The Pd-Catalyzed Fluorination of (Hetero) Aryl Bromides and Triflates

by

Phillip J. Milner

B.A. Chemistry, B.A. Mathematics
Hamilton College (2010)

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy in Organic Chemistry

at the
Massachusetts Institute of Technology

May 2015

© 2015 Massachusetts Institute of Technology
All Rights Reserved

Signature redacted
Signature of Author: ____________________________
Department of Chemistry
April 13, 2015

Signature redacted
Certified by: ____________________________
Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Signature redacted
Accepted by: ____________________________
Robert W. Field
Haslam and Dewey Professor of Chemistry
Chairman, Departmental Committee on Graduate Students
DISCLAIMER NOTICE

Due to the condition of the original material, there are unavoidable flaws in this reproduction. We have made every effort possible to provide you with the best copy available.

Thank you.

Despite pagination irregularities, this is the most complete copy available.

Pages 541-580 are not included due to pagination irregularities.
This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Timothy M. Swager:  
Thesis Committee Chair

Professor Stephen L. Buchwald:  
Thesis Supervisor

Professor Jeremiah A. Johnson:
The Pd-Catalyzed Fluorination of (Hetero)Aryl Bromides and Triflates

by

Phillip J. Milner

Submitted to the Department of Chemistry on May 8, 2015
in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy
at the Massachusetts Instituted of Technology

Abstracts

Chapter 1: This chapter details mechanistic work regarding the reductive elimination of electron-rich aryl fluorides from \textit{L}\textperiodcentered\textperiodcentered\textit{Pd}(\textit{Ar})F species. An unexpected dearomatization/arylation process of \textit{Pd}(II) complexes bearing bulky biaryl phosphines was discovered, resulting in ligand arylation during the catalytic fluorination of aryl triflates. This process must occur prior to C–F reductive elimination. Further experimental studies of this rearrangement revealed that it likely proceeds via a concerted migratory insertion into the bottom ring of the ligand.

Chapter 2: This chapter describes extensive work to understand the mechanism by which regioisomeric mixtures of products form during the Pd-catalyzed fluorination of electron-rich aryl triflates lacking ortho-substituents. Deuterium labeling experiments suggest that ortho-deprotonation of \textit{L}\textperiodcentered\textperiodcentered\textit{Pd}(\textit{Ar})OTf intermediates by CsF competes with the transmetallation step of the desired catalytic process. Additional studies investigating the previously observed formation of regioisomeric products in the absence of CsF (Chapter 1) are also presented.

Chapter 3: This chapter describes the key discovery that di-adamantyl ligands are superior to \textit{tBuBrettPhos} for promoting the Pd-catalyzed fluorination of aryl triflates. While previously described 2-aminobiphenyl-based sulfonate precatalysts were ineffective, readily activated [(\textit{L}\textperiodcentered\textperiodcentered\textit{Pd})\textsubscript{2}COD] (COD = cyclooctadiene) complexes proved to be general precatalysts for these reactions. Further structural and reactivity studies of this new family of precatalysts are presented.

Chapter 4: The first general method for the Pd-catalyzed fluorination of aryl bromides and iodides is described using a combination of AgF and various additives, most commonly KF. Preliminary studies suggest that the additive is necessary to promote an otherwise difficult transmetallation step. In addition, the use of a "pre-modified" ligand, HGPhos, allows for the Pd-catalyzed fluorination of 6-membered nitrogen-containing heterocycles. An investigation of ligand structural effects on this reaction is also included.
Chapter 5: An in-depth investigation of the Pd-catalyzed fluorination of 5-membered heteroaryl bromides is described. Preliminary crystallographic and computational evidence suggest that reductive elimination of 5-membered heteroaryl fluorides from Pd(II) is extremely difficult. Nonetheless, it was found that heteroaryl bromides bearing *ortho*-phenyl groups, as well as highly activated 2-bromoazoles, can be efficiently fluorinated using a catalyst based on the recently developed ligand AlPhos.

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

If you do the math, this thesis represents somewhere in the realm of 14,000 hours (60 hours a week × 48 weeks a year × 4.75 years) of my life. It hasn't always been easy – I'm not sure it's ever been easy – but I am proud of this work. Obviously, I could not have undertaken the creation of this monstrosity without a lot of help from people both inside and outside the Buchwald lab. Here I want to thank them for their support, help, and friendship, over the last years.

First, I want to thank Steve for giving me freedom to work on projects I (and, as it turns out, other people!) find important. In the third floor of building 18, Steve has put together a gathering place for some of the greatest minds in the chemistry world. I am very grateful that I got to spend the last 5 years in this chemistry playground! I would also like to thank my thesis chair Prof. Timothy Swager, as well as Profs. Jeremiah Johnson and Timothy Jamison, for being helpful and informative during my time here.

In the Buchwald lab, I owe a lot of thanks to "my post-docs", Prof. Thomas "The Master" Maimone and Dr. Hong Geun Lee. Tom took me under his wing when I first joined the lab and helped me navigate an extremely challenging project. He is probably the most brilliant chemist I have met, and I learned a lot from him. It is amazing how far this project has come since I joined it with Tom all those years ago! During my second year, the focus of my graduate work switched from mechanistic work (Chapters 1-2) to more synthetic work (Chapters 3-5), and a big part of that is thanks to Hong Geun. He changed the way I and many other people in the lab view the fluorination project. We made an excellent team and complemented each other very well! I can honestly say he is responsible for most of the improvement in my synthetic skills during my time in the lab.

I also owe a lot of thanks to other post-docs I have collaborated with, both in this group and in others. Dr. Aaron Sather, the newest recruit to the fluorination project, has been a fun and awesome addition to our lab. He has taken fluorination to new heights and will continue to kick ass. I owe many thanks to my other collaborators Drs. Tom Kinzel, Yong Zhang, and Takashi Takada. I also had the pleasure of collaborating with three physical chemists: Dr. Jiahao Chen (van Voorhis lab), as well as Drs. Michael Covin and Loren Andreas (Griffin lab). I would also like to thank Dr. Michael Placzek at Massachusetts General Hospital, who taught Hong Geun and I most of what we know about positron emission tomography. His advisor and our collaborator, Prof. Jacob Hooker, has also been a great source of knowledge; I hope our collaboration continues. Unfortunately, due to length restrictions I could not include this work within this thesis.

There are plenty of other current and former post-docs from the Buchwald lab that I would like to thank (in somewhat chronological order). Drs. Timothy Noël, Naoyuki Hoshiya, Satoshi Ueda, Meredith McGowan, Tom Barton, Jean-Baptiste Langlois, Mao Chen, and Prof. Alex Spokony were inspiring chemists who were always a joy to chat with. Dr. Matthias Oberli taught me all of my (Swiss) German swear words. Dr. Alex Düffert was one of my good friends in lab, and even though our attempted project together ended up being a bust, I did learn a lot from him and enjoyed hanging out with him. I will always remember late-night car rides/chemistry chats with Dr. Natalia Chernyak. Dr. Katrin Niedermann was one of the most interesting people I have ever met, and I miss her every day! We had a great time in New Orleans together. Dr. Ye Zhu was one of my best friends in lab, and I always enjoyed our weekly lunches, chemistry chats, and
memorable times at the Muddy. Out of everybody, Dr. Thierry Leon is my brownie and espresso buddy (or should I say putita?). Drs. Kurt Armbrust, John Nguyen, Erhad Ascic, Kashif Khan, Sandra King, Dawn Niu, Esben Olsen, Michael Pirnot, Timothy Senter, Yiming Wang, and Shaolin Zhu have been tons of fun to hang out with, and I'm going to miss them. And of course, I have to thank Christine Nguyen for keeping this lab running; they should give you a hundred awards a year for that!

Now to graduate students. First I have to say thank you thank you thank you!! to some of the best friends I've ever had: Paula Ruiz-Castillo (Renita, Markush, Patata...), Dr. Nootaree Niljianskul (Noot Noot), and Dr. Mingjuan Su (Moooommm!). Paula has been an inspiration and a friendly voice every day, and is easily one of the most amazing, open, silly, and fun people I've ever met. I'm going to miss her so much when I move. Over the past year and a half or so, Nootaree has become one of my best friends in the lab, and is great to grab a drink (or three) with and gossip about anything and everything. I'm going to miss her too. Mingjuan was my mom, and even though I was accidentally mean to her she was always the nicest person in the lab to me. Our lab is so much quieter now! Dr. Nicholas Bruno has also been a good friend during our PhD – it hasn't always been easy, but we made it through! Can you believe we used to eat at the student center every day? Blech. I have also had tons of (totally sober, I swear) fun with the rest of my fellow fifth years: James Colombe, Nathan Park, Dr. Ekaterina Vinogradova, and Dr. Rong Zhu. We're almost done! The same goes for Spencer Shinaberry, Anthony Rojas, Jeffrey Yang, and Saki Ichikawa - the future of the lab is in your hands! I especially want to wish good luck to my fellow fluorination students, Yuxuan Ye and Bryan Ingoglia. This project isn't easy but I have faith in you. The graduate students are what make this place special, no matter what post-docs say. Lastly I should thank the graduate students who somehow managed to teach me something, Drs. Georgiy Teverovskiy and Todd Senecal, as well as Prof. Brett Fors, who I wish I had overlapped with more.

As for graduate students outside of the Buchwald lab, first and foremost I have to thank one of my other best friends, Elizabeth Kelley. She always tells me like it is, and I think we're a great influence on each other! I also have to give a shout out to my many friends who helped me learn how to relax, especially Sarah Tasker, Minyuan Li, David Grimes, Luigi DeMarco, and Mik Minier, among others. I have to give a special shout out to my roommates for the past four years, Sam Teitelbaum and Thomas Bischof. They've probably been a bad influence on my work ethic, but they've made these years some of the best of my life. Lastly, Andrew Beyler, my roommate (hah!) and best friend for the last 9 years, deserves a lot of credit for getting me through this. Thanks man. The same goes for the third member of the trio, Kathryn Arpino.

Lastly, the non-chemists in my life deserve a lot of credit for putting up with my baloney all these years. Maggie has been a good friend for the past 10+ years. Kelsey is another one of those people who keeps me grounded. The same with my nieces Harmony and Melody. Joanna has also been one of the best things to happen to me in graduate school and has helped me more than she knows during my last year at MIT. Thank you. Lastly, a lot of credit goes to my parents, first and foremost for having me! But also for encouraging a curiosity and drive that has carried through college and graduate school.

I'm sure I've missed people on this list, for which I apologize! This is truly a work to which many people have contributed in some small way or another. Thank you all. Enjoy the read.
Respective Contributions

This work is the result of extensive collaborations between the author and other researchers, both at MIT and at Massachusetts General Hospital (MGH). The specific contributions of the author are outlined below.

Chapter 1: Dr. Thomas Maimone (Buchwald lab, MIT) uncovered the rearrangement process and carried out the first reductive elimination of an electron-rich aryl fluoride from Pd(II). The author carried out the in-depth investigation of the dearomatization of biaryl phosphine-ligated Pd(II) complexes, with Dr. Thomas Maimone assisting with some experiments. Dr. Jiahao Chen (Van Voorhis lab, MIT) and Dr. Mingjuan Su (Buchwald lab, MIT) carried out corroborating DFT calculations. X-ray structures in this chapter were solved either by Dr. Michael Takase or Dr. Peter Müller.

Chapter 2: Dr. Yong Zhang (Buchwald lab, MIT) carried out the original deuterium labeling experiment using tBuOD. Dr. Tom Kinzel (Buchwald lab, MIT) assisted with analysis of the results and carried out additional kinetic studies. The author carried out all of the experiments presented in this chapter.

Chapter 3: Efforts to use 2-aminobiphenyl-based precatalysts for Pd-catalyzed fluorination were carried out in collaboration with Nicholas Bruno (Buchwald lab, MIT). The discovery of the first [(L•Pd)2COD] species was made by Dr. Hong Geun Lee (Buchwald lab, MIT). Studies of the structure and reactivity of these species were carried out in collaboration with Dr. Lee. Solid-state NMR studies were carried out by Dr. Michael T. Colvin (Griffin lab, MIT) and Loren Andreas (Griffin lab, MIT). X-ray structures in this chapter were solved either by Dr. Stacey Smith or Dr. Peter Müller.

Chapter 4: This work was carried out in collaboration with Dr. Hong Geun Lee. Dr. Lee carried out the first synthesis of HGPhos, and isolated most of the aryl fluoride products described in this chapter. The author discovered the original additive effect and carried out the synthesis and evaluation of other di-adamantyl ligands. X-ray structures in this chapter were solved either by Dr. Stacey Smith or Dr. Peter Müller. AlPhos was developed by Dr. Aaron Sather (Buchwald lab, MIT).

Chapter 6: This work was carried out by the author. X-ray structures in this chapter were solved by Dr. Peter Müller.
Preface

Parts of this thesis have been adapted from the following published articles co-written by the author. In all cases, the articles are adapted with permission from the appropriate journal.

Chapter 1:


Chapter 2:

Chapter 3:

These authors contributed equally to this work.


These authors contributed equally to this work.

Chapter 4:
Fluorine atoms are present in an estimated 20% of pharmaceuticals and 30% of agrochemicals, making organofluorines a privileged class of biologically and medicinally relevant compounds.\(^1\) This is primarily due to the improved metabolic stability and membrane permeability of fluorinated compounds compared to their non-fluorinated analogues.\(^1\) In addition, molecules labeled with the radioactive isotope \(^{18}\text{F}\)-deoxyglucose (Figure 1), are the most widely-used radiotracers for Positron Emission Tomography (PET).\(^2\) Aryl fluorides (Ar–F), in particular, are found in a number of top-selling drugs, such as Januvia (sitagliptin, antidiabetic),\(^3\) Lipitor (atorvastatin, dyslipidemia treatment),\(^4\) Isentress (raltegravir, antiretroviral),\(^5\) and the 6-fluoroquinolone class of antibiotics,\(^6\) with Cipro (ciprofloxacin) as a representative example (Figure 1). Commonly used pesticides, such as Epoxiconazole,\(^7\) also contain aryl fluorides (Figure 1). Despite their importance, until the 21st century there were only two general methods for the preparation of aryl fluorides: 1) the Balz-Schiemann reaction (Figure 2A),\(^8\) which involves thermalizing explosive and unstable diazonium salts and typically gives only modest yields; and 2) the Halex reaction (Figure 2B),\(^9\) which only works for extremely electron-deficient substrates. Due to these limitations, aryl fluorides are typically

---

**Figure 1.** Examples of biologically active compounds containing fluorine atoms.
installed early in a synthetic sequence, increasing the difficulty of preparing fluorinated compounds of interest. Thus, their remains a need for the development of a general, user-friendly, safe, and clean method for the late-stage introduction of aromatic C–F bonds.¹⁰

There are two main modes of fluorine's reactivity, nucleophilic ("F⁻") and electrophilic ("F⁺"), that one could exploit to introduce C–F bonds. One approach that has found some success for the synthesis of aryl fluorides is to react organometallic reagents with electrophilic fluorinating agents. Thus, various Ag-,¹¹ Cu-,¹² and Pd-mediated,¹³ as well as transition metal-free,¹⁴ electrophilic fluorination reactions of aryl organometallic reagents have been developed. As a complementary approach, directed C–H electrophilic fluorination reactions have also been developed.¹⁵ Notably, these reactions are postulated to occur through high-valent transition metal intermediates (i.e., Cu(III), Ag(III), Pd(III-IV)). However electrophilic fluorination suffers from key drawbacks, including: 1) electrophilic fluorine sources are expensive, unstable, and strongly oxidizing; 2) densely functionalized aryl organometallic reagents are typically difficult to prepare, toxic, and/or unstable; 3) stoichiometric amounts of transition metals are often required; 4) significant formation of reduced arene products (Ar–H), which are inseparable from the desired aryl fluoride, occurs in many cases; 5) ¹⁸F-¹⁹F, the precursor to all electrophilic fluorinating reagents for the synthesis of PET radiotracers, produces
radiotracers with low specific activity (that is, the ratio of $^{18}\text{F}$-labelled radiotracer to $^{19}\text{F}$-labelled byproduct).16

In contrast, nucleophilic fluoride salts are readily available, stable, and can be produced with much higher specific activity than electrophilic $^{18}\text{F}$-sources.13d,16 These properties make nucleophilic fluorination methods an important, albeit less well-studied, complement to electrophilic methods.17 However, nucleophilic fluoride sources are not without their drawbacks: MF ($\text{M}=\text{K, Cs, Ag}$) salts are hygroscopic, poorly soluble, weakly nucleophilic, and basic under anhydrous conditions, and tetraalkylammonium fluoride ($\text{R}_4\text{NF}$) salts are unstable to heating.9b,17 Nonetheless, several methodologies for aromatic fluorination using MF salts have been developed. As an early example, Ribas used AgF to facilitate the room temperature fluorination of an in situ formed Cu(III) species (not shown).18 Hartwig later extended to a general method for the Cu-mediated fluorination of aryl iodides, although significant formation of inseparable arene side products ($\text{Ar-H}$) was observed (Figure 3A).19 Based on the same mechanistic scheme, Sanford showed that Cu(OTf)$_2$ can catalyze the nucleophilic fluorination of diaryliodonium salts20 and mediate the fluorination of potassium aryltrifluoroborates, with KF as the nucleophilic fluoride source in both cases (Figure 3B).21 In a unique example of Ni-promoted fluorination, Ritter demonstrated that aryl-Ni complexes can be fluorinated with aqueous K$^{18}\text{F}$ in the presence of a hypervalent iodine oxidant (Figure 3C).22 Daugulis23 and Liu24 found that directing-groups allow for the Cu-catalyzed fluorination of arenes and aryl bromides, respectively, using AgF (Figure 3D), though in Daugulis' case the addition of an external oxidant (NMO) was required. Lastly, Ritter has shown that the combination of hygroscopic, unstable Phenofluor and CsF can effect
the direct fluorination of phenols through an activated intermediate (Figure 3E).\textsuperscript{25} It is worth noting that many of these reactions require specialized starting materials, the addition of external oxidants, and/or the use of a glovebox to handle hygroscopic MF or Cu salts, which limits their generality. Thus, there remains a need for the further development of simple and general methods for the synthesis of aryl fluorides using desirable nucleophilic fluoride sources.

\begin{align*}
\text{A)} & \quad \text{Cu-mediated fluorination of aryl iodides;} \\
\text{B)} & \quad \text{Cu-mediated fluorination of diaryliodonium salts and potassium aryltrifluoroborates;} \\
\text{C)} & \quad \text{Fluorination of Ni(II) complexes with aqueous KF with an oxidant;} \\
\text{D)} & \quad \text{directing group-assisted C–H and C–Br fluorinations;} \\
\text{E)} & \quad \text{deoxyfluorination of phenols with Phenofluor.}
\end{align*}

Figure 3. Examples of aryl fluorination reactions using nucleophilic fluoride salts. A) Cu-mediated fluorination of aryl iodides; B) Cu-mediated fluorination of diaryliodonium salts and potassium aryltrifluoroborates; C) Fluorination of Ni(II) complexes with aqueous KF with an oxidant; D) directing group-assisted C–H and C–Br fluorinations; E) deoxyfluorination of phenols with Phenofluor.

As a complement to these methods, the Pd-catalyzed cross-coupling of aryl (pseudo)halides with a nucleophilic metal fluoride (MF) salt, involving oxidative addition (OA), transmetallation (TM), and C–F reductive elimination (RE), is desirable in terms of simplicity and generality (Figure 4). That being said, elegant investigations by Grushin\textsuperscript{26} and Yandulov\textsuperscript{27} showed that Ar–F reductive elimination from phosphine-ligated Ln\textsuperscript{*}Pd(Ar)F species is extremely difficult, with other processes, such as $\mu$-F dimer
formation and P–F reductive elimination, dominating. The transmetallation step of this cycle would also involve a virtually insoluble MF salt. In the Buchwald laboratory, we have found bulky dialkyl biarylmonophosphines (Figure 4) to be excellent supporting ligands for Pd-catalyzed cross-coupling reactions.\textsuperscript{28,29} Indeed, in the only reported example of net reductive elimination of Ar–F from Pd(II) (Ar = 4-NO\textsubscript{2}Ph), tBuXPhos (L\textsubscript{1}, Figure 4) was found to be a crucial additive.\textsuperscript{27} Although direct C–F reductive elimination has been called into doubt in this case,\textsuperscript{30} it indicated that biaryl phosphines might be capable of promoting Pd-catalyzed fluorination.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Mechanism of Pd-catalyzed cross-coupling to produce aryl fluorides, involving oxidative addition (OA), transmetallation (TM), and reductive elimination (RE); biaryl phospine ligands L\textsubscript{1-3}.}
\end{figure}

In 2009, our laboratory reported that complexes 1a-b form low yields of aryl fluoride upon heating,\textsuperscript{31} with improved yields observed in the presence of added aryl bromide (Figure 5A).\textsuperscript{32} These findings represent the first reliable examples of stoichiometric C–F reductive elimination from a L•Pd(Ar)F complex. Key to successful reductive elimination was the use of the bulky ligand BrettPhos (L\textsubscript{2}, Figure 4), which forms sterically hindered monomeric L•Pd(Ar)F complexes. The catalytic fluorination of aryl bromides, utilizing AgF, could also be achieved, although it was limited to ortho-substituted, electron-deficient substrates (Figure 5B). Using the bulkier ligand tBuBrettPhos (L\textsubscript{3}, Figure 4) and CsF as the nucleophilic fluoride source, the Pd-
catalyzed fluorination of aryl triflates, which produce more cationic Pd(II) complexes upon oxidative addition, could also be achieved and demonstrated a much broader scope than the reaction of aryl bromides (Figure 5C).

Figure 5. First examples of aryl fluoride formation via Pd-catalyzed cross-coupling. A) Stochiometric reductive elimination from 1a-b (yields in parentheses with added aryl bromide); B) Pd-catalyzed fluorination of an ortho-substituted, electron-deficient aryl bromide; C) Pd-catalyzed fluorination of aryl triflates.

Although this process was a breakthrough for the synthesis of aryl fluorides, it suffered from some drawbacks. These included: 1) poor yields for highly electron-rich and heteroaryl triflates; 2) little to no product for all but the most activated aryl bromides (Figure 5B); 3) formation of the corresponding aryl chloride side product resulting from activation of [(cinnamyl)PdCl]_2; 4) the need to employ a glovebox to handle hygroscopic CsF; 5) poor mass balance in certain cases; 6) formation of inseparable mixtures of regioisomeric aryl fluorides with electron-rich aryl triflates (2-3), but not with electron-deficient (4) or ortho-substituted (5) substrates (Figure 6). The mechanism of undesired regioisomer formation was initially unclear, but suggested that the simple Pd-catalyzed cross-coupling process shown in Figure 4 was not occurring for some substrates. In order to understand and ultimately overcome these problems, an in-depth mechanistic investigation was required before improved catalysts for carrying out this important transformation could be prepared. This work describes our efforts to understand the
mechanistic intricacies of the fluorination of electron-rich aryl triflates, which led to the discovery of a hitherto unnoticed ligand modification process (Chapter 1), as well as efforts to understand the mechanism of regioisomer formation (Chapter 2). After these undesired pathways were elucidated, we were able to prepare new catalyst systems for carrying out the fluorination of densely functionalized aryl triflates (Chapter 3) and (hetero)aryl bromides (Chapter 4), including 5-membered heteroaryl bromides (Chapter 5). Ultimately, the work described herein represents the first steps towards transforming the Pd-catalyzed fluorination of aryl (pseudo)halides into a general method that can be used for late-stage fluorination of complex molecules.

![Reaction scheme](image)

**Figure 6.** Formation of regioisomers with electron-rich aryl triflates lacking ortho-substituents.

**References.**


7 Grohe, K.; Zeiler, H.-J.; Metzger, K. G. 7-amino-1-cyclopropyl-4-oxo-1,4-dihydroquinoline- and naphthyridine-3-carboxylic acids and antibacterial agents containing these compounds. U.S. Patent 4670444, May 29, 1984.


10 For a review, see: Campbell, M. G.; Ritter, T. Chem. Rev. 2015, 115, 612.


Grushin, V. V.; Marshall, W. J. Organometallics 2007, 26, 4997.


Chapter 1. Ligand Modification in Pd-Catalyzed Fluorination via the Dearomative Rearrangement of Biaryl Phosphine-Ligated Pd(II) Complexes
1.1. Introduction.

![Figure 1.1](image)

**Figure 1.1.** Previous C–F reductive elimination studies with 1-3 (yields in parentheses are with added aryl bromide), and ligands L1-3 for Pd-catalyzed fluorination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>CN</td>
<td>25% (45%)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>CF₃</td>
<td>15% (55%)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>nBu</td>
<td>0% (0%)</td>
</tr>
</tbody>
</table>

*L1: R = Cy, R' = OMe (BrettPhos)*
*L2: R = tBu, R' = OMe (tBuBrettPhos)*
*L3: R = tBu, R' = Me (RockPhos)*

During our initial investigation of Pd-catalyzed fluorination, we found that bulky, monodentate biaryl phosphines (L1-3, Figure 1.1) were necessary to promote reductive elimination.¹ While C–F reductive elimination was demonstrated from L1•Pd(Ar)F complexes, it was observed only when the aryl group was both electron-deficient and ortho-substituted (1-2, Figure 1.1), two structural features known to favor reductive elimination.² When the aryl group was electron-rich, no product was observed (3, Figure 1).¹ In addition, only catalysts derived from the di-tert-butyl ligand tBuBrettPhos (L2) were shown to be capable of transforming a wide range of aryl triflates to the corresponding aryl fluorides. We have since discovered that catalysts based on the structurally similar ligand RockPhos (L3)³ also perform well in fluorination reactions, with yields similar to L2 (*vide infra*). Although we hypothesized that a discrete L•Pd(Ar)F complex was involved in the fluorination of electron-rich aryl triflates, the failed stoichiometric C–F reductive elimination from 3, as well as the formation of regioisomeric mixtures of aryl fluorides in the corresponding catalytic reactions (see Introduction),¹ cast doubt on this possibility. To address this question, a better
understanding of C–F reductive elimination from electron-rich L•Pd(Ar)F complexes supported by ligands relevant to the catalytic reaction (L2-L3) was required.

1.2. Attempted reductive elimination from L3•Pd(4-(nBu)Ph)F. In general, complexes derived from L3 proved superior to those originating from L2 in terms of isolation, characterization, and synthetic manipulation. Simply by stirring [(1,5-COD)Pd(CH2TMS)2],4 L3, and 4-(nBu)PhBr in a minimum quantity of cyclohexane, the desired oxidative addition complex 4a could be obtained (Figure 1.2). This simple procedure has since been used to prepare a large number of oxidative addition complexes of biaryl phosphine ligands. Additionally, 4a was one of the first oxidative addition complexes of a di-tert-butyl biaryl phosphine ligand to be fully characterized. X-ray crystallographic analysis showed that 4a adopts a C-bound conformation in the solid state (Figure 1.2). Unlike with L1, oxidative addition complexes derived from L3 show no

![Chemical structure diagram](image_url)

**Figure 1.2.** Preparation of L3•Pd(4-(nBu)Ph)F (5) from 4a, X-ray crystallographic structure of 4a (ellipsoids at 50% probability), and failed reductive elimination of 4-(nBu)PhF (6a) from 5.
signs of an O-bound conformation in solution.\textsuperscript{5} Transmetallation of \textit{4a} with AgF afforded the desired complex \textbf{L3}\textsuperscript{•}Pd(4-(\textit{nBu})Ph)F (\textit{5}) (Figure 1.2).

When complex \textit{5} was heated in toluene, either alone or in the presence of 4-(\textit{nBu})PhX (X = Br or OTf) or additional \textbf{L3}, no formation of \textit{6a} by C–F reductive elimination was observed, despite \textit{5} being fully consumed (Figure 1.2). \textsuperscript{19}F and \textsuperscript{31}P NMR analysis of the crude reaction mixture showed no formation of aryl fluorides had taken place. The major fluorine-containing species detected by \textsuperscript{19}F NMR (δ = -136 and -148 ppm) disappeared upon the addition of Et\textsubscript{3}N, and thus likely correspond to HF and HF\textsubscript{2}\textsuperscript{−} (\textit{vide infra}). Along with our failed reductive elimination of \textit{6a} from \textit{3} (Figure 1.1), this finding cast doubt on the feasibility of C–F reductive elimination of electron-rich aryl fluorides from \textbf{L}\textsuperscript{•}Pd(Ar)F complexes.

\textbf{1.3. Discovery of dearomative rearrangement of L2\textsuperscript{•}Pd(Ar)Br complexes.} The analogous \textbf{L2}-ligated complex \textit{7a} could be prepared in a manner similar to \textit{4a}; X-ray crystallography confirmed its structural similarity to \textit{4a} in the solid state (Figure 1.3). However, the initially formed bright yellow complex 7\textit{a} (\textsuperscript{31}P NMR: δ 69 ppm) rapidly converted to a dark red-colored compound (\textsuperscript{31}P NMR: δ 83 ppm) upon dissolution in CD\textsubscript{2}Cl\textsubscript{2}, reaching equilibrium (K\textsubscript{eq} = 5.71 ± 0.10) after approximately 3 h as determined by \textsuperscript{1}H NMR (Figure 1.4, top). From this mixture, the major component could be crystallized, which X-ray analysis identified as dearomatized Pd(II) complex \textit{7b} with Pd–C bond lengths of 2.0713(16) (Pd-C2') and 2.2974(16) Å (Pd-C3'), respectively (Figure 1.3). Despite its twisted, dearomatized structure, \textit{7b} is stable to air and heating up to 100 °C in solution. Dissolving pure crystalline \textit{7b} in CD\textsubscript{2}Cl\textsubscript{2} re-established the same
equilibrium ratio of 7a and 7b, confirming that these two compounds are interconverting in solution (Figure 1.4, bottom). The activation parameters for the rearrangement of 7a to 7b were determined by Eyring analysis (10-42 °C, CD₂Cl₂, Figure 1.5) to be ΔH° = 22.1 ± 1.3 kcal/mol, ΔS° = 16 ± 4 cal/K•mol, and ΔG°(20 °C) = 17.4 ± 1.3 kcal/mol (see Supporting Information Table S1 for kinetic data). The positive entropy of activation suggests that extensive reorganization of the species leading to the rate-determining transition state is not necessary, and is consistent with the relief of steric interactions as a driving force for the rearrangement process (vide infra). Notably, upon closer inspection the analogous complex 4a was also found to undergo the same rearrangement process in solution, albeit to a much lesser degree (Kₑq = 0.08, CD₂Cl₂).

Concurrent with our work, Doyle reported a similar dearomatized L1-ligated Ni(II) complex (8),⁶ and Allgeier and Shaw reported the decomposition of a tBuXPhos complex to give 9, purportedly by a carbene insertion mechanism originating from

![Image of chemical structures]

**Figure 1.3.** Synthesis and isomerization of tBuBrettPhos oxidative addition complex 7a to 7b, with X-ray crystallographic structures of 7a and 7b (ellipsoids at 50% probability). The numbering scheme used throughout this chapter for 7b and related complexes is shown.
Figure 1.4. Kinetic plots of the conversion of pure 7a (top) and pure 7b (bottom) to the equilibrium mixture of 7a and 7b in CD$_2$Cl$_2$, as determined by $^1$H NMR.
dichloromethane (Figure 1.6).\textsuperscript{7} In both of these cases, dearomatization occurs at the 4' position of the lower arene (Figure 1.6), whereas 7b is dearomatized at the 3'-position (Figure 1.3). Reactions wherein a transition metal-bound arene undergoes nucleophilic attack are well-established,\textsuperscript{8} as are a number of dearomatization reactions using Pd and Pt catalysts.\textsuperscript{9} However, the reversible rearrangement of 7a/7b, which formally represents an aryl migratory insertion into an aromatic ring, is quite unusual. Concerted aryl migratory insertion processes from Pd(II) have been proposed as a potential pathway in C-H arylation reactions,\textsuperscript{10} but little is known experimentally about the viability of this process, and the direct observation of the product of the insertion of an aryl group into an aromatic ring from Pd(II) had never, to our knowledge, been reported prior to this finding.
Likewise, the reverse of this process (Figure 1.4, bottom) represents a rare example of β-aryl elimination from an isolated Pd(II) complex. Due to possible relevance of this process to C-H arylation and Pd-catalyzed fluorination reactions, we further investigated the mechanistic features of this rearrangement.

Several possible mechanisms for the rearrangement of 7a to 7b are shown in Scheme 1.1. Numerous mechanistic studies of aryl migratory insertions into alkenes using bidentante ligands or small monodentate ligands have been conducted. Most relevant to this study, Brown found that intramolecular migratory insertions of electron-rich Pd(II) complexes are incredibly facile, and with monodentate phosphine ligands the insertion most likely proceeds directly from the L•Pd(aryl)X(alkene) species. In the solid-state structure of 7a, the aryl group and lower ring of the ligand are trans, but a concerted insertion requires the π system and migrating groups to be cis. Therefore, isomerization (possibly by pseudo-rotation of a tricoordinate 14-electron Pd-species) to cis 7a' must occur before a concerted 1,4-migratory insertion into the arene (Pathway I) or a concerted 1,2-migratory insertion to form 10 followed by a 1,3-allylic shift (Pathway II). Several cationic mechanisms (Pathways III-IV), wherein halide disassociation to 11 precedes 1,2- or 1,4-migratory insertion (III) as from 7a', or Friedel-Crafts-type electrophilic palladation to give 11' followed by 1,2- or 1,4-aryl migration (IV), could also be envisioned. With these mechanistic possibilities in mind, we investigated the effect of solvent, halide, aryl substituent, and ligand structure on the rate and extent of rearrangement to determine which pathway is most likely operative in the dearomatization of 7a.
Scheme 1.1. Plausible pathways (I-IV) for the rearrangement of 7a to 7b.

1.4. Experimental Investigation of Dearomatization Process.

1.4.1. Solvent Effects. The $^{31}$P NMR spectrum of 7a displays only one resonance, but it is unusually broad, especially when compared to that of 4a (Figure 1.7). The broad $^{31}$P NMR resonance of 7a is indicative of multiple rapidly equilibrating species being present in solution, consistent with the presence of both 7a and 7a' (Scheme 1.1). However, low temperature (−80 °C) decoalescence and NOESY NMR experiments could not
definitively establish the identity of the species present in solution (see Figure 1.21 in the Experimental).

Solvent effects on the rate and extent of rearrangement of 7a to 7b were also examined (Table 1.1). The relative rates of isomerization ($k_{f+r}$) and equilibrium ($K_{eq}$) constants were determined in THF-d$_8$, C$_6$D$_6$, 1,4-dioxane-d$_8$, and CD$_2$Cl$_2$. From these two parameters, the $k_f$ rate constants for the forward rearrangement process could be determined. These findings suggest that solvation has a minor effect on the relative stabilities of 7a and 7b, yet there is no discernible trend between solvent polarity and equilibrium concentration or rate of rearrangement. Because halide dissociation must be rate-determining or precede the rate-determining step in Pathways III and IV, these results are inconsistent with an ion-dissociation pathway, which previous studies suggest should be uniformly accelerated by more coordinating solvents such as THF and 1,4-dioxane. The observation that the addition of 5 eq. of soluble Br$^-$ (nBu$_4$NBr) did not

![Figure 1.6. $^{31}$P NMR (CD$_2$Cl$_2$) comparison of 7a and 4a.](image)

27
Table 1.1. Solvent effects on rearrangement.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$k_{rt} a$</th>
<th>$k_1 a$</th>
<th>$K_{eq}$</th>
<th>$\Delta G_{exp}$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD$_2$Cl$_2$</td>
<td>1.22 ± 0.06</td>
<td>1.16 ± 0.05</td>
<td>5.71 ± 0.10</td>
<td>-1.01 ± 0.01</td>
</tr>
<tr>
<td>THF-d$_8$</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.03</td>
<td>8.71 ± 0.15</td>
<td>-1.26 ± 0.01</td>
</tr>
<tr>
<td>C$_6$H$_6$</td>
<td>1.44 ± 0.04</td>
<td>1.50 ± 0.06</td>
<td>13.5 ± 0.24</td>
<td>-1.51 ± 0.01</td>
</tr>
<tr>
<td>dioxane-d$_8$</td>
<td>1.14 ± 0.04</td>
<td>1.18 ± 0.04</td>
<td>13.5 ± 0.24</td>
<td>-1.51 ± 0.01</td>
</tr>
</tbody>
</table>

$a$ Relative to 7a in THF-d$_8$.

decrease the rate of rearrangement is also consistent with this premise. In addition, DFT calculations of this process, carried out in collaboration with the van Voorhis lab (MIT), which are beyond the scope of this work, are consistent with a concerted 1,2-insertion pathway (Pathway II).

1.4.2. Aryl Substituent Effects. A range of para-substituted aryl bromide oxidative addition complexes based on L$_3$ were synthesized using the same general procedure used to prepare 4a and 7a (Table 1.2). The kinetic profiles for the rearrangements of these species are shown in Figure 1.7, and the parameters corresponding to these profiles are shown in Table 1.3. In all cases, first-order decay of the initially formed oxidative addition complex to the dearomatized isomer was observed. A Hammett plot of the $K_{eq}$ values in Table 1.3 was linear, with $r = -2.56 ± 0.13$ (Figure 1.8). Only with substituents that are electron-withdrawing by both resonance and induction (18a, 19a) is the oxidative addition complex lower in energy than its dearomatized isomer. Because the aryl group is bound to a sp$^3$-hybridized carbon in the dearomatized complex, but interacts directly
with the Pd center in the corresponding oxidative addition complexes, its identity should
be of more consequence to the stability of 7,12-19a than to 7,12-19b; that is, it is likely
that electron-donating substituents destabilize oxidative addition complexes of \( \text{L2} \)
relative to their dearomatized counterparts. The solid-state structures of 7a, 14a, 16a,
and 19a\(^{13}\) provide insight into why this might be (Figure 1.9). No significant changes in
the length of Pd-Br (2.46-2.47 Å) and Pd-P (2.34-2.35 Å) bond lengths were found
among the four complexes, and the expected changes in the Ar-Pd-Br bond angles based
on the relative ease of reductive elimination were observed.\(^2\) The Pd-C1' (ipso carbon of
the lower ring) distance grows longer as the aryl group becomes more electron-rich
(Figure 1.9), due to the stronger trans influence of electron-rich aryl ligands. Likewise,
the Pd-Ar bond lengthens slightly as the aryl substituent becomes more electron-rich,
likely due to the weaker \( \pi \)-accepting ability of more electron-rich aryl substituents.
Therefore, increasing the electron-donating ability of the aryl group weakens stabilization
of the oxidative addition complex by the lower ring, making oxidative addition
complexes with electron-rich aryl substituents less stable than those with electron-

**Table 1.2.** Synthesis of \( \text{L2-Pd(Ar)Br} \) complexes.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield(^b)</th>
<th>Entry</th>
<th>R</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>NMe(_2)</td>
<td>57%</td>
<td>16a</td>
<td>F</td>
<td>47%</td>
</tr>
<tr>
<td>13a</td>
<td>OMe</td>
<td>52%</td>
<td>17a</td>
<td>Cl</td>
<td>73%</td>
</tr>
<tr>
<td>7a</td>
<td>nBu</td>
<td>59%</td>
<td>18a</td>
<td>CHO</td>
<td>67%</td>
</tr>
<tr>
<td>14a</td>
<td>H</td>
<td>66%</td>
<td>19a</td>
<td>CN</td>
<td>66%</td>
</tr>
<tr>
<td>15a</td>
<td>Ph</td>
<td>73%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1.0 eq. (1,5-cyclooctadiene)Pd(CH\(_2\)TMS)\(_2\), 1.0 eq. L2, 1.1-5.0 eq. aryl bromide, cyclohexane, 12 h. Isolated yields.
Figure 1.7. Growth of dearomatized product in the rearrangement of various L2•Pd(Ar)Br complexes. A first-order kinetic model is overlaid for each.

withdrawing aryl substituents. This effect could also facilitate the proposed cis/trans isomerization step in Pathways I-II (Scheme 1.1) if lower-ring disassociation is necessary for this process to occur.

Similarly, the Hammett plot of the $k_f$ values was linear, yielding $r = -1.58 \pm 0.16$ (Figure 1.10), confirming that electron-donating groups on the aryl substituent increase the rate of dearomatization. This is likely due in part to the aforementioned
Table 1.3. Aryl substituent effects on rearrangement.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>$\alpha$</th>
<th>$K_{eq}$</th>
<th>$\Delta G_{\text{exp}}$ (kcal/mol)</th>
<th>$k_{ftr}^a$</th>
<th>$k_{r}^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>12b</td>
<td>NMe$_2$</td>
<td>-0.83</td>
<td>(40.5)$^b$</td>
<td>&gt;10</td>
<td>&gt;11</td>
</tr>
<tr>
<td>13a</td>
<td>13b</td>
<td>OMe</td>
<td>-0.27</td>
<td>19.4 ± 0.34</td>
<td>3.35 ± 0.13</td>
<td>3.93 ± 0.14</td>
</tr>
<tr>
<td>7a</td>
<td>7b</td>
<td>nBu</td>
<td>-0.16</td>
<td>8.71 ± 0.15</td>
<td>1.50 ± 0.05</td>
<td>1.66 ± 0.06</td>
</tr>
<tr>
<td>14a</td>
<td>14b</td>
<td>H</td>
<td>0.00</td>
<td>4.32 ± 0.08</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.04</td>
</tr>
<tr>
<td>15a</td>
<td>15b</td>
<td>Ph</td>
<td>0.01</td>
<td>3.24 ± 0.06</td>
<td>1.02 ± 0.04</td>
<td>0.96 ± 0.03</td>
</tr>
<tr>
<td>16a</td>
<td>16b</td>
<td>F</td>
<td>0.06</td>
<td>3.61 ± 0.06</td>
<td>1.01 ± 0.05</td>
<td>0.97 ± 0.03</td>
</tr>
<tr>
<td>17a</td>
<td>17b</td>
<td>Cl</td>
<td>0.23</td>
<td>1.48 ± 0.03</td>
<td>0.86 ± 0.04</td>
<td>0.63 ± 0.02</td>
</tr>
<tr>
<td>18a</td>
<td>18b</td>
<td>CHO</td>
<td>0.42</td>
<td>0.24$^c$</td>
<td>0.83 ± 0.01</td>
<td>0.99 ± 0.05</td>
</tr>
<tr>
<td>19a</td>
<td>19b</td>
<td>CN</td>
<td>0.66</td>
<td>0.09$^c$</td>
<td>1.43 ± 0.01</td>
<td>$^d$</td>
</tr>
</tbody>
</table>

$^a$Relative to 14a in THF-d$_8$. $^b$From a first-order kinetic model. $^c$Estimated error is less than ± 0.01. $^d$Kinetics unreliable due to small change in [19a] over time.

Figure 1.8. Hammett plot of equilibrium constants for the rearrangement of L$_2$·Pd(Ar)Br complexes (Table 1.3).
Figure 1.9. Pd-Ar and Pd-\(\text{ipso}\) bond lengths, and Ar-Pd-Br bond angles for 7a, 14a, 16a, and 19a, as determined by X-ray crystallographic analysis.

<table>
<thead>
<tr>
<th>R</th>
<th>(\theta (\degree))</th>
<th>Pd-(\text{ipso}) (Å)</th>
<th>Pd-Ar (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBu (7a)</td>
<td>81.3(3)</td>
<td>2.50(4)</td>
<td>2.01(6)</td>
</tr>
<tr>
<td>H (14a)</td>
<td>80.0(0)</td>
<td>2.50(0)</td>
<td>2.01(4)</td>
</tr>
<tr>
<td>F (16a)</td>
<td>80.0(0)</td>
<td>2.47(0)</td>
<td>2.01(2)</td>
</tr>
<tr>
<td>CN (19a)</td>
<td>79.8(8)</td>
<td>2.45(2)</td>
<td>2.00(0)</td>
</tr>
</tbody>
</table>

Figure 1.10. Hammett plot of the forward rate constants \(k_f\) for the rearrangement of L3-Pd(Ar)Br complexes (Table 1.3).

ground state weakening of the Pd-C\(_{Ar}\) and Pd-C1' bonds as the aryl substituent becomes more electron-rich, as these bonds must be cleaved for the insertion to occur. In addition, in the transition state of a concerted insertion C\(_{Ar}\) migrates from Pd to C2', which is more electronegative than Pd, and thus C\(_{Ar}\) would be expected to become more electron-deficient as the insertion occurs. Electron-donating groups on the aryl substituent would mitigate this loss in electron density and thus facilitate the proposed concerted
rearrangement. Therefore, the Hammett plot in Figure 1.10 is also consistent with a concerted insertion process.

1.4.3. Halide Effect. We next investigated the influence of the halide ligand on the rearrangement of L2-ligated oxidative addition complexes. The chloride (20a), iodide (21a), and triflate (22a) analogues of 7a were prepared in the same manner as 7a (Table 1.4). In all three cases, rearrangement to the corresponding dearomatized complexes 20-22b could be observed in solution. An X-ray structure of 20b (Figure 1.11) was obtained and shows similar structural features to the corresponding Br complex 7b, suggesting that switching from Br to Cl does not have a significant effect on structure of the dearomatized complex, although the Pd–Cl bond in 20b (2.39(4) Å) is significantly shorter than the Pd–Br bond in 7b (2.51(1) Å). Iodide complex 21a proved unstable in CD₂Cl₂, THF-d₈ and C₆D₆, as free ligand slowly appeared with concomitant generation of Pd black. Nonetheless, X-ray quality crystals of 21a could be obtained (Figure 1.11), and analysis of the solid-state structure of 21a show that it is nearly identical to that of 7a, although the Pd–I bond in 21a (2.61(6) Å) is significantly longer than the Pd–Br bond in 7a (2.46(0) Å). Thus, it is likely that 21a decomposes in solution by dissociation of I⁻. Thus, we hesitate to assign definite kinetic or thermodynamic parameters to the rearrangement of 21a to 21b due to its decomposition in solution. Pd(II) complexes bearing Cl, Br, and I ligands all feature ³¹P NMR resonances in the δ 65-70 ppm range (CD₂Cl₂); however, triflate complex 22a possesses a much further downfield ³¹P resonance (δ 111 ppm, C₆D₆), suggesting the triflate group is dissociated in solution. Indeed, X-ray crystallographic analysis revealed that 22a-Ph, the phenyl analogue of 22a,
is cationic at Pd in the solid state, with additional stabilization provided by the lower ring of L2 compared to other complexes (Figure 1.11). Not surprisingly, 22a was found to be susceptible to solvent coordination, so its rearrangement to 22b was studied in C6D6 instead of THF-d8.

Table 1.4. Halide Effects on Rearrangement.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yielda</th>
<th>k_{th}b</th>
<th>kfb</th>
<th>K_{eq}</th>
<th>ΔG_{exp} (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20a</td>
<td>Cl</td>
<td>73%</td>
<td>2.84 ± 0.08</td>
<td>2.18 ± 0.07</td>
<td>2.15 ± 0.04</td>
<td>-0.44 ± 0.01</td>
</tr>
<tr>
<td>7a</td>
<td>Br</td>
<td>59%</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.03</td>
<td>8.71 ± 0.15</td>
<td>-1.26 ± 0.01</td>
</tr>
<tr>
<td>21a</td>
<td>I</td>
<td>53%</td>
<td>.c</td>
<td>.c</td>
<td>.c</td>
<td>.c</td>
</tr>
<tr>
<td>22a</td>
<td>OTf</td>
<td>37%</td>
<td>.c</td>
<td>.c</td>
<td>0.04*</td>
<td>1.87 ± 0.01</td>
</tr>
</tbody>
</table>

aIsolated yield, prepared in the same manner as in Table 1.2. bRelative to 7a in THF-d8. cDecomposed in solution. dKinetics unreliable due to small change in [22a] over time. eValue in C6D6; estimated error is less than ± 0.01.

Figure 1.11. Solid-state structures of 20b, 21a, and L2-Pd(Ph)OTf (22a-Ph) (ellipsoids at 50% probability).
The observed trend for equilibrium constants is \( \text{Br} > \text{Cl} >> \text{OTf} \) (Table 1.4), which follows the trend observed in Table 1.3, as Cl is inductively more electron-withdrawing than Br, and 22a is cationic at Pd. Although 21a eventually decomposed in solution, we observed minimal formation of 21b (~16%) during the first hour in THF-d8, consistent with a tentative rate trend of Cl > Br > I. Exchanging the bromide ligand in 7a for a chloride ligand in 20a accelerates the rate of rearrangement (as with an electron-donating aryl substituent) but reduces the extent of rearrangement (as with an electron-withdrawing aryl substituent). Although Cl is inductively more electron-withdrawing than Br, it is a stronger \( \pi \)-donor to the Pd center; thus, the interplay of these two effects likely causes the observed difference in reactivity between 7a and 20a. However, at this time we cannot determine the exact role of the halide ligand in the rearrangement process.

1.4.4. Ligand Structure Effects: Groups on Phosphorus. The alkyl groups bound to phosphorus in biaryl phosphine ligands play a key role in determining the catalytic activity of their Pd complexes; bulkier ligands, \textit{i.e.} those bearing \textit{tert}-butyl and adamantyl groups, are typically used in cross-coupling reactions with difficult reductive elimination steps. Thus, we decided to investigate the behavior of complexes of ligands analogous to L2 with different substituents on the phosphorus atom. Several oxidative addition complexes of the di-cyclohexyl ligand BrettPhos (L1) have been previously reported\(^5\)\(^,\)\(^18\). In none of these reports was any rearrangement of the corresponding oxidative addition complexes observed. Considering Doyle’s recent observation of 8 (Figure 1.6),\(^6\) we decided to monitor the solution stability of \( \text{L1} \cdot \text{Pd(4-(nBu)Ph)} \text{Br} \) (23a)\(^{18a}\) by \(^1\)H NMR.
Even after 10 days in solution, no rearrangement to 23b was observed. Oxidative addition complexes of other di-cyclohexyl biaryl phosphine ligands have also been prepared or detected *in situ* with no report of anomalous behavior.\(^\text{19}\)

To further test the effect of the substituents on phosphorus, the di-adamantyl ligand AdBrettPhos (L4, Figure 1.12)\(^\text{20}\) was used to prepare oxidative addition complex 24a (Table 1.5). In solution, this complex rearranges to 24b with kinetic and thermodynamic parameters similar to those observed for the conversion of 7a to 7b (Table 1.5). Unfortunately, a solid-state structure of 24a or 24b could not be obtained for comparison to that of 7a or 7b. The structurally similar ligand AdRockPhos\(^\text{21}\) (L5, Figure 1.12) could be used to prepare X-ray quality crystals of L5\(\cdot\)Pd(4-(nBu)Ph)Br (25a, Figure 1.12) for comparison with the structure of 4a (Figure 1.2). The only major structural difference between the solid-state structures of 4a and 25a is the significantly smaller Ar-Pd-Br angle in 25a (79.(5)\(^{\circ}\)) compared to that in 4a (81.(8)\(^{\circ}\)), a trend that has been previously observed.\(^\text{20}\) Based on this information, the relief of unfavorable steric interactions between the aryl group and *tert*-butyl (or adamantyl) groups on the ligand is likely a driving force for rearrangement, as it is for reductive elimination. This finding is consistent with the positive \(\Delta S^\ddagger\) of the rearrangement process as the rearranged species should possess more rotational degrees of freedom for both the *tert*-butyl and aryl substituents than in the corresponding oxidative addition complex.

1.4.5. Ligand Structure Effects: Substituents on the Biaryl Backbone. Due to the radically different behavior of complexes of tBuBrettPhos (L2) and RockPhos (L3), we decided to also investigate the effect of substituents on the phosphine-containing ring of
Table 1.5. Phosphine Substituent Effects on Rearrangement

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>$k_{f+rb}$</th>
<th>$k_{rb}$</th>
<th>$K_{eq}$</th>
<th>$\Delta G_{exp}$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23a</td>
<td>Cy</td>
<td>72%</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.03</td>
<td>8.71 ± 0.15</td>
<td>-1.26 ± 0.01</td>
</tr>
<tr>
<td>7a</td>
<td>tBu</td>
<td>59%</td>
<td>1.00 ± 0.04</td>
<td>0.87 ± 0.03</td>
<td>9.00 ± 0.16</td>
<td>-1.28 ± 0.01</td>
</tr>
<tr>
<td>24a</td>
<td>Ad</td>
<td>37%</td>
<td>0.87 ± 0.04</td>
<td>0.87 ± 0.03</td>
<td>9.00 ± 0.16</td>
<td>-1.28 ± 0.01</td>
</tr>
</tbody>
</table>

$^a$Isolated yield, prepared in the same manner as in Table 1.2. $^b$Relative to 7a in THF-d8. $^c$Rearranged product 23b was not observed. Ad = adamantyl.

Figure 1.12. Di-adamantyl ligands L4-L5, and X-ray crystallographic structure of 25a (ellipsoids at 50% probability).

The biaryl backbone. Because a change from a methoxy group in the 6-position of 7a to a methyl group in 4a greatly decreased the $K_{eq}$ and rate of rearrangement (~5% rearrangement after 6 hours for 4a), we hypothesized that bulkier substituents in the 6-position of the ligand might retard rearrangement. Similarly, the fact that the corresponding complex of tBuXPhos (L6, Table 1.6), L6•Pd(4-(nBu)Ph)Br (26a), was found to rearrange to 26b to only a small degree, suggests that the substituent in the 3-position found in 7a but not in 26a promotes rearrangement (Table 1.6). Thus, a variety of complexes were synthesized in order to test the effect of substituents in the 3- and 6-positions on the rate of rearrangement and the equilibrium ratio of complexes (Table 1.6).
When attempting to prepare 27a, the oxidative addition complex of a BrettPhos-type ligand with no substituent in the 6-position, we observed that the product that precipitated from the reaction mixture was already an equilibrium mixture heavily favoring rearranged complex 27b (Table 1.6). To probe whether the enhancement of rearrangement by a substituent in the 3-position was due to either a steric or electronic effect, we attempted to prepare 28a (R = Me). As with 27a, only an equilibrium mixture favoring 28b could be obtained (Table 1.6). An equilibrium constant (Keq) of 15 was determined for this complex and is the largest value seen for any ligand in the series of oxidative addition complexes with Ar = 4-(nBu)Ph. Finally, 29a, which has a methyl group in the 6-position but no substituent in the 3-position of the ligand, was prepared. In accordance with previous findings, only trace amounts (~1%) of 29b could be detected in solution by ¹H NMR, even after allowing 29a to stand at room temperature in solution for 24 h (Table 1.6).

Table 1.6. Ligand substituent effects on rearrangement.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yielda</th>
<th>₁₀⁻¹₅ b</th>
<th>₁₀⁻¹₅ b</th>
<th>Keq</th>
<th>ΔG&lt;sub&gt;exp&lt;/sub&gt; (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>OMe</td>
<td>OMe</td>
<td>59%</td>
<td>1.00 ± 0.03</td>
<td>1.00 ± 0.03</td>
<td>6.71 ± 0.15</td>
<td>-1.26 ± 0.01</td>
</tr>
<tr>
<td>4a</td>
<td>OMe</td>
<td>Me</td>
<td>76%</td>
<td>_c</td>
<td>_c</td>
<td>0.19&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.97 ± 0.01</td>
</tr>
<tr>
<td>26a</td>
<td>H</td>
<td>H</td>
<td>77%</td>
<td>3.77 ± 0.54</td>
<td>0.87 ± 0.07</td>
<td>0.26&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.78 ± 0.01</td>
</tr>
<tr>
<td>27a</td>
<td>OMe</td>
<td>H</td>
<td>58%</td>
<td>_c</td>
<td>_c</td>
<td>10.0 ± 0.2</td>
<td>-1.34 ± 0.01</td>
</tr>
<tr>
<td>28a</td>
<td>Me</td>
<td>H</td>
<td>35%</td>
<td>_c</td>
<td>_c</td>
<td>15.0 ± 0.3</td>
<td>-1.58 ± 0.01</td>
</tr>
<tr>
<td>29a</td>
<td>H</td>
<td>Me</td>
<td>34%</td>
<td>_c</td>
<td>_c</td>
<td>0.01&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.68 ± 0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields; prepared in the same manner as in Table 1.2. <sup>b</sup>Relative to 7a in THF-d₈. <sup>c</sup>Kinetics unreliable due to slow appearance of rearranged complex over time. <sup>d</sup>Estimated error is less than ± 0.01. <sup>e</sup>Obtained at equilibrium.
Overall, these results confirm that substituents in the 3-position promote both the rate and extent of dearomatization, whereas substituents in the 6-position inhibit this process.\textsuperscript{23,24} Based on the observed trend in $K_{eq}$ when varying the substituent in the 3-position (Me (28a) $>\text{OMe (27a)} >\text{H (26a)}$), the promotion of rearrangement by these substituents appears to be steric in nature, likely arising from this substituent "pushing" the $\tau$butyl groups closer to the Pd center. This effect has been previously proposed to promote reductive elimination as well.\textsuperscript{3} On the other hand, the solid state structures of 7a, 4a, and 7b provide an explanation for the retarding effect of substituents in the 6-position on the equilibrium extent of rearrangement. Viewing 7a and 4a along the axis that contains the biaryl bond and bisects both the lower and phosphine-containing rings (as shown in Figure 1.13, left and center), the lower and phosphine-containing rings are almost perfectly perpendicular to one another, as would be expected. Due to the near perpendicularity of the two rings, the distance between the \textit{ortho}-isopropyl groups and the substituent at the 6-position (OMe in 7a, Me in 4a) is similar, with an observed average distance of 3.55 Å in 7a and 3.77 Å in 4a. The longer observed distance in 4a compared to 7a reflects the longer bond length of the C–C bond in 4a (1.51(4) Å) compared to the C–O bond in 4a (1.37(6) Å) (Figure 1.13).

However, viewing the solid-state structure of 7b in the same manner reveals that the lower ring is significantly tilted relative to the phosphine-containing ring after dearomatization (Figure 1.13, right). This tilting effectively positions the isopropyl group adjacent to the Pd-center farther from the OMe goup at the 6-position, but, more importantly, positions the other isopropyl group (highlighted in yellow in Figure 1.13) roughly 0.56 Å closer to the methoxy group than it was in 7a. The decrease in distance
between these two substituents upon dearomatization should result in a stronger
disfavorable steric interaction between them. In 4b the substituent at the 6-position is
significantly larger than in 7a, suggesting that the increase in steric repulsion following
dearomatization should be even more dramatic for 4b than for 7b and could be enough to
significantly destabilize 4b relative to 4a. This ground state effect is the most likely
explanation for why 4a dearomatizes to such a lesser extent than 7a. The effect of the
substituent at the 6-position on transition states, and thus its effect on the relative rates of
rearrangement for the two complexes, is more difficult to determine, but it is likely similar in nature to the observed ground state effects.

1.4.6. Ligand Structure Effects: Further Studies of Complexes of L3 and L6. In order to determine if the trends we observed for complexes of L2 were generalizable to the other commonly employed di-tert-butyl biaryl phosphine ligands (L6) and RockPhos (L3). Thus, additional complexes of L6 (30a-32a) and L3 (33-35a) were synthesized to compare with the corresponding complexes of L2 (Table 1.7). Crystal structures of all of these complexes were obtained and show similar structural features and trends to those of L2, including the lengthening of the Pd-ipso interaction as the arene becomes more electron-rich (not shown). The aryl substituent equilibrium constant trend of NMe 2 > nBu > H > CN demonstrated for complexes of L2 in Table 1.3 was also observed for even after several days in solution (Table 1.7). In addition, the observed trend in extent of rearrangement for varying the phosphine ligand in the 4-(nBu)PhBr oxidative addition complex series, namely L2 > L6 > L3 (Table 1.6), also held true for the 4-(NMe2)PhBr and PhBr series of complexes. Thus, the results and analysis we described for complexes of L2 likely hold true for complexes of L3 and L6 as well.

1.5. Base-Mediated 3'-arylation of Pd(II) Complexes. Having full investigated the experimental parameters regarding the rearrangement of Pd(II) complexes ligated by L2, we next turned our attention to investigating what effect, if any, this dearomatization complexes of L3 and L6, with no detectable rearrangement of 32a and 35a observed process has on Pd-catalyzed fluorination. In this vein, we found that treating 7a with
Table 1.7. Equilibrium parameters for the rearrangement of various aryl-substituted complexes derived from L3 and L6.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Yield</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
<td>R</td>
<td></td>
<td>K&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>ΔG&lt;sub&gt;exp&lt;/sub&gt; (kcal/mol)</td>
</tr>
<tr>
<td>30a</td>
<td>30b</td>
<td>NMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>77%</td>
<td>2.15 ± 0.04</td>
<td>-0.45 ± 0.01</td>
</tr>
<tr>
<td>26a</td>
<td>26b</td>
<td>nBu</td>
<td>77%</td>
<td>0.26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.76 ± 0.01</td>
</tr>
<tr>
<td>31a</td>
<td>31b</td>
<td>H</td>
<td>70%</td>
<td>0.11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.28 ± 0.01</td>
</tr>
<tr>
<td>32a</td>
<td>32b</td>
<td>CN</td>
<td>87%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Yield</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
<td>R</td>
<td></td>
<td>K&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>ΔG&lt;sub&gt;exp&lt;/sub&gt; (kcal/mol)</td>
</tr>
<tr>
<td>33a</td>
<td>33b</td>
<td>NMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>75%</td>
<td>1.08 ± 0.02</td>
<td>-0.05 ± 0.01</td>
</tr>
<tr>
<td>4a</td>
<td>4b</td>
<td>nBu</td>
<td>76%</td>
<td>0.19&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.97 ± 0.01</td>
</tr>
<tr>
<td>34a</td>
<td>34b</td>
<td>H</td>
<td>76%</td>
<td>0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.47 ± 0.01</td>
</tr>
<tr>
<td>35a</td>
<td>35b</td>
<td>CN</td>
<td>70%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields; prepared in the same manner as in Table 1.2. <sup>b</sup>Estimated absolute error is less than 0.01. <sup>c</sup>Rearranged species not detected by <sup>1</sup>H NMR.

DBU (1.2 equiv.) in THF led to clean abstraction of HBr and concomitant rearomatization of the lower ring of the ligand to provide 3'-arylated Pd(0) intermediate 36, which could not be isolated (Figure 1.14). However, 36 could be trapped by external 4-(nBu)PhBr (3 equiv.) to produce 3'-arylated oxidative addition complex 37, which was characterized by X-ray crystallography (Figure 1.14). In contrast to 7a, 37 could be heated to 100 °C without undergoing any detectable dearomatization, as determined by <sup>31</sup>P NMR.
Interestingly, the main structural difference between 7a and 37 is a distortion from ideal square-planar geometry observed in 7a (and in all solid state structures that have been obtained for oxidative addition complexes of L2, L3, and L6) that is not observed in the solid-state structure of 37 (Figure 1.15).\textsuperscript{25} When 7a is viewed down the biaryl axis as shown in Figure 1.13, it becomes clear that the angle between the \textit{ipso} carbon and the aryl substituent (\textit{ipso}-Pd-Ar) is not 180 ° as it would be in an ideal square planar complex; instead, this angle is approximately 158 ° due to tilting of the aryl substituent towards one side of the lower ring of the ligand. In addition, the P-Pd-Br angle is distorted approximately 13 ° from linearity (Figure 1.13). This "tilting" likely indicates a ground-state predilection towards dearomatization. However, when 37 is viewed in the same manner, no significant distortion of the \textit{ipso}-Pd-Ar angle (178 °) from linearity is observed, and the P-Pd-Br is significantly closer to linearity (176 °) than it is in 7a (Figure 1.15). Thus, the 3'-aryl substituent imposes a stronger square planar geometry at the metal center, which seems to prevent a second dearomatization event from occurring.

Not surprisingly, 26a and 4a could also be converted to the corresponding 3'-arylated complexes 38 and 39 using the same procedure, although in the latter case long reaction times (60 h) were needed to overcome the sluggish rearrangement of 4a (Figure 1.16). A solid-state structure of 39 was obtained and found to be very similar to that of 37 (Figure 1.16). In particular, the \textit{ipso}-Pd-Ar angle is also close to linearity as in 37 (Figure 1.15).

With the 3'-arylation of complexes of L2 and L3 brought to light, we began to probe the potential relevance of this process to Pd-catalyzed fluorination. In particular, we wondered if the 3'-arylated analogue of L2, namely L7 (Figure 1.17), could be the actual
Figure 1.14. Base-mediated rearomatization of 7a to 36 with concomitant oxidative addition of 4-(nBu)PhBr to produce 37, which was characterized by X-ray crystallography (ellipsoids at 50% probability).

Figure 1.15. The solid state structure of 37 shows no significant distortions of the ipso-Pd-Ar and P-Pd-Br angles from linearity and contains a more ideal square planar geometry than 7a (compare to Figure 1.13).
Figure 1.16. Base-mediated 3'-arylation of 26a and 4a to produce 38 and 39, respectively. The latter was characterized by X-ray crystallography (two views, ellipsoids at 50% probability).

supporting ligand during the catalytic fluorination of 4-(nBu)PhOTf (6-OTf). Although L7 could not be isolated from the crude reaction mixture of the Pd-catalyzed fluorination of 6-OTf, the complete conversion of L2 into L7 was confirmed by $^{31}$P NMR and LC/MS (Figure 1.17). The very similar $^{31}$P NMR chemical shifts of L7 relative to L2 (~1.3 ppm difference) prevented us from previously noticing that ligand modification had occurred. In fact, the catalytic fluorination reaction of every aryl triflate we have examined to date results in complete conversion of L2 into the corresponding 3'-arylated ligand. Importantly, L8 could be isolated from the reaction mixture when L3 was used.
as the supporting ligand for the Pd-catalyzed fluorination of 3-OTf, and its structure and connectivity were confirmed by X-ray analysis (Figure 1.17).

![Diagram](image)

**Figure 1.17.** 3'-arylated ligands L7 and L8 formed during the catalytic fluorination of 6-OTf, and the X-ray structure of L8 (ellipsoids at 50% probability).

The kinetic profile of the Pd-catalyzed fluorination of 6-OTf using L3 (or L2) shows a substantial initial mass loss without the formation of an equivalent amount of aryl fluorides (Figure 1.18). During this stage, 4-(nBu)PhCl (arising from the Cl- generated upon activation of [(cinnamyl)PdCl]2) and (4-(nBu)Ph)2O (arising from adventitious water) are the only detectable products. After this induction period, zeroth-order overall decay of the remaining 6-OTf to 6a-b is observed. It is now evident that this initial mass loss is in part due to the *in situ* conversion of L3 to L8. Indeed, when using ligand L8, the initial mass loss 6-OTf is less and the zeroth-order conversion of 6-OTf to 6a-b begins more quickly (Figure 1.18). Furthermore, we found an improvement in yield of 13% in the fluorination of 6-OTf when using L8 instead of L3 (73% vs. 60%, Figure 1.18).27 No further arylation of L8 was detected by 31P NMR or LC/MS, consistent with our previous observation that 37 does not undergo further rearrangement, even upon heating. Consistent with our catalytic studies, upon closer inspection we also found that substantial quantities of L8 were formed during the attempted reductive elimination of 5 shown in Figure 1.2. Although we were unable to directly observe a rearranged Pd(II)
OTf 3

eq CsF F
2.5% [(cinnamyl)PdCl]2
7.5% L3 or L8
tol, 120 °C, 12 h

with L3: 60% (6a:6b = 2.4:1)
with L8: 73% (6a:6b = 2.4:1)

Figure 1.18. Comparison of L3 and L8 in the Pd-catalyzed fluorination of 6-OTf.

fluoride species, the net loss of HF had taken place to produce L8 and Pd(0). Overall, our catalytic and stoichiometric studies suggest that rapid ligand modification of L2 and L3 to L7 and L8, respectively, occurs during the Pd-catalyzed fluorination of 6-OTf.

1.6. Reductive elimination from 3'-arylated Pd–F complexes. Having established that complexes of L2-L3 undergo dearomatization/3'-arylation in the catalytic fluorination of aryl triflates, we wondered if electron-rich 3'-arylated L•Pd(Ar)F complexes were capable of undergoing C–F reductive elimination. 3'-arylated complex L7•Pd(4-(nBu)Ph)F (40) was readily prepared from 37 and AgF, and its reactivity was compared to 5 (Table 1.8). In contrast to 5, heating 40 in toluene or cyclohexane led to formation of
4-(nBu)PhF (6a) in yields of 15% and 20%, respectively (entries 1-2, Table 1.8). In both cases, no 3-(nBu)PhF (6b) could be detected by $^{19}$F NMR, suggesting that when isolated 40 is a competent intermediate in the catalytic reaction. Indeed, 40 was found to be catalytically competent in the fluorination of 4-(nBu)PhOTf (6-OTf) with the highest yield observed at this point (84% combined yield of 6a-b). Interestingly, attempting to increase the yield of 6a by heating 40 in the presence of 4-(nBu)PhOTf (entry 3) led to a 1.6:1 mixture of 6a and 6b in 52% combined yield, which is nearly the same ratio of products seen in the catalytic reaction (entry 3, Table 1.8). This finding suggests that the formation of regioisomeric mixtures of aryl fluorides in the catalytic fluorination of 6-OTf may not require the presence of highly basic CsF nor any other additional fluoride source to occur (see Chapter 2). Notably, if this stoichiometric reaction was conducted in cyclohexane instead of toluene, a slightly improved ratio (2:1) of 6a to 6b was observed, similar to the improvement we have previously observed by carrying out the catalytic reaction in cyclohexane (entry 4, Table 1.8). If 4-(nBu)PhBr was used in place of 4-(nBu)PhOTf (6-OTf) (entry 5, Table 1.8), very little 6b was formed, but the yield of 6a was still low. This experiment suggests that regioisomer formation in these stoichiometric experiments likely involves in situ formed L•Pd(4-(nBu)Ph)X (X = Br, OTf) species (see Chapter 2). In addition, attempted trapping of Pd(0) species with other agents such as diphenylacetylene, 1,5-cyclooctadiene, or 4-(nBu)PhCl, did not led to an improvement in the yield of 6a (not shown). Nonetheless, the findings in Table 1.8 represent the first unambiguous reductive elimination of an electron-rich aryl fluoride from an isolated L•Pd(Ar)F complex.
Table 1.8. Reductive elimination of 6a from 3'-arylated complex 40°

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Aryl Fluoride Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tol</td>
<td>None</td>
<td>nBu-(\text{F}) 15%</td>
</tr>
<tr>
<td>2</td>
<td>cy</td>
<td>None</td>
<td>nBu-(\text{F}) 20%</td>
</tr>
<tr>
<td>3</td>
<td>tol</td>
<td>nBu-(\text{OTf})</td>
<td>nBu-(\text{F}) 32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nBu-(\text{F}) 20%</td>
</tr>
<tr>
<td>4</td>
<td>cy</td>
<td>nBu-(\text{OTf})</td>
<td>nBu-(\text{F}) 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nBu-(\text{F}) 13%</td>
</tr>
<tr>
<td>5</td>
<td>tol</td>
<td>nBu-(\text{Br})</td>
<td>nBu-(\text{F}) 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nBu-(\text{F}) 3%</td>
</tr>
<tr>
<td>6</td>
<td>tol</td>
<td>(\text{Br})</td>
<td>(\text{F}) 40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nBu-(\text{F}) 6%</td>
</tr>
<tr>
<td>7</td>
<td>tol</td>
<td>(\text{OTf})</td>
<td>(\text{F}) 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nBu-(\text{F}) &lt;3%</td>
</tr>
</tbody>
</table>

° Yields based on 40 and determined by \(^{19}\text{F}\) NMR.

1.7. Halide cross-over in stoichiometric experiments. As an interesting aside, attempting to improve the yield of the reductive elimination of 6a by heating 40 in the presence of excess PhBr produced primarily PhF (40%) and only a small amount of 4-
(nBu)PhF (6%) (entry 6, Table 1.8). Similarly, in the presence of 1-naphthyl triflate, 1-fluoronaphthalene was formed nearly exclusively 75% yield (entry 7, Table 1.8). An explanation for the near exclusive formation of cross-over products in the presence of PhBr (entry 6, Table 1.8) is depicted in Figure 1.19. After slow C–F reductive elimination from 40, the formed \textbf{L7}•Pd(0) species (36) would undergo oxidative addition into the excess PhBr, leading to \textbf{L7}•Pd(Ph)Br (41). This complex could then undergo halide exchange with the remaining 40 to produce the cross-over complexes \textbf{L7}•Pd(Ph)F (42) and 37. Reductive elimination from 42 would produce PhF. Because reductive elimination from 43 would be faster than from 37,\textsuperscript{2} the reaction should funnel through 42 and produce predominantly PhF.

This Curtin-Hammett situation would depend on F/Br exchange between 41 and 40 being rapid and reversible under the reaction conditions.\textsuperscript{29} In order to investigate this likelihood, we independently prepared complex 41 from 7b, PhBr, and DBU (Figure 1.20). Complex 41 could be prepared in >95% purity, and its structure was confirmed by X-ray crystallography (Figure 1.20). The corresponding fluoride complex 42 was also prepared (Figure 1.20). When 40 and 41, or 42 and 37, were combined in toluene, a 1:1:1:1 mixture of 40, 41, 42, and 37 was formed in less than 10 min. at rt (not shown), as judged by 3\textsuperscript{1}P NMR. This result confirms that F/Br exchange of biaryl phosphine-ligated L•Pd(Ar)X complexes is extremely rapid.

1.8. Conclusion. In this chapter, we have demonstrated that L•Pd(Ar)X (L = L2-3) complexes undergo an unprecedented dearomative rearrangement in solution. The rearrangement of biaryl phosphine-ligated Pd(II) complexes is heavily dependent on the
steric parameters of both the phosphine-containing ring of the ligand and well as the alkyl groups on the phosphorus atom. It is important to note that nearly all studied complexes bearing di-tert-butyl biaryl phosphine ligands show at least some ability to rearrange in
solution. The presented experimental work is consistent with a Pd(II)-mediated, direct aryl insertion reaction into an arene; until now, this reactivity mode had only been proposed in certain C-H arylation reactions. We have found that not only is this process viable, but that it can occur under mild conditions. The relief of unfavorable steric interactions between the alkyl groups on phosphorus and the aryl substituent is a powerful factor in promoting the rate and extent of rearrangement, as is the electronic nature of the aryl group. Taken together, these experimental results suggest that the structural features that make bulky biaryl phosphine ligands effective for promoting challenging reductive eliminations from Pd(II) also enable the rearrangement of their oxidative addition complexes to the corresponding dearomatized isomers.

This rearrangement process is important because it leads to 3'-arylation of the ligand, which is necessary before C–F reductive elimination can occur. The results presented herein confirm that arylated ligands such as L7-8 are the actual supporting ligands during catalytic fluorination reactions. Thus, there is a slightly different catalyst for each individual substrate, and reactions employing catalysts based on di-tert-butyl biaryl phosphines may be more complex than previously assumed. Preliminary investigations in our lab suggest that while ligand modification occurs to some degree in other reactions involving L2 and L3, it does not have as dramatic an impact on the success of these reactions as it does for fluorination. With this ligand modification process brought to light, it finally became possible for us to investigate the intricacies of the catalytic fluorination reaction and, most importantly, to determine the mechanism of regioisomer formation.
1.9. Experimental

1.9.1. General Procedures. All reactions were carried out in a nitrogen-filled glovebox using oven-dried glassware and anhydrous degassed solvents unless otherwise noted. Dry, oxygen-free toluene, dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), and ether (Et₂O) were obtained by passage through activated alumina columns followed by an argon sparge. Other solvents were purchased from Aldrich in Sure-Seal™ bottles and were purged with argon before use. CD₂Cl₂ (99.9%), THF-d₈ (99.5%), and dioxane-d₈ (99.0%) were purchased in sealed ampules from Cambridge Isotopes. C₆D₆ (99.5%) was purchased from Cambridge Isotopes and distilled from CaH₂, degassed by three freeze-pump-thaw sequences, and then transferred to a nitrogen-filled glovebox for storage. Celite was dried at 200 °C under high vacuum before use. The preparations of tBuBrettphos,3⁰ RockPhos,3 di-tert-butyl-(2′-4′-6′-triisopropyl-3-methoxy-[1,1′-biphenyl]-2-yl)phosphine,3 Me₄tBuXPhos,3¹ di-tert-butyl-(2′-4′-6′-triisopropyl-3-methyl-[1,1′-biphenyl]-2-yl)phosphine,2² AdBrettPhos,2⁰ and AdRockPhos²¹ have been previously described. tBuXPhos and BrettPhos were purchased from commercial sources or received as gifts and used without further purification. [(cinnamyl)PdCl]₂ was purchased from Aldrich and used as received. Cesium fluoride (99.9%) was purchased from Aldrich (or Strem) and was dried at 200°C under high-vacuum for 24 hours. The dried CsF was then transferred to a nitrogen-filled glovebox where it was thoroughly ground using an oven-dried mortar and pestle. The finely ground CsF was then filtered through a 45 μm stainless-steel sieve (purchased from Cole Parmer) and the smaller particles collected. All other reagents were purchased from commercial sources and used without further purification. Isolated yields refer to spectroscopically pure materials, unless otherwise
stated. All yields stated for fluorination reactions are based on \(^{19}\text{F}\) NMR relative to an internal standard of 1-fluoronaphthalene. \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra were recorded on Varian XL 300 MHz, Bruker AMX 400 MHz, and Varian Inova 500 MHz spectrometers and were calibrated using residual solvent as an internal reference (CD\(_2\)Cl\(_2\): \(\delta\) 5.32 (\(^1\text{H}\)), \(\delta\) 53.8 (\(^{13}\text{C}\)) ppm; THF-d\(_8\): \(\delta\) 3.58 (\(^1\text{H}\)), \(\delta\) 67.6 (\(^{13}\text{C}\)) ppm; C\(_6\)D\(_6\): \(\delta\) 7.16 (\(^1\text{H}\)), \(\delta\) 128.1 (\(^{13}\text{C}\)) ppm). \(^{19}\text{F}\) and \(^{31}\text{P}\) spectra were recorded on Varian XL 300 MHz or Bruker AMX 400 MHz spectrometers. \(^{19}\text{F}\) NMR spectra were calibrated to an external standard of CFCl\(_3\) (\(\delta\) 0.0 ppm). \(^1\text{H}\)-decoupled \(^{31}\text{P}\) NMR spectra were calibrated to an external standard of \(\text{aq. H}_3\text{PO}_4\) (\(\delta\) 0.0 ppm). Variable temperature NMR experiments were performed on a Varian Inova 500 MHz spectrometer equipped with two RF channels and pulse field gradients, capable of a VT range of -100°C to +150°C. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, pt = pseudo triplet. Fluorination reactions were carried out in Fisher 16 x 125 mm tubes (Cat. No. 1495925C) using Thermo Scientific SPTA PTFE/SIL F/15-425 10 septa (Cat. No. 03394A). All reactions performed in sealed reaction tubes should be carried out behind a blast shield or a closed hood sash.
Figure 1.21. Decoalescence and $^1$H NOESY spectra (CD$_2$Cl$_2$, 400 MHz, 20 °C) of 19a.
1.9.2. Procedures for catalytic fluorination reactions.

General Procedure for Catalytic Fluorination Using L2 or L3. To an oven-dried screw cap tube equipped with a stir bar was added (in this order) CsF (91.1 mg, 0.60 mmol, 3.00 eq.), L2 or L3 (0.02 mmol, 7.5%), [(cinnamyl)PdCl]2 (2.6 mg, 0.005 mmol, 5% “Pd”), aryl triflate (0.2 mmol, 1 eq.), and toluene (2.0 mL). The tube was capped, removed from the glovebox, and placed into an oil bath that had been pre-heated to 120 °C and allowed to stir vigorously for 12 h. The reaction mixture was cooled to room temperature, 1-fluoronapthalene (40 μL, 1.55 eq.) was added, and the reaction mixture was analyzed directly by $^{19}$F NMR. Reactions conducted with [(cinnamyl)PdCl]2/L8 or with 40 as the Pd source were carried out using the same procedure.

Procedure for Initial Rate Comparison Between L3 and L8 (Figure 1.18): To an oven-dried vial was added [(cinnamyl)PdCl]2 (32.5 mg, 0.06 mmol) and toluene (25 mL). The vial was vigorously shaken to dissolve the solid, and the resulting mixture was used as a stock solution. Meanwhile, two oven-dried screw top reaction tubes equipped with stir bars were charged with the following:

Tube #1: CsF (455 mg, 2.99 mmol, 3.00 eq.), L3 (35.0 mg, 0.08 mmol, 7.5%), 1-fluoronaphthalene (110 μL, 1.00 mmol, 1.00 eq.), and 4-nBuPhOTf (228 μL, 1.00 mmol, 1.00 eq).

Tube #2: CsF (455 mg, 2.99 mmol, 3.00 eq.), L8 (45.0 mg, 0.08 mmol, 7.5%), 1-fluoronaphthalene (110 μL, 1.00 mmol, 1.00 equiv), and 4-nBuPhOTf (228 μL, 1.00 mmol, 1.00 eq).
Next, 10 mL of the [(cinnamyl)PdCl]₂ stock solution (which corresponds to 5 % “Pd”) was added to each reaction tube. The tubes were capped, removed from the glovebox, and placed into an oil bath that had been pre-heated to 120 °C and allowed to stir vigorously. Every 30 min., aliquots (~ 200-300 µl) were rapidly removed, quenched with EtOAc, and analyzed directly for conversion by ¹⁹F NMR.

1.9.3. Synthesis of new ligands.

**di-tert-butyl-(2'-4'-6'-triisopropyl-6-methyl-[1,1'-biphenyl]-2-yl)phosphine:** Magnesium turnings (2.96 g, 122 mmol, 5.00 eq.) were added to a 250 mL three-necked roundbottom flask equipped with a stir bar and a reflux condenser. The flask was flame-dried under vacuum with vigorous stirring of the turnings. The flask was cooled to room temperature, and then back-filled with argon. THF (50 mL) and 2,4,6-triisopropylbromobenzene (12.3 mL, 48.7 mmol, 2.00 eq.) were added, and the reaction mixture was heated to reflux. 1,2-dibromoethane (50 µL) was added dropwise once reflux was achieved, and the reaction mixture was stirred at reflux for 3 h. At this time the reaction mixture was cooled to room temperature and diluted with THF (50 mL). 2-bromo-3-chlorotoluene (5.00 g, 24.3 mmol, 1.00 eq.) in THF (25 mL) was added via cannula over 30 min the solution of the Gringard reagent. The reaction mixture was then brought back up to reflux and allowed to stir overnight. The reaction mixture was cooled to 0°C using an ice bath, and iodine (12.4 g, 48.7 mmol, 2.00 eq.) in THF (50 mL) was added dropwise over 15 min with vigorous stirring; afterwards, the reaction mixture was allowed to stir for 1 h while slowly warming to room temperature. Saturated aqueous
sodium thiosulfate (200 mL) and ethyl acetate (200 mL) were added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (200 mL), and the combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate, and filtered. The solvent was removed in vacuo. The resulting brown non-homogeneous material was triturated from hexanes (10 mL) and filtered, yielding a brown-yellow solid. This solid was recrystallized from hot ethyl acetate to yield exclusively the undesired 3-methyl regioisomer (2-iodo-2',4',6'-triisopropyl-3-methyl-1,1'-biphenyl), which was set aside. The mother liquor from the recrystallization was concentrated in vacuo, and the resulting solid was purified by flash chromatography (hexanes) to yield a nearly 1:1 mixture of 2-iodo-2',4',6'-triisopropyl-3-methyl-1,1'-biphenyl and 2-iodo-2',4',6'-triisopropyl-6-methyl-1,1'-biphenyl (432 mg, 4% yield total) as a white crystalline solid. The mixture of regioisomeric biaryl iodides (420 mg, 1.00 mmol, 1.00 eq.) was then transferred to an oven-dried 25 mL Schlenk flask equipped with a magnetic stir bar and fitted with a rubber septum. The flask was evacuated and backfilled with argon (this process was repeated a total of three times). Toluene (10 mL) was then added, and the reaction mixture was cooled to -78°C. t-BuLi (1.7 M in pentane, 1.30 mL, 2.20 mmol) was added drop-wise via syringe, and the reaction mixture was stirred for 1 h at -78°C. At this time, the septum was removed from the flask and CuCl (99.0 mg, 1.00 mmol, 1.00 mmol), which was weighed out in a nitrogen-filled glovebox, was added in one portion, followed by (tBu)2PCl (190 uL, 1.50 mmol, 1.500 eq.). The septum was replaced with a Teflon screw cap and the reaction mixture was warmed to room temperature, at which time it turned dark purple. The reaction mixture was then heated to 140°C for 24 h, and then cooled to room temperature, diluted with EtOAc (20
mL), and washed repeatedly with \textit{aq.} \text{NH}_4\text{OH} until the aqueous layer was no longer blue in color. The organic layer was then washed with brine (10 mL), dried over MgSO$_4$, and concentrated \textit{in vacuo}. The resulting yellow solid was purified by flash chromatography (0 $\rightarrow$ 2% Et$_2$O/hexanes) to give a white crystalline solid. This solid was recrystallized from hot methanol under argon to yield di-\textit{tert}-butyl-(2'-4'-6'-triisopropyl-6-methyl-[1,1'-biphenyl]-2-yl)phosphine (58.0 mg, 0.5 \% overall) as a white crystalline solid. Melting point: 119°C. \textsuperscript{1}H NMR (300 MHz, CD$_2$Cl$_2$): \textit{\delta} 7.76 (d, \textit{J} = 6.3 Hz, 1H), 7.22-7.29 (m, 2H), 7.05 (s, 2H), 2.95 (p, \textit{J} = 6.9 Hz, 1H), 2.43 (p, \textit{J} = 6.6 Hz, 2H), 1.88 (s, 3H), 1.32 (d, \textit{J} = 6.9 Hz, 6H), 1.19 (d, \textit{J} = 6.9 Hz, 6H), 1.16 (d, \textit{J} = 11.4 Hz, 18H), 0.97 (d, \textit{J} = 6.9 Hz, 6H) ppm; \textsuperscript{13}C NMR (75 MHz, CD$_2$Cl$_2$): \textit{\delta} 148.7, 148.1, 146.7, 138.7, 138.6, 138.0, 137.6, 136.5, 136.5, 134.2, 134.1, 131.2, 125.6, 121.5, 34.5, 33.5, 33.2, 31.4, 31.2, 31.1, 25.5, 24.9, 24.9, 24.2, 22.8, 22.8 ppm (observed complexity is due to C-P coupling); \textsuperscript{31}P NMR (121 MHz, CD$_2$Cl$_2$): \textit{\delta} 22.5 ppm. IR: 2950, 2926, 2889, 2863, 1466, 1443, 1382, 1362, 877, 776, 762 cm$^{-1}$.

To an oven-dried schlenk tube was added 4-nBuPhOTf (744 mg, 2.63 mmol, 1.00 eq.), RockPhos (L3) (250 mg, 0.53 mmol, 0.20 eq.), [(cinnamyl)PdCl]$_2$ (138 mg, 0.27 mmol, 0.100 equiv.), CsF (1.22 g, 8.00 mmol, 3.00 eq.) and toluene (25 ml). The tube was sealed and placed into and oil bath that had been pre-heated to 120 °C and allowed to stir vigorously for 20 h. At this time, the reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The organic phase was washed with saturated \textit{aq.} \text{NaHCO}_3 (100 mL) and brine (100 mL), dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. 

59
The crude reaction mixture was purified by flash chromatography (hexanes → CH₂Cl₂ → Et₂O) to obtain a light brown foam that proved to be a 5:1 mixture of L₈ (δ 37.0 ppm) and L₈ (δ 35.8 ppm), as determined by ³¹P NMR. Recrystallization of this mixture from hot MeOH/EtOAc afforded L₈ (75.0 mg, 24% based on starting L₃) as an off-white solid. [Note: under identical conditions, tBuBrettPhos (L₂) (δ 34.8 ppm) is quantitatively converted to L₇ (δ 36.0 ppm); however all re-crystalization attempts to date have failed to deliver analytically pure L₇]. ¹H NMR (400 MHz, CD₂Cl₂) δ 7.25 – 7.21 (m, 3 H), 7.17 (d, J = 9.1 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.3 Hz, 1 H), 3.81 (s, 3 H), 2.77 (septet, J = 8.2 Hz, 1 H), 2.68 (t, J = 6.8 Hz, 2 H), 2.56 – 2.45 (m, 2 H), 1.80 (s, 3 H), 1.71 – 1.65 (m, 2 H), 1.43 – 1.38 (m, 2 H), 1.28 – 1.13 (m, 24 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.99 – 0.93 (m, 6 H), 0.81 (d, J = 7.2 Hz, 3 H), 0.61 (d, J = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CD₂Cl₂) δ 160.7, 160.7, 152.0, 151.7, 147.6, 145.8, 142.8, 141.4, 139.1, 138.8, 138.8, 132.9, 132.3, 131.8, 131.0, 130.9, 127.2, 127.1, 125.3, 124.9, 120.4, 108.8, 54.0, 35.8, 34.7, 34.6, 34.4, 34.3, 34.2, 32.8, 32.8, 32.4, 32.4, 32.3, 32.2, 31.3, 31.3, 29.8, 25.4, 24.9, 24.7, 24.3, 23.6, 22.9, 22.5, 22.5, 14.2 (observed complexity is due to C–P splitting); ³¹P NMR (121 MHz, CD₂Cl₂) δ: 36.9. X-ray quality crystals of L₈ were obtained by vapor diffusion of a MeOH/Et₂O solution of L₈ with pentane.

1.9.4. Synthesis of new complexes.

Standard procedure for synthesis of oxidative addition complexes. Ligand (1.00-1.10 eq.) and aryl halide (1.10-5.00 eq.) were added to an oven-dried vial. Cyclohexane was added dropwise with stirring until all of the ligand dissolved. (1,5-
cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (1.00 eq.) was added in one portion, and the reaction mixture was allowed to stir overnight at room temperature, during which time a precipitate formed. Pentane was added, and the reaction mixture was stored at $-20^\circ$C for 1 h, at which time it was filtered through a sintered glass frit. The resulting solid was washed with pentane three times, yielding the oxidative addition complex without any further purification.$^7$

Following the standard procedure, RockPhos (250 mg, 0.53 mmol, 1.10 eq.), 1-bromo-4-nbutylbenzene (565 mg, 2.65 mmol, 5.00 eq.) and (COD)Pd(CH$_2$TMS)$_2$ (205 mg, 0.53 mmol, 1.00 eq.) were combined to yield 4a as a yellow solid (320 mg, 76%). X-ray quality crystals of 4a were obtained by dissolving 4a in a minimal quantity of CH$_2$Cl$_2$, layering with pentane, and cooling the sample to $-20^\circ$C. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.26 (d, $J = 8.8$ Hz, 1 H), 7.11 (s, 2 H), 6.93 (d, $J = 7.4$ Hz, 2 H), 6.87 (d, $J = 7.8$ Hz, 1 H), 6.63 (d, $J = 7.9$ Hz, 2 H), 3.81 (s, 3 H), 3.07 (septet, $J = 6.8$ Hz, 1 H), 2.69 (septet, $J = 6.8$ Hz, 2 H), 2.45 (t, $J = 7.6$ Hz, 2 H), 1.66 (d, $J = 6.7$ Hz, 6 H), 1.55 – 1.47 (m, 2H), 1.41 (s, 9 H), 1.37 (d, $J = 6.8$ Hz, 6 H), 1.37 (s, 9 H), 1.32 – 1.25 (m, 2 H), 1.18 (s, 3 H), 0.93 (d, $J = 6.6$ Hz, 6 H), 0.89 (t, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$ 159.5, 157.8, 152.7, 148.5, 148.3, 139.8, 139.7, 136.7, 135.5, 133.0, 132.9, 129.8, 129.7, 126.2, 126.1, 126.0, 125.6, 122.7, 122.6, 110.2, 54.0, 41.6, 41.5, 34.9, 34.8, 34.2, 32.9, 32.9, 31.7, 27.3, 26.9, 24.9, 24.5, 22.7, 19.9, 14.2 (observed complexity is due to C–P splitting); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) $\delta$ 70.8.
Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 4b could not be obtained due to the small amount of it present at equilibrium. It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 8.91 ppm (dd, $J = 8.0, 2.0$ Hz, 1H), 7.38 (d, $J = Hz, 1H$), 7.31 (dd, $J = 7.6, 1.9$ Hz, 1H), 7.19 (dd, $J = 8.1, 1.7$ Hz, 1H), 5.81 (s, 1H), 3.82 (s, 3H), 2.60 (t, $J = 7.8$ Hz, 2H), 2.29 (s, 3H), 1.09 (d, $J = 6.9$ Hz, 3H), 0.71 (d, $J = 6.5$ Hz, 3H), 0.02 (d, $J = 7.0$ Hz, 3H) ppm.

4a (150 mg, 0.19 mmol, 1.00 eq.) was dissolved in DCM (5.0 mL) in an oven-dried vial. The vial was wrapped in aluminum foil, AgF (180 mg, 1.43 mmol, 7.50 equiv.) was added in one portion, and the mixture was rapidly stirred for 7 h while protected from light. Pentane (10 ml) was added and the mixture placed in a -20 °C freezer for 12 hours [this step precipitates unwanted black particles]. The mixture was filtered through a small (1 cm), tightly packed plug of celite and the solvent was removed under reduced pressure to yield a brown film. Pentane (5 mL) was added and the solvent removed under reduced pressure. This process was repeated two more times to afford 5 as a dark yellow solid (120 mg, 88%). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) $\delta$ 7.31 (d, $J = 7.4$ Hz, 1H), 7.14 (s, 2 H), 7.03 (dd, $J = 8.0, 1.6$ Hz, 2 H), 6.90 (d, $J = 8.6$ Hz, 1 H), 6.66 (d, $J = 6.2$ Hz, 2 H), 3.83 (s, 3 H), 2.94 (septet, $J = 7.3$ Hz, 1 H), 2.69 (septet, $J = 6.7$ Hz, 2 H), 2.44 (t, $J = 7.2$ Hz, 2 H), 1.74 (d, $J = 7.4$ Hz, 6 H), 1.54 – 1.24 (m, 13 H), 1.44 (s, 9 H), 1.41 (s, 9 H), 0.99 (d, $J = 6.4$ Hz, 6 H), 0.88 (t, $J = 6.5$ Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$ 159.0, 157.9, 152.8, 148.5 (b), 142.0 (b), 137.2, 135.6, 132.4, 132.3,
129.2, 127.0, 126.2, 124.5, 120.5, 110.4, 66.0, 40.7 (b), 35.0, 34.9, 34.3, 32.9, 32.8, 31.7, 28.8, 28.6, 27.1, 24.8, 24.2 (b), 22.7, 20.4, 15.5, 14.2, 14.1 (observed complexity is due to C=P splitting); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) $\delta$ 78.1 (d, $J = 163.1$ Hz); $^{19}$F NMR (282 MHz, CD$_2$Cl$_2$) $\delta$ -215.1 (d, $J = 165.3$ Hz).

Following the standard procedure, tBuBrettPhos (2) (500 mg, 1.03 mmol, 1.05 eq.), 1-bromo-4-nbutylbenzene (1.10 g, 5.16 mmol, 5.00 eq.), and (COD)Pd(CH$_2$TMS)$_2$ (400 mg, 1.03 mmol, 1.00 eq.) were combined to yield 7a as a bright yellow solid (490 mg, 61%). Clean $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 7a could not be obtained due to its isomerization to 7b in solution. It was detected by $^1$H NMR (400 MHz, CD$_2$Cl$_2$) signals at $\delta$ 7.04 (s, 2 H), 6.93 – 6.92 (m, 3 H), 6.87 (d, $J = 8.8$, 1 H), 6.61 (d, $J = 8.0$ Hz, 2 H), 3.78 (s, 3 H), 3.34 (s, 3 H), 3.01 (bs, 1 H), 2.62 – 2.52 (m, 2 H), 2.43 (at, $J = 7.7$ Hz, 2 H), 1.57 (d, $J = 6.7$ Hz, 6 H), 1.54 – 1.47 (m, 4 H), 1.38 (s, 9 H), 1.34 (s, 9 H), 1.33 (d, $J = 7.2$ Hz, 6 H), 0.88 (t, $J = 7.3$ Hz, 3 H), 0.82 (d, $J = 6.6$ Hz, 6 H), $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) $\delta$ 67.6 (bs). X-ray quality crystals of 7a were obtained by suspending 7a in pentane in a vial, adding CH$_2$Cl$_2$ dropwise until all of the solid dissolved, and then immediately putting the vial into a freezer at -20°C.

7a (490 mg, 0.61 mmol, 1.00 eq.) was dissolved in CH$_2$Cl$_2$ (10 mL) and allowed to stand for 12 hours, during which period a color change from yellow to dark red was observed. The solvent was removed under
reduced pressure, and the resulting dark-red solid was triturated with pentane (2 mL) and filtered. The solid was washed with pentane (2 x 5 mL) and dried under reduced pressure to afford 7b as a red solid (420 mg, 86%), which contained small amounts of 7a. Trituration with a minimal quantity of CH₂Cl₂ afforded 7b (purity > 95%) as a red crystalline solid. X-ray quality crystals of 7b were obtained by dissolving 7b in a minimal quantity of CH₂Cl₂, layering with pentane, and cooling to −20 °C. ¹H NMR (400 MHz, CD₂Cl₂) δ 8.60 (dd, J = 8.0, 1.7 Hz, 1 H), 7.30 (dd, J = 7.5, 1.9 Hz, 1 H), 7.19 (dd, J = 8.0, 2.0 Hz, 1 H), 7.10 (dd, J = 7.8, 2.0 Hz, 1 H), 7.05 (d, J = 9.0 Hz, 1 H), 6.93 (dd, J = 9.0, 2.4 Hz, 1 H), 5.79 (s, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.08 (d, J = 39.3 Hz, 1 H), 2.60 (t, J = 7.7 Hz, 2 H), 2.37 (septet, J = 6.8 Hz, 1 H), 1.91 (septet, J = 6.8 Hz, 1 H), 1.63 - 1.57 (m, 2 H), 1.52 (d, J = 15.0 Hz, 9 H), 1.41 (d, J = 14.8 Hz, 9 H), 1.36 - 1.30 (m, 3 H), 1.23 (d, J = 6.7 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 6 H), 1.07 (d, J = 6.9 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H), 0.73 (d, J = 6.5 Hz, 3 H), - 0.06 (d, J = 6.9 Hz, 3 H); ¹³C NMR (100 MHz, CD₂Cl₂) δ 174.9, 174.9, 155.2, 155.2, 151.7, 151.6, 142.2, 136.8, 136.6, 136.3, 136.3, 136.2, 136.0, 131.7, 129.0, 128.7, 127.8, 119.1, 118.9, 114.1, 110.5, 98.6, 68.3, 68.2, 55.1, 54.5, 52.2, 52.2, 40.1, 39.9, 39.4, 39.4, 35.5, 33.0, 32.8 (b), 32.5, 30.5, 30.5, 22.7, 22.6, 22.3, 21.4, 21.4, 20.2, 20.0, 19.9, 14.1 (observed complexity is due to C—P splitting); ³¹P NMR (121 MHz, CD₂Cl₂) δ 82.6.

Following the standard procedure, tBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-bromo-N,N-dimethylaniline (43.0 mg, 0.22 mmol, 1.05 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 12a (94 mg,
57%) as an orange solid. Clean $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 12a could not be obtained due to its very rapid isomerization to 12b in solution (3:1 mixture of 12b and 12a after 15 min). It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 6.96 (d, J = 9.2 Hz, 1H), 6.26 (d, J = 8.7 Hz, 2H), 3.14 (s, 3H) ppm. $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 69.7 ppm (bs). Anal. Calcd. for C$_{39}$H$_{59}$BrNO$_2$PPd: C, 59.20; H, 7.52. Found: C, 59.84; H, 7.60.

12b was allowed to stand for approximately 1 h in CD$_2$Cl$_2$, yielding 12b in greater than 98% purity. $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 8.45 (d, J = 6.8 Hz, 1H), 7.24 (dd, J = 8.6, 2 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.95 (dd, J = 9.2, 2.4 Hz, 1H), 6.76 (dd, J = 4.8, 2.4 Hz, 1H), 6.65 (dd, J = 8.0, 2.4 Hz, 1H), 5.77 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.0 (d, 1H), 2.94 (s, 6H), 2.38 (m, 1H), 1.98 (m, 1H), 1.55 (m, 1H), 1.53 (d, J = 16 Hz, 9H), 1.42 (d, J = 16 Hz, 9H), 1.24 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 0.04 (d, J = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ 176.6, 176.5, 155.7, 152.3, 152.2, 150.7, 137.5, 137.4, 137.3, 132.7, 126.8, 119.8, 119.6, 114.3, 113.4, 112.0, 110.8, 110.7, 98.5, 68.8, 68.7, 54.8, 52.2, 41.2, 40.4, 39.8, 39.7, 33.5, 33.4, 30.9, 27.7, 23.1, 23.0, 22.7, 21.9, 21.8, 20.7, 20.6, 20.5 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 81.0 ppm.
Following the standard procedure, tBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-bromoanisole (52.0 uL, 0.41 mmol, 2.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 13a (83.0 mg, 52%) as a tan solid. Clean ¹H, ¹³C, and ³¹P NMR spectra for 13a could not be obtained due to its very rapid isomerization to 13b in solution (1:1 mixture of 13a and 13b after 15 min). It was detected by ¹H NMR signals (400 MHz, THF-d₈) at δ 6.97 (d, J = 8.9 Hz, 1H), 6.83 (d, J = 8.2 Hz, 2H), 6.37 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.59 (s, 3H), 2.63 (p, J = 7.6 Hz, 2H), 1.58 (d, J = 7.7 Hz, 3H), 1.36 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H) ppm. ³¹P NMR (121 MHz, CD₂Cl₂): δ 70.0 ppm (bs).

13b was allowed to stand for approximately 3 h in CD₂Cl₂, yielding 13b in greater than 95% purity. ¹H NMR (400 MHz, CD₂Cl₂): δ 8.63 (dd, J = 8.7, 2.3 Hz, 1H), 7.29 (dd, J = 8.3, 2.3 Hz, 1H), 7.06 (d, J = 9.1 Hz, 1H), 6.90-6.95 (m, 2H), 6.82 (dd, J = 8.3, 2.8 Hz, 1H), 5.78 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.06 (d, J = 39.4 Hz, 1H), 2.38 (p, J = 6.9 Hz, 1H), 1.88-1.95 (m, 1H), 1.51 (d, J = 115.7 Hz, 9H), 1.40 (d, J = 14.8 Hz, 9H), 1.34-1.37 (m, 1H), 1.23 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H), -0.01 (d, J = 7.0 Hz, 3H) ppm; ¹³C NMR (100 MHz, CD₂Cl₂): δ 175.2, 175.1, 159.3, 155.3, 155.2, 151.8, 151.7, 136.9, 136.7, 136.4, 136.3, 132.9, 132.7, 132.1, 130.9, 129.0, 119.3, 119.1, 114.0, 113.7, 113.6, 110.5, 110.4, 98.6, 98.6, 68.4, 68.4, 68.3, 65.6, 55.6, 55.1, 54.4, 51.8, 51.7, 40.1, 40.0, 39.5, 39.4, 34.0, 34.0, 33.0, 32.8, 32.7, 32.6, 31.6, 30.5, 30.5, 27.3, 24.6, 22.7, 22.6,
22.6, 22.4, 22.3, 21.4, 21.3, 20.3, 20.2, 20.1, 14.2 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 81.2 ppm.

Following the standard procedure, $t$BuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), bromobenzene (109 µL, 1.04 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 14a (102 mg, 66%) as a yellow solid. Clean $^1$H, $^31$P, and $^{13}$C NMR spectra for 14a could not be obtained due to its isomerization to 14b in solution (9% isomerized to 14b after 15 min). $^1$H NMR (300 MHz, CD$_2$Cl$_2$): $\delta$ 7.11 (s, 2H), 7.06-7.16 (m, 2H), 6.91-7.03 (m, 2H), 6.82 (pt, $J$ = 7.8 Hz, 2H), 6.70-6.75 (m, 1H), 3.85 (s, 3H), 3.94 (s, 3H), 3.09 (p, $J$ = 6.9 Hz, 1H), 2.65 (p, $J$ = 6.6 Hz, 2H), 1.65 (d, $J$ = 6.6 Hz, 6H), 1.44 (d, $J$ = 15 Hz, 18H), 1.41 (d, $J$ = 6.9 Hz, 6H), 0.88 (d, $J$ = 6.6 Hz, 6H) ppm; $^{31}$P (121 MHz, CD$_2$Cl$_2$): $\delta$ 70.1 (bs) ppm. Anal. Calcd. for C$_{37}$H$_{54}$BrO$_2$PPd: C, 59.40; H, 7.28. Found: C, 59.62; H, 7.30. Crystals suitable for X-ray analysis were obtained by suspending 14a in a small amount of ether in a vial and then adding CH$_2$Cl$_2$ dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 14b could not be obtained due to large amount of 14a still present at equilibrium (4:1 mixture of 14b and 14a). It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 8.93 (d, $J$ = 7.8 Hz, 1H), 7.42 (d, $J$ = 7.2 Hz, 1H), 7.30-7.33 (m, 1H), 7.19-7.27 (m, 2H), 7.17 (d, $J$ = 9.3 Hz, 1H).
Hz, 1H), 5.79 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.15 (d, J = 40.1 Hz, 1H), 2.37-2.43 (m, 1H), 1.86-1.94 (m, 2H), 1.54 (d, J = 15.5 Hz, 9H), 1.43 (d, J = 14.6 Hz, 9H), 1.24 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 6H), 1.06 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H), -0.04 (d, J = 7.0 Hz, 3H) ppm. $^{31}$P NMR (121 MHz, CD$_{2}$Cl$_{2}$): $\delta$ 81.7 ppm.

After 6 h in solution, a roughly 4:1 mixture of 20b and 20a was obtained. $^{13}$C NMR (100 MHz, CD$_{2}$Cl$_{2}$): $\delta$ 174.5, 174.5, 155.3, 151.8, 151.7, 140.4, 139.2, 139.1, 136.9, 136.7, 136.1, 135.9, 132.1, 131.9, 129.3, 128.7, 128.0, 127.5, 127.4, 125.7, 119.3, 119.1, 114.1, 113.7, 110.5, 110.5, 99.0, 99.0, 68.3, 68.2, 55.1, 54.7, 54.5, 54.4, 52.7, 52.6, 41.4, 40.2, 40.0, 39.6, 39.5, 34.8, 34.1, 34.1, 33.1, 33.0, 32.9, 32.7, 32.6, 31.6, 30.6, 30.5, 25.8, 24.8, 24.7, 22.7, 22.7, 22.6, 22.4, 22.3, 22.3, 21.4, 21.4, 20.3, 20.1, 20.0 ppm (observed complexity is due to C-P coupling and the presence of two species at equilibrium).

Following the standard procedure, tBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-bromobiphenyl (96.5 mg, 0.41 mmol, 2.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 15a (124 mg, 73%) as a yellow solid. Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 15a could not be obtained due to its isomerization to 15b in solution (8% isomerized to 15b after 15 min). $^1$H NMR (400 MHz, CD$_{2}$Cl$_{2}$): $\delta$ 7.56 (d, J = 7.4 Hz, 2H), 7.37 (pt, J = 7.5 Hz, 2H), 7.22-7.26 (m, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.06-7.12 (m, 4H), 6.95 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 3.79 (s, 3H), 3.35 (s, 3H), 3.06 (m, 1H), 2.63 (p, J = 6.5 Hz, 2H), 1.64 (d, J = 6.5 Hz,
6H), 1.36-1.48 (m, 24H), 0.86 (d, J = 6.3 Hz, 6H) ppm; \(^{31}\)P NMR (161 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 70.6 ppm.

Clean \(^1\)H, \(^{31}\)P, and \(^{13}\)C NMR spectra for 15b could not be obtained due to large amount of 15a still present at equilibrium (3:1 mixture of 15b and 15a). It was detected by \(^1\)H NMR signals (400 MHz, THF-d\(_8\)) at \(\delta\) 9.03 (ddd, J = 8.7, 5.7, 2.4 Hz, 1H), 7.44 (ddd, J = 8.3, 5.3, 2.5 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 7.04-7.08 (m, 2H), 5.80 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.18 (d, J = 39.2 Hz, 1H), 2.42-2.45 (m, 1H), 1.83-1.91 (m, 2H), 1.54 (d, J = 15.8 Hz, 9H), 1.42 (d, J = 15.3 Hz, 9H), 1.23 (d, J = 7.3 Hz, 3H), 1.15-1.19 (m, 6H), 1.07 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H), 0.00 (d, J = 6.4 Hz, 3H) ppm. \(^{31}\)P NMR (161 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 81.7 ppm.

After 6 h in solution, an approximately 3:1 mixture of 15b and 15a was obtained. \(^{13}\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 174.3, 174.2, 155.2, 155.2, 154.3, 154.1, 152.2, 152.1, 151.8, 151.7, 141.5, 140.9, 140.5, 140.0, 138.4, 138.3, 136.8, 136.6, 136.0, 135.9, 134.9, 132.4, 132.3, 129.3, 129.0, 128.9, 127.4, 127.2, 126.8, 126.7, 126.4, 123.8, 119.2, 119.0, 117.4, 117.3, 114.1, 113.8, 110.9, 110.6, 110.5, 99.0, 99.0, 68.3, 68.2, 55.1, 54.7, 54.5, 54.2, 52.2, 52.1, 41.5, 41.3, 40.2, 40.0, 39.5, 39.5, 34.8, 34.1, 34.1, 33.1, 33.0, 33.0, 32.8, 32.7, 32.6, 31.6, 30.6, 30.5, 25.8, 24.8, 24.7, 22.7, 22.6, 22.4, 22.3, 21.4, 21.4, 20.3, 20.2, 14.2 ppm (observed complexity is due to C-P coupling and the presence of two species at equilibrium).
Following the standard procedure, tBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 1-bromo-4-fluorobenzene (82.4 μL, 0.75 mmol, 3.60 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 16a (74 mg, 47%) as a pale yellow solid. Clean ¹H, ³¹P, and ¹³C NMR spectra for 16a could not be obtained due to its rapid isomerization to 16b in solution (9% isomerized to 16b after 15 min). ¹H NMR (300 MHz, CD₂Cl₂): δ 6.87-7.13 (m, 6H), 6.61 (pt, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.36 (s, 3H), 2.97-3.04 (m, 1H), 2.59 (p, J = 6.7 Hz, 2H), 1.58 (d, J = 6.7 Hz, 6H), 1.32-1.46 (m, 24H), 0.83 (d, J = 6.4 Hz, 6H) ppm; ³¹P NMR (121 MHz, CD₂Cl₂): δ 70.5 ppm; ¹⁹F NMR (282 MHz, CD₂Cl₂): δ −126.4 ppm. Crystals suitable for X-ray analysis were obtained by suspending 16a in a small amount of ether in a vial and then adding CH₂Cl₂ dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.

Clean ¹H, ³¹P, and ¹³C NMR spectra for 16b could not be obtained due to large amount of 16a still present at equilibrium (4:1 mixture of 16b and 16a). It was detected by ¹H NMR signals (400 MHz, THF-d₈) at δ 9.03 (dd, J = 8.2, 2.0 Hz, 1H), 7.67 (d, J = 7.3 Hz, 3H), 7.58 (dd, J = 8.1, 2.3 Hz, 1H), 7.37 (pt, J = 7.3 Hz, 2H), 7.18 (d, J = 9.0 Hz, 1H), 7.06 (dd, J = 8.9, 3.0 Hz, 1H), 5.82 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.21 (d, J = 40.0 Hz, 1H), 2.41-2.48 (m, 2H), 1.93-2.01 (m, 1H), 1.55 (d, J = 15.4 Hz, 9H), 1.45 (d, J = 14.9 Hz, 9H), 1.25 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 6.8 Hz, 6H), 1.10 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H), 0.05 (d, J =
6.7 Hz, 3H) ppm. $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 81.8 ppm; $^{19}$F NMR (282 MHz, CD$_2$Cl$_2$): $\delta$ -116.9 ppm.

After 8 h in solution, a roughly 4:1 mixture of 16b and 16a was obtained. $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 173.7, 173.6, 163.3, 161.4, 155.0, 154.2, 151.5, 151.4, 139.9, 136.4, 136.3, 135.4, 135.3, 134.6, 133.6, 132.9, 132.8, 129.2, 118.9, 118.8, 116.7, 115.6, 115.4, 114.4, 114.2, 114.0, 110.5, 110.4, 68.1, 68.0, 55.0, 54.4, 51.5, 51.4, 41.2, 41.1, 39.9, 39.8, 39.3, 39.3, 34.6, 33.8, 33.8, 32.7, 32.7, 32.4, 32.4, 31.4, 30.3, 30.3, 25.5, 24.4, 22.4, 22.3, 22.2, 21.2, 21.2, 20.0, 20.0 ppm (observed complexity is due to C-P and C-F coupling and the presence of two species at equilibrium).

Following the standard procedure, tBuBrettPhos (50.0 mg, 0.104 mmol, 1.00 eq.), 1-bromo-4-chlorobenzene (49.8 mg, 0.26 mmol, 2.50 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (40.0 mg, 0.10 mmol, 1.00 eq.) were combined to yield 17a (124 mg, 73%) as a golden-yellow solid. Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 17a could not be obtained due to its isomerization to 17b in solution (4% isomerized to 17b after 15 min). $^1$H (400 MHz, CD$_2$Cl$_2$): $\delta$ 7.04 (s, 2H), 7.00-7.06 (m, 2H), 6.93 (dd, $J = 8.9$, 2.4 Hz, 1H), 6.87 (d, $J = 8.9$ Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 2H), 3.79 (s, 3H), 3.32 (s, 3H), 3.03 (p, $J = 6.8$ Hz, 1H), 2.58 (p, $J = 6.7$ Hz, 2H), 1.57 (d, $J = 6.8$ Hz, 6H), 1.38 (d, $J = 14.9$ Hz, 18H), 1.35 (d, $J = 7.0$ Hz, 6H), 0.81 (d, $J = 6.6$ Hz, 6H) ppm; $^{31}$P (163 MHz, CD$_2$Cl$_2$): $\delta$ 71.1 ppm.
Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 17b could not be obtained due to large amount of 17a still present at equilibrium (1.5:1 mixture of 17b and 17a). It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 9.04 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.45 (dd, $J$ = 4.1, 2.3 Hz, 1H), 7.34 (dd, $J$ = 8.5, 2.4 Hz, 1H), 7.28 (dd, $J$ = 8.1, 2.3 Hz, 1H), 7.18 (d, $J$ = 9.1 Hz, 1H), 5.80 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.19 (d, $J$ = 39.7 Hz, 1H), 1.82-1.89 (m, 1H), 1.23 (d, $J$ = 6.7 Hz, 3H), 1.16 (pt, $J$ = 6.6 Hz, 6H), 1.06 (d, $J$ = 6.9 Hz, 3H), 0.76 (d, $J$ = 6.5 Hz, 3H), 0.02 (d, $J$ = 6.9 Hz, 3H) ppm. $^{31}$P (163 MHz, CD$_2$Cl$_2$): $\delta$ 82.0 ppm.

After 7 h in solution, a 1.5:1 mixture of 17b and 17a was obtained. $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ 173.5, 173.4, 155.3, 155.3, 154.7, 154.3, 152.3, 152.1, 151.8, 151.7, 141.2, 137.9, 137.7, 136.6, 136.5, 135.4, 135.3, 133.6, 133.2, 133.1, 129.7, 129.0, 128.1, 125.2, 119.2, 119.0, 116.7, 114.2, 113.8, 110.7, 110.6, 100.4, 99.5, 99.4, 68.3, 68.2, 65.2, 57.0, 55.1, 54.7, 54.5, 54.2, 51.9, 51.8, 41.5, 41.4, 40.2, 40.1, 39.7, 39.6, 34.9, 34.1, 34.1, 33.0, 33.0, 32.8, 32.7, 31.7, 30.6, 30.5, 25.8, 24.8, 24.6, 22.6, 22.5, 22.4, 22.4, 21.4, 21.4, 20.4, 20.4, 20.3 ppm (observed complexity is due to C-P coupling and the presence of two species at equilibrium).

Following the standard procedure, tBuBrettPhos (120 mg, 0.25 mmol, 1.00 eq.), 4-bromobenzaldehyde (48.0 mg, 0.26 mmol, 1.05 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (96.0 mg, 0.25 mmol, 1.00 eq.) were combined to yield 18a (130 mg, 67%) as a yellow solid. $^1$H and $^{31}$P NMR are contaminated with a trace (<5%) of 18b.
$^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 9.76 (s, 1H), 7.39 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.05 (s, 2H), 6.94 (dd, J = 8.9, 2.6 Hz, 1H), 6.87 (d, J = 8.9 Hz, 1H), 3.79 (s, 3H), 3.32 (s, 3H), 3.03 (p, J = 6.9 Hz, 1H), 2.59 (p, J = 6.8 Hz, 2H), 1.59 (d, J = 6.8 Hz, 6H), 1.40 (s, 9H), 1.37 (s, 9H), 1.35 (d, J = 7.0 Hz, 6H), 0.82 (d, J = 6.7 Hz, 6H) ppm; $^{13}$C (100 MHz, CD$_2$Cl$_2$): $\delta$ 192.9, 158.5, 155.1, 154.3, 154.3, 152.2, 152.0, 151.7, 151.6, 141.1, 138.2, 138.0, 135.0, 132.9, 132.8, 132.4, 131.7, 128.8, 127.6, 127.4, 125.3, 125.2, 120.5, 119.0, 116.2, 116.2, 114.2, 113.9, 111.0, 111.0, 110.8, 100.0, 68.1, 55.1, 54.7, 54.5, 54.1, 41.6, 41.5, 40.2, 40.1, 39.7, 39.6, 34.8, 34.5, 34.2, 33.0, 32.7, 32.6, 31.7, 30.5, 30.5, 27.3, 25.8, 24.9, 24.6, 22.7, 22.5, 22.4, 21.4, 21.3, 20.4, 20.3, 20.2, 14.2 ppm (observed complexity is due to C-P coupling and the presence of a trace of 18b); $^{31}$P (121 MHz, CD$_2$Cl$_2$): $\delta$ 72.0 ppm. Anal. Calcd. for C$_{38}$H$_{54}$BrO$_3$PPd: C, 58.81; H, 7.01. Found: C, 58.36; H, 7.09.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 18b could not be obtained due to the small amount of it present at equilibrium (4:1 mixture of 18a and 18b). It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 9.97 (s, 1H), 9.29 (dd, J = 8.1, 1.5 Hz, 1H), 7.88 (dd, J = 8.0, 1.6 Hz, 1H), 7.82 (dd, J = 7.8, 1.8 Hz, 1H), 7.67 (d, J = 6.2 Hz, 1H), 7.19 (d, J = 9.1 Hz, 1H), 5.84 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.32 (d, J = 39.4 Hz, 1H), 1.57 (s, 9H), 1.53 (s, 9H), 1.25 (d, J = 6.7 Hz, 3H), 1.17 (pt, J = 8.4 Hz, 6H), 0.77 (d, J = 6.5 Hz, 3H), 0.03 (d, J = 7.0 Hz, 3H) ppm. $^{31}$P (121 MHz, CD$_2$Cl$_2$): $\delta$ 82.5 ppm.
19a was prepared according to the literature procedure.\textsuperscript{20} Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 19b could not be obtained due to the small amount of it present at equilibrium (8%). It was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 9.31 (d, $J = 8.0$ Hz, 1H), 7.65-7.68 (m, 3H), 7.19 (d, $J = 9.1$ Hz, 1H), 2.44 (s, 3H), 1.24 (d, $J = 7.0$ Hz, 6H), 1.16 (d, $J = 6.8$ Hz, 6H), 1.07 (d, $J = 6.9$ Hz, 6H), -0.03 (d, $J = 6.9$ Hz, 3H) ppm.

Following the standard procedure, tBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-nbutyl-1-chlorobenzene (61.7 $\mu$L, 0.41 mmol, 2.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 20a (114 mg, 73%) as an pale yellow solid. Clean $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 20a could not be obtained due to its rapid isomerization to 20b in solution (15% isomerized after 15 min). $^1$H (400 MHz, THF-d$_8$): $\delta$ 6.97-7.08 (m, 4H), 6.89 (d, $J = 8.2$ Hz, 2H), 6.52 (d, $J = 8.0$ Hz, 2H), 3.81 (s, 3H), 3.35 (s, 3H), 2.95 (p, $J = Hz$, 1H), 2.57-2.66 (m, 2H), 2.39 (t, $J = 7.7$ Hz, 2H), 1.59 (d, $J = 6.8$ Hz, 6H), 1.40 (d, $J = 14.6$ Hz, 18H), 1.34 (d, $J = 6.9$ Hz, 6H), 1.24-1.32 (m, 2H), 1.12-1.16 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 6H) ppm, $^{31}$P NMR (121 MHz, THF-d$_8$): $\delta$ 70.5 ppm.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 20b could not be obtained due to the large amount of 20a still present at equilibrium (2:1 mixture of 20b and 20a). It was
detected by $^1$H NMR signals (400 MHz, THF-$d_8$) at $\delta$ 8.81 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.30 (d, $J = 6.0$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.15 (d, $J = 9.1$ Hz, 1H), 7.07 (d, $J = 7.4$ Hz, 1H), 5.81 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.20 (d, $J = 40.1$ Hz, 1H), 2.59 (t, $J = 6.4$ Hz, 2H), 1.96-2.01 (m, 1H), 1.52 (d, $J = 15.9$ Hz, 9H), 1.42 (d, $J = 14.2$ Hz, 9H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.14 (pt, $J = 6.8$ Hz, 6H), 1.05 (d, $J = 7.4$ Hz, 3H), 0.92 (t, $J = 9.1$ Hz, 3H), 0.77 (d, $J = 6.2$ Hz, 3H), -0.04 (d, $J = 6.8$ Hz, 3H) ppm. $^{31}$P NMR (121 MHz, THF-$d_8$): $\delta$ 79.6 ppm. Unstable in CD$_2$Cl$_2$. Crystals of 20b suitable for X-ray analysis were obtained by suspending 20a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.

After 5 h in solution, an approximately 2:1 mixture of 20b and 20a was obtained. $^{13}$C NMR (100 MHz, THF-$d_8$): $\delta$ 172.3, 172.2, 157.5, 156.0, 155.9, 155.2, 153.5, 153.1, 152.9, 152.6, 152.4, 142.4, 139.6, 139.3, 139.1, 137.6, 137.5, 137.3, 136.3, 135.5, 135.0, 134.8, 132.8, 132.2, 129.6, 129.5, 128.9, 128.6, 128.0, 126.1, 125.3, 120.1, 119.9, 118.7, 114.8, 114.4, 111.5, 111.5, 111.3, 111.3, 98.8, 98.8, 80.4, 68.0, 67.8, 67.6, 66.6, 66.5, 55.2, 54.8, 54.6, 54.2, 52.9, 52.9, 41.3, 41.1, 40.6, 40.5, 39.7, 39.6, 36.2, 35.6, 35.5, 34.9, 34.7, 34.1, 34.1, 33.6, 33.6, 33.0, 33.0, 32.9, 32.0, 30.8, 30.8, 27.8, 26.0, 25.9, 25.7, 25.5, 25.2, 25.0, 23.3, 23.2, 23.1, 22.8, 22.8, 22.7, 22.7, 22.6, 22.6, 21.9, 21.8, 20.7, 20.4, 20.4, 14.4, 14.3 ppm (observed complexity is due to C-P coupling and the presence of two species at equilibrium).
Following the standard procedure, nBuBrettPhos (150 mg, 0.31 mmol, 1.00 eq.), 4-nbutyl-1-iodobenzene (165 µL, 0.93 mmol, 3.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (120 mg, 0.21 mmol, 1.00 eq.) were combined to yield 21a (139 mg, 53%) as a golden-brown solid. This compound proved unstable in every solvent examined, generating a new species by ³¹P NMR (121 MHz, THF-d₈) at δ 124.5 ppm after only 15 min in solution. For this reason, a ¹³C spectrum was not obtained. ¹H NMR (400 MHz, THF-d₈): δ 7.07 (s, 2H), 7.00-7.06 (m, 1H), 6.94-6.97 (m, 1H), 6.89 (d, J = 7.9 Hz, 2H), 6.49 (d, J = 8.0 Hz, 2H), 3.80 (s, 3H), 3.32 (s, 3H), 3.08 (m, 1H), 2.64 (p, J = 6.8 Hz, 2H), 2.40 (t, J = 7.7 Hz, 2H), 1.75-1.81 (m, 2H), 1.61 (d, J = 6.8 Hz, 6H), 1.15-1.48 (m, 26H), 0.88 (t, J = 7.2 Hz, 3H), 0.80 (d, J = 6.6 Hz, 6H) ppm; ³¹P NMR (121 MHz, THF-d₈): δ 62.9 ppm. Crystals of 21a suitable for X-ray analysis were obtained by suspending 21a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.

Clean ¹H, ¹³C, and ³¹P NMR spectra for 21b could not obtained due to the decomposition of 21a in solution. It was detected by ¹H NMR (400 MHz, THF-d₈) signals at δ 8.80 (d, J = 7.3 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H) ppm. ³¹P NMR (121 MHz, THF-d₈): δ 84.3 ppm.
Following the standard procedure, nBuBrettPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-nbutylphenyl triflate (175 mg, 0.62 mmol, 3.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 22a (66 mg, 37%) as a light orange solid. $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 7.29 (d, J = 8.0 Hz, 1H), 7.16-7.20 (m, 3H), 7.01-7.05 (m, 2H), 6.79 (d, J = 6.8 Hz, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 2.58 (p, J = 6.6 Hz, 2H), 2.49 (t, J = 7.7 Hz, 2H), 2.37 (p, J = 5.5 Hz, 1H), 1.54 (d, J = 7.3 Hz, 6H), 1.47-1.55 (m, 2H), 1.35 (d, J = 17.2 Hz, 18H), 1.24-1.33 (m, 2H), 1.15 (d, J = 6.6 Hz, 6H), 0.90 (t, J = 7.4 Hz, 3H), 0.84 (d, J = 6.9 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 154.1, 152.4, 150.2, 147.9, 140.6, 139.0, 137.5, 135.8, 130.5, 128.4, 118.3, 115.6, 115.5, 55.1, 54.8, 41.3, 41.2, 34.9, 33.9, 33.4, 31.4, 31.3, 27.0, 25.2, 23.2, 22.3, 21.9, 13.9 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, C$_6$D$_6$): $\delta$ 111.9 ppm; $^{19}$F NMR (282 MHz, C$_6$D$_6$): $\delta$ –77.4 ppm.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 21b could not be obtained due to the small amount of it present at equilibrium (<5%). It was detected by $^1$H NMR signals (400 MHz, C$_6$D$_6$) at $\delta$ 8.70 ppm (d, J = 8.5 Hz, 1H), 6.56 (d, J = 10.0 Hz, 1H), 6.37 (dd, J = 9.4, 2.4 Hz, 1H), 6.11 (s, 1H), 3.16 (d, J = 51.8 Hz, 1H), 0.26 (d, J = 6.8 Hz, 3H) ppm.
Following the standard procedure, tBuBrettphos (100 mg, 0.21 mmol, 1.00 eq.), phenyl triflate (101 μL, 0.62 mmol, 3.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 22a-Ph (108 mg, 64%) as a bright yellow solid. 'H NMR (400 MHz, CD₂Cl₂): δ 7.30 (d, J = 9.0 Hz, 1H), 7.20 (s, 2H), 7.15-7.21 (m, 3H), 7.00-7.04 (m, 1H), 6.93-6.97 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.58 (p, J = 6.6 Hz, 2H), 2.36 (p, J = 6.8 Hz, 1H), 1.51 (d, J = 6.6 Hz, 6H), 1.35 (d, J = 17.3 Hz, 18H), 1.15 (d, J = 6.6 Hz, 6H), 0.86 (d, J = 6.9 Hz, 6H) ppm; ¹³C NMR (100 MHz, CD₂Cl₂): δ 154.6, 152.9, 152.8, 150.6, 147.7, 147.7, 139.7, 139.6, 139.4, 131.8, 131.7, 129.5, 129.2, 128.5, 128.5, 126.4, 117.6, 116.6, 115.6, 114.1, 114.1, 55.4, 55.1, 42.1, 42.0, 33.9, 31.8, 31.7, 27.3, 23.5, 23.5, 22.1 ppm; ³¹P NMR (121 MHz, CD₂Cl₂): δ 111.9 ppm; ¹⁹F NMR (282 MHz, CD₂Cl₂): δ -79.2 ppm. Crystals of 22a-Ph suitable for X-ray analysis were obtained by suspending 22a-Ph in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. Hexanes was then layered on top, and the vial was allowed to stand at –20 °C.

23 was prepared according to the literature procedure.¹⁸a

Following the standard procedure using pentane instead of cyclohexane, AdBrettPhos (40.0 mg, 0.06 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (55.0 μL, 0.31 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (24.0 mg, 0.06 mmol, 1.00 eq.) were combined to yield 24a (22 mg, 37%) as a bright yellow solid. Clean 'H, ¹³C,
and $^{31}\text{P}$ NMR spectra for 24a could not be obtained due to its rapid isomerization to 24b in solution (20% isomerized after 15 min). It was detected by $^1\text{H}$ NMR (400 MHz, THF-d$_8$) signals at $\delta$ 7.05 (s, 2H), 7.02-7.06 (m, 1H), 6.94-6.99 (m, 3H), 6.54 (d, $J = 7.8$ Hz, 2H), 3.85 (s, 3H), 3.33 (s, 3H), 2.61 (p, $J = 6.9$ Hz, 1H), 2.38-2.49 (m, 4H), 2.26-2.37 (m, 6H), 2.17-2.26 (m, 6H), 1.24-1.82 (m, 31H), 0.88 (d, $J = 7.4$ Hz, 6H), 0.82 (d, $J = 6.6$ Hz, 6H) ppm; $^{31}\text{P}$ NMR (121 MHz, THF-d$_8$): $\delta$ 65.8 ppm.

**24b** was allowed to stand in THF-d$_8$ for 20 h, yielding a 9:1 mixture of 24b and 24a. Spectra for 24b are contaminated with ~10% of 24a. $^1\text{H}$ NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 8.47 (d, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 7.0$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 9.0$ Hz, 1H), 6.94 (dd, $J = 9.0$, 2.0 Hz, 1H), 5.82 (s, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.44 (bm, 3H), 3.08 (d, $J = 37.0$ Hz, 1H), 2.57-2.59 (m, 2H), 1.86-2.48 (m, 18H), 1.78 (m, 6H), 1.45-1.71 (m, 11H), 1.25-1.35 (m, 6H), 1.18 (d, $J = 7.0$ Hz, 2H), 1.15 (d, $J = 6.5$ Hz, 2H), 1.08 (d, $J = 7.0$ Hz, 2H), 0.88 (t, $J = 7.5$ Hz, 3H), 0.73 (d, $J = 6.5$ Hz, 2H), -0.11 (d, $J = 6.5$ Hz, 3H) ppm; $^{31}\text{P}$ NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 84.4 ppm.

After 5 h in solution, an approximately 9:1 mixture of 24b and 24a was obtained. $^{13}\text{C}$ NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 174.5, 174.4, 155.2, 151.7, 151.7, 142.2, 137.5, 137.4, 136.4, 136.3, 136.0, 135.9, 131.6, 131.6, 129.3, 128.6, 127.2, 117.7, 117.6, 113.6, 110.0, 110.0, 99.2, 67.5, 67.4, 55.0, 54.4, 51.9, 51.9, 45.0, 44.9, 44.9, 44.8, 40.3, 36.9, 36.8, 36.5, 35.4, 34.1, 34.0, 33.9, 33.2, 32.8, 32.8, 31.9, 30.2, 30.1, 29.8, 29.5, 29.4, 29.1, 29.4,
Following the standard procedure using pentane instead of cyclohexane, AdRockPhos (27.5 mg, 0.044 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (24.0 µL, 0.132 mmol, 3.00 eq.) and CODPd(CH₂TMS)₂ (17.1 mg, 0.044 mmol, 1.00 eq.) were combined to yield 25a (31.6 mg, 76%) as a yellow solid. ¹H, ¹³C, and ³¹P NMR spectra of 25a are contaminated with ~6% of the corresponding rearranged complex, detected by ³¹P NMR at δ 78.2 ppm. ¹H NMR (500 MHz, CD₂Cl₂): δ 7.24 (d, J = 9 Hz, 1H), 7.09 (s, 2H), 7.00 (d, J = 8 Hz, 2H), 6.87 (d, J = 9 Hz, 1H), 6.64 (d, J = 8 Hz, 2H), 3.84 (s, 3H), 3.00-3.08 (m, 1H), 2.67 (septet, J = 7 Hz, 2H), 2.44 (t, J = 8 Hz, 2H), 2.26 (bs, 6H), 2.16 (bs, 6H), 1.61-1.76 (m, 23H), 1.47 (p, J = 8 Hz, 2H), 1.24-1.37 (m, 9H), 1.17 (s, 3H), 0.86-0.93 (m, 9H); ¹³C NMR (125 MHz, CD₂Cl₂): δ 159.5, 159.5, 153.0, 139.8, 139.8, 135.2, 132.9, 132.9, 126.3, 125.7, 110.0, 47.7, 47.7, 41.7, 36.7, 34.8, 34.5, 344, 31.6, 30.1, 30.0, 27.4, 24.9, 24.7, 22.7, 22.6, 20.3, 14.2, 14.1 ppm; ³¹P NMR (202 MHz, CD₂Cl₂): δ 67.8 ppm. Anal. Calcd. for C₅₃H₇₄BrOPp: C, 67.40; H, 7.90; found: C, 66.00, H, 7.96. Crystals of 25a suitable for X-ray analysis were obtained by suspending 25a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.
Following the standard procedure using pentane instead of cyclohexane, tBuXPhos (200 mg, 0.47 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (166 μL, 0.94 mmol, 2.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (183 mg, 0.47 mmol, 1.00 eq.) were combined to yield 26a (270 mg, 77%) as a bright yellow solid. Clean ¹H, ¹³C, and ³¹P NMR spectra for 26a could not be obtained due to its rapid isomerization to 26b (12% isomerized to 26b after 15 min). ¹H NMR (400 MHz, CD₂Cl₂): δ 7.97-8.02 (m, 1H), 7.37-7.40 (m, 2H), 7.09 (s, 2H), 6.94 (dd, J = 8.2, 1.8 Hz, 2H), 6.74-6.78 (m, 1H), 6.67 (d, J = 8.0 Hz, 2H), 3.06 (p, J = 6.9 Hz, 1H), 2.50-2.61 (m, 2H), 2.45 (t, J = 7.8 Hz, 2H), 1.57 (d, J = 6.8 Hz, 6H), 1.34-1.39 (d + d overlap, 24H), 0.89 (d, J = 6.9 Hz, 6H) ppm; ³¹P NMR (121 MHz, CD₂Cl₂): δ 49.8 ppm. Anal. Calcd. for C₃₀H₅₈BrPd: C, 62.94; H, 7.86. Found: C, 62.71; H, 7.65.

After 1 h in solution, an approximately 4:1 mixture of 26a and 26b was obtained. ¹H NMR (400 MHz, THF-d₈) signals at δ 8.61 (d, J = 8.4 Hz, 1H), 7.88-7.92 (m, 2H), 5.81 (s, 1H), 3.35 (d, J = 37.0 Hz, 1H), 1.98 (p, J = 5.2 Hz, 1H), 1.12 (d, J = 7.1 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H), -0.04 (bs, 3H) ppm. ³¹P NMR (121 MHz, CD₂Cl₂): δ 68.3 ppm.

After 1 h in solution, an approximately 4:1 mixture of 26a and 26b was obtained. ¹³C NMR (100 MHz, CD₂Cl₂): δ 177.5, 156.9, 151.9, 147.7, 147.5, 142.6, 138.7, 138.7, 138.7,
Following the standard procedure, di-tert-butyl-(2',4',6'-triisopropyl-3-methoxy-[1,1'-biphenyl]-2-yl)phosphine (75.0 mg, 0.17 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (146 μL, 0.83 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)$_₂$ (64.2 mg, 0.17 mmol, 1.00 eq.) were combined to yield 27b (74.0 mg, 58%) as a dark red solid. $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 27b are contaminated with 9% of 27a. $^1$H NMR (400 MHz, THF-d₈): δ 8.71 (d, $J$ = 7.9 Hz, 1H), 7.45 (pt, $J$ = 8.3 Hz, 1H), 7.31 (d, $J$ = 7.4 Hz, 1H), 7.20 (d, $J$ = 8.0 Hz, 1H), 7.07-7.12 (m, 2H), 6.96-6.99 (m, 1H), 5.78 (s, 1H), 3.89 (s, 3H), 3.24 (d, $J$ = 38.3 Hz, 1H), 3.06-3.10 (m, 1H), 2.59 (t, $J$ = 7.8 Hz, 2H), 2.67-2.38 (m, 1H), 1.89-1.96 (m, 1H), 1.56 (d, $J$ = 15.5 Hz, 9H), 1.48-1.61 (m, 2H), 1.40 (d, $J$ = 14.7 Hz, 9H), 1.30-1.44 (m, 2H), 1.24 (d, $J$ = 6.7 Hz, 3H), 1.19 (d, $J$ = 6.9 Hz, 3H), 1.12 (d, $J$ = 6.7 Hz, 3H), 1.06 (d, $J$ = 6.9 Hz, 3H), 0.92 (t, $J$ = 7.3 Hz, 3H), 0.71 (d, $J$ = 6.4 Hz, 3H), 0.01 (d, $J$ = 2.6 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, THF-d₈): δ 174.5, 174.4, 162.3, 162.3, 151.4, 149.7, 149.6, 142.8, 140.5, 137.4, 137.3, 135.3, 134.1, 134.0, 132.9, 132.3, 132.1, 129.7, 128.4, 126.2, 126.2, 126.0, 126.0, 118.6, 118.5, 112.1, 112.1, 110.6, 100.4, 68.1, 67.2, 67.1, 54.9, 54.6, 52.7, 52.6, 41.4,
41.3, 40.8, 40.7, 39.7, 39.6, 36.4, 35.6, 35.5, 35.1, 34.9, 34.8, 34.8, 33.2, 32.9, 32.9, 32.9, 32.9, 32.2, 32.2, 32.0, 28.8, 28.0, 26.0, 25.3, 24.8, 24.8, 23.5, 23.4, 23.4, 23.3, 23.0, 22.9, 22.1, 22.1, 21.8, 21.7, 20.6, 14.5 ppm (observed complexity is due to C-P coupling and the presence of ~9% of 27a); $^{31}$P NMR (121 MHz, THF-d$_8$): $\delta$ 83.9 ppm. Unstable in CD$_2$Cl$_2$.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 27a could not be obtained due to the small amount of it present at equilibrium (~10:1 mixture of 27b and 27a), and the fact that 27b is the dominant species that precipitates from cyclohexane following the standard procedure. 27a was detected by $^1$H NMR signals (400 MHz, THF-d$_8$) at $\delta$ 6.88 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.2 Hz, 2H), 6.31 (d, J = 6.7 Hz, 1H) ppm. $^{31}$P (121 MHz, THF-d$_8$): $\delta$ 67.2 ppm.

Following the standard procedure using pentane instead of cyclohexane, di-tert-butyl-(2',4',6'-triisopropyl-3-methyl-[1,1'-biphenyl]-2-yl)phosphine (56.8 mg, 0.13 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (68.5 gL, 0.39 mmol, 3.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (50.0 mg, 0.13 mmol, 1.00 eq.) were combined to yield 28b (34 mg, 35%) as a purple solid. $^1$H, $^{13}$C, and $^{31}$P NMR of 28b are contaminated with 4% of 28a. $^1$H NMR (400 MHz, THF-d$_8$): $\delta$ 8.73 (d, J = 7.7 Hz, 1H), 7.34-7.36 (m, 2H), 7.29 (d, J = 7.4 Hz, 1H), 7.17-7.19 (m, 2H), 7.05-7.08 (m, 1H), 5.80 (s, 1H), 3.15 (d, J = 40.1 Hz, 1H), 2.98-3.02 (m, 2H), 2.75 (s, 3H),
2.60 (t, J = 7.8 Hz, 2H), 1.90-1.95 (m, 1H), 1.68 (d, J = 15.4 Hz, 9H), 1.58-1.62 (m, 2H), 1.47 (d, J = 14.6 Hz, 9H), 1.32-1.38 (m, 2H), 1.24 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.71 (d, J = 6.4 Hz, 3H), -0.01 (d, J = 6.8 Hz, 3H) ppm; \(^1\)C NMR (100 MHz, THF-\(d_8\)): \(\delta\) 174.3, 174.3, 149.2, 143.7, 142.8, 137.4, 137.4, 135.6, 133.7, 133.1, 132.4, 131.6, 130.1, 129.8, 128.4, 126.3, 100.7, 52.7, 41.5, 41.4, 39.5, 36.4, 34.9, 34.8, 34.3, 33.6, 33.4, 32.5, 31.0, 28.1, 23.5, 23.4 22.9, 21.8, 20.5, 14.5 ppm (observed complexity is due to C-P coupling); \(^{31}\)P NMR (121 MHz, THF-\(d_8\)): \(\delta\) 87.9 ppm.

Clean \(^1\)H, \(^{31}\)P, and \(^{13}\)C NMR spectra for 28a could not be obtained due to the small amount of it present at equilibrium (4%), and the fact that 28b is the dominant species that precipitates out of cyclohexane following the standard procedure. 28a was detected by \(^1\)H NMR signals (400 MHz, THF-\(d_8\)) at \(\delta\) 6.53 (d, J = 7.1 Hz, 2H), 6.29 (s, 1H) ppm. \(^{31}\)P NMR (121 MHz, THF-\(d_8\)): \(\delta\) 76.5 ppm.

Following the standard procedure, di-\textit{tert}-butyl-(2'-4'-6'-triisopropyl-6-methyl-[1,1'-biphenyl]-2-yl)phosphine (109 mg, 0.25 mmol, 1.00 eq.), 1-bromo-4-nbutylbenzene (219 \textmu L, 1.24 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH\(_2\)SiMe\(_3\))\(_2\) (97.0 mg, 0.25 mmol, 1.00 eq.) were combined to yield 29a (64 mg, 34%) as a yellow solid. \(^1\)H NMR (400 MHz, THF-\(d_8\)): \(\delta\) 7.92 (m, 1H), 7.34-7.37 (m, 2H), 7.14 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.05 (p, J = 6.9 Hz, 1H), 2.64 (p, J = 6.8 Hz, 2H),
2.42 (t, J = 7.7 Hz, 2H), 1.65 (d, J = 7.4 Hz, 6H), 1.44-1.52 (m, 2H), 1.41 (s, 9H), 1.37-1.39 (m, 18H), 1.22-1.33 (m, 2H), 0.92 (d, J = Hz, 6H), 0.87 (t, J = 7.0 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): δ 157.7, 152.9, 146.7, 146.5, 141.1, 139.0, 138.0, 137.8, 137.3, 133.8, 127.9, 126.6, 125.5, 123.8, 40.2, 40.1, 34.9, 34.2, 32.0, 31.7, 27.0, 24.9, 24.6, 22.7, 21.1, 14.1 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): δ 50.6 ppm.

Clean $^1$H, $^{31}$P, and $^{13}$C NMR spectra for 29b could not be obtained due to the small amount of it present at equilibrium (1% at equilibrium). It was detected by a $^1$H NMR signals (400 MHz, THF-d$_8$) at δ 8.78 (d, J = 8.0 Hz, 1H), 5.84 (s, 1H) ppm.

Following the standard procedure, tBuXphos (87.8 mg, 0.21 mmol, 1.00 eq.), 4-bromo-N,N-dimethylaniline (43.5 mg, 0.22 mmol, 1.05 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 30a (117 mg, 77%) as a bright orange solid. Clean $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 30a could not be obtained due to its rapid isomerization to 30b in solution (nearly 1:1.5 mixture of 30a and 30b after 15 min). 30a was detected by $^1$H NMR (400 MHz, CD$_2$Cl$_2$) signals at δ 7.98-8.02 (m, 1H), 7.37-7.45 (m, 1H), 7.08 (s, 2H), 6.82 (d, J = 7.8 Hz, 2H), 6.74-6.77 (m, 2H), 6.40 (d, J = 7.6 Hz, 2H), 3.02-3.09 (m, 1H), 2.79 (s, 6H), 1.98-2.06 (m, 2H), 1.56 (d, J = 6.8 Hz, 6H), 1.36-1.41 (m, 24H), 0.88 (d, J = 6.6 Hz, 6H) ppm. $^{31}$P NMR (121 MHz,
CD$_2$Cl$_2$): δ 49.6 ppm. Crystals of 30a suitable for X-ray analysis were obtained by suspending 30a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane, and the larger vial was capped.

Clean 1H, $^{13}$C, and $^{31}$P NMR spectra for 30b could not be obtained due to the large amount of 30a still present at equilibrium (approximately 1.5:1 mixture of 30b and 30a).

30b was detected by $^1$H NMR (400 MHz, CD$_2$Cl$_2$) signals at δ 8.27 (bs, 1H), 7.81 (pt, J = 5.9 Hz, 1H), 7.37-7.47 (m, 3H), 7.30-7.34 (m, 1H), 7.21 (bs, 1H), 6.65 (bs, 1H), 5.79 (s, 1H), 3.20 (d, J = 36.7 Hz, 1H), 3.06 (p, J = 6.9 Hz, 1H), 2.93 (s, 6H), 2.53 (p, J = 6.7 Hz, 2H), 1.52 (d, J = 14.4 Hz, 9H), 1.36-1.41 (d + d overlap, 12H), 1.22 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.68 (d, J = 6.4 Hz, 3H), -0.10 (bs, 3H) ppm. $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): δ 67.7 ppm.

After 1 h in solution, a 1:1.5 mixture of 30a and 30b was obtained. $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): δ 156.8, 151.8, 150.3, 147.8, 147.7, 147.5, 147.1, 146.9, 138.7, 138.6, 136.7, 136.5, 136.4, 135.8, 135.1, 134.8, 134.7, 134.2, 132.3, 132.3, 131.6, 130.3, 129.9, 129.4, 129.1, 127.0, 127.0, 126.3, 126.2, 125.9, 125.9, 125.0, 114.5, 113.0, 112.7, 111.7, 97.7, 97.7, 67.7, 67.6, 51.5, 41.2, 40.7, 39.7, 39.6, 38.5, 38.3, 37.8, 37.7, 34.7, 34.3, 34.3, 32.7, 32.4, 32.4, 31.8, 31.8, 31.7, 31.3, 31.2, 29.7, 25.6, 24.8, 24.7, 23.2, 22.8, 22.8, 22.0, 22.0, 21.3, 21.3, 20.7, 20.4 ppm (observed complexity is due to C-P coupling and the presence of two species at equilibrium).
Following the standard procedure, tBuXPhos (88.0 mg, 0.21 mmol, 1.00 eq.), bromobenzene (109 µL, 1.04 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 31a (99 mg, 70%) as a bright yellow solid.¹H, ¹³C, and ³¹P NMR spectra for 31a are contaminated with ~5% of the corresponding rearranged complex, detected by ³¹P NMR (121 MHz, CD₂Cl₂) at δ 68.5 ppm. ¹H NMR (400 MHz, CD₂Cl₂): δ 7.98-8.02 (m, 1H), 7.38-7.41 (m, 2H), 7.09 (s, 2H), 7.05-7.09 (m, 2H), 6.70-6.83 (m, 4H), 3.06 (p, J = 6.9 Hz, 1H), 2.54 (p, J = 6.7 Hz, 2H), 1.57 (d, J = 6.8 Hz, 6H), 1.38 (d, J = 14.0 Hz, 18H), 1.37 (d, J = 7.0 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H) ppm; ¹³C NMR (100 MHz, CD₂Cl₂): δ 157.1, 152.2, 147.6, 147.4, 139.4, 136.5, 136.3, 135.9, 134.9, 134.8, 132.1, 130.4, 126.4, 126.0, 125.1, 122.9, 98.6, 39.9, 39.7, 34.7, 32.8, 32.4, 31.8, 31.7, 29.7, 25.6, 24.9, 24.7 ppm (observed complexity is due to C-P coupling and the presence of the rearranged complex at equilibrium); ³¹P NMR (121 MHz, CD₂Cl₂): δ 50.1 ppm. Crystals of 31a suitable for X-ray analysis were obtained by crystallization from cyclohexane using pentane.

Following the standard procedure, tBuXPhos (88.0 mg, 0.21 mmol, 1.00 eq.), 4-bromobenzonitrile (39.6 mg, 0.22 mmol, 1.05 eq.), and (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 32a (99 mg, 67%) as a pale yellow solid. The corresponding rearranged complex was not detected by ¹H NMR after 24 h in solution. ¹H NMR (400 MHz, CD₂Cl₂): δ 7.96-8.00 (m, 1H), 7.40-7.42 (m,
Following the standard procedure, RockPhos (100 mg, 0.21 mmol, 1.00 eq.), 4-bromo-N,N-dimethylaniline (45.0 mg, 0.22 mmol, 1.05 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (83.0 mg, 0.21 mmol, 1.00 eq.) were combined to yield 33a (125 mg, 75%) as a tan solid. $^1$H, $^{13}$C, and $^{31}$P NMR spectra for 33a are contaminated with 10-15% of the corresponding rearranged complex, detected by $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) at δ 82.9 ppm. $^1$H NMR (400 MHz, CD$_2$Cl$_2$): δ 7.25 (d, J = 8.4 Hz, 1H), 7.09 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 6.37 (d, J = 7.4 Hz, 2H), 3.81 (s, 3H), 3.03 (p, J = 6.9 Hz, 1H), 2.79 (s, 6H), 2.68 (p, J = 6.7 Hz, 2H), 1.65 (d, J = 6.8 Hz, 6H), 1.40 (d, J = 14.7 Hz, 18H), 1.36 (d, J = 7.0 Hz, 6H), 1.16 (s, 3H), 0.91 (d, J = 6.6 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): δ 159.5, 157.7, 152.7, 150.3, 148.5, 148.4, 147.0, 139.8, 135.4, 134.8, 133.0, 132.9, 132.5, 130.7, 126.2, 126.1, 125.5, 122.6, 118.3, 112.9, 112.3, 111.5, 110.4, 110.2, 98.0, 67.1, 54.0, 51.8, 41.5, 41.4, 40.8, 40.2, 40.0, 39.7, 34.8, 34.0,
33.0, 32.9, 32.6, 31.7, 31.5, 31.0, 30.9, 27.3, 26.8, 24.9, 24.5, 23.3, 23.0, 23.0 22.6, 22.1, 20.4, 20.3, 20.3, 19.9 ppm (observed complexity is due to C-P coupling, and the presence of the corresponding rearranged complex); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 69.4 ppm.

Crystals suitable for X-ray analysis were obtained by suspending 33a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.

Following the standard procedure, RockPhos (96.8 mg, 0.21 mmol, 1.00 eq.), bromobenzene (109 $\mu$L, 1.04 mmol, 5.00 eq.), and (1,5-cyclooctadiene)Pd(CH$_2$SiMe$_3$)$_2$ (80.0 mg, 0.21 mol, 1.00 eq.) were combined to yield 34a (115 mg, 76%) as a pale yellow solid. The corresponding rearranged complex was not detected by $^1$H NMR after 1 h in solution. $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 7.25 (d, $J$ = 8.4 Hz, 1H), 7.10 (s, 2H), 7.06 (d, $J$ = 8.1 Hz, 2H), 6.87 (dd, $J$ = 8.4, 2.0 Hz, 1H), 6.76 (pt, $J$ = 7.4 Hz, 2H), 6.65-6.69 (m, 1H), 3.81 (s, 3H), 3.05 (p, $J$ = 6.8 Hz, 1H), 2.68 (p, $J$ = 6.8 Hz, 2H), 1.66 (d, $J$ = 6.8 Hz, 3H), 1.40 (s, 9H), 1.34-1.37 (d + s overlap, 15H), 1.16 (s, 3H), 0.92 (d, $J$ = 6.7 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ 159.6, 159.6, 158.0, 153.0, 148.5, 148.3, 140.5, 140.5, 135.6, 135.5, 134.6, 134.5, 133.1, 133.0, 126.2, 126.0, 125.7, 125.6, 122.4, 122.4, 122.3, 110.3, 110.2, 54.0, 41.6, 41.5, 34.9, 33.0, 32.9, 31.8, 26.8, 24.9, 24.5, 19.9 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 70.2 ppm.

Crystals of 34a suitable for X-ray analysis were obtained by suspending 34a in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane.
Following the standard procedure, RockPhos (100 mg, 0.213 mmol, 1.03 eq.), 4-bromobenzonitrile (73 mg, 0.40 mmol, 1.94 eq.), and (1,5-cyclooctadiene)Pd(CH2SiMe3)2 (80 mg, 0.21 mmol, 1.00 eq.) were combined to yield 35a (111 mg, 70%) without the final addition of pentane and freezing at -20°C in the standard procedure. The corresponding rearranged complex was not detected by 1H NMR even after 60 h in solution. 1H NMR (400 MHz, THF-d8): δ 7.28 (m, 3H), 7.11 (s, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.88 (dd, J = 8.4, 2.0 Hz, 1H), 3.80 (s, 3H), 3.03 (q, J = 7.0 Hz, 1H), 2.66 (q, J = 6.8 Hz, 2H), 2.12 (s, 3H), 1.64 (d, J = 6.8 Hz, 6H), 1.34-1.40 (m, 24H), 0.92 (d, J = 6.7 Hz, 6H) ppm; 13C NMR (100 MHz, CD2Cl2): δ 159.1, 158.7, 153.7, 147.7, 147.5, 146.6, 140.9, 135.6, 132.8, 132.7, 132.3, 1128.1, 127.2, 125.5, 125.3, 120.5, 120.4, 119.9, 110.1, 105.2, 51.4, 41.5, 34.6, 32.6, 32.6, 31.6, 26.9, 26.4, 26.0, 24.6, 24.0, 19.3 ppm (observed complexity is due to C-P coupling); 31P NMR (121 MHz, CD2Cl2): δ 72.4 ppm. Crystals of 35a suitable for X-ray analysis were obtained by dissolving 35a in a minimal amount of DCM in a vial, layering the resulting solution with pentane, and placing the vial in a freezer at -20°C.

7a (152 mg, 0.19 mmol, 1.00 eq.) and 4-bromo-1-nbutylbenzene (100 µL, 0.57 mmol, 3.00 eq.) was dissolved in THF (3.0 mL) in an oven-dried vial equipped with a stir bar. 1,8-Diazabicycloundec-7-ene (34.5 µL, 0.23 mmol, 1.20 eq.) was added, and the reaction mixture was allowed to stir at room temperature for 12 h, during which time a color change from dark red to yellow was observed, along with
formation of an insoluble white solid. The crude reaction mixture was filtered through an oven-dried glass frit, and the solvent was removed under reduced pressure to afford a yellow oil. Ether (3 mL) was added and then removed under reduced pressure. This process was repeated two additional times to afford a yellow solid that was triturated with pentane (3 mL), filtered, and washed with additional pentane (3 x 5 mL), which afforded 37 as a bright yellow solid (158 mg, 90%). $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.72 (d, $J$ = 9.4 Hz, 1 H), 7.17 – 7.12 (m, 3 H), 7.08 (d, $J$ = 7.6 Hz, 1 H), 6.96 (d, $J$ = 9.4 Hz, 2 H), 6.93 – 6.85 (m, 2 H), 6.64 (d, $J$ = 7.6 Hz, 2 H), 3.78 (s, 3 H), 3.40 (s, 3 H), 2.94 (septet, $J$ = 7.3 Hz, 1 H), 2.66 (t, $J$ = 7.8 Hz, 2 H), 2.58 (septet, $J$ = 6.4 Hz, 1 H), 2.51 – 2.44 (m, 3 H), 1.69 – 1.63 (m, 2 H), 1.60 (d, $J$ = 7.7 Hz, 3 H), 1.56 – 1.48 (m, 2 H), 1.47 – 1.25 (m, 25 H), 1.04 – 1.00 (m, 6 H), 0.95 (t, $J$ = 7.7 Hz, 3 H), 0.89 (t, $J$ = 6.4 Hz, 3 H), 0.78 (d, $J$ = 6.4 Hz, 3 H), 0.64 (d, $J$ = 7.7 Hz, 3 H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) δ 158.0, 154.4, 154.4, 153.8, 152.3, 152.2, 151.8, 141.5, 140.3, 139.6, 139.4, 139.4, 139.4, 138.5, 136.6, 132.4, 131.8, 130.0, 129.9, 127.9, 127.8, 127.2, 126.5, 126.0, 123.7, 118.3, 118.3, 113.7, 110.6, 110.5, 66.0, 54.7, 41.7, 41.5, 41.4, 41.2, 35.8, 34.9, 34.3, 34.1, 33.5, 33.0, 32.7, 32.6, 31.6, 30.3, 25.6, 25.4, 25.2, 24.6, 22.8, 22.7, 22.3, 15.5, 14.2, 14.2 (observed complexity is due to C–P splitting); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) δ 71.7. Crystals of 37 suitable for X-ray analysis were obtained by dissolving 37a in a minimal amount of DCM in a vial, layering the resulting solution with pentane, and placing the vial in a freezer at –20°C.

26a (100 mg, 0.14 mmol, 1.00 eq.) and 1-bromo-4-$n$butylbenzene (47.4 µL, 0.27 mmol, 2.00 eq.) were
dissolved in THF (2.0 mL) in an oven-dried vial equipped with a stir bar. 1,8-Diazabicycloundec-7-ene (22.0 μL, 0.15 mmol, 1.10 eq.) was added, and the reaction mixture was allowed to stir at room temperature for 12 h, during which time a color change from dark red to yellow was observed, along with formation of an insoluble white solid. The crude reaction mixture was filtered through an oven-dried glass frit, and the solvent was removed under reduced pressure to afford a yellow oil. Ether (3 mL) was added and then removed under reduced pressure. This process was repeated two additional times to afford a yellow solid that was triturated with pentane (3 mL), filtered, and washed with additional pentane (3 x 5 mL), which afforded 38 (87.0 mg, 73%) as a bright yellow solid. ¹H NMR (300 MHz, CD₂Cl₂): δ 7.99 (pt, J = 7.2 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.34-7.43 (m, 2H), 7.10-7.22 (m, 4H), 6.99 (d, J = 6.9 Hz, 2H), 6.84-6.89 (m, 1H), 6.70 (d, J = 8.1 Hz, 2H), 3.32-3.50 (m, 1H), 2.83 (p, J = 7.2 Hz, 1H), 2.66 (t, J = 8.1 Hz, 2H), 2.40-2.52 (m, 3H), 1.62-1.69 (m, 2H), 1.57 (d, J = 6.6 Hz, 3H), 1.48-1.54 (m, 2H), 1.43 (d, J = 14.1 Hz, 9H), 1.30 (d, J = 14.1 Hz, 9H), 1.25-1.35 (m, 5H), 1.12-1.18 (m, 2H), 1.03 (d, J = 6.9 Hz, 3H), 0.85-0.98 (m, 12H), 0.79 (d, J = 6.9 Hz, 3H) ppm; ¹³C NMR (100 MHz, CD₂Cl₂): δ 157.3, 151.9, 149.4, 148.6, 148.4, 141.7, 140.1, 139.2, 138.6, 138.2, 137.6, 136.7, 136.4, 135.9, 135.5, 135.4, 135.0, 132.6, 131.4, 130.2, 127.4, 127.2, 126.8, 126.7, 126.7, 126.5, 125.8, 125.8, 123.6, 49.1, 48.1, 40.0, 39.9, 39.8, 39.7, 35.8, 35.3, 34.9, 34.5, 34.3, 34.2, 33.6, 32.1, 32.1, 31.8, 31.7, 31.7, 30.4, 25.6, 25.5, 25.2, 24.8, 23.4, 22.8, 22.7, 22.7, 14.2, 14.2 ppm (observed complexity is due to C–P coupling); ³¹P NMR (121 MHz, CD₂Cl₂): δ 50.2 ppm.
4a (50.0 mg, 0.06 mmol, 1.00 eq.) and 1-bromo-4-nbutylbenzene (56.0 μL, 0.32 mmol, 5.00 eq.) were dissolved in THF (1.5 mL) in an oven-dried vial equipped with a stir bar. 1,8-diazabicycloundec-7-ene (10.4 μL, 0.070 mmol, 1.1 eq.) was added, and the reaction was stirred at room temperature with monitoring by $^{31}$P NMR. After 12 and 36 hours, additional 1,8-diazabicycloundec-7-ene (10.4 μL, 0.07 mmol, 1.10 eq.) was added. After 60 h, the crude reaction mixture was filtered through an oven-dried glass frit, and the solvent was removed under reduced pressure to afford a yellow oil. Ether (3 mL) was added and then removed under reduced pressure. This process was repeated two additional times to afford a yellow solid that was triturated with pentane (3 mL), filtered, and washed with additional pentane (3 x 5 mL), which afforded 39 (50.0 mg, 86%) as a bright yellow solid. $^1$H NMR (400 MHz, CD$_2$Cl$_2$): δ 7.74 (d, J = 7.9 Hz, 1H), 7.25-7.28 (d + s overlap, 2H), 7.13-7.18 (m, 2H), 7.07-7.10 (m, 1H), 6.96 (d, J = 6.8 Hz, 2H), 6.86 (dd, J = 8.5, 1.9 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 3.79 (s, 3H), 3.30 (t, J = 5.8 Hz, 2H), 3.03 (p, J = 7.2 Hz, 1H), 2.63-2.74 (m, 2H), 2.44-2.50 (m, 2H), 1.63-1.70 (m, 5H), 1.49-1.55 (m, 2H), 1.26-1.45 (m, 25H), 1.11 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.86-0.92 (m, 6H), 0.68 (d, J = 7.0 Hz, 3H) ppm; $^{13}$C (125 MHz, CD$_2$Cl$_2$): δ 159.7, 158.1, 152.4, 150.0, 149.4, 149.2, 141.8, 140.4, 140.2, 139.7, 138.0, 136.8, 135.6, 133.5, 132.4, 131.6, 129.8, 129.7, 127.4, 126.7, 126.3, 126.1, 124.4, 110.1, 110.1, 110.1, 108.1, 104.0, 91.0, 90.0, 89.0, 88.0, 87.0, 86.0, 85.0, 84.0, 83.0, 82.0, 81.0, 80.0, 79.0, 78.0, 77.0, 76.0, 75.0, 74.0, 73.0, 72.0, 71.0, 70.0, 69.0, 68.0, 67.0, 66.0, 65.0, 64.0, 63.0, 62.0, 61.0, 60.0, 59.0, 58.0, 57.0, 56.0, 55.0, 54.0, 53.0, 52.0, 51.0, 50.0, 49.0, 48.0, 47.0, 46.0, 45.0, 44.0, 43.0, 42.0, 41.0, 40.0, 39.0, 38.0, 37.0, 36.0, 35.0, 34.0, 33.0, 32.0, 31.0, 30.0, 29.0, 28.0, 27.0, 26.0, 25.0, 24.0, 23.0, 22.0, 21.0, 20.0, 19.0, 18.0, 17.0, 16.0, 15.0, 14.0, 13.0, 12.0, 11.0, 10.0, 9.0, 8.0, 7.0, 6.0, 5.0, 4.0, 3.0, 2.0, 1.0 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (121 MHz,
Crystals of 39 suitable for X-ray analysis were obtained by suspending 39 in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane, and the larger vial was capped and placed in a freezer at -20°C.

37 (145 mg, 0.16 mmol, 1.00 eq.) was dissolved in CH₂Cl₂ (5 mL) in an oven-dried vial wrapped in aluminum foil. AgF (100 mg, 0.79 mmol, 5.00 eq.) was added in one portion. The mixture was rapidly stirred for 4 h while protected from light. Pentane (10 mL) was then added, and the vial was placed in a -20 °C freezer for 12 h (this step precipitates unwanted black particles). The mixture was filtered through a small (1 cm), tightly-packed plug of celite and the solvent was removed under reduced pressure to afford a light brown oil. Pentane (5 mL) was added and then removed under reduced pressure; this process was repeated two additional times to afford 40 as a yellow solid (117 mg, 86%).

³¹P NMR (100 MHz, CD₂Cl₂) δ 70.5 ppm. Crystals of 39 suitable for X-ray analysis were obtained by suspending 39 in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane, and the larger vial was capped and placed in a freezer at -20°C.

³¹C NMR (100 MHz, CD₂Cl₂) δ 157.4, 154.1, 152.3, 152.1, 148.9, 142.5, 141.9, 141.3, 139.9, 139.7, 139.5, 138.9, 137.4, 137.1, 133.9, 131.5, 130.8, 130.6, 128.2, 127.9, 127.4,
126.4, 126.2, 122.6, 118.2, 113.7, 110.5, 54.6, 40.9, 40.7, 40.4, 40.2, 35.9, 35.3, 35.1, 34.4, 34.2, 33.9, 33.4, 33.0, 32.9, 32.6, 32.5, 31.6, 30.4, 26.2, 25.9, 25.0, 24.9, 24.1, 22.9, 22.8, 22.6, 14.2, 14.2 (observed complexity is due to C–P splitting); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$) δ 78.1 (d, $J = 163.7$ Hz); $^{19}$F NMR (282 MHz, CD$_2$Cl$_2$) δ -210.6 (d, $J = 166.9$ Hz).

A 6:1 mixture of 7b and 7a (300 mg, 0.37 mmol, 1.00 eq.) and bromobenzene (118 µL, 1.12 mmol, 3.00 eq.) were dissolved in THF (5.0 mL) in an oven-dried vial equipped with a stir bar. 1,8-Diazabicyclo[5.4.0]undec-7-ene (61.6 µL, 0.41 mmol, 1.10 eq.) was added in one portion, and the reaction mixture was stirred at room temperature for 16 h, during which time a color change from red to yellow was observed, along with precipitation of a white solid. After 16 h, the crude reaction mixture was filtered through a short (1 cm) celite plug, and the solvent was removed under reduced pressure to afford a yellow oil. Ether (3 mL) was added and then removed under reduced pressure. This process was repeated two additional times to afford a yellow solid that was triturated with pentane (3 mL), filtered, and washed with additional pentane (3 x 5 mL), which afforded 41 (277 mg, 84%) as a bright yellow solid. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.72 (d, $J = 7$ Hz, 1H), 7.08-7.20 (m, 6H), 6.86-6.94 (m, 2H), 6.78-6.81 (m, 2H), 6.69 (pt, $J = 7$H), 3.79 (s, 3H), 3.39 (s, 3H), 2.95 (p, $J = 7$H, 1H), 2.66 (t, $J = 8$ Hz, 2H), 2.60 (p, $J = 7$ Hz, 1H), 2.48 (p, $J = 7$ Hz, 1H), 1.63-1.68 (m, 2H), 1.61 (d, $J = 7$ Hz, 3H), 1.44 (d, $J = 15$ Hz, 9H), 1.37-1.40 (m, 2H), 1.33 (d, $J = 15$ Hz, 3H), 1.26 (d, $J = 7$ Hz, 3H), 1.01-1.05 (m, 6H), 0.96 (t, $J = 8$ Hz, 3H), 0.79 (d, $J = 7$ Hz, 3H), 0.65 (d, $J = 7$ Hz,
3H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 158.3, 154.4, 154.4, 154.1, 152.3, 152.2, 152.1, 141.6, 141.0, 140.3, 139.6, 139.4, 138.5, 135.5, 134.8, 134.8, 132.7, 132.4, 131.9, 131.9, 130.5, 128.0, 127.9, 127.9, 127.4, 127.3, 126.5, 125.9, 125.7, 125.6, 123.8, 122.3, 122.2, 118.0, 118.0, 114.0, 113.7, 110.6, 110.6, 54.7, 54.1, 41.7, 41.6, 41.5, 41.4, 35.8, 34.5, 34.2, 33.6, 33.1, 33.0, 32.8, 32.7, 31.7, 30.3, 29.6, 27.5, 25.6, 25.4, 25.2, 24.6, 22.9, 22.9, 22.8, 22.7, 22.3, 14.2 ppm (observed complexity is due to C-P coupling); $^{31}$P{${}^1$H} NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 70.6 ppm (a minor contaminant was detected at 71.1 ppm). Anal. Calcd. for C$_{47}$H$_{66}$BrO$_2$PPd: C, 64.12, H, 7.56; Found C, 64.34, H, 7.79. Crystals of 41 suitable for X-ray analysis were obtained by suspending 41 in a small amount of ether in a vial and then adding DCM dropwise until all of the solid dissolved. This uncapped vial was then placed in a larger vial containing pentane, and the larger vial was capped and placed in a freezer at $-20^\circ$C.

![41](image)

41 (75.0 mg, 0.09 mmol, 1.00 eq.) was dissolved in CH$_2$Cl$_2$ (3.0 mL) in an oven-dried vial equipped with a stir bar. The vial was wrapped in aluminum foil and AgF$_2$Pr$_2$ (54.0 mg, 0.42 mmol, 5.00 eq.) was added in one portion. The reaction mixture was stirred for 6 h protected from light. At this time, pentane (5 mL) was added and the non-homogenous mixture was allowed to stand for 12 h at $-20^\circ$C (this step precipitates unwanted black particles). The mixture was filtered through a small (1 cm), tightly-packed plug of celite and the solvent was removed under reduced pressure to afford a light brown oil. Pentane (5 mL) was added and then removed under reduced pressure; this process was repeated two additional times to afford 42 as a yellow solid.
(117 mg, 86%). $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.51 (d, J = 8 Hz, 1H), 7.10-7.31 (m, 6H), 6.93 (s, 2H), 6.77-6.85 (m, 3H), 3.79 (s, 3H), 3.47 (s, 3H), 2.85-2.91 (m, 1H), 2.66 (t, J = 8 Hz, 2H), 2.48-2.55 (m, 1H), 2.41-2.46 (m, 1H), 1.62-1.67 (m, 5H), 1.47 (d, J = 15 Hz, 9H), 1.36-1.42 (m, 2H), 1.31 (d, J = 15 Hz, 9H), 0.99-1.07 (m, 6H), 0.96 (t, J = 7 Hz, 3H), 0.84-0.87 (m, 3H), 0.78-0.81 (m, 3H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 157.6, 154.2, 152.4, 148.9, 146.5, 141.3, 139.9, 138.8, 137.9, 133.9, 131.8, 127.9, 127.4, 127.0, 126.9, 126.5, 126.4, 126.0, 122.7, 118.5, 118.0, 111.8, 113.7, 110.6, 54.6, 54.1, 40.9, 40.7, 40.4, 40.2, 35.8, 34.5, 34.2, 33.4, 32.9, 32.5, 31.7, 30.4, 29.7, 28.6, 28.5, 26.2, 25.9 25.0, 24.2, 24.1, 23.7, 22.9, 22.7, 14.2, 14.2 ppm (observed complexity is due to C-P and C-F coupling); $^{31}$P{^1}H NMR (121 MHz, CD$_2$Cl$_2$): δ 78.1 (d, J = 163 Hz) ppm (a contaminant was detected at 62.8 ppm); $^{19}$F NMR (470 MHz, CD$_2$Cl$_2$): δ −210.7 (d, J = 164 Hz) ppm.

Sample halogen exchange reaction:

1.9.5. Thermolysis experiments of 5 (Figure 1.2) and 40 (Table 1.8).

General Procedure: In a nitrogen-filled glovebox, an oven-dried screw cap NMR tube was charged with L•Pd(Ar)F complex (15-35 mg), toluene (or cyclohexane) (800 μL), and additive (where appropriate) (10 eq.). The tube was capped, removed from the glovebox, and placed in a oil bath that had been pre-heated to 120 °C. After 2 h, the reaction was cooled, the internal standard (1-fluoronaphthalene or 3-fluoroanisole, where
appropriate, 1.00 eq. relative to Pd) was added, and the product mixture was analyzed by
$^{19}$F NMR.

Entry 1, Table 1.8: Following the general procedure, 40 (12.5 mg, 0.01 mmol, 1.00 eq.)
was heated at 120 °C in toluene for 3 h. After cooling and addition of 1-
fluoronaphthalene, $^{19}$F NMR analysis showed 15% of 4-nBuPhF (6a) (δ -118.4 ppm).
This experiment has been repeated three times and consistently yields 15-20% of 6a.

Entry 2, Table 1.8: Following the general procedure, 40 (15.0 mg, 0.02 mmol, 1.00 eq.)
was heated at 120 °C in toluene for 3 h. After cooling and addition of 1-
fluoronaphthalene, $^{19}$F NMR analysis showed 20% of 4-nBuPhF (6a) (δ -118.4 ppm).

Entry 3, Table 1.8: Following the general procedure, 40 (19.0 mg, 0.02 mmol, 1.00 eq.)
and 4-nBuPhOTf (61.0 mg, 0.22 mmol, 10.0 eq.) were heated at 120 °C in toluene for 3 h.
After cooling and addition of 1-fluoronaphthalene, $^{19}$F NMR analysis showed 32% of 4-
nBuPhF (6a) (δ -118.4 ppm) and 20% of 3-nBuPhF (6b) (δ -114.4 ppm).

Entry 4, Table 1.8: Following the general procedure, 40 (20.0 mg, 0.02 mmol, 1.00 eq.)
and 4-nBuPhOTf (64.0 mg, 0.23 mmol, 10.0 eq.) were heated at 120 °C in cyclohexane
for 3 h. After cooling and addition of 1-fluoronaphthalene, $^{19}$F NMR analysis showed
27% of 4-nBuPhF (6a) (δ -118.4 ppm) and 17% of 3-nBuPhF (6b) (δ -114.4 ppm).

Entry 5, Table 1.8: Following the general procedure, 40 (25.0 mg, 0.03 mmol, 1.00 eq.)
and 4-nBuPhBr (61.0 mg, 0.30 mmol, 10.0 eq.) were heated at 120 °C in toluene for 3 h.
After cooling and addition of 1-fluoronaphthalene, $^{19}$F NMR analysis showed 24% of 4-
nBuPhF (6a) (δ -118.4 ppm) and 3% of 3-nBuPhF (6b) (δ -114.4 ppm).

Entry 6, Table 1.8: Following the general procedure, 40 (19.0 mg, 0.02 mmol, 1.00 eq.)
and bromobenzene (34.0 mg, 0.20 mmol, 10.0 eq.) were heated at 120 °C in toluene for 3
h. After cooling and addition of 1-fluoronaphthalene, $^{19}$F NMR analysis showed 40% of fluorobenzene ($\delta$ –113.3 ppm) and 7% of 4-nBuPhF (6a) ($\delta$ –118.4 ppm).

Entry 7, Table 1.8: Following the general procedure, 40 (34.0 mg, 0.04 mmol, 1.00 eq.) and 1-naphthyltriflate (107 mg, 0.40 mmol, 10.0 eq.) were heated at 120 °C in toluene for 2 h. After cooling and addition of 3-fluoroanisole, $^{19}$F NMR analysis showed 75% of 1-fluoronaphthalene ($\delta$ –124.0 ppm) and a trace (~3%) of 4-nBuPhF (6a) ($\delta$ –118.4 ppm).

1.9.6. Kinetic Data for Rearrangement Processes

**General Procedure to Monitor the Kinetics of Rearrangement.** The complex being studied (12.4 µmol, 1.0 eq.) and trimethoxybenzene (5 mg, 29.7 µmol, 2.4 eq.) were added to a screw-cap NMR tube. The deuterated solvent (1 ampule, 1.0 g) was added quickly, and the tube was capped. $^1$H NMR (400 MHz) integrations relative to the trimethoxybenzene internal standard were used to monitor the change in starting material and product over time. The sum of the starting material and rearranged complex was normalized to 1. For each set of data, the plot of relative amounts of oxidative addition complex and rearranged complex are shown, followed by the plot of ln((A-Ae)/(A+1)) (where A is the ratio of the starting oxidative addition complex to the rearranged isomer, for example [7a]/[7b], and Ae is the equilibrium ratio) vs. time is shown. It should be noted that because absolute concentrations were not used to make these plots that the slopes determined from these plots are not the absolute rate constants. All kinetic runs were conducted in THF-d$_8$ unless otherwise specified. Equilibrium constants were obtained either by allowing the reaction to come to equilibrium (several data points in a row with nearly identical relative amounts of the two species) or by collection of a data
point after the solution had stood for 20 h. A reference temperature of 20°C was used in all analyses.

**Procedure for Eyring Plot (Figure 1.5).** Kinetic runs and the processing of the data were carried out in the same way as described above. The first data point collected at each temperature was arbitrarily chosen to be 0 min. Kinetic data was obtained by first allowing the NMR spectrometer to reach the desired temperature (measured via an internal digital thermometer), followed by rapid preparation of the sample in a nitrogen-filled glovebox and delivery to the NMR spectrometer. The sample was allowed to equilibrate to the internal temperature of the spectrometer while the sample was locked, shimmed, and tuned (approximately 15 min), at which time data collection was begun. The total time between sample preparation and the beginning of data collection never exceeded 20 min. Rate constants relative to the reaction at 22°C were used in the Eyring Plot to cancel out the transmission coefficient; the calculated $k_f$ values were used in the Eyring Plot. The kinetic plots at 10 °C, 22 °C, and 38 °C were reproduced within estimated errors.
10 °C:

$K_{eq} \approx 0.84$ (after approximately 10 h at 10 °C)

![Graph showing ln(\(A-A_e)/(A+1)\) vs. time for 10 °C with a linear fit equation $y = -0.0047x - 0.5514$, $R^2 = 0.99753$.]

16 °C:

$K_{eq} \approx 0.81$ (after approximately 8 h at 16 °C)

![Graph showing ln(\(A-A_e)/(A+1)\) vs. time for 16 °C with a linear fit equation $y = -0.0072x - 0.3829$, $R^2 = 0.9917$.]
$22^\circ C$:

![Graph](image1)

$y = -0.0249x - 0.4182$

$R^2 = 0.99853$

$26^\circ C$:

![Graph](image2)

$y = -0.0242x - 0.4736$

$R^2 = 0.99749$
$30^\circ C$: 

![Graph showing the relationship between time and ln(Ae/(A+1)) for 30°C.](image)

$y = -0.0518x - 1.217$

$R^2 = 0.9995$

$34^\circ C$: 

![Graph showing the relationship between time and ln(Ae/(A+1)) for 34°C.](image)

$y = -0.0897x - 1.0029$

$R^2 = 0.99772$
38 °C:

\[ y = -0.1238x - 0.4269 \]
\[ R^2 = 0.98271 \]

42 °C:

\[ y = -0.2535x - 1.2386 \]
\[ R^2 = 0.97405 \]
1.10. References.

5 “O-bound” refers to binding of the Pd(II) center to the oxygen of the OMe group in the 3 position as opposed to the lower arene (i.e. “C-bound”). see: Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. J. Am. Chem. Soc. 2008, 130, 13552-13554.
\[\text{\textcopyright 12} \beta\text{-aryl elimination from isolated Rh(I) complexes has been demonstrated: (a) Zhao, P. J.; Incarvito, C. D.; Hartwig, J. F. J. Am. Chem. Soc. 2006, 128, 3124; (b) Zhao, P. J.; Hartwig, J. F. J. Am. Chem. Soc. 2005, 127, 11618.}\\]


We ruled out an unlikely radical chain mechanism because the addition of BHT (5.0 eq.) had no effect on the rate of rearrangement of \textit{7a} to \textit{7b}.

\[\text{\textcopyright 14} \text{7a proved unstable for extended periods of time in highly coordinating solvents such as CD}_3\text{CN and CD}_3\text{NO}_2.\]


Preliminary experiments carried out by Dr. Luca Salvi in our group confirm that oxidative addition complexes of ligands with cyclohexyl groups on the bottom ring of the ligand also show evidence of rearrangement in solution.

Despite numerous attempts, to date we have not been able to prepare an oxidative addition complex of \textit{Me}_4\textit{tBuXPhos}, the bulkiest known di-\textit{tert}-butyl biaryl phosphine ligand.

While \textit{L2}-ligated complexes bearing electron-rich aryl groups are more "tilted" than those bearing electron-deficient aryl groups, the same trend does not hold true across all ligand classes.

In situ ligand modification has been documented during Pd-catalyzed cross-coupling processes in the past, with Hartwig's QPhos system being a notable example. See: Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. J. \textit{Am. Chem. Soc.} 2000, 122, 10718-10719.

The prevention of ligand modification when using \textit{L8} over \textit{L3} should result in only a 7.5% yield increase (corresponding to the ligand loading of the reaction).
of the yield increase when switching from \textbf{L3} to \textbf{L8} is likely due to the decreased generation of HF.


\textsuperscript{29} For an example of halide exchange between two Pd(II) centers, see: Hunt, C. T.; Balch, A. L. \textit{Inorg. Chem.} 1982, 21, 1641.


1.11 NMR Spectra.

[Image of NMR spectra with two chemical structures and ppm scale]
$^{1}H$, 300 MHz, CD$_2$Cl$_2$
$^{13}$C, 75 MHz, CD$_2$Cl$_2$
\(^{13}\text{C NMR}, 100 \text{ MHz, CD}_2\text{Cl}_2\)
$^1$H NMR, 400 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 122 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 100 MHz, CD$_2$Cl$_2$
$^1\text{H NMR, 400 MHz, CD}_2\text{Cl}_2$
$^{19}$F NMR, 282 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 122 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 100 MHz, CD$_2$Cl$_2$
<5 min. after dissolving

$^1$H NMR, 400 MHz, CD$_2$Cl$_2$
<5 min. after dissolving

\( ^{31}\text{P NMR, 122 MHz, CD}_2\text{Cl}_2 \)
$^1$H NMR, 400 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 122 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 100 MHz, CD$_2$Cl$_2$
2 hours after dissolving
$^1$H, 400 MHz, CD$_2$Cl$_2$
2 hours after dissolving

$^{31}$P, 121 MHz, CD$_2$Cl$_2$
2 hours after dissolving
$^{13}\text{C}, 100 \text{ MHz, CD}_2\text{Cl}_2$
OCH₃

Pd

N

i-Pr

Br

CH₃O

< 20 minutes after dissolving

¹H, 400 MHz, CD₂Cl₂
<20 minutes after dissolving

$^{31}$P, 121 MHz, CD$_2$Cl$_2$
~ 3 hours after dissolving
\(^1\text{H}, 400 \text{ MHz, CD}_2\text{Cl}_2\)
~ 3 hours after dissolving
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
~ 3 hours after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 300 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
~ 1 hour after dissolving
$^{13}\text{C}$, 100 MHz, CD$_2$Cl$_2$
~6 hours after dissolving

$^1$H, 300 MHz, CD$_2$Cl$_2$
~7 hours after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
~7 hours after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving

$^{31}$P, 161 MHz, CD$_2$Cl$_2$
6 hours after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
6 hours after dissolving
$^{31}$P, 161 MHz, CD$_2$Cl$_2$
7 hours after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 300 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving $^{31}$P, 121 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving
$^{19}\text{F}, 282\text{ MHz, CD}_2\text{Cl}_2$
6 hours after dissolving
$^1$H, 500 MHz, CD$_2$Cl$_2$
6 hours after dissolving
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
6 hours after dissolving

$^{19}$F, 282 MHz, CD$_2$Cl$_2$
8 hours after dissolving
$^{13}$C, 125 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving

$^{31}$P, 163 MHz, CD$_2$Cl$_2$
6 hours after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
6 hours after dissolving
$^{31}\text{P}$, 163 MHz, CD$_2$Cl$_2$
6 hours after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
~ 2 hours after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
~ 2 hour after dissolving
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
~1 hour after dissolving

$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1H$, 400 MHz, THF-d$_8$
< 20 minutes after dissolving

$^{31}$P, 121 MHz, THF-d$_8$
5 hours after dissolving
$^1$H, 400 MHz, THF-d$_8$
5 hours after dissolving
$^{31}$P, 121 MHz, THF-$d_8$
5 hours after dissolving 13C, 100 MHz, THF-d8
< 20 minutes after dissolving

\(^1\text{H}, 400 \text{ MHz, THF-d}_8\)

Decomposition detected
< 20 minutes after dissolving

$^{31}$P, 121 MHz, THF-$d_8$

Decomposition detected
$^1$H, 400 MHz, CD$_2$Cl$_2$
n-BuCH$_3$O$<_{7}$Pd Pd i-Pr OTf CH$_3$Oi-Pr

$^{31}$P, 121 MHz, C$_6$D$_6$

7.0 11.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0 55.0 60.0 65.0 70.0 75.0 80.0 85.0 90.0 95.0 100.0 105.0 ppm

Diagram of molecular structure
$^{13}\text{C}, 100\text{ MHz, C}_6\text{D}_6$
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
$^{19}$F, 282 MHz, CD$_2$Cl$_2$
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
1 hour after dissolving
$^1\text{H}, 400 \text{ MHz, CD}_2\text{Cl}_2$
n-Bu-Pd-I
Pr, d Sr-i-Pr-I

49.8 ppm i-Pr

1 hour afterdissolving
${}^{31}P$, 121 MHz, CD$_2$Cl$_2$
1 hour after dissolving

$^{13}$C, 100 MHz, CD$_2$Cl$_2$
$n$-Bu$\text{CH}_3\text{O}p_4r1/n$-Bu$\text{O}_2\text{Pd CH}_3$ $\text{Br}$, $\text{H}$ $i$-Pr $\text{N}_2$-Pr $\text{Pd}$ $\text{Br}$ $\text{H}$ $i$-Pr $\text{H}$ $i$-Pr $\delta$ 67.2 ppm $\delta$ 83.9 ppm

$^{31}$P, 121 MHz, THF-$d_8$
$^{13}C$, 125 MHz, THF-d$_8$
$^{1}$H, 400 MHz, THF-d$_8$
$^3$P, 121 MHz, CD$_2$Cl$_2$
$^{13}C$, 100 MHz, $CD_2Cl_2$
$^{1}H$, 400 MHz, THF-d$_8$
\[ \delta 76.5 \text{ ppm} \quad \delta 87.9 \text{ ppm} \]

\[ ^{31}\text{P}, 121 \text{ MHz}, \text{THF-d}_8 \]
\[ \text{Spectrum: } ^{13}\text{C, 125 MHz, THF-d}_8 \]
<20 minutes after dissolving
$^1$H, 400 MHz, THF-d$_8$
$^{31}$P, 121 MHz, THF-d$_8$

< 20 minutes after dissolving
n-Bu
CH₃O
Ad
Ad
/
Ad Ad
Br
-But

P
--
CH₃
0
P,
/
i-Pr

Pd

i-Pr
Pd
H

CH₃
i-Pr

i-Pr
ICH₃
0
i-Pr

20 hours after dissolving

¹H, 400 MHz, THF-d₈
20 hours after dissolving

$^{31}$P, 121 MHz, THF-$d_8$
20 hours after dissolving
$^{13}$C, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 202 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
<20 minutes after dissolving
$^1$H, 400 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^{31}$P, 121 MHz, CD$_2$Cl$_2$
1 hour after dissolving
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
δ 50.1 ppm \text{^i-Pr}

< 20 minutes after dissolving

\textsuperscript{31}P, 121 MHz, CD\textsubscript{2}Cl\textsubscript{2}
1 hour after dissolving

$^{13}\text{C}$, 100 MHz, CD$_2$Cl$_2$
$^1$H, 400 MHz, CD$_2$Cl$_2$
$^{31}\text{P}, 121\text{ MHz}, \text{CD}_2\text{Cl}_2$
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^1$H, 400 MHz, CD$_2$Cl$_2$
< 20 minutes after dissolving

$^{31}$P, 121 MHz, CD$_2$Cl$_2$
1 hour after dissolving

$^{13}$C, 100 MHz, CD$_2$Cl$_2$
$^{1}H$, 400 MHz, CD$_2$Cl$_2$
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
$^1$H, 400 MHz, THF-d$_8$
$^{31}$P, 121 MHz, CD$_2$Cl$_2$
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
$^1\text{H NMR, 400 MHz, CD}_2\text{Cl}_2$
$^{13}$C NMR, 100 MHz, CD$_2$Cl$_2$
$^{1}H$ NMR, 400 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 122 MHz, CD$_2$Cl$_2$
$^{19}$F NMR, 282 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 100 MHz, CD$_2$Cl$_2$
n-BuPdPrBr

H, 300 MHz, CD2Cl2
$^{13}$C, 100 MHz, CD$_2$Cl$_2$
$^1\text{H}, 400 \text{ MHz, CD}_2\text{Cl}_2$
$^{1}$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^{1}H$ NMR, 500 MHz, CD$_2$Cl$_2$
$^{31}$P NMR, 121 MHz, $CD_2Cl_2$
$^{19}$F NMR, 470 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
Chapter 2. Studying the Formation of Regioisomers in the Pd-Catalyzed Fluorination of Electron-Rich Aryl Triflates by Deuterium Labeling
2.1. Introduction. As described in the introduction to this work, a catalyst based on the biaryl phosphine ligand iBuBrettPhos (1) can effect the conversion of aryl triflates to the corresponding aryl fluorides using CsF, but, surprisingly, the fluorinations of electron-rich substrates lacking ortho-substituents, such as 2-OTf and 3-OTf, yield regioisomeric products 2b and 3b in addition to desired products 2a and 3a (Figure 2.1). In contrast, electron-deficient (4-OTf) and ortho-substituted substrates (5-OTf) convert cleanly to the desired products 4a and 5a, respectively (Figure 2.1).

![Figure 2.1. Regioisomer formation in the Pd-catalyzed fluorination of aryl triflates 2-5-OTf, and ligands (1, 6) for this process. tol = toluene.](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>R'</th>
<th>% Yield (a + b)</th>
<th>a : b</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-OTf</td>
<td>H</td>
<td>OMe</td>
<td>55</td>
<td>1 : 2.7</td>
</tr>
<tr>
<td>3-OTf</td>
<td>H</td>
<td>nBu</td>
<td>70</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>4-OTf</td>
<td>H</td>
<td>CN</td>
<td>80</td>
<td>&gt; 99 : 1</td>
</tr>
<tr>
<td>5-OTf</td>
<td>Me</td>
<td>H</td>
<td>80</td>
<td>&gt; 99 : 1</td>
</tr>
</tbody>
</table>

Intriguingly, attempting to increase the yield by adding 4-(nBu)PhOTf (3-OTf) to trap the L-Pd(0) species formed after reductive elimination led to regioisomeric mixtures of 3a and 3b (Figure 2.2). Together, these results confirm that: a) potential catalytic intermediate 7a does not generate significant quantities of regioisomeric 3-
(nBu)PhF (3b) on its own, and b) regioisomer formation in the catalytic reaction may not require the presence of basic CsF to occur. Based on the findings presented in Chapter 1, the catalytic cycle shown in Figure 2.2, involving oxidative addition of the aryl triflate to 8 to form 9, transmetallation with CsF to form 7, and C–F reductive elimination from 7, is a feasible pathway to form aryl fluorides from aryl triflates. Thus, in the case of aryl triflates such as 2-OTf and 3-OTf, a separate pathway must be occurring to generate the regioisomeric products 2b and 3b. In the present work, we provide evidence that the process in Figure 2.2 occurs to convert 3-OTf to 3a, and that the analogous pathway is operative during the fluorination of other aryl triflates. However, in cases where regioisomeric mixtures of products are observed, ortho-deprotonation of L•Pd(Ar)OTf intermediates (9) to generate Pd-aryne intermediates, which recombine with HF to ultimately produce regioisomeric mixtures of aryl fluorides, competes with this process. Although our previously reported stoichiometric studies show that L•Pd(Ar)F complexes are capable of effecting this ortho-deprotonation process as well, the studies presented in this chapter suggest that CsF is the more likely culprit for this process in the catalytic reaction. By selectively deuterating aryl fluoride products generated from Pd-aryne intermediates, we can estimate the contribution of this pathway to the outcome of catalytic fluorination reactions.

2.2. Evidence for Pd-aryne intermediate. The most straightforward mechanism for regioisomer formation in this reaction would involve ortho-deprotonation of the starting material or product(s) by a basic fluoride species without direct involvement of the catalyst. The aryne so generated would lead to both aryl fluoride products by
nucleophilic attack of external fluoride at two distinct sites.\(^3\) Because regioisomer formation is not observed in the absence of catalyst, we consider this pathway unlikely.\(^4\)

A more plausible scenario is ortho-deprotonation of a catalytic intermediate, such as 9 or 7, by an external basic fluoride species to generate a Pd-aryne\(^5\) intermediate such as 10 (Figure 2.3). The basic fluoride source could be either CsF or a second molecules of 7, as suggested by our previous stoichiometric experiments (Figure 2.2).\(^6\) The nonselective

![Diagram](image_url)

**Figure 2.2.** Observed stoichiometric C–F reductive elimination from 7a, with regioisomer formation observed only in the presence of 3-OTf (top, see Chapter 1 for details),\(^8b\) and the proposed catalytic cycle for the formation of aryl fluorides from aryl triflates (bottom). n/o = not observed.
reaction of 10 with HF would provide regioisomeric \( \text{L\textbullet Pd(Ar)F} \) complexes 7 and 7', which could in turn independently undergo C–F reductive elimination to generate the observed mixture of regioisomeric aryl fluorides (a and b). Consistent with this hypothesis, we have reported that the fluorinations of 2,6-dideuterated aryl triflates show improved regioselectivity compared to their non-deuterated analogues, suggesting that scission of the C-H bond adjacent to the triflate group occurs before or during the regioselectivity-determining step.\(^8\)^\(^9\)

To investigate the plausibility of this mechanism, we reasoned that the addition of an exchangeable deuterium source to the reaction mixture would form \( \text{DF} \) \textit{in situ}, which could recombine with 10 to allow deuterium incorporation into the aryl fluoride products. However, any product resulting from the desired direct C–F reductive elimination pathway outlined in Figure 2.2 would not show evidence of deuterium incorporation under these conditions. When 1.0 equiv of \( t\text{BuOD} \) was added to the catalytic fluorination of 3-OTf, 20% deuterium labeling of the aryl fluoride products was detected by GC/MS.\(^10\)^\(^{11}\)^\(^{12}\) In addition to the normally observed \(^19\text{F} \) NMR signals for 3a (30%) and 3b (14%) in the product mixture were two new signals for aryl fluoride species 3c (3%) and 234
3d (8%) (Figure 2.4). The structures of these compounds were confirmed by their independent synthesis using the routes in Scheme 2.1. Compound 3a was prepared from 11 by adapting previously reported conditions for the Balz-Schiemann reaction via diazonium salt 12, which was not isolated. Negishi coupling of 13 with nBuZnCl in the presence of XantPhos-based 2-aminobiphenyl mesylate precatalyst 15 gave 14, which could be converted to 3c by lithium-halogen exchange with tBuLi followed by quenching with CD3OD at −78°C. Similar routes were used to prepare 3b and 3d (not shown). The presence of 3b in the product mixture suggests that deuteration of products originating from 10a was not complete, and therefore that some of the desired product 3a likely comes from 10a as well. By assuming that the two sites of 10a are similarly susceptible to deuterium incorporation upon reaction with DF (see experimental for details), we estimate that 5% of the observed 3a comes from the aryne intermediate 10a, and the other 25% originates from a pathway for which no deuterium labeling or regioisomer formation is possible. In other words, 56% of the aryl fluoride products likely originate from 10a, and the other 45%, exclusively 3a, likely comes from the desired C-F cross-coupling pathway outlined in Figure 2.2. This study provides the first tangible evidence that formation of 10a (Figure 2.3), leading to 3a-b, and C-F cross-coupling (Figure 2.2), leading only to 3a, are directly competing processes during the catalytic fluorination of 3-OTf.

2.3. Kinetic profiles of Pd-catalyzed fluorinations of 1-naphthyl and 4-(nbutyl)phenyl triflates. To determine the kinetic parameters of the two pathways occurring during the
fluorination of 3-OTf, it is helpful to compare the Pd-catalyzed fluorinations of 1-naphthyl triflate (16-OTf, Figure 2.5), which proceeds cleanly to 1-fluoronaphthalene (16e) and thus likely by a pathway analogous to that outlined in Figure 2.2, with that of
3-OTf, which produces both 3a and 3b. Notably, the addition of tBuOD to the fluorination of 16-OTf did not result in deuterium incorporation into the formed 1-fluoronaphthalene 16e, indicating that competitive Pd-aryne formation is likely not occurring in this case (Figure 2.5A; see Section 2.8 for discussion). The fluorination of 16-OTf is zeroth order in [ArOTf], first order in [Pd] ($k_{10\%{Pd}}/k_{5\%{Pd}} = 1.82 \pm 0.18$, Figure 2.5B), and, as we have previously reported, shows a positive order in CsF.$^{17,18}$ Thus, the rate law for the desired cross-coupling process (at least in this case) follows a rate $= k[Pd][CsF]^n (n > 0)$. These findings are consistent with L·Pd(1-naphthyl)OTf species 17a or 17b (Figure 2.5C) being the resting state of the catalyst. Thus, for the desired cross-coupling reaction, the resting state of the catalyst is likely a L·Pd(Ar)OTf species ($L = 1$ or 6), and either transmetallation or reductive elimination is the rate-determining step of the catalytic cycle.$^{19}$

The fluorination of 3-OTf shows many of the same features as that of 16-OTf (Figure 2.6). In Chapter 1 we showed that this reaction is zeroth order in aryl triflate. Indeed, the growth of both products over time is linear (Figure 2.6A), with the relative rates for their formation ($k_{4-nBu}/k_{3-nBu} = 1.67 \pm 0.34$) approximately equal to the final observed regioselectivity (3a:3b $\approx 1.7:1$). This finding is consistent with our hypothesis that formation of the undesired regioisomer 3b occurs competitively with formation of 3a, and suggests that both products ultimately originate from the same intermediate. In addition, the rate of starting material consumption during the Pd-catalyzed fluorination of 3-OTf shows a nearly identical dependence on [Pd] ($k_{10\%{Pd}}/k_{5\%{Pd}} = 1.71 \pm 0.18$, Figure 2.6B) as the reaction of 16-OTf ($k_{10\%{Pd}}/k_{5\%{Pd}} = 1.82 \pm 0.18$, Figure 5B). This finding suggests that the rate dependence on [Pd] of the pathways occurring during the
Figure 2.5. Analysis of the Pd-catalyzed fluorination of 16-OTf, which proceeds cleanly to 16e. A) No deuterium incorporation to form 16f is observed in the presence of tBuOD. B) Rate of starting material consumption during the fluorination of 16-OTf with 5% "Pd" (blue diamonds) or 10% "Pd" (red squares). Conversions determined by GC analysis. C) The resting state of the catalyst during the catalytic fluorination reaction is likely 17a or 17b.
fluorination of 3-OTf is nearly equal, as otherwise this reaction would show a different rate dependence on [Pd] than the fluorination of 16-OTf \textit{(vide infra)}. Indeed, when the catalytic fluorination of 3-OTf was conducted using varying amounts of [(cinnamyl)PdCl]$_2$ (2.50–10.0 %) and 1 (3.75–15.0 %) while maintaining the 1:1.5 ratio of Pd:1, no significant change in the extent of deuterium incorporation was observed (see Table 2.8A in the Experimental). Likewise, changing the amount of 1 (5.00-10.0%) while holding the quantity of [(cinnamyl)PdCl]$_2$ constant (see Table 2.8B in the Experimental), or conducting the same experiment using varying amounts of 9a (5.00-
10.0 %) (see Table 2.8C in the Experimental), showed no significant dependence of regioselectivity or % aryne on catalyst or ligand loading.

Similar to the results previously reported for the fluorination of 16-OTf, the Pd-catalyzed fluorination of 3-OTf displays a small but statistically significant positive order in [CsF] \((k_{3\text{eq CsF}}/k_{1.5\text{eq CsF}} = 1.24 \pm 0.09, \text{Figure 2.6B)}\). The observed zeroth order dependence on [ArOTf] but positive order in [CsF] suggests that 9a is likely the resting state of the catalyst during this reaction. Additionally, low temperature \(^{19}\text{F NMR}\) (470 MHz, \(-78^\circ\text{C}\)) studies of the catalytic fluorination reaction of 3-OTf run to partial...
conversion (see Experimental Figure 2.13) support that 9a is the resting state of the catalyst, with 7a present in too low of a concentration to be reliably observed.\textsuperscript{21} From all of the experiments we have conducted to date, we can reliably conclude that: a) the resting state of the catalyst in these reactions is a L•Pd(Ar)OTf species; b) regioisomer formation and the desired cross-coupling reaction show a similar rate dependence on [Pd]; 3) both reactions show a positive, non-linear dependence on [CsF]; and 4) ortho-deprotonation is the rate-determining step of regioisomer formation (vide supra). Based on these conclusions, we next investigated which species were directly involved in Pd-aryne formation during the catalytic fluorination of 3-OTf.

2.4. Species undergoing ortho-deprotonation. We initially hypothesized that 9a is the major species undergoing ortho-deprotonation competitively with transmetallation because: a) 9a is the resting state of the catalyst, and so is present in a much higher concentration than 7a; b) the protons in 9a adjacent to the cationic Pd center should be more acidic than the corresponding protons in 7a; and c) in our previously reported stoichiometric reductive elimination experiments with 7a (Figure 2.2), regioisomer formation was observed only when 3-OTf was added to trap the L•Pd(0) species formed after reductive elimination from 7a.\textsuperscript{8b,22} In addition, the lack of multiply deuterated products in the product mixture is consistent with ortho-deprotonation of 9a instead of 7a. The deprotonation of 9a to form 10a should be irreversible, because the reverse process would require three species – namely, 10a, HF, and CsOTf – to react together in the transition state.\textsuperscript{23} Thus, if 7a (and the corresponding meta-substituted isomer 7a') cannot be deprotonated during the catalytic reaction, only one deuterium incorporation
event could take place before formation of the desired aryl fluorides, leading to 3a-d. However, if ortho-deprotonation of 7a (or 7a') in competition with reductive elimination were possible, than multiple deuterium atoms could be incorporated into the aryl fluoride products. The lack of multiply deuterated products is consistent with the reaction of 10a with HF being irreversible. In other words, ortho-deprotonation of 7a likely does not directly compete with reductive elimination.24

2.5. F⁻ source involved in Pd-aryne formation. We also investigated whether CsF or 7a was more likely to be the base responsible for Pd-aryne formation. Although significantly more CsF (~ 40-60 eq. relative to 9a) is present than 7a during the catalytic reaction, our previous stoichiometric studies corroborate that 7a is capable of deprotonating 9a.22 Our kinetic studies with 16-OTf suggest that the rate law of the desired cross-coupling process is rate = k[Pd][CsF]ⁿ (n > 0). In addition, the improved regioselectivity observed with 2,6-dideuterated substrates suggests that ortho-deprotonation occurs before or during the rate-limiting step of regioisomer formation.1 If rate-limiting ortho-deprotonation involved one molecule of 7a reacting with a molecule of 9a, then the rate of ortho-deprotonation would follow rate = k[Pd]². In this case, the extent of regioisomer formation and % aryne would increase with catalyst loading, as the rate of ortho-deprotonation would be greatly accelerated over that of cross-coupling. However, if ortho-deprotonation involved deprotonation of 9a by CsF, the rate of ortho-deprotonation would follow rate = k[Pd][CsF]ᵐ (m > 0, m and n are not necessarily equal). In this case, increasing the catalyst loading would equally raise the rate of the competing cross-coupling process (Figure 2.2) and Pd-aryne formation (Figure 2.3),

242
resulting in no change in regioselectivity at higher catalyst loadings. As we previously showed (Section 2.3), changing the catalyst loading of the Pd-catalyzed fluorination of 3-OTf does not affect the regioselectivity or % aryne of the reaction. These results suggest that regioisomer formation and the pathway shown in Figure 2.2 have the same rate dependence on [Pd]. This result is consistent with CsF, not a L•Pd(Ar)F intermediate, acting as the base responsible for ortho-deprotonation of 9a. Nonetheless, stoichiometric experiments confirm that 7a is capable of reacting with 9a to generate 10a. Therefore, it is likely only the extremely low concentration of 9a present during the catalytic reaction that limits its involvement in regioisomer formation. We cannot entirely rule out that a small portion of the 10a formed during the catalytic reaction comes from ortho-deprotonation of 9a by 7a.

**Table 2.1.** Stoichiometric transmetallation experiments with 12 and CsF in toluene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CsF eq.</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>12</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>0.5</td>
<td>85</td>
<td>55</td>
</tr>
</tbody>
</table>

We also investigated the stoichiometric reaction between 9a and CsF to search for evidence of formation of 10a. When CsF (5 eq.) was added to a solution of 9a (1 eq.) in toluene, minimal conversion to 7a was observed, even after 12 h (entry 1, Table 2.1). This finding is likely due to the poor solubility of CsF in toluene, especially at room temperature. When the CsF:Pd ratio was increased to that found at the beginning of the
Figure 2.7. Complex 9 can either undergo transmetalation to yield 7 (Figure 2.2) and ultimately aryl fluoride a, or ortho-deprotonation to yield 10 (Figure 2.3) and ultimately aryl fluorides a (from 7) and b (from 7'), during the catalytic fluorination reaction.

catalytic reaction (60:1), significant conversion (85%) of 9a occurred in only 0.5 h, but a lower yield of 7a than expected (55% yield relative to an internal standard) was observed (entry 2, Table 2.1). No other fluorine- or phosphorus-containing species could be detected by NMR, as the generated HF was likely rapidly trapped as CsHF2. However, analysis of the reaction mixture by GC/MS showed unidentified high molecular weight compounds to be present. Thus far, our unsuccessful efforts to isolate 10a (not shown) suggest that it is extremely reactive towards trimerization and oligimerization in
solution.⁸ Thus, the discrepancy in conversion and yield when 9a is reacted with CsF is indirect evidence that 10a is forming in situ along with 7a.²⁵ Based on these findings, the mechanism shown in Figure 7, involving competitive transmetallation (leading ultimately to a) and deprotonation (leading ultimately to a and b) of a L•Pd(Ar)OTf intermediate with CsF, is the most likely scenario for regioisomer formation in the Pd-catalyzed fluorination of aryl triflates.

2.6. Para-substituent effects We next applied our deuterium labeling protocol to other para-substituted substrates to gain insight into the effect of aryl triflate substitution patterns on the formation and behavior of 10 (Table 2.2). For each substrate, two Pd-catalyzed fluorinations were conducted: one without tBuOD added to determine the combined yield (a + b)¹⁰ and regioselectivity (a : b) of the reaction, and one with tBuOD added to determine the total deuterium incorporation into the aryl fluoride products (% D) and the estimated fraction of aryl fluoride products originating from 10 (% aryne). In a series of para-substituted aryl triflates (Table 2.2), deuterium incorporation (% D) and % aryne steadily decrease as the substituent becomes more electron-withdrawing, so that electron-deficient aryl fluorides 4a, 21a, and 22a are formed without any corresponding deuterated or regioisomeric products. The observed reactivity of para-substituted aryl triflates is consistent with the mechanistic scenario presented in Figure 2.7. This is because catalytic intermediates bearing electron-rich aryl groups would undergo slower transmetallation than those bearing electron-deficient aryl groups, providing a greater
Table 2.2. Effect of \textit{para}-substituents on fluorination.

\begin{table}[h]
\centering
\begin{tabular}{cccccc}
\hline
Substrate & R & Combined \% Yield (a + b)$^\text{a,10}$ & \textit{para} : \textit{meta} (a : b)$^\text{a}$ & a : c : b : d$^\text{b}$ & \% D$^\text{b}$ & \% aryne$^\text{b}$ \\
\hline
3-OTf & nBu & 70 & 1.5 : 1 & 30 : 3 : 14 : 8 & 20 ± 1 & 56 ± 3 \\
18-OTf & H & 61 & – & 51 : 10 & 16 ± 1 & 16-33$^c$ \\
19-OTf & Ph & 75 & 8.5 : 1 & 66 : 5 : 5 : 5 & 12 ± 1 & 25 ± 3 \\
20-OTf & Cl & 37 & 7.8 : 1 & 31 : 2 : 2 : 2 & 11 ± 1 & 20 ± 3 \\
21-OTf & CO$_2$Me & 94 & > 99 : 1 & 94 : n/o : n/o : n/o & < 1 & < 1 \\
4-OTf & CN & 80 & > 99 : 1 & 80 : n/o : n/o : n/o & < 1 & < 1 \\
22-OTf & NO$_2$ & 80 & > 99 : 1 & 80 : n/o : n/o : n/o & < 1 & < 1 \\
\hline
\end{tabular}
\end{table}

$^a$0.2 mmol scale, reactions without tBuOD added. $^b$0.2 mmol scale, reactions with tBuOD added. $^{19}$F NMR yields. $^c$Estimated range assuming that between 0\% of 18a (16\% aryne) and 10\% of 18a (33\% aryne) originates from 10. n/o = not observed.

opportunity for competitive \textit{ortho}-deprotonation by CsF (or 7) to occur. Notably, multiply deuterated products were not observed in the product mixtures for these \textit{para}-substituted substrates, consistent with our hypothesis that conversion of 10 to 7 is irreversible.$^{26}$

We have previously reported that Pd-catalyzed fluorination reactions conducted in cyclohexane instead of toluene result in improved regioselectivity for formation of the desired product.$^1$ However, using cyclohexane as the reaction solvent typically requires higher temperatures and/or catalyst loadings, presumably due to the even lower solubility of CsF in cyclohexane compared to toluene.$^{27}$ As the results in Table 2.3 show, for 3-OTf and 19-OTf more of the aryl fluoride product a originates from the desired cross-coupling process (Figure 2.2) and less from Pd-aryne 10 (Figure 2.3), leading to an improved regioselectivity for the desired products 3a and 19a, respectively.$^{28}$ Notably, the fluorination reactions of substrates with more electron-withdrawing \textit{para}-substituents
proceed to a single regioisomer of product in cyclohexane as well as in toluene (not shown). The two most likely explanations for increased regioselectivity in cyclohexane are: 1) less of Pd-aryne 10 is forming in cyclohexane, or 2) 10 forms to an equal degree in both solvents, but is converted into non-fluorine-containing side products, such as aryne-derived trimmers or oligomers, instead of aryl fluoride products, in cyclohexane.

Because the overall yields for the reactions in Table 2.3 are close to those in Table 2.2, and no increase in potential aryne-derived byproducts occurs in cyclohexane, the second explanation is unlikely. Thus, switching the solvent to cyclohexane likely slows down ortho-deprotonation more than it does transmetallation, leading to the observed increase in regioselectivity. The reason for this change remains unclear, although a subtle change in the nature of the reaction occurring between 9 and the surface of CsF nanoparticles is the most likely explanation. Nonetheless, switching to the non-polar solvent cyclohexane has the general benefit of decreasing the amount of aryl fluorides originating from Pd-aryne 10.

Table 2.3. Deuterium labeling results with cyclohexane as solvent.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>Combined % Yield (a + b)a,10</th>
<th>a : b : c : d10</th>
<th>% D10</th>
<th>% aryneb</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-OTf</td>
<td>nBu</td>
<td>6.0</td>
<td>5.7 : 1</td>
<td>30 : 2 : 6 : 4</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>19-OTf</td>
<td>Ph</td>
<td>79</td>
<td>12 : 1</td>
<td>64 : 3 : 2 : n/o</td>
<td>4 ± 1</td>
</tr>
</tbody>
</table>

0.2 mmol scale, reactions without tBuOD added. 19F NMR yields. 0.2 mmol scale, reactions with tBuOD added. 19F NMR yields. Estimated range assuming that between 0% of 19a (7% aryne) and 3% of 19a (12% aryne) originates from 10. cy = cyclohexane.

2.7. Meta-substituent effects. In the case of meta-substituted substrates, the desired C–F cross-coupling process (Pathway A, Figure 2.8) leads to the meta-substituted product b.
Figure 2.8. Meta-substituted 9’ can either undergo transmetalation to yield 7’ and ultimately aryl fluoride b (Pathway A), and/or ortho-deprotonation to yield 10 (Figure 2.3) and ultimately products a and b from 7 and 7’, respectively (Pathway B), and/or ortho-deprotonation to yield 10’ and ultimately aryl fluorides b and e from 7’ and 7”, respectively (Pathway C). Ortho-substituted products e are not observed.

This pathway could be intercepted at intermediate 9’ by the formation of two Pd-aryne intermediates, either "away" from R (Pathway B) or "towards" R (Pathway C) (Figure 2.8). Deprotonation "away" from R provides 10, the same intermediate formed by deprotonation of the corresponding para-substituted substrate. Reaction of this intermediate with HF would provide complexes 7’ and 7, leading to the desired product b and the undesired para-substituted regioisomer a, respectively. Deprotonation between the Pd center and R would generate Pd-aryne 10’, which could in turn react with HF to form regioisomeric L•Pd(Ar)F complexes 7’ and 7”. Reductive elimination from 7’ and 7” would produce b and e, respectively (Figure 2.8). Preliminary isotopic labeling studies suggest that for the majority of meta-substituted substrates, all three pathways are operative during the catalytic reaction.29

Although determination of estimated % aryne values for reactions of meta-substituted substrates was not possible,29 we were able to investigate the effect of meta-substituents on regioisomer formation (Table 2.4). Notably, ortho-substituted products e30
Table 2.4. The effect of meta-substituents on the outcome of fluorination.$^a$

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$R$</th>
<th>Combined % Yield (b + a)</th>
<th>$meta : para$ (b : a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-OTf</td>
<td>nBu</td>
<td>73</td>
<td>14 : 1</td>
</tr>
<tr>
<td>24-OTf</td>
<td>tBu</td>
<td>76</td>
<td>16 : 1</td>
</tr>
<tr>
<td>25-OTf</td>
<td>CO$_2$Et</td>
<td>72</td>
<td>11 : 1</td>
</tr>
<tr>
<td>26-OTf</td>
<td>CN</td>
<td>76</td>
<td>16 : 1</td>
</tr>
<tr>
<td>27-OTf</td>
<td>NO$_2$</td>
<td>75</td>
<td>12 : 1</td>
</tr>
<tr>
<td>28-OTf</td>
<td>OMe</td>
<td>60</td>
<td>&gt; 99 : 1</td>
</tr>
<tr>
<td>29-OTf</td>
<td>NMe$_2$</td>
<td>59</td>
<td>&gt; 99 : 1</td>
</tr>
</tbody>
</table>

$^a0.2$ mmol scale. $^{19}$F NMR yields.

resulting from 7$''$ (Pathway C, Figure 2.8) were not observed in any case. With alkyl-substituted substrates 23-OTf ($R = nBu$) and 24-OTf ($R = tBu$), small amounts of para-substituted products 23-24a were observed along with the desired meta-substituted products 23-24b, which is consistent with formation of 10 (Pathway B, Figure 2.8) during the reaction (Table 2.4). Substrates bearing electron-withdrawing ester (25-OTf), nitrile (26-OTf), and nitro (27-OTf) groups in the meta-position also generate meta-substituted products (25-27b) with high regioselectivity over para-substituted aryl fluorides (25-27a) (Table 2.4). However, the identity of the electron-withdrawing group does not have a significant effect on the yield or extent of regioisomer formation. A different result was observed with OMe (28-OTf) or NMe$_2$ (29-OTf) groups in the meta position (28-OTf): in both cases, only the desired products 28-29b were observed by $^{19}$F NMR (Table 2.4). The absence of para-substituted products confirms that Pathway B (Figure 2.8) is not operative in these cases. Studies aimed at understanding the mechanistic intricacies of
the Pd-catalyzed fluorination of meta-substituted aryl triflates are ongoing in our laboratory. We note that similar to the results in Table 2.3, the fluorinations of 24-OTf (R = tBu) and 25-OTf (R = CO_2Et) could be carried out in cyclohexane to cleanly provide 24b and 25b, respectively, in high yield, with no evidence of regioisomer formation or deuterium incorporation in the presence of tBuOD (Figure 2.9).^1

Figure 2.9. Using cyclohexane as the reaction solvent improves the regioselectivity of the fluorinations of 24–25-OTf. cy = cyclohexane.

2.8. Ortho-substituent effects. In the case of ortho-substituted substrates, only one Pd-aryne intermediate, 10' (Figure 2.10), could conceivably form by competitive ortho-deprotonation of L•Pd(Ar)OTf complex 9'' (Pathway B, Figure 2.10) during the desired cross-coupling process (Pathway A, Figure 2.10). However, as for the fluorination of 16-OTf (Figure 2.5), meta-substituted regioisomers do not form during the Pd-catalyzed fluorination of any ortho-substituted aryl triflate tested to date (Table 2.5).^117 Indeed, substrates bearing ortho-alkoxy (30-OTf) and alkyl (31-OTf) substituents proceed cleanly to the desired ortho-substituted aryl fluorides without deuterium labeling in the presence of tBuOD (Table 2.5). Even ortho-substituted substrates bearing an electron-withdrawing group in the meta position (32-OTf) or an electron-donating group in the para position (33-OTf) do not undergo deuterium labeling or regioisomer formation, confirming that ortho-substitution overrules substituent patterns that normally result in regioisomer formation and deuterium incorporation (Tables 2.2 and 2.4).
Because we observed that a $L\cdot$Pd(Ar)OTf species was the resting state of the catalyst in both the fluorinations of 3-OTf (Figure 2.5) and 16-OTf (Figure 2.6), it is likely not a change in resting state or rate-determining step that explains the lack of regioisomer formation in the latter case. In general, we have observed that the Pd-catalyzed fluorinations of ortho-substituted substrates are much faster than those of other substrates (compare Figure 2.5B with Figure 2.6B). It is well-known that ortho-substituents accelerate the rate of reductive elimination. This could account for the complete regioselectivity of the reactions in Table 2.5 if reductive elimination is the rate-determining step of Pathway A (Figure 2.10) and transmetallation is reversible, as the reaction would rapidly funnel towards the desired product e without allowing for ortho-deprotonation of 9''.

**Figure 2.10.** Formation of Pd-aryne 10' from 9'' (Pathway B) does not occur during the Pd-catalyzed fluorination of ortho-substituted aryl triflates (Pathway A).

An alternative explanation for the complete regioselectivity of the reactions in Table 2.5 is that in an effort to minimize steric interactions between the ortho-substituent and the tBu groups of the phosphine ligand, 9'' would likely preferentially adopt a
Table 2.5. Fluorinations of ortho-substituted aryl triflates.$^{10,a}$

\[
\begin{align*}
\text{OTf} & \quad \text{R} \\
\text{F} & \quad \text{OMe} \\
\text{F} & \quad \text{Cy} \\
\text{F} & \quad \text{NO}_2 \\
\text{F} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{Me} \\
\text{F} & \quad \text{F} \\
\end{align*}
\]

$^{0.2}$ mmol scale. $^{19}$F NMR yields.

Figure 2.11. The shielding effect of $\text{tBu}$ groups on the ligand could decelerate ortho-deprotonation of preferred conformer A of $9''$; conformer B is disfavored due to steric interactions between R on the aryl group and the $\text{tBu}$ groups on the ligand.

conformation with the R group pointing away from the phosphine ligand (A, Figure 2.11), as pointing the R group towards the $\text{tBu}$ groups would be highly disfavored (B, Figure 2.11). This conformation would leave the only proton ortho to the Pd center (H*, Figure 2.11) very close to the bulky phosphine ligand, making deprotonation by CsF difficult. Similarly, increased steric interactions between the bulky phosphine ligand and R in 10' compared to 9'' could disfavor formation of this high energy intermediate and
thus decelerate the rate of Pd-aryne formation (Pathway B, Figure 2.10). In short, ortho-substituted aryl triflates are a general class of substrates that show no evidence of deuterium incorporation, suggesting that competitive formation of a Pd-aryne intermediate is not occurring under catalytic conditions.

2.9. Conclusion. In this chapter, we have demonstrated that deuterium labeling can be used to estimate the amount of Pd-aryne intermediates generated during the catalytic fluorination of a variety of ortho- and para-substituted aryl triflates. Using this method, we have revealed that the transmetallation step of the desired C–F cross-coupling process (Figure 2.2) likely competes with ortho-deprotonation to form a Pd-aryne intermediate (Figure 2.3). The substrate classes for which regioisomer formation remains a significant challenge are those bearing electron-donating groups in the para position, and those bearing certain electron-donating or withdrawing groups in the meta position, with no other substituents present. Switching the solvent to cyclohexane can prove beneficial in these cases by reducing the extent of products originating from Pd-aryne intermediates.\(^1\) Most importantly, the results in the preceding two chapters provide corroborating evidence that the mechanism that was our original goal to promote – C–F cross-coupling (Figure 2.2) – occurs to some degree during the Pd-catalyzed fluorination of aryl triflates. With strong confirmation that C–F reductive elimination from Pd(II) is a feasible step in Pd-catalyzed fluorination reactions, and a firm understanding of the mechanism of these reactions, our goal became to design a new catalyst capable of promoting the fluorination of a wider range of substrates under milder conditions.
2.10. Experimental.

2.10.1. General Procedures. All reactions were set up and carried out in a nitrogen-filled glovebox using oven-dried glassware and anhydrous degassed solvents unless otherwise noted. Anhydrous, oxygen-free toluene, dichloromethane (CH$_2$Cl$_2$), and tetrahydrofuran (THF) were obtained by passage through activated alumina columns under argon pressure before use. Cyclohexane was purchased from Aldrich in Sure-Seal™ bottles. CD$_2$Cl$_2$ (99.9%) and other deuterium sources (Table SI) were purchased in sealed ampules from Cambridge Isotopes. tBuOD (99%) and CDCl$_3$ were purchased from Cambridge Isotopes. Cesium fluoride (99.9%) was purchased from Strem and dried at 200 °C under high vacuum for 24 h. The dried cesium fluoride was then transferred to a nitrogen-filled glovebox where it was thoroughly ground using an oven-dried mortar and pestle. The finely ground cesium fluoride was filtered through a stainless-steel sieve (purchased from Cole Parmer) to obtain cesium fluoride with particle size of < 45 μm. The preparation of tBuBrettPhos (I) has been previously described, some of the I used in this work was received as a gift from Dr. Naoyuki Hoshiya (MIT), for which we are grateful. All other reagents were purchased from commercial sources and used without further purification. All $^{19}$F NMR yields stated for fluorination reactions are calculated from $^{19}$F NMR (282 MHz) spectra relative to an internal standard of 1-fluoronaphthalene. All compounds were analyzed by $^1$H, $^{13}$C, $^{31}$P, and $^{19}$F NMR, IR spectroscopy, as well as GC/MS or elemental analysis. Copies of NMR data are attached at the end of the Supporting Information. $^1$H and $^{13}$C NMR spectra were recorded on Varian XL 300 MHz or Varian Inova 500 MHz spectrometers and calibrated using residual solvent as internal reference. The following abbreviations were used to explain multiplicities: s = singlet, d
= doublet, \textit{t} = triplet, \textit{pt} = pseudotriplet, \textit{q} = quartet, \textit{p} = pentet, \textit{m} = multiplet. $^{19}$F NMR spectra were recorded on Varian XL 300 MHz or Varian Inova 500 MHz spectrometers and calibrated to an external standard of CFCl$_3$ ($\delta$ 0.0 ppm). $^{31}$P-$^1$H NMR spectra were recorded on Varian XL 300 MHz or Varian Inova 500 MHz spectrometers calibrated to an external standard of \textit{aq}. H$_3$PO$_4$ ($\delta$ 0.0 ppm). Low temperature $^{19}$F and $^{31}$P-$^1$H NMR experiments were conducted on a variable temperature Varian Inova 500 MHz spectrometer capable of a temperature range of $-100 \, ^\circ\text{C}$ to $+150 \, ^\circ\text{C}$. IR spectra were recorded on a Thermo Scientific Nicolet iS5 Fourier Transform IR Spectrometer. GC/MS spectra were recorded on an Agilent 5975 Inert Mass Selective Detector. Elemental analysis was performed by Atlantic Microlabs Inc., Norcross, GA. High Resolution Mass Spectrometry (HRMS) data were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform ion cyclotron resonance mass spectrometer. Unless specified otherwise, reactions were carried out in oven-dried Fisher Scientific 16 x 125 mm screw-cap tubes (Cat. No. 1495925C) using Thermo Scientific PTFE/silicon F/15-425 10 septa (Cat. No. 03394A). All reactions performed in sealed reaction tubes should be carried out behind a blast shield or a closed hood sash.

2.10.2. Synthesis of Aryl Triflates. The preparations of 4-(\textit{n}butyl)phenyl (3-OTf)$_3$, 4-biphenyl (19-OTf)$_3$, 4-chlorophenyl (20-OTf)$_3$, methyl 4-carboxyphenyl (21-OTf)$_3$, 4-cyanophenyl (4-OTf)$_3$, 3-\textit{n}butyl) (24-OTf)$_3$, ethyl 3-carboxyphenyl (25-OTf)$_3$, 3-cyanophenyl (26-OTf)$_3$, 3-nitrophenyl (27-OTf)$_3$, 3-methoxyphenyl (28-OTf)$_3$, 3-(N,N-dimethylamino)phenyl (29-OTf)$_3$, 2-tolyl (5)$_3$, 2-methoxyphenyl (30-OTf)$_3$, 2-cyclohexyl (31-OTf)$_3$, and 2-methyl-5-nitrophenyl (32-OTf)$_3$ triflates have been
previously reported. 3-(nbutyl)phenyl triflate was prepared from 3-(nbutyl)phenol, which was prepared according to the literature procedure. 44 4-methoxyphenyl (2-OTf), phenyl (18-OTf), 4-nitrophenyl (22-OTf), and 1-naphthyl (16-OTf) triflates are commercially available.

Pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35 (td, $J = 8$, 1 Hz, 1H), 7.22 (d, $J = 8$ Hz, 1H), 7.08-7.12 (m, 2H), 2.67 (t, $J = 6$ Hz, 2H), 1.63 (m, 2H), 1.38 (sextet, $J = 5$Hz, 2H), 0.96 (t, $J = $ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 149.8, 146.1, 130.0, 128.6, 121.3, 118.9 (q, $J = 319$ Hz), 118.5, 35.4, 33.4, 22.3, 13.9 ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –73.2 ppm. IR (neat): 2960, 2934, 2863, 1615, 1581, 1486, 1421, 1206, 1139, 1116, 943, 924, 835, 785, 688, 605 cm$^{-1}$. Anal. Calcd. for C$_{11}$H$_{13}$F$_3$O$_3$S: C, 46.80, H, 4.64; found C, 46.72, H, 4.82.

Pale yellow oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.10-7.14 (m, 2H), 7.02-7.08 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 146.6, 138.4, 132.8, 130.5, 128.2, 121.0, 118.8 (q, $J = 318$ Hz), 20.9, 16.4 ppm; $^{19}$F NMR (CDCl$_3$, 282 MHz): $\delta$ –74.4 ppm. IR: 2930, 1992, 1418, 1247, 1203, 1173, 1138, 1087, 931, 869, 814, 691, 618 cm$^{-1}$. Anal. calcd. for C$_9$H$_9$O$_3$SF$_3$: C, 42.52, H, 3.57; found C, 42.81, H, 3.46.

Pale yellow oil. $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –73.2 ppm. IR: 1553, 1421, 1359, 1246, 1204, 1139, 1092, 888, 860, 814, 716, 609 cm$^{-1}$. No signals were detected by $^1$H NMR (500 MHz, CDCl$_3$). GC/MS: m/z calcd. for C$_7$D$_5$O$_3$SF$_3$: 231.1; found 231.1.

256
2.10.3. Synthesis of Aryl Fluorides. Most of the aryl fluorides prepared during the course of this work are commercially available or have been previously prepared; when not available, authentic samples were prepared as detailed below. \(^{19}\text{F} \text{NMR}\) (282 MHz) chemical shifts and MS spectra were compared to reported values or authentic samples (when available) to confirm the identity of the products.

\[
\begin{align*}
\text{NH}_2 
\begin{array}{c}
\text{11} \\
\text{nBu}
\end{array} \rightarrow \begin{array}{c}
\text{N}_2\text{BF}_4 \\
\text{12}
\end{array} \rightarrow \begin{array}{c}
\text{F} \\
\text{3a}
\end{array}
\end{align*}
\]

4-\((\text{nbutyl})\)aniline (11, 790 \(\mu\)L, 5.00 mmol, 1.00 eq.) was converted into the intermediate diazonium salt 12, a red oil, following a literature procedure.\(^{13}\) The diazonium salt was decomposed to 3a following the literature procedure with cyclohexane as the solvent.\(^{13}\) After completion of the reaction, saturated NaHCO\(_3\) (aq.) (10 mL) was added dropwise (this step decomposes any diazonium salts that may still be present in the crude reaction mixture). Hexanes (10 mL) was added, the layers were separated, and the aqueous layer was extracted with hexanes (2 x 10 mL). The combined organic layers were washed with saturated NaHCO\(_3\) (aq.) (10 mL), water (10 mL), and brine (10 mL), and then dried over MgSO\(_4\). The resulting solution was filtered through a short plug of silica gel, eluting with hexanes (50 mL). The solvent was carefully removed with the aid of a rotary evaporator, yielding 4-\((\text{nbutyl})\)fluorobenzene (3a, 698 mg, 92%) as a yellow oil. \(^1\text{H} \text{NMR}\) (300 MHz, CDCl\(_3\)):

\[\delta\ 7.10-7.17\ \text{(m, 2H)},\ 6.93-7.01\ \text{(m, 2H)},\ 2.60\ \text{(t, J = 8 Hz, 2H)},\ 1.60\ \text{(pentet, J = 8 Hz, 2H)},\ 1.36\ \text{(sextet, J = 8 Hz, 2H)},\ 0.95\ \text{(t, J = 7 Hz, 3H)}\ \text{ppm};\ \(^{13}\text{C} \text{NMR}\) (75 MHz, CDCl\(_3\)):

\[\delta\ 161.3\ \text{(d, J = 241 Hz)},\ 138.6\ \text{(d, J = 3 Hz)},\ 129.9\ \text{(d, J = 8 Hz)},\ 115.1\ \text{(d, J = 21 Hz)},\ 35.0,\]

257
34.0, 22.5, 14.1 ppm; $^{19}$F NMR (CDCl$_3$, 282 MHz): $\delta$ –118.6 ppm. IR: 3040, 2957, 2930, 2859, 1600, 1509, 1467, 1220, 1157, 1106, 1016, 823, 756, 735, 700 cm$^{-1}$. GC/MS: m/z calcd. for C$_{10}$H$_{13}$F: 152.2; found 152.2. These spectra are consistent with those reported in the literature.$^{46}$ (Note: this compound should not be placed under high vacuum due to its volatility).

An oven-dried Fisher Scientific 20 x 125 mm screw-cap tube (cat. no. 1495937A) equipped with a stir bar was charged with zinc chloride (272 mg, 2.00 mmol, 2.00 eq.) and lithium chloride (105 mg, 2.50 mmol, 2.50 eq.) in a nitrogen-filled glovebox. THF (5.0 mL) was added, and the reaction mixture was stirred vigorously for 5 min to dissolve the zinc chloride. The tube was capped and removed from the glovebox, and an inlet of argon was added. Next, the reaction mixture was cooled to 0 °C using an ice-water bath, and nBuLi (2.5 M solution in hexanes, 0.80 mL, 2.00 mmol, 2.00 eq.) was added dropwise. The ice-water bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 h. Under a stream of argon, 13 (300 mg, 1.00 mmol, 1.00 eq.), 15$^{15}$ (38.0 mg, 4%), and XantPhos (24.0 mg, 4%) were added to the tube, and the septum was replaced for a Fischer Scientific PTFE/SIL septum (cat. no. 03394B) that had not been punctured. The reaction mixture was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir vigorously for 12 h. At the time, the reaction mixture was cooled to room temperature and diluted with hexanes (20 mL) and water (10 mL).
phases were separated, and the aqueous phase was extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and filtered through a plug of silica gel, eluting with additional hexanes (30 mL). Careful evaporation of the solvent yielded 14 (206 mg, 90%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 7.36 (dd, J = 7, 2 Hz, 1H), 6.98-7.10 (m, 2H), 2.56 (t, J = 8 Hz, 2H), 1.51-1.62 (m, 2H), 1.34 (sextet, J = Hz, 2H), 0.93 (t, J = 7 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 157.5 (d, J = 243 Hz), 140.4 (d, J = 4 Hz), 133.3, 128.9 (d, J = 6 Hz), 116.2 (d, J = 22 Hz), 108.8 (d, J = 21 Hz), 34.8, 33.7, 22.4, 14.1 ppm; ¹⁹F NMR (CDCl₃, 282 MHz): δ −112.6 ppm. IR (neat): 2958, 2930, 2859, 1494, 1242, 1046, 872, 817, 767, 724, 671 cm⁻¹. GC/MS: m/z calcd. for C₁₀H₁₂Br: 230.0, 232.0; found 230.0, 232.0. (Note: this compound should not be placed under high vacuum due to its volatility).

An oven-dried reaction tube equipped with a stir bar was charged with 14 (90.0 mg, 0.38 mmol, 1.00 eq.) and THF (1.0 mL). The reaction mixture was cooled to −78 °C, and tBuLi (1.7 M solution in pentane, 0.69 mL, 1.17 mmol, 3.00 eq.) was added dropwise over 5 min, and the reaction mixture was allowed to stir at −78 °C for 30 min. Next, CD₃OD (158 μL, 3.80 mmol, 10.0 eq.) was added dropwise over 5 min, and the reaction mixture was allowed to stir at −78 °C for 15 min and then warmed to room temperature. The reaction mixture was quenched with water (3 mL) and pentane (3 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 x 3 mL). The combined organic phases were washed with saturated NaHCO₃ (aq.) (3 mL) and brine (3 mL), dried over MgSO₄, and filtered through
a silica plug, eluting with additional pentane (20 mL). Careful evaporation of the solvent yielded 3c (55 mg, 92%) as a colorless oil contaminated with <5% of the protonated analogue 3a. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.10-7.17 (m, 2H), 6.96 (pt, $J = 9$ Hz, 1H), 2.59 (t, $J = 8$ Hz, 2H), 1.53-1.64 (m, 2H), 1.36 (sextet, $J = 7$ Hz, 2H), 0.94 (t, $J = 7$ Hz, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.3 (d, $J = 242$ Hz), 138.7, 129.6-130.0 (m), 115.1 (d, $J = 21$ Hz), 35.0, 34.0, 22.5, 14.2 ppm (the $^{13}$C NMR signal for the deuterated carbon could not be observed); $^{19}$F NMR (CDCl$_3$, 282 MHz): $\delta$ -118.7 ppm. IR: 2958, 2929, 2860, 1594, 1492, 1220, 1126, 1027, 909, 598, 733 cm$^{-1}$. GC/MS: m/z calcd. for C$_{10}$H$_{12}$DF: 153.1; found 153.1. (Note: this compound should not be placed under high vacuum due to its volatility).

converted into the intermediate diazonium salt 12', a red oil, following a literature procedure.$^{13}$ The diazonium salt was decomposed to 3b following the literature procedure with cyclohexane as the solvent.$^{13}$ After completion of the reaction, saturated NaHCO$_3$ (aq.) (10 mL) was added dropwise (this step decomposes any diazonium salts that may still be present in the crude reaction mixture). Hexanes (10 mL) was added, the layers were separated, and the aqueous layer was extracted with hexanes (2 x 10 mL). The combined organic layers were washed with saturated NaHCO$_3$ (aq.) (10 mL), water (10 mL), and brine (10 mL), and then dried over MgSO$_4$. The resulting solution was filtered through a short plug of silica gel, eluting with hexanes (30 mL). The solvent was
carefully removed with the aid of a rotary evaporator, yielding 3-(n-butyl)fluorobenzene (3b, 361 mg, 95%) as a golden yellow oil. \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.17-7.27 (m, 1H), 6.84-6.98 (m, 3H), 2.62 (t, \(J = 8\) Hz, 2H), 1.55-1.67 (m, 2H), 1.37 (sextet, \(J = 7\) Hz, 2H), 0.95 (t, \(J = 7\) Hz, 3H) ppm; \(^1^3^C\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 163.1 (d, \(J = 232\) Hz), 145.6 (d, \(J = 7\) Hz), 129.7 (d, \(J = 8\) Hz), 124.2, 115.3 (d, \(J = 21\) Hz), 112.5 (d, \(J = 21\) Hz), 35.5, 33.5, 22.4, 14.1 ppm; \(^1^9^F\) NMR (CDCl\(_3\), 282 MHz): \(\delta\) -114.5 ppm. IR: 2958, 2931, 2860, 1614, 1591, 1488, 1448, 1253, 1140, 943, 875, 777, 689 cm\(^{-1}\). GC/MS: \(m/z\) calcd. for C\(_{10}\)H\(_{13}\)F: 152.2; found 152.2. (Note: this compound should not be placed under high vacuum due to its volatility).

An oven-dried Fisher Scientific 20 x 125 mm screw-cap tube (cat. no. 1495937A) was charged with zinc chloride (272 mg, 2.00 mmol, 2.00 eq.) and lithium chloride (105 mg, 2.50 mmol, 2.50 eq.) in a nitrogen-filled glovebox. THF (5.0 mL) was added, and the reaction mixture was stirred vigorously for 5 min to dissolve the zinc chloride. The tube was capped and removed from the glovebox, and an inlet of argon was added. Next, the reaction mixture was cooled to 0 °C using an ice-water bath, and \(n\)BuLi (2.5 M solution in hexanes, 0.80 mL, 2.00 mmol, 2.00 eq.) was added dropwise. The ice-water bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 h. Under a stream of argon, 13' (300 mg, 1.00 mmol, 1.00 eq.), 15\(^1^5\) (38.0 mg, 4%), and XantPhos (24.0 mg, 4%) were added to the tube, and the septum was replaced for a
Fischer Scientific PTFE/SIL septum (Cat. No. 03394B) that had not been punctured. The reaction mixture was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir vigorously for 12 h. At the time, the reaction mixture was cooled to room temperature and diluted with hexanes (20 mL) and water (10 mL). The phases were separated, and the aqueous phase was extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and filtered through a plug of silica gel, eluting with additional hexanes (30 mL). Careful evaporation of the solvent yielded 14' (180 mg, 78%) as a pale yellow oil. "H NMR (300 MHz, CDCl₃): δ 7.42 (pt, J = 7 Hz, 1H), 6.95 (dd, J = 10, 2 Hz, 1H), 6.84 (dd, J = 8, 2 Hz, 1H), 2.57 (t, J = 8 Hz), 1.52-1.63 (m, 2H), 1.34 (sextet, J = 8 Hz, 2H), 0.93 (t, J = 7 Hz, 3H) ppm; "C NMR (75 MHz, CDCl₃): δ 159.1 (d, J = 245 Hz), 145.0 (d, J = 7 Hz), 133.2, 125.6 (d, J = 3 Hz), 116.6 (d, J = 21 Hz), 105.7 (d, J = 21 Hz), 35.2, 33.4, 22.4, 14.1 ppm; "F NMR (CDCl₃, 282 MHz): δ -108.6 ppm. IR: 2956, 2930, 2860, 1577, 1484, 1419, 1241, 1152, 1039, 950, 862, 813, 634 cm⁻¹. GC/MS: m/z calcd. for C₁₀H₁₂Br: 230.0, 232.0; found 230.0, 232.0. (Note: this compound should not be placed under high vacuum due to its volatility).

An oven-dried reaction tube equipped with a stir bar was charged with 14' (90.0 mg, 0.38 mmol, 1.00 eq.) and THF (1.0 mL). The reaction mixture was cooled to -78 °C, and tBuLi (1.7 M solution in pentane, 0.69 mL, 1.17 mmol, 3.00 eq.) was added dropwise over 5 min, and the reaction mixture was allowed to stir at -78 °C for 30 min. Next, CD₃OD (158 μL, 3.80 mmol, 10.0 eq.) was
added dropwise over 5 min, and the reaction mixture was allowed to stir at -78 °C for 15 min and then warmed to room temperature. The reaction mixture was quenched with water (3 mL) and pentane (3 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 x 3 mL). The combined organic phases were washed with saturated NaHCO₃ (aq.) (3 mL) and brine (3 mL), dried over MgSO₄, and filtered through a silica plug, eluting with additional pentane (20 mL). **Careful** evaporation of the solvent yielded 3d (55 mg, 92%) as a colorless oil contaminated with <5% of the protonated analogue 3b. **¹H NMR** (300 MHz, CDCl₃): δ 7.25 (pt, J = 7 Hz, 1H), 6.96 (dd, J = 8, 3 Hz, 1H), 6.90 (d, J = 9 Hz, 1H), 2.62 (t, J = 8 Hz, 2H), 1.55-1.67 (m, 2H), 1.37 (sextet, J = 7 Hz, 2H), 0.94 (t, J = 7 Hz, 3H) ppm; **¹³C NMR** (75 MHz, CDCl₃): δ 163.1 (d, J = 244 Hz), 145.7 (d, J = 7 Hz), 129.7 (d, J = 8 Hz), 124.2, 115.4 (d, J = 20 Hz), 35.6, 33.6, 22.5, 14.1 ppm (the **¹³C NMR** signal for the deuterated carbon could not be observed); **¹⁹F NMR** (CDCl₃, 282 MHz): δ -114.6 ppm. IR: 2957, 2930, 2860, 1612, 1580, 1479, 1425, 1237, 1133, 990, 865, 834, 730, 652 cm⁻¹. GC/MS: m/z calcd. for C₁₀H₁₂DF: 153.1; found 153.1. (Note: this compound should not be placed under high vacuum due to its volatility).

To an oven-dried reaction screw-cap tube equipped with a stir bar was added (in this order) cesium fluoride (338 mg, 2.25 mmol, 3 eq.), 1 (27 mg, 7.5%), palladium cinnamyl chloride dimer (9.8 mg, 2.5 %), 24-OTf (212 mg, 0.75 mmol, 1 eq.), and cyclohexane (7.5 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C. The reaction mixture was allowed to stir at this temperature for 24 h, at which time it was cooled to
room temperature and filtered through a short celite plug, eluting with Et₂O (20 mL). The solvent was carefully removed with the aid of a rotary evaporator, and the crude product was purified by flash chromatography (pentane) to yield 3-(t-butyl)fluorobenzene (94 mg, 82%) as a colorless oil. Contaminated with <2 % of 4-(t-butyl)fluorobenzene by ¹⁹F NMR. ¹H NMR (300 MHz, CDCl₃): δ 7.25-7.32 (m, 1H), 7.17-7.21 (m, 1H), 7.08-7.14 (m, 1H), 6.86-6.93 (m, 1H), 1.35 (s, 9H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 163.0 (d, J = 243 Hz), 154.1 (d, J = 6 Hz), 129.5 (d, J = 8 Hz), 121.0 (d, J = 3 Hz), 112.6 (d, J = 21 Hz), 112.3 (d, J = 21 Hz), 31.4 ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -114.1 ppm; IR (neat): 2965, 2906, 2870, 1615, 1589, 1482, 1441, 1425, 1364, 1272, 1212, 1199, 1162, 910, 869, 813, 780, 697, 687 cm⁻¹. Anal. Calcd. for C₁₀H₁₃F: C, 78.91, H, 8.61; Found C, 78.69, H, 8.47. (Note: this compound should not be placed under high vacuum due to its volatility).

2.10.4. Synthesis of new complexes.

6a·Pd(4-(nBu)Ph)Br (75.0 mg, 0.08 mmol, 1.00 eq., prepared as in Chapter 1) was dissolved in CH₂Cl₂ (3.0 mL) in a 20 mL scintillation vial equipped with a stir bar. The vial was wrapped in aluminum foil and AgOTf (25.0 mg, 0.01 mmol, 1.20 eq.) was added in one portion. The reaction mixture was stirred for 16 h, at which time pentane (5 mL) was added and the non-homogenous mixture was allowed to stand for 24 h at -20 °C.
The reaction mixture was then filtered through a long (2 cm) plug of celite, and the solvent was removed in vacuo to yield a brown oil. Pentane (4 x 2 mL) was added and removed in vacuo to crystallize 9a (78.0 mg, 94%) as a red-brown solid. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.36 (dd, J = 8, 2 Hz, 1H), 7.17-7.31 (m, 7H), 7.11 (dd, J = 8, 2 Hz, 1H), 6.86 (d, J = 8 Hz, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 2.60-2.72 (m, 4H), 2.51 (t, J = 8 Hz, 2H), 2.29 (septet, J = 7 Hz, 1H), 1.61-1.68 (m, 2H), 1.60 (d, J = 7 Hz, 3H), 1.48-1.54 (m, 2H), 1.42 (d, J = 17 Hz, 9H), 1.37 (d, J = 17 Hz, 9H), 1.25-1.34 (m, 4H), 1.21 (d, J = 7 Hz, 3H), 1.13 (d, J = 7 Hz, 3H), 0.95 (t, J = 7 Hz, 3H), 0.85-0.91 (m, 6H), 0.63 (d, J = 7 Hz, 3H), 0.28 (d, J = 7 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 154.3, 154.3, 153.0, 152.9, 151.5, 151.5, 149.8, 148.5, 143.9, 143.9, 142.0, 140.0, 137.5, 135.7, 135.6, 133.2, 133.1, 133.0, 131.6, 131.4, 130.6, 130.3, 128.2-128.4 (m), 118.5, 118.5, 116.5, 116.5, 114.0, 114.0, 113.8, 113.8, 55.2, 55.1, 49.1, 42.5, 42.3, 42.3, 42.1, 42.0, 38.8, 35.6, 35.3, 35.0, 34.2, 33.9, 33.2, 32.3, 32.3, 32.2, 32.1, 32.1, 31.9, 31.8, 30.6, 29.3, 26.9, 25.7, 24.9, 24.7, 24.6, 34.2, 23.9, 22.7, 22.5, 20.8, 14.1, 14.0 ppm (observed complexity is due to C-P and C-F coupling); $^{31}$P{$^1$H}NMR (121 MHz, CD$_2$Cl$_2$): δ 114.4 ppm; $^{19}$F NMR (282 MHz, CD$_2$Cl$_2$): δ -78.2 ppm. HRMS: Calcd. M$^+$ for C$_{51}$H$_{74}$O$_2$PPd (M – CF$_3$SO$_3^-$), 855.4477; found, 855.4487.
17a was prepared using the standard procedure developed for the synthesis of oxidative addition complexes (see Chapter 1). An oven-dried vial equipped with a stir bar was charged with 1 (100 mg, 0.21 mmol, 1.00 eq.) and 16-OTf (122 μL, 0.62 mmol, 3.00 eq.). A minimal amount of cyclohexane necessary to dissolve 1 (~3 mL) was added. Next, (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂ (80.0 mg, 0.21 mmol, 1.00 eq.) was added in one portion, and the reaction mixture was allowed to stir overnight at room temperature, during which time an orange precipitate formed. Pentane (3 mL) was added, and the reaction mixture was stored at -20°C for 1 h, at which time it was filtered through a sintered glass frit. The resulting solid was washed with pentane (3 x 2 mL), yielding 17a (132 mg, 74%) as a bright orange solid. 

¹H NMR (500 MHz, CD₂Cl₂): δ 8.29 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.50 (pt, J = 7 Hz, 1H), 7.45 (pt, J = 7 Hz, 1H), 7.36-7.40 (m, 1H), 7.35 (s, 1H), 7.30 (bs, 1H), 7.25 (dd, J = 9, 4 Hz, 1H), 7.06-7.13 (m, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 2.82 (bs, 1H), 2.55 (bs, 1H), 1.71-1.79 (m, 4H), 1.15-1.53 (m, 27H), 0.76 (bs, 3H), 0.25 (bs, 3H) ppm; ¹³C NMR (125 MHz, CD₂Cl₂): δ 155.2, 154.7, 152.9, 152.8, 147.9, 145.9, 145.9, 140.5, 139.1, 139.0, 137.3, 135.5, 132.4, 132.3, 131.5, 131.4, 129.6, 129.4, 129.0, 126.8, 126.5, 125.8, 125.1, 124.7, 124.7, 117.9, 117.9, 116.8, 116.8, 116.0, 114.8, 114.5, 114.4, 55.4, 55.1, 41.8, 33.5, 32.3, 31.8, 31.3, 27.3, 26.3, 25.6, 24.2, 23.1, 22.8, 19.3 ppm (observed complexity is due to C-P and C-F coupling); ³¹P{¹H} NMR (121 MHz, CD₂Cl₂): δ 112.6 ppm; ¹⁹F NMR (282 MHz, CD₂Cl₂): δ -112.6 ppm.
MHz, CD₂Cl₂): δ -79.1 ppm. HRMS: Calcd. M⁺ for C₄₁H₅₆O₂PPd (M - CF₃SO₃⁻), 717.3066; found, 717.3072.

17b-1 was prepared using the standard procedure developed for the synthesis of oxidative addition complexes (see Chapter 1). An oven-dried vial equipped with a stir bar was charged with 1 (250 mg, 0.52 mmol, 1.00 eq.) and 1-bromonaphthalene (218 µL, 1.56 mmol, 3.00 eq.). A minimal amount of cyclohexane necessary to dissolve 1 (~ 10 mL) was added. Next, (1,5-cyclooctadiene)Pd(CH₂SiMe₃)₂46 (201 mg, 0.52 mmol, 1.00 eq.) was added in one portion, and the reaction mixture was allowed to stir overnight at room temperature, during which time a yellow precipitate formed. Pentane (5 mL) was added, and the reaction mixture was stored at -20°C for 1 h, at which time it was filtered through a sintered glass frit. The resulting solid was washed with pentane (3 × 4 mL), yielding 17b-1 (317 mg, 76%) as a bright yellow solid. Clean ¹H, ³¹P, and ¹³C NMR spectra for 17b-1 could not be obtained due to its poor solubility in deuterated organic solvents (CD₂Cl₂, THF-d₈, tol-d₈) and its isomerization to 17b-2¹⁹ once dissolved in solution. ³¹P NMR (121 MHz, CD₂Cl₂): δ 70.0 ppm. HRMS: Calcd. M⁺ for
Complex 17b-1 (239 mg, 0.30 mmol, 1.00 eq.) was suspended in THF (20 mL) in an oven-dried vial equipped with a stir bar. 1-bromonaphthalene (126 μL, 0.90 mmol, 3.00 eq.) was added, followed by 1,8-diazabicycloundec-7-ene (45.6 μL, 0.33 mmol, 1.10 eq.), and the reaction mixture was allowed to stir vigorously for 72 h. During this time, the suspended 17b-1 dissolved, the solution changed from yellow to brown in color, and a gray solid precipitated from solution. Analysis of an aliquot of the reaction mixture by 31P NMR at this time indicated the complete consumption of 17b-1 and 17b-2. The vial was stored at −20 °C for 12 h, and then filtered through a plug of celite, eluting with THF (10 mL). The solvent was removed in vacuo. Pentane (3 x 5 mL) was added and then
removed *in vacuo* to help solidify the desired product. Cyclohexane (5 mL) and pentane (5 mL) were added, resulting in precipitation of an orange-brown solid, which was filtered and further washed with pentane (3 x 5 mL) to yield **17b-3** (244 mg, 88%) as a pale orange solid. The $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$) spectrum of **17b-3** contains two signals in a 1:4 ratio (major, $\delta$ 70.3 ppm; minor, $\delta$ 69.7 ppm), indicating the presence of atropisomers from hindered rotation around the 1-naphthyl group on the bottom ring of the ligand. Thus, the $^1$H NMR (500 MHz, CD$_2$Cl$_2$) and $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) spectra of **17-b3** are extremely complex, and the $^1$H NMR spectrum (500 MHz, C$_6$D$_6$) shows evidence of signal coalescence and broadening upon heating (20 °C → 80 °C). The $^1$H NMR (500 MHz, CD$_2$Cl$_2$, rt), $^1$H NMR (500 MHz, C$_6$H$_6$, 20 °C → 80 °C), $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$, rt), and $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$, rt) spectra of **17b-3** are included below for reference. HRMS: Calcd. M$^+$ for C$_{51}$H$_{61}$O$_2$PPdBr (M – H), 923.2638; found, 923.2625.

17b-3 (125.0 mg, 0.14 mmol, 1.00 eq.) was dissolved in CH$_2$Cl$_2$ (5.0 mL) in a 20 mL scintillation vial equipped with a stir bar. The vial was wrapped in aluminum foil and AgOTf (38.3 mg, 0.15 mmol, 1.10 eq.) was added in one portion. The reaction mixture was stirred for 16 h, at which time pentane (5 mL) was added and the non-homogenous mixture was allowed to stand for 24 h at −20 °C. The reaction mixture was then filtered
through a long (2 cm) plug of celite, and the solvent was removed in vacuo to yield a brown oil. Pentane (4 x 2 mL) was added and removed in vacuo to crystallize 17b (132 mg, 95%) as a red-brown solid. \(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 8.69 (d, \(J = 9\) Hz, 1H), 7.89-7.95 (m, 2H), 7.84-7.88 (m, 1H), 7.77 (pt, \(J = 7\) Hz, 1H), 7.72 (d, \(J = 8\) Hz, 1H), 7.67 (d, \(J = 8\) Hz, 1H), 7.44-7.64 (m, 6H), 7.43 (s, 1H), 7.34 (d, \(J = 9\) Hz, 1H), 7.24 (dd, \(J = 10,\) 4 Hz, 1H), 7.18 (d, \(J = 7\) Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.38-3.42 (m, 1H), 2.85 (septet, \(J = 7\) Hz, 1H), 2.65-2.74 (m, 1H), 2.01 (d, \(J = 7\) Hz, 3H), 1.58 (d, \(J = 17\) Hz, 9H), 1.33 (d, \(J = 18\) Hz, 9H), 1.24 (d, \(J = 7\) Hz, 3H), 1.18 (d, \(J = 7\) Hz, 3H), 0.74 (d, \(J = 7\) Hz, 3H), 0.23 (d, \(J = 7\) Hz, 3H), –0.40 (d, \(J = 7\) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CD\(_2\)Cl\(_2\)): complex spectrum, see attached; \(^{31}\)P NMR (122 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 121.0 ppm; \(^{19}\)F NMR (282 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) –79.2 ppm. HRMS: Calcd. M\(^+\) for C\(_{51}\)H\(_{62}\)O\(_2\)PPd (M – CF\(_3\)SO\(_3\)^–), 843.3538; found, 843.3556.

### 2.10.5. Experimental Procedures.

**General procedure for fluorination reactions (Tables 2.2-2.5):** To an oven-dried screw-cap tube equipped with a stir bar was added (in this order) cesium fluoride (90.0 mg, 0.60 mmol, 3.00 eq.), 1 (7.20 mg, 7.50 %), aryl triflate (0.20 mmol, 1.00 eq.), palladium cinnamyl chloride dimer (2.60 mg, 2.50 %), and toluene (2.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C. The reaction mixture was allowed to stir at this temperature for 12 h. The reaction mixture was then cooled to room temperature, and 1-fluoronaphthalene (40.0 µL, 1.55 eq.) was added. The crude reaction mixtures were analyzed directly by
$^{19}$F NMR (282 MHz) to determine conversion, yield, and regioselectivity, as necessary. The same procedure was used for reactions carried out in cyclohexane.

**General procedure for fluorinations with tBuOD (Tables 2.2-2.3, 2.5):** To an oven-dried screw-cap tube equipped with a stir bar was added (in this order) cesium fluoride (90.0 mg, 0.6 mmol, 3.00 eq.), 1 (7.20 mg, 7.50 %), aryl triflate (0.20 mmol, 1.00 eq.), tBuOD (19.1 uL, 0.20 mmol, 1.00 eq., as a solution in 0.2 mL toluene), palladium cinnamyl chloride dimer (2.60 mg, 2.50 %), and toluene (1.8 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C. The reaction mixture was allowed to stir at this temperature for 12 h. The reaction mixture was then cooled to room temperature, and 1-fluoronaphthalene (40.0 µL, 1.55 eq.) was added. The crude reaction mixtures were analyzed directly by $^{19}$F NMR (282 MHz) to determine conversion, yield, and regioselectivity, as necessary. The same procedure was used for reactions carried out in cyclohexane.

For every substrate discussed in this work, the signals for all products could be cleanly resolved by $^{19}$F NMR. In general, at least 32 scans were collected; we estimate that the absolute error in the NMR integrations is 1%. Using standard error propagation techniques, this results in an absolute error in % deuterium calculations of 2%, and an absolute error in % aryne calculation of 5%.

When analyzing the results of the experiment in Figure 2.4, 3b-d must come from 10a. However, some portion of 3a likely originates from 10a as well; we designate this quantity A. To determine the value of A, we rationalized that the two sites of the aryne intermediate should undergo deuterium incorporation at similar rates. This assumption is
likely valid because H/D exchange should be much faster than reaction of 10a with H/DF. Based on this assumption, the ratio of the fraction of 3-(nBu)PhF that is deuterated (3d) to the portion that is not deuterated (3b) should be similar to the ratio of the fraction of 4-(nBu)PhF that is deuterated (3c) to the undeuterated 4-(nBu)PhF originating from 10a (A); note that this does not include the 3a formed via C–F cross-coupling. In other words, 3c/A ≈ 3d/3b. In the case of the fluorination of 3, A = 5% of the 30% observed yield for 3a. A similar analysis was used in all cases to estimate the fraction of the product originating from Pd-aryne intermediates.

Table 2.6. Alternative deuterium sources.

<table>
<thead>
<tr>
<th>Source</th>
<th>% D</th>
<th>Source</th>
<th>% D</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBuOD</td>
<td>20</td>
<td>dioxane-d8</td>
<td>0</td>
</tr>
<tr>
<td>acetone-d6</td>
<td>13</td>
<td>anisole-d8</td>
<td>0</td>
</tr>
<tr>
<td>CD3CN</td>
<td>4</td>
<td>tol-d8 (as solvent)</td>
<td>0</td>
</tr>
</tbody>
</table>

"0.2 mmol scale. 19F NMR yields.

These reactions were conducted using the same procedure described for reactions utilizing tBuOD as the deuterium source. Other potential deuterium sources, including CD3NO2, CD3OD, and DMSO-d6, either inhibited the reaction or underwent competitive cross-coupling processes with the starting material.

Procedure for crossover experiment between C6D5OTf and 3-OTf (Figure 2.12): To an oven-dried screw-cap tube equipped with a stir bar was added (in this order) cesium fluoride (120 mg, 0.60 mmol, 3.00 eq.), 1 (7.20 mg, 7.50 %), 4-(nbutyl)phenyl triflate (3-
OTf, 56.0 mg, 0.20 mmol, 1.00 eq.), C₆D₅OTf (46.0 mg, 0.20 mmol, 1.00 eq.), palladium cinnamyl chloride dimer (2.60 mg, 2.50 %), and toluene (2.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C. The reaction mixture was allowed to stir at this temperature for 12 h. The reaction mixture was then cooled to room temperature, and 1-fluoronaphthalene (40.0 μL, 1.55 eq.) was added. The crude reaction mixture was analyzed directly by ¹⁹F NMR (282 MHz); the results are summarized in Figure 2.12.

**Figure 2.12.** Crossover deuterium incorporation experiment with C₆D₅OTf and 3-OTf. 0.2 mmol scale, ¹⁹F NMR yields.
Table 2.7. Effect of Pd source on the fluorination of 3-OTf.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Ligand</th>
<th>Combined Yield (a + b)</th>
<th>para : meta (a : b)</th>
<th>a : c : b : d</th>
<th>% Aryne</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[(cinnamyl)PdCl(_2)]</td>
<td>1</td>
<td>70</td>
<td>1.5 : 1</td>
<td>30 : 3 : 14 : 8</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$</td>
<td>1</td>
<td>65</td>
<td>1.9 : 1</td>
<td>31 : 2 : 16 : 9</td>
<td>19 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>9a</td>
<td>-</td>
<td>58</td>
<td>1.6 : 1</td>
<td>23 : 3 : 13 : 10</td>
<td>28 ± 1</td>
</tr>
</tbody>
</table>

*a* 1.5 eq. of ligand relative to Pd source was added. *b* 0.2 mmol scale, reactions without rBuOD added. *c* 0.2 mmol scale, reactions with rBuOD added. *d* NMR yields. *f* 0.2 mmol scale, reactions with rBuOD added. 19F NMR yields.

These reactions were conducted using the same procedure described for reactions utilizing [(cinnamyl)PdCl\(_2\)] and 1, except in entry 3, where no additional ligand was added.

**Procedure for determining the order of the Pd-catalyzed fluorination of 16-OTf in [Pd] (Figure 2.5):** A stock solution of 16-OTf (414 µL, 1.50 mmol, 3.00 eq.) and dodecane (342 µL, 1.50 mmol, 3.00 eq.) in toluene (6 mL) was prepared. An aliquot (~100 µL) was removed from this stock solution and used as the t = 0 min reference. Meanwhile, two separate oven-dried reaction tubes equipped with stir bars were charged with cesium fluoride (228 mg, 1.50 mmol, 3.00 eq.), as well as the appropriate amount of 1 (5% "Pd": 18.2 mg, 7.5%; 10% "Pd": 36.4 mg, 15%) and cinnamyl palladium chloride dimer (5% "Pd": 6.50 mg, 2.5%; 10% "Pd": 13.0 mg, 5.0%). Next, 2.0 mL of the prepared stock solution (corresponding to 0.50 mmol, 1.00 eq. of 16-OTf and dodecane) was added to each tube, and the sides of the tubes were washed down with additional toluene (0.5 mL). The tubes were capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 110 °C, where they were allowed to stir vigorously.
After 10, 20, 30, 40, 50, 60, and 110 min, an aliquot (~100 μL) of the reaction mixture was carefully removed by syringe (through a plug of teflon tape to cover the hole in the septume), quenched into ethyl acetate, and subjected to analysis by GC to determine conversion.

Slopes of linear regressions (errors reported are standard deviations of the slopes of the linear regressions):

5% "Pd": -0.8995 ± 0.1090
10% "Pd": -0.4934 ± 0.0351

Using standard error propagation techniques, we calculate that $k_{\text{rel}} = k_{10\% \text{ Pd}}/k_{5\% \text{ Pd}} = 1.82 ± 0.18$, and so the reaction is nearly first order in Pd.

**Procedure for kinetics in Figure 2.6A:** To an oven-dried screw-cap tube equipped with a stir bar was added (in this order) CsF (450 mg, 3.00 mmol, 3.00 eq.), 1 (36.4 mg, 7.5%), 3-OTf (282 mg, 1.00 mmol, 1.00 eq.), palladium cinnamyl chloride dimer (13.0 mg, 2.5%), 1-fluoronaphthalene (110 μL, 1.00 mmol, 1.00 eq.) and toluene (10 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been preheated to 120 °C. Aliquots (200-300 μL) were carefully removed by syringe (through a plug of teflon tape to cover the hole in the cap) at the designated time points, quenched into EtOAc, and analyzed by $^{19}$F NMR (282 MHz) for yields of 3a and 3b.

Slopes of linear regressions (errors reported are standard deviations of the slopes of the linear regressions):

4-(nBu)PhF: 0.0835 ± 0.0099
3-(nBu)PhF: 0.0501 ± 0.0044
Using standard error propagation techniques, we calculate that $k_{rel} = \frac{k_{4-\text{nBu}}}{k_{3-\text{nBu}}} = 1.67 \pm 0.34$. The final regioselectivity of the reaction is 1.7:1.

**Procedure for determining the order of the Pd-catalyzed fluorination of 3-OTf in [Pd] and [CsF] (Figure 2.6B).** A stock solution of 3-OTf (565 mg, 2.00 mmol, 4.00 eq.) and dodecane (456 µL, 2.00 mmol, 3.00 eq.) in toluene (8 mL) was prepared. An aliquot (~ 100 µL) was removed from this stock solution and used as the $t = 0$ min reference. Meanwhile, three separate oven-dried reaction tubes equipped with stir bars were charged with the appropriate amount of cesium fluoride (3.00 eq.: 228 mg, 1.50 mmol; 1.50 eq.: 114 mg, 0.75 mmol) as well as the appropriate amount of 1 (5% "Pd": 18.2 mg, 7.5%; 10% "Pd": 36.4 mg, 15%) and cinnamyl palladium chloride dimer (5% "Pd": 6.50 mg, 2.5%; 10% "Pd": 13.0 mg, 5.0%). Next, 2.0 mL of the prepared stock solution (corresponding to 0.50 mmol, 1.00 eq. of 4-(nbutyl)phenyl triflate and dodecane) was added to each tube, and the sides of the tubes were washed down with additional toluene (0.5 mL). The tubes were capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C, where they were allowed to stir vigorously. After 30, 60, 120, 170, 240, 295, and 360 min, an aliquot (~ 100 µL) of the reaction mixture was removed by syringe (through a plug of teflon tape to cover the hole in the cap), quenched into ethyl acetate, and subjected to analysis by GC to determine conversion.

Slopes of linear regressions (errors reported are standard deviations of the slopes of the linear regressions):

3 eq. CsF, 5% "Pd": $-0.2308 \pm 0.0113$  
3 eq. CsF, 10% "Pd": $-0.3944 \pm 0.0384$
1.5 eq. CsF, 5% "Pd": $-0.1863 \pm 0.0044$

Order in [Pd]: Using standard error propagation techniques, we calculate that $k_{rel} = k_{10\% Pd}/k_{5\% Pd} = 1.71 \pm 0.18$.

Order in [CsF]: Using standard error propagation techniques, we calculate that $k_{rel} = k_{3\text{ eq.} CsF}/k_{1.5\text{ eq.} CsF} = 1.24 \pm 0.09$, and so the reaction seems to show a small, positive order in [CsF].

Table 2.8A. Effect of catalyst loading on the outcome of fluorination using [(cinnamyl)PdCl]$_2$ and 1.

<table>
<thead>
<tr>
<th>% Pd</th>
<th>% Yield$^a$</th>
<th>$\text{para:meta}^a$</th>
<th>$a:b:d$</th>
<th>% D$^a$</th>
<th>% arynes$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>55</td>
<td>1.6:1</td>
<td>29:5:12:9</td>
<td>26 ± 1</td>
<td>59 ± 3</td>
</tr>
<tr>
<td>5.0</td>
<td>54</td>
<td>1.5:1</td>
<td>30:3:14:8</td>
<td>20 ± 1</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>7.5</td>
<td>52</td>
<td>1.4:1</td>
<td>28:3:14:8</td>
<td>21 ± 1</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>1.2:1</td>
<td>26:3:14:9</td>
<td>23 ± 1</td>
<td>59 ± 3</td>
</tr>
</tbody>
</table>

$^a$0.2 mmol scale. $^{19}$F NMR yields.

Table 2.8B. Effect of ligand loading on the outcome of fluorination using [(cinnamyl)PdCl]$_2$ and 1.

<table>
<thead>
<tr>
<th>% 1</th>
<th>1:Pd</th>
<th>% Yield$^a$</th>
<th>$\text{para:meta}^a$</th>
<th>$a:b:d$</th>
<th>% D$^a$</th>
<th>% arynes$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>1:1</td>
<td>45</td>
<td>1.5:1</td>
<td>22:4:10:9</td>
<td>29 ± 1</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>7.5</td>
<td>1.5:1</td>
<td>54</td>
<td>1.5:1</td>
<td>30:3:14:8</td>
<td>20 ± 1</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>10</td>
<td>2:1</td>
<td>48</td>
<td>1.4:1</td>
<td>24:4:12:8</td>
<td>25 ± 1</td>
<td>60 ± 3</td>
</tr>
<tr>
<td>15</td>
<td>3:1</td>
<td>62</td>
<td>1.3:1</td>
<td>30:5:17:11</td>
<td>25 ± 1</td>
<td>63 ± 3</td>
</tr>
</tbody>
</table>

$^a$0.2 mmol scale. $^{19}$F NMR yields.
Table 2.8C. Effect of catalyst loading on the outcome of fluorination using 9a.

<table>
<thead>
<tr>
<th>% 9a</th>
<th>% Yield</th>
<th>para : meta</th>
<th>a : c : b : d</th>
<th>% D</th>
<th>% aryls</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>50</td>
<td>1.2 : 1</td>
<td>23 : 3 : 13 : 10</td>
<td>27 ± 1</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>7.5</td>
<td>45</td>
<td>1.2 : 1</td>
<td>22 : 3 : 11 : 9</td>
<td>28 ± 1</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>10.0</td>
<td>44</td>
<td>1.2 : 1</td>
<td>20 : 4 : 11 : 9</td>
<td>29 ± 1</td>
<td>61 ± 3</td>
</tr>
</tbody>
</table>

*0.2 mmol scale. 19F NMR yields.

These reactions were conducted using the same procedure described for reactions with tBuOD, and changing the catalyst and/or ligand loading as indicated.

Table 2.9. Effect of equivalents of cesium fluoride on the outcome of fluorination.

<table>
<thead>
<tr>
<th>Equiv CsF</th>
<th>% Yield</th>
<th>para : meta</th>
<th>a : c : b : d</th>
<th>% D</th>
<th>% aryls</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>60</td>
<td>1.0 : 1</td>
<td>25 : 5 : 19 : 12</td>
<td>28 ± 1</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>3.0</td>
<td>54</td>
<td>1.5 : 1</td>
<td>30 : 3 : 14 : 8</td>
<td>20 ± 1</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>6.0</td>
<td>43b</td>
<td>2.3 : 1</td>
<td>27 : 3 : 8 : 5</td>
<td>18 ± 1</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>9.0</td>
<td>36b</td>
<td>2.6 : 1</td>
<td>24 : 2 : 6 : 4</td>
<td>16 ± 1</td>
<td>36 ± 3</td>
</tr>
</tbody>
</table>

*0.2 mmol scale, reaction with tBuOD added. 19F NMR yields. b4-(nBu)PhOH detected by GC/MS.

These reactions were conducted using the same procedure described for reactions with tBuOD, and changing the equivalents of cesium fluoride as indicated.

The combined yield of aryl fluorides significantly decreases as more cesium fluoride is added, with the majority of starting material being converted to biaryl ether side products and 4-(nBu)PhOH. These side products likely result from contamination of the cesium fluoride with CsOH (and water), of which more would also be present as the amount of cesium fluoride is increased. The CsOH could undergo Pd-catalyzed C-O cross-coupling to yield 4-(n-Bu)PhOH, which could then react with a second molecule of...
starting material to generate products such as (4-(nBu)Ph)₂O. Furthermore, we observe multiple regioisomers of the biaryl ether products by GC/MS, suggesting that CsOH may react directly with the Pd-aryne intermediate to generate these side products and/or that Pd-aryne formation can precede conversion of the starting material to phenolic side products. Thus, it is not necessarily the case that less of 10a is forming when more cesium fluoride is added to the reaction mixture; instead, more 10a could be intercepted by CsOH and water, with less leading to the regioisomeric mixture of aryl fluoride products. This would account for the observed loss in aryl fluoride yield but increase in regioselectivity as more cesium fluoride is added.

Procedure for in situ ¹⁹F NMR and ³¹P NMR experiments (Figure 2.13, 2.13', and 2.14). To an oven-dried screw-cap tube equipped with a stir bar was added (in this order) cesium fluoride (90.0 mg, 0.60 mmol, 3.00 eq.), 1 (7.20 mg, 7.50 %), aryl triflate (0.20 mmol, 1.00 eq.), palladium cinnamyl chloride dimer (2.60 mg, 2.50 %), and toluene (2.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been preheated to 110 °C (for 16-OTf) or 120 °C (for 3-OTf). After 15 (for 16-OTf) or 90 (for 3-OTf) min, the reaction tube was quickly transferred to a dry ice/acetone bath, where it was allowed to cool to −78 °C for 5 min. Under an atmosphere of argon, approximately 0.75 mL of the reaction mixture was transferred to a screw cap NMR tube (also in the dry ice/acetone bath and under an atmosphere of argon) with a syringe, and the NMR tube was transported to a NMR spectrometer. The ¹⁹F NMR experiment was conducted at −78 °C. Allowing the NMR tube to warm to 20 °C and collecting the ¹⁹F NMR spectrum at this temperature gave a nearly identical looking spectrum. The
identification of cinnamyl fluoride was made by comparison to an authentic sample. The spectrum observed for the fluorination of 3-OTf in shown in Figure 2.13, and the spectrum observed for the fluorination of 16-OTf is shown in Figure 2.14.

The corresponding $^{31}$P NMR (202 MHz) spectrum for the fluorination of 3-OTf is shown in Figure 2.13'. Although the signal in the $^{31}$P NMR spectrum at δ ~80 ppm corresponds to the chemical shift of 7a, this species was not detected by $^{19}$F NMR. Thus, this signal likely corresponds to 10a or to a hitherto unidentified decomposition product of 1.

**Figure 2.13.** $^{19}$F NMR (470 MHz, −78 °C) of the Pd-catalyzed fluorination of 3-OTf run to partial conversion shows only starting material (3-OTf), products (3a-b), cinnamyl fluoride, and 9a present in the reaction mixture.
Figure 2.13. $^{31}$P NMR (202 MHz, $-78$ °C) spectrum of the Pd-catalyzed fluorination of 3-OTf run to partial conversion.

Figure 2.14. $^{19}$F NMR (470 MHz, $-78$ °C) of the Pd-catalyzed fluorination of 16-OTf run to partial conversion shows only starting material (16-OTf), product (16e), cinnamyl fluoride, and 17a and/or 17b present in the reaction mixture.

Procedure for thermolysis experiments of 7a in the presence of 9a. To an oven-dried screw-cap NMR tube was added (in this order) 7a (10.0 mg, 0.01 mmol, 1.00 eq.), 9a
(0.50 equiv or 1.00 equiv), and toluene (0.75 mL). The NMR tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C, where it was allowed to stand for 2 h. At this time, the reaction mixture was allowed to cool to room temperature, and 1-fluoronaphthalene (1.95 µL, as a solution in 0.1 mL toluene) was added, and the crude reaction mixture was analyzed directly by $^{19}$F NMR (470 MHz). When 1.00 equiv of 9a was added, 2% of 3a and 1% of 3b were detected, along with significant formation of HF (δ –138 ppm). When 0.50 equiv of 9a was added, 26% of 3a and 17% of 3b were detected.

**Procedure for thermolysis experiment of 7a in the presence of CsF.** To an oven-dried reaction tube equipped with a stir bar was added (in this order) 7a (10.0 mg, 0.01 mmol, 1.00 eq.), CsF (7.60 mg, 0.05 mmol, 5.00 eq.), and toluene (0.75 mL). The reaction tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 120 °C, where it was allowed to stir vigorously for 2 h. At this time, the reaction mixture was allowed to cool to room temperature, and 1-fluoronaphthalene (1.95 µL, as a solution in 0.1 mL toluene) was added, and the crude reaction mixture was analyzed directly by $^{19}$F NMR (470 MHz). Only 3a (7%) was observed.

**Procedure for experiments in Table 2.1:** To an oven-dried vial equipped with a stir bar was added (in this order) 9a (15.0 mg, 0.02 mmol, 1.00 eq.), CsF (11.3 mg, 0.08 mmol, 5.00 eq., or 136 mg, 0.9 mmol, 60.0 eq.), 1-fluoronaphthalene (1.95 µL, as solution in 0.5 ml toluene), and toluene (1.5 mL). The vial was capped and allowed to vigorously stir for 12 h (5.00 eq. CsF) or 30 min (60.0 eq.) at room temperature. The crude reaction
mixture was analyzed directly by \(^{19}\)F NMR (470 MHz) for conversion and yield. Only 9a and 7a could be detected by both \(^{19}\)F and \(^{31}\)P NMR. Analysis of the crude reaction mixture by GC/MS revealed the primary organic byproducts to be high molecular weight compounds (likely oligomers derived from 10a).

### Table 2.10. Results of deuterium incorporation experiments with 2.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Combined % Yield (a + b)</th>
<th>para : meta (a : b)</th>
<th>a : c : b : d : e</th>
<th>% (^1)D</th>
<th>% (^2)D</th>
<th>% aryne (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>toluene</td>
<td>50</td>
<td>1 : 2.7</td>
<td>6 : 1 : 16 : 19 : 6</td>
<td>54%</td>
<td>13%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>cyclohexane</td>
<td>44</td>
<td>1.1 : 1</td>
<td>19 : 1 : 12 : 6 : n/o</td>
<td>54%</td>
<td>13%</td>
<td>55 ± 3</td>
</tr>
</tbody>
</table>

\(^a\)0.2 mmol scale, reactions without tBuOD added. \(^b\)0.2 mmol scale, reactions with tBuOD added. \(^\)\(^{19}\)F NMR yields. Estimate assuming that 2e underwent Pd-aryne formation at least once before forming. n/o = not observed.

Unexpectedly, incorporation of two deuterium atoms into aryl fluoride products resulting from the fluorination of \(2\)-OTf was observed by GC/MS and \(^{19}\)F NMR, leading to dideuterated products \(2e-\alpha\) and/or \(2e-\beta\) in addition to \(2a-d\) (Table 2.10). Unfortunately, we could not distinguish the exact regioselectivity of the double deuteration, as the observed \(^{19}\)F NMR signal could correspond to \(2e-\alpha\), \(2e-\beta\), or a mixture of both (Figure 2.15). In addition, the regioselectivity for the reaction without tBuOD (1:3) is better than that for the reaction with tBuOD added (1:5), suggesting that the addition of tBuOD adversely affects the regioselectivity of this reaction. In this one case, deuterium labeling must be reversible and/or lead to another species that can be deprotonated under the reaction conditions. The mechanism presented in Figure 2.7 would not account for this behavior. Our proposed mechanism that would account for formation of \(2e-\alpha\) is shown in Figure 2.15. If reversible ortho-deprotonation of very
electron-rich L•Pd(Ar)F complexes is possible under the reaction conditions, then multiple deuterium atoms could be incorporated into the aryl fluoride products. For example, deuterated intermediate 7b-D (Figure 2.15), formed by reaction of Pd-aryne 10b with DF, could undergo reductive elimination to form 2c, although this process would be slow due to the very electron-rich aryl group. Therefore, we propose that 7b-D could also competitively undergo a second ortho-deprotonation with cesium fluoride to form deuterated Pd-aryne intermediate 10b-D, which could in turn react with a second molecule of DF to form dideuterated L•Pd(Ar)F intermediate 7b-D₂ (Figure 2.15). The presence of tBuOD could exacerbate the slow reductive elimination from 7b-D. It is also possible that 7b-D can be converted to 10b-D by disassociation of fluoride from the Pd center followed by ortho-deprotonation. Reductive elimination from 7b-D₂ would provide 2e-α (Figure 2.15). The other possible di-deuterated product 2e-β could conceivably form by a similar mechanism. Overall, this finding suggests that very electron-rich substrates such as 2-OTf can undergo ortho-deprotonation at multiple stages during the catalytic cycle, which likely explains the poor regioselectivity (1:3) and high estimated % aryne (>90 %) for the fluorination of 2-OTf.
Figure 2.15. Dideuterated 2e forms during the fluorination of 2. The proposed mechanism for its formation, involving ortho-deprotonation of deuterated complex 7b-D followed by recombination with DF to give 7b-D₂, followed by reductive elimination, is shown.
2.11. References.

3 Ortho-deprotonation of aryl chlorides and bromides by anhydrous fluoride has been previously reported. See: Grushin, V. V.; Marshall W. J. Organometallics 2008, 27, 4825. However, the ratios of products obtained using Grushin’s methodology differ greatly from those observed using the Pd-catalyzed fluorination reaction.
4 To rule out the possibility of deprotonation of the aryl fluoride product by a species generated in situ, we added 4-(OMe)PhF to the catalytic fluorination reaction of 3-OTf. No isomerization to 3-(OMe)PhF was observed; the added 4-(OMe)PhF was recovered quantitatively.
7 An alternative possibility is that 10 reacts with HF directly to produce the aryl fluoride products without the intermediacy of 7 and 7'. We consider this possibility unlikely, because direct reaction of 10 with HF would require either a) reaction with the p orbitals that are part of the aromatic system, or b) disassociation of the Pd center to form a free aryne species, which then would react with HF. Nonetheless, these possibilities cannot be entirely ruled out.
9 Attempts to trap the Pd-aryne intermediate by adding 1,2-diphenylacetylene, oct-4-yne, 2,5-diphenylfuran, or cyclopentadiene to the Pd-catalyzed fluorination of 3-OTf were unsuccessful.
10 The addition of tBuOD also resulted in approximately 15% yield loss due to an increase in the amount of biaryl ether formed by reaction with adventitious water.
11 Other acidic deuterium sources were also evaluated, but none proved superior to tBuOD. See Table 2.6 in the Experimental.
12 To confirm that the presence of tBuOD does not induce formation of 10a, and that free H/DF forms in situ as a result of regioisomer formation, we also carried out a crossover experiment by subjecting C₅D₅OTf and 4-(nBu)PhOTf to the reaction conditions together. Deuterium incorporation into the nBu-containing products was observed. See Figure 2.12 in the Experimental.
Several traditional ligands were evaluated for this reaction, including XPhos (2-dicyclohexylphosphino-2',4',6'-trisopropylbiphenyl), CPhos (2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl), PPh₃, and dppf (1,1'-bis(diphenylphosphino)ferrocene), but only a catalyst based on XantPhos provided the desired product free from biaryl byproducts, which were difficult to separate from 14. For a previous example of the use of XantPhos in Negishi couplings, see: Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* 2007, 1, 31.

It is worth noting that the estimated portion of 3a-b originating from 10 (% aryne) was similar whether [(cinnamyl)PdCl]₂/1, Pd₂(dba)₃/1, or independently prepared 9a, was used as the catalyst source (see Table 2.7 in the Experimental).

Determining the exact order in CsF is difficult due to its near insolubility in toluene. In general, Pd-catalyzed fluorination reactions are non-homogenous, and therefore factors such as stirring rate, reaction scale, and average CsF particle size, can affect the yields and rates of reactions.

Preliminary computational work carried out in our group suggests that transmetallation is a highly thermodynamically favored step in the catalytic cycle, and that the barrier to reductive elimination is lower (<20 kcal/mol) than might be initially expected based on previous work by Yandulov (see ref. 4). These preliminary calculations suggest that transmetallation, not reductive elimination, is the rate-determining step of the catalytic cycle shown in Figure 2.2.

Determining the effect of increasing [CsF] on the rate of the fluorination of 3-OTf or the extent of Pd-aryne generation is difficult due to its poor solubility in toluene, as well as contamination of the CsF with CsOH, which results in lowering of the overall product yield when more CsF is added to the reaction mixture. See Table 2.9 and the subsequent discussion in the Experimental for details.

An *in situ* ¹⁹F NMR (470 MHz) investigation of the Pd-catalyzed fluorination of 16-OTf run to partial conversion was also carried out (see Figure 2.14 in the Experimental). The major species observed were 16-OTf, a 30:1 mixture of two L·Pd(Ar)OTf species (minor, δ ~77.3 ppm, major, δ ~77.9 ppm), 16e, and cinnamyl fluoride. Comparison with independently prepared samples of 17a and 17b suggests that complete modification of the ligand had not occurred after 15 minutes of reaction time. Notably, significant quantities of L·Pd(Ar)F species (~ δ ~210 ppm) were not detected.

Consistently, heating a mixture of 7a (1.0 equiv.) and 9a (0.5 equiv.) led to formation of both 3a (26%) and 3b (17%) in a similar ratio (1.5:1) as heating 7a with 3-OTf (1.6:1).

Reversion of 10a to 9a could also hypothetically occur by direct reaction of 10a with triflic acid (HOTf), but given the low pKa of HOTf (0.3 in DMSO) compared to HF (15 in DMSO) its generation *in situ* is highly disfavored.

When 4 or more equiv of tBuOD are added to the fluorination of 3-OTf, doubly deuterated products can be observed by GC/MS and ¹⁹F NMR. However, the yields of these reactions are significantly lower than the standard catalytic fluorination of 3, so it is likely that tBuOD adversely affects the cross-coupling process at such high concentrations. The presence of hydrogen-bond donors can greatly affect the reactivity.
of Pd–F complexes; for example, see: Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.

Repeating the reductive elimination of 7a in the presence of 5.0 equiv of CsF led only to 3a (7% yield); 3b was not detected. See Experimental for details.

Although multiply deuterated products were observed in the product mixture resulting from the fluorination of 2-OTf in the presence of tBuOD, analysis of this reaction was complicated by the fact that this reaction proceeds almost exclusively through a Pd-aryne intermediate. See Table 2.10, Figure 2.15, and the associated discussion, in the Experimental.

The fluorination of 3-OTf does not go to full conversion at temperatures below 130 °C in cyclohexane (or below 120 °C in toluene), limiting our ability to examine temperature effects on the regioselectivity of the reaction.

This improvement in regioselectivity is also observed for reactions conducted with 2-OTf.

Analysis of the ratios of deuterium incorporation was complicated because the desired product can form by all three pathways in Figure 2.8, with deuterium incorporation possible at two distinct sites to form d and/or f (see below) by Pathway B or Pathway C, respectively. We have found that we cannot reliably distinguish between d and f by $^{19}$F NMR.

```
R  
|   
|---
| D   Pathway B  
| F Figure 2.8 (with DF)  
| R

R  
|   
|---
|   Pathway C  
| OTf Figure 2.8 (with DF)  
| R

R  
|   
|---
| D   Pathway B  
| F Figure 2.8 (with DF)  
| R
```

```
30
```


The effect of ortho-substitution on the rate of transmetallation has never, to our knowledge, been thoroughly studied.


47 McAtee, J. R.; Martin, S. E. S.; Ahneman, D. T.; Johnson, K. A.; Watson, D. A. Angew. Chem. Int. Ed. 2012, 51, 3663. This compound was stored at -20 °C in a glovebox when not in use.
$^{1}$$H$ NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^{19}$F NMR, 282 MHz, CDCl$_3$
F

\textsuperscript{1}H, 300 MHz, CDCl\textsubscript{3}

\begin{center}
\textsuperscript{1}H, 300 MHz, CDCl\textsubscript{3}
\end{center}
$^{13}$C, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^{19}$F NMR, 282 MHz, CDCl$_3$
$^{1}H$ NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^{19}$F NMR, 282 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^{1}H$ NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
MeO$_2$Pd, ...Pr$_2$Br

$^{1}$H NMR, 300 MHz, CD$_2$Cl$_2$
13C NMR, 125 MHz, CD2Cl2
$^{31}$P NMR, 122 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^{1}$H NMR, 500 MHz, $C_6D_6$
$^1$H NMR: 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
Chapter 3. New Precatalysts for the Fluorination of (Hetero)Aryl Triflates
3.1. Introduction. The work presented in the previous two chapters confirms that the desired C–F cross-coupling cycle shown in Figure 3.1 is possible with the right supporting ligand, and likely proceeds during the Pd-catalyzed fluorination of most aryl triflates. Our original catalyst system of [(cinnamyl)PdCl]_2/L1 facilitates the catalytic fluorination of a variety of aryl triflates with minimal formation (<5%) of the corresponding reduction product. However, the substrate scope with L1 as the supporting ligand is limited, especially with regard to very electron-rich and heteroaryl triflates (see Section 3.2). In addition, the use of [(cinnamyl)PdCl]_2 as the Pd precursor requires 1.5 equiv. of L1 relative to Pd to be added and results in generation of one equivalent of "Cl", which participates in a competitive cross-coupling process to produce the corresponding aryl chloride. In some cases, this side product can be difficult to separate from the desired aryl fluoride product.

**Figure 3.1.** Mechanism of the Pd-catalyzed fluorination of aryl triflates, supporting ligands for this reaction, and chlorination of the starting material from the [(cinnamyl)PdCl]_2 catalyst precursor.

Generation of the catalytically active L•Pd(0) species is a necessary but often overlooked first step in most Pd-catalyzed cross-coupling processes. Traditionally, Pd(0) species are accessed by combining the desired ligand (e.g., L1) with either a Pd(II) precursor such as PdCl₂, Pd(OAc)₂, or [(cinnamyl)PdCl]₂ (Figure 3.2, left) or a stable Pd(0) precursor such as Pd₂(dba)₃ or Pd(dba)₂ (Figure 3.2, center). However, both of
these methods have drawbacks: the use of Pd(II) precursors requires \textit{in situ} reduction to Pd(0), which is inefficient in many cases\textsuperscript{2} and generates potentially reactive byproducts such as Cl\textsuperscript{-} and AcO\textsuperscript{-}, while commercially available samples of Pd\textsubscript{m}(dba)\textsubscript{m} species are of variable quality\textsuperscript{3} and release dba upon activation, which is known to have an inhibitory effect on some cross-coupling reactions.\textsuperscript{4} In addition, both methods require an excess of the desired ligand relative to Pd. As an alternative to these methods, our laboratory has developed stable pre-ligated Pd(II) species that activate in the presence of base to release the desired L\textsuperscript{-}Pd(0) species without the requirement for additional ligand relative to Pd.\textsuperscript{5} However, our third generation precatalyst for L\textsubscript{1}, 1 (Figure 3.2, right),\textsuperscript{6} generates one equivalent of both carbazole\textsuperscript{7} and acid upon activation, which are potentially reactive byproducts under fluorination conditions. Despite extensive efforts, we have found that 1 is not an effective precatalyst for Pd-catalyzed fluorination reactions (not shown). This chapter describes the preparation and evaluation of a new family of Pd(0) precatalysts that activate at room temperature by disassociation of a weakly bound 1,5-cyclooctadiene ligand without the generation of reactive byproducts.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.2.png}
\caption{Traditional methods for generation of the active L\textsuperscript{-}Pd(0) species in Pd-catalyzed reactions.}
\end{figure}
3.2. Initial Ligand and Pd source investigation. Our original Pd-catalyzed fluorination method suffers from poor reactivity with highly electron-rich and heteroaryl substrates, as represented by estrone (3-OTf) and 3-quinolinyl (4-OTf) triflates (entry 1, Table 3.1). After an extensive investigation of new ligands for this reaction, AdBrettPhos (L2) (Figure 3.1) was found to be more capable in the fluorination of these substrates (entry 2, Table 1), though formation of two regioisomeric aryl fluorides was observed in the case of estrone triflate. The effectiveness of a catalyst based on L2 is likely due to the faster rate of reductive elimination from Pd–F intermediates bearing L2 compared to those bearing L1, which should accelerate the desired reaction over decomposition of the aryl triflate. However, the use of [(cinnamyl)PdCl]2 as the source of active Pd still produced the corresponding aryl chloride in both cases, as described in Figure 3.1. Thus, we evaluated alternative Pd sources in conjunction with L2. Other Pd sources such as Pd(OAc)2 (entry 3, Table 1), Pd2(dba)3 (entry 4, Table 1), and Pd(dba)2 (entry 5, Table 1), did not prove as effective as [(cinnamyl)PdCl]2 for one or both of these substrates. Notably, when 0.1 eq. of dba was added to the reactions in entry 1, an identical yield of fluorodeoxyestrone (66%, α:β = 5:1) but a diminished yield of 3-fluoroquinoline (40%) was observed. Thus, in the case of fluorination of heteroaryl triflates, dba likely inhibits the desired transformation.

In contrast to the use of separate sources of Pd and ligand, we have found that precatalysts are superior in terms of convenience, efficiency of catalyst generation, and the use of only one equivalent of ligand relative to Pd (Figure 3.2, right). However, when our third generation palladacycle precatalyst 2 (Figure 3.2) was employed in the fluorination of 3-OTf or 4-OTf, low yields of the desired products were obtained (entry
6, Table 1). The low yields result both from arylation of the carbazole generated as byproduct of catalyst activation, which consumes 1 eq. of the starting material relative to Pd, and the overall formation of 2 eq. of HF relative to Pd, which experiments in Chapter 1 suggest is detrimental to the reaction yield (Figure 3.3). Only when oxidative addition complex $\text{L2-Pd}(4-\text{nBuPh})\text{OTf}$ (5) was employed as catalyst could high yields of these aryl fluoride products be obtained without formation of the aryl chloride side product or the need for excess L2 relative to Pd (entry 7, Table 1). Based on these results, a precatalyst bearing L2 that activates without producing reactive and/or inhibitory byproducts such as chloride, dba, carbazole, or HF, would be ideal for this transformation.

Table 3.1. The Pd-catalyzed fluorination of estrone (3-OTf) and 6-quinolinyl (4-OTf) triflates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Ligand (L:Pd = 1.5:1)</th>
<th>ArF Yield</th>
<th>ArF Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[(cinnamy)PdCl]$_2$</td>
<td>L1</td>
<td>&lt;20%</td>
<td>30%$^b$</td>
</tr>
<tr>
<td>2</td>
<td>[(cinnamy)PdCl]$_2$</td>
<td>L2</td>
<td>75% ($\alpha$:$\beta = 8:1)^b$</td>
<td>70%$^b$</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>L2</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$</td>
<td>L2</td>
<td>58% ($\alpha$:$\beta = 7:1$)</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)$_2$</td>
<td>L2</td>
<td>73% ($\alpha$:$\beta = 5:1$)</td>
<td>47%</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>-</td>
<td>35%</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>L2•Pd(4-\text{nBuPh})\text{OTf} (5)</td>
<td>-</td>
<td>63% (8:1 $\alpha$:$\beta$)</td>
<td>66%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: Aryl triflate (0.10 mmol), CsF (0.30 mmol), 4$^\circ$ "Pd", tol (0.1 M), 120 °C, 12 h. $^{19}F$ NMR yields. $^b$Corresponding ArCl detected by GC.
Figure 3.3. Carbazole and HF generation diminish the yield of Pd-catalyzed fluorination reactions using precatalyst 2.

3.3. Preparation and reactivity of \((\text{L}_2\text{Pd})_2(1,5\text{-COD})\) precatalyst. While attempting to form oxidative addition complexes of 2,6-disubstitued aryl triflates for use as precatalysts, we found that simply combining equimolar quantities of \(\text{L}_2\) and \([\text{1,5-COD}\text{Pd(CH}_2\text{TMS)}_2]\) (COD = cyclooctadiene) \(^9\) together in pentane resulted in precipitation of a pale yellow solid (6) (Figure 3.4); due to the lack of oxidant present in this reaction, we anticipated that 6 was an isolable Pd(0) species. Although many biaryl phosphine-ligated Pd(II) complexes have been isolated, there exist only a few examples of related Pd(0) complexes.\(^{10}\) This is due to the high reactivity of electron-rich phosphine-ligated Pd(0) complexes\(^5\) and their tendency to decompose \textit{via} oxidation or Pd nanoparticle formation. The filtrate of this reaction mixture contained 53\% of the starting amount of 1,5-COD\(^{11}\) and minimal quantities of \(\text{L}_2\), confirming that 6 possesses a 2:2:1 ratio of \(\text{L}_2\):Pd:1,5-COD. Based on this information, we propose a \(C_2\)-symmetric structure for 6, wherein two trigonal-planar Pd(0) centers, each ligated by a molecule of \(\text{L}_2\), are coordinated to a double bond of the 1,5-COD ligand (Figure 3.4); a similar structure has been proposed for the complex \([\text{1,5-COD}(\text{dippePd})_2]\) (dippe = 1,2-bis(diisopropylphosphino)ethane).\(^{12}\) Despite containing two reactive tri-coordinate Pd(0) centers, 6 is indefinitely stable at room temperature in a glovebox or when stored under \(N_2\) in a benchtop desiccator.
Figure 3.4. Preparation of Pd(0) species 6.

We quickly found that 6 was insoluble in most organic solvents, which limited our ability to corroborate the proposed structure by NMR. To circumvent this problem, 6 was characterized by solid-state $^1$H, $^{13}$C and $^1$H-$^{13}$C correlation NMR experiments (Figure 3.5). The number of observed signals in the $^{13}$C NMR spectrum suggests that 6 is symmetrical, which is in agreement with our proposed C$_2$-symmetric structure. Although the solid-state $^1$H NMR spectrum of 6 was not detailed enough to yield clear structural information, no signals downfield of $\delta$ 10 ppm or upfield of $\delta$ 0 ppm were observed. Complex 6 was also analyzed by cross polarization based $^1$H-$^{13}$C correlation NMR using two different length second cross polarization steps ("short" and "long") to detect $^1$H-$^{13}$C contacts (Figure 3.5). These spectra are also consistent with the proposed structure, as most of the contacts are between aromatic $^1$H and $^{13}$C signals, and aliphatic $^1$H and $^{13}$C signals. The unusual signal observed in the $^{13}$C NMR spectrum at $\delta$ 83 ppm does not correspond to any signals in isolated samples of L2 or 1,5-cyclooctadiene, and thus likely corresponds to the alkene carbons of the 1,5-COD ligand bound to the Pd center in 6. Indeed, this signal only shows $^1$H-$^{13}$C contacts with signals in the aliphatic region ($\delta <$5 ppm) in the $^1$H NMR dimension, as would be expected for the alkene carbons of the central 1,5-COD ligand. The signal for this carbon is shifted significantly upfield from where it is normally observed for free 1,5-cyclooctadiene ($\delta \sim$130 ppm), an effect likely due to significant $\pi$-backbonding with the metal center. In all, the solid-state NMR
spectra presented here are wholly consistent with the proposed structure of 6. However, at this time the preferred conformation of the central 1,5-COD ligand in the solid state remains unclear.

![Figure 3.5. Solid-state $^{13}$C NMR (left) and cross polarization based $^1$H-$^{13}$C correlation NMR spectra (right), with 1.5 ms contact time for the initial cross polarization and 0.2 ms and 0.5 ms for the second cross polarization step, of 6.](image)

We also examined processes in which 6 loses 1,5-COD to act as a source of L2•Pd(0). Although 6 is insoluble in most organic solvents, it readily dissolves in CDCl$_3$ to generate 0.5 equiv. of 1,5-cyclooctadiene relative to Pd and what X-ray crystallographic analysis revealed to be dearomatized Pd(II) complex 7 (Figure 3.6). A nearly identical species bearing a related ligand and also possessing $\eta^3$-binding of the dearomatized ring to the Pd center has been previously reported.$^{13}$ This species likely does not form by oxidative addition of L2•Pd(0) to CDCl$_3$ followed by the dearomative rearrangement reported in Chapter 1 because the CDCl$_2$ and Pd center are bound to opposite faces of the lower ring of the ligand. Instead, a carbene mechanism is likely involved in the formation of 7.$^{13}$

328
Figure 3.6. Reaction of 6 with CDCl₃ to produce 7 and 1,5-COD. Ellipsoids at 50% probability.

The 1,5-COD ligand in 6 could also be exchanged with the more π-acidic olefin N-phenylmaleimide to form 8 (Figure 3.7), which was significantly more soluble in organic solvents than 6. Thus, 8 could be characterized by solution-state NMR and X-ray crystallography (Figure 3.7). Complex 8 possesses a trigonal planar structure at the Pd(0) center, which is coordinated to the phosphine and the ipso carbon of the lower ring of 8, as well as to the N-phenylmaleimide ligand. As expected, the Pd–C₂ (2.13(6) Å) and Pd–C₃ (2.11(6) Å) bond lengths are similar. This complex also possesses a much shorter Pd–ipso distance (2.03(4) Å) than that reported for L₂•Pd(4-CNPh)Br (2.49(6) Å), indicating stronger binding of the Pd center to the lower ring of the ligand in the case of 8. The improved stability and solubility of 8 compared to 6 is likely due to the stronger π-backbonding ability of N-phenylmaleimide compared to 1,5-COD. Consistent with this hypothesis, the C₂–C₃ bond length in 8 is elongated (1.41(7) Å) relative to that of a typical double bond (1.34 Å), and the $^{13}$C NMR (125 MHz, CD₂Cl₂) resonance for the C=O carbon in 8 is shifted ~35 ppm upfield from where it is normally observed. Due to these effects, 8 is significantly less reactive than 6. An extensive study of the stability and reactivity of olefin-ligated Pd(0) complexes was carried out, but none proved as reactive as 6 (not shown).
Lastly, when exposed to 4-(nBu)PhOTf in toluene-d₈, 6 quantitatively converts to the corresponding oxidative addition complexes L₂•(4-(nBu)Ph)PdOTf (5) in less than 10 min. at room temperature under neutral conditions, generating 0.5 eq. of 1,5-COD relative to Pd in the process. Significantly, when this experiment was repeated using 6 that had been exposed to air for 24 h on the benchtop, the ¹H NMR yield of 5 produced was only diminished to 83%, suggesting that the half-life of 6 in air is on the order of days. Similarly, exposing 6 to 4-(nBu)PhBr produced L₂•Pd(4-nBuPh)PdBr (9) in quantitative yield. Collectively, these results suggest that dissociation of the 1,5-COD ligand from 6 is very facile at room temperature, even though 6 itself is relatively stable and easy to handle. Thus, 6 behaves as a functional equivalent of the unstable intermediate L₂•Pd(0), and should be an ideal precatalyst for Pd-catalyzed cross-coupling reactions.
Figure 3.8. Facile oxidative addition of 4-(nBu)PhOTf or 4-(nBu)PhBr to 6.

3.4. 6 as a precatalyst for the fluorination of aryl triflates. Most importantly, 6 is also an excellent precatalyst for the fluorination of estrone (3-OTf, Table 3.2) and 3-quinolinyll (4-OTf) triflates (Table 3.3), providing yields comparable to those obtained with [(cinnamyl)PdCl]2/L2 but without generation of aryl chloride byproducts.\(^\text{1814}\) By GC analysis, the only side products observed were trace amounts (<5% in all cases) of reduction product and the corresponding biaryl ethers. In light of these results, the ability of 6 to function as a precatalyst for the fluorination of aryl triflates derived from heterocyclic and biologically active phenols, the substrates for which incorporation of fluorine centers is most important, was further investigated (Tables 3.2-3.3).

Fluorination could be cleanly carried out on the triflate derivatives of various naturally occurring phenols (Table 3.2). These include estrone (10), the diethyl amide of isovanillin (11), the N-methyl derivative of nonivamide (pseudocapsaicin, 12), the plant-derived antioxidant methyl p-coumarate (16), and δ-tocopherol (19). In addition, the fluorinated derivatives of a number of phenol-containing pharmaceuticals could be accessed, including the antimicrobial chloroxylenol (13),\(^\text{15}\) the chloretic 4-methylumbelliferone (Hymecromone, 15),\(^\text{16}\) the N-methyl derivative of the analgesic acetaminophen (17), the antidepressant (des)venlaflaxine (18),\(^\text{17}\) and N-methylnonivamide (12), whose relative, capsaicin, has a number of promising medicinal
uses (Table 3.2).\textsuperscript{18} The des-aminofluorinated analog of the anti-bacterial dapsone (Aczone)\textsuperscript{19} could also be prepared (14). Additionally, the aryl nonaflate of 4-methylumbelliferone could be used in place of the triflate to access 15 in comparable yield (89\% vs. 92\%). Although in general substrates containing free NH or OH groups were not tolerated in this reaction because they undergo competitive cross-coupling processes, the hindered tertiary carbinol present in (des)venlaflaxine (18) did not need to be protected. Regiosiomerically mixtures of products were observed for the fluorinations leading to electron-rich aryl fluorides 10, 17, 18, and 19 when the reactions were conducted in toluene. As we have previously reported, switching the solvent to cyclohexane in these cases led to an increase in regioselectivity for the desired product (see Chapter 2). We briefly investigated if the formation of regioisomers with 6 follows the same trends we outlined for [(cinnamyl)PdCl]$_2$/L1 in Chapter 2. Similar to our previous results, the fluorination of 4-(nBu)PhOTf yielded a nearly 1:1 mixture of para and meta regioisomers of 20. Likewise, the addition of tBuOD to this reaction led to deuterium incorporation (30 $\pm$ 1 \%) into both regioisomers, resulting in an estimated \% aryne of 69 $\pm$ 3 \% (not shown). Thus, regioisomer formation in these reactions likely proceeds by a similar mechanism as that described in Chapter 2. Notably, when the preparations of electron-rich aryl fluorides 10, 11, 17, and 19, were attempted using our previous catalyst system of [(cinnamyl)PdCl]$_2$/L1, lower yields of the desired products were observed in each case (Table 3.2), demonstrating the superiority of our new catalyst system. Even in the case of electron-deficient 16, an improved yield was observed when using 6 in place of [(cinnamyl)PdCl]$_2$/L1 (Table 3.2).
We also examined the application of 6 to the synthesis of heteroaryl fluorides, which are typically more difficult to access using transition metal-mediated fluorination.

Table 3.2. Fluorination of aryl triflates derived from biologically active aryl triflates, and 4-(nBu)PhOTf, using 6.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone</td>
<td>74% b (20:1 α:β)</td>
<td>2% &quot;Pd&quot;, 120 °C</td>
</tr>
<tr>
<td>Isovanillamide</td>
<td>91% c</td>
<td>2% &quot;Pd&quot;, 100 °C</td>
</tr>
<tr>
<td>N-methylnicotamide</td>
<td>85% d</td>
<td>3% &quot;Pd&quot;, 130 °C</td>
</tr>
<tr>
<td>Chloroxylenol</td>
<td>84%</td>
<td>2% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>Dapsone (des-amino)</td>
<td>82% e</td>
<td>6% &quot;Pd&quot;, 130 °C</td>
</tr>
<tr>
<td>4-Methylumbelliferone</td>
<td>92%</td>
<td>2% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>Methyl p-coumarate</td>
<td>92% (53%) c</td>
<td>2% &quot;Pd&quot;, 80 °C</td>
</tr>
<tr>
<td>N-methylacetaminophen</td>
<td>71% (58%) c</td>
<td>4% &quot;Pd&quot;, 120 °C</td>
</tr>
</tbody>
</table>

*Isolated yields, average of two runs. Reaction conditions unless otherwise noted: Aryl triflate (1.00 mmol), CsF (3.00 mmol), 6 (1-3%), tol (0.1 M). aAryl triflate (0.5 mmol), CsF (1.5 mmol), 6 (1%), cy (0.1 M). bYield when reaction was conducted under the same reaction conditions using [(cinnamyl)PdCl]2/L2 (Pd:L2 = 1:1.5) instead of 6. Aryl triflate (0.10 mmol), CsF (0.30 mmol), tol (0.1 M). 19F NMR yields. dAryl triflate (0.50 mmol), CsF (1.50 mmol), 6 (1.5-3%), tol (0.1 M). eAryl triflate (0.5 mmol), CsF (3 mmol), 6 (3%), tol (0.1 M). fAryl triflate (1 mmol), 6 (1.5-2%), cy (0.1 M). gAryl triflate (0.10 mmol), CsF (0.30 mmol), tol (0.1 M). 19F NMR yield.
methods (Table 3.3). Precatalyst 6 is competent for the synthesis of 4- and 3-quinolinyl fluorides alike (21-22). Although fluorination of 3-pyridyl triflate to produce 23 proceeded in low yield, electron-deficient 3-pyridyl triflates, such as that corresponding to methyl nicotinate (24), provided somewhat higher yields of the desired aryl fluoride. In addition, 2,6-disubstituted 3-pyridyl fluorides can be accessed in good yield using this reaction (25). Lastly, substrates containing the 5-membered heterocycles pyrrole (26), furan (27), and thiophene (28) could also be fluorinated, confirming that decomposition of these electron-rich 5-membered heterocycles does not occur under the reaction conditions. As before, when the fluorinations of 21, 25, and 28 were carried out using [(cinnamyl)PdCl]$_2$/L1, lower yields of the desired products were observed in every case (Table 3.3), although the improvements when switching to 6 were not dramatic.

**Table 3.3.** Fluorination of heteroaryl and heterocycle-containing aryl triflates using 6.$^a$

<table>
<thead>
<tr>
<th>Aryl Triflate</th>
<th>Yield</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>21, 70% (30%)$^b$</td>
<td>4% &quot;Pd&quot;, 120 °C</td>
<td>4% &quot;Pd&quot;, 120 °C</td>
</tr>
<tr>
<td>22, 87%</td>
<td>2% &quot;Pd&quot;, 90 °C</td>
<td>2% &quot;Pd&quot;, 90 °C</td>
</tr>
<tr>
<td>23, 30%$^c$</td>
<td>4% &quot;Pd&quot;, 120 °C</td>
<td>4% &quot;Pd&quot;, 120 °C</td>
</tr>
<tr>
<td>24, 44%</td>
<td>methyl nicotinate</td>
<td>methyl nicotinate</td>
</tr>
<tr>
<td>25, 64% (55%)$^b$</td>
<td>4% &quot;Pd&quot;, 130 °C</td>
<td>4% &quot;Pd&quot;, 130 °C</td>
</tr>
<tr>
<td>26, 71%</td>
<td>3% &quot;Pd&quot;, 120 °C</td>
<td>3% &quot;Pd&quot;, 120 °C</td>
</tr>
<tr>
<td>27, 91% (&gt;20:1 $\alpha:\beta$)</td>
<td>2% &quot;Pd&quot;, 100 °C</td>
<td>2% &quot;Pd&quot;, 100 °C</td>
</tr>
<tr>
<td>28, 89% (&gt;20:1 $\alpha:\beta$) (71%)$^b$</td>
<td>2% &quot;Pd&quot;, 130 °C</td>
<td>2% &quot;Pd&quot;, 130 °C</td>
</tr>
</tbody>
</table>

$^a$Isolated yields, average of two runs. Reaction conditions unless otherwise noted: Aryl triflate (1.00 mmol), CsF (3.00 mmol), 6 (1-3%), tol (0.1 M). $^b$Yield when reaction was conducted under the same reaction conditions using [(cinnamyl)PdCl]$_2$/L2 (Pd:L2 = 1:1.5) instead of 6. Aryl triflate (0.10 mmol), CsF (0.30 mmol), tol (0.1 M). $^c$Yield when reaction was conducted under the same reaction conditions using [(cinnamyl)PdCl]$_2$/L2 (Pd:L2 = 1:1.5) instead of 6. Aryl triflate (0.10 mmol), CsF (0.30 mmol), 6 (2%), tol (0.1 M). $^{19}$F NMR yield.
Other nitrogen-containing heteroaryl triflates, such as those derived from 5-membered heteroaryl phenols, could not be fluorinated under these conditions. An inhibition study\textsuperscript{20} of the conversion of δ-tocopherol triflate to 19 in the presence of various sp\textsuperscript{2}-hybridized nitrogen-containing additives suggests that these species inhibit this transformation to some degree, which may explain why such heteroaryl triflates remain challenging substrates for this reaction (see Table 3.7 in the experimental).

3.5 Preparation of other [(1,5-COD)(L•Pd)\textsubscript{n}] (n = 1-2) species. Inspired by the powerful reactivity of 6, we next investigated how general this precatalyst framework is by preparing the analogous Pd(0) complexes of other biaryl phosphine ligands. When combined with [(1,5-COD)Pd(CH\textsubscript{2}TMS)\textsubscript{2}] in pentane, the bulky di-\textit{tert}-butyl ligands tBuBrettPhos (L\textsubscript{1}, Figure 3.1), RockPhos (L\textsubscript{3}), and tBuXPhos (L\textsubscript{4}) also form isolable complexes 29-31 with concomitant loss of 0.5 eq. of 1,5-COD (Figure 3.9). Like 6, these complexes are insoluble in most organic solvents and rapidly undergo oxidative addition to 4-(nBu)PhBr to produce the corresponding oxidative addition complexes 32-34, generating an additional 0.5 eq. of 1,5-COD relative to Pd in the process (Figure 3.9).

\begin{equation*}
\text{Pd(CH}_2\text{TMS)}_2 \quad \text{Pd(4-nBu)PhBr} \\
\text{Pr} \quad \text{Pd-L} \\
\text{Pd} \quad \text{Pd-L} \\
\text{L-Pd(4-nBuPh)Br}
\end{equation*}

29: L = L\textsubscript{1} (79\%) 30: L = L\textsubscript{3} (75\%) 31: L = L\textsubscript{4} (98\%)

\textbf{Figure 3.9.} Reaction of L\textsubscript{1}, L\textsubscript{3}-L\textsubscript{4} with [(1,5-COD)Pd(CH\textsubscript{2}TMS)\textsubscript{2}] to produce [(1,5-COD)(L•Pd)\textsubscript{2}] species 29-31, which react with 4-(nBu)PhBr to produce 32-34, respectively.
In contrast, when the smaller di-cyclohexyl ligand BrettPhos (L5) was combined with [(1,5-COD)Pd(CH₂TMS)₂], only trace amounts of 1,5-COD could be detected in the mother liquor of the reaction, suggesting that the generated species 35 possesses a 1:1:1 ratio of L5:Pd:1,5-COD (Figure 3.10). Indeed, when 35 was exposed to 4-(nBu)PhBr in toluene-d₈, full conversion to the previously reported complex 36 was observed in less than 10 min. with concomitant generation of 1 eq. of 1,5-cyclooctadiene (Figure 3.10). Instead of the general structure of [(1,5-COD)(L•Pd)₂] shared by 6 and 29–31, 35 is likely monomeric in nature, with only one Pd center coordinated to each molecule of 1,5-COD. Nonetheless, 35 still effectively behaves as a highly reactive source of L5•Pd(0). Unfortunately, smaller di-cyclohexyl ligands such as XPhos, SPhos, and RuPhos, do not form stable complexes with 1,5-COD, nor do extremely bulky ligands such as Me₄BuXPhos (not shown).

![Figure 3.10. Reaction of L5 with [(1,5-COD)Pd(CH₂TMS)₂] to produce [(1,5-COD)(L5•Pd)] species 35, which reacts with 4-(nBu)PhBr to produce 36.](image)

3.6 Conclusion. Driven by the need for a new Pd source for the Pd-catalyzed fluorination of aryl triflates, we have developed a family of new Pd(0) precatalysts that activate at room temperature under neutral conditions, generating only innocent 1,5-COD in the process. Further insight into the principal reactivity of 6 as a source of L2•Pd(0) revealed that dissociation of 1,5-COD from this complex occurs readily at room
temperature. Despite its high reactivity, 6 is thermally stable at room temperature and reasonably air/moisture stable, making it an ideal precatalyst for Pd-catalyzed cross-coupling reactions. Overall, these precatalysts should be effective for Pd-catalyzed reactions that are inhibited by the byproducts resulting from activation of other Pd sources, as well as those reactions for which the addition of base is not necessary. Together with this key discovery, we found that the di-adamantyl ligand L2 is superior to L1 for carrying out the Pd-catalyzed fluorination of aryl triflates. Taken together, these findings have brought this reaction to a level where it could be used to cleanly fluorinate a variety of triflates derived from biologically active phenols and heterocycles. With such a reactive precatalyst in hand, we next set out to develop Pd-catalyzed fluorination reactions that were not possible with the combination of [(cinnamyl)PdCl]2/L1.

3.7. Experimental.

3.7.1. General Procedures. Anhydrous, oxygen-free toluene, tetrahydrofuran, diethyl ether, and dichloromethane (CH2Cl2) were purchased from J. T. Baker and passed through two activated alumina columns followed by sparging with argon before use. Cyclohexane and pentane were purchased from Aldrich in Sure-Seal™ bottles and sparged with argon before use. CD2Cl2 and tol-d8 were purchased in sealed ampules from Cambridge Isotopes. CDCl3 was purchased from Cambridge Isotopes. Cesium fluoride (99.9%) was purchased from Strem and dried at 200 °C under high vacuum for 24 h. The dried CsF was then transferred to a nitrogen-filled glovebox where it was thoroughly ground using an oven-dried mortar and pestle. The finely ground CsF was then filtered through a 45 μm stainless-steel sieve (purchased from Cole Parmer) to
obtain CsF with particle size of < 45 μm. Preparations of \( \textbf{L}1 \), \( \textbf{L}2 \), \( \textbf{L}3 \) have been previously described; the \( \textbf{L}1 \) used in this work was received as a gift from Dr. Naoyuki Hoshiya (MIT), for which we are grateful. The BrettPhos (\( \textbf{L}4 \)) used in this work was purchased from Sigma Aldrich. The \( \text{tBuXPhos} \) (\( \textbf{L}5 \)) used in this work was received as a gift from Sigma Aldrich, for which we are grateful. All other reagents were purchased from commercial sources and used without further purification. Compounds were analyzed by \( ^1\text{H}, ^{13}\text{C}, ^{31}\text{P}, ^{19}\text{F} \) NMR, and IR, as well as by elemental analysis in some cases. All \( ^{19}\text{F} \) NMR yields stated for fluorination reactions are calculated from \( ^{19}\text{F} \) NMR spectra relative to an internal standard of 1-fluoronaphthalene. \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometers and were calibrated using residual solvent as an internal reference. \( ^{19}\text{F} \) and \( ^{31}\text{P} \{ ^1\text{H} \} \) spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometer. \( ^{19}\text{F} \) NMR spectra were calibrated to an external standard of PhCF\(_3\) (\( \delta -63.72 \) ppm). All \( ^{19}\text{F} \) and \( ^{31}\text{P} \) NMR are proton decoupled. \( ^{31}\text{P} \) NMR spectra were calibrated to an external standard of \( \text{aq. H}_3\text{PO}_4 \) (\( \delta 0.0 \) ppm). The following abbreviations were used to explain multiplicities: \( s = \) singlet, \( d = \) doublet, \( t = \) triplet, \( \text{pt} = \) pseudotriplet, \( q = \) quartet, \( p = \) pentet, \( m = \) multiplet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 Fourier Transform IR Spectrometer.

Solid-state NMR spectra were recorded at 750 MHz \( ^1\text{H} \) frequency using a home-built spectrometer courtesy of David Rubin (MIT) and a triple channel Bruker 1.3 mm triple resonance probe (Bruker Biospin, Billerica, MA). Spectra acquired at 750 MHz were rotated at a MAS frequency of 60 kHz. 15 kHz TPPM proton decoupling was used in all experiments. Protons were suppressed prior to cross polarization to minimize the
contributions from protons not bonded to $^{13}$C. The pulse sequence used to acquire $^1$H-$^{13}$C spectra is as follows: polarization was transferred from $^1$H to $^{13}$C by cross polarization (CP), which then evolved on $^{13}$C for a time $t_1$ with 15 kHz of $^1$H decoupling. The $^{13}$C signal was then stored along z and proton signal was saturated to minimize the signal from protons not bonded to $^{13}$C. A second CP transferred signal from $^{13}$C to $^1$H, which is then detected. The cross polarization contact time is 1.5 ms for the transfer from $^1$H to $^{13}$C and contact times of 0.2 ms and 0.5 ms for the transfer from $^{13}$C to $^1$H, respectively. The indirect $^{13}$C dimension was sampled to 12.5 ms, and the $^1$H dimension for 40 ms. The $^1$H dimension was apodized with a 90 Hz gaussian filter, and the $^{13}$C dimension was apodized with a 50 Hz gaussian filter. All spectra were referenced to the water peak of an external sample at 4.8 ppm. $^{13}$C shifts are reported on the DSS scale. Spectra were processed, displayed and assigned using the NMRPipe software package (Goddard and Kneller, University of California, San Francisco).

### 3.7.2. Synthesis of new complexes.

In a nitrogen-filled glovebox, AdBrettPhos (641 mg, 1.00 mmol, 1.00 eq.) was suspended in pentane (10 mL). To this suspension was added [(COD)Pd(CH$_2$TMS)$_2$] (389 mg, 1.00 mmol, 1.00 eq.) in one portion, followed by 4-nbutylphenyl triflate (565 mg, 2.00 mmol, 2.00 eq.). The non-homogenous mixture was stirred vigorously at room temperature for 48 h, during which time a bright yellow solid precipitated from solution. At this time, the non-homogenous mixture was filtered though a fine sintered glass frit. The filter cake was washed with pentane (20 mL) and dried
under vacuum to yield 5 (937 mg, 91%) as a yellow solid. $^1$H NMR (500 MHz, CD$_2$Cl$_2$):

$\delta$ 7.29 (d, $J = 9$ Hz, 1H), 7.15-7.73 (m, 3H), 7.10-7.14 (m, 2H), 6.81 (d, $J = 8$ Hz, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 2.57 (septet, $J = 7$ Hz, 2H), 2.50 (t, $J = 8$ Hz, 2H), 2.35 (septet, $J = 6$ Hz, 1H), 2.00-2.09 (bs, 12H), 1.90-1.98 (bs, 6H), 1.63-1.69 (bs, 12H), 1.49-1.56 (m, 7H), 1.22-1.34 (m, 4H), 1.08-1.14 (m, 5H), 0.79-0.92 (m, 9H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 154.5, 153.0, 152.9, 150.5, 148.5, 148.4, 141.4, 139.3, 135.3, 135.2, 132.3, 132.2, 128.8, 127.9, 127.8, 117.5, 117.4, 116.3, 116.0, 113.9, 55.3, 55.1, 47.5, 47.4, 41.8, 36.3, 35.0, 34.5, 34.2, 34.0, 31.7, 29.6, 29.5, 25.5, 23.7, 22.7, 22.5, 22.5, 22.2, 14.2, 14.1 ppm (observed complexity is due to C-P coupling); $^{31}$P NMR (121 MHz, CD$_2$Cl$_2$): $\delta$ 113.2 ppm; $^{19}$F NMR (470 MHz, CD$_2$Cl$_2$): $\delta$ -79.3 ppm. Anal. Calcd. for: C$_{54}$H$_{74}$O$_3$F$_3$PPdS: C, 62.99, H, 7.24; found C, 61.19, H, 7.29.

In a nitrogen-filled glovebox, AdBrettPhos (1.28 g, 2.00 mmol, 1.00 eq.) and [(COD)Pd(CH$_2$TMS)$_2$] (778 mg, 2.00 mmol, 1.00 eq.) were suspended in pentane (30.0 mL). The reaction mixture was stirred vigorously at room temperature for 48 h, during which time a pale yellow solid precipitated from solution. At this time, the non-homogenous mixture was filtered though a sintered glass frit. The filter cake was washed with pentane (3 x 10 mL) to yield 6 (1.56 g, 96%) as a pale yellow solid. When dodecane was added to the filtrate as an internal standard, 11%, of 1,3-COD and 33% of 1,5-COD were detected, respectively, by GC analysis (upon comparison to a standard curve). A third species, which we assumed was 1,4-COD and had an identical response factor to
that of 1,5-COD, was also present (9%). IR (neat): 2950, 2900, 2847, 1575, 1456, 1418, 1375, 1342, 1301, 1157, 1090, 1048, 1015, 930, 866, 804, 748, 715, 617 cm⁻¹. 6 is almost completely insoluble in cyclohexane, pentane, toluene, benzene, THF, Et₂O, 1,2-dimethoxyethane, cyclopentyl methyl ether, methyl tert-butyl ether, DMSO, DMF, and acetone. 6 is unstable in chlorinated solvents, pyridine, and methanol. Pd(0) complexes 29-31 and 35 were prepared using the same procedure with yields in the range of 75-95%, are similarly insoluble in most organic solvents, and are also unstable in chlorinated solvents.

In a nitrogen-filled glovebox, 6 was dissolved in CDCl₃ (0.5 mL). The resulting suspension was vigorously stirred for 10 min. to give a dark yellow solution. The solvent was then removed under high vacuum. Pentane (1 mL) was added to the resulting brown oil, and the mixture was vigorously stirred for 1 min., at which time the solvent was removed under vacuum. The process was repeated a total of three times to yield 7 as bright yellow powder. ¹H NMR (500 MHz, CDCl₃): δ 6.88 (s, 2H), 5.31 (s, 1H), 5.29 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.12-2.22 (m, 12H), 1.92-1.95 (m, 6H), 1.79-1.86 (m, 3H), 1.58-1.70 (m, 12H), 1.32 (d, J = 7 Hz, 6H), 1.13 (d, J = 7 Hz, 6H), 1.04 (d, J = 7 Hz, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 154.7, 151.0, 150.8, 139.8, 139.6, 137.9, 137.9, 132.0, 131.8, 113.1, 110.8, 103.6, 103.5, 87.8, 87.8, 54.4, 54.1, 53.7, 53.7, 53.7, 43.0, 41.5, 37.7, 36.6, 31.0, 29.2, 29.1, 24.7, 23.9, 22.4, 19.3, 14.2 ppm (observed complexity is due to C-P coupling); ³¹P NMR (202 MHz, CDCl₃): δ 86.5 ppm. X-ray quality crystals of 7 were grown by vapor diffusion of a solution of 7 in MTBE using 341
pentane.

In a nitrogen-filled glovebox, N-phenylmaleimide (19.0 mg, 0.11 mmol, 2.20 eq.) was suspended in pentane (10 mL). To this suspension was added 6 (80.0 mg, 0.050 mmol, 1.00 eq.). The non-homogenous solution was allowed to vigorously stir at room temperature for 48 h, during which time a color change from pale yellow to bright yellow was observed. The mixture was cooled to −20 °C and kept at this temperature for 1 h, at which time it was filtered through a sintered glass frit. The filter cake was washed thoroughly with pentane (3 x 5 mL) to yield 8 (80 mg, 84%) as a bright yellow solid. \( ^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)): δ 7.27-7.33 (m, 2H), 7.17-7.21 (m, 3H), 7.00-7.50 (bs, 2H), 6.94 (d, J = 9 Hz, 1H), 6.86 (d, J = 9 Hz, 1H), 4.17-4.47 (bs, 2H), 3.86 (s, 3H), 3.39 (s, 3H), 3.13 (septet, J = 9 Hz, 1H), 2.03-2.30 (m, 13H), 1.92 (bs, 6H), 1.70 (bs, 12H), 1.42 (bs, 6H), 1.17-1.35 (m, 7H), 0.68-0.95 (m, 7H) ppm; \( ^{13}\)C NMR (125 MHz, CD\(_2\)Cl\(_2\)): δ 155.3, 155.3, 152.4, 152.3, 148.4, 140.2, 139.9, 134.7, 128.4, 128.3, 128.2, 126.8, 126.2, 116.3, 116.3, 113.0, 110.3, 110.3, 60.1, 54.5, 54.5, 42.9, 42.3, 37.1, 34.1, 31.7, 29.7, 25.8, 24.9 ppm (observed complexity is due to C–P coupling); \( ^{31}\)P NMR (202 MHz, CD\(_2\)Cl\(_2\)): δ 82.5 ppm. HSQC and HMBC spectra (CD\(_2\)Cl\(_2\), 500 MHz) were collected to aid in structural assignment. The \( ^{13}\)C resonances at δ 134.7 ppm and δ 128.3 ppm are for quaternary carbons (by HSQC) that show no long range coupling to any \(^1\)H signals on the phosphine ligand but do show correlation to the \(^1\)H signals for the 5H on the Ph group (HSQC). These are the most likely signals for the C=O carbonyl and the N-bound carbon of the Ph group. IR (neat): 2904, 2847, 1727, 1681, 1597, 1579,
1497, 1459, 1419, 1352, 1259, 1202, 1120, 1091, 1045, 1016, 946, 873, 807, 791, 753, 696, 619 cm\(^{-1}\). X-ray quality crystals of 8 were grown by vapor diffusion of a solution of 8 in 1:1 TBME:CH\(_2\)Cl\(_2\) using pentane.

3.7.3. Oxidative addition experiments of [(L-Pd)\(_n\)(1,5-COD)] (n = 1-2) species.

Procedure for reaction between 6 and 4-(nBu)PhOTf: In a nitrogen-filled glovebox, 6 (16.0 mg, 0.01 mmol, 1.00 eq.) was suspended in tol-d\(_8\) (1.0 mL) in an oven-dried screw-cap NMR tube. 4-(nBu)PhOTf (6.30 mg, 0.02 mmol, 2.20 eq.) was then added, and the NMR tube was capped and removed from the glovebox. After <10 min. at room temperature, complete conversion of 6 to 5 was observed by \(^{31}\)P NMR (121 MHz), and 0.5 eq. of 1,5-cyclooctadiene could be detected by \(^1\)H NMR integration (300 MHz, tol-d\(_8\), see below). The reaction mixture was also homogenous and red in color.

Procedure to estimate the air stability of 6. In a nitrogen-filled glovebox, 6 (20.0 mg, 13.0 \(\mu\)mol, 1.00 eq.) was weighed out in a vial and then removed from the glovebox. The
vial was placed uncapped on the benchtop for a period of 24 h. The vial was transferred back to the glovebox and suspended in tol-d$_8$ (1.8 mL). 4-(nBu)PhOTf (7.80 mg, 28 μmol, 2.20 eq.) was added, and the vial was vigorously shaken for 10 min. At this point the mixture turned homogeneous and red in color. Then, 1,3,5-trimethoxybenzene (2.10 mg, 13 μmol, 1.00 eq.) in tol-d$_8$ (0.2 mL) was added, and the reaction mixture was analyzed by $^{31}$P (121 MHz) and $^1$H (300 MHz) NMR. By $^{31}$P NMR, the only signals observed were at δ 113 ppm (5) and a weak signal at δ 55 ppm for an unidentified species. By $^1$H NMR, an 83% yield of 5 was observed; the spectrum was very similar to that shown above for the reaction conducted with material stored in a glovebox.

**General procedure for reaction of 6, 29-31 with 4-(nBu)PhBr:** In a nitrogen-filled glovebox, the precatalyst (0.01 mmol, 1.00 eq.) was suspended in toluene-d$_8$ (1.0 mL) in an oven-dried screw-cap NMR tube. 4-(nBu)PhBr (3.90 μL, 22 μmol, 2.20 eq.) was then added, and the NMR tube was capped and removed from the glovebox. After <10 min. at room temperature, the homogenous reaction mixture was analyzed by $^{31}$P NMR (121 MHz) and $^1$H (300 MHz, toluene-d$_8$) and compared to the spectra for the corresponding oxidative addition complex reported in the literature. In every case, 0.5 eq. of 1,5-COD could be detected by $^1$H NMR integration (300 MHz, toluene-d$_8$).

**Procedure for reaction of 35 with 4-(nBu)PhBr:** In a nitrogen-filled glovebox, 35 (15.0 mg, 0.020 mmol, 1.0 eq.) was suspended in toluene-d$_8$ (1.0 mL) in an oven-dried screw-cap NMR tube. 4-nBuPhBr (3.9 μL, 0.022 mmol, 1.1 eq.) was then added, and the NMR tube was capped and removed from the glovebox. After <10 min. at room
temperature, the homogenous reaction mixture was analyzed by $^{31}$P NMR (121 MHz) and $^1$H (300 MHz, tol-$d_8$) and compared to the spectra for the corresponding oxidative addition complex reported in the literature. In this case, 1.0 eq. of 1,5-COD could be detected by $^1$H NMR integration (300 MHz, toluene-$d_8$).

3.7.4. Synthesis of phenols and aryl triflates.

Unless specified otherwise, aryl triflates were prepared from the corresponding phenols following the method of Ritter.$^{25}$ Aryl nonaflates were prepared via the same method using perfluorobutanesulfonyl fluoride in place of triflic anhydride. $p$-Coumaric acid methyl ester,$^{26}$ $N$-(4-hydroxyphenyl)-$N$-methylacetamide,$^{27}$ and 3-hydroxyquinoline$^{28}$ were prepared according to literature procedures. Unless specified otherwise, all other phenols were purchased from commercial sources. The triflates derived from estrone,$^{40}$ $\delta$-tocopherol,$^{40}$ 4-methylumbelliferone,$^{29}$ 4-chloro-3,5-dimethylphenol,$^{30}$ and 8-trifluoromethyl-4-quinolinol,$^{31}$ have been previously described.

White solid. Melting Point: 33-34 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.66 (d, J = 15 Hz, 1H), 7.56-7.60 (m, 2H), 7.27-7.31 (m, 2H), 6.44 (d, J = 16 Hz, 1H), 3.75 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.9, 150.4, 142.5, 136.0, 129.9, 122.0, 120.1, 118.8 (q, J = 319 Hz), 52.0 ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ −73.1 ppm. IR: 2960, 1704, 1641, 1598, 1504, 1423, 1326, 1248, 1216, 1198, 1173, 1135, 1019, 977, 947, 880, 844, 832, 775, 750, 739, 704, 687, 609, 593 cm$^{-1}$. Anal. Calcd. for C$_{11}$H$_9$F$_3$O$_5$S: C, 42.58, H, 2.92; found C, 42.80, H, 2.87.
Yellow solid. Melting Point: 40 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$
7.22 (d, $J = 8$ Hz, 1H), 7.05 (d, $J = 2$ Hz, 1H), 6.95 (dd, $J = 8$, 2 Hz, 1H),
3.90 (s, 3H), 3.52 (bs, 2H), 3.24 (bs, 2H), 1.23 (bs, 3H), 1.13 (bs, 3H)
ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 169.5, 151.7, 139.1, 138.5, 122.6, 118.6, 118.8 (q,
$J = 319$ Hz), 111.8, 56.4, 43.5, 39.5, 14.3, 12.9 ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –
74.5 ppm. IR: 2977, 2941, 1630, 1601, 1463, 1420, 1295, 1265, 1248, 1202, 1137,
1107, 1029, 882, 817, 760, 609 cm$^{-1}$. Anal. Calcd. for C$_{13}$H$_{16}$F$_3$NO$_5$S: C, 43.94 , H, 4.54;
found C, 44.06, H, 4.56.

White crystalline solid. Melting Point: 121 °C. $^1$H NMR
(500 MHz, CDCl$_3$): $\delta$ 8.07 (dd, $J = 9$, 1 Hz, 4H), 7.46 (dd, $J$
= 9, 1 Hz, 4H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 152.8, 141.1,
130.6, 123.0, 118.7 (q, $J = 319$ Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –72.9 ppm. IR (neat): 3104, 1583,
1486, 1429, 1406, 1326, 1291, 1251, 1205, 1133, 1103, 1014, 878, 841, 725, 658 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_8$O$_8$F$_6$S$_3$: C, 32.69, H, 1.57; found C, 32.83, H, 1.57.

Fluffy white crystalline solid. Melting Point: 95 °C. $^1$H NMR
(500 MHz, CDCl$_3$): $\delta$ 7.70 (d, $J = 9$ Hz, 1H), 7.22-7.27 (m, 2H),
6.33 (s, 1H), 2.45 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$
159.6, 154.2, 151.4, 151.1, 126.5, 120.1, 117.5, 116.0, 110.6, 18.8 ppm (the signals for
the C$_4$F$_9$ group are omitted due to complex C-F coupling); $^{19}$F NMR (470 MHz, CDCl$_3$):
$\delta$ –81.1, –108.9, –121.2, –126.2 ppm. IR (neat): 3082, 1722, 1629, 1603, 1433, 1384,
1350, 1235, 1194, 1112, 1068, 1030, 1015, 977, 899, 839, 825, 806, 732, 696, 629, 581 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_{7}$O$_{5}$F$_{9}$S: C, 36.69; H, 1.54; found C, 36.83, H, 1.43.

To a solution of nonivamide (1.47 g, 5.00 mmol, 1.00 eq.) in CH$_2$Cl$_2$ (20 mL) in a 100 mL roundbottom flask was added triethylamine (0.84 mL, 6.00 mmol, 1.20 eq.), followed by $n$-butyldimethylsilyl chloride (829 mg, 5.50 mmol, 1.10 eq.). The reaction mixture was then vigorously stirred under an inert atmosphere for 14 h. At this time, the reaction mixture was quenched with water (20 mL) and the organic and aqueous phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL), and the organic extracts were combined and dried over MgSO$_4$. After concentration, the crude product was purified by flash chromatography (1:4 EtOAc:hexanes $\rightarrow$ 1:3 EtOAc:hexanes) to yield 12a (2.01 g, 99\%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.78 (dd, J = 8, 2 Hz, 1H), 6.75-6.77 (m, 1H), 6.68-6.71 (m, 1H), 5.71 (bs, 1H), 4.35 (d, J = 5 Hz, 2H), 3.78 (s, 3H), 2.20 (t, J = 7 Hz, 2H), 1.65 (p, J = 8 Hz, 2H), 1.23-1.31 (m, 10H), 0.98 (s, 9H), 0.87 (t, J = 7 Hz, 3H), 0.14 (s, 6H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.1, 151.3, 144.7, 132.1, 121.1, 120.4, 112.1, 55.7, 43.7, 37.1, 32.1, 29.6, 29.4, 26.1, 25.9, 22.9, 22.6, 18.7, 14.3, −4.4 ppm. IR (in CHCl$_3$): 3289, 2927, 2856, 1642, 1512, 1464, 1418, 1281, 1250, 1233, 1157, 1126, 1039, 898, 839, 781 cm$^{-1}$.
A solution of 12a (1.45 g, 3.60 mmol, 1.00 eq.) in anhydrous THF (20 mL) was cooled to −78 °C. 2.50 M solution of nBuLi in hexane (1.56 mL, 3.90 mmol, 1.10 eq.) was added dropwise, and the reaction mixture was allowed to stir for 1 h at −78 °C. At this time, iodomethane (0.331 mL, 5.30 mmol, 1.50 eq.) was added. The reaction mixture was warmed to room temperature over 1 h, and then allowed to stir at room temperature for an addition 8 h. The reaction was then quenched with saturated \( \text{aq. NH}_4\text{Cl} \) (20 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). After concentration, the crude product was dissolved in methanol (10 mL) and 2.0 M hydrochloric acid (0.1 mL) was added. The mixture was heated to 60 °C and stirred at this temperature for 2 h. The reaction mixture was cooled to room temperature, the solvent was removed, and the resulting oil was quenched with saturated \( \text{aq. NaHCO}_3 \) (10 mL) and diluted with ethyl acetate (20 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, dried over MgSO\(_4\), and concentrated. The crude product was purified by flash chromatography to yield 12b (887 mg, 81% over two steps) as a colorless oil. 12b exists as a 1.5:1 mixture of rotamers in solution. \( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): major rotamer: \( \delta \) 6.84 (d, \( J = 8 \text{ Hz}, 1\text{H} \)), 6.80 (s, 1\text{H}), 6.72 (d, \( J = 8 \text{ Hz}, 1\text{H} \)), 5.66 (bs, 1\text{H}), 4.50 (s, 2H), 3.86 (s, 3H), 2.89 (s, 3H), 2.33-2.39 (m, 2H), 1.64-1.68 (m, 2H), 1.25-1.30 (m, 10H), 0.85-0.89 (m, 3H) ppm; minor rotamer: \( \delta \) 6.90 (d, \( J = 8 \text{ Hz}, 1\text{H} \)), 6.66 (d, \( J = 8 \text{ Hz}, 1\text{H} \)), 6.61 (s, 1\text{H}), 4.45 (s, 2H), 3.87 (s, 3H), 2.92 (s, 3H), 2.33-2.39 (m, 2H), 1.64-1.68 (m, 2H), 1.25-1.30 (m, 10H), 0.85-0.89 (m, 3H) ppm; \( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)): \( \delta \) 173.4, 146.9, 145.1, 129.7, 121.4, 119.4, 114.8, 114.1, 110.9, 108.7, 56.1, 53.3, 50.7, 34.7, 33.8, 33.4, 32.0, 29.7, 29.6, 29.3, 25.7, 25.4, 22.8, 14.2 ppm
(observed complexity is due to the presence of two rotamers in solution). IR (in CHCl₃): 3950, 3010, 2855, 1627, 1456, 1432, 1402, 1273, 1238, 1215, 1152, 1125, 1037 cm⁻¹.

Thick yellow oil. This compound exists as a 2.5:1 mixture of rotamers in solution. ¹H NMR (500 MHz, CDCl₃): major rotamer: δ 7.11 (d, J = 8 Hz, 1H), 6.92 (d, J = 2 Hz, 1H), 6.79 (dd, J = 8, 2 Hz, 1H), 4.54 (s, 2H), 3.84 (s, 3H), 2.93 (s, 3H), 2.35 (t, J = 8 Hz, 2H), 1.59-1.68 (m, 2H), 1.18-1.36 (m, 10H), 0.81-0.88 (m, 3H) ppm; minor rotamer: δ 7.17 (d, J = 8 Hz, 1H), 6.77 (s, 1H), 6.74 (d, J = 9 Hz, 1H), 4.51 (s, 2H), 3.86 (s, 3H), 2.92 (s, 3H), 2.30 (t, J = 8 Hz, 2H), 1.59-1.68 (m, 2H), 1.18-1.36 (m, 10H), 0.81-0.88 (m, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 173.6, 173.5, 151.9, 151.5, 139.6, 138.8, 137.9, 122.9, 122.3, 120.1, 120.0, 118.3, 117.5, 112.8, 110.7, 56.2, 56.2, 53.0, 50.6, 35.1, 34.0, 33.5, 33.1, 31.9, 31.8, 29.5, 29.5, 29.5, 29.2, 29.2, 25.4, 25.2, 22.7, 22.7, 14.1, 14.1 ppm (observed complexity is due to the presence of two rotamers in solution); ¹⁹F NMR (470 MHz, CDCl₃): δ -74.1 ppm (major rotamer), δ -74.1 ppm (minor rotamer). IR (neat): 2925, 2855, 1645, 1601, 1504, 1464, 1419, 1285, 1248, 1203, 1139, 1104, 1032, 875, 704, 614 cm⁻¹. Anal. Calcd. for C₁₉H₂₈O₅F₃NS: C, 51.92, H, 6.42; found C, 52.03, H, 6.34.

White crystalline solid. Melting Point: 70 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.30 (d, J = 9 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 3.23 (s, 3H), 1.85 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 170.5, 148.6, 144.9, 129.5,
A 20 mL reaction tube was charged with desvenlafaxine (793 mg, 3.01 mmol, 1.00 eq.), N-phenyl-bis(trifluoromethanesulfonimide) (1.18 g, 3.31 mmol, 1.10 eq.), and K$_2$CO$_3$ (832 mg, 6.02 mmol, 2.00 eq.). The tube was evacuated under high vacuum and backfilled with nitrogen. This procedure was repeated a total of three times. THF (10 mL) was added, and the heterogeneous mixture was stirred at 70 °C for 12 h. At this time the mixture was cooled to room temperature and filtered through a pad of Celite, eluting with EtOAc (50 mL). After concentration, the crude product was purified by flash chromatography (hexanes → EtOAc → 1:20 acetone:EtOAc → 1:10 acetone:EtOAc → 1:20 MeOH:CH$_2$Cl$_2$ → 1:10 MeOH:CH$_2$Cl$_2$) to yield desvenlafaxine triflate (1.10 g, 92%) as a white solid. Melting Point: 90 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.21 (d, J = 9 Hz, 2H), 7.17 (d, J = 9 Hz, 2H), 5.86 (bs, 1H), 3.28 (pt, J = 12 Hz, 1H), 3.03 (dd, J = 13 Hz, 3 Hz, 1H), 2.29-2.35 (m, 7H), 1.63-1.77 (m, 3H), 1.47-1.60 (m, 3H), 1.34-1.42 (m, 1H), 1.22 (ptd, J = 12, 4 Hz, 1H), 0.81-0.97 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 148.4, 141.5, 131.0, 120.9, 118.8 (q, J = 319 Hz), 74.1, 60.9, 52.1, 45.6, 38.3, 31.4, 26.0, 21.6, 21.3 ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): δ –73.2 ppm. IR: 3148 (broad), 2943,

Off-white crystalline solid. Melting Point: 38 °C. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 8.84 (d, \(J = 3\) Hz, 1H), 8.17 (d, \(J = 9\) Hz, 1H), 8.08 (d, \(J = 3\) Hz, 1H), 7.86 (d, \(J = 9\) Hz, 1H), 7.78-7.82 (m, 1H), 7.64 (m, 1H) ppm; \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 147.2, 143.8, 143.3, 130.8, 129.8, 128.5, 128.1, 127.7, 127.0, 118.9 (q, \(J = 319\) Hz); \(^{19}\)F NMR (282 MHz, CDCl₃): \(\delta\) -72.8 ppm. IR (neat): 3065, 1601, 1505, 1421, 1329, 1243, 1204, 1131, 1114, 971, 912, 903, 850, 829, 785, 758, 751, 700, 645, 603 cm⁻¹. Anal. Calcd. for: C₁₀H₆O₃F₃NS: C, 43.33, H, 2.18; found C, 43.58, H, 2.21.

Pale yellow oil. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 7.43 (d, \(J = 8\) Hz, 1H), 7.05 (d, \(J = 9\) Hz, 1H), 2.87 (q, \(J = 8\) Hz, 2H), 2.54 (s, 3H), 1.30 (t, \(J = 8\) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 158.3, 155.3, 143.0, 129.1, 122.1, 118.7 (q, \(J = 318\) Hz), 25.9, 24.2, 12.8 ppm; \(^{19}\)F NMR (282 MHz, CDCl₃): \(\delta\) -74.1 ppm. IR: 2978, 2942, 2884, 1592, 1455, 1422, 1250, 1207, 1137, 1097, 910, 865, 824, 714, 697, 644, 627 cm⁻¹. Anal. Calcd. for C₉H₁₀F₃NO₃S: C, 40.15, H, 3.74; found C, 40.44, H, 3.73.

3-aminophenol (1.09 g, 11.0 mmol, 1.10 eq.) and 2,5-dimethoxytetrahydrofuran (1.30 mL, 10.0 mmol, 1.00 eq.) were
dissolved in dioxane (6 mL) in a two-neck roundbottom flask equipped with a reflux condenser. Acetic acid (4 mL) was added, and the reaction mixture was stirred at reflux for 6 h, during which time the reaction solution turned dark brown. The reaction mixture was cooled to room temperature and the solvent was removed. The resulting brown sludge was partitioned between CH₂Cl₂ (100 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The non-homogenous organic layers were combined, dried over MgSO₄, and filtered to give a homogenous solution. The solvent was removed with the aid of a rotary evaporator, and the crude product was purified by flash chromatography (1:4 EtOAc:hexanes) to yield 3-((1H-pyrrol-1-yl)phenol (848 mg, 53%) as a light brown solid. Melting point: 62-64 °C.

$$^1$$H NMR (500 MHz, CDCl₃) δ 7.28 (pt, J = 8 Hz, 1H), 7.09 (td, J = 2, 1 Hz, 2H), 6.98-7.01 (m, 1H), 6.86 (td, J = 2, 1 Hz, 1H), 6.69-6.72 (m, 1H), 6.38 (td, J = 2, 1 Hz, 2H), 5.29 (s, 1H) ppm; $$^{13}$$C NMR (125 MHz, CDCl₃) δ 156.4, 142.0, 130.7, 119.4, 113.0, 112.6, 110.5, 107.8 ppm. IR (neat): 2800-3500 (broad), 1615, 1591, 1513, 1483, 1398, 1336, 1296, 1203, 1172, 1131, 1091, 1078, 1065, 1024, 952, 847, 769, 714 cm⁻¹.

White crystalline solid. Melting Point: 46 °C. $$^1$$H NMR (500 MHz, CDCl₃): δ 7.51 (pt, J = 8 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 7.32 (s, 1H), 7.16 (d, J = 8 Hz, 1H), 7.10 (s, 2H), 6.41 (s, 2H) ppm; $$^{13}$$C NMR (125 MHz, CDCl₃): δ 150.2, 142.4, 131.3, 120.0, 119.3, 118.9 (q, J = 319 Hz), 118.0, 113.5, 111.7 ppm; $$^{19}$$F NMR (470 MHz, CDCl₃): δ -73.1 ppm. IR (neat): 3134, 3077, 1614, 1589, 1505, 1417, 1338, 1318, 1249, 1197, 1138, 1087, 1069, 1027, 952, 878, 856, 796,
781, 761, 730, 647 cm\(^{-1}\). Anal. Calcd. for C\(_{11}\)H\(_8\)O\(_3\)NS: C, 45.36; H, 2.77; found C, 45.92, H, 2.68.

This procedure is adapted from the literature.\(^5\)a 2-bromo-6-hydroxynaphthalene (892 mg, 4.00 mmol, 1.00 eq.), 3-furanyl boronic acid (896 mg, 8.00 mmol, 2.00 eq.), and XPhos OMs\(^5\)a (136 mg, 0.160 mmol, 0.0400 eq.) were added to a roundbottom flask equipped with a stir bar. The flask was capped with a septum. Next, the flask was evacuated under high vacuum and backfilled with nitrogen. This procedure was repeated a total of three times. THF (8 mL) and degassed \( \text{aq. } \text{K}_3\text{PO}_4 \) (2M, 16.0 mL, 8.00 mmol, 2.00 eq.) were then added, and then hole in the septum was covered with teflon tape. The reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature, quenched with saturated \( \text{aq. } \text{NH}_4\text{Cl} \) (40 mL), and diluted with Et\(_2\)O (40 mL). The two phases were separated, and the aqueous phase was extracted with Et\(_2\)O (4 x 40 mL). The combined organic layers were dried over MgSO\(_4\) and concentrated. Purification by flash chromatography (1:10 EtOAc:hexanes → 1:5 EtOAc: hexanes) yielded 6-(furan-3-yl)-2-hydroxynaphthalene (776 mg, 92%) as a light brown powder. Melting Point: 169 °C. \(^1\)H NMR (500 MHz, CD\(_3\)OD): \( \delta \) 7.93 (dd, J
= 2, 1 Hz, 1H), 7.85-7.87 (m, 1H), 7.70 (d, J = 9 Hz, 1H), 7.62 (d, J = 9 Hz, 1H), 7.58 (d, J = 2 Hz, 2H), 7.56 (dd, J = 3, 2 Hz, 1H), 7.09 (d, J = 3 Hz, 1H), 7.07 (dd, J = 9, 3 Hz, 1H), 6.87 (dd, J = 1, 1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 156.4, 145.0, 139.8, 135.5, 130.4, 130.1, 128.3, 128.0, 127.8, 125.7, 124.7, 119.6, 109.9, 109.6 ppm. IR (neat): 3436 (broad), 3140, 3125, 1635, 1619, 1519, 1475, 1287, 1202, 1150, 1135, 1051, 897, 888, 867, 813, 782 cm$^{-1}$.  

White solid. Melting Point: 72 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.93 (s, 1H), 7.82-7.90 (m, 3H), 7.68-7.74 (m, 2H), 7.54-7.57 (m, 1H), 7.37 (dd, J = 9, 3 Hz, 1H), 6.82-6.84 (m, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 147.1, 144.3, 139.5, 132.9, 132.5, 131.5, 130.6, 128.8, 126.4, 126.1, 124.0, 120.3, 119.3, 119.1 (q, J = 319 Hz), 109.9 ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ -73.2 ppm. IR (neat): 3132, 1608, 1470, 1419, 1397, 1210, 1184, 1163, 1130, 1109, 1054, 1016, 969, 947, 885, 871, 846, 815, 785, 743, 715, 709, 695, 644, 594 cm$^{-1}$.

354
This procedure is adapted from the literature.\textsuperscript{5a} 2-bromo-6-hydroxynaphthalene (892 mg, 4.00 mmol, 1.00 eq.), 3-thienyl boronic acid (1.06 g, 8.00 mmol, 2.00 eq.), and XPhos OMs\textsuperscript{5a} (136 mg, 0.160 mmol, 0.0400 eq.) were added to a 100 mL roundbottom flask equipped with a stir bar. The flask was capped with a septum. Next, the flask was evacuated under high vacuum and backfilled with nitrogen. This procedure was repeated a total of three times. THF (8 mL) and degassed \textit{aq.} K\textsubscript{3}PO\textsubscript{4} (2 M, 16.0 mL, 8.00 mmol, 2.00 eq.) were then added, and then hole in the septum was covered with teflon tape. The reaction mixture was stirred at 40 °C for 4 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature, quenched with saturated \textit{aq.} NH\textsubscript{4}Cl (40 mL), and diluted with Et\textsubscript{2}O (40 mL). The two phases were separated, and the aqueous phase was extracted with Et\textsubscript{2}O (3 x 40 mL). The combined organic layers were dried over MgSO\textsubscript{4} and concentrated. Purification by flash chromatography (1:10 EtOAc:hexanes \(\rightarrow\) 1:5 EtOAc: hexanes) yielded 6-(thiophen-3-yl)-2-hydroxynaphthalene 756 mg, 84%) as a light brown powder. Melting Point: 195 °C. \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD): \(\delta\) 7.97 (s, 1H), 7.60-7.74 (m, 4H), 7.53 (dt, J = 5, 1 Hz, 1H), 7.46 (ddd, J = 5, 3,
1 Hz, 1H), 7.05-7.10 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CD$_3$OD): $\delta$ 156.5, 143.7, 135.5, 131.8, 130.7, 130.1, 127.8, 127.2, 127.1, 126.2, 125.4, 120.6, 119.7, 109.8 ppm. IR (neat): 3249 (broad), 3094, 1630, 1603, 1575, 1516, 1479, 1456, 1398, 1305, 1247, 1202, 1148, 1090, 965, 885, 868, 813, 776, 764 cm$^{-1}$.

White solid. Melting Point: 110 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.07 (s, 1H), 7.93 (d, $J = 9$ Hz, 1H), 7.89 (d, $J = 9$ Hz, 1H), 7.84 (dd, $J = 9$, 2 Hz, 1H), 7.74 (d, $J = 3$ Hz, 1H), 7.61 (dd, $J = 3$, 1 Hz, 1H), 7.52 (dd, $J = 6$, 1 Hz, 1H), 7.46 (dd, $J = 5$, 3 Hz, 1H), 7.38 (dd, $J = 9$, 3 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 147.1, 141.6, 134.7, 132.8, 132.5, 130.8, 128.7, 126.9, 126.4, 124.7, 121.5, 120.2, 119.2, 117.7 ppm (the signal corresponding to the CF$_3$ group could not be readily observed); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –73.1 ppm. IR (neat): 3099, 1602, 1508, 1473, 1421, 1360, 1204, 1133, 1109, 963, 935, 883, 848, 809, 778, 712, 672, 636, 604, 584 cm$^{-1}$. Anal. Calcd. for C$_{18}$H$_9$O$_3$F$_3$S$_2$: C, 50.27, H, 2.53; found C, 50.21, H, 2.36.

3.7.5. Experimental Procedures for Fluorination Reactions.

General procedure for reactions in Table 3.1: In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with cesium fluoride (45.6 mg, 0.30 mmol, 3.00 eq.), L1 or L2 (6.00 μmol, 0.060 eq., where appropriate), aryl triflate (0.10 mmol, 1.00 eq.). Pd source (4.00 μmol, 0.04 eq., 4% "Pd"), and toluene (1.0 mL) were added (in this order) to an oven-dried reaction tube equipped with a stir bar. The tube was capped, removed from the glovebox, placed in an oil bath that had been
pre-heated to 120 °C, and allowed to stir vigorously for 14 h. At this time, the reaction mixture was cooled to room temperature and 1-fluoronaphthalene was added. The reaction mixture was analyzed directly by $^{19}$F NMR (300 MHz) for conversion and yield. Reactions carried out with added inhibitors were carried out using the same procedure.

**General Procedure using 6 (Tables 3.2-3.3):** In a nitrogen-filled glovebox, cesium fluoride (456 mg, 3.00 mmol, 3.00 eq.), 6 (1-2%), and solvent (10 mL) were added to an oven-dried screw-cap reaction tube equipped with a stir bar. The reaction mixture was stirred at room temperature for 1 min., at which time the aryl triflate (1.00 mmol, 1.00 eq.) was added in one portion. The tube was capped, removed from the glovebox, placed in an oil bath that had been pre-heated to the desired reaction temperature, and allowed to vigorously stir at that temperature for 14 h (the stirring rate should be maintained at over 1000 rpm for optimal results). The reaction mixtures typically turned dark red during this period, and no significant formation of Pd nanoparticles was observed, although the reaction mixture remained non-homogenous due to the poor solubility of CsF and CsOTf in organic solvents. At this time, the reaction mixture was cooled to room temperature and passed through a plug of celite, eluting with Et$_2$O or EtOAc (40 mL). The solvent was removed with the aid of a rotary evaporator and the resulting crude products were purified directly by flash chromatography. All isolated yields are an average of two runs.
Table 3.7. Effect of nitrogen-containing additives on the conversion of δ-tocopherol triflate to 19.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion</th>
<th>ArF Yield (α:β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>100%</td>
<td>80% (&gt;20:1)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>80%</td>
<td>15% (n.d.)</td>
</tr>
<tr>
<td>3</td>
<td>R = Me</td>
<td>80%</td>
<td>28% (n.d.)</td>
</tr>
<tr>
<td>4</td>
<td>R = NMe₂</td>
<td>100%</td>
<td>68% (10:1)</td>
</tr>
<tr>
<td>5</td>
<td>R = CN</td>
<td>30%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>40%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>100%</td>
<td>35% (n.d.)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>100%</td>
<td>44% (10:1)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>100%</td>
<td>46% (6:1)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>50%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>100%</td>
<td>77% (&gt;20:1)</td>
</tr>
<tr>
<td>12</td>
<td>Bu₃N</td>
<td>100%</td>
<td>75% (&gt;20:1)</td>
</tr>
</tbody>
</table>

*0.10 mmol scale, ¹⁹F NMR yields.
General procedure for inhibitor screen (Table 3.7): In a nitrogen-filled glovebox, cesium fluoride (45.6 mg, 0.30 mmol, 3.00 eq.), 6 (3.20 mg, 20.0 μmol, 0.02 eq.), and cyclohexane (1.0 mL) were added to an oven-dried reaction tube equipped with a stir bar. The reaction mixture was stirred at room temperature for 1 min, at which time δ-tocopherol triflate (53.5 mg, 0.10 mmol, 1.00 eq.) was added in one portion, followed by the indicated additive (0.10 mmol, 1.00 eq.). The tube was capped, removed from the glovebox, placed in an oil bath that had been pre-heated to 130 °C, and allowed to stir vigorously for 14 h. At this time, the reaction mixture was cooled to room temperature and 1-fluoronaphthalene was added. The reaction mixture was analyzed directly by $^{19}$F NMR (300 MHz) for conversion and yield.


Following the general procedure, CsF (228 mg, 1.50 mmol, 3.00 eq.), estrone triflate (201 mg, 0.500 mmol, 1.00 eq.), 6 (8.0 mg, 0.005 mmol, 0.010 eq., 2% "Pd"), and cyclohexane (5 mL) were combined and heated at 120 °C. The crude product mixture was purified by flash chromatography (1:10 EtOAc:hexanes → 1:5 EtOAc:hexanes) to yield fluoro-deoxyestrone (97.4 mg, 70%) as a white solid. Melting Point: 179–180 °C (Lit. 178–180 °C). $^{1}$H NMR (500 MHz, CDCl$_3$): δ 7.22 (dd, J = 9, 6 Hz, 1H), 6.83 (ptd, J = 9, 3 Hz, 1H), 6.78 (dd, J = 10 Hz, 3 Hz), 2.87-2.92 (m, 2H), 2.50 (dd, J = 20, 9 Hz, 1H), 2.34-241 (m, 1H), 2.22-2.27 (m, 1H), 1.94-2.18 (m, 4H), 1.40-1.67 (m, 6H), 0.91 (s, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ 220.7, 161.1 (d, J = 243 Hz), 138.8 (d, J = 7 Hz), 135.4 (d, J = 3 Hz), 126.9 (d, J = 8 Hz), 115.2 (d, J = 20 Hz), 359
112.6 (d, J = 21 Hz), 50.4, 48.0, 44.1, 38.2, 35.9, 31.6, 29.6, 26.4, 26.0, 21.7, 13.9 ppm; 

$^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ –118.4 ppm. Contaminated with ~4% of a compound with $^{19}$F NMR shift of $\delta$ –117.6 ppm, which is likely a regioisomer of the desired compound. IR (neat): 3043, 2927, 2866, 1739, 1610, 1585, 1494, 1451, 1427, 1419, 1404, 1377, 1230, 1211, 1148, 1052, 1008, 916, 907, 889, 816, 784 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{40}$

Following the general procedure, CsF (228 mg, 1.50 mmol, 3.00 eq.), N-methylnonivamide triflate (220 mg, 0.50 mmol, 1.00 eq.), 6 (12.0 mg, 0.0075 mmol, 0.015 eq., 3% "Pd"), and toluene (5 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (1:3 EtOAc:hexanes $\rightarrow$ 1:2 EtOAc:hexanes) to yield fluoro-deoxy-N-methylnonivamide (132 mg, 85%) as a yellow oil. 12 exists as a 2:1 mixture of rotamers in solution. $^1$H NMR (500 MHz, CDCl$_3$): major rotamer: $\delta$ 6.95 (dd, J = 12, 7 Hz, 1H), 6.85 (dd, J = 8, 2 Hz, 1H), 6.68-6.72 (m, 1H), 4.49 (s, 2H), 3.82 (s, 3H), 2.88 (s, 3H), 2.30-2.35 (m, 2H), 1.61-1.67 (m, 2H), 1.20-1.32 (m, 10H), 0.81-0.85 (m, 3H) ppm; minor rotamer: $\delta$ 7.01 (dd, J = 11, 8 Hz), 6.68-6.72 (m, 1H), 6.62-6.66 (m, 1H), 4.45 (s, 2H), 3.83 (s, 3H), 2.89 (s, 3H), 2.30-2.35 (m, 2H), 1.61-1.67 (m, 2H), 1.20-1.32 (m, 10H), 0.81-0.85 (m, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.6, 173.3, 152.7, 150.8, 148.1, 148.0, 147.8, 147.7, 134.1, 134.1, 133.2, 133.1, 120.4, 120.3, 118.5, 118.4, 116.4, 116.2, 115.8, 115.6, 113.2, 113.2, 111.2, 111.2, 56.2, 56.2, 53.0, 50.4, 34.8, 33.8, 33.6, 33.1, 31.9, 31.8, 29.7, 29.5, 29.5, 29.4, 29.2, 29.2, 25.5, 25.2, 22.7, 14.1, 14.1 ppm (observed complexity is due to C-F coupling and the presence of two rotamers
in solution; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ -137.7 ppm (major rotamer), $\delta$ -137.1 ppm (minor rotamer). Coalescence of the two sets of $^1$H NMR (500 MHz, DMSO-$d_6$) signals was observed between 70 °C and 80 °C (see attached). The assignment of the multiplet signal at $\delta$ 6.68-6.72 as containing signals for both the major and minor rotamers was confirmed by a $^1$H-$^1$H COSY NMR experiment (see attached), which showed coupling between this signal and the signals for the N-CH$_2$-Ar protons present in both rotamers. IR (neat): 2954, 2923, 2854, 1643, 1516, 1464, 1417, 1280, 1216, 1150, 1119, 1032, 922, 808, 785, 730 cm$^{-1}$.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 4- (diethylcarbamoyl)-2-methoxyphenyl triflate (355 mg, 1.00 mmol, 1.00 eq.), 6 (16.0 mg, 0.010 mmol, 0.010 eq., 2% "Pd"), and toluene (10 mL) were combined and heated at 100 °C. The crude product mixture was purified by flash chromatography (1:2 EtOAc:hexanes $\rightarrow$ 1:1 EtOAc:hexanes) to yield N,N-diethyl-4-fluoro-3-methoxybenzamide (205 mg, 91%) as an amber oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.00 (dd, $J$ = 11, 8 Hz, 1H), 6.95 (dd, $J$ = 8, 2 Hz, 1H), 6.81-6.85 (m, 1H), 3.83 (s, 3H), 3.44 (bs, 2H), 3.2 (bs, 2H), 1.16 (bs, 3H), 1.07 (bs, 3H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 170.4, 152.8 (d, $J$ = 247 Hz), 147.7 (d, $J$ = 11 Hz), 133.7 (d, $J$ = 4 Hz), 118.9 (d, $J$ = 7 Hz), 115.9 (d, $J$ = 19 Hz), 112.2 (d, $J$ = 2 Hz), 56.3, 43.4 (bs), 39.5 (bs), 14.4 (bs), 13.1 (bs) ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ -134.1 ppm. IR (neat): 2973, 2937, 1627, 1605, 1518, 1461, 1426, 1316, 1290, 1263, 1213, 1165, 1119, 1092, 1030, 920, 819, 787, 727, 609 cm$^{-1}$.
Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 4-chloro-3,5-dimethylphenyltrifluoromethanesulfonate (289 mg, 1.00 mmol, 1.00 eq.), 5 (16.0 mg, 0.0100 mmol, 0.0100 eq., 2% "Pd"), and toluene (10 mL) were combined and heated at 110 °C for 14 h. The crude product mixture was purified by flash chromatography (pentane) to yield 1-chloro-4-fluoro-2,6-dimethylbenzene (133 mg, 84%) as colorless oil. Contaminated with <5% toluene. 

\[ \text{1H NMR (500 MHz, CDCl}_3\text{): } \delta 6.81 \text{ (d, } J = 9 \text{ Hz, } 2\text{H}), 2.37 \text{ (s, } 6\text{H)} \text{ ppm; } \]
\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 160.7 \text{ (d, } J = 243 \text{ Hz), 138.2 (d, } J = 8 \text{ Hz), 129.6 (d, } J = 3 \text{ Hz), 115.3 (d, } J = 22 \text{ Hz), 21.1 (d, } J = 1 \text{ Hz)} \text{ ppm; } \]
\[ \text{19F NMR (282 MHz, CDCl}_3\text{): } \delta -118.0 \text{ (t, } J = 9 \text{ Hz)} \text{ ppm. IR (neat): 2957, 1607, 1579, 1467, 1437, 1412, 1312, 1137, 1063, 1022, 856, 730, 697, 627 \text{ cm}^{-1}. \text{ Note: This compound should not be placed under high vacuum due to its volatility.} \]

Following the general procedure, CsF (456 mg, 3.00 mmol, 6.00 eq.), 4,4'-sulfonylbis(phenyltrifluoromethanesulfonate) (257 mg, 0.500 mmol, 1.00 eq.), 6 (24.0 mg, 0.015 mmol, 0.030 eq., 6% "Pd"), and toluene (5 mL) were combined and heated at 130 °C for 14 h. The crude product mixture was purified by flash chromatography (1:10 EtOAc:hexanes → 1:5 EtOAc:hexanes) to yield 4,4'-sulfonylbis(fluorobenzene) (104 mg, 82%) as white crystalline solid. Melting Point: 98 °C (Lit. 97-98 °C). 

\[ \text{1H NMR (500 MHz, CDCl}_3\text{): } \delta 7.92-7.96 \text{ (m, } 4\text{H), 7.15-7.20 (m, } 4\text{H)} \text{ ppm; } \]
\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 165.6 \text{ (d, } J = 255 \text{ Hz), 137.6 (d, } J = 3 \text{ Hz), 130.5 (d, } J = 10 \text{ Hz), 116.8 (d, } J = 23 \text{ Hz)} \text{ ppm; } \]
\[ \text{19F NMR (470 MHz, } \text{ppm; } \]

362
Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 4-methylumbelliferone trflate (308 mg, 1.00 mmol, 1.00 eq.), and toluene (10 mL) were combined and heated at 110 °C. The crude product mixture was purified by flash chromatography (1:5 EtOAc:hexanes → 1:3 EtOAc:hexanes) to yield 7-fluoro-4-methyl-coumarin (164 mg, 92%) as a pale yellow solid. Melting Point: 130 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.56–7.59 (m, 1H), 6.99–7.04 (m, 2H), 6.22 (s, 1H), 2.42 (d, $J = 1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 164.5 (d, $J = 252$ Hz), 160.5, 154.8 (d, $J = 13$ Hz), 152.1 (d, $J = 1$ Hz), 126.4 (d, $J = 10$ Hz), 116.8 (d, $J = 3$ Hz), 114.0 (d, $J = 3$ Hz), 112.3 (d, $J = 23$ Hz), 104.6 (d, $J = 25$ Hz), 18.9 ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): δ −106.2 ppm. IR (neat): 3083, 3060, 2919, 1713, 1609, 1575, 1501, 1418, 1383, 1370, 1272, 1143, 1122, 1067, 1015, 978, 873, 809, 797, 747, 705, 623 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{35}$

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 4-methylumbelliferone nonaflate (458 mg, 1.00 mmol, 1.00 eq.), 6 (16.6 mg, 0.010 mmol, 0.010 eq.), and toluene (10 mL) were combined and heated at 110 °C. The crude product mixture was purified by flash chromatography (1:5 EtOAc:hexanes → 1:3 EtOAc:hexanes) to yield 7-fluoro-4-methyl-coumarin (158 mg, 89%) as a pale yellow...
solid. The spectra obtained for this compound are identical with those reported in the previous entry.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), (E)-methyl 3-(4-(triflate)phenyl)acrylate (310 mg, 1.00 mmol, 1.00 eq.), 5 (16.0 mg, 0.010 mmol, 0.010 eq., 2% "Pd"), and toluene (10 mL) were combined and heated at 80 °C. The crude product mixture was purified by flash chromatography (hexanes → 1:10 EtOAc:hexanes) to yield (E)-methyl 3-(4-fluorophenyl)acrylate (166 mg, 92%) as a pale yellow solid. Melting Point: 45 °C (Lit. 45–47 °C).\(^{16}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.60 (d, \(J = 16\) Hz, 1H), 7.43-7.48 (m, 2H), 7.00-7.05 (m, 2H), 6.31 (d, \(J = 16\) Hz, 1H), 3.75 (s, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 167.2, 163.9 (d, \(J = 250\) Hz), 143.5 (d, \(J = 1\) Hz), 130.6, 130.0 (d, \(J = 8\) Hz), 117.5, 116.1 (d, \(J = 23\) Hz), 51.7 ppm; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta\) -109.9 ppm. IR (neat): 3036, 2956, 1705, 1632, 1599, 1509, 1435, 1317, 1282, 1223, 1202, 1171, 1160, 1005, 939, 832, 782 cm\(^{-1}\). These spectra are with those reported in the literature.\(^{16}\) This compound should not be placed under high vacuum due to its predilection towards sublimation.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 4-(N-methylacetamido)phenyl triflate (297 mg, 1.00 mmol, 1.00 eq.), 6 (32.0 mg, 0.020 mmol, 0.020 eq., 4% Pd"), and cyclohexane (10 mL) were combined and heated at 120 °C. The crude product mixture was purified by flash chromatography (1:1 EtOAc:hexanes) to yield N-(4-fluorophenyl)-N-
methylacetamide (119 mg, 71%) as a yellow solid. Melting Point: 64–66 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta \) 7.10-7.15 (m, 2H), 7.02-7.07 (m, 2H), 3.18 (s, 3H), 1.80 (s, 3H) ppm; \(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta \) 170.5, 161.7 (d, \(J = 236\) Hz), 140.7, 128.9 (d, \(J = 9\) Hz), 116.7 (d, \(J = 23\) Hz), 37.2, 22.4 ppm; \(^19\)F NMR (282 MHz, CDCl\(_3\)): \(\delta \) –113.9 ppm. IR (neat): 3072, 3047, 3012, 2933, 1659, 1502, 1417, 1385, 1305, 1218, 1160, 1142, 1086, 974, 844, 815, 731, 587, 557 cm\(^{-1}\). Anal. Calcd. for C\(_9\)H\(_{10}\)ONF: C, 64.66, H, 6.03; found, 64.97, H, 6.19.

Following the general procedure, CsF (228 mg, 1.50 mmol, 3.00 eq.), desvenlaflaxine triflate (198 mg, 0.50 mmol, 1.00 eq.), 6 (24.0 mg, 0.015 mmol, 0.030 eq., 6% "Pd"), and toluene (5 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (1st column (silica gel): EtOAc → MeOH:CH\(_2\)Cl\(_2\) 1:20 → 1:10 → 1:7; 2nd column (alumina): EtOAc:hexanes 1:10 → 1:5 → 1:3) to yield 18 (178 mg, 67%) as a white solid. 18 was obtained as a 3:1 mixture of regioisomers by \(^19\)F NMR. Melting Point: 91-95 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): major regioisomer: \(\delta \) 7.07 (dd, \(J = 7, 2\) Hz, 2H), 6.94 (pt, \(J = 9\) Hz, 2H), 3.25 (pt, \(J = 13\) Hz, 1H), 2.94-3.00 (m, 1H), 2.28-2.32 (m, 7H), 0.79-1.88 (m, 10H) ppm; minor regioisomer: \(\delta \) 7.18-7.27 (m, 2H), 7.11 (d, \(J = 7\) Hz, 1H), 6.80-6.92 (m, 1H), 3.28-3.35 (m, 1H), 2.28-2.32 (m, 7H), 0.79-1.88 (m, 10H) ppm; \(^1\)C NMR (125 MHz, CDCl\(_3\)): complex spectrum due to C-F coupling and presence of two regioisomers, see attached; \(^19\)F NMR (282 MHz, CDCl\(_3\)): major regioisomer: \(\delta \) –116.5 ppm; minor regioisomer: \(\delta \) –113.7 ppm. IR (neat): 3135
(broad), 2981, 2929, 2859, 2828, 2782, 1606, 1587, 1511, 1464, 1445, 1323, 1370, 1249, 1037, 1011, 969, 903, 876, 849 cm\(^{-1}\). The assignation of the desired product to the major regioisomer was made based on the resemblance of the \(^1\)H and \(^{13}\)C NMR spectra of the major product to a para-substituted aromatic system, and that of the minor regioisomer to a meta-substituted aromatic system. In addition, the \(^{19}\)F NMR shift for the major regioisomer is upfield from that of the minor regioisomer, which is consistent with the electron-donating group being para to the fluorine atom in the major regioisomer and meta in the minor regioisomer.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), \(\delta\)-tocopherol triflate (535 mg, 1.00 mmol, 1.00 eq.), 6 (24.0 mg, 0.015 mmol, 0.015 eq., 3% "Pd"), and cyclohexane (10 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (hexanes) to yield fluoro-deoxy-\(\delta\)-tocopherol (352 mg, 88%) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.70 (dd, \(J = 9, 3\) Hz, 1H), 6.61 (dd, \(J = 9, 2\) Hz, 1H), 2.68-2.79 (m, 2H), 2.17 (s, 3H), 1.74-1.84 (m, 2H), 1.04-1.64 (m, 27H), 0.86-0.92 (m, 11H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 155.9 (d, \(J = 235\) Hz), 148.0 (d, \(J = 2\) Hz), 127.9 (d, \(J = 8\) Hz), 121.5 (d, \(J = 8\) Hz), 115.1 (d, \(J = 22\) Hz), 112.4 (d, \(J = 22\) Hz), 76.1, 40.1, 39.6, 37.6, 37.6, 37.6, 37.5, 33.0, 32.8, 31.3, 28.2, 25.0, 24.6, 24.3, 22.9, 22.8, 22.7, 21.1, 19.9, 19.8 ppm; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)): \(\delta\) –126.7 ppm. Contaminated with ~5% of a compound with \(^{19}\)F NMR shift of \(\delta\) –129.1 ppm, which is likely a regioisomer of the desired compound. IR (neat): 2925, 2867, 1743, 1377, 1219, 1126,
1046, 990, 931, 915, 856, 735, 711 cm⁻¹. These spectra are consistent with those reported in the literature.⁴⁰

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 3-quinolinyl triflate (277 mg, 1.00 mmol, 1.00 eq.), 6 (32.0 mg, 0.020 mmol, 0.020 eq., 4% "Pd"), and toluene (10 mL) were combined and heated at 120 °C. The crude product mixture was purified by flash chromatography (hexanes → 1:10 EtOAc:hexanes) to yield 3-fluoroquinoline (103 mg, 70%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.77 (d, J = 3 Hz, 1H), 8.08 (d, J = 9 Hz, 1H), 7.66-7.72 (m, 2H), 7.62 (pt, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 156.2 (d, J = 255 Hz), 145.4 (d, J = 2 Hz), 141.5 (d, J = 28 Hz), 129.7, 128.7, 127.8 (d, J = 6 Hz), 127.4 (d, J = 5 Hz), 118.5 (d, J = 16 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -128.5 ppm. IR (neat): 3059, 1611, 1497, 1464, 1426, 1336, 1270, 1210, 1154, 1138, 983, 889, 857, 779, 749, 709, 610 cm⁻¹. These spectra are consistent with those reported in the literature.⁴⁰ This compound should not be placed under high vacuum due to its volatility.

Following the general procedure, CsF (228 mg, 1.50 mmol, 3.00 eq.), 8-(trifluoromethyl)quinolin-4-yl triflate (173 mg, 0.50 mmol, 1.00 eq.), 6 (8.0 mg, 0.005 mmol, 0.010 eq., 2% "Pd"), and toluene (5 mL) were combined and heated at 90 °C. The crude product mixture was purified by flash chromatography (hexanes → 1:10 EtOAc:hexanes) to yield 4-fluoro-8-trifluoromethylquinoline (94 mg, 87%) as a white solid. Melting Point: 97 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.98 (dd, J = 9, 5 Hz, 1H), 8.23 (d, J = 9 Hz, 1H), 8.09 (d, J = 7 Hz,
1H), 7.60 (pt, J = 8 Hz, 1H), 7.17 (dd, J = 9, 5 Hz, 1H) ppm; 13C NMR (75 MHz, CDCl₃): Complex spectra due to C-F coupling; 19F NMR (282 MHz, CDCl₃): δ -60.8, -111.4 ppm. IR (neat): 3064, 1631, 1609, 1577, 1504, 1479, 1423, 1312, 1294, 1263, 1231, 1214, 1129, 1096, 1071, 883, 861, 821, 805, 768, 717 cm⁻¹. Anal. Calcd. for C₁₀H₅NF₄: C, 55.83, H, 2.34; found C, 56.09, H, 2.40. This compound should not be placed under high vacuum due to its predilection towards sublimation.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), methyl 5-triflatonicotinate (285 mg, 1.00 mmol, 1.00 eq.), 6 (32.0 mg, 0.020 mmol, 0.020 eq., 4% "Pd"), and toluene (10 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (1:5 EtOAc:hexanes → 1:3 EtOAc:hexanes) to yield methyl 5-fluoronicotinate (68 mg, 44%) as an off-white solid. Melting Point: 51 °C (Lit. 48 °C).³⁷ ¹H NMR (500 MHz, CDCl₃): δ 9.01 (s, 1H), 8.62 (d, J = 4 Hz, 1H), 7.94-7.98 (m, 1H), 3.94 (s, 3H) ppm; 13C NMR (75 MHz, CDCl₃): δ 164.7 (d, J = 2 Hz), 159.2 (d, J = 257 Hz), 146.7 (d, J = 4 Hz), 142.2 (d, J = 23 Hz), 127.4 (d, J = 3 Hz), 123.7 (d, J = 19 Hz), 52.8 ppm; 19F NMR (282 MHz, CDCl₃): δ -126.3 ppm. IR (neat): 3062, 2967, 1723, 1599, 1571, 1446, 1440, 1417, 1308, 1294, 1215, 1162, 1093, 1018, 973, 940, 901, 796, 767, 689, 688 cm⁻¹. These spectra are consistent with those reported in the literature.⁵² This compound should not be placed under high vacuum due to its predilection for sublimation.
Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 2-ethyl-6-methyl-3-triflatopyridine (269 mg, 1.00 mmol, 1.00 eq.), 6 (32.0 mg, 0.020 mmol, 0.020 eq., 4% "Pd"), and toluene (10 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (pentane → 1:10 Et₂O/pentane → 1:5 Et₂O/pentane) to yield methyl 2-ethyl-3-fluoro-6-methylpyridine (89 mg, 64%) as a sweet-smelling colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.15 (pt, J = 9 Hz, 1H), 6.91 (dd, J = 9, 3 Hz, 1H), 2.80 (qd, J = 8, 2 Hz, 1H), 2.47 (s, 3H), 1.23 (t, J = 8 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 156.0 (d, J = 250 Hz), 153.3 (d, J = 5 Hz), 150.6 (d, J = 16 Hz), 122.7 (d, J = 20 Hz), 121.7 (d, J = 3 Hz), 25.3 (d, J = 2 Hz), 23.8 (d, J = 2 Hz), 13.2 (d, J = 2 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ -132.6 ppm. IR (neat): 2974, 2938, 2878, 1598, 1466, 1238, 1155, 1120, 1050, 909, 820, 733 cm⁻¹. This compound should not be placed under high vacuum due to its volatility.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 3-(1H-pyrrol-1-yl)phenyl triflate (291 mg, 1.00 mmol, 1.00 eq.), 6 (24.0 mg, 0.015 mmol, 0.015 eq., 3% "Pd"), and toluene (10 mL) were combined and heated at 120°C. The crude product mixture was purified by flash chromatography (1:40 EtOAc:hexanes → 1:20 EtOAc:hexanes → 1:10 EtOAc:hexanes) to yield 1-(3-fluorophenyl)-1H-pyrrole (115 mg, 71%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.40 (dd, J = 16, 9 Hz, 1H), 7.22 (dd, J = 9, 2 Hz, 1H), 7.11-7.17 (m, 3H), 6.95-7.00 (m, 1H), 6.41-6.42 (m, 2H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 163.4 (d, J = 245 Hz), 142.2 (d, J = 10 Hz), 130.9 (d, J = 10 Hz), 119.3, 115.3, 112.4 (d, J = 21 Hz), 111.1,
107.8 (d, J = 25 Hz) ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ – 111.5 ppm. IR (neat): 3106, 3075, 1612, 1598, 1503, 1479, 1455, 1342, 1316, 1251, 1172, 1160, 1107, 1066, 1025, 954, 844, 775, 719, 680 cm$^{-1}$. Anal. Calcd. for C$_{10}$H$_8$NF$_6$: C, 74.52, H, 5.00; found C, 73.48, H, 5.09. The sensitivity of this pyrrole-containing compound is likely responsible for the discrepancy in elemental analysis.

Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 6-(furan-3-yl)-2-naphthyl triflate (342 mg, 1.00 mmol, 1.00 eq.), 6 (16.0 mg, 0.0100 mmol, 0.0100 eq., 2% "Pd"), and toluene (10 mL) were combined and heated at 100 °C. The crude product mixture was purified by flash chromatography (hexanes) to yield 6-(furan-3-yl)-2-fluoronaphthalene (193 mg, 91%) as an off-white solid. Melting Point: 99-101 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.91 (s, 1H), 7.75-7.87 (m, 3H), 7.65 (d, J = 9 Hz, 1H), 7.56-7.58 (m, 1H), 7.47 (dd, J = 10, 3 Hz, 1H), 7.30 (td, J = 9, 3 Hz, 1H), 6.84 (dd, J = 2, 2 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.6 (d, J = 244 Hz), 144.0, 138.9, 133.2 (d, J = 9 Hz), 130.8, 130.2 (d, J = 9 Hz), 129.2 (d, J = 3 Hz), 127.9 (d, J = 5 Hz), 126.3, 125.6, 124.0 (d, J = 1 Hz) 116.7 (d, J = 25 Hz), 110.9 (d, J = 20 Hz), 108.9, 99.8 ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ – 115.3 ppm. Contaminated with ~2% of a compound with $^{19}$F NMR shift of $\delta$ – 114.7 ppm, which is likely a regioisomer of the desired compound. IR (neat): 3133, 1610, 1559, 1514, 1501, 1474, 1365, 1249, 1237, 1198, 1164, 1142, 1092, 1052, 971, 891, 881, 814, 782, 740, 632 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_6$OF: C, 79.23, H, 4.27; found C, 78.98, H, 4.17.
Following the general procedure, CsF (456 mg, 3.00 mmol, 3.00 eq.), 6-(thiophen-3-yl)-2-naphthyl triflate (358 mg, 1.00 mmol, 1.00 eq.), 6 (16.0 mg, 0.010 mmol, 0.010 eq., 2% "Pd"), and toluene (10 mL) were combined and heated at 130 °C. The crude product mixture was purified by flash chromatography (hexanes) to yield 6-(thiophen-3-yl)-2-fluoronaphthalene (203 mg, 89%) as a white solid. Melting Point: 147 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.03 (s, 1H), 7.76-7.86 (m, 3H), 7.55-7.57 (m, 1H), 7.52 (dd, $J = 5$, 1 Hz, 1H), 7.43-7.49 (m, 2H), 7.30 (td, $J = 9$, 3 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 160.7 (d, $J = 245$ Hz), 142.0, 133.3 (d, $J = 9$ Hz), 132.7 (d, $J = 3$ Hz), 130.8 (d, $J = 1$ Hz), 130.5 (d, $J = 9$ Hz), 127.9 (d, $J = 5$ Hz), 126.6, 126.5, 126.2 (d, $J = 1$ Hz), 124.8 (d, $J = 1$ Hz), 120.7, 116.8 (d, $J = 25$ Hz), 110.9 (d, $J = 20$ Hz) ppm; $^{19}$F NMR (282 MHz, CDCl$_3$): δ -115.0 ppm. Contaminated with ~3% of a compound with $^{19}$F NMR shift of δ -114.6 ppm, which is likely a regioisomer of the desired compound. IR (neat): 3095, 1602, 1575, 1507, 1500, 1407, 1364, 1234, 1205, 1189, 1140, 1116, 1092, 967, 871, 810, 777, 727, 623 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_9$FS: C, 73.66, H, 3.97; found C, 73.97, H, 4.21.

3.8. References.

3 Zelesskiy, S. S.; Ananikov, V. P. Organometallics, 12, 31, 2302.
It should be noted that, to date, we have been unable to prepare N-substituted precatalysts of Li (as well as L2). See: Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. J. Org. Chem. 2014, 79, 4161.


McAtee, J. R.; Martin, S. E. S.; Ahneman, D. T.; Johnson, K. A.; Watson, D. A. Angew. Chem. Int. Ed. 2012, 51, 3663. This compound was stored at −20 °C in a glovebox when not in use.


Unlike with dba, when 1,5-COD was added to the reactions in entry 1, Table 1, comparable yields of both fluorodeoxyestrone (67%, α:β = 5:1) and 3-fluoroquinoline (73%) to reactions conducted in the absence of 1,5-COD were observed. Thus, 1,5-COD does not show an inhibitory effect on these reactions.


Although to our knowledge the isomerization of alkenes in the presence of a Pd(0) species has never been reported, isomerization in the presence of Pd(II) species is well-known. In this case the isomerization could be mediated by a Pd(II) species present...
before reductive elimination of (TMSCH$_2$)$_2$. However, at this time it is unclear exactly what is the mechanism of 1,5-COD isomerization to 1,4- and 1,3-COD.

29 Koever, J.; Antus, S. Zeitschrift fuer Naturforschung, B: Chemical Sciences 2005, 60, 792.
$^{1}$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
1H NMR, 500 MHz, CDCl₃
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}\text{C NMR, 125 MHz, CD}_2\text{Cl}_2$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{H NMR, 500 MHz, CDCl}_3$

[Chemical structure image]

$^1\text{H NMR, 500 MHz, CDCl}_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
Me
NC
8 H 1 7
MeON
8l
0
19F NMR, 470 MHz, CDCl₃
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
19F NMR, 282 MHz, CDCl₃
$\text{F} \quad \text{Me}$

$\text{MeO} \quad \text{N} \quad \text{C}_2\text{H}_7$

$^1\text{H} \text{NMR, 500 MHz, } \text{CDCl}_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{19}$F NMR, 470 MHz, CDCl₃
$^{13}$C NMR, 75 MHz, CDCl$_3$
\[ \text{OH OH} \quad \text{NMe}_2 \quad \text{NMe}_2 \]

\[ + \quad \text{F} \quad \text{F} \]

\[ ^1\text{H NMR, 500 MHz, CDCl}_3 \]

\[ \text{fl (ppm)} \]

\[ 10.0 \quad 9.5 \quad 9.0 \quad 8.5 \quad 8.0 \quad 7.5 \quad 7.0 \quad 6.5 \quad 6.0 \quad 5.5 \quad 5.0 \]

\[ \text{Al} / \text{Im} \quad 4.5 \quad 4.0 \quad 3.5 \quad 3.0 \quad 2.5 \quad 2.0 \quad 1.5 \quad 1.0 \quad 0.5 \quad 0.0 \]

\[ \text{\textit{OH} NMR, 500 MHz, CDCl}_3 \]
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^19$F NMR, 282 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}\text{C NMR, 75 MHz, CDCl}_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{19}$F NMR, 470 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$

![NMR Spectrum Image]
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{19}$F NMR, 470 MHz, CDCl$_3$
Chapter 4. Pd-Catalyzed Fluorination of (Hetero)Aryl Bromides and Iodides.
4.1. Introduction. Among the various strategies for the preparation of (hetero)aryl fluorides (Ar–F), the Pd-catalyzed nucleophilic fluorination of the heavier aryl halides (Ar–X, X = Cl, Br, I) with a metal fluoride salt (MF) would be ideal due to the improved availability, synthetic tractability, and stability of aryl halides compared to aryl triflates (Scheme 4.1, left).¹ In our original report, only highly activated (i.e., ortho-substituted and electron-deficient) aryl bromides could be successfully fluorinated due to the challenging nature of this transformation (see Introduction).² Similarly, prior to the work described in this chapter, only the Cu-mediated fluorination of aryl iodides³ and the Cu-catalyzed fluorination of highly activated 2-pyridyl aryl bromides⁴ had been described. However, the former reaction is hampered by formation of the corresponding reduction (Ar–H) products, which are usually difficult to separate from the desired aryl fluorides, and a limited substrate scope, whereas the latter method is very limited in scope and provides only modest yields of the desired aryl fluoride products. Given our improved understanding of the fluorination of aryl triflates (Chapters 1 and 2), as well as the discovery that AdBrettPhos (L₁, Scheme 4.1, right) and L₁-based Pd(0) precatalyst 1 (Figure 4.1, right) provide significantly more active catalysts for the fluorination of aryl triflates, we re-investigated the Pd-catalyzed nucleophilic fluorination of (hetero)aryl bromides not activated towards direct nucleophilic substitutions or transition metal-mediated reactions.
Scheme 4.1. General catalytic cycle of Pd-catalyzed fluorination (left), and potential ligand (L1) and precatalyst (1) for this transformation.

4.2. Fluoride source and additive effects. To expand our previously reported method (X = OTf, M = Cs, Scheme 4.1) to the fluorination of aryl halides (X = I, Br, Cl, Scheme 4.1), we investigated the catalytic fluorination of 3-bromo-\(N,N\)-dimethylaniline (2-Br) with 1 as the source of active catalyst (Table 4.1). However, with 2 eq. of CsF, no product 2 was observed; only starting material was recovered (entry 1, Table 4.1). Thus, at least one of the steps in the catalytic cycle shown in Scheme 4.1 must not be operative in this reaction. The change from aryl triflate to bromide should not affect the C–F reductive elimination step of the catalytic cycle, but would affect the rates of oxidative addition and transmetallation. Given our previous observation of rapid oxidative addition of aryl bromides with 1 at room temperature (Chapter 3), and the known reactivity of L1-based catalysts with aryl bromides,\(^5\) we did not expect that oxidative addition would be a challenging step in the catalytic cycle. Based on this analysis, and the fact that the Pd center of a L•Pd(Ar)Br species should be less reactive than that of a cationic L•Pd(Ar)OTf species, we hypothesized that transmetallation might be the limiting process in this reaction. Therefore, the judicious choice of fluoride source should facilitate transmetallation, and, by extension, the Pd-catalyzed fluorination of aryl bromides.\(^6\)
The most promising fluoride source in our mind was AgF, which had been previously employed in the Cu-mediated fluorinations of aryl halides\(^3\)\(^4\) and our catalytic fluorination of activated aryl bromides.\(^2\) In addition, we\(^7\) and others\(^8\) have used AgF to stoichiometrically convert Pd–X (X = Br, I) species to the corresponding Pd–F species, typically at room temperature. This reaction is likely driven forward by the irreversible precipitation of insoluble AgBr (or AgI) from solution. However, the fluorination of 2-Br with AgF and a catalytic amount of 1 did not produce 2; as with CsF, only starting material was recovered. Because AgF should be able to effect the transmetallation step, we expected that something more complicated was going on in this reaction.

In Chapter 1, we showed that base induces an \textit{in situ} ligand modification during the catalytic fluorination of aryl triflates (Scheme 4.2, A to B to C, X = OTf), and that the catalyst is effective only when it is supported by the 3'-arylated ligand 3.\(^{10}\) Our next hypothesis was that AgF might not be basic enough to induce the elimination of HX (Scheme 4.2, B to C), rendering the ligand modification inefficient and thus stymying the desired reaction. Therefore, we surmised that the introduction of a substoichiometric amount of base could promote the formation of C (3•Pd(0)) and allow for the desired reaction to take place. To test the hypothesis, the fluorination of 2-Br was attempted using AgF (2.0 eq.) in conjunction with a substoichiometric amount of "base". Because CsF is definitely capable of effecting ligand modification, we began our investigation by adding CsF to the reaction (entry 3, Table 4.1). In accord with our hypothesis, the desired product 2 was formed in good yield. Alternatively, less hygroscopic KF was also found to be effective for promoting the reaction in similar yield (entry 4, Table 4.1),\(^{9,10}\) although insoluble NaF was not (entry 5, Table 4.1).\(^{11}\) It should be noted that KF on its
own was not a competent fluoride source for this reaction (entry 6, Table 4.1), indicating that the fluoride that ends up in 2 likely originates from AgF (*vide infra*).

While investigating this base effect further, we found that using AgF in combination with other moderately strong inorganic bases, such as K$_2$CO$_3$, K$_3$PO$_4$, or KOrBu, afforded little to no 2 under these conditions (entries 7-9, Table 4.1). Similarly, organic bases such as DBU, Bu$_3$N, and 2,6-lutidine, were ineffective at promoting this reaction (entries 10-12, Table 4.1). Curiously, DABCO, which is lower in pK$_a$ than Bu$_3$N but considerably more nucleophilic, was more capable in promoting this reaction (entry 13, Table 4.1). This finding led us to suspect that the nucleophilicity of the "base" additive was more important than its basicity for promoting the desired transformation. To look into this possibility further, we attempted the fluorination of 2 promoted by KX (X = Cl, Br, I, entries 14-16, Table 4.1) and CsX (X = Cl, Br, I, entries 17-19, Table 4.1) salts. Other than the fluoride salts discussed above, only the iodide salts were effective at promoting this transformation, both of them more efficiently than more basic additives (entries 7-13, Table 4.1). Considering that I$^-$ is an extremely poor base (pKa $\sim 10$ in H$_2$O), but is highly polarizable and nucleophilic, it is likely that our original reasoning for adding CsF to promote the conversion of 2-Br to 2, as outlined above, was incorrect. Instead, the addition of nucleophilic additives such as fluoride, iodide, or DABCO, likely promotes the transmetallation step, either by interacting with AgF or the L$^*$Pd(Ar)Br intermediate. This interesting promoting effect has been previously observed, and remains a matter of investigation. Nonetheless, inexpensive and moisture stable KF was chosen as the promoter of this reaction for reasons of practicality and cost.
Table 4.1. Additive effects in the Pd-catalyzed fluorination of aryl bromides.\(^a\)

\[
\begin{array}{ccc}
\text{Entry} & \text{MF} & \text{"Base"} & \text{Yield Ar-F} & \text{Entry} & \text{MF} & \text{"Base"} & \text{Yield Ar-F} \\
1 & \text{CsF} & \text{None} & 0\% & 11 & \text{AgF} & \text{Bu}_3\text{N} & \text{Trace} \\
2 & \text{AgF} & \text{None} & 0\% & 12 & \text{AgF} & 2,6-\text{lutidine} & \text{Trace} \\
3 & \text{AgF} & \text{CsF} & 65\% & 13 & \text{AgF} & \text{DABCO} & 24\% \\
4 & \text{AgF} & \text{KF} & 71\% & 14 & \text{AgF} & \text{CsBr} & 0\% \\
5 & \text{AgF} & \text{NaF} & 0\% & 15 & \text{AgF} & \text{CsCl} & 0\% \\
6 & \text{KF} & \text{None} & 0\% & 16 & \text{AgF} & \text{CsI} & 48\% \\
7 & \text{AgF} & \text{K}_2\text{CO}_3 & 11\% & 17 & \text{AgF} & \text{KCl} & 0\% \\
8 & \text{AgF} & \text{K}_3\text{PO}_4 & 21\% & 18 & \text{AgF} & \text{KCl} & 0\% \\
9 & \text{AgF} & \text{KO}_{\text{tBu}} & 0\% & 19 & \text{AgF} & \text{KI} & 80\% \\
10 & \text{AgF} & \text{DBU} & 0\% & \\
\end{array}
\]

\(^a\)Reaction conditions: 0.10 mmol 2-Br, 0.20 mmol AgF, 0.05 mmol "base", 2\% 1, cy (0.1 M), 130 °C, 12 h. \(^{19}\)F NMR yields.

Scheme 4.2. Ligand modification during the catalytic fluorination.

4.3. Fluorination of aryl bromides. The optimized reaction conditions were applied to the fluorination of a variety of aryl bromides and iodides (Table 4.2). Substrates with ortho- (4-5), meta- (6-13), and para-substituents (14-19) were fluorinated with comparable efficiencies regardless of the electronic nature of the substituents. Importantly, base-sensitive functional groups such as methyl sulfone (6), fluorene (10), and ketones (14 and 15) are tolerated, as are nitrile (7), ester (8), and amide (16) groups, which are common in pharmaceutical compounds. In addition, substrates that are not
amenable to electrophilic fluorination due to potential oxidation, such as a sulfide (9) or electron-rich amines (12 and 13), were also fluorinated in good yields. Unactivated aryl iodides were also viable substrates for this reaction (10, 14, and 17). Although this reaction was a breakthrough, it has several limitations. Analogous to the fluorination of aryl triflates (see Chapter 2), electron-rich substrates such as 4-bromoanisole (19-Br) and 4-(nBu)PhBr (20-Br) provided regioisomeric mixtures of products under the reaction

Table 4.2. Pd-catalyzed fluorination of aryl halides using precatalyst 2.

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Yield (%)</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>94% (X = Br)</td>
<td>4% Pd, 90 °C</td>
</tr>
<tr>
<td>5</td>
<td>73% (X = Br)</td>
<td>4% Pd, 130 °C</td>
</tr>
<tr>
<td>6</td>
<td>75% (X = Br)</td>
<td>2% Pd, 110 °C</td>
</tr>
<tr>
<td>7</td>
<td>73% (X = Br)</td>
<td>3% Pd, 110 °C</td>
</tr>
<tr>
<td>8</td>
<td>93% (X = Br)</td>
<td>2% Pd, 110 °C</td>
</tr>
<tr>
<td>9</td>
<td>69% (X = Br)</td>
<td>4% Pd, 110 °C</td>
</tr>
<tr>
<td>10</td>
<td>76% (X = I)</td>
<td>α:β = 17:1</td>
</tr>
<tr>
<td>11</td>
<td>88% (X = Br)</td>
<td>m:p = 3:1</td>
</tr>
<tr>
<td>12</td>
<td>86% (X = Br)</td>
<td>2% Pd, 120 °C</td>
</tr>
<tr>
<td>13</td>
<td>86% (X = Br)</td>
<td>m:p = 0:1</td>
</tr>
<tr>
<td>14</td>
<td>87% (X = I)</td>
<td>2% Pd, 110 °C</td>
</tr>
<tr>
<td>15</td>
<td>87% (X = Br)</td>
<td>2% Pd, 110 °C</td>
</tr>
<tr>
<td>16</td>
<td>92% (X = Br)</td>
<td>3% Pd, 90 °C</td>
</tr>
<tr>
<td>17</td>
<td>92% (X = Br)</td>
<td>3% Pd, 90 °C</td>
</tr>
<tr>
<td>18</td>
<td>95% (X = Br)</td>
<td>2% Pd, 130 °C</td>
</tr>
<tr>
<td>19</td>
<td>70% (p:m = 1:3)</td>
<td>4% Pd, 130 °C</td>
</tr>
<tr>
<td>20</td>
<td>85% (p:m = 3:1)</td>
<td>4% Pd, 130 °C</td>
</tr>
<tr>
<td>21</td>
<td>73% (X = Br)</td>
<td>4% Pd, 130 °C</td>
</tr>
</tbody>
</table>

"Isolated yields, average of two runs. Reaction conditions: Aryl halide (1.00 mmol), AgF (2.00 mmol), KF (0.50 mmol), 1 (0.010-0.020 mmol), cyclohexane (10 mL), 14 h. Toluene was used as solvent. '0.50 mmol scale; yields determined by 19F NMR."
conditions. Preliminarily, we have found that the addition of tBuOD to the fluorination of 20-Br leads to deuterium incorporation into the aryl fluoride products (not shown), suggesting that the formation of regioisomers in these cases likely proceeds through a Pd-aryne intermediate as with aryl triflates (see Chapter 2). In addition, we have found that although this reaction can tolerate small ortho-substituents, such as methoxy (5) and ethyl (21) groups, larger ortho-substituents (i.e., phenyl) greatly retard the rate of fluorination (not shown). In addition, free N–H and O–H groups are, in general, not tolerated in this reaction due to their predilection for undergoing competitive cross-coupling processes. Lastly, aryl chlorides are also not viable substrates for this reaction (not shown).

Most importantly, in contrast to other reactions this process does not result in significant reduction of the aryl halide. Reduction products were not observed for a majority of the examples, as judged by GC analysis; in those cases for which reduction products were formed, the amount of Ar–H ranged from 0.10% to 1.6%, with an average of 0.5%. In only one case was the reduction product formed in greater than 1% yield (see Experimental for details).

4.4. Fluorination of heteroaryl bromides. We next tried to extend this methodology to the fluorination of heteroaryl bromides using 3-bromo-5-cyanopyridine (22-Br) as a representative substrate. Initially, we found that ethereal solvents such as 2MeTHF and methyl tbutyl ether (MTBE) provided superior results compared to cyclohexane and toluene, which is likely due to the improved solubility of nitrogen-containing heterocycles in more polar ethereal solvents. Even though the addition of KF significantly improved the reaction, the conditions failed to provide the fluorinated
heteroarene 22 in satisfactory yield (Table 4.3, entries 1-2). We postulated that with heteroaryl substrates, either the ligand modification process in Scheme 4.2 is not facile and/or the resulting modified ligand (3, Scheme 4.2) is not effective for the fluorination reaction. To remedy this situation, we decided to use a precatalyst with a new ligand, which is 3'-arylated ex situ (Scheme 4.3). By using a pre-modified ligand such as 3, we could circumvent the modification process altogether, allowing us to take full advantage of the established system.

Table 4.3. Precatalyst and KF effect in the Pd-catalyzed fluorination of heteroaryl bromide 23-Br.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>&quot;Base&quot;</th>
<th>Yield Ar-F</th>
<th>Entry</th>
<th>Precatalyst</th>
<th>&quot;Base&quot;</th>
<th>Yield Ar-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>None</td>
<td>11%</td>
<td>3</td>
<td>25</td>
<td>None</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>KF</td>
<td>48%</td>
<td>4</td>
<td>25</td>
<td>KF</td>
<td>72%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 22-Br (0.10 mmol), AgF (0.20 mmol), KF (0.050 mmol), 1 or 25 (2%), 2MeTHF (1 mL), 130 °C, 12 h. 19F NMR yields.*

A robust and scalable synthesis was developed to access to 3 bearing a 4-(nBu)Ph group (L2, Scheme 4.3), which we have designated HGPhos. The 4-nbutylphenyl moiety was installed by Suzuki-Miyaura cross coupling of commercially available 4-nbutylphenylboronic acid with 1-bromo-2,4,6-triisopropylbromobenzene in the presence of XPhos-based precatalyst 23. The resulting biaryl 24 was selectively monobrominated to furnish 25, which was converted to triaryl bromide 26 using a protocol analogous to that used to prepare a number of biaryl phosphine ligands. Lastly, lithium/halogen exchange of triaryl bromide 26 followed by reaction with Ad2PCI afforded HGPhos (L2). This process is amenable to preparation of L2 on multigram scale. Analogous to L1 (see
Chapter 3), L2 reacts with [(1,5-COD)Pd(CH2TMS)2] at room temperature to afford Pd(0) precatalyst 27.17

**Scheme 4.3.** Scalable synthesis of HGPhos (L2) and Pd(0) precatalyst 27.

The new precatalyst, 27 showed improved reactivity (entry 3, Table 4.3) compared to 1 (entry 1, Table 4.3). Notably, the use of 27 alone with AgF was not as effective as the combined use of 1 with KF and AgF (entry 2, Table 4.3). Only when a combination of AgF and KF was used with 27 as the Pd source was 22 obtained in high yield (entry 4, Table 4.3). This result is consistent with our hypothesis that s KF plays a role beyond assisting the modification of 1 (Section 4.2). Interestingly, we have found that 27 is not a completely general precatalyst for Pd-catalyzed fluorination reactions, as some of the substrates in Table 4.2 provide higher yields of the desired product using precatalyst 1 in place of 27. This result suggests that the 4-(nBu)Ph group is not the ideal substituent for the 3'-position of the ligand (see Section 4.5).
By employing 27, fluorinated heteroarenes that are not accessible through traditional 
SNAr reactions were successfully prepared (Table 4.4). Importantly, the use of 27 rather 
than 1 for the fluorination of heteroaryl bromides provides superior results in almost all 
instances (yields obtained using 1 under identical conditions are shown in parentheses for 
selected cases). In addition, reduction products were not observed in the purified samples

Table 4.4. Pd-catalyzed fluorination of heteroaryl bromides using precatalyst 27.a

| R         | 
|------------|--------|
| 22         | 
| 28         | 
| 29         | 
| 30         | 
| 31         | 
| 32         | 
| 33         | 
| 34         | 
| 35         | 
| 36         | 
| 37         | 
| 38         | 
| 39         |

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>76%</td>
<td>4% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>MeO</td>
<td>89% (18%b,c)</td>
<td>2% &quot;Pd&quot;, 90 °C</td>
</tr>
<tr>
<td>PMBO</td>
<td>71% (16%b,c)</td>
<td>6% &quot;Pd&quot;, 150 °C</td>
</tr>
<tr>
<td>30</td>
<td>86% (19%b,c)</td>
<td>4% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>31</td>
<td>75% (46%b,c)</td>
<td>4% &quot;Pd&quot;, 130 °C</td>
</tr>
<tr>
<td>32</td>
<td>84% (73%b,c)</td>
<td>3% &quot;Pd&quot;, 90 °C</td>
</tr>
<tr>
<td>33</td>
<td>96%</td>
<td>3% &quot;Pd&quot;, 90 °C</td>
</tr>
<tr>
<td>34</td>
<td>90% (75%b,c)</td>
<td>3% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>35</td>
<td>88%</td>
<td>2% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>36</td>
<td>51% (9%b,c)</td>
<td>6% &quot;Pd&quot;, 150 °C</td>
</tr>
<tr>
<td>37</td>
<td>90%</td>
<td>4% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>38</td>
<td>73% (68%b,c)</td>
<td>3% &quot;Pd&quot;, 110 °C</td>
</tr>
<tr>
<td>39</td>
<td>69%</td>
<td>4% &quot;Pd&quot;, 130 °C</td>
</tr>
</tbody>
</table>

n-Cyclohexane was used as solvent. MTBE was used as solvent. 0.50 mmol scale.

Isolated yields, average of two runs. Reaction conditions: heteroaryl halide (1.00 
mmol), AgF (2.0 mmol), KF (0.50 mmol), 27 (0.010-0.030 mmol), 2-MeTHF (10 mL), 
14 h. 0.10 mmol scale. Yield determined by 19F NMR. MTBE was used as solvent.

In any case, with the exception of 30, for which 0.10% Ar–H was observed, as 
determined by GC analysis. 3-Fluoropyridine derivatives with varying electronic 
properties were prepared from the corresponding bromides (22, 28-29), although 3-
bromopyridine itself furnished a 1:1 (p:m) mixture of aryl fluoride regioisomers (not shown). In line with our previous observations (see Chapter 3), forcing conditions were required to synthesize electron-rich fluoropyridine 29. Indole (30), quinoline (31-33), and isoquinoline (34-35) derivatives were also prepared in high yields. Heteroaryl bromides with more than one nitrogen atom, such as pyrimidine (36), indazole (37), and quinoxaline (38) were also suitable substrates. Finally, the vascular disorder drug Nicergoline (Sermion)18 was fluorinated to provide analogue 39. This result suggests that our methodology should be viable for the late-stage fluorination of advanced intermediates in which reactive functional groups are present.

4.5. Ligand structure effects. Having developed conditions for the Pd-catalyzed fluorination of aryl (Section 4.3) and heteroaryl (Section 4.4) bromides, we next investigated the effect on these reactions of modifying the ligand's structure (Table 4.5-4.6).19 In doing so, we hoped to (a) design a catalyst system capable of effecting these reactions under milder conditions and with lower catalyst loadings, (b) mitigate regioisomer formation, and (c) find a single ligand capable of promoting the fluorination of a wide array of (hetero)aryl triflates and bromides.

We began our investigation by systematically varying the substituents of AdBrettPhos (L1) to determine what effect, if any, changing specific substituents on the biaryl backbone would have on the fluorination of 4-(nBu)PhBr (20-Br) (Table 4.5). With tBuBrettPhos (L3) in lieu of L1, no reaction was observed (entry 2, Table 4.5), suggesting that the bulky adamantyl groups on the phosphine are necessary for the fluorination of aryl bromides. Notably, only one adamantyl group appears to be
necessary: the previously reported ligand \( \text{Ad(tBu)BrettPhos}^{5\text{c}} \) (L4) provided similar yields and moderately improved regioselectivity for \( 4-(nBu)\text{PhF} \) (20a) over \( 3-(nBu)\text{PhF} \) (20b) (entry 3, Table 4.5).

We next investigated the role of substituents on the phosphine-containing ring of the ligand on the outcome of the Pd-catalyzed fluorination of 20-Br (entries 4-7, Table 4.5). Consistent with our previous findings (Chapter 1), switching the ligand from L1 to the closely related ligand \( \text{AdRockPhos}^{20} \) (L5) had only a minimal effect (entry 4, Table 4.5). In fact, a reaction conducted with the newly prepared ligand \( \text{desOMeAdBrettPhos} \) (L6), which lacks a substituent at the 6-position of the top ring, showed similar yield but slightly improved regioselectivity compared to AdBrettPhos (4:1 for L6, 3:1 for L1) (entry 5, Table 4.5). Subsequently, have found that L6 is similar to or slightly better than AdBrettPhos for a number of fluorination reactions (not shown). This is interesting because the precursor to 64 is 3-fluoroanisole, which is much more readily available than 1-fluoro-2,4-dimethoxybenzene required to prepare L1. In addition, previous work had suggested that a substituent at the 6-position of the phosphine-containing ring was necessary to promote reductive elimination.\(^{21}\) It should be noted that the methoxy group at the 3-position of the top ring is required for the desired reaction to occur, as a catalyst based on \( \text{AdXPhos} \) (L7) provided no aryl fluorides under these conditions (entry 6, Table 4.5).

As the bulky ligand AdBrettPhos (L1) is superior to its di-\( \text{tert-} \)butyl analogue L3, we wondered if increasing the steric influence of the substituent adjacent to the phosphine would further promote C–F reductive elimination and thus improve the rate of catalytic fluorination. Thus, the 3-\( \text{iso-} \)propoxy analogue of AdBrettPhos (L8) was
prepared. Unfortunately, this ligand does not form a stable Pd(0) precatalyst upon reaction with [(1,5-COD)Pd(CH2TMS)2]; a similar outcome was observed while attempting to make Pd(0) precatalysts of ligands with tetramethyl-substituted top rings (see Chapter 3). This finding suggests that increasing the size of the substituent in the 3-position of the top ring has a detrimental effect on the ligand's ability to bind to Pd. Nonetheless, L8 was evaluated by using it in conjunction with [Pd(cinnamyl)Cl]2. Unfortunately, only low yields of the desired aryl fluoride 20a were obtained (entry 7, Table 4.5).22 Similarly, all ligands with tetramethyl-substituted top rings that have been evaluated provide little to no product in the Pd-catalyzed fluorinations of both aryl triflates and bromides (not shown). Thus, at this point it seems that a methoxy group adjacent to the phosphine is both necessary and optimal for promoting fluorination.

We also investigated the effect of changing the substituents on the bottom ring of the ligand (entries 8-9, Table 4.5). Again, we wondered if larger substituents might be able to accelerate C–F reductive elimination. However, the ligand bearing tert-butyl groups at the 2',4',6'-positions of the bottom ring (L9) did not form a stable Pd(0) precatalyst, and in conjunction with [(cinnamyl)PdCl]2 did not promote the fluorination of 20-Br (entry 8, Table 4.5). Moving in the opposite direction, we also prepared and evaluated the ligand with no substituents on the bottom ring of the ligand (L10). Previous findings in our lab suggest that the 2,4,6-tri-iso-propyl ring found in L1 and related ligands promotes both catalytic activity and catalyst stability by limiting potential C–H activation of the 2',6'-positions of the ligand.23 Thus, we initially expected that L10 would be ineffective. Surprisingly, using L10 in conjunction with [(cinnamyl)PdCl]2 (entry 9, Table 4.5) or Pd2(dba)3 (entry 10, Table 4.5) afforded a low yield of the desired
product 20a as a single regioisomer. This result suggested to us that while the iso-propyl groups on the bottom ring of the ligand in L1 promote the desired transformation, they are not required for catalytic activity.

Based on this finding, we wondered if non-biaryl phosphine ligands bearing di-adamantyl groups would be capable of effecting fluorination (entries 11-14, Table 4.5). However, the use of BuPAd₂ (L11, entry 11, Table 4.5), BnPAd₂ (L12, entry 12, Table

Table 4.5. Ligand structure effects on the fluorination of 20-Br.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Yield (20a:20b)</th>
<th>Entry</th>
<th>Ligand</th>
<th>% Yield (20a:20b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>L1 (R = R’ = Ad)</td>
<td>85% (3:1)</td>
<td>8-10</td>
<td>L9 (R = fBu)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>L3 (R = R’ = fBu)</td>
<td>0%</td>
<td></td>
<td>L10 (R = H)</td>
<td>11%b</td>
</tr>
<tr>
<td></td>
<td>L4 (R = Ad, R’ = fBu)</td>
<td>85% (4:1)</td>
<td></td>
<td>L10 (R = H)</td>
<td>16%c</td>
</tr>
<tr>
<td>4-7</td>
<td>L5 (R = OMe, R’ = Me)</td>
<td>70% (4:1)</td>
<td>11-12</td>
<td>L11 (R = Bu)</td>
<td>0%b</td>
</tr>
<tr>
<td></td>
<td>L6 (R = OMe, R’ = H)</td>
<td>90% (4:1)</td>
<td></td>
<td>L12 (R = Bn)</td>
<td>0%b</td>
</tr>
<tr>
<td></td>
<td>L7 (R = H)</td>
<td>0%</td>
<td>13</td>
<td>L13</td>
<td>0%b</td>
</tr>
<tr>
<td></td>
<td>L8 (R = OMe, R’ = OMe)</td>
<td>21% (2:1)b</td>
<td>14</td>
<td>L14</td>
<td>0%b</td>
</tr>
</tbody>
</table>

*aReaction conditions: 20-Br (0.10 mmol), AgF (0.20 mmol), KF (0.050 mmol), [(L·Pd)₂(1,5-COD)] (2%), cyclohexane (1 mL), 130 °C, 12 h.  

b¹⁹F NMR yields.  

[cinnamyl]PdCl₂ (2%), ligand (6%) was used.  bPd₂dba₁ (2%), ligand (6%) was used.

448
4.5), or DalPhos (L13, entry 13, Table 4.5), in conjunction with [(cinnamyl)PdCl]2 afforded none of the desired product under the reaction conditions. Similarly, the related ligand AdBippyPhos (L14) was incapable of promoting the fluorination of 20-Br (entry 14, Table 4.5). Taken together, these findings suggest that the key components of L1 needed to promote the fluorination of aryl bromides are (a) the di-adamantyl groups on the phosphine, (b) the methoxy group in the 3-position of the top ring, and (c) the biaryl phosphine backbone.

We also briefly investigated the effects of modifying substituents on 3'-arylated ligand L2 (Table 4.6). Similar to our findings for L1, switching the methoxy group at the 6-position of the top ring in L2 to a methyl group (L15, entry 2) or a hydrogen atom (L16, entry 3)24 afforded ligands that formed Pd(0) precatalysts with similar activity as L2 (entry 1) for the fluorination of 22-Br. We also prepared a number of ligands bearing different para-substituted aryl groups at the 3'-position, but none of the catalysts derived from them showed superior reactivity compared to L2 (not shown). Concurrent with this

Table 4.6. Ligand structure effects for 3'-arylated ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% Yield</th>
<th>Entry</th>
<th>Ligand</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>L2 (R = OMe)</td>
<td>72%</td>
<td>4</td>
<td>L17</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>L15 (R = Me)</td>
<td>59%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L16 (R = H)</td>
<td>51%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aReaction conditions: 20-Br (0.10 mmol), AgF (0.20 mmol), KF (0.050 mmol), [(L•Pd)2(1,5-COD)] (2%), cyclohexane (1 mL), 130 °C, 12 h. 19F NMR yields.
work, coworkers in our lab discovered that the ligand bearing a 2,3,5,6-tetrafluoro-4-nbutylphenyl group at the 3'-position, designated AlPhos (L17), shows equal or superior reactivity for the fluorination of both (hetero)aryl triflates and bromides (entry 4, Table 4.6). In fact, L17 can be used to carry out the fluorination of 20-Br to 20a with only minimal formation of 20b. Thus, L17 affords the most active catalyst seen to date for the Pd-catalyzed fluorination of aryl (pseudo)halides.

4.6. Conclusion. We have developed reaction conditions for converting unactivated (hetero)aryl bromides and iodides to the corresponding fluorides. The reaction proceeds without significant formation of reduction byproducts. The success of the reaction stems from the use of AgF with added KF to promote the reaction, and from control of the ligand modification process described in Chapter 1. At this time, however, the role of the added nucleophile remains unclear. Although this work was a breakthrough for the synthesis of heteroaryl fluorides, several limitations remain, including the use of superstoichiometric amounts of Ag to carry out the reaction, and the need for a glovebox to set up these reactions. Lastly, a preliminary investigation suggested that 5-membered heteroaryl bromides are, in general, not suitable substrates for this reaction. Thus, a deeper investigation of this challenging transformation was carried out (Chapter 5).

4.7. Experimental.

4.7.1. General Procedures. Anhydrous, oxygen-free toluene, tetrahydrofuran, and dichloromethane (CH2Cl2) were purchased from J. T. Baker and passed through two activated alumina columns followed by sparging with argon before use. All other
anhydrous solvents were purchased from Aldrich in Sure-Seal™ bottles and sparged with argon before use. Cesium fluoride (99.0 %) was purchased from Aldrich and dried at 180 °C under vacuum for 24 h. The dried KF was then transferred to a nitrogen-filled glovebox where it was thoroughly ground using an oven-dried mortar and pestle. The finely ground KF was then filtered through a 45 μm stainless-steel sieve (purchased from Cole Parmer) to obtain KF with particle size of < 45 μm. Potassium fluoride (99.0%) was purchased from Sigma-Aldrich and dried using the procedure described for CsF. Di(1-adamantyl)chlorophosphine and di(1-adamantyl)phosphine were received as gifts from Sigma-Aldrich, for which we are grateful. [(1,5-COD)Pd(CH₂TMS)₂] was prepared according to the literature procedure and stored at −20 °C in a nitrogen filled glovebox when not in use. 1-(3-bromophenyl)-1H-pyrrole and 4-bromo-1-tosyl-1H-indole were prepared according to the literature procedures. All other reagents were purchased from commercial sources and used as received, or prepared as described below. Compounds were analyzed by ¹H, ¹³C, ³¹P, ¹⁹F NMR, and IR, where appropriate. New compounds were also analyzed by elemental analysis or high resolution ESI-MS. All ¹⁹F NMR yields stated for fluorination reactions are calculated from ¹⁹F NMR spectra relative to an internal standard of 1-fluoronaphthalene. ¹H and ¹³C NMR spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometers and were calibrated using residual solvent as an internal reference. ¹⁹F and ³¹P{¹H} spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometer. ¹⁹F NMR spectra were calibrated to an external standard of neat PhCF₃ (δ = 63.72 ppm). ³¹P{¹H} NMR spectra were calibrated to an external standard of neat H₃PO₄ (δ = 0.0 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, pt =
pseudotriplet, q = quartet, p = pentet, m = multiplet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 Fourier Transform IR Spectrometer. Screw-cap reaction tube refers to Fisher 16 x 125 mm tubes (Cat. No. 1495925C) or Fisher 20 x 150 mm tubes (Cat. No. 1495937C) tubes equipped with SPTA PTFE/SIL F/15-425 10 (Cat. No. 03394A) septa or SPTA PTFE/SIL F/18-400 10 (Cat. No. 03394B), respectively. All reactions carried out at high temperatures should be performed behind a blast shield or closed hood sash.

The contents of arene reduction product were evaluated by analysis of the crude reaction mixture (for compounds 5, 7, 8, 9, 14, 19, and 36) or purified products (for compounds 4, 6, 10, 11, 12, 13, 15, 16, 17, 18, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37, and 38) with dodecane as the internal standard. Agilent 7890A series GC systems was used. The content of reduction product in 39 was evaluated by comparison of $^1$H NMR spectra.

4.7.2. Procedures for Pd-catalyzed fluorination reactions.

General Procedure for Reactions in Table 4.1. The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with metal fluoride (0.20 mmol, 2.0 equiv.), base (0.05 mmol, 0.5 equiv.), 1 (3.2 mg, 0.0020 mmol, 0.020 equiv.), and cyclohexane (1.0 mL), in that order. Then, 3-bromo-$N,N$-dimethylaniline (14.7 μL, 0.10 mmol, 1.0 equiv.) was added with a micropipette. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 130 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the reaction mixture was cooled to room temperature and 1-fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired
product.

**General Procedure for Reactions in Table 4.3.** The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (25.4 mg, 0.20 mmol, 2.0 equiv.), with or without KF (2.9 mg, 0.050 mmol, 0.50 equiv.), 1 or 27 (0.0020 mmol, 0.020 equiv.), 2-MeTHF (1 mL), and 3-bromo-5-cyanopyridine (18.3 mg, 0.10 mmol, 1.0 equiv.), in that order. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 130 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the reaction system was cooled to room temperature and 1-fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired product.

**Table 4.7. Evaluation of Pd sources.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(PdCinnCl)$_2$</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$</td>
<td>0</td>
</tr>
<tr>
<td>3$^a$</td>
<td>Pd$_2$(dba)$_3$</td>
<td>47/19% (p/m)</td>
</tr>
<tr>
<td>4</td>
<td>AdBP 3rd gen. precat.</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Preactivated at 130 °C for 1.5 min.

**General Procedure for Reactions in Table 4.7.** The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (25 mg, 0.20 mmol, 2.0 equiv.), KF (2.9 mg, 0.05 mmol, 0.50 equiv.), Pd source (0.004 mmol, 0.04 equiv.), L1 (3.8 mg, 0.006 mmol, 0.06 equiv.), and cyclohexane (1.0 mL). For entry 4, $^{28}$ 4% of
precatalysts were used, respectively. Then 1-bromo-4-n-butylbenzene (18 \mu L, 0.10 mmol, 1.0 equiv.) was added with a micropipette. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 130 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 12 h. At this time, the reaction mixture was cooled to room temperature and 1-fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired product.

Table 4.8. The effect of equivalents of KF on reaction yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>KF equiv.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>31</td>
</tr>
</tbody>
</table>

The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (25.4 mg, 0.20 mmol, 2.0 equiv.), KF, 1 (3.2 mg, 0.0020 mmol, 0.020 equiv.), cyclohexane (1.0 mL), and 3-bromo-N,N-dimethylaniline (14.7 \mu L, 0.10 mmol, 1.0 equiv.), in that order. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 130 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the reaction mixture was cooled to room temperature and 1-
fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired product.

4.7.3. Synthesis of aryl fluorides.

For compounds 4, 6, 10, 11, 12, 13, 15, 16, 17, and 18:

The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (254 mg, 2.00 mmol, 2.00 equiv.), KF (29.1 mg, 0.500 mmol, 0.500 equiv.), 1, reaction solvent (10 mL), and aryl halide (1.00 mmol, 1.00 equiv.), in that order. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to the designated temperature in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite, eluting with diethyl ether. After concentration, the crude product was purified by silica gel chromatography.

Purified by silica gel column chromatography (hexanes) to provide 4 as a white solid (1st: 181 mg, 92%; 2nd: 187 mg, 95%). Melting Point: 51 °C (Lit. 51 °C). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.69 (d, J = 7 Hz, 1H), 8.62-8.67 (m, 1H), 8.22 (d, J = 8 Hz, 1H), 7.82-7.86 (m, 1H), 7.66-7.77 (m, 2H), 7.59-7.65 (m, 2H), 7.40 (d, J = 12 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 157.3 (d, J = 250 Hz), 132.0 (d, J = 9 Hz), 132.0 (d, J = 4 Hz), 128.2 (d, J = 6 Hz), 128.0 (d, J = 1 Hz), 127.8, 127.4, 127.1 (d, J = 1 Hz), 126.8, 126.0 (d, J = 2 Hz), 124.4 (d, J = 19 Hz), 122.9 (d, J = 3 Hz), 122.9 (d, J = 1 Hz), 121.5 (d, J = 6 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): δ -125.4 ppm. IR (neat): 3055, 1951, 1923, 1811, 1639, 1604, 1500, 1450, 1400, 1311, 1220,
Purified by silica gel column chromatography (diethyl ether/pentane = 1/2 to 1/1) to provide 6 as a white solid (1st: 183 mg, 76%; 2nd: 177 mg, 73%). Melting Point: 81 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.01 (s, 1H), 7.84-7.87 (m, 1H), 7.62 (m, 1H), 3.11 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.6 (d, J = 255 Hz), 144.1 (d, J = 6 Hz), 134.4 (qd, J = 34, 7 Hz), 120.5-120.7 (m), 118.7 (d, J = 24 Hz), 118.5 (dq, J = 24, 4 Hz), 122.4 (qd, J = 272, 3 Hz), 44.4 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -63.1, -105.9 ppm. IR (neat): 3070, 2939, 1620, 1446, 1411, 1333, 1301, 1217, 1179, 1134, 1103, 1085, 971, 930, 890, 836, 761, 699, 636, 585 cm$^{-1}$. Anal. Calcd. for: C$_8$H$_6$O$_2$SF$_4$: C, 39.67, H, 2.50; found C, 40.02, H, 2.51.

Purified by silica gel column chromatography (pentane) to provide 10 as a white solid (1st: 139 mg, 76%; 2nd: 139 mg, 76%). Melting Point: 97-98 °C (Lit. 100 °C). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.76 (d, J = 8 Hz, 1H), 7.73 (dd, J = 9, 5 Hz, 1H), 7.56 (d, J = 7 Hz, 1H), 7.43 (pt, J = 8 Hz, 1H), 7.35 (ptd, J = 7, 1 Hz, 1H), 7.25-7.29 (m, 1H), 7.13 (ptd, J = 9, 3 Hz, 1H), 3.88 (s, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.5 (d, J = 243 Hz), 145.4 (d, J = 9 Hz), 143.1 (d, J = 2 Hz), 141.0, 137.9 (d, J = 2 Hz), 127.0, 126.5, 125.1, 120.8 (d, J = 9 Hz), 119.7, 114.0 (d, J = 23 Hz), 112.4 (d, J = 23 Hz), 37.1 (d, J = 2 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -116.0 (major regioisomer), -116.6 (minor regioisomer) ppm. IR (neat): 3052, 2907, 1611, 1590, 1484, 1449, 1424, 1349, 1305, 1273, 1249, 1207, 1192, 1177, 1121, 1091, 951, 926, 860, 821, 760, 728, 712 cm$^{-1}$. 456
Purified by silica gel column chromatography (diethyl ether/hexanes = 1/100 to 1/20) to provide 11 as a pale yellow oil (1st: 169 mg, 84%; 2nd: 186 mg, 92%). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.36-7.51 (m, 5H), 7.23-7.32 (m, 1H), 6.68-6.85 (m, 3H), 5.08 (s, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ 163.8 (d, J = 244 Hz), 160.3 (d, J = 11 Hz), 136.6, 130.4 (d, J = 10 Hz), 128.8, 128.3, 127.7, 110.8 (d, J = 3 Hz), 107.9 (d, J = 21 Hz), 102.8 (d, J = 25 Hz), 70.4 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): δ -111.7 ppm. IR (neat): 3066, 3032, 2913, 2868, 1609, 1592, 1488, 1454, 1381, 1313, 1277, 1262, 1164, 1131, 1025, 959, 937, 831, 760, 733, 695, 679 cm$^{-1}$.

Purified by silica gel column chromatography (diethyl ether/hexanes = 1/9 to 1/4) to provide 12 as a colorless oil (1st: 154 mg, 85%; 2nd: 156 mg, 86%). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.21 (ddd, J = 17, 8, 1 Hz, 1H), 6.67 (ddd, J = 9, 2, 1 Hz, 1H), 6.54-6.61 (m, 2H), 3.85 (td, J = 5, 2 Hz, 4H), 3.15 (td, J = 5, 2 Hz, 4H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 164.0 (d, J = 242 Hz), 153.1 (d, J = 10 Hz), 130.4 (d, J = 8 Hz), 110.9 (d, J = 3 Hz), 106.4 (d, J = 21 Hz), 102.6 (d, J = 25 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): δ -112.2 ppm. IR (neat): 2963, 2854, 2828, 1680, 1581, 1494, 1448, 1380, 1262, 1250, 1180, 1163, 1120, 1069, 999, 971, 933, 881, 832, 759, 682, 643 cm$^{-1}$. Anal. Calcd. for: C$_{10}$H$_{12}$FON: C, 66.28, H, 6.67; found C, 66.37, H, 6.67.

Purified by silica gel column chromatography (diethyl ether/hexanes = 0/1 to 1/100) to provide 13 as a colorless oil (1st: 139 mg, 86%; 2nd: 138 mg, 86%). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.40 (dd, J = 16, 8 Hz, 1H), 7.22
(dd, J = 9, 2 Hz, 1H), 7.11-7.17 (m, 3H), 6.95-7.01 (m, 1H), 6.39-6.43 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 163.5 (d, J = 245 Hz), 142.3 (d, J = 10 Hz), 131.0 (d, J = 9 Hz), 119.3, 115.9 (d, J = 3 Hz), 112.4 (d, J = 21 Hz), 111.1, 107.9 (d, J = 25 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ -111.2 ppm. IR (neat): 3105, 2925, 1612, 1599, 1502, 1455, 1343, 1251, 1198, 1160, 1117, 1073, 1025, 954, 845, 772, 719, 681, 624 cm$^{-1}$.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/20 to 1/15) to provide 15 as a white solid (1$^{st}$: 158 mg, 88%; 2$^{nd}$: 155 mg, 86%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.94-7.98 (m, 2H), 7.06-7.12 (m, 2H), 2.91 (t, J = 8 Hz, 2H), 1.69 (pentet, J = 7 Hz, 2H), 1.38 (sextet, J = 8 Hz, 2H), 0.92 (t, J = 7 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.0, 165.7 (d, J = 253 Hz), 133.6 (d, J = 3 Hz), 130.8 (d, J = 9 Hz), 115.7 (d, J = 22 Hz), 38.4, 26.6, 22.6, 14.1 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -105.9 ppm. IR (neat): 2959, 2933, 2872, 1683, 1596, 1505, 1467, 1409, 1227, 1205, 1155, 1099, 1012, 969, 842, 819, 734 cm$^{-1}$.

Purified by silica gel column chromatography (EtOAc) to provide 16 as a golden-yellow solid (1$^{st}$: 150 mg, 90%; 2$^{nd}$: 157 mg, 94%). Melting Point: 65 $^\circ$C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.38-7.43 (m, 2H), 7.03-7.09 (m, 2H), 3.08 (s, 3H), 2.96 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.8, 164.4 (d, J = 248 Hz), 132.5 (d, J = 4 Hz), 129.5 (d, J = 8 Hz), 115.6 (d, J = 22 Hz), 39.8, 35.7 ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ -110.8 ppm. IR (neat): 3064, 3045, 3013, 2929, 1619, 1592, 1490, 1456, 1407, 1393, 1262, 1223, 1161, 1083, 1013, 922, 849, 814, 760, 721, 690 cm$^{-1}$.
From aryl bromide: Purified by silica gel column chromatography (hexanes) to provide 17 as a white solid (1st: 160 mg, 93%; 2nd: 155 mg, 87%). Melting Point: 72 °C (Lit. 69-71 °C). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.55-7.59 (m, 4H), 7.44-7.49 (m, 2H), 7.35-7.39 (m, 1H), 7.13-7.18 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.7 (d, J = 245 Hz), 140.5, 137.5 (d, J = 3 Hz), 129.0, 128.9 (d, J = 8 Hz), 127.5, 127.2, 115.8 (d, J = 21 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -116.0 (major regioisomer), -113.3 (minor regioisomer) ppm. IR (neat): 3064, 3041, 1596, 1518, 1484, 1234, 1194, 1106, 835, 757, 706, 687 cm$^{-1}$.

From aryl iodide: Purified by silica gel column chromatography (pentane) to provide 17 as white solid (1st: 156 mg, 91%; 2nd: 158 mg, 92%). The spectra obtained for this compound were identical with those obtained when using the corresponding aryl bromide as the substrate.

Purified by silica gel column chromatography (diethyl ether/hexanes = 1/20) to provide 18 as a white solid (1st: 219 mg, 96%; 2nd: 217 mg, 95%). Melting Point: 100 °C (Lit. 100-102 °C). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.05-8.11 (m, 3H), 7.90 (d, J = 8 Hz, 1H), 7.50 (pt, J = 8 Hz, 1H), 7.39 (pt, J = 7 Hz, 1H), 7.16-7.21
(m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): d 166.9, 164.6 (d, J = 250 Hz), 154.3, 135.2, 130.1 (d, J = 3 Hz), 129.7 (d, J = 9 Hz), 126.6, 125.4 (d, J = 4 Hz), 123.4, 121.8, 116.3 (d, J = 22 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): δ -109.0 ppm. IR (neat): 3055, 3031, 2992, 1602, 1519, 1479, 1456, 1435, 1406, 1315, 1296, 1252, 1226, 1153, 1097, 1073, 1013, 963, 834, 808, 754, 728, 700, 623 cm$^{-1}$.

For compounds 5, 7, 8, 9, 14, 19, 20, 21:

The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (127 mg, 1.00 mmol, 2.00 equiv.), KF (14.5 mg, 0.250 mmol, 0.500 equiv.), 1, and 5 mL of reaction solvent, successively. The aryl halide (0.500 mmol, 1.00 equiv.) was then added to the reaction tube. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to the designated temperature in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the reaction mixture was cooled to room temperature and 1-fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired product.

4.7.4. Synthesis of heteroaryl fluorides.

For compounds 27, 28, 29, 30, 31, 32, 38, 33, 34, 35, 37, and 38:

The reactions were set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (254 mg, 2.00 mmol, 2.00 equiv.), KF (29.1 mg, 0.500 mmol, 0.500 equiv.), 27, and reaction solvent (10 mL), in that order. Then aryl halide (1.00 mmol, 1.00 equiv.) was added to the reaction tube. The tube was sealed with a Teflon cap, removed from the
glovebox, and heated to the designated temperature in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the mixture was cooled to room temperature and filtered through a pad of Celite eluting with diethyl ether. After concentration, the crude product was purified by silica gel column chromatography.

\[ \text{NC} \]

Purified by silica gel column chromatography (diethyl ether/pentane = 1/5 to 1/3) to provide 22 as a white solid (1\textsuperscript{st}: 95 mg, 78%; 2\textsuperscript{nd}: 89 mg, 73%). Melting Point: 56 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 8.70 (bs, 1H), 8.68 (d, \( J = 3 \) Hz, 1H), 7.70 (ddd, \( J = 8, 3, 2 \) Hz, 1H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 158.3 (d, \( J = 260 \) Hz), 148.4 (d, \( J = 5 \) Hz), 142.4 (d, \( J = 23 \) Hz), 126.0 (d, \( J = 21 \) Hz), 115.2 (d, \( J = 2 \) Hz), 110.8 (d, \( J = 5 \) Hz) ppm; \textsuperscript{19}F NMR (280 MHz, CDCl\textsubscript{3}): \( \delta \) -123.0 ppm. IR (neat): 3056, 2243, 1596, 1574, 1454, 1421, 1319, 1270, 1228, 1156, 1024, 940, 904, 706, 693 cm\textsuperscript{-1}. Anal. Calcd. for: C\textsubscript{6}H\textsubscript{3}N\textsubscript{2}F: C, 59.02, H, 2.48; found C, 59.06, H, 7.80.

\[ \text{MeO}_2\text{C} \]

Purified by silica gel column chromatography (diethyl ether/pentane = 1/2 to 1/1) to provide 28 as a pale yellow solid (1\textsuperscript{st}: 140 mg, 90%; 2\textsuperscript{nd}: 137 mg, 88%). Melting Point: 60 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 8.49 (d, \( J = 3 \) Hz, 1H), 8.11 (dd, \( J = 10, 5 \) Hz, 1H), 7.46 (ptdd, \( J = 9, 3, 1 \) Hz, 1H), 3.92 (s, 3H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 164.6, 161.2 (d, \( J = 262 \) Hz), 144.1 (d, \( J = 4 \) Hz), 138.5 (d, \( J = 25 \) Hz), 127.0 (d, \( J = 6 \) Hz), 123.6 (d, \( J = 19 \) Hz), 53.0 ppm; \textsuperscript{19}F NMR (280 MHz, CDCl\textsubscript{3}): \( \delta \) -119.4 ppm. IR (neat): 3110, 3089, 2964, 1716, 1582, 1479, 1438, 1386, 1314, 1280, 1256, 1228, 1198, 1128, 1103, 1021, 957, 913, 854, 790, 692, 638, 607.
Purified by silica gel column chromatography (diethyl ether/pentane = 1/3 to 1/2 to 1/1.5) to provide 29 as a white solid (1st: 168 mg, 72%; 2nd: 160 mg, 69%). Melting Point: 88-90 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.21 (bs, 1H), 8.10 (bs, 1H), 7.33 (d, J = 9 Hz, 2H), 6.99 (dpt, J = 10 Hz, 3 Hz, 1H), 6.92 (d, J = 9 Hz, 2H), 5.00 (s, 2H), 3.80 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 159.9 (d, J = 256 Hz), 159.9, 155.9, 134.4 (d, J = 3 Hz), 130.2 (d, J = 23 Hz), 129.5, 127.6, 114.3, 109.4 (d, J = 21 Hz), 70.7, 55.4 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): d −126.1 ppm. IR (neat): 3067, 3008, 2943, 2878, 2844, 1615, 1576, 1516, 1456, 1435, 1383, 1318, 1307, 1285, 1254, 1236, 1183, 1152, 1024, 1000, 973, 859, 827, 781, 700, 603 cm$^{-1}$. Anal. Calcd. for C$_{13}$H$_{12}$O$_2$NF: C, 66.94, H, 5.19; found C, 67.17, H, 5.25.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/20 to 1/15 to 1/10) to provide 30 as a white solid (1st: 241 mg, 83%; 2nd: 255 mg, 88%). Melting Point: 88 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.76-7.80 (m, 3H), 7.55 (d, J = 4 Hz, 1H), 7.20-7.27 (m, 3H), 6.90 (dd, J = 11, 8 Hz, 1H), 6.75 (dd, J = 4, 1 Hz, 1H), 2.32 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 156.0 (d, J = 248 Hz), 145.5, 137.0 (d, J = 10 Hz), 135.1, 130.1, 127.0, 126.5, 125.5 (d, J = 2 Hz), 119.9 (d, J = 22 Hz), 109.7, 108.7 (d, J = 18 Hz), 104.7, 21.7 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ −120.9 ppm. IR (neat): 3141, 3121, 2933, 1626, 1582, 1488, 1429, 1371, 1362, 1304, 1245, 1164, 1131, 1087, 1031, 946, 811, 749, 704, 688, 635, 574 cm$^{-1}$. Anal. Calcd. for C$_{15}$H$_{12}$O$_2$NSF: C, 62.27, H, 4.18; found C, 62.10, H, 4.20.

462
Purified by silica gel column chromatography (diethyl ether/pentane = 1/10 to 1/8) to provide 31 as a yellow oil (1st: 111 mg, 76%; 2nd: 108 mg, 73%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.81 (d, \(J = 3\) Hz, 1H), 8.11 (d, \(J = 10\) Hz, 1H), 7.73-7.79 (m, 2H), 7.63-7.69 (m, 1H), 7.54-7.59 (m, 1H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 156.3 (d, \(J = 243\) Hz), 145.5 (d, \(J = 2\) Hz), 141.6 (d, \(J = 27\) Hz), 129.6, 128.6 (d, \(J = 10\) Hz), 128.5 (d, \(J = 5\) Hz), 127.7, 127.4 (d, \(J = 5\) Hz), 118.4 (d, \(J = 16\) Hz) ppm; \(^{19}\)F NMR (280 MHz, CDCl\(_3\)): \(\delta -128.3\) ppm. IR (neat): 3057, 1611, 1497, 1464, 1426, 1336, 1270, 1210, 1154, 1138, 984, 889, 857, 779, 749, 709, 610 cm\(^{-1}\).

Purified by silica gel column chromatography (diethyl ether/pentane = 1/3 to 1/2) to provide 32 as a pale yellow oil (1st: 127 mg, 86%; 2nd: 121 mg, 82%). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.91 (dd, \(J = 5, 2\) Hz, 1H), 8.36 (d, \(J = 9\) Hz, 1H), 7.87 (d, \(J = 9\) Hz, 1H), 7.55-7.62 (m, 1H), 7.39 (dd, \(J = 9, 4\) Hz, 1H), 7.16 (pt, \(J = 9\) Hz, 1H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 157.9 (d, \(J = 253\) Hz), 151.3, 149.0, 129.4, 129.0 (d, \(J = 9\) Hz), 125.4 (d, \(J = 4\) Hz), 121.3 (d, \(J = 3\) Hz), 119.2, 110.2 (d, \(J = 19\) Hz) ppm; \(^{19}\)F NMR (280 MHz, CDCl\(_3\)): \(\delta -123.0\) ppm. IR (neat): 3071, 1635, 1598, 1500, 1470, 1400, 1250, 1235, 1199, 1143, 1068, 1044, 1008, 793, 742, 639 cm\(^{-1}\).

Purified by silica gel column chromatography (diethyl ether/pentane = 1/3 to 1/2) to provide 33 as a pale yellow solid (1st: 155 mg, 96%; 2nd: 155 mg, 96%). Melting Point: 52 °C (Lit. 52-53 °C). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.93 (dd, \(J = 10, 5\) Hz, 1H), 7.86 (d, \(J = 8\) Hz, 1H), 7.36 (ptd, \(J = 9, 4\) Hz, 1H) ppm.
Hz, 1H), 7.27 (dd, J = 10, 3 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 2.65 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.0 (d, J = 245 Hz), 158.3 (d, J = 3 Hz), 144.9 (d, J = 1 Hz), 135.5 (d, J = 5 Hz), 131.0 (d, J = 9 Hz), 127.0 (d, J = 10 Hz), 122.8, 119.4 (d, J = 25 Hz), 110.5 (d, J = 21 Hz), 25.2 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -115.0 ppm. IR (neat): 3050, 2922, 1628, 1608, 1564, 1498, 1371, 1343, 1302, 1223, 1137, 1107, 964, 927, 896, 822, 755, 654, 669, 584 cm$^{-1}$.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/3 to 1/2) to provide 34 as a pale yellow solid (1st: 131 mg, 89%; 2nd: 132 mg, 90%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.04 (s, 1H), 8.36 (d, J = 2 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H), 7.74 (ddd, J = 10, 8, 1 Hz, 1H), 7.64 (ddd, J = 9, 8, 1 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 155.3 (d, J = 258 Hz), 148.5 (d, J = 5 Hz), 130.8, 130.0 (d, J = 3 Hz), 128.5, 128.3, 127.1 (d, J = 1 Hz), 126.6 (d, J = 15 Hz), 119.7 (d, J = 4 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -140.0 ppm. IR (neat): 3056, 1632, 1589, 1503, 1452, 1386, 1276, 1247, 1147, 1110, 1066, 880, 859, 791, 772, 751, 707, 632, 573 cm$^{-1}$. Anal. Calcd. for C$_9$H$_6$NF: C, 73.46; found C, 71.02.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/1 to 1/0) to provide 35 as a yellow solid (1st: 132 mg, 90%; 2nd: 126 mg, 86%). Melting Point: 50 ºC. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.18 (s, 1H), 8.48 (d, J = 6 Hz, 1H), 7.93 (dd, J = 10, 6 Hz, 1H), 7.55 (d, J = 6 Hz, 1H), 7.36 (dd, J = 10, 3 Hz, 1H), 464
7.31 (ptd, J = 9, 3 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 163.3 (d, J = 251 Hz), 152.3, 143.9, 137.3 (d, J = 11 Hz), 130.8 (d, J = 10 Hz), 126.0, 120.1, 118.0 (d, J = 26 Hz), 110.0 (d, J = 21 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -106.5 ppm. IR (neat): 3065, 3020, 1632, 1561, 1494, 1468, 1391, 1330, 1274, 1251, 1222, 1174, 1141, 1118, 1032, 964, 825, 704, 647, 633 cm$^{-1}$. Anal. Calcd. for C$_9$H$_6$NF: C, 73.46, H, 4.11; found C, 73.55, H, 4.27.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/10 to 1/5 to 1/4) to provide 37 as a light beige solid (1$^{st}$: 135 mg, 90%; 2$^{nd}$: 134 mg, 89%). Melting Point: 40 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.03 (d, J = 1 Hz, 1H), 7.24-7.28 (m, 1H), 7.11 (d, J = 8 Hz, 1H), 6.75 (dd, J = 10, 8 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 155.9 (d, J = 251 Hz), 142.6 (d, J = 9 Hz), 129.3 (d, J = 2 Hz), 127.2 (d, J = 7 Hz), 114.4 (d, J = 23 Hz), 105.1 (d, J = 4 Hz), 104.8 (d, J = 18 Hz), 35.9 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -118.3 ppm. IR (neat): 3106, 2948, 1912, 1632, 1575, 1508, 1433, 1407, 1385, 1265, 1231, 1204, 1150, 980, 878, 850, 775, 728, 676, 633 cm$^{-1}$. Anal. Calcd. for C$_8$H$_7$N$_2$F: C, 63.99, H, 4.70; found C, 64.44, H, 4.89.

Purified by silica gel column chromatography (diethyl ether/pentane = 1/2) to provide 38 as a beige solid (1$^{st}$: 102 mg, 69%; 2$^{nd}$: 113 mg, 77%). Melting Point: 34-35 °C (Lit. 33-34 °C). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.78 (d, J = 2 Hz, 1H), 8.76 (d, J = 2 Hz, 1H), 8.04 (dd, J = 10, 6 Hz, 1H), 7.66 (dd, J = 9, 3 Hz, 1H), 7.49 (ptd, J = 9, 3 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.8 (d, J = 251 Hz), 145.8, 144.4 (d, J = 3 Hz), 143.9 (d, J = 13 Hz), 140.3, 131.7 (d, J = 10 Hz), 465
120.7 (d, J = 26 Hz), 113.0 (d, J = 21 Hz) ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): $\delta$ -107.8 ppm. IR (neat): 3093, 3062, 3037, 1626, 1421, 1368, 1355, 1297, 1239, 1209, 1133, 1110, 1023, 966, 930, 873, 828, 769, 725, 645, 609 cm$^{-1}$.

For compound 36:

The reaction was set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (127 mg, 1.00 mmol, 2.00 equiv.), KF (14.5 mg, 0.250 mmol, 0.500 equiv.), 2-MeTHF (5 mL), and 5-bromopyrimidine (0.500 mmol, 1.00 equiv.), in that order. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 150 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the reaction system was cooled to room temperature and 1-fluoronaphthalene was added as an internal standard. The reaction mixture was analyzed by $^{19}$F NMR (280 MHz) to determine the yield of the desired product.

For compound 39:

The reaction was set up in a nitrogen-filled glovebox. A reaction tube was charged with AgF (127 mg, 1.00 mmol, 2.00 equiv.), KF (14.5 mg, 0.250 mmol, 0.500 equiv.), 2-MeTHF (5 mL), and nicergoline (0.500 mmol, 1.00 equiv.), in that order. The tube was sealed with a Teflon cap, removed from the glovebox, and heated to 130 °C in a pre-heated oil bath. The reaction mixture was vigorously stirred for 14 h. At this time, the mixture was cooled to room temperature and filtered through a pad of Celite, eluting with EtOAc. After concentration, the crude product was purified by alumina column.
chromatography (hexanes/EtOAc = 1/2 to 0/1) to provide the title compound as yellow solid (1st: 146 mg, 69%; 2nd: 144 mg, 68%). The purified product contained <5% of an unidentified impurity. The corresponding reduction product was not detected based on $^1$H NMR analysis. Preparation of the corresponding reduction product (see below) confirmed that it is not the observed contaminant. Decomposes upon heating above 50 °C in air. $^1$H NMR (500 MHz, CDCl$_3$): δ 9.06 (s, 1H), 8.66 (d, J = 3 Hz, 1H), 7.99 (ddd, J = 9, 3, 2 Hz, 1H), 7.17-7.28 (m, 2H), 7.05 (d, J = 7 Hz, 1H), 6.79 (s, 1H), 4.42 (dd, J = 13, 5 Hz, 1H), 4.30 (dd, J = 11, 7 Hz, 1H), 3.77 (s, 3H), 3.21 (dd, J = 13, 4 Hz, 1H), 3.01-3.04 (m, 2H), 3.00 (s, 3H), 2.60-2.67 (m, 1H), 2.48 (s, 3H), 2.35 (d, J = 10 Hz, 1H), 2.10 (pt, J = 10 Hz, 1H), 1.18-1.44 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 164.3 (d, J = 2 Hz), 159.3 (d, J = 257 Hz), 146.7 (d, J = 4 Hz), 142.4 (d, J = 23 Hz), 135.3, 129.8, 127.6, 126.5, 123.8, 123.6 (d, J = 22 Hz), 121.6, 115.1, 110.4, 109.2, 73.7, 70.2, 68.7, 60.7, 49.7, 44.1, 33.0, 31.7, 30.3, 22.5 ppm; $^{19}$F NMR (280 MHz, CDCl$_3$): δ -125.7 ppm. IR (neat): 2941, 2819, 2772, 1723, 1599, 1578, 1463, 1421, 1365, 1286, 1208, 1155, 1092, 1071, 1048, 975, 898, 816, 766, 746, 690, 608 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{24}$H$_{27}$O$_3$N$_3$F [M+H$^+$]: 424.2031; found 424.2013.

The corresponding reduction product was prepared according to published conditions. A reaction tube was charged with nicergoline (100 mg, 0.21 mmol, 1.00 equiv.), sodium formate (42.8 mg, 0.63 mmol, 3.00 equiv.), palladium(II) acetate (2.36 mg, 0.01 mmol, 0.05 equiv.), and 2-(di-tert-butylphosphino)biphenyl (6.27 mg, 0.02 mmol, 0.01 equiv.), successively. The tube was capped and evacuated and backfilled with argon three times.
Then, methanol (1.0 mL) was added. The reaction tube was heated to 80 °C in an oil bath with vigorous stirring for 2 h. At this time, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (5.0 mL), and filtered through a pad of celite, rinsing with EtOAc (5.0 mL x 2). After concentration, the crude product was purified by alumina column chromatography (hexanes/EtOAc = 0/1 to 1/3 to 1/1 to 3/1 to 0/1) to provide the title compound as a viscous yellow oil (24.0 mg, 28%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.28 (d, $J = 2$ Hz, 1H), 8.82 (dd, $J = 5$, 2 Hz, 1H), 8.33 (dpt, $J = 8$, 2 Hz, 1H), 7.43 (dd, $J = 8$, 5 Hz, 1H), 7.20-7.29 (m, 2H), 7.08 (d, $J = 7$ Hz, 1H), 6.82 (s, 1H), 4.44 (dd, $J = 12$, 3 Hz, 1H), 4.32 (dd, $J = 10$, 7 Hz, 1H), 3.80 (s, 3H), 3.24 (m, 1H), 3.04-3.09 (m, 2H), 3.03 (s, 3H), 2.61-2.71 (m, 1H), 2.50 (s, 3H), 2.38 (dd, $J = 11$, 5 Hz, 1H), 2.13 (pt, $J = 11$ Hz, 1H), 1.18-1.44 (m, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 165.3, 153.6, 151.0, 137.2, 135.2, 129.8, 126.4, 126.2, 123.5, 123.3, 121.5, 115.1, 110.5, 109.0, 73.7, 70.2, 68.3, 60.7, 52.6, 49.6, 33.0, 31.7, 30.3, 22.5 ppm. HRMS (ESI) m/z calcd. for $C_{24}H_{28}O_{3}N_3$ [M+H$^+$]: 406.2131; found 406.2144.

4.7.5. Preparation of new ligands.

\[ \begin{array}{c}
\text{4-n-Butylphenylboronic acid} \quad \text{23} \\
\text{NH}_2 \quad 1\% \\
\text{Pd-XPhos} \\
\text{n-Bu} \\
\text{i-Pr Br} \\
\text{n-OfBu} \\
\text{Pi-Pr +} \\
\text{(HO)$_2$B} \text{THE HWRON, 12 h i-Pr} \\
\text{99%} \\
\text{A 100 mL Schlenk tube was charged with 4-n-butylphenylboronic acid (2.14 g, 12.0 mmol, 1.20 equiv.) and 23 (84.6 mg, 0.100 mmol, 0.0100 equiv.). The tube was capped} \\
\end{array} \]

468
with a rubber septum and evacuated. It was then backfilled with argon. This process was repeated a total of three times. To the tube was transferred degassed THF (5 mL), degassed 2.0 M aqueous solution of K$_3$PO$_4$ (10 mL), and 1-bromo-2,4,6-triisopropylbenzene (2.53 mL, 10.0 mmol, 1.00 equiv.), successively. The septum was replaced with a Teflon stopper under a flow of argon, and the reaction vessel was heated to 80 °C in an oil bath. The mixture was vigorously stirred for 12 h. At this time, the mixture was cooled to room temperature and quenched with 50 mL of water. The aqueous phase was extracted with hexanes (100 mL × 3) and the combined organic phases were dried over anhydrous MgSO$_4$. After concentration, the crude product was filtered through a 5 cm pad of silica gel (diameter = 6 cm) eluting with hexanes. Removal of solvent provided biaryl 24 as a white solid (3.32 g, 99%). Melting Point: 63-65 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.24 (d, J = 9 Hz, 2H), 7.13 (dd, J = 8, 2 Hz, 2H), 7.11 (d, J = 2 Hz, 1H), 2.99 (septet, J = 7 Hz, 1H), 2.64-2.75 (m, 4H), 1.73 (pentet, J = 6 Hz, 2H), 1.47 (sextet, J = 7 Hz, 2H), 1.36 (dd, J = 8, 2 Hz, 6H), 1.13 (dd, J = 7, 2 Hz, 12H), 1.02 (t, J = 7 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 147.8, 146.9, 141.0, 138.1, 137.4, 129.8, 128.1, 120.7, 35.7, 34.5, 33.8, 30.4, 24.5, 24.3, 22.8, 14.3 ppm. IR (neat): 3049, 3020, 2954, 2926, 2863, 1606, 1569, 1512, 1456, 1381, 1362, 1316, 1070, 1056, 1007, 877, 838, 811, 782, 733, 652 cm$^{-1}$. Anal. Calcd. for C$_{25}$H$_{36}$: C, 89.22, H, 10.78; found C, 89.32, H, 10.78.

\[\begin{align*}
\text{24} & \quad \text{Br}_2 \\
& \quad \text{DMF / CH}_2\text{Cl}_2 \\
& \quad 0 \degree \text{C, 10 min.} \\
\end{align*}\]

\[
\begin{array}{c}
\text{24} \quad \text{Br}_2 \\
\quad \text{DMF / CH}_2\text{Cl}_2 \\
\quad 0 \degree \text{C, 10 min.} \\
\end{array}
\]

24 (3.32 g, 9.86 mmol, 1.00 equiv.) was dissolved in CH$_2$Cl$_2$ (30 mL) and cooled to 0 °C.
In a separate flask, bromine (2.03 mL, 39.4 mmol, 4.00 equiv.) was added to DMF (10 mL) over 5 min at 0 °C. After 10 min, the DMF solution was cannulated to the 0 °C solution of 24 over 10 min. The resulting red mixture was vigorously stirred for 30 min at 0 °C. At this time, the mixture was quenched with saturated Na₂SO₃ (aq.) solution until the red color of bromine disappeared. The aqueous phase was extracted with hexanes (100 mL x 3) and the combined organic phases were dried over anhydrous MgSO₄. After concentration, the crude product was filtered through a 5 cm pad of silica gel (diameter = 6 cm) eluting with hexanes. Removal of solvent provided bromoarene 25 as a white solid (3.11 g, 76%). Melting Point: 107-109 °C. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 7.25 \text{ (d, } J = 8 \text{ Hz, } 2\text{H}), 7.18 \text{ (s, } 1\text{H}), 7.07 \text{ (d, } J = 8 \text{ Hz, } 2\text{H}), 3.64 \text{ (pentet, } J = 7 \text{ Hz, } 1\text{H}), 3.07 \text{ (pentet, } J = 7 \text{ Hz), 2.72 \text{ (t, } J = 8 \text{ Hz, } 2\text{H}), 2.56 \text{ (septet, } J = 7 \text{ Hz, } 1\text{H}), 1.73 \text{ (pentet, } J = 8 \text{ Hz, } 2\text{H), 1.47 \text{ (sextet, } J = 7 \text{, } 2\text{H), 1.38 \text{ (d, } J = 7 \text{ Hz, } 6\text{H), 1.34 \text{ (d, } J = 7 \text{ Hz, } 6\text{H), 1.10 \text{ (d, } J = 7 \text{ Hz, } 6\text{H), 1.02 \text{ (t, } J = 7 \text{ Hz, } 3\text{H)} \text{ ppm; } ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 147.8, 146.6, 144.2, 141.4, 141.0, 138.8, 131.0, 129.0, 128.4, 127.4, 122.7, 121.2, 35.7, 33.8, 33.6, 33.3, 30.7, 24.3, 23.5, 22.8, 20.2, 14.3 \text{ ppm. IR (neat): 2957, 2926, 2865, 1512, 1456, 1363, 1172, 1111, 1080, 1056, 1028, 1012, 884, 840, 808, 784, 684, 601 cm}^{-1}. \text{Anal. Calcd. for C}_{25}\text{H}_{35}\text{Br: C, 72.28, H, 8.49; found C, 72.31, H, 8.63.}

\[ \text{A 500 mL round bottom flask was charged with 2-fluoro-1,4-dimethoxybenzene (5.08 g,} \]
32.5 mmol, 0.900 equiv.) and THF (100 mL). The flask was cooled to −78 °C and 2.5 M n-BuLi solution in hexane (13.0 mL, 32.5 mmol, 0.900 equiv.) was added drop-wise over 10 min. The mixture was stirred at −78 °C for 1 h (A). In another 500 mL flask, 25 (15.0 g, 36.1 mmol, 1.00 equiv.) was dissolved in THF (120 mL). The flask was cooled to −78 °C and 1.6 M t-BuLi solution in pentane (44.6 mL, 75.8 mmol, 2.10 equiv.) was added drop-wise over 10 min. The mixture was stirred at −78 °C for 1 h (B). B was cannulated to A over 15 min at −78 °C. An additional 5 mL of THF was used to rinse the reaction vessel. The combined reaction mixture was slowly warmed to 0 °C and vigorously stirred for 2 h. At this time, bromine (3.72 mL, 72.2 mmol, 2.00 equiv.) was added drop-wise over 5 min, then the reaction mixture was stirred for 30 min. Then, the mixture was quenched with saturated Na₂SO₃ (aq.) solution until the red color of bromine disappeared. The aqueous phase was extracted with Et₂O (100 mL × 3) and the combined organic phases were dried over anhydrous MgSO₄. After concentration, the crude product was purified by silica gel chromatography (EtOAc:hexanes=0/1 to 1/20 to 1/15) to provide triaryl 26 as a white solid (11.6 g, 65%). Melting Point: 51-54 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.24 (s, 1H), 7.16-7.22 (m, 4H), 6.89 (dd, J = 9, 1 Hz, 1H), 6.86 (dd, J = 9, 1 Hz, 1H), 3.90 (d, J = 1 Hz, 3H), 3.70 (d, J = 1 Hz, 3H), 2.67-2.77 (m, 3H), 2.58 (septet, J = 7 Hz, 1H), 2.41 (septet, J = 6 Hz, 1H), 1.71 (pentet, J = 8 Hz, 2H), 1.44 (sextet, J = 7 Hz, 2H), 1.23 (d, J = 7 Hz, 3H), 1.11-1.16 (m, 6H), 1.08 (d, J = 7 Hz, 3H), 0.99 (t, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H), 0.76 (d, J = 7 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 152.8, 150.4, 147.5, 145.7, 142.5, 140.9, 138.9, 138.0, 133.7, 133.1, 131.5, 131.0, 127.1, 119.6, 116.7, 114.8, 110.2, 109.0, 56.7, 55.5, 35.6, 33.9, 32.8, 31.8, 31.0, 29.9, 24.8, 14.4, 14.0, 22.9, 22.9, 22.7, 14.3, 14.2 ppm. IR (neat): 2958, 2929, 2867,
1461, 1432, 1409, 1360, 1260, 1240, 1090, 1038, 883, 841, 793, 709 \text{ cm}^{-1}. \text{ Anal. Calcd. for } \text{C}_{33}\text{H}_{43}\text{O}_2\text{Br}: \text{C}, 71.86, \text{H}, 7.86; \text{found } \text{C}, 71.37, \text{H}, 7.80.

A 100 mL Schlenk tube was charged a solution of 26 (3.28 g, 5.95 mmol, 1.00 equiv.) in THF (20 mL). To the solution was added 1.6 M solution of t-BuLi in pentane (7.35 mL, 12.5 mmol, 2.10 equiv.) at \(-78^\circ\text{C}\) over 10 min. After 1 h, the septum was replaced with a Teflon stopper under a flow of argon, and the pentane from the t-BuLi solution was removed under vacuum. When the solvent level reached 2/3 of the initial volume, the Schlenk flask was back-filled with argon and CuCl (648 mg, 6.55 mmol, 1.10 equiv.) was added under a flow of argon. After addition of CuCl, the flask was sealed with a rubber septum and slowly warmed to room temperature over 30 min. Then, a solution of di(1-adamantyl)chlorophosphine (2.20 g, 6.55 mmol, 1.10 equiv.) in 20 mL of toluene was cannulated to the reaction mixture. An additional 5 mL of toluene was used to rinse the reaction vessel. The rubber septum was replaced with a Teflon stopper under a flow of argon and the reaction system was heated to 140 °C in an oil bath. The mixture was vigorously stirred for 48 h. At this time, the flask was cooled to room temperature and diluted with water (50 mL) and EtOAc (300 mL), and the layers were separated. The organic phase was washed with 10% NH₄OH (aq.) (50 mL × 5), and brine (20 mL), successively. The combined aqueous phases were extracted with additional EtOAc (100 mL). The combined organic phases were dried over anhydrous MgSO₄ and filtered. After
concentration, the crude product was filtered through a 5 cm pad of alumina (diameter = 6 cm) eluting with hexanes to 1:10 mixture of EtOAc/hexanes. This process removes most of polar byproducts. The collected material was concentrated and dried under vacuum. To the crude product was added 20 mL of MeOH and the flask was sonicated until a white powder precipitated. The powder was filtered and the filter cake was rinsed with MeOH (5 mL). This process removes most of triaryl compounds that do not contain a diadamantylphosphine group. The filter cake was over 90% pure by \(^1\)H and \(^{31}\)P NMR.

To obtain pure crystalline \(\text{L2}\), the white powder was recrystallized from EtOAc/MeOH. First crop: 1.31 g. Second crop: 0.86 g. Third crop: 0.30 g (combined 2.47 g, 54%). The final filtrate contained approximately 0.22 g of crude product. Melting Point: 237 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.08-7.18 (m, 4H), 7.06 (s, 1H), 6.85 (d, \(J = 9\) Hz, 1H), 6.80 (d, \(J = 9\) Hz, 1H), 3.80 (s, 3H), 3.58 (s, 3H), 2.63-2.73 (m, 3H), 2.48 (pentet, \(J = 7\) Hz, 1H), 2.39 (pentet, \(J = 7\) Hz, 1H), 1.80-1.91 (m, 18H), 1.58-1.70 (m, 15H), 1.38 (sextet, \(J = 7\) Hz, 2H), 1.22 (d, \(J = 7\) Hz, 3H), 1.04-1.10 (m, 6H), 0.92-0.98 (m, 5H), 0.88 (d, \(J = 7\) Hz, 3H), 0.49 (d, \(J = 7\) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 156.2, 152.9, 152.8, 146.9, 146.6, 143.5, 142.5, 142.2, 140.9, 139.9, 137.1, 134.4, 132.6, 131.2, 127.1, 126.0, 125.6, 118.9, 110.8, 107.9, 54.4, 42.5, 52.4, 42.4, 42.3, 39.4, 39.1, 38.9, 37.6, 35.9, 34.2, 33.3, 31.8, 29.8, 29.7, 29.7, 29.7, 26.1, 25.2, 24.8, 24.6, 24.5, 24.1, 23.0, 14.5 ppm (observed complexity is due to C-P coupling). \(^{31}\)P NMR (121 MHz, CDCl\(_3\)): \(\delta\) 37.8 ppm.

IR (neat): 2900, 2869, 2848, 1742, 1583, 1456, 1425, 1354, 1298, 1249, 1146, 1088, 1045, 970, 885, 843, 798, 775, 720 cm\(^{-1}\). Anal. Calcd. for C\(_{53}\)H\(_{73}\)O\(_2\)P: C, 82.34, H, 9.52; found C, 82.37, H, 9.68.
General Procedure A. Synthesis of di-adamantyl ligands. A flame-dried Schlenk tube equipped with a stir bar was charged with the appropriate aryl halide (1.00 eq.), evacuated, and backfilled with argon. The cap was removed, and the tube was fitted with a septum. Anhydrous toluene (10-15 mL/mmol) was added. The tube was cooled to $-78^\circ$C and tBuLi (1.7 M in pentane, 2.20 eq.) was added dropwise, and the reaction mixture was allowed to stir at $-78^\circ$C for 30 min. At this time, the septum was removed, and CuCl (1.00 eq., weighed out in a nitrogen-filled glovebox) and Ad$_2$PCl (1.10 eq., weighed out in a nitrogen-filled glovebox) were added under a stream of argon. The reaction mixture was allowed to warm to room temperature, at which time the septum was exchanged for a screw-cap and the tube was placed in an oil bath that had been pre-heated to $140^\circ$C and allowed to stir for 24-48 h. The reaction mixture was allowed to cool to room temperature, and diluted with EtOAc and a 1:1 mixture of saturated aq. NH$_4$OH and brine. The phases were separated, and the aqueous phase was further extracted with EtOAc. The combined organic phases were alternately washed with saturated aq. NH$_4$OH and brine until the aqueous phase was no longer blue. At this point, the organic phase was washed one more time with brine, dried over MgSO$_4$, filtered, and concentrated. The resulting material was purified as described to provide the desired ligand.

![Diagram](image)

This compound was prepared according to General Procedure A. Thus, 2-iodo-2',4',6'-triisopropyl-3-methoxy-1,1'-biphenyl (655 mg, 1.50 mmol, 1.00 eq.), tBuLi (1.7 M in pentane, 1.94 mL, 3.30 mmol, 2.20 eq.), CuCl (149 mg, 1.50 mmol, 1.00 eq.), Ad$_2$PCl (556 mg, 1.65 mmol, 1.10 eq.), and toluene (20 mL) were combined and allowed to stir at $140^\circ$C for 24
h. Purification of the crude reaction mixture by recrystallization from hot EtOAc/MeOH afforded di(adamantan-1-yl)(2',4',6'-triisopropyl-3-methoxy-[1,1'-biphenyl]-2-yl)phosphine (269 mg, 29%) as a fluffy white solid. Melting Point: 224 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 7.30 (pt, $J = 8$ Hz, 1H), 7.01 (s, 2H), 6.91 (d, $J = 8$ Hz, 1H), 6.72 (dd, $J = 8, 4$ Hz, 1H), 3.87 (s, 3H), 2.95 (septet, $J = 7$ Hz, 1H), 2.58 (septet, $J = 7$ Hz, 2H), 1.83-1.99 (m, 18H), 1.61-1.74 (bs, 12H) 1.33 (d, $J = 7$ Hz, 6H), 1.22 (d, $J = 7$ Hz, 6H), 0.92 (d, $J = 7$ Hz, 6H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 162.2, 152.0, 151.7, 149.4, 147.7, 146.7, 129.3, 126.3, 126.3, 120.8, 108.8, 54.2, 42.5, 42.4, 39.3, 39.1, 37.4, 34.4, 31.1, 31.1, 29.8, 29.8, 26.5, 24.2, 23.1 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): $\delta$ 35.8 ppm. IR: 3052, 2881, 1456, 1427, 1335, 1194, 1071, 1028, 937, 825, 755, 741, 723, 685 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{42}$H$_{60}$OP (M+H$^+$): 611.4376; found: 611.4356.

An oven-dried screw-cap reaction tube equipped with a stir bar was charged with Mg shavings (60.0 mg, 2.50 mmol, 2.50 eq.). The tube was flame-dried under vacuum with vigorous stirring of the Mg shavings. The tube was allowed to cool to room temperature and back-filled with argon. 1-bromo-2,4,6-triisopropylbenzene (253 μL, 1.00 mmol, 1.00 eq.) and THF (4.0 mL) were added, followed by 1 drop of 1,2-dibromoethane. The septum was replaced with one that had not been punctured, and the reaction tube was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir for 1.5 h. The reaction tube was cooled to room temperature, and 1-bromo-2-chlorobenzene (129 mL, 1.10 mmol, 1.10 eq.) was carefully added dropwise via syringe. The septum was replaced with one
that had not been punctured, and the reaction tube was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir for 2 h. The reaction tube was cooled to room temperature. Under a stream of argon, CuCl (99.0 mg, 1.00 mmol, 1.00 eq., weighed out in a nitrogen-filled glovebox) and Ad$_2$PCl (421 mg, 1.25 mmol, 1.25 eq., weighed out in a nitrogen-filled glovebox) were added. The septum was replaced with one that had not been punctured, and the reaction tube was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir for 48 h. The reaction mixture was allowed to cool to room temperature, and diluted with EtOAc (10 mL and a 1:1 mixture of saturated $aq.$ NH$_4$OH (10 mL) and brine (10 mL). The phases were separated, and the aqueous phase was further extracted with EtOAc (2 x 20 mL). The combined organic phases were alternately washed with saturated $aq.$ NH$_4$OH and brine until the aqueous phase was no longer blue. At this point, the organic phase was washed one more time with brine (20 mL), dried over MgSO$_4$, filtered, and concentrated. The resulting material was triturated with hot EtOAc/MeOH to afford di(adamantan-1-yl)(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (131 mg, 23%) as a white solid. Melting Point: 200-205 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.87-7.91 (m, 1H), 7.31-7.37 (m, 2H), 7.16 (dd, J = 10, 4 Hz, 1H), 7.02 (s, 2H), 2.94 (septet, J = 7 Hz, 1H), 2.52 (septet, J = 7 Hz, 2H), 1.86-1.94 (m, 17H), 1.67 (bs, 13H), 1.32 (d, J = 7 Hz, 6H), 1.19 (d, J = 7 Hz, 6H), 0.93 (d, J = 7 Hz, 6H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 151.3, 148.0, 147.0, 137.8, 133.0, 128.0, 125.4, 120.8, 100.2, 42.1, 42.0, 38.1, 37.9, 37.3, 37.3, 34.5, 31.2, 29.5, 29.4, 26.5, 24.2, 22.9 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): δ 24.8 ppm. IR: 2901, 2445, 1453, 1342, 1301, 873, 782, 766, 751 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{41}$H$_{58}$P (M+H$^+$): 581.4274; found: 581.4279
A flame-dried 100 mL roundbottom flask equipped with a stir bar was charged with 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl,\textsuperscript{44} evacuated, and backfilled with argon. Anhydrous CH\textsubscript{2}Cl\textsubscript{2} (30 mL) was added, and the flask was cooled to \(-78^\circ\text{C}\). BBr\textsubscript{3} (1M in CH\textsubscript{2}Cl\textsubscript{2}, 11 mL, 11 mmol, 1.1 eq.) was added dropwise, and the reaction mixture was allowed to slowly warm to room temperature and stir for 12 h. The flask was cooled to 0 \(^\circ\text{C}\) and \textit{carefully} quenched with saturated \textit{aq.} NH\textsubscript{4}Cl (50 mL). The phases were separated, and the aqueous phase was further extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO\textsubscript{4}, filtered, and concentrated, to afford 2-iodo-2',4',6'-triisopropyl-6-methoxy-[1,1'-biphenyl]-3-ol (4.37 g, 97\%) as pale orange solid. Melting Point: 199 \(^\circ\text{C}\). \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{2}Cl\textsubscript{2}): \(\delta\) 7.10 (s, 2H), 7.02 (d, \(J = 9\) Hz, 1H), 6.93 (d, \(J = 9\) Hz, 1H), 5.17 (s, 1H), 3.69 (s, 3H), 2.98 (septet, \(J = 7\) Hz, 1H), 2.40 (septet, \(J = 7\) Hz, 2H), 1.34 (d, \(J = 7\) Hz, 6H), 1.18 (d, \(J = 7\) Hz, 6H), 1.01 (d, \(J = 7\) Hz, 6H) ppm; \textsuperscript{13}C NMR (125 MHz, CD\textsubscript{2}Cl\textsubscript{2}): \(\delta\) 152.0, 149.5, 149.0, 146.5, 136.6, 134.5, 121.4, 113.3, 112.0, 96.5, 56.0, 34.6, 31.3, 24.7, 24.2, 23.8 ppm. IR: 3481, 2958, 2898, 1457, 1434, 1415, 1380, 1358, 1254, 1190, 1173, 1026, 875, 801, 758, 712 cm\(^{-1}\). Anal. Calcd. for C\textsubscript{22}H\textsubscript{29}I\textsubscript{2}O\textsubscript{2}: C, 58.41; H, 6.46; found: C, 58.68, H, 6.47.

A flame-dried 50 mL roundbottom flask equipped with a stir bar was charged with 2-iodo-2',4',6'-triisopropyl-6-methoxy-[1,1'-biphenyl]-3-ol (2.0 g, 4.40 mmol, 1.00 eq.). The flask was placed under vacuum and backfilled with nitrogen. Anhydrous DMF (10 mL) was added, followed by K\textsubscript{2}CO\textsubscript{3} (1.22 g, 8.80 mmol, 2.00 eq.) under a stream of nitrogen. The
reaction mixture was allowed to stir vigorously for 5 min., at which time 2-bromopropane (1.24 mL, 13.2 mmol, 3.00 eq.) was added. The reaction mixture was placed in an oil-bath that had been pre-heated to 80 °C and allowed to stir vigorously overnight. The reaction mixture was cooled to room temperature, and diluted with ether (20 mL) and saturated \( \text{aq. NaHCO}_3 \) (20 mL). The phases were separated, and the aqueous phase was further extracted with ether (2 x 20 mL). The combined organic phases were washed with saturated \( \text{aq. NaHCO}_3 \) (20 mL), water (20 mL), and brine (20 mL), dried over MgSO\(_4\), filtered, and concentrated. The resulting solid was purified by flash chromatography (10% Et\(_2\)O/hexanes) to afford 2-iodo-3-isopropoxy-2',4',6'-triisopropyl-6-methoxy-1,1'-biphenyl (1.57 g, 72%) as a white solid. Melting Point: 134-136 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.05 (s, 2H), 6.86 (s, 2H), 4.49 (septet, \( J = 6 \) Hz, 1H), 3.66 (s, 3H), 2.94 (septet, \( J = 7 \) Hz, 1H), 2.39 (septet, \( J = 7 \) Hz, 2H), 1.42 (d, \( J = 6 \) Hz, 6H), 1.32 (d, \( J = 7 \) Hz, 6H), 1.19 (d, \( J = 7 \) Hz, 6H), 1.01 (d, \( J = 7 \) Hz, 6H) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 152.7, 151.3, 148.2, 145.8, 136.2, 136.0, 120.8, 114.7, 110.2, 100.3, 73.7, 55.7, 34.2, 31.0, 24.7, 24.2, 23.8, 22.4 ppm. IR: 2957, 2864, 1568, 1457, 1432, 1380, 1256, 1236, 1108, 1064, 1052, 1030, 970, 951, 874, 834, 811, 790, 759, 654 cm\(^{-1}\).

Anal. Calcd. for \( \text{C}_{25}\text{H}_{35}\text{I}_{2}\text{O}_2 \): C, 60.73; H, 7.13; found: C, 60.93, H, 7.20.

This compound was prepared according to General Procedure A. Thus, 2-ido-3-isopropoxy-2',4',6'-triisopropyl-6-methoxy-1,1'-biphenyl (540 mg, 1.00 mmol, 1.00 eq.), tBuLi (1.7 M in pentane, 1.29 mL, 2.20 mmol, 2.20 eq.), CuCl (99.0 mg, 1.00 mmol, 1.00 eq.), \( \text{Ad}_3\text{PCl} \) (371 mg, 1.10 mmol, 1.10 eq.), and toluene (8 mL) were combined and allowed
to stir at 140 °C for 24 h. Purification of the crude reaction mixture by recrystallization from hot EtOAc/MeOH afforded di(adamantan-1-yl)(3-isopropoxy-2',4',6'-triisopropyl-6-methoxy-[1,1'-biphenyl]-2-yl)phosphine (115 mg, 17%) as a white solid. Melting Point: 221-224 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 7.00 (s, 2H), 6.84-6.92 (m, 2H), 4.72 (septet, $J = 6$ Hz, 1H), 3.53 (s, 3H), 2.97 (septet, $J = 7$ Hz, 1H), 2.50 (septet, $J = 7$ Hz, 2H), 2.02 (d, $J = 11$ Hz, 6H), 1.91 (d, $J = 11$ Hz, 6H), 1.86 (bs, 6H), 1.70 (d, $J = 12$ Hz, 6 Hz), 1.64 (d, $J = 13$ Hz, 6H), 1.52 (d, $J = 6$ Hz, 6H), 1.35 (d, $J = 7$ Hz, 6H), 1.21 (d, $J = 7$ Hz, 6H), 0.89 (d, $J = 7$ Hz, 6H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): $\delta$ 154.7, 151.8, 151.7, 147.4, 147.4, 147.1, 141.1, 140.8, 134.6, 134.5, 125.9, 125.6, 120.6, 111.5, 109.8, 54.5, 42.7, 42.6, 39.1, 38.9, 37.4, 34.2, 31.4, 29.8, 29.7, 25.6, 24.1, 23.9, 22.3 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): $\delta$ 36.4 ppm.

IR: 2899, 2844, 1447, 1427, 1245, 1115, 1040, 962, 871, 796, 758, 723 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{45}$H$_{66}$O$_2$P (M+H$^+$): 669.4795; found: 669.4786.

This compound was prepared according to General Procedure A. Thus, 2',4',6'-tri-tert-butyl-2-iodo-3,6-dimethoxy-1,1'-biphenyl $^4$ (382 mg, 0.75 mmol, 1.00 eq.), tBuLi (1.7 M in pentane, 0.97 mL, 1.65 mmol, 2.20 eq.), CuCl (74.3 mg, 0.75 mmol, 1.00 eq.), Ad$_2$PCl (278 mg, 0.83 mmol, 1.10 eq.), and toluene (8 mL) were combined and allowed to stir at 140 °C for 24 h. Purification of the crude reaction mixture by trituration with cold methanol afforded di-(adamantan-1-yl)(2',4',6'-tri-tert-butyl-3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (267 mg, 52%) as a fluffy white solid. Melting Point: 227-231 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta$ 7.35 (s, 2H), 6.81 (d, $J = 9$ Hz, 1H), 6.72 (d, $J = 9$ Hz, 1H), 3.79 (s, 3H), 3.70
(s, 3H), 1.78-1.88 (m, 18H), 1.62 (bs, 12H), 1.34 (s, 9H), 1.12 (s, 18H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 157.0, 1570, 154.5, 154.4, 151.3, 148.0, 147.8, 147.7, 144.8, 144.6, 131.6, 131.5, 128.4, 128.0, 123.1, 110.3, 110.2, 108.2, 54.6, 54.2, 42.0, 41.9, 39.9, 39.6, 39.2, 37.4, 34.9, 33.8, 33.8, 33.1, 31.5, 29.9, 29.8 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): δ 40.2 ppm (additional signals were detected at 39.6, 38.4, and 37.7 ppm; these could be due to impurities or rotoisomeric species).

IR: 2959, 2899, 2847, 1458, 1419, 1249, 1173, 1086, 1040, 1018, 873, 794, 741, 707 cm$^{-1}$

HRMS (ESI) m/z calcd. for C$_{46}$H$_{68}$O$_2$P (M+H$^+$): 683.4951; found: 683.4944.

A flame-dried 100 mL round-bottom flask equipped with a stir bar was charged with 2-fluoro-1,4-dimethoxybenzene (659 μL, 5.00 mmol, 1.00 eq.) and THF (25 mL) under argon. The reaction mixture was cooled to −78 °C, and nBuLi (2.5M in hexanes, 2.20 mL, 5.50 mmol, 1.10 eq.) was added dropwise. The reaction mixture was allowed to stir at −78 °C for 1 h. At this time, phenylmagnesium bromide (3M in ether, 3.33 mL, 10.0 mmol, 2.00 eq.) was added dropwise, and the reaction mixture was allowed to warm to room temperature and stir for 12 h. The reaction mixture was cooled to 0 °C, and Br$_2$ (516 μL, 10.0 mmol, 2.00 eq.) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 30 min., and then was quenched carefully with saturated aq. Na$_2$SO$_3$ (30 mL) and ether (30 mL). The phases were separated, and the aqueous phase was further extracted with ether (2 x 30 mL). The combined organic phases were washed with saturated aq. Na$_2$SO$_3$ (30 mL) and brine (30 mL), dried over MgSO$_4$, filtered, and concentrated. The resulting oil was triturated with cold hexanes (5 mL), which resulted in precipitation of a brown solid from
solution. The solid was filtered and washed with cold hexanes (2 x 5 mL). The resulting brown solid was ~95% pure by $^1$H NMR. This brown solid was triturated with cold EtOAc (5 mL), filtered, and washed with cold EtOAc (2 x 3 mL), to afford 2-bromo-3,6-dimethoxy-1,1'-biphenyl (528 mg, 36%) as an off-white solid. Melting Point: 123-126 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.47 (pt, J = 8 Hz, 2H), 7.41 (t, J = 7 Hz, 1H), 7.27 (d, J = 7 Hz, 2H), 3.92 (s, 3H), 3.69 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 152.0, 150.6, 137.7, 133.8, 130.1, 128.0, 127.6, 114.9, 111.2, 110.6, 57.0, 56.6 ppm. IR: 2900, 2836, 1571, 1471, 1428, 1251, 1092, 1029, 1014, 793, 756, 712, 699 cm$^{-1}$. Anal. Caled. for C$_{14}$H$_{13}$BrO$_2$: C, 57.36; H, 4.47; found: C, 57.56, H, 4.44.

OMe

This compound was prepared according to General Procedure A. Thus, 2-bromo-3,6-dimethoxy-1,1'-biphenyl (293 mg, 1.00 mmol, 1.00 eq.), tBuLi (1.7 M in pentane, 1.29 mL, 2.20 mmol, 2.20 eq.), CuCl (99.0 mg, 1.00 mmol, 1.00 eq.), Ad$_2$PCl (371 mg, 1.10 mmol, 1.10 eq.), and toluene (8 mL) were combined and allowed to stir at 140 °C for 24 h. Purification of the crude reaction mixture by recrystallization from hot EtOAc/MeOH afforded di(adamantan-1-yl)(3,6-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (119 mg, 23%) as a white solid. Melting Point: 194-196 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.25-7.35 (m, 3H), 7.05 (d, J = 7 Hz, 2H), 6.97 (d, J = 9 Hz, 1H), 6.88 (d, J = 9 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 1.75-1.93 (m, 18H), 1.66 (s, 12H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 156.1, 156.1, 151.7, 140.9, 140.8, 132.0, 132.0, 127.2, 126.0, 124.6, 124.3, 113.2, 109.0, 56.5, 54.3, 42.6, 42.5, 38.3, 38.1, 37.4, 29.7, 29.7 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): δ 33.2 ppm. IR: 2901, 2873, 2845, 1582, 1453, 1426, 1344, 1299,
1241, 1176, 1155, 1100, 1046, 1020, 843, 790, 769, 747, 718, 701 cm⁻¹. Anal. Calcd. for C₃₄H₄₃O₂P: C, 79.34; H, 8.42; found: C, 79.05; H, 8.54.

In a nitrogen-filled glovebox, an oven-dried reaction tube equipped with a stir bar was charged with LiCl (151 mg, 3.60 mmol, 1.20 eq.). The tube was capped, removed from the glovebox, and an inlet of argon was added. Under a stream of argon, Mg shavings (108 mg, 4.50 mmol, 1.50 eq.) were added, followed by THF (0.5 mL). The resulting slurry was allowed to stir for 5 min. Meanwhile, a separate oven-dried reaction tube was charged with 3-bromo-4'-butyl-2,4,6-triisopropyl-1,1'-biphenyl (1.50 g, 3.60 mmol, 1.20 eq.), evacuated, and backfilled with argon. THF (5.0 mL) was added, and the resulting solution was added dropwise to the previously prepared slurry of Mg and LiCl. The cap of the reaction tube was replaced with one that had not been punctured, and the reaction mixture was placed in an oil bath that had been pre-heated to 80 °C and allowed to stir vigorously for 1.5 h. Meanwhile, to a separate flame-dried 100 mL roundbottom flask was added 2-fluoro-1,4-dimethoxybenzene (421 mg, 3.00 mmol, 1.00 eq.) and THF (15 mL) under argon. This reaction mixture was cooled to −78 °C, and nBuLi (2.5 M in hexanes, 1.32 mL, 3.30 mmol, 1.10 eq.) was added dropwise. This reaction mixture was allowed to stir at −78 °C for 1 h. At this time, the previously prepared Gringard reagent, which had been cooled to room temperature, was added dropwise to the second solution via cannula at −78 °C. The combined reaction mixture was allowed to warm to room temperature and stir for 12 h. The reaction mixture was cooled to 0 °C, and Br₂ (309 μL, 6.00 mmol, 2.00 eq.) was
added dropwise. The reaction mixture was allowed to stir at 0 °C for 30 min., at which time it was carefully quenched with saturated aq. Na$_2$SO$_3$ (30 mL) and ether (30 mL). The phases were separated, and the aqueous phase was further extracted with ether (2 x 30 mL). The combined organic phases were washed with saturated aq. Na$_2$SO$_3$ (30 mL) and brine (30 mL), dried over MgSO$_4$, and concentrated, to afford an oil. This oil was purified by flash chromatography (3% EtOAc/hexanes) to afford 2-bromo-4''-butyl-2',4',6'-triisopropyl-3-methoxy-6-methyl-1,1':3',1''-terphenyl (800 mg, 50%) as an off-white solid. Melting Point: 123-125 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.22 (s, 1H), 7.09-7.18 (m, 4H), 6.82 (d, J = 9 Hz, 1H), 3.93 (s, 3H), 2.60-2.69 (m, 3H), 2.52 (septet, J = 7 Hz, 1H), 2.32 (septet, J = 7 Hz, 1H), 2.02 (s, 3H), 1.67 (pentet, J = 8 Hz, 2H), 1.40 (sextet, J = 8 Hz, 2H), 1.18 (d, J = 7 Hz, 3H), 1.06-1.10 (m, 9H), 0.96 (t, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H), 0.73 (d, J = 8 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 154.3, 147.9, 144.9, 144.0, 141.8, 141.0, 138.5, 138.4, 135.9, 131.6, 131.4, 131.0, 129.0, 127.0, 126.9, 120.1, 115.2, 110.0, 56.4, 35.6, 33.8, 32.6, 32.2, 30.9, 29.6, 24.8, 24.6, 24.6, 24.5, 23.4, 23.3, 22.6, 21.0, 14.2 ppm. IR: 2955, 2928, 2870, 1463, 1359, 1297, 1278, 1250, 1085, 1027, 888, 839, 796, 782, 757, 724 cm$^{-1}$. Anal. Calcd. for C$_{33}$H$_{43}$BrO: C, 74.00; H, 8.09; found: C, 74.29, H, 8.25.

Following General Procedure A, 2-bromo-4''-butyl-2',4',6'-triisopropyl-3-methoxy-6-methyl-1,1':3',1''-terphenyl (300 mg, 0.56 mmol, 1.00 eq.), iBuLi (1.7 M in pentane, 0.72 mL, 1.23 mmol, 2.20 eq.), CuCl (55.4 mg, 0.56 mmol, 1.00 eq.), Ad$_2$PCl (207 mg, 0.62 mmol, 1.10 eq.), and toluene (6.0 mL) were combined and allowed to stir...
at 140 °C for 48 h. Purification of the crude reaction mixture by trituration with cold methanol (with sonication) afforded di(adamantan-1-yl)(4"-butyl-2',4',6'-triisopropyl-3-methoxy-6-methyl-[1,1':3',1"-terphenyl]-2-yl)phosphine (250 mg, 59%) as a white solid. Melting Point: 182-185 °C. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.19-7.25 (m, 3H), 7.16 (d, J = 9 Hz, 2H), 7.07 (d, J = 7 Hz, 1H), 6.84 (d, J = 9 Hz, 1H), 3.84 (s, 3H), 2.76 (septet, J = 8 Hz, 1H), 2.67 (t, J = 8 Hz, 2H), 2.46-2.58 (m, 2H), 1.92-2.03 (m, 12H), 1.83-1.91 (m, 6H), 1.59-1.80 (m, 17H), 1.39 (sextet, J = 8 Hz, 2H), 1.26 (d, J = 7 Hz, 3H), 1.17 (d, J = 7 Hz, 3H), 1.02 (d, J = 7 Hz, 3H), 0.93-0.98 (m, 6H), 0.79 (d, J = 7 Hz, 3H), 0.60 (d, J = 8 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 160.5, 160.5, 151.3, 147.6, 145.9, 142.9, 141.4, 139.1, 138.9, 132.8, 132.3, 131.8, 127.2, 127.1, 120.5, 108.6, 42.8, 42.7, 42.6, 40.0, 40.0, 39.8, 39.7, 37.5, 37.4, 35.8, 34.2, 32.8, 31.4, 30.0, 29.9, 29.9, 29.9, 29.7, 25.8, 25.4, 25.2, 24.7, 24.2, 23.5, 22.8, 22.7, 22.7, 14.2 ppm (observed complexity is due to C–P coupling); $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): δ 39.8 ppm. IR: 2959, 2900, 2845, 1560, 1452, 1422, 1359, 1289, 1265, 1245, 1087, 1052, 1027, 972, 887, 839, 802 cm$^{-1}$. Anal. Calcd. for C$_{53}$H$_{73}$OP: C, 84.08; H, 9.72; found: C, 83.78, H, 9.85.

4.7.7. Preparation of Pd complexes.

27 was prepared in a manner identical to that described in Chapter 3 for the preparation of Pd(0) precatalysts. In a nitrogen-filled glovebox, an oven-dried 20 mL vial was charged with L2 (773 mg, 1.00 mmol, 1.00 equiv.) and [(COD)Pd(CH$_2$TMS)$_2$] (389 mg, 1.00 mmol, 1.00 equiv.). The mixture was suspended in 15 mL of pentane, and vigorously stirred for 48 h at ambient temperature. Upon completion of the reaction, the heterogeneous mixture was filtered over a fine sintered glass filter and the filter cake was

484
washed with pentane (5 mL), yielding 27 as a beige solid (740 mg, 79%). 27 is insoluble in all organic solvents that have been tested to date. All other Pd(0) precatalysts described in this Chapter were prepared using the same procedure and were similarly insoluble in all tested organic solvents.

**Reaction of 27 with 4-\((nBu)\text{PhBr}\).**

In a nitrogen-filled glovebox, a vial was charged with 27 (11 mg, 0.0059 mmol, 1.0 equiv.) and 0.50 mL of toluene-d8. To the suspension was added 1-bromo-4-nbutylbenzene (10 μL, 0.057 mmol, 9.6 equiv.), and the mixture was vigorously stirred for 1 min, during which time it became homogeneous and yellow in color. The reaction mixture was transferred to an NMR tube and analyzed by \(^1\)H NMR. \(^1\)H NMR integration showed that the mixture contained 2:1 ratio of L2•Pd(4-(nBu)Ph)Br (synthesis of authentic sample described below) and 1,5-cyclooctadiene.

This procedure is adapted from Chapter 1. In a nitrogen-filled glovebox, L1•Pd(4-(nBu)Ph)Br (96.0 mg, 0.100 mmol, 1.00 equiv.), was dissolved in THF (5.0 mL). To the solution was added 1-bromo-4-nbutyl benzene (52.9 μL, 0.300 mmol, 3.00 equiv.), followed by 1,8-diazabicyclounde-7-ene (17.9 μL, 0.120 mmol, 1.20 equiv.). After addition, the reaction mixture turned bright yellow. The heterogeneous mixture was

485
vigorously stirred for 12 h. At the end of the reaction, the solvent was removed under reduced pressure. To the crude product was added 2 mL of Et₂O, and the volatiles were evaporated. This process was repeated a total of three times, during which, a bright yellow solid precipitated. The crude product was filtered through a fine fritted glass filter and the filter cake was washed with pentane (2 mL × 3). The product was isolated as a bright yellow solid (89 mg, 81%). ¹H NMR (500 MHz, CD₂Cl₂): δ 7.72 (bs, 1H), 7.01-7.21 (m, 6H), 6.94 (d, J = 9 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 6.69 (d, J = 8 Hz, 2H), 3.83 (s, 3H), 3.37-3.48 (m, 4H), 2.92-3.05 (m, 1H), 2.66 (t, J = 8 Hz, 2H), 2.43-2.56 (m, 4H), 2.17-2.38 (m, 8H), 2.02-2.12 (m, 3H), 1.95 (s, 4H), 1.75-1.86 (m, 6H), 1.48-1.78 (m, 16H), 1.40 (sextet, J = 8 Hz, 2H), 1.23-1.33 (m, 5H), 0.99-1.07 (m, 5H), 0.96 (t, J = 8 Hz, 3H), 0.90 (t, J = 7 Hz, 3H), 0.80 (bs, 3H), 0.68 (bs, 3H) ppm; ¹³C NMR (125 MHz, CD₂Cl₂): δ 157.6, 154.5, 154.4, 152.3, 152.2, 141.5, 140.5, 139.4, 138.7, 136.5, 132.4, 131.8, 129.6, 127.2, 126.8, 126.6, 126.5, 126.3, 123.9, 118.9, 113.4, 113.3, 110.3, 54.7, 54.6, 47.8, 47.8, 47.5, 47.4, 42.0, 41.3, 38.3, 36.8, 36.6, 35.8, 34.9, 34.5, 34.4, 34.2, 33.3, 32.5, 31.6, 30.3, 30.1, 30.5, 30.0, 29.4, 27.2, 26.0, 25.7, 25.4, 25.3, 27.8, 22.8, 22.7, 22.6, 19.9, 14.2, 14.1 ppm (observed complexity is due to C-P coupling); ³¹P NMR (121 MHz, CD₂Cl₂): δ 67.8 ppm (minor peaks were observed at δ 70.0 and 67.6 ppm).
4.8. References.


6 An extensive screen of commercially available MF₄ and R₄NF sources was undertaken to promote the fluorination of 2-Br with catalytic amounts of 1, but none afforded detectable amounts of 2 (not shown).


9 Other sources of the active catalyst were also evaluated; we found that precatalyst 1 is the most effective Pd source. See Table 4.7 in the experimental.

10 0.5 equivalents was identified to be optimal loading of KF. See Table 4.8 in the experimental.

11 Likewise, other insoluble fluoride salts such as LiF, MgF₂, CaF₂, and CuF₂, did not promote this reaction.

12 Other potentially nucleophilic or coordinating additives, such as PhSMe, 1,4-dithiane, 1,4-dioxane, TMEDA, MeCN, DMA, and 18-crown-6, were not effective.


17 Similar to 1, precatalyst 27 is insoluble in most organic solvents. Therefore, spectroscopic characterization was not possible. However, it readily forms the oxidative addition complex L₂-Pd(4-(nBu)Ph)Br and 1,5-COD upon exposure to 4-(nBu)PhBr. See Experimental for details.


19 A similar investigation was carried out using the corresponding aryl triflate and CsF as the fluoride source. See Table 4.8 in the experimental.

2 The use of other Pd sources, such as Pdₐdbaₐ species and Pd(OAc)₂, in conjunction with L8, provided no product.
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1\text{H NMR, 500 MHz, CDCl}_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^\text{13}C$ NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}C$ NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{\textsuperscript{1}H NMR, 500 MHz, CDCl}_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR. 125 MHz. CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
OMe
MeO
Br
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
\( \mu \text{Pr} \)
n-Bu

\(^1\text{H NMR, 500 MHz, CDCl}_3\)
$^{13}$C NMR, 125 MHz, CDCl$_3$
1H NMR, 500 MHz, CDCl₃
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR. 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CD$_2$Cl$_2$
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$. 

[Chemical structure image]
$^{13}$C NMR, 125 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
n-Bu
Ad
n-flu
/\Meo
P-Pd-Br
i-Pr /&Pr
OMe

$^1$C NMR, 125 MHz, CD$_2$Cl$_2$
DISCLAIMER NOTICE

Due to the condition of the original material, there are unavoidable flaws in this reproduction. We have made every effort possible to provide you with the best copy available.

Thank you.

Despite pagination irregularities, this is the most complete copy available.

Pages 541-580 are not included due to pagination irregularities.
Chapter 5. Assessment of the Pd-Catalyzed Fluorination of 5-Membered Heteroaryl Bromides.
5.1. Introduction. Five-membered heterocycle-containing compounds are widely prevalent in active pharmaceuticals. For example, a number of top-selling drugs, including sitagliptin (Januvia), clopidogrel (Plavix), celecoxib (Celebrex), and tiotropium bromide (Spiriva), contain at least one 5-membered heterocycle (Figure 5.1). Additionally, a number of important biomolecules, such as serotonin, histidine, and thiamine, contain 5-membered heterocyclic cores (Figure 5.1). Thiophenes are also frequently employed as conducting organic materials and agrochemicals (not shown). The commonality of 5-membered heterocycles in so many areas of research is due to their enormous structural diversity and interesting biological, steric, and electronic properties.

Despite the independent importance of 5-membered heterocycles (Figure 5.1) and aryl fluorides (see Introduction), there is a surprising lack of 5-membered heteroaryl fluorides that have been prepared and studied. This is likely due to the limited methods available for the efficient preparation of 5-membered heteroaryl fluorides. The easiest
way to prepare these compounds is by heterocyclization reactions of fluorinated precursors.\(^8\) However, this approach is not generalizable and does not allow for late-stage fluorination of advanced intermediates, which is a key component of evaluating structure-activity relationships. As with 6-membered ring heteroaryl fluorides, the most general methods for the synthesis of 5-membered heteroaryl fluorides are the Balz-Schiemann and Halex reactions (examples are shown in Figure 5.2). However, the thermal or photochemical Balz-Schiemann reaction involves harsh reaction conditions, the intermediacy of potentially explosive diazonium salts, and low yields for many 5-membered heteroaryl fluorides.\(^9\) In addition, many 5-membered aminoheteroarenes, such as 4-aminoimidazoles, are unstable, and so in these cases the amine must be generated, diazotized, and irradiated in one pot, as shown in Figure 5.2A for the low-yielding synthesis of protected 4-fluorohistidine.\(^10\) In addition, as with 6-membered ring systems, the Halex reaction is limited to highly activated 5-membered heteroaryl halides (Figure 5.2B).\(^11\) Due to their electron-richness, 5-membered heterocycles can also be directly fluorinated with strongly oxidizing fluorinating agents such as \(\text{F}_2\) or \(\text{XeF}_2\), although these reactions do not tolerate many functional groups and typically produce complex mixtures of fluorinated regioisomers and starting material.\(^6\) A more controlled approach is to prepare organometallated species by lithium\(^{12}\) or magnesium/halogen exchange,\(^{13}\) or direct deprotonation,\(^{14}\) and then react these species with an electrophilic fluorinating agent such as \(\text{N-fluorobenzenesulfonylimide (NFSI)}\) (Figure 5.2C). While this method avoids the possibility of regioisomer formation in typical electrophilic fluorination reactions (assuming clean metallation takes place), it has poor functional group tolerance.
and usually provides mixtures of the desired product and the corresponding reduced heteroarene.

Unfortunately, extension of recently developed transition metal-mediated aryl fluorination methods to the synthesis of 5-membered heteroaryl fluorides has proven disappointing thus far. For example, Sanford's recent report of the Cu-catalyzed fluorination of diaryliodonium salts required harsh conditions and 1 eq. of Cu(OTf)₂ to produce only a modest yield of 2-fluorothiophene (Figure 2D). Similarly, recently developed methods for C–H fluorination of 6-membered heteroarenes and deoxyfluorination of phenols are explicitly incompatible with 5-membered heterocycle-containing substrates. Thus, there remains significant need for the development of a general, mild, and clean, method for the fluorination of 5-membered heterocycles.

We wondered if our success in the Pd-catalyzed fluorination of 6-membered heteroaryl bromides (Chapter 4) would translate to the fluorination of 5-membered heteroaryl bromides. Many of the properties that make 5-membered heterocycles fascinating substrates, including their size, coordinating ability, and electron-richness,
make the corresponding heteroaryl halides challenging substrates for Pd-catalyzed cross-coupling reactions. For example, previous stoichiometric and computational work in our lab suggests that C–N reductive elimination of 5-membered heteroaryl groups is more difficult than it is for 6-membered aryl groups. This is likely due both to the smaller size and increased electron-richness of 5-membered heteroarenes. Based on this analysis, our lab has found that very bulky ligands are needed to facilitate reductive elimination and, by extension, cross-coupling reactions of 5-membered heteroaryl halides. In addition, we and others have found that nitrogen-containing heterocycles can inhibit Pd-catalyzed reactions by coordinating to the Pd center, necessitating the use of high catalyst loadings and reaction temperatures in many cases. In all, 5-membered heteroaryl halides remain among the most challenging electrophiles for Pd-catalyzed cross-coupling processes. Herein, we describe our initial successes and failures regarding this challenging transformation and the first examples of the use of a Pd catalyst to prepare 5-membered heteroaryl fluorides. To do so, we systematically studied substituent effects on the 5-membered heterocycle to determine which substitution patterns, if any, would allow for Pd-catalyzed fluorination to occur.

5.2. Heterocycles containing one heteroatom (thiophenes, furans, pyrroles)

5.2.1. Bromothiophenes and Bromobenzothiophenes. We began our investigation with bromothiophenes, because they tend to be well-behaved in Pd-catalyzed cross-coupling reactions, are less electron-rich than most 5-membered heterocycles, lack potentially coordinating sp²-hybridized nitrogen atoms, and are synthetically tractable, with many methods available for their synthesis and functionalization. Pd-catalyzed fluorination reactions were conducted with the three ligands that have displayed acitivity
Figure 5.3. Ligands (L1-L3) and Pd(0) precatalysts (1-3) for the Pd-catalyzed fluorination of aryl bromides.

Table 5.1. Failed Pd-catalyzed fluorinations of simple 2- and 3-bromothiophenes.\(^a\)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Reaction</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4b (R = Me)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4c (R = OMe)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4d (R = CN)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4e (R = NO₂)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4f (R = SO₂NEt₂)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4h: R = Me: 0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4i: R = OMe: 0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4j: R = Ph: 0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>4k</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 0.10 mmol heteroaryl bromide, 0.20 mmol AgF, 0.05 mmol KF, 2% L-Pd (1,5-COD) precatalysts (1-3) as sources of the active catalyst (Figure 5.3). The results of our first efforts to prepare heteroaryl fluorides are summarized in Table 5.1. We quickly found that simple 2- and 3-bromothiophenes, unsubstituted (4a, 4g) or bearing a variety of electron-withdrawing (4b-4f, 4h-i) or other (4j-4k) substituents, were not converted to the corresponding aryl fluorides under the standard reaction conditions employed for the fluorination of 6-membered heteroaryl bromides. No change in ligand (L1-L3), solvent, additive (in place of KF), reaction temperature, or catalyst loading, could promote these transformations. Notably, in all cases primarily starting material was recovered, with trace amounts of reduction product (Ar-H) observed in some cases by GC/MS.
Based on our previous work in this area, we anticipated that C–F reductive elimination was the challenging step in these reactions. To investigate this possibility, L1-ligated oxidative addition complexes of 2-bromothiophene (5) and 2-bromo-5-acetylthiophene (6) were prepared using the standard procedure outlined in Chapter 1 (Figure 5.4). The structure of both complexes was confirmed by X-ray crystallography, indicating at the very least that oxidative addition of electron-rich 5-membered heteroaryl bromides is feasible at room temperature. Unfortunately, both complexes proved to be either poorly soluble (C₆D₆) or unstable for extended periods of time (CDCl₃, CD₂Cl₂, THF-d₈) in organic solvents, which precluded their complete characterization by solution-state NMR. The structures of 5 and 6 are very similar, indicating that, in contrast to our previous findings regarding the oxidative addition complexes of 6-membered aryl bromides (Chapter 1), the addition of an electron-withdrawing group on the thiophene ring does not have a significant impact on the structure of the oxidative addition complex. In addition, comparison of these solid-state structures to those previously reported for di-adamantyl biaryl phosphine-ligated oxidative addition complexes of or 4-(CN)PhBr (7)¹⁹ or 4-(nBu)PhBr (8, Chapter 1) confirms that the Ar–Pd–Br bond angle is significantly larger with 5-membered heteroaryl groups (~81 °, 5-6) compared to 6-membered ring aryl groups (~79 °, 7-8) (Figure 5.5). This larger angle reflects the increased difficulty of reductive elimination of 5-membered heteroaryl fluorides from Pd(II). Additionally, although there is no noticeable trend in the Pd–Ar bond lengths among the four complexes, the Pd-ipsō distance is on average 0.04 Å shorter with 5-membered heteroaryl groups (Figure 5.5), indicating increased stabilization of the Pd center by the bottom ring of the ligand in these cases, an effect that
could also slow down the rate of reductive elimination. Overall, these findings are consistent with our hypothesis that the rate-limiting step in the fluorination of heteroaryl bromides is reductive elimination.

**Figure 5.4.** Synthesis and solid-state structures of 5 and 6 (ellipsoids at 50% probability).

<table>
<thead>
<tr>
<th>Complex</th>
<th>R</th>
<th>Ar</th>
<th>$\theta$ (°)</th>
<th>Pd-Ar (Å)</th>
<th>Pd-ipso (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>OMe</td>
<td>$\text{C}_6\text{H}_4\text{CN}$</td>
<td>79.03(8)</td>
<td>2.015(3)</td>
<td>2.496(3)</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>$\text{C}_6\text{H}_4\text{Bu}$</td>
<td>79.53(4)</td>
<td>2.014(1)</td>
<td>2.487(2)</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>$\text{C}_6\text{H}_4\text{Ac}$</td>
<td>81.2(1)</td>
<td>2.028(6)</td>
<td>2.440(5)</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>$\text{C}_6\text{H}_4\text{Bu}$</td>
<td>81.48(4)</td>
<td>2.006(2)</td>
<td>2.457(1)</td>
</tr>
</tbody>
</table>

**Figure 5.5.** Aryl group effects on the solid-state structure of di-adamantyl biaryl phosphine-ligated oxidative addition complexes.

In an effort to find 5-membered heteroaryl bromides that would undergo Pd-catalyzed fluorination, we prepared a number of *ortho*-substituted bromothiophenes and
subjected them to the reaction conditions, because *ortho*-substituents are known to promote reductive elimination (Table 5.2). Unfortunately, reactions of bromothiophenes bearing *ortho*-methyl, ethyl, or *n*-octyl groups yielded no aryl fluoride products (9a-d). However, when 2-bromo-3-phenylthiophene was subjected to the reaction conditions, a trace amount of 9e could be detected by $^{19}$F NMR and GC/MS, as confirmed by comparison to an independently prepared sample (see Experimental for details). This result represented the first indication that 5-membered heteroaryl bromides could be converted to the corresponding heteroaryl fluorides under these conditions. In addition, the regioisomeric heteroaryl bromide, 3-bromo-2-phenylthiophene, provided the desired product 9f in higher yield (22% vs. 1%, Table 5.2). Although it is well-known that 2-halothiophenes undergo oxidative addition more rapidly than 3-halothiophenes, little is known about the relative rates of reductive elimination of Pd(II) complexes bearing 3-thiophenyl groups compared to 2-thiophenyl groups. Therefore, the origin of this discrepancy in rate merits further investigation. While in this case catalysts based on HGPhos (L2) and AlPhos (L3) afforded similar yields of 9f, in most cases catalysts based on AlPhos provide higher yields and conversion. Additionally, a screen of ethereal (MTBE, 2MeTHF, CPME, 1,4-dioxane, Bu$_2$O) and hydrocarbon (toluene, cyclohexane) solvents at this stage revealed that the use of MTBE was optimal for this reaction.

Based on this result, we prepared substrates bearing bulkier aryl groups in the 2-position (9g-h, Table 5.2) to determine if we could further promote the rate of C–F reductive elimination. Unfortunately, no aryl fluoride products were detected in these cases, with only starting material recovered. Presumably, the presence of such a bulky group adjacent to the C–Br bond likely impedes oxidative addition. Lastly, a substrate
bearing an ester in the ortho-position was also prepared and evaluated in the reaction; again, none of the desired product 9i was observed. It should be noted that to date we have struggled to carry out fluorinations of aryl (pseudo)halides bearing adjacent carbonyl groups. Nonetheless, these findings suggested that bromothiophenes bearing phenyl groups in the ortho-position might be promising substrates for this reaction.

Based on this hypothesis, we prepared a variety of ortho-substituted bromothiophenes bearing additional electron-withdrawing groups in order to further promote reductive elimination and, by extension, the desired transformation (Table 5.3). The addition of electron-withdrawing ester (10a), phenyl ketone (10b), sulfonamide (10c), and amide (10d) groups at the 5-position of the thiophene ring greatly increased the yield of the desired aryl fluoride products (Table 5.3, compare to 9f in Table 5.2).

Although the reactions to produce 10c and 10d could be carried out on a 0.50 mmol scale to provide the isolated products in good yields, the reactions to produce 10a and 10b did not proceed to full conversion on larger scale (~60% conv. for 10a, ~80% conv. for 10b), producing an inseparable mixture of starting material and product in both cases. Nonetheless, the desired products 10a-b could be isolated from the crude reaction.

**Table 5.2.** Pd-catalyzed fluorinations of ortho-substituted bromothiophenes.\(^a\)

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>2 eq. AgF</th>
<th>0.5 eq. KF</th>
<th>2% (L-Pd)(_2)(1,5-COD)</th>
<th>MTBE, 130 °C, 12 h</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a (R = Me): n/o(^b)</td>
<td>9d: n/o(^b)</td>
<td>9e: 1%(^b,c)</td>
<td>9f (Ar = Ph): 22% (45% conv.)(^b,c,d)</td>
<td>9g (Ar = 2,6-(Me)(_2)Ph): n/o(^b,c)</td>
<td>9h (Ar = 1-naphthyl): n/o(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 0.10 mmol heteroaryl bromide, 0.20 mmol AgF, 0.05 mmol KF, 2% 2 or 3, MTBE (0.1 M), 130 °C, 12 h. \(^b\)2 was used as the catalyst. \(^c\)3 was used as the catalyst. \(^d\)Conversion determined by GC. n/o = not observed.
mixtures on small scale (0.20 mmol) to confirm their identity (see Experimental for details). A substrate bearing a phenyl group at the 5-position also underwent efficient fluorination under these conditions to produce 10e in high yield (Table 5.3). This finding may be due to a remote steric effect between the 5-phenyl group and the di-adamantyl groups on the phosphine, which would promote reductive elimination. Unfortunately, substrates bearing formyl (10f), acetyl (10g), nitro (10h), and cyano (10i) groups at the 5-position of the thiophene ring underwent significant decomposition during the reaction, which made analysis of the results of these reactions challenging (Table 5.3). It is likely that these sensitive functional groups do not survive the highly basic reaction conditions, although the latter three are tolerated in Pd-catalyzed fluorinations of 6-membered (hetero)aryl bromides and triflates (see Chapters 2 and 4).

Intriguingly, in the cases of 10a-10d, a small amount of a second fluorothiophene product with the same molecular weight as the desired product, as determined by GC/MS, was observed in the crude reaction mixtures (Table 5.3). This side product is likely the undesired regioisomer with the fluorine atom adjacent to the electron-withdrawing group, considering a) no corresponding side product was observed during the preparation of 10e, wherein the proposed regioisomer and the desired product would be the same compound, and b) the use of AlPhos (L3) generally affords higher selectivity for the desired product compared to HGPhos (L2) (as shown for 10a in Table 5.3), which is also the case with 6-membered ring substrates that undergo regioisomer formation.27 In the cases of 10a-b, and 10d, the undesired regioisomer could be chromatographically separated from the desired product. However, it should be noted that the addition of tBuOD to the reaction mixture (Chapter 2) did not result in deuterium incorporation into
aryl fluoride products, as judged by $^{19}$F NMR and GC/MS. This finding suggests either that regioisomer formation in these cases proceeds through a different mechanism than that outlined in Chapter 2, or that the involved Pd-thiophyne intermediates are too short-lived to allow for adequate H/D exchange prior to re-protonation and reductive elimination. Further study of this phenomenon is required.

We further investigated the breadth of these findings with other substituted bromothiophenes (Table 5.3). In the case of more challenging 2-bromo-3-phenyl-5-substituted thiophenes (10j-10l, Table 5.2), an ester at the 5-position allowed for the formation of the desired product 10j. However, electron-neutral (10k) or donating (10l) groups at this position did not significantly promote the reaction compared to the unsubstituted case (9e, Table 5.2). In addition, it should be noted that the presence of an electron-withdrawing group on the thiophene ring does not supersede the need for an

Table 5.3. Pd-catalyzed fluorinations of ortho-substituted bromothiophenes bearing additional substituents.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Conversion</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a (R = CO$_2$Me)</td>
<td>2 eq AgF, 0.5 eq KF, 2% 3 (4% ^{19}Pd) MTBE, 130 °C, 12 h</td>
<td>HetArF</td>
<td>80% ^{a} (α:β &gt; 50:1, 95% conv.) $^{b}$</td>
<td></td>
</tr>
<tr>
<td>10b (R = C(O)Ph)</td>
<td>81% $^{a}$ (α:β = 26:1, &gt;98% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10c (R = SO$_2$NET$_2$)</td>
<td>93% (α:β = 30:1) $^{d,e}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10d (R = C(O)NET$_2$)</td>
<td>94% (α:β &gt; 99:1) $^{d}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10e (R = Ph)</td>
<td>80% $^{a}$ (&gt;98% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10f (R = CHO)</td>
<td>Decomp. (&gt;95% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10g (R = Ac)</td>
<td>Decomp. (63% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10h (R = NO$_2$)</td>
<td>Decomp. (90% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10i (R = CN)</td>
<td>Decomp. (78% conv.) $^{b}$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^{a}$0.10 mmol scale. $^{19}$F NMR yield. Confirmed by comparison to an authentic sample. $^{b}$Conversion determined by GC. *2 was used in place of 3. $^{d}$Isolated yield, 0.50 mmol scale. $^{e}$Toluene was used as the solvent. $^{f}$Conversion determined by GC. $^{g}$Contaminated with 4% of the corresponding reduction product, as judged by GC and $^{1}$H NMR analysis. n/o = not observed
phenyl group in the ortho-position to promote reductive elimination, as analogous substrates bearing methyl groups in the ortho-position (10m-10n) yielded little or no product under the reaction conditions (Table 5.3). Lastly, reactions of trisubstituted 3-bromothiophenes bearing an additional methyl (10o) or phenyl (10p) group adjacent to the bromine atom produced diminished yields compared to the corresponding substrate lacking substitution at the 4-position (10e). Similar to the results observed for 9g-9h, this finding is likely due to slow oxidative addition of the aryl bromide. Overall, these studies revealed several key trends for the fluorination of 5-membered heteroaryl bromides: a) 3-bromothiophenes are fluorinated in higher yields than homologous 2-bromothiophenes; b) only substrates bearing both ortho-phenyl and electron-withdrawing groups on the thiophene ring provide synthetically useful yields; c) overwhelming steric hindrance (as in the cases of 9g-h, Table 5.2, 10o-p, Table 5.3) limits oxidative addition and thus the desired transformation. It should be noted that <1% of the corresponding reduction product was observed in the purified products 10c-d, as judged by GC analysis. However, 10j was contaminated with approximately 4% of the corresponding reduction product (see Experimental for details).

We next investigated how well these trends extrapolate to bromobenzo[b]thiophenes (Table 5.4). Consistent with the findings in Table 5.1, simple 2- and 3-bromobenzo[b]thiophenes provided no product (11a-11b) under the standard reaction conditions. Unfortunately, reactions of substrates bearing methyl groups at the 2- or 3-position (11c, e) produced significant amounts of HF, suggesting that deprotonation of the methyl group by a basic fluoride species is occurring in these cases.
In addition, only low yields of the desired products 11c and 11e could be observed. Lastly, although 2-bromo-3-phenylbenzo[b]thiophene was converted to the corresponding aryl fluoride 11d in low yield, the regioisomeric substrate bearing a Br atom in the 3-position provided the desired product 11f in higher yield (Table 5.4). Unfortunately, as with 10a-b this reaction failed to reach full conversion, producing an chromatographically inseparable mixture of starting material and product. Based on these results, it appears that the trends described for the fluorination of bromothiophenes should hold for bromobenzo[b]thiophenes as well.

Table 5.4. Pd-catalyzed fluorinations of bromobenzo[b]thiophenes.\(^a\)

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 eq. AgF 0.5 eq. KF</td>
<td>2% 3 (4% &quot;Pd&quot;)</td>
</tr>
<tr>
<td>MTBE, 130 °C, 12 h</td>
<td></td>
</tr>
<tr>
<td>11a: n/o</td>
<td>11b: n/o</td>
</tr>
<tr>
<td>11c (R = Me): Decomp.</td>
<td>11d (R = Ph): 3%(^b)</td>
</tr>
<tr>
<td>11e (R = Me): Decomp.</td>
<td>11f (R = Ph): 67% (69% conv.)(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions unless otherwise noted: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 3 (2%), MTBE (1.0 mL), 130 °C, 12 h. \(^b\)\(^{19}\)F NMR yield. Confirmed by comparison to an authentic sample. \(^c\)Conversion determined by GC. n/o = not observed.

5.2.2. Bromofurans and Bromobenzo[b]furans. We next investigated the effect of switching the sulfur atom in bromothiophenes to an oxygen atom by studying the Pd-catalyzed fluorination of bromo(benzo)furans (Table 5.5). Because furans are substantially less aromatic than thiophenes, halogenated furans suffer from stability issues.\(^7b\) Indeed, all of the bromofurans we investigated, from simple ones bearing electron-withdrawing groups (12a) to those corresponding to bromothiophenes that readily undergo Pd-catalyzed fluorination (12b-12c), decomposed under the reaction conditions to produce a complex mixture of products in both MTBE and toluene.
Similarly, an ortho-alkylated 3-bromobenzo[b]furan did not furnish 12d under the reaction conditions, instead undergoing decomposition to a number of fluorinated compounds. Only 3-bromo-2-phenylbenzo[b]furan could be converted into the corresponding aryl fluoride (12e) in good yield (Table 5.5). Thus, at this time the Pd-catalyzed fluorination of bromofurans remains extremely limited in scope.

Table 5.5. Pd-catalyzed fluorinations of bromo(benzo)furans. 

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>2 eq. AgF</th>
<th>0.5 eq. KF</th>
<th>2% 3 (4% &quot;Pd&quot;)</th>
<th>MTBE or toluen, 130 °C, 12 h</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOC(=O)Br</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a: Decomp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhOC(=O)Br</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12b: Decomp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOC(=O)Ph</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12c: Decomp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12d (R = Et): Decomp.</td>
<td>12e (R = Ph): 88%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aReaction conditions unless otherwise noted: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 3 (2%), MTBE or toluene (1.0 mL), 130 °C, 12 h. b0.50 mmol scale, isolated yield.

5.2.3. Pyrroles and Indoles. We also briefly examined the fluorination of heterocycles containing a single nitrogen atom (Table 5.6). Because pyrroles and indoles represent the most electron-rich classes of 5-membered heterocycles, we expected that these substrates would not readily undergo fluorination. In addition, cleanly accessing functionalized monobromopyrroles is challenging due to their high reactivity towards polybromination under even mild conditions, as well as their inherent instability. Preliminarily, we found that fluorination of a bromopyrrole substituted with an electron-withdrawing ester did not provide 13a under the standard reaction conditions (Table 5.6). Indoles are more synthetically tractable than pyrroles, but it has been shown that 3-fluoroindoles are unstable unless substituted with electron-withdrawing sulfonyl groups on the nitrogen center. Thus, we focused on 3-bromo-N-sulfonyl indoles as substrates for this reaction.
(13b-13d, Table 5.6). Unfortunately, 3-bromoindoles protected with arylsulfonyl groups on the nitrogen atom (13b), even those further substituted with electron-withdrawing (13c) or ortho-phenyl (13d) groups, provided no product Table 5.6). It should be noted that significant desulfonylation or decomposition was not observed (vide infra). Therefore, further catalyst development is needed to promote the reductive elimination of these very electron-rich heteroaryl fluorides from Pd(II).

Table 5.6. Failed Pd-catalyzed fluorinations of bromopyrroles and bromoindoles.\textsuperscript{a}

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>2 eq. Ag\textsuperscript{+}</th>
<th>0.5 eq. KF</th>
<th>2% 2 or 3 (4% “Pd)</th>
<th>MTBE, 130 °C, 12 h</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a: n/o</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13b: n/o</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13c: n/o</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13d: n/o</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 3 (2\%), MTBE (1.0 mL), 130 °C, 12 h.

5.3. Azoles.

5.3.1. Inhibition studies. Having achieved at least promising results in the synthesis of fluorinated (benzo[b])thiophenes, we next turned our attention to azoles, which are challenging substrates because they contain a potentially coordinating sp\textsuperscript{2}-hybridized nitrogen center. As a first experiment, we assessed potential inhibition of this reaction by various azoles using the fluorination of 4-(nBu)PhOTf (14-OTf) to 14a-b with L2 as the supporting ligand as a model case (entry 1, Table 5.7). We chose this reaction because cationic L·Pd(Ar)OTf intermediates should be especially susceptible to binding of nitrogen-containing heterocycles. We were surprised to find that, in contrast to reactions carried out with L1 (see Chapter 3), most nitrogen-containing heterocycles did not diminish the conversion and yield of this transformation. For example, the presence of 1
eq. of thiazole (entry 2), 2-phenylbenzothiazole (entry 3), or N-alkyl (tBu or Me) pyrazoles (entries 4-5) did not significantly decrease the yield of 14a-b. However, a more electron-rich thiazole (entry 6) did inhibit the reaction to some degree. Additionally, N-methylimidazole (entry 7) dramatically decreased the conversion of this reaction and prevented formation of the desired products. Likewise, N-methylimidizole completely impedes the Pd-catalyzed fluorination of (hetero)aryl bromides using both L2 and L3 as supporting ligands (not shown). This finding suggests that the 3'-aryl group found in L2 and L3 helps to restrict binding of coordinating nitrogen atoms to the Pd.

Table 5.7. Inhibition of the fluorination of 14-OTf by 5-membered heteroarenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion</th>
<th>Combined ArF Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>100%</td>
<td>86%</td>
</tr>
<tr>
<td>2</td>
<td>3 eq. CsF (1 \text{ eq. Additive} ) (2% ) (2)</td>
<td>100%</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph} )</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{tBu} )</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>(\text{Me} )</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
<td>6</td>
<td>(\text{tBu} )</td>
<td>70%</td>
<td>62%</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Me} )</td>
<td>50%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(a\)Reaction conditions: 14-OTf (0.10 mmol), CsF (0.30 mmol), 2 (2%), cyclohexane (1.0 mL), 130 °C, 12 h. \(^{19}\)F NMR conversions and yields.
center, and is consistent with our finding that L2 is superior to L1 for carrying out the fluorination of heteroaryl bromides (Chapter 4). With these encouraging results in hand, we investigated the fluorination of various bromothiazoles, with a focus on thiazoles and pyrazoles, due to the inhibition of the desired reaction by imidazoles.

5.3.2. Bromothiazoles. Thiazoles are the most common 5-membered heterocycle subunit in active pharmaceuticals,1a and reports of the direct fluorination of thiazoles are rare.32 Thus, we were interested in the Pd-catalyzed fluorination of substituted bromothiazoles (Table 5.8). Although 2-bromothiazole itself could not be fluorinated under the reaction conditions (15a), reaction of the 4-phenyl-substituted derivative produced 15b in low yield. Notably, no reaction occurred in the absence of 3, ruling out

Table 5.8. Pd-catalyzed fluorinations of bromothiazoles.\textsuperscript{a}

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 eq. AgF, 0.5 eq. KF, 2% 3 (4% “Pd”)</td>
<td></td>
</tr>
<tr>
<td>MTBE or toluene, 130 °C, 12 h</td>
<td></td>
</tr>
</tbody>
</table>

2-Br: 15a: n/o 15b: 19%\textsuperscript{b, d} (76% conv.\textsuperscript{d}) (0% w/o Pd) 15c: 67%\textsuperscript{c, f} (5% w/o Pd) 15d: Decomp. 15e: n/o 15f: 17%\textsuperscript{b, f} (29% conv.\textsuperscript{f})

4-Br: 15d: Decomp. 15e: n/o

5-Br: 15g: Decomp. 15h: n/o 15i: 8%\textsuperscript{b} 15j: n/o

\textsuperscript{a}Reaction conditions unless otherwise noted: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 3 (2%), MTBE or toluene (1.0 mL), 130 °C, 12 h. \textsuperscript{b}\textsuperscript{19}F NMR yield. Confirmed by comparison to an authentic sample. \textsuperscript{c}Toluene was used as the solvent. \textsuperscript{d}Conversion determined by GC. \textsuperscript{e}0.50 mmol scale, isolated yield. \textsuperscript{f}45% yield of 15f was obtained with 2. n/o = not observed.
the possibility of a background Halex reaction (Table 5.8). Based on our successful fluorination of bromothiophenes bearing electron-withdrawing groups (Table 5.3), we also prepared a 2-bromothiazole derivative bearing an ester group at the 5-position. As expected, a dramatically improved yield of 15c was observed compared to 15b (Table 5.7). Notably, <1% of the corresponding reduction product was observed by GC analysis (see Experimental for details). This finding represents the first successful Pd-catalyzed fluorination of a 5-membered heteroaryl bromide lacking an ortho-phenyl group, and is likely possible because of the highly activated nature of the C–2 position of thiazoles. Consistently, more activated 2-bromobenzothiazole underwent significant fluorination in the absence of 3, likely by a Halex process (not shown). It should be noted that in the cases of 15b-e, significant formation of side products occurred using MTBE as the solvent, and so these reactions were carried out in toluene.

We next investigated the fluorination of 4- (15d-f) and 5- (15g-j) bromothiazoles (Table 5.8). Unsubstituted 4- and 5-bromothiazole underwent significant decomposition under the reaction conditions instead of producing 15d or 15g, respectively (Table 5.8). Indeed, we have found that all bromothiazoles lacking substituents in the 2-position undergo rapid decomposition under fluorination conditions, likely by deprotonation at C–2 by a base fluoride source followed by decomposition or Pd-catalyzed oligimerization. However, simply blocking this position did not allow for fluorination to take place (15e and 15h). As with bromothiophenes (Table 5.2), only with substrates bearing phenyl groups adjacent to the Br center could the desired aryl fluorides 15f and 15i be detected, although in both cases low yields were observed. Unfortunately, to date we have been unable to prepare 4-bromo-5-phenyl and 5-bromo-4-phenylthiazoles bearing electron-
withdrawing groups at the 2-position because of the sluggish reactivity of electron-deficient thiazoles (not shown). Although a substrate bearing both a 2-acetyl and ortho-methyl group could be prepared, none of the desired product 15j could be detected at the end of the reaction (Table 5.7). This discrepancy should be addressed because, based on the results in Tables 5.3 and 5.8, these types of substrates should undergo efficient Pd-catalyzed fluorination.

5.3.3. Bromopyrazoles and Bromoindazoles. Bromopyrazoles are highly electron-rich substrates that have proven challenging for Pd-catalyzed cross-coupling reactions. Nonetheless, we hoped that appropriately substituted bromopyrazoles could be successfully fluorinated to produce potentially useful fluoropyrazole products (Table 5.9). In contrast to our finding with 3-bromoindole substrates (Table 5.6), phenylsulfonyl (16a), tosyl (16e, 16i), and even 2,4,6-triisopropylphenylsulfonyl (trisyl) (16j) protecting groups are readily cleaved from bromopyrazoles under the reaction conditions, as confirmed by detection of the corresponding sulfonyl fluorides by $^{19}$F NMR and GC/MS (Table 5.9). This process occurs in the absence of catalyst. Similarly, pivalyl groups are cleaved under the reaction conditions (not shown). Because of this, we were limited to electron-releasing alkyl, aryl, and trityl protecting groups on the nitrogen center. Unfortunately, none of the prepared 4-bromo-1H-pyrazoles, either unsubstituted (16b-d) or bearing adjacent 3-phenyl (16f-g), 3-methyl (16h), or 3,5-dimethyl (16k-16l) groups, underwent significant fluorination under the reaction conditions (Table 5.9). Changing the solvent, ligand, and additive (in place of KF), had no effect on this outcome. For most of these substrates, the potentially coordinating sp$^2$-hybridized nitrogen atom is flanked by two bulky substituents (e.g., a trityl and phenyl group in 16f), which should
prevent it from readily coordinating the Pd center. Thus, the failure of these reactions cannot simply be attributed to inhibition of the catalyst by the starting material. Instead, as with 3-bromoindoles (Table 5.5), it is likely the extreme electron-richness of 4-bromo-1H-pyrazoles that makes them poor substrates for this reaction.

**Table 5.9. Failed Pd-catalyzed fluorinations of pyrazoles and indazoles.**

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>2 eq. AgF</th>
<th>0.5 eq. KF</th>
<th>MTBE or tol, 130 °C, 12 h</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>16a (R = SO₂Ph): n/o</td>
<td>16e (R = Ts): n/o</td>
<td>16h: n/o</td>
<td>16i (R = Ts): n/o</td>
<td>16m (R = H): n/o</td>
</tr>
<tr>
<td>16b (R = Me): n/o</td>
<td>16f (R = C₆H₅): n/o</td>
<td>16g (R = 4-NO₂Ph): n/o</td>
<td>16j (R = Trisyl): n/o</td>
<td>16n (R = NO₂): n/o</td>
</tr>
<tr>
<td>16c (R = C₆H₅): n/o</td>
<td>16k (R = C₆H₅): n/o</td>
<td>16l (R = Me): n/o</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aReaction conditions unless otherwise noted: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 2 or 3 (2%), MTBE or toluene (1.0 mL), 130 °C, 12 h. bFormation of ArSO₂PhF detected by ¹⁹F NMR and GC/MS.

Similar to bromopyrazoles, 3-bromoindazoles substituted with N-tosyl groups undergo rapid de-tosylation during the reaction (not shown). Due to the challenge of selectively protecting N1 of indazoles, 2-tetrahydropyranyl (THP) groups were chosen to prepare potentially viable 3-bromoindazole substrates. Unfortunately, neither produced significant quantities of the corresponding aryl fluorides 16m-n when subjected to fluorination conditions (Table 5.9).

**5.3.4. Bromimidazoles.** Given the inhibition of fluorination reaction by imidazoles (entry 7, Table 5.7), we only briefly investigated the fluorination of bromimidazoles (Table 5.10). As expected, simple 4- and 5-bromimidazoles did not produce any of the desired aryl fluorides under the reaction conditions (17a-c). Additionally, 3-fluoroimidazo[1,2-α]pyridine (17d) and 3-fluoroimidazo[1,2-α]pyrimidine (17e) could
not be accessed from the corresponding heteroaryl bromides under these conditions. Based on our successful fluorination of 2-bromothiazoles (Table 5.8), we also attempted the fluorination of 2-bromo-1\(H\)-imidazoles (17f-17h). However, 2-bromo-1-methyl-1\(H\)-imidazole decomposed under the reaction conditions (17f), and a 2-bromoimidazole substituted with an electron-withdrawing nitro group provided none of the aryl fluoride 17g. Considering these results, we were surprised to find that 8-bromocaffeine could be converted to 8-fluorocaffeine (17h) in high yield under the standard fluorination conditions using 3, without any obvious decomposition or inhibition of the catalyst being observed. Despite being a potentially interesting biologically active molecule, to the best of our knowledge 17h has never been isolated and characterized. Notably, <1% of 17h formed in the absence of 3, indicating that this reaction does not simply occur via a Halex process. In addition, no caffeine was observed in the purified product as judged by GC analysis (see Experimental for details). Overall, despite the challenge of cross-coupling bromoimidazoles, we were able to find at least one substrate from this family that could be fluorinated in high yield.

**Table 5.10.** Pd-catalyzed fluorination of bromoimidazoles.\(^a\)

<table>
<thead>
<tr>
<th>HetArBr</th>
<th>2 eq. AgF</th>
<th>0.5 eq. KF</th>
<th>2% 2 or 3 (2% &quot;Pd&quot;)</th>
<th>MTBE or toluene, 130 °C, 12 h</th>
<th>HetArF</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a (R = Me): n/o</td>
<td>17c: n/o</td>
<td>17d (R = CH): n/o</td>
<td>17e (R = N): n/o</td>
<td>17f: Decomp.</td>
<td>17g: n/o</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions unless otherwise noted: heteroaryl bromide (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), 2 or 3 (2%), MTBE or toluene (1.0 mL), 130 °C, 12 h. \(^b\)0.50 mmol, isolated yield.

602
5.4. Conclusion and outlook. By systematically studying the effect of substituents on the fluorination of 5-membered heteroaryl bromides, we were able to find a number of hitherto unknown 5-membered heteroaryl fluorides that could be prepared in synthetically useful yields using a catalyst system based on L3. In particular, electron-deficient thiophenes, benzo[b]thiophenes, and benzo[b]furans substituted with phenyl groups in the ortho-position, as well as highly activated 2-bromoazoles, are viable substrates for this reaction. However, despite these advances, the scope of this reaction remains extremely limited, especially with respect to bromoazole substrates. Although our previous work in this area suggests that increasing the steric bulk of the ligand could potentially help overcome this problem, it is difficult to imagine a bulkier ligand than L3 that can still effectively bind to the Pd center, especially given our findings regarding ligand structure effects (Chapter 4). Thus, it is likely that a more fundamental change to the reaction, such as a change in mechanism, transition metal catalyst, or ligand architecture, is necessary to access a broader scope of fluorinated 5-membered heterocycles. Given the potential importance of these compounds in a number of fields, this area will likely remain an area of intense research for the foreseeable future.

5.5. Experimental.

5.5.1. General Procedures. Anhydrous, oxygen-free toluene, tetrahydrofuran, and dichloromethane (CH2Cl2) were purchased from J. T. Baker and passed through two activated alumina columns followed by sparging with argon before use. All other anhydrous solvents were purchased from Aldrich in Sure-Seal bottles and sparged with argon before use. Potassium fluoride (99.0 %) was purchased from Aldrich and dried at
180 °C under vacuum for 24 h. The dried KF was then transferred to a nitrogen-filled glovebox where it was thoroughly ground using an oven-dried mortar and pestle. The finely ground KF was then filtered through a 45 μm stainless-steel sieve (purchased from Cole Parmer) to obtain KF with particle size of < 45 μm. Potassium fluoride (99.0%) was purchased from Sigma-Aldrich and dried using the procedure described for CsF. Preparations of L1, L3, and 3 have been previously described. Di(1-adamantyl)chlorophosphine and di(1-adamantyl)phosphine were received as gifts from Sigma-Aldrich, for which we are grateful. The preparation of XPhos precatalyst 18 and XantPhos precatalyst 19 have been previously described. Degassed aq. K3PO4 solutions were obtained by dissolving K3PO4 in deionized water, and degassing the solution by performing several evacuation/argon refill cycles while sonicating the solution. N-bromosuccinimide was recrystallized from water and stored at 0 °C when not in use. [(1,5-COD)Pd(CH2TMS)2] was prepared according to the literature procedure and stored at −20 °C in a nitrogen filled glovebox when not in use. All other reagents were purchased from commercial sources and used as received, or prepared as described below. Compounds were analyzed by 1H, 13C, 31P, 19F NMR, and IR, where appropriate. New compounds were also analyzed by elemental analysis or high resolution ESI-MS. All 19F NMR yields stated for fluorination reactions are calculated from 19F NMR spectra relative to an internal standard of 1-fluoronaphthalene. 1H and 13C NMR spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometers and were calibrated using residual solvent as an internal reference. 19F and 31P{1H} spectra were recorded on a Varian XL 300 MHz or Varian Inova 500 MHz spectrometer. 19F NMR spectra were calibrated to an external standard of neat PhCF3 (δ −63.72 ppm). 31P{1H}
NMR spectra were calibrated to an external standard of neat H₃PO₄ (δ 0.0 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, pt = pseudotriplet, q = quartet, p = pentet, m = multiplet. IR spectra were recorded on a Thermo Scientific Nicolet iS5 Fourier Transform IR Spectrometer. Screw-cap reaction tube refers to Fisher 16 x 125 mm tubes (Cat. No. 1495925C) or Fisher 20 x 150 mm tubes (Cat. No. 1495937C) tubes equipped with SPTA PTFE/SiL F/15-425 10 (Cat. No. 03394A) septa or SPTA SPTA PTFE/SiL F/18-400 10 (Cat. No. 03394B), respectively. All reactions carried out at high temperatures should be performed behind a blast shield and/or closed hood sash.

5.5.2. Synthesis of new complexes.

\[
\begin{align*}
\text{Pd} & \quad \text{TMS} \\
\text{L1} & \quad \text{Br} \\
\text{pentane} & \quad \text{rt} \\
48 \text{h} & \quad \text{MeO Ad AdS} \\
\end{align*}
\]

In a nitrogen-filled glovebox, an oven-dried 20 mL vial equipped with a stir bar was charged with L1 (133 mg, 0.21 mmol, 1.00 eq.) and 2-bromothiophene (60.1 μl, 062 mmol, 3.00 eq.). Pentane (5 mL) was added, and the non-homogenous reaction mixture was vigorously stirred as [(1,5- )Pd(CH₂TMS)₂] (80.0 mg, 0.21 mmol, 1.00 eq.) was added in one portion. The reaction mixture was allowed to stir vigorously for 48 h, at which time it was filtered through a sintered glass frit. The resulting yellow solid was thoroughly washed with pentane (3 x 5 mL), affording 5 (130 mg, 65%) as a dark yellow solid. Clean ¹H, ¹³C, and ³¹P NMR spectra of 5 could not be obtained due to its slow decomposition (CD₂Cl₂, CDCl₃, THF-d₈) or poor solubility (C₆D₆) in solution. It was
detected by $^1$H NMR (500 MHz, CD$_2$Cl$_2$) signals at $\delta$ 7.37 (d, $J = 6$ Hz, 1H), 6.88-7.15 (m, 5H), 6.60 (bs, 1H), 3.85 (s, 3H), 3.42 (bs, 3H), 2.91 (bs, 1H), 2.57 (bs, 2H), 2.33 (bs, 6H), 2.13 (bs, 6H), 1.94 (bs, 6H), 1.58-1.78 (bs, 17H), 1.25 (bs, 6H), 0.88 (bs, 6H) ppm.

$^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): $\delta \sim$76 ppm (bs). Anal. Calcd. for C$_{47}$H$_{64}$BrO$_2$PPdS: C, 62.01; H, 7.09; found: C, 62.20; H, 7.04. X-ray quality crystals of 5 were obtained by layering a CH$_2$Cl$_2$/Et$_2$O solution of 5 with pentane and cooling the mixture to $-20$ °C in a nitrogen-filled glovebox.

In a nitrogen-filled glovebox, an oven-dried 20 mL vial equipped with a stir bar was charged with L1 (200 mg, 0.31 mmol, 1.00 eq.) and 2-bromo-5-acetylthiophene (69.7 mg, 0.31 mmol, 1.10 eq.). Pentane (10 mL) was added, and the non-homogenous reaction mixture was vigorously stirred as [(1,5-COD)Pd(CH$_2$TMS)$_2$] (121 mg, 0.31 mmol, 1.00 eq.) was added in one portion. The reaction mixture was allowed to stir vigorously for 48 h, at which time it was filtered through a sintered glass frit. The resulting yellow solid was thoroughly washed with pentane (3 x 5 mL), affording 6 (206 mg, 70%) as a yellow solid. Clean $^1$H, $^{13}$C, and $^{31}$P NMR spectra of 6 could not be obtained due to its slow decomposition (CD$_2$Cl$_2$, CDCl$_3$, THF-d$_8$) or poor solubility (C$_6$D$_6$) in solution. It was detected by $^1$H NMR (500 MHz, CD$_2$Cl$_2$) signals at $\delta$ 7.46 (d, $J = 4$ Hz, 1H), 7.08 (s, 2H), 6.97 (dd, $J = 9$, 3 Hz, 1H), 6.89 (d, $J = 9$ Hz), 6.78 (d, $J = 4$ Hz), 3.84 (s, 3H), 3.34 (s, 3H), 6.06
3.01 (septet, J = 7 Hz), 2.34-2.39 (m, 9H), 2.08-2.17 (m, 6H), 1.95 (bs, 7H), 1.59-1.79 (m, 19H), 1.34 (d, J = 7 Hz, 6H), 0.83 (bs, 6H) ppm. $^{31}$P NMR (202 MHz, CD$_2$Cl$_2$): δ ~73.8 ppm (bs) (free L1 was also detected). Anal. Calcd. for C$_{49}$H$_{66}$BrO$_3$PPdS: C, 61.79; H, 6.98; found, C, 60.79; H, 7.13. X-ray quality crystals of 6 were obtained by layering a CH$_2$Cl$_2$/Et$_2$O solution of 6 with pentane and cooling the mixture to −20 °C.

5.5.3. Synthesis of heteroaryl bromides. When available, heteroaryl bromides were purchased from commercial suppliers and used without further purification. In cases where the commercially available aryl bromide was an oil, it was filtered through a short plug of non-basic alumina in a nitrogen-filled glovebox prior to use. 2-bromo-3-ethylthiophene (9b-Br), 36 2-bromo-3-phenylthiophene (9e-Br), 37 5-bromo-N,N-diethylthiophene-2-sulfonamide, 38 2-methylbenzo[b]thiophene, 39 3-bromo-2-methylbenzo[b]thiophene (11e-Br), 40 methyl 3-bromo-1-tosyl-1H-indole-5-carboxylate (13c-Br), 41 tert-butyl 4-methylthiazole-5-carboxylate, 42 2-iso-butyl-5-phenylthiazole, 43 5-bromo-2-phenylthiazole (15h-Br), 44 4-bromo-1-trityl-1H-pyrazole (16c-Br), 45 4-bromo-3-phenyl-1H-pyrazole, 46 4-bromo-3-methyl-1-trityl-1H-pyrazole, 40c 4-bromo-3,5-dimethyl-1-trityl-1H-pyrazole, 40c and 2-bromo-1-methyl-1H-benzimidazole 47 were prepared according to literature procedures. 2-methyl-3-fluorobenzo[b]thiophene has been previously prepared. 13

General Procedure A (Suzuki-Miyaura Coupling). This procedure is adapted from the literature. 48 To a reaction tube equipped with a stir bar was added precatalyst 18 or 19 (2-10%), additional ligand (if necessary), and boronic acid (1.10-3.50 eq.) (if the aryl halide
was a solid, it was also added at this point). The tube was capped, placed under high vacuum, and backfilled with argon. This process was repeated a total of three times. THF and degassed aq. K$_3$PO$_4$ solution (2.0-4.0 eq.) were then added (if the aryl halide was a liquid, it was added at this point). The cap was replaced with one that had not been punctured, and the reaction tube was placed in an oil bath that had been pre-heated to the desired temperature and allowed to stir vigorously overnight. At this time, the reaction mixture was cooled to room temperature and diluted with ether and water. The phases were separated, and the aqueous phase was extracted with additional ether. The combined organic phases were dried over MgSO$_4$, filtered through a short celite plug, and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified as described. 

General Procedure B (Bromination with NBS). The heteroarene (1.00 eq.) was dissolved in DMF in a roundbottom flask equipped with a stir bar and open to air. The roundbottom flask was heated/cooled to the indicated temperature and N-bromosuccinimide (1.10-2.00 eq.) was added portionwise. The reaction was allowed to stir for 12 h at the indicated temperature. At this time, the reaction mixture was brought to room temperature and diluted with water and either hexanes or ether. The phases were separated, and the aqueous phase was extracted with additional ether or hexanes. The
combined organic phases were washed with H$_2$O (3×) and brine (1×), dried over MgSO$_4$, filtered through a short silica gel plug, and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified as indicated.

**General Procedure C (Bromination with Br$_2$).** The heteroarene (1.00 eq.) was dissolved in DMF in a roundbottom flask equipped with a stir bar and open to air. The roundbottom flask was cooled to 0 °C. An equal volume of DMF was added to a separate roundbottom flask equipped with a stir bar and cooled to 0 °C. Br$_2$ (4.00 eq.) was added dropwise to the second flask, which was allowed to stir at 0 °C for 2 min. At this time, the Br$_2$/DMF solution was cannulated dropwise to the first flask, maintaining the temperature of the reaction mixture near 0 °C. The reaction mixture was allowed to stir for the indicated time, and then diluted with Et$_2$O and carefully quenched with saturated aq. Na$_2$SO$_3$. The phases were separated, and the aqueous phase was extracted with additional ether. The combined organic phases were washed with H$_2$O (2×) and brine (1×), dried over MgSO$_4$, filtered through a short silica gel plug, and concentrated using a rotary evaporator. In indicated cases, additional purification was carried out.

**General Procedure D (N-Protection of Azoles).** The azole (1.00 eq.) was dissolved in CH$_2$Cl$_2$ in a roundbottom flask equipped with a stir bar. Then, triethylamine (2.00 eq.) and the arylsulfonyl chloride (1.10 eq.) or trityl chloride (1.50 eq.) was added in one portion, and the reaction mixture was allowed to stir at room temperature for 12 h. At this time, water was added, and the phases were separated. The aqueous phase was
further extracted with CH₂Cl₂, dried over MgSO₄, and filtered through a silica gel plug, eluting with CH₂Cl₂, and concentrated. The product was further purified as indicated.

\[
\begin{align*}
\text{Br} & \quad \text{PhB(OH)}_2 \\
\text{Br} & \quad \text{cat. 18} \\
\text{THF/H}_2\text{O, rt, 12 h} & \quad \text{Ph} \\
\text{Br} & \quad \text{4k-Br}
\end{align*}
\]

4k-Br was prepared according to General Procedure A. Thus, 2,4-dibromothiophene (110 μL, 1.00 mmol, 1.00 eq.), phenylboronic acid (135 mg, 1.00 mmol, 1.10 eq.), 18 (17.0 mg, 0.02 mmol, 2%), THF (1.0 mL), and aq. K₃PO₄ (1.0 M, 2.0 mL, 2.0 mmol, 2.0 eq.) were combined in a reaction tube and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by flash chromatography (hexanes) yielded 3-bromo-5-phenylthiophene (120 mg, 50%) as a white solid. Melting Point: 65-67 °C (Lit. 45-46 °C).\(^4\)\(^9\) \(^1\)H NMR (500 MHz, CDCl₃): δ 7.56 (dd, J = 8, 2 Hz, 2H), 7.40 (pt, J = 8 Hz, 2H), 7.32 (tt, J = 8, 2 Hz, 1H), 7.21 (d, J = 2 Hz, 1H), 7.18 (d, J = 2 Hz, 1H) ppm; \(^{13}\)C NMR (125 MHz, CDCl₃): δ 145.6, 133.3, 129.2, 128.4, 125.9 125.8, 122.1, 110.6 ppm. IR: 3108, 3089, 3054, 3031, 1596, 1567, 1485, 1447, 1340, 1332, 1299, 1192, 1070, 1028, 960, 903, 860, 827, 812, 752, 707, 686, 625, 587 cm⁻¹. These spectra are consistent with those reported in the literature.\(^4\)\(^9\)

\[
\begin{align*}
\text{Br} & \quad \text{PhB(OH)}_2 \\
\text{Br} & \quad \text{cat. 18} \\
\text{THF/H}_2\text{O, rt, 12 h} & \quad \text{Ph} \\
\text{Br} & \quad \text{9f-Br}
\end{align*}
\]

9f-Br was prepared according to General Procedure A.\(^2\)\(^5\)\(^b\) Thus, 2,3-dibromothiophene (1.13 mL, 10.0 mmol, 1.00 eq.), phenylboronic acid (1.34 g, 11.0 mmol, 1.10 eq.), 18 (169 mg,
0.20 mmol, 2%), THF (20 mL), and \( \text{aq. } \) \( \text{K}_3\text{PO}_4 \) (1.0 M, 20 mL, 20 mmol, 2.0 eq.) were combined in a 100 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by flash chromatography (pentane) yielded 3-bromo-2-phenylthiophene (1.58 g, 66%) as a colorless oil. \(^1\)H NMR (500 MHz, \( \text{CDCl}_3 \)): \( \delta \) 7.67 (d, \( J = 8 \) Hz, 2H), 7.45 (pt, \( J = 8 \) Hz, 2H), 7.39 (t, \( J = 8 \) Hz, 1H), 7.29 (dd, \( J = 5, 2 \) Hz, 1H), 7.07 (dd, \( J = 5, 3 \) Hz, 1H) ppm; \(^{13}\)C NMR (125 MHz, \( \text{CDCl}_3 \)): \( \delta \) 138.3, 133.0, 131.8, 129.2, 128.6, 128.4, 125.1, 107.6 ppm. IR: 3106, 3056, 1523, 1484, 1444, 1343, 1146, 1073, 863, 690, 624, 608 cm\(^{-1}\). These spectra are consistent with those reported in the literature.\(^{25b}\) A comparison of the \(^1\)H spectra of this compound with that of 2-bromo-3-phenylthiophene\(^{37}\) is included.

\[
\begin{array}{cc}
\text{Br} & \text{Me} \\
\text{Br} & \text{Me}
\end{array}
\xrightarrow{\text{cat. 18, XPhos}}
\begin{array}{c}
\text{Br} \\
\text{Me}
\end{array}
\]

\( \text{9g-Br} \) was prepared according to General Procedure A. Thus, 2,3-dibromothiophene (566 µL, 5.00 mmol, 1.00 eq.), 2,6-dimethylphenylboronic acid (904 mg, 6.00 mmol, 1.20 eq.), 18 (85.0 mg, 0.10 mmol, 2%), XPhos (48.0 mg, 0.10 mmol, 2%), THF (10 mL), and \( \text{aq. } \) \( \text{K}_3\text{PO}_4 \) (0.5 M, 20 mL, 10 mmol, 2.0 eq.) were combined in a 100 mL roundbottom flask and allowed to stir at room temperature for 12 h. Under these conditions, the reaction did not proceed to full conversion, but no diarylation was observed. Purification of the crude reaction mixture by flash chromatography (hexanes) yielded 3-bromo-2-(2,6-dimethylphenyl)thiophene (311 mg, 23%) as a greasy colorless solid that melts near room temperature. The regioselectivity is assumed based on that observed for the preparation of 3-bromo-2-phenylthiophene. \(^1\)H NMR (500 MHz,
CDCl₃): δ 7.37 (d, J = 5 Hz), 7.24 (d, J = 8 Hz), 7.14 (d, J = 7 Hz), 7.09 (d, J = 5 Hz), 2.12 (s, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 138.8, 137.2, 131.8, 130.3, 129.0, 127.4, 126.1, 110.1, 20.5 ppm. IR: 3106, 3022, 2944, 2914, 1463, 1441, 1376, 1339, 114, 1031, 957, 866, 775, 732, 708, 656, 634 cm⁻¹. HRMS (ESI) m/z calcd. for C₁₂H₁₂BrS [M+H⁺, M+2+H⁺]: 266.9838, 268.9823; found: 266.9846, 268.9792.

![Chemical structure](image)

**9h-Br** was prepared according to General Procedure A. Thus, 2,3-dibromothiophene (566 μL, 5.00 mmol, 1.00 eq.), 1-naphthylboronic acid (946 mg, 5.50 mmol, 1.10 eq.), 18 (85.0 mg, 0.10 mmol, 2%), XPhos (48.0 mg, 0.10 mmol, 2%), THF (10 mL), and aq. K₃PO₄ (0.5 M, 20 mL, 10 mmol, 2.0 eq.) were combined in a 100 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by flash chromatography (hexanes) yielded 3-bromo-2-(1-naphthyl)thiophene (848 mg, 59%) as a white solid. The regioselectivity is assumed based on that observed for the preparation of 3-bromo-2-phenylthiophene. Melting Point: 80 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.93-7.98 (m, 2H), 7.79-7.82 (m, 1H), 7.43-7.58 (m, 4H), 7.44 (d, J = 5 Hz), 7.19 (d, J = 5 Hz) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 136.7, 133.7, 132.2, 130.6, 130.3, 129.6, 129.5, 128.5, 126.7, 126.3, 126.2, 126.2, 125.2, 111.1 ppm. IR: 3040, 1591, 1503, 1385, 1341, 1146, 1014, 858, 794, 777, 708, 683, 617 cm⁻¹. Anal. Calcd. for C₁₄H₉BrS: C, 58.15; H, 3.14; found: C, 58.69; H, 3.28.
A 50 mL roundbottom flask equipped with a stir bar was charged with MgSO₄ (1.44 g, 12.0 mmol, 4.00 eq.) and anhydrous CH₂Cl₂ (12 mL) under an atmosphere of N₂. Concentrated H₂SO₄ (~170 μL, ~3.00 mmol, ~1.00 eq.) was added dropwise, and the mixture was allowed to stir at rt for 10 min. Next, 3-bromothiophene-2-carboxylic acid (621 mg, 3.00 mmol, 1.00 eq.) was added under a positive pressure of N₂, followed immediately by tBuOH (1.4 mL, 15 mmol, 5.0 eq.). The reaction mixture was allowed to stir at room temperature for 12 h. At this time, saturated aq. NaHCO₃ (10 mL) was carefully added, followed by additional CH₂Cl₂ (20 mL). The phases were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 × 20 mL). The combined organic phases were washed with saturated aq. NaHCO₃ (20 mL), H₂O (20 mL), and brine (20 mL), dried over MgSO₄, filtered, and concentrated. The crude product mixture was purified by flash chromatography (0 → 5% EtOAc/hexanes) to yield tert-butyl 3-bromothiophene-2-carboxylate (9i-Br) (308 mg, 39%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 2.67 (s, 3H), 1.54 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 160.2, 159.3, 139.1, 127.7, 83.2, 28.3, 17.3 ppm. IR: 2978, 2931, 1714, 1697, 1532, 1401, 1368, 1331, 1303, 1255, 1163, 1090, 1050, 1015, 841, 827, 762 cm⁻¹. Anal. Calcd. for C₉H₁₁BrO₂S: C, 41.08; H, 4.21; found: C, 41.33; H, 4.15.
10a-Br was prepared according to General Procedure A. Thus, methyl 4,5-dibromo-2-carboxylate (1.20 g, 4.00 mmol, 1.00 eq.), phenylboronic acid (540 mg, 4.40 mmol, 4.40 eq.), 19 (190 mg, 0.20 mmol, 5%), XantPhos (116 mg, 0.20 mmol, 5%), THF (4.0 mL), aq. K3PO4 (1M, 8.0 mL, 8.0 mmol, 2.0 eq.) were combined in a 50 mL Schlenk flask and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (5% EtOAc/hexanes) yielded methyl 4-bromo-5-phenylthiophene-2-carboxylate (1.04 g, 88%) as a white solid. The regioselectivity was confirmed by comparison of the 'H NMR spectrum with that of the potentially formed regioisomeric compound methyl 5-bromo-4-phenylthiophene-2-carboxylate (10j-Br). Melting Point: 70 °C. 'H NMR (500 MHz, CDCl3): δ 7.73 (s, 1H), 7.64-7.68 (m, 2H), 7.41-7.48 (m, 3H), 3.90 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3): δ 162.4, 145.9, 137.9, 132.7, 132.6, 129.9, 129.7, 129.4, 108.7, 53.2 ppm. IR: 3100, 3025, 2960, 1728, 1714, 1528, 1450, 1438, 1291, 1182, 1080, 1069, 924, 862, 840, 755, 746, 714, 692, 669, 629, 611 cm⁻¹. HRMS (ESI) for C12H13BrNO2S (M+NH4⁺, M+2+NH4⁺): 313.9845, 315.9825; found: 313.9858, 315.9842.

This procedure was adapted from the literature. 2-benzoylthiophene (1.00 g, 5.31 mmol, 1.00 eq.), Pd(OAc)2 (119 mg, 0.53 mmol, 10%), tricyclohexylphosphine tetrafluoroborate
(293 mg, 0.80 mmol, 15%), and K_2CO_3 (1.10 g, 7.97 mmol, 1.50 eq.) were combined in a 100 mL Schlenk tube equipped with a stir bar. The tube was placed under high vacuum and backfilled with argon. This process was repeated a total of three times. The screw-cap was replaced with a septum, and bromobenzene (558 μL, 5.31 mmol, 1.00 eq.), pivalic acid (183 μL, 1.59 mmol, 0.30 eq.), and DMA (25 mL) were added. The septum was replaced with the screw-cap, and the tube was placed in an oil bath pre-heated to 100 °C and allow to stir for 12 h. At this time, the tube was cooled to room temperature, and the reaction mixture was diluted with ether (50 mL) and water (50 mL). The phases were separated, and the aqueous phase was further extracted with ether (2 × 25 mL). The combined organic phases were washed with water (2 × 25 mL) and brine (25 mL), dried over MgSO_4, filtered through a silica gel plug, eluting with ether, and concentrated. The resulting brown solid was recrystallized from hot methanol to afford 2-benzoyl-5-phenylthiophene (10b-H) (889 mg, 63%) as a pale yellow solid. Melting Point: 130 °C (Lit. 132 °C).\(^{51}\) ¹H NMR (500 MHz, CDCl₃): δ 7.89 (d, J = 7 Hz, 2H), 7.70 (d, J = 9 Hz, 2H), 7.58-7.63 (m, 2H), 7.51 (pt, J = 8 Hz, 2H), 7.44 (pt, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 1H), 7.36 (d, J = 4 Hz, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 188.2, 153.4, 142.4, 138.2, 136.1, 133.4, 132.3, 129.3, 129.2, 128.6, 126.5, 124.0 ppm. IR: 2951, 2849, 1617, 1495, 1462, 1318, 1211, 1177, 1077, 1037, 1005, 909, 754, 703, 668 cm⁻¹. These spectra are consistent with those reported in the literature.\(^{52}\)

10b-Br was prepared according to General Procedure C. Thus, 2-benzoyl-5-phenylthiophene (211 mg, 0.80 mmol, 1.00 eq.), Br₂ (163 μL, 3.20 mmol, 4.00 eq.), and DMF (8 mL) were combined in a 25 mL roundbottom flask and allowed to stir at 0 °C for
1 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, followed by recrystallization of the resulting solid from MeOH, afforded 5-benzoyl-3-bromo-2-phenylthiophene (163 mg, 59%) as a pale yellow solid.

Melting Point: 84 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.89 (dd, \(J = 8, 2\) Hz, 2H), 7.72 (dd, \(J = 8, 2\) Hz, 2H), 7.63 (tt, \(J = 8, 2\) Hz, 1H), 7.59 (s, 1H), 7.54 (pt, \(J = 8\) Hz, 2H), 7.4-7.51 (m, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 187.2, 147.3, 141.5, 138.5, 137.4, 132.8, 132.2, 126.9, 129.3, 129.2, 128.9, 128.8, 108.2 ppm. IR: 3057, 1630, 1596, 1575, 1520, 1447, 1426, 1426, 1324, 1286, 1223, 1152, 1115, 1075, 874, 764, 709, 694, 652, 631 cm\(^{-1}\). Anal. Calcd. for C\(_{17}\)H\(_{13}\)BrOS: C, 59.49; H, 3.23; found: C, 59.45; H, 3.39.

This compound was prepared according to General Procedure A. Thus, 5-bromo-N,N-diethylthiophene-2-sulfonamide\(^3\) (2.00 g, 6.71 mmol, 1.00 eq.), phenylboronic acid (1.23 g, 10.1 mmol, 1.50 eq.), \(\text{Pd(Br)}_2\) cat. 18 (114 mg, 0.13 mmol, 2%), THF (7 mL), and \(aq.\) K\(_3\)PO\(_4\) (1 M, 13.4 mL, 13.4 mmol, 2.0 eq.) were combined in a 100 mL Schlenk tube and allowed to stir at 60 °C overnight. Purification of the crude reaction mixture by flash chromatography (10 \(\rightarrow\) 20% EtOAc/hexanes) afforded 5-phenyl-N,N-diethylthiophene-2-sulfonamide (\(10c\)-H) (1.41 g, 71%) as a brown solid. Melting Point: 80-81 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.59 (d, \(J = 7\) Hz, 2H), 7.50 (d, \(J = 4\) Hz, 1H), 7.41 (pt, \(J = 7\) Hz, 2H), 7.36 (t, \(J = 7\) Hz, 1H), 7.24 (d, \(J = 4\) Hz, 1H), 3.28 (q, \(J = 8\) Hz, 4H), 1.20 (t, \(J = 7\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 150.4, 139.0, 132.9, 132.3, 129.3, 129.1,
126.2, 122.9, 42.8, 14.4 ppm. IR: 2983, 2941, 2873, 1448, 1334, 1294, 1243, 1201, 1143, 1011, 940, 812, 791, 754, 704, 685, 647, 579 cm\(^{-1}\). Anal. Calcd. for \(\text{C}_{14}\text{H}_{17}\text{NO}_{2}\text{S}_{2}\): C, 56.92; H, 5.80; found: C, 57.15; H, 5.76.

\textbf{10c-Br} was prepared according to General Procedure C. Thus, 5-phenyl-\(\text{N},\text{N}\)-diethylthiophene-2-sulfonamide (1.41 g, 4.77 mmol, 1.00 eq.), \(\text{Br}_2\) (984 \(\mu\)L, 19.1 mmol, 4.00 eq.), and DMF (20 mL) were combined in a 100 mL roundbottom flask at 0 °C and allowed to stir at 0 °C overnight. The crude product mixture was purified by flash chromatography (5% EtOAc/hexanes) to afford 4-bromo-5-phenyl-\(\text{N},\text{N}\)-diethylthiophene-2-sulfonamide (1.67 g, 93%) as a yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.62-7.65 (m, 2H), 7.42-7.49 (m, 4H), 3.20 (q, \(J = 8\) Hz, 4H), 1.23 (t, \(J = 7\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 144.0, 139.6, 134.8, 131.5, 129.6, 129.2, 129.0, 107.5, 43.1, 14.6 ppm. IR: 2974, 2935, 2873, 1445, 1431, 1339, 1305, 1298, 1200, 1149, 1019, 934, 828, 784, 757, 718, 691, 580 cm\(^{-1}\). Anal. Calcd. for \(\text{C}_{14}\text{H}_{16}\text{BrNO}_{2}\text{S}_{2}\): C, 44.92; H, 4.31; found: C, 44.91; H, 4.21.

![Diagram](image_url)

An oven-dried 100 mL roundbottom flask equipped with a stir bar was charged with 2-bromothiophene carboxylic acid (2.00 g, 9.66 mmol, 1.00 eq.). The roundbottom flask was placed under high vacuum and backfilled with nitrogen. Then, anhydrous CH\(_2\)Cl\(_2\) (30 mL) and DMF (2.5 mL) were added (the solid should dissolve at this point). The septum was fitted with a vent needle, and oxalyl chloride (1.66 mL, 19.3 mmol, 2.00 eq.)...
was added dropwise (Caution: evolution of toxic gases!). The reaction mixture was allowed to stir at room temperature for 1 h, at which time it was concentrated with the aid of a rotary evaporator. The roundbottom flask was placed under high vacuum and backfilled with nitrogen. The resulting thick yellow oil was redissolved in anhydrous CH$_2$Cl$_2$ (30 mL) and the flask was cooled to 0 °C. Then, diethylamine (4.99 mL, 48.3 mmol, 5.00 eq.) was added dropwise (Caution: evolution of HCl!). The reaction mixture was allowed to stir at room temperature for 12 h. At this time, the reaction mixture was diluted with CH$_2$Cl (40 mL), and saturated aq. NaHCO$_3$ (50 mL) was carefully added. The phases were separated, and the aqueous phase was further extracted with CH$_2$Cl$_2$ (2 × 40 mL). The combined organic phases were washed with water (2 × 50 mL) and brine (50 mL), dried over MgSO$_4$, filtered, and concentrated. The resulting material was purified by flash chromatography (10 → 20% → 30% EtOAc/hexanes) to afford 5-bromo-N,N-diethyl-thiophene-2-carboxamide (1.27 g, 52%) as a greasy pale yellow solid that melted close to room temperature. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.08 (d, J = 4 Hz, 1H), 6.99 (d, J = 4 Hz, 1H), 3.52 (q, J = 7 Hz, 4H), 1.24 (t, J = 7 Hz, 6H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 146.1, 132.4, 130.9, 130.4, 129.2, 107.4, ~43 (bs), ~15 (bs) ppm. IR: 3068, 2982, 2964, 2934, 1600, 1528, 1433, 1383, 1313, 1281, 1223, 1050, 969, 940, 843, 824, 748, 726, 692, 633 cm$^{-1}$. Anal. Calcd. for C$_9$H$_{12}$BrNOS: C, 41.23; H, 4.61; found: C, 41.38; H, 4.52.

**10d-H** was prepared according to General Procedure A. Thus, 5-bromo-N,N-diethyl-thiophene-2-carboxamide (800 mg, 3.05 mmol, 1.00 eq.), phenylboronic acid (558 mg, 4.58 mmol, 1.50 eq.), 18 (51.6 mg, 0.06 mmol, 2%), THF (3 mL), and aq. K$_3$PO$_4$ (1M,
6.0 mL, 6.0 mmol, 2.0 eq.) were combined in a 50 mL Schlenk tube and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (10 → 20 → 30% EtOAc/hexanes) afforded 5-phenyl-\(N,N\)-diethyl-thiophene-2-carboxamide (587 mg, 74%) as a white solid. Melting Point: 45-47 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.60-7.63 (m, 2H), 7.39 (pt, \(J = 8\) Hz, 2H), 7.29-7.34 (m, 2H), 7.22 (d, \(J = 4\) Hz, 1H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 146.1, 132.4, 130.9, 130.4, 129.2, 129.2, 107.4 ~43 (bs), ~15 (bs) ppm. IR: 3061, 2986, 1601, 1538, 1459, 1385, 1367, 1307, 1285, 1180, 1103, 1054, 915, 845, 822, 750, 731, 703, 688, 675, 622 cm\(^{-1}\). Anal. Calcd. for C\(_{15}\)H\(_{17}\)NOS: C, 69.46; H, 6.61; found: C, 69.69; H, 6.63.

10d-Br was prepared according to General Procedure C. Thus, 5-phenyl-\(N,N\)-diethyl-thiophene-2-carboxamide (1.14 mg, 4.40 mmol, 1.00 eq.), Br\(_2\) (906 \(\mu\)L, 17.6 mmol, 4.00 eq.), and DMF (20 mL) were combined at 0 °C and allowed to stir at 0 °C for 1 h. Purification of the crude reaction mixture by flash chromatography (20% EtOAc/hexanes) afforded 4-bromo-5-phenyl-\(N,N\)-diethyl-thiophene-2-carboxamide (1.29 mg, 87%) as a thick pale yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.64-7.67 (m, 2H), 7.38-7.47 (m, 3H), 7.26 (s, 1H), 3.57 (q, \(J = 7\) Hz, 4H), 1.28 (t, \(J = 7\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 162.4, 141.5, 137.5, 132.2, 131.9, 129.1, 128.9, 128.8, 106.7, ~43 (bs), ~15 (bs) ppm. IR: 2971, 2932, 1609, 1529, 1440, 1380, 1319, 1277, 1216, 1056, 844, 815, 758, 729, 693, 628 cm\(^{-1}\). Anal. Calcd. for C\(_{15}\)H\(_{16}\)BrNOS: C, 53.26; H, 4.77; found: C, 53.53; H, 4.83.
**10e-H** was prepared according to General Procedure A. Thus, 2,5-dibromothiophene (1.13 mL, 10.0 mmol, 1.00 eq.), phenylboronic acid (3.05 g, 25.0 mmol, 2.50 eq.), 18 (169 mg, 0.20 mmol, 2%), THF (10 mL), and aq. K$_3$PO$_4$ (1.5 M, 20 mL, 30 mmol, 3.0 eq.) were combined in a 100 Schlenk flask and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (1% EtOAc/hexanes) yielded 2,5-diphenylthiophene (1.13 g, 48%) as a pale yellow crystalline solid. Melting Point: 153 °C (Lit. 152-153 °C).$^{53}$ 1H NMR (500 MHz, CDCl$_3$): δ 7.63-7.66 (m, 4H), 7.38-7.42 (m, 4H), 7.26-7.31 (m, 4H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 143.8, 134.4, 129.1, 127.7, 125.8, 124.1 ppm. IR: 3055, 3017, 1593, 1480, 1454, 1273, 1157, 1079, 1028, 940, 902, 804, 747, 683 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{54}$

**10e-Br** was prepared according to a slightly modified General Procedure B. Thus, 2,5-diphenylthiophene (1.12 g, 4.75 mmol, 1.00 eq.), N-bromosuccinimide (934 mg, 5.22 mmol, 1.10 eq.), DMF (10 mL), and CH$_2$Cl$_2$ (20 mL, added to solubilize the starting material) were combined and allowed to stir at room temperature for 12 h. Purification by flash chromatography (hexanes), followed by recrystallization of the resulting solid from hot MeOH, yielded 3-bromo-2,5-diphenylthiophene (725 mg, 48%) as a pale yellow solid. Melting Point: 42-43 °C (Lit. 43-44 °C).$^{55}$ 1H NMR (500 MHz, CDCl$_3$): δ 7.73 (d, J = 9 Hz, 2H), 7.61 (d, J = 9 Hz, 2H), 7.40-7.49 (m, 5H), 7.31-7.37 (m, 1H), 7.29 (s, 1H)
ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 143.3, 137.4, 133.2, 133.0, 129.2, 129.0, 128.7, 128.4, 128.3, 127.5, 125.6, 108.0 ppm. IR: 3055, 3026, 1598, 1533, 1496, 1442, 1326, 1275, 1156, 1036, 969, 908, 824, 752, 715, 624, 608 cm\(^{-1}\). These spectra are consistent with those reported in the literature.\(^5\)\(^6\)

![Chemical reaction diagram]

10f-Br was prepared according to General Procedure A. Thus, 4,5-dibromothiophene-2-carboxaldehyde (540 mg, 2.00 mmol, 1.00 eq.), phenylboronic acid (270 mg, 2.20 mmol, 1.10 eq.), 19 (95 mg, 0.1 mmol, 5%), THF (2 mL), and \(aq.\) K\(_3\)PO\(_4\) (1.0 M, 4.0 mL, 4.0 mmol, 2.0 eq.) were combined in a 25 mL roundbottom flask and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (0 → 2 → 4 → 6% EtOAc/hexanes) yielded 4-bromo-5-phenylthiophene-2-carboxaldehyde (370 mg, 69%) as a pale yellow solid. The regioselectivity is assumed based on that observed for the preparation of methyl 3-bromo-2-phenylthiophene-5-carboxylate. Melting Point: 83 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 9.86 (s, 1H), 7.73 (s, 1H), 7.68-7.70 (m, 2H), 7.46-7.50 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 182.2, 148.5, 141.7, 140.3, 132.2, 130.1, 129.4, 129.2, 109.2 ppm. IR: 3309, 3082, 3054, 2847, 1678, 1663, 1450, 1432, 1306, 1219, 1125, 1076, 915, 848, 837, 754, 724, 690, 662, 633 cm\(^{-1}\). HRMS (ESI) m/z calcd. for C\(_{11}\)H\(_8\)BrOS (M+H\(^+\), M+2+H\(^+\)): 266.9474, 268.9454; found: 266.9476, 268.9451.
10g-H was prepared according to General Procedure A. Thus, 2-acetyl-5-bromothiophene (1.03 g, 5.00 mmol, 1.00 eq.), phenylboronic acid (914 mg, 7.50 mmol, 1.50 eq.), 18 (85 mg, 0.10 mmol, 2%), THF (5 mL), and aq. K$_3$PO$_4$ (1.0 M, 10 mL, 20 mmol, 2.0 eq.) were combined in a 50 mL roundbottom flask and allowed to stir at 60 ºC for 12 h. Purification of the crude reaction mixture by flash chromatography (0 → 2.5 → 5 → 7.5% EtOAc/hexanes) yielded 2-acetyl-5-phenylthiophene (840 mg, 83%) as a pale yellow solid. Melting Point: 114-116 ºC (Lit. 115 ºC).$^57$ ¹H NMR (500 MHz, CDCl$_3$): δ 7.64-7.67 (m, 3H), 7.42 (pt, J = 7 Hz, 2H), 7.37 (tt, J = 8, 2 Hz, 1H), 7.32 (d, J = 4 Hz, 1H), 2.57 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl$_3$): δ 190.7, 152.9, 143.2, 133.6, 133.4, 129.2, 126.4, 124.0, 26.7 ppm. IR: 3081, 3001, 1645, 1530, 1441, 1362, 1275, 1087, 1036, 926, 908, 809, 756, 687, 661, 611, 586 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^57$

10g-Br was prepared according to General Procedure B. Thus, 2-phenyl-5-acetylthiophene (700 mg, 3.46 mmol, 1.00 eq.), N-bromosuccinimide (862 mg, 4.84 mmol, 1.40 eq.), and DMF (10 mL) were combined in a 25 mL roundbottom flask and allowed to stir at 50 ºC overnight. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, followed by recrystallization of the resulting solid from MeOH, yielded 2-acetyl-4-bromo-5-phenylthiophene (925 mg, 95%) as a pale yellow solid. Melting Point: 70 ºC. ¹H NMR (500 MHz, CDCl$_3$): δ 7.67 (dd, J = 8, 2
Hz, 2H), 7.63 (s, 1H), 7.43-7.48 (m, 3H), 2.56 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.8, 146.9, 142.3, 136.4, 132.1, 129.5, 129.1, 128.8, 108.1, 26.5 ppm. IR: 3077, 1652, 1431, 1359, 1312, 1270, 1155, 1078, 1046, 922, 882, 861, 831, 760, 697, 682, 632, 608, 595 cm$^{-1}$. Anal. Calcd. for C$_{12}$H$_9$BrOS: C, 51.26; H, 3.23; found: C, 51.08; H, 3.07. It should be noted that the $^1$H NMR shift of the proton located on the thiophene ring in the potentially formed regioisomeric compound 2-acetyl-3-bromo-5-phenylthiophene is predicted to be more than 0.5 ppm (~7.2 ppm) upfield from where it is observed (~7.7 ppm), suggesting that the desired product formed exclusively.

$^{10}$h-H was prepared according to General Procedure A. Thus, 2-bromo-5-nitrothiophene (1.64 g, 8.00 mmol, 1.00 eq.), phenylboronic acid (1.46 g, 12.0 mmol, 1.50 eq.), $^{18}$ (272 mg, 0.32 mmol, 4%), THF (8.0 mL), and aq. K$_3$PO$_4$ (1.0 M, 16.0 mL, 16 mmol, 2.0 eq.) were combined in a 100 mL roundbottom flask and allowed to stir at 60 $^\circ$C overnight. The crude reaction mixture was purified by flash chromatography (2 $\rightarrow$ 4 $\rightarrow$ 6% EtOAc/hexanes); all of the fractions containing the desired product were collected and concentrated to provide a brown solid. This solid was recrystallized from hot MeOH to afford 5-phenyl-2-nitrothiophene (927 mg, 57 %) as an orange-brown solid. Melting Point: 126 $^\circ$C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J$ = 4 Hz, 1H), 7.61-7.64 (m, 2H), 7.42-7.48 (m, 3H), 7.24 (d, $J$ = 5 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 152.2, 132.2, 130.2, 129.8, 129.5, 126.4, 122.5 ppm (the $^{13}$C-NO$_2$ signal could not be readily
observed). IR: 3110, 1536, 1449, 1425, 1353, 1326, 1248, 1043, 1028, 958, 812, 755, 731 cm\(^{-1}\). Anal. Calcd. for C\(_{10}\)H\(_7\)NO\(_2\)S: C, 58.52; H, 3.44; found: C, 58.46; H, 3.54.

**10h-Br** was prepared according to General Procedure B. Thus, 5-phenyl-2-nitrothiophene (920 mg, 4.52 mmol, 1.00 eq.), Br\(_2\) (932 \(\mu\)L, 18.1 mmol, 4.00 eq.), and DMF (20 mL) were combined at 0 °C and allowed to stir at room temperature for 12 h. The crude reaction mixture was filtered through a silica gel plug, eluting with ether, and concentrated to afford an orange solid. This solid was triturated with cold methanol, filtered, and washed with additional cold methanol, to afford 4-bromo-5-phenyl-2-nitrothiophene (897 mg, 70%) as a bright yellow solid. Melting Point: 69 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.91 (s, 1H), 7.64-7.69 (m, 2H), 7.48-7.32 (m, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 146.1, 132.4, 130.9, 130.4, 129.2, 129.2, 107.4 ppm (the \(^{13}\)C-NO\(_2\) signal could not be readily observed). IR: 3110, 1596, 1525, 1299, 1289, 1489, 1446, 1421, 1350, 1319, 1218, 1162, 1084, 1071, 1033, 1000, 960, 910, 855, 842, 804, 753, 779, 718, 689 cm\(^{-1}\). Anal. Calcd. for C\(_{10}\)H\(_7\)BrNO\(_2\)S: C, 42.27; H, 2.13; found: C, 42.01; H, 2.12. It should be noted that the \(^1\)H NMR shift of the proton located on the thiophene ring in the potentially formed regioisomeric compound 3-bromo-2-nitro-5-phenylthiophene is predicted to be more than 0.8 ppm (~7.1 ppm) upfield from where it is observed (~7.9 ppm), suggesting that the desired product formed exclusively.
10i-H was prepared according to General Procedure A. Thus, 2-bromo-5-cyanothiophene (940 mg, 5.00 mmol, 1.00 eq.), phenylboronic acid (915 mg, 7.50 mmol, 1.50 eq.), 18 (169 mg, 0.20 mmol, 4%), THF (5.0 mL), and aq. K$_3$PO$_4$ (1.0 M, 10 mL, 10 mmol, 2.0 eq.) were combined in a 50 mL Schlenk tube and allowed to stir at 40 °C for 12 h. The crude reaction mixture was purified by flash chromatography (0 → 4% EtOAc/hexanes); all of the fractions containing the desired product were collected and concentrated to afford a yellow solid, which was recrystallized from hot hexanes to afford 2-cyano-5-phenylthiophene (387 mg, 42%) as a yellow solid. Melting Point: 85-87 °C (Lit. 86-87 °C).$^{58}$ $^1$H NMR (500 MHz, CDCl$_3$): 8 7.59-7.62 (m, 3H), 7.38-7.46 (m, 3H), 7.28 (d, J = 4 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): 8 152.0, 138.5, 132.4, 129.6, 129.4, 126.5, 123.4, 114.5, 108.3 ppm. IR: 3097, 2219, 1493, 1455, 1254, 1239, 1157, 1058, 999, 954, 909, 816, 753, 684 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{58}$

10i-Br was prepared according to General Procedure C. Thus, 2-cyano-5-phenylthiophene (463 mg, 2.50 mmol, 1.00 eq.), Br$_2$ (516 μL, 10.0 mmol, 4.00 eq.), and DMF (10 mL) were combined at 0 °C and allowed to stir at room temperature for 12 h. The crude reaction mixture was filtered through a silica gel plug, eluting with ether, and concentrated. The resulted yellow solid was recrystallized from hot hexanes to afford 4-bromo-2-cyano-5-phenylthiophene (355 mg, 54%) as a fluffy pale yellow solid. Melting
Point: 76-78 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.61-7.65 (m, 2H), 7.57 (s, 1H), 7.46-7.50 (m, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 145.8, 141.0, 130.9, 130.0, 129.3, 129.1, 113.2, 108.2, 99.9 ppm IR: 3093, 2223, 1448, 1433, 1321, 1220, 1167, 1116, 1073, 868, 838, 753, 721, 688, 629 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{11}$H$_{10}$BrN$_2$S (M+NH$_4^+$, M+2+NH$_4^+$): 280.9743, 282.9723; found: 280.9745, 282.9721. It should be noted that the $^1$H NMR shift of the proton located on the thiophene ring in the potentially formed regioisomeric compound 3-bromo-2-cyano-5-phenylthiophene is predicted to be more than 0.4 ppm (~7.2 ppm) upfield from where it is observed (~7.6 ppm), suggesting that the desired product formed exclusively.

10j-H was prepared according to General Procedure A. Thus, methyl 4-bromo-thiophene-2-carboxylate (1.00 g, 4.52 mmol, 1.00 eq.), phenylboronic acid (827 mg, 6.80 mmol, 1.50 eq.), 18 (77.0 mg, 0.09 mmol, 2%), THF (4.5 mL), and aq. K$_3$PO$_4$ (1 M, 9.0 mL, 9.0 mmol, 2.0 eq.) were combined in a Schlenk tube and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (0 → 2.5 → 5% EtOAc/hexanes) yielded methyl 4-phenylthiophene-2-carboxylate (689 mg, 70%) as an off-white solid. Melting Point: 95 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.09 (d, J = 2 Hz, 1H), 7.65 (d, J = 2 Hz, 1H), 7.59 (d, J = 7 Hz, 2H), 7.42 (pt, J = 8 Hz, 2H), 7.33 (t, J = 7 Hz, 1H), 3.92 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.7, 143.0, 134.9, 134.2, 132.3, 129.1, 127.9, 127.0, 126.4, 52.4 ppm. IR: 3099, 2950, 1705, 1547, 1440, 1259, 626

10j-Br was prepared according to General Procedure B. Thus, methyl 4-phenylthiophene-2-carboxylate (600 mg, 2.75 mmol, 1.00 eq.), N-bromosuccinimide (684 mg, 3.85 mmol, 1.40 eq.), and DMF (10 mL) were combined in a 25 mL roundbottom flask and allowed to stir at room temperature overnight. Filtration of the crude reaction mixture through a silica gel plug, eluting with ether, was sufficient to provide methyl 5-bromo-4-phenylthiophene-2-carboxylate (770 mg, 94%) as a pale yellow solid. Recrystallization from MeOH could provide the desired material as an off-white solid. Melting Point: 80 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.72 (s, 1H), 7.54 (d, J = 9 Hz, 2H), 7.45 (pt, J = 9 Hz, 2H), 7.39 (t, J = 7 Hz, 1H), 3.90 (s, 3) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 161.8, 142.4, 134.7, 134.2, 133.1, 128.7, 128.6, 128.3, 116.5, 52.5 ppm. IR: 3099, 2950, 1705, 1547, 1440, 1259, 1205, 1084, 869, 853, 791, 748, 688 cm⁻¹. Anal. Calcd. for C₁₂H₉BrO₂S: C, 48.50; H, 3.05; found: C, 48.59; H, 3.03.

Br
\[ \text{PhB(OH)}_2 \]
\[ \text{K}_3\text{PO}_4 \]
\[ \text{THF/H}_2\text{O, 60 °C, 24 h} \]
\[ \text{Ph} \]
\[ \text{10k-H} \]
\[ \text{NBS} \]
\[ \text{DMF, 0 °C, 2.5 h} \]
\[ \text{Ph} \]
\[ \text{10k-Br} \]

10k-H was prepared according to General Procedure A. Thus, 2,4-dibromothiophene (1.12 mL, 10.0 mmol, 1.00 eq.), phenylboronic acid (3.05 g, 25.0 mmol, 2.50 eq.), 18 (169 mg, 0.20 mmol, 2%), THF (10 mL), and aq. K₃PO₄ (1 M, 20 mL, 10 mmol, 3.0 eq.) were combined in a 100 mL Schlenk tube and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (0 → 1%
EtOAc/hexanes) yielded a white solid that was ~95% 10k-H, as judged by $^1$H NMR. Recrystallization of this material from MeOH yielded 2,4-diphenylthiophene (1.88 g, 80%) as a white crystalline solid. Melting Point: 120 °C (Lit. 124-125 °C).$^{59}$ $^1$H NMR (500 MHz, CDCl$_3$): δ 7.63-7.70 (m, 4H), 7.62 (d, J = 2 Hz, 1H), 7.40-7.46 (m, 5H), 7.31-7.36 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 145.2, 143.3, 136.0, 134.4, 129.1, 129.0, 127.8, 127.4, 126.4, 126.0, 122.5, 119.8 ppm. IR: 3053, 3037, 1595, 1481, 1447, 1365, 1198, 1155, 1075, 1028, 965, 910, 885, 834, 751, 734, 691 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{60}$

10k-Br was prepared according to a modification of General Procedure B to prevent formation of dibrominated and regioisomeric monobrominated side products. 2,4-diphenylthiophene (945 mg, 4.00 mmol, 1.00 eq.) was dissolved in CH$_2$Cl$_2$ (10 mL) and DMF (10 mL) in a 50 mL roundbottom flask wrapped in aluminum foil. The flask was cooled to 0 °C. N-bromosuccinimide (1.07 g, 6.00 mmol, 1.50 eq.) was added in one portion, and the reaction mixture was allowed to stir at 0 °C for 2.5 h. At this time, saturated aq. Na$_2$SO$_3$ (20 mL) and ether (20 mL) were added, and the organic phase was carefully removed with the aid of a rotary evaporator. The resulting suspension was diluted with ether (20 mL), and the phases were separated. The aqueous phase was further extracted with ether (2 × 20 mL), and the combined organic phases were washed with water (2 × 20 mL) and brine (20 mL), dried over MgSO$_4$, filtered, and concentrated, to afford 2-bromo-3,5-diphenylthiophene (1.18 g, 94%) as a thick yellow oil that solidified upon standing at 0 °C. Melting Point: 54-56 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.62 (dd, J = 9, 2 Hz, 2H), 7.57 (dd, J = 9, 1 Hz, 2H), 7.47 (t, J = 8 Hz, 2H), 7.38-7.43
(m, 3H), 7.34 (t, J = 8, 2 Hz, 1H), 7.25 (s, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 144.3, 142.3, 131.2, 133.6, 129.3, 128.7, 128.6, 128.2, 127.9, 125.7, 124.8, 107.9 ppm. IR: 3054, 3023, 1598, 1505, 1487, 1446, 1215, 1072, 1030, 992, 951, 837, 751, 687 cm$^{-1}$. Anal. Calcd. for C$_{16}$H$_{11}$BrS: C, 60.96; H, 3.52; found: C, 60.98; H, 3.59.

$^{101}$-H was prepared according to General Procedure A. Thus, 3-bromo-5-methylthiophene (336 μL, 3.00 mmol, 1.00 eq.), phenylboronic acid (549 mg, 4.50 mmol, 1.50 eq.), 18 (51.0 mg, 0.10 mmol, 2%), XPhos (48.0 mg, 0.06 mmol, 2%), THF (3 mL), and $aq.$ K$_3$PO$_4$ (1 M, 6.0 mL, 6.0 mmol, 2.0 eq.) were combined in a reaction tube and allowed to stir at 60 ºC for 12 h. Purification of the crude reaction mixture by flash chromatography (hexanes) yielded 3-phenyl-5-methylthiophene (380 mg, 73%) as a white solid. Melting Point: 75 ºC (Lit. 75-77 ºC).$^{61}$ $^1$H NMR (500 MHz, CDCl$_3$): δ 7.58 (d, J = 8 Hz, 2H), 7.40 (pt, J = 8 Hz, 2H), 7.29 (t, J = 8 Hz, 1H) (d, J = 2 Hz, 1H), 7.08 (bs, 1H), 2.55 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 142.2, 140.6, 136.2, 128.9, 127.1, 126.4, 124.8, 118.1, 15.6 ppm. IR: 3102, 3011, 2917, 1501, 1458, 1205, 1149, 1028, 893, 851, 830, 770, 728, 687, 644 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{61}$

$^{101}$-Br was prepared according to General Procedure B. Thus, 3-phenyl-5-methylthiophene (261 mg, 1.50 mmol, 1.00 eq.), N-bromosuccinimide (295 mg, 1.65 mmol, 1.10 eq.), and DMF (6 mL) were combined in a 25 mL roundbottom flask and
allowed to stir at room temperature overnight. Purification of the crude product mixture by flash chromatography (hexanes) yielded 2-bromo-5-methyl-3-phenylthiophene (225 mg, 59%) as a colorless oil contaminated with ~4% of 10l-H.\(^{62}\)\(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.54-7.57 (m, 2), 7.44 (pt, \(J = 9\) Hz, 2H), 7.36 (tt, \(J = 8, 2\) Hz, 1H), 6.74 (t, \(J = 1\) Hz, 1H), 2.47 (t, \(J = 1\) Hz, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 141.0, 140.1, 135.4, 128.7, 128.4, 127.6, 127.3, 105.1, 15.7 ppm. IR: 3058, 2917, 1736, 1601, 1503, 1436, 1229, 1144, 1030, 986, 827, 759, 695, 640, 605 cm\(^{-1}\). HRMS (ESI) m/z calcd. for C\(_{11}\)H\(_{10}\)BrS [M+H\(^{+}\), M+2+H\(^{+}\)]: 252.9681, 254.9660; found: 252.9696, 254.9675.

\[
\begin{array}{c}
\text{MeO}_2\text{C} & \text{S} & \text{NBS} & \text{DMF,} 50^\circ\text{C, 12 h} & \text{MeO}_2\text{C} \\
\text{Me} & \text{Br} & \text{10m-Br} & \text{Me}
\end{array}
\]

10m-Br was prepared according to General Procedure B. Thus, methyl 5-methylthiophene-2-carboxylate (312 mg, 2.00 mmol, 1.00 eq.), N-bromosuccinimide (712 mg, 4.00 mmol, 2.00 eq.), and DMF (5 mL) were combined in a 25 mL roundbottom flask and allowed to stir at 50 °C overnight. Purification of the crude product mixture by filtration through a silica gel plug, eluting with Et\(_2\)O, provided methyl 4-bromo-5-methylthiophene-2-carboxylate (395 mg, 84%) as an amber solid. Melting Point: 42-44 °C. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.58 (s, 1H), 3.86 (s, 3H), 2.42 (s, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 161.8, 142.4, 135.9, 130.2, 110.4, 99.9, 52.4, 15.5 ppm. IR: 3091, 2950, 1706, 1452, 1334, 1244, 1151, 1081, 1002, 806, 750, 631 cm\(^{-1}\). Anal. Calcd. for C\(_7\)H\(_7\)BrO\(_2\)S: C, 35.76; H, 3.00; found: C, 35.80; H, 2.98. It should be noted that the \(^{1}\)H NMR shift of the proton located on the thiophene ring in the potentially formed regioisomeric compound methyl 3-bromo-5-methylthiophene-2-carboxylate is
predicted to be more than 1 ppm (~6.5 ppm) upfield from where it is observed (~7.6 ppm), suggesting that the desired product formed exclusively.

\[
\begin{align*}
\text{MeO}_2C &= \\
\text{S} &= \\
\text{NBS} &= \\
\text{DMF, rt, 12 h} &= \\
\text{MeO}_2C &= \\
\text{S} &= \\
\text{Br} &= \\
\end{align*}
\]

**10n-Br** was prepared according to General Procedure B. Thus, methyl 4-methylthiophene-2-carboxylate (312 mg, 2.00 mmol, 1.00 eq.), N-bromosuccinimide (463 mg, 2.60 mmol, 1.30 eq.), and DMF (2 mL) were combined in a 10 mL roundbottom flask and allowed to stir at room temperature for 12 h. Filtration of the crude product mixture through a silica gel plug, eluting with EtO, provided methyl 5-bromo-4-methylthiophene-2-carboxylate (407 mg, 87%) as an off-white solid. Melting Point: 39 °C. \(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.46 (s, 1H), 3.85 (s, 3H), 2.19 (s, 3H) ppm; \(^13C\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 161.9, 138.6, 135.0, 132.3, 117.8, 52.4, 15.3 ppm. IR: 3074, 3000, 2950, 2924, 1717, 1556, 1438, 1419, 1354, 1241, 1191, 1075, 1021, 980, 877, 782, 743, 704, 585 cm\(^{-1}\). HRMS (ESI) m/z calcd. for \(C_7H_{11}BrO_2SN\) (M+\(NH_4^+\), M+2+\(NH_4^+\)): 251.9688, 253.9709; found: 251.9688, 253.9663.

\[
\begin{align*}
\text{Br S S Br} &= \\
\text{cat. 18} &= \\
\text{THF/H}_2\text{O, 60 °C, 12 h} &= \\
\text{PhS S Ph} &= \\
\text{NBS} &= \\
\text{DMF, rt, 12 h} &= \\
\text{PhS S Ph} &= \\
\end{align*}
\]

**10o-H** was prepared according to General Procedure A. Thus, 2,5-dibromo-3-methylthiophene (1.50 g, 5.90 mmol, 1.00 eq.), phenylboronic acid (1.79 g, 14.7 mmol, 2.50 eq.), **18** (250 mg, 0.30 mmol, 5%), THF (6 mL), and \(aq.\) \(K_3PO_4\) (2M, 9 mL, 18.0 mmol, 3 eq.) were combined in a 50 mL Schlenk tube and allowed to stir at 60 °C for 12
h. Purification of the crude reaction mixture by flash chromatography (hexanes) provided 2,5-diphenyl-3-methylthiophene (780 mg, 53%) as an off-white solid. Melting Point: 85 °C (Lit. 86-87 °C).\textsuperscript{63} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.65 (dd, J = 9, 2 Hz, 2H), 7.56 (dd, J = 7, 1 Hz, 2H), 7.46 (pt, J = 8 Hz, 2H), 7.41 (pt, J = 7 Hz, 2H), 7.36 (tt, J = 8, 2 Hz, 1H), 7.31 (tt, J = 8, 1 Hz, 1H), 7.20 (s, 1H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 141.9, 137.5, 134.8, 134.4, 134.3, 129.0, 128.9, 128.7, 127.5, 127.4, 127.3, 125.6, 15.3 ppm. IR: 3049, 2926, 1596, 1486, 1448, 1182, 1075, 1012, 838, 755, 722, 695, 627 cm\textsuperscript{-1}. These spectra are consistent with those reported in the literature.\textsuperscript{63}

\textbf{10o-Br} was prepared according to a slightly modified General Procedure B. Thus, 2,5-diphenyl-3-methylthiophene (3200 mg, 0.80 mmol, 1.00 eq.), N-bromosuccinimide (214 mg, 1.20 mmol, 1.50 eq.), DMF (2 mL), and CH\textsubscript{2}Cl\textsubscript{2} (1 mL, to solubilize the starting material) were combined and allowed to stir at room temperature overnight. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with hexanes, provided 3-bromo-2,5-diphenyl-4-methylthiophene (154 mg, 59%) as a crystalline white solid. Melting Point: 104 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.71 (d, J = 8 Hz, 2H), 7.44-7.50 (m, 6H), 7.40 (pt, J = 7 Hz, 2H), 2.37 (s, 3H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 137.4, 136.7, 134.3, 133.8, 133.5, 129.3, 129.2, 128.8, 128.6, 128.3, 128.0, 112.0, 15.9 ppm. IR: 3049, 2994, 2916, 1597, 1485, 1440, 1346, 1251, 1178, 1080, 1035, 1024, 1010, 919, 810, 753, 698, 586 cm\textsuperscript{-1}. HRMS (ESI) m/z calcd. for C\textsubscript{17}H\textsubscript{14}BrS [M+H\textsuperscript{+}, M+2+H\textsuperscript{+}]: 328.9994, 330.9979; found: 328.9996, 330.9977.
10p-H was prepared according to General Procedure A. Thus, 2,3,5-tribromothiophene (646 μL, 5.00 mmol, 1.00 eq.), phenylboronic acid (2.13 g, 17.5 mmol, 3.50 eq.), 18 (212 mg, 0.25 mmol, 5%), THF (5 mL), and aq. K₃PO₄ (1M, 20 mL, 20 mmol, 4.0 eq.) were combined in a 100 mL Schlenk tube and allowed to stir at 60 °C for 12 h. Purification of the crude reaction mixture by flash chromatography (hexanes → 1% EtOAc/hexanes) yielded 2,3,5-triphenylthiophene (1.23 g, 79%) as a fluffy yellow solid. Melting Point: 139-141 °C (Lit. 144-145 °C).¹ H NMR (500 MHz, CDCl₃): δ 7.66 (d, J = 7 Hz, 2H), 7.37-7.43 (m, 3H), 7.25-7.36 (m, 11H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 142.7, 139.1, 138.1, 136.7, 134.3, 134.2, 129.3, 129.2, 129.1, 128.6, 128.6, 127.8, 127.6, 127.2, 126.7, 125.7 ppm. IR: 3058, 3021, 1597, 1484, 1446, 1070, 1029, 914, 846, 754, 695 cm⁻¹. These spectra are consistent with those reported in the literature.²

10p-Br was prepared according to a slightly modified General Procedure B. Thus, 2,3,5-triphenylthiophene (625 mg, 2.00 mmol, 1.00 eq.), N-bromosuccinimide (392 mg, 2.20 mmol, 1.10 eq.), DMF (5 mL), and CH₂Cl₂ (2 mL) were combined and allowed to stir at room temperature overnight. The crude reaction mixture was filtered through a silica gel plug, eluting with CH₂Cl₂, and concentrated. The resulting solid was recrystallized from hot methanol to afford 4-bromo-2,3,5-triphenylthiophene (590 mg, 75%) as a pale yellow solid. Melting Point: 129 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.75 (dd, J = 7, 2 Hz, 2H), 7.49 (pt, J = 8 Hz, 2H), 7.36-7.44 (m, 5H), 7.32 (dd, J = 8, 2 Hz, 2H), 7.23 (bs, 5H) ppm;
$^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\text{)}$: $\delta$ 139.4, 139.1, 137.2, 136.0, 133.7, 133.4, 130.9, 129.5, 128.9, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 111.2 ppm. IR: 3058, 3021, 1598, 1484, 1446, 1070, 1029, 914, 846, 754, 695 cm$^{-1}$. Anal. Calcd. for C$_{22}$H$_{15}$BrS: C, 67.52; H, 3.86; found: C, 67.56; H, 3.94.

$\text{Br Ph Ph} / \text{PhB(OH)}_2$ cat. 18

$11c$-Br was prepared according to General Procedure B. Thus, 3-methylbenzo[b]thiophene (1.96 g, 11.0 mmol, 1.10 eq.), and DMF (10 mL) were combined in a 50 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with hexanes, provided 2-bromo-3-methylbenzo[b]thiophene (1.86 g, 82%) as a colorless oil. $^1\text{H} \text{NMR (500 MHz, CDCl}_3\text{)}$: $\delta$ 7.71-7.74 (m, 1H), 7.62-7.65 (m, 1H), 7.31-7.39 (m, 2H), 2.39 (d, $J = 1$ Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.7, 139.0, 131.9, 124.6, 124.6, 121.9, 121.8, 112.6, 13.2 ppm. IR: 3060, 2914, 2853, 1936, 1899, 1779, 1569, 1530, 1458, 1425, 1377, 1256, 1136, 1097, 1052, 1011, 944, 747, 724, 707, 604, 585 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{65}$

$11d$-H was prepared according to General Procedure A. Thus, 3-bromobenzo[b]thiophene (1.31 mL, 10.0 mmol, 1.00 eq.), phenylboronic acid (1.46 g, 12.0 mmol, 1.20 eq.), 18 (170 mg, 0.20 mmol, 2%), THF (10 mL), $aq$ K$_3$PO$_4$ (2M, 10
mL, 20 mmol, 2 eq.) were combined in a 100 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by flash chromatography (hexanes) provided 3-phenylbenzo[b] thiophene (1.85 g, 88%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.95-7.99 (m, 2H), 7.62-7.65 (m, 2H), 7.53 (pt, $J = 10$ Hz, 2H), 7.42-7.47 (m, 4H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 140.8, 138.2, 138.0, 136.1, 128.9, 128.8, 127.7, 124.5, 124.5, 123.5, 123.0 ppm. IR: 3055, 1600, 1524, 1483, 1441, 1425, 1347, 1259, 1073, 1061, 1027, 940, 914, 833, 760, 729, 696, 637, 573 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{66}$

11d-Br was prepared according to General Procedure B. Thus, 3-phenylbenzo[b] thiophene (1.05 g, 5.00 mmol, 1.00 eq.), N-bromosuccinimide (979 mg, 5.50 mmol, 1.10 eq.), and DMF (10 mL) were combined in a 50 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with hexanes, provided 2-bromo-3-phenylbenzo[b] thiophene (511 mg, 35%) as a white solid. Melting Point: 72 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.79 (ddd, $J = 8, 2, 1$ Hz, 1H), 7.47-7.61 (m, 7H), 7.32-7.40 (m, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.9, 138.9, 137.2, 134.0, 130.1, 1128.7, 128.2, 124.9, 123.0, 121.8, 113.4 ppm. IR: 3052, 1598, 1482, 1455, 1440, 1427, 1332, 1259, 1153, 1130, 1071, 1027, 990, 886, 858, 758, 729, 710, 696, 640, 609 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_9$BrS: C, 58.15; H, 3.14; found: C, 58.42; H, 3.25.
This procedure was adapted from the literature. Pd(OAc)$_2$ (90.0 mg, 0.40 mmol, 5%), tricyclohexylphosphine tetrafluoroborate (220 mg, 0.60 mmol, 6%), and K$_2$CO$_3$ (2.08 g, 15.0 mmol, 1.50 eq.) were combined in a 100 mL Schlenk tube equipped with a stir bar. The tube was placed under high vacuum and backfilled with argon. This process was repeated a total of three times. The screw-cap was replaced with a septum, and benzo[b]thiophene (1.17 mL, 10.0 mmol, 1.00 eq., warmed gently prior to use), bromobenzene (1.05 mL, 10.0 mmol, 1.00 eq.), pivalic acid (345 tL, 3.00 mmol, 0.30 eq.), and DMA (25 mL) were added. The septum was replaced with the screw-cap, and the tube was placed in an oil bath pre-heated to 100 °C and allow to stir for 12 h. At this time, the tube was cooled to room temperature, and the reaction mixture was diluted with hexanes (50 mL) and water (50 mL). The phases were separated, and the aqueous phase was further extracted with hexanes (2 × 25 mL). The combined organic phases were washed with water (2 × 25 mL) and brine (25 mL), dried over MgSO$_4$, filtered through a silica gel plug, eluting with hexanes, and concentrated. The resulting brown solid was recrystallized from hot hexanes to afford 2-phenylbenzo[b]thiophene (11f-H) (1.15 g, 55%) as an off-white solid. Melting Point: 172 °C (Lit. 168-169 °C).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J = 8$ Hz, 1H), 7.79 (d, $J = 8$ Hz, 1H), 7.74 (d, $J = 8$ Hz, 2H), 7.56 (s, 1H), 7.44 (t, $J = 8$ Hz, 2H), 7.30-7.38 (m, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.4, 140.8, 139.6, 134.4, 129.1, 128.4, 126.6, 124.7, 124.5, 123.7, 122.4.
119.6 ppm. IR: 3052, 1486, 1446, 1335, 1194, 1071, 1028, 944, 825, 756, 724, 685 cm\(^{-1}\). These spectra are consistent with those reported in the literature.\(^6\)

**11f-Br** was prepared according to General Procedure B. Thus, 2-phenylbenzo[b]thiophene (1.00 g, 4.76 mmol, 1.00 eq.), N-bromosuccinimide (933 mg, 5.24 mmol, 1.10 eq.), and DMF (10 mL) were combined in a 50 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, followed by recrystallization of the resulting solid from MeOH, provided 3-bromo-2-phenylbenzo[b]thiophene (1.27 g, 92%) as a pale yellow solid. Melting Point: 62 °C (Lit. 62-63 °C).\(^6\)

\(^{1}H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.91 (d, \(J = 8\) Hz, 1H), 7.83 (d, \(J = 8\) Hz, 1H), 7.79 (dd, \(J = 9\), 2 Hz, 2H), 7.41-7.47 (m, 2H) ppm; \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 139.9, 138.9, 137.2, 134.0, 130.1, 128.7, 128.2, 124.9, 123.0, 121.8, 113.4 ppm. IR: 3055, 3021, 1600, 1481, 1443, 1431, 1299, 1249, 1015, 886, 794, 743, 723, 686 cm\(^{-1}\).

These spectra are consistent with those reported in the literature.\(^6\)

![Chemical structure](image)

A 25 mL roundbottom flask equipped with a stir bar and wrapped in aluminum foil was charged with 2,5-diphenylfuran (220 mg, 1.00 mmol, 1.00 eq.). CHCl\(_3\) (6 mL) was added, followed by N-bromosuccinimide (214 mg, 1.20 mmol, 1.20 eq.), and the reaction mixture was allowed to stir at room temperature for 12 h. The solvent was removed, and the resulting solid was partitioned between Et\(_2\)O (10 mL) and water (10 mL). The phases
were separated, and the aqueous phase was further extracted with Et₂O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and filtered through a silica gel plug, eluting with Et₂O. The solvent was removed in vacuo, and the resulting yellow solid was recrystallized from hot MeOH, which yielded 3-bromo-2,5-diphenylfuran (12b-Br) (127 mg, 43%) as a pale orange solid. Melting Point: 82 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, J = 6 Hz, 2H), 7.71 (d, J = 7 Hz, 2H), 7.40-7.49 (m, 4H), 7.30-7.38 (m, 2H), 6.79 (s, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 152.8, 148.2, 129.9, 129.8, 129.0, 128.7, 128.3, 128.1, 125.6, 124.0, 111.5, 98.1 ppm. IR: 3125, 3055, 2981, 1589, 1448, 1193, 1068, 1053, 1034, 953, 911, 802, 757, 685, 662 cm⁻¹. Anal. Calcd. for C₁₆H₁₂BrO: C, 64.24; H, 3.71; found: C, 64.21; H, 3.84.

MeO₂C      PhB(OH)₂
O       cat. 18
Br       K₃PO₄
THF/H₂O, 60 °C, 12 h

12c-H was prepared according to General Procedure A. Thus, methyl 5-bromofuran-2-carboxylate (820 mg, 4.00 mmol, 1.00 eq.), phenylboronic acid (731 mg, 6.00 mmol, 1.50 eq.), 18 (67.7 mg, 0.08 mmol, 2%), THF (4 mL), and aq. K₃PO₄ (1M, 8.0 mL, 8.0 mmol, 2.0 eq.) were combined in a 50 mL Schlenk flask and allowed to stir at 60 °C overnight. Purification of the crude reaction mixture by flash chromatography (0 → 2.5 → 5% EtOAc/hexanes) yielded methyl 5-phenylfuran-2-carboxylate (666 mg, 82%) as a white solid. Melting Point: 66 °C (Lit. 58-60°C). ¹H NMR (500 MHz, CDCl₃): δ 7.78 (dd, J = 9, 1 Hz, 2H), 7.40-7.44 (m, 2H), 7.35 (tt, J = 8, 2 Hz, 1H), 7.25 (d, J = 4 Hz, 1H), 6.74 (d, J = 4 Hz, 1H), 3.92 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 159.3, 157.7, 143.7, 129.6, 129.1, 128.9, 124.9, 120.2, 107.0, 52.0 ppm. IR: 3124, 3030, 2954, 1713, 638
1525, 1475, 1452, 1434, 1374, 1308, 1276, 1224, 1196, 1145, 1035, 989, 917, 811, 797, 758, 764, 670 cm⁻¹. These spectra are consistent with those reported in the literature.⁶⁹

**12c-Br** was prepared according to General Procedure C. Thus, methyl 5-phenylfuran-2-carboxylate (408 mg, 2.00 mmol, 1.00 eq.), Br₂ (412 μL, 8.00 mmol, 4.00 eq.), and DMF (10 mL) were combined and allowed to stir at 0 °C for 30 min. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, provided 4-bromo-5-phenylfuran-2-carboxylate (461 mg, 82%) as a white solid. Melting Point: 89 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.05 (dd, J = 7, 2 Hz, 2H), 7.46 (pt, J = 7 Hz, 2H), 7.41 (tt, J = 8, 2 Hz, 1H), 7.26 (s, 1H), 3.92 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 152.5, 142.8, 129.5, 128.7, 128.7, 126.6, 123.4, 97.2, 52.3 ppm. IR: 3128, 2953, 2845, 1723, 1568, 1532, 1473, 1444, 1368, 1303, 1196, 1116, 990, 956, 881, 798, 772, 758, 688, 665 cm⁻¹. Anal. Calcd. for C₁₂H₉BrO₃: C, 51.27; H, 3.23; found: C, 51.00; H, 3.31.

![Chemical Reaction Diagram](attachment:image.png)

**12d-Br** was prepared according to General Procedure B. Thus, 2-ethylbenzo[b]furan (292 mg, 2.00 mmol, 1.00 eq.), N-bromosuccinimide (463 mg, 2.60 mmol, 1.30 eq.), and DMF (2.0 mL) were combined in a 10 mL roundbottom flask and allowed to stir at room temperature overnight.⁷⁰ Purification of the crude reaction mixture by flash chromatography (hexanes) afforded 3-bromo-2-ethylbenzo[b]furan (185 mg, 41%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.47 (m, 2H), 7.27-7.31 (m, 2H), 2.87
(q, J = 8 Hz, 2H), 1.34 (t, J = 8 Hz, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 156.8, 153.5, 128.5, 124.5, 123.2, 119.2, 111.2, 93.5 ppm. IR: 2975, 2939, 2877, 1599, 1450, 1261, 1173, 1106, 1010, 999, 838, 739 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{10}$H$_8$BrO [M-H$^+$, M+2-H$^+$]: 222.9753, 224.9738; found: 222.9779, 224.9759.

This procedure was adapted from the literature.$^{71}$ Benzo[b]furan (576 μL, 5.20 mmol, 1.30 eq.) and THF (10 mL) were added to an oven-dried 50 mL roundbottom flask under an atmosphere of argon. The flask was cooled to −78 °C, and nBuLi (2.5 M in hexanes, 2.28 mL, 5.72 mmol, 1.43 eq.) was added dropwise. The nonhomogenous reaction mixture was allowed to stir vigorously at −78 °C for 1 h, at which time ZnCl$_2$ (1.9 M in 2MeTHF, 3.28 mL, 6.24 mmol, 1.56 eq.) was added dropwise. The reaction mixture was allowed to warm to rt and stir for 1 h, during which time it turned yellow and became homogenous. Next, bromobenzene (420 μL, 4.00 mmol, 1.00 eq.) was added via syringe. The septum was removed, and under a positive pressure of argon 18 (72.8 mg, 0.08 mmol, 2%) and XPhos (38.4 mg, 0.08 mmol, 2%) were added quickly. The reaction mixture was allowed to stir at rt for 12 h. At this time, ether (20 mL) and water (20 mL) were added, and the phases were separated. The aqueous phase was further extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried over MgSO$_4$, filtered through a plug of celite, eluting with ether, and concentrated. Purification of the crude reaction mixture by flash chromatography (hexanes) afforded 2-phenylbenzo[b]furan (12e-H) (492 mg, 60%) as a fluffy white solid.
Melting Point: 120 °C (Lit. 118-119).72 \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.88\) (dd, \(J = 8, 2\) Hz, 2H), 7.60 (ddd, \(J = 8, 2, 1\) Hz, 1H), 7.54 (d, \(J = 8\) Hz, 1H), 7.46 (pt, \(J = 8\) Hz, 2H), 7.36 (tt, \(J = 8, 1\) Hz, 1H), 7.22-7.32 (m, 2H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 156.0, 155.0, 130.6, 129.3, 128.9, 128.7, 125.1, 124.4, 123.1, 121.0, 111.3, 101.4\) ppm. IR: 3035, 1491, 1470, 1455, 1259, 1208, 1169, 1105, 1038, 1020, 919, 882, 806, 762, 739, 689, 646 cm\(^{-1}\). These spectra are consistent with those reported in the literature.72

\textbf{12e-Br} was prepared according to a modified General Procedure B. Thus, 2-phenylbenzo[b]furan (1.30 g, 6.69 mmol, 1.00 eq.), N-bromosuccinimide (1.52 g, 8.70 mmol, 1.30 eq.), DMF (15 mL) and CH\(_2\)Cl\(_2\) (15 mL, to dissolve the starting material) were combined in a 100 mL roundbottom flask and allowed to stir at room temperature for 12 h. At this time, the CH\(_2\)Cl\(_2\) was removed with the aid of a rotary evaporator. The resulting solution was diluted with water (30 mL) and ether (30 mL), and the phases were separated. The aqueous phase was further extracted with ether (2 × 30 mL). The combined organic phases were washed with water (2 × 30 mL) and brine (30 mL), dried over MgSO\(_4\), filtered, and concentrated. The resulting yellow oil was purified by flash chromatography (hexanes) to afford 3-bromo-2-phenylbenzo[b]furan (1.33 g, 73%) as a colorless oil that solidified to a white solid upon standing at 0 °C. Melting Point: 63 °C (Lit. 62-63 °C).73 \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.19\) (dd, \(J = 8, 1\) Hz, 2H), 7.58 (ddd, \(J = 8, 2, 1\) Hz, 1H), 7.48-7.53 (m, 3H), 7.43 (tt, \(J = 8, 1\) Hz, 1H), 7.31-7.39 (m, 2H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 153.3, 150.4, 129.7, 129.7, 1299.2, 128.7, 126.9, 125.7, 123.6, 120.0, 111.4, 94.0\) ppm. IR: 3060, 1490, 1452, 1442, 1254, 1205, 1082, 1065.
1029, 986, 890, 820, 763, 738, 686, 581 cm\(^{-1}\). These spectra are consistent with those reported in the literature.\(^7\) 

![Chemical Reaction Diagram]

This procedure was adapted from the literature.\(^7\) 1-(phenylsulfonyl)-1\(H\)-indole (1.42 g, 5.50 mmol, 1.10 eq.) and THF (10 mL) were added to an oven-dried 50 mL roundbottom flask under an atmosphere of argon. The flask was cooled to \(-78\) °C, and \(nBuLi\) (2.5 M in hexanes, 2.42 mL, 6.05 mmol, 1.21 eq.) was added dropwise, resulting in a color change from blue to red. The reaction mixture was allowed to stir vigorously at \(-78\) °C for 1 h, at which time \(ZnCl_2\) (1.9 M in 2MeTHF, 3.47 mL, 6.60 mmol, 1.32 eq.) was added dropwise. The reaction mixture was allowed to warm to rt and stir for 1 h. Next, bromobenzene (527 μL, 5.00 mmol, 1.00 eq.) was added via syringe. The septum was removed, and under a positive pressure of argon 18 (84.6 mg, 0.10 mmol, 2%) and XPhos (47.7 mg, 0.10 mmol, 2%) were added quickly. The reaction mixture was allowed to stir at room temperature for 12 h. At this time, ether (20 mL) and water (20 mL) were added, and the phases were separated. The aqueous phase was further extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (2 × 20 mL), dried over MgSO\(_4\), filtered through a plug of celite, eluting with ether, and concentrated. The crude reaction mixture was purified by flash chromatography (2.5 → 5% EtOAc/hexanes); all of the fractions containing the desired product were collected and concentrated to afford a yellow solid, which was recrystallized from hot MeOH to afford 2-phenyl-1-(phenylsulfonyl)-1\(H\)-indole (13d-H) (936 mg, 56%) as an off-white solid. Melting Point:
95-97 °C (Lit. 103-104 °C).\textsuperscript{74} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.33 (d, J = 9 Hz, 1H), 7.35-7.52 (m, 10H), 7.24-7.30 (m, 3H), 6.56 (d, J = 1 Hz, 1H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 142.2, 138.4, 137.6, 133.7, 132.4, 130.7, 130.5, 128.8, 128.7, 127.7, 126.9, 125.0, 124.5, 120., 116.8, 113.9 ppm (the signal observed at 100 ppm is a transmitter glitch). IR: 3057, 1449, 1372, 11070, 1089, 1049, 979, 836, 761, 732, 698, 682, 635 cm\textsuperscript{-1}. These spectra are consistent with those reported in the literature.\textsuperscript{74}

\textbf{13d-Br} was prepared according to General Procedure B. Thus, 2-phenyl-1-(phenylsulfonyl)-1\textit{H}-indole (400 mg, 1.20 mmol, 1.00 eq.), N-bromosuccinimide (235 mg, 1.32 mmol, 1.10 eq.), and DMF (5.0 mL) were combined at room temperature and allowed to stir overnight. The crude reaction mixture was filtered through a silica gel plug, eluting with ether, and concentrated to yield a red foam. Trituration of this foam with cold MeOH (4 mL) resulted in precipitation of a white solid from solution. The resulting non-homogenous mixture was filtered, and the filtrate was washed with cold MeOH (2 × 2 mL) to afford 3-bromo-2-phenyl-1-(phenylsulfonyl)-1\textit{H}-indole (376 mg, 76%) as a white solid. Melting Point: 109-111 °C (Lit. 107-108 °C).\textsuperscript{75} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.36 (d, J = 8 Hz, 1H), 7.36-7.53 (m, 11H), 7.30 (pt, J = 7 Hz, 2H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 137.7, 137.7, 134.0, 131.7, 130.0, 129.9, 129.4, 129.0, 127.7, 127.0, 126.3, 124.9, 120.1, 116.3, 104.0 ppm. IR: 3066, 1446, 1373, 1183, 1121, 1086, 1009, 770, 751, 731, 684, 632, 589 cm\textsuperscript{-1}. These spectra are consistent with those reported in the literature.\textsuperscript{75}
A 50 mL roundbottom flask equipped with a stir bar was charged with MgSO₄ (1.08 g, 9.00 mmol, 4.00 eq.) and flame-dried under high vacuum. The flask was backfilled with nitrogen, and anhydrous CH₂Cl₂ (15 mL) was added. Concentrated H₂SO₄ (~128 µL, ~2.25 mmol, ~1.00 eq.) was added dropwise, and the mixture was allowed to stir at for 10 min. Next, 2-bromo-4-methylthiazole-5-carboxylic acid (500 mg, 2.25 mmol, 1.00 eq.) was added under a positive pressure of N₂, followed immediately by tBuOH (1.05 mL, 11.3 mmol, 5.00 eq.). The reaction mixture was allowed to stir at room temperature for 12 h. At this time, saturated aq. NaHCO₃ (10 mL) was carefully added, followed by additional CH₂Cl₂ (20 mL). The phases were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with saturated aq. NaHCO₃ (20 mL), H₂O (20 mL), and brine (20 mL), dried over MgSO₄, filtered, and concentrated. The crude product mixture was purified by flash chromatography (5% EtOAc/hexanes) to yield tert-butyl 2-bromo-4-methylthiazole-5-carboxylate (15c-Br) (334 mg, 53%) as a colorless oil that solidified to a pale yellow solid upon standing at 0 °C. Melting Point: 48 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.67 (s, 3H), 1.54 (s, 9H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 160.2, 159.3, 139.1, 127.7, 83.2, 28.3, 17.3 ppm. IR: 2978, 2931, 1714, 1697, 1532, 1401, 1368, 1331, 1303, 1255, 1163, 1090, 1050, 1015, 841, 827, 762 cm⁻¹. HRMS (ESI) m/z calcd. for C₉H₁₅BrNO₂S (M+H⁺, M+2+H⁺): 277.9845, 279.9825; found: 277.9833, 279.9817.
This compound was prepared according to General Procedure B. Thus, 2-iso-butyl-5-phenylthiazole\(^4\) (611 mg, 2.87 mmol, 1.00 eq.), N-bromosuccinimide (668 mg, 3.73 mmol, 1.30 eq.), and DMF (5 mL) were combined and allowed to stir at room temperature for 12 h. The crude reaction mixture was filtered through a silica gel plug, eluting with ether, and concentrated. The resulting oil was further purified by flash chromatography (2% EtOAc/hexanes) to afford 4-bromo-2-iso-butyl-5-phenylthiazole (867 mg, quant.) as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.62 (dd, \(J = 9, 2\) Hz, 2H), 7.36-7.45 (m, 3H), 2.86 (d, \(J = 8\) Hz, 2H), 2.13 (nonet, \(J = 7\) Hz, 1H), 1.03 (d, \(J = 7\) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 169.8, 132.4, 130.5, 129.2, 128.8, 128.7, 121.0, 42.7, 29.9, 22.4 ppm. IR: 2956, 2928, 2868, 1519, 1480, 1386, 1206, 1157, 1066, 965, 853, 755, 692 cm\(^{-1}\). Anal. Calcd. for C\(_{13}\)H\(_{14}\)BrNS: C, 52.71; H, 4.76; found: C, 52.98; H, 4.78.

\[\begin{align*}
\text{Ph} & \quad \text{Bu} \\
\text{S} & \quad \text{N} \\
\text{Br} & \quad \text{Ph} \\
\text{NBS} & \quad \text{DMF, rt, } 12\text{ h}
\end{align*}\]

\[\begin{align*}
\text{Ph} & \quad \text{Bu} \\
\text{S} & \quad \text{N} \\
\text{Br} & \quad \text{Ph} \\
\text{NBS} & \quad \text{DMF, rt, } 12\text{ h}
\end{align*}\]

\[15\text{f-Br}\]

\(15\text{i-H}\) was prepared according to General Procedure A. Thus, 2-bromo-4-phenylthiazole (720 mg, 3.00 mmol, 1.00 eq.), phenylboronic acid (549 mg, 4.50 mmol, 1.50 eq.), \(18\) (102 mg, 0.12 mmol, 4%), THF (3.0 mL), and \(aq.\) K\(_3\)PO\(_4\) (1M, 6.0 mL, 6.0 mmol, 2.0 eq.) were combined in a 50 mL Schlenk tube and allowed to stir at 60 °C overnight. Purification of the crude reaction mixture by flash chromatography (0 → 2% EtOAc/hexanes) afforded 2,4-diphenylthiazole (640 mg, 90%) as a white crystalline solid.
Melting Point: 92 °C (Lit. 91-92 °C).\textsuperscript{76} \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 8.06 (dd, \( J = 9, 2 \) Hz, 2H), 8.01 (dd, \( J = 9, 2 \) Hz, 2H), 7.43-7.49 (m, 6H), 7.37 (tt, \( J = 8, 1 \) Hz, 1H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 168.0, 156.4, 134.6, 133.8, 130.2, 129.0, 128.9, 128.3, 126.7, 126.6, 112.8 ppm. IR: 3116, 3047, 1479, 1443, 1070, 1056, 1027, 974, 921, 837, 757, 733, 714, 686, 671, 595 cm\textsuperscript{-1}. These spectra are consistent with those reported in the literature.\textsuperscript{76}

\textbf{15i-Br} was prepared according to General Procedure B. Thus, 2,4-diphenylthiazole (500 mg, 2.11 mmol, 1.00 eq.), N-bromosuccinimide (450 mg, 2.53 mmol, 1.20 eq.), and DMF (5.0 mL) were combined and allowed to stir at 40 °C for 12 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, followed by recrystallization of the resulting solid from MeOH, provided 5-bromo-2,4-diphenylthiazole (540 mg, 81%) as a white solid. Melting Point: 88 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 8.04 (d, \( J = 8 \) Hz, 2H), 7.94 (dd, \( J = 7, 2 \) Hz, 2H), 7.40-7.51 (m, 6H) ppm; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 167.3, 153.3, 133.6, 133.2, 130.7, 129.2, 128.8, 128.7, 128.5, 126.4, 103.5 ppm. IR: 3064, 1477, 1443, 1271, 1245, 1068, 997, 975, 907, 857, 757, 710, 676, 633, 598 cm\textsuperscript{-1}. Anal. Calcd. for C\textsubscript{15}H\textsubscript{10}BrNS: C, 56.97; H, 3.19; found: C, 56.88; H, 3.28.

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{S} \quad \text{O} \\
\text{Me} & \quad \text{N} \quad \text{S} \quad \text{O} \\
\text{Br} & \quad \text{Br} \\
\end{align*}
\]

\textbf{15j-Br} was prepared according to General Procedure C. Thus, 2-acetyl-4-methylthiazole (183 mg, 1.30 mmol, 1.00 eq.), Br\textsubscript{2} (268 mL, 5.20 mmol, 4.00 eq.), and DMF (6 mL) were combined at 0 °C and allowed to warm to room temperature and stir for 2 h.
Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, afforded 2-acetyl-5-bromo-4-methylthiazole (188 mg, 66%) as a bright yellow solid. Melting Point: 45 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 2.63 (s, 3H), 2.47 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 191.0, 165.6, 154.6, 114.4, 25.5, 16.0 ppm. IR: 924, 1678, 1502, 1425, 1372, 1356, 1282, 1261, 1060, 1033, 1015, 929,727, 604 cm$^{-1}$. Anal. Calcd. for C$_6$H$_6$BrNOS: C, 32.74; H, 2.75; found: C, 33.04; H, 2.81.

16-Br was prepared according to General Procedure D. Thus, 4-bromo-3-phenyl-1H-pyrazole (669 mg, 3.00 mmol, 1.00 eq.), triethylamine (0.80 mL, 6.00 mmol, 2.00 eq.), 4-toluenesulfonyl chloride (630 mg, 3.30 mmol, 1.10 eq.), and CH$_2$Cl$_2$ (10 mL) were combined and allowed to stir at room temperature overnight. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with CH$_2$Cl$_2$, afforded 4-bromo-3-phenyl-1-(4-toluenesulfonyl)-1H-pyrazole (1.05 g, 93%) as a white solid. Melting Point: 111-113 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.19 (s, 1H), 7.94 (d, J = 9 Hz, 2H), 7.83-7.86 (m, 2H), 7.39-7.44 (m, 3H), 7.34 (d, J = 9 Hz, 2H), 2.42 (s, 3H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 154.2, 146.4 133.6, 132.4, 130.3, 129.5, 128.5, 128.3, 96.8, 21.9 ppm. IR: 3126, 3056, 1594, 1531, 1500, 1440, 1381, 1301, 1175, 1149, 1071, 981, 816, 764, 693, 671, 591, 567 cm$^{-1}$. Anal. Calcd. for C$_{16}$H$_{13}$BrN$_2$O$_2$S: C, 50.94; H, 3.47; found: C, 51.09; H, 3.52.
**16f-Br** was prepared according to General Procedure D. Thus, 4-bromo-3-phenyl-1*H*-pyrazole (223 mg, 1.00 mmol, 1.00 eq.), triethylamine (420 µL, 3.00 mmol, 3.00 eq.), trityl chloride (420 mg, 1.50 mmol, 1.50 eq.), and CH$_2$Cl$_2$ (2.0 mL) were combined in a 10 mL roundbottom flask and allowed to stir at room temperature overnight. The crude reaction mixture was purified by filtration through a silica gel plug, eluting with CH$_2$Cl$_2$, and concentrated to a minimal volume of CH$_2$Cl$_2$ (~5 mL). This solution was slowly triturated with methanol, which resulted in precipitation of a white crystalline solid from solution. Filtration of the non-homogenous mixture and washing the resulting solid with cold methanol (2 × 5 mL) afforded 4-bromo-3-phenyl-1-trityl-1*H*-pyrazole (398 mg, 69 %) as a white crystalline solid. Melting Point: 182-184 °C (Lit. 181-183 °C).$^{46}$ $^1$H NMR (500 MHz, CDCl$_3$): δ 7.94 (dd, J = 7, 2 Hz, 1H), 7.221-7.43 (m, 20H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 148.4, 142.9, 134.5, 132.4, 130.4, 128.3, 128.1, 128.0, 127.9, 127.8, 91.1, 79.6 ppm. IR: 3129, 3059, 1604, 1490, 1446, 1363, 1186, 1161, 1111, 1086, 1030, 1000, 903, 871, 813, 749, 693, 654, 642 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{46}$
This procedure was adapted from the literature. Copper (I) iodide (38.0 mg, 0.20 mmol, 10%), K₂CO₃ (580 mg, 4.20 mmol, 2.10 eq.), 3-phenyl-1H-pyrazole (346 mg, 2.40 mmol, 1.20 eq.), and 1-iodo-4-nitrobenzene (498 mg, 2.00 mmol, 1.00 eq.) were combined in a reaction tube equipped with a stir bar. The tube was placed under high vacuum and backfilled with argon. This process was repeated a total of three times. Then, (±)-trans-1,2-diaminocyclohexane (96.0 µL, 0.40 mmol, 20%) and 1,4-dioxane (4.0 mL) were added to the tube. The cap was replaced with one that had not been punctured, and the tube was placed in an oil bath that had been pre-heated to 130 °C and allowed to stir for 12 h. At this time, the reaction mixture was cooled to room temperature and diluted with EtOAc (10 mL). The reaction mixture was filtered through a silica gel plug, eluting with EtOAc, and concentrated, to afford 1-(4-nitrophenyl)-3-phenyl-1H-pyrazole (16g-H) (300 mg, 57%) as a yellow solid. Melting Point: 169-171 °C. 

\(^1\)H NMR (500 MHz, CDCl₃): δ 8.35 (dt, J = 9, 3 Hz, 2H), 8.07 (d, J = 3 Hz, 1H), 7.91-7.97 (m, 4H), 7.47 (t, J = 8 Hz, 2H), 7.39 (tt, J = 8, 1 Hz, 1H), 6.88 (d, J = 3 Hz, 1H) ppm; \(^13\)C NMR (125 MHz, CDCl₃): δ 154.7, 145.4, 144.5, 132.3, 128.9, 128.4, 126.2, 125.6, 118.4, 107.1 ppm. IR: 3143, 3120, 1599, 1534, 1509, 1456, 1394, 1364, 1329, 1308, 1286, 1183, 1111, 1045, 951, 855, 840, 751, 746, 691, 683 cm\(^{-1}\). Anal. Calcd. for C₁₅H₁₁N₃O₂: C, 67.92; H, 4.18; found: C, 67.63; H, 4.25.

649
16g-Br was prepared according to General Procedure B. Thus, 1-(4-nitrophenyl)-3-phenyl-1H-pyrazole (265 mg, 1.00 mmol, 1.00 eq.), N-bromosuccinimide (196 mg, 1.10 mmol, 1.10 eq.), and DMF (4.0 mL) were combined in a 25 mL roundbottom flask and allowed to stir at room temperature for 12 h. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with ether, afforded 1-(4-nitrophenyl)-3-phenyl-1H-pyrazole (263 mg, 76%) as a golden yellow solid. Melting Point: 169 °C. \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.34 (d, \( J = 9 \), 2 Hz, 2H), 8.12 (s, 1H), 8.00 (dt, \( J = 7 \), 1 Hz, 2H), 7.89 (dt, \( J = 10 \), 3 Hz, 2H), 7.43-7.51 (m, 3H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 151.7, 145.8, 143.6, 131.0, 129.2, 129.1, 128.6, 127.9, 125.6, 118.3, 96.6 ppm. IR: 3151, 1598, 1509, 1448, 1394, 1332, 1310, 1183, 1111, 1058, 970, 950, 843, 796, 767, 474, 680 cm\(^{-1}\). Anal. Calcd. for C\(_{15}\)H\(_{10}\)BrN\(_3\)O\(_2\): C, 52.35; H, 2.93; found: C, 52.36; H, 2.99.

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{N} \\
\text{Br} & \quad \text{Me} \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt}, 12 \text{ h}
\end{align*}
\]

16i-Br was prepared according to General Procedure D. Thus, 4-bromo-3,5-dimethyl-1H-pyrazole (875 mg, 5.00 mmol, 1.00 eq.), triethylamine (1.40 mL, 10.0 mmol, 2.00 eq.), 4-toluenesulfonyl chloride (1.05 g, 5.50 mmol, 1.10 eq.), and CH\(_2\)Cl\(_2\) (30 mL) were combined and allowed to stir at room temperature overnight. Purification of the crude reaction mixture by filtration through a silica gel plug, eluting with CH\(_2\)Cl\(_2\), afforded 4-bromo-3,5-dimethyl-1-(4-toluenesulfonyl)-1H-pyrazole (1.26 g, 76%) as a white solid. Melting Point: 130-133 °C. \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.82 (d, \( J = 9 \) Hz, 2H), 7.30 (d, \( J = 8 \) Hz, 2H), 2.49 (s, 3H), 2.40 (s, 3H), 2.20 (s, 3H), 1.16 (d, \( J = 7 \) Hz, 12H) ppm;
\[ ^{13}C\text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 152.1, 145.8, 141.1, 134.7, 130.1, 127.8, 101.0, 21.8, 12.9, 12.3 ppm. IR: 2930, 1592, 1562, 1449, 1386, 1368, 1296, 1188, 1175, 1141, 1058, 1015, 975, 813, 779, 702, 668, 604, 585 cm}^{-1}. \text{ Anal. Calcd. for C}_{12}H_{13}BrN_{2}O_{2}S: C, 43.78; H, 3.98; found: C, 44.01; H, 4.00. }\]

\[ \text{16j-Br was prepared according to General Procedure D. Thus, 4-bromo-3,5-dimethyl-1H-pyrazole (525 mg, 3.00 mmol, 1.00 eq.), triethylamine (0.80 mL, 6.00 mmol, 2.00 eq.), 2,4,6-triisopropylphenyl-1-sulfonyl chloride (1.00 g, 3.30 mmol, 1.10 eq.), and CH}_2\text{Cl}_2\text{ (10 mL) were combined and allowed to stir at room temperature overnight. Purification of the crude reaction mixture by flash chromatography (0 } \rightarrow \text{ 20 } \rightarrow \text{ 40 } \rightarrow \text{ 60\% CH}_2\text{Cl}_2/\text{hexanes) afforded 4-bromo-3,5-dimethyl-1-(2,4,6-triisopropylphenyl-1-sulfonyl)-1H-pyrazole (157 mg, 12\%) as an oil that solidified to a white solid upon standing at 0}^\circ\text{C. Melting Point: 68-70 }^\circ\text{C. }^1H\text{ NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 7.19 (s, 2H), 4.13 (septet, J = 7 Hz, 2H), 2.92 (septet, J = 7 Hz, 1H), 2.39 (s, 3H), 2.20 (2, 3H), 1.26 (d, J = 7 Hz, 6H) ppm; } ^{13}C\text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 155.0, 152.2, 150.1, 140.1, 124.3, 99.8, 34.3, 29.8, 24.6, 23.6, 12.8, 11.9 ppm. IR: 2958, 2929, 2866, 1595, 1558, 1425, 1373, 1343, 1299, 1176, 1141, 1115, 1062, 1034, 977, 879, 784, 672, 588 cm}^{-1}. \text{ Anal. Calcd. for C}_{20}H_{28}BrN_{2}O_{2}S: C, 54.42; H, 6.62; found: C, 54.62; H, 6.71.}\]
3-bromo-1H-indazole (500 mg, 2.54 mmol, 1.00 eq.) was suspended in CH$_2$Cl$_2$ (10 mL) in a 50 mL roundbottom flask equipped with a stir bar. 3,4-Dihydro-2H-pyran (694 µL, 7.61 mmol, 3.00 eq.) and p-TsOH (43.0 mg, 0.25 mmol, 0.10 eq.) were added, and the reaction mixture was allowed to stir at room temperature for 1 h, during which time all of the starting material dissolved and the solution turned dark brown. The reaction mixture was diluted with CH$_2$Cl$_2$ (40 mL) and saturated aq. NaHCO$_3$ (50 mL) was added. The phases were separated, and the aqueous phase was further extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic phases were washed with saturated aq. NaHCO$_3$ (50 mL) and brine (50 mL), dried over MgSO$_4$, filtered, and concentrated. Purification of the crude reaction mixture by flash chromatography (0 → 2 → 4% EtOAc/hexanes) afforded 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (16m-Br) (585 mg, 82%) as a white solid. Melting Point: 66 °C (Lit. 65 °C).$^{78}$ $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.51 (d, J = 10 Hz, 1H), 7.47 (d, J = 9 Hz, 1H), 7.34 (pt, J = 9 Hz, 1H), 7.13 (pt, J = 8 Hz, 1H), 5.58 (dd, J = 10, 3 Hz, 1H), 3.90-3.94 (m, 1H), 3.63 (td, J = 12, 2 Hz, 1H), 2.42-2.49 (m, 1H), 2.00-2.09 (m, 1H), 1.93-2.00 (m, 1H), 1.60-1.70 (m, 2H), 1.51-1.59 (m, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 140.7, 127.9, 124.5, 122.2, 122.1, 120.5, 110.4, 85.6, 67.6, 29.4, 25.1, 22.6 ppm. IR: 2952, 2850, 1617, 1496, 1462, 1444, 1411, 1318, 1211, 1181, 1123, 1077, 1052, 1038, 1005, 963, 909, 874, 754, 654, 627, 579 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{78}$
3-bromo-5-nitro-1H-indazole (1.00 g, 4.13 mmol, 1.00 eq.) was suspended in CH₂Cl₂ (40 mL) in a 100 mL roundbottom flask equipped with a stir bar. 3,4-Dihydro-2H-pyran (1.13 mL, 12.4 mmol, 3.00 eq.) and p-TsOH (71.0 mg, 0.41 mmol, 0.10 eq.) were added, and the reaction mixture was allowed to stir at room temperature for 12 h, during which time all of the starting material dissolved and the solution turned dark brown. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and saturated aq. NaHCO₃ (50 mL) was added. The phases were separated, and the aqueous phase was further extracted with CH₂Cl₂ (2 × 30 mL). The combined organic phases were washed with saturated aq. NaHCO₃ (50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated. The crude reaction mixture was purified by flash chromatography (10 → 20% EtOAc/hexanes), which afforded an off-white solid after removal of the solvent. This solid was triturated with ether (5 mL), filtered, and washed with cold ether (2 × 5 mL), which provided 3-bromo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (16n-Br) (583 mg, 43%) as a white crystalline solid. Melting Point: 115 °C (Lit. 121 °C).¹ ¹H NMR (500 MHz, CDCl₃): δ 8.56 (d, J = 2 Hz, 1H), 8.28 (dd, J = 9, 2 Hz, 1H), 7.68 (d, J = 9 Hz, 1H), 5.72 (dd, J = 9, 3 Hz, 1H), 3.96-4.01 (m, 1H), 8.72-8.78 (m, 1H), 2.43-2.51 (m, 1H), 2.07-2.17 (m, 2H), 1.65-1.81 (m, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 143.2, 142.5, 124.5, 124.1, 122.7, 118.2, 111.5, 86.3, 67.5, 29.3, 24.9, 22.0 ppm. IR: 3098, 2949, 2845, 2158, 1516, 1445, 1343, 1199, 1080, 1038, 1004, 912, 815, 787, 751, 731, 608 cm⁻¹. These spectra are consistent with those reported in the literature.⁷⁸
A reaction tube equipped with a stir bar was charged with 2-bromo-4-nitro-1H-pyrazole (384 mg, 2.00 mmol, 1.00 eq.), K$_2$CO$_3$ (415 mg, 3.00 mmol, 1.50 eq.), and tetrabutylammonium iodide (148 mg, 0.40 mmol, 0.20 eq.). The tube was placed under high vacuum and backfilled with nitrogen. Next, benzyl bromide (262 µL, 2.20 mmol, 1.10 eq.) and EtOH (5.0 mL) were added, and the reaction mixture was placed in an oil bath that had been preheated to 80 °C and allowed to stir vigorously for 12 h. The reaction mixture was allowed to cool to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over MgSO$_4$, filtered, and concentrated. The resulting yellow oil was purified by flash chromatography (20 → 40% EtOAc/hexanes) to afford a colorless oil, which was triturated with a minimal amount of ether, resulting in precipitation of a white solid from solution. The non-homogenous mixture was filtered, and the filtrate was washed with cold ether (2 × 5 mL) to afford 1-benzyl-2-bromo-4-nitro-1H-pyrazole (17g-Br) (248 mg, 44%) as a white solid. Melting Point: 91-93 °C.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.70 (s, 1H), 7.40-7.44 (m, 3H), 7.23-7.26 (m, 2H), 5.17 (s, 2H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 133.1, 129.6, 129.5, 128.1, 121.5, 120.7, 52.8 ppm. IR: 3152, 3112, 1535, 1504, 1443, 1393, 1370, 1337, 1279, 1179, 1160, 1136, 1090, 1079, 992, 824, 781, 753, 709 cm$^{-1}$. Anal. Calcd. for C$_{10}$H$_8$BrN$_3$O$_2$: C, 42.58; H, 2.86; found: C, 42.59; H, 2.91.
5.5.4. Synthesis of heteroaryl fluorides.

**General Procedure for Pd-catalyzed fluorination reactions.** In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with silver fluoride (26 mg, 0.20 mmol, 2.00 eq.), additive (0.05 mmol, 0.50 eq.), 1-3 (4.0 mg, 2%), aryl bromide (0.10 mmol, 1.00 eq.), and solvent (1.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 ºC and allowed to stir vigorously for 14 h. At this time, the tube was allowed to cool to room temperature, and 1-fluoronaphthalene (20 µL, 1.55 eq.) was added. The reaction mixture was analyzed directly by $^{19}$F NMR.

**General Procedure E. Pd-catalyzed fluorination reactions.** In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), aryl bromide (0.50 mmol, 1.00 eq.), and solvent (5.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 ºC and allowed to stir vigorously for 14 h. At this time, the tube was allowed to cool to room temperature, and the reaction mixture was diluted with EtOAc (10 mL), and filtered through a pad of celite, eluting with EtOAc (20 mL). The resulting solution was concentrated, and the crude reaction mixture was purified by flash chromatography.
10c was prepared according to General Procedure E. Thus, 4-bromo-5-phenyl-N,N-diethylthiophene-2-sulfonamide (187 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), and toluene (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (5 → 10% Et2O/hexanes) afforded 4-fluoro-5-phenyl-N,N-diethylthiophene-2-sulfonamide (146 mg, 93%) as a yellow oil. Contaminated with <5 % of a second fluorothiophene with the same mass as the desired product, which is likely 3-fluoro-5-phenyl-N,N-diethylthiophene-2-sulfonamide. 1H NMR (500 MHz, CDCl3): δ 7.62 (d, J = 8 Hz, 2H), 7.41-7.49 (m, 2H), 7.37 (tt, J = 8 Hz, 2 Hz, 1H), 7.31 (s, 1H), 3.29 (bq, J = 8 Hz, 4H), 1.22 (bt, J = 7 Hz, 6H) ppm; 13C NMR (125 MHz, CDCl3): δ 152.0 (d, J = 264 Hz), 136.1, 134.8, 128.9-129.9 (m), 127.3 (d, J = 5 Hz), 121.9 (d, J = 27 Hz), 43.0, 14.5 ppm; 
19F NMR (470 MHz, CDCl3): δ –126.3 ppm (a minor contaminant was detected at –126.4 ppm). IR: 2975, 2937, 2873, 1724, 1557, 1443, 1386, 1340, 1201, 1145, 1024, 984, 934, 839, 758, 725, 697, 583 cm⁻¹. HRMS (ESI) m/z calcd. for C14H17FNO2S2 (M+H⁺): 314.0679; found: 314.0661.
10d was prepared according to General Procedure E. Thus, 4-bromo-5-phenyl-\( N,N \)-diethylthiophene-2-sulfonamide (169 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), and MTBE (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (10 → 20% EtOAc/hexanes) afforded 4-fluoro-5-phenyl-\( N,N \)-diethylthiophene-2-carboxamide (131 mg, 94%) as a yellow solid. Melting Point: 47 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.65 (dd, \( J = 9, 2 \) Hz, 2H), 7.41 (pt, \( J = 8 \) Hz), 7.33 (tt, \( J = 7 \) Hz, 1H), 7.11 (bs, 1H), 3.56 (bq, \( J = 7 \) Hz, 4H), 1.28 (bt, \( J = 7 \) Hz, 6H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 162.5, 152.0 (d, \( J = 261 \) Hz), 133.8 (d, \( J = 7 \) Hz), 130.5 (d, \( J = 4 \) Hz), 129.1, 128.3 (d, \( J = 1 \) Hz), 127.2 (d, \( J = 5 \) Hz), 125.2 (d, \( J = 11 \) Hz), 119.3 (d, \( J = 27 \) Hz), ~42 (bs), ~13 (bs) ppm; \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \( \delta \) –127.4 ppm. IR: 2970, 2931, 2871, 1599, 1575, 1522, 1468, 1428, 1390, 1363, 1335, 1311, 1283, 1259, 1169, 1087, 1058, 1007, 981, 939, 905, 854, 829, 759, 728, 684, 641 cm\(^{-1}\). Anal. Calcd. for C\(_{15}\)H\(_{16}\)FNOS: C, 64.96; H, 5.81; found: C, 64.90; H, 5.91.
10j was prepared according to General Procedure E. Thus, methyl 5-bromo-4-phenylthiophene-2-carboxylate (149 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), and MTBE (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (2 → 4% Et₂O/hexanes) afforded methyl 5-fluoro-4-phenylthiophene-2-carboxylate (115 mg, 97%) as a pale yellow solid. Contaminated with 4% of the corresponding reduction product 10j-H, as confirmed by ¹H NMR (see attached) and GC/MS analysis, which could not be readily separated from the desired product by flash chromatography. Melting Point: 57 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.80 (d, J = 5 Hz), 7.59 (dd, J = 8, 1 Hz, 2H), 7.44 (pt, J = 8 Hz, 2H), 7.34 (tt, J = 8, 2 Hz, 1H), 3.90 (s, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 164.4 (d, J = 298 Hz), 162.4, 131.7 (d, J = 2 Hz), 131.4 (d, J = 4 Hz), 129.0, 128.0 (d, J = 1 Hz), 127.4 (d, J = 4 Hz), 123.6 (d, J = 5 Hz), 120.2 (d, J = 4 Hz), 52.5 ppm; ¹⁹F NMR (470 MHz, CDCl₃): δ −123.4 ppm. IR: 3063, 2954, 1711, 1603, 1585, 1569, 1469, 1443, 1374, 1257, 1127, 1073, 956, 892, 870, 764, 743, 725, 689, 613 cm⁻¹. HRMS (ESI) m/z calcd. for C₁₂H₁₀FO₂S (M+H⁺): 237.0380; found: 237.0389.
12e was prepared according to General Procedure E. Thus, 3-bromo-2-phenylbenzo[b]furan (137 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), and MTBE (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (hexanes) afforded 3-fluoro-2-phenylbenzo[b]furan (93 mg, 88%) as a white solid. Melting Point: 61 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.93 (d, J = 9 Hz, 2H), 7.62 (d, J = 9 Hz, 1H), 7.46-7.52 (m, 3H), 7.25-7.38 (m, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 151.3 (d, J = 9 Hz), 144.7 (d, J = 256 Hz), 138.2 (d, J = 20 Hz), 128.9, 128.8 (d, J = 5 Hz), 128.3 (d, J = 2 Hz), 125.5 (d, J = 1 Hz), 124.9 (d, J = 6 Hz), 123.123.4, 120.8 (d, J = 19 Hz), 117.8 (d, J = 3 Hz), 111.9 (d, J = 2 Hz) ppm; ¹⁹F NMR (470 MHz, CDCl₃): δ -170.4 ppm. IR: 3063, 1631, 1497, 1454, 1443, 1390, 1258, 1210, 1136, 1112, 1073, 1028, 1007, 913, 895, 830, 768, 743, 688, 654, 615 cm⁻¹. Anal. Calcd. for C₁₄H₉FO: C, 79.23; H, 4.27; found: C, 79.17; H, 4.35.

15c was prepared according to General Procedure E. Thus, tert-butyl 2-bromo-4-methylthiazole-5-carboxylate (139 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg,
0.01 mmol, 2%), and toluene (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (5% Et2O/hexanes) afforded tert-butyl 2-fluoro-4-methylthiazole-5-carboxylate (73 mg, 67%) as a yellow oil. 1H NMR (500 MHz, CDCl3): δ 2.58 (s, 3H), 1.55 (s, 9H) ppm; 13C NMR (125 MHz, CDCl3): δ 170.2 (d, J = 286 Hz), 160.8, 154.1 (d, J = 14 Hz), 120.4 (d, J = 2 Hz), 83.1, 28.3, 17.4 ppm; 19F NMR (470 MHz, CDCl3): δ –74.4 ppm. IR (in CDCl3): 2981, 1702, 1557, 1493, 1370, 1343, 1313, 1241, 1166, 905, 728, 650 cm⁻¹. Anal. Calcd. for C9H12FNO2S: C, 49.75; H, 5.57; found: C, 49.63; H, 5.62.

17h was prepared according to General Procedure E. Thus, 8-bromocaffeine (137 mg, 0.50 mmol, 1.00 eq.), silver fluoride (127 mg, 1.00 mmol, 2.00 eq.), potassium fluoride (14.5 mg, 0.25 mmol, 0.50 eq.), 3 (19.5 mg, 0.01 mmol, 2%), and toluene (5.0 mL) were combined and allowed to stir at 130 °C for 14 h. Purification of the crude reaction mixture by flash chromatography (1:1 EtOAc/hexanes) afforded 8-fluorocaffeine (91 mg, 86%) as an off-white solid. Melting Point: 158-162 °C. 1H NMR (500 MHz, CDCl3): δ 3.83 (s, 3H), 3.49 (s, 3H), 3.37 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3): δ 154.2 (d, J = 230 Hz), 151.5, 151.3, 144.5 (d, J = 15 Hz), 103.8 (d, J = 3 Hz), 30.7, 30.0, 28.0 ppm; 19F NMR (470 MHz, CDCl3): δ –107.8 ppm. IR (in CDCl3): 2959, 1704, 1654, 1614, 1539,
1456, 1329, 1288, 1212, 1041, 971, 821, 783, 742, 733, 666 cm$^{-1}$. Anal. Calcd. for C$_8$H$_9$FN$_4$O$_2$: C, 45.28; H, 4.28; found: C, 45.58; H, 4.18.

5.5.5. Preparation of authentic aryl fluoride samples.

**General Procedure F. Fluorination of lithiated heteroarenes.** An oven-dried reaction tube equipped with a stir bar was charged with the heteroaryl bromide (0.20 mmol, 1.00 eq.) and evacuated. The tube was backfilled with argon, and anhydrous THF (1.0 mL) was added. The tube was cooled to $-78 \, ^\circ$C, and nBuLi (2.5 M in hexanes, 0.08 mL, 0.22 mmol, 1.10 eq.) was added dropwise. The reaction mixture was allowed to stir at $-78 \, ^\circ$C for 30 min. At this time, a separately prepared solution of N-fluorobenzenesulfonimide (NFSI) (75.8 mg, 0.24 mmol, 1.20 eq.) in anhydrous THF (0.5 mL) was added dropwise to the heteroaryllithium reagent, and the reaction mixture was allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with saturated aq. NaHCO$_3$ (2 mL) and EtOAc (5 mL), and the phases were separated. The aqueous phase was further extracted with EtOAc (2 × 5 mL), and the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated. Purification of the crude reaction mixtures by preparative thin layer chromatography afforded the desired heteroaryl fluoride.

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{1) \text{nBuLi, } -78 \, ^\circ\text{C}} \quad \text{Ph} \\
\text{S} & \quad \xrightarrow{2) \text{NFSI, } -78 \, ^\circ\text{C} \to \text{rt}} \quad \text{Ph}
\end{align*}
\]

**9e** was prepared according to a slightly modified General Procedure F. Thus, 2-bromo-3-phenylthiophene (47.8 mg, 0.20 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.08 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were
combined and allowed to stir at −78 °C for 1 h (allowing the reaction to warm to room
temperature led to a complex mixture of products). Purification of the crude reaction
mixture by preparative thin layer chromatography (pentane) afforded 2-fluoro-3-
phenylthiophene (19 mg, 53%) as a pale yellow oil. Contaminated with ~4% of a second
fluorothiophene with the same mass as the desired product, which is likely 2-fluoro-4-
phenylthiophene. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.60 (d, J = 9 Hz, 2H), 7.43 (pt, J = 8
Hz, 2H), 7.31 (tt, J = 8, 2 Hz, 1H), 7.00 (dd, J = 7, 4 Hz, 1H), 6.70 (dd, J = 7, 4 Hz, 1H)
ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 160.7 (d, J = 288 Hz), 132.6 (d, J = 4 Hz), 128.9,
127.4 (d, J = 4 Hz), 127.4, 124.8 (d, J = 3 Hz), 121.6 (d, J = 48 Hz), 112.6 (d, J = 3 Hz)
ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): δ −136.2 ppm (a minor contaminant was detected at −
130.4 ppm). IR (in CDCl$_3$): 3058, 1605, 1585, 1568, 1498, 1442, 1275, 1188, 1124, 907,
880, 732, 707 cm$^{-1}$. GC/MS M/z for C$_{10}$H$_7$FS: 178.0, found, 178.0. (Note: this
compound should not be placed under high vacuum due to its volatility).

![Reaction Scheme]

9f was prepared according to a slightly modified General Procedure F. An oven-dried
reaction tube equipped with a stir bar was charged with 9f-Br (47.8 mg, 0.20 mmol, 1.00
eq.) and evacuated. The tube was backfilled with argon, and anhydrous Et$_2$O (1.0 mL)
was added. The tube was cooled to −78 °C, and nBuLi (2.5 M in hexanes, 0.08 mL, 0.22
mmol, 1.10 eq.) was added dropwise. The reaction mixture was allowed to stir at −78 °C
for 30 min. At this time, a separately prepared solution of N-fluorobenzenesulfonimide
(NFSI) (75.8 mg, 0.24 mmol, 1.20 eq.) in anhydrous THF (0.5 mL) was added dropwise
to the heteroaryllithium reagent, and the reaction mixture was allowed to stir for at – 78 °C for 2 h (allowing the reaction to warm to room temperature led to a complex mixture of products). The reaction mixture was quenched with saturated aq. NaHCO₃ (2 mL) and EtOAc (5 mL), and the phases were separated. The aqueous phase was further extracted with EtOAc (2 × 5 mL), and the combined organic extracts were dried over MgSO₄, filtered, and concentrated. Purification of the crude reaction mixture by preparative thin layer chromatography (pentane) afforded 9f (24.0 mg, 67%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 7.66 (dd, J = 8, 2 Hz, 2H), 7.41 (pt, J = 8 Hz, 2H), 7.30 (tt, J = 8, 1 Hz, 1H), 7.13 (dd, J = 6, 3 Hz, 1H), 6.89 (d, J = 6 Hz, 1H) ppm; ¹³C NMR (150 MHz, CDCl₃): δ 154.1 (d, J = 259 Hz), 131.4 (d, J = 4 Hz), 129.0, 127.6, 126.9 (d, J = 5 Hz), 122.1 (d, J = 10 Hz), 121.5 (d, J = 13 Hz), 118.9 (d, J = 28 Hz) ppm; ¹⁹F NMR (282 MHz, CDCl₃): δ −130.5 ppm. IR (in CDCl₃): 3062, 1557, 1494, 1448, 1395, 983, 905, 760, 730, 690, 633 cm⁻¹. GC/MS m/z calcd. for C₁₀H₇FS: 178.0; found: 178.0. (Note: this compound should not be placed under high vacuum due to its volatility).

In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with silver fluoride (50.8 mg, 0.40 mmol, 2.00 eq.), potassium fluoride (5.80 mg, 0.10 mmol, 0.50 eq.), 3 (8.00 mg, 0.004 mmol, 2%), methyl 4-bromo-5-phenylthiophene-2-carboxylate (59.4 mg, 0.20 mmol, 1.00 eq.), and MTBE (1.0 mL).
The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 °C and allowed to stir vigorously for 14 h. At this time, the tube was allowed to cool to room temperature, and the reaction mixture was diluted with EtOAc (10 mL), and filtered through a pad of celite, eluting with EtOAc (20 mL). The resulting solution was concentrated and purified by preparative thin layer chromatography (5% EtO/pentane) to afford methyl 4-fluoro-5-phenylthiophene-2-carboxylate (16.0 mg, 34%) as a white solid. Contaminated with <5% of the corresponding aryl bromide, as judged by 1H NMR and GC analysis. Melting Point: 45 °C. 1H NMR (500 MHz, CDCl3): δ 7.67 (dd, J = 8, 2 Hz, 2H), 7.53 (s, 1H), 7.43 (pt, J = 8 Hz, 2H), 7.36 (tt, J = 8, 2 Hz, 1H), 3.91 (s, 3H) ppm; 13C NMR (125 MHz, CDCl3): δ 162.6, 153.6 (d, J = 261 Hz), 130.9 (d, J = 4 Hz), 129.8, 129.5 (d, J = 1 Hz), 128.5 (d, J = 9 Hz), 127.9 (d, J = 5 Hz), 125.5, 124.4 (d, J = 26 Hz), 53. 2 ppm; 19F NMR (470 MHz, CDCl3): δ -126.6 ppm. IR (in CDCl3): 3097, 3000, 1713, 1576, 1561, 1461, 1434, 1400, 1287, 1246, 1166, 1069, 1006, 852, 758, 722, 687, 645 cm⁻¹. HRMS (ESI) m/z calcd. for C12H10FO2S (M+H⁺): 237.0380; found: 237.0378.

In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with silver fluoride (102 mg, 0.80 mmol, 4.00 eq.), potassium fluoride (11.6 mg, 0.20 mmol, 1.00 eq.), 3 (8.00 mg, 0.004 mmol, 2%), 5-benzoyl-3-bromo-2-phenylthiophene (68.6 mg, 0.20 mmol, 1.00 eq.), and MTBE (1.0 mL). The tube was
capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 °C and allowed to stir vigorously for 14 h. At this time, the tube was allowed to cool to room temperature, and the reaction mixture was diluted with EtOAc (10 mL), and filtered through a pad of celite, eluting with EtOAc (20 mL). The resulting solution was concentrated and purified by preparative thin layer chromatography (5% Et$_2$O/pentane) to afford 5-benzoyl-3-fluoro-2-phenylthiophene (41.0 mg, 73%) as a yellow solid. Melting Point: 83 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.88 (d, J = 7 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.63 (pt, J = 8 Hz, 1H), 7.53 (pt, J = 8 Hz, 2H), 7.46 (pt, J = 8 Hz, 2H), 7.43 (s, 1H), 7.39 (pt, J = 7 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 187.2 (d, J = 2 Hz), 153.1 (d, J = 263 Hz), 137.3, 137.1 (d, J = 6 Hz), 132.8, 130.3 (d, J = 4 Hz), 129.2, 129.2, 128.7, 127.5 (d, J = 5 Hz), 126.9 (d, J = 5 Hz), 125.1 (d, J = 26 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): δ −125.8 ppm. IR (in CDCl$_3$): 3061, 1634, 1599, 1575, 1555, 1455, 1398, 1287, 1170, 1118, 1007, 906, 860, 730, 661, 647 cm$^{-1}$. Anal. Calcd. for C$_{17}$H$_{11}$FOS: C, 72.32; H, 3.93; found: C, 72.27; H, 4.01.

![Chemical Structure](image)

10e was prepared according to General Procedure F. Thus, 3-bromo-2,5-diphenylthiophene (63.0 mg, 0.20 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.08 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude reaction mixture by preparative thin layer chromatography (pentane) afforded 3-fluoro-

---

665
2,5-diphenylthiophene (33 mg, 65%) as a white solid. Melting Point: 96 °C. \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta 7.68 \) (dd, \( J = 9 \), 2 Hz, 2H), 7.60 (dd, \( J = 9 \), 2 Hz, 2H), 7.39-7.45 (m, 4H), 7.28-7.36 (m, 2H), 7.12 (s, 1H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta 153.9 \) (d, \( J = 260 \) Hz), 139.8 (d, \( J = 9 \) Hz), 133.6, 131.3 (d, \( J = 4 \) Hz), 129.1, 129.0, 128.4, 127.6 (d, \( J = 1 \) Hz), 126.8 (d, \( J = 5 \) Hz), 125.2, 120.8, 114.5 (d, \( J = 28 \) Hz), ppm; \( ^{19}F \) NMR (470 MHz, CDCl\(_3\)): \( \delta -126.7 \) ppm. IR: 3053, 1596, 1573, 1562, 1487, 1466, 1449, 1395, 1331, 1307, 1184, 1074, 1011, 966, 910, 818, 754, 720, 690, 641 cm\(^{-1}\). HRMS (ESI) m/z calcd. for C\(_{16}\)H\(_{11}\)FS (M): 254.0560; found: 254.0579.

\( \text{Ph} \text{S} \text{Br} \text{Ph} \) 1 was prepared according to General Procedure F. Thus, 2-bromo-3,5-diphenylthiophene (63.0 mg, 0.20 mmol, 1.00 eq.), \( n \text{BuLi} \) (2.5 M in hexanes, 0.08 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude reaction mixture by preparative thin layer chromatography (pentane) afforded 2-fluoro-3,5-diphenylthiophene (44 mg, 86%) as a white solid. Melting Point: 94-96 °C. \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta 7.64 \) (d, \( J = 9 \) Hz, 2H), 7.54 (dd, \( J = 7 \), 2 Hz, 2H), 7.44 (pt, \( J = 8 \) Hz, 2H), 7.40 (pt, \( J = 8 \) Hz, 2H), 7.29-7.35 (m, 2H), 7.21 (d, \( J = 4 \) Hz, 1H) ppm; \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta 159.6 \) (d, \( J = 291 \) Hz), 133.9, 132.5 (d, \( J = 4 \) Hz), 131.0 (d, \( J = 3 \) Hz), 129.1, 128.9, 127.8 (d, \( J = 1 \) Hz), 127.5 (d, \( J = 1 \) Hz), 127.4 (d, \( J = 33 \) Hz), 125.4 (d, \( J = 2 \) Hz), 122.4 (d, \( J = 4 \) Hz), 120.1 (d, \( J = 1 \) Hz) ppm; \( ^{19}F \) NMR (470 MHz, CDCl\(_3\)):
δ –133.1 ppm. IR (in CDCl₃): 3063, 1587, 1513, 1494, 1476, 1368, 1234, 1142, 905, 729, 691, 652 cm⁻¹. HRMS (ESI) m/z calcd. for C₁₆H₁₂FS (M+H⁺): 255.0638; found: 255.0631.

10o was prepared according to General Procedure F. Thus, 3-bromo-4-methyl-2,5-diphenylthiophene (50.0 mg, 0.15 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.06 mL, 0.17 mmol, 1.10 eq.), NFSI (58.3 mg, 0.18 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude reaction mixture by preparative thin layer chromatography (pentane) afforded 3-fluoro-4-methyl-2,5-diphenylthiophene (32 mg, 80%) as a white solid. Melting Point: 104-106 °C. 

¹H NMR (500 MHz, CDCl₃): δ 7.57 (dd, J = 9 Hz, 2H), 7.24-7.41 (m, 7H), 7.19 (tt, J = 8, 2 Hz, 1H), 2.17 (d, J = 1 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 152.7 (d, J = 262 Hz), 134.5 (d, J = 7 Hz), 134.4 (d, J = 2 Hz), 131.6 (d, J = 4 Hz), 129.0, 128.9, 128.6, 1278.0, 127.4 (d, J = 1 Hz), 126.8 (d, J = 5 Hz), 124.2 (d, J = 24 Hz), 11.6 ppm; ¹⁹F NMR (470 MHz, CDCl₃): δ –126.9 ppm. IR (in CDCl₃): 3050, 2926, 1598, 1487, 1434, 1405, 1295, 1113, 974, 902, 753, 731, 694 cm⁻¹. HRMS (ESI) m/z calcd. for C₁₇H₁₄FS (M+H⁺): 269.0795; found: 269.0803.
11d was prepared according to General Procedure F. Thus, 2-bromo-3-phenylbenzo[b]thiophene (57.8 mg, 0.20 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.09 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude reaction mixture by preparative thin layer chromatography (pentane) afforded 2-fluoro-3-phenylbenzo[b]thiophene (42 mg, 92%) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.73-7.76 (m, 2H), 7.60 (d, \(J = 8\) Hz, 2H), 7.54 (pt, \(J = 8\) Hz, 2H), 7.35-7.47 (m, 3H) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 159.8 (d, \(J = 290\) Hz), 136. (d, \(J = 4\) Hz), 131.2 (d, \(J = 42\) Hz), 129.5 (d, \(J = 2\) Hz), 128.9, 128.0, 125.8, 125.3, 124.7 (d, \(J = 5\) Hz), 122.7, 122.7, 117.1 (d, \(J = 7\) Hz) ppm; \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta\) -131.0 ppm. IR: 3058, 1605, 1586, 1492, 1460, 1443, 1435, 1351, 1207, 1149, 1020, 907, 859, 763, 748, 728, 696, 679, 640, 622 cm\(^{-1}\). HRMS (ESI) m/z calcd. for C\(_{14}\)H\(_9\)FS (M): 228.0404; found: 228.0403.

11f was prepared according to General Procedure F. Thus, 3-bromo-2-phenylbenzo[b]thiophene (57.8 mg, 0.20 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.09 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude
reaction mixture by preparative thin layer chromatography (pentane) afforded 3-fluoro-2-phenylbenzo[b]thiophene (34 mg, 75%) as a white solid. Melting Point: 94 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.74-7.80 (m, 4H), 7.34-7.49 (m, 5H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 147.6 (d, J = 264 Hz), 134.3 (d, J = 9 Hz), 131.3 (d, J = 4 Hz), 130.8 (d, J = 24 Hz), 129.1, 128.2, 127.6 (d, J = 3 Hz), 125.8, 124.9, 122.8, 120.9 (d, J = 14 Hz), 120.2 (d, J = 2 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ -135.5 ppm. IR: 3062, 1586, 1491, 1445, 1370, 1277, 1088, 1018, 955, 850, 749, 726, 691, 595 cm$^{-1}$. Anal. Calcd. for C$_{14}$H$_9$FS: C, 73.66; H, 3.97; found: C, 73.40; H, 4.07.

In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with cesium fluoride (152 mg, 1.00 mmol, 5.00 eq.), 2-bromo-4-phenylthiazole (48.0 mg, 0.20 mmol, 1.00 eq.), and anhydrous DMF (2.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 °C and allowed to stir for 14 h. The reaction tube was allowed to cool to room temperature and dilute with ether (5 mL) and water (5 mL). The phases were separated, and the aqueous phase was further extracted with ether (2 $\times$ 5 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO$_4$, filtered, and concentrated. The resulting yellow solid was purified by preparative thin layer chromatography (2% Et$_2$O/hexanes) to afford 2-fluoro-4-phenylthiazole (23 mg, 64%) as a white solid. Melting Point: 65 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.80 (dd, J = 8, 2 Hz, 2H), 7.42 (t, J = 8 Hz, 2H), 7.35 (tt, J = 7, 2 Hz, 1H), 7.06 (d, J = 2 Hz) ppm; $^{13}$C
NMR (125 MHz, CDCl₃): δ 169.9 (d, J = 281 Hz), 148.4 (d, J = 15 Hz), 133.6, 128.9, 128.7, 126.0 (d, J = 1 Hz), 10.9 (d, J = 4 Hz) ppm; ¹⁹F NMR (470 MHz, CDCl₃): δ -79.5 ppm. IR: 3096, 3063, 3034, 1540, 1525, 1480, 1445, 1323, 1301, 1235, 1197, 1064, 1025, 914, 843, 743, 688, 669, 656 cm⁻¹. HRMS (ESI) m/z calcd. for C₉H₇FNS (M+H⁺): 180.0278; found: 180.0283.

In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged with silver fluoride (50.8 mg, 0.40 mmol, 2.00 eq.), potassium fluoride (5.80 mg, 0.10 mmol, 0.50 eq.), 2 (7.40 mg, 0.004 mmol, 2%), 4-bromo-2-iso-butyl-5-phenylthiazole (59.2 mg, 0.20 mmol, 1.00 eq.), and MTBE (1.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been pre-heated to 130 °C and allowed to stir vigorously for 14 h. At this time, the tube was allowed to cool to room temperature, and the reaction mixture was diluted with EtOAc (10 mL), and filtered through a pad of celite, eluting with EtOAc (20 mL). The resulting solution was concentrated and purified by preparative thin layer chromatography (5% Et₂O/hexanes) to afford 2-iso-butyl-4-fluoro-5-phenylthiazole (13.0 mg, 28%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 7.56 (dd, J = 9, 2 Hz, 2H), 7.40 (t, J = 8 Hz, 2H), 7.29 (tt, J = 7, 2 Hz, 1H), 2.77 (d, J = 7 Hz, 2H), 2.13 (septet, J = 7 Hz, 1H), 1.02 (d, J = 7 Hz, 6H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 164.8 (d, J = 19 Hz), 155.8 (d, J = 249 Hz), 129.5 (d, J = 6 Hz), 129.1, 127.8 (d, J = 1 Hz), 127.0 (d, J = 5 Hz), 112.2 (d, J = 26 Hz), 43.0, 29.7,
22.4 ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –107.9 ppm. IR (in CDCl$_3$): 2959, 1559, 1357, 1017, 907, 732, 692 cm$^{-1}$. HRMS (ESI) m/z calcd. for C$_{13}$H$_{13}$FNS (M+H$^+$): 236.0904; found: 236.0877.

![Reaction Scheme](image)

15i was prepared according to General Procedure F. Thus, 5-bromo-2,4-diphenylthiazole (63.2 mg, 0.20 mmol, 1.00 eq.), nBuLi (2.5 M in hexanes, 0.09 mL, 0.22 mmol, 1.10 eq.), NFSI (75.8 mg, 0.24 mmol, 1.20 eq.), and THF (1.5 mL) were combined and allowed to stir at room temperature for 1 h. Purification of the crude reaction mixture by preparative thin layer chromatography (15% CH$_2$Cl$_2$/hexanes) afforded 5-fluoro-2,4-diphenylthiazole (29 mg, 57%) as a white solid. Melting Point: 78 °C (Lit. 84-85 °C).$^{79}$ $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.03 (d, J = 8 Hz, 2H), 7.89-7.93 (m, 2H), 7.44-7.51 (m, 5H), 7.37 (tt, J = 8, 1 Hz, 1H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 157.4 (d, J = 301 Hz), 154.9 (d, J = 10 Hz), 135.9 (d, J = 5 Hz), 133.7, 132.1 (d, J = 6 Hz), 130.3 (d, J = 1 Hz), 129.1, 128.8, 128.2 (d, J = 2 Hz), 127.1 (d, J = 6 Hz), 126.0 (d, J = 2 Hz) ppm; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –147.1 ppm. IR: 3053, 3029, 1581, 1490, 1475, 1447, 1349, 1301, 1195, 1183, 1072, 1029, 1002, 973, 911, 871, 756, 683, 658, 591 cm$^{-1}$. These spectra are consistent with those reported in the literature.$^{80}$
5.6. References.


8 For an example, see: Bumgardner, C. L.; Sloop, J. C. *J. Fluorine Chem.* **1992**, *56*, 141.


In addition, we have found that significantly higher catalyst loadings (10% vs. 2%) are required for Suzuki-Miyaura couplings of bromothiazoles compared to bromothiophenes.


Dolle, Roland E.; Le Bourdonnec, Bertrand; Ajello, Christopher W.; Gu, Minghua; Chu, Guo-Hua; Tuthill, Paul Anson; Leister, Lara K.; Zhou, Jean Q. Preparation of 3-azaspiro[5.5]undecanes and related compounds as δ opioid receptor ligand. WO2005033073, Apr 14, 2005


Yumoto, K.; Irie, M.; Matsuda, K. *Org. Lett*. **2008**, *10*, 2051. It should be noted that the regioisomeric product 2-bromo-4-phenylthiophene is reported to have a distinct ¹H NMR spectrum (Funaki, K.; Sato, T.; Oi, S. *Org. Lett*. **2012**, *14*, 6186).

In the case of 4,5-dibromothiophenes bearing electron-withdrawing groups at the 5-position, a catalyst based on XantPhos was found to provide superior regioselectivity as well as improved selectivity for the monoarylation product compared to a catalyst based on XPhos.


The addition of extra N-bromosuccinimide to increase conversion to the desired product led to dibrominated products, as judged by GC/MS.


Under these conditions, the starting material is not fully consumed, but dibrominated side products are not observed.


Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. J. Org. Chem. 2007, 72, 5731.


$^1$H NMR, 500 MHz, CD$_2$Cl$_2$
$^{1}H$ NMR, 500 MHz, CD$_2$Cl$_2$
$^1$H NMR, 500 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
\[ ^{13}\text{C NMR, 125 MHz, CDCl}_3 \]
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$\text{Br}$

$\text{13C NMR, 125 MHz, CDCl}_3$

![Chemical Structure](image)
$^1$H NMR, 500 MHz, $\text{CDCl}_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR. 500 MHz, CDCl$_3$. 
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
\[ \text{Et}_2\text{N}^+\text{S}^-\text{Ph} \]
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz. CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz. CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
\( \text{H}^1 \text{NMR, 500 MHz, CDCl}_3 \)

\[
\begin{align*}
\text{Hb} & \quad \text{Hc} \quad \text{Hd, e} \\
\text{Hb} & \quad \text{Hc} \quad \text{Hd, e}
\end{align*}
\]
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz. CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$\text{MeO}_2\text{C}$

$\text{Ph}$

$\text{Br}$

$^{13}\text{C NMR, 125 MHz, CDCl}_3$
$^1H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}{H}$ NMR, 500 MHz, CDCl$_3$
$\text{Bu}_2\text{C}_6\text{S} - \text{Br}$

\[ \text{Me} \]

$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz. CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR. 500 MHz, CDC$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{Me}_{2}N$N$Pr'$

$\text{O}$

$\text{Me}$

$\text{Br}$

$\text{Me}$

$\text{H NMR, 500 MHz, CDCl}_3$

$\Delta$ (Ppm)
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{El}_N^+$

$^{1}H$ NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}H$ NMR, 500 MHz, CDCl$_{3}$
MeO₂C-S-F
Ph

$^{1}H$ NMR, 500 MHz, CDCl₃

MeO₂C-S
Ph

$^{1}H$ NMR, 500 MHz, CDCl₃
$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{MeO}_2\text{C}$

$\text{S}$

$\text{F}$

$\text{Ph}$

$\text{C}$

$\text{NMR, 125 MHz, CDCl}_3$

$\text{MeO}_2\text{C}\quad \ast 0\quad \text{Ph}$

$\text{13C NMR, 125 MHz, CDCl}_3$

$I\quad I\quad I\quad I\quad 166$

$I\quad I\quad I\quad 164$

$I\quad I\quad 162\ 160\ 158\ 156$

$I\quad I\quad 148\ 146\ 144\ 142\ 140$

$I\quad 138\ 136$

$I\quad 134$

$F\quad 132$

$I\quad I\quad I\quad 130$

$I\quad I\quad 128\ 126$

$I\quad I\quad 124\ 122$

$I\quad I\quad 120$

$I\quad I\quad 118$

$I\quad 116$

$748$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
\[ ^1H \text{ NMR, 500 MHz, CDCl}_3 \]
$^{13}$C NMR, 125 MHz, CDCl$_3$
Ph\n
$\text{H NMR, 500 MHz, CDCl}_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{19}\text{F NMR, 470 MHz, CDCl}_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 150 MHz, CDCl$_3$
MeO₂C

$^1$H NMR, 500 MHz, CDCl₃

$^1$H NMR. 500 MHz. CDCl₃
$\text{MeO}_2C\text{S} - \text{Ph}$

$^13C$ NMR. 125 MHz. CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
Ph

T/F

Ph

H NMR, 500 MHz, CDCl₃
$\text{Ph} \quad \text{S} \quad \text{F} \quad \text{Ph}$

$^{13}$C NMR, 125 MHz, CDCl$_3$
$\text{PhMePhF} \quad \text{H NMR, 500 MHz. CDC$_3$} \quad \text{H}$

Chemical shift values:
- 10.0 ppm
- 9.5 ppm
- 9.0 ppm
- 8.5 ppm
- 8.0 ppm
- 7.5 ppm
- 7.0 ppm
- 6.5 ppm
- 6.0 ppm
- 5.5 ppm
- 5.0 ppm
- 4.5 ppm
- 4.0 ppm
- 3.5 ppm
- 3.0 ppm
- 2.5 ppm
- 2.0 ppm
- 1.5 ppm
- 1.0 ppm
- 0.5 ppm
- 0.0 ppm
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^1$H NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^13$C NMR, 125 MHz, CDCl$_3$
Ph  S  N  F

$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 1.25 MHz, CDCl$_3$