Synthesis of PET Imaging Agents and Analogues Thereof Utilizing Microwave and Microfluidic Technology

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B.S. in Chemistry, Lewis University

A thesis submitted to

The Faculty of the College of Science
Of Northeastern University
In partial fulfillment of the requirements
For the degree of Master of Science

December 11th, 2015

Thesis directed by

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Acknowledgements

My time at Northeastern has been a rewarding and humbling experience that has helped shape me into the person I am today. First and foremost I need to thank my family for beginning the shaping process and teaching me to follow my heart and be the best person I can be. I will always be grateful to my parents for their support and love, and I know I am luckier than most to have people like them to look up to. As for my sister Sara, over the past few years you have become my best friend, and I truly appreciate all of the input and advice you have given me over the years about life, love, and happiness. Sam, I became a chemist to be just like my big brother. You may not know how much I look up to you, but that alone should speak volumes. You are strong, smart, and giving and someone I’ve aspired to be like for as long as I can remember.

I also want to thank my advisor Dr. Graham Jones. You only want what is best for your students, and it’s inspiring to witness you share your love for science and education with others around you. You’ve been patient and kind with me while I’ve decided what path I want to take, and I cannot express how much I appreciate your support and understanding. To the Jones group past and present, I could not have made it anywhere without your friendship and guidance. We’ve laughed, cried, and wanted to punch walls in frustration, but we made it through together and will accomplish great things.

Finally I’d like to thank Dr. James Aggen and Dr. George O’Doherty for being on my thesis committee and for providing professional input and guidance as well as the Department of Chemistry and Chemical Biology for the opportunity to pursue my degree.
Abstract

In recent years, $^{18}$F labeled ligands have played a key role in positron emission tomography (PET) imaging. Due to the short half-life of these radiolabeled compounds, microwave and continuous flow microreactor techniques have proven extremely useful by accelerating reactions in under ten minutes with high purity. With the production of radiotracers and radiopharmaceuticals relying on automated synthesis platforms for production, multi-step reactions performed in a continuous flow process are of great significance. When developing central nervous system (CNS) imaging agents, optimizing lipophilicity of the drug to maximize blood brain barrier penetration is vital, and typically, the addition of even one methylene spacer or a change in hybridization can have an extreme impact on the drug's properties. Palladium catalyzed Sonogashira couplings of $\omega$-alkynyl tosylates, particularly propargyl tosylates, with aryl halides have being developed in a continuous flow process under copper, ligand, and amine-free conditions. Homologs of CNS imaging agents nifrolidine and fallypride are being investigated as well as additional analogues involving the rapid hydrogenation products under microwave conditions.
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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>CT</td>
<td>X-ray computed tomography</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
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<td>DIEA</td>
<td>Diisopropylethylamine</td>
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<td>DMF</td>
<td>Dimethylformamide</td>
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<tr>
<td>EDC</td>
<td>1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide</td>
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<td>EWG</td>
<td>Electron withdrawing group</td>
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<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
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<td>HOBT</td>
<td>1-Hydroxybenzotriazole</td>
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<tr>
<td>IPA</td>
<td>Isopropyl alcohol</td>
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<tr>
<td>LAH</td>
<td>Lithium aluminum hydride</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MW</td>
<td>Microwave</td>
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<tr>
<td>PEEK</td>
<td>Polyether ether ketone</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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TsCl  4-Toluenesulfonyl chloride
TH   Transfer hydrogenation
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Chapter 1

Introduction

1.1 Applications of Fluorine in Medicinal Chemistry

Fluorine-containing chemicals have existed since the late 1800’s; however, after the first fluoropharmaceutical, fludrocortisone, was produced in 1953\(^1\), the market has boomed considerably with up to 25% of all drugs containing fluorine.\(^2\) From 2001-2011 alone 40 new fluoropharmaceuticals entered the market, a market in which 3 of the top 10 selling pharmaceuticals contained fluorine. Lipitor, Pfizer’s lipid lowering agent, is the best-selling drug of all time making roughly $125 billion between 1997 and 2012.\(^3\) Fluoropharmaceuticals target many areas including anti-cancer, anti-inflammatory, cardiovascular and gastrointestinal issues, infectious diseases, and central nervous system (CNS) diseases among others.\(^1\)

The benefits of fluorinated pharmaceuticals are discussed in great detail in many reviews over the past 15 years.\(^4\) The effects of fluorine’s electronegativity, lipophilicity, size, and polarizability make it very attractive to synthetic chemists in small molecule drug development.\(^1\) The special qualities of fluorine have been shown to enhance binding properties, make for easier penetration of the blood brain barrier (BBB), and increase metabolic stability for certain drugs.\(^2\) A large utility of fluorine has always been its high electronegativity and steric resemblance to hydrogen, which allowed drug developers to mimic a C-H bond with a C-F bond to fool receptors.\(^5\) The much stronger C-F...
bond drastically affects the metabolism by either delaying excretion or slowing metabolism of the fluorine-containing compound, allowing more time for the drug to make its full impact. However, many times the effect of the fluorine on biological activity can be subtle and difficult to predict.  

A large spectrum of methods exist for highly selective fluorinations and fluoroalkylations despite the difficulties in C-F bond formation. The downsides of using fluorine in medicinal chemistry are as notorious as its benefits including the relatively low availability of “F” sources and the high reactivity of fluorine gas. A series of direct fluorinating agents, deoxofluorinating (nucleophilic) agents, and electrophilic fluorinating agents have been developed since the 1960s as seen in Figure 1.3. A very common and useful method of fluorination is the use of quaternary ammonium cations because they can enhance the weak nucleophilicity of fluoride. Alkynl, allylic, benzylic, and alkyl fluorides as well as many PET imaging agents can be synthesized using this method.
Positron emission tomography (PET) imaging has become one of the leading methods of imaging largely due to its ability to deliver high-resolution images of radiotracer distribution and metabolism. Anatomical techniques such as MRI and CT have heavily impacted clinical trials of investigational new drugs by joint use with PET imaging. More metabolic and physiological information can be drawn from this combination than ever before. However, the short half-lives of radiotracers place special limitations on the development of radiotracers. While $^{18}$F is by far the most widely used isotope, there are numerous applications with $^{11}$C, $^{13}$N, and others.
Zimmer developed the first tomographic imaging and computed imaging device in the 1960s using a single photon emitter, $^{99m}$Tc. As the technology advanced, various radioisotopes and radiotracers were developed prioritizing $^{11}$C, $^{15}$O, $^{13}$N, $^{68}$Ga, and $^{18}$F. As seen in Table 1.1, $^{18}$F, $^{11}$C, $^{13}$N, and $^{15}$O have shorter half-lives and a smaller maximum position energy (MeV).

The maximum energy emitted by each radionuclide directly relates to the length the positron must travel. In theory, the shorter the positron linear range, the higher resolution image it is able to provide. For this reason, and the fact that it has a longer half-life (Table 1.1) and a multitude of desirable pharmacological properties, $^{18}$F is by far the most widely used radionuclide.

It has been reasoned that one of the driving forces behind the eventual acceptance of PET imaging was the development and success of the advanced radiotracer 2-deoxy-2-[$^{18}$F]fluoro-D-glucose, ($^{18}$FDG). For over twenty years, the production of $^{18}$FDG has relied on commercial automated systems. That said, the discovery process for new compounds has been slow. Factors include the time constraints involved in synthesis and purification, the need for high specific activity, and the toxicity of reagents employed.
As a guideline, the time it takes to complete the synthesis and purification of a radiotracer should be shorter than three half-lives of the radionuclide being used. Ideally the radionuclide is introduced at the last possible step to provide more time for any modifications and minimizing the steps required in the hot cell. Compounding the difficulty, purification and analysis (quality control) times can greatly impact the overall process. Normally, HPLC is used to analyze and purify radiopharmaceuticals; however, studies show that it is possible to purify with solid phase extraction methods. Other challenges in radiopharmaceutical development include safety, as operators are dealing with ionizing radiation, miniaturization for the use of extremely small-scale quantities, and the generally limited variety of suitable starting materials and reagents.

1.2.1 PET and Central Nervous System Diseases

Central to PET imaging is the development of appropriate PET imaging probes for CNS diseases. Today, even after 25 years of research and development, only a handful of established radiopharmaceuticals exist for the investigation of CNS diseases, and for a vast majority of these CNS targets, no radioligand exists. The established difficulties of specificity, affinity, stability, and pharmacokinetics are largely unknown, making the successful development of new radiopharmaceuticals nearly impossible. The added difficulty of having to collaborate with radiochemists, clinicians, and pharmacologists has deterred the desire to produce effective radioactive probes for CNS diseases.

Figure 1.5: PET image of the brain at various stages of cognitive impairment

![Figure 1.5: PET image of the brain at various stages of cognitive impairment](image)
The CNS disease that has seen the most progress in the field of PET imaging is Alzheimer’s disease (AD). Alzheimer’s is a neurodegenerative disease that accounts for nearly 70% of all cases of dementia and has no known cure. Common symptoms include disorientation, difficulty remembering events or people, mood swings, and behavioral issues, and gradually bodily functions are lost, leading to death. Because of the need for constant caregiving in the late stages of the disease, AD is one of the financially devastating diseases in the world, and PET imaging may be a source of preventative care.

The cause of this devastating disease is largely unknown; however, it is generally agreed upon that an accumulation of beta(\(\beta\))-amyloid plaques in the brain is a large factor.\(^\text{14}\) As of 2014, three \(\beta\)-amyloid imaging agents, Amyvid (florbetapir), Vizamyl (flutemetamol) and Neuraceq (florbetaben), have been approved by the Food and Drug Administration (FDA), while many others, including D2/D3 dopamine receptor antagonist Fallypride and \(\alpha4\beta2\)-nicotinic receptor antagonist Nifrolidine, are in AD clinical trials.\(^\text{15}\)

Figure 1.6: Structures of FDA-approved PET imaging agents used for AD
1.3 Technology Assisted Synthesis of Fluoropharmaceuticals

The multi-billion dollar pharmaceutical industry is constantly looking for effective ways to make drugs in a cleaner, safer, cheaper, and faster. With these goals in mind, technology assisted synthesis has flourished since the mid-1980s. The first record of using a microwave in organic synthesis was in 1986; however, the age of using microwave ovens has long since passed. The enhanced purity profile made for more uniform heating, faster reaction times, the ability to heat beyond a solvent’s boiling point, and higher conversion rates. As microwave chemistry was still in its infancy however, microfluidic and flow chemistry began as another, perhaps more effective, way of quickly and efficiently synthesizing an array of compounds.

1.3.1. Microwave Reactions

Microwave reactions rely on two mechanisms to be successful: dipolar polarization and conduction (Scheme 1.1). The electromagnetic force applied on polar molecules when put in a microwave causes them to disorient and realign themselves, which is what creates heat. Dipolar polarization occurs when the dipoles of the solvent try to align themselves with the wave creating heat as they rotate. The other mechanism is electrical conduction, which is when ions separate based on charge and proceed to opposite ends of the wave. Once the waves pass, the ions collide creating heat. While cosmetic changes for microwaves have inevitably happened since the first use of microwaves for chemistry, these principles have remained largely intact. The inability to scale up reactions, however, has led to an increase in the use of microfluidic systems in recent years. Many microfluidic systems also allow safer, faster, and more efficient syntheses with the added benefit of increased scalability.
1.3.2. Microfluidic Reaction

Microfluidic systems have many advantages over both microwave and conventional batch reactions including scalability, computer-controlled setups, better management of pressure, and increased interaction between reagent and vessel, which in turn greatly improves the mixing process. These advantages expedite reaction rates, improve heat transfer, and aide reproducibility, making it highly desirable in many areas of chemistry.

The use of continuous flow techniques in organic synthesis began in the late 1970s; however, in the past 10 years the method has received widespread attention and adoption. The basis of the method involves synthesis in a pressurized system, which contains a high surface-to-volume
ratio and an efficient mixing process producing compounds in mere minutes with high purity profiles. Typically, reagents of interest are pumped through channels that are 10-300 micrometers in diameter, allowing for better control over heat transfer and reaction kinetics, along with complete control over temperature, pressure, and volume.\textsuperscript{17} In many cases, an automated “on-chip” method is used as seen in Figure 2. Here, reagents are pumped through the channels at different intervals depending on the reaction, and the product exits the chip when completed.

A key advantage in a microfluidic system is the application of laminar flow to control fluid mixing and reaction processes. Laminar flow is defined as parallel layers or streamlines in the direction of the flow, which proceed uninterrupted. Under these conditions, diffusion controlled mixing of reagents occurs, and while this can be a slow process in batch conditions, with small reactor channels and even shorter diffusion distances, laminar flow provides much more controlled mixing than the turbulent, or ‘active’ conventional mixing methods.\textsuperscript{10}

Microfluidic methods have become relevant in various fields of synthesis including solid-phase chemistry, library synthesis, protein synthesis, production scale synthesis, and drug candidate synthesis.\textsuperscript{17} In the field of drug candidate synthesis, microfluidic techniques have recently been instrumental in creating new approaches to PET image contrast agents. When developing radiotracers, the principal difficulties arise from extended reaction time and low product purity (necessitating additional time consuming purifications). Based on the above principles, microfluidic techniques have proven efficient in addressing these problems.

As discussed, the advantages of microfluidics make the technique ideal for certain reactions; however, disadvantages play a part in determining whether or not the use of microfluidics is an ideal solution. Solubility of reagents is often the most difficult obstacle to
overcome when performing a reaction under microfluidic conditions. If a reagent is not completely soluble the tubing clogs up, halting the reaction. Solubility involves reagent compatibility with solvent, but it is also important that the reagents and solvents are compatible with the tubing and chip system. Some solvents, especially those that are either highly basic or highly acidic, can degrade the tubing\textsuperscript{17}. A more pressing disadvantage is the low radioactivity that microfluidic conditions utilize\textsuperscript{18}. The low concentration levels of radioactivity can be remedied with prolonged production time, however, this is not an ideal scenario for the production of radiotracers\textsuperscript{19}.

Flow and microwave chemistry have proven themselves as effective tools in producing novel compounds safer, faster, and cleaner than conventional batch methods. The following work showcases the full utility of these methods through a multi-step synthesis of PET radiotracers in flow as well as a subsequent transfer hydrogenation under microwave conditions. These methods have allowed for previously difficult to make compounds to be synthesized quickly where variations in chain length and hybridization. The areas of fluorine chemistry, PET imaging, and technology assisted synthesis towards the development of fluoropharmaceuticals will be discussed.
1.4 References


Chapter 2

The use of microfluidic techniques to synthesize Fallypride and Nifrolidine analogues

2.1 Background of work done using flow to synthesize $^{18}$F compounds

Technology-assisted synthesis has advanced in recent years with the help of microwave and microfluidic technology because these methods allow for more precise control of reaction parameters. Microwave chemistry has been applied to a variety of areas of chemistry since the 1980s, showing a large amount of versatility; however, more recently flow chemistry and microfluidics have shown an even greater ability to fine tune reaction parameters offering an enhanced purity profile to both microwave and conventional batch reactions.

It should be stressed at the outset that this application of fluid dynamics and nanotechnology allows for the miniaturization of the conventional production of PET radiotracers. Radiochemical reactions on a chip or in a microscale environment do not require nearly as much laboratory space or resources as is the case with the conventional hot cell production. The reduction of required resources (typically space in hospital radiopharmacies is very limited) coupled with the high degree of control of reaction conditions, has led to substantial interest in the method in clinical settings.

Microfluidic technology has the ability to revolutionize the development of PET radiotracers due to its ability to control pressure, temperature, time, and mixing from a completely automated system. The diversity of the technique has many applications, and the use of microfluidics in radiopharmaceutical development is now progressing.
2.2 Techniques used to make short-chained analogues

Many conventional methods of fluorination involve use of diatomic fluorine gas, which requires extreme care as it is explosive in the presence of oxygen. Alternative methods have been developed, but many of these still require use of volatile reagents and conditions. Based on the fact that the reactor is pressurized, the use of microflow techniques greatly alleviates safety and toxicity concerns during these particular reactions.  

Placzek et al. utilized a microfluidic system to produce a library of compounds containing hexynyl fluoride chains (Figure 3.4). The method was effective both for electron rich and electron poor activating groups, underscoring the versatility of the method. The method involved a multi-step synthesis in flow with a fluorination of an alkynyl tosylate using tetrabutylammonium fluoride (TBAF), followed by a Sonogashira coupling using palladium acetate and tetrabutylammonium acetate (TBA acetate). This method was used to synthesize analogues of Fallypride that contained a 6-carbon, fluorinated alkynl chain in high yield. An important point to note is that a copper-free synthesis was used because copper can be known to degrade the polyether ether ketone (PEEK) tubing that all of the flow reactions are run in, and the lack of copper provides a greener, more attractive synthesis in medicinal chemistry.
A number of prescription pharmaceutical drugs contain fluoroalkyl chains due to the increased lipophilicity and bioavailability that the fluorine moiety imparts. A synthetic route that can be used to accommodate varying chain lengths and hybridization is now a reality based on the use of microfluidic processes. The method utilizes both on-chip and off-chip microfluidic techniques. Oftentimes, and especially when solid phase catalysts are used, clogging affects the process. In these cases, using an on-chip method may not be ideal, and hybrid off-chip methods are engaged.

With these methods established, the exploration into synthesizing shorter chain analogues started. However, it was discovered that the shorter chain analogues provided much more difficulty than the longer chained analogues due to the extremely low boiling points of the fluorinated alkynl chains. A 3-carbon fluorinated alkynl chain has a boiling point of roughly $15^\circ C$, and a 4-carbon chain is not much better, at around room temperature. The vitality and

Scheme 2.1: Fluorination of alkynyl sulfonates and subsequent coupling with aryl halides in flow
applicability of microfluidic systems became necessary for the synthesis at this point due to its ability to keep the gas within the walls of the system, as opposed to a batch or microwave system where the gas would escape to the headspace of the reaction vessel.

Due to unavailability of temperature control, a chip was not used when synthesizing the shorter chained analogues. As seen in Scheme 2.2, both the fluorination of the alkynyl tosylate as well as the copper-free Sonogashira coupling were performed at 115°C. First, the alkynyl tosylate was fluorinated using TBAF as a fluorinating agent to synthesize a fluoro-alkynyl chain. A method developed by Kim et al, employed the use of alkali metal fluorides, such as TBAF, to fluorinate aliphatic leaving groups in a nonpolar, protic tertiary alcohol medium to tame the basicity of the fluoride. 5 This “taming” was shown to drastically decrease the amount of biproducts; however, the use of acetonitrile as a solvent across the entire reaction showed similar results to tert-amyl alcohol. Keeping both the temperature and solvent constant throughout the flow system provides a simpler, more reproducible method, therefore, acetonitrile was used as the only solvent in the flow system after initial tests were done as seen in Table 2.1.

2.3 Optimization of 3 and 4-chained analogues

With the basic parameters for 6-carbon alkynyl chained analogues established, the focus was set to adapt these parameters for a Labtrix® Start. Plazcek et al performed the previous syntheses in flow using a Labtrix®-S1 (Chemtrix NL) system, and the synthesis for the short-chained analogues had to adapted to be used on a Labtrix® Start. The Labtrix®-S1 is a completely automated system with temperature control and the ability to set multiple reactions up at a time. The Labtrix® Start was not automated and did not have temperature control;
however, the pumps could flow at the same speed as the Labtrix®-S1 which became a large factor in reproducibility.

Figure 2.1: Labtrix® Start

Figure 2.2: Labtrix®-S1

Experimental optimization done by Plazcek et al concluded that the best yield was seen when the concentration of the arene is .1M with the alkyne, TBAF, TBA acetate, and palladium acetate be at 1, 1.5, 1.5, and .05 equivalents respectively. The reaction reached full completion in roughly ten minutes with high yield. Based on this information and the equipment at hand, optimization was done to synthesize a three-carbon fluoroalkyl compound using 4-iodoacetophenone as a model substrate.

Scheme 2.2: Fluorination of short-chained alkynyl sulfonates and subsequent coupling with aryl halides in flow
Optimized conditions showed that a temperature of 115 °C at a rate of .5 uL/min in ACN synthesized the desired product at 71% yield in 14 minutes. With this established, multiple analogues were synthesized including 3 and 4 chained analogues of fallypride and nifrolidine. However, the synthesis of the fallypride and nifrolidine precursors proved to be a lengthy process.

Table 2.1: Continuous flow palladium-catalyzed coupling of alkynes with aryl halides: Optimization Results

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<th>Flow A (uL/min)</th>
<th>Flow B (uL/min)</th>
<th>Flow C (uL/min)</th>
<th>Flow D (uL/min)</th>
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2.4 Synthesis of fallypride and nifrolidine precursors

The synthesis of the fallypride analogues began with the synthesis of the 5-iodo precursor. Plazcek and co-workers developed a modified synthesis of Abrams, starting with the synthesis of the aromatic core. Electrophilic iodination of 3-methoxy salicylic acid with iodine monochloride activated by silver nitrate yielded the corresponding arene followed by a methylation using methyl iodide in DMF to yield 2,3-dimethoxymethylsalicylate with no purification necessary in between steps. The methyl ester was then saponified with lithium hydroxide and compound 2.3. Standard amide coupling conditions coupled this arene to the alkylated pyrrolidine. To synthesize the pyrrolidine core, we started with L-proline methyl ester hydrochloride and alkylated with allyl bromide to produce compound 2.5. The alkylated L-proline methyl ester was then reduced with LAH to afford the primary alcohol.

A Gabriel type synthesis under Mitsunobu conditions yielded the final primary amine after a problematic intermediate step. The triphenylphosphine oxide formed in the reaction was difficult to remove; however, through column chromatography it was possible to still get a reasonable yield.

The synthesis of the nifrolidine precursor was much more simple, beginning with the aryl ether formation under Mitsonobu conditions of a boc-protected L-prolinol. We opted to keep the protecting group attached throughout the production of analogues in order to ease the synthesis and to provide a good proof-of-concept for the reaction.
Scheme 2.3: Synthesis of fallypride precursor

Scheme 2.4: Synthesis of boc-protected nifrolidine precursor
2.5 Synthesis of Sonogashira-coupled compounds under continuous flow conditions

With conditions optimized using 4-iodoacetophenone as a model substrate, we wanted to examine if the synthesis allowed for the use of electron poor as well as electron rich arenes in the same way that Placzek had proven. The short-chained compounds were not quite as successful in proving versatility of the method; however, weakly activating, weakly deactivating, and strongly deactivating groups all showed moderate to good yields with a strongly deactivating substrate being the most successful. The heteroaromatic nifroldiene analogue also provided decent yield with a bromine leaving group, showing promise that multiple leaving groups could be successful along with iodoarenes. As stated previously, nifroldiene is an α4β2-nicotinic receptor used in PET imaging studies. The α4β2-nicotinic receptor subtype has been implicated in AD, lung cancer, schizophrenia, and addiction disorders, and the development of a promising imaging agent of nifroldiene could advance the study of these devastating disorders. Unfortunately, the other AD PET imaging agent we wanted to analyze, fallypride, did not prove successful using this method. Due to the difficulty of the synthesis of the precursor, there was not much material to work with to perform the coupling of the iodoarene with alkynl tosylate; however, we do believe with more time and an adequate amount of precursor, this synthesis will be successful in making fallypride analogues.
Scheme 2.5: Fluorination of short-chained alkynyl tosylates and subsequent coupling with aryl halides

Yields were determined by HPLC vs. an internal standard.
2.6 Conclusion

A continuous flow microreactor method has been developed for the synthesis of fluoroalkynated arenes from the corresponding 3 and 4 carbon chained alkynyl tosylates and aryl halides. The method proved most effective for electron poor aryl halides; however, it still showed promising results with a moderately electron rich aryl halide as well as a heteroaromatic drug analogue with a bromine leaving group. This $\alpha 4\beta 2$-nicotinic receptor, nifrolidine, analogue has shown promise in PET imaging studies with AD, schizophrenia, lung cancer, and addictive disorders. Logical further reactions employing this methodology is expanding the range of substrates to include more electron rich substrates, as well as looking into reactions that can readily couple fluorinated chains with $sp^2$ and $sp^3$ hybridization. Even one methylene spacer or variation in hybridization can drastically affect the binding and transport properties of a drug, so developing a method that can manipulate those at ease would be of great interest.
2.7 References


2.8 Experimental

General Methods

Reagents were purchased from common suppliers including Sigma-Aldrich, Inc. (St. Louis, MO), Fisher Scientific, Frontier Scientific Services, Inc. (Newark, DE), and TCI (Portland, OR) and were used as received unless otherwise noted. All anhydrous reactions were performed under argon. Solvents were dried through a distillation apparatus and stored over 4A molecular sieves. LC/MS analysis was conducted using a Waters Micromass ZQ mass spectrometer in positive mode with 254 nm UV detection by a Waters 2489 UV/visible detector. GC/MS analysis was performed on a Hewlett Packard 6890 Plus GC with 5973 Mass Selective Detector. Samples were analyzed by HPLC-UV (Waters Alliance; Agilent Eclipse Plus C18 Column; 254 nm), and yields for continuous flow reactions were determined by the use of an internal standard. Column chromatography was done with silica gel from Silicycle.
5-iodo-3-methoxysalicylic acid (2.1)

Iodine monochloride (2.03 g, 12.48 mmol) was added to a solution of pyridine (40 mL) and silver nitrate (2.12 g, 12.48 mmol) in chloroform (100 mL). After 15 minutes at room temperature, 3-methoxysalicylic acid was added to the reaction and stirred for 3 hours. Upon completion ether (50 mL) was added and the reaction was filtered. The solid was washed with chloroform and ether, and the filtrate was concentrated in vacuo. It was then washed with 5% HCl, 5% sodium thiosulfate, and brine to dry. It was then dried further over MgSO₄, filtered, and concentrated. The crude mixture was purified via column chromatography on silica gel eluting with 10% Methanol/DCM to give the title compound as a beige solid (97%). Spectroscopically identical to that reported.⁸

¹H NMR (400 MHz, CDCl₃): δ 11.01 (OH, brs, 1H), 7.77 (s, 1H), 7.22 (s, 1H), 3.88 (s, 3H).

5-iodo-2,3-dimethoxysalicylic acid (2.2)

To a solution of 2.1 (3.5 g, 12.1 mmol) in acetone was added cesium carbonate (11.8 g, 36.3 mmol) and iodomethane (2.2 mL, 36.3 mmol). This reaction was heated under reflux overnight, cooled, and washed with sodium carbonate solution. It was then washed with ethyl acetate,
washed with brine, and dried over MgSO₄, filtered, and concentrated in vacuo. The mixture was
diluted with THF and a 5M lithium hydroxide (60.5 mmol) solution was added. This was stirred
overnight at room temperature then acidified with 5% HCl. The organic layer was extracted with
ethyl acetate, washed with brine, and dried over MgSO₄. The product was a white solid (82%).

\[^1\text{H} \text{NMR (400MHz, CDCl}_3\text{)}: \delta 7.98 \text{ (s, 1H), 7.38 \text{ (s, 1H), 4.02 \text{ (s, 3H), 3.92 \text{ (s, 3H)}}. LCMS found 308.96 [M+H]^+\] (S)-methyl 1-allylpyrroolidine-2-carboxylate (2.3)

Triethylamine (TEA) (20 mL) and allyl bromide (6.9 mL, 57 mmol) were added to a solution of
L-proline methyl ester hydrochloride (5.0 g, 30.2 mmol) in anhydrous DMF. The reaction stirred
at room temperature overnight after which water was added, and the organic layer was extracted
with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO₄, and
concentrated in vacuo. The compound was purified by column chromatography on silica gel
eluting with 50% ethyl acetate/hexanes to afford 4.69 g of the title compound as a clear oil.

\[^1\text{H} \text{NMR (400MHz, CDCl}_3\text{)}: \delta 5.83-5.9 \text{ (m, 1H), 5.1-5.17 \text{ (m, 2H), 3.71 \text{ (s, 3H), 3.3-3.39 \text{ (m, 1H), 3.1-3.21 \text{ (m, 3H), 2.38 \text{ (q, J=8Hz, 1H), 2.05-2.1 \text{ (m, 1H), 1.75-1.9 \text{ (m, 3H)}}. LCMS found 169.85 [M+H]^+}\] (L)-1-allylpyrroolidine-2-carboxylate (2.3)

\[^1\text{H} \text{NMR (400MHz, CDCl}_3\text{)}: \delta 5.83-5.9 \text{ (m, 1H), 5.1-5.17 \text{ (m, 2H), 3.71 \text{ (s, 3H), 3.3-3.39 \text{ (m, 1H), 3.1-3.21 \text{ (m, 3H), 2.38 \text{ (q, J=8Hz, 1H), 2.05-2.1 \text{ (m, 1H), 1.75-1.9 \text{ (m, 3H)}}. LCMS found 169.85 [M+H]^+\] (S)-1-allylpyrroolidine-2-carboxylate (2.3)
(S)-(1-allylpyrrolidin-2-yl)methanol (2.4)

Lithium aluminum hydride (LAH) (3.2 g, 83.7 mmol) was suspended in anhydrous ether at 0°C while 2.3 (4.7 g, 27.9 mmol) was also dissolved in anhydrous ether in an adjacent round bottom flask. The (S)-methyl 1-allylpyrrolidine-2-carboxylate in ether was slowly added to the LAH suspension over 30 minutes. The reaction slowly warmed to room temperature over 4-5 hours before adding cold methanol dropwise followed by cold ethyl acetate and finally ice cold water. The aqueous layer was extracted with ethyl acetate, and the organic layers were combined, washed with brine, and dried over MgSO₄. The compound was concentrated in vacuo and purified by column chromatography with silica gel. The title compound eluted with 50% ethyl acetate/hexanes and was a colorless oil. Spectroscopically identical to that reported.⁹

¹H NMR (400MHz, CDCl₃): δ 5.83-5.93 (m, 1H), 5.1-5.2 (m, 2H), 3.24-3.30 (m, 1H), 3.06-3.15 (m, 3H), 2.38 (q, J=8Hz, 1H), 2.05-2.1 (m, 1H), 1.75-1.9 (m, 3H).

(S)-2-((1-allylpyrrolidin-2-yl)methyl)isoindoline-1,3-dione (2.5)

To a solution of 2.4 (2.3 g, 16.7 mmol) phthalimide (2.7 g, 18.3 mmol), and PPh₃ (4.8 g, 18.3 mmol) in anhydrous THF at 0°C was added DIAD (3.7 g, 18.31 mmol) slowly. The reaction slowly warmed to room temperature overnight, was filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel eluting with 50% ethyl acetate/hexanes to afford the title compound (1.8 g, 40%) as a yellow oil. LCMS found 271.14 [M+H]⁺
\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.83 \text{ (dd, J=6.3 Hz, 2H)}, 7.71 \text{ (dd, J=6.3 Hz, 2H)}, 5.83-5.93 \text{ (m, } 1\text{H)}, 5.1-5.2 \text{ (m, } 2\text{H)}, 3.72 \text{ (dd, J=14, 4 Hz, } 1\text{H)}, 3.64 \text{ (dd, J=14, 4 Hz, } 1\text{H)}, 3.53 \text{ (m, } 1\text{H)}, 3.05-3.10 \text{ (m, } 1\text{H)}, 2.97 \text{ (dd, J=13, 8 Hz, } 1\text{H)}, 2.22-2.28 \text{ (m, } 1\text{H)}, 1.62-1.80 \text{ (m, } 4\text{H}). \]

(S)-(1-allylpyrrolidin-2-yl)methanamine (2.6)

Hydrazine hydrate (.63 mL, 20 mmol) was added to a solution of 2.5 (1.8 g, 6.6 mmol) in ethanol and heated at reflux for 3 hours. The reaction was cooled to 0°C and filtered, and the filtrate was washed with cold ethyl acetate and concentrated in vacuo. The crude material was purified by column chromatography on silica eluting with 50% ethyl acetate/hexanes to afford the title compound as a colorless oil (2.4 g, 17 mmol).

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta 5.81-5.90 \text{ (m, } 1\text{H)}, 5.0-5.21 \text{ (m, } 2\text{H)}, 3.33-3.39 \text{ (m, } 1\text{H)}, 3.02-3.06 \text{ (m, } 1\text{H)}, 2.80-2.88 \text{ (m, } 1\text{H)}, 2.61-2.70 \text{ (m, } 2\text{H)}, 2.35-2.41 \text{ (m, } 1\text{H)}, 2.14-2.20 \text{ (m, } 1\text{H)}, 1.48-1.88 \text{ (m, } 6\text{H}). \] LCMS found 141.64 [M+H]^+ 

(S)-N-((1-allylpyrrolidin-2-yl)methyl)-5-iodo-2,3-dimethoxybenzamide (2.7)
To a mixture of 2.6 (0.54 g, 3.8 mmol) in anhydrous chloroform was added 2.2 (0.91 g, 2.95 mmol) and HOBT (0.44 g, 3.2 mmol). EDC (0.62 g, 3.2 mmol) was slowly added at 0°C followed by DIEA (1.1 mL, 6.5 mmol) and the reaction was stirred overnight as it slowly warmed to room temperature. Water was used to quench the reaction, and the organic layer was extracted with chloroform, washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo. The crude reaction was purified by column chromatography on TEA neutralized silica eluting with 60% ethyl acetate/hexanes and afforded the title compound as a yellow oil in 53% yield (1.26 g).

1H NMR (400MHz, CDCl₃): δ 8.32 (brs, 1H), 8.03 (s, 1H), 7.28 (s, 1H), 5.87-5.95 (m, 1H), 5.20 (d, J=20 Hz, 1H), 5.10 (d, J=8 Hz, 1H), 3.89 (s, 6H), 3.76 (ddd, J=10, 5, 2.5 Hz, 1H), 3.42-3.47 (m, 1H), 3.3-3.34 (m, 1H), 3.10-3.13 (m, 1H), 2.87-2.91 (m, 1H), 2.66-2.71 (m, 1H), 2.22-2.27 (m, 1H), 1.88-1.96 (m, 1H), 1.62-1.77 (m, 3H). LCMS found 431.08, 433.11 [M+H]⁺

(S)-tert-butyl 2-((5-bromopyridin-3-yloxy)methyl)pyrrolidine-1-carboxylate (2.8)

To a mixture of 2-bromo-5-hydroxypyridine (0.94 g, 5.4 mmol), PPh₃ (1.4 g, 5.4 mmol), and (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (1 g, 4.9 mmol) in anhydrous THF at 0°C was added DIAD (1.1 g, 5.4 mmol) slowly over 30 minutes. The reaction stirred overnight at room temperature before concentrating in vacuo and was purified by column chromatography on silica gel eluting in 50% ethyl acetate/hexanes to afford the title compound as a white solid in 77% yield (1.35 g), m.p. 63°C. LCMS found 357.00, 359.02 [M+H]⁺
$^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.24 (d, $J=2$ Hz, 1H), 8.22 (m, 1H), 7.35-7.40 (m, 1H), 3.80-4.01 (m, 3H), 3.15 (m, 2H), 2.4 (s, 9H), 1.84-2.04 (m, 4H). LCMS found 357.00, 359.02 [M+H]$^+$.

General procedure for continuous flow syntheses

Flow chemistry was performed using Labtrix® Start available from Chemtrix BV. Scheme 2.5 shows a representation of the microfluidic setup. More specifically, the reaction proceeded as follows: from left to right, syringe 1 was loaded with .15 M alkynyl tosylate in ACN. Syringe 2 was loaded with a .2 M solution of TBAF in ACN. Syringes 1 and 2 were combined and heated in a 115°C oil bath with a combined flow rate of 1 $\mu$L/min in a 45$\mu$L PEEK loop. Syringes 1 and 2 were then combined with the aryl halide (syringe 3, .05 M) and palladium acetate/tetrabutylammonium acetate (syringe 4, .005 M/.2 M) and pumped again through a 45$\mu$L PEEK loop in a 115°C oil bath at a combined rate of 2 $\mu$L/min. The reaction dispensed into an HPLC vial containing ACN/.1% formic acid and an internal standard. The reactions were then analyzed by HPLC. To purify the compounds, 1 mL of reaction mixture was collected, concentrated in vacuo, and purified by column chromatography eluting with ethyl acetate/hexanes.
1-(4-3-Fluoroprop-1-ynyl)phenylethanone (2.9)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.92 (d, J=8 Hz, 2H), 7.58 (d, J=8 Hz, 2H), 5.21 (dt, J=48, 6 Hz, 2H), 2.59 (s, 3H). LCMS found 177.19 [M+H]$^+$

![Chemical structure](image)

1-(4-4-Fluorobut-1-ynyl)phenylethanone (2.10)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.87 (d, J=8 Hz, 2H), 7.51 (d, J=8 Hz, 2H), 4.63 (dt, J=48, 6 Hz, 2H), 2.85 (t, J=8 Hz, 2H), 2.59 (s, 3H). LCMS found 190.89 [M+H]$^+$

![Chemical structure](image)

1-(4-Fluorobut-1-ynyl)-4-methylbenzene (2.11)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.23 (d, J=8 Hz, 2H), 7.05 (d, J=8 Hz, 2H), 4.45 (dt, J=40, 5.8 Hz, 2H), 2.61 (t, J=8 Hz, 2H), 2.59 (s, 3H). GCMS found 162.08 [M$^+$]

![Chemical structure](image)
1-(4-Fluorobut-1-ynyl)-4-nitrobenzene (2.12)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.19 (d, J=8 Hz, 2H), 7.61 (d, J=8 Hz, 2H), 5.20 (dt, J=48, 6 Hz, 2H). GCMS found 178.9 [M$^+$]


Tert-butyl (S)-2(((5-(6-fluorobut-1-ynyl)pyridine-3-yl)oxy)methyl)pyrrolidine-1-carboxylate (2.13)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.23 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.20 (s, 1H), 4.52 (dt, J=48, 6 Hz, 2H), 4.15-4.23 (m, 2H), 3.85-3.90 (m, 1H), 3.34 (t, J=8 Hz, 2H), 2.46 (t, J=6.5 Hz, 2H), 1.69-2.19 (m, 3H), 1.32 (s, 9H). 45% yield. LCMS found 349.13 [M+H]$^+$


Tert-butyl (S)-2(((5-(6-fluoropent-1-ynyl)pyridine-3-yl)oxy)methyl)pyrrolidine-1-carboxylate (2.14)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.23 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.20 (s, 1H),
4.52 (dt, J=48.6 Hz, 2H), 4.15-4.23 (m, 2H), 3.85-3.90 (m, 1H), 3.34 (t, J=8 Hz, 2H), 2.46 (t, J=6.5 Hz, 2H), 1.69-2.19 (m, 5H), 1.32 (s, 9H). 55% yield. LCMS found 363.45 [M+H]^+
Chapter 3

Transfer hydrogenations of Nifrolidine and Fallypride analogues under microwave conditions

3.1 Transfer hydrogenations in medicinal chemistry

Hydrogenation is an important synthetic catalytic method in both academic and industry laboratories alike that effectively reduces or saturates organic compounds. Many functional groups can be hydrogenated with high conversions under relatively mild conditions with a very clean reducing agent, hydrogen.¹

Knoevenagel, who demonstrated that palladium black promoted the reduction of dimethyl 1,4-dihydrorteraphthalate to dimethyl terephthalate, performed the first direct hydrogenation in 1903. Close to 50 years later, Braude and Linstead separated hydrogenations into three categories: (1) reduction taking place within one molecule, (2) hydrogen disproportionation involving hydrogen transfer between identical donor and acceptor units, and (3) hydrogenation occurring between non identical donor and acceptor units. The third category, known as transfer hydrogenation (TH)-dehydrogenation, is by far the most widely used subfield. Direct hydrogenation employs the use of H₂ gas, a very effective process, however direct hydrogenation also requires the use of elaborate experimental setups as well as potentially hazardous pressurized hydrogen gas.² A much safer alternative is the cost effective, “green”, and generally mild TH-dehydrogenation.

The field of TH has grown rapidly in recent years due to the high demand for safe, green methods of the reduction of organic compounds employing non-H₂ hydrogen sources and generally a mild catalyst. This reaction is of particular interest in the field of pharmaceuticals as
well as bioactive molecules and agricultural compounds, and variety of catalysts, ligands, solvents, bases, and hydrogen sources have been explored to find the most effective route. In pharmaceuticals, ruthenium and palladium based catalysts have been of much interest due to the greener and more economical catalytic systems.

As explained previously, the efficacy of AD drugs can vary greatly with even the smallest changes in methylene spacers and hybridization. We looked into the idea of synthesizing the fluorinated alkynyl nifrolidine and fallypride analogues by flow then reducing those to provide multiple analogues in a short amount of time.

3.2 Techniques and approach to perform a quick transfer hydrogenation of fluorinated compounds

In 2011, Han et al. developed a facile selective hydrogenation of alkynes with formic acid. This method showed promise as a method to reduce our fluorinated alkynes due to the readily available reagents and mild catalyst. The general method can be seen in scheme 3.1, and a microwave method was developed based on those conditions.

![Scheme 3.1: Selective transfer hydrogenation using formic acid as the hydrogen source](image-url)
Han’s method was attractive because it provided a safe and selective transfer hydrogenation with relatively subtle change in the reaction conditions to synthesize cis and trans-alkenes and alkane compounds. According to the literature, the method proceeded in dioxane over 15 hours at 80°C; however, we thought adapting the conditions to be successful in the microwave in under ten minutes would be advantageous to the synthesis of PET imaging agents. However, upon employing the method there was minimal selectivity in the method, and a suitable solvent could not be found for microwave conditions. Dioxane is not an ideal microwave solvent, so the temperature had to reach upwards of 200°C, oftentimes exceeding pressure in the closed microwave system. While we did see conversion to the desired product, the conditions were harsher than expected and other options were explored.

In 2009 Tran\textsuperscript{4} and associates developed a method for the reduction of alkynes and alkenes to alkanes using acetic acid, a palladium catalyst, and sodium borohydride to produce hydrogen gas \textit{in situ}. The substrates gave the desired alkanes in under 15 minutes at room temperature in a variety of solvents. The ease of handling of all the reagents, high conversion rates, and relatively fast rate of reaction made this particular method great to adapt for microwave use for our fluorinated alkynes.

\begin{center}
\begin{tikzpicture}
\node (a) {Alkene or Alkyne};
\node (b) [right of=a] {Alkane};
\node (c) [above of=a] {NaBH\textsubscript{4}, Acetic Acid};
\node (d) [right of=c, yshift=-1cm] {Pd/C};
\node (e) [right of=d] {IPA, RT, 15 min};
\draw[->] (c) -- (d) -- (e) -- (b);
\end{tikzpicture}
\end{center}

\textit{Scheme 3.2: Sodium borohydride reduction of alkynes and alkenes}

The exact mechanism for this reaction is unknown; however, it is suggested that a catalytic hydrogenation on the metal surface is the mechanism of action for reductions of alkenes with borohydrides and metal salts. The extremely rapid rate of reduction can be somewhat
explained by alkyne or alkene adsorption on the metal surface after the palladium metal catalyzes the hydrolysis of the sodium borohydride at the metal surface to release hydrogen gas. Another possibility would be that the reduction may occur through ionic hydrogenation wherein a carbocation is generated by the acid and is in turn reduced with a nucleophilic hydride to synthesize the reduced product.\(^4\)

3.3 Synthesis of fluorinated alkanes from previously made alkynes

Tran’s synthesis was adapted for microwave use fairly easily and retained excellent yields for a variety of substrates as well as for analogues of fallypride and nifrolidine.

Optimization was done on 6-phenylhexyn-1-ol. Alcohols are believed to act similarly to fluorines mechanistically in the body due to a similar size and electronegativity. It was much easier to synthesize large amounts of 6-phenylhexyn-1-ol to use as a model substrate than repeatedly make a fluorinated alternative, and longer chained substrates provided much higher yields than the 3 and 4-chained analogues discussed in the previous chapter. Once high yields of 6-phenylhexanol were achieved through a microwave synthesis, fluorinated alkanes were synthesized following Plazcek’s method\(^5\) of fluorinating hex-5-ynyl-4-methylbenzenesulfonate (3.3) and subsequently coupling the fluorinated alkynyl chain to an aryl halide. Following the

Scheme 3.3: General reduction of fluoroalkylated compounds and reduction of 6-phenylhexyn-1-ol
subsequently coupling the fluorinated alkynyl chain to an aryl halide. Following the reduction of the simple substrates were reductions of fallypride and nifrolidine analogues.
Scheme 3.4: Transfer hydrogenations of fluoroalkylated substrates including fallypride and nifrolidine analogues
3.4 Conclusion

A robust method was developed for a rapid transfer hydrogenation to reduce fluorinated aryl alkynes. As seen by the reduction of 3.1, the carbonyl is not affected; however, the reduction of 3.12 not only affected the alkyne but also reduced the allyl pyrrolidine. Also, a quick addition of trifluoroacetic acid (TFA) successful removed the tert-butyloxy carbonyl protecting group while simultaneously reducing the alkyne to the alkane nifrolidine analogue. Both electron rich and electron poor substrates showed good yields, and LC/MS analysis showed the formation of the cis-alkene after roughly 30 seconds of reaction time. Isolation of the alkene could not successfully be optimized; however, with further work it is highly likely that a reaction could be improved to form the cis-alkene exclusively in a very short amount of time. This reaction could be especially helpful in the synthesis of PET imaging agents due to the vast amount of pharmaceuticals with sp and sp\(^2\) bonds as well as the dramatic changes that could result in the modification of hybridization. Ideally we would like to perform these reductions on alkynes with variety in the length of the carbon chain, successfully linking the microfluidic and microwave work in this thesis.
3.5 References


3.6 Experimental

6-phenylhexyn-5-ol (3.1)

To a round bottom flask was added iodobenzene (6 mmol, .672 g), propargyl alcohol (5 mmol, .291 mL), bis(triphenylphosphine)palladium(II) (.068 mmol, .047 g), in TEA (40 mL). The reaction stirred for 5 mins then copper iodide (.034 mmol, .006 g) was added. The reaction stirred overnight at room temperature in open air. Upon completion the reaction was quenched with water, washed three times with ethyl acetate, dried over MgSO₄, and concentrated in vacuo. The compound was purified by column chromatography and eluted with ethyl acetate/hexanes to afford a 79% yield of the desired product.

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.43 (m, 2H), 7.20-7.32 (m, 3H), 4.14 (s, 1H), 3.75 (d, J=8 Hz, 2H), 2.46 (d, J=8 Hz, 2H), 1.74-1.95 (m, 4H). LCMS found 174.89 [M+H]^+

6-phenylhexanol (3.2)

To a mixture of 6-phenylhexyn-5-ol (.2 mmol, .034g), palladium acetate (.01 mmol, .002 g), acetic acid (.4 mmol, .025 mL) and IPA (1 mL) in a microwave vial was added sodium
borohydride (.8 mmol, .03 g), and the reaction mixture was subjected to microwave irradiation for 2 minutes at 40°C. Upon completion, the reaction mixture was filtered to remove excess sodium borohydride and concentrated en vacuo to provide a colorless oil in 89% yield.

^1^H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.34-7.43 (m, 2H), 7.20-7.32 (m, 3H), 4.14 (s, 1H), 3.75 (d, J=8 Hz, 2H), 2.46 (d, J=8 Hz, 2H), 1.74-1.95 (m, 4H), 1.29-1.43 (m 4H). LCMS found 179.28 [M+H]^+ 

\[ \text{Hex-5-ynyl-4-methylbenzenesulfonate (3.3)} \]

In a round bottom flask at 0°C, 5-hexyn-1-ol (2 g, 20.40 mmol) was added to tosyl chloride (4.66 g, 24.5 mmol) in DCM. Triethylamine (3.41 mL, 24.5 mmol) was slowly added over five minutes and the reaction was stirred overnight. Upon completion, water was added until the reaction turned clear and was washed with ethyl acetate. The organic layers were combined, washed with brine, dried over MgSO\textsubscript{4}, and concentrated en vacuo. The compound was purified with column chromatography and eluted with hexanes/ethyl acetate to afford the desired product in 91% yield. Colorless oil.

^1^H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.79 (d, J= 8 Hz, 2H), 7.36 (d, J= 8 Hz, 2H), 4.03 (t, J= 6 Hz, 2H), 2.45 (s, 3H), 2.18 (td, J = 8, 4 Hz, 2H), 1.92 (t, J = 4, 1H), 1.74-1.81 (m, 2H), 1.51-1.60 (m, 2H)
General method for the synthesis of 3.4-3.9 in batch

\[
\begin{align*}
\text{Hex-5-ynyl-4-methylbenzenesulfonate} & \quad \text{(.63 mmol, .158 g)} \\
\end{align*}
\]

In a flame-dried microwave vial under argon, hex-5-ynyl-4-methylbenzenesulfonate (.63 mmol, .158 g) was stirred with anhydrous t-amyl alcohol and 1M TBAF in THF (.6 mL) was added. The reaction mixture was subjected to microwave irradiation for 10 minutes at 90°C. Upon completion the reaction was cooled to 0°C in an ice bath. Anhydrous DMF (1 mL) and the aryl halide (.63 mmol) were added, and the reaction mixture was sparged with argon for twenty minutes. After twenty minutes TBAA (945 mmol, .284 g) and palladium acetate (.03 mmol, .007 g) were added and the reaction warmed to room temperature overnight. Distilled water was added and the reaction mixture was washed 5 times with ethyl acetate, and the combined organic layer was washed with brine, dried with MgSO₄, and concentrated en vacuo. The compound compound was purified via column chromatography and eluted with hexanes/ethyl acetate to afford the desired fluoroalkynylated product.
1-(4-(6-fluorohex-1-ynyl)phenyl)ethanone (3.4)

Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (d, J=8 Hz, 2H), 7.43 (d, J=8 Hz, 2H), 4.52 (dt, J=48 Hz, 6 Hz, 2H), 2.59 (s, 3H), 2.52 (t, J=8 Hz, 2H), 2.74-2.94 (m, 4H) 21% yield. LCMS found 190.88 [M+H]$^+$

1-(6-fluorohex-1-ynyl)4-methylbenzene (3.5)

Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.25 (d, J= 8 Hz, 2H), 7.05 (d, J=8 Hz, 2H), 4.52 (dt, J=48 Hz, 6 Hz, 2H) 2.47 (t, J=8 Hz, 2H), 2.32 (s, 3H), 2.74-2.94 (m, 4H) 16% yield. LCMS found 219.03 [M+H]$^+$

3-(6-fluorohex-1-ynyl)pyridine (3.6)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.59 (s, 1H), 8.45 (d, J=6 Hz, 1H), 7.65 (d, J=8 Hz, 1H), 7.20 (dd, J=8, 6 Hz, 1H), 4.52 (dt, J= 48, 6 Hz, 2H), 2.51 (t, J=8 Hz, 2H), 1.74-1.95 (m, 4H)
26% yield. LCMS found 177.91 [M+H]^+

1-fluoro-4-(6-fluorohex-1-ynyl)benzene (3.7)

Colorless oil. \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.37 (dd, J=8, 6 Hz, 2H), 6.98 (t, J=8 Hz, 2H), 4.52 (dt, J= 48, 6 Hz, 2H), 2.46 (t, J=8 Hz, 2H), 1.74-1.95 (m, 4H) 23% yield. GCMS found 194.0 [M]^+

Tert-butyl \((S)-2(((5-(6-fluorohex-1-ynyl)pyridine-3-yl)oxy)methyl)pyrrolidine-1-carboxylate (3.8)

Yellow oil. \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.23 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.20 (s, 1H), 4.52 (dt, J=48,6 Hz, 2H), 4.15-4.23 (m, 2H), 3.85-3.90 (m, 1H), 3.34 (t, J=8 Hz, 2H), 2.46 (t, J= 6.5 Hz, 2H), 1.69-2.19 (m, 8H), 1.32 (s, 9H). 45% yield. LCMS found 377.15 [M+H]^+
(S)-N-((1-allylpyrrolidin-2-yl)methyl)-S-(6-fluorohex-1-ynyl)-2,3-dimethoxybenzamide (3.9)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.31 (br, s, 1H), 7.75 (s, 1H), 7.03 (s, 1H), 5.85-5.95 (m, 1H), 5.15 (d, J=16 Hz, 1H), 5.05 (d, J=16 Hz, 1H), 4.52 (dt, J=48, 6 Hz, 2H), 3.89 (s, 6H), 3.77 (ddd, J=14, 8, 3 Hz, 1H), 3.44 (m, 1H), 3.31-3.35 (m, 1H), 2.84-2.89 (m, 1H), 2.65-2.71 (m, 1H), 2.42-2.49 (m, 2H), 2.20-2.27 (m, 1H), 1.69-1.99 (m, 8H). LCMS found 403.10 [M+H]$^+$

General procedure for the synthesis of 3.10-3.16 (excluding 3.15)

To a microwave vial with a Teflon coated stir bar was added the fluoroalkylated substrate (.2 mmol), palladium acetate (5% eqv), acetic acid (.4 mmol, 2 eqv) and IPA (1 mL). Let stir a few seconds then add sodium borohydride (.8 mmol, 4 eqv). The reaction was subjected to microwave irradiation for 2 minutes at 40°C. The compound was then filtered to remove excess sodium borohydride, washed with IPA and concentrated en vacuo.
1-(4-6-fluorohexyl)phenyl)ethanone (3.10)
Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.58 (d, J= 8 Hz, 2H), 7.34 (d, J=8 Hz, 2H), 4.52 (dt, J=48, 6 Hz, 2H), 2.65 (m, 2H), 2.59 (s, 3H), 1.64-1.74 (m, 4H), 1.21-1.34 (m, 2H). 97% yield. LCMS found 223.06 [M+H]$^+$

1-(6-fluorohexyl)-4-methylbenzene (3.11)
Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.25 (d, J=8 Hz, 2H), 7.05 (d, J=8 Hz, 2H), 4.52 (dt, J=48, 6 Hz, 2H), 2.60-2.65 (m, 2H), 3.59 (s, 3H), 1.64-1.74 (m, 4H), 1.15-1.39 (m, 4H). 90% yield. GCMS found 194.1 [M]$^+$

3-(6-fluorohexyl)pyridine (3.12)
Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.50 (s, 1H), 7.57 (d, J= 6Hz, 1H), 7.20 (m, 2H),
4.52 (dt, J=48, 6 Hz, 2H), 2.63 (d, J=8 Hz, 2H), 1.74-1.89 (m, 4H), 1.15-1.29 (m, 4H). 75% yield. LCMS found 181.94 [M+H]^+

1-fluoro-4-(6-fluorohexyl)benzene (3.13)

Colorless oil. ^1^H NMR (400 MHz, CDCl₃): δ 7.38 (dd, J=8, 6 Hz, 2H), 6.98 (t, J=8 Hz, 2H), 4.52 (dt, J=48, 6 Hz, 2H), 2.53 (d, J=8 Hz, 2H), 1.64-1.88 (m, 4H), 1.21-1.34 (m, 2H). 63% yield. GCMS found 198.26 [M]^+

Tert butyl (S)-2-(((5-(6-fluorohexyl)pyridine-3-yl)oxy)methyl)pyrrolidine-1-carboxylate (3.14)

Colorless oil. ^1^H NMR (400 MHz, CDCl₃): δ 8.23 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.20 (s, 1H), 4.52 (dt, J=48, 6 Hz, 2H), 4.15-4.23 (m, 2H), 3.34 (s, 1H), 3.10-3.20 (t, J=8 Hz, 2H), 2.63 (d, J=8 Hz, 2H), 1.69-2.01 (m, 11 H), 1.32 (s, 9H). 52% yield. LCMS found 381.24 [M+H]^+
(S)-3-(6-fluorohexyl)-5-(pyrrolidin-2-yl-methoxy)pyridine (3.15)

The general reaction conditions were done followed by the addition of TFA (.050 mL). The reaction mixture was subjected to microwave irradiation for another two minutes to give the desired product in 45% yield.

Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.23 (s, 1H), 8.20 (s, 1H), 8.18 (s, 1H), 7.20 (s, 1H), 4.52 (dt, J=48, 6 Hz, 2H), 4.15-4.23 (m, 2H), 3.34 (s, 1H), 3.10-3.20 (t, J=8 Hz, 2H), 2.63 (d, J=8 Hz, 2H), 1.69-2.01 (m, 11 H), 1.32. 45% yield. LCMS found 281.17 [M+H]$^+$

(S)-5-(6-fluorohexyl)-2,3-dimethoxy-N-((1-propylpyrrolidin-2-yl)methyl)benzamide (3.16)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.31 (br, s, 1H), 7.75 (s, 1H), 7.03 (s, 1H), 4.52 (dt, J=48, 6 Hz, 2H), 3.89 (s, 6H), 3.77 (ddd, J=14, 8, 3 Hz, 1H), 3.44 (m, 1H), 3.31-3.35 (m, 1H), 2.84-2.89 (m, 1H), 2.65-2.71 (m, 1H), 2.42-2.49 (m, 2H), 2.20-2.27 (m, 1H), 2.01-2.08 (m, 2H), 1.29-1.99 (m, 12H), .87-.97 (m, 3H) LCMS found 409.24 [M+H]$^+$
4.1 Representative NMR spectra

2.1
Pulse Sequence: 62pu1
Solvent: CDCl3
Ambient temperature
Mercury-7000 "mar400"

Relax. delay 1.898 sec
Pulse 54.0 degrees
Acq. time 1.395 sec

320000 repetitions

Obs. 32.0000 ppm

Line broadening 8.2 Hz
SP 

Total time 32 min, 27 sec
Pulse Sequence: s2pop
Solvent: CDCl3
Ambient temperature
Mercury-400B "NE4000"

Relax. delay 1.000 sec
Pulse 78.8 degrees
Acq. time 1.305 sec
Width 6002.4 Hz
24 repetitions

Spectrum: 1H, 399.1216210 MHz

Data Processing

Total time 13 min, 22 sec
KH-Z-92-pure IR CDC13

Pulse Sequence: s2pa1
Solvent: CDC13
Ambient temperature
Mercury=60088 "nm=600"

Relax. delay 1.000 sec
Pulse 54.0 degrees
Acq. time 1.385 sec
Width 6002.4 kHz
136 repetitions
OBSERVE H1, 399.1316673 MHz
DATA PROCESSING
Line broadening 0.2 Hz
117, 12888
Total time 22 min, 27 sec
4H nmr

KIS-3-89_clean

Pulse Sequence: sinc
Solvent: CDCl3
Ambient temperature
Mercury-600SB "unknown"

Relax. delay 1.008 sec
Polariz 54.0 degrees
Avg. time 1.253 sec
Width 002.4 Hz

Observ. - Hi 391.1213301 MHz

Data Processing
Line broadening 0.2 Hz
FID scale 10000
Total time 22 min, 27 sec
Pulse Sequence: s2pol
Solvent: CDC19
Ambient Temperature
Mercury-4000B "pronto"
Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.280 sec
Width 6092.4 Hz
2 repetitions
Scale factor 184.125388 MHz
DATA PROCESSING
Line broadening 9.2 Hz
FT slice 16384
Total time 22 min, 27 sec
fatty alcohol
ICH-3-68

Pulse Sequence: uzpu1
Solvent: CDCl3
Ambient temperature
Mercury-40000 "unknown"

Relax. delay 1.000 sec
Pulse 54.3 degrees
Acc. time 1.000 sec
Width 1000.0 Hz
Repetitions 1000

Reference: 1H: 399.1216301 MHz

DNP 180 degrees
Line broadening 8.0 Hz
FT size 1024
Total time 22 min, 17 sec

3.9
HK-1-25_bottom
Pulse Sequence: a3pul
Nucleus: COC19
Ambient Temperature
Mercury-400MHz "unknown"

Relax. delay 1.001 sec
Pulse 64.0 degrees
Acq. time 1.385 sec
Width 0.011 1 Hz
35 repetitions
COCCYCE 61, 391.121581 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FF size 16384
Total time 22 min, 27 sec
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