Development of Copper(II)-Mediated Methods for PET Imaging Applications

by

Katarina Jade Makaravage

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Doctoral Committee:

Professor Melanie S. Sanford, Chair
Professor John Montgomery
Research Associate Professor Peter J. H. Scott
Professor John P. Wolfe

Katarina J. Makaravage

kjmak@umich.edu

ORCID iD: 0000-0002-1225-5305

Dedication

To Jimmy and my family

Acknowledgements

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18-c-6	1,4,7,10,13,16-hexaoxacyclooctadecane
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Å	Angstrom
Ac	Acetyl
AD	Alzheimer's disease
Ar	Aryl
B_2pin_2	bis(pinacolato)diboron
Bn	benzyl
Boc	tert-Butyloxycarbonyl
Bu	butyl
C	Celsius
[^{11}C]CFN	[^{11}C]carfentanil
cGMP	Current Good Manufacturing Practice
Ci	Curie (unit)
CT scan	Computerized tomography scan
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene
DC	decay corrected
DCM	dichloromethane
DG	Directing group
DMA	*N,N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EOB	End of bombardment
EoS	end of synthesis
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
[^{18}F]FDG	[^{18}F]fluorodeoxygluocose
[^{18}F]F-PEB	[^{18}F]3-fluoro-5-[(pyridine-3-yl)ethynyl]benzonitrile
g	gram
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
[^{11}C]HED	[^{11}C]-(−)-*m*-hydroxyephedrine
HPLC	High performance liquid chromatography

HRMS	High-resolution mass spectrometry
Hz	Hertz
KOR	kappa opioid receptors
Kryptofix	4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane
L-DOPA	L-DOPA L-3,4-dihydroxyphenylalanine
M	Molarity
Me	Methyl
Mes	Mesityl
[^{18}F]4F-MHPG	4-[^{18}F]Fluoro-m-hydroxyphenethylguanidine
[^{123}I]MIBG	[^{123}I]meta-Iodobenzylguanidine
mL	milliliter
MOR	mu opioid receptors
mp	melting point
MPPF	2'-methoxyphenyl-(*N*-2'-pyridinyl)-p-fluorobenzamidoethyipiperazine
MRI	Magnetic resonance imaging
MTBE	methyl tert-butyl ether
NDC	non-decay corrected
NET	norepinephrine transporter
NEt_3	Triethylamine
NFSI	*N*-Fluorobenzenesulfonimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
OAc	Acetate
OTf	Trifluoromethane sulfonate
OTs	tosylate
PDE	Permitted daily exposure
PET	Positron Emission Tomography
PG	Protecting group
Ph	phenyl
PhF	fluorobenzene
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
QC	quality control
QMA	quaternary ammonium
RCC	Radiochemical conversion
RCY	Radiochemical yield
R_f	Retention factor
SA	Specific activity
S_NAr	Nucleophilic aromatic substitution

$t_{1/2}$	Half-life
TBA	tetrabutylammonium
*t*BuCN	Trimethylacetonitrile
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxyl
TFA	Trifluoroacetatic acid
THF	tetrahydrofuran
TLC	Thin-layer chromatography
TMS	trimethylsilane

Abstract

Positron emission tomography (PET) is an imaging technique that uses a radioactive small molecule to monitor biological processes. As the radioactive molecule moves throughout the body, it emits positrons that allow it to be tracked using a PET scan. Key information can be learned during this scan, including how the molecule engages the target of interest, ability to cross the blood-brain barrier, how quickly it is cleared from the body, etc. As PET imaging becomes more prevalent, the need for more diverse tracers increases. This thesis describes several new methods for forming C–^{18}F and C–^{11}C bonds that have and will continue to be utilized for the synthesis of new PET imaging tracers.

Chapter 1 describes the importance of fluorinated arenes and their importance in PET imaging. Current methods for radiolabeling these substrates are discussed. Challenges for developing PET methodologies and labeling molecules with other radioactive isotopes are discussed.

Chapter 2 focuses on the development of copper-mediated [^{18}F]radiofluorination methodologies using aryl boron acids and arylstannanes derivatives as precursors. Both methods have wide substrate scopes and were fully automated to provide clinical doses of [^{18}F]MPP-F.

Chapter 3 details the development of a copper-mediated [^{11}C]radiocyanation method that is applicable to various aryl boron and arylstannanes derivatives. This methodology was utilized to produce [^{11}C]perampanel and [^{11}C]LY2795050 on a clinical scale. [^{11}C]LY2795050 was used for a non-human primate imaging study and is currently undergoing clinical trials.

Chapter 4 focuses on the development of a copper-mediated directed C(sp^2)–H [^{18}F]radiofluorination method. Chapters 2 and 3 used pre-functionalized precursors, which can hinder application to more complicated substrates. The development of a C–H activation method that uses a removable directing group could be highly advantageous for molecules in clinical trials.

Chapter 5 details three incomplete projects: (1) [^{18}F]radiofluorination of aryl iodides, (2) directed fluorination of other removable directing groups, and (3) improved [^{18}F]radiofluorination of [^{18}F]4F-MHPG. Preliminary results and future directions are discussed.

This dissertation describes new methodologies that have been developed and how they have been applied in our lab and others. New methodologies to form C–^{18}F and C–^{11}C bonds will become more pertinent as the field of PET continues to grow and new targets are identified. We believe the methods discussed herein will serve an important role for helping the PET community diagnose and monitor diseases earlier and more effectively than alternative imaging techniques.

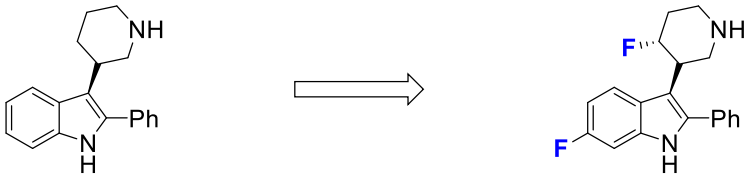
Chapter 1

Introduction

1.1. Significance of Aryl Fluorides

Since the appearance of the first fluorine-containing drug on the market, approved by the FDA in 1955, there has been an increase in the number of fluorinated molecules approved.[1–3] In 2005, as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market contained fluorine including half of the top 10 drugs sold.[4] Introducing a fluorine atom onto a drug candidate can impart many new properties of interest, such as lipophilicity, pK_a, and metabolism, while minimally effecting changes in molecular size.[5] For instance, Figure 1.1 shows an example of a fluorinated lead compound compared to the proto-compound where the addition of two fluorine atoms (1) decrease the basicity of the amine, improving bioavailability, and (2) block a site of metabolism.[6] These two minor modifications lead to an increased binding affinity by an order of magnitude in addition to an increased bioavailability.[6,7] Due to the rarity of organofluorine in nature, there are limited metabolic pathways for C–F functionalities allowing the drug to circulate in the body for longer periods.[4,8]

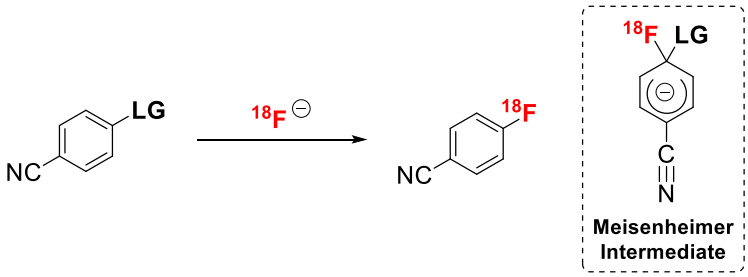
Figure 1.1. Effect of Fluorinate Addition on Antipsychotic Drug Candidates



To incorporate a fluorine atom onto a molecule there are two approaches (1) start with fluorine in a building block or (2) introduce fluorine during the synthesis.[4] Although new methods to introduce fluorine in a late-stage approach are being developed, this problem remains challenging due to fluorine being the most electronegative element.[6] Fluoride can form strong interactions with hydrogen bonds in water, alcohols, and amines and in addition, in the presence of hydrogen bond donors, fluoride is only weakly nucleophilic.[9] Furthermore, in anhydrous conditions, fluoride is more nucleophilic but also demonstrates strong basic character which can lead to undesired reactions.[9] An alternative to nucleophilic fluoride would be to use electrophilic fluorine, which can come in many forms. F_2 is highly reactive and presents poor selectivity in fluorination reactions, but N–F fluorine sources have been used under more mild and selective conditions; however, they are generally more expensive than nucleophilic sources.

A common method to install an aryl fluoride is to use the halogen exchange (Halex) process. The Halex process (S_NAr fluorination) has several notable limitations including using metal fluoride sources that have poor solubility, requiring forcing reaction conditions (>100 °C), or requiring additives such as phase transfer reagents. For S_NAr reactions to be productive, electron-withdrawing arenes are needed to help stabilize intermediates formed during the transition state (Scheme 1.1).

Scheme 1.1. S_NAr Fluorination



1.2. Transition Metal-Mediated and -Catalyzed Aromatic Fluorination

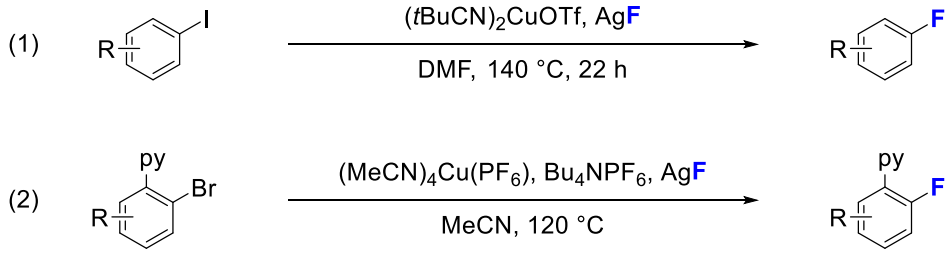
Many of the challenges associated with S_NAr fluorination could be overcome using a transition metal to mediate and/or catalyze the fluorination reaction.[10] Over the past several years, several transition metal-catalyzed or -mediated methods have been

developed for C–F bond formation. Stoichiometric reactions with Pd have shown that the reductive elimination step is challenging.[11] In 2009, a Pd-catalyzed method was reported using a nucleophilic fluorine source with aryl triflates.[12] This methodology was later expanded to include aryl iodides and bromides.[13] Since this initial report, other metal-mediated and -catalyzed methods have been developed.[9,10,14,15]

1.2.1. Cu-Mediated and -Catalyzed Nucleophilic Fluorination

As an alternative to Pd, Cu is a relatively inexpensive option that has been shown to form aryl–F bonds. In 2011, Ribas and coworkers reported the first example of C–F bond forming reductive elimination from a well-defined aryl-Cu(III) complex.[16] Following the initial report, a C–H fluorination method was reported using KF via a Cu(III) route.[17] In 2012, Hartwig and coworkers reported a copper-mediated fluorination of aryl iodides using a large excess of a Cu(I) complex and AgF (Scheme 1.2, reaction 1).[18] The reaction was effective for electron-rich and -poor arenes as well as sterically hindered substrates, but the formation of a hydrodeiodinated side product rendered the purification challenging.[18] The methodology performed best for aryl iodides, but aryl bromides could be used to obtain low yields of product (<20%).[18] An alternative method was published in 2013 by Liu and coworkers that used 2-phenyl pyridine derivatives and catalytic copper to fluorinate aryl bromides with an excess of AgF (Scheme 1.2, reaction 2).[19] This method was limited to 2-pyridine substrates or similar motifs and could not be extended to additional directing groups.

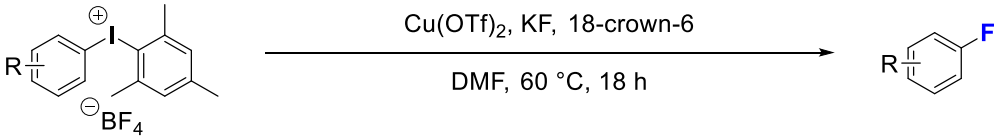
Scheme 1.2. Cu-Mediated Fluorination of Aryl–X Bonds



Copper catalysis has also been developed for an S_NAr-type nucleophilic fluorination of diaryliodonium salts. Nucleophilic fluorination of diaryliodonium salts has

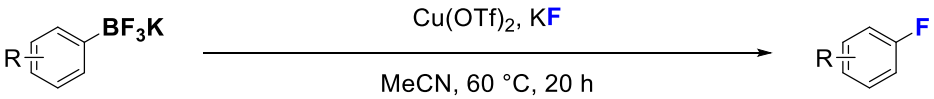
been known since the early 1980s using KF as the fluoride source.[20] The products can be formed in good yield, but typically as a mixture with the corresponding aryl iodide and reduced arene side products. A limitation of this methodology is the need to prepare the diaryliodonium substrates. Unsymmetrical diaryliodonium salts are preferred for enhanced selectivity, however they prove to be a synthetic challenge when targeting functionalized aryl fluorides. In 2013, a copper catalyzed method was utilized with unsymmetrical (mesityl)iodoniums salts and KF [21], which concluded the fluorination of the less sterically hindered arenes was preferred, allowing for use of a bulky mesityl group as a separable byproduct formation (Scheme 1.3).

Scheme 1.3. Cu-Catalyzed Fluorination of (Mesityl)(aryl)iodonium Salts[21]



Employing excess copper and KF were shown to fluorinate aryl trifluoroborate salts with good yields (Scheme 1.4).[22] This was the first example showing organoborane derivatives undergo transmetallation and reductive elimination with nucleophilic fluoride and copper to give the desired C–F bond. The reaction could tolerate electron-poor substrates, while electron-rich substrates gave trace product.

Scheme 1.4. Cu-Mediated Fluorination of Aryl Trifluoroborate Salts[22]



1.3. PET Chemistry

There is a wealth of modern imaging techniques that have been transformative for how maladies are detected, diagnosed, and treated. A PET scan is an *in vivo* imaging technique that uses a radioactive, positron-emitting molecule (known as a tracer) to monitor biological processes.[23] Unlike a magnetic resonance imaging (MRI) or computerized tomography (CT) scan that provide structure information, a PET scan can

provide functional information about how the tracer is interacting with a desired target. The tracer is monitored in real-time giving a picture of the biochemical and physiological processes that are occurring. This can be a valuable diagnostic tool to help determine the nature of particular internal species, including whether a mass means a returned tumor or cell death. PET scans can be used to diagnose tumors, validate lead compounds that can cross blood-brain barrier and engage with the desired target, as well as monitor side pathways and metabolic processes.

The radioactive agent is equipped with a radionuclide that has a half-life intrinsic to the isotope used (Table 1.1). New tracers are generally developed as [^{11}C]radiotracer. This is due to the ubiquitous presence of carbon in natural products and drug compounds, which provide a multitude of possible incorporation sites. Exchanging a ^{12}C atom for a position-emitting ^{11}C atom should ensure that the molecule of interest behaves the same chemically and biologically.[23,24] Due to the short half-life (20 min), syntheses have to be efficient and short, but multiple scans can be performed in the same day. Carbon-11 is typically generated as [^{11}C]CO_2 but can quickly be converted to [^{11}C]CH_4 and is generally used as a methylating reagent in the form of [^{11}C]MeI or [^{11}C]MeOTf.[23] The other common form of [^{11}C]radiotracers is a [^{11}C]carbonyl group. This can be incorporated by a few methods, [^{11}C]CO_2, [^{11}C]CO, or [^{11}C]CN followed by hydrolysis. [^{11}C]Cyanide offers an advantage because it can be readily generated from [^{11}C]CO_2.[23,24] Chapter 3 describes an improved copper-mediated [^{11}C]radiocyanation method utilizing aryl borane derivatives and arylstannanes.[25]

Fluorine-18 is the most commonly used radionuclide due to its' relatively long half-life (110 min) and favorable imaging properties.[23] Fluorine-18 is generated and available as electrophilic fluorine or nucleophilic fluoride. Nucleophilic fluoride is commonly accessible and provides high specific activity (ratio of ^{19}F/^{18}F) but is generated as an aqueous solution, diminishing the nucleophilicity of the fluoride. Electrophilic fluorine is generated as [^{18}F]F_2 with [^{19}F]F_2 as a carrier gas causing the specific activity (ratio of ^{19}F to ^{18}F) to be low. High specific activity is critical for imaging certain biological targets with low concentrations, such as neurotransmitter receptors in the brain.[24] [^{18}F]F_2 is very reactive and requires specialized systems that are not common. Electrophilic fluorination methods have been developed with ^{19}F that would be desirable as an ^{18}F analogue. There

have been recent methodologies developed to form these electrophilic fluorine sources for the PET scale.[26,27]

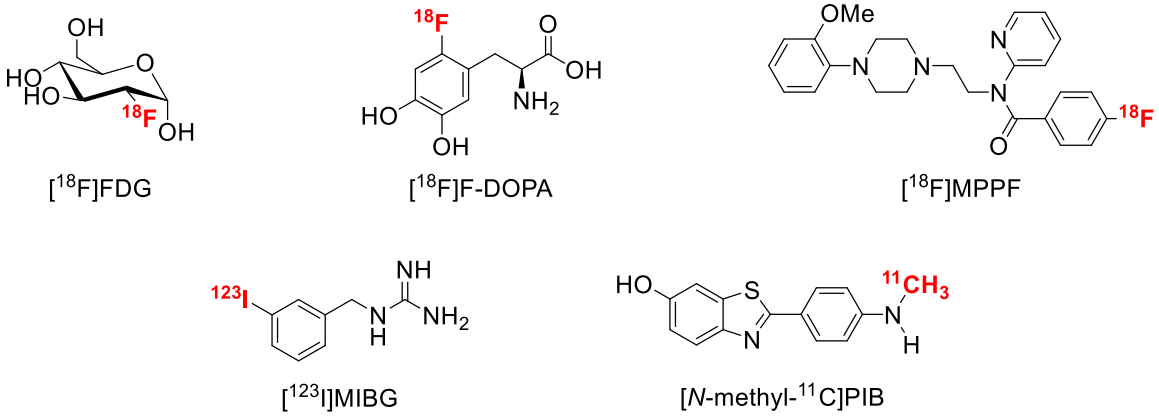
In addition to ^{11}C and ^{18}F, other short-lived isotopes are used, such as ^{13}N and ^{15}O. Due to the short half-lives, these radionuclides are usually generated in a simple form and used for limitation imaging applications. On the other hand, iodine has a few long-lived radioactive isotopes with iodine-124 being commonly used for PET imaging.

Table 1.1. Commonly Used Isotopes

Radionuclide	Half-life, $t_{1/2}$ (min)
^{18}F	110
^{11}C	20
^{13}N	10
^{15}O	2
^{124}I	4.2 d

In regards to the radiotracers, [^{18}F]FDG ([^{18}F]fluorodeoxygluocose) is the most commonly used radiotracer (Figure 1.2). It has favorable properties that allow it to image many varieties of diseases and can be easily synthesized *via* an S_N2 mechanism. FDG is processed in the body similarly to glucose, making it an unselective radiotracer due to large background noise as a function of unspecific absorption. To image a wider variety of biochemical and physiological processes, more scaffolds need to be accessed (Figure 1.2). For each tracer, the radionuclide needs to be incorporated in the last steps of the synthesis prior to a deprotection (if needed) because of the short half-lives of the radionuclides. New methods need to be designed so that a vast number of novel radiotracers can be synthesized and tested.

Figure 1.2. Known Radiotracers



1.3.1. Challenges for methodology development for PET chemistry

A major limitation of PET imaging is the number and diversity of fluorine-18 imaging agents that can be synthesized. Currently, one of the major obstacles to accessing more imaging agents lies in the source of fluorine-18, which is most commonly nucleophilic fluoride formed in water through cyclotron irradiation ($^{18}O(p,n)^{18}F$). The low concentration of fluorine-18 that is generated under these conditions (pmol quantities) in combination with the limited scope of fluorination methods that employ nucleophilic fluoride have both prevented the development of a unified radiofluorination method. As PET imaging becomes more common, there are many interesting potential imaging agents that cannot currently be accessed. The development of new nucleophilic fluorination methods that employ common intermediates would open-up more synthetic pathways to be assessed, and should ultimately allow the for identification of the most effective synthetic routes. The operational simplicity of a new method is another key consideration in the development process. Reaction conditions must be operationally simple, such that a non-expert chemist can reproduce these reactions on demand in a production setting. In addition, air sensitive methods are difficult to develop given that reactions employ a fluoride source that has been azeotropically dried from water and that reaction hot cells used in commercial radiochemistry are under ambient conditions. As such, for reproducibility all reagents should be bench stable. In order for a new method to be successful, it needs to provide access to more scaffolds and also be simple to implement in the existing radiopharmaceutical infrastructure.

For drug molecules, the fluorine atom is typically introduced as a building block in the original synthesis. For PET imaging, the radionuclide must be introduced in the last steps of the synthesis and generally some pre-functionalized (usually an aryl halide) has to be carried through the synthesis in place of the aryl fluoride. In recent years, there have been several late-stage fluorination methodologies developed that address this limitation, but there is still more to be done. The new methodologies have to have short reaction times because of the half-life of [^{18}F]fluorine. C–H activation would serve as an alternative approach to requiring a pre-functionalized motif to be carried through a synthesis. Chapter 4 describes a copper-mediated C–H activation method for [^{18}F]radiofluorination of 8-aminoquinoline directed arenes.[28] Chapter 5 includes some preliminary results of translating an aryl iodide fluorination method to aryl–^{18}F.

In the case of nucleophilic fluoride, [^{18}F]fluoride is generated in an aqueous solution and has to be azeotropically dried. Trace amounts of water can affect the nucleophilicity of the fluoride and can affect the metal-mediated methods negatively. New methodologies developed need to have mild water and air tolerance.

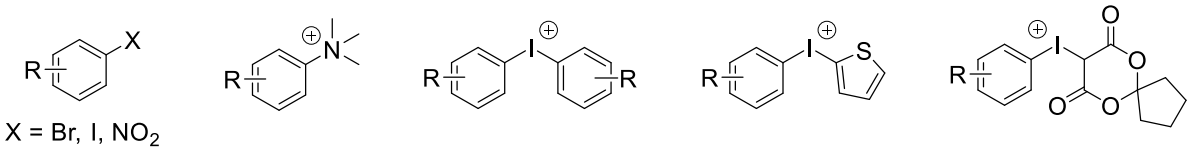
1.3.2. Current Methodologies to Form a C(sp^2)–^{18}F Bond

There have been several in-depth reviews that cover the methodologies developed to install an aryl–^{18}F bond.[9,23,24,29–33] One of the most reliable methods is S_NAr using aryl halides or trimethylammonium salts as the leaving group (Figure 1.3). S_NAr requires the R group to be electron-withdrawing, limiting the scaffolds that could be applied. To label an electron-rich molecule via S_NAr, several post-fluorine modifications must occur, increasing the time of the synthesis, decreasing the yield, and chances of reproducibility.

A commonly used alternative to S_NAr is employing diaryliodonium salts as precursors (Figure 1.3).[34–36] Symmetrical iodonium salts are easier to make for simple molecules, but are synthetically challenging for more complex molecules.[37–39] Additionally, the side products of the symmetrical iodonium salts can be challenging to separate (protodeiodinated and aryl iodide arenes). There are several limitations for diaryliodonium salts including sensitivity to both steric- and electronic-effects.[40] Some of these limitations can be addressed by using a 2-thienyl diaryliodonium precursor.[41] The incorporation of the 2-thienyl group as the sacrificial arene helps address selectivity.

In 2014, a more activated iodonium(III) precursor was designed.[42] The spirocyclic hypervalent iodine(III) precursors were designed with an auxiliary on the iodine to avoid the limitations of the previous diaryliodonium methods, including the *ortho*-substitution. Both 2-thienyl and spirocyclic iodonium salts have been used for clinical applications.[43–47] A limitation of these methods is the requirement of high temperatures where [29]most reactions require >150 °C leading to a limited scope due to the instability of some sensitive functional groups.

Figure 1.3. Common Metal-Free Precursors

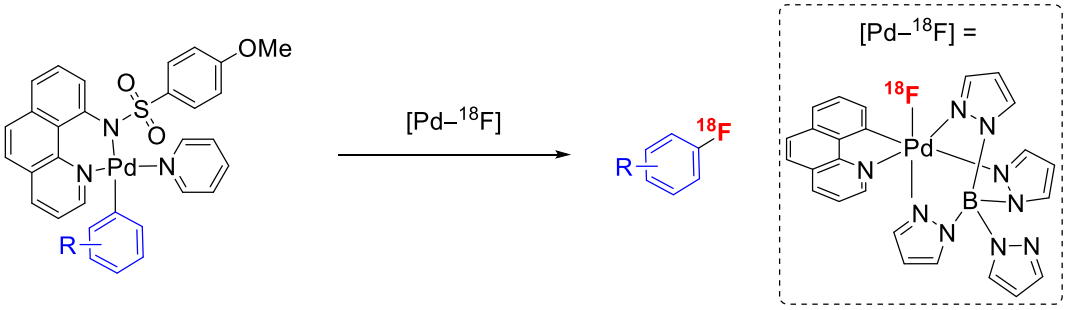


New methodologies have been introduced that have not been widely implemented. A recently developed reagent, PhenoFluor, has been shown to do [^{18}F]deoxyfluorination of phenols in a two-step method.[48] Triarylsulfonium salts react in a similar manner to diaryliodonium salts and have similar limations.[49] A derivative of this methodology uses dibenzothiophene sulfonium salts that undergo a ring-closing reaction to form a good leaving group for the incoming [^{18}F]fluoride to attack the arene.[50] Other [^{18}F]radiofluorination methodologies include electrochemical fluorination of benzene,[51] phosphane-catalysed fluorination of iodanes,[52] anilines *via* isolated *N*-arylsydnone intermediates,[53] and a metal-free oxidative fluorination of phenols with *t*Bu as a leaving group.[54]

As with ^{19}F fluorination methods, a way to overcome the challenges above are developing metal-mediated and -catalyzed methods to help increase the rate and yields of [^{18}F]radiofluorination. In 2011, Ritter and coworkers developed a Pd-mediated methodology to perform [^{18}F]radiofluorination.[55] The key to this transformation is disguising nucleophilic fluorine to react as an electrophilic fluorine source by creating a Pd–^{18}F complex that can react with the Pd–Ar complex to give the desired product (Scheme 1.5).[55] The next generation methodology improved upon the initial methodology by using aqueous [^{18}F]fluoride instead of a Pd–^{18}F complex and used aryl-Ni complexes.[56] Although these methodologies have been shown to be compatible to produce radiotracers

for non-human primate imaging studies,[57–59] they have not been widely implemented for several reasons. The most likely reason is due to the non-trivial synthesis of the Pd complexes, as PET radiotracers are typically synthesized by non-experts. Additionally this methodology has a lower efficiency of fluorination with *ortho*-substituted precursors.[29] Another Pd methodology that has been developed is a carrier-added Pd mediated [^{18}F]radiofluorination of aryl triflates[60] inspired by a newly developed fluorination methodology.[12] Carrier-added is a limitation because it generates a low specific activity due to the excess of ^{19}F in the reaction. In 2017, Ritter and coworkers developed a Ru-mediated [^{18}F]deoxyfluorination methodology that implemented phenols as starting materials.[61] This methodology was applied used to radiolabel [^{18}F]Bavarostat to image in rodent and non-human primates.[62]

Scheme 1.5. Ritter and Coworker's Pd-Mediated [^{18}F]Radiofluorination



Copper-catalyzed and -mediated methods are a relatively less expensive and less toxic alternative to the Pd and Ni transformations developed. In 2014, a copper-mediated method addressed some of the issues related with the diaryliodonium salts.[63] Unsymmetrical (mesityl)(aryl)iodonium salts were used a lower temperatures (<100 °C) with high yields and better selectivity. Similar to previous reports, *ortho*-substituted precursors are a limitation of this methodology. Recently, a C(sp^2)–H activation method was developed that formed an iodonium salt *in situ* before performing the [^{18}F]radiofluorination.[64] This methodology addresses the limitation of some unstable iodonium salts, but introduces more limitations with the relatively harsh reaction conditions. Chapter 2 describes a mild copper-mediated nucleophilic [^{18}F]radiofluorination method of aryl boronic acids and arylstannanes as an alternative to using iodonium salts.[65,66]

1.4. References

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Chapter 2

Cu-Mediated [^{18}F]Fluorination of Organometallic Reagents[1–3]

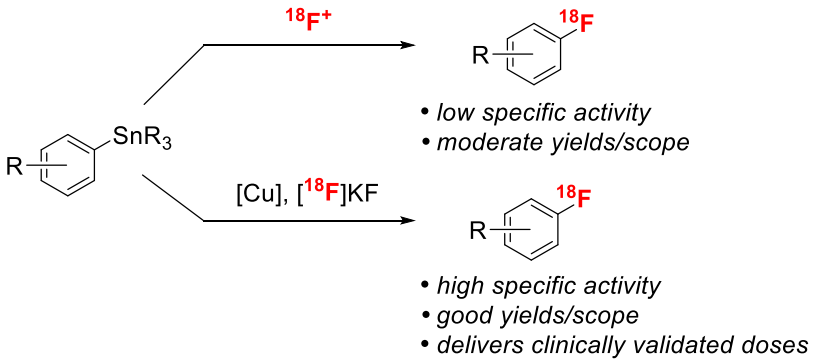
2.1. Electrophilic Fluorination of Organometallic Reagents

Transition metal-mediated and/or -catalyzed methods have been developed to fluorinate organometallic reagents with electrophilic fluorine sources. Pd and Ag methods have been developed for both arylboronic acids and arylstannanes.[4–7] These methods were shown to fluorinate a diverse array of starting materials and had some late stage fluorination properties that made their translation amendable to PET chemistry.[8] Changing from Pd and Ag to a more earth abundant metal, such as Cu, is desirable for PET chemistry because the metals have to be removed from the product at the end of synthesis.[9] According to ICH guidelines, Cu has a larger allowable dose relative to Pd and Ag, making purification easier. Fluorination of arylboron derivatives was achieved with Cu in good yields.[9] This method uses a specialized Cu catalyst that is not commercially available. This method was further extended to include arylstannanes and aryltrifluoroborane substrates.[10]

In PET chemistry, electrophilic fluorination is not widely utilized due to the specialized equipment that is required.[11] Furthermore, electrophilic radiofluorination methods result in products with dramatically lower specific activity (ratio of ^{18}F/^{19}F), which greatly reduces imaging sensitivity.[12] Electrophilic methods for PET require the use of [^{18}F]F_2 whereas the ^{19}F reactions that have been recently developed use F^+ sources like Selectfluor or NFSI. To overcome this limitation there has been work to create [^{18}F]NFSI[13] and [^{18}F]Selectfluor[14] from [^{18}F]F_2. While this transformation turns [^{18}F]F_2 into a more useful F^+ reagent, [^{18}F]F_2 still requires the customized equipment and has a low specific activity that makes imaging challenging. For electrophilic fluorination, arylstannanes are

the state-of-the-art substrate (Scheme 2.1).[11,15–19] Arylboron reagents have also been shown to form the fluorinated product with electrophilic ^{18}F sources.[20] Additionally, arylstannanes have already been validated as precursors to radiopharmaceuticals for human clinical trials,[21–24] thereby mitigating concerns about toxicity and the feasibility of Sn removal.

Scheme 2.1. Radiofluorination of Arylstannanes



2.2. Nucleophilic Fluorination of Organometallic Reagents

While nucleophilic fluorine sources are generally inexpensive and the preferred source of ^{18}F, there are few examples that use organometallic reagents (Scheme 2.1). Early work by Ritter's group developed Pd and Ni complexes that were formed from organometallic reagents and used [^{18}F]fluoride to form the desired product.[8,25] This seminal work transformed nucleophilic fluoride into an electrophilic fluorine source without the limitations mentioned in the previous section, but the Pd and Ni complexes are not commercial and not trivial to make, leading to limited implementation of this procedure.[26,27] A translation of an electrophilic method to a nucleophilic method using Cu and [^{18}F]KF was the basis for the following method development.[28]

2.3. Initial Results and Optimization for Aryl-B(OH)$_2$ Precursors[A]

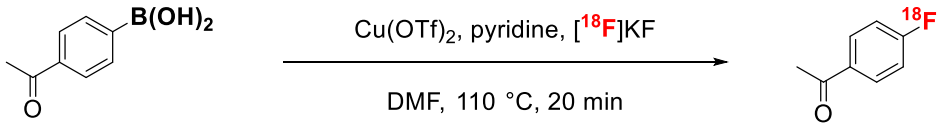
The copper-mediated fluorination of aryl trifluoroborates with [^{19}F]KF was the inspiration for the initial studies using [^{18}F]KF.[28] Our radiochemistry studies focused on implementing conditions similar to those used for [^{19}F]fluorination (4 equiv Cu(OTf)$_2$, 4 equiv KF in MeCN at 60 °C for 20 h), where it was found that both potassium trifluoroborate salts and boronate esters undergo Cu-mediated radiofluorination. Trifluoroborate substrates contain exogenous ^{19}F that could exchange with the ^{18}F and dilute the specific activity of the product. To avoid this, boronate esters and boronic acids were investigated. Concomitant with the initial studies, Gouverneur reported a closely related radiofluorination of pinacol boronate esters;[26] however, in our hands, this method proved less reproducible and generally afforded low RCCs. Boronic acids were chosen as substrates due to their ready availability and stability. When [^{18}F]fluoride is generated from the cyclotron (^{18}O(*p,n*)^{18}F), it is produced as a solution in water. For the trifluoroborate chemistry, it was found that the yield was decreased in the presence of water.[28] To generate an anhydrous [^{18}F]fluoride source, the solution is azeotropically dried with MeCN. It has been found that adding various bases to the QMA (quaternary ammonium) eluent increases the efficiency of [^{18}F]KF produced over [^{18}F]HF which evaporates.[3] As the methodology progresses from manual reactions to automated reactions, the amount of base in the reaction increases which can have detrimental effects on [^{18}F]radiofluorination chemistry.

During the optimization, we found that the presence of K_2CO_3 (which is typically used in the preparation of [^{18}F]KF) resulted in low RCCs of the fluorinated products (Table 2.1, entry 1).[29] Investigating other bases that could be used as eluents lead to pyridinium *p*-toluenesulfonate (PPTS) and a mixture of KOTf/K_2CO_3 (Table 2.1, entries 2–3). During the production of [^{18}F]KF, it was noted that when PPTS was used,[3] only 50-60% of ^{18}F was retained, likely due to volatile H^{18}F forming, but with the mixture of KOTf/K_2CO_3 (73:1 molar ratio) 80% of the ^{18}F was preserved. As expected, no product was detected without pyridine or Cu (Table 2.1 entries 4 and 5, respectively). Other copper sources including

[A] Dr. Andrew Mossine performed most of the optimizations for the arylboronic acid radiofluorination reactions

the copper(I) source used for the previously developed iodonium chemistry did not give any product (Table 2.1 entry 6).[30]

Table 2.1. Optimization of Radiofluorination of **1-B(OH)$_2$**



(**1-B(OH)$_2$**) (**[^{18}F]1**)

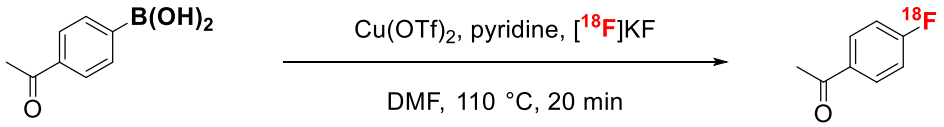
entry	QMA eluent	[Cu]	[^{18}F]1 (% RCC)
1	K_2CO_3	$Cu(OTf)_2$	nd
2	PPTS	$Cu(OTf)_2$	48
3	KOTf/K_2CO_3	$Cu(OTf)_2$	61
4[a]	KOTf/K_2CO_3	$Cu(OTf)_2$	3
5	KOTf/K_2CO_3	--	nd
6	KOTf/K_2CO_3	$(MeCN)_4CuOTf$	nd

Conditions: **1-B(OH)$_2$** (4 µmol, 1 equiv), $Cu(OTf)_2$ (20 µmol, 5 equiv), pyridine (0.5 mmol, 125 equiv), and [^{18}F]KF in DMF (4 mM) at 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2). Nd = not detected. [a]no pyridine

Using MeCN as the solvent instead of DMF did not give any product and using a mixture of DMF/MeCN gave decreased RCCs with increasing MeCN (Table 2.2, entry 2). This is particularly interesting because DMF was not an effective solvent under the ^{19}F conditions (1 equiv aryl trifluoroborate, 4 equiv of $Cu(OTf)_2$, 4 equiv of KF in MeCN at 60 °C for 20 h).[28] Furthermore, it was found that pyridine was critical for the success of the [^{18}F]radiofluorination. The role of pyridine is being investigated, but it is likely serving as a base source and/or as a ligand on the copper species. Other pyridine derivatives gave increased or similar RCCs with electron-rich 4-phenyl or 4-methoxypyridine, but other electron-deficient pyridine derivatives or other bases gave trace product (Table 2.2, entry 3). Investigation into the stoichiometry of Cu and pyridine showed that pyridine ≥75 equiv and Cu ≤5 equiv, relative to the arylboronic acid, were optimal (Table 2.2, entries 4-6). Temperature studies showed that ≥100 °C was sufficient (Table 2.2, entry 7). Unlike the aryl trifluoroborate chemistry,[28] this transformation was found to be tolerant of water (Table 2.2, entry 8). For most substrates attempted, the arylboronate ester gave a higher

RCC than the aryl boronic acid (Table 2.2, entry 9). The main byproduct observed in all cases is the protodeboronated product.

Table 2.2. Stoichiometry of Reagents



(**1-B(OH)$_2$**) (**[^{18}F]1**)

entry	Cu(OTf)$_2$ (equiv)	pyridine (equiv)	conditions	[^{18}F]1 (% RCC)
1	5	125	--	61
2	5	125	10% MeCN	49
3	5	125	4-Ph-pyridine	58
4	5	75	--	64
5	10	125	--	53
6	2.5	125	--	69
7	5	125	100 °C	58
8	10	125	8 equiv H_2O	45
9	5	125	Ar-Bpin	70

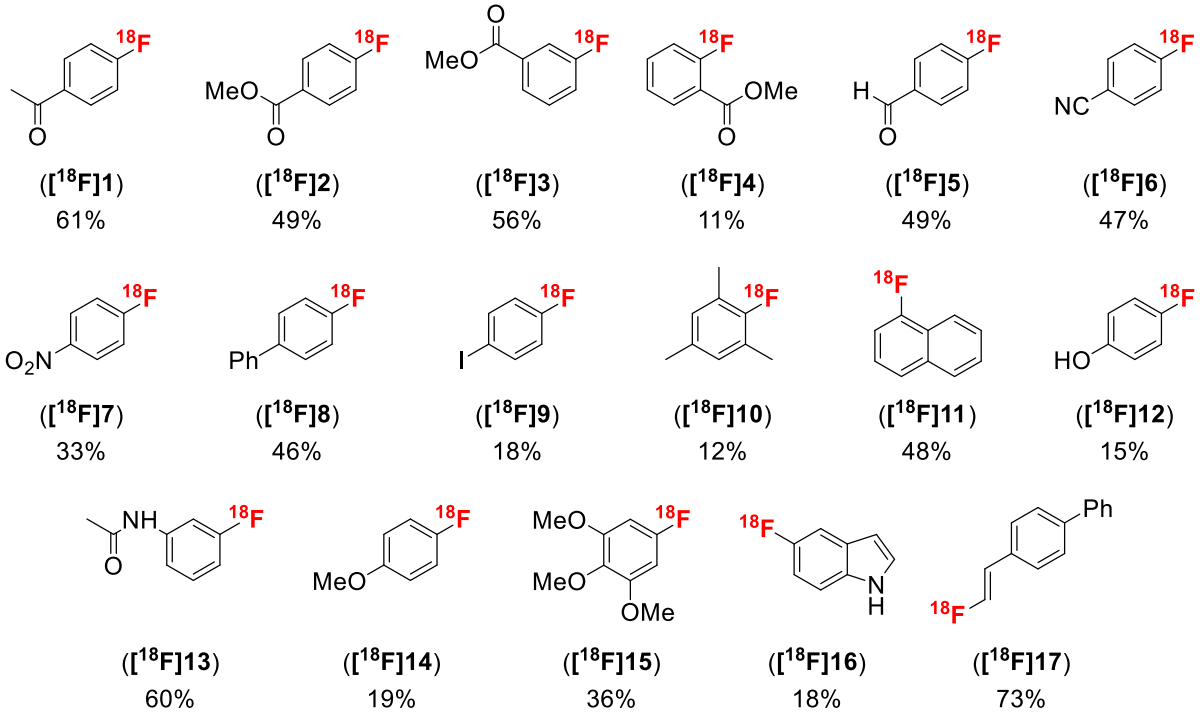
Entry 1 conditions: **[^{18}F]1** (4 μmol, 1 equiv), Cu(OTf)$_2$ (20 μmol, 5 equiv), pyridine (0.5 mmol, 125 equiv), and [^{18}F]KF in DMF (4 mM) at 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2).

2.4. Substrate Scope for Ar-B(OH)$_2$

The substrate scope of aryl boronic acid [^{18}F]radiofluorination was explored. As summarized in Figure 2.1, this method is compatible with a range of functional groups. The reaction proceeds in moderate to high RCC with arylboronic acids bearing electron-withdrawing (**[^{18}F]2**–**[^{18}F]7**), electroneutral (**[^{18}F]8**–**[^{18}F]11**), and electron-donating (**[^{18}F]12**–**[^{18}F]15**) substituents. Electron-rich **[^{18}F]15** was formed in 36% RCC, significantly higher than the yield obtained in the corresponding copper-mediated (mesityl)(aryl)iodonium chemistry (14% RCC).[30] *Meta* (**[^{18}F]3**, **[^{18}F]13**, and **[^{18}F]15**) and *ortho*-substituents (**[^{18}F]4** and **[^{18}F]10**) were tolerated, although with lower RCC, likely due to slower transmetalation of the more sterically hindered aryl boronic acids. This method is also compatible with heteroaromatic (**[^{18}F]16**) and vinylic (**[^{18}F]17**) boronic acids. While the yield of **[^{18}F]16** was lower than that for many of the other substrates (18%

RCC), this substrate and **[^{18}F]12** demonstrate that this radiofluorination reaction proceeds without the need for protection of protic functional groups.

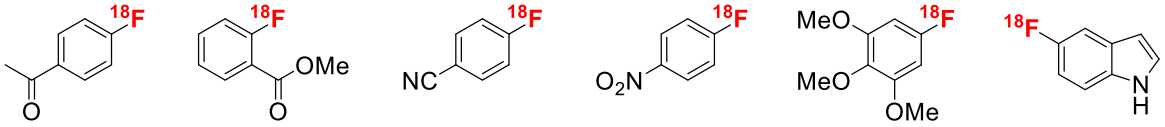
Figure 2.1. Substrate Scope of Ar-B(OH)$_2$



Conditions: arylboronic acid (4 µmol, 1 equiv), Cu(OTf)$_2$ (20 µmol, 5 equiv), pyridine (0.5 mmol, 125 equiv), and [^{18}F]KF in DMF (4 mM) at 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2).

As mentioned above, the RCCs with aryl pinacol boronate esters are generally similar or higher than the boronic acid alternatives (Figure 2.2). The radiofluorination of aryltrifluoroborate substrates formed the desired product **[^{18}F]6**, but in a low RCC (Figure 2.2).

Figure 2.2. Substrate Scope with Various Boronate Derivatives



([**^{18}F]1**) **$B(OH)_2$:** 61% **Bpin:** 70%

([**^{18}F]4**) **$B(OH)_2$:** 11% **Bpin:** 40%

([**^{18}F]6**) **$B(OH)_2$:** 47% **Bpin:** 74% **BF_3K:** 5%

([**^{18}F]7**) **$B(OH)_2$:** 33% **Bpin:** 58%

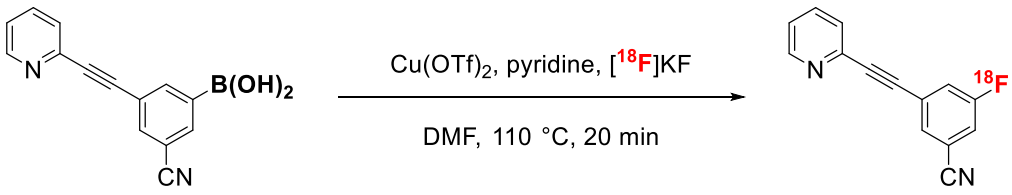
([**^{18}F]15**) **$B(OH)_2$:** 36% **Bpin:** 55%

([**^{18}F]16**) **$B(OH)_2$:** 18% **Bpin:** 11%

Conditions: arylboronate derivatives (4 µmol, 1 equiv), $Cu(OTf)_2$ (20 µmol, 5 equiv), pyridine (0.5 mmol, 125 equiv), and [^{18}F]KF in DMF (4 mM) at 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2).

[^{18}F]F-PEB (**[^{18}F]18**) was used as an example of a biologically relevant molecule. This is an important radiotracer for quantifying metabotropic glutamate 5 receptors,[31–35] and it has been historically challenging to synthesize. As shown in Scheme 2.2, this method gave [^{18}F]F-PEB in a moderate RCC of 8%. While this is relatively low, it would be more than enough for an animal or patient study, due to the low amounts of radiotracer needed for a PET scan. The synthesis of [^{18}F]F-PEB was automated to give the product in 4% RCC and a specific activity of 750 Ci/mmol. Notably, automated yields are always lower than manual results because the automation accounts for any loss during ^{18}F formation and purification starting from the amount produced from target irradiation.

Scheme 2.2. Synthesis of [^{18}F]F-PEB



(**18-$B(OH)_2$**)

([**^{18}F]18**)
manual: 8%
automated: 4%
SA: 750 Ci/mmol

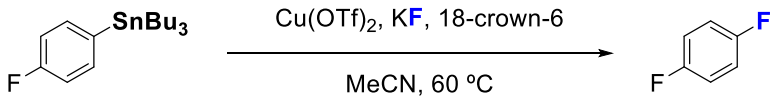
Conditions: **18-$B(OH)_2$** (4 µmol, 1 equiv), $Cu(OTf)_2$ (20 µmol, 5 equiv), pyridine (0.5 mmol, 125 equiv), and [^{18}F]KF in DMF (4 mM) at 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2).

2.5. Initial Results and Optimization for Aryl-SnR_3 Precursors with KF

While the first-generation method involving arylboron [^{18}F]radiofluorination was quite effective, it still has some significant limitations. First, the arylboron [^{18}F]radiofluorination worked well with electron-deficient substrates, but afforded lower RCCs with electron-rich substrates. Electron-deficient substrates can be made through alternative methods but forming C–^{18}F bonds on electron-rich aromatic rings remains a challenge. Secondly, there was a large amount of protodeboronated product formed. This product can be difficult to separate, as it elutes at a similar retention time as the desired fluorinated product. Furthermore, this side product could competitively interact with the target during imaging, thus effectively lowering the specific activity by competing with the radioligand of interest for the target protein. Minimizing this side product formation was a key goal. We hypothesized that one way to minimize the protodeboronated species would be to use an arylstannane. Arylstannanes are known to undergo faster transmetalation than arylboron derivatives, which should lead to less side product formation.[36]

The initial investigations focused on the $Cu(OTf)_2$-mediated fluorination of **19-$SnBu_3$** with KF under conditions analogous to those demonstrated for aryl trifluoroborate substrates.[28] After 18 h at 60 °C with 4 equiv KF in MeCN, the fluorinated product **19** was obtained in 42% yield as determined by ^{19}F NMR spectroscopy (Table 2.3, entry 1). While this yield is lower than that reported with **19-BF_3K** under closely analogous conditions (70%, 20 h), the addition of 18-crown-6 as a phase transfer catalyst could be used to boost the yield with **19-$SnBu_3$** to 55% (entry 2). Furthermore, as predicted, the fluorination of **19-$SnBu_3$** is significantly faster than that of **19-BF_3K**. For example, **19-$SnBu_3$** affords 51% yield after just 15 min under these conditions. In contrast, the analogous reaction of **19-BF_3K** requires more than 2 h to afford 50% yield. The faster rate with **19-$SnBu_3$** is highly desirable for PET applications. The stoichiometry of fluoride was next investigated. Notably, this is another key consideration for translation, because [^{18}F]fluoride is typically the limiting reagent during radiofluorination. With KF as the limiting reagent, the reaction still proceeded albeit in reduced yield (Table 2.3, entry 6).

Table 2.3. Cu-Mediated Nucleophilic Fluorination of **19-SnBu$_3$** in Acetonitrile



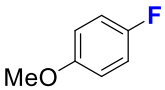
(**19-SnBu$_3$**) (**19**)

entry	time (h)	18-crown-6 (equiv)	yield 20 (%)
1	18	--	42
2	18	4	55
3	2	--	42
4	2	4	53
5	0.25	4	51
6[b]	0.25	4	15

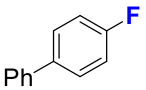
General conditions: **19-SnBu$_3$** (0.025 mmol, 1 equiv), $Cu(OTf)_2$ (4 equiv), KF (4 equiv), and 18-crown-6 (4 equiv) in MeCN (0.083 M) at 60 °C. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard. [b]KF (0.5 equiv) used. Yield based on KF.

This method was next applied to a small set of arylstannanes (Figure 2.3). The objectives here were twofold: (1) to establish the effectiveness of the 15 min nucleophilic fluorination protocol for electronically diverse arylstannanes and (2) to examine the impact of the alkyl substituents on tin on the reaction. As shown in Figure 2.3, stannanes bearing electron donating (*p*-MeO), electron-neutral (*p*-Ph), and electron-withdrawing (*p*-Ac) substituents react to form fluorinated products in moderate to good yields in just 15 min at 60 °C. The *p*-MeO derivative is particularly noteworthy, as the corresponding aryltrifluoroborate is poorly reactive, affording <5% yield under any of the fluorination conditions examined.[28] Substitution of the alkyl group on the stannane had a significant impact on the yield over this short reaction time, with the Me-substituted stannanes affording comparable or higher yield than the Bu derivatives in all cases. This likely reflects the faster transmetalation from the less hindered tin center.[37]

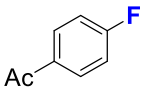
Figure 2.3. Mini Substrate Scope in Acetonitrile



SnBu$_3$: 23%
SnMe$_3$: 24%



SnBu$_3$: 34%
SnMe$_3$: 64%

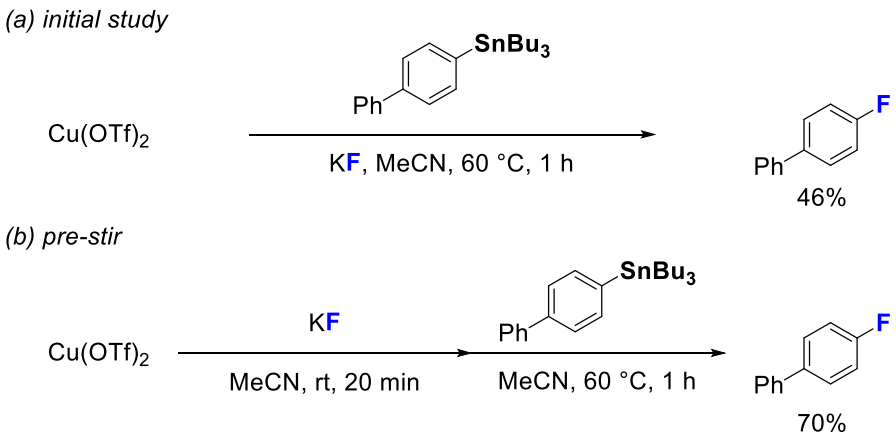


SnBu$_3$: 57%
SnMe$_3$: 65%

Conditions: arylstannane (0.025 mmol, 1 equiv), $Cu(OTf)_2$ (4 equiv), KF (4 equiv) and 18-crown-6 (4 equiv) in MeCN (0.083 M) at 60 °C for 15 min. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard.

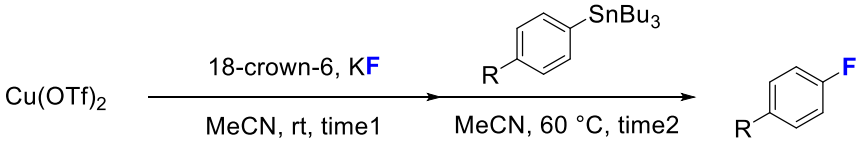
During this method development, a paper reporting a similar transformation was published by Jennifer Murphy.[38] This paper showed that pre-stirring the copper and fluoride source provided higher yields (Scheme 2.3). In their SI, the same reaction with 2 equiv of $Cu(OTf)_2$ and 2 equiv of KF afforded a 46% yield with no pre-stir and a 58% yield with a 10 or 20 min pre-stir. These results mirror the results below in Table 2.4 where pre-stirring increases the yield for some substrates, although not universally. For the 4-F substrate, the addition of 18-crown-6 replaced the need for pre-stirring (Table 2.4, entries 1, 2, 5, and 6). This trend was not observed for the 4-BnO substrate (Table 2.4, entries 3, 4, 7, and 8). The pre-stirring and addition of 18-crown-6 likely improves the reproducibility of this reaction as the standard conditions varied greatly (26-52% without 18-crown-6 versus 48-63% with 18-crown-6).

Scheme 2.3. Effects of Pre-Stir from Murphy's Report[38]



Conditions: $Cu(OTf)_2$ (4 equiv), KF (4 equiv) and 18-crown-6 (4 equiv) were pre-stirred in MeCN (0.2 mL) at rt for the selected time. Arylstannane (0.025 mmol, 1 equiv) in MeCN (0.1 mL, 0.083 M) were added to the mixture, heated to 60 °C for the selected time. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture with an internal standard.

Table 2.4. Pre-stirring Effects on Optimized Conditions



entry	R	time1	time2	18-crown-6 (equiv)	yield (%)
1	F	0	2 h	4	55
2	F	1 h	1 h	4	50
3	BnO	0 h	2 h	4	15
4	BnO	1 h	1 h	4	43
5	F	0	2 h	--	45
6	F	1 h	1 h	--	52
7	BnO	0 h	2 h	--	12
8	BnO	1 h	1 h	--	52

Conditions: $Cu(OTf)_2$ (4 equiv), KF (4 equiv) and 18-crown-6 (4 equiv) were pre-stirred in MeCN (0.2 mL) at rt for the selected time. Arylstannane (0.025 mmol, 1 equiv) in MeCN (0.1 mL, 0.083 M) were added to the mixture, heated to 60 °C for the selected time. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard.

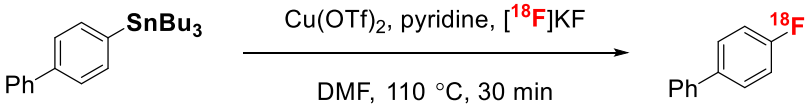
2.6. Initial Results and Optimization for Aryl-SnR_3 Precursors with [^{18}F]KF[B]

Translation of this nucleophilic fluorination method to achieve the ^{18}F-fluorination of **8-$SnBu_3$** was the next objective. As is common in the radiofluorination field,[12,39] significant reoptimization was required, as the best ^{19}F fluorination conditions afforded no detectable ^{18}F-labeled product (Table 2.5, entry 1). This is likely a consequence of the dramatic change in fluoride stoichiometry (from 0.3 M with KF to approximately 0.1 nM with [^{18}F]KF).[40] Even with the addition of pyridine and switching to DMF as the solvent, no product was detected until the temperature was increased to 110 °C (Table 2.5, entries 2-4). Less pyridine was found to give a similar result (Table 2.5, entry 5). This is particularly noteworthy because for automated reactions, all chemical impurities have to be removed. The only other Cu source that worked other than $(py)_4Cu(OTf)_2$ was $(MeCN)_4Cu(OTf)$ (Table 2.5, entries 6-7). Increasing the temperature to 140 °C increased the RCC for most substrates (Table 2.5, entry 8). At least 2 equiv of $Cu(OTf)_2$ was found

[B]The work in this section was performed with the assistance of Dr. Allen Brooks.

to best (Table 2.5, entry 9). Increasing the Cu equiv did not increase the RCC. Changing the solvent from DMF to DMA was found to give a large increase in RCC for most substrates (Table 2.5, entry 10). The reaction was tolerant of trace amounts of water (Table 2.5, entry 11). As observed with ^{19}F, this reaction was rapid, affording **[^{18}F]8** in 65% RCC within just 5 min (entry 12).

Table 2.5. Cu-Mediated Nucleophilic Fluorination of **8-SnBu$_3$** with [^{18}F]KF



(**8-SnBu$_3$**) (**[^{18}F]8**)

entry	changes in conditions	[^{18}F]8 (% RCC)
1	pyridine (0 equiv), MeCN, 60 °C	nd
2	pyridine (50 equiv), MeCN, 60 °C	nd
3	pyridine (50 equiv), 60 °C	nd
4	pyridine (50 equiv)	22
5	--	20
6	(py)$_4$Cu(OTf)$_2$ (2 equiv)	14
7	(MeCN)$_4$Cu(OTf) (2 equiv)	2
8	140 °C	42
9	Cu(OTf)$_2$ (1 equiv), 140 °C	29
10	DMA, 140 °C	55
11	H_2O (0.5% v/v)	32
12	DMA, 140 °C, 5 min	65

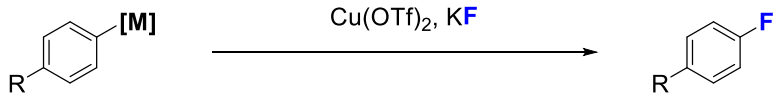
Conditions: **8-SnBu$_3$** (0.01 mmol, 1 equiv), Cu(OTf)$_2$ (2 equiv), pyridine (15 equiv), and [^{18}F]KF in DMF (0.01 M) at 110 °C for 30 min. RCC determined by radio-TLC (n ≥ 2). nd = no product detected by radio-TLC or HPLC.

2.7. Additional Optimization for Aryl-SnR$_3$ Precursors with KF

With the optimized [^{18}F]radiofluorination conditions determined, an array of arylstannane derivatives were examined with KF (Table 2.6). The previous report[28] and all attempts after gave no product in DMF or DMA without pyridine. The DMA conditions (condition C) gave similar yields as the above MeCN and MeCN with 18-crown-6 conditions (Table 2.6 entries 1-3). The anisole substrate gave no product with the trifluoroboroate substrate (Table 2.6, entry 4) and gave low yields in MeCN (Table 2.6,

entries 1-2). Now in the DMA conditions, moderate yield is observed with anisole (Table 2.6, entry 3).

Table 2.6. Comparison of Substrates in Various Fluorination Methods

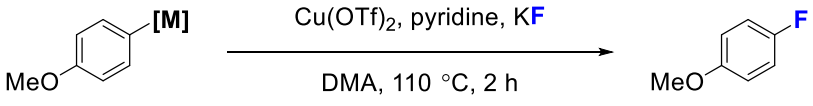


entry	conditions	[M]	R = F	R = MeO	R = Ph
1	A	$SnBu_3$	42	11	29
2	B	$SnBu_3$	53	16	30
3	C	$SnBu_3$	33	40	38
4	D	BF_3K	70	n/a	48[a]

Conditions: Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard. (**A**) arylstannane (0.04 mmol, 1 equiv), $Cu(OTf)_2$ (4 equiv), and KF (4 equiv) in MeCN (0.083 M) at 60 °C for 2 h. (**B**) Condition **A** with 18-crown-6 (4 equiv). (**C**) arylstannane (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and KF (4 equiv) in DMA (0.01 M) at 110 °C for 2 h. (**D**) aryltrifluoroborate (0.025 mmol, 1 equiv), $Cu(OTf)_2$ (4 equiv), and KF (4 equiv) in MeCN (0.083 M) at 60 °C for 20 h. Conditions and results are from the literature.[28] [a]Isolated yield: aryltrifluoroborate (0.5 mmol)

Given that the **14-$SnBu_3$** provided the desired fluorinated product in moderate yield in the DMA conditions (Table 2.6, entry 3), a comparison with boron derivatives was performed (Table 2.7). The Ar–Bpin and Ar–BF_3K derivatives both gave moderate yields of the desired fluorinated product **14**.

Table 2.7. Methoxy Substrates in DMA Conditions



(**14-M**) (**14**)

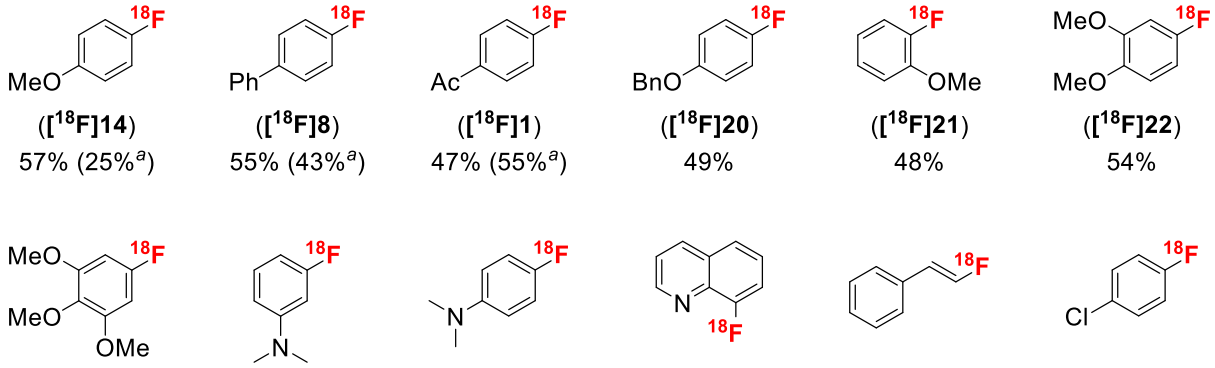
entry	[M]	yield 15 (%)
1	$SnBu_3$	40
2	BF_3K	28
3	Bpin	44

Conditions: substrate (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and KF (4 equiv) in DMA (0.01 M) at 110 °C for 2 h. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard.

2.8. Substrate Scope for Ar-SnR_3 with [^{18}F]KF

The optimal conditions were applied to a series of aryl-, heteroaryl-, and vinylstannane precursors. As summarized in Figure 2.4, this method is compatible with aromatic substrates bearing electron-neutral (**[^{18}F]8**), electron-withdrawing (**[^{18}F]1, [^{18}F]27**), and electron-donating substituents (**[^{18}F]14-[^{18}F]15, [^{18}F]20−[^{18}F]24**) as well as heteroaromatic (**[^{18}F]25**) and vinylstannane (**[^{18}F]26**) derivatives. Substrates such as **27-$SnBu_3$** include a functional handle that can be used for further elaboration. *Ortho*-substitution was well-tolerated, with the *o*-MeO substrate **21-$SnBu_3$** affording a yield comparable to that of the *p*-MeO substrate **14-$SnBu_3$** (RCC = 57% versus 48%, respectively). The electron-rich substrates (**[^{18}F]14-[^{18}F]15, [^{18}F]20−[^{18}F]24**) are noteworthy, as they are challenging to radiofluorinate using traditional S_NAr reactions.[41]

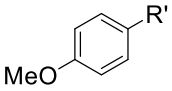
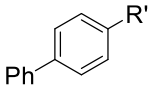
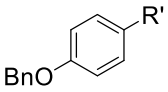
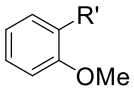
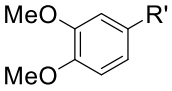
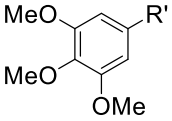
Figure 2.4. Substrate Scope for Arylstannane Precursors



Conditions: aryltributyltin substrate (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and [^{18}F]KF in DMA (0.01 M) at 140 °C for 30 min. RCC determined by radio-TLC (n ≥ 2). [a]Ar-$SnMe_3$ used as substrate [b]100 °C; [c]*18*-crown-6 (0.5 equiv); [d]30 equiv of pyridine.

When this method was compared to other metal-mediated nucleophilic radiofluorination methods, overall the RCCs were comparable and, in many cases, significantly higher. Notably, the *ortho*-methoxy and 1,2,3-trimethoxy products were produced with a much higher RCC than the other metal-mediated methods.

Table 2.8. Comparison of Substrates by Other metal-Mediated Methods

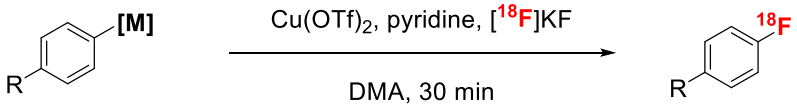
substrate	R'	conditions	yield (RCC)
	-$SnBu_3$	A	56 ± 4%
	-$IMesBF_4$	B	79 ± 8%
	-$B(OH)_2$	C	19 ± 3%
	-$SnBu_3$	A	55 ± 10%
	-$IMesBF_4$	B	51 ± 8%
	-$B(OH)_2$	C	46 ± 6%
	-Bpin	D	74 ± 5%
	-[Ni]	E	42 ± 8%
	-$SnBu_3$	A	50 ± 3%
	-Bpin	D	43 ± 5%
	-$SnBu_3$	A	48 ± 4%
	-$IMesBF_4$	B	30 ± 8%
	-Bpin	D	11 ± 2%
	-$SnBu_3$	A	54 ± 8%
	-$IMesBF_4$	B	51 ± 6%
	-Bpin	D	54 ± 3%
	-$SnBu_3$	A	59 ± 3%
	-$IMesBF_4$	B	14 ± 1%
	-$B(OH)_2$	C	36 ± 11%

References: condition A (Cu-mediated with arylstannanes),[2] condition B (Cu-mediated with diaryliodonium salts),[30] condition C (Cu-mediated with arylboronic acids),[1] condition D (Cu-catalyzed with arylboron pinacol esters, note: decay-corrected "RCY"),[26] and condition E (Ni-mediated method).[25]

A few arylboron derivatives were tested under the optimal conditions. For the 4–Ac substrate, a lower temperature was found to be optimal and the arylboronic acid gave a similar result to the arylstannane, which was a slight improvement on the original report (Table 2.9, entries 1-2).[1] The anisole starting material in the form of the arylboronic acid

or the arylpinacol borane was analyzed to see if there was a difference in RCC. With this substrate, an improvement is seen by increasing the temperature and again an improvement in RCC over prior methods (Table 2.9, entries 3-4).

Table 2.9. Comparison of Arylboron Derivative to Arylstannane Derivatives



entry	R	temp (°C)	[M] = $SnBu_3$ (% RCC)	[M] = $B(OH)_2$ (% RCC)	[M] = Bpin (% RCC)
1	Ac	100	73	72 (61*)	--
2	Ac	140	48	48	--
3	MeO	100	30	35 (19*)	28
4	MeO	140	57	48	35
5	Ph	100	51	41 (46*)	--
6	Ph	140	55	65	--

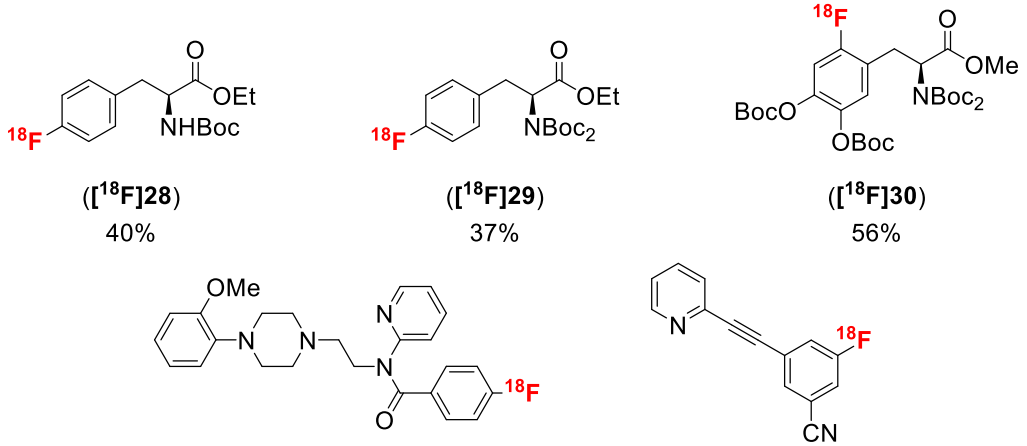
Conditions: substrate (0.01 mmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and KF (4 equiv) in DMA (0.01 M) at 110 °C for 2 h. Yield determined by ^{19}F NMR spectroscopic analysis of the crude reaction mixture using 1,2-difluorobenzene as an internal standard. *Reported values from the literature.[1]

The method was then applied to the preparation of products currently being evaluated as radiotracers that are FDA approved or are currently in clinical trials.[42,43] Initial studies were conducted via manual synthesis, which afforded useful RCCs (Figure 2.5). For instance, this method is effective for the synthesis of protected phenylalanine derivatives (**[^{18}F]28** and **[^{18}F]29**) for studying amino acid transport.[44] [^{18}F]F-PEB (**[^{18}F]18**), whose previous radiosyntheses suffer from low yields (1−5% RCY, nondecay corrected), was also targeted.[1,31,32] Metal-free fluorination of an iodonium ylide afforded 20% RCY; however, these precursors can be challenging to prepare.[45] Our new method, starting from the readily available and stable arylstannane precursor **18-$SnBu_3$**, delivers the product in 11% RCC.

This method is also effective for the radiofluorination of the protected L-DOPA stannane **30-$SnMe_3$**, affording **[^{18}F]30** in 56% RCC. This result is noteworthy for several reasons. First, nucleophilic methods for radiolabeling L-DOPA remain highly sought

after,[41,44,46,47] and the obtained RCC is among the best reported for this type of transformation.[2] Second, the precursor **30-SnMe$_3$** is a single step from a commercial stannane whose derivatives have been used in the clinical production of [^{18}F]F-DOPA via electrophilic radiofluorination.[21,22] As such, the successful radiofluorination of **30-SnMe$_3$** offers the potential for a direct nucleophilic replacement for this method.

Figure 2.5. Substrate Scope of Biologically Relevant Radiotracers



Conditions: aryltrimethylstannane (0.01 mmol, 1 equiv), Cu(OTf)$_2$ (2 equiv), pyridine (15 equiv), and [^{18}F]KF in DMA (0.01 M) at 100 °C for 30 min. RCC determined by radio-TLC (n ≥ 2). [a]aryltributylstannane substrate was used

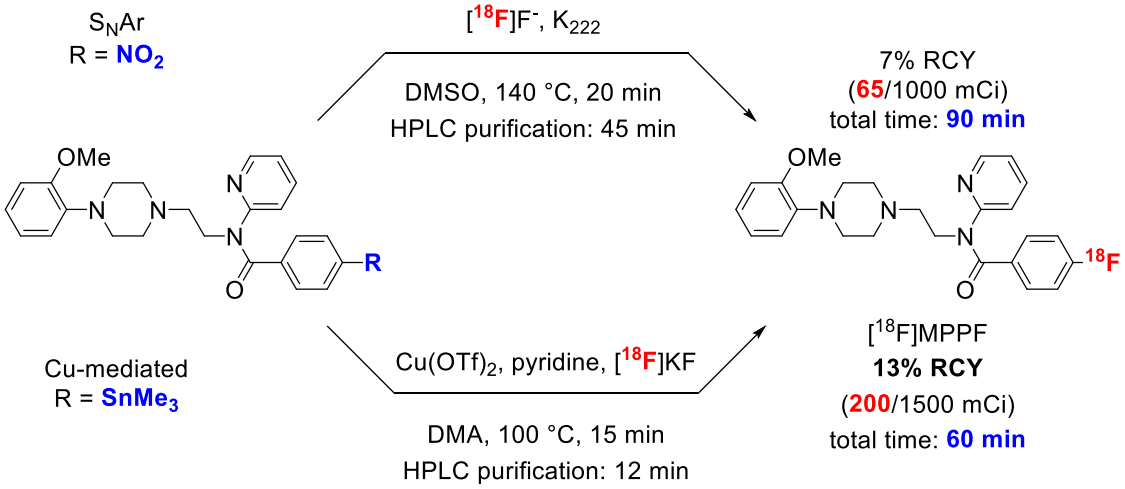
2.9. Automation of [^{18}F]MPP-F[C]

Finally, [^{18}F]MPPF (**[^{18}F]31**), a serotonin receptor ligand currently synthesized by S$_N$Ar radiofluorination of the NO$_2$ precursor (Scheme 2.4a), was targeted. Our manual Cu-mediated procedure from stannane **31-SnMe$_3$** delivered **[^{18}F]31** in 33% RCC. The [^{18}F]MPPF synthesis was scaled and automated using a TRACERLab FXFN module (Scheme 2.4b). The reaction using 1500 mCi of initial activity afforded a formulated and validated 200 mCi dose (13% RCY) after radiolabeling and HPLC purification. (A typical clinical scan uses 10 mCi of [^{18}F]MPPF.) The dose prepared by this method passed all

[C] The work in this section was performed with the assistance of Dr. Allen Brooks.

cGMP quality control testing necessary for clinical use, as outlined in the US Pharmacopeia and 21CFR212, including residual Cu and Sn levels below the allowed limits specific in the ICH Guidelines.[48,49] As shown in Scheme 2.4, our new method affords nearly double the RCY and reduces the overall time from EOB to end of purification by one-third relative to the current commercial synthesis of this tracer.[50]

Scheme 2.4. Comparison of Current Methods to Syntehsize [^{18}F]MPPF (**[^{18}F]31**)[43,50]



2.10. Conclusion

This chapter detailed the development of a mild and general Cu-mediated method for the radiofluorination of aryl boronic acids and arylstannane substrates with [^{18}F]KF. This method represents the first high-yielding nucleophilic fluorination of boronic acids and stannanes, is compatible with aryl, heteroaryl, and vinyl boronic acids, and fills an important gap in the field of late-stage fluorination. This process can be readily automated and scaled on a commercial radiochemistry synthesis module and applied to clinically relevant radiotracers. The method is tolerant of a reasonable number of functional groups frequently found in common drug targets.

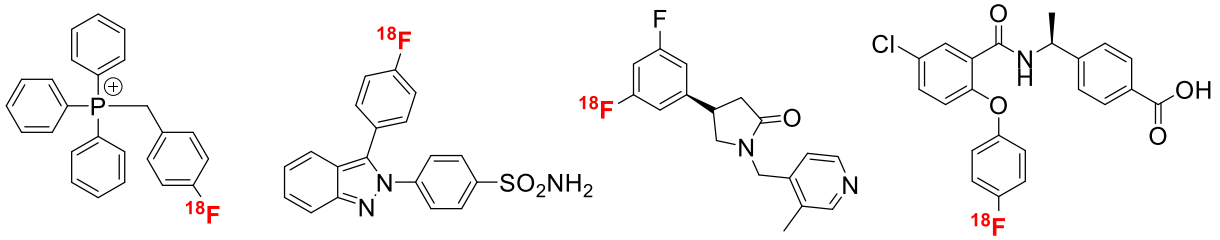
2.11. Outlook

During the course of this work, two related methods were published, as discussed above. Gouverneur's radiofluorination of aryl pinacol boranes[26] was impactful, but had

reproducibility issues due to unique reaction setups. The method used a large amount of starting material (60 μmol) as opposed to the ≤10 μmol that is more common. To address the reproducibility issues, eight radiotracers were made with Gouverneur's method using different laboratories and synthetic platforms.[46] To further test the limitations of this method, Gouverneur published fragments to analyze what functional groups could be tolerated.[51] Furthermore, the large amount of base used in the reaction makes automation of this method challenging. A "low base" approach and minimization of Kryptofix 222 have been developed to improve the translation to automation.[29,52] This modified method has been used to study the effect of pyridine addition.[53] The arylboronic acid method gave low automation yields and a large amount of protoarene side product that was difficult to separate by HPLC from the desired product. Both of these limitations were investigated and addressed in a follow-up report.[54]

Murphy's fluorination of arylstannanes was thorough, but still used MeCN, and therefore they were not able to translate it to a radiofluorination method.[38] The pre-stirring that was critical in their reaction did not seem to make a large impact in the DMA reaction conditions. Neumaier published a modified method for the arylstannane [^{18}F]radiofluorination method.[55] A recent review covers all the commonly used methods and organizes the highlights and limitations of each method.[56] Since the initial publications, these methods have been used to produce radiotracers that were previously inaccessible or gave low RCYs (Figure 2.6).[57–62] Conditions have been slightly adjusted based on the needs of the radiotracer.

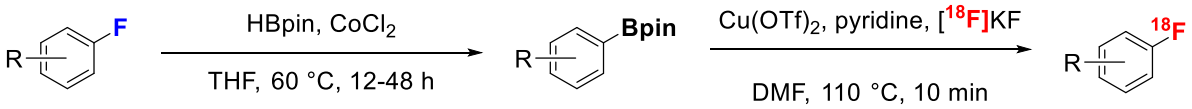
Figure 2.6. New Radiotracers Made with Recent Methods



^{18}F-FBnTP ^{18}F COX-2 Inhibitor ^{18}F-SDM-8 ^{18}F-CH-042794

This transformation was used as inspiration for the development of methods for forming other types of Ar–X bonds, including the topic of Chapter 3.[63,64] Arylstannanes are commonly used to make SPECT radiotracers with ^{123}I. A Cu-mediated transformation using arylboron derivatives was developed to make Ar–^{123}I products.[65] Another method was developed that transforms aryl fluorides into aryl pinacol boranes.[66] This could be a complementary way to go from an Ar–^{19}F to an Ar–^{18}F compound in just two steps (Scheme 2.5).

Scheme 2.5. Co-Catalyzed Borylation of Aryl Fluorides Followed By Radiofluorination[66]



2.12. Experimental Details

2.12.1. Instrumental Information

NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^{1}H; 100.71 MHz for ^{13}C; 376.87 MHz for ^{19}F), a Varian VNMRS 500 (500.10 MHz for ^{1}H), or a Varian VNMRS 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced based on an internal standard, 1,d-difluorobenzene (–140.53 ppm). ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ICP-OES data was obtained from Cerium Laboratories, LLC in Austin, TX. Melting point data (mp) were collected on an OptiMelt Automated Melting Point System. HPLC was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

2.12.2. Materials and Methods

All commercial products were used as received unless otherwise stated. Boronic acid precursors were purchased from Frontier Scientific, Oakwood Products and Sigma Aldrich. Fluorine-19 reference standards were also sourced commercially. Arylstannane precursors were purchased from Frontier Scientific, Oakwood Products and Sigma Aldrich or synthesized in the following sections. Fluorine-19 reference standards were sourced commercially. Boc-Phe(4-I)-OH (CAS 62129-44-6) was purchased from Fisher. TriBoc-L-DOPA methyl ester (CAS: 857502-21-7) was obtained from ABX. HPLC grade acetonitrile, anhydrous N,N-dimethylformamide, potassium trifluoromethanesulfonate and potassium carbonate were purchased from Fisher Scientific. Pyridinium p-toluenesulfonate was purchased from Sigma-Aldrich. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 90 mg/mL potassium trifluoromethanesulfonate solution, and finally 10 mL of sterile water prior to use.

2.12.3. Synthesis of [^{18}F]KF

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron (40 μA beam for 2–5 min generated ca. 150–375 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the synthesis module in a 1.5 mL bolus of [^{18}O]water and trapped on a QMA-light Sep-Pak to remove [^{18}O]water and other impurities. [^{18}F]Fluoride was eluted into the reaction vessel using 550 μL of aqueous solution containing 5 mg potassium trifluoromethanesulfonate and 50 μg of potassium carbonate. Acetonitrile (1.0 mL) was added to the reaction vessel, and the resulting solution was dried by azeotropic distillation to provide anhydrous [^{18}F]KF. Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 °C and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min. Overall, 70% of activity remained after

azeotropic drying (68%; calculated from TRACERLab FX_{FN} reactor radiation detector by comparing activity before and after azeotropic drying). DMF (6 mL) was added to the dried reagent, and heated at 120 °C with stirring for 5 min. The resulting solution was cooled to 40 °C and was transferred to a sterile vial for subsequent use in reactions (% activity recovery into dose vial: 40%; calculated by comparing activity of recovered solution by Capintec with final reading from TRACERLab FX_{FN} reactor radiation detector. As an example, approx. 80 mCi of prepared [^{18}F]KF in 6 mL DMF is isolated with a 5 min beam. It should be noted that % recovery data is only relevant for manual reactions, not automated one-pot syntheses).

For the arylstannane conditions: (same as above) azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min. DMA (8 mL) was added to the dried reagent, and the sample was cooled to 40 ºC and was transferred to a sterile vial for subsequent use in reactions. As an example, approximately 80 mCi of prepared [^{18}F]KF in 8 mL DMA is isolated with a 5 min cyclotron beam. It should be noted that percent recovery data is only relevant for manual reactions, not automated one-pot syntheses.

2.12.4. Manual Synthesis of ^{18}F-Labeled Molecules for Arylboronic Acids

This procedure was used for the synthesis of the [^{18}F] fluorinated substrates described in the substrate scope. Stock solutions of boronic acid precursor (40 mM), $Cu(OTf)_2$ (200 mM), and pyridine (1 M) in DMF were prepared immediately prior to the start of the reaction. Aliquots of these solutions were used to carry out subsequent [^{18}F]fluorination reactions. In a typical reaction, a 100 µL (20 µmol, 5 equiv) of $Cu(OTf)_2$ aliquot was mixed with a 500 µL (500 µmol, 25 equiv) pyridine aliquot in a colorless borosilicate 4 mL scintillation vial. The solution was briefly agitated using a vortex shaker (Barnstead® Thermolyne Type 16700), then a 100 µL (4 µmol, 1 equiv) aliquot of boronic acid precursor was added. The reaction vial was sealed under an atmosphere of ambient air with a PTFE/Silicone septum cap, and a 100–300 µL aliquot of [^{18}F]KF (150–3000 µCi, depending on the time required for HPLC analysis) was added to the reaction vial through

the septum via a syringe. Additional anhydrous DMF was also added (as required) to bring the total solution volume to 1000 µL. The vial was then heated in an aluminum block (Chemglass Part# CG-1991-04) without stirring at 110 ºC for 20 min. After 20 min, the reaction was allowed to cool to room temperature. Radio-TLC analysis was conducted to determine RCC. Crude reaction mixture was spotted onto standard silica coated glass plates and developed with 1:1 hexane/ethyl acetate in a glass TLC chamber. The RCC was determined by dividing the integrated area under the fluorinated product spot by the total integrated area of the TLC plate. To prepare samples for HPLC analysis, 50 µL of the reaction mixture was mixed with 50 µL acetonitrile or spiked with 50 µL of 1 mg/mL fluorinated standard solution in acetonitrile.

2.12.5. Manual Synthesis of ^{18}F-Labeled Molecules for Arylstannanes

This procedure was used for the synthesis of the [^{18}F]fluorinated substrates described in main text. Stock solutions of arylstannane precursor (0.1 M), $Cu(OTf)_2$ (0.2 M), and pyridine (1M) in DMA were prepared immediately prior to the start of the reaction. Aliquots of these solutions were used to carry out subsequent [^{18}F]fluorination reactions. In a typical reaction, a 0.1 mL (0.020 mmol, 2 equiv) aliquot of $Cu(OTf)_2$ was mixed with a 0.15 mL (0.15 mmol, 15 equiv) aliquot of pyridine in a 4 mL vial. Next, a 0.1 mL (0.01 mmol, 1 equiv) aliquot of aryl stannane precursor was added along with the remaining solvent volume (0.55 mL DMA, total volume 1 mL). The reaction vial was sealed under an atmosphere of ambient air with a PTFE/Silicone septum cap, and a 0.1 mL aliquot of [^{18}F]KF (150-3000 µCi, depending on the time required for HPLC analysis) was added to the reaction vial through the septum via a syringe. The vial was then heated in an aluminum block without stirring at 140 ºC for 30 min. After 30 min, the reaction was allowed to cool to room temperature. Radio-TLC analysis was conducted to determine radiochemical conversion (% RCC). The crude reaction mixture was spotted onto a standard silica-coated glass plate and run using 1:1 hexane/ethyl acetate in a glass TLC chamber. The RCC was then determined by dividing the integrated area under the fluorinated product spot by the total integrated area of the fluorine-18 on the TLC plate. To prepare samples for HPLC analysis: 0.1 mL of the reaction mixture or for the co-

injection analysis 0.1 mL of the reaction mixture spiked with 0.1 mL of 1 mg/mL fluorinated standard solution were transferred to an HPLC autosampler vial.

2.12.6. Automated Synthesis of [^{18}F]F-PEB ([^{18}F]18)

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron. [^{18}F]KF was produced as indicated above. A solution containing $Cu(OTf)_2$ (20 µmol, 5 equiv, 0.02 M), pyridine (500 µmol, 125 equiv, 0.5 M), and boronic acid (4 µmol, 1 equiv, 0.004 M) precursor in 1 mL anhydrous DMF (prepared from separate stock solutions of the three reagents) was added to the reactor containing dry [^{18}F]KF by applying Ar gas through the valve containing the reagent solution. Open valves leading out of the reactor were closed and the mixture was stirred for 20 min at 110 ºC. The mixture was then cooled to 50 ºC with compressed air cooling and 5 mL of DMF was added to the reactor. Mixture was allowed to stir for approximately 1 min and was then transferred to an 8 mL sterile product vial with Ar gas. The dose vial was transferred out of the synthesis module in a lead pig. Total activity, RCC, and identity were then determined by a capintec dose calibrator, Radio-TLC scanner, and HPLC, respectively and as described previously.

2.12.7. Automated Synthesis of [^{18}F]MPPF ([^{18}F]31)

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron. [^{18}F]KF was produced as indicated above. A solution containing aryl stannane precursor (0.01 mmol, 1 equiv, 0.1M stock) in 0.4 mL of anhydrous DMA in vial 3 and $Cu(OTf)_2$ (0.02 mmol, 2 equiv, 0.2 M stock), pyridine (0.015 mmol, 15 equiv, 1 M stock), in 0.25 mL of DMA from vial 4 (prepared from separate stock solutions of the three reagents) were added to a reactor containing dry [^{18}F]KF by applying

Argon (Ar) gas through the valve containing the reagent solution for a final reaction volume of 1 mL of DMA. Open valves leading out of the reactor were closed, and the mixture was stirred for 15 min at 100 ºC. The mixture was then cooled to 50 ºC with compressed air cooling, and 2 mL of HPLC buffer (50% MeCN, 10 mM NH_4OAc, pH 6.0) was added to the reactor. This mixture was allowed to stir for approximately 1 min and was then transferred to an HPLC loop for injection and purification by semi-preparative chromatography (250 x 10 mm, 10µ, 4 mL/min). The product peak (retention time ~12 min) was collected and diluted into 50 mL of MQ H_2O. The product was trapped on a C18 extraction disk, washed with 10 mL of sterile water, eluted with 1 mL of EtOH, and then rinsed with 9 mL of saline solution. The resulting 10 mL solution was passed through a sterile filter and submitted to standard quality control tests (tests and results are described in detail below). [^{18}F]MPPF was produced in a 13% RCY (200 mCi).

2.12.8. Specific Activity Calculation

The specific activity of radiofluorinated products was determined by the following method. A sample of known volume of the crude reaction mixture was transferred to a vial, and the activity of the vial was counted using a calibrated CAPINTEC (CRC-15R) detector. The activity in the vial was then multiplied by the RCC (obtained from radio-TLC analysis) to determine the total activity of the product in the vial. A concentration of activity in Ci/mL was thus obtained. An aliquot of the sample was then injected onto the HPLC using one of the four isocratic methods listed above. The UV peak corresponding to the radiofluorinated product was determined by overlaying the UV and RAD traces (with a 0.1 min offset). The UV area was then used to calculate the concentration of the product based on linear regression analysis of appropriate [^{19}F]fluoroarene standard. A standard curve was generated from standard solutions, each performed in duplicate (1 mg/mL to 10 µg/mL). This, in turn, was used to determine the concentration of the product in mmol/mL. Dividing the activity concentration (Ci/mL) by the HPLC-derived concentration of product (mmol/mL) provided the specific activity in Ci/mmol. This reflects an EoS specific activity. [^{18}F]MPPF was produced with a specific activity 2,400 Ci/mmol.

2.12.9. QC Validation for [^{18}F]MPPF ([^{18}F]31)

Radiochemical Purity (> or = to 95%): 98.4%

Total Chemical Content (< or = to 10 µg/mL): Pass

MPPF Concentration (N/A (µg/mL)): 4.26 µg/mL

Specific Activity (N/A (Ci/mmol)): 1915 Ci/mmol

pH (4.5-7.5): 5.0

Visual Inspection (clear, colorless, no ppt): Pass

Kryptofix Analysis (< or = to 50 µg/mL): < 50 µg/mL

Residual Solvent Analysis for Acetone, 5000 µg/mL: Pass

Methanol < 3000 µg/mL: Pass

THF < 5000 µg/mL: Pass

MeCN < 410 µg/mL: Pass

DMSO < 5000 µg/mL: Pass

Radionuclide Identity (105-115 min half-life): 108.30 min

Endotoxin Analysis (<17.5 EU/mL): <2.00 EU/mL

Filter Bubble Point Test (>40 psi): >40 psi

Radiochemical Identity (0.9-1.10): 1.001

Analysis for Residual Copper and Tin: conformed to ICH guidelines

Detection limits were 0.019 ppm for Cu and 0.395 ppm for Sn

Both Sn and Cu were below the limit of detection

See “Analytical Report” below for more information

Analytical Report

Title:

Cu & Sn in Buffered Catalyst Solution

Date:

August 18, 2016

Prepared For:

Katarina Makaravage
University of Michigan

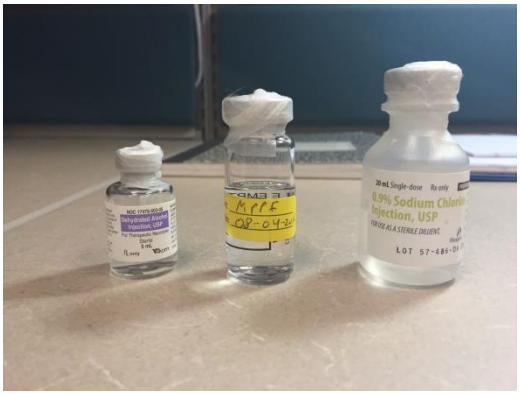
Prepared By:

Chemistry Team
Cerium Laboratories
Austin, TX

Sample Description:

Sample #	Sample ID
MPPF	MPPF, 8ml product solution <1mM substrate

Samples as received:



Only the yellow labeled sample was analyzed. The other two bottles are extra solvent and buffer just in case more analysis is needed.

Analytical Equipment:

- *Varian* Liberty Series II Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES).

Instrument Conditions:

- ICP-OES:
    1. Inlet: HF resistant torch with V-groove type pneumatic nebulizer.
    2. Plasma Flow: 15.0L/min.
    3. Aux Flow: 1.50L/min.
    4. Nebulizer Pressure: 260kPa.
    5. PMT Voltage: 660V.
    6. Method: Custom just for Cu and Sn lines.

Test Method:

1. Sample was diluted 10 times in 10% HNO_3 then analyzed by ICPOES.
2. Tool sensitivity and calibrations performed using NIST traceable standards.

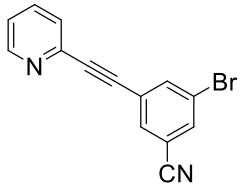
Data:

"nd" implies the analyte was not detected.

Technique	Analyte	Units	MPP	Detection Limits
ICPOES-HFI	Cu	ppm	nd	0.019
ICPOES-HFI	Sn	ppm	nd	0.395

2.13. Synthesis and Characterization

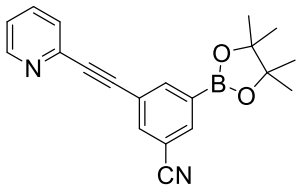
2.13.1. Boronic Acid Substrates



(**S1**)

3-bromo-5-(pyridin-2-ylethynyl)-benzonitrile (Br-PEB, **S1**) was prepared by the following procedure adapted from the literature.[67] In a glovebox, 2-((trimethylsilyl)ethynyl)pyridine (873.7 mg, 5.0 mmol, 1.0 equiv), 3,5-dibromobenzonitrile (1304.4 mg, 5.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (350.0 mg, 0.50 mmol, 0.1 equiv), CuI (182.6 mg, 1.0 mmol, 0.2 equiv), and Et_3N (1.4 mL, 2.0 mmol, 0.4 equiv) were placed in a 25 mL flask equipped with a stir bar. DMF (8.6 mL, 0.6 M) was added to the mixture and the flask was capped with a septum and taken out of the glovebox. Under N_2, the flask was stirred at 80 °C for 30 minutes. A solution of $(n\text{-}Bu)_4NF$ (1.695 g, 6.1 mmol, 1.2 equiv) in THF (1.0 M, 6.0 mL) was added dropwise. The reaction mixture was stirred at 80 °C until TLC showed no starting material was present (average time 4 hours). The reaction mixture was cooled to room temperature and diluted with methyl tert-butyl ether (MTBE, 10 mL) and poured into

aqueous NH_4OH (1.0 M, 15 mL). The aqueous layer was washed with MTBE (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (15% EtOAc/hexanes), which afforded Br-PEB **S1** as a yellow powder (687.0 mg, 2.4 mmol, 49 % yield). The ^{1}H and ^{13}C NMR spectroscopic data for **S1** were identical to that reported.[68] HRMS (ESI+) [$M+H^+$] Calculated for $C_{14}H_7BrN_2$: 282.9865; Found 282.9865.



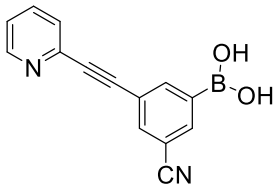
(**S2**)

(3-cyano-5-(pyridin-2-ylethynyl)phenyl)boronic acid, pinacol ester (Bpin-PEB, **S2**) was prepared by the following procedure adapted from the literature.[69] In a glovebox, Br-PEB (**S1**) (297.5 mg, 1.1 mmol, 1 equiv), B_2pin_2 (295.0 mg, 1.2 mmol, 1.1 equiv), KOAc (308.1 mg, 3.1 mmol, 3.0 equiv), and $Pd(dppf)Cl_2$ (116.6 mg, 0.14 mmol, 0.14 equiv) were placed in a 20 mL vial equipped with a stir bar. DMSO (5.8 mL, 0.2 M) was added to the mixture and the vial was sealed with a Teflon cap and taken out of the glovebox. The vial was stirred at 80 °C for 15 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether (10 mL) and filtered through Celite®. The organic layer was washed with H_2O (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The product was washed with $NaHCO_3$ (2 x 10 mL) to remove excess pinacol, which afforded substrate **S2** as a black oil (200.7 mg, 0.6 mmol, 58% yield).

^{1}H NMR (700 MHz, CDCl3): δ 8.63 (d, *J* = 4.9 Hz, 1H) 8.23 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.70 (td, *J* = 7.7, 2.1 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.28 (dd, *J* = 4.9, 2.1 Hz, 1H), 1.33 (s, 12H)

^{13}C NMR (176 MHz, CDCl3): δ 150.2, 142.7, 142.2, 138.0, 137.0, 136.3, 127.3, 123.3, 123.3, **117.9**, **112.6**, 90.5, 86.5, 84.7, 25.0, 24.8. C-CN and CN carbons in **bold**.

HRMS (ESI+) [M+H+] Calculated for $C_{20}H_{19}BN_2O_2$: 331.1612; Found 331.1617



(**18-B(OH)$_2$**)

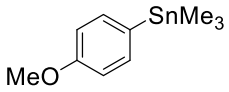
(3-cyano-5-(pyridin-2-ylethynyl)phenyl)boronic acid (B(OH)$_2$-PEB, **18-B(OH)$_2$**) was prepared by the following procedure adapted from the literature.[70] Bpin-PEB (**S2**) (271.9 mg, 0.8 mmol, 1 equiv) and sodium periodate (529.9 mg, 2.5 mmol, 3 equiv) were stirred in 6.7 mL of a 4:1 mixture of THF/H_2O for 30 minutes at room temperature. After that time, aqueous hydrochloric acid (1N, 0.6 mL) was added to the suspension. The solution was stirred at ambient temperature overnight (18 hr). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (2 x 20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was washed with hexanes to give **18-B(OH)$_2$** as a yellow solid (109.2 mg, 54 % yield).

^{1}H NMR (700 MHz, CD_3OD and 1 drop of CD_3COOD): δ 8.63 (d, *J* = 4.9 Hz, 1H) 8.15 (s, 1H), 8.03 (s, 1H), 7.97 (t, *J* = 1.4 Hz, 1H), 7.91 (td, *J* = 7.7, 2.1 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.47 (ddd, *J* = 7.7, 5.3, 1.4, 0.7 Hz, 1H)
^{13}C NMR (176 MHz, CDCl3): δ 150.20, 142.65, 142.20, 138.02, 137.02, 136.27, 127.29, 123.28, **117.93**, **112.57**, 90.55, 86.48, 84.72. C-CN and CN carbons in **bold**.
HRMS (ESI+) [M+H$^+$] Calculated for $C_{14}H_9BN_2O_2$: 248.0830; Found 248.0834

2.13.2. Arylstannane Substrates

General Procedure for Preparation of Trialkylaryl Stannanes: The general procedure is adapted from the literature.[30,71] In a nitrogen atmosphere glovebox, a 20 mL vial was charged with aryl iodide (1 mmol), $Pd(PPh_3)_4$ (224.6 mg, 0.19 mmol), and lithium chloride (202.9 mg, 4.8 mmol). The combined solids were dissolved in toluene (12.5 mL, 0.08 M) at room temperature. Hexabutylditin (2.6 mL, 5.2 mmol) or hexamethylditin (1.1 mL, 5.2 mmol) was added via syringe, and the vial was sealed and removed from the glovebox. The sealed vial was heated to 100 °C using an aluminum block. Once the reaction mixture

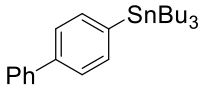
turned black (generally 2-4 h), it was cooled to room temperature. Aqueous potassium fluoride (5.0 mL, 2 M solution) was added, and the mixture was stirred vigorously. After 30 min, the mixture was filtered through a plug of Celite (eluting with hexanes or toluene). The filtrate was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified via flash column chromatography.



(**14-SnMe$_3$**)

4-Trimethylstannylanisole (14-SnMe$_3$)

The published procedure was followed with small modifications.[72] Under nitrogen atmosphere, 4-methoxyaniline (491.7 mg, 4.0 mmol, 1 equiv) and TsOH•H_2O (929.0 mg, 4.9 mmol, 1.2 equiv) were weighed into an oven-dried round bottom flask. 1,2-Dichloroethane (DCE) (20 mL, 0.2 M) was added, and the flask was cooled to 0 °C. *t*-BuONO (0.4 mL, 8.2 mmol, 2.0 equiv) and Sn_2Me_6 (0.9 mL, 4.3 mmol, 1.1 equiv) were added in succession. The resulting reaction solution was stirred for 4 h at 0 °C under nitrogen. The solution was then filtered through a silica plug and concentrated under reduced pressure. Purification by flash column chromatography eluting with 20% diethyl ether in pentanes afforded **14-SnMe$_3$** as a colorless oil (59.3 mg, 22% yield, R_f = 0.8 in 10% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[72] HRMS (EI) [M–CH_3^+] Calculated for $C_9H_{13}OSn$: 256.9989; Found 256.9979.

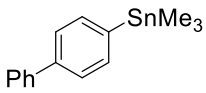


(**8-SnBu$_3$**)

4-Tributylstannyl-1,1'-biphenyl (8-SnBu$_3$)

The general procedure was followed using 4-iodo-1,1'-biphenyl (279.5 mg, 1.0 mmol) and heating for 3 h. Purification by flash column chromatography eluting with hexanes afforded **8-SnBu$_3$** as a colorless oil (191.0 mg, 43% yield, R_f = 0.6 in 100% hexanes). The

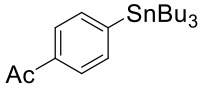
^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[73] HRMS (EI) [M–$C_4H_9^+$] Calculated for $C_{20}H_{27}Sn$: 387.1135; Found 387.1135.



(**8-SnMe$_3$**)

4-Trimethylstannyl-1,1'-biphenyl (8-SnMe$_3$)

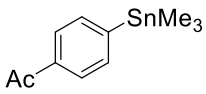
The general procedure was followed using 4-iodo-1,1'-biphenyl (280.1 mg, 1.0 mmol) and heating for 2 h. Purification by flash column chromatography eluting with hexanes afforded **8-SnBu$_3$** as a colorless oil (275.0 mg, 87% yield, R_f = 0.5 in 100% hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[74] HRMS (EI) [M^+] Calculated for $C_{15}H_{18}Sn$: 318.0430; Found 318.0415.



(**1-SnBu$_3$**)

4-Tributylstannylacetophenone (1-SnBu$_3$)

The general procedure was followed using 4-iodoacetophenone (246.3 mg, 1.0 mmol) and heating for 4 h. Purification by flash column chromatography eluting with hexanes afforded **1-SnBu$_3$** as a colorless oil (284.3 mg, 69 %, R_f = 0.56 in 5% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[73] HRMS (ESI$^+$) [M+K^+] Calculated for $C_{20}H_{34}KOSn$: 449.1263; Found 449.1263.

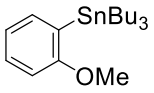


(**1-SnMe$_3$**)

4-Trimethylstannylacetophenone (1-SnMe$_3$)

The general procedure was followed using 4-iodoacetophenone (245.9 mg, 1.0 mmol) and heating for 4 h. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **1-SnMe$_3$** as a colorless oil (147.0 mg, 52% yield, R_f = 0.7 in 10% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported

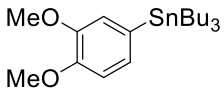
previously in the literature.[72] HRMS (EI) [M–CH_3^+] Calculated for $C_{10}H_{13}OSn$: 268.9988; Found 268.9984.



(**21-SnBu$_3$**)

2-Tributylstannylanisole (21-SnBu$_3$)

The general procedure was followed using 2-iodoanisole (0.32 mL, 2.5 mmol) and heating for 6 h. Purification by flash column chromatography eluting with hexanes afforded **21-SnBu$_3$** as a colorless oil (604.2 mg, 62% yield, R_f = 0.6 in 100% hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[73] HRMS (EI) [M–$C_4H_9^+$] Calculated for $C_{15}H_{25}OSn$: 341.0927; Found 341.0934.



(**22-SnBu$_3$**)

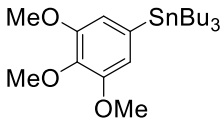
(3,4-dimethoxyphenyl)tributylstannane (22-SnBu$_3$)

The general procedure was followed using 1-iodo-3,4-dimethoxybenzene (265.2 mg, 1.0 mmol) and heating for 2.5 h. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **22-SnBu$_3$** as a colorless oil (171.7 mg, 40% yield, R_f = 0.5 in 10% ethyl acetate in hexanes). The ^{1}H NMR spectra matched that reported previously in the literature.[75]

^{1}H NMR ($CDCl_3$): δ 6.99 (d, *J* = 7.7 Hz, 1H), 6.94 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 3.89 (s, 3H), 2.87 (s, 3H), 1.56-1.52 (multiple peaks, 6H), 1.36-1.30 (multiple peaks, 6H), 1.05-1.03 (multiple peaks, 6H), 0.89 (t, *J* = 7 Hz, 9H)

^{13}C NMR ($CDCl_3$): δ 149.12, 148.65, 132.52, 129.17, 118.63, 111.20, 55.83, 55.62, 29.10, 27.37, 13.90, 9.67

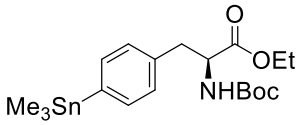
HRMS (ESI) [M+Na^+] Calculated for $C_{20}H_{36}NaO_2Sn$: 451.1629; Found 451.1629



(**15-SnBu$_3$**)

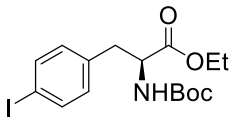
Tributyl(3,4,5-trimethoxy)stannane (15-SnBu$_3$)

The general procedure was followed using 5-iodo-1,2,3-trimethoxybenzene (294.5 mg, 1.0 mmol) and heating for 2 h. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **15-SnBu$_3$** as a colorless oil (326.7 mg, 71% yield, R_f = 0.7 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[76] HRMS (ESI) [M+H$^+$] Calculated for $C_{21}H_{39}O_3Sn$: 459.1916; Found 459.1915.



(**28-SnMe$_3$**)

NHBoc-Phe(4-SnMe$_3$) ethyl ester (28-SnMe$_3$) was prepared by the following 2 step procedure.



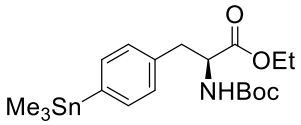
(**S3**)

Step 1:

Iodide **S3** was prepared via a modification of a literature procedure.[77] To an oven-dried flask, Boc-Phe(4-I)-OH (1016.6 mg, 2.6 mmol, 1.0 equiv) was dissolved in dichloromethane (22 mL) at room temperature. DMAP (34.3 mg, 0.3 mmol, 0.1 equiv) and ethanol (0.3 mL, 5.1 mmol, 2.0 equiv) were added to the solution, and the reaction was placed under nitrogen and cooled to 0 °C. DCC (862.5 mg, 4.2 mmol, 1.6 equiv) was added slowly. The mixture was allowed to warm up to room temperature and react overnight at room temperature under nitrogen. The white precipitate formed was filtered off and the organic filtrate was washed with brine (1 x 20 mL), dried using magnesium

sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) affording the product (**S3**) as a white solid (1.01 g, 93% yield, R_f = 0.2 in 20% ethyl acetate in hexanes, mp = 91–92 °C).

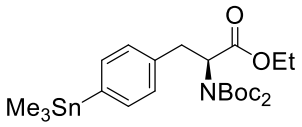
^{1}H NMR ($CDCl_3$): δ 7.57 (d, *J* = 7.7 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 5.00 (d, *J* = 7.0 Hz, 2H), 4.49 (d, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.03 (m, 2H), 1.37 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 3H)
^{13}C NMR ($CDCl_3$): δ 171.45, 154.90, 137.40, 135.76, 131.30, 92.32, 79.86, 61.38, 54.14, 37.82, 28.21, 14.06
HRMS (ESI+) [M+Na^+] Calculated for $C_{16}H_{22}INNaO_4$: 442.0486; Found 442.0489



(**28-SnMe$_3$**)

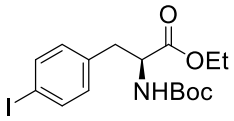
Step 2:
The general procedure for stannane synthesis was followed using **S3** (404.8 mg, 1.0 mmol) and heating for 2 h. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **28-SnBu$_3$** as a colorless oil (73.4 mg, 17% yield, R_f = 0.5 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.39 (d, *J* = 10.5 Hz, 2H), 7.09 (d, *J* = 10.5 Hz, 2H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.14 (q, *J* = 9.8 Hz, 2 H), 3.03 (m, 2H), 1.39 (s, 9H), 1.22 (t, *J* = 9.8 Hz, 3H), 0.25 (s, 9H)
^{13}C NMR ($CDCl_3$): δ 171.59, 155.00, 135.95, 134.63, 130.70, 128.58, 61.47, 54.31, 37.79, 28.29, 14.13, –0.97, –9.61
HRMS (ESI) [M+H^+] Calculated for $C_{19}H_{32}NO_4Sn$: 458.1348; Found 458.1352



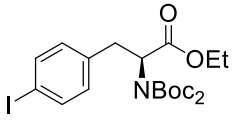
(**29-SnMe$_3$**)

NBoc$_2$-Phe(4-SnMe$_3$) ethyl ester (29-SnMe$_3$) was prepared by the following 3 step procedure.



(**S3**)

Step 1: see above procedure



(**S4**)

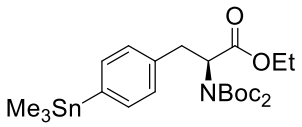
Step 2:

Iodide **S4** was prepared via a modified literature procedure.[78] To a solution of **S3** (546.0 mg, 1.3 mmol) in dry acetonitrile (25 mL) under nitrogen was added DMAP (75.3 mg, 0.6 mmol) in dry acetonitrile (10 mL) and then di-*tert*-butyl dicarbonate (0.7 mL, 3.1 mmol) in dry acetonitrile (10 mL). The mixture was stirred at room temperature overnight and then concentrated under vacuum. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **S4** as a colorless oil (407.9 mg, 60% yield, R_f = 0.54 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.56 (d, *J* = 11.9 Hz, 2H), 6.91 (d, *J* = 11.9 Hz, 2H), 5.05 (dd, *J* = 14.2, 7.3 Hz, 1H), 4.18 (m, 2H), 3.35 (dd, *J* = 19.6, 7.3 Hz, 1H), 3.13 (dd, *J* = 19.6, 14.2 Hz, 1H), 1.38 (s, 18H), 1.25 (t, *J* = 9.8 Hz, 3H)

^{13}C NMR ($CDCl_3$): δ 170.08, 151.79, 137.42, 137.32, 131.62, 91.82, 83.04, 61.40, 59.11, 35.63, 27.84, 14.11

HRMS (ESI+) [M+Na$^+$] Calculated for $C_{21}H_{30}INNaO_6$: 542.0101; Found 542.0102



(**29-SnMe$_3$**)

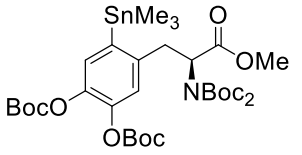
Step 3:

The general procedure for stannane synthesis was followed using **S4** (407.9 mg, 0.8 mmol) and heating for 2 h. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **29-SnBu$_3$** as a yellow oil (230.4 mg, 53% yield, R_f = 0.6 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.36 (d, *J* = 7.7 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 5.08 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.18 (m, 2H), 3.38 (dd, *J* = 14.0, 4.9 Hz, 1H), 3.18 (dd, *J* = 14.0, 10.5 Hz, 1H) 1.36 (s, 18H), 1.25 (t, *J* = 7 Hz, 3H), 0.22 (s, 9H)

^{13}C NMR ($CDCl_3$): δ 170.38, 151.66, 139.78, 137.71, 135.82, 129.35, 82.83, 61.34, 59.60, 36.07, 27.86, 14.15, –9.71

HRMS (ESI) [M+H$^+$] Calculated for $C_{24}H_{40}NO_6Sn$: 558.1883; Found 558.1883



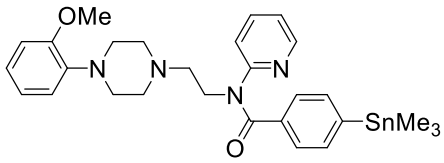
(**30-SnMe$_3$**)

Boc$_4$DOPA(2-SnMe$_3$) methyl ester (30-SnMe$_3$)

Aryl stannane **30-SnMe$_3$** was prepared via a modified literature porcedure.[78] To a solution of Boc$_3$DOPA-SnMe$_3$ (445.1 mg, 0.7 mmol) in dry acetonitrile (10 mL) under nitrogen was added DMAP (32.3.0 mg, 0.28 mmol, 0.4 equiv) in dry acetonitrile (4.6 mL) and di-*tert*-butyl dicarbonate (0.3 mL, 1.3 mmol, 2 equiv) in dry acetonitrile (4.4 mL). The reaction was stirred at room temperature overnight and then concentrated under vacuum. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes

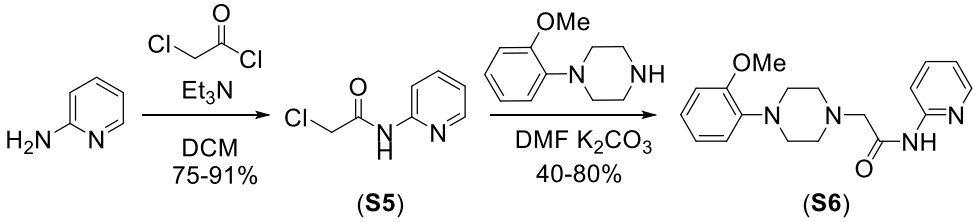
afforded **30-SnMe$_3$** as a yellow oil (407.6 mg, 80% yield, R_f = 0.46 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 7.01, (s, 1H), 5.03 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.73 (s, 3H), 3.38 (dd, *J* = 14.7, 4.2 Hz, 1H), 3.29 (dd, *J* = 14.7, 10.5 Hz, 1H) 1.52 (s, 9H), 1.50 (s, 9H), 1.37 (s, 18H), 0.31 (s, 9H)
^{13}C NMR ($CDCl_3$): δ 170.59, 151.79, 150.72, 150.59, 142.95, 142.44, 141.28, 140.50, 130.00, 123.82, 83.44, 83.36, 83.19, 59.24, 52.36, 37.98, 27.84, 27.62, 27.61, –8.13
HRMS (ESI) [M+Na$^+$] Calculated for $C_{33}H_{53}NNaO_{12}Sn$: 798.2482; Found 798.2491

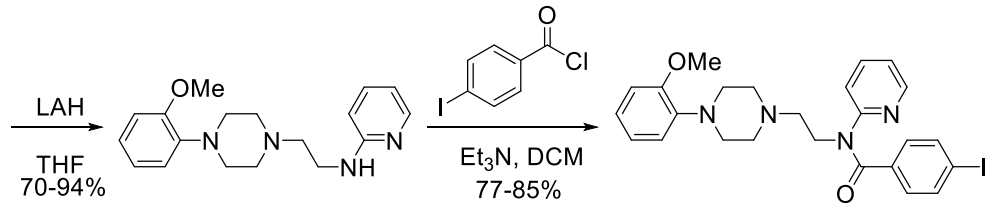


(**31-SnMe$_3$**)

MPP-SnMe$_3$ (31-SnMe$_3$) was prepared by the following 5-step procedure.[2D]

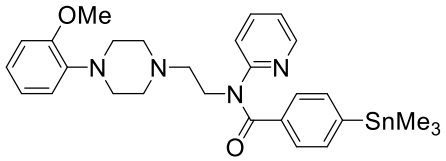


(**S5**) (**S6**)



(**S7**) (**S8**)

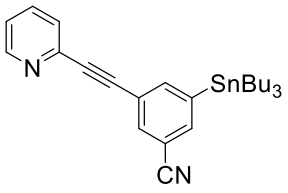
[D] Reactions performed and products isolated by Jason Miller.



(**31-SnMe$_3$**)

The general procedure was followed using **S8** (200.0 mg, 0.37 mmol) and heating for 2 h. Purification by flash column chromatography eluting with 50% ethyl acetate in hexanes afforded **31-SnMe$_3$** as a white solid (132.8 mg, 62% yield, R_f = 0.16 in 50% ethyl acetate in hexanes, mp = 140–141 °C).

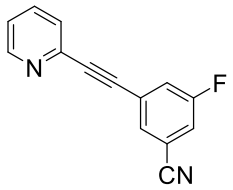
^{1}H NMR ($CDCl_3$): δ 8.41 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.37 (td, *J* = 7.7, 2.1 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 6.84-7.00 (multiple peaks, 5H), 6.82 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.27 (t, *J* = 7.0 Hz, 2 H), 3.82 (s, 3H), 2.90 (broad peak, 4H), 2.73 (t, *J* = 7.0 Hz, 2 H), 2.61 (broad peak, 4H), 0.22 (s, 9H)
^{13}C NMR ($CDCl_3$): δ 170.72, 156.59, 152.22, 148.52, 145.70, 141.39, 136.94, 135.97, 135.30, 127.93, 122.91, 122.73, 120.90, 120.70, 118.05, 111.17, 56.41, 55.32, 53.32, 50.62, 45.49, –9.56
HRMS (ESI+) [M+H$^+$] Calculated for $C_{28}H_{37}N_4O_2Sn$: 581.1933; Found 581.1950



(**18-SnBu$_3$**)

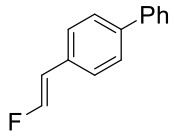
The general procedure was followed using **S1** (263.9 mg, 0.93 mmol) and heating for 7 h. Purification by flash column chromatography eluting with 30% ethyl acetate in hexanes afforded **18-SnBu$_3$** as a yellow oil (245.8 mg, 54% yield, R_f = 0.43 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[68] HRMS (EI) [M+H$^+$] Calculated for $C_{26}H_{35}N_2Sn$: 495.1817; Found 495.1820.

2.13.3. Fluorinated Standards



(**18**)

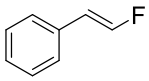
3-fluoro-5-(pyridin-2-ylethynyl)benzonitrile (F-PEB, **18**) was prepared by the following procedure adapted from the literature.[67] In a glovebox, 2-((trimethylsilyl)ethynyl)pyridine (177.7 mg, 1.0 mmol, 1.0 equiv), 3,5-dibromobenzonitrile (205.6 mg, 1.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (74.4 mg, 0.10 mmol, 0.10 equiv), CuI (39.5 mg, 0.2 mmol, 0.20 equiv),and Et_3N (0.3 mL, 2.1 mmol, 2.1 equiv) were placed in a flask with DMF (1.75 mL, 0.6 M). The flask was placed under N_2 flow and stirred at 80 °C for 30 min. A solution of $(n\text{-}Bu)_4NF$ (1.129 g, 4.0 mmol, 4.0 equiv) in THF (1.0 M, 4.0 mL,1.1 equiv) was added dropwise. The reaction mixture was stirred at 80 °C until TLC showed no starting material was present. The reaction mixture was cooled to room temperature and diluted with MTBE (10 mL) and poured into aqueous NH_4OH (1.0 M, 15 mL). The aqueous layer was washed with MTBE (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (15% EtOAc/hexanes), which afforded F-PEB **18** as a brown solid (142.9 mg, 0.64 mmol, 63% yield). The ^1H and ^{13}C NMR spectroscopic data for S3 were identical to that reported.[79] ^{19}F NMR (658 MHz, CDCl3): δ –108.9. HRMS (ESI+) $[M+H^+]$ Calculated for C14H7FN2: 223.0666; Found 223.0664.



(**17**)

4-(2-fluorovinyl)-1,1'-biphenyl (**17**) was prepared by the following procedure adapted from literature.[6] 2-([1,1'-biphenyl]-4-yl)vinyl boronic acid (46 mg, 0.21 mmol, 1.0 equiv) was dissolved with a 0.24 M methanolic NaOH solution (1 mL, 0.24 mmol, 2.4 equiv) in a flask. The mixture was capped with a septum and stirred for 15 min at room temperature, then cooled to 0 °C in an ice water bath. Silver trifluoromethanesulfonate (156 mg, 0.61 mmol,

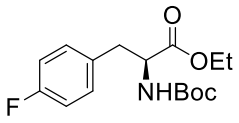
3.0 equiv) was added to the reaction mixture, and the mixture was capped and stirred for an additional 30 min at 0° C. Solvent was then evaporated under reduced pressure using a rotary evaporator at 3 °C. Then acetone aliquots (2 x 1mL) were added to the reaction mixture and evaporated to remove any additional volatile components. The dry residue was dissolved in 1 mL of acetone and approx. 300 mg of 4 Å molecular sieves were added to the solution, followed by Selectfluor (75 mg, 0.21 mmol, 1.0 equiv). The mixture was capped with a septum and stirred at 0 °C for 60 min. The reaction was quenched with 30 mL water and extracted with DCM (3 x 30 mL). The organic layer was washed twice with brine and passed through silica, thereby decolorizing it. The filtrate was loaded onto silica and purified by flash chromatography on silica gel (hexanes). The solvent was removed *in vacuo* to afford the product **17** as a white powder (12 mg, 0.06 mmol, 29% yield). The ^{1}H and ^{13}C NMR spectroscopic data for **17** were identical to that previously reported.[6] ^{19}F NMR (470 MHz, CDCl3): δ –129.5. HRMS (ESI+) [$M+H^{+}$] Calculated for $C_{14}H_{11}F$: 198.0845; Found 198.08444.



(**26**)

(*E*)-Fluorostyrene (26)

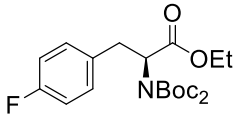
In a nitrogen atmosphere glovebox, tributyl(phenylethenyl)tin (415.9 mg, 1.1 mmol, 1 equiv), $Cu(OTf)_2$ (766.2 mg, 2.1 mmol, 2 equiv), KF (245.3 mg, 4.2 mmol, 4 equiv), and pyridine (1.3 mL, 16.1 mmol, 15 equiv) were weighed into a flask equipped with a magnetic stir bar. DMA (100 mL) was added. The reaction mixture was allowed to stir at 140 ºC for 4 h. The resulting solution was cooled to room temperature, diluted with diethyl ether and washed with water (2 x 200 mL), and brine (200 mL). The organic extracts were dried and concentrated. Purification by flash column chromatography eluting with 20% diethyl ether in pentane afforded **26** as a colorless oil. The ^{19}F NMR spectroscopic data was identical to that reported.[80]



(**28**)

NHBoc-Phe(4-F) ethyl ester (28)

Authentic standard **28** was prepared by the following procedure via a modification of a literature procedure.[77] To an oven-dried flask, NHBoc-Phe(4-F)-OH (509.4 mg, 1.8 mmol, 1.0 equiv) was dissolved in dichloromethane (15 mL, 0.12 M) at room temperature. DMAP (22.2 mg, 0.18 mmol, 0.1 equiv) and ethanol (0.21 mL, 3.6 mmol, 2.0 equiv) were added to the solution and the reaction was placed under nitrogen and cooled to 0 °C. DCC (595.0 mg, 2.9 mmol, 1.6 equiv) was added slowly. The mixture was allowed to warm to room temperature and was then stirred overnight at room temperature under nitrogen. Over this time, a white precipitate formed and was removed by filtration. The filtrate was washed with brine (1 x 20 mL), dried over magnesium sulfate, and concentrated. The crude residue was purified by column chromatography (silica gel, 20% ethyl acetate in hexane) affording the product (**28**) as a colorless oil (453.1 mg, 81% yield, R_f = 0.44 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported previously in the literature.[81] ^{19}F NMR ($CDCl_3$): δ –116.01. HRMS (ESI) [M+H$^+$] Calculated for $C_{16}H_{23}FNO_4$: 312.1606; Found 312.1611.



(**29**)

NBoc$_2$-Phe(4-F) ethyl ester (29)

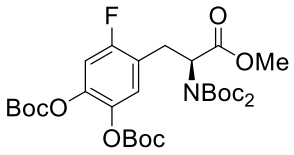
Authentic standard **29** was prepared via a modification of a literature procedure.[78] To a solution of **28** (334.5 mg, 1.07 mmol, 1 equiv) in dry acetonitrile (20 mL) under nitrogen was added 4-dimethylaminopyridine (DMAP) (54.0 mg, 0.44 mmol, 0.4 equiv) in dry acetonitrile (5 mL) and di-*tert*-butyl dicarbonate (0.5 mL, 2.2 mmol, 2.0 equiv) in dry acetonitrile (5 mL). The mixture was stirred at room temperature overnight and then concentrated under nitrogen. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **29** as a colorless oil (81.5 mg, 18% yield, R_f = 0.5 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.12 (dd, *J* = 8.4, 4.9 Hz, 2H), 6.93 (t, *J* = 8.4 Hz, 2H, 5.06 (dd, *J* = 9.8, 4.9 Hz, 1H), 4.18 (m, 2H), 3.37 (dd, *J* = 14.0, 4.9 1H), 3.16 (dd, *J* = 14.0, 9.8 Hz, 1H), 1.38 (s, 18H), 1.25 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR ($CDCl_3$): δ 170.24, 162.42, 161.03, 151.83, 133.46, 133.44, 131.00, 130.96, 115.14, 115.02, 82.98, 61.39, 59.39, 35.27, 27.88, 14.14

^{19}F NMR ($CDCl_3$): δ –116.93

HRMS (ESI) [M+H$^+$] Calculated for $C_{21}H_{31}FNO_6$: 412.2130; Found 412.2136



(**30**)

Boc$_4$DOPA(2-F) methyl ester (30)

In a nitrogen atmosphere glovebox, **30-SnMe$_3$** (311.0 mg, 0.4 mmol, 1 equiv), $Cu(OTf)_2$ (290.0 mg, 0.8 mmol, 2 equiv), KF (93.3 mg, 1.6 mmol, 4 equiv), and pyridine (0.5 mL, 6.2 mmol, 15 equiv) were weighed into a flask equipped with a magnetic stir bar. DMA (40 mL, 0.01M) was added. The reaction mixture was allowed to stir at 100 ºC for 2 h. The resulting solution was cooled to room temperature, diluted with diethyl ether, and washed with water (2 x 200 mL) and brine (200 mL). The organic extracts were dried over magnesium sulfate and concentrated. Purification by flash column chromatography eluting with 20% ethyl acetate in hexanes afforded **30** as a colorless oil (19.1 mg, 8% yield, R_f = 0.6 in 40% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.05 (d, *J* = 9.8 Hz, 1H), 6.97 (d, *J* = 13.3 Hz, 1H), 5.18 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.73 (s, 3H), 3.43 (dd, *J* = 19.6, 7.0 Hz, 1H), 3.21 (dd, *J* = 19.6, 14.0 Hz, 1H), 1.51 (s, 18H), 1.38 (s, 18H)

^{13}C NMR ($CDCl_3$): δ 170.45, 158.88, 157.46 151.55, 150.57, 150.09, 141.80, 138.39, 125.37, 122.66, 110.43, 84.05, 83.76, 83.29, 57.73, 52.34, 29.45, 27.81, 27.57

^{19}F NMR ($CDCl_3$): δ –117.64

HRMS (ESI) [M+NH_4^+] Calculated for $C_{30}H_{48}FN_2O_{12}$: 647.3186; Found 647.3184

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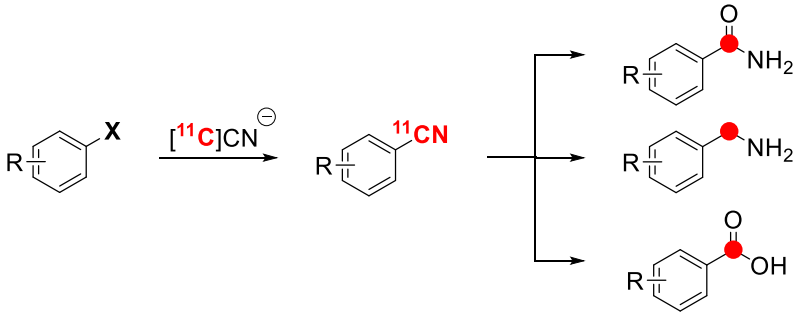
Chapter 3

Cu-Mediated [^{11}C]Cyanation of Organometallic Reagents[1,2]

3.1. Background

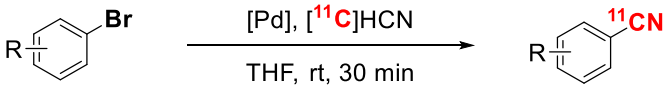
Carbon-11 ($t_{1/2}$ = 20 min) is a radioisotope that is commonly used for positron emission tomography (PET) imaging.[3,4] A number of methods have been developed for [^{11}C]radiolabeling, most involve introducing a [^{11}C]methyl group onto a molecule of interest.[5] Recently, new methods have been developed to generate [^{11}C]CN.[6] [^{11}C]Cyanide offers two advantages, (1) it can be readily generated from [^{11}C]CO_2,[3,4] allowing for ease of implementation; and (2) the nitrile functionality is common in bioactive molecules[7] and can be rapidly transformed into other prevalent functional groups, including amides, carboxylic acids, and amines (Scheme 3.1).

Scheme 3.1. Diversification of [^{11}C]Nitrile Substrates



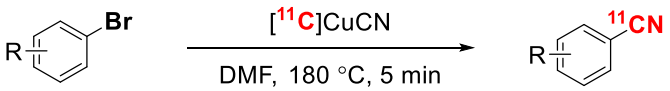
There are currently two major methods for the [^{11}C]cyanation of aromatic and heteroaromatic substrates. The first uses aryl halide precursors in combination with a Pd catalyst to engage [^{11}C]cyanide in aryl–CN cross coupling (Scheme 3.2).[8–11] These reactions often provide high yields, exhibit broad scope, and proceed under mild conditions. However, Pd is relatively toxic, having a PDE of 10 µg/day in parenteral drugs, considerably lower than Cu (PDE = 340 µg/day) or Sn (PDE = 640 µg/day).[12] Due to the very low PDE for Pd, more time and specialized equipment is needed to ensure residual Pd levels in radiotracer doses are below the allowable limit. Furthermore, the Pd-aryl intermediates and phosphine ligands required for these reactions are often not air stable,[9,11] which needs to be accounted for in radiotracer synthesis. For example, to prevent loss in RCY due to oxidation, Pd is commonly added at the last possible moment.[9] However, this is not possible when working with multi-Curie production scale levels of ^{11}C in automated synthesis modules which are set up prior to delivery of ^{11}C to the hot-cell.

Scheme 3.2. [^{11}C]-Cyanation Using Biaryl Phosphine Pd(0) Complexes[11]



The other major [^{11}C]radiocyanation method involves the reaction of aryl halides with [^{11}C]CuCN (*e.g.*, the Rosenmund-von Braun reaction).[13–15] This transformation offers the advantages of operational simplicity (*e.g.,* no phosphine ligands, no requirement to pre-form organometallic intermediates, no need to remove palladium) and the relatively low toxicity of Cu.[12] However, it suffers from low yields, modest scope, and forcing reaction conditions, often requiring temperatures of 150–250 °C (Scheme 3.3).[4] This Chapter describes the development of an alternative Cu-mediated [^{11}C]radiocyanation that leverages the advantages, while addressing the limitations of the existing Cu method.

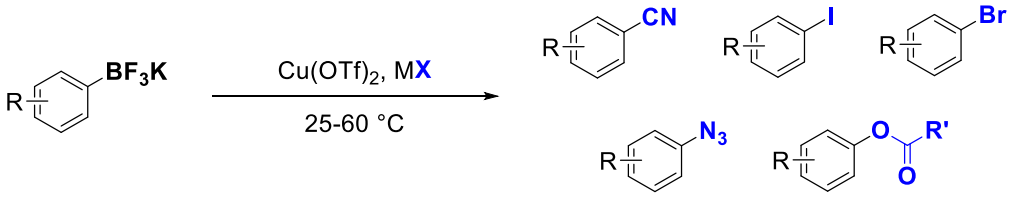
Scheme 3.3. [^{11}C]Cyanation Using [^{11}C]CuCN[15]



3.2. Initial Studies and Optimization with [^{12}C]KCN

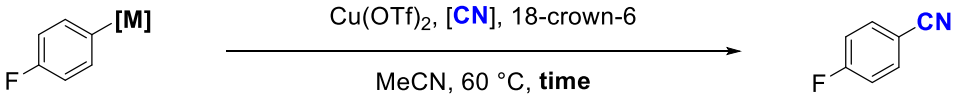
Our group has shown aryl trifluoroborates were competent substrates for diverse Cu-mediated functionalization with a variety of nucleophiles including cyanide, halides, azide, carboxylates, and sulfonates.[16,17] The fluorination conditions (4 equiv of $Cu(OTf)_2$ and 4 equiv of KF in MeCN at 60 °C for 20 h)[18] were modified for other nucleophiles, which should proceed via a similar mechanism (Scheme 3.4).

Scheme 3.4. Copper-Mediated Functionalization of Aryl Trifluoroborates



Preliminary results show that aryl trifluoroborates form 22% of the desired product under similar conditions to the previously describe fluorination conditions (4 equiv of $Cu(OTf)_2$ and 4 equiv of KCN in MeCN at 60 °C for 20 h, (Table 3.1, entry 1).[16,17] Arylstannanes gave similar yields to the aryltrifluoroborate substrate, but these reactions required a shorter time (Table 3.1, entries 2-5), which is highly desirable for radiolabeling. Methods to generate [^{11}C]KCN were known, so further optimizations revolved around using KCN.

Table 3.1. Initial Attempts in MeCN

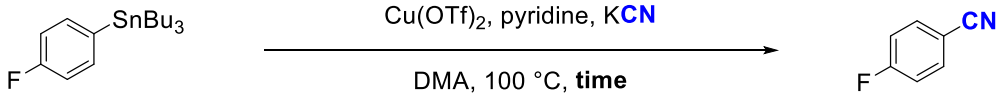


entry	[M]	[CN]	18-crown-6	time (h)	yield (%)
1	BF_3K	KCN	--	20	22
2	$SnBu_3$	KCN	--	2	14
3	$SnBu_3$	TBACN	--	2	21
4	$SnBu_3$	KCN	✓	2	14
5	$SnBu_3$	TBACN	✓	2	15

Conditions: substrate (25 µmol), $Cu(OTf)_2$ (4 equiv), [CN] (4 equiv), and 18-crown-6 (4 equiv), in MeCN (0.083 M) at 60 ºC for the indicated time. Yield was determined by ^{19}F NMR spectroscopy with 1,2-difluorobenzene as an internal standard.

Changing from the MeCN conditions above to modified [^{18}F]radiofluorination conditions (2 equiv $Cu(OTf)_2$, 15 equiv pyridine, 4 equiv KF in DMA at 110 °C for 2 h)[19] gave an increase in yield. Using a slight excess of KCN did not increase the yield of product over two hours (Table 3.2, entries 1-3). A similar result is observed when 1 equiv of KCN was used (Table 3.2, entry 4), confirming that this transformation is fast and does not require an excess of KCN.

Table 3.2. Initial Attempts in DMA



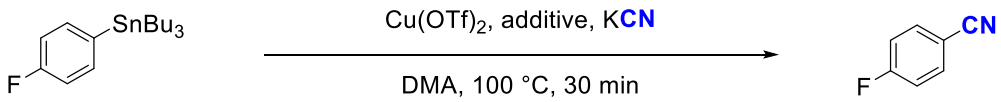
Entry	KCN (equiv)	time (h)	yield (%)
1	2	0.5	35
2	2	1	38
3	2	2	36
4	1	1	36

Conditions: arylstannane (10 µmol), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and KCN (X equiv) in DMA (10 mM) at 100 ºC for the indicated time. Yield was determined by ^{19}F NMR spectroscopy with 1,2-difluorobenzene as an internal standard.

A time study showed that the reaction stalls after 15 min (Table 3.3, entries 1-2). Increasing the temperature increased the yield up to 47% (Table 3.3, entry 3). However, to save time with [^{11}C]CN ($t_{1/2}$ = 20 min), 100 °C was chosen as the temperature to save time heating the reaction vessel (the system requires ~1 min per 50 °C). Several other copper sources were shown to be competent for this transformation (Table 3.3, entries 4-5). The reaction was found to give desired product without pyridine, but adding pyridine to the reaction increased the yield (Table 3.3, entry 6). Other additives/bases either had no effect or gave a slight increase in yield over the control without additives (Table 3.3,

entry 7). Using a crown ether increased the yield slightly (Table 3.3, entry 8). Finally, using DMF, rather than DMA, as a solvent also gave a small boost in yield (Table 3.3, entry 9).

Table 3.3. Optimization Results with KCN

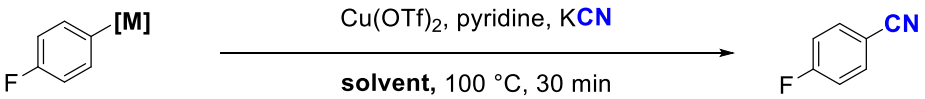


entry	[Cu]	additive	yield (%)
1[a]	$Cu(OTf)_2$	pyridine	40
2	$Cu(OTf)_2$	pyridine	41
3[b]	$Cu(OTf)_2$	pyridine	47
4	$Cu(BF_4)_2$ $6H_2O$	pyridine	39
5	$(MeCN)_4Cu(BF_4)$	pyridine	18
6	$Cu(OTf)_2$	--	17
7	$Cu(OTf)_2$	2,6-lutidine	21
8	$Cu(OTf)_2$	pyridine, 18-c-6	42
9[c]	$Cu(OTf)_2$	pyridine	52

Conditions: arylstannane (10 µmol), $Cu(OTf)_2$ (2 equiv), additive (15 equiv), and KCN (2 equiv) in DMA (10 mM) at 100 ºC for the indicated time. Yield was determined by ^{19}F NMR spectroscopy with 1,2-difluorobenzene as an internal standard. [a]Reaction time: 15 min. [b]Reaction temperature: 120 °C. [c]Solvent: DMF

A small substrate scope was used to analyze the effects of DMA versus DMF as the solvent. While DMF was a better solvent for the arylstannane precursor (Table 3.4, entry 1), DMA gave higher yields for the boronate derivatives (Table 3.4, entries 2-4). The boronate ester only reacted to form the desired product in a modest yield. However, the yield with the boronate ester could be increased to 41% by the addition of KF. This additive likely promotes transmetalation via the formation of a borate intermediate. The effect of water in the reaction was analyzed and it was found that small amounts of water were tolerated in this reaction (Table 3.4, entry 7).

Table 3.4. Comparison of Substrates in DMF and DMA



entry	[M]	additive	yield (%)
1	$SnBu_3$	--	44 (52)
2	$B(OH)_2$	--	65 (62)
3	BF_3K	--	61 (59)
4	Bpin	--	15 (12)
5	Bpin	KF (1 equiv)	41
6	Bpin	KF (2 equiv)	40
7	$SnBu_3$	DMA/H_2O (9:1)	45

Conditions: substrate (10 µmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and KCN (2 equiv) in DMA at 100 ºC for 30 min. Yields in parenthesis were performed in DMF. Yield was determined by ^{19}F NMR spectroscopy with 1,2-difluorobenzene as an internal standard.

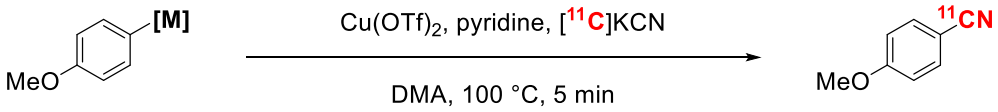
3.3. Initial Studies and Optimization with [^{11}C]KCN

After preliminary studies with KCN, the optimal conditions were translated to [^{11}C]KCN. Starting with analogous conditions to the previously reported [^{18}F]KF conditions (2 equiv $Cu(OTf)_2$, 15 equiv pyridine in DMA at 100 °C for 5 min) provided the desired product in 42% RCC as determined by radio-TLC, with identity confirmed by radio-HPLC (Table 3.5, entry 1). Subsequent studies revealed that anhydrous conditions (which were essential for the analogous [^{18}F]radiofluorination with [^{18}F]KF) are not necessary for [^{11}C]radiocyanation. For example, a comparable 41% RCC was obtained upon the addition of exogenous water (0.2 mL, 17% v/v) to the anhydrous [^{11}C]KCN reaction mixture (Table 3.5, entry 2). Furthermore, an even higher yield (66% RCC, Table 3.5, entry 3) was observed when the [^{11}C]KCN was prepared and used directly as an aqueous solution. Importantly, this modification decreased the overall synthesis time by 4 min (approximately 20% of the ^{11}C half-life). The improved RCC under these conditions is likely due to increased solubility of [^{11}C]KCN.

Analogous to the KCN conditions, using DMF as a solvent gave lower RCC (Table 3.5, entry 4) and the boron derivatives gave a higher conversion than the arylstannane (Table 3.5, entries 5-7). Interestingly, the aryl pinacol borane substrate gave comparable

yields and did not require activating KF, likely due to the decreased amount of KCN available in the reactions. Other optimization did not lead to an increase in RCC. Notably, while this work was underway, the team of Hooker, Vasdev, and Liang published a related method for the Cu-mediated [^{11}C]cyanation of arylboronic acids (for more discussion, see Section 3.8).[20]

Table 3.5. Optimization with [^{11}C]KCN



entry	[M]	[^{11}C]KCN conditions	RCC (%)
1	$SnBu_3$	anhydrous in DMA	42
2	$SnBu_3$	anhydrous in DMA, H_2O[a]	41
3	$SnBu_3$	[^{11}C]KCN in H_2O	66
4[b]	$SnBu_3$	[^{11}C]KCN in H_2O	48
5	$B(OH)_2$	[^{11}C]KCN in H_2O	79
6	BF_3K	[^{11}C]KCN in H_2O	93
7	Bpin	[^{11}C]KCN in H_2O	76

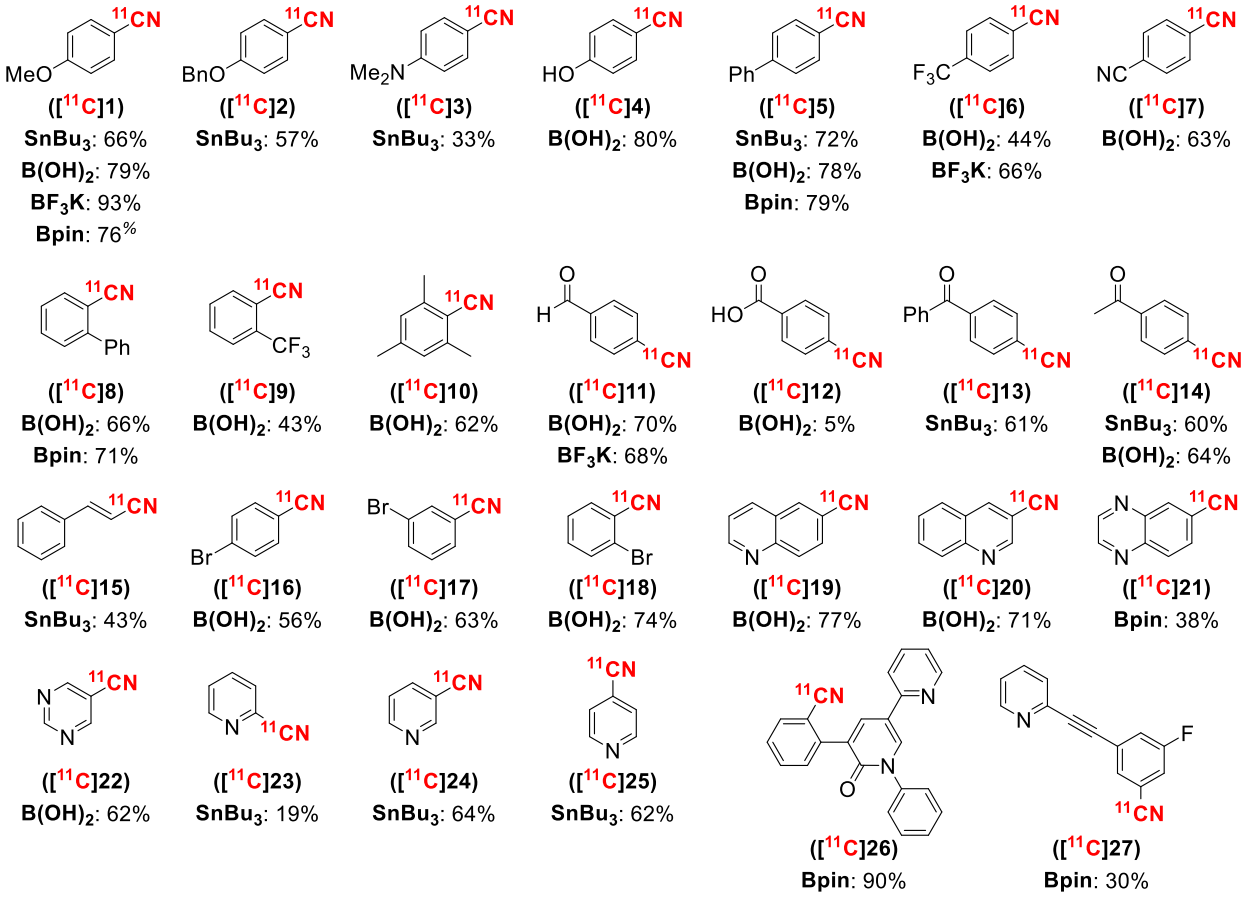
Conditions: **2-[M]** (10 μmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and [^{11}C]KCN in DMA (1 mL, 10 mM) at 100 °C, 5 min. Reported values indicate RCC determined by radio-TLC (n ≥ 2). [a]H_2O (0.2 mL, 17% v/v). [b]Reaction solvent: DMF.

3.4. Substrate Scope

The scope of this transformation was evaluated using a variety of organoboron and organostannane substrates (denoted by the footnotes in Figure 3.1). These studies show that electron-donating (**[^{11}C]1-4**), -neutral (**[^{11}C]5**), and -withdrawing (**[^{11}C]6-7**) substituents on the aromatic ring are all well-tolerated. *Ortho*-substituted substrates undergo [^{11}C]radiocyanation in comparable yields to their unsubstituted counterparts (compare **[^{11}C]8-10**).[20] In addition, carbonyl-containing groups (**[^{11}C]11-14**) are compatible with the reaction conditions, but minimal uncharacterized side products were observed by radio-HPLC. All of these side products were formed in small amounts and could be easily separated from the desired product. Significantly, precursors containing unprotected benzoic acid (**[^{11}C]12**) and phenol (**[^{11}C]4**) substituents also afford modest to excellent yields. Aryl bromides are tolerated at various sites around the phenyl ring

(**[^{11}C]16-18**), and these could serve as handles for further elaboration of the products. Pyridine derivatives and related nitrogen heterocycles also undergo [^{11}C]radiocyanation in moderate to high yields (**[^{11}C]19-25**). Finally, it is noteworthy that a number of the products in Figure 3.1 have not been labeled with [^{11}C]CN before, including **[^{11}C]3-[^{11}C]4**, **[^{11}C]6**, **[^{11}C]8-[^{11}C]9**, **[^{11}C]12**, **[^{11}C]14-[^{11}C]15**, **[^{11}C]17-[^{11}C]19**, **[^{11}C]22**, **[^{11}C]25**, and **[^{11}C]27**.

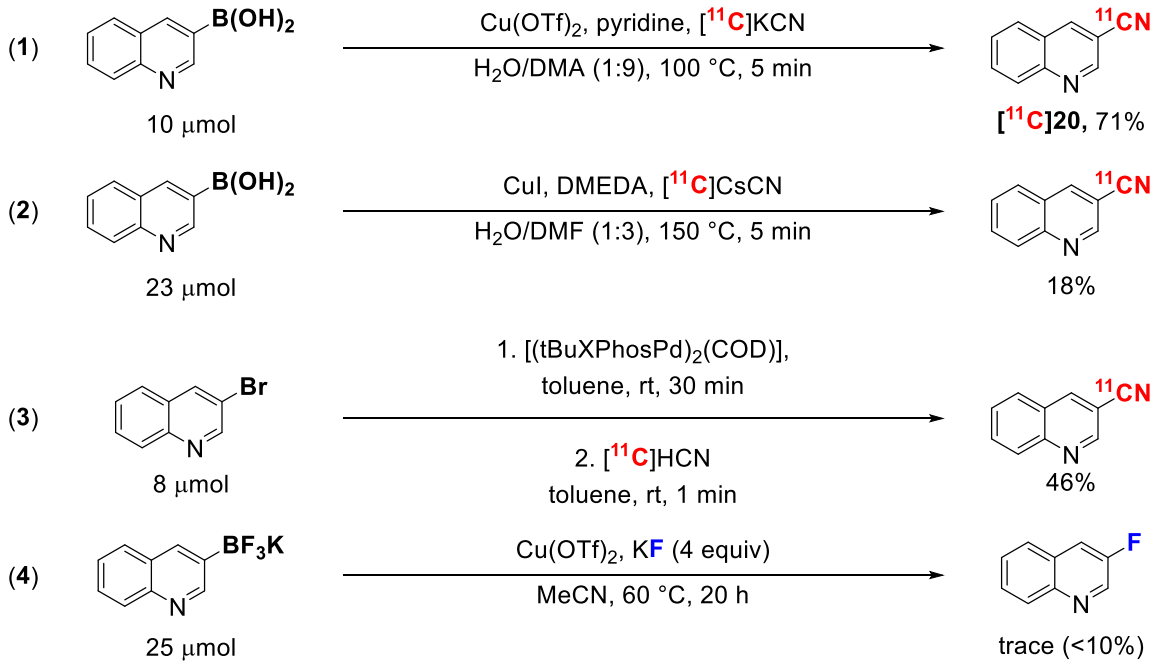
Figure 3.1. Substrate Scope



Reported values indicate RCC determined by radio-TLC (n ≥ 2). General conditions: substrate (10 μmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and [^{11}C]KCN (in H_2O) in DMA (10 mM) at 100 °C for 5 min.

Overall, the scope of this transformation is broader, and many of the RCCs are higher than those of previously reported methods for the [^{11}C]radiocyanation of aromatic substrates.[11,20] As an example, this method affords quinoline product **[^{11}C]20** in 71% RCC from **20-B(OH)$_2$** (Scheme 3.5, reaction 1), while recently reported Cu-catalyzed [^{11}C]radiocyanation conditions provide 18% RCC for the same substrate (Scheme 3.5, reaction 2),[20] and a Pd-catalyzed method affords 46% RCC from the analogous aryl bromide (Scheme 3.5, reaction 3).[11] Notably, subjecting **20-B(OH)$_2$** to the related Cu-mediated fluorination affords only trace amounts of product (<10% ^{19}F NMR yield, Scheme 3.5, reaction 4),[17] demonstrating that this cyanation reaction also has an improved scope relative to fluorination.

Scheme 3.5. Comparison of **[^{11}C]20** via Recent Methodologies



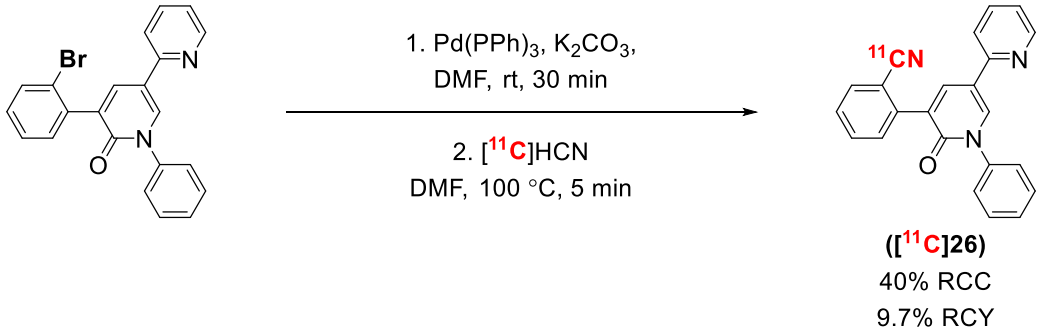
3.5. Automation of [^{11}C]Perampanel[A]

As a final demonstration of this method, the automation of [^{11}C]perampanel was pursued. Perampanel, an FDA-approved drug for epilepsy, has been [^{11}C]radiolabeled once before using a Pd-catalyzed method with an aryl bromide precursor to afford **[^{11}C]26**

[A]Automation was performed with the assistance of Dr. Allen Brooks and Dr. Xia Shao.

in 40% RCC (manual, radio-TLC) and 9.7% RCY (isolated, non-decay corrected), (Scheme 3.6).[11]

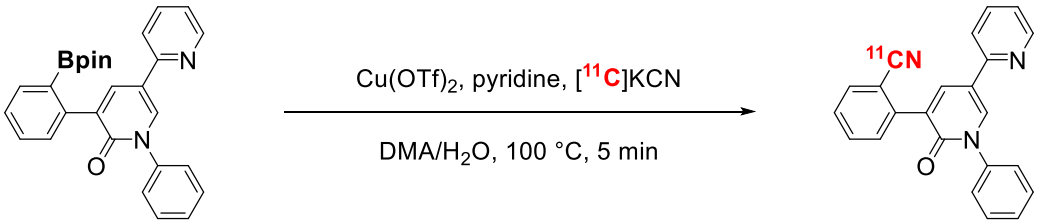
Scheme 3.6. Pd-Catalyzed [^{11}C]Cyanation of Perampanel[11]



([^{11}C]26)
40% RCC
9.7% RCY

Our manual method provided 90% RCC of **[^{11}C]26** from the arylboronate ester using approximately 1 mCi of [^{11}C]KCN per reaction. The synthesis was scaled to 450 mCi of [^{11}C]KCN, and the [^{11}C]radiocyanation and subsequent HPLC purification of **[^{11}C]26** were conducted using an automated radiosynthesis module. Without further optimization, this procedure afforded **[^{11}C]26** in 10.4% non-decay corrected RCY (Scheme 3.7). The fully automated synthesis lasted approximately 32 min from the end of bombardment.

Scheme 3.7. Automation of [^{11}C]Perampanel



26-Bpin

[^{11}C]26
RCY, NDC: 10.4%
RCY, DC: 29%
SA: 1860 Ci/mmol

General conditions: **26-Bpin** (10 µmol, 1 equiv), $Cu(OTf)_2$ (2 equiv), pyridine (15 equiv), and [^{11}C]KCN (in H_2O) in DMA at 100 °C for 5 min. RCY determined by isolated material

after preparative-HPLC. QC was performed to confirm the correct product was formed and purify was >95%.

3.6. Automation of [^{11}C]LY2795050[B]

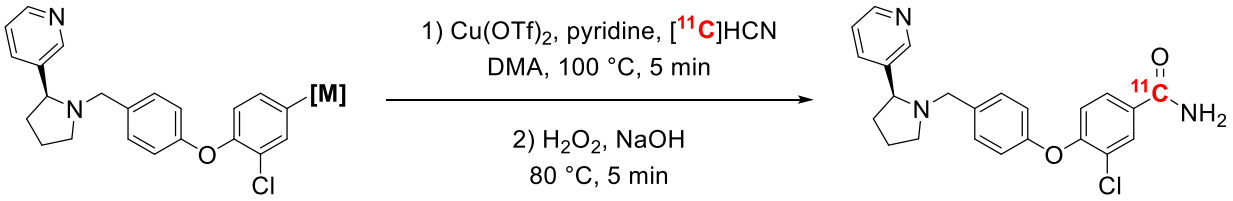
Opioid receptors are involved in a variety of neuropsychiatric diseases, and remain popular targets for imaging and drug development.[21] These receptors were first imaged in humans using PET in the 1980s. Since these early studies, significant work has been undertaken to develop radiotracers for quantifying the major opioid receptor subtypes (mu, delta, kappa, ORL-1).[22] Given that popular opioid pain killers, such as morphine, codeine and fentanyl, all act preferentially at MORs,[23,24] significant work has been undertaken to understand the pharmacology of this receptor. [^{11}C]CFN has been used for decades to image the mu opioid system.[25]

While mu opioid agonists are some of the most effective pain killers used in modern medicine,[26] they have been heavily abused, leading to a serious crisis in the US.[27] This crisis has led a strong motivation to develop opioid painkillers that have fewer side effects, such as dependence. One approach for improvement is to develop drugs (and PET radiotracers) that target the other opioid subtypes.[28] The KOR structure has been recently revealed,[29] and this is expected to spur development of new drugs for this target.[30] Reflecting this, there is a desire to access to a KOR-selective PET radiotracer manufactured according to cGMP and suitable for clinical use.

The method described in this chapter was modified for a clinical preparation of [^{11}C]LY2795050, a promising KOR antagonist.[2,31] During the course of the study, it was found that [^{11}C]HCN could be used instead of [^{11}C]KCN. As with **[^{11}C]2**, **28-Bpin** provided higher RCCs than **28-SnMe$_3$** (Scheme 3.8).

[B] Automation was performed by Dr. Xia Shao and Lingyun Yang

Scheme 3.8. Radiosynthesis of [^{11}C]LY2795050

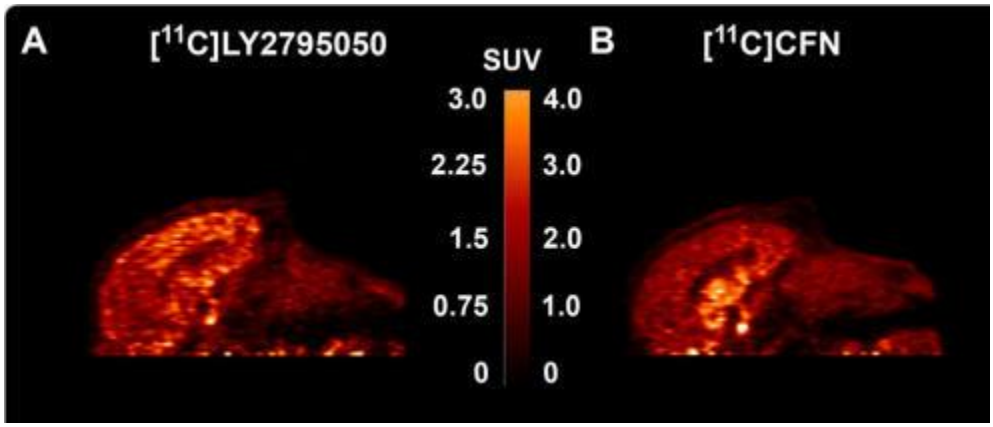


28-[M]

[^{11}C]LY2795050 ([^{11}C]28)
28-Bpin: 50%
28-SnMe$_3$: 31%

Using the copper-mediated [^{11}C]cyanation developed in this chapter to produce a clinical scale of [^{11}C]LY2795050, further animal studies were performed including rodent and non-human primate studies (Figure 3.2). Comparison with [^{11}C]CFN imaging of MOR identified regional brain distribution differences consistent with the known distribution of opioid receptors in primates. Preparation is ongoing to prepare for a clinical trial.

Figure 3.2. Primate PET images of [^{11}C[LY2795050 (A) and [^{11}C]CFN (B)[2]



3.7. Conclusion

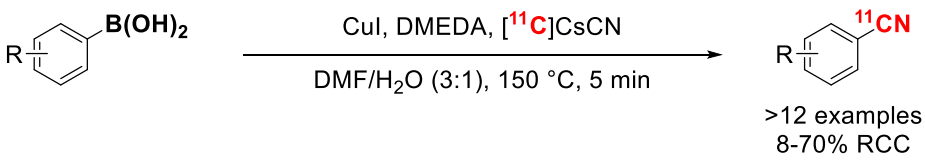
In conclusion, this chapter describes a Cu-mediated [^{11}C]radiocyanation of diverse aryl organometallic reagents. This method is compatible with a wide range of substrates, including those containing carboxylic acids, phenols, aldehydes, and heterocycles. This method is also amenable to automation on a clinically relevant scale, as demonstrated in the synthesis of [^{11}C]perampanel and further applied to [^{11}C]LY2795050. The automation of [^{11}C]LY2795050, represents the first validation of the Cu-mediated cyanation of pinacol borane esters for the cGMP synthesis of a PET radiotracer for preclinical and clinical

applications. The synthesis of [^{11}C]LY2795050, a PET radiotracer for the KOR, was fully automated using a commercial radiochemistry synthesis module. Doses met all QC criteria for preclinical and clinical use and were used to image rodents and nonhuman primates.

3.8. Outlook

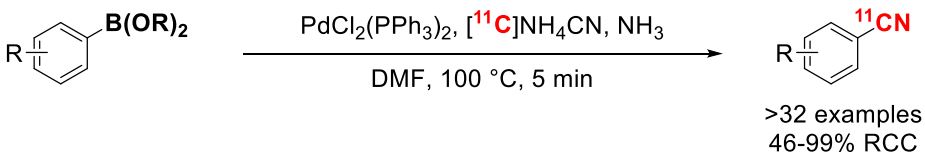
Concomitant with this report, Vasdev and coworkers reported a similar system for [^{11}C]aryl cyanation.[20] The combination of arylboronic acids, CuI, and base in a DMF/H_2O mixture yielded moderate RCCs (Scheme 3.9). Additionally, the automation of anisole was reported with a low RCY of 4% (non-decay corrected).

Scheme 3.9. Cu-Mediated [^{11}C]Cyanation Method Developed by Vasdev and Coworkers[20]



Since this report on the Cu(OTf)$_2$-mediated cyanation of aryl organometallic reagents,[1] a palladium method utilizing arylboron derivatives was also published.[32] The reaction was first studied with copper, but homocoupling was a major side product under the conditions examined. The optimal conditions used a bench-stable Pd(II) catalyst (Scheme 3.10). This method was used to automate and isolate PET tracers in good RCY. One limitation of this method is that it uses a relativity large amount of the starting precursor (20 µmol, as opposed to the <10 µmol that is commonly used).

Scheme 3.10. Pd-Catalyzed [^{11}C]Cyanation Method Developed by Zhang and Coworkers



3.9. Experimental Details

3.9.1. Instrumental Information

NMR spectra were obtained on a Varian vnmrs700 (699.76 MHz for 1H; 175.95 MHz for ^{13}C), a Varian vnmr500 (500.09 MHz for 1H; 470.56 MHz for ^{19}F; 125.75 MHz for ^{13}C), or a Varian MR400 (400.53 MHz for 1H; 376.87 MHz for ^{19}F) spectrometer. All ^{13}C NMR data presented are proton-decoupled ^{13}C NMR spectra, unless noted otherwise. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to TMS with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced based on the internal standard 1,2-difluorobenzene, which appears at –140.53 ppm. ^{1}H and ^{19}F NMR multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Melting point data (mp) were collected on an OptiMelt Automated Melting Point System and are uncorrected. HPLC was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analyses were performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

3.9.2. Materials and Methods

Unless otherwise stated, reagents and solvents were commercially available and used without further purification. Arylstannane and arylboronic acid precursors were purchased from Frontier Scientific, Oakwood Products, Acros Organics, Synthonix, and Sigma Aldrich or synthesized in the following sections. Arylnitrile reference standards were sourced commercially. 3-Bromo-1-phenyl-5-(pyridine-2-yl)-1,2-dihydropyridin-2-one (CAS 381248-06-2) was purchased from Key Organics and used as received. Perampanel (CAS 380917-97-5) was purchased from AChemBlock. HPLC-grade acetonitrile, anhydrous DMF, anhydrous DMA, potassium trifluoromethanesulfonate, and potassium carbonate were purchased from Fisher Scientific. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 90 mg/mL potassium trifluoromethanesulfonate solution, and finally 10 mL of sterile water prior to use. Sodium chloride, 0.9% USP and sterile water for Injection, USP were purchased from Hospira; Dehydrated Alcohol for Injection, USP was obtained from Akorn

Inc.; Ammonium acetate and acetic acid (glacial) were obtained from Fisher Scientific; HPLC columns were acquired from Phenomenex. Other synthesis components were obtained as follows: sterile filters were acquired from Millipore; C18 Vac 1cc Sep-Paks were purchased from Waters Corporation; Sep-Paks were flushed with 5 mL of ethanol followed by 10 mL of sterile water prior to use.

3.9.3. General Procedures for Synthesis and Characterization of Substrates

General Procedure A: Preparation of Trialkylarylstannane Substrates

General procedure A was adapted from the literature.[19,33,34] In a nitrogen atmosphere glovebox, a 20 mL vial was charged with aryl iodide or aryl bromide (1 mmol), $Pd(PPh_3)_4$ (0.1–0.25 mmol), and lithium chloride (4.8 mmol). The combined solids were dissolved in toluene (12.5 mL, 0.08 M) at room temperature. Hexabutylditin (2.6 mL, 5.2 mmol) or hexamethylditin (1.1 mL, 5.2 mmol) was added via syringe, and the vial was sealed and removed from the glovebox. The sealed vial was heated at 100 ºC. Once the reaction mixture turned black (generally 2–4 h), it was cooled to room temperature. Aqueous potassium fluoride (5.0 mL, 2 M solution) was added, and the mixture was stirred vigorously. After 30 min, the mixture was filtered through a plug of Celite (eluting with hexanes or toluene). The filtrate was washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified via flash column chromatography.

General Procedure B: Preparation of Arylboronic Acid Substrates

General procedure B was adapted from the literature.[35] *n*-BuLi (1.2 equiv, 2.48 M in hexane) was added dropwise to a solution of the aryl bromide (1 equiv) in anhydrous THF (0.1 M) at –78 ºC under a nitrogen atmosphere in an oven-dried 20 mL vial. The reaction was then stirred at –78 ºC for ~1 h. An excess of $B(OMe)_3$ (10 equiv) was added slowly under a nitrogen atmosphere via syringe. The resulting solution was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched with distilled water and acidified with HCl (1 M solution, pH <3), and the product was extracted into EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum.

3.9.4. General Procedure for Copper-Mediated Fluorination

Stock solutions of the aryl organometallic substrate (0.1 mL, 0.1 M solution, 10 μmol, 1 equiv), $Cu(OTf)_2$ (20 μmol, 2 equiv), pyridine (0.15 mL, 1.0 M solution,150 μmol, 15 equiv), and KCN (1.5 mg, 20 μmol, 2 equiv) were added to a 4 mL vial and diluted with DMA (to 1.0 mL total volume). The vial was sealed with a Teflon-lined cap and the reaction mixture was stirred at 100 ºC for 30 min. The resulting solution was cooled to room temperature, 1,2-difluorobenzene was added as an internal standard, and the crude reaction was analyzed by ^{19}F NMR spectroscopy.

Experimental Details for the Radiosynthesis of [^{11}C]LY2795050.

No carrier added [^{11}C]HCN was bubbled into a mixture of pyridine (15 equiv) in DMA (0.25 mL) and H_2O (0.05 mL) directly. $Cu(OTf)_2$ (4 equiv) was added followed by **28-Bpin** or **28-SnMe$_3$** (1 equiv) and the reaction was heated at 100 °C for 5 min to generate cyano intermediate. The reaction mixture was cooled down to 5 °C and hydrolysis with 30% H_2O_2 (0.2 mL) and 5.0 M NaOH (0.2 mL) at 80 °C for 5 min to generate **[^{11}C]LY2795050 [^{11}C]28**). The reaction mixture was quenched with HPLC buffer and analyzed by radio-HPLC (Phenomenex Luna C18(2), 150 x 4.6 mm, 20:80 MeCN:H_2O, 10 mM NH_4OAc, 0.2% acetic acid, pH = 4.5, flow rate = 2.0 mL/min, UV = 254 nm) to determine RCC.

3.9.5. Synthesis of [^{11}C]HCN

A GE Medical Systems PETtrace cyclotron (40 μA for 30 min) was used to produce [^{11}C]CO_2 by the $^{14}N(p,\alpha)^{11}C$ reaction. [^{11}C]HCN was synthesized from [^{11}C]carbon dioxide by “gas phase” method utilizing a GE PETtrace Carbon-11 Process Panel as previously reported.[6] Briefly, [^{11}C]CO_2 (3,000 mCi) from the target was trapped on molecular sieves at room temperature. The [^{11}C]CO_2 was released and mixed with hydrogen gas at 350 ºC then passed through a preheated nickel oven at 420 ºC for conversion to [^{11}C]CH_4. The [^{11}C]CH_4 gas was purified by passing it through Ascarite and Sicapent columns to remove water and unreacted [^{11}C]CO_2. The [^{11}C]CH_4 was mixed with anhydrous ammonia and passed through a high temperature (950 ºC) platinum oven, resulting in the formation of [^{11}C]HCN (non-decay corrected radiochemical yields of ~800 mCi starting from 3000 mCi of [^{11}C]CO_2).

3.9.6. Synthesis of [^{11}C]KCN[6]

Modifications were made to a commercial GE TRACERLab FX_M. Two electronic valves were installed in the front of the chemistry module to direct [^{11}C]HCN from the GE process panel to the FX_M. V30 and V31 were removed from the HPLC pump and connected to a system to capture the [^{11}C]HCN from the process panel. The system consists of a helically shaped platinum wire in a Teflon tube inserted between V30 and V31. To capture and purify [^{11}C]HCN (removal of excess NH_3), the helical platinum wire was treated with 0.2 mL of a 1 M solution of KOH followed by 2 mL of dry air. The [^{11}C]HCN was trapped on the platinum wire, and then the flow was switched from the process panel to N_2, which removed the ammonia. This purification was carried out because it was hypothesized that residual NH_3 could have a negative effect on the reaction conditions. The [^{11}C]CN was then eluted as [^{11}C]KCN by directing the three way valve from waste to the reactor and eluting with H_2O.

3.9.7. Synthesis of ^{11}CN-Labeled Molecules (Manual Synthesis)

Unless otherwise noted, this procedure was used for all [^{11}C]cyanation reactions. Stock solutions of precursor (0.1 M), $Cu(OTf)_2$ (0.2 M) and pyridine (1.0 M) in DMA were prepared immediately prior to the start of the reaction. Aliquots of these solutions were used to carry out subsequent [^{11}C]cyanation reactions. Reactions were typically set up in the following order: $Cu(OTf)_2$ (0.1 mL, 20 μmol, 2 equiv) and pyridine (0.15 mL, 0.15 mmol, 15 equiv) were mixed in a 4 mL vial at room temperature. The resulting solution was diluted with DMA (0.55 mL, 1.0 mL total volume) and then charged with substrate (0.1 mL, 0.01 mmol, 1 equiv). The reaction vial was sealed under an atmosphere of ambient air with a PTFE/Silicone septum cap, and a 0.1 mL aliquot of [^{11}C]KCN (150–3000 μCi, depending on the time required for HPLC analysis) was added to the reaction vial through the septum via a syringe. The vial was heated in an aluminum block without stirring at 100 ºC for 5 min and then immediately cooled to room temperature. Radio-TLC analysis was conducted to determine the radiochemical conversion (% RCC). The crude reaction mixture was spotted onto a standard silica-coated glass plate and the TLC was conducted using 1:1 hexane/EtOAc or 100% EtOAc as the eluant. The RCC was then

determined by dividing the integrated area under the cyanated product spot by the total integrated area of the carbon-11 on the TLC plate. To prepare samples for HPLC analysis: 0.1 mL of the reaction mixture (or for the co-injection analysis 0.1 mL of the reaction mixture spiked with 0.1 mL of 1 mg/mL cyanation authentic standard solution) were transferred to an HPLC autosampler vial. Eluent systems and columns used for HPLC analysis are described below.

RCC = integration of ^{11}C product peak / sum of integration of all ^{11}C peaks

3.9.8. General Procedure/Methods for Automated Syntheses

All loading operations were conducted under an ambient atmosphere. Nitrogen was used as a pressurizing gas during automated sample transfers. [^{11}C]Cyanide was produced via the ^{14}N(p,α)^{11}C nuclear reaction using a GE PETTrace cyclotron and process panel. [^{11}C]KCN was produced as indicated above. A solution containing precursor (0.1 mL, 0.1 M stock, 10 µmol, 1 equiv) in 0.4 mL of anhydrous DMA was prepared in vial 2. $Cu(OTf)_2$ (0.1 mL, 0.2 M stock, 20 µmol, 2 equiv) and pyridine (0.15 mL, 1.0 M stock, 150 µmol, 15 equiv) in 0.25 mL of DMA was mixed in the reaction vessel. H_2O (0.2 mL in vial 1) was used to wash the [^{11}C]KCN into the reaction vessel containing the catalyst solution. After vial 2 was added, the mixture was heated at 100 ºC for 4 min (it took approximately 1 min to heat to 100 ºC). After 4 min, the reaction was cooled to 40 ºC and vial 4 containing 0.5 mL of buffer was added. The mixture was then transferred to an HPLC loop for injection and purification by semi-preparative chromatography (Phenomenex Luna C18, 250 x 10 mm, 10µ, 4 mL/min). The product peak (retention time ~12 min) was collected and transferred out of the hot cell. Time from EOB ~30–32 min.

Specific Activity Calculation. An aliquot of the purified sample was injected onto an analytical HPLC. The UV peak corresponding to the [^{11}C]radionitrile product was determined by overlaying the UV and RAD traces (with a 0.2 min offset as described in the HPLC section). The UV area was then used to calculate the concentration of the product based on linear regression analysis of appropriate arylnitrile standards. A standard curve was generated from the standard solutions, each performed in duplicate

(0.0001 mg/mL to 1.0 mg/mL). This provided the concentration of the product in mmol/mL. Dividing the activity concentration (Ci/mL) by the HPLC-derived concentration of product (mmol/mL) provided the specific activity in Ci/mmol. This reflects an EoS specific activity.

Automated Synthesis of [^{11}C]4-methoxybenzonitrile ***([^{11}C]1****)*
Starting material: **1-SnBu$_3$**
Activity Isolated, non-decay corrected: 16 mCi/220 mCi
RCY, non-decay corrected: 7%
RCY, decay corrected: 22%
Specific Activity: 1800 Ci/mmol

*Automated Synthesis of [^{11}C]4-methoxybenzonitrile (****[^{11}C]1****)*
Starting material: **1-B(OH)$_2$**
Activity Isolated, non-decay corrected: 71 mCi/400 mCi
RCY, non-decay corrected: 18%
RCY, decay corrected: 53%
Specific Activity: 4400 Ci/mmol

*Automated Synthesis of [^{11}C]Perampanel (****[^{11}C]26****)*
Starting material: **26-Bpin**
Activity Isolated, non-decay corrected: 46 mCi/450 mCi
RCY, non-decay corrected: 10%
RCY, decay corrected: 29%
Specific Activity: 1900 Ci/mmol

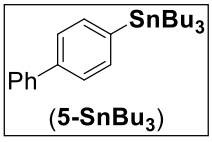
3.9.9. Automated Radiosynthesis of [^{11}C]LY2795050

Pyridine (0.15 mL, 1.0 M DMA stock, 150 μmol, 15 equiv) in 0.1 mL of DMA was mixed in the reactor. No carrier added [^{11}C]HCN was bubbled into the reactor directly. Then Cu(OTf)$_2$ (0.2 mL, 0.2 M DMA stock, 40 μmol, 4 equiv) through V31 and **28-Bpin** (4.9 mg in 0.4 mL DMA, 10 μmol,1 equiv) from vial 1 were added. The reaction was allowed to heat to 100 °C for 5 min. After the temperature was cooled to 5 °C by liquid nitrogen, 30%

H_2O_2 (0.2 mL) in vial 2 and NaOH (5M, aq, 0.2 mL) in vial 3 were added to the reactor. The hydrolysis was performed at 80 °C for 5 min, followed by cooling to 25 °C and quenching with acetic acid (0.4 mL, glacial) in vial 4. The reaction mixture was stirred for 2 min and then injected onto a semi-preparative HPLC column for purification (Phenomenex Prodigy C8, 10 µm, 150 x 10 mm, 25:75 MeCN:H_2O, 100 mM NH_4OAc, 1.0% acetic acid, pH = 4.8, flow rate = 5.0 mL/min, UV = 254 nm). The product peak at ~5–7 minutes was collected into 55 mL of water and passed through a C-18 sep-pak to remove HPLC solvent. The sep-pak was rinsed with 4 mL of USP water and the product was then eluted with 0.5 mL of ethanol followed by 9.5 mL of USP saline for injection. The final dose was filtered into a dose vial via a 0.22 µm sterile filter, then submitted for quality control testing as outlined below. Total synthesis time was approximately 45 min from end of beam. The non-decay radiochemical yield was 48 mCi (6%) based on [^{11}C]HCN with radiochemical purity of >99% and specific activity of 914 mCi/µmol.

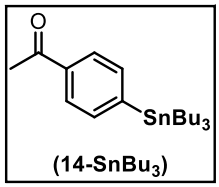
3.10. Synthesis and Characterization

3.10.1. Starting Materials



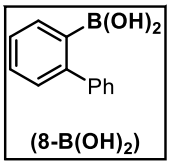
(**5-SnBu$_3$**)

*4-Tributylstannyl-1,1'-biphenyl (**5-SnBu$_3$**).* General procedure A was followed using 4-iodo-1,1'-biphenyl (279.5 mg, 1.0 mmol) and heating for 3 h. Purification by flash column chromatography eluting with hexanes afforded **5-SnBu$_3$** as a colorless oil (191.0 mg, 43% yield, R_f = 0.6 in 100% hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[36] HRMS (EI) $[M - C_4H_9]^+$ Calculated for $C_{20}H_{27}Sn$: 387.1135; Found 387.1135.



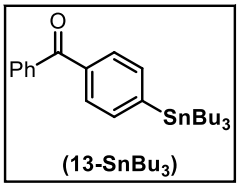
(**14-SnBu$_3$**)

*4-Tributylstannylacetophenone (**14-SnBu$_3$**).* General procedure A was followed using 4-iodoacetophenone (246.3 mg, 1.0 mmol) and heating for 4 h. Purification by flash column chromatography eluting with hexanes afforded **14-SnBu$_3$** as a colorless oil (284.3 mg, 69% yield, R_f = 0.56 in 5% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[36] HRMS (ESI$^+$) $[M+K]^+$ Calculated for $C_{20}H_{34}KOSn$: 449.1263; Found 449.1263.



(8-B(OH)$_2$)

*[1,1'-Biphenyl]-2-ylboronic Acid (**8-B(OH)$_2$**).* 2-Bromobiphenyl (0.25 mL, 1.45 mmol) was dissolved in 15 mL of anhydrous THF (0.1 M), and *n*-BuLi (0.7 mL, 1.75 mmol, 1.2 equiv, 2.48 M in hexane) and then $B(OMe)_3$ (1.6 mL, 14.4 mmol, 10 equiv) were added sequentially according to general procedure B. Triturating the resulting mixture with pentanes and a small amount of EtOAc yielded the desired boronic acid (**8-B(OH)$_2$**) as an off-white solid (220.3 mg, 77% yield, mp = 184–185 ºC). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[35] HRMS (EI) $[M]^+$ Calculated for $C_{12}H_{11}BO_2$: 198.0852; Found 198.0858.



(13-SnBu$_3$)

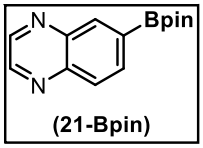
*4-Tributylstannylbenzophenone (**13-SnBu$_3$**)*. In a nitrogen atmosphere glovebox, a 20 mL vial was charged with 4-iodobenzopheone (308.6 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (175.3 mg, 0.25 mmol, 0.25 equiv) and dioxane (12.5 mL, 0.08 M) at room temperature. Hexabutylditin (1.3 mL, 2.6 mmol) was added via syringe and the vial was sealed and removed from the glovebox. The sealed vial was heated at 100 ºC for 4 h. After cooling to room temperature, the reaction mixture was filtered through a silica plug that was washed with EtOAc. The solvent was removed under vacuum, and the crude product was

purified via preparative TLC (5% ethyl acetate in hexanes) affording the product (**13-$SnBu_3$**) as a yellow oil (231.5 mg, 59% yield, R_f = 0.5 in 5% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 7.82 (m, 2H), 7.73 (m, 2H), 7.57–7.63 (multiple peaks, 3H), 7.48 (m, 2H), 1.56 (m, 6H), 1.35 (m, 6H), 1.11 (m, 6H), 0.90 (m, 9H)

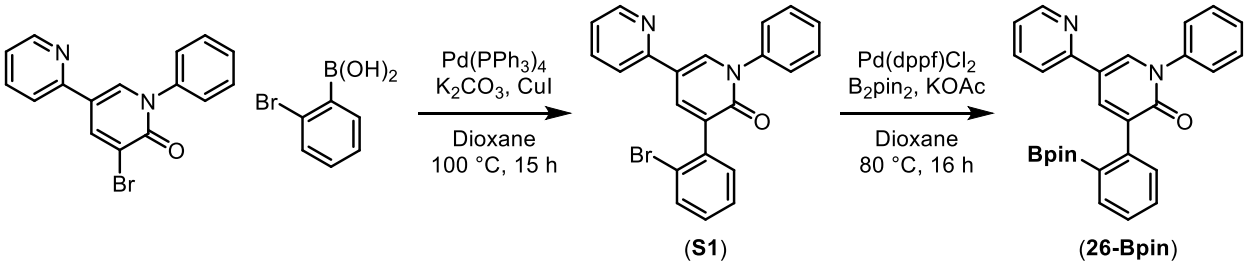
^{13}C NMR ($CDCl_3$): δ 197.05, 149.22, 137.70, 136.92, 136.26, 132.24, 130.04, 128.94, 128.18, 29.04, 27.34, 13.66, 9.66

HRMS (ESI+) $[M+K]^+$ Calculated for $C_{25}H_{36}KOSn$: 511.1420; Found 511.1418

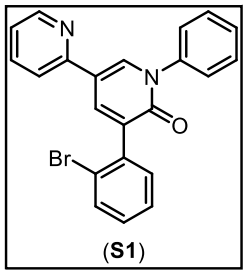


(21-Bpin)

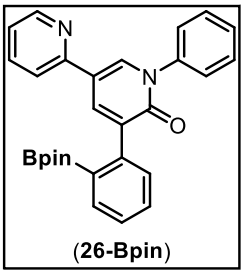
*6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline (**21-Bpin**).* The following procedure was adapted from the literature.[37] In a nitrogen atmosphere glovebox, a 20 mL vial was charged with 6-bromoquinoxaline (419 mg, 2.0 mmol, 1 equiv), Pd(dppf)Cl_2 dichloromethane complex (186.0 mg, 0.23 mmol, 0.11 equiv), KOAc, (394.2 mg, 4.0 mmol, 2.0 equiv), bis(pinacoloato)diboron (612.5 mg, 2.4 mmol, 1.2 equiv) and dioxane (10 mL, 0.2 M). The resulting solution was heated at 90 ºC for 1.5 h. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and filtered through a plug of celite. After removing the CH_2Cl_2 under vacuum, the product was purified by column chromatography (20% ethyl acetate in hexane), affording **21-Bpin** as a yellow oil (103.2 mg, 15% yield, R_f = 0.3 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[37] HRMS (ESI+) $[M+H]^+$ Calculated for $C_{14}H_{18}BN_2O_2$: 257.1456; Found 257.1463.



Perampanel-Bpin (**26-Bpin**) was prepared via the following 2 step procedure that was adapted from the literature.[11,38]



Step 1: Aryl bromide **S1** was prepared via a literature procedure. In a nitrogen-filled glovebox, the pyridine bromide (319.2 mg, 0.98 mmol, 1 equiv), 2-bromophenylboronic acid (1651.6 mg, 8.2 mmol, 8.4 equiv), tetrakis(triphenylphosphine)palladium(0) (180.5 mg, 0.16 mmol, 0.16 equiv), copper(I) iodide (48.9 mg, 0.26 mmol, 0.26 equiv), and potassium carbonate (1653.6 mg, 12.0 mmol, 12.3 equiv) were dissolved in dioxane (6 mL, 0.16 M) at room temperature. This solution was heated at 100 ºC for 15 h with vigorous stirring. The reaction was cooled to room temperature and quenched with water (5 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to afford **S1** as a yellow oil (210.0 mg, 53% yield, R_f = 0.4 in 50% ethyl acetate in hexanes). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[11] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{22}H_{16}BrN_2O$: 403.0441; Found 403.0444.



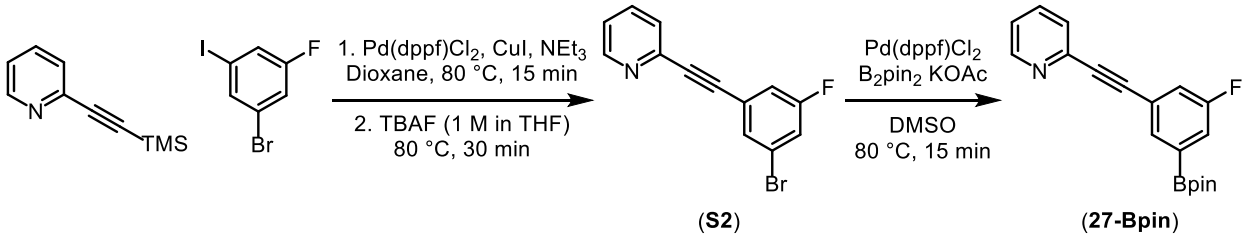
(**26-Bpin**)

Step 2: In a nitrogen-atmosphere glovebox, a suspension of aryl bromide (**S1**, 60.8 mg, 0.15 mmol), Pd(dppf)Cl_2 dichloromethane complex (20.3 mg, 0.02 mmol, 0.16 equiv), KOAc, (372.9 mg, 1.5 mmol, 9.7 equiv), and bis(pinacoloato)diboron (214.8 mg, 2.2 mmol, 14.5 equiv) in dioxane (3.8 mL, 40 mM) was heated at 80 ºC for 16 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and washed with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by column chromatography (20% ethyl acetate in hexane with 1–5% NEt_3) to afford **26-Bpin** as a white solid (31.7 mg, 47% yield, R_f = 0.2 in 70% ethyl acetate in hexanes with 15% NEt_3, melting point: decomposes above 138 ºC).

^{1}H NMR ($CDCl_3$): δ 8.84 (d, *J* = 1.3 Hz, 1H), 8.66 (dt, *J* = 0.8, 2.5, 1H), 8.35 (d, *J* = 1.3 Hz, 1H), 7.80–7.83 (multiple peaks, 3H), 7.72 (d, *J* = 4.6 Hz, 1H), 7.52–7.57 (multiple peaks, 5H), 7.37 (dtd, *J* = 18.0, 7.4, 0.8 Hz, 2H), 7.30 (dd, *J* = 2.5, 9.8 Hz, 1H), 1.11 (s, 12H)

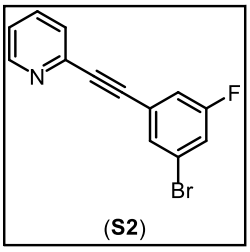
^{13}C NMR ($CDCl_3$): δ 161.1, 152.3, 150.0, 140.4, 137.3, 134.6, 133.7, 133.5, 133.2, 129.6, 129.4, 129.0, 127.9, 127.5, 126.8, 123.4, 123.0, 122.9, 122.8, 119.3, 80.49, 25.89

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{28}H_{28}BN_2O_3$: 451.2187; Found 451.2175



(**S2**) (**27-Bpin**)

PEB-Bpin,F (**27-Bpin**) was prepared by the following 2 step procedure adapted from the literature.[39–41]



(**S2**)

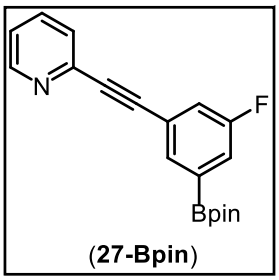
Step 1: In a nitrogen filled glovebox, 2-((trimethylsilyl)ethynyl)pyridine (177.0 mg, 1.01 mmol, 1 equiv), 1-bromo-3-fluoro-5-iodobenzene (316.9 mg, 1.05 mmol, 1 equiv), $Pd(PPh_3)Cl_2$ (87.1 mg, 0.12 mmol, 0.1 equiv), CuI (43.0 mg, 0.23 mmol, 0.2 equiv), and NEt_3 (0.3 mL, 2.2 mmol, 2.1 equiv) were dissolved in dioxane at room temperature. The reaction mixture was heated to 80 ºC under nitrogen for 15 min. TBAF (1 M solution in THF, 1.1 mL, 1.2 mmol, 1.1 equiv) was added dropwise over 10 min via syringe through a septum. The resulting solution was allowed to stir for an additional 30 min at 80 ºC under nitrogen before being cooled to room temperature. The reaction was filtered through a celite plug, concentrated under vacuum, and dissolved in DCM. The organic later was washed with H_2O (2 x 25 mL) and brine, dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purified by column chromatography (5% ethyl acetate in hexanes) to afford **S2** as a yellow oil (182.2 mg, 65% yield, R_f = 0.43 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 8.63 (m, 1H), 7.70 (m, 1H), 7.52–7.54 (multiple peaks, 2H), 7.26–7.29 (multiple peaks, 2H), 7.23 (m, 1H)

^{13}C NMR ($CDCl_3$): δ 162.11, 150.24, 142.57, 136.28, 130.84, 127.38, 125.41, 123.35, 122.44, 119.99, 117.76, 90.45, 86.07

^{19}F NMR ($CDCl_3$): δ –110.46

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{13}H_8BrFN$: 275.9819; Found 275.9821



(**27-Bpin**)

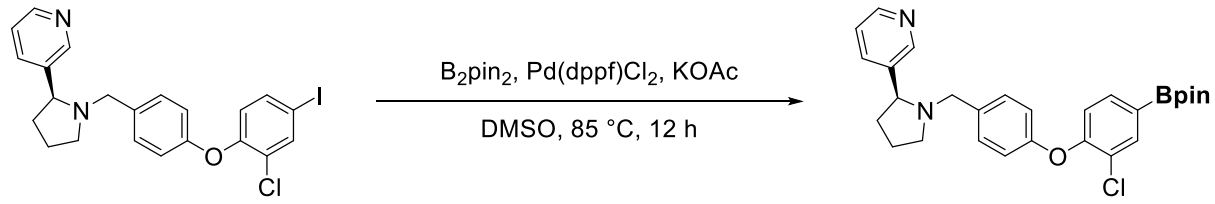
Step 2: In a nitrogen atmosphere glovebox, aryl bromide (**S2**, 430.8 mg, 1.6 mmol), Pd(dppf)Cl_2 dichloromethane complex (179.4 mg, 0.02 mmol, 0.14 equiv), KOAc (459.7 mg, 4.7 mmol, 3.0 equiv), and bis(pinacoloato)diboron (436.3 mg, 1.7 mmol, 1.1 equiv) were suspended in DMSO (8.8 mL, 0.18 M). The reaction mixture was heated at 80 ºC for 15 h. The reaction was allowed to cool to room temperature and quenched with water, and the product was extracted into EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Triturating the resulting mixture with pentanes and a few drops of EtOAc yielded **27-Bpin** as a yellow solid (386.1 mg, 76% yield, R_f = 0.32 in 20% ethyl acetate in hexanes, mp = 77–78 °C).

^{1}H NMR ($CDCl_3$): δ 8.62 (dq, *J* = 4.9, 1.0 Hz, 1H), 7.84 (s, 1H), 7.68 (td, *J* = 7.7, 2.0 Hz, 1H), 7.50 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.35 (dq, *J* = 8.9, 1.3 Hz, 1H), 7.24 (dd, *J* = 4.9 1.3 Hz, 1H), 1.34 (s, 12H)

^{13}C NMR ($CDCl_3$): δ 161.98, 150.11, 143.10, 136.16, 134.38, 127.18, 123.71, 122.93, 121.66, 121.00, 89.27, 87.74, 84.32, 29.68, 24.83

^{19}F NMR ($CDCl_3$): δ –113.84

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{19}H_{20}BFNO_2$: 324.1566; Found 324.1575



(S3) **(28-Bpin)**

Aryl-I (**S3**) was prepared[2] and used to synthesize **28-Bpin**. In a nitrogen atmosphere glovebox, aryl iodide (**S3**, 430.8 mg, 1.6 mmol), $Pd(dppf)Cl_2$ dichloromethane complex (179.4 mg, 0.02 mmol, 0.14 equiv), KOAc (459.7 mg, 4.7 mmol, 3.0 equiv), and bis(pinacoloato)diboron (436.3 mg, 1.7 mmol, 1.1 equiv) were suspended in DMSO (8.8 mL, 0.18 M). The reaction mixture was heated at 80 ºC for 15 h. The reaction was allowed to cool to room temperature and quenched with water, and the product was extracted into EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Triturating the resulting mixture with pentanes and a few drops of EtOAc yielded **28-Bpin** as a yellow solid (386.1 mg, 76% yield, R_f = 0.32 in 20% ethyl acetate in hexanes, mp = 77–78 °C).

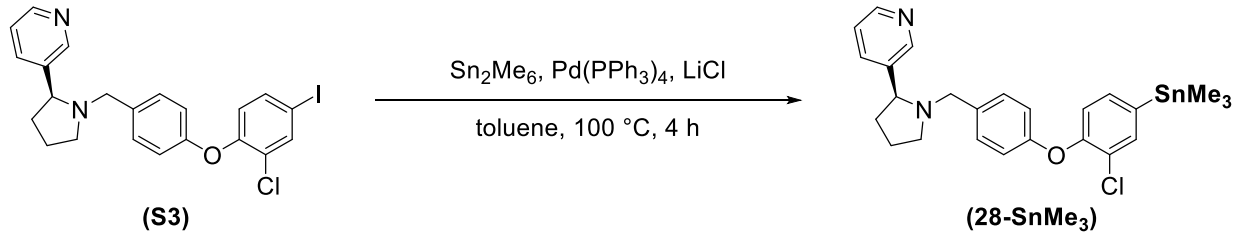
To a mixture of (S)-3-(1-(4-(2-chloro-4-iodophenoxy)benzyl)pyrrolidin-2-yl)pyridine 5 (0.54 g, 1.1 mmol), bis(pinacolato)-diboron (0.36 g, 1.4 mmol), Pd(dppf)Cl (0.048 g, 0.066 mmol) and potassium acetate (0.32 g, 3.3 mmol) in DMSO (6.0 mL) was reacted at 85 °C under argon atmosphere for 12 h. Then the mixture was diluted with saturated ammonium chloride solution and EtOAc, and the insoluble material was filtered through Celite. The organic layer of the filtrate was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (MeOH:DCM, 1:100 to 1:30) to give **28-Bpin** (0.35 g, 65%) as a brown oily product.

^{1}H NMR ($CDCl_3$): δ: 8.62 (d, J = 1.6 Hz, 1H), 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.88 (d, J = 1.4 Hz, 1H), 7.80 (dt, J = 7.8, 1.8 Hz, 1H), 7.60 (dd, J = 8.1, 1.5 Hz, 1H), 7.31–7.27 (m,

1H), 7.22 (d, J = 8.4 Hz, 2H), 6.92–6.82 (m, 3H), 3.74 (d, J = 13.1 Hz, 1H), 3.41 (t, J = 8.2 Hz, 1H), 3.16–3.08 (m, 2H), 2.29–2.19 (m, 2H), 1.97–1.87 (m, 1H), 1.86–1.78 (m, 1H), 1.76–1.66 (m, 1H), 1.24 (s, 12H)

^{13}C NMR ($CDCl_3$): δ 160.09, 159.37, 154.93, 152.26, 150.51, 141.40, 134.87 (2C), 128.47 (2C), 125.68, 115.15, 112.92, 112.77, 107.77, 107.61, 105.86, 83.74 (2C), 62.07, 51.09, 49.46, 27.19, 24.89 (4C), 18.66

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{28}H_{33}BClN_2O_3$: 491.2267; Found 491.2276



(S3) **(28-SnMe$_3$)**

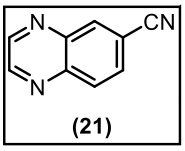
Aryl-I (**S3**) was prepared[2] and used to synthesize **28-SnMe$_3$**. In a nitrogen atmosphere glovebox, aryl iodide (**S3,** 0.11 g, 0.21 mmol), $(Me_3Sn)_2$ (0.084 g, 0.26 mmol), $Pd(PPh_3)_4$ (0.025 g, 0.021 mmol) and lithium chloride (0.014 g, 0.32 mmol) in toluene (15 mL) was reacted at 100 °C under nitrogen atmosphere for 4 h. Then the mixture was diluted with water and EtOAc, and the insoluble material was filtered through Celite. The organic layer of the filtrate was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (MeOH:DCM, 1:100 to 1:30) to give **28-SnMe$_3$** (0.086 g, 76%) as a brown oily product.

^{1}H NMR ($CDCl_3$): δ: : 8.62 (d, *J* = 1.7 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.79 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.66 (dd, *J* = 12.0, 1.4 Hz, 1H), 7.58–7.52 (m, 1H), 7.47 (dd, *J* = 7.6, 2.9 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.92–6.85 (m, 3H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.41 (t, *J* = 8.1 Hz, 1H), 3.15–3.07 (m, 2H), 2.25 (d, *J* = 8.8 Hz, 2H), 1.96–1.87 (m, 1H), 1.86–1.79 (m, 1H), 1.75–1.67 (m, 1H), 0.31 (s, 9H)

^{13}C NMR ($CDCl_3$): δ 155.72, 152.75, 149.63, 148.80, 139.39, 138.37, 137.48, 135.00, 134.34, 132.12, 129.90 (2C), 128.51, 123.56, 120.21, 117.84 (2C), 66.93, 57.51, 53.54, 35.28, 22.54, –9.36 (3C)

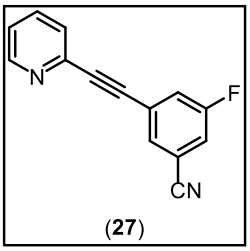
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{25}H_{30}ClN_2OSn^+$: 529.1063; Found 529.1055

3.10.2. Arylnitrile Standards



(21)

Quinoxaline-6-carbonitrile (**21**) was prepared via an adapted literature procedure.[42] In a nitrogen atmosphere glovebox, $Pd(PPh_3)_4$ (110.7 mg, 0.10 mmol, 0.1 equiv) was added to a vial and removed from the glovebox. The same vial was charged with 6-bromoquinoxaline (210.6 mg, 1.0 mmol, 1 equiv) and $K_4[Fe(CN)_6]\bullet 3H_2O$ (174.5 mg, 0.41 mmol, 0.4 equiv). The vial was placed under N_2. A solution of *t*-BuOH/H_2O (1:1, 3 mL, 0.33 M) and DBU (0.05 mL, 0.33 mmol, 0.33 equiv) was added via syringe, and the resulting mixture was stirred at room temperature for 10 min and then at 85 ºC for 15 h. The reaction mixture was allowed to cool to room temperature and filtered through a celite plug that was washed with methanol and DCM. The organic solution was washed with H_2O and brine, was dried over $MgSO_4$, and was then concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexanes), which afforded **21** as a white solid (55.0 mg, 21% yield R_f = 0.4 in 50% ethyl acetate in hexanes, mp = 173–174 ºC). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[43] HRMS (ESI+) $[M+H]^+$ Calculated for $C_9H_6N_3$: 156.0562; Found 156.0553.



(**27**)

F-PEB (**27**) was prepared via a literature procedure.[19,39] The product was purified by flash chromatography on silica gel (15% ethyl acetate in hexanes), to afford **27** as a brown solid (142.9 mg, 63% yield R_f = 0.15 in 20% ethyl acetate in hexanes, mp = 75–77 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[39,44] ^{19}F NMR ($CDCl_3$): δ –108.9. HRMS (ESI+) $[M+H]^+$ Calculated for $C_{14}H_8FN_2$: 223.0666; Found 223.0664

3.11. References

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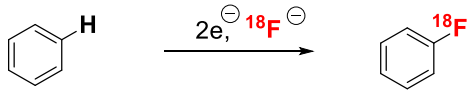
Chapter 4

Cu-Catalyzed [^{18}F]Fluorination *via* Directed C(sp^2)–H Functionalization[1]

4.1. Background

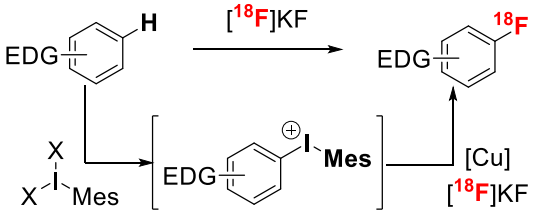
Current methods for arene radiofluorination require pre-functionalized starting materials, which can limit the accessibly of complex radiotracer targets. A complementary approach would involve the direct radiofluorination of C(sp^2)–H bonds. Several strategies have been developed for the radiofluorination of aliphatic[2,3] and benzylic[4–6] C–H bonds; however, analogous transformations of C(sp^2)–H substrates have proven considerably more challenging. The development of nucleophilic C(sp^2)–H radiofluorination methods has proven elusive due to the inertness of C(sp^2)–H bonds and the electronic mismatch between nucleophilic $^{18}F^-$ and most arene substrates. There are two known examples that have overcome these challenges. The first involves electrochemical [^{18}F]radiofluorination (Scheme 4.1).[7] This method works best for benzene, as there are selectivity issues when substituted arenes are used.[8,9] Additionally, common functional groups, such as bromoarenes, undergo decomposition during the course of the reaction.[8]

Scheme 4.1. Electrochemical [^{18}F]Radiofluorination[7]



An alternative method uses electrophilic aromatic substitution (S_EAr) to generate an aryliodonium salt *in situ* (Scheme 4.2).[10] From there, previously developed chemistry was utilized to produce the desired product.[11] This method worked well for a variety of substrates, but the relatively harsh conditions limited the functional group tolerance.

Scheme 4.2. Cu-Mediated C−H [^{18}F]Fluorination of Electron-Rich Arenes[10]



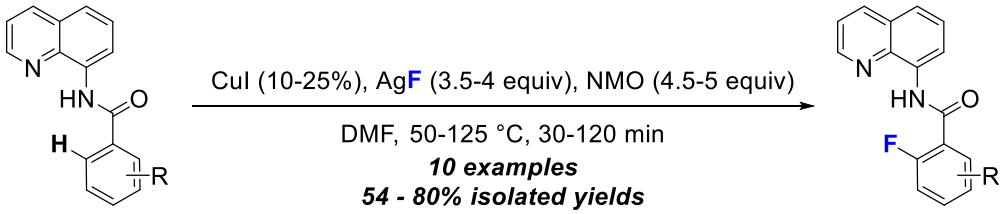
Removable directing groups have been successfully utilized for directed C(sp^2)–H fluorination, but there are currently no examples of the translation to [^{18}F]radiofluorination.[12,13] When considering nucleophilic fluorine sources, AgF is commonly used, but it is challenging for [^{18}F]radiofluorination applications due to the limited solubility. To overcome this limitation, a method was developed to generate [^{18}F]AgF in a soluble way that is necessary for PET chemistry.[14]

4.2. Initial Results and Optimization with ^{18}F[A]

In 2013, the Daugulis group successfully employed 8-aminoquinoline as a directing group with catalytic copper, excess oxidant (NMO), and AgF for the fluorination of C(sp^2)–H bonds (Scheme 4.3).[15] To achieve difluorination, a larger excess of all reagents can be used. This method was limited to AgF as the fluorinating reagent.[15]

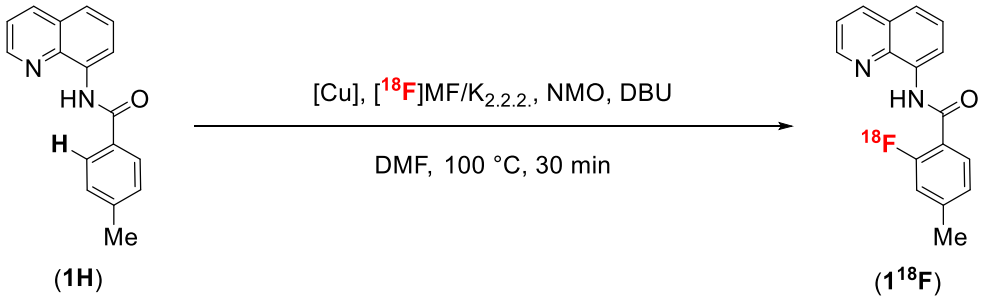
[A] The work in this section was done in collaboration with Dr. So Jeong Lee. Most of the radiofluorination optimization was performed by her except for the glovebox reactions in **Table 4.1**

Scheme 4.3. Daugulis' Conditions for Directed C–H Fluorination[15]



Initially, conditions analogous to Daugulis' reported conditions were analyzed with [^{18}F]AgF.[14] However, these did not afford detectable quantities of **1^{18}F** as determined by radio-TLC and radio-HPLC analysis (Table 4.1, entry 1). Notably, the Ag^{19}F likely serves two roles in the original Daugulis reaction. First, it acts as the nucleophile to install the C(sp^2)–F bond. Second, it serves as a base to sequester the proton that is generated during C–H activation. Since Ag^{19}F is present in 3- to 4-fold excess relative to **1H**, there is sufficient fluoride available for both of these functions. In contrast, under the radiofluorination conditions, the [^{18}F]AgF is the limiting reagent. It was hypothesized that an exogeneous base might be needed to sequester protons while preserving a reservoir of nucleophilic fluoride for the desired C(sp^2)–F coupling reaction. Consistent with this hypothesis, the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv relative to **1H**) led to the formation of the desired product **1^{18}F** in 26 ± 1% RCC as determined by radio-TLC and confirmed by radio-HPLC (Table 4.1, entry 2). Further optimization revealed that switching from CuI to more soluble (MeCN)$_4$CuOTf resulted in a slightly improved RCC (29 ± 0%; Table 4.1, entry 3). Under these conditions, the [^{18}F]fluoride source could be changed to readily accessible [^{18}F]KF[16] to afford 33 ± 0% RCC of **1^{18}F** (Table 4.1, entry 4). In the Ag^{19}F reaction (which is conducted under inert atmosphere), NMO acts as the terminal oxidant for Cu. However, the radiochemical reactions are conducted under ambient air, which could directly oxidize the Cu. Indeed, excluding NMO from the [^{18}F]KF reaction under otherwise identical conditions resulted in a comparable RCC (52 ± 17%, entry 5), although it did negatively impact the run-to-run reproducibility. When Table 4.1, entry 5 was set up in a glovebox and kept under an inert atmosphere the RCC dropped prohibitively (Table 4.1, entry 6), consistent with the role of air as the oxidant.

Table 4.1. Initial Results with Daugulis-like Conditions



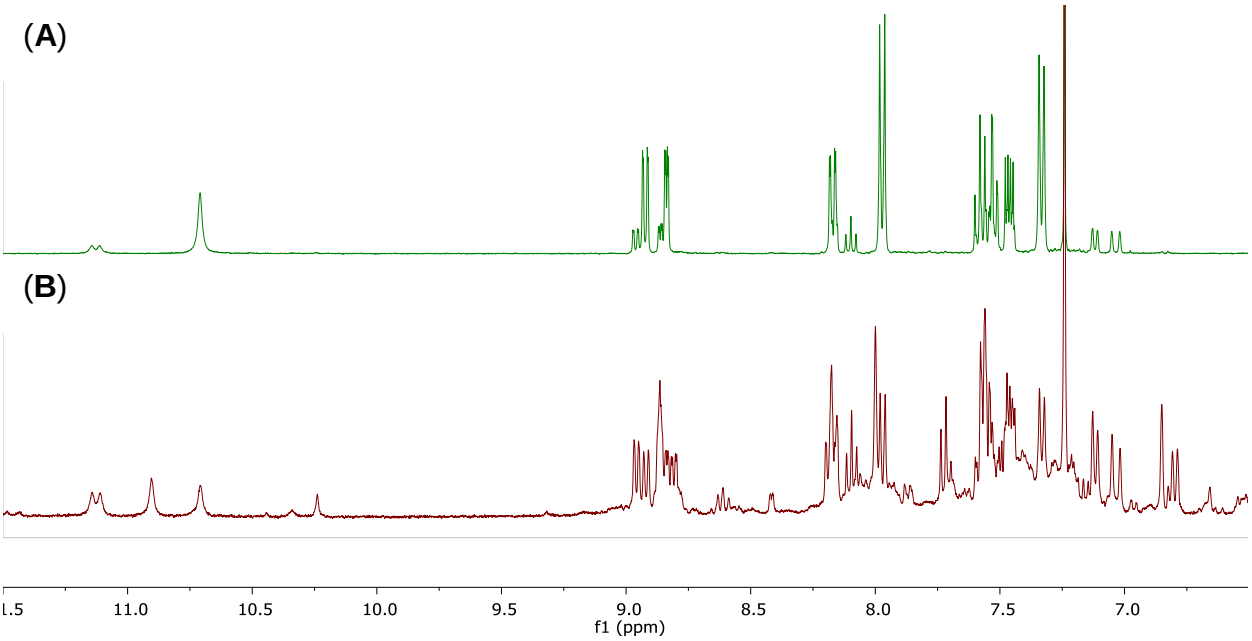
(**1H**) (**1**^{18}**F**)

entry	[Cu]	[^{18}F]MF	condition notes	**1**^{18}**F (% RCC)**
1	CuI	[^{18}F]AgF	no DBU	Nd
2	CuI	[^{18}F]AgF	--	26 ± 1
3	$(MeCN)_4CuOTf$	[^{18}F]AgF	--	29 ± 0
4	$(MeCN)_4CuOTf$	[^{18}F]KF	--	33 ± 0
5	$(MeCN)_4CuOTf$	[^{18}F]KF	no NMO	52 ± 17
6	$(MeCN)_4CuOTf$	[^{18}F]KF	inert atmosphere	6 ± 4

Conditions: **1H** (20 µmol), Cu source (0.25 equiv), NMO (4.5 equiv), $K_{2.2.2}$ (0.067 equiv), DBU (1 equiv), M^{18}F (2.5–3.5 mCi), DMF (1 mL). RCC was determined by radio-TLC (n ≥ 3); nd = not detected. The identity of **1**^{18}**F** was confirmed by radio-HPLC.

The inert reaction conditions in entry 6 were conducted to confirm an observation that was made when the analogous reactions were performed using [^{19}F]AgF. The original [^{19}F]AgF reaction conditions (0.25 equiv CuI, 4.5 equiv NMO, and 3.5 equiv AgF at 105 °C for 75 min) were set up in a glovebox and kept inert during the reaction.[15] The crude NMR spectrum of this reaction mixture shows the starting material, the mono-fluorinated product, the di-fluorinated product, and various other unidentified species (**B**, Figure 4.1). Modified [^{18}F]radiofluorination reaction conditions (0.25 equiv $(MeCN)_4Cu(OTf)$, 4.5 equiv NMM, 1 equiv DBU, and 3.5 equiv AgF at 140 °C for 30 min) provided a clean crude NMR spectrum, showing only starting material and monofluorinated product (**A**, Figure 4.1). When [^{19}F]KF was used instead of [^{19}F]Ag^{19}F, no product was observed in the glovebox reactions. If the glovebox reaction was open air for <3 min then trace product was observed. No change in product formation was observed when setting up the reaction on the bench top compared to an inert atmosphere. In the absence of DBU, trace product is observed.

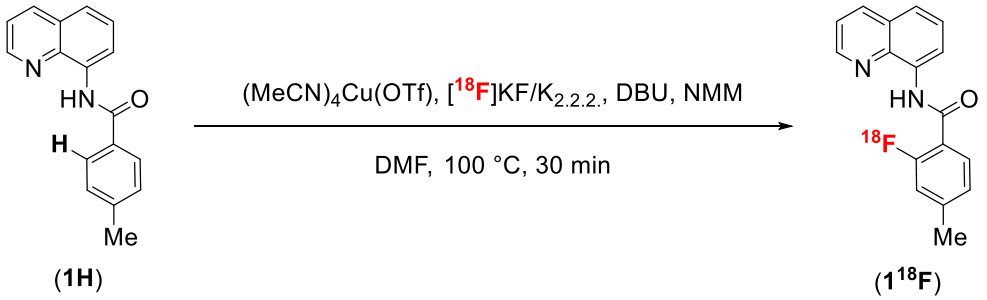
Figure 4.1. NMR Reactions Using AgF



Conditions: (**A**) **1H** (50 µmol), $(MeCN)_4Cu(OTf)$ (0.3 equiv), DBU (1 equiv), NMM (4.5 equiv), AgF (4 equiv), DMF (0.3 mL), 140 °C, 30 min. (**B**) **1H** (50 µmol), CuI (0.3 equiv), NMO (4.5 equiv), AgF (3 equiv), DMF (0.3 mL), 105 °C, 75 min.

Reproducibility is critical for radiochemical labeling reactions, and the reaction in Table 4.1, entry 5 showed poor reproducibility. To address this issue, several additives were evaluated (Table 4.2, entry 1), and it was found that the addition of the reduced form of NMO, *N*-methylmorpholine (NMM) resulted in enhanced reproducibility (Table 4.2, entry 2). Other bases were screened to investigate the role of DBU. Daugulis proposed that adding pyridine to the difluorination reactions slowed the decomposition of the starting material.[15] Upon addition of pyridine, no product was detected (Table 4.2, entry 3). DMAP provided some of the desired product and DBN also gave comparable results (Table 4.2, entries 4–5). Other Cu sources gave product with [^{18}F]AgF and [^{18}F]KF (Table 4.2, entries 6–8). Other solvents gave product, but DMF was the highest yielding (Table 4.2, entry 9).

Table 4.2. Optimization of C–H Radiofluorination



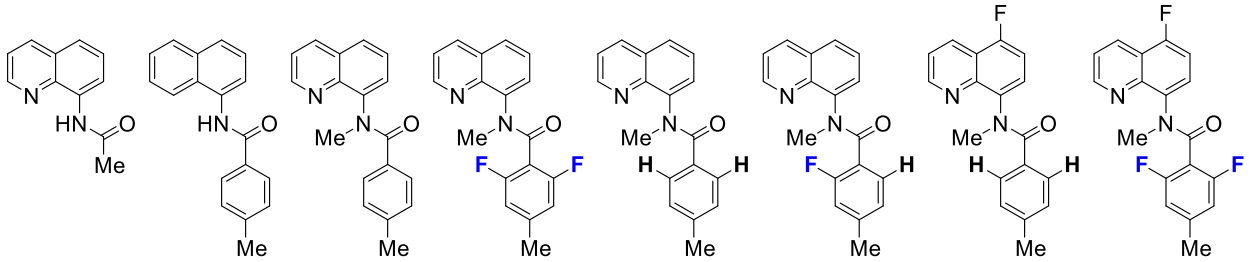
(**1H**) (**1**^{18}**F**)

entry	conditions	**1**^{18}**F (% RCC)**
1	no NMM	52
2	--	50
3	no DBU, pyridine (1 equiv)	nd
4	no DBU, DMAP	10
5	no DBU, DBN	46
6	$(MeCN)_4Cu(BF_4)$	44
7	$Cu(OAc)_2$	19
8	CuI	24
9	DMA	37

Conditions: **1H** (20 µmol), $(MeCN)_4Cu(OTf)$ (0.25 equiv), $K_{2.2.2}$ (0.067 equiv), DBU (1 equiv), NMM (4.5 equiv), [^{18}F]KF (2.5–3.5 mCi), DMF (1 mL). RCC was determined by radio-TLC (n ≥ 3); nd = not detected. The identity of **1**^{18}**F** was confirmed by radio-HPLC.

To confirm that the desired C–H fluorination product was being generated, a series of control reactions were conducted. All control reactions indicated that the expected product was being formed (Figure 4.2). Removing the arene ring (**S1**), the quinoline motif (**S2**), and blocking the N–H group (**S3**) resulted in no detectable products in a range of conditions. If both *ortho* sites were blocked (**3F**), no radiofluorination was detected, indicating that fluorination was not occurring on the quinoline ring and further that the ^{19}F atoms were not exchanging with the ^{18}F atoms. To further confirm this, five different regioisomers (**1H**, **1F**, **3F**, **14H**, **14F**) were synthesized and separated on HPLC. As suspected **3F** and **14H** were challenging to get baseline separation. A co-injection with the crude reaction mixture showed that the desired *ortho*-fluorination product was formed selectively.

Figure 4.2. Control Reactions

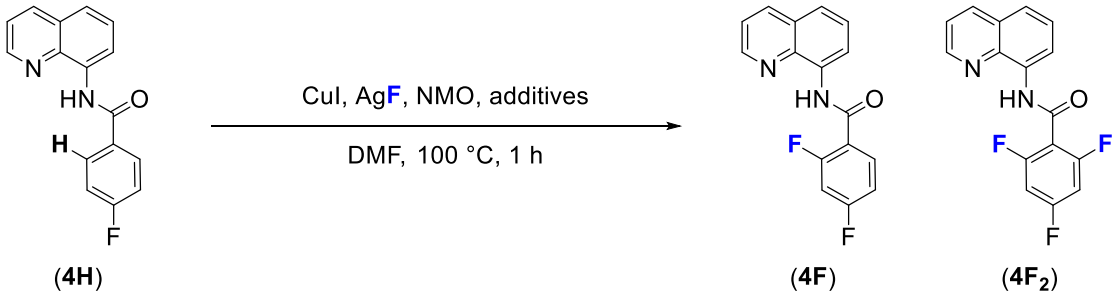


Conditions: substrate (20 μmol, 1 equiv), $(MeCN)_4CuOTf$ (0.25 equiv), DBU (1 equiv), NMM (4.5 equiv), $[^{18}F]KF/K_{2.2.2.}$, DMF (1mL), 70–140 ºC, 30 min.

4.3. Effects of DBU

The effects of DBU in this reaction were investigated in the context of the analogous $[^{19}F]AgF$ reaction. The Daugulis report used pyridine to achieve difluorination.[15] Their hypothesis was that the pyridine slowed down the rate of decomposition of the starting material, but also slowed down the rate of the reaction. The requirement for the glovebox was also investigated. For the first set of reactions, *p*-fluoro substrate **4H** was investigated. The control reaction (Table 4.3, entry 1) showed some product (mono and difluorination) as well as unreacted starting material. Opening the reaction to air decreased the amount of monofluorinated product and increased the difluorinated product (Table 4.3, entry 2). Adding pyridine to the reaction slowed the rate of the reaction to where trace product was detected (Table 4.3, entry 3). Notably, there is no detectable starting material present, which conflicts with Daugulis's hypothesis.[15] Adding DBU to the reaction led to a large increase in the yield of difluorinated product with some monofluorinated product obtained. To study this effect further, a substrate was chosen that could only produce the monofluorinated product. Substrate **4H** was shown in the original report to undergo difluorination preferentially over monofluorination.

Table 4.3. Effects of DBU with **4H**



(**4H**) (**4F**) (**4F$_2$**)

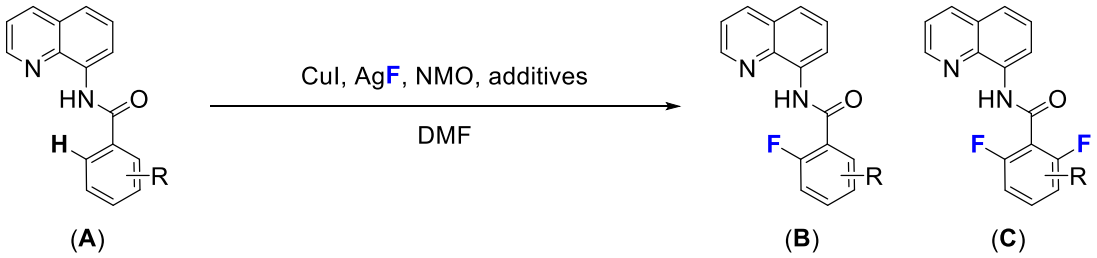
entry	additives	4F (%)	4F$_2$ (%)	4H (%)
1	--	17	6	4
2[a]	--	7	12	nd
3	pyridine	1	5	nd
4	DBU	8	25	nd

Conditions: **4H** (20 µmol), CuI (0.25 equiv), NMO (5 equiv), AgF (4 equiv), additives [pyridine (2 equiv), DBU (2 equiv)], DMF (1 mL). [a]open to air <5 min at rt. Crude reaction analyzed by NMR with 1,2-difluorobenzene as an internal standard. Nd = not detected

The effect of DBU was investigated with a substrate that could only give the monofluorinated product (Table 4.4, entries 1–4). The original conditions were performed on a 10-fold scale and gave 80% of the monofluorinated product.[15] Under the control reaction, 52% of the monofluorinated product was obtained (Table 4.4, entry 1). With this substrate, there was a stark difference on the glovebox reaction versus the reaction open to air (Table 4.4, entry 2). Additionally, pyridine had no effect on this reaction, but DBU gave a large increase in product (Table 4.4, entries 3–4).

Next a substrate that gave monofluorination and difluorination product was investigated (Table 4.4). A similar trend was found with the standard conditions giving 36% of the desire product with a large amount of starting material remaining (Table 4.4, entry 5). Exposing the reaction to air deceased the yield of the desired product and pyridine had no effect on the reaction (Table 4.4, entries 6–7). The addition of DBU increased the yield of the desired product significantly as well as increased the amount of difluorinated product present (Table 4.4, entry 8).

Table 4.4. Effects of DBU



Entry	R	additives	temperature (°C)	time (h)	A (%)	B (%)	C (%)
1	2-CF_3	--	120	1.5	23	52	--
2[a]	2-CF_3	--	120	1.5	15	33	--
3	2-CF_3	pyridine	120	1.5	23	54	--
4	2-CF_3	DBU	120	1.5	trace	72	--
5	4-CF_3	--	80	0.5	52	36	2
6[a]	4-CF_3	--	80	0.5	63	19	3
7	4-CF_3	pyridine	80	0.5	33	38	3
8	4-CF_3	DBU	80	0.5	11	67	15

Conditions: substrate (20 µmol), CuI (0.25 equiv), NMO (5 equiv), AgF (4 equiv), additives [pyridine (2 equiv), DBU (2 equiv)], DMF (1 mL). [a]open to air <5 min at rt. Crude reaction analyzed by NMR with 1,2-difluorobenzene as an internal standard.

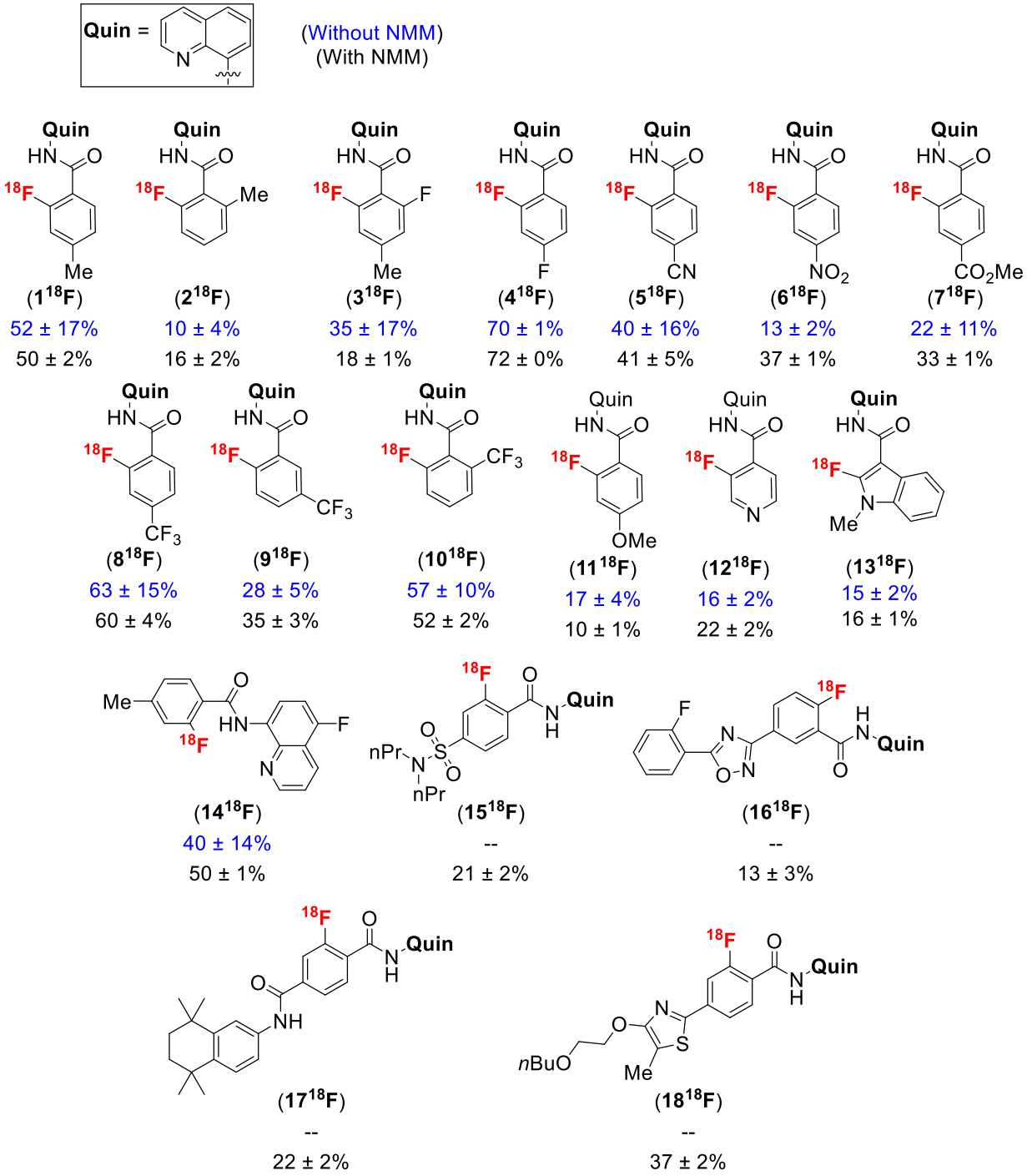
4.4. Substrate Scope

The scope of this reaction was examined using aminoquinolines derived from a variety of substituted benzoic acids. Product identities were confirmed by radio-HPLC. As shown in Figure 4.3, electron-neutral (**1**^{18}**F**–**4**^{18}**F**), -withdrawing (**5**^{18}**F**–**10**^{18}**F**), and -donating (**11**^{18}**F**) substituents were well tolerated. Some arenes bearing electron-withdrawing substituents give rise to minor side products. The formation of side products derived from competing S_NAr reactions were ruled out, but the unknown side products have not been positively identified to date. Many functional groups, including benzylic C–H bonds, trifluoromethyl, cyano, nitro, ester, amide, and sulfonamide substituents, were compatible. This C(sp^2)–H radiofluorination was also effective on pyridine- and indole-derived substrates, providing **12**^{18}**F** and **13**^{18}**F** in moderate RCC. A substrate containing a fluorine substituent at the activated 4-position on the quinoline reacted to afford the *ortho*-^{18}F-labelled product **14**^{18}**F** in 50% RCC.[17,18]

This method was applied to the late-stage radiofluorination of a series of biologically relevant molecules. Four carboxylic acid-containing drugs, Probenecid (**15H**),

Ataluren (**16H**), Tamibarotene (**17H**), and AC261066 (**18H**), were converted to the corresponding 8-aminoquinoline benzamides and then subjected to the optimal conditions. The [^{18}F]fluorinated analogues (**15^{18}F**–**18^{18}F**, respectively) were obtained in 13–37% RCC. Products **15^{18}F–18^{18}F** contain functional groups that could potentially direct C–H fluorination elsewhere in the molecule (*e.g.* **17H** contains 2 amide groups). Small impurity peaks were detected in the crude radio-HPLC traces of these products; however, **15^{18}F**–**18^{18}F** were the major products in each case, and they appear to be readily separable from the side products formed in the reaction. Performed as part of the optimization and similar to the Ag^{19}F reaction,[15] temperature was optimized for each substrate. For most substrates, the reaction was performed with and without NMM to analyze if there are any effects with NMM. Several substrates had a large standard deviation when NMM was excluded, indicating that this reagent could be increasing reproducibility. Most substrates had the same RCC with or without NMM except **3^{18}F** (large increase without NMM) and **6^{18}F** (large increase with NMM).

Figure 4.3. Substrate Scope



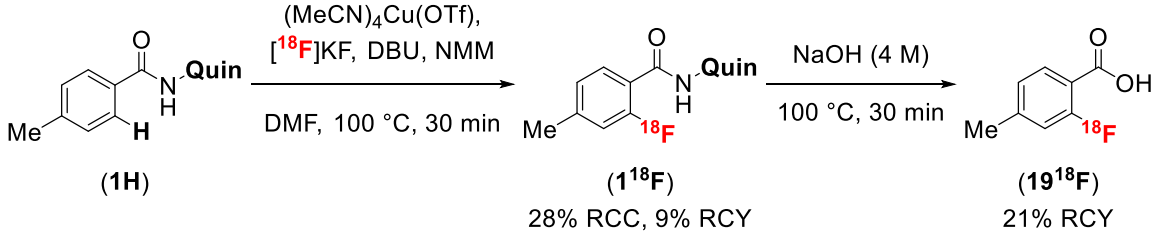
Conditions: Substrate (20 µmol), $(MeCN)_4Cu(OTf)$ (5 µmol), NMM (90 µmol), $K_{2.2.2}$ (1.33 µmol), DBU (20 µmol), [^{18}F]KF (2.5–3.5 mCi), DMF (1.0 mL), 90–110 °C, 30 min. Reported values indicate RCC determined by radio-TLC for n ≥ 3 runs. The identity of all

products was confirmed by radio-HPLC. In cases where other products were observed by radio-HPLC analysis, RCCs from radio-TLC analysis were corrected.

4.5. Automation[B]

For automation, two substrates were analyzed for their efficiency of radiofluorination and hydrolysis. Initial automated studies were conducted with **1H**, and afforded **1^{18}F** in 28% automated RCC or, by incorporating semi-preparative HPLC purification, 9% isolated decay-corrected RCY and >98% radiochemical purity. Starting with 1.7 Ci of [^{18}F]fluoride **1^{18}F** was obtained in 42 mCi with high specific activity (6 Ci μmol^{-1}). Hydrolysis of the aminoquinoline protecting group was then achieved with 4M NaOH to afford **19^{18}F** in 90% RCC from **1^{18}F** (manual) and 21% RCC based upon starting [^{18}F]fluoride (Scheme 4.4).

Scheme 4.4. Automation of **1H**

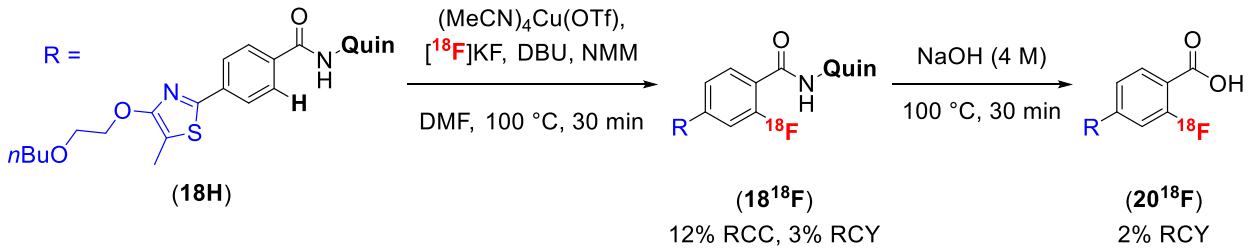


An analogous method was applied to the synthesis of [^{18}F]AC261066 (**20^{18}F**), a RARβ2 agonist (Scheme 4.5).[19] Subjecting **18H** to the C–H radiofluorination conditions afforded **18^{18}F** in 12% automated RCC. Starting with 1.7 Ci of [^{18}F]fluoride, **18^{18}F** was obtained in 36 mCi after sep-pak purification, corresponding to 3% isolated decay-corrected RCY. Manual hydrolysis of the amide with 4M NaOH formed [^{18}F]AC261066 (**20^{18}F**) in 98% RCC from **18^{18}F** (determined by radio-TLC). Overall, the isolated decay-corrected RCY of **20^{18}F** was 9 mCi (2% based upon starting [^{18}F]fluoride). The product was obtained in high chemical and radiochemical (>98%) purity and high specific activity (0.80 Ci μmol^{-1}). These unoptimized automation results demonstrate that this method can

[B] All reactions performed by So Jeong Lee

be used to prepare sufficient amounts of radiotracers for pre-clinical evaluation in rodents and non-human primates. The yields could be further improved through careful optimization of the automated method.

Scheme 4.5. Automation of **18H**



(**18H**)

(**18^{18}F**)
12% RCC, 3% RCY

(**20^{18}F**)
2% RCY

4.6. Conclusion

In summary, a Cu-catalyzed, 8-aminoquinoline-directed C(sp^2)–H radiofluorination method of arene C(sp^2)–H bonds with [^{18}F]KF is reported. The method has been applied to a variety of substrates, including the active pharmaceutical ingredients of Probenecid, Ataluren, and Tamibarotene. In addition, it has been translated to an automated synthesis of high specific activity doses of RARβ2 agonist [^{18}F]AC261066. Further optimization will be required to make the automation and subsequent deprotection efficient for a clinical scale. However, overall this operationally simple procedure demonstrates proof-of-concept that metal-catalyzed nucleophilic C(sp^2)–H radiofluorination is feasible, and that this approach shows promise for the late-stage radiofluorination of bioactive molecules.

4.7. Outlook

This transformation serves as inspiration for using other directing groups to achieve (radio)fluorination (Chapter 5). The effects of NMM and DBU on the reaction will be investigated more thoroughly.

4.8. Experimental Details

4.8.1. Instrumental Information

NMR spectra were obtained on a Varian vnmrs700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), a Varian vnmr500 (500.09 MHz for ^{1}H; 470.56 MHz for ^{19}F; 125.75 MHz for ^{13}C), or

a Varian MR400 (400.53 MHz for ^{1}H; 376.87 MHz for ^{19}F) spectrometer. All ^{13}C NMR data presented are proton-decoupled ^{13}C NMR spectra, unless noted otherwise. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to TMS with the residual solvent peak used as an internal reference. ^{1}H and ^{19}F NMR multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Melting point data (mp) were collected on an OptiMelt Automated Melting Point System and are uncorrected. HPLC was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analyses were performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

4.8.2. Materials and Methods

All commercial products were used as received and reagents were stored under ambient conditions unless otherwise stated. 8-aminoquinonline was purchased from Synthonix. Acid chlorides and benzoic acid derivatives were purchased from Frontier Scientific, Oakwood Products, Acros Organics, Synthonix, Chem Impex, TCI America, Matrix Scientific, Alfa Aesar, Ark Pharm, and Sigma Aldrich. Oxalyl chloride was purchased from Acros Organics. Silver fluoride was purchased from Oakwood. NMO, CuI, and probenecid were purchased from Sigma Aldrich. Tamibarotene was purchased from AAChemPharm. Ataluren was purchased from ArkPharm. 4-[4-(2-butoxyethoxy)-5-methyl-1,3-thiazol-2-yl]benzoic acid (CAS 920269-72-3) and 4-[4-(2-butoxyethoxy)-5-methyl-1,3- thiazol-2-yl]benzoic acid (AC261066, CAS: 920269-72-3) were purchased from Atomax Chemicals Co., Ltd. The manipulation of solid reagents was conducted on the benchtop unless otherwise stated. Reactions were conducted under an ambient atmosphere unless otherwise stated. Reaction vessels were sealed with either a septum (flask) or a Teflon-lined cap (4 mL or 20 mL vial). Reactions conducted at elevated temperatures were heated on a hot plate using an aluminum block. Temperatures were regulated using an external thermocouple. For TLC analysis, RF values are reported based on normal phase silica plates with fluorescent indicator.

HPLC grade acetonitrile, potassium trifluoromethanesulfonate, and anhydrous dimethylformamide were purchased from Fisher Scientific. Silver trifluoromethanesulfonate, sodium bicarbonate, Kryptofix® 2.2.2 ($K_{2.2.2}$), anhydrous acetonitrile, *N,N*-dimethylacetamine, *N*-methylmorpholine (NMM), *N*-methylmorpholine *N*-oxide (NMO), and 1,8-diazabicyclo[5.4.0]undec-7-ene were purchased from Sigma-Aldrich. Sterile product vials (10 mL) were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 90 mg/mL of an aqueous solution of potassium trifluoromethanesulfonate, and rinsed with 10 mL of MQ water prior to use for the generation of [^{18}F]AgF. QMA-light Sep-Paks were flushed with ethanol (10 mL), 0.5 M aqueous sodium bicarbonate (10 mL), and MQ water (10 mL) prior to use for the generation of [^{18}F]KF.

4.8.3. Synthesis of ^{18}F

Generation of [^{18}F]AgF. All loading operations were conducted under ambient atmosphere. Automated sample transfers utilized argon gas. Silver [^{18}F]fluoride was prepared with a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electronic, GE). [^{18}F]Fluoride was produced via the proton beam bombardment of ^{18}O-target water (^{18}O(p,n)^{18}F) using a GE PETTrace cyclotron (40 μA beam for 5–10 min generated ca. 315–620 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the automated synthesis module in a 1.5 mL bolus of [^{18}F]target water and trapped on the preconditioned QMA-light Sep-Pak to remove [^{18}O]target water and other aqueous impurities. [^{18}F]Fluoride was eluted into the reaction vessel using silver trifluoromethanesulfonate in MQ water (10 mg, 0.5 mL, 0.08 M) and $K_{2.2.2}$ in acetonitrile (15 mg, 1 mL, 0.04 M). Azeotropic drying was achieved by heating to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min to produce anhydrous [^{18}F]AgF/$K_{2.2.2}$.. Overall 70% of radioactivity remained after azeotropic drying (66%; calculated from TRACERLab FX_{FN} reactor radiation detector by comparing radioactivity in the reaction vessel before and after azeotropic drying process). The reaction vessel was cooled to room temperature via an argon stream, and anhydrous dichloromethane (3.5 mL) was

added to dissolve the dried reagents. The mixture was heated to 37 °C with stirring for 5 min to suspend the Ag[^{18}F]F/$K_{2.2.2}$. The resulting solution was cooled to room temperature and transferred to a sterile vial.

Generation of [^{18}F]KF. [^{18}F]Fluoride was produced by the same protocol described in generation of [^{18}F]AgF (above). The [^{18}F]fluoride was delivered to the automated synthesis module (TRACERLab FX_{FN}, GE) in a 1.5 mL bolus of [^{18}F]target water and was trapped on the preconditioned QMA-light Sep-Pak to remove [^{18}O]target water and other aqueous impurities. [^{18}F]Fluoride was eluted into the reaction vessel using potassium trifluoromethanesulfonate (5 mg, 0.5 mL, 0.05 M) and $K_{2.2.2}$ in acetonitrile (15 mg, 1 mL, 0.04 M). Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 ºC and drawing vacuum for 6 min. Azeotropic drying was achieved by heating to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min to produce anhydrous [^{18}F]KF/$K_{2.2.2}$. The reaction vessel was cooled to room temperature under an argon stream, and anhydrous DMF (6 mL) was added. The mixture was heated to 50 °C with stirring for 5 min to suspend the [^{18}F]KF/ $K_{2.2.2}$. The resulting solution was cooled to room temperature and was transferred to a sterile vial.

4.8.4. Manual Synthesis of ^{18}F-Labeled Molecules

A stock solution of each of the following reagents, the quinoline benzamide precursor (0.2 M), $(MeCN)_4CuOTf$ (0.05 M), DBU (0.2 M), and NMM (0.9 M), in DMF was prepared. To a 4 mL vial containing a stir bar were added 0.1 mL aliquots of each stock solution [quinoline benzamide precursors (20 μmol, 1 equiv), $(MeCN)_4CuOTf$ (5 μmol, 0.25 equiv), DBU (20 μmol, 1 equiv), and NMM (90 μmol, 4.5 equiv)]. [^{18}F]KF/$K_{2.2.2}$ in 0.2 mL of DMF (2.5–3.5 mCi of radioactivity) was used for each manual reaction, and additional DMF (0.4 mL) was also added to bring the total solution volume to 1 mL. The reaction vial was sealed and pre-stirred (1500 rpm) at room temperature for 5 min. The reaction vial was heated in an aluminum block with vigorous stirring (1500 rpm) at 90–110 °C for 30 min. After 30 min, the reaction was cooled to room temperature and the radiochemical conversion (RCC, %) was determined by radio-TLC analysis. The crude reaction mixture

was spotted onto standard silica-coated glass plates and developed with hexanes:ethyl acetate (1:1) in a glass TLC chamber. The RCC was determined by dividing the integrated area of radiation under the fluorinated product spot by the total integrated area of radiation on the TLC plate. In reactions where the radio-HPLC traces show multiple peaks, the RCC (determined by radio-TLC) was corrected by dividing the integrated area of radiation under the desired F-18 labeled product peak by the total integrated area of radiation on the analytical radio-HPLC. To prepare samples for HPLC analysis, 80 µL of the reaction mixture was spiked with 20 µL of 2 mg/mL fluorinated standard solution in DMF.

*Manual Synthesis of **20^{18}F***

[^{18}F]Fluorination of **18H** was carried out according to the procedure described above. The reaction was cooled to room temperature and a portion of the crude mixture (80 µL) was used for radio-TLC (hexanes:ethyl acetate = 1:1) and HPLC analysis. The crude reaction was then diluted with DI water (50 mL) and loaded onto a preconditioned QMA-C18 light Sep-Pak [EtOH (10 mL), D.I water (10 mL)]. The organic portions were eluted with EtOH (1 mL). The eluent quality was confirmed by radio-TLC analysis (hexanes:ethyl acetate = 1:1). To the eluent in EtOH (0.5 mL) was added 4 M NaOH (1 mL). The reaction was heated to 100 °C for 30 min with stirring at 1500 rpm. The reaction was cooled to room temperature, and the crude mixture was acidified with 1 N HCl (4 mL). The organic portion was extracted with ethyl acetate (1 mL). The RCC of the final product was determined by radio-TLC (hexanes:ethyl acetate = 1:1). A portion of the reaction mixture (80 µL) was spiked with 20 µL of 2 mg/mL AC 261066 standard in DMF.

4.8.5. Automated Synthesis

*Automated synthesis of **1^{18}F** followed by semi-preparative HPLC purification.*

All loading operations were conducted under ambient atmosphere. Argon gas and vacuum were used for automated sample transfers. [^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F nuclear reaction using a General Electronic (GE) PETTrace cyclotron (40 µA beam for 3 min generated ca. 200 mCi of [^{18}F]fluoride, and 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). [^{18}F]KF was produced as described in **Generation of [^{18}F]KF** using a GE TRACERLab FX_{FN} automated synthesis module. DMF (0.5 mL) was added to the dried

[^{18}F]KF in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **1H** (5.3 mg, 20 μmol, 1 equiv), $(MeCN)_4CuOTf$ (2 mg, 5 μmol, 0.25 equiv), DBU (3 μL, 20 μmol, 1 equiv), and NMM (10 μL, 90 μmol, 4.5 equiv) in 0.8 mL of anhydrous DMF was added to the reactor containing 0.5 mL of a [^{18}F]KF solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was pre-stirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The mixture was cooled to 30 ºC with compressed air cooling, and the resulting mixture was diluted by 3 mL of semipreparative HPLC buffer (60% acetonitrile in water, 0.1% (v/v) trifluoroacetic acid) then loaded onto the HPLC injection loop by passing through a Sep-Pak alumina N plus light cartridge to remove unreacted residual [^{18}F]fluoride. The diluted mixture was injected onto the semi-prep HPLC for purification. The peak for the desired ^{18}F-labeled organic product was collected for 2 min (t_R = 16.5 min, collected volume: 8 mL) in a 10 mL sterile product vial. The dose vial was transferred out of the synthesis module product identity were then determined using a Capintec dose calibrator and analytical HPLC (Table 4.5).

Table 4.5. Automated Synthesis of **1^{18}F**

entry	starting activity (mCi)	final activity (mCi)	RCY, NDC (%)	total time (min)	RCY, DC (%)
1	194	12	6	104	12
2	194	12	6	103	12
3	194	13	7	102	13
4	1700	40	2	110	5
5	1700	40	2	98	4
6	1700	45	3	104	5

*Automated synthesis of **1^{18}F** followed by manual hydrolysis to provide **19^{18}F**.*

All loading operations were conducted under ambient atmosphere. Argon gas and vacuum was used for automated sample transfers. [^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F nuclear reaction using a GE PETTrace cyclotron (40 μA beam for 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). [^{18}F]KF was produced as described in **Generation of [^{18}F]KF** using an automated synthesis module, TRACERLab FX_{FN} (General Electronic,

GE). DMF (0.2 mL) was added to the dried [^{18}F]KF in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **1H** (5.3 mg, 3.8 µmol, 1 equiv), $(MeCN)_4CuOTf$ (2 mg, 0.1 µmol, 0.25 equiv), DBU (3 µL, 3.8 µmol, 1 equiv), and NMM (10 µL, 17 µmol, 4.5 equiv) in 0.8 mL of anhydrous DMF was added to the reactor containing 0.2 mL of a [^{18}F]KF solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was pre-stirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The RCC of **1^{18}F** from **1H** was determined by radio-TLC (28%), and product identity was determined using analytical HPLC. The mixture was cooled to 30 ºC with compressed air cooling, and for 3 runs the resulting mixture was transferred to the dilution flask containing 50 mM of EDTA solution (70 mL). The diluted mixture was slowly loaded onto the Sep-Pak C18 plus cartridge to trap ^{18}F-labeled organic products by removing unreacted residual [^{18}F]fluoride and copper. Radiochemical purity of **1^{18}F** following this purification was 83%. The trapped **1^{18}F** was eluted with ethanol (2 mL) and collected in an 8 mL sterile product vial. An aliquot of the collected **1^{18}F** in ethanol (0.5 mL) was then added to 4 M NaOH (1 mL) in a 4 mL vial. The reaction vial was transferred to a hot plate and stirred for 30 min at 100 ºC. The resulting mixture was cooled to room temperature and neutralized by the addition of 6 N HCl (0.7 mL). Ethyl acetate (1 mL) was used to extract the organic portion from the mixture. The RCC of **19^{18}F** from **1^{18}F** was determined by radio-TLC (90%) and the product identity was determined using analytical HPLC. The overall RCC to **19^{18}F** from [^{18}F]fluoride was 21%.

*Automated synthesis of **18^{18}F** followed by manual hydrolysis to provide **20^{18}F**.*

All loading operations were conducted under ambient atmosphere. Argon gas and vacuum was used for automated sample transfers. [^{18}F]Fluoride was produced via the $^{18}O(p, n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron (40 µA beam for 30 min generated ca. 1.7 Ci of [^{18}F]fluoride). [^{18}F]KF was produced as described in Generation of [^{18}F]KF using an automated synthesis module, TRACERLab FX_{FN} (General Electronic, GE). DMF (0.5 mL) was added to the dried [^{18}F]KF in the reactor, and the solution was stirred for 5 min at room temperature. A solution containing **18H** (3.5 mg, 7.8 µmol, 1

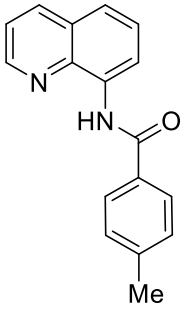
equiv), $(MeCN)_4CuOTf$ (0.76 mg, 2 μmol, 0.25 equiv), DBU (1.14 μL, 7.8 μmol, 1 equiv), and NMM (3.6 μL, 34 μmol, 4.5 equiv) in 1 mL of anhydrous DMF was added to the reactor containing 0.5 mL of a [^{18}F]KF solution in DMF by applying Ar gas through the valve containing the reagent solution. The open valves leading out of the reactor were closed, and the reaction mixture was pre-stirred for 5 min at room temperature. The mixture was heated to 100 ºC and stirred for 30 min. The mixture was cooled to 30 ºC with compressed air cooling, and the resulting mixture was transferred to the dilution flask containing DI water (70 mL) by passing through a Sep-Pak alumina N plus light cartridge to remove unreacted residual [^{18}F]fluoride. DI water (3 mL) was added to the reactor and transferred by argon gas to the dilution flask to rinse the residue from the reactor. The diluted mixture was allowed to stir for approximately 1 min then slowly loaded onto the Sep-Pak C18 1cc vac cartridge. The trapped ^{18}F-labeled organic products were eluted with ethanol (1 mL) and collected in an 8 mL sterile product vial. The dose vial was transferred out of the synthesis module in a lead pig. Total activity of **18^{18}F** (36 mCi, 3% RCY, decay-corrected) and product identity were then determined using a Capintec dose calibrator and analytical HPLC (Table 4.6). The automated synthesis time of **18^{18}F** was 100 min. The collected **18^{18}F** in ethanol (1 mL) was then added to 4 M NaOH (2 mL) in a 4 mL vial. The reaction vial was transferred to a hot plate and stirred for 30 min at 100 ºC. The resulting mixture was cooled to room temperature and neutralized by the addition of 2 N HCl (2 mL). Ethyl acetate (1 mL) was used to extract the organic portion from the mixture. The RCC of **20^{18}F** from **18^{18}F** (98%) was determined by radio-TLC. The isolated decay-corrected RCY of **20^{18}F** at EOS was also determined to be 2% and RCP (>98%) was determined by analytical HPLC. Total synthesis time of **20^{18}F** from **18H** was 155–160 min.

Table 4.6. Automated Synthesis of **18^{18}F** and **20^{18}F**

entry	starting activity (mCi)	activity of 18^{18}F (mCi)	activity of 20^{18}F (mCi)	total time (min)	RCY, DC (%)
1	1700	30	5	155	1
2	1700	32	5	160	1
3	1700	45	17	155	3

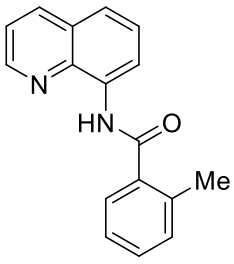
4.9. Synthesis and Characterization

4.9.1. Preparation and characterization of starting materials



(**1H**)

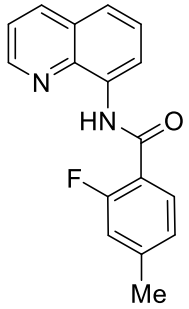
***N*-(4-Methylbenzoyl)-8-aminoquinoline** (**1H**) was prepared according to the literature procedure.[15] 8-Aminoquinoline (290.1 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.34 M) followed by a dropwise addition of 4-methylbenzoyl chloride (0.34 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**1H**) as a white solid (474.1 mg, 90% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 119–120 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[20] HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{15}N_2O$: 263.1179; Found 263.1186.



(**2H**)

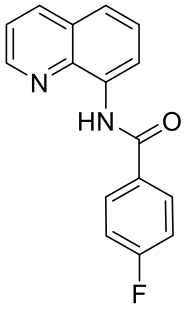
***N*-(2-Methylbenzoyl)-8-aminoquinoline** (**2H**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (434.4 mg, 3.0 mmol, 1 equiv) and NEt_3 (0.55 mL, 4.0 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (9.0 mL, 0.33 M) followed by a dropwise addition of 2-methylbenzoyl chloride (0.52 mL, 4.0 mmol, 1.3 equiv). The

resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**2H**) as a white solid (709.4 mg, 90% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 94–95 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[20] HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{15}N_2O$: 263.1179; Found 262.1177.



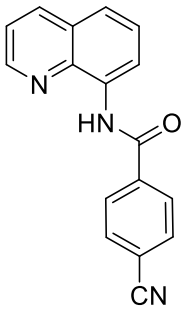
(**3H**/**1F**)

2-Fluoro-4-methyl-*N*-(quinolin-8-yl)benzamide (**3H**/**1F**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (290.5 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (7.0 mL, 0.29 M), followed by a dropwise addition of 2-fluoro-4-methylbenzoyl chloride (408.0 mg, 2.4 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3H**/**1F**) as a white solid (199.1 mg, 35% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 131–132 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.8 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1088.



(**4H**)

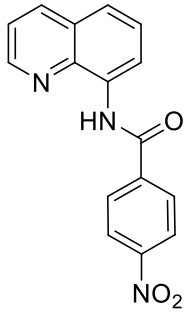
***N*-(4-Fluorobenzoyl)-8-aminoquinoline (4H)** was prepared according to the literature procedure.[21] 8-Aminoquinoline (146.1 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.34 M) followed by a dropwise addition of 4-fluorobenzoyl chloride (0.16 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (6% ethyl acetate in hexanes), affording the product (**4H**) as a white solid (257.6 mg, 96% yield, R_f = 0.54 in 30% ethyl acetate in hexanes, mp = 117–118 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[21] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –107.7 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{16}H_{12}FN_2O$: 267.0928; Found 267.0930.



(**5H**)

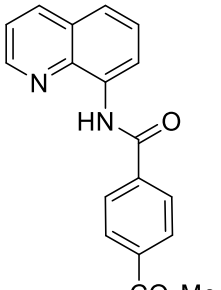
***N*-(4-Cyanobenzoyl)-8-aminoquinoline** (**5H**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (1.44 g, 10 mmol, 1 equiv) and NEt_3 (1.8 mL, 13 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (70 mL, 0.14 M) followed by a dropwise addition of 4-cyanobenzoyl chloride (2.4 g, 13 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl (2 x 15

mL), saturated aqueous $NaHCO_3$ (2 x 15 mL), and brine (25 mL). The organic layers were combined, dried over $NaSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient of 100% hexanes to 40% ethyl acetate in hexanes), affording the product (**5H**) as an off-white solid (2.49 g, 91% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 182–183 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{11}N_3O$: 274.0975; Found 274.0975.



(**6H**)

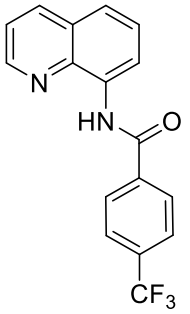
***N*-(4-Nitrobenzoyl)-8-aminoquinoline** (**6H**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (1 g, 6.94 mmol, 1 equiv) and NEt_3 (1.26 mL, 9.02 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (50 mL, 0.14 M) followed by a dropwise addition of 4-nitrobenzoyl chloride (1.5 g, 9.02 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl (2 x 15 mL), saturated aqueous $NaHCO_3$ (2 x 15 mL), and brine (25 mL). The organic layers were combined, dried over $NaSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (gradient of 100% hexanes to 40% ethyl acetate in hexanes), affording the product (**6H**) as a yellow solid (1.91 g, 94% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 178–179 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{16}H_{11}N_3O_3$: 294.0873; Found 294.0873.



(**7H**)

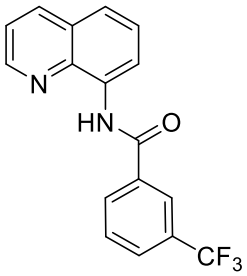
Methyl 4-(quinolin-8-ylcarbamoyl)benzoate (**7H**) was prepared according to the literature procedure.[22] To an oven-dried vial, monomethyl terephthalate (359.9 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo* and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (384.2 mg, 2.7 mmol, 1.3 equiv) and NEt_3 (0.56 mL, 4.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.67 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 6.0 mL total, 0.44 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (20% ethyl acetate in hexanes), affording the product (**7H**) as an off-white solid (421.6 mg, 69% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 125–126 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[22] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{18}H_{14}N_2O_3$: 307.1077; Found 307.1084



(**8H**)

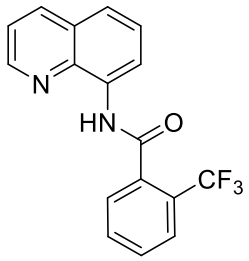
***N*-(4-Trifluorobenzoyl)-8-aminoquinoline** (**8H**) was prepared according to the literature procedure.[23] 8-Aminoquinoline (533 mg, 3.7 mmol, 1 equiv) and NEt_3 (0.67 mL, 4.8 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (11 mL, 0.33 M) followed by a dropwise addition of 4-trifluoromethylbenzoyl chloride (0.71 mL, 4.8 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. Recrystallization from hexanes/ethyl acetate (4:1) afforded the product (**8H**) as an off-white solid (995 mg, 85% yield, mp = 84–85 ºC). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[23] ^{19}F NMR (470 MHz, $CDCl_3$, ppm): δ –63.07 (s, 3F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{11}F_3N_2O$: 317.0896; Found 317.0899.



(**9H**)

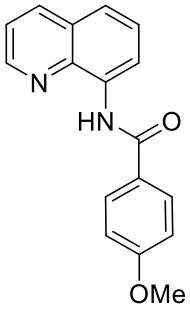
***N*-(3-Trifluoromethylbenzoyl)-8-aminoquinoline** (**9H**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (288.7 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.33 M) followed by a dropwise addition of 3-(trifluoromethyl)benzoyl chloride (0.39 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were

combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**9H**) as a white solid (586.9 mg, 93% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 80–81 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[22] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –62.7 (s, 3F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{12}F_3N_2O$: 317.0896; Found 317.0899.



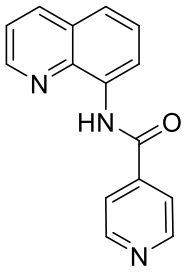
(**10H**)

***N*-(2-Trifluoromethylbenzoyl)-8-aminoquinoline** (**10H**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (290.1 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.36 mL, 2.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.34 M) followed by a dropwise addition of 2-(trifluoromethyl)benzoyl chloride (0.38 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**10H**) as a white solid (609.8 mg, 96% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 105–106 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[24] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –58.9 (d, J = 4 Hz, 3F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{12}F_3N_2O$: 317.0896; Found 317.0904.



(**11H**)

4-Methoxy-*N*-(quinolin-8-yl)benzamide (**11H**) was prepared according to the literature procedure.[15] 8-Aminoquinoline (286.6 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (6.0 mL, 0.33 M) followed by a dropwise addition of 4-methyoxybenzoyl chloride (0.35 mL, 2.6 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (1% ethyl acetate in dichloromethane), affording the product (**11H**) as a white solid (370.9 mg, 67% yield, R_f = 0.31 in 20% ethyl acetate in hexanes, mp = 113–114 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[22] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{15}N_2O_2$: 301.0947; Found 301.0950.

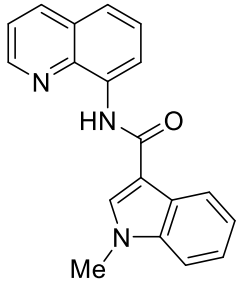


(**12H**)

***N*-(Quinolin-8-yl)isonicotinamide** (**12H**) was prepared according to the literature procedure.[25] To an oven dried vial, isonicotinic acid (245.0 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to

room temperature under N_2 and stirred for 3 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (324.8 mg, 2.3 mmol, 1.1 equiv) and 4-dimethylaminopyridine (24.9 mg, 0.20 mmol, 0.1 equiv) were placed under N_2. Anhydrous CH_2Cl_2 (7.0 mL, 0.32 M) was added and the solution was cooled to 0 °C. NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) was added at 0 °C. A solution of acid chloride in CH_2Cl_2 (4.0 mL, 11.0 mL total, 0.2 M) was added dropwise. The resulting mixture was allowed to warm to room temperature and left to stir overnight. The mixture was diluted with CH_2Cl_2 and washed with brine. Saturated aqueous $NaHCO_3$ was added to the brine layer to raise the pH from 5 to 7. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**12H**) as a peach solid (323.8 mg, 65% yield, R_f = 0.3 in 75% ethyl acetate in hexanes, mp = 122–123 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[25] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{15}H_{12}N_3O$: 250.0975; Found 250.0978.

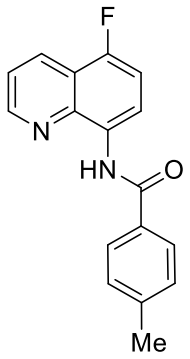


(**13H**)

1-Methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide (13H) was prepared according to the literature procedure.[22] To an oven-dried vial, 1-methyl-1H-indole-3-carboxylic acid (351.5 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 6 h. The solvent was

removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

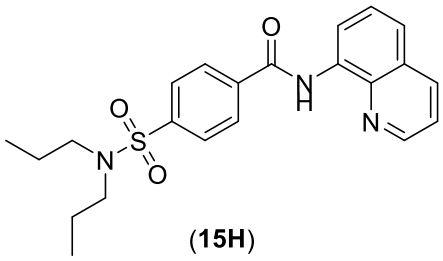
To another oven-dried vial, 8-aminoquinoline (376.7 mg, 2.6 mmol, 1.3 equiv) and NEt_3 (0.55 mL, 4.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.65 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 8.0 mL total, 0.33 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, HCl (1 N), and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (30% ethyl acetate in hexanes), affording the product (**13H**) as an off-white solid (370.8 mg, 61% yield, R_f = 0.15 in 30% ethyl acetate in hexanes, mp = 182–183 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{19}H_{16}N_3O$: 302.1288; Found 302.1295



(**14H**)

***N*-(5-Fluoroquinolin-8-yl)-4-methylbenzamide** (**14H**) was prepared according to the literature procedure.[21] 5-Fluoro-8-aminoquinoline (193.9 mg, 1.2 mmol, 1 equiv) and NEt_3 (0.22 mL, 1.6 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.6 mL, 0.33 M), followed by a dropwise addition of 4-methylbenzoyl chloride (0.2 mL, 1.5 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**14H**)

as a white solid (243.4 mg, 73% yield, R_f = 0.5 in 20% ethyl acetate in hexanes, mp = 131–132 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[17] ^{19}F NMR (470 MHz, $CDCl_3$, ppm): δ –129.3 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1090.



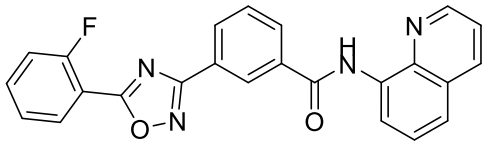
(**15H**)

4-(*N,N*-Dipropylsulfamoyl)-*N*-(quinolin-8-yl)benzamide (**15H**) was prepared according to the literature procedure.[22] To an oven-dried vial, Probenecid (580.3 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (324.1 mg, 2.3 mmol, 1.1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.2 equiv) were dissolved in anhydrous CH_2Cl_2 (4.0 mL, 0.56 M). A solution of acid chloride in CH_2Cl_2 (3.0 mL, 7.0 mL total, 0.32 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine, and the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (15% ethyl acetate in hexanes), affording the product (**15H**) as a white solid (589.0 mg, 70% yield, R_f = 0.4 in 30% ethyl acetate in hexanes, mp = 125–126 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.75 (s, 1H), 8.88 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.83 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.15–8.18 (multiple peaks, 3H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.54–7.58 (multiple peaks, 2H), 7.47 (dd, *J* = 7.7, 4.2 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 4H), 1.55 (m, *J* = 7.7 Hz, 4H), 0.87 (t, *J* = 7.7 Hz, 6H)

^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 163.73, 148.40, 143.15, 138.62, 138.40, 136.44, 134.03, 127.93, 127.941, 127.42, 127.33, 122.19, 121.81, 116.69, 50.00, 21.97, 11.13
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{22}H_{26}N_3O_3S$: 412.1689; Found 412.1689



(**16H**)

3-(5-(2-Fluorophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(quinolin-8-yl)benzamide (**16H**) was prepared according to the literature procedure.[22] To an oven-dried vial, Ataluren (284.0 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.2 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to slowly warm to room temperature under N_2 and stirred for 4.5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

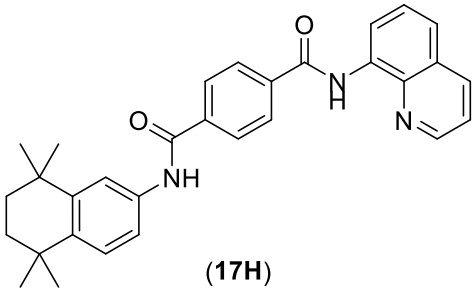
To another oven-dried vial, 8-aminoquinoline (170.4 mg, 1.2 mmol, 1.2 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.6 mL, 0.74 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 5.6 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (5% ethyl acetate in dichloromethane), affording the product (**16H**) as a white solid (317.3 mg, 77% yield, R_f = 0.63 in 40% ethyl acetate in hexanes, mp = 170–171 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.80 (s, 1H), 8.94 (d, *J* = 7.7 Hz, 1H), 8.88 (s, 1H), 8.86 (d, *J* = 4.2 Hz, 1H), 8.37 (d, *J* = 7.0 Hz, 1H), 8.24 (t, *J* = 7.0 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.58–7.62 (multiple peaks, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 9.5 Hz, 1H)

^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 173.02 (d, *J* = 5.3 Hz), 168.14, 164.63, 160.81 (d, *J* = 261 Hz), 148.40, 138.77, 136.37, 136.07, 134.69 (d, *J* = 7.0 Hz), 134.41, 130.97, 130.68, 129.97, 129.44, 217.98, 217.56, 127.42, 126.46, 124.72 (d, *J* = 3.5 Hz), 121.82 (d, *J* = 31.7 Hz), 117.18 (d, *J* = 21.1 Hz), 116.72, 112.77, 112.70

^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.16 (m, 1F)

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{24}H_{16}FN_4O_2$: 411.1252; Found 411.1259

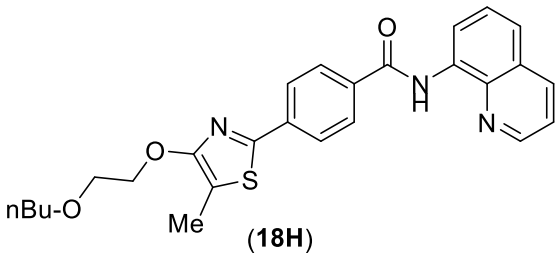


(**17H**)

***N*^{1}-(Quinolin-8-yl)-*N*^{4}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide** (**17H**) was prepared according to the literature procedure.[22] To an oven-dried vial, Tamibarotene (360.5 mg, 1.0 mmol, 1 equiv) were placed under N_2. DMF (5 drops) and CH_2Cl_2 (5.4 mL, 0.2 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 4.5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (169.4 mg, 1.2 mmol, 1.2 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.6 mL, 0.73 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 5.6 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (20% ethyl acetate in hexanes), affording the product (**17H**) as an off-white solid (184.3 mg, 38% yield, R_f = 0.67 in 40% ethyl acetate in hexanes, mp = 155–156 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.74 (s, 1H), 8.86 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.80 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.29 (s, 1H), 8.14 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.62 (s, 1H), 7.49–7.54 (multiple peaks, 3H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 1.68 (s, 4H), 1.29 (s, 6H), 1.27 (s, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 164.92, 164.39, 148.36, 145.76, 141.59, 138.63, 138.24, 137.57, 136.35, 135.26, 134.13, 127.91, 127.55, 127.31, 127.21, 122.03, 121.74, 118.28, 118.22, 116.63, 35.03, 34.99, 34.41, 33.98, 31.83, 31.78
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{31}H_{32}N_3O_2$: 478.2489; Found 478.2499



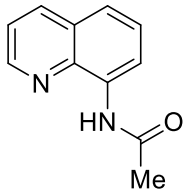
(**18H**)

4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-*N*-(quinolin-8-yl)benzamide (**18H**) was prepared according to the literature procedure.[22] To an oven-dried vial, 4-[4-(2-butoxyethoxy)-5-methyl-1,3-thiazol-2-yl]benzoic acid (332.9 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to slowly warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo* and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (200.9 mg, 1.4 mmol, 1.4 equiv) and NEt_3 (0.30 mL, 2.2 mmol, 2.2 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.70 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 4.0 mL total, 0.35 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (15% ethyl acetate in hexanes), affording the

product (**18H**) as a yellow solid (366.5 mg, 80% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 78–79 °C).

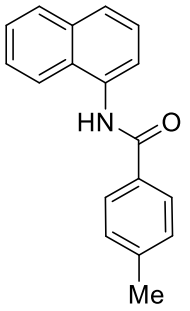
^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.75 (s, 1H), 8.91 (d, *J* = 7.7 Hz, 1H), 8.82 (d, *J* = 4.2 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.4, 1H), 7.44 (dd, *J* = 7.7, 4.2 Hz, 1H), 4.51 (t, *J* = 4.9 Hz, 2H), 3.77 (t, *J* = 4.9 Hz, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.58 (m, *J* = 7.1 Hz, 2H), 1.38 (m, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 164.60, 159.99, 157.68, 148.26, 138.67, 136.87, 136.31, 135.16, 134.41, 127.92, 137.80, 127.40, 125.41, 121.71, 121.67, 116.48, 108.63, 71.15, 69.74, 69.43, 31.72, 19.25, 13.91, 9.41
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{26}H_{28}N_3O_3S$: 462.1846; Found 462.1848



(**S1**)

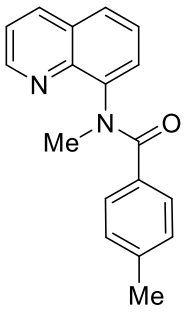
***N*-(Quinolin-8-yl)acetamide** (**S1**) was prepared according to the literature procedure.[26] 8-Aminoquinoline (144.3 mg, 1.0 mmol, 1 equiv) was dissolved in acetic anhydride (5.0 mL, 0.2 M) and stirred overnight at room temperature. The mixture was concentrated and washed with brine and CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*, affording the product (**S1**) as a white solid (171.1 mg, 94% yield, R_f = 0.2 in 20% ethyl acetate in hexanes, mp = 94–96 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 9.75 (bs, 1H), 8.76 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.73 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.7, 4.2 Hz, 1H), 2.32 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 168.67, 148.03, 137.17, 136.29, 134.47, 127.85, 127.33, 121.51, 121.37, 116.33, 25.07
HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{11}H_{10}N_2O$: 187.0866; Found 187.0866



(**S2**)

4-Methyl-*N*-(naphthalen-1-yl)benzamide (**S2**) was prepared according to the literature procedure.[21] 1-Aminonaphthalene (215.0 mg, 1.5 mmol, 1 equiv) and NEt_3 (0.3 mL, 2.2 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (4.6 mL, 0.33 M), followed by a dropwise addition of 4-methylbenzoyl chloride (0.25 mL, 1.9 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**S2**) as an off-white solid (266.0 mg, 67% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 170–171 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[27] HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{18}H_{16}NO$: 262.1226; Found 262.1231.



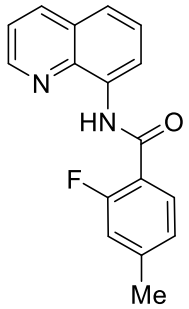
(**S3**)

***N*,4-Dimethyl-*N*-(quinolin-8-yl)benzamide** (**S3**) was prepared according to the modified literature procedure.[28] A suspension of sodium hydride (43.5 mg, 1.8 mmol, 3.0 equiv) in DMF (3.0 mL) was added to a solution of 4-methyl-*N*-(quinolin-8-yl)benzamide (154.0 mg, 0.60 mmol, 1 equiv) in DMF (3.0 mL, 6.0 mL total, 0.10 M) in an oven-dried vial at 0 °C under N_2. The reaction mixture was warmed to room temperature and stirred for 3 h. Methyl iodide (0.05 mL, 0.80 mmol, 1.4 equiv) was added, and the reaction was stirred

an additional 1 h at room temperature under N_2. The reaction was diluted with CH_2Cl_2 (40 mL), washed with water (40 mL), dried over $MgSO_4$, and concentrated *in vacuo*, affording the product (**S3**) as a colorless oil (49.7 mg, 31% yield, R_f = 0.12 in 40% ethyl acetate in hexanes).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 8.96 (d, *J* = 4.2 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 7.0, 2.1, 1H), 7.39 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.31–7.35 (multiple peaks, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 7.7 Hz, 2H), (s, 3H), 2.10 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 172.09, 150.51, 143.87, 142.68, 139.34, 136.18, 133.66, 129.20, 129.12, 128.05, 128.01,127.39, 126.21, 121.62, 38.49, 21.17
HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{18}H_{17}N_2O$: 277.1335; Found 277.1341

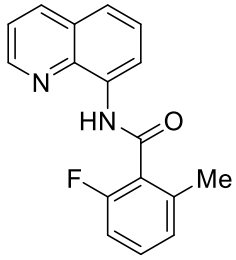
4.9.2. Preparation and characterization of fluorinated standards



(**3H**/**1F**)

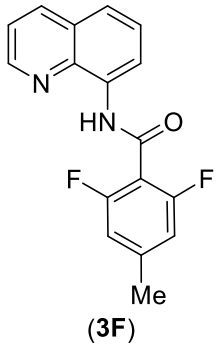
2-Fluoro-4-methyl-*N*-(quinolin-8-yl)benzamide (**3H**/**1F**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (290.5 mg, 2.0 mmol, 1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (7.0 mL, 0.29 M), followed by a dropwise addition of 2-fluoro-4-methylbenzoyl chloride (408.0 mg, 2.4 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3H**/**1F**) as a white solid (199.1 mg, 35% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 131–132 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F

NMR (377 MHz, $CDCl_3$, ppm): δ –112.8 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{14}FN_2O$: 281.1085; Found 281.1088.



(**2F**)

2-Fluoro-6-methyl-*N*-(quinolin-8-yl)benzamide (**2F**) was prepared according to the literature procedure.[15] In a glovebox, 2-methyl-*N*-(quinolin-8-yl)benzamide (129.0 mg, 0.5 mmol, 1 equiv), copper(I) iodide (24.0 mg, 0.13 mmol, 0.26 equiv), silver fluoride (245.2 mg, 1.9 mmol, 3.9 equiv), and *N*-methylmorpholine oxide (295.8 mg, 2.5 mmol, 5.1 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min. The reaction was then heated to 120 °C for 20 min. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**2F**) as a white solid (27.5 mg, 20% yield, R_f = 0.5 in 20% ethyl acetate in hexanes, mp = 122–123 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –115.9 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{15}N_2O$: 281.1085; Found 281.1087.



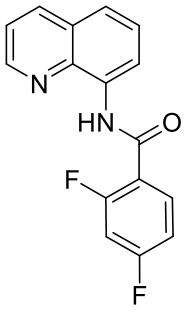
(**3F**)

2,6-Difluoro-*N*-(quinolin-8-yl)-4-methylbenzamide (**3F**) was prepared according to the literature procedure.[22] To an oven-dried vial, 2,6-difluoro-4-methylbenzoic acid (197.7

mg, 1.2 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.3 mL, 0.5 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.12 mL, 1.4 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

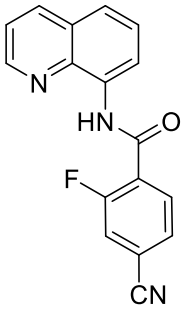
To another oven-dried vial, 8-aminoquinoline (232.1 mg, 1.6 mmol, 1.4 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 2.20 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.80 M). A solution of acid chloride in CH_2Cl_2 (3.2 mL, 5.2 mL total, 0.31 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**3F**) as a white solid (97.2 mg, 28% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 136–137 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.34 (s, 1H), 8.92 (dd, *J* = 7.0, 1.4 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.14 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.57–7.52 (multiple peaks, 2H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 2.38 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 160.80 (d, *J* = 7.0 Hz), 159.37 (d, *J* = 7.0 Hz), 158.75, 148.33, 143.71 (t, *J* = 10.6 Hz), 138.40, 136.28, 134.25, 127.89, 127.34, 122.16, 121.66, 116.95, 112.79 (d, *J* = 3.5 Hz), 112.67 (d, *J* = 3.5 Hz), 111.76 (t, *J* = 19.4 Hz), 21.52
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.7 (d, *J* = 8 Hz, 2F)
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{17}H_{13}F_2N_2O$: 299.0990; Found 299.0990



(**4F**)

2,4-Difluoro-*N*-(quinolin-8-yl)benzamide (4F) was prepared according to the literature procedure.[15] 8-Aminoquinoline (145.2 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.34 M) followed by a slow dropwise addition of 2,4-difluorobenzoyl chloride (0.15 mL, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature exposed to air overnight. The mixture was washed with 1 N HCl, sat. $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (8% ethyl acetate in hexane) affording the product (**4F**) as a white solid (261.4 mg, 49% yield, R_f = 0.58 in 20% ethyl acetate in hexanes, mp = 136–137 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[29] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –103.69 (m, 1F), –107.49 (m, 1F). HRMS (ESI+) $[M+H]^+$ Calculated for $C_{16}H_{11}F_2N_2O$: 285.0834; Found 285.0834.

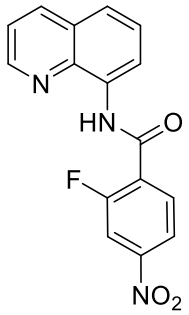


(**5F**)

4-Cyano-2-fluoro-*N*-(quinolin-8-yl)benzamide (**5F**) was prepared according to the literature procedure.[22] To an oven-dried vial, 4-cyano-2-fluorobenzoic acid (165.5 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.50 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature

under N_2 and stirred for 5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

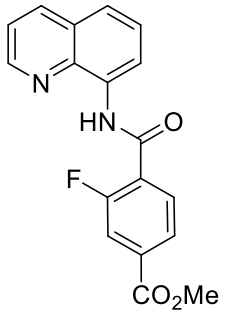
To another oven-dried vial, 8-aminoquinoline (209.8 mg, 1.5 mmol, 1.5 equiv) and NEt_3 (0.28 mL, 2.0 mmol, 2.0 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.73 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 7.0 mL total, 0.21 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**5F**) as an off-white solid (13.3 mg, 5% yield, R_f = 0.8 in 20% ethyl acetate in hexanes, mp = 205–206 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –109.59 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{11}FN_3O$: 292.0881; Found 292.0887.



(**6F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-nitrobenzamide (**6F**) was prepared according to the literature procedure.[22] To an oven-dried vial, 2-fluoro-4-nitrobenzoic acid (191.5 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.52 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.1 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 5 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

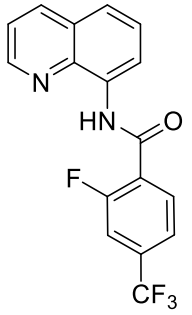
To another oven-dried vial, 8-aminoquinoline (196.3 mg, 1.4 mmol, 1.3 equiv) and NEt_3 (0.28 mL, 2.0 mmol, 1.9 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.68 M). A solution of acid chloride in CH_2Cl_2 (3.0 mL, 5.0 mL total, 0.27 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**6F**) as a yellow solid (10.6 mg, 3% yield, R_f = 0.9 in 20% ethyl acetate in hexanes, mp = 200–201 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.04 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{16}H_{11}FN_3O_3$: 312.0779; Found 312.0776.



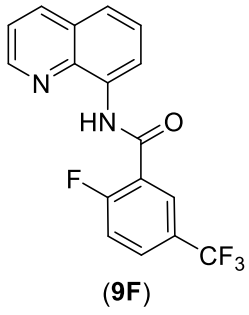
(**7F**)

Methyl 3-fluoro-4-(quinolin-8-ylcarbamoyl)benzoate (**7F**) was prepared according to the literature procedure.[15] In a glovebox, methyl 4-(quinolin-8-ylcarbamoyl)benzoate (228.1 mg, 0.74 mmol, 1 equiv), copper(I) iodide (16.5 mg, 0.09 mmol, 0.12 equiv), silver fluoride (390.3 mg, 3.1 mmol, 4.1 equiv), and *N*-methylmorpholine oxide (441.3 mg, 3.8 mmol, 5.1 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min at room temperature. The reaction was heated to 90 °C for 1 h. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**7F**) as an off-white solid (13.2 mg, 6% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 142–143 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –

111.56 (s, 1F). HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{18}H_{14}FN_2O_3$: 325.0983; Found 325.0985.

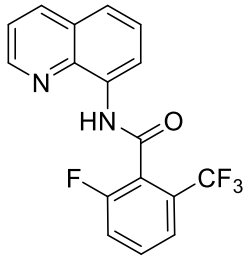

(**8F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-trifluorobenzamide (**8F**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (144 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.33 M) followed by a dropwise addition of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (0.2 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (8% ethyl acetate in hexanes), affording the product (**8F**) as an off-white solid (304 mg, 91% yield, R_f = 0.32 in 10% ethyl acetate in hexanes, mp = 82–84 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –63.14 (s, 3F), –110.13 (m, 1F). HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{10}F_4N_2O$: 335.0802; Found 335.0805.


(**9F**)

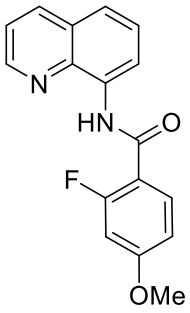
2-Fluoro-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (**9F**) was prepared according to the literature procedure.[21] 8-Aminoquinoline (145.3 mg, 1.0 mmol, 1 equiv) and NEt_3

(0.18 mL, 1.3 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3 mL, 0.34 M), followed by a dropwise addition of 2-fluoro-5-(trifluoromethyl)benzoyl chloride (0.2 mL, 1.3 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**9F**) as a white solid (251.8 mg, 75% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 143–140 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –62.26 (s, 3F), –107.21 (m, 1F). HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{11}F_4N_2O$: 335.0802; Found 335.0811.



(**10F**)

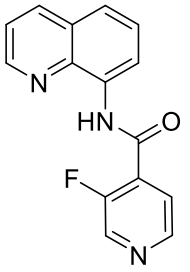
2-Fluoro-*N*-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (**10F**) was prepared according to the literature procedure.[15] In a glovebox, *N*-(quinolin-8-yl)-2-(trifluoromethyl)benzamide (155.0 mg, 0.49 mmol, 1 equiv), copper(I) iodide (19.3 mg, 0.10 mmol, 0.21 equiv), silver fluoride (254.4 mg, 2.0 mmol, 4.1 equiv), and *N*-methylmorpholine oxide (300.5 mg, 2.6 mmol, 5.2 equiv) were dissolved in DMF in the dark. The mixture was allowed to stir for 5 min at room temperature. The reaction was heated to 120 °C for 90 min. The solution was cooled to room temperature, diluted with ethyl acetate, filtered through a celite plug, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**10F**) as a white solid (20.0 mg, 12% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 173–174 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –59.24 (s, 3F), –113.14 (m, 1F). HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{11}F_4N_2O$: 335.0802; Found 335.0806.



(**11F**)

2-Fluoro-*N*-(quinolin-8-yl)-4-methoxybenzamide (**11F**) was prepared according to the literature procedure.[22] To an oven-dried vial, 2-fluoro-4-methoxybenzoic acid (171.1 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.2 mL, 0.46 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h and then slowly warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

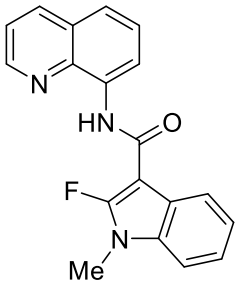
To another oven-dried vial, 8-aminoquinoline (159.7 mg, 1.1 mmol, 1.1 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (1.4 mL, 0.79 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 3.4 mL total, 0.33 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$, 1 N HCl, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (100% dichloromethane), affording the product (**11F**) as a white solid (187.5 mg, 63% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 147–148 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[30] ^{19}F NMR (377 MHz,s $CDCl_3$, ppm): δ –109.1 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{17}H_{14}FN_2O_2$: 297.1034; Found 297.1037.



(**12F**)

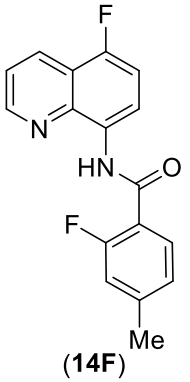
3-Fluoro-*N*-(quinolin-8-yl)isonicotinamide (**12F**) was prepared according to the literature procedure.[22] To an oven-dried vial, 3-fluoroisonicotinic acid (140.7 mg, 1.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (2.0 mL, 0.50 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.1 mL, 1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature under N_2 and stirred for 4 h. The solvent was removed *in vacuo*, and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (206.3 mg, 1.4 mmol, 1.4 equiv) and NEt_3 (0.30 mL, 2.2 mmol, 2.2 equiv) were dissolved in anhydrous CH_2Cl_2 (2.0 mL, 0.72 M). A solution of acid chloride in CH_2Cl_2 (4.0 mL, 6.0 mL total, 0.24 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**12F**) as an off-white solid (30.6 mg, 12% yield, R_f = 0.4 in 50% ethyl acetate in hexanes, mp = 155–156 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –127.46 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{15}H_{11}FN_3O$: 268.0881; Found 268.0887.



(**13F**)

2-Fluoro-1-methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide (13F) was prepared according to the literature procedure.[15] In a glovebox, a 1 dram vial was charged with 1-methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide **(13H)** (75.3 mg, 0.25 mmol, 1 equiv), copper(I) iodide (5.7 mg, 0.030 mmol, 0.12 equiv), *N*-methylmorpholine oxide (152.9 mg, 1.3 mmol, 5.2 equiv) and AgF (129.3 mg, 1.0 mmol, 4.1 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 50 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 10 mL). The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**13F**) as a yellow solid (11.5 mg, 14% yield, R_f = 0.38 in 30% ethyl acetate in hexanes, mp >210 °C). The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.[15] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –124.0 (m, 1F). HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{19}H_{15}FN_3O$: 320.1194; Found 320.1198.

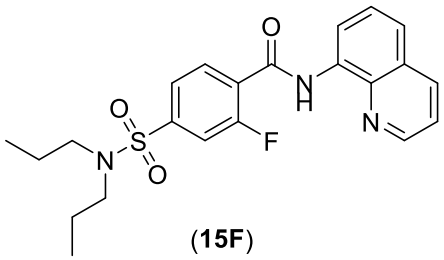


(**14F**)

2-Fluoro-*N*-(5-fluoroquinolin-8-yl)-4-methylbenzamide (**14F**) was prepared according to the literature procedure.[21] 5-Fluoro-8-aminoquinoline (101.6 mg, 0.63 mmol, 1.4 equiv)

and NEt_3 (0.11 mL, 0.79 mmol,1.7 equiv) were dissolved in anhydrous CH_2Cl_2 (2.2 mL, 0.78 M), followed by a dropwise addition of a solution of 2-fluoro-4-methylbenzoyl chloride (136.0 mg, 0.46 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 mL, 2.2 mL total, 0.21 M). The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexanes), affording the product (**14F**) as a white solid (113.7 mg, 48% yield, R_f = 0.6 in 20% ethyl acetate in hexanes, mp = 177–178 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 10.97 (d, *J* = 14 Hz, 1H), 8.94 (d, *J* = 5.6 Hz, 1H), 8.92 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.45 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.11 (t, *J* = 8.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.26 (t, *J* = 4.2 Hz, 1H), 7.13 (d, *J* = 5.6 Hz, 1H), 7.04 (d, *J* = 14 Hz, 1H), 2.44 (s, 3H)
^{13}C NMR (175 MHz, $CDCl_3$, ppm): δ 161.58 (d, *J* = 3.5 Hz), 160.49 (d, *J* = 248.2 Hz), 153.11 (d, *J* = 249.9 Hz), 149.27, 145.08 (d, *J* = 8.8 Hz), 139.05 (d, *J* = 1.8 Hz), 131.83 (d, *J* = 1.8 Hz), 131.48 (d, *J* = 3.5 Hz), 129.66 (d, *J* = 3.5 Hz), 125.73 (d, *J* = 3.5 Hz), 121.69 (d, *J* = 1.8 Hz), 118.88 (d, *J* = 12.3 Hz), 118.75 (d, *J* = 17.6 Hz), 116.70 (d, *J* = 3.5 Hz), 116.61 (d, *J* = 12.3 Hz), 110.42 (d, *J* = 19.4 Hz), 21.38
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.97 (m, 1F), –128.97 (m, 1F)
HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{17}H_{12}F_2N_2O$: 299.0990; Found 299.0992



(**15F**)

4-(*N,N*-Dipropylsulfamoyl)-2-fluoro-*N*-(quinolin-8-yl)benzamide (**15F**) was prepared according to the literature procedure.[15] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **13H** (104.0 mg, 0.25 mmol, 1 equiv), copper(I) iodide (4.7 mg, 0.025 mmol, 0.10 equiv), *N*-methylmorpholine oxide (118.4 mg, 1.0 mmol, 4.0 equiv) and AgF (94.1 mg, 0.74 mmol, 2.9 equiv). The solids were dissolved in anhydrous DMF (1.0

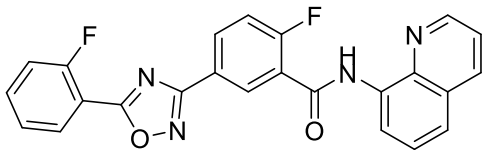
mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 30 min. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 1 mL). The crude residue was purified by column chromatography (8% ethyl acetate in hexanes), affording the product (**15F**) as a white solid (29.3 mg, 27% yield, R_f = 0.3 in 20% ethyl acetate in hexanes, mp = 176–177 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 12 Hz, 1H), 8.93 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.87 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.32 (t, *J* = 7.7 Hz, 1H), 8.19 (dd, *J* = 7.7, 2.1 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.69 (dd, *J* = 10.5, 1.4 Hz, 1H), 7.57–7.60 (multiple peaks, 2H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.13 (t, *J* = 7.7 Hz, 4H), 1.57 (m, *J* = 7.7 Hz, 4H), 0.88 (t, *J* = 7.7 Hz, 6H)

^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 160.36 (d, *J* = 100.3 Hz), 160.06, 159.20, 148.64, 145.09 (d, *J* = 7.0 Hz), 138.72, 136.37, 134.36, 133.10, 133.09, 127.99, 127.34, 125.49 (d, *J* = 10.6 Hz), 123.08 (d, *J* = 3.5 Hz), 122.58, 121.84, 117.45, 115.54, 115.38, 50.05, 21.99, 11.16

^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –109.41 (m, 1F)

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{22}H_{25}FN_3O_3S$: 430.1595; Found 430.1591

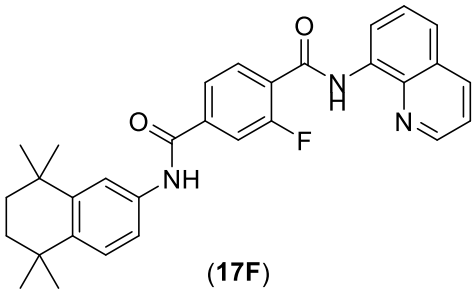


(**16F**)

2-Fluoro-5-(5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl)-*N*-(quinolin-8-yl)benzamide (**16F**) was prepared according to the literature procedure.[15] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **16H** (98.2 mg, 0.24 mmol, 1 equiv), copper(I) iodide (6.2 mg, 0.03 mmol, 0.14 equiv), *N*-methylmorpholine oxide (120.5 mg, 1.0 mmol, 4.3 equiv), and AgF (93.1 mg, 0.73 mmol, 3.1 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.24 M). The sealed vial was stirred at room temperature for

5 min, covered with aluminum foil, and then heated to 75 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 20 mL). The crude residue was purified by column chromatography (4% ethyl acetate in dichloromethane), affording the product (**16F**) as a white solid (27.2 mg, 20% yield, R_f = 0.50 in 30% ethyl acetate in hexanes, mp = 201–202 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 4.9 Hz, 1H), 9.04 (d, *J* = 7.7 Hz, 1H), 8.99 (d, *J* = 7.7 Hz, 1H), 8.87 (d, *J* = 4.2, 1H), 8.35 (m, 1H), 8.24 (t, *J* = 7.7 Hz,1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.56–7.63 (multiple peaks, 3H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39 (t, *J* = 9.8 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 9.8 Hz, 1H)
^{13}C NMR (176 MHz, d_7-DMF, 75 °C, ppm): δ 173.54, 167.60, 161.59, 160.61, 160.12, 149.40, 138.85, 136.90, 135.87 (d, *J* = 10.6 Hz), 134.87, 132.99 (d, *J* = 10.6 Hz), 131.27, 131.04, 128.51, 127.28, 125.63 (d, *J* = 5.3 Hz), 124.24, 123.44 (d, *J* = 12.3 Hz), 122.91, 122.53, 118.18 (d, *J* = 22.9 Hz), 117.46 (d, *J* = 22.9 Hz), 117.21, 112.48 (d, *J* = 12.3 Hz),
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –108.15 (m, 1F), –108.41 (m, 1F)
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{24}H_{15}F_2N_4O_2$: 429.1158; Found 429.1158

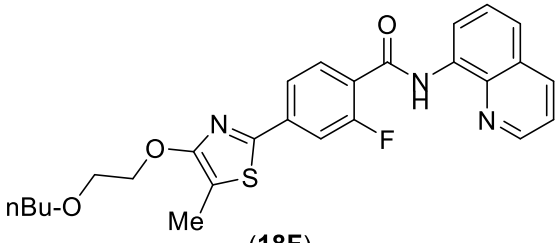


(**17F**)

2-Fluoro-*N*^{1}-(quinolin-8-yl)-*N*^{4}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)terephthalamide (**15F**) was prepared according to the literature procedure.[15] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **17H** (118.0 mg, 0.25 mmol, 1 equiv), copper(I) iodide (4.1 mg, 0.02 mmol, 0.09 equiv), *N*-methylmorpholine oxide (119.7 mg, 1.0 mmol, 4.1 equiv), and AgF (99.0 mg, 0.78 mmol, 3.2 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.25 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 1

h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 20 mL). The crude residue was purified by column chromatography (18% ethyl acetate in hexanes), affording the product (**17F**) as a white solid (16.5 mg, 12% yield, R_f = 0.52 in 30% ethyl acetate in hexanes, mp = 190–191 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.19 (d, *J* = 14.0 Hz, 1H), 8.94 (m, 1H), 8.86 (m, 1H), 8.28 (m, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.91 (m, 1H), 7.78 (d, *J* = 10.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.54–7.58 (multiple peaks, 3H), 7.44–7.48 (multiple peaks, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 1.68 (s, 4H), 1.29 (s, 6H), 1.27 (s, 6H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 163.35, 161.11, 160.62, 159.68, 148.61, 145.91, 141.98, 140.27 (d, *J* = 7.0 Hz), 138.72, 136.28, 134.81, 134.46, 132.58, 127.95, 127.34, 127.30, 124.64 (d, *J* = 12.3 Hz), 122.60, 122.43, 121.79, 118.26 (d, *J* = 19.4 Hz), 117.36, 115.92 (d, *J* = 26.4 Hz), 34.99, 34.96, 34.44, 34.03, 31.83, 31.80
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –110.5 (m, 1F)
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{31}H_{31}FN_3O_2$: 496.2395; Found 496.2396



(**18F**)

4-(4-(2-Butoxyethoxy)-5-methylthiazol-2-yl)-2-fluoro-*N*-(quinolin-8-yl)benzamide (**18F**) was prepared according to the literature procedure.[15] In a glovebox, a 1 dram vial was charged with *N*-(8-quinolinyl)benzamide **18H** (109.5 mg, 0.24 mmol, 1 equiv), copper(I) iodide (5.2 mg, 0.03 mmol, 0.12 equiv), *N*-methylmorpholine oxide (141.6 mg, 1.2 mmol, 5.1 equiv), and AgF (127.5 mg, 1.0 mmol, 4.2 equiv). The solids were dissolved in anhydrous DMF (1.0 mL, 0.24 M). The sealed vial was stirred at room temperature for 5 min, covered with aluminum foil, and then heated to 75 °C for 1 h. The reaction was cooled to room temperature, diluted with ethyl acetate (2 mL), filtered through a pad of celite, and then the solid phase was washed with ethyl acetate (2 x 1 mL). The crude

residue was purified by column chromatography (9% ethyl acetate in hexanes), affording the product (**18F**) as a yellow solid (44.7 mg, 39% yield, R_f = 0.4 in 20% ethyl acetate in hexanes, mp = 96–97 °C).

^{1}H NMR (700 MHz, $CDCl_3$, ppm): δ 11.15 (d, *J* = 14 Hz, 1H), 8.96 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.22 (t, *J* = 8.4, 1H), 8.16 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.71–7.74 (multiple peaks, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.51 (t, *J* = 4.9 Hz, 2H), 3.77 (t, *J* = 4.9 Hz, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.58 (m, *J* = 7.1 Hz, 2H), 1.38 (m, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (176 MHz, $CDCl_3$, ppm): δ 161.3 (d, *J* = 74 Hz), 161.06, 160.26, 160.08, 156.14 (d, *J* = 3.5 Hz), 148.51, 139.00 (d, *J* = 10.6 Hz), 138.80, 136.26, 134.81, 132.66 (d, *J* = 1.8 Hz), 127.98, 127.38, 122.09, 121.89 (d, *J* = 10.6 Hz), 121.69, 121.32 (d, *J* = 1.8 Hz), 117.28, 112.67 (d, *J* = 28 Hz), 109.56, 71.20, 69.83, 69.44, 31.76, 19.28, 13.92, 9.47
^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –111.48 (m, 1F)
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{26}H_{27}FN_3O_3S$: 480.1752; Found 480.1753

4.10. References

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Chapter 5

Cu-Mediated Fluorination of Aryl Iodides and Other Applications

This chapter includes projects that are incomplete. Each section will have a brief introduction, the results of the project to date, and an outlook of where these projects could go when complete.

5.1. [^{18}F]Radiofluorination of Aryl Iodides

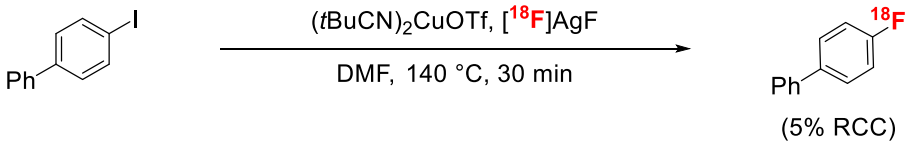
Most commonly used precursors for PET imaging are synthesized from an aryl iodide starting material (see Chapter 1 for more details). Instead of transforming the aryl iodide into a more complex starting material, utilizing the aryl iodide would be advantageous. They are commonly used to make other precursors and are known to be stable to various other chemical transformations. Thus, a method that involves a [^{18}F]radiofluorination of aryl iodides would be ideal, allowing for a quick screening of drug candidate and preliminary radiotracers. A target could be synthesized and initial studies performed even if the overall yield of the reaction is low; confirming that the target is worth pursuing.

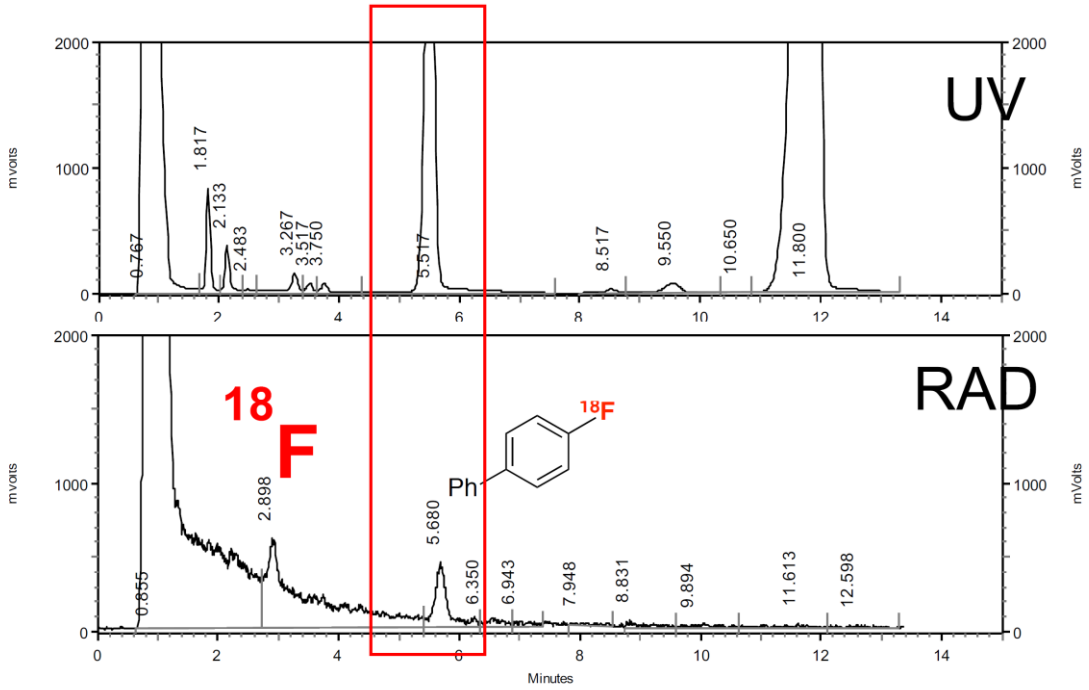
In 2012, Hartwig and coworkers developed a fluorination method using aryl iodides and a specialized Cu(I) complex.[1] This reported methodology used a large excess of AgF and Cu(I) complex, required high temperatures, and long reaction times. The reaction had good functional group tolerance but formed the dehalogenated side products which made the purification difficult.

5.1.1. Initial Results and Optimization[A]

One of the main challenges in the Hartwig method was the long reaction time relative to a PET time scale (the reported conditions required 22 hours).[1] An initial result discovered by Dr. Naoko Ichiishi found that the desired product was formed in 5% RCC (confirmed by a HPLC co-injection with the authentic standard, Scheme 5.1).[2]

Scheme 5.1. Preliminary Hit[2]



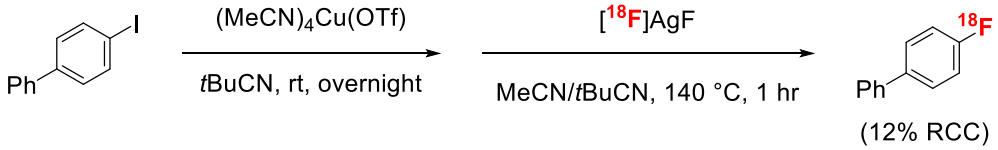


It was hypothesized that the low RCC observed was due to slow reaction rates. The main strategy investigated was to make the Cu catalyst more reactive. Various ligands were screened but most of them produced unstable Cu-^{18}F complexes or [^{18}F]side product that could not be isolated and yielded no desired product. To overcome the slow oxidative addition, the Cu catalyst and the substrate were pre-stirred overnight at room

[A]The work this section was done in collaboration with Dr. Naoko Ichiishi and Dr. Allen Brooks.

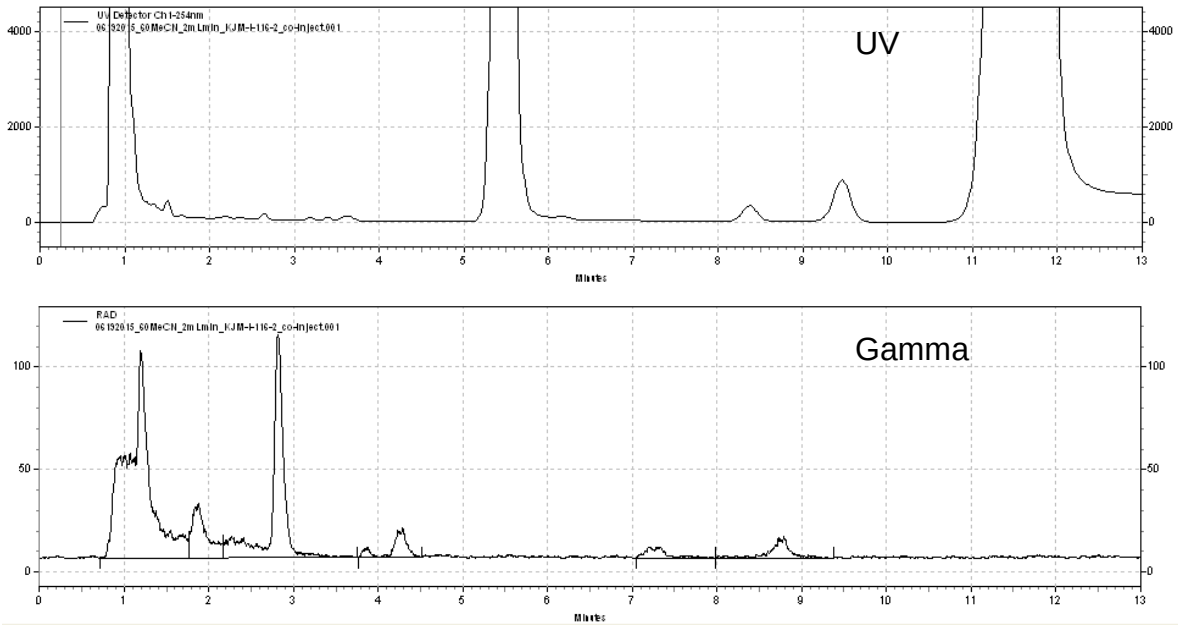
temperature. At the point, when I joined the project, there had been several attempts to optimize the reaction that raised the radio-TLC conversion, but later found that the desired product was not being formed (by radio-HPLC, Scheme 5.2). The conditions when I took over the product are depicted in Scheme 5.2. Radio-TLC provided a 12% RCC, but when subjected to radio-HPLC, the desired product was not formed (Scheme 5.2).

Scheme 5.2. Initial "Optimized" Conditions



(12% RCC)

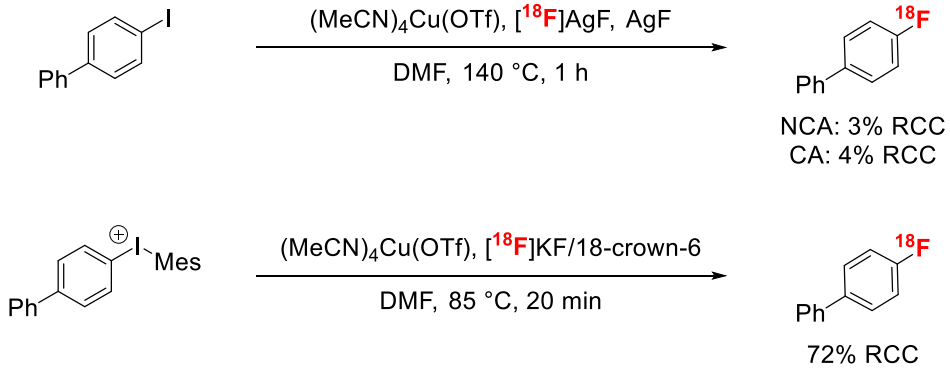
Conditions: aryl iodide (10 µmol) and $(MeCN)_4Cu(OTf)$ (1.5 equiv) were stirred in *t*BuCN (0.3 mL) at room temperature overnight. [^{18}F]AgF in MeCN (0.1 mL) was added and the reaction was set to 140 °C for 1 h. RCC was determined by radio-TLC. HPLC traces of the crude reaction mixture with a co-inject of the authentic product are included below:



To confirm that the reaction was feasible for [^{18}F]radiofluorination, the initial conditions discovered by Dr. Naoko Ichiishi were re-investigated. The commercially available Cu catalyst $(MeCN)_4Cu(OTf)$ was found to form the desired product with and without AgF carrier (Scheme 5.3). HPLC co-injection confirmed the desired product was

being formed. To further ascertain the formation of the product, the same [^{18}F]product was made via the iodonium salt method[3] and the authentic [^{18}F]product was spiked in the reaction conditions (Scheme 5.3).

Scheme 5.3. Investigation of [^{18}F]Radiofluorination of Aryl Iodides



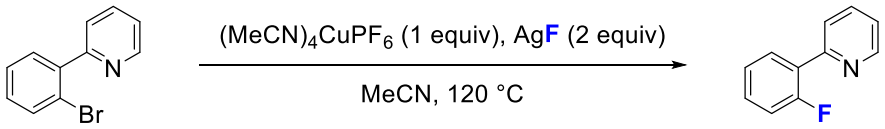
Conditions: aryl iodide (50 µmol), $(MeCN)_4Cu(OTf)$ (3 equiv), and AgF (2 equiv) were stirred in DMF (0.3 mL) at room temperature overnight. [^{18}F]AgF in DMF (0.1 mL) was added and the reaction was set to 140 °C for 1 h. RCC was determined by radio-TLC and product identity was confirmed by radio-HPLC.

In summary, this transformation could be possible with further optimization. The methodology currently suffers from low RCC (<5%). The strategies listed above could still be used to address the limitations, but careful consideration will need to be made to ensure the correct product is being formed.

5.1.2. Directed [^{18}F]Radiofluorination of Aryl Iodides

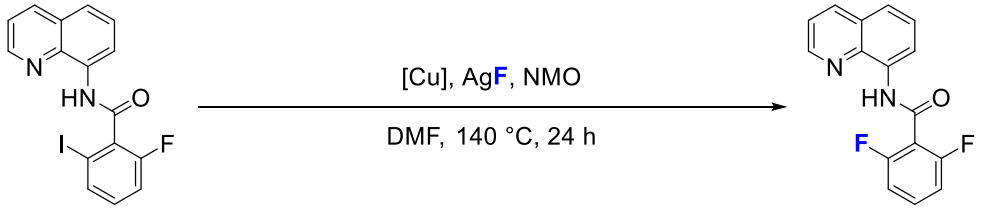
As shown above, Hartwig's conditions were limited to aryl iodides, needed high temperatures, long reaction times, an excess of an activated metal salt, and excess fluoride.[1] Our attempts at [^{18}F]radiofluorination encountered similar limitations. In 2013, Liu and coworkers had demonstrated that catalytic Cu(I) could be used for aryl bromide fluorination with AgF, but required coordinating directing groups such as pyridine (Scheme 5.4).[4] Previous attempts found that this methodology was specific for pyridine directing groups and could not be extended to other removeable groups.[5]

Scheme 5.4. Liu and Coworkers Pyridine Assisted Fluorination[4]



Inspired by the 8-aminoquinoline directed fluorination[6] and subsequent [^{18}F]radiofluorination developed in Chapter 4,[7] we sought to develop a general Cu-mediated fluorination of aryl halides. The model substrate, with blocked *ortho* C–H positions, formed no product when subjected to Hartwig's optimized conditions (Table 5.1, entry 1). Daugulis's optimized conditions gave a 14% of the product (Table 5.1, entry 2). A more soluble copper source ($Cu(OAc)_2$) gave a similar yield of desired product (Table 5.1, entry 3). To further optimize the reaction, a shorter time point was analyzed on half scale reaction (Table 5.1, entry 4), which boosted the yield to 37%. Ar-Br substrates were also amenable to this reaction and gave a slight increase in the NMR yield (Table 5.1, entry 5).

Table 5.1. Initial Results with Directed Fluorination of Aryl Iodides



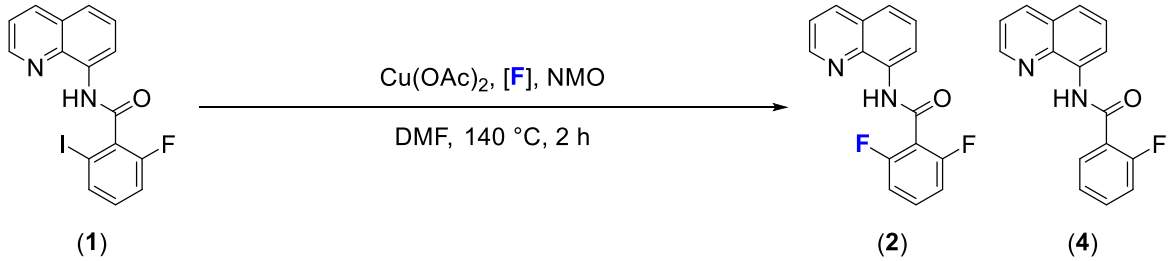
(**1**) (**2**)

entry	[Cu]	AgF (equiv)	NMO (equiv)	yield 2 (%)
1	(*t*BuCN)$_2$Cu(OTf)	2	--	nd
2	CuI	3.5	4.5	14
3	$Cu(OAc)_2$	3.5	4.5	12
4[a]	$Cu(OAc)_2$	3.5	4.5	37
5[b]	$Cu(OAc)_2$	3.5	4.5	54

Conditions: Substrate **1** (0.1 mmol), Cu source [(*t*BuCN)$_2$Cu(OTf) (3 equiv), CuI (0.25 equiv), $Cu(OAc)_2$ (0.25 equiv)], AgF (X equiv), and NMO (4.5 equiv) were stirred in DMF (0.5 mL, 0.2 M) at 140 ºC for 24 h. Yields determined by ^{19}F NMR spectroscopy using 1,2-difluorobenzene as standard. [a]Substrate **1** (0.05 mmol), heated at 140 ºC for 2 h. [b]Aryl-Br (**3**, 0.05 mmol) was used.

With preliminary conditions in hand, other fluoride sources were investigated. KF gave no product except when an excess of 18-crown-6 was used and only trace product was observed with a large amount of protodehalogenated product formed as the major product (Table 5.2, entries 2-3). More soluble CsF gave product with and without NMO and decreased the amount of protodehalogenated side product formed (Table 5.2, entries 4-6). As seen with AgF, when Ar─Br was used as a substrate, a slight increase in yield was obtained (Table 5.2, entry 6). Anhydrous TMAF also gave product and no protodehalogenated side product that was observed with the other fluoride sources (Table 5.2, entry 7). The addition of AgOTf with the alternative fluoride sources gave a decrease of yield in all cases.

Table 5.2. Optimization with other fluoride sources



(**1**) (**2**) (**4**)

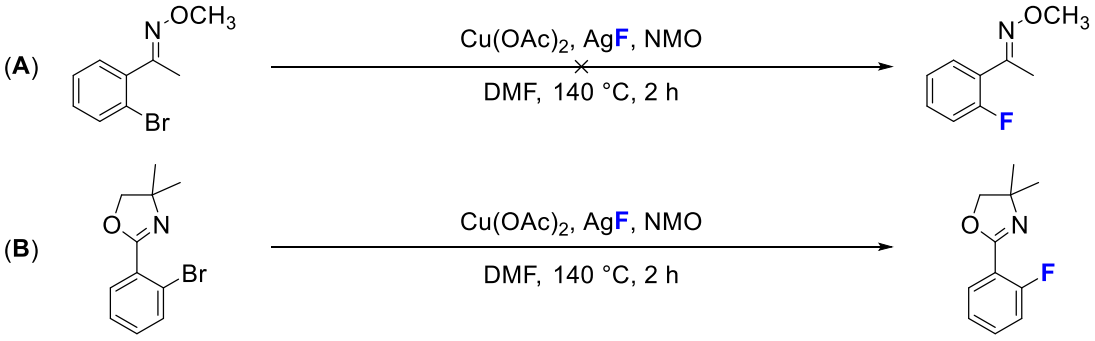
entry	[F]	yield 2 (%)	yield 4 (%)
1	AgF	37	nd
2	KF	nd	20
3[a]	KF	4	31
4	CsF	18	12
5[b]	CsF	16	17
6[bc]	CsF	22	11
7	TMAF	21	nd

Conditions: Substrate **1** (0.05 mmol), $Cu(OAc)_2$ (0.25 equiv), [F] source (3.5 equiv), and NMO (4.5 equiv) were stirred in DMF (0.5 mL, 0.1 M) at 140 ºC for 2 h. Yields determined by ^{19}F NMR spectroscopy using 1,2-difluorobenzene as standard. [a]18-crown-6 (3 equiv). [b]no NMO added. [c]Aryl-Br (**3**, 0.05 mmol) was used.

5.1.3. Outlook for Fluorination of Aryl Iodides

More optimization is needed to fully understand the above scaffold. Preliminary results with the following cleavable directing groups were investigated with both C–H and C–Br bonds. Using similar conditions as above did not form any product for an oxime ether directing group (Reaction A, Scheme 5.5), but did for oxazoline (Reaction B). An internal standard was not included to determine how much was formed.

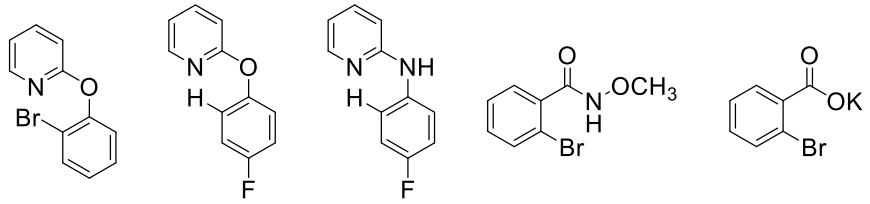
Scheme 5.5. Fluorination of Other Directing Groups



Conditions: Substrates (0.02 mmol), $Cu(OAc)_2$ (0.25 equiv), AgF (3.5 equiv), and NMO (4.5 equiv) were stirred in DMF (0.5 mL, 0.1 M) at 140 ºC for 2 h.

Other directing groups that could potentially be used for this chemistry were tried but yielded no detectable product in the above conditions (Figure 5.1). These substrates might need further optimization of their own to determine if these reagents are feasible for this transformation.

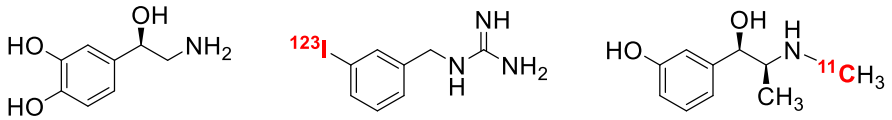
Figure 5.1. Other Directing Groups



5.2. [^{18}F]4F-MHPG Background and Clinical Studies

As of 2016, the leading cause of death in the US was heart disease.[8] Cardiac autonomic dysfunction contributes to the morbidity by changing in the outflow of nervous impulses to the parasympathetic and sympathetic branches of the autonomic nervous system.[9] This regional degeneration of the nerve fibers in the heart is a complicated interaction that often evolves with the progression of the disease.[10] This imbalance leads to chronically elevated levels of the neurotransmitter norepinephrine which contribute to the heart failure.[10] Derivatives of the endogenous neurotransmitter norepinephrine (Figure 5.2) have been radiolabeled to study the cardiac sympathetic nerves, such as [^{123}I]MIBG for SPECT imaging and [^{11}C]HED for PET imaging.[10–12] Norepinephrine and analogues are transferred into the nerve terminals by NET and NET expression is only associated with sympathetic nerves levels; therefore, the retention of these tracers can be used to measure the regional sympathetic nerve density.[10] Clinical trials with these two tracers have demonstrated that cardiac sympathetic denervation is associated with a significant increased risk of sudden cardiac death.[10] Specifically the sympathetic denervation in the left ventricle was the strongest predictor of sudden cardiac arrest among all imaging parameters measured.[10]

Figure 5.2. Norepinephrine Derivatives for SPECT and PET Imaging



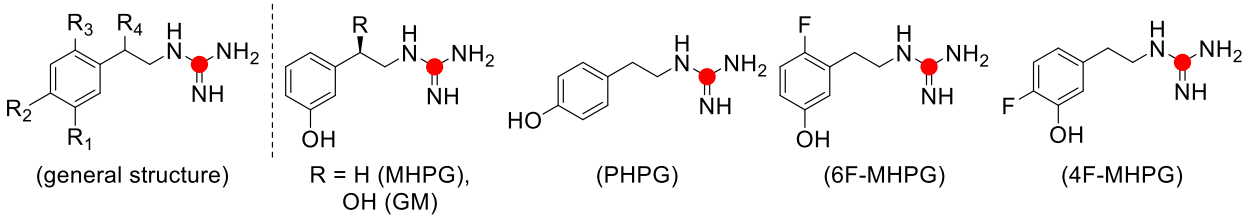
norepinephrine [^{123}I]MIBG [^{11}C]HED

The key component successful radiotracers need to address are: slow NET transport rates, vulnerability to intraneuronal enzyme metabolism, efficiency of vesicular storage, and diffusion rates from the neurons.[13] As of early 2000s, the known radiotracers all suffered the same limitation: rapid uptake rates into cardiac sympathetic neurons. This rapid uptake cannot allow for a robust and reliable compartmental modeling of their kinetics, limiting the quantitative information that can be obtained from clinical studies with these tracers.[13] When designing the next generation of cardiac sympathetic nerve tracers,

certain kinetic properties are needed in the tracer for an ideal quantitative analyses: (1) a slower neuronal uptake rate, providing more favorable kinetic data and (2) a very long neuronal retention time, through trapping inside norepinephrine storage vesicles.[13] A slower neuronal uptake rate paired with efficient trapping of the tracer intraneuronally would maximize the amount of radioactivity retained in the neurons, increasing image quality and providing better kinetic modeling data.[13] Additionally, complete trapping of the tracer in the neuron following its neuronal uptake allows a simpler kinetic model to be used, reducing the number of parameters that need to be estimated from this data.[13] This allows the new tracer to be more compatible with current PET practices.[13] Since neuronal transport rate by NET is highly sensitive to changes in nerve density, accurate estimates of the rate constant would effectively provide quantitative regional estimates of cardiac sympathetic nerve density, a major advance in this branch of nuclear cardiology since it could be used to provide truly quantitative measures of regional nerve density.[13]

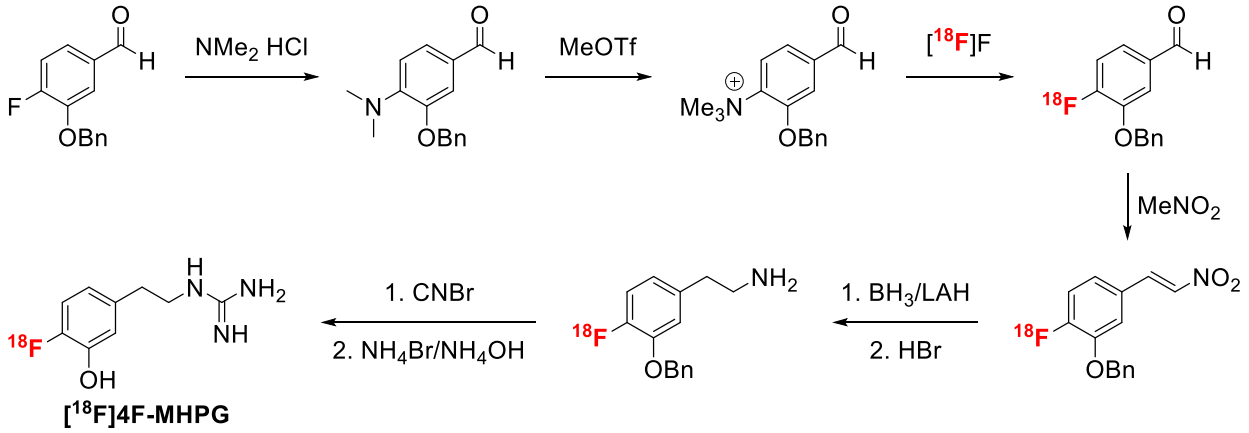
Towards this goal, phenethylguanidines are known to have a high vesicular retention and be potent depletors of cardiac norepinephrine stores *in vivo*, but have been vastly understudied as imaging agents.[14] Initial scaffolds were designed as [^{11}C]tracers, but incorporated fluorine and iodine atoms on the molecule during SAR studies for future labeling opportunities. Several derivatives were studied and all were found to have slower neuronal uptake rates than [^{11}C]HED and [^{123}I]MIBG. Almost half of the substrates analyzed had the desired long retention times (Figure 5.3). It was found that the hydroxy group on the arene was a key component to a long retention time, but it did not affect the uptake rate.[13] In contrast, a fluorine on the arene slowed both the uptake and reduced the retention time.[13] The transport kinetics and binding affinity for the human norepinephrine transporter were studies for the five promising leads in Figure 5.3 compared to [^{11}C]HED, [^{3}H]dopamine, and [^{3}H] norepinephrine.[15] It was found that [^{11}C]4F-MHPG had the desired properties of a slower NET transport rate, long neuronal retention time, and favorable *in vivo* imaging properties.[15,16] These favorable properties led to more studies that required a longer imaging time than was possible with ^{11}C ($t_{1/2}$ = 20 min).[10,17]

Figure 5.3. [^{11}C]Phenethylguanidines With Favorable Imaging Properties



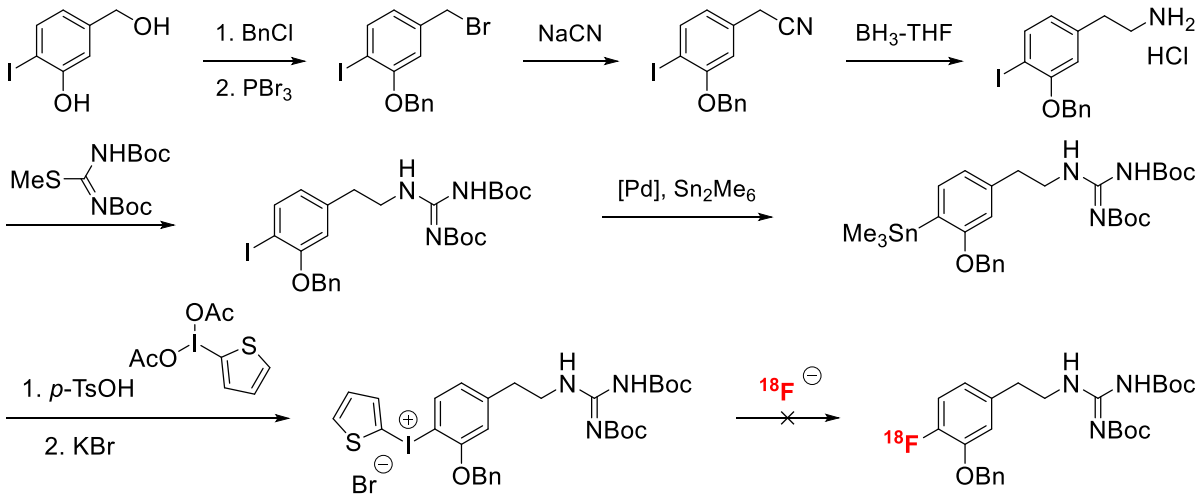
Progressing with [^{18}F]4F-MHPG, the first-generation synthesis was modified from the ^{11}C synthesis (Scheme 5.6).[16] The synthesis introduces [^{18}F]fluoride early via S_NAr with five step post introducing and had a total time of 200-220 min with the overall decay-corrected RCY of 1–2%.[16] There are several opportunities for improvement, besides the overall yield and time. The late-stage introduction of the guanidine proved to be troublesome leading to the use of cyanogen bromide, which is highly toxic.

Scheme 5.6. First-Generation Synthesis of [^{18}F]4F-MHPG[16]



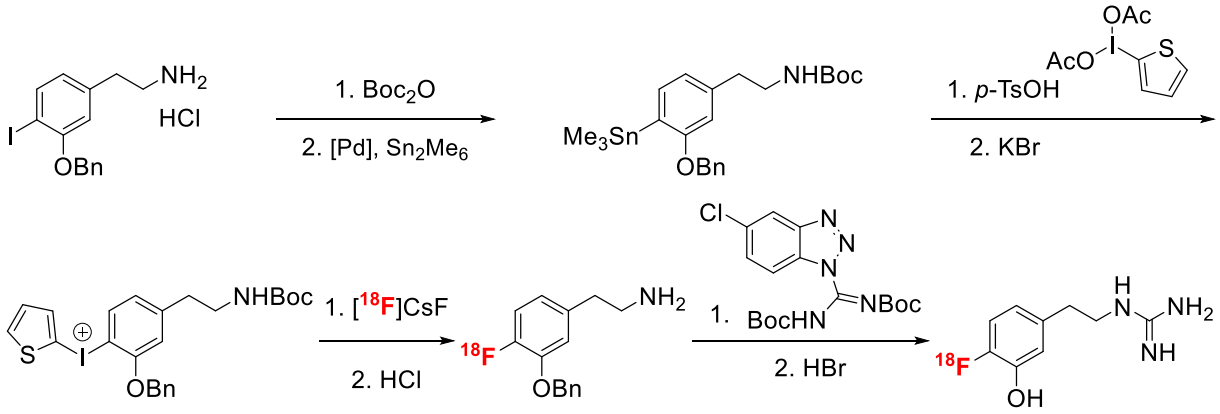
The second-generation synthesis of [^{18}F]4F-MHPG uses a (2-thienyl)iodonium salt precursor. Initial attempts to [^{18}F]radiofluorinate the protected precursor were not successful using multiple [^{18}F]fluoride sources, conventional and microwave heating, various temperature and solvents, with and without H_2O, and with and without TEMPO (Scheme 5.7).[18]

Scheme 5.7. First Attempt at Second-Generation Synthesis of [^{18}F]4F-MHPG[18]



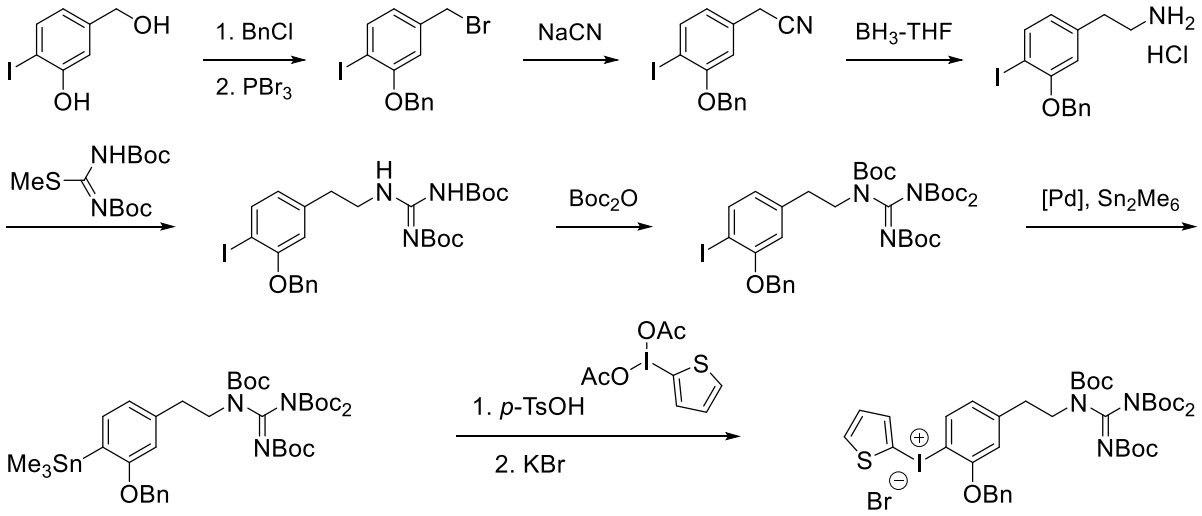
To overcome this limitation an earlier intermediate was used for the [^{18}F]radiofluorination, followed by a three step structure elaboration to get to the final product (Scheme 5.8).[18] This set-up required two radiosynthesis modules in adjacent hot cells.[18] The total time was ~150 min and could produce an overall decay-corrected RCY of 7% (55–125 mCi) of [^{18}F]4F-MHPG.[18] While this is an improvement upon the first-generation synthesis, the complexity of the [^{18}F]radiosynthesis has increased due to the duel hot cell set-up, causing reproducibility issues. Additionally, time, yield, and reproducibility could be improved by limiting the number of steps post [^{18}F]fluoride introduction to include only a deprotection step.

Scheme 5.8. Second-Generation Synthesis of [^{18}F]4F-MHPG[18]



The third-generation, and current synthesis for [^{18}F]4F-MHPG is shown in Scheme 5.9. While the previous intermediate was unable to undergo [^{18}F]radiofluorination, creating a tetraBoc protected intermediate provided [^{18}F]4F-MHPG. The constitutional isomer, [^{18}F]3F-PHPG, has shown favorable imaging results and can be synthesized in a similar manner.[10] The new improved synthesis has a total time of 90 min and could produce an overall decay-corrected RCY of 7% (16–54 mCi) of [^{18}F]4F-MHPG and 8% (27–64 mCi) of [^{18}F]3F-PHPG.[10] The current synthesis greatly reduces the total time, but the yield and reproducibility of the overall system could still be improved.

Scheme 5.9. Current Synthesis for [^{18}F]4F-MHPG



As the synthetic routes were being optimized, kinetics were performed throughout and found the [^{18}F]4F-MHPG behaved similarly to the initial reports with [^{11}C]4F-MHPG in terms of neuronal uptake and retention times (a large improvement upon [^{123}I]MIBG, [^{11}C]HED, and other radiotracers being used at the time).[16] Notably, [^{18}F]4F-MHPG had a lower background in other organs than observed with [^{11}C]4F-MHPG, which is again an improvement on currently used radiotracers.[16] Kinetic studies in isolated rat hearts and rhesus macaque monkeys showed a uniform uptake through the left ventricle with little background activity in the heart, lungs, and liver, and no uptake of free fluorine-18 was observed in the vertebral bones of the spine, indicating that the tracer did not undergo defluorination in non-human primates.[10,18] Selectivity was analyzed by adding increasing

amounts of a potent inhibitor and the results showed that [^{18}F]4F-MHPG was highly selective for presynaptic sympathetic nerve terminals.[18]

Comparing the kinetic results for [^{18}F]4F-MHPG and [^{18}F]3F-PHPG showed similar uptake rates and long clearance times with $T_{1/2}$ of >50 h for [^{18}F]3F-PHPG and >24 h for [^{18}F]4F-MHPG.[10] The long neuronal retention times of these compounds are due to their efficient uptake and storage in norepinephrine storage vesicles.[10] The metabolic pathway of [^{18}F]3F-PHPG was analyzed and found to be different than [^{18}F]4F-MHPG.[10] Both tracers are currently undergoing first-in-human clinical trials (ClinicalTrials.gov, NCT02385877) and have minor differences, such as a more rapid clearance rate from the liver with [^{18}F]4F-MHPG, improving the image interpretation and reducing spillover from the liver to the left ventricle.[19] On the contrary, the prolonged accumulation of [^{18}F]3F-PHPG in the sympathetic neurons may be advantageous in accurately measuring low nerve densities in areas of severe denervation.[19] Because both tracers have advantages over the other, they continue to be compared head-to-head in heart failure patients staged for implantable cardioverter defibrillator placement to determine which is better for clinical assessments of regional denervation in diseased hearts.[19]

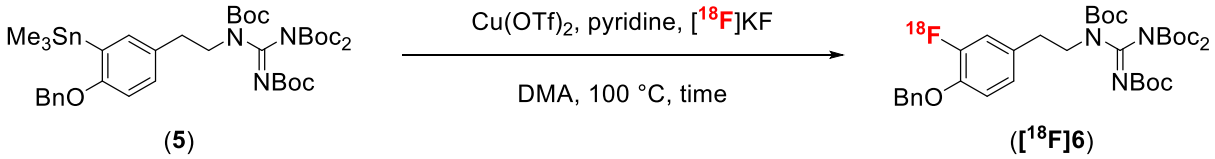
5.2.1. Manual Results with [^{18}F]4F-MHPG and [^{18}F]3F-PHPG[B]

As [^{18}F]3F-PHPG and [^{18}F]4F-MHPG progress through clinical trials, an improved and reliable synthesis is required. The current synthesis provides both tracers in relatively low quantities (ideally >50 mCi will be produced at the end of synthesis, non-decay corrected). We hypothesized that our recently developed methods could be used as an alternative synthesis to help produce these radiotracers as they progress through clinical trials. Initial optimization was performed with PHPG-$SnMe_3$ (**5**). The initial conditions of the [^{18}F]radiofluorination of arylstannanes[20] provided the desired protected product in 58% RCC in 30 min (Table 5.3, entry 1). Increasing the amount of $Cu(OTf)_2$ or pyridine did not increase the amount of product formed (Table 5.3, entries 2-4). Decreasing the time from 30 min to 10 min and decreasing the scale to 5 µmol of **5** gave similar RCC of

[B]The work this section was done in collaboration with Dr. Allen Brooks.

product **6** (Table 5.3, entries 5-6). MHPG-$SnMe_3$ under similar conditions gave a decreased RCC of 26% (Table 5.3, entries 7-8).

Table 5.3. Preliminary Results with PHPG-$SnMe_3$



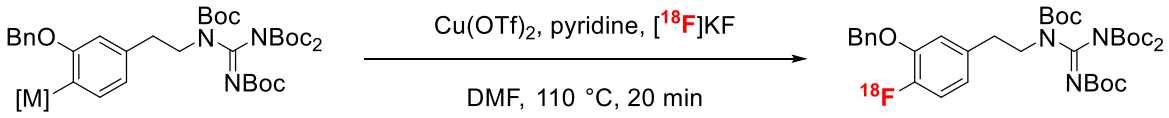
(**5**) ([^{18}F]**6**)

entry	$Cu(OTf)_2$ (equiv)	pyridine (equiv)	time (min)	[^{18}F]6 (% RCC)
1	2	15	30	58
2	4	15	30	42
3	2	30	30	39
4	4	30	30	24
5	2	15	10	61
6[a]	2	15	10	52
7[b]	2	15	10	26
8[bc]	2	15	10	26

Conditions: PHPG-$SnMe_3$ (**5**, 10 µmol), $Cu(OTf)_2$, and pyridine were stirred in DMA (1.0 mL, 10 mM). [^{18}F]KF in DMA (0.1 mL) was added and the reaction was set to 100 ºC for the indicated time. RCC was determined by radio-TLC (n ≥ 2). [a]PHPG-$SnMe_3$ (**5**, 5 µmol), DMA (1.0 mL, 5 mM). [b]MHPG-$SnMe_3$ (**7**, 10 µmol), DMA (1.0 mL, 10 mM). [c]MHPG-$SnMe_3$ (**7**, 5 µmol), DMA (1.0 mL, 5 mM).

As [^{18}F]4F-MHPG offered more opportunities for improvement, a series of analogous were made to analyze our previously designed methodologies.[3,20,21] MHPG-Bpin and MHPG-$SnMe_3$ were tested for fluorination in DMF (Table 5.4) and DMA (Table 5.5) conditions.[20,21] For every entry, MHPG-Bpin gave a higher RCC than MHPG-$SnMe_3$.

Table 5.4. Aryl Boronic Acid Conditions to Generate [^{18}F]4F-MHPG[21]



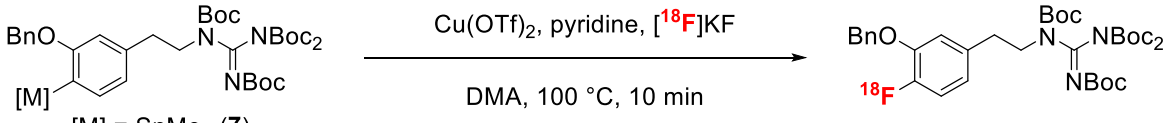
[M] = $SnMe_3$ (**7**), Bpin (**8**)

([^{18}F]**9**)

entry	[M]	[M] (μmol)	$Cu(OTf)_2$ (equiv)	pyridine (equiv)	[^{18}F]9 (% RCC)
1	Bpin	4	5	125	8
2	$SnMe_3$	4	5	125	4
3	Bpin	10	2	15	6
4	$SnMe_3$	10	2	15	5

Conditions: MHPG-[M], $Cu(OTf)_2$, and pyridine were stirred in DMF (1.0 mL, 10 mM). [^{18}F]KF in DMF (0.1 mL) was added and the reaction was set to 110 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2). Radio-HPLC co-injection was performed to confirm product identity.

Table 5.5. Arylstannane Conditions to Generate [^{18}F]4F-MHPG[20]



[M] = $SnMe_3$ (**7**), Bpin (**8**)

([^{18}F]**9**)

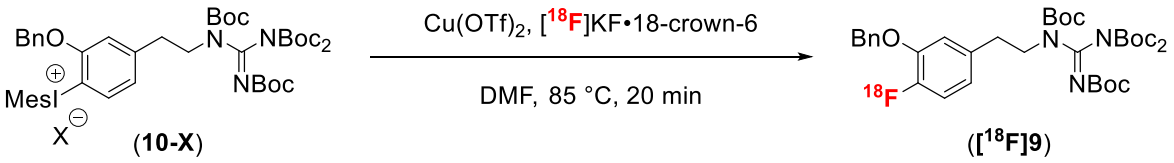
entry	[M]	[M] (μmol)	$Cu(OTf)_2$ (equiv)	pyridine (equiv)	[^{18}F]9 (% RCC)
1	Bpin	4	5	125	24
2	$SnMe_3$	4	5	125	2
3	Bpin	10	2	15	27
4	$SnMe_3$	10	2	15	13

Conditions: MHPG-[M], $Cu(OTf)_2$, and pyridine were stirred in DMF (1.0 mL, 10 mM). [^{18}F]KF in DMF (0.1 mL) was added and the reaction was set to 100 ºC for 10 min. RCC was determined by radio-TLC (n ≥ 2). Radio-HPLC co-injection was performed to confirm product identity.

The iodonium salt of MHPG was synthesized with various counteranions. As observed before, using OTs as the counterion gave trace product (<5%). PF_6 was better than BF_4, but both were similar in yield (Table 5.6). Both yields were lower than was previously obtained.[2] While using the (mesityl)iodonium salt could be a solution to the

current synthesis, the overall steps would be the same, substituting one diaryliodonium salt for another and adding Cu to the reaction.

Table 5.6. (Mesityl)diaryliodonium Conditions to Generate [^{18}F]4F-MHPG[2,3]



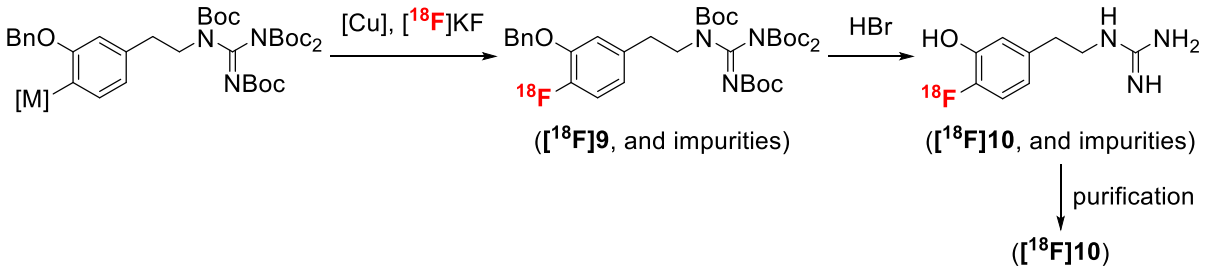
entry	[X]	[^{18}F]9 (% RCC)
1	OTs	trace
2	PF_6	23
3	BF_4	16

Conditions: MHPG-IMes and $Cu(OTf)_2$ were stirred in DMF (0.75 mL, 10 mM). [^{18}F]KF•18-crown-6 in DMF (0.1 mL, 5 mM) was added and the reaction was set to 85 ºC for 20 min. RCC was determined by radio-TLC (n ≥ 2). Radio-HPLC co-injection was performed to confirm product identity.

5.2.2. Automation Results[C]

After the promising manual reactions, the reaction was transitioned from a manual method to a semi-automated reaction. As shown in Scheme 5.10, there are several steps to consider for this automation process. First the reaction to get the crude protected product, then a deprotection and purification. All three stages have the chance of failure and need to be studied individually first.

Scheme 5.10. Automation Considerations for [^{18}F]4F-MHPG



[C] The work this section was done in collaboration with Dr. Allen Brooks.

Taking into account the overall synthetic automation steps and the ease of implication, the arylstannane or aryl boronic acid would be the best precursors to pursue. The arylstannane is already an intermediate in the current route.[10] Alternatively, the arylboronic acid could be easily synthesized from the current route. Investigating the first step in Scheme 5.10 produced **[^{18}F]9** in 24% RCC from MHPG-$SnMe_3$ and 7% RCC form MHPG-Bpin (Table 5.7, entries 1–2). A recently improved automation method was published for the Ar-Bpin reactions with DOPA which uses a different preparation of [^{18}F]KF.[22] This preparation provided trace of the desired product (Table 5.7, entry 3). Although MHPG-Bpin gave higher RCC manual, the use of these precursors requires more optimization while MHPG-$SnMe_3$ performed better than the manual conditions.

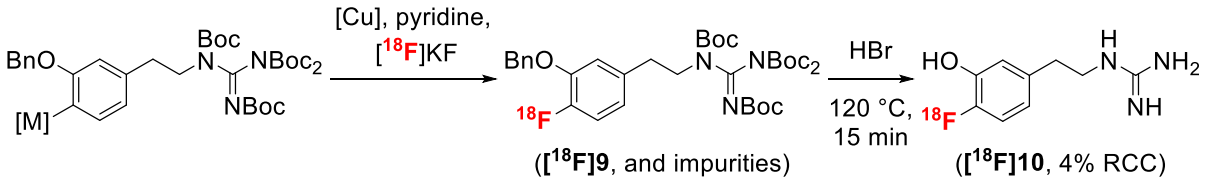
Table 5.7. Semi-Automated Attempts to Generate Protected [^{18}F]4F-MHPG

entry	precursor	[^{18}F]9 (% RCC)
1[a]	MHPG-$SnMe_3$	24
2[b]	MHPG-Bpin	7
3[bc]	MHPG-Bpin	trace

Conditions: The reaction was performed in the hot cell module. [^{18}F]KF, MHPG-[M], $Cu(OTf)_2$, and pyridine were stirred in DMF. RCC was determined by radio-HPLC, with similar values obtained from radio-TLC. Radio-HPLC co-injection was performed to confirm product identity. [a]100 ºC for 10 min. [b]110 ºC for 20 min. [c]TBAOTf and Cs_2CO_3 preparation of [^{18}F]KF.

Now that step 1 of the full automation procedure worked, it was time to test the deprotection method. In original procedure, the reaction was performed in MeCN and the deprotection was heated to 120 ºC, well above the boiling point of MeCN (bp = 82 ºC).[10] These reactions are performed in DMA (bp = 165 ºC) and copper and pyridine are present in the mixture, making the deprotection step complicated. Ascorbic acid was added to the reaction to help keep the Cu soluble. Upon subjecting this mixture to reaction conditions, the desired product **[^{18}F]10** was obtained in 4% RCC, confirmed by HPLC co-injection with the authentic standard (Scheme 5.11). This proved that the deprotection step is highly inefficient as is and needs to be improved before new methodologies could be utilized for this reaction.

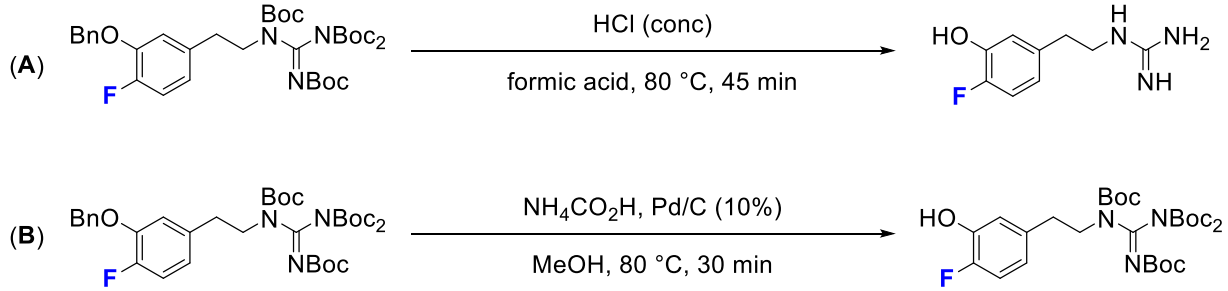
Scheme 5.11. Semi-Automated Deprotection of MHPG-$SnMe_3$



5.2.3. Outlook for [^{18}F]4F-MHPG

The improvement of the reaction not only depends on the improvement of the initial [^{18}F]radiofluorination conditions, but also on the deprotection reaction. Preliminary results for alternative deprotection pathways seem promising. A deprotection method using concentrated HCl and formic acid at 80 °C for 45 min achieved a global deprotection of the fully protected standard of 4F-MHPG (Scheme 5.12, reaction A).[23] A Pd/C method selectively cleaved the Ar-OBn group leaving the Boc groups intact (Scheme 5.12, reaction B).[24] With the selective Ar-OBn group cleavage, a new easier deprotected group, could be installed on the PhOH so that HBr is not required for deprotection. Since the HCl/formic acid conditions were successful, it was attempted with in a solution with $Cu(OTf)_2$, pyridine and DMA under the reported conditions, but no deprotection was observed.

Scheme 5.12. Preliminary Deprotection Results



5.3. Experimental Details

5.3.1. Instrumental Information

NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^{1}H; 100.71 MHz for ^{13}C; 376.87 MHz for ^{19}F), a Varian VNMRS 500 (500.10 MHz for ^{1}H), or a Varian VNMRS 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR spectra are referenced based on an internal standard, 1,d-difluorobenzene (–140.53 ppm). ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Melting point data (mp) were collected on an OptiMelt Automated Melting Point System. HPLC was performed using a Shimadzu LC-2010A HT system equipped with a Bioscan B-FC-1000 radiation detector. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner with EMD Millipore TLC silica gel 60 plates (3.0 cm wide x 6.5 cm long).

5.3.2. Materials and Methods

All commercial products were used as received unless otherwise stated. Aryl iodide precursors were purchased from Frontier Scientific, Oakwood Products and Sigma Aldrich. Fluorine-19 reference standards were sourced commercially. HPLC grade acetonitrile, anhydrous *N,N*-dimethylformamide, potassium trifluoromethanesulfonate, silver trifluoromethanesulfonate, and potassium carbonate were purchased from Fisher Scientific. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation.

5.3.3. Synthesis of [^{18}F]

Generation of [^{18}F]AgF. All loading operations were conducted under ambient atmosphere. Automated sample transfers utilized argon gas. Silver [^{18}F]fluoride was prepared with a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electronic, GE). [^{18}F]Fluoride was produced via the proton beam bombardment of ^{18}O-target water (^{18}O(p,n)^{18}F) using a GE PETTrace cyclotron (40 μA beam for 5–10 min generated ca. 315–620 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the automated synthesis module in a 1.5 mL bolus of [^{18}F]target water and trapped on the

preconditioned QMA-light Sep-Pak to remove [^{18}O]target water and other aqueous impurities. [^{18}F]Fluoride was eluted into the reaction vessel using silver trifluoromethanesulfonate in MQ water (11 mg, 1.0 mL, 0.04 M). MeCN (1.0 mL) was added and the mixture was azeotropically dried to produce anhydrous [^{18}F]AgF.. The reaction vessel was cooled to room temperature via an argon stream, and anhydrous DMF or MeCN (4 mL) was added to dissolve the dried reagents. The resulting solution was cooled to room temperature and transferred to a sterile vial.

Generation of [^{18}F]KF•18-crown-6•K_2CO_3 Complex for (Mestyl)Iodonium Salts. All loading operations were conducted under ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction using a GE PETTrace cyclotron (40 μA beam for 2 min generated ca. 150 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the synthesis module in a 1.5 mL bolus of [^{18}O]water and trapped on a QMA-light Sep-Pak to remove [^{18}O]water. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 900 mg/mL potassium trifluoromethanesulfonate solution, and finally 10 mL of sterile water prior to use. [^{18}F]Fluoride was eluted into the reaction vessel using aqueous potassium carbonate (3.5 mg in 0.5 mL of water). A solution of 18-crown-6 (15 mg in 1 mL of acetonitrile) was added to the reaction vessel, and the resulting solution was dried by azeotropic distillation to give dry [^{18}F]KF•18-crown-6•K_2CO_3. Evaporation was achieved by heating the reaction vessel to 100 °C and drawing vacuum for 4 min. After this time, the reaction vessel was subjected to an argon stream and simultaneous vacuum draw for an additional 4 min. Finally, DMF (4 mL) was added to the dried reagent, and the resulting solution was transferred to a sterile vial for subsequent use in reactions.

Generation of [^{18}F]KF (KOTf Prep). All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via

the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron (40 μA beam for 2–5 min generated ca. 150–375 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the synthesis module in a 1.5 mL bolus of [^{18}O]water and trapped on a QMA-light Sep-Pak to remove [^{18}O]water and other impurities. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 900 mg/mL KOTf solution, and finally 10 mL of sterile water prior to use. [^{18}F]Fluoride was eluted into the reaction vessel using 550 μL of aqueous solution containing 5 mg KOTf and 50 μg of K_2CO_3. Acetonitrile (1.0 mL) was added to the reaction vessel, and the resulting solution was dried by azeotropic distillation to provide anhydrous [^{18}F]KF. Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 °C and drawing vacuum for 6 min. The reaction vessel was then subjected to an argon stream and simultaneous vacuum draw for an additional 6 min. Overall, 70% of activity remained after azeotropic drying (68%; calculated from TRACERLab FX_{FN} reactor radiation detector by comparing activity before and after azeotropic drying). DMF or DMA (6 mL) was added to the dried reagent, and heated at 120 °C with stirring for 5 min. The resulting solution was cooled to 40 °C and was transferred to a sterile vial for subsequent use in reactions.

5.3.4. General Procedures for [^{18}F]Radiofluorination Reactions (Manual Scale)

Experimental Details for [^{18}F]Fluorination Reactions Reported in Scheme 5.2

In a drybox, 4-iodobiphenyl (10 μmol, 1 equiv) and $(MeCN)_4Cu(OTf)$ (1.5 equiv) were weighed into a 4 mL vial equipped with a micro stir-bar. *t*BuCN (0.3 mL, 0.03 M) was added and the reaction vial was sealed with a septa lined cap, removed from the drybox, and stirred overnight at room temperature. [^{18}F]AgF in MeCN (0.1 mL) was added and the reaction was set to 140 °C for 1 h. The reaction was cooled to room temperature and analyzed by radio-TLC to determine RCC and radio-HPLC to confirm product identity.

Experimental Details for [^{18}F]Fluorination Reactions Reported in Scheme 5.3

In a drybox, 4-iodobiphenyl (50 μmol, 1 equiv), $(MeCN)_4Cu(OTf)$ (3 equiv), and AgF (2 equiv) were weighed into a 4 mL vial equipped with a micro stir-bar. DMF (0.3 mL, 0.17 M) was added and the reaction vial was sealed with a septa lined cap, removed from the drybox, and stirred overnight at room temperature. [^{18}F]AgF in DMF (0.1 mL) was added

and the reaction was set to 140 °C for 1 h. The reaction was cooled to room temperature and analyzed by radio-TLC to determine RCC and radio-HPLC to confirm product identity.

(Mesityl)(4-biphenyl)iodonium tetrafluoroborate (6 μmol, 1 equiv) was weighed into a 4 mL vial equipped with a micro stir-bar and dissolved in DMF (0.35 mL, 0.17 M). A stock solution of $(MeCN)_4Cu(OTf)$ in DMF (0.15 mL, 38 μmol in 1.0 mL, 38 mM) was added and the reaction vial was sealed with a septa lined cap. [^{18}F]KF•18-crown-6•K_2CO_3 in DMF (0.1 mL) was added and the reaction was set to 85 °C for 20 min. The reaction was cooled to room temperature and analyzed by radio-TLC to determine RCC and radio-HPLC to confirm product identity.

Experimental Details for [^{18}F]Fluorination Reactions Reported in Table 5.3
Stock solutions were made of PHPG-$SnMe_3$ (**5**, 0.1 M), MHPG-$SnMe_3$ (**7**, 0.1 M), $Cu(OTf)_2$ (0.2 M), and pyridine (1.0 M). Solutions of $Cu(OTf)_2$ (0.1 mL, 2 equiv) and pyridine (0.15 mL, 15 equiv) were diluted in DMA (0.55 mL) and Ar-$SnMe_3$ solution (0.1 mL, 1 equiv) was added. [^{18}F]KF in DMA (0.1 mL) was added to the reaction via a septa cap and the reaction was heated to 100 °C, for 10–30 min. Note: no stir-bars were used.

Experimental Details for [^{18}F]Fluorination Reactions Reported in Table 5.4 and Table 5.5, entries 1–2. Stock solutions were made of MHPG-$SnMe_3$ (**7**, 40 mM), MHPG-Bpin (**8**, 40 mM), $Cu(OTf)_2$ (0.1 M), and pyridine (1.0 M). A vial was charged with solutions of $Cu(OTf)_2$ (0.2 mL, 5 equiv), pyridine (0.5 mL, 125 equiv) and Ar-[M] (0.1 mL, 1 equiv). [^{18}F]KF in DMF/DMA (0.2 mL) was added to the reaction via a septa cap and the reaction was heated to 110 °C for 20 min (Table 5.4) or 100 °C, for 10 min (Table 5.5). Note: no stir-bars were used.

Experimental Details for [^{18}F]Fluorination Reactions Reported in Table 5.4 and Table 5.5, entries 3–4. Stock solutions were made of MHPG-$SnMe_3$ (**7**, 40 mM), MHPG-Bpin (**8**, 40 mM), $Cu(OTf)_2$ (0.1 M), and pyridine (0.5 M). A vial was charged with solutions $Cu(OTf)_2$ (0.2 mL, 2 equiv), pyridine (0.3 mL, 15 equiv), DMF/DMA (0.05 mL) and Ar-[M] (0.25 mL, 1 equiv). [^{18}F]KF in DMF/DMA (0.2 mL) was added to the reaction via a septa cap and

the reaction was heated to 110 °C for 20 min (Table 5.4) or 100 °C, for 10 min (Table 5.5). Note: no stir-bars were used.

Experimental Details for [^{18}F]Fluorination Reactions Reported in Table 5.6

MHPG-IMes were weighed into 4 mL vial and dissolved in DMF (0.3 mL, 0.75 mL total volume, 5 mM). [^{18}F]KF•18-crown-6 in DMF (0.25 mL) was added to the reaction via a septa cap and the reaction was heated to 85 °C for 20 min.

5.3.5. General Procedures for Fluorination Reactions

Experimental Details for Fluorination Reactions Reported in Table 5.1

In a drybox, substrate **1** (0.1 mmol, 1.0 equiv), Cu source [(*t*BuCN)$_2$Cu(OTf) (3 equiv), CuI (0.25 equiv), Cu(OAc)$_2$ (0.25 equiv)], NMO (4.5 equiv), and AgF (added in the dark) were weighed into a 4 mL vial equipped with a micro stirbar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at the 140 ºC for 24 h. The reaction was then cooled to room temperature, diluted with EtOAc (2 mL), filtered through celite and an internal standard (1, 2-difluorobenzene, 200 µL of a 0.25 M solution in EtOAc) was added. An aliquot was removed for analysis by ^{19}F NMR spectroscopy. For the 0.05 mmol scale reactions, 100 µL of a 0.25 M solution of internal standard was added.

Experimental Details for Fluorination Reactions Reported in Table 5.2

In a drybox, substrate **1** (0.05 mmol, 1.0 equiv), Cu(OAc)$_2$ (0.25 equiv), NMO (4.5 equiv), and [F] source (3.5 equiv) were weighed into a 4 mL vial equipped with a micro stirbar. DMF (0.5 mL) was added, and the reaction vial was sealed with a Teflon-lined cap, removed from the drybox, and stirred at the 140 ºC for 2 h. The reaction was then cooled to room temperature, diluted with EtOAc (2 mL), filtered through celite and an internal standard (1, 2-difluorobenzene, 100 µL of a 0.25 M solution in EtOAc) was added. An aliquot was removed for analysis by ^{19}F NMR spectroscopy.

5.3.6. Semi-Automated Synthesis of Protected [^{18}F]4F-MHPG

All loading operations were conducted under an ambient atmosphere. Argon was used as a pressurizing gas during automated sample transfers. Potassium [^{18}F]fluoride was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron. [^{18}F]KF was produced as indicated above. A 10 min beam was used for the semi-automated reaction, generally providing ~900–1000 mCi of activity for each reaction.

Experimental Details Reported in Table 5.7

A solution containing MHPG-$SnMe_3$ or MHPG-Bpin (0.01 mmol, 1 equiv, 0.1 M stock) in 0.4 mL of anhydrous DMA in vial 3 and $Cu(OTf)_2$ (0.02 mmol, 2 equiv, 0.2 M stock), pyridine (0.015 mmol, 15 equiv, 1 M stock), in 0.25 mL of DMA from vial 4 (prepared from separate stock solutions of the three reagents) were added to a reactor containing dry [^{18}F]KF (KOTf prep) by applying Ar gas through the valve containing the reagent solution for a final reaction volume of 1 mL of DMA. Open valves leading out of the reactor were closed, and the mixture was stirred for 10 min at 100 ºC (for entry 1) or 20 min at 110 ºC (for entry 2). The mixture was then cooled, extra DMA (2 mL from vial 6) was added to aid in the removal and the crude reaction was analyzed manually.

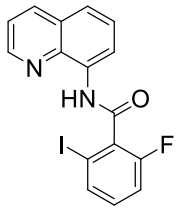
Experimental Details Reported in Scheme 5.11

A solution containing MHPG-$SnMe_3$ (0.01 mmol, 1 equiv, 0.1 M stock) in 0.4 mL of anhydrous DMA in vial 3 and $Cu(OTf)_2$ (0.02 mmol, 2 equiv, 0.2 M stock), pyridine (0.015 mmol, 15 equiv, 1 M stock), in 0.25 mL of DMA from vial 4 (prepared from separate stock solutions of the three reagents) were added to a reactor containing dry [^{18}F]KF (KOTf prep) by applying Ar gas through the valve containing the reagent solution for a final reaction volume of 1 mL of DMA. Open valves leading out of the reactor were closed, and the mixture was stirred for 10 min at 100 ºC. The mixture was then cooled to 50 °C. A mixture of ascorbic acid (0.2 mL, 0.25 M), HBr (48%, 0.5 mL), and DMA (0.5 mL) in vial 5 were added to the reactor and the mixture was stirred for 15 min at 120 ºC. The mixture

was cooled, extra DMA (2 mL from vial 6) was added to aid in the removal and the crude reaction was analyzed manually.

5.4. Synthesis and Characterization

5.4.1. Substrates



(**1**)

2-fluoro,6-iodo-*N*-(quinolin-8-yl)benzamide (1) was prepared according to the literature procedure.[25] To an oven-dried vial, 2-fluoro-6-iodobenzoic acid (523.3 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 2 h. The solvent was removed i*n vacuo* and the resulting acid chloride was used immediately without further purification.

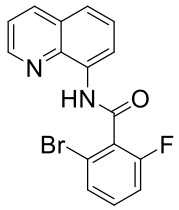
To another oven-dried vial, 8-aminoquinoline (323.1 mg, 2.2 mmol, 1.1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.75 M). A solution of acid chloride in CH_2Cl_2 (3.0 mL, 6.0 mL total, 0.37 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (100% dichloromethane), affording the product (**1**) as a yellow solid (602.9 mg, 78% yield, R_f = 0.82 in hexanes, mp = 209–210 °C).

^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H), 8.94 (d, *J* = 7.0 Hz, 1H), 8.76 (d, *J* = 0.9 Hz, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.56–7.61 (multiple peaks, 2H), 7.44 (m, 1H), 7.11–7.18 (multiple peaks, 2H)

^{13}C NMR ($CDCl_3$): δ 163.04, 158.76 (d, *J* = 251.7 Hz), 148.37, 138.41, 136.35, 135.31 (d, *J* = 3.5 Hz), 133.97, 132.14 (d, *J* = 8.8 Hz), 131.44 (d, *J* = 21.1 Hz), 127.96, 127.35, 122.45, 121.74, 117.14, 115.99 (d, *J* = 21.1 Hz), 93.65 (d, *J* = 3.5 Hz)

^{19}F NMR ($CDCl_3$): δ –110.77 (m, 1F)

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{16}H_{11}FIN_2O$: 392.9822; Found 392.9892



(**3**)

2-bromo,6-fluoro-*N*-(quinolin-8-yl)benzamide (3) was prepared according to the literature procedure.[25] To an oven-dried vial, 2-bromo-6-fluorobenzoic acid (431.1 mg, 2.0 mmol, 1 equiv) was placed under N_2. DMF (5 drops) and CH_2Cl_2 (4.4 mL, 0.45 M) were added, and the solution was cooled to 0 °C. Oxalyl chloride (0.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise at 0 °C, resulting in vigorous bubbling. The mixture was allowed to warm to room temperature under N_2 and stirred for 6 h. The solvent was removed *in vacuo* and the resulting acid chloride was used immediately without further purification.

To another oven-dried vial, 8-aminoquinoline (323.0 mg, 2.2 mmol, 1.1 equiv) and NEt_3 (0.35 mL, 2.5 mmol, 1.3 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.75 M). A solution of acid chloride in CH_2Cl_2 (2.0 mL, 5.0 mL total, 0.45 M) was added dropwise at room temperature. The resulting mixture was stirred at room temperature overnight. The mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography (100% dichloromethane), affording the product (**3**) as an off-white solid (573.6 mg, 84% yield, R_f = 0.29 (20% ethyl acetate in hexanes, mp = 194–196 °C).

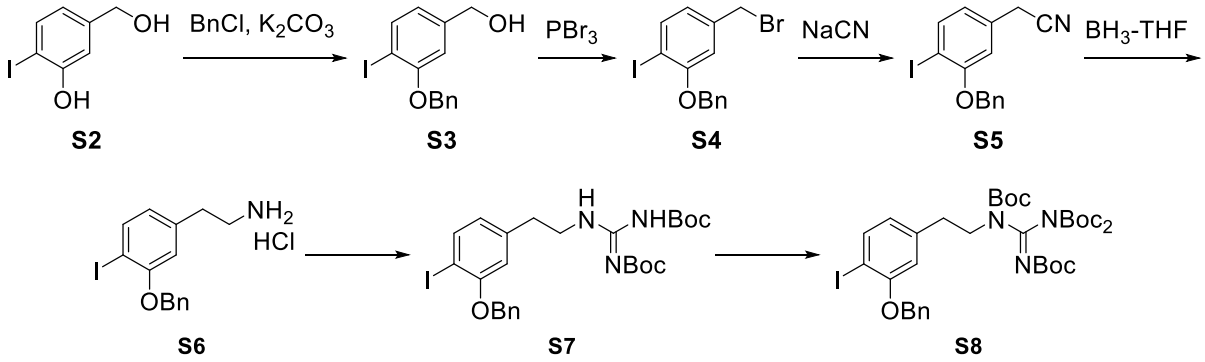
^{1}H NMR ($CDCl_3$): δ 10.10 (s, 1H), 8.94 (d, *J* = 6.3 Hz, 1H), 8.76 (d, *J* = 1.1 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 7.56–7.60 (multiple peaks, 2H), 7.42–7.46 (multiple peaks, 2H), 7.30 (m, 1H), 7.15 (m, 1H)

^{13}C NMR ($CDCl_3$): δ 161.39, 159.53 (d, *J* = 251.7 Hz), 148.36, 138.38, 136.35, 133.96, 131.69 (d, *J* = 8.8 Hz), 128.85 (d, *J* = 3.5 Hz), 127.94, 127.70 (d, *J* = 22.9 Hz), 127.34, 122.45, 121.74, 120.83 (d, *J* = 3.5 Hz), 117.10, 115.19 (d, *J* = 22.9 Hz)

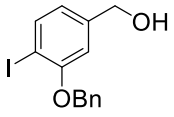
^{19}F NMR ($CDCl_3$): δ –111.61 (m, 1F)

HRMS (ESI+) $[M+H]^+$ Calculated for $C_{16}H_{11}BrFN_2O$: 345.0033; Found 345.0037

4I-MHPG (S8) was prepared by the following 6-step procedure.



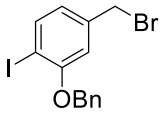
S2 **S3** **S4** **S5** **S6** **S7** **S8**



S3

Step 1:

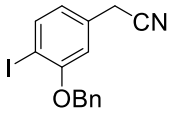
Intermediate **S3** was prepared according to a literature procedure.[18] The product was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes), which afforded **S3** as a white solid (5.76 g, 85% yield, R_f = 0.48 in 50% ethyl acetate in hexanes, mp = 62–63 °C). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[18] HRMS $[M+Na]^+$ Calculated for $C_{14}H_{13}INaO_2$: 362.9852; Found 362.9848.



S4

Step 2:

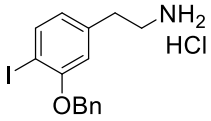
Intermediate **S4** was prepared according to a literature procedure.[18] The product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes), which afforded **S4** as a white solid (0.76 g, 72% yield, R_f = 0.77 in 100% hexanes, mp = 89–90 °C). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[18] HRMS $[M]^+$ Calculated for $C_{14}H_{12}BrIO$: 401.9116; Found 401.9126.



S5

Step 3:

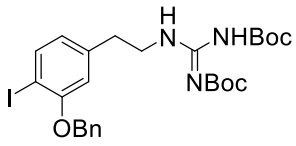
Intermediate **S5** was prepared according to a literature procedure.[18] The product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes), which afforded **S5** as a yellow solid (1.57 g, 72% yield, R_f = 0.26 in 20% ethyl acetate in hexanes, mp = 49–51 °C). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[18] HRMS $[M]^+$ Calculated for $C_{15}H_{12}INO$: 348.9964; Found 348.9965.



S6

Step 4:

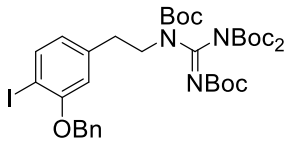
Intermediate **S6** was prepared according to a literature procedure.[18] After the crude reaction was quenched with methanol and concentrated to remove solvent, HCl (4.0 M HCl in dioxane, 1 mL) and excess diethyl ether was added. The precipitate was filtered and washed with diethyl ether to afford **S6** as a white solid (1.21 g, 53% yield, mp = 155–156 °C). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[18] HRMS [M–HCl] Calculated for $C_{15}H_{16}INO$: 354.0349; Found 354.0354.



S7

Step 5:

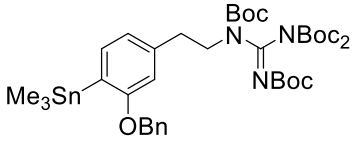
Intermediate **S7** was prepared according to a literature procedure.[18] The product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes), which afforded **S7** as a white solid (1.92 g, 87% yield, R_f = 0.38 in 20% ethyl acetate in hexanes, mp = 99–100 °C). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[18] HRMS $[M+H]^+$ Calculated for $C_{26}H_{34}IN_3O_5$: 596.1616; Found 596.1613.



S8

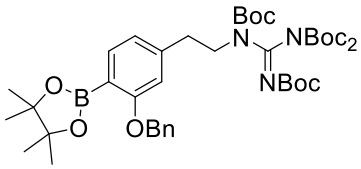
Step 6:

Intermediate **S8** was prepared according to a literature procedure.[10] The product was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes), which afforded **S8** as a clear oil (1.55 g, 65% yield, R_f = 0.68 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[10] HRMS $[M+H]^+$ Calculated for $C_{36}H_{50}IN_3O_9$: 796.2664; Found 796.2657.



(**7**)

MHPG-$SnMe_3$ (**7**) was prepared according to a literature procedure.[10] The product was purified by flash column chromatography on silica gel (15% diethyl ether in pentanes), which afforded **7** as a colorless oil (576.3 mg, 72% yield, R_f = 0.52 in 20% ethyl acetate in hexanes). The ^{1}H and ^{13}C NMR spectra matched that reported previously in the literature.[10] HRMS $[M+H]^+$ Calculated for $C_{39}H_{59}N_3O_9Sn$: 834.3346; Found 834.3349.



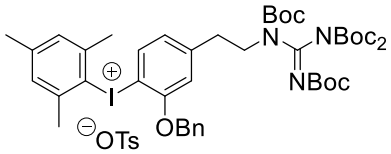
(**8**)

MHPG-Bpin (**8**) was prepared according to a modified literature procedure.[26] In a glovebox, a 20 mL vial was charged with intermediate **S8** (845.9 mg, 1.1 mmol), pinacoldiboron ester (297.7 mg, 1.2 mmol, 1.1 equiv), potassium acetate (311.9 mg, 3.2 mmol, 3.0 equiv), and Pd(dppf)Cl_2 dichloromethane complex (86.4 mg, 0.11 mmol, 0.1 equiv), and DMSO (5.8 mL, 0.18 M). The vial was sealed and set to 80 °C. After 3 h, the reaction was cooled to room temperature, filtered through a silica plug with Et_2O. The Et_2O later was washed with H_2O (150 mL x 3). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (20% ethyl acetate in hexane) affording the product **8** as a white solid (435.3 mg, 52% yield, R_f = 0.57 in 25% ethyl acetate in hexanes, mp = 54–55 °C).

^{1}H NMR ($CDCl_3$): δ 7.63 (m, 3H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.0 Hz, 1H), 6.86 (s, 1H), 5.13 (s, 2H), 3.97 (t, *J* = 8.4 Hz, 2H), 2.95 (t, *J* = 8.4 Hz, 2H), 1.52 (s, 9H), 1.51 (s, 9H), 1.49 (s, 18H), 1.36 (s, 12H)

^{13}C NMR ($CDCl_3$): δ 163.63, 157.78, 151.19, 147.34, 143.84, 143.57, 137.66, 136.92, 128.06, 127.22, 126.78, 121.20, 112.75, 83.60, 83.53, 83.31, 81.99, 69.94, 48.56, 33.63, 28.02, 27.96, 27.89, 25.00, 24.90

HRMS (ESI$^+$) $[M+H]^+$ Calculated for $C_{42}H_{63}BN_3O_{11}$: 796.4550; Found 796.4558

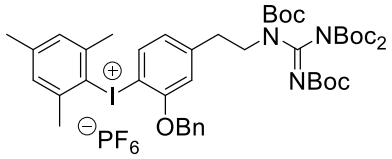


(**10-OTs**)

MHPG-IMes OTs (**10-OTs**) was prepared according to a modified thesis procedure.[2] In an oven-dried flask, iodomesitylene diacetate (200.4 mg, 0.55 mmol, 1.6 equiv) was added with CH_3CN (2.0 mL, 0.28 M) and cooled to 0 °C using an ice bath under N_2. To the cooled solution, *p*-TsOH•H_2O (78.5 mg, 0.41 mmol, 1.2 equiv) was added in one

portion, and the solution immediately turned yellow and was allowed to stir for 10 min. MHPG-$SnMe_3$ dissolved in DCM (2 mL, 0.17M) was added dropwise. An additional 15 mL of DCM was added. The reaction was warmed up to room temperature and stir for 2 days. The product was purified by flash column chromatography on silica gel (5% methanol in DCM), which afforded **10-OTs** as a white solid (172.1 g, 54% yield, mp = 95–96 °C).

^{1}H NMR (CD_3OD): δ 7.92 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.37–7.38 (multiple peaks, 3H), 7.26–7.28 (multiple peaks, 2H), 7.25 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.11 (s, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 5.25 (s, 2H), 3.96 (t, *J* = 7.4 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 2.46 (s, 6H), 2.36 (s, 3H), 2.34 (s, 3H), 1.49 (s, 9H), 1.46 (s, 18H), 1.37 (s, 9H)
^{13}C NMR (CD_3OD): δ 159.34, 157.86, 152.44, 149.26, 148.35, 145.34, 145.25, 143.88, 143.62, 141.56, 138.21, 136.47, 131.16, 129.90, 129.85, 129.76, 126.95, 125.55, 120.82, 116.25, 100.73, 85.58, 85.28, 83.58, 73.01, 34.38, 28.31, 28.25, 28.19, 26.74, 21.32, 20.96
HRMS (ESI+) $[M–OTs]^+$ Calculated for $C_{45}H_{61}IN_3O_9$: 914.3452; Found: 914.3452



(**10-PF$_6$**)

MHPG-IMes OTs (**10-OTs**, 97.5 mg) was dissolved in DCM (5 mL) and saturated KPF_6 (aq, 5 mL) was added and vigorously stirred for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with DCM twice and concentrated. The product was purified by flash column chromatography on silica gel (100% DCM), which afforded **10-PF$_6$** as a white solid (88.8 mg, 93% yield, R_f = 0.28 in 4% methanol in DCM, mp = 92–93 °C).

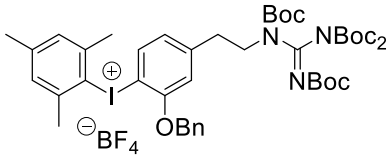
^{1}H NMR (CD_3OD): δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.40–7.42 (multiple peaks, 3H), 7.30–7.31 (multiple peaks, 2H), 7.28 (s, 1H), 7.15 (s, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 2H), 4.00

(t, *J* = 7.7 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 6H), 2.37 (s, 3H), 1.53 (s, 9H), 1.49 (s, 18H), 1.41 (s, 9H)

^{13}C NMR (CD_3OD): δ 159.36, 157.87, 152.45, 149.28, 148.42, 145.36, 145.32, 143.88, 138.16, 136.47, 131.19, 129.91, 129.85, 129.78, 125.59, 120.75, 116.28, 100.65, 85.59, 85.30, 83.59, 73.04, 34.38, 28.31, 28.28, 28.24, 28.18, 26.73, 20.95

^{19}F NMR (CD_3OD): δ –74.00 (m, 1F), –75.88 (m, 1F)

HRMS (ESI+) $[M–PF_6]^+$ Calculated for $C_{45}H_{61}IN_3O_9$: 914.3452; Found: 914.3442



(**10-BF$_4$**)

MHPG-IMes OTs (**10-OTs**, 107.0 mg) was dissolved in DCM (5 mL) and saturated $NaBF_4$ (aq, 5 mL) was added and vigorously stirred for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with DCM twice and concentrated. The product was purified by flash column chromatography on silica gel (7% methanol in DCM), which afforded **10-BF$_4$** as a white solid (92.4 mg, 94% yield, R_f = 0.19 in 4% methanol in DCM, mp = 96–97 °C).

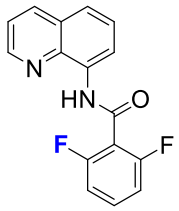
^{1}H NMR (CD_3OD): δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.40–7.42 (multiple peaks, 3H), 7.29–7.31 (multiple peaks, 2H), 7.28 (s, 1H), 7.15 (s, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 2H), 3.99 (t, *J* = 7.7 Hz, 2H), 3.04 (t, *J* = 7.7 Hz, 2H), 2.49 (s, 6H), 2.37 (s, 3H), 1.52 (s, 9H), 1.49 (s, 18H), 1.40 (s, 9H)

^{13}C NMR (CD_3OD): δ 159.35, 157.87, 152.45, 149.28, 148.42, 145.35, 145.31, 143.88, 138.18, 136.47, 131.18, 129.91, 129.86, 129.78, 125.58, 120.77, 116.28, 100.68, 85.59, 85.30, 83.59, 73.04, 34.38, 28.31, 28.25, 28.19, 26.73, 20.95

^{19}F NMR (CD_3OD): δ –155.21 (m, 4F)

HRMS (ESI+) $[M–BF_4]^+$ Calculated for $C_{45}H_{61}IN_3O_9$: 914.3452; Found: 914.3447

5.4.2. Standards



(**2**)

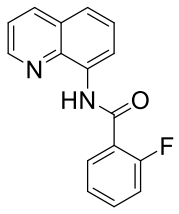
2,6-difluoro-*N*-(quinolin-8-yl)benzamide (2) was prepared according to the literature procedure.[27] 8-Aminoquinoline (141.7 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.5 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.33 M) followed by a slow dropwise addition of 2,6-difluorobenzoyl chloride (0.15 mL, 1.2 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature exposed to air overnight. The mixture was washed with 1 N HCl, sat. $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (10% ethyl acetate in hexane) affording the product (**2**) as a white solid (175.6 mg, 62% yield, R_f = 0.31 in 20% ethyl acetate in hexanes, mp = 173–174 °C).

^{1}H NMR ($CDCl_3$): δ 10.32 (s, 1H), 8.92 (d, *J* = 7.0 Hz, 1H), 8.76 (d, *J* = 0.5 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 7.53–7.57 (multiple peaks, 2H), 7.34–7.43 (multiple peaks, 2H), 7.00 (m, 2H)

^{13}C NMR ($CDCl_3$): δ 160.16 (d, *J* = 253.4 Hz), 160.12 (d, *J* = 253.4 Hz), 158.47, 148.34, 138.32, 136.28, 134.06, 131.96 (t, *J* = 9.7 Hz), 127.87, 127.27, 122.33, 121.69, 116.99, 114.78 (t, *J* = 19.4 Hz), 112.22 (d, *J* = 3.5 Hz), 112.10 (d, *J* = 5.3 Hz)

^{19}F NMR ($CDCl_3$): δ –111.76 (m, 1F)

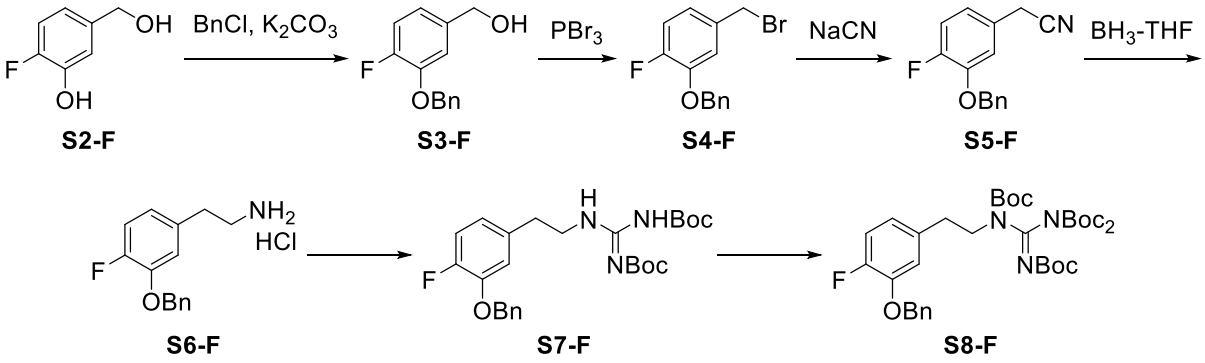
HRMS (ESI+) $[M+H]^+$ Calculated for $C_{16}H_{11}F_2N_2O$: 285.0834; Found 285.0837

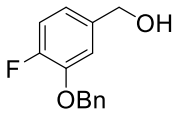


(**4**)

2-Fluoro-*N*-(quinolin-8-yl)benzamide (4) was prepared according to the literature procedure.[27] 8-Aminoquinoline (147.6 mg, 1.0 mmol, 1 equiv) and NEt_3 (0.20 mL, 1.4 mmol, 1.4 equiv) were dissolved in anhydrous CH_2Cl_2 (3.0 mL, 0.34 M) followed by a slow dropwise addition of 2-fluorobenzoyl chloride (0.15 mL, 1.3 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature exposed to air overnight. The mixture was washed with 1 N HCl, sat. $NaHCO_3$, and brine. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude residue was purified by column chromatography (5% ethyl acetate in hexane) affording the product (**4**) as a white solid (243.8 mg, 92% yield, R_f = 0.42 in 20% ethyl acetate in hexanes, mp = 126–127 °C). The ^1H and ^{13}C NMR spectra matched those reported in the literature.[28] ^{19}F NMR (377 MHz, $CDCl_3$, ppm): δ –112.10 (m, 1F). HRMS (ESI+) $[M+H]^+$ Calculated for $C_{16}H_{12}FN_2O$: 267.0928; Found 267.0922.

4F-MHPG (**S8-F**) was prepared by the following 6-step procedure.





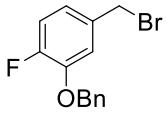
S3-F

Step 1:

Intermediate **S3-F** was prepared according to the modified literature procedure.[18] 2-fluoro-5-(hydroxymethyl)phenol **S2-F** (2.45 g, 17.2 mmol) was dissolved in DMF (30.0 mL, 0.58 M) at room temperature open to air. K_2CO_3 (3.58 g, 25.9 mmol) and benzyl chloride (2.2 mL, 19.1 mmol) was added and the reaction was heated to 130 °C. After 2 h the reaction was cooled to room temperature and washed with a saturated NH_4Cl

solution (200 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Mg_2SO_4, and concentrated. The crude residue was purified by column chromatography (15% ethyl acetate in hexane) affording the product (**S3-F**) as a white solid (3.57 g, 89% yield, R_f = 0.48 in 40% ethyl acetate in hexanes, mp = 36–37 °C).

^{1}H NMR ($CDCl_3$): δ 7.43 (d, *J* = 7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.04 (multiple peaks, 2H), 6.85 (m, 1H), 5.12 (s, 2H), 4.57 (s, 2H), 1.83 (br s, 1H)
^{13}C NMR ($CDCl_3$): δ 152.21 (d, *J* = 246.4 Hz), 146.69 (d, *J* = 10.9 Hz), 137.09, 136.37, 128.57, 128.09, 127.43, 119.66 (d, *J* = 7.0 Hz), 116.07 (d, *J* = 18.7 Hz), 114.20, 71.21, 64.73
^{19}F NMR ($CDCl_3$): δ –135.28 (m, 1F)
HRMS (ESI+) $[M+NH_4]^+$ Calculated for $C_{14}H_{17}FNO_2$: 250.1238; Found 25.1236



S4-F

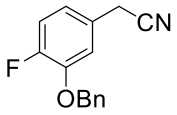
Step 2:
Intermediate **S4-F** was prepared according to the modified literature procedure.[18] A solution of PBr_3 (2.6 mL, 28.6 mL total, 0.1 M in CH_2Cl_2) was added a solution of alcohol **SF-3** (3.14 g, 13.5 mmol) in CH_2Cl_2 (100 mL, 0.14 M) dropwise over 1.5 h at room temperature open to air. After 4 h, TLC showed no starting material remaining. The reaction was quenched slowly with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Mg_2SO_4, and concentrated. The crude residue was used without further purification to afford the product (**S4-F**) as a white solid (3.71 g, 93% yield, R_f = 0.70 in 20% ethyl acetate in hexanes, mp = 72–73 °C).

^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.03 (multiple peaks, 2H), 6.92 (m, 1H), 5.13 (s, 2H), 4.41 (s, 2H)

^{13}C NMR ($CDCl_3$): δ 152.72 (d, *J* = 248.2 Hz), 146.80 (d, *J* = 10.6 Hz), 136.14, 134.01 (d, *J* = 5.3 Hz), 128.61, 128.19, 127.50, 122.00 (d, *J* = 7.0 Hz), 116.39 (d, *J* = 8.8 Hz), 116.32 (d, *J* = 7.0 Hz), 71.36, 33.03

^{19}F NMR ($CDCl_3$): δ –133.20 (m, 1F)

HRMS (EI) $[M]^+$ Calculated for $C_{14}H_{12}BrFO$: 294.0056; Found 294.0065



S5-F

Step 3:

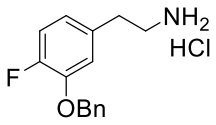
Intermediate **S5-F** was prepared according to the modified literature procedure.[18] Sodium cyanide (337.6 mg, 6.9 mmol, 1.2 equiv) was added portion-wise over 15 min to a solution of the bromide **S4-F** (1.71 g, 5.8 mmol, 1 equiv) in DMSO (21.5 mL, 0.27 M) at room temperature open to air. After 45 min TLC showed no starting material remaining. The reaction was poured over ice water (250 mL). The aqueous solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Mg_2SO_4, and concentrated. The crude residue was purified by column chromatography (8% ethyl acetate in hexane) affording the product (**S5-F**) as a white solid (1.14 g, 82% yield, R_f = 0.30 in 20% ethyl acetate in hexanes, mp = 37–38 °C).

^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.38 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.06 (dd, *J* = 14.0, 7.0 Hz, 1H), 6.96 (dd, *J* = 7.0, 7.0 Hz, 1H), 6.84 (m, 1H), 5.13 (s, 2H), 3.65 (s, 2H)

^{13}C NMR ($CDCl_3$): δ 152.44 (d, *J* = 248.2 Hz), 147.05 (d, *J* = 12.3 Hz), 135.94, 128.62, 128.23, 127.45, 125.95 (d, *J* = 3.5 Hz), 120.77 (d, *J* = 7.0 Hz), 117.58, 116.72 (d, *J* = 19.4 Hz), 115.22 (d, *J* = 1.8 Hz), 71.39, 23.14

^{19}F NMR ($CDCl_3$): δ –134.19 (m, 1F)

HRMS (EI) $[M]^+$ Calculated for $C_{15}H_{12}FNO$: 241.0903; Found 241.0909



S6-F

Step 4:

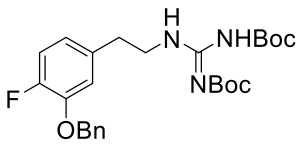
Intermediate **S6-F** was prepared according to a modified literature procedure.[18] BH_3-THF (17 mL, 1.0 M solution in tetrahydrofuran, 17 mmol, 2.8 equiv) was added dropwise to a solution of the cyanide **S5-F** (1.4434 g, 6.0 mmol, 1 equiv) in anhydrous tetrahydrofuran (45 mL, 0.13 M) at room temperature under a nitrogen atmosphere. The reaction was heated to 70 °C for 4.5 h and excess BH_3 was quenched with the cautious addition of methanol until effervescence ceased. The solvent was removed under reduced pressured and the residue was taken up in HCl solution (4.0 M HCl in dioxane, 3 mL) with excess diethyl ether (200 mL). The precipitate was filtered, washed with excess diethyl ether, and dried *in vacuo* to give the desired product **S6-F** as a white solid (1.4482 g, 86% yield, mp = 194–196 °C).

^{1}H NMR (CD_3OD with 1 drop of d_6-DMSO): δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.07 (m, 1H), 6.85 (m, 1H), 5.16 (s, 2H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H)

^{13}C NMR (CD_3OD with 1 drop of d_6-DMSO): δ 153.46 (d, *J* = 246.0 Hz), 148.31 (d, *J* = 12.3 Hz), 138.26, 134.62 (d, *J* = 3.5 Hz), 129.70, 129.27, 128.88, 122.81 (d, *J* = 7.0 Hz), 117.57, 117.43 (d, *J* = 17.6 Hz), 72.37, 42.03, 34.19

^{19}F NMR (CD_3OD with 1 drop of d_6-DMSO): δ –138.32 (m, 1F)

HRMS (ESI^+) $[M]^+$ Calculated for $C_{15}H_{17}FNO$: 246.1289; Found 2461292



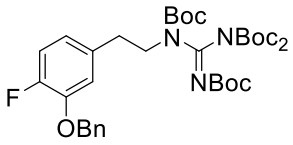
S7-F

Step 5:

Intermediate **S7-F** was prepared according to a modified literature procedure.[18] To a cooled (0 °C) solution of **S6-F** (1.32 g, 4.7 mmol, 1 equiv) and triethylamine (2.6 mL, 18.7

mmol, 4 equiv) in anhydrous DMF (13 mL, 0.36 M) was added in portion 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.442 g, 5.0 mmol, 1.1 equiv). The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate (50 mL), washed with saturated NH_4Cl solution (200 mL), and extracted with ethyl acetate (2 × 250 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes), which afforded **S7-F** as a colorless oil (1.986 g, 87% yield, R_f = 0.40 in 20% ethyl acetate in hexanes).

^{1}H NMR ($CDCl_3$): δ 11.47 (bs, 1H), 8.34 (bs, 1H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 9.4 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.72 (m, 1H), 5.11 (s, 2H), 3.61 (m, 2H), 2.77 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H)
^{13}C NMR ($CDCl_3$): δ 163.49, 156.03, 153.12, 151.56 (d, *J* = 227.0 Hz), 146.56 (d, *J* = 8.8 Hz), 136.46, 134.73 (d, *J* = 3.5 Hz), 128.48, 127.99, 127.43, 121.42 (d, *J* = 7.0 Hz), 116.12 (d, *J* = 17.6 Hz), 115.98, 83.02, 79.21, 71.21, 42.09, 34.79, 28.22, 27.95
^{19}F NMR ($CDCl_3$): δ –137.12 (m, 1F)
HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{26}H_{35}FN_3O_5$: 488.2555; Found 488.2555



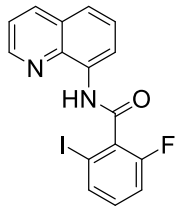
S8-F

Step 6:
Intermediate **S8-F** was prepared according to a modified literature procedure.[10] A solution of $(Boc)_2O$ (3.9 mmol, 0.9 mL of 1.0 M solution in THF, 6.3 equiv) was added to a solution of **S7-F** (305.2 mg, 0.63 mmol, 1 equiv), DMAP (46.9 mg, 0.38 mmol, 0.6 equiv) and triethylamine (0.55 mL, 3.9 mmol, 6.3 equiv) in anhydrous THF (7.5 mL, 84 mM) at room temperature. The mixture was stirred for 48 h and then poured over water (75 mL). The mixture was diluted with ethyl acetate (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated

under reduced pressure. The product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes), which afforded **S8-F** as a white solid (391.4 mg, 91% yield, R_f = 0.73 in hexanes, mp = 113–114 °C).

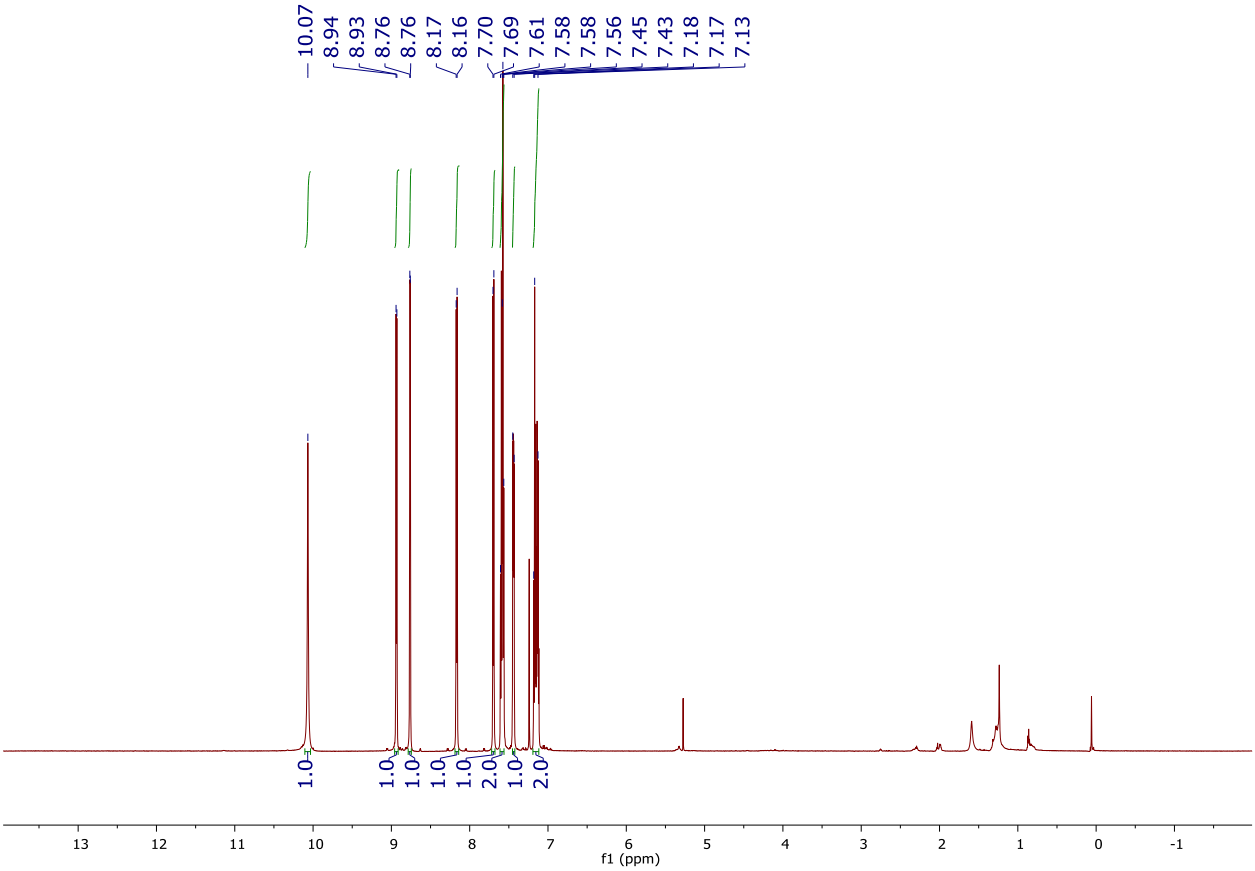
^{1}H NMR ($CDCl_3$): δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 6.94–6.99 (multiple peaks, 2H), 6.77 (m, 1H), 5.11 (s, 2H), 3.91 (m, 2H), 2.87 (m, 2H), 1.50 (s, 9H), 1.47 (s, 27H)
^{13}C NMR ($CDCl_3$): δ 159.69, 151.66 (d, *J* = 244.6 Hz), 151.14, 147.36, 146.47 (d, *J* = 10.6 Hz), 143.60, 136.50, 135.06 (d, *J* = 3.5 Hz), 128.50, 128.02, 127.60, 121.61, (d, *J* = 7.0 Hz), 116.43, 115.98 (d, *J* = 17.6 Hz), 83.61, 83.55, 81.97, 71.35, 48.73, 32.81, 27.95 (d, *J* = 12.3 Hz), 27.85
^{19}F NMR ($CDCl_3$): δ –137.27 (m, 1F)
HRMS (ESI^+) $[M+H]^+$ Calculated for $C_{36}H_{51}FN_3O_9$: 688.3604; Found 688.3601

5.5. NMR Spectra

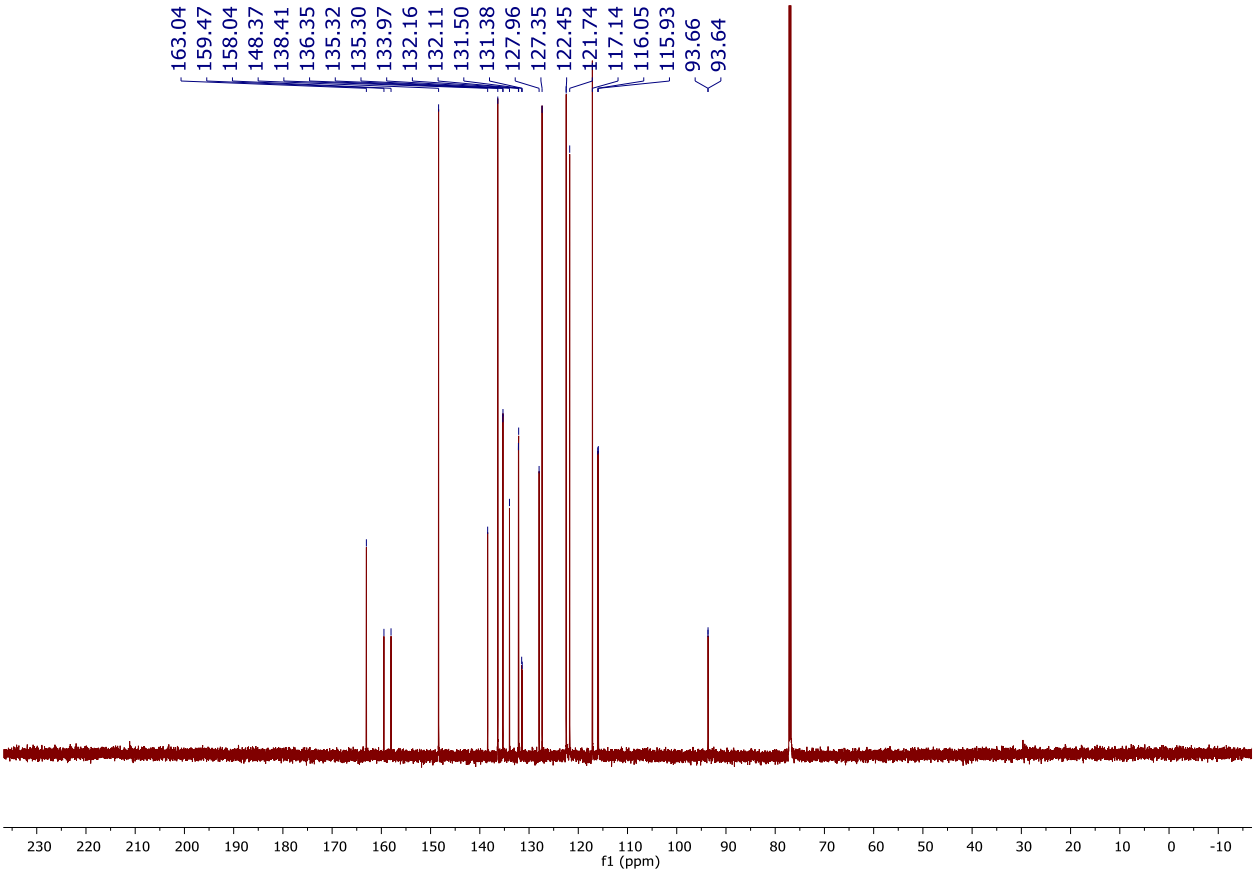


(**1**)

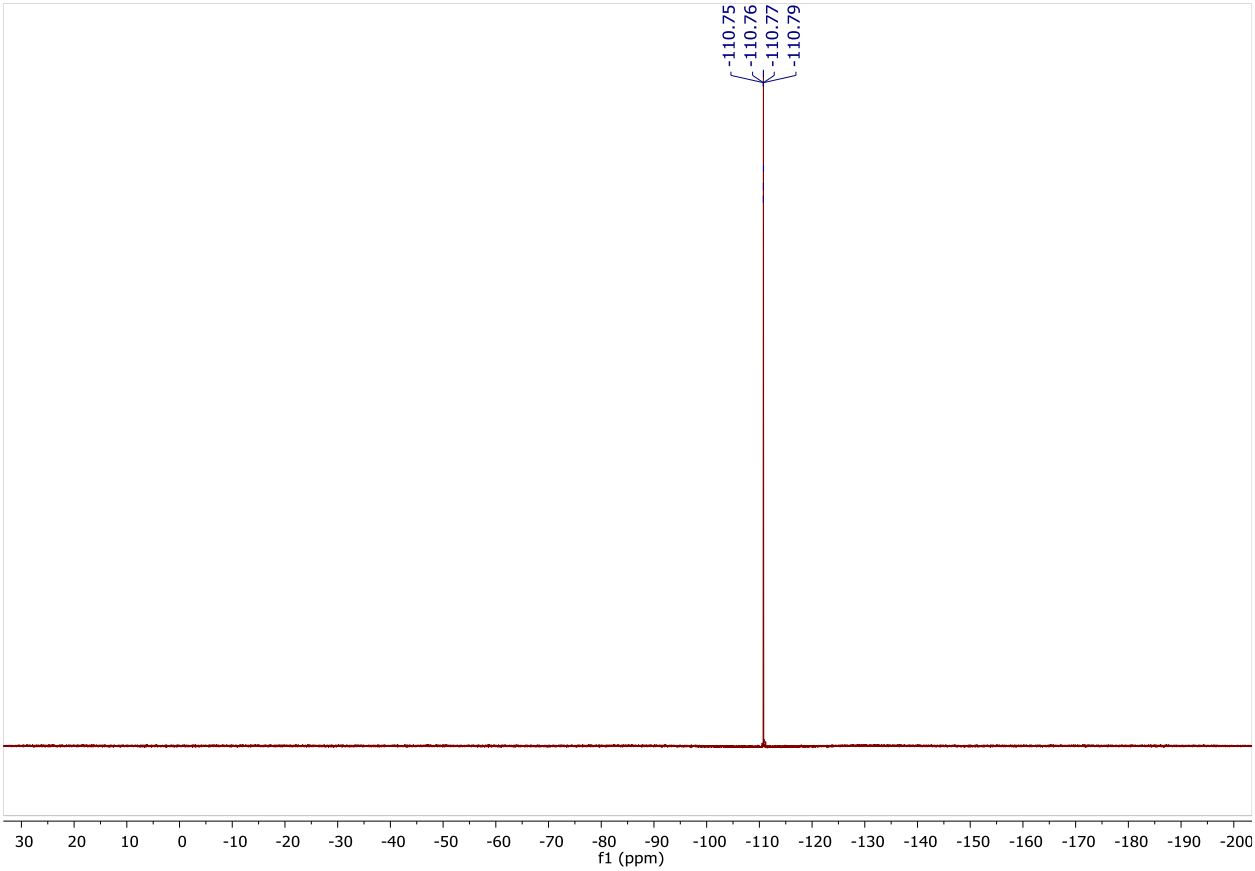
^{1}H NMR:

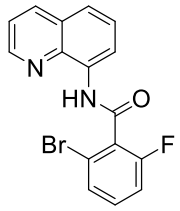


^{13}C NMR:


163.04
159.47
158.04
148.37
138.41
136.35
135.32
135.30
133.97
132.16
132.11
131.50
131.38
127.96
127.35
122.45
121.74
117.14
116.05
115.93
93.66
93.64
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

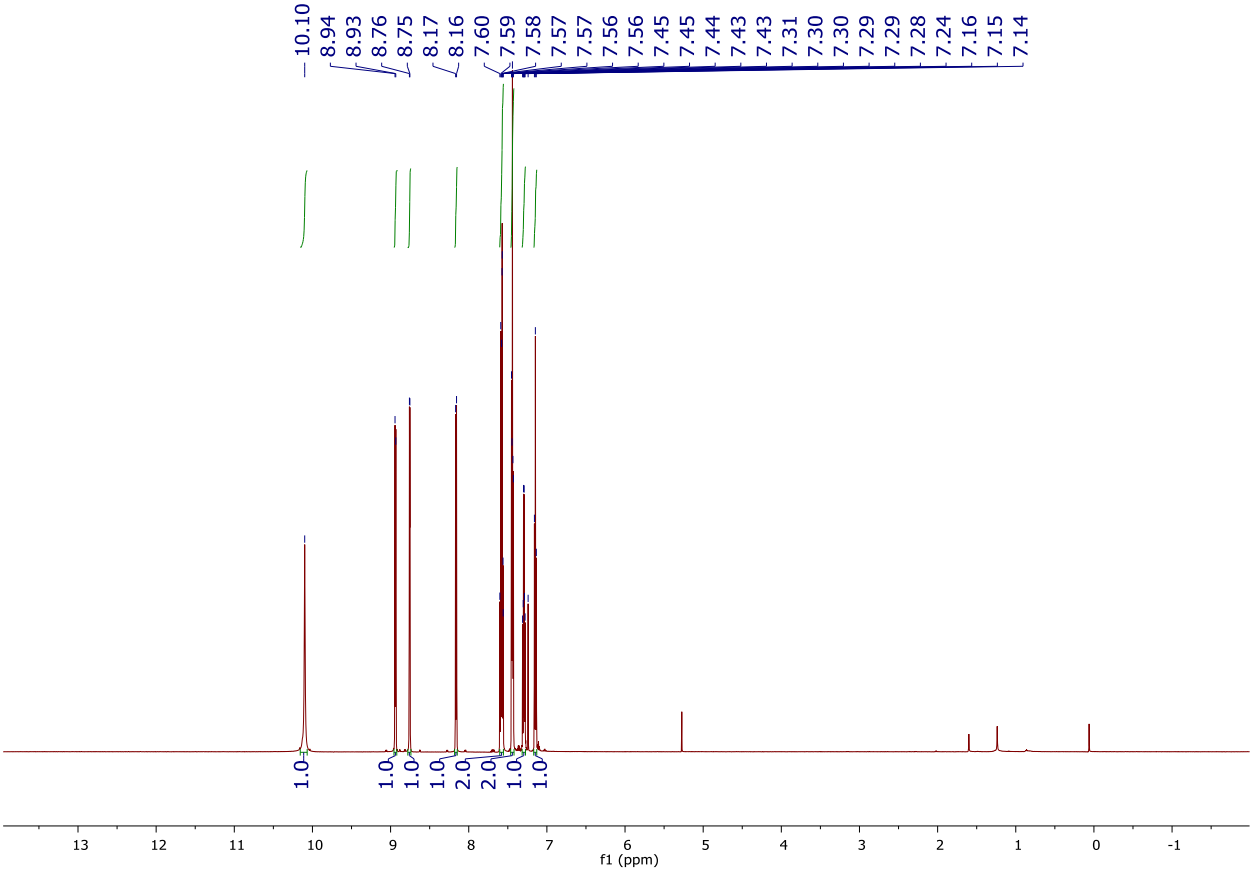
^{19}F NMR:


-110.75
-110.76
-110.77
-110.79
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

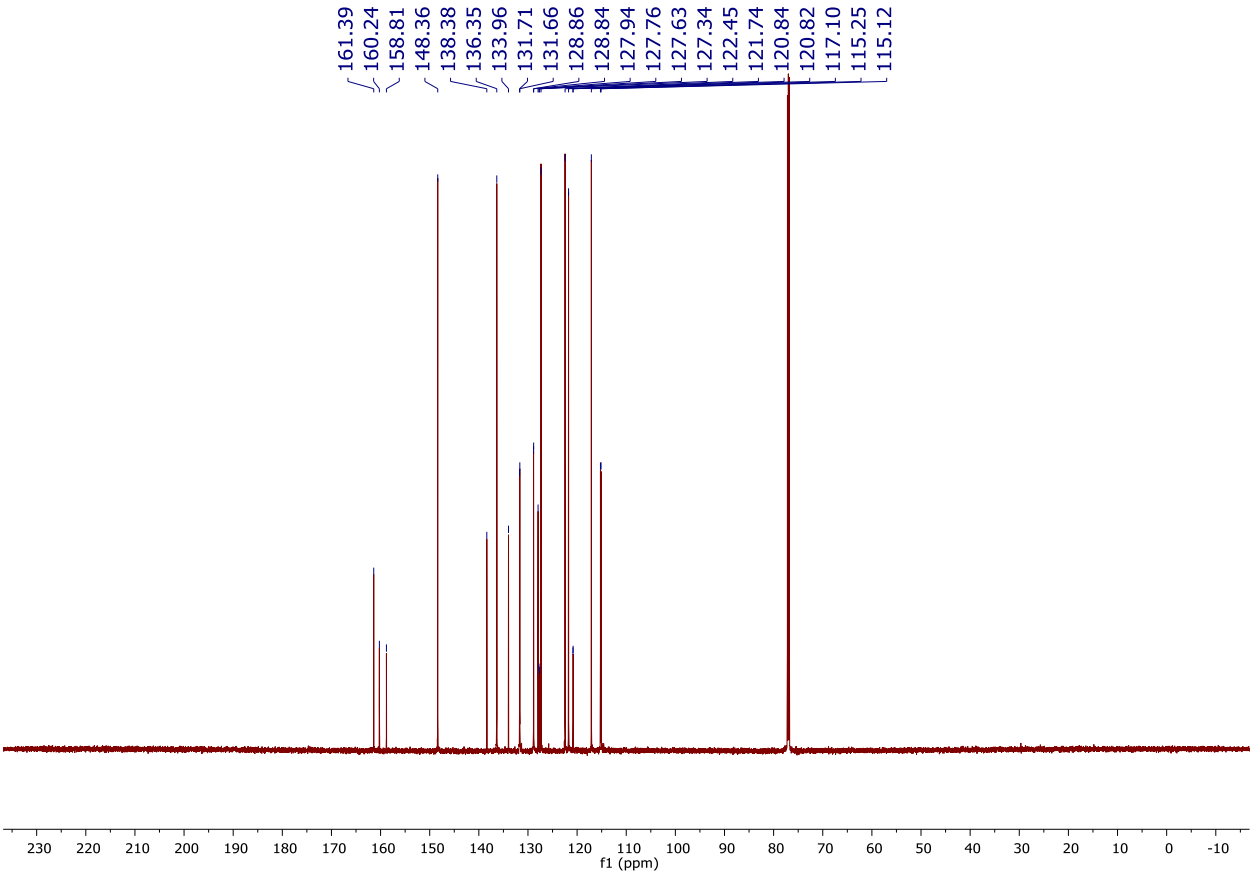

N
HN
O
Br
F

(**3**)

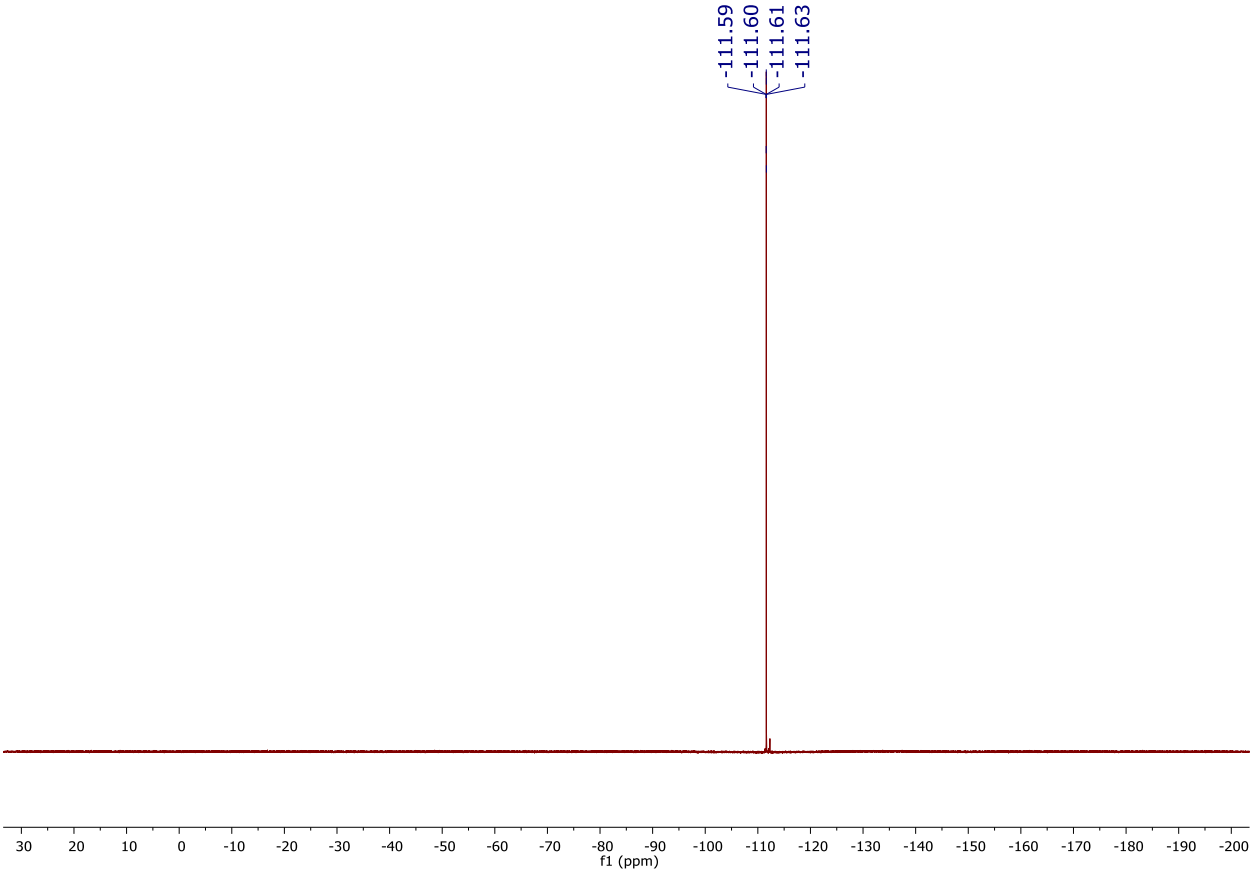
^{1}H NMR:

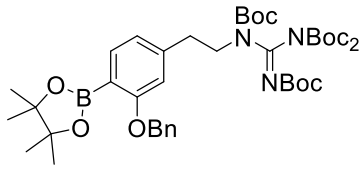

10.10
8.94
8.93
8.76
8.75
8.17
8.16
7.60
7.59
7.58
7.57
7.57
7.56
7.56
7.45
7.45
7.44
7.43
7.43
7.31
7.30
7.30
7.29
7.29
7.28
7.24
7.16
7.15
7.14
1.0
1.0
1.0
1.0
2.0
2.0
1.0
1.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


161.39
160.24
158.81
148.36
138.38
136.35
133.96
131.71
131.66
128.86
128.84
127.94
127.76
127.63
127.34
122.45
121.74
120.84
120.82
117.10
115.25
115.12
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

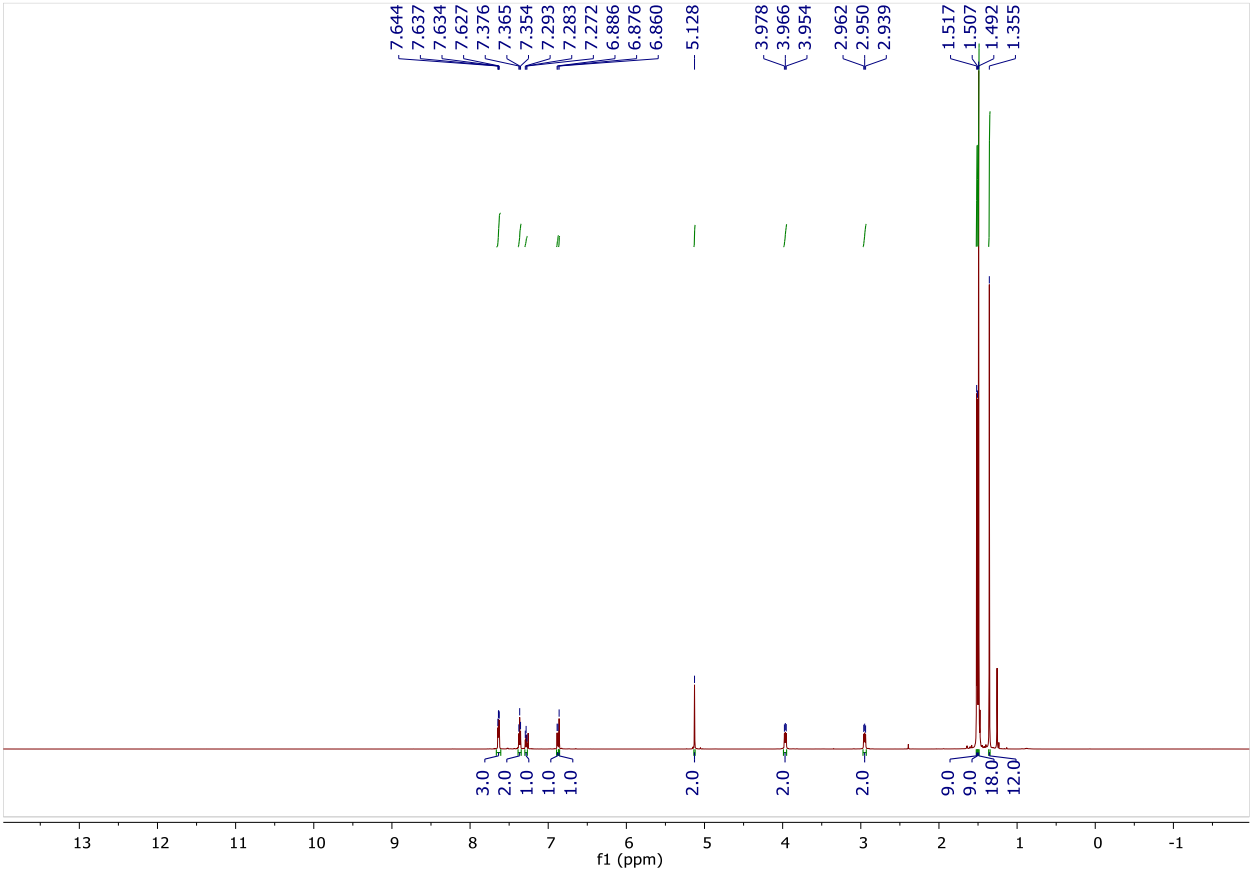
^{19}F NMR:


-111.59
-111.60
-111.61
-111.63
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

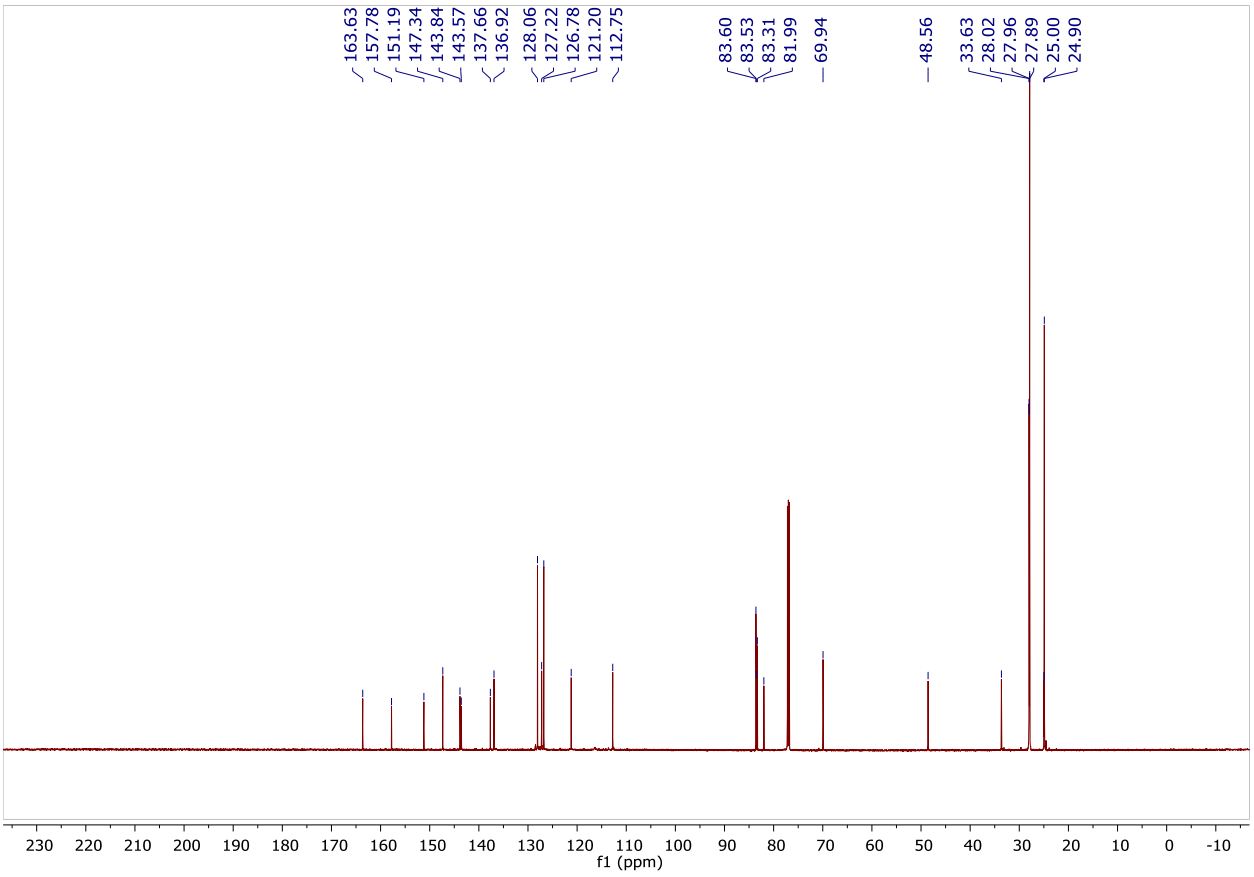

Boc
N
NBoc2
NBoc
O
B
O
OBn

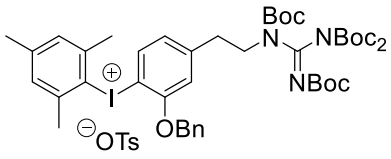
(**8**)

^{1}H NMR


7.644
7.637
7.634
7.627
7.376
7.365
7.354
7.293
7.283
7.272
6.886
6.876
6.860
5.128
3.978
3.966
3.954
2.962
2.950
2.939
1.517
1.507
1.492
1.355
3.0
2.0
1.0
1.0
1.0
2.0
2.0
2.0
9.0
9.0
18.0
12.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

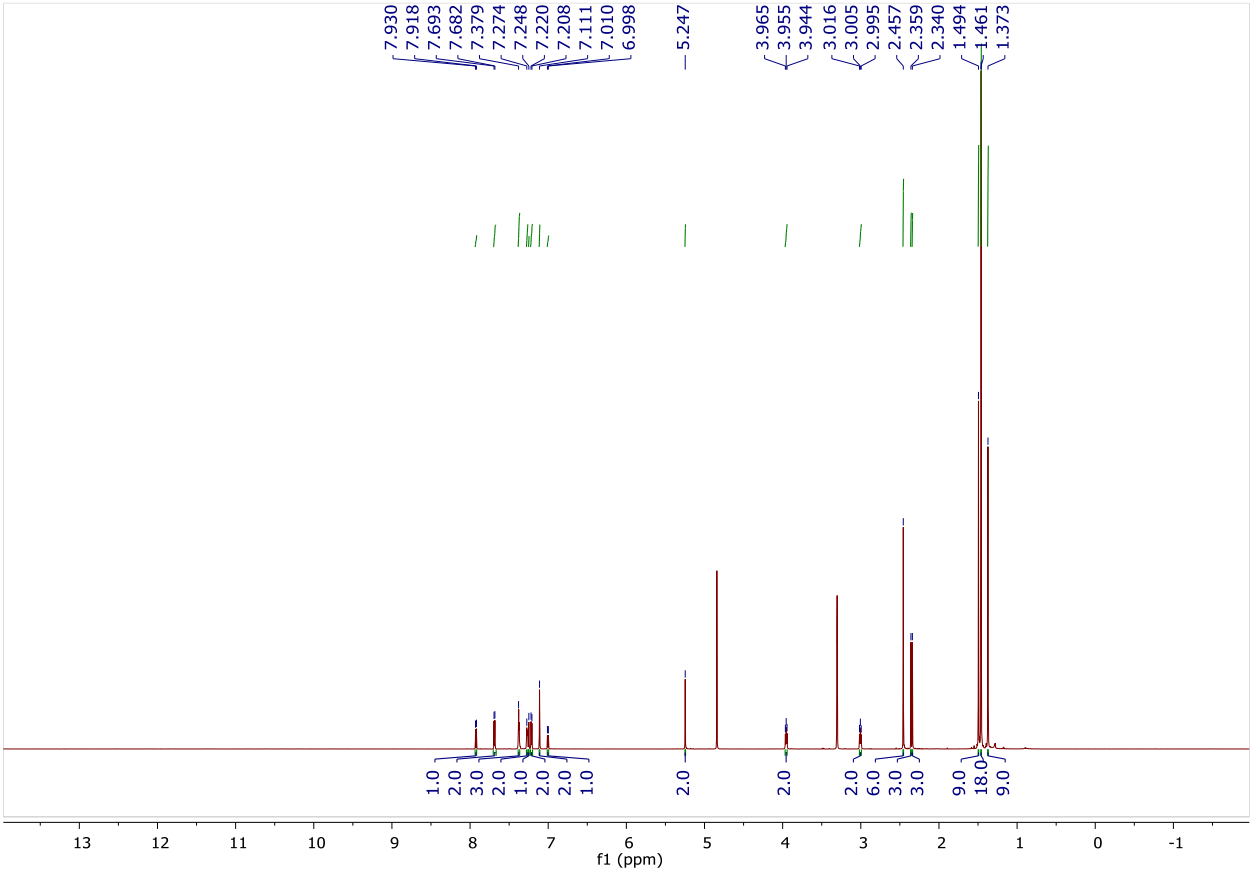
^{13}C NMR


163.63
157.78
151.19
147.34
143.84
143.57
137.66
136.92
128.06
127.22
126.78
121.20
112.75
83.60
83.53
83.31
81.99
69.94
48.56
33.63
28.02
27.96
27.89
25.00
24.90
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

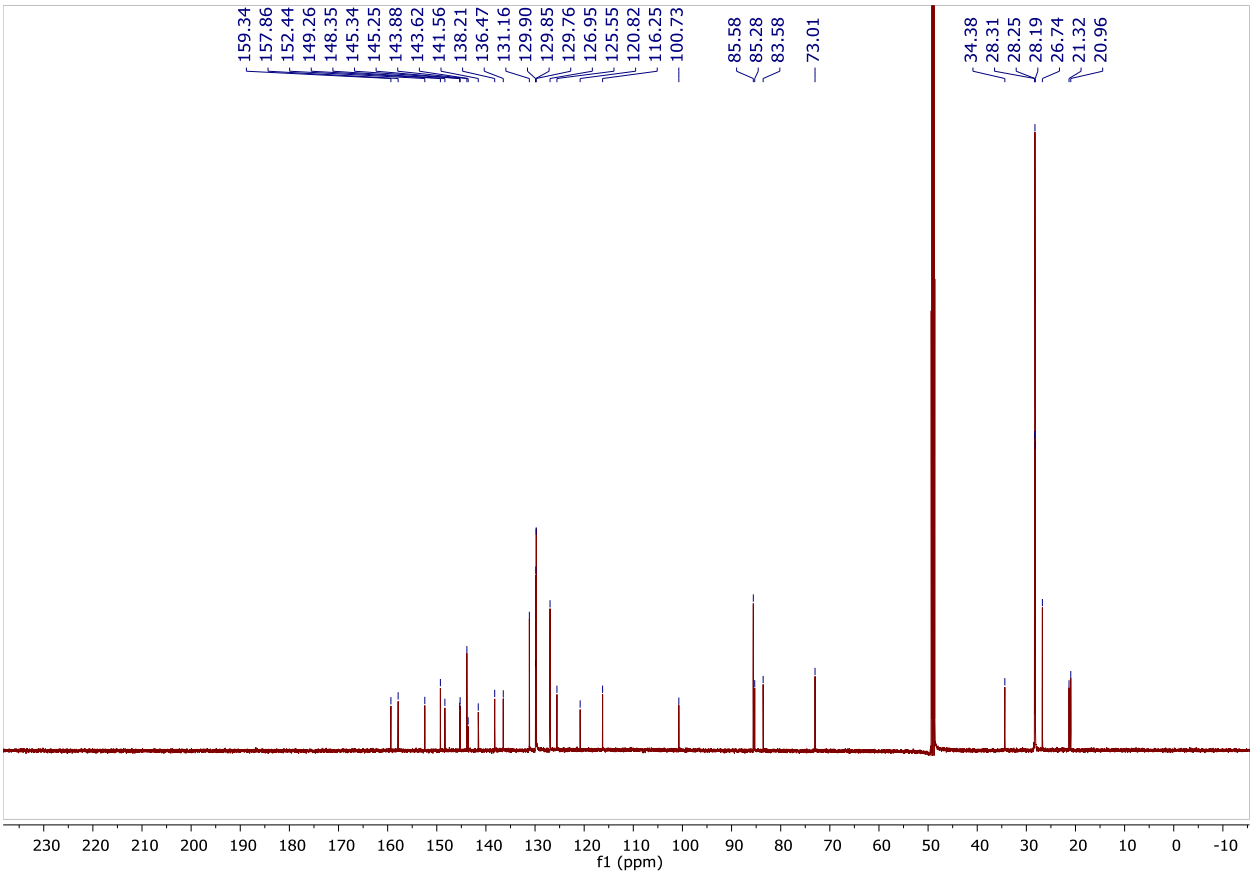

Boc
N
NBoc2
NBoc
OTs
OBn

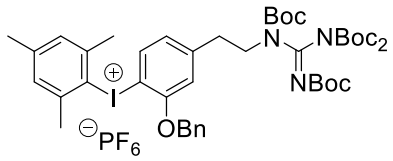
(**10-OTs**)

^{1}H NMR


7.930
7.918
7.693
7.682
7.379
7.274
7.248
7.220
7.208
7.111
7.010
6.998
5.247
3.965
3.955
3.944
3.016
3.005
2.995
2.457
2.359
2.340
1.494
1.461
1.373
1.0
2.0
3.0
2.0
1.0
2.0
2.0
1.0
2.0
2.0
2.0
6.0
3.0
3.0
9.0
18.0
9.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

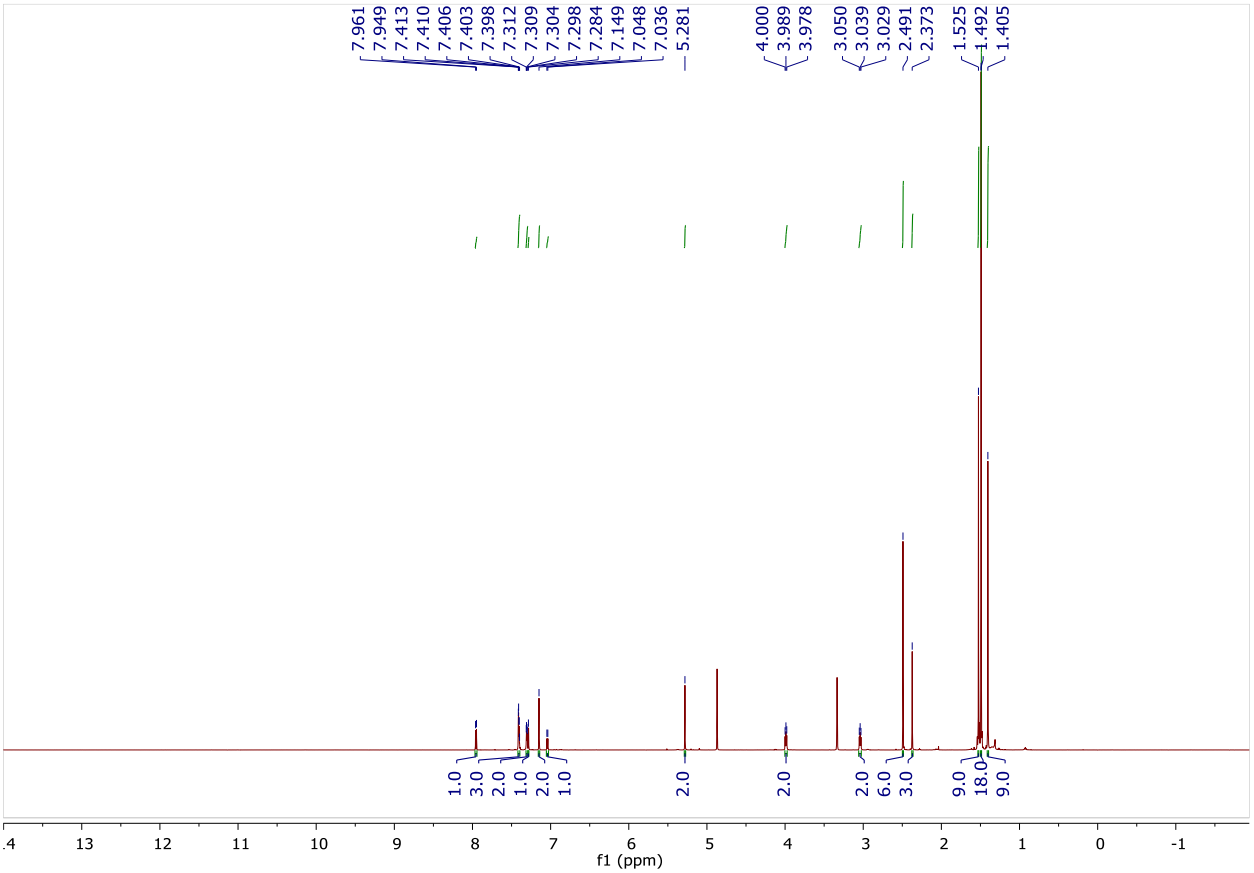
^{13}C NMR


159.34
157.86
152.44
149.26
148.35
145.34
145.25
143.88
143.62
141.56
138.21
136.47
131.16
129.90
129.85
129.76
126.95
125.55
120.82
116.25
100.73
85.58
85.28
83.58
73.01
34.38
28.31
28.25
28.19
26.74
21.32
20.96
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

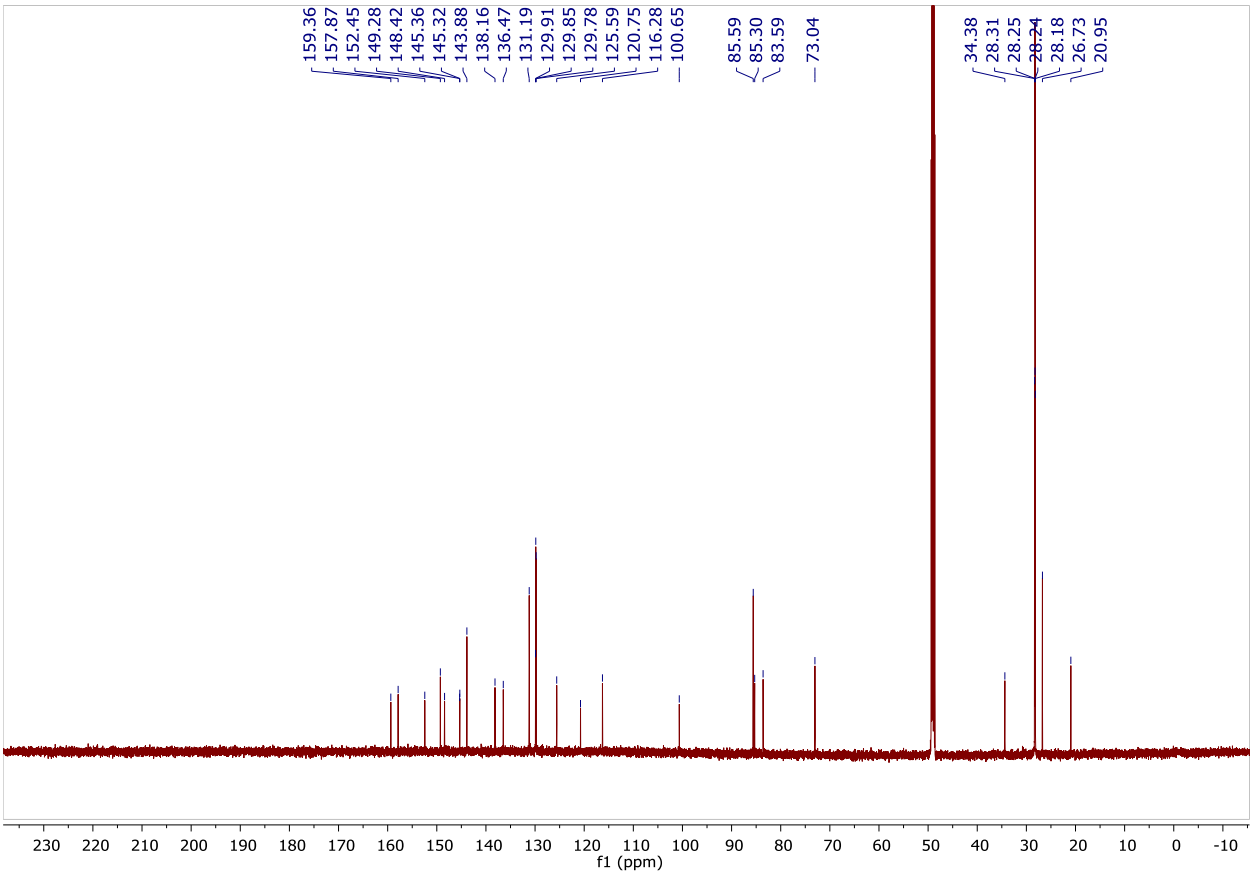

Boc
N
NBoc2
NBoc
OBn
PF6

(**10-PF$_6$**)

^{1}H NMR


7.961
7.949
7.413
7.410
7.406
7.403
7.398
7.312
7.309
7.304
7.298
7.284
7.149
7.048
7.036
5.281
4.000
3.989
3.978
3.050
3.039
3.029
2.491
2.373
1.525
1.492
1.405
1.0
3.0
2.0
1.0
2.0
1.0
2.0
2.0
2.0
6.0
3.0
9.0
18.0
9.0
f1 (ppm)

^{13}C NMR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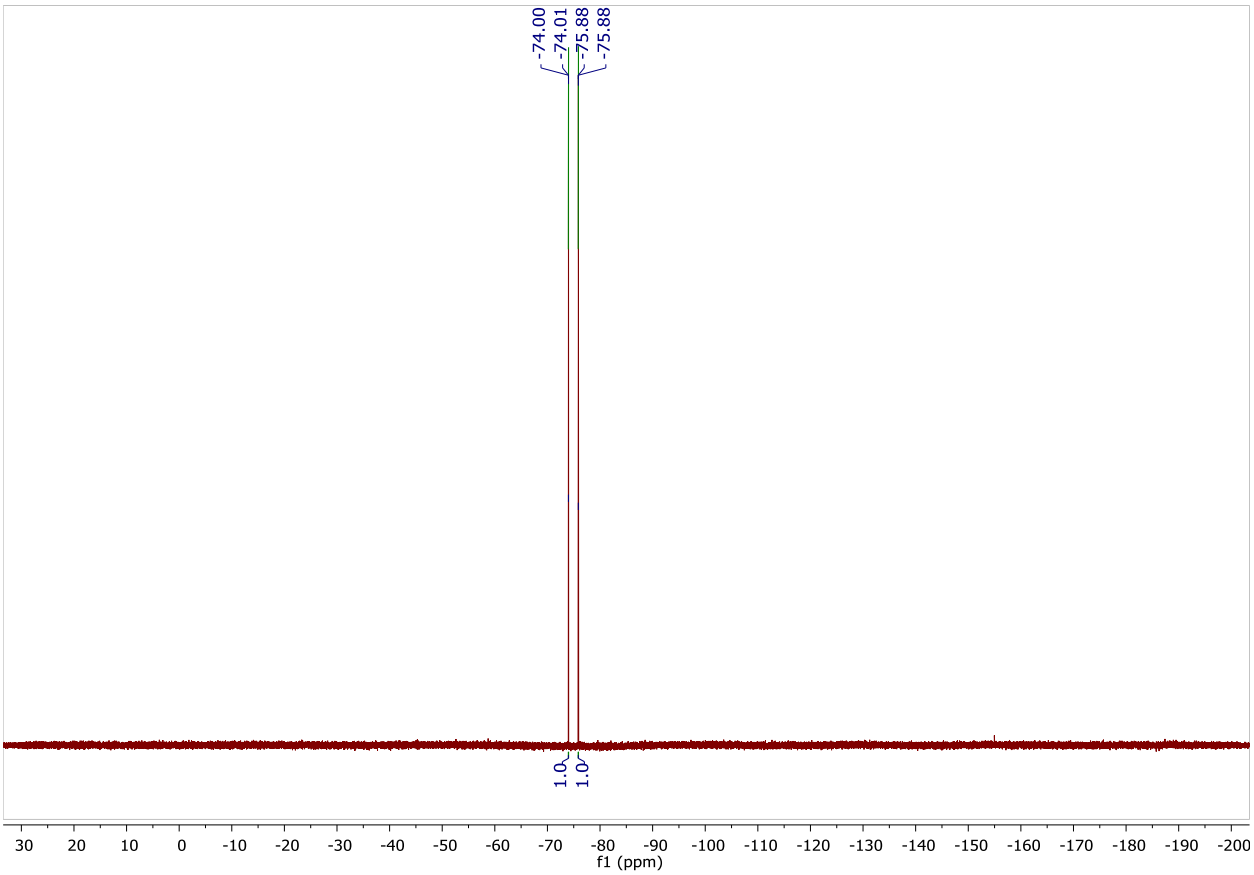
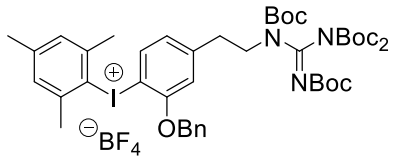
157.87
152.45
149.28
148.42
145.36
145.32
143.88
138.16
136.47
131.19
129.91
129.85
129.78
125.59
120.75
116.28
100.65
85.59
85.30
83.59
73.04
34.38
28.31
28.25
28.24
28.18
26.73
20.95
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

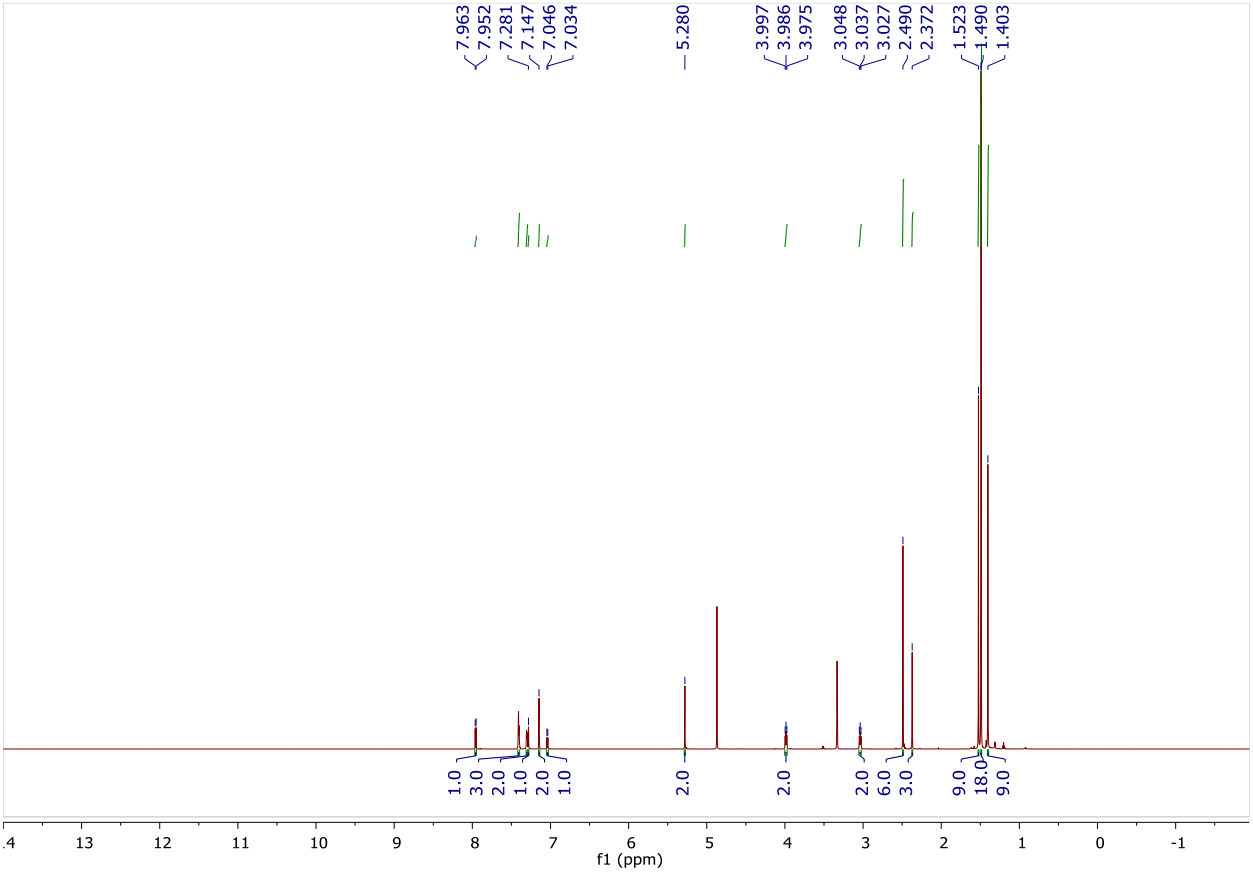
^{19}F NMR


-74.00
-74.01
-75.88
-75.88
1.0
1.0
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

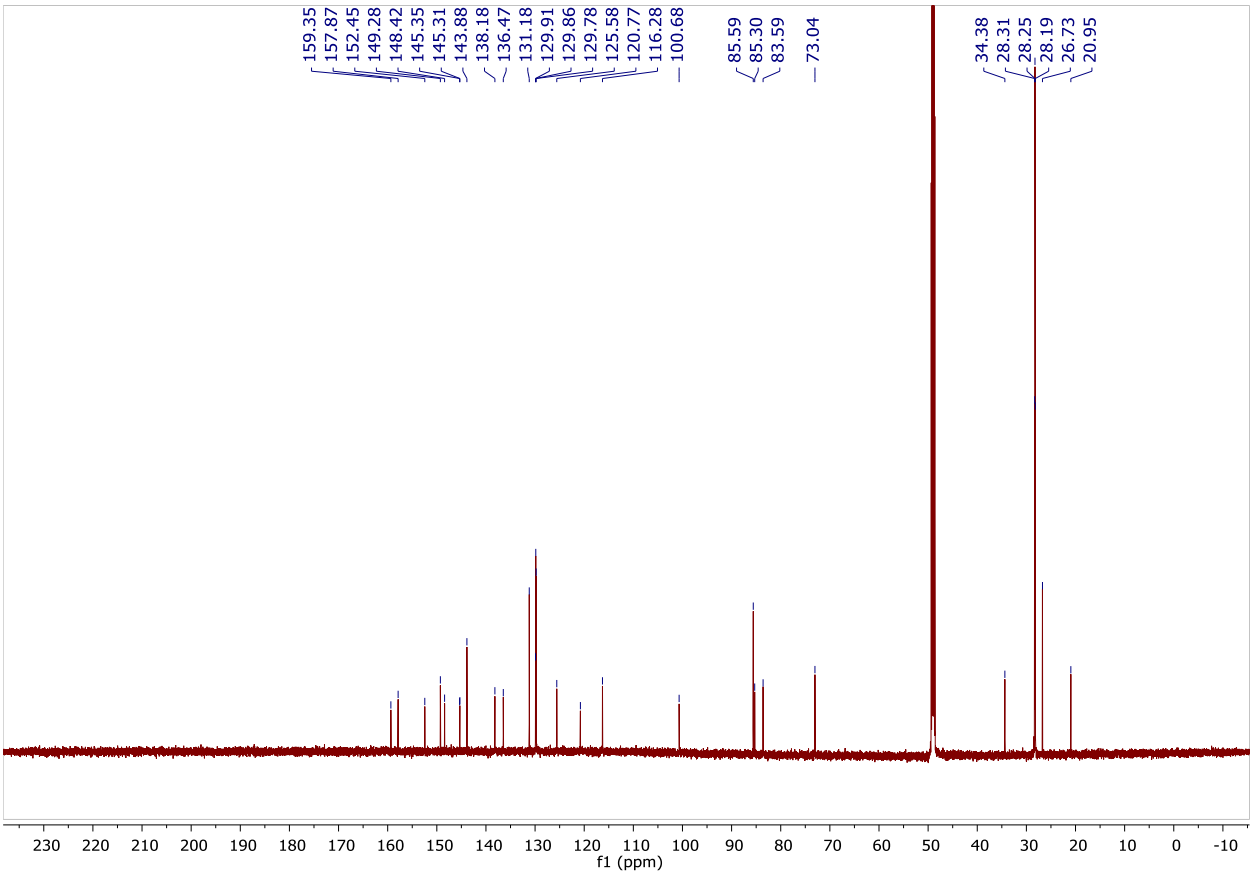

Boc
N
NBoc2
NBoc
OBn
BF4

(**10-BF_4**)

^{1}H NMR


7.963
7.952
7.281
7.147
7.046
7.034
5.280
3.997
3.986
3.975
3.048
3.037
3.027
2.490
2.372
1.523
1.490
1.403
1.0
3.0
2.0
1.0
2.0
1.0
2.0
2.0
2.0
6.0
3.0
9.0
18.0
9.0
f1 (ppm)

^{13}C NMR


159.35
157.87
152.45
149.28
148.42
145.35
145.31
143.88
138.18
136.47
131.18
129.91
129.86
129.78
125.58
120.77
116.28
100.68
85.59
85.30
83.59
73.04
34.38
28.31
28.25
28.19
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20.95
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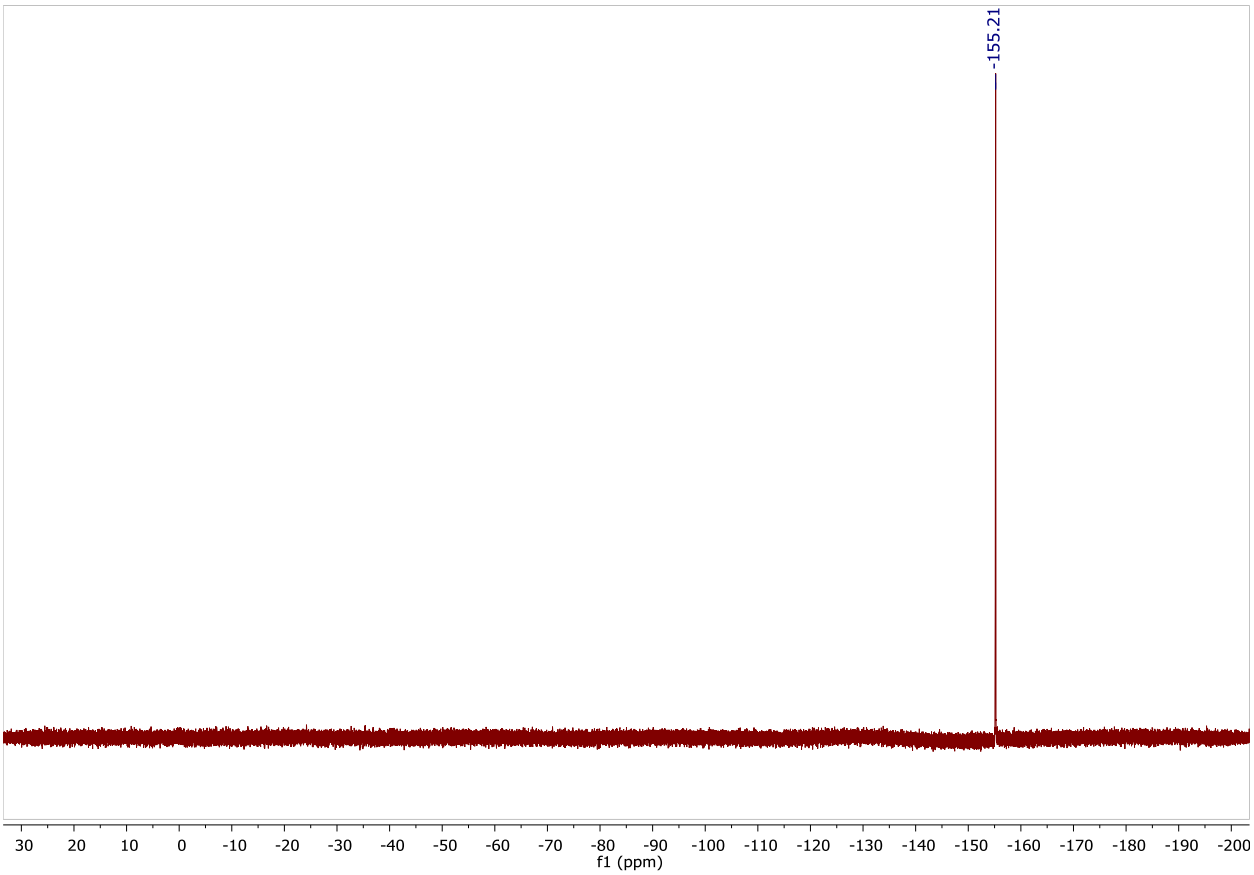
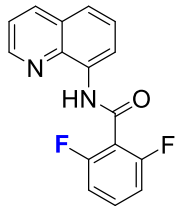
f1 (ppm)

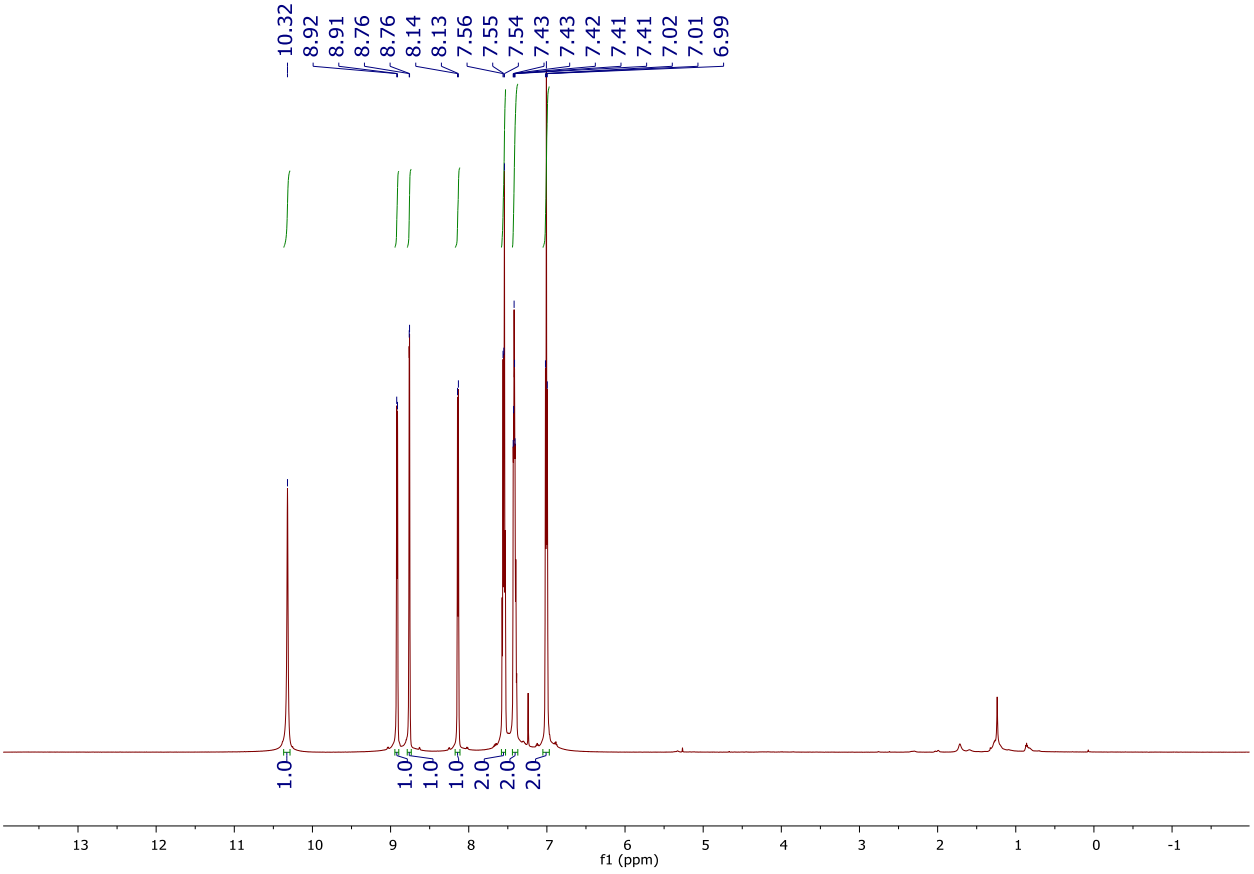
^{19}F NMR


-155.21
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

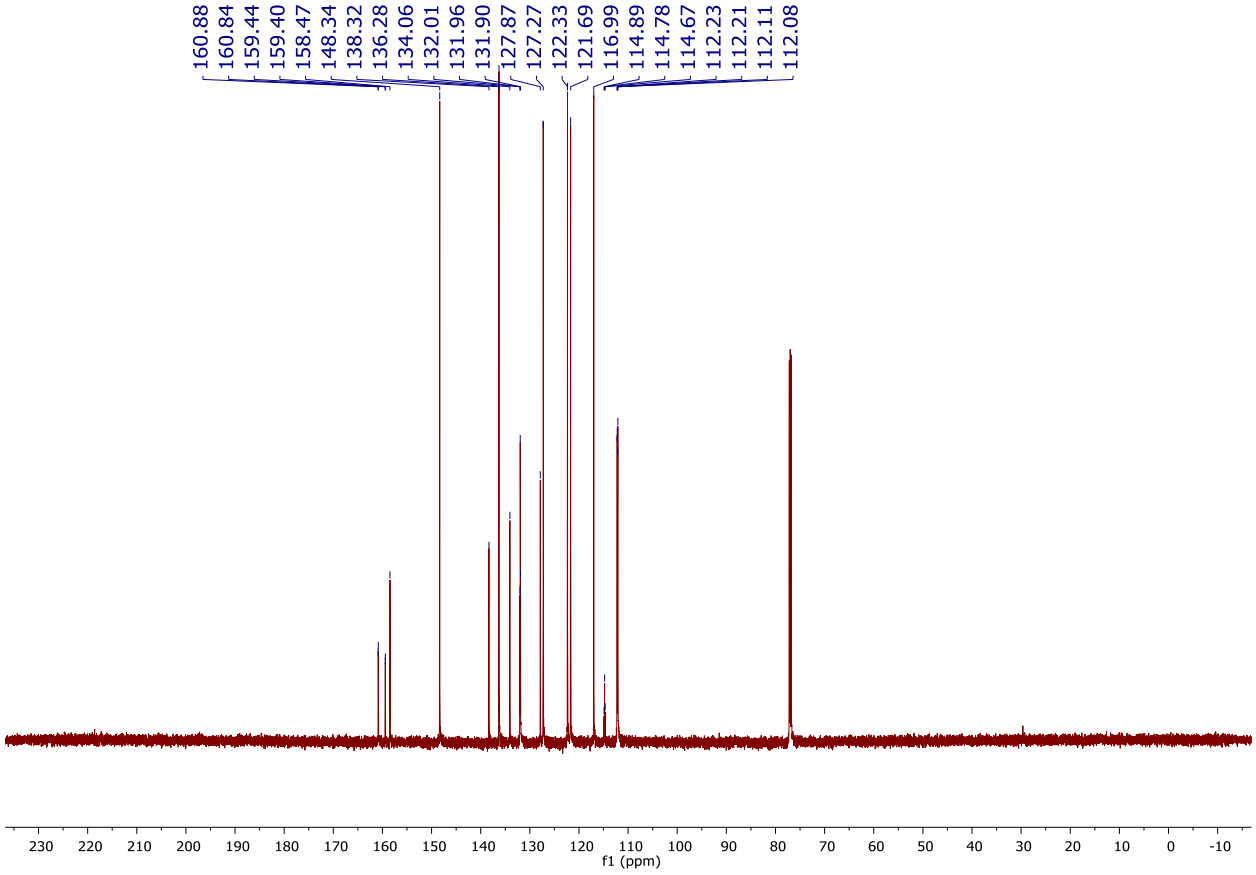

N
HN
O
F
F

(**2**)

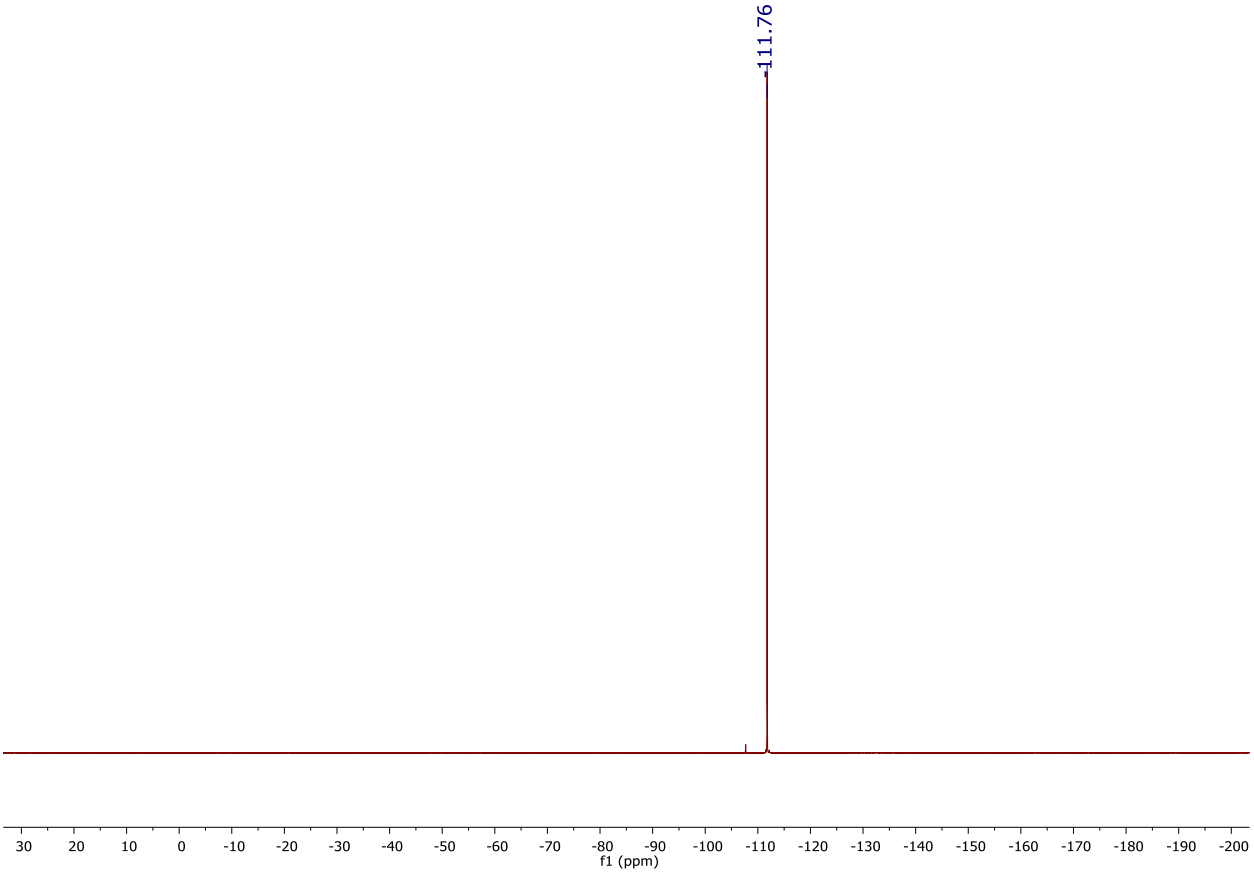
^{1}H NMR

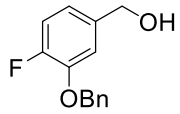

10.32
8.92
8.91
8.76
8.76
8.14
8.13
7.56
7.55
7.54
7.43
7.43
7.42
7.41
7.41
7.02
7.01
6.99
1.0
1.0
1.0
1.0
2.0
2.0
2.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR


160.88
160.84
159.44
159.40
158.47
148.34
138.32
136.28
134.06
132.01
131.96
131.90
127.87
127.27
122.33
121.69
116.99
114.89
114.78
114.67
112.23
112.21
112.11
112.08
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

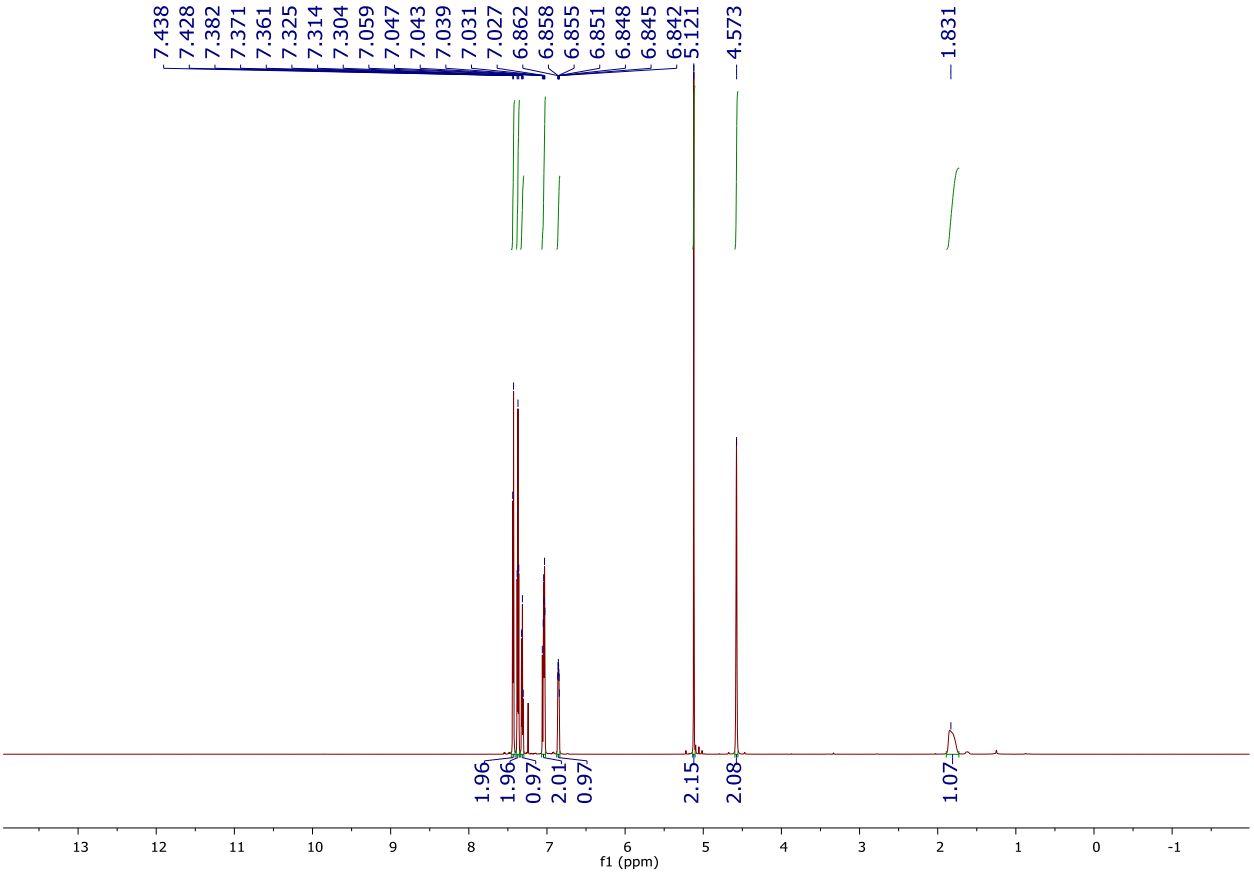
^{19}F NMR


-111.76
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

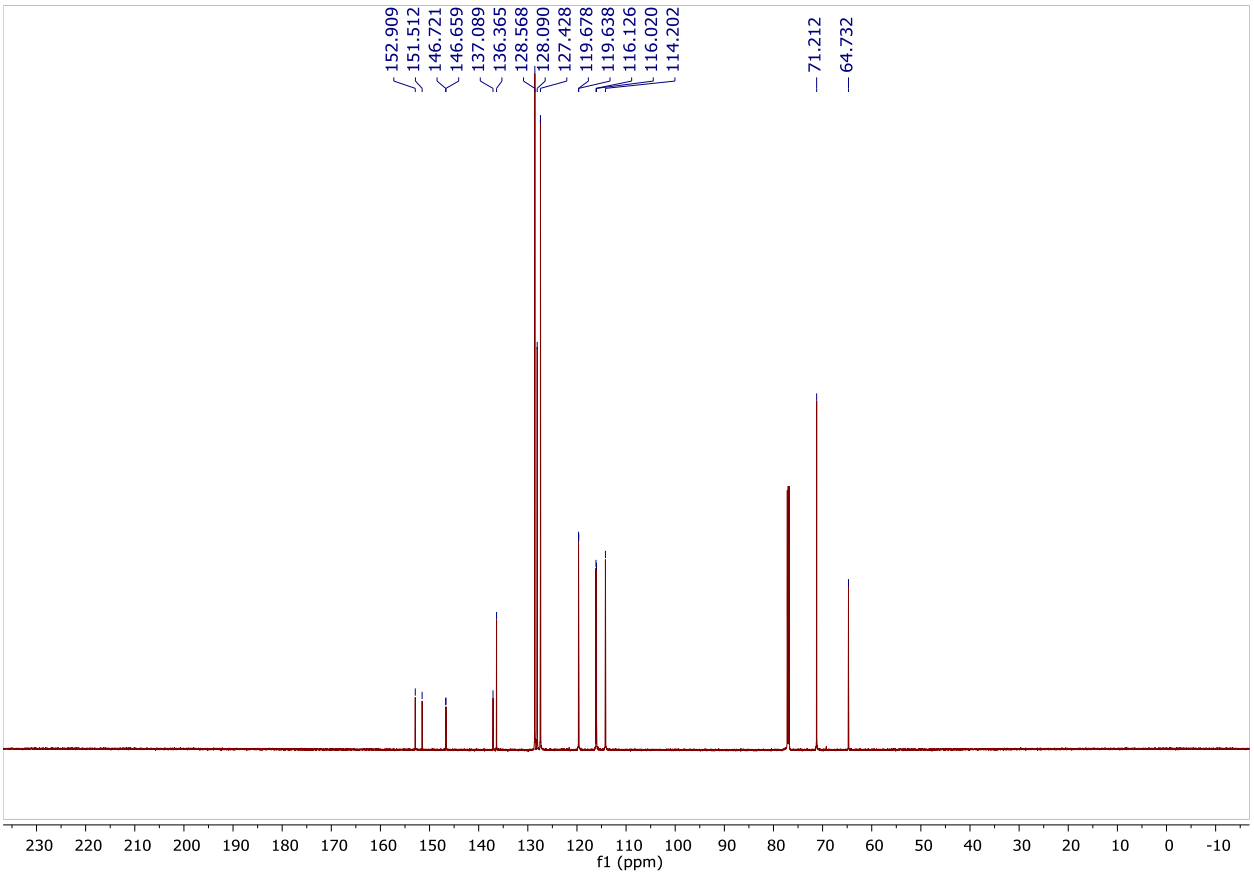

OH
F
OBn

S3-F

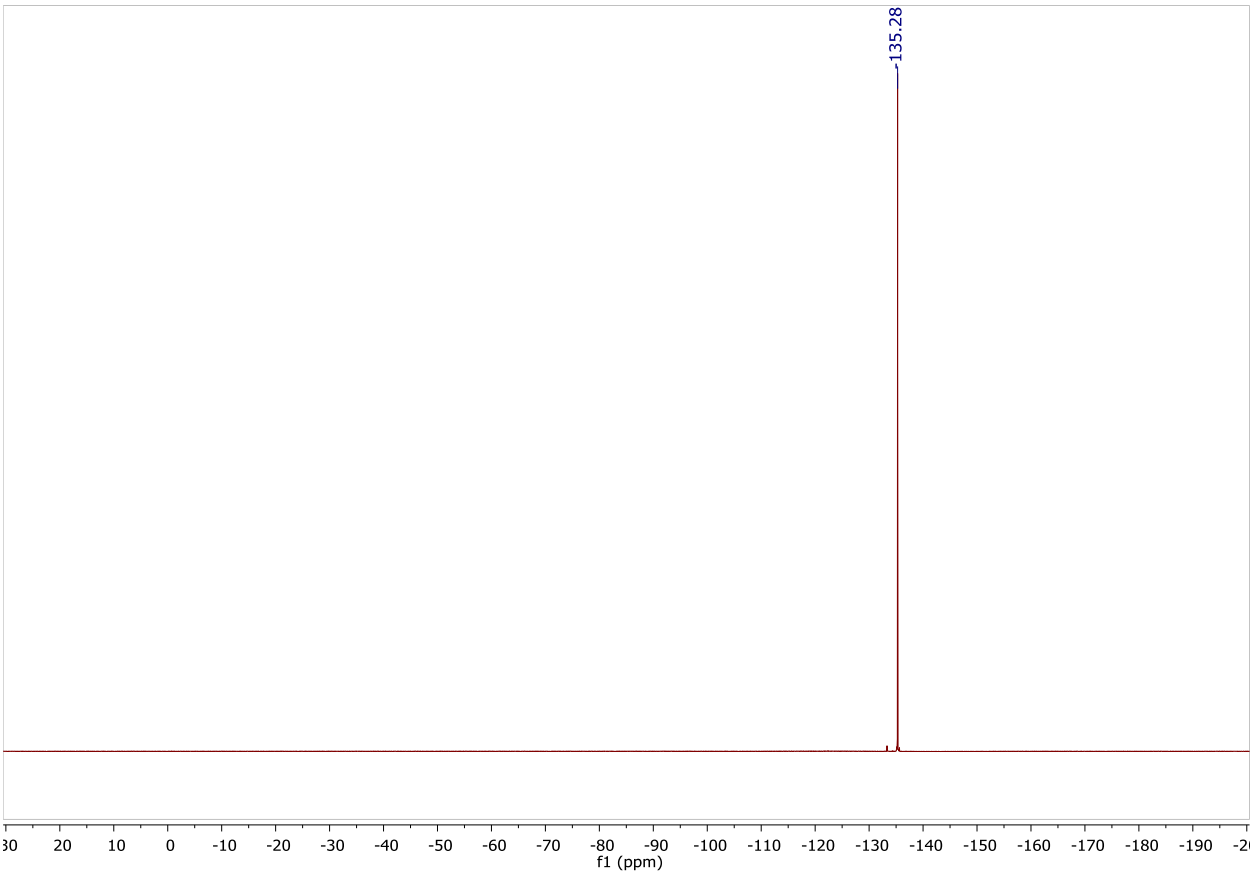
^{1}H NMR:

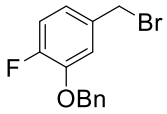

7.438
7.428
7.382
7.371
7.361
7.325
7.314
7.304
7.059
7.047
7.043
7.039
7.031
7.027
6.862
6.858
6.855
6.851
6.848
6.845
6.842
5.121
4.573
1.831
1.96
1.96
0.97
2.01
0.97
2.15
2.08
1.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


152.909
151.512
146.721
146.659
137.089
136.365
128.568
128.090
127.428
119.678
119.638
116.126
116.020
114.202
71.212
64.732
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

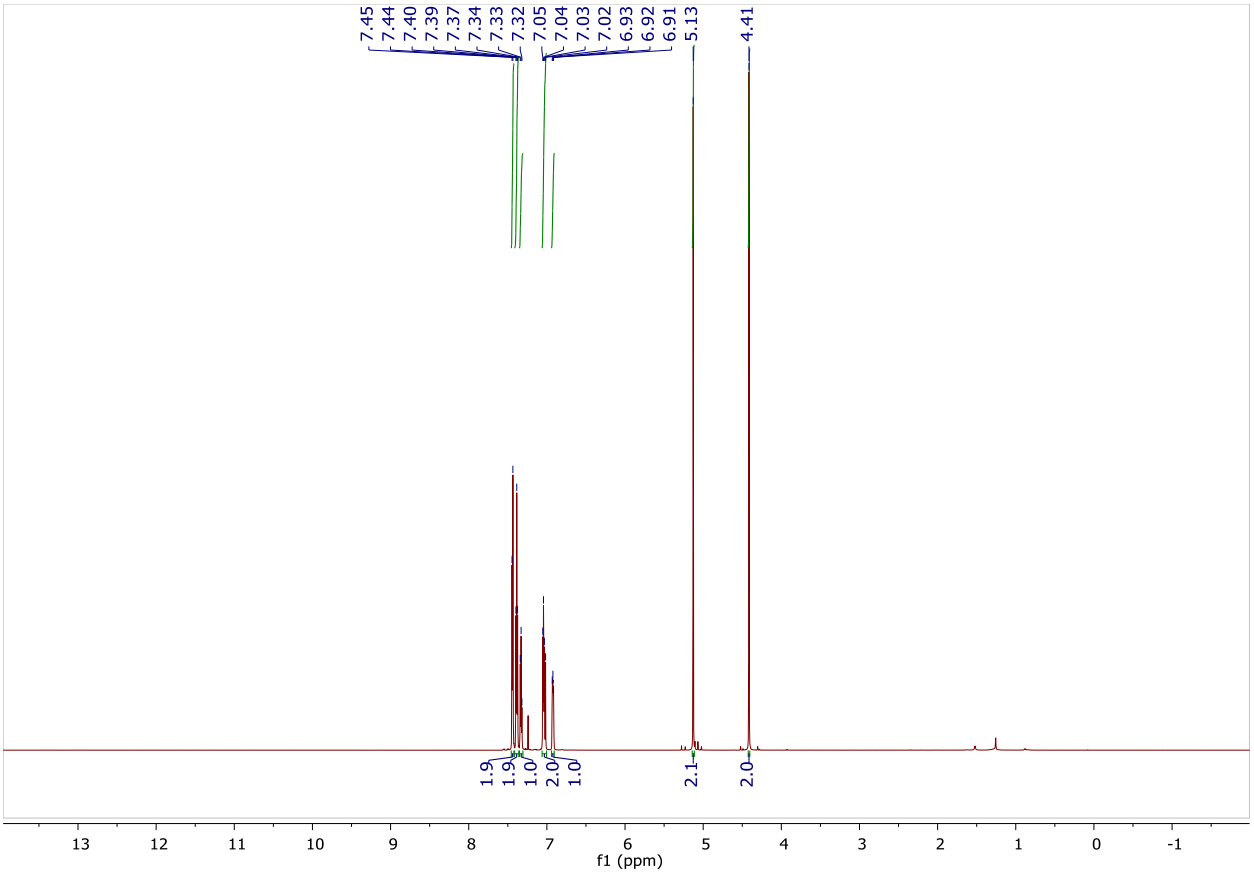
^{19}F NMR:


-135.28
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

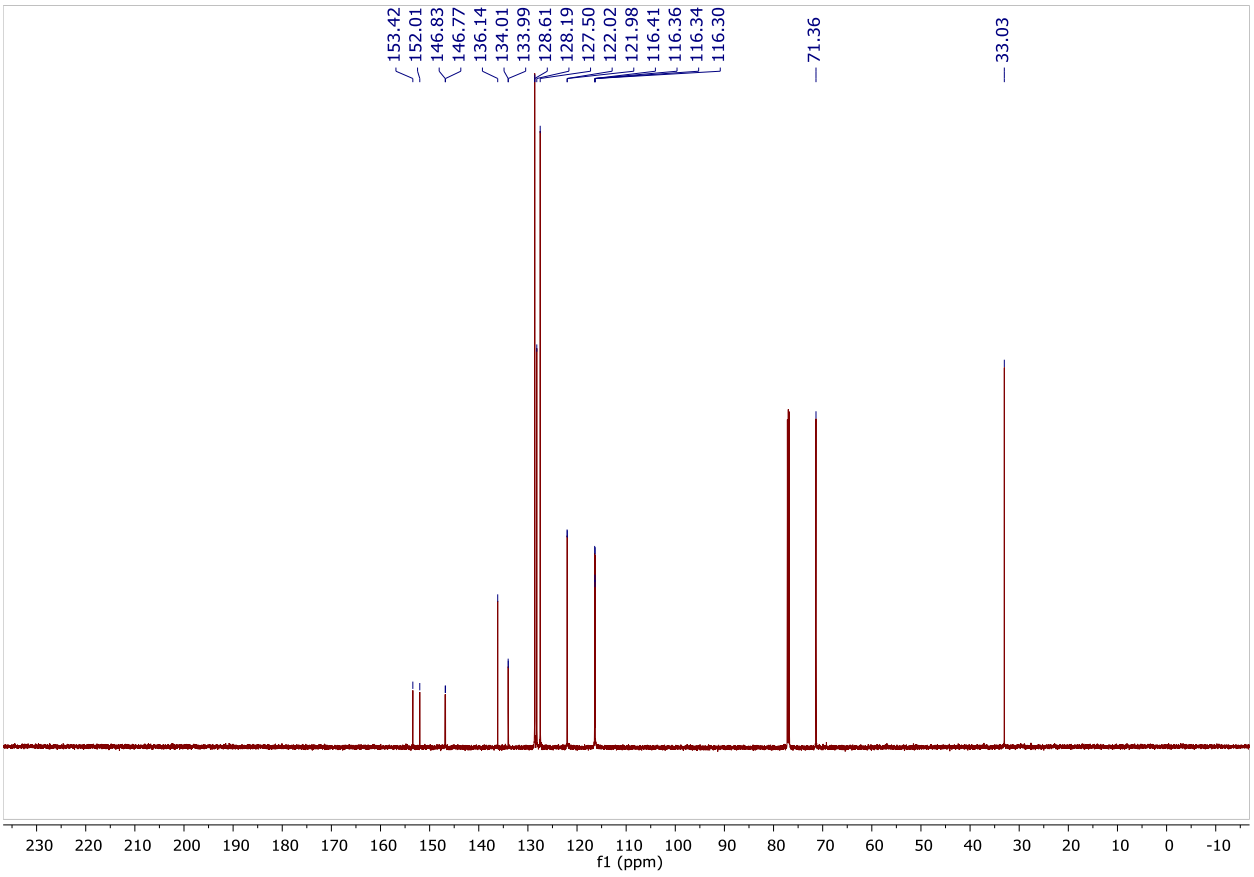

Br
F
OBn

S4-F

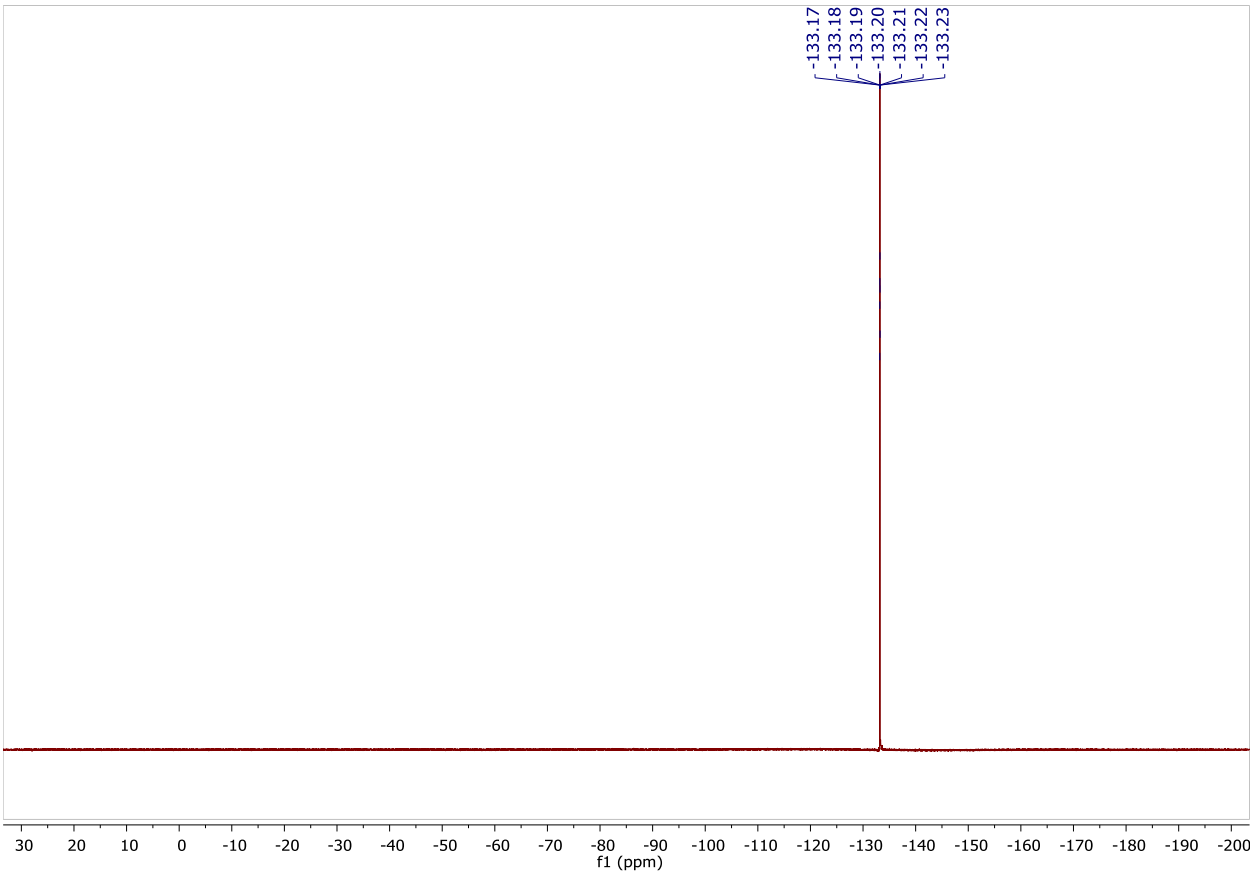
^{1}H NMR:

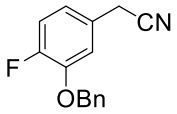

7.45
7.44
7.40
7.39
7.37
7.34
7.33
7.32
7.05
7.04
7.03
7.02
6.93
6.92
6.91
5.13
4.41
1.9
1.9
1.0
2.0
1.0
2.1
2.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


153.42
152.01
146.83
146.77
136.14
134.01
133.99
128.61
128.19
127.50
122.02
121.98
116.41
116.36
116.34
116.30
71.36
33.03
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

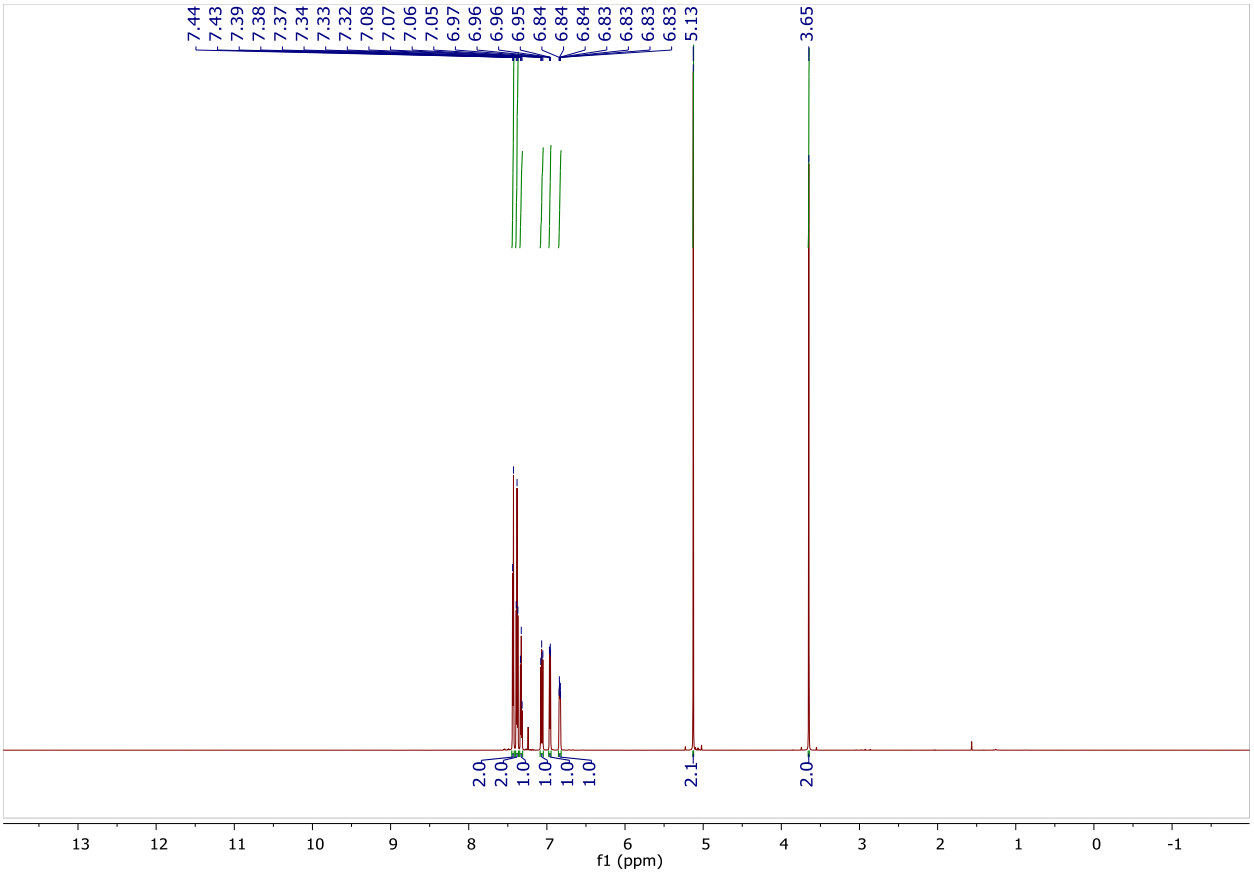
^{19}F NMR:


-133.17
-133.18
-133.19
-133.20
-133.21
-133.22
-133.23
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

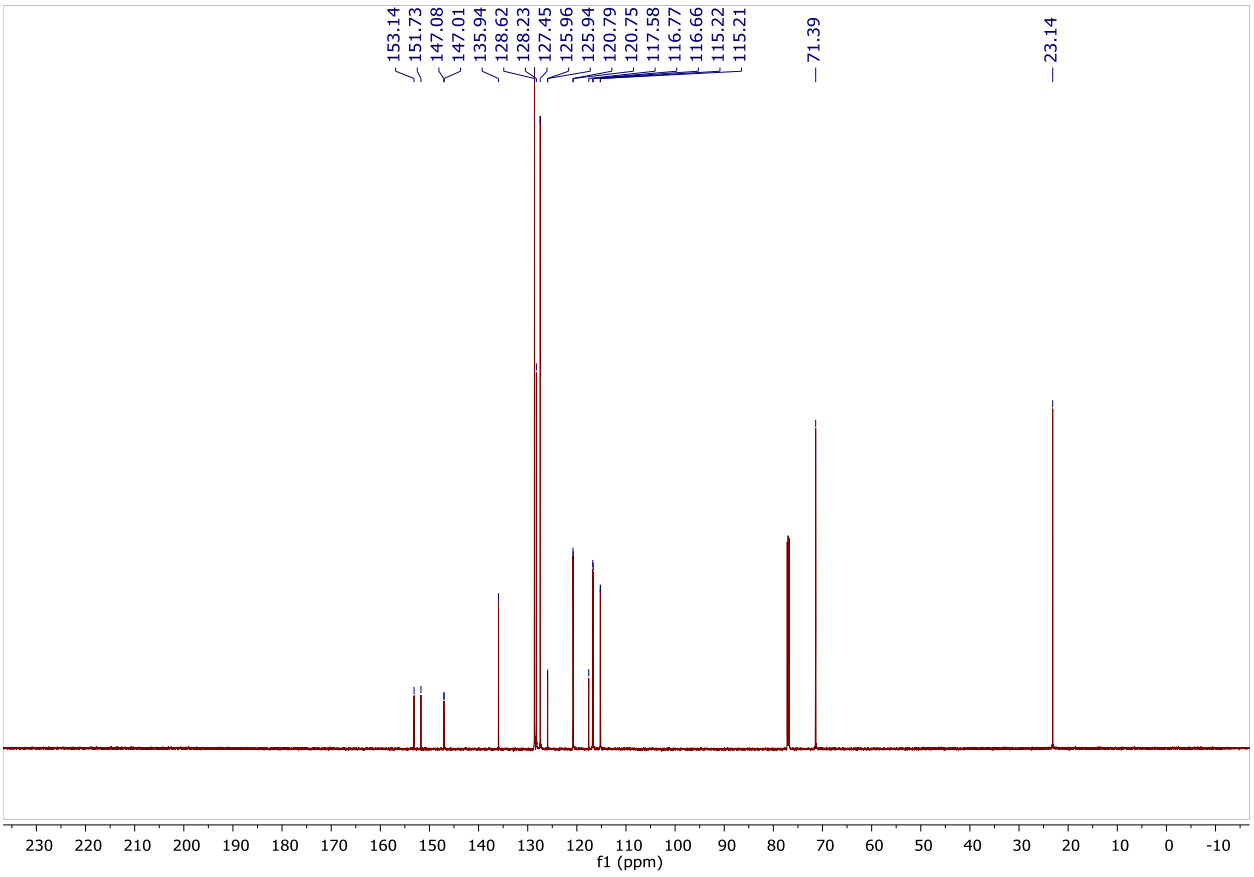

CN
F
OBn

S5-F

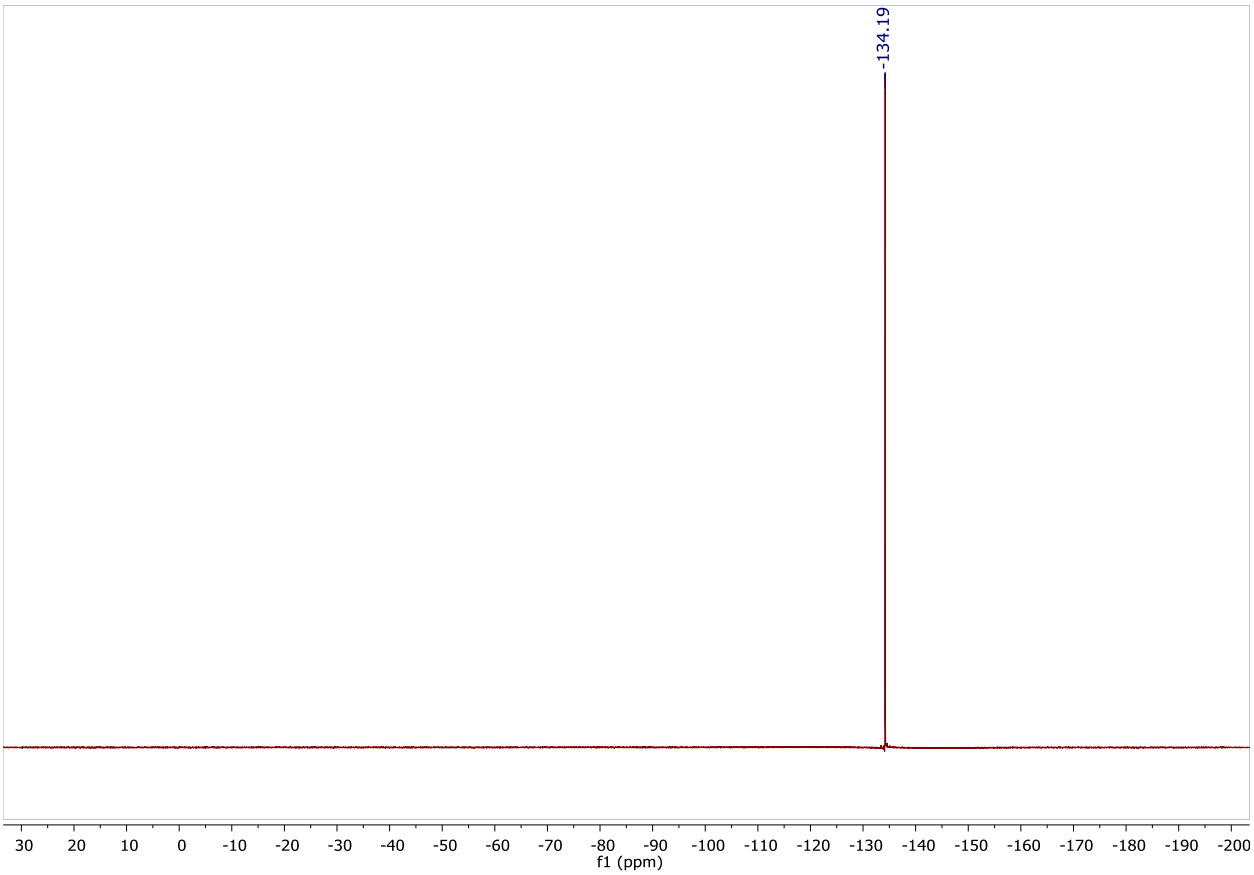
^{1}H NMR:

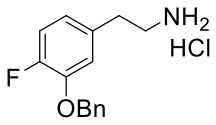

7.44
7.43
7.39
7.38
7.37
7.34
7.33
7.32
7.08
7.07
7.06
7.05
6.97
6.96
6.96
6.95
6.84
6.84
6.84
6.83
6.83
6.83
6.83
5.13
3.65
2.0
2.0
1.0
1.0
1.0
1.0
2.1
2.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


153.14
151.73
147.08
147.01
135.94
128.62
128.23
127.45
125.96
125.94
120.79
120.75
117.58
116.77
116.66
115.22
115.21
71.39
23.14
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

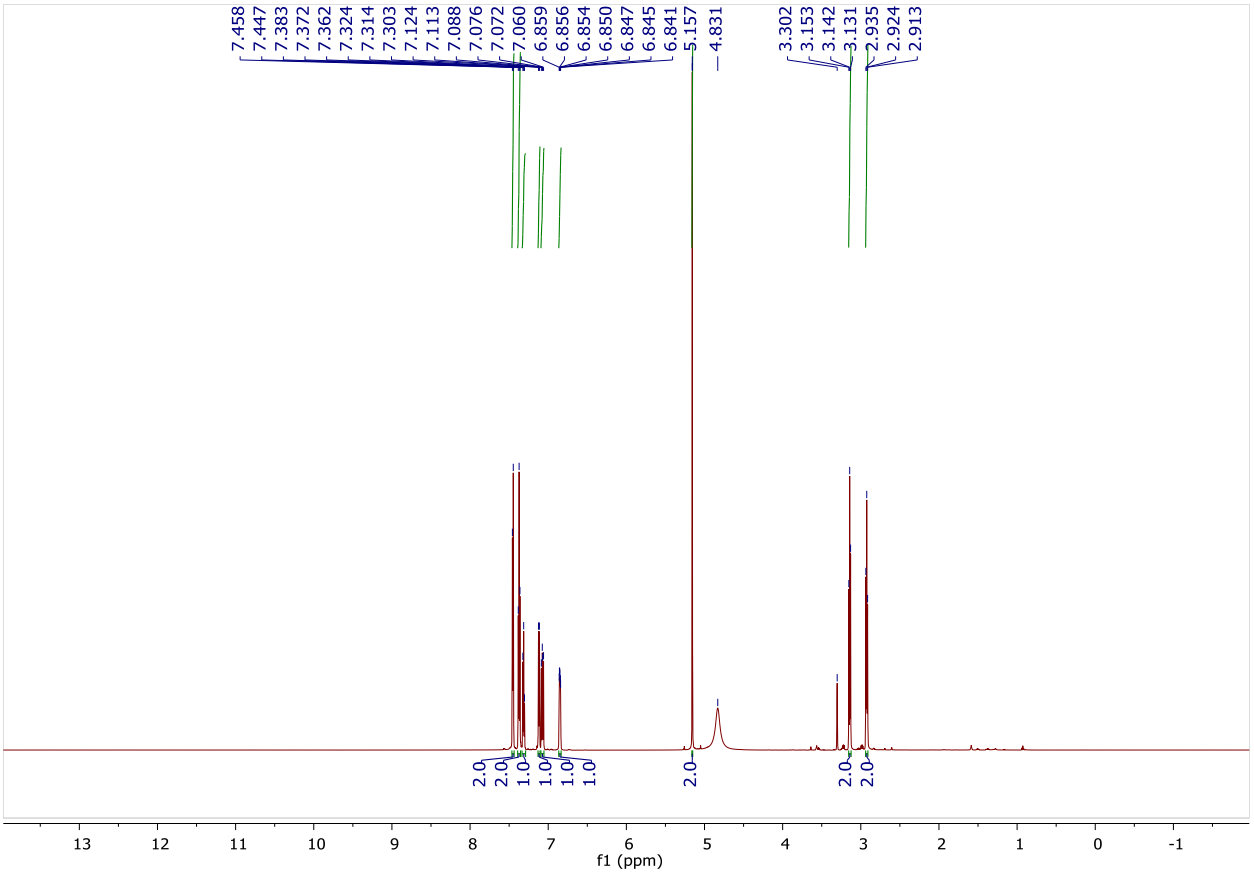
^{19}F NMR:


-134.19
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

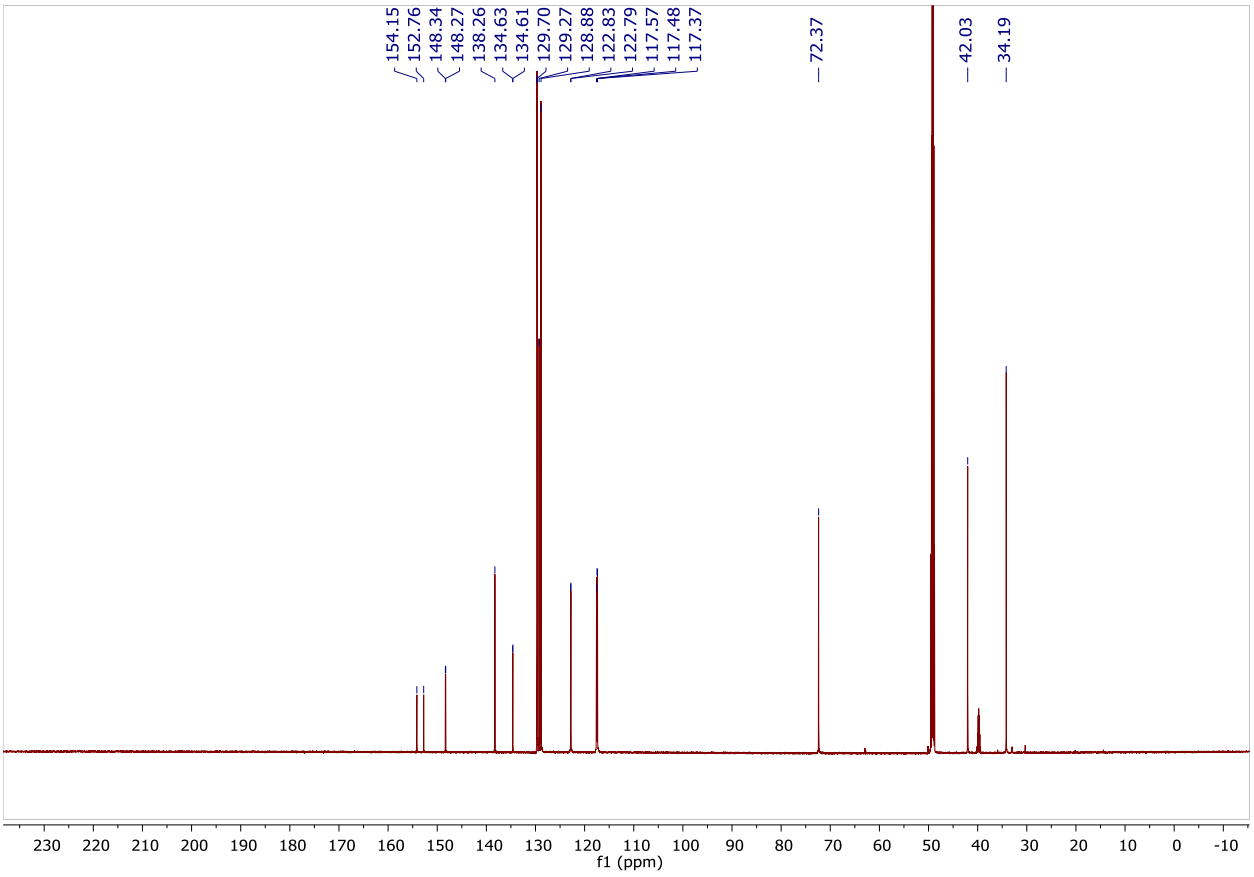

NH2
HCl
F
OBn

S6-F

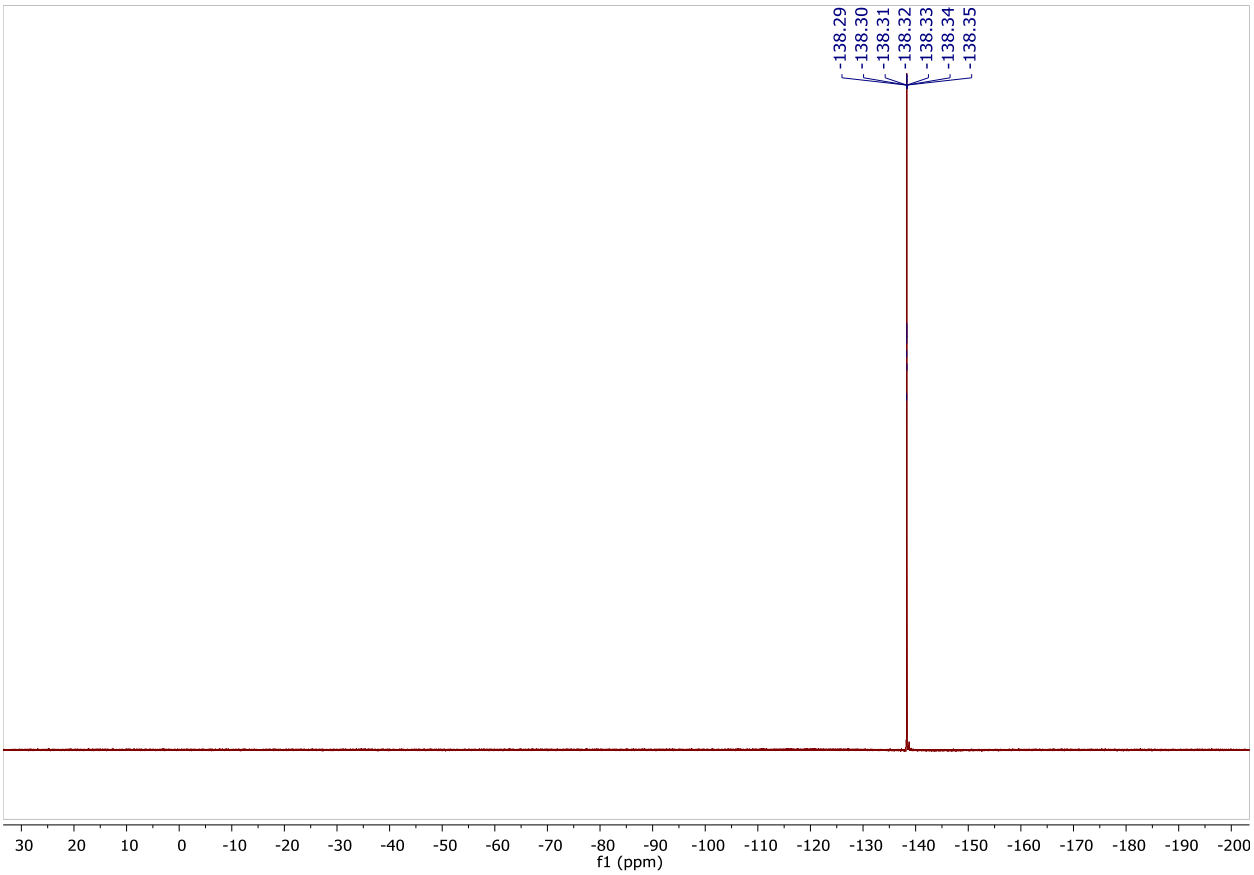
^{1}H NMR:

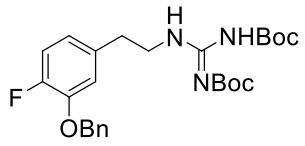

7.458
7.447
7.383
7.372
7.362
7.324
7.314
7.303
7.124
7.113
7.088
7.076
7.072
7.060
6.859
6.856
6.854
6.850
6.847
6.845
6.841
5.157
4.831
3.302
3.153
3.142
3.131
2.935
2.924
2.913
2.0
2.0
1.0
1.0
1.0
1.0
2.0
2.0
2.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


154.15
152.76
148.34
148.27
138.26
134.63
134.61
129.70
129.27
128.88
122.83
122.79
117.57
117.48
117.37
72.37
42.03
34.19
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

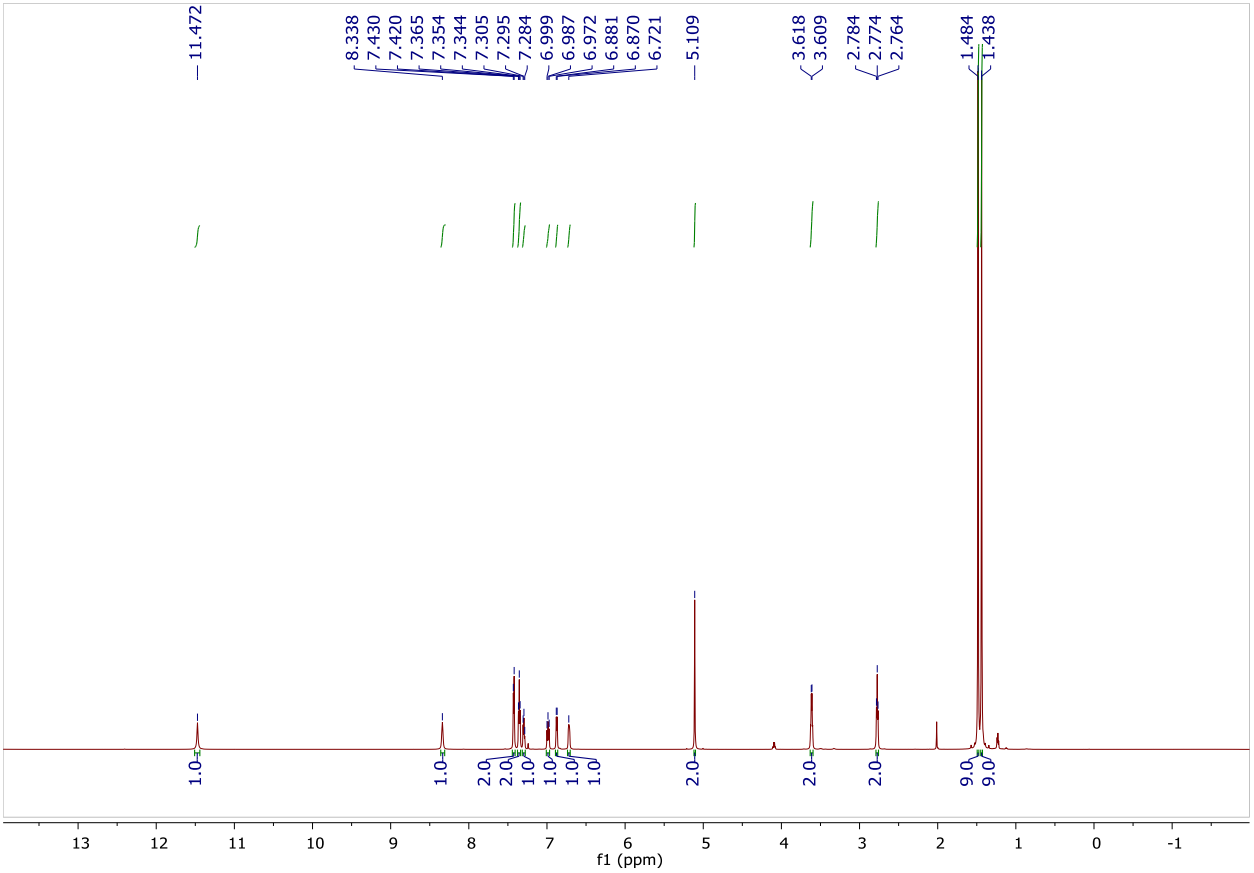
^{19}F NMR:


-138.29
-138.30
-138.31
-138.32
-138.33
-138.34
-138.35
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

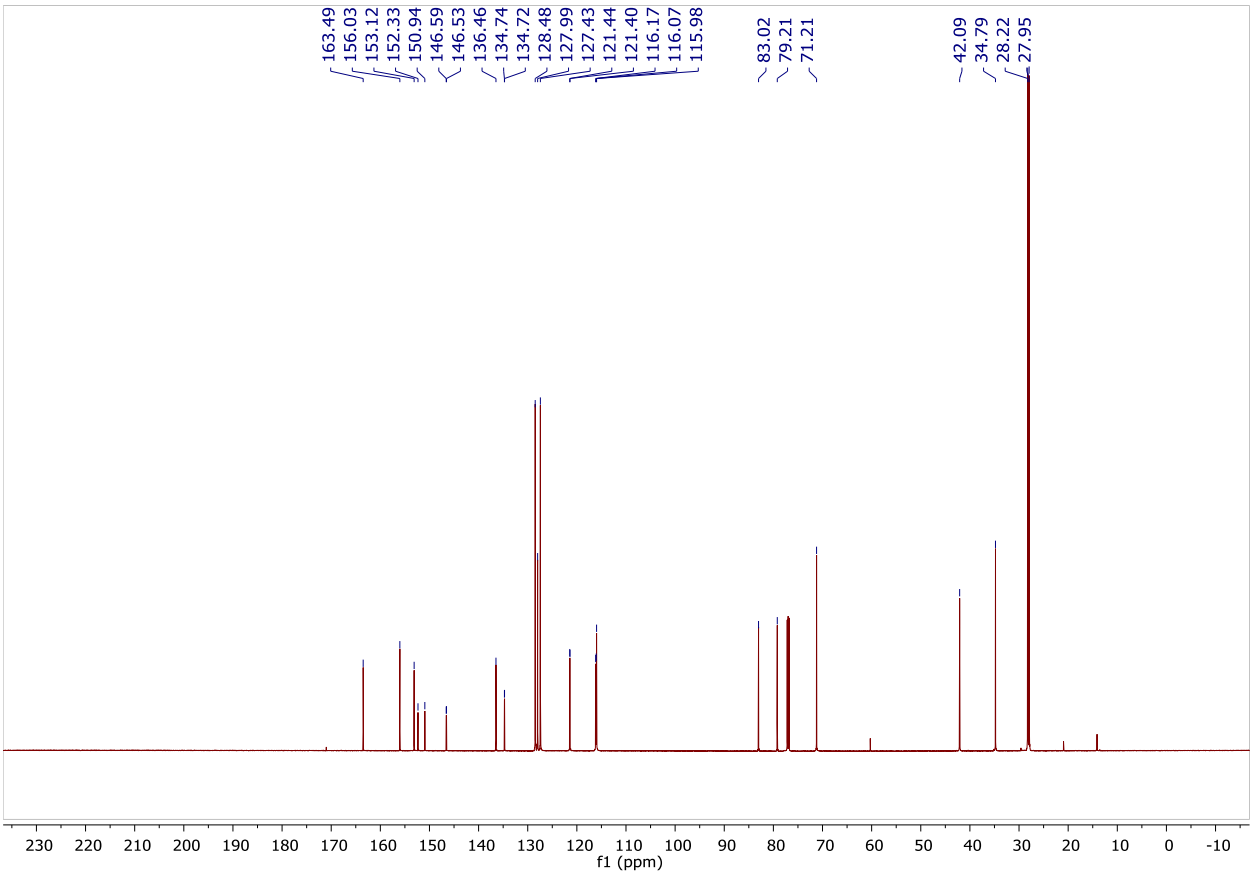

H
N
NHBoc
NBoc
F
OBn

S7-F

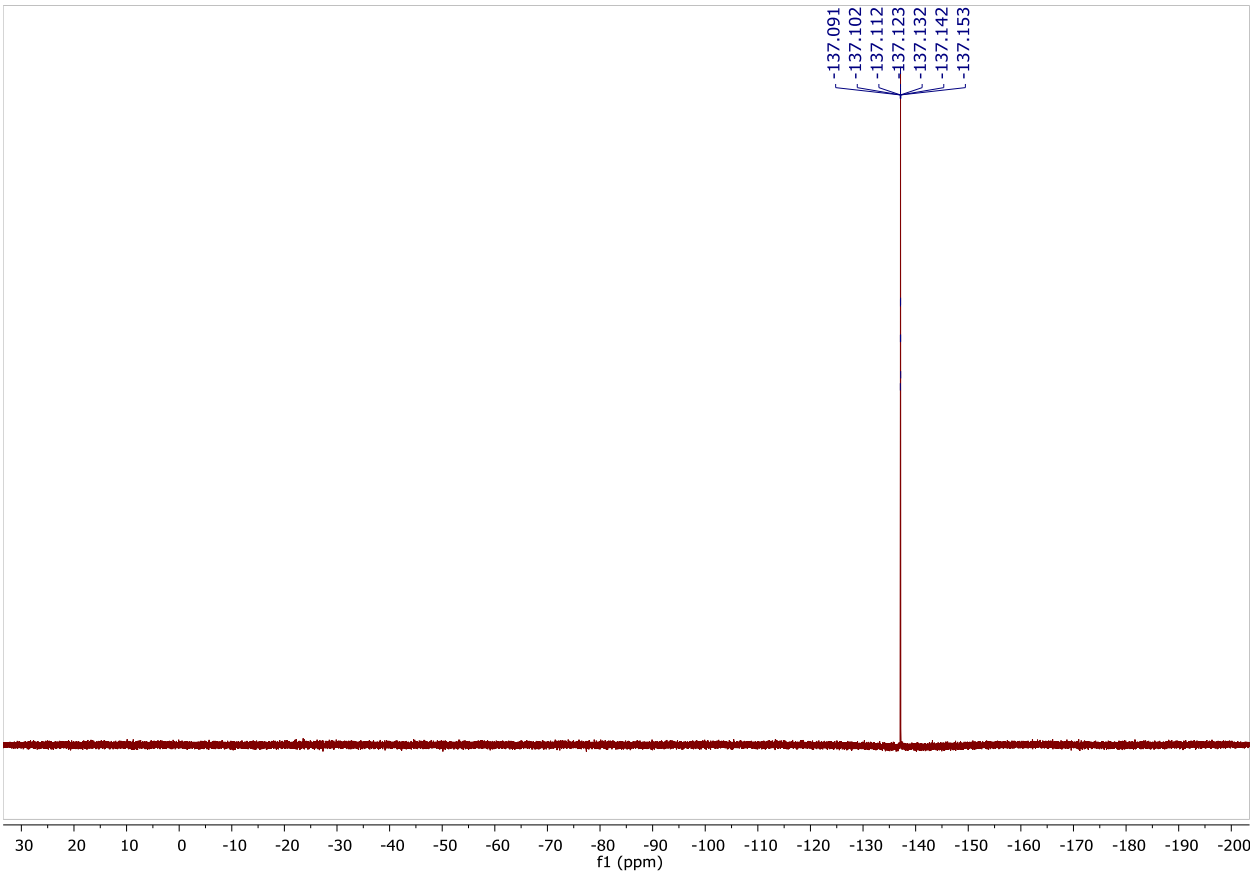
^{1}H NMR:

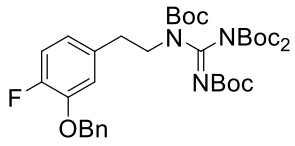

11.472
8.338
7.430
7.420
7.365
7.354
7.344
7.305
7.295
7.284
6.999
6.987
6.972
6.881
6.870
6.721
5.109
3.618
3.609
2.784
2.774
2.764
1.484
1.438
1.0
1.0
2.0
2.0
1.0
1.0
1.0
1.0
2.0
2.0
2.0
9.0
9.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


163.49
156.03
153.12
152.33
150.94
146.59
146.53
136.46
134.74
134.72
128.48
127.99
127.43
121.44
121.40
116.17
116.07
115.98
83.02
79.21
71.21
42.09
34.79
28.22
27.95
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

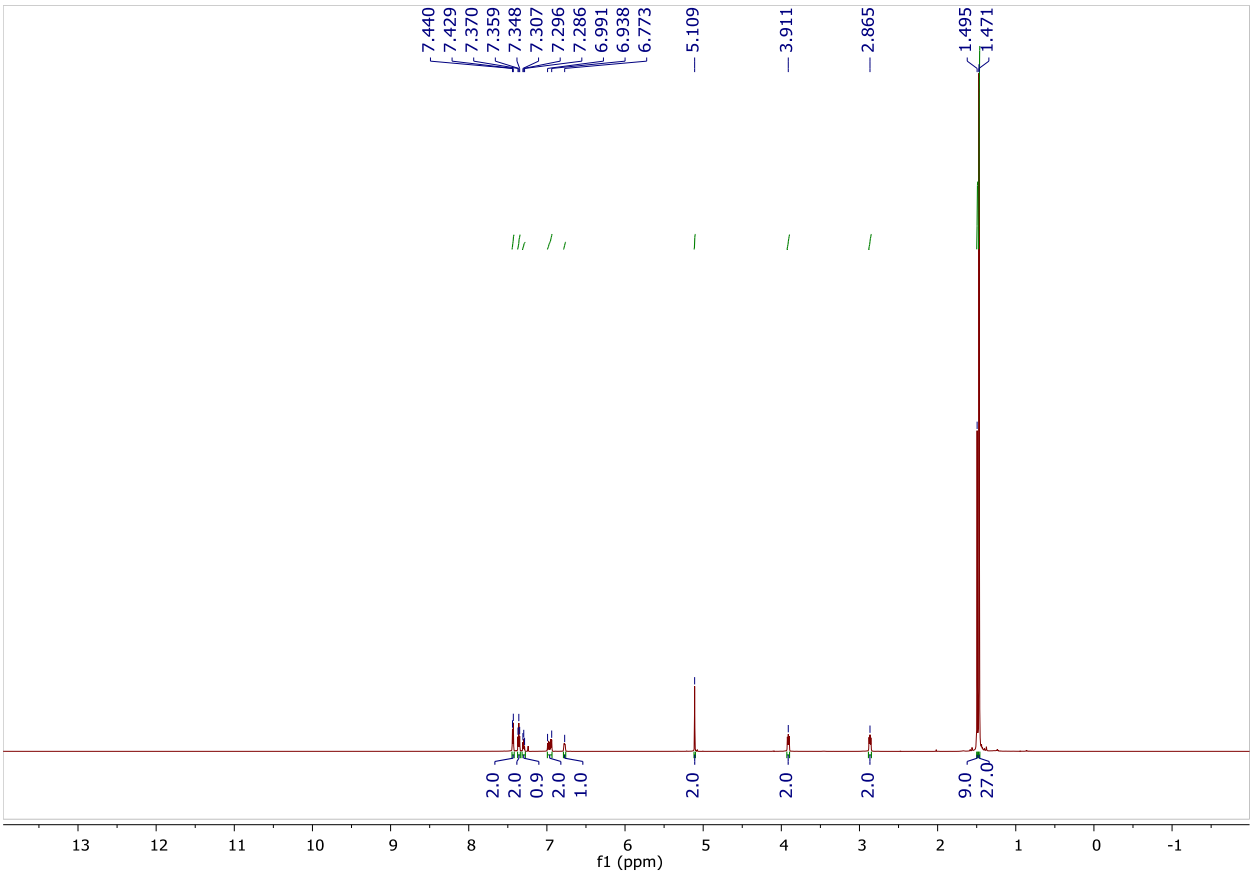
^{19}F NMR:


-137.091
-137.102
-137.112
-137.123
-137.132
-137.142
-137.153
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

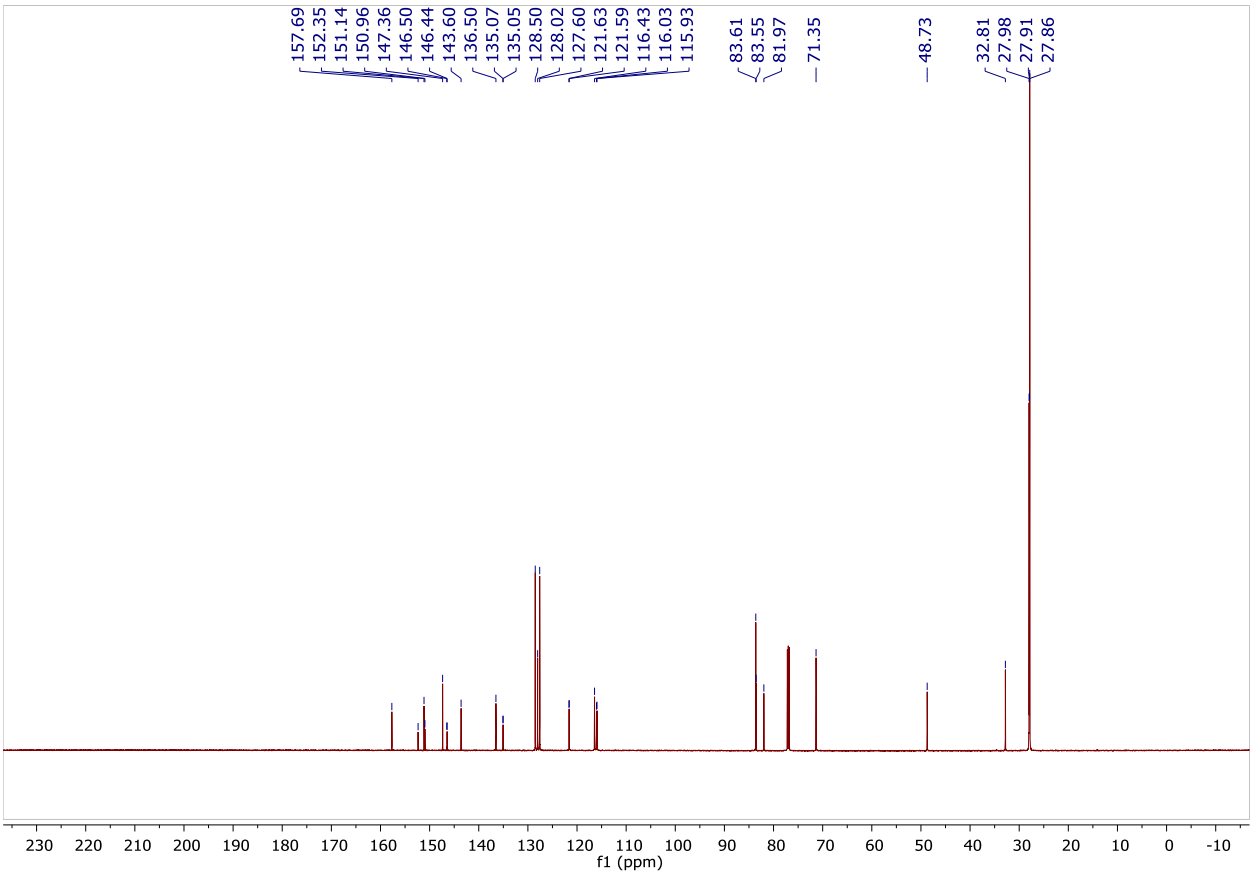

Boc
N
NBoc2
NBoc
F
OBn

S8-F

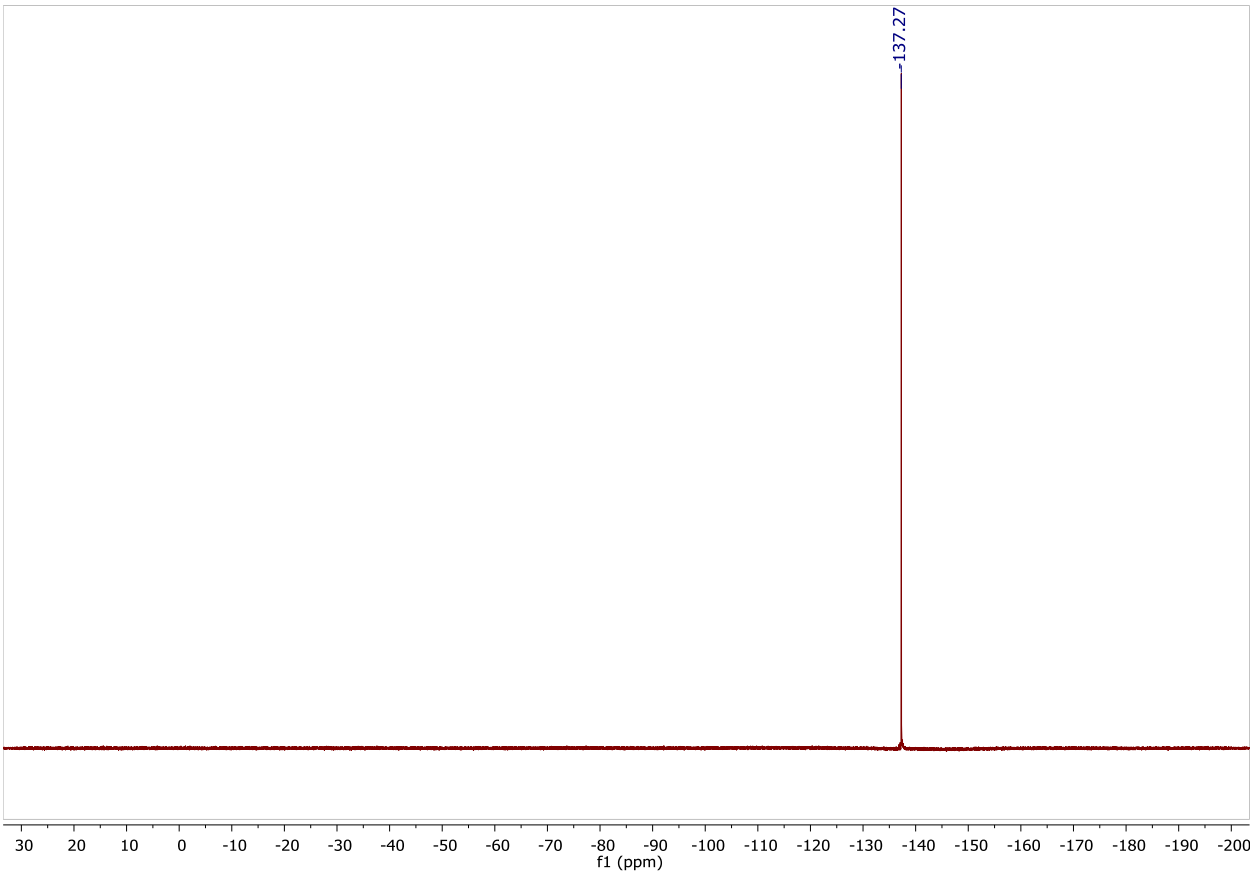
^{1}H NMR:


7.440
7.429
7.370
7.359
7.348
7.307
7.296
7.286
6.991
6.938
6.773
5.109
3.911
2.865
1.495
1.471
2.0
2.0
0.9
2.0
1.0
2.0
2.0
2.0
9.0
27.0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

^{13}C NMR:


157.69
152.35
151.14
150.96
147.36
146.50
146.44
143.60
136.50
135.07
135.05
128.50
128.02
127.60
121.63
121.59
116.43
116.03
115.93
83.61
83.55
81.97
71.35
48.73
32.81
27.98
27.91
27.86
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

^{19}F NMR:


-137.27
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

5.6. Radio-HPLC Data

5.6.1. General HPLC Conditions

To confirm the identity of the radiolabeled substrate, a HPLC co-injection of the crude reaction mixture with an aliquot of the authentic product was performed. The two HPLC traces show the RAD and UV trace (254 nm or 280 nm) from the crude reaction mixture spiked with an authentic standard of the product. The wavelength shown is the wavelength where the analyte compound exhibited greatest absorptivity. Because of the physical separation of the two detectors, the two traces are offset by 0.2 min.

HPLC Conditions A

Condition: 70% MeCN/H_2O, 10 mM NH_4OAc, pH 7

Flow Rate: 2 mL/min

Column: Luna C-18 Column 150 x 4.6 mm; 5 µm

HPLC Conditions B

Condition: 75% MeCN/H_2O, 10 mM NH_4OAc, pH 7

Flow Rate: 2 mL/min

Column: Luna C-18 Column 150 x 4.6 mm; 5 µm

HPLC Conditions C

Condition: 95% MeCN/H_2O, 10 mM NH_4OAc, pH 7

Flow Rate: 2 mL/min

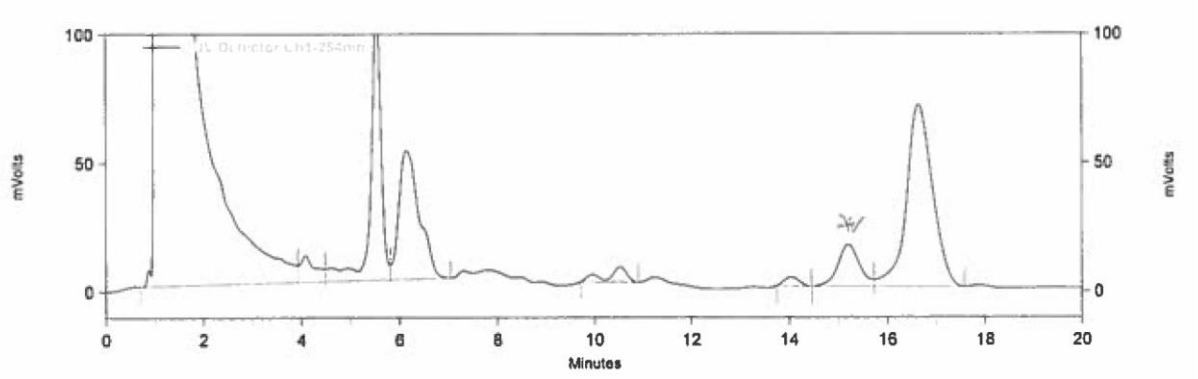
Column: Luna NH_2 Column 150 x 4.6 mm; 5 µm

5.6.2. Radio-HPLC Co-Injections with Authentic Standards

Table 5.4, entry 1

HPLC Conditions A

HPLC – UV



HPLC – Gamma

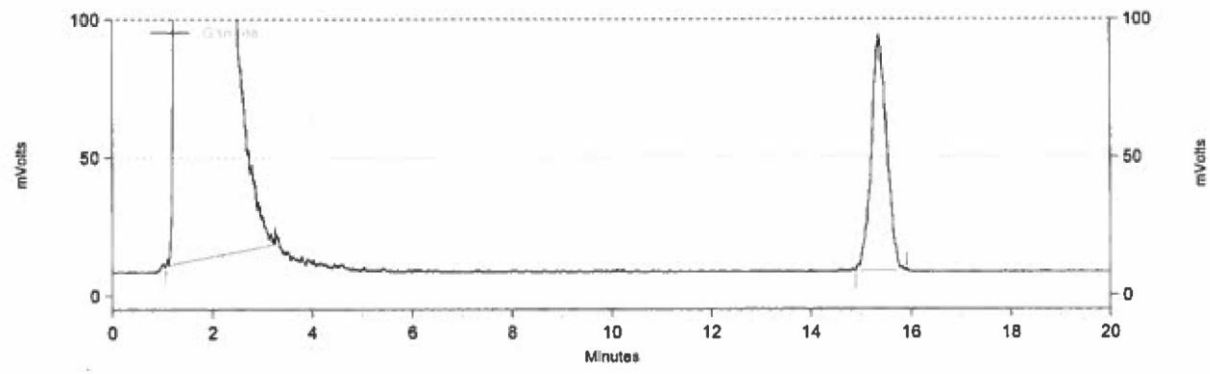
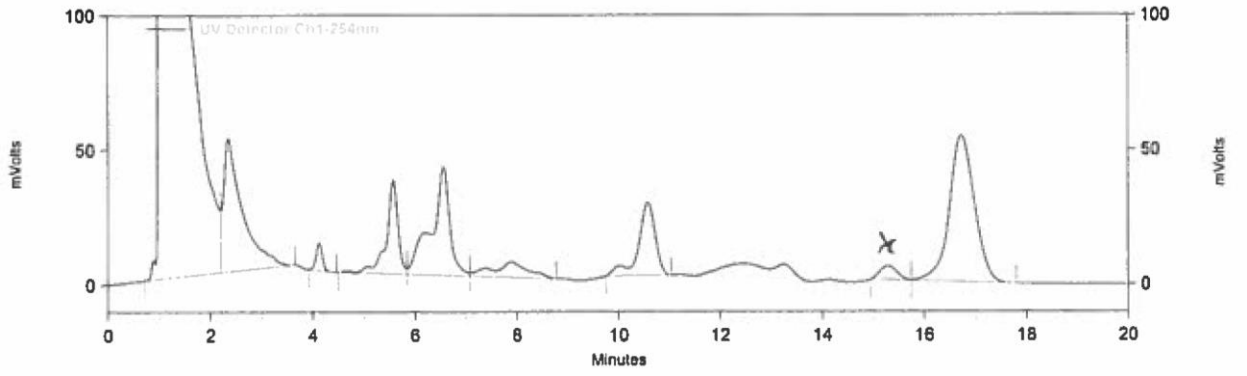


Table 5.4, entry 4

HPLC Conditions A

HPLC – UV



HPLC – Gamma

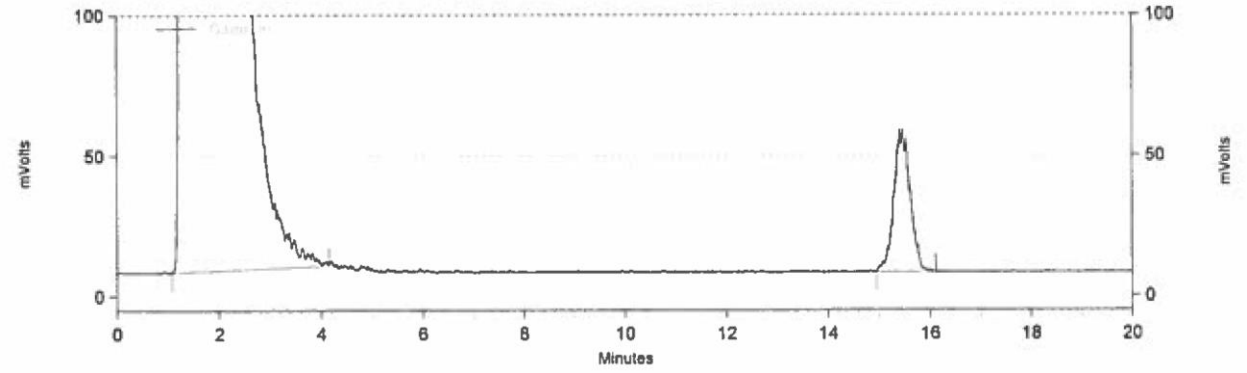
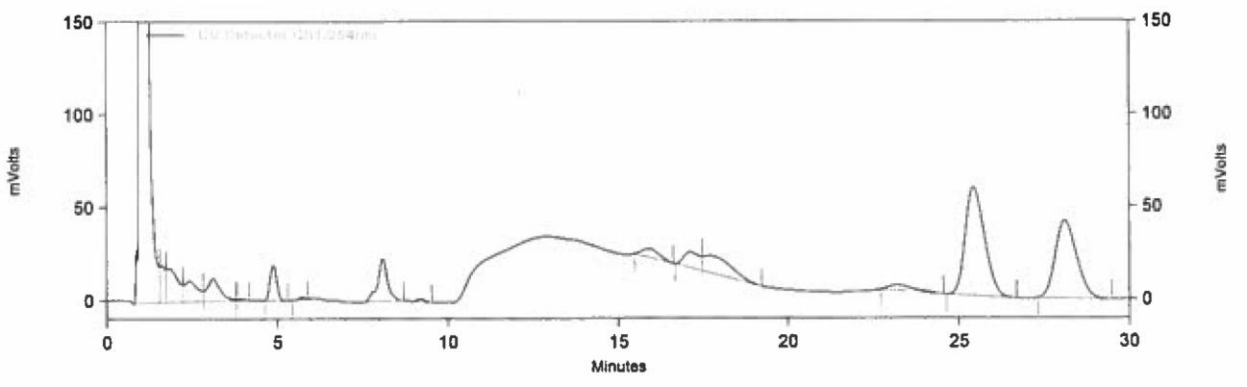


Table 5.5, entry 3

HPLC Conditions A

HPLC – UV



HPLC – Gamma

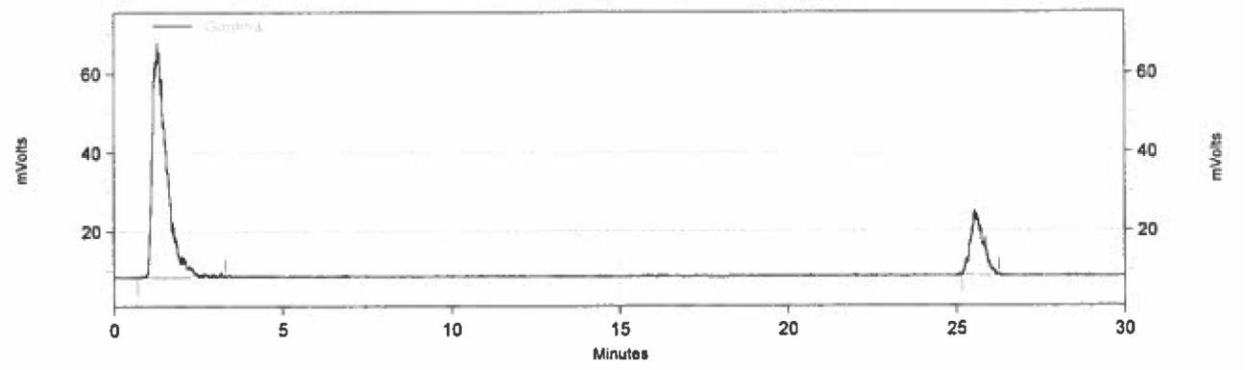
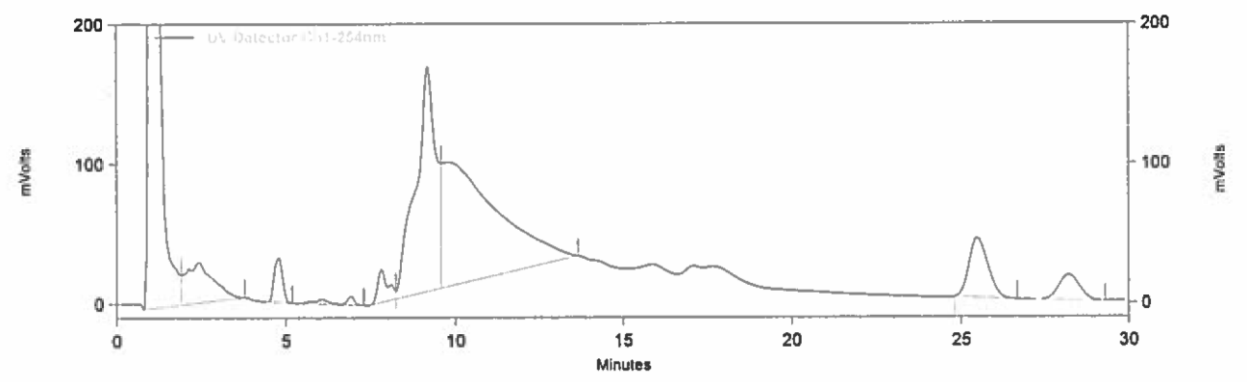


Table 5.5, entry 4

HPLC Conditions A

HPLC – UV



HPLC – Gamma

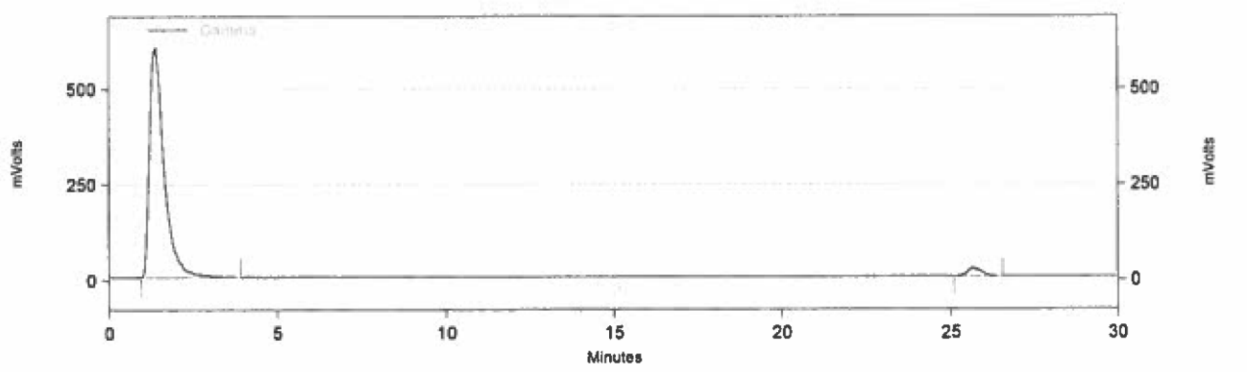
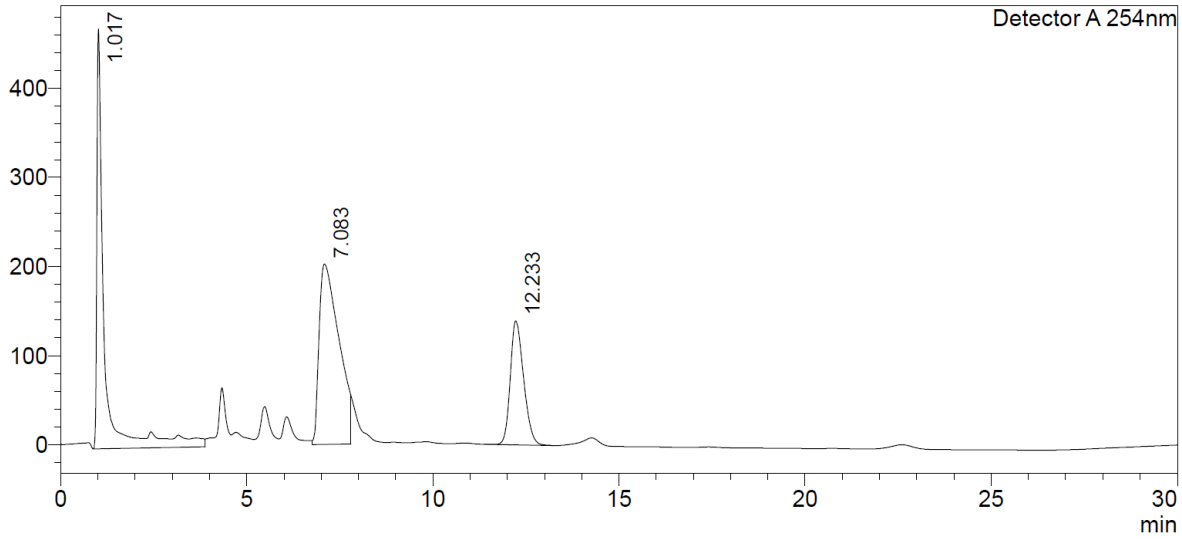


Table 5.6, entry 2

HPLC Conditions B

HPLC – UV



HPLC – Gamma

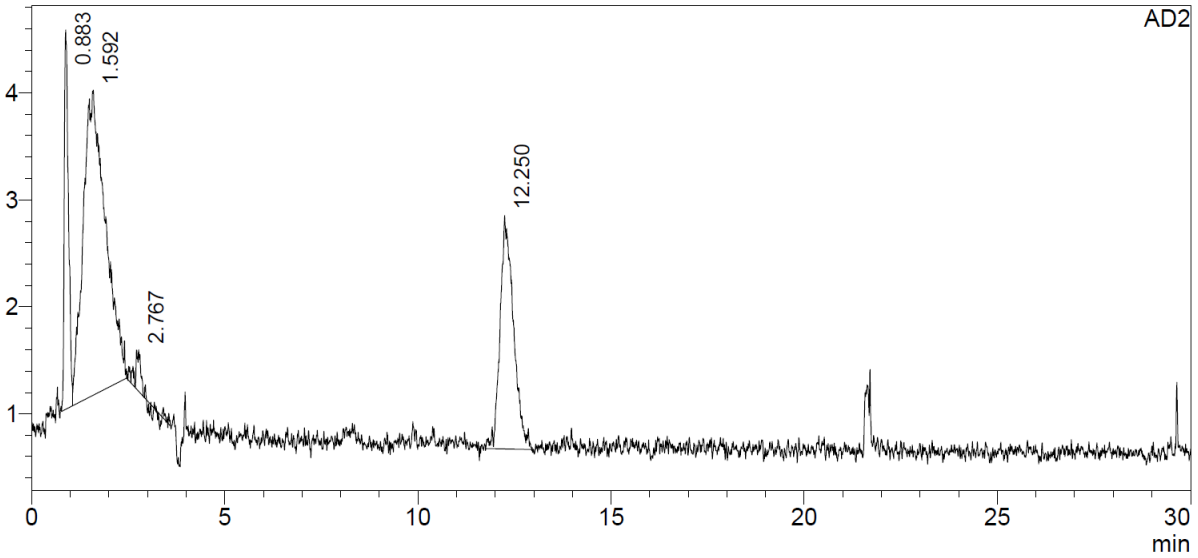
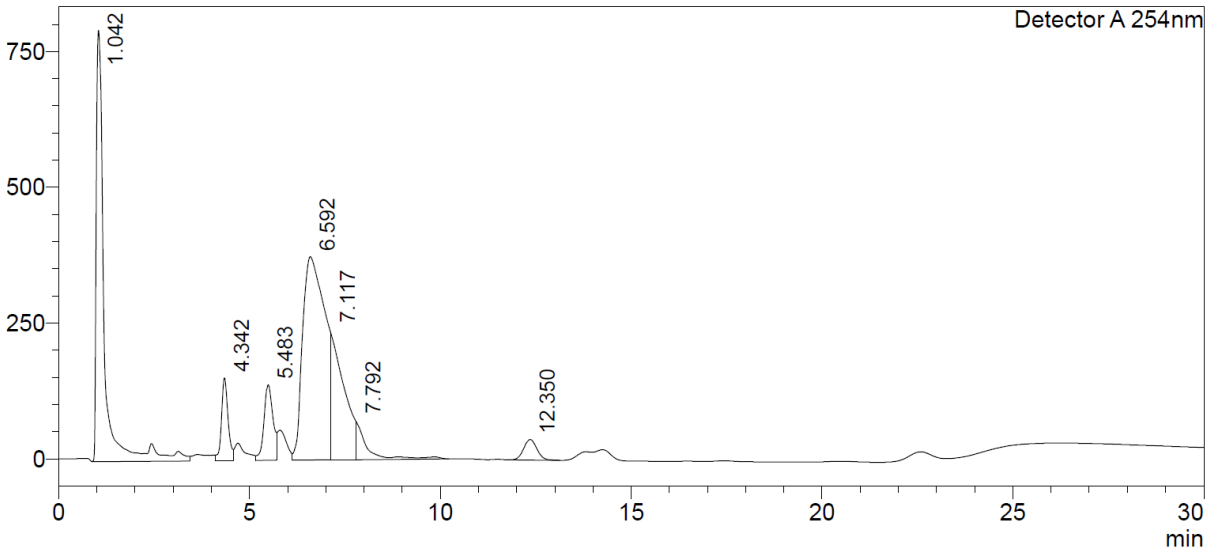


Table 5.6, entry 3

HPLC Conditions B

HPLC – UV



HPLC – Gamma

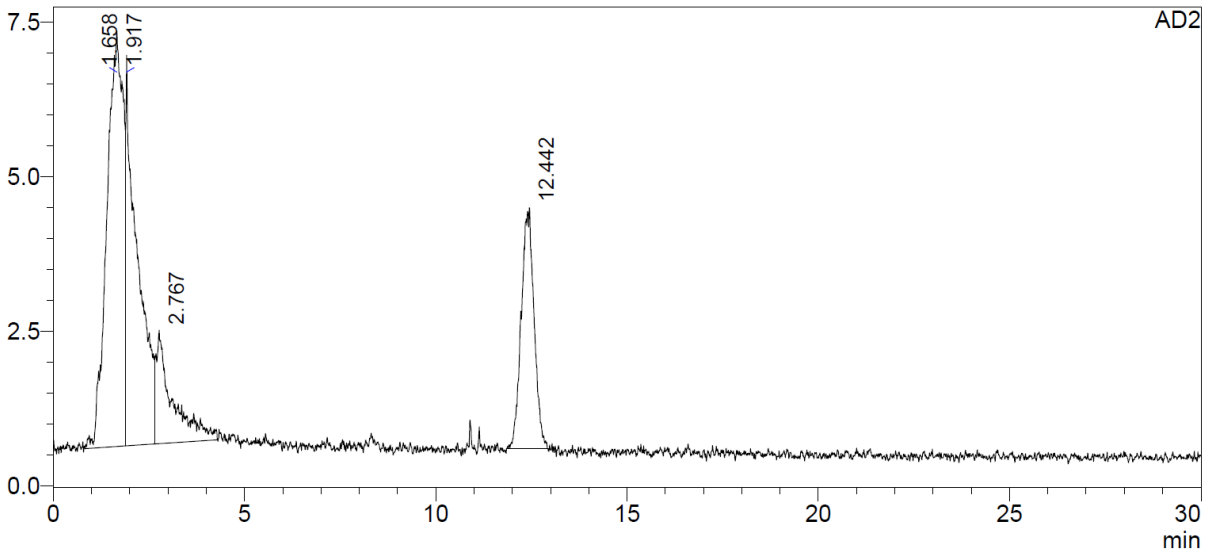
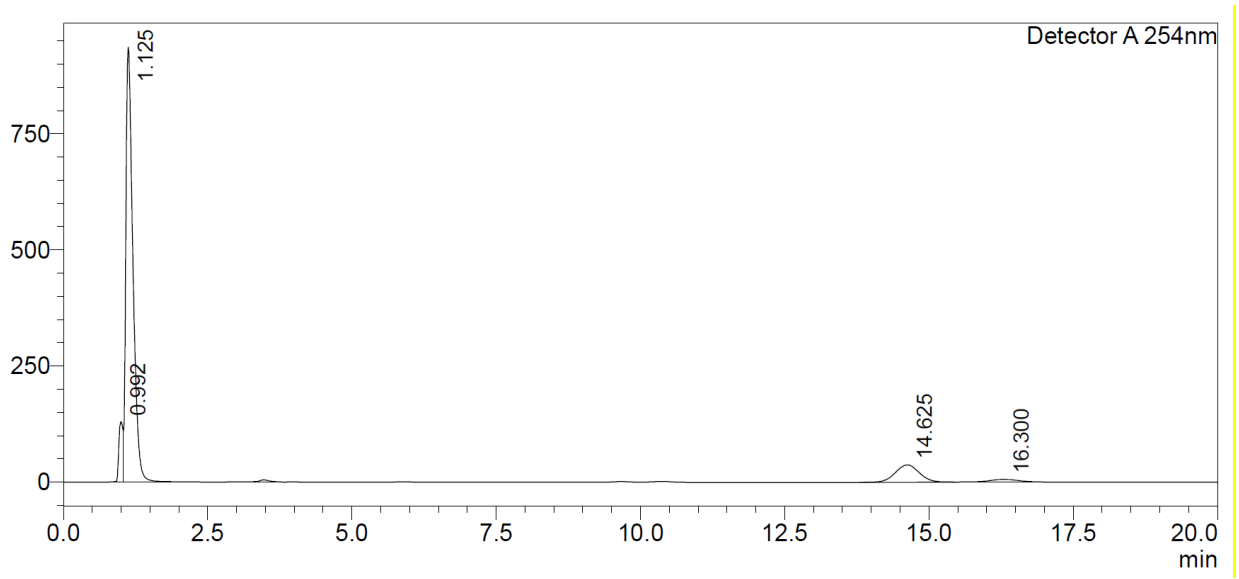


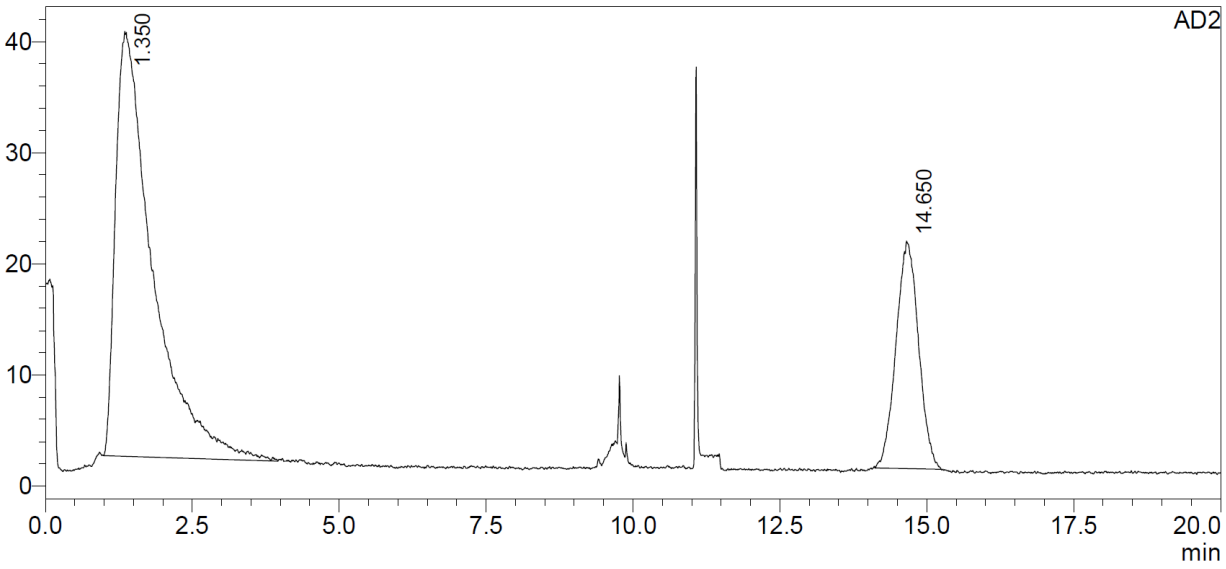
Table 5.7, entry 1

HPLC Conditions B

HPLC – UV



HPLC – Gamma

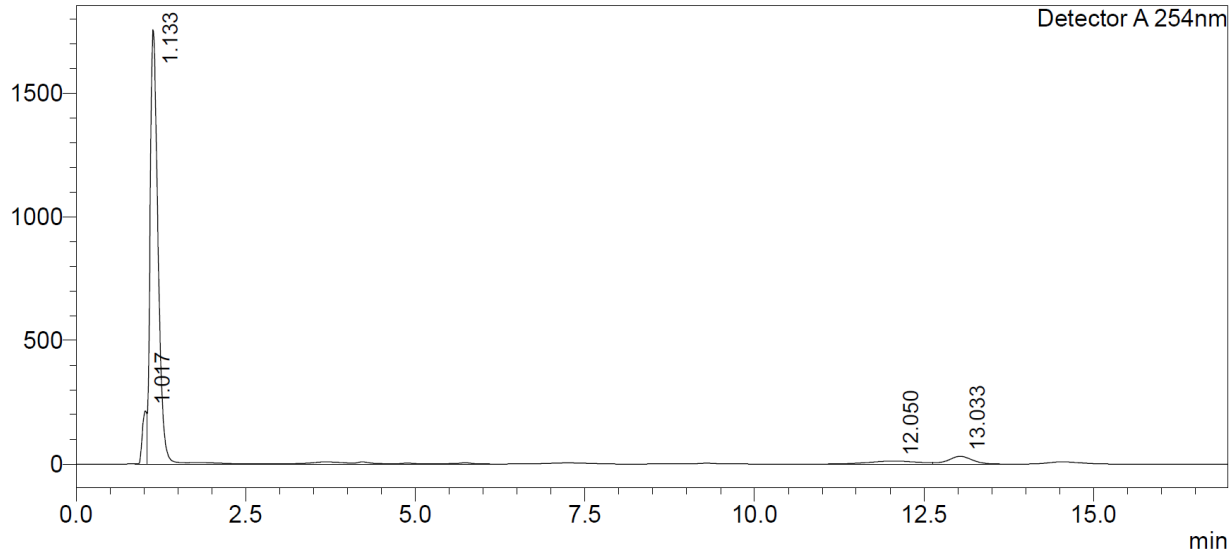


(peak at 10 and 11 min are background activity from production)

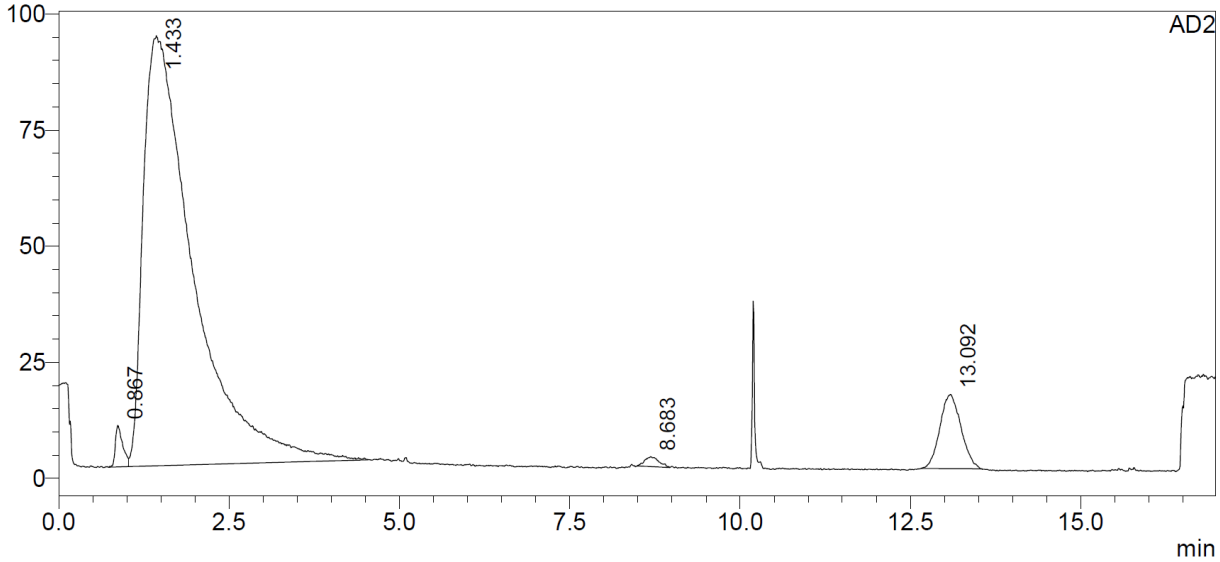
Table 5.7, entry 2

HPLC Conditions B

HPLC – UV



HPLC – Gamma



(peak at 10 min is background activity from production)

5.7. References

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