Synthesis and Reactivity of Palladium Trifluorides and Fluorides Towards Aryl C–CF$_3$ and C–F Bond Formation

by

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"Vouloir c'est pouvoir"
– French Proverb

Dedication

To my three heroes:

James A. Ball Jr. (Father)

Dorothea G. Ball (Mother)

Dorothy J. Garrett (Grandmother)

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Abbreviations

AcOH	acetic acid
Ar	aryl
bpy	2,2'-bipyridine
ºC	temperature in degrees centigrade
CDCl$_3$	deutrated chloroform
Cy	cyclohexyl
d	day(s)
dba	dibenzylidene acetone
DCE	1,2-dichloroethane
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridine
Et	ethyl
equiv	equivalent
GCMS	gas chromatography mass spectrometry
h	hour(s)
i-Pr	isopropyl
ºK	temperature in degrees Kelvin
MS	Mass Spectroscopy
Me	methyl
min	minute(s)
NBu$_4$OAc	tetrabutylammonium acetate

NBu$_4$OTf   tetrabutylammonium triflate

NO$_2$Ph-*d*$_5$ nitrobenzene-*d*$_5$

Ph   phenyl

rt   room temperature

TBAF   tetrabutylammonium fluoride

t-Bu   *tert*-butyl

THF   tetrahydrofuran

tol   tolyl

Abstract

The installation of carbon–fluorine and carbon-trifluoromethyl bonds in organic compounds can have a significant effect on the chemical and biological of the molecules. However, synthetically the selective incorporation of C–F/C–CF$_3$ bonds into important biological targets remains a significant challenge. Palladium catalysis has been extremely successful in the selective incorporation of C-X (X = Cl, Br, I, OAc, Ar, N) bonds into molecules. Thus, an attractive strategy would be to utilize palladium C–X coupling methodologies to promote C–F/C–CF$_3$ bond formation.

This dissertation will discuss structural and mechanistic studies of palladium intermediates modeling Pd(0)/Pd(II) and Pd(II)/Pd(IV) catalytic systems towards aryl fluorination and trifluoromethylation. Structural analysis of Pd(II)-fluoride complexes will be presented focusing on the affects of steric and electronics on the metal center and the implications towards Pd(0)/Pd(II) aryl C–F coupling. Additionally, the reactivity of aryl Pd(II)–F and Pd(II)–CF$_3$ complexes with stoichiometric quantities of electrophilic fluorinating agents resulting in Aryl–F and Aryl–CF$_3$ bond coupling will be discussed. These reactions proceed to generate both electron rich and electron poor aryl fluorides and trifluorides in good yield. Observation of C–F/C–CF$_3$ bond coupling from isolated σ-aryl Pd^{IV}–F and Pd^{IV}–CF$_3$ complexes will emphasize the viability of C–F/C–CF$_3$ bond formation in a Pd(II)/Pd(IV) catalytic system.

Chapter 1

Introduction

Carbon-trifluoromethyl and carbon–fluorine bond formation has been a transformation of high interest due to the utility of these bonds in an array of applications from PET imaging, agrochemicals and pharmaceuticals. Nearly 25% of pharmaceuticals and 40% of agrochemicals currently in development contain C–CF$_3$ or C–F bonds underscoring their importance in these fields (Scheme 1.1).[1,2]

Lipitor
(Cholesterol, rank #1)
$ 13.7 billion

Crestor
(Cholesterol, rank #16)
$ 3.9 billion

Celebrex
(Arthritis, rank #37)
$2.5 billion

Fluoropyram
(Fungicide)
$200 milion

Trifluralin
(herbicide)
$300 milion

Scheme 1.1 – Representative Examples of Fluorinated Pharmaceuticals and Agrochemicals and Their Annual Sales (2008)

Although organofluorine compounds are not commonly found in nature, there is a

need to develop practical methodologies for the selective incorporation of fluorine into both simple and complex molecules. A variety of synthetic methods exist to create aliphatic sp^3 and olefinic sp^2 C–CF$_3$ and C–F bonds,[3,4] however few general and practical approaches for the formation of benzotrifluorides and aryl fluorides are currently available. As an alternative, the use of transition metal catalysts for the construction of aryl C–CF$_3$ and C–F offers several key advantages. (1) Catalysis would lower the activation barrier to form the desired C–CF$_3$ and C–F bonds thus allowing the usage of milder reagents and conditions. (2) Metal-catalyzed method would selectively install C–CF$_3$ and C–F bonds on specific carbons. (3) Catalysis would allow the use of sub-stoichiometric quantities of metal in the reactions. The following sections will describe the key synthetic challenges of forming aryl C–CF$_3$ and C–F bonds and contextualize how conducting the stoichiometric and mechanistic studies described in this thesis have been instrumental in providing evidence for novel Pd^{II}/Pd^{IV}-catalyzed C–CF$_3$ and C–F couplings.

1.1 Synthesis of Benzotrifluorides and Aryl Fluorides

The development of general synthetic methods for the installation of the CF$_3$ groups poses a considerable challenge for synthetic organic chemists. Traditionally, benzotrifluorides have been formed either through the Swarts reaction[5] or oxidative desulfurization-fluorination (Scheme 1.2).[6] The Swarts reaction involves a two-step conversion of toluenes to benzotrifluorides through radical chlorination followed by treatment with a metal fluoride (e.g. SbF$_5$) or anhydrous hydrogen fluoride (Scheme 1.2-a). Alternatively benzotrifluoride can be synthesized through oxidative desulfurization-fluorination. For example aryldithiolates can be converted to benzotrifluorides using 1,3-dibromo-5,5-dimethylhydantoin (DBH) as an oxidant (Scheme 1.2-b). There have also been reports of using aryl trifluoromethylsulfonium reagents as a source of CF$_3^+$ to directly trifluoromethylated arenes (e.g. *p*-hydroquinone); however, this transformation is only compatible with electron-rich aromatic systems (Scheme 1.2-c).[7] These approaches require the use of toxic, corrosive reagents and suffer with modest yields and poor regioselectivity. These features render them incompatible with many functional groups and thus undesirable for towards the construction of complex molecules.

Scheme 1.2 – Common Methods of Aryl Trifluoromethylation: (a) Swarts Reaction, (b) Oxidative Desulfurization-Fluorination and (c) Electrophilic Substitution of Arenes

Installation of a fluorine atom into an aromatic system also remains a challenge for synthetic chemists. The two most common methods to generate aryl fluorides are the Balz-Schiemann reaction[8] and the Halex process.[9] The Balz-Schiemann reaction, similar to the Sandmeyer reaction involves the conversion of anilines to aryl diazonium salts using HBF_4 and HNO_2. Thermolysis of the diazonium salts then leads to the desired aryl fluoride (Scheme 1.3-a). The Halex (halogen exchange) process involves the reaction of a highly activated arene (e.g. 1-chloro-2,4-dinitrobenzene) with a fluoride source through a nucleophilic aromatic substitution (Scheme 1.3-b). In addition, there are examples of the synthesis of aryl fluorides using thallium compounds and diaryliodonium salts (Scheme 1.3-c and d).[10,11]

Scheme 1.3 – Common Methods of Aryl Fluorination: (a) Balz-Schiemann Reaction, (b) Halex Process, (c) Fluorination of Aryl Tl(III) Reagents, and (d) Fluorination of Diaryliodonium Salts

Similar to the methods to produce benzotrifluorides, these aryl fluorination protocols are very limited in substrate scope, involve corrosive and explosive reagents, and are thus incompatible with many functional groups. Recent efforts have been made to address these issues by using a milder fluorinating reagent such as tetramethylammonium fluorine ($[Me_4N]_3F$), and by synthesizing aryl fluorides from aryl bromides (via benzyne intermediate). However, poor regioselectivity remains a challenge for these systems (Scheme 1.4).[12]

Scheme 1.4 – Fluorination of 2-Bromonapthlene by $[NMe_4]^+F^-$ via a Benzyne Intermediate

Provided these issues were resolved, a notable hurdle remains. In a multi-step synthetic sequence of a complex organic molecule the installation of C–CF$_3$/C–F bonds significantly alters the reactivity of the molecules towards subsequent reactions. This is a considerable challenge especially in medicinal chemistry where the fluorinated analogue of a target compound for high-throughput screening requires unique synthesis. Additionally, these syntheses are limited to the commercial availability of the fluorinated starting materials. Therefore, there is extreme interest in developing robust methods that permit the late stage incorporation of fluorine. To address these challenges, transition metal catalyzed cross-coupling reactions towards aryl C–CF$_3$/C–F bond formation would be an attractive approach. These metal-catalyzed transformations could lower the activation barrier towards C–CF$_3$/C–F coupling thereby affording conditions more amenable to a wide array of substrates. To date, however, these transformations have proven difficult.

1.2 Metal-Mediated Aryl Trifluoromethylation

The most extensively studied aryl C–CF$_3$ cross-coupling from transition metals has been with copper.[13] Early work by Urata showed that copper halides, like CuI, could be used along with CF$_3$SiMe$_3$, and KF to convert aryl iodides to benzotrifluorides (Scheme 5).[14] While promising, this method is limited to being stoichiometric in metal and has a modest substrate scope. Recently, Amii and co-workers have been able to use this strategy to develop a Cu-catalyzed cross-coupling reaction that converts aryl iodides to benzotrifluorides using copper(I) iodide (CuI) and phenanthroline.[15] However, similar to the stoichiometric example by Urata, this transformation is also limited in scope, primarily requiring electron-withdrawing arenes (Scheme 1.5).

Scheme 1.5 – Cu-mediated Formation of Benzotrifluorides

Implicated in both systems is the *in situ* generation of a "CuCF$_3$" from the reaction of R$_3$SiCF$_3$ with F$^-$. Yet, such species have been difficult to isolate. Towards this goal, Vicic and co-workers have shown that the isolable *N*-heterocyclic carbene (NHC) copper complexes (NHC)Cu−CF$_3$ react stoichiometrically with aryl iodides to generate Ar−CF$_3$ products. The mechanism of this transformation is still currently under investigation (Scheme 1.6).[16]

Scheme 1.6 – Conversion of Aryl Iodides to Benzotrifluorides using (NHC)Cu–CF$_3$

As an alternative, several researchers have focused on using palladium to promote aryl C–CF$_3$ cross-coupling. Palladium is particularly attractive due to its known broad applications in cross-coupling reactions to form carbon–carbon bonds. Two general strategies have been proposed for promoting Aryl–CF$_3$ bond formation from palladium: 1) modifying the ancillary ligands on palladium towards the development of a Pd^0/Pd^{II} catalytic cycle and, 2) changing the metal center through oxidation for Pd^{II}/Pd^{IV} catalysis (Scheme 1.7).

Modify ancillary ligand(s) by sterics

Modify the metal center

Scheme 1.7 – Two Strategies Towards Ar–CF$_3$ Bond Formation from Pd

Early efforts in this area focused on the conversion of aryl halides to benzotrifluorides following a Pd^0/Pd^{II} mechanism. This mechanism involves the following: (i) an oxidative addition of Ar-X (X = I, Br, Cl, or OTf) to the Pd^0 center resulting in an σ- aryl Pd^{II} halide compound (**2-1**), (ii) transmetallation of CF_3 from a R_3SiCF_3 reagent (R = alkyl group) to **2-1** generating Pd^{II}–CF_3 (**2-2**) and finally (iii) reductive elimination of the Ar-CF_3 from **2-2** and regeneration of the Pd^0 catalyst (Scheme 1.8).[17]

(i)   oxidative addition
(ii) transmetallation
(iii) reductive elimination

Scheme 1.8 – Pd^0/Pd^{II} Catalytic Cycle for Aryl Trifluoromethylation

All the steps of the proposed catalytic cycle have significant precedent except for the C–CF_3 bond-forming reductive elimination. To this end, considerable efforts have been invested in promoting C–CF_3 bond-forming reductive elimination from Pd^{II} complexes by using bulky ligands. These efforts are predicated on the hypothesis that steric congestion introduced at the metal center by the bulky ligand should force reductive elimination by relieving steric strain on the complex. In 2006, Grushin and co-workers provided the first demonstration of this concept by showing that the thermolysis of [(Xantphos) Pd(Ph)(CF_3)] in the presence of Xantphos in benzene at 80 °C leads to the nearly quantitative yield of trifluorotoluene (Scheme 1.9).[18] Inspired by Grushin's work, Buchwald and co-workers using sterically encumbering monodentate phosphine ligands

(Brettphos or Ruphos) developing a Pd-catalyzed system that converts aryl chlorides to benzotrifluorides at 130 - 140 °C (Scheme 1.10).[19]

Scheme 1.9 – Aryl–CF$_3$ Bond Formation from (Xantphos)Pd(Ar)(CF$_3$) at 80 °C

Scheme 1.10 – Pd-catalyzed Conversion of Aryl Chlorides to Benzotrifluorides

Although an important discovery in metal-catalyzed Aryl–CF$_3$ cross-coupling reactions, the requirement for expensive ligands, high temperatures, and Et$_3$SiCF$_3$ leave substantial room for improvement. This work underscores the need for future catalytic systems that can utilize a larger array of ligands and different sources of CF$_3$.

Since 2004, our group and others have been highly successful in using palladium catalysts to promote the conversion of aryl C–H bonds to C–X bonds (X = aryl, F, Cl, Br, I, OAc, N, etc.) using electrophilic reagents as oxidants.[20] This oxidative C–H activation/functionalization transformation proceeds through the following Pd^{II}/Pd^{IV} mechanism: (i) C–H activation by Pd forming an aryl Pd^{II} species (**2-3**), (ii) oxidation of **2-3** by oxidant–X (X = aryl, F, Cl, Br, I, OAc, N, etc.) generating a Pd^{IV} intermediate (**2-4**) and finally C–X bond-forming reductive elimination (Scheme 1.11).

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(i)   C–H activation
(ii) Oxidation
(iii) Reductive elimination

Scheme 1.11 – Mechanism of Oxidative C–H Activation/Functionalization

Our goal was to see if we could exploit this Pd^{II}/Pd^{IV} manifold to promote Aryl–CF_3 bond formation (Scheme 1.12). A significant advantage to this strategy is that we could expand the scope of the starting material from aryl halides and triflates to any arene (though C–H activation or transmetallation with aryl boronic acid, stannanes or silanes). However, at the onset of this project, there were no examples of Aryl–CF_3 bond-forming oxidative coupling and no evidence of the viability of a Pd^{IV}–CF_3 intermediate.

Scheme 1.12 – General Transformation of Oxidative Trifluoromethylation

Chapter 2 discusses the synthesis and isolation of a $Pd^{IV}(Ar)(CF_3)$ complex and its reactivity towards the first example of C–CF_3 bond formation from Pd^{IV}.[21] Kinetic and computational studies (DFT calculations were performed by J. Brannon Gary) have been used to elucidate the mechanism of C–CF_3 bond-forming reductive elimination. Finally, ligand optimization has allowed for the first demonstration of C–CF_3 coupling from

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palladium at room temperature in high yield. Chapter 3 describes collaboration with Yingda Ye, where the isolation and characterization of another monomeric $Pd^{IV}(Ar)(CF_3)$ compound from a cyclometallated dimer is demonstrated to be catalytically-relevant in a Pd-catalyzed C–H trifluoromethylation reaction.[22]

1.3 Metal-Mediated Aryl Fluorination

Transformations from transition metals silver and palladium have also seen studied in the formation of aryl fluorides. Ritter and co-workers reported a novel Ag-mediated conversion of aryl stannanes to aryl fluorides using an excess of AgOTf and F-TEDA-PF_6 (Scheme 1.13).[23]

Scheme 1.13 – Ag-Mediated Conversion of Aryl Stannanes to Aryl Fluorides

The mechanism was proposed to involve a transmetallation of the aryl group from tin to silver forming an aryl-silver•AgOTf adduct (**2-5**). Subsequent oxidation of the aryl-silver species with F-TEDA BF_4 followed by C–F bond-forming reduction elimination resulted in the aryl fluoride product (Scheme 1.14).

Scheme 1.14 – Mechanism of Silver-Mediated Aryl Fluorination

Recently, further optimization of this reaction has lead to a silver-catalyzed system where the treatment of aryl stannanes with Ag_2O, F-TEDA-PF_6 and sodium salts leads to aryl fluorides with excellent yield (Scheme 1.15).[24]

Scheme 1.15 – A Example of Silver-Catalyzed Aryl Fluorination

Analogous aryl-fluoride coupling reactions have also been pursued at Pd centers. This approach is particularly attractive since Pd is a versatile catalyst in other carbon-halogen (e.g. Cl, Br, or I) couplings. Compared to silver, C–F couplings from palladium could also occur from a wider scope of starting materials (e.g. aryl halides, boronic acids, silanes, in addition to stannanes). Moreover, the ability of palladium to catalyze C–H activation/functionalization chemistry is another advantage over silver; circumventing the need for pre-functionalized arenes.[20a]

In the literature there are two main proposed mechanisms for aryl fluorination using palladium: reductive fluorination and oxidative fluorination.[25] More commonly, reductive fluorination involving a Pd^0/Pd^{II} cycle has been proposed where there is (i) an oxidative addition of Ar-X (X = I, Br, Cl) to the Pd^0 center to form σ- aryl Pd^{II} halide complex (**2-6**) , (ii) a salt metathesis at **2-6** converting Pd–X to Pd–F and finally (iii) a Ar–F bond-forming reductive elimination from **2-6** and regeneration of the Pd^0 catalyst (Scheme 1.16). Although the first two steps have successfully been demonstrated, reductive elimination from Pd^{II} to form Ar-F bonds has proven difficult to achieve.[26]

Scheme 1.16 – Pd^0/Pd^{II} Catalytic Cycle for Aryl Fluorination

(i) oxidative addition
(ii) halide exchange
(iii) reductive elimination

The thermolysis of $(L)_2Pd^{II}(Ar)(F)$ complexes (L = phosphine ligands) have been reported to undergo competitive P–F, P–P and Aryl–Aryl reductive eliminations instead of generating the C–F product.[26] For example the thermolysis of $(Ph_3)_2Pd(Ph)(F)$ in toluene afforded Ph_3P^+–F, Ph_3PF_2, Ph–Ph, Ph_2P–Ph_3 and Pd^0 the products (Scheme 1.17).

Scheme 1.17 – Thermolysis of $(Ph_3)_2Pd(Ph)(F)$ in Toluene.

Recently, Buchwald and co-workers were able to demonstrate aryl C–F bond-forming reductive elimination from $(L)Pd^{II}(Ar)(F)$ compound, **5.16** (L = *t*BuBrettPhos and Ar = 4-fluoro-3-methylbenzonitrile). Upon thermolysis of **5.16**, the corresponding aryl fluoride product was achieved in 25% yield (Scheme 1.18).[27] Similar to their strategy of Aryl–CF_3 coupling from Pd^{II}, Buchwald used the *t*Brettphos ligand to introduce sufficient steric congestion around the Pd center to promote C–F formation and suppress the undesired P–F product.

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Scheme 1.18 – C–F Bond-Forming Reductive Elimination from Pd^{II}

Building on this initial success, a Pd-catalyzed conversion of aryl triflates to aryl fluorides was developed using Brettphos as a ligand (Scheme 1.19).[27] While this was a significant advance in Pd-catalyzed Aryl–F coupling this transformation from a Pd^{II} remains rare; further highlighting the difficulty in C–F reductive elimination from Pd^{II}.[26a]

Scheme 1.19 – Pd-Catalyzed Aryl Fluorination Using Reductive Fluorination

One alternative to circumvent the undesired side-products generated upon thermolysis of these phosphine complexes is to use different ancillary ligands. A prime candidate for this modification would include nitrogen-donor ligands because the unproductive P–F bond-forming reductive elimination would not be possible in this system. Thus, these new complexes may favor C–F bond formation. Chapter 4 discusses the synthesis of novel aryl and alkyl palladium(II) fluorides with sp^2 and sp^3 nitrogen donor ligands. While no C–F bond formation was observed from these compounds, X-ray crystallographic characterization revealed interesting characteristics in comparison to their phosphine-containing analogues. These studies provide significant insight on the effect of ancillary

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ligand on the nature of the Pd–F bonds.[28]

Another approach to palladium-catalyzed aryl fluorination is through oxidative fluorination via a Pd^{II}/Pd^{IV} manifold. To this end, our laboratory has recently reported a Pd-catalyzed ligand-directed C-H activation/fluorination reaction using *N*-fluoropyridinium salts as an oxidant (Scheme 1.20).[29] However, at the time it was not clear if the mechanism proceeded via a Pd^{II}/Pd^{IV} mechanism or an electrophilic cleavage of the aryl–palladium bond.

R = F, CF$_3$, Me, OMe

(33-70%)

Scheme 1.20 – Ligand-Directed Pd-Catalyzed Fluorination of Aryl C–H Bonds

To this end, Ritter and coworkers isolated a (bzq)Pd^{IV} fluoride complex (bzq = benzo[*h*]quinoline) and demonstrated direct aryl C–F reductive elimination. This model served as an example that oxidative fluorination could indeed proceed through a Pd^{II}/Pd^{IV} mechanism (Scheme 1.21).[30]

(58%)

(97%)

Scheme 1.21 – Synthesis of an Isolable Pd^{IV}–F by Oxidative Fluorination and C–F Bond-Forming Reductive Elimination

While the ability to regioselectively convert aryl C–H bonds to C–F bonds represents a significant advance to synthesize aryl fluorides; the need for a tethered chelating group on the arene is a critical limitation of this method. Towards this goal, recent stoichiometric studies have focused on a palladium-mediated oxidative fluorination of σ-

aryl Pd[II] species where the arene does not contain a chelating group (Scheme 1.22).[31]

Scheme 1.22 – Oxidative Fluorination of a Pd(Ar)(F) Species Without a Chelating Group on the Arene

Although these transformations were proposed to proceed through a Pd[II]/Pd[IV] mechanism, the isolation of an aryl Pd[IV] fluoride complex without a tethered chelating group on the arene has proven challenging.

Chapter 5 will describe the isolation of an σ-aryl Pd[IV]–bifluoride where the arene does not have a chelating ortho substituent. The reactivity of this complex towards Aryl–F bond forming reductive elimination is discussed.[32] With this mechanistic evidence, a catalytic C–F bond forming reaction can be envisioned that can convert aryl stannanes, silanes and boronic acids to aryl fluorides. The ease of synthesis of these metal arene reagents permits the installation of aryl fluoride anywhere an Aryl–M can be incorporated. Each chapter addresses critical challenges towards promoting aryl C–CF$_3$ and C–F bond-forming reductive elimination from Pd. The research described herein not only represent advances in the synthesis and reactivity of Pd[IV] complexes, but establishes a foundation to explore new organometallic transformations.

1.4 References

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Chapter 2

Mechanistic Studies on Aryl–CF$_3$ Formation from Palladium(IV) Complexes: Rational Design Towards Room Temperature Aryl Trifluoromethylation

2.1 Introduction

The formation of C–CF$_3$ bonds is an extremely important transformation for the construction of numerous pharmaceuticals and agrochemicals.[1] The replacement of a CH$_3$ for a CF$_3$ group can have a profound effect on the physical and biological properties of a molecule and is a highly important strategy in increasing its bioavailability.[2] As a result, there is a high demand for versatile synthetic methods for generating C–CF$_3$ bonds. While there has been remarkable progress in the construction of sp^3 C–CF$_3$ linkages, [3] there are comparatively fewer methods for Aryl–CF$_3$ bond formation.[4] Several methods have been developed to access benzotrifluorides, including the Swarts reaction[5] and oxidative desulfurization-fluorination[6]. In addition, the direct C–H trifluoromethylation of arenes with aryl trifluoromethylsulfonium reagents has been reported for electron-rich systems (Scheme 2.1).[7] However, these methods are incompatible with many functional groups and are thus not generally applicable for the modification of complex molecules. Transition metal catalyzed cross-coupling reactions for the transformation would provide a potentially attractive alternative for Aryl–CF$_3$ bond construction. However, Aryl–CF$_3$ bond-forming reductive elimination (a key step of any catalytic cycle for cross-coupling) has proven exceptionally challenging.[8]

Scheme 2.1 – (a) Swarts Reaction, (b) Oxidative Desulfurization-Fluorination and (c) Electrophonic Substitution of Arenes

Palladium-catalyzed Aryl–CF_3 is a particularly attractive target, since Pd is a versatile catalysts for a variety of other C–C bond-forming reactions. There are two general strategies for promoting Aryl–CF_3 bond formation from palladium: (1) modifying the ancillary ligands to achieve a Pd^0/Pd^{II} catalytic cycle and 2) changing the metal center through oxidation for Pd^{II}/Pd^{IV} catalysis. In 2006, Grushin demonstrated that $(Xantphos)Pd^{II}(Ar)(CF_3)$ undergoes high yielding Ph–CF_3 bond-forming reductive elimination at 80 °C. This was the first reported example of Aryl–CF_3 coupling from a well-defined transition metal complex (Scheme 2.2).[9] Key to their strategy was the use of sterically bulky phosphine ligand Xantphos to facilitate C–CF_3 bond formation.

Scheme 2.2 – Ar–CF_3 Bond Formation From $(Xantphos)Pd(Ar)(CF_3)$ at 80 °C

Recently, using a similar approach, Buchwald and co-workers developed a catalytic system for converting aryl chlorides to benzotrifluorides using Pd complexes containing sterically large monodentate phosphine ligands (Brettphos or Ruphos, Scheme 2.3).[10] While this was an exceptional breakthrough in metal-catalyzed Ar–CF$_3$ cross coupling reactions, the reaction is limited by the requirement for specialized phosphine ligands, high temperatures (130 - 140 °C) and, expensive Et$_3$SiCF$_3$ (1 mol = $13,500).[11]

Scheme 2.3 – Pd-catalyzed Conversion of Aryl Chlorides to Benzotrifluorides

Our group[12] and others[13] have demonstrated that high oxidation state palladium complexes mediate a number of challenging Aryl–X (X = Ar, Cl, Br, I, N, OAc, and OMe) bond-forming reactions. These studies have shown that high energy Pd^{III} and Pd^{IV} intermediates greatly facilitate reductive elimination relative to analogous transformations at Pd^{II} centers. Adopting this approach, we envisioned that modification of the palladium center via oxidation to Pd^{IV} could promote C–CF$_3$ bond forming reductive elimination. The key benefit of this method is that the putative Pd^{IV} can be accessed through either arene C–H activation[14] or transmetallation[15] and with nucleophilic (CF$_3^-$),[16] electrophilic (CF$_3^+$),[17] or radical (CF$_3^•$)[18] -based trifluoromethylation sources. As such, this would significantly expand available types of catalytic Ar–CF$_3$ bond-forming reactions (Scheme 2.4). This chapter discusses our work demonstrating the first example of Ar–CF$_3$ bond forming reductive elimination from a fully characterized Pd^{IV}(Ar)(CF$_3$) compound.[19] A full account of our studies including a ligand screen, oxidant scope, and description of a new ligand system that promotes Ar–CF$_3$ bond formation at room temperature are presented. Additionally, kinetic and DFT studies that provide insights into the mechanism of Aryl–CF$_3$ bond-forming reductive elimination in this system are described.

Scheme 2.4 – General Transformations of Oxidative Trifluoromethylation

2.2 Synthesis and Reactivity of (dtbpy)Pd(Ar)(CF$_3$) Complexes

Our studies began with the synthesis of a series of Pd^{II}–CF$_3$ complexes of general structure (dtbpy)Pd(Aryl)(CF$_3$) (**2-1a-j**, dtbpy = di-*tert*-butylbipyridine). These complexes were prepared by the sequential treatment of (dtbpy)Pd(Ar)(I) with CsF followed by TMSCF$_3$ in THF at 23 °C (Table 2.1). The products were isolated as yellow solids in 32-70% yield. [19]

Table 2.1 – Synthesis of (dtbpy)Pd(Aryl)(CF$_3$) Complexes **2-1a** – **2-1k**

Entry	Compound	Aryl	Yield
1	**2-1a**	*p*-FC$_6$H$_4$	70%
2	**2-1b**	*p*-CNC$_6$H$_4$	54%
3	**2-1c**	*p*-CF$_3$C$_6$H$_4$	63%
4	**2-1d**	*p*-(C(O)Ph)C$_6$H$_4$	51%
5	**2-1e**	*p*-PhC$_6$H$_4$	58%
6	**2-1f**	*p*-CH$_3$OC$_6$H$_4$	32%
7	**2-1g**	C$_6$H$_5$	47%
8	**2-1h**	*p*-tol	49%
9	**2-1i**	*m*-tol	42%
10	**2-1j**	*o*-tol	70%
11	**2-1k**	*o*-FC$_6$H$_4$	36%

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These Pd^{II} complexes are remarkably stable towards direct Aryl–CF$_3$ bond-forming reductive elimination. For example, <5% of 4-fluorobenzotrifluoride **2-2a** was formed upon heating complex **2-1a** at 130 °C in nitrobenzene-d_5 (NO$_2$Ph-d_5) for 72 h. The Pd^{II} starting material remained largely intact (>80% recovery) even after these forcing conditions (Scheme 2.5). This observation is consistent with literature reports showing that related (P~P)Pd^{II}(Aryl)(CF$_3$) complexes (P~P = dppe, dppbz and dppp) are similarly inert toward C–CF$_3$ bond forming reductive elimination.[16a,16b] The only successful example of Aryl–CF$_3$ bond-forming reductive elimination from Pd^{II}–CF$_3$ complexes have involved sterically bulky phosphine ligands like Xantphos, RuPhos and BrettPhos.[9,10]

Scheme 2.5 – Thermolysis of **2-1a** at 130 °C in NO$_2$Ph-d_5

We reasoned that a 2e^- oxidation of (dtbpy)Pd(Aryl)(CF$_3$) would produce a Pd^{IV}(Aryl)(CF$_3$) adduct that might be significantly more reactive towards Aryl–CF$_3$ bond-forming reductive elimination. We first examined the reaction of **2-1a** with NBS, NCS, and PhI(OAc)$_2$, which are well known to promote the oxidation of Pd^{II} to Pd^{IV}.[12] As shown in Table 2.2, entries 1-3, these oxidants all reacted rapidly with **2-1a** in NO$_2$Ph-d_5 at 80 ºC to produce functionalized arenes. However, in all cases, the major organic product contained a nucleophile derived from the oxidant (Br, Cl, or OAc, respectively), and the desired trifluoromethylated compound (**2-2a**) was formed in <5% yield. These results suggest that upon oxidation, C–X (X = OAc, Br, and Cl) bond-forming reductive elimination is significantly faster than C–CF$_3$ coupling with these oxidants (Scheme 2.6).

Scheme 2.6 – Competitive C–CF$_3$ versus C–X Reductive Elimination From **2-1a**

Table 2.2 – Reaction of **2-1a** with *N*-Halosuccinimides and PhI(OAc)$_2$

Entry	Oxidant	Yield 2-2a	Yield 2-3a (X)
1	Br—N(succinimide)	<5%	75% (Br)
2	Cl—N(succinimide)	<5%	70% (Cl)
3	AcO—I—OAc (Ph)	<5%	20% (OAc)

3 equiv of oxidant was used in the reaction.
Yields are determined by ^{19}F NMR spectroscopy and are an average of two runs.

On the basis of these results, we reasoned an oxidant was needed that could introduce ligands to the putative Pd^{IV} intermediate from which C–X bond forming reductive elimination is significantly slower than C–CF$_3$ coupling. This approach should render our desired transformation more kinetically accessible. As such, we explored the use of electrophilic fluorinating reagents (F$^+$) since C–F bond-forming reductive elimination at Pd has been demonstrated to be significantly slower than other carbon-heteroatom coupling reactions (Scheme 2.7).[20]

Scheme 2.7 – Competitive C–CF$_3$ Versus C–F Reductive Elimination from **2-1a**

Gratifyingly, this transformation worked as predicted. A variety of different F$^+$ reagents reacted with **2-1a** to afford modest to excellent yields of the trifluoromethylated product **2-2a** after 3 h at 80 °C (Table 2.3, entries 4-10). The optimal electrophilic fluorinating

reagent was *N*-fluoro-1,3,5-trimethylpyridium triflate (NFTPT), which provided **2-2a** in 70% yield (as determined by ^{19}F NMR spectroscopy, entry 7).[21] Importantly, <5% of the corresponding fluorine or triflate-containing products were formed under these conditions.

Table 2.3 – Reaction of **2-1a** with Electrophilic Fluorinating Oxidants

Entry	Oxidant	Yield 2-2a
1		<5%[a]
2		60%
3		53%
4		69%
5		55%
6		68%
7		73%
10	XeF_2	65%

3 equiv of oxidant was used in the reaction.
Yields are determined by ^{19}F NMR spectroscopy and are an average of two runs.
[a] **2-1a** accounted for the remaining mass balance.

We next examined the efficacy of this transformation with complexes **2-1b – 2-1k** that contain sterically and electronically diverse aryl groups (Table 2.1). In general, the yield

of Aryl–CF$_3$ coupling was relatively insensitive to the electronic properties of the arene and these reactions proceeded in good to excellent yield with both electron withdrawing (*e.g.,* CN, C(O)Ph) and electron donating (*e.g.,* CH$_3$, OCH$_3$) *para-* and *meta*-substituents on the aromatic ring. Interestingly, attempts to promote oxidative Ar–CF$_3$ bond formation from Pd^{II}–CF$_3$ with *ortho* methyl (*o*-tol) substitution (**2-1j**) yielded a reversal in chemoselectivity of the reaction favoring the C–F coupled product 2-fluorotoluene in a 4.4:1 ratio relative to 2-methylbenzotrifluoride (**2-2j**) (Table 2.4, entry 10). Ortho–F substituted arene (**2-k**) did not undergo clean Aryl–CF$_3$ bond formation. Instead, a complex mixture of products was observed by ^{19}F NMR spectroscopy (entry 11). This reversal in chemoselectivity highlights how slight steric changes of the σ-aryl ligand can have a significant effect on the chemoselectivity of reductive elimination from Pd^{IV} (*vide infra)*.

Table 2.4 – Aryl–CF$_3$ Coupling at Complexes **2-1a** – **2-1k** Promoted by NFTPT

Entry	Compound	Aryl	Yield
1	**2-1a**	*p*-FC$_6$H$_4$	70%
2	**2-1b**	*p*-CNC$_6$H$_4$	25%
3	**2-1c**	*p*-CF$_3$C$_6$H$_4$	55%
4	**2-1d**	*p*-(C(O)Ph)C$_6$H$_4$	56%
5	**2-1e**	*p*-PhC$_6$H$_4$	70%
6	**2-1f**	*p*-CH$_3$OC$_6$H$_4$	72%
7	**2-1g**	C$_6$H$_5$	66%
8	**2-1h**	*p*-tol	70%
9	**2-1i**	*m*-tol	64%
10	**2-1j**	*o*-tol[a]	13%
11	**2-1k**	*o*-FC$_6$H$_4$[b]	<5%

3 equiv of NFTPT was used in the reaction.
Yields are determined by ^{19}F NMR spectroscopy and are an average of two runs
[a] 2-fluorotoluene was the major product in 62% [b] product could not be determined

2.3 Synthesis of (dtbpy)Pd^{IV}(p-FPh)(CF$_3$)(F)(OTf), 2-4

Our efforts next focused on the detecting intermediates in this Aryl–CF$_3$ bond-forming process. The reactions in Tables 2.2 and 2.3 were conducted at 80 ºC, we reasoned that intermediates might be detectable at lower temperatures. As such, we examined the oxidation of **2-1a** by NFTPT at room temperature. In both DCE (1,2-dichloroethane) and nitrobenzene, a single major product inorganic intermediate (**2-4**) was observed by ^{1}H and ^{19}F NMR spectroscopy. This species was isolated from DCE as a yellow solid in 53% yield (Scheme 2.8). Analysis of **2-4** by ^{19}F NMR spectroscopy in MeCN-d_3 showed four characteristic broad resonances: a doublet at –30.9 ppm (Pd–**CF$_3$**), a singlet at –79.4 ppm (Pd–**OTf**), a multiplet at –117.1 ppm (Pd–Ar**F**), and a quartet at –256.5 ppm (Pd–**F**) in a 3 : 3 : 1 : 1 ratio. In nitrobenzene-d_5 broad resonances were observed with similar chemical shifts in the same 3 :3 :1 :1 ratio.[22] in nitrobenzene-d_5 showed four resonances at –31.8 ppm (Pd–**CF$_3$**), –77.9 ppm (Pd–**OTf**), –115.7 ppm (Pd–**ArF**), and –246.7 ppm (Pd**F**) in a 3:3:1:1 ratio (Figure 2.1). ^{1}H NMR spectroscopy showed singlets at 8.83 ppm and 8.70 ppm corresponding to the 5 and 5' protons of the dtbpy ligand. Additionally, two singlets for the *t*-butyl groups appeared at 1.49 and 1.41 ppm implicating an unsymmetrical compound (Figure 2.2).[23] Thermolysis of **2-4** at 80 ° C in NO$_2$Ph-d_5 for 3h resulted in 77% conversation to 1-fluoro-4-benzotrifluoride **2-2a** (Scheme 2.9).

Scheme 2.8 – Synthesis of **2-4** at 23 °C in DCE

Figure 2.1 – ^{19}F NMR of **2-4** in NO_2Ph-d_5

VARIAN

(2-4)

Nitrobenzene overlapping with peaks of compound

Figure 2.2 – ^{1}H NMR of **2-4** in NO$_2$Ph-d_5

Scheme 2.9 – Thermolysis of **2-4** at 80 °C in NO$_2$Ph-d_5

X-ray quality crystals of **2-4** were obtained via vapor diffusion of pentanes into a DCE solution of **2-4**. The X-ray crystal structure in Figure 2.3 confirms the unsymmetrical octahedral structure (dtbpy)Pd(p-FPh)(CF$_3$)(F)(OTf) (Figure 2.3).

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Figure 2.3 – ORTEP Drawing Of Complex **2-4**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogen Atoms Are Omitted For Clarity Unless Otherwise Noted. Selected Bond Lengths (Å): Pd–C(1) 2.009(5), Pd–C(25) 2.018(5), Pd–N(1) 2.038(4), Pd–N(15) 2.082(4), Pd–O(1) 2.226(3). Selected Bond Angles (°): C(19)–Pd–C(25) 91.09(15), C(19)–Pd–N(15) 92.18(16), C(25)–Pd–N(15) 175.68(17), C(19)–Pd–F(1) 91.09(15), C(25)–Pd–F(1) 83.31(16), C(19)–Pd(1)–O(1) 175.74 (16), C(25)–Pd(1)–O(1) 95.15 (16).

For structural comparison, X-ray quality crystals of Pd^{II}–CF_3 complex **2-1a** were obtained by vapor diffusion of pentanes into a solution of dichloromethane. The X-ray structure of this square planar Pd^{II} compound is shown in Figure 2.4. Intriguingly, the Pd–CF_3 bond lengths of **2-1a** (2.005(3) Å) is nearly identical to that found in Pd^{IV}–CF_3 **2-4** (2.009(4) Å).[19] However, the Pd–N bond lengths of **2-4** (2.038(4) and 2.082(4) Å) are significantly shorter than those in the corresponding Pd^{II} complex **2-1a** (2.107(2) and 2.143(3) Å). This implicates stabilization of the high oxidation state Pd center through π-electron donation from the rigid bidentate sp^2 N-donor ligand to the more electron deficient Pd^{IV}.[24, 25]

Figure 2.4 – ORTEP Drawing Of Complex **2-1a**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogen Atoms Are Omitted For Clarity Unless Otherwise Noted. The Structure Was Solved As Two Identical Structures In A Unit Cell (Only One Is Shown, See Section 2.12). Selected Bond Lengths (Å): Pd–C(1) 2.005(3), Pd–C(25) 2.007(4), Pd–N(1) 2.107(2), Pd–N(2) 2.143(3). Selected Bond Angles (°): C(1)–Pd–C(25) 89.99(13), C(1)–Pd–N(1) 95.58(11), C(1)–Pd–N(2) 169.99(11), C(25)–Pd–N(1) 173.92(12), C(25)–Pd–N(2) 96.67(11).

2.4 Ligand Scope of Oxidative Aryl Trifluoromethylation

We next sought to explore the scope of this oxidative trifluoromethylation reaction with respect to the L-type donor ligands. Importantly, related Aryl–CF$_3$ coupling reactions at Pd^{II} are very sensitive to ligand structure. For example, Pd^{II} aryl trifluorides with bulky ligands (e.g. Xantphos[26], Brettphos and Ruphos[10]) undergo Ar–CF$_3$ bond-forming reductive elimination quantitatively at 80 °C. However, replacing the ligand with less sterically hindered ligands (dppe, dppp and dppbz) resulted extremely low yields of benzotrifluoride.[27] Thus, it would be highly advantageous to have a metal-mediated trifluoromethylation method that tolerated diversity of L-type ligands. The Pd^{II} complexes used in these studies (**2-1f** and, **2-5** – **2-10** in Table 2.5) were prepared in modest to

excellent yield either by the reaction of $L_2Pd^{II}(AryI)(I)$ with CsF followed by TMSCF$_3$ (compounds **2-1f** and **2-7 – 2-11**) or (TMEDA)Pd(Ar)(CF$_3$) with KHSO$_4$ followed by phosphine in CH$_2$Cl$_2$ (compounds **2-5** and **2-6)** (see Section 2.12.).

Table 2.5 – Synthesis of (L)$_2$Pd(Ph)(CF$_3$) Complexes

$$\text{L}\!\!>\!\!\text{Pd}^{II}\!\!<^{\text{Aryl}}_{\text{I}} \xrightarrow[\text{2. TMSCF}_3\text{, THF, 23 °C}]{\text{1. CsF, THF, 23 °C}} \text{L}\!\!>\!\!\text{Pd}^{II}\!\!<^{\text{Aryl}}_{\text{CF}_3}$$

Entry	Compound	L	Ar	Yield Ar–CF$_3$
1	**2-5**	Ph$_2$P⌒PPh$_2$	Ph	Ref. 16b
2	**2-6**	Ph$_2$P⌒PPh$_2$ (benzene backbone)	*o*-tol	Ref. 16a
3	**2-1f**	tBu / tBu bipyridine	Ph	47%
4	**2-7**	bipyridine	Ph	37%
5	**2-8**	N⌒N (cyclohexyl)	Ph	81%
6	**2-9**	N⌒N (propyl)	Ph	67%
7	**2-10**	N⌒N (isopropyl)	Ph	Ref. 16b

Treatment of the phosphine complexes **2-5** and **2-6** with NFTPT in NO$_2$Ph at 80 °C for 3 h resulted in complete consumption of starting material and the liberation of <5% to 20% of benzotrifluoride **2-2h** and **2-2j**, respectively (Table 2.6, entries 1-3). While these yields are relatively modest, they are still higher yielding than analogous reactions at Pd^{II} with these same simple ligands. In most cases the starting material was the major product.

Complexes containing bidentate N-donor ligands afforded good to excellent yields of trifluorotoluene at 80 °C in the presence of NFTPT (Table 2.6, entries 4-7). Tmeda (*N,N,N',N'*-tetramethylethylene diamine) appears to be the optimal ligand for this transformation[28], as (tmeda)Pd^{II}(Ph)(CF$_3$) (**2-10)** reacted with NFTPT to afford 90% yield of trifluorotoluene after 3 h at 80 °C (entry 7). *Remarkably, this complex also provided excellent yield of Ph–CF$_3$ coupling after 1 h at room temperature (entry 8).* To our knowledge this is first example of room temperature arene trifluormethylation at a Pd center.[29]

Table 2.6 – Aryl–CF$_3$ Coupling from Complexes **2-1f** and **2-5 – 2-10** Promoted by NFTPT

Entry	Compound	L	Ar	Yield Ph–CF$_3$
1	2-5	Ph$_2$P⌒PPh$_2$	Ph	20%
2	2-6	Ph$_2$P⌒PPh$_2$ (o-phenylene)	o-tol	<5%
3	2-1f	tBu / tBu bipyridine	Ph	66%
4	2-7	bipyridine	Ph	62%
5	2-8	N⌒N (dipiperidyl)	Ph	99%
6	2-9	Et$_2$N⌒NEt$_2$	Ph	40%
7	2-10	Me$_2$N⌒NMe$_2$	Ph	90%
8	2-10	Me$_2$N⌒NMe$_2$	Ph	83%^{a}

3 equiv. of NFTPT was used in the reaction.
Yields are determined by ^{19}F NMR spectroscopy and are an average of two runs.
^{a} Reaction was conducted at room temperature.

2.5 Synthesis and Reactivity of (tmeda)Pd(Ar)(CF$_3$) Complexes

With these optimized conditions in hand, a series of (tmeda)Pd^{II}(Ar)(CF$_3$) complexes with electronically and sterically different σ-aryl ligands were synthesized by the reaction of (tmeda)Pd^{II}(Aryl)(I) with CsF followed by TMSCF$_3$ in THF at 23 °C. The compounds were isolated yellow or white solids in 10 to 76% yield (**2-10a** – **2-10j** in Table 2.7).

Table 2.7 – Synthesis of (tmeda)Pd(Ar)(CF$_3$) Complexes

Entry	Compound	Aryl	Yield
1	**2-10a**	p-FC$_6$H$_4$	76%
2	**2-10b**	p-CNC$_6$H$_4$C$_6$H$_4$	51%
3	**2-10c**	p-CF$_3$C$_6$H$_4$	42%
4	**2-10d**	p-OCH$_3$C$_6$H$_4$	34%
5	**2-10e**	C$_6$H$_5$	Ref. 16b
6	**2-10f**	p-tol	57%
7	**2-10g**	m-tol	42%
8	**2-10h**	o-tol	59%
9	**2-10i**	o-FC$_6$H$_4$	81%
10	**2-10j**	o-OCH$_3$C$_6$H$_4$	10%

We next explored the scope of oxidatively induced trifluoromethylation from tmeda complexes **2-10a** to **2-10j** at 80 °C and at room temperature. Overall, yields of benzotrifluorides were significantly improved using tmeda versus dtbpy as the ancillary ligand. As shown in Table 2.8, complexes with electron neutral or electron donating substituents on the σ-aryl ligand (entries 4-7), underwent Aryl–CF$_3$ bond formation at 80 °C and at room temperature in comparable yields. Complexes with electron withdrawing groups required higher temperatures for better conversion of the desired trifluoromethylated arene (Table 2.8, entries 1-3). Unlike the dtbpy system (Table 2.4, entries 10 and 12), tmeda complexes with *ortho*-substituted aromatic groups reacted to form the corresponding benzotrifluorides in modest to excellent yields (Table 2.8, entries 8-10). Remarkably, the *o*-tol-substituted Pd^{II}–CF$_3$ complex (entry 8) resulted in very high yield (88%) of trifluoromethylated arene product. This is in contrast to the same complex in the dtbpy series, where aryl fluorination was predominated (Table 2.4, entry 10, *vide infra)*. The 2-fluoro substitution (Table 2.8, entries 9) underwent trifluoromethylation in low yield, with the major product being 2-fluorobenzene. This is presumably due to adventitious water in the solvent. However, the yield could be improved by heating this substrate at 80 °C for 3 h.

Table 2.8 – Aryl–CF$_3$ Coupling from Tmeda Complexes **2-10a – 2-10j** Promoted by NFTPT at 80 ºC and 23 ºC

(2-10a – 2-10j)

Entry	Compound	Aryl	Yield Ar–CF$_3$ (80 ºC)	Yield Ar–CF$_3$ (23 ºC)
1	**2-10a**	p-FC$_6$H$_4$	81%	78%
2	**2-10b**	p-CNC$_6$H$_4$C$_6$H$_4$	60%	22%
3	**2-10c**	p-CF$_3$C$_6$H$_4$	76%[a]	52%[b]
4	**2-10d**	p-OCH$_3$C$_6$H$_4$	94%	88%
5	**2-10e**	C$_6$H$_5$	90%	83%
6	**2-10f**	p-tol	92%	95%
7	**2-10g**	m-tol	95%	95%
8	**2-10h**	o-tol	85%	88%
9	**2-10i**	o-FC$_6$H$_4$	44%[b]	13%[c]
10	**2-10j**	o-OCH$_3$C$_6$H$_4$	90%	99%

These reactions were conducted with 3 equiv. of oxidant at 80 °C for 3 h and at 23 °C for 1 h. Yields are determined by ^{19}F NMR spectroscopy and are an average of two runs. Reactions were run in duplicate and all of the starting material was consumed. [a] At both temperatures, trifluorotoluene is present at 13%. [b] At 80 °C, fluorobenzene is present at 46%. [c] At 23 °C, fluorobenzene is present at 45%.

2.6 Mechanistic Study of C–CF$_3$ Bond Forming Reductive Elimination From 2-4

There are at least three potential pathways Aryl–CF$_3$ bond-forming reductive elimination from **2-4**, paths **A**, **B**, and **C** (Figure 2.5). Pathway **A** involves triflate dissociation from complex **2-4**, resulting in a cationic five-coordinate Pd^{IV} species and subsequent Aryl–CF$_3$ bond formation. Pathway **B** involves fluoride dissociation, following a similar transformation as pathway **B**. Pathway **C** involves concerted C–CF$_3$ bond-forming reductive elimination. Notably, there is significant literature precedent for ionic (paths **A** and **B**)[30,31] and concerted (path **C**) reductive elimination mechanisms from octahedral Pd^{IV} complexes.[32]

PATH A

−TfO⁻ → ... +TfO⁻

Aryl ⌐+
N Pd^IV ·CF₃
N F

−[Pd^II]

Aryl
N Pd^IV ·CF₃
N F
OTf

[N~N = dtbpy]
[Aryl = *p*-FC₆H₄]

(2-4)

PATH B
−F⁻ ⇌ +F⁻

Aryl ⌐+
N Pd^IV ·CF₃
N OTf

−[Pd^II] → Aryl–CF₃

PATH C
−[Pd^II]

Figure 2.5 – Three Potential Mechanisms for Ar–CF₃ Bond Formation from **2-4**.

We first sought to explore the kinetics of Aryl–CF₃ bond-forming reductive elimination from **2-4** by observing the formation of **2-2a** over time (Figure 2.6). At first glance, a plot of [**2-2a**] versus time seemingly followed an exponential first order growth (Figure 2.7). However, as shown in Figure 2.7, the rate of C–CF₃ bond formation changes as the reaction progresses. This is most clearly seen at the beginning of the reaction (highlighted in the box in Figure 2.7). As shown in Table 2.8, the initial rate of product formation (Ar–CF₃) decreased at higher conversions implicating inhibition by of the products of reductive elimination. This observation is consistent with a dissociative mechanism (path **A** or **B**) where higher conversion of product leads to higher concentration of TfO⁻ or F⁻ anion, which then slows the rates of C–CF₃ bond-forming reductive elimination. For these reasons, we used initial rates (first 10% conversion) for all subsequent rate studies.

Figure 2.6 – Array Spectrum Demonstrating the Reductive Elimination of **2-4** to from **2-2a** in NO$_2$Ph-d_5 at 60 °C

Figure 2.7 – Representative Kinetics for the Reductive Elimination

of **2-5** in d_5-NO$_2$Ph at 60 °C

Table 2.9 – Initial Rates versus Percent Conversion of the **2-4** to **2-2a**

in d_5-NO$_2$Ph at 60 °C

Conversion to 2-2a	Initial rate (M s^{-1})
0-10%	2.20 x 10^{-4}
10-20%	1.91 x 10^{-4}
20-30%	1.66 x 10^{-4}
40-50%	1.64 x 10^{-4}
50-60%	1.31 x 10^{-4}
60-70%	1.11 x 10^{-4}
70-80%	1.16 x 10^{-4}
80-90%	1.18 x 10^{-4}
90-100%	1.34 x 10^{-4}

We first sought to investigate mechanism **A** by examining the rate of C–CF$_3$ bond-forming reductive elimination as function of [TfO$^-$].

2.7 Order Studies with 2-4

Thermolysis of **2-4** in NO$_2$Ph-d_5 at 50 °C in the presence of 1 equiv of NBu$_4$OTf significantly slowed the initial rate of formation of **2-2a** from 2.21 x 10^{-5} M s^{-1} to 1.35 x 10^{-5} M s^{-1}. Furthermore, an excellent linear fit was obtained for a plot of initial rate

versus 1/[NBu$_4$OTf]. This is consistent with a reaction that is inverse first-order in triflate ion (Figure 2.8). To discern whether the decrease in rate was due to the triflate anion and not a change in polarity of the reaction medium, complex **2-4** was heated at 50 °C in the presence of 1 equiv of NBu$_4$PF$_6$. The initial rate was 5.57 x 10^{-5} M s^{-1} indicating the change in rate with NBu$_4$OTf was not due to change in polarity of the reaction medium but to the triflate anion. Additionally, the increase rate in the presence of NBu$_4$PF$_6$ versus no additive is consistent with a less coordinating ligand (e.g. PF$_6$) favoring a cationic Pd^{IV} intermediate thus, facilitating faster reductive elimination. We next wanted to explore path **B** by studying the initial rate of reductive elimination as a function of [F$^-$]. However, the reaction of **2-4** in NO$_2$Ph-d_5 at 23 °C in the presence of 1 equiv Me$_4$NF produced a compound array of Pd–CF$_3$ and Pd–F peaks (as determined by ^{19}F NMR spectroscopy). As such, we could not fully explore path **B**.[33]

Figure 2.8 –Plot of Initial Rates Versus 1/[OTf $^-$] for Reductive Elimination From **2-4** in PhNO$_2$-d_5 at 50 °C. y = 1.91 x 10^{-7} + 9.86 x 10^{-6}; R^2 = 0.998.

2.8 – Activation Parameters of Reductive Elimination of 2-4

The initial rates of C–CF$_3$ bond-forming reductive elimination from **2-4** were determined at temperatures ranging from 30 °C to 60 °C in NO$_2$Ph-d_5. An Eyring plot resulted in the following values for the activation parameters: $\Delta H^{\ddagger}$ = 29.1 ± 0.2 kcal mol^{-1} and $\Delta S^{\ddagger}$ = 9.48 ± 0.8 eu and, $\Delta G^{\ddagger}_{298}$ = 26.2 ± 0.1 kcal mol^{-1}.

Figure 2.9. Eyring Plot for the Reductive Elimination of **2-4** in PhNO$_2$-d_5. y = -1.45 x 10^{-7} + 2.85 x 10^{-6}; R^2 = 0.999

Previous reports have demonstrated that reductive eliminations from Pd^{IV} following dissociative mechanisms like paths **A** and **B** can have rather different entropies of activation ($\Delta S^{\ddagger}$). For example, Canty and co-workers reported that sp^3 C-Se bond-forming reductive elimination from Pd^{IV} has highly negative $\Delta S^{\ddagger}$ values ranging from -40 to 49 eu in acetone. The authors attribute these $\Delta S^{\ddagger}$ values to the overall stabilization of the transition state via orientation of polar and coordinating solvent molecules around the cationic Pd^{IV} transition state. Conversely, recent reports by our group and Ritter have reported $\Delta S^{\ddagger}$ values for aryl C–O and C–F bond forming reductive elimination from Pd^{IV} that were significantly higher with $\Delta S^{\ddagger}$ ranging from -1.4 to 4.2 eu (CDCl$_3$ and DMSO-d_5 respectively) and 12.4 eu (MeCN) respectively.[12e,13f,30c] The $\Delta S^{\ddagger}$ value in the current system demonstrates that the nature of the transition state is less ionized than Canty's system suggesting an early or late transition state. Furthermore, the values are inconsistent with activation entropy values for a concerted reductive elimination, which should be nearer to zero. [32b]

With the results of the order and activation parameter studies in hand, we propose that path **A** is the predominant pathway of C–CF$_3$ bond-forming reductive elimination from **2-4**. The order studies demonstrate inverse-first order dependence on [TfO$^-$] (Scheme 2.10). However, inconclusive attempts to study the dependence of [F$^-$] on reductive elimination of **2-4** preclude us from eliminating path **B**. Finally, the entropy of activation suggests that a concerted mechanism (Path **C**) is not likely in this system.

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Scheme 2.10 – Proposed Mechanism (Path **A**) and Derived Rate Expression

2.9 Synthesis and Reactivity of Pd^{IV}(Ar)(CF$_3$) Compounds 2-11 and 2-12

Scheme 2.11 – Pd^{IV}–CF$_3$ compounds **2-11** and **2-12**

We next wanted to examine whether the electronics of the σ-aryl group has an effect on the rate of reductive elimination. We synthesized two new mono aryl Pd^{IV}–CF$_3$ complexes (dtbpy)Pd(*p*–CF$_3$Ph)(CF$_3$)(F)(OTf) (**2-11**) and (dtbpy)Pd(tol)(CF$_3$)(F)(OTf) (**2-12**) in a similar manner to **2-4** (see Section 2.12 for experimental details, Scheme 2.11). Thermolysis of these complexes at 80 °C in NO$_2$Ph-*d$_5$* for 3h led to quantitative conversion to their respective benzotrifluorides. Next, we observed the initial rates of Aryl–CF$_3$ bond-forming reductive elimination from these complexes. Upon thermolysis in NO$_2$Ph-*d$_5$* at 50 **°**C, the initial rate for **2-11** was 1.43 x 10^{-5} M s^{-1}, nearly two times slower than reductive elimination from **2-4** (pF) (2.21 x 10^{-5} M s^{-1}). With the more electron-rich **2-12**, the initial rate *was* more than *20 times faster* (4.59 x 10^{-4} M/s^{-1}) than that from **2-4**. At first glance these results suggest that electron-donating groups promote faster Ar–CF$_3$ bond formation and therefore that there is a positive charge buildup in the transition state. However, due to the *trans* effect of the aryl group on triflate dissociation, electron-donating arenes could serve to promote more facile dissociation to form five-coordinate

Pd[IV] intermediate and thus promote faster formation of product. Therefore, it was difficult to discern if the increased initial rate for **2-12** was due to the stronger *trans* effect of a tolyl group (versus a p-Fphenyl or p-CF$_3$ phenyl group) or an actual charge buildup in the transition state. These synergistic phenomena would make a Hammett plot from these hexacoordinate complexes challenging to interpret. Notably, related studies by Buchwald and co-workers on σ-aryl Pd[II] complexes did not show a significant electronic effect for the aryl group on aryl–CF$_3$ bond forming reductive elimination.[10]

2.10 Density Functional Theory (DFT) studies

We next turned to computational analysis to glean information on two key aspects of our mechanism of reductive elimination from Pd[IV]: (a) the electronic effect of the aryl ligand towards C–CF$_3$ bond-forming reductive elimination and (b) the chemoselectivity of C–F bond formation over C–CF$_3$ bond formation in the case of the oxidative fluorination of (dtbpy)Pd(*o*-tol)(CF$_3$) (**2-1j**). J. Brannon Gary assisted with this analysis and performed the DFT calculations. We first focused on exploring the effect of arene electronics on C–CF$_3$ bond-forming reductive elimination.

Our experimental studies demonstrated that the rate of C–CF$_3$ bond-forming reductive elimination from (dtbpy)Pd[IV](Aryl)(CF$_3$)(F)(OTf) complexes followed a trend where initial rate for *p*-CH$_3$> F > CF$_3$, indicating electron-donating aryl groups at Pd[IV] facilitated faster reductive elimination. However, the kinetics involved in bond forming reductive elimination involve a loss of $^-$OTf to form a pentacoordinate intermediate before rate-determining reductive elimination (Figure 2.5, path A). As discussed above, this complicates analysis of the effect of aryl electronics in the fundamental bond-forming step. To ameliorate this complication, we decided to analyze reductive elimination from the five-coordinate intermediate using DFT calculations. [Pd(bipy)(Ph)(CF$_3$)F]$^+$ (**2-13**) (bipy = 2,2'-bipyridyl) was chosen as our model for computational analysis (Scheme 2-12). From complex (**2-13**), we found a transition state corresponding to Ar-CF$_3$ reductive elimination with an energy ($\Delta G^{\ddagger}_{298}$) of 17.1 kcal mol^{-1}. The charge distribution of intermediate **2-13** using Natural Bond Order Analysis (NBO)[34] indicated that CF$_3$ carbon carries a significant positive charge (+1.03) along with the Ph carbon having a charge of +0.02.[35] This charge difference is amplified in the transition state for reductive elimination. In the transition state, the CF$_3$ carbon carries an enhanced positive charge

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of +1.14, while the Ph carbon charge decreases to -0.14. These data imply that the Ph group is acting as the nucleophile in the fundamental bond-forming step. This is in sharp contrast to other reports of reductive elimination from Pd[IV] in which the Ar group typically serves as the electrophilic coupling partner.[12,13]

We next explored computationally how the electronics of the aryl ring affected the transition state energy for reductive elimination. With a buildup of negative charge on the aryl carbon, we hypothesized that electron-donating groups should accelerate C–CF$_3$ bond-forming reductive elimination. Our hypothesis was validated as a Hammett plot of log(k_X/k_H) versus $\sigma+$ resulted in a ρ value of −1.16. This demonstrates that electron-donating groups increase the rate of reaction (Figure 2.11).

Scheme 2.12 – Model Pd[IV]–CF$_3$ Complexes **2-14**, **2-15**, and **2-16** for DFT Calculations

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Figure 2.10 – Plot of log(k_X/k_H) Versus σ+ Using Computational Analysis at 298 K. y = -1.16 x + 0.65; R^2 = 0.840.

Notably, the fit of the Hammett data to σ+ (R^2 = 0.840; ρ = -1.16) was significantly better than sigma (R^2 = 0.557; ρ = -1.70) and σ– (R^2 = 0.602; ρ = -1.30) indicating a significant π-contribution from the *para*-substituent.

With this data in hand, we next explored the chemoselectivity of Ar-CF$_3$ versus Ar-F bond formation. Using **2-13** to the model a transition state for Ar-CF$_3$ reductive elimination with an activation energy ($\Delta G^{\ddagger}_{298}$) of 17.1 kcal mol^{-1} was found. In contrast, the transition state energy for Ar-F reductive elimination is ($\Delta G^{\ddagger}_{298}$) 14.0 kcal mol^{-1}. This indicates a mixture of products should be observed with the Ar-F product being the major product. This is in sharp contrast to our experimental results where Ar–CF$_3$ product is the major species observed.[36] Using this data as a benchmark calculation to explain reactivity and selectivity, we next explored the consequence of changing the bipy ligand for tmeda in the two transition states. Using the model complex [Pd(tmeda)(Ph)(CF$_3$)F]$^+$ (**2-14**), resulted in a transition state energy ($\Delta G^{\ddagger}_{298}$) of 13.8 kcal mol^{-1} for Ar-CF$_3$ reductive elimination and ($\Delta G^{\ddagger}_{298}$) of 13.0 kcal mol^{-1} Ar-F reductive elimination. These results accurately predict that exchanging tmeda for dtbpy would lower the activation barrier toward C–CF$_3$ bond formation as seen with the oxidative trifluoromethylation of (tmeda)Pd(Ar)(CF$_3$) compounds at room temperature.

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Next, in an effort to understand the chemoselectivity seen with the *ortho*-tolyl substrate, [Pd(bipy)(*o*-tol)(CF$_3$)F]$^+$ (**2-15**) was used a model complex. In comparison with model **2-13**, the addition of steric bulk had little effect on the transition state energies for Ar-CF$_3$ bond formation ($\Delta G^{\ddagger}_{298}$ = of 17.3 kcal mol^{-1}). In contrast, the corresponding Ar-F bond formation showed a pronounced lowering of the transition state energy $\Delta G^{\ddagger}_{298}$ = 10.9 kcal mol^{-1} compared to $\Delta G^{\ddagger}_{298}$ = 14.0 kcal mol^{-1} for bipy **2-13**. These results suggest that in our *ortho*-tolyl system there should be an increase in the amount of Ar-F coupled product. This was indeed their result in the oxidative fluorination of **2-1j** with NFTPT resulting in a 4.4:1 ratio of Ar-F to Ar-CF$_3$ (Scheme 2.13).

Scheme 2.13 – Oxidative Fluorination of **2-1j** with NFTPT

While these DFT studies broadly corroborate our empirical findings, the fact that our model still calculates the transition state of C–F bond formation as lower in energy is of concern. Therefore further studies are ongoing to explore this issue.

2.11 Conclusion

This chapter demonstrates the first evidence of C–CF$_3$ bond formation from Pd^{IV} Aryl–CF$_3$ complexes. Oxidative trifluoromethylation of several aryl Pd^{II}–CF$_3$ compounds has demonstrated that Aryl–CF$_3$ bond formation is feasible with a variety of phosphorus and nitrogen ancillary ligands and electrophilic fluorinating oxidants. Most notably, using tmeda as the ancillary ligand resulted in the first example of Aryl–CF$_3$ bond formation from palladium at room temperature. Extensive kinetic and DFT calculations have provided significant evidence that Aryl–CF$_3$ bond forming reductive elimination from these Pd^{IV} complexes occurs via a dissociative mechanism that is inverse first-order in TfO$^-$ and involves the aryl group as the nucleophilic coupling partner. This work provides the basis for the development novel Pd-catalyzed C–CF$_3$ coupling reactions via C–H activation or transmetallation with aryl boronic acid, stannanes or silanes.

2.12 Experimental Procedures

General Considerations

NMR spectra were obtained on a Varian Inova 400 (399.96 MHz for ^{1}H; 376.34 MHz for ^{19}F; 100.57 MHz for ^{13}C), a vnmr500 (500.09 MHz for ^{1}H: 470.56 MHz for ^{19}F; MHz for ^{13}C) spectrometer, or MR400 (400.53 MHz for ^{1}H: 376.87 MHz for ^{19}F; 100.71 MHz for ^{13}C) spectrometer. ^{1}H, ^{19}F and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced on a unified scale, where the single primary reference is the frequency of the residual solvent peak in the ^{1}H NMR spectrum.[37] ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), quartet (q), multiplet (m), and broad resonance (br). Atlantic Microlabs in Norcross, Georgia, conducted elemental analyses. Mass spectral data were obtained on a Micromass magnetic sector mass spectrometer or on a Micromass LCT mass spectrometer with an electrospray ionization mode.

Materials and Methods

Pd(dba)$_2$,[38] (dtbpy)Pd(Cl)$_2$,[39] (dtbpy)Pd(I)$_2$ (see Chapter 5, Section 5.7), (bpy)Pd(Ph)(I)[40], (dtbpy)Pd(Ar)(I) (Ar = *p*-F, *p*-CF$_3$ and *p*-OMe see Chapter 5, Section 5.7), (teeda)Pd(Ph)(I),[41] (dpe)Pd(Ph)(I),[41] (dppe)Pd(tol)(CF$_3$) (**2-5**),[16b] (dppbz)Pd(Ph)(CF$_3$) (**2-6**),[16a] (tmeda)Pd(Ph)(CF$_3$) (**2-10**),[16b] 1,2-dipiperdinoethane (dpe)[42] were prepared according to literature procedures. All aryl iodides were purchased from commercial sources. Authentic samples of all of the Ar–CF$_3$ reductive elimination products were purchased from commercial sources. Rupert's reagent (TMSCF$_3$), 1-fluoro-4-benzotrifluoride were obtained from Matrix Chemicals. 1,2-bis(diphenylphosphino)ethane (dppe), 1.2-bis(diphenylphosphino)benzene (dppbz), triphenylphosphine, *N,N',N'',N'''*-tetramethylethylenediamine (TMEDA), *N,N',N'',N'''*-tetraethylethylenediamine (TEEDA), 1,4-(bis) and 4,4′-di-*tert*-butyl-2,2′-bipyridine, were obtained from Aldrich. 1-Fluoro-2,4,6-trimethylpyridinium triflate and was obtained from TCI America. Unless otherwise noted, all reagents were used as received. Nitrobenzene-*d*$_5$, CD$_2$Cl$_2$, CD$_3$CN and CDCl$_3$ were obtained from Cambridge Isotope

Laboratories. All other solvents were obtained from Fisher Chemicals. Tetrahydrofuran, toluene and pentane were purified using an Innovative Technologies (IT) solvent purification system consisting of a copper catalyst, activated alumina, and molecular sieves. Dichloroethane was distilled from CaH_2. Nitrobenzene-d_5 was distilled from P_2O_5 and then stored over 4 Å molecular sieves. All syntheses were conducted using standard Schlenk techniques or in an inert atmosphere glovebox unless otherwise stated.

General procedure for the synthesis of (dtbpy)Pd(Ar)(I): Complexes were synthesized according to previously reported literature procedure (3g scale).

(dtbpy)Pd(*p*-FPh)(I) – Product was isolated as an orange solid (1.6 g, 31% yield). ^{1}H NMR (CDCl$_3$): δ 9.47 (d, *J* = 6 Hz, 1H), 7.95 (multiple peaks, 2H), 7.53 (d, *J* = 6 Hz, 1H), 7.48 (d, *J* = 6 Hz, 1H), 7.30 (multiple peaks, 3H), 6.81 (multiple peaks, 2H), 1.40 (s, 9H), 1.37 (s, 9H); ^{19}F NMR (CDCl$_3$): δ −123.2 (m, 1F); ^{13}C NMR (CDCl$_3$): δ 163.33, 163.27, 160.93 (d, *J* = 239.8 Hz), 155.91, 153.86, 152.52, 149.55, 138.52, 136.67 (d, *J* = 5 Hz), 123.86 (br s), 123.54, 118.43, 118.01, 113.98 (d, *J* = 19 Hz), 35.53, 35.48, 30.38, 30.26. Anal. Calc. for C$_{24}$H$_{28}$FIN$_2$Pd: C, 48.30, H, 4.73, N, 4.69; Found: C, 48.09, H, 4.75, N, 4.72. Notably, small amounts (~7%) of (dtbpy)Pd(I)$_2$ were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(*p*-FPh)(I).**

(dtbpy)Pd(*p*-CNPh)(I) – Product was isolated as an orange solid (1.38g, 66%). ^{1}H NMR (CDCl$_3$, 500.09 MHz): δ 9.47 (d, 6Hz, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.58 (d, 8Hz, 2H), 7.50 (dd, 5 Hz, 2Hz, 1H), 7.43 (d, 6Hz, 1H), 7.34 (dd, 6Hz, 2Hz, 1H), 7.25 (d, 10 Hz, 2H), 1.41 (s, 9H), 1.38 (s, 9H). .^{13}C NMR (CDCl$_3$, 125.75 MHz): δ 163.78, 163.59, 158.15, 155.94, 153.77, 152.59, 149.26, 137.67, 129.18, 124.02, 123.71, 120.14, 118.64, 118.20, 106.32, 35.55, 35.47, 30.31, 30.18. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{25}$H$_{28}$IN$_3$Pd, 626.0255; Found, 626.0256 amu. Notably, small amounts (~5%) of (dtbpy)Pd(I)$_2$ were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(*p*-CNPh)(I).**

(dtbpy)Pd(*p*-C(O)Ph–Ph)(I) – Product was isolated as an orange solid (2.20 g, 62 %). ^{1}H NMR (CDCl$_3$): δ 9.45 (d, 6Hz, 1H), 7.97 (apparent singlet, 2H), 7.80-7.78 (multiple peaks, 2H), 7.58 (d, 8Hz, 2H), 7.53-7.42 (multiple peaks, 7H), 7.30 (dd, 6Hz, 2Hz, 1), 1.40 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 197.34, 163.53, 163.41, 158.45, 155.86, 153.80, 152.49, 149.56, 138.51, 136.63, 132.73, 131.56, 129.85, 128.17, 127.95, 123.89, 123.64, 118.51, 118.08, 35.49, 35.44, 30.32, 30.10. HRMS-electrospray (m/z): [M – I + MeCN]$^+$ calcd for C$_{33}$H$_{36}$N$_3$OPd, 596.1880. Found, 596.1900 amu. Notably, small amounts (~5%) of [(*t*-Bu-bpy)Pd(I)$_2$] were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(I)$_2$.**

(dtbpy)Pd(*m*–tol)(I) – Product was isolated as an orange solid (0.72g, 23%). ^{1}H NMR (CDCl$_3$): δ 9.50 (d, *J* = 6Hz, 1H), 7.98 (s, 2H), 7.59 (d, *J* = 6Hz 1H), 7.51 (m, 1H), 7.35 (m, 1H), 7.28 (s, 1H), 7.20 (d, *J* = 7Hz, 1H), 6.93 (t, *J* = 7 Hz, 1H), 6.74 (d, *J* = 7 Hz, 1H), 1.44 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 163.21, 163.16, 155.92, 153.91, 152.57, 150.00, 146.54, 137.20, 136.54, 133.51, 126.99, 124.19, 123.90, 123.65, 118.37, 117.99, 35.61, 35.56, 30.52, 30.39, 21.65. HRMS-electrospray (m/z): [M – I – MeCN]$^+$ calcd for C$_{25}$H$_{31}$IN$_2$Pd, 506.1782; Found, 506.1798 amu. Notably, small amounts (~4%) of (dtbpy)Pd(I)$_2$ were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(*m*–tol)(I).**

(dtbpy)Pd(*o*–tol)(I) – Product was isolated as an orange solid (0.60 g, 19%). ^{1}H NMR (CDCl$_3$,): δ 9.45 (d, 6 Hz, 1H), 7.94 (s, 2H), 7.48 (d, 6Hz, 1H), 7.39-7.34 (multiple peaks, 2H), 7.26 (m, 1H), 6.94 (m, 1H), 6.84-6.82 (multiple peaks, 2H), 2.57 (s, 3H), 1.40 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 163.06, 163.02, 155.86, 153.70, 152.28, 149.18, 147.26, 141.28, 136.10, 128.65, 123.98, 123.82, 123.64, 123.09, 118.33, 117.86, 35.45. 35.41, 30.27, 30.23, 26.90. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{25}$H$_{31}$IN$_2$Pd, 615.0464; Found, 615.0477 amu. Notably, small amounts (~7%) of (dtbpy)Pd(I)$_2$ were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(*o*–tol)(I).**

(dtbpy)Pd(*o*–FPh)(I) – Product was isolated as an orange solid (0.89 g, 29%). ^{1}H NMR (CDCl$_3$,): δ 9.57 (d, *J* = 6Hz, 1H), 7.95 (s, 2H), 7.61 (d, *J* = 6Hz, 1H), 7.51 (dd, *J* = 6Hz, 2Hz, 1H), 7.45 (m, 1H), 7.32 (dd, *J* = 6Hz, 2Hz, 1H), 6.97-6.89 (multiple peaks, 2H), 6.80 (m, 1H), 1.43 (s, 9H), 1.39 (s, 9H) . ^{19}F NMR (CDCl$_3$): δ –93.07 (m, 1F) 1^{13}C NMR (CDCl$_3$): δ 164.58 (d, *J* = 230 Hz), 163.54, 156.29, 154.37, 153.08, 149.97, 139.08 (d, *J* = 15 Hz), 127.73 (d, *J* = 38 Hz), 124.98 (d, *J* = 7 Hz), 124.16, 123.84, 123.30 (d, *J* = 2 Hz), 118.63, 118.14, 114.62, 114.35, 35.69, 35.64, 30.52, 30.40. HRMS-electrospray (m/z): [M – I + MeCN]$^+$ calcd for C$_{24}$H$_{28}$FIN$_2$Pd, 510.1531; Found, 510.1543 amu. Notably, small amounts (~5%) of (dtbpy)Pd(I)$_2$ were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **(dtbpy)Pd(*o*–FPh)(I).**

General procedure for the synthesis of (tmeda)Pd(Ar)(I): Under nitrogen, Pd(dba)$_2$ (2.0 g, 3.48 mmol, 1 equiv) was weighed into a 250 mL round bottom flask and dissolved in THF (50 mL). TMEDA (1.1 g, 9.06 mmol, 2.6 equiv) was added, and the resulting mixture was stirred at 25 ºC for 15 min. The aryl iodide (9.74 mmol, 2.8 equiv) was added, and the reaction was warmed for 60 ºC for 30 min. In air, the reaction mixture was filtered through a plug of Celite, and the solvent was removed under reduced pressure. The resulting solid was washed with hexanes (3 x 20 mL) and then diethyl

ether (3 x 50 mL) removing all residual dibenzylidene acetone (dba). The product was then dried *in vacuo*.

(tmeda)Pd(*p*–FPh)(I) – The complex was isolated as an orange solid (1.8 g, 78% yield). ^{1}H NMR (CDCl$_3$): δ 7.11-7.08 (multiple peaks, 2H), 6.67-6.63 (multiple peaks, 2H), 2.63-2.61(multiple peaks, 2H), 2.59 (s, 6H), 2.48-2.46 (multiple peaks, 2H), 2.22 (s, 6H). ^{19}F NMR (CDCl$_3$): δ –124.02 (m, 1F). ^{13}C NMR (CDCl$_3$): δ 160.41 (d, *J* = 239 Hz), 136.75 (d, *J* = 2 Hz), 136.14 (d, *J* = 5 Hz), 112.90 (d, *J* = 19 Hz), 61.82, 57.98, 49.61, 49.48. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{20}$IFN$_2$Pd, 466.9588; Found, 466.9588. Anal. Calc. for C$_{12}$H$_{20}$FIN$_2$Pd: C, 32.42, H, 4.53, N, 6.30; Found: C, 32.13, H, 4.48, N, 6.07.

(tmeda)Pd(*p*–CNPh)(I) –Product was isolated as an orange solid (0.95g scale, 0.51g, 68%). ^{1}H NMR (CDCl$_3$): δ 7.42 (d, 8Hz, 2H), 7.12 (d, 8Hz, 2H), 2.70 (broad singlet, 2H), 2.65 (s, 6H), 2.55 (broad singlet, 2H), 2.29 (6H). ^{13}C NMR (CDCl$_3$): δ 156.99, 137.40, 128.46, 119.99, 105.90, 62.12, 58.31, 49.98, 49.86 HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{20}$IN$_3$Pd, 473.9634; Found, 473.9644 amu

(tmeda)Pd(*p*–CF$_3$Ph)(I) –Product was isolated as an orange solid (1.02 g, 39%). ^{1}H NMR (CDCl$_3$): δ 7.35 (d, 8 Hz, 2H), 7.06 (d, 8 Hz, 2H), 2.59 (s, 9H), 2.45 (apparent s, 4H), 2.20 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –61.81 (s, 3F). ^{13}C NMR (CDCl$_3$): δ 152.69, 136.48, 124.77 (q, 271 Hz), 124.56 (q, 32 Hz), 121.90 (q, 4Hz), 61.93, 58.08, 49.76, 49.60. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{20}$F$_3$IN$_2$Pd, 516.9556; Found, 516.9573.

(tmeda)Pd(*p*–OCH$_3$Ph)(I) – Product was isolated as an orange solid (1.23 g, 77%). ^{1}H NMR (CDCl$_3$, 500.09 MHz): δ 7.08 (d, 9 Hz, 2H), 6.61 (d, 9 Hz, 2H), 3.69 (s, 3H), 2.72-2.70 (multiple peaks, 2H), 2.66 (s, 6H), 2.56-2.54 (multiple peaks, 2H), 2.31 (s, 6H). ^{13}C NMR (CDCl$_3$, 125.75 MHz): δ 156.22, 135.90, 131.70, 112.64, 61.92, 58.09, 54.90, 49.69, 49.53. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{23}$IN$_2$OPd, 478.9788; Found, 478.9782 amu.

(tmeda)Pd(p–CH$_3$Ph)(I) – Product was isolated as an orange solid (1.18g, 51%). ^{1}H NMR (CDCl$_3$): δ 7.06 (d, J = 8Hz, 2H), 6.72 (d, J = 8Hz, 2H), 2.68 – 2.66 (multiple peaks, 4H), 2.62 (s, 6H), 2.52 –2.49 (multiple peaks, 4H), 2.28 (s, 6H), 2.18 (s, 3H). ^{13}C NMR (CDCl$_3$): δ 139.49, 135.89, 131.43, 127.43, 61.98, 58.10, 49.77, 49.56, 20.48. HRMS-electrospray (m/z): [M – I + MeCN]$^+$ calcd for C$_{13}$H$_{23}$IN$_2$Pd, 354.1162; Found, 354.1166.

(tmeda)Pd(m–CH$_3$Ph)(I) – Product was isolated as an orange solid (1.24g, 81%). ^{1}H NMR (CDCl$_3$): δ 7.05 (s, 1H), 7.00 (d, J = 8 Hz, 1H), 6.77 (m, 1H), 6.58 (d, J = 7 Hz, 1H), 2.69 (br. multiplet, 2H), 2.63 (s, 6H), 2.53 (br multiplet, 2H), 2.29 (s, 6H), 2.18 (s, 3H). ^{13}C NMR (CDCl$_3$): δ 144.46, 136.77, 135.31, 133.21, 125.86, 123.41, 61.92, 58.03, 49.76, 49.67, 49.49, 21.29. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{23}$IN$_2$Pd, 462.9838; Found, 462.9843.

(tmeda)Pd(o–CH$_3$Ph)(I) – Product was isolated as an orange solid (1g scale, 0.52g, 68%). ^{1}H NMR (CDCl$_3$): δ ^{1}H NMR (CDCl$_3$): δ 7.17 (d, J = 7 Hz, 1 Hz, 1H), 6.82 (m, 1H), 6.77-6.72 (multiple peaks, 2H), 2.86-2.82 (multiple peaks, 2H), 2.70-2.66 (multiple peaks, 9H), 2.45 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (CDCl$_3$): δ 144.55, 141.63, 135.31, 127.76, 123.62, 122.62, 62.03, 58.09, 50.21, 48.77, 48.52, 27.50. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{23}$IN$_2$Pd, 462.9838; Found, 462.9844.

(tmeda)Pd(o–FPh)(I) – Product was isolated as an orange solid (0.90g, 53%). ^{1}H NMR (CDCl$_3$): δ 7.22 (m, 1H), 6.84-6.79 (multiple peaks, 2H), 6.65 (m, 1H), 2.79 (m, 1H), 2.75 (s, 3H), 2.73 (s, 3H), 2.67-2.40 (multiple peaks, 3H), 2.42 (s, 3H), 2.39 (s, 3H) . ^{19}F NMR (CDCl$_3$): δ –93.97 (s, 3F).^{13}C NMR (CDCl$_3$): δ 164.68 (d, J = 229Hz), 138.39 (d, J = 16Hz), 125.69 (d, J = 38Hz), 124.32 (d, J = 7Hz), 122.82 (d, J = 2Hz),

113.66 (d, J = 28Hz), 62.18, 58.78, 50.59, 50.43, 49.74 . HRMS-electrospray (m/z): [M–I + MeCN]$^+$ calcd for $C_{12}H_{20}FIN_2Pd$, 358.0911; Found, 358.0915.

(tmeda)Pd(*o*–CH₃OPh)(I) – Product was isolated as an orange solid (0.61 g, 38%). ^{1}H NMR (CDCl₃): δ 7.16 (d, J = 7 Hz, 1H), 6.82 (t, J = 7 Hz, 1H), 6.63 (t, J = 7 Hz, 1H), 6.47 (d, 8 Hz, 1H), 3.82 (s, 3H), 2.74 – 2.62 (multiple peaks, 4H), 2.70 (s, 3H), 2.69 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (CDCl₃): 161.80, 137.50, 129.74. 123.62, 119.95, 110.13, 61.98, 58.41, 55.75, 50.09 (2 overlapping carbons), 49.73, 49.27. HRMS-electrospray (m/z): [M + I]$^+$ calcd for $C_{13}H_{23}IN_2OPd$, 329.0845; Found, 329.0848.

General procedure for the synthesis of (dtbpy)Pd(Ar)(CF₃): Complexes were synthesized according to previously reported literature procedure.

(dtbpy)Pd(*p*-FPh)(CF₃) (2-1a) – Product was obtained as a yellow solid (0.65 g, 70% yield). ^{1}H NMR (CDCl₃): δ 9.02 (m, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.62 (d, J = 6 Hz, 1H), 7.53-7.50 (multiple peaks, 3H), 7.25 (m, 1H), 6.87 (m, 2H), 1.42 (s, 9H), 1.36 (s, 9H). ^{19}F NMR (CDCl₃): δ -20.75 (s, 3F), -122.35 (m, 1F); ^{13}C NMR (CDCl₃): δ 163.55, 163.48, 160.61 (d, J = 239 Hz), 155.40, 154.38, 151.74 (dd, J = 9 Hz, 4 Hz), 150.40, 150.28, 136.08 (d, J = 5 Hz), 135.04 (q, J = 363 Hz), 123.56, 123.27, 118.13, 117.97, 113.65 (d, J = 18 Hz), 35.40 (app. s, overlapping carbons, 2C), 30.31, 30.25. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for $C_{25}H_{28}F_4N_2Pd$, 561.1121; Found, 561.1127. Anal. Calc. for $C_{25}H_{28}F_4N_2Pd$: C, 55.72, H, 5.24, N, 5.20; Found: C, 55.59, H, 5.31, N, 5.19. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF₃)₂ was observed.

(dtbpy)Pd(*p*-CNPh)(CF₃) (**2-1b**) – Product was isolated as an yellow solid (1.2g scale, 0.59g, 54%). ^{1}H NMR (CDCl$_3$): δ 9.00 (app. d, *J* = 6 Hz 1H), 7.99 (s, 1H), 7.96 (s, 1H), 7.76 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 6 Hz, 1H), 7.50 (d, *J* = 6 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 6 Hz, 1H), 1.43 (s, 9H), 1.36 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –21.25. ^{13}C NMR (CDCl$_3$): δ 168.76, 164.00, 163.81, 155.40, 154.33, 151.71 (br q, *J* = 4 Hz), 150.13, 136.94, 134.57 (q, *J* = 364 Hz), 129.37, 123.71, 123.45, 120.60, 118.33, 118.25, 106.20, 35.46 (2 overlapping carbons), 30.30, 30.23. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C$_{26}$H$_{28}$F$_3$N$_2$Pd, 568.1162; Found, 568.1166. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(*p*-CF₃Ph)(CF₃) (**2-1c**) – Product was obtained as a yellow solid (0.57 g, 63% yield). Samples of **2-1c** could be further purified by recrystallization from warm MeCN. ^{1}H NMR (CDCl$_3$): δ 9.02 (br d, *J* = 4 Hz, 1H), 7.98 (s, 1H), 7.95 (s, 1H), 7.73 (d, *J* = 8 Hz, 2H), 7.55-7.53 (multiple peaks, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.27 (dd, *J* = 6 Hz, 2 Hz, 1H), 1.42 (s, 9H), 1.36 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –21.1 (s, 3F), –61.8 (s, 1F). ^{13}C NMR (CDCl$_3$): δ 164.40 (q, *J* = 10 Hz), 163.77, 163.66, 155.41, 154.39, 151.76 (q, *J* = 4 Hz), 150.35, 136.12, 134.63 (q, *J* = 364 Hz), 125.24 (q, *J* = 271 Hz), 125.18 (q, *J* = 32 Hz), 123.65, 123.46, 122.85 (app. br d), 118.22, 118.09, 35.45 (app. s, overlapping carbons, 2C), 30.32, 30.25. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{28}$H$_{28}$F$_6$N$_2$Pd, 611.1089; Found, 611.1111. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(*p*-C(O)Ph–Ph)(CF₃) (**2-1d**) – Product was isolated as an yellow solid (0.47 g, 51%). ^{1}H NMR (CDCl$_3$): δ 9.02 (br multiplet, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.83 (d, *J* = 7 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H), 7.59-7.51 (multiple peaks, 5H), 7.48-7.43 (multiple peaks, 2H), 7.23 (resonance overlaps with CDCl$_3$ peak, 1H), 1.42 (s, 9H), 1.35 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –20.86. ^{13}C NMR (CDCl$_3$): δ 197.68,

169.14 (q, J = 11 Hz), 163.78, 163.66, 155.39, 154.39, 151.73 (q, J = 5 Hz), 150.44, 138.75, 135.99, 134.15 (q, J = 364 Hz), 132.63, 131.50, 129.91, 128.12, 127.96, 123.60, 123.39, 118.21, 118.08, 35.43 (2 carbon resonances overlapping), 30.31, 30.24. HRMS electrospray (m/z): [M + Na]$^+$ calcd for $C_{32}H_{33}F_3N_2OPd$, 605.1596; Found, 605.1603. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed

(dtbpy)Pd(*p*-Ph–Ph)(CF$_3$) (**2-1e**) **–** Product was obtained as a yellow solid (0.53 g, 58% yield). ^{1}H NMR (CDCl$_3$): δ 9.06 (dd, J = 6 Hz, 2 Hz, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.73 (d, J = 6 Hz, 1H), 7.66-7.63 (multiple peaks, 4H), 7.53 (d, J = 6 Hz, 1H), 7.41-7.37 (multiple peaks, 4H), 7.27-7.24 (multiple peaks, 2H), 1.43 (s, 9H), 1.35 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –20.54 (m, 3F). ^{13}C NMR (CDCl$_3$): δ 163.44, 163.40, 157.31 (q, J = 4 Hz), 155.38, 154.39, 151.73 (q, J = 4 Hz), 150.65, 142.12, 136.19, 135.55, 135.53 (q, J = 364 Hz), 128.50, 126.65, 126.11, 125.35, 123.52, 123.31, 118.09, 117.90, 35.40 (app. s, overlapping carbons, 2C), 30.33, 30.25. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for $C_{31}H_{33}F_3N_2Pd$, 619.1528; Found, 619.1547. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(*p*-CH$_3$OPh)(CF$_3$) (**2-1f**) **–** This compound was prepared by a modification of the general method where the reaction was stirred for 3 d, and an additional 3 equiv of CsF and 2 equiv of Me$_3$SiCF$_3$ were added after each 24 h period. Product **2-1f** was obtained as a yellow solid (0.22 g, 32% yield). ^{1}H NMR (CDCl$_3$): δ 9.03 (br d, J = 4 Hz, 1H), 8.00 (s, 1H), 7.92 (s, 1H), 7.67 (d, J = 6 Hz, 1H), 7.51 (d, J = 6 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.23 (m, 1H), 6.76 (d, J = 8 Hz, 2H), 3.77 (s, 3H), 1.41 (s, 9H), 1.34 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –20.45 (m, 3F). ^{13}C NMR (CDCl$_3$): δ 163.34, 163.32, 156.29, 155.40, 154.41, 151.80 (q, J = 4 Hz), 150.66, 146.12 (q, J = 11 Hz), 135.82, 135.56 (q, J = 364 Hz), 123.49, 123.20, 118.04, 117.83, 113.05, 55.02, 35.28 (app. s, overlapping carbons, 2C), 30.35, 30.28. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for $C_{26}H_{31}F_3N_2OPd$, 573.1321; Found, 573.1328. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(Ph)(CF₃) (**2-1g**) – Product was isolated as an yellow solid (0.53g scale, 0.23g, 47%). ¹H NMR (CDCl₃): ¹H NMR (CDCl₃): δ 8.95 (app. s, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.59-7.45 (multiple peaks, 3H), 7.17 (br d, J = 4 Hz, 1H), 7.04-7.00 (multiple peaks, 2H), 6.94 (m, 1H), 1.37 (s, 9H), 1.29 (s, 9H). ¹⁹F NMR (CDCl₃): δ –20.45. ¹³C NMR (CDCl₃): δ 163.40, 163.39, 157.66 (q,

J = 10 Hz), 155.33, 154.33, 151.62 (q, J = 4 Hz), 150.48, 135.90, 135.73 (q, J = 369 Hz), 126.86, 123.44, 123.21, 122.94, 118.12, 117.92, 35.36, 35.34, 30.28, 30.21. HRMS electrospray (m/z): [M + Na]⁺ calcd for $C_{25}H_{29}F_3N_2Pd$, 543.1215; Found, 543.1223.

By ¹H, ¹⁹F, ¹³C NMR spectroscopy, <5% of (dtbpy)Pd(CF₃)₂ was observed.

(dtbpy)Pd(Ph)(CF₃) (**2-1h**) – This compound was prepared by a modification of the general method where the reaction was stirred for 2 d, and an additional 3 equiv of CsF and 2 equiv of Me₃SiCF₃ were added after the first 24 h period. Product **1e** was obtained as a yellow solid (0.45 g, 49% yield). ¹H NMR (CDCl₃): δ 9.00 (dd, J = 6 Hz, 2 Hz, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.67 (d, J = 6 Hz, 1H), 7.49 (dd, J = 6 Hz, 2 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.22 (dd, J = 6 Hz, 2 Hz, 1H), 6.90 (d, J = 8 Hz, 2H), 2.26 (s, 3H), 1.39 (s, 9H), 1.32 (s, 9H). ¹⁹F NMR (CDCl₃): δ –20.50 (s, 3F). ¹³C NMR (CDCl₃): δ 163.31, 155.35, 154.35, 152.89 (q, J = 10 Hz), 151.70 (q, J = 4 Hz), 150.60, 135.55, 135.82 (q, J = 364 Hz), 135.60, 131.87, 127.87, 123.44, 123.21, 118.05, 117.84, 35.56 (app. s, overlapping carbons, 2C), 30.31, 30.24, 21.02. HRMS-electrospray (m/z): [M + Na]⁺ calcd for $C_{31}H_{33}F_3N_2Pd$, 557.1372; Found, 557.1391. By ¹H, ¹⁹F, ¹³C NMR spectroscopy, <5% of (dtbpy)Pd(CF₃)₂ was observed.

(dtbpy)Pd(Ph)(CF₃) (**2-1i**) – Product was isolated as an yellow solid (0.72g scale, 0.35g, 54%). ¹H NMR (CDCl₃): δ 8.94 (br d, 4Hz, 1H), 7.93 (s, 1H), 7.89 (s, 1H), 7.59 (d, 6Hz, 1H), 7.44 (br d, 5Hz, 1H), 7.37 (s, 1H), 7.30 (br d, 8Hz, 1H), 7.17 (br d, 6Hz, 1H), 6.90 (m, 1H), 6.74 (br d, 7 Hz, 1H), 1.36 (s, 9H), 1.29 (s,

9H). ^{19}F NMR (CDCl$_3$): δ –20.33. ^{13}C NMR (CDCl$_3$): δ 163.35, 157.41 (q, 10 Hz), 155.30, 154.31, 151.58 (q, 4Hz), 150.55, 135.93 (q, 364 Hz), 136.48, 132.74, 126.48, 123.83, 123.58, 123.41, 123.20, 118.08, 117.89, 35.34, 35.33, 30.27, 30.19. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{26}$H$_{31}$F$_3$N$_2$Pd, 557.1372; Found, 557.1383 amu. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(o-tol)(CF$_3$) (**2-1j**) **–** Product was isolated as an yellow solid (0.50 g scale, 0.20 g, 45%). ^{1}H NMR (CDCl$_3$): δ 9.05 (br d, 4Hz, 1H), 7.98 (s, 1H), 7.93 (s, 1H), 7.58 (d, 7 Hz, 1H), 7.53 (d, 6Hz, 1H), 7.46 (d, 6Hz, 1H), 7.22 (m, 1H), 7.03 (d, 6Hz, 1H), 6.96-6.89 (multiple peaks, 2H), 2.61 (s, 3H), 1.42 (s, 9H), 1.32 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –20.51. ^{13}C NMR (CDCl$_3$): δ 163.29, 159.17 (J = 10 Hz), 155.43, 154.28, 151.71, 151.67, 150.06, 141.58, 136.08 (J = 361 Hz), 135.45, 127.90, 123.55 (two overlapping carbons), 123.38, 122.59, 118.03, 117.92, 35.38 (two overlapping carbons), 30.34, 30.26, 26.46. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{26}$H$_{31}$F$_3$N$_2$Pd, 557.1372; Found, 557.1384 amu. Calc. for C$_{23}$H$_{31}$F$_3$N$_2$Pd: C, 58.37, H, 5.84, N, 5.24; Found: C, 58.29, H, 5.95, N, 5.24. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

(dtbpy)Pd(o-FPh)(CF$_3$) (**2-1k**) **–** Product was isolated as an yellow solid (0.50 g scale, 0.20 g, 36%). ^{1}H NMR (CDCl$_3$): δ 8.99 (br d, J = 6Hz, 1H), 7.97 (s, 1H), 7.93 (s, 1H), 7.64 (d, J = 6 Hz, 1H), 7.56 (dd, J = 7Hz, 2Hz, 1H), 7.51 (d, J = 6Hz, 1H), 7.21 (dd, J = 6Hz, 2Hz 1H), 7.00 (m, 1H), 6.91 (m, 1H), 6.82 (m, 1H) 1.40 (s, 9H), 1.32 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –20.17 (s, 3F), –92.66 (s, 1F). ^{13}C NMR (CDCl$_3$): δ 165.13 (d, J = 227 Hz), 163.86, 155.54, 154.75, 151.74 (q, J = 4 Hz), 150.51, 140.00 (dq, J = 44 Hz, 11 Hz), 138.07 (d, J = 18 Hz), 133.52 (qd, J = 364 Hz, 6Hz), 124.68 (d, J = 7 Hz), 123.75, 123.51, 123.03, 118.41, 118.31, 113.78 (d, J = 29 Hz), 35.55, 35.52, 30.38, 30.31. HRMS-electrospray (m/z): [M – F]$^+$ calcd for C$_{25}$H$_{28}$F$_4$N$_2$Pd, 519.1234; Found, 519.1241 amu. By ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, <5% of (dtbpy)Pd(CF$_3$)$_2$ was observed.

General procedure for the synthesis of (tmeda)Pd(Ar)(CF$_3$): Under nitrogen, (TMEDA)Pd(Ar)(I) (1.0 g, 2.02-2.30 mmol, 1 equiv) and CsF (3 equiv) were suspended

in THF (0.145 M) in a 25 mL Schlenk flask for 10 min, then Me_3SiCF_3 (2 equiv) was added. The reaction was stirred vigorously for 3 h at 22 °C. The solvent was then removed under reduced pressure. CH_2Cl_2 (15 mL) was added to dissolve the product, and the resulting suspension was filtered through a plug of Celite. The plug was washed with CH_2Cl_2 (2 x 5 mL) the filtrate was concentrated under reduced pressure to (~ 2 mL) and hexanes (60 mL) was added to precipitate the product. The resulting solid was collected on fritted Buchner funnel, washed with hexanes (3 x 10 mL), diethyl ether (2 x 2 mL) and dried *in vacuo*.

(tmeda)Pd(*p*–CN)(CF$_3$) (**2-10a**) – Product was obtained as an off-white solid (0.49 g, 76% yield). ^{1}H NMR (CDCl$_3$): δ 7.38 (m, 2H), 6.74 (m, 2H), 2.65 (s, 6H), 2.53 (app. br s, 4H), 2.17 (s, 6H). ^{19}F NMR (CDCl$_3$): δ –20.90 (s, 3F), –123.0 (s, 1F). ^{13}C NMR (CDCl$_3$): δ 160.50 (d, J = 239 Hz), 149.22 (dd, J = 11 Hz, 3 Hz), 135.95 (d, J = 5 Hz), 134.09 (d, J = 365 Hz), 113.02 (d, J = 18 Hz), 60.36, 59.82, 49.03, 48.64. Anal. Calc. for C$_{13}$H$_{20}$F$_4$N$_2$Pd: C, 40.37, H, 5.21, N, 7.24; Found: C, 40.19, H, 5.07, N, 7.30.

(tmeda)Pd(*p*–CN)(CF$_3$) (**2-10b**) – Product was isolated as a yellow solid (0.47 scale, 0.21 g, 51%). ^{1}H NMR (CDCl$_3$) δ 7.64 (d, J = 7 Hz, 2H), 7.22 (d, J = 7 Hz, 2H), 2.69 (s, 6H), 2.60 (apparent s, 4H), 2.21 (s, 6H). ^{19}F NMR (CDCl$_3$): δ –21.60. ^{13}C NMR (CDCl$_3$): δ 168.37 (q, 10 Hz), 136.91, 133.12 (q, 365 Hz), 128.65, 120.55, 105.86, 60.40, 59.96, 49.12, 48.82. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{14}$H$_{30}$F$_3$N$_3$Pd, 416.0542 Found, 416.0537 amu.

(tmeda)Pd(*p*–CF$_3$)(CF$_3$) (**2-10c**) – Product was isolated as a yellow solid (0.37 g, 42%). ^{1}H NMR (CDCl$_3$): δ 7.61 (d, 8Hz, 2H), 7.19 (d, 8Hz, 2H), 2.69 (s, 6H), 2.59 (apparent singlet, 4H), 2.20 (s, 6H). ^{19}F NMR (CDCl$_3$): δ –21.14 (s, 3F), –61.67. ^{13}C NMR (CDCl$_3$): δ 163.82 (q, 11 Hz), 136.05, 133.69 (q, 365 Hz), 125.19 (q, 271 Hz), 124.81 (q, 32 Hz), 122.44, 60.37, 59.84, 49.03, 48.72. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{14}$H$_{20}$ F$_6$N$_2$Pd, 417.0581; Found, 417.0586.

(tmeda)Pd(*p*–OCH₃)(CF₃) (**2-10d**) – Product was isolated as a yellow solid (0.89, 34%). ^{1}H NMR (CDCl₃): δ 7.33 (d, 8 Hz, 2H), 6.64 (d, 8 Hz, 2H), 3.72 (s, 3H), 2.67 (s, 6H), 2.56 (apparent singlet, 4H), 2.20 (s, 6H). ^{19}F NMR (CDCl₃): δ –20.80 (s, 3F). ^{13}C NMR (CDCl₃): δ 155.94, 144.95 (q, 11Hz), 135.65, 134.74 (q, 365 Hz), 112.24, 60.23, 59.63, 54.80, 48.87, 48.52. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C₁₄H₂₃F₃N₂Pd, 421.0695; Found, 421.0699.

(tmeda)Pd(*p*–tol)(CF₃) (**2-10f**) – Product was isolated as a yellow solid (0.51g, 57%). ^{1}H NMR (CDCl₃): δ 7.33 (d, *J* = 8 Hz, 2H), 6.81 (d, *J* = 8 Hz, 2H), 2.67 (s, 6H), 2.56 (br multiplet, 4H), 2.22 (s, 6H), 2.20 (s, 3H). ^{19}F NMR (CDCl₃): δ –20.86 (s, 3F). ^{13}C NMR (CDCl₃): δ 151.74 (q, *J* = 11 Hz), 135.52, 134.93 (q, *J* = 365 Hz), 127.17, 60.33, 59.66, 48.91, 48.63, 20.85. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C₁₄H₂₃F₃N₂Pd, 363.0864; Found, 363.0863.

(tmeda)Pd(*m*-tol)(CF₃) (**2-10g**) – Product was isolated as a yellow solid (0.37 g, 42%). ^{1}H NMR (CDCl₃): δ 7.30 (s, 1H), 7.24 (d, *J* = 7 Hz, 1H), 6.85 (m, 1H), 6.70 (d, *J* = 7 Hz, 1 H), 2.65 (s, 6H), 2.54 (app. s, 4H), 2.23 (s, 3H), 2.19 (s, 3H). ^{19}F NMR (CDCl₃): δ –20.82 (s, 3F). ^{13}C NMR (CDCl₃): δ 156.30 (q, *J* = 10 Hz), 136.49, 134.92 (q, *J* = 365 Hz), 135.05, 132.83, 125.82, 123.48, 60.40, 48.96, 48.70, 21.54. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C₁₄H₂₃F₃N₂Pd, 405.0746; Found, 405.0758.

(tmeda)Pd(*o*-tol)(CF₃) (**2-10h**) – Product was isolated as a yellow solid (1.5g scale, 0.89g, 59%). ^{1}H NMR (CDCl₃): δ 7.42 (d, *J* = 7 Hz, 1H), 6.91 (m, 1H), 6.85-6.81 (multiple peaks, 2H), 2.72-2.67 (multiple peaks, 11 H), 2.48-2.45 (multiple peaks, 2H), 2.32 (s, 3H), 2.09 (s, 3H). ^{19}F NMR (CDCl₃): δ –20.71 (s, 3F). ^{13}C NMR (CDCl₃): δ 157.67 (q, *J* = 11 Hz), 141.76, 135.30, 134.98 (q, *J* = 365 Hz), 123.01, 122.27, 60.24, 59.56, 49.38, 47.93, 47.78, 26.33. HRMS electrospray (m/z): [M + Na]$^+$ calcd for C₁₄H₂₃F₃N₂Pd, 405.0746; Found, 405.0734.

(tmeda)Pd(*o*-F)(CF₃) (2-10i) – Product was isolated as a yellow solid (0.89 g scale, 0.61g, 81%). ^{1}H NMR (CDCl₃, 500 MHz): δ 7.43 (m, 1H), 6.92 (m, 1H), 6.84 (m, 1H), 6.71 (m, 1H), 2.73 (s, 3H), 2.69 (s, 3H), 2.62-2.59 (multiple peaks, 2H), 2.55-2.49 (multiple peaks, 2H), 2.24 (s, 3H), 2.237 (s, 3H). ^{19}F NMR (CDCl₃): δ –20.45 (s, 3F), –93.69 (m, 1F). ^{13}C NMR (CDCl₃): δ 165.20 (d, J = 227 Hz), 138.20 (dq, J = 44 Hz, 11 Hz), 137.94 (d, J = 19 Hz), 132.30 (dq, J = 365 Hz, 7 Hz), 124.09 (d, J = 7 Hz), 122.54, 113.18 (d, J = 29 Hz), 60.27, 60.19, 49.56, 49.10, 48.72, 48.36. HRMS electrospray (m/z): [M + Na]$^+$ calcd for $C_{13}H_{20}F_4N_2Pd$, 409.0492; Found, 409.0490.

(tmeda)Pd(*o*-OCH₃)(CF₃) (2-10j) – Product was isolated as a yellow solid (0.50 g scale, 0.04g, 10%). ^{1}H NMR (CDCl₃): δ 7.40 (d, 7Hz, 1H), 6.93 (m, 1H), 6.69 (m, 1H), 6.58 (d, 8 Hz, 1H), 3.82 (s, 3H), 2.73 (s, 3H), 2.69 (s, 3H), 2.65-2.60 (multiple peaks, 2H), 2.53-2.46 (multiple peaks, 2H), 2.25 (s, 3H), 2.21 (s, 3H). ^{19}F NMR (CDCl₃): δ –20.74 (s, 3F). ^{13}C NMR (CDCl₃): δ 162.26, 143.25 (q, 11 Hz), 136.83, 133.79 (q, 365 Hz), 123.44, 119.76, 109.70, 60.22, 60.00, 55.61, 49.57, 49.03, 48.48, 48.36. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for $C_{14}H_{23}F_3N_2OPd$, 421.0695; Found, 421.0699.

(bpy)Pd(Ph)(CF₃) (2-7) – Product was isolated as a pale yellow solid (0.49g scale, 0.16g, 37%). Further purification was achieved by recrystallizing the compound from hot MeCN. Upon cooling, the resulting yellow crystals were washed with MeCN (~5 mL) and dried *in vacuo*. ^{1}H NMR (CDCl₃, 40 °C): δ 9.14 (apparent s, 1H), 8.08-8.00 (multiple peaks, 4H), 7.90 (t, J = 8Hz, 1H), 7.76 (br d, J = 4Hz, 1H), 7.58 (br d, J = 7Hz, 2H), 7.52 (m, 1H), 7.11-7.07 (multiple peaks, 2H), 7.01 (m, 1H). ^{19}F NMR (CDCl₃): δ –20.56. HRMS-electrospray (m/z): [M – CF₃ + MeCN]$^+$ calcd for $C_{17}H_{13}F_3N_2Pd$, 380.0379; Found, 380.0377. Anal. Calc. for $C_{17}H_{13}F_3N_2Pd$: C, 49.96, H, 3.21, N, 6.85 Found: C, 49.69, H, 3.20, N, 6.92.

(dpe)Pd(Ph)(CF₃) (2-8) – Product synthesized from (dpe)Pd(Ph)(CF₃) according the procedure described for (TMEDA)Pd(Ar)(CF₃). The product was isolated as a pale yellow solid (0.59 g, 67%). ^{1}H NMR (CDCl₃): δ 7.42 (d, 7Hz, 2H), 6.97-6.93 (multiple peaks, 2H), 6.87 (m, 1H), 3.56-2.63 (multiple peaks, 12H), 1.77-0.99

(multiple peaks, 12H). ^{19}F NMR (CDCl$_3$): δ –21.02 (s, 3F).^{13}C NMR (CDCl$_3$): δ 159.27 (q, 10 Hz), 136.37, 135.14 (q, 365 Hz), 126.38, 122.59, 54.42, 54.16, 50.82, 49.73, 24.34, 24.11, 19.63, 19.16. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{19}$H$_{29}$F$_3$N$_2$Pd, 471.1215; Found, 471.1203.

(teeda)Pd(Ph)(CF$_3$) **(2-9)** – Product synthesized from (TEEDA)Pd(Ph)(CF$_3$) according the procedure described for (TMEDA)Pd(Ar)(CF$_3$). The product was isolated as a yellow solid (0.4 g scale, 0.20g, 56%). ^{1}H NMR (CD$_2$Cl$_2$): δ 7.42 (d, 8 Hz, 2H), 6.90 (m, 2H), 6.82 (m, 1H), 3.07-2.98 (multiple peaks, 2H), 2.82-2.73 (multiple peaks, 2H), 2.62 (s, 4H), 2.51-2.39 (multiple peaks, 2H), 1.36 (t, 7 Hz, 6H), 1.29 (t, 7 Hz, 6H). ^{19}F NMR (CD$_2$Cl$_2$): δ –21.10 (s, 3F). ^{13}C NMR (CD$_2$Cl$_2$): δ 157.88 (q, 10 Hz), 134.54 (366 Hz), 136.26, 126.12 (q, 12 Hz), 122.46, 51.50, 51.38, 49.82, 48.40, 11.13, 11.06. HRMS-electrospray (m/z): [M + Na]$^+$ calcd for C$_{17}$H$_{29}$F$_3$N$_2$Pd, 447.1215; Found, 447.1219 amu.

(dtbpy)Pd(CF$_3$)$_2$ – Under N$_2$, (dtbpy)Pd(Cl)$_2$ (0.3 g, 0.67 mmol, 1 equiv) and CsF (1.1 g, 7.4 mmol, 1 equiv) were dissolved in CH$_2$Cl$_2$ (9.6 mL) in a 25 mL Schlenk flask. This mixture was stirred for 5 min, and then Me$_3$SiCF$_3$ (0.77 mL, 7.4 mmol, 8 equiv) was added. The reaction was stirred vigorously for 3 d. The solvent was then removed under reduced pressure. CH$_2$Cl$_2$ (5 mL) was added to dissolve the product, and the resulting suspension was filtered through a plug of Celite. The filtrate was concentrated under reduced pressure to (~1 mL), and hexanes (30 mL) were added to precipitate the product. The resulting solid was collected on a fritted filter, washed with hexanes (2 x 5 mL) and dried *in vacuo*. Analytically pure samples were obtained by recrystallization from warm MeCN, which yielded the product as a yellow crystalline solid (0.21 g, 61% yield). ^{1}H NMR (CDCl$_3$): δ 8.86 (d, *J* = 6 Hz, 2H), 7.96 (s, 2H), 7.51 (dd, *J* = 6 Hz, 2 Hz, 2H), 1.41 (s, 9H). ^{19}F NMR (CDCl$_3$): δ –25.17 (s, 6F). HRMS-electron ionization (m/z): [M – F]$^+$ calcd for C$_{20}$H$_{24}$F$_5$N$_2$Pd, 493.0894; Found, 493.0911. Anal. Calc. for C$_{20}$H$_{24}$F$_6$N$_2$Pd: C, 46.84, H, 4.72, N, 5.46; Found: C, 46.81, H, 4.68, N, 5.32.

(dtbpy)Pd(4-CF₃C₆H₅)(CF₃)(F)(OTf) (2-4) – Under N₂, a solution of **1a** (60 mg, 0.11 mmol, 1 equiv) in DCE (1 mL) was added to a suspension of 1-fluoro-2,4,6-trimethylpyridium triflate (NFTPT) (45 mg, 0.15 mmol, 1.4 equiv) in DCE (1 mL). An additional 0.8 mL of DCE was added, and the reaction mixture was stirred at 23 °C for 45 min. The solvent was then removed *in vacuo*, and the residue was taken up in a mixture of DCE (0.5 mL) and toluene (2 mL). This suspension was filtered through a plug of Celite, which was washed with additional toluene (0.5 mL). Pentanes (10 mL) were then added, and the resulting suspension was sonicated for 5 min. The solids were allowed to settle, and then the solution was removed by decantation. Fresh pentanes (10 mL) were added, and the sonication process was repeated. The residue was dried *in vacuo*, yielding **4** as a yellow solid (42 mg, 53% yield). ¹H NMR (CD₃CN): δ 8.86-8.85 (multiple peaks, 2H), 8.47 (s, 1H), 8.40 (s, 1H), 7.98 (dd, *J* = 6 Hz, 2 Hz, 1H), 7.89 (dd, *J* = 6 Hz, 2 Hz, 1H), 6.90 (m, 2H), 6.81 (m, 2H), 1.49 (s, 9H), 1.41 (s, 9H). ¹⁹F NMR (CDCl₃): δ –30.90 (d, *J* = 10 Hz, 3F), –79.40 (s, 3F), –117.4 (m, 1F), –256.5 (br q, *J* = 9 Hz, 1F). At room temperature in nitrobenzene-*d₅* the peaks are broadened significantly; however, at 40 °C the resonances are better resolved. ¹H NMR (nitrobenzene-*d₅*, 40 °C): δ 9.49 (app. br s, 1H), 9.42 (app. br s, 1H), 8.83 (s, 1H), 8.72 (s, 1H), 8.13 (br d, *J* = 5 Hz, 1H), 7.98 (app. br s, 1H), 7.50 (br m, 2H), 6.80 (m, 2H), 1.50 (s, 9H), 1.35 (s, 9H). ¹⁹F NMR (nitrobenzene-*d₅*, 40 °C): δ –31.78 (app. s, 3F), –77.93 (br s, 3F), –115.65 (br m, 1F), –246.70 (br s, 1F). Anal. Calc. for C₂₆H₂₈F₈N₂O₃PdS: C, 44.17, H, 3.99, N, 3.96 Found: C, 43.89, H, 4.00, N, 4.03.

(dtbpy)Pd(4-CF₃C₆H₅)(CF₃)(F)(OTf) (2-11) – Under N₂, a solution of **2-1c** (60 mg, 0.09 mmol, 1 equiv) in DCE (0.5 mL) was added to a suspension of 1-fluoro-2,4,6-trimethylpyridium triflate (NFTPT) (38 mg, 0.13 mmol, 1.4 equiv) in DCE (0.5 mL). An additional 0.5 mL of DCE was added, and the reaction mixture was stirred at 23 °C for 45 min. The solvent was then removed *in vacuo*, and the residue was taken up in a mixture of DCE (0.5 mL) and toluene (2 mL). This suspension was filtered through a plug of Celite, which was washed with additional toluene (0.5 mL). Pentanes (10 mL) were then added, and the resulting suspension was sonicated for 5 min. The solids were

allowed to settle, and then the solution was removed by decantation. Fresh pentanes (10 mL) were added, and the sonication process was repeated. The residue was dried *in vacuo*, yielding **4** as a yellow solid (4.3 mg, 2% yield). ^{1}H NMR (CD$_3$CN): δ 8.88 (d, 6 Hz, 1H), 8.85 (d, 6Hz, 1H), 8.49 (s, 1H), 8.41 (s, 1H), 8.00 (m, 1H), 7.90 (m, 1 H), 7.32 (d, 9Hz, 2H), 7.10 (d, 9Hz, 2H), 1.50 (s, 9H), 1.41 (s, 9H). ^{19}F NMR (CD$_3$CN): δ –30.72 (d, *J* = 8 Hz, 3F, Pd^{IV}–**CF$_3$**), –63.10 (s, 3F, Pd^{IV}–**ArCF$_3$**), –79.35 (s, 3F, Pd^{IV}–**OTf**), –254.55 (br q, *J* = 10 Hz, 1F, Pd^{IV}–**F**). Calc. for C$_{27}$H$_{28}$F$_{10}$N$_2$O$_3$PdS: C, 42.84, H, 3.73, N, 3.70 Found: C, 42.55, H, 3.83, N, 3.78.

Figure 2.11 – ^{1}H NMR Spectrum of Complex **2-11** in CD$_3$CN at 23 °C

Figure 2.12 – ^{19}F NMR Spectrum of Complex **2-11** in CD$_3$CN at 23 ºC

(dtbpy)Pd(4-CF$_3$C$_6$H$_5$)(CH$_3$)(F)(OTf) **(2-12)** – Product was isolated as a yellow solid (21.0 mg, 27%). Under N$_2$, a **2-1h** (60 mg, 0.11 mmol, 1 equiv) in DCE (1 mL) was added to a suspension of 1-fluoro-2,4,6-trimethylpyridium triflate (NFTPT) (45 mg, 0.15 mmol, 1.4 equiv) in DCE (1 mL). An additional 0.8 mL of DCE was added, and the reaction mixture was stirred at 23 °C for 45 min. The solvent was then removed *in vacuo*, and the residue was taken up in a mixture of DCE (0 mL) and toluene (2 mL). This suspension was filtered through a plug of Celite, which was washed with additional toluene (0.5 mL). Pentanes (10 mL) were then added, and the resulting suspension was sonicated for 5 min. The solids were allowed to settle, and then the solution was removed by decantation. Fresh pentanes (10 mL) were added, and the sonication process was repeated. The residue was dried *in vacuo*, yielding 4 as a yellow solid (xx mg, 2% yield). ^{1}H NMR (CD$_3$CN): δ 8.93-8.91 (multiple peaks, 2H), 8.53 (s, 1H), 8.46 (s, 1H), 8.403 (m, 1H), 7.95 (m, 1H), 6.87-6.85 (multiple peaks, 2H),

6.81-6.79 (multiple peaks, 2H), 2.24 (s, 3H), 1.55 (s, 9H), 1.47 (s, 9H). ^{19}F NMR (CD$_3$CN): δ −31.23 (d, J = 9 Hz, 3F, Pd–**CF$_3$**), , −79.30 (s, 3F, Pd–**OTf**), −256.42 (br q, 1F, Pd–**F**). Calc. for C$_{27}$H$_{31}$F$_7$N$_2$O$_3$PdS: C, 46.13, H, 4.42, N, 3.98 Found: C, 45.87, H, 4.51, N, 4.12.

Figure 2.13 – ^{1}H NMR spectrum of complex **2-12** in CD$_3$CN at 23 ºC

Figure 2.14 – ^{19}F NMR spectrum of complex **2-12** in CD$_3$CN at 23 ºC

General procedure for oxidatively induced Ar–CF$_3$ coupling from 2-1a – 2-1k, 2-10a –2-10k, and 2-5 – 2-9: The Pd^{II} trifluoromethyl complex (40 mg, 1 equiv) was dissolved in an appropriate volume of nitrobenzene to make a 0.084 M solution. The solution was added to a 4 mL scintillation vial containing 1-fluoro-2,4,6-trimethylpyridium triflate (2 equiv) and a Teflon®-coated stir bar. The vial was purged with nitrogen, sealed with a Teflon®-lined cap, shaken vigorously, and then heated at 23 °C for 1 h or 80 °C or 3h. The resulting light to dark brown mixture was cooled to room temperature, 4-fluoroanisole was added as an internal standard (under air), and the reactions were analyzed by ^{19}F NMR spectroscopy. The identities of the organic reductive elimination products were confirmed by comparison to authentic samples of these materials. The authentic sample was spiked in to the crude reaction mixtures, and, in each case, the ^{19}F NMR resonances were coincident. Reactions with complexes **2-1a –2-1j**, **2-2a, 2-2f and 2-2g** were conducted on a 50 mg scale.

Example protocol for the preparation of 4-fluoroanisole standard solution in nitrobenzene for analysis of oxidative trifluoromethylation of 2-2c: To add an equamolar amount of standard to product (0.092 mmol, 1 equiv) to the reaction in 50 μL, 208 μL of 4-fluoroanisole was added to 792 μL d^5-nitrobenzene for a total solution volume of 1 mL. The addition of 50 μL of this standard solution to the reaction represents 100% conversion to product. The integration of the standard peak is set to 1 and the integration of the Ar–CF_3 product peak in the ^{19}F spectrum is divided by 3 and multiplied by 100 to give the % yield.

It is important to note that the optimal conditions for ^{19}F NMR spectroscopic analysis of these reactions were as follows: spectral with -10 to -150 ppm, relaxation delay = 2 s, and acquisition time = 2s. These conditions were required due to the faster relaxation time of the standard relative to the trifluoromethylated arene products.

Determining Rate of Reductive Elimination from Pd^{IV} complex 2-4: In a N_2-filled drybox, complex **2-4** (14 mg, 0.0198 mmol, 1.0 equiv) was added to a screw-cap NMR tube and dissolved in dry NO_2Ph-d_5 (0.4 mL). The internal standard, 4-fluoroanisole was syringed into the NMR tube (50 μL of a stock solution in dry DCE, 0.0198 mmol, 1 equiv) and the tube was sealed with a Teflon® cap. The spectrometer was heated to 60 °C. Once at temperature, the tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The data was fit to a first order kinetics plot using Sigma Plot 10.

Determining Inverse Order in Triflate with 2-4 at 50 °C in NO$_2$Ph-d_5: In a N_2-filled drybox, complex **2-4** (14 mg, 0.0198 mmol, 1.0 equiv) and NBu_4OTf (0.004 – 0.04 mmol, 0.01M – 0.1M) was added to a screw-cap NMR tube and dissolved in dry NO_2Ph-d_5 (0.4 mL). The internal standard, 4-fluoroanisole was syringed into the NMR tube (50 μL of a stock solution in dry d^5-NO_2Ph, 0.0198 mmol, 1 equiv) and the tube was sealed with a Teflon® cap. The spectrometer was heated to 50 °C. Once at temperature, the tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The reaction was followed to 10% conversion of **2-4** to 1-fluoro-4-benzotrifluoride (**2-2a**). The data plotted as a function of **[2-2a]** versus time, fitted to a linear regression, and the slope of the line

was deemed the initial rate. Each experiment was carried out in duplicate, and the initial rates values reported in Table 2.10 represent an average of two runs.

Table 2.10 – Rate Data for Triflate Order Study with **2-4** at 50 °C.

[OTf⁻]	1/[OTf⁻]	initial rate ($M\ s^{-1}$)	Error in ± initial rate ($M\ s^{-1}$)
0.01	100	2.91×10^{-5}	3.4×10^{-7}
0.03	33.3	1.68×10^{-5}	4.4×10^{-7}
0.05	20.0	1.35×10^{-5}	8.4×10^{-8}
0.07	14.3	1.25×10^{-5}	9.1×10^{-8}
0.1	10.0	1.18×10^{-5}	5.6×10^{-8}

$y = 2.2179E-05x + 1.0486E-02$
$R^2 = 9.9090E-01$

Figure 2-15 – Representative Kinetics for the Reductive Elimination of **2-4** in the Presence of 0.07M of NBu_4OTf at 50 in $PhNO_2$-d_5 at 50 °C

Determining Eyring Plot of from Pd^{IV} complex 2-4: In a N_2-filled drybox, complex **2-4** (14 mg, 0.0198 mmol, 1.0 equiv) was added to a screw-cap NMR tube and dissolved in dry NO_2Ph-d_5 (0.4 mL). The internal standard, 4-fluoroanisole was syringed into the NMR tube (50 µL of a stock solution in dry d^5-NO_2Ph, 0.0198 mmol, 1 equiv) and the tube was sealed with a Teflon® cap. The NMR spectrometer was heated to the desired temperature, the tube was placed in an NMR spectrometer, and the reaction was

allowed to equilibrate for three minutes. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The rate was followed to 10% conversion of **5** to 1-fluoro-4-benzotrifluoride (**2-2a**) at 30 °C, 40 °C, 50 °C and, 60 °C. The data was fitted to an inverse first order plot. The rate reported in Table 2.11 represent an average of two runs.

Table 2.11 – Rate Data for Reductive Elimination of **2-4** in PhNO$_2$-d_5 as a Function of Temperature

Temperature	Initial rate (M s^{-1})	±Error of initial rate (M s^{-1})	Ln(k/T)	1/T °K
303.2	1.15 x 10^{-6}	2.1 x 10^{-8}	-19.39	0.0033
313.2	5.15 x 10^{-6}	5.4 x 10^{-8}	-17.92	0.0032
323.2	2.21 x 10^{-5}	7.5 x 10^{-7}	-16.50	0.0031
333.2	9.59 x 10^{-5}	1.0 x 10^{-6}	-15.06	0.0030

y = 2.2179E-05x + 1.0486E-02
R^2 = 9.9090E-01

Figure 2.16 – Representative Kinetics for the Reductive Elimination of **2-4** at 50 °C in NO$_2$Ph-d_5

Determining Initial Rates of Reductive Elimination from Complexes 2-11 and 2-12 at 50 °C in d_5-PhNO$_2$: In a N$_2$-filled drybox, complex **2-11** or **2-12** (14 mg, 1.0 equiv)

dissolved in dry NO_2Ph-d_5 (0.4 mL). The internal standard, 4-fluoroanisole was syringed into the NMR tube (50 µL of a stock solution in dry NO_2Ph-d_5, 0.0198 mmol, 1 equiv) and the tube was sealed with a Teflon® cap. The spectrometer was heated to 50 °C. Once at temperature, the tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The reaction was followed to 10% conversion of Pd^{IV} complex to product. The data plotted as a function of [**product**] versus time, fitted to a linear regression, and the slope of the line was deemed the initial rate. Each experiment was carried out in duplicate, and the initial rate values reported in Table 2.12 represent an average of two runs.

Table 2.12 – Rate Data for Reductive Elimination of **2-11** and **2-12** in NO_2Ph-d_5 at 50 °C

Compound	Initial rate (M s^{-1})	± Error in initial rate (M s^{-1})
12	4.58×10^{-4}	1.6×10^{-6}
13	1.43×10^{-5}	2.0×10^{-8}

Figure 2.17 – Representative Kinetics for the Reductive Elimination of **2-11** in NO_2Ph-d_5 at 50 °C

Figure 2.18 – Representative Kinetics for the Reductive Elimination of **2-12** in NO$_2$Ph-*d$_5$* at 50 °C

Computational Methods: Using Gaussian 03 suite of programs,[43] all density functional theory (DFT) calculations were performed with the B3LYP (Becke's

three-parameter hybrid functional[44] using the LYP correlational functional containing both local and nonlocal terms of Lee, Yang, and Parr)[45] functional along with the Stevens (CEP-31G) valence basis sets with effective core potentials.[46,47] The CEP-31G basis sets are triple-ξ for Pd and double-ξ for all main group elements. A d-polarization function was added to all non-hydrogen main group elements: ξ_d =0.8 for carbon, nitrogen, oxygen, and fluorine and ξ_d =0.65 for sulfur. All geometries were optimized without symmetry constraints using the restricted Kohn-Sham formalism for all complexes. All minima were confirmed by the absence of imaginary frequencies and all transitions states were verified by visual inspection of the single imaginary frequency vibration and optimization along the reaction coordinate in each direction. Thermochemical data was calculated using default parameters at 298.15 K and 1 atm.

2.13 References

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(23)   Additionally, in CD_3CN, there is an observable coupling of CF_3 to F with CF_3 being a doublet (*J* = 10 Hz) and F as a broad quartet (*J* = 9 Hz). To our knowledge, this is a rare example of this type of coupling at any metal center.

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(26)   Ar–CF$_3$ bond formation occurs from (Xantphos)Pd(Ph)(CF$_3$) at 80 °C in the presence of access Xantphos ligand. See ref 16b.

(27) Grushin at al. reported $PhCF_3$ formation from $(L{\sim}L)Pd(Ph)(CF_3)$ ($L{\sim}L$ = dppe and dppp) in the presence of ligand at 145 °C after 64h in 10-60% yield. See ref 16b.

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Chapter 3

Synthesis and Reactivity of Catalytically Competent Monomeric Pd(IV) Aquo Complex

3.1 – Introduction

Over that past decade the field of Pd-catalyzed ligand-directed C–H activation/functionalization has grown exponentially.[1] Considerable efforts have focused on using strong oxidants (e.g. hypervalent iodine reagents and electrophilic halogenating reagents) in conjunction with Pd catalysts to promote C–C and C-heteroatom couplings.[1] Despite extraordinary progress in the development of these methodologies, very little is known about the key Pd intermediates and their role in catalysis.[2,3] Most commonly implicated in these catalytic systems are high oxidation palladium intermediates. These can be monomeric,[4,5] dimeric[6,7] or trimeric[8] ranging from +2 to +4 oxidation state.[2] Furthermore, while co-solvents and additives are used to promote these transformations their roles in catalysis are poorly understood.[1,2] Therefore, there is significant interest in performing studies to garner more mechanistic insights of these catalytic reactions. Such work would facilitate further optimization and rational design towards future catalytic systems.

Towards this goal there have been several recent reports focused on the role of cyclometallated dimers in Pd-catalyzed C–H activation/functionalization reactions.[6,7] Our group has demonstrated that upon oxidation of cyclometallated Pd^{II} dimer **3-1** with [Ph$_2$I]BF$_4$, the resulting Pd^{III}-dimer **3-2** was found to be the kinetically competent intermediate in C–H activation/arylation reactions (Scheme 2.1-a).[6] Related Pd^{III} species (**3-4**) have been isolated by the reaction of Pd^{II} dimer **3-3** with PhI(Cl)$_2$ and PhI(OAc)$_2$ (Scheme 2.1-b).[7] Although often implicated as catalytically relevant intermediates in C–H

activation/functionalization reactions,[1–4] monomeric Pd^{IV} intermediates have yet to be detected in the oxidation of catalytically relevant dimers such as **3-1** and **3-3**.[5]

This chapter will describe work done in collaboration with lab member Yingda Ye towards the isolation, reactivity and mechanistic studies of the monomeric Pd^{IV} species $(bzq)Pd(OAc)_2(OH_2)(CF_3)$ (bzq = benzo[*h*]quinoline). This Pd^{IV} compound undergoes C–CF_3 bond-forming reductive elimination and, Lewis and Brønsted acid additives can be used to tune both the rate and yield of this transformation. Mechanistic investigations of the C–CF_3 bond forming process provide insight into the role of acidic additives in C–H activation/functionalization chemistry.[9] Finally, we provide evidence that this Pd^{IV} species is a catalytic competent intermediate in Pd-catalyzed C–H trifluoromethylation reactions. Yingda Ye will describe a full detailed account of this work in his thesis. Thus, in the discussion of this project I will highlight my contributions focusing on the mechanism of C–CF_3 bond formation.[10]

Scheme 3.1 – Oxidation of Cyclometallated Dimers Generating High Oxidation State Palladium

3.2 – Isolation of (bzq)Pd(OAc)$_2$(OH$_2$)(CF$_3$), 3-6

Our investigations began my exploration of oxidizing Pd^{II} cyclometallated dimer **3-3** with a variety of CF$_3$+ reagents **3-5a– 3-5e**[11] in AcOH. Heating these reactions at 40 °C for 1h resulted in a new Pd–CF$_3$ species (**3-6**, as determined by ^{19}F NMR spectroscopy) in 2 – 60% yield (Table 3.1, entries 1 – 5 all). Conducting the reaction under anhydrous AcOH led to similar yields of **3-6**. With these results in hand, Yingda Ye optimized the reaction towards isolation of the new species **3-6**. Heating **3-3** in the presence of **3-5b** in DCE resulted in the formation of **3-6** in <2% yield (Table 3.1, entry 6). However, it was found that conducting the same reaction with different equivalents (1 – 20 equiv) of AcOH in DCE produced **3-6** in good yield (Table 3.1, entries 7 – 9). Complex **3-6** was isolated in 60% yield from the reaction of **3-3** in the presence of 3 equiv of **3-5b** in AcOH as a pale yellow solid. ^{1}H and ^{19}F NMR spectroscopy suggested a palladium species with one benzo[*h*]quinoline ligand, two different acetate ligands, a CF$_3$ group and a water molecule. This structure was confirmed by X-ray crystallography and indicated a monomeric Pd^{IV} complex.

Table 3.1 – Oxidation of **3-3** by Different "CF₃⁺" Reagents

Entry	Solvent	Oxidant	Yield 6 [a]
1	AcOH	**5a**	45%
2	AcOH	**5b**	60%
3	AcOH	**5c**	27%
4	AcOH	**5d**	2%
5	AcOH	**5e**	4%
6	DCE	**5b**	<2%
7	DCE/1 equiv AcOH	**5b**	48%
8	DCE/5 equiv AcOH	**5b**	56%
9	DCE/20 equiv AcOH	**5b**	65%

[a] Yields were determined by ¹⁹F NMR spectroscopy and represent an average of at least two independent runs. All yields are based on the reaction stoichiometry of 1 equiv of **3-3** reacting to form **3-6**.

3.3 – C–CF₃ Bond Forming Reductive Elimination from 3-6

Reductive elimination from **3-6** could produce at least three products: bzq–CF₃ (**3-7**), bzq-OAc (**3-8**), or bzq–OH (**3-9**). While there is significant literature precedent for C–O bond formation from Pd^{IV} [5b,12] and other metal centers,[13] C–CF₃ couplings from metals remain rare.[14,15] Interestingly, Yingda Ye demonstrated that the thermolysis of **6** in several solvents (CHCl₃, DCE, and nitrobenzene) selectively produced the bzq–CF₃ product (**3-7**) in 54 – 62% yield with just trace amounts of the C–O products **3-8** and **3-9** (Table 3.2). We propose that the high chemoselectivity for C–CF₃ bond formation could be due to hydrogen bonding between the coordinated H₂O and OAc ligands, which slows competing C–O bond formation. Intriguingly, Yingda Ye also found that the thermolysis of **3-6** in DCE in the presence of 50 equiv of pyridine resulted in C–O

coupled product **3-9** in 84% yield (Table 3.2, entry 5). Our hypothesis is that addition of pyridine disrupts hydrogen bonding by either displacement of the H_2O ligand with pyridine or deprotonation favoring C–O bond formation.

Table 3.2 – Product Distribution as a Function of Solvent

Entry	Solvent	Yield 7	Yield 8a	Yield 8b [a]
1	CD_3CO_2D	56%	<2%	<2%
2	DCE	54%	<2%	<2%
3	$CHCl_3$	62%	<2%	<2%
4	NO_2Ph	57%	<2%	<2%
5	DCE[a]	<2%	<2%	84%

[a] Yields were determined by ^1H and ^{19}F NMR spectroscopy and represent an average of at least two independent runs.

3.4 – Mechanism of C–CF$_3$ Bond-Forming Reductive Elimination from 3-6

There are at least three potential mechanisms for C–CF$_3$ bond formation from **3-6**, path **A**, **B**, and **C** (Figure 2.1). Path **A** involves the dissociation of acetate ligand from **3-6** resulting in a five-coordinate Pd^{IV} intermediate (**I**) and subsequent Aryl–CF$_3$ bond formation. Pathway **B** proceeds through H_2O dissociation generating a neutral five-coordinate intermediate **II** followed by the formation of **3-7**. Finally, path **C** involves direct C–CF$_3$ bond-forming reductive elimination. These mechanisms invoking ionic[16,17], neutral[18], and concerted pathways[19] are well precedented in the literature with Pd^{IV} and Pt^{IV} intermediates.

Figure 3.1 – Three Possible Mechanisms for C–CF$_3$ Bond-Forming Reductive Elimination from **3-6**

Yingda Ye initiated our mechanistic studies by examining the feasibility of the carboxylate dissociation (step i, in path **A**) by seeing if we could observe ion exchange. Adding 20 equiv of AcOH-d_4 or NMe$_4$OAc-d_3 to a solution of **3-6** in DCE-d_4 at room temperature resulted in complete exchange of both acetate ligands within minutes (as observed by ^{1}H NMR spectroscopy). These results provide evidence that carboxylate exchange is faster than C–CF$_3$ bond formation from **3-6**.

Scheme 3.2 – Acetate Dissociation and Exchange with **3-6**

Yingda Ye and I next explored the influence of exogenous acetate on C–CF$_3$ bond-forming reductive elimination from **3-6**. Intriguingly, addition of 1 equiv of NBu$_4$OAc completely suppressed C–CF$_3$ coupling, with the major products being the C–O products **3-8** and **3-9** (Table 3.3, entry 3). Addition of fewer equivalents of NBu$_4$OAc resulted in slightly improved yield of C–CF$_3$ product. However, significantly less product was formed than in the absence of additive (26% versus 54% yield, Table 3.3, entries 2 and 1 respectively).

Table 3.3 – Product Distribution as a Function of Additive

Entry	Additive	Yield 3-7	Yield 3-8	Yield 3-9 [a]
1	none	54%	<2%	<2%
2	0.2 equiv of NBu$_4$OAc	26%	<2%	<2%
3	1 equiv of NBu$_4$OAc	2%	16%	16%
4	1 equiv of NBu$_4$PF$_6$	56%	<2%	<2%
5	1 equiv of H$_2$O	50%	<2%	2%
6	10 equiv of H$_2$O	50%	<2%	2%

[a] Yields were determined by ^{1}H and ^{19}F NMR spectroscopy and represent an average of at least two independent runs.

I next focused on the quantitative kinetic analysis of C–CF$_3$ bond-forming reductive elimination from **3-6**. However, this proved challenging due to an induction period. It was then useful to compare the reaction profile (yield versus time) in the presence or absence of NBu$_4$OAc. Addition of NBu$_4$OAc significantly increased the induction period of the reaction and decreased the yield of **3-7** (Figure 3.2). In contrast, the addition of NBu$_4$PF$_6$ had no significant effect on the yield (Table 3.3, entry 4) or reaction profile compared to the reaction without additive (Figure 3.2). This demonstrates that the dramatic effect observed with NBu$_4$OAc was due to the acetate ligand and in conjunction with the aforementioned exchange experiments, are consistent with the inverse first-order dependence on [AcO$^-$] predicted by path **A** (Scheme 3.3).

Figure 3.2 – Reaction Profile for the Reductive Elimination from **3-6** in DCE at 60 °C in the Presence of No Additive (Black Squares), 1 Equiv of H_2O (Blue Triangles), and 0.2 Equiv of NBu_4OAc (Red Diamonds)

$$\text{Rate} = \frac{k_1 k_2 [\textbf{3-6}]}{k_2 + k_{-1}[\text{AcO}^-]}$$

Scheme 3.3 – Derived Rate Expression of Pathway **A**.

Finally, we wanted to investigate the role of H_2O on reductive elimination from **3-6** (path **B**). If the H_2O dissociation pathway was viable (path **B**), upon addition of excess H_2O we would predict a decrease in yield and rate of reductive elimination similar to what was observed with exogenous acetate. Yingda Ye found that the thermolysis of **3-6** at 60 °C in the presence of 1 – 10 equiv of H_2O resulted in similar overall yields of **3-7** (Table 3.3, entries 5 and 6). In the presence of 1 equiv of H_2O, the rate of reductive elimination decreased and the induction period increased (Figure 3.2). However this effect was much smaller than the effect observed in the presence 0.2 equiv of NBu_4OAc. While these results do not completely rule out paths **B** or **C**, they are consistent with path **A** being the predominant mechanism in this reaction. Notably, this mechanism is similar to that of C–CF_3 bond-forming reductive elimination from Pd^{IV} compound

(dtbpy)Pd(p-FPh)(CF$_3$)(F)(OTf) that involves a comparable TfO$^-$ dissociation (Chapter 2).[14a]

3.5 – Additive Effect on C–CF$_3$ Bond-Forming Reductive Elimination from 3-6

Our initial attempts to conduct quantitative kinetic analysis of C–CF$_3$ coupling from **3-6** were complicated by an induction period. With mechanistic evidence in hand suggesting a pre-equilibrium acetate dissociation from **3-6** (path **A**) as the predominant pathway, we hypothesized that if we could improve the pre-equilibrium to favor the five-coordinate Pd^{IV} species (**I**), we could eliminate the induction period (Scheme 3.4).

Scheme 3.4 – Favoring Intermediate **I** by the Addition of an Acidic Additive

On the basis of several literature reports,[5b,13c] we proposed the addition of Brønsted [e.g., trifluoroacetic acid (TFA)], Lewis acids (e.g. Yb(OTf)$_3$) and, other regents (e.g. trifluoroacetic anhydride) that would scavenge free AcO$^-$ would achieve this goal. To this end, Yingda Ye and I both studied the effect of several additives on the reductive elimination from **3-6**. As predicted, the addition of 10 equiv of TFA or TFAA (trifluoroacetic anhydride) or Yb(OTf)$_3$ eliminated the induction period and resulted in first-order kinetics for bzq–CF$_3$ coupling (Figure 3.3). Interestingly, the addition of these additives allowed for higher yield of C–CF$_3$ product **3-7**, with Yb(OTf)$_3$ resulting in near quantitative yield of **3-7**. This is a significant improvement from 56% yield with no additive (Table 3-4). These results corroborate our evidence supporting mechanism **A** as the predominant pathway for C–CF$_3$ bond-forming reduction elimination from **3-6**. The improved mass balance also suggests that the role of these acidic additives may involve the sequestration of reactive coordinatively unsaturated Pd intermediates formed as a result of reductive elimination.

Table 3-4 – Effect of Lewis and Brønsted Acid Additives on the Reductive Elimination from **3-6** at 60 °C

Entry	Additive	k_{obs} (s^{-1})	Yield of 3-7[a]
1	none	nd[b]	54%
2	10 equiv TFA	$3.308 \times 10^{-4} \pm 4.143 \times 10^{-6}$	73%
3	10 equiv TFAA	$1.430 \times 10^{-3} \pm 1.660 \times 10^{-5}$	84%
4	1 equiv Yb(OTf)$_3$	$2.918 \times 10^{-4} \pm 2.874 \times 10^{-6}$	99%

[a] Yields were determined by ^{1}H and ^{19}F NMR spectroscopy and represent an average of at least two independent runs. [b] k_{obs} could not be determined for the reaction because of an induction period.

Figure 3.3 – Reaction Profile for the Reductive Elimination from **3-6** in DCE at 60 °C in the Presence of no Additive (Black Squares), 10 Equiv of TFA (Blue Diamonds), and 10 Equiv of TFAA (Green Circles) and, 1 equiv of Yb(OTf)$_3$ (Red Triangles)

3.6 – Catalytic Competence of 3-6 in Pd-Catalyzed C–H Trifluoromethylation

During the progression of this work a communication by Yu et al. reported a Pd-catalyzed C–H trifluoromethylation reaction of benzo[*h*]quinoline with oxidants **3-5b**, **3-**

5d, and **3-5e** in DCE.[20] In this reaction, the addition of Cu(OAc)$_2$ and TFA were essential promoters. However, no mechanistic information concerning their role in catalysis was provided. Additionally, although a Pd^{II}/Pd^{IV} mechanism was suggested, there was no exploration of the mechanism. We hypothesized that **3-6** could be a catalytic intermediate in Yu's system, especially, since the compound could be generated using conditions similar to the catalytic transformation (Table 3.1, entries 7 – 9). Yingda Ye explored this possibility by comparing the initial rates of the trifluoromethylation of benzo[*h*]quinoline with oxidant **3-5e** using 10 mol% of Pd(OAc)$_2$ and 10 mol% of **3-6** under otherwise identical conditions. The initial rate with **3-6** was 18 times faster than with Pd(OAc)$_2$ clearly demonstrating that **3-6** is a kinetically competent intermediate in Pd-catalyzed C–H trifluoromethylation (Scheme 3.5). These results represent the first example of a Pd^{IV} species that serves as a catalytically competent intermediate for Pd-catalyzed C–H functionalization.

$$[Pd] = Pd(OAc)_2;\ \text{Initial Rate} = 0.08 \times 10^{-4}\ \text{M/s}$$
$$[Pd] = \textbf{3-6};\ \text{Initial Rate} = 1.40 \times 10^{-4}\ \text{M/s}$$

Scheme 3.5 – Initial Rates of C–H Trifluoromethylation of Pd(OAc)$_2$ and **3-6**

3.7 – The Role of Promoters in Catalytic Trifluoromethylation

The demonstration that **3-6** is a catalytically relevant intermediate in catalytic C–H trifluoromethylation provided an opportunity to elucidate the role of the promoters Cu(OAc)$_2$ and TFA in the catalytic cycle. All of the aforementioned studies have shown that these additives are critical in both the formation of and C–CF$_3$ reductive elimination from **3-6**. Our initial oxidation studies of dimer **3-3** demonstrated that least 1 equiv of AcOH was essential in the formation of Pd^{IV} compound **3-6** (Table 3.1). In the catalytic system, equivalences of AcOH could be generated by the reaction of Cu(OAc)$_2$ and TFA through the equilibrium shown in Scheme 3.6.

$$Cu(OAc)_2 \ + \ TFA \ \rightleftharpoons \ Cu(TFA)_2 \ + \ AcOH$$

Scheme 3.6 – The Generation of AcOH from $Cu(OAc)_2$ and TFA

Acidic additives were demonstrated to increase the rate, yield and mass balance of C–CF_3 bond-forming reductive elimination from **3-6** (Table 3.4). Next I investigated whether catalytically relevant amounts of $Cu(OAc)_2$ and TFA have a similar effect. The thermolysis of **6** in the presence of 10 equiv of $Cu(OAc)_2$ and 100 eq of TFA resulted in very rapid reductive elimination and nearly quantitative conversion to **3-7** (94% compared to 54% without any additive) (Figure 3.4). In line with our conclusions about the role of other Lewis and Brønstead acidic additives, $Cu(OAc)_2$/TFA seems to be crucial for accelerating reductive elimination and limiting unproductive competitive pathways that attenuate the yields of Bzq–CF_3.

Figure 3.4 – Reaction Profile for the Reductive Elimination from **3-6** in DCE at 60 °C in the Presence of No Additive (Black Squares), 10 Equiv of $Cu(OAc)_2$/100 equiv of TFA (Red Circles)

3.8 – Conclusion

This chapter describes the synthesis and isolation of monomeric Pd^{IV} trifluoromethylated compound **3-6** by the oxidation of cyclometallated dimer [(bzq)Pd(OAc)]$_2$ (**3-3**) with CF_3^+ reagents. This complex undergoes chemoselective C–CF_3 bond-forming reductive elimination upon thermolysis and acidic additives enhanced

the yield and rate of this transformation. Complex **3-6** is a kinetically competent catalyst for the Pd-catalyzed trifluoromethylation of benzo[*h*]quinoline with CF_3^+ reagents. New insights into the role of $Cu(OAc)_2$ and TFA in the catalytic transformation demonstrate that these additives serve two principal roles: (1) they serve as a source of AcOH, critical for the oxidation of dimer $[(bzq)Pd(OAc)]_2$ to monomeric **3-6** and (2) enhance yield of **3-6** and mass balance in C–CF_3 coupling. From these data, we propose that **3-6** is a catalytically relevant intermediate in C–H trifluoromethylation. In light of recent literature examples that suggest C–H functionalization predominantly proceeds via Pd^{III} intermediates,[7] these studies substantiate the existence of Pd^{IV} intermediate in this system and highlight how the speciation of Pd is highly dependent on solvent, oxidant structure, temperature and ancillary ligands. We envision this and other organometallic/mechanistic investigation of catalytic systems will facilitate the rational design and development of new transformations.

3.9 – Experimental Procedures

Oxidation of 3 with Different Electrophilic Trifluoromethylating Reagents: In air, $[(bzq)Pd^{II}(OAc)]_2$ (**3-3**) (20 mg, 0.03 mmol, 1 equiv) was dissolved in CD_3CO_2D (0.4 mL) in a 4 mL vial. The appropriate "CF_3^+" reagent (0.09 mmol, 3 equiv) was added. The vial was then sealed with a Teflon-lined cap, and the reaction was heated at 40 °C for 1 h. The resulting dark brown mixture was cooled to room temperature, 4-(trifluoromethyl)anisole was added as an internal standard, and the reaction was analyzed by ^{19}F NMR spectroscopy.

Oxidation of 3-3 with 5b in DCE with Different Equivalents of AcOH: In air, $[(bzq)Pd^{II}(OAc)]_2$ (**3-3**) (20 mg, 0.029 mmol, 1 equiv) and reagent **3-5b** (0.087 mmol, 3 equiv) were dissolved in DCE-d_4 (0.4 mL) in a 4 mL vial. AcOH (0-58 mmol, 0-20 equiv) was added. The vial was sealed with a Teflon-lined cap, and the reaction was stirred at 40 °C for 1 h. 4-Trifluoromethylanisole was added as an internal standard, and the reaction was analyzed by ^{19}F NMR spectroscopy. The results of these experiments are summarized in Table 3.5.

Table 3.5 – Yield of **3-6** as a Function of Equivalents of AcOH

Entry	Equiv AcOH	Yield 3-6
1	0	<2%
2	1	48%
3	5	56%
4	20	65%

Effect of Additives on the Reaction Profile and Rate of Reductive Elimination from 3-6

   Additive = Trifluoroacetic acid: In a N_2-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) was dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. TFA (15.16 µL, 0.204 mmol, 1.0 equiv) and 4-(trifluoromethyl)anisole (50 µL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) were then added through the septum. The tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 60 °C before acquisition was started. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The data was fit to a first order kinetics plot using Sigma Plot 10. A representative reaction profile is shown in Figure 3.5.

Figure 3.5 – Representative Reaction Profile of Reductive Elimination from **3-6** in the Presence of 10 equiv of TFA at 60 °C. Fit to the Function f = a(1-exp(-bx)); a = 83.84 ± 0.3356, b = 3.308 x10^{-4} ± 4.143*10^{-6}, R^2 = 0.9904. [k_{obs} = b]

Additive = Trifluoroacetic Anhydride: In a N_2-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) was dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. Trifluoroacetic anhydride (28.4 µL, 0.204 mmol, 1.0 equiv) and 4-(trifluoromethyl)anisole (50 µL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) were then added through the septum. The tube was immediately placed in the NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 60 °C before acquisition was started. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. The data was fit to a first order kinetics plot using Sigma Plot 10. A representative reaction profile is shown in Figure 3.6.

Figure 3.6 – Representative Reaction Profile of Reductive Elimination from **3-6** in the Presence of 10 equiv of TFAA at 60 °C. Fit to the Function f = a(1-exp(-bx)); a = 88.80 ± 0.1990, b = 1.430 x 10^{-3} ± 1.660*10^{-5}, R^2 = 0.9884. [k_{obs} = b].

Additive = Cu(OAc)$_2$ and TFA: In a N$_2$-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) and Cu(OAc)$_2$ (37.2 mg, 0.204 mmol, 10 equiv) were dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. TFA (152 μL, 2.04 mmol, 100 equiv) and 4-(trifluoromethyl)anisole (50 μL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) were then added through the septum. The tube was immediately placed in the NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 60 °C before acquisition was started. A representative reaction profile is shown in Figure 3.7. This reaction did not follow a 1st order kinetic profile.

Figure 3.7 Representative Reaction Profile of Reductive Elimination from **3-6** in the Presence of 10 Equiv of Cu(OAc)$_2$ and 100 Equiv of TFA at 60 ºC

Additive = NBu$_4$OAc: In a N$_2$-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) and NBu$_4$OAc (1.23 mg, 0.0041 mmol, 0.2 equiv) were dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. 4-(Trifluoromethyl)anisole (50 µL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) was then added through the septum. The tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 60 ºC before acquisition was started. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. This reaction showed a significant induction period and did not follow a 1st order kinetic profile.

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Figure 3.8 – Representative Reaction Profile of Reductive Elimination from **3-6** in the Presence of 0.2 Equiv of NBu$_4$OAc at 60 °C

Additive = NBu$_4$PF$_6$: In a N$_2$-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) and NBu$_4$PF$_6$ (7.9 mg, 0.0204 mmol, 1 equiv) were dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. 4-(Trifluoromethyl)anisole (50 μL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) was then added through the septum. The tube was immediately placed in an NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 60 °C before acquisition was started. The kinetics of reductive elimination was studied using ^{19}F NMR spectroscopy by monitoring the appearance of the product signal. This reaction showed a significant induction period and did not follow a 1st order kinetic profile.

Figure 3.9 – Representative Reaction Profile of Reductive Elimination from **3-6** With NBu$_4$PF$_6$ at 60 ºC

Additive = None: In a N$_2$-filled drybox, complex **3-6** (10 mg, 0.0204 mmol, 1.0 equiv) was dissolved in dry DCE (0.5 mL) in a 4 mL vial and then transferred to a screw cap NMR tube fitted with a septum. The NMR tube was removed from the glovebox. 4-(Trifluoromethyl)anisole (50 µL of a stock solution in dry DCE, 0.0204 mmol, 1 equiv) was then added through the septum. The tube was immediately placed in the NMR spectrometer, and the reaction was allowed to equilibrate for three minutes at 23 ºC before acquisition was started. A representative reaction profile is shown in Figure 3-10. This reaction showed a significant induction period and did not follow a 1st order kinetic profile.

Figure 3-10 – Representative Reaction Profile of Reductive Elimination from **3-6** at 60 ºC

3.10 – References

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Chapter 4

Synthesis, Structure and Reactivity of Pd(II)-Fluorides with Nitrogen Ligands

4.1 Introduction

Organopalladium complexes containing fluoride ligands are currently of significant interest due to their proposed intermediacy in both C–F activation[1,2] and, C–F bond-forming transformations.[3] Efforts towards Pd-catalyzed formation of aryl fluorides have focused on a Pd^0/Pd^{II} reductive fluorination mechanism involving nucleophilic fluorine. This mechanism involves the following steps: (i) oxidative addition of Ar-X (X = I, Br, Cl) to a Pd^0 center, (ii) metathesis of Pd–X for Pd–F at the σ- aryl Pd^{II} halide complex and finally (iii) reductive elimination of the Ar-F and regeneration of the Pd^0 catalyst (Scheme 4.1). A key advantage to this approach is that inexpensive and easy to handle fluoride salts (e.g. NaF, KF or LiF) serve as the source of fluorine in these reactions.

Scheme 4.1 – Palladium (II) Fluorides with Phosphine Ligands

While the first two steps have successfully been demonstrated, reductive elimination from Pd^{II} to form Ar-F bonds has proven to be quite challenging. Grushin and co-workers published the first example of an isolable aryl palladium fluoride complex, *trans*-$(PPh_3)_2Pd^{II}(Ph)(F)$, in 1997.[4] Subsequent extensive studies by Grushin focused on the isolation and reactivity of diverse σ-aryl Pd^{II} fluoride complexes. These investigations have demonstrated that such compounds are stabile to air and trace amounts of water. In addition, these complexes react with CO to form aryl acyl fluorides (Scheme 4.2).

Scheme 4.2 – Formation of Acyl Fluorides from $(PPh_3)_2Pd(Ph)(F)$

Following this seminal report, a variety of related compounds bearing phosphine supporting ligands have been prepared and characterized (Scheme 4.3).[5] In addition to the complexes described in Scheme 4.3, there are several examples of organopalladium fluorides in which the Pd–F bond is a part of a Lewis acid/base complex (*e.g.,* Pd–**F**BF_3 or Pd–**F**HF). However, the Pd–F bonds are arguably perturbed by the coordinating atoms thereby their relevance in C–F bond–forming

reactions is not straightforward. Therefore they will not be included in this discussion.[6]

Scheme 4.3 – Palladium (II) Fluorides with Phosphine Ligands

In order to achieve the ultimate goal of generating C–F aryl fluorides from palladium, the thermal decomposition of these complexes was studied in detail. However, this transformation has proven challenging from these Pd^{II} phosphine complexes, as P–F bond-formation typically predominantes over the desired C–F coupling. For example, thermolysis of $(Ph_3)_2Pd(Ph)(F)$ in toluene at 110 °C resulted in a complex mixture of Pd^0, C–C and P–P and P–F coupling products (Scheme 4.4).[5,7]

Scheme 4.4 – Thermolysis of $(PPh_3)_2Pd(Ph)(F)$ in Toluene

In contrast to the extensive literature on Pd^{II}(R)(F) phosphine complexes, palladium fluorides bearing nitrogen-donor ligands remain rare.[8] A key advantage of $(N)_2Pd^{II}(Ar)(F)$ intermediates is that P–F bond-forming reductive elimination is not possible, thereby hopefully favoring C–F bond formation. Notably, with nitrogen ligands the competing N–F bond formation is unlikely. This is because typically N–F reagents (i.e. *N*-fluorinated reagents: Selectfluor®, *N*-fluoropyridinium salts and *N*-fluorobenzenesulfanimde) are often formed using F_2 (a source of F$^+$) and in the aryl

Pd[II]–F complexes the fluorine is considered the nucleophile in C–F coupling from Pd[II].[3b]

R = H or *tert*-butyl

Scheme 4.5 – Palladium(II) Fluorides with Nitrogen Ligands

Grushin initially suggested that phosphines are essential to stabilize the Pd–F bond in (L)$_2$Pd[II](Ar)(F);[8] however, in a later report he amended his comments by isolating Pd[II](Ar)(F) species with sp^2 nitrogen-donors ligands (Scheme 4.5).[9] With this initial precedent in hand, we wanted to further explore the feasibility of Pd[II] complexes with nitrogen ligands. This chapter discusses the synthesis, characterization, and reactivity of a series of novel aryl and alkyl palladium (II) fluorides containing both sp^2 and sp^3 nitrogen donor ligands. X-ray crystallographic characterization of many of these complexes has allowed structural comparisons to related phosphine-containing species. In addition, the thermal decomposition of the new complexes has been investigated. By studying the structure and reactivity of these new complexes we hoped to glean insight into the feasibility of catalytic phosphine-free Pd^0/Pd[II] C–F coupling reactions.[10]

4.2 Synthesis of Palladium(II) Fluoride Compounds

The synthetic approach to the palladium(II) fluoride complexes involved the sonication of the corresponding Pd[II] iodides with AgF at 20 - 25 °C in benzene, following a procedure developed by Grushin.[2a] It should be noted that these complexes are extremely sensitive to water. In the presence of water, the resulting hydrated (L)$_2$Pd[II](Ar)(F) compound has a Pd–F bond that is labile on a NMR time scale (as indicated by broad Pd–F resonances).[3a, 11] As a result the isolation of the palladium(II) fluorides were performed in a glovebox. The palladium(II) iodide precursors were prepared using three different synthetic strategies. The cyclometalated C~N complexes **4-2** - **4-5** were prepared by reaction of the readily

available cyclopalladated dimers [(phpy)Pd(I)]$_2$ [12] (**4-1a**) and [(bzq)Pd(I)]$_2$ (**4-1b**) (phpy = 2-phenylpyridine; bzq = benzo[*h*]quinoline) with 2,6-lutidine, 4-*tert*-butylpyridine (tpy), or PPh$_3$, respectively in acetone. Complex **4-6** was generated by reaction of NaI with a solution of known pincer complex (NCN)Pd(Br) in acetone [13] (NCN = *N,N,N′,N′*-tetramethyl-1,3-xylylenediamine). Finally, **4-7** was accessed by reaction of (dtbpy)Pd(Me)$_2$ [14] (dtbpy = 4,4'-di-*tert*-butylbipyridine) with MeI (Scheme 4.6).

(4-1a)

L = 2,6-lutidine (**4-2**, 83%)
L = 4-^{t}Bu-pyridine (**4-3**, 69%)

(4-1b)

L = 2,6-lutidine (**4-4**, 82%)
L = PPh$_3$ (**4-5**, 65%)

(4-6, 90%)

(4-7, 52%)

Scheme 4.6 – Synthesis of Palladium(II) Iodide Complexes **4-2 – 4-7**.

Synthesis of *trans*-(phpy)Pd(lutidine)(F), 4-8 and *trans*-(phpy)Pd(tbpy)(F), 4-9

The cyclometalated 2-phenylpyridine complexes **4-8** and **4-9** were prepared by sonication of **4-2** and **4-3** respectively with AgF in benzene under an N$_2$ atmosphere for 5 h at 25 °C. Notably, it was important for the temperature of these reactions to not exceed 25 °C. Higher temperatures resulted in considerable decomposition of the complexes to Pd^0 (as indicated by Pd plating out on the reaction vessel). The desired products were isolated by filtration through Celite, removal of solvent, and recrystallization from CH$_2$Cl$_2$ and pentanes to afford **4-8** as a yellow solid (47%) and **4-9** as a white solid (45%) (Scheme 4.7).

Analysis of **4-8** and **4-9** by ^{19}F NMR spectroscopy showed characteristic Pd[II] fluoride resonances as broad singlets at –261.0 ppm and –243.4 ppm, respectively. The ^{1}H NMR spectrum of **4-8** revealed signals indicative of an unsymmetrical square planar complex, with H_a and H_b of the 2-phenylpyridine ligand appearing as doublets at 8.08 and 5.77 ppm, respectively. Similar diagnostic upfield and downfield resonances were observed in the ^{1}H NMR spectrum of **4-9** at 8.96 (H_a) and 6.50 ppm (H_b), respectively. Notably, the ^{1}H NMR chemical shifts for H_a in **4-8** and **4-9** appear approximately 1 ppm upfield from those in the corresponding palladium(II) iodides **4-2** and **4-3** (9.89 and 9.91 ppm, respectively). Literature precedent suggests that this large $\Delta\delta$ is indicative of a *trans* orientation between the fluoride ligand and the σ-aryl group (Scheme 4.7). This is proposed to be due to the sterics of the halogen atom pushing the H_a into the ring current of the 2-phenylpyridine ligand.[12]

The synthesis of **4-3** and **4-9** are particularly notable because previous reports have suggested that methyl substituents at the 2- and/or 6-positions of the pyridine ligand were crucial in preventing an equibrium to the halogenated dimer.[8] The stability of both **4-3** and **4-9** towards isolation and characterization suggest that the methyl substution of the pyridine is not necessary to prevent formation of halide bridged dimers.[12]

(**4-8**, L = 2,6-lutidine, 47%)
(**4-9**, L = 4-[t]Bu-pyridine, 45%)

Scheme 4.7 – Synthesis of Complexes **4-8** and **4-9**

Recrystallization of **4-8** was performed by slow diffusion of pentanes into a THF solution at –35 °C to afford colorless needles suitable for X-ray crystallographic analysis. The X-ray structure of **4-8** in Figure 3.1 confirms the *trans* configuration of the σ-aryl group and the fluoride ligand. Intriguingly, the Pd–F bond distance in **4-8** (2.1024(17) Å) is the longest Pd–F bond known for an isolable monomeric Pd[II](Ar)(F) complex, with the next longest being in $(PPh_3)_2PdF(Ph)$ (Pd–F = 2.085(3) Å).[4, 15]

Figure 4.1 – X-ray Crystal Structure of **4-8**. Thermal Ellipsoids are Drawn at 50% Probability, Hydrogens Are Omitted for Clarity. Selected Bond Length (Å): Pd1-C11 1.960(3), Pd1-N1 2.017(2), Pd1-N2 2.055(2), Pd1-F1 2.1024(17). Selected Bond Angles (°): C11-Pd1-N1 82.13(11), C11-Pd1-N2 93.68(10), N1-Pd1-N2 175.36(9), C11-Pd1-F1 173.88(9), N1-Pd1-F1 92.32(8), N2-Pd1-F1 91.95(8), C11-C6-C5-N1 6.16.

Synthesis of *trans*-(bzq)Pd(lutidine)(F), 4-10

Using an analogous procedure to the synthesis of **4-8** and **4-9,** Compound **4-10** was prepared as a yellow solid (57% yield) (Scheme 4.8). Its ^{19}F NMR spectrum contained a broad singlet at –270.4 ppm for the Pd-bound fluoride ligand. The ^{1}H NMR spectrum of **4-10** showed signals indicating an unsymmetrical square planar complex, with H_a and H_b of the benzo[*h*]quinoline ligand appearing as doublets at 9.03 and 5.95 ppm, respectively. Similar to **4-8** and **4-9**, the chemical shift of H_a in **4-10** is nearly 1 ppm upfield from that of the corresponding Pd iodide (**4-4**), indicative of a *trans* orientation of the fluoride and σ-aryl ligands.

Scheme 4.8 – Synthesis of Complexes **4-10** and **4-11**

Slow diffusion of pentanes into a CH_2Cl_2 solution of **4-10** at –35 °C provided yellow blocks of this complex. An X-ray crystal structure was obtained of **4-10** (Figure 4.2).

As predicted on the basis of the NMR spectral data, this complex contains *trans* fluoride and aryl substituents. Notably, the sole difference between complexes **4-8** and **4-10** is the nature of the cyclometallated ligand. However, intriguingly, **4-10** exhibits a significantly shorter Pd–F bond (2.0604(12) Å) and a correspondingly longer Pd–C bond (1.9769(19) Å) than **4-8**. This Pd–C bond length difference of ca. 0.017 Å is likely due to the increased rigidity of benzo[*h*]quinoline versus 2-phenylpyridine.[16] The Pd–N1 bond length (2.0325(15) Å) is also shorter than the corresponding bond found in **4-8**. The crystal structure of **4-10** clearly demonstrates the effect of rigidity of the cyclometallated ligand by the Pd–C, and Pd–F bond lengths. The C11-C12-C13-N1 dihedral angle in **4-10** is 0.75 ° indicating a nearly planar benzo[*h*]quinline ligand. In contrast, complex **4-8** has a dihedral angle of 6.16 ° corresponding with the more flexible nature of the 2-phenylpyridine ligand. This ability of 2-phenylpyridine to twist out of plane allows for better Pd/C orbital overlap thus shorter a Pd–C bond and concomittanly a longer Pd–F bond than **4-10**.

Figure 4.2 – X-ray Crystal Structure of **4-10**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogens Are Omitted for Clarity. Selected Bond Lengths (Å): Pd1-C11 1.9769(19), Pd1-N1 2.0325(15), Pd(1)-N(2) 2.0519(15), Pd1-F1 2.0604(12). Selected Bond Angles (°): C11-Pd1-N1 82.89(7), C11-Pd1-N2 92.46(7), N1-Pd1-N2 174.46(6), C11-Pd1-F1 174.14(6), N1-Pd1-F1 91.29(6), N2-Pd1-F1 93.32(5), C11-C12-C13-N1 0.75.

Synthesis of *trans*-(bzq)Pd(PPh₃)(F), 4-11

Compound **4-11** was isolated as a pale yellow solid in 84% yield from the reaction

of **4-5** with AgF (Scheme 4.8). In this case, the fluoride ligand appeared as a broad doublet at –245.2 ppm by ^{19}F NMR spectroscopy. In addition, the ^{31}P NMR spectrum of **4-11** showed a corresponding doublet at 39.7 ppm. The ^{31}P/^{19}F coupling constant (J_{PF} = 9 Hz) is similar to that observed for other *cis* fluoride and phosphine ligands at Pd[II] centers.[4,5a,5c]

X-ray quality crystals of **4-11** were obtained by slow diffusion of pentanes into a CH_2Cl_2 solution at –35 °C. The X-ray crystal structure of **4-11** is shown in Figure 3–3. Compound **4-11** is unusual in that it is the first example of a Pd[II] aryl fluoride containing both P and N donor ligands. The Pd–F (2.1024(17) Å) and Pd–C (1.960(3) Å) bond lengths are significantly smaller than those found in **4-10**. Notably, the C11-C12-C13-N1 dihedral angle (0.09°) is considerably smaller than **4-11** (0.75°) further emphasizing the effect of rigidity of the cyclometallated ligand on Pd–F and Pd–C bond lengths.

Figure 4.3 – X-ray Crystal Structure of **4-11**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogens Are Omitted For Clarity. Two Polymorphs Were Present. Selected Bond Lengths (Å): Pd1-C11 2.004(2), Pd1-F1 2.0301(15), Pd1-N1 2.0762(19), Pd1-P1 2.2458(6), Pd2-C42 2.012(2), Pd2-F(2) 2.0290(15), Pd2-N7 2.070(2), Pd2-P2 2.2448(6). Selected Bond Angles (°): C11-Pd1-F1 169.77(8), C11-Pd1-N1 82.52(9), F1-Pd1-N1 87.36(7), C11-Pd1-P1 96.97(7), F1-Pd1-P1 93.23(5), N2-Pd1-P1 176.20(6), C42-Pd2-F2 170.46(8), C42-Pd2-N7 82.57(9), F2-Pd2-N7 87.91(7), C42-Pd2-P2 96.08(7), F2-Pd2-P2 93.46(5), N7-Pd2-P2 177.32(6), C11-C12-C13-N1 0.09, C42-C43-C44-N7 0.26.

Synthesis of (NCN)Pd(F), 4-12

Pincer complex **4-12** was synthesized in 63% yield using an analogous procedure to that for **4-8 – 4-11**. Complex **4-12** is the first example of an isolable palladium fluoride containing sp^3 N donor ligands.[17] This molecule shows a broad singlet at –243.7 ppm for the Pd–F bond by ^{19}F NMR spectroscopy.

Colorless crystals of **4-12** were generated by slow diffusion of pentanes in a CH_2Cl_2 solution of this compound at –35 °C. An X-ray crystal structure was obtained and (Figure 4.4). Intriguingly, the Pd–F bond length (2.0959(7) Å) of **4-12** is identical to that of **4-8** resulting in both complexes consisting of the reported longest Pd–F bonds of any monomeric Pd^{II} aryl fluoride.[15] The Pd–N (2.0954(9) and 2.1019(9) Å) and Pd–C bond lengths (1.9068(11) Å) are similar to those found in (NCN–CH_2OH)Pd(Cl) (Pd–N = 2.1083(15) and 2.1066(15) Å) and Pd-C = 1.9174 (18) Å).[18] Notably, the Pd–C bond length of 1.9068(11) Å is the shortest reported for a Pd^{II}(Ar)(F) with the next closest being in (PPh$_3$)$_2$Pd(Ph)(F) (Pd–C = 1.998 (5) Å) (Figure 1).[4]

Figure 4.4 – X-ray Crystal Structure of **4-12**. Thermal Ellipsoids are Drawn at 50% Probability, Hydrogens are Omitted For Clarity. Selected Bond Lengths (Å): Pd1-C7 1.9068(11), Pd1-N1 2.0954(9), Pd(1)-N(2) 2.1019(9), Pd1-F1 2.0959(7). Selected Bond Angles (°): C7-Pd1-N1 81.69(4), C7-Pd1-N2 81.61(4), N1-Pd1-N2 163.27(4), C7-Pd1-F1 176.62(4), N1-Pd1-F1 96.89(3), N2-Pd1-F1 99.74(3).

Synthesis of *cis*-(dtbpy)Pd(4-FC₆H₄)(F), 4-13

(**4-13**, X = *p*-FC₆H₄, 83%)
(**4-14**, X = CH₃, 69%)
(**4-15**, X = F, 35%)

Scheme 4.9 – Synthesis of complexes **4-13**, **4-14** and **4-15**

Complex **4-13** was prepared by reaction of (dtbpy)Pd(*p*-FC₆H₄)(I) with AgF (Scheme 4.9).[3i] The ¹⁹F NMR spectrum of **4-13** shows two resonances: a broad singlet at –340.7 ppm for the Pd–**F** and a multiplet at –122.9 ppm for the Aryl–**F**. Crystallization of **4-13** was achieved by diffusion of pentanes into a fluorobenzene solution of this complex at –35 °C. This afforded yellow blade-like crystals, which were used to obtain an X-ray crystal structure (Figure 4.5). This X-ray structure confirms the square planar geometry of **4-13** as well as the *cis* orientation of the *p*-F phenyl and fluoride ligands. Complex **4-13** is a rare example of a monomeric Pd–F compound with the F *trans* to an L-type ligand.[7,19] Notably, the Pd–F bond in **4-13** (1.999(4) Å) is significantly shorter than that in the closely related *trans*-configured complexes *trans*-(py)₂Pd(Ph)(F) and *trans*-(tpy)₂Pd(Ph)(F) (Pd–F = 2.077(4) Å and 2.079(2) Å, respectively). Indeed, **4-13** contains the shortest known Pd–F bond for a Pdᴵᴵ(Ar)(F) complex.[15] The closest is in *trans*-(ⁱPr₃P)₂Pd(F)(4-C₅F₄N), where Pd–F = 2.0158(16) Å.[1e] The contraction of the Pd–F bond in **4-13** versus *trans*-(ⁱPr₃P)₂Pd(F)(4-C₅F₄N) is likely due to weaker *trans* influence of the pyridyl ligand versus the σ-aryl group C₅F₄N. Interestingly, the Pd–C bond length in **4-13** of 1.981(8) Å is nearly identical to that in *trans*-(py)₂Pd(Ph)(F) and *trans*-(tpy)₂Pd(Ph)(F) (1.982(3) and 1.978(2) Å, respectively).[9]

Figure 4.5 – X-ray Crystal Structure of **4-13**. Thermal Ellipsoids Are Drawn At 50% Probability, Hydrogens and CH_2Cl_2 Were Omitted For Clarity. The Structure was Solved as Two Identical Structures in a Unit Cell (Only One is Shown, See Section 3.5 for More Information). Selected Bond Lengths (Å): Pd1-C1 1.981(8), Pd1-F1 1.999(4), Pd1-N2 2.026(6), Pd1-N1 2.086(7), Pd2-C25 1.983(9), Pd2-F(3) 1.983(4), Pd2-N3 1.998(7), Pd2-N4 2.073(7). Selected Bond Angles (°): C1-Pd1-F1 89.9(3), C1-Pd1-N2 96.6(3), F1-Pd1-N2 173.5(2), C1-Pd1-N1 174.3(3), F1-Pd1-N1 93.8(2), N2-Pd1-N1 79.7(3), C25-Pd2-F3 90.9(3), C25-Pd(2)-N3 97.9(3), F3-Pd2-N3 171.0(2), C25-Pd2-N4 176.8(3), F3-Pd2-N4 91.6(2), N3-Pd2-N4 79.5(2).

Synthesis of *cis*-(dtbpy)Pd(CH₃)(F), 4-14

Compound **4-14** was synthesized in 69% yield by similar methods to **4-8 − 4-13** by sonication of palladium iodide **4-7** with AgF in benzene (Scheme 4.9). ^{19}F NMR spectroscopy shows a resonance for the fluorine bound to palladium as a broad singlet at –347.4 ppm. The ^{1}H NMR spectrum shows the methyl ligand as a doublet at 0.84 ppm with J_{HF} = 6 Hz. The ^{13}C NMR signal for the methyl group appears as a doublet at 0.0039 ppm with J_{CF} = 1.3 Hz. Notably **4-14** is the first example of an alkyl Pd^{II}–F with nitrogen-donor ligands.[5a]

Synthesis of *cis*-(dtbpy)Pd(F)₂, 4-15

Compound **4-15** was accessed by stirring Pd^{II} diiodide **7** and AgF in CH_2Cl_2

according to a previously reported procedure (Scheme 4.9).[2m] Analysis by ^{19}F NMR spectroscopy revealed a broad singlet at –354.06 ppm corresponding to Pd–**F**. The ^{1}H NMR spectrum showed signals indicative of a symmetrical square planar complex with the protons at the 6-position of the *t*Bu-bpy ligand appearing at 8.51 ppm.

Figure 4.6 – X-ray Crystal Structure of **4-15**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogens Are Omitted For Clarity. Selected Bond Lengths (Å): Pd1-F1 1.9708(11), Pd1-F1A 1.9708(11), Pd1-N1 1.9722(15), Pd1-N1A 1.9722(15). Selected Bond Angles (°): F1-Pd1-F1A 91.70(7), F1-Pd1-N1A 174.52(6), F1A-Pd1-N1A 93.64(6), F1-Pd1-N1 93.64(6), F1A-Pd1-N1 174.52(6), N1A-Pd1-N1 81.04(9).

Complex **4-15** was crystallized by vapor diffusion of pentanes into an acetone solution of the compound at –35 °C to afford colorless blocks for X-ray analysis. The resulting crystal structure confirmed the *cis* orientation of the two fluorides along with the square planar geometry of **4-15** (Figure 4.6). The Pd–F bond lengths are, within error, identical at 1.9708(11) and 1.9722(15) Å. Intriguingly, the Pd–F distances observed in **4-15** are very similar to those in *trans*-(*t*Bu-py)$_2$Pd(F)$_2$ (1.947(4) and 1.958(4) Å), which contains the shortest Pd–F bonds ever observed in a molecular Pd fluoride compound. [9]

In the case of *trans*-(tpy)$_2$Pd(F)$_2$, (tpy = 4-*tert*-butylpyridine) Grushin and Marshall reasonably argued that the short Pd–F distances resulted from field/inductive effects

associated with the two *trans* fluoride ligands. They hypothesized that these ligands increased the ionic character of the Pd[II]–F interaction and thereby enhanced electrostatic contributions to the bonding.[9] The observation of nearly identical Pd–F bond lengths in the *cis* complex **4-15** suggests that Pd–F bonds lengths might be independent of ligand geometry and that Columbic forces are predominent. Figure 3.7 compares the new complexes with the shortest and longest Pd–F described within to those previously found in the literature. Additionally Figure 4.8 compares the all Pd–F bond lengths of all known complexes, highlighting those new complexes described in this chapter.

(R = tert-butyl; Ar = p-FC$_6$H$_4$; pic = 2,6-picoline)

Figure 4.7 – Comparison of Pd–F Bond Lengths of Selected Literature Pd[II]–F Compounds (Grey) and Compounds (4-15, 4-13, 4-8, green). Error Bars Demonstrate Three Standard Deviations (95 % Confidence Level) in the Error of the Bond Lengths.

Figure 4.8 – Comparison of Pd–F bond Lengths of Literature Pd^{II}–F Compounds (Grey) and Compounds (Green in Order from Left to Right **4-15**, **4-13, 4-11, 4-10, 4-12** and, **4-8**). Literature Crystallographic Information Was Obtained from the Cambridge Crystallographic Database (July 1, 2009).

4.3 Thermolysis of Aryl Pd^{II}–Fluorides

Palladium fluorides **4-8 – 4-14** are potential intermediates in C–F bond forming reactions.[2] Thermolysis of compounds **4-8 – 4-14** in nitrobenzene at 150 °C for 16h gave no C–F products, instead favoring the biaryl products. These C–C products were confirmed by GC or ^{19}F NMR using the authentic samples. This process likely occurs via a well-precedented Ar tranfer between to palladium centers following by C–C bond-forming reductive elimination.[20] Additionally, the thermolysis of **4-14** at 80 °C for 1 h did not result in the formation of methyl fluoride. The reactions after completion gave significant amounts of palladium black indicating reduction to Pd^0. This was confirmed by ^{1}H NMR spectroscopy, where there was no trace of Pd–F species or the coordinated cyclometallated ligand. Interestingly, thermolysis of **4-13** and **4-14** resulted in a new Pd species with the dtbpy coordinated to Pd center by ^{1}H NMR, however, the product could not be identified. This reactivity is similar to what is seen in the literature,[7] further highlighting the challenge of C–F bond forming reductive elimination from Pd^{II}.

4.4 Conclusions

In summary, we have described the synthesis, characterization and reactivity a series of Pd[II]–F complexes with sp^2 and sp^3 nitrogen donor ligands.[21] These complexes represent the first examples of Pd[II]–fluorides with: (1) sp^3 nitrogen ligands (**4-12**), (2) an alkyl and nitrogen ligands (**4-14**), and (3) both phosphorus and nitrogen ligands (**4-11**). Structural analysis of these compounds by X-ray crystallography have revealed both the longest (**4-8**) and shortest Pd–F bonds (**4-13**) of any monomeric Pd[II] aryl fluoride previously reported. Structural comparison of a *cis* Pd[II]–difluoride to a *trans* Pd[II]–difluoride demonstrated nearly identical Pd–F bond lengths suggesting *trans* fluoride ligands are not integral to achieve short Pd–F bond length. Thermolysis of this complexes did not result in C–F bond formation instead favoring C–C bond formation. Even though we were able to demonstrate the feasibility of Pd[II]–F complexes with nitrogen ligands and observe very interesting structural characteristic compared to the phosphine systems, the reactivity of these compounds are very similar to their phosphine counterparts. These results emphasize the difficulty of promoting C–F bond forming reductive elimination from Pd[II] centers.

4.5 Experimental Procedures

General Considerations

NMR spectra were obtained on a Varian Inova 400 (399.96 MHz for ^{1}H; 376.34 MHz for ^{19}F; 100.57 MHz for ^{13}C) or MR400 (400.53 MHz for ^{1}H: 376.87 MHz for ^{19}F; 100.71 MHz for ^{13}C) spectrometer. ^{1}H, ^{19}F and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced on a unified scale, where the single primary reference is the frequency of the residual solvent peak in the ^{1}H NMR spectrum.[22] Several ^{19}F NMR experiments were conducted using "No-D" parameters and are noted accordingly.[23] ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), and multiplet (m). Elemental analyses were conducted by Atlantic Microlabs in Norcross, Georgia. Microanalysis for the Pd–F complexes described herein was consistently low in C. This may be due to the hygroscopic nature of these materials because of the possibility of strong H-bonding interactions between the Pd–F and H_2O.[2a, 2i] The amount of water could not accurately

be quantified by ^{1}H NMR analysis due to likely broading of the signal *via* rapid exchange. Full ^{1}H, ^{19}F and ^{13}C NMR spectra are detailed for these Pd–F compounds in the electronic supporting information. Gas chromatographs were obtained on a Shimadzu 17A using Restek Rtx®-5 (crossbond 5% diphenyl polysiloxane, 15 m, 0.25 mm ID, 0.25 mm ID, 0.25μm df) column. Sonication was performed using a VWR Model 75H7 ultrasound bath, with the temperature regulated by a Neslab RTE-111 recirculating chiller.

Materials and Methods

The palladium complexes Pd(dba)$_2$,[23] (NCN)PdBr,[13] (dtbpy)PdMe$_2$,[14] [(phpy)Pd(OAc)]$_2$,[24] [(bzq)Pd(OAc)]$_2$,[25] (bzq)$_2$[26], (phpy)$_2$[27], and (4,4'-difluoro-1,1'-biphenyl) [28] were prepared according to literature procedures. Palladium fluorides (dtbpy)Pd(p-FC$_6$H$_4$)(F) and (dtbpy)PdF$_2$ were prepared according to previously reported procedures.[3i] AgF and 1-fluoro-4-iodobenzene were obtained from Matrix Chemicals. MeI, dtbpy, 2,6-lutidine, and LiI were obtained from Aldrich. dtbpy was obtained from TCI America. PPh$_3$ was obtained from Strem Chemicals. All reagents were used as received. Nitrobenzene-d_5, CD$_2$Cl$_2$, and CDCl$_3$ were obtained from Cambridge Isotope Laboratories. All other solvents were obtained from Fisher Chemical. Dichloromethane and pentane were purified using an Innovative Technologies (IT) solvent purification system consisting of a copper catalyst, activated alumina, and molecular sieves. Benzene was distilled from Na^0/benzophenone and stored over activated 4 Å molecular sieves. Acetone was distilled from CaSO$_4$. All syntheses were conducted using standard Schlenk techniques or in an inert atmosphere glovebox unless otherwise stated.

[(phpy)Pd(I)]$_2$ (4-1a) – In air, [(phpy)Pd(OAc)]$_2$ (1.5 g, 2.2 mmol, 1 equiv) was weighed into a 250 mL Erlenmeyer flask and dissolved in acetone (100 mL). In a separate flask, LiI (1.2 g, 8.8 mmol) was dissolved in water (50 mL). The aqueous LiI solution was added slowly to the stirring solution of [(phpy)Pd(OAc)]$_2$ in acetone, and the resulting solution was stirred at room temperature overnight. The reaction mixture was filtered, and the solid obtained was washed with a 1:1 mixture of MeOH/H$_2$O (3 x 10 mL) followed by a 1:1 mixture of hexanes/Et$_2$O (3 x 3 mL). The solid was dried *in vacuo*, yielding the product (3-**1a**)

as a yellow solid (1.7 g, 95% yield). Spectroscopic data for this complex matched that reported in the literature.[11]

[(bzq)Pd(I)]₂ (4-1b) – Complex **4-1b** was synthesized via an analogous procedure to the preparation of **4-1a**, with [(bzq)Pd(OAc)]₂ (1.5 g, 2.2 mmol) as the starting material. The product was obtained as a dark yellow solid (1.6 g, 88% yield). ^{1}H NMR (95% CDCl₃, 5% C₅D₅N): δ 9.87 (br s, 2H), 8.17 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 9 Hz, 2H), 7.52 (d, *J* = 9 Hz, 4H), 7.54 (m, 2H), 7.21 (d, *J* = 8 Hz, 2H), 6.14 (br s, 2H); ^{13}C NMR (CDCl₃, 1 drop of C₅D₅N): δ 154.84, 149.34, 141.34, 136.95, 135.43, 133.42, 128.62, 128.42, 126.84, 123.50, 123.11, 121.72 (two aromatic ^{13}C resonances appear to be coincidentally overlapping). (Found: C, 38.07, H, 1.93, N, 3.50. $C_{22}H_{16}I_2N_2Pd_2$ requires 37.94, H, 1.96, N, 3.40).

***trans*-(phpy)Pd(lutidine)(I) (4-2)** – Complex **4-2** was prepared under ambient conditions using a modification of the literature procedure.[12] To a stirring suspension of dimer **4-1a** (0.50 g, 0.65 mmol, 1 equiv) in acetone (16 mL) was added 2,6-lutidine (0.30 mL, 4 equiv) dropwise. The resulting clear solution was stirred for 15 min. The solvent was then removed under vacuum, and the resulting solid was recrystallized from CH₂Cl₂/hexanes and dried in vacuo yielding **4-2** as a yellow solid (0.53 g, 83% yield). ^{1}H NMR (CDCl₃): δ 9.89 (d, *J* = 5 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 7.66 (multiple peaks, 2H), 7.43 (d, *J* = 8 Hz, 1H), 7.22 (multiple peaks, 2H), 7.10 (multiple peaks, 2H), 6.85 (t, *J* = 8 Hz, 1H), 5.58 (d, *J* = 6 Hz, 1H), 3.12 (s, 6H). ^{13}C NMR (CDCl₃): δ 165.07, 159.79, 156.94, 154.03, 145.92, 138.29, 130.25, 129.65, 124.97, 123.37, 123.02, 122.83, 118.48, 28.57 (two aromatic ^{13}C resonances appear to be coincidentally overlapping). (Found: C, 43.44, H, 3.31, N, 5.88. $C_{18}H_{17}IN_2Pd$ requires C, 43.70, H, 3.36, N, 5.63).

***trans*-(phpy)Pd(dtbpy)(I) (4-3)** – Complex **4-3** was prepared via an analogous procedure to the preparation of **4-2**, using **4-1a** (1.0 g, 1.3 mmol, 1 equiv) and tpy (1.5 mL, 5.1 mmol, 4 equiv)

as starting materials The product was obtained as a pale yellow solid (0.93 g, 69% yield). ^{1}H NMR (CDCl$_3$): δ 9.91 (d, J = 5 Hz, 1H), 8.80 (d, J = 6 Hz, 2H), 7.76 (m, 1H), 7.64 (d, J = 8 Hz, 1H), 7.43-7.39 (multiple peaks, 3H), 7.10-7.07 (multiple peaks, 2H), 6.92 (m, 1H), 5.87 (d, J = 8 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 165.24, 162.67, 157.36, 155.96, 153.02, 145.88, 138.37, 131.28, 129.47, 125.05, 123.42, 122.71, 118.55, 35.22, 30.32 (two aromatic ^{13}C resonances appear to be coincidentally overlapping). (Found: C, 45.65, H, 4.15, N, 5.26. C$_{22}$H$_{21}$IN$_2$Pd requires C, 45.95, H, 4.05, N, 5.36).

trans-(bzq)Pd(lutidine)(I) (4-4) – Complex **4-4** was prepared via an analogous procedure to the preparation of **4-2**, using **4-1b** (0.50 g, 0.61 mmol, 1 equiv) and 2,6-lutidine (0.30 mL, 4.5 equiv) as starting materials. The product was obtained as a yellow solid (0.52 g, 82% yield). ^{1}H NMR (CDCl$_3$): δ 10.1 (d, J = 6 Hz, 1H), 8.27 (d, J = 8 Hz, 1H), 7.71 (multiple peaks, 2H), 7.59 (multiple peaks, 2H), 7.47 (m, 1H), 7.28-7.19 (multiple peaks, 3H), 5.81 (d, J = 8 Hz, 1H), 3.12 (s, 6H). ^{13}C NMR (CDCl$_3$): δ 160.09, 155.39, 155.19, 152.63, 141.59, 138.32, 136.92, 133.54, 128.64, 128.58, 127.33, 126.96, 123.71, 123.12, 123.03, 122.11, 28.67. (Found: C, 45.12, H, 3.19, N, 5.48. C$_{20}$H$_{17}$IN$_2$Pd requires C, 46.31, H, 3.30, N, 5.40).

trans-(bzq)Pd(PPh$_3$)(I) (**4-5**) – Complex **4-5** was prepared via an analogous procedure to the preparation of **4-4**, using **4-1b** (0.50 g, 0.61 mmol, 1 equiv) and PPh$_3$ (0.72 g, 2.7 mmol, 4.5 equiv) as starting materials. The product was obtained as a yellow solid (0.53 g, 65% yield). ^{1}H NMR (CDCl$_3$): δ 10.46 (br s, 1H), 8.27 (d, J = 8 Hz, 1H), 7.85 (multiple peaks, 6H), 7.70 (m, 1H), 7.60 (m, 1H), 7.50 (m, 1H), 7.42 (multiple peaks, 4H), 7.34 (multiple peaks, 6H), 6.87 (t, J = 8 Hz, 1H), 6.65 (t, J = 8 Hz, 1H). ^{31}P NMR (CDCl$_3$): δ 44.67. ^{13}C NMR (CDCl$_3$): δ 155.41, 155.18, 154.46, 143.06, 137.19, 135.82, 135.63 (d, J = 12 Hz), 133.92, 133.43 (d, J = 52 Hz), 130.74, 129.07, 128.01 (d, J = 11 Hz), 127.87, 127.17, 123.42, 123.31, 122.12 (d, J = 3 Hz). (Found C, 55.01, H, 3.39, N, 2.14. C$_{31}$H$_{23}$INPPd requires C, 55.26, H, 3.44, N, 2.08).

(NCN)Pd(I) – 4-6. In air, (NCN)PdBr (2.0 g, 3.1 mmol, 1.0 equiv) was weighed into a 250 mL Erlenmeyer flask and dissolved in acetone (141 mL). In a separate 100 mL Erlenmeyer flask, LiI (1.7 g, 13 mmol, 4 equiv) was dissolved in water (71 mL). The aqueous LiI solution was added slowly to the stirring solution of (NCN)PdBr in acetone, and the resulting solution was stirred at 23 °C for an additional 12 h. The reaction mixture was then filtered through a frit, and the resulting solid washed with water (3 x 5 mL) and diethyl ether (3 x 5 mL). The solvent was removed *in vacuo*, and the resulting solid was further purified by recrystallization from CH_2Cl_2/hexanes. The product was obtained as a microcrystalline yellow solid (0.71 g, 90% yield). ^{1}H NMR (CDCl$_3$): δ 6.97 (t, *J* = 8 Hz, 1H), 6.74 (d, *J* = 8 Hz, 2H), 3.98 (s, 4H), 2.99 (s, 12H); ^{13}C NMR (CDCl$_3$): δ 159.19, 145.15, 124.60, 119.75, 73.94, 54.84. (Found C, 33.95, H, 4.34, N, 6.59. $C_{12}H_{19}IN_2Pd$ requires C, 33.94, H, 4.51, N, 6.60).

(dtbpy)Pd(Me)(I) (4-7) – In the glovebox, (dtbpy)PdMe$_2$ (0.77 g, 3.1 mmol, 1.9 equiv) was weighed into a 20 mL scintillation vial and dissolved in acetone (2 mL). MeI was added dropwise to this solution. The reaction was stirred for 30 min, during which time it changed from a clear yellow solution to a cloudy suspension. Pentanes (8 mL) was added to completely precipitate the product, and the solids were collected, and washed with pentanes (3 x 2 mL). The resulting material was dried *in vacuo* to yield **4-7** as a yellow solid. Further purification by recrystallization from CH_2Cl_2/hexanes afforded analytically pure compound (0.86 g, 52% yield). ^{1}H NMR (CDCl$_3$): δ 9.29 (d, *J* = 6 Hz, 1H), 8.46 (d, *J* = 6 Hz, 1H), 8.08 (d, *J* = 2 Hz, 1H), 8.02 (d, *J* = 2 Hz, 1H), 7.59 (dd, *J* = 6, 2 Hz, 1H), 7.44 (dd, *J* = 6, 2 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 0.738 (s, 3H). ^{13}C NMR (CDCl$_3$): δ 163.93, 163.27, 157.29, 154.01, 152.21, 146.93, 124.39, 123.94, 120.09, 118.98, 36.01, 35.87, 30.63, 30.57, 7.63. (Found C, 44.19, H, 5.31, N, 5.61. $C_{19}H_{27}IN_2Pd$ requires C, 44.16, H, 5.27, N, 5.42).

***trans*-(phpy)Pd(lutidine)(F) (4-8) –** Complex **4-8** was prepared in the glovebox, by weighing **4-2** (0.66 g 1.3 mmol, 1 equiv) and AgF (0.66 g, 5.2 mmol, 3.9 equiv) into a amber glass jar and 27 mL of benzene was added. The reaction was sonicated for 5 h. In the glovebox the reaction mixture was filtered through Celite and washed with CH_2Cl_2 (3 x 5 mL). This filtration

was repeated and the solvent removed *in vacuo*. The resulting solid was recrystalized from CH_2Cl_2/pentanes. The product was obtained as a yellow solid (0.23 g, 47% yield). ^{1}H NMR (CDCl₃): ^{1}H NMR (CDCl₃): δ 8.70 (br d, *J* = 6 Hz 1H), 7.72 (t, *J* = 8 Hz, 1H), 7.58-7.52 (multiple peaks, 2H), 7.32 (d, *J* = 8 Hz, 1H), 7.13-7.08 (multiple peaks, 3H), 6.93 (m, 1H), 6.70 (m, 1H), 5.77 (d, *J* = 8 Hz, 1H), 3.13 (s, 6H). ^{19}F NMR (CDCl₃): δ –260.3 (br s, 1F). ^{13}C NMR (CDCl₃): δ 164.55, 160.11, 149.35, 145.72, 138.71, 138.31, 133.12, 129.19, 128.12, 124.07, 123.09, 122.76, 121.80, 117.80, 27.76. (Found C, 53.40, H, 4.66, N, 6.61. $C_{18}H_{17}FN_2Pd$ requires C, 55.90, H, 4.43, N, 7.24%).

trans-(phpy)Pd([t]Bu-py)(F) (4-9) – Complex **4-9** was prepared via an analogous procedure to the preparation of **4-8**, using **4-3** (0.60 g, 1.2 mmol, 1 equiv), AgF (0.57 g, 4.5 mmol, 3.9 equiv), and benzene (23 mL) as starting materials and conducting the sonication for 3 h. The product was obtained as a white solid (0.22 g, 45% yield). ^{1}H NMR (CDCl₃): δ 8.96 (d, *J* = 5 Hz, 1H), 8.82 (d, *J* = 6 Hz, 2H), 7.82 (m, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.42 (multiple peaks, 3H), 7.17 (m, 1H), 7.06 (m, 1H), 6.94 (m, 1H), 6.50 (d, *J* = 8 Hz, 1H), 1.34 (s, 9H); ^{19}F NMR (CD₂Cl₂): δ –243.4; ^{13}C NMR (CD₂Cl₂): δ 164.71, 162.80, 152.06, 149.56, 145.98, 138.73, 133.76, 129.10, 128.21, 124.19, 123.17, 122.45, 121.69, 117.83, 35.08, 30.18. (Found : C, 57.95, H, 5.01, N, 6.67. $C_{20}H_{21}FN_2Pd$ requires C, 57.91, H, 5.10, N, 6.75).

trans-(bzq)Pd(lutidine)(F) (4-10) – Complex **4-10** was prepared via an analogous procedure to the preparation of **4-8**, using **4-4** (0.40 g, 0.77 mmol, 1 equiv) and AgF (0.38 g, 3.0 mmol, 3.9 equiv) as starting materials and conducting the sonication for 5 h. The product was obtained as a yellow solid (0.18 g, 57% yield). ^{1}H NMR (CDCl₃): δ 9.03 (br d, *J* = 5 Hz, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.62-7.59 (multiple peaks, 2H), 7.50 (d, *J* = 8 Hz, 1H), 7.46-7.40 (multiple peaks, 2H), 7.17 (d, *J* = 8 Hz, 2H), 7.05 (d, *J* = 8 Hz, 1H), 5.95 (d, *J* = 8 Hz, 1H), 3.20 (s, 6H). ^{19}F NMR (CDCl₃): δ -270.4. ^{13}C NMR (CDCl₃): δ 160.52, 154.66, 148.40, 141.58, 138.45, 137.04, 133.15, 130.19, 128.69, 128.38, 128.27, 126.31, 123.31, 122.88, 122.29, 121.15, 27.99. Found : C 54.76; H, 4.53 N, 6.35. $C_{20}H_{17}FN_2Pd$ requires 58.48; H, 4.17 N, 6.82.

***trans*-(bzq)Pd(PPh₃)(F), 4-11.** Complex **4-11** was prepared via an analogous procedure to the preparation of **4-8**, using **4-5** (0.40 g, 0.59 mmol, 1 equiv) and AgF (0.29 g, 2.3 mmol, 3.9 equiv) as starting materials and conducting the sonication for 5 h. The product was obtained as white solid (0.28 g, 84% yield). ^{1}H NMR (CDCl$_3$): δ 9.30 (m, 1H), 8.29 (d, J = 8 Hz, 1H), 7.82-7.77 (multiple peaks, 6H), 7.70 (d, J = 9 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.55 (m, 1H) 7.47-7.42 (multiple peaks, 4H), 7.39-7.34 (multiple peaks, 6H), 7.33 (s, C$_6$H$_6$, 6H), 6.79 (t, J = 8 Hz 1H), 6.54 (m, 1H). ^{19}F NMR (CDCl$_3$): δ –247.2 (apparent s, 1F). ^{31}P NMR (CDCl$_3$): δ 40.7 (d, J = 8 Hz, 1P). ^{13}C NMR (CDCl$_3$): δ 153.34, 147.37, 147.31, 142.94, 137.52, 135.37 (d, J = 12 Hz), 133.67, 130.85, 130.82, 129.91 (d, J = 50 Hz), 129.04, 128.32 (C$_6$H$_6$), 128.23 (d, J = 8 Hz), 128.07, 126.46, 123.09, 122.64, 121.16 (J = 4 Hz). Found : C, 68.43, H, 4.47, N, 2.38. C$_{31}$H$_{23}$FNPPd•1 C$_6$H$_6$ requires C, 69.00, H, 4.54, N, 2.95.

(NCN)Pd(F) (4-12) – In the glovebox, **4-6** (0.50 g, 1.2 mmol, 1 equiv) and AgF (0.59 g, 4.6 mmol, 3.9 equiv) were dissolved in benzene (23 mL) in a 50 mL amber glass jar. The jar was sealed with a Teflon-lined cap, and the reaction was sonicated in the dark at 25 °C for 3 h. The resulting suspension was filtered through a plug of Celite in the drybox. The plug was washed with benzene (1 x 5 mL) and then with CH$_2$Cl$_2$ (5 x 2 mL). The solvent was removed under reduced pressure. The solid was collected and dried *in vacuo* affording the product (**4-12**) as a white solid (0.24 g, 63% yield). ^{1}H NMR (CD$_2$Cl$_2$): δ 6.90 (t, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 2H), 3.95 (s, 4H), 2.84 (s, 12H). ^{19}F NMR (CD$_2$Cl$_2$): δ –243.72 (br s, 1F). ^{13}C NMR (CD$_2$Cl$_2$): δ 145.76, 129.48, 124.14, 119.97, 74.57, 52.28. (Found : C, 42.55, H, 6.30, N, 8.04. C$_{12}$H$_{19}$FN$_2$Pd requires C, 45.51, H, 6.05, N, 8.85).

(dtbpy)Pd(Me)(F) (4-14) – Complex **4-14** was prepared via an analogous procedure to the preparation of **4-8**, using **7** (0.40 g, 0.77 mmol, 1 equiv) and AgF (0.38 g, 3.0 mmol, 3.9 equiv) as starting materials and conducting the sonication for 3 h. The product was obtained as a yellow solid (0.22 g, 69% yield). ^{1}H NMR (CDCl$_3$): δ 8.69 (d, J = 6 Hz, 1H), 8.48 (d, J = 6 Hz, 1H), 7.98 (s, 1H), 7.97 (s, 1H), 7.59 (dd, J = 5 Hz, 2 Hz, 1H), 7.42 (dd, J = 6 Hz, 2 Hz, 1H), 1.43 (s, 9H), 0.84 (d, J = 6 Hz, 3H). ^{19}F NMR (CD$_3$Cl): δ –243.7 (br s, 1F). ^{13}C NMR (CD$_3$Cl): δ 163.96, 163.37, 157.75,

152.92, 150.75, 148.08, 124.15, 124.02, 119.77, 118.32, 36.01, 35.92, 30.72, 30.49, 0.039 (d, J = 1.3 Hz). Found : C, 54.04, H, 6.65, N, 6.56. $C_{19}H_{27}FN_2Pd$ requires C, 55.82, H, 6.66, N, 6.85.

X-ray structure determination of *trans*-(phpy)Pd(lutidine)(F) – (4-8). Colorless needles of **3-8** were crystallized from a pentane/tetrahydrofuran solution at -35 deg. C. A crystal of dimensions 0.33 x 0.14 x 0.07 mm was mounted on a standard Bruker SMART-APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(2) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 3630 frames were collected with a scan width of 0.5° in w and 0.45°in with an exposure time of 20 s/frame. Indexing was performed by use of the CELL_NOW program, which indicated that the crystal was a non-merohedral twin. The frames were integrated with the Bruker SAINT software package with a narrow frame algorithm. The integration of the data yielded a total of 39833 reflections to a maximum 2q value of 52.88° of which 4339 were independent and 3953 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9958 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with TWINABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P2(1)/c with Z = 4 for the formula $C_{18}H_{17}N_2FPd$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. The twin domains are related by a 4.2 degree rotation about the direct (0.900 0.100 1) axis or reciprocal (0.048 0.031 1) axis and a refined twin volume fraction of 0.281(1). Full-matrix least-squares refinement based on F^2 converged at R1 = 0.0323 and wR2 = 0.0797 [based on I > 2sigma(I)], R1 = 0.0383 and wR2 = 0.0842 for all data.[29]

X-ray structure determination of *trans*-(bzq)Pd(lutidine)(F) (4-10) – Yellow blocks of **3-10** were crystallized from a dichloromethane/pentane solution at -35 deg. C. A crystal of dimensions 0.34 x 0.20 x 0.16 mm was mounted on a standard Bruker SMART 1K CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (l = 0.71073 A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 108(2) K; the detector was placed at a

distance 4.912 cm from the crystal. A total of 3000 frames were collected with a scan width of 0.5° in w and phi with an exposure time of 25 s/frame. The integration of the data yielded a total of 44848 reflections to a maximum 2q value of 56.72° of which 5037 were independent and 4299 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9227 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P2(1)/c with Z = 4 for the formula $C_{20}H_{17}N_2FPd$•(CH_2Cl_2). All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0214 and wR2 = 0.0508 [based on I > 2sigma(I)], R1 = 0.0307 and wR2 = 0.0551 for all data.

X-ray structure determination of *trans*-(bzq)Pd(PPh₃)(F) (4-11) – Colorless plates **3-11** were grown from a pentanes/dichloromethane solution at -35 deg. C. A crystal of dimensions 0.25 x 0.24 x 0.05 mm was mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(1) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 5190 frames were collected with a scan width of 0.5° in w and 0.45° in phi with an exposure time of 25 s/frame. The integration of the data yielded a total of 128348 reflections to a maximum 2q value of 56.66° of which 14487 were independent and 13303 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9709 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group P1bar with Z = 4 for the formula $C_{31}H_{23}NFPPd$, $CHCl_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. There are two independent palladium complexes and two independent dichloromethane solvates in the asymmetric unit. One of the solvates is disordered over three sites. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0376 and wR2 = 0.0934 [based on I > 2sigma(I)], R1 = 0.0403 and wR2 = 0.0961 for all data.

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X-ray structure determination of (NCN)Pd(F) (4-12) – Colorless plates **4-12** were grown from a pentanes/dichloromethane solution at -35 deg. C. A crystal of dimensions 0.32 x 0.30 x 0.22 mm was mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(1) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 5190 frames were collected with a scan width of 0.5° in w and 0.45° in phi with an exposure time of 10 s/frame. The integration of the data yielded a total of 38567 reflections to a maximum 2q value of 60.18° of which 4384 were independent and 4326 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9935 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group P1bar with Z = 2 for the formula $C_{12}H_{19}N_2FPd$, $CHCl_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0147 and wR2 = 0.0386 [based on I > 2sigma(I)], R1 = 0.0150 and wR2 = 0.0387 for all data.

X-ray structure determination of *cis*-(^tBu-bpy)Pd(F)_2 (4-15) – Yellow cubes of **4-15** were crystallized from a pentane/dichloromethane solution at -30 deg. C. A crystal of dimensions 0.10 x 0.10 x 0.10 mm was mounted on a standard Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low-temperature device and fine- focus Mo-target X-ray tube (l = 0.71073 A) operated at 2000 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(2) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 3100 frames were collected with a scan width of 0.5° in w and 0.45°infwith an exposure time of 25 s/frame. Indexing was performed by use of the CELL_NOW program, which indicated that the crystal was a two-component, non-merohedral twin. The frames were integrated with the Bruker SAINT software package with a narrow frame algorithm. The integration of the data yielded a total of 92957 reflections to a maximum 2q value of 56.66° of which 6735 were independent and 3768 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9448 reflections above 10s(I). Analysis of the data showed negligible decay

during data collection; the data were processed with TWINABS and corrected for absorption. For this refinement, reflections from both components were used in the refinement and well as reflections containing contributions from both domains. Merging of the data was performed in TWINABS and an HKLF 5 format file used for refinement. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group Pccn with Z = 4 for the formula $C_{18}H_{24}N_2F_2Pd \cdot CH_2Cl_2$. The complex lies on a two-fold axis of the crystal lattice. The dichloromethane is disordered over an alternate two-fold axis. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. The twin domains are related by a 180 degree rotation about the direct (1 1 0) axis) and a refined twin volume fraction of 0.886(2). Full-matrix least-squares refinement based on F^2 converged at R1 = 0.0386 and wR2 = 0.1032 [based on I > 2sigma(I)], R1 = 0.0507 and wR2 = 0.102 for all data.

Table 4.1 – Crystallographic Data, Details of Data Collection and Refinement for **4-8**, **4-10 – 4-13**, and **4-15**

	4-8	**4-10**[a]	**4-11**[a]
Molecular Formula	$C_{18}H_{17}FN_2Pd$	$C_{21}H_{19}Cl_2FN_2Pd$	$C_{32}H_{25}Cl_2FNPPd$
M	386.74	495.68	650.80
Crystal System	Monoclinic	Monoclinic	Triclinic
Space group (standard setting)	$P2_1/c$	$P2_1/c$	P-1
a/Å	9.6607(11)	13.904(4)	8.7399(5)
b/ Å	9.2742(10)	11.409(3)	17.2959(9)
c/ Å	17.810(2)	14.366(4)	20.3468 (11)
α/°			96.861(1)
β/°	96.023(2)	117.158(3)	98.293(1)
γ/°			104.123(1)
V/ Å^3	1586.9(3)	2027.8(9)	2913.0(3)
Z, calculated density (Mg/m^3)	4, 1.619	4, 1.619	4, 1.484
Absorption coefficient/mm^{-1}	1.177	1.195	0.904
Crystal size/mm	0.33 x 0.14 x 0.07	0.34 x 0.20 x 0.16	0.25 x 0.24 x 0.05
T/K	85	108	85
Reflection collected	39833	44848	128348
Independent reflections (R_{int})	4339 (0.0578)	5037 (0.0379)	14487 (0.0328)
Data/parameters	4339/211	5037/246	14487/79
wR_2 (obs. and all data)	0.0797 and 0.0842	0.0508 and 0.0551	0.0934 and 0.0961
R_1 (obs. and all data)	0.0323 and 0.0383	0.0214 and 0.0307	0.0367 and 0.0403

[a] Crystal structure contains an equivalent of CH_2Cl_2

Table 4.2 – Crystallographic Data, Details of Data Collection and Refinement for 4-12 – 4-15

	4-12[c]	4-13[b]	4-15[a]
Molecular Formula	$C_{13}H_{21}Cl_2FN_2Pd$	$C_{57}H_{65}F_4N_4Pd_2$	$C_{19}H_{26}Cl_2F_2N_2Pd$
M	401.62	1094.93	497.72
Crystal System	Triclinic	Monoclinic	Orthorhombic
Space group (standard setting)	P-1	Ia	Pccn
a/Å	8.4407(6)	17.9592(12)	11.1616(9)
b/ Å	9.5451(6)	17.5332(12)	11.9919(9)
c/ Å	11.5693(8)	20.2950(14)	15.6096(10)
α/°	105.314(1)		
β/°	95.629(1)	95.135(1)	90
γ/°	116.010(1)		
V/ Å^3	782.97(9)	6364.9(8)	2089.3(3)
Z, calculated density (Mg/m^3)	2, 1.704	4, 1.143	4, 1.582
Absorption coefficient/mm^{-1}	1.525	0.610	1.166
Crystal size/mm	0.32 x 0.30 x 0.22	0.25 x 0.10 x 0.09	0.10 x 0.10 x 0.10
T/K	85	85	85
Reflection collected	38567	70232	92957
Independent reflections (R_{int})	4384 (0.0282)	11189 (0.0652)	6735 (0.0631)
Data/parameters	4084/176	11189/682	6735/128
wR_2 (obs. and all data)	0.0386 and 0.0387	0.1553 and 0.1651	0.1032 and 0.1102
R_1 (obs. and all data)	0.0147 and 0.0150	0.0552 and 0.0700	0.0386 and 0.0507

[a] Crystal structure contains an equivalent of CH_2Cl_2 [b] There are two independent palladium complexes in the asymmetric unit. [c] There are two independent palladium complexes and the equivalents of CH_2Cl_2 in the unit cell

General procedure for the thermolysis of compounds 4-8 – 4-13 – In the glovebox Pd–F (10 mg) was weighed into a 4 mL scintillation vial and d^5-nitrobenzene (0.03M) with a Teflon stirbar and sealed with a Teflon-lined cap. The reaction stirred at 150 °C for 16 h. Compound **14** was heated at 80 °C for 1 h. The reaction was cooled to room temperature, 4-fluoronitrobenzene was added as an internal standard and the reaction mixture was analyzed by ^{19}F NMR spectroscopy and gas chromatography.

4.6 – References

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Chapter 5

Aryl C–F Bond Formation from a Pd(IV)-FHF Compound

5.1 Introduction

Aryl fluorides are important components of many biologically active molecules, including pharmaceuticals, agrochemicals, and PET imaging agents.[1,2] While a diversity of synthetic approaches are exist for generating sp^3 C–F bonds,[2–4] relatively few general and practical methods are available for the formation of aryl fluorides.[2] To date, the most common routes to these molecules involve fluorination of aryl diazonium salts (the Balz-Schiemann reaction)[3a] and other nucleophilic aromatic substitution reactions with F$^-$.[3b,4] However, these transformations have significant limitations (*e.g.,* modest scope, the requirement for potentially explosive reagents, low yields, and long reaction times), and new synthetic methods are of great current interest.

An attractive approach to address this challenge would be the development of Pd-catalyzed coupling reactions to produce aryl fluorides. The extraordinary success of other C–X bond forming reactions using Pd catalysis provides reasonable precedent to pursue the use of Pd towards the generation of aryl fluorides. In the literature there are two main proposed mechanisms for aryl fluorination using palladium: reductive fluorination and oxidative fluorination. More commonly pursued, reductive fluorination involves a Pd^0/Pd^{II} mechanism in which the essential step to introduce fluorine into the arene features the reduction of Pd^{II} to Pd^0 (for more detailed discussion see Chapters 1 and 4).[4] This mechanism is commonly implicated in the conversion of aryl halides and triflates to aryl fluorides.

Alternatively, oxidative fluorination is often invoked in the conversion of aryl boronic acids, stannanes, silanes and C–H bonds to aryl fluorides. [5,6] The key step in introducing fluorine into the arene involves an oxidation of Pd^{II} to Pd^{IV} by an electrophilic fluorine reagent (F^+). This mechanism involves the following: (i) C–H activation or transmetallation to Pd^{II}, (ii) oxidation of Pd^{II} by F^+ to Pd^{IV} and finally (iii) C–F bond forming reductive elimination (Scheme 5.1).

(i) C–H activation or transmetallation
(ii) oxidation by F^+
(iii) reductive elimination

Scheme 5.1 – Mechanism of Oxidative Fluorination

As shown in Scheme 5.2, both processes would involve the formation of a Pd(Ar)(F) species as a key intermediate.

Scheme 5.2 – Reductive (a) and Oxidative Aryl Fluorination (b)

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Aryl–X (X = Cl, Br, and I) bond-forming reactions using a reductive halogenation strategy is well-precedented from $Pd^{II}(Ar)(X)$ complexes;[7,8] however, achieving Aryl–F coupling from $Pd^{II}(Ar)(F)$ adducts has proven extremely challenging. Instead, upon thermolysis most Pd^{II} complexes are prone to a variety of side reactions that do not result in the desired aryl fluoride (for more detail, refer to Chapter 4, Scheme 4.4).[4,9] The first suggestion of Aryl–F bond formation from Pd^{II} was reported by Yandulov in 2007. That report described C–F bond-forming reductive elimination from a $Pd^{II}(Ar)(F)$ dimer with a highly activated p-NO$_2$-substituted aryl group in the presence of Buchwald's ligand (BL) in 10% yield (Scheme 5.3).[9] Interestingly, a subsequent investigation by Grushin determined that $Pd^{II}(Ar)(F)$ dimers with more electron-donating arenes did not produce aryl fluorides. As such, he argued that the aryl fluorination in Yandulov's system was not due to direct Aryl–F bond-forming reductive elimination, but a result of nucleophilic aromatic substitution (Scheme 5.3). These examples further highlight the challenges of the reductive fluorination strategy.

Scheme 5.3 –Reductive Fluorination from Palladium(II) Dimers

In contrast, several recent reports have shown that aryl fluorides can be formed by reacting Pd^{II}–Ar complexes with electrophilic fluorination reagents via oxidative fluorination. In 2006, our group demonstrated a Pd^{II}-catalyzed ligand-directed fluorination of Aryl–H bonds with N-fluoropyridinium reagents as an oxidant under microwave conditions (Scheme 5.4).[5] However, it was unclear whether the oxidative fluorination proceeded via a Pd^{II}/Pd^{IV} mechanism or by oxidative cleavage of the Pd–C bond.

Scheme 5.4 – Ligand-Directed Pd-Catalyzed Fluorination of Aryl C–H Bonds

In 2008, Ritter provided significant evidence towards a Pd^{II}/Pd^{IV} mechanism in our group's Pd-catalyzed ligand directed C–H activation/fluorination reaction by demonstrating C–F bond-forming reductive elimination from an analogus $Pd^{IV}(Ar)(F)$ complex, (Scheme 5.5).[6c]

Scheme 5.5 – Aryl C–F Bond-Forming Reductive Elimination from a Pd^{IV} Compound

Our group's goal was to expand the scope of Pd-catalyzed oxidative fluorination beyond arenes with a tethered chelating group to a more general transformation where the source of arene could vary from benzene to an aryl boronic acid (Scheme 5.6).

Scheme 5.6 – Conversion of a Variety of Arenes to Aryl Fluorides Using Oxidative Fluorination

Towards this goal, stoichiometric reactions of Pd^{II} σ-aryl species containing an aryl ligand without a chelating group with *N*-fluoropyridinium salts were shown to afford

modest yields of aryl fluorides (Scheme 5.7-a),[6a] and a related stoichiometric reaction with Selectfluor was recently optimized (Scheme 5.7-b).[6b] While these transformations were proposed to proceed through a Pd^{II}/Pd^{IV} mechanism, the isolation of an aryl Pd^{IV} fluoride complex without a tethered chelating group on the arene has proven challenging. [10,11]

Scheme 5.7 – Stoichiometric Examples of Oxidative Fluorination at Palladium

My research goal was to design such an isolable $Pd^{IV}(Ar)(F)$ species and study its reactivity towards Aryl–F bond-formation. This chapter will describe the design, synthesis, and reactivity of an isolable $Pd^{IV}(Ar)(FHF)$ complex. This work provides a basis for the development of new $Pd^{II/IV}$-catalyzed Aryl–F coupling reactions.[12]

5.2 – Synthesis of Aryl Pd^{II}–F Precursor

Our efforts focused on the design of a stable Pd^{IV}–F complex that would balance stability with reactivity. Prior work by our group and Canty provided evidence that Pd^{IV} complexes can be stabilized by rigid bidentate sp^2 N-donor ligands such as 2,2′-bipyridine (bpy).[11,13] We also reasoned that multiple fluoride ligands would enhance the stability of the desired intermediate, as PdF_4 was one of the first reported compounds with Pd in the +4 oxidation state.[14] Finally, the use of a *p*–fluorophenyl group as the arene would help us account for the inorganic/organic products by ^{19}F NMR

spectroscopy. We anticipated that these features would allow us to obtain a Pd^{IV}–F intermediate that is amenable to isolation but sufficiently reactive to promote C–F bond formation. Based on these considerations, (bpy)Pd^{IV}(Ar)(F)$_3$ (bpy = 2,2'-bipyridine) was identified as our initial synthetic target.

R = H   X = F   (**5-1a**)

R = tBu   X = F   (**5-3a**)
                CF$_3$ (**5-3b**)
                OMe (**5-3c**)

(**5-2a**), 8%

(**5-4a**), 83%
(**5-4b**), 77%
(**5-4c**), 45%

Scheme 5.8 – Synthesis of (L~L)Pd(p-XPh)(F) complexes

The Pd^{II} precursor (bpy)Pd^{II}(p-FC$_6$H$_4$)(F) (**5-2**) was prepared by sonication of (bpy)Pd^{II}(p-FC$_6$H$_4$)(I) (**5-1**) with AgF in benzene for 3 h at 40 °C (Scheme 8).[14a] Unfortunately, **5-2** was isolated in only 8% yield due to the low solubility of this complex. The isolated yellow solid also contained an unidentified side-product and was insoluble in many solvents. To ameliorate this issue of solubility, we switched from bpy to dtbpy (dtbpy = 4,4'-di-$tert$-butyl-2,2'-bipyridine). Gratifyingly, (dtbpy)Pd^{II}(p-FC$_6$H$_4$)(F) (**5-4a**) could be prepared from the corresponding iodide (**5-3**) in 83% isolated yield (Scheme 5.8). Additionally other (dtbpy)Pd(p-XPh)(F) complexes where X = CF$_3$ (**5-4b**) and OMe (**5-4c**) were prepared similarly in 77% and 45% yield respectively.

Analysis of **5-4a** by ^{19}F NMR spectroscopy showed a characteristic broad resonance at –340.7 ppm (Pd**F**) along with a peak at –122.9 ppm (Ar**F**) in a 1 : 1 ratio. The ^{1}H NMR spectrum of **5-4a** contained signals indicative of an unsymmetrical square planar Pd^{II} complex, with the 6- and 6'-protons of the dtbpy ligand appearing at 8.08 ppm and 8.74 ppm, respectively. Notably, (dtbpy)Pd(F)$_2$ was also present in 8% yield (see Section 5.7).

5.3 – Oxidative Fluorination of Aryl Pd(II) Fluorides

We next examined the reactivity of **5-4a** with XeF$_2$ in order to introduce additional fluorine ligands to stabilize a Pd^{IV} intermediate. Gratifyingly, the combination of **5-4a** with 3 equiv of XeF$_2$ in nitrobenzene at 90 °C for 1 h afforded **5-5a**, in 57% yield (Table 5.3,

entry 1). In addition, the biaryl species **5-6a** and fluorobenzene were also generated as minor side products in 7% and 5% yield, respectively. Aryl–F bond formation was not observed at lower temperatures (Table 5.1). At lower temperatures a mixture of starting material **5-4a** and XeF$_2$ were observed by ^{19}F NMR spectroscopy. It was only upon heating to higher temperatures the starting material disappeared and **5-5a** was formed cleanly. Lower equivalents of XeF$_2$ resulted in decreased yield of **5-5a** and higher yield of the biaryl **5-6a** (Table 5.2, entry 2). Additional equivalents of XeF$_2$ also did not improve the yield of Aryl–F bond product (Table 5.2, entries 3 – 6). Importantly, without oxidant, thermolysis of **5-4a** in nitrobenzene at 90 °C did not yield **5-5a** (Table 5.2, entry 1).

Table 5.1 – Temperature Study of the Reaction of **5-4a** with XeF$_2$

Entry	Temperature (°C)	5-5a	5-6a
1	25	<2%	<2%
2	40	<2%	<2%
3	60	<2%	<2%
4	90	57%	7%

Table 5.2 – Optimization of XeF$_2$ Equivalents in the Reaction of **5-4a** with XeF$_2$

Entry	Eq of XeF$_2$	5-5a	5-6a
1	0	0%	0%
2	1	2%	14%
3	3	57%	7%
4	5	48%	8%
5	10	45%	6%
6	15	46%	5%

Other solvents were screened for this reaction. However, XeF_2 reacted vigorously with these solvents resulting in fluorination of the solvent molecules (e.g. CH_2Cl_2, $CHCl_2$, most aromatic solvents and acetone). It was very important for all solvents to be as dry as possible due to the violent reaction of XeF_2 with water. However, due to the hygroscopic nature of the (dtbpy)Pd(Ar)(F) complexes (see Section 5.5 for more details) and despite rigorous attempts to dry nitrobenzene (see Section 5.5), water could not be eliminated completely from the system. As a consequence, it was demonstrated that oxidative fluorination was indeed sensitive to the amount of water present in the reaction. Nearly identical yields of aryl fluoride **5-5a** and biaryl **5-6a** were obtained when 1 equiv of H_2O was added to the reaction of **5-4a** with XeF_2. However, the addition of 5 equiv of H_2O led to an erosion of the yield of **5-5a** (to 3%) and a significant increase in the formation of **5-6a** (75%).

This C–F bond-forming reaction also proceeded efficiently with electronically diverse Ar groups. For example, Pd^{II}(Ar)(F) complexes containing electron withdrawing (**5-4b**) and donating (**5-4c**) substituents on the Ar rings also reacted with XeF_2 to afford aryl fluorides (**5-5b** and **5-5c**) in comparable yields to **5-5a** (Table 5.3).[15]

Table 5.3 – C–F Bond Formation with Electronically Diverse Ar Groups

Entry	X	compound	Yield 4-5	Yield 4-6
1	F	**5-4a**	57%	7%
2	CF$_3$	**5-4b**	60%	3%
3	OMe	**5-4c**	45%	6%

5.4 – Isolation of (dtbpy)Pd(*p*-FPh)(F)$_2$(FHF), 5-7

The fluorination of **5-4a** was monitored at lower temperatures in an effort to observe a reactive intermediate. We were pleased to find that stirring **5-4a** with XeF_2 at 70 °C for 2.5 min afforded a new organometallic species (**5-7**), which was isolated in 38% yield by

recrystallization from THF/pentanes (Scheme 5.9). ^{1}H NMR spectroscopy of **5-7** revealed five aromatic protons and one resonance at 1.42 ppm (18 H, *tert*-butyl groups) indicating a symmetric complex (Figure 5.1). The ^{19}F NMR spectrum of **5-7** at 25 °C showed three broad resonances in a 1 : 1 : 2 ratio at –117.2 (Ar**F**), –206.3 (Pd**F**), and –257.4 (Pd**F**) ppm, respectively (Figure 5.2).

Scheme 5.9 – Synthesis of (dtbpy)Pd(*p*-FPh)(F)$_2$(FHF), **5-7**

Figure 5.1 – ^{1}H NMR spectrum of **5-7** in d_5-PhNO$_2$

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Figure 5.2 – ^{19}F NMR spectrum of **5-7** in d_5-PhNO$_2$

Interestingly, a resonance corresponding to the bifluoride ligand proton was observed in d_5–PhNO$_2$ at room temperature as a very broad singlet in the baseline spanning from ~12 – 13 ppm. This broadening is most likely due to the dynamic nature of the bifluoride ligand in solution to form several species in fast equilibrium. Grushin and Perutz have reported this behavior with several Pd^{II} and Pt^{II} bifluoride complexes concluding that the equilibria are fast on a NMR time scale, thereby leading to significant signal broadening.[16] However, the broad proton and fluorine resonances were resolved into their respective doublet of doublet and doublet by lowering the temperature of the NMR sample.

To whether a similar phenomenon was observed in our system, we conducted low temperature NMR spectroscopy studies of **5-7** in CD$_2$Cl$_2$. CD$_2$Cl$_2$ was chosen as an NMR solvent because of the high freezing point of d$_5$-nitrobenzene (~4 °C). A solution of **5-7** in CD$_2$Cl$_2$ was cooled to –60 °C. By ^{19}F NMR spectroscopy a fourth resonance was observed as a doublet of doublets at –177.6 ppm; furthermore, the Pd–F peaks sharpened considerably and appeared as a multiplet (–204.4 ppm) and doublet (–256.9

ppm), respectively (Figure 5.3). This spectroscopic data, along with a doublet of doublets at 12.7 ppm in the low temperature ^{1}H NMR spectrum (Figure 5.4), is consistent with the formulation of **5-7** as (dtbpy) Pd^{IV}(Ar)(F)$_2$(FHF).[16] It is to be noted that **5-7** demonstrated significant reactivity with CD$_2$Cl$_2$ at room temperature (Figure 5.4) as indicated by the extra aromatic protons seen in Figure 5.4 corresponding to a side product that could not be identified.

Figure 5.3 – ^{19}F NMR spectrum of **5-7** in CD$_2$Cl$_2$ at –60 °C.

Figure 5.4 – ^{1}H NMR spectrum of **5-7** in CD$_2$Cl$_2$ at 22 °C and –80 °C.

X-ray quality crystals were obtained as colorless blocks from a solution of **5-7** in acetone/pentanes at – 30 °C. The structure was determined by X-ray crystallography corroborating the proposed structure by the solution-phase NMR studies (Figure 4.5). The reaction of XeF$_2$ with water produces Xe gas, 2 equivalents of HF, and O$_2$.[17] The HF observed in this system is likely due to the reaction of XeF$_2$ to adventitious water present in the reaction (section 5.3), Bifluoride ligands in similar systems are often polarized with one F–H bond longer than the other. This results in a bifluoride ligand with characteristics of a M–F bond hydrogen bonded to HF (M–F...HF). In **5-7** the fluoride bound to Pd^{IV} is 1.29 Å from the H. This distance is longer than that of the terminal fluoride bound to the same hydrogen (1.07 Å). These values are consistent with similar Pd and Pt systems with polarized bifluoride ligands.[16] This polarization is even more pronounced in the solution phase. At –80 °C by ^{1}H NMR spectroscopy, we observe drastically different coupling constants (J = 386 and 38 Hz). This polarization will have

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important consequences for the reactivity of **5-7** discussed in Section 5.5. Notably, this is the first reported example of a Pd[IV] bifluoride and a rare example of a mono-aryl Pd[IV] complex that is not stabilized by an σ-aryl ligand with an ortho chelating group.[18]

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Figure 5.5 – ORTEP Drawing of Complex **5-7**. Thermal Ellipsoids Are Drawn at 50% Probability, Hydrogen Atoms Are Omitted For Clarity Unless Otherwise noted. Selected Bond Lengths (Å): Pd–C(19) 1.883(10), Pd–C(25) 1.983(9), Pd–N(1) 1.968(3), Pd–N(2) 1.977(2), Pd–F(1) 1.9307(19), Pd–F(2) 1.9226(18), Pd–F(3) 2.113(2). Hydrogen Bonds of Bifluoride Ligand: F(5)-H(5F)…F(3) 2.344(3), F(5)-H(5F) 1.05(7), H(5F)….F(3) 1.29(7). Selected Bond Angles (°): C(19)–Pd(1)–F(1) 84.5(3), C(19)–Pd(1)–F(2) 87.1(3), C(19)–Pd(1)–F(3) 174.9(3), F(1)–Pd(1)–F(2) 92.11(9), C(19)-Pd(1)-N(1) 95.0(3), C(19)-Pd(1)-N(2) 95.5(3), F(1)-Pd(1)-N(1) 175.21(8), F(2)-Pd(1)-N(1) 175.21(8), F(5)-H(5F)…F(3) 176(7).

5.5 – Aryl Fluoride Formation from (dtbpy)Pd(*p*-FPh)(F)$_2$(FHF), 5-7

We next investigated the reactivity of **5-7** towards Aryl–F bond-forming reductive elimination. Intriguingly, heating this complex at 80 °C for 1 h in nitrobenzene led to only

traces of aryl fluoride **5-3a**. Instead, significant quantities (35%) of biaryl **5-6a** were observed (Table 5.4, entry 1).[19] This is in surprising contrast to a related Pd[IV] aryl fluoride, which underwent quantitative C–F bond-forming reductive elimination upon thermolysis (Scheme 5.5-c).[6c] This result suggests that direct C–F coupling at **5-7** is slow relative to σ-aryl/F⁻ exchange between Pd centers (which is the likely pathway to Aryl–Aryl coupling).[19] The aryl exchange process is likely facilitated in this system because the σ-aryl group is not stabilized by a chelating group (Scheme 5.10).[6c,19]

Scheme 5.10 – Potential Pathway to Biaryl **5-6a** Formation by Ar/F ⁻ Exchange Between Two Equivalences of **5-7**

Table 5.4 – Reactivity of **5-7** with Electrophilic Oxidants

(5-7)

Entry	Oxidant–X	X	Yield of 5a
1	none	-	<2% [a]
2	XeF_2	F	92%
3	PhO_2S, $N–F$, PhO_2S	F	83%
4	(N-fluoro-2,6-dimethylpyridinium BF_4^-)	F	50%
5	(N-bromosuccinimide)	Br	≥95%
6	Cl—I—Cl (Ph)	Cl	65% [b]
7	AcO—I—OAc (Ph)	OAc	9% [c]

[a] 4,4'-difluorobiphenyl (**5-6a**) was formed in 35% yield [b] 1-chloro-4-fluorobenzene was formed in 18% yield. [c] 1-acetoxy-4-fluorobenzene was formed in 87% yield.

Our oxidant studies of (dtbpy)Pd(*p*-FPh)(F) compound (**5-4a**) demonstrated that with 1 equiv of XeF_2, trace amounts of C–F bond-forming product **5-5a** were formed (2%) (Table 5.2, entry 2). However an excess of oxidant relative to **5-4a** significantly increased the yield (Table 5.2). We hypothesized that perhaps XeF_2 was not only needed for the formation of Pd^{IV} intermediate **5-7** but also for C–F bond formation. In addition, this would be a comparable scenario in any catalytic C–F bond-forming reaction where there would be an excess of electrophilic fluorinating reagent relative to the Pd^{IV}(Ar)(F) intermediate. As such, we next investigated the thermolysis of **5-7** in the

presence of the electrophilic fluorinating reagents XeF$_2$, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, and *N*-fluorosulfanamide. We were delighted to find that under these conditions, the C–F coupled product **5-5a** was obtained in good to excellent yield, along with only trace amount (<5%) of **5-6a** (Table 5.4, entries 2-4).

The Aryl–F bond formation from **5-7** in the presence of excess F$^+$ could occur by electrophilic cleavage of the Pd^{IV}–aryl bond instead of direct C–F bond forming reductive elimination. To test this hypothesis, **5-7** was heated in the presence of a variety of electrophilic–X reagents (X = Br, Cl and OAc). Thermolysis in the presence of *N*-bromosuccimide (NBS) resulted in ≥95% of **5-5a** indicating the fluorine in the organic product does not originate from the electrophilic reagent. In contrast, heating **7** with PhI(Cl)$_2$ and PhI(OAc)$_2$ resulted in significant amounts of 1-chloro-4-fluorobenzene and 1-acetoxy-4-fluorobenzene, respectively (Table 5.4, entries 6-7).

5.6 – Potential Mechanisms Explaining the Role of Excess Electrophilic Reagent in C–F Bond Formation from 5-7.

There are several possible mechanisms for the role of an additional electrophilic reagent towards the promotion Aryl–F formation from **5-7**. Additionally, mechanisms for each reagent can be similar or proceed through their own pathways. With this in mind, a report by Perutz et al. provides an example of the reactivity of a Pt bifluoride compound [Pt(PCy$_3$)$_2$H(FHF)] with a variety of electrophiles.[16a] For example [Pt(PCy$_3$)$_2$H(FHF)] in the presence of acetyl chloride (CH$_3$COCl) in THF results in the formation of acetyl fluoride (CH$_3$COF) and [Pt(PCy$_3$)$_2$H(Cl)] (Scheme 5.11). This transformation is proposed to occur by a nucleophilic substitution mechanism. In the mechanism, an attack of the acetyl chloride by F$^-$ from the bifluoride ligand releases a chloride ion that coordinates to the Pt by-product and results in the acetyl fluoride.

Scheme 5.11 – Reaction of (PCy$_3$)$_2$Pt(H)(FHF) with Acetyl Chloride in THF

Electrophilic Fluorinating Reagents and 5-7

This type of reactivity is also demonstrated with other electrophiles including CH_3I, $(CH_3)_3SiOTf$ and $(CH_3)_3SiN_3$ (Scheme 5.12-a and b). A comparable mechanism could be operational in our system where the bifluoride ligand of **5-7** undergoes a nucleophilic substitution with F^+ reagents, NBS, $PhI(Cl)_2$, and $PhI(OAc)_2$ acting as the electrophiles. The following paragraphs will discuss how the mechanism implicated by Perutz could explain the results found in Table 5.4 with each of these electrophilic reagents. During this discussion there will be initial results and proposed future experiments that probe this mechanism.

$$\text{(a)} \quad \underset{\underset{PCy_3}{|}}{\overset{\overset{PCy_3}{|}}{H{-}Pt{-}F}}{\cdots}HF \;+\; CH_3I \;\xrightarrow[\;-HF\;]{}\; \underset{\underset{PCy_3}{|}}{\overset{\overset{PCy_3}{|}}{H{-}Pt{-}I}} \;+\; CH_3F$$

$$\text{(b)} \quad \underset{\underset{PCy_3}{|}}{\overset{\overset{PCy_3}{|}}{H{-}Pt{-}F}}{\cdots}H_2F \;+\; (CH_3)_3SiX \;\xrightarrow[\;-HF\;]{}\; \underset{\underset{PCy_3}{|}}{\overset{\overset{PCy_3}{|}}{H{-}Pt{-}X}} \;+\; (CH_3)_3SiF$$

X = OTf
or N_3

Scheme 5.12 – Reaction of $(PCy_3)_2Pt(H)(FHF)$ with Other Electrophiles

The mechanism involving C–F bond formation from **5-7** in the presence of electrophilic fluorinating agents could proceed through the aforementioned nucleophilic substitution mechanism purposed by Perutz or through F^+ cleavage. In a nucleophilic substitution mechanism involving **5-7** and *N*-fluoro-2,4,6-trimethylpyridium tetrafluoroborate (NFTPTB) the N–F bond could be attacked at the fluorine resulting in the formation of F_2 and a cationic Pd^{IV} species (**5-8**) with the 2,4,6-collidine ligand bound (Scheme 5.13).

Scheme 5.13 – Mechanism of *N*-Fluoro-2,4,6-Trimethylpyridium Tetrafluoroborate Reacting with **5-7**

Similarly, the reaction of **5-7** and *N*-fluorobenzosulfonimide would result in a neutral Pd^{IV} complex (**5-9**) with the benzosulfonimide ligand on the palladium (Scheme 5.14). Aryl C–F bond-forming reductive elimination from either **5-8** or **5-9** would result in the C–F product **5-5a.**

Scheme 5.14 – Mechanism of *N*-fluorosulfonimide Reacting with **5-7**

Unlike the other electrophilic fluorinating reagents, XeF$_2$ can undergo significantly different chemistry. More specifically, XeF$_2$ is known to be a good fluoride ion (F$^-$) donor. This characteristic would also allow it to be a good hydrogen bond acceptor.[20] In our system, this potential interaction might result in competitive hydrogen bonding between a fluoride of XeF$_2$ and the Pd^{IV}–fluoride with HF (Scheme 5.15). The XeF$_2$ fluorines could out-compete that of Pd^{IV}–F in hydrogen bonding to HF, resulting in the formation of (dtbpy)Pd(*p*–FPh)(F)$_3$ (**5-10**) and [XeF$^+$][FHF $^-$] (Scheme 5.15).[20] This transformation would be favored thermodynamically since the hydrogen bond of a bifluoride ion (e.g. F--
--HF) is one of the strongest found in chemistry with a bond strength >155 kJ mol^{-1}.[21] From **5-10** Aryl–F bond-forming reductive elimination would occur. Other bifluoride salts

like $[XeF^+][FHF^-]$ have been reported in the literature. For example $[Ru(dmpe)_2H^+][HF^-]$ at $-85\ °C$ by ^{19}F NMR spectroscopy has a resonance at -150.9 ppm as a broad doublet. At the end the oxidative fluorination reactions of **5-4a** with XeF_2 we also observe a broad resonance (singlet) at ~ -150 ppm (at $23\ °C$) by ^{19}F NMR spectroscopy suggesting that a $[XeF^+][FHF^-]$ could be present. This preliminary observation provides some evidence towards the proposed mechanism. Further experiments focused on the isolation of the inorganic product after oxidative fluorination of **5-4a** would be instrumental in providing addition support towards the proposed mechanism.

Scheme 5.15 – Mechanism of the Reaction of XeF_2 and **5-7** Towards the Ar C–F Bond Formation

Hypervalent Iodine Reagents and 5-7

Nucleophilic substitution with F^- of hypervalent iodine reagents has been demonstrated previously in the literature with the quantitative conversion of $PhI(OAc)_2$ to $PhI(F)_2$ with excess TBAF (tetra-*N*-butylammonium fluoride) (Scheme 5.16).[22] With this precedent in hand, one can envision a similar mechanism with F^- (from the bifluoride ligand of **5-7**) and electrophilic hypervalent iodine reagents $PhI(Cl)_2$ and $PhI(OAc)_2$. The attack of F^- on the iodide of $PhI(X)_2$ (X = Cl or OAc) could result in the formation of $PhI(X)(F)$ and $(dtbpy)Pd^{IV}(pFPh)(F)_2(X)$ **(5-11)** (Scheme 5.17). From $(dtbpy)Pd^{IV}(pFPh)(F)_2(X)$ either direct C–F bond-forming reductive elimination would occur, or a reversible dissociation of X^- from **5-11** and isomerization forming **5-12**. This isomerization of **5-11** to **5-12** would orient the aryl group *cis* to X resulting in either C–F or C–X bond formation (Scheme 5.17).

Scheme 5.16 – Conversion of PhI(OAc)$_2$ to PhI(F)$_2$ with TBAF in MeCN

Scheme 5.17 – Mechanism of the Reaction of **5-7** with Hypervalent Iodine Reagents Towards the Production of C –F (**5-5a**) and C–X (X = Cl or OAc) products

The C–X (X= Cl or OAc) bond formation could also result from electrophilic cleavage of the Pd^{IV}–aryl bond (Scheme 5.17). This mechanism would obviate the need for X to be coordinated to Pd^{IV} in order to achieve C–X bond forming reductive elimination. To explore this possibility, we reacted (dtbpy)Pd(*p*-FPh)(Cl) (**5-13**) and (dtbpy)Pd(*p*-FPh)(I) (**5-3a**) with XeF$_2$ under our oxidative fluorination conditions. In order to couple the aryl and X ligands in reductive elimination, the two groups must be in a *cis* configuration about the metal. There is considerable literature precedent that XeF$_2$ oxidation of Pd and

Pt compounds occur with *cis* addition.[6c,23] Therefore in these reactions, an intermediate similar to **5-12** with the aryl and X groups in a *cis* orientation is plausible allowing C–X bond-forming reductive elimination (Scheme 5.18). This is in contrast to a Pd[IV] intermediate **5-11** where the aryl group and X are *trans* across the metal center eliminating the possibility of C–X coupling (Scheme 5.18).

Scheme 5.18 – C–F Reductive Elimination from Pd(IV) Isomers **5-11** and **5-12**

Subjecting (dtbpy)Pd(*p*-FPh)(Cl) (**5-13**) and (dtbpy)Pd(*p*-FPh)(I) (**5-3a**) under the oxidative fluorination conditions resulted in 73% and 53% yield respectively of the C-Cl and C-I products with trace amounts of C–F product **5-5a** (Table 5.5). While these experiments do not completely rule out C–X bond-forming electrophilic cleavage, it lends further support toward the hypothesis that C–X bond formation from **5-7** in the presence of hypervalent iodine reagents can occur from direct C–X bond reductive elimination from Pd[IV].

Table 5.5 – Chemoselectivity Study of **5-13** and **5-3a** with XeF$_2$

Entry	Compound	X	Yield of 5-5a	Yield of C–X
1	**5-13**	Cl	11	73
2	**5-3a**	I	3	53

N-Bromosuccinimide and 5-7

The reagent NBS has the ability to react either in an ionic mechanism or radical mechanism with a variety of reagents.[24] The reaction of **5-7** with NBS (Table 5.4, entry 5) lead exclusively to high yields of Aryl–F bond formation with no C–Br product observed. Unlike with the hypervalent iodine reagents, the absence of C–Br produce suggest that Br coordination to Pd^{IV} is unlikely. Alternatively, if NBS assisted Aryl–F bond formation from **5-7** proceeded through an analogous mechanism proposed for the hypervalent iodine reagents, F$^-$ attack on Br would yield "BrF", HF and succinimide anion resulting in Pd^{IV} succinimide intermediate, (dtbpy)Pd^{IV}(pFPh)(F)$_2$(succinimide) (**5-14)** or isomer **5-15** (Scheme 5.19).

Scheme 5.19 – Proposed Mechanism of the Reaction of **5-7** with NBS to Yield of **5-5a**

The same products can also be envisioned for a radical mechanism. An analogous example from our group is the compound $(phpy)_2Pd^{IV}(Cl)(succinimide)$ (phpy = 2-phenylpyridine). Thermolysis of this compound resulted in highly chemoselective C–Cl bond formation (67% yield) over C–N bond formation (Scheme 5.20).

Scheme 5.20 – Reaction of $(phpy)_2Pd^{IV}(Cl)(succinimide)$

With this precedent in hand, it is reasonable to propose that a $(dtbpy)Pd^{IV}(pFPh)(F)_2(succinimide)$ intermediate (**5-14** or **5-15**) would exhibit similar reactivity and also favor C–F bond-forming reductive elimination over C–N. This would also be the case in the reaction of *N*-fluorosulfonimide with **5-7** (Scheme 5.14) where C–

N bond formation would not be likely. Future work to obtain evidence towards this mechanism could be pursued focusing on the isolation of an intermediate like **5-14** or **5-15** and demonstrating the production of **5-5a**.

5.7 – Conclusion

In conclusion, this chapter describes the synthesis of a stable $Pd^{IV}(Ar)(F)_2(FHF)$ complex that undergoes Aryl–F bond formation in the presence of "F$^+$" sources. The results presented herein are remarkable for several reasons. First, the facile formation of **5-7** suggests that the intermediacy of such Pd^{IV} bifluoride species should be considered in catalytic C–F coupling processes, particularly where water has not been rigorously excluded. Second, the fact that the σ-aryl ligand of **5-7** is not stabilized as part of a chelate makes this complex directly relevant to the development of Pd-catalyzed coupling reactions to form electronically diverse simple aryl fluorides. Third, the oxidant-promoted C–F coupling at **5-7** demonstrates the viability of this step in stoichiometric[9] and catalytic[5] oxidative fluorination reactions. The observed stability of **5-7** at room temperature also suggests that Aryl–F formation may be turnover-limiting in $Pd^{II/IV}$-catalyzed fluorinations. Finally, the similar reactivity of electron rich and electron deficient Pd–Ar species provides further precedent for the generality of these transformations.[6b] This work serves as a foundation for the development of $Pd^{II/IV}$-catalyzed couplings between electrophilic fluorinating reagents and aryl stannanes, boronic acids, and/or silanes.

5.8 – Recent Advances

Since the publication of this work there have been two major reports regarding reductive and oxidative fluorination. In 2009, Buchwald and co-workers reported the Pd-catalyzed conversion of aryl triflates to aryl fluorides using a CsF and BrettPhos (Scheme 5.21). Additionally, they were able to isolate a $(L)Pd^{II}(Ar)(F)$ complex **5.16** (L = *t*BuBrettPhos, Ar = 4-fluoro-3-methylbenzonitrile) where upon thermolysis, the corresponding aryl fluoride formation was achieved in 25% yield. This was the first example of Ar C–F bond-forming reductive elimination from Pd^{II} (Scheme 5.22). This landmark example is the first report of Pd^0/Pd^{II}-catalyzed formation of aryl fluoride.[25]

Scheme 5.21 – Pd-catalyzed Conversion of Aryl Triflate to Aryl Fluoride

Scheme 5.22 – C–F Bond-Forming Reductive Elimination from Pd^{II}

Yu and co-workers report an additional example of ligand-direct C–H activation/fluorination through oxidative fluorination using triflamide-protected benzylamines, *N*-fluoro-2,4,6-trimethylpyridium triflate (NFTPT), and *N*-methypyrrolidinone (NMP) as a promoter. This report was an improvement over a similar reaction reported by our group because it did not require microwave conditions and the protected amine directing group could be readily cleaved and converted to other functional group (e.g. aldehydes, azides, and cyanates) (Scheme 5.23).[26]

Scheme 5.21 Pd-Catalyzed Fluorination of a Triflamide-Protected Benzylamine

5.9 – Experimental Procedures

General Considerations

NMR spectra were obtained on a Mercury 300 (300.00 MHz for ^{1}H; 282.35 MHz for ^{19}F), Varian Inova 400 (399.96 MHz for ^{1}H; 376.34 MHz for ^{19}F; 100.57 MHz for ^{13}C), a MR400 (400.53 MHz for [1]H: 376.87 MHz for ^{19}F; 100.71 MHz for ^{13}C) spectrometer. [1]H, ^{19}F and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced on a unified scale, where the single primary reference is the frequency of the residual solvent peak in the ^{1}H NMR spectrum.[27] Several ^{19}F NMR experiments were conducted using "No-D" parameters and are noted accordingly.[28] [1]H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), quartet (q), and multiplet (m). Atlantic Microlabs in Norcross, Georgia, conducted elemental analyses. Sonication was performed using a VWR Model 75H7 ultrasound bath, with the temperature regulated by a Neslab RTE-111 recirculating chiller. IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer.

Materials and Methods

The palladium complexes Pd(dba)$_2$[29] and (dtbpy)PdCl$_2$[30] were prepared according to literature procedures. Authentic samples of biaryl products **5a–c** were prepared as described in the literature by McClure and co-workers.[31] AgF, XeF$_2$, 1-fluoro-4-iodobenzene, 1-iodobenzotrifluoride, 1,4-difluorobenzene (**5-5a**), and 4-fluorobenzotrifluoride (**5-5b**) were obtained from Matrix Chemicals. 4,4′-Di-*tert*-butyl-2,2′-bipyridine, 4-iodoanisole, 1-chloro-4-fluorobenzene, 1-fluoro-2,4,6-trimethylpyridium tetrafluoroborate, and *N*-fluorosulfanimide were obtained from Aldrich. 4-Fluoroanisole (**5-5c**) was obtained from Acros. All reagents were used as received. Nitrobenzene-d_5, CD$_2$Cl$_2$, and CDCl$_3$ were obtained from Cambridge Isotope Laboratories, and nitrobenzene was obtained from Acros. All other solvents were obtained from Fisher Chemical. Tetrahydrofuran, dichloromethane, and pentane were purified using an Innovative Technologies (IT) solvent purification system consisting of a copper catalyst, activated alumina, and molecular sieves. CD$_2$Cl$_2$ was distilled from CaH$_2$. Acetone was distilled from CaSO$_4$. Nitrobenzene and nitrobenzene-d_5 were distilled from P$_2$O$_5$ and placed over 4Å molecular sieves. Benzene and hexanes were distilled from

Na[0]/benzophenone. All syntheses were conducted using standard Schlenk techniques or in an inert atmosphere glovebox unless otherwise stated.

General procedure for the synthesis of complexes **5-3a – 5-3c**: Under nitrogen, Pd(dba)$_2$ (2.9 g, 5.1 mmol, 1.0 equiv) was weighed into a 250 mL round bottom flask and dissolved in THF (72 mL). 4, 4′-Di-*tert*-butylbipyridine (1.9 g, 6.6 mmol, 1.3 equiv) was added, and the resulting mixture was stirred at 25 °C for 15 min. The aryl iodide (7.1 mmol, 1.4 equiv) was added, and the reaction was warmed to 60 °C for 3 h. The reaction mixture was filtered through a plug of Celite, and the solvent was removed under reduced pressure. The resulting solid was washed with hexanes (3 x 50 mL) and then with a 50:50 mixture of ether and hexanes (~400 mL) until residual dibenzylidene acetone (dba) was completely removed. The product was then redissolved in CH$_2$Cl$_2$ (20 mL) and stirred with activated charcoal for 30 min. This suspension was filtered through a plug of Celite, and the solvent was removed *in vacuo* to yield the products as orange solids.

(dtbpy)Pd(*p*-FPh)(I) (5-3a) – Product was isolated as an orange solid (1.6 g, 31% yield). ^{1}H NMR (CDCl$_3$): δ 9.47 (d, *J* = 6 Hz, 1H), 7.95 (multiple peaks, 2H), 7.53 (d, *J* = 6 Hz, 1H), 7.48 (d, *J* = 6 Hz, 1H), 7.30 (multiple peaks, 3H), 6.81 (multiple peaks, 2H), 1.40 (s, 9H), 1.37 (s, 9H); ^{19}F NMR (CDCl$_3$): δ –123.2 (m, 1F); ^{13}C NMR (CDCl$_3$): δ 163.33, 163.27, 160.93 (d, *J* = 239.8 Hz),

155.91, 153.86, 152.52, 149.55, 138.52, 136.67 (d, *J* = 5 Hz), 123.86 (br s), 123.54, 118.43, 118.01, 113.98 (d, *J* = 19 Hz), 35.53, 35.48, 30.38, 30.26. Anal. Calc. for C$_{24}$H$_{28}$FIN$_2$Pd: C, 48.30, H, 4.73, N, 4.69; Found: C, 48.09, H, 4.75, N, 4.72. Notably, small amounts (~7%) of [(*t*-Bu-bpy)Pd(I)$_2$] were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **5-3a**.

(dtbpy)Pd(*p*-CF$_3$Ph)(I) (5-3b) – Product was isolated as an orange solid (1.1 g, 33% yield). ^{1}H NMR (CDCl$_3$): δ 9.49 (d, *J* = 6 Hz, 1H), 7.95 (multiple peaks, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.48 (multiple peaks, 2H), 7.34 (m, 1H), 7.25 (d, *J* = 8 Hz, 2H), 1.41 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CDCl$_3$): δ –61.8 (s, 3F); ^{13}C NMR

(CDCl$_3$): 163.54, 163.43, 155.94, 153.84, 153.60, 152.65, 149.52, 136.82, 125.48 (q, J = 32 Hz), 124.99 (q, J = 272 Hz), 123.97, 123.73, 123.02 (q, J = 4 Hz), 118.49, 118.05, 35.54, 35.48, 30.56, 30.23. Anal. Calc. for C$_{25}$H$_{28}$F$_3$IN$_2$Pd: C, 46.42, H, 4.36, N, 4.33; Found: C, 46.36, H, 4.33, N, 4.35. Notably, small amounts (~8%) of [(t-Bu-bpy)Pd(I)$_2$] were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **5-3b**.

(dtbpy)Pd(p-OMePh)(I) (5-3c) – Product was isolated as an orange solid (1.0 g, 33% yield) ^{1}H NMR (CDCl$_3$): δ 9.49 (d, J = 6 Hz, 1H), 7.94 (multiple peaks, 2H), 7.61 (dd, J = 6, 2 Hz, 1H), 7.48 (dd, J = 6, 2 Hz, 1H), 7.31 (dd, J = 5, 2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 6.73 (d, J = 8 Hz, 2H), 3.76 (s, 3H), 1.41 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 163.09, 163.05, 156.64, 155.87, 153.87, 153.77, 152.58, 149.86, 136.36, 134.06, 123.81, 123.46, 117.84, 113.58, 55.16, 35.48, 35.43, 30.38, 30.26. Anal. Calc. for C$_{25}$H$_{31}$IN$_2$OPd: C, 49.32, H, 5.13, N, 4.60; Found: C, 49.12, H, 5.19, N, 4.60. Notably, small amounts (~8%) of [(t-Bu-bpy)Pd(I)$_2$] were observed in the ^{1}H, and ^{13}C NMR spectra of most isolated samples of **5-3c**.

General procedure for the synthesis of complexes 5-4a – 5-4c: [(dtbpy)Pd(Ar)(I)] (3.6-3.8 mmol, 1 equiv) and AgF (3.9 equiv) were dissolved in benzene (20 mL) in a 50 mL amber glass jar. The jar was sealed with a Teflon-lined cap, and the reaction was sonicated in the dark at 25 °C for 1.5-4 h. The resulting mixture was filtered through a plug of Celite in the drybox. The plug was washed with benzene (1 x 5 mL) and then with CH$_2$Cl$_2$ (5 x 2 mL). This filtration was repeated to remove residual silver salts. The solvent was then removed under reduced pressure, and pentane was added to precipitate a yellow solid. The solid was collected and dried *in vacuo* to afford the product as a yellow solid. It should be noted that without the second filtration, the filtrate changes color from yellow to gold over several minutes, which is indicative of impurities in the product (as confirmed by ^{1}H and ^{19}F NMR spectroscopy).

(dtbpy)Pd(p-FPh)(F) (5-4a) – Product was isolated as an yellow solid (0.42 g, 83% yield). ^{1}H NMR (CD$_2$Cl$_2$): δ 8.74 (d, J = 6 Hz, 1H), 8.08 (d, J = 6 Hz, 1H), 8.00 (d, J = 2 Hz, 1H), 7.98 (d, J = 2 Hz, 1H), 7.62 (dd, J = 4, 2 Hz, 1H), 7.40 (multiple peaks, 2H), 7.29 (dd, J = 4, 2 Hz, 1H), 6.85 (dd, J = 11, 9 Hz, 2H), 1.44 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CD$_2$Cl$_2$): δ –122.9 (m,

1F), −340.67 (br s, 1F); ^{13}C NMR (CD$_2$Cl$_2$): δ 164.71, 163.88, 161.75 (d, J = 238 Hz), 157.34, 153.44, 153.05, 148.49 (d, J = 3 Hz), 146.60, 135.80 (d, J = 5 Hz), 124.27, 124.11, 119.66, 118.59, 113.54 (d, J = 19 Hz), 36.13, 35.98, 30.72, 30.47. Complex **5-4a** is extremely hygroscopic, and even after extensive drying under vacuum, ^{1}H NMR spectroscopic analysis in dry CD$_2$Cl$_2$ showed the presence of 0.60 equiv of H$_2$O/complex (observed as a broad resonance at 1.42 ppm). The microanalysis results are consistent with this stoichiometry. Anal. Calc. for C$_{24}$H$_{28}$F$_2$N$_2$Pd•0.60 H$_2$O: C, 57.68, H, 5.77, N, 5.61; Found: C, 57.89, H, 5.87, N, 5.31. Notably, traces (~3%) of [(t-Bu-bpy)Pd(F)$_2$] were observed in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of most isolated samples of **5-4a**.

(dtbpy)Pd(p-CF$_3$Ph)(F) (5-4b) – Product was isolated as an yellow solid (0.39 g, 77% yield). ^{1}H NMR (CD$_2$Cl$_2$): δ 8.74 (d, J = 6 Hz, 1H), 8.01 (multiple peaks, 3H), 7.64 (multiple peaks, 3H), 7.30 (multiple peaks, 3H), 1.45 (s, 9H), 1.39 (s, 9H); ^{19}F NMR (CD$_2$Cl$_2$): −62.10 (s, 3F), −341.6(s, 1F); ^{13}C NMR (CD$_2$Cl$_2$): δ 164.94, 164.17, 157.31, 153.45, 152.96, 148.44 (q, J = 4 Hz), 136.84, 135.87 (q, J = 3 Hz), 126.10 (q, J = 31 Hz), 125.80 (q, J = 271 Hz), 124.37, 124.11, 122.84 (q, J = 4 Hz), 119.87, 118.77, 36.17, 36.02, 30.71, 30.46. Complex **5-4b** is extremely hygroscopic, and even after extensive drying under vacuum, ^{1}H NMR spectroscopic analysis in dry CD$_2$Cl$_2$ showed the presence of 0.67 equiv of H$_2$O/complex (observed as a broad resonance at 1.41 ppm). The microanalysis results are consistent with this stoichiometry. Anal. Calc. for C$_{25}$H$_{28}$F$_4$N$_2$Pd•0.67 H$_2$O: C, 54.42, H, 5.23, N, 5.07; Found: C, 54.28, H, 5.43, N, 5.05. Notably, trace amounts (~4%) of [(t-Bu-bpy)Pd(F)$_2$] were observed in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of most isolated samples of **5-4b**.

(dtbpy)Pd(p-OMePh)(F) (5-4c) – Product was isolated as an yellow solid (0.21 g, 45% yield). Notably, trace amounts (~6%) of [(t-Bu-bpy)Pd(F)$_2$] were observed in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of most isolated samples of **5-4c**. ^{1}H NMR (CD$_2$Cl$_2$): δ 8.77 (d, J = 6 Hz, 1H), 8.17 (d, J = 6 Hz, 1H), 8.02 (d, J = 2 Hz,

1H), 7.99 (d, J = 2 Hz, 1H), 7.61 (dd, J = 4, 2 Hz, 1H), 7.31 (d, J = 8 Hz, 2H), 7.28 (d, J = 8, 2 Hz, 1H), 6.72 (d, J = 8 Hz, 2H), 3.77 (s, 3H), 1.44 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CD$_2$Cl$_2$): –338.7 (s, 1F); ^{13}C NMR (CD$_2$Cl$_2$): 164.53, 163.65, 157.64, 157.30, 153.41, 153.18, 148.48, 135.86, 135.31, 124.17, 124.05, 119.57, 118.52, 113.06, 55.63, 36.10, 35.94, 30.72, 30.47. Complex **5-4c** is extremely hygroscopic, and even after extensive drying under vacuum, ^{1}H NMR spectroscopic analysis in dry CD$_2$Cl$_2$ showed the presence of 0.86 equiv of H$_2$O/complex (observed as a broad resonance at 1.41 ppm). The microanalysis results are consistent with this stoichiometry. Anal. Calc. for C$_{25}$H$_{31}$FN$_2$OPd•0.86 H$_2$O: C, 58.26, H, 6.23, N, 5.44; Found: C, 58.02, H, 6.18, N, 5.29. Notably, trace amounts (~4%) of [(dtbpy)Pd(F)$_2$] were observed in the ^{1}H, ^{19}F, and ^{13}C NMR spectra of most isolated samples of **5-4c**.

(dtbpy)Pd(p-FPh)(F)$_2$(FHF) (5-7) – In a glovebox, **5-7** (10 mg, 0.02 mmol, 1 equiv) was dissolved in nitrobenzene (1 mL) and added to a 4 mL scintillation vial containing XeF$_2$ (10 mg, 0.06 mmol, 3 equiv). The vial was sealed with a Teflon-lined cap and stirred for 25 °C for 10 s to yield an orange solution. The reaction mixture was then stirred at 80 °C for 2 min to afford a yellow solution. Hexanes (10 mL) were added to precipitate the crude inorganic product. The resulting yellow solid was collected, washed with hexanes (3 x 2 mL), and dried *in vacuo* to yield the crude product. This material was further purified by recrystallization from THF/hexanes and was obtained as a pale yellow solid (4.1 mg, 38% yield).

^{1}H NMR (d_5-nitrobenzene): δ 9.48 (d, J = 6 Hz, 2H), 8.76 (s, 2H), 8.03 (d, 6Hz), 7.58 (m, 2H), 6.88 (m, 2H), 1.42 (s, 18H); ^{19}F NMR (d_5-nitrobenzene): δ –116.7 (m, 1F), –204.8 (m, 1F, Pd–F *trans* from C), –253.2 (br s, 2F, Pd–F *trans* from N). A minor impurity with ^{19}F NMR resonances at δ –116.6 and –247 ppm proved extremely challenging to remove completely from samples of **5-7**. ^{1}H NMR (CD$_2$Cl$_2$, 22 °C): δ12.86 (very br s, 1H, Pd–F*HF*); (CD$_2$Cl$_2$, -70 °C): 12.71 (dd, 368, 38Hz, 1H, Pd–F*HF*); ^{19}F NMR (CD$_2$Cl$_2$, 22 °C): -117.2 (m, 1F), -206.3 (br m, 1F, Pd–F *trans* from Ar), -257.4 (br s, 2F, Pd–F *trans* from N); (CD$_2$Cl$_2$, -70 °C): -116.7 (m, 1F), -177.6 (dd, 364, 116 Hz, 1F, Pd–FH*F*), -204.5 (m, 1F, Pd–*F*HF), -256.9 (d, 60Hz, 2F, *trans* from N).

(dtbpy)Pd(I)₂.[32] – Using standard air-free techniques, (dtbpy)PdCl₂ (500 mg, 1.1 mmol, 1 equiv) was dissolved in acetone (15 mL). NaI (0.49 g, 3.0 mmol, 2.7 equiv) was added, and the reaction mixture was stirred for 2 h. The resulting purple precipitate was collected on a frit and washed with copious amounts of acetone (~50 mL).[33] The crude product was then dissolved in CH_2Cl_2 (20 mL) and stirred with charcoal for 30 min. This suspension was filtered through a plug of Celite and washed with CH_2Cl_2 (20 mL). The solvent was removed *in vacuo* to afford the product as a purple solid (0.64 g, 91% yield). ^{1}H NMR (CDCl₃): δ 9.89 (d, *J* = 6 Hz, 2H), 7.93 (d, *J* = 2 Hz, 2H), 7.53 (dd, *J* = 6, 2 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (CDCl₃): δ 164.00, 156.28, 153.77, 124.39, 119.00, 35.68, 30.28. Anal. Calc. for $C_{18}H_{24}I_2N_2Pd$: C, 34.39, H, 3.85, N, 4.46; Found: C, 34.49, H, 3.77, N, 4.49.

(dtbpy)Pd(F)₂ – Using a modification of Vigalok's procedure,[33] (dtbpy)Pd(I)₂ (90 mg, 0.14 mmol, 1.0 equiv) and AgF (50 mg, 0.42 mmol, 3.0 equiv) were weighed into a 20 mL scintillation vial and dissolved in CH_2Cl_2 (4 mL). The vial was covered in aluminum foil, and the mixture was stirred for 3 h at room temperature. The resulting suspension was filtered through a plug of Celite, concentrated, and the product was precipitated with pentane. This solid was collected and washed with pentane (3 x 2 mL). It was then redissolved in CH_2Cl_2 (2 mL), and the suspension was filtered through a plug of Celite. The solvent was removed *in vacuo*, to yield the product as a pale yellow solid (20 mg, 35% yield). ^{1}H NMR (CD₂Cl₂): δ 8.51 (d, *J* = 6 Hz, 2H), 7.88 (s, 2H), 7.54 (d, *J* = 6 Hz, 2H), 1.42 (s, 18H); ^{19}F NMR (CD₂Cl₂): δ –354.06 (s, 2F); ^{13}C NMR (CD₂Cl₂): δ 165.95, 156.05, 149.49, 124.19, 119.46, 36.37, 30.59. Complex (dtbpy)Pd(F)₂ is extremely hygroscopic, and even after extensive drying under vacuum, ^{1}H NMR spectroscopic analysis in dry CD₂Cl₂ showed the presence of 0.86 equiv of H_2O/complex (observed as a broad resonance at 1.45 ppm). The microanalysis results are consistent with this stoichiometry. Anal. Calc. for $C_{18}H_{24}F_2N_2Pd$•0.86 H_2O: C, 50.47, H, 5.85, N, 6.54; Found: C, 50.70, H, 5.92, N, 6.41.

(dtbpy)Pd(*p*-FPh)(Cl) – (5-13) This product was prepared using a modification of a procedure by Osakada.[34] In the glovebox, **5-3a** (0.40 g, 0.67 mmol, 1 equiv) and AgBF$_4$ (0.20g, 1.0 mmol, 1.5 equiv) were weighed into separate 20 mL scintillation vials. To the vial of **5-3a**, 5.2 mL of MeCN was added and 1.4 mL was added to the AgBF$_4$ vial. The AgBF$_4$ solution was added to the vial of **5-3a** and MeCN, covered with Al foil and stirred vigorously for 30 min. After 30 min., NaCl (0.12g, 2.2 mmol, 3.3 equiv) was added and stirred for 5 min. After 5 min., the suspension was filtered over Celite in air, washed with (3 x 5 mL of CH$_2$Cl$_2$), and filtrate solvent was removed under reduced pressure. The resulting yellow solid was dissolved in minimal amount of acetone then, treated with water (~15 mL). The suspension was treated with two scoops of NaCl to precipitate all the solids and sat at room temperature for 3 hours. The resulting precipitate was filtered over a frit, washed with water (3 x 10 mL) and dried *in vacuo* over P$_2$O$_5$ to yield the product as a pale yellow solid (0.20 mg, 58% yield). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 9.13 (d, *J* = 5 Hz, 1H), 7.95 – 7.92 (multiple peaks, 2H), 7.87 (d, *J* = 7 Hz, 1H), 7.52 (dd, 6Hz, 2Hz, 1H), 7.38 – 7.28 (multiple peaks, 3H), 6.88 – 6.82 (multiple peaks, 2H), 1.42 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CDCl$_3$, 282 MHz): δ −122.73.

General procedure for oxidative fluorination of 5-4a – 5-4c: In a glovebox, the Pd^{II} fluoride (**5-4a – 5-4c**) (10 mg, 1 equiv) was dissolved in nitrobenzene (1 mL). This solution was added to a 4 mL scintillation vial containing XeF$_2$ (3 equiv). The vial was sealed with a Teflon-lined cap, vigorously shaken, and then heated at 90 °C for 1 h. The resulting mixture was cooled to room temperature, hexafluorobenzene was added as an internal standard, and the reactions were analyzed by ^{19}F NMR spectroscopy. The identities of the organic products were confirmed by the synthesis of authentic samples of these materials.

It is important to note that the optimal conditions for ^{19}F NMR spectroscopic analysis of these reactions were as follows: spectral width = −80 to −180 ppm, relaxation delay = 5 s, and acquisition time = 6.4 s. These conditions were required due to the faster relaxation time of the standard relative to the fluoroarene products.

Studies of the reactivity of 5-7: In a glovebox, **5-7** (1 equiv) was dissolved in nitrobenzene (0.012 M solution). Hexafluorobenzene was added as an internal standard,

the NMR tube was sealed with a Teflon-lined cap, and the reaction mixture was shaken vigorously. This reaction was then analyzed by ^{19}F NMR spectroscopy to determine the ratio of starting material to standard. The NMR tube was the returned to the glovebox, and the oxidant (3 equiv) was added as a solid. The tube was shaken vigorously, removed from the glovebox, and heated in an oil bath at 80 °C for 1 h. After cooling, the reaction was again analyzed by ^{19}F NMR to determine the percent conversion of the starting material to the product.

Structure Determination of Complex 5-7. – Colorless blocks of **5-7** were grown from an acetone/pentane solution at 25 deg. C. A crystal of dimensions 0.28 x 0.16 x 0.16 mm mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (l = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(2) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 3336 frames were collected with a scan width of 0.5° in w and 0.45° in phi with an exposure time of 20 s/frame. The integration of the data yielded a total of 44156 reflections to a maximum 2q value of 56.74° of which 7631 were independent and 6810 were greater than 2s(I). The final cell constants (Table 1) were based on the xyz centroids of 9998 reflections above 10s(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL software package, using the space group P1bar with Z = 4 for the formula $C_{24}H_{29}F_5N_2Pd$, $2(C_3H_6O)$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. The para-fluorophenyl ligand is disordered over two positions modeled by placement of partial occupancy atoms.   Restraints (SADI/SIMU/DELU) were employed to maintain chemically sensible geometries.   Full matrix least-squares refinement based on F^2 converged at R1 = 0.0448 and wR2 = 0.1019 [based on I > 2sigma(I)], R1 = 0.0524 and wR2 = 0.1088 for all data.

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Chapter 6

Conclusion and Outlook

The work described in this thesis represents key advancements towards the promotion of aryl C–CF$_3$ and C–F bond formation from palladium. Concomitant with these advancements is the opportunity to address other current and future challenges.

6.1 Outlook on Future Investigations with Pd^{IV} intermediates

Chapter 2 described the synthesis of a novel aryl Pd^{IV}–CF$_3$ complexes from the oxidation of aryl Pd^{II}–CF$_3$ complexes with an electrophilic fluorinating regent. From these complexes subsequent Ar-CF$_3$ bond-forming reduction elimination was observed. Key to the stability of these aryl Pd^{IV}–CF$_3$ intermediates was the slow coupling of the aryl and CF$_3$ ligands. Future work could exploit this stability to explore other transformations at Pd^{IV}.

One transformation of intense interest is C–H activation at Pd^{IV}. While proposed as a transformation in several Pd–catalyzed C–H activation/functionalization reactions, direct evidence of this transformation from Pd^{IV} have yet to be demonstrated.[1] To this end, future work could focus on the oxidation of a series of Pd^{II}–CF$_3$ complexes with C–H bonds in an appropriate proximity to the Pd center. These complexes upon oxidation with F$^+$ could allow for an intramolecular C–H activation at Pd^{IV}, resulting in a stable Pd^{IV} product (Scheme 6.1).

Scheme 6.1 – Proposed Intramolecular C–H Activation at Pd^{IV}

This proposed transformation could be performed with a variety of aryl Pd^{II}–CF$_3$ complexes like **6-1**, **6-2** and **6-3** providing models for sp^2 and sp^3 C–H activation at Pd^{IV} (Scheme 6.2).

(6-1)   **(6-2)**   **(6-3)**

Scheme 6.2 – Proposed Aryl Pd^{II}–CF$_3$ Complexes to Study Sp^2 and Sp^3 C–H Activation at Pd^{IV}

Joy Racowski in our group has preliminary evidence towards this strategy with the oxidation of **6-1** with *N*-fluoro-2,4,6-trimethylpyridium triflate in acetonitrile forming HF and isolable Pd^{IV} complex **6-4** in 62% yield (Scheme 6.3).

(6-1)   **(6-4)**

Scheme 6.3 – Oxidatively Induced C–H Activation at Pd^{IV}

Chapter 2 also describes mechanistic studies that provide evidence suggesting reductive elimination occurs through a reversible dissociation of a TfO$^-$ anion from Pd^{IV}–CF$_3$ complex **6-5** to cationic Pd^{IV} intermediate (**6-6**). This is followed by an irreversible C–

CF$_3$ reductive elimination (Scheme 6.4).

Scheme 6.4 – Proposed Mechanism of Ar–CF$_3$ Bond-Forming Reductive Elimination from Pd^{IV}–CF$_3$ Complex.

Future work could exploit this mechanism to demonstrate other novel aryl C–X bond forming reductive eliminations from Pd^{IV}. One C–X bond formation that has not been demonstrated to occur from Pd^{IV} complex is C–N bond-forming reductive elimination.[2] Aryl Pd–CF$_3$ complex **6-5** in the presence of an amine could displace TfO$^-$ and coordinate to palladium resulting in a cationic Pd^{IV} intermediate (**6-7**). Intramolecular deprotonation of the amine with the F$^-$ ligand (for precedent see Scheme 6.3) would result in another cationic Pd^{IV} intermediate (**6-8**) followed by Aryl–N bond-forming reductive elimination (Scheme 6.4).

Scheme 6.5 – Proposed Strategy to Demonstrate C–N Bond Formation from Pd^{IV}

In addition, this equilibrium could be exploited to achieve intermolecular C–H activation. Heating **6-5** in the presence of arene (e.g. with benzene or veratrole) could result in an intermolecular C–H activation yielding Pd^{IV} intermediate **6-9** followed by aryl-aryl bond-forming reduction elimination (Scheme 6.6).

Scheme 6.6 – Proposed Strategy to Demonstrate Intermolecular C–H Activation at Pd^{IV}

Chapters 3 and 5 highlighted examples of C–CF$_3$ or C–F bond forming reductive elimination from Pd^{IV} complexes **6-10** and **6-11** that required the addition of either Lewis or Brønsted acids or extra oxidant (Scheme 6.7).

Scheme 6.7 – Aryl–CF$_3$ and Aryl–F Bond-Forming Reductive Elimination from Pd^{IV} in the Presence of Additives

These additives not only increased the overall yield of the desired product, but in the case of C–CF$_3$ bond formation, increased the rate of the reaction. Previous literature examples of C–X (X = Halogen, aryl, alkyl, N, O, S, etc.) bond formation from Pd^{IV} have focused on observing the transformation upon thermolysis.[3] However, in Pd^{II}/Pd^{IV} catalysis the Pd^{IV} intermediates exist in the presence of an excess of oxidant, substrate, co-catalyst, and other reagents. Thus, future studies of Pd^{IV} complexes that focus on the reactivity in the presence of additives may prove to be an attractive alternative to optimize stoichiometric results into catalytic systems. For example in Chapter 3, Pd^{IV}–

CF_3 complex **6-10** was demonstrated to be a kinetically competent intermediate in a Pd-catalyzed C–H/trifluoromethylation reaction. Since **6-10** was a catalytic intermediate, studies to explore its reactivity and rate of reaction in the presence of different components of the catalytic reaction (oxidant, inorganic by-product(s), organic product, etc.) could give valuable insight into which components promote or inhibit catalysis. Using this strategy to optimize other catalytic C-H activation/functionalization reactions could lead to improved catalytic systems (Scheme 6.8).

Scheme 6.8 – Optimization of C–H Activation/Trifluoromethylation Reactions in the Presence of Different Components of the Catalytic System

6.2 Outlook on Pd-catalyzed Aryl Trifluoromethylation and Fluorination

While the studies highlighted in Chapters 2 and 3 give promise to the development of future Pd^{II}/Pd^{IV} aryl trifluoromethylation reactions, a key challenge to this strategy centers on the limitations of current trifluoromethylating reagents. Transmetallation of CF_3^- from R_3SiCF_3 (R = Me or Et) reagents to palladium can be slow and upon heating often result in decomposition of the silylating reagent.[4] Additionally, sources of CF_3^+ (e.g. diarylsulfonium salts and hypervalent iodine reagents) are very expensive.[5] Ultimately, the use of trifluoroacetic acid (TFA) would be a very cheap and more environmentally friendly alternative source of CF_3^- (Scheme 6.9).

Scheme 6.9 – Cost of Various Trifluoromethylating Reagents

A considerable advance in Pd-catalyzed aryl trifluormethylation would be a system that coupled Pd-catalyzed aryl C–H activation with the decarboxylation of TFA to form CO_2 and CF_3^-.[6] Using either a Pd^0/Pd^{II} or Pd^{II}/Pd^{IV} manifold, this aryl–CF_3 coupling from palladium could potentially provide a cost-effective method of metal-catalyzed C–CF_3 bond formation.

Despite significant progress by Buchwald in promoting Pd^0/Pd^{II} aryl fluorination, Chapter 4 demonstrates how this reductive fluorination strategy is still very sensitive to ligand structure. Oxidative fluorination is an attractive alternative, however the cost of electrophilic fluorinating reagents is also an issue towards the development of future Pd^{II}/Pd^{IV} aryl fluorination reactions. Fluoride salts (e.g. metal salts or tetraalkylammonium salts) are a significantly cheaper source of fluorine (Scheme 6.10).[7]

Scheme 6.10 – Cost of Various Fluorinating Reagents

Similar to our nucleophilic trifluormethytlation strategy (Chapter 2), future work could focus on the usage of an oxidant-X that would introduce a ligand that upon oxidation would not competitively undergo C–X versus C–F reductive elimination (Scheme 6.11). Upon oxidation, F^- could coordinate to Pd^{IV}, followed by subsequent C–F bond reductive elimination. This orthogonal approach would eliminate the need for expensive electrophilic fluorinating reagents. Kate Butler in the laboratory is currently pursuing this strategy.

Scheme 6.11 – A Strategy Towards Oxidative Fluorination Using A F⁻ Source

6.3 References

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