SELECTIVE, CATALYTIC C-F ACTIVATION AS A ROUTE TO METHYL- AND ETHER- FUNCTIONALIZED POLYFLUOROARYLIMINES

by

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Abstract

Platinum (II) complexes were used to achieve catalytic C-F bond activation and cross-coupling of a series of polyfluoroarylimines.

PtCl$_2$(SMe$_2$)$_2$ (21) was found to be active for coupling to obtain Ar-CH$_3$ bonds, a reaction which had been previously reported using Pt$_2$Me$_4$(SMe$_2$)$_2$ (1) as a catalyst. The yields of the two reactions are comparable, and 21 is a significantly easier compound to prepare. This reaction is postulated to have a similar reaction mechanism to that determined for the C-C cross-coupling achieved using 1. In addition, a new example of cross-coupling of a polyfluoroarylimine not possessing a 2,6-difluorination pattern (imine 26) was demonstrated.

Platinum complex 1 was demonstrated to be active for a new catalytic cross-coupling reaction to generate aryl methyl ethers from the same series of polyfluoroarylimines. The imine products were characterized by $^1$H and $^{19}$F NMR spectroscopy, and their corresponding aldehydes were fully isolated and characterized by $^1$H, $^{13}$C and $^{19}$F NMR spectroscopy and elemental analysis. The structure of aldehyde 46 was further confirmed by X-ray crystallography. The substrate limitations of this reaction are greater, with electron withdrawing groups required at the 2, 4, and 6 positions. A preliminary mechanistic investigation revealed that the mechanism is different from that reported for the corresponding C-C cross-coupling reaction, but that the platinum catalyst is required and the reaction does not proceed through a traditional organic chemistry mechanism. This reaction may be the first example of catalytic C-O reductive elimination from a platinum (IV) centre.
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min = minutes
mL = millilitre
mmol = millimole
mol = mole
μ = mu, micro
NMR = nuclear magnetic resonance
ORTEP = Oakridge Thermal Ellipsoid Plot
Ph = phenyl
π = pi
ppm = parts per million
R, R’, R” = generic substituent, alkyl or otherwise
rt = room temperature
s = singlet
SNAr = nucleophilic aromatic substitution
t = triplet
TBAF = tetrabutylammonium fluoride
t-Bu = tert-butyl
td = triplet of doublets
THF = tetrahydrofuran
X = generic element; generic halogen unless otherwise defined
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Ideas are the lifeblood of research. Any project, no matter how big or small, begins because someone has both the vision and drive to turn that idea into a reality. My supervisor, Dr. Jennifer Love, has provided the vision and drive to set this project in motion, and has challenged me throughout it to think in new ways. Along the way she has been a source of support, encouragement, and optimistic pragmatism.

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Ideas are the lifeblood of research; friends are the lifeblood of happiness. Thank you to all of you.

- HLB, April 24, 2009
Chapter 1 – Introduction

1.1 Introduction

Transition metals are widely used in the activation of carbon-element bonds. The cleavage of a bond by a metal centre has many applications ranging from the creation of new organometallic complexes to cross-coupling reactions that generate synthetically useful functionalized organic molecules.

In this thesis, the application of a platinum (II) catalyst to the selective activation of a carbon-fluorine bond and subsequent catalytic cross-coupling are described. The precedent for this work is discussed in the first chapter, beginning with the activation of carbon-element bonds by platinum centres. Cross-coupling reactions are then highlighted, followed by an overview of the various applications of functionalized organofluorides. This leads to a discussion of the activation of C-F bonds, both stoichiometrically and catalytically. The first examples of selective, platinum-catalyzed C-F activation of a polyfluorinated arene are highlighted here. A broader range of cross-coupling reactions is discussed next. From this point the focus shifts to the formation of C-heteroatom bonds. The emphasis is on the currently established methods of C-O bond formation, both via metal-catalyzed cross-coupling and by other methods.

In the second chapter, the application of a new platinum catalyst to C-C cross-coupling of polyfluoroarylimines is discussed. We have discovered that PtCl$_2$(SMe$_2$)$_2$, an air- and water-stable precursor to the Pt complex used in our previous work, reacts in situ to generate an active catalyst for the same C-C cross-coupling reactions previously reported by our group (eq. 1.1). The ease of synthesis of this catalyst precursor has potential cost and environmental benefits in C-F activation reactions.
An entirely new reaction is presented in the third chapter. The platinum species Pt$_2$(CH$_3$)$_4$(SMe)$_2$ catalyzes the formation of aryl methyl ethers via selective C-F bond activation of polyfluoroarylimines (eq. 1.2). We explore the substrate scope of this reaction and demonstrate that it is both selective and functional-group tolerant. This chapter ends with a preliminary exploration of the mechanism of this novel C-O cross-coupling reaction.

The thesis concludes with a discussion of possible future directions for catalytic C-F activation chemistry. The proposed work includes an exploration of a broader range of substrates, further reactivity at the various functional groups tolerated in this reaction, and elucidation of the complete mechanism of the C-O cross-coupling reaction.

Catalytic C-F activation is a reaction in its infancy. As it gradually emerges amongst the cross-coupling strategies established for other halocarbons, there is great potential for the development of new organometallic and organic species, and for new methodologies based on the strong, but clearly reactive, carbon-fluorine bond.

### 1.2 Bond Activation with Platinum

Transition metals are widely used for bond activation.\(^1\) In the case of carbon-element bonds (C-E bonds, E = H, Cl, Br, F, O, etc.), the most ubiquitous mode for activation is...
through oxidative addition of the C-E bond across the metal centre (eq. 1.3). This leads to oxidation of the metal and the generation of two formally anionic ligands. Alternately, bond activation through a metal centre can proceed via electrophilic attack, where the C-E bond undergoes heterolytic cleavage and the anionic moiety binds to the metal centre without a change in oxidation state (eq. 1.4).

\[
\begin{align*}
C-E & + M^{n+} \rightarrow C \overset{\text{E}}{\underset{\text{M}^{(n+2)+}}{\text{M}}} & (1.3) \\
C-E & + M^{n+} \rightarrow \overset{\text{C}}{\text{M}^{n+}} + E^+ & (1.4)
\end{align*}
\]

Platinum complexes are used in the activation and functionalization of a wide variety of such carbon-element bonds. Carbon-hydrogen bond activation has been applied as a method to generate interesting platinum organometallics,\textsuperscript{2-23} as well as to impart functionality at a previously unfunctionalized site. It is interesting to note that some of the earliest C-H activation chemistry at platinum was in fact via heterolytic cleavage (electrophilic activation, as in eq. 1.4), where the reaction was initiated by loss of a proton and coordination of the carbanion to the platinum centre.\textsuperscript{24} Much of the more recent work in C-H activation has involved an oxidative addition reaction. In the majority of cases, redox chemistry at homogeneous platinum centres occurs between Pt(II) and Pt(IV).

C-H bond activation by platinum has been applied to the derivatization of unfunctionalized carbon chains, typically via reductive elimination of a carbon-carbon or carbon-element bond from the platinum centre. These reactions have been demonstrated to occur both stoichiometrically and catalytically.\textsuperscript{25}
A widely used application of C-H bond activation by platinum is dehydrogenation chemistry. Saturated, unfunctionalized hydrocarbons are both cheap and abundant feedstocks, and the ability to selectively remove the saturation from these compounds can provide more useful, functionalized organic compounds for further synthetic application. For instance, Goldberg and coworkers\textsuperscript{26} demonstrate the ability to stoichiometrically generate alkenes from both cyclohexane and 2,2-dimethylpentane using β-diketiminate complexes of platinum (II) (Scheme 1.1).

![Scheme 1.1 Dehydrogenation of alkanes using a platinum (II) β-diketiminate complex](image)

Activation of a variety of other carbon-element bonds by platinum has been demonstrated in recent years. This has led to the synthesis of several organoplatinum complexes of heavier-element species,\textsuperscript{27-29} as well as the generation of chemosensors for SO\textsubscript{2}\textsuperscript{30-34} and other gasses,\textsuperscript{35} biosensors,\textsuperscript{36} and photochemical products.\textsuperscript{37-39} In the realm of synthetic chemistry, however, the most significant advances have been in the activation of carbon-halogen bonds.
1.2.1 Cross-Coupling Reactions

Transition metal-catalyzed cross-coupling reactions are ubiquitous in modern organic chemistry. In such a reaction, the basic motif is the activation of an aryl halide by a transition metal centre, followed by transmetallation with an organometallic reagent, and reductive elimination (Scheme 1.2).\(^1\)

![Scheme 1.2 General scheme for catalytic cross-coupling](image)

The earliest cross-coupling reactions, such as the Ullmann\(^40\) and Glaser couplings, made use of copper as the catalytic metal centre. Today, palladium and nickel are the most widely used metals for these reactions, although copper also finds use in the Cadiot-Chodkeiwicz\(^41\) and Sonogashira\(^42\) couplings. The stoichiometric organometallic reagent can be any of a variety of main group compounds.

Oxidative addition and cross-coupling of carbon-halogen bonds to group X metals is an essential reaction to modern synthetic organic chemistry. The bulk of this chemistry
occurs at palladium(0) or nickel(0), which are the metals responsible for a wealth of C-C cross-coupling reactions of aryl halides, including Kumada-Corriu,\textsuperscript{43,44} Heck,\textsuperscript{45} Sonogashira,\textsuperscript{42} Negishi,\textsuperscript{46} and Suzuki-Miyaura\textsuperscript{47} reactions, among others. While less widely used, stoichiometric activation of C-X bonds by platinum is known, and again leads to interesting metal complexes.\textsuperscript{3,4,28,48-51} Given the success of these reactions with other metals of the same group, carbon-halogen bond activations by platinum have great potential.

1.2.2 The Significance of Fluoroaromatics

Despite the relatively high abundance of inorganic fluorine in the earth’s crust, naturally occurring organofluorides are virtually unknown.\textsuperscript{52} Only thirteen have been identified at this point, and eight of these are derivatives of fluoroacetic acid. With such a deficiency of naturally occurring fluorinated compounds, it is clear that synthetic methods to produce them are needed if they are to be widely used in industrial applications.

Indeed, there are many uses for fluorinated organic compounds in current industrial applications. They are frequently lipophilic, hydrophilic, metabolically stable, and capable of forming strong hydrogen bonds. It is for this reason that 30\% of new agrochemicals and 20\% of new pharmaceuticals contained fluorine in 2007.\textsuperscript{53,54} Among many pharmaceuticals that contain a fluoroaromatic functionality, some of the best known include the antibacterial Cipro, the cholesterol-lowering drug Lipitor, the antidepressant Paxil, and the antifungal Difulcan (Figure 1.1).
Given this high prevalence of synthetic organofluorides in these two industries, it is clear that the ability to generate and functionalize these species is important. A variety of methods exist for the generation of C-F bonds, with various electrophilic and nucleophilic substitutions predominant in the generation of aliphatic organofluorides. Reactions with alkali and transition metal fluoride salts and complexes are the primary method for generating aryl fluorides.²⁵,₅₆,₅₇

While the aforementioned methods are valuable in producing C-F bonds, it is generally desirable to have other functionalities present on a compound as well. Selectively functionalized fluorinated compounds are valuable both as synthons and as final products of a total synthesis. Thus the ability to derivatize C-F bonds is a highly valuable tool. One method of doing this is via activation of C-F bonds using transition metals.

1.2.3 C-F Bond Activation

While activation of C-F bonds by transition metals is not as widespread as the activation of other carbon-halogen bonds, a number of both stoichiometric and catalytic examples of this reaction do exist. Most common are reactions that utilize nickel.²⁰,₅₈-₆⁰
and palladium. A wide range of reactions demonstrating stoichiometric C-F activation with nickel and palladium have been observed, as well as a number of catalytic reactions, such as the cross-coupling of octafluorotoluene reported by Schaub et al. in 2006 (Scheme 1.3).

![Scheme 1.3 Catalytic C-F activation and cross-coupling with a nickel catalyst](image)

While catalytic reactions of this sort are becoming increasingly common, they tend to have very limited substrate scope, and the above reaction is one of a small number that demonstrate cross-coupling of polyfluoroaromatics and therefore directly generate functionalized fluorinated products. This reaction is also unique as it is one of very few reactions that generates a “true” cross-coupling product and does not simply lead to hydrodefluorination of the activated bond.

In addition to reactions on transition metals (which have also been observed at Rh, Ru, W and other metals) C-F activation chemistry on silyl species has progressed significantly in recent years. The strength of the silicon-fluorine bond has led to the use of stabilized silylium cations to effect heterolytic C-F bond activation.  

### 1.2.4 Stoichiometric C-F Bond Activation with Platinum

Much of the work to-date involving platinum-mediated carbon-halogen bond activation has relied on intramolecular activation. Initial coordination of a
nitrogen lone pair generates a system where the C-X bond is in a favourable position for reaction with the metal, and oxidative addition then leads to a chelating ring.

This same principle has been applied by Crespo, Martinez and coworkers to the stoichiometric activation of a carbon-fluorine bond.\textsuperscript{2,4,72,73} Throughout the course of their work, they have explored several alternatives for the chelating nitrogen group; the compounds that were ultimately of the most interest to our group were a set of polyfluoroarylimines (Figure 1.2).

\[ F \quad F \quad N \quad Ph \quad F \quad n \quad F \quad n = 3,4,5-F_3 \\
\quad 3-F, 4-F \]

**Figure 1.2** Polyfluoroarylimines subjected to C-F bond activation by Pt(II)

The reactions of these imines with Pt\(_2\)(CH\(_3\))\(_4\)(SMe\(_2\))\(_2\) is notable because, unlike many of the other C-F activation reactions reported, it is highly selective for activation of the aryl C-F bond positioned *ortho* to the imine directing group to generate complex A (eq. 1.5). This reaction is irreversible,\textsuperscript{2,74} and generates a platinum (IV) species. The dimethyl sulphide ligand undergoes facile dissociation from this species, as was demonstrated by exchange with a triphenylphosphine ligand.\textsuperscript{74} This is believed to be significant to the mechanism of the oxidative addition, which may actually occur onto a transiently-present three-coordinate platinum (II) complex.
Our interest in this C-F oxidative addition reaction was largely due to the potential of following this with a reductive elimination of a C-C bond. The non-reversibility of the C-F activation meant that complex A could not simply revert to starting materials. This meant that the most probable type of further reactivity was through cross-coupling of the Pt-bound carbon with another species. Based on the C-F activation work performed by Crespo and Martinez, our goal was to achieve selective, catalytic cross-coupling with polyfluoroaromatics.

1.2.5 Catalytic C-F Bond Activation with Platinum

While heating of complex A was not sufficient to generate any sort of cross-coupling product, we anticipated that this species might undergo transmetallation at the Pt-F bond, provided that the resultant M-F bond was sufficiently strong for the reaction to be thermodynamically favourable (eq. 1.6).

While we initially predicted that the most facile cross-coupling reactions would occur between two sp²-hybridized carbon centres due to better orbital overlap, we found that cross-coupling actually occurred to generate aryl-methyl bonds even when sources of phenyl were introduced (Table 1.1). Of greatest significance in this chemistry, though, was the requirement for platinum to catalyze the conversion; the reaction did not proceed
through a simple nucleophilic aromatic substitution (SNAr) reaction. This reaction constitutes the first example of platinum-catalyzed C-F activation and cross-coupling of a polyfluoroarene.\textsuperscript{75}

**Table 1.1 Optimization of Conditions for Catalytic Methylation of Polyfluoroarylimines\textsuperscript{75}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (equiv)</th>
<th>Solvent</th>
<th>mol % Pt</th>
<th>Yield\textsuperscript{a}</th>
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<tr>
<td>1</td>
<td>PhSi(OMe)\textsubscript{3} (1.2)</td>
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<td>88%</td>
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<td>Me\textsubscript{2}Zn (1.2)</td>
<td>CD\textsubscript{3}CN</td>
<td>0</td>
<td>0%</td>
</tr>
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<td>5</td>
<td>Me\textsubscript{2}Zn (0.6)</td>
<td>CD\textsubscript{3}CN</td>
<td>5</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>6</td>
<td>MeLi (1.2)</td>
<td>THF-\textsubscript{d\textsubscript{8}}</td>
<td>5</td>
<td>complex mix</td>
</tr>
<tr>
<td>7</td>
<td>MeLi (1.2)</td>
<td>THF-\textsubscript{d\textsubscript{8}}</td>
<td>0</td>
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\textsuperscript{a} Yields based on \textsuperscript{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Studies of the scope of this reaction further demonstrated its selectivity and functional group tolerance (Table 1.2). Exclusively the ortho-methylated product formed in good-to-excellent yields, even in the presence of weaker C-Br bonds (imines 8 and 13) and functionalities such as nitrile groups (imine 6) at any location other than that ortho to the imine substituent. The only evident requirement for reactivity of these polyfluoroarylimines (in addition to the imine directing group) is the presence of three electron withdrawing groups on the aryl ring involved in the cross-coupling reaction in order to make the ring sufficiently electron deficient. This is presumably necessary for
polarization of the C-F bond for activation. Consistent with this hypothesis, Crespo and Martinez did not observe stoichiometric C-F activation of imine 15.²

**Table 1.2** Scope of Pt-Catalyzed Methylation of Fluoroimines²⁷⁵

![Chemical Structures](image)

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<th>entry</th>
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<th>yield (%)</th>
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<tr>
<td>2</td>
<td><img src="image3" alt="Structure" /> 4</td>
<td><img src="image4" alt="Structure" /> 5</td>
<td>91%</td>
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<td>3</td>
<td><img src="image5" alt="Structure" /> 6</td>
<td><img src="image6" alt="Structure" /> 7</td>
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<tr>
<td>4</td>
<td><img src="image7" alt="Structure" /> 8</td>
<td><img src="image8" alt="Structure" /> 9</td>
<td>85%</td>
</tr>
<tr>
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<td><img src="image9" alt="Structure" /> 10</td>
<td><img src="image10" alt="Structure" /> 11</td>
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</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Structure" /> 12</td>
<td><img src="image12" alt="Structure" /> 11</td>
<td>&gt;95%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Structure" /> 13</td>
<td><img src="image14" alt="Structure" /> 14</td>
<td>86%</td>
</tr>
</tbody>
</table>
Several of these products are well suited towards further functionalization, which supports our goal of developing synthetically useful methodologies. For example, the brominated imines 8 and 13 (entries 4 and 7) could be substrates for palladium-catalyzed cross-coupling. The nitrile group of imine 6 (entry 3) could be hydrolyzed to a carboxylic acid or reduced to a variety of different functional groups. Any C-F activation products generated from these species would possess the same reactivity as their precursors. The imine itself can readily undergo hydrolysis to the corresponding aldehyde, which in turn can be converted into a wide range of functional groups.

Our group conducted extensive mechanistic studies on this platinum-catalyzed C-F activation and cross-coupling reaction. The similarity of the stoichiometric reaction products observed in a reaction of 21 (complex A, generated with 2,4,6-trifluorinated imine 2) with dimethylzinc and the catalytic reaction observed when starting with imine and 5 mol % Pt$_2$(CH$_3$)$_4$(SMe)$_2$ strongly suggested the involvement of 21 or a closely
related species in the catalytic cycle. Complex 24 was observed by $^1$H NMR spectroscopy, and the triphenylphosphine adduct was isolated and characterized by X-ray crystallography. The addition of excess SMe$_2$ suppressed reactivity, supporting the idea that the active species was in fact a five coordinate platinum (IV) complex, which is common for Pt(IV) alkyl complexes. Finally a full catalytic cycle was elucidated (Scheme 1.4).

Scheme 1.4 Proposed mechanism for catalytic C-C cross coupling$^{74}$
The reaction proceeds via initial coordination of the imine to platinum (II), followed by intramolecular oxidative addition of the C-F bond, and transmetallation with dimethylzinc. The strong (~380 kJ/mol) Zn-F bond formed in this reaction is believed to be a major thermodynamic driving force for the overall process, allowing turnover of the strong Pt-F bond. The Pt-F bond was likely a thermodynamic sink in previous C-F activation chemistry. The cycle completes with reductive elimination of the aryl methyl bond, producing the functionalized polyfluoroarylimine and regenerating the catalyst. As previously mentioned, the active species 22 and 23 in the catalytic process are five-coordinate, but facile dissociation of SMel₂ means that they are in rapid equilibrium with their inactive six-coordinate analogues.

With a solid understanding of the mechanism of this reaction, our group identified the potential to extend its scope beyond the generation of aryl-methyl bonds. The synthesis of aryl methyl ethers, which is the subject of Chapter 2, is a result of our exploration of other possible cross-coupling reactions that could stem from carbon-fluorine bond activation.

1.3 Cross-Coupling as a Route to Aryl Ether Formation

Traditionally, the definition of cross-coupling has been limited to the formation of carbon-carbon bond as shown in Scheme 1.2 and discussed in Section 1.2.1. However, the increasing prevalence of fundamentally similar reactions that yield carbon-heteroatom bonds has led to an extension of this definition. The research groups of both Buchwald and Hartwig have shown the use of cross-coupling to generate amines and sulphides,⁷⁶ and, of greatest relevance to the research presented here, ethers.⁷⁷-⁸³
1.3.1 Aryl Ether Synthesis

Aryl ethers have inspired considerable synthetic efforts because of their prevalence in bioactive molecules\(^{84-94}\) and materials.\(^{95,96}\) They have also been applied recently as cross-coupling reagents to aryl boronic acids (eq. 1.7).\(^{97}\) This is a somewhat unusual application as it removes the ether functionality, but it provides another method for the formation of a C-C bond; bonds between carbon atoms are still a cornerstone of synthetic methodology.

\[
\begin{align*}
\text{OMe} & \quad \underset{10 \text{ mol}\% [\text{Ni(COD)}_2]}{\text{Ph-B-O}} \quad \underset{20 \text{ mol}\% \text{PCy}_3}{\text{CsF, Toluene}} \quad 12 \text{h, 120 °C} \\
& \quad \text{Ph} \quad 93\% 
\end{align*}
\]  

(1.7)

In organic synthesis, one method for generating aryl ethers is via a nucleophilic aromatic substitution reaction.\(^{98,99}\) This is indeed an application of aryl fluoride reactivity, where a nucleophilic alkoxide or phenoxide (which is often protected by a silyl group) attacks an aryl-F bond to generate an ether product (eq. 1.8).

\[
\begin{align*}
R_n & \quad \underset{\text{TBAF, solvent}}{\text{F}} \quad R'_3\text{SiOR}'' \\
& \quad \text{OR}'' \quad (1.8)
\end{align*}
\]

Better conversion can be achieved by the use of TBAF\(^{100,101}\) and related reagents, which can either activate the siloxane or generate the more reactive alkoxide. However, the ability to generate similar products by metal-mediated reactions lends itself towards milder conditions and selective reactions.
1.3.2 Generation of Aryl Ethers by Cross-Coupling

Historically, a version of the Ullmann coupling has seen extensive use in metal-mediated aryl ether synthesis, but harsh conditions and the need for excess Cu salts make new approaches desirable.\(^{40}\) A new reaction involving catalytic Ullmann coupling has been put forward,\(^{102-104}\) however, this reaction still requires high temperatures for the reaction to occur. Alternative room-temperature couplings require an excess of copper to generate aryl ether products.

Notably, Pd-catalyzed cross-coupling of alkoxides and phenoxides has been advanced independently by both Hartwig and Buchwald as the first method of generating aryl ethers through a conventional cross-coupling cycle.\(^{77-83}\) On certain substrates these reactions can be performed under mild conditions, which increases the potential to apply this reaction to more functionalized substrates.

While significant advances in aryl ether synthesis have been reported, methods to generate fluorinated aryl methyl ether building blocks, which could have considerable bioactivity, are as yet unknown. The aim of the work presented in Chapter 3 of this thesis is to provide a means to generate these products selectively and catalytically.

1.4 Conclusion

Carbon-element bond activation by transition metal centres is a valuable reaction that can lead to interesting metal complexes and valuable cross-coupling products. While this field has progressed significantly in recent years, the sheer number of elements available in the periodic table means that many viable options have not yet been explored. There is great potential for fluorine to be the element cleaved from carbon, and for platinum to be the metal centre engaged in a new series of cross-coupling reactions.
Chapter 2 – A New Catalyst for Catalytic C-F Activation

2.1 Introduction

Recent work in the field of carbon-fluorine bond activation has met with a great deal of success. As discussed in Chapter 1, a range of transition metal species\textsuperscript{2-4,20,58,61,67,71-73,105} and several main-group compounds\textsuperscript{68,69} that have been successful in the activation of C-F bonds now exist. Although catalytic hydrodefluorination reactions and several examples of catalytic cross-coupling have been achieved,\textsuperscript{59,60,62,63,66,106-120} our group has demonstrated the only reported examples of C-C cross coupling with platinum. Moreover, our system has the broadest substrate scope of cross-coupling involving polyfluoroaryenes.\textsuperscript{74,75}

The catalyst we have used for all of our C-F activation chemistry to date has been the bis-platinum complex Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1). This complex has been highly successful for C-C cross-coupling reactions as discussed in Chapter 1 (see eq. 2.1). In Chapter 3, we will demonstrate its further application for C-O cross-coupling reactions to form aryl ethers.

\[
\begin{align*}
\text{F} & \quad \text{N} & \quad \text{R}' \\
\text{R} & \quad \text{F} & \quad \text{F} \\
& \quad \text{5 mol \% Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2 & \quad \text{0.6 equiv ZnMe}_2 \\
& \quad \text{CH}_3\text{CN, 60 °C} & \quad \text{R} & \quad \text{F} & \quad \text{N} & \quad \text{R}' \\
\end{align*}
\]

Because Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1) is generated through the reaction of PtCl$_2$(SMe)$_2$ (25) and methyllithium, we hypothesized that 25 might also react with another methyl organometallic to generate 1. Alternately, it may generate another Pt-methyl species that is the same or similar to the active species, 21, reported in our previous work.\textsuperscript{74} Because
dimethylzinc was the transmetalation reagent of choice in the catalytic cross-coupling (eq. 2.1), we sought to explore the possibility that this reagent would generate 1 or a comparably catalytically active species in situ. As such, we tested PtCl$_2$(SMe)$_2$ (25) as an alternative precatalyst for catalytic C-F activation and cross-coupling of polyfluoroarylimines (eq. 2.2).

With only a single catalyst (1) currently known for catalytic C-F activation and cross-coupling of these systems, the potential for an alternative is very promising. In this chapter, we discuss the application of PtCl$_2$(SMe)$_2$ to catalyze C-F activation and compare it to our previous work with Pt$_2$(CH$_3$)$_4$(SMe)$_2$. The chapter ends with the discussion of a substrate with a new and interesting functionalization pattern and a foray into further expanding the scope of the reaction.

2.2 Results and Discussion

2.2.1 Synthesis of Imines and Platinum Complexes

The starting materials for all of the imines generated are fluorinated benzaldehydes and primary benzyl or aryl amines. The imines are produced by a condensation reaction following a literature procedure.\textsuperscript{75} PtCl$_2$(SMe)$_2$ (25) and Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1) were synthesized using modified literature procedures.\textsuperscript{121}
2.2.2 Imine Scope

To compare the catalytic activity of PtCl$_2$(SMe)$_2$ (25) to that of Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1) for the cross-coupling of polyfluoroarylimines, we tested 25 on a range of substrates that had previously been tested with 1. By using similar conditions to those previously reported, we are able to draw direct comparisons between the catalysts based on both our own results and previously collected data. In addition, we tested two imine substrates that have not been previously reported. For these substrates, we completed the experiments with both platinum complexes in order to compare their reactivities. The majority of this work was done via NMR-scale reactions; the products were known, and so full isolation and characterization were not necessary. New products were generated and isolated on a preparative scale. Additionally, one known product generated using 25 as the precatalyst was isolated to confirm that the isolation methods previously reported were indeed applicable to the new system.

2.2.2.1 Reaction Protocol for Imine Scope Studies

All reactions were carried out in a nitrogen-filled glovebox. Both NMR-scale and preparative-scale reaction were performed. NMR-scale reactions were monitored periodically by $^1$H and $^{19}$F{$^1$H} NMR spectroscopy. Yields are based on integration of the imine CH=N peak of the product in the $^1$H NMR spectrum versus the Ar-H peaks of 1,3,5-trimethoxybenzene.

2.2.2.2 Results of Imine Scope Studies

Table 2.1 shows a comparison of the yields of reactions catalyzed by PtCl$_2$(SMe)$_2$ (25) to those catalyzed by Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1). In most cases the yields
obtained using 25 are lower than those obtained with 1, suggesting that PtCl₂(SMe₂)₂ is a less active catalyst than Pt₂(CH₃)₄(SMe₂)₂. Nevertheless, most reactions proceed in good-to-excellent yields and in one case, complex 25 provides the cross-coupling product in superior yield to 1.

**Table 2.1** Scope of Imine Reactivity with Two Platinum Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
<th>PtCl₂(SMe₂)₂&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pt₂(CH₃)₄(SMe₂)₂&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>60%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
<td>63%</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>7</td>
<td>97%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>9</td>
<td>63%</td>
<td>85%</td>
<td></td>
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<td>5</td>
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<td>92%</td>
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</tr>
<tr>
<td>6</td>
<td>12</td>
<td>11</td>
<td>&gt;95%</td>
<td>&gt;95%&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 10 mol % [Pt], ZnMe₂, CD₃CN, 60 °C, 24 h

<sup>b</sup> Pt₂(CH₃)₄(SMe₂)₂ is a less active catalyst than PtCl₂(SMe₂)₂.
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>CF₃NPh</td>
<td>CF₃NCH₃</td>
<td>60%</td>
</tr>
<tr>
<td>8</td>
<td>ClF₂NPh</td>
<td>ClF₂CH₃</td>
<td>30%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>F₂NBr</td>
<td>F₂NCH₃</td>
<td>30%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>F₂NPh</td>
<td>F₂NCH₃</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td>F₃NPh</td>
<td>F₃NCH₃</td>
<td>20%</td>
</tr>
</tbody>
</table>

*<sup>a</sup> 10 mol % PtCl₂(SMe₂)₂, 1.2 equiv. ZnMe₂, 24 h. Yields based on <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard unless otherwise indicated. <sup>b</sup> 5 mol % Pt₂(CH₃)₄(SMe₂)₂, 0.6 equiv ZnMe₂, 4-12 h. Isolated yields reported unless otherwise indicated. <sup>c</sup> Isolated yield. <sup>d</sup> Yields based on <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>e</sup> Reaction run using 1.2 equiv. ZnMe₂, 80° C, 24 h.*

To the extent that it has been tested, the substrate scope of reactions with the monoplatinum catalyst (25) is the same as that of the Pt₂(CH₃)₄(SMe₂)₂ system (1). The reaction proceeds in good yield for all substrates except for the 2,6-difluorinated imine 15 (entry 10), which also failed to react appreciably with 1. The low reactivity of 15 is consistent with the idea that a minimum of three electron-withdrawing groups in addition to the imine are required for C-F activation to occur.
In the case of imine 6 (entry 3) the C-C cross-coupling reaction with PtCl$_2$(SMe$_2$)$_2$ (25) produces better yield than in our previously reported work with Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1). When run on a preparative scale, this reaction generated imine 7 in 97% isolated yield. Thus, for substrate 6, the new precatalyst is a better choice.

Selective C-F activation at the ortho-position occurs even in the presence of other carbon-halogen bonds as in imines 8, 28, and 13 (entries 4, 8 and 9). Carbon-chlorine and carbon-bromine bonds are weaker than carbon-fluorine bonds, but at remote positions they are unreactive. When a chlorine substituent is present in the ortho position as in imine 12 (entry 6), however, exclusive carbon-chlorine bond activation is observed. This confirms that this reaction is highly selective for reactivity at the position ortho to the imine directing group, and points towards preferential reactivity at a site with an adjacent electron withdrawing group, as is also the case with imine 10.

The selectivity observed in the reaction of imine 10 (entry 5) is consistent with our previous results. Activation exclusively at the 2-position of the 2,3,6-trifluorinated substrate has been attributed to the electron withdrawing nature of the adjacent fluorine atom.

In the case of pentafluoroimine 17 (entry 11), only monomethylation products are observed in the reaction with platinum chloride complex 25. This is consistent with our previous work using Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1). Under forcing conditions with an excess of dimethylzinc, the 2,6-dimethylated product has been generated; we did not attempt to replicate this reaction in the course of these studies.

In the majority of the platinum-mediated C-F activation chemistry reported to this point by our group and by others who have studied similar systems, the
polyfluoroarylimine substrates have been fluorinated at the 2- and 6- positions on the phenyl ring where C-F activation occurs. Substitution at the 3, 4, and 5 positions of this ring has been varied and has included a variety of different electron withdrawing groups, whereas our efforts to-date have largely focused on the reactivity of imines with fluoro-substituents in both the 2- and 6- positions. Variation at the 2- and 6-positions has been attempted only for a second methylation of pentafluoroimine 17.

In an effort to expand the scope of the reaction beyond this substitution pattern, imine 26 (entry 7), which possesses a trifluoromethyl group, was evaluated. Unlike substituents such as chloro- (as in imine 12) or bromo-, the C-CF₃ bond is not expected to be susceptible to activation by the platinum species, and should be sufficiently electron-withdrawing to permit facile activation of the ortho C-F bond. The reaction of 26 is also interesting as it demonstrates the selective activation of an aromatic C-F bond over an aliphatic. This is likely due to the favourable geometry of C-F activation in the position ortho to a chelating imine. Like the majority of other substrates tested here, 26 was less reactive with PtCl₂(SMe₂)₂ than with Pt₂(CH₃)₄(SMe₂)₂. The reaction with Pt₂(CH₃)₄(SMe₂)₂ resulted in complete conversion to the methylated product, allowing for easier isolation of the product (27).

It is interesting to note that Pt-CH₃ signals are observed in ¹H NMR spectra of reaction mixtures involving PtCl₂(SMe₂)₂ (25). These signals are highly distinctive due to the large coupling constant and 34% abundance of ¹⁹⁵Pt, which is NMR active with a spin of ½. Although the platinum species responsible for this catalytic reaction process is not identical to that observed in reactions involving Pt₂(CH₃)₄(SMe₂)₂, it is clearly similar (vide infra).
The comparable scope of the reactions catalyzed by PtCl$_2$(SMe)$_2$ (25) and Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1), as well as spectroscopic evidence pointing to the formation of Pt-CH$_3$ bonds in the reactions of 25, suggests that the reaction mechanisms are the same or similar. The lower yields obtained with 25 may be due to incomplete formation of the active catalytic species or side reactions that lead to decomposition of the active catalyst. The mechanism of C-F activation with Pt$_2$(CH$_3$)$_4$(SMe)$_2$ was previously described in Chapter 1.

Given the similar scope of C-F activations using 1 and 25, there are practical advantages to 25 that may offset the lower reactivity of this complex. PtCl$_2$(SMe)$_2$ (25) is a yellow solid that is trivially prepared in >85% yield and can be stored for months under air at ambient conditions. It is the synthetic precursor to Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1). The preparation of the latter compound, while still reasonably straightforward, is more difficult and recrystallization inevitably reduces the yield. This species also requires storage under nitrogen at -35 °C and degrades over time. For reactions that do proceed in reasonable yield when using 25 as the catalyst, it may be more environmentally friendly and cost effective to use the complex that is more synthetically accessible.

2.2.3 Stoichiometric Reactions

The initial studies of C-F activation using PtCl$_2$(SMe)$_2$ (25) were catalytic in nature, following on the precedent of successful catalytic C-F activation chemistry performed in our group using Pt$_2$(CH$_3$)$_4$(SMe)$_2$. Given the success of the catalytic reaction, it has been of interest to examine the stoichiometric reactions between 25, dimethylzinc, and imine. These reactions do not constitute a complete mechanistic study,
but provide valuable preliminary insight into the nature of the active catalyst generated from PtCl$_2$(SMe)$_2$.

An obvious question that arises from this chemistry relates to the stringency of the conditions under which a C-F bond can be activated. It is clear from our earlier work$^{74}$ and the work of Crespo and Martinez$^2$ that 1 is capable of C-F activation to generate complex A (eq. 2.3). We sought to test whether PtCl$_2$(SMe)$_2$ was also capable of C-F activation. Imine 2 was heated with a stoichiometric amount of 25 in CD$_3$CN, but no reaction was observed (eq. 2.4).

\[
\text{Imine 2} \quad \text{CD}_3\text{CN, 60°C, 5h} \quad \text{No Reaction (2.4)}
\]

In contrast, reaction of the platinum chloride complex 25 with dimethylzinc showed clear evidence of formation of Pt-CH$_3$ bonds in the $^1$H NMR spectrum (eq. 2.5). The species generated here was only observed spectroscopically and was not isolated. As mentioned previously, Pt$_2$(CH$_3$)$_4$(SMe)$_2$ is not observed in this product mixture. It is also worth noting that the Pt-CH$_3$ species observed in the reaction between 1 and dimethylzine in the presence of imine 2 is not the resting state of the catalyst observed in our previous work. In our previous work, the resting complex included a coordinated
imine; no evidence of an imine proton coupled to $^{195}$Pt is observed in the $^1$H NMR spectrum of the complex produced in eq. 2.5.

$$\text{1.0 equiv } \text{PtCl}_2(\text{SMe}_2)_2 + \text{CD}_3\text{CN} \xrightarrow{60^\circ\text{C}, 24 \text{ h}} \text{Uncharacterized [Pt-CH}_3\text{]} \text{Complex}$$

(2.5)

With Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1), the addition of stoichiometric (or even substoichiometric) amounts of dimethylzinc to a stoichiometric mixture of imine and bisplatinum complex led to generation of the C-C cross-coupling product. In contrast, when imine 2 was reacted with stoichiometric amounts of platinum complex 25 and dimethylzinc, no cross-coupling product was observed and there was no evidence that C-F activation was occurring (eq. 2.6). There was, however, evidence once again of the formation of several species with Pt-CH$_3$ bonds.

$$\text{1.0 equiv } \text{PtCl}_2(\text{SMe}_2)_2 + \text{1.2 equiv } \text{ZnMe}_2, \text{CD}_3\text{CN} \xrightarrow{60^\circ\text{C}, 24 \text{ h}} \text{No Cross-Coupling Reaction}$$

(2.6)

When excess dimethylzinc is added to the reaction mixture in eq. 2.6, formation of the C-C cross-coupling product is indeed observed. This result, along with the observation of a species containing Pt-CH$_3$ (vide supra), suggests that the first equivalent of dimethylzinc may be consumed in the generation of an active species.
2.2.4 Preliminary Forays Toward a Broader Substrate Scope

Previous work in our group has included several preliminary attempts to apply directed C-F activation to substrates other than imines and to organometallics contributing R-groups other than the methyl from dimethylzinc. In one case, this has led to the synthesis of the series of polyfluoroaryl ethers that will be discussed in Chapter 3. In many other cases, attempted C-F activation and cross-coupling reactions using \( \text{Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2 \) have been unsuccessful.

The bench top stability of \( \text{PtCl}_2(\text{SMe}_2)_2 \) and its reactivity with the imines listed in Table 2.1 led us to speculate that substrates that did not react with \( \text{Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2 \) might be activated with this complex. This was not highly likely because in general the reactivity of \( \text{PtCl}_2(\text{SMe}_2)_2 \) had proven to be lower, but was still a worthwhile investigation.

Table 2.2 shows the substrates tested in catalytic reactions with the monoplatinum species 25. Where the results are available, the catalytic activity of 25 is compared to that of bisplatinum complex 1.
Table 2.2 Attempts to Expand the Substrate Scope of Catalytic C-F Activation Chemistry Using Catalytic PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2} and Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>MR\textsubscript{n}</th>
<th>yield (%)</th>
<th>PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2}\textsuperscript{a}</th>
<th>Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2}\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnMe\textsubscript{2}</td>
<td>60%</td>
<td>&gt;95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ZnPh\textsubscript{2}</td>
<td>&lt;5%</td>
<td>&lt;5%\textsuperscript{c}</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>ZnPh\textsubscript{2} + 0.1 ZnMe\textsubscript{2}</td>
<td>&lt;5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Si(OMe\textsubscript{4})</td>
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<td></td>
<td></td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td>ZnMe\textsubscript{2}</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>ZnMe\textsubscript{2}</td>
<td>unknown\textsuperscript{d}</td>
<td>&lt;5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} 10 mol % PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2}, 1.2 equiv. MR\textsubscript{n} unless otherwise indicated, 24 h. Yields based on \textsuperscript{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

\textsuperscript{b} 5 mol % Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2}, 1.2 equiv MR\textsubscript{n} unless otherwise indicated, 24 h. Yields based on \textsuperscript{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

\textsuperscript{c} 0.6 equiv. ZnMe\textsubscript{2} used.

\textsuperscript{d} Significant byproducts were formed.

Early attempts in our group to achieve catalytic C-F activation and cross-coupling reactions made use of diphenylzinc in the anticipation that coupling two sp\textsuperscript{2}-hybridized carbon centres would be more facile than the coupling of an sp\textsuperscript{2} with an sp\textsuperscript{3} centre.\textsuperscript{75} This proved not to be the case when using 1 as a catalyst. The lack of success of cross coupling with diphenylzinc resulted in a search for alternative organometallics. Dimethylzinc was found to be reactive, and a series of imines including those presented in Table 2.1 was synthesized for the first time. Diphenylzinc is similarly unreactive when
25 is used as a catalyst precursor (Table 2.2, entry 2) and no cross-coupling product was generated from this reaction.

In a further attempt to generate the phenylated cross-coupling product, a catalytic amount of dimethylzinc was added to a reaction mixture of imine, diphenylzinc, and platinum complex 25 (entry 3). It was theorized that reaction of the platinum complex with dimethylzinc might generate a species that could undergo subsequent transmetallation with the diphenylzinc. However, this reaction was not successful.

Catalytic C-O cross-coupling to generate aryl methyl ethers was also attempted (entry 4). While this reaction works very well with complex 1 as the catalyst, as will be discussed in Chapter 3, no ether product was observed by NMR spectroscopy when 25 was used.

Both 2,4,6-trifluorobenzaldehyde (30) and 2,4,6-trifluorobenzoic acid (31) are completely unreactive when combined with bisplatinum complex 1 and dimethylzinc. When reacted with 25, the benzaldehyde again demonstrates no reactivity (entry 5). Pt-CH$_3$ peaks do appear in this reaction spectrum, however, demonstrating again that there is an interaction between the platinum species and the dimethylzinc.

The reaction of the benzoic acid 31 (entry 6) generates considerably more complicated $^1$H NMR spectra. Poor resolution makes these spectra difficult to interpret; the substrate is likely present in its ionic form. Pt-CH$_3$ peaks are visible along with a second set of peaks that appear similar to those of the substrate. The $^{19}$F NMR spectrum is subject to similar broadening of peaks and a poorly defined signal appears over time in the aryl-F region. The same changes to the NMR spectrum occur when benzoic acid 31 and dimethylzinc are reacted in the absence of any platinum species. It is possible that C-
F activation is occurring with this substrate, but the evidence suggests a benzoate-zinc ion pair is forming and that platinum is not involved. This chemistry may be worth pursuing further in a buffered environment or with an alternative substrate where purely electrostatic interactions are less likely. Pre-formation of the benzoate or the use of a larger excess of dimethylzinc to first generate the benzoate in situ may also provide conditions amenable to C-F activation chemistry.

2.3 Conclusions

In this chapter, the catalytic cross-coupling of polyfluoroarylimines has been demonstrated with a new platinum catalyst, PtCl$_2$(SMe$_2$)$_2$ (25). This reaction generates C-C cross coupling products in moderate-to-excellent yields. Although these yields are not typically as good as those achieved with previously reported Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1), the advantages in terms of ease of preparation and cost of the catalyst make this a viable alternative route to the use of 1 in platinum-catalyzed C-F bond activation.

2.4 Experimental

2.4.1 General Methods

Manipulation of all compounds was carried out using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled MBraun glovebox (O$_2$ < 2 ppm). Reactions were heated in an oil bath and those at preparative scale were stirred with a Teflon-coated magnetic stir bar. Reaction mixtures were concentrated either using rotary evaporation methods or by use of a Schlenk line. Glassware was cleaned by soaking in a base bath of potassium hydroxide, water, and isopropanol, (100 g : 100 mL : 1 L) followed by sequential rinsing with deionized water and acetone. When necessary,
glassware was first cleaned with aqua regia, consisting of nitric acid and hydrochloric acid freshly mixed in a 1:3 ratio, and then rinsed with water.

2.4.2 Reagents and Solvents

All organic reagents were obtained from commercial sources and used as received, unless otherwise stated. Potassium tetrachloroplatinate (II) was purchased from Strem Chemicals and used as received. All silicon reagents were purchased from commercial sources, degassed, and used under inert atmosphere. ZnMe$_2$ (2.0 M in toluene), was purchased from Aldrich, titrated with LiCl and I$_2$ according to a literature procedure$^{122}$ and used as received. CD$_3$CN was purchased in 1 g ampules and degassed prior to use. CH$_3$CN was dried over molecular sieves and degassed prior to use. 1,3,5-Trimethoxybenzene was sublimed prior to use.

2.4.3 Chromatography

Flash chromatography was used to isolate imine products. The solvent was eluted using either nitrogen or air pressure at an approximate rate of two inches per minute. Basified columns were prepared by eluting a 1:1 triethylamine:hexanes mixture, followed by elution of an equal volume of pure hexanes.

2.4.4 Physical and Spectroscopic Measurements

NMR spectra were recorded on Bruker Avance 300 ($^1$H at 300 MHz and $^{19}$F{$^1$H} at 282 MHz) or Bruker Avance 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) magnetic resonance spectrometers. $^1$H and $^{13}$C chemical shifts are reported in parts per million and referenced to residual solvent. $^{19}$F NMR spectra are reported in parts per million and referenced to C$_6$H$_5$F (-113.1 ppm). Coupling constant values ($J$) were extracted assuming
first-order coupling and are reported in Hertz (Hz). Spin multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets. All spectra were obtained at 25 °C. 1,3,5-trimethoxybenzene was used as an internal standard to determine NMR yields. Elemental analyses were obtained using a Carlo Erba Elemental Analyzer EA 1108.

2.4.5 Synthesis and Characterization of Platinum Species

\( \text{PtCl}_2(\text{SMe})_2 \) (25) was synthesized using a modified literature procedure.\(^{121}\) \( \text{K}_2[\text{PtCl}_4] \) (2.01 g, 4.84 mmol) was weighed into a 100 mL 3-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a rubber septum, a stopper, and a gas inlet adaptor. Deionized water (50 mL) was added by pipette to the flask. The flask was placed under vacuum briefly and then refilled with \( \text{N}_2 \). This process was repeated two more times. Dimethyl sulphide (2.58 mL, 35.07 mmol) was then added via syringe and a pink-brown suspension was formed. The suspension was heated to 90 °C. After approx. 20 min, a clear yellow solution was observed. The solution was heated for an additional 5-10 min and was then cooled to room temperature, followed by extraction with methylene chloride (5 x 30 mL). The combined organic extracts were dried over MgSO\(_4\), filtered and concentrated to dryness under vacuum to give a yield of 1.664 g (88%). Characterization data is consistent with previously reported data.\(^{121}\)

\( \text{Pt}_2(\text{CH}_3)_4(\text{SMe})_2 \) (1) was synthesized using a modified literature procedure.\(^{121}\) \( \text{PtCl}_2(\text{SMe})_2 \) (25) (1.00 g, 2.56 mmol) was weighed into an oven-dried 250 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a rubber septum, and a gas inlet adaptor. The flask was placed under vacuum briefly and then refilled with \( \text{N}_2 \).
This process was repeated two more times. Dry diethyl ether (50 mL) was then added via syringe and the solid was dissolved. The solution was cooled to 0 °C and methyllithium (8.54 mL of 1.5 M solution in diethyl ether, 12.80 mmol) was added via syringe. The reaction was stirred for 40 min at 0 °C. A chilled 1:9 solution of saturated aqueous ammonium chloride: distilled water (45 mL) was added. The reaction was extracted with diethyl ether (3 x 50 mL), also chilled to 0 °C. The combined organic extracts were dried over MgSO₄ for 10 min and then further treated with decolourizing charcoal for an additional 5 min. The organic extracts were then filtered and concentrated to dryness under vacuum. The white solid was recrystallized in acetone at -35 °C to obtain a white crystalline solid in 25-30% yield (~0.2 g). Characterization data is consistent with previously reported data.¹²¹

2.4.6 Synthesis and Characterization of Imines

\[
\text{N-(2,4,6-trifluorophenylbenzyldene)benzylimine (2)}
\]

was synthesized according to a literature procedure.⁷⁵ 2,4,6-trifluorobenzaldehyde (0.65 g, 4.06 mmol) was weighed into a 100 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (60 mL) was added by pipette. Benzyl amine (0.465 mL, 4.26 mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with \( \text{N}_2 \). This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The
residue was extracted with \( n \)-pentane (3 x 20 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation. The product was further purified by Kugelrohr distillation to give a light yellow oil (0.88 g, 87%). Characterization data is consistent with previously reported data.\(^{75}\)

\[
\text{N-}(4\text{-cyano-2,6-difluorophenylbenzylidene})\text{benzylimine (6)}
\]

was synthesized according to a literature procedure.\(^{75}\) 4-cyano-2,6-difluorobenzaldehyde (0.25 g, 1.50 mmol) was weighed into a 25 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (12 mL) was then added by pipette. Benzyl amine (0.171 mL, 1.57 mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with \( \text{N}_2 \). This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The residue was extracted with \( n \)-pentane (3 x 15 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation to give a yellow solid (0.34 g, 88%). Characterization data is consistent with previously reported data.\(^{75}\)

\[
\text{N-}(4\text{-bromo-2,6-difluorophenylbenzylidene})\text{benzylimine (8)}
\]

was synthesized according to a literature procedure.\(^{75}\) 4-bromo-2,6-difluorobenzaldehyde (0.66 g, 3.00
mmol) was weighed into a 50 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (12 mL) was added by pipette. Benzyl amine (0.343 mL, 3.15 mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with N₂. This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The residue was extracted with \(n\)-pentane (3 x 15 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation to give a light yellow solid (0.88 g, 95%). Characterization data is consistent with previously reported data.\(^{75}\)

![Chemical Structure](image)

\textit{N-(2,4,6-trifluorophenylbenzylidene)-4-bromobenzylimine} (13) was synthesized according to a literature procedure.\(^{75}\) 2,4,6-trifluorobenzaldehyde (0.32 g, 2.00 mmol) was weighed into a 100 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (30 mL) was added by pipette. 4-bromobenzyl amine (0.39 g, 2.10 mmol) was then added. The flask was placed under vacuum briefly and then refilled with N₂. This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The residue was extracted with \(n\)-pentane (3 x 20 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation to give a white solid (0.45 g, 69%). Characterization data is consistent with previously reported data.\(^{75}\)
**N-(2,3,6-trifluorophenylbenzylidene)benzylimine (10)** was synthesized according to a literature procedure.\(^{75}\) 2,3,6-trifluorobenzaldehyde (0.48 g, 3.00 mmol) was weighed into a 50 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (20 mL) was added by pipette. Benzyl amine (0.343 mL, 3.15 mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with N\(_2\). This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The residue was extracted with \(n\)-pentane (3 x 20 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation. The product was further purified by Kugelrohr distillation to give a yellow solid (0.91 g, 90%). Characterization data is consistent with previously reported data.\(^{75}\)

**N-(3-chloro-2-fluoro-6-trifluoromethylbenzylidene)benzylimine (26)** was synthesized according to a modified literature procedure.\(^{75}\) 3-chloro-2-fluoro-6-trifluoromethyl benzaldehyde (0.2 g, 0.131 mL, 0.88 mmol) was weighed into a 25 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (10 mL) was added by pipette. Benzyl amine (0.10 mL, 0.93
mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with N₂. This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum overnight. The residue was extracted with n-pentane (3 x 15 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation. The product was further purified by Kugelrohr distillation to give a yellow oil (0.16 g, 57 %). ¹H NMR (CD₃CN, 300 MHz): δ 8.62 (s, 1H), 7.69 (t, 1H, J = 7.8 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.37-7.25 (m, Ar-H, 5H), 4.87 (s, 2H). ¹⁹F NMR (CD₃CN, 282 MHz): δ -59.2 (s, 3F), δ -116.6 (s, 1F). ¹³C-APT NMR (CD₃CN, 100 MHz): δ 158.8 (s), 156.3 (s) 154.9 (s, HCN), 139.4 (s), 132.7 (s), 129.8 (s), 129.3 (s), 128.4 (s), 126.4 (s, C₃), 124.0 (m, CF₃), 123.3 (s, C₃), 66.8 (s, NCH₂Ph).

N-(2,4,6-trifluorophenylbenzylidene)phenylimine (4), N-(2,4,6-trifluorophenylbenzylidene)-2-chlorobenzylimine (28), N-(2,6-difluorophenylbenzylidene)benzylimine (15), N-(2,3,4,5,6-pentafluorophenylbenzylidene)benzylimine (17), and N-(2-chloro-3,6-difluorophenylbenzylidene)benzylimine (12) were generously contributed by Tongen Wang. Characterization matched previously reported data.⁷⁵
2.4.7 Imine Scope

2.4.7.1 NMR Scale Reactions

All reactions for imine scope studies were performed on a 0.34 mmol of imine scale in an NMR tube with a screw cap. Stock solutions of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (I), PtCl$_2$(SMe)$_2$ (25) 1,3,5-trimethoxybenzene, and all imines were prepared in CD$_3$CN.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with ZnMe$_2$ using PtCl$_2$(SMe)$_2$.** 0.1 mL of PtCl$_2$(SMe)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. N-(2,4-Difluoro-6-methylbenzylidene)benzylimine (3) was generated in 60% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.$^{75}$
Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)phenylimine (4) with ZnMe$_2$ using PtCl$_2$(SMe$_2$)$_2$. 0.1 of mL PtCl$_2$(SMe$_2$)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of $N$-(2,4,6-trifluorophenylbenzylidene)phenylimine (4) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(2,4-Difluoro-6-methylbenzylidene)phenylimine (5) was generated in 63% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.$^{75}$

Reaction of $N$-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) with ZnMe$_2$ using PtCl$_2$(SMe$_2$)$_2$. 0.1 mL of PtCl$_2$(SMe$_2$)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of $N$-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C.
and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(4-Cyano-2-fluoro-6-methylbenzylidene)benzylimine (7) was generated in >95% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.\textsuperscript{75}

![Chemical structure of 7](image)

**Reaction of $N$-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) with ZnMe\textsubscript{2} using PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2}**. 0.1 mL of PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2} solution (0.034 mmol in 1.0 mL CD\textsubscript{3}CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\textsubscript{3}CN, 0.33 equiv), 0.18 mL CD\textsubscript{3}CN, 0.1 mL of $N$-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) solution (0.34 mmol in 1.0 mL CD\textsubscript{3}CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(4-Bromo-2-fluoro-6-methylbenzylidene)benzylimine (9) was generated in 63% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.\textsuperscript{75}

![Chemical structure of 9](image)

**Reaction of $N$-(2,3,6-trifluorophenylbenzylidene)benzylimine (10) with ZnMe\textsubscript{2} using PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2}**. 0.1 mL of PtCl\textsubscript{2}(SMe\textsubscript{2})\textsubscript{2} solution (0.034 mmol in 1.0 mL CD\textsubscript{3}CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-
trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of N-(2,3,6-trifluorophenylbenzylidene)benzylimine (10) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. N-(3,6-Difluoro-2-methylbenzylidene)benzylimine (11) was generated in 50% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.$^{75}$

![Chemical Reaction Diagram]

**Reaction of N-(2-chloro-3,6-difluorophenylbenzylidene)benzylimine (12) with ZnMe$_2$ using PtCl$_2$(SMe)$_2$.** 0.1 mL of PtCl$_2$(SMe)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of N-(2-chloro-3,6-difluorophenylbenzylidene)benzylimine (12) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. N-(3,6-Difluoro-2-methylbenzylidene)benzylimine (11) was generated in >95% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data.$^{75}$
**Reaction of \(N\)-(3-chloro-2-fluoro-6-trifluoromethylphenylbenzylidene)benzylimine (26) with ZnMe\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\).**

0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.18 mL CD\(_3\)CN, 0.1 mL of \(N\)-(3-chloro-2-fluoro-6-trifluoromethylphenylbenzylidene)benzylimine (26) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h. \(N\)-(3-Chloro-2-methyl-6-trifluoromethylphenylbenzylidene)benzylimine (27) was generated in 60% yield based on NMR spectroscopy. 

\(^1\)H NMR (CD\(_3\)CN, 300 MHz): \(\delta\) 8.62 (s, 2H), 7.58 (s, 1H), 7.37 (s, 1H), 7.36 (s, 2H), 7.32-7.29 (m, Ar-H, 2H), 4.87 (s, 2H), 2.40 (s, 3H).

\(^{19}\)F NMR (CD\(_3\)CN, 282 MHz): \(\delta\) -58.9 (s, 3F).

\(^{13}\)C-APT NMR (CD\(_3\)CN, 100 MHz): \(\delta\) 160.3 (s, HCN), 130.5 (s) 129.6 (s), 129.3 (s), 128.1 (s), 126.5 (s), 125.7 (s), 66.4 (s, NCH\(_2\)Ph), 17.7 (s, CH\(_3\)).

Reaction of \(N\)-(2,4,6-trifluorophenylbenzylidene)-2-chlorobenzylimine (28) with ZnMe\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\). 0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.18 mL CD\(_3\)CN, 0.1 mL of \(N\)-(2,4,6-trifluorophenylbenzylidene)-2-chlorobenzylimine (28) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h. \(N\)-(2,4-Difluoro-6-methylbenzylidene)-2-chlorobenzylimine (29) was generated in 30% yield based on NMR spectroscopy, along with the formation of significant byproducts. Characterization data is consistent with previously reported data.\(^{75}\)

Reaction of \(N\)-(2,4,6-trifluorophenylbenzylidene)-4-bromobenzylimine (13) with ZnMe\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\). 0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.18 mL CD\(_3\)CN, 0.1 mL of \(N\)-(2,4,6-trifluorophenylbenzylidene)-4-bromobenzylimine (13) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.02 mL dimethylzinc solution
(2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(2,4-Difluoro-6-methylbenzylidene)-4-bromobenzylimine (14) was generated in 30% yield based on NMR spectroscopy, along with the formation of significant byproducts. Characterization data is consistent with previously reported data.\textsuperscript{75}

$\begin{align*}
\text{Reaction of } N$-\text{(2,6-difluorophenylbenzylidene)}\text{benzylimine (15) with ZnMe$_2$ using } \\
\text{PtCl$_2$(SMe$_2$)$_2$. } 0.1 \text{ mL of PtCl$_2$(SMe$_2$)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of } N$-\text{(2,6-difluorophenylbenzylidene)}\text{benzylimine (15) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated less than 5% product yield. The product was not characterized.}
\end{align*}$

$\begin{align*}
\text{Reaction of } N$-\text{(2,3,4,5,6-pentafluorophenylbenzylidene)}\text{benzylimine (17) with ZnMe$_2$ using } \\
\text{PtCl$_2$(SMe$_2$)$_2$. } 0.1 \text{ mL of PtCl$_2$(SMe$_2$)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of}
\end{align*}$
1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.18 mL CD$_3$CN, 0.1 mL of N-(2,3,4,5,6-pentafluorophenylbenzylidene)benzylimine (17) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. N-(2,3,4,5-Tetrafluoro-6-methylbenzylidene)benzylimine (18) was generated in 20% yield based on NMR spectroscopy. Characterization data is consistent with previously reported data. 

2.4.7.2 Preparative Scale Reactions

Reaction of N-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) with ZnMe$_2$ using PtCl$_2$(SMe)$_2$. Under an atmosphere of nitrogen, PtCl$_2$(SMe)$_2$ (0.1 mL, 0.175 M in CH$_3$CN, 0.0175 mmol) was measured by micropipet into a 25 mL 2-necked round bottom flask equipped with a stirbar, a rubber septum and a vacuum inlet adaptor. CH$_3$CN (7 mL) was added to the flask and the solid was dissolved. N-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) (0.0448 g, 0.175 mmol) and ZnMe$_2$ (0.210 mL, 1.0 M in Toluene, 0.210 mmol) were then added sequentially by syringe. The resulting solution was heated at 60 °C for 24 h. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was washed with petroleum ether (35-60) (3 x 20 mL). The combined organic extracts were filtered through Celite and concentrated by rotary evaporation to provide the crude imine.
product. The product was further purified by flash column chromatography on a basified column (SiO\textsubscript{2}, 70-230 mesh, 10% ethyl acetate in hexanes as eluent) to generate \textit{N}-(4-cyano-2-fluoro-6-methylbenzylidene)benzylimine (7) in 97% yield. Characterization data is consistent with previously reported data.\textsuperscript{75}

\[
\begin{align*}
\text{CF}_3 & \quad \text{N} \quad \text{Ph} \\
\text{Cl} & \quad \text{F} \quad 26 \\
\end{align*}
\]

\[
\begin{align*}
5 \text{ mol \% Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2 & \quad 1.2 \text{ equiv ZnMe}_2, \text{CH}_3\text{CN} \\
60 \degree \text{C}, 24 \text{ h} & \quad 27 \\
\end{align*}
\]

**Reaction of \textit{N}-(3-chloro-2-fluoro-6trifluoromethylphenylbenzylidene)benzylimine (26) with ZnMe\textsubscript{2} using Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2}.** Under an atmosphere of nitrogen, Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2} (0.1 mL, 0.079 M in CH\textsubscript{3}CN, 0.0079 mmol) was measured by micropipet into a 25 mL 2-necked round bottom flask equipped with a stirbar, a rubber septum, and a vacuum inlet adaptor. CH\textsubscript{3}CN (7 mL) was added to the flask and the solid was dissolved. \textit{N}-(3-chloro-2-fluoro-6-trifluoromethylphenylbenzylidene)benzylimine (26) (0.0497 g, 0.16 mmol) and ZnMe\textsubscript{2} (0.189 mL, of 1.0 M in Toluene, 0.189 mmol) were then added sequentially by syringe. The resulting solution was heated at 60 \degree \text{C} for 24 h. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was washed with petroleum ether (35-60) (3 x 20 mL). The combined organic extracts were filtered through Celite and concentrated by rotary evaporation to provide the crude imine product. The product was further purified by flash column chromatography on a basified column (SiO\textsubscript{2}, 70-230 mesh, 10% ethyl acetate in hexanes as eluent) to generate \textit{N}-(3-chloro-2-methyl-6-trifluoromethylphenylbenzylidene)benzylimine (27) in 71% yield. Characterization data is reported above.
2.4.7.3 Stoichiometric Reactions for Mechanistic Investigations

Stock solutions of Pt₂(CH₃)₄(SMe₂)₂ (1), PtCl₂(SMe₂)₂ (25), 1,3,5-trimethoxybenzene, and imine (2) were prepared in CD₃CN.

![Reaction 2](image)

Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with PtCl₂(SMe₂)₂ (25). 0.1 mL of PtCl₂(SMe₂)₂ solution (0.185 mmol in 1.0 mL CD₃CN, 1.0 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.062 mmol in 1.0 mL CD₃CN, 0.33 equiv), 0.3 mL CD₃CN, and 0.1 mL of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.185 mmol in 1.0 mL CD₃CN, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by ¹H and ¹⁹F NMR spectroscopy over 24 h, but no reaction was observed.

![Reaction 3](image)

Reaction of PtCl₂(SMe₂)₂ (25) and ZnMe₂. 0.1 mL of PtCl₂(SMe₂)₂ solution (0.185 mmol in 1.0 mL CD₃CN, 1.0 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.062 mmol in 1.0 mL CD₃CN, 0.33 equiv), 0.31 mL CD₃CN, and 0.093 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the
reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. Multiple Pt-CH$_3$ peaks were observed by $^1$H NMR spectroscopy ($^1$H NMR (CD$_3$CN, 300 MHz): $\delta$ 1.2-0.75 (several s, $J_{Pt-H}$ clearly visible)), but products were not further characterized.

![Chemical Structure](image)

**Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with PtCl$_2$(SMe$_2$)$_2$ and ZnMe$_2$.** 0.1 mL PtCl$_2$(SMe$_2$)$_2$ solution (0.185 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.062 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.21 mL CD$_3$CN, and 0.1 mL of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.185 mmol in 1.0 mL CD$_3$CN, 1.0 equiv), and 0.093 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h, but no cross-coupling product was observed.

**2.4.7.4 Substrate Scope Exploration**

All reactions for substrate were performed on a 0.34 mmol of fluoroorganic scale in an NMR tube with a screw cap. Stock solutions of Pt$_2$(CH$_3$)$_4$(SMe$_2$)$_2$ (1), PtCl$_2$(SMe$_2$)$_2$ (25) 1,3,5-trimethoxybenzene, and all fluoroorganics were prepared in CD$_3$CN.
Reaction of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) with ZnPh\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\). 0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.18 mL CD\(_3\)CN, 0.1 mL of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.0088 g diphenylzinc (0.40 mmol, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) with ZnPh\(_2\) using Pt\(_2\)(CH\(_3\))\(_4\)(SMe\(_2\))\(_2\). 0.1 mL of Pt\(_2\)(CH\(_3\))\(_4\)(SMe\(_2\))\(_2\) solution (0.017 mmol in 1.0 mL CD\(_3\)CN, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.3 mL CD\(_3\)CN, 0.1 mL of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.0088 g diphenylzinc (0.40 mmol, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by
\(^1\)H and \(^19\)F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of \(N\)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with ZnPh\(_2\) and ZnMe\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\). 0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.18 mL CD\(_3\)CN, 0.1 mL of \(N\)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL CD\(_3\)CN, 1.0 equiv) and 0.0088 g diphenylzinc (0.40 mmol, 1.2 equiv), and 0.0034 mL dimethylzinc solution (2.0 M in toluene, 0.1 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by \(^1\)H and \(^19\)F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of 2,4,6-trifluorophenylbenzaldehyde (30) with ZnMe\(_2\) using PtCl\(_2\)(SMe\(_2\))\(_2\). 0.1 mL of PtCl\(_2\)(SMe\(_2\))\(_2\) solution (0.034 mmol in 1.0 mL CD\(_3\)CN, 0.10 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_3\)CN, 0.33 equiv), 0.28 mL CD\(_3\)CN, 0.1 mL of 2,4,6-
trifluorophenylbenzaldehyde (30) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of 2,4,6-trifluorophenylbenzaldehyde (30) with ZnMe$_2$ using Pt$_2$(CH$_3$)$_4$(SMe)$_2$. 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL CD$_3$CN, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.28 mL CD$_3$CN, 0.1 mL of 2,4,6-trifluorophenylbenzaldehyde (30) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of 2,4,6-trifluorophenylbenzoic acid (31) with ZnMe$_2$ using PtCl$_2$(SMe)$_2$. 0.1 mL of PtCl$_2$(SMe)$_2$ solution (0.034 mmol in 1.0 mL CD$_3$CN, 0.10 equiv) was
measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.28 mL CD$_3$CN, 0.1 mL of 2,4,6-trifluorophenylbenzoic acid (31) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.

Reaction of 2,4,6-trifluorophenylbenzoic acid (31) with ZnMe$_2$ using Pt$_2$(CH$_3$)$_4$(SMe)$_2$. 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL CD$_3$CN, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.28 mL CD$_3$CN, 0.1 mL of 2,4,6-trifluorophenylbenzoic acid (31) solution (0.34 mmol in 1.0 mL CD$_3$CN, 1.0 equiv) and 0.02 mL dimethylzinc solution (2.0 M in toluene, 1.2 equiv). The tube was fitted with a screw cap. The tube was heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated product in <5% yield. The product was not characterized.
Chapter 3 – Catalytic C-F Activation as a Route to Polyfluoroaryl Ethers

3.1 Introduction

Aryl ethers are valuable synthetic targets. A variety of methods to access aryl ethers has been generated; several of these are discussed in Chapter 1. Cross-coupling reactions represent a significant advance in the generation of alkyl aryl ethers, as these methods typically operate under mild conditions. While improvements in cross-coupling protocols have rendered a wide range of ethers synthetically accessible, there is still a need for new methodologies to produce the diverse targets of organic and organometallic chemistry.

Previous research performed in our group has demonstrated efficient platinum (II)-catalyzed methylation of polyfluoroaryl imines with dimethylzinc (eq. 3.1 and Chapter 2). This reaction is already highly selective, and consequently one of our major goals has been to expand the substrate scope to generate cross-coupling products with new substituents other than methyl.

\[
\begin{align*}
\text{R}^{\prime} &\quad \underset{5 \text{ mol } \% \text{ Pt}_2(\text{CH}_3)_4(\text{SMe})_2}{\text{R}}^{\prime} \quad \text{0.6 equiv Me}_2\text{Zn, CH}_3\text{CN} \\
&\quad \text{F} \quad \text{F} \quad \text{N} \quad \text{R}^{\prime} \quad \text{CH}_3 \quad \text{N} \quad \text{R}^{\prime} \quad \text{R} \\
&\quad \text{60 °C, 8-24h} \\
\end{align*}
\]

In the early stages of substrate scope exploration, we tested phenyltrimethoxysilane as a transmetallation reagent in the hopes that the phenyl group could be transferred catalytically to the aryl fluoride (eq. 3.2). We anticipated that such \(\text{sp}^2-\text{sp}^2\) bond formation would be even more facile than the already successful cross-coupling between \(\text{sp}^2\)- and \(\text{sp}^3\)-hybridized carbons when using dimethylzinc.
The reaction of \( N-(2,4,6\text{-trifluorobenzylidene})\text{benzylimine} \) \( \text{2} \) with \( \text{PhSi(OMe)}_3 \) initially generated the aryl-methyl cross-coupling product \( \text{3} \), but in less than 5% yield. This suggested that a methyl group from the precatalyst was transferred stoichiometrically. The contribution of the methyl group from the catalyst was confirmed by isotopic labeling studies.\(^{74}\) Upon retesting under slightly altered conditions, we found that a new imine, \( \text{33} \), was generated as the major product, in addition to \( N-(2,4\text{-difluoro-6-methylbenzylidene})\text{benzylimine} \) \( \text{3} \) (eq. 3.3).

The new imine was identified as the aryl ether \( N-(2,4\text{-difluoro-6-methoxybenzylidene})\text{benzylimine} \), \( \text{33} \), demonstrating that a catalytic carbon-oxygen bond-forming reaction had occurred. This reaction, which is an unusual example of Pt-catalyzed C-O bond formation, demonstrates the potential versatility of Pt-catalyzed selective, catalytic carbon-fluorine bond activation chemistry. We consequently were motivated to explore the scope of this process. This chapter describes the optimization of this reaction and the application of this chemistry to a range of silanes and imines. The chapter ends with a discussion of our efforts towards understanding the unique reaction mechanism of this carbon-oxygen cross-coupling reaction.
3.2 Synthetic Studies – Optimization and Substrate Scope

3.2.1 Silane Scope

In the initial reaction shown in eq. 3.3, a significant amount of the aryl methyl ether was generated. However, at only 46% conversion from starting material to product this reaction was certainly not optimal for synthetic application. As such, our first goal was to optimize the reaction conditions. We began by studying a range of silanes that would be potentially applicable to this reaction.

Table 3.1 presents a summary of our studies of silane substrate scope. Several different silanes were tested in a number of solvents.
### Table 3.1 Silane Substrate Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSi(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>60</td>
<td>24 h</td>
<td>46%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>PhSi(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>35</td>
<td>44 h</td>
<td>39%</td>
</tr>
<tr>
<td>3</td>
<td>PhSi(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
<td>24 h</td>
<td>36%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>60</td>
<td>24 h</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>35</td>
<td>24 h</td>
<td>39%</td>
</tr>
<tr>
<td>6</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
<td>24 h</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>THF</td>
<td>35</td>
<td>24 h</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>8</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt; (0.6 equiv)</td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
<td>24 h</td>
<td>55%</td>
</tr>
<tr>
<td>9</td>
<td>Si(OMe)&lt;sub&gt;4&lt;/sub&gt; (0.3 equiv)</td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
<td>24 h</td>
<td>44%</td>
</tr>
<tr>
<td>10</td>
<td>MeSi(OMe)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>35</td>
<td>24 h</td>
<td>64%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;Si(OMe)</td>
<td>THF</td>
<td>35</td>
<td>24 h</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>MeSi(OEt)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>THF</td>
<td>35-60&lt;sup&gt;d&lt;/sup&gt;</td>
<td>44 h</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>13</td>
<td>Si(OEt)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>THF</td>
<td>35</td>
<td>19 h</td>
<td>15%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields based on <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard and integration of CHN proton.  
<sup>b</sup> A small amount (<10%) of aryl-methyl cross-coupling product (3) also observed.  
<sup>c</sup> Remaining 36% is unidentified imine byproduct.  
<sup>d</sup> Reaction mixture heated to 35°C for 24 h, then 60°C for an additional 20 h.

The use of PhSi(OMe)<sub>3</sub> under different conditions gave modest yields of aryl methyl ether product (Table 3.1, entries 1-3). The best results were those initially obtained in CD<sub>3</sub>CN at 60 °C (entry 1), although at 35 °C in CD<sub>3</sub>CN the C-C cross-coupling product is not observed (entry 2). Nearly the same result is obtained in CD<sub>2</sub>Cl<sub>2</sub>, although in this case 3 is again a byproduct of the reaction.

The use of Si(OMe)<sub>4</sub> in CD<sub>3</sub>CN generated higher yields than PhSi(OMe)<sub>3</sub> at 60 °C (entry 4) and comparable yields at 35 °C (entry 5). A preliminary exploration of
alternate solvents revealed that yields were further improved by the use of \( \text{CD}_2\text{Cl}_2 \) (entry 6) or THF (entry 7) as a solvent. These solvents were thus used in further studies of substrate scope. A more exhaustive solvent study is presented later in this chapter.

Reduced loadings of \( \text{Si(OMe)}_4 \) (at 0.6 and 0.3 equiv, entries 8 and 9, respectively) were also tested. Our previous work has shown that dimethylzinc is able to contribute both of its methyl groups to the C-C cross-coupling reaction.\(^{75}\) Also, silanes have been shown to react more than once in addition-elimination reactions, allowing sub-stoichiometric amounts of tetramethoxysilane to lead to quantitative product formation.\(^{101}\) However, in the case of our reaction, the use of substoichiometric amounts of silane gave lower yields, which may suggest that the silicon-oxygen bond of the silane byproduct is significantly less labile than that of tetramethoxysilane.

Several other silanes were also tested, with \((\text{CH}_3)_n\text{Si(OMe)}_{4-n} \) (entries 10 and 11) giving lower yields of 33 than tetramethoxysilane, but still generating the aryl ether as the major imine product, as detected by NMR spectroscopy. In an effort to extend the scope of products generated beyond aryl methyl ethers, two different ethoxysilanes were tested (entries 11 and 12). While the yields on these reactions are very low, small amounts of an imine product were identified in the NMR spectrum of entry 12. The product is believed to be imine 34, and is likely a result of stoichiometric cross-coupling. This reaction merits further study. Once this ether is generated in higher yields, it should be possible to isolate and characterize the product.
3.2.2 Solvent and Temperature Optimization

In the process of exploring the silane scope for the ether synthesis reaction, a strong solvent dependence was noticed, with yields ranging from <40 to >95% depending on the conditions. Because of this variation, we set out to do a more exhaustive study of solvent and temperature conditions for this reaction.

In Section 2.2.3 it was demonstrated that Si(OMe)$_4$ was a better substrate than phenyltrimethoxysilane for the aryl ether synthesis. Reactions with Si(OMe)$_4$ give higher yields (with the best >95%), and does not lead to the generation of the C-C cross coupling product. As such, Si(OMe)$_4$ was the silane used for solvent optimization studies. Table 3.2 shows a range of solvents and temperatures that were tested with the imine $N$-(2,4,6-trifluorobenzylidene)benzylimine 2.
Table 3.2 Optimization of Conditions for C-O Cross Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Equiv. Silane</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD$_3$CN</td>
<td>35</td>
<td>1.2</td>
<td>39%</td>
</tr>
<tr>
<td>2</td>
<td>CD$_3$CN</td>
<td>60</td>
<td>1.2</td>
<td>63%</td>
</tr>
<tr>
<td>3</td>
<td>d$_6$-DMSO</td>
<td>35</td>
<td>1.2</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$D$_6$</td>
<td>35</td>
<td>1.2</td>
<td>37%</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$D$_6$</td>
<td>60</td>
<td>1.2</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>CD$_2$Cl$_2$</td>
<td>35</td>
<td>1.2</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>CD$_2$Cl$_2$</td>
<td>rt (17)</td>
<td>1.2</td>
<td>58%</td>
</tr>
<tr>
<td>8</td>
<td>CD$_2$Cl$_2$/THF</td>
<td>35</td>
<td>1.2</td>
<td>80%</td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>35</td>
<td>1.2</td>
<td>&lt;10%b</td>
</tr>
<tr>
<td>10</td>
<td>DCE</td>
<td>80</td>
<td>1.2</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>35</td>
<td>1.2</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>60</td>
<td>1.2</td>
<td>61%</td>
</tr>
</tbody>
</table>

a Yields based on $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard and integration of CHN proton.  
b Conversion estimated based on $^{19}$F{$^1$H}NMR spectroscopy by integration of starting material and product peaks.

Due to the potential for certain solvents to interact with the platinum complex, only aprotic solvents were used. As discussed previously, there was a strong dependence on temperature for the yield observed in CD$_3$CN (entries 1 and 2). The reaction in d$_6$-DMSO (entry 3) produced no significant amount of product, likely due to coordination of the solvent and resultant deactivation of the platinum centre. Reactions in d$_6$-benzene (entries 4 and 5) proceeded in lower yield than the reactions in CD$_3$CN, but still produced a significant amount of product and also exhibited temperature-dependent reactivity. d$_2$-Methylene chloride (entry 6) produced quite good (85%) yield at 35 °C, whereas the yield in d$_2$-methylene chloride at room temperature was slightly lower (entry 7).
The best yield was obtained with THF at 35 °C (entry 11). THF was thus used in the majority of the preparative scale reactions and in some NMR studies. For $^1$H NMR spectroscopy, there is no overlap between the solvent peaks of THF and the aryl peak of trimethoxybenzene and the characteristic imine $HC=N$ peaks. This made it possible to use proteo-THF for some studies, while in others $d_8$-THF was employed. It is interesting to note that in THF, this reaction proceeds at a higher yield at 35 °C than at the elevated temperature of 60 °C (entry 12). This is likely due to competitive formation of a platinum complex that is not catalytically active in the aryl ether synthesis.

3.2.3 Imine Scope

In Tables 3.1 and 3.2, optimized conditions for the generation of aryl ethers were established. A series of imines were subjected to these conditions to test for their reactivity towards catalytic generation of aryl ethers.

All of these reactions were initially run on an NMR scale in THF or $d_2$-methylene chloride, and those that gave significant yield in THF were repeated in $d_8$-THF to provide cleaner spectra and more reliable integration. The results are reported in Table 3.3.
Table 3.3 Scope of Imines for C-O Cross-Coupling

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>product</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Imine 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Imine 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>92%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Imine 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Imine 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>71%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Imine 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>32%$^b$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Imine 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>76%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Imine 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>12%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Imine 8" /></td>
<td><img src="image16" alt="Product 8" /></td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Conditions: 5 mol % Pt$_2$(CH$_3$)$_4$(SMe)$_2$, 1.2 equiv Si(OCH$_3$)$_4$, $d_8$-THF, 35°C, 24 h.
Excellent yields were obtained for the reactions of imines 2 and 4 (entries 1 and 2), demonstrating that phenyl and benzyl substituents on the imine are both compatible with this reaction. Imine 6 (entry 3) also reacted to generate the ether in excellent yield; no reaction of the cyano- group was observed.

Bromo-substituted imine 8 (entry 4) also reacted to generate the ether product in very good yield. This result is significant because it demonstrates that even in the presence of the more labile C-Br on the same ring, C-F activation occurs selectively with no byproducts generated. Similarly, imines 28 and 13 (entries 5 and 6) react cleanly in the presence of C-Br and C-Cl bonds, again demonstrating the high selectivity of ortho-C-F activation in this reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>product</th>
<th>yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td><img src="image" alt="Imine 15" /></td>
<td><img src="image" alt="Product 43" /></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Imine 17" /></td>
<td><img src="image" alt="Product 44" /></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Imine 12" /></td>
<td><img src="image" alt="Product 42" /></td>
<td>~15(^c)</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Imine 26" /></td>
<td><img src="image" alt="Product 45" /></td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

\(^a\) Yields based on \(^1\)H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard and integration of CHN proton, averaged over several runs. \(^b\) Reaction run in \(d_2\)-methylene chloride. \(^c\) Conversion estimated based on \(^19\)F\(^\{\text{1H}\}\)NMR spectroscopy by integration of starting material and product peaks.
Interestingly, reactions that successfully generate the aryl ether product in significant yield seem to feature a 2,4,6-substitution pattern on the aryl imine. The only substrate with a different substitution pattern that produced any measurable amount of product is imine 40 (entry 7). However, at 12% yield on NMR scale and no isolable product generated on a larger scale reaction, this reaction is not synthetically useful at this point.

Previous C-C cross-coupling work in our group has demonstrated the requirement for substrates to be 2,6-difluorinated in nearly all cases, and to possess at least one additional electron withdrawing group at any other position. Although 2,6-difluorinated imines such as 15 (entry 9) do not react to generate a C-C cross coupling product, substitution at any (or all) of the 3-, 4-, or 5- positions appears to facilitate the methylation reaction. In contrast, the present etherification study has a more restricted substrate scope. The apparent limitations on reactivity seen in substrates 10, 17, and 26 (entries 8, 10 and 12) is a source of further questions. This requirement of 2,4,6-substitution of the phenyl ring may be due to steric constraints, or may be related to more complex mechanistic considerations.

Substrates 12 and 26 (entries 11 and 12) are unique as they are the only imines tested that do not possess fluorine substituents at the 2- and 6- positions. The reaction of 12 appears to generate some product. If optimized, the etherification of 12 may be useful for mechanistic studies as it would provide access to a species with a 2,3,6-substitution pattern. However, this reaction was not studied further because C-Cl bond activation is not the focus of this study. The reaction of 26 was unsuccessful. It is not clear whether this is due to the 2,3,6-substitution pattern that seems to preclude reactivity on other
substrates or whether the CF$_3$ substituent at the 6- position significantly affects the chemistry of this reaction. This deserves further exploration.

### 3.2.3.1 Isolation of Aldehydes from Preparative Scale Reactions

When reactions were performed on a preparative scale, isolating the products required the use of flash silica column chromatography. Alternative methods, particularly recrystallization, were attempted, however, the presence of excess silanes and silane byproducts made this difficult. Additionally, in many cases the imine products were likely oils, or were generated from crystalline starting material that could easily co-crystallize even from an otherwise pure sample.

For isolation of C-C coupling products (such as 3) presented in Chapter 2, the use of a silica column basified with 1:1 triethylamine: hexanes was sufficient to stabilize the imine product against hydrolysis. However, the presence of the ether functionality appears to labilize the C=N bond sufficiently that even on a basified column, the product fraction contains more than 50% aldehyde in variable mixtures. The simplest solution to this has been to run a column without pre-treatment, which results in nearly complete hydrolysis of the imine and isolation of the pure aldehyde. The aldehydes that have been isolated are all solids, and in some cases can be recrystallized from pentanes at -35°C to separate them from the trace imine residual in the chromatographic product fraction.

It should be noted that 2,4-difluoro-6-methoxybenzaldehyde 46 is the isolated product from the reactions of imines 2, 4, 28, and 13 (Table 3.3, Entries, 1, 2, 5 and 6). Thus the three distinct aldehydes isolated are compounds 46, 47, and 48 (Table 3.4).
Table 3.4 Aldehydes Produced by Cross-Coupling of Polyfluoroarylimes with Si(OMe)$_4$ Followed by Hydrolysis

1. 5 mol% Pt$_2$(CH$_3$)$_4$(SMe)$_2$ \\
2. Column chromatography

<table>
<thead>
<tr>
<th>entry</th>
<th>imine</th>
<th>aldehyde product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{R}^1 \text{N}^+ \text{R}^2$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$\text{R}^1 \text{N}^+ \text{Ph}$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$\text{R}^1 \text{N}^+ \text{Cl}$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>$\text{R}^1 \text{N}^+ \text{Ph}$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$\text{NC} \text{N}^+ \text{Ph}$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$\text{Br} \text{N}^+ \text{Ph}$</td>
<td></td>
</tr>
</tbody>
</table>
3.3 Preliminary Mechanistic Investigations

3.3.1 Background – Mechanism of C-C Cross-Coupling of Polyfluoroarylimines

An understanding of the mechanism of a new reaction is an essential counterpart to studies towards the broad application of the methodology. The mechanism provides insight into the limitations on scope, yield, and conditions. It also increases the potential for accurately predicting the applicability of similar chemistry to fundamentally different systems.

As discussed in Chapter 1, previous work in our group has involved the same imine substrates as used in this study. The reaction of these imines with dimethylzinc leads to the formation of a carbon-carbon bond (see eq. 3.1). Extensive studies on this reaction have led to the determination of a mechanism.$^{74}$

Work by Crespo and Martinez demonstrated oxidative addition of the carbon-fluorine bond to platinum, generating the Pt(IV)-F complex $A$ (eq. 3.4).$^{2,3,73}$ Complex $A$ can also serve as a catalyst for the same cross-coupling reaction shown in eq. 3.1 (see eq. 3.5); this observation has led to the conclusion that the catalytic reaction does involve C-F activation as a step in the cycle.

![Chemical Structure](image-url)
Further work in our group ultimately led to the elucidation of the catalytic cycle for the transformation of imine 2 into product 3, which is shown in Scheme 3.1. The C-C cross-coupling reaction is proposed to proceed through initial coordination of the imine, followed by oxidative addition of the C-F bond to the platinum centre. This is followed by transmetallation with dimethylzinc, and reductive elimination of the aryl-methyl bond accompanied by dissociation of the chelating imine.
Scheme 3.1 Proposed mechanism for catalytic C-C cross-coupling$^{74}$

Two particularly important observations support this proposed mechanistic cycle. The lability of the Pt-S bond throughout the reaction, combined with the suppression of reactivity by the addition of excess dimethyl sulphide strongly supports the idea that the active form of the catalyst is a five-coordinate species, and that complex A is not itself the active catalyst in eq. 3.5. The non-reversibility of the initial C-F activation (as was demonstrated by the mixing of complex 21 and the pentafluorinated imine 17, a substrate
with a more labile C-F bond) is significant in that it provides conclusive evidence that some derivative of A does undergo catalytic turnover in this C-C cross coupling reaction.

### 3.3.2 C-F Activation as a Mechanistic Hypothesis for Catalytic Ether Formation

Given the similarities in the C-C and C-O bond forming processes, we initially hypothesized that the mechanisms of C-C and C-O bond formation would be similar. The same Pt complex catalyzes both reactions. The reactions have similar substrate scope, although the ether-forming reaction is more limited. In both C-C and C-O cross coupling, a minimum of three electron withdrawing groups on the aryl ring is necessary. This is demonstrated by the lack of reactivity of imine 15 (Table 3.3, entry 9) under both sets of reaction conditions.

To test the hypothesis that the mechanisms of C-C and C-O coupling were similar, the C-F activated complex 21 was generated in situ and then reacted with a slight excess of tetramethoxysilane (eq. 3.6). A similar experiment was conducted in the mechanistic studies of C-C bond coupling (discussed in Section 2.3.1); in that case dimethylzinc was the organometallic reagent.

\[
\begin{align*}
\text{NCH}_2\text{Ph} & \quad \text{Pt} \quad \text{Me}^+ \quad \text{F} \quad \text{H}_3\text{C} \quad \text{SM}\text{e}_2 \quad \text{F} \\
\text{F} & \quad \text{F} \quad \text{NCH}_2\text{Ph} & \quad \text{Pt} \quad \text{Me}^+ \quad \text{F} \quad \text{H}_3\text{C} \quad \text{SM}\text{e}_2 \quad \text{F} \\
\text{1.2 equiv} \text{Si(OMe)}_4 & \quad \text{CD}_3\text{CN, 60 °C} & \quad \text{3 equiv} \text{Si(OMe)}_4 & \quad \text{CD}_3\text{CN, 60 °C} \\
\text{21} & \quad \text{Me}^- & \quad \text{F} \quad \text{H}_3\text{C} \quad \text{SM}\text{e}_2 \quad \text{F} & \quad \text{NCH}_2\text{Ph} & \quad \text{Pt} \quad \text{Me}^+ \quad \text{F} \quad \text{H}_3\text{C} \quad \text{SM}\text{e}_2 \quad \text{F} \quad \text{OCH}_3 \\
\text{33} & \quad \text{F} \quad \text{OCH}_3 & \quad \text{3 equiv} \text{Si(OMe)}_4 & \quad \text{CD}_3\text{CN, 60 °C} \\
\end{align*}
\]

Given that the reaction of complex 21 with dimethylzinc generated the expected C-C cross-coupling product rapidly and quantitatively, we anticipated that addition of Si(OMe)_4 to 21 would generate the aryl ether product. To our surprise, only a minimal
amount of the methyl aryl ether product was formed. This demonstrated that, contrary to what we had predicted, the Pt(IV) complex (21, or 22 in the active form) that was shown to be catalytically active for our previous work does not play a role in any catalytic cycle that leads to the generation of these aryl methyl ethers.

3.3.3 Nucleophilic Aromatic Substitution (S\textsubscript{N}Ar) as a Mechanistic Hypothesis for Catalytic Ether Formation

With a new mechanism needed to explain the observed reactivity, we first sought to test some obvious alternatives, and at the same time to determine whether the platinum complex was necessary to the reaction. One common method for generating aryl ethers from fluoroaromatics is through an addition-elimination (S\textsubscript{N}Ar) pathway (Scheme 3.2).\textsuperscript{98} In nucleophilic aromatic substitution, the nucleophile attacks an aromatic carbon, causing the benzene ring to go through a non-aromatic intermediate before the stepwise elimination of the leaving group from the same carbon which was initially attacked. To determine whether this process is operative in the conversion of 2 to 33, the reaction of 2 under standard S\textsubscript{N}Ar conditions was compared to the Pt-catalyzed process.

![Scheme 3.2 Formation of aryl ethers by nucleophilic aromatic substitution](image)

A simple nucleophilic aromatic substitution reaction was first attempted with excess sodium methoxide and compared to the reaction in the presence of platinum catalyst. The results of these experiments are shown in Table 3.5.
Table 3.5 Possible S\textsubscript{N}Ar Reactions with NaOMe

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time (h)</th>
<th>reagents</th>
<th>product\textsuperscript{b} (%)</th>
<th>byproduct\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>24</td>
<td>NaOMe (3.0)</td>
<td>&lt;5%</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>24</td>
<td>NaOMe (3.0)</td>
<td>&lt;5%</td>
<td>88%</td>
</tr>
<tr>
<td>3</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}/MeOH</td>
<td>24</td>
<td>NaOMe (3.0)</td>
<td>20%</td>
<td>20%\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>24</td>
<td>Pt\textsubscript{2}(CH\textsubscript{3})\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2}, (0.05), Si(OOMe)\textsubscript{4} (1.2) NaOMe (3.0)</td>
<td>75%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>24</td>
<td>NaOMe (0.05)</td>
<td>-</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>15 min</td>
<td>KOt-Bu (3.0)</td>
<td>-</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Byproduct is an isomer of 2 unless otherwise indicated, denoted as 49 in the Experimental section. \textsuperscript{b} Conversions based on \textsuperscript{1}H NMR spectroscopy by integration of CHN proton. \textsuperscript{c} Mixture of several byproducts apparent by \textsuperscript{1}H NMR spectroscopy.

In \textsubscript{d2}-methylene chloride (entry 1) only a trace amount of the ether product was formed and a significant amount of an isomer of the imine. This isomer is believed to be imine 49, shown in Figure 3.1. Similar results were found in THF (entry 2), where the majority (88\%) of the starting material was converted to the isomer and again a trace amount of the aryl methyl ether was formed.

Figure 3.1 Proposed isomerization product 49
When methanol was added to the mixture (entry 3), 20% of the substrate was converted to the aryl methyl ether over 24 h, with a further 20% being converted into several byproducts which were not characterized. This demonstrated that a reaction with sodium methoxide is not the preferred means of generating aryl methyl ethers from aryl fluorides. This reaction lacks both the yield and selectivity of the platinum-catalyzed reaction. When excess sodium methoxide was added to an otherwise standard catalytic reaction mixture (entry 4), it had very little effect on the reaction, showing that it is a poor competitor with the catalytic aryl ether synthesis. Catalytic sodium methoxide also had a minimal effect with less than 5% conversion achieved (entry 5). As confirmation of the fact that the methoxy group from sodium is not incorporated in any way into the isomeric byproduct (and therefore, that it is an isomer as confirmed by mass spectrometry), the imine substrate was also reacted with potassium tert-butoxide under the same conditions (entry 6). In this case the isomerization product formed exclusively with complete conversion occurring within a 15 min period.

An alternative form of nucleophilic aromatic substitution was tested next. This reaction involves the activation of Si(OMe)₄ by a non-platinum reagent, and so has potential to more closely resemble the reaction conditions of the solvent optimization and substrate scope studies. The results are shown in Table 3.6.
Table 3.6 Alternative SNAr Pathway and Other Mechanisms for Ether Formation

![Chemical structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time (h)</th>
<th>reagents (equiv.)</th>
<th>productb (%)</th>
<th>byproductb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>17</td>
<td>TBAF (3.0), Si(OMe)₄ (1.2)</td>
<td>-</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2</td>
<td>CD₂Cl₂</td>
<td>24</td>
<td>CsF (3.6), Si(OMe)₄ (1.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>2.5</td>
<td>TBAF (3.0)</td>
<td>-</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>24</td>
<td>TBAF (0.05)</td>
<td>-</td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>1.5</td>
<td>Pt₂(CH₃)₄(SMe)₂ (0.05), Si(OMe)₄ (1.2), TBAF (3.0)</td>
<td>&lt;5%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>6</td>
<td>CD₂Cl₂</td>
<td>24</td>
<td>Si(OMe)₄ (1.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>24</td>
<td>BF₃·Et₂O (1.0), Si (1.2)</td>
<td>-</td>
<td>&gt;95%c</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>24</td>
<td>BF₃·Et₂O (0.1), Si (1.2)</td>
<td>-</td>
<td>&lt;5%c</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>24d</td>
<td>PtCl₂(SMe)₂ (0.1), Si(OMe)₄ (1.2)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a Byproduct is an isomer of 2 unless otherwise indicated, denoted as 49 in the Experimental section. b Conversions based on ¹H NMR spectroscopy by integration of CHN proton. c Appears to be B-N adduct. d Reaction was heated to 35 °C for the first 8 h and then to 60 °C for the remaining 16 h.

Initially, imine 2 was reacted with a combination of tetramethoxysilane and excess tetrabutyl ammonium fluoride (entry 1).¹⁰⁰,¹⁰¹,¹²³,¹²⁶ The expectation in this reaction was that the fluoride ion would react with the silane, generating a five-coordinate silicon species. This species would thus be activated toward transmetalation. Alternatively, cleavage of the Si-O bond would generate a methoxy anion as shown in Scheme 3.3, which is highly reactive in SNAr.
Scheme 3.3 Reaction of fluoride anion with tetramethoxysilane to formally generate a methoxy anion

The same reaction was also attempted using cesium fluoride (entry 2);\textsuperscript{124,125} this had no effect, but lack of solubility of cesium fluoride in \(d_2\)-methylene chloride may be responsible for the lack of reactivity in this case. This reaction, if successful, had particular mechanistic significance to platinum-mediated aryl ether synthesis because one of the major byproducts identified by \textit{in situ} \(^{19}\text{F}\{^1\text{H}\}\) NMR spectroscopy was fluorotrimethoxysilane. Reaction of tetramethoxysilane with a fluoride anion would be one very straightforward way to generate this byproduct.

The reaction with TBAF did not generate the aryl ether product, but instead led to nearly quantitative conversion in 17 h to the same isomerization product identified as the major product in entries 1, 2 and 6 of Table 3.5. In the absence of tetramethoxysilane, reaction of the imine and excess tetrabutyl ammonium fluoride led to quantitative conversion to the isomer in just 2.5 h (entry 3). With catalytic TBAF, the reaction proceeded more slowly, but the isomer was generated with 87% conversion over 24 h (entry 4). As mentioned above, a similar reaction with 5 mol % sodium methoxide had led to only 5% conversion over 24 h (Table 3.5, entry 5). Similarly, addition of TBAF to a standard catalytic reaction mixture (Table 3.6, entry 5) led rapidly to generation of the isomerization product, confirming again that TBAF mediates the isomerization more effectively than does sodium methoxide. It is worthwhile to note that heating a mixture
of the imine and unactivated tetramethoxysilane also did not lead to any formation of the ether product (entry 6).

As a final foray into the exploration of alternate mechanistic hypotheses, addition of the borane etherate BF₃·Et₂O was also tested (entries 7 and 8). The goal was to determine if platinum was simply serving as a Lewis acid in catalysis, changing the electronics of the aryl imine through coordination of the nitrogen. In the stoichiometric reaction (entry 7) evidence of the quantitative formation of a borane-imine adduct was observed, but no further reaction with the silane occurred. When sub-stoichiometric borane was added (entry 8), a small amount of the adduct appeared to form.

Having concluded that the platinum complex is an essential component of this catalytic reaction and that none of the additives tested appeared to enhance the reaction, we attempted a reaction with PtCl₂(SMe₂)₂ (25) (entry 9) the platinum species that was used as a catalyst in Chapter 2. PtCl₂(SMe₂)₂ is the synthetic precursor of the bis-platinum species 1. No product was generated from this reaction, further supporting the idea that the ether synthesis is mechanistically distinct from the C-C cross-coupling reactions.

### 3.3.4 Alternative Mechanistic Hypotheses

There are several alternate mechanisms that merit consideration. Our first proposal was that this reaction may proceed through a benzyne intermediate,¹²⁷ which could be activated by coordination of the imine to platinum.

As shown in Table 3.3, all substrates that have successfully undergone this reaction in significant yields have a 2,4,6-substitution pattern on the aryl ring where C-F activation occurs. The apparent need for a hydrogen substituent ortho to the activated C-
F bond supports the idea of a benzyne mechanism. However, several other observations regarding the substrate scope call the idea of a benzyne intermediate into question. The failure of this reaction to work on the 2,6-disubstituted ring of imine 29 (Table 3.3, entry 9) is not in support of this hypothesis. The apparently complete selectivity of the reaction for substitution ortho to the imine group likewise does not support this hypothesis. Formation of the 2,3-benzyne and the 3,4-benzyne would be expected to occur comparably well – the reaction observed would account only for formation of the 2,3-benzyne. Furthermore, bromide is known to be a vastly superior leaving group over fluoride in reported examples of the benzyne mechanism;\textsuperscript{127} leaving group preference is often used as a diagnostic between addition-elimination and benzyne mechanisms of nucleophilic aromatic substitution when both are possible based on products formed. Finally, the observation of selective elimination of fluoride over bromide for imine 8 (Table 3.3, entry 4) is inconsistent with a benzyne mechanism.

When Pt\textsubscript{2}Me\textsubscript{4}(SMe\textsubscript{2})\textsubscript{2} and a stoichiometric amount of Si(OMe)\textsubscript{4} are mixed and heated, an unidentified Pt-CH\textsubscript{3} intermediate forms (eq. 3.7). The addition of imine 2 leads to the rapid generation of 33, suggesting that some form of preactivation between the silane and the platinum complex may be involved in the catalytic reaction.

\[
\text{Me}_2\text{PtS}\text{Me}_2 + 2.4 \text{ equiv Si(OMe)}_4 \xrightarrow{\text{THF, 35°C, 6h}} \text{Unidentified intermediate} \xrightarrow{2 \text{ equiv Si(OMe)}_4, \text{THF, 35°C, 30 min}} \text{33, >95% conversion}
\]

The most plausible mechanism at this point seems to be one similar to that elucidated for carbon-carbon cross coupling with the same series of aryl fluoride substrates, but which enters the catalytic cycle through a different active species. While no reaction of the platinum species is observed upon mixing with Si(OMe)\textsubscript{4}, the
premixing of these two and subsequent addition of stoichiometric imine does lead to product formation. As previously mentioned, FSi(OMe)$_3$ is also observed in the $^{19}$F NMR spectrum as a reaction product. While this could be a byproduct in many mechanisms, it is a likely product of any mechanism involving a transmetallation or metathesis-like step.

Recently published work by Goldberg and coworkers suggests that reductive elimination of carbon-oxygen bonds from platinum (IV) species can proceed by dissociation of alkoxide anion and then nucleophilic attack on the electrophilic carbon.$^{128}$ Goldberg’s work applies specifically to reactions at electrophilic sp$^3$-hybridized carbons. However, the ease of cross-coupling between sp$^2$ and sp$^3$ hybridized carbon centres demonstrated in our previous work makes it plausible that the same mechanism of indirect reductive elimination may apply to our system.

3.3.5 Ongoing Mechanistic Studies

The next step in this project is to launch a full-fledged investigation into the mechanism of platinum catalyzed aryl ether synthesis. While further work and information are required, we present here a speculated catalytic cycle and several experiments that will directly highlight its merits or faults. Graphical representations of two variants of the proposed cycle are shown in Scheme 3.4.
Scheme 3.4 Two possible catalytic cycles. In both, the aryl ether is generated by C-F activation, transmetallation, and reductive elimination, but the order of these steps and therefore the intermediates involved are different. The imine is denoted by $N^C$ for simplicity.

The proposed mechanisms are fundamentally similar in that they propose C-F activation onto a platinum centre bearing a methoxy ligand. They differ in the order of reaction (i.e., whether transmetallation occurs before or after reductive elimination). Further studies will be necessary to determine whether a variant of these mechanisms is active in the selective, catalytic transformation of C-F bonds into C-O bonds.
3.4 Conclusions

The results presented in this chapter demonstrate the first reported examples of catalytic C-O bond formation via C-F activation. This reaction has been optimized and successfully applied to a series of 2,4,6-trisubstituted polyfluoroarylimines, generating novel, functionalized fluoroaryl methyl ethers.

Mechanistic studies support the requirement for a platinum catalyst to this reaction. These studies have allowed us to eliminate several potential pathways and to propose two possible mechanisms, which will be the subject of future investigation in our group.

3.5 Experimental Procedures

3.5.1 General Methods

Manipulation of all compounds was carried out using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled MBraun glovebox (O$_2$ < 2 ppm). Reactions were heated in an oil bath and those at preparative scale were stirred with a Teflon-coated magnetic stir bar. Reaction mixtures were concentrated either using rotary evaporation methods or by use of a Schlenk line. Glassware was cleaned by soaking in a base bath of potassium hydroxide, water, and isopropanol, (100 g : 100 mL : 1 L) followed by sequential rinsing with deionized water and acetone. When necessary, glassware was first cleaned with aqua regia, consisting of nitric acid and hydrochloric acid freshly mixed in a 1:3 ratio and then rinsed with water.
3.5.2 Reagents and Solvents

All organic reagents were obtained from commercial sources and used as received, unless otherwise stated. Potassium tetrachloroplatinate (II) was purchased from Strem Chemicals and used as received. All silicon reagents were purchased from commercial sources, degassed, and used under inert atmosphere. CsF, KOtBu, NaOMe were dried under vacuum overnight and used under inert atmosphere. ZnMe$_2$ (2.0 M in toluene) was purchased from Aldrich, titrated with LiCl and I$_2$ according to a literature procedure$^{122}$ and used as received. TBAF (1.0 M in THF) and BF$_3$·Et$_2$O (1.0 M in Et$_2$O) were purchased from Aldrich and used as received. Hexanes and toluene were dried by passage through solvent purification columns. Tetrahydrofuran (THF) and dichloroethane (DCE) were dried on molecular sieves and degassed prior to use. CD$_2$Cl$_2$, and CD$_3$CN were purchased in 1 g ampules and degassed prior to use. $d_6$-DMSO, C$_6$D$_6$ and $d_8$-THF were purchased in 1 g ampules and used as received. 1,3,5-trimethoxybenzene was sublimed prior to use.

3.5.3 Chromatography

Flash chromatography was used to isolate aldehyde products. The solvent was eluted using either nitrogen or air pressure at an approximate rate of two inches per minute.

3.5.4 Physical and Spectroscopic Measurements

NMR spectra were recorded on Bruker Avance 300 ($^1$H at 300 MHz and $^{19}$F{$^1$H}) at 282 MHz) or Bruker Avance 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) magnetic resonance spectrometers. $^1$H and $^{13}$C chemical shifts are reported in parts per million and
referenced to residual solvent. $^{19}$F NMR spectra are reported in parts per million and referenced to C$_6$H$_5$F (-113.1 ppm). Coupling constant values ($J$) were extracted assuming first-order coupling and are reported in Hertz (Hz). Spin multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets. All spectra were obtained at 25 °C. 1,3,5-trimethoxybenzene was used as an internal standard to determine NMR yields. Elemental analyses were obtained using a Carlo Erba Elemental Analyzer EA 1108.

3.5.5 Synthesis and Characterization of Platinum Species

Platinum complex 1 was prepared as described in section 2.4.5.

3.5.6 Synthesis and Characterization of Imines

Imines 2, 6, 8, 10, 13, and 26 were prepared as described in section 2.4.6. Imines 4, 12, 15, 17, and 28 were generously contributed by Tongen Wang.

\[ \text{N-(3-chloro-2,6-difluorobenzylidene)benzylimine (40)} \]

was synthesized according to a modified literature procedure. $^{75}$ 3-chloro-2,6-difluorobenzaldehyde (0.2 g, 1.13 mmol) was weighed into a 25 mL 2-necked round bottom flask equipped with a Teflon coated magnetic stirbar, a septum and a gas inlet adaptor. Absolute ethanol (10 mL) was added by pipette. Benzyl amine (0.13 mL, 1.19 mmol) was then added by syringe. The flask was placed under vacuum briefly and then refilled with N$_2$. This process was repeated two more times. The solution was then heated to reflux (90 °C) for 3 h. The solution was then cooled to room temperature and the solvent was removed under vacuum.
overnight. The residue was extracted with n-pentane (3 x 15 mL). The combined organic extracts were filtered through Celite, then concentrated by rotary evaporation. The imine product was further purified by Kugelrohr distillation to produce a yellow oil (0.18 g, 60%). $^1$H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta$ 8.58 (s, 1H), 7.48-7.24 (m, Ar-H, 6H), 6.95 (td, J = 9.2 Hz, J = 1.8 Hz, 1H), 4.87 (s, 3H). $^{19}$F NMR (CD$_2$Cl$_2$, 282 MHz): $\delta$ -113.1 (d, J = 5.6 Hz, 1F), $\delta$ -114.0 (d, J = 5.6 Hz, 1F). $^{13}$C-APT NMR (CD$_2$Cl$_2$, 100 MHz): $\delta$ 152.3.6 (s, HCN), 139.4 (s), 132.3 (broad s), 132.2 (d, J = 1.5 Hz), 129.1 (s), 128.5 (s), 127.7 (s), 113.1 (dd, J = 23 Hz, J = 4.6 Hz), 67.1 (s, NCH$_3$Ph). Anal. Calcd for C$_{14}$H$_{10}$ClF$_2$N: C, 63.29, H, 3.79, N, 5.27; found: C, 63.05, H, 3.90, N 5.30.

3.5.7 Solvent and Temperature Optimization and Silane Scope

All reactions for solvent and temperature optimization were performed on a 0.34 mmol of imine scale in an NMR tube with a screw cap. The solvents tested in this optimization study were CD$_3$CN, $d_6$-DMSO, C$_6$D$_6$, CD$_2$Cl$_2$, THF, and dichloroethane (DCE). Stock solutions of Pt$_2$(CH$_3$)$_4$(SMe)$_2$)$_2$ (I), 1,3,5-trimethoxybenzene, Si(OMe)$_4$, and N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) were prepared in each of these solvents. Temperatures tested were 17 °C (room temperature), 35 °C, 60 °C, and 80 °C. Not all solvents were tested for all conditions.
Reactions of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$. 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL solvent, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL solvent, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL solvent, 1.2 equiv unless otherwise indicated in Table 3.2 in the manuscript), 0.2 mL solvent (in the cases of entries 13 and 14 of Table 3.2, in which case the volume of solvent was increased to account for the smaller amount of silane solution), and 0.1 mL of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL solvent, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. The reactions generated 33 in yields ranging from <5% to >95%.

Reactions of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with PhSi(OMe)$_3$. 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL solvent, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL solvent, 0.33 equiv), 0.1 mL of PhSi(OMe)$_3$ solution (0.40 mmol in 1.0 mL solvent, 1.2 equiv) 0.2 mL solvent, and 0.1 mL of $N$-(2,4,6-
trifluorophenylbenzylimine (2) solution (0.34 mmol in 1.0 mL solvent, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy. The reactions generated 33 in yields ranging from 36% to >46% and in some cases also generated 3 in <10% yield.

Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with MeSi(OMe)$_3$.

0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of MeSi(OMe)$_3$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv) 0.2 mL THF, and 0.1 mL of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. The reaction generated 33 in 64% yield in addition to an unidentified imine byproduct.

Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Me$_3$Si(OMe)$_3$.

0.1 mL Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene
solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Me_3Si(OMe) solution (0.40 mmol in 1.0 mL THF, 1.2 equiv) 0.2 mL THF, and 0.1 mL of \( N \)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by \(^1\)H and \(^19\)F NMR spectroscopy over 24 h. The reaction generated **33** in 10% yield.

\[
\begin{align*}
\text{F} & \quad \text{N} \quad \text{Ph} \\
\text{F} & \quad 5 \text{ mol\% Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2 \\
\text{F} & \quad \text{1.2 equiv MeSi(OEt)}_3, \\
\text{THF, 44 h, 35°C/60°C} & \quad \text{2} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{N} \quad \text{Ph} \\
\text{F} & \quad \text{OEt} \\
\text{2} & \quad \text{34} \\
\end{align*}
\]

**Reaction of \( N \)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with MeSi(OEt)_3.** 0.1 mL \( Pt_2(\text{CH}_3)_4(\text{SMe}_2)_2 \) solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of MeSi(OEt)_3 solution (0.40 mmol in 1.0 mL THF, 1.2 equiv) 0.2 mL THF, and 0.1 mL of \( N \)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C over 24 h and then to 60 °C for an additional 20 h, and the reaction monitored by \(^1\)H and \(^19\)F NMR spectroscopy. The reaction generated a product that is likely **34** in <5% yield. \(^1\)H NMR (THF, 300 MHz): \( \delta \) 8.56 (s, 1H), 4.72 (s, 2H). \(^19\)F NMR (THF, 282 MHz): \( \delta \) -106.1 (d, \( J = 9.6 \) Hz, 1F), \( \delta \) -107.9 (d, \( J = 9.6 \) Hz, 1F). Some peaks are obscured by starting material and solvent, and so this product is not conclusively identified.
Reaction of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) with Si(OEt)\(_4\). 0.1 mL \(\text{Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2\) solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Si(OEt)\(_4\) solution (0.40 mmol in 1.0 mL THF, 1.2 equiv) 0.2 mL THF, and 0.1 mL of \(N-(2,4,6\text{-trifluorophenylbenzylidene})\)benzylimine (2) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by \(^1\text{H}\) and \(^{19}\text{F}\) NMR spectroscopy over 24 h. The reaction generated a product that is likely 34 in 15% yield. Some peaks are obscured by starting material and solvent, and so this product is not conclusively identified.

3.5.8 Imine Scope

3.5.8.1 NMR Scale Reactions

All reactions for substrate were performed on a 0.34 mmol of imine scale in an NMR tube with a screw cap. Stock solutions of \(\text{Pt}_2(\text{CH}_3)_4(\text{SMe}_2)_2\) (1), 1,3,5-trimethoxybenzene, and all imines were prepared in the appropriate solvents.
Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)₄. 0.1 mL of Pt₂(CH₃)₄(SMe₂)₂ solution (0.017 mmol in 1.0 mL THF-d₈, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-d₈, 0.33 equiv), 0.1 mL of Si(OMe)₄ solution (0.40 mmol in 1.0 mL THF-d₈, 1.2 equiv), 0.1 mL THF-d₈, and 0.1 mL of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) solution (0.34 mmol in 1.0 mL THF-d₈, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by ¹H and ¹⁹F NMR spectroscopy over 24 h. N-(2,4-difluoro-6-methoxybenzylidene)benzylimine (33) was generated in >95% yield based on NMR spectroscopy. ¹H NMR (THF-d₈, 300 MHz): δ 8.58 (s, 1H), 7.40-7.10 (m, Ar-H), 6.72 (dt, J = 10.8 Hz, 2.0 Hz, 1H), 6.60 (m, 1H) 4.76 (s, 2H), 3.88 (s, 3H). ¹⁹F NMR (THF-d₈, 282 MHz): δ -105.9 (d, J = 9.1 Hz, 1F), -107.9 (d, J = 9.1 Hz, 1F).

Reaction of N-(2,4,6-trifluorophenylbenzylidene)phenylimine (4) with Si(OMe)₄. 0.1 mL of Pt₂(CH₃)₄(SMe₂)₂ solution (0.017 mmol in 1.0 mL THF-d₈, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-d₈, 0.33 equiv), 0.1 mL of Si(OMe)₄ solution (0.40 mmol in 1.0 mL THF-d₈, 1.2 equiv), 0.1 mL THF-d₈, and 0.1 mL of N-(2,4,6-trifluorophenylbenzylidene)phenylimine (4) solution (0.34 mmol in 1.0 mL THF-d₈, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by ¹H and ¹⁹F NMR spectroscopy over 24 h. N-(2,4-difluoro-6-
methoxybenzylidene)phenylimine (35) was generated in 92% yield based on NMR spectroscopy. $^1$H NMR (THF-$d_8$, 300 MHz): $\delta$ 8.64 (s, 1H), 7.35-7.00 (m, Ar-H), 6.78 (dt, J = 11.1 Hz, 1.8 Hz, 1H), 6.66 (m, 1H), 3.91 (s, 3H). $^{19}$F NMR (THF-$d_8$, 282 MHz): $\delta$ -104.2 (d, J = 9.3 Hz, 1F), -106.5 (d, J = 9.3 Hz, 1F).

Reaction of $N$-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) with Si(OMe)$_4$. 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF-$d_8$, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-$d_8$, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF-$d_8$, 1.2 equiv), 0.1 mL THF-$d_8$, and 0.1 mL of $N$-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) solution (0.34 mmol in 1.0 mL THF-$d_8$, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(4-cyano-2-fluoro-6-methoxybenzylidene)benzylimine (36) was generated in 85% yield based on NMR spectroscopy. $^1$H NMR (THF-$d_8$, 300 MHz): $\delta$ 8.63 (s, 1H), 7.40-7.00 (m, Ar-H), 4.82 (s, 2H), 3.94 (s, 3H). $^{19}$F NMR (THF-$d_8$, 282 MHz): $\delta$ -109.7 (s, 1F).
Reaction of \( N\)-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) with Si(OMe)\(_4\). 0.1 mL of Pt\(_2\)(CH\(_3\))\(_4\)(SMe\(_2\))\(_2\) solution (0.017 mmol in 1.0 mL THF-\(d_8\), 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-\(d_8\), 0.33 equiv), 0.1 mL of Si(OMe)\(_4\) solution (0.40 mmol in 1.0 mL THF-\(d_8\), 1.2 equiv), 0.1 mL THF-\(d_8\), and 0.1 mL of \( N\)-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) solution (0.34 mmol in 1.0 mL THF-\(d_8\), 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h. \( N\)-(4-bromo-2-fluoro-6-methoxybenzylidene)benzylimine (37) was generated in 71% yield based on NMR spectroscopy. \(^1\)H NMR (THF-\(d_8\), 300 MHz): \( \delta \) 8.58 (s, 1H), 7.40-6.85 (m, Ar-H), 4.77 (s, 2H), 3.89 (s, 3H). \(^{19}\)F NMR (THF-\(d_8\), 282 MHz): \( \delta \) -110.0 (s, 1F).

\[
\begin{align*}
\text{F} & \quad \text{N} & \quad \text{Cl} \\
\text{F} & \quad \text{Cl} & \quad \text{OCH}_3
\end{align*}
\]

Reaction of \( N\)-(2,4,6-trifluorophenylbenzylidene)-2-chlorobenzylimine (28) with Si(OMe)\(_4\). 0.1 mL of Pt\(_2\)(CH\(_3\))\(_4\)(SMe\(_2\))\(_2\) solution (0.017 mmol in 1.0 mL CD\(_2\)Cl\(_2\), 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD\(_2\)Cl\(_2\), 0.33 equiv), 0.1 mL of Si(OMe)\(_4\) solution (0.40 mmol in 1.0 mL CD\(_2\)Cl\(_2\), 1.2 equiv), 0.1 mL CD\(_2\)Cl\(_2\), and 0.1 mL of \( N\)-(2,4,6-trifluorophenylbenzylidene)-2-chlorobenzylimine (28) solution (0.34 mmol in 1.0 mL CD\(_2\)Cl\(_2\), 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h. \( N\)-(2,4-difluoro-6-methoxybenzylidene)-2-chlorobenzylimine (38) was generated in 32% yield.
based on NMR spectroscopy. $^1$H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta$ 8.62 (s, 1H), 6.5-7.5 (m, Ar-H), 4.87 (s, 2H), 3.87 (s, 3H). $^{19}$F NMR (CD$_2$Cl$_2$, 282 MHz): $\delta$ -105.3 (d, $J = 9.3$ Hz, 1F), -109.3 (d, $J = 9.3$ Hz, 1F).

**Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)-4-bromobenzylimine (13) with Si(OMe)$_4$.** 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF-$d_8$, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-$d_8$, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF-$d_8$, 1.2 equiv), 0.1 mL THF-$d_8$, and 0.1 mL of $N$-(2,4,6-trifluorophenylbenzylidene)-4-bromobenzylimine (13) solution (0.34 mmol in 1.0 mL THF-$d_8$, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(2,4-difluoro-6-methoxybenzylidene)-4-bromobenzylimine (39) was generated in 76% yield based on NMR spectroscopy. $^1$H NMR (THF-$d_8$, 300 MHz): $\delta$ 8.58 (s, 1H), 7.44 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 6.73 (td, $J = 10.5$ Hz, $J = 1.8$ Hz, 1H), 6.61 (m, 1H) 4.72 (s, 2H), 3.88 (s, 3H). $^{19}$F NMR (THF-$d_8$, 282 MHz): $\delta$ -105.6 (d, $J = 9.3$ Hz, 1F), -108.0 (d, $J = 9.3$ Hz, 1F).
Reaction of \(N-(3\text{-chloro-2,6-difluorobenzylidene})\)benzylimine (40) with Si(OMe)\(_4\).

0.1 mL of \(Pt_2(CH_3)_4(SMe)_2\) solution (0.017 mmol in 1.0 mL THF-\(d_8\), 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-\(d_8\), 0.33 equiv), 0.1 mL of Si(OMe)\(_4\) solution (0.40 mmol in 1.0 mL THF-\(d_8\), 1.2 equiv), 0.1 mL THF-\(d_8\), and 0.1 mL of \(N-(3\text{-chloro-2,6-difluorobenzylidene})\)benzylimine (40) solution (0.34 mmol in 1.0 mL THF-\(d_8\), 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy over 24 h. \(N-(3\text{-chloro-6-fluoro-2-methoxybenzylidene})\)benzylimine (41) was generated in 12% yield based on NMR spectroscopy. \(^1\)H NMR (THF-\(d_8\), 300 MHz): \(\delta\) 8.62 (s, 1H), 7.60-6.80 (buried peaks, Ar-H), 4.80 (s, 2H), 3.88 (s, 3H). \(^{19}\)F NMR (THF-\(d_8\), 282 MHz): \(\delta\) -113.2 (s, 1F).

Reaction of \(N-(2,3,6\text{-trifluorophenylbenzylidene})\)benzylimine (10) with Si(OMe)\(_4\).

0.1 mL of \(Pt_2(CH_3)_4(SMe)_2\) solution (0.017 mmol in 1.0 mL THF-\(d_8\), 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF-\(d_8\), 0.33 equiv), 0.1 mL of Si(OMe)\(_4\) solution (0.40 mmol in 1.0 mL THF-\(d_8\), 1.2 equiv), 0.1 mL THF-\(d_8\), and 0.1 mL of \(N-(2,3,6\text{-trifluorophenylbenzylidene})\)benzylimine (42) solution (0.34 mmol in 1.0 mL THF-\(d_8\), 1.0 equiv).
trifluorophenylbenzylidene)benzylimine (10) solution (0.34 mmol in 1.0 mL THF-d8, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by ¹H and ¹⁹F NMR spectroscopy over 24 h but generated less than 5% product yield. The product was not characterized.

Reaction of N-(2,6-difluorophenylbenzylidene)benzylimine (15) with Si(OMe)₄. 0.1 mL of Pt₂(CH₃)₄(SMe₂)₂ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Si(OMe)₄ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.2 mL THF, and 0.1 mL of N-(2,6-difluorophenylbenzylidene)benzylimine (15) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by ¹H and ¹⁹F NMR spectroscopy over 24 h but generated less than 5% product yield. The product was not characterized.

Reaction of N-(2,3,4,5,6-pentafluorophenylbenzylidene)benzylimine (17) with Si(OMe)₄. 0.1 mL of Pt₂(CH₃)₄(SMe₂)₂ solution (0.017 mmol in 1.0 mL THF, 0.05
equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.2 mL THF, and 0.1 mL of $N$-(2,3,4,5,6-pentafluorophenylbenzylimidene)benzylimine (17) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated less than 5% product yield. The product was not characterized.

![Chemical Reaction](image)

**Reaction of $N$-(2-chloro-3,6-difluorobenzylimidene)benzylimine (12) with Si(OMe)$_4$.**

0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.2 mL THF, and 0.1 mL of $N$-(3-chloro-2,6-difluorobenzylimidene)benzylimine (12) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h. $N$-(3,6-difluoro-2-methoxybenzylimidene)benzylimine (42) was generated in ~15% conversion based on $^{19}$F NMR spectroscopy. $^1$H NMR (THF, 300 MHz): δ 8.62 (s, 1H), 7.50-7.00 (buried peaks, Ar-H), 4.87 (s, 2H), OCH$_3$ peak buried in THF signal. $^{19}$F NMR (THF, 282 MHz): δ -107.2 (m, 1F), -119.7 (m, 1F).
Reaction of *N*-({3-chloro-2-fluoro-6-trifluoromethylbenzylidene})benzylimine (26) with Si(OMe)$_4$. To 0.1 mL of Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv), 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.2 mL THF, and 0.1 mL of *N*-({3-chloro-2-fluoro-6-trifluoromethylbenzylidene})benzylimine (26) solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap. The tube was heated to 35 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 24 h but generated less than 5% product yield. The product was not characterized.

3.5.8.2 Preparative Scale Reactions

Reaction of *N*-({2,4,6-trifluorophenylbenzylidene})benzylimine (2) with Si(OMe)$_4$. Under an atmosphere of nitrogen, Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (0.1 mL, 0.40 M in THF, 0.040 mmol) was measured by micropipet into a 50 mL 2-necked round bottom flask equipped with a stirbar, a rubber septum and a vacuum inlet adaptor. THF (20 mL) was added to the flask. Si(OMe)$_4$ (0.144 mL, 0.96 mmol) was then added by syringe, followed by *N*--
(2,4,6-trifluorophenylbenzylidene)benzylimine (2) (0.2 g, 0.80 mmol). The resulting solution was heated at 35°C for 24 h. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was washed with n-pentane (3 x 20 mL). The combined organic extracts were filtered through Celite and concentrated by rotary evaporation to provide the crude imine product. Flash column chromatography (SiO₂, 70-230 mesh, 10% ethyl acetate in hexanes as eluent) provided clean 2,4-difluoro-6-methoxybenzaldehyde (46) (white solid, 85%). ¹H NMR (CD₂Cl₂ methylene-d₂-chloride, 300 MHz): δ 10.30 (s, 1H), 6.58-6.45 (m, Ar-H, 2H), 3.91 (s, 3H). ¹⁹F{¹H} NMR (CD₂Cl₂, 282 MHz): δ -98.0 (d, J = 12.4 Hz, 1F), -111.2 (d, J = 12.4 Hz, 1F). ¹³C-APT NMR (CD₂Cl₂, 100 MHz): δ 186.1 (s, CHO), 97.8 (t, J = 26.1 Hz), 96.6 (dd, J = 26.1 Hz, J = 3.8 Hz), 57.3 (s, OCH₃). Anal. Calcd for C₈H₆F₂O₂: C, 55.82, H, 3.51; found: C, 56.08, H, 3.79.

**Reaction of N-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) with Si(OMe)₄.** Under an atmosphere of nitrogen, Pt₂(CH₃)₄(SMe)₂ (0.1 mL, 0.098 M in THF, 0.0098 mmol) was measured by micropipet into a 50 mL 2-necked round bottom flask equipped with a stirbar, a rubber septum and a vacuum inlet adaptor. THF (10 mL) was added to the flask. Si(OMe)₄ (0.0348 mL, 0.234 mmol) was then added by syringe, followed by N-(4-cyano-2,6-difluorophenylbenzylidene)benzylimine (6) (0.05 g, 0.195 mmol). The resulting solution was heated at 35 °C for 24 h. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was washed
with petroleum ether 35-65 (3 x 10 mL). The combined organic extracts were filtered through Celite and concentrated by rotary evaporation to provide the crude imine product. Flash column chromatography (SiO₂, 70-230 mesh, 10% ethyl acetate in hexanes as eluent) provided clean 3-fluoro-4-formyl-5-methoxybenzonitrile (47) (white-yellow solid, 10%). ¹H NMR (CD₂Cl₂, 400 MHz): δ 10.39 (s, 1H), 7.10 (s, 1H), 7.05 (d, J = 10.4 Hz 1H), 3.97 (s, 3H). ¹⁹F NMR (CD₂Cl₂, 282 MHz): δ -109.3 (s, 1F). ¹³C-APT NMR (CD₂Cl₂, 100 MHz): δ 186.5 (s, CHO), 113.2 (d, J = 25.1 Hz), 112.0 (d, J = 3.8 Hz), 57.6 (s, OCH₃).

1. 5 mol% Pt₂(CH₃)₄(SMe₂)₂
2. Column chromatography

Reaction of N-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) with Si(OMe)₄. Under an atmosphere of nitrogen, Pt₂(CH₃)₄(SMe₂)₂ (0.1 mL, 0.145 M in THF, 0.0145 mmol) was measured by micropipet into a 50 mL 2-necked round bottom flask equipped with a stirbar, a rubber septum and a vacuum inlet adaptor. THF (10 mL) was added to the flask. Si(OMe)₄ (0.0506 mL, 0.34 mmol) was then added by syringe, followed by N-(4-bromo-2,6-difluorophenylbenzylidene)benzylimine (8) (0.00 g, 0.29 mmol). The resulting solution was heated at 35°C for 24 h. The solution was cooled to room temperature and the solvent was removed under vacuum. The residue was washed with petroleum ether 35-65 (3 x 10 mL). The combined organic extracts were filtered through Celite and concentrated by rotary evaporation to provide the crude imine product. Flash column chromatography (SiO₂, 70-230 mesh, 10% ethyl acetate in hexanes as eluent) provided clean 4-bromo-2-fluoro-6-methoxybenzaldehyde (48) (white...
solid, 71%). $^{1}$H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta$ 10.32 (s, 1H), 7.00 (s, 1H), 6.96 (d, J = 10.2 Hz, 1H), 3.92 (s, 3H). $^{19}$F NMR (CD$_2$Cl$_2$, 282 MHz): $\delta$ -106.5 (s, 1F). $^{13}$C-APT NMR (CD$_2$Cl$_2$, 100 MHz): $\delta$ 186.6 (s, CHO), 164.5 (s), 129.9 (d, J = 13.8 Hz), 113.1 (d, J = 25.2 Hz), 112.2 (d, J = 3.8 Hz), 57.4 (s, OCH$_3$).

3.5.9 In Situ Generation of Complex 21 and Stoichiometric Reactions

**Synthesis of Complex 21.** 0.1 mL Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.093 mmol in 1.0 mL CD$_3$CN, 0.5 equiv) was measured into each of two NMR tubes via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.062 mmol in 1.0 mL CD$_3$CN, 0.33 equiv), 0.3 mL CD$_3$CN, and 0.1 mL of 2 N-(2,4,6-trifluorobenzylidene)benzylimine (2) solution (0.185 mmol in 1.0 mL CD$_3$CN, 1.0 equiv). The tubes was fitted with screw caps and heated to 60 °C and the reaction monitored by $^1$H and $^{19}$F NMR spectroscopy over 5 h. Complex 21 was generated in ~95% yield. In situ characterization data is consistent with previously reported data.$^{75}$

**Reaction of Complex 21 with ZnMe$_2$.** 0.0111 mL of ZnMe$_2$ solution (2.0 M in toluene, 1.2 equivalents) was added to one of the above NMR tubes via syringe. The reaction was heated to 60 °C and monitored by $^1$H and $^{19}$F NMR spectroscopy. After 0.5 h, imine 3 was generated in 68% yield.

**Reaction of Complex 21 with Si(OMe)$_4$.** 0.0033 mL of Si(OMe)$_4$ (0.022 mmol, 1.2 equivalents) was added to the other of the above NMR tubes via syringe. The reaction was heated to 60 °C and monitored by $^1$H and $^{19}$F NMR spectroscopy. A small amount of ether imine 33 was generated but predominantly decomposition was observed.
3.5.10 Mechanistic Alternatives

Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with excess NaOMe. NaOMe (0.102 mmol, 3.0 equiv) was weighed into an NMR tube. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL solvent, 0.33 equiv) was added via syringe, followed by 0.4 mL solvent, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL solvent, 1.0 equiv). A faint pink colour was observed immediately in all cases and persisted throughout the reaction. The tube was fitted with a screw cap and heated to 35 °C over 24 h. Reactions were monitored by $^1$H and $^{19}$F NMR spectroscopy.

In CD$_2$Cl$_2$, the reaction generated 33 in <5% conversion and 49 in 50% conversion. In THF, the reaction generated 33 in <5% conversion and 49 in 88% conversion. In CD$_2$Cl$_2$/MeOH, the reaction generated 33 in 20% conversion and 49 in 20% conversion.

Available characterization data for proposed isomerism product 49. $^1$H NMR (CD$_2$Cl$_2$, 300 MHz): δ 8.37 (s, 1H), 7.72 (m, 2H), 7.42 (m, 3H) 6.72 (t, J = 8.7 Hz, 2H), 4.78 (s, 2H). $^{19}$F NMR (CD$_2$Cl$_2$, 282 MHz): δ -110.1 (d, 1F), -113.4, (d, 1F).

Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with catalytic NaOMe. NaOMe (0.0017 mmol, 0.05 equiv) was weighed into an NMR tube. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was added via syringe, followed by 0.4 mL THF, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap and heated to 35 °C over 24 h.
The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. The reaction generated 49 in <5% conversion.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$, Pt$_2$(CH$_3$)$_4$(SMe)$_2$, and excess NaOMe.** NaOMe (0.102 mmol, 3.0 equiv) was weighed into an NMR tube. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_2$Cl$_2$, 0.33 equiv) was added via syringe, followed by, 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL CD$_2$Cl$_2$, 1.2 equiv), 0.1 mL Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL CD$_2$Cl$_2$, 0.05 equiv), 0.2 mL CD$_2$Cl$_2$, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL CD$_2$Cl$_2$, 1.0 equiv). The tube was fitted with a screw cap and heated to 35 °C over 24 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. The reaction generated 33 in 75% conversion, and 49 in <5% conversion.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with excess KOT-Bu.** KOT-Bu (0.102 mmol, 3.0 equiv) was weighed into an NMR tube. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was added via syringe, followed by 0.4 mL THF, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). A dark pink colour was immediately observed. The tube was fitted with a screw cap and heated to 35 °C for 15 min. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. The reaction generated 49 in >95% conversion.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$ and TBAF.** 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33
equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.198 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), 0.102 mL TBAF solution (1.0 M in THF, 3.0 equiv). A dark pink colour was immediately observed. The tube was fitted with a screw cap and heated to 35 °C over 17 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. The reaction generated 49 in >95% conversion.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$ and excess CsF.** CsF (0.122 mmol, 3.6 equiv) was weighed into an NMR tube. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_2$Cl$_2$, 0.33 equiv) was added via syringe, followed by 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL CD$_2$Cl$_2$, 1.2 equiv), 0.3 mL CD$_2$Cl$_2$, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL CD$_2$Cl$_2$, 1.0 equiv). The tube was fitted with a screw cap and heated to 35 °C. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. No significant reaction was observed.

**Reaction of N-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with excess TBAF.** 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was measured into an NMR tube via syringe, followed by 0.298 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), 0.102 mL TBAF solution (1.0 M in THF, 3.0 equiv). A dark pink colour was immediately observed. The tube was fitted with a screw cap and heated to 35 °C over 2.5 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. The reaction generated 49 in >95% conversion.
Reaction of \( N\)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with catalytic TBAF. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was measured into an NMR tube via syringe, followed by 0.398 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), 0.0017 mL TBAF solution (1.0 M in THF, 0.05 equiv). A faint pink colour was immediately observed. The tube was fitted with a screw cap and heated to 35 °C over 24 h. The reaction was monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy. The reaction generated 49 in 87% conversion.

Reaction of \( N\)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$, Pt$_2$(CH$_3$)$_4$(SMe)$_2$, and excess TBAF. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was measured into an NMR tube via syringe, followed by, 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.1 mL Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.017 mmol in 1.0 mL THF, 0.05 equiv), 0.098 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), and 0.102 mL TBAF solution (1.0 M in THF, 3.0 equiv). The tube was fitted with a screw cap and heated to 35 °C over 1.5 h. The reaction was monitored by \(^1\)H and \(^{19}\)F NMR spectroscopy. The reaction generated 33 in <5% conversion, and 49 in >95% conversion.

Reaction of \( N\)-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$. 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL CD$_2$Cl$_2$, 0.33 equiv) was measured into an NMR tube via syringe, followed by, 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL CD$_2$Cl$_2$, 1.2 equiv), 0.3 mL CD$_2$Cl$_2$, and 0.1 mL of imine solution (0.34 mmol in 1.0 mL CD$_2$Cl$_2$, 1.0 equiv). The tube was fitted with a screw cap and heated to
35 °C over 24 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. No significant reaction was observed.

**Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$ and stoichiometric BF$_3$·Et$_2$O.** 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.296 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), and 0.043 mL BF$_3$·Et$_2$O (0.034 mmol, 1.0 equiv.). The tube was fitted with a screw cap and heated to 35 °C over 24 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. What appeared to be a B-N adduct was formed in >95% conversion.

**Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$ and catalytic BF$_3$·Et$_2$O.** 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF, 0.33 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.296 mL THF, 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv), and 0.0043 mL BF$_3$·Et$_2$O (0.0034 mmol, 0.1 equiv). The tube was fitted with a screw cap and heated to 35 °C over 24 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. What appeared to be a B-N adduct was formed in <5% conversion.

**Reaction of $N$-(2,4,6-trifluorophenylbenzylidene)benzylimine (2) with Si(OMe)$_4$, and PtCl$_2$(SMe)$_2$.** 0.1 mL of 1,3,5-trimethoxybenzene solution (0.11 mmol in 1.0 mL THF,
0.33 equiv) was measured into an NMR tube via syringe, followed by 0.1 mL of Si(OMe)$_4$ solution (0.40 mmol in 1.0 mL THF, 1.2 equiv), 0.1 mL PtCl$_2$(SMe)$_2$$_2$ solution (0.034 mmol in 1.0 mL THF, 0.10 equiv), 0.098 mL THF and 0.1 mL of imine solution (0.34 mmol in 1.0 mL THF, 1.0 equiv). The tube was fitted with a screw cap and heated to 35 °C over 8 h, then to 60 °C for an additional 16 h. The reaction was monitored by $^1$H and $^{19}$F NMR spectroscopy. No significant reaction was observed.

**Premixing Pt$_2$(CH$_3$)$_4$(SMe)$_2$ (1) and Si(OMe)$_4$ followed by the addtion of imine 2.**

0.1 mL Pt$_2$(CH$_3$)$_4$(SMe)$_2$ solution (0.093 mmol in 1.0 mL THF, 0.5 equiv) was measured into each of two NMR tubes via syringe, followed by 0.1 mL of 1,3,5-trimethoxybenzene solution (0.062 mmol in 1.0 mL THF, 0.33 equiv), 0.3 mL THF, and 0.0033 mL of Si(OMe)$_4$ (0.022 mmol, 1.2 equivalents). The reaction was heated to 35 °C and monitored by $^1$H and $^{19}$F NMR spectroscopy. After 6 h, 0.1 mL of 2 N-(2,4,6-trifluorobenzylidene)benzylimine (2) solution (0.185 mmol in 1.0 mL THF, 1.0 equiv) was added. The reaction was heated to 35 °C and monitored by $^1$H and $^{19}$F NMR spectroscopy. 33 was generated in >95% conversion after 30 min.
Chapter 4 – Summary, Conclusions, and Future Work

4.1 Summary

In this thesis, two projects are presented. Both are based on the selective activation of aryl C-F bonds in a series of polyfluoroarylimines. These reactions use a platinum catalyst, and are effectively applied to catalytic cross-coupling to generate functionalized fluoroaromatics.

In the first project, a new monoplatinum catalyst PtCl$_2$(SMe)$_2$ (25) was employed in the selective ortho C-F activation of a series of imines. The generation of Ar-CH$_3$ bonds for these substrates had been previously established by our group; this reaction demonstrated the ability to use a more synthetically accessible catalyst to achieve the same transformation. Based on preliminary evidence, we propose that this reaction undergoes a very similar catalytic cycle to that established in our previous work.

The second project involves catalytic conversion of aryl C-F bonds to aryl C-O bonds, generating aryl methyl ethers. Preliminary mechanistic studies established that the mechanism of this reaction is different from that in our previous work. However, it is a platinum-mediated cross-coupling and not simply $S_{N}Ar$ or a benzyne mechanism. If this reaction does proceed through reductive elimination from the platinum centre, it will be the first example of catalytic reductive elimination of a C-O bond from platinum.

4.2 Future Work

The work presented in this thesis and in our earlier work is only the tip of the iceberg in terms of platinum-catalyzed C-F activation chemistry. There is a wealth of
mechanistic and synthetic work to be studied within the systems we have already established for catalytic cross-coupling, as well as many new areas to explore.

An understanding of the mechanism of the C-O cross coupling reaction presented in Chapter 3 will be essential to broadening the scope of that chemistry. One option for the study of potential intermediates will be to generate a platinum-methoxide species through reaction of PtCl$_2$(SMe$_2$)$_2$ with sodium methoxide or another reagent. This could generate a complex similar in structure to the current Pt precatalyst for the ether synthesis.

Another reaction that should be studied in more detail is that of the imine and platinum catalyst with phenyltrimethoxysilane (eq. 3.3). The fact that this reaction generates a stoichiometric amount of the C-C cross coupling product suggests that it may go through a slightly different mechanism or enter the same catalytic cycle in a different way. The timeline for formation of this product, as well as the products of a stoichiometric reaction, should be investigated.

Generation of a catalytically active C-F activated species such as complex 21 from imine and the platinum precatalyst 1 has been unsuccessful in generating the ether product, and consequently we propose another approach. An alternate approach would be to study the possibility of reductive elimination from the platinum. If this reductive elimination does prove to be possible, then it will be worthwhile to identify the mechanism by which Pt$_2$(CH$_3$)$_4$(SMe)$_2$ enters into the catalytic cycle.

One plausible route to a complex which may undergo reductive elimination is through C-Cl activation as demonstrated with the 2-chloro substituted imine 12 (Table 3.3, entry 11). Work by Hartwig et al suggests that replacing a chloro-ligand with
methoxy should be facile;\textsuperscript{77,79,82} this would generate a platinum species with chelated imine and both the carbon and oxygen which we are aiming to cross-couple (Scheme 4.1). Depending on the propensity for isomerization, geometrical constraints may limit reactivity. Either naturally or through the introduction of another chelating ligand, the hope is that this complex would reductively eliminate a carbon-oxygen bond, generating the aryl methyl ether product and confirming the mechanism proposed above.

\begin{center}
\includegraphics[width=\textwidth]{Scheme41.png}
\end{center}

\textbf{Scheme 4.1} Proposed alternative method of accessing a platinum species from which a C-O bond could reductively eliminate.

There are several ways in which the scope of this reaction could be broadened. The first is through variation of the directing group. While replacement of the imine with an aldehyde or carboxylic acid has been unsuccessful to-date, these groups may be successful directing groups under slightly altered conditions or with a different catalyst. Additionally, directing groups such as ketones, 2-pyridiniums, oxazolines, and pyrazolyls may find application here.\textsuperscript{129-132}

The second potential route to a broadened substrate scope is through variation of the organometallic. In our early work, phenyltrimethoxysilane was proposed as a source of phenyl;\textsuperscript{75} while this was unsuccessful it did lead to our discovery of the C-O cross coupling reaction. A wide range of aromatic and aliphatic organometallics are
commercially available, and could be similarly applied to generate fluoroarylimes with larger functional groups. Along these same lines, the potential to generate catalysts $\text{Pt}_2\text{R}_4(\text{SMe}_2)_2$, where $R$ is not a methyl group, may facilitate cross coupling to generate different products. A number of these platinum species are known, but have not been tested for catalytic activity.

A final direction that may be considered for this project is the application of catalytic C-F activation as a step in a synthesis of a bioactive target molecule. The tolerance demonstrated by this reaction for remote halogen and nitrile functionalities suggests that subsequent to a C-F cross-coupling, a further reaction could occur; a Suzuki coupling or any other chemistry at these functional groups are all viable alternatives. Indeed, it will be through application to synthetic problems, be they for organic chemistry, materials, or environmental applications, that this new methodology will become a part of the synthetic toolkit.
References


(2) Crespo, M.; Martinez, M.; Sales, J. *Organometallics* 1993, 12, 4297-4304.


(64) Edelbach, B. L.; Jones, W. D. Organometallics 1994, 13, 385-396.


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Appendix I: X-ray Crystallographic Data for Aldehyde 46

Figure 1. ORTEP diagram of compound 46. Thermal ellipsoids are drawn at the 50% probability level.
A. Crystal Data

Empirical Formula  \( \text{C}_8\text{H}_6\text{F}_2\text{O}_2 \)
Formula Weight  172.13
Crystal Color, Habit  colourless, needle
Crystal Dimensions  0.05 X 0.10 X 0.50 mm
Crystal System  orthorhombic
Lattice Type  primitive
Lattice Parameters  
\[
\begin{align*}
a &= 13.825(5) \ \text{Å} \\
b &= 7.234(3) \ \text{Å} \\
c &= 14.469(5) \ \text{Å} \\
\alpha &= 90.0^\circ \\
\beta &= 90.0^\circ \\
\gamma &= 90.0^\circ
\end{align*}
\]
\( V = 1447.1(9) \ \text{Å}^3 \)
Space Group  \( P \ bc a \ (\#61) \)
Z value  8
\( D_{\text{calc}} \)  1.580 g/cm\(^3\)
\( F_{000} \)  704.00
\( \mu(\text{MoK } \alpha) \)  1.46 cm\(^{-1}\)

B. Intensity Measurements

Diffractometer  Bruker X8 APEX II
Radiation  \( \text{MoK } \alpha (\lambda = 0.71073 \ \text{Å}) \)
graphite monochromated
Data Images  1350 exposures @ 30.0 seconds
Detector Position  36.00 mm
\( 2\theta_{\text{max}} \)  50.0\(^\circ\)
No. of Reflections Measured  
Total: 9978
Unique: 1244 (\( R_{\text{int}} = 0.050 \))
Corrections  
Absorption (\( T_{\text{min}} = 0.608, \ T_{\text{max}} = 0.993 \))
Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution  Direct Methods (SIR97)
Refinement  Full-matrix least-squares on \( F^2 \)
Function Minimized \[ \Sigma w (F_o^2 - F_c^2)^2 \]
Least Squares Weights \[ w = 1/(\sigma^2(F_o^2) + (0.0578P)^2 + 0.5219P) \]
Anomalous Dispersion All non-hydrogen atoms
No. Observations (I>0.00 (I)) 1244
No. Variables 110
Reflection/Parameter Ratio 11.31
Residuals (refined on F^2, all data): R1; wR2 0.062; 0.114
Goodness of Fit Indicator 1.06
No. Observations (I>2.00 \( \sigma \) (I)) 934
Residuals (refined on F): R1; wR2 0.041; 0.098
Max Shift/Error in Final Cycle 0.00
Maximum peak in Final Diff. Map 0.17 e^-/Å^3
Minimum peak in Final Diff. Map -0.29 e^-/Å^3

Table 1. Atomic coordinates (\( x 10^4 \)) and equivalent isotropic displacement parameters (Å^2 x \( 10^2 \)) (U(eq) is defined as one third of the trace of the orthogonalized Uij tensor)

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**Table 2. Bond Lengths [Å]**

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**Table 3. Bond Angles [°]**

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H(10A)-C(10)-H(10C)  109.5
H(10B)-C(10)-H(10C)  109.5
C(8)-O(9)-C(10)  117.88(15)

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Table 4. Anisotropic displacement parameters (Å$^2 \times 10^3$)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å$^2 \times 10^3$).

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