Transition Metal-Facilitated C—C and C—F Bond Forming Processes

By

Ian B. Perry

Submitted to the Department of Chemistry on December 1st, 2016 in Partial Fulfillment of the Requirements for the Degree of Bachelor of Science at the Massachusetts Institute of Technology

ABSTRACT

Chapter 1. Copper-Catalyzed Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones

A copper (I) catalyzed coupling of olefins and ketones has been developed for the diastereo- and enantioselective generation of homopropargyl alcohols bearing vicinal stereocenters. This method allows for the generation of enantioenriched tertiary alcohols with a high degree of functional group compatibility. The utility of the process is further illustrated by a large scale synthesis with extremely low catalyst loading as well as the late stage modification of several pharmaceuticals.

Chapter 2. Copper-Catalyzed Enantioselective Addition of Styrene-Derived Nucleophiles to Imines

We describe the catalytic generation of amines bearing vicinal stereocenters with a moderate degree of diastereoselectivity. The stereoselective hydrocupration of an unactivated olefinic component is followed by nucleophilic addition of the organocuprate to an N-phosphinoyl protected imine. The mild and general process tolerates a broad-range of functionality, and the process was shown to be successful at a gram-scale synthesis.

The preliminary findings regarding an aryl and heteroaryl halide fluorination process facilitated by palladium as a reagent is described. Stoichiometric studies illustrate the utility of the method in producing aryl fluorides with unprecedented regioselectivity, and preliminary studies into the fluorination of five- and six-membered heteroaryl bromides are described. Halogen atom substitution as a route to irreversible oxidative addition of aryl and heteroaryl halides is discussed. This strategy may serve to facilitate the fluorination of particularly problematic heteroaryl bromide and chloride substrates.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry
ACKNOWLEDGEMENT

First and foremost, I would like to thank Professor Stephen Buchwald for his guidance and support throughout my time in his lab. Professor Buchwald and the members of the Buchwald research lab have been a tremendous influence in shaping me as a scientist and as a person over the past two years. Thanks to their patience and understanding, I have developed and accomplished more than I thought was possible during my time as an undergraduate student. I hope I have the pleasure to work with any of the members of the Buchwald group in the future.

I owe a great deal of gratitude to Professor Christopher “Kit” Cummins, who provided me with a research opportunity very early in my undergraduate career, an experience that provided me with a foundation upon which my scientific career has been built. I am especially grateful for Dr. Yang Yang’s mentorship. I hope to carry with me his incredible work ethic and vast understanding of the science as I pursue my own scientific endeavors. I would like to thank Dr.’s Aaron Sather and Mycah Uehling for their guidance during my semester of independent research. I am incredibly grateful for their help and advice in conducting my research and preparing my thesis.

Finally, I would like to thank my brother Robert, my parents, and my step parents as exemplary pillars of support for my scientific curiosity throughout my childhood. I likewise would like to thank my wonderful fiancé Maddie for her unyielding support through all the challenges of life.
PREFACE

Parts of this thesis have been adapted from the following articles co-written by the author.


RESPECTIVE CONTRIBUTIONS

This thesis is the result of collaborative effort of the author and other colleagues at MIT. The specific contributions of the author are detailed below.

The author performed the experiments in chapters 1 and 2 in collaboration with Dr. Yang Yang. The computational investigations briefly discussed in chapter 1 were carried out by Dr. Gang Lu and Prof. Peng Liu in collaboration with Dr. Yang Yang.

The author performed all of the experiments in chapter 3.
TABLE OF CONTENTS

Chapter 1. Copper-Catalyzed Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones

1.1 – Introduction 10
1.2 – Results and Discussion 13
1.3 – Conclusion 19
1.4 – Experimental 19
1.5 – References 23

Chapter 2. Copper-Catalyzed Enantioselective Addition of Styrene-Derived Nucleophiles to Imines

2.1 – Introduction 24
2.2 – Results and Discussion 26
2.3 – Conclusion 30
2.4 – Experimental 31
2.5 – References 34

Chapter 3. Palladium-facilitated Regioselective Nucleophilic Fluorination of Aryl and Heteroaryl Halides

3.1 – Introduction 35
3.2 – Results and Discussion 37
3.3 – Conclusion 43
3.4 – Experimental 44
3.5 – References 47
3.6 – Spectra 48
Chapter 1: Copper-catalyzed Asymmetric Addition of Olefin-derived Nucleophiles to Ketones.

1.1 – Introduction

Enantiomerically enriched alcohols are a common structural motif in pharmaceutical and biological chemistry. These molecules participate in a variety of biological functions, and consequently many methods of chiral alcohol synthesis have been developed in recent years. Among the most common methods is the addition of organometallic nucleophiles to ketones and aldehydes to yield substituted alcohols. This is widely regarded as one of the cornerstones of organic synthesis, with Grignard reagents being the most versatile and widely used nucleophiles for this process. The development and application of these preformed organometallic reagents as nucleophiles has given rise to a plethora of synthetically valuable chemistry, and more recent advances have been made to incorporate a high degree of stereoselectivity to these organometallic nucleophilic addition processes.

Despite the significant advances made in the development and application of organometallic nucleophiles as precursors to chiral alcohols, there have been limitations in their usefulness and practicality. Firstly, the use of Grignard reagents as nucleophiles requires preformation of a stoichiometric equivalent of the organometallic reagent, which predicates an additional synthetic step. Secondly, the use of Grignard reagents to induce chirality requires full or near-full equivalents of chiral auxiliaries or additives, likewise complicating synthetic pathways. Lastly, the strongly basic and nucleophilic nature of the reagents often limits the functional group compatibility of these processes, which often makes late stage modification of drug candidates by nucleophilic addition of Grignard reagents to ketones and aldehydes difficult.
or impossible. A general process by which nucleophilic attack of ketones is facilitated using catalytic quantities of both chiral molecules and metals to yield enantioenriched alcohols would have a significant impact on pharmaceutical chemistry as well as the field of chemistry as a whole.

By utilizing olefins as latent carbanion equivalents in lieu of preformed organometallic nucleophiles, we can bypass the limitations of Grignard reagents and develop a synthetically useful method for enantioselective nucleophilic addition to carbonyls with high degrees of functional group compatibility. Enantioselective reductive coupling of both olefins and alkynes with carbonyls have been previously reported by Krische and coworkers.\textsuperscript{5-6} The copper catalyzed borylative coupling of enynes with aldehydes by Hoveyda and coworkers marks an important development in this chemistry as well,\textsuperscript{7,8} however the synthesis of sterically complex alcohols from ketones via catalytically generated organometallic nucleophiles has thus far remained elusive.

We envisioned that such a process was possible through the \textit{in situ} generation of stereochemically enriched alkylcopper nucleophiles via the hydrocupration of olefins. The subsequent addition of these organocuprates to ketones to generate tertiary alcohols with vicinal highly-substituted stereocenters would mark the first catalytic nucleophilic addition of olefin-derived nucleophiles to ketones (Figure 1). Although the proposed process is novel, the metallofunctionalization of olefins and subsequent trapping by electrophiles has been independently reported by Hirano and coworkers\textsuperscript{9} as well as our lab.\textsuperscript{10} In these cases, an electrophilic amine was employed to intercept the organocopper nucleophile and generate the enantioenriched amine product. The use of ketones to facilitate this interception represents a novel challenge for copper chemistry.
Traditional approach: alkylation using stoichiometric quantities of organometallic reagents

\[ \text{[M]} + \text{R} \rightarrow \text{R'} \]

(i) Use of stoichiometric organometallic reagents
(ii) C-C bond forming nucleophilic addition generally sets one stereocenter

Our approach: alkylation using easily accessible olefins as latent carbanion equivalents

\[ \text{RC} = \text{C} \rightarrow \text{OH} \]

(i) Use of catalytically generated organometallic species via olefin hydrometalation
(ii) Rapid access to tertiary alcohols bearing contiguous tri- and tetrasubstituted stereocenters
(iii) Room temperature, free of acidic or basic additives, exceptional functional group compatibility

Figure 1- Strategies for accessing enantioenriched tertiary alcohols via nucleophilic addition to carbonyl electrophiles. From "Copper-catalyzed Asymmetric Addition of Olefin-derived Nucleophiles to Ketones." Science 353.6295 (2016): 144-50. Reprinted with permission from AAAS.

The proposed mechanism is illustrated in figure 2. Addition of the copper hydride species (I) across the olefin (II) yields an enantioenriched alkylcopper intermediate (III). Subsequent diastereoselective addition to the ketone (IV) affords an organocopper intermediate (V). Tert-butanol (VI) facilitates the release of the product (VII) via ligand exchange with V and generates a copper tert-butoxide intermediate (VIII), which undergoes \( \sigma \)-bond metathesis with the silane (IX) to regenerate catalytically active copper-hydride species (I). The lack of acidic or basic additives required in this mechanism provides for a highly versatile process, and the substrate scope consequently contains multiple sensitive functional groups.
1.2 – Results and Discussion

There are several challenges associated with this process, mainly the selective hydrocupration of the olefin component over the undesired reduction of the ketone. Lipschutz and coworkers have demonstrated the capability of phosphine-ligated copper-hydride species to reduce carbonyls with high levels of enantioselectivity, but the analogous pathway must be limited for our proposed process to afford the desired product in good yield, and we envisioned
that the appropriate choice of ligand would facilitate the desired olefin hydrometalation over ketone reduction. We commenced our study by examining different ligands and their propensity for the undesired reduction of the ketone component. As expected based on the findings of Lipschutz and coworkers, DTBM-SEGPHOS was capable of facilitating the undesired transformation of acetophenone 1 to the reduced secondary alcohol product 2a quite readily, with a \( \Delta G \) of 9.9 kcal/mol, and a relative rate of \( 5.3 \times 10^2 \) compared to (S,S)-Ph-BPE (L2) (Figure 3a). The effectiveness of L2 at facilitating the desired transformation is illustrated in figure 3b. L1 afforded the desired product in poor yield (48% yield by NMR), and instead slightly favored reduction of the ketone electrophile to the benzylic alcohol 4b (52% yield by NMR). Our optimized reaction conditions afford the product in 97% yield with excellent diastereo- and enantioselectivity. In an attempt to explain the selectivity afforded by our process, we conducted computational studies using density functional theory. The DFT calculations indicate a 5.5 kcal/mol free energy difference between the enantiomeric transition states, and a 2.7 kcal/mol free energy difference between the diastereomeric transition states (Figure 4a). These differences
arise as a result of unfavorable steric interactions between the ligand and the conformation of the substrate required to provide the disfavored product (Figure 4b-c).

Figure 4- DFT-calculated enantio- and diastereochemical-determining transition states for the copper-catalyzed addition of enyne (12)-derived nucleophile (13a-b) to ketone 1. From "Copper-catalyzed Asymmetric Addition of Olefin-derived Nucleophiles to Ketones." Science 353.6295 (2016): 144-50. Reprinted with permission from AAAS.

The scope of the transformation is shown in figure 5. Electron rich (5b) and electron poor (5c) aryl ketones are well tolerated. Ketones bearing aryl bromide (5d) and chloride (5e) substituents are compatible, which allows for further transformation through cross-coupling
methodologies. A variety of 5- and 6-membered heterocycles (5h-k) are feasible substrates, all of which provide excellent ee and dr and moderate to excellent isolated yield. Dialkyl ketones (5l-o), an α-ketoester (5q), and an enone (5r) are also tolerated. The enyne substrate scope is likewise quite broad, with both aromatic and aliphatic (5s-v) enynes being tolerated. An enyne with substitution at the olefinic terminus (5y) also provided high diastereo- and enantioselectivities, albeit with moderate yield. The reaction proceeds at room temperature and does not require acidic or basic additives, which allows for the inclusion of several sensitive functional groups into the substrate scope. A thioether (5f), a Boc-protected amine (5m), and a tertiary amine (5w) were all tolerated with moderate to excellent yields and excellent chemoselectivities. The functional tolerance of the process extended to an unprotected secondary amine (6a), a secondary amide (6b), an unprotected primary aliphatic alcohol (6c), a free phenol (6d), and most strikingly a carboxylic acid (6e), all while retaining excellent chemoselectivities with moderate yields.

Finally, we would like to report that this copper-catalyzed coupling process is scalable, and the homopropargyl alcohols are versatile intermediates that can be easily modified. We conducted a 50 mmol synthesis using 0.2 mol% catalyst loading without lowering the yield or selectivity of the transformation (82% yield, 98% ee, 10:1 dr). We were able to reduce the resultant homopropargyl alcohol 5c to either the aliphatic alcohol 9a, or the homoallylic alcohol 9b with in good yield while retaining the achieved selectivity (Figure 6a). The demonstrated scalability and robustness of the process makes it a viable tool for use on an industrial scale for the late-stage modification of pharmaceutical or agrochemical agents. To further demonstrate the synthetic applicability of our process, we subjected two pharmaceuticals to the coupling conditions. Lamisil (10a), an enyne, was coupled with acetophenone to give the homopropargyl
Figure 5 – Substrate scope of the copper-catalyzed addition of enyne-derived nucleophiles to ketones.

Reaction conditions (unless otherwise specified): Cu(OAc)$_2$ (5 mol %), (S,S)-Ph-BPE (6 mol %), ketone (0.5 mmol, 1.0 eq.), enyne (0.75 mmol, 1.5 eq.), t-BuOH (0.5 mmol, 1 eq.), (MeO)$_2$MeSiH (2.5 mmol, 5 eq.), RT, 12h. Yields refer to the isolated yield of the major diastereomer. Yields in parentheses refer to the combined yields of both diastereomers determined $^1$H NMR spectroscopy of the crude reaction mixture. Values for ee were determined by chiral HPLC. TBS, tert-butyldimethylsilyl; Ts, tosyl; Et, ethyl. From "Copper-catalyzed Asymmetric Addition of Olefin-derived Nucleophiles to Ketones." Science 353.6295 (2016): 144-50. Reprinted with permission from AAAS.
alcohol in moderate yield with good selectivity. Tricor (10b), a ketone, was likewise subjected to our conditions to yield the product in good yield with excellent enantioselectivity, yet lacking the same diastereoselectivity seen through much of our substrate scope.

Figure 6 - Scalability and application of the copper-catalyzed asymmetric addition of olefin-derived nucleophiles. (A) a: Pd(OH)$_2$/C, H$_2$ (balloon pressure). MeOH, RT, 12 hours. b: 5 mol% IPrCuCl, 6 mol% LiOtBu, (MeO)$_2$MeSiH, t-BuOH, toluene, RT, 48 hours. (B) c: 5 mol% Cu(OAc)$_2$, 6 mol% (S,S)-Ph-BPE, (MeO)$_2$MeSiH, t-BuOH, cyclohexane, RT, 12 hours.
1.3 – Conclusion

In summary, we have developed a copper-catalyzed coupling of olefin-derived nucleophiles with ketones which achieves excellent enantio- and diastereoselectivity. The process circumvents the need for preformed organometallic intermediates, as is common for nucleophilic addition to carbonyls. The mild and general transformation proceeds at room temperature and does not require basic additives, which allows for unprecedented functional group tolerance. The transformation is scalable, and our strategy is applicable to a range of commercially available pharmaceutical agents. We anticipate that further transformations will become possible with the advent of more complex ligand scaffolds that allow for functionalization of increasingly unactivated olefins, developments that will provide olefin-derived nucleophiles of remarkable synthetic utility.

1.4 – Experimental

**General Information:** All reactions were carried out under an inert atmosphere of argon or nitrogen gas. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina and copper (II) oxide. Cyclohexane (anhydrous, 99.5%) and methyl tert-butyl ether (MTBE) (anhydrous, 99.5%) were purchased from Sigma Aldrich in a SureSeal® bottle and was used without further purification. Copper(II) acetate, (S,S)- and (R,R)-Ph-BPE were purchased from Strem or Sigma-Aldrich and were used as received. (R)-DTBM-SEGPHOS was purchased from Takasago and was used as received. Dimethoxymethylsilane ((MeO)₂MeSiH, moisture-sensitive) was
purchased from TCI-America and was stored in a -20 °C freezer. All of the other reagents were purchased from Sigma Aldrich, Alfa Aesar, Strem, TCI America, Combi-Blocks or Matrix Scientific and were used as received. Flash column chromatography was performed with the aid of a Biotage Isolera Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g). Enynes were prepared according to literature procedure.\textsuperscript{a,b}

**General Analytical Information:** All compounds were characterized by \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and \textsuperscript{19}F NMR (when applicable). New compounds were also characterized by IR spectroscopy, melting point (if solids), elemental analysis and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 or 600 MHz instrument. All \textsuperscript{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals of residual chloroform (7.26 ppm) or dichloromethane (5.32 ppm) in the deuterated solvent. All \textsuperscript{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) or dichloromethane-d\textsubscript{2} (53.84 ppm) and all were obtained with \textsuperscript{1}H decoupling. All \textsuperscript{19}F NMR spectra are reported in ppm relative to CFC\textsubscript{13} (0.00 ppm). All IR spectra were taken on a Thermo Scientific Nicolet iS5 spectrometer. (iD5 ATR, diamond). Enantiomeric excess (ee) values were determined by high performance liquid chromatography (HPLC) analysis using a chiral stationary phase. Racemic samples were prepared using racemic ligand prepared by mixing a 1:1 ratio of (S,S)- and (R,R)-Ph-BPE. Optical rotations were measured on a Jasco P-1010 polarimeter with [α]D values reported in degrees; concentration (c) is in g/100 mL. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ESI-HRMS and DART-HRMS


spectrometric data were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). DART-MS spectrometric data were recorded on an IonSense Inc. DART SVP (Direct Analysis in Real Time, Standardized Voltage and Pressure) mass spectrometer.

1.4.1 – Experimental Procedures

General Procedure for Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones (Unless Otherwise Noted): In a nitrogen-filled glovebox, an oven-dried 20 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with Cu(OAc)$_2$ (4.6 mg, 0.025 mmol, 5.0 mol %), (S,S)-Ph-BPE (15.2 mg, 0.03 mmol, 6.0 mol %), the enyne substrate (0.75 mmol, 1.5 equiv), the ketone substrate (0.50 mmol, 1 equiv), t-BuOH (48 µL, 0.5 mmol, 1 equiv) and cyclohexane (1.00 mL, 0.5 M). The mixture was stirred for 5 minutes at room temperature before the addition of dimethoxymethylsilane (307 µL, 2.5 mmol, 5.0 equiv). The reaction vessel was capped, removed from the glovebox and allowed to stir for 12 h. Upon completion, a saturated solution of NH$_4$F in MeOH (ca. 6 mL) was carefully added to quench the reaction (Caution: gas evolution was observed). The reaction was allowed to stir at room temperature for 20 minutes, diluted with EtOAc (ca. 10 mL), and allowed to stir for an additional 10 minutes. The reaction mixture was filtered through a short plug of celite (ca. 1 cm) and rinsed thoroughly with EtOAc (ca. 50 mL). Solvent was removed under vacuum with the aid of a rotary evaporator. Combined yield and dr were determined by $^1$H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The reaction mixture was purified by flash column chromatography with the aid of Biotage Isolera.
**Large scale (50 mmol) Synthesis with Low Catalyst Loading:** In a nitrogen-filled glovebox, an oven-dried 300 mL round-bottom flask was equipped with a stir bar and charged with Cu(OAc)$_2$ (18.2 mg, 0.1 mmol, 0.20 mol %), (S,S)-Ph-BPE (101 mg, 0.2 mmol, 0.4 mol %), but-3-en-1-yn-1-ylbenzene (10 mL, 75 mmol), 4'-( trifluoromethyl)acetophenone (50 mmol, 1 equiv), t-BuOH (4.8 mL, 50 mmol, 1 equiv) and cyclohexane (100 mL, 0.5 M). The mixture was stirred vigorously at room temperature for 10 min until most of the phosphine ligand had dissolved. (MeO)$_2$MeSiH (30.0 mL, 250 mmol, 5.0 equiv) was added dropwise while stirring the reaction mixture. The S29 reaction vessel was then capped with a rubber septum, removed from the glove box and allowed to stir at room temperature for 24 h. After completion, the reaction mixture was carefully transferred to a saturated solution of NH$_4$F in MeOH (ca. 150 mL) while stirring (Caution: gas evolution was observed). The reaction mixture was allowed to stir for 10 min at room temperature, diluted with EtOAc, stirred for an additional 10 min at room temperature and then filtered through a short plug of celite (ca. 5 cm) eluting with EtOAc (ca. 200 mL). Solvent was removed under reduced pressure with the aid of a rotary evaporator to yield the crude product as an off-white solid. The crude product was recrystallized from hot hexanes to give the title product as a white crystalline solid (12.1 g, 76% yield). The mother liquor was collected, concentrated under reduced pressure and further recrystallized from hexanes to give the title product as a white crystalline solid (1.2 g, 7% yield). HPLC analysis (AD-H column, 3% i-PrOH/hexanes, 0.80 mL/min, 254 nm) indicated 98% ee for both crops of product.

*For detailed information on substrate preparation, individual reaction conditions, and spectroscopic data, please see Y. Yang, Perry, I. B., Lu, G., Liu, P., and Buchwald, S. L. “Copper-Catalyzed Asymmetric Addition of Olefin-Derived Nucleophiles to Ketones.” Science, 2016.*
1.5 – References


Chapter 2: Copper-Catalyzed Enantioselective Addition of Styrene-Derived Nucleophiles to Imines

2.1–Introduction

Among the most important structural motifs in biologically relevant small molecules are chiral amines. Enantiomerically enriched amines can be found in a wide variety of pharmaceutically relevant small molecules,¹ and consequently the synthesis of such chiral amines has long been a focus of synthetic organic chemistry. Although there are several methods of asymmetric amine synthesis, the addition of nucleophiles to prochiral imines is often employed as a convenient method of α-chiral amine synthesis.²⁻⁴

However, limitations to this nucleophilic attack of the C—N double bond do exist. Particularly, a stoichiometric quantity of a preformed organometallic reagent and the use of a chiral auxiliary group limit the feasibility of the method. Highly basic organometallic compounds such as Grignard reagents can limit the functional group tolerance of these methods as well. Furthermore, the use of Grignard or organozinc reagents generally requires the additional synthetic step of preparing such reagents, most usually from the organic halide or olefin. If a method of in situ generation of organometallic nucleophile from olefins as latent carbanion equivalents was possible, some of these problems could be remediated. In recent years, Krische and coworkers have demonstrated that polyunsaturated olefins could be employed as latent carbanion equivalents for the nucleophilic attack of carbonyls through transition metal catalysis.⁵⁻⁶ The success of these processes, however, has been primarily limited to aldehydes,⁷⁻⁸ and relatively few examples exist for the generation of chiral amines via catalytically-generated nucleophiles adding to imines.⁹⁻¹⁰
Our lab has recently become interested in copper(I) hydride catalysis as a means for accessing enantioenriched organocopper nucleophiles via the hydrocupration of readily available precursor chemicals.\textsuperscript{11} By capturing thesis enantioenriched species with electrophiles, our laboratory\textsuperscript{11} and Hirano and Miura\textsuperscript{12} have independently developed a novel method for the hydroamination of olefins. We have also developed a method for an enantioselective intramolecular $\text{C}--\text{C}$ bond forming process demonstrating the feasibility of utilizing organocuprates as potent enough nucleophiles to engage in $\text{C}--\text{C}$ bond forming processes with imines as electrophiles (Figure 1A).\textsuperscript{13} We have aimed to develop the analogous intermolecular process, utilizing styrenes as latent carbanions for nucleophilic addition to imine electrophiles, and the proposed mechanism is shown in Figure 1B. Ligand-bound copper hydride species I hydrocuprates the styrene substrate II to yield the enantioenriched organocuprate III. Subsequent nucleophilic attack on the $N$-protected imine substrate IV yields the amine-bound copper species V, which through interaction with tert-butanol VI releases the product VII and copper tert-butoxide species VIII. Sigma-bond metathesis with the hydrosilane IX regenerates the active copper hydride catalyst I.\textsuperscript{14} Notably, this strategy requires no acidic or basic additives, which allows for a broad substrate scope and potentially tolerates sensitive functional groups.
Figure 1 – (A) Previous work involving the analogous intermolecular addition of olefin-derived organocuprates to imine-based electrophiles. (B) Copper catalyzed enantioselective addition of styrene-derived nucleophiles to imines. (C) Hydrocupration of olefins in the presence imines represents a challenge, due to the propensity for imines to undergo undesired 1,2-reduction.

2.2 - Results and Discussion

Several difficulties are apparent with this transformation. Notably, the hydrocupration of a styrene in the presence of an N-protected imine presents a significant challenge, due to the thermodynamic favorability of reduction of the C—N N-protected double bond (Figure 1C). Selection of an appropriate protecting group could substantially influence the propensity of the polarized 2π component to undergo undesired reduction. Compiled in Table 1 is our survey of
Table 1 – Reaction optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>variation from the “standard conditions”</th>
<th>yield of 3 (dr)</th>
<th>ee of 3</th>
<th>yield of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>95% (3:1)</td>
<td>99% ee (99% ee)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5%</td>
</tr>
<tr>
<td>2</td>
<td>L1 instead of L6</td>
<td>9% (1:1)</td>
<td>95% ee (99% ee)</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>L2 instead of L6</td>
<td>&lt;5%</td>
<td>n.d.</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>L3 instead of L6</td>
<td>&lt;5%</td>
<td>n.d.</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>L4 instead of L6</td>
<td>56% (1:1)</td>
<td>86% ee (83% ee)</td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td>L5 instead of L6</td>
<td>46% (1:1)</td>
<td>78% ee (70% ee)</td>
<td>54%</td>
</tr>
<tr>
<td>7</td>
<td>no t-BuOH</td>
<td>41% (3:1)</td>
<td>99% ee (99% ee)</td>
<td>31%</td>
</tr>
<tr>
<td>8</td>
<td>2b instead of 2a</td>
<td>5%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n.d.</td>
<td>36%</td>
</tr>
<tr>
<td>9</td>
<td>2c instead of 2a</td>
<td>6%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n.d.</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 1 (0.2 mmol), 2 (0.1 mmol), Cu(OAc)<sub>2</sub> (5 mol %), L (6 mol %), t-BuOH (2 equiv), (MeO)<sub>2</sub>MeSiH (5 equiv), THF (0.5 M), rt, 12 h. Yields were determined by 1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as the internal standard. Enantiomeric excess values were determined by chiral HPLC analysis.

<sup>b</sup>The ee of the major diastereomer is shown in parentheses. 

reaction conditions. It was found that N-phosphinoyl imines performed most favorably among imine protecting groups tested, and Ph-BPE (L1) was found to selectively hydrocuprate the olefin substrate over the imine substrate with far more success than any other ligand tested, and with higher ee and yield (Table 1, entry 1). Several ligands (L1, L4, L5) were found to facilitate
the hydrocupration with moderate to excellent enantioselectivity (entries 2, 5 and 6), but at the cost of diastereoselectivity. Ligands L2 and L3 were incapable of facilitating the desired transformation (entries 2 and 3). The omission of tert-butanol was found to dramatically reduce the yield (Table 1, entry 7). Lastly, phenyl or phenylsulfonyl protecting groups could not be employed in the desired transformation, and failed to yield adequate amounts of product (Table 1, entries 8 and 9).

We next investigated and compiled a substrate scope for this reaction, shown in Table 2. The scope of styrenes (Table 2A) contains styrenes with a variety of electronic properties (5a-d)

Table 2 – (A) Styrene substrate scope. (B) Imine substrate scope

![Table 2](image)

⁹Yields are of isolated product as a mixture of two diastereomers on a 0.5 mmol scale. The relative and absolute chemistry of both diastereomers was determined by X-ray crystallography or further derivatization of the product. Minor diastereomer ee is shown in parentheses.
as well as examples of halogenated styrenes (5e-f) which can be further functionalized through coupling processes. These substrates yield the desired product with excellent enantioselectivity and in good yield. An ortho-substituted styrene (5g) as well as two examples of nitrogen heterocycles (5h-i) are included in the scope, and these substrates exhibit the same excellent enantioselectivity with moderate to good yields. Lastly, a $\beta$-substituted styrene was found to yield the desired product with equally excellent stereocontrol despite a subpar yield. The scope of the imine substrate (Table 2B) was then examined. Again, imines with a variety of electronic properties were found to be compatible with the reaction (6a-d). Examples of nitrogen and sulfur-containing heterocycles were demonstrated to be feasible substrates for this strategy, both in terms of yield and enantioselectivity (6e-i). An $\alpha$-$\beta$ unsaturated imine (6j) was likewise found to be a suitable substrate for our strategy, and was not subject to the undesired 1,4-reduction. Several ketimines were tested (6k-m) and found to be reasonable coupling partners as well, providing the desired enantiomer in good to excellent ee, albeit with varying yields.

We next set out to show the scalability of our copper-catalyzed enantioselective imine addition to further demonstrate the utility of this strategy. We found that the process was scalable and required very low catalyst loadings. In Figure 2, the gram-scale synthesis of enantioenriched amine from 3-chlorostyrene (7) and imine 2a is shown to proceed with equally excellent yield and enantioselectivity as the smaller-scale reactions (eq. 1). Also shown is the use of a chiral sulfinimine auxiliary to influence the addition of the benzylcopper intermediate to proceed in a diastereoselective fashion, improving the product ratio to 18:1:0.2:0.7 (eq. 2).
**2.3– Conclusion**

In summary, we have developed a mild and general method for the enantioselective addition of styrene-derived nucleophiles to imines. The functional group tolerance of this strategy is very broad, allowing for a variety of electronic properties and heterocycles in both the imine and styrene substrates. This method allows for the generation of vicinal stereocenters with excellent enantiocontrol, and the use of chiral N-protecting groups positively influences the product ratio further. As more ligand scaffolds become available, the strategy of employing olefins as latent nucleophiles will surely develop further, and transformations involving unactivated olefins will become more possible.
2.4 – Experimental

**General Information:** All reactions were carried out under an inert atmosphere of argon or nitrogen gas. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina and copper (II) oxide. Cyclohexane (anhydrous, 99.5%) and methyl tert-butyl ether (MTBE) (anhydrous, 99.5%) were purchased from Sigma Aldrich in a SureSeal® bottle and was used without further purification. Copper(II) acetate, (S,S)- and (R,R)-Ph-BPE were purchased from Strem or Sigma-Aldrich and were used as received. (R)-DTBM-SEGPHOS was purchased from Takasago and was used as received. Dimethoxymethylsilane ((MeO)₂MeSiH, moisture-sensitive) was purchased from TCI-America and was stored in a -20 °C freezer. All of the other reagents were purchased from Sigma Aldrich, Alfa Aesar, Strem, TCI America, Combi-Blocks or Matrix Scientific and were used as received. Flash column chromatography was performed with the aid of a Biotage Isolera Automated Flash Chromatography System using prepacked SNAP silica cartridges (10-100 g).

**General Analytical Information:** All compounds were characterized by 
^1^H NMR, 
^1^3^C NMR and 
^1^9^F NMR (when applicable). New compounds were also characterized by IR spectroscopy, melting point (if solids), elemental analysis and/or high-resolution mass spectrometry. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 or 600 MHz instrument. All 
^1^H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals of residual chloroform (7.26 ppm) or dichloromethane (5.32 ppm) in the deuterated solvent. All 
^1^3^C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) or dichloromethane-d2 (53.84 ppm) and all were obtained with 
^1^H decoupling. All 
^1^9^F NMR spectra are reported in ppm relative to CFCl3 (0.00 ppm). All IR spectra were taken on a Thermo Scientific Nicolet iS5 spectrometer. (iD5 ATR, diamond). Enantiomeric excess (ee) values were determined by high performance liquid chromatography (HPLC) analysis using a chiral stationary phase. Racemic samples were prepared using racemic ligand prepared by mixing a 1:1 ratio of
(S,S)- and (R,R)-Ph-BPE. Optical rotations were measured on a Jasco P-1010 polarimeter with $[\alpha]$D values reported in degrees; concentration ($c$) is in g/100 mL. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ESI-HRMS and DART-HRMS spectrometric data were recorded on a Bruker Daltonics APEX IV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). DART-MS spectrometric data were recorded on an IonSense Inc. DART SVP (Direct Analysis in Real Time, Standardized Voltage and Pressure) mass spectrometer.

### 2.4.1 Experimental Procedures

#### General Procedure for the Asymmetric Addition of Styrene-Derived Nucleophiles to Imines (Unless Otherwise Noted):

In a nitrogen-filled glovebox, an oven-dried 20 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with Cu(OAc)$_2$ (4.6 mg, 0.025 mmol, 5.0 mol %), (S,S)-Ph-BPE (15.2 mg, 0.03 mmol, 6.0 mol %), the styrene substrate (0.75 mmol, 1.5 equiv), the imine substrate (0.50 mmol, 1 equiv), t-BuOH (96 µL, 1.0 mmol, 2 equiv) and THF (1.00 mL, 0.5 M). The mixture was stirred for 5 minutes at room temperature before the addition of dimethoxymethylsilane (307 µL, 2.5 mmol, 5.0 equiv). The reaction vessel was capped, removed from the glovebox and allowed to stir for 12 h. Upon completion, the reaction mixture was transferred to a 50 mL round bottom flask. The solvent was removed *in vacuo* with the aid of a rotary evaporator. At the point, the combined yield and the diastereomeric ratio (dr) were determined by $^1$H NMR using 1,3,5-trimethoxybenzene or 1,1,2,2-tetrachloroethane as an internal standard. The reaction mixture was purified by flash column chromatography with the aid of Biotage Isolera.

#### General Procedure for Gram-Scale synthesis:

Following the general procedure, Cu(OAc)$_2$ (2.3 mg, 0.0125 mmol, 0.2 mol %), (S,S)-Ph-BPE (9.5 mg, 0.01875 mmol, 0.75 mol %), 3-chlorostyrene (0.64 mL, 5.0 mmol), N-benzylidine-$P,P$-diphenylphosphinic amide (0.763 g, 2.5 mmol), t-BuOH (0.475 mL, 5.0 mmol, 2 equiv) and THF (5.00 mL) were added to a 20 mL reaction tube under inert atmosphere and
allowed to stir for 5 minutes. At this point, dimethoxymethylsilane (1.54 mL, 12.5 mmol) was added to the vial. The reaction tube was sealed and allowed to stir at room temperature for 12 h.

Major diastereomer: m.p. = 219 – 220 ºC. 1 H NMR (400 MHz, CDCl3) δ: 7.57 – 7.41 (m, 5H), 7.41 – 7.30 (m, 3H), 7.27 – 7.22 (m, 7H), 7.08 – 7.07 (m, 1H), 7.04 – 7.01 (m, 3H), 4.22 (q, J = 8.9 Hz, 1H), 3.21 (dd, J = 9.8, 6.7 Hz, 1H), 3.08 (p, J = 7.2 Hz, 1H), 1.15 (d, J = 7.0 Hz, 3H) ppm. 31P NMR (162 MHz, CDCl3) δ: 22.3 ppm. 13C NMR (101 MHz, CDCl3) δ: 145.4, 142.19, 142.16, 134.3, 133.4, 133.1, 132.5, 132.4, 132.1, 131.9, 131.79, 131.78, 131.75, 131.70, 131.67, 129.8, 128.7, 128.5, 128.39, 128.34, 128.32, 128.2, 127.40, 127.39, 127.2, 127.1, 126.7, 61.20, 61.19, 47.66, 47.60, 18.53 ppm (Observed complexity is due to C–P splitting). IR: 3188 (N-H), 3055, 2961, 1435, 1181, 723, 691 cm⁻¹. Anal. Calcd. for C27H25ClNOP: C, 72.72; H, 5.65. Found: C, 72.70; H, 5.82. [α]D 24 = +45.6, (c = 1.00, CHCl3). HPLC analysis (IC column, 10% iPrOH/hexanes, 1.0 mL/min, 210 nm) indicated 99% ee: tR (minor) = 20.9 min, tR (major) = 85.6 min

2.5 – References

Chapter 3: Palladium-facilitated Regioselective Nucleophilic Fluorination of Aryl and Heteroaryl Halides.

3.1– Introduction

The abundance of the aryl fluoride moiety in medicinal and agrochemical agents can be partially attributed to the robustness of fluorinated organic compounds to oxidative metabolism by biological systems. However, the efficacy of organofluorides is not solely rooted in their resistance to catabolism. Fluorination of biologically active molecules can modulate a variety of physical properties including lipophilicity and electrostatic interactions between the small molecule and its binding site. Currently, the synthesis of many fluorinated drugs begins with fluorinated starting materials, as late stage fluorination of many drug candidates is an outstanding challenge. In recent years, a variety of methods for the catalytic nucleophilic fluorination of aryl halides have been developed. Our lab has reported a method for the room temperature fluorination of aryl bromides and triflates, as well as some selected examples of heteroaryl halide fluorination.

Although advances have been made toward a general process for the fluorination of aryl halides and pseudohalides, current methods are limited in scope, with a general method for the regioselective fluorination of protic substrates, five-membered heteroarenes, and electron rich arenes not yet available. Such a method for the fluorination of aryl halides and particularly heteroaryl halides is of great interest to the field of medicinal chemistry, due to the prevalence of both fluorinated organic compounds and heterocycles in pharmaceuticals. However, several significant challenges have hindered the development of such a method. Firstly, while processes exist for the regioselective fluorination of electron poor aryl halides, electron rich aryl halides...
have a tendency to form regioisomers through a palladium-benzyne intermediate.\textsuperscript{3} Secondly, only selected examples of the fluorination of heteroaryl halides exist, very few of which are five-membered heterocycles.\textsuperscript{5} For bromothiophenes, this was shown to be a result of the relatively high barrier to reductive elimination,\textsuperscript{3} yet for five-membered nitrogen heterocycles, it was found that the substrates themselves may have an inhibiting role on the reaction.\textsuperscript{5}

By utilizing a stoichiometric equivalent of palladium, we envisioned that it would be possible to remediate substrate inhibition of the reaction. Given the high cost of synthesizing a late-stage pharmaceutical from feedstock chemicals, the analogous synthesis with fluorinated starting materials is far too expensive and time consuming to be practical. Even with the relatively high cost of stoichiometric quantities of palladium and phosphine ligands, a general method for the fluorination of complex aryl and heteroaryl bromides would be of substantial value to the medicinal chemistry industry. Such a method would allow for late stage fluorination of drug candidates, giving medicinal chemists a tool for the rapid synthesis of aryl and heteroaryl fluorides for high-throughput screening.

The proposed mechanism is illustrated in figure 1. Palladium (0) species (I), present in a stoichiometric quantity, inserts into the (hetero)aryl—halide (II) bond, removing free (hetero)aryl halide from solution entirely. Oxidative addition complex III reacts with fluoride source IV to yield palladium-fluoride species V. Thermolysis of this species provides the (hetero)aryl fluoride product (VI). This mechanism relies on the favorable and irreversible nature of oxidative addition to permanently remove any heteroaryl bromide from the reaction, which may have an inhibitory effect on the reaction.
3.2 – Results and Discussion

We commenced our study by synthesizing two AlPhos (L1)-based oxidative addition complexes ((L1)Pd(Ar)(Br)) bearing electron rich (3a) and electron deficient (3b) aryl groups (Figure 2A). Oxidative addition complexes were prepared conveniently by allowing the AlPhos precatalyst P1 ((AlPhosPd)₂COD) to react with aryl bromides at room temperature in THF. Complexes 3a and 3b were isolated as yellow solids in 70-90% yield.

The conversion of 3a and 3b to the corresponding palladium fluoride species 3c and 3d (Figure 2B) afforded the resultant palladium fluoride species, which was isolated, characterized by $^{19}$F NMR, and stored at -20°C away from light. Stoichiometric reductive elimination studies were then performed. It was found that upon heating complex 3c in toluene at 100°C, the desired product was afforded in 21% yield, with 6% undesired meta-regioisomer detected by $^{19}$F NMR. However, the addition of 2 equivalents of 4-bromo-n-butylbenzene to the reaction mixture prior to heating afforded the product in 50% yield with 7% regioisomer formation by $^{19}$F NMR. This improvement in yield prompted us to examine the use of an aryl halide trap in further stoichiometric studies, the results of which are documented in table 1. Most significantly, it was found that a decrease in temperature from 100°C to 80°C resulted in a complete shutdown of the pathway to regioisomer (3f) formation, and only formation of the desired para-isomer (3e) was
observed in cyclohexane. Moreover, it was found that in contrast to stoichiometric reductive elimination studies, the addition of a trapping agent (Ar-X) did not prove to aid the reaction, and in some cases reduced the yield. In contrast to the analogous catalytic reaction\textsuperscript{1}, it was found that the addition of KF was not required and typically resulted in diminished yields (entries 17-18, 20).
Table 1 - Reaction optimization. Yields were determined by 19F NMR with 1-Fluoronaphthalene as an internal standard. Product chemical shifts were taken from literature data\(^3\text{-}^5\). Standard conditions highlighted in yellow.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-X</th>
<th>equiv. Ar-X</th>
<th>equiv. AgF</th>
<th>solvent</th>
<th>temperature</th>
<th>% yield 3e</th>
<th>% yield 3f</th>
<th>additives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
<td>2-MeTHF</td>
<td>100</td>
<td>42</td>
<td>11</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>31</td>
<td>&lt;2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5</td>
<td>Tol</td>
<td>110</td>
<td>27</td>
<td>&lt;2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5</td>
<td>2-MeTHF</td>
<td>100</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>5</td>
<td>2-MeTHF</td>
<td>100</td>
<td>37</td>
<td>15</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>55</td>
<td>&lt;2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>5</td>
<td>Tol</td>
<td>110</td>
<td>43</td>
<td>11</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>67</td>
<td>7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4-CF\textsubscript{3}-PhBr</td>
<td>1</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>60</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>0.5</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>63</td>
<td>9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>58</td>
<td>12</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.5</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>60</td>
<td>9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>2</td>
<td>Cy</td>
<td>80</td>
<td>21</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0.5</td>
<td>2</td>
<td>Cy</td>
<td>80</td>
<td>27</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>5</td>
<td>Cy</td>
<td>80</td>
<td>43</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.5</td>
<td>5</td>
<td>Cy</td>
<td>80</td>
<td>45</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0.5</td>
<td>2</td>
<td>Cy</td>
<td>80</td>
<td>31</td>
<td>0</td>
<td>0.5 eq. KF</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>2</td>
<td>Cy</td>
<td>80</td>
<td>11</td>
<td>0</td>
<td>0.5 eq. KF</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>5</td>
<td>Cy</td>
<td>100</td>
<td>54</td>
<td>12</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>2</td>
<td>Cy</td>
<td>80</td>
<td>34</td>
<td>0</td>
<td>0.5 eq. KF</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>5</td>
<td>Cy</td>
<td>80</td>
<td>62</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

For general procedure and selected \(^{19}\text{F} \text{NMR spectra, see experimental section.}

Despite this promising result, it was determined that there was a solvent-dependent effect as we varied substrates. 5-bromonicotinitrile (3h) and 8-bromocaffeine (3i) were found to be incompatible with the fluorination conditions, affording 0% product in both cases. However, this
problem was remediated by a solvent switch. Results are compiled in table 2. These initial results are promising in that the yields are comparable to those in the analogous catalytic reactions. Further studies are required to determine the applicability of this strategy to heterocycles that are incompatible with the catalytic reaction.

**Table 2** - Solvent dependence in fluorination of heterocycles. Values reported are percent yields as determined by $^{19}$F NMR against an internal standard. All reactions run at the boiling point of the solvent. N/d = no data

<table>
<thead>
<tr>
<th>Entry</th>
<th>HetArBr</th>
<th>Cyclohexane</th>
<th>2-MeTHF</th>
<th>Toluene</th>
<th>MTBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3g</td>
<td>12</td>
<td>0</td>
<td>&lt;2</td>
<td>&lt;2</td>
<td></td>
</tr>
<tr>
<td>3h</td>
<td>0</td>
<td>77</td>
<td>55</td>
<td>n/d</td>
<td></td>
</tr>
<tr>
<td>3i</td>
<td>0</td>
<td>36</td>
<td>66</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

For general procedure and selected $^{19}$F NMR spectra, see experimental section 1.4.1

### 3.2.1 – Preliminary Results in Halogen Exchange Studies

Analysis of a reaction mixture by GC-MS indicated that in some instances, (L1)Pd(Ar)(Br) is capable of reductive elimination of aryl bromide. Moreover, reductive elimination of aryl halides from phosphine-ligated Pd(II) species has been previously documented. Although further exploration of the mechanism and scope of this process is
required, this finding prompted the exploration of additional conditions that would limit this reversibility, which could have an inhibitory effect on the fluorination of heteroaryl bromides\(^5\).

Inspired by the cationic nature of aryl triflate oxidative addition complexes\(^8\), it was proposed that a silver(I) triflate facilitated halogen atom abstraction step could be performed, a process which would be unique to the stoichiometric reaction. Initial studies indicated that both silver tetrafluoroborate and silver triflate were capable of the necessary substitution to yield the cationic palladium species. This reaction, shown in scheme 1, afforded a product with a unique \(^{31}\)P NMR chemical shift at 120 ppm (see supplementary information).

**Scheme 1**

If this cationic palladium species \(\text{3j}\) could be generated *in situ* stoichiometrically and irreversibly, the fluorination of aryl and heteroaryl halides could proceed in a similar fashion to fluorination of triflates. In addition to the removal of heteroaryl bromides from solution, this could open up the substrate scope to include aryl chlorides, which have historically been more difficult substrates to fluorinate. Preliminary testing showed a variety of promising results in terms of regioselectivity in the fluorination of aryl halides. Given that these studies are still in their infancy, further optimization could make this stoichiometric halogen exchange a viable method for the rapid fluorination of a variety of electron rich aryl bromides and chlorides (Table 3A) as well as the possibility of fluorination of five and six-membered heterocycles (Table 3B).
Table 3 - (A) regioselective fluorination of aryl halides by halogen atom substitution. (B) Fluorination of heteroaryl bromides by halogen atom substitution

A

1) P1, solvent, 80°C, 20 minutes
2) AgBF₄, MF, 80°C, 12h

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>solvent</th>
<th>M⁺</th>
<th>% yield (para)</th>
<th>% yield (meta)</th>
<th>Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>n-Bu</td>
<td>Cy</td>
<td>Cs</td>
<td>46</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>n-Bu</td>
<td>Cy</td>
<td>Me₄N</td>
<td>14</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>OMe</td>
<td>Cy</td>
<td>Cs</td>
<td>26</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>n-Bu</td>
<td>Cy</td>
<td>Cs</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>n-Bu</td>
<td>Cy</td>
<td>Me₄N</td>
<td>26</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>n-Bu</td>
<td>2-MeTHF</td>
<td>Cs</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>n-Bu</td>
<td>2-MeTHF</td>
<td>Cs</td>
<td>20</td>
<td>0</td>
<td>2.5 eq. KF</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>n-Bu</td>
<td>Cy</td>
<td>Cs</td>
<td>57</td>
<td>0</td>
<td>2.5 eq. KF</td>
</tr>
</tbody>
</table>

B

1) P1, solvent, 80°C, 20 minutes
2) AgX, CsF, temp, 12h

<table>
<thead>
<tr>
<th>Entry</th>
<th>HetArBr</th>
<th>Solvent</th>
<th>X</th>
<th>temp</th>
<th>% yield HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3g</td>
<td>2-MeTHF</td>
<td>OTf</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>3g</td>
<td>Cy</td>
<td>OTf</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>3g</td>
<td>Tol</td>
<td>OTf</td>
<td>110</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>3h</td>
<td>2-MeTHF</td>
<td>OTf</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>13</td>
<td>3h</td>
<td>Cy</td>
<td>OTf</td>
<td>80</td>
<td>41</td>
</tr>
<tr>
<td>14</td>
<td>3h</td>
<td>Tol</td>
<td>OTf</td>
<td>110</td>
<td>48</td>
</tr>
<tr>
<td>15</td>
<td>3i</td>
<td>2-MeTHF</td>
<td>OTf</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>16</td>
<td>3i</td>
<td>Cy</td>
<td>OTf</td>
<td>80</td>
<td>52</td>
</tr>
<tr>
<td>17</td>
<td>3i</td>
<td>Tol</td>
<td>OTf</td>
<td>110</td>
<td>71</td>
</tr>
<tr>
<td>18</td>
<td>3g</td>
<td>Cy</td>
<td>BF₄</td>
<td>80</td>
<td>&lt;2</td>
</tr>
<tr>
<td>19</td>
<td>3i</td>
<td>Cy</td>
<td>BF₄</td>
<td>80</td>
<td>68</td>
</tr>
</tbody>
</table>

For general procedure and selected ¹⁹F NMR spectra, see experimental section 1.4.1
Future directions for this research include studies at higher temperatures, as heteroaryl fluorination is not consistently plagued by the same regioisomerization problems as aryl fluorination. In addition to this, fluorination of heteroaryl chlorides should be tested, as the prevalence of aryl and heteroaryl chlorides in drug molecules exceeds that of bromides.

3.3 – Conclusion

In summary, we have developed the initial groundwork for a fluorination process facilitated by palladium as a reagent. Although in its infancy, this strategy has given promising results, such as the fluorination of 4-bromoanisole with unprecedented regioselectivity. Studies into halogen exchange have indicated that this step, which would be unique to stoichiometric use of palladium, could help to enable fluorination of historically difficult substrates by removing free substrate from solution permanently. These findings mark a small step forward in the notoriously difficult problem of transition metal facilitated fluorination chemistry.
3.4– Experimental

**General Information:** All reactions were carried out under an inert atmosphere of argon or nitrogen gas. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina and copper (II) oxide. Cyclohexane (anhydrous, 99.5%), 2-methyltetrahydrofuran (2-MeTHF) (anhydrous, 99.5%), and methyl tert-butyl ether (MTBE) (anhydrous, 99.5%) were purchased from Sigma Aldrich in a SureSeal® bottle and was used without further purification. AlPhos and P1 were synthesized according to literature procedures. All of the other reagents were purchased from Sigma Aldrich, Alfa Aesar, Strem, TCI America, Combi-Blocks or Matrix Scientific and were used as received.

**General Analytical Information:** All compounds were characterized by $^{19}$F NMR. Nuclear Magnetic Resonance spectra were recorded on a Bruker 300 MHz instrument. All $^{19}$F NMR spectra are reported in ppm relative to 1-fluoronapthalene (-124.00 ppm). Yields were determined by integration relative to 1-fluoronapthalene, and literature values for all fluorinated compounds were used to characterize reaction mixtures, in addition to GC-MS verification.

3.4.1– Experimental Procedures

**General Procedure for Substrates in Figure 2:** (A) In a nitrogen-filled glovebox, an oven-dried 10 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with (AlPhosPd)$_2$COD (195 mg, 0.1 mmol, 1 equiv Pd) and THF (3.00 mL, 0.033 M).
The suspension was stirred for 3 minutes. The aryl bromide substrate (0.4 mmol, 2 equiv) was added and the reaction was allowed to stir for 15 minutes. Upon completion, solvent was removed and the resulting oil was suspended in 5 mL pentane. After stirring for 5 minutes, the suspension was filtered and the solids were washed with pentane (3 x 3 mL) to give a yellow powder (70-93% yield). (B) In a nitrogen-filled glovebox, an oven-dried 10 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with the oxidative addition complex (0.183 mmol, 1 equiv), AgF (162 mg, 1.28 mmol, 7 equiv), and DCM (4.00 mL, 0.045 M). The reaction tube was wrapped in aluminum foil to shield the reaction mixture from light, and allowed to stir for 12h. Upon completion, pentane (6 mL) was added to the reaction mixture and the suspension was placed in the freezer for 1 h. The suspension was then filtered through celite, and the filtrate was concentrated under vacuum. The resulting oil was suspended in pentane (3 mL) and solvent was again removed. This process was repeated twice. The solids were suspended in pentane and isolated on a fine porosity frit and stored under inert atmosphere at -20°C. (50-70% yield).

**General Procedure for Substrates in Tables 1 and 2:** In a nitrogen-filled glovebox, an oven-dried 10 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with (AlPhosPd)2COD (9.7 mg, 0.005 mmol, 0.5 equiv – 1 equiv Pd), the (hetero)aryl bromide substrate (0.01 mmol, 1 equiv), and solvent (1.00 mL, .01 M). The mixture was stirred for 15 minutes at r.t. Upon full solvation of all reagents, AgF (6.3 mg, 0.05 mmol, 5 equiv) and “trap” aryl-bromide was added. If necessary, KF (0.3 mg, 0.005 mmol, 0.5 equiv) was added to the reaction mixture. The vial was sealed and removed from the box. The reaction mixture was heated for 12 h. Upon completion, 1-fluoronaphthalene (1.3 μL, 0.01 mmol, 1 equiv) was added.
to the reaction mixture and the reaction mixture was allowed to stir for 3 minutes. The crude reaction mixture was analyzed by $^{19}$F NMR, and yields were determined by integration against 1-fluoronaphthalene ($\delta = -124$ ppm).

**General Procedure for Substrates in Table 3:** In a nitrogen-filled glovebox, an oven-dried 10 mL screw-cap reaction tube equipped with a magnetic stir bar and a Teflon cap was charged with (AlPhosPd)$_2$COD (9.7 mg, 0.005 mmol, 0.5 equiv – 1 equiv Pd), the (hetero)aryl bromide substrate (0.01 mmol, 1 equiv), and solvent (1.00 mL, 0.01 M). The reaction was allowed to stir until all reagents were in solution. If the solution remained a suspension for longer than 10 minutes, the reaction mixture was heated to 80°C for 5 minutes. Upon solvation of all reagents, AgOTf (3.8 mg, 0.015 mmol, 1.5 equiv) or AgBF$_4$ (3.0 mg, 0.015 mmol, 1.5 equiv) was added to the reaction mixture, and the reaction vessel was shielded from light and allowed to stir for 3 minutes. At this point, CsF (7.6 mg, 0.05 mmol, 5 equiv) or Me$_4$NF (4.7 mg, 0.05 mmol, 5 equiv), and (if necessary) KF (1.5 mg, 0.025 mmol, 2.5 equiv) was added to the reaction mixture, and the solution was heated for 12 hours. Upon completion, 1-fluoronaphthalene (1.3 μL, 0.01 mmol, 1 equiv) was added to the reaction mixture and the reaction mixture was allowed to stir for 3 minutes. The crude reaction mixture was analyzed by $^{19}$F NMR, and yields were determined by integration against 1-fluoronaphthalene ($\delta = -124$ ppm).
3.5 – References


3.6-Selected Relevant $^{19}$F and $^{31}$P NMR Spectra
Table 1 Entry 1
Table 1 Entry 6
Table 1 Entry 12
Table 1 Entry 21 ("Standard Conditions")
Table 2 Entry 3h (2-MeTHF)
Table 2 Entry 3i (Toluene)
Table 3 Entry 1

IBP-1-165B
19F OBSERVE
STANDARD PARAMETERS

<table>
<thead>
<tr>
<th>n-Bu</th>
<th>F</th>
<th>4.4</th>
<th>114</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>1.18</td>
<td>118</td>
</tr>
</tbody>
</table>

Chemical shifts (ppm)
Table 3 Entry 5

IBP-1-166A
19F OBSERVE
STANDARD PARAMETERS

![Chemical Structure Image]
Table 3 Entry 9
Table 3 Entry 12