STUDIES TOWARDS THE SYNTHESIS OF FUNCTIONALIZED ARYL FLUORIDES: TRANSITION METAL CATALYZED CROSS-COUPLING AND FLUORINATION OF ORGANOBORON REAGENTS

by

Duo Sun

B.Sc., Simon Fraser University, 2006

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
in

THE FACULTY OF GRADUATE STUDIES

(Chemistry)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

January 2013

Abstract

This thesis covers several synthetic approaches to the generation of highly functionalized aryl fluorides. $PtCl_2(SMe_2)_2$ and $PtCl_2(DMSO)_2$ have been applied to catalytic methylation of polyfluoroaryl imines as user-friendly precatalysts. These complexes have demonstrated high selectivity for ortho C-F activation and subsequent functionalization, exhibiting high functional group tolerance while proving more thermal, moisture and air stable than our original catalyst, $[Me_2Pt(SMe_2)]_2$. Nickel-catalyzed Suzuki-Miyaura and Negishi cross-coupling reactions allow rapid functionalization of C-F bonds; we have been able to obtain a variety of highly functionalized aryl-, heteroaryl-, and alkyl-substituted aryl fluoride molecules under mild reaction conditions. Furthermore, we have described a novel fluorination procedure that employs organoboron reagents and electrophilic fluorine sources. This method is rapid, high yielding and can be carried out without inert atmosphere protection and dry solvents.

Preface

I have designed, in consultation with my supervisor Dr. Jennifer A. Love, the research projects presented herein; furthermore, I have carried out nearly all of the experimental work, data collection/analysis, and manuscript preparation.

Any work referred to in the text of this thesis that I did not directly carry out has been clearly referenced.

A version of section 2.2 in chapter 2 has been published. Buckley, H. L., Sun, A. D., Love, J. A. *Organometallics* **2009**, *28*, 6622-6624. Heather L. Buckley initiated the project and obtained the data for Table 2.1 except numbers in parentheses, which were determined by me. All other work in this chapter was obtained by me.

A version of section 2.3 in chapter 2 has been published. Sun, A. D.; Love, J. A. *J. Fluorine Chem.* **2010**, *131*, 1237-1240. The first drafts of the paper were written by me.

A version of chapter 3 has been published. Sun, A. D.; Love, J. A. *Org. Lett.* **2011**, *13*, 2750-2753. The first drafts of the paper were written by me.

A version of chapter 4 has been submitted for publication. Sun, A. D.; Leung, K.; Restivo, A. D.; Love, J. A. I performed the majority of the work presented and wrote the first drafts of the paper. Nicholas Cowper and Philip P. Provencher, who were undergraduate students, conducted research under my supervision and collected data for Scheme 4.1 in section 4.2.1. After I optimized the reactions, Kaylyn Leung and Anita D. Restivo, who were also undergraduate students, assisted with the data collection for section 4.2.2, under my supervision.

Margaret Hwu assisted with the experiments and the data collection in chapter 5.

Dr. Brian Patrick of the Department of Chemistry at UBC performed the X-ray crystallography data collection, analysis and generated the report attached in Appendix. Mr. Marshall Lapawa, Mr. David Wong and Mr. Derek Smith of the Department of Chemistry at UBC performed all high-resolution mass spectrometry.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

acac	Acetylacetone
Ar	Aryl
BDE	Bond dissociation energy
Bn	Benzyl
Bu	Butyl
COD	Cyclooctadiene
Cp	Cyclopentadienyl
Cy	Cyclohexanyl
d	Doublet, in NMR spectroscopy
dba	Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets, in NMR spectroscopy
ddd	Doublet of doublet of doublets, in NMR spectroscopy
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
dmpe	1,2-Bis(dimethylphosphino)ethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dt	Doublet of triplets, in NMR spectroscopy
EDGs	Electron-donating-groups
eq	Equation
equiv	Equivalent
Et	Ethyl
EWGs	Electron-withdrawing-groups
FG	Functional group
h	Time in hours
HPLC	High-performance liquid chromatography
HRMS	High resolution-mass spectrometry

Hz	Hertz
^{i}Pr	Isopropyl
J	Coupling constant, in NMR spectroscopy
L	i) Ligand
	ii) Liter
M	i) Metal atom
	ii) Concentration, in molarity
m	Multiplet, in NMR spectroscopy
Me	Methyl
min	Time in minutes
MIDA	*N*-methyliminodiacetic acid
MHz	Megahertz
mmol	Millimole
mol	Mole
MS	Mass spectrometry
MW	Microwave
m/z	Mass-to-charge ratio, in mass spectrometry
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMP	Methylpyrrolidone
NMR	Nuclear magnetic resonance
OAc	Acetate
OTf	Triflate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
P^{t}Bu$_2$Me	Di-*tert*-butyl(methyl)phosphine
PCy_3	Tricyclohexanylphosphine
Ph	Phenyl
Pin	Pinacol
PMe_3	Trimethylphosphine
PPh_3	Triphenylphosphine
ppm	Parts per million, in NMR spectroscopy
P(^{t}Bu)$_3$	Tri-*tert*-butylphosphine

q	Quartet, in NMR spectroscopy
R	Organic group
RT/rt	Room temperature
s	Singlet, in NMR spectroscopy
SMe_2	Dimethylsulfide
SET	Single electron transfer
t	Triplet, in NMR spectroscopy
TBAF	Tetra-*n*-butylammonium fluoride
^{t}Bu	*t*-Butyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
©	Copyright
Δ	Heating, in reaction equation
δ	Chemical shift in NMR spectroscopy, in ppm
hv	Energy of light

Acknowledgements

First and foremost, I would like to thank Professor Jennifer A. Love for all of her support, guidance and patience over the years. I also owe her tremendous gratitude for always answering my questions and allowing me to freely explore chemistry.

I would also like to thank the members of my advisory committee: Professors Raymond J. Andersen, Gregory R. Dake and Pierre Kennepohl, for their valuable advice and discussions over the years.

I would like to thank all past and present members of the Love group; Paul Bichler, Heather Buckley, Lauren Fraser, Lauren Keyes, Erica Kiemele, Tin Nguyen, Anthony Sabbrre, Shiva Shoai Thomson, and Jun Yang have helped and encouraged me in numerous ways. I would also like to thank Alex Dauth and Matt Wathier for taking the time to read my thesis. Special thanks go to Tongen Wang for introducing me to the wonderful world of organofluorine chemistry.

I would like to express my profound gratitude to all the undergraduate students I have had the privilege of working with: Nicholas Cowper, Helen He, Margaret Hwu, Amy Kim, Dayle Larson, Kaylyn Leung, Philip Provencher, and Anita Restivo. I thank all of you for your hard work and wish you the best in your future endeavors.

I would also thank the various shops and services in the Department of Chemistry at UBC. Only their outstanding services and products can make the work presented herein possible. I am grateful to UBC, the Department of Chemistry, NSERC (Collaborative Research and Development Grant, Research Tools and Instrumentation Grant, Discovery Grant), the Canada Foundation for Innovation, the British Columbia Knowledge

Development Fund, Merck Canada, AstraZeneca Canada, and the Canada Knowledge Development Fund for their support and funding.

My Ph.D work has not been possible without the love of my Mom and Dad. Thank you for always supporting me, even when you probably had no idea what I was doing.

Finally, I would like to thank my wife Christina Muyi Tan, for her generous, unwavering support throughout the years, not to mention for being the love of my life. I could not have done this without her.

To Christina

Chapter 1: Introduction[a]

1.1 Introduction to fluorinated compounds

Over the last 50 years, the chemistry of fluorine-containing compounds has developed rapidly. While fluorine appears in no more than 50 natural products, approximately 20% of pharmaceutical and 35% of agrochemical molecules contain one or more fluorine atoms.[1] Fluorine-containing compounds have found wide applications in areas such as refrigerants, solvents, pesticides and pharmaceuticals.[2-4] Simple fluorine-containing molecules, such as dichlorodifluoromethane (Freon-12) and polytetrafluoroethylene (Teflon), have been well known to the general public for decades.[5] Several top selling drugs, including Pfizer's Lipitor (#1 by sales in 2010) and AstraZeneca's Crestor (#8 by sales in 2010), contain C-F bonds (Figure 1.1).[6]

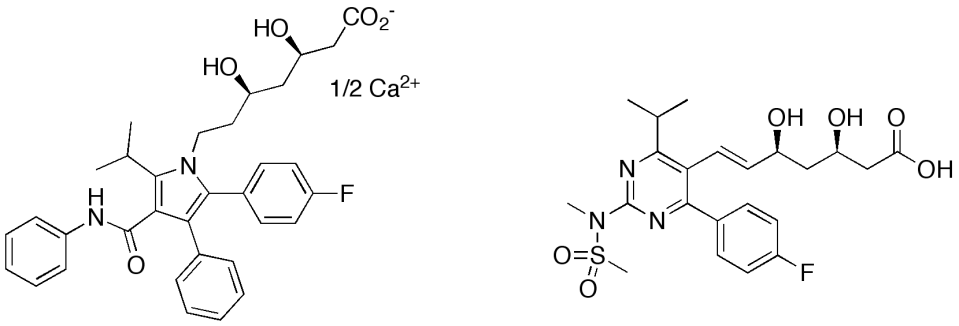


Figure 1.1 Popular fluorine-containing pharmaceuticals

Fluorine is the most electronegative element on the Pauling scale and C-F bonds are highly polarized.[7] The electrostatic interaction between these partially charged atoms results in a net contraction in bond length. A typical carbon-fluorine bond is about 135

[a] A version of section 1.4.4 has been published. Sun, A. D.; Love, J. A. (2010) Cross Coupling Reactions of Polyfluoroarenes via C-F Activation. Dalton Trans. 39: 10362-10374.

pm.[7] Fluorine also forms the strongest single bond to carbon, with bond dissociation energies (BDE) of up to 544 kJ/mol, which is significantly higher than other carbon-halogen bonds.[7,8]

The proliferation of fluorinated compounds is explained by their unique physical and chemical properties, such as solubility and lipophilicity.[2] Despite the fact that the sizes of fluorine and hydrogen are quite different (covalent radius: hydrogen: 31 pm; fluorine: 57 pm)[9], fluorine has often been used to replace hydrogen in organic molecules.[10] For example, fluorine atoms are introduced at certain positions on active pharmaceutical ingredients to block degenerative cytochrome P450 enzymatic oxidation.[11] A large number of novel compounds with highly valuable and desirable properties have been successfully synthesized.[2,12]

1.2 Methods to incorporate fluorine into organic compounds

Less than 50 organofluorine compounds have been isolated and identified in nature, with most of them synthesized biologically from fluoroacetic acid as the common precursor.[13] They are found in only a handful of microorganisms and plants, and cover a very narrow spectrum of structural diversity. Thus, due to the lack of natural sources of fluorinated compounds, chemical synthesis is required to generate fluorine-containing compounds. Efficient introduction of C-F bonds into target compounds, especially at a late stage of their synthesis, has been a longstanding challenge in synthetic chemistry. Certain highly fluorinated or perfluorinated compounds can be synthesized from direct fluorination of hydrocarbons with HF and/or F_2 (*vide infra*). Unfortunately, the extreme reactivity, toxicity and non-selectivity of these reagents put significant limitations on the application of this methodology. Since the 1970s, a number of mild fluorinating reagents, such as those shown in Figure 1.2, have been developed to be compatible with common functional groups and ordinary laboratory equipment.[14] Increasingly, such reagents can

be purchased from commercial suppliers at reasonable prices, and protocols to synthesize fluorinated compounds, even asymmetrically, are rapidly expanding.[15]

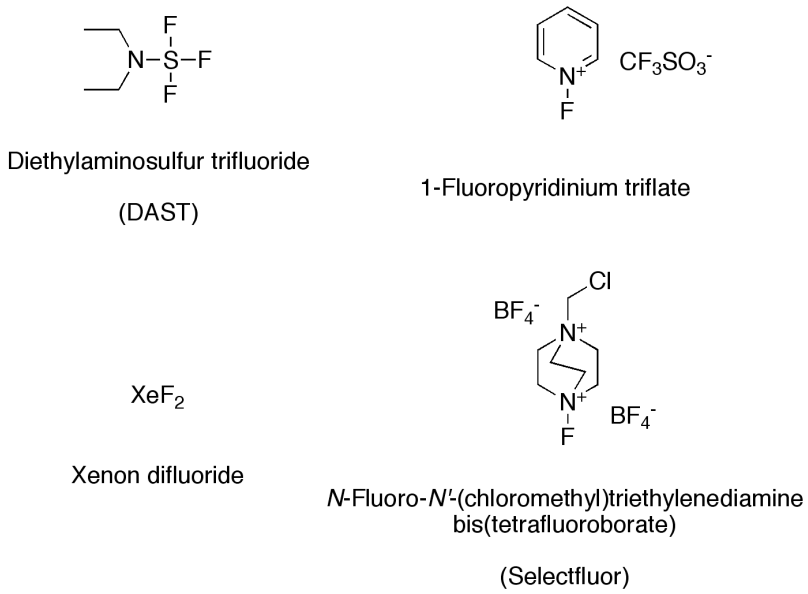


Figure 1.2 Structures of some common fluorinating agents

Compared to organofluorine synthesis in general, however, aryl fluoride synthesis presents more challenges. Its development has been hindered by a number of factors. For one, because no aryl fluorides have been found in nature to date,[13] no naturally occurring enzymatic C-F bond formation provides a template for study. Also, fluoride ions are highly solvated in aqueous solution and/or in certain polar solvents, rendering them inactive under typical nucleophilic aromatic substitution conditions. A common pathway to introduce chlorine, bromine and iodine atoms into aryl rings in biological systems is to oxidize them into corresponding electrophilic halogens ("Cl^+", "Br^+", and "I^+") for electrophilic aromatic substitution.[16] In contrast, fluorine, being the most electronegative atom, does not readily form "F^+" under biological conditions; hence, electrophilic aromatic substitution cannot be used easily as a strategy to synthesize fluorinated arenes. The most common method to synthesize such complex fluorinated molecules, such as Lipitor or Crestor industrially is to incorporate existing fluorinated starting materials

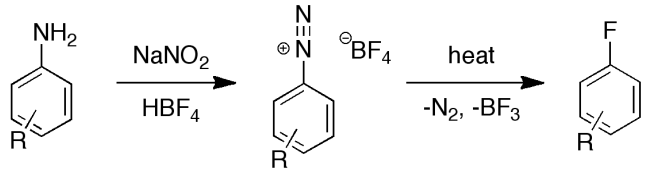
(Lipitor from 4-fluorobenzaldehyde[17] and Crestor from 4-fluorobenzoyl chloride[18], respectively).

This thesis focuses on methods to generate functionalized aryl fluoride building blocks. As such, contemporary methods for generating aryl fluorides will be discussed. A number of approaches have been taken over the years to address the challenges associated with aryl fluoride synthesis. In the next section, the scope and limitations of these methodologies will be described in more detail.

1.3 Methods for synthesizing aryl fluorides

1.3.1 Nucleophilic fluorination

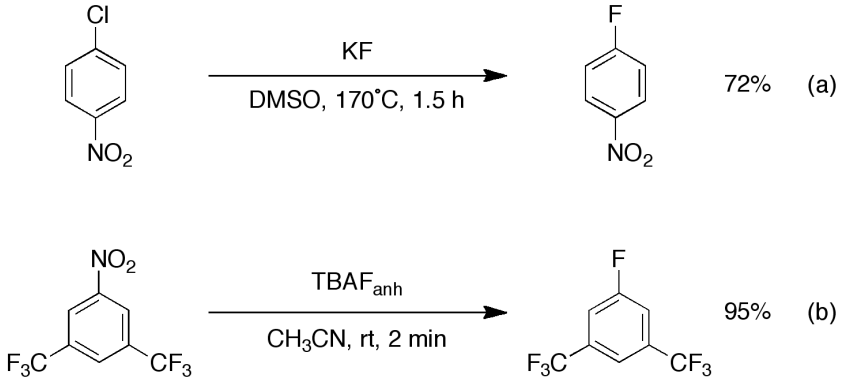
One method to generate aryl fluorides is the classical Balz-Schiemann reaction, shown in Scheme 1.1. This reaction generates aryl diazonium tetrafluoroborate intermediates, which release N_2 and BF_3 upon heating to generate functionalized aryl fluorides.[19] Although this reaction has been the method of choice to generate aryl fluorides for many years and gives good results in general, its harsh preparatory conditions and the potentially explosive nature of diazonium ions significantly limit the synthetic utility and make large scale reactions problematic.



Scheme 1.1 Balz-Schiemann reaction

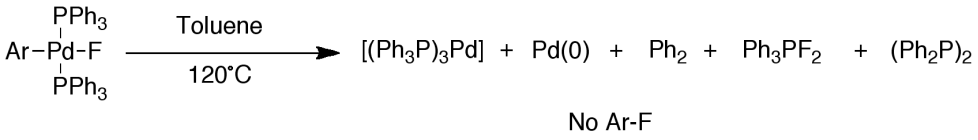
Another method is by nucleophilic aromatic substitution. Electron-withdrawing groups are required to stabilize the Meisenheimer intermediates. Classical reaction conditions, such as those shown in Scheme 1.2a (high temperature, basic fluoride ion) are

harsh and incompatible with many sensitive functional groups.[20] More recently, the development of anhydrous fluoride sources has dramatically decreased the requirements for reaction temperature and duration, and allowed reactions, such as the one shown in Scheme 1.2b, to proceed under mild conditions, although the number of examples is limited.[21]



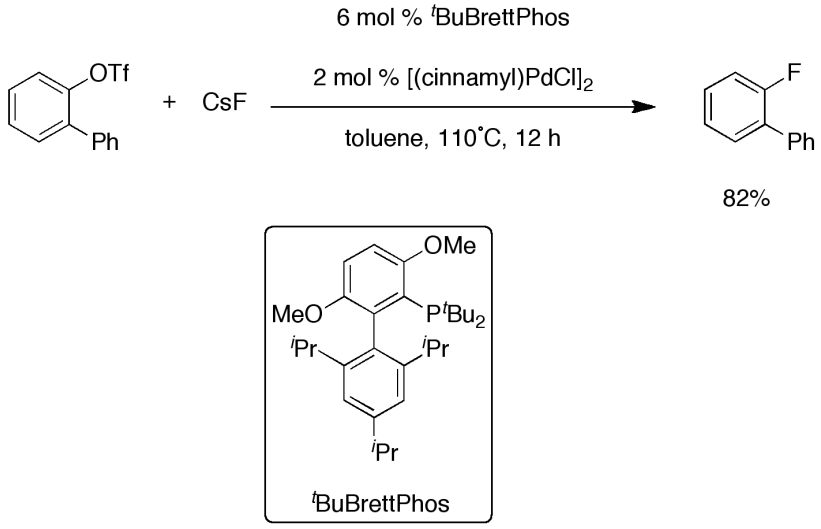
Scheme 1.2 Nucleophilic aromatic substitution

A third method is transition metal-mediated/catalyzed nucleophilic fluorination via C-F reductive elimination. Much of the focus has been on the generation of carbon-fluorine bonds from readily available carbon-iodine, -bromine and -chlorine bonds. The general mechanism of this process involves oxidative addition of the C-X bond to the metal (X = I, Br, Cl, etc.), followed by a nucleophilic exchange of the halogen for fluoride at the metal center. Finally, reductive elimination of the C-F bond releases the fluorinated product. After many years of study, researchers have realized that the bottleneck for this transformation is the reductive elimination of Ar-M-F species.[22] In many instances, only side products, resulting from carbon-carbon reductive elimination, are observed (Scheme 1.3).[23]



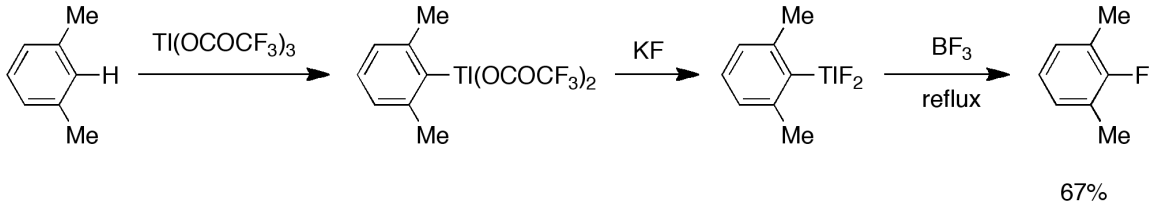
Scheme 1.3 Attempted nucleophilic C-F reductive elimination

More recently, Buchwald and co-workers demonstrated that the combination of a Pd(II) salt and a highly electron-rich, sterically demanding ligand was capable of converting aryl triflates to aryl fluorides catalytically, using cesium fluoride (Scheme 1.4).[24]

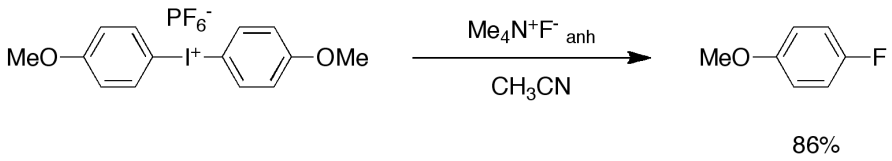


Scheme 1.4 Nucleophilic C-F reductive elimination

There are other protocols to utilize nucleophilic fluorine sources to synthesize aryl fluorides, but they either employ stoichiometric amounts of toxic metals, such as thallium (Scheme 1.5),[25] or require uncommon starting materials, such as hypervalent iodine species (Scheme 1.6).[26] Unfortunately, such constraints limit the ready extension of these methods to the general synthesis of aryl fluorides.



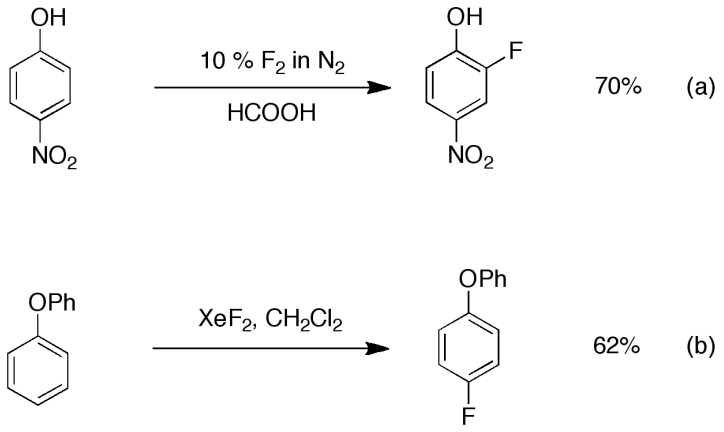
Scheme 1.5 Tl-mediated aryl fluoride synthesis



Scheme 1.6 Aryl fluoride synthesis from diaryliodonium salts

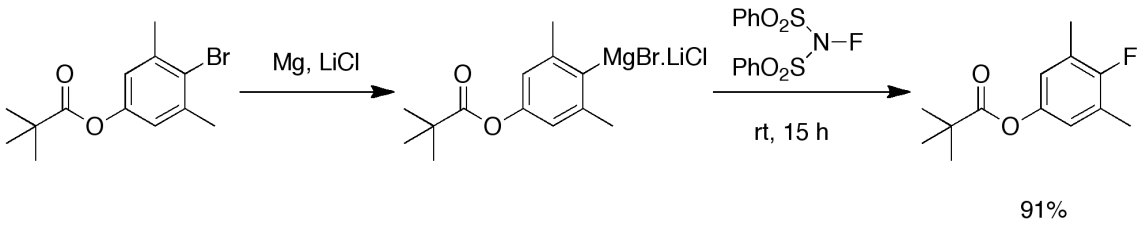
1.3.2 Electrophilic fluorination

Elemental fluorine or hydrogen fluoride can be employed for generating aryl fluorides.[27] In particular, these reagents have high abundance and low cost. However, due to the high reactivity and toxic nature of these reagents, great care must be taken to ensure the safety of operations. In addition, such reactions are often unselective. One recent example that proceeds with high selectivity is shown in Scheme 1.7a.[28] Moreover, xenon difluoride (XeF_2) can be used to achieve similar results (Scheme 1.7b); however, its instability and high cost have made it less popular.[29]



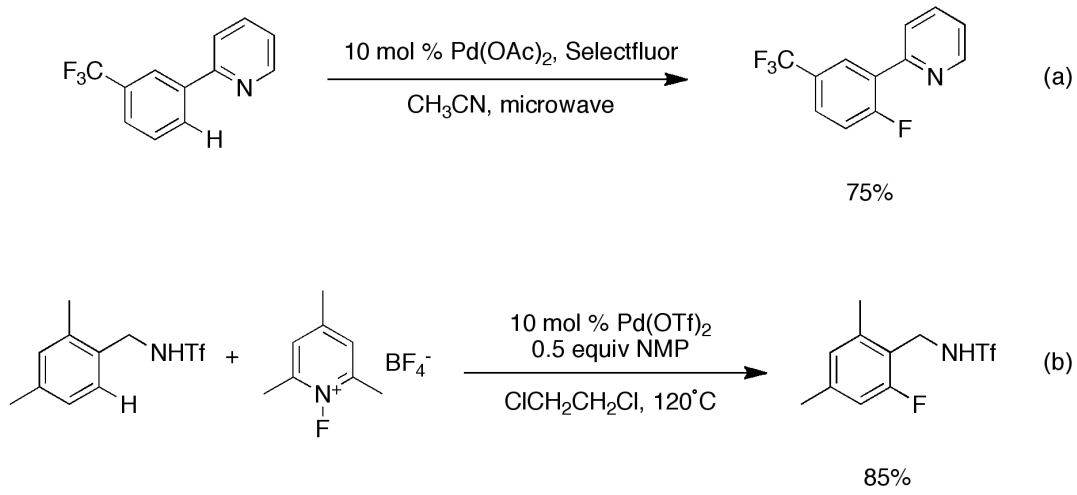
Scheme 1.7 Direct fluorination

In response to the reactive and unselective nature of fluorine gas and hydrogen fluoride, milder electrophilic fluorinating agents have been developed. A large variety are now commercially available and generally do not require special equipment and/or expertise to handle. While many of these are still sensitive towards light, moisture and heat, these reagents have been successfully applied in nucleophilic substitution reactions involving organometallic species, such as lithium-, magnesium- or zinc-based reagents. Although originally suffering from low functional group compatibility, electrophilic fluorination via organometallic reagents has now been established as a viable method to generate highly functionalized aryl fluorides.[30] A recent example developed by the Knochel group is shown in Scheme 1.8. The authors were able to generate the Grignard reagent by the direct insertion of Mg metal into the C-Br bond in the presence of LiCl. Subsequent reaction with *N*-fluorobenzenesulfonimide (NFSI) gave the corresponding aryl fluoride in 91% yield.[31]



Scheme 1.8 Electrophilic fluorination via organometallic reagents

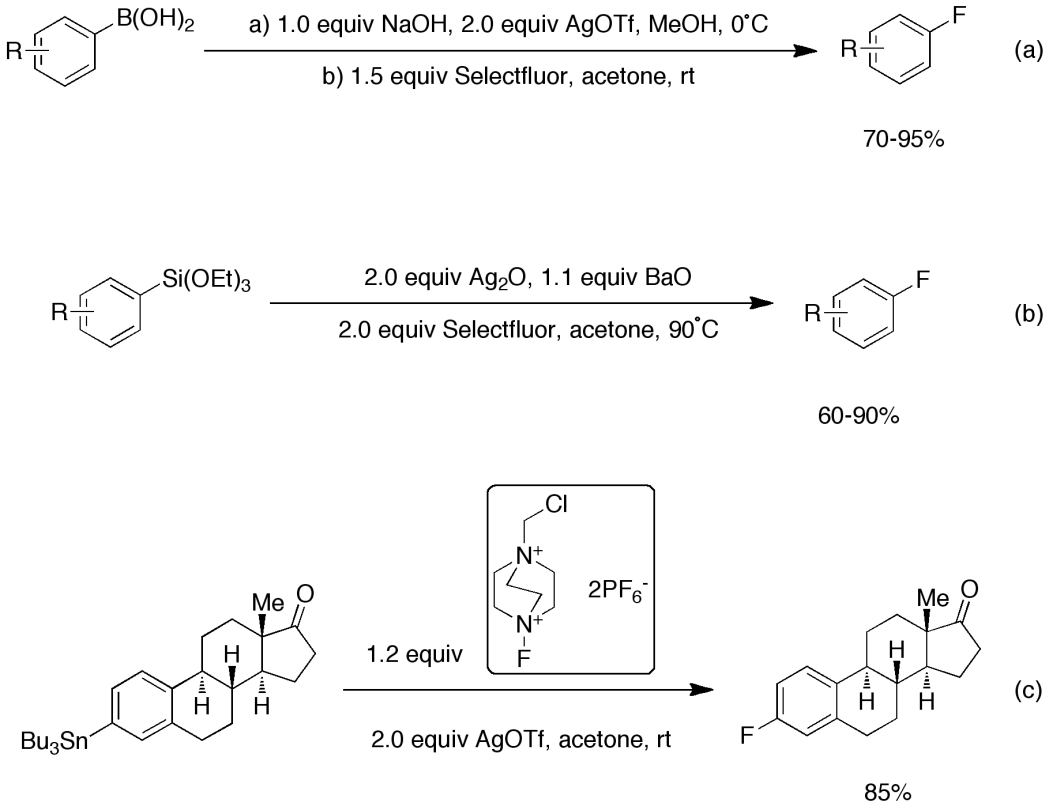
Another method is transition metal-mediated/catalyzed electrophilic fluorination via C-F reductive elimination. Because electrophilic fluorine sources are used, different catalytic cycles are involved to overcome the difficult nucleophilic C-F reductive elimination process. These reactions do not employ organohalides as starting materials, but rather use hydrocarbons or other readily available species. For example, the Sanford group (Scheme 1.9a)[32] and the Yu group (Scheme 1.9b)[33] independently reported Pd-catalyzed aryl fluoride synthesis with electrophilic fluorine sources. After the initial directing group-assisted C-H activation, electrophilic fluorine reagents oxidize the Pd(II) centers to Pd(IV). C-F reductive elimination releases the fluorinated products and re-generates the Pd(II) catalysts.



Scheme 1.9 Electrophilic C-F reductive elimination via C-H activation

Recently, Ritter and co-workers developed a series of methods to generate aryl fluorides from organometallic reagents. Unlike lithium- or magnesium-based reagents, these boron-, tin-, and silicon-based reagents do not react with electrophilic reagents directly; instead, transition metals are required to activate those carbon-metal bonds. As shown in Scheme 1.10a and 1.10b, aryl boron[34] and aryl silicon[35] compounds are used as starting materials in Ag-mediated reactions to synthesize functionalized aryl fluorides in high yields under mild conditions. Fluorinated estrogen derivative is generated from

organotin starting material, demonstrating that this methodology is compatible with complex structures and potentially reactive functional groups (Scheme 1.10c).[36]

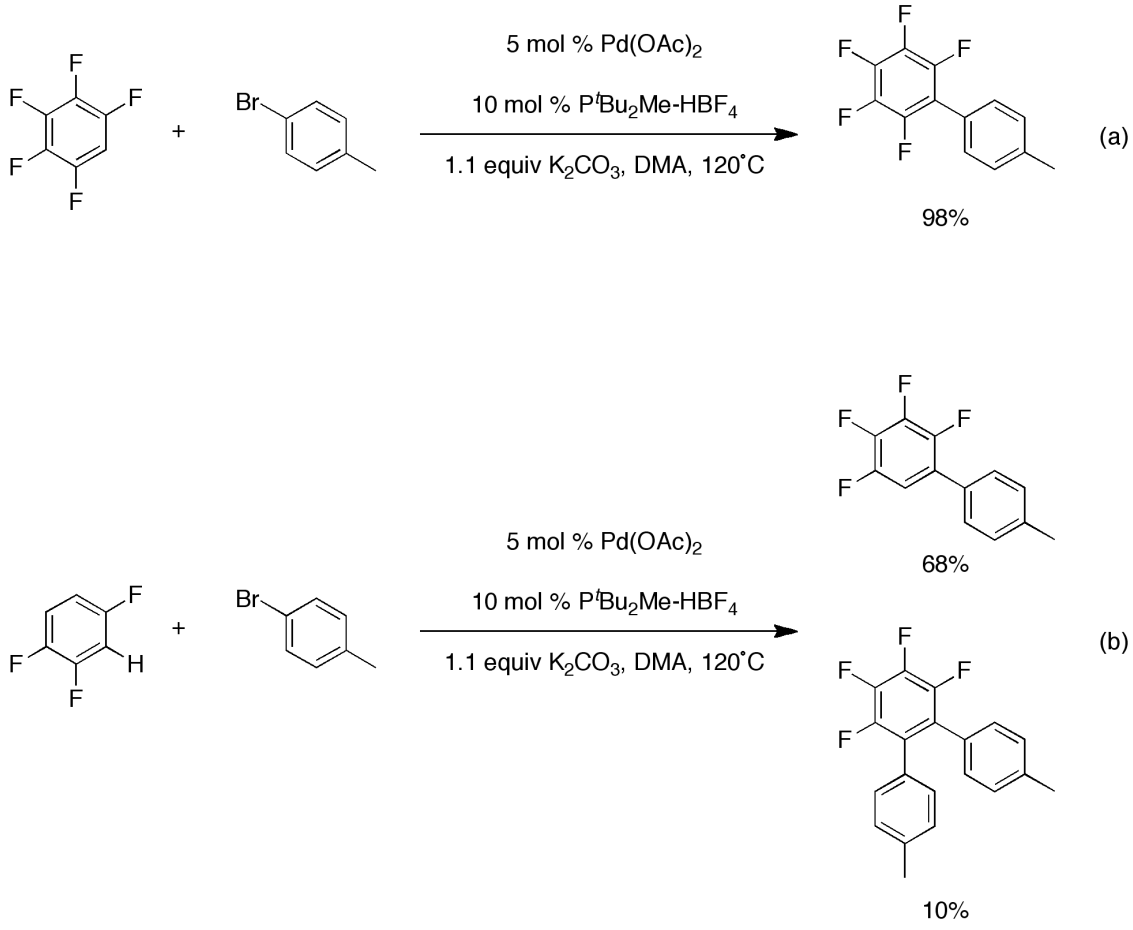


Scheme 1.10 Electrophilic C-F reductive elimination via C-M activation

1.3.3 Direct arylation

Direct arylation of fluorinated arenes has been developed as a contemporary approach to generate aryl fluorides.[37] This strategy involves the activation of an aryl C-H bond and subsequent functionalization. Many groups have made significant contributions in this field, and their results have been reviewed extensively.[38] One example by the late professor Fagnou is shown in Scheme 1.11a in which a near quantitative isolated yield was reported. In several instances, over-arylation is observed (Scheme 1.11b).[39] It is

notable that in many cases, the strategy for generating functionalized aryl fluorides outlined in this thesis provides products that are not easily accessible by a direct arylation strategy. As such, the methods are complementary.

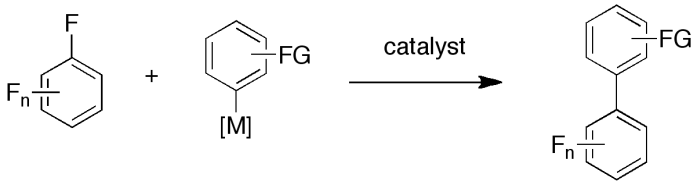


Scheme 1.11 Direct arylation

1.3.4 Potential for selective cross-coupling of polyfluoroarenes

In spite of extensive efforts in the synthesis of functionalized aryl fluorides, there are still significant limitations in each of the cases discussed above. Many of them suffer from harsh conditions and/or functional group incompatibility; others require special starting materials or ligands to achieve synthetically acceptable yields. Given these

limitations, we argue that it is reasonable to consider selective carbon-fluorine cross-coupling of polyfluoroarenes as an alternative approach to synthesize functionalized aryl fluoride compounds. The challenge is to activate one C-F bond in the presence of one or more additional C-F bonds under mild conditions. In principle, these products could be generated by cross-coupling reactions of more reactive C-X bonds (X = Cl, Br, etc.). The mixed halo compounds, however, are often not commercially available; those that are can be more expensive than the polyfluoroarenes. For example, 2,4,6-trifluorobenzaldehyde, an aryl fluoride starting material we used extensively in our research, is commercially available, whereas 2-chloro-4,6-difluorobenzaldehyde is not. These mixed halo compounds must be synthesized by one of the methods mentioned above. Due to the high cost of electrophilic fluorinating reagents, most fluorinated building blocks are still formed by nucleophilic pathways. As fluorine atoms are introduced into target compounds, the products become more electron-deficient and more reactive than the starting materials, which make synthesizing mixed halo compounds challenging and expensive. For example, nucleophilic substitution of 1,4-dichlorobenzene by fluorine will generate 1-chloro-4-fluorobenzene first, which is more reactive than the starting material. As a consequence, 1,4-difluorobenzene is the major product instead of 1-chloro-4-fluorobenzene.



Scheme 1.12 Hypothetical selective C-F cross-coupling of polyfluoroarenes

1.4 Catalytic carbon-fluorine activation of aryl fluorides

1.4.1 Introduction

Transition metal-catalyzed cross-coupling of fluoroarenes would presumably follow a typical cross-coupling mechanism involving oxidative addition of the C-F bond, transmetalation and reductive elimination. The challenge in this reaction is that C-F activation by transition metals is relatively underdeveloped compared to other C-X bonds.

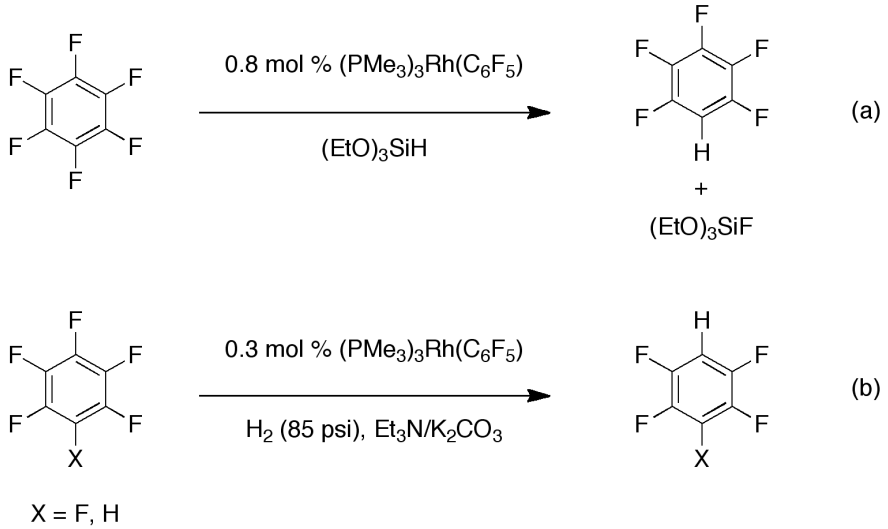
Even so, many transition metals (Ti, Zr, Nb, Ta, W, Mn, Fe, Ru, Co, Rh, Ir, Ni, Pd, Pt) have been shown to be capable of activating C-F bonds. The chemistry of stoichiometric C-F activation has been reviewed by Richmond (general C-F bond activation),[40] Crabtree (general C-F bond activation),[41] Braun and Perutz (C-F bond activation by Ni),[42] Braun and Perutz (general C-F bond activation),[43] Jones (C-F bond activation by Zr),[44] and Torrens (C-F bond activation by platinum group metals).[45]

Catalytic C-F activation reactions are much more limited in scope. They can be classified into two types of reactions: hydrodefluorination (the replacement of C-F bonds with C-H bonds) and cross-coupling of fluoroarenes, which includes cross-coupling of monofluoroarenes and polyfluoroarenes. In this section, relevant literature on catalytic C-F activation is presented. First, hydrodefluorination is discussed, followed by a discussion of cross-coupling of monofluoroarenes. Since the focus of this thesis is to synthesize highly functionalized aryl fluorides via C-F activation, cross-coupling of polyfluoroarenes will be examined and discussed in detail. A number of reviews have been published that discuss catalytic hydrogenolysis of C-F bonds,[46] catalytic activation of fluorocarbons,[47] C-F bonds in organic synthesis[48] and C-F bond functionalization by Rh.[49]

1.4.2 Catalytic hydrodefluorination

Hydrodefluorination replaces C-F bonds with C-H bonds. No new C-C bond is formed. If polyfluorinated aromatics are used, new fluoroarenes are generated, assuming not all C-F bonds are cleaved. This is potentially a convenient method to synthesize asymmetrical fluorinated compounds from symmetrical starting materials, but since it is not the focal point of this thesis, only a few representative examples will be reviewed here.

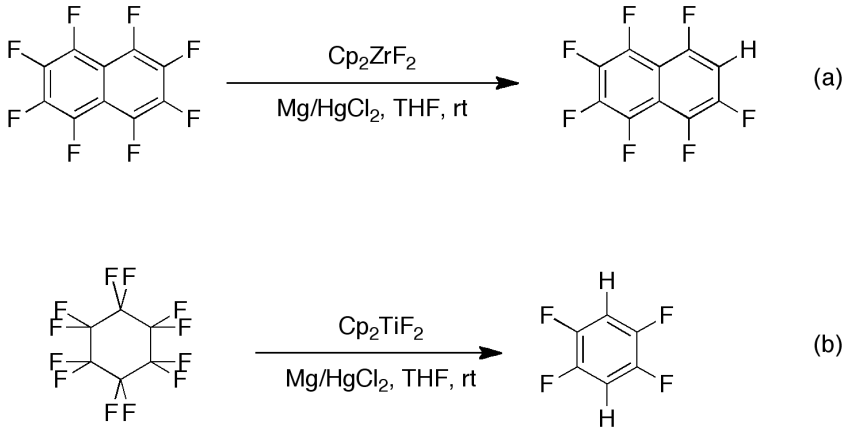
Milstein and co-workers reported the first examples of homogeneous catalytic hydrodefluorination of fluoroarenes in the early 1990s.[50] $(PMe_3)_3Rh(C_6F_5)$ catalyzed the conversion of hexafluorobenzene and pentafluorobenzene to pentafluorobenzene and 1,2,4,5-tetrafluorobenzene, respectively, employing $(EtO)_3SiH$ (Scheme 1.13a) or H_2 (Scheme 1.13b) as the hydrogen source.



Scheme 1.13 Rh-catalyzed hydrodefluorination by Milstein

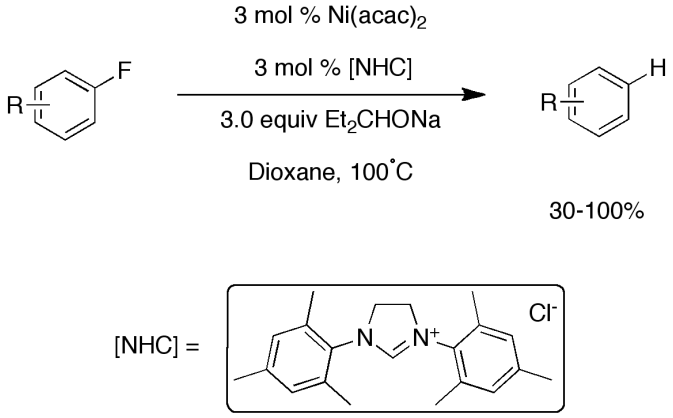
Kiplinger and Richmond developed a catalytic procedure to reduce fluoroarenes using group 4 metallocenes (Cp_2TiF_2/Cp_2ZrF_2) as catalysts. Perfluoronaphthalene was reduced to 1,3,4,5,6,7,8-heptafluoronaphthalene in the presence of Cp_2ZrF_2, $HgCl_2$ and

magnesium turnings as the reducing agent (Scheme 1.14a). This procedure could also be used to reduce alkyl C-F bonds. Perfluorocyclohexane was reduced to afford 1,2,4,5-tetrafluorobenzene (Scheme 1.14b).[51]



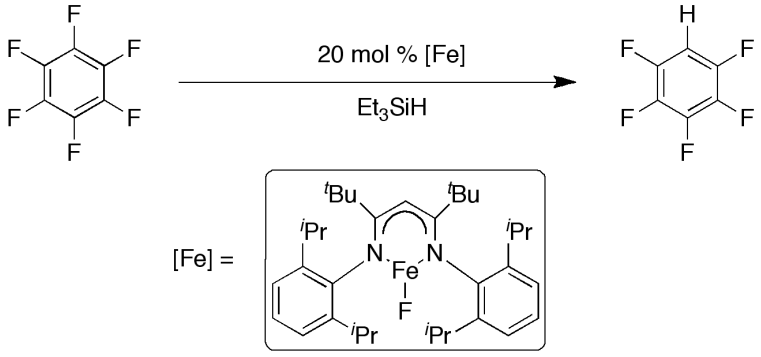
Scheme 1.14 Zr/Ti-catalyzed hydrodefluorination by Richmond

Fort and co-workers studied the catalytic hydrogen transfer reactions with metal alkoxides containing β-hydrogens. They reported that a common *N*-heterocyclic carbene precursor (IMes-HCl), combined with *in situ* generated Ni(0) from $Ni(acac)_2$, were capable of catalyzing hydrodefluorination of various fluorinated aromatics. The reactions were conducted under very mild conditions, and used sodium isopropoxide as the hydride source. A number of fluoroarenes were tested; the results were generally good but showed strong substrate dependency (Scheme 1.15).[52]



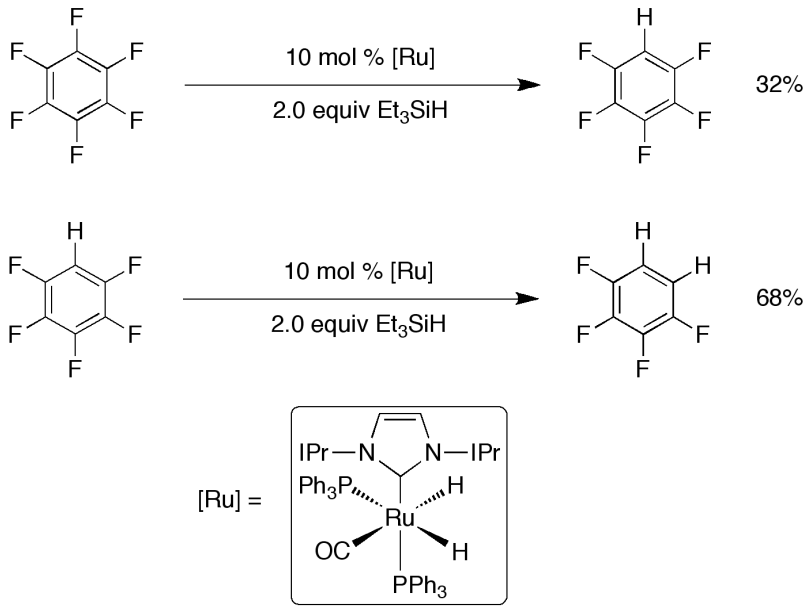
Scheme 1.15 Ni-catalyzed hydrodefluorination by Fort

In 2005, the Holland group reported the synthesis and reactivity of low-coordinate Fe(II) fluoride complexes and their application in catalytic hydrodefluorination reactions. These diketiminate species were very stable under ambient conditions. While the catalytic loading was high, mono-hydrodefluorination of fluoroarenes was observed in the presence of silanes as the hydrogen source (Scheme 1.16).[53]



Scheme 1.16 Fe-catalyzed hydrodefluorination by Holland

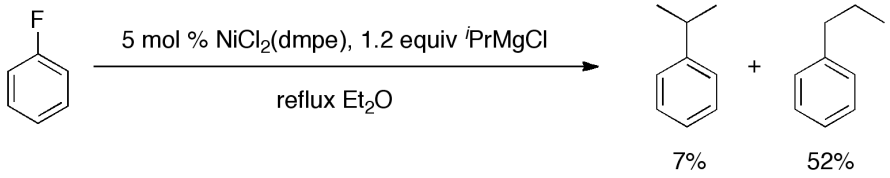
A catalytic hydrodefluorination of fluoroarenes with silanes was realized by Whittlesey and co-workers using ruthenium *N*-heterocyclic carbene (NHC) complexes. Hexafluorobenzene and pentafluorobenzene were readily reduced to pentafluorobenzene and 1,2,3,4-tetrafluorobenzene, respectively (Scheme 1.17).[54]



Scheme 1.17 Ru-catalyzed hydrodefluorination by Whittlesey

1.4.3 Cross-coupling of monofluoroarenes

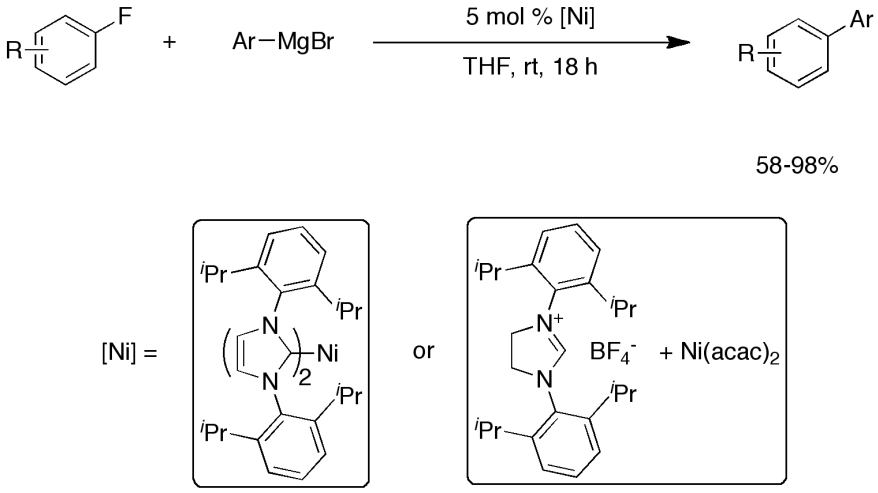
Kumada and co-workers published the first example of catalytic C-F cross-coupling in 1973.[55] The reaction between fluorobenzene and isopropyl magnesium chloride, catalyzed by a Ni(II)/phosphine complex, produced 7% of the expected branched product and 52% of the linear isomer. The mechanistic details were not elucidated. Although this reaction was not particularly synthetically useful, it demonstrated that cross-coupling of aryl fluorides was possible (Scheme 1.18).



Scheme 1.18 Ni-catalyzed Kumada cross-coupling by Kumada

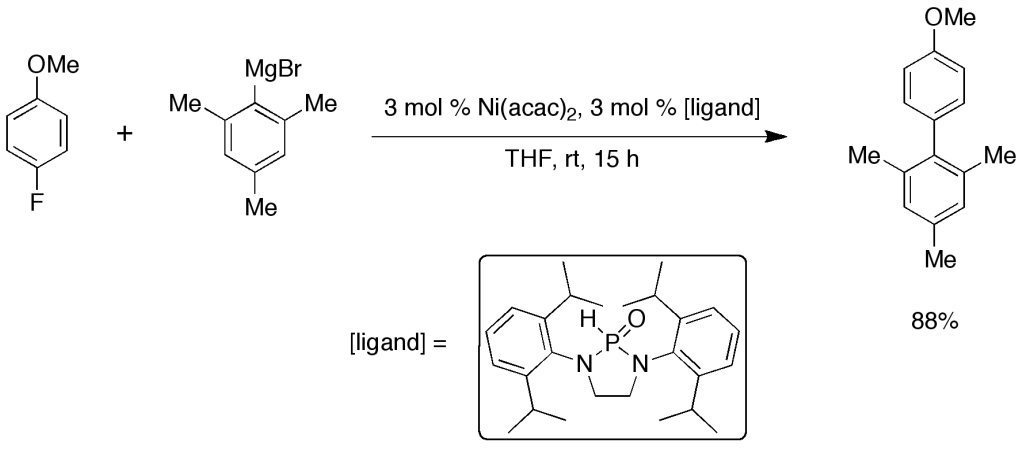
In 2001, the Herrmann group developed a highly successful cross-coupling of aryl C-F bonds using a bis[1,3-di(2',6'-diisopropylphenyl)imindazolin-2-ylidene] nickel(0)

complex that generated biaryl products in good-to-excellent yields. The authors observed high activity even at room temperature. Both electron-rich and electron-poor fluoroarenes worked well (Scheme 1.19).[56]



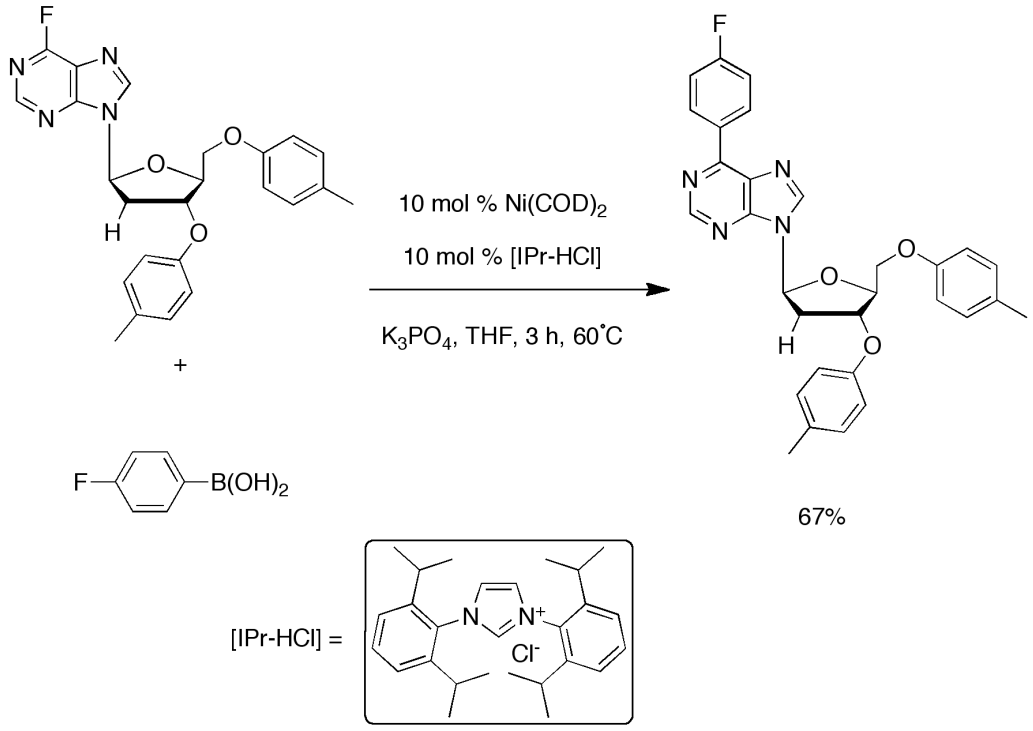
Scheme 1.19 Ni-catalyzed Kumada cross-coupling by Hermann

Ackermann and co-workers reported a Ni-catalyzed Kumada C-F cross-coupling of aryl fluorides. The reactions were catalyzed by $Ni(acac)_2$ and a diaminophosphine oxide ligand (Scheme 1.20). Reactions were conducted at room temperature and yields were good-to-excellent.[57]



Scheme 1.20 Ni-catalyzed Kumada cross-coupling by Ackermann

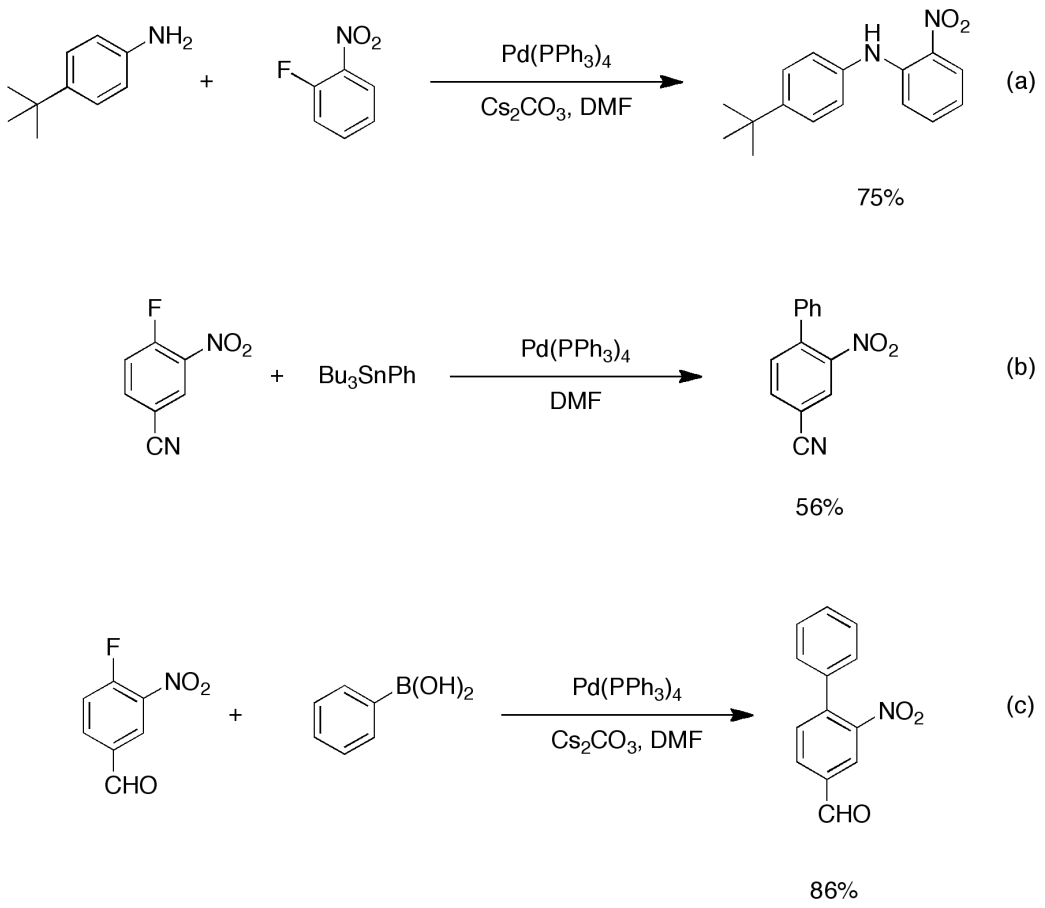
In their research of protected 2'-deoxynucleosides and nucleosides, Robins and co-workers discovered a Ni-catalyzed C-F cross-coupling between boronic acids and electron-poor 6-fluoropurine derivatives. Both electron-donating and electron-withdrawing arylboronic acids underwent coupling reactions in good yield. It is noteworthy that the C-F bond from 4-fluorobenzeneboronic acid was unaffected, confirming that only C-F bonds on electron-poor substrates were sufficiently reactive towards the coupling conditions (Scheme 1.21).[58]



Scheme 1.21 Ni-catalyzed Suzuki-Miyaura cross-coupling by Robins

The Yu group studied Pd(0)-catalyzed amination, Suzuki-Miyaura coupling and Stille coupling reactions of electron-poor fluoroarenes.[59] The amination reaction between 4-*tert*-butylaniline and 2-fluoronitrobenzene resulted in a reasonable yield (Scheme 1.22a). For Suzuki-Miyaura (Scheme 1.22b) and Stille coupling (Scheme 1.22c), cross-coupling reactions took place only when nitro groups were adjacent to the C-F bonds, and electron-withdrawing groups occupied the positions para to the C-F bonds.

The authors believed that there was a change in the mechanism in cross-coupling relative to amination, but no detail was given.



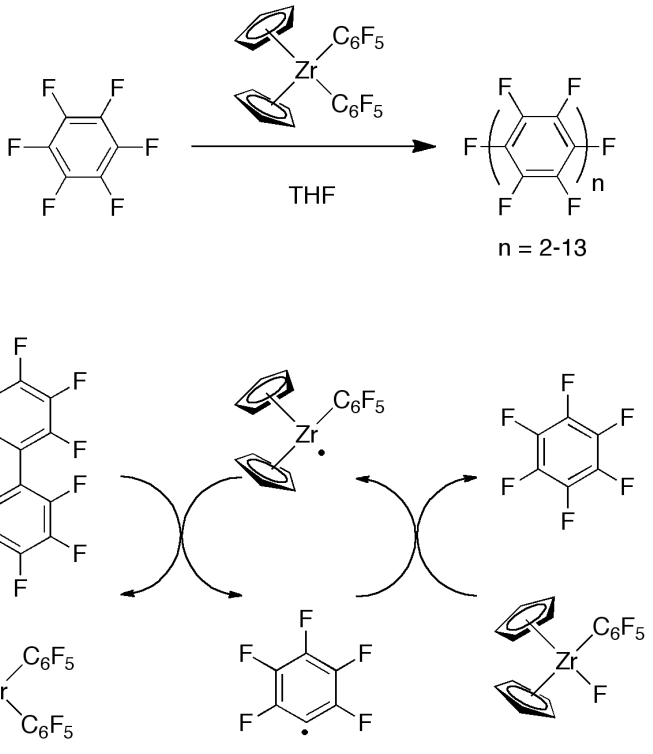
Scheme 1.22 Pd-catalyzed amination, Stille and Suzuki-Miyaura cross-coupling by Yu

1.4.4 Cross-coupling of polyfluoroarenes

Compared to the development of cross-coupling of monofluoroarenes, there is less research done on cross-coupling of polyfluoroarenes. The key challenge in cross-coupling reactions with polyfluoroarenes is to activate one or more C-F bonds without activating all available C-F bonds, as the products can be more reactive than the starting materials.

The Jones group reported the first catalytic carbon-fluorine activation of polyfluoroarenes to form C-C bonds in 1999 (Scheme 1.23). They realized that thermal

decomposition of $Cp_2Zr(C_6F_5)_2$ in the presence of C_6F_6 generated a series of linear oligomers of fluorinated polyphenylenes. C-F bonds were activated in a radical mechanism, with the Zr complexes acting as electron transfer agents.[60]



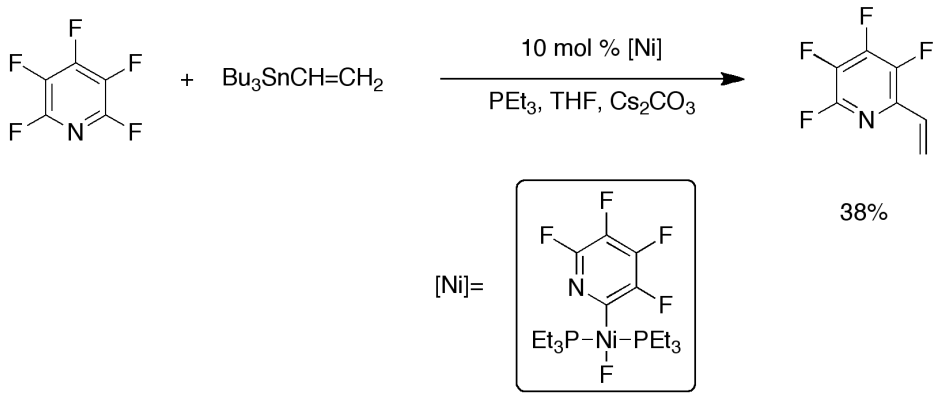
Scheme 1.23 Zr-catalyzed homocoupling by Jones

The use of early transition metals in catalytic C-F cross-coupling reaction of polyfluoroarenes catalyzed is rare. Takahashi and co-workers reported that hexafluorobenzene underwent clean cross-coupling with 2-phenethylmagnesium chloride in the presence of 5 mol % $TaCl_5$. The authors observed complete isomerization from the linear to the branched isomer,[61] whereas Kumada *et al.* observed partial isomerization from the branched to the linear isomer.[53] The two catalytic systems showed opposite isomerization patterns despite having similar reaction conditions (fluorobenzene in reflux diethyl ether for Kumada *et al.*, hexafluorobenzene in THF/DME mixture at 50°C for Takahashi *et al.*). The cause of this isomerization was not determined. The ratio between

mono-coupled and di-coupled products could be controlled by the amount of organometallic reagents added (Scheme 1.24).

Scheme 1.24 Ta-catalyzed Kumada cross-coupling by Takahashi

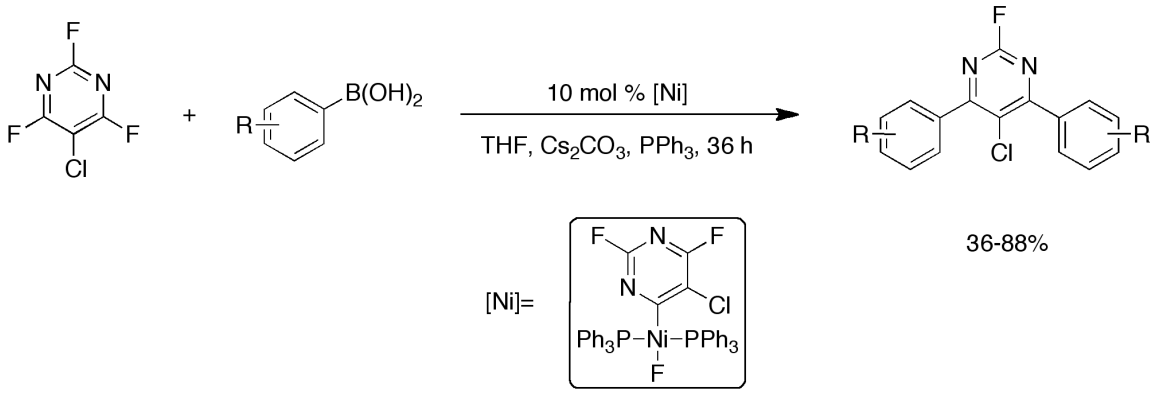
Group 10 metals have been commonly applied in catalytic C-F activation. In 2001, Perutz and Braun reported a Ni-catalyzed Stille cross-coupling of fluoropyridines. In the presence of a base (Cs_2CO_3) and a catalytic amount of a Ni(II)-F complex, pentafluoropyridine reacted with tributyl(vinyl)tin to activate one of the C-F bonds ortho to the nitrogen atom. The vinyl-substituted product was isolated in 38% yield (Scheme 1.25).[62]



Scheme 1.25 Ni-catalyzed Stille cross-coupling by Perutz

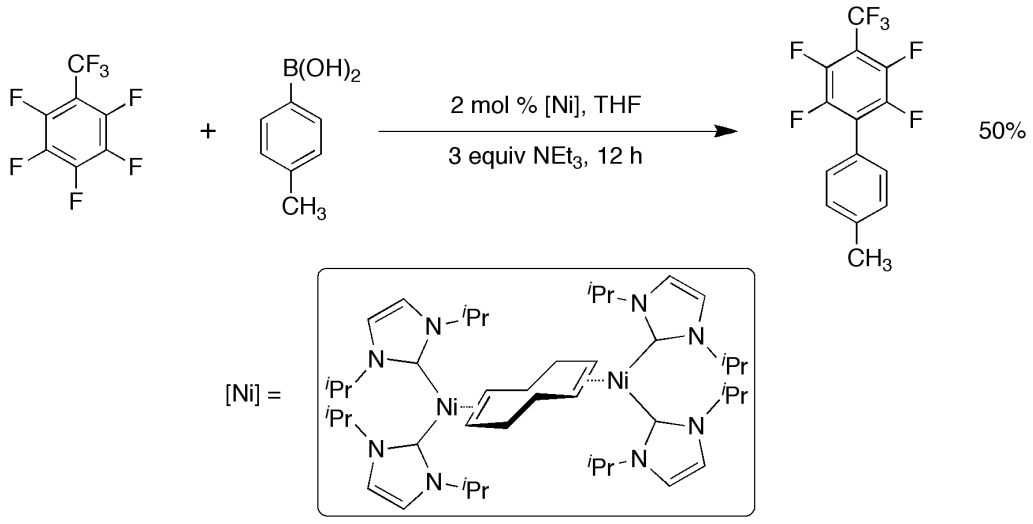
Braun and co-workers subsequently reported that a slightly different Ni(II)-F complex was capable of catalyzing Suzuki-Miyaura cross-coupling reactions. The reaction

required the addition of PPh_3 and Cs_2CO_3. The selectivity of this reaction is noteworthy. The C-F bonds at the 4- and 6-positions on the fluorinated pyrimidine were activated preferentially, whereas the 2-position C-F bond and a much weaker C-Cl bond remained intact (Scheme 1.26).[63]



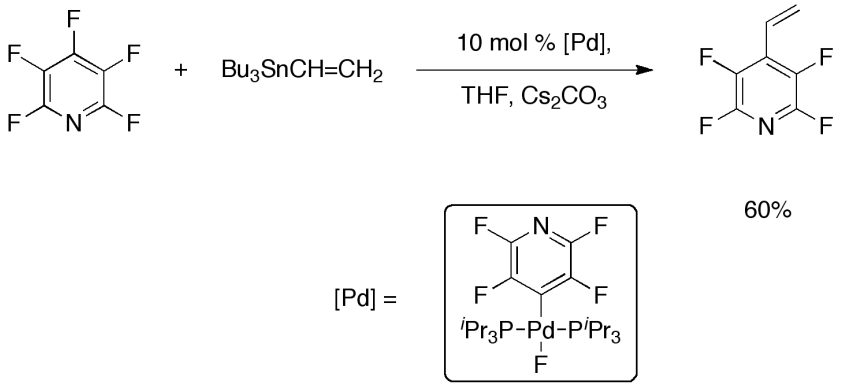
Scheme 1.26 Ni-catalyzed Suzuki-Miyaura cross-coupling by Braun

Radius and co-workers were able to achieve a Suzuki-Miyaura C-F cross-coupling of polyfluoroarenes, catalyzed by Ni(0)-NHC complexes. C-F activation took place preferentially at the C-F bonds para to the CF_3 groups, and yields were moderate for most arylboronic acids explored (Scheme 1.27).[64]



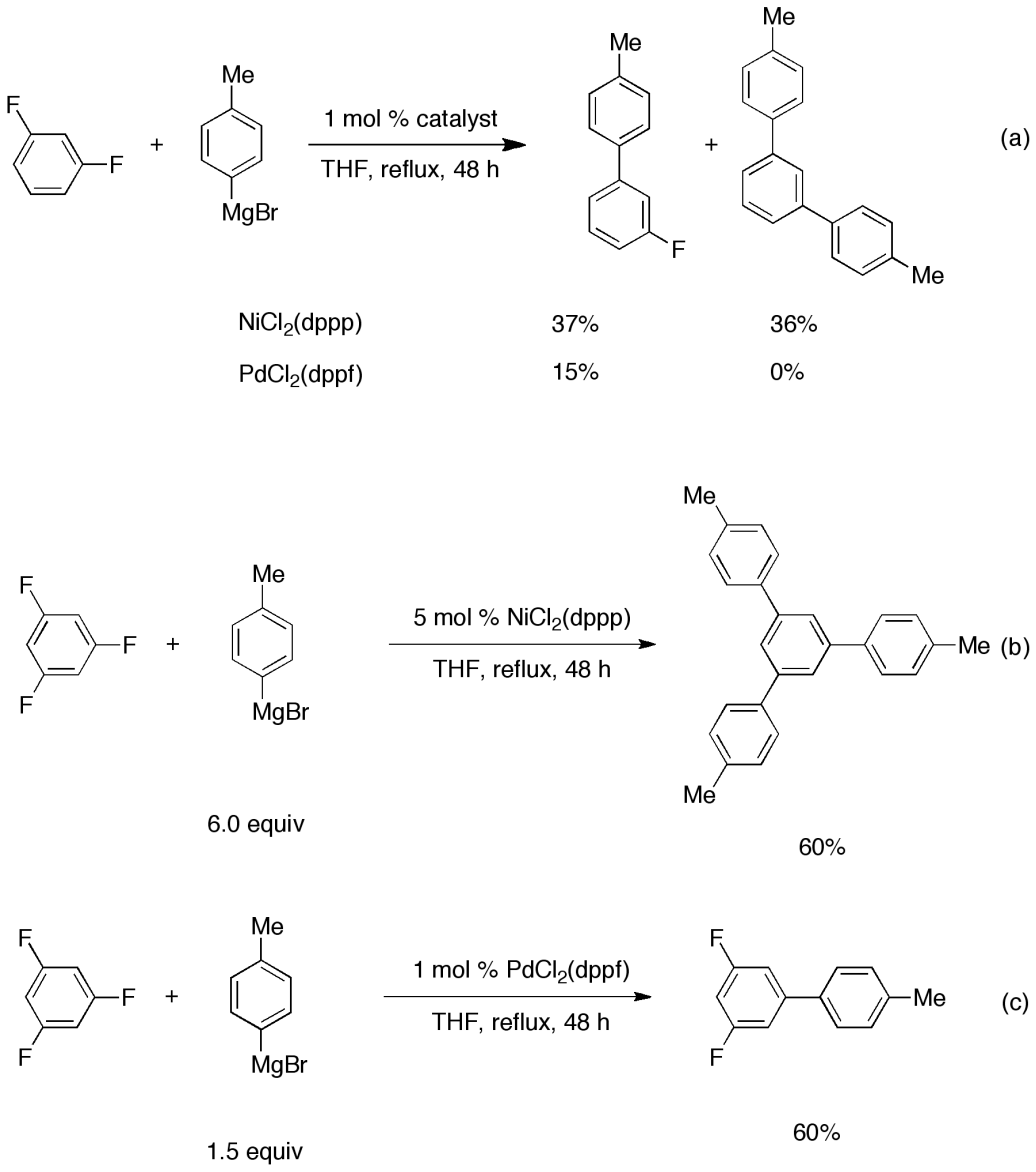
Scheme 1.27 Ni-catalyzed Suzuki-Miyaura cross-coupling by Radius

The Braun group developed a Pd-catalyzed Stille cross-coupling of polyfluoroarenes. Pentafluoropyridine reacted with tributyl(vinyl)tin in the presence of Cs_2CO_3 and a catalytic amount of a Pd(II) complex (Scheme 1.27).[65] It is noteworthy that in this case, the C-F bond para to the nitrogen atom was activated (Scheme 1.28), whereas in the previously disclosed Ni-catalysis, cross-coupling took place at the ortho C-F bonds (Scheme 1.25).[62]



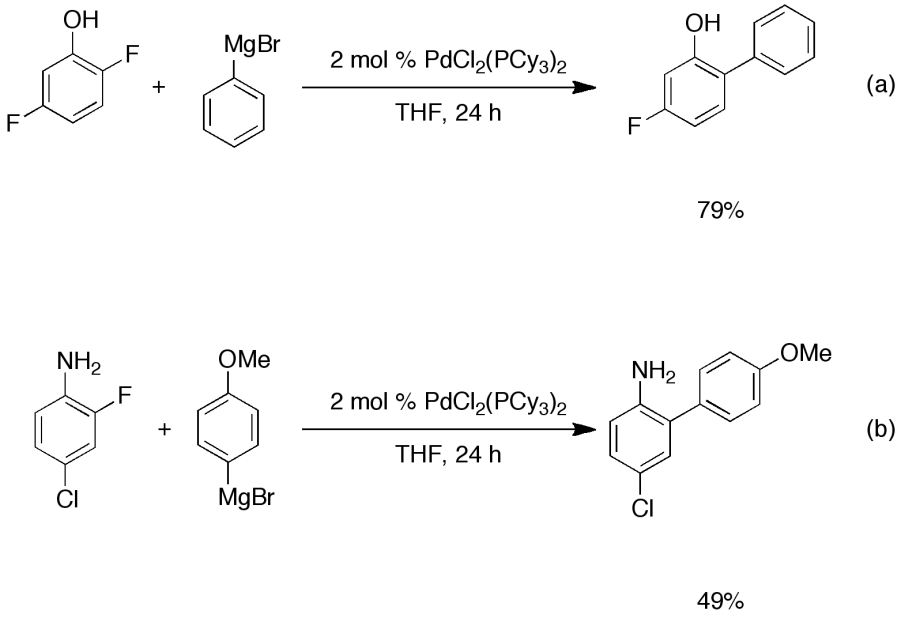
Scheme 1.28 Pd-catalyzed Stille cross-coupling by Braun

Tamao and co-workers reported their Ni- and Pd-catalyzed Kumada cross-coupling reactions of polyfluoroarenes. By changing the catalyst and controlling the catalytic loadings, they were able to synthesize mono-, di-, and tri-substituted benzene derivatives in moderate yields. They found that Ni-catalysis was generally suitable for poly-substitution (Scheme 1.29b), whereas Pd-catalysis was more effective for mono-substitution (Scheme 1.29c).[66]



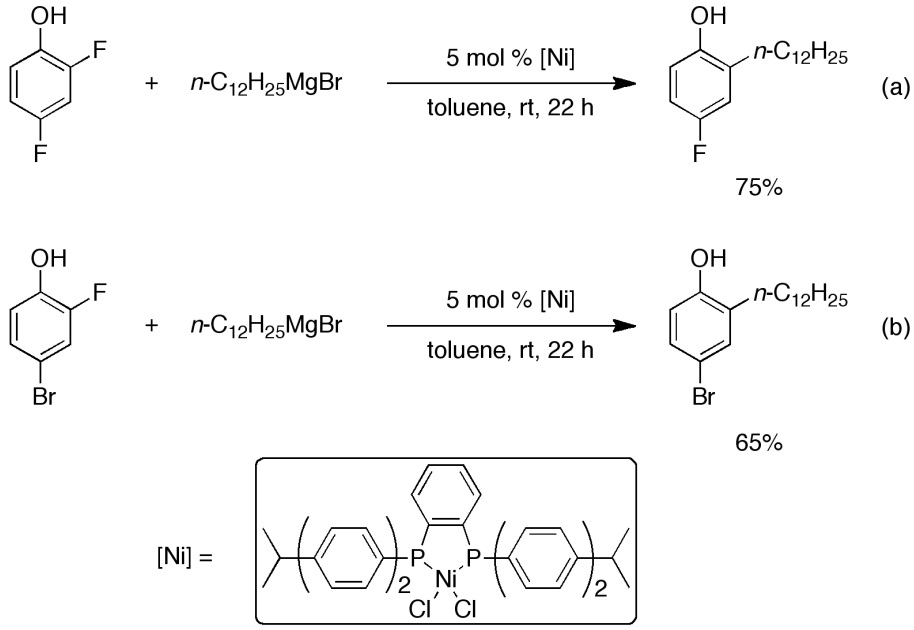
Scheme 1.29 Ni/Pd-catalyzed Kumada cross-coupling by Tamao

Manabe and co-workers published a Pd-catalyzed Kumada cross-coupling of polyfluoroarenes. They utilized commercially available $PdCl_2(PCy_3)_2$ as catalyst and obtained good-to-excellent yields with aryl, heteroaryl, alkenyl and benzyl Grignard reagents. A wide range of directing groups, including hydroxyl, hydroxymethyl, and amino groups could be used (Scheme 1.30).[67] Alkyl Grignard reagents with β-hydrogens were not compatible, as they resulted in a net reduction of the polyfluorinated arenes.



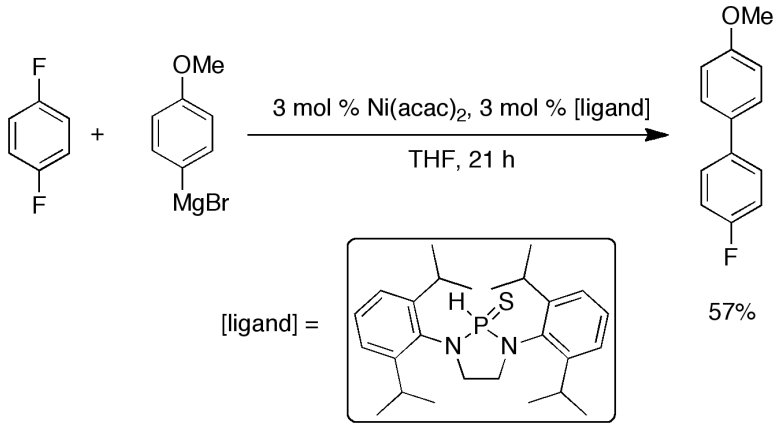
Scheme 1.30 Pd-catalyzed Kumada cross-coupling by Manabe

In order to overcome this limitation, the Manabe group employed a Ni(II) complex instead. A free hydroxyl directing group was crucial for this reaction. Not only were the authors able to selectively replace an ortho C-F bond with an alkyl group in the presence of another C-F bond (Scheme 1.31a), they were also able to activate an ortho C-F bond in the presence of a much weaker para C-Br bond (Scheme 1.31b).[68]



Scheme 1.31 Ni-catalyzed Kumada cross-coupling by Manabe

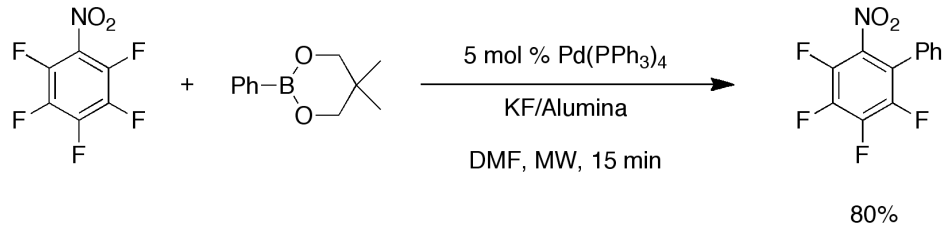
The Ackermann group reported a Ni-catalyzed cross-coupling between aryl/heteroaryl fluorides and Grignard reagents. The authors were able to synthesize fluorinated biaryl products with their diaminophosphine sulfide ligand under mild conditions (Scheme 1.32).[69]



Scheme 1.32 Ni-catalyzed Kumada cross-coupling by Ackermann

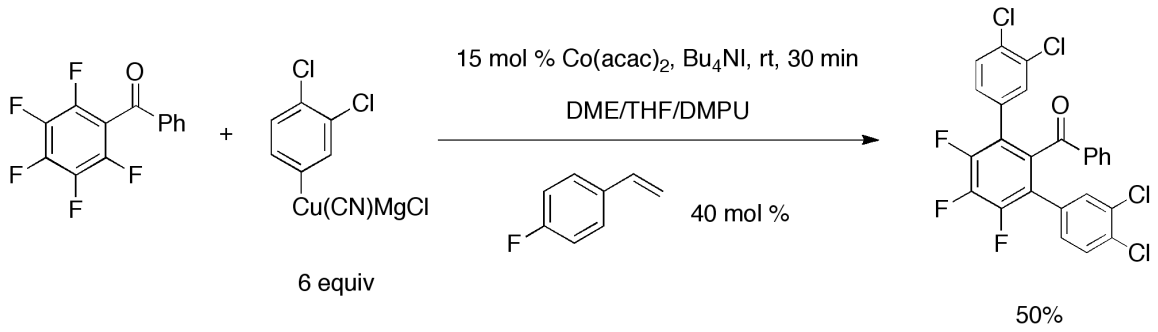
Recently, Sandford and co-workers published a Pd-catalyzed Suzuki-Miyaura

cross-coupling of polyfluoronitrobenzenes. While this protocol required highly electron-deficient substrates such as the one shown in Scheme 1.33, the yields were good. Because these reactions were highly selective towards ortho C-F bonds, the authors suggested that significant interactions between the nitro group and the incoming Pd catalyst might be present.[70]



Scheme 1.33 Ni-catalyzed Suzuki-Miyaura cross-coupling by Sandford

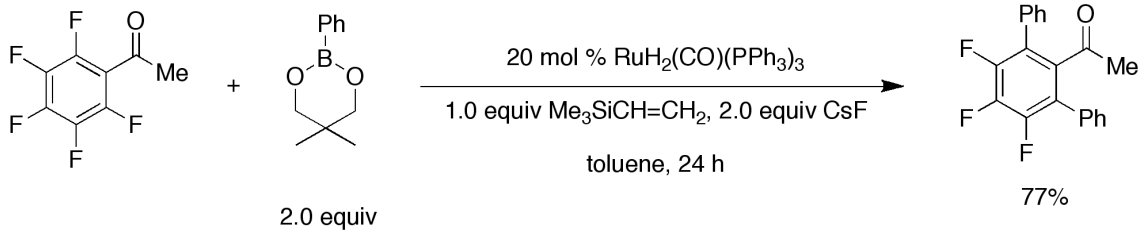
Knochel and co-workers reported that polyfluorinated aryl ketones could be used in cross-coupling reactions catalyzed by a cobalt salt (Scheme 1.34). Arylcopper reagents were used as coupling partners. Using pentafluorobenzophenone as an example, the authors were able to activate both C-F bonds adjacent to the carbonyl group under very mild conditions, and isolate the di-arylated ketone in 50% yield. Interestingly, the C-F bond on 4-fluorostyrene (used as an additive) was not activated, suggesting that a directing group was required in such C-F cross-coupling reactions.[71]



Scheme 1.34 Co-catalyzed cross-coupling by Knochel

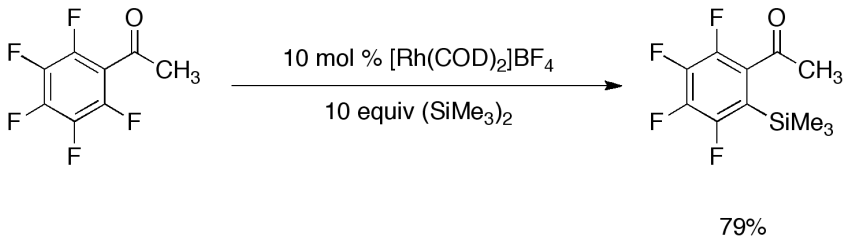
The Kakiuchi group reported a Ru-catalyzed Suzuki-Miyaura cross-coupling of

polyfluorinated aromatic ketones. In the case of pentafluorinated acetophenone, both C-F bonds adjacent to the carbonyl group were activated and the yield was very good (Scheme 1.35).[72]



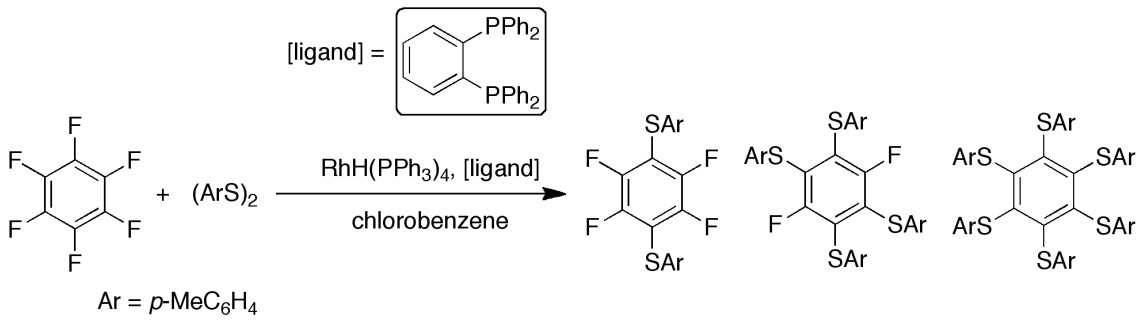
Scheme 1.35 Ru-catalyzed Suzuki-Miyaura cross-coupling by Kakiuchi

Polyfluoroarenes have also been used as substrates to synthesize carbon-heteroatom bonds. Murai and co-workers reported a C-Si exchange reaction catalyzed by a Rh complex. Unlike the last two examples mentioned above, only mono-substitution was observed, leaving the other ortho C-F bond intact (Scheme 1.35).[73]



Scheme 1.36 Rh-catalyzed C-F activation/C-Si formation by Murai

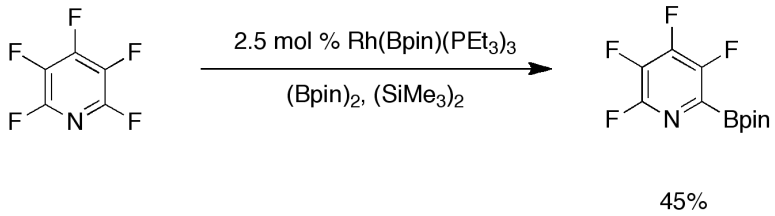
Yamaguchi and co-workers reported a catalytic C-S bond formation from polyfluoroarenes and diaryl disulfides. The polyarylthiolation of hexafluorobenzene took place in the presence of a catalytic amount of $RhH(PPh_3)_4$ and 1,2-bis(diphenylphosphino) benzene (Scheme 1.37). The product distribution was influenced by the ratio between the two starting materials. Rapid second, fourth and sixth thiolations were observed with respect to first, third and fifth reactions. The cause of this phenomenon was not established.[74]



0.5 equiv	95%	5%	0%
2.0 equiv	0%	95%	5%
3.0 equiv	3%	3%	92%

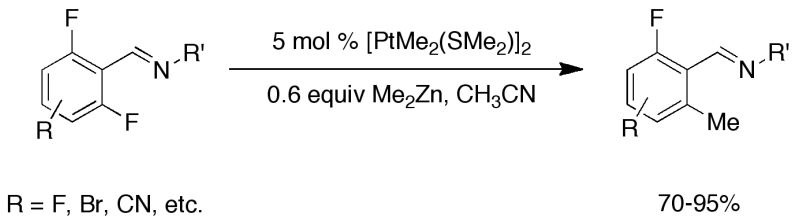
Scheme 1.37 Rh-catalyzed C-F activation/C-S formation by Yamaguchi

Braun and co-workers published a catalytic C-F activation/C-B formation procedure. They were able to selectively activate one of the C-F bonds ortho to the nitrogen atom in pentafluoropyridine using a Rh(I)-Bpin complex to generate a boryl-substituted product, which has the potential to be used in further transformations (Scheme 1.38).[75]



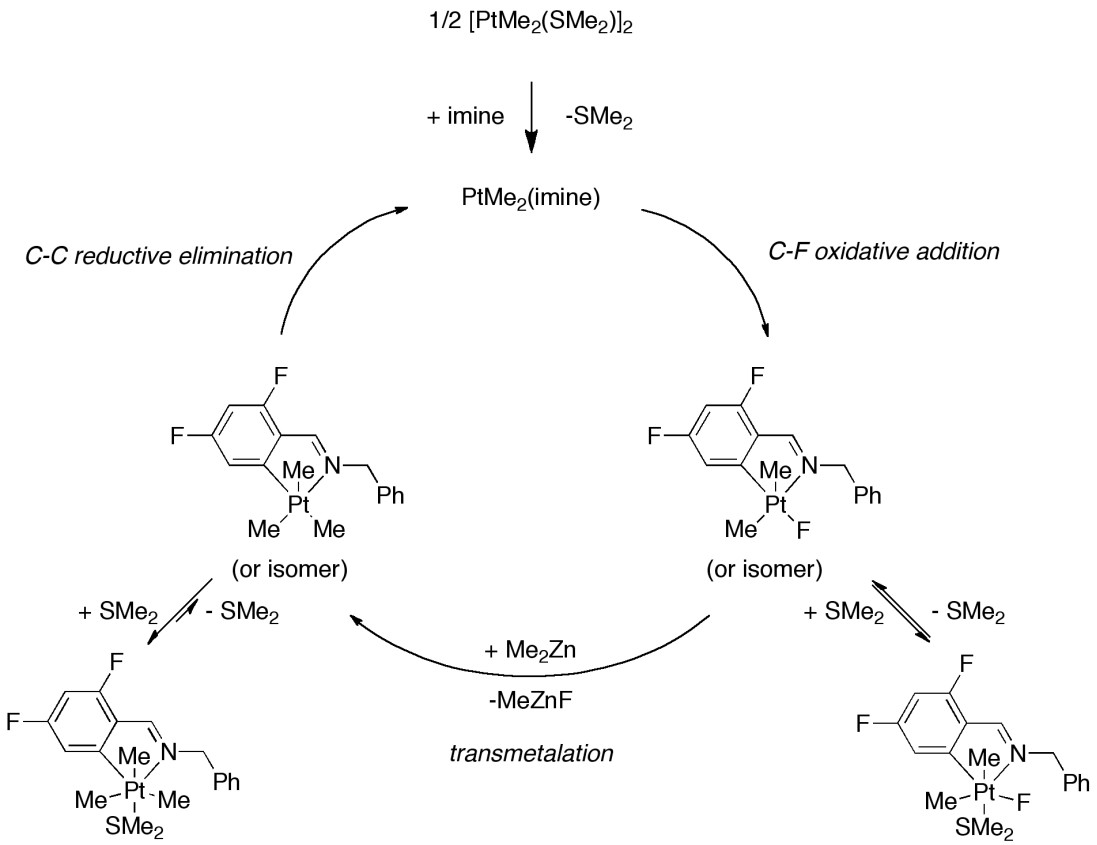
Scheme 1.38 Rh-catalyzed C-F activation/C-B formation by Braun

In 2007, the first example of Pt-catalyzed cross-coupling of polyfluoroaryl imines was reported by the Love group (Scheme 1.39). The main products, mono-methylated fluoroaryl imines, have been produced in high yields under mild conditions. Ortho C-F activation, directed by the imine moiety, took place even in the presence of weaker but remote C-Br, C-Cl and C-CN bonds.[76]



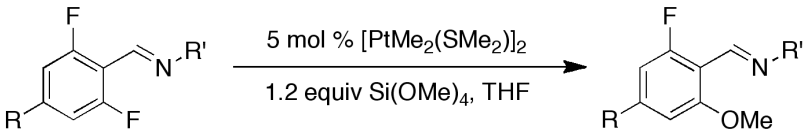
Scheme 1.39 Pt-catalyzed C-F methylation by Love

The mechanism of this Pt-catalyzed methylation of polyfluoroaryl imines has been studied. The catalytic reaction was believed to involve the following steps: C-F oxidative addition to the Pt(II) center; transmetalation by dimethylzinc; and C-C reductive elimination to form the product and regenerate the active catalyst (Scheme 1.40).[77] This catalytic cycle and its implications shall be discussed further in chapter 2.



Scheme 1.40 Proposed mechanism of Pt-catalyzed C-F methylation

This methodology has also been extended to methoxylation of polyfluoroaryl imines, and the corresponding mono-methoxylated products were isolated in high yields (Scheme 1.41). It is noteworthy that the preliminary mechanistic investigation revealed a different reaction mechanism than for methylation.[78]



R = F, Br, CN, etc. 32-95%

Scheme 1.41 Pt-catalyzed C-F methoxylation by Love

1.4.5 Summary

Cross-coupling of fluoroarenes, especially polyfluoroarenes, has been an active research area for the last 40 years. Not only are these important reactions in organometallic chemistry, but they also provide an alternative route towards the synthesis of highly functionalized aryl fluorides. Recent examples indicate that cross-coupling reactions of polyfluoroarenes catalyzed by transition metal complexes are feasible; however, these reactions are still quite limited in terms of substrates and coupling partners, and are not always compatible with many functional groups.

1.5 Our proposal

Given our results in Pt-catalyzed cross-coupling of polyfluoroaryl imines (*vide supra*), we would like to expand our portfolio in the following fashion: 1) The current precatalyst is both air- and moisture-sensitive; it would be preferable to have a more user-friendly catalyst that can be handled without the need for Schlenk techniques. 2) Platinum is a very expensive metal to be used in large scale; we would like to employ other complexes

based on low-cost metals. 3) The current cross-coupling methodology is limited to methylation and methoxylation; expanding the coupling partner scope further is highly desirable. 4) There cannot be a C-H bond at the other ortho position in the Pt-based system; having a catalyst that activates the C-F bond preferentially is very important.

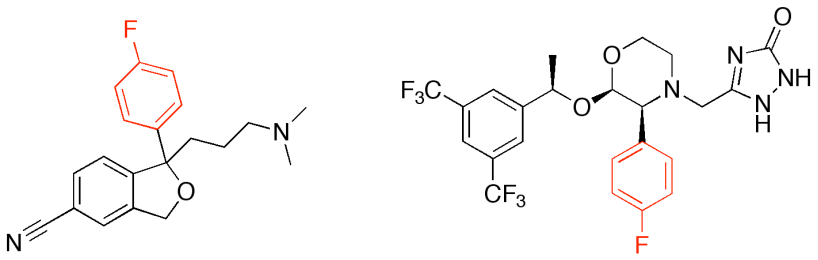
1.6 Content of thesis

The following sections describe our recent research on various methods to generate highly functionalized aryl fluoride molecules. The development of user-friendly precatalysts for Pt-catalyzed cross-coupling of polyfluoroaryl imines is described in chapter 2. In chapter 3, a Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroarenes is presented. A Ni-catalyzed Negishi cross-coupling of polyfluoroarenes is discussed in chapter 4. A new synthetic method of generating functionalized aryl fluorides from arylboronic reagents is introduced in chapter 5. Finally, conclusions and future work are given in Chapter 6. The appendix includes X-ray data of a new compound **3P** reported in chapter 3.

Chapter 2: Pt-Catalyzed Cross-Coupling of Polyfluoroaryl Imines with User-friendly Precatalysts[b]

2.1 Introduction

Due to their physical and chemical properties, in particular the relative inertness of carbon-fluorine bonds, organic fluorinated compounds have been widely used in practical applications.[1-4] These same properties also make the activation of carbon-fluorine bonds an ongoing challenge. Organic and organometallic chemists have devoted considerable attention to the stoichiometric and catalytic activation of C-F bonds, and their successes have been highlighted in a number of recent reviews and book chapters.[40-49] Selective cross-coupling of polyfluorinated arenes has also used as an alternative route towards the synthesis of fluorinated small molecules. Two common pharmaceuticals, Celexa by Lundbeck and Emend by Merck contain highly functionalized aryl fluorides (Figure 2.1).



Celexa

Anti-depressant

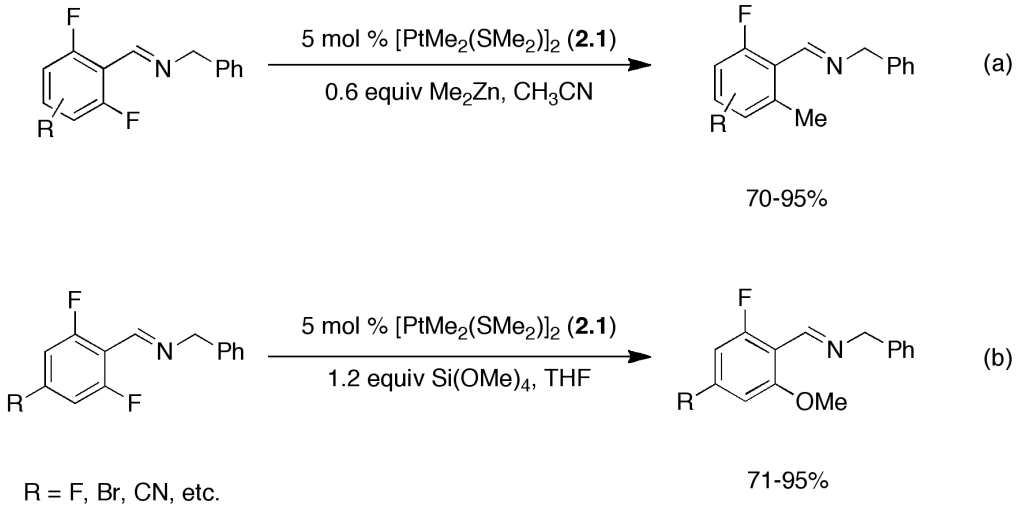
Emend

Anti-emetic

Figure 2.1 Structures of Celexa and Emend

[b] A version of section 2.2 has been published. Buckley, H. L.; Sun, A. D.; Love, J. A. (2009) User-Friendly Precatalyst for the Methylation of Polyfluoroaryl Imines. Organometallics. 28:6622-6624. A version of section 2.3 has been published. Sun, A. D.; Love, J. A. (2010) $Pt(II)Cl_2(DMSO)_2$-Catalyzed Cross-Coupling of Polyfluoroaryl Imines. J. Fluorine Chem. 131: 1237-1240.

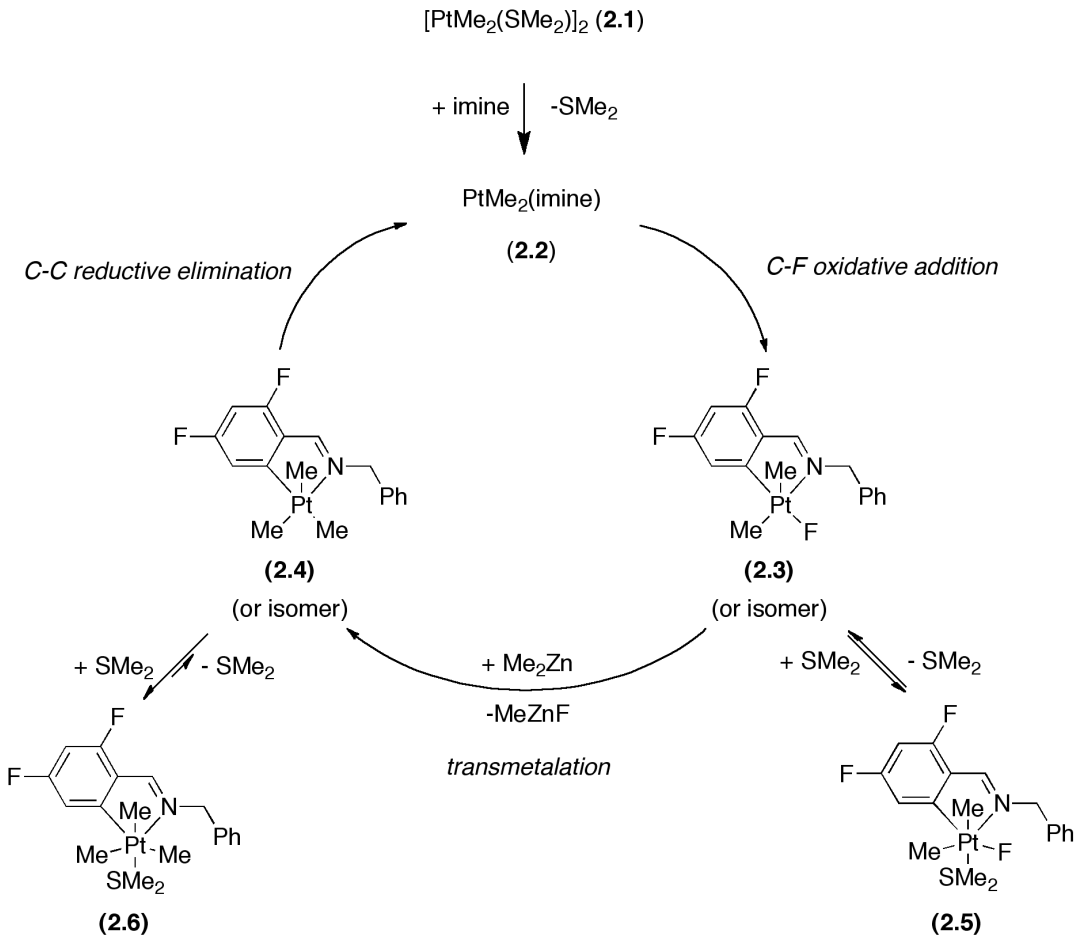
Our group has recently demonstrated that under mild conditions, $[PtMe_2(SMe_2)]_2$ (**2.1**) is a highly efficient precatalyst for the methylation (Scheme 2.1a) and methoxylation (Scheme 2.1b) of a variety of polyfluoroaryl imines.[76,78] A large number of fluorine-containing products have been successfully isolated and characterized, and the precatalyst shows excellent functional group tolerance and selectivity for the ortho C-F bond in the presence of other C-F bond(s) and/or potentially reactive C-Cl, C-Br and C-CN bonds on the same molecule.



Scheme 2.1 Pt-catalyzed methylation and methoxylation of polyfluoroaryl imines

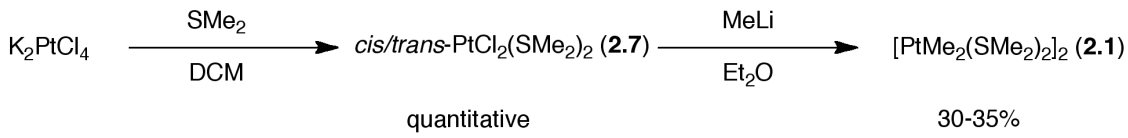
In a subsequent paper, the mechanism of Pt-catalyzed methylation was proposed to be consistent with the following steps: 1) oxidative addition of the ortho C-F bond from an imine-bonded, electron-rich Pt(II) complex (**2.2**) to form a Pt(IV)-F species (**2.3**); 2) transmetalation with dimethylzinc to generate a Pt(IV)-Me (**2.4**) species; and 3) reductive elimination to generate the aryl-methyl coupled product and release an active species that will enter the next catalytic cycle (Scheme 2.2). In addition to the 5-coordinate species **2.3** and **2.4**, we believed that there were two dimethyl sulfide-bonded, 6-coordinate species (**2.5** and **2.6**) in equilibrium with **2.3** and **2.4**, respectively. The 6-coordinate

species were not part of the catalytic cycle, but could enter the cycle upon the loss of SMe_2.[77]



Scheme 2.2 Proposed mechanism of Pt-catalyzed methylation of polyfluoroaryl imines

Complex **2.1** was synthesized in two steps from commercially available K_2PtCl_4, based on a modified literature procedure (Scheme 2.3).[79] Complex **2.1** turned out to be quite sensitive to heat, moisture and air, which made it hard to store for extended periods of time. For practical purposes, it thereby proves a rather poor precatalyst to be employed widely. Consequently, we initiated a search for more user-friendly precatalyst(s) with greater thermal, moisture and air stability.



Scheme 2.3 Synthesis of $[PtMe_2(SMe_2)]_2$

The results of methylation of polyfluoroaryl imines catalyzed by $PtCl_2(SMe_2)_2$ will be presented in section 2.2. Methylation of polyfluoroaryl imines catalyzed by $PtCl_2(DMSO)_2$ will be illustrated in Section 2.3. Finally, we provide a conclusion in section 2.4.

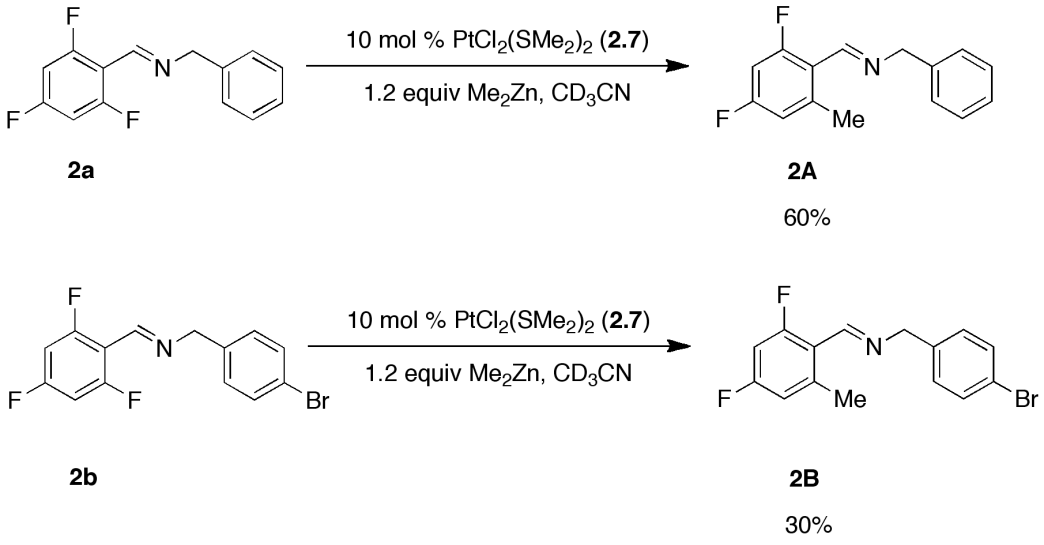
2.2 Methylation of polyfluoroaryl imines catalyzed by $PtCl_2(SMe_2)_2$

2.2.1 Proposal

This part of the chemistry was conducted collaboratively with Heather Buckley, an M.Sc student from our group. Our research objective was to find robust, alternative precatalyst(s) with the ability to generate an active catalyst *in situ*. Heather decided to test *cis/trans*-$PtCl_2(SMe_2)_2$ (**2.7**) in C-F methylation for the following reasons. First, *cis/trans*-$PtCl_2(SMe_2)_2$ (**2.7**) is synthesized from K_2PtCl_4 and dimethyl sulfide as a yellow solid in near quantitative yields.[79] Further, it is stable under ambient conditions and does not react with water or oxygen. Finally, it has been used previously as an intermediate to generate $[PtMe_2(SMe_2)]_2$ (**2.1**) upon reaction with methyl lithium. Consequently, it was hypothesized that this complex would be able to replace its chloride ligands with methyl groups from dimethylzinc under the catalytic conditions. We proposed that the resulting species would be similar to **2.1**, and would be able to catalyze C-F cross-coupling of polyfluoroaryl imines.

2.2.2 Results and discussion

Heather subjected $PtCl_2(SMe_2)_2$ (**2.7**) to the reaction conditions previously reported for $[PtMe_2(SMe_2)]_2$ (**2.1**). She was able to obtain the methylated product from 2,4,6-trifluoroimine **2a** in 60% yield. Several other substrates were also tested and the yields were generally lower than those obtained from using $[PtMe_2(SMe_2)]_2$ (**2.1**) as the precatalyst. In addition, there was no background reaction in the absence of $PtCl_2(SMe_2)_2$ (**2.7**) (Scheme 2.4).[80]



Scheme 2.4 Methylation of polyfluoroaryl imines catalyzed by $PtCl_2(SMe_2)_2$

My task was to optimize the reaction conditions to see if the yields can be improved. To do so, different reaction conditions were explored. In a representative reaction, the stock solutions of 2,4,6-trifluoroimine **2a** (0.034 mmol, 1.0 equiv); $PtCl_2(SMe_2)_2$ (**2.7**) (0.0034 mmol, 10 mol %); and 1,3,5-trimethoxybenzene (0.034 mmol, 1.0 equiv, internal standard) were mixed in a CD_3CN solution (1 mL) of dimethylzinc (0.041 mmol, 1.2 equiv). The reaction mixture was transferred to a screw-cap NMR tube, then taken out of the glovebox and heated at 60°C for 24 hours. Reaction progress was monitored by ^1H

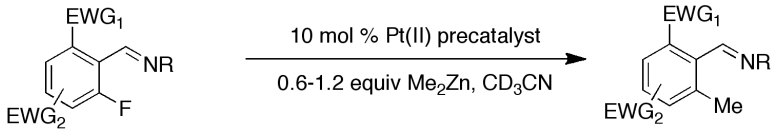
and $^{19}F\{^{1}H\}$ NMR spectroscopy. I discovered that if $PtCl_2(SMe_2)_2$ (**2.7**) was permitted to react with dimethylzinc for 6 hours at room temperature prior to heating, either with or without the addition of imine, a significant increase in yields was observed. A yield of 95% was reached in the cases of 2,4,6-trifluorimine **2a**, a result comparable to one obtained using $[PtMe_2(SMe_2)]_2$ (**2.1**).

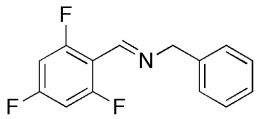
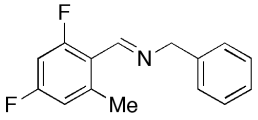
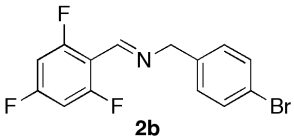
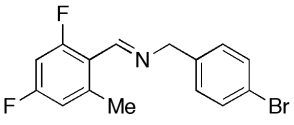
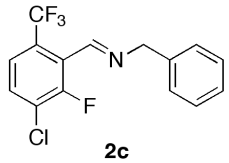
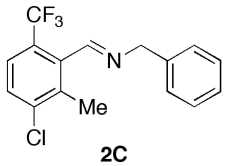
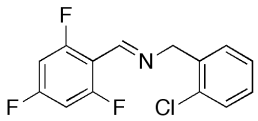
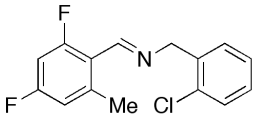
Several scenarios were tested to determine the optimal conditions of the pretreatment. The first, using 2,4,6-trifluoroimine **2a** as substrate, and then mixing $PtCl_2(SMe_2)_2$ (**2.7**) and dimethylzinc at 4°C (inside a refrigerator) for 6 hours, did not produce any observable changes in the NMR spectra or benefit in the subsequent C-F cross-coupling. The second, which left $PtCl_2(SMe_2)_2$ (**2.7**) and dimethylzinc (1.2 equiv or 2.4 equiv) without imine at 60°C for an extended period of time, generated unidentified decomposition products that retarded subsequent C-F cross-coupling. Ultimately, it was determined that treating $PtCl_2(SMe_2)_2$ (**2.7**) with dimethylzinc for 6 hours at room temperature provided the highest yield. In addition, it was revealed early on that, unlike $[PtMe_2(SMe_2)]_2$ (**2.1**), 0.6 equiv of dimethylzinc was not sufficient for $PtCl_2(SMe_2)_2$-catalyzed methylation; a synthetically useful yield was only achieved with 1.2 equiv of dimethylzinc. This increased need for dimethylzinc was attributed to the exchange between chloride and methyl groups on the precatalyst prior to entering the catalytic cycle.

Subsequently, the substrate scope of the methylation of polyfluoroaryl imines catalyzed by $PtCl_2(SMe_2)_2$ was studied. Reactions of polyfluoroaryl imines were carried out under both standard conditions by Heather and modified conditions with pretreatment by me. As shown in Table 2.1, in general, the yields were significantly lower than using $PtCl_2(SMe_2)_2$ (**2.7**) as the precatalyst. Reactions typically stopped once certain yields were reached, even though there were starting materials left. On the other hand, results comparable to those obtained using $[PtMe_2(SMe_2)]_2$ (**2.1**) were obtained using the modified procedure. In all cases, $PtCl_2(SMe_2)_2$ (**2.7**) demonstrated identical functional

group tolerance and selectivity for the ortho C-F bonds. Potentially reactive bonds C-Br (entry 2) and C-Cl (entry 3 and 4) remained intact under catalytic conditions. In addition, spectroscopic data for all compounds were consistent with the characterization data obtained independently using $[PtMe_2(SMe_2)]_2$ (**2.1**) in our earlier work.[76]

Table 2.1 Comparison of $[PtMe_2(SMe_2)]_2$ (**2.1**) and $PtCl_2(SMe_2)_2$ (**2.7**) in Pt-catalyzed methylation



entry	substrate	product	(**2.1**)[a,b]	(**2.7**)[a,c]
1	 **2a**	 **2A**	95%	60%(95%)[d]
2	 **2b**	 **2B**	86%	30%(95%)[d]
3	 **2c**	 **2C**	95%	60%(95%)[d]
4	 **2d**	 **2D**	85%	30%(85%)[d]

[a] Yields based on ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Taken from reference 76; conditions: 0.6 equiv Me_2Zn, 8 h. [c] Taken from Heather Buckley's thesis (reference 80) except numbers in parentheses, which were determined by Duo Sun; conditions: 1.2 equiv Me_2Zn, 24 h. [d] Pre-treated with Me_2Zn for 6 h at room temperature.

To generate insight into the mechanism of $PtCl_2(SMe_2)_2$-catalyzed methylation, we chose to study the stoichiometric C-F activation first, in order to probe the nature of the active species formed *in situ* under catalytic conditions. As Crespo and Martinez had found,[81] and we had later confirmed,[77] $[PtMe_2(SMe_2)]_2$ (**2.1**) could readily activate the C-F bond in polyfluoroaryl imines, which is the first step in the catalytic cycle. At the

same time, $PtCl_2(SMe_2)_2$ (**2.7**) did not undergo any C-F activation, either at room temperature or at 60°C. In addition, the imine starting material could be recovered after 24 hours. Catalytic cross-coupling took place only after dimethylzinc was added to the reaction mixture. While no Pt-F containing species were observed in the $^{19}F\{^1H\}$ NMR spectrum, characteristic chemical shifts (0.5-1 ppm) with J_{Pt-H} coupling constant (70-80 Hz) were observed in ^1H NMR spectrum, which were consistent with the formation of $Pt-CH_3$ species, supporting our hypothesis that a catalytically active $Pt-CH_3$ species was generated *in situ*.

Heather and I independently demonstrated that methoxylation of 2,4,6-trifluoroimine **2a** with tetramethoxysilane catalyzed by $PtCl_2(SMe_2)_2$ (**2.7**) was unsuccessful; no methoxylated product was detected and the imine starting material **2a** was recovered. This observation confirmed our early speculation that Pt-catalyzed methoxylation operated with a different mechanism than the one outlined in Scheme 2.2.[77]

In summary, $PtCl_2(SMe_2)_2$ (**2.7**) is a practical methylation precatalyst in C-F cross-coupling of polyfluoroaryl imines. Pretreatment of it with dimethylzinc for 6 hours generates an active species *in situ* that is as effective as $[PtMe_2(SMe_2)]_2$ (**2.1**).

2.3 Methylation of polyfluoroaryl imines catalyzed by $PtCl_2(DMSO)_2$

2.3.1 Proposal

Recognizing the shortcomings of our previous precatalysts, namely the low stability of $[PtMe_2(SMe_2)]_2$ (**2.1**) and the low reactivity of $PtCl_2(SMe_2)_2$ (**2.7**), we speculated that there were two possible ways to increase the reactivity of Pt-catalyzed methylation. The first was to replace the chloride ligands on $PtCl_2(SMe_2)_2$ (**2.7**) with other groups. This idea was abandoned because we were concerned that any ligand exchange would require additional synthetic steps, running counter to the idea of a user-friendly precatalyst. The

second option involved replacing the SMe_2 ligand on $PtCl_2(SMe_2)_2$ (**2.7**) with dimethyl sulfoxide. Such a complex would prove superior to $PtCl_2(SMe_2)_2$ (**2.7**) for two reasons. First, in order for $[PtMe_2(SMe_2)]_2$ (**2.1**) or $PtCl_2(SMe_2)_2$ (**2.7**) to enter the catalytic cycle, they must lose their SMe_2 ligands to generate an imine-bonded species along the lines of **2.2**. Dimethyl sulfoxide, being less coordinating, would facilitate this dissociation step.[82] Secondly, 5-coordinate complexes (**2.3** and **2.4**) are the species involved in the catalytic cycle, whereas 6-coordinate species (**2.5** and **2.6**) are off-cycle species. Because **2.6** is believed to be the resting state of this catalytic cycle, any effort to suppress the formation of **2.6** would be beneficial. A less-coordinating ligand such as DMSO would shift the equilibrium away from **2.5** and **2.6** and facilitate the reaction by keeping more Pt species within the catalytic cycle.

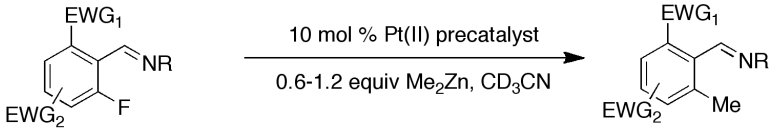
2.3.2 Results and discussion

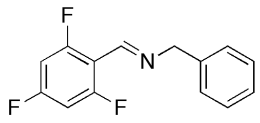
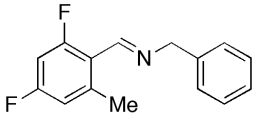
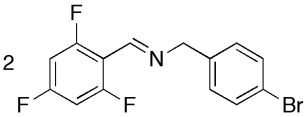
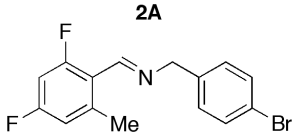
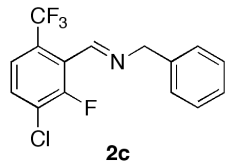
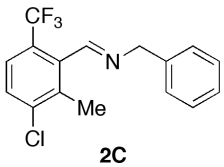
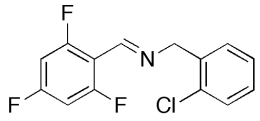
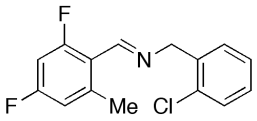
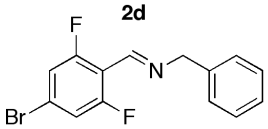
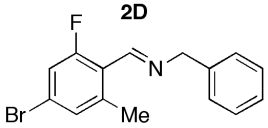
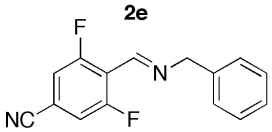
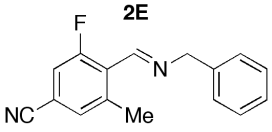
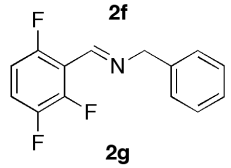
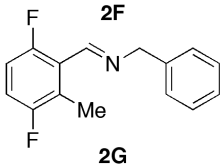
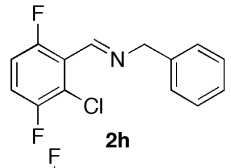
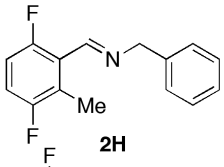
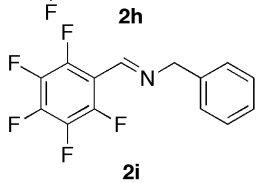
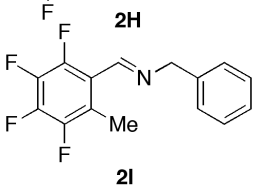
Cis-$PtCl_2(DMSO)_2$ (**2.8**) is synthesized from K_2PtCl_4 and dimethyl sulfoxide as an off-yellow microcrystalline solid.[82] It proves stable over extended periods of time and does not react with water or oxygen. Applying the same catalytic conditions developed for $PtCl_2(SMe_2)_2$ (**2.7**), the stock solutions of 2,4,6-trifluoroimine **2a** (0.034 mmol, 1.0 equiv); $PtCl_2(DMSO)_2$ (**2.8**) (0.0034 mmol, 10 mol %) and 1,3,5-trimethoxybenzene (0.034 mmol, 1.0 equiv, internal standard) were added to a CD_3CN solution (1 mL) of dimethylzinc (0.041 mmol, 1.2 equiv) in a nitrogen-filled glovebox. The reaction mixture was then transferred to a screw-cap NMR tube, taken out of the glovebox, and heated at 60°C for 24 hours. The reaction progress was monitored by ^1H and $^{19}F\{^1H\}$ NMR spectroscopy. The reaction proceeded smoothly to 95% yield in 12 hours. Under their respective optimal conditions, reactions catalyzed by $[PtMe_2(SMe_2)]_2$ (**2.1**) resulted in the same yield in approximately 8 hours, whereas reactions catalyzed by $PtCl_2(SMe_2)_2$ (**2.7**) produced only 60% of the methylated product, even after 24 hours. We have also found

that increased yields could be achieved for $PtCl_2(SMe_2)_2$ (**2.7**) if it was allowed to be pre-treated with dimethylzinc for 6 hours. In summary, $PtCl_2(DMSO)_2$ (**2.8**) demonstrated the same reactivity without the need of pretreatment. Importantly, there is no background reaction in the absence of the precatalyst.

The reactivity of $PtCl_2(DMSO)_2$ (**2.8**) in methylation of polyfluoroaryl imines was examined and compared to that of $[PtMe_2(SMe_2)]_2$ (**2.1**) and $PtCl_2(SMe_2)_2$ (**2.7**). Table 2.2 shows a direct comparison of these three complexes. Spectroscopic data for all compounds obtained from reactions catalyzed by $PtCl_2(DMSO)_2$ (**2.8**) were consistent with the characterization data obtained in our earlier studies.[76] $PtCl_2(DMSO)_2$ (**2.8**) demonstrated the same level of selectivity for the ortho C-F bonds, as well as functional group tolerance. Reactions catalyzed by $PtCl_2(DMSO)_2$ (**2.8**) resulted in yields comparable to those of $[PtMe_2(SMe_2)]_2$ (**2.1**), and significantly higher than those of $PtCl_2(SMe_2)_2$ (**2.7**). In summary, $PtCl_2(DMSO)_2$ (**2.8**) proved to be a highly efficient alternative to both $[PtMe_2(SMe_2)]_2$ (**2.1**) and $PtCl_2(SMe_2)_2$ (**2.7**).

Table 2.2 Comparison of $[PtMe_2(SMe_2)]_2$ (**2.1**), $PtCl_2(SMe_2)_2$ (**2.7**) and $PtCl_2(DMSO)_2$ (**2.8**) in Pt-catalyzed methylation



entry	substrate	product	(**2.1**)[a,b]	(**2.7**)[a,c]	(**2.8**)[a,e]
1	 **2a**	 **2A**	95%	60%(95%)[d]	95%
2	 **2b**	 **2B**	86%	30%(95%)[d]	85%
3	 **2c**	 **2C**	95%	60%(95%)[d]	95%
4	 **2d**	 **2D**	85%	30%(85%)[d]	85%
5	 **2e**	 **2E**	85%	63%	85%
6	 **2f**	 **2F**	94%	95%	95%
7	 **2g**	 **2G**	92%	50%	90%
8	 **2h**	 **2H**	99%	30%	95%
9	 **2i**	 **2I**	74%	20%	70%

[a] Yields based on ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Taken from reference 76; conditions: 0.6 equiv Me_2Zn, 8 h. [c] Taken from Heather Buckley's thesis

(reference 80) except numbers in parentheses, which were determined by Duo Sun; conditions: 1.2 equiv Me_2Zn, 24 h. [d] Pre-treated with Me_2Zn for 6 h at room temperature. [e] Conditions: 1.2 equiv Me_2Zn, 24 h.

We next investigated the nature of the catalytically active species in methylation of polyfluoroaryl imines catalyzed by $PtCl_2(DMSO)_2$. Heating stoichiometric amounts of $PtCl_2(DMSO)_2$ (**2.8**) and imine **2a** failed to achieve any C-F activation under the reaction conditions (24 hours at 60°C). This observation is consistent with the finding that $PtCl_2(SMe_2)_2$ (**2.7**) is also unable to activate C-F bonds, and reaffirms the hypothesis that only electron-rich late transition metal complexes are capable of promoting oxidative addition of aryl C-F bonds.

We observed peaks in the ^1H NMR spectrum associated with Pt-CH_3 species in the stoichiometric reaction between dimethylzinc and $PtCl_2(DMSO)_2$ (**2.8**) at room temperature. The same observation was made in the methylation of polyfluoroaryl imines catalyzed by $PtCl_2(DMSO)_2$. Hence, the overall picture suggests that the active catalyst is generated from $PtCl_2(SMe_2)_2$ (**2.7**) or $PtCl_2(DMSO)_2$ (**2.8**) *in situ* upon reaction with dimethylzinc, and that the mechanism proposed in Scheme 2.2 is operative for complexes $[PtMe_2(SMe_2)]_2$ (**2.1**), $PtCl_2(SMe_2)_2$ (**2.7**) and $PtCl_2(DMSO)_2$ (**2.8**).

Methoxylation of 2,4,6-trifluoroimine **2a** with tetramethoxysilane catalyzed by $PtCl_2(DMSO)_2$ (**2.8**) was also unsuccessful; no methoxylated product was detected and starting material **2a** was recovered.

2.4 Conclusions

In this chapter, we have presented two user-friendly precatalysts for Pt-catalyzed methylation of polyfluoroaryl imines. Unlike $[PtMe_2(SMe_2)]_2$ (**2.1**), both precatalysts are stable under ambient conditions. $PtCl_2(DMSO)_2$ (**2.8**) shows comparable reactivity to $[PtMe_2(SMe_2)]_2$ (**2.1**), whereas $PtCl_2(SMe_2)_2$ (**2.7**) shows lower reactivity unless

pre-treated with dimethylzinc. Both these precatalysts have the same high selectivity for ortho C-F activation, and both enjoy the same level of functional group tolerance. Finally, we have proposed that the active catalyst is generated *in situ* from $PtCl_2(SMe_2)_2$ (**2.7**) and $PtCl_2(DMSO)_2$ (**2.8**).

2.5 Experimental

General Procedures. Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled glovebox (O_2 < 2 ppm). NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 spectrometers. ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts are reported in parts per million and referenced to residual solvent. $^{19}F\{^{1}H\}$ NMR spectra are reported in parts per million and referenced to $CFCl_3$ (0 ppm). Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets. All spectra were obtained at 25°C.

Materials and Methods. Acetonitrile-d_3 and all organic reagents were obtained from commercial sources and used as received. K_2PtCl_4 was purchased from Strem Chemicals and was used without further purification. All imines were prepared according to a published procedure.[76] *cis/trans*-$PtCl_2(SMe_2)_2$ (**2.7**) and *cis*-$PtCl_2(DMSO)_2$ (**2.8**) were prepared according to published procedures.[79,82] Dimethyl zinc (2.0 M solution in toluene) was purchased from Aldrich and used without further purification.

Experimental procedure for Pt(II)-catalyzed methylation of polyfluoroaryl imines

In a 20 mL vial in the glovebox, 0.1 mL of imine solution (0.34 mmol in 1.0 mL of CD_3CN, 1.0 equiv), 0.1 mL of $PtCl_2(SMe_2)_2$ (**2.7**) or $PtCl_2(DMSO)_2$ (**2.8**) solution (0.0034 mmol in 1.0 mL of CD_3CN, 10 mol %), dimethylzinc (0.02 mL of 2.0 M in toluene, 0.040 mmol, 1.2 equiv) and 0.1 mL of 1,3,5-trimethoxybenzene solution (0.34 mmol in 1.0 mL of CD_3CN, 1.0 equiv, internal standard) were added in CD_3CN (1 mL) in a nitrogen-filled glovebox. The reaction mixture was transferred to a screw-cap NMR tube, taken out of the glovebox and heated at 60°C for 24 hours. Reactions were

monitored by ^{1}H and $^{19}F\{^{1}H\}$ NMR spectroscopy. The yield of the reaction was based on integration of the methyl resonance of the product with the aryl resonance of the internal standard (1,3,5-trimethoxybenzene) in the ^{1}H NMR spectrum. Analytic data for **2A**-**2I** matches previously reported data.

Note: There is no background reaction in the absence of the catalyst.

Experimental procedure for Pt(II)-catalyzed methylation of polyfluoroaryl imines (pretreatment of $PtCl_2(SMe_2)_2$ (2.7) with dimethylzinc)

In a 20 mL vial in the glovebox, 0.1 mL of imine solution (0.34 mmol in 1.0 mL of CD_3CN, 1.0 equiv), 0.1 mL of $PtCl_2(SMe_2)_2$ (**2.7**) solution (0.0034 mmol in 1.0 mL of CD_3CN, 10 mol %), dimethylzinc (0.02 mL of 2.0 M in toluene, 0.040 mmol, 1.2 equiv) and 0.1 mL of 1,3,5-trimethoxybenzene solution (0.34 mmol in 1.0 mL of CD_3CN, 1.0 equiv, internal standard) were added to CD_3CN (1 mL) in a nitrogen-filled glovebox. The reaction mixture was transferred to a screw-cap NMR tube and taken out of the glovebox. The contents were allowed to react at room temperature for 6 hours. The tube was then heated at 60°C for 24 hours. Reactions were monitored by ^{1}H and $^{19}F\{^{1}H\}$ NMR spectroscopy. The yield of the reaction was based on integration of the methyl resonance of the product with the aryl resonance of the internal standard (1,3,5-trimethoxybenzene) in the ^{1}H NMR spectrum. This procedure was used for **2A**, **2B**, **2C** and **2D** in Table 2.1.

Note: The imine could be added after $PtCl_2(SMe_2)_2$ (**2.7**) had been pretreated with dimethyl zinc at room temperature for 6 hours. Whether imine was added at the same time as other regents or added later had no impact on the reactivity.

Chapter 3: Ni-Catalyzed Suzuki-Miyaura Carbon-Fluorine Cross-Coupling[c]

3.1 Introduction

Our group has reported Pt-catalyzed cross-coupling reactions of polyfluoroaryl imines. Methylation with zinc reagents and methoxylation with silicon reagents produced fluorinated aromatic compounds in high yields under mild conditions.[76,78] Potentially reactive functional groups were well-tolerated, and the reactions showed high selectivity for the fluorine adjacent to the imine directing group. There were, however, a number of limitations that would severely hinder any potential large-scale synthetic application.[83] 1) An ortho C-H bond resulted in competitive C-H activation, which was favored under catalytic conditions. 2) C-F oxidative addition, which was the first and rate-determining step, required at least three electron-withdrawing groups (EWGs) in addition to the imine to proceed. 3) The coupling partners were principally limited to methyl and methoxyl groups (Figure 3.1). Diethylzinc and diphenylzinc did not produce any ethyl- or phenyl-substituted compounds and only resulted in catalyst degradation. In light of these limitations, we concluded that a new catalytic system was required to develop a viable strategy of functionalized fluoroarene generation via selective cross-coupling of polyfluoroarenes.

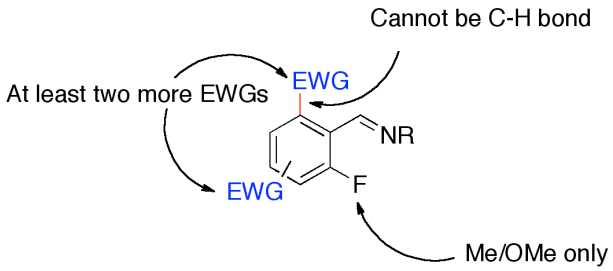
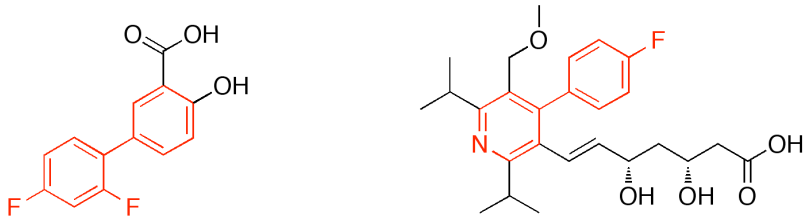


Figure 3.1 Limitations of Pt-catalyzed C-F activation

[c] A version of this chapter has been published. Sun, A. D.; Love, J. A. (2011) Nickel-Catalyzed Selective Defluorination to Generate Partially Fluorinated Biaryls. Org. Lett. 13:2750-2753.

We were interested in developing methods to generate biaryl and heteroaryl-aryl fluorinated molecules via C_{sp2}-C_{sp2} cross-coupling reactions. These molecules can be highly valuable synthetic targets. The two drugs shown below in Figure 3.2, Diflunisal by Merck and Cerivastation by Bayer, contain such structures.



Diflunisal

Anti-inflammatory

Cerivastation

Lowers cholesterol

Figure 3.2 Structures of Diflunisal and Cerivastation

A review of the literature supplies many interesting examples of Ni-mediated C-F activation.[84] Numerous nickel-fluorine complexes have been generated under mild conditions. At the same time, most Ni-catalyzed cross-coupling of fluoroarenes do not exhibit broad substrate scope, and the Grignard reagents they employ as coupling partners have limited functional group compatibility.

In 3.2, the section that follows, we present a Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroaryl imines. A Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroarenes with different directing groups is demonstrated in section 3.3, followed by a preliminary mechanistic investigation in section 3.4.

3.2 Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroaryl imines

We decided to start our investigation of Ni-catalyzed cross-coupling reaction of polyfluoroarenes with polyfluoroaryl imines for several reasons. They are readily synthesized from commercially available polyfluorinated aldehydes, and are easily

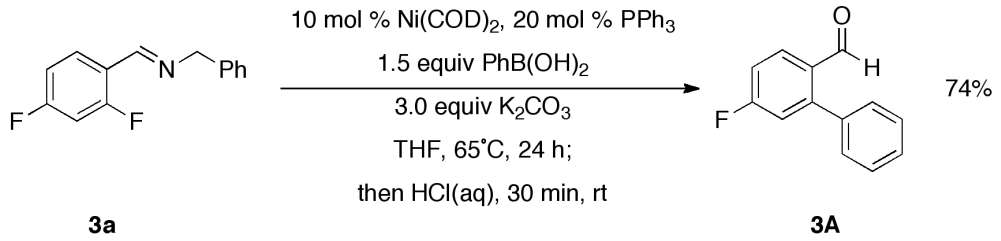
purified and handled, either on the benchtop or in the glovebox. Further, the imine moiety can be converted easily into other functional groups if desired.

3.2.1 Initial results with organoboron reagents

Our first goal was to find an appropriate transmetalation reagent to generate aryl-aryl bonds under mild conditions. There are a number of phenyl-containing reagents readily available. In the presence of catalytic amounts of various nickel salts, phenylmagnesium bromide, diphenylzinc and phenylboronic acid all reacted with 2,4,6-trifluoroimine to replace the ortho C-F bond with a phenyl group. Although phenylmagnesium bromide has been applied extensively in transition metal-mediated/catalyzed C-F activation, it does not tolerate many functional groups due to its high reactivity. On the other hand, while generally less reactive, organozinc and organoboron reagents offer superior functional group tolerance. While both types of reagents have found widespread application in cross-coupling reactions in general, we initially opted to employ organoboron reagents over organozinc reagents because 1) highly-functionalized boronic acids and derivatives are abundantly available from commercial sources and 2) they are not particularly sensitive towards light, water or temperature fluctuation and can be stored for extended periods of time. (The chemistry of organozinc reagents in Ni-catalyzed C-F activation shall be discussed further in chapter 4.)

Our study started with the Ni-catalyzed cross-coupling of 2,4-difluoroimine **3a**. The substrate was selected for reaction optimization because it was unsuccessful in Pt-catalyzed methylation and methoxylation reactions.[76,78,83] The ortho C-H bond was activated instead of the ortho C-F bond. This substrate underwent cross-coupling smoothly, with phenylboronic acid in THF, in the presence of 10 mol% $Ni(COD)_2$, 20 mol% PPh_3 and 3.0 equiv of K_2CO_3. Activation of the ortho C-F bond occurred selectively to generate the phenyl-substituted product. We have also discovered that the

corresponding aldehyde was much easier to isolate and store than the parent imine, which tends to undergo spontaneous hydrolysis over time. The corresponding aldehyde was successfully isolated in 74% yield after hydrolysis and column chromatography. All of the limitations of the previous Pt-based system were overcome: 1) there was no evidence of imine-assisted C-H activation, as the ortho C-F activation occurred preferentially over C-H activation; 2) an aryl group could be installed; and 3) a relatively unactivated polyfluoroarene under catalytic conditions proved sufficiently active to yield the corresponding biaryl product (Scheme 3.1).

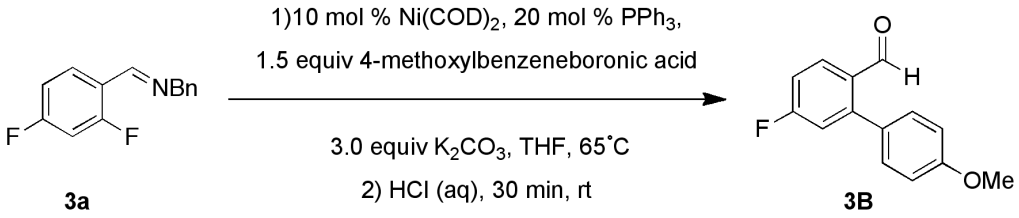


Scheme 3.1 Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroaryl imines

We next examined the various reaction parameters to achieve optimal yield. In order to better separate the biaryl product from unreacted starting material using column chromatography, we used 4-methoxybenzeneboronic acid instead of phenylboronic acid. The results are summarized in Table 3.1 and there are a few notable observations. First, only Ni(0) sources were able to catalyze the C-F activation so far. While the literature cites instances of Ni(0) generation from Ni(II) salts in the presence of boronic acids *in situ*,[85] we did not observe this and two Ni(II) complexes tested failed to produce any observable C-F activation product (entry 3). As well, phosphine ligands proved important in the catalysis, as no reaction took place without them (entry 4). We also noted that aryl phosphines, alkyl phosphines or bidentate phosphines showed similar reactivity (entries 1, 5 and 6). We selected PPh_3 for subsequent study because it is considerably cheaper than the other phosphines investigated. In addition, having a base is important, as

Suzuki-Miyaura cross-coupling reactions generally require base to proceed.[86] A quick scan of common organic and inorganic bases determined that K_2CO_3 was a suitable candidate (entry 7). The imine moiety proved very important as the aldehyde from which the imine is derived showed no reactivity at all under the catalytic conditions (entry 8).

Table 3.1 Screening for Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroaryl imines



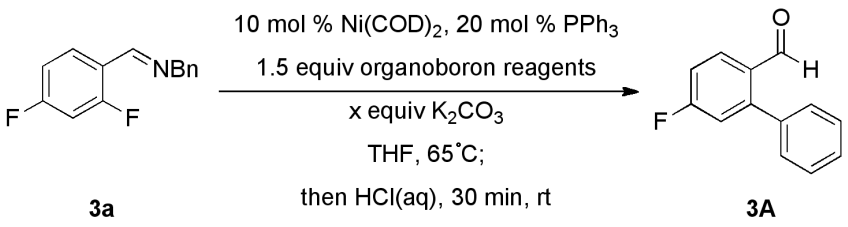
3a **3B**

entry	changes from conditions listed above	yield[a]
1	no change	85%
2	no Ni(COD)	0%
3	$NiCl_2(PPh_3)_2$ or $NiCl_2(PEt_3)_2$ instead of $Ni(COD)_2/PPh_3$	0%
4	no PPh_3	0%
5	20 mol % PEt_3 instead of PPh_3	79%
6	10 mol % DPPF instead of PPh_3	81%
7	no K_2CO_3	0%
8	aldehyde instead of imine	0%

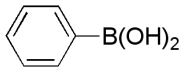
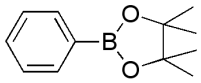
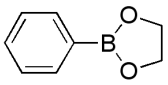
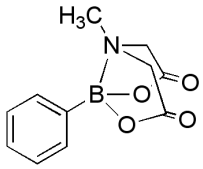
[a] Isolated yields.

Next, we investigated the scope and limitations of organoboron reagents. A review of the literature reveals that in addition to organoboronic acids, organoboronic esters and trifluoroborate salts have also been utilized in transition metal-catalyzed cross-coupling reactions.[87] Not only are many commercially available, but others are easily generated by various means.[88] Compared to organoboronic acids, they offer improved stability. We were pleased to note that phenylboronic pinacol ester (entry 2), phenylboronic 1,3-propanediol ester (entry 3) and potassium phenyltrifluoroborate (entry 5) all reacted under catalytic conditions without compromising the yield (Table 3.2). In particular, the use of trifluoroborate salt eliminated the need for added base. One class of boronic esters that did not yield any product was the *N*-methyliminodiacetic acid (MIDA) ester (entry 4).[89]

Table 3.2 Organoboron reagents for Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroaryl imines



3a **3A**

entry	organoboron reagents	reaction conditions[a]	yield[b]
1		A	74%
2		A	75%
3		A	70%
4		A	0%
5	$K[PhBF_3]$	B	69%

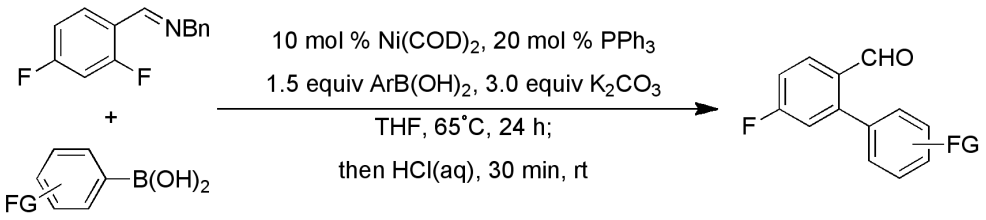
[a] A: 24 h, 3.0 equiv K_2CO_3. B: 48 h, no base added. [b] Isolated yield.

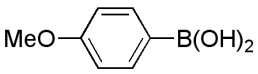
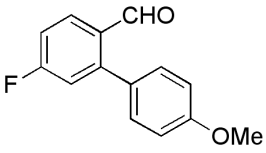
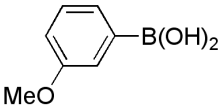
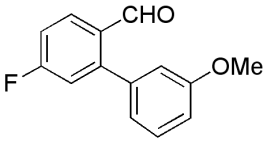
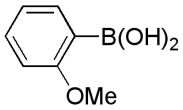
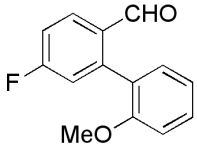
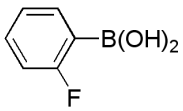
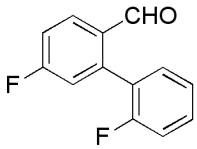
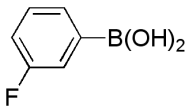
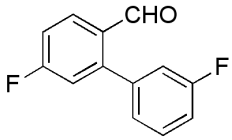
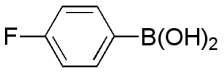
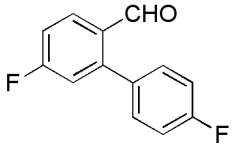
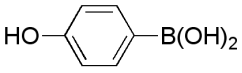
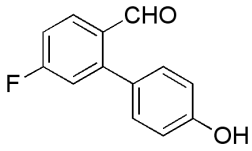
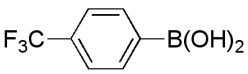
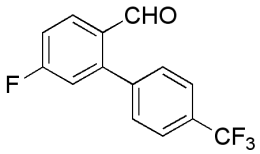
Alkyl boron reagents, unfortunately, did not react under the conditions tested. Methyl and *n*-butyl boronic acids, pinacol esters and trifluoroborate salts were tested but no cross-coupling was observed, which is not unexpected, given the general trend of lower reactivity of alkyl compared to aryl boronic acids, demonstrating the need to develop an alternative route for aryl-alkyl cross-coupling (Chapter 4).[90]

3.2.2 Scope and limitations of arylboronic reagents

After demonstrating successful Ni-catalyzed Suzuki-Miyaura cross-coupling reaction via C-F activation, we sought to probe the scope and limitations of various arylboronic acids. Most arylboronic acids tested were found to be compatible with the reaction conditions (Table 3.3). At the end of the reactions, aqueous HCl was introduced and the biaryl aldehydes were isolated in good yields after hydrolysis and column chromatography. Arylboronic acids with both electron-donating (entries 1 and 2) and electron-withdrawing groups (entries 5 and 6) were well tolerated. A methoxy group at the ortho position prohibited the reaction, likely due to its steric hindrance (entry 3), while an ortho fluoro group only mildly decreased the yield (entry 4). An unprotected 4-hydroxyl group did not inhibit the reaction (entry 7). In addition, biaryl molecules containing 4-fluoro and 4-trifluoromethyl groups were successfully generated. All of these products are 1,2,4-trisubstituted arenes, which is a common motif in pharmaceutical compounds.[91]

Table 3.3 Scope and limitations of arylboronic acids



entry	boronic acid	product		yield[a]
1			**3B**	85%
2			**3C**	74%
3				<5%
4			**3D**	72%
5			**3E**	84%
6			**3F**	77%
7			**3G**	88%
8			**3H**	85%

[a] Isolated yield.

There were a number of arylboronic acids that failed in Ni-catalyzed cross-coupling (Figure 3.3). 4-Bromo- and chlorobenzeneboronic acids resulted in Ni-catalyzed boronic acid homocoupling, presumably due to the faster rate of C-Br and C-Cl oxidative addition. This result was to be expected, as in the literature, Ni/phosphine systems have been widely employed in C-Br and C-Cl cross-coupling.[92] 4-Nitrobenzeneboronic acid and 4-cyanobenzeneboronic acid showed no reactivity. It is commonly accepted that for Suzuki-Miyaura cross-coupling reactions, electron-withdrawing groups on the arylboronic acids accelerate the overall rate by accelerating the transmetalation step, which is normally the rate-determining step.[86] It was somewhat surprising then to see that while the 4-trifluoromethyl group had no impact on the yield (entry 8), the 4-nitro and 4-cyano groups had such detrimental effects, despite their similar Hammett sigma constants.[93] 4-(Methylthio)benzeneboronic acid (4-thioanisoleboronic acid) also failed to produce any coupling product. The 4-methylthio group is neither strongly electron donating nor withdrawing and should have no steric effect at all.[93] It is speculated that the sulfur atom poisons the active species in the catalytic cycle. In addition, both aryl nitriles[94] and sulfides[95] have been reported to participate in Ni-catalyzed cross-coupling reactions.

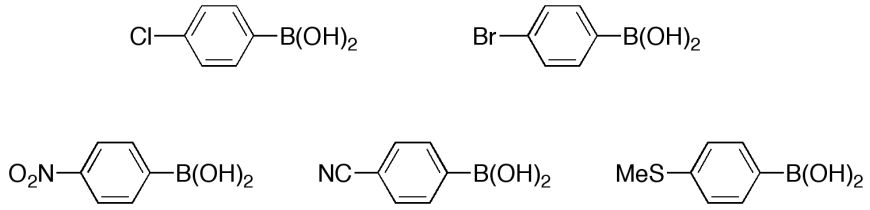


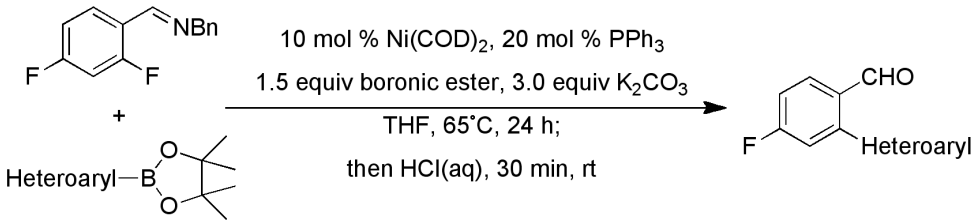
Figure 3.3 List of arylboronic acids that failed in Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroaryl imines

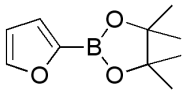
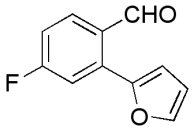
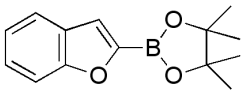
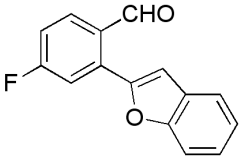
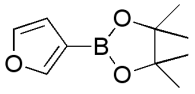
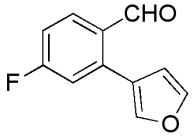
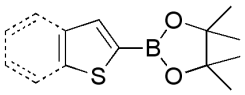
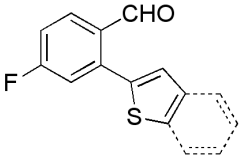
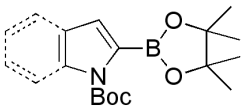
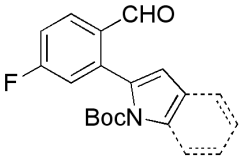
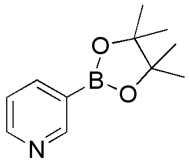
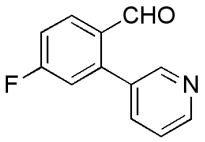
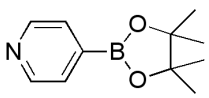
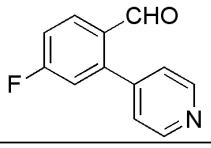
3.2.3 Scope and limitations of heteroaryl boronic reagents

Having established the feasibility of Ni-catalyzed Suzuki-Miyaura C-F cross-coupling to generate biaryl molecules, we next undertook an investigation of the cross-coupling

reactions using heteroarylboronic reagents. Repeated attempts using furan-2-boronic acid resulted in no C-F activation or cross-coupling. Heteroarylboronic acids, especially those boron atoms adjacent to the hetero atoms, are prone to hydrolysis under basic conditions due to their weak C-B bonds.[96] It is well-documented that oxygen-, nitrogen-, and sulfur-containing heterocyclic boronic acids can undergo hydrodeboronation. Thus, the most convenient solution to this problem is to mask the boronic acids as derivatives that undergo hydrolysis, such as boronic esters, MIDA boronates, trifluoroborate salts, etc., so as to slowly release the free boronic acids.[97] Given that arylboronic pinacol esters are more convenient to handle and purify than other boronic derivatives, we chose them as the coupling partners. The results are summarized in Table 3.4.

Table 3.4 Scope and limitations of heteroarylboronic acid esters



entry	Heteroarylboronic ester	product	yield[a]
1			0%
2			**3l** 74%
3			**3J** 90%
4			0%
5			N/A[b]
6			N/A[b]
7			N/A[b]

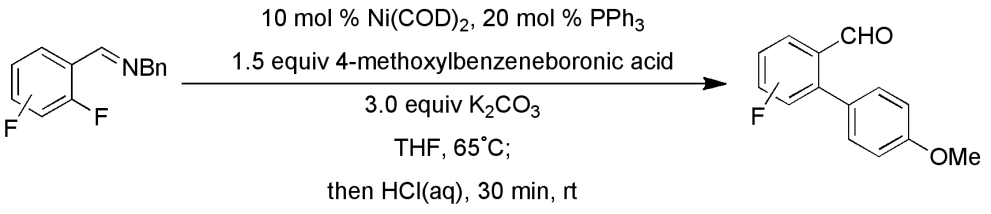
[a] Isolated yield. [b] Detected by ^{19}F NMR spectroscopy and mass spectrometry but not isolated.

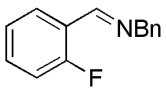
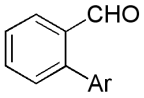
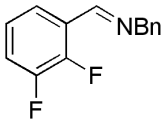
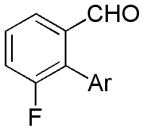
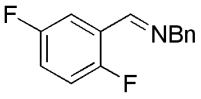
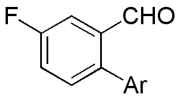
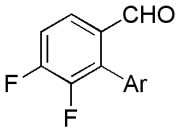
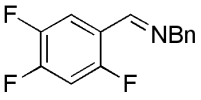
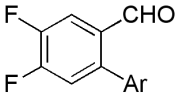
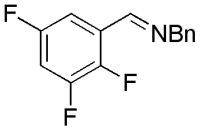
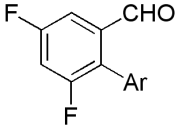
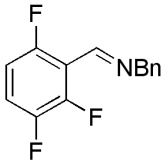
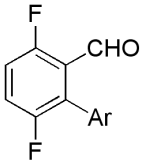
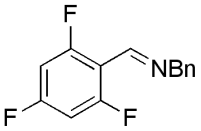
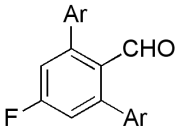
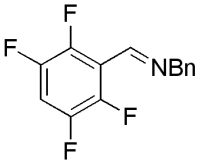
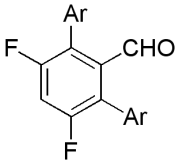
We found that furan-2-boronic pinacol ester (entry 1) persistently failed to yield any product, while benzofuran-2-boronic pinacol ester (entry 2) and furan-3-boronic pinacol ester (entry 3) resulted in almost quantitative conversions and 74% and 90% isolated yields, respectively. Thiophene and benzothiophene boronic esters (entry 4) did not work under the reaction conditions and no C-F activation was observed. It is hypothesized that they poison the catalytic system the same way that 4-(methylthio)benzeneboronic acid does. Nitrogen-containing heterocyclic boronic esters (entries 5, 6, and 7) reacted very sluggishly. While all of them generated a small amount of products observable by $^{19}F\{^{1}H\}$ NMR spectroscopy and mass spectrometry, the products could not be isolated in sufficient quantity or purity. We are currently investigating the cause of this difference in reactivity.

3.2.4 Scope and limitations of fluorine substitution patterns

We next explored the scope and limitations of the fluorine substitution patterns on polyfluoroaryl imines. We chose to use 4-methoxybenzeneboronic acid in our investigation of the fluorine substitution pattern since it produces compounds that are easily separated from starting materials using column chromatography. A broad range of fluorine substitution patterns was tested. Most of them provided good-to-excellent yield, with two notable exceptions (Table 3.5).

Table 3.5 Scope and limitations of polyfluoroaryl imines



entry	imine	product[a]		conditions (A or C), yield[b,c]
1			**3K**	A, 82%
2			**3L**	A, 78%
3				A or C, <5%
4			**3M**	A, 91%
5			**3N**	A, 75%
6			**3O**	A, 70%
7			**3P**	A or C, 70%
8			**3Q**	C, 81%
9			**3R**	C, 84%

[a] Ar = 4-methoxylbenzene. [b] A: 1.5 equiv boronic acid, 24 h, C: 3.0 equiv boronic acid, 48 h. [c] Isolated yield.

First, no reaction took place in the case of 2,5-difluoroimine (entry 3), and the imine was recovered at the end of each run. Second, in the case of 2,3,6-trifluoroimine (entry 7), with two inequivalent ortho C-F bonds, only the 2-position C-F bond underwent activation, resulting in mono-arylation. Repeated attempts using more than 3 equiv of boronic acid and more forcing conditions resulted in no di-arylation. This mono-arylated product was analyzed by ^{1}H, $^{19}F\{^{1}H\}$, $^{13}C\{^{1}H\}$ NMR spectroscopy and the structure was unambiguously confirmed by X-ray crystallography (Figure 3.4). The product of this reaction has the same 2,5-difluoro substitution pattern as the substrate in entry 3, so it appears that this substitution pattern is not tolerated in C-F activation for yet unknown reasons. In comparison, two other substrates with chemically equivalent ortho C-F bonds (entries 8 and 9) underwent di-arylation smoothly. The mono-arylation products from these reactions were only detected as minor products at incomplete conversion, suggesting that the second arylation is competitive with or faster than the initial arylation reaction. We later utilized this unsymmetrical reactivity of 2,3,6-trifluoroimine in Ni-catalyzed sequential C-F cross-coupling (Chapter 4).

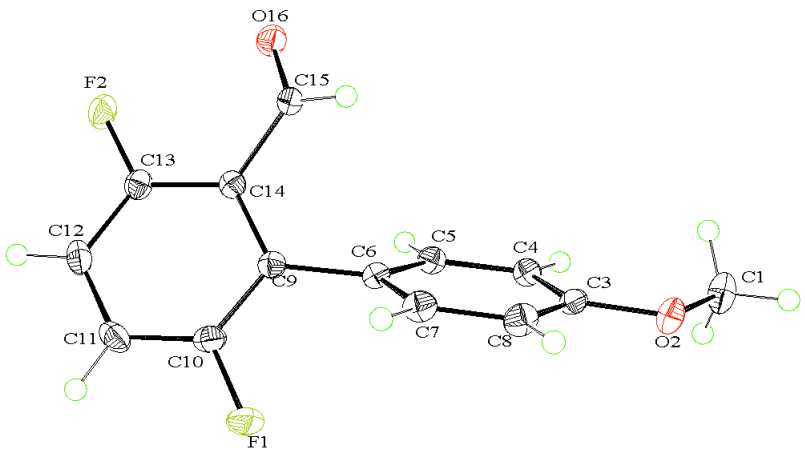
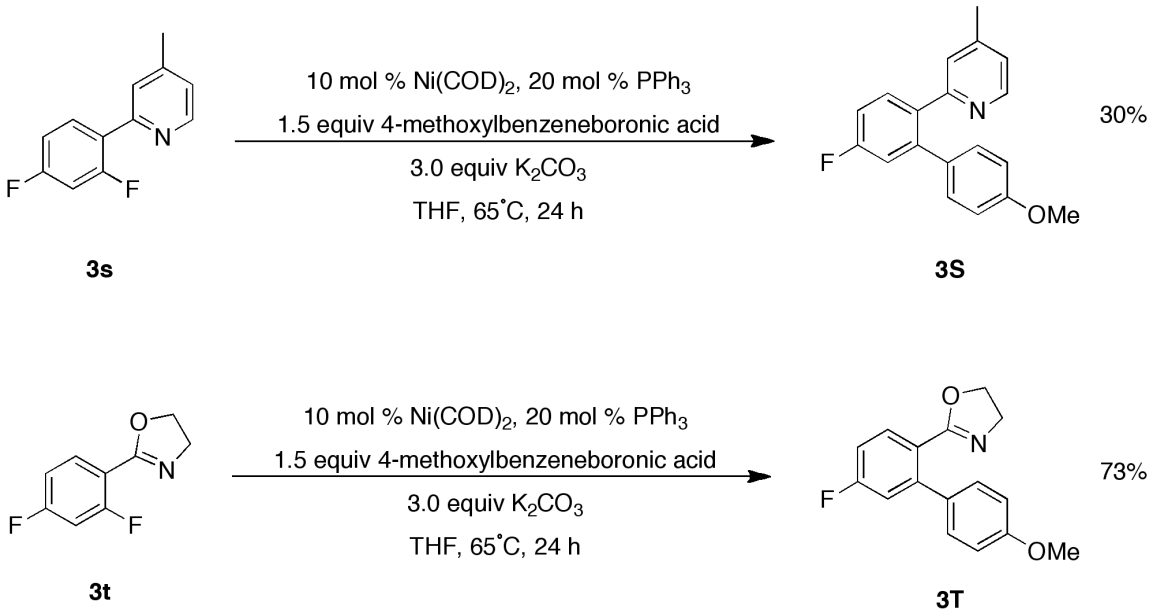


Figure 3.4 ORTEP diagram of product **3P**. Thermal ellipsoids are drawn at the 50% probability level. The full characterization data is listed in the appendix section included at the end of this thesis.

3.3 Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroarenes with different directing groups

As demonstrated above, the imine moiety served as an efficient ortho directing group for Suzuki-Miyaura cross-coupling, and we were satisfied with its easy removal and synthetic versatility. In order to further expand the scope of polyfluoroarenes, we examined other commonly employed directing groups in C-F activation. Recently, we determined that Pt-catalyzed methylation and methoxylation reactions are limited in substrate scope to imine, oxazoline and imidazole directing groups.[98] We were thus pleased to note that for Ni-catalyzed cross-coupling, pyridine and oxazoline-based directing groups showed very promising results. The catalytic conditions were applied to both of them without further optimization. The coupling products were isolated in 30% and 73% yields, respectively; the remaining mass balances were recovered starting

materials (Scheme 3.2). Exploration of other directing groups and further reaction optimization will be conducted in the near future.



Scheme 3.2 Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroarenes

3.4 Mechanistic investigation of Ni-catalyzed Suzuki-Miyaura cross-coupling

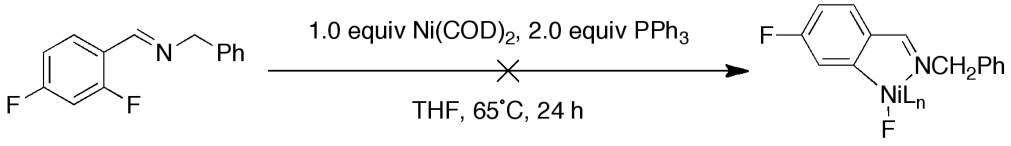
At this stage, we do not have a complete mechanistic picture of Ni-catalyzed C-F cross-coupling. Compared to its heavier cousin palladium, nickel tends to attract less attention as a catalyst in cross-coupling reactions. Several reasons may explain why. For one, during the early stages of transition metal-catalyzed cross-coupling reactions, nickel salts have been found to be less reactive towards C-I and C-Br bond activation, and they carry a higher possibility of homocoupling.[99] From a mechanistic point of view, the most common oxidation state of nickel is Ni(II), but compounds of Ni(0), Ni(I), and Ni(III) are well-documented, and Ni(IV) complexes have also been reported.[100] They may participate in two-electron redox cycles involving [Ni(0)/(II)], [Ni(I)/(III)], or [Ni(II)/(IV)] or one-electron single-electron-transfer (SET) processes involving [Ni(0)/(I)], [Ni(I)/(II)], [Ni(II)/(III)], or [Ni(III)/(IV)].[101] The number of possible oxidation states permits a much

wider range of mechanisms than are typically seen for Pd catalysis. In addition, the presence of paramagnetic species in Ni catalysis greatly complicates the analysis of the mechanism of nickel-catalyzed cross-coupling reactions.

We present here a few observations we made during the course of the study. It has been suggested that 4-nitrophenylboronic acid works well in Pd(0)/(II)-catalyzed cross-coupling because it assists the rate-determining transmetalation step, but that owing to SET, it is not compatible with nickel-phosphine catalysts.[102] We observed in our reactions that 4-trifluoromethylphenylboronic acid worked well but 4-nitrophenylboronic acid did not. It should be noted that while this observation is not evidence in favor of a particular mechanism, it is consistent with the involvement of SET.

Another observation we made early on in the optimization process was that while the reaction is not particularly sensitive towards water or acidic protons, it is sensitive towards oxygen. Commercially available THF (containing up to 0.02% H_2O) can be used after degasification without further drying, but the reverse prohibits the catalytic cycle entirely. Even the presence of a small amount of oxygen is enough to completely prevent the reaction.

The third observation is the absence of any observable Ni-F species, unlike in many Ni-mediated C-F activations reported in the literature.[84] Monitoring the reaction by $^{19}F\{^1H\}$ NMR spectroscopy revealed only the peaks associated with starting materials and products. In Pt-catalyzed C-F activation, an imine-bound Pt(IV)-F complex is formed from oxidative addition; this species was found to be capable of re-entering the catalytic cycle (Scheme 2.2).[77] In comparison, there is no such species observed from the stoichiometric reaction of 2,4-difluoroimine and $Ni(COD)_2/PPh_3$.

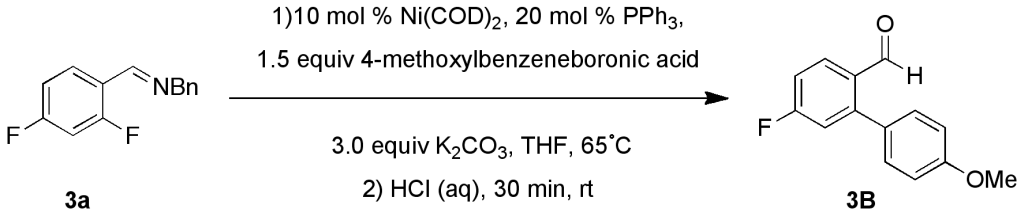


Scheme 3.3 Attempted stoichiometric C-F activation by a Ni complex

The fourth observation is the absence of imine-assisted C-H activation. While stoichiometric and catalytic C-H activation in fluoroarenes have been reported recently[103], we did not observe any evidence of such reactions. We cannot however definitely rule out the possibility of C-H activation under the reaction conditions, as such processes could be fast and reversible.

Finally, we observed catalytic poisoning by sulfur. We tested a number of sulfur-containing additives to determine the effect of such poisoning and the results are summarized in Table 3.6. Dimethyl sulfide and dimethyl sulfoxide have negative effects on the reaction outcome. At 20 mol % loading, a significant drop in yield was observed (entries 2 and 4) but the full effect was perceived only when more than one equivalent of these reagents were added to the reaction mixture (entries 3 and 5), thereby stopping the reaction completely. In contrast, dimethyl sulfone, up to 120 mol %, did not have any observable effect on the reaction.

Table 3.6 Effect of sulfur poisoning in Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroaryl imines



3a **3B**

entry	addtives	yield[a]
1	none	85%
2	20% SMe_2	17%
3	120% SMe_2	0%
4	20% DMSO	21%
5	120% DMSO	0%
6	20% dimethyl sulfone	80%
7	120% dimethyl sulfone	82%

[a] Isolated yield.

3.5 Conclusions

This chapter describes a novel method to generate highly functionalized fluorinated biaryl and aryl-heteroaryl molecules via Ni-catalyzed C-F activation under mild conditions. The method is selective to ortho C-F bonds, compatible with various fluorine substitution patterns, and results in good-to-excellent yields. Aryl, heteroaryl boronic acids, esters and trifluoroborate salts can be used as coupling partners, and different

electron-donating and electron-withdrawing groups are incorporated into the products. This method addresses the key limitations of our previously reported Pt-catalyzed C-F cross-coupling reactions and it demonstrates the successful synthesis of a large number of fluorinated building blocks. Additional work is needed to fully understand the mechanism of this catalytic system and it will be conducted in the near future.

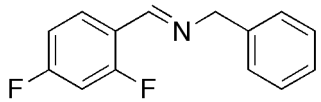
3.6 Experimental

General Procedures. Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled glovebox (O_2 < 2 ppm). NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 600 spectrometers. ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts are reported in parts per million and referenced to residual solvent. $^{19}F\{^{1}H\}$ NMR spectra are reported in parts per million and referenced to $CFCl_3$ (0 ppm). Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets. All spectra were obtained at 25°C. Mass spectra were recorded on a Kratos MS-50 mass spectrometer.

Materials and Methods. Acetone-d_6 and acetonitrile-d_3 were purchased from Cambridge Isotope Laboratories and used as received. All boronic acids, esters, trifluoroborate salts and potassium bicarbonate were obtained from commercial sources and used as received except heteroaryl boronic pinacol esters used in Table 3.4. Heteroaryl boronic pinacol esters were synthesized according to a literature procedure.[104] Anhydrous tetrahydrofuran (THF) was purchased from Aldrich and freeze-pump-thawed three times before bringing into the glovebox and was used without further purification. Bis(cyclooctadiene)nickel(0) [$Ni(COD)_2$] was purchased from Strem Chemicals and was used without further purification. Triphenylphosphine was recrystallized from ethanol. All imines were prepared by published procedures and were purified before use.[76] Three new imines were synthesized using the same procedure and their analytical data is reported here. 2-(2,4-Difluorophenyl)-4-methylpyridine **(3s)** and 2-(2,4-difluorophenyl)-4,5-dihydrooxazole **(3t)** were synthesized according to literature procedures.[105, 106]

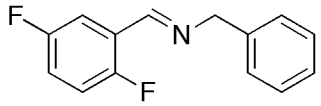
Analytical data for starting materials:

(*E*)-N-(2,4-difluorobenzylidene)(phenyl)methanamine (colorless oil)



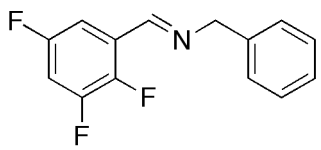
^{1}H NMR (acetonitrile-d_3, 300 MHz): δ 8.63 (s, 1H), 7.99-7,97 (m, 1H), 7.40-7.28 (m, 5H), 7.00-6.98 (m, 2H), 4.78 (s, 2H). ^{19}F{^{1}H} NMR (acetonitrile-d_3, 282 MHz): δ -107.4 (d, 1F, J = 9.2 Hz), -118.7 (d, 1F, J = 9.2 Hz). ^{13}C{^{1}H} NMR (acetonitrile-d_3, 150 MHz): δ 165.5 (dd, J = 190.2 Hz, J = 12.3 Hz), 163.0 (dd, J = 190.2 Hz, J = 12.3 Hz), 154.5 (d, J = 3.1 Hz), 140.4 (s), 130.1 (d, J = 4.6 Hz), 130.0 (d, J = 4.6 Hz), 129.3 (s), 128.3 (s), 127.8 (s), 112.9 (d, J = 18.4 Hz), 104.8 (t, J = 26.0 Hz), 65.6 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}NF_2$: 231.0860; found: 231.0860.

(*E*)-N-(2,5-difluorobenzylidene)(phenyl)methanamine (colorless oil)



^{1}H NMR (acetonitrile-d_3, 300 MHz): δ 8.64 (s, 1H), 7.66-7.64 (m, 1H), 7.36-7.25 (m, 5H), 7.18-7.17 (m, 2H), 4.81 (s, 2H). ^{19}F{^{1}H} NMR (acetonitrile-d_3, 282 MHz): δ -120.1 (s, 1F), -129.0 (s, 1F). ^{13}C{^{1}H} NMR (acetonitrile-d_3, 150 MHz): δ 160.9 (d, J = 56.7 Hz), 158.4 (d, J = 56.7 Hz), 154.9 (s), 140.4 (s), 129.5 (s), 129.0 (s), 128.1 (s), 126.4 (m), 120.0 (dd, J = 24.5 Hz, J = 9.2 Hz), 118.5 (dd, J = 24.5 Hz, J = 9.2 Hz), 114.0 (dd, J = 24.5 Hz, J = 3.1 Hz), 65.7 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}NF_2$: 231.0860; found: 231.0859.

(*E*)-phenyl-N-(2,3,5-trifluorobenzylidene)methanamine (yellow solid)



^{1}H NMR (acetonitrile-d_3, 300 MHz): δ 8.66 (s, 1H), 7.49-7.47 (m, 1H), 7.36-7.20 (m, 4H), 4.83 (s, 2H). ^{19}F{^{1}H} NMR (acetonitrile-d_3, 282 MHz): δ -116.6 (s, 1F), -136.1 (s, 1F), -153.1 (s, 1F). ^{13}C{^{1}H} NMR (acetonitrile-d_3, 150 MHz): δ 162.7 (s), 158.7 (ddd, J = 243.8 Hz, J = 10.3 Hz, J = 2.9 Hz), 154.1 (m), 151.5 (ddd, J = 248.4 Hz, J = 13.8 Hz, J = 12.6 Hz), 148.0 (ddd, J = 248.9 Hz, J = 13.8 Hz, J = 4.0 Hz), 140.1 (s), 129.5 (s), 129.0 (s), 128.1 (s), 109.2 (m), 108.4 (dd, J = 28.7 Hz, J = 21.2 Hz), 65.6 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}NF_3$: 249.0765; found: 249.0767.

General experimental procedure for catalytic C-F cross-coupling reactions:

Reaction conditions A: In a 20 mL vial, imine (0.5 mmol, 1.0 equiv), $Ni(COD)_2$ (13.8 mg, 0.05 mmol, 10 mol %), PPh_3 (26.2 mg, 0.1 mmol, 10 mol %) and boronic acid/ester (0.75 mmol, 1.5 equiv) were dissolved in THF (10 mL). K_2CO_3 (150 mg, 1.5 mmol, 3.0 equiv) was added to the resulting solution. The vial was capped, removed from the glovebox and subsequently heated at 65°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further column separation provides clean products (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

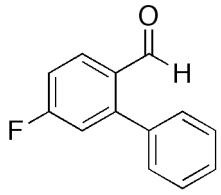
Reaction conditions B: Identical to condition A, except 0.75 mmol trifluoroborate salt was used instead of boronic acid, no base was added, and the resulting mixture was heated for 48 h.

Reaction conditions C: Identical to condition A, except 3.0 mmol boronic acid was added and the resulting mixture was heated for 48 h.

Analytical data for products of C-F cross-coupling:

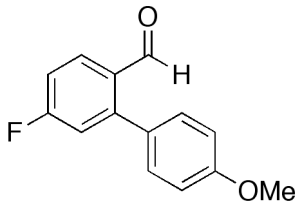
The resonances at δ 2.84 in acetone-d_6 and δ 2.13 in acetonitrile-d_3 are due to residual H_2O from the solvent (the peaks appear in the absence of cross-coupling products). The exact amount depends on the batch.

(3A) 5-fluoro-[1,1'-biphenyl]-2-carbaldehyde (colorless oil, 74%)



^{1}H NMR (acetone-d_6, 300 MHz): δ 9.87 (s, 1H), 8.04 (dd, 1H, J = 8.68 Hz, J = 5.94 Hz), 7.58-7.47 (m, 5H), 7.38-7.31 (m, 1H), 7.27 (dd, J = 9.59 Hz, J = 2.51 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.5 (s). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.5 (d, J = 4.0 Hz), 166.2 (d, J = 254.1 Hz), 149.6 (d, J = 9.2 Hz), 137.5 (d, J = 1.7 Hz), 131.6 (d, J = 2.3 Hz), 131.5 (s), 131.4 (s), 130.9 (s), 129.5 (d, J = 1.7 Hz), 118.2 (d, J = 22.4 Hz), 116.0 (d, J = 22.4 Hz). HRMS (EI) m/z calculated for $C_{13}H_9FO$: 200.0637; found: 200.0636.

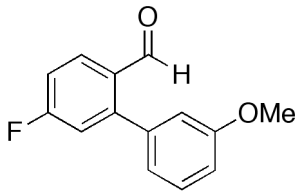
(3B) 5-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 85%)



^{1}H NMR (acetone-d_6, 300 MHz): δ 9.89 (s, 1H), 8.01 (dd, 1H, J = 8.68 Hz, J = 6.17 Hz), 7.41 (d, 2H, J = 8.68 Hz), 7.34-7.21 (m, 2H), 7.10 (d, 2H, J = 8.68 Hz), 3.88 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.7 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150

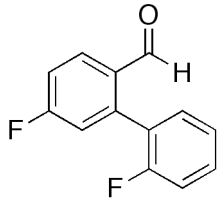
MHz): δ 190.7 (d, J = 4.0 Hz), 166.2 (d, J = 253.5 Hz), 161.2 (s), 149.4 (d, J = 9.7 Hz), 132.2 (s), 131.5 (d, J = 2.9 Hz), 131.4 (d, J = 9.5 Hz), 129.6 (d, J = 1.7 Hz), 118.1 (d, J = 21.8 Hz), 115.7 (d, J = 21.8 Hz), 115.0 (s), 55.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO_2$: 230.0743; found: 230.0742.

(3C) 5-fluoro-3'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 74%)



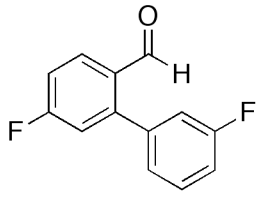
^{1}H NMR (acetone-*d*$_6$, 300 MHz): δ 9.89 (s, 1H), 8.02 (dd, 1H, J = 8.68 Hz, J = 6.17 Hz), 7.47-7.41 (m, 1H), 7.37-7.26 (m, 2H), 7.09-6.99 (m, 3H), 3.88 (s, 3H). ^{19}F{^{1}H} NMR (acetone-*d*$_6$, 282 MHz): δ -106.5 (s, 1F). ^{13}C{^{1}H} NMR (acetone-*d*$_6$, 150 MHz): δ 190.5 (d, J = 4.0 Hz), 166.2 (d, J = 253.5 Hz), 160.8 (s), 149.4 (d, J = 9.7 Hz), 138.9 (d, J = 1.7 Hz), 131.6 (d, J = 2.3 Hz), 131.2 (d, J = 9.7 Hz), 130.5 (s), 123.3 (s), 118.1 (d, J = 22.4 Hz), 116.2 (s), 116.1 (d, J = 21.8 Hz), 115.2 (s), 55.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO_2$: 230.0743; found: 230.0743.

(3D) 2',5-difluoro-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 72%)



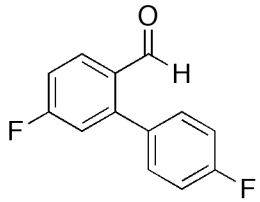
^{1}H NMR (acetone-*d*$_6$, 300 MHz): δ 9.83 (s, 1H), 8.09-8.07 (m, 1H), 7.58-7.52 (m, 2H), 7.43-7.41 (m, 2H), 7.32-7.30 (m, 2H). ^{19}F{^{1}H} NMR (acetone-*d*$_6$, 282 MHz): δ -106.2 (s, 1F), -117.8 (s, 1F). ^{13}C{^{1}H} NMR (acetone-*d*$_6$, 150 MHz): δ 190.2 (s), 166.4 (d, J = 254.1 Hz), 160.4 (d, J = 244.9 Hz), 142.4 (d, J = 9.8 Hz), 132.8 (d, J = 2.9 Hz), 132.1 (d, J = 8.0 Hz), 131.8 (d, J = 2.9 Hz), 130.6 (d, J = 10.3 Hz), 125.8 (s), 119.1 (d, J = 22.9 Hz), 116.6 (q, J = 24.1 Hz). HRMS (EI) m/z calculated for $C_{13}H_8F_2O$: 218.0543; found: 218.0540.

(3E) 3',5-difluoro-[1,1'-biphenyl]-2-carbaldehyde (colorless oil, 84%)



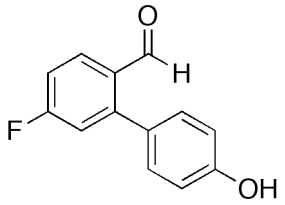
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.90 (s, 1H), 8.06 (dd, 1H, J = 8.68 Hz, J = 5.94 Hz), 7.62-7.54 (m, 1H), 7.42-7.26 (m, 5H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.3 (s, 1F), -114.6 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.3 (d, J = 3.4 Hz), 166.2 (d, J = 254.1 Hz), 163.5 (J = 245.5 Hz), 148.0 (dd, J = 9.2 Hz, J = 1.7 Hz), 140.0 (dd, J = 8.0 Hz, J = 1.7 Hz), 131.7 (d, J = 9.8 Hz), 131.5 (d, J = 2.3 Hz), 131.3 (d, J = 8.6 Hz), 127.1 (d, J = 2.9 Hz), 118.3 (d, J = 22.9 Hz), 117.6 (d, J = 22.4 Hz), 116.5 (d, J = 22.4 Hz), 116.3 (d, J = 21.2 Hz) . HRMS (EI) m/z calculated for $C_{13}H_8F_2O$: 218.0543; found: 218.0542.

(3F) 4',5-difluoro-[1,1'-biphenyl]-2-carbaldehyde (colorless oil, 77%)



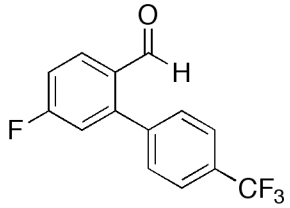
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.87 (s, 1H), 8.03 (dd, 1H, J = 8.68 Hz, J = 6.17 Hz), 7.57-7.50 (m, 2H), 7.37-7.24 (m, 4H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.3 (s, 1F), -115.3 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.4 (d, J = 4.0 Hz), 166.2 (d, J = 254.1 Hz), 163.9 (d, J = 246.7 Hz), 148.3 (d, J = 9.2 Hz), 133.8 (q, J = 1.7 Hz), 132.9 (d, J = 8.6 Hz), 131.6 (d, J = 10.3 Hz), 131.5 (s), 118.4 (d, J = 22.4 Hz), 116.3 (d, J = 22.4 Hz), 116.2 (d, J = 21.8 Hz). HRMS (EI) m/z calculated for $C_{13}H_8F_2O$: 218.0543; found: 218.0542.

(3G) 5-fluoro-4'-hydroxy-[1,1'-biphenyl]-2-carbaldehyde (colorless oil, 88%)



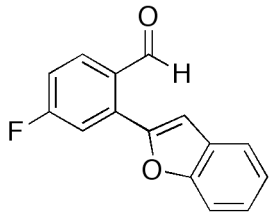
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.91 (s, 1H), 8.00 (dd, 1H, J = 8.45 Hz, J = 5.94 Hz), 7.32 (d, 2H, J = 8.68 Hz), 7.29-7.21 (m, 2H), 7.00 (d, 2H, J = 8.68 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.8 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.8 (d, J = 4.0 Hz), 166.2 (d, J = 253.5 Hz), 159.0 (s), 149.7 (d, J = 9.7 Hz), 132.3 (s), 131.5 (d, J = 2.9 Hz), 131.3 (d, J = 10.3 Hz), 128.5 (d, J = 1.7 Hz), 118.0 (d, J = 21.8 Hz), 116.4 (s), 115.5 (d, J = 22.3 Hz). HRMS (EI) m/z calculated for $C_{13}H_9FO_2$: 216.0587; found: 216.0584.

(3H) 5-fluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (colorless oil, 85%)



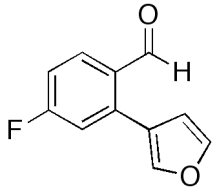
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.90 (s, 1H), 8.12-8.06 (m, 1H), 7.90 (d, 2H, J = 7.99 Hz), 7.75 (d, 2H, J = 7.99 Hz), 7.46-7.31 (m, 2H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -63.5 (s, 3F), -106.1 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.1 (d, J = 4.0 Hz), 166.2 (d, J = 254.7 Hz), 147.7 (d, J = 9.2 Hz), 141.9 (t, J = 1.1 Hz), 132.1 (d, J = 10.3 Hz), 131.7 (s), 131.6 (d, J = 2.9 Hz), 130.9 (q, J = 32.1 Hz), 126.3 (q, J = 4.0 Hz), 125.3 (q, J = 271.3 Hz), 118.5 (d, J = 23.0 Hz), 116.8 (d, J = 21.8 Hz). HRMS (EI) m/z calculated for $C_{14}H_8F_4O$: 268.0511; found: 268.0509.

(3I) 2-(benzofuran-2-yl)-4-fluorobenzaldehyde (colorless solid, 74%)



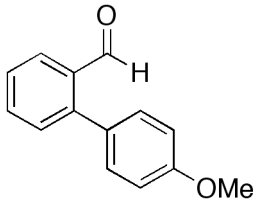
^{1}H NMR (acetone-d_6, 300 MHz): δ 10.45 (s, 1H), 8.09-8.07 (m, 1H), 7.75-7.64 (m, 3H), 7.44-7.33 (m, 4H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -105.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.8 (s), 166.3 (d, J = 253.0 Hz), 156.5 (s), 152.7 (s), 136.2 (d, J = 9.8 Hz), 132.3 (d, J = 9.8 Hz), 131.7 (s), 129.6 (s), 126.6 (s), 124.6 (s), 122.8 (s), 117.3 (d, J = 22.4 Hz), 116.5 (d, J = 24.1 Hz), 112.3 (s), 109.8 (s). HRMS (EI) m/z calculated for $C_{15}H_9FO_2$: 240.0587; found: 240.0588.

(3J) 4-fluoro-2-(furan-3-yl)benzaldehyde (colorless solid, 90%)



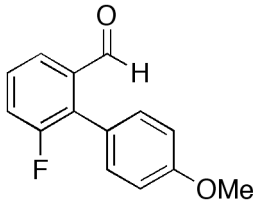
^{1}H NMR (acetone-d_6, 300 MHz): δ 10.16 (s, 1H), 8.03-8.01 (m, 1H), 7.94 (s, 1H), 7.77 (s, 1H), 7.34-7.33 (m, 2H), 6.83 (s, 1H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): -105.5 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.5 (s), 166.4 (d, J = 253.6 Hz), 145.1 (s), 143.3 (s), 140.3 (d, J = 9.8 Hz), 131.7 (d, J = 2.9 Hz), 131.6 (d, J = 10.3 Hz), 122.2 (s), 117.9 (d, J = 22.9 Hz), 115.9 (d, J = 22.4 Hz), 112.9 (s). HRMS (EI) m/z calculated for $C_{11}H_7FO_2$: 190.0430; found: 190.0429.

(3K) 4'-methoxybiphenyl-2-carbaldehyde (colorless solid, 82%)



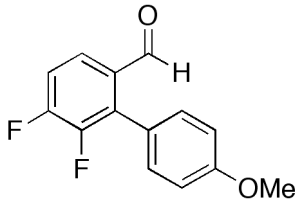
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.97 (s, 1H), 7.93 (d, 1H, J= 7.70 Hz), 7.71 (dt, 1H, J = 7.70 Hz, J = 1.51 Hz), 7.54-7.49 (m, 2H), 7.38 (d, 2H, J = 8.68 Hz), 7.10 (d, 2H, J = 8.68 Hz), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 192.3 (s), 160.8 (s), 146.4 (s), 134.7 (s), 134.5 (s), 132.2 (s), 131.8 (s), 130.8 (s), 128.3 (s), 128.0 (s), 114.8 (s), 55.7 (s). HRMS (EI) m/z calculated for $C_{14}H_{12}O_2$: 212.0837; found: 212.0838.

(3L) 6-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 78%)



^{1}H NMR (acetone-d_6, 300 MHz): δ 9.81 (s, 1H), 7.78-7.76 (m, 1H), 7.62-7.49 (m, 2H), 7.38 (d, 2H, J = 8.68 Hz), 7.10 (d, 2H, J = 8.68 Hz), 3.88 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -118.0 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.2 (t, J = 3.4 Hz), 161.1 (s), 160.9 (d, J = 245.5 Hz), 137.0 (d, J = 2.3 Hz), 133.5 (d, J = 16.6 Hz), 133.1 (d, J = 1.7 Hz), 130.0 (d, J = 8.0 Hz), 123.9 (d, J = 3.4 Hz), 123.3 (s), 121.6 (d, J = 23.5 Hz), 114.8 (s), 55.7 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO_2$: 230.0743; found: 230.0743.

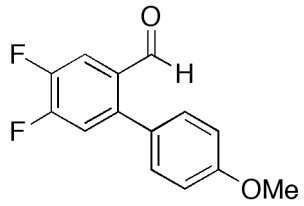
(3M) 5,6-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 91%)



^{1}H NMR (acetone-d_6, 300 MHz): δ 9.75 (s, 1H), 7.83-7.81 (m, 1H), 7.52-7.50 (m, 1H), 7.42 (d, 2H, J = 8.68 Hz), 7.13 (d, 2H, J = 8.68 Hz), 3.90 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -131.3 (d, 1F, J = 20.6 Hz), -142.8 (d, 1F, J = 20.6 Hz). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.0 (s), 161.4 (s), 154.7 (dd, J = 255.3 Hz, J = 14.3 Hz), 148.5 (dd, J = 246.7 Hz, J = 12.6 Hz), 136.0 (d, J = 14.9 Hz), 133.0 (s), 132.5

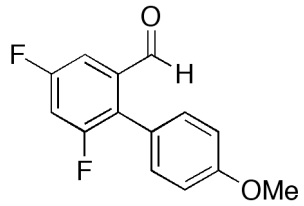
(d, J = 2.9 Hz), 125.1 (dd, J = 8.6 Hz, J = 4.6 Hz), 122.1 (d, J = 2.9 Hz), 117.5 (d, J = 18.4 Hz), 114.9 (s), 55.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O_2$: 248.0649; found: 248.0651.

(3N) 4,5-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 75%)



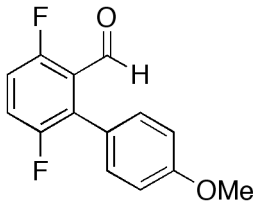
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.84 (d, 1H, J = 3.20 Hz), 7.85 (dd, 1H, J = 10.74 Hz, J = 8.45 Hz), 7.50-7.38 (m, 3H), 7.10 (d, 2H, J = 8.91 Hz), 3.88 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -131.7 (d, 1F, J = 20.6 Hz), -141.1 (d, 1F, J = 20.6 Hz). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 189.8 (s), 161.1 (s), 152.1 (dd, J = 256.1 Hz, J = 13.8 Hz), 152.0 (ddd, J = 331.3 Hz, J = 256.1 Hz, J = 13.8 Hz), 144.3 (d, J = 7.7 Hz), 132.2 (s), 131.7 (t, J = 3.1 Hz), 128.5 (s), 120.4 (d, J = 18.4 Hz), 116.4 (s), 114.8 (s), 55.6 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O_2$: 248.0649; found: 248.0650.

(3O) 4,6-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 70%)



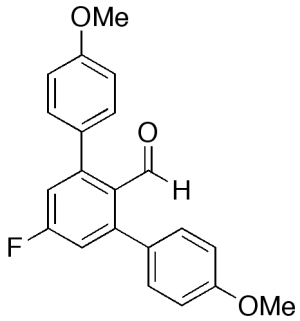
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.79 (d, 1H, J = 3.43 Hz), 7.50-7.37 (m, 4H), 7.11 (d, 2H, J = 8.68 Hz), 3.89 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -111.8 (s, 1F), -112.9 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 190.0 (dt, J = 4.0 Hz, J = 2.3 Hz), 162.0 (ddd, J = 249.0 Hz, J = 199.6 Hz, J = 12.0 Hz), 161.2 (s), 137.9 (dd, J = 6.9 Hz, J = 3.4 Hz), 133.2 (s), 130.9 (d, J = 361.9 Hz), 130.3 (dd, J = 17.2 Hz, J = 3.4 Hz), 122.4 (s), 114.9 (s), 110.1 (dd, J = 22.4 Hz, J = 4.0 Hz), 109.8 (dd, J = 27.5 Hz, J = 26.4 Hz), 55.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O_2$: 248.0649; found: 248.0648.

(3P) 3,6-difluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 75%)



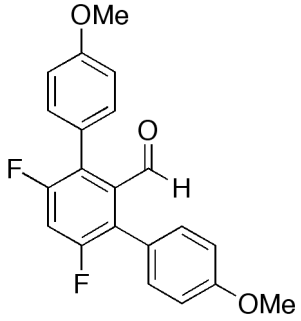
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.79 (s, 1H), 7.57-7.50 (m, 1H), 7.34-7.32 (m, 3H), 7.09 (d, 2H, J = 8.68 Hz), 3.88 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -122.4 (d, 1F, J = 18.4 Hz), -123.4 (d, 1F, J = 18.4 Hz). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 188.6 (s), 161.2 (s), 158.8 (d, J = 207.0 Hz), 156.4 (d, J = 191.7 Hz), 133.5 (d, J = 16.9 Hz), 132.8 (s), 125.1 (d, J = 7.7 Hz), 123.3 (s), 122.3 (dd, , J = 27.6 Hz, J = 10.7 Hz), 117.6 (dd, J = 24.5 Hz, J = 9.2 Hz), 114.8 (s), 55.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O_2$: 248.0649; found: 248.0648.

(3Q) 5'-fluoro-4,4''-dimethoxy-[1,1':3',1''-terphenyl]-2'-carbaldehyde (colorless solid, 81%)



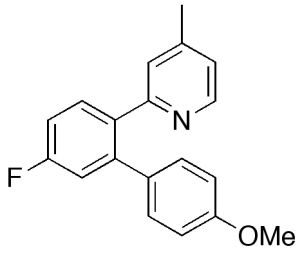
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.87 (s, 1H), 7.73 (d, 4H, J = 8.68 Hz), 7.14 (d, 2H, J = 9.37 Hz), 7.01 (d, 4H, J = 8.68 Hz), 3.86 (s, 6H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -109.6 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 192.5 (s), 164.0 (d, J = 252.4 Hz), 160.7 (s), 147.8 (d, J = 9.2 Hz), 131.8 (s), 131.7 (s), 131.3 (d, J = 2.3 Hz), 117.3 (d, J = 21.2 Hz), 114.5 (s), 55.7 (s). HRMS (EI) m/z calculated for $C_{21}H_{17}FO_3$: 336.1162; found: 336.1160.

(3R) 4',6'-difluoro-4,4"-dimethoxy-[1,1':3',1"-terphenyl]-2'-carbaldehyde (colorless solid, 84%)



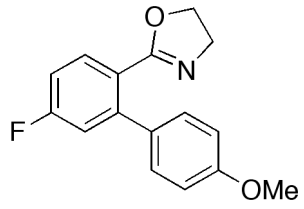
^{1}H NMR (acetone-d_6, 300 MHz): δ 9.74 (s, 1H), 7.41 (t, 1H, J = 9.37 Hz), 7.27 (d, 4H, J = 8.68 Hz), 7.02 (d, 4H, J = 8.68 Hz), 3.85 (s, 6H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -114.0 (s, 2F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 192.2 (s), 160.7 (s), 159.9 (dd, J = 247.8 Hz, J = 12.6 Hz), 138.5 (t, J = 2.9 Hz), 132.7 (s), 127.4 (dd, J = 15.5 Hz, J = 6.3 Hz), 124.2 (s), 114.5 (s), 107.9 (t, J = 27.5 Hz), 55.7 (s). HRMS (EI) m/z calculated for $C_{21}H_{16}F_2O_3$: 354.1068; found: 354.1067.

(3S) 2-(5-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4-methylpyridine (colorless oil, 30%)



^{1}H NMR (acetone-d_6, 300 MHz): δ 8.40 (d, 1H, J = 5.12 Hz), 7.66-7.64 (m, 1H), 7.21-7.14 (m, 2H), 7.07 (d, 2H, J = 8.71 Hz), 7.04-7.02 (m, 1H), 6.83 (d, 2H, J = 8.70 Hz), 6.78 (s, 1H), 3.77 (s, 3H), 2,12 (s, 3H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -115.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 163.4 (d, J = 246.1 Hz), 160.1 (s), 159.3 (s), 150.0 (s), 147.2 (s), 143.5 (s), 137.2 (s), 133.7 (s), 133.5 (s), 131.5 (s), 126.7 (s), 123.4 (s), 117.4 (d, J = 21.8 Hz), 114.5 (d, J = 21.2 Hz), 114.5 (s), 55.6 (s), 20.9 (s). HRMS (ESI) [m/z+1] calculated for $C_{19}H_{17}NFO$: 294.1294; found: 294.1295.

(3T) 2-(5-fluoro-4'-methoxy-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (colorless solid, 73%)

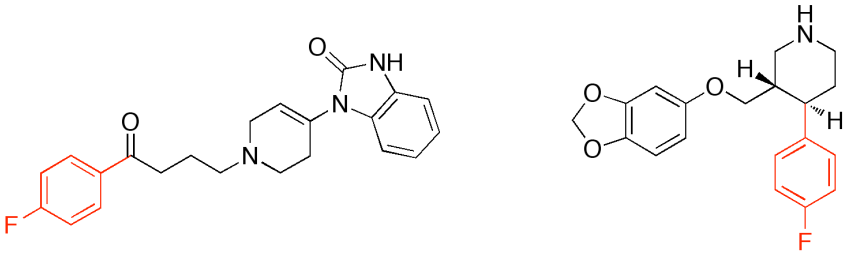


^{1}H NMR (acetone-d_6, 300 MHz): δ 7.77-7.75 (m, 1H), 7.33 (d, 2H, J = 9.22 Hz), 7.17-7.15 (m, 2H), 6.96 (d, 2H, J = 9.22 Hz), 4.13-4.10 (m, 2H), 3.85-3.83 (m, 2H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -111.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 165.4 (s), 164.7 (d, J = 248.4 Hz), 160.5 (s), 145.0 (d, J = 8.6 Hz), 133.5 (d, J = 9.2 Hz), 133.2 (s), 130.3 (s), 125.2 (s), 117.5 (s), 116.0 (q, J = 170.9 Hz), 114.0 (s), 68.4 (s), 55.7 (d, J = 18.4 Hz). HRMS (ESI) [m/z+1] calculated for $C_{16}H_{15}NFO_2$: 272.1087; found: 272.1089.

Chapter 4: Ni-Catalyzed Negishi Carbon-Fluorine Cross-Coupling[d]

4.1 Introduction

In chapter 3, we discussed a novel Ni-catalyzed Suzuki-Miyaura C-F cross-coupling of polyfluoroarenes that proves to be a highly efficient method to synthesize a wide range of highly functionalized, fluorinated biaryl or aryl-heteroaryl compounds under mild conditions. Unfortunately, despite our efforts, cross-coupling reactions employing alkyl boron reagents have not come to fruition; in other words, our method does not permit the construction of C_{sp2}-C_{sp3} bonds. Aryl-alkyl cross-coupling methodologies may provide convenient methods to synthesize certain aryl fluoride compounds. For example, two drugs shown here, Johnson & Johnson's Droperidol and GlaxoSmithKline's Paroxetine, contain alkyl-substituted aryl fluoride moieties that cannot be prepared by our Suzuki-Miyaura cross-coupling (Figure 4.1).



Droperidol

Anti-emetic and anti-psychotic

Paroxetine

Anti-depressant

Figure 4.1 Structures of Droperidol and Paroxetine

In the section to follow, we present a Ni-catalyzed Negishi cross-coupling of polyfluoroaryl imines for generating C_{sp2}-C_{sp3} bonds. Next, Ni-catalyzed sequential

[d] A version of this chapter has been submitted for publication. Sun, A. D.; Leung, K.; Restivo, A. D.; Love, J. A. Nickel-Catalyzed Csp2-Csp3 Bond Formation via C-F Activation.

reactions of polyfluoroaryl imines will be reported in section 4.3. Finally, Ni-catalyzed Negishi cross-coupling of polyfluoroarenes with different directing groups are presented in section 4.4.

4.2 Ni-catalyzed Negishi cross-coupling of polyfluoroaryl imines

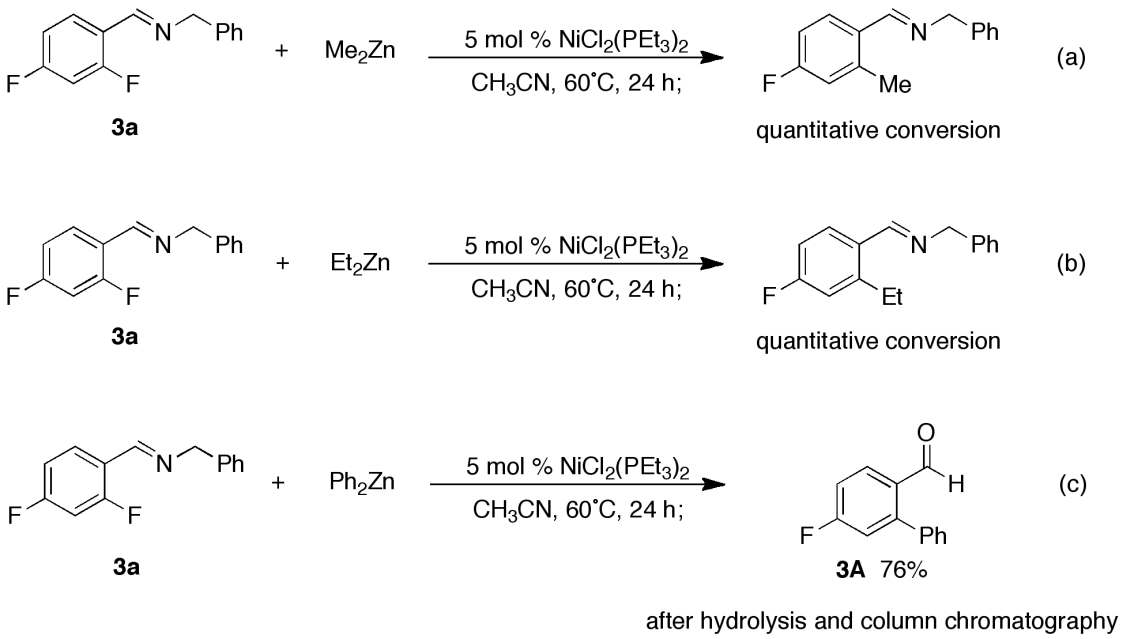
Our approach was to develop a Ni-catalyzed cross-coupling method of polyfluoroarenes using an alkyl-containing reagent as a coupling partner. Our previous research had indicated that Pt-catalyzed C-F cross-coupling was unable to achieve this result because Pt(IV) intermediates were prone to β-hydride elimination.[83] In addition, the Ni-catalyzed Suzuki-Miyaura cross-coupling procedure we had recently discovered did not produce any C_{sp2}-C_{sp3} coupling product with methyl- or *n*-butyl- boronic reagents. At the same time, we were encouraged by literature examples that showed promising results for either transition metal-mediated[107] or catalyzed[108] reactions between aryl fluorides and alkyl-organometallics reagents.

Consequently, our decision to investigate cross-coupling with organozinc reagents (Negishi coupling) was informed by two factors: 1) although for practical reasons we had chosen organoboron reagents over organozinc reagents in the biaryl synthesis, diphenylzinc was equally effective in those Ni-catalyzed reactions and 2) compared to more reactive organometallic reagents (organolithium, Grignard, etc.), organozinc reagents offered excellent functional group compatibility and could be synthesized from commercially available starting materials in high yields under mild conditions.[109,110]

We chose to use polyfluoroaryl imines in our initial investigation because that would help us compare reaction conditions, yields and functional group tolerance with our Pt-catalyzed and Ni-catalyzed cross-coupling reactions. These polyfluoroaryl imines are readily synthesized from polyfluorinated aldehydes, easy to handle, and can be easily functionalized if desired.

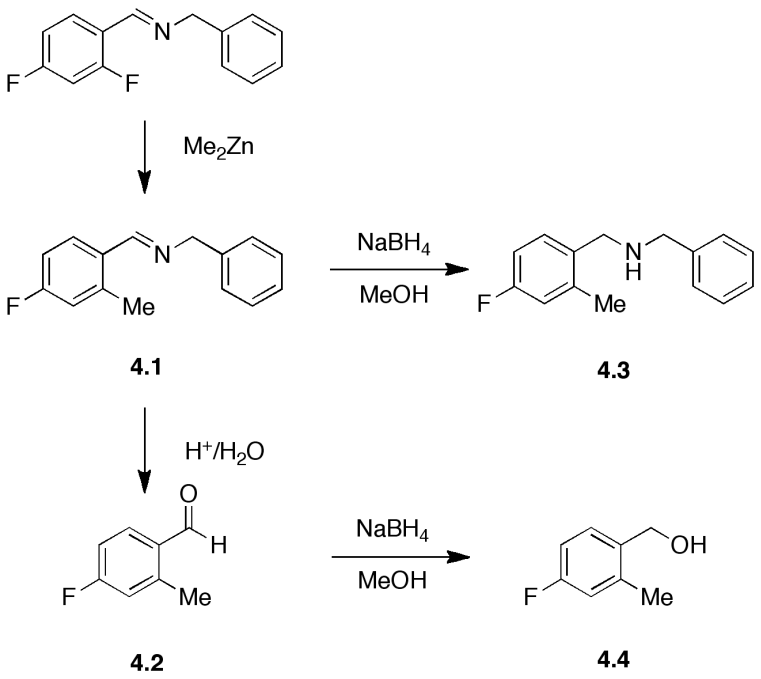
4.2.1 Initial results with diorganozinc reagents

Our investigation began by testing the reaction between 2,4-difluoroimine and dimethylzinc in CH_3CN with catalytic amounts of nickel salts. We were glad to find that a number of them proved to be efficient precatalysts. For example, with $NiCl_2(PEt_3)_2$ as the precatalyst, the signals in the ^1H NMR spectrum corresponding to 2,4-difluoroimine completely disappeared over the course of the reaction, and the methylated product was formed quantitatively according to ^1H, $^{19}F\{^1H\}$ NMR spectroscopy and mass spectrometry. No apparent imine-assisted C-H activation was observed (Scheme 4.1a). Diethylzinc was equally productive, also offering the ethyl-substituted product in quantitative conversion. There was no evidence of any C-F activation/C-H bond formation from potential β-hydride elimination, which can be a significant problem in cross-coupling reactions involving ethyl groups (Scheme 4.1b). Moreover, diphenylzinc also produced phenyl-substituted imine, which after hydrolysis and purification, was identical to the compound **3A** obtained from the reaction between 2,4-difluoroimine and phenylboronic acid in Ni-catalyzed Suzuki-Miyaura cross-coupling (Scheme 4.1c).



Scheme 4.1 Ni-catalyzed Negishi C-F cross-coupling of polyfluoroaryl imines

Isolating these newly formed compounds from the reaction mixtures turned out to be a greater challenge than we originally anticipated. While the phenyl-substituted product could be isolated in the form of aldehyde after hydrolysis and column chromatography, the same procedure could not be applied to the methylated and ethylated aldehydes. Their low molecular weights made them so volatile that solvents and other starting materials could not be fully removed without significantly compromising the yields. Isolating the products in the original imine form was not an option either as they were prone to hydrolysis in NMR solvent and upon column chromatography. Other attempts to increase the stability of these compounds, such as converting the imine (**4.1**) to the amine (**4.3**) or converting the aldehyde (**4.2**) to the alcohol (**4.4**), were successful as both **4.3** and **4.4** were detected by $^{19}F\{^{1}H\}$ NMR spectroscopy and mass spectrometry. Unfortunately, as a result of their polar functional groups, these final products and those compounds derived from starting material have very similar physical properties. Therefore, **4.3** and **4.4** could not be fully purified and analyzed.



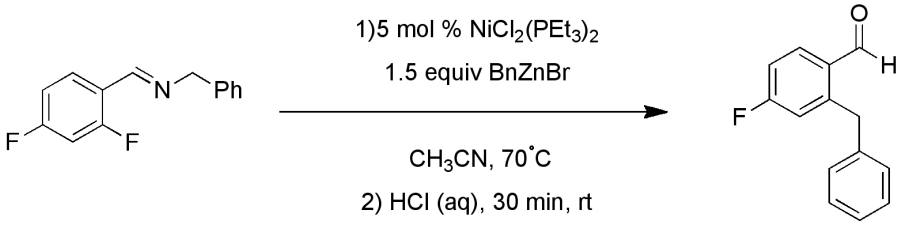
Scheme 4.2 Attempts to isolate the methylated products of C-F cross-coupling

4.2.2 Reactions with pre-formed organozinc halides

After demonstrating that Ni-catalyzed C-F cross-coupling could be used to generate alkyl-substituted aryl fluorides with organozinc reagents, we sought to test a variety of zinc reagents. Compared with diorganozinc reagents, there are more organozinc halide reagents commercially available. Among them, benzylzinc bromide is a relatively stable and inexpensive choice. The reaction between 2,4-difluoroimine, benzylzinc bromide and a catalytic amount of $NiCl_2(PEt_3)_2$ went smoothly to produce the benzyl-substituted compound in 85% yield after hydrolysis and purification. C-F activation took place exclusively at the ortho position, and no C-H activation was observed.

With this result at hand, we then looked at a number of parameters with the hope of optimizing reaction conditions so as to maximize the yield. The results are summarized in Table 4.1.

Table 4.1 Screening for Ni-catalyzed Negishi C-F cross-coupling of polyfluoroaryl imines



3a **4A**

entry	changes from conditions listed above	yield[a]
1	no change	85%
2	no $NiCl_2(PEt_3)_2$	0%
3	$NiCl_2(PPh_3)_2$ instead of $NiCl_2(PEt_3)_2$	27%
4	5 mol % $Ni(COD)_2$/ 10 mol % PEt_3	82%
5	1 mol % $NiCl_2(PEt_3)_2$	53%
6	5 mol % $Ni(COD)_2$/1,3-diisopropyl-imidazol-2-ylidene	17%
7	60˚C instead of 70˚C	0%
8	aldehyde instead of imine	0%

[a] Isolated yields.

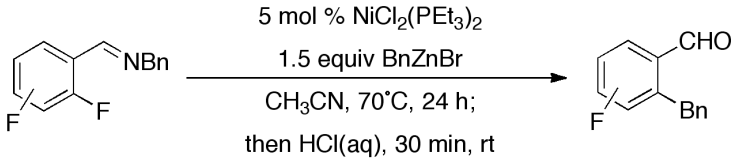
A number of Ni complexes were able to catalyze the cross-coupling. Unlike the Suzuki-Miyaura cross-coupling, in which only Ni(0) complexes were suitable for the reactions, both Ni(II) and Ni(0) complexes were competent precatalysts; however the reaction yields were influenced by the nature of the ligand. Triethylphosphine showed superior reactivity both as a preformed complex (entry 1) and when reacted with $Ni(COD)_2$ *in situ* (entry 4). On the other hand, triphenylphosphine (entry 3) and

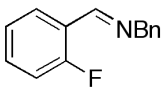
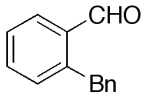
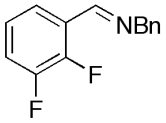
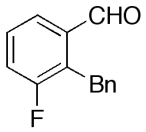
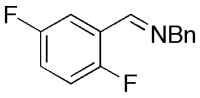
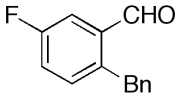
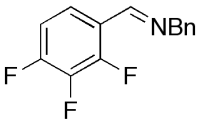
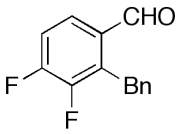
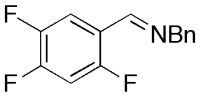
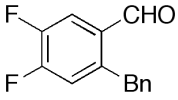
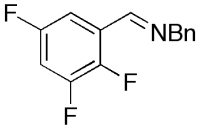
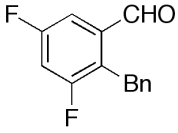
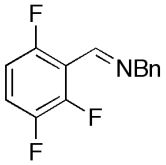
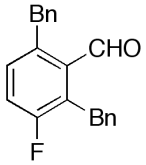
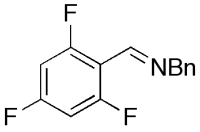
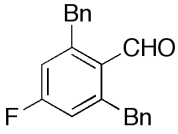
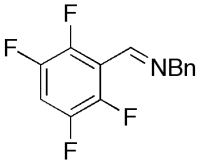
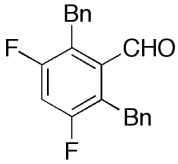
N-heterocyclic carbene (entry 6) were not as effective. For practical purposes, we chose $NiCl_2(PEt_3)_2$ as our preferred precatalyst because it was convenient to synthesize[111] and offered excellent results.

The reaction temperature played a surprisingly important role in this reaction. While 60°C was the optimal temperature for Pt-catalyzed methylation (Tables 2.1 and 2.2) and Ni-catalyzed Negishi cross-coupling of diorganozinc reagents (Scheme 4.1), no reaction took place at this temperature with benzylzinc bromide. Rather, a temperature of 70°C was required to achieve C-F cross-coupling in the latter case (entry 7). On the other hand, running reaction at 70°C instead of 60°C for diorganozinc reagents completely inhibited the product formation. Although starting materials were consumed, the strong basicity of diorganozinc reagents under these conditions resulted in the isomerization of the starting material. This observation demonstrated this reaction's sensitivity to subtle changes in the reaction conditions. Reactions were generally completed overnight (~12-14 hours), but certain substrates required longer reaction times. Reactions were carried out over 24 hours, ensuring that all of them were completed with satisfactory yields. Further extension of the reaction duration offered no additional benefits.

Our next task was to explore the scope of the fluorine substitution pattern on these polyfluoroaryl rings. Those results are summarized in Table 4.2.

Table 4.2 Scope and limitations of polyfluoroaryl imines



entry	imine	product		yield[a]
1			**4B**	84%
2			**4C**	91%
3			**4D**	33%
4			**4E**	88%
5			**4F**	84%
6			**4G**	79%
7			**4H**	90%[b]
8			**4I**	86%[b]
9			**4J**	83%[b]

[a] Isolated yield. [b] 3.0 equiv. benzylzinc bromide was used.

For all substrates, only the products of ortho C-F cross-coupling were observed. There was no evidence of C-H activation. A variety of substitution patterns were tolerated. Most substrates underwent clean cross-coupling reactions in high yields. In the case of a 2,5-difluoroimine (entry 3), the yield was considerably lower than those of other substrates, providing the expected product **4D** in only 33% yield. This was the same substrate that failed to react at all under Suzuki-type reaction conditions (entry 3, Table 3.5). Currently, we do not have a definitive explanation of why this particular substrate is so problematic in Ni-catalyzed C-F activation. Although we did not observe any nickel-hydride species in the ^{1}H NMR spectrum, it is possible that this substrate underwent rapid irreversible C-H bond activation, which would consume the Ni precatalyst.[103] This substrate had a C-H bond adjacent to both the imine directing group and a fluorine substituent, both of which had been speculated to promote C-H activation.[112] The same 2,5-difluoro substitution pattern was also present in entries 5 and 6, but these substrates underwent clean cross-coupling. If any C-H activations occurred, they were probably more easily reversible for those substrates than for 2,5-difluoroimine. More kinetic and mechanistic studies are currently underway.

For substrates with two chemically equivalent ortho C-F bonds (entries 8 and 9), di-alkylation took place. The mono-alkylated compounds for each substrate could be detected as minor products by NMR spectroscopy and mass spectrometry at incomplete conversion, but could not be isolated due to very similar physical and chemical properties. The 2,3,6-trifluoroimine (entry 7) also resulted in di-alkylation in high yield. This result is especially noteworthy because only the C-F bond at the 2-position reacted under the Suzuki-Miyaura arylation conditions (entry 7, Table 3.5). Ni-catalyzed Negishi cross-coupling was able to achieve the second C-F activation while Ni-catalyzed Suzuki-Miyaura cross-coupling was not for yet unknown reasons. We anticipated that this difference in reactivity between the two different catalytic systems would provide a

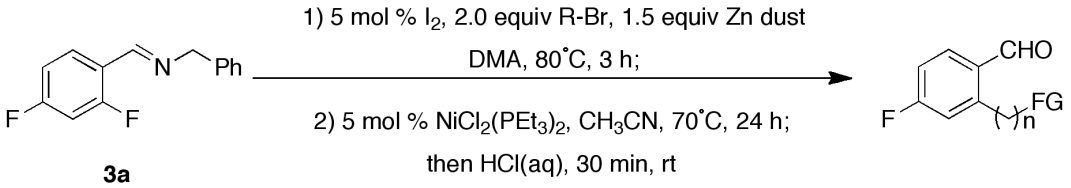
valuable opportunity for sequential Suzuki-Miyaura arylation and Negishi alkylation (*vide infra*).

We also found that this Ni-catalyzed Negishi cross-coupling procedure does not tolerate other carbon-halide bonds. Weaker C-Br and C-Cl bonds reacted first under the reaction conditions and consumed organozinc reagents.

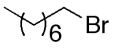
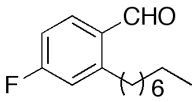
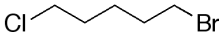
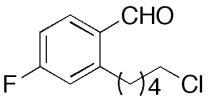
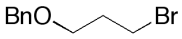
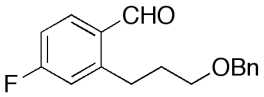
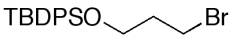
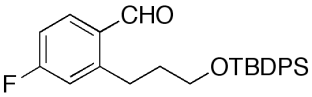
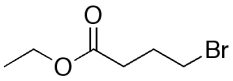
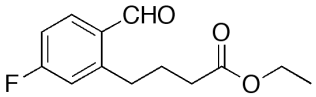
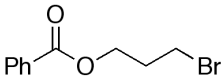
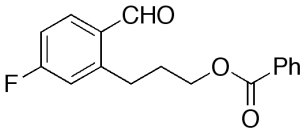
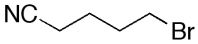
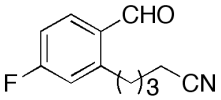
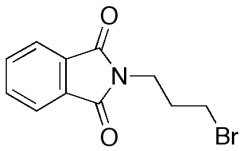
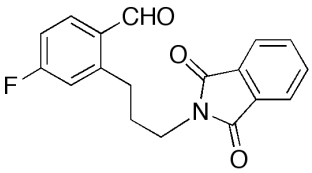
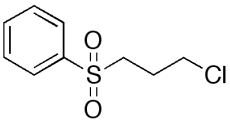
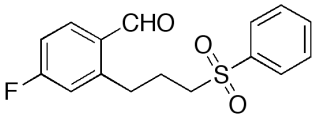
4.2.3 Reactions with organozinc halides generated *in situ*

Zinc reagents are significantly less reactive towards functional groups than lithium or magnesium reagents, offering higher synthetic utility. In addition to the limited number of diorganozinc and organozinc halides that are commercially available, the vast majority of organozinc reagents are synthesized using well-established protocols.[109] In order to test the reactivity of different organozinc reagents, we decided to utilize the Huo protocol, as it is a highly efficient general procedure for the preparation of alkylzinc halide reagents from unactivated alkyl bromides and chlorides.[110] For example, benzylzinc bromide was prepared *in situ* using 5 mol % I_2, 2.0 equiv of benzyl bromide and 1.5 equiv of zinc dust in dimethylacetamide (DMA) at 80°C for 3 hours. The resulting mixture was then added to a solution of 1.0 equiv of 2,4-difluoroimine and 5 mol % $NiCl_2(PEt_3)_2$ in CH_3CN, while maintaining the temperature at 70°C for 24 hours. The substrate underwent cross-coupling reaction, and upon hydrolysis, the same aldehyde **4A** was isolated in comparable yield (87% vs. 85% from commercially available BnZnBr solution, Scheme 4.3a and b).

Table 4.3 Scope and limitations of organozinc reagents



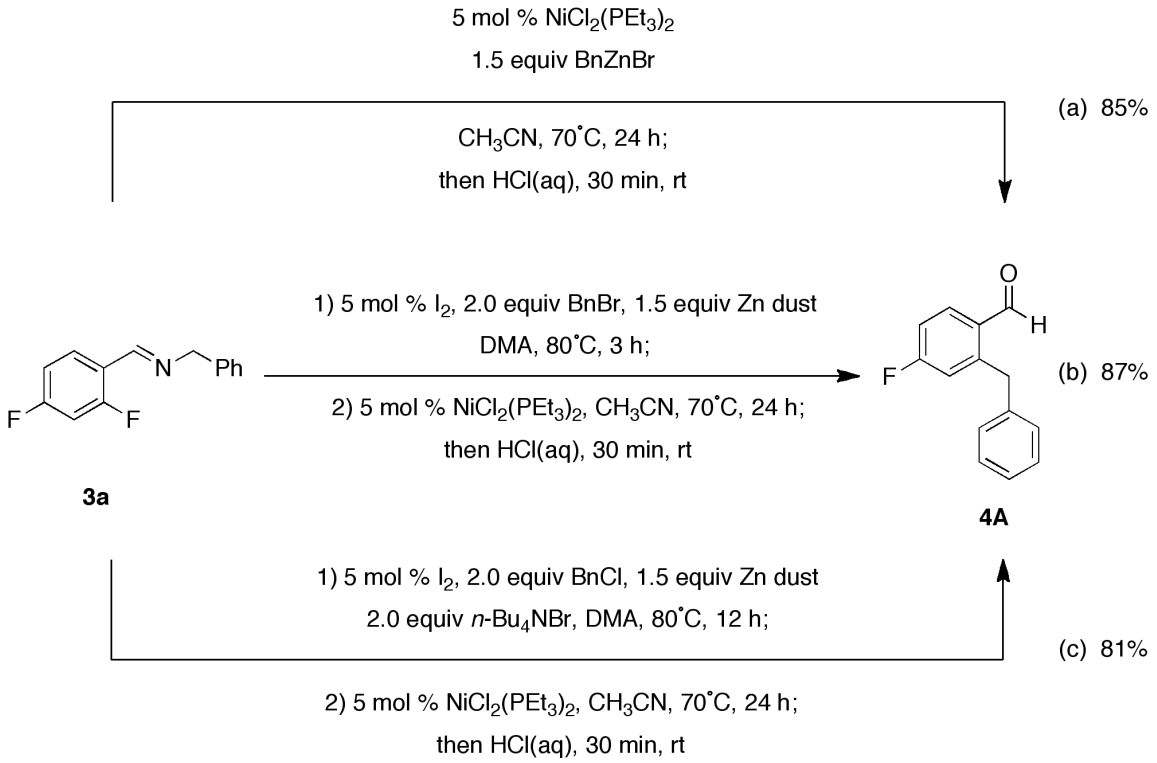
3a

entry	R-Br	product		yield[a]
1			**4K**	90%
2			**4L**	86%
3			**4M**	84%
4			**4N**	92%
5			**4O**	83%
6			**4P**	81%
7			**4Q**	75%
8			**4R**	78%
9[b]			**4S**	69%

[a] Isolated yield. [b] 2.0 equiv. *n*-tetrabutylammonium bromide was added, heated for 12 h in DMA.

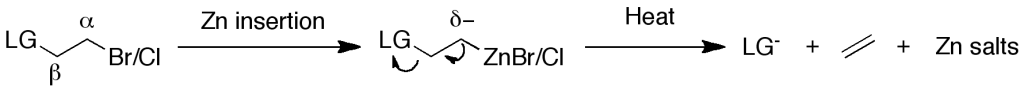
A number of alkyl bromides were subject to the catalytic conditions and the results are summarized in Table 4.3. In general, they offered good-to-excellent yields and excellent functional group compatibility. An un-functionalized alkyl bromide (entry 1) reacted in high yield. The remote alkyl chloride functionality that could have participated in alkyl-alkyl cross-coupling reactions did not react under the reaction conditions and product **4L** was successfully isolated (entry 2). The resulting exclusive coupling at the C-Br bond over the C-Cl bond was consistent with the generation of alkyl zinc reagents from alkyl bromides being faster than from chlorides. Two kinds of commonly employed protected alcohols were tested. Both benzyl (entry 3) and *t*-butyldiphenylsilyl (entry 4) groups resulted in excellent isolated yields. Both of the ester substrates tested (entries 5 and 6) reacted smoothly to generate their corresponding products. Of great concern were the remote cyano groups (entry 7) because they are generally sensitive to basic conditions and there were recent examples of them participating in cross-coupling reactions.[94] Thus, we were delighted to note that the cyano group remained intact at the end of the reaction. In addition, this methodology was compatible with phthalimide-protected amino groups (entry 8).

Having established the procedure using alkyl zinc bromides as coupling partners, we sought to further extend its synthetic utility by using alkyl chlorides as starting materials. Using benzyl chloride as the alkyl chloride source, and *n*-tetrabutylammonium bromide as the halide transfer salt, the benzylzinc reagent was successfully generated and applied in Ni-catalyzed C-F cross-coupling. The aldehyde **4A** was isolated in yield (81%, Scheme 4.3c), comparable to that obtained using the corresponding alkyl bromide (87%, Scheme 4.3a). This method could be used in cases in which alkyl bromides were not readily available, such as entry 9 in Table 4.3. Although the yield was slightly lower than in the other cases, the sulfone-containing substrate nevertheless underwent clean transformation and resulted in a synthetically useful yield.



Scheme 4.3 Summary of Ni-catalyzed Negishi cross-coupling with different organozinc reagents

There are several functional groups/moieties that were not compatible with our Ni-catalyzed C-F activation. First, this method did not tolerate acidic protons, such as unprotected O-H, N-H or S-H bonds. Although C-Zn bonds have significantly more covalent character than C-Li or C-Mg bonds,[113] acidic X-H bonds would still protonate the organozinc halide reagent. Second, this method did not tolerate substrates in which a potential leaving group was attached to the β-carbon (Scheme 4.4). When this particular moiety was present in alkyl halides, Bernet-Vasella-type reaction took place, and no C-F activation occurred. Third, some sulfur-containing functional groups proved once again problematic. Remote sulfide and sulfoxide groups had prohibitive effect; no C-F activation took place and starting materials were recovered. On the other hand, a sulfone group could be incorporated efficiently without interference with the catalytic system (entry 9 in Table 4.3).



LG = OR, OC(O)R, NR_2, CN

Scheme 4.4 Decomposition of organozinc halides

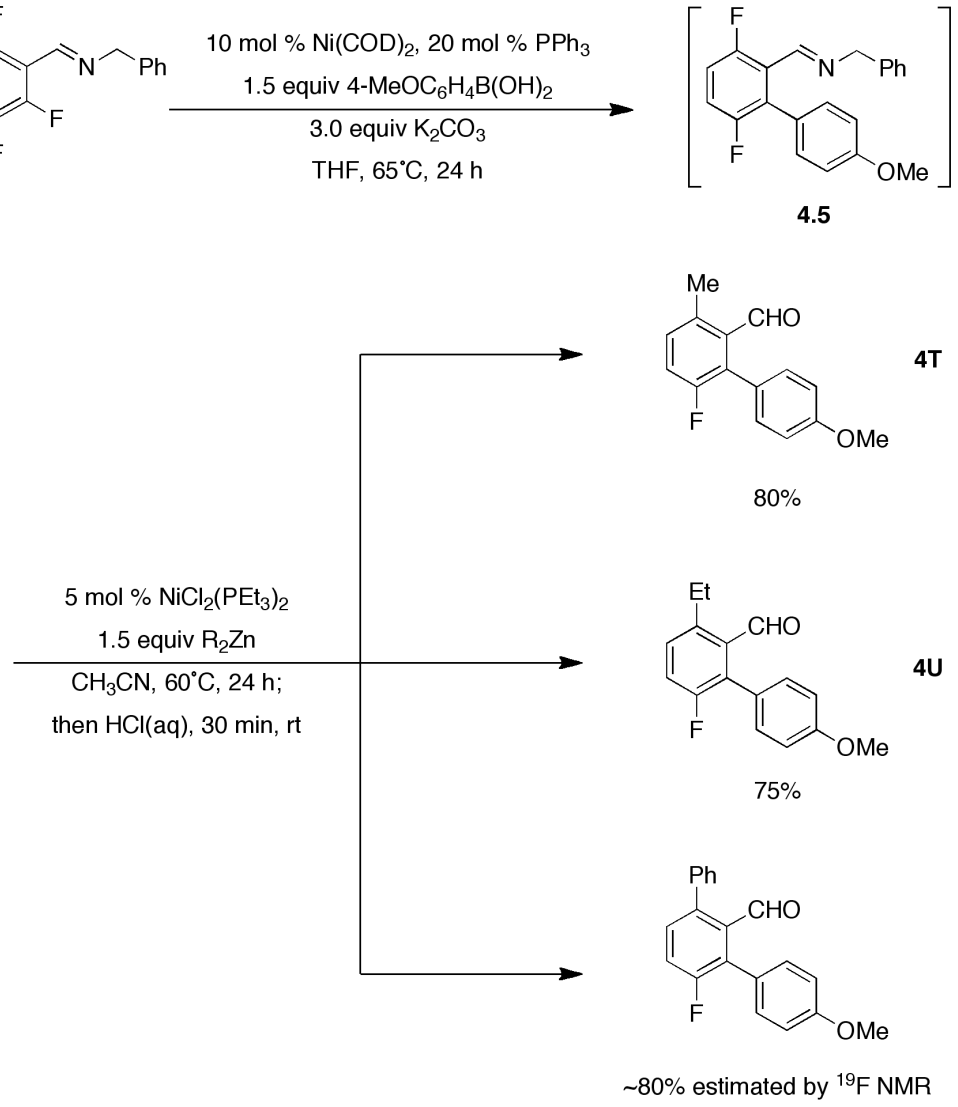
The reaction conditions were more accommodating than those of Ni-catalyzed Suzuki-Miyaura reactions. Rigorously dried solvents were not required, since DMA and CH_3CN could be used as received from commercial sources, without further drying or purification. In addition, though the reactions were not inhibited by trace amounts of air deliberately introduced before the reaction commenced, the reactions could not be successfully carried out under open reflux conditions.

4.3 Ni-catalyzed sequential C-F cross-coupling of polyfluoroaryl imines

Given that 2,3,6-trifluoroimine underwent mono-arylation under Suzuki-Miyaura conditions but underwent di-alkylation under Negishi conditions, we envisioned using two different coupling partners as a means to generate highly functionalized fluorine-containing building blocks, even though the exact cause of the difference in reactivity of the C-F bonds at the 2- and 6- position was unclear.

2,3,6-Trifluoroimine was subjected to Suzuki-Miyaura cross-coupling conditions in THF with 4-methoxyphenylboronic acid, and C-F activation took place exclusively at the 2-position. After removing the solvent under reduced pressure and re-dissolving the crude intermediate **4.5** in CH_3CN, we subjected the crude material to Negishi cross-coupling conditions with dimethylzinc, diethylzinc and diphenylzinc. Upon hydrolysis, aldehydes **4T** and **4U** were isolated in 80% and 75%, respectively. In the case of diphenylzinc, the phenyl-substituted aldehyde was produced in ~80% conversion, but could not be fully

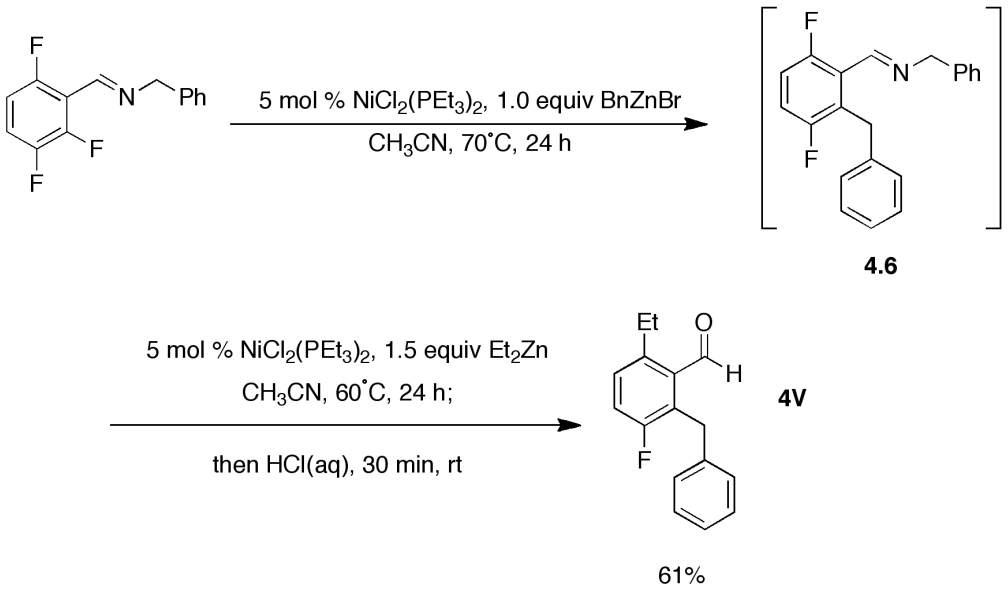
separated from the aldehyde derived from **4.5** by column chromatography due to their similar physical properties.



Scheme 4.5 Sequential Ni-catalyzed Suzuki-Miyaura/Negishi cross-coupling

The same starting material could also be subjected to two sequential Negishi reactions; however, the reactions were executed differently due to a number of practical considerations. In Ni-catalyzed alkylation (Table 4.2), 2,4,6-trifluoroimine and 2,3,5,6-tetrafluoroimine have two chemically equivalent ortho C-F bonds; the second C-F activation proceeds at a rate comparable with that of the first C-F activation. This is not

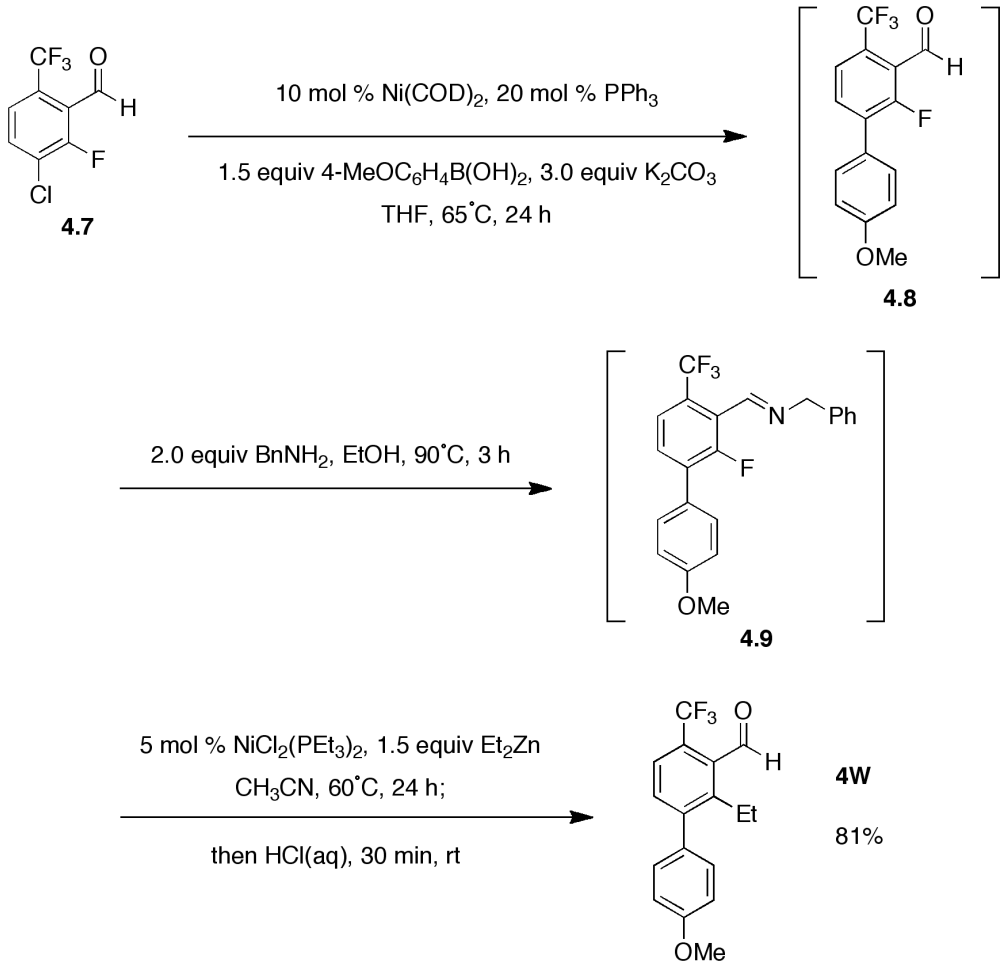
the case for 2,3,6-trifluoroimine however; the C-F bond at the 2-position is significantly more reactive than the C-F bond at the 6-position. The activation of the latter only begins once the activation of the former is almost complete. Based on this observation, we decided to limit the amount of benzylzinc bromide to 1.0 equiv as we tried to minimize the presence of di-alkylation. After the first reaction, the crude product contained approximately 80-85% mono-alkylation product and 15-20% unreacted starting material. After removing solvent and re-dissolving intermediate **4.6** in CH_3CN, we subjected it to an excess amount of diethylzinc in the presence of a catalytic amount of $NiCl_2(PEt_3)_2$. ^1H and $^{19}F\{^1H\}$ NMR spectroscopy, as well as mass spectrometry, indicated that all remaining ortho C-F bonds were replaced with ethyl groups. The final product **4V** was isolated in 61% yield after column chromatography.



Scheme 4.6 Sequential Ni-catalyzed Negishi/Negishi cross-coupling

We decided to combine C-F cross-coupling with cross-coupling of different carbon-halide bonds in order to synthesize highly functionalized, structurally diverse fluorine-containing molecules. In the first example, aldehyde **4.7** was subjected to Suzuki-Miyaura cross-coupling conditions to activate the aryl C-Cl bond and forge a new

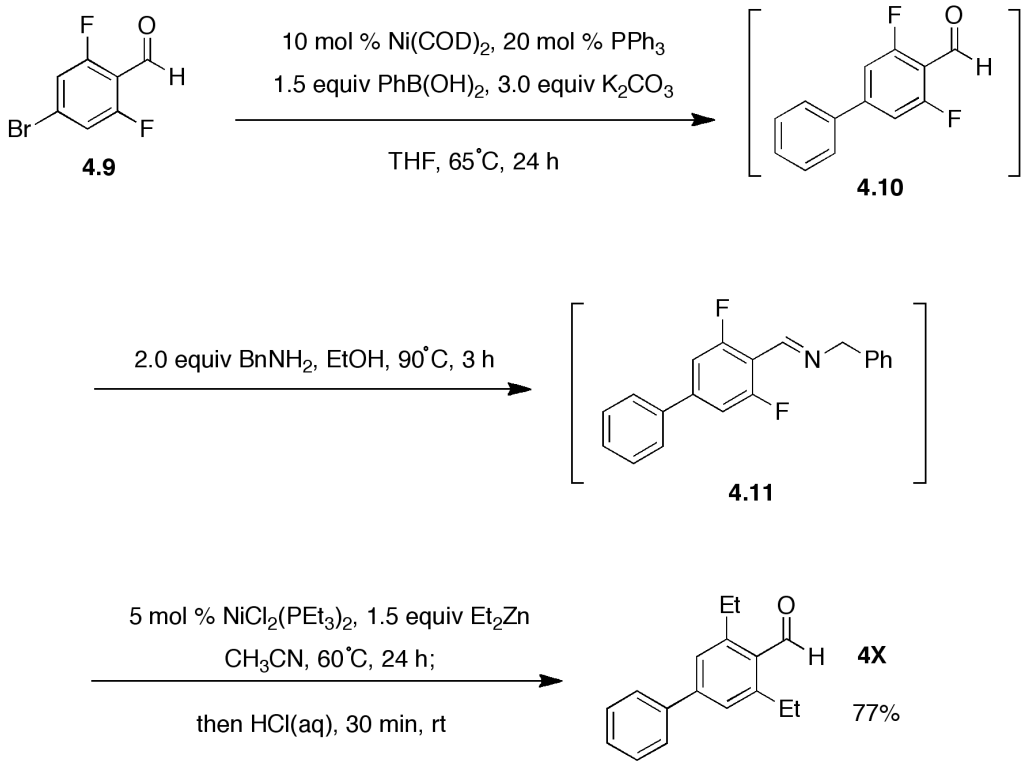
C-C bond while leaving C-F bonds intact. After converting the crude aldehyde **4.8** to imine **4.9**, it was then subjected to Negishi conditions to activate the ortho C-F bond. The final product **4W** contained a highly functionalized biaryl bearing a trifluoromethyl group, which is increasingly common in pharmaceutical agents.[91]



Scheme 4.7 Sequential Ni-catalyzed C-Cl/C-F cross-coupling

In the second example, the C-Br bond was activated first and replaced by a phenyl group. The crude aldehyde was converted into the corresponding imine, and both ortho C-F bonds were replaced with ethyl groups under Negishi coupling conditions. Although the final aldehyde **4X** no longer contained an aryl fluoride moiety, its

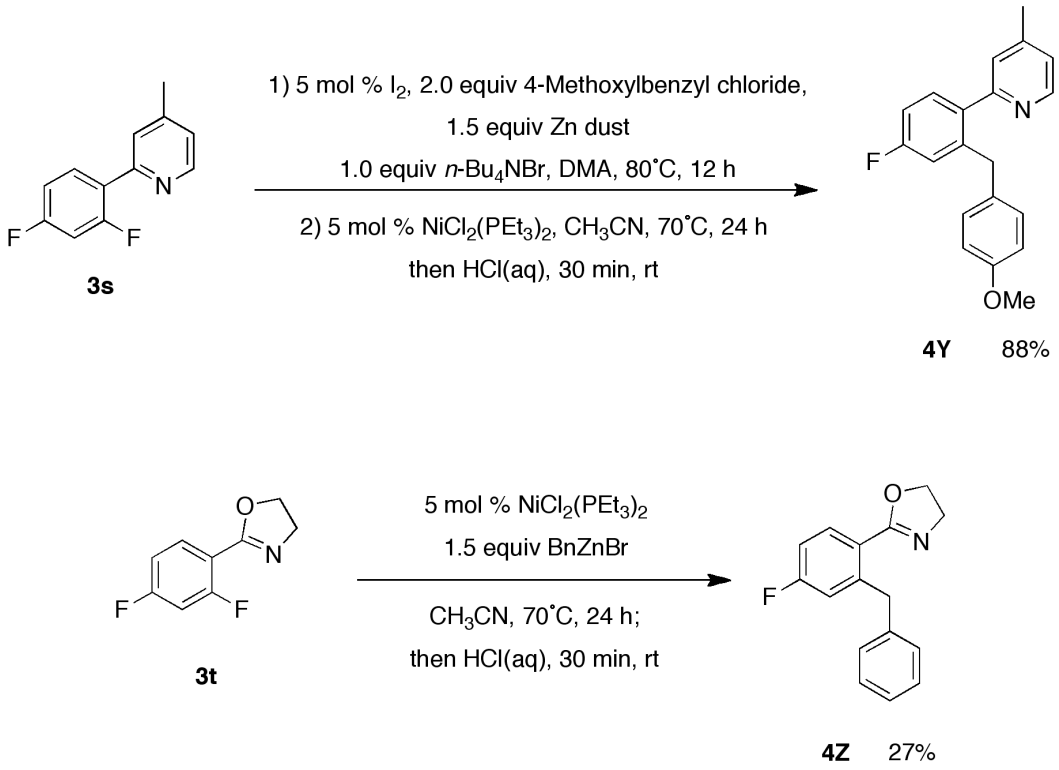
1,2,3,5-tetrasubstituted benzene structure was complementary to our previously synthesized 1,2,3,4-tetrasubstituted benzene rings.



Scheme 4.8 Sequential Ni-catalyzed C-Br/C-F cross-coupling

4.4 Ni-catalyzed Negishi cross-coupling of polyfluoroarenes with different directing groups

In order to expand substrate scope beyond imines, we tested two commonly employed directing groups. As in the case of Ni-catalyzed Suzuki-Miyaura cross-coupling, appropriate catalytic conditions were applied without further optimization. Whereas pyridine-directed 2,4-difluoroarene reacted smoothly with 4-methoxybenzyl zinc chloride to generate **4Y** in 88% yield, oxazoline-directed 2,4-difluoroarene underwent clean coupling reaction with benzylzinc bromide, resulting in the formation of **4Z** in 27% yield. The remaining mass balances were recovered starting materials.



Scheme 4.9 Ni-catalyzed Negishi C-F cross-coupling of polyfluoroarenes

4.5 Conclusions

This chapter describes a new way to generate alkyl-substituted aryl fluorides via Ni-catalyzed Negishi cross-coupling. It reveals how polyfluoroaryl imines with diverse fluorine substitution patterns are able to react with organozinc reagents with various functional groups, and how this methodology has high selectivity for ortho C-F activation and excellent functional group tolerance. Sequential cross-coupling reactions incorporating different carbon-halide bonds and coupling partners are also described. Moreover, it shows how directing groups other than imine can be employed to produce highly functionalized aryl fluorides.

4.6 Experimental

General Procedures. Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled glovebox (O_2 < 2 ppm). NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 600 spectrometers. ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts are reported in parts per million and referenced to residual solvent. $^{19}F\{^{1}H\}$ NMR spectra are reported in parts per million and referenced to $CFCl_3$ (0 ppm). Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets. All spectra were obtained at 25°C. Mass spectra were recorded on a Kratos MS-50 mass spectrometer.

Materials and Methods. Acetone-d_6 and methanol-d_4 were purchased from Cambridge Isotope Laboratories and used as received. Anhydrous acetonitrile (CH_3CN) was purchased from Aldrich and freeze-pump-thawed three times before bringing into the glovebox and was used without further purification. All imines were prepared by a published procedure.[76] Benzylzinc bromide solution (0.5 M in THF), dimethylzinc solution (2.0 M in toluene), diethylzinc solution (1.0 M in hexane), diphenylzinc, zinc dust (>99% powder), *N*-dimethylacetamide (DMA), *n*-tetrabutylammonium bromide, benzyl 3-bromopropyl ether, thiophenol, 1-bromo-3-chloropropane, 4-methoxylbenzyl chloride were purchased from Aldrich and used without further purification. 1-bromooctane, (2-bromoethyl)benzene, 1-bromo-5-chloropentane, ethyl 3-bromobutanoate, 3-bromo-1-propanol, benzoic acid, 5-bromovaleronitrile, N-(3-bromopropyl)phthalimide, 3-chloro-2-fluoro-6-(trifluoromethyl)benzaldehyde were purchased from Alfa Aesar and used without further purification. *Tert*-butyldiphenylchlorosilane was purchased from TCI America and used without

further purification. 4-methoxyphenylboronic acid was purchased from Matrix Scientific and used without further purification. Bis(triethylphosphine)nickel(II) chloride [$Ni(PEt_3)_2Cl_2$],[111] (3-bromopropoxy)(*t*-butyl)diphenylsilane,[114] ((3-chloropropyl)sulfonyl)benzene[115] were synthesized according to literature procedures.

General experimental procedure for catalytic C-F cross coupling reactions:

Reaction conditions A (reaction with benzylzinc bromide solution/Table 4.2/Scheme 4.3a): In a 20 mL vial, imine (0.5 mmol, 1.0 equiv), $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %), and benzylzinc bromide solution (0.5 M in THF) (1.5 mL, 0.75 mmol, 1.5 equiv) (3.0 mL, 1.5 mmol, 3.0 equiv for entries 8, 9 and 10 in Table 4.2) were dissolved in acetonitrile (10 mL). The vial was capped, removed from the glovebox and subsequently heated to 70°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

Compound **4Z** was synthesized in a similar manner from **3t** and benzylzinc bromide. After aqueous HCl addition, saturated aqueous sodium bicarbonate ($NaHCO_3$) was added at the end of the stirring to neutralize the acid. Column chromatography was performed using *n*-pentane: ethyl acetate = 20: 3 as eluant.

Reaction conditions B (reaction with organozinc halide generated *in situ*/Table 4.3/Scheme 4.3b/c): This protocol was adopted from a previously reported procedure.[110]

A dry 25 mL one-neck round-bottom flask was charged with dry DMA (5 mL), I_2 (7 mg, 0.025 mmol, 5 mol %) and zinc dust (50 mg, 0.75 mmol, 1.5 equiv) under N_2. The mixture was stirred at room temperature for 5 min until the iodine color disappeared. Alkyl bromide (1.0 mmol, 2.0 equiv) was added via syringe either neat or dissolved in 1 mL of DMA and the resulting mixture was heated for 3 h at 80°C. The mixture was then added to a 10 mL CH_3CN solution of 2,4-difluoroimine (116 mg, 0.5 mmol, 1.0 equiv) and $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %), while maintaining the temperature at 70°C for 24 hours. The mixture was cooled to room temperature and stirred for 30 min following the addition of aqueous hydrochloric acid (3 M). The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluent unless otherwise specified). For entry 3 and 4, *n*-pentane: ethyl acetate = 25: 1 was used as eluent; for entry 5 and 6, *n*-pentane: ethyl acetate = 50: 1 was used as eluent; for entry 8, *n*-pentane: ethyl acetate = 10: 1 was used as eluent; for entry 9, additional *n*-tetrabutylammonium bromide (87 mg, 1.0 mmol, 2.0 equiv) was added and the DMA mixture was heated for 12 h at 80°C instead of 3 h, and *n*-pentane: ethyl acetate = 10: 1 was used as eluent.

Compound **4Y** was synthesized in a similar manner from **3s** and 4-methoxylbenzyl chloride. Additional *n*-tetrabutylammonium bromide (87 mg, 1.0 mmol, 2.0 equiv) was added and the DMA mixture was heated for 12 h at 80°C instead of 3 h. After aqueous HCl addition, saturated aqueous sodium bicarbonate ($NaHCO_3$) was added at the end of the stirring to neutralize the acid. Column chromatography was performed using *n*-pentane: ethyl acetate = 20: 1 as eluant.

Reaction conditions C (sequential reaction/Scheme 4.5): In a 20 mL vial, 2,3,6-trifluoroimine (125 mg, 0.5 mmol, 1.0 equiv), $Ni(COD)_2$ (13.8 mg, 0.05 mmol, 10 mol %), PPh_3 (26.2 mg, 0.1 mmol, 20 mol %) and 4-methoxyphenylboronic acid (115 mg, 0.75 mmol, 1.5 equiv) were dissolved in THF (10 mL). K_2CO_3 (150 mg, 3.0 equiv) was added to the resulting solution. The vial was capped, removed from the glovebox and subsequently heated to 65°C for 24 h. The solution was cooled to room temperature and then partitioned between water (100 mL) and diethyl ether (50 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude imine product. The compound was brought back to the glovebox, dissolved in an acetonitrile solution (10 mL) of $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %) and diorganozinc (0.75 mmol, 1.5 equiv) in a 20 mL vial. The vial was capped, removed from the glovebox and subsequently heated to 60°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

Reaction conditions D (sequential reaction/Scheme 4.6): In a 20 mL vial, 2,3,6-trifluoroimine (125 mg, 0.5 mmol, 1.0 equiv), $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %), and benzylzinc bromide solution (0.5 M in THF) (1.0 mL, 0.5 mmol, 1.0 equiv) were dissolved in acetonitrile (10 mL). The vial was capped, removed from the glovebox and subsequently heated to 70°C for 24 h. The solution was cooled to room temperature and then partitioned between water (100 mL) and diethyl ether (50 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude imine product. The compound was brought back to the

glovebox, dissolved in an acetonitrile solution (10 mL) of $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %) and diethyl zinc (0.375 mL, 0.75 mmol, 1.5 equiv) in a 20 mL vial. The vial was capped, removed from the glovebox and subsequently heated to 60°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

Reaction conditions E (sequential reaction/Scheme 4.7): In a 20 mL vial, 3-chloro-2-fluoro-6-(trifluoromethyl)benzaldehyde (113 mg, 0.5 mmol, 1.0 equiv), $Ni(COD)_2$ (13.8 mg, 0.05 mmol, 10 mol %), PPh_3 (26.2 mg, 0.1 mmol, 20 mol %) and 4-methoxyphenylboronic acid (115 mg, 0.75 mmol, 1.5 equiv) were dissolved in THF (10 mL). K_2CO_3 (150 mg, 3.0 equiv) was added to the resulting solution. The vial was capped, removed from the glovebox and subsequently heated to 65°C for 24 h. The solution was cooled to room temperature and then partitioned between water (100 mL) and diethyl ether (50 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude C-Cl cross-coupling product. The corresponding imine was synthesized and brought back to the glovebox. The imine was then dissolved in an acetonitrile solution (10 mL) of $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %) and diethyl zinc (0.375 mL, 0.75 mmol, 1.5 equiv) in a 20 mL vial. The vial was capped, removed from the glovebox and subsequently heated to 60°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude

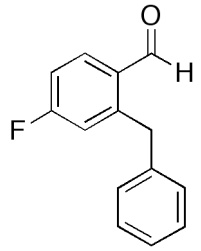
aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

Reaction conditions F (sequential reaction/Scheme 4.8): In a 20 mL vial, 4-bromo-2,6-difluorobenzaldehyde (111 mg, 0.5 mmol, 1.0 equiv), $Ni(COD)_2$ (13.8 mg, 0.05 mmol, 10 mol %), PPh_3 (26.2 mg, 0.1 mmol, 20 mol %) and phenylboronic acid (92 mg, 0.75 mmol, 1.5 equiv) were dissolved in THF (10 mL). K_2CO_3 (150 mg, 3.0 equiv) was added to the resulting solution. The vial was capped, removed from the glovebox and subsequently heated to 65°C for 24 h. The solution was cooled to room temperature and then partitioned between water (100 mL) and diethyl ether (50 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude C-Br cross-coupling product. The corresponding imine was synthesized and brought back to the glovebox. The imine was then dissolved in an acetonitrile solution (10 mL) of $NiCl_2(PEt_3)_2$ (9.1 mg, 0.025 mmol, 5 mol %) and diethyl zinc (0.375 mL, 0.75 mmol, 1.5 equiv) in a 20 mL vial. The vial was capped, removed from the glovebox and subsequently heated to 60°C for 24 h. The solution was cooled to room temperature, aqueous hydrochloric acid (3 M) was added, and the mixture was stirred at room temperature for 30 minutes. The mixture was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to provide the crude aldehyde product. Further separation by column chromatography provided clean product (SiO_2, 230-400 mesh, *n*-pentane: ethyl acetate = 100: 1 as eluant).

Analytical data for products of C-F cross-coupling:

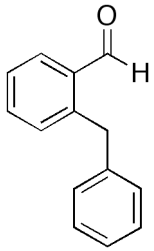
The resonances at δ2.84 in d_6-acetone and δ4.87 in d_4-methanol are due to residual H_2O from the solvent (the peaks appear in the absence of cross-coupling products). The exact amount depends on the batch.

(4A) 2-benzyl-4-fluorobenzaldehyde (colorless oil, 87%)



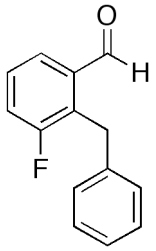
^{1}H NMR (methanol-d_4, 600 MHz): δ 10.18 (s, 1H), 7.94 (dd, 1H, J = 8.70 Hz, J = 6.14 Hz), 7.29-7.26 (m, 2H), 7.21-7.16 (m, 4H), 7.03 (dd, 1H, J = 9.73 Hz, J = 2.56 Hz), 4.47 (s, 2H). ^{19}F{^{1}H} NMR (methanol-d_4, 282 MHz): δ -105.8 (s, 1F). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 192.7 (s), 167.4 (d, J = 254.7 Hz), 148.5 (d, J = 8.6 Hz), 141.2 (s), 136.2 (d, J = 9.7 Hz), 132.3 (s), 130.0 (s), 129.8 (s), 127.6 (s), 119.4 (d, J = 22.4 Hz), 115.2 (d, J = 21.8 Hz), 38.6 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO$: 214.0794; found: 214.0794.

(4B) 2-benzylbenzaldehyde (colorless oil, 84%)



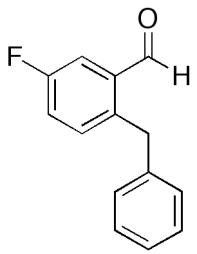
^{1}H NMR (methanol-d_4, 600 MHz): δ 10.20 (s, 1H), 7.85 (d, 1H, J = 7.68 Hz), 7.54 (t, 1H, J = 8.70 Hz), 7.41 (t, 1H, J = 7.68 Hz), 7.30 (d, 1H, J = 7.68 Hz), 7.23-7.21 (m, 2H), 7.16-7.14 (m, 3H), 4.43 (s, 2H). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 194.2 (d, J = 6.88 Hz), 144.7 (s), 142.2 (s), 135.5 (s), 135.2 (s), 133.1 (s), 133.0 (s), 129.9 (s), 129.6 (s), 128.2 (s), 127.3 (s), 38.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{12}O$: 196.0888; found: 196.0889.

(4C) 2-benzyl-3-fluorobenzaldehyde (colorless oil, 91%)



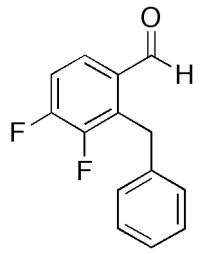
^{1}H NMR (methanol-*d*$_4$, 600 MHz): δ 10.21 (s, 1H), 7.73 (d, 1H, J = 7.68 Hz), 7.51-7.49 (m, 1H), 7.43 (t, 1H, J = 9.43 Hz), 7.23-7.21 (m, 2H), 7.16-7.14 (m, 3H), 4.49 (s, 2H). ^{19}F{^{1}H} NMR (methanol-*d*$_4$, 282 MHz): δ -118.4 (s, 1F). ^{13}C{^{1}H} NMR (methanol-*d*$_4$, 150 MHz): δ 193.2 (d, J = 6.88 Hz), 163.0 (d, J = 245.5 Hz), 141.3 (s), 137.4 (d, J = 4.0 Hz), 131.0 (d, J = 16.0 Hz), 129.8 (d, J = 8.6 Hz), 129.6 (s), 129.5 (s), 129.3 (d, J = 3.4 Hz), 127.4 (s), 122.1 (s), 29.9 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO$: 214.0794; found: 214.0795.

(4D) 2-benzyl-5-fluorobenzaldehyde (colorless oil, 33%)



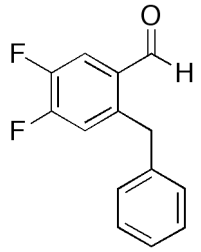
^{1}H NMR (methanol-*d*$_4$, 600 MHz): δ 10.23 (s, 1H), 7.58-7.57 (m, 1H), 7.27-7.25 (m, 3H), 7.18-7.09 (m, 5H), 4.44 (s, 2H). ^{19}F{^{1}H} NMR (methanol-*d*$_4$, 282 MHz): δ -119.2 (s, 1F). ^{13}C{^{1}H} NMR (methanol-*d*$_4$, 150 MHz): δ 192.6 (s), 163.2 (d, J = 246.1 Hz), 135.1 (s), 130.0 (s), 129.8 (s), 129.6 (s), 127.4 (d, J = 35.0 Hz), 122.0 (d, J = 21.2 Hz), 117.6 (d, J = 22.4 Hz), 115.8 (d, J = 21.2 Hz), 113.7 (d, J = 23.5 Hz), 38.0 (s). HRMS (EI) m/z calculated for $C_{14}H_{11}FO$: 214.0794; found: 214.0794.

(4E) 2-benzyl-3,4-difluorobenzaldehyde (colorless oil, 88%)



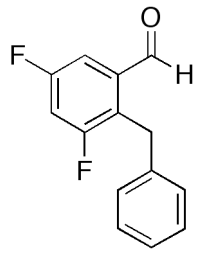
^{1}H NMR (methanol-*d*$_4$, 600 MHz): δ 10.12 (s, 1H), 7.77-7.75 (m, 1H), 7.38 (dd, 1H, J = 17.4 Hz, J = 9.22 Hz), 7.25-7.23 (m, 2H), 7.16-7.14 (m, 3H), 4.53 (s, 2H). ^{19}F{^{1}H} NMR (methanol-*d*$_4$, 282 MHz): δ -130.1 (d, 1F, J = 18.4 Hz), 143.0 (d, 1F, J = 20.6 Hz). ^{13}C{^{1}H} NMR (methanol-*d*$_4$, 150 MHz): δ 192.2 (s), 155.4 (dd, J = 271.3 Hz, J = 14.3 Hz), 150.7 (dd, J = 246.7 Hz, J = 12.6 Hz), 140.6 (s), 134.0 (d, J = 12.6 Hz), 130.4 (dd, J = 8.6 Hz, J = 4.0 Hz), 129.8 (s), 129.6 (s), 129.4 (s), 127.6 (s), 117.0 (d, J = 18.4 Hz), 30.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O$: 232.0700; found: 232.0700.

(4F) 2-benzyl-4,5-difluorobenzaldehyde (colorless oil, 84%)



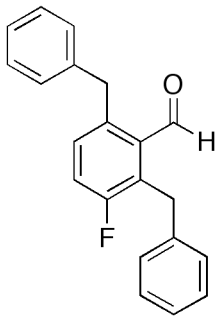
^{1}H NMR (methanol-*d*$_4$, 600 MHz): δ 10.16 (s, 1H), 7.77-7.76 (m, 1H), 7.28-7.14 (m, 6H), 4.42 (s, 2H). ^{19}F{^{1}H} NMR (methanol-*d*$_4$, 282 MHz): δ -131.1 (d, 1F, J = 22.9 Hz), 141.8 (d, 1F, J = 20.6 Hz). ^{13}C{^{1}H} NMR (methanol-*d*$_4$, 150 MHz): δ 192.2 (s), 154.9 (dd, J = 256.4 Hz, J = 13.2 Hz), 150.2 (dd, J = 248.4 Hz, J = 13.2 Hz), 141.3 (s), 130.0 (s), 129.8 (s), 127.7 (s), 121.6 (d, J = 17.8 Hz), 120.5 (d, J = 17.8 Hz), 120.2 (d, J = 17.8 Hz), 117.3 (d, J = 18.9 Hz), 30.8 (s). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O$: 232.0700; found: 232.0700.

(4G) 2-benzyl-3,5-difluorobenzaldehyde (colorless oil, 79%)



^{1}H NMR (methanol-d_4, 600 MHz): δ 10.19 (s, 1H), 7.47-7.45 (m, 1H), 7.32-7.30 (m, 1H), 7.23 (t, 2H, J = 7.2 Hz), 7.15-7.14 (m, 3H), 4.44 (s, 2H). ^{19}F{^{1}H} NMR (methanol-d_4, 282 MHz): δ -113.2 (d, 1F, J = 9.2 Hz), 114.4 (d, 1F, J = 6.9 Hz). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 191.5 (s), 163.0 (ddd, J = 248.4 Hz, J = 21.8 Hz, J = 10.9 Hz), 141.0 (s), 138.2 (dd, J = 6.9 Hz, J = 4.6 Hz), 129.8 (s), 129.3 (s), 129.2 (s), 127.7 (d, J = 4.0 Hz), 127.6 (s), 114.4 (d, J = 21.8 Hz, J = 3.4 Hz), 110.2 (dd, J = 28.1 Hz, J = 25.8 Hz), 29.6 (d, J = 4.0 Hz). HRMS (EI) m/z calculated for $C_{14}H_{10}F_2O$: 232.0700; found: 232.0700.

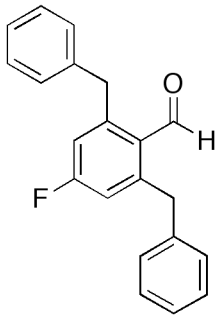
(4H) 2,6-dibenzyl-3-fluorobenzaldehyde (colorless oil, 90%)



^{1}H NMR (methanol-d_4, 600 MHz): δ 10.40 (s, 1H), 7.32 (t, 1H, J = 8.70 Hz), 7.26-7.20 (m, 5H), 7.16-7.08 (m, 6H), 4.37 (s, 2H), 4.32 (s, 2H). ^{19}F{^{1}H} NMR (methanol-d_4, 282 MHz): δ -120.5 (s, 1F). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 194.5 (m), 161.5 (d, J = 244.4 Hz), 142.2 (s), 141.3 (s), 141.0 (d, J = 4.0 Hz), 135.5 (s), 132.9 (d, J = 8.0 Hz), 131.1 (d, J = 16.1 Hz), 130.2 (s), 129.8 (s), 129.7 (s), 129.6 (s), 129.4 (s), 127.4 (d, J =

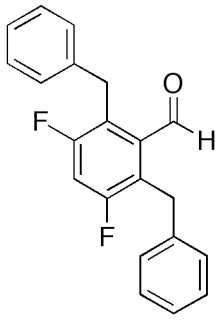
13.8 Hz), 120.9 (d, J = 23.5 Hz), 39.1 (s), 30.7 (d, J = 5.2 Hz). HRMS (EI) m/z calculated for $C_{21}H_{17}FO$: 304.1263; found: 304.1265.

(4I) 2,6-dibenzyl-4-fluorobenzaldehyde (colorless oil, 86%)



^{1}H NMR (methanol-d_4, 600 MHz): δ 10.42 (s, 1H), 7.26 (t, 4H, J = 7.70 Hz), 7.18 (t, 2H, J = 7.20 Hz), 7.12 (d, 4H, J = 7.20 Hz), 4.38 (s, 4H). ^{19}F{^{1}H} NMR (methanol-d_4, 282 MHz): δ -107.0 (s, 1F). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 193.4 (m), 166.3 (d, J = 254.1 Hz), 149.3 (d, J = 9.6 Hz), 141.6 (s), 130.2 (s), 130.0 (s), 129.8 (s), 127.6 (s), 118.0 (d, J = 21.8 Hz), 39.7 (s). HRMS (EI) m/z calculated for $C_{21}H_{17}FO$: 304.1263; found: 304.1265.

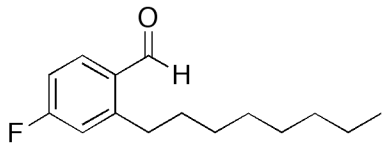
(4J) 2,6-dibenzyl-3,5-difluorobenzaldehyde (colorless oil, 83%)



^{1}H NMR (methanol-d_4, 600 MHz): δ 10.37 (s, 1H), 7.32 (t, 1H, J = 9.22 Hz), 7.24-7.22 (m, 4H), 7.16-7.09 (m, 6H), 4.33 (s, 4H). ^{19}F{^{1}H} NMR (methanol-d_4, 282 MHz): δ -110.8 (s, 2F). ^{13}C{^{1}H} NMR (methanol-d_4, 150 MHz): δ 193.6 (m), 161.5 (dd, J = 247.2 Hz, J = 13.2 Hz), 141.0 (s), 129.7 (s), 129.4 (s), 129.3 (s), 129.3 (s), 127.5 (s), 108.9 (t, J

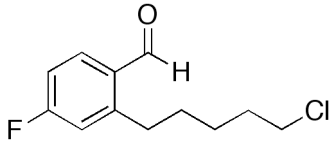
= 28.1 Hz), 30.3 (s). HRMS (EI) m/z calculated for $C_{21}H_{16}F_2O$: 322.1169; found: 322.1169.

(4K) 4-fluoro-2-octylbenzaldehyde (colorless oil, 90%)



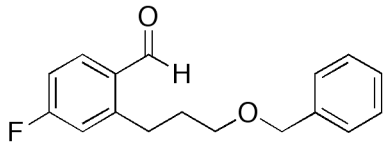
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.25 (s, 1H), 7.94 (d, 1H, J = 6.14 Hz), 7.18-7.16 (m, 2H), 1.14-1.08 (m, 14H), 0.88 (t, 3H, J = 6.14 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.0 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.4 (s), 166.5 (d, J = 253.6 Hz), 150.1 (d, J = 9.2 Hz), 135.3 (d, J = 10.3 Hz), 131.7 (d, J = 2.3 Hz), 118.4 (d, J = 21.2 Hz), 114.4 (d, J = 22.4 Hz), 32.9 (s), 32.8 (s), 32.8 (s), 32.7 (s), 32.4 (s), 30.3 (s), 23.4 (s), 14.4 (s). HRMS (EI) m/z calculated for $C_{15}H_{21}FO$: 236.1576; found: 236.1576.

(4L) 2-(5-chloropentyl)-4-fluorobenzaldehyde (colorless oil, 86%)



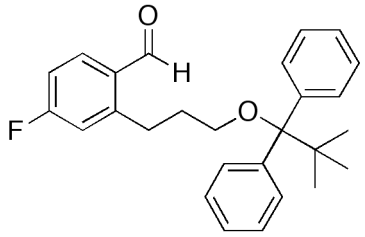
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.25 (s, 1H), 7.97-7.95 (m, 1H), 7.20-7.18 (m, 2H), 3.62 (t, 2H, J = 6.66 Hz), 3.12 (t, 2H, J = 7.68 Hz), 1.83 (q, 2H, 6.66 Hz), 1.67 (q, 2H, J = 7.68 Hz), 1.56 (q, 2H, J = 7.17 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -107.0 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.6 (s), 166.5 (d, J = 253.6 Hz), 149.8 (d, J = 8.6 Hz), 135.7 (d, J = 10.3 Hz), 131.8 (d, J = 2.3 Hz), 118.5 (d, J = 21.8 Hz), 114.5 (d, J = 21.8 Hz), 45.7 (s), 33.2 (s), 32.7 (s), 31.9 (s), 27.4 (s). HRMS (EI) m/z calculated for $C_{12}H_{14}FO^{35}Cl$: 228.0717; found: 228.0716.

(4M) 2-(3-(benzyloxy)propyl)-4-fluorobenzaldehyde (colorless solid, 84%)



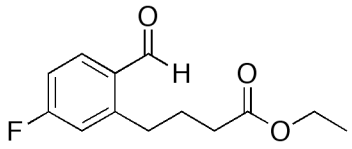
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.26 (s, 1H), 7.94 (dd, 1H, J = 8.70 Hz, J = 6.14 Hz), 7.37-7.35 (m, 4H), 7.29-7.27 (m, 1H), 7.17-7.14 (m, 2H), 4.50 (s, 2H), 3.52 (t, 2H, J = 6.14 Hz), 3.19 (t, 2H, J = 7.68 Hz), 1.96-1.91 (m, 2H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.3 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.5 (s), 166.5 (d, J = 253.6 Hz), 149.5 (d, J = 9.2 Hz), 139.9 (s), 135.3 (d, J = 10.3 Hz), 131.9 (s), 129.1 (s), 128.4 (s), 128.2 (s), 118.5 (d, J = 21.2 Hz), 114.5 (d, J = 21.8 Hz), 73.3 (s), 69.8 (s), 32.5 (s), 29.4 (s). HRMS (EI) m/z calculated for $C_{17}H_{17}FO_2$: 272.1213; found: 272.1212.

(4N) 2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-4-fluorobenzaldehyde (colorless solid, 92%)



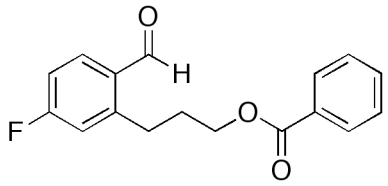
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.28 (s, 1H), 7.94 (dd, 1H, J = 8.70 Hz, J = 6.14 Hz), 7.71 (dd, 4H, J = 8.19 Hz, J = 1.54 Hz), 7.45-7.43 (m, 6H), 7.19-7.17 (m, 2H), 3.78 (t, 2H, J = 6.14 Hz), 3.24 (t, 2H, J = 7.68 Hz), 1.93-1.92 (m, 2H), 1.07 (s, 9H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.8 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.4 (s), 166.5 (d, J = 253.6 Hz), 149.5 (d, J = 9.2 Hz), 136.3 (s), 135.4 (d, J = 9.8 Hz), 134.6 (s), 131.8 (d, J = 2.3 Hz), 130.7 (s), 128.7 (s), 118.5 (d, J = 21.8 Hz), 114.5 (d, J = 21.8 Hz), 63.9 (s), 35.3 (s), 30.7 (s), 27.3 (s), 19.8 (s). HRMS (EI) m/z calculated for $C_{22}H_{20}FO_2Si$ (M – *t*-Bu): 363.1216; found: 363.1214.

(4O) ethyl 4-(5-fluoro-2-formylphenyl)butanoate (colorless solid, 83%)



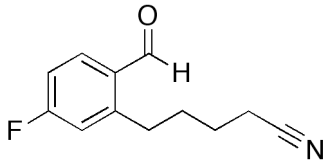
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.27 (s, 1H), 7.96 (dd, 1H, J = 8.70 Hz, J = 6.14 Hz), 7.36-7.34 (m, 2H), 4.09 (q, 2H, J = 7.17 Hz), 3.15-3.14 (m, 2H), 2.39 (t, 2H, J = 7.17 Hz), 1.93-1.91 (m, 2H), 1.21 (t, 3H, J = 7.17 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -105.5 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.6 (s), 173.3 (s), 166.5 (d, J = 253.5 Hz), 149.0 (d, J = 8.6 Hz), 139.6 (d, J = 10.3 Hz), 131.9 (s), 118.5 (d, J = 21.8 Hz), 114.7 (d, J = 21.8 Hz), 60.7 (s), 34.1 (s), 32.0 (s), 27.9 (s), 14.6 (s). HRMS (EI) m/z calculated for $C_{13}H_{15}FO_3$: 238.1005; found: 238.1004.

(4P) 3-(5-fluoro-2-formylphenyl)propyl benzoate (colorless solid, 81%)



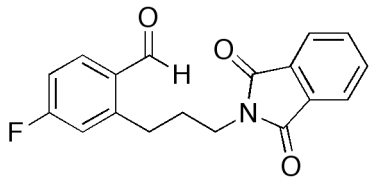
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.27 (s, 1H), 8.05-7.97 (m, 3H), 7.64 (t, 1H, J = 7.17 Hz), 7.52 (t, 2H, 8.19 Hz), 7.26-7.20 (m, 2H), 4.39 (t, 2H, J = 6.66 Hz), 3.32 (t, 2H, 9.22 Hz), 2.16-2.12 (m, 2H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.8 (s), 166.8 (s), 166.5 (d, J = 253.6 Hz), 148.8 (d, J = 8.6 Hz), 136.4 (d, J = 10.3 Hz), 133.9 (s), 131.9 (s), 131.4 (s), 130.3 (s), 129.4 (s), 118.7 (d, J = 21.8 Hz), 114.7 (d, J = 21.8 Hz), 65.0 (s), 31.4 (s), 30.7 (s). HRMS (EI) m/z calculated for $C_{17}H_{15}FO_3$: 286.1005; found: 286.1003.

(4Q) 5-(5-fluoro-2-formylphenyl)pentanenitrile (colorless oil, 75%)



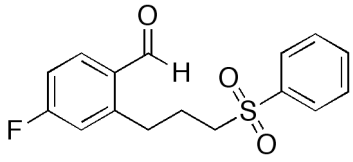
^{1}H NMR (acetone-d_6, 600 MHz): δ 10.25 (s, 1H), 7.99-7.98 (m, 1H), 7.23-7.21 (m, 2H), 3.17 (t, 2H, J = 7.17 Hz), 2.53 (t, 2H, J = 6.66 Hz), 1.76-1.73 (m, 4H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -106.1 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.7 (s), 166.5 (d, J = 253.5 Hz), 149.0 (d, J = 8.6 Hz), 136.1 (d, J = 10.3 Hz), 129.1 (d, J = 14.9 Hz), 120.6 (s), 118.6 (d, J = 21.8 Hz), 114.7 (d, J = 21.8 Hz), 32.0 (s), 34.1 (s), 31.6 (s), 26.0 (s), 17.0 (s). HRMS (EI) m/z calculated for $C_{12}H_{12}FNO$: 205.0903; found: 205.0901.

(4R) 2-(3-(1,3-dioxoisoindolin-2-yl)propyl)-4-fluorobenzaldehyde (colorless solid, 78%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 10.18 (s, 1H), 7.94 (dd, 1H, J = 8.70 Hz, J = 6.14 Hz), 7.86-7.83 (m, 4H), 7.25 (dd, 1H, J = 10.24 Hz, J = 2.56 Hz), 7.18 (dt, J = 8.19 Hz, J = 2.56 Hz), 3.77 (t, 2H, J = 6.66 Hz), 3.18 (t, 2H, J = 8.19 Hz), 2.03-2.01 (m, 2H). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -10.7 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 191.7 (s), 169.0 (s), 166.4 (d, J = 253.5 Hz), 148.7 (d, J = 8.5 Hz), 136.5 (d, J = 10.3 Hz), 135.0 (s), 133.0 (s), 131.8 (d, J = 2.9 Hz), 123.7 (s), 118.6 (d, J = 21.8 Hz), 114.6 (d, J = 21.8 Hz), 38.3 (s), 31.8 (s), 30.5 (s). HRMS (EI) m/z calculated for $C_{18}H_{14}FNO_3$: 311.0958; found: 311.0956.

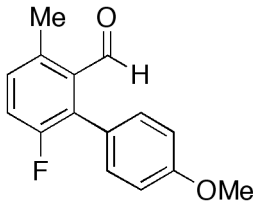
(4S) 4-fluoro-2-(3-(phenylsulfonyl)propyl)benzaldehyde (colorless solid, 69%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 10.17 (s, 1H), 7.95 (dd, 1H, J = 8.71 Hz, J = 6.14 Hz), 7.93-7.91 (m, 2H), 7.74 (t, 1H, 7.68 Hz), 7.66 (t, 2H, J = 7.68 Hz), 7.22 (dt, 1H, J = 8.19

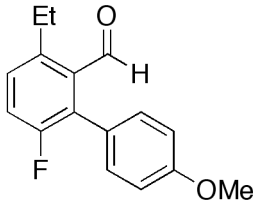
Hz, J = 2.56 Hz), 7.17 (dd, 1H, J = 10.24 Hz, J = 2.56 Hz), 3.30 (t, 2H, J = 7.68 Hz), 3.21 (t, 2H, J = 7.68 Hz), 2.00-1.98 (m, 2H). $^{19}F\{^{1}H\}$ NMR (acetone-d_6, 282 MHz): δ -105.9 (s, 1F). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 191.9 (s), 166.4 (d, J = 253.5 Hz), 147.6 (d, J = 8.6 Hz), 140.7 (s), 136.7 (d, J = 9.8 Hz), 134.6 (s), 131.8 (d, J = 2.9 Hz), 130.3 (s), 128.9 (s), 118.8 (d, J = 21.8 Hz), 115.0 (d, J = 21.8 Hz), 55.8 (s), 31.2 (s), 25.6 (s). HRMS (EI) m/z calculated for $C_{16}H_{15}FSO_3$: 306.0726; found: 306.0724.

(4T) 3-methyl-6-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 80%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 9.81 (s, 1H), 7.39-7.37 (m, 2H), 7.30 (d, 2H, J = 8.70 Hz), 7.09 (d, 2H, J = 8.70 Hz), 3.88 (s, 3H), 2.54 (s, 3H). $^{19}F\{^{1}H\}$ NMR (acetone-d_6, 282 MHz): δ -120.4 (s, 1F). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 193.6 (s), 161.0 (s), 159.2 (d, J = 242.6 Hz), 136.0 (s), 135.4 (s), 133.8 (d, J = 16.7 Hz), 133.0 (s), 132.9 (s), 124.4 (s), 120.0 (d, J = 23.0 Hz), 114.8 (s), 55.8 (s), 20.7 (s). HRMS (EI) m/z calculated for $C_{15}H_{13}FO_2$: 244.0900; found: 244.0902.

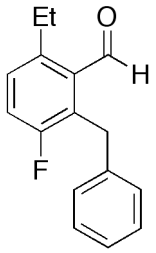
(4U) 3-ethyl-6-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (colorless solid, 75%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 9.81 (s, 1H), 7.41-7.39 (m, 2H), 7.31-7.30 (m, 2H), 7.08-7.07 (m, 2H), 3.88 (s, 3H), 2.95 (q, 2H, J = 7.31 Hz), 1.21 (t, 3H, J = 7.31 Hz). $^{19}F\{^{1}H\}$ NMR (acetone-d_6, 282 MHz): δ -121.4 (s, 1F). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 193.6 (s), 161.0 (s), 159.0 (d, J = 242.7 Hz), 142.2 (d, J = 3.4 Hz), 135.3 (s), 133.6 (d, J = 16.6 Hz), 133.0 (s), 131.8 (d, J = 8.0 Hz), 124.5 (s), 120.3 (d, J = 22.5 Hz),

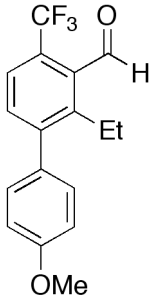
114.7 (s), 55.8 (s), 27.0 (s), 16.6 (s). HRMS (EI) m/z calculated for $C_{16}H_{15}FO_2$: 258.1056; found: 258.1057.

(4V) 2-benzyl-6-ethyl-3-fluorobenzaldehyde (colorless oil, 61%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 10.54 (s, 1H), 7.77-7.75 (m, 2H), 7.25 (t, 2H, J = 7.68 Hz), 7.17 (d, 3H, J = 7.17 Hz), 4.41 (s, 2H), 2.95 (t, 2H, J = 7.17 Hz), 1.20 (t, 3H, J = 7.68 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -120.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 194.0 (s), 160.7 (d, J = 242.7 Hz), 144.2 (s), 141.1 (s), 134.9 (d, J = 2.9 Hz), 131.4 (d, J = 8.0 Hz), 130.1 (d, J = 15.5 Hz), 129.5 (s), 129.3(s), 127.1 (s), 120.8 (d, J = 23.5 Hz), 26.6 (s), 17.2 (s). HRMS (EI) m/z calculated for $C_{16}H_{15}FO$: 242.1107; found: 242.1105.

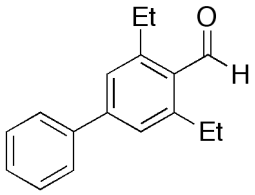
(4W) 2-ethyl-4'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-3-carbaldehyde (colorless solid, 81%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 10.66 (q, 1H, J = 2.56 Hz), 7.75 (d, 1H, J = 8.19 Hz), 7.53 (d, 1H, J = 8.19 Hz), 7.29-7.27 (m, 2H), 7.07-7.04 (m, 2H), 3.87 (s, 3H), 3.82 (q, 2H, J = 7.17 Hz), 0.98 (t, 3H, J = 7.68 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -56.2 (s,

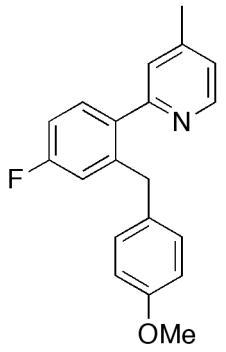
3F). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 194.4 (s), 160.5 (s), 148.4 (s), 144.4 (s), 134.4 (s), 132.9 (s), 131.0 (s), 128.6 (q, J = 31.5 Hz), 125.2 (q, J = 273.1 Hz), 124.7 (q, J = 5.7 Hz), 114.7 (s), 55.7 (s), 23.3 (s), 16.3 (s). HRMS (EI) m/z calculated for $C_{17}H_{15}F_3O_2$: 308.1024; found: 308.1025.

(4X) 3,5-diethyl-[1,1'-biphenyl]-4-carbaldehyde (colorless solid, 77%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 10.63 (s, 1H), 7.75 (d, 1H, J = 8.19 Hz), 7.76-7.73 (m, 2H), 7.50-7.48 (m, 4H), 7.42-7.41 (m, 1H), 3.08 (t, 4H, J = 7.68 Hz), 1.27 (t, 6H, J = 7.68 Hz). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 193.8 (s), 148.9 (s), 146.2 (s), 140.8 (s), 131.6 (s), 130.0 (s), 129.2 (s), 128.1 (s), 127.8 (s), 27.4 (s), 17.2 (s). HRMS (EI) m/z calculated for $C_{17}H_{18}O$: 238.1358; found: 238.1355.

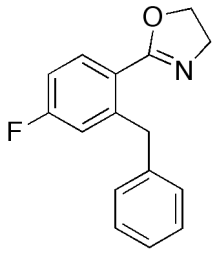
(4Y) 2-(4-fluoro-2-(4-methoxybenzyl)phenyl)-4-methylpyridine (colorless liquid, 88%)



^{1}H NMR (acetone-d_6, 600 MHz): δ 8.53-8.52 (m, 1H), 7.41-7.39 (m, 1H), 7.20 (s, 1H), 7.16-7.14 (m, 1H), 7.05-7.03 (m, 2H), 6.99-6.97 (m, 2H), 6.77 (d, 2H, J = 8.70 Hz), 4.11 (s, 2H), 3.70 (s, 3H), 2.34 (s, 3H). $^{19}F\{^{1}H\}$ NMR (acetone-d_6, 282 MHz): δ -115.3 (s, 1F). $^{13}C\{^{1}H\}$ NMR (acetone-d_6, 150 MHz): δ 163.3 (d, J = 244.9 Hz), 159.7 (s), 159.0 (s), 149.7 (s), 148.3 (s), 143.8 (s), 138.0 (s), 133.6 (s), 132.6 (d, J = 8.0 Hz), 130.8 (s), 125.9

(s), 123.7 (s), 117.4 (d, J = 21.2 Hz), 114.5 (s), 113.5 (d, J = 21.2 Hz), 55.4 (s), 38.4 (s), 21.0 (s). HRMS (ESI) [m/z+1] calculated for $C_{20}H_{19}FNO$: 308.1451; found: 308.1450.

(4Z) 2-(2-benzyl-4-fluorophenyl)-4,5-dihydrooxazole (colorless solid, 27%)

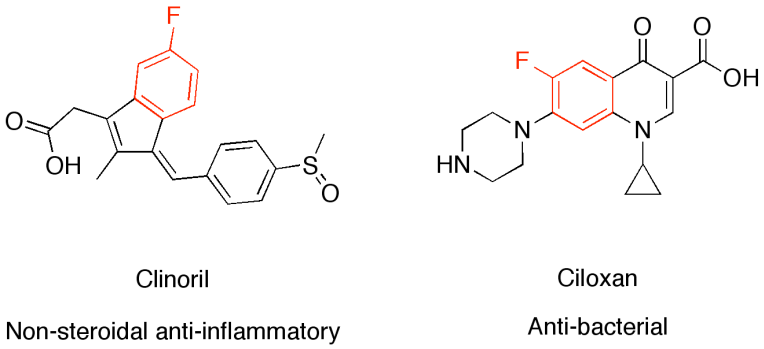


^{1}H NMR (acetone-d_6, 600 MHz): δ 7.87-7.85 (m, 1H), 7.28-7.17 (m, 5H), 7.07-7.05 (m, 1H), 7.01-6.99 (m, 1H), 4.52 (s, 2H), 4.34 (t, 2H, J = 9.22 Hz), 4.02 (t, 2H, J = 9.22 Hz). ^{19}F{^{1}H} NMR (acetone-d_6, 282 MHz): δ -111.4 (s, 1F). ^{13}C{^{1}H} NMR (acetone-d_6, 150 MHz): δ 164.5 (d, J = 248.5 Hz), 163.7 (s), 146.2 (d, J = 8.0 Hz), 141.7 (s), 133.3 (d, J = 9.2 Hz), 130.0 (s), 129.3 (s), 127.0 (s), 124.8 (s), 118.4 (d, J = 21.8 Hz), 113.8 (d, J = 21.8 Hz), 67.4 (s), 56.2 (s), 39.8 (s). HRMS (ESI) [m/z+1] calculated for $C_{16}H_{15}FNO$: 256.1138; found: 256.1137.

Chapter 5: Carbon-Fluorine Bond Formation from Aryl Boron Reagents

5.1 Introduction

In previous chapters, we discussed three procedures for synthesizing functionalized aryl fluorides via selective catalytic C-F cross-coupling. Obtained were a variety of compounds that have potential use as fluorine-containing building blocks in pharmaceutical and materials chemistry. Certain aryl fluorides, however, have structures that so far cannot be readily synthesized by cross-coupling methods, such as Clinoril by Merck and Ciloxan by Bayer, as shown in Figure 5.1. Due to their complex structures, in such cases, a late stage carbon-fluorine bond formation may be the method of choice.



Clinoril

Non-steroidal anti-inflammatory

Ciloxan

Anti-bacterial

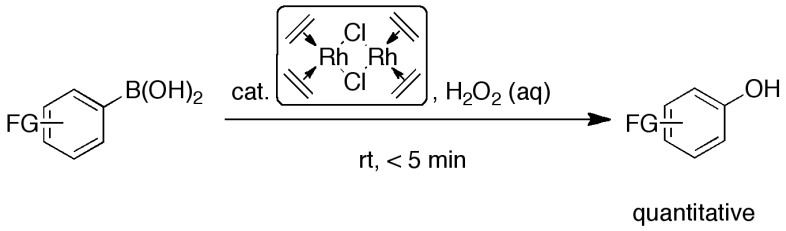
Figure 5.1 Structures of Clinoril and Ciloxan

In this chapter, we present a synthetic method for generating functionalized aryl fluorides from aryl boron reagents. We describe its background, then its scope and limitations, and finally discuss future work and conclusions.

5.2 Aryl fluoride bond formation from aryl boron reagents

5.2.1 Background

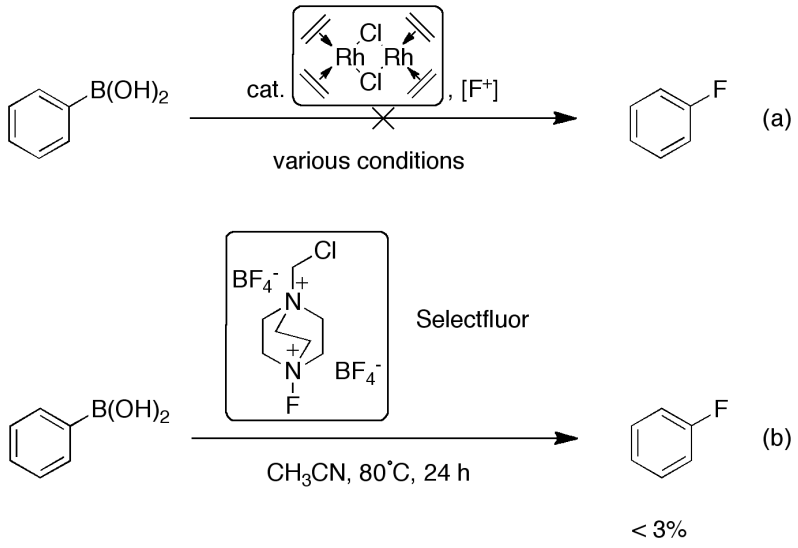
The first objective of our research was to find a convenient method of generating functionalized aryl fluorides from readily available starting materials. We were initially inspired by an observation made in our group by Alex Dauth, who discovered that arylboronic acids were almost instantaneously converted into phenols at room temperature, in the presence of hydrogen peroxide and a catalytic amount of an Rh(I) compound (Scheme 5.1).[116] Although reactions to generate phenols using arylboronic acids and hydrogen peroxide are hardly new, most of them require acid or base to facilitate this process.[117]



Scheme 5.1 Rh-catalyzed phenol formation

While the mechanistic details remain elusive, we speculated that phenols were formed from aryl groups attacking electrophilic oxygen atoms (from hydrogen peroxide), hypothesizing that the Rh(I) compound acted as a catalyst to facilitate the break-up of the C-B bonds in arylboronic acids. Following this logic, if these reactive aryl groups could be intercepted by appropriate electrophilic fluorine source (F^+), aryl fluorides would be generated. There are recent examples in the literature based on the same principle. The Ritter group developed a strategy converting aryl boronic acids to aryl fluorides using stoichiometric amount of silver,[34] whereas the Lemaire group reported a metal-free electrophilic fluorination method that was only effective for electron-rich boronic acids

and derivatives.[118] Unfortunately, under various conditions, with common electrophilic fluorine sources catalyzed by the Rh(I) complex, repeated attempts to react phenylboronic acid were unsuccessful (Scheme 5.2a). Surprisingly, when we conducted standard background reactions, phenylboronic acid and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate (Selectfluor) produced a small amount of fluorobenzene (<3%) in CH_3CN at 80°C after 24 hours in the absence of the Rh(I) salt (Scheme 5.2b). We decided to pursue this interesting and rather unexpected result further.



Scheme 5.2 C-F bond formation from phenylboronic acid and Selectfluor

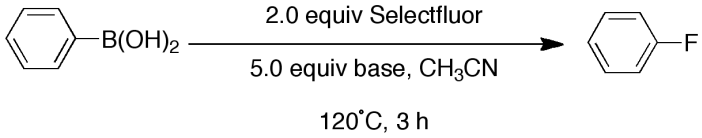
5.2.2 Reaction optimization

We first confirmed that fluorobenzene was formed between phenylboronic acid and Selectfluor in the absence of any transition metal catalysis; we tested several batches of phenylboronic acid, Selectfluor and CH_3CN from different suppliers purchased at different times, to consistent results (1~3% yield). In addition, while fluorobenzene was generated in only a minimal amount, a significant amount of benzene was detected by

HPLC. We speculated that after a transient phenyl anion or its equivalent was first generated from the decomposition of phenylboronic acid, fluorobenzene was formed when electrophilic fluorine was available; otherwise, benzene was formed from phenyl anion reacting with acidic proton in the system. Therefore, we sought to find appropriate conditions wherein the formation of aryl anion was accelerated but the side reaction was suppressed, so that aryl fluorides could be generated in synthetically useful yields.

We first turned our attention to the effects of additives on the yield. We believed any additive that could facilitate the breaking-up of arylboronic acid could potentially facilitate the formation of fluorobenzene. At the same time, a drying agent was desirable to absorb moisture, so as to keep the formation of benzene to a minimum. It is commonly known that a base is required in Suzuki-Miyaura cross-coupling to activate the arylboronic acid, in order to generate the boron "ate" complex that releases the aryl group;[86] thus we believed that an appropriate base would activate the arylboronic acid in this reaction as well. A systematic screening of common bases was conducted and the results are shown in Table 5.1.

Table 5.1 Screening of common bases for aryl fluoride synthesis



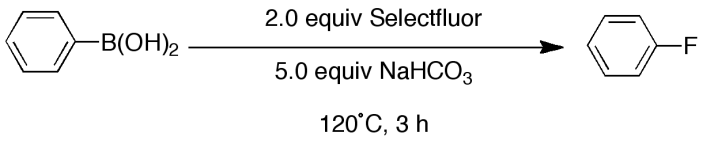
Entry	Base	Yield[a]
1	NaOH	0%
2	KOH	0%
3	K_3PO_4	< 5%
4	NEt_3	0%
5	$NaHCO_3$	80%
6	$MgSO_4$	< 5%
7	Na_2SO_4	< 5%
8	Na_2CO_3	33%
9	NaOMe	< 5%
10	K_2CO_3	< 5%

[a] Yields based on ^{19}F NMR spectroscopy using 3-nitrofluorobenzene as an internal standard.

Sodium bicarbonate (entry 5) provided the best result in 80% yields. Not only was it found to be a sufficient base to activate the boronic acid, but it also suppressed the side reaction that would otherwise generate benzene; ^{1}H and $^{19}F\{^{1}H\}$ NMR spectroscopy revealed the remaining mass balance as an unidentified complex mixture that does not contain fluorine.

Re-examination of the choice of solvent in the presence of $NaHCO_3$ confirmed that CH_3CN was the optimal solvent, as shown in Table 5.2. Increasing the amounts of Selectfluor and/or $NaHCO_3$ offered no additional benefits.

Table 5.2 Screening of solvent for aryl fluoride synthesis

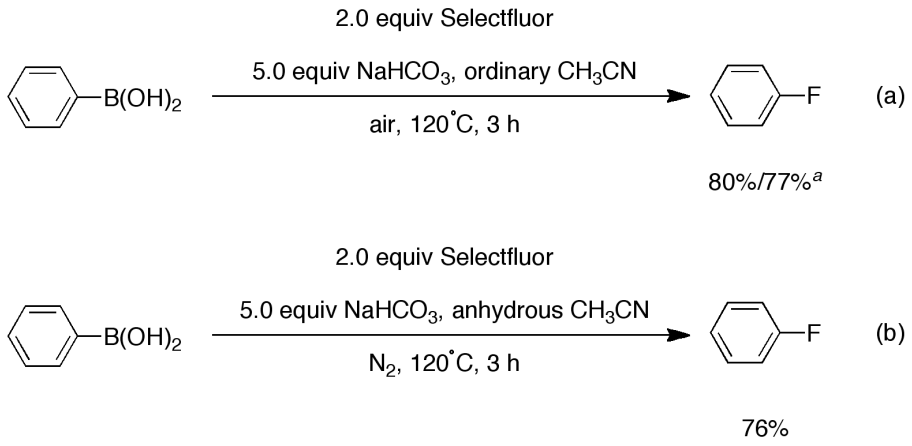


Entry	Solvent	Yield[a]
1	CH_3CN	80%
2	Toluene	11%
3	Acetone	27%
4	DMF	14%
5	THF	< 5%
6	DMSO	< 5%
7	Benzene	< 5%
8	Methanol	< 5%
9	Ethyl acetate	< 5%

[a] Yields based on ^{19}F NMR spectroscopy using 3-nitrofluorobenzene as an internal standard.

In order to better understand the reaction, we attempted to monitor its progress by determining the yield of fluorobenzene after various time intervals. We were glad to see that fluorobenzene was formed in ~60% yield after 1 h, 80% after 2 h, and showed no improvement after 3 h.

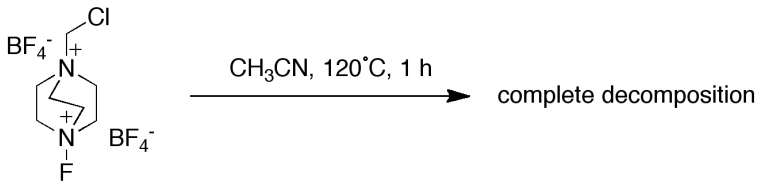
Our methodology does not require sophisticated working conditions. All previous data was collected using regular solvents and under no nitrogen protection. As shown in Scheme 5.3b, reactions conducted under strictly anhydrous conditions with nitrogen protection did not offer higher yield. Neither the presence of moisture nor oxygen during the reaction had any effect on the reaction outcome. Furthermore, an undergraduate student was able to repeat these reactions and obtain similar results after completing basic training (Scheme 5.3a).



[a] Data collected by Margaret Hwu

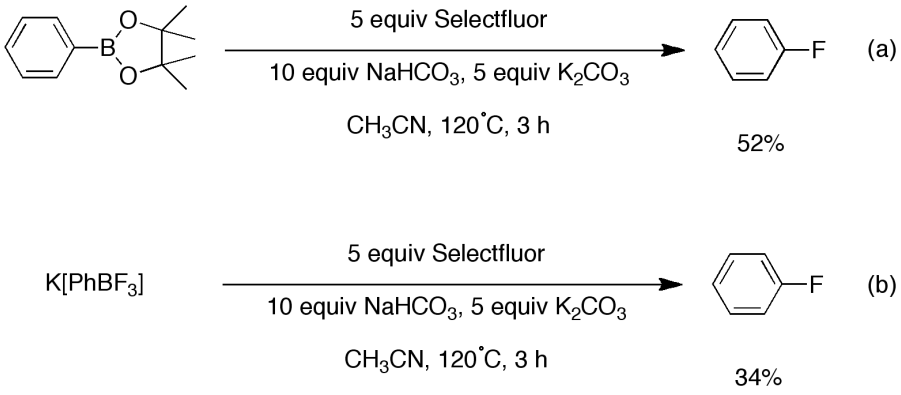
Scheme 5.3 Aryl fluoride synthesis under different conditions

An interesting observation was that, in the absence of arylboronic acids, Selectfluor decomposed rapidly under the reaction conditions; the signal corresponding to the electrophilic fluorine atom disappeared after 1 h at 120°C regardless of the presence or absence of $NaHCO_3$. On the other hand, we always detected the presence of some Selectfluor left at the end of reactions, as it was always used in excess. The disappearance of electrophilic fluorine source is not unexpected as there are a number of pathways through which it can be consumed,[119] but this observation raised a curious mechanistic question: if Selectfluor decomposed in the absence of boronic acid, why did it not do so in the presence of it? It appears as though arylboronic acid decreases the rate of the decomposition so that the electrophilic fluorine can be trapped by the transient aryl anion. We are currently designing experiments to probe this unexpected result.



Scheme 5.4 Decomposition of Selectfluor

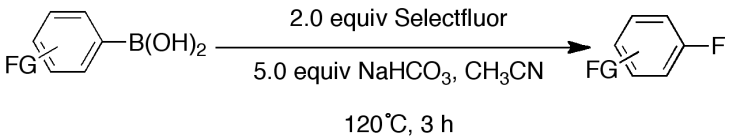
In order to broaden the substrate scope, we examined the possibility of employing boronic esters and potassium trifluoroborate. They are considered to be masked boronic acids and have been employed extensively in Suzuki-Miyaura cross-coupling reactions.[87] These molecules can either be purchased from commercial sources or generated as intermediates in multistep synthesis.[88] We found that reactions with phenylboronic derivates were considerably more sluggish and resulted in 52% yield with boronic ester (Scheme 5.5a) and 34% yield with trifluoroborate salt (Scheme 5.5b), despite employing a higher equiv of Selectfluor and $NaHCO_3$, and with additional K_2CO_3. The lower reactivity of boronic ester can be rationalized due to increased steric demand; however the low reactivity of trifluoroborate is surprising, since it is thought to be "activated" because of the tetra-coordinated boron atoms.

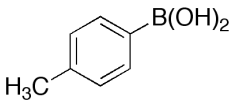
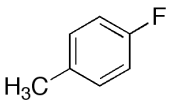
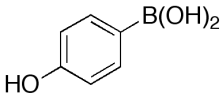
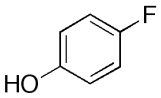
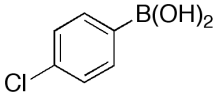
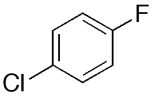
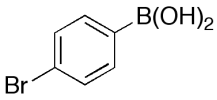
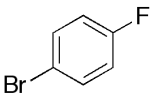
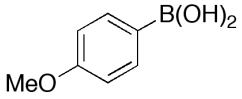
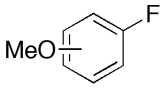


Scheme 5.5 Aryl fluoride from arylboronic acid derivates

To tolerate potentially reactive functional groups, it is very important for any aryl fluoride synthesis to have a broad substrate scope, especially when such methodology is needed at a late stage in synthesis. We tested our standard conditions with arylboronic acids containing common functional groups and the results are summarized in Table 5.3.

Table 5.3 Scope and limitations of boronic acids in aryl fluoride synthesis



Entry	Substrate	Product	Yield[a]
1			57%
2			74%
3			~ 40%
4			~ 40%
5			isomers

[a] Yields based on ^{19}F NMR spectroscopy using 3-nitrofluorobenzene as an internal standard.

As expected, a *para*-methyl group had only a small effect on the yield (entry 1). A free hydroxyl group did not appear to interfere with the reaction despite the presence of an acidic proton, which might have led to phenol formation (entry 2). C-Br and C-Cl bonds were tolerated, but the yields were much lower and showed significant variation between individual runs (entries 3 and 4).

The reaction of 4-methoxybenzeneboronic acid produced an unlikely result (entry 5). When we compared the peaks observed in ^{1}H and $^{19}F\{^{1}H\}$ NMR spectroscopy to authentic samples obtained from commercial sources, it was clear that all possible

isomers of mono-fluoroanisole were formed in various quantities. We do not have an explanation for this observation and more kinetic and mechanistic studies are currently underway.

5.3 Conclusions and future work

In this chapter, we have demonstrated a convenient method to generate aryl fluorides from boron reagents. This method is rapid, high yielding, and can be performed using routine organic laboratory equipment without inert atmosphere protection or dry solvents. We are in the process of further optimizing reaction conditions, testing more functional group compatibility, and elucidating the mechanism.

5.4 Experimental

General Procedures. Synthesis of aryl fluorides was performed with commercially available solvents and reagents without further purification and inert atmosphere protection unless otherwise noticed. NMR spectra were recorded on Bruker Avance 300 spectrometer. $^{19}F\{^{1}H\}$ NMR spectra are reported in parts per million and referenced to $CFCl_3$ (0 ppm). All spectra were obtained at 25°C. $^{19}F\{^{1}H\}$ NMR spectra comparisons were made with authentic samples obtained from commercial sources in the same solvent.

Materials and Methods. All organic solvents were obtained from commercial sources and used as received unless otherwise described. CH_3CN used in glovebox was distilled from molecular sieves and freeze-pump-thawed three times before bringing into the glovebox. All organoboron reagents, fluorination reagents were obtained from commercial sources and used as received. Reaction vials were purchased from Biotage (Biotage microwave reaction kit, 0.5-2 mL, code number: 352016).

General procedure of synthesis of aryl fluorides

Phenylboronic acid (0.122 g, 1 mmol, 1.0 equiv), Selectfluor (0.710 g, 2 mmol, 2.0 equiv), $NaHCO_3$ (0.420 g, 5 mmol, 5.0 equiv), and 1 mL CH_3CN were added to a 0.5-2 mL Biotage reaction vial, along with a Teflon coated magnetic stir bar. The vial was capped and the reaction mixture was subsequently stirred at 120°C for 3 hours. The vial was then cooled to room temperature, and 3-nitrofluorobenzene (0.140 g, 1 mmol, 1.0 equiv) was added. The yield was determined by comparing the integration of the $^{19}F\{^{1}H\}$ NMR resonance of fluorobenzene with that of 3-nitrofluorobenzene.

General procedure of synthesis of aryl fluorides under inert atmosphere

Phenylboronic acid (0.122 g, 1 mmol, 1.0 equiv), Selectfluor (0.710 g, 2 mmol, 2.0 equiv), $NaHCO_3$ (0.420 g, 5 mmol, 5.0 equiv), and 1 mL dry CH_3CN were added to a pre-dried 0.5-2 mL Biotage reaction vial, along with a Teflon coated magnetic stir bar in a glovebox. The vial was capped, removed from the glovebox and the reaction mixture was subsequently stirred at 120°C for 3 hours. The vial was then cooled to room temperature, and 3-nitrofluorobenzene (0.140 g, 1 mmol, 1.0 equiv) was added. The yield was determined by comparing the integration of the $^{19}F\{^1H\}$ NMR resonance of fluorobenzene with that of 3-nitrofluorobenzene.

Chapter 6: Conclusions and Future Work

6.1 Conclusions

We have presented several procedures for selective carbon-fluorine cross-coupling of polyfluoroarenes. These reactions produce highly functionalized aryl fluorides that can potentially be used as fluorine-containing building blocks in pharmaceutical and materials chemistry. $PtCl_2(SMe_2)_2$ and $PtCl_2(DMSO)_2$ prove highly efficient precatalysts in catalytic methylation of polyfluoroaryl imines. They show similar selectivity towards ortho C-F bonds and functional group tolerance in comparison with $[PtMe_2(SMe_2)]_2$, but present significant practical advantages due to their thermal, water and air stabilities.

We have developed a novel Ni-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroarenes. This process offers a variety of fluorinated biaryl and heteroaryl-aryl molecules in high yields under mild conditions. Arylboronic acids with electron-donating and electron-withdrawing groups provide comparable yields. A diverse group of functionalized fluoroaryl pyridine, oxazoline and imines have been generated. We have also successfully employed arylboronic derivatives such as boronic esters and trifluoroborate salts.

In addition, we have demonstrated a Ni-catalyzed Negishi cross-coupling of polyfluoroarenes, synthesizing and characterizing a large number of alkyl-substituted aryl fluorides. Various fluorine substitution patterns and functional groups have proven capable of incorporation into target molecules. Sequential reactions, involving different catalytic protocols and coupling partners, have been successfully developed and these examples have further broadened the synthetic utility of our discovery.

We have also discovered a convenient method to generate aryl fluorides from aryl boron reagents. This protocol permits rapid synthesis of fluorinated compounds from commercial starting materials that are readily available.

6.2 Future work

Our work opens up areas of further research in several directions. First, an exploration of transmetalation reagents other than boron and zinc will further enhance the synthetic utility of our findings. Helen He, a member of our group, is studying Kumada cross-coupling using organomagnesium halides, including aryl, heteroaryl and alkyl groups. Though less compatible with functional groups, organomagnesium reagents certainly deserve our attention as so many are commercially available and inexpensive.

The mechanistic detail of Ni-catalyzed cross-coupling reactions will provide another area of investigation. Preliminary results indicate a different mechanism than the one we proposed for the Pt(II) system. A better understanding of this mechanism will no doubt help us to design a better catalytic system and improve synthetic utility.

An additional line of inquiry is the optimization and expansion of our C-F formation protocol. So far, there are limitations on the substrate scope and functional group tolerance that prevent it from being synthetically useful. We would like to address these concerns and apply this procedure in the synthesis of highly functionalized aryl fluorides for pharmaceutical and materials chemistry.

References

1) Muller, K., Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881-1886.
2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320-330.
3) Strunecka, A.; Patocka, J.; Connett, P. *J. Appl. Biomed*. **2004**, *2*, 141-150.
4) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013-1029.
5) Okazoe, T. *Proc. Jpn. Acad., Ser. B* **2009**, *85*, 276-289.
6) http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010
7) O'Hagan, D. *Chem. Soc. Rev*. **2008**, *37*, 308-319.
8) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res*. **2003**, *36*, 255-263.
9) Cordero, B.; Gomez, V.; Platero-Prats, A. E.; Reves, M.; Echeverria, J.; Cremades, E.; Barragan, F.; Alvarez, S. *Dalton Trans.* **2008**, 2832-2838.
10) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem*. **1999**, *100*, 127-133.
11) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071-1081.
12) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15-24.
13) Murphy, C. D.; Schaffrath, C.; O'Hagan, D. *Chemosphere* **2003**, *52*, 455-461.
14) www.alfa.com/en/docs/FluorinatingAgents.pdf
15) (a) Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231. (b) Kirk, K. L. *Org. Process Res. Dev*. **2008**, *12*, 305-321. (c) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1-PR43.
16) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364-3378.
17) Roth, B. D. *Prog. Med. Chem.* **2002**, *40*, 1-22.
18) Cameron, N. E.; Cotter, M. A. Use of 3-hydroxy-3-methylglutaryl coenzym A reductase inhibitors for the manufacture of a medicament for the treatment of diabetic

neuropathy. WO 00/45818. August 10, 2000.

19) Baltz, G.; Schiemann, G. *Ber. Dtsch. Chem. Ges*. **1927**, *60*, 1186-1190.

20) (a) Gottlieb, H. B. *J. Am. Chem. Soc*. **1936**, *58*, 532-533. (b) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc*. **1956**, *78*, 6034-6037.

21) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc*. **2005**, *127*, 2050-2051.

22) Grushin, V. V. *Acc. Chem. Res*. **2010**, *43*, 160-171.

23) (a) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc*. **2007**, *129*, 1342-1358. (b) Grushin, V. V.; Marshall, W. J. *Organometallic* **2007**, *26*, 4997-5002.

24) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661-1664.

25) Taylor, E. C.; Bigham, E. C.; Johnson, D. K.; McKillop, A. *J. Org. Chem*. **1977**, *42*, 362-363.

26) Wang, B.; Qin, L.; Neumann, K. D.; Uppaluri, S.; Cerny, R. L.; DiMagno, S. G. *Org. Lett*. **2010**, *12*, 3352-3355.

27) Lai, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737-1756.

28) Sandford, G. *J. Fluorine Chem*. **2007**, *128*, 90-104.

29) Zupan, M.; Iskra, J.; Stavber, S. *J. Org. Chem.* **1998**, *63*, 878-880.

30) (a) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed*. **2010**, *49*, 2219-2222. (b) Yamada, S.; Knochel, P. *Synthesis* **2010**, *14*, 2490-2494.

31) Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed*. **2010**, *49*, 2215-2218.

32) Hull, K. L., Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc*. **2006**, *128*, 7134-7135.

33) (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc*. **2009**, *131*, 7520-7521. (b) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2011**, *50*, 9081-9084.

34) (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 5993-5996. (b) Furuya, T.; Ritter, T. *Org. Lett*. **2009**, *11*, 2860-2863.

35) Tang, P.; Ritter, T. *Tetrahedron* **2011**, *67*, 4449-4454.

36) (a) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc*. **2009**, *131*, 1662-1663. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc*. **2010**, *132*, 12150-12154.

37) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton. Trans.* **2010**, *39*, 10352-10361.

38) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc*. **2008**, *130*, 1128-1129. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc*. **2008**, *130*, 15185-15192. (c) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc*. **2008**, *130*, 16170-16171. (d) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc*. **2010**, *132*, 4506-4507.

39) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.*, **2006**, *128*, 8757-8756.

40) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev*. **1994**, *94*, 373-431.

41) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber*. **1997**, *130*, 145-154.

42) Braun, T.; Perutz, R. N. *Chem. Commun*. **2002**, 2749-2757.

43) Perutz, R. N.; Braun, T. Transition Metal-mediated C-F Bond Activation. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P.; Crabtree, R. H., Eds.; Elsevier, **2007**; Vol. 1, pp. 725-758.

44) Jones, W. D. *Dalton Trans*. **2003**, 3991-3995.

45) Torrens, H. *Coord. Chem. Rev*. **2005**, *249*, 1957-1985.

46) Hudlicky, M. *J. Fluorine Chem*. **1989**, *44*, 345-359.

47) Richmond, T. G. *Angew. Chem. Int. Ed*. **2000**, *39*, 3241-3244.

48) Amii, H.; Uneyama, K. *Chem. Rev*. **2009**, *109*, 2119-2183.

49) Braun, T.; Wehmeier, F. *Eur. J. Inorg. Chem*. **2011**, 613-625.

50) (a) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359-361. (b) Aizenberg, M.; Milstein, D. *J. Am. Chem. Soc*. **1995**, *117*, 8674-8675.

51) (a) Kiplinger, J. L.; Richmond, T. G. *J. Am. Chem. Soc*. **1996**, *118*, 1805-1806. (b) Kiplinger, J. L.; Richmond, T. G. *Chem. Commun*. **1996**, 1115-1116.

52) (a) Desmarets, C.; Kuhl, S.; Schneider, R.; Fort, Y. *Organometallic* **2002**, *21*, 1554-1559. (b) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal*. **2003**, *345*, 341-344.

53) Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L. *J. Am. Chem. Soc*. **2005**, *127*, 7857-7870.

54) (a) Reade, S. P.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc*. **2009**, *131*, 1847-1861. (b) Reade, S. P.; Acton, A. L.; Mahon, M. F.; Martin, T. A.; Whittlesey, M. K. *Eur. J. Inorg. Chem*. **2009**, 1774-1785.

55) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973**, *50*, C12-C14.

56) Bohm, V. P. W.; Gstottmayr, C. W. K. Weskamp, T.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3387-3389.

57) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 7216-7219.

58) Liu, J.; Robins, M. J. *Org. Lett.* **2005**, *7*, 1149-1151.

59) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696-1697.

60) Edelbach, B. L.; Kraft, B. M.; Jones, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 10327-10331.

61) Guo, H.; Kong, F.; Kanno, K.-I.; He, J.; Nakajima, K.; Takahashi, T. *Organometallics* **2006**, *25*, 2045-2048.

62) Braun, T.; Perutz, R. N.; Sladek, M. I. *Chem. Comm.* **2001**, 2254–2255.

63) Steffen, A.; Sladek, M. I.; Braun, T.; Neumann, B.; Stammler, H.-G. *Organometallics* **2005**, *24,* 4057-4064.

64) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964-15965.

65) Braun, T.; Izundu, J.; Steffen, A.; Neumann, B.; Stammler, H.-G. *Dalton Trans*. **2006**, 5118-5123.

66) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, *7*, 1771-1774.

67) (a) Manabe, K.; Ishikawa, S. *Synthesis* **2008**, *16*, 2645-2649. (b) Ishikawa, S.;

Manabe, K. *Synthesis* **2008**, *19*, 3180-3182.

68) Wang, J.-R.; Manabe, K. *Org. Lett.* **2009**, *11*, 741-744.

69) Ackermann, L.; Wechsler, C.; Kapdi, A.; Althammer, A. *Synlett* **2010**, *2*, 294-298.

70) Cargill, M. R.; Sandford, G.; Tadeusiak, A. J.; Yufit, D. S.; Howard, J. A. K.; Kilickiran, P.; Nelles, G. *J. Org. Chem*. **2010**, *75*, 5860-5866.

71) (a) Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P. *Org. Lett.* **2006**, *8*, 725-728. (b) Korn, T. J.; Schade, M. A.; Cheemala, M. N.; Wirth, S.; Guevara, S. A.; Cahiez, G.; Knochel, P. *Synthesis* **2006**, *21*, 3547–3574.

72) Kawamoto, K.; Kochi, T.; Sato, M.; Mizushima, E.; Kakiuchi, F. *Tetrahedron Lett*. **2011**, *52*, 5888-5890.

73) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett*. **1998**, 157-158.

74) Arisawa, M.; Suzuki, T.; Ishikawa, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **2008**, *130*, 12214-12215.

75) Teltewskoi, M.; Panetier, J. A.; Macgregor, S. A.; Braun, T. *Angew. Chem. Int. Ed*. **2010**, *49*, 3947-3951.

76) Wang, T.; Alfonso, B. J.; Love, J. A. *Org. Lett*. **2007**, *9*, 5629-5631.

77) Wang, T.; Love, J. A. *Organometallic* **2008**, *27*, 3290-3296.

78) Buckley, H. L.; Wang, T.; Tran, O.; Love, J. A. *Organometallics* **2009**, *28*, 2356-2359.

79) Hill, G. S.; Irwin, M. J.; Levy, C. J.; Rendina, L. M.; Puddephatt, R. J.; Andersen, R. A. and McLean, L. *Inorg. Synth.* **1998**, *32*, 149-151.

80) Buckley, H. L. Selective, Catalytic C-F Activation as a Route to Methyl- and Ether-Functionalized Polyfluoroarylimines. M.Sc. Dissertation, University of British Columbia, Vancouver, BC, Canada, 2009.

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

82) Price, J. H.; Williamson, A. N.; Schramm, R. F.; Wayland, B. B. *Inorg. Chem.* **1972**, *11*, 1280-1284.

83) Wang, T. Pt-Catalyzed Cross-Coupling of Arylfluorides: Reaction Development and Mechanistic Analysis. Ph.D. Dissertation, University of British Columbia, Vancouver, BC, Canada, 2009.

84) (a) Fahey, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 1101-1108. (b) Braun, T.; Perutz, R. N. *Chem. Commun.* **2002**, 2749-2757. (c) Cronin, L.; Higgitt, C. L.; Karch, R.; Perutz, R. N. *Organometallics* **1997**, *16*, 4920-4928. (d) Archibald, S. J.; Braun, T.; Gaunt, J. A.; Hobson, J. E.; Perutz, R. N. *J. Chem. Soc., Dalton Trans.* **2000**, 2013-2018. (e) Braun, T.; Foxon, S. P.; Perutz, R. N.; Walton, P. H. *Angew. Chem. Int. Ed.* **1999**, *38*, 3326-3329. (f) Burling, S.; Elloitt, P. I. P.; Jasim, N. A.; Lindup, R. J.; McKenna, J.; Perutz, R. N.; Archibald, S. J.; Whitwood, A. C. *Dalton Trans.* **2005**, 3686-3695. (g) Schaub, T.; Radius, U. *Chem. Eur. J.* **2005**, *11*, 5024-5030. (h) Schaub, T.; Fischer, P.; Steffen, A.; Braun, T.; Radius, U.; Mix, A. *J. Am. Chem. Soc.* **2008**, *130*, 9304-9317. (i) Yamamoto, T.; Abla, M. *J. Organomet. Chem.* **1997**, *535*, 209-211. (j) Johnson, S. A.; Huff, C. W.; Mustafa, F.; Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 17278-17280. (k) Johnson, S. A.; Taylor, E. T. Cruise, S. J. *Organometallic* **2009**, *28*, 3842-3855. (l) Johnson, S. A.; Mroz, N. M.; Valdizon, R.; Murray, S. *Organometallic* **2011**, *30*, 441-457. (m) Hatnean, J. A.; Johnson, S. A. *Organometallic* **2012**, *31*, 1361-1373.

85) (a) Indolese, A. F. *Tetrahedron Lett*. **1997**, *38*, 3513-3515. (b) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447-3452.

86) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2483.

87) (a) Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 3565-3568. (b) Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7164-7165. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286. (d) Miyaura, N. *Bull. Chem. Soc. Jpn*. **2008**, *81*,1535-1553.

88) (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890-931. (b) Pilarsko, L. T.; Szabo, K. J. *Angew. Chem. Int. Ed.*

2011, *50*, 8230-8232. (c) Newhouse, T.; Baran, P. S. *Angew. Chem,. Int. Ed*. **2011**, *50*, 3362-3374.

89) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc*. **2007**, *129*, 6716-6717.

90) (a) Saito, G.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602-9603. (b) Kirchhoff, J. H.; Netherton, M. R.; Hill, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662-13663. (c) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154-8157. (d) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813-3818.

91) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F. III.; Schenck, R. J.; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443-4451.

92) (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, **2004**; Vols 1 and 2. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, 2 Vol. Set*; Wiley-VCH: New York, **2004**.

93) (a) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96-103. (b) Hammett, L. P. *Chem. Rev*. **1935**, *17*, 125-136. (c) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165-195.

94) (a) Schaub, T.; Doring, C.; Radius, U. *Dalton Trans*. **2007**, 1993-2002. (b) Yu, D.-G.; Yu, M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, *11*, 3374-3377.

95) (a)Takei, H.; Miiura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447-1450. (b) Wenkert, E.; Hanna, J. M.; Leftin, M. H.; Michelotti, E. I.; Potts, K. T.; Usifer, D. *J. Org. Chem.* **1985**, *50*, 1125-1126. (c) Kanemura, S.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Synthesis* **2008**, 2659-2664.

96) (a) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *Can. J. Chem*. **1963**, *41*, 3081-3090. (b) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A.; *J. Am. Chem. Soc.* **1964**, *86*, 2666-2670.

97) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.

98) Keyes, L.; Sun, A. D.; Love, J. A. *Eur. J. Org. Chem*. **2011**, 3985-3994.

99) (a) Rosen, B. M.; Quasdof, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.; Garg, N. K.; Percec, V. *Chem. Rev*. **2011**, *111*, 1346-1416. (b) Lin, S.; Agapie, T. *Synlett* **2011**, *1*, 1-5.

100) Cotton, F. A.; Wilkinson, G. In *Advanced Inorganic Chemistry;* Wiley-Interscience: **1980**, pp. 375-376.

101) Tamao, K.l.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1976**, *49*, 1958-1969.

102) Slagt, V. F.; De Vries, A. H. M.; De Vries, J. G.; Kellogg, R. M. *Org. Process Res. Dev.* **2010**, *14*, 30-47.

103) (a) Johnson, S. A., Huff, C. A., Mustafa, F., Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 17278-17280. (b) Johnson, S. A., Taylor, E. T., Cruise, S. J. *Organometallic* **2009**, *28*, 3842-3855. (c) Doster, M. E., Hatnean, J. A., Jeftic, T., Modi, S., Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923-11925. (d) Hatnean, J. A., Beck, R., Borrelli, J. D., Johnson, S. A. *Organometallics* **2010**, *29*, 6077-6091. (e) Johnson, S. A., Mroz, N. M., Valdizon, R., Murray, S. *Organometallics* **2011**, *30*, 441-457. (f) Campeau, L.-C., Fagnou, K. *Chem. Commun.* **2006,** 1253-1264. (g) Nakao, Y., Kashihara, N., Kanyiva, K. S., Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170-16171. (h) Kanyiva, K. S., Kashihara, N., Nakao, Y., Hiyama, T. *Dalton Trans.* **2010**, *39*, 10483-10494.

104) Morandi, S.; Caselli, E.; Forni, A.; Bucciarelli, M.; Torre, G.; Prati, F. *Tetrahedron: Asymmetry*. **2005**, *16*, 2918-2926.

105) Wu, F.; Yang, W.; Wang, Q.; Zhang, M.; Ding, Y.-Q. *Chinese J. Synth. Chem*. **2011**, *19*, 109-110.

106) Karade, N. N.; Tiwari, G. B.; Gampawar, S. V. *Synlett* **2007**, *12*, 1921-1924.

107) (a) Noveski, D.; Braun, T.; Neumann, B.; Stammler, A.; Stammler, H.-G. *Dalton Trans.* **2004**, 4106-4119. (b) Braun, T.; Parsons, S.; Perutz, R. N.; Voith, M.

Organometallics **1999**, *18*, 1710-1716.

108) (a) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973**, *50*, C12-C14. (b) Guo, H.; Kong, F.; Kanno, K.-i.; He, J.; Nakajima, K.; Takahashi, T. *Organometallics* **2006**, *25*, 2045-2048. (c) Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. Synthesis 1999, 12, 2138-2144. (d) Wang, J.-R.; Manabe, K. Org. Lett. 2009, 11, 741-744. (d) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem. Int. Ed*. **2008**, *47*, 10124-10127. (e) Xie, L.-G.; Wang, Z.-X. *Angew. Chem. Int. Ed*. **2011**, *50*, 4901-4904.

109) (a) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117-2188. b) Rieke, R. D. *Aldrichimica Acta* **2000**, *33*, 52-60. (c) Knochel, P.; Schade, M. A.; Bernhardt, S.; Manolikaes, G.; Metzger, A.; Piller, F. M.; Rohbogner, C. J.; Mosrin, M. *Beilstein J. Org. Chem.* **2011**, *7*, 1261-1277.

110) Huo, S. *Org. Lett*. **2003**, *5*, 423-425.

111) Stanger, A.; Vollhardt, K. P. C. *Organometallic* **1992**, *11*, 317-320.

112) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; McGrady, J. E.; Perutz, R. N. *Acc. Chem. Res*. **2011**, *44*, 333-348.

113) (a) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417-731. (b) Phapale, V. B.; Cardenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598-1607.

114) Meyer, Y.; Richard, J.-A.; Massonneau, M.; Renard, P.-Y.; Romieu, A. *Org. Lett*. **2008**, *10*, 1517-1520.

115) Sonda, S.; Katayama, K.; Kawahara, T.; Sato, N.; Asano, K. *Bioorg. Med. Chem*. **2004**, *12*, 2737-2747.

116) (a) Dauth, A.; Love, J. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9219-9224. (b) Dauth, A. Personal communication.

117) Hall, D. G. Structure, Properties, and Preparation of Boronic Acid Derivates. Overview of Their Reactions and Applications. In *Boronic Acids - Preparation and*

Applications in Organic Synthesis and Medicine; Hall, D. G., Eds.; Wiley-VCH: Weinheim, **2005**; pp 1-99.

118) Cazorla, C.; Metay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 3936-3938.

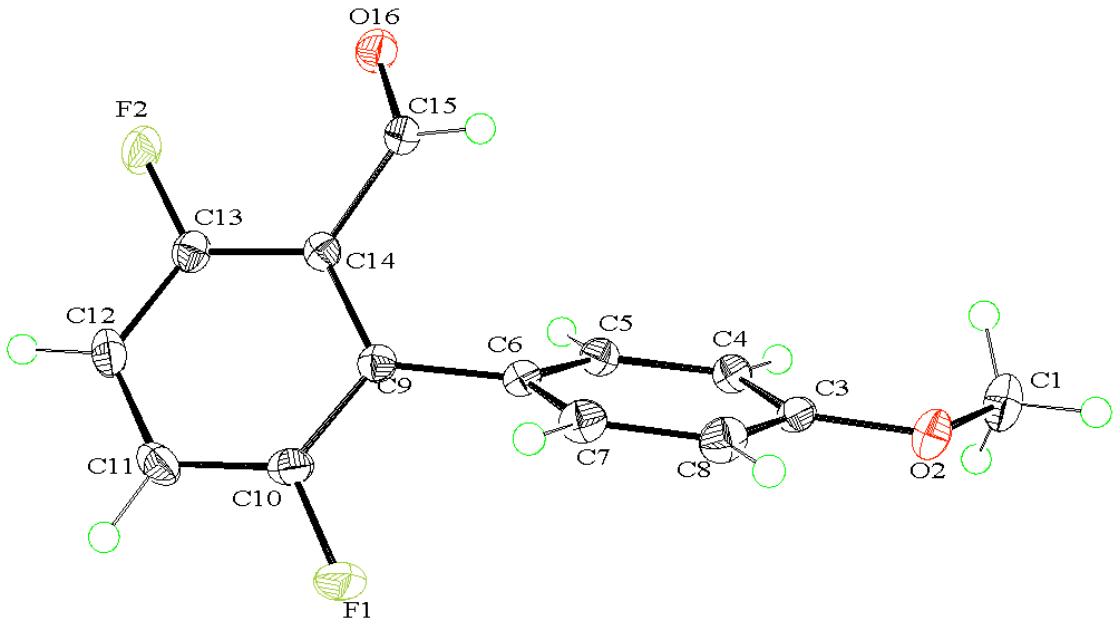
119) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2006**, *44*, 192-212.

Appendix: X-ray data for compound **3P**

Data Collection

A colorless blade crystal of $C_{14}H_{10}F_2O_2$ having approximate dimensions of 0.08 x 0.13 x 0.25 mm was mounted on a glass fiber. All measurements were made on a Bruker X8 APEX II diffractometer with graphite monochromated Mo-Kα radiation.

The data were collected at a temperature of -173.0 ± 0.1°C to a maximum 2θ value of 56.1°. Data were collected in a series of ϕ and ω scans in 0.50° oscillations with 20.0-second exposures. The crystal-to-detector distance was 40.02 mm.



A. Crystal Data

Empirical Formula	$C_{14}H_{10}F_2O_2$
Formula Weight	248.22
Crystal Colour, Habit	colourless, blade
Crystal Dimensions	0.08 X 0.13 X 0.25 mm
Crystal System	orthorhombic
Lattice Type	primitive
Lattice Parameters	a = 20.909(3) Å b = 7.4692(9) Å c = 7.1368(8) Å α = 90 β = 90 γ = 90 V = 1114.6(2) Å^3
Space Group	*P ca*2_1 (#29)
Z value	4
D_{calc}	1.479 g/cm^3
F_{000}	512.00
μ(MoKα)	1.20 cm^{-1}

B. Intensity Measurements

Diffractometer	Bruker X8 APEX II
Radiation	MoKa (λ = 0.71073 Å) graphite monochromated
Data Images	2811 exposures @ 20.0 seconds
Detector Position	40.02 mm
$2\theta_{max}$	56.1
No. of Reflections Measured	Total: 25961
	Unique: 2695 (R_{int} = 0.028; Friedels not merged)
Corrections	Absorption (T_{min} = 0.907, T_{max}= 0.990)
Lorentz-polarization	

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	S w (Fo^2 - Fc^2)^2
Least Squares Weights	w=1/($s^2(Fo^2)$+(0.0418P) ^{2}+ 0.2203P)
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (l>0.00σ(l))	2695
No. Variables	164
Reflection/Parameter Ratio	16.43
Residuals (refined on F^2, all data): R1; wR2	0.028; 0.074
Goodness of Fit Indicator	1.05
No. Observations (I>2.00σ(I))	2583
Residuals (refined on F): R1; wR2	0.027; 0.072
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.27 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.20 $e^-/Å^3$