Copper Catalysis in Organic Synthesis of Alkyl Fluorides, Sterically Hindered Anilines, and 1,4-Dienes

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Abstract

Copper-Catalyzed Synthesis of Alkyl Fluorides, Sterically Hindered Anilines, and 1,4-Dienes

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Copper is a versatile transition metal and has been used as a catalyst for constructing a variety of bonds in organic synthesis. It is relatively abundant, cheap, and less toxic than other transition metals, making it an advantageous catalyst. Presented in this thesis are three new copper-catalyzed reactions for the preparation of alkyl fluorides, sterically hindered anilines, and 1,4-dienes. These classes of compounds can be found in nature and have important application in medicinal chemistry and the pharmaceutical industry. Finally, we have also demonstrated the utility of these reactions in the construction of useful organic compounds.

Chapter 1 describes the copper-catalyzed fluorination of alkyl triflates for the synthesis of alkyl fluorides. This reaction uses a transition-metal complex as an efficient phase-transfer catalyst under mild reaction conditions. No elimination byproducts were observed when using the optimized reaction conditions. This addresses a long standing issue in alkyl fluoride synthesis.

Chapter 2 describes the copper-catalyzed coupling of aryl boronic esters with *O*-benzoyl hydroxylamines for the synthesis of sterically hindered *N*,*N*-dialkyl anilines and *N*-alkyl anilines. This reaction uses an air stable and commercially available precatalyst and a mild turn over reagent, thus making this reaction a practical method to synthesize anilines.

Chapter 3 describes the anti-Markovnikov hydroallylation of terminal alkynes and nonsymmetrical dialkyl substituted alkynes to provide a variety of 1,4-dienes and trisubstituted alkenes. The hydroallylation is syn-stereospecific and highly-regioselective allowing access to stereodefined trisubstituted olefins.

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List of Abbreviations

Ac:	Acetyl
Ar:	Aryl
BINAP:	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn:	Benzyl
Boc:	*tert*-Butyloxycarbonyl
Bz:	Benzoyl
C:	Celsius
Cl_2IPr:	1,3-Bis-[2,6-diisopropylphenyl)-4,5dichloroimidazolium
CsF	Cesium fluoride
Cy:	Cyclohexyl
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
Equiv:	Equivalent
EtOAc:	Ethyl acetate
Et_2O	Diethyl ether
ESI-MS:	Electrospray ionization mass spectrometry
Et:	Ethyl
FTIR:	Fourier transform infrared spectroscopy
Abbreviations for FTIR peaks	
s:	strong
m:	medium
w:	weak
b:	broad
h:	Hour
HPLC:	High performance liquid chromatography
HRMS:	High resolution mass spectrometry

Hz:	Hertz
ICy:	1,3-dicyclohexyl imidazolium
IMes:	1,3-Bis-(2,4,6-trimethylphenyl)imidazolium
*i*Pr:	isopropyl
IPr:	1,3-Bis-(2,6-diisopropylphenyl)imidazolium
IPr^*:	1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazolium
ItBu:	1,3-Bis-(*tert*-butyl)imidazolium
KF	Potassium fluoride
$LiAlD_4$	Lithium aluminum deuteride
Me:	Methyl
Mes:	Mesityl
MHz:	Megahertz
mol:	Mole
NHC:	N-heterocyclic carbene
NMR:	Nuclear magnetic resonance
Abbreviations for NMR splitting patterns	
s:	singlet
d:	doublet
t:	triplet
q:	quartet
p:	pentet
m:	multiplet
br:	broad
dd:	doublet of doublets
dt:	doublet of triplets
ddt:	doublet of doublet of triplets
OTf:	Trifluoromethanesulfonate
OTFA:	Trifluoroacetate
OTs:	*p*-Toluenesulfonate

Ph:	Phenyl
pin:	pinacol
PMHS:	polymethylhydrosiloxane
ppm:	parts per million
rt:	room temperature
*t*Bu:	*tert*-butyl
TBDPS:	*Tert*-butyldiphenylsilyl
TBS:	*Tert*-butyldimethylsilyl
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
TIPS:	Triisopropylsilyl
TLC:	Thin layer chromatography
TMB:	1,3,5-Trimethoxy benzene
TMDSO:	Tetramethyldisiloxane
TMS:	Trimethylsilyl
tol:	Tolyl
Ts:	*p*-Toluenesulfonyl
SIPr:	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium
Xantphos:	4,5-bis(dipheylphosphino)-9,9-dimethylxanthene

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Dedication

To my parents for supporting me.

Chapter 1: Copper-Catalyzed Fluorination of Alkyl Triflates

Parts of this chapter was reproduced from the following manuscript: Dang, H.; Mailig, M.; Lalic, G. *Angew. Chem. Int. Ed.* **2014**, *126*, 6591–6594.

1.1 Introduction

Organofluorine compounds have attracted a considerable amount of attention in the last few decades as a result of the numerous applications of these compounds in the pharmaceutical industry, agrochemical industry, materials science, and as radiotracers for positron emission tomography (PET).[1–4] The synthetic interest in organofluorine chemistry is due in part to the fact that incorporation of fluorine, which is highly electronegative and small, into organic molecules imparts unique molecular properties.[1] These characteristics can dramatically influence chemical reactivity, stability, and conformation. For instance, the strong inductive effect of fluorine can have an impact on the acidity and basicity of neighboring functional groups. Fluorine substitution is often used to increase metabolic stability, enhance binding interactions, and alter lipophilicity which can be beneficial in the context of drug development.[1] In fact, approximately 20% of commercially available pharmaceuticals contain C-F bonds (Figure 1.1).[5]

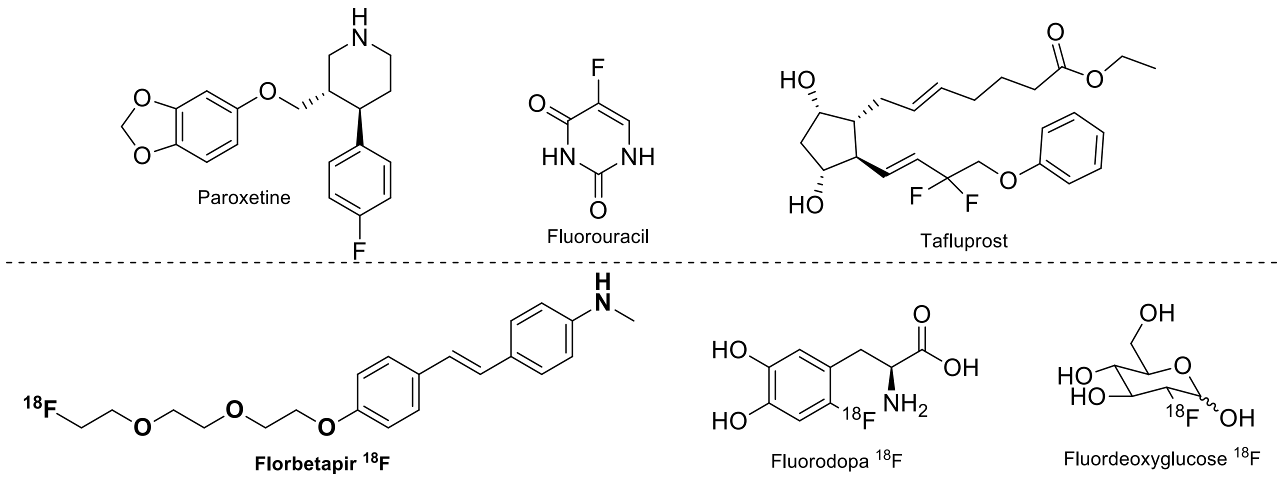
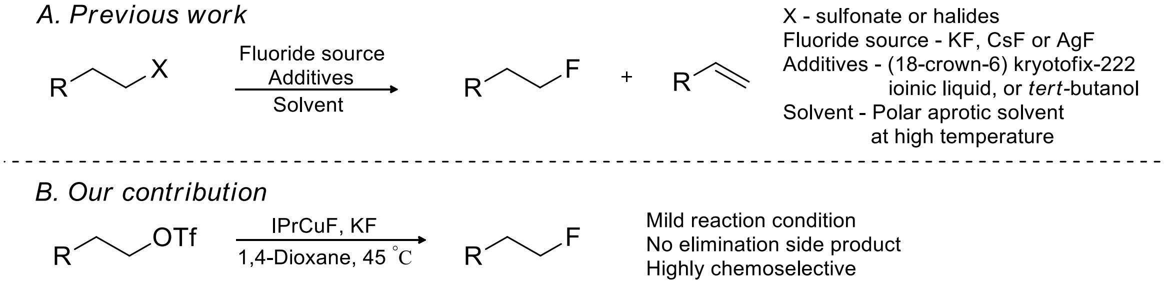


Figure 1.1. *Top:* Marketed drugs that contain C-F bonds *Bottom:* Examples of PET tracers with ^{18}F.

In addition, a more specialized application of fluorination is in the formation of C-^{18}F bonds. ^{18}F serves as an important radiotracer label for PET molecular imaging (Figure 1.1). This non-invasive technique allows for real time imaging of biological process and has been used to diagnose diseases. The use of ^{18}F is advantageous over other radioactive nuclei because of its low positron energy (0.64 eV), and relatively long half-life (110 min). This allows for longer studies and higher resolution images.[6] The application of fluorine in PET imaging and the high prevalence of organofluorine compounds in medicine and agrochemicals continues to inspire the continued development of methods for the synthesis of organofluorine compounds.

A number of methods for the incorporation of fluorine atoms into organic molecules have been developed.[7–11] Numerous methods for the synthesis of aryl fluorides have been developed with pioneering work led by Buchwald, Sanford, and Ritter among others.[12,13,9,14,15] On the other hand, Doyle & co-workers pioneered the allyl fluoride synthesis.[16–19] Significant advancements in the synthesis of aryl[9,12–14,20,21] fluoride and allyl[16–19,22–28] fluoride have been established, but efficient methods for the synthesis of alkyl[11,29–38] fluorides are still lacking.

A typical method for introducing a fluorine atom at an aliphatic site is accomplished by nucleophilic fluorination which involves the displacement of a halide or sulfonate leaving group by a fluoride anion (Scheme 1.1A).[39] Alkali metal fluoride salts such as KF, CsF or NaF are the commonly used fluoride anion source due to their abundance and low cost. Due to low solubility and low nucleophilicity of alkali metal fluorides, high reaction temperatures (often >100 °C) in high boiling polar aprotic solvents (e.g. DMF, DMSO NMP or ethylene glycol) along with the use of phase transfer additive (e.g. quaternary ammonium salts,[39] ionic liquids,[40–42] or *tert*-butanol[43]) is required to generate a soluble and reactive fluoride or naked fluoride. Unfortunately, the utility of these naked fluoride ions is limited due to the formation of olefinic byproducts via E2 elimination.[43] Crown ether Kryptofix-222,[44] is the most common phase transfer additive used for the synthesis of PET probes, it allows for the fluorination of alkyl electrophiles using KF at a high rate (under 10 min) at high temperature (>110 °C), but a considerable amount of elimination side product[45] is observed along with the aliphatic fluoride. This impurity can be challenging to remove on the timescale of radioactive decay. It is therefore desirable to develop a practical method that avoids the formation of alkene side product.



Scheme 1.1. Synthesis of alkyl fluorides.

This chapter describes the copper-catalyzed synthesis of aliphatic fluorides through the nucleophilic fluorination of alkyl triflates. This reaction proceeds under mild reaction conditions

(Scheme 1.1B) and as a result, no elimination side products were detected. In addition, the reaction is compatible with a wide range of functional groups. Interestingly, the transition metal complex involved is believed to function as a phase-transfer catalyst.

1.2 Fluorination of Alkyl Triflates

1.2.1 Reaction Optimization

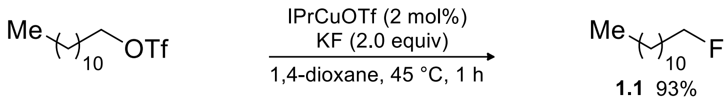
The key challenges during the reaction development were 1) to identify an efficient fluorinating agent along with a compatible alkyl electrophile, and 2) to have the reaction proceed through mild reaction conditions in order to avoid the formation of the alkene side product. Meeting these challenges would enable the reaction to proceed with high chemoselectivity and to afford high yield of the desired product.

We began our investigation by studying IPrCuF as a fluorinating agent. We were inspired by the idea that the sigma-donating ability of the NHC ligand might cause the copper fluoride species to be highly nucleophilic. In addition, IPrCuF is soluble in organic solvents and has been shown to be a relevant catalytic intermediate in a few other organic reactions.[46,47] Because IPrCuF is soluble in organic solvents and the alkali fluoride nucleophiles (LiF, NaF, KF, etc) from which it is derived are generally not, the use of this catalyst allows for the possibility of phase separation between the electrophile and alkali fluoride source. This in theory should suppress the uncatalyzed background elimination reaction pathway.

We found that IPrCuOTf reacts with KF in dioxane at 45 °C to give IPrCuF in 10 minutes in 88% yield (Scheme 1.2). With this result, we then explored the catalytic reaction. First, we looked for a suitable alkyl electrophile and found that dodecyl triflate reacts with high efficiency (Table 1.1, entries 2-3). A control experiment shows that the copper catalyst is necessary for the reaction

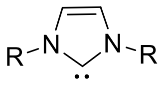
(Table 1.1, entry 4). Different NHC copper complexes gave the desired product, but in low yield (Table 1.1, entries 5-6). The choice of solvent is crucial in the reaction. For example, THF, an ethereal solvent like 1,4-dioxane, gave very little product, while chlorinated solvents gave a much better yield (Table 1.1, entries 7-9). In addition, it is necessary to use dried KF (Table 1.1, entry 10). It is important to note that by increasing the catalyst loading to 10 mol% the reaction is done in 10 min (Table1.1, entries 11-12). This is on a timescale that is suitable for preparation of ^{18}F radio labeled compounds.

Table 1.1. Reaction optimization for the synthesis of alkyl fluorides.

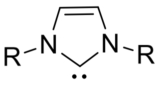


entry	change from standard conditions	yield[a]
1.	none	93%
2.	alkyl tosylate as an electrophile	<1%[b]
3.	alkyl iodide as an electrophile	<1%[b]
4.	no catalyst	<1%
5.	I*t*-BuCuOTf as catalyst	63%
6.	SIPrCuOtf as catalyst	85%
7.	THF	<1%
8.	1,2-dichloroethane	18%[c]
9.	CH_2Cl_2	7%
10.	non-dried KF	6%[d]
11.	0.2 mol% of IPrCuOTf for 16 h	94%
12.	10 mol% of IPrCuOTf for 10 min	92%

[a] GC Yields are reported. KF was dried for 5 mins prior to use (See the Supporting Information for details. [b] The electrophile remained unchanged. [c] 95% yield after 3 h with 10 mol% catalyst. [d] After 12 h.



IPr R = 2,6-diisopropylphenyl
I*t*-Bu R = *tert*-butyl



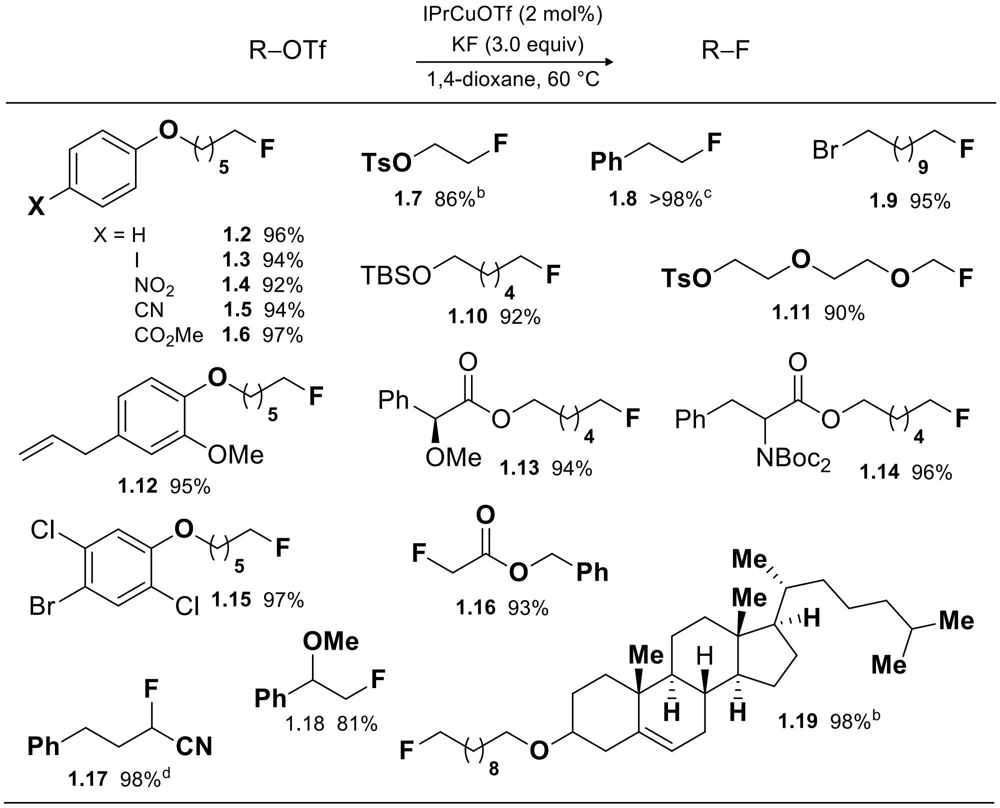
SIPr R = 2,6-diisopropylphenyl

Overall, the best results were obtained using 2 mol% of IPrCuOTf as phase transfer catalyst, KF as the fluoride source in 1,4-dioxane at 45 °C. The reaction is typically done within 16 h.

1.2.2 Reaction Scope

The scope of the alkyl fluoride synthesis is shown in Table 1.2. Our optimized reaction conditions exhibits high chemoselectivity. We were able to prepare alkyl fluorides in the presence of a wide variety of functional groups. Iodoarenes, nitroarenes, nitriles, esters, protected alcohols, alkyl tosylates, alkenes, and imides were all compatible. It's also important to note that the reaction tolerates the presence of an ester bearing an acidic alpha stereocenter, which typically epimerizes under basic conditions. The alkyl fluoride product was formed as a single enantiomer showing the mildness of the reaction conditions towards base sensitive functional groups (Table 1.2, compound **1.13**). In addition, by using a copper catalyst supported by smaller NHC ligand, we can synthesized a secondary alkyl fluoride (Table 1.2, compound **1.17**).

Table 1.2. Reaction scope for fluorination of alkyl triflates.



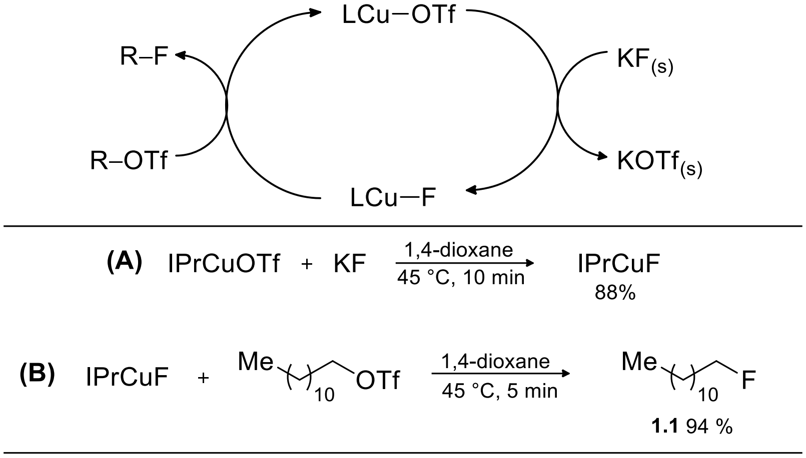
[a] Unless otherwise noted, yield of the isolated alkyl fluoride. [b] Reaction was completed in 10 min using 10 mol% of the catalyst. [c] Yield determined by NMR spectroscopy bacause ofthe volatility of the product. [d] Used 10 mol% of IMeCuCl as a catalyst, at 100 °C.

It is important to note that ^{18}F analogues of alkyl bromides, tosylates, and PEG (poly-ethylene glycol) based compounds are common prosthetic groups used in convergent synthesis of PET probes.[48] Lastly showing a direct comparison between this method and other developed protocols, product **1.19** labeled with ^{18}F was formed in only in 4% yield through nucleophilic fluorination of the corresponding tosylates. Using our optimized protocol, we were able to synthesize the alkyl fluoride **1.19** in excellent yield and selectivity.[49]

Importantly, the only products observed in the reactions reported in Table 1.2 were alkyl fluorides. There was no evidence of elimination or any other side reactions. Even compounds **1.8** and **1.18**, which are typically prone to undergo elimination, were successfully fluorinated.

1.3 Mechanism

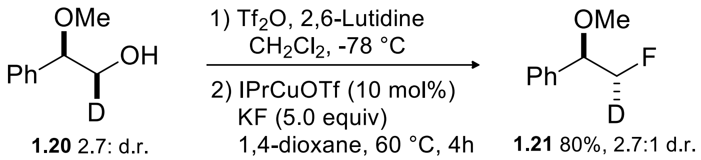
We proposed that the fluorination reaction proceeds according to the mechanism shown in Scheme 1.2. The reaction involves formation of an IPrCuF complex from IPrCuOTf, followed by nucleophilic substitution of the alkyl triflate and IPrCuF complex.



(A) Stoichiometric reaction of IPrCuOTf with KF to form IPrCuF. (B) Stoichiometric reaction of IPrCuF with alkyltriflate to form alkylfuoride.

Scheme 1.2. Proposed mechanism for fluorination of alkyl triflates.

To provide evidence in support of this proposed catalytic cycle, we performed stoichiometric reactions for each of the elementary steps. We showed the stoichiometric reaction of IPrCuOTf with KF resulted in 86% yield of IPrCuF complex in 10 min at 45 °C (Scheme 1.2A). This isolable IPrCuF complex allowed us to investigate the potential role of this transition metal complex in the second step of the proposed catalytic cycle. The stoichiometric reaction of the IPrCuF complex with alkyl triflate provides 94% yield of the desired product in 5 min (Scheme 1.2B). In addition, when a deuterium labeled alcohol **1.20** was subjected to the reaction condition, we observed an inversion of configuration (Scheme 1.3).



Scheme 1.3. Fluorination of deuterium-labled compound **1.20** showed inversion of configuration.

Finally, we also looked at the kinetics of the reaction. When the reaction is performed without stirring only trace amount of the desired product was observed after 12 min, while with vigorous stirring (1500 rpm) about 40% of the desired product was observed after 12 min (Figure 1.2). These results showed that the rate of the reaction depends on rate of stirring, suggesting that the phase transfer of fluoride ion is part of the rate law and contributes to the overall rate of the reaction.

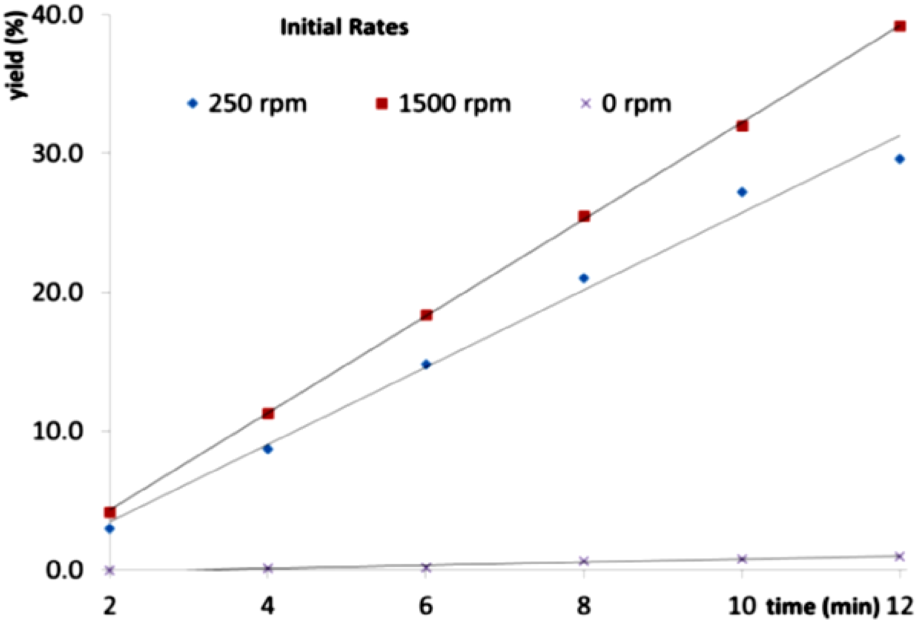


Figure 1.2. Initial rate measurement of catalytic fluorination of alkyl triflate at different stir rates.

1.4 Conclusion

We developed an efficient copper-catalyzed method for the synthesis of alkyl fluorides from alkyl triflates using KF as a fluoride source under mild reaction conditions. Phase separation of the electrophile and KF prevented elimination side products from forming and we have shown that the copper catalyst used enables phase transfer of the fluoride anion. Our method is compatible with a wide range of functional groups such as alkyl tosylates, alkyl bromides and alkyl iodides. We have shown that by using 10 mol % of the catalyst, the desired product is formed in less than 10 min.

1.5 Experimental

1.5.1 General

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.

<u>Materials:</u> 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.[50] IPrCuF was prepared according to the published procedure.[46]

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 vacuum 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.

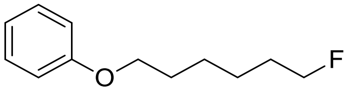
1.5.2 General Procedure for Reaction Optimization (Table 1.1).

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, KF (58.1 mg, 1.0 mmol, 2.0 equiv), catalyst (0.010 mmol, 0.02 equiv), Solvent (1.0 mL), electrophile (0.5 mmol, 1.0 equiv) and a solution of TMB (42.0 mg, 0.25mmol, 0.5 equiv) in a solvent of choice (1.5 mL). The reaction mixture was vigorously stirred at 45 °C.

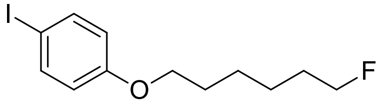
1.5.3 General Procedure for Fluorination of Alkyl Triflates (Table 1.2).

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, KF (58.1 mg, 1.0 mmol, 3.0 equiv), IPrCuOTf (6.0 mg, 0.01 mmol, 0.02 equiv), 1,4-dioxane, (2.5 mL), alkyl triflate (0.5 mmol, 1.0 equiv). The reaction mixture was vigorously stirred at 45 °C. After 1 h, the reaction mixture was filtered through a pad of silica gel and wash with 20 mL of Et_2O. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel column.

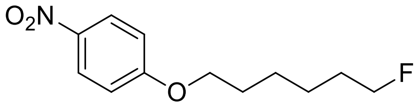
1.5.4 Characterization Data for Alkyl Fluorides



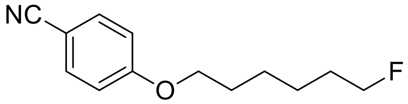
[(6-fluorohexyl)oxy]benzene (Table 1.2, compound 1.2), compound was isolated as a colorless oil (94.0 mg, 96% yield). ^{1}H NMR (300 MHz, CD2Cl2) δ 7.34 – 7.19 (m, 2H), 7.02 – 6.75 (m, 3H), 4.44 (dt, J = 47.4, 6.1 Hz, 2H), 3.95 (t, J = 6.5 Hz, 2H), 1.98 – 1.61 (m, 4H), 1.58 – 1.37 (m, 4H). ^{13}C NMR (126 MHz, C6D6) 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, C6D6) 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).



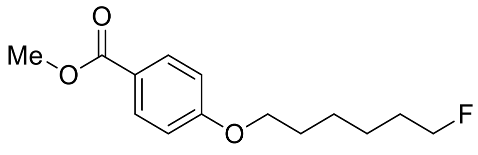
1-[(6-fluorohexyl)oxy]-4-iodobenzene (Table 1.2, compound 1.3), compound was isolated as a colorless oil (148.0 mg, 94% yield). ^{1}H NMR (300 MHz, C6D6) δ 7.40 (d, J = 8.9 Hz, 2H), 6.39 (d, J = 8.9 Hz, 2H), 4.08 (dt, J = 47.5, 6.0 Hz, 2H), 3.37 (t, J = 6.4 Hz, 2H), 1.58 – 1.24 (m, 4H), 1.24 – 1.03 (m, 4H). ^{13}C NMR (126 MHz, C6D6) 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, C6D6) 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).



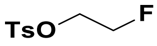
1-[(6-fluorohexyl)oxy]-4-nitrobenzene (Table 1.2, compound 1.4), compound was isolated as a colorless oil (111.0 mg, 92% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.93 (d, *J* = 9.2 Hz, 2H), 6.33 (d, *J* = 9.2 Hz, 2H), 4.10 (dt, *J* = 47.5, 5.9 Hz, 2H), 3.28 (t, *J* = 6.4 Hz, 2H), 1.57 – 1.23 (m, 4H), 1.21 – 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).



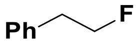
4-[(6-fluorohexyl)oxy]benzonitrile (Table 1.2, compound 1.5), compound was isolated as a colorless oil (104.0 mg, 94% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 7.04 (d, *J* = 8.9 Hz, 2H), 6.35 (d, *J* = 8.9 Hz, 2H), 4.09 (dt, *J* = 47.5, 5.9 Hz, 2H), 3.27 (t, *J* = 6.4 Hz, 2H), 1.51 – 1.22 (m, 4H), 1.20 – 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).



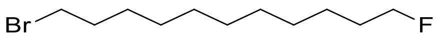
methyl 4-[(6-fluorohexyl)oxy]benzoate (Table 1.2, compound 1.6), compound was isolated as a colorless oil (120.8 mg, 97% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 8.18 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 4.09 (dt, *J* = 47.5, 6.0 Hz, 2H), 3.55 (s, 3H), 3.43 (t, *J* = 6.4 Hz, 2H), 1.51 – 1.23 (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).



2-fluoroethyl 4-methylbenzene-1-sulfonate (Table 1.2, compound 1.7), compound was isolated as a colorless oil (100.0 mg, 92%). **17** is a known compound and spectral data match the reported literature values.[51]

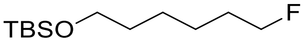


2-fluoroethylbenzene (Table 1.2, compound 1.8), Yield was determined by NMR analysis using 1,3,5 – trimethoxybenzene as an internal standard. **19** is a known compound and spectral data match the reported literature values.[52]

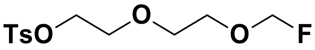


1-bromo-11-fluoroundecane (Table 1.2, compound 1.9), compound was isolated as a colorless oil (120.2 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ

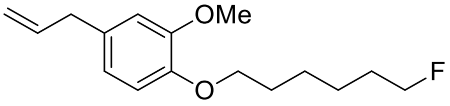
4.44 (dt, J = 47.4, 6.2 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.78 – 1.57 (m, 2H), 1.52 – 1.17 (m, 14H). ^{13}C NMR (126 MHz, C_6D_6) δ 83.9 (d, J = 165.7 Hz), 33.9 (s), 33.3 (s), 31.0 (d, J = 19.5 Hz), 30.0 (s), 30.0 (s), 29.9 (s), 29.8 (s), 29.2 (s), 28.6 (s), 25.7 (d, J = 5.1 Hz). GCMS (EI) calculated for $[M]^+$ 252.09, found 251.95. FTIR (neat, cm-1): 2930(s), 1465 (m), 1266 (s), 741 (s).



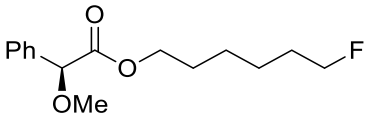
tert-butyl[(6-fluorohexyl)oxy]dimethylsilane (Table 1.2, compound 1.10), compound was isolated as a colorless oil (106.0 mg, 92% yield). ^{1}H NMR (300 MHz, C_6D_6) δ 4.10 (dt, J = 47.5, 6.1 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 1.52 – 1.31 (m, 4H), 1.30 – 1.12 (m, 4H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C 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).



(2-fluoroethoxy)ethoxy]ethyl 4-methylbenzene-1-sulfonate (Table 1.2, compound 1.11), 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.[52]



1-[(6-fluorohexyl)oxy]-2-methoxy-4-(prop-2-en-1-yl)benzene (Table 1.2, compound 1.12), 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 1.2, compound 1.13), 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 column. Conditions: 5% IPA/Hexanes, 1 mL/min.

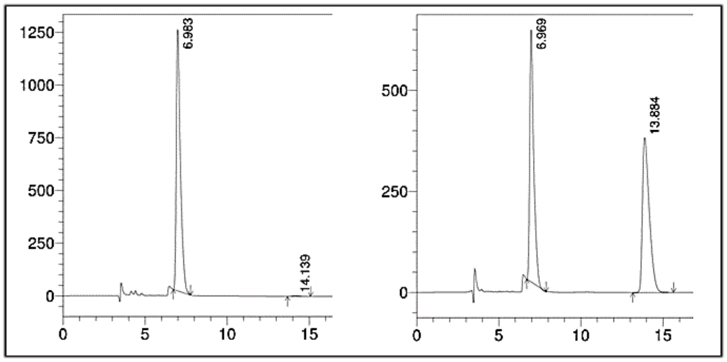
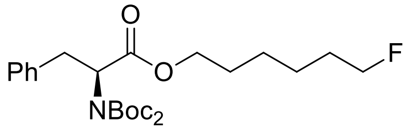
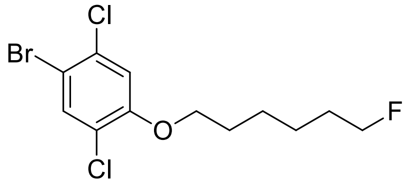


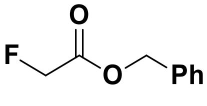
Figure 1.3. HPLC trace for analysis of enantiopurity of compound **1.13**.



6-fluorohexyl 2-{bis[(tert-butoxy)carbonyl]amino}-3-phenylpropanoate (Table 1.2, compound 1.14), 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).

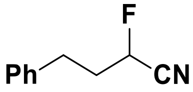


1-bromo-2,5-dichloro-4-[(6-fluorohexyl)oxy] (Table 1.2, compound 1.15), compound was isolated as a white solid (162.3 mg, 97% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 (s, 1H), 6.99 (s, 1H), 4.46 (dt, *J* = 47.3, 6.0 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 2.04 – 1.64 (m, 4H), 1.61 – 1.39 (m, 4H). ^{13}C NMR (126 MHz, C$_6$D$_6$) 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$_6$D$_6$) 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).

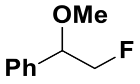


benzyl 2-fluoroacetate (Table 1.2, compound 1.16), compound was isolated as a colorless oil (80.0 mg, 95% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (s, 5H), 5.25 (s, 2H), 4.89

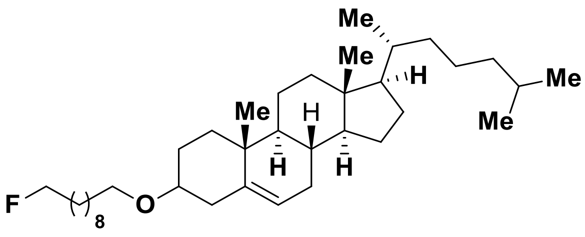
(d, *J* = 47.0 Hz, 2H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 168.2 (d, *J* = 21.9 Hz), 135.7, 129.2, 129.1, 129.0, 78.4 (d, *J* = 181.1 Hz), 67.5. ^{19}F GCMS (EI) calculated for $[M]^+$ 168.06, found 168.10. FTIR (neat, cm-1): 3054 (m), 2986 (w), 1769 (s), 1265 (s), 1215 (m), 1082 (m), 961 (w).



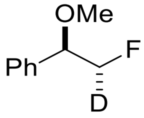
2-fluoro-4-phenylbutanenitrile (Table 1.2, compound 1.17), compound was isolated as a colorless oil (80 mg, 98% yield). Compound **1.17** is a known compound and spectral data match the reported literature values.[53]



2-Fluoro-1-methoxyethyl)benzene (Table 1.2, compound 1,18), 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, $CDCl_3$) 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.[54]



(8S,9S,10R,13R,14S,17R)-3-((10-fluorodecyl)oxy)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene (Table 1.2, compound 1.19), compound was isolated as a white solid (264.3 mg, 95% yield). Compound **1.19** is a known compound and spectral data match the reported literature values.[49]



(2-Fluoro-2-deutero-1-methoxyethyl)benzene (compound 21), 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.

1.5.5 Reaction of IPrCuOTf with KF (Scheme 1.2A).

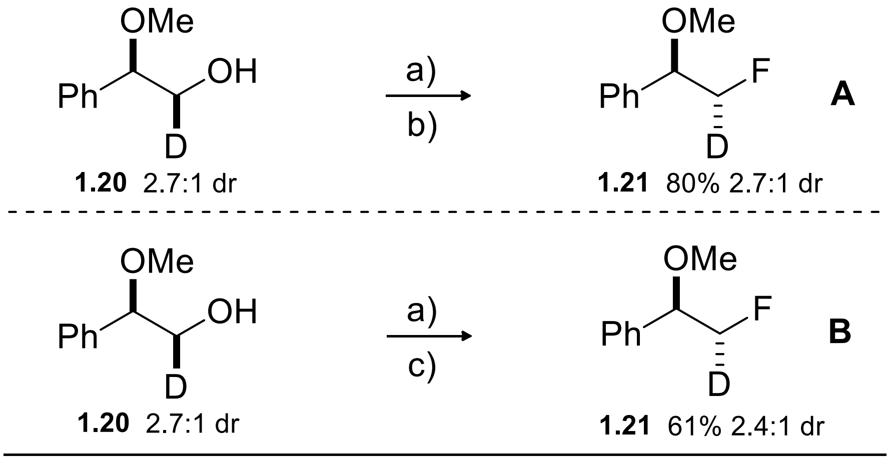
In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, KF (5.8 mg, 0.100 mmol, 5.00 equiv), IPrCuOTf (24.0 mg, 0.020 mmol, 1.00 equiv), a stock solution of the internal standard, hexafluorobenzene (1.1 mg, 0.006 mmol, 0.300 equiv), in 1,4-dioxane (440 µL). The reaction mixture was stirred at 45 °C. After 10 min 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.

1.5.6 Reaction of IPrCuF with Dodecyl Triflate (Scheme 1.2B).

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuF (23.6 mg 0.050 mmol, 1.00 equiv), 1,4-dioxane (500 µL), 1-dodecyl triflate (31.8 mg, 0.100 mmol, 2.00 equiv), and TMB (4.2 mg, 0.025 mmol, 0.5 equiv). The reaction mixture was stirred at 45 °C. After 5 min, aliquot was taken. A 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1500 µL of Et_2O before GC analysis.

1.5.7 Stereochemistry of Fluorination Reaction (Scheme 1.3).

The stereochemistry of the fluorination reaction was determined based on the results of experiments described in Scheme 1.4. The diastereomeric mixture of the mono-deuterated alcohol **20** (see below for the synthesis of **20**) was transformed into the corresponding triflates and subsequently into a mixture of alkyl fluorides **21**. 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 Scheme 1.4B. Using the conditions shown in Scheme 1.4B, the fluorination of **20** can only proceed through the SN_2 mechanism and result in the inversion of the configuration. Using the conditions shown in Scheme 1.4A, the diastereoisomer of **21** obtained as the major product was the same as the one obtained as the major product in the reaction shown in Scheme 1.4B. 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 Scheme 1.4B 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.

Scheme 1.4. Determination of stereochemistry of fluorination reaction.

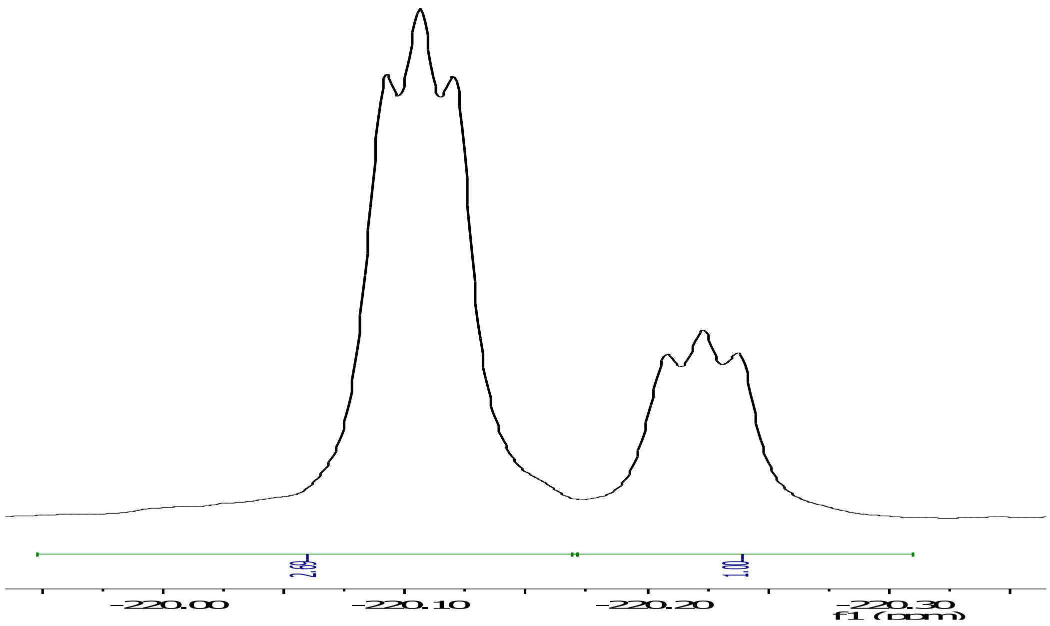
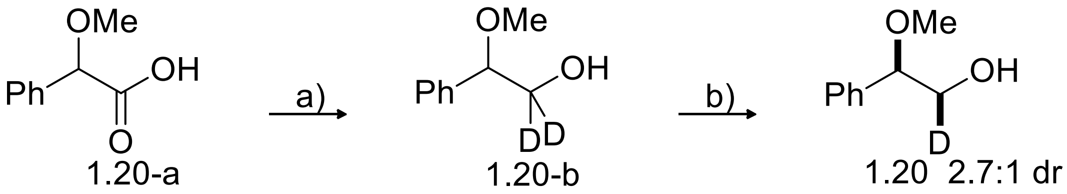


Figure 1.4 NMR showing a 2.7:1 d.r of product **21** obtained in reaction shown on Scheme 1.4A.

Compound 1.**20** was synthesized according known chemistry with slight modifications.



Scheme 1.5. Synthesis of compound **1.20**.

a) To a suspension of $LiAlD_4$ (923.6 mg, 22.0 mmol, 1.1 equiv) in dry diethyl ether (60.0 mL) was added **1.20-a** (3.3 g, 20.0 mmol, 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 H_2O, followed by 1.9 mL of 2 M aq. NaOH. Finally, 2.8 mL of H_2O 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% EtOAc in hexanes to afford a clear colorless oil (2.6 g, 16.7 mmol, 83% yield), **1.20-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). **1.20-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. $NaHCO_3$, followed by 1M aq. HCl, and with a final wash with saturated aq. $NaHCO_3$. The organic layer was then dried over $MgSO_4$, filtered, concentrated to afford a crude mixture containing **1.20-c**. This was used in the subsequent step without further purification. Crude mixture containing **1.20-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 **20** as a clear colorless oil (422 mg, 2.8 mmol, 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).

1.5.8 Initial Rate Measurement of Catalytic Fluorination of Alkyl Triflate (Figure 1.2).

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, KF (87.2 mg, 1.50 mmol, 3.00 equiv), 1,4-dioxane (1.40 mL), a solution of IPrCuOTf (6.0 mg in 143 µL 1,4-dioxane, 0.010 mmol, 0.02 equiv), a solution of 1-dodecyl triflate (159 mg in 955 µL 1,4-dioxane, 0.500 mmol, 1.00 equiv), and TMB (42 mg, 0.25 mmol, 0.5 equiv). The reaction mixture was stirred at the desired stir rate at 45 °C. Aliquots were taken every 2 min for the first 12 min of the reaction. The 60 µL aliquot was diluted with 500 µL of saturated Et_2O of sodium *tert*-pentoxide and pipetted onto silica gel plug and rinsed through with 1000 µL of Et_2O before GC analysis.

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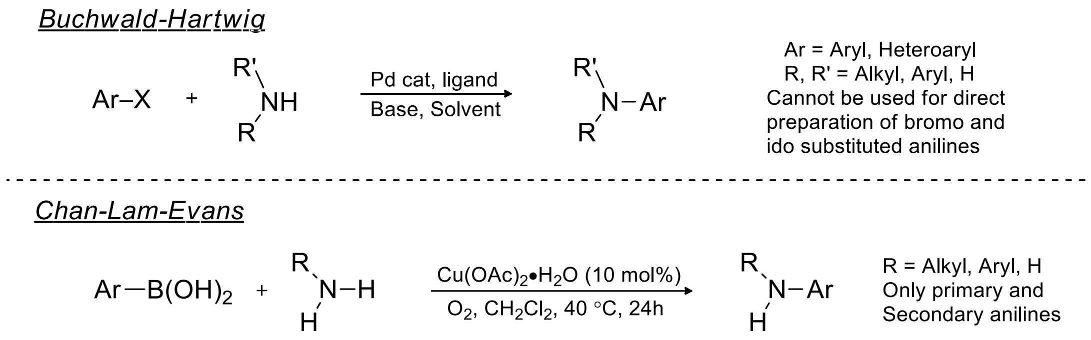
Chapter 2: Practical Method for the Synthesis of Sterically Hindered Anilines

Parts of this chapter was reproduced from the following manuscript: Mailig, M.; Rucker, R. P.; Lalic, G. *Chem. Commun.* **2015**, *51*, 11048–11051.

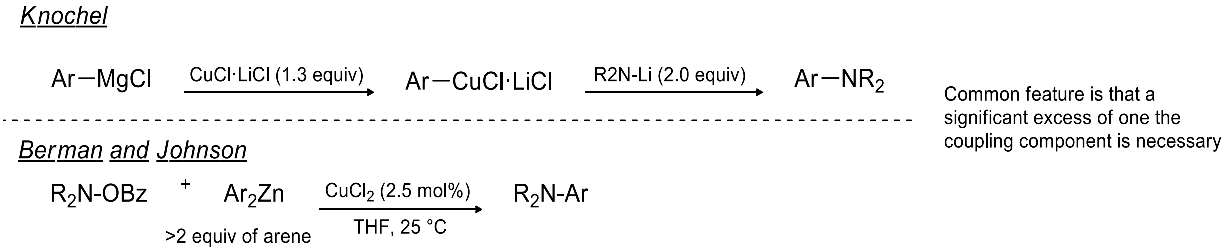
2.1 Introduction

Aromatic amines and heteroaromatic amines are found in a wide range of naturally occurring compounds. In addition, these motifs are found in many biologically active compounds and medicinal chemistry targets.[1,2] In fact 5% of the top selling drugs in 2013 contain the aromatic amine functional group.[3] As a result, extensive research interests in transition-metal catalyzed coupling of aryl halides with amines to synthesize anilines and heteroaromatic amines has been demonstrated in recent years. Two commonly used methods found in the literature are the Lam-Chan-Evans oxidative coupling of boronic acids and amines using copper catalyst and the Buchwald-Hartwig coupling of amines and aryl halides using palladium catalysis (Scheme 2.1). Although both provide a practical method for preparing a wide range of anilines, some challenges remain. For example, the Chan-Lam-Evans reaction is highly sensitive to the steric properties of amine substrates and can only be used for the synthesis of primary and unhindered secondary anilines.[4–7] The Buchwald-Hartwig reaction cannot be used for the direct preparation of bromo and iodo substituted anilines and this reaction is also sensitive to the steric environment of both the amine and aryl halide.[8–10]



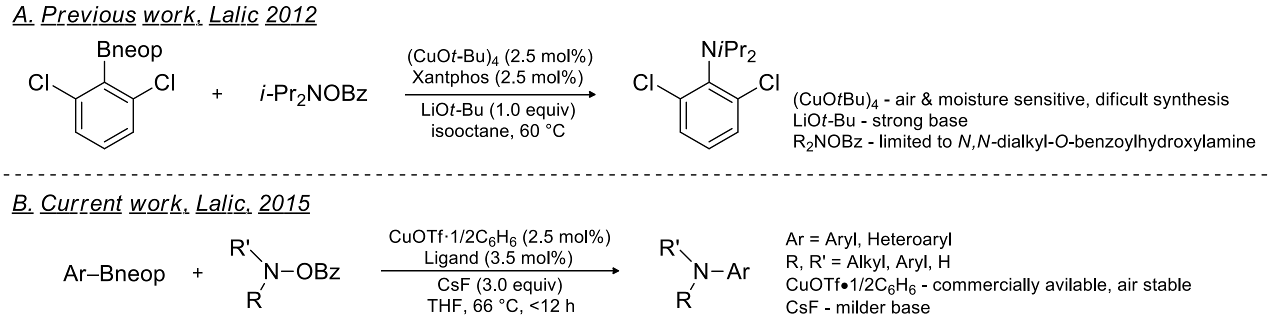
Scheme 2.1. Previous work: Synthesis of anilines.

There are several methods for the synthesis of hindered amines. Knochel and coworkers developed an oxidative coupling of organometallic reagents with hindered lithium amides in the presence of stoichiometric amounts of copper to synthesized hindered aniline. In addition to significant amount of metal waste generated in this reaction, the synthesis of the reactive intermediates makes the method incompatible with a number of functionalities. On the other hand, Berman and Johnson developed an electrophilic amination of aryl zinc reagents by hindered electrophiles, but a highly reactive Grignard reagents are needed to prepare the aryl zinc nucleophile.



Scheme 2.2. Previous work: Synthesis of hindered anilines.

Lalic and coworkers successfully developed a copper-catalyzed synthesis of sterically hindered anilines by electrophilic amination of aryl and heteroaryl boronic ester with *N*,*N*-dialkyl-*O*-benzoyl hydroxylamine esters (Scheme 2.3A).[11] The reaction conditions developed were shown to be tolerant of a wide range of functional groups such as iodo, bromo, nitro, and even the most sterically hindered anilines. However, the catalyst precursor used in this reaction, CuO*t*-Bu tetramer, is highly sensitive to air and water and extremely difficult to synthesize. In addition, the turnover reagent, LiO*t*-Bu, prevents the use of protic functional groups in either coupling partner and the reaction is limited to *N*,*N*-dialkyl-*O*-benzoyl hydroxylamine.



Scheme 2.3. Lalic's Lab: Synthesis of sterically hindered anilines.

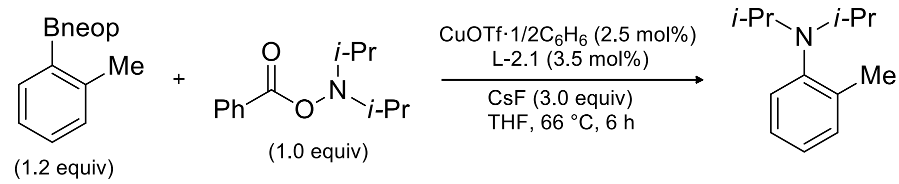
In this chapter, I describe our success in the development of a practical catalytic method for the synthesis of highly sterically hindered tertiary and secondary anilines through electrophilic amination of aryl and heteroaryl boronic esters (Scheme 2.3B). We have developed the reaction to a level where we can use a commercially available copper catalyst that is air stable and we can use a mild turnover reagent, CsF. Moreover, the reaction is tolerant of a wide variety of functional groups and can be used to prepare monoalkyl anilines.

2.2 Electrophilic Amination of Boronic Esters

2.2.1 Reaction Optimization

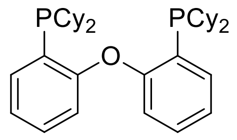
We knew from the previous work in our lab focused on the synthesis of sterically hindered anilines that CsF is a suitable turn-over additive, but the reaction proceeded at a low rate. Our investigation started by screening for different catalyst precursors while using CsF as a turn-over additive. We found that copper (I) triflate benzene complex is the best catalyst precursor. Although several commercially available copper (I) and copper (II) salts work, the reaction either gave a low yield or proceeded at a low rate (Table 2.1, entries 2-5). A variety of bidentate phosphine ligands perform well in this reaction, but the best yield was obtained if bis(dicyclohexylphosphinophenyl) ether **L-2.1** was used. Ligands that have a smaller bite angle have a detrimental effect on the reaction (Table 2.1, entries 6-7). We found that our reaction worked well with ethereal solvents (Table 2.1., entries 8-11). We also looked at different turn-over reagents, but CsF is the one that is superior (Table 2.1, entry 12).

Table 2.1. Reaction optimization for synthesis of sterically hindered anilines.

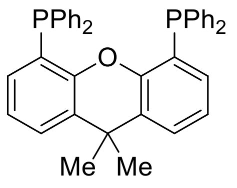


entry	change from standard conditions	yield[a]
1.	none	96%
2.	$[Cu(MeCN)_4]OTf$ as a catalyst	79%
3.	$[Cu(MeCN)_4]BF_4$ as a catalyst	86%
4.	$Cu(i\text{-}BuCO_2)_2$ as a catalyst	60%[b]
5.	$CuCO_3$ as a catalyst	1%
6.	Xantphos as a ligand	84%
7.	BINAP as a ligand	<5%
8.	2-Me-THF	95%
9.	1,4-dioxane	83%
10.	Toluene	6%
11.	Acetonitrile	16%
12.	KF as a turn over reagent	<5%

[a] GC Yields are reported. [b] 1.5 equiv of sodium ascorbate was used. neop = neopentyl glycol

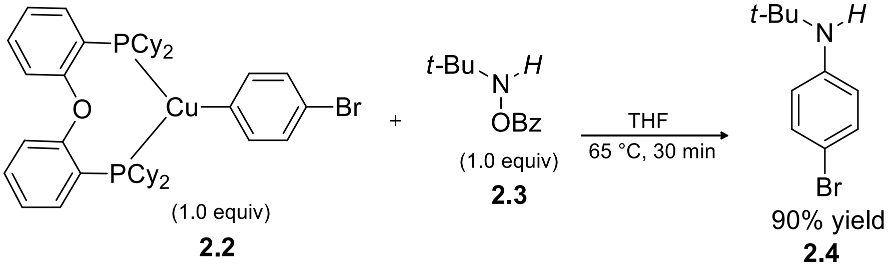


L-2.1



Xantphos

We were also interested with the synthesis of *N*-alkyl anilines. We began our investigation by stoichiometric reaction of *N*-alkyl-*O*-benzoyl hydroxylamine **2.3** with diphosphine-supported copper aryl complex **2.2** and we found that 90% of the desired aniline was produced in 30 min at 65 °C (Scheme 2.4). However, in an attempt to establish a catalytic protocol using the similar conditions to entry 1 of Table 2.1, we were disappointed that no desired product was formed. However, we found that the desired *N*-alkyl aniline was formed when the electrophile was slowly added to the reaction mixture.



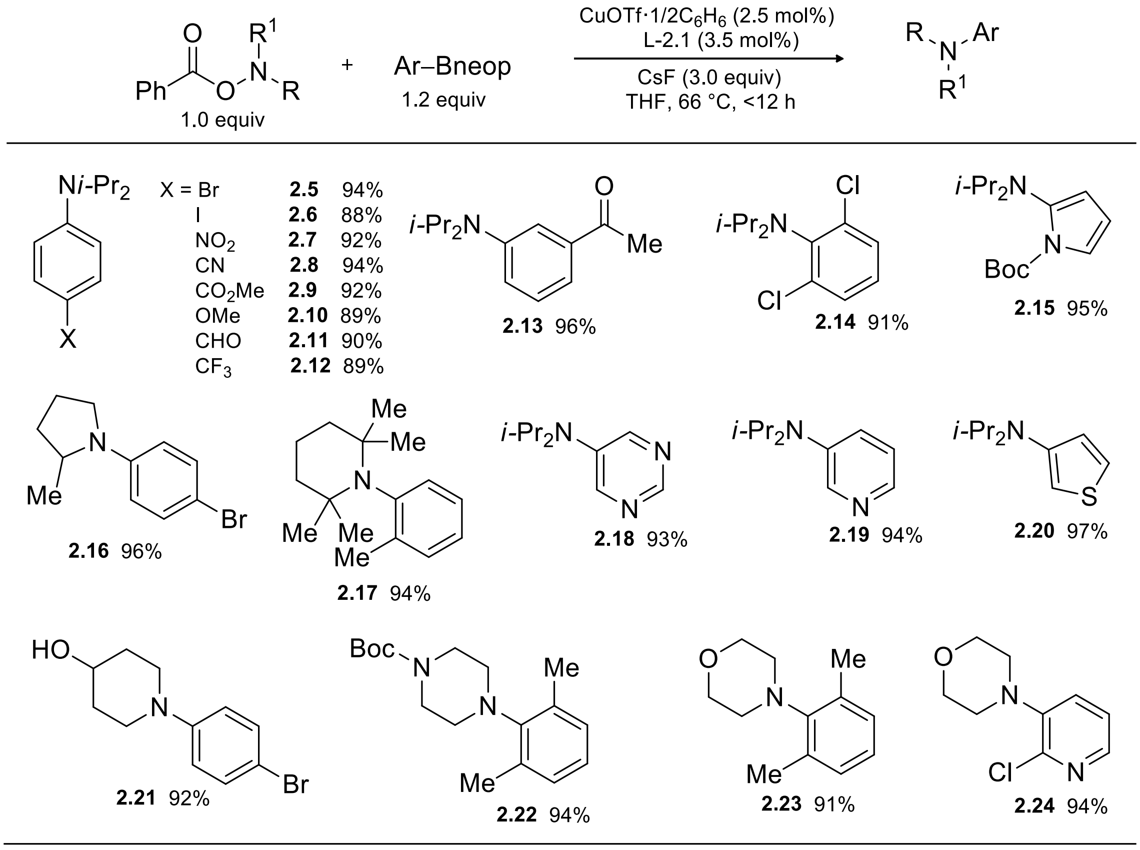
Scheme 2.4. Stoichiometric synthesis of *N*-alkyl anilines.

The best conditions for amination using *N*,*N*-dialkyl-*O*-benzoyl hydroxylamine electrophile was achieved using copper (I) triflates benzene complex as precatalyst, bis(dicyclohexylphosphinophenyl) ether as the ligand, CsF as the turn-over additive, and THF as the solvent at 66 °C. The reaction is complete in <12 h. For reaction with *N*-alkyl-*O*-benzoyl hydroxylamine electrophile, we found that by adding the electrophile to the reaction mixture over three hours the desired product could be achieved in a good yield.

2.2.2 Reaction Scope

The optimized reaction conditions proved to be remarkably general. We found that reactions with diisopropylamine-derived electrophiles worked well in the presence of a number of functional groups on the arene, including bromo, iodo, nitro, cyano, and carbomethoxy, alkoxy, ketone, and aldehyde. Highly electron-rich arenes such as *p*-methoxy and hindered boronic esters are well tolerated in the reaction (Table 2.2, compounds **2.10, 2.14**). In addition, a variety of heteroaromatic boronic esters such as thiophine, pyridine, pyrimidine, and Boc protected pyrrole can be used in the reaction.

Table 2.2. Reaction scope for tertiary anilines.

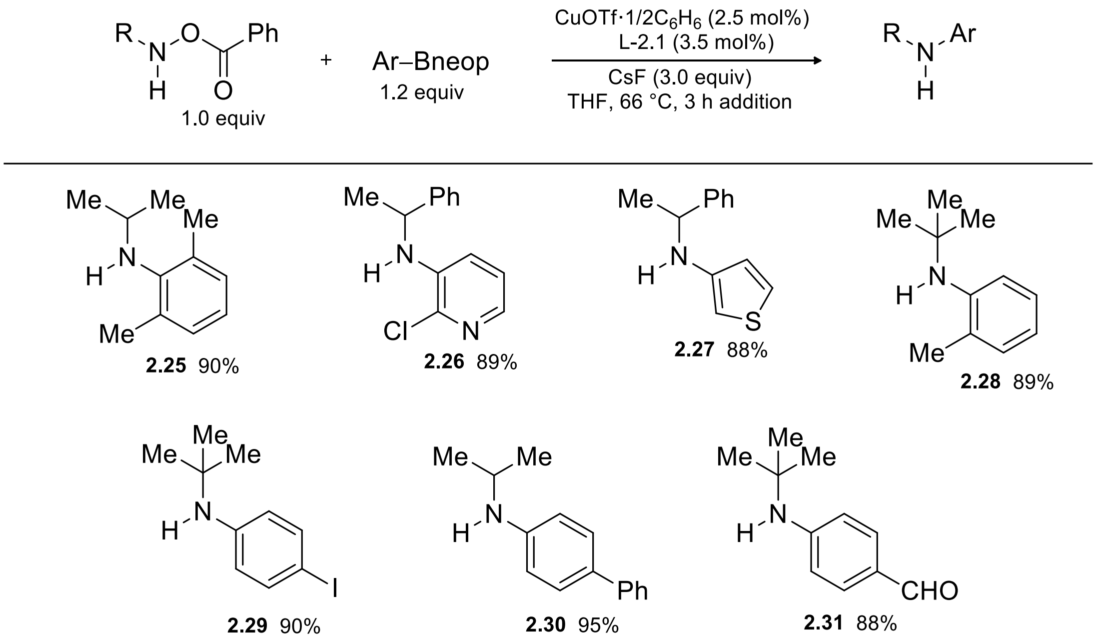


All reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. neop = neopentyl glycol

To establish the full scope of the amination reaction, we explored the reactivity of various electrophiles. Electrophiles derived from common heterocyles such as piperazines, piperidines, morpholines, and pyrrolidines worked well in the reaction (Table 2.2, compounds **2.16, 2.17, 2.21-2.24**). Even, a sterically hindered 2,2,6,6-tetramethylpiperidine electrophile is well tolerated in the reaction (Table 2.2, compound **2.17**). It is important to note that the presence of acidic functional group have no effect on the outcome of the reaction (Table 2.2, compound **2.21**).

We also explored the reactivity of *N*-alkyl-*O*-benzoyl hydroxylamine electrophiles with a variety of boronic esters. The scope is shown in Table 2.3. We found that reaction with *N*-alkyl-*O*-benzoyl hydroxylamine electrophiles could be performed in the presence of a number of functional groups such as thiophenes, pyridine, sterically hindered arenes, and arenes containing an iodide, or aldehyde functional group.

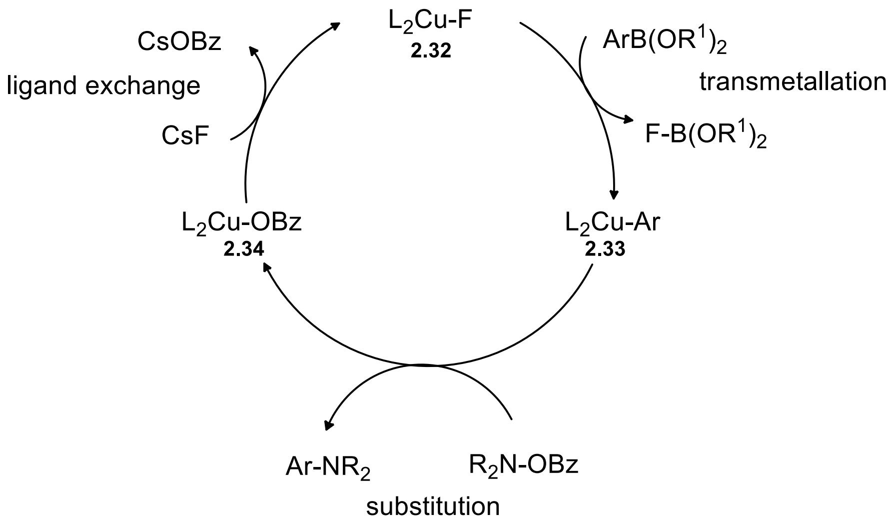
Table 2.3. Reaction scope for secondary anilines.



All reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. neop = neopentyl glycol

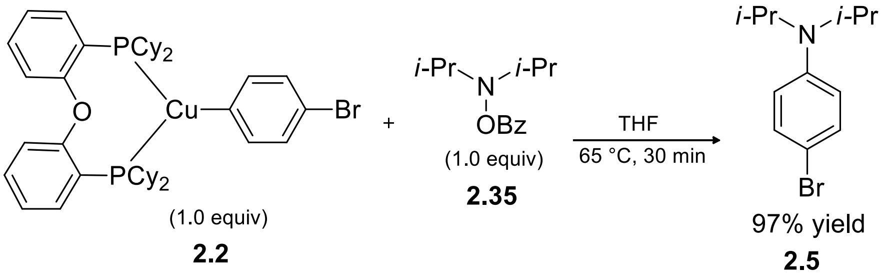
2.3 Mechanism

We propose that the amination reaction proceeds according to the mechanism shown in Scheme 2.5. The reaction involves transmetallation of the aryl group of an aryl boron reagent with copper fluoride followed by electrophilic amination of the aryl copper intermediate. Finally, the regeneration of copper fluoride with cesium fluoride completes the catalytic cycle.



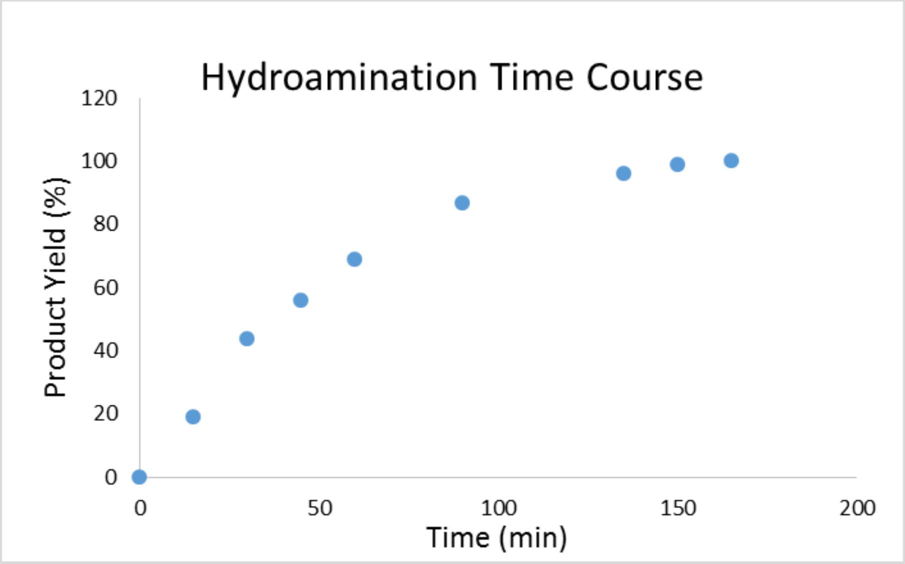
Scheme 2.5. Proposed mechanism for electrophilic amination of boronic esters.

The transmetallation of arenes from boron to copper and formation of copper fluoride complexes from various copper salts in the presence of CsF and or KF are well documented in the literature.[15,16] We focused our attention on the electrophilic amination of the putative aryl copper intermediate. We showed that the reaction of *N*,*N*-isopropyl-*O*-benzoyl hydroxylamine **2.32** with diphopshine-supported copper aryl complex **2.2** resulted in a 97% yield of aniline **2.5**, in 30 min at 65 °C (Scheme 2.6).

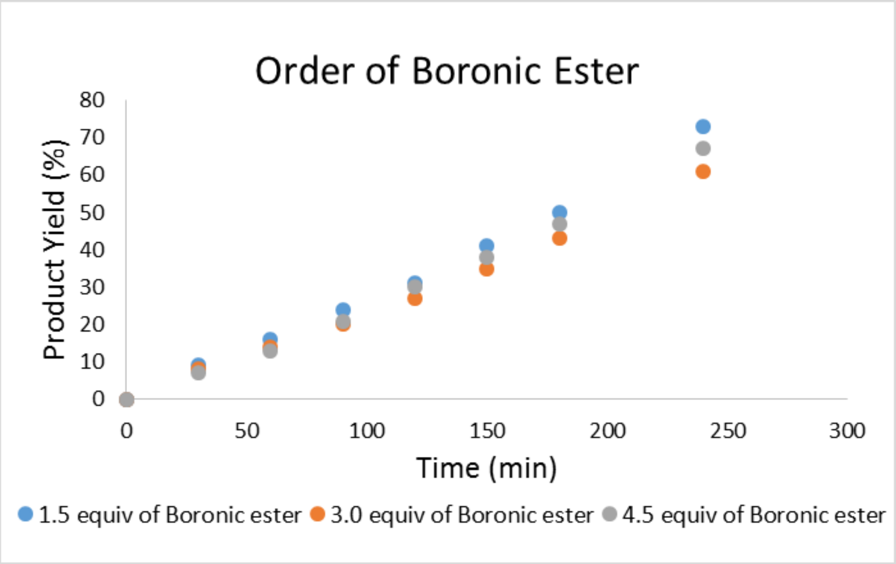


Scheme 2.6. Stiochiometric synthesis of *N,N*-dialkyl anilines.

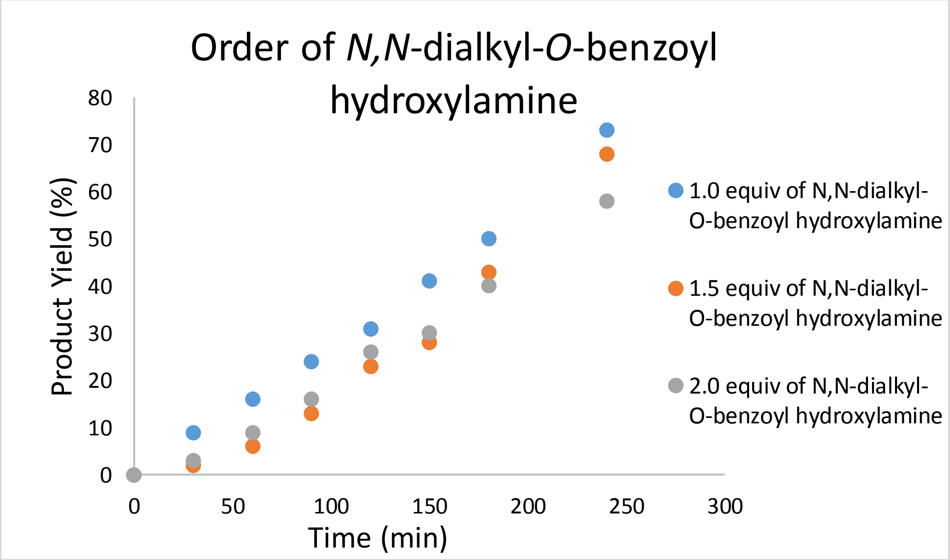
We monitored the rate of product formation over time until the full conversion of the electrophile was achieved. We found that the overall rate of the reaction does not significantly change over time (Figure 2.1A). In addition, the initial rate of the reaction does not depend on the concentration of either the aryl boronic ester or the concentration of the electrophile (Figure 2.1B and 2.1C). These observations and the fact that CsF has low solubility in organic solvents indicate that the rate-limiting step is the formation of the copper fluoride intermediate **2.32** and that the resting state is the copper benzoate intermediate **2.34**.



A. Yield of the aniline product as a function of time. Reaction conditions: 4-BrC_6H_4Bneop (1.2 equiv), *i*-Pr_2NOBz (1.0 equiv), CuOTf●1/2C_6H_6 (2.5 mol%), L-**2.1** (3.5 mol %), CsF (3.0 equiv), 80 °C, THF



B. Yield of the aniline product as a function of time. Reaction conditions: 4-BrC$_6$H$_4$Bneop (1.5 equiv, 3.0 equiv, 4.5 equiv), *i*-Pr$_2$NOBz (1.0 equiv), CuOTf●1/2C$_6$H$_6$ (2.5 mol%), L-**2.1** (3.5 mol %), CsF (3.0 equiv), 80 °C, THF



C. Yield of the aniline product as a function of time. Reaction conditions: 4-BrC$_6$H$_4$Bneop (1.5 equiv), *i*-Pr$_2$NOBz (1.0 equiv, 1.5 equiv, or 2.0 equiv), CuOTf●1/2C$_6$H$_6$ (2.5 mol%), L-**2.1** (3.5 mol %), CsF (3.0 equiv), 80 °C, THF

Figure 2.1. Kinetics of electrophilic amination reaction.

2.4 Conclusion

We have developed a practical and mild catalytic method for the synthesis of sterically hindered anilines. The catalyst precursor and ligand are commercially available and air stable allowing this reaction to be performed without the use of a glove box. The method is compatible with a wide range of functional groups such as carbomethoxy, nitro, cyano, hydroxyl, and formyl. Also, the tolerance of aryl chlorides, bromides and iodides demonstrates that the method provides a valuable compliment to the established palladium-catalyzed methods. Overall, our method provides a significant addition to existing methods for the synthesis of anilines.

2.5 Experimental

2.5.1 General and Materials

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. ^1H- 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. Cesium fluoride was purchased from Sigma-Aldrich and used as received, unless otherwise noted. *O*-benzoyl hydroxyl amine[13] and aryl boronic esters[17] were prepared according to a literature procedure.

2.5.2 General Procedure for Reaction Optimization (Table 2.1.)

In a nitrogen-filled glove box, a dram vial was charged with a stir bar, copper catalyst (0.025 equiv), ligand (0.035 equiv), cesium fluoride (3.0 equiv), aryl boronic ester (1.2 equiv), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.0 equiv), 1,3,5-trimethoxybenzene (0.5 equiv), and solvent (0.2 M) respectively. The reaction mixture was allowed to stir for 6 h at 66 °C. A 30 µL aliquot was taken. The aliquot was diluted with 500 µL DCM and pipetted onto silica gel plug and rinsed through with 1000 µL DCM before GC analysis. Cesium fluoride used for the optimization was dried rigorously by flame-drying under vacuum followed by grinding with mortar and pestle in a glovebox.

2.5.3 General Procedure for Hydroamination

General procedure for the synthesis of tertiary aniline: An air-free reaction flask charged with a stir bar was flame dried under vacuum, allowed to cool under nitrogen. To the flask was added CsF (227.9 mg, 1.5 mmol, 3.0 equiv), boronic ester (0.6 mmol, 1.2 equiv), *O*-benzoyl-*N,N*-dialkyl hydroxylamine (0.5 mmol, 1.0 equiv), Bis(2-dicyclohexylphosphinophenyl)ether (9.8 mg, 0.018 mmol, 0.035 equiv), copper(I) trifluoromethanesulfonate benzene complex (3.1 mg, 0.013 mmol, 0.025 equiv), and THF (2.5 mL, 0.2 M). The mixture was allowed to stir at 66 °C until complete conversion of the hydroxylamine by TLC (all reactions were complete in less than 12 h). The mixture was then filtered through a plug of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography.

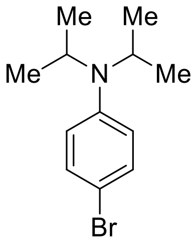
Synthesis of secondary anilines**:** Synthesis of secondary anilines can be performed without use of a glove box as all of the materials used in the reaction are sufficiently stable in air. CsF is highly hygroscopic and should be used either from a freshly opened bottle of dried CsF or should be flame dried under vacuum for several minutes in the reaction flask before the use. Copper(I) trifluoromethanesulfonate benzene complex does slowly oxidize in air and should be manipulated quickly when exposed to air. We found that with older bottles of copper(I) trifluoromethanesulfonate benzene complex we had to use higher catalyst loadings to achieve the same rate of the reaction. For convenience, we have performed the majority of the reactions described in table 3 using a glove box. However, as the results shown below demonstrate there is no significant difference in yields obtained in reactions that are setup using a glovebox and those set up outside of a glovebox.

<u>General procedure for secondary aniline outside the glovebox</u>: An air-free reaction flask charged with a stir bar was flame dried under vacuum, allowed to cool under nitrogen. To the flask was added CsF (227.9 mg, 1.5 mmol, 3.0 equiv), boronic ester (0.6 mmol, 1.2 equiv), bis(2-dicyclohexylphosphinophenyl)ether (9.8 mg, 0.018 mmol, 0.035 equiv), copper(I) trifluoromethanesulfonate benzene complex (3.1 mg, 0.013 mmol, 0.025 equiv), and THF (1.5 mL 0.1 M). The mixture was allowed to stir vigorously at 66 °C. Solution of *O*-benzoyl-*N*-alkyl hydroxylamine (0.250 mmol, 1.0 equiv, 0.5 M) in THF was added using a syringe pump over three hours under inert atmosphere. After 30 minutes, the reaction was filtered through a plug of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified using ion exchange chromatography.

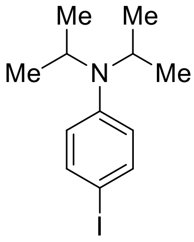
<u>General procedure for secondary aniline using glove box</u>: In a glove box, a 5 mL Schlenk flask was charged with a stir bar, copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 3.1 mg, 0.013 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 9.8 mg, 0.018 mmol), cesium fluoride (3.00 equiv, 1.500 mmol), 5,5-dimethyl-2-(2-methylphenyl)-1,3,2-dioxaborinane (1.20 equiv, 0.300 mmol) and THF (1.5 mL). The reaction flask was then brought outside of the glove box and vigorously stirred in an oil bath at 66 °C. Solution of *O*-benzoyl-*N*-alkyl hydroxylamine (1.00 equiv, 0.250 mmol, 0.5 M) in THF was added using a syringe pump over three hours under inert atmosphere. After 30 minutes, the reaction was filtered through a plug

of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified using ion exchange chromatography.

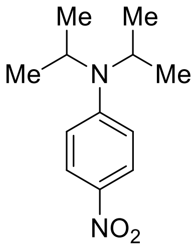
2.5.4 Characterization Data for Aniline



4-bromo-*N,N*-diisopropylaniline (Table 2.2, compound 2.5), compound was isolated as a white solid (120.2 mg, 94% yield). Compound **2.5** is a known compound and spectral data match the reported literature values.[11]

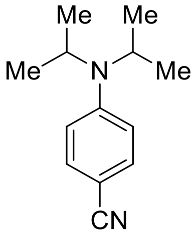


4-iodo-*N,N*-diisopropylaniline (Table 2.2, compound 2.6), compound was isolated as a white solid (133.2 mg, 88% yield). Compound **2.6** is a known compound and spectral data match the reported literature values.[11]

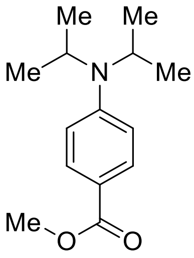


4-nitro-*N,N*-bis(propan-2-yl)aniline (Table 2.2, compound 2.7), compound was isolated as an orange powder (102.4 mg, 92% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 8.14 – 7.99 (m, 2H), 6.30 – 6.19 (m, 2H), 3.28 (hept, J = 6.8 Hz, 2H), 0.80 (d, J = 6.9 Hz, 12H). ^{13}C NMR (126

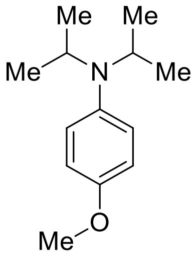
MHz, C_6D_6) δ 152.8, 137.3, 125.7, 113.4, 47.8, 20.4. GCMS (EI) calculated for $[M]^+$ 222.14, found 222.10. FTIR (neat, cm-1): 2976(w), 1598(s), 1310(s), 1294(s).



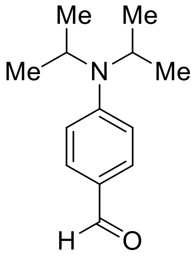
4-[bis(propan-2-yl)amino]benzonitrile (Table 2.2, compoun2.8), compound was isolated as a white powder (95.2 mg, 94% yield) ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 6.82 – 6.71 (m, 2H), 3.93 (hept, J = 13.8, 6.9 Hz, 2H), 1.30 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 151.0, 133.0, 120.6, 115.0, 98.1, 47.4, 20.5. GCMS (EI) calculated for [M]+ 202.15, found 202.10 FTIR (neat, cm-1): 3436(s), 2218(w),1636(s), 1516(s), 1265(s). The spectral data matched the literature.[11]



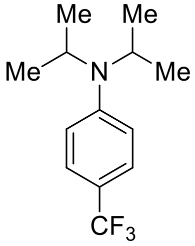
methyl 4-(diisopropylamino)benzoate (Table 2.2, compound 2.9), compound was isolated as a white solid (108.2 mg, 92% yield). Compound **2.9** is a known compound and spectral data match the reported literature values.[11]



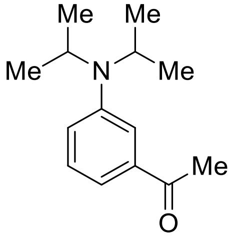
***N,N*-diisopropyl-4-methoxyaniline (Table 2.2, compound 2.10),** compound was isolated as a white solid (92.5 mg, 89% yield). Compound **2.20** is a known compound and spectral data match the reported literature values.[11]



4-(diisopropylamino)benzaldehyde (Table 2.2, compound 2.11), compound was isolated as a white solid (92.8 mg, 90% yield). Compound **2.11** is a known compound and spectral data match the reported literature values.[11]

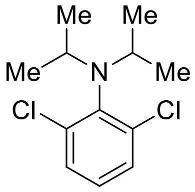


***N,N*-bis(propan-2-yl)-4-(trifluoromethyl)aniline (Table 2.2, compound 2.12),** compound was isolated as a colorless oil (108 mg, 89% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.61 – 7.28 (m, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.39 (hept, J = 6.9 Hz, 2H), 0.92 (d, J = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 126.0 (q, J = 3.7 Hz), 125.4 (q, J = 269.9 Hz), 117.5 (q, J = 32.5 Hz), 115.0, 47.5, 21.1. GCMS (EI) calculated for [M]+ 245.14, found 245.10. FTIR (neat, cm-1): 2962(m), 2877(m), 1618(s), 1524(s), 1321(s), 1109(s).

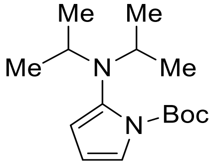


1-{3-[bis(propan-2-yl)amino]phenyl}ethan-1-one (Table 2.2, compound 2.13), compound was isolated as a yellow oil (105.2 mg, 96% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.77 (dd, J = 2.7, 1.6 Hz, 1H), 7.23 (dt, J = 7.5, 1.3 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.93 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 3.51 (hept, J = 6.8 Hz, 2H), 2.23 (s, 3H), 1.01 (d, J = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 197.2, 148.8, 138.3, 128.8, 123.1, 118.6, 117.7, 47.7, 26.4, 21.3. GCMS

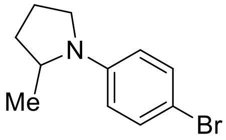
(EI) calculated for [M]+ 219.16, found 219.20. FTIR (neat, cm-1): 3054(w), 2973(w), 1680(m),1593(m), 1491(m), 1265(s).



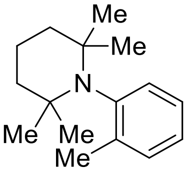
2,6-dichloro-*N,N*-diisopropylaniline (Table 2.2, compound 2.14), compound was isolated as a white solid (112.1 mg, 91% yield). Compound **2.14** is a known compound and spectral data match the reported literature values.[11]

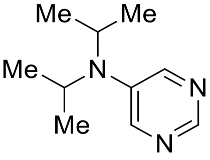


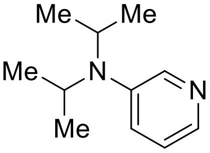
***tert*-butyl 2-[bis(propan-2-yl)amino]-1H-pyrrole-1-carboxylate (Table 2.2, compound 2.15),** compound was isolated as a colorless oil (125.9 mg, 95% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.29 (dd, J = 3.7, 1.9 Hz, 1H), 6.06 (t, J = 3.6 Hz, 1H), 5.89 (dd, J = 3.4, 1.9 Hz, 1H), 3.35 (hept, J = 6.4 Hz, 2H), 1.37 (s, 9H), 1.05 (d, J = 6.4 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 149.3, 138.1, 119.0, 112.0, 108.8, 81.9, 50.8, 28.0, 21.6. GCMS (EI) calculated for [M]+ 266.20, found 266.10. FTIR (neat, cm-1): 3106(w), 2970(s), 2871(m), 1729(s), 1330(s).

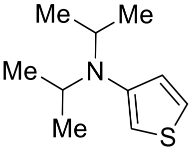


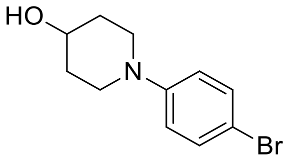
1-(4-bromophenyl)-2-methylpyrrolidine (Table 2.2, compound 2.16), compound was isolated as a white powder (114.8 mg, 96% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.44 – 7.23 (m, 2H), 6.37 – 6.02 (m, 2H), 3.35 (tt, J = 6.4, 3.2 Hz, 1H), 2.87 (ddd, J = 9.5, 7.6, 2.5 Hz, 1H), 2.69 – 2.54 (m, 1H), 1.70 – 1.33 (m, 3H), 1.29 – 1.05 (m, 1H), 0.81 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 131.8, 113.4, 106.9, 53.8, 48.3, 33.2, 23.4, 19.1. GCMS (EI) calculated for [M]+ 239.03, found 239.10. FTIR (neat, cm-1): 3053(w), 2986(w), 1593(w), 1422(w), 1265(s).

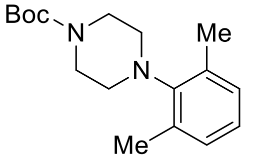

2,2,6,6-tetramethyl-1-(o-tolyl)piperidine (Table 2.2, compound 2.17), compound was isolated as a white solid (109.2 mg, 94% yield). Compound **2.17** is a known compound and spectral data match the reported literature values.[11]

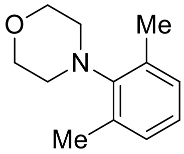

***N,N*-diisopropylpyrimidin-5-amine (Table 2.2, compound 2.18),** compound was isolated as a white solid (103.8 mg, 93% yield). Compound **2.18** is a known compound and spectral data match the reported literature values.[11]

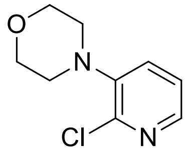

***N,N*-bis(propan-2-yl)pyridin-3-amine (Table 2.2, compound 2.19),** compound was isolated as a colorless oil (117.9 mg, 94%) ^{1}H NMR (500 MHz,C_6D_6) δ 8.48 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 4.5, 1.6 Hz, 1H), 6.92 – 6.75 (m, 2H), 3.39 (hept, J = 6.7 Hz, 2H), 0.92 (d, J = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.3, 142.2, 140.1, 124.9, 123.1, 47.6, 21.2. GCMS (EI) calculated for [M]+ 178.15, found 178.20. FTIR (neat, cm-1): 3046(m), 2972(s), 2875(m), 1583(s), 1265(s).


***N,N*-diisopropylthiophen-3-amine (Table 2.2, compound 2.20),** compound was isolated as a white solid (111.1 mg, 97% yield). Compound **2.20** is a known compound and spectral data match the reported literature values.[11]

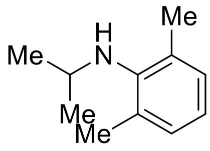

1-(4-bromophenyl)piperidin-4-ol (Table 2.2, compound 2.21), compound was isolated as a yellow powder (117.3 mg, 92% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.30 – 7.21 (m, 2H), 6.42 – 6.33 (m, 2H), 3.28 (s, 1H), 3.13 – 2.94 (m, 2H), 2.38 (ddd, J = 12.7, 9.5, 3.3 Hz, 2H), 1.48 (dddt, J = 12.9, 5.3, 3.7, 2.0 Hz, 2H), 1.27 (dtd, J = 12.8, 9.0, 3.9 Hz, 2H), 0.63 (s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 150.9, 132.3, 118.4, 111.4, 68.0, 47.5, 34.5. GCMS (EI) calculated for [M]+ 255.03, found 255.10. FTIR (neat, cm-1): 3287(b), 3054(w), 2818(w), 1589(s), 1494(s), 1265(s).


***tert*-butyl 4-(2,6-dimethylphenyl)piperazine-1-carboxylate (Table 2.2, compound 2.22),** compound was isolated as a white powder (190.2 mg, 94% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 6.91 (s, 3H), 3.40 (s, 4H), 2.98 – 2.41 (m, 4H), 2.10 (s, 6H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.8, 148.6, 136.9, 129.4, 125.7, 79.1, 49.9, 28.6, 19.7. GCMS (EI) calculated for [M]+ 290.20, found 290.20. FTIR (neat, cm-1): 3053(s), 2985(w), 1675(s), 1642(s), 1266(s).

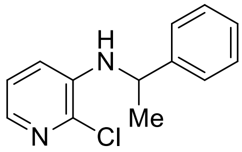

4-(2,6-dimethylphenyl)morpholine (Table 2.2, compound 2.23), compound was isolated as a white powder (121.3 mg, 91% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 6.95 (s, 3H), 3.58 (t, 4H), 2.78 (t, 4H), 2.22 (s, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 148.4, 137.0, 129.5, 125.7, 68.2, 50.4, 19.7. GCMS (EI) calculated for [M]+ 191.13, found 191.20. FTIR (neat, cm-1): 3053(s), 1631(s), 1264(s), 1111(w).



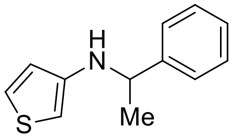
4-(2-chloropyridin-3-yl)morpholine (Table 2.2, compound 2.24), compound was isolated as a yellow oil (129.9 mg, 94% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.88 (t, J = 3.1 Hz, 1H), 6.53 (d, J = 3.2 Hz, 2H), 4.02 – 3.10 (m, 4H), 3.02 – 2.05 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 145.7, 143.0, 128.0, 123.0, 66.9, 51.2. GCMS (EI) calculated for [M]+ 198.06, found 198.10. FTIR (neat, cm-1): 3053(m), 2860(m), 1447(s), 1409(s), 1267(s), 1375(s).



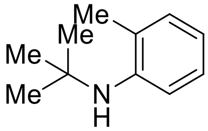
2,6-dimethyl-*N*-(propan-2-yl)aniline (Table 2.2, compound 2.25), compound was isolated as a colorless oil (102.5 mg, 90% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.00 (d, J = 7.3 Hz, 2H), 6.87 (dd, J = 8.0, 6.8 Hz, 1H), 3.26 (hept, J = 6.3 Hz, 1H), 2.57 (s, 1H), 2.13 (s, 6H), 0.93 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.4, 129.3, 128.9, 121.4, 48.6, 24.0, 19.1. GCMS (EI) calculated for [M]+ 163.14, found163.15. FTIR (neat, cm-1); 3370(s), 2965(s), 1595(m), 1475(s), 1380(m).



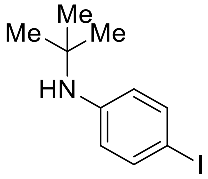
2-chloro-*N*-(1-phenylethyl)pyridin-3-amine (Table 2.2, compound 2.26), compound was isolated as a yellow solid (103.0 mg, 89% yield) ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.61 (dd, J = 4.6, 1.6 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.18 (m, 1H), 6.92 (dd, J = 8.0, 4.6 Hz, 1H), 6.64 (dd, J = 8.1, 1.6 Hz, 1H), 4.79 (s, 1H), 4.64 – 4.34 (m, 1H), 1.58 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 139.9, 137.1, 136.6, 129.0, 127.5, 125.7, 123.3, 118.9, 77.2, 53.4, 25.2. GCMS (EI) calculated for [M]+ 232.08, found 232.20. FTIR (neat, cm-1): 350 (s), 1652(m), 149(w).



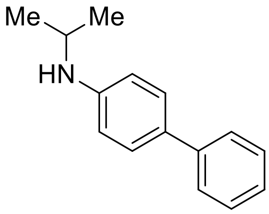
***N*-(1-phenylethyl)thiophen-3-amine (Table 2.2, compound 2.27),** compound was isolated as a brown oil (89.0 mg, 88% yield) ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.52 – 7.17 (m, 5H), 7.08 (dd, J = 5.1, 3.0 Hz, 1H), 6.61 (dd, J = 5.1, 1.5 Hz, 1H), 5.66 (dd, J = 3.0, 1.5 Hz, 1H), 4.36 (q, J = 6.7 Hz, 1H), 4.14 (s, 1H), 1.48 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz,CD_2Cl_2) δ 148.1, 146.1, 129.1, 129.0, 127.5, 125.0, 121.0, 97.9, 56.3, 25.3. GCMS (EI) calculated for [M]+ 203.08, found 203.00. FTIR (neat, cm-1): 3402(w), 3050(w) 2977(w), 2867(w), 1558(s), 1261(s).



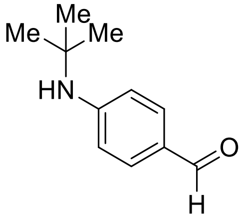
***N-tert*-butyl-2-methylaniline (Table 2.2, compound 2.28),** compound was isolated as an orange solid (101.2 mg, 89% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.12 (d, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 3.23 (s, 1H), 1.90 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.1, 130.6, 126.7, 123.7, 117.2, 114.3, 51.3, 30.3, 18.3. GCMS (EI) calculated for [M]+ 163.14, found 163.10. FTIR (neat, cm-1): 3440(m), 3050(s), 2975(s), 1586(S), 1482(S), 1320(s).



***N-tert*-butyl-4-iodoaniline (Table 2.2, compound 2.29),** compound was isolated as a white solid (124.8 mg, 91% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.53 – 7.20 (m, 2H), 6.29 – 5.93 (m, 2H), 3.01 (s, 1H), 0.99 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.5, 137.5, 118.8, 78.8, 51.4, 29.9. GCMS (EI) calculated for [M]+ 275.02, found 275.00. FTIR (neat, cm-1): 3416(s), 2978(w), 1636(m), 1458(m), 1219(m).



4-phenyl-*N*-(propan-2-yl)aniline (Table 2.2, compound 2.30), compound was isolated as a yellow solid (100.4 mg, 95% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.74 – 7.53 (m, 2H), 7.53 – 7.45 (m, 2H), 7.27 (t, J = 7.6 Hz, 2H), 6.45 (d, J = 8.6 Hz, 2H), 3.49 – 3.20 (m, 1H), 3.01 (s, 1H), 0.90 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 147.9, 141.9, 130.0, 129.3, 128.4, 126.7, 126.6, 114.0, 44.9, 23.4. GCMS (EI) calculated for [M]+ 211.14, found 211.20. FTIR (neat, cm-1): 3412(s), 2097(m), 1645(m), 1264(m).



4-(*tert*-butylamino)benzaldehyde (Table 2.2, compound 2.31), compound was isolated as an orange oil (111.2 mg, 90% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 9.80 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 8.8 Hz, 2H), 3.62 (s, 1H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.2, 152.5, 132.1, 125.7, 113.8, 51.4, 29.5. GCMS (EI) calculated for [M]+ 177.12, found 177.15. FTIR (neat, cm-1): 3357(w), 2978(m), 2812(m), 1670(s), 1598(s), 1310(m), 1208(m), 1164(s).

2.5.5 Stoichiometric Reaction of Organocopper Complexes (Scheme 2.5 & 2.7).

In a nitrogen-filled glove box, a dram vial charged with a stir bar, Cy_4DPE-Phos-Cu-(4-bromo)Ph (0.250 mmol, 1.0 equiv), either, *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (0.250 mmol, 1.0 equiv), or *O*-benzoyl-*N*-tertbutyl hydroxylamine (0.250 mmol, 1.0 equiv), and THF (1.25 mL, 0.2 M). The reaction mixture was allowed to stir for 30 min at 65 °C. A 30 µL aliquot was taken. The aliquot was diluted with 500 µL DCM and pipetted onto silica gel plug and rinsed through with 1400 µL DCM before GC analysis.

2.5.6 Kinetics Experiments (Figure 2.1).

Hydroamination Time Course: In a nitrogen-filled glovebox, a dram vial was charged with stir bar, CsF (113.95 mg, 0.750 mmol, 3.0 equiv), copper (I) trifluoromethanesulfonate benzene complex (250 µL of a 0.025 M stock solution, 0.025 equiv), Bis(2-dicyclohexylphosphinophenyl)ether (250 µL of a 0.035 M stock solution, 0.035 equiv), 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (250 µL of a 1.2 M stock solution, 0.3 equiv), *O*-benzoyl-*N,N*-diisopropyl hydroxylamine (0.250 mmol, 250 µL of a 1 M stock solution, 1.0 equiv), dodecane (10.6 mg, 0.063 mmol, 0.25 equiv), and THF (0.2 M). The reaction mixture was stirred at 80 °C. Aliquot was taken at the desired time point. The 30 µL was diluted in 500 µL of DCM and pipetted onto silica gel plug and rinsed through with 1400 µL of DCM to quench the reaction before GC analysis.

Order of Boronic ester: In a nitrogen-filled glovebox, a dram vial was charged with stir bar, CsF (113.95 mg, 0.750 mmol, 3.0 equiv), copper (I) trifluoromethanesulfonate benzene complex (250 µL of a 0.025 M stock solution, 0.025 equiv), Bis(2-dicyclohexylphosphinophenyl)ether (250 µL of a 0.035 M stock solution, 0.035 equiv), varying amounts of 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (a: 1.5 equiv, b: 3.0 equiv, c: 4.5 equiv), *O*-benzoyl-*N,N*-diisopropyl hydroxylamine (1.0 equiv), dodecane (10.6 mg, 0.063 mmol, 0.25 equiv), and THF (0.2 M). The reaction mixture was stirred at 80 °C. Aliquot was taken at the desired timepoint. The 30 µL was diluted in 500 µL of DCM and pipetted onto silica gel plug and rinsed through with 1400 µL of DCM to quench the reaction before GC analysis.

Order of Amine: In a nitrogen-filled glovebox, a dram vial was charged with stir bar, CsF (113.95 mg, 0.750 mmol, 3.0 equiv), copper (I) trifluoromethanesulfonate benzene complex (250 µL of a

0.025 M stock solution, 0.025 equiv), Bis(2-dicyclohexylphosphinophenyl)ether (250 µL of a 0.035 M stock solution, 0.035 equiv), 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (1.50 equiv), varying amount of *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (a:1.0 equiv, b: 1.5 equiv, c: 2.0 equiv), dodecane (10.6 mg, 0.063 mmol, 0.25 equiv), and THF (0.2 M). The reaction mixture was stirred at 80 °C. Aliquot was taken at the desired time point. The 30 µL was diluted in 500 µL of DCM and pipetted onto silica gel plug and rinsed through with 1400 µL of DCM to quench the reaction before GC analysis.

2.6 References

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Chapter 3: Copper Catalyzed Synthesis of 1,4-Dienes and Trisubstituted Alkenes by Anti-Markovnikov Hydroallylation of Terminal and Functionalized Internal Alkynes

Parts of this chapter was reproduced from the following manuscript: Mailig, M.; Hazra, A.; Armstrong, M. K.; Lalic, G. *J. Am. Chem. Soc.* **2017,** *139*, 6969-6977.

3.1 Introduction

1,4-Diene motif is regularly observed in natural products.[1,2] One example is the essential fatty acid, linoleic acid, which is a vital precursor to many bioactive natural products such as arachidonic acid, docosahexaenoic acid, and epilachnadiene (Figure 3.1).[3,4] 1,4-Diene containing natural products are known to be involved in many important biological functions such as cell signaling, anti-inflammatory process, and are important as anti-cancer compounds.[2]

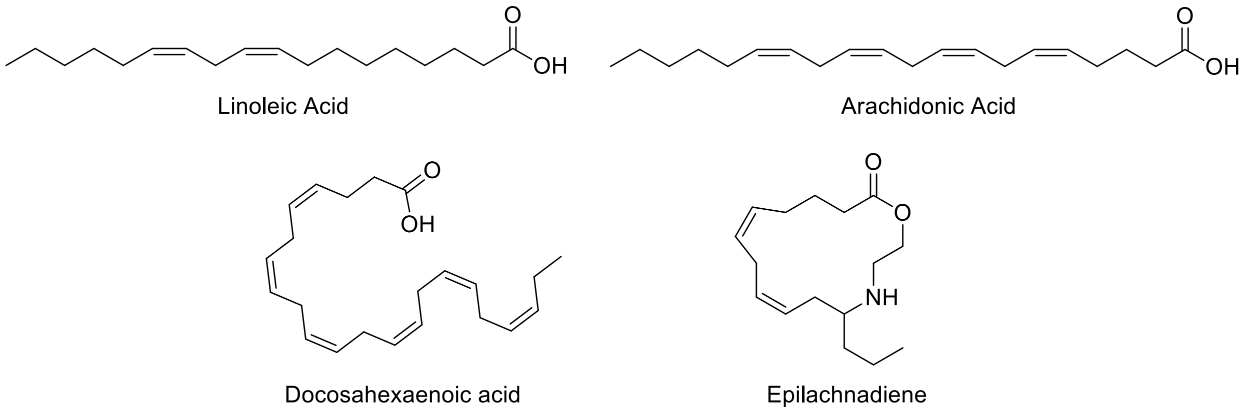
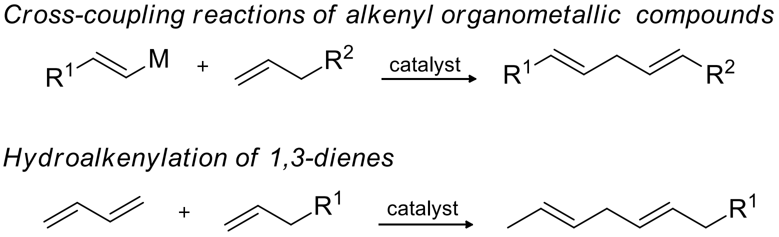

Linoleic Acid
Arachidonic Acid
Docosahexaenoic acid
Epilachnadiene

Figure 3.1. Natural products containing 1,4-diene motif.

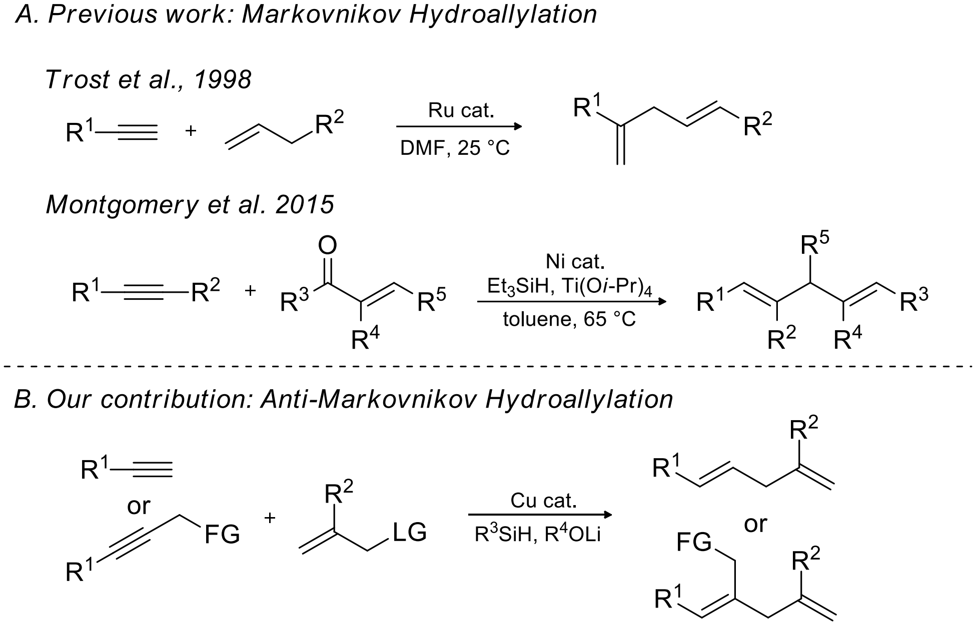
1,4-Dienes are also important synthetic intermediates for the synthesis of useful molecules.[5] Their significance as synthetic targets is shown by continued effort to design new techniques for their synthesis. There are variety of different approaches, both stoichiometric and catalytic that have been reported over the past few decades. An elegant stoichiometric synthesis of 1,4 dienes was recently reported by Micalizio et al. using titanium-promoted reductive coupling of vinyl cyclopropanes and alkynes or vinylsilanes.[6–9]

Recently, the development for synthesis of 1,4-diene has been focused on catalytic methods using a transition metal catalysts. Two of the most common methods are cross coupling[10–18] reactions of alkenyl organometallic reagents with allylic electrophiles and hydroalkenylation of 1,3-dienes.[19–24] Hydroalkenylation methods offer a significant advantage over cross coupling methods (Scheme 3.1). The substrates for hydroalkenylation does not need to be functionalized and this method can be used to make highly substituted 1,4-dienes, although a mixture of diastereomers is obtained in the hydroalkenylation method.



Scheme 3.1. Catalytic reactions for the synthesis of 1,4-dienes

Another approach is hydroallylation of alkynes.[5,25,26] Although less common, this method is highly effective. For example, Trost et al. reported a ruthenium-catalyzed hydroallylation of terminal alkynes which proceeds with Markovnikov selectivity (Scheme 3.2A).[25] This method has exceptional substrate scope and functional group compatibility. A more recent example was reported by Montgomery et al. which uses nickel as a catalyst to reductively couple internal alkynes or alkyl aryl alkynes with enals or enones to provide 1,4-dienes with excellent regio- and diastereoselectivity over a wide range of substrates (Scheme 3.2A).[27] Similarly, high regioselectivity can be obtained using boro-,[28] silyl-,[29] and alkynyl-[30] substituted internal alkynes as substrates.



Scheme 3.2. Hydroallyation of alkynes for the synthesis of 1,4-dienes.

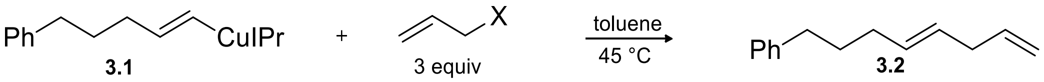
In this chapter, I describe our success in development of anti-Markovnikov hydroallylation of terminal and functionalized internal alkynes for the synthesis of 1,4-dienes (Scheme 3.2B). Our technique was based on the hydrofunctionalization of alkynes. Our lab has worked on copper-catalyzed hydrofunctionalization of alkyne to achieved semireduction,[31] hydrobromination,[32] and hydroalkylation.[33,34] Common to these catalytic reactions is the syn-diastereospecific hydrocupration[35] of the alkynes described by Sadighi and coworkers, followed by electrophilic functionalization. In theory, if an allyl electrophile is able to react with alkenyl copper, we could achieved 1,4-dienes as a product.

In addition to terminal alkynes we developed a technique for hydroallylation of internal alkynes. The regioselectivity issue is one of the major challenges with hydroallylation of internal alkynes. To overcome this issue, fine tuning the steric and electronic properties of the internal alkyne is common. This limits the reaction to aryl-,[27] alkenyl-,[30] and silyl-[35]substituted alkyl acetylenes as substrates to synthesize 1,4-dienes. Our technique uses substrates that contain polar functional group at the propargylic position and we can obtain compounds with high regio- and diasteroselectivty.

3.2 Anti-Markovnikov Hydroallylation of Alkynes

3.2.1 Reaction Optimization

Our investigation began with a need to understand which type of electrophile to use in the catalytic reaction. To understand this, we designed an experiment where we would allow an alkenyl copper complex, the proposed nucleophile in the hydroallylation reaction, to react with different types of allylic electrophiles. The results of this experiment showed that allyl chloride and allyl phosphate are efficient electrophiles in this stoichiometric reaction with alkenyl copper complex **3.1** (Scheme 3.3). The less reactive allyl carbonate and allyl acetate gave very little to no desired product.

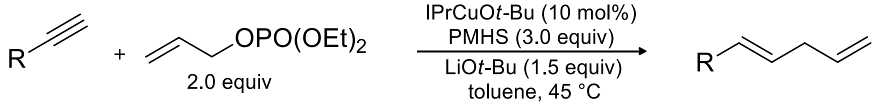


X = OP(O)(OEt)$_2$	98% (12 h)
Cl	96% (12h)
OAc	0% (24 h)
OBoc	9% (24 h)

Scheme 3.3. Stoichiometric reaction of alkenyl copper complex **3.1** with allyl electrophiles.

After understanding what type of electrophile to use, we then explored the catalytic reaction and found that the best results can be obtained when using IPrCuO*t*-Bu as a catalyst precursor, PMHS as hydride source, LiO*t*-Bu as a turn over reagent, and toluene as solvent at 45 °C. The reaction is typically complete after 16 h. During the course of finding the most optimal conditions, we found that allyl phosphate works best as an electrophile even though both allyl chloride and allyl phosphate gave good results in the stoichiometric reaction (Table 3.1, entries 1-2). NHC copper(I) *tert*-butoxide works better than NHC copper(I) chloride as catalyst precursor (Table 3.1, entry 3). Other NHC copper(I) chlorides also gave the desired product, but in much lower yield (Table 3.1, entries 4-7). A variety of copper complexes supported by phosphine ligands gave little to no product (Table 3.1, entries 8-11). PMHS and $(Me_2HSi)_2O$ both gave the desired product in high yield (Table 3.1, entry 1 and 12). The highly reactive $(EtO)_3SiH$ gave a significantly lower yield while a variety of other di or trialkyl substituted silanes also gave little to no desired product (Table 3.1, entries 13-15). The reaction works in a variety of solvents, but the best results are obtained in toluene, chlorobenzene and isooctane (Table 3.1, entries 16-20).

Table 3.1. Reaction optimization for hydroallylation of terminal alkynes.



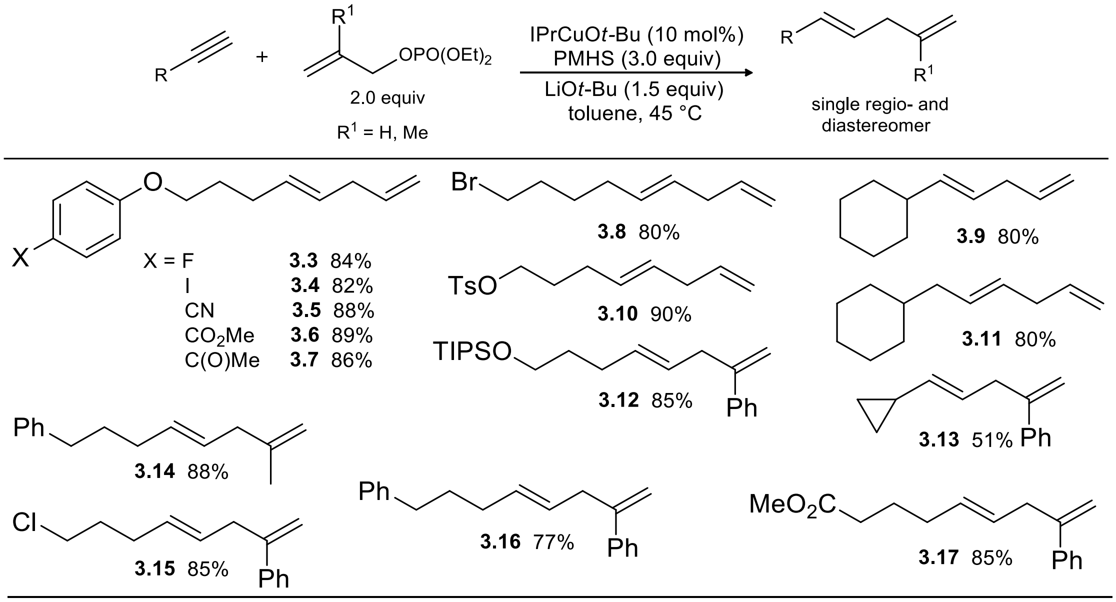
entry	change from standard conditions	yield^a
1.	none	89%^{b}
2.	allyl chloride as an electrophile	44%
3.	IPrCuCl as catalyst	69%
4.	SIPrCuCl as catalyst	59%
5.	Cl_2IPrCuCl as catalyst	31%
6.	ICyCuCl as catalyst	42%
7.	IPr*CuCl as catalyst	36%
8.	BINAP^c	1%
9.	SEPHOS^c	0%
10.	PCy_3^{c}	3%
11.	DPPF^c	1%
12.	$(Me_2HSi)_2O$ instead of PMHS	86%
13.	t-Bu_2SiH_2 instead of PMHS	28%
14.	$(EtO)_3SiH$ instead of PMHS	16%
15.	Et_3SiH instead of PMHS	0%
16.	chlorobenzene	88%
17.	THF	76%
18.	dioxane	72%
19.	isooctane	88%
20.	acetonitrile	50%

[a] GC Yields are reported. All reactions performed on 0.1 mmol scale. [b] Yield of the pure isolated product is reported. [c] Copper (I) triflate benzene complex was used as catalyst instead of IPrCuO*t*-Bu.

3.2.2 Reaction Scope

We first explored the scope of the reaction with variety of terminal alkynes. Using the optimized reaction conditions shown in entry 1 of Table 3.1, we were able to synthesize a variety of 1,4-dienes in good yield and these results are shown in Table 3.2. A wide variety of functional groups on the terminal alkyne were tolerated by the reaction condition. The hydroallylation can be achieved in the presence of aryl halides, nitriles, esters, alkyl halides, tosylates, and protected alcohols. It is important to note that even a ketone, which under very similar conditions have been reduced, was well tolerated using the optimal reaction conditions.[36,37]

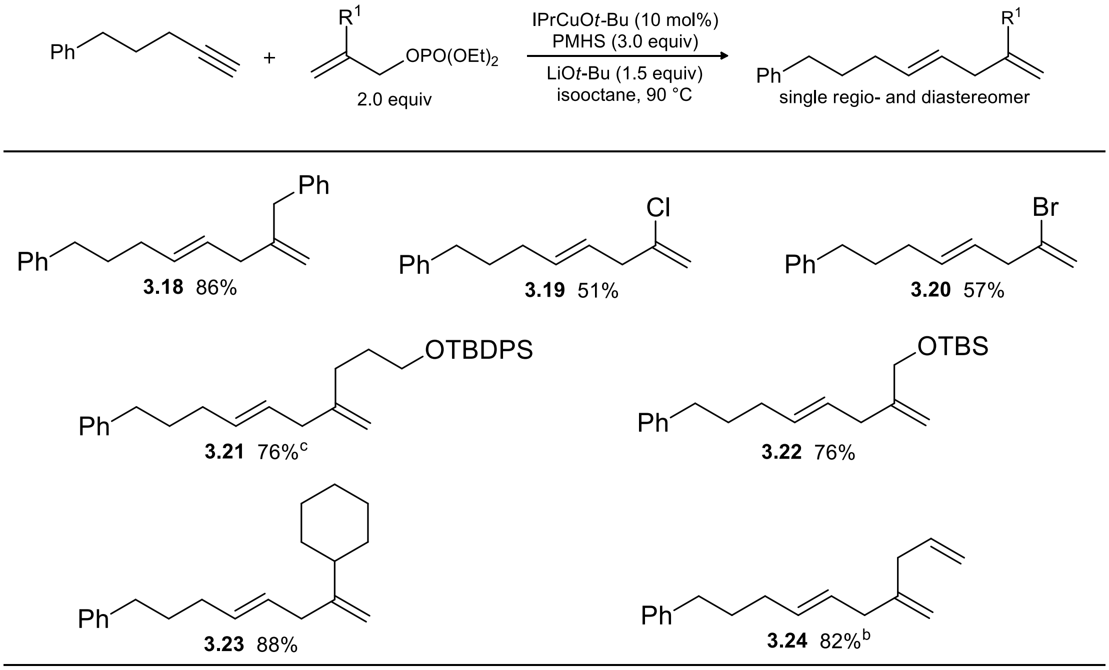
Table 3.2. Reaction scope for hydroallylation of terminal alkynes.



All reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported.

We next explored the scope of the allylic electrophile. However, when the optimized conditions were used for hydroallylation of terminal alkynes with allylic electrophiles that have substitution on the central carbon, the yield was significantly decreased along with the formation of undesired products. Only 2-phenyl and 2-methyl substituted allylic electrophiles worked well when using the optimized conditions as shown in Table 3.2, compounds **3.12-3.17**. After further optimization, we found that the yield increased when isooctane was used as solvent and the reaction was stirred at 90 °C. The scope of the allylic electrophile is shown in Table 3.3. A variety of 2-substituted allylic electrophiles, such as benzyl, sterically hindered cyclohexane, alkenes, halides, and protected alcohols were well tolerated using our reaction conditions. It is important to note that chloro- and bromo- substituted electrophiles can provide a synthetic handle for further derivatization.

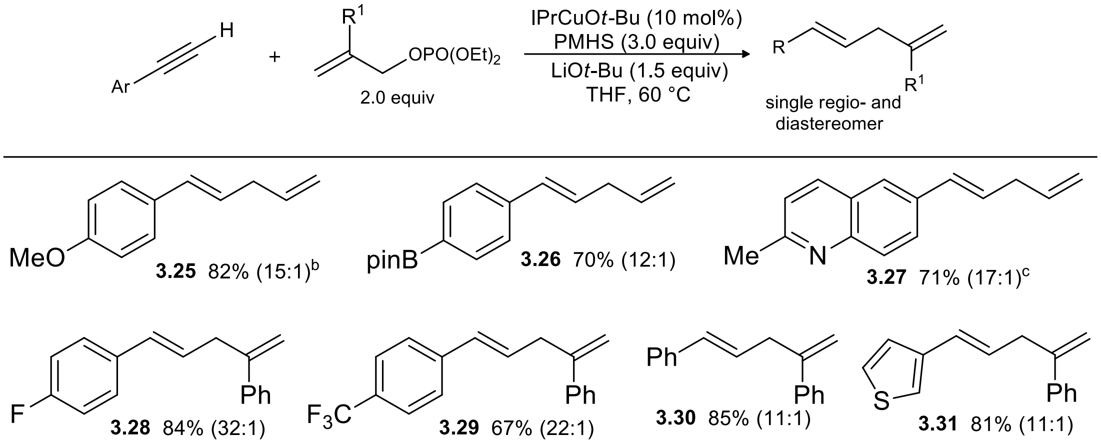
Table 3.3. Reaction scope for hydroallylation of terminal alkynes with 2-substituted allylic electrophiles.



[a] Unless otherwise noted, all reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. [b] Reaction performed on 0.15 mmol scale. [c] Reaction performed on 0.25 mmol scale.

We also explored the scope of the reaction with a variety of aryl alkynes. Aryl alkynes are known to be a challenging substrate for reactions that are catalyzed by late transition metal complexes. This is due to the increased acidity of the alkyne and the regioselectivity of the hydrometallation step. When the optimized reaction conditions shown in entry 1 of Table 3.1 were used, the yield was significantly decreased along with the formation of undesired products. After further optimization, we found that using THF at 60 °C increased the yield significantly. The scope of the hydroallylation of aryl alkynes is shown in Table 3.4. Heteroaryl alkyne such as quinolines and thiophenes and aryl alkynes bearing electron-donating and electron-withdrawing groups were well tolerated. Although, lower yield was obtained with highly acidic aryl alkynes (Table 3.4, compounds 3.28 and 3.29). It is important to note that in all reactions, only one diastereomer is formed and good anti-Markovnikov regioselectivity is observed.

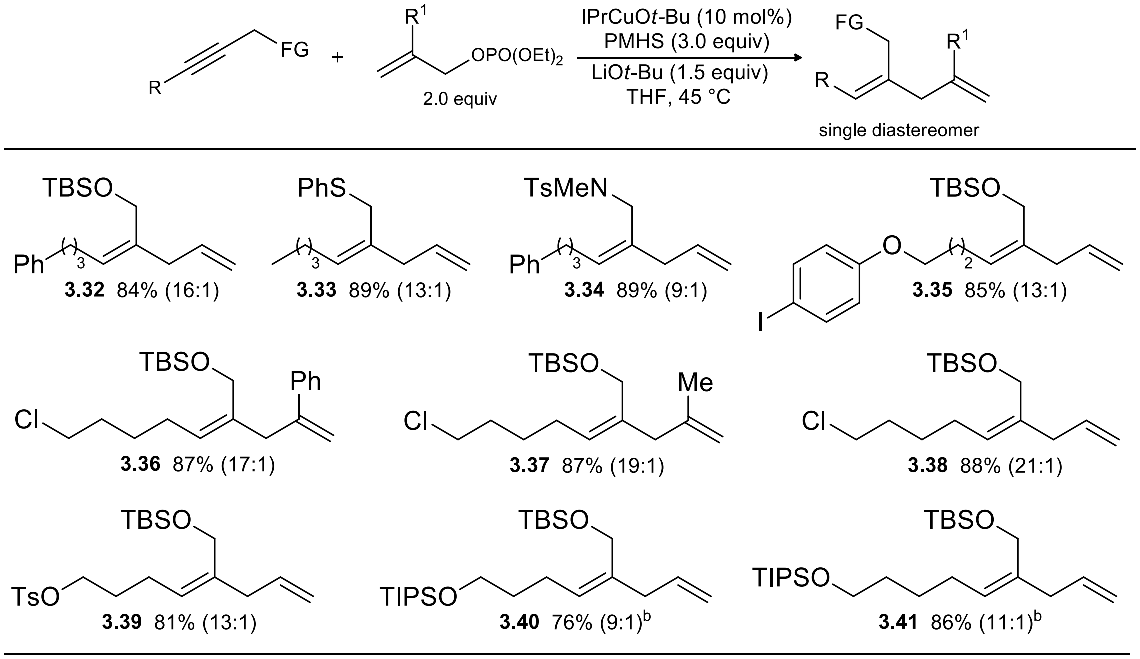
Table 3.4. Reaction scope of hydroallylation of aryl alkynes.



[a] Unless otherwise noted, all reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. Regioselectivity reported in parenthesis was determinded by GC analysis of the crude reaction mixture. [b] 3.0 equiv of phosphate was used.
[c] Reaction performed on 0.25 mmol scale.

To establish the full scope of the hydroallylation reaction, we explored the reactivity of internal alkynes. We found that having a polar functional group at the propargylic position and through a minor change in the optimized conditions; we were able to achieve high regio- and diasteroselectivty with high yield. The scope of the hydroallylation of internal alkynes is shown in Table 3.5. The scope mimics the scope observed for hydroallylation of terminal alkynes. Derivatives of propargylic alcohols, thiols, and amines were also well tolerated (Table 3.5 compounds **3.32-3.34**). It is important to note that for substrates containing polar functional group on both sides, the selectivity is controlled by the polar group closer to the alkyne.

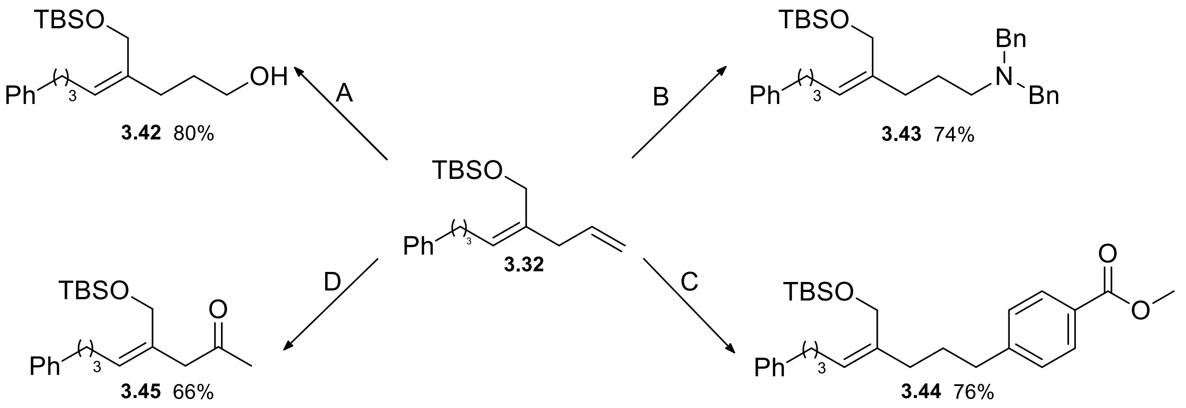
Table 3.5. Reaction scope of hydroallylation of internal alkynes.



[a] Unless otherwise noted, all reactions performed on 0.5 mmol scale. Yields of pure isolated products are reported. Regioselectivity reported in parenthesis was determinded by GC analysis of the crude reaction mixture. [b] Reactions performed in isooctane at 60 °C.

3.3 Functionalization of the Trisubstituted Alkene

The hydroallylation of internal alkynes allows the synthesis of a skipped diene containing a trisubstituted alkene. This skipped diene can be used to access a complex trisubstituted alkene by taking advantage of the terminal alkene as a good synthetic handle. To demonstrate the synthetic utility of the terminal alkene, we performed hydration, hydroamination, hydroarylation and oxidation (Scheme 3.4).

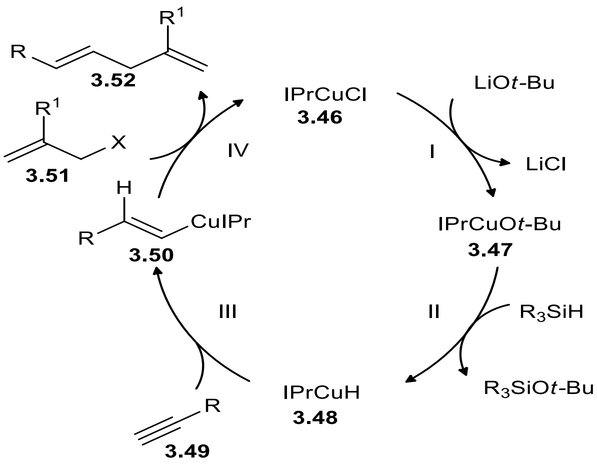


Conditions: a) 9-BBN (1.1 equiv), 1,4-dioxane, 60 °C, 12 h; then $NaBO_3$ (3.3 equiv), THF, 25 °C, 4h; b) 9-BBN (1.0 equiv), 1,4-dioxane, 60 °C, 12 h; then ICyCuCl (5 mol%), LiOtBu (1.1 equiv), Bn_2NOBz (1.0 equiv), toluene, 60 °C; c) 9-BBN (1.0 equiv), 1,4-dioxane, 100 °C, 24 h; then $Pd(OAc)_2$ (1 mol%), PCy_3 (2 mol%), Cs_2Co_3 (3.0 equiv), 1,4-dioxane, 100 °C, 24 h. d) $PdCl_2$ (15 mol%), CuCl (1.4 equiv), O_2, DMF:H_2O (7:1), 24 h.

Scheme 3.4. Functionalization of terminal alkene to synthesized a more complex trisubstituted alkenes.

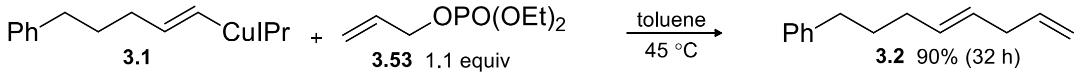
3.4 Mechanism

We proposed that the copper-catalyzed hydroallylation of alkynes proceeds according to the mechanism depicted in Scheme 3.5. In the first step, a copper chloride **3.46** transmetallates with LiO*t*-Bu to form a copper (I) alkoxide **3.47** which undergo transmetallation with a silane to form a copper (I) hydride complex **3.48**. Complex **3.48** reduces the alkyne to form alkenyl copper complex **3.50**. Allylation of complex **3.50** with allyl phosphate **3.51** produces the skipped diene **3.52**.



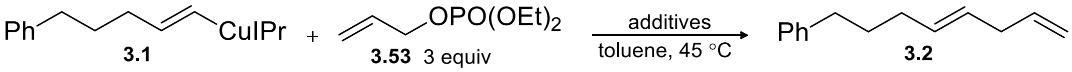
Scheme 3.5. Proposed mechanism for hydroallylation.

The stoichiometric reactions performed by Sadighi[38] and us[31–33] support the feasibility of the elementary steps I, II, and III in the proposed catalytic reaction. However, we observed that the stoichiometric reaction of alkenyl copper complex **3.1** with 1.1 equiv of allyl phosphate **3.53** took 32 h to complete, while the catalytic reaction is done within 16 h (Scheme 3.6). This observation indicates that the proposed allylation of complex **3.1** is kinetically inconsistent with the proposed hydroallylation reaction.



Scheme 3.6. Stoichiometric reaction of alkenyl copper complex **3.1** with allyl phosphate **3.53.**

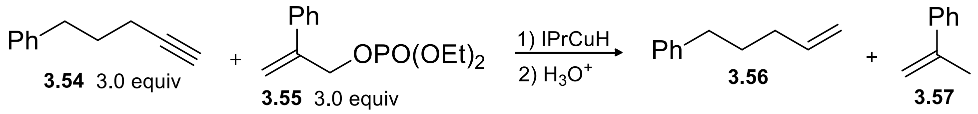
We therefore explored the effect of the individual components of the catalytic reaction. We observed that in a stoichiometric reaction of complex **3.1** and **3.53** in the presence of LiO*t*Bu, the initial rate is 4.7 times faster than in the absence of LiO*t*Bu (Scheme 3.7). In addition, we also observed that in the presence of both LiO*t*Bu and 12-crown-4, the initial rate is 4.3 times faster than in their absences (Scheme 3.7). These observations indicate that it is likely not the Li ion that is responsible with the rate increase, but the alkoxide. In the presence of alkoxide, alkenyl copper could possibly form an alkoxycuprate intermediate, which can act as the reactive nucleophile. Alkoxycuprates have been postulated as the reactive intermediate for asymmetric alkylation of alkyl lithium reagents in the presence of a stoichiometric amount of copper and chiral alkoxide.[39–44]



additives	relative initial rate
none	1
LiO*t*-Bu	4.7
LiO*t*-Bu + 12-crown-4	4.3

Scheme 3.7. Effect of additives on the allylation of alkenyl copper complex **3.1.**

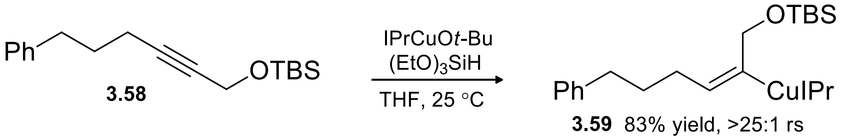
Several groups, including ours, have shown that the (NHC)CuH complexes are known to reduce a variety of electrophiles such as alkyl iodides,[45] alkyl triflates,[45] propargylic epoxides,[46] and carbonates.[47] We performed a competition experiment between terminal alkyne **3.54** and allyl phosphate **3.55** with IPrCuH (Scheme 3.8). We observed that the alkyne reduction is about two times faster than the allyl phosphate reduction. This observation indicates that the slow reduction of allyl phosphate allows the hydrocupration of alkyne to happen first followed by the hydroallylation. In addition, this observation is consistent with the fact that two equivalent of allyl phosphate is necessary for our hydroallylation reaction.



product	yield	relative rate
3.56	61%	2.3
3.57	27%	1

Scheme 3.8. Hydrocupration of alkyne **3.54** in the presence of allyl phosphate **3.55.**

Given the broad scope and high regioselectivity of the hydroallylation of internal alkyne, we looked at the regioselectivity and stability of the alkenyl copper complexes from internal alkynes. We were able to isolate and obtain an X-ray crystal structure of the alkenyl copper complex **3.59** from the stoichiometric reaction of OTBS-substituted alkyne **3.58** and IPrCuH (Scheme 3.9).[48] We found that complex **3.59** is quite stable in C_6D_6 at 45 °C. In addition, we observed by ^1H NMR high regioselectivity (rs > 25:1) from the crude stoichiometric reaction. The X-ray structure of complex **3.59** reveals that there is no interaction between the OTBS and copper (Cu-O distance is 3.22 Å). Based on this observation, we can conclude that the regioselectivity is not a result of the direct interaction between the OTBS and the catalyst. A possible explanation for high selectivity is the inductive effect of the OTBS group, which polarizes the alkyne.



Scheme 3.9. Stoichiometric hydrocupration of internal alkyne **3.58**

3.5 Conclusion

We have developed a method to synthesized 1,4-dienes by anti-Markovnikov hydroallylation of terminal, aryl and functionalized internal alkynes. This method is *syn*-stereospecific and highly regioselective. In addition, this method allows us to synthesize trisubstituted alkenes from functionalized internal alkynes. The reaction has a broad substrate scope and can be performed in the presence of a variety of functional groups including nitriles, ketones, esters, sulfonate esters, alkyl halides, aryl halides, sulfonamides, thioesters, and silyl ethers. We also demonstrated that the terminal alkene of the hydroallylation product is a good synthetic handle for further functionalization. In addition, we discovered that LiO*t*-Bu plays a special role in the allylation step of the catalytic cycle.

3.6 Experimental

3.6.1 General and Materials

General: All reactions were performed under a nitrogen atmosphere with flame-dried or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a 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. 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. 1H- and 13C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. 1H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak (CDCl3 (7.26 ppm), or C6D6 (7.16 ppm)). 13C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent (CDCl3: δ 77.2 ppm, C6D6: δ 128.1 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, 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, CH2Cl2, acetonitrile, DME, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled over calcium hydride, degassed, and stored over 4Å molecular sieves. Isooctane, chlorobenzene, and DCE were degassed and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. Commercial reagents were purchased from Sigma-Aldrich, TCI America, GFS-Chemicals, and AK-Scientific. Polymethylhydrosiloxane (PMHS) was purchased from Acros Organic and was degassed and stored over 4Å molecular sieves.

3.6.2 Stoichiometric Reaction of Alkenyl Copper with Different Electrophiles

In a nitrogen-filled glovebox, a stock solution of alkenyl copper complex **5** (191.2 mg, 0.32 mmol, 1.0 equiv) and internal standard TMB (26.8 mg, 0.16 mmol, 0.5 equiv) in 2000 µL toluene was prepared before the experiment. A 500 µL aliquot of the alkenyl copper/TMB stock solution was added to dram vial charged with stir bar and 300 µL of toluene. To this solution was added allyl electrophile (0.240 mmol, 3.0 equiv). The reaction mixture was stirred at 45 °C. A 50 µL aliquot was taken. The aliquot was diluted with 500 µL EtOAc and pipetted onto silica gel plug and rinsed through with 1000 µL EtOAc before GC analysis. Table S6 shows the product yield of the reaction.

Table 3.6. Yield of compound **3.2** with different electrophile.

Electrophile	**% Yield 12h**
Allyl phosphate (1.1 equiv)	90% (After 32 h)
Allyl phosphate	98%
Allyl chloride	96%
Allyl acetate	0% (After 24 h)
Allyl carbonate	9% (After24 h)

3.6.3 General Procedure for Reaction Optimization (Table 3.1)

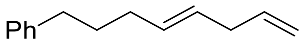
In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, LiO*t*-Bu, catalyst (either a copper complex (Table 3.1, entries 3-7), or copper (I) triflate benzene complex and ligand (Table 3.1, entries 8-11), solvent, silane, and alkyne respectively. The reaction mixture was allowed to stir at 25 °C until the yellow color disappears. The allyl diethyl phosphate and TMB (as internal standard) were added and the reaction mixture was vigorously stirred at 45 °C.

3.6.4 General Procedure for Hydroallylation of Alkynes (Table 3.2-3.5)

In a nitrogen-filled glovebox, a scintillation vial was charged with a stir bar, LiOt-Bu (60.0 mg, 0.750 mmol, 15 equiv), IPrCuOt-Bu (26.3 mg, 0.050 mmol, 0.10 equiv) and indicated solvent (5 mL, 0.1 M). To this reaction mixture was added PMHS (1.5 mmol, 3.0 equiv) and alkyne (0.5 mmol, 1.0 equiv). The reaction mixture was stirred at 25 °C until the yellow color disappeared. To this reaction mixture was added allyl diethyl phosphate (1.0 mmol, 2.0 equiv) and the reaction mixture was vigorously stirred at the indicated temperature. After 20 h, the reaction mixture was filtered through a pad of silica gel and washed with EtOAc. The crude mixture was concentrated under reduced pressure and purified by silica gel column.

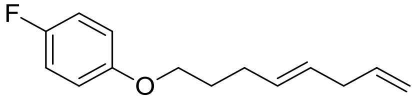
The regioselectivity of the hydroallylation of internal alkynes and aryl alkynes was determined by GC analysis of the crude reaction mixture.

3.6.5 Characterization date for 1,4-Diene

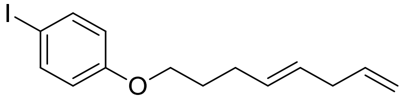


(E)-octa-4,7-dien-1-ylbenzene (Compound 3.2), compound was isolated as a clear colorless liquid (129.0 mg, 89% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.20 – 7.17 (m, 2H), 7.12 – 7.00 (m, 3H), 5.81 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.48 – 5.28 (m, 2H), 5.14 – 4.88 (m, 2H), 2.70 – 2.66 (m, 2H), 2.47 (t, *J* = 7.7 Hz, 2H), 1.97 – 1.91 (m, 2H), 1.58 (p, *J*

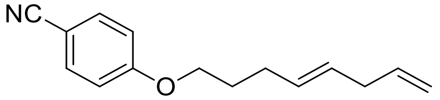
= 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.7, 137.5, 131.4, 128.6, 128.4, 128.3, 125.8, 114.9, 36.9, 35.5, 32.2, 31.3. GCMS (EI) calculated for [M]+ 186.14, found 186.20. FTIR (neat, cm^{-1}): 3064(m), 3028(s), 2931(s), 1958(w), 1638(m), 678(s).



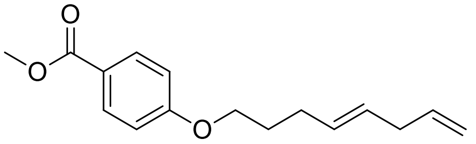
(E)-1-fluoro-4-(octa-4,7-dienyloxy)benzene (Table 3.2, compound 3.3), compound was isolated as a clear colorless liquid (130.0 mg, 84% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_6$) δ 6.82 – 6.74 (m, 2H), 6.61 – 6.54 (m, 2H), 5.78 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.46 – 5.28 (m, 2H), 5.07 – 4.95 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.69 – 2.59 (m, 2H), 2.07 – 1.99 (m, 2H), 1.62 (p, *J* = 7.5, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.2 (d, *J* = 237.8 Hz), 155.3 (d, *J* = 1.6 Hz), 137.3, 130.5, 128.8 , 115.8 (d, *J* = 23.0 Hz), 115.6 (d, *J* = 8.0 Hz), 115.1, 68.0, 36.8, 29.1, 29.0. ^{19}F NMR (471 MHz, CDCl$_3$) δ -124.41. GCMS (EI) calculated for [M]+ 220.13 found 220.20. FTIR (neat, cm^{-1}): 1726(m), 1693(m), 1636(m), 1505(s), 1474(s), 1434(m), 1293(s), 1248(s), 1209(s).



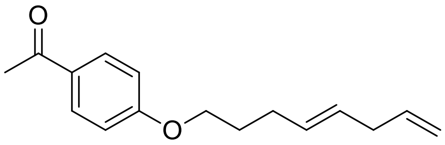
(E)-1-iodo-4-(octa-4,7-dienyloxy)benzene (Table 3.2, compound 3.4), compound was isolated as a clear colorless liquid (134.0 mg, 82% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_6$) δ 7.37 (d, *J* = 8.9 Hz, 2H), 6.38 (d, *J* = 8.9 Hz, 2H), 5.77 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.44 – 5.24 (m, 2H), 5.08 – 4.90 (m, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.72 – 2.58 (m, 2H), 2.02 – 1.96 (m, 2H), 1.58 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.1, 138.3, 137.3, 130.4, 128.9, 117.1, 115.1, 82.6, 67.4, 36.8, 29.0. GCMS (EI) calculated for [M]+ 328.03, found 328.10. FTIR (neat, cm^{-1}): 3084(m), 2940(s), 2871(m), 1636(s), 1586(s), 1484(s), 1282(s), 1244(s), 988(s), 712(s).



(E)-4-(octa-4,7-dien-1-yloxy)benzonitrile (Table 3.2, compound 3.5), compound was isolated as a clear colorless liquid (114.2 mg, 88% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_{6}$) δ 7.01 (d, *J* = 8.8 Hz, 2H), 6.34 (d, *J* = 8.8 Hz, 2H), 5.77 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.41 – 5.35 (m, 1H), 5.32 – 5.26 (m, 1H), 5.04 – 4.93 (m, 2H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 1.96 – 1.92 (m , 2H), 1.50 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_{3}$) δ 162.5, 137.2, 134.1, 130.1, 129.2, 119.4, 115.3, 115.1, 103.9, 67.7, 36.8, 28.9, 28.8. GCMS (EI) calculated for [M]+ 227.13, found 227.20. FTIR (neat, cm^{-1}): 3072(m), 3036(m), 2943(m), 2226(s), 1720(w), 1606(s), 1478(m), 680(s).

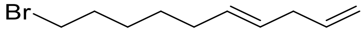


(E)-methyl 4-(octa-4,7-dien-1-yloxy)benzoate (Table 3.2, compound 3.6), compound was isolated as a clear colorless liquid (100.8 mg, 89% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_{6}$) δ 8.15 (d, *J* = 8.9 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 5.78 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 1H), 5.45 – 5.25 (m, 2H), 5.08 – 4.94 (m, 2H), 3.54 (s, 3H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.67 – 2.63 (m, 2H), 2.01– 197 (m, 2H), 1.57 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_{3}$) δ 167.0, 163.0, 137.2, 131.7, 130.3, 129.0, 122.5, 115.1, 114.2, 67.5, 51.9, 36.8, 28.9, 28.9. GCMS (EI) calculated for [M]+ 260.14, found 260.20. FTIR (neat, cm^{-1}): 3079(m), 3000(m), 2950(s), 1750(w), 1718(s),1637(m), 1450(m), 1315(s), 771(s).

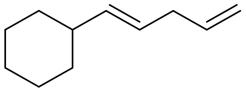


(E)-1-(4-(octa-4,7-dien-1-yloxy)phenyl)ethanone (Table 3.2, compound 3.7), compound was isolated as a clear colorless liquid (105.2 mg, 86% yield). ^{1}H NMR (300 MHz, Benzene-*d*$_{6}$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.79 (ddt, *J* =

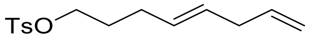
16.6, 10.1, 6.4 Hz, 1H), 5.46 – 5.28 (m, 2H), 5.07 – 4.98 (m, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.16 (s, 3H), 2.05 – 1.98 (m, 2H), 1.60 (p, *J* =7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 163.1, 137.2, 130.6, 130.2, 130.1, 128.9, 115.0, 114.1, 67.4, 36.7, 28.9, 28.8, 26.4. GCMS (EI) calculated for [M]+ 244.15, found 244.10. FTIR (neat, cm^{-1}): 3075(w), 3002(w), 2942(w), 2849(w), 1678(s), 1637(w), 1601(s), 1508(s), 1470(w), 1420(w), 1358(s), 1306(s), 1255(s), 1171(s), 1115(w), 1075(w), 970(w), 914(w), 834(s).



(E)-10-bromodeca-1,4-diene (Table 3.2 compound 3.8), compound was isolated as a clear colorless liquid (81.0 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 5.82 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.47 – 5.25 (m, 2H), 5.14 – 4.96 (m, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 2.79 – 2.57 (m, 2H), 1.90 – 1.77 (m, 2H), 1.46 (p, *J* = 6.6 Hz, 2H), 1.23 – 0.99 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4, 131.3, 128.1, 114.9, 36.8, 34.0, 32.8, 32.4, 28.7, 27.8. GCMS (EI) calculated for [M]+ 216.05, found 216.10. FTIR (neat, cm-^{1}): 2933(s), 2856(s), 1637(s), 1459(s), 1437(s), 1337(w), 970(s), 757(s).

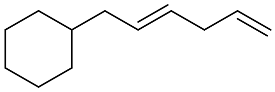


(E)-penta-1,4-dienylcyclohexane (Table 3.2, compound 3.9), compound was isolated as a clear colorless liquid (60.0 mg, 80% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_6$) δ 5.89 – 5.77 (m, 1H), 5.61 – 5.31 (m, 2H), 5.23 – 4.76 (m, 2H), 2.70 (d, *J* = 5.4 Hz, 2H), 1.87 (t, *J* = 12.8 Hz, 1H), 1.78 – 1.51 (m, 4H), 1.58 (d, *J* = 14.5 Hz, 1H), 1.29 – 0.95 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.7, 125.1, 114.8, 40.8, 36.9, 33.3, 26.4, 26.3. GCMS (EI) calculated for [M]+ 150.14, found 150.10. FTIR (neat, cm^{-1}): 3085 (w), 2926(s), 2851(s), 1718(s), 1638(s), 1449(m), 1334(m), 736(s).

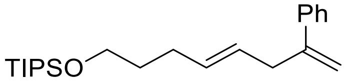


(E)-octa-4,7-dien-1-yl 4-methylbenzenesulfonate (Table 3.2, compound 3.10), compound was isolated as a clear colorless liquid (190.1 mg, 90% yield). ^{1}H

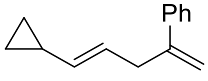
NMR (300 MHz, Benzene-d_6) δ 7.76 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 5.77 – 5.64 (m, 1H), 5.25 – 4.94 (m, 4H), 3.81 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 6.3 Hz, 2H), 1.84 (s, 3H), 1.84 – 1.73 (m, 2H), 1.33 (p, *J* = 7.5 Hz , 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 137.0, 133.3, 129.9, 129.4, 129.3, 127.9, 115.0, 69.9, 36.6, 28.6, 28.2, 21.7. GCMS (EI) calculated for [M]+ 280.11, found 280.10. FTIR (neat, cm^{-1}): 3072(m), 3035(m), 2924(m), 1750(w), 1638(m), 1479(m),1362(s).



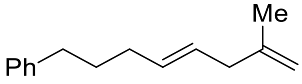
(E)-hexa-2,5-dienylcyclohexane (Table 3.2, compound 3.11), compound was isolated as a clear colorless liquid (66.0 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.83 (ddt, *J* = 16.6, 10.0, 6.3 Hz, 1H), 5.52 – 5.33 (m, 2H), 5.19 – 4.83 (m, 2H), 2.74 – 2.69 (m, 2H), 1.90 (t, *J* = 5.3 Hz, 2H), 1.79 – 1.51 (m, 5H), 1.31 – 1.00 (m, 4H), 0.93 – 0.76 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 137.7, 130.4, 128.6, 114.8, 40.8, 38.1, 36.9, 33.2, 26.8, 26.5. GCMS (EI) calculated for [M]+ 164.16, found 164.20. FTIR (neat, cm^{-1}): 3079(m), 2922(s), 2851(s), 1638(s), 1448(s), 969(s).



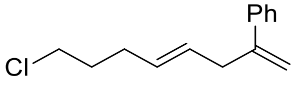
(E)-triisopropyl((7-phenylocta-4,7-dien-1-yl)oxy)silane (Table 3.2, compound 3.12), compound was isolated as a clear colorless liquid (228.0 mg, 85% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.40 – 7.37 (m, 2H), 7.16 – 7.06 (m, 3H), 5.64 – 5.41 (m, 2H), 5.39 (s, 1H), 5.11 (s, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.14 (d, *J* = 5.8 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.58 (p, *J* = 7.5 Hz, 2H), 1.11 – 1.03 (m, 21H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 141.2, 132.3, 128.3, 127.8, 127.5, 126.1, 112.8, 62.9, 38.4, 32.8, 29.0, 18.2, 12.1. GCMS (EI) calculated for [M]+ 282.24, found 358.30. FTIR (neat, cm^{-1}): 3090(m), 3035.7(m), 2942(s), 1811.7(m),1627.1(m), 1366.1(m), 1106.4(s).



(E)-(5-cyclopropylpenta-1,4-dien-2-yl)benzene (Table 3.2, compound 3.13), compound was isolated as a clear colorless liquid (72.0 mg, 51% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.12 – 7.06 (m, 3H), 5.59 (dt, *J* = 14.2, 6.8 Hz, 1H), 5.37 (s, 1H), 5.11 (s, 1H), 4.98 (dd, *J* = 14.2, 8.4 Hz, 1H), 3.12 (d, *J* = 6.8 Hz, 2H), 1.24 – 1.12 (m, 1H), 0.49 – 0.42 (m, 2H), 0.23 – 0.18 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 141.3, 136.1, 128.3, 127.5, 126.1, 125.3, 112.8, 38.3, 13.7, 6.6. GCMS (EI) calculated for [M]+ 184.13, found 184.10. FTIR (neat, cm^{-1}): 2936(m), 3058(w), 1723(s), 1685(s), 1448(s), 1266(s), 1025(s), 736(s), 701(s).

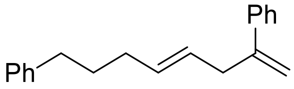


(E)-(7-methylocta-4,7-dien-1-yl)benzene (Table 3.2, compound 3.14), compound was isolated as a clear colorless liquid (114.2 mg, 88% yield). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.18 (t, *J* = 7.9 Hz, 2H), 7.10 – 7.06 (m, 3H), 5.46 – 5.36 (m, 2H), 4.85 (s, 1H), 4.82 (s, 1H), 2.66 (d, *J* = 5.8 Hz, 2H), 2.50 – 2.46 (t, 2H), 1.97 – 193 (m, 2H), 1.66 (s, 3H), 1.60 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 142.7, 131.9, 128.6, 128.4, 128.3, 125.8, 110.4, 41.4, 35.5, 32.2, 31.4, 22.5. GCMS (EI) calculated for [M]+ 200.16, found 200.20. FTIR (neat, cm^{-1}): 3072(m), 3028(m), 2933(s), 1813(w), 1650(m), 1470(m), 677(s).

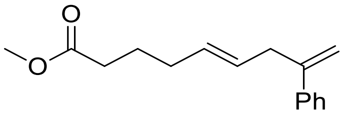


(E)-(8-chloroocta-1,4-dien-2-yl)benzene (Table 3.2, compound 3.15), compound was isolated as a clear colorless liquid (94.0 mg, 85% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 1H), 5.56 (dt, *J* = 14.5, 6.3 Hz, 1H), 5.45 (dt, *J* = 14.5, 6.4 Hz, 1H), 5.36 (s, 1H), 5.08 (s, 1H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.20 (d, *J* = 6.3 Hz, 2H), 2.20 – 2.12 (m 2H), 1.80 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.0, 141.1, 130.6, 129.2, 128.3, 127.5, 126.1, 113.0, 44.4, 38.4, 32.2, 29.9. GCMS

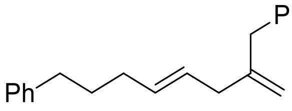
(EI) calculated for [M]+ 220.10, found 220.20. FTIR (neat, cm^{-1}): 3058(m), 3027(w), 2930(s), 1724(m), 1685(s), 1597(s), 1494(s), 1447(s), 1027(s), 700(s).

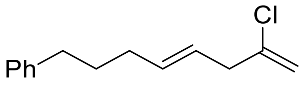


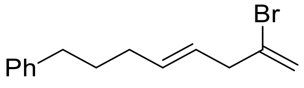
(E)-octa-4,7-diene-1,7-diyldibenzene (Table 3.2, compound 3.16), compound was isolated as a clear colorless liquid (101.0 mg, 77% yield). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 7.49 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 7.19 – 6.75 (m, 5H), 5.56 – 5.39 (m, 2H), 5.38 (s, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 3.14 (d, *J* = 5.7 Hz, 2H), 2.41 (t, 2H), 2.05 – 1.76 (m, 2H), 1.54 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.3, 142.6, 141.3, 132.3, 128.6, 128.6, 128.3, 128.2, 127.5, 126.2, 125.7, 112.8, 38.5, 35.4, 32.2, 31.3. GCMS (EI) calculated for [M]+ 262.17, found 262.20. FTIR (neat, cm^{-1}): 3061(m), 3025(m), 2926(s), 2854(s), 1643(s), 1602(s), 1494(s), 1452(s), 1074(s), 894(s), 698(s).



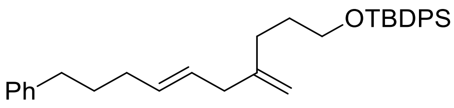
(E)-methyl 8-phenylnona-5,8-dienoate (Table 3.2, compound 3.17), compound was isolated as a clear colorless liquid (155.0 mg, 85% yield). ^{1}H NMR (500 MHz, Benzene-*d*$_6$) δ 7.36 (d, *J* = 7.7 Hz, 2H), 7.14 – 7.06 (m, 3H), 5.44 (dt, *J* = 14.0, 6.7 Hz, 1H), 5.37 (s, 1H), 5.29 (dt, *J* = 14.0, 6.8 Hz, 1H), 5.07 (s, 1H), 3.32 (s, 3H), 3.08 (d, *J* = 6.6 Hz, 2H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.84 – 1.80 (q, *J* = 7.2 Hz, 2H), 1.55 (p, *J* = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.3, 147.0, 141.1, 131.4, 128.8, 128.3, 127.5, 126.1, 112.9, 51.6, 38.4, 33.4, 31.9, 24.6. GCMS (EI) calculated for [M]+ 244.15, found 244.20. FTIR (neat, cm^{-1}): 3090(m), 30359(m), 2950(s), 1740(s), 1627(m), 1480(m), 1173(m), 680(s).


(E)-(2-methyleneoct-4-ene-1,8-diyl)dibenzene (Table 3.3, compound 3.18), compound was isolated as a clear colorless liquid (119.0 mg, 86% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.22 – 7.16(m, 6H), 7.13 – 7.04 (m, 4H), 5.50 – 5.25 (m, 2H), 4.94 (s, 1H), 4.83 (s, 1H), 3.28 (s, 2H), 2.65 (d, J = 5.7 Hz, 2H), 2.48 (t, J = 7.4, 2H), 2.02 – 1.87 (m, 2H), 1.59 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.4, 142.7, 139.8, 132.3, 129.2, 128.6, 128.4, 128.1, 126.2, 125.8, 111.9, 42.9, 39.0, 35.5, 32.2, 31.4. GCMS (EI) calculated for [M]+ 276.19, found 276.30. FTIR (neat, cm^{-1}): 3083(m), 3025(s), 2928(s), 2854(s), 1643(s), 1602(s), 1494(s), 1452(s), 1029(m), 895(m), 739(s), 698(s).

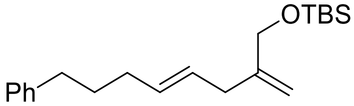

(E)-(7-chloroocta-4,7-dienyl)benzene (Table 3.3, compound 3.19), compound was isolated as a clear colorless liquid (50.0 mg, 51% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.19 (d, J = 7.7 Hz, 2H), 7.12 – 7.01 (m, 3H), 5.43 – 5.21 (m, 2H), 5.07 (s, 1H), 4.88 (s, 1H), 2.81 (d, J = 5.2 Hz, 2H), 2.45 (t, J = 7.7 Hz, 2H), 1.94 – 1.80 (m, 2H), 1.54 (p, J = 7.5, 7.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.5, 141.9, 134.1, 128.6, 128.4, 125.8, 125.3, 112.3, 42.5, 35.4, 32.1, 31.1. GCMS (EI) calculated for [M]+ 220.10, found 220.20. FTIR (neat, cm^{-1}): 3089(m), 3033(m), 2932(s), 1633(s), 1478(s), 1128(m), 968(m), 699(s), 677(s).


(E)-(7-bromoocta-4,7-dienyl)benzene (Table 3.3, compound 3.20), compound was isolated as a clear colorless liquid (75.0 mg, 57% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.24 – 7.17 (m 2H), 7.14 – 7.02 (m 3H), 5.50 – 5.07 (m, 4H), 2.91 (d, J = 5.3 Hz, 2H), 2.45 (t, J = 7.4 2H), 2.00 – 1.75 (m, 2H), 1.54 (p, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.5, 134.1, 133.3, 128.6, 128.4, 125.9, 125.8, 116.7, 44.8, 35.4, 32.1, 31.0. GCMS

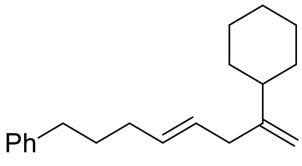
(EI) calculated for [M]+ 264.05, found 264.10. FTIR (neat, cm^{-1}): 3084(m), 3025(m), 2930(s), 1720(s), 1628(s), 1602(m), 1452(s), 750(s), 609(s).

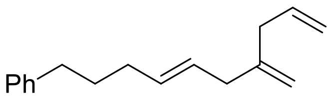


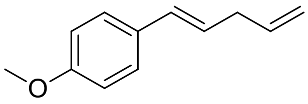
(E)-tert-butyl(4-methylene-10-phenyldec-6-enyloxy)diphenylsilane (Table 3.3, compound 3.21), compound was isolated as a clear colorless liquid (101.0 mg, 76% yield). The reaction was performed on 0.25 mmol scale. ^{1}H NMR (300 MHz, Benzene-d_6) δ 8.02 – 7.48 (m, 4H), 7.28 – 7.19 (m, 6H), 7.20 – 7.15 (m, 2H), 7.13 – 7.02 (m, 3H), 5.58 – 5.20 (m, 2H), 4.87 (s, 1H), 4.83 (s, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.68 (d, *J* = 4.9 Hz, 2H), 2.49 (t, *J* = 7.7 Hz, 2H), 2.13 (t, *J* = 7.8 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.78 – 1.67 (m, 2H), 1.61 (p, *J* = 7.6 Hz, 2H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.8, 142.7, 135.7, 134.2, 131.9, 129.6, 128.6, 128.4, 128.3, 127.7, 125.8, 109.6, 63.7, 39.8, 35.5, 32.2, 32.2, 31.4, 30.8, 27.0, 19.4. GCMS (EI) calculated for [M]+ 482.30, found 482.30. FTIR (neat, cm^{-1}): 3069(s), 3025(m), 2930(s), 2856(s), 1644(s), 1495(s), 1427(s), 1187(s), 1111(s), 890(m), 700(s).



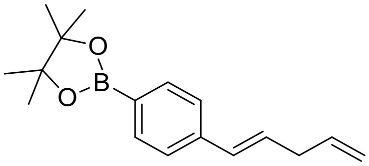
(E)-tert-butyldimethyl(2-methylene-8-phenyloct-4-enyloxy)silane (Table 3.3, compound 3.22), compound was isolated as a clear colorless liquid (125.0 mg, 76% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.32 – 7.15 (m, 2H), 7.13 – 6.98 (m, 3H), 5.66 – 5.32 (m, 2H), 5.24 (s, 1H), 4.97 (s, 1H), 4.08 (s, 2H), 2.74 (d, *J* = 4.3 Hz, 2H), 2.48 (t, *J* = 7.7 Hz, 2H), 2.09 – 1.84 (m, 2H), 1.60 (p, *J* = 7.5 Hz, 2H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.8, 142.6, 132.1, 128.6, 128.4, 127.8, 125.8, 109.2, 65.8, 36.3, 35.5, 32.2, 31.3, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 330.24, found 330.30. FTIR (neat, cm^{-1}): 3083(w), 3026(m), 2954(s), 2928(s), 2856(s), 1653(s), 1604(w), 1453(m), 1251(s), 1111(s), 1080(s), 836(s), 775(s).


(E)-(7-cyclohexylocta-4,7-dienyl)benzene (Table 3.3, compound 3.23), compound was isolated as a clear colorless liquid (118.0 mg, 88% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29 (m 2H), 7.18 (m, 3H), 5.63 – 5.16 (m, 2H), 4.74 (s, 1H), 4.70 (s, 1H), 2.80 – 2.69 (m, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.07 (m, 2H), 1.96 – 1.58 (m, 8H), 1.36 – 1.04 (m, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 154.6, 142.7, 131.7, 128.9, 128.6, 128.4, 125.7, 107.7, 44.1, 38.5, 35.9, 32.5, 32.2, 31.4, 26.9, 26.6. GCMS (EI) calculated for [M]+ 268.22, found 268.20. FTIR (neat, cm^{-1}): 3084(s), 3026(s), 2925(s), 2851(s), 1956(w), 1811(w), 1640(s), 1603(s), 1495(s), 1451(s), 909(s), 887(s), 743(s), 698(s).

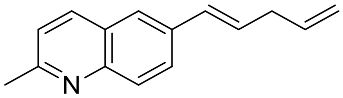

(E)-(7-methylenedeca-4,9-dien-1-yl)benzene (Table 3.3, compound 3.24), compound was isolated as a clear colorless liquid (28.0 mg, 82% yield). The reaction was performed on 0.1 mmol scale. ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 7.26 – 7.17(m, 2H), 7.13 – 7.02 (m, 3H), 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.51 – 5.28 (m, 2H), 5.10 – 4.97 (m, 2H), 4.91 (s, 1H), 4.88 (s, 1H), 2.77 – 2.65 (m, 2H), 2.48 (t, *J* = 7.7 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.60 (p, *J* = 7.5, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 147.5, 142.7, 136.4, 132.2, 128.8, 128.4, 128.1, 125.8, 116.3, 110.7, 40.6, 39.5, 35.5, 32.2, 31.4. GCMS (EI) calculated for [M]+ 226.17, found 226.20. FTIR (neat, cm^{-1}): 3078 (m), 3026(m), 1700(w), 1641(s), 1603(m), 1217(s), 754(s).


(E)-1-methoxy-4-(penta-1,4-dien-1-yl)benzene (Table 3.4, compound 3.25), compound was isolated as a colorless liquid (71.2 mg, 82% yield, rs = 15:1). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.33 (d, *J* = 15.8 Hz, 1H),

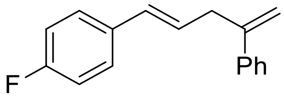
6.00 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.84 (ddt, *J* = 16.6, 10.1, 6.7 Hz, 1H), 5.21 – 4.89 (m, 2H), 3.30 (s, 3H), 2.93 – 2.56 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.0, 136.9, 130.6, 130.4, 127.3, 126.1, 115.6, 114.1, 55.4, 37.1. GCMS (EI) calculated for [M]+ 174.10, found 174.10. FTIR (neat, cm^{-1}): 3070(m), 3034(m), 2835(m), 1637(m), 1464(s), 1126(s), 679(s)



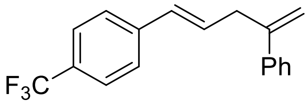
(E)-4,4,5,5-tetramethyl-2-(4-(4-phenylpenta-1,4-dien-1-yl)phenyl)-1,3,2-dioxaborolane (Table 3.4, compound 3.26), compound was isolated as a colorless liquid (94.6 mg, 70% yield, rs = 12:1). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 8.16 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.27 (d, *J* = 15.9 Hz, 1H), 6.06 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.75 (ddt, *J* = 16.7, 10.1, 6.4 Hz, 1H), 5.13 – 4.86 (m, 2H), 2.78 – 2.53 (m, 2H), 1.14 (s, 12H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.5, 136.4, 135.2, 131.0, 129.5, 125.6, 125.5, 115.9, 83.8, 25.0.GCMS (EI) calculated for [M]+ 270.10, found 270.10. FTIR (neat, cm^{-1}): 3077(m), 3026(m), 2977(s), 1741(s), 1637(m), 1464(m), 963(m).



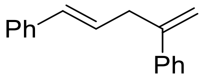
(E)-2-methyl-6-(penta-1,4-dien-1-yl)quinolone (Table 3.4, compound 3.27), compound was isolated as a pale yellow liquid (37.1mg, 71% yield, rs = 17:1). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 8.21 (d, *J* = 8.8 Hz, 1H), 7.63 – 7.41 (m, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.12 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.84 (ddt, *J* = 16.7, 10.1, 6.7 Hz, 1H), 5.21 – 4.94 (m, 2H), 2.85 – 2.76 (m, 2H) 2.56 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.6, 147.4, 136.3, 136.2, 135.2, 130.4, 129.5, 128.8, 127.4, 126.8, 124.9, 122.4, 116.0, 37.2, 25.3. GCMS (EI) calculated for [M]+ 209.12, found 209.10. FTIR (neat, cm^{-1}): 3060(m), 3055(m), 1637(s). 1750(m), 968(s), 755(s)



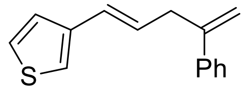
(E)-1-fluoro-4-(4-phenylpenta-1,4-dien-1-yl)benzene (Table 3.4, compound 3.28), compound was isolated as a white solid (100.2 mg, 84% yield, rs = 32:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.37 (m, 2H), 7.22 – 7.18 (m, 2H), 7.15 – 7.13 (m, 1H), 7.12 – 7.06 (m, 3H), 7.06 – 6.98 (m, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.21 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.40 (s, 1H), 5.09 (s, 1H),3j.22 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.2 (d, *J* = 245.8 Hz), 146.6, 141.0, 133.8 (d, *J* = 2.9 Hz), 130.6, 128.5 , 127.9 , 127.9 , 127.7 (d, *J* = 7.5 Hz), 126.1, 115.5 (d, *J* = 21.9 Hz), 113.5, 38.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ -113.29. GCMS (EI) calculated for [M]+ 238.12, found 238.10. FTIR (neat, cm^{-1}): 3057(m), 3025(m), 1920(w), 1625(m), 970(s), 895(s).



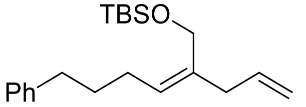
(E)-1-(4-phenylpenta-1,4-dien-1-yl)-4-(trifluoromethyl)benzene (Table 3.4, compound 3.29), compound was isolated as a white solid (97 mg, 67% yield, rs = 22:1). ^{1}H NMR (300 MHz, Benzene-*d*$_6$) δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H),7.20 – 7.18 (m, 2H), 7.13 – 7.07 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 6.21 – 6.01 (m, 2H), 5.40 (s, 1H), 5.04 (s, 1H), 3.16 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 146.2 , 141.1 , 140.8 , 131.1 , 130.6 , 129.1 (q, *J* = 32.2 Hz), 128.5 , 127.8 , 126.4 , 126.1 , 125.6 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 271.8 Hz), 113.8 , 38.8 . ^{19}F NMR (471 MHz, $CDCl_3$) δ -65.60. GCMS (EI) calculated for [M]+ 288.11, found 288.20. FTIR (neat, cm^{-1}):3054(m), 2987(m), 1921(w), 1650(m), 741(s), 706(s).



(E)-penta-1,4-diene-1,4-diyldibenzene (Table 3.4, compound 3.30), compound was isolated as a white solid (94.0 mg, 85% yield, rs = 11:1). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.15 – 7.13 (m, 2H), 7.13 – 7.06 (m, 3H), 7.06 – 6.98 (m, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.40 (s, 1H), 5.09 (s, 1H), 3.22 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 141.1, 137.7, 131.8, 128.6, 128.5, 128.2, 127.6, 127.2, 126.2, 126.1, 113.5, 38.8. GCMS (EI) calculated for [M]+ 220.13, found 220.20. FTIR (neat, cm^{-1}): 3082(m), 3053(s), 2985(m), 1951(w), 1626(m), 1447(m), 746(s).

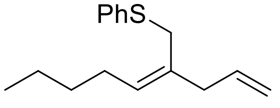


(E)-3-(4-phenylpenta-1,4-dien-1-yl)thiophene (Table 3.4, compound 3.31), compound was isolated as a white solid (91.6 mg, 81% yield, rs = 11:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.47 – 7.32 (m, 2H), 7.32 – 7.19 (m, 2H), 7.13 – 7.06 (m, 1H), 6.91 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.79 (dd, *J* = 5.1, 2.9 Hz, 1H), 6.67 (dd, *J* = 3.1, 1.2 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 6.02 (dt, *J* = 15.9, 6.7 Hz, 1H), 5.40 (s, 1H), 5.08 (s, 1H), 3.18 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 141.1, 14038, 128.5, 128.1, 127.6, 126.1, 126.1, 125.9, 125.2, 121.1, 113.5, 38.7. GCMS (EI) calculated for [M]+ 226.08, found 226.10. FTIR (neat, cm^{-1}): 3060(m), 3052(s), 1755(w), 1624(m), 968(s), 896(s).

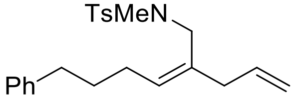


(Z)-((2-allyl-6-phenylhex-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (Table 3.5, compound 3.32), compound was isolated as a clear colorless liquid (181.9 mg, 84% yield, rs = 16.1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.23 – 7.18 (m, 2H), 7.12 – 7.03 (m, 3H), 5.92 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.26 (t, *J* = 7.4 Hz, 1H), 5.18 – 5.03 (m, 2H), 4.15 (s, 2H), 2.99 (d, *J* = 6.3 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.59 (p, *J* = 7.6 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 137.6, 137.2, 128.5, 128.4, 127.3, 125.8, 115.8, 60.3, 38.9, 35.5, 31.7, 27.2, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+

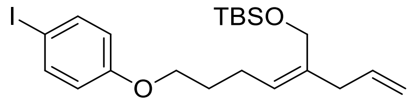
330.24, found 330.20. FTIR (neat, cm^{-1}): 3072(m), 2955(s), 2857(s), 1813(m), 1637(m), 1470(m), 1251(s).



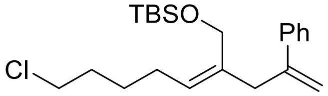
(Z)-nona-1,4-dien-4-yl(phenyl)sulfane (Table 3.5, compound 3.33), compound was isolated as a colorless liquid (110.0 mg, 89% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.07 – 6.87 (m, 3H), 5.79 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.15 – 4.96 (m, 2H), 3.49 (s, 2H), 2.95 (d, *J* = 6.8 Hz, 2H), 1.85 (q, *J* = 7.0 Hz, 2H), 1.50 – 1.00 (m, 4H), 0.82 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 136.7, 132.4, 130.9, 130.7, 128.8, 126.5, 116.4, 40.5, 34.6, 32.0, 27.8, 22.5, 14.1. GCMS (EI) calculated for [M]+ 246.14, found 246.20. FTIR (neat, cm^{-1}): 3089.8(s), 3034(s), 2957.2(m),1814.6(m), 1478.4(s), 1392.8(w), 668.9(s).



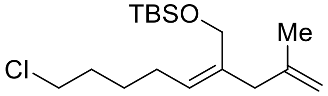
(Z)-N-(2-allyl-6-phenylhex-2-en-1-yl)-N,4-dimethylbenzenesulfonamide (Table 3.5, compound 3.34), compound was isolated as a clear colorless liquid (134.0 mg, 89% yield, rs = 9:1). ^{1}H NMR (500 MHz, Benzene-d_6) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 7.8 Hz, 2H), 5.90 (ddt, *J* = 16.7, 9.3, 7.0 Hz, 1H), 5.27 (t, *J* = 7.4 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 3.53 (s, 2H), 2.89 (d, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 2.31 (t, *J* = 7.7 Hz, 2H), 1.88 (s, 3H), 1.68 (q, *J* = 7.5 Hz, 2H), 1.40 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 142.0, 136.1, 134.1, 132.4, 131.4, 129.7, 128.4, 128.3, 127.6, 125.8, 116.6, 48.5, 38.9, 35.3, 33.8, 31.3, 27.0, 21.6. GCMS (EI) calculated for [M]+ 383.55, found 383.30. FTIR (neat, cm^{-1}): 3062.4(m), 3027(m), 2925(s), 1809(w), 1637(m), 1455(s), 1340(s), 753(s).



(Z)-((2-allyl-6-(4-iodophenoxy)hex-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (Table 3.5, compound 3.35), compound was isolated as a colorless liquid (200.0 mg, 85% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.14 (s, 1H), 6.83 – 6.88 (m, 3H), 5.89 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.22 (t, *J* = 7.4 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.19 (s, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 2.97 (d, *J* = 6.8 Hz, 2H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.64 (p, *J* = 6.6 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.2, 138.4, 137.01, 129.5, 126.4, 120.6, 115.8, 114.6, 67, 60.3, 38.9, 29.6, 26.1, 24.2, 18.5, -5.2. GCMS (EI) calculated for [M]+ 472.13, found 472.00. FTIR (neat, cm^{-1}): 3073.0(m), 2953.7(s), 2855.6(s), 1636.3(m), 1471.3(m), 1246.0(s),1079.0(m).

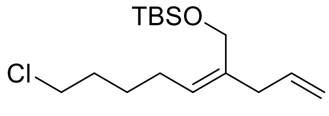


(Z)-tert-butyl((7-chloro-2-(2-phenylallyl)hept-2-en-1-yl)oxy)dimethylsilane (Table 3.5, compound 3.36), compound was isolated as a colorless liquid (164.5 mg, 87% yield, rs = 17:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.46 (d, *J* = 7.1 Hz, 1H), 7.14 – 7.19 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.48 (d, *J* = 1.7 Hz, 1H), 5.28 – 4.92 (m, 2H), 4.13 (s, 2H), 3.41 (s, 2H), 3.03 (t, *J* = 6.5 Hz, 2H), 1.83 (q, *J* = 7.2 Hz, 2H), 1.39 – 1.21 (m, 2H), 1.23 – 1.09 (m, 2H), 0.99 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 146.1, 141.2, 136.9, 128.6, 128.2, 127.3, 126.4, 114.3, 60.2, 45.0, 40.2, 31.9, 27.0, 26.7, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 378.21, found 378.30. FTIR (neat, cm^{-1}): 2954.0 (s), 2855.7(s), 1625.5(w), 1444.2(m), 1250.7(m), 1073.3(s).

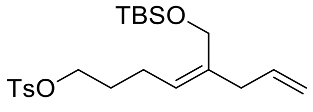


(Z)-tert-butyl((7-chloro-2-(2-methylallyl)hept-2-en-1-yl)oxy)dimethylsilane (Table 3.5, compound 3.37), compound was isolated as a colorless liquid

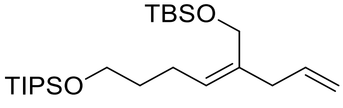
(131.6 mg, 87% yield, rs = 19:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.17 (t, *J* = 7.4 Hz, 1H), 4.91 (s, 2H), 4.12 (s, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 2.91 (s, 2H), 1.92 (q, *J* = 7.4 Hz, 2H), 1.70 (s, 3H), 1.45 (p, *J* = 6.6 Hz, 2H), 1.26 (p, *J* = 7.5 Hz, 2H), 0.99 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 137.1, 128.3, 112.0, 59.8, 45.0, 43.5, 32.3, 27.3, 26.9, 26.1, 22.2, 18.5, -5.2. GCMS (EI) calculated for [M]+ 316.20, found 316.20. FTIR (neat, cm^{-1}): 2954.9(s), 286.7(s), 1647.59m), 1472.0(m), 1250.7(m), 1075.69(m).



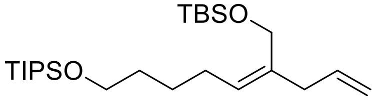
(Z)-((2-allyl-7-chlorohept-2-en-1-yl)oxy)(tert-butyl)dimethylsilane (Table 3.5, compound 3.38), compound was isolated as a colorless liquid (133.1 mg, 88% yield, rs = 21:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.89 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.19 – 5.02 (m, 3H), 4.15 (s, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 2.96 (d, *J* = 6.8 Hz, 2H), 1.89 (q, *J* = 7.4 Hz, 2H), 1.43 (p, *J* = 6.6 Hz, 2H), 1.24 (p, *J* = 7.2, 6.8 Hz, 2H), 0.99 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.1, 126.9, 115.8, 60.3, 45.0, 32.3, 30.0, 27.3, 26.9, 26.1, 18.5, -5.2. GCMS (EI) calculated for [M]+ 302.18, found 302.20 FTIR (neat, cm^{-1}): 3076.5(m), 2954.3(s), 2856.4(s), 1636.1(m), 1471.89(m), 1250.9(m), 1706.0(m).



(Z)-5-(((tert-butyldimethylsilyl)oxy)methyl)octa-4,7-dien-1-yl 4-methylbenzenesulfonate (Table 3.5, compound 3.39), compound was isolated as a colorless liquid (171.0 mg, 81% yield, rs = 13:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.76 (d, *J* = 7.9 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 5.81 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.24 – 4.86 (m, 3H), 4.10 (s, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 2.88 (d, *J* = 6.8 Hz, 2H), 1.91 (q, *J* = 7.5 Hz, 2H), 1.84 (s, 3H), 1.36 (p, *J* = 6.7 Hz, 2H), 0.97 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 138.9, 136.8, 133.4, 129.9, 127.9, 125.2, 115.9, 69.9, 60.3, 38.9, 29.2, 26.0, 23.5, 21.7, 18.4, -5.2. GCMS (EI) calculated for [M]+ 424.21, found 424.20. FTIR (neat, cm^{-1}): 3072.8(m),2954.9(s), 2855.5(s), 1635.8(m), 1471.9(m), 1363.3(s), 1250.9(m), 1075.1(s).

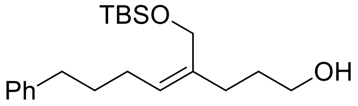


(Z)-6-allyl-12,12-diisopropyl-2,2,3,3,13-pentamethyl-4,11-dioxa-3,12-disilatetradec-6-ene (Table 3.5, compound 3.40), compound was isolated as a colorless liquid (162.0 mg, 76% yield, rs = 9:1). ^{1}H NMR (300 MHz, Benzene-d_6) δ 5.93 (ddt, *J* = 16.9, 9.9, 6.8 Hz, 1H), 5.31 (t, *J* = 7.4 Hz, 1H), 5.22 – 4.96 (m, 2H), 4.27 (s, 2H), 3.61 (t, *J* = 6.2 Hz, 2H), 3.00 (d, *J* = 6.8 Hz, 2H), 2.34 – 2.04 (m, 2H), 1.70 – 1.45 (m, 2H), 1.27 – 1.03 (m, 21H), 1.00 (s, 9H), 0.11 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.6, 137.3, 127.2, 115.7, 63.0, 60.4, 38.9, 33.4, 26.1, 24.2, 18.5, 18.2, 12.2, -5.1. GCMS (EI) calculated for [M]+ 426.33, found 426.40. FTIR (neat, cm^{-1}): 2943(s), 2865(s), 1744(w), 1636(w), 1506(w), 1471(s), 1462(s), 1388(w), 1361(w), 1250(s), 1106(s), 1073(s), 1005(m), 913(s), 882(s), 836(s), 774(s).

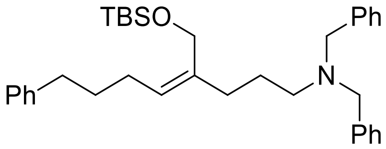


(Z)-6-allyl-13,13-diisopropyl-2,2,3,3,14-pentamethyl-4,12-dioxa-3,13-disilapentadec-6-ene (Table 3.5, compound 3.41), compound was isolated as a colorless liquid (189.4 mg, 86% yield, rs = 11:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.25 (t, *J* = 7.3 Hz, 1H), 5.08 – 4.97 (m, 2H), 4.15 (s, 2H), 3.68 (t, *J* = 6.5 Hz, 2H), 2.84 (d, *J* = 6.8 Hz, 2H), 2.06 – 2.10 (m, 2H), 1.52 – 1.58(m, 2H), 1.42 (p, *J* = 7.5 Hz, 2H), 1.05 – 1.07 (m, 21H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.3, 137.3, 127.7, 115.7, 63.4, 60.4, 38.9, 32.8, 27.5, 26.4, 26.1, 18.5, 18.2, 12.2, -5.1. GCMS (EI) calculated for [M]+440.35, found 440.40. FTIR (neat, cm^{-1}): 2945 (s), 2867(s), 1636(w), 1471(s), 1462(s), 1388(m), 1360(w), 1250(s), 1105(s), 1071(s), 1013(s), 912(s), 882(s), 836(s).

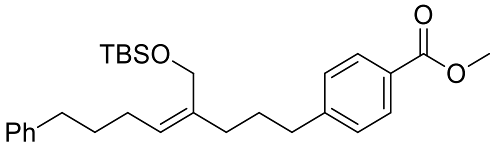
3.6.6 Elaboration of Trisubstituted Alkenes Prepared by Hydroallylation



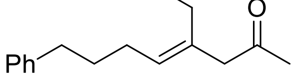
(Z)-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-ol (Scheme 3.4, compound 3.42), Compound **3.32** was subjected to hydroboration using a known procedure and then the alkylborane product was subjected to oxidation using a known procedure.[45,46] In a nitrogen-filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (61.0 mg, 0.25 mmol, 0.55 equiv), 1, 4-dioxane (1 mL, 0.5 M) and compound **3.32** (165.3 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred overnight at 60 °C. The solvent was removed under reduced pressure. To the resulting reaction mixture was added a solution $NaBO_3*H_2O$ (159.7 mg, 1.6 mmol, 3.3 equiv) in $THF:H_2O$ (910 µL, 1:1, 0.5 M). The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was dilute with water and was extracted with diethyl ether. The combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column. The compound was isolated as a colorless liquid (140.2 mg, 80% yield). ^{1}H NMR (300 MHz, Benzene-d_6) δ 7.25 – 7.14 (m, 2H), 7.14 – 7.03 (m, 3H), 5.36 – 5.17 (t, *J* = 6.3 Hz, 1H), 4.12 (s, 2H), 3.47 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.00 (q, *J* = 7.4 Hz, 2H), 1.76 – 1.50 (m, 4H), 0.97 (s, 10H), 0.06 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.4, 128.5, 128.40, 127.1, 125.8, 62.6, 60.8, 35.5, 31.7, 31.4, 31.0, 27.2, 26.1, 18.4, -5.2. GCMS (EI) calculated for [M]+ 348.25, found 348.20. FTIR (neat, cm^{-1}): 3340(br,s), 3026(m), 2927(s), 2855(s), 1471(s), 1070(s), 836(s).



(Z)-N,N-dibenzyl-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-amine (Scheme 3.4, compound 3.43), Compound **3.32** was subjected to hydroamination using a known procedure.[49] In a nitrogen-filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (61.0 mg, 0.25 mmol, 0.5 equiv), 1, 4-dioxane (1 mL, 0.5 M) and compound **3.32** (165.3 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred overnight at 60 °C. The solvent was removed under reduced pressure. The reaction mixture was transferred to a 25 mL reaction flask. To the reaction mixture was added LiO*t*Bu (44 mg, 0.55 mmol, 1.1 equiv), ICyCuCl (8.3 mg, 0.025 mmol, 0.05 equiv), and Toluene (10 mL, 0.05M). The reaction flask was taken out of the glove box and put on the manifold using standard air-free techniques. A solution of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (158.7 mg in 400 µL Toluene, 0.500 mmol, 1.0 equiv) was added over 4 hours to the stirred reaction mixture at 60 °C. After addition of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine, the reaction mixture was allowed to stirred at 60 °C and the consumption of *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine was monitored by TLC. The reaction mixture was filtered through a plug of silica gel with DCM. The solvent was removed under reduced pressure and the crude product was purify by a silica gel column. The compound was isolated as a pale yellow liquid (195 mg, 74% yield). ^{1}H NMR (300 MHz, Benzene-d6) δ 7.41 (d, J = 7.2 Hz, 4H), 7.27 – 7.18 (m, 6H), 7.12 – 7.04 (m, 5H), 5.12 (t, J = 7.3 Hz, 1H), 4.12 (s, 2H), 3.51 (s, 4H), 2.70 – 2.31 (m, 4H), 2.22 (t, J = 7.7 Hz, 2H), 1.98 (q, J = 7.4 Hz, 2H), 1.73 (p, J = 7.5 Hz, 2H), 1.56 (p, J = 7.5 Hz, 2H), 0.98 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 142.5, 140.2, 139.0, 128.9, 128.5, 128.4, 128.2, 126.8, 126.2, 125.8, 60.6, 58.5, 53.5, 35.6, 32.4, 31.7, 27.2, 26.1, 25.8, 18.5, -5.1. FTIR (neat, cm^{-1}): 3026(m), 2928(s), 2855(s), 1602(m), 1360(m), 1070(s), 836(s).



(Z)-methyl 4-(4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-1-yl)benzoate (Scheme 3.4, compound 3.44), Compound **3.32** was subjected to hydroboration using a known procedure and then the alkylborane product was subjected to Suzuki c[46]oupling using a known procedure.[50] In a nitrogen filled glovebox, a dram vial was charged with stir bar, 9-BBN-H dimer (36.6 mg, 0.15 mmol, 0.5 equiv), 1,4-dioxane (550 µL, 0.5 M) and compound **3.32** (99.2 mg, 0.3 mmol, 1 equiv). The reaction mixture was stirred at 100 °C for 24 hours. To the reaction mixture was added Pd(OAc)2 (0.7 mg, 0.003 mmol, 0.01 equiv), tricyclohexylphosphine (1.7 mg, 0.006 mmol, 0.02 equiv), cesium carbonate (293.2 mg, 0.9 mmol, 3 equiv), and 4-bromo-methylbenzoate (71 mg, 0.33 mmol, 1.1 equiv) respectively. The reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with EtOAc and filtered through a plug of silica. The solvent was removed under reduced pressure and the crude product was purify by a silica gel. The compound was isolated as a colorless liquid. The yield was determined by ^{1}H NMR analysis of the crude product using TMB as internal standard (76 % yield). ^{1}H NMR (300 MHz, Benzene-d6) δ 8.15 (d, J = 8.2 Hz, 2H), 7.25 – 7.15 (m, 2H), 7.13 – 6.99 (m, 5H), 5.20 (t, J = 7.4 Hz, 1H), 4.14 (s, 2H), 3.52 (s, 3H), 2.63 – 2.36 (m, 4H), 2.19 (t, J = 7.7 Hz, 2H), 2.02 (q, J = 7.4 Hz, 2H), 1.83 – 1.36 (m, 4H), 0.96 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 148.4, 142.5, 138.7, 129.8, 128.6, 128.5, 128.4, 127.9, 126.7 125.8, 60.6, 52.0, 35.9, 35.6, 34.5, 31.8, 29.9, 27.2, 26.1, 18.4, -5.2. GCMS (EI) calculated for [M]+ 466.29, found 466.40. FTIR (neat, cm^{-1}): 3026 (m), 2950(s), 2856(s), 1724(s), 1610(m), 1360(m), 836(m).



(Z)-4-(((tert-butyldimethylsilyl)oxy)methyl)-8-phenyloct-4-en-2-one (Scheme 3.4, compound 3.45), Compound **3.32** was subjected to standard wacker oxidation procedure.[51] A scintillation vial was charged with stir bar, $PdCl_2$ (6.7 mg, 0.037 mmol, 0.15 equiv), CuCl (32.3 mg, 0.33 mmol, 1.4 equiv), and DMF:H_2O (3 mL, 7:1, 0.1 M). The reaction mixture was stirred at room temperature for 1 hour under oxygen atmosphere. To this reaction mixture was added compound **3.32** (82.56 mg, 0.25 mmol, 1.0 equiv) and the reaction mixture was stirred at room temperature under oxygen atmosphere for 24 hours. The reaction mixture was dilute with water and was extracted with diethyl ether. The combined organic phase was dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified on a silica gel column. The compound was isolated as a colorless liquid (57.2 mg, 66% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 5.34 (t, *J* = 7.3 Hz, 1H), 4.17 (s, 2H), 3.16 (s, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.15 (s, 3H), 2.14 – 2.07 (m, 2H), 1.72 (p, *J* = 7.5 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 142.2, 133.7, 130.4, 128.5, 128.4, 125.9, 60.8, 49.8, 35.4, 31.4, 29.4, 27.2, 26.0, 18.4, -5.4. GCMS (EI) calculated for [M]+ 346.23, found 346.30. FTIR (neat, cm^{-1}): 3063(m), 3026(m), 2953(s), 1716(s), 938(m).

3.6.7 Initial Rate Experiment (Scheme 3.7)

Reaction with Lithium *tert*-butoxide. In a nitrogen-filled glovebox, a dram vial was charged with stir bar, alkenyl copper **3.1** (47.8 mg, 0.08 mmol, 1.0 equiv), and LiO*t*-Bu (7.0 mg, 0.088 mmol, 1.10 equiv). The mixture was suspended with toluene (600 µL) and then allyl diethyl phosphate **3.53** (46.6 mg, 0240 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 1 min for the first 10 min of the reaction. The 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1400 µL of Et_2O to quench the reaction before GC analysis. This reaction was done three times. Table 3.7 shows the product yield for the first 10 minutes of the reaction. Table S10 shows the initial rates and the relative rate.

Table 3.7. Product yield for the first 10 minutes of the reaction of alkenyl copper **3.1** with allyl phosphate **3.53** and LiO*t*-Bu.

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Trial 1	2%	4%	6%	9%	11%	13%	16%	18%	20%	21%
Trial 2	2%	4%	7%	10%	12%	14%	16%	18%	20%	22%
Trial 3	2%	4%	6%	9%	12%	14%	16%	18%	20%	21%

Reaction without Lithium *tert*-butoxide. In a nitrogen-filled glovebox, a dram vial was charged with stir bar and alkenyl copper **3.1** (47.8 mg, 0.08 mmol, 1.0 equiv). The mixture was suspended with toluene (600 µL) and then allyl diethyl phosphate **3.53** (46.6 mg, 0240 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added. The reaction mixture was stirred at 45 °C. Aliquots were taken every 5 min for the first 50 min of the reaction. The 50- µL aliquot was pipetted onto silica gel plug and rinse through with 1400 µL of Et_2O to quench the reaction before GC analysis. This reaction was done three times. Table 3.8 shows the product yield for the first 50 minutes of the reaction. Table 3.10 shows the initial rates and the relative rate.

Table 3.8. Product yield for the first 50 minutes of the reaction of alkenyl copper **3.1** with allyl phosphate **3.53**.

Time (min)	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**
Trial 1	2%	5%	7%	9%	12%	14%	17%	19%	21%	24%
Trial 2	2%	5%	7%	10%	12%	14%	17%	19%	22%	24%
Trial 3	2%	4%	7%	9%	11%	14%	16%	18%	21%	23%

Reaction with Lithium *tert*-butoxide and 12-crown-4. In a nitrogen-filled glovebox, a dram vial was charged with stir bar, alkenyl copper **3.1** (47.8 mg, 0.08 mmol, 1.0 equiv), and LiO*t*-Bu (7.0 mg, 0.088 mmol, 1.10 equiv). The mixture was suspended with toluene (600 µL) and then 12-crown-4 (15.5 mg, 0.088 mmol, 1.10 equiv), allyl diethyl phosphate **3.53** (46.6 mg, 0240 mmol, 2.0 equiv) and a solution of TMB (0.04 mmol) in toluene (200 µL) were added respectively. The reaction mixture was stirred at 45 °C. Aliquots were taken every 1 min for the first 10 min of the reaction. The 50 µL aliquot was pipetted onto silica gel plug and rinsed through with 1400 µL of Et_2O to quench the reaction before GC analysis. Table 3.9 shows the product yield for the first 10 minutes of the reaction. Table 3.10 shows the initial rate and the relative rate.

Table 3.9. Product yield for the first 10 minutes of the reaction of alkenyl copper **3.1** with allyl phosphate **3.53**, LiO*t*-Bu, and 12-crown-4.

Time (min)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Trial 1	2%	4%	6%	8%	10%	12%	15%	17%	18%	20%

Table 3.10 The rate, average rate and the relative rate of the allylation of alkenyl complex **3.1** with or without the additive.

Additive	**Trial 1**	**Trial 2**	**Trial 3**	**Average**	**Relative initial rate**
None	0.0048	0.0048	0.0047	0.0048	1.0
LiOtBu	0.0222	0.0222	0.0222	0.0222	4.7
LiOtBu & 12-crown-4	0.0205				4.3

3.6.8 Competition Experiment (Scheme 3.8)

In a nitrogen-filled glovebox, a dram vial was charged with IPrCuO*t*-Bu (42.0 mg, 0.08 mmol, 1 equiv) and C_6D_6 (550 µL). To the reaction mixture was added triethoxysilane (14.5 µL, 0.084 mmol, 1.05 equiv) which resulted to a bright orange color. The reaction mixture was stirred at 25

°C for 90 s. The reaction mixture was transferred to a dram vial containing phenylpentyne (**7**) (34.6 mg, 0.32 mmol, 3.0 equiv), phosphate **3.55** (64.9 mg, 0.32 mmol, 3.0 equiv), internal standard TMB (6.7 mg, 0.04 mmol, 0.5 equiv) and C_6D_6 (2.0 mL). The reaction solution was vigorously stirred at 45 °C. After 5 minutes, 50 µL aliquots were taken and was diluted with 500 µL of 1:1 mixture of 0.1 M HCl and ether. The ether layer was extracted and pipetted onto silica plug and rinsed through with 1500 µL of EtOAc.

3.6.9 Stoichiometric Reaction for the Synthesis of OTBS-substituted Alkenyl Copper **3.59** (Scheme 3.9)

In a nitrogen filled glovebox, IPrCuO*t*-Bu (184.2 mg, 0.350 mmol, 1.0 equiv) was weighed in a 20 mL scintillation vial, followed by 500 µL THF. Triethoxysilane (60.4 mg, 0.368 mmol, 1.05 equiv) was weighed into a shell vial and transferred to the reaction with 3 aliquots of 330 µL THF, this mixture was pre-stirred at 25 °C for 15 s resulting in a bright orange solution. Then OTBS-substituted alkyne **3.58** (111.1 mg, 0.385 mmol, 1.10 equiv) was weighed into a shell vial and washed into the reaction mixture with 3 aliquots of 330 µL THF. The reaction was vigorously stirred (1500 rpm) at 25 °C for 30 min after which the reaction turned clear. The reaction was concentrated in vaccuo, and recrystallized from pentane. Due to the high solubility of the alkenyl copper complex, crystals were obtained at -35 °C and had to be washed with cold pentane and stored on dry ice for X-ray Crystallography.

3.7 References

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