

January 01, 2009

New methodologies for the preparation of fluorine containing medicinal agents

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Recommended Citation

Lapointe, Blair T., "New methodologies for the preparation of fluorine containing medicinal agents" (2009). *Chemistry Master's Theses*. Paper 7. <http://hdl.handle.net/2047/d2000022>

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New Methodologies for the Preparation of Fluorine Containing Medicinal Agents

A thesis presented

by

Blair T. Lapointe

to

The Department of Chemistry and Chemical Biology

In partial fulfillment of the requirements for the degree of

Master of Science

in the field of

Chemistry

Northeastern University
Boston, Massachusetts
April, 2009

New Methodologies for the Preparation of Fluorine Containing Medicinal Agents

by

Blair T. Lapointe

ABSTRACT OF THESIS

Submitted in partial fulfillment of the requirements
for the degree of Master of Science in Chemistry
in the Graduate School of Arts and Sciences of
Northeastern University, April 2009

ABSTRACT

Fluorine has a long history as an important and useful tool in the development of new pharmaceuticals. Fluorine is able to modulate physical properties like solubility and facilitate stronger binding interactions within the binding pocket, while also having the added benefit in that one of its isotopes, ^{18}F , can be employed as a radiotracer for PET and SPECT imaging. Thus, there is a renewed need for technologies that allow fluorine to be easily introduced into pharmaceutical agents to take advantage of the many benefits available.

During the course of a recent medicinal chemistry program there was a need to be able to install a difluoroketone moiety. Currently, the best viable option for reaching this objective was using Percy's difluorostannane derivative, which was coupled to respective aromatic rings through Stille coupling conditions.^{1,2} Since removal of tin during the purification steps can be problematic, and is a known neurotoxin, a boron based alternative was explored. Herein I present the work of the optimization, scope and application of the Suzuki-Miyaura coupling of a novel potassium trifluoroborate salt with various aryl halide coupling partners. This work identified our agent as an effective and efficient precursor for difluoroketone substituted compounds, and viable alternative to the analogous tin reagent.

The fluorodenitration reaction has been developed as a routine way to install nucleophilic fluorine onto aromatic rings. This technology was adopted to microwave acceleration for the use in the synthesis of radio-labeled pharmaceuticals. This method decreased reaction time dramatically and allowed the radioactive fluorine to be installed

well within its half-life of 110 min. This procedure worked well for compounds already containing a nitro group, but due to its reactive nature difficulties arose when trying to carry out a full synthesis with a nitro group present. Thus, time was dedicated to exploring a recently published nitrodehalogenation reaction, but under microwave conditions.³ After determining the optimum reaction conditions, this method was applied to series of substituted aryl-halides. With these two technologies in hand it would be possible to carry out two sequential microwave reactions to obtain the final radio-labeled pharmaceutical agent.

ACKNOWLEDGEMENTS

First and foremost I would like to acknowledge and thank Dr. Graham B. Jones. Dr. Jones always made time to talk with me about my research as well as my professional and even some of my personal goals. He catalyzed both my attendance at Northeastern University and my ability to graduate in four years with a combined MS/BS. Dr. Jones has had a direct impact on how far I have come over the past four years and I can not thank him enough for the opportunities he has afforded me. In addition to Dr. Jones, I would like to thank the Jones research group for all their help and support while I completed my thesis work in their lab.

I would also like to thank Dr. Jason Katz and the Medicinal Chemistry Department of Merck Pharmaceuticals for giving me the chance to intern with them. The experience was life changing and really allowed me to appreciate the field I have decided to pursue. Specifically, Dr. Katz has acted as a mentor for me and taught me a lot of new ways to approach and think about chemistry. While under Dr. Katz I was able to grow as a chemist and really find my confidence as a synthetic chemist.

Although I can thank Dr. Jones and Dr. Katz for refining my skills as a chemist, I would not be a chemist at all today without my high school chemistry teachers, Mrs. McCormick and Mr. Murawski. These two people opened my eyes to the possibilities and opportunities that chemistry allows. They taught the subject in a fun and stress-free manner that really allowed me to appreciate the subject without getting laden down with the fact that we were actually beginning to learn some rather technical subjects. I can

honestly say that I would not be where I am today without having taken their classes and listening and following their advice.

Lastly, I would like to thank all my family and friends who have supported me over the past four years. They have had to hear about both my triumphs and hardships, and it's the latter of which I thank them for getting me through. Specifically I would like to acknowledge my parents, Jeff and Cheryl, and my sister, Michelle, for the love and support they give me while I pursue all of my goals.

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GLOSSARY OF ABBREVIATIONS

APCI	Atmospheric pressure chemical ionization
app	Approximate
BF ₃ K-salt	Potassium trifluoroborate salt
CDCl ₃	Deuterated chloroform
CuI	Copper iodide
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
Et ₃ N	Triethylamine
EtOAc	Ethyl Acetate
FDG	Fluorodeoxyglucose
g	gram
HCl	Hydrogen chloride
HF	Hydrogen fluoride
hr	Hour
<i>J</i>	Joule
KHF ₂	Potassium hydrogen fluoride
L	Liter

LDA	Lithium diisopropylamide
LC/MS	Liquid Chromatography/ Mass Spectroscopy
Me	Methyl
MEM	Methoxyethoxymethyl
MeCN	Acetonitrile
mg	Milligram
MHz	Megahertz
mL	Milliliter
mol	Mole
mmol	Millimole
NMR	Nuclear Magnetic Resonance
n-PrOH	Normal propanol
PET	Positron Emission Tomography
PdCl ₂	Palladium(II) chloride
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
ppm	Parts per million
PSI	Pounds per square inch
R _f	Retention factor
Ruphos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
SPECT	Single Photon Emission Computed Tomography
t _{1/2}	Half-life
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
UV/Vis	Ultra violet-visible spectroscopy
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
μL	Microliter
μm	Micrometer
18-crown -6	1,4,7,10,13,16-hexaoxacyclooctadecane

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Chapter 1

Introduction

1.1 Fluorine in Pharmaceuticals

Fluorine has become increasingly exploited through incorporation into synthetic pharmaceutical agents over the past 50 years since the introduction of 5-fluorouracil in 1957.⁴ This increase in fluorine implementation has been extremely noteworthy within the past 5 years, with 44 fluorinated drug candidates currently under studies in clinical trials.⁵ The steric changes associated with the substitution of fluorine for hydrogen is rather small due to their similar atomic radii, but the difference in electronegativity can greatly affect the pharmacological effects of the drug candidate.⁶ The site and extent of fluorine substitution will determine how greatly the candidate's binding interactions, stability, selectivity, and physical properties, like pK_a and $\log P$, are affected.^{4,5} Due to fluorine's wide array of effects, its incorporation is often considered during the optimization of a pharmaceutical agent in order to address potential issues with drug development, such as metabolism, solubility, and pharmacokinetics. For example, fluorine can be substituted into aromatic rings to increase stability by preventing oxidation on the ring.⁴ Fluorine has become one of the most important elements in the development of new pharmacological agents and its use will continue to grow, especially with the potential for ^{18}F incorporation and use as a radiotracer for PET and SPECT scans.

A variety of methods exist to install fluorine into organic molecules. Fluorine can be installed directly, using either a nucleophilic or an electrophilic fluorinating agent, or

as part of a larger functional group, using a variety of synthetic reagents.⁷ The first reagent available as a source for electrophilic fluorine was elemental fluorine.^{7,8} From here, a series of *O*-F reagents and *N*-F reagents were developed for the installation of electrophilic fluorine. Of these new reagents, Selectfluor® (Figure 1.1) and its related derivatives have become one of the more popular reagents because of their stability and ease of use.⁷

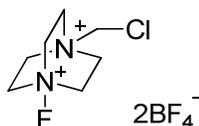
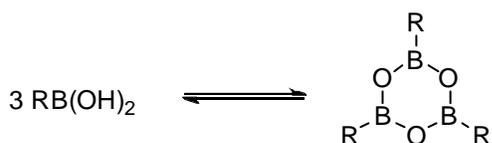


Figure 1.1: Selectfluor®

Fluorine can also be installed by direct displacement with a fluoride source. There are many reagents that can be used to deliver nucleophilic fluorine, including but not limited to hydrogen fluoride, tetrabutylammonium fluoride, and DAST.^{7,9} Additionally, nucleophilic fluorination reactions allow ¹⁸F to be installed for use in PET and SPECT scans, both of which are part of the rapidly growing functional imaging field. If ¹⁸F capabilities are not required, there are a variety of reagents available to couple groups already containing fluorine to various organic molecules. One of the most popular reagents in this class of fluorine reagents is trimethyl(trifluoromethyl)silane, which allows a trifluoromethyl group to be transferred from the silicon to an appropriate electrophile, such as a carbonyl carbon.

1.2 Molander Organotrifluoroborates

Of the available organoboron reagents, boronic acids can often be difficult to work with. They are often waxy solids, can be chemically unstable, and can form nonreactive trimers (Scheme 1.1).¹⁰



Scheme 1.1: Trimerization of boronic acid

Boronic acids can be protected by converting them to their respective esters, using various diols. These boronic esters still have a limited stability and are sometimes difficult to store, since residual water can convert them back to the original boronic acid. These problems led to the development of the class of boron reagents known as the potassium trifluoroborate salts. These salts are often stable when stored on the bench top, and are usually synthetic analogues to the corresponding boronic acids, as they are likely converted back into the acid *in situ*.¹⁰

Gary Molander has devoted a large portion of his research toward the development of the organoboron reagents, specifically the trifluoroborate salts, used in Suzuki-Miyaura coupling. Molander has developed and explored a wide variety of alkenyl-, alkyl-, alkynyl-, aromatic-, and vinyl- trifluoroborate salts.¹¹⁻¹⁸ Furthermore, the Molander group has demonstrated the versatility of each reagent by exploring and

varying the variety of coupling partners that are compatible with each class of BF_3K -salt.¹⁰

1.3 PET/SPECT Labeling

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are two similar imaging techniques that recently have become increasingly popular for mapping drug targets within the body. These noninvasive imaging options are especially important when mapping the brain. These techniques work by detecting the decay of a radioactive tracer injected into the subject. During a SPECT scan, when the decay occurs a gamma ray is emitted, which is then measured by a gamma camera. PET differs from SPECT in that when the radio-tracer decays it emits a positron that travels a short distance before it collides with an electron. This annihilation generates two anti-parallel photons which are then detected by the scanning unit. Examples of some radio-labeled pharmaceutical agents used for PET scans are displayed in (Figure 1.2). The largest factor in determining which elemental radiotracer is used for these tests is their respective half-lives. Currently the most popular radiotracers for PET are ^{18}F ($t_{1/2} = 110$ min) and ^{11}C ($t_{1/2} = 20$ min). Within the first few half lives the tracer has to be incorporated into a pharmaceutical agent, purified, injected into the patient, and a full scan taken. Since the limiting factor is time, radiotracer incorporation has to be the final step of the agent's synthesis and has to be a clean straightforward reaction.

There are three general ways in which PET/SPECT scans are currently used to map the human body: monitoring metabolism rates, occupancy studies and monitoring

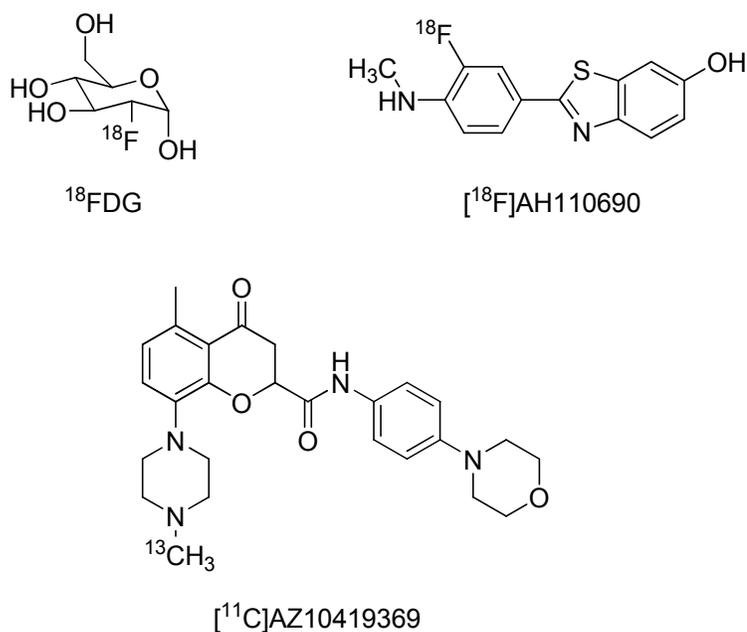


Figure 1.2: Radio labeled pharmaceutical agents

drug distribution. For monitoring metabolism one of the most well known radio tracers, ^{18}F FDG, is used to show areas with increased or decreased rates of metabolism. This technique is popular when mapping a patient with cancer, as tumors tend to consume glucose at a faster rate than normal tissue. This method is also used for mapping the activity of the brain pre- and post- Alzheimer's disease.¹⁹ The second method, occupancy studies, is a way to indirectly monitor how effective a drug is at binding to its target. A ligand with high affinity for the drug's target is labeled with a radiotracer and injected into the patient. Following this injection the non-radio labeled drug is injected and the physician is able to watch the ligand bind to the target and then sequentially watch how effective the drug replaces the ligand in the binding site. The last method employed for PET/SPECT scans is to directly label the drug with a radiotracer and monitor whether it

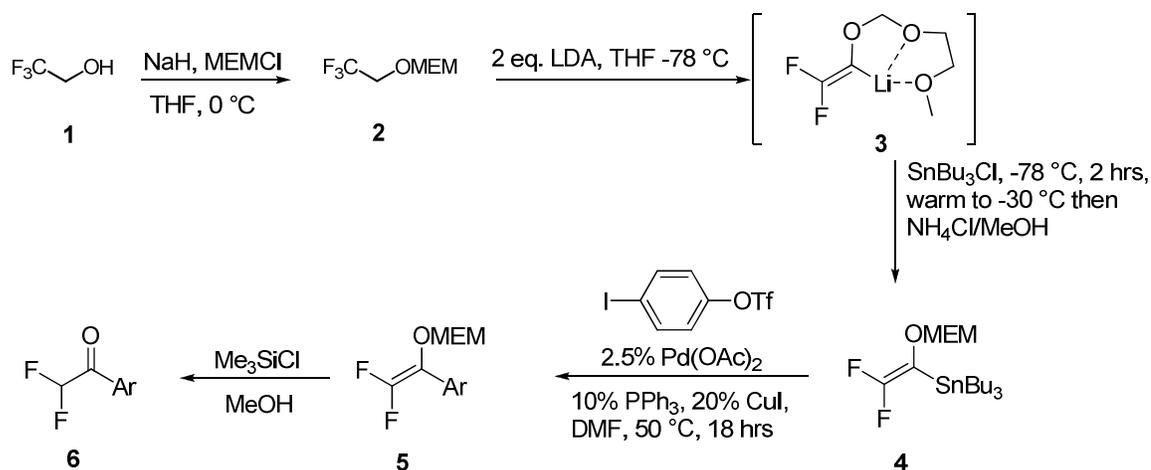
reaches its desired target, how long it stays there, and how it is metabolized within the body. This method is the newest application and is ideal for determining directly the course of the drug while in the body.

Chapter 2

Development of a Novel Trifluoroborate Salt

2.1 Objective

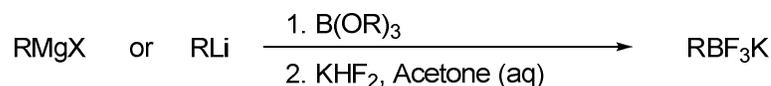
In a recent medicinal chemistry program there was a need to quickly and efficiently install a difluoroketone moiety onto larger molecular skeletons that was applicable to both small scale and large scale syntheses. When this project was started the best viable option for reaching this goal was using Percy's difluorostannane derivative, **4**, which is then coupled to respective aromatic rings through Stille coupling conditions (Scheme 2.1).²



Scheme 2.1: Synthesis of difluoroketone substituted aromatic using Percy's difluoroketostannane reagent

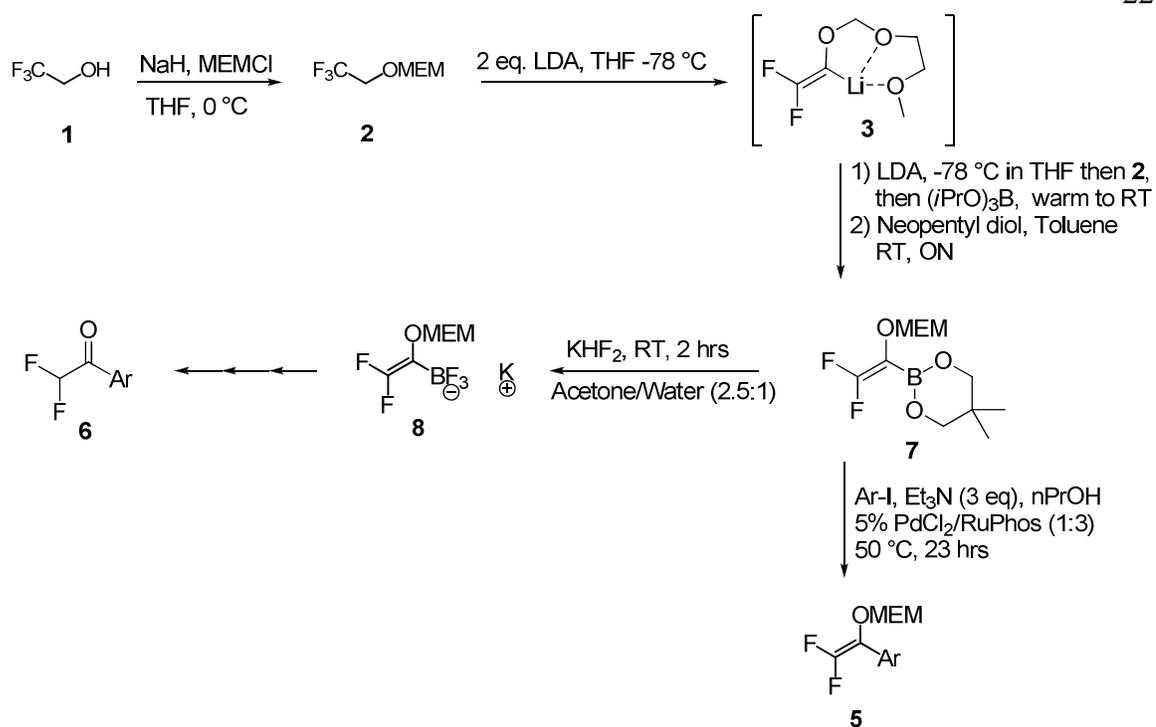
When the scope of reagent **4** was explored the results were excellent when displacing certain iodotriflates, up to 96% isolated for 4-iodophenyl trifluoromethanesulfonate, but

wasn't really expanded to displacing other halides.¹ Another downside of this reagent is the difficulty encountered when trying to purify the product, **5**, from the tin salts. Due to the large scale that reagent **5** would need to be produced on it was impractical and a potential safety issue; therefore a suitable alternative for this stannane based reagent would have to be developed. Recently, Gary Molander has published his extensive work on the discovery and development of new organotrifluoroborate salts. Molander demonstrated that trifluoroborate salts were accessible through a transmetalation step with an appropriate boron electrophile, followed by conversion to the organotrifluoroborate salt (Scheme 2.2).



Scheme 2.2: Transmetalation step in potassium trifluoroborate salt synthesis

Previous work by researchers at Merck has shown that it was possible to prepare the boronic ester **7** derivative of the Percy stannane **4** (Scheme 2.3). This boronic ester was successfully used in the cross coupling to an aryl-iodide. However, this ester was unpredictably unstable and required iodides as the coupling partner. The subject of this work was to explore the possibility of preparing the corresponding trifluoroborate salt **8**.



Scheme 2.3: Projected synthetic route to BF_3K -salt **8**

2.2 Synthesis of Trifluoroborate Salt

The synthesis of the BF_3K -salt **8** began with the protection of the 2,2,2-trifluoroethanol as an ether using methoxyethoxymethyl chloride. The MEM-protected alcohol was then deprotonated twice at the alpha position, which most likely forms the lithium salt intermediate **3**. At this point, instead of quenching with a tin reagent like Percy, we quenched with a boron based electrophile, triisopropyl borate. After work-up this gave us the boronic acid, which was sequentially converted to its respective ester using neopentyl diol. Performing these steps sequentially allowed us to avoid losing any acid to trimerization. The conversion from protected alcohol **2** to boronic ester **7** resulted in a

51% conversion. Boronic ester **7** was successfully coupled to give products with the general structure of **5** by researchers at Merck, but it was determined that the reagent was unstable on the bench top. To alleviate this problem it was thought that if boronic ester **7** could be advanced to the boronic salt **8** it may be bench top stable and therefore easier to use. This conversion was done by using the standard method of treatment with an excess of potassium hydrogen fluoride and stirred overnight. After recrystallization with acetonitrile and ether, potassium trifluoroborate salt **8** was isolated with an excellent 91% isolated yield.

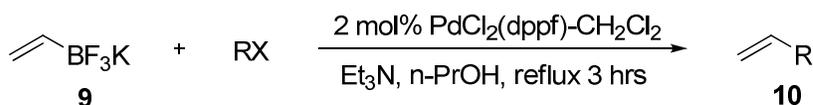
A degradation study was performed for both the boronic ester and BF_3K -salt over four months. For the boronic ester we set up two separate lots for study. The first lot was stored in a dilute toluene solution under an inert atmosphere at a $0\text{ }^\circ\text{C}$, while the second was stored the same way but with the addition of potassium carbonate as a drying reagent. The second lot with potassium carbonate degraded overnight, while the first lot was stable for up to four months in the freezer without any appreciable degradation. When the boronic salt's stability was examined it was stored neat in a scintillation vial on the bench top. Over the four months that its stability was examined, there was no degradation. Since the boronic ester had to be thawed and concentrated before each use the BF_3K -salt was the reagent of choice for the Suzuki-Miyaura coupling reaction due to its ease of use.

2.3 Optimization

With the the salt in hand, it was possible to explore potential coupling conditions. The coupling optimization of our trifluoroborate salt was done with 1-bromonaphthalene

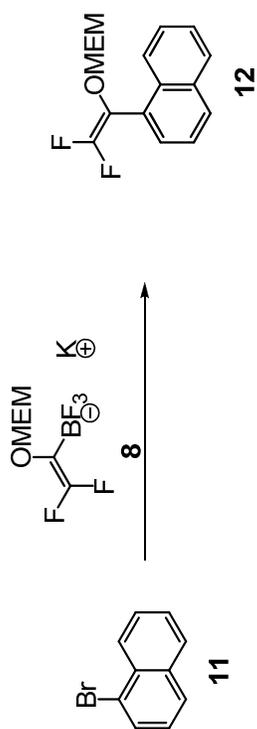
as the coupling partner since bromides are more versatile than their respective iodides.

We started our optimization by using the conditions determined to be optimal by the Molander group for the coupling of potassium vinyltrifluoroborate with simple aromatics (Scheme 2.4).¹²



Scheme 2.4: Molander's optimized coupling conditions for a generic vinylic BF₃K-salt

These conditions delivered the desired vinyl naphthalene **12** in a 70% isolated yield (Figure 2.1) (entry 1). Previous work with ester **7** had shown that the reagent was unstable to reaction conditions; using excess reagent led to higher yields. However, increasing the equivalents of salt **8** (entries 1-3) under these conditions did not have any effect on the yield. Additionally, since the boronic ester **7** was sensitive to temperature we investigated whether lower temperatures could increase the yield. This proved incorrect, as decreasing the temperature negatively affected the yield (entries 4-5). When we monitored the reaction at different time points, the reaction appeared to be mostly over after 2 hrs (entries 6-8). The length of this reaction was revisited after the ideal catalyst/ligand system was determined (entries 15-16). This second investigation showed the reaction was still proceeding after 4 hrs, with a 70% conversion at that time point compared to the 91 % yield at 23 hrs.



entry	Catalyst system	Catalyst loading	Solvent	Equiv. of salt	Base	Temp (°C)	Reaction time (hr)	Isolated yield (%)
1	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	90	24	70
2	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.5	Et_3N	90	24	69
3	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	2	Et_3N	90	24	68
4	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	50	24	4
5	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	70	24	53
6	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	90	2	66
7	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	90	4	66
8	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	Et_3N	90	6	65
9	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	CsCO_3	90	26	-
10	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	K_3PO_4	90	26	-
11	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	nPrOH	1.1	KOAc	90	25	12
12	$\text{PdCl}_2\text{-Xphos (1:3)}$	0.05	nPrOH	1.1	Et_3N	90	23	86
13	$\text{PdCl}_2\text{-RuPhos (1:3)}$	0.05	nPrOH	1.1	Et_3N	90	23	91
14	$\text{PdCl}_2\text{-PPh}_3 (1:3)$	0.05	nPrOH	1.1	Et_3N	90	23	39
15	$\text{PdCl}_2\text{-RuPhos (1:3)}$	0.05	nPrOH	1.1	Et_3N	90	2	58
16	$\text{PdCl}_2\text{-RuPhos (1:3)}$	0.05	nPrOH	1.1	Et_3N	90	4	69
17	$\text{PdOAc}_2\text{-Ruphos}$	0.05	nPrOH	1.1	Et_3N	90	25	86
18	$\text{Pd(dba)}_2\text{-RuPhos}$	0.05	nPrOH	1.1	Et_3N	90	25	69
19	$\text{PdCl}_2\text{-(dppf)-CH}_2\text{Cl}_2$ Adduct	0.05	<i>t</i> Amyl-OH	1.1	Et_3N	90	23	10

Figure 2.1: Optimization of Coupling Conditions for Trifluoroborate Salt **8**

We also explored another solvent, *t*-amyl alcohol, which due to its steric bulk should alleviate any possible problems caused from solvent addition into the enol, but it did not improve the yield over *n*-propanol (entry 19). During our exploration of different bases, inorganic bases proved extremely detrimental to the course of the reaction. Both Cs_2CO_3 and K_3PO_4 resulted in no observable product, and KOAc resulted in only a 12% isolated yield.

Buchwald ligands have also been shown to be effective in similar Molander couplings.¹² We explored the more standard ligand triphenylphosphine as well as XPhos and RuPhos (Figure 2.2) of the Buchwald ligand set (entries 12-14).^{20, 21} Of the ligands tested, RuPhos resulted in the best conversions, with an isolated yield of 91% (entry 13). With our ligand in hand we investigated whether delivering palladium(II) with a different counter-ion or palladium(0) had an effect on the coupling (entries 17-18). Palladium(II) acetate gave a similar yield to palladium(II) chloride while $\text{Pd}_2(\text{dba})_3$ gave a decreased yield of 69 %.

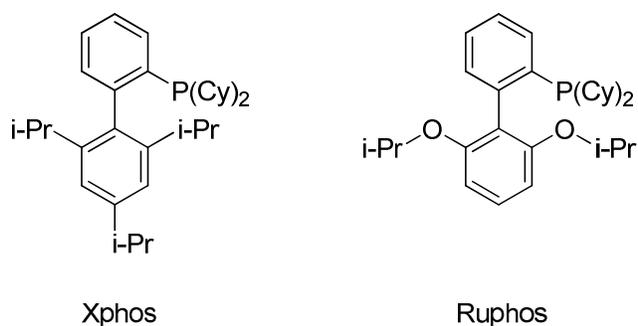
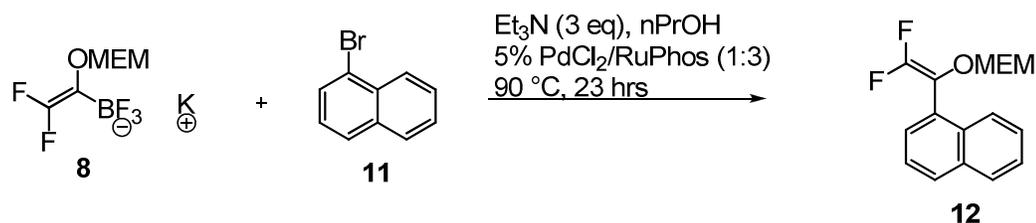


Figure 2.2: Structures of Xphos and RuPhos

2.4 Scope

Using the optimized conditions the scope of the coupling partners for trifluoroborate salt **8** was explored (Scheme 2.5).

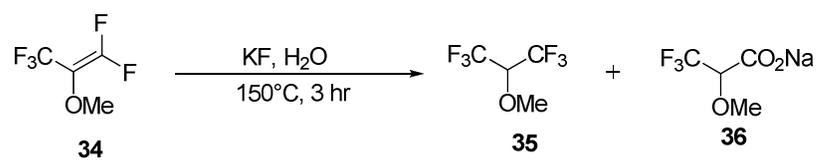


Scheme 2.5: Optimized conditions for coupling of novel potassium trifluoroborate salt

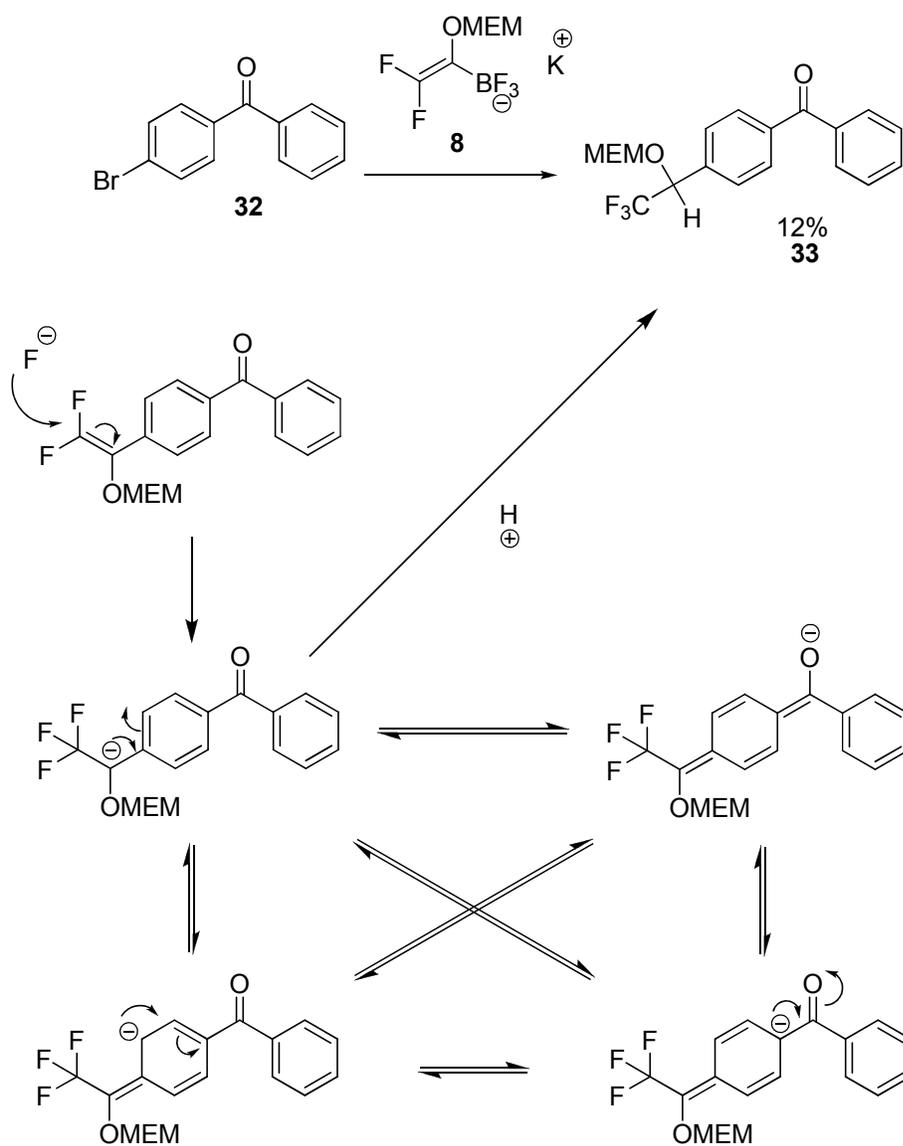
First, the halides on the aromatic ring were compared (iodo- vs. bromo- vs. chloro-naphthalene) (Figure 2.3). Bromine proved to be the best halide for this coupling reaction. 1-chloronaphthalene (**14**) gave a 78% isolated yield, which was expected since it is less reactive towards oxidative insertion than bromine. The iodide (**15**) was expected to give a higher yield because it is more susceptible to oxidative insertion, but actually only gave a 48% isolated yield. The free iodide that may be generated during the course of this reaction has the ability decompose the salt or product, which would lead to lower yields. Next the three isomers of bromoanisole were used to explore the electronic effects of ring substitution on the coupling reaction. Ortho-, Para-, and Meta- (**16-18**) substitution resulted in similar results, 86%, 76%, and 83% isolated yields respectively. When steric effects were explored, they also proved to have a minimal effect on the coupling reaction. For example, 1-bromo-2-isopropylbenzene (**21**) resulted in a moderate yield of 66%, while 2-bromomesitylene (**20**) gave a 72% isolated yield.

The scope was pursued further to explore a larger range of electronic effects. Of the heteroatomics that worked well, 7-bromo-1H-indole (**25**) afforded a 65% yield and 3-bromopyridine (**26**) gave a 77% yield, meanwhile 2-bromothiazole (**29**) allowed no desired product. Of the other substituents that worked with this coupling, 4-bromobenzotrifluoride (**24**) generated a 82% yield while 4'-bromoacetophenone (**23**) resulted in a 66% yield and 4'-bromobenzophenone (**22**) gave a 62% yield. The substrates that didn't work well included the nitro substituted aromatic rings (**27-28**) as well as 2-acetyl-5-bromothiophene (**30**).

One of the notable side-products that was observed while exploring the scope of these reactions occurred with the 4-carbonyl substituted substrates, such as 4'-bromobenzophenone. During this reaction we were able to isolate a side-product where HF had added into the enol ether portion of the product. A literature search revealed some precedent for this reaction where at elevated temperatures when HF is present it has the ability to add into a difluoroenoether moiety (Scheme 2.6).²² It seems reasonable that during the *in situ* conversion of the BF₃K-salt into the corresponding boronic acid some HF is evolved which would then be available to participate in a similar reaction with either the boron reagent or the product. These substrates are most likely more prone to this substitution because after the presumable first step of fluorine insertion the resulting negative charge can then be delocalized throughout the ring system (Scheme 2.7). Although this mechanism seems plausible for the 4'-bromobenzophenone substrate, it is also possible that this side reaction occurs with other electron withdrawing substituents, but we were unable to isolate those respective side-products.



Scheme 2.6: Precedent for HF insertion



Scheme 2.7: Benzophenone by-product formation

In an attempt to circumvent the HF addition and increase the yield of the 4'-bromobenzophenone coupling, we decided to explore the analogous reaction using the boronic ester **7**. This reaction only resulted in a 29% isolated yield, which was much less than that observed during the coupling using the BF₃K-salt **8** (Figure 2.3). For comparison, the coupling of 1-bromonaphthalene was also done with the boronic ester **7**, which gave a 25% isolated yield. At first this yield was unimpressive. When the reaction was repeated, adding a second equivalent of the ester after two hours the yield increased to 62%. This result showed that ester degradation was probably occurring faster than the insertion, and a slow addition of the ester would negate this problem. The ester coupling was also attempted with 1-bromo-3-nitrobenzene and 2-bromothiazole, both of which resulted in no conversion with the BF₃K-salt coupling. The nitro-substituted product was able to be isolated with a 41% isolated yield while the thiazole substrate still resulted in no yield.

2.5 Applications and Future Directions

Some work was done into the applicability of this reaction to both microwave accelerated synthesis and benzyl coupling reactions. A small exploration of microwave coupling conditions revealed that heating the reaction at 150°C for ten minutes, using two equivalents of the BF₃K-salt, resulted in the best conversion to the desired product. The results for the scope attempted with these conditions are listed in Figure 2.4. Using 1-bromonaphthalene as the coupling partner revealed that there is about a 50% decrease in yield when conducting this reaction in the microwave using the previously optimized

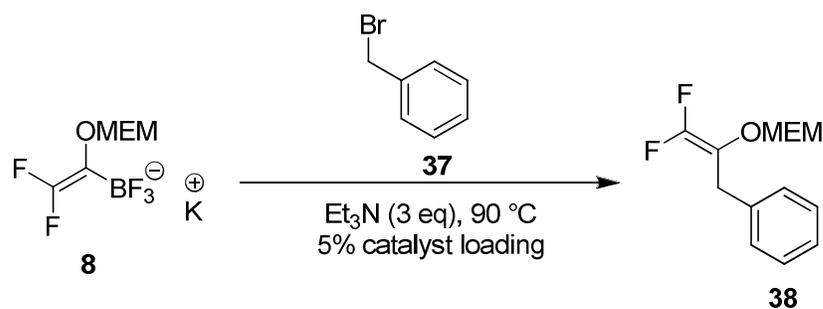
conditions (entry 1). However, under these reaction conditions, the reaction time is decreased from 23 hours to ten minutes, a 99 % decrease in reaction time, which makes this a viable option for time sensitive applications. A positive that came from this study was the result for 2-bromoanisole, which gave an 83% isolated yield (entry 3). This result was nearly identical to that of the conventional coupling, lending some feasibility to the microwave application of this reaction. With greater exploration of microwave conditions this method could prove to be a quick and effective alternative of the conventional method.

entry	Starting material	Isolated Yield (%)	
		Conventional	Microwave
1	1-bromonaphthalene	91	43
2	2-bromoanisole	76	38
3	4-bromoanisole	86	83
4	4-bromobenzotrifluoride	82	57
5	2-bromotoluene	78	56

Figure 2.4: Comparison of microwave and conventional syntheses

When attempting to expand the coupling of BF_3K -salt **8** from aryl-halides to benzyl-halides, some difficulty was encountered. An initial survey of reaction conditions was attempted to get the coupling to proceed, but none gave satisfactory results (Figure 2.5). However, during this initial study, it was observed that the benzyl-halide was being completely consumed within the first twenty minutes of the reaction. After reassessing the reaction conditions, it is likely that the benzyl-halide is alkylating triethylamine,

rather than coupling to the desired substrate. Going forward with research in this area, changing to a more hindered base may allow the reaction to proceed as expected. The fact that some desired product (entry 4) was able to be isolated, even with this dominant side reaction, lends the reaction some feasibility.



entry	catalyst system	solvent	reaction time (hr)	Isolated yield (%)
1	PdCl ₂ -RuPhos (1:3)	n-PrOH	24	4
2	PdCl ₂ -dppf (1:3)	n-PrOH	24	7
3	PdCl ₂ -RuPhos (1:3)	dioxane	24	6
4	PdCl ₂ -RuPhos (1:3)	n-PrOH	4	13
5	PdCl ₂ -dppf (1:3)	n-PrOH	2	6
6	PdCl ₂ -RuPhos (1:3)	n-PrOH	2	2

Figure 2.5: Initial investigation into benzyl-halide coupling

The work within this thesis examined the preparation of a new organotrifluoroborate salt, and the scope of its reactivity with a number of coupling partners. This work provides the researcher with the MEM-protected difluoroketone moiety and although there are standard methods for removing such moieties, such as MeOH and TMS-Cl to generate HCl *in situ*, some work will have to be done to optimize

these conditions for this specific substrate.¹ These conditions, coupled with what has been presented herein, combine to give a simple and direct route to difluoroketone substituted pharmaceutical agents.

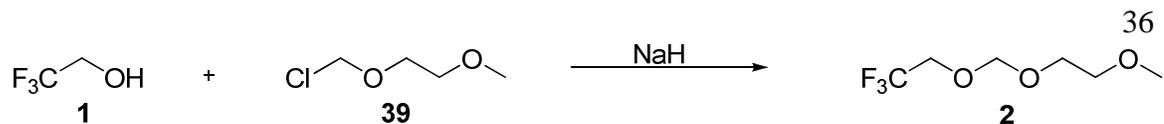
2.6 Experimentals

General Information

Commercial reagents were obtained from reputable suppliers and used as received. All solvents were purchased in septum-sealed bottles stored under an inert atmosphere; those used in palladium cross-couplings were degassed prior to use by sparging with nitrogen for 5 minutes. All reactions were sealed with septa through which a nitrogen atmosphere was introduced unless otherwise noted. Liquid reagents and solvents were transferred under a positive pressure of nitrogen via syringe. Reactions were conducted in microwave vials or round bottomed flasks containing Teflon-coated magnetic stir bars. Microwave reactions were performed with a Biotage Initiator.

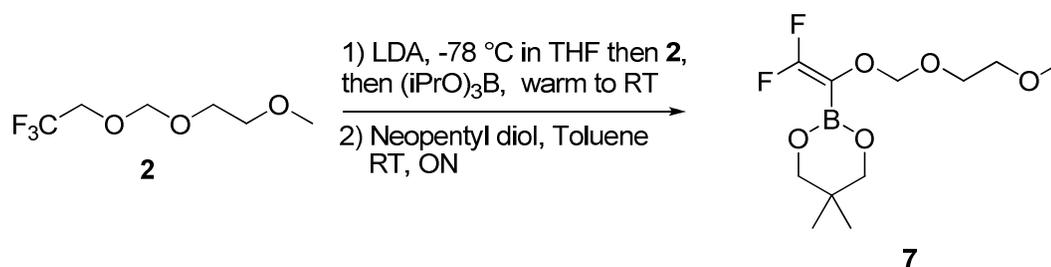
Reactions were monitored by thin layer chromatography (TLC) on precoated TLC glass plates (silica gel 60 F254, 250 μm thickness) or by LC/MS (30 mm x 2 mm 2 micron column + guard; 2 mL injection; 3% to 98% MeCN/water + 0.05% TFA gradient over 2.3 minutes; 0.9 mL/min flow; APCI; positive ion mode; UV detection at 254 nm). Visualization of the developed TLC chromatogram was performed by fluorescence quenching. Flash chromatography was performed on an automated purification system using pre-packed silica gel columns. ^1H and ^{13}C NMR were recorded on a 500 MHz spectrometer; chemical shifts (δ) are reported relative to residual protio solvent signals.

Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR spectra are reported by chemical shift (δ ppm).



1,1,1-trifluoro-2-((2-methoxyethoxy)methoxy)ethane

Sodium hydride (60% dispersion in mineral oil) (20 g, 494 mmol) was suspended in tetrahydrofuran (57 mL) at 0 °C. Trifluoroethanol (41.2 g, 412 mmol, 30 mL) in tetrahydrofuran (57 mL) was added drop wise with an addition funnel over one hour. The solution was then allowed to stir for an additional hour at 0 °C. MEM-Cl, **39**, (61.5 g, 494 mmol, 56 mL) in tetrahydrofuran (57 mL) was then added drop wise over 1 hr using an addition funnel. The white suspension was allowed to warm to room temperature and stir overnight. The reaction was then quenched with water (425 mL) and stirred well to dissolve all of the salt. The solution was diluted with diethyl ether and the organic layer was rinsed with water (2x with 400 mL) and brine (1x with 300 mL) and dried over magnesium sulfate, filtered and concentrated (50 °C, 100 torr). Purification by fractional distillation (100 torr) delivered desired product. Literature value for product is 110 °C at 100 torr. Fractions were collected between 117-121°C. First few drops collected were not saved. Two aliquots, with identical ¹H NMR spectra, were collected after the initial fraction. The first aliquot was 48.93 g and second aliquot was 15.06 g. (63.99 g, 340 mmol, 83% yield). ¹H NMR (500 MHz, CDCl₃) δ 4.79 (s, 2H), 3.93 (q, *J* = 8.9, 2H), 3.75–3.72 (m, 2H), 3.6–3.55 (m, 2H), 3.39 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 124.16 (q, *J* = 277.7), 95.78, 71.73, 67.62, 64.60 (q, *J* = 34.4), 59.20

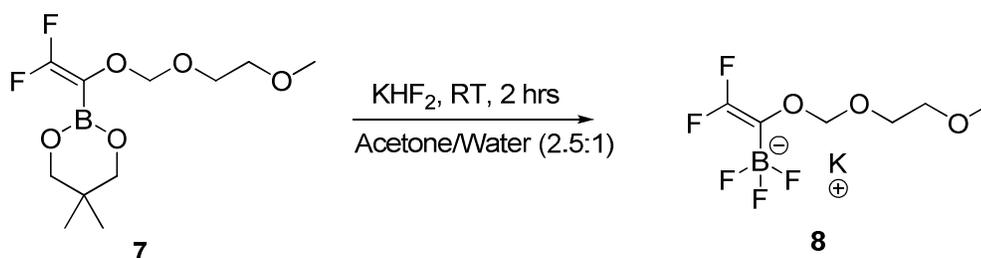


2-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-5,5-dimethyl-1,3,2-dioxaborinane

Di-isopropyl amine (11.29 g, 112 mmol, 15.91 ml) in tetrahydrofuran (57.5 mL) was cooled to -78 °C. Butyl lithium (1.6 M in hexanes) (7.17 g, 112 mmol, 69.8 ml) was added drop wise via addition funnel over 35 min yielding a pale yellow slurry. The addition funnel was rinsed with tetrahydrofuran (8 mL) after initial addition. After 10 min, **2** (10 g, 53.2 mmol) in tetrahydrofuran (10 mL) was added drop wise via addition funnel over 30 minutes such that the internal temperature is less than -65 °C. This addition was also followed by a rinse with tetrahydrofuran (5 mL). The solution turned an orange-brown color towards end of addition of **2**. The reaction mixture was allowed to stand at -78 °C for one hour. Tri-isopropyl Borate (19.99 g, 106 mmol, 24.68 ml) was then added drop wise via addition funnel over 30 min, again keeping the temperature below -65 °C. This addition gave a brown solution. The mixture was allowed to warm to -30 °C over 1 hr. The reaction was then quenched by the addition of saturated ammonium chloride (50 mL), during which a white precipitate formed, and allowed to warm to room temperature. The reaction mixture was diluted in diethyl ether (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with water (2x 50 mL), and the organic layer was discarded. The pH of combined aqueous layers was 10.

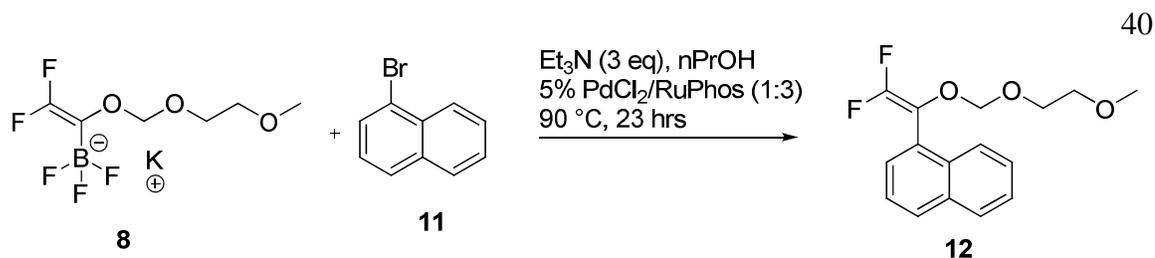
Concentrated HCl was added to the solution until the pH was between 5.5-6. Organics were extracted from aqueous solution with ether (125 mL + 100 mL + 75 mL), combined and dried over sodium sulfate, filtered and concentrated. This yielded an orange oil. The crude material was dissolved in toluene (250 mL) and then neopentyl diol (5.54 g, 53.2 mmol) was added to the solution. This solution was allowed to stir overnight.

The reaction mixture was then concentrated down to about 100 mL and diluted in diethyl ether. This mixture was then washed with water (1x 75 mL) and brine (1x 75 mL), then dried over sodium sulfate giving the first organic layer. The aqueous layer was concentrated with sodium chloride and then back extracted with diethyl ether. This second organic layer was combined with the first over sodium sulfate. Together the organic layer was filtered and concentrated to yield 7.623 g (27.2 mmol, 51.2%) of an orange oil. ^1H NMR (500 MHz, DMSO- d_6) δ 4.78 (s, 2H), 3.62–3.68 (m, 6H), 3.40–3.45 (m, 2H), 3.18 (s, 3H), 0.90 (s, 6H)



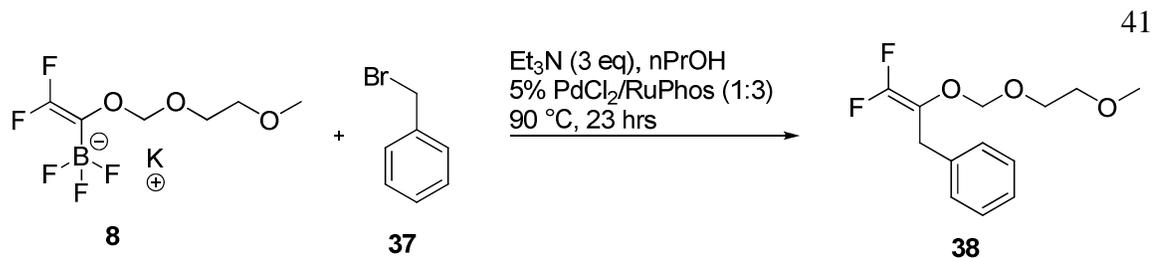
Potassium 2-(difluoromethylene)-1,1,1-trifluoro-3,5,8-trioxa-1-boranuidanonane

7 (6.032 g, 21.54 mmol) was dissolved in water (70 mL)/Acetone (175 mL). Potassium hydrogen fluoride (10.09 g, 129 mmol) was added and the mixture was allowed to stir for 2 hrs. The reaction was concentrated in vacuo, azeotroped 3x with toluene and once with acetone. The solid was suspended in hot acetone, filtered and concentrated. The resulting solid was dissolved in MeCN (40 mL) and diethyl ether (100 mL) was slowly added to mixture. The mixture was then cooled to 0 °C and the solid was filtered off and rinsed with cold diethyl ether. Yield 5.344 g. (19.50 mmol, 91%). ¹H NMR (500 MHz, Acetone-d₆) δ 4.80 (s, 2H), 3.65–3.75 (m, 2H), 3.45–3.55 (m, 2H), 3.60 (s, 3H); ¹⁹F NMR (470, DMSO-d₆) –98.43 (d, *J* = 74.7), –114.08 (dq, *J* = 10.8, 74.7), –137.79– 38.2 (m); ¹³C NMR (125 MHz, DMSO-d₆) δ 94.71, 71.81, 67.37, 58.65



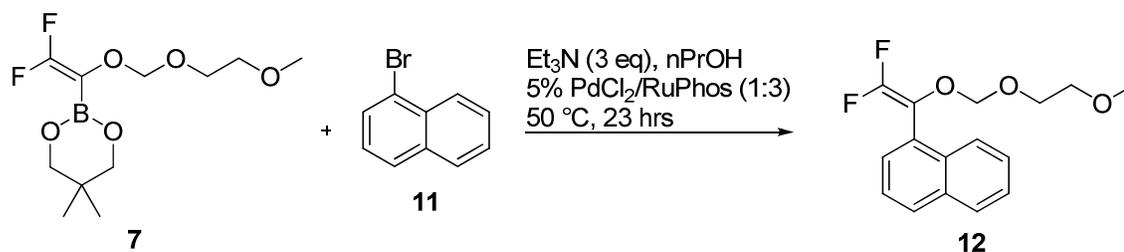
1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)naphthalene

8 (150 mg, 0.550 mmol), Palladium(II) Chloride (4.43 mg, 0.025 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (35.0 mg, 0.075 mmol) were added to a 2-5 mL microwave vial with stir bar, capped and sparged for 5 min. 1-bromonaphthalene (104 mg, .5mmol, 70.0 μ l), triethylamine (152 mg, 1.500 mmol, 209 μ l), n-PrOH (2500 μ l) were then added to the vial and the mixture was sparged for 10 min. The reaction mixture was heated to 90 °C and allowed to stir for 23 hrs. Afterwards, the reaction mixture was diluted in ethyl acetate. The organic layer was rinsed first with sodium hydrogen carbonate then with brine and then back extracted once. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography of silica gel (EtOAc/Hexanes gradient, 0-14 %) to give 133.6 mg (0.454 mmol, 91%) as a clear colorless oil. R_f = 0.181 (7.5% EtOAc/92.5% Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.10 (d, J = 8.0, 1H), 7.94–7.84 (m, 2H), 7.6 – 7.44 (m, 4H), 4.71 (d, J = 1.0, 2H), 3.83–3.75 (m, 2H), 3.53 – 3.48 (m, 2H), 3.36 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 155.32 (dd, J = 290.3, 281.0), 133.91, 132.08 (app. d, J = 3.27), 130.38, 129.76, 128.64, 126.98, 126.46, 126.07 (dd, J = 4.2, 1.9), 125.54, 125.35, 114.34 (dd, J = 40.9, 18.6), 94.05–93.65 (m), 71.76, 68.12, 59.23 (d, J = 2.76)



(3,3-difluoro-2-((2-methoxyethoxy)methoxy)allyl)benzene

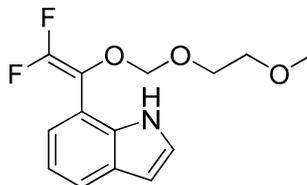
8 (150 mg, 0.550 mmol), Palladium(II) Chloride (4.43 mg, 0.025 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (35.0 mg, 0.075 mmol) were added to a 2-5 mL microwave vial with stir bar and cap and then sparged for 5 min. Benzyl bromide (86 mg, 0.5 mmol, 59.4 μL), triethylamine (152 mg, 1.500 mmol, 209 μl), n-PrOH (2500 μl) were then added to the vial and sparged for 10 min. The reaction mixture was heated to 90 $^\circ\text{C}$ and allowed to stir for 23 hrs. After reaction period, the mixture was diluted in ethyl acetate. The organic layer was rinsed once with sodium hydrogen carbonate and once with brine, and back extracted once with ethyl acetate. The organic layers were combined, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography of silica gel (EtOAc/Hexanes gradient, 0-20 %) to give 16 mg (0.063 mmol, 13%). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.24–7.28 (m, 2H), 7.19–7.22 (m, 3H), 4.81 (s, 2H), 3.65–3.70 (m, 2H), 3.53 – 3.47 (m, 4H), 3.37 (s, 3H)



1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)naphthalene

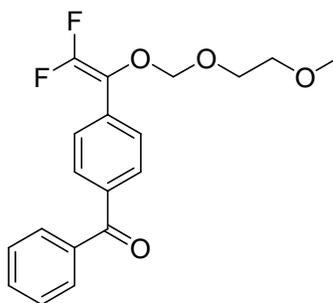
Palladium(II) Chloride (4.43 mg, 0.025 mmol), 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (35.0 mg, 0.075 mmol) were added to a 2-5 mL microwave vial with stir bar and cap and then sparged for 5 min. 1-bromo-naphthalene (104 mg, 0.5 mmol, 70.0 μ L), triethylamine (152 mg, 1.500 mmol, 209 μ l), n-PrOH (2500 μ l) and 1 equivalent of **7** (280 mg, 1.00 mmol) were then added to the vial and sparged for 10 min. The reaction mixture was allowed to stir at 50 °C for 2 hrs and then a second equivalent of **7** (280 mg, 1 mmol) was introduced into the vial. The reaction mixture was allowed to stir overnight at 50 °C. After allotted reaction time the mixture was allowed to cool to room temperature and then diluted in ethyl acetate. The organic layer was rinsed once with sodium hydrogen carbonate and once with brine and then back extracted once with ethyl acetate. The organic layers were combined and dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography of silica gel (EtOAc/Hexanes gradient, 3-15 %) to give 91.1 mg (0.310 mmol, 62%).

Spectral Data for Compounds



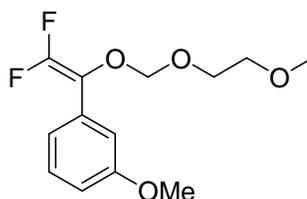
7-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-1H-indole

Flash Column Chromatography (3-30% EtOAc/Hexanes gradient) (92.5 mg, 65%), Yellow oil; $R_f = 0.17$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 9.08 (s, 1H), 7.67 (d, $J = 8.0$, 1H), 7.30 – 7.18 (m, 2H), 7.13 (app. t, $J = 8$, 1H), 6.57 (app t., $J = 2.5$ 1H), 4.82 (s, 2H), 3.90 – 3.79 (m, 2H), 3.64 – 3.53 (m, 2H), 3.43 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 155.11 (dd, $J = 289.8$, 285.5), 134.14 (d, $J = 3.8$), 128.77, 124.89, 122.43 – 122.39 (m), 122.07, 119.77, 114.18 (dd, $J = 38.6$, 19.1), 112.33 (dd, $J = 5.2$, 1.9), 102.74–102.59 (m), 95.0–94.6 (m), 71.86, 68.39 (d, $J = 1.9$), 59.22 (d, $J = 3.6$)



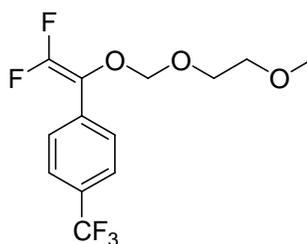
(4-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)phenyl)(phenyl)methanone

Flash Column Chromatography (3-30% EtOAc/Hexanes gradient) (108.5 mg, 62%), Pale yellow oil; $R_f = 0.2$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.81 (dd, $J = 14$, 5.5, 4H), 7.64-7.58 (m), 7.50 (app. t, $J = 7.5$, 2H), 4.92 (s, 2H), 3.91 – 3.86 (m, 2H), 3.59 – 3.54 (m, 2H), 3.39 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 196.19, 156.25 (app. t, $J = 292.5$), 137.6, 137.24, 134.45 (dd, $J = 6.4$, 1.9), 132.80, 130.55, 130.22, 128.58, 126.52, 115.50 (dd, $J = 34.4$, 19.1), 96.08–96.01 (m), 71.77, 68.89, 59.29 (d, $J = 3.3$).



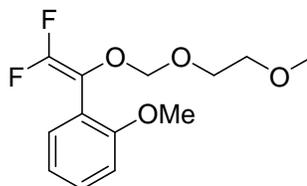
1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-3-methoxybenzene

Flash Column Chromatography (3-30% EtOAc/Hexanes gradient) (114.5 mg 83%), Orange oil; $R_f = 0.3$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.29 (app. t, $J = 8$, 1H), 7.05 (d, $J = 7.5$, 1H), 7.00 (s, 1H), 6.85 (dd, $J = 2$, 6.5, 1H), 4.87 (s, 2H), 3.89 – 3.83 (m, 2H), 3.81 (s, 3H), 3.59 – 3.51 (m, 2H), 3.38 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 159.89, 155.78 (app. T, $J = 289.6$) 131.45 (dd, $J = 6.$, 1.9), 129.81, 119.47 (dd, $J = 6.0$, 3.3), 115.69 (dd, $J = 34.4$, 18.0), 114.16, 112.5 (dd, $J = 5.7$, 3.3), 95.7–95.4 (m), 71.80, 68.67 (d, $J = 1.9$), 59.24 (d, $J = 3.3$), 55.48 (d, $J = 5.5$).



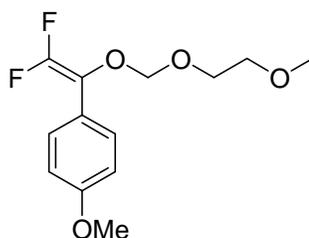
1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-4-(trifluoromethyl)benzene

Flash Column Chromatography (0-15% EtOAc/Hexanes gradient) (128 mg, 82%), Clear colorless oil; $R_f = 0.21$ (7.5% EtOAc/92.5% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.61 (dd, $J = 24.4$, 8.5, 4H), 4.88 (s, 2H), 3.92 – 3.78 (m, 2H), 3.61 – 3.49 (m, 2H), 3.37 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 156.16 (app t, $J = 292.2$), 134.1 (d, $J = 6.5$), 130.34 (q, $J = 65.6$, 32.5), 127.2–126.8 (m), 125.74 (d, $J = 3.64$), 125.19, 123.03, 120.86, 115.15 (dd, $J = 34.0$, 19.1), 96.4–95.8 (m), 71.74, 68.88 (d, $J = 1.9$), 59.25 (d, $J = 3.3$).



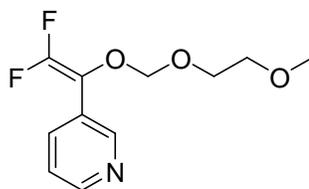
1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-2-methoxybenzene

Flash Column Chromatography (3-30% EtOAc/Hexanes gradient) (118.1 mg, 86%), Clear colorless oil; $R_f = 0.22$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.39 – 7.29 (m, 2H), 6.99 – 6.90 (m, 2H), 4.77 (s, 2H), 3.85 (s, 3H), 3.82 – 3.76 (m, 2H), 3.55 – 3.51 (m, 2H), 3.37 (s, 3H), $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 158.15 – 157.95 (m), 154.72 (dd, $J = 288.8$, 281.8), 131.95, 131.17, 120.42, 118.06 (dd, $J = 4.3$, 2.4), 112.45 (dd, $J = 41.9$, 19.5), 111.37, 94.26 – 94.22 (m), 71.77, 68.08 (d, $J = 1.4$), 59.20 (d, $J = 3.3$), 55.88 (d, $J = 5.0$).



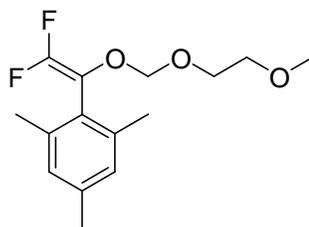
1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-4-methoxybenzene

Flash Column Chromatography (3-30% EtOAc/Hexanes gradient) (96 mg, 70%), Clear colorless oil; $R_f = 0.29$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.38 (dd, $J = 9, 1$ 2H), 6.94–6.87 (m, 2H), 4.85 (s, 2H), 3.90 – 3.83 (m, 2H), 3.81 (s, 3H), 3.59 – 3.51 (m, 2H), 3.38 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 159.85 – 159.68 (m), 155.31 (dd, $J = 288.4, 286.54$), 128.58, 122.18 (dd, $J = 6.0, 1.4$), 115.49 (dd, $J = 36.0, 18.6$), 114.23, 95.4 – 95.0 (m), 71.82, 68.59 (d, $J = 1.9$), 59.25 (d, $J = 3.3$), 55.5 (d $J = 5.5$)



3-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)pyridine

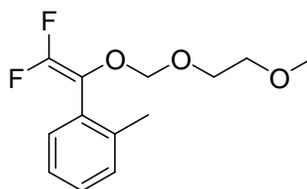
Flash Column Chromatography (15-100% EtOAc/Hexanes gradient) (95 mg, 77%), Orange oil; $R_f = 0.28$ (50% EtOAc/50% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.76–8.69 (m, 1H), 8.55 (dd, $J = 5.0, 2.0$, 1H), 7.81–7.73 (m, 1H), 7.36–7.28 (m, 4.8, 1H), 4.90 (s, 2H), 3.88 – 3.84 (m, 2H), 3.57 – 3.52 (m, 2H), 3.37 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 155.90 (app. t, $J = 292.1$), 149.42, 148.07 – 148.05 (m), 134.18 (dd, $J = 6.0, 3.3$), 126.56 (app. d, $J = 8.4$), 123.48, 113.71 (dd, $J = 36.2, 20$), 96.1–95.6 (m), 71.67, 68.81 (d, $J = 1.4$), 59.2.



2-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-1,3,5-trimethylbenzene

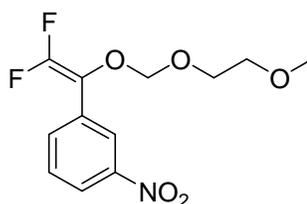
Flash Column Chromatography (0-14% EtOAc/Hexanes gradient) (103 mg, 72%), Clear colorless oil; $R_f = 0.478$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 6.88 (s, 2H), 4.64 (d, $J = 1.0$, 2H), 3.82 – 3.75 (m, 2H), 3.59 – 3.50 (m, 2H), 3.37 (s, 3H), 2.29 (app. d, $J = 8.7$, 9H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 153.99 (dd, $J = 290.3, 277.2$),

139.61, 139.31 (dd, $J = 3.3, 1.9$), 128.71, 124.12 (app d, $J = 1.8$), 112.58 (dd, $J = 44.1, 17.2$), 92.75–92.6 (m), 71.80, 67.81 (d, $J = 1.4$), 59.21, 21.35, 19.86 (d, $J = 1.0$)



1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-2-methylbenzene

Flash Column Chromatography (0-14% EtOAc/Hexanes gradient) (102.5 mg, 79%), Clear colorless oil; $R_f = 0.3$ (7.5% EtOAc/92.5% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.36–7.15 (m, 4H), 4.70 (s, 2H), 3.81 – 3.76 (m, 2H), 3.55 – 3.50 (m, 2H), 3.38 (s, 3H), 2.34 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 154.39 (dd, $J = 289.8, 280.5$), 138.62 (dd, $J = 2.7, 1.4$), 130.90, 130.67, 129.70, 128.20 (dd, $J = 4.2, 2.3$), 125.94, 114.46 (dd, $J = 41.8, 17.7$), 93.7–93.3 (m), 71.77, 68.03 (d, $J = 1.9$), 59.23 (d, $J = 2.8$), 19.9–19.5 (m)



1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-3-nitrobenzene

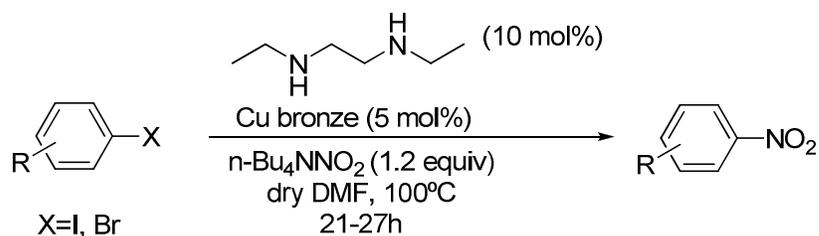
Flash Column Chromatography (0-18% EtOAc/Hexanes gradient) (59.6 mg, 41%), Yellow Oil; $R_f = 0.167$ (15% EtOAc/85% Hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.35 (app. t, $J = 2.0, 1\text{H}$), 8.16 (dd, $J = 8.5, 2.0, 1\text{H}$), 7.80 (dd, $J = 8.0, 1.0, 1\text{H}$), 7.57 (t, $J = 8.0, 1\text{H}$), 4.92 (s, 2H), 3.91 – 3.84 (m, 2H), 3.58 – 3.50 (m, 2H), 3.37 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 156.19 (app. t, $J = 292.5$), 148.72, 132.7 – 132.2 (m), 129.87, 123.14, 121.62 (dd, $J = 6.53, 4.15$), 114.72 (dd, $J = 34.4, 19.9$), 96.45–96.2 (m), 71.69, 69.01 (d, $J = 1.88$), 59.24

Chapter 3

Microwave Accelerated Nitrodehalogenation

3.1 Introduction

The fluorodenitration reaction has been widely used as a convenient method to install fluorine into aromatic scaffolds.²³⁻²⁵ This technology was successfully adopted to microwave conditions, and the resulting decrease in reaction time makes it ideal for installing radio labeled fluorine onto pharmaceutical agents used in PET and SPECT imaging.²⁶ However, carrying out full syntheses with nitro groups can be problematic, due to their high reactivity under a variety of conditions. Saito has shown that it is possible to reach nitro substituted aromatic compounds from their respective aryl-halides.³ Saito's group explored a variety of catalysts, ligands, and nitrite salts to arrive at their optimized conditions (Scheme 3.1).



Scheme 3.1: Saito's optimized nitrodehalogenation conditions

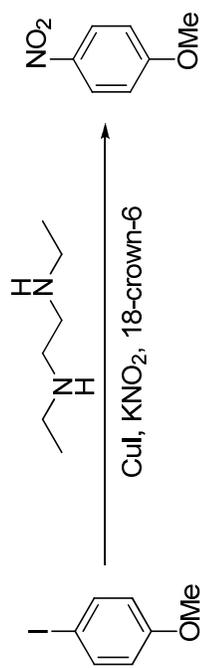
This procedure seems to be a promising tool in the synthesis of nitro containing compounds, but there existed a need for a reaction that was complete much quicker than the 21-27 hrs dictated by the Saito conditions. The Jones group had previously

demonstrated that similar aromatic nucleophilic substitution reactions could be conducted under microwave conditions, and this seemed a feasible option for the nitrodehalogenation.^{24, 26} The work herein is the optimization and scope of the microwave expediated nitrodehalogenation reaction.

3.2 Optimization

The optimization of this coupling was performed using slightly different reagents than those in Saito's optimized conditions due what was easily available. For example copper iodide was used as the catalyst rather than copper bronze, and potassium nitrite as the nitro source rather than tetrabutylammonium nitrite (Figure 3.1). Saito group's work set a good precedent for the optimization of the microwave reaction conditions since he had already done some previous optimization.³ The initial entries, 1-6, were an exploration into varying the equivalents of the catalyst, ligand, and salt, as well as varying the temperature and time. From these reactions it was determined that a larger ratio of catalyst, ligand and salt relative to the substrate gave respectable yields in the microwave, with the greatest yield being entry 4 at 74%. This initial result was promising since it was comparable to the conventional conditions.

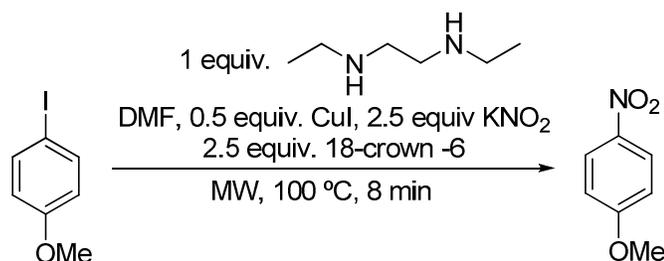
Since Saito only did a small exploration into the effect of solvent on this coupling reaction, we felt it prudent to investigate this effect further, especially since solvent plays an important role in the effectiveness of microwave acceleration. Entries 7-13 in Figure 3.1 demonstrate that our initial solvent of DMF is the best solvent for this coupling. The solvent's polarity and ability to dissolve all of the reactants probably played the largest



Entry	Catalyst (mol %)	Ligand (%)	Solvent	KNO ₂ equivs	Temperature	Time (min)	Concentration	Yield
1	CuI (100)	N,N'-diethylethylenediamine (100%)	DMF	1	140 °C	20	.5 M	32
2	CuI (100)	N,N'-diethylethylenediamine (100%)	DMF	1	160 °C	8	.5 M	19
3	CuI (100)	N,N'-diethylethylenediamine (100%)	DMF	2	100 °C	16	.5 M	61
4	CuI (100)	N,N'-diethylethylenediamine (100%)	DMF	2.5	100 °C	7	.5 M	74
5	CuI (15)	N,N'-diethylethylenediamine (30%)	DMF	2.5	100 °C	40	.5 M	64
6	CuI (15)	N,N'-diethylethylenediamine (30%)	DMF	2.5	100 °C	8	.5 M	19
7	CuI (100)	N,N'-diethylethylenediamine (100%)	DMSO	2.5	100 °C	8	.5 M	55
8	CuI (100)	N,N'-diethylethylenediamine (100%)	DCM	2.5	100 °C	8	.5 M	0
9	CuI (100)	N,N'-diethylethylenediamine (100%)	THF	2.5	100 °C	8	.5 M	11
10	CuI (100)	N,N'-diethylethylenediamine (100%)	H ₂ O	2.5	100 °C	8	.5 M	0
11	CuI (100)	N,N'-diethylethylenediamine (100%)	Methanol	2.5	100 °C	8	.5 M	5
12	CuI (100)	N,N'-diethylethylenediamine (100%)	Acetonitrile	2.5	100 °C	8	.5 M	50
13	CuI (100)	N,N'-diethylethylenediamine (100%)	Toluene	2.5	100 °C	8	.5 M	0
14	CuI (50)	N,N'-diethylethylenediamine (100%)	DMF	2.5	100 °C	8	.5 M	76
15	CuI (50)	N,N'-diethylethylenediamine (100%)	DMF	2.5	120 °C	4	.5 M	47

Figure 3.1: Optimization of nitrodehalogenation coupling

role in determining how well it performed. The last two entries, 14-15, in Figure 3.1 were an attempt to lower the catalyst loading and reduce the reaction time. Entry 14 gave the highest yield of 76% and was determined to be the optimized conditions, Scheme 3.2.

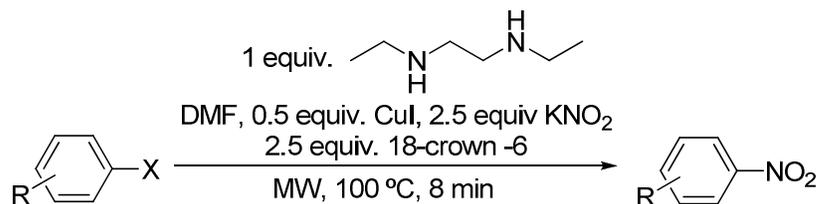


Scheme 3.2: Optimized microwave conditions for nitrodehalogenation

3.3 Scope

The optimized conditions in Scheme 3.2 were then applied to exploring the scope of the microwave accelerated nitrodehalogenation (Figure 3.2). First, some substitution effects around the ring were explored with the anisole series (entries 1, 3 and 4). Both the meta and para substituted anisole's gave yields, 62 % and 76 %, comparable to the conventional yields, 65 % and 71% respectively. The ortho-substituted anisole gave the lowest yield of this set, resulting in only a 16 % conversion. Additionally, 4-bromoanisole gave a yield of 60 %, which is better than the conventional method and may allow the scope to be further increased to include a variety of bromine substituted substrates. The substituted toluene derivatives also afforded promising results. 1-methyl-

3-iodobenzene had a yield of 60 %, which was comparable to the conventional yield of 69 %, and 1-methyl-4-iodobenzene afforded a yield of 48 %, which was much better than



Entry	R	X	MW yield	Conventional yield
1	4-MeO	I	76	71 ^a
2	4-MeO	Br	60	53 ^b
3	2-MeO	I	16	-
4	3-MeO	I	62	65 ^b
5	3-Me	I	60	69 ^b
6	4-Me	I	48	25 ^b
7	2-t-But	I	76	91 ^b
8	H	I	25	65 ^b
9	4-NH ₂	I	0	45 ^b
10	4-COCH ₃	I	7	-
11	3-pyridine	I	0	-
12	2-OH	I	0	-

Figure 3.2: Scope of microwave accelerated nitrodehalogenation

^a - reported yield but with same reagents;
^b - reported yield for conditions in Figure 3.1

the conventional yield of 25 %. While these substrates performed well in the microwave, others resulted in poor or no conversion to product. Iodobenzene and 4-iodoaniline resulted in respectable yields with the conventional method, but poor yields under microwave irradiation. Furthermore, 3-iodopyridine and 2-iodophenol gave no yield while 4-iodoacetophenone gave only a 7% yield.

The scope explored within this work has yielded some preliminary insight into what type of substituents are viable substrates for microwave acceleration. From the

anisole and toluene sets, it seems that non-reactive, non-protic, and slightly electron donating substituents work well in the microwave. Meanwhile electron withdrawing and protic substituents retard the reaction during microwave acceleration. Furthermore, it is possible that some of the coupling partners, like the pyridine and phenol substrates, may be chelating to the copper retarding the reaction. On the other hand, some of these yields may be increased slightly if a longer hold time was used during the microwave procedure. Some substrates, like 3-iodoanisole and 3-iodotoluene, had trace amounts of starting material left as observed by TLC. So although these reactions were aborted to get comparable yields, in practice they can be reacted under microwave irradiation for slightly longer and the yield should increase slightly.

3.4 Future Directions

This research demonstrates another application of microwave technology to the acceleration of metal catalyzed coupling reactions. Although the relative ratios of reagents were increased relative to the substrate, this seems a fair trade off for the 99.5 % decrease in reaction time from upwards of 27 hours with conventional methods down to about 8 min with microwave acceleration. Although the microwave acceleration shared limited scope in this initial substrate set, it still lends itself to application in larger syntheses. To help elucidate this, a slightly larger scope should be attempted to give a clearer picture of substrate compatibility. This expansion of scope shouldn't just include other simple aryl-halides, but also larger molecular skeletons, to demonstrate the technology's applicability. Lastly, these refined microwave conditions should be

attempted during the synthesis of radio labeled pharmaceuticals. It is not impossible to imagine two consecutive microwave reactions conditions yielding a radio labeled pharmaceutical that only needs to be purified and prepared before being using for PET/SPECT scans.

3.5 Experimentals

General Information

All reactions were carried out in dry glassware (dried in the oven at 135°C overnight and immediately sealed with a rubber septum and cooled under argon). All syringes and needles were stored overnight in an oven and allowed to cool in a dessicator before use. Reactions were stirred with Teflon coated magnetic stir bars. Reactions were monitored by TLC. DMF stirred overnight with 4 Å molecular sieves and magnesium sulfate, distilled and then stored over 4 Å molecular sieves. All other reagents were purchased from reputable suppliers and used as received. For all microwave reactions, a CEM brand Discover microwave reactor was used at 300 watts, with a maximum pressure of 275 PSI and a run time of 1 minute.

^1H and ^{13}C NMR spectra were recorded on a 300 MHz Varian Mercury instrument. Both ^1H and ^{13}C NMR data were presented in ppm down field relative to tetramethylsilane as an internal standard. The ^1H NMR data were presented in the order: multiplicity, number of protons, and the coupling constant (Hz). TLC analyses were carried out on general purpose silica gel on polyester TLC plates and visualized with UV

fluorescence. Chromatographic separations were made using SilicaFlash 40-63 μm 60 \AA silica gel purchased from Silicycle.

General Procedure

To a dry, argon filled microwave vial with stir bar add (if solid) 0.5 mmol of aryl halide, copper iodide (47.6 mg, 0.25 mmol), potassium nitrate (106.4 mg, 1.25 mmol), and 18-crown-6 (330.2 mg, 1.25 mmol) and cap with rubber septum. Purge the vial with argon for approximately five minutes. Add 1 mL of dimethylformamide, N,N'-diethylethylenediamine (58.1 mg, 0.5 mmol, 71.6 μL) (and aryl halide if liquid). Cap the microwave vial with appropriate microwave cap and insert into CEM microwave reactor. Optimized conditions for microwave are 300W, 250 PSI, 100°C, and 8 min hold time. Load reaction mixture directly onto column and run column with a gradient from 5-30% EtOAc in hexanes to yield desired product after concentration.

1-methoxy-4-nitrobenzene

58.1 mg isolated (76 % yield, 0.379 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.21 (d, $J = 9$, 2H), 6.96 (d, $J = 9$, 2H), 3.90 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 164.83, 150.73, 126.13, 114.23, 56.18

1-methyl-4-nitrobenzene

32.7 mg isolated (48 % yield, 0.238 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.12 (d, $J = 8.7$, 2H), 7.32 (d, $J = 8.1$, 2H), 2.47 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 146.159, 130.024, 123.744, 21.83

1-methyl-3-nitrobenzene

41.3 mg isolated (60 % yield, 0.301 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.2–7.9 (m, 2H), 7.6–7.3 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 150.73, 140.01, 135.563, 129.28, 124.06, 120.88, 21.45

1-methoxy-3-nitrobenzene

47.8 mg isolated (62 % yield, 0.312 mmol); ^1H NMR (300 MHz, CDCl_3) δ 7.82 (d, $J = 7.5$, 1H), 7.725 (s, 1H), 7.429 (t, $J = 8.1$, 1H), 7.23 (d, $J = 8.1$, 1H), 3.894 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 160.36, 150.73, 130.14, 121.47, 115.95, 108.35, 56.034

1-(4-nitrophenyl)ethanone

6.1 mg isolated (7.4 % yield, 0.036 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.32 (d, $J = 8.7$, 2H), 8.12 (d, $J = 8.7$, 2H), 2.69 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 196.54, 150.73, 141.60, 129.539, 124.08, 27.20

nitrobenzene

15.4 mg isolated (25 % yield, 0.125 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.13 (d, $J = 9$, 2H), 7.648 (t, $J = 7.5$, 1H), 7.48 (t, $J = 7.5$, 2H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 150.74, 134.87, 129.53, 123.57

1-methoxy-2-nitrobenzene

12.0 mg isolated (16% yield, 0.0784 mmol); ^1H NMR (300 MHz, CDCl_3) δ 7.85 (dd, $J = 1.8, 7.8$, 1H), 7.65–7.45 (m, 1 H), 7.2–7.15 (m, 2H), 3.965 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 150.74, 134.417, 125.94, 120.49, 113.694, 56.69

1-tert-butyl-4-nitrobenzene

68.2 mg isolated (76% yield, 0.380 mmol); ^1H NMR (300 MHz, CDCl_3) δ 8.144 (d, $J = 9$, 2H), 7.537 (d, $J = 9$, 2H), 1.363 (s, 9H); ^{13}C NMR (75.4 MHz, CDCl_3) δ 159.08, 150.72, 126.458, 123.546, 35.60, 31.245

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