested, and all gave results significantly inferior to the results obtained in 1,4-dioxane. A few

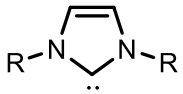
representative results are shown in entries 6, 7, and 8. We also found that while drying KF for 5 minutes is sufficient, KF that has not been dried could not be successfully used in the reaction (entry 9).

Table 2.3. Development of catalytic fluorination of alkyl triflates reaction

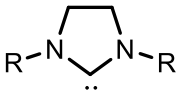


Entry	Change from standard conditions	Yield (%)[b]
1.	no catalyst	<1
2.	ROTs instead of ROTf	<1
3.	RI instead of ROTf	<1
4.	ItBuCuOTf instead of IPrCuOTf	63
5.	SIPr instead of IPrCuOTf	85
6.	1,2-dichloroethane as solvent	18[c]
7.	CH_2Cl_2 as solvent	7
8.	THF as solvent	<1
9.	non-dried KF	6[d]
10.	0.2 mol % of IPrCuOTf for 16 h	94
11.	10 mol % of IPrCuOTf for 10 min	92

[a] KF was dried for 5 minutes prior to use (see SI for details). [b] GC yields are reported. [c] 95% yield after 3 h with 10 mol % catalyst. [d] After 12 h.



IPr R = 2,6-diisopropylphenyl
ItBu R = *tert*-butyl



SIPr R = 2,6-diisopropylphenyl

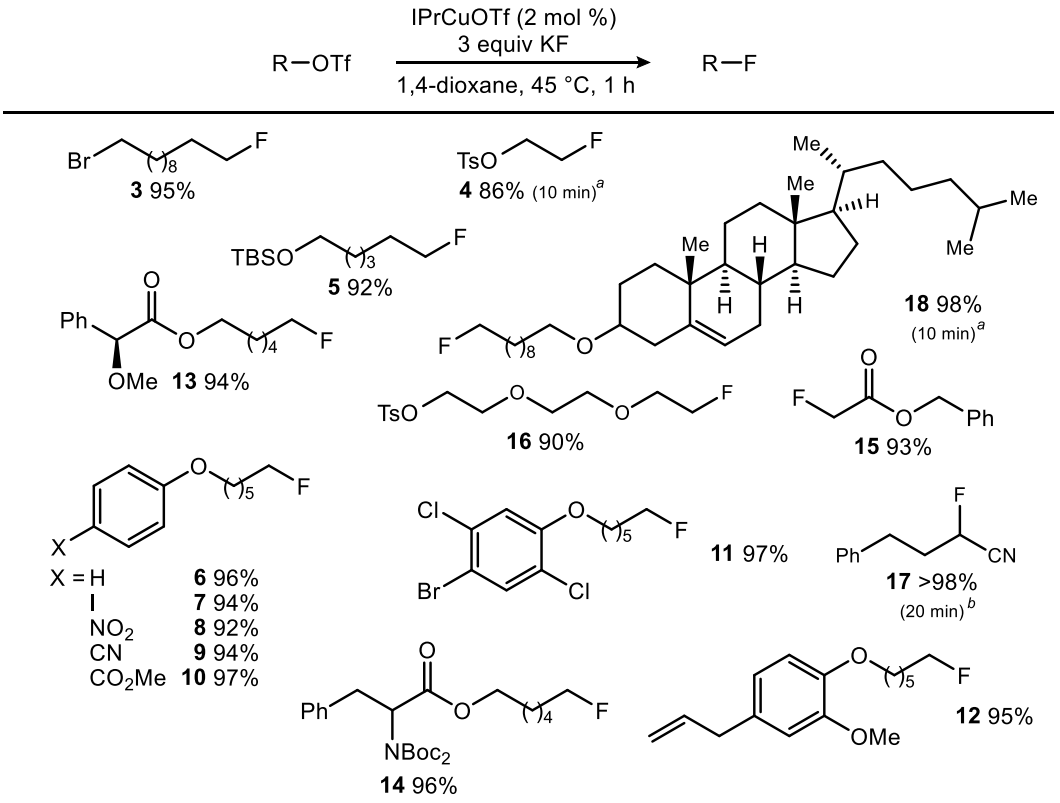
Finally, a catalyst loading of just 0.2 mol % is sufficient to accomplish full conversion of the alkyl triflate within 16 h. On the other hand, with 10 mol % of the catalyst complete conversion is achieved in less than 10 minutes at 45 °C.

2.2.2 *Scope of the reaction*

Using the standard conditions shown in Table 2.4, we explored the scope of the catalytic fluorination reaction, and found that the reaction can be performed in the presence of a wide

range of functional groups. The reaction is compatible with esters, nitriles, protected alcohols, nitro arenes, iodo arenes, alkenes, ethers, imides, alkyl bromides and tosylates. This level of chemoselectivity has not been documented in other methods for synthesis of alkyl fluorides. The fluorination can also be accomplished in the presence of a stereocenter bearing an acidic proton, as demonstrated by the synthesis of a single enantiomer of **13**.

Table 2.4. Scope of catalytic fluorination of alkyl triflates reaction



[a] 10 mol % of the catalyst was used [b] 10 mol % of IMeCuCl used as a catalyst, at 100 °C.

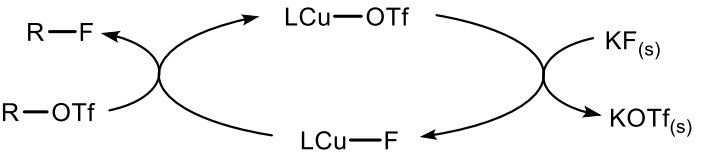
Interestingly, we found that the stereocenter in **13** epimerizes in the presence of TBAF (see supporting information). Products **3**, **4**, and **16**, are particularly interesting, as their ^{18}F analogues are common prosthetic groups[69] used in convergent synthesis[70] of PET probes. These ^{18}F-labeled electrophiles are often used in synthesis of radiolabeled tertiary alkyl amines[71] and other complex probes for which nucleophilic precursors are easier to prepare.[59] We have also prepared

18 from the corresponding triflate in excellent yield after 10 minutes with 10 mol % of the catalyst. The only reported synthesis of the ^{18}F-labeled cholesterol-derived probe **18** was previously accomplished in 4% yield, by nucleophilic fluorination of the tosylate precursor performed at 165 °C for 10 minutes.[72] We have also discovered that secondary alkyl triflates can be converted to alkyl fluorides in excellent yield and without even a trace amount of the elimination product (Table 2.4, compound **17**). The use of a copper catalyst supported by a smaller NHC ligand was essential for the success of this reaction. Finally, it is important to note that the only products observed in reactions reported in Table 2.4 were alkyl fluorides, and that we found no signs of elimination or other side reactions as commonly observed in reaction of metal fluorides with alkyl electrophiles.

2.2.3 *Mechanistic Studies*

After the exploration of the reaction scope we turned our attention to the mechanism of the reaction and the role that the copper catalyst plays in the fluorination reaction. Considering the low solubility and low nucleophilicity of KF in organic solvents,[73] the high rate of the fluorination reaction that we observed is quite surprising. We speculated that the fluorination reaction involves the formation of IPrCuF from IPrCuOTf and KF, followed by the fluorination of alkyl triflate by the IPrCuF (see Figure 2.1, eq 1).[65] According to this proposal, the copper catalyst functions as a phase transfer catalyst that provides a soluble and nucleophilic source of fluoride from the rather insoluble KF. To test this hypothesis, we prepared IPrCuF[64] and explored its reactivity in the presence of alkyl triflates. We found that in a stoichiometric reaction, alkyl fluoride is formed quantitatively in less than 10 minutes at room temperature (Fig. 2.1, eq 2). We also found that IPrCuOTf in a reaction with KF performed in 1,4-dioxane, provides IPrCuF in 88% yield after 10 minutes (eq 3). The same reaction performed in $CDCl_3$

afforded only a trace amount of IPrCuF. These results provide evidence for the mechanism shown in figure 2.1, and are consistent with the pronounced solvent effect described earlier (see Table 2.1, entries 6, 7, and 8).



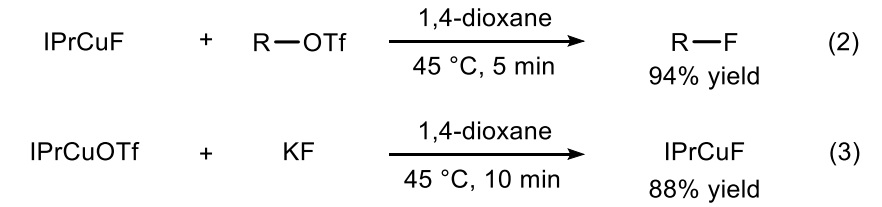


Figure 2.1. Proposed catalytic cycle for the copper-catalyzed fluorination of alkyl triflates

Consistent with the mechanism shown in Figure 2.1 is also the observation that the rate of the reaction depends on the rate at which the reaction mixture is stirred. Very little fluorination is observed within 20 minutes without stirring of the reaction mixture. The difference in the rates of fluorination is also noticeable for stir rates of 250 and 1500 rpm. While it remains unclear whether the formation of IPrCuF occurs on the surface of solid KF or in solution, these experiments indicate that the phase transfer is a part of the rate law and contributes to the overall rate of the reaction.

2.2.4 *Conclusion*

In conclusion, we have developed an efficient copper-catalyzed fluorination of alkyl triflates with KF as a fluoride source. With as little as 10 mol% of the cooper catalyst reaction can be accomplished within 10 minutes at 45 °C. The fluorination reaction is compatible with a wide range of functional groups including alkyl tosylates and alkyl bromides. Finally, we have described the preliminary study of the reaction mechanism that provides insight into the role of

the copper catalyst and shows that transition metal complexes can be used as efficient phase transfer catalysts.

2.3 EXPERIMENTAL

2.3.1 *General*

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

2.3.1.1 *Materials*

Toluene and benzene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. All other solvents were used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., TCI Chemicals USA, or STREM Chemicals, Inc., and were used as received.

Dry KF was prepared by flame-drying grounded KF (mortar and pestle) at 100 mtorr for 5 minutes. Wet KF refers to anhydrous KF that was not spray dried and that has been handled in ambient atmosphere.

IPrCuOTf was prepared from commercially available IPrCuCl (Strem) according to the reported procedure.[14] IPrCuF was prepared according to the published procedure.[15]

11-bromoundecan-1-ol, 2-methoxy-2-phenylethan-1-ol, 2-phenylethanol, and benzyl 2-hydroxyacetate are commercially available compounds from Sigma-Aldrich and were used without further purification

Triflic anhydride obtained from Oakwood was vaccum transferred from P_2O_5 prior to use. The purified material could be stored at -20 °C for weeks. When triflic anhydride is used as received, minor impurities were observed in alkyl triflates.

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[14] Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446.
[15] Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486.

2.3.2 *Standard Procedures used for reactions shown in Tables 2.3 and 2.4*

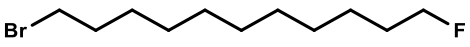
2.3.2.1 *Standard procedure used for reactions shown in Table 2.3:*

In a nitrogen-filled glove box, a 1 dram vial was charged with a stir bar. KF (58.1 mg, 2.00 equiv) was added to the reaction vessel followed by the catalyst (0.02 equiv). This mixture was suspended in 1.00 mL of the solvent. Next, the electrophile (1.00 equiv) and internal standard, 1,3,5-trimethoxybenzene, were added to the reaction vessel as a solution (1.50 mL) in the solvent of choice. Finally, the vial was capped and heated at 45 °C with stirring.

2.3.2.2 *Standard Procedure for Catalytic Fluorination of Alkyl Triflates- Reaction Scope (Table 2.4)*

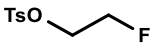
In a nitrogen-filled glovebox, a 1 dram vial was charged with a stirbar. KF (58.1 mg, 1.00 mmol, 2.00 equiv) was added, followed by IPrCuOTf (6.0 mg, 0.01 mmol, 0.02 equiv). The mixture was suspended in 1.00 mL of 1,4-dioxane, and the alkyl triflate (0.500 mmol), was added as a solution (1.50 mL) in 1,4-dioxane. The reaction was stirred for 1 hour at 45 °C, and then filtered through a plug of silica gel. After a 20 mL Et_2O wash of the filter, the filtrate was concentrated and then chromatographed on a 25 g silica gel column with a solvent gradient of 0→10% EtOAc in hexanes over 8 CVs.

2.3.3 *Characterization Data for Alkyl Fluoride Products*

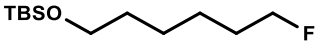


1-bromo-11-fluoroundecane (Table 2, 3): Compound was isolated as a colorless oil (120.2 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (dt, *J* = 47.4, 6.2 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.78 – 1.57 (m, 2H), 1.52 – 1.17 (m, 14H). ^{13}C NMR (126 MHz, C_6D_6) δ 83.9 (d, *J* = 165.7 Hz), 33.9 (s), 33.3 (s), 31.0 (d, *J* =

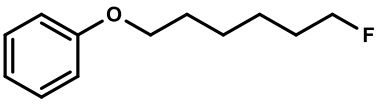
19.5 Hz), 30.0 (s), 30.0 (s), 29.9 (s), 29.8 (s), 29.2 (s), 28.6 (s), 25.7 (d, *J* = 5.1 Hz). GCMS (EI) calculated for $[M]^+$ 252.09, found 251.95. FTIR (neat, cm-1): 2930(s),1465 (m), 1266 (s), 741 (s).



2-fluoroethyl 4-methylbenzene-1-sulfonate (Table 2, 4): Compound was isolated as a colorless oil (100.0 mg, 92%). **17** is a known compound and spectral data match the reported literature values.[16]



tert-butyl[(6-fluorohexyl)oxy]dimethylsilane (Table 2, 5) : Compound was isolated as a colorless oil (106.0 mg, 92% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 4.10 (dt, *J* = 47.5, 6.1 Hz, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 1.52 – 1.31 (m, 4H), 1.30 – 1.12 (m, 4H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 83.8 (d, *J* = 165.8 Hz), 63.3 (s), 33.2 (s), 30.9 (d, *J* = 19.6 Hz), 26.4 (s), 26.0 (s), 25.5 (d, *J* = 5.4 Hz), 18.7 (s), -5.0 (s). ^{19}F NMR (282 MHz, C6D6) δ -218.89 – -222.00 (m, *J* = 47.9, 24.1 Hz). GCMS (EI) calculated for $[M]^+$ 234.18, found 233.90. FTIR (neat, cm-1): 2933(s),1463 (m), 1265 (s), 1093 (s).



[(6-fluorohexyl)oxy]benzene (Table 2, 6): Compound was isolated as a colorless oil (94.0 mg, 96% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.34 – 7.19 (m, 2H), 7.02 – 6.75 (m, 3H), 4.44 (dt, *J* = 47.4, 6.1 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 1.98 – 1.61 (m, 4H), 1.58 – 1.37 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 159.8, 129.7, 120.8, 114.8, 83.6 (d, *J* = 165.7 Hz), 67.6, 30.6 (d, *J* = 19.6 Hz), 29.4, 26.0, 25.2 (d, *J* = 5.3 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -217.82 – -222.77 (m). GCMS (EI) calculated for $[M]^+$ 196.13, found 196.10. FTIR (neat, cm-1): 3055 (m), 2942 (m), 2865 (m), 1600 (s), 1450 (s), 1265 (s), 1035 (m).

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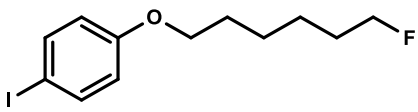
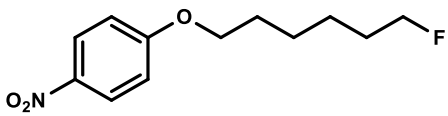
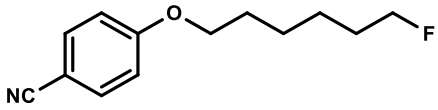
[16] Fujinaga, M., Yamasaki T., Yui J., Hatori, A. Xie, L., Kawamura, K.. Asagawa C., Kumata, K. , Yoshida, Y., Ogawa, M., Nengaki, N., Fukumura, T., Zhang, M.R., *J. Med. Chem.* **2012**, *55*, 2342-2352.



1-[(6-fluorohexyl)oxy]-4-nitrobenzene (Table 2, 7): Compound was isolated as a colorless oil (148.0 mg, 94% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 8.9 Hz, 2H), 6.39 (d, *J* = 8.9 Hz, 2H), 4.08 (dt, *J* = 47.5, 6.0 Hz, 2H), 3.37 (t, *J* = 6.4 Hz, 2H), 1.58 – 1.24 (m, 4H), 1.24 – 1.03 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 159.4, 138.5, 117.2, 83.6 (d, *J* = 165.8 Hz), 82.8, 67.7, 30.6 (d, *J* = 19.6 Hz), 29.2, 25.9, 25.2 (d, *J* = 5.3 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -218.74 – -221.60 (m). GCMS (EI) calculated for $[M]^+$ 322.02, found 321.95. FTIR (neat, cm-1): 3053 (m), 2941 (s), 1587 (s), 1472 (s), 1282 (s), 1175 (s), 998 (s).

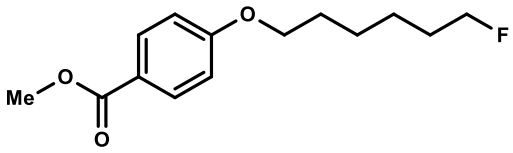


1-[(6-fluorohexyl)oxy]-4-nitrobenzene (Table 2, 8): Compound was isolated as a colorless oil (111.0 mg, 92% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.93 (d, *J* = 9.2 Hz, 2H), 6.33 (d, *J* = 9.2 Hz, 2H), 4.10 (dt, *J* = 47.5, 5.9 Hz, 2H), 3.28 (t, *J* = 6.4 Hz, 2H), 1.57 – 1.23 (m, 4H), 1.21 – 0.99 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.1, 141.8, 125.9, 114.4, 83.6 (d, *J* = 165.6 Hz), 68.5, 30.6 (d, *J* = 19.6 Hz), 29.0, 25.7, 25.2 (d, *J* = 4.9 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -219.63 – -220.56 (m). GCMS (EI) calculated for $[M]^+$ 241.11, found 241.00. FTIR (neat, cm-1): 3055(w), 2945 (m), 1594 (m), 1514 (m), 1342 (s), 1265 (s), 1112 (w).

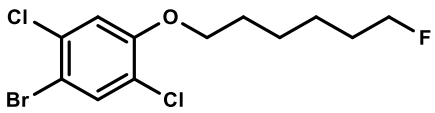


4-[(6-fluorohexyl)oxy]benzonitrile (Table 2, 9): Compound was isolated as a colorless oil (104.0 mg, 94% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.04 (d, *J* = 8.9 Hz, 2H), 6.35 (d, *J* = 8.9 Hz, 2H), 4.09 (dt, *J* = 47.5, 5.9 Hz, 2H), 3.27 (t, *J* = 6.4 Hz, 2H), 1.51 – 1.22 (m, 4H), 1.20 – 0.97 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 162.3, 133.9, 119.3, 115.2, 104.4, 83.6 (d, *J* = 165.7 Hz), 68.0, 30.5 (d, *J* = 19.7 Hz), 29.0, 25.7, 25.2 (d, *J* = 5.2 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -218.26 – -222.49 (m, *J*

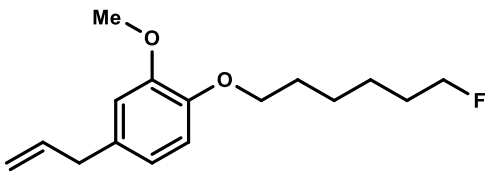
= 47.5, 24.9 Hz). GCMS (EI) calculated for $[M]^+$ 221.12, found 220.95. FTIR (neat, cm-1): 3055 (m), 2944 (m), 2226 (m), 1606 (s), 1509 (s), 1265 (s), 1172 (s), 1000 (w).



methyl 4-[(6-fluorohexyl)oxy]benzoate (Table 2, 10): Compound was isolated as a colorless oil (120.8 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 4.09 (dt, *J* = 47.5, 6.0 Hz, 2H), 3.55 (s, 3H), 3.43 (t, *J* = 6.4 Hz, 2H), 1.51 – 1.23 (m, 4H), 1.22 – 1.03 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 163.2, 132.0, 123.3, 114.4, 83.6 (d, *J* = 166.0 Hz), 67.9, 51.4, 30.6 (d, *J* = 19.7 Hz), 29.2, 25.8, 25.2 (d, *J* = 4.9 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -218.23 – -221.97 (m). GCMS (EI) calculated for $[M]^+$ 254.13, found 254.05. FTIR (neat, cm-1): 3055 (m), 2947 (m), 1713 (s), 1606 (s), 1436 (m), 1265 (s), 1009 (m).

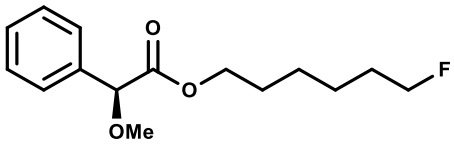


1-bromo-2,5-dichloro-4-[(6-fluorohexyl)oxy] (Table 2, 11): Compound was isolated as a white solid (162.3 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.99 (s, 1H), 4.46 (dt, *J* = 47.3, 6.0 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 2.04 – 1.64 (m, 4H), 1.61 – 1.39 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.6, 134.1, 133.4, 122.6, 114.7, 112.7, 83.6 (d, *J* = 165.8 Hz), 69.1, 30.5 (d, *J* = 19.6 Hz), 28.8, 25.7, 25.1 (d, *J* = 5.0 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -217.70 – -222.09 (m). GCMS (EI) calculated for $[M]^+$ 341.96, found 341.58. FTIR (neat, cm-1): 3055 (m), 2943 (s), 1579 (s), 1467 (s), 1347 (s), 1265 (s), 1003 (s), 876 (m).

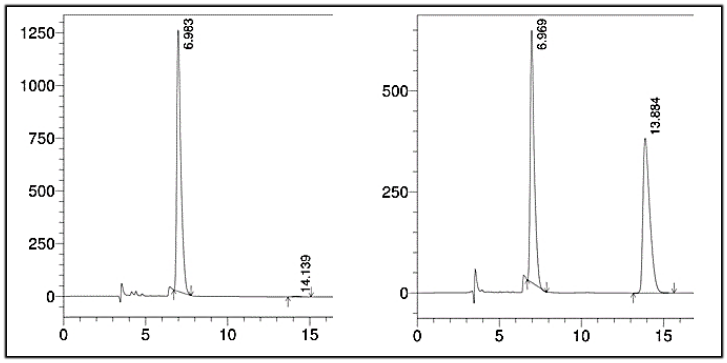


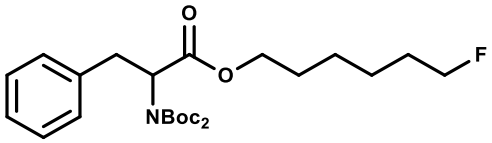
1-[(6-fluorohexyl)oxy]-2-methoxy-4-(prop-2-en-1-yl)benzene (Table 2, 12): Compound was isolated as a colorless oil (124.0 mg, 95% yield). ^{1}H NMR (300 MHz,

C_6D_6) δ 6.75 (s, *J* = 7.4 Hz, 2H), 6.65 (s, 1H), 5.97 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.17 – 4.95 (m, 2H), 4.07 (dt, *J* = 47.5, 6.1 Hz, 1H), 3.72 (t, *J* = 6.3 Hz, 2H), 3.44 (s, 3H), 3.26 (d, *J* = 6.6 Hz, 2H), 1.68 – 1.51 (m, 2H), 1.45 – 1.01 (m, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.5, 148.1, 138.3, 132.9, 121.0, 115.5, 114.1, 113.3, 83.6 (d, *J* = 165.7 Hz), 69.0, 55.5, 40.2, 30.6 (d, *J* = 19.5 Hz), 29.7, 26.1, 25.2 (d, *J* = 5.2 Hz). ^{19}F NMR (282 MHz, C_6D_6) δ -218.08 – -221.83 (m). GCMS (EI) calculated for $[M]^+$ 266.17, found 266.05. FTIR (neat, cm-1): 3055 (m), 2940 (s), 1513 (s), 1265 (s), 1140 (s), 1037 (s).

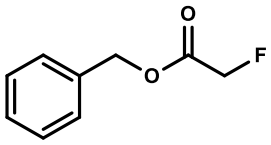


6-fluorohexyl (2S)-2-methoxy-2-phenylacetate (Table 2, 13): Compound was isolated as a colorless oil (130.1 mg, 97% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.27 (m, 5H), 4.76 (s, 1H), 4.38 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.13 (t, *J* = 6.6 Hz, 2H), 3.41 (s, 3H), 1.78 – 1.48 (m, 4H), 1.43 – 1.09 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 136.5, 128.8, 128.7, 127.3, 84.0 (d, *J* = 164.4 Hz), 82.7, 65.1, 57.5, 30.3 (d, *J* = 19.5 Hz), 28.5, 25.4, 24.8 (d, *J* = 5.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -213.3 – -236.9 (m). GCMS (EI) calculated for $[M]^+$ 268.15, found 268.10. FTIR (neat, cm-1): 3054 (m), 2940 (m), 2304 (w), 1754 (s), 1455 (w), 1264 (s), 1178 (m), 998 (m). Enantiopurity is greater than 99% as determined by HPLC analysis using a Chiralcel OD-H analytical columm. Conditions: 5% IPA/Hexanes, 1 mL/min.

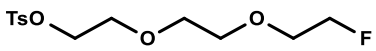




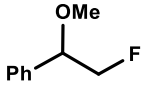
6-fluorohexyl 2-{bis[(tert-butoxy)carbonyl]amino}-3-phenylpropanoate (Table 2, 14): Compound was isolated as a colorless oil (157.0 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 6.94 (m, 5H), 5.13 (dd, *J* = 10.2, 5.1 Hz, 1H), 4.43 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.25 – 4.00 (m, 2H), 3.31 (m, *J* = 24.3, 14.0, 7.7 Hz, 2H), 1.87 – 1.56 (m, 4H), 1.50 – 1.21 (m, *J* = 8.2 Hz, 22H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 151.8, 137.8, 129.6, 128.4, 126.6, 84.6, 83.9 (d, *J* = 164.4 Hz), 65.3, 59.6, 36.1, 30.3 (d, *J* = 19.5 Hz), 28.5, 27.9, 25.6, 24.9 (d, *J* = 5.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -219.0 – -224.0 (m). FTIR (neat, cm-1): 3411 (w), 2980 (s), 1737 (s), 1457 (m), 1368 (s), 1265 (s), 1137 (s), 989 (m).



benzyl 2-fluoroacetate (Table 2, 15): Compound was isolated as a colorless oil (80.0 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 5H), 5.25 (s, 2H), 4.89 (d, *J* = 47.0 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 168.2 (d, *J* = 21.9 Hz), 135.7, 129.2, 129.1, 129.0, 78.4 (d, *J* = 181.1 Hz), 67.5. 19F GCMS (EI) calculated for $[M]^+$ 168.06, found 168.10. FTIR (neat, cm-1): 3054 (m), 2986 (w), 1769 (s), 1265 (s), 1215 (m), 1082 (m), 961 (w).



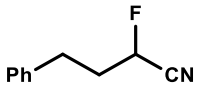
(2-fluoroethoxy)ethoxy]ethyl 4-methylbenzene-1-sulfonate (Table 2, 16): Compound was isolated as a colorless oil (141.0 mg, 92% yield). **16** is a known compound and spectral data match the reported literature values.[17]



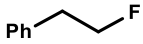
(2-Fluoro-1-methoxyethyl)benzene (Table 2, 17): Compound was isolated as a light yellow oil (61.5 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H), 4.79 – 4.02 (m, 3H), 3.34 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 136.9 (d, *J* = 8.2 Hz), 128.9, 128.8 , 127.3 , 86.2 (d, *J* = 177.7 Hz), 82.7 (d, *J* = 19.1 Hz), 57.3. ^{19}F NMR (282 MHz,

[17] Snow, A. W., Foos E. E., Coble M. M., Jernigan, G. G., Ancona, M. G., *Analyst*, **2009**, *134*, 1790-1801.

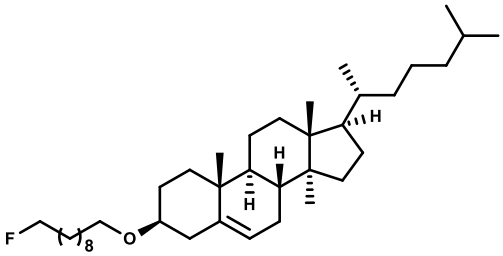
$CDCl_3$) δ -219.74 – -220.54 (m). GCMS (EI) calculated for $[M]^+$ 154.18, found 154.00. FTIR (neat, cm-1): 3053 (m), 2931 (m), 1769 (s), 2305 (w), 1454 (w), 1216 (m), 1124 (w). **17** is a known compound and spectral data match the reported literature values.[18]



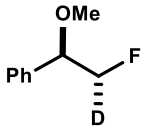
2-fluoro-4-phenylbutanenitrile (Table 2, 18): Compound was isolated as a colorless oil (80 mg, 98% yield). **18** is a known compound and spectral data match the reported literature values.[19]



2-fluoroethylbenzene (Table 2, 19): Yield was determined by NMR analysis using 1,3,5 – trimethoxybenzene as an internal standard. **19** is a known compound and spectral data match the reported literature values.[20]



(1S,2R,5S,10R,11S,14R,15R)-5-[(10-fluorodecyl)oxy]-2,11,15-trimethyl-4[(2R)6 methylheptan-2-yl]tetracyclo[8.7.0.0^{2,7}.0^{11,15}] heptadec-7-ene (Table 2, 20): Compound was isolated as a white solid (264.3 mg, 95% yield). Compound **20** is a known compound and spectral data match the reported literature values.[21]



(2-Fluoro-2-deutero-1-methoxyethyl)benzene (22): Compound was isolated as a light yellow oil (61.2 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 – 7.28 (m, 5H), 4.87 – 3.99 (m, 2H), 3.34 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -213.72 – -214.47 (m). GCMS (EI) calculated for $[M]^+$ 155.09, found 155.10.

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[18] Uemoto, T., Fukami, S., Tomizawa, G., Harasawa, K., Kawada, K., Tomita, K., *J. Am. Chem. Soc*, **1990**, *112*, 8563-8575.
[19] L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J., J. Org. Chem.* **2010**, *75*, 3401-3411.
[20] Taylor, S. L., Lee, D. Y., Martin, J. C., *J. Org. Chem*. **1983**, *48*, 4158-4159.
[21] Jensen, A. T. I., Binderup, T., Andresen, T. L., Kjaer, A., Rasmussen, P. H., *J. Lipos. Res.* **2012**. *22*, 295-305.

2.3.4 *Formation and the Reactivity of IPrCuF (equations 2 and 3)*

2.3.4.1 Formation of IPrCuF (equation 3)

In a nitrogen-filled glovebox, KF (5.8 mg, 0.100 mmol, 5.00 equiv) was added to a 1 dram vial containing a stirbar. Next, IPrCuOTf (24.0 mg, 0.020 mmol, 1.00 equiv) was added, followed by a stock solution of the internal standard, hexafluorobenzene (1.1 mg, 0.006 mmol, 0.300 equiv), in 1,4-dioxane (440 μL). The vial was then capped and stirred at 45 °C for 10 minutes. At this time, the reaction mixture was diluted in 800 μL of $CDCl_3$ and filtered through a glass wool. ^{19}F NMR shows that 88% of IPrCuF was formed and 11% of IPrCuOTf was present.

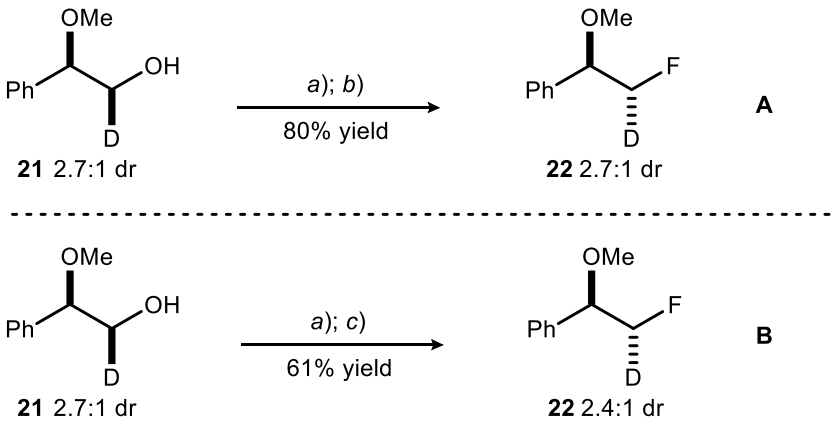
2.3.4.2 *Reaction of IPrCuF with dodecyl triflate (equation 2)*

In a nitrogen-filled glovebox, IPrCuF (23.6 mg 0.050 mmol, 1.00 equiv) was added to a 1 dram vial charged with a stirbar. 1-dodecyl triflate (31.8 mg, 0.100 mmol, 2.00 equiv), and 1,3,5-trimethoxybenzene as the internal standard was then added to the reaction vessel as a solution in 1,4-dioxane (500 μL). The vessel was then capped and stirred at 45°C. A 94% yield of 1-fluorododecane at the reaction time of five minutes was calculated using GC analysis.

2.3.5 *Stereochemistry of fluorination reaction*

The stereochemistry of the fluorination reaction was determined based on the results of experiments described in figure 2.2. The diastereomeric mixture of the mono-deuterated alcohol **21** (see below for the synthesis of **21**) was transformed into the corresponding triflates and subsequently into a mixture of alkyl fluorides **22**. The diastereomeric ratio of the fluorides was determined by the analysis of the proton-decoupled ^{19}F NMR (see the included spectrum). Considering that diastereomeric ratio remained unchanged through the triflation and fluorination reactions, the fluorination reaction is stereospecific. To determine whether the reaction proceeds

with retention or inversion of configuration, we transformed the same alcohol into a mixture of alkyl fluorides according to the reaction shown in figure 2.2. Using the conditions shown in figure 2.2 B, the fluorination of **21** can only proceed through the SN2 mechanism and result in the inversion of the configuration. Using the conditions shown in figure 2.2 A, the diastereoisomer of **22** obtained as the major product was the same as the one obtained as the major product in the reaction shown in figure 2.2 B. This finding allowed us to conclude that the reaction proceeds with the inversion of configuration. (Note: The somewhat lower diastereoselectivity of the fluoride (relative to the dr of the staring alcohol) obtained in reaction shown in figure 2.2 B is consistent with the decomposition of the product observed under the reaction conditions and the lower yield.



a) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C; b) IPrCuOTf (10 mol %), KF (5 equiv), 1,4-dioxane, 60 °C, 4 h. c) 18-crown-6 (1.1 equiv), KF (5 equiv), 1,4-dioxane, 45 °C, 16 h. Yield determined by NMR.

Figure 2.2. Stereochemistry of fluorination

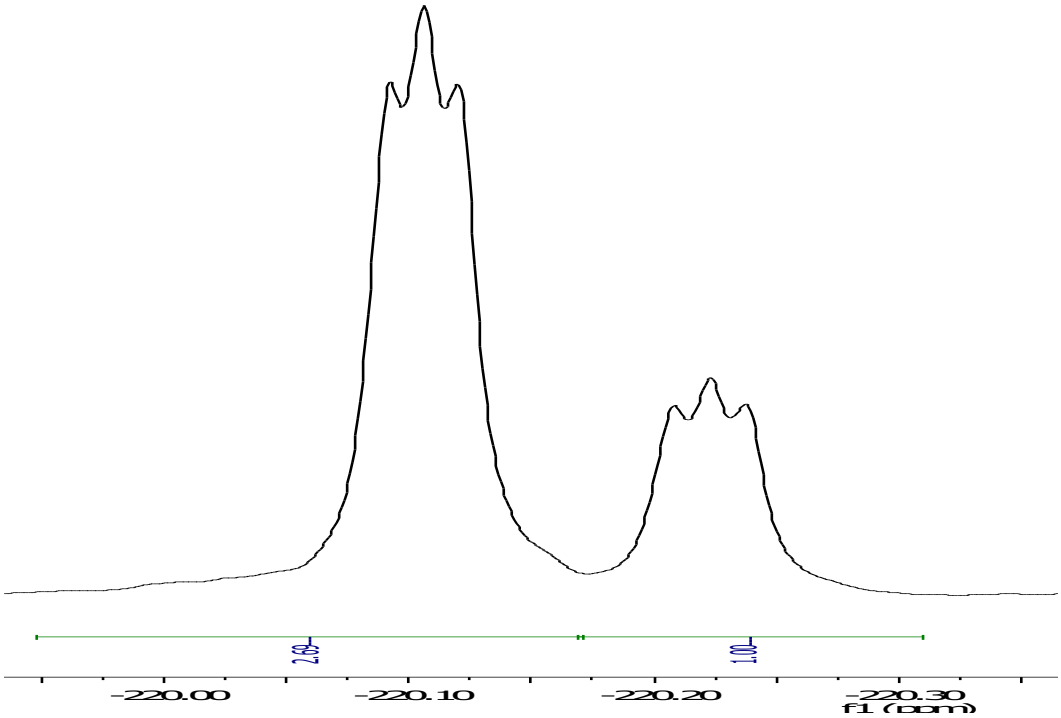
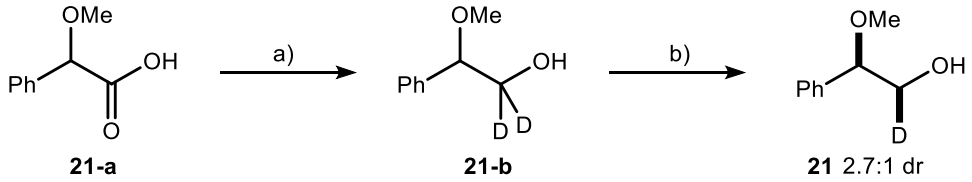


Figure 2.3. NMR showing a 2.7:1 d.r of product **22** formed in catalytic reaction

Compound **21** was synthesized according known chemistry with slight modifications.



21-a **21-b** **21** 2.7:1 dr

Figure 2.4. Synthesis of compound 21

a) To a suspension of LiAlD4 (923.6 mg, 22.0 mmols, 1.1 equiv) in dry diethyl ether (60.0 mL) was added **21-a** (3.3 g, 20.0 mols, 1.0 equiv) as a solution in dry THF (20.0 mL) at 0°C. The reaction was allowed to warm up and stir overnight. When determined to be done using NMR analysis, the reaction chilled to 0°C and quenched with 923.6 mL of H2O, followed by 1.9 mL of 2 M aq. NaOH. Finally, 2.8 mL of H2O causing white precipitation. The reaction mixture was then filtered through a pad of celite and concentrated. The resulting yellow oil was then purified

by flash chromatography using 35% ethyl acetate in hexanes to afford a clear colorless oil (2.6 g, 16.7 mmols, 83% yield), **21-b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 6.80 (m, *J* = 27.2 Hz, 5H), 4.30 (s, 1H), 3.31 (s, 3H), 2.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.7, 128.2, 127.0, 84.7, 69.6 – 63.1 (m), 57.0. $[M]^{+}$154.10, found 154.10 . FTIR (neat, cm-1): 3434 (br), 3028 (m), 2934 (s), 2213 (s), 2083 (s), 1602 (w), 1492 (m), 1453 (s) 1101 (s).

b) To a flame dried reaction flask was added TEA (4.9 mL, 35.0 mmol, 5 equiv), followed by dry DCM (52.5 mL) and DMSO (17.5 mL). **21-b** (999.5 μL, 7.0 mmol, 1.0 equiv) was then added and the reaction was chilled to 0°C before the addition of pyridine sulfur trioxide (3.9 g, 24.5 mmol, 3.5 equiv). When determined to be done by TLC, the reaction was diluted with hexanes:ether, 5:1. The mixture was then washed with saturated aq. NaHCO3, followed by 1M aq. HCl, and with a final wash with saturated aq. $NaHCO_3$. The organic layer was then dried over MgSO4, filtered, concentrated to afford a crude mixture containing **21-c**. This was used in the subsequent step without further purification. Crude mixture containing **21-c** (987.2 mg, 6.5 mmol, 1.0 equiv), was suspended in dry DCM and chilled to -78°C. Red-Al (1.8 mL, 6.5 mmol, 1.0 equiv) was then added as a 3.6 M solution in toluene. The reaction was maintained at -78°C for two hours and then quenched with a saturated aq. solution of Rochelle's salt. This mixture was allowed to stir until two clear layers formed. The organic layer was washed several times with water and the organic layer was dried over sodium sulfate. Filtration, concentration, and finally purification by flash chromatography afforded **21** as a clear colorless oil (422 mg, 2.8 mmols, 42% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.14 – 6.95 (m, 5H), 4.32 – 3.94 (m, 1H), minor isomer 3.61 (d, *J* = 33.6, 9 Hz, 1H), major isomer (d, *J* = 9 Hz, 1H), 2.99 (s, 3H), 2.07 (d, *J* = 9.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.7, 128.3, 127.0, 84.7, 68.7 – 63.7 (t),

57.0. GC/MS (EI) calculated for [M]+ 153.09, found 153.00 . FTIR (neat, cm-1): 3424 (br), 3028 (m), 2934 (s), 1602 (w), 1492 (m), 1453 (m) 110 (s).

2.3.6 *Initial rate measurements of catalytic fluorination of alkyl triflates reaction*

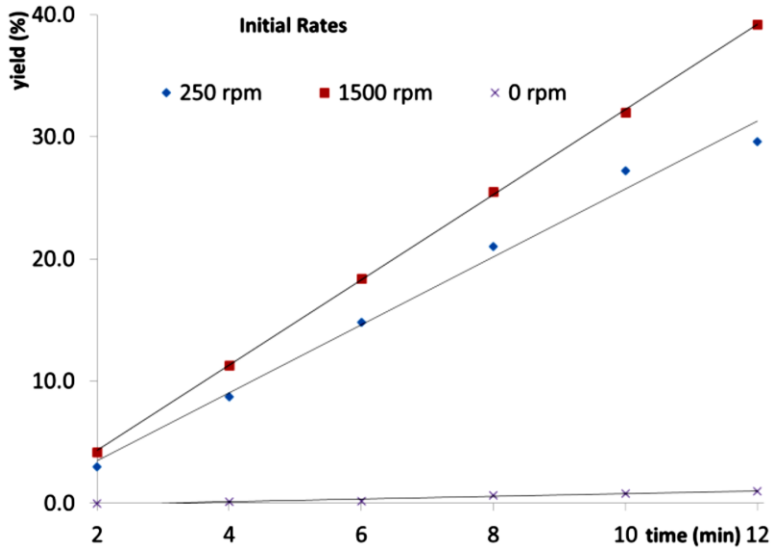


Figure 2.5. Initial rate measurements for catalytic fluorination of alkyl triflates

In a nitrogen-filled glovebox, a 1 dram vial was charged with a stirbar. KF (87.2 mg, 1.50 mmol, 3.00 equiv) was added, followed by the addition of 1,4-dioxane (1.40 mL). IPrCuOTf (6.0 mg, 0.010 mmol, 0.02 equiv) was added as a solution in 1,4-dioxane (0.143 mL). Finally, 1-dodecyl triflate (159 mg, 0.500 mmol, 1.00 equiv), was added as a solution in 1,4-dioxane (0.955 mL). The reaction was stirred at 45 ˚C. Aliquots (0.060 mL) were taken and immediately quenched by a saturated diethyl ether solution of sodium *tert*-pentoxide every two minutes for 20 minutes. These aliquots were then further prepared for GC analysis by filtration through a small plug of silica gel, using diethyl ether as the eluent.

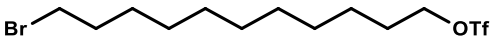
2.3.7 *Synthesis of Alkyl Triflates*

General procedure: A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and a primary alcohol (2.00 mmol, 1.00 equiv). The alcohol was dissolved in CH_2Cl_2 (5.0 mL) and cooled to −78 °C before adding 2,6-lutidine (370 µL, 3.20 mmol, 1.60 equiv). While stirring, triflic anhydride (455 µL, 2.4 mmol, 1.20 equiv) was added drop-wise over five minutes, and then the reaction mixture was allowed to stir for 15 min while remaining at −78 °C. We found that in order to achieve high yields, it was particularly important to make sure that the workup was conducted as quickly as possible, and that the material remained cold. While the flask was still in a −78 °C bath, 0.5 M H_2SO_4 aq (20 mL) and hexanes (15 mL) was added. Quenching the reaction with base, such as $NaHCO_3$, results in diminished yields. Quenching the reaction with HCl (aq) results in the formation of alkyl chloride byproducts that cannot be separated for the alkyl fluorides obtained in the subsequent fluorination step. It is important to note that quenching the reaction at ambient temperature or even 0 °C resulted in diminished yield. The flask was removed from the cold bath and transferred to a separatory funnel and extracted 5× with 15 mL of CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, then filtered and concentrated under vacuum, resulting in a clear, yellow liquid. This material was then filtered through a 10 g plug of silica gel with 10% EtOAc in hexanes. In order to maximize recovery of the triflate, fractions of the filtrate were analyzed by thin-layer chromatography to ensure that no triflate remained in the silica gel plug. The filtrate was then concentrated under vacuum and used without further purification.

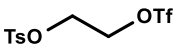
In most cases the triflate was obtained in greater than 95% purity. Minor impurities found in some triflates were found to be of no consequence in a subsequent fluorination reaction. ^{1}H

NMR spectra for the crude triflate products are provided. No further attempt was made to purify or characterize the triflate products.

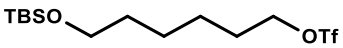
2.3.8 *Characterization data for Alkyl Triflates*



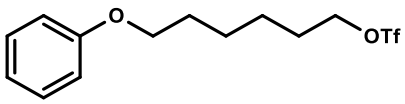
11-bromoundecyl trifluoromethanesulfonate (S3): Compound was isolated as a clear colorless oil (510.0 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (t, *J* = 6.5 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.17 – 1.71 (m, 4H), 1.52 – 1.14 (m, 14H).



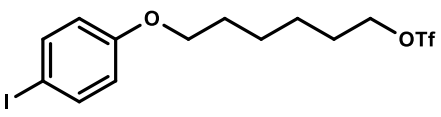
2-[(4-methylbenzenesulfonyl)oxy]ethyl trifluoromethanesulfonate (S4): Compound was isolated as a pale pink oil (633.2 mg, 73%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.76 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 7.9 Hz, 2H), 3.68 – 3.54 (m, *J* = 7.9, 3.2 Hz, 4H), 1.90 (s, 3H).



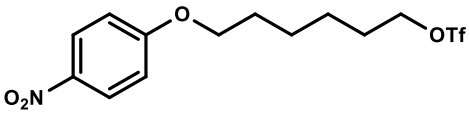
[(tert-butyldimethylsilyl)oxy]hexyl trifluoromethanesulfonate (S5): Compound was isolated as a clear colorless oil (482.7 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (t, *J* = 6.5 Hz, 2H), 3.61 (t, *J* = 6.2 Hz, 1H), 2.19 – 1.68 (m, *J* = 14.1, 6.9 Hz, 2H), 1.68 – 1.25 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H).



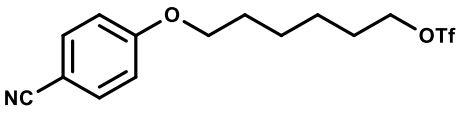
6-phenoxyhexyl trifluoromethanesulfonate (S6): Compound was isolated as a clear colorless oil (385.0 mg, 98%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.34 – 7.22 (m, 2H), 6.93 – 6.42 (m, *J* = 10.8, 4.4 Hz, 2H), 3.79 (t, *J* = 6.4 Hz, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 1.38 (m, *J* = 8.4, 6.5 Hz, 2H), 1.18 – 0.72 (m, 6H).



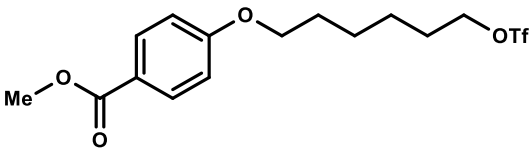
6-(4-iodophenoxy)hexyl trifluoromethanesulfonate (S7): Compound was isolated as a clear colorless oil (1202 mg, 89%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.42 (d, *J* = 9.0 Hz, 2H), 6.41 (d, *J* = 9.0 Hz, 2H), 3.79 (t, *J* = 6.3 Hz, 2H), 3.34 (t, *J* = 6.3 Hz, 2H), 1.30 (dq, *J* = 12.7, 6.4 Hz, 2H), 1.18 – 0.72 (m, 6H).



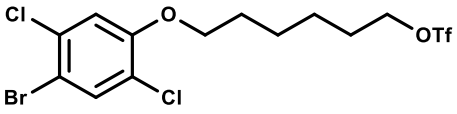
6-(4-nitrophenoxy)hexyl trifluoromethanesulfonate (S8): Compound was isolated as an orange oil (339.0 mg, 76%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.95 (d, *J* = 9.2 Hz, 2H), 6.36 (d, *J* = 9.2 Hz, 2H), 3.82 (t, *J* = 6.3 Hz, 2H), 3.26 (t, *J* = 6.3 Hz, 2H), 1.65 – 0.31 (m, 8H).



6-(4-cyanophenoxy)hexyl trifluoromethanesulfonate (S9): Compound was isolated as a clear colorless oil (1400 mg, 99%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.05 (d, *J* = 8.9 Hz, 2H), 6.38 (d, *J* = 8.8 Hz, 2H), 3.80 (t, *J* = 6.3 Hz, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 1.53 – 0.43 (m, 8H).

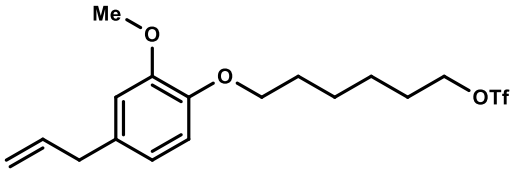


methyl4-{[6-(trifluoromethanesulfonyloxy)hexyl]oxy} benzoate (S10): Compound was isolated as a clear colorless oil (391.4 mg, 85%). ^{1}H NMR (300 MHz, C_6D_6) δ 8.19 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 3.55 (s, 3H), 3.40 (t, *J* = 6.3 Hz, 2H), 1.51 – 1.13 (m, 2H), 1.20 – 0.46 (m, 8H).

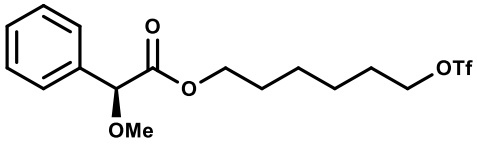


6-(4-bromo-2,5-dichlorophenoxy)hexyl trifluoromethanesulfonate (S11): Compound was isolated

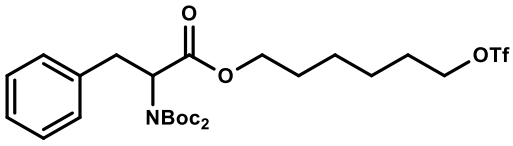
as a clear colorless oil (558.2 mg, 98%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.32 (s, 1H), 6.54 (s, 1H), 3.82 (t, *J* = 6.3 Hz, 2H), 3.08 (t, *J* = 6.1 Hz, 2H), 1.46 – 0.68 (m, 8H).



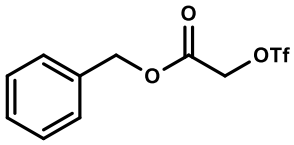
6-[2-methoxy-4-(prop-2-en-1-yl)phenoxy]hexyl Trifluoromethanesulfonate (S12): Compound was isolated as a clear yellow oil (770.0 mg, 99%). ^{1}H NMR (300 MHz, C_6D_6) δ 6.75 (s, 2H), 6.65 (s, 1H), 6.21 – 5.61 (m, *J* = 16.7, 10.0, 6.6 Hz, 1H), 5.32 – 4.86 (m, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.68 (t, *J* = 6.2 Hz, 2H), 3.45 (s, 3H), 3.27 (d, *J* = 6.6 Hz, 2H), 1.52 – 1.29 (m, 2H), 1.22 – 0.98 (m, 4H), 0.86 (d, *J* = 7.1 Hz, 2H).



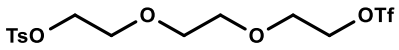
6-(trifluoromethanesulfonyloxy)hexyl (2S)-2-methoxy-2-phenylacetate (S13): Compound was isolated as a clear colorless oil (500 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.33 (m, 5H), 4.76 (s, 1H), 4.47 (t, *J* = 6.4 Hz, 2H), 4.13 (t, *J* = 6.5, 2.0 Hz, 2H), 3.41 (s, 3H), 1.91 – 0.71 (m, 8H).



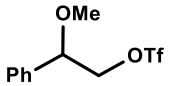
6-(trifluoromethanesulfonyloxy)hexyl 2-{bis[(tert-butoxy)carbonyl]amino}-3-phenylpropanoate (S14): Compound was isolated as a clear yellow oil (695.0 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.05 (m, *J* = 11.6 Hz, 5H), 5.16 – 5.04 (m, *J* = 10.2, 5.1 Hz, 1H), 4.53 (t, *J* = 6.4 Hz, 2H), 4.21 – 3.99 (m, *J* = 16.2, 8.0 Hz, 2H), 3.60 – 3.34 (m, 1H), 3.20 (dd, *J* = 13.9, 10.3 Hz, 1H), 1.92 – 1.18 (m, 32H).



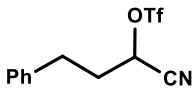
benzyl 2-(trifluoromethanesulfonyloxy)acetate (S15): Compound was isolated as clear colorless oil (483.2 mg, 55%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.05 (s, 5H), 4.74 (s, 2H), 3.92 (s, 2H).



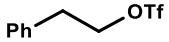
2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)ethyl trifluoromethanesulfonate (S16): Compound was isolated as brown oil (571.0 mg, 65%). Synthesis of this particular compound was done in accordance to a reported literature procedure.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 21.4 Hz, 2H), 4.51 (t, 2H), 4.06 (t, 2H), 3.75 – 3.15 (m, 8H), 2.35 (s, 3H).



(2-methoxy-2-phenylethyl) methanesulfonate (S17): Compound was isolated as a yellow oil (564 mg, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.28 (m, 5H), 4.82 – 3.66 (m, *J* = 19.4, 6.6 Hz, 3H), 3.33 (s, 1H).

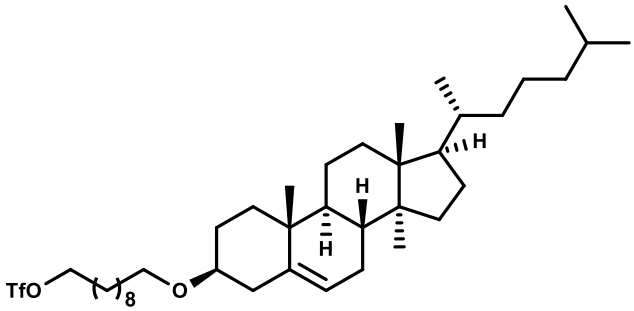


(1-cyano-3-phenylpropyl) trifluoromethanesulfonate (S18): Compound was isolated as a clear colorless oil (524.9mg, 89% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.11 – 6.87 (m, 3H), 6.70 – 6.49 (m, *J* = 1.5 Hz, 2H), 4.82 – 4.00 (m, *J* = 7.2, 6.1 Hz, 1H), 2.18 (dt, *J* = 9.3, 7.0 Hz, 2H), 1.76 – 1.24 (m, 2H).

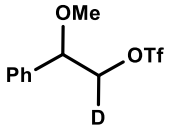


[2-(Trifluoromethylsulfonyloxy)ethyl]benzene (S19): Compound was isolated as a clear colorless oil (2474.4 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.13 – 6.94 (m, 3H), 6.77 – 6.59 (m, 2H), 3.94 (t, *J* = 7.0 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 2H).

[22] Stadler, A. L., Santos, J. O. D., Strensrud, E. S., Dembska, A., Silva, G. L., *Bioconjugate Chem.* **2011**, *22*, 1491-1502.

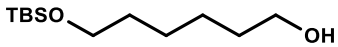


10-{[(1S,2R,5S,10R,11S,14R,15R)-2,11,15-trimethyl-14-[(2R)-6-methylheptan-2-yl]tetracyclo[8.7.0.0^{2},^{7}.0^{11},^{15}]heptadec-7-en-5- yl]oxy}decyl trifluoromethanesulfonate (S20): Isolated as a white solid (1328 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.53 (t, *J* = 6.5 Hz, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.25 – 2.93 (m, 1H), 2.57 – 0.48 (m, 61H).

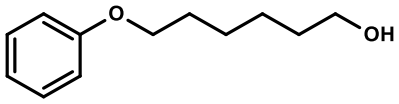


(1-deutero-2-methoxy-2-phenylethyl) methanesulfonate (S22): Compound was isolated as a yellow oil (493 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.31 (m, 5H), 4.48 (d, *J* = 23.1 Hz, 2H), 3.33 (s, 3H).

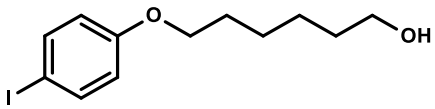
2.3.9 *Preparation of Alcohol Substrates*



6-[(tert-butyldimethylsilyl)oxy]hexan-1-ol (S'5): This compound is known and was isolated as a cloudy colorless oil. Spectral data for **S'5** match reported literature values.[23]



6-phenoxyhexan-1-ol (S'6): Compound was isolated as a white solid. **S'6** is a known compound and spectral data match reported literature values.[24]

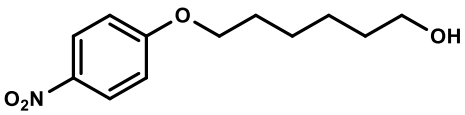


6-(4-iodophenyl)oxyhexan-1-ol (S'7): Compound was isolated as a white powder. **S'7** is a known compound and

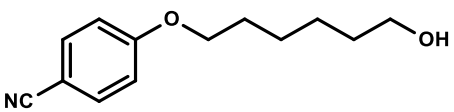
[23] Snyder, S. A., Truitler, D. S., Brucks, A. P., Sattler, W., *J. Am. Chem. Soc.* **2011**, *133*,15898-15901.
[24] S. J. Leiris, O. M. Khdour, Z. J. Segerman, K. S. Tsosie, J.-C. Chapuis, S. M. Hecht,

Bioorg. Med. Chem. **2010**, *18*, 3481-3493.

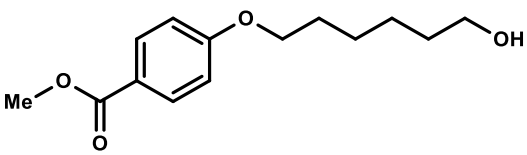
spectral data match the reported literature values.[25]



1-[(6-fluorohexyl)oxy]-4-nitrobenzene (S'8): This compound was synthesized from known procedures with slight modifications and was isolated as an pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.3 Hz, 2H), 6.93 (d, *J* = 9.3 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.67 (q, *J* = 9.8, 5.9 Hz, 2H), 1.99 – 1.71 (m, 2H), 1.71 – 1.34 (m, 6H), 1.28 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 103.8, 83.2, 82.5, 71.7, 63.9, 61.8, 18.3, 11.6, -18.0, -21.9, -25.0, -25.1. GCMS (EI) calculated for $[M]^+$ 239.12, found 239.10. FTIR (neat, cm-1): 3466 (br), 3053 (m), 1593 (m), 1515 (m), 1342 (m), 1266 (s), 1112 (w).



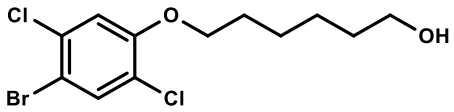
6-(4-cyanophenyl)oxyhexan-1-ol (S'9): Compound was isolated as a white solid. **S'9** is a known compound and spectral data match reported literature values. [74 74 74 74 74 74 73 73 72 72 72 72 72 72 72 72 72 72 7226]



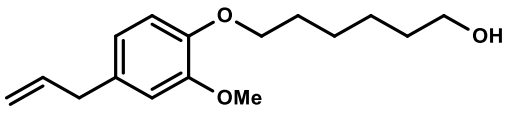
methyl 4-[(6-hydroxyhexyl)oxy]benzoate (S'10): This compound was synthesized from known procedures with slight modifications and was isolated as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.88 (s, 3H), 3.67 (q, *J* = 11.8, 6.3 Hz, 2H), 2.01 – 1.72 (m, 2H), 1.68 – 1.33 (m, 6H), 1.25 (t, *J* = 5.3 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.6, 163.2, 131.8, 123.0, 114.3, 67.9, 62.4, 51.3, 32.9, 29.2, 25.9, 25.8. GC/MS (EI) calculated for $[M]^+$ 252.14, found 252.10. FTIR (neat, cm^{-1}): 3479(br), 3054 (m), 2940 (m), 1713 (s), 1606 (s), 1265 (s), 1169 (s).

[25] R. Gimenez, M. Millaruelo, M. Pinol, J. L. Serrano, A. Vinuales, R. Rosenhauer, T. Fischer, J. Stumpe, *Polymer* **2005**, *46*, 9230-9242.

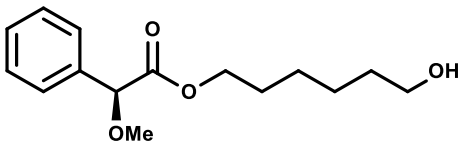
[26] T. Pierro, C. Gaeta, C. Talotta, A. Casapullo, P. Neri, *Org. Lett*. **2011**, *13*, 2650-2653.



1-bromo-2,5-dichloro-4-[(6-fluorohexyl)oxy]benzene (S'11): This compound was synthesized from known procedures with slight modifications and was isolated as a white solid. ^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (s, 1H), 6.53 (s, 1H), 3.39 – 3.27 (m, 2H), 3.14 (t, *J* = 6.3 Hz, 2H), 1.48 – 0.92 (m, 8H), 0.58 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 103.8, 83.2, 82.5, 71.7, 63.9, 61.8, 18.3, 11.6, -18.0, -21.9, -25.0, -25.1. GCMS (EI) calculated for $[M]^+$ 339.96, found 340.00. FTIR (neat, cm-1): 3465 (br), 3053 (m), 2940 (m), 1568 (w), 1468 (m), 1347 (m), 1265 (s), 1075 (m).

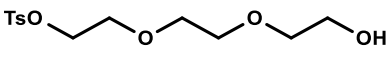


1-(6-hydroxyhexyl)oxy-2-methoxy-4-(prop-2-en-1-yl)benzene (S'12): This compound was synthesized from known procedures with slight modifications and was isolated as a clear yellow liquid. ^{1}H NMR (500 MHz, C_6D_6) δ 6.75 (s, 2H), 6.65 (s, 1H), 5.97 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.06 (dd, *J* = 13.7 Hz, 2H), 3.75 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 3H), 3.35 – 3.29 (m, 2H), 3.29 – 3.20 (m, 2H), 1.75 – 1.55 (m, 2H), 1.43 – 1.27 (m, 4H), 1.27 – 1.13 (m, 2H), 0.59 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.5, 148.2, 138.3, 132.8, 121.0, 115.5, 114.1, 113.3, 69.2, 62.6, 55.6, 40.2, 33.1, 29.8, 26.3, 25.9. GC/MS (EI) calculated for $[M]^+$ 264.17, found 264. FTIR (neat, cm^{-1}): 3419 (br), 3053 (m), 2938 (s), 1675 (w), 1589 (m), 1513 (s), 1265 (s), 1139 (m), 1036 (m), 917 (w), 742 (s).

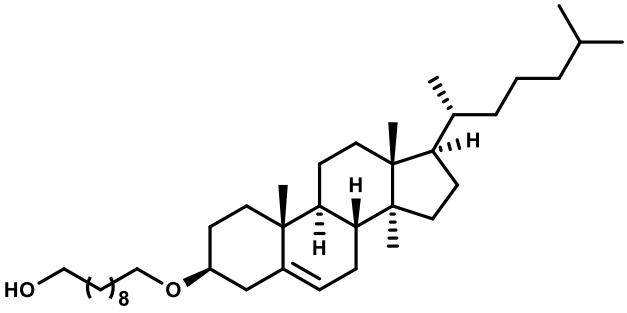


6-hydroxyhexyl (2'S)-2-methoxy-2-phenylacetate (S13): This compound was synthesized from known procedures with slight modifications and was isolated as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.29 (m, 1H), 4.76 (s, 1H), 4.13 (t, *J* = 6.6 Hz, 1H), 3.83 – 3.33 (m, 1H), 3.41 (s, 1H), 2.16 – 0.57 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 136.4, 128.8, 128.7, 127.3, 82.7, 65.2, 62.8, 57.4,

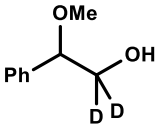
32.6, 28.5, 25.5, 25.3. GC/MS (EI) calculated for $[M]^+$ 266.15, found 266.10 . FTIR (neat, cm^{-1}): 3054 (m), 2940 (m), 1745 (s), 1264 (s), 998 (m).



2-(2-{2-[(4-methylbenzenesulfonyl)oxy]ethoxy}ethoxy)ethan-1-ol (S'16): This compound was synthesized from known procedures with slight modifications and was isolated as a clear colorless oil. **S'16** is known compound and spectral data match the reported literature values.[27]

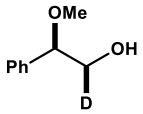


10-{[(1S,2R,5S,10R,11S,14R,15R)-2,11,15-trimethyl-14-[(2R)-6-methylheptan-2-yl]tetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadec-7-en-5-yl]oxy}decan-1-ol (S'20): Compound was isolated as a white solid. **S'18** is a known compound and spectral data match the reported literature values.[28]



(21-b) Compound was isolated as a clear colorless oil (422.6mg, 42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 6.80 (m, *J* = 27.2 Hz, 5H), 4.30 (s, 1H), 3.31 (s, 3H), 2.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 128.7, 128.2, 127.0, 84.7, 69.6 – 63.1 (m), 57.0. $[M]^+$ 154.10, found 154.10 . FTIR (neat, cm^{-1}): 3434 (br), 3028 (m), 2934 (s), 2213 (s), 2083 (s), 1602 (w), 1492 (m), 1453 (s) 1101 (s).

[27] T. Pierro, C. Gaeta, C. Talotta, A. Casapullo, P. Neri, *Org. Lett.* **2011**, *13*, 2650-2653.
[28] Stadler, A. L., Santos, J. O. D., Strensrud, E. S., Dembska, A., Silva, G. L., *Bioconjugate Chem.* **2011**, *22*, 1491-1502.



(21) 1H NMR (300 MHz, C6D6) δ 7.14 – 6.95 (m, 5H), 4.32 – 3.94 (m, 1H), 3.56 (dd, *J* = 33.6, 9.1 Hz, 1H), 2.99 (s, 3H), 2.07 (d, *J* = 9.6 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 138.4, 128.7, 128.3, 127.0, 84.7, 68.7 – 63.7 (t), 57.0. GC/MS (EI) calculated for $[M]^+$ 153.09, found 153.00 . FTIR (neat, cm^{-1}): 3424 (br), 3028 (m), 2934 (s), 1602 (w), 1492 (m), 1453 (m) 110 (s).

2.3.10 *Synthesis of 13*

Compound **13** was prepared by two separate synthetic sequences. Depending on the conditions of the deprotection, **13** was obtained either enantiopure or in racemic form. These results suggest racemization of the substrate when TBAF is used as a reagent in the deprotection step.

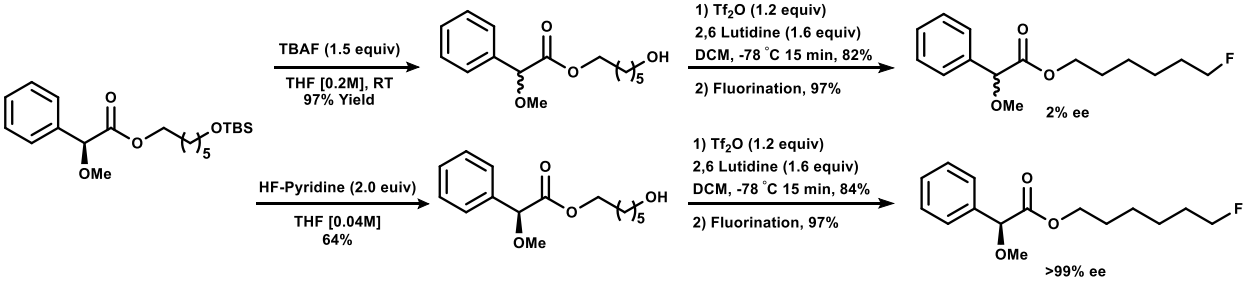
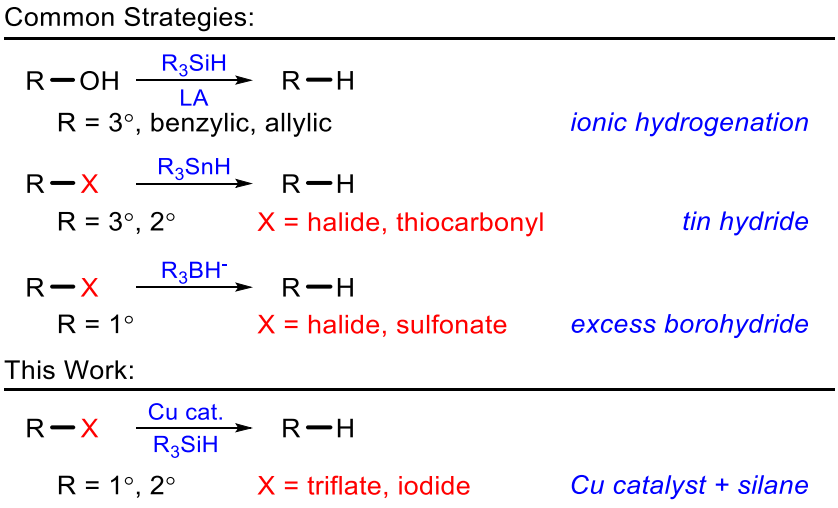


Figure 2.6. Effect of TBAF and HF-pyridine on the racemization of **13**

Chapter 3. COPPER-CATALYZED REDUCTION OF ALKYL TRIFLATES AND IODIDES: AN EFFICIENT METHOD FOR THE DEOXYGENATION OF PRIMARY AND SECONDARY ALCOHOLS[63]

3.1 INTRODUCTION

The selective reduction of alcohols to alkanes is commonly used in the synthesis of complex organic molecules.[75] However, it remains a difficult transformation in organic chemistry due to the inherent difficulties associated with C−O bond activation.[76, 77] Furthermore, current techniques for reducing primary alcohols are inefficient and employ reducing reagents that are both toxic and difficult to remove.[78] These challenges provide motivation for the development of new techniques for the practical and efficient deoxygenation of alcohols.



Scheme 3.1. Strategies for the deoxygenation of alcohols

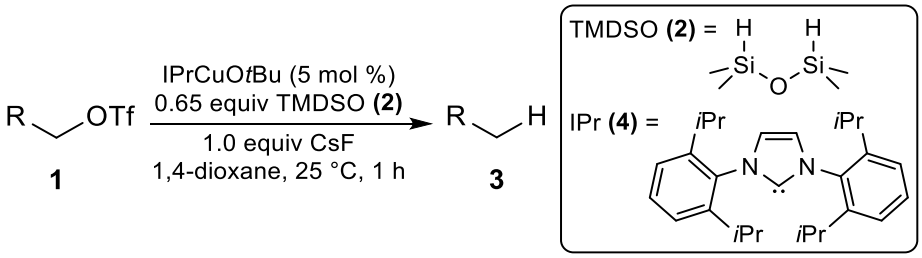
Current strategies for alcohol deoxygenation can be categorized into single-step and two-step procedures. Single-step procedures reduce alcohols directly without prior chemical manipulation. While there are several varied strategies for single-step alcohol deoxygenation,[79-80]

ionic hydrogenation is the most widely used technique.[81-82] This procedure is best suited for the reduction of alcohols that can generate a stabilized carbenium ion, such as benzylic, allylic, or tertiary alcohols. For the reduction of unactivated primary and secondary alcohols, the Barton McCombie deoxygenation reaction, a two-step protocol, is the most widely used technique.[83-84] The alcohol group is first converted into a thioester group prior to the radical reduction step using tin hydride reagents. While other hydride sources have been successfully used, in practice, alkylstannanes remain the reagent of choice despite their toxicity and problems associated with purification.[85-86] Furthermore, even with extensive development of the Barton-McCombie reaction, the reduction of primary alcohols using this procedure is still difficult to achieve.[18]

In contrast to the reduction of secondary or tertiary alcohols, there are few practical approaches to primary alcohol deoxygenation. Recently, Stephenson has reported an efficient light-mediated reduction of complex primary alkyl iodides using Hantzsch ester and a stoichiometric source of hydride.[87] In practice, however, the deoxygenation of primary alcohols typically involves the reduction of halides or sulfonates using powerful borohydride reagents, [88-89] such as Superhydride.[90] Even the mildest variant of this approach requires prolonged heating with multiple equivalents of $NaBH_4$ in DMSO,[91] making this strategy an impractical option for the reduction of molecules bearing sensitive functional groups.[92,93] Overall, the deoxygenation of complex primary alcohols remains a particularly challenging task.

We were surprised to find that relatively few attempts have been made to address these challenges through the use of transition metal catalysis, especially given its role in the selective reduction of alkenes, alkynes, and carbonyls. Thus far, investigations into the reduction of halides and sulfonates using Pd,[94-95] Ni,[96, 97] and Ir[98, 99] have tended to focus on substrates bearing unsubstituted alkyl or aryl substituents. We recently reported a copper-catalyzed semi-reduction

of alkynes to alkenes which is highly selective and compatible with many different functional groups.[100] Considering that copper hydride complexes have been shown to reduce unfunctionalized alkyl halides and sulfonates in moderate yield when used in stoichiometric quantities,[101-102] we reasoned that the catalytic system developed in our laboratory could provide a new approach to the deoxygenation of alcohols. In this paper, we describe a copper-catalyzed reduction of alkyl triflates and iodides that is practical, efficient, and functional-group-tolerant.



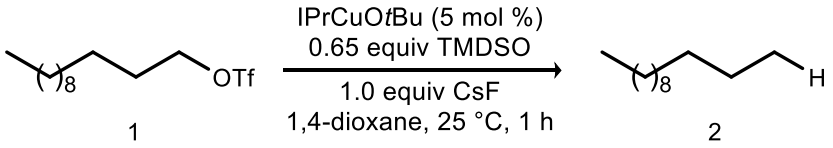
Scheme 3.2. Conditions for the copper-catalyzed reduction of 1° triflates

3.2 REACTION DEVELOPMENT

Alkyl sulfonates can be readily accessed from primary alcohols, and their reactivity can be easily tuned through adjustment of their electronic properties.[103,104] For these reasons, we anticipated that they would be useful in exploring the copper-catalyzed two-step deoxygenation of primary alcohols. We found that primary triflates can be reduced using IPrCuO*t*Bu as the catalyst, tetramethyldisiloxane **2** (TMDSO) as the hydride source, and CsF as an additive that aids catalyst turnover (Scheme 3.2).[105,106,107] The reduction occurs in high yield in less than 1 hour at ambient temperature, and without competing elimination. Tosylates and nosylates were found to be significantly less reactive, illustrating the mild nature of the reducing reagent (Table 3.5, entries 2-3). In the absence of catalyst no reaction took place (entry 4). Furthermore, IPrCuO*t*Bu performed significantly better than catalysts supported by phosphines or less sterically demanding NHC ligands (entries 5-7). In general, we observed a higher rate of

reduction when more reactive silanes such as poly(methylhydrosiloxane) (PMHS) or Ph_2SiH_2 were used. Surprisingly, the highest rate of reduction was achieved with TMDSO (entries 8-10).[108] Although alkoxide additives are commonly employed in copper catalyzed reactions of silanes to aid in catalyst turnover,[105,106,107] we found thattheir use resulted in unproductive side-reactions of the triflate starting material, and that the use of CsF was essential (entries 11-12).

Table 3.5. Reaction development



Entry	Changes from optimized conditions	Yield [%][a] after 1h	Yield [%][a] after 48h
1	None	96	100
2	ROTs instead of ROTf		10
3	RONs instead of ROTf		0
4	No catalyst		0
5	Cy_3PCuI instead of IPrCuO*t*Bu		59
6	XantphosCuI instead of IPrCuO*t*Bu		52
7	IMesCuO*t*Bu instead of IPrCuO*t*Bu		54
8	1.3 equiv Et_3SiH instead of TMDSO		71
9	1.3 equiv PMHS instead of TMDSO	10	98
10	Ph_2SiH_2 instead of TMDSO	89	100
11	NaO*t*Bu instead of CsF		16[b]
12	LiO*t*Bu instead of CsF		13[b]

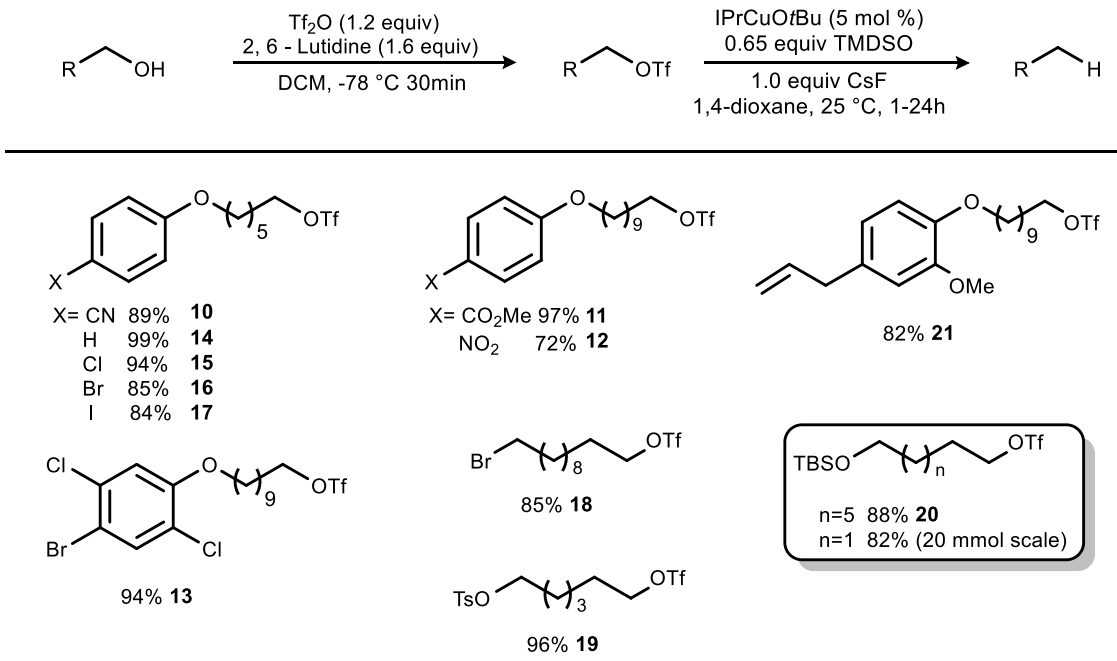
[a] GC yield based on internal standard. [b] Complete conversion observed. Additional Information: Cy= cyclohexyl, Ns= Nosyl, Ts= Tosyl, Xantphos= 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene

3.3 REACTION SCOPE

3.3.1 *Reduction of primary alkyl triflates and iodides*

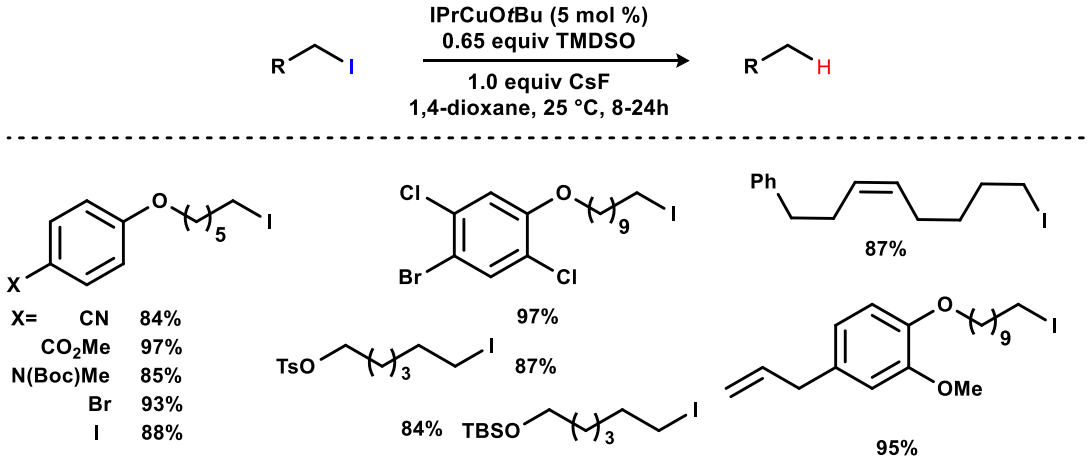
We turned our attention to the development of a two-step procedure for deoxygenation of primary alcohols based on the copper-catalyzed reduction of alkyl triflates. The practical utility of this procedure depends on the efficient functionalization of alcohols, and we found that with slight modifications to existing protocols, primary triflates can be efficiently prepared with minimal purification. As shown in Table 3.6, the overall deoxygenation of alcohols occurs in high yield over two steps and is compatible with many functional groups. High yields were obtained in the presence of substituents that are commonly susceptible to reduction, including cyano, ester, nitro, and olefin groups (compounds **10-12** and **21**). The reaction is compatible with aryl chlorides, bromides, and iodides—functional groups which are typically reactive in both transition metal-catalyzed and free-radical reductions (compounds **14-17**). The reduction of compounds **18** and **19** shows that the selective reduction of triflates can be accomplished even in the presence of alkyl bromides or tosylates. Finally, no deprotection of silyl-protected alcohols was observed although a stoichiometric amount of CsF is used in the reaction, (compound **20**). Overall, the two-step procedure illustrated in Table 3.6 is a practical approach to primary alcohol deoxygenation that addresses key limitations of existing methods.

Table 3.6. Two-step procedure for the reduction of primary alcohols



We also found that the reaction conditions developed for triflate reduction were effective in the reduction of primary alkyl iodides. The results in Table 3.7 show that iodides can be reduced by extending the reaction time to 24 hours while maintaining the functional group compatibility observed in the reduction of triflates. Nitriles, esters, carbamates, amides, aryl halides, tosylates, silyl ethers, and alkenes are well-tolerated.

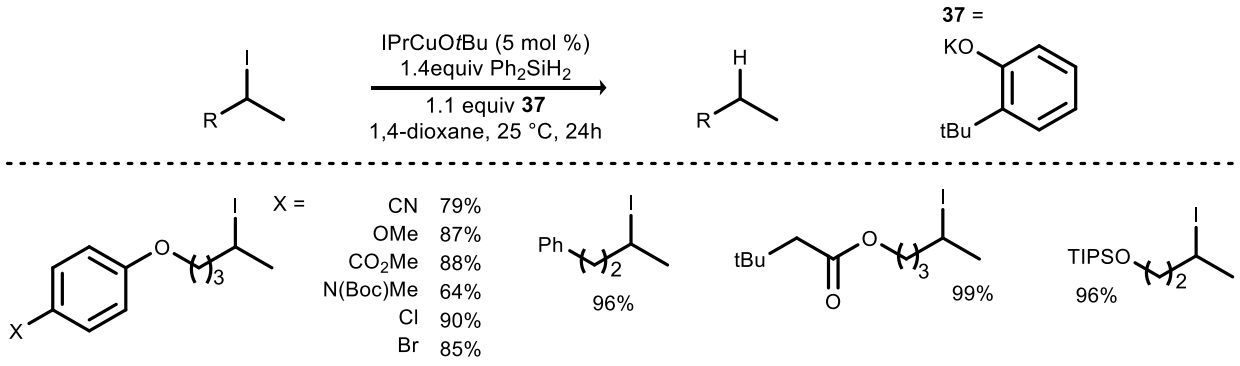
Table 3.7. Catalytic reduction of primary iodides



3.3.2 *Reduction of secondary iodides*

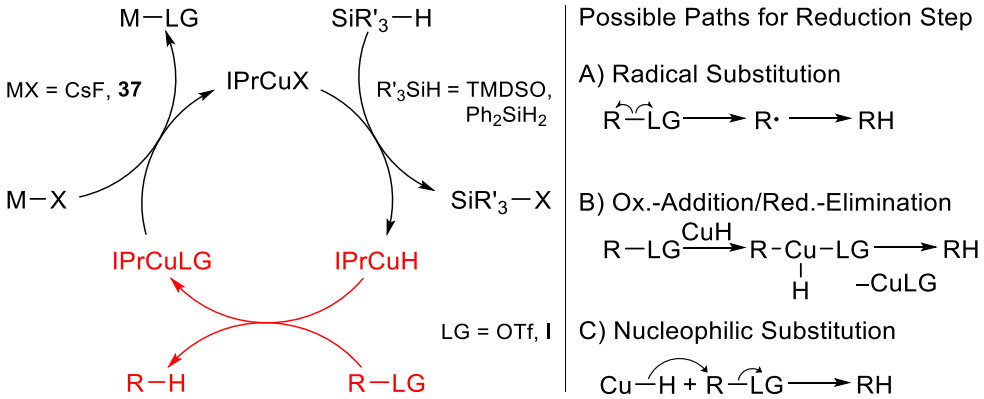
When we turned our attention to the reduction of secondary iodides, we found that a competing elimination reaction produced trace amounts of an undesired alkene along with the reduced product. In order to address this problem, we explored the use of alternative hydride sources and additives. Ultimately, we found that switching from TMDSO to Ph_2SiH_2 and from CsF to potassium 2-*tert*-butylphenoxide (**37**) allowed us to achieve high yield in the reduction of secondary iodides without alkene formation. As shown in Table 3.8, these slight changes to the reaction conditions allowed the successful reduction of secondary iodides bearing a variety of functional groups, including ester, silyl ether, cyano, methoxy, carbamate and aryl halide.

Table 3.8. Catalytic reduction of secondary iodides



3.4 MECHANISTIC STUDIES

We propose that the copper-catalyzed reduction of triflates and iodides proceeds according to the mechanism depicted in Scheme 3.3. Given the precedence for the formation of copper(I) hydrides through silicon-to-copper transmetallation,[100,109] we chose to focus our



Scheme 3.3. Plausible mechanisms for the reduction step

investigation of the mechanism on the proposed copper hydride reduction step, which had not been studied in detail. We reasoned that the reduction step is likely to occur by one of three pathways: A) the formation of alkyl radical intermediates, B) an oxidative-addition/reductive-elimination sequence, or C) direct S_N2-type substitution of the leaving group by copper hydride. The reduction of triflates by copper hydride is unlikely to proceed by a radical mechanism, as is it would involve the homolytic cleavage of the strong C−O bond.[110] However, considering the facile homolytic cleavage of the C−I bond, it is possible that the reduction of iodides involves the formation of free-radical intermediates (Scheme 3.3 A).

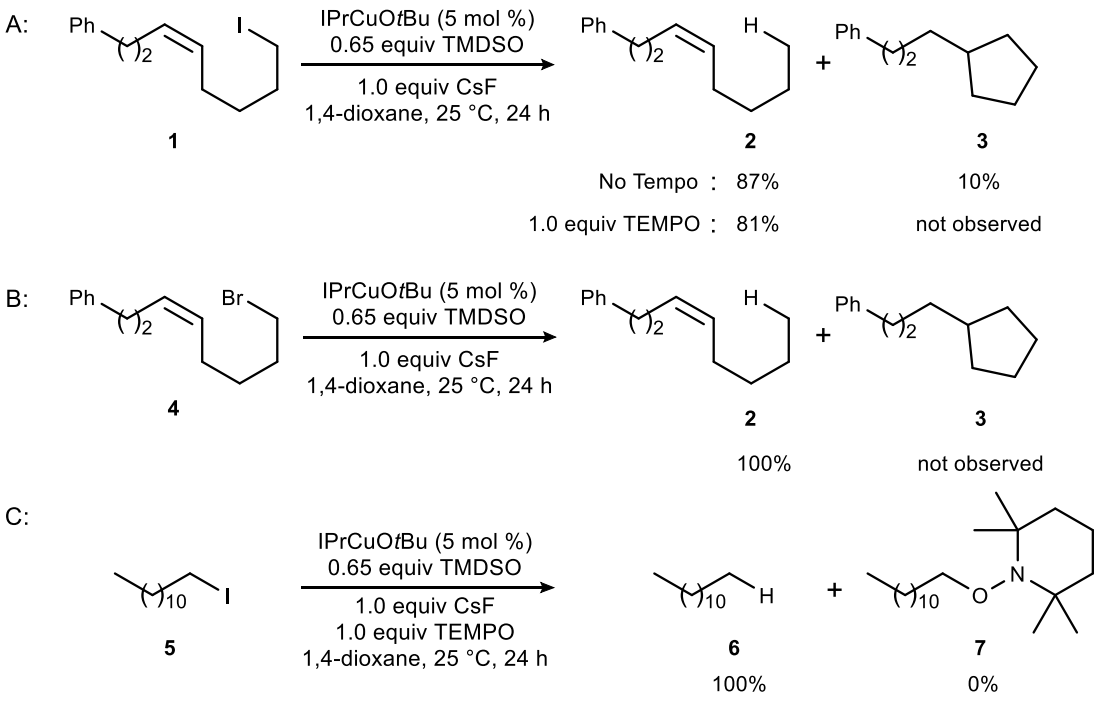


Figure 3.1. Mechanistic studies on the reduction of alkyl halides

To explore this possibility, we conducted the experiments shown in Figure 3.1. We found that in the copper-catalyzed reduction of alkenyl iodide **1**, the ratio of reduced product to cyclization product was 9:1 (Fig. 3.1 A).[45] Furthermore, when alkenyl bromide **4** was submitted to the reaction conditions, reduction product **2** was formed in quantitative yield and cyclization product **3** was not observed, suggesting that free-radical formation is not the dominant pathway (Fig. 3.1 B). Finally, when we carried out the reduction of iodide **5** in the presence of a stoichiometric amount of TEMPO, the reduction product **6** was observed in quantitative yield and the TEMPO-alkyl adduct **7** was not detected (Fig. 3.1 C). While it is inherently difficult to rule out the possibility of free-radical formation, we believe that taken collectively, these results suggest that a radical mechanism is not the major pathway in the copper-catalyzed reduction of halides, and that paths B and C in Scheme 3.3 are more likely. Further investigation into the mechanism is ongoing.

3.5 CONCLUSION

In conclusion, we have developed a copper-catalyzed deoxygenation of primary and secondary alcohols that is convenient, versatile, and compatible with many functional groups. We have demonstrated that the reduction of alcohols can be achieved through a practical two-step procedure in which the alcohol is converted either to a triflate or iodide prior to a highly efficient copper-catalyzed reduction step. Initial investigation of the mechanism suggests that free-radical formation is not the dominant reaction pathway, and that the reduction step is more likely to occur either by oxidative-addition/reductive-elimination or nucleophilic substitution. Overall, this technique is particularly well-suited to deoxygenation of functionalized primary alcohols, which has traditionally been a challenging transformation.

3.6 EXPERIMENTAL

3.6.1 *General*

All reactions were performed under a nitrogen atmosphere, using flame-dried glassware unless otherwise indicated. Column chromatography was performed on a Biotage Iso-1SV flash purification system using silica gel (Agela Technologies Inc., 60Å, 40-60 μm, 230-400 mesh). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual $CHCl_3$ (7.26 ppm), C_6H_6 (7.16 ppm), CH_2Cl_2 (5.32 ppm), or CH_3CN (1.94 ppm). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent $CDCl_3$ (δ 77.2 ppm), C_6D_6 (128.1), or CD_2Cl_2 (54.0). Data

are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a Bruker Esquire 1100 Liquid Chromatograph – Ion Trap Mass Spectrometer, or a Hewlett Packard 5971A gas chromatograph – Mass Spectrometer. GC analysis was performed on a Shimadzu GC-2010 with a flame ionization detector and a SHRXI-5MS column (15 m x 0.25 mm x 0.25 μm).

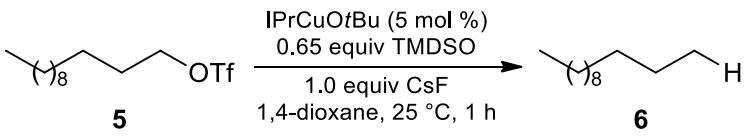
Materials: THF, CH_2Cl_2, and Et_2O were degassed and dried on columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl, and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. IPrCuO*t*Bu[100] and IMesCuO*t*Bu[111] were prepared according to existing procedures. Primary and secondary alcohols were prepared according to standard techniques. All other commercially available reagents were purchased from AK Scientific, Inc., Oakwood Products, Inc., Sigma-Aldrich Co., STREM Chemicals, Inc., Tokyo Chemical Industry Co., Ltd., or VWR international, LLC. and were used as received.

3.6.2 *Reduction of Primary Triflates*

3.6.2.1 *Reaction Optimization*

In a nitrogen-filled glovebox, catalyst (0.005 mmol, 0.05 equiv), ligand (0.005 mmol, 0.05 equiv; only added separately in the case of phosphine-copper iodide catalysts) and additive (0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335 µL). At this point, silane (0.065 mmol, 0.65 equiv in the case of dihydride, 0.130 mmol, 1.30 equiv in the case of monohydride), 1,4-dioxane (335 µL) and dodecyl triflate[112,] **5** (31.8 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C. Aliquots were taken at various time points as indicated in Table 3.9. Yield was determined based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard: SHRXI-5MS column.

Table 3.9. optimization



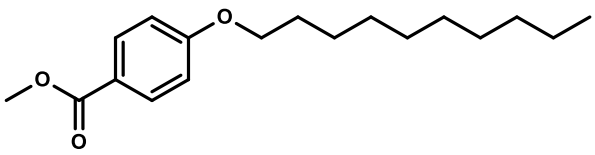
Entry	Change From Optimized Conditions	1 h Yield (%)[a]	48 h Yield (%)[a]
1	None	96	100
2	ROTs instead of ROTf	-	10
3	RONs instead of ROTf	-	0
4	No catalyst instead of IPrCuO*t*Bu	-	0
5	Cy_3PCuI instead of IPrCuO*t*Bu	-	59
6	XantphosCuI instead of IPrCuO*t*Bu	-	52
7	IMesCuO*t*Bu instead of IPrCuO*t*Bu	-	54

8	1.3 equiv Et_3SiH instead of TMDSO	-	71
9	1.3 equiv PMHS instead of TMDSO	10	98
10	Ph_2SiH_2 instead of TMDSO	89	100
11	NaO*t*Bu instead of CsF	-	16[b]
12	LiO*t*Bu instead of CsF	-	13[b]

[a] Yield was determined by GC based on an internal standard. [b] Complete conversion of the starting material was observed.

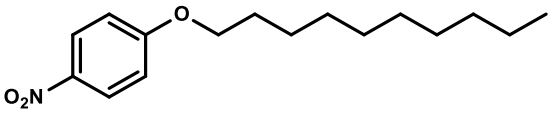
3.6.2.2 Reduction Step

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, IPrCuO*t*Bu (13.1 mg, 0.025 mmol, 0.05 equiv), and CsF (76.0 mg, 0.500 mmol, 1.00 equiv). The mixture was suspended in 1,4-dioxane (1.67 mL) and then tetramethyldisiloxane (TMDSO; 58.2 µL, 0.325 mmol, 0.65 equiv) was added. At this point alkyl triflate (0.500 mmol, 1.00 equiv) was added as a solution in 1,4-dioxane (1.67 mL). The mixture was stirred for 4 h at 25 °C, then filtered through a plug of silica gel and the filter was rinsed with Et_2O (20 mL). The filtrate was concentrated and then chromatographed on a 25 g silica gel column with a solvent gradient of 0→10% EtOAc in hexanes over 8 CVs.

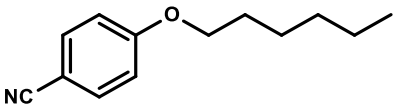


methyl 4-(dec-1-yl)oxybenzoate (S1): Compound was isolated as a white solid (142 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.14 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.9 Hz, 2H), 3.67 – 3.41 (m, 5H), 1.65 – 1.43 (m, 2H), 1.40 – 1.11 (m, 14H), 0.92 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 167.2, 163.6, 132.0, 123.0, 114.6, 68.9, 52.2, 32.5, 30.2, 30.2, 30.0, 29.9, 29.7, 26.6, 23.3, 14.5. GC/MS (EI)

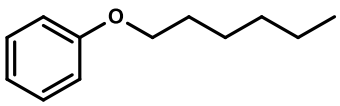
calculated for $[M]^+$ 292.20, found 292. FTIR (neat, cm^{-1}): 3053 (m), 2926 (s), 1715 (s), 1605 (s), 1511 (s), 1435 (s), 1258 (s), 1010 (m), 647 (w).



1-(4-nitrophenyl)oxydecane (S2): Compound was isolated as a clear yellow liquid (100.3 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.3 Hz, 2H), 6.94 (d, *J* = 9.3 Hz, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 1.91 – 1.69 (m, 2H), 1.51 – 1.16 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.1, 141.9, 125.9, 114.4, 68.7, 32.3, 30.0, 30.0, 29.8, 29.7, 29.2, 26.2, 23.1, 14.4. GC/MS (EI) calculated for $[M]^+$ 279.18, found 279. FTIR (neat, cm^{-1}): 3053 (m), 2928 (s), 1593 (s), 1521 (s), 1342 (s), 1264 (s), 1172 (m), 1111 (m), 845 (m).

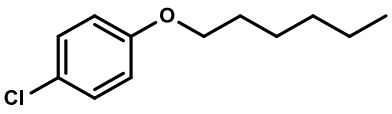


1-(4-cyanophenyl)oxyhexane (S3): Compound was isolated as a clear colorless liquid (90.2 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 1.87 – 1.70 (m, 2H), 1.51 – 1.40 (m, 2H), 1.39 – 1.29 (m, 4H), 0.91 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6, 134.1, 119.5, 115.3, 103.8, 68.5, 31.6, 29.1, 25.7, 22.7, 14.1. GC/MS (EI) calculated for $[M]^+$ 203.13, found 203. FTIR (neat, cm^{-1}): 3054 (m), 2932 (s), 2225 (s), 1899 (w), 1606 (s), 1506 (s), 1264 (s), 1171 (s), 1017 (m), 835 (s).

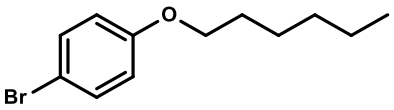


1-phenoxyhexane (S4): Compound was isolated as a clear colorless liquid (88.6 mg, 99% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.39 – 7.12 (m, 2H), 6.99 – 6.76 (m, 3H), 3.94 (t, *J* = 6.6 Hz, 2H), 1.89 – 1.64 (m, 2H), 1.62 – 1.18 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 159.8, 129.9, 120.9, 114.9, 68.4, 32.2, 29.8, 26.3, 23.2, 14.4. GC/MS (EI) calculated for $[M]^+$ 178.14, found 178. FTIR (neat, cm^{-}

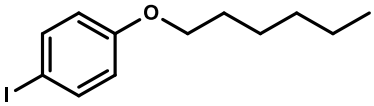
^{1}): 3039 (m), 2932 (s), 1923 (w), 1844 (w), 1772 (w), 1684 (w), 1601 (s), 1244 (s), 752 (s), 690 (s).



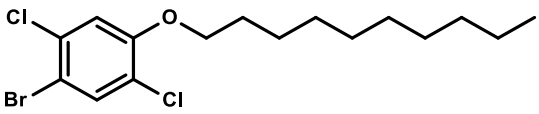
1-(4-chlorophenyl)oxyhexane (S5): Compound was isolated as a clear colorless liquid (99.9 mg, 94% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 3.92 (t, *J* = 6.6 Hz, 2H), 1.87 – 1.66 (m, 2H), 1.49 – 1.19 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 159.8, 129.9, 120.9, 114.9, 68.4, 32.2, 29.8, 26.3, 23.2, 14.4. GC/MS (EI) calculated for $[M]^+$ 212.10, found 212. FTIR (neat, cm^{-1}): 3072 (w), 2932 (s), 1869 (w), 1597 (s), 1472 (s), 1245 (s), 1092 (s), 823 (s), 668 (s).



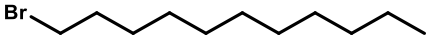
1-(4-bromophenyl)oxyhexane (S6): Compound was isolated as a clear colorless liquid (108.9 mg, 85% yield). **S6** is a known compound and spectral data matches reported literature values.[113]



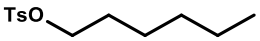
1-(4-iodophenyl)oxyhexane (S7): Compound was isolated as a clear colorless liquid (128.1 mg, 84% yield). **S7** is a known compound and spectral data matches reported literature values.[114]



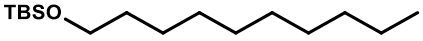
1-(4-bromo-2,5-dichlorophenyl)oxydecane (S8): Compound was isolated as a white solid (179.7 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.99 (s, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.94 – 1.73 (m, 2H), 1.53 – 1.40 (m, 2H), 1.40 – 1.16 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.7, 134.1, 133.4, 122.6, 114.7, 112.6, 69.3, 32.4, 30.0, 30.0, 29.8, 29.7, 29.1, 26.2, 23.2, 14.4. GC/MS (EI) calculated for $[M]^+$ 380.03, found 380. FTIR (neat, cm^{-1}): 3050 (w), 2924 (s), 1575 (m), 1464 (s), 1346 (m), 1264 (s), 1123 (m), 1075 (m), 739 (s).



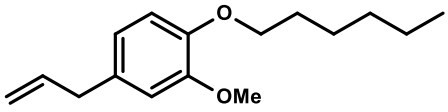
1-bromoundecane (S9): Compound was isolated as a clear colorless liquid (100.0 mg, 85% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 2.97 (t, *J* = 6.8 Hz, 2H), 1.62 – 1.43 (m, 2H), 1.43 – 1.00 (m, 16H), 0.92 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 33.7, 33.1, 32.3, 30.0, 30.0, 29.8, 29.8, 29.1, 28.4, 23.1, 14.4. GC/MS (EI) calculated for $[M]^+$ 234.10, found 234. FTIR (neat, cm^{-1}): 2920 (s), 1465 (s), 1377 (m), 1259 (m), 721 (m), 647 (m), 565 (m).



***p*-toluenesulfonic acid, hexyl ester (S10):** Compound was isolated as a clear colorless liquid (122.5 mg, 96% yield). **S10** is a known compound and spectral data matches reported literature values.[115]



1-(*tert*-butyldimethylsilyl)oxydecane (S11): Compound was isolated as a clear colorless liquid (124.4 mg, 91% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 3.58 (t, *J* = 6.3 Hz, 2H), 1.66 – 1.49 (m, 2H), 1.46 – 1.21 (m, 14H), 1.01 (s, 9H), 0.91 (t, *J* = 6.7 Hz, 3H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 63.4, 33.3, 32.3, 30.1, 30.1, 29.9, 29.8, 26.3, 26.2, 23.1, 18.6, 14.4, -5.1. FTIR (neat, cm^{-1}): 3065 (m), 2931 (s), 1917 (w), 1723 (w), 1598 (s), 1465 (s), 1363 (s), 1176 (s), 1097 (s), 787 (m).



1-hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene (S12): Compound was isolated as a clear colorless liquid (102.3 mg, 82% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.75 (d, *J* = 2.8 Hz, 2H), 6.65 (s, 1H), 6.10 – 5.81 (m, 1H), 5.26 – 4.98 (m, 2H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.45 (s, 3H), 3.26 (d, *J* = 6.6 Hz, 2H), 1.82 – 1.56 (m, 2H), 1.53 – 1.31 (m, 2H), 1.31 – 1.05 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.6, 148.3, 138.4, 132.7, 121.0, 115.5, 114.1, 113.4, 69.2, 55.6, 40.2, 32.0,

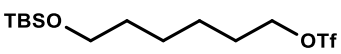
29.9, 26.2, 23.0, 14.3. GC/MS (EI) calculated for $[M]^+$ 248.18, found 247.75. FTIR (neat, cm^{-1}): 3059 (w), 2932 (s), 2280 (m), 1639 (m), 1590 (s), 1466 (s), 1260 (s), 1141 (s), 1040 (s), 914 (m), 812 (s).

3.6.2.3 *Triflation Step*

A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and a primary alcohol (2.00 mmol, 1.00 equiv). The alcohol was dissolved in CH_2Cl_2 (5.0 mL) and cooled to −78 °C before adding 2,6-lutidine (370 µL, 3.20 mmol, 1.60 equiv). While stirring, triflic anhydride (455 µL, 2.4 mmol, 1.20 equiv) was added drop-wise, and then the reaction mixture was allowed to stir for 15 min while remaining at −78 °C. We found that in order to achieve high yields, it was particularly important to make sure that the workup was conducted as quickly as possible, and that the material remained cold. While the flask was still in a −78 °C bath, 1 M HCl_{aq} (15 mL) and brine (15 mL) was added and allowed to freeze in the flask. It is important to note that quenching the reaction at ambient temperature or even 0 °C resulted in diminished yield. The flask was removed from the cold bath, and as soon as the mixture had thawed slightly, it was transferred to a separatory funnel and extracted 5× with 15 mL of CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, then filtered and concentrated under vacuum, resulting in a clear, yellow liquid. This material was then filtered through a 10 g plug of silica gel with 10% EtOAc in hexanes. In order to maximize recovery of the triflate, fractions of the filtrate were analyzed by thin-layer chromatography to ensure that no triflate remained in the silica gel plug. The filtrate was then concentrated under vacuum and used without further purification or isolation.Although minor impurities remained, we found that these did not affect the outcome of the 2-step deoxygenation procedure. No further attempt was made to purify or characterize the triflate products.

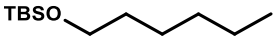
3.6.3 *Multi-Gram Scale Deoxygenation*

3.6.3.1 *Preparation of Alkyl Triflate*



6-(*tert*-butyldimethylsilyl)oxyhex-1-yl trifluoromethanesulfonate (20b): A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and 6-(*tert*-butyldimethylsilyl)oxyhexan-1-ol (5.68 g, 24.4 mmol, 1.00 equiv). The alcohol was dissolved in CH_2Cl_2 (61.0 mL) and cooled to −78 °C before adding 2,6-lutidine (4.52 mL, 39.1 mmol, 1.60 equiv). While stirring, triflic anhydride (5.56 mL, 29.3 mmol, 1.20 equiv) was added drop-wise, and then the reaction mixture was allowed to stir for 30 min while remaining at −78 °C. While the flask was still in a −78 °C bath, 0.5 M H_2SO_{4aq} (20 mL) was added and allowed to freeze in the flask. The flask was removed from the cold bath, and as soon as the mixture had thawed slightly, it was transferred to a separatory funnel and extracted 3× with 50 mL of CH_2Cl_2. The organic layers were combined and washed 1× 50mL of distilled water. The collected organic layers were then dried over Na_2SO_4, then filtered and concentrated under vacuum, resulting in a cloudy yellow liquid. This material was then filtered through a 125 g plug of silica gel with 10% EtOAc in hexanes. In order to maximize recovery of the triflate, fractions of the filtrate were analyzed by thin-layer chromatography to ensure that no triflate remained in the silica gel plug. The filtrate was then concentrated under vacuum to afford a clear, colorless liquid (8.16 g, 92% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 3.81 (t, J = 6.4 Hz, 2H), 3.45 (t, J = 6.2 Hz, 2H), 1.38 – 1.16 (m, 4H), 1.19 – 1.02 (m, 4H), 1.00 (s, 9H), 0.95 – 0.82 (m, 4H), 0.07 (s, 6H).

3.6.3.2 Reduction Step

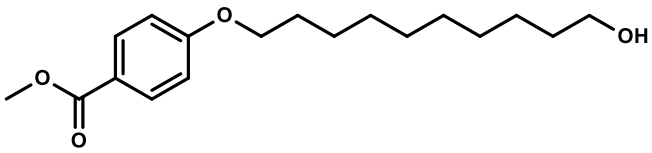


1-(*tert*-butyldimethylsilyl)oxyhexane (S13): A dry 500 mL reaction

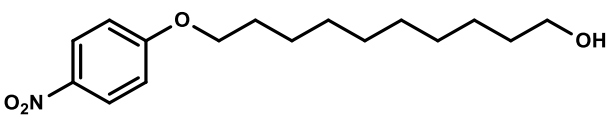
flask was charged with a stir bar, IPrCuO*t*Bu (210 mg, 0.40 mmol, 0.02 equiv), and CsF (3.04 g, 20.0 mmol, 1.00 equiv). The mixture was suspended in 1,4-dioxane (133 mL). While stirring at 0 °C, tetramethyldisiloxane (TMDSO; 2.33 mL, 13.0 mmol, 0.65 equiv) was added, producing a clear yellow solution. To this was added alkyl triflate (7.29 mL, 20.0 mmol, 1.00 equiv). After warming up to 25 °C, the reaction was allowed to stir for an additional 6 hours. At this point, the reaction mixture was filtered through a 125 g plug of silica gel and the filter was rinsed with Et_2O (200 mL). The filtrate was concentrated and then pushed through an 85 g plug of silica gel with 100% hexanes as the eluent. Concentration of the filtrate resulted in a clear colorless oil (3.57 g, 82% yield). **S13** is a known compound and spectral data matches reported literature values.[116]

3.6.4 *Characterization of Primary Alcohols*

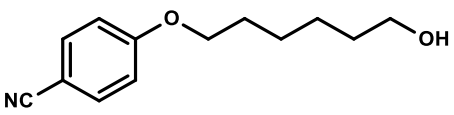
Primary alcohols that were used as starting materials in the triflation step were prepared according to standard protocols.



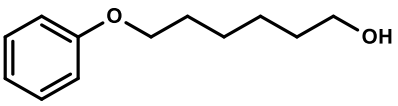
methyl 4-(10-hydroxydec-1-yl)oxybenzoate (S14): Compound was isolated as a white solid. ^{1}H NMR (300 MHz, C_6D_6) δ 8.17 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 3.67 – 3.46 (m, 5H), 3.46 – 3.28 (m, 2H), 1.66 – 1.46 (m, 2H), 1.46 – 1.34 (m, 2H), 1.34 – 1.16 (m, 12H), 0.51 (t, *J* = 5.4 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.7, 163.3, 132.0, 114.5, 68.1, 62.7, 51.5, 33.2, 30.0, 29.9, 29.9, 29.7, 29.4, 26.3, 26.3. GC/MS (EI) calculated for $[M]^+$ 308.20, found 308. FTIR (neat, cm^{-1}): 3612 (br), 3053.5 (s), 2931 (s), 1712 (s), 1606 (s), 1511 (m), 1436 (s), 1264 (s), 1010 (w).



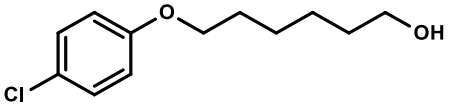
10-(4-nitrophenyl)oxydecan-1-ol (S15): Compound was isolated as a white solid. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.18 (d, *J* = 9.3 Hz, 2H), 6.96 (d, *J* = 9.3 Hz, 2H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.68 – 3.50 (m, 2H), 1.90 – 1.70 (m, 2H), 1.56 (s, 1H), 1.55 – 1.39 (m, 4H), 1.38 – 1.24 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 141.4, 126.0, 114.5, 69.0, 63.2, 32.9, 29.6, 29.6, 29.5, 29.4, 29.1, 26.0, 25.8. GC/MS (EI) calculated for $[M]^+$ 295.18, found 295. FTIR (neat, cm^{-1}): 3513 (br), 3053 (m), 2931 (m), 1594 (m), 1505 (m), 1342 (m), 1265 (s), 1173 (w), 1111 (w), 738 (s).



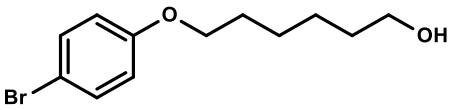
6-(4-cyanophenyl)oxyhexan-1-ol (S16): Compound was isolated as a white solid. **S16** is a known compound and spectral data matches reported literature values.[74]



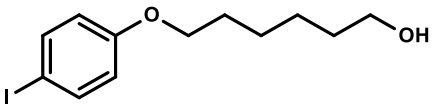
6-phenoxyhexan-1-ol (S17): Compound was isolated as a white solid. **S16** is a known compound and spectral data matches reported literature values.[117]



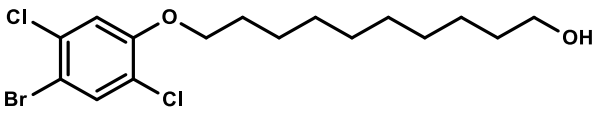
6-(4-chlorophenyl)oxyhexan-1-ol (S18): Compound was isolated as a white powder. ^{1}H NMR (500 MHz, C_6D_6) δ 7.08 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 3.38 – 3.22 (m, 2H), 1.58 – 1.43 (m, 2H), 1.42 – 1.28 (m, 2H), 1.28 – 1.14 (m, 4H), 0.56 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 158.2, 129.6, 125.7, 116.1, 68.1, 62.5, 33.0, 29.4, 26.1, 25.9. GC/MS (EI) calculated for $[M]^+$ 228.09, found 228. FTIR (neat, cm^{-1}): 3346 (br), 2936 (s), 1869 (w), 1734 (w), 1596 (s), 1492 (s), 1391 (w), 1169 (s), 1092 (s), 738 (m).



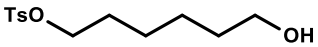
6-(4-bromophenyl)oxyhexan-1-ol (S19): Compound was isolated as a white powder. ^{1}H NMR (300 MHz, C_6D_6) δ 7.22 (d, *J* = 9.0 Hz, 2H), 6.49 (d, *J* = 9.0 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 3.36 – 3.23 (m, 2H), 1.57 – 1.41 (m, 2H), 1.38 – 1.26 (m, 2H), 1.26 – 1.11 (m, 4H), 0.48 (t, *J* = 5.2 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 158.7, 132.6, 116.6, 113.0, 68.0, 62.5, 33.0, 29.4, 26.1, 25.9. GC/MS (EI) calculated for $[M]^+$ 272.04, found 272. FTIR (neat, cm^{-1}): 3609 (br), 3052 (m), 2938 (s), 1873 (w), 1591 (s), 1489 (s), 1171 (s), 1002 (s), 823 (s), 641 (m).



6-(4-iodophenyl)oxyhexan-1-ol (S20): Compound was isolated as a white powder. **S20** is a known compound and spectral data matches reported literature values.[118]

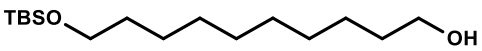


10-(4-bromo-2,5-dichlorophenyl)oxydecan-1-ol (S21): Compound was isolated as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.99 (s, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 1.94 – 1.72 (m, 2H), 1.65 – 1.43 (m, 7H), 1.43 – 1.21 (m, 8H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.7, 134.1, 133.4, 122.6, 114.7, 112.7, 69.3, 62.7, 33.2, 30.0, 29.9, 29.9, 29.6, 29.1, 26.3, 26.2. GC/MS (EI) calculated for $[M]^+$ 396.03, found 396. FTIR (neat, cm^{-1}): 3446 (br), 3052 (m), 2931 (m), 1579 (w), 1457 (w), 1344 (w), 1261 (s), 1073 (m), 895 (w), 738 (s).

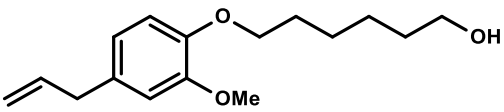


***p*-toluenesulfonic acid, 6-hydroxyhexyl ester (S22):** Compound was isolated as a clear colorless liquid. ^{1}H NMR (300 MHz, C_6D_6) δ 7.77 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 3.80 (t, *J* = 6.4 Hz, 2H), 3.34 – 3.14 (m, 2H), 1.83 (s, 3H), 1.35 – 1.21 (m, 2H), 1.21 – 1.05 (m, 2H), 1.05 – 0.82 (m, 4H), 0.51 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8,

133.2, 129.9, 127.9, 70.6, 62.6, 32.5, 28.8, 25.2, 25.1, 21.7. FTIR (neat, cm^{-1}): 3379 (br), 3064 (m), 2935 (s), 1920 (w), 1737 (w), 1597 (s), 1462 (s), 1359 (s), 1176 (s), 666 (s).



10-(*tert*-butyldimethylsilyl)oxydecan-1-ol (S23): Compound was isolated as a clear colorless liquid. **S23** is a known compound and spectral data matches reported literature values.[119]

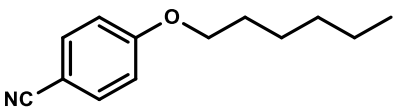


1-(6-hydroxyhexyl)oxy-2-methoxy-4-(prop-2-en-1-yl)benzene (S24): Compound was isolated as a clear yellow liquid. ^{1}H NMR (500 MHz, C_6D_6) δ 6.75 (s, 2H), 6.65 (s, 1H), 5.97 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.06 (dd, *J* = 13.7 Hz, 2H), 3.75 (t, *J* = 6.4 Hz, 2H), 3.44 (s, 3H), 3.35 – 3.29 (m, 2H), 3.29 – 3.20 (m, 2H), 1.75 – 1.55 (m, 2H), 1.43 – 1.27 (m, 4H), 1.27 – 1.13 (m, 2H), 0.59 (s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 150.5, 148.2, 138.3, 132.8, 121.0, 115.5, 114.1, 113.3, 69.2, 62.6, 55.6, 40.2, 33.1, 29.8, 26.3, 25.9. GC/MS (EI) calculated for $[M]^+$ 264.17, found 264. FTIR (neat, cm^{-1}): 3419 (br), 3053 (m), 2938 (s), 1675 (w), 1589 (m), 1513 (s), 1265 (s), 1139 (m), 1036 (m), 917 (w), 742 (s).

3.6.5 *Reduction of Primary Iodides*

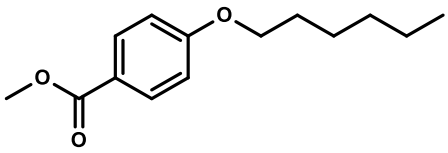
3.6.5.1 Reduction Step

The procedure used for the reduction of primary iodides was exactly the same as the procedure for the reduction of primary triflates, with the exception that the reaction was allowed to stir at 25 °C for 24 h before the workup.

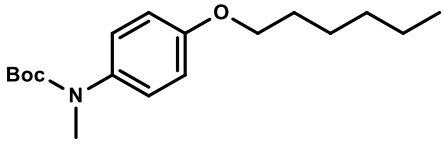


1-(4-cyanophenyl)oxyhexane (S3): Compound was isolated as a clear colorless liquid (87.1 mg, 84% yield). Spectral data

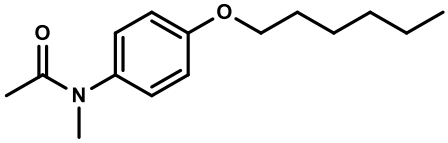
matches that reported previously for **S3**.



methyl 4-(hex-1-yl)oxybenzoate (S25): Compound was isolated as a white solid (114.3 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.17 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 3.54 (s, 3H), 3.48 (t, *J* = 6.5 Hz, 2H), 1.63 – 1.38 (m, 2H), 1.35 – 1.03 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 163.3, 132.0, 123.2, 114.4, 68.1, 51.4, 31.9, 29.4, 26.0, 23.0, 14.2. GC/MS (EI) calculated for $[M]^+$ 236.14, found 236.20. FTIR (neat, cm^{-1}): 3053 (m), 2076 (w), 1916 (w), 1715 (s), 1606 (s), 1512 (s), 1392 (m), 1252 (s), 1167 (s), 1105 (s), 1022 (s), 847 (s).

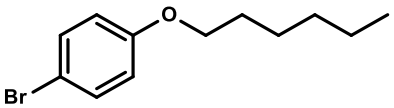


carbamic acid, *N*-(4-(hex-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester (S26): The procedure used was exactly the same as the procedure for the reduction of secondary iodides. Compound was isolated as a clear colorless liquid (130.7 mg, 85% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.11 (s, 3H), 1.68 – 1.50 (m, 2H), 1.43 (s, 9H), 1.40 – 1.12 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 157.3, 154.8, 137.5, 127.3, 114.6, 79.4, 68.1, 37.7, 31.9, 29.6, 28.4, 26.1, 23.0, 14.3. GC/MS (EI) calculated for $[M]^+$ 307.21, found 307.2. FTIR (neat, cm^{-1}): 2931 (s), 2362 (w), 2280 (m), 1700 (s), 1612 (w), 1514 (s), 1476 (m), 1366 (s), 1244 (s), 1152 (s), 1031 (m), 976 (m), 833 (m).

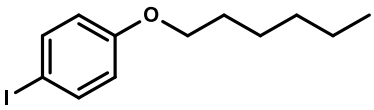


***N*-methyl-*N*-(4-(hex-1-yl)oxyphenyl)acetamide (S27):** Compound was isolated as a clear colorless liquid (124.6 mg, >98% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.63 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.0 Hz, 2H),

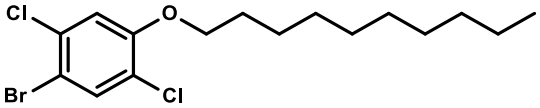
3.55 (t, J = 6.4 Hz, 2H), 3.14 (s, 3H), 1.77 (s, 3H), 1.64 – 1.49 (m, 2H), 1.42 – 1.11 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 158.5, 137.4, 128.2, 115.4, 68.4, 37.4, 31.7, 29.3, 25.8, 22.7, 22.5, 14.1. GC/MS (EI) calculated for $[M]^+$ 249.17, found 249. FTIR (neat, cm^{-1}): 3461 (w), 3298 (w), 3050 (m), 2931 (s), 2537 (w), 2305 (w), 2055 (w), 1885 (w), 1655 (s), 1512 (s), 1025 (m).



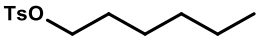
1-(4-bromophenyl)oxyhexane (S6): Compound was isolated as a clear colorless liquid (119.1 mg, 93% yield). **S6** is a known compound and spectral data matches reported literature values.[113]



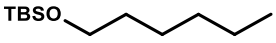
1-(4-iodophenyl)oxyhexane (S7): Compound was isolated as a clear colorless liquid (133.9 mg, 88% yield). **S7** is a known compound and spectral data matches reported literature values.[114]



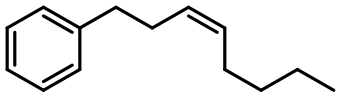
1-(4-bromo-2,5-dichlorophenyl)oxydecane (S8): Compound was isolated as a white solid (185.2 mg, 97% yield). Spectral data matches that reported previously for **S8**.



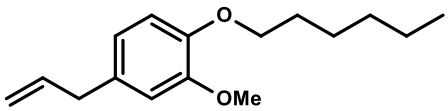
***p*-toluenesulfonic acid, hexyl ester (S10):** Compound was isolated as a clear colorless liquid (111.6 mg, 87% yield). **S10** is a known compound and spectral data matches reported literature values.[115]



1-(*tert*-butyldimethylsilyl)oxyhexane (S13): Compound was isolated as a clear colorless liquid (90.9 mg, 84% yield). **S13** is a known compound and spectral data matches reported literature values.[116]



(*Z*)-1-phenyloct-3-ene (47): Compound was isolated as a clear colorless liquid (279.36 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 2H), 7.24 – 7.11 (m, 3H), 5.56 – 5.21 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.46 – 2.23 (m, 2H), 2.10 – 1.87 (m, 2H), 1.41 – 1.15 (m, 4H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 130.8, 128.8, 128.6, 128.4, 125.9, 36.2, 32.0, 29.3, 27.1, 22.5, 14.1. GC/MS (EI) calculated for $[M]^+$ 188.16, found 188. FTIR (neat, cm^{-1}): 3063 (m), 2925 (s), 1604 (m), 1495 (m), 1453 (m), 1377 (w), 1030 (w), 697 (s), 584 (w).



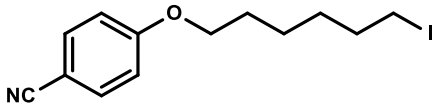
1-hexyloxy-2-methoxy-4-(prop-2-en-1-yl)benzene (S12): Compound was isolated as a clear colorless liquid (120.1 mg, 97% yield). Spectral data matches that reported previously for **S12**.

3.6.6 *Iodination Step*

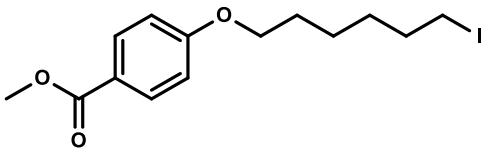
Primary alkyl iodides were obtained from the corresponding primary alcohols, which were prepared according to standard protocols. A representative procedure for the iodination step conducted on a 2.00 mmol scale is described below.

A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and iodine (660 mg, 2.60 mmol, 1.30 equiv). This was dissolved in Et_2O (4.0 mL) and stirred vigorously while triphenylphosphine (630 mg, 2.40 mmol, 1.20 equiv) was added slowly, resulting in the formation of a yellow precipitate. To this mixture was added a primary alcohol (2.00 mmol, 1.00 equiv) as a solution in CH_2Cl_2 (4.0 mL), followed by imidazole (204 mg, 3.00 mmol, 1.50 equiv). The resulting opaque red mixture was stirred at ambient temperature until disappearance of the alcohol was observed by thin-layer chromatography (between 12 and 24 h). At this point, the reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (5 mL) and transferred to

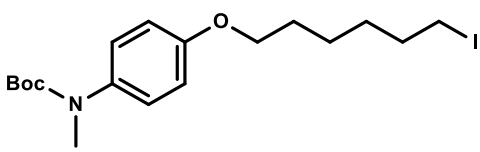
a separatory funnel, then extracted 3× with EtOAc (30 mL) and washed with brine. The organic layers were dried over $MgSO_4$, then filtered. The filtrate was concentrated and then chromatographed on a 100 g silica gel column with a solvent gradient of 5→20% EtOAc in hexanes over 8 CVs.



1-(4-cyanophenyl)oxy-6-iodohexane (24): Compound was isolated as a white solid (1.16 g, 91% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, *J* = 9.0 Hz, 2H), 6.36 (d, *J* = 9.0 Hz, 2H), 3.25 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 1.45 – 1.16 (m, 4H), 1.11 – 0.94 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 134.0, 119.3, 115.2, 103.7, 68.2, 33.3, 30.1, 28.8, 24.9, 7.0. GC/MS (EI) calculated for $[M]^+$ 329.03, found 329. FTIR (neat, cm^{-1}): 3053 (s), 2940 (s), 2225 (s), 1606 (s), 1508 (s), 1420 (w), 1264 (s), 1171 (s), 896 (m), 835 (m).

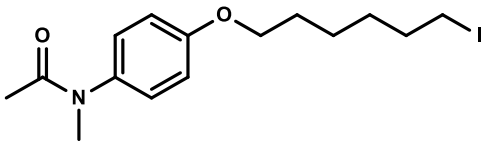


methyl 4-(6-iodohex-1-yl)oxybenzoate (25): Compound was isolated as a white solid (782 mg, 99% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 3.55 (s, 3H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 7.0 Hz, 2H), 1.49 – 1.28 (m, 4H), 1.14 – 0.93 (m, 4H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 163.2, 132.0, 123.4, 114.4, 67.8, 51.4, 33.5, 30.2, 29.0, 25.1, 6.5. GC/MS (EI) calculated for $[M]^+$ 362.04, found 362. FTIR (neat, cm^{-1}): 3053 (m), 2944 (m), 1712 (s), 1605 (s), 1511 (m), 1435 (m), 1234 (s), 1169 (m), 1114 (w).

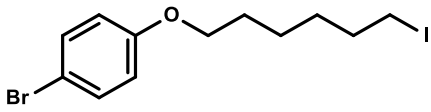


carbamic acid, *N*-(4-(6-iodohex-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester (26): Compound was isolated as a white solid (1.02 g, 79% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.13 – 6.96 (m, 2H),

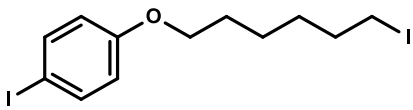
6.76 (d, *J* = 8.9 Hz, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.12 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 1.54 – 1.31 (m, 13H), 1.22 – 0.86 (m, 4H). ^{13}C NMR (75 MHz, C_6D_6) δ 157.1, 154.8, 137.4, 127.3, 114.6, 79.4, 67.8, 37.7, 33.6, 30.4, 29.3, 28.5, 25.3, 6.9. GC/MS (EI) calculated for $[M]^+$ 433.11, found 433.10. FTIR (neat, cm^{-1}): 3377 (w), 2933 (s), 2280 (m), 1698 (s), 1513 (s), 1433 (s), 1368 (s), 1244 (s), 1148 (s), 976 (m), 833 (s).



***N*-methyl-*N*-(4-(6-iodohex-1-yl)oxyphenyl)acetamide (27):** Compound was isolated as a white solid (795 mg, 96% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.75 – 6.50 (m, 4H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.15 (s, 3H), 2.69 (t, *J* = 7.0 Hz, 2H), 1.78 (s, 3H), 1.54 – 1.29 (m, 4H), 1.22 – 0.96 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 158.4, 137.5, 128.2, 115.4, 68.1, 37.4, 33.4, 30.3, 29.1, 25.1, 22.5, 7.0. GC/MS (EI) calculated for $[M]^+$ 375.07, found 375. FTIR (neat, cm^{-1}): 3471 (w), 3283 (w), 3037 (m), 2934 (s), 1652 (s), 1514 (s), 1298 (s), 1170 (s), 975 (m), 836 (s), 558 (s).

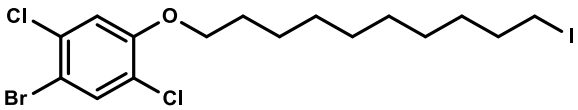


1-(4-bromophenyl)oxy-6-iodohexane (28): Compound was isolated as a clear colorless liquid (705.5 mg, 78% yield). **28** is a known compound and spectral data matches reported literature values.[87]

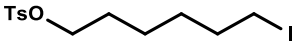


1-(4-iodophenyl)oxy-6-iodohexane (29): Compound was isolated as a clear colorless liquid (859.3 mg, 68% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 9.0 Hz, 2H), 6.40 (d, *J* = 9.0 Hz, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 1.50 – 1.23 (m, 4H), 1.16 – 0.88 (m, 4H). ^{13}C NMR (75 MHz, C_6D_6) δ 159.3, 138.5, 117.2, 83.0, 67.8, 33.6, 30.4, 29.1, 25.2, 7.1. GC/MS (EI) calculated for

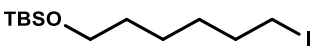
$[M]^+$ 429.93, found 429.85. FTIR (neat, cm^{-1}): 2941 (s), 1587 (m), 1486 (s), 1392 (w), 1285 (m), 1243 (s), 1168 (s), 1025 (w), 997 (w), 821 (s), 740 (s).



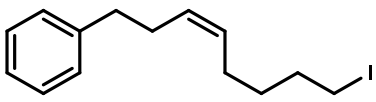
1-(4-bromo-2,5-dichlorophenyl)oxy-10-iododecane (30): Compound was isolated as a white solid (1.30 g, 98% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.60 (s, 1H), 7.04 (s, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.71 (m, 4H), 1.51 – 1.23 (m, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.7, 134.1, 133.4, 122.6, 114.7, 112.7, 69.3, 33.8, 30.7, 29.8, 29.7, 29.5, 29.1, 28.8, 26.2, 6.9. GC/MS (EI) calculated for $[M]^+$ 505.93, found 505. FTIR (neat, cm^{-1}): 3052.1 (m), 2931.4 (m), 1574.5 (w), 1463.2 (m), 1392.5 (w), 1347.3 (m), 1263.7 (s). 1124.6 (w), 1075.6 (m).



***p*-toluenesulfonic acid, hexyl ester (31):** Compound was isolated as a clear colorless liquid (315.1 mg, 34% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.77 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.84 (s, 3H), 1.32 – 1.04 (m, 4H), 0.92 – 0.70 (m, 4H). ^{13}C NMR (75 MHz, C_6D_6) δ 144.4, 134.4, 129.9, 128.1, 70.2, 33.4, 29.8, 28.7, 24.4, 21.2, 6.6. FTIR (neat, cm^{-1}): 2935 (s), 2860 (s), 2280 (m), 1599 (m), 1460 (m), 1361 (s), 1178 (s), 1098 (m), 947 (s), 907 (m), 814 (s), 664 (s).

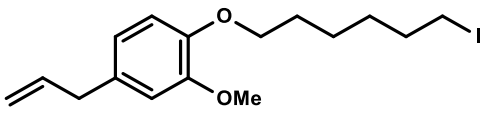


1-(*tert*-butyldimethylsilyl)oxydecane (32): Compound was isolated as a clear colorless liquid (650.3 mg, 63% yield). **32** is a known compound and spectral data matches reported literature values.[120]

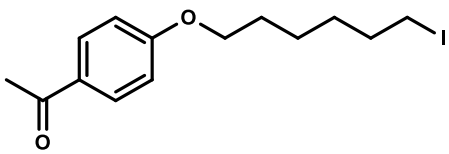


(*Z*)-8-iodo-1-phenyloct-3-ene (33): Compound was isolated as a clear colorless liquid (310.4 mg, 99% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.21 – 7.13 (m, 2H), 7.12 – 7.02 (m, 3H), 5.46 – 5.31 (m, 1H), 5.29 – 5.15 (m, 1H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.23 (dt, *J* = 7.8, 7.4 Hz, 2H), 1.72 (dt, *J* = 7.4, 7.3

Hz, 2H), 1.46 – 1.27 (m, 2H), 1.17 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 142.2, 129.9, 129.6, 128.9, 128.6, 126.2, 36.3, 33.2, 30.5, 29.6, 26.3, 6.6. GC/MS (EI) calculated for $[M]^+$ 314.05, found 314. FTIR (neat, cm^{-1}): 3007 (m), 2931 (s), 1497 (m), 1210 (m), 1169 (w).



1-(6-iodohexyl)oxy-2-methoxy-4-(prop-2-en-1-yl)benzene (34): Compound was isolated as a white solid (574.7 mg, 77% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.75 (d, *J* = 0.8 Hz, 2H), 6.65 (s, 1H), 6.11 – 5.82 (m, 1H), 5.17 – 4.95 (m, 2H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.44 (s, 3H), 3.26 (d, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 7.1 Hz, 2H), 1.63 – 1.48 (m, 2H), 1.48 – 1.32 (m, 2H), 1.28 – 1.12 (m, 2H), 1.12 – 0.94 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6) δ 150.5, 148.1, 138.3, 132.9, 120.9, 115.5, 114.1, 113.3, 68.9, 55.6, 40.2, 33.7, 30.4, 29.5, 25.3, 6.8. GC/MS (EI) calculated for $[M]^+$ 374.07, found 373.90. FTIR (neat, cm^{-1}): 3075 (w), 2935 (s), 2279 (w), 1638 (m), 1590 (s), 1513 (s), 1465 (s), 1260 (s), 1233 (s), 1140 (s), 1038 (s), 914 (m), 805 (m).

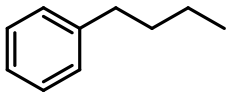


methyl 4-(6-iodohexyl)oxyphenyl ketone[121] (S28): Compound was isolated as a white solid (526.9 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.55 (s, 3H), 1.97 – 1.72 (m, 4H), 1.57 – 1.38 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 163.1, 130.7, 130.3, 114.2, 68.1, 33.4, 30.3, 29.0, 26.4, 25.1, 7.0. GC/MS (EI) calculated for $[M]^+$ 346.04, found 346.80. FTIR (neat, cm^{-1}): 3054 (s), 2941 (m), 2306 (m), 1674 (s), 1265 (s), 1060.2 (w), 592 (m).

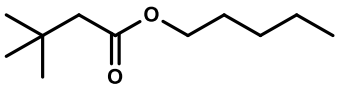
3.6.7 *Reduction of Secondary Iodides*

3.6.7.1 Reduction Step

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, IPrCuO*t*Bu (13.1 mg, 0.025 mmol, 0.05 equiv), and potassium 2-*tert*-butylphenoxide **37** (103.6 mg, 0.550 mmol, 1.10 equiv). The mixture was suspended in 1,4-dioxane (3.33 mL) and then Ph_2SiH_2 (129.9 µL, 0.700 mmol, 1.40 equiv) was added. At this point alkyl iodide (0.500 mmol, 1.00 equiv) was added as a solution in 1,4-dioxane (3.33 mL) and the mixture was stirred for 24 h at 25 °C. For compounds that were isolated, the mixture was filtered through a plug of alumina and the filter was rinsed with Et_2O (20 mL). The filtrate was concentrated and then chromatographed on a 25 g alumina column with a solvent gradient of 0→10% EtOAc in hexanes over 8 CVs.

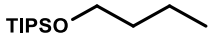


butylbenzene (S29): Compound could not be isolated due to volatility. Yield was therefore determined by GC based on the use of 1,3,5-trimethoxybenzene as an internal standard (96% yield). **S29** is a commercially available compound and retention time of the product matched that of a product standard.

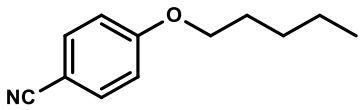


pentyl 3,3-dimethylbutyrate (S30): Compound was isolated as a clear colorless liquid, but was found to be slightly volatile under reduced pressure. Yield was therefore determined by GC based on the use of 1,3,5-trimethoxybenzene as an internal standard (99% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 4.00 (t, *J* = 6.7 Hz, 2H), 2.11 (s, 2H), 1.55 – 1.32 (m, 2H), 1.25 – 1.09 (m, 4H), 1.01 (s, 9H), 0.80 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 171.7, 64.0, 48.0, 30.6, 29.7, 28.8, 28.4, 22.6, 14.1.

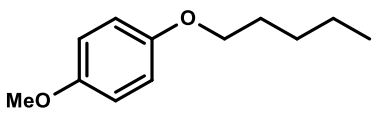
GC/MS (EI) calculated for $[M]^+$ 186.16, found 186.00. FTIR (neat, cm^{-1}): 2955 (s), 1732 (s), 1468 (s), 1325 (s), 1230 (s), 1130 (s), 1050 (s), 998 (m), 728 (w).



1-(triisopropylsilyl)oxybutane (S31): Compound was isolated as a clear colorless liquid (89.6 mg, 78% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 3.63 (t, *J* = 6.2 Hz, 2H), 1.63 – 1.46 (m, 2H), 1.46 – 1.30 (m, 2H), 1.21 – 1.01 (m, 21H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 63.4, 35.6, 19.5, 18.3, 14.2, 12.4. GC/MS (EI) calculated for $[M]^+$ 230.21, found 230.10. FTIR (neat, cm^{-1}): 2944 (s), 2727 (w), 2281 (m), 1464 (s), 1383 (m), 1248 (m), 1104 (s), 996 (m), 884 (s), 773 (m), 721 (m), 677 (s).

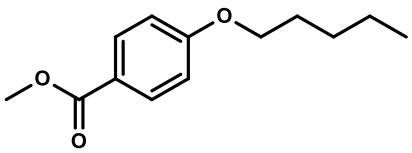


1-(4-cyanophenyl)oxypentane (S32): Compound was isolated as a clear colorless liquid (75.0 mg, 79% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, *J* = 8.9 Hz, 2H), 6.36 (d, *J* = 8.9 Hz, 2H), 3.31 (t, *J* = 6.5 Hz, 2H), 1.57 – 1.28 (m, 2H), 1.28 – 1.03 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 162.3, 133.9, 119.2, 115.2, 104.5, 68.2, 28.9, 28.3, 22.7, 14.2. GC/MS (EI) calculated for $[M]^+$ 189.12, found 188.70. FTIR (neat, cm^{-1}): 2957 (s), 2873 (s), 2281 (s), 2226 (s), 1607 (s), 1574 (m), 1509 (s), 1469 (s), 1393 (w), 1330 (m), 1302 (s), 1259 (s), 1174 (s), 1113 (w), 1050 (m), 1014 (m), 835 (s), 704 (w), 680 (w).

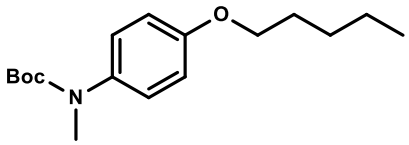


1-(4-methoxyphenyl)oxypentane (S33): Compound was isolated as a clear colorless liquid (84.3 mg, 87% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.95 – 6.68 (m, 4H), 3.65 (t, *J* = 6.5 Hz, 2H), 3.35 (s, 3H), 1.74 – 1.50 (m, 2H), 1.44 – 1.08 (m, 4H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 154.4, 154.0, 115.7, 115.0, 68.4, 55.2, 29.5, 28.6, 22.8, 14.2. GC/MS (EI) calculated for $[M]^+$ 194.13, found 194.10. FTIR (neat, cm^{-1}): 3046 (m), 2934 (s), 2280 (m), 2061 (w), 1849 (w), 1739 (w), 1592 (m), 1509

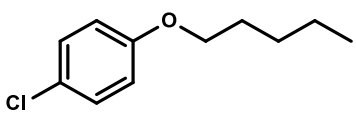
(s), 1467 (s), 1390 (m), 1288 (m), 1232 (s), 1181 (s), 1107 (m), 1041 (s), 911 (w), 824 (s), 789 (m), 742 (m).



methyl 4-(pent-1-yl)oxybenzoate (S34): Compound was isolated as a clear colorless liquid (97.8 mg, 88% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.17 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 3.55 (s, 3H), 3.46 (t, *J* = 6.5 Hz, 2H), 1.60 – 1.42 (m, 2H), 1.29 – 1.11 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 166.5, 163.3, 132.0, 123.1, 114.4, 68.1, 51.4, 29.1, 28.4, 22.7, 14.2. GC/MS (EI) calculated for $[M]^+$ 222.13, found 222.05. FTIR (neat, cm^{-1}): 2954 (s), 2872 (s), 2280 (s), 1918 (w), 1720 (s), 1607 (s), 1511 (s), 1435 (s), 1392 (m), 1255 (s), 1169 (s), 1105 (s), 1012 (s), 911 (w), 847 (s), 813 (m), 771 (s), 697 (m), 648 (m).

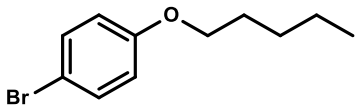


carbamic acid, *N*-(4-(pent-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester (S35): Compound was isolated as a clear colorless liquid (94.4 mg, 64% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, *J* = 7.7 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.11 (s, 3H), 1.67 – 1.48 (m, 2H), 1.43 (s, 9H), 1.32 – 1.15 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 157.3, 154.9, 137.5, 127.3, 114.6, 79.4, 68.0, 37.7, 29.3, 28.5, 28.4, 22.8, 14.2. GC/MS (EI) calculated for $[M]^+$ 293.20, found 293.15. FTIR (neat, cm^{-1}): 2931 (s), 2280 (m), 1875 (w), 1702 (s), 1366 (s), 1286 (s), 1244 (s), 1151 (s), 1029 (m), 976 (m), 928 (w), 869 (m), 833 (s), 769 (s), 646 (m).



1-(4-chlorophenyl)oxypentane (S36): Compound was isolated as a clear colorless liquid (89.7 mg, 90% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.08 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* = 9.0 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 1.64 – 1.44

(m, 2H), 1.32 – 1.08 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 158.3, 129.6, 125.6, 116.0, 68.1, 29.2, 28.4, 22.8, 14.2. GC/MS (EI) calculated for $[M]^+$ 198.08, found 198.05. FTIR (neat, cm^{-1}): 2934 (s), 2280 (m), 1870 (w), 1741 (w), 1598 (s), 1493 (s), 1391 (m), 1287 (s), 1244 (s), 1170 (s), 1093 (s), 1006 (m), 910 (w), 823 (s), 666 (s).

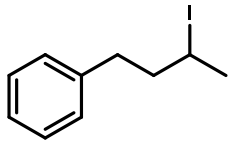


1-(4-bromophenyl)oxypentane (S37): Compound was isolated as a clear colorless liquid (102.8 mg, 85% yield). **S37** is a known compound and spectral data matches reported literature values.[122,123]

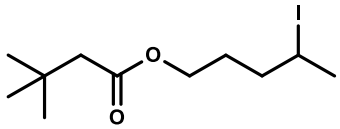
3.6.7.2 Iodination Step

Secondary alkyl iodides were obtained from the corresponding secondary alcohols, which were prepared according to standard protocols. A representative procedure for the iodination step conducted on a 2.00 mmol scale is described below.

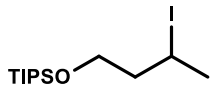
A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and iodine (1.02 g, 4.00 mmol, 2.00 equiv). This was dissolved in C_6H_6 (3.0 mL) and stirred vigorously while triphenylphosphine (1.05 g, 4.00 mmol, 2.00 equiv) was added slowly, resulting in the formation of a yellow precipitate. To this mixture was added a secondary alcohol (2.00 mmol, 1.00 equiv) as a solution in C_6H_6 (3.0 mL), followed by imidazole (204 mg, 3.00 mmol, 1.50 equiv). The resulting opaque red mixture was refluxed until disappearance of the alcohol was observed by thin-layer chromatography (between 24 and 36 h). At this point, the reaction mixture was cooled to ambient temperature and diluted with hexanes (50 mL) while stirring. The mixture was then filtered through celite to facilitate the removal of an orange, waxy precipitate. The filtrate was concentrated and then chromatographed on a 100 g silica gel column with a solvent gradient of 5→20% EtOAc in hexanes over 8 CVs.



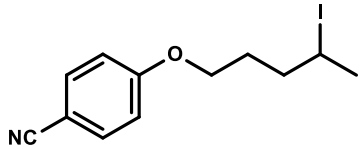
3-iodobutylbenzene (38): Compound was isolated as a clear colorless liquid (3.89 g, 100% yield). **38** is a known compound and spectral data matches reported literature values.[87]



4-iodopentyl 3,3-dimethylbutyrate (39): Compound was isolated as a clear colorless liquid (769 mg, 89% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 3.85 (t, *J* = 6.3 Hz, 2H), 3.74 – 3.57 (m, 1H), 2.07 (s, 2H), 1.70 – 1.46 (m, 5H), 1.45 – 1.32 (m, 1H), 1.32 – 1.15 (m, 1H), 0.98 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 171.5, 62.9, 47.8, 39.5, 30.6, 29.8, 29.4, 29.0, 28.9. ESI MS calculated for $[M + Na]^+$ 335.05, found 335.20. FTIR (neat, cm^{-1}): 2959 (s), 2361 (w), 1736 (s), 1466 (s), 1367 (s), 1323 (s), 1228 (s), 1130 (s), 1047 (m), 1003 (m), 868 (w), 752 (w).

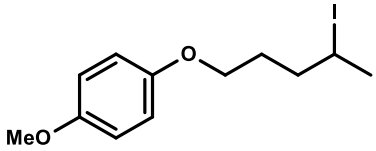


(triisopropylsilyl)oxybutane(40): Compound was isolated as a clear colorless liquid (1.82 g, 73% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 4.33 – 4.18 (m, 1H), 3.70 – 3.59 (m, 2H), 1.89 – 1.72 (m, 1H), 1.67 (d, *J* = 6.9 Hz, 3H), 1.61 – 1.48 (m, 1H), 1.18 – 0.91 (m, 21H). ^{13}C NMR (75 MHz, C_6D_6) δ 63.4, 45.9, 29.3, 26.4, 18.4, 12.3. GC/MS (EI) calculated for $[M]^+$ 356.10, found 356.10. FTIR (neat, cm^{-1}): 2950 (s), 2727 (w), 2361 (w), 1857 (w), 1463 (s), 1379 (s), 1301 (w), 1238 (m), 1168 (s), 1114 (s), 995 (s), 883 (s), 826 (w), 775 (w), 740 (s), 680 (s).

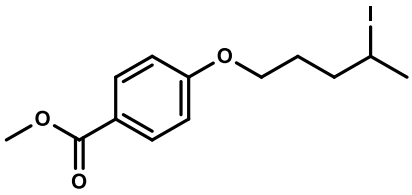


4-iodo-1-(4-cyanophenyl)oxypentane (41): Compound was isolated as a clear colorless liquid (665.6 mg, 55% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.02 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 8.7 Hz, 2H), 3.77 – 3.56 (m, 1H), 3.16 (t, *J* = 5.3 Hz, 2H), 1.71 – 1.16 (m, 7H). ^{13}C NMR (75 MHz,

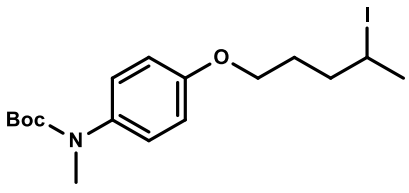
C_6D_6) δ 162.1, 133.9, 119.2, 115.2, 104.6, 67.1, 39.3, 29.5, 29.4, 29.0. GC/MS (EI) calculated for $[M]^+$ 315.01, found 314.80. FTIR (neat, cm^{-1}): 2952 (m), 2280 (s), 2225 (s), 1606 (s), 1509 (s), 1470 (m), 1392 (w), 1301 (s), 1259 (s), 1172 (s), 1020 (m), 934 (w), 835 (s), 812 (s).



4-iodo-1-(4-methoxyphenyl)oxypentane (42): Compound was isolated as a clear colorless liquid (922.3 mg, 68% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 6.78 (s, 4H), 3.90 – 3.62 (m, 1H), 3.62 – 3.43 (m, 2H), 3.35 (s, 3H), 1.84 – 1.38 (m, 7H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.5, 153.6, 115.7, 115.0, 67.3, 55.3, 39.7, 30.1, 29.8, 29.0. GC/MS (EI) calculated for $[M]^+$ 320.03, found 320.00. FTIR (neat, cm^{-1}): 3044 (m), 2949 (s), 2336 (w), 2061 (w), 1851 (w), 1592 (m), 1505 (s), 1442 (s), 1390 (m), 1289 (s), 1227 (s), 1131 (s), 1042 (s), 980 (m), 936 (m), 824 (s), 771 (m), 727 (s).

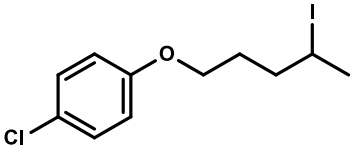


methyl 4-(4-iodopent-1-yl)oxybenzoate (43): Compound was isolated as a clear colorless liquid (892.4 mg, 57% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.17 (d, *J* = 9.0 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.81 – 3.62 (m, 1H), 3.55 (s, 3H), 3.40 – 3.23 (m, 2H), 1.71 – 1.26 (m, 7H). ^{13}C NMR (75 MHz, C_6D_6) δ 166.4, 163.0, 131.9, 123.3, 114.4, 67.0, 51.5, 39.4, 29.7, 29.5, 29.0. GC/MS (EI) calculated for $[M]^+$ 348.12, found 348.00. FTIR (neat, cm^{-1}): 3077 (m), 2950 (s), 2080 (w), 1919 (w), 1716 (s), 1606 (s), 1511 (s), 1435 (s), 1391 (m), 1255 (s), 1169 (s), 1105 (s), 1023 (s), 935 (m), 847 (s), 771 (s), 737 (s), 697 (s).

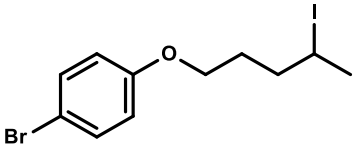


carbamic acid, *N*-(4-(4-iodopent-1-yl)oxyphenyl)-*N*-methyl, 1,1-dimethylethyl ester (44): Compound was isolated as a

clear colorless liquid (826.5 mg, 67% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.03 (d, *J* = 7.7 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 3.84 – 3.63 (m, 1H), 3.51 – 3.37 (m, 2H), 3.11 (s, 3H), 1.75 – 1.59 (m, 2H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.54 – 1.45 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6) δ 156.9, 154.7, 137.5, 127.2, 114.6, 79.4, 67.0, 39.6, 37.7, 29.9, 29.1, 28.5. GC/MS (EI) calculated for $[M]^+$ 419.10, found 419.10. FTIR (neat, cm^{-1}): 3378 (w), 2976 (s), 2280 (m), 1876 (w), 1698 (s), 1610 (m), 1514 (s), 1434 (s), 1365 (s), 1241 (s), 1153 (s), 1036 (m), 977 (s), 935 (m), 833 (s), 769 (s), 647 (m).



4-iodo-1-(4-chlorophenyl)oxypentane (45): Compound was isolated as a clear colorless liquid (674.4 mg, 78% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.07 (d, *J* = 9.1 Hz, 2H), 6.48 (d, *J* = 9.0 Hz, 2H), 3.80 – 3.60 (m, 1H), 3.37 – 3.18 (m, 2H), 1.74 – 1.25 (m, 7H). ^{13}C NMR (75 MHz, C_6D_6) δ 157.9, 129.6, 125.7, 116.0, 67.0, 39.4, 29.8, 29.6, 29.0. GC/MS (EI) calculated for $[M]^+$ 323.98, found 323.90. FTIR (neat, cm^{-1}): 3063 (w), 2948 (s), 2870 (s), 2279 (m), 1871 (w), 1742 (w), 1597 (s), 1492 (s), 1492 (s), 1390 (s), 1286 (s), 1244 (s), 1169 (s), 1093 (s), 1029 (s), 935 (m), 824 (s), 746 (m), 667 (s).



4-iodo-1-(4-bromophenyl)oxypentane (46): Compound was isolated as a clear colorless liquid (743.2 mg, 75% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.21 (d, *J* = 9.0 Hz, 2H), 6.42 (d, *J* = 9.0 Hz, 2H), 3.84 – 3.56 (m, 1H), 3.38 – 3.16 (m, 2H), 1.73 – 1.27 (m, 7H). ^{13}C NMR (75 MHz, C_6D_6) δ 158.4, 132.5, 116.5, 113.1, 67.0, 39.4, 29.7, 29.5, 29.0. GC/MS (EI) calculated for $[M]^+$ 367.93, found 369.90. FTIR (neat, cm^{-1}): 3070 (w), 2957 (s), 2279 (w), 1872 (w), 1591 (s), 1487 (s),

1389 (m), 1287 (s), 1236 (s), 1171 (s), 1131 (m), 1072 (s), 1027 (s), 927 (m), 820 (s), 748 (m), 696 (m), 643 (s).

3.6.8 *Mechanism Experiments*

3.6.8.1 *Radical Reductive Cyclization Experiments*

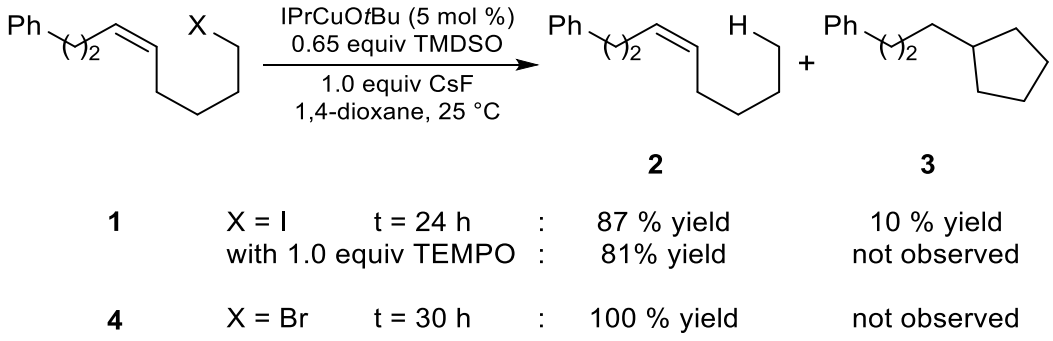


Figure 3.2. Copper-catalyzed reduction of alkenyl halides

3.6.8.2 *Reduction of Alkenyl Iodide*

In a nitrogen-filled glovebox, IPrCuO*t*Bu (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335 µL). At this point, TMDSO (11.6 µL, 0.065 mmol, 0.65 equiv), 1,4-dioxane (335 µL), and alkenyl iodide **1** (31.4 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C for 24 h. Yield of reduction product **2** was 87%, and yield of cyclization product **3** was 10% based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard.

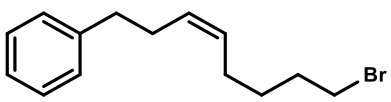
The same reaction was carried out only with the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO; 16.5 mg, 0.100 mmol, 1.00 equiv). After 24 h, yield of reduction product **2** was 81%, and cyclization product **3** was not detected.

3.6.8.3 *Reduction of Alkenyl Bromide*

In a nitrogen-filled glovebox, IPrCuO*t*Bu (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335 µL). At this point, TMDSO (11.6 µL, 0.065 mmol, 0.65 equiv), 1,4-dioxane (335 µL), and alkenyl bromide **4** (26.7 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C for 24 h. Yield of reduction product **3** was quantitative, and cyclization product **3** was not observed based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard.

3.6.8.4 *Synthesis of Alkenyl Bromide*

Alkenyl bromide **4** was obtained from the corresponding alkenyl alcohol, 8-phenyloct-5-en-1-ol **S38**, which was prepared according to standard protocols.



A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and **S38** (303 mg, 1.48 mmol, 1.00 equiv). This was dissolved in THF (3.0 mL) and then CBr_4 (615 mg, 1.85 mmol, 1.25 equiv) and triphenylphosphine (486 mg, 1.85 mmol, 1.25 equiv) was added slowly, resulting in the formation of a white precipitate. This mixture was stirred at ambient temperature until disappearance of the alcohol was observed by thin-layer chromatography (12 h). At this point, the reaction mixture concentrated under vacuum and then diluted with hexanes (20 mL) and stirred vigorously for 1 h. The mixture was then filtered through celite to facilitate the removal of a white, crystalline precipitate (Ph_3PO). The filtrate was concentrated and then chromatographed on a 50 g silica gel column with a solvent gradient of 0→5% EtOAc in hexanes over 5 CVs. Compound **4** was isolated as a clear colorless liquid (83.2 mg, 21% yield).

^{1}H NMR (300 MHz, C_6D_6) δ 7.22 – 7.11 (m, 2H), 7.11 – 7.02 (m, 3H), 5.46 – 5.31 (m, 1H), 5.31 – 5.14 (m, 1H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.23 (dt, *J* = 7.4, 7.2 Hz, 2H), 1.73 (dt, *J* = 7.4, 7.3 Hz, 2H), 1.50 – 1.30 (m, 2H), 1.22 – 0.99 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 142.2, 129.9, 129.6, 128.9, 128.6, 126.2, 36.3, 33.5, 32.5, 29.6, 28.2, 26.5. GC/MS (EI) calculated for $[M]^+$ 266.07, found 266. FTIR (neat, cm^{-1}): 3052.0 (m), 2934.9 (s), 1602.1 (m), 1495.0 (m), 1453.1 (m), 1263.3 (s), 1029.9 (w), 896.3 (m).

3.6.9 *Radical Trap Experiment*

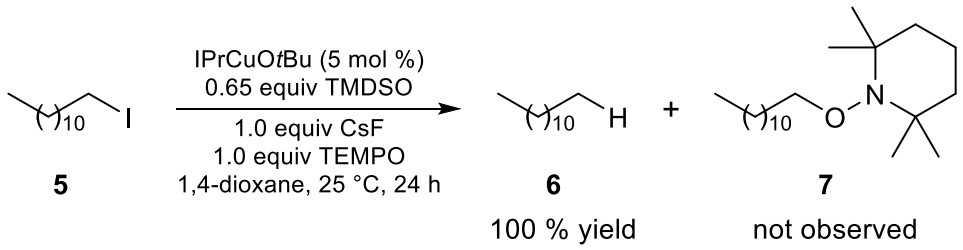
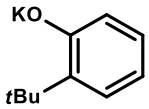


Figure 3.3. Copper-catalyzed Reduction of Alkenyl Iodide in the Presence of TEMPO

Dodecyl iodide **5** was prepared according to an existing procedure[124] and used in the radical trap experiment as described below.

In a nitrogen-filled glovebox, IPrCuO*t*Bu (2.6 mg, 0.005 mmol, 0.05 equiv) and CsF (15.2 mg, 0.100 mmol, 1.00 equiv) were combined in a 1-dram vial then suspended in 1,4-dioxane (335 µL). At this point, TMDSO (11.6 µL, 0.065 mmol, 0.65 equiv), 1,4-dioxane (335 µL), dodecyl iodide **5** (29.6 mg, 0.100 mmol, 1.00 equiv), and TEMPO (16.5 mg, 0.100 mmol, 1.00 equiv) were added to the vial. The reaction mixture was stirred at 25 °C for 24 h. Yield of reduction product **6** was quantitative based on GC analysis with reference to 1,3,5-trimethoxybenzene internal standard. No TEMPO-alkyl adduct **7** was detected by ^{1}H NMR of the crude reaction mixture.

3.6.10 *Preparation of Potassium 2-Tert-butylphenoxide* **37**



A flame-dried air-free flask was placed under an atmosphere of nitrogen and charged with a stir bar and potassium bis(trimethylsilyl)amide (KHMDS; 4.90 g, 32.7 mmol, 1.00 equiv). This was suspended in pentane (65 mL), cooled to 0 °C and stirred vigorously while 2-*tert*-butylphenol (6.50 g, 32.7 mmol, 1.00 equiv) was slowly added. The mixture was allowed to warm to ambient temperature and stir for 20 min, then the flask was transferred to a nitrogen-filled glovebox and filtered on a frit. The solid was collected, re-suspended in Et_2O (60 mL), then stirred vigorously for 20 min. At this time, pentane (120 mL) was added resulting in the precipitation of a light pink solid. The solid was filtered off and the ether wash/filtration steps were repeated once more. The pink solid was then collected and placed under vacuum for several hours to facilitate the removal of residual solvent. Compound **37** was isolated as a light pink solid (4.0 g, 64% yield). ^{1}H NMR (300 MHz, CD_3CN) δ 6.85 (dd, J = 7.4, 2.1 Hz, 1H), 6.74 – 6.62 (m, 1H), 6.08 (dd, J = 8.0, 1.4 Hz, 1H), 5.96 – 5.82 (m, 1H), 1.36 (s, 9H).

Chapter 4. SYNTHESIS OF HINDERED ANILINES: COPPER-CATALYZED ELECTROPHILIC AMINATION OF ARYL BORONIC ESTERS[125]

4.1 INTRODUCTION

Aromatic and heteroaromatic amines have attracted considerable attention in the last two decades as a result of the numerous applications in the pharmaceutical industry and medicinal chemistry.[126,127] The development of several transition metal-catalyzed couplings of aryl halides with amines[128,129] has provided practical methods for the preparation of a variety of anilines.[130-135] Despite the progress made, there are still no practical methods for making sterically congested anilines. [136] This is illustrated by Baran et al in the total synthesis of (+)-psychotetramine (Figure 4.1).[137]

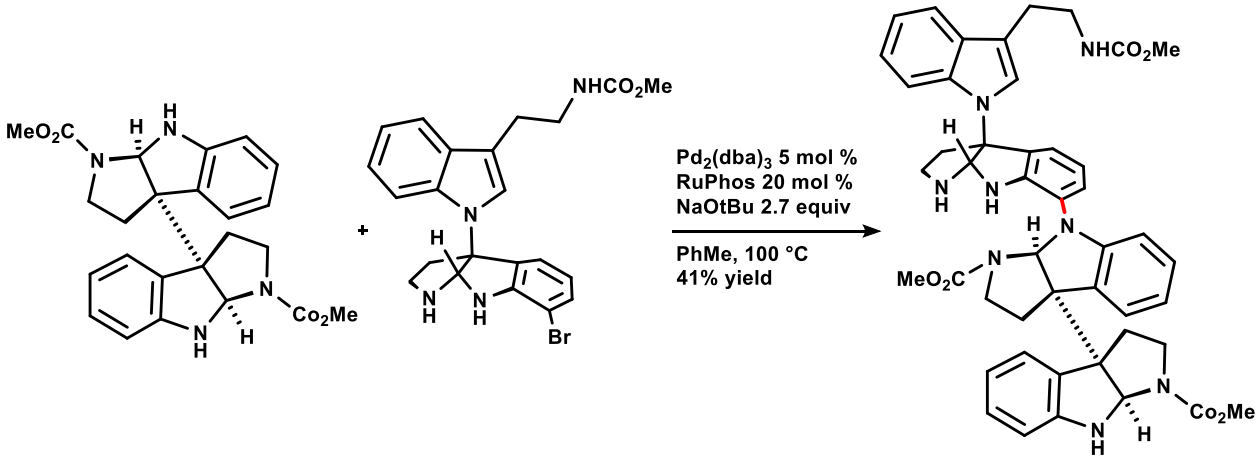
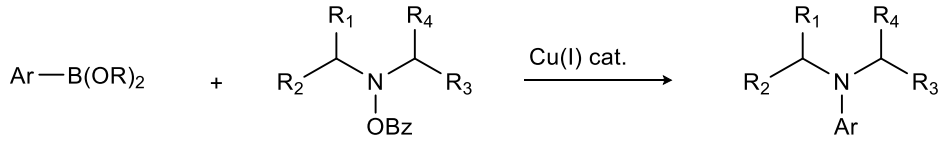


Figure 4.1. Towards the synthesis of (+)-psychotetramine and the Buchwald-Hartwig amination reaction

Current methods for synthesizing hindered anilines involves the formation of highly reactive intermediates, such as benzynes,[138-141] or organometallic reagents.[142-146] The most general of these reactions was reported by Knochel, and involves oxidative coupling of organometallic reagents with hindered lithium amides in the presence of stoichiometric amounts

of copper.[145] In a rare instance of *catalytic* synthesis of hindered anilines, Johnson reported three examples of electrophilic amination of aryl zinc reagents with hindered electrophiles.[147-150] However, the yields were significantly lower than with less hindered substrates. A common feature of the procedures reported by Johnson and Knochel is that a significant excess (≥ 2 equivalents) of one of the coupling components is necessary. Furthermore, both methods require stoichiometric amounts of reactive organometallic reagents, *i.e.,* grignard and organo lithium reagents.

Aryl boronic acids and their derivatives offer significant advantages over the organometallic reagents currently used in the synthesis of hindered anilines. Unlike most organometallic reagents, aryl boronic acids and esters are stable, readily available, and compatible with a wide range of functional groups. However, previous attempts by Johnson and others[151] to develop electrophilic amination of these compounds have been unsuccessful. A related oxidiative amination of organoboron reagents developed by the group of Lam,[152] Chan,[153] Evans,[154] and others[155,156] is highly sensitive to the steric properties of amine substrates and cannot be used for the synthesis of hindered anilines.



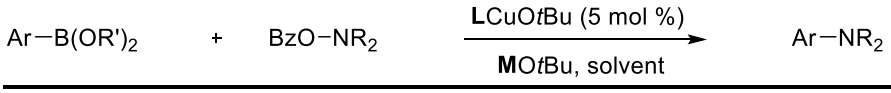
(1)

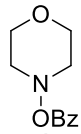
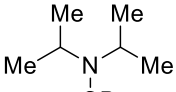
In this communication, we describe a catalytic method for the synthesis of hindered anilines from readily available aryl and heteroaryl boronic esters [Eq. (1); Bz=benzoyl]. The method allows for the preparation of even the most hindered anilines under mild reaction conditions and in the presence of a wide variety of functional groups, including aryl iodides and bromides.

4.2 COPPER-CATALYZED ELECTROPHILIC AMINATION OF ARYL BORONIC ESTERS

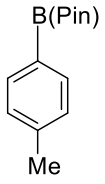
4.2.1 *Reaction Development*

Table 4.10. Reaction development

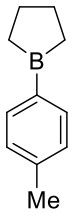


Entry[a]	BzO−NR$_2$	Ar−B(OR')$_2$	Ligand	M	Solvent	% Yield[b]
1		**3**	IMes	Na	THF	<5
2		**4**	IMes	Na	THF	16
3		**5**	IMes	Na	THF	72
4[c]		**5**	Xantphos	Na	1,4-dioxane	99
5	**1**	**6**	Xantphos	Na	1,4-dioxane	8
6		**6**	Xantphos	Li	1,4-dioxane	56
7		**6**	Xantphos	Li	toluene	74
8[d]		**6**	Xantphos	Li	toluene	81
9[e]	**2**	**6**	Xantphos	Li	isooctane	94

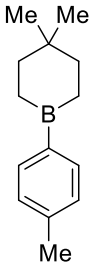
[a] ArB(OR')$_2$ (1.2 equiv), BzONR$_2$ (1.0 equiv), MO*t*Bu (1.0 equiv), 25 °C, 12h. [b] Determined by GC analysis. [c] Catalyst was formed in situ from Xantphos and (CuOtBu)$_4$ [d] Reaction temperature was 45 °C [e] 60 °C, 1.0 M, toluene was used to prepare the catalyst.



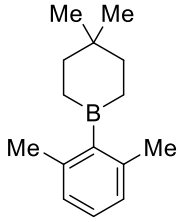
3



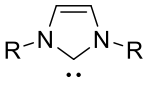
4



5

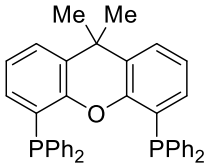


6



IMes

R = 2,4,6-trimethylphenyl



XantPhos

In an initial experiment, we explored the reactivity of aryl boronic ester **3** in a reaction with 4-benzoyloxymorpholine **1**. Based on our experience with copper-catalyzed transformations of aryl boronic esters,[157] we used IMesCuO*t*-Bu as a catalyst in the presence of sodium *t*-

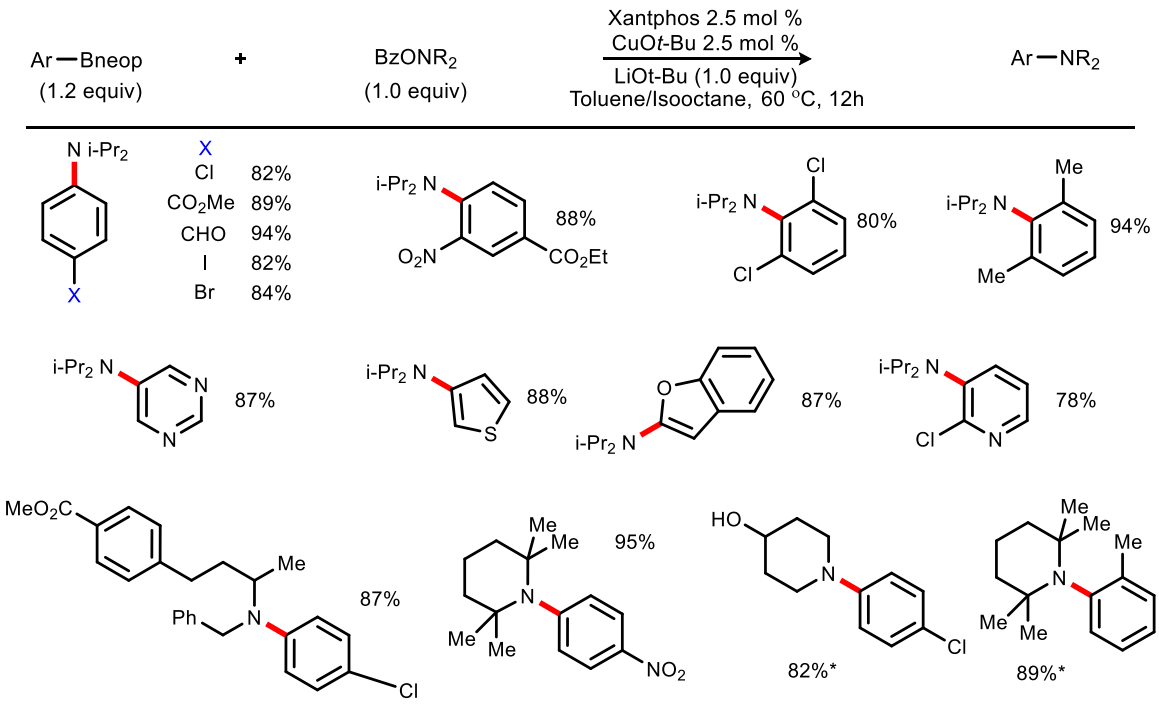
butoxide. Upon full conversion of the electrophile, the desired aniline was obtained in less than 5% yield (Table 4.10, entry 1).

We speculated that the low yield of the aniline was a consequence of slow transmetallation of the aryl boronic ester. Indeed, reactions with ethylene glycol **4** and neopentyl glycol **5** esters, which are known to undergo transmetallation faster than the corresponding pinacol esters,[158-160] provided the aniline product in 16 and 72% yield, respectively (Table 4.10, entry 2 and 3). In a catalyst screen performed with boronic ester **5** and electrophile **1**, we identified XantPhosCuO*t*Bu, a complex prepared in situ from XantPhos ligand and $(CuO\textit{t}Bu)_4$[161], as the best catalyst. In a reaction performed in 1,4-dioxane, it provided the desired aniline in 99% yield (Table 4.10, entry 4). Unfortunately, a reaction with more hindered boronic ester **6** resulted in the formation of the desired aniline in only 8% yield, together with 83% yield of *t*-butyl benzoate (Table 4.10, entry 5).

In fact, a control experiment revealed that *t*-butylbenzoate forms in nearly quantitative yield in a reaction of 4-benzoyloxymorpholine **1** with sodium *t*-butoxide after only 10 minutes at room temperature. However, we found that this background reaction of the electrophile can be suppressed if less reactive lithium *t*-butoxide is used in a non-coordinating solvent. Consistent with these findings, a reaction with boronic ester **6** and electrophile **1** performed in toluene in the presence of lithium *t*-butoxide afforded the desired aniline in 74% yield (Table 4.10, entry 7). The same conditions could also be used to prepare highly hindered *N*,*N*-diisopropyl-2,6-dimethyl aniline from boronic ester **6** and electrophile **2** (Table 4.10, entry 8). Finally, the best result (94% yield) was obtained when this reaction was performed in a concentrated isooctane solution using a catalyst prepared from Xantphos and $(CuO\textit{t}Bu)_4$ in toluene (Table 4.10, entry 9).

4.2.2 *Reaction Scope*

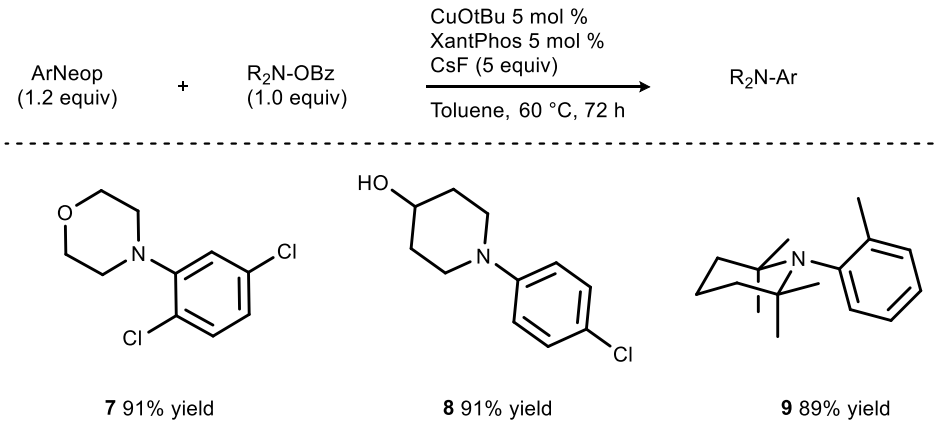
Table 4.11. Reaction scope



The optimized reaction conditions proved to be remarkably general. We found that reactions with diisopropylamine-derived electrophile **2** could be performed in the presence of a number of functional groups, including formyl, carbomethoxy, nitro, methoxy, trifluormethyl, iodo, and bromo. As the synthesis of anilines from hindered boronic esters are well tolerated in the reaction. In addition, a variety of heteroaromatic boronic esters, including 2-chloropyridine-3-boronic ester, can also be used as nucleophiles (Table 4.11). In most reactions, 2.5 mol% of the catalyst was sufficient to accomplish the full conversion in less than 12 h, while the sterically hindered boronic esters required a higher catalyst loading (5 mol%). To establish the full scope of the amination reaction, we explored the reactivity of various electrophiles. *O*-benzoyl hydroxylamines derived from common cyclic amines, such as pyrrole, piperidine, morpholine, and piperazine can be used in the reaction. Electrophiles bearing functional groups, such as nitro,

carbomethoxy, bromo, and chloro, are also viable substrates and provide the aniline products in excellent yields. The steric properties of an electrophile have no significant effect on the outcome of the reaction. Both 2-methylpyrrole and decahydroquinoline-derived electrophiles provide the expected anilines in high yield. Even a highly hindered electrophile derived from 2,2,6,6-tetramethylpiperidine could be coupled with nitrophenyl boronic ester in 87% yield, while the 2-methylphenyl boronic ester afforded the desired product in 60% yield.

Table 4.12. Reaction scope

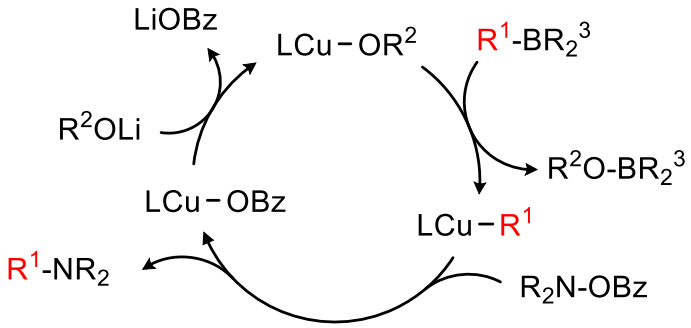


7 91% yield **8** 91% yield **9** 89% yield

An extension of the substrate scope could be achieved if lithium *t*-butoxide is replaced with CsF. This change was particularly beneficial in coupling hindered boronic esters with base-sensitive electrophiles (Table 4.12). Furthermore, CsF allowed the reaction to be performed in the presence of acidic functional groups, as demonstrated by the reaction of 4-hydroxypiperidine-derived electrophile to produce **8**. Finally, the extremely hindered aniline **9** could be prepared in 89% yield using this procedure. While the transformation requires 72 h and 5 equivalents of CsF, the result is still remarkable considering that an extremely hindered aniline is prepared in excellent yield and under relatively mild reaction conditions.

4.2.3 *Mechanistic Studies*

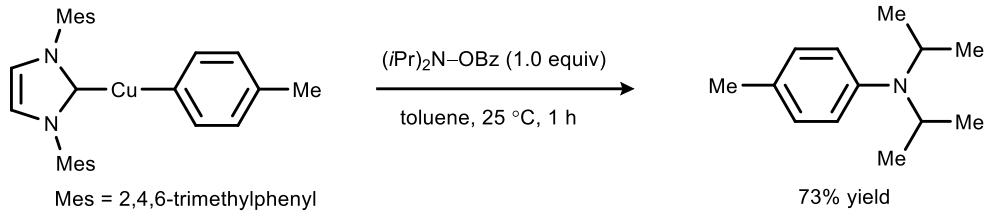
Based on the known copper-catalyzed reactions of aryl boronic esters (see references 157-159) and the mechanism of copper-catalyzed electrophilic amination reactions,[8] we propose that the amination reaction proceeds according to the mechanism shown in Scheme 4.1. The reaction involves transmetallation from boron to copper, followed by electrophilic amination of the aryl copper intermediate. Finally, the reactive copper alkoxide is regenerated in the reaction with lithium alkoxide.



Scheme 4.1. Proposed catalytic cycle

With the transmetallation step of aryl boronic ester and copper having precedence in the literature,[162] we instead focused our attention on the electrophilic amination of the putative aryl copper intermediate (Scheme 4.2). A reaction of electrophile **2** with IMes-supported copper aryl complex (**37**)[29] resulted in a 73% yield of aniline **38**, in less than 30 minutes, at room temperature. In addition, when used as a catalyst, **37** provided results indistinguishable from those obtained with IMesCuO*t*Bu catalyst.[19]

[29] IMesCuOtBu provides results comparable to those obtained with Xantphos-based catalyst (XantophosCuOtBu) with less hindered boronic esters. See Supporting information for further information.



Scheme 4.2. Electrophilic amination of proposed aryl copper intermediate

4.2.4 *Conclusion*

In conclusion, we have developed a mild copper-catalyzed reaction for the synthesis of sterically hindered anilines from aryl and heteroaryl boronic esters. This method allowed us to prepare some of the most hindered anilines ever made. Furthermore, the new method is compatible with a wide range of functional groups, including chloro, bromo, iodo, carbomethoxy, nitro, hydroxyl, formyl, and methoxy. Overall, an exceptionally broad scope and reliability of this new procedure, together with the availability of a wide variety of aryl boronic esters, makes it a significant breakthrough in the synthesis of hindered anilines.

4.3 EXPERIMENTAL

4.3.1 *General*

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Ion Exchange Chromatography was performed using analytical grade cation exchange resin from sulfonic acid functionalized styrene (Bio-Rad Laboratories, 200-400 mesh, 5.2 meq/g). General method for purification by ion exchange chromatography is as follows: crude product was adsorbed on the cation exchange resin (200 mg resin/mmol product) using MeOH, and the resin was subsequently washed with

10% dichloromethane in MeOH over 4 CV, then 10% Et_3N in MeOH over 4 CV to elute the product. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm, CD_3CN: δ 1.3 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 µm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

Materials

THF, CH_2Cl_2, diethyl ether, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., or

STREM Chemicals, Inc., and were used as received. Aryl boronic esters were prepared according to a literature procedure.[30]

4.3.2 *Reaction Optimization*

4.3.2.1 General

All optimization reactions were performed in a glove box. A 1-dram vial was charged with a stir bar. To the vial was added alkoxide additive (1.00 equiv), aryl boronic ester (1.20 equiv), copper catalyst (0.05 equiv), *n*-dodecane (0.10 equiv), and solvent (0.1 M). To the resulting mixture was added *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv). The reaction vial was capped and stirred for 24 h with heating at the indicated temperature. Product yield was determined by GC comparison against *n*-dodecane as an internal standard.

4.3.2.2 Optimization of the aryl boronic ester backbone (Entries 1 – 3, Table 4.13)

Reactions were conducted according to the General Procedure using IMesCu-O*t*Bu (0.003 mmol, 1.1 mg), Na-O*t*Bu (0.050 mmol, 4.8 mg), and either 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane (0.060 mmol, 13.8 mg), 2-(*p*-tolyl)-1,3,2-dioxaborolane (0.060 mmol, 9.7 mg), or 5,5-dimethyl-2-(*p*-tolyl)-1,3,2-dioxaborinane (0.060 mmol, 12.2 mg) with THF as solvent (0.5 mL). To the resulting solution was added 4-benzoyloxymorpholine (0.050 mmol, 10.4 mg). Reactions were heated at 25 °C with stirring for 24 h.

4.3.2.3 Optimization of the catalyst (Entries 4 – 12, Table 4.13)

Reactions were conducted according to the General Procedure using the indicated copper catalysts (0.003 mmol), Na-O*t*Bu (0.050 mmol, 4.8 mg), and dimethyl-2-(*p*-tolyl)-1,3,2-dioxaborinane (0.060 mmol, 12.2 mg) with THF as solvent (0.5 mL). To the resulting solution

[30] Schnürch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green. Chem.* **2007**, *9*, 139.

was added 4-benzoyloxymorpholine (0.050 mmol, 10.4 mg). Reactions were heated at 25 °C with stirring for 24 h.

Note on Preparation of XantPhosCu-OtBu from XantPhos and (Cu-OtBu)$_4$:

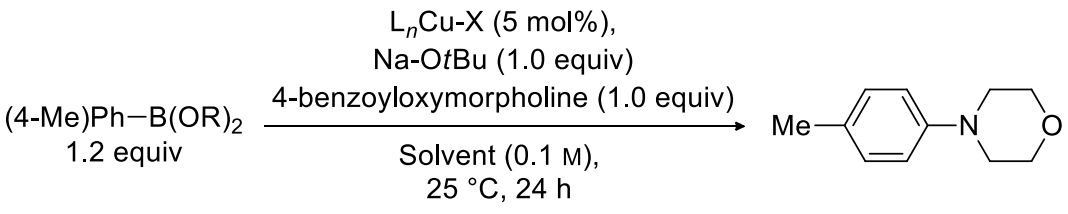
In a glove box, a 1-dram reaction vial was charged with a stir bar. To the vial was added Cu-O*t*Bu tetramer[31] (0.25 equiv), XantPhos ligand (1.00 equiv) and solvent (0.1 M). The resulting mixture was allowed to stir at 45°C for 0.5 h. The mixture was used as a stock solution of the catalyst.

4.3.2.4 Optimization of the solvent (Entries 13 – 15, Table 4.13)

Reactions were conducted according to the General Procedure using XantPhosCu-O*t*Bu (0.003 mmol, 25 µL of a 0.1 M stock solution), Na-O*t*Bu (0.050 mmol, 4.8 mg), and 2-(*p*-tolyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.060 mmol, 12.4 mg) with either diethyl ether, dichloromethane, or 1,4-dioxane as solvent (0.475 mL). To the resulting mixture was added 4-benzoyloxymorpholine (0.050 mmol, 10.4 mg). Reactions were heated at 25 °C with stirring for 24 h.

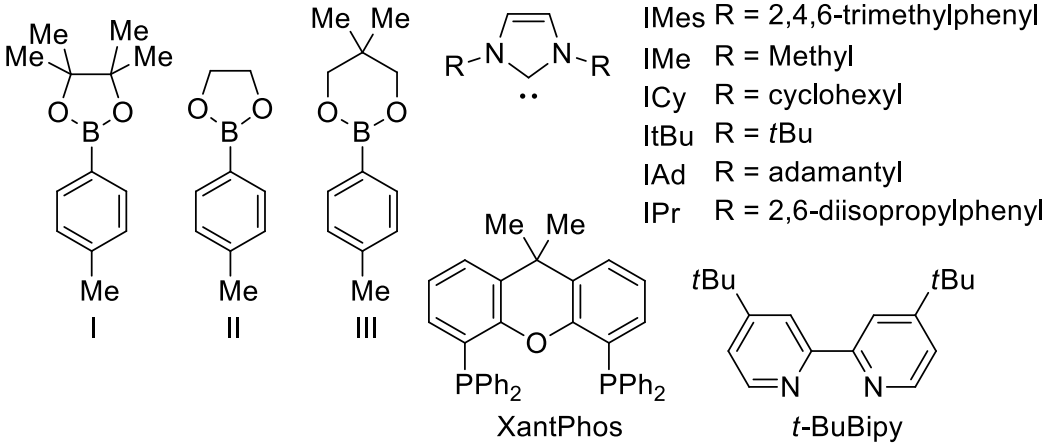
[31] Lemmon, T. H.; Goeden, G. V.; Huffman, J. C.; Geerts, R. L.; Kaulton, K. G. *Inorg. Chem.* **1990**, *29*, 3680.

Table 4.13. Reaction development



Entry	(4-Me)Ph-B(OR)$_2$	L_nCu-X[a]	Solvent	Yield
1	I	IMesCu-O*t*Bu	THF	< 5
2	II	IMesCu-O*t*Bu	THF	16
3	III	IMesCu-O*t*Bu	THF	72
4	III	CyIBoxCu-Cl	THF	< 1
5	III	IMeCu-Cl	THF	< 1
6	III	ICyCu-O*t*Bu	THF	< 1
7	III	I*t*BuCu-Cl	THF	48
8	III	IAdCu-Cl	THF	60
9	III	IPrCu-O*t*Bu	THF	0
10	III	*t*BuBipyCu-O*t*Bu	THF	52
11	III	dppeCu-O*t*Bu	THF	0
12	III	XantPhosCu-O*t*Bu	THF	92
13	III	XantPhosCu-O*t*Bu	diethyl ether	5
14	III	XantPhosCu-O*t*Bu	DCM	0
15	III	XantPhosCu-O*t*Bu	1,4-dioxane	99

[a] XantPhosCu-O*t*Bu is formed in situ from (Cu-O*t*Bu)$_4$ and XantPhos.



4.3.2.5 *Optimization of solvent, alkoxide additive, and concentration with 2-(2,6-dimethylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (Table 4.14):*

***With* 4-benzoyloxymorpholine:**

Reactions were conducted according to the General Procedure using XantPhosCu-O*t*Bu (0.003 mmol, 25 µL of a 0.1 M stock solution prepared in either 1,4-dioxane or toluene), Na-O*t*Bu (0.050 mmol, 4.8 mg) or Li-O*t*Bu (0.050 mmol, 4.0 mg), and 2-(2,6-dimethylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.06 mmol, 13.1 mg) with either 1,4-dioxane or toluene as solvent (0.475 mL). To the resulting mixture was added 4-benzoyloxymorpholine (0.050 mmol, 10.4 mg). The reaction vial was capped and stirred for 24 h at the indicated temperature.

***With O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine:**

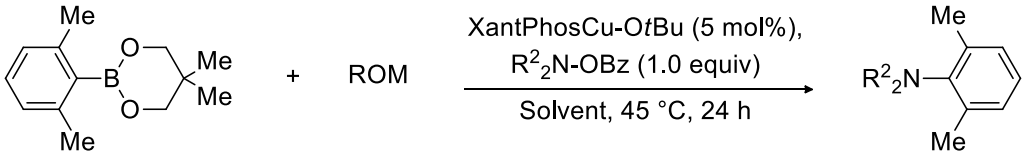
Reactions were conducted according to the General Procedure using XantPhosCu-O*t*Bu (0.003 mmol, 25 µL of a 0.1 M stock solution prepared in toluene), Li-O*t*Bu (0.050 mmol, 4.0 mg), and 2-(2,6-dimethylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.06 mmol, 13.1 mg) with either toluene or isooctane as solvent (0.475 mL). To the resulting mixture was added *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (0.050 mmol, 11.1 mg). The reaction vial was capped and stirred for 24 h at the indicated temperature.

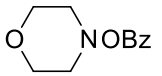
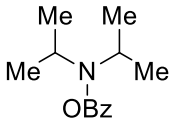
4.3.2.6 *Optimization of Concentration with O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine *and* isooctane:

The 0.5 M scale reaction (Table S2, entry 5) was conducted according to the General Procedure using XantPhosCu-O*t*Bu (0.010 mmol, 100 µL of a 0.1 M stock solution prepared in toluene), Na-O*t*Bu (0.200 mmol, 16.0 mg), and 2-(2,6-dimethylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.240 mmol, 52.3 mg) with isooctane as solvent (0.3 mL, 0.5 M) The 1.0 M scale reaction (Table S2, entry 6) was conducted according to the General Procedure using XantPhosCu-O*t*Bu

(0.010 mmol, 40 µL of a 0.25 M stock solution prepared in toluene), Na-O*t*Bu (0.200 mmol, 16.0 mg), and 2-(2,6-dimethylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.240 mmol, 52.3 mg) with isooctane as solvent (0.16 mL, 1.0 M). To the resulting mixture for both entries was added *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (0.200 mmol, 44.3 mg). The reaction vial was capped and heated to 60 °C with stirring for 24 h.

Table 4.14. Solvent and additive effect



Entry[a]	R^2_2N-OBz	ROM	Solvent	Concentration (M)	Yield (%)
1[b]		Na-O*t*Bu	1,4-dioxane	0.1	8
2		Li-O*t*Bu	1,4-dioxane	0.1	56
3		Li-O*t*Bu	toluene	0.1	74
4		Li-O*t*Bu	toluene	0.1	81
5[c]		Li-O*t*Bu	toluene/isooctane	0.5	87
6[c]		Li-O*t*Bu	toluene/isooctane (1:4)	1.0	94

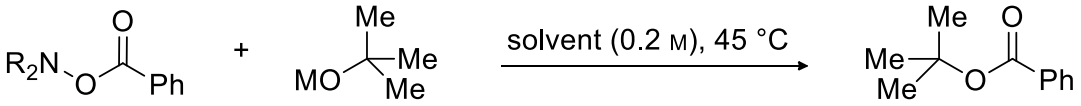
[a] Reactions conducted with 1.2 equiv of boronic ester and 1.0 equiv of ROM. XantPhosCu-O*t*Bu is formed in situ from $(Cu\text{-}OtBu)_4$ and XantPhos. [b] Reaction is conducted at 25 °C and electrophile is completely consumed within 3 h. [c] Reaction conducted at 60 °C and toluene is used to prepare XantPhosCu-O*t*Bu catalyst.

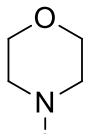
Reactions of *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine with sodium *tert*-butoxide and lithium *tert*-butoxide (Table 4.15).

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added either Li-O*t*Bu or Na-O*t*Bu (1.00 equiv, 0.100 mmol), and 1,3,5-trimethoxybenzene as an internal standard. To the resulting mixture was added *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.100 mmol) and solvent (0.50 mL). The resulting mixture was capped and heated at 45 °C with stirring.

Conversion of *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. To obtain data for each time point in Table S3, aliquots (0.05 mL) were withdrawn from the reaction mixture and were diluted to 0.50 mL with benzene-d^6.

Table 4.15. Solvent and additive effects on the formation of *t*-butyl ester by-product



Entry	NR_2	M	Solvent	% Conversion Electrophile & % Yield *t*-butyl benzoate Timepoint (min) 10		120	
1[a]		Na	1,4-dioxane-d^8	94	92	100	97
2		Li	1,4-dioxane-d^8	57	34	86	85
3		Li	benzene-d^6	21	22	66	33
4	$(iPr)_2N-OBz$	Li	benzene-d^6	0	0	0	0

[a] Reaction conducted at 25 °C.

4.3.3 *Amination of Aryl Boronic Esters:*

4.3.3.1 General procedure using alkoxides

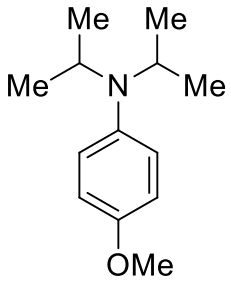
In a glove box, a dram vial was charged with a stir bar. To the vial was added Cu-O*t*Bu tetramer (0.025 equiv, 1.7 mg, 0.0125 mmol), xantphos (0.025 equiv, 7.2 mg, 0.0125 mmol), and toluene (100 µL). After stirring for 30 min at 25 °C, the mixture was transferred to a dram vial containing the boronic ester (1.20 equiv, 0.600 mmol), Li-O*t*Bu (1.00 equiv, 40.0 mg, 0.500 mmol), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.500 mmol), and isooctane (300 µL). An additional 100 µL of isooctane was used to rinse the dram vial containing the catalyst into the reaction vial. The mixture was allowed to stir at the specified temperature until complete conversion of the hydroxylamine by TLC. The mixture was then diluted in dichloromethane (2

mL), and filtered through a silica plug using successively dichloromethane (5 mL) and then diethyl ether (5 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography or ion exchange chromatography.

4.3.3.2 General procedure using CsF

In a glove box, a dram vial was charged with a stir bar. To the vial was added Cu-O*t*Bu tetramer (0.025 equiv, 1.7 mg, 0.0125 mmol), xantphos (0.025 equiv, 7.2 mg, 0.0125 mmol), and toluene (100 µL). After stirring for 30 min at 25 °C, the mixture was transferred to a dram vial containing the boronic ester (1.20 equiv, 0.600 mmol), CsF (5.00 equiv, 379.7 mg, 2.500 mmol), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.500 mmol), and toluene (400 µL). The mixture was allowed to stir at 60 °C for 72 h. The mixture was then diluted in dichloromethane (2 mL), and filtered through a silica plug using successively dichloromethane (5 mL) and then diethyl ether (5 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography.

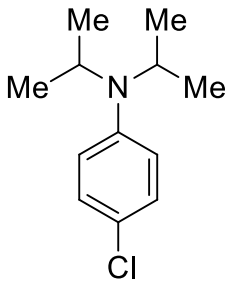
4.3.4 *Characterization Data for Aniline Products shown in table 4.11*



***N*,*N*-diisopropyl-4-methoxyaniline**

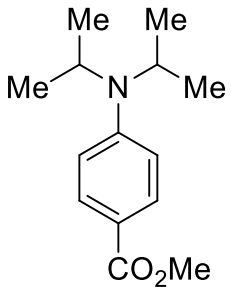
Compound was isolated as a yellow oil (105.6 mg, 85% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 6.94 (d, *J* = 9.1 Hz, 2H), 6.77 (d, *J* = 9.1 Hz, 2H), 3.75 (s, 3H), 3.60 – 3.46 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 12H) ^{13}C NMR (126 MHz, $CDCl_3$) δ

155.5, 140.6, 127.6, 113.4, 55.5, 48.6, 21.4. HRMS calculated for $[M]^+$ 207.1622, found 207.1619. FTIR (neat, cm^{-1}): 3037(m), 2971(s), 1464(m), 1359(m), 1286(m), 1241(s).



4-chloro-*N*,*N*-diisopropylaniline

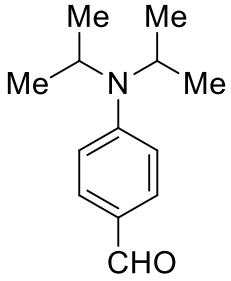
Compound was isolated as a colorless oil (870.4 mg, 82% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 7 CV). ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.73 (sept, *J* = 6.7 Hz, 2H), 1.19 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 128.3, 123.1, 120.4, 47.7, 21.3. HRMS calculated for $[M+H]^+$ 212.1206, found 212.1213. FTIR (neat, cm^{-1}): 3051(m), 2972(s), 1595(m), 1499(s), 1265(s), 740(s).



methyl 4-(diisopropylamino)benzoate

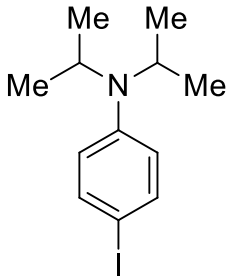
Compound was isolated as a white solid (104.8 mg, 89% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 7 CV). ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 9.2 Hz, 2H), 4.00 – 3.86 (m, 2H), 3.84 (s, 3H), 1.30 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 152.3, 131.1, 117.1, 114.5,

51.7, 48.0, 21.1. HRMS calculated for $[M+H]^+$ 236.1652, found 236.1646. FTIR (neat, cm^{-1}): 2971(s), 2875(m), 2251(m), 1705(s), 1605(s), 1434(s), 1278(s).



4-(diisopropylamino)benzaldehyde

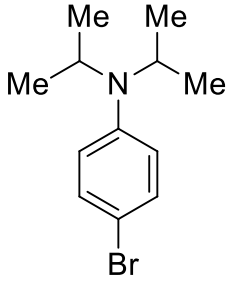
Compound was isolated as a yellow oil (106.0 mg, 94% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.67 (s, 1H), 7.64 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 4.00 (hept, *J* = 6.8 Hz, 2H), 1.33 (d, *J* = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 190.1, 153.6, 131.7, 125.5, 114.6, 48.3, 21.1. HRMS calculated for $[M+H]^+$ 206.1545, found 206.1543. FTIR (neat, cm^{-1}): 2972(s), 2930(s), 2872(m), 2853(m), 1867(w), 1681(s), 1423(s).



4-iodo-*N*,*N*-diisopropylaniline

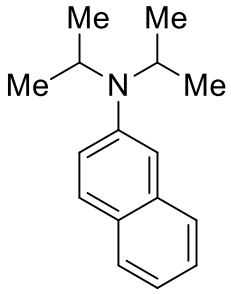
Compound was isolated as a white-pink solid (125.0 mg, 83% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 9.0 Hz, 2H), 3.76 (hept, *J* = 6.8 Hz, 2H), 1.21 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 148.5, 137.6, 120.4, 78.4, 48.1, 21.5. ESI-MS

calculated for $[M]^+$ 303.0, found 303.0. FTIR (neat, cm^{-1}): 3047(w), 2970(s), 2873(m), 2611(w), 1582(s), 1495(s), 1367(s), 1328(s), 1288(s), 591(w), 553(m).



4-bromo-*N*,*N*-diisopropylaniline

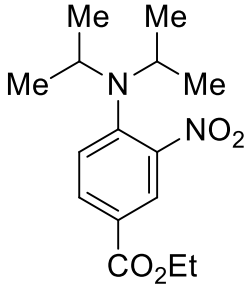
Compound was isolated as off white solid (107.6 mg, 84% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, *J* = 9.1 Hz, 2H), 6.51 (d, *J* = 9.1 Hz, 2H), 3.32 (hept, *J* = 6.7 Hz, 2H), 0.91 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 131.3, 120.6, 110.2, 47.8, 21.4. ESI-MS calculated for $[M+H]^+$ 256.1, found 257. FTIR (neat, cm^{-1}): 3038(w), 2970(s), 2872(m), 2612(w), 1588(s), 1496(s), 1367(s), 1287(s), 732(m).



***N*,*N*-diisopropylnaphthalen-2-amine**

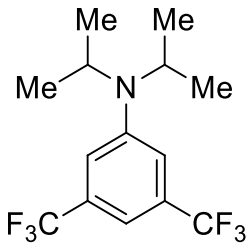
Compound was isolated as a yellow oil (94.9 mg, 84% yield) after purification by ion exchange chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.57 (m, 3H), 7.46 – 7.33 (m, 1H), 7.32 – 7.17 (m, 2H), 7.16 (d, *J* = 2.1 Hz, 1H), 3.90 (hept, *J* = 6.6 Hz, 2H), 1.30 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.0, 135.4, 128.0, 127.9, 127.7, 126.7, 126.3, 122.7, 122.1,

112.8, 48.3, 21.8. HRMS calculated for $[M]^+$ 227.1671, found 227.2675. FTIR (neat, cm^{-1}): 3053(s), 2970(s), 1823(w), 1627(s), 1388(s), 1283(s), 1236(s), 1147(s), 1016(m).



ethyl 4-(diisopropylamino)-3-nitrobenzoate

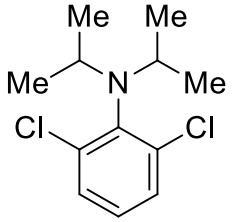
Compound was isolated as an orange oil (129.0 mg, 88% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.22 (hept, *J* = 6.6 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 165.4, 150.4, 146.6, 132.4, 130.2, 126.8, 125.7, 62.2, 51.4, 21.7, 14.5. HRMS calculated for $[M+H]^+$ 295.1655, found 295.1660. FTIR (neat, cm^{-1}): 3690(w), 3053(s), 2985(s), 2684(w), 1719(m), 1610(m), 1367(w).



***N*,*N*-diisopropyl-3,5-bis(trifluoromethyl)aniline**

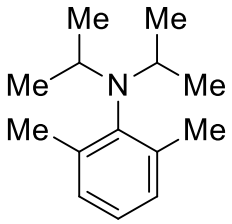
Compound was isolated as a yellow oil (133.6 mg, 85% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.28 (s, 1H), 7.11 (s, 2H), 3.26 (hept, *J* = 6.8 Hz, 2H), 0.80 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.5, 132.2 (q, *J* = 32.2 Hz), 124.7 (q, *J* = 272.4 Hz), 115.5, 109.3 (m),

48.5, 21.3. ESI-MS calculated for $[M]^+$ 313.2, found 313.1. FTIR (neat, cm^{-1}): 3054(m), 2976(s), 1615(s), 1550(w), 1488(s), 1429(s), 1361(s), 1276(s), 1179(s), 1130(s).



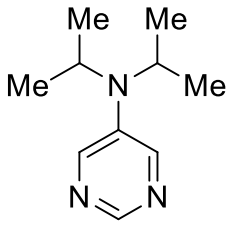
2,6-dichloro-*N*,*N*-diisopropylaniline

Compound was isolated as a white solid (103.7 mg, 84% yield) after purification by silica gel column chromatography (100% hexanes over 1 CV). ^{1}H NMR (500 MHz, C_6D_6) δ = 7.01 (d, *J*= 8.0, 2H), 6.41 (t, *J* = 8.0, 1H), 3.75 – 3.62 (hept, *J* = 6.5 Hz, 2H), 1.11 (d, *J* = 6.5, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ = 144.2, 140.9, 128.5, 126.9, 50.0, 22.9. ESI-MS calculated for $[M+H]^+$ 246.2, found 246.2. FTIR (neat, cm^{-1}): 3052(m), 2971(s), 1429(s), 1264(s), 1192(m), 743(s).



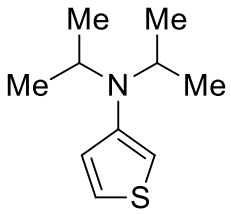
***N*,*N*-diisopropyl-2,6-dimethylaniline**

Compound was isolated as a yellow oil (96.7 mg, 94% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.02 – 6.96 (m, 2H), 6.96 – 6.90 (m, 1H), 3.55 (hept, *J* = 6.6 Hz, 2H), 2.26 (s, 6H), 1.02 (d, *J* = 6.4 Hz, 12H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.0, 141.4, 128.3, 125.4, 50.2, 23.7, 20.7. ESI-MS calculated for $[M+H]^+$ 206.2, found 206.1. FTIR (neat, cm^{-1}): 4197(w), 3054(s), 2987(s), 2855(m), 2855(w), 2305(m), 1422(m), 1266(s),



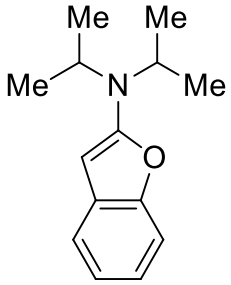
***N*,*N*-diisopropylpyrimidin-5-amine**

Compound was isolated as a yellow solid (77.8 mg, 87% yield) after purification by silica gel column chromatography (0 → 30% ethyl acetate/hexanes over 12 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 (s, 1H), 8.29 (s, 2H), 3.84 (hept, *J* = 6.8 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 147.9, 144.6, 48.0, 21.0. ESI-MS calculated for $[M+H]^+$ 180.1, found 180.1. FTIR (neat, cm^{-1} 3052(s), 2985(s), 2886(m), 2688(w), 1367(w), 1264(s).



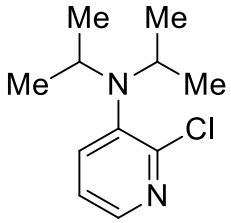
***N*,*N*-diisopropylthiophen-3-amine**

Compound was isolated as a yellow brown oil (80.8 mg, 88% yield) after purification by silica gel column chromatography (0 → 10% diethyl ether/hexanes over 6 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 6.89 (dd, *J* = 5.2, 3.1 Hz, 1H), 6.72 (dd, *J* = 5.2, 1.5 Hz, 1H), 6.06 (dd, *J* = 3.1, 1.5 Hz, 1H), 3.34 (hept, *J* = 6.7 Hz, 2H), 0.99 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 148.9, 124.2, 124.0, 102.6, 49.2, 21.4. ESI-MS calculated for $[M+H]^+$ 183.1, found 183.1. FTIR (neat, cm^{-1}): 3052(s), 2971(s), 2871(m), 1537(s), 1264(s), 1126(m).



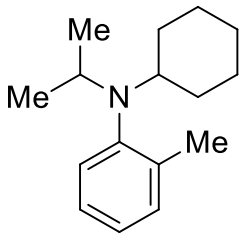
***N*,*N*-diisopropylbenzofuran-2-amine**

Compound was isolated as a light orange solid (95.0 mg, 87% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.20 (d, *J* = 7.6 Hz, 2H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 – 6.82 (m, 1H), 5.34 (s, 1H), 3.76 (hept, *J* = 6.7 Hz, 2H), 1.30 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 161.5, 151.0, 132.3, 123.5, 119.9, 118.0, 109.9, 79.7, 49.1, 21.4. ESI-MS calculated for $[M]^+$ 217.2, found 217.1. FTIR (neat, cm^{-1}): 3853(s), 2984(s), 2305(m), 1581(s), 1368(m), 1264(s), 1130(m).



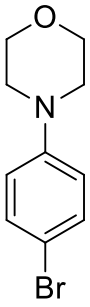
2-chloro-*N*,*N*-diisopropylpyridin-3-amine

Compound was isolated as a yellow oil (82.4 mg, 78% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (500 MHz, C_6D_6) δ 7.98 (dd, *J* = 4.5, 1.7 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.51 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.28 (hept, *J* = 6.6 Hz, 2H), 0.89 (d, *J* = 6.5 Hz, 12H). ^{13}C NMR (126 MHz, CD_3CN) δ 155.2, 146.7, 142.9, 141.2, 123.5, 51.0, 21.5. ESI-MS calculated for $[M+H]^+$ 213.1, found 213.0. FTIR (neat, cm^{-1}): 3053(s), 2974(s), 1443(m), 1398(s), 1265(s).



***N*-cyclohexyl-*N*-isopropyl-2-methylaniline**

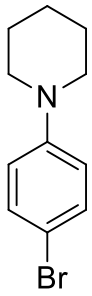
Compound was isolated as a yellow oil (110.0 mg, 95% yield) after purification by ion exchange chromatography. ^{1}H NMR (300 MHz, CD_3CN) δ 7.26 – 7.18 (m, 2H), 7.12 – 7.00 (m, 2H), 3.53 (hept, *J* = 6.8 Hz, 1H), 3.06 (tt, *J* = 10.7, 3.3 Hz, 1H), 2.14 (s, 3H), 1.90 – 1.80 (m, 2H), 1.74 – 1.59 (m, 2H), 1.59 – 1.48 (m, 1H), 1.37 – 1.10 (m, 2H), 1.04 (m, 3H), 0.94 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 147.5, 140.8, 130.7, 130.3, 125.8, 125.3, 59.4, 49.8, 32.1, 26.9, 26.5, 21.4, 19.4. ESI-MS calculated for $[M]^+$ 231.2, found 231.2. FTIR (neat, cm^{-1}): 3052(m), 2931(s), 1379(m), 1361(w), 1264(s), 1109(m), 1066(w).



4-(4-bromophenyl)morpholine

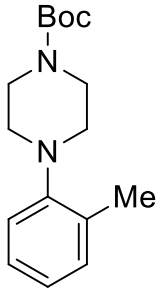
Compound was isolated as a white solid (98.1 mg, 81% yield) after purification by silica gel column chromatography (0 → 17% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.91 – 3.66 (m, 4H), 3.21 – 2.94 (m, 4H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.1, 132.4, 117.7, 112.2, 67.3, 49.6. ESI-MS calculated

for $[M+H]^+$ 242.1, found 242.9. FTIR (neat, cm^{-1}): 3684(w), 3053(s), 2986(s), 1494(m), 1265(s), 522(w).



1-(4-bromophenyl)piperidine

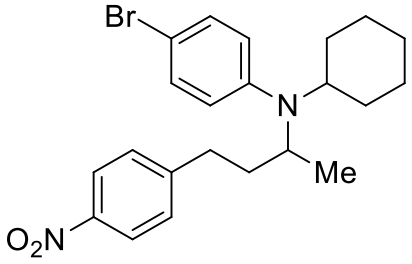
Compound was isolated as a white solid (96.2 mg, 80% yield) after purification by ion exchange chromatography. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.30 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.15 – 3.08 (m, 4H), 1.71 – 1.64 (m, 4H), 1.62 – 1.54 (m, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 151.9, 132.2, 118.3, 111.0, 50.8, 26.3, 24.8. ESI-MS calculated for $[M]^+$ 240.1, found 240.0. FTIR (neat, cm^{-1}): 3053(s), 2986(s), 2940(s), 1856(m), 2827(m), 2305(s), 1588(m), 1421(s), 1264(s), 1130(m), 895(s).



***tert*-butyl 4-(*o*-tolyl)piperazine-1-carboxylate**

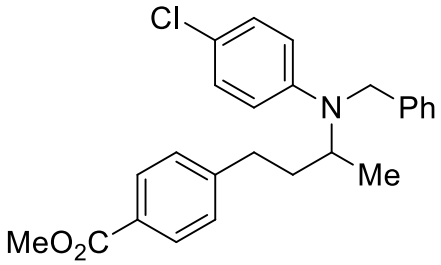
Compound was isolated as a yellow solid (105.2 mg, 76% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 6 CV). ^{1}H NMR (300 MHz, MeOD) δ 7.25 – 7.11 (m, 2H), 7.03 – 6.77 (m, 2H), 3.61 – 3.54 (m, 4H), 2.98 – 2.56 (m, 4H), 2.31 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, CD_3CN) δ 155.5, 152.5, 133.5, 131.9, 127.6,

124.3, 120.1, 80.0, 52.6, 28.5, 21.8, 17.9. ESI-MS calculated for $[M]^+$ 276.2, found 276,0. FTIR (neat, cm^{-1}): 3053(s), 2984(m), 2053(m), 1685(m), 1366(m), 1265(s), 1171(m).



4-bromo-*N*-cyclohexyl-*N*-(4-(4-nitrophenyl)butan-2-yl)aniline

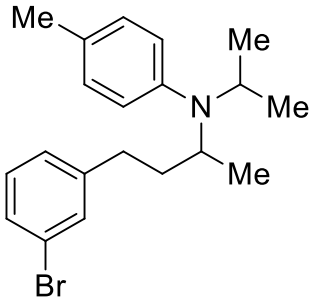
Compound was isolated as a yellow oil (86.8 mg, 80% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 3.48 – 3.39 (m, 1H), 3.19 – 3.09 (m, 1H), 2.59 (t, *J* = 8.1 Hz, 2H), 1.92 – 1.82 (m, 1H), 1.79 – 1.63 (m, 5H), 1.59 – 1.52 (m, 1H), 1.42 – 1.35 (m, 2H), 1.25 – 1.14 (m, 5H), 1.05 – 0.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 147.4, 146.4, 131.4, 129.1, 123.7, 121.0, 110.7, 58.7, 52.1, 37.2, 33.6, 32.8, 31.9, 26.3, 26.0, 25.9, 19.8. HRMS calculated for $[M+H]^+$ 431.1334, found 431.1342. FTIR (neat, cm^{-1}): 3053(m), 2988(w), 1420(w), 1267(s), 918(s).



methyl 4-(3-(benzyl(4-chlorophenyl)amino)butyl)benzoate

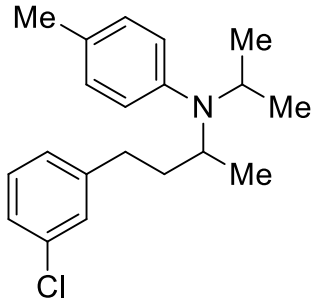
Compound was isolated as a colorless oil (178.2 mg, 87% yield) after purification by silica gel column chromatography (0 → 20% ethyl acetate/hexanes over 8 CV), then ion exchange

chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.16 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 9.1 Hz, 2H), 4.38 (s, 2H), 3.98 (dq, *J* = 13.6, 6.7 Hz, 1H), 3.89 (s, 3H), 2.69 (t, *J* = 7.9 Hz, 2H), 1.99 – 1.91 (m, 1H), 1.83 – 1.74 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 147.9, 147.3, 139.6, 129.8, 128.9, 128.6, 128.4, 128.1, 126.8, 126.5, 121.7, 115.2, 53.6, 52.0, 48.4, 36.2, 33.4, 17.8. HRMS calculated for $[M+H]^+$ 408.1730, found 408.1738. FTIR (neat, cm^{-1}): 3053(m), 2986(w), 1718(s), 1496(m), 1265(s), 738(s).



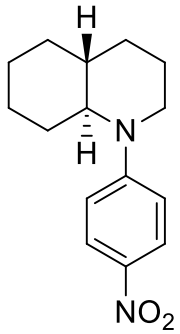
***N*-(4-(3-bromophenyl)butan-2-yl)-*N*-isopropyl-4-methylaniline**

Compound was isolated as a colorless oil (166.3 mg, 92% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.79 – 6.70 (m, 2H), 3.50 – 3.36 (m, 1H), 3.28 – 3.17 (m, 1H), 2.49 – 2.29 (m, 2H), 2.21 (s, 3H), 1.78 – 1.65 (m 1H), 1.47 – 1.34 (m, 1H), 1.16 – 0.91 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 145.0, 131.5, 129.9, 129.1, 128.9, 128.7, 127.1, 122.5, 121.0, 52.2, 48.4, 37.7, 33.2, 22.6, 21.4, 20.6, 19.2. HRMS calculated for $[M+H]^+$ 360.1326, found 360.1325. FTIR (neat, cm^{-1}): 3047(w), 2968(m), 1514(m), 1265(s), 739(s).



***N*-(4-(3-chlorophenyl)butan-2-yl)-*N*-isopropyl-4-methylaniline**

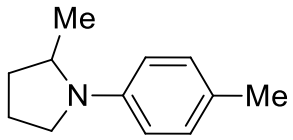
Compound was isolated as a colorless oil (128.9 mg, 81% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 7 CV, then 0 → 5% Et_2O/hexanes over 7 CV. ^{1}H NMR (300 MHz, C_6D_6) δ 7.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.52 (dq, *J* = 13.2, 6.6 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.53 – 2.46 (m, 2H), 2.31 (s, 3H), 1.85 – 1.75 (m, 1H), 1.59 – 1.45 (m, 1H), 1.25 – 1.00 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 144.7, 134.1, 129.5, 129.1, 128.7, 128.6, 126.6, 125.9, 121.0, 52.2, 48.4, 37.6, 33.2, 22.5, 21.5, 20.5, 19.1. ESI-MS calculated for $[M+H]^+$ 315.2, found 315.3. FTIR (neat, cm^{-1}): 3054(m), 2987(w), 1419(w), 1265(s), 741(s).



(4aR,8aS)-1-(4-nitrophenyl)decahydroquinoline

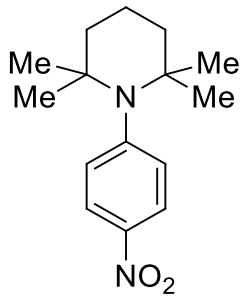
Compound was isolated as a yellow solid (123.7 mg, 95% yield) after purification by silica gel column chromatography (0 → 4% ethyl acetate/hexanes over 4 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 8.03 (d, *J* = 9.3 Hz, 2H), 6.32 (d, *J* = 9.3 Hz, 2H), 2.94 – 2.92 (m, 2H), 2.84 – 2.58 (m, 1H),

2.34 (td, *J* = 10.6, 3.0 Hz, 1H), 1.77 – 1.22 (m, 6H), 1.22 – 0.95 (m, 3H), 0.95 – 0.63 (m, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.5, 138.2, 126.2, 114.5, 65.0, 44.1, 40.1, 33.7, 30.5, 27.7, 26.8, 25.8, 23.5. ESI-MS calculated for $[M+H]^+$ 260.1, found 260.1. FTIR (neat, cm^{-1}): 3053(m), 2986(m), 2934(m), 1594(m), 1421(m), 1312(m), 1264(s), 1113(w), 895(m), 705(s).



2-methyl-1-(*p*-tolyl)pyrrolidine

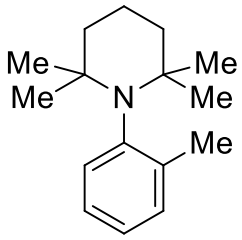
Compound was isolated as a colorless oil (79.1 mg, 90% yield) after purification by silica gel column chromatography (0 → 5% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.13 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.80 – 3.49 (m, 1H), 3.13 (dt, *J* = 12.4, 6.1 Hz, 1H), 2.88 (dt, *J* = 14.6, 6.9 Hz, 1H), 2.28 (s, 3H), 1.74 – 1.57 (m, 2H), 1.55 – 1.42 (m, 1H), 1.32 – 1.18 (m, 1H), 0.98 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 129.7, 124.3, 112.0, 53.8, 48.5, 33.2, 23.4, 20.3, 19.6. HRMS calculated for $[M+H]^+$ 176.1439, found 176.1441. FTIR (neat, cm^{-1}): 3053(m), 2985(w), 1521(w), 1265(s).



2,2,6,6-tetramethyl-1-(4-nitrophenyl)piperidine

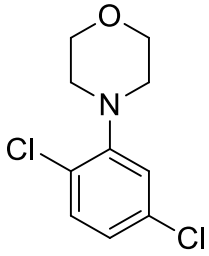
Compound was isolated as a yellow oil (114.3 mg, 87% yield) after purification by silica gel column chromatography (100% hexanes over 2CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 1.74 (m, 2H), 1.67 – 1.46 (m, 4H), 1.03 (s, 12H).^{13}C NMR

(126 MHz, $CDCl_3$) δ 154.5, 145.7, 134.8, 123.2, 54.7, 42.1, 29.8, 18.3. HRMS calculated for $[M+H]^+$ 263.1761, found 263.1759. FTIR (neat, cm^{-1}): 3085(w), 2968(s), 2869(m), 1586(s), 1345(s), 1277(s), 1174(m), 1130(s), 1036(m),



2,2,6,6-tetramethyl-1-(*o*-tolyl)piperidine (Table 4.13)

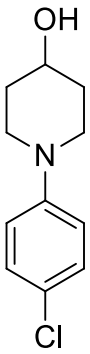
Compound was isolated as a yellow oil (102.9 mg, 89% yield) after purification by silica gel column chromatography (100% hexanes over 2 CV). ^1H NMR (300 MHz, C_6D_6) δ 7.34 – 7.27 (m, 1H), 7.21 (dd, *J* = 5.5, 3.8 Hz, 1H), 7.10 – 7.01 (m, 2H), 2.37 (s, 3H), 1.93 – 1.71 (m, 1H), 1.70 – 1.42 (m, 5H), 1.25 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 141.5, 132.4, 130.9, 125.8, 125.5, 55.3, 42.4, 32.0, 25.7, 19.9, 19.0. ESI-MS calculated for $[M]^+$ 231.2, found 231.2. FTIR (neat, cm^{-1}): 3053(s), 2971(s), 1486(m), 1349(m), 1265(s), 895(m).



4-(2,5-dichlorophenyl)morpholine (Table 4.13)

Compound was isolated as a colorless oil (105.8 mg, 91% yield) after purification by silica gel column chromatography (0 → 5% Et_2O/hexanes over 7 CV). ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.64 – 3.43 (m, 4H),

2.60 – 2.36 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 133.2, 131.5, 127.0, 123.7, 120.8, 67.0, 51.5. ESI-MS calculated for $[M+H]^+$ 232.0, found 232.1. FTIR (neat, cm^{-1}): 3054(s), 2986(m), 1421(w), 1265(s), 736(s).



4-hydroxy-1-(4-chlorophenyl)piperidine (Table 4.13)

Compound was isolated as white needles (79.2 mg, 75% yield) after purification by silica gel column chromatography (40 → 70% Et_2O/hexanes over 7 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.13 (d, *J* = 9.1 Hz, 2H), 6.43 (d, *J* = 9.0 Hz, 2H), 3.29 (m, 1H), 3.15 – 2.97 (m, 2H), 2.39 (ddd, *J* = 12.6, 9.6, 3.2 Hz, 2H), 1.61 – 1.41 (m, 2H), 1.36 – 1.21 (m, 2H), 0.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 129.1, 124.4, 117.8, 67.8, 47.4, 34.1. HRMS calculated for $[M+H]^+$ 212.0842, found 212.0846. FTIR (neat, cm^{-1}): 3404(br), 2951(m), 1635(br), 1495(s), 1041(s), 733(s).

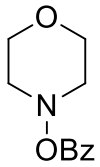
4.3.5 *Synthesis of O-benzoyl-N,N-dialkyl hydroxylamines:*

General:

The *O*-benzoyl-*N*,*N*-dialkyl hydroxylamines were synthesized according to a modified literature procedure.[32] To a reaction flask under nitrogen was added potassium hydrogen phosphate (5.00 equiv) and benzoyl peroxide (1.20 equiv) followed by DMF (1.0 M). With vigorous stirring, the

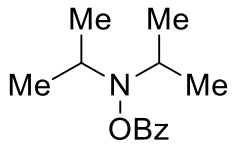
[32] Ashley M. Berman and Jeffrey S. Johnson. *J. Org. Chem.* **2006**, *71*, 219.

secondary amine (1.00 equiv) was added, and the resulting mixture stirred at 25 °C until complete conversion of the amine, as indicated by TLC. The solids were separated by filtration through a silica plug using diethyl ether as the eluent. The organic layer was concentrated, and the crude product was purified by silica gel chromatography or ion-exchange chromatography.



4-benzoyloxymorpholine (Table 1, 1)

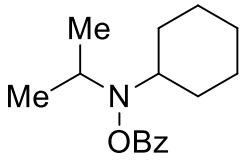
Compound was isolated as a white solid (2942.1 mg, 71% yield) after purification by silica gel column chromatography (0 → 50% diethyl ether/hexanes over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 7.80 (m, 2H), 7.57 (dd, *J* = 10.5, 4.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz,2H), 4.08 – 3.76 (m, 4H), 3.46 (d, *J* = 9.9 Hz, 2H), 3.05 (t, *J* = 10.7 Hz, 2H ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 133.2, 129.5, 129.2, 128.5, 65.9, 57.0. GC-MS calculated for $[M]^+$ 207, found 207. FTIR (neat, cm^{-1}): 3053(s), 2986(s), 2858(m) 1691(m), 1264(s), 1160(w), 895(m).



***O*-benzoyl-*N*,*N*-diisopropylhydroxylamine (Table 1, 2)**

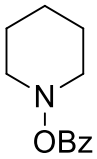
Compound was isolated as a pale yellow oil which solidified into a white crystalline product (1992.1 mg, 60% yield) after purification by silica gel column chromatography (0 → 20% ethyl acetate/hexanes over 9 CV). ^{1}H ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 – 7.92 (m, 2H), 7.57 (dd, *J* = 10.4, 4.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 3.85 – 2.97 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 133.0, 129.6, 129.5, 128.5, 53.6, 19.9, 17.7. ESI-MS

calculated for $[M]^+$ 221.3, found 221.1. FTIR (neat, cm^{-1}): 3053(s), 2984(s), 2939.8(m), 1737(s), 1601(w), 1584(w), 1421(s), 1384(m), 1264(s), 1025(s), 895(s), 746(s).



_O_-benzoyl-_N_-cyclohexyl-_N_-isopropylhydroxylamine (S1)

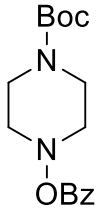
Compound was isolated as a white solid (991.7 mg, 40% yield) after purification by silica gel column chromatography (0 → 15% ethyl acetate/hexanes over 9CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 – 7.94 (m, 2H), 7.64 – 7.52 (m, 1H), 7.50 – 7.38 (m, 2H), 3.72 – 3.33 (m, 1H), 3.27 – 2.83 (m, 1H), 1.85 (dd, *J* = 33.2, 11.2 Hz, 4H), 1.63 (d, *J* = 11.6 Hz, 1H), 1.52 – 0.94 (m, 11H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 132.8, 129.5, 129.4, 128.4, 61.7, 52.5, 29.7, 28.7, 25.8, 25.2, 19.9, 16.5. GC-MS calculated for $[M]^+$ 261, found 261. FTIR (neat, cm^{-1}): 3053(s), 2986(s), 2684(m), 1710(m), 1601(w), 1266(s), 1158(w), 1082(w), 1063(w), 894(s), 743(s).



piperidin-1-yl benzoate (S2)

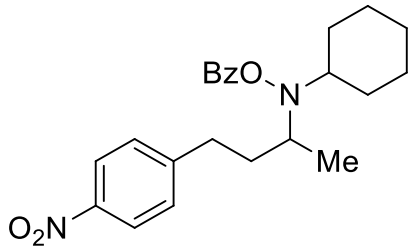
Compound was isolated as a white solid (2627.0 mg, 64% yield) after purification by silica gel column chromatography (0 → 20% diethyl ether/hexanes over 9CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.87 (m, 2H), 7.61 – 7.51 (m, 1H), 7.49 – 7.36 (m, 2H), 3.62 – 3.35 (m, 2H), 2.78 (m, *J* = 8.9, 8.3 Hz, 2H), 1.97 – 1.77 (m, 4H), 1.75 – 1.54 (m, 1H), 1.45 – 0.94 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 133.0, 129.8, 129.5, 128.5, 57.6, 25.1, 23.4. GC-MS

calculated for $[M]^+$ 205, found 205. FTIR (neat, cm^{-1}): 3943(w), 3053(s), 2985(s), 1732(s), 1421(m), 1264(s), 1177(w), 1068(m), 1016(m), 895(m),745(s).



***tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (S3)**

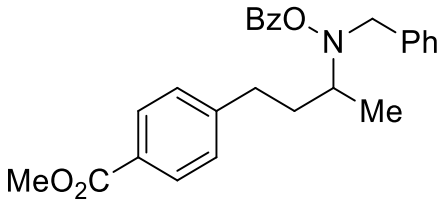
Compound was isolated as a white solid (1166.6 mg, 71% yield) after purification by silica gel column chromatography (0 → 20% ethyl acetate/hexanes over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 7.77 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 4.05 (s, 2H), 3.53 – 3.26 (m, 4H), 2.92 (s, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 154.0, 132.8, 129.0, 128.8, 128.1, 79.7, 55.4, 41.6, 28.0. ESI-MS calculated for $[M+H]^+$ 307.4, found 307.8. FTIR (neat, cm^{-1}): 3053(s), 2986(s), 2938(m), 2857(w), 2830(w), 2684(m), 1739(m), 1601(w), 1421(s), 1265(s).



***O*-benzoyl-*N*-cyclohexyl-*N*-(4-(4-nitrophenyl)butan-2-yl)hydroxylamine (S4)**

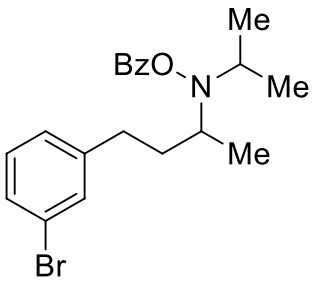
Compound was isolated as a colorless oil (235.0 mg, 29% yield) after purification by silica gel column chromatography (0 → 15% Et_2O/hexanes over 7 CV, then 0 → 30% ethyl acetate/hexanes over 7 CV), then ion exchange chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (dd, *J* = 7.6, 8.4

Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 3.42 – 3.21 (m, 1H), 3.16 – 2.95 (m, 2H), 2.95 – 2.70 (m, 1H), 1.94 – 1.69 (m, 4H), 1.69 – 1.49 (m, 3H), 1.44 – 1.14 (m, 8H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.5, 151.1, 146.7, 133.5, 130.0, 129.8, 129.6, 128.9, 124.0, 62.0, 56.5, 31.0, 30.7, 26.2, 25.3, 25.1, 24.9. HRMS calculated for $[M+H]^+$ 397.2127, found 397.2112. FTIR (neat, cm^{-1}): 2984(m), 2940(w), 1738(s), 1448(m), 1374(s), 1245(s), 908(s).



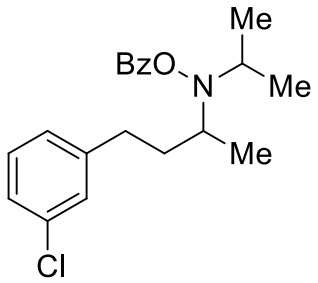
methyl 4-(3-((benzoyloxy)(benzyl)amino)butyl)benzoate (S5)

Compound was isolated as a colorless oil (1151.4 mg, 75% yield) after purification by silica gel column chromatography (0 → 15% Et_2O/hexanes over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 4H), 7.59 – 7.50 (m, 1H), 7.48 – 7.37 (m, 4H), 7.33 – 7.23 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 4.27 (d, *J* = 13.2 Hz, 1H), 4.09 (d, *J* = 13.2 Hz, 1H), 3.87 (s, 3H), 3.24 – 3.02 (m, 1H), 2.95 – 2.80 (m, 2H), 2.08 – 1.87 (m, 1H), 1.79 – 1.63 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 165.2, 148.0, 136.4, 132.9, 129.7, 129.5, 129.3, 128.6, 128.5, 128.4, 128.3, 127.7, 127.6, 59.3, 58.9, 51.9, 35.7, 32.6, 14.1. HRMS calculated for $[M+H]^+$ 418.2018, found 418.2011. FTIR (neat, cm^{-1}): 3030(w), 2949(m), 1742(s), 1720(s), 1279(s).



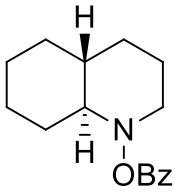
***O*-benzoyl-*N*-(4-(3-bromophenyl)butan-2-yl)-*N*-isopropylhydroxylamine (S6)**

Compound was isolated as a colorless oil (486.0 mg, 67% yield) after purification by silica gel column chromatography (0 → 10% Et_2O/hexanes over 7 CV), then ion exchange chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.34 (s, 1H), 7.32 – 7.27 (m, 1H), 7.11 (d, *J* = 4.9 Hz, 2H), 3.43 – 3.38 (m, 1H), 3.23 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.86 – 2.72 (m, 2H), 1.93 – 1.84 (m, 1H), 1.70 – 1.60 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 166.6, 145.2, 133.4, 132.0, 130.3, 130.0, 129.7,129.3, 128.9, 127.6, 122.8, 57.4, 54.1, 32.6, 20.8. ESI-MS calculated for $[M+H]^+$ 390.1, found 390.2. FTIR (neat, cm^{-1}): 2979(m), 2876(w), 1739(s), 1451(m), 1257(s), 910(s).



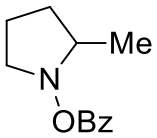
_O_-benzoyl-_N_-(4-(3-chlorophenyl)butan-2-yl)-_N_-isopropylhydroxylamine (S7)

Compound was isolated as a colorless oil (612.2 mg, 80% yield) after purification by silica gel column chromatography (0 → 10% Et_2O/hexanes over 7 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.27 – 7.01 (m, 4H), 3.53 – 3.30 (m, 1H), 3.23 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.85 – 2.75 (m, 2H), 1.94 – 1.83 (m, 1H), 1.69 – 1.58 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 144.5, 134.0, 133.0, 129.6, 129.4, 128.7, 128.5, 126.8, 125.9, 57.1, 53.7, 36.7, 32.2, 20.4, 12.9. HRMS calculated for $[M+H]^+$ 346.1573, found 346.1583. FTIR (neat, cm^{-1}): 2979(m), 2875(w), 1740(s), 1451(m), 1256(s), 908(s).



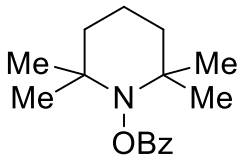
(4aR,8aS)-octahydroquinolin-1(2H)-yl benzoate (S8)

Compound was isolated as a white solid (1829.4 mg, 54% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes with 3% toluene as an additive over 9 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 3.58 (d, *J* = 9.5 Hz, 1H), 2.88 – 2.60 (m, 1H), 2.42 (t, *J* = 10.2 Hz, 1H), 1.97 (dt, *J* = 16.4, 11.6 Hz, 2H), 1.83 – 1.44 (m,6H), 1.46 – 0.90 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 133.0, 129.7, 129.5, 128.4, 71.7, 58.1, 41.4, 32.6, 31.4, 29.9, 25.8, 24.9, 24.7. GC-MS calculated for $[M]^+$ 261, found 261. FTIR (neat, cm^{-1}): 3049(s), 2982(s), 1738(s), 1603(w), 1424(m), 1262(s), 1024(w), 704(s).



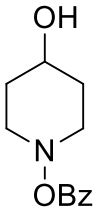
2-methylpyrrolidin-1-yl benzoate (S9)

Compound was isolated as a colorless oil (529.4 mg, 56% yield) after purification by silica gel column chromatography (0 → 30% ethyl acetate/hexanes over 7 CV), then ion exchange chromatography. ^{1}H NMR (300 MHz, C_6D_6) δ 8.10 (d, *J* = 6.8 Hz, 2H), 7.12 – 6.98 (m, 3H), 3.65 – 3.40 (m, 1H), 3.22 – 2.92 (m, 1H), 2.74 (dt, *J* = 19.1, 8.7 Hz, 1H), 1.65 – 1.36 (m, 3H), 1.33 – 1.17 (m, 1H), 1.14 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 132.9, 129.6, 129.5, 128.4, 63.7, 56.3, 28.8, 20.5, 17.9. HRMS calculated for $[M+H]^+$ 206.1181, found 206.1186. FTIR (neat, cm^{-1}): 3054(s), 2986(m), 1734(m), 1420(m), 1265(s).



2,2,6,6-tetramethylpiperidin-1-yl benzoate (S10)

Compound was isolated as a white solid (2522.0 mg, 64% yield) after purification by silica gel column chromatography (0 → 10% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 7.95 (m, 2H), 7.62 – 7.54 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 1.85 – 1.35 (m, 6H), 1.28 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 133.0, 129.9, 129.8, 128.6, 60.6, 39.3, 32.2, 21.1, 17.2. ESI-MS calculated for $[M]^+$ 261.4, found 261.1. FTIR (neat, cm^{-1}): 3944(w), 3053(s), 2983(m), 2304(w), 1742(s), 1584(w), 1450(m), 1380(w), 1264(s), 1084(m), 1065(m), 1025(m).

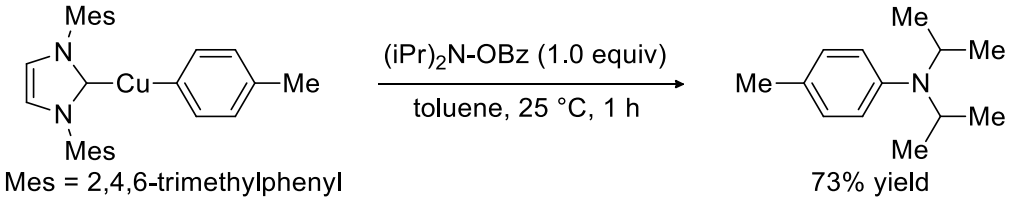


4-hydroxy piperidin-1-yl benzoate (Scheme 1, 35)

Compound was isolated as a white powder (759.0 mg, 79% yield) after purification by silica gel column chromatography (50 → 80% ethyl acetate/hexanes over 8 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 3.92 (s, 1H), 3.63 - 3.52 (m, 1H), 3.39- 3.22 (m, 2H), 2.94 - 2.83 (m, 1H), 2.16 - 2.00 (m, 2H), 1.94 - 1.82 (m, 2H), 1.54 - 1.45 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 164.9, 133.1, 129.4, 128.4, 67.1, 63.8, 54.3, 52.1, 33.0, 31.5. HRMS calculated for $[M+H]^+$ 222.1130, found 222.1140. FTIR (neat, cm^{-1}): 3417(br), 3057(m), 2952(s), 1734(s), 1601(w), 1450(m), 1258(s), 1063(m).

4.3.6 *Stoichiometric Reactions of Organocopper Complexes*

4.3.6.1 *With* IMesCu-(4-Me)Ph[33]:



Mes = 2,4,6-trimethylphenyl

73% yield

All reactions were performed in a glove box. A 1-dram vial was charged with a stir bar. To the vial was added *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine (1.00 equiv, 0.100 mmol, 22.1 mg), 1,3,5-trimethoxybenzene, and toluene (0.2 mL). To a shell vial was added IMesCu-(4-Me)Ph (1.00 equiv, 0.100 mmol, 45.9 mg) and toluene (0.2 mL). This solution was then added over 1 min to the stirred solution of *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine and the shell vial rinsed with toluene (0.1 mL).The reaction vial was capped and stirred at 25 °C. Yield of *N*,*N*-diisopropyl-4-methylaniline was determined by GC using 1,3,5-trimethoxybenzene as an internal standard. The reaction was completed within 1 h. This complex was also substituted for IMesCu-O*t*Bu as a catalyst in a reaction using *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine and tolyl boronic ester under the conditions described (Table S1, Entry 15). After 24 h reaction time, an 82% yield of product was obtained.

[33] Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216.

Chapter 5. COPPER-CATALYZED AMINATION OF ALKYL BORANES: DEVELOPMENT OF A PROTOCOL FOR ANTI-MARKOVNIKOV HYDROAMINATION OF TERMINAL ALKENES[163]

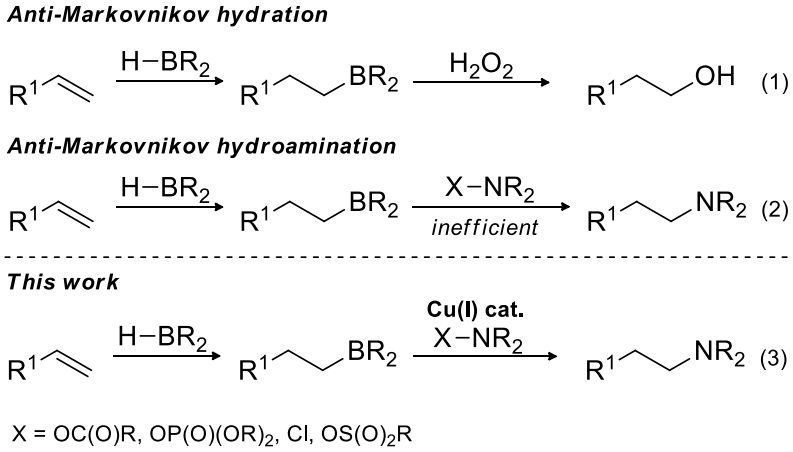
5.1 INTRODUCTION

The hydroamination of alkenes is a highly desirable transformation and has received considerable attention over the last two decades[164] Despite the progress made in developing this transformation, regioselectivity remains a problem with terminal alkenes substrates.[165-171] In these metal-catalyzed intermolecular hydroamination reactions, the formation of Markovnikov products is generally favoured. As a result, anti-Markovnikov selectivity has been observed only with special substrates, such as activated alkenes[172-176] and styrenes.[177-181] Approaches to anti-Markovnikov hydroamination that do not rely on transition metals have also been explored. Studer has reported a free-radical hydroamination that provides protected primary amines, in moderate yields (~50%).[182,183] Beauchemin has reported the reverse-Cope elimination as a method for hydroamination of alkenes.[184,185] However, low regioselectivity is generally observed in reactions of simple alkenes in both cases.

In practice, the anti-markovnikov hydroamination of olefins can be prepared using a hydroboration-amination sequence (Scheme 5.1, eq 2). This is illustrated in Kabalka's work for the synthesis of primary amines.[186] It is a synthetic transformation based on Brown's important work on the hydroboration-oxidation of alkenes for the anti-Markovnikov hydration of olefins (Scheme 5.1, eq 1).[187,188] Whereas the hydroboration-oxidation sequence is characterized by excellent regioselectivity, efficiency, and reliability, the hydroboration-amination sequence suffers from low yields of the desired amine product. This is due to the inefficient amination of

the trialkylborane intermediate where one, and at most two, of the three alkyl groups on the trialkyl borane intermediate can be aminated in this process.

Secondary amines can be prepared from alkyl boronic esters after conversion to trifluoroborates, followed by a reaction with excess Lewis acid (BF_3 or $SnCl_4$) and alkyl azide.[189-192] Unfortunately, while these methods are still the best option for anti-Markovnikov hydroamination of alkenes because of their excellent regioselectivity, they often provide the amination products in low yield (<50% based on the alkene). Furthermore, strong Lewis acids are usually used for the reaction of organoboron compounds with azides, and this method has rarely been used for the synthesis of secondary amines from alkenes. *Finally, none of the existing procedures for anti-Markovnikov hydroamination allows the preparation of tertiary alkyl amines from alkenes.*



Scheme 5.1. Hydroboration in the anti-Markovnikov hydrofunctionalization of alkenes

5.2 COPPER-CATALYZED ELECTROPHILIC HYDROAMINATION OF ALKYL BORANES

5.2.1 *Reaction Development*

We recently reported a catalytic method for the synthesis of hindered anilines featuring copper-catalyzed electrophilic amination of aryl boronic esters.[125] At the same time, we were

exploring the possibility that the analogous copper-catalyzed amination of alkyl boranes could be used to achieve a direct synthesis of tertiary alkyl amines from alkenes (Scheme 5.1, eq 3).

We decided to explore the reactivity of **1-Me**[193] in stoichiometric reactions with reagents commonly used in electrophilic amination of organometallic nucleophiles.[143,147,149,151,194-197] In a reaction with *N*,*N*-dibenzyl-*N*-chloroamine (**2**) we observed complete conversion of **1-Me**, and the formation of a small amount (7%) of the amination product (Figure 5.1, eq 4).

More insight into the reactivity of *N*-chloroamine **2** was obtained from its reaction with **1-Ar** (Scheme 5.1, eq 5), in which the oxidative homocoupling product was obtained in 70% yield. Gratifyingly, in a reaction of **1-Me** with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**3**) the desired amination product was obtained in 99% yield (eq 4). *O*-Benzoyl-*N*,*N*-dialkylhydroxylamines are readily available[143,194] and have previously been used in copper-catalyzed electrophilic amination of organozinc and Grignard reagents.

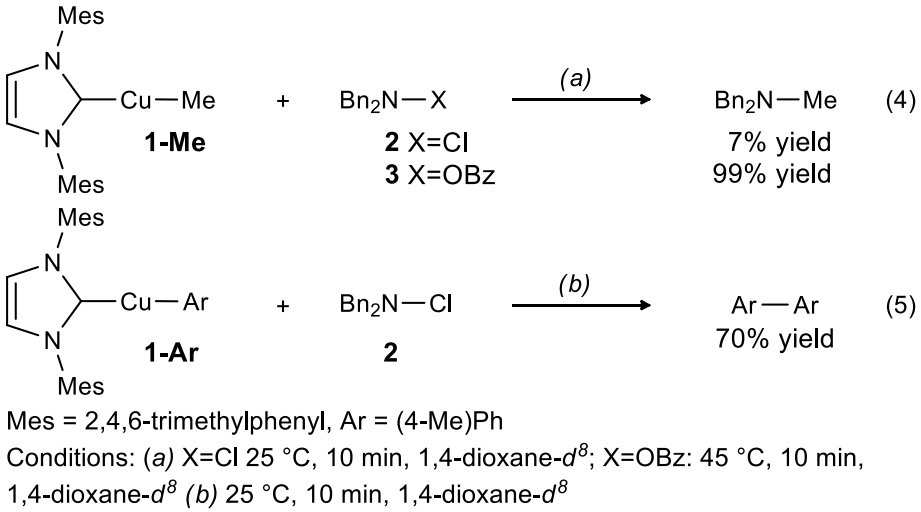
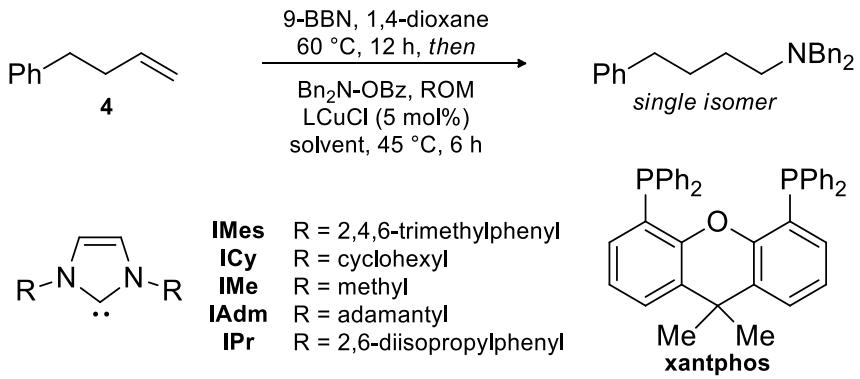


Figure 5.1. Electrophilic amination of organocopper complexes

Having identified a suitable electrophile for amination of NHC-Cu alkyl complexes, we turned our attention to the development of copper-catalyzed amination of alkyl boranes and its application in hydroamination of terminal alkenes.

Table 5.16. Reaction development



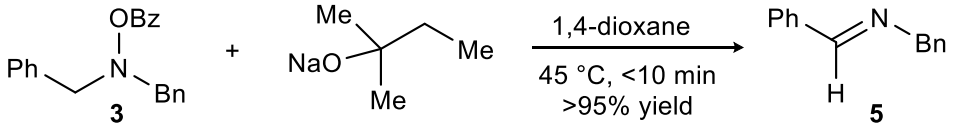
Entry[a]	Solvent	ROM	L	Yield[b]
1	1,4-dioxane	NaO*t*-Pent	IMes	<5%
2	1,4-dioxane	NaO*t*-Pent	ICy	16%
3	1,4-dioxane	LiO*t*-Bu	ICy	56%
4	pentane	LiO*t*-Bu	ICy	78%
5	pentane	LiO*t*-Bu	IMe	39%
6	pentane	LiO*t*-Bu	IAdm	43%
7	pentane	LiO*t*-Bu	IPr	<5%
8[c]	pentane	LiO*t*-Bu	xantphos	<5%
9[d]	pentane	LiO*t*-Bu	ICy	97%

[a] alkene (1.0 equiv), 9-BBN (1.0 equiv), Bn_2N-OBz (1.0 equiv), ROM (1.0 equiv) [b] determined by GC [c] Catalyst was formed in situ from xantphos and $(CuO\text{-}t\text{Bu})_4$ [d] Bn_2N-OBz (1.3 equiv), ROM (1.3 equiv) were used

We decided to explore electrophilic amination of the 9-alkyl-9-BBN derivative prepared by hydroboration of 4-phenyl-1-butene (**4**) with 9-BBN. Hydroboration was performed in 1,4-dioxane at 60 °C for 12 h, after which all components required for electrophilic amination were

added to the reaction flask. Under conditions previously used in allylic alkylation with alkyl boranes, the hydroamination product was obtained in less than 5% yield (Table 5.16, entry 1). However, when ICyCuCl was used as a catalyst the desired product was obtained in 16% yield (entry 2).[157,198,34]

Analysis of the crude reaction mixtures obtained in catalytic reactions indicated complete consumption of the electrophile and the formation of a single major product. After column chromatography, we isolated a significant amount of benzaldehyde, which suggested that the major product of the reaction might be the imine formed by elimination of benzoate from *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine.[35] A control experiment confirmed fast formation of imine **5** in a reaction of the electrophile with sodium *tert*-pentoxide (Fig.5.2, eq 6). While the elimination reaction was slower in the presence of alkyl borane ($t_{1/2}$~10 min at 45 °C), it still effectively competed with the desired electrophilic amination. Further experiments revealed that the consumption of the electrophile was significantly slower in a reaction with lithium *tert*-butoxide, under otherwise identical conditions ($t_{1/2}$~120 min). The reaction with lithium *tert*-butoxide was even slower if less polar benzene was used as a solvent instead of 1,4-dioxane (4% conversion after 2 h, at 45 °C).



(6)

Figure 5.2. Formation of imine **5**

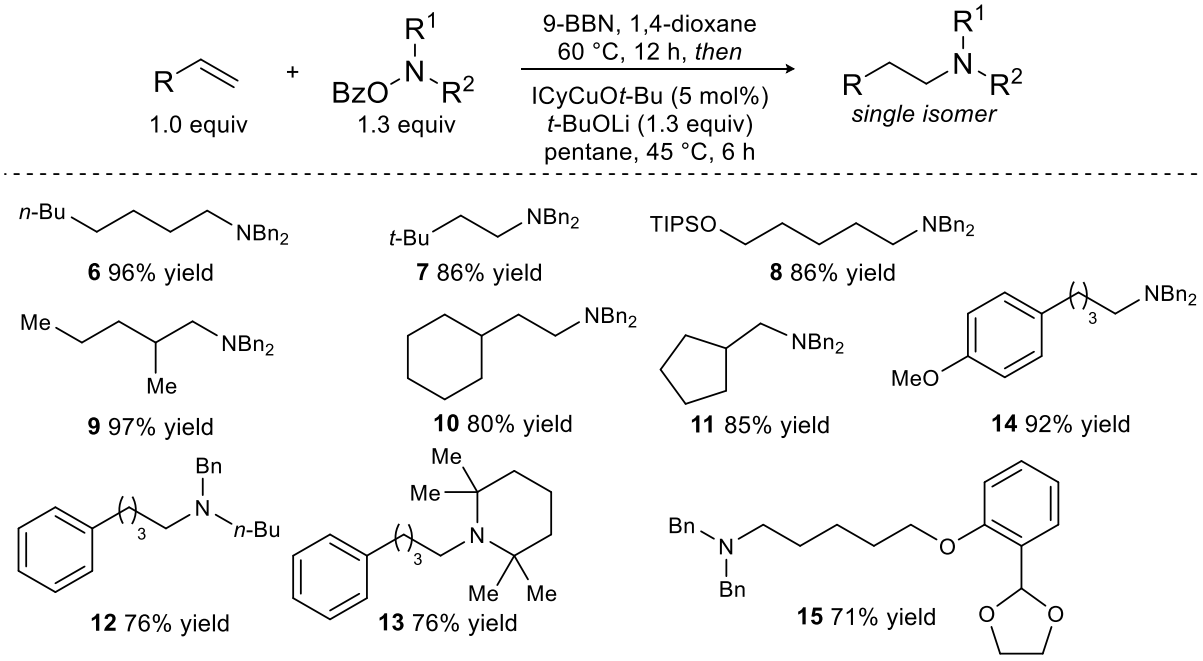
[34] In the absence of copper catalyst of the alkoxide additive, the hydroamination product was obtained in less than 5% yield.

[35] Reaction mixtures formed by adding lithium tert-butoxide to a 0.2 M solution of the electrophile in 1,4-dioxane or benzene at 45 °C are homogeneous, suggesting that the difference in reactivity is not simply a result of the difference in solubility of the alkoxide.

Based on these experiments, we were able to significantly improve the efficiency of the hydroamination procedure. In a reaction performed with lithium *tert*-butoxide instead of sodium *tert*-pentoxide, the desired product was obtained in 56% yield (Table 5.16, entry 3). Even higher yield (78%) was obtained when pentane was used as a co-solvent in the amination step of the reaction (entry 4). In a catalyst screen performed using the new reaction conditions, ICyCuCl (entries 5-8) was again identified as the best catalyst, and was used in further reaction optimization. Finally, if 1.3 equivalents of both the electrophile and alkoxide are used in the reaction, the desired product is obtained in 97% yield, as a single regioisomer.[32]

5.2.2 *Reaction Scope*

Table 5.17. Reaction Scope

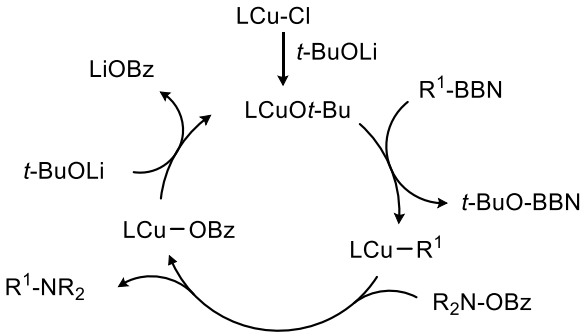


Using the optimized hydroamination procedure, a number of monosubstituted alkenes can be effectively converted to benzyl protected primary amines (Table 5.17). A variety of substituents on the alkene component are tolerated, including a sterically demanding *tert*-butyl substituent (see **7**). 2,2-Disubstituted alkenes can also be successfully used as substrates without

decrease in the yield of the desired product (see **9** and **11**). Finally, in addition to the protected primary amines, both benzyl-protected secondary amines (**12**) and tertiary amines, including the highly sterically-hindered tetramethyl piperidine derivative **13**, can be prepared using the same general procedure. A single regioisomer of the hydroamination product was obtained in all reactions.

5.2.3 *Mechanistic Studies*

Based on the results of the stoichiometric experiments and the mechanism of related copper-catalyzed reactions of organoboron compounds with other electrophiles, we propose that the copper-catalyzed amination of alkyl boranes proceeds by the mechanism shown in Scheme 5.2. According to this proposal, copper alkoxide, formed in the reaction with lithium *tert*-butoxide, reacts with alkyl borane to form an alkyl copper intermediate.[157,198-203] The intermediate reacts with *O*-benzoyl hydroxylamine to produce the amine product and copper carboxylate, which is converted to copper alkoxide in reaction with lithium *tert*-butoxide.[109]



Scheme 5.2. Proposed mechanism

Mechanistic studies of related reactions involving hydroxylamine derivatives and carbon-based nucleophiles suggest that electrophilic amination of the proposed organocopper intermediate may proceed by an S_N2 mechanism.[146] The most intriguing aspect of the proposed

mechanism is the presence of a neutral copper(I) alkyl intermediate in a reaction performed at a relatively high temperature. Such complexes are known to decompose quickly above −35 °C, [193,204] and to the best of our knowledge, there are no examples of fully characterized neutral copper(I) alkyl complexes containing β-hydrogen substituents. While similar intermediates have previously been proposed in copper-catalyzed reactions of alkyl boranes, there is little experimental evidence for their involvement.[198,199]

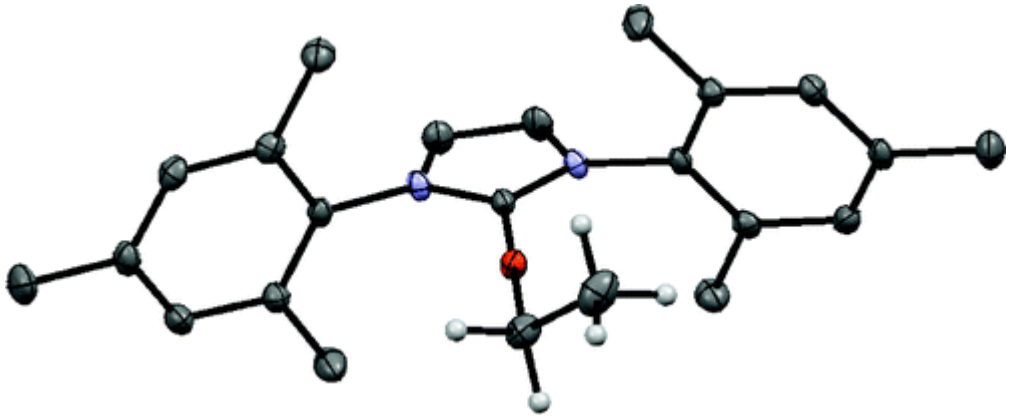
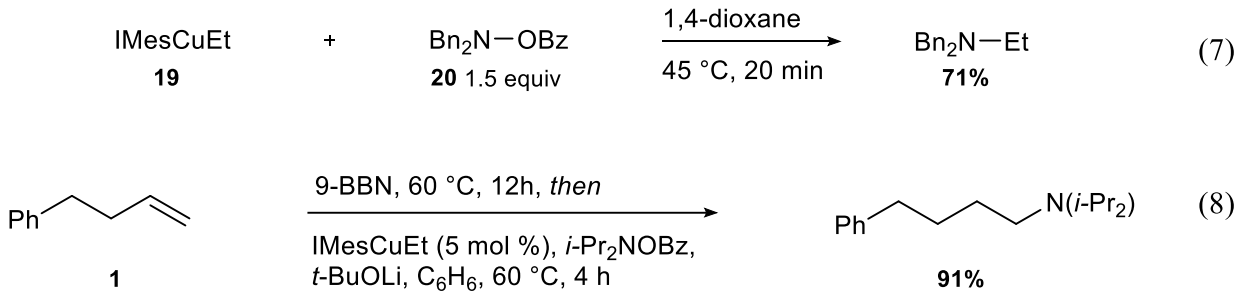


Figure 3. Crystal structure of IMesCuEt **(19)**

In an effort to explore the role of copper(I) alkyl complexes in the amination reaction, we prepared IMesCuEt (**19**) by addition of ethyllithium to IMesCuCl at low temperature. To our surprise, we were able not only to isolate the IMesCuEt complex, albeit in low yield (37%), but also to characterize it by X-ray diffraction (Figure 28). We discovered that the complex is stable in benzene for at least 4 h at 60 °C if kept in the dark. However, it decomposes quite readily at room temperature upon exposure to light (~50% conversion after 4 h).



Scheme 5.3. The role of 19 in the copper-catalyzed electrophilic amination reactions of organoboranes

We also showed that IMesCuEt reacts at 45 °C with electrophile **20** to produce the expected amination product in 71% yield (eq. 7 in Scheme 5.3). Furthermore, when **19** was used as the catalyst in the hydroamination of **1**, the desired product was obtained in 91% yield (eq. 8 in Scheme 5.3). The results of these experiments provide support for the proposed participation of neutral copper(I) alkyl complexes in the catalytic amination of alkyl boron compounds.

5.2.4 *Conclusion*

In conclusion, we have developed a practical protocol for anti-Markovnikov hydroamination of terminal alkenes. Using a one-pot hydroboration/electrophilic amination sequence, hydroamination products are obtained in good yield and with excellent regioselectivity. Considering the lack of alternative methods for anti-Markovnikov hydroamination of terminal alkenes, we expect this transformation to be of considerable utility in organic synthesis. Furthermore, we anticipate that copper-catalyzed electrophilic functionalization of alkyl boranes used in the hydroamination reaction will be useful in the development of other anti-Markovnikov hydrofunctionalization reactions, such as hydrocyanation and hydroazidation.)

5.3 EXPERIMENTAL

5.3.1 *General*

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Ion Exchange Chromatography was performed using analytical grade cation exchange resin from sulfonic acid functionalized styrene (Bio-Rad Laboratories, 200-400 mesh, 5.2 meq/g). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

Materials

Toluene and benzene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. All other solvents were used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., TCI Chemicals USA, or STREM Chemicals, Inc., and were used as received, except for 9-BBN (9-borabicyclo[3.3.1]nonane) dimer, which was recrystallized from dimethoxyethane (glyme).

O-benzoyl-*N*,*N*-dialkyl hydroxylamines were synthesized according to a literature procedure.[36] Terminal alkenes were all commercially available with the exception of triisopropyl(pent-4-en-1-yloxyl)silane,[37] 1-(but-3-en-1-yl)-4-methoxybenzene,[38] 1-bromo-4-(but-3-en-1-yl)benzene,[39] and 2-(2-(pent-4-en-1-yloxy)phenyl)-1,3-dioxolane,[40] which were prepared according to literature procedures.

5.3.2 *Reaction optimization*

5.3.2.1 *Hydroboration of Terminal Alkenes:*

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv), alkene (1.00 equiv), and solvent. The vial was capped and heated at 60℃ with stirring for 12 h.

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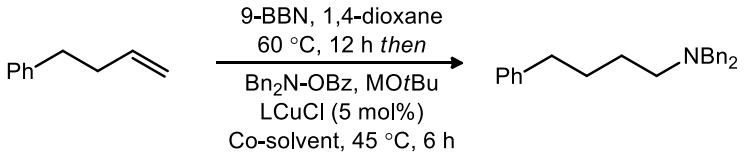
[36] Rucker, R. P., Whittaker, A. M., Dang, H., Lalic, G. *Angew. Chem. Int. Ed.* **2012**, *xxx*, xxx-xxx.
[37] Procedure: Huang, J.; Wu, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 13366-13367. Spectral Data: Phukan, P.; Bauer, M.; Maier, M. E. *Synthesis*, **2003**, *9*, 1324-1328.
[38] Procedure: Gary A. Molander and Deidre L. Sandrock. *J. Am. Chem. Soc.* **2008**, *130*, 15792-15793. Spectral Data: Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294-9295.
[39] Gary A. Molander and Deidre L. Sandrock. *J. Am. Chem. Soc.* **2008**, *130*, 15792-15793.
[40] Coulter, M.M.; Dornan, P.K.; Dong, V.M. *J. Am. Chem. Soc.* **2009**, *131*, 6932-6933.

5.3.2.2 *Using O-benzoyl-N,N-dibenzyl hydroxylamine:*

In a glove box, 4-phenylbut-1-ene (1.00 equiv, 0.017 mL, 0.110 mmol) was subjected to the standard hydroboration conditions described above using 9-BBN dimer (0.50 equiv, 13.4 mg, 0.055 mmol), *n*-dodecane as internal standard, and 1,4-dioxane (0.20 mL, [alkene] = 0.55 M). After 12 h at 60℃, the reaction vial was allowed to reach room temperature, and MO*t*Bu (M = Na, K, Li; 1.00 equiv, 0.110 mmol), copper catalyst (0.05 equiv, 0.006 mmol), *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.00 equiv, 36.2 mg, 0.110 mmol), 1,4-dioxane (0.075 ml) and the reaction co-solvent (0.275 ml) were added as indicated in **Table 5.18**. The vial was capped and stirred at 45 °C for 6 h. Yield of the desired product was determined by gas chromatography using *n*-dodecane as an internal standard.

Table 5.18. Reaction optimization

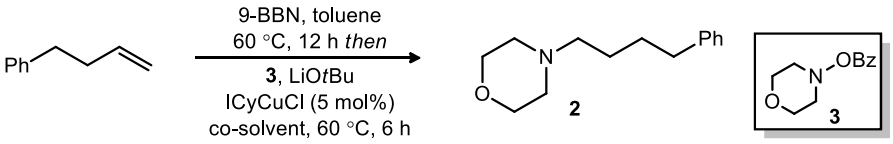


Entry[a]	M	L	Co-solvent	Yield[b]
1.	Na	IMes	1,4-dioxane	< 5%
2.	Na	ICy	1,4-dioxane	16%
3.	K	ICy	1,4-dioxane	11%
4.	Li	ICy	1,4-dioxane	56%
5.	Li	ICy	pentane	78%
6.	Li	IMe	pentane	39%
7.	Li	IAdm	pentane	43%
8.	Li	IPr	pentane	<5%
9.[c]	Li	xantphos	pentane	<5%
10.[d]	Li	ICy	pentane	97%

[a] All reactions conducted with 1.0 equiv each Bn_2N-OBz and MO*t*Bu at 0.2 M concentration. [b] Yield determined by GC analysis using *n*-dodecane as internal standard. [c] Catalyst formed in situ from xantphos and $(CuOtBu)_4$. [d] After 3 h, 0.3 equiv each Bn_2N-OBz and LiO*t*Bu was added to the reaction mixture.

5.3.2.3 Using 4-benzoyloxymorpholine:

Table 5.19. Further reaction optimization



Entry[a]	Reaction Concentration (M)	**S2** Add'n Time (h)	Co-solvent	Yield[b]
1.[c,d]	0.20	N/A[d]	pentane	< 5%
2.[c,e]	0.20	6	pentane	52%
3.[c]	0.20	6	1,4-dioxane	78%
4.	0.35	6	toluene	74%
5.	0.20	6	toluene	85%
6.	0.10	6	toluene	86%
7.[f]	0.10	6	toluene	90%
8.[f]	0.05	3	toluene	99%

[a] Unless otherwise specified, all reactions conducted with 1.3 equiv each **3** and LiO*t*Bu. [b] Yield determined by GC analysis of crude reaction mixture obtained after initial workup described in the Optimization Text. [c] 1,4-Dioxane substituted for toluene as hydroboration solvent. [d] Reaction was conducted according to procedure outlined in **Table S1**. [e] Reaction temperature = 45 °C. [f] 1.1 equiv each **S2** and LiO*t*Bu were used.

For all optimization reactions, 4-phenylbut-1-ene (1.00 equiv, 0.060 mL, 0.400 mmol) was subjected to the standard hydroboration conditions described above using 9-BBN dimer (0.50 equiv, 48.8 mg, 0.400 mmol) and solvent (1.00 mL, 0.40 M). After 12 h at 60℃, the dram vial was allowed to reach room temperature, and the contents were transferred to a 15 mL Schlenk tube. To the resulting solution was added lithium *tert*-butoxide (1.3 equiv, 41.6 mg, 0.520 mmol), ICyCuCl (0.05 equiv, 6.6 mg, 0.020 mmol), and solvent. Separately, a stock solution of the electrophile was prepared (0.400 mL of reaction co-solvent) and taken up in a gas-tight syringe (500 µL size). The Schenk tube assembly was put on the manifold using standard air-free techniques. The electrophile was added over the period indicated in **Table 5.19** to the stirred reaction mixture at 60 °C. After addition of the electrophile, the reaction was stopped and

allowed to cool to room temperature. The crude product was isolated by diluting the reaction mixture with ether (5 mL) and then washing with aqueous saturated $NaHCO_3$ solution. The aqueous layer was then extracted with diethyl ether (2 x 10 mL), and the combined organic fractions were dried over sodium sulfate. After filtering, 1,3-dinitrobenzene was added as an internal standard to the ether solution, and the yield of the product was determined by GC analysis of an aliquot of this solution.

5.3.3 *Reactions of O-benzoyl-N,N-dibenzyl hydroxylamine with sodium tert-pentoxide and lithium tert-butoxide.*

For the following reactions, conversion of *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. To obtain data for each time point in **Table 5.20**, aliquots (0.05 mL) were withdrawn from the reaction mixture and were diluted to 0.50 mL with benzene-d^6.

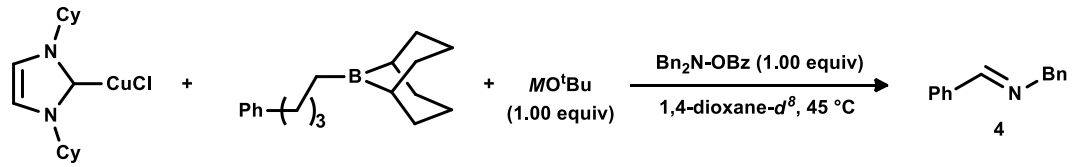
Entries 1, *4*, and *6*: In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added either LiO^tBu or NaO^tBu (1.00 equiv, 0.110 mmol), 1,3,5-trimethoxybenzene as an internal standard, and 1,4-dioxane-d^8 (0.35 mL). To the resulting mixture was added *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.00 equiv, 0.110 mmol) and 1,4-dioxane-d^8 (0.15 mL). The resulting mixture was capped and heated to 45 ℃ under stirring.

Entries 2 and *7*: The reactions were set up exactly as described for *Entries 1* and *4* except that ICyCuCl catalyst (0.05 equiv, 0.006 mmol) was added before addition of *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine.

Entries 3, *5*, and *8*: In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv, 13.4 mg, 0.055 mmol) , 4-phenyl-but-1-ene (1.00 equiv,

1.65x10^{-2} mL, 0.110 mmol), and 1,4-dioxane-d^8 (0.20 mL, 0.5 M). The vial was heated at 60 ℃ for 12 h and then cooled to room temperature. To the resulting solution was added either LiO^{t}Bu or NaO^{t}Bu (1.00 equiv, 0.110 mmol), 1,3,5-trimethoxybenzene, *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.00 equiv, 0.110 mmol) and 1,4-dioxane-d^8 (0.30 mL). The resulting mixture was capped and heated to 45 ℃ with stirring

Table 5.20. Imine formation



Entry[a]	ICyCuCl (mol%)	9-(4-phenylbutyl)-9-borabicyclo[3.3.1]nonane (equiv)	*M*	% conversion of Bn$_2$N-OBz (min) 10	30	60	120	1020
1	0	0	Li	7	14	37	53	100
2	5	0	Li	35	50	61	71	100
3	0	1.00	Li	2	17	32	49	100
4[b]	0	0	Li	0	NA	NA	5	NA
5[b]	0	1.00	Li	0	NA	NA	2	NA
6	0	0	Na	93	100	100	100	100
7	5	0	Na	100	100	100	100	100
8	0	1.00	Na	50	67	74	81	100

[a] All reaction concentrations are 0.2 M. [b] Benzene-d^6 was used as reaction solvent.

5.3.4 *Hydroamination of terminal alkenes*

General procedure:

In a glove box, a one-dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv, 48.8 mg 0.200 mmol), toluene (1.00 mL, 0.40 M), and the alkene (1.00 equiv, 0.400 mmol). After 12 h at 60 °C, the reaction mixture was cooled to room temperature and

transferred to a 15 mL Schlenk tube. To the resulting solution was added lithium *tert*-butoxide (1.10 equiv, 35.2 mg, 0.440 mmol), ICyCuCl (0.05 equiv, 6.6 mg, 0.020 mmol), and toluene (6.60 mL, 7.60 mL total volume, 0.05 M). Separately, a stock solution of the electrophile was prepared (0.400 mL of reaction co-solvent) and taken up in a gas-tight syringe (500 µL size). The Schenk tube assembly was put on the manifold using standard air-free techniques. The electrophile was added over 4 h to the stirred reaction mixture at 60 °C. After addition of the electrophile, the reaction was allowed to stir at 60 °C and the consumption of electrophile was monitored by tlc. Upon complete consumption of the electrophile, the reaction was cooled to room temperature. The crude product was isolated by diluting the reaction mixture with ether (5 mL) and then washing with aqueous saturated $NaHCO_3$ solution. The aqueous layer was then extracted with diethyl ether (2 x 10 mL), and the combined organic fractions were dried over sodium sulfate. After filtration and removal of the solvent under reduced pressure, the crude product was obtained as an oil, which was further purified according to one of the following three procedures:

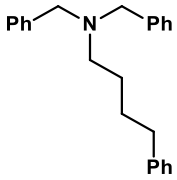
Purification Procedure **A**: Acid/Base Extraction

The crude product was transferred to a 60 mL separatory funnel using 2.5 mL portions of diethyl ether and hexane (5 mL total volume). The organic layer was extracted three times with 5 mL of a 3 M aqueous HCl solution. The organic layer was discarded. The *p*H of the aqueous layer was adjusted by dropwise addition of an aqueous 3 M NaOH solution until *p*H 10 was achieved. The resulting solution was then extracted three times with 10 mL portions of dichloromethane. The organic extracts were washed with 5 mL of saturated brine and then dried over sodium sulfate. Upon filtration and removal of solvent, the purified tertiary amine product was obtained as an oil.

Purification Procedure **B**: Acid-sensitive functional groups, such as the *tert*-butyl carbamate (BOC)-protected amine used in product **8**, and the tris(isopropyl)siloxy (TIPS)-protected alcohol used in product **9**, require the substitution of a weaker acid in place of aqueous HCl. This is readily accomplished by use of an aqueous 3 M sodium acetate and acetic acid solution buffered at *p*H 4. The purification procedure is identical to A except for this substitution.

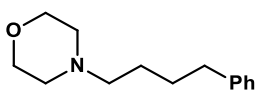
Purification Procedure **C**: Ion-Exchange Chromatography

The crude product was loaded on the cation exchange resin (200 mg resin/mmol product) using MeOH. The resin was subsequently washed with 4 CV of 2% dichloromethane in MeOH, then with 4 CV of 20% Et_3N in MeOH to elute the product.



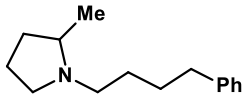
***N,N*-dibenzyl-4-phenylbutan-1-amine (S1)**

Compound was isolated as a colorless oil (147.5 mg, 90% yield) after purification by silica gel column chromatography (0 → 30% benzene/hexanes over 3 CV, then 0 → 15% Et_2O/hexanes over 7 CV). ^{1}H NMR (300 MHz, C_6D_6) δ 7.37 (d, J = 7.4 Hz, 4H), 7.28 – 6.90 (m, 11H), 3.41 (s, 4H), 2.52 – 2.27 (m, 4H), 1.60 – 1.26 (m, 4H). ^{13}C NMR (125 MHz, C_6D_6) δ 142.8, 140.4, 129.1, 128.8, 128.6, 128.5, 127.2, 126.0, 58.8, 53.3, 35.9, 29.2, 26.9. HRMS calculated for $[M]^+$ 330.2212, found 330.2217. FTIR (neat, cm^{-1}): 3084(w), 2933(m), 1494(m), 1452(m), 1028(w).



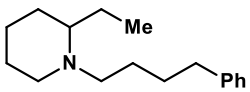
4-(4-phenylbutyl)morpholine (Table 2, 4)

Compound was isolated as a colorless oil (82.8 mg, 94% yield) after purification by ion exchange chromatography. Reaction time was 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 2H), 7.30 – 7.10 (m, 3H), 3.88 – 3.65 (m, 4H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.59 – 2.32 (m, 6H), 1.84 – 1.45 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 128.5, 128.4, 125.8, 67.1, 59.1, 53.9, 35.9, 29.4, 26.3. HR-MS calculated for $[M+H]^+$ 220.1701, found 220.1693. FTIR (neat, cm^{-1}): 3083(w), 3024(w), 2935(s), 1603(w), 1453(s), 1118(s).



2-methyl-1-(4-phenylbutyl)pyrrolidine (Table 2, 5)

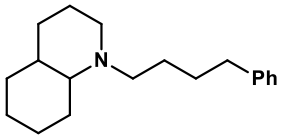
Compound was isolated as a colorless oil (73.1 mg, 84% yield) after purification by ion exchange chromatography. Reaction time was 3 h. ^{1}H NMR (300 MHz, MeOD) δ 7.39 – 7.05 (m, 5H), 3.24 – 3.00 (m, 1H), 2.94 – 2.73 (m, 1H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.49 – 2.25 (m, 1H), 2.25 – 1.85 (m, 3H), 1.87 –3 1.34 (m, 7H), 1.11 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 128.6, 128.4, 125.8, 60.5, 54.2, 54.1, 36.0, 32.8, 29.8, 28.5, 21.7, 19.0. HRMS calculated for $[M+H]^+$ 218.1908, found 218.1915. FTIR (neat, cm^{-1}): 3062(w), 3025(w), 2936(s), 1603(w), 1453(s), 1374(m), 746(s).



2-ethyl-1-(4-phenylbutyl)piperidine (Table 2, 6)

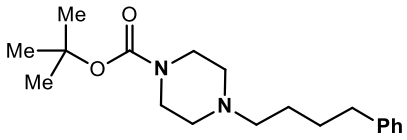
Compound was isolated as a colorless oil (89.6 mg, 91% yield) after acid base extraction **A**. Reaction time was 3 h. ^{1}H NMR (300 MHz, MeOD) δ 7.43 – 7.00 (m, 5H), 2.96 – 2.80 (m, 1H), 2.79 – 2.57 (m, 3H), 2.57 – 2.42 (m, 1H), 2.42 – 2.15 (m, 2H), 1.82 – 1.44 (m, 9H), 1.44 – 1.21 (m, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 142.1, 128.1, 128.0, 125.4, 61.7, 52.8, 51.7, 35.3, 29.2, 28.7, 24.5, 23.8, 23.2, 23.0, 9.2. HRMS calculated for $[M+H]^+$

246.2221, found 246.2215. FTIR (neat, cm^{-1}): 3054(w), 2933(s), 1734(m), 1437(s), 1265(s), 738(s).



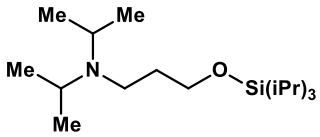
1-(4-phenylbutyl)decahydroquinoline (Table 5.17, 7)

Compound was isolated as a colorless oil (105.8 mg, 97% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.33 – 7.18 (m, 2H), 7.15 – 7.05 (m, 3H), 2.93 – 2.82 (m, 1H), 2.78 – 2.60 (m, 1H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.35 – 2.12 (m, 1H), 2.12 – 1.94 (m, 2H), 1.83 – 1.31 (m, 11H), 1.30 – 1.05 (m, 4H), 1.06 – 0.76 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 143.0, 128.8, 128.6, 126.0, 66.8, 54.2, 52.9, 42.6, 36.3, 33.6, 33.3, 30.9, 29.9, 26.6, 26.5, 26.2, 26.0. HR-MS calculated for $[M+H]^+$ 272.2378, found 272.2378. FTIR (neat, cm^{-1}): 3062(w), 3026(m), 2921(s), 1603(w), 1447(m), 1239(m), 698(s).



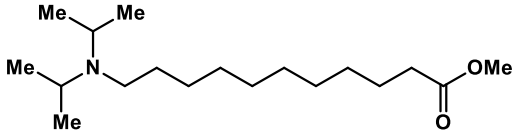
***tert*-butyl 4-(4-phenylbutyl)piperazine-1-carboxylate (Table 5.17, 8)**

Compound was isolated as a pale yellow oil (119.7 mg, 94% yield) after purification by acid/base extraction **B**. Reaction time was 4 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 2H), 7.07 (t, *J* = 7.1 Hz, 3H), 3.38 – 3.25 (m, 4H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.36 – 2.13 (m, 6H), 1.60 – 1.39 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, C_6D_6) δ 154.7, 142.8, 128.7, 128.7, 126.1, 79.0, 58.5, 53.3, 46.2, 44.6, 43.7, 36.1, 29.4, 28.5, 26.7. HR-MS calculated for $[M+H]^+$ 319.2385, found 319.2392. FTIR (neat, cm^{-1}): 3062(w), 3026(m), 2933(s), 1688(s), 1442(m), 1247(m), 1171(m), 1123(m), 1006(m).



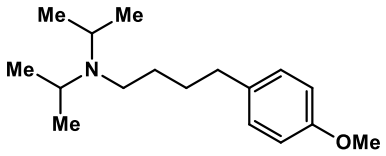
***N*,*N*-diisopropyl-3-((triisopropylsilyl)oxy)propan-1-amine (Table 5.17, 9)**

Compound was isolated as a pale yellow oil (101.0 mg, 80% yield) after purification by acid/base extraction **B**. Reaction time was 6 h. ^{1}H NMR (300 MHz, C_6D_6) δ 3.74 (t, *J* = 6.2 Hz, 2H), 3.07 – 2.85 (m, 2H), 2.68 – 2.47 (m, 2H), 1.80 – 1.65 (m, 2H), 1.21 – 1.10 (m, 21H), 1.00 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 70.7, 62.0, 48.5, 41.6, 34.8, 32.4, 26.7, 22.5, 21.0, 18.4, 12.4. HR-MS calculated for $[M+H]^+$ 316.3035, found 316.3045. FTIR (neat, cm^{-1}): 2962(s), 2865(s), 1464(m), 1106(s).



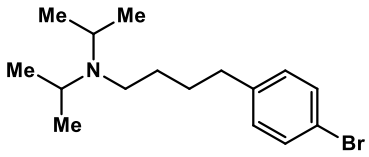
methyl 11-(diisopropylamino)undecanoate (Table 5.17, 10)

Compound was isolated as a colorless oil (96.8 mg, 81% yield) after purification by acid/base extraction **A**. Reaction time was 6 h. ^{1}H NMR (300 MHz, C_6D_6) δ 3.46 (s, 3H), 3.15 – 2.97 (m, 2H), 2.60 – 2.41 (m, 2H), 2.30 – 2.15 (m, 2H), 1.79 – 1.54 (m, 4H), 1.47 – 1.18 (m, 12H), 1.10 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 173.3, 50.9, 48.3, 45.1, 34.2, 31.7, 30.2, 30.1, 29.9, 29.7, 29.5, 28.2, 27.8, 25.3, 21.1. HR-MS calculated for $[M+H]^+$ 300.2902, found 300.2913. FTIR (neat, cm^{-1}): 2928(s), 2855(m), 1743(s), 1465(m), 1204(m), 1172(m).



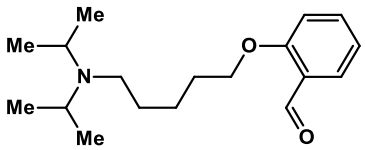
***N*,*N*-diisopropyl-4-(4-methoxylphenyl)butan-1-amine (Table 5.17, 11)**

Compound was isolated as a pale yellow oil (88.7 mg, 84% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.06 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.34 (s, 3H), 2.92 (hept, *J* = 6.6 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.55 (m, 2H), 1.54 – 1.35 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 158.5, 135.1, 129.6, 114.2, 54.8, 48.1, 44.7, 35.5, 30.9, 29.8, 21.0. HR-MS calculated for $[M+H]^+$ 264.2327, found 264.2339. FTIR (neat, cm^{-1}): 3033(w), 2962(s), 1751(w), 1465(m), 1245(s), 1039(m).



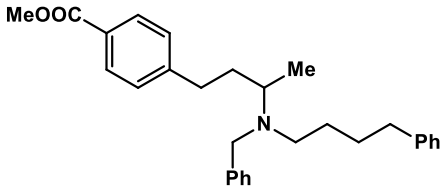
4-(4-bromophenyl)-*N*,*N*-diisopropylbutan-1-amine (Table 5.17, 12)

Compound was isolated as a pale yellow oil (104.7 mg, 84% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 2.99 – 2.76 (m, 2H), 2.39 – 2.21 (m, 4H), 1.53 – 1.26 (m, 4H), 0.95 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 131.6, 130.5, 119.8, 48.1, 44.6, 35.6, 30.7, 29.2, 21.0. HR-MS calculated for $[M+H]^+$ 312.1326, found 312.1320. FTIR (neat, cm^{-1}): 3035(w), 2963(s), 1892(w), 1751(w), 1488(m), 1072(m), 1011(m), 829(m), 677(m).



2-((5-(diisopropylamino)pentyl)oxy)benzaldehyde (Table 5.17, 13)

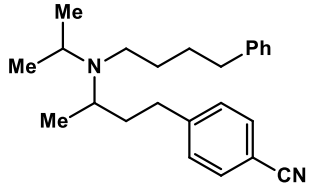
Compound was isolated as a colorless oil (123.9 mg, 92% yield) after purification by acid/base extraction **A**. Reaction time was 5 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.52 (d, *J* = 0.8 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.10 – 6.89 (m, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.40 (s, 2H), 2.11 – 1.77 (m, 2H), 1.48 (d, *J* = 7.1 Hz, 4H), 1.00 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 161.7, 136.0, 128.3, 125.0, 120.6, 112.6, 68.6, 48.5, 45.2, 31.3, 29.2, 24.0, 20.8. HR-MS calculated for $[M+H]^+$ 292.2276, found 292.2281. FTIR (neat, cm^{-1}): 3076(w), 2952(s), 2811(w), 2758(w), 1694(s), 1458(m), 1243(m), 1042(m).



methyl 4-(3-(benzyl(4-phenylbutyl)amino)butyl)benzoate (Table 5.17, 14)

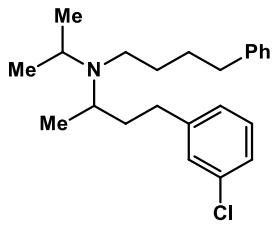
Compound was isolated as a colorless oil (161.0 mg, 94% yield) after purification by column chromatography (0-30% ethyl acetate in hexanes over 8 CV). Reaction time was 4 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 2H), 7.27 – 7.19 (m, 4H), 7.16 – 7.07 (m, 4H), 6.95 (d, *J* = 8.3 Hz, 2H), 3.60 – 3.52 (m, 4H), 3.21 (d, *J* = 13.9 Hz, 1H), 2.75 – 2.54 (m, 2H), 2.43 – 2.35 (m, 4H), 2.28 – 2.14 (m, 1H), 1.70 – 1.25 (m, 6H), 0.80 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 148.7, 142.7, 141.3, 129.7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.6, 126.6, 125.6, 54.1, 53.4, 52.0, 49.1, 35.9, 35.8, 33.4, 29.2, 28.3, 13.5.

HRMS calculated for $[M+H]^+$ 430.2746, found 430.2735. FTIR (neat, cm^{-1}): 3061(w), 3026(w), 2929(s), 1721(s), 1609(m), 1453(m), 1279(s), 738(m).



4-(3-(isopropyl(4-phenylbutyl)amino)butyl)benzonitrile (Table 5.17, 15)

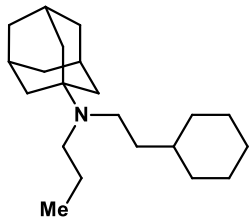
Compound was isolated as a colorless oil (124.8 mg, 90% yield) after acid/base extraction **A**. Reaction time was 8 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.16 (m, 7H), 3.15 – 2.90 (m, 1H), 2.82 – 2.75 (m, 2H), 2.67 – 2.32 (m, 5H), 1.78 – 1.32 (m, 6H), 1.12 – 0.90 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 142.9, 132.2, 129.3, 128.5, 128.4, 125.8, 119.4, 109.4, 51.9, 48.0, 44.4, 37.6, 36.1, 34.0, 30.1, 29.5, 22.7, 19.6, 17.5. HRMS calculated for $[M+H]^+$ 349.2643, found 349.2646. FTIR (neat, cm^{-1}): 3086(w), 2961(s), 2226(m), 1606(s), 1453(s), 1152(m), 737(m).



***N*-(4-(3-chlorophenyl)butan-2-yl)-*N*-isopropyl-4-phenylbutan-1-amine (Table 5.17, 16)**

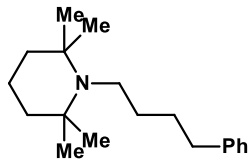
Compound was isolated as a colorless oil (108.6 mg, 76% yield) after purification by column chromatography (0-20% MeOH in CH_2Cl_2 over 8 CV with 0.1% acetic acid as an additive) followed by acid/base extraction **A**. Reaction time was 6 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.21 – 7.10 (m, 5H), 6.96 – 6.90 (m, 2H), 2.92 – 2.86 (m, 1H), 2.78 – 2.54 (m, 4H), 2.48 – 2.24 (m, 3H), 1.86 – 1.24 (m, 6H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 146.6, 143.9, 135.0, 130.8, 129.5,

129.4, 129.3, 127.8, 126.7, 126.6, 53.3, 49.5, 45.8, 38.3, 36.9, 31.0, 30.5, 22.5, 20.1, 17.4. HRMS calculated for $[M+H]^+$ 358.2301, found 358.2296. FTIR (neat, cm^{-1}): 3062(w), 2961(s), 1597(m), 1453(m), 1079(w), 908(s), 733(s).



***N*-(2-cyclohexylethyl)-*N*-propyladamantan-1-amine (Table 5.17, 17)**

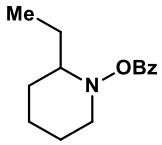
Compound was isolated as a colorless oil which solidified upon standing (101.2 mg, 83% yield) after acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 2.66 – 2.54 (m, 2H), 2.54 – 2.39 (m, 2H), 2.02 (s, 3H), 1.85 – 1.39 (m, 20H), 1.39 – 1.10 (m, 3H), 1.04 – 0.84 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.5, 46.2, 40.0, 37.0, 36.8, 36.5, 33.7, 29.8, 29.7, 26.8, 26.5, 12.1, 12.0. ESI-MS calculated for $[M+H]^+$ 304.3, found 304.3. FTIR (neat, cm^{-1}): 2917(s), 2849(s), 1447(m), 1084(s) 1154(m).



2,2,6,6-tetramethyl-1-(4-phenylbutyl)piperidine (Table 5.17, 18)

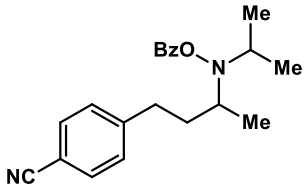
Compound was isolated as a colorless oil (93.7 mg, 86% yield) after purification by acid/base extraction **A**. Reaction time was 4 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.25 – 7.13 (m, 2H), 7.13 – 7.04 (m, 3H), 2.53 (t, J = 7.4 Hz, 2H), 2.45 – 2.25 (m, 2H), 1.69 – 1.28 (m, 10H), 1.01 (s, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ 143.1, 128.7, 128.6, 126.0, 54.5, 45.3, 41.6, 36.4, 36.1, 29.7, 27.7, 18.2. HRMS calculated for $[M]^+$ 274.2535, found 274.2527. FTIR (neat, cm^{-1}): 3082(w), 2928(s), 1377(m), 1262(m), 1129(m).

5.3.5 *Synthesis of O-benzoyl Hydroxylamines:*



2-ethylpiperidin-1-yl benzoate (S2)

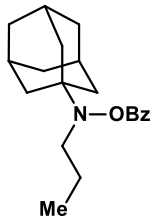
Compound was isolated as a colorless oil (880.0 mg, 78% yield) after purification by column chromatography (0-20% ethyl acetate in hexanes over 8 CV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.1 Hz, 2H), 7.15 – 6.95 (m, 3H), 3.60 – 3.49 (m, 1H), 2.46 – 2.62 (m, 2H), 1.73 – 1.28 (m, 8H), 1.03 – 0.77 (d, *J* = 36.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 132.9, 129.6, 129.4, 128.4, 68.1, 58.1, 30.0, 25.9, 25.5, 23.7, 9.6. HRMS calculated for $[M+H]^+$ 234.1494, found 234.1493. FTIR (neat, cm^{-1}): 3062(w), 2938(s), 1740(s), 1451(m), 1244(s), 708(s).



***O*-benzoyl-*N*-(4-(4-cyanophenyl)butan-2-yl)-*N*-isopropylhydroxylamine (S3)**

Compound was isolated as a colorless oil (1443.3 mg, 53% yield) after removal of the amine through ion exchange chromatography followed by purification by column chromatography (0-20% diethyl ether in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 8.11 (d, *J* = 8.2, 2H), 7.15 – 6.95 (m, 5H), 6.83 (d, *J* = 8.0 Hz, 2H), 3.16 – 3.02 (m, 2H), 2.92 – 2.60 (m, 1H), 2.74 – 2.54 (m, 1H), 1.75 – 1.43 (m, 1H), 1.44 – 1.28 (m, 1H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 148.3, 133.1, 132.1, 129.5, 129.4, 128.5, 128.3, 119.1, 109.5, 57.0, 53.7, 53.5, 36.4, 32.7, 20.6, 12.5. HRMS calculated for

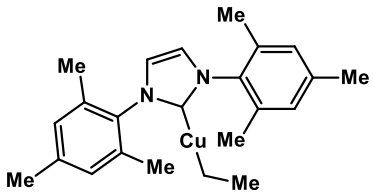
$[M+H]^+$ 337.1916, found 337.1899. FTIR (neat, cm^{-1}): 3062(w), 2977(s), 2226(m), 1743(s), 1606(w), 1245(s), 709(s).



***O*-benzoyl-*N*-(adamantan-1-yl)-*N*-propylhydroxylamine (S4)**

Compound was isolated as a colorless oil (683.8 mg, 37% yield), which solidified upon standing, after purification by column chromatography (0 – 10% Et_2O in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H), 7.60 – 7.53 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 2.99 – 2.86 (m, 2H), 2.10 (s, 3H), 1.90 – 1.80 (m, 6H), 1.71 – 1.59 (m, 6H), 1.57 – 1.45 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ 165.6, 132.8, 130.6, 129.8, 128.7, 60.2, 51.7, 38.6, 36.9, 29.7, 21.6, 12.1. ESI-MS calculated for $[M+Na]^+$ 336.2, found 336.2. FTIR (neat, cm^{-1}): 3045(m), 2911(s), 1739(s), 1265(s), 740(s).

5.3.6 *Synthesis of (IMes)Cu(Et)* ***(19)***



(ethyl)[1,2-dihydro-1,3-bis(2,4,6-trimethylphenyl)-2H-imidazol-2-ylidene]-Copper

The title compound was synthesized according to a modified literature procedure.[41] A 15 mL Schlenk bomb was charged with a stir bar and flame-dried under vacuum. The flask was then

[41] Goj, L. A.; Blue, E.D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* 2006, *22*, 9032-9045.

transferred into a glove box and IMesCuCl (1.0 equiv, 400 mg, 1.0 mmol) followed by THF (8.0 mL, 0.1 M) were added. Out of the glove box, the flask was cooled to -78 °C at which point ethyl lithium (1.0 equiv, 2.0 mL, 1.0 mmol) was added dropwise over 30 min. The reaction was allowed to stir for 1 h before warming to 0 °C. The reaction was transfered into the glove box, and stirred at 20 °C for 10 min and the mixture was filtered through a pad of celite. The solvent was then removed and toluene (10 mL) was added to the dark brown solid which was stirred for 10 min before 20 mL of pentane was added. The mixture was filtered through a pad celite and concentrated to dryness. The resulting brown solution was taken up in THF (ca. 5 mL) and pentane was added until the solution became cloudy (ca. 20 mL). The mixture was filtered through a pad of celite, resulting in a transparent solution, and a white powder upon concentration (144 mg, 37% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 6.86 (s, 4H), 6.16 (s, 2H), 2.21 (s, 6H), 2.17 (s, 12H), 1.80 (t, J = 8.0 Hz, 3H), 0.70 (q, J = 8.0 Hz, 2H). ^{13}C NMR (126 MHz, THF-d^8) δ 183.9, 138.3, 136.2, 134.7, 128.8, 121.5, 20.2, 17.2, 13.4, 0.6. Crystals suitable for x-ray analysis were obtained by vapor diffusion of pentane into a saturated solution of THF. Upon exposure of a solution of IMesCuEt in C_6D_6 to ambient light at 25 °C in a sealed NMR tube, 50% decomposition was observed. The decomposition was indicated by ^{1}HNMR upon the disappearance of the ethyl signals and the appearance of a signal corresponding to ethane. Alternatively, at 60 °C in a sealed NMR tube protected from light, no decomposition of IMesCuEt was observed after 4 h. However, complete decomposition occurred after 24 h.

5.3.7 *Stoichiometric Reaction of IMesCu(Et) (Equation 2):*

In a glove box, a 1 dram vial was charged with a stir bar. To the vial was added *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.50 equiv, 11.7 mg, 0.037 mmol) and 1,4-dioxane-d^8 (0.25 mL). Separately, to a shell vial was added IMesCu-Et (1.0 equiv, 9.8 mg, 0.025 mmol) and 1,4-

dioxane-d^8 (0.25 mL). The resulting solution was then added dropwise over 10 min to the reaction vial containing *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine with stirring at 45℃. After 1 h 1,3,5-trimethoxybenzene as internal standard was added and the reaction yield was determined by NMR comparison against 1,3,5-trimethoxybenzene.

5.3.8 *Hydroamination of phenyl butene using IMesCu(Et) as a catalyst (Equation 3):*

In a glove box, a one-dram vial was charged with a stir bar. To the vial was added 9-BBN dimer (0.50 equiv, 12.2 mg 0.050 mmol), toluene (0.20 mL, 0.40 M), and phenyl butene (1.00 equiv, 13.2 mg, 0.100 mmol). After 12 h at 60 °C, the reaction mixture was cooled to room temperature and lithium *tert*-butoxide (1.10 equiv, 8.8 mg, 0.110 mmol), *O*-benzoyl-*N*,*N*-dibenzyl hydroxylamine (1.10 equiv, 24.3 mg, 0.110 mmol), and toluene (1.3 mL) were added. Finally IMesCuEt (0.050 equiv, 2.0 mg, 0.005 mmol) in toluene (0.5 mL, 2.0 mL total) was added dropwise over 1 min at 60 °C. The reaction vial was capped and allowed to stir at 60 °C for 4 h before 1,3,5-trimethoxybenzene as internal standard was added and the reaction yield was determined by GC analysis.

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Author's Note:

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