

11-2016

Thermolysis of Hypervalent Iodine Complexes: Synthesis of Fluorinated Radiotracers for Positron Emission Tomography and Synthesis of Quaternary α -Alkyl α -Aryl Amino Acids

Jayson J. Kempinger

University of Nebraska-Lincoln, jkempinger@huskers.unl.edu

Follow this and additional works at: <http://digitalcommons.unl.edu/chemistrydiss>

 Part of the [Organic Chemistry Commons](#)

Kempinger, Jayson J., "Thermolysis of Hypervalent Iodine Complexes: Synthesis of Fluorinated Radiotracers for Positron Emission Tomography and Synthesis of Quaternary α -Alkyl α -Aryl Amino Acids" (2016). *Student Research Projects, Dissertations, and Theses - Chemistry Department*. 76.

<http://digitalcommons.unl.edu/chemistrydiss/76>

This Article is brought to you for free and open access by the Chemistry, Department of at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Student Research Projects, Dissertations, and Theses - Chemistry Department by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.

THERMOLYSIS OF HYPERVALENT IODINE COMPLEXES: SYNTHESIS OF
FLUORINATED RADIOTRACERS FOR POSITRON EMISSION TOMOGRAPHY
AND SYNTHESIS OF QUATERNARY α -ALKYL α -ARYL AMINO ACIDS

by

Jayson J. Kempinger

A THESIS

Presented to the Faculty of
The Graduate College at the University of Nebraska
In Partial Fulfillment of Requirements
For the Degree of Master of Science

Major: Chemistry

Under the Supervision of Professor Stephen G. DiMagno

Lincoln, Nebraska

November, 2016

THERMOLYSIS OF HYPERVALENT IODINE COMPLEXES: SYNTHESIS OF
FLUORINATED RADIOTRACERS FOR POSITRON EMISSION TOMOGRAPHY
AND SYNTHESIS OF QUATERNARY α -ALKYL α -ARYL AMINO ACIDS

Jayson J. Kempinger, M.S.

University of Nebraska, 2016

Adviser: Stephen G. DiMagno

Hypervalent iodine complexes can be used to deliver a variety of functional groups to arenes. Delivery of fluorine-18, in a manner compatible with positron emission tomography (PET), is especially attractive. VizamylTM, an injectable solution of [¹⁸F]Flutemetamol, is currently used to diagnose and monitor the progression of Alzheimer's Disease (AD), the most common form of dementia. AD affects 47.5 million people across the world as of 2015, and is projected to affect 1 in 85 people by 2050. An improved radiosynthesis of [¹⁸F]Flutemetamol via a diaryliodonium salt is described. The use of nonpolar solvents minimizes disproportionation and other side reactions, leading to higher fluorination yields. The use of an electron-withdrawing protecting group allows functionalization of the highly electron-rich aniline ring. Upon initial testing, thermolysis of this salt provides radiochemical yields (RCY) of more than twice that of the best previously reported syntheses. Another class of heterocycles, 2-aryl-5-fluorobenzimidazoles, was also investigated. A variety of these suspected anti-tumor,

anti-microbial, and anti-inflammatory compounds were fluorinated for screening and additionally synthesized by thermolysis of diaryliodonium salts, suitable for radiosynthesis.

Hypervalent iodine complexes involving stabilized α -nitroester enolates were developed and studied. Thermolysis of these diaryliodonium salts leads to selective formation of α -alkyl α -aryl α -nitroesters, which can be reduced and hydrolyzed to form the analogous quaternary α -alkyl α -aryl amino acids. These unnatural quaternary amino acids have no enolizable proton, so racemization is not possible, and oxidation pathways that involve abstraction of the proton on the α -carbon are also prevented. This convergent, rapid synthesis provides access to a variety of unnatural quaternary amino acids that can be used for screening and studying biological pathways. Synthesis of an enantiopure cyclophanyl-substituted diaryliodonium salt was investigated as a potential method for stereoselectively generating these compounds.

ACKNOWLEDGMENTS

I would like to thank my adviser, Prof. Stephen DiMagno, for the opportunity to work in your lab and for sharing your wisdom with me. I would like to thank the members of my supervisory committee, Prof. Patrick Dussault, Prof. David Berkowitz, Prof. Barry Cheung, and Prof. Paul Blum for following my progress over the years. I would like to thank the late Prof. Thomas “Adrian” George; I will always appreciate the guidance you gave me and the patience you showed. I would also like to thank Dr. Joseph Dumais and Dr. Martha Morton; you have taught me so much and given me support and guidance over the years.

I would like to thank my current and former colleagues in the DiMagno group, Ethan Linstad, Jordan Veness, Dr. Bijia Wang, Dr. Linlin Qin, Daniel Moore, Mark Craddock, Dr. Haoran Sun, Dr. Bao Hu, SaraAnne Lovell, Dr. Kiel Neumann, Katelynn McCauley, and Joseph Graskemper; you have worked with me over the years with patience, support, and friendship. I would especially like to thank Dr. Shri Harsha Uppaluri, for being an exceptional mentor and friend. I would like to thank my other colleagues, Dr. Monica Kinde, Dr. John Persons, and especially Judy Schmitt and Sara Basiaga. You have been such amazing friends.

I would like to thank all of my friends in Wisconsin, Nebraska, and now Pennsylvania; you have given me support throughout my life. A simple thank you does not do justice to the appreciation I have for my family. You have stood by me throughout my life, giving me advice, support, and love. To my late grandparents, thank you for your wisdom and your compassion. To my parents, I cannot begin to describe the

selfless love you have shown me; I could not have made it where I am in life without you. To my wife, you have been my strength, giving me the support and love I need to get through the stressful times in life. With you by my side I know I can accomplish anything.

Most importantly, I would like to thank God. You have given me life; you have given me everything. I would not be the man I am today without your Holy Spirit guiding me.

TABLE OF CONTENTS

LIST OF FIGURES	viii
LIST OF SCHEMES	x
LIST OF TABLES	xiii
CHAPTER 1 IMPROVED METHODOLOGY FOR FLUORINATION OF ANILINES VIA HYPERVALENT IODINE COMPLEXES: APPLICATION TO THE SYNTHESIS OF [¹⁸ F]FLUTEMETAMOL	14
1.1 Introduction.....	14
1.2 Results and Discussion	31
1.3 Conclusion	46
1.4 References.....	48
1.5 Experimental.....	58
1.6 NMR Spectra	75
CHAPTER 2 SYNTHESIS OF A VARIETY OF QUATERNARY α -ALKYL α -ARYL AMINO ACIDS	96
2.1 Introduction.....	96
2.2 Results and Discussion	99
2.3 Conclusion	140
2.4 References.....	142
2.5 Experimental.....	150
2.6 NMR Spectra	197

CHAPTER 3 SYNTHESIS OF A VARIETY OF 2-ARYL-5- FLUOROBENZIMIDAZOLES.....	225
3.1 Introduction.....	225
3.2 Results and Discussion	228
3.3 Conclusion	252
3.4 References.....	254
3.5 Experimental.....	266
3.6 NMR Spectra	327

LIST OF FIGURES

Figure 1.1: Thioflavin T chemical structure and Thioflavin T Congo Red stain of β -amyloid plaques in brain tissue.....	16
Figure 1.2: Pittsburgh compound B, [<i>N</i> -methyl- ^{11}C]6-Me-BTA-1	16
Figure 1.3: Diagram of the annihilation event.....	18
Figure 1.4: A cyclotron (<i>left</i>) and an automated synthesis module (<i>right</i>).....	21
Figure 1.5: Diagram of unsymmetrical diaryliodonium salt thermolysis.....	28
Figure 1.6: Examples of $\text{A}\beta$ plaque PET imaging agents.....	29
Figure 1.7: Diagram of the aryl swapping process	40
Figure 1.8: Radio-TLC of run 4 (<i>left</i>); HPLC trace of ^{19}F standard (<i>top right</i>); HPLC trace of run 4 (<i>bottom right</i>)	44
Figure 2.1: Resonance of the enolate, 3	100
Figure 2.2: 3D orbital map of malonic acid HOMO (B3LYP/6-311G)	101
Figure 2.3: List of diaryliodonium salts used	107
Figure 2.4: Amino acids at varying pH.....	114
Figure 2.5: Thermolysis of a cyclophane-containing diaryliodonium salt	116
Figure 2.6: Cyclophane phenyl iodonium salt enantiomers.....	117
Figure 2.7: Racemic aryl-cylophanyl iodonium salts synthesized.....	123
Figure 2.8: Synthesis of enantiopure iodonium salt, 43	128
Figure 2.9: Initial structures used for ground state geometry optimizations	131
Figure 2.10: Initial ground state energy calculations.....	132

Figure 2.11: Example structure generated from higher level calculation.....	133
Figure 2.12: Chiral HPLC separations of ethyl 2-nitro-2-phenylpropionate (13) (<i>top</i> : Chirex 3126; <i>bottom</i> : Lux Cellulose-1).....	135
Figure 3.1: Numbering convention for benzimidazole (<i>left</i>) and some 2-arylbenzimidazoles used as biological agents (<i>right</i>).....	223
Figure 3.2: Some current PET radiotracers used for imaging β -amyloid plaques.....	224
Figure 3.3: Acid chlorides used	229
Figure 3.4: Proposed mechanism of ring closure.....	231
Figure 3.5: Proposed mechanism of tautomerization	232
Figure 3.6: Methods for synthesizing diaryliodonium salts.....	233
Figure 3.7: Diaryliodonium triflates (16) analyzed	244
Figure 3.8: Two regiochemical pathways for thermolysis of diaryliodonium salts	246
Figure 3.9: Meisenheimer-like transition state	247

LIST OF SCHEMES

Scheme 1.1: Process to capture $^{18}\text{F}^-$	24
Scheme 1.2: Generation of aryl fluoride from Nickel complex.....	25
Scheme 1.3: Synthesis of 1-bromo- ^{18}F fluorobenzene.....	27
Scheme 1.4: Initial patented synthesis of ^{18}F Flutemetamol.....	30
Scheme 1.5: Improved synthesis of Flutemetamol.....	31
Scheme 1.6: Initial retrosynthesis of ^{19}F Flutemetamol.....	32
Scheme 1.7: Final synthesis of ^{19}F Flutemetamol.....	33
Scheme 1.8: Kumada coupling (R=Me, EtOCH ₂ ; X=I, H; PG=OAc, Boc).....	34
Scheme 1.9: Addition of butyllithium (R=Me, EtOCH ₂ ; R'=n-Bu, s-Bu, t-Bu)	34
Scheme 1.10: Sonogoshira-style coupling used.....	35
Scheme 1.11: Coupling with 4-bromo-N-methylaniline.....	36
Scheme 1.12: Iodination under basic conditions	37
Scheme 1.13: Magnesium-halogen exchange reaction.....	38
Scheme 1.14: Thermolysis reaction.....	39
Scheme 1.15: Synthesis of ^{19}F HPLC standards.....	42
Scheme 1.16: Initial synthesis of 6-ethoxymethoxybenzothiazole (21).....	46
Scheme 2.1: Synthesis of aryl nitro esters and their reduction/hydrolysis	97
Scheme 2.2: Synthesis of dimethyl methylmalonate	100
Scheme 2.3: Synthesis of dimethyl 2-(4-methoxyphenyl)-2-methylmalonate (4).....	102
Scheme 2.4: Synthesis of α -nitroesters	103

Scheme 2.5: Formation of nitrobenzene	104
Scheme 2.6: Synthesis of bis(4-methoxyphenyl)iodonium triflate (1).....	105
Scheme 2.7: Synthesis of racemic diaryliodonium salts (R=H, OMe).....	118
Scheme 2.8: Attempts to form cyclophane salt	120
Scheme 2.9: Synthesis of aldehyde 38	125
Scheme 2.10: Synthesis of enantiopure <i>N,N,N</i> -trimethyl-1-phenylethylammonium hexafluorophosphate salts (45 and 46)	137
Scheme 2.11: Synthesis of <i>tert</i> -butyl 2-nitropropionate (48)	138
Scheme 3.1: Retrosynthesis of 2-aryl-5-fluorobenzimidazoles	227
Scheme 3.2: General forward synthesis of 2-aryl-5-fluorobenzimidazoles.....	227
Scheme 3.3: Milder nitration conditions.....	228
Scheme 3.4: Formation of <i>N</i> -cyclohexyl-4-fluoro-2-aminoaniline (6m).....	230
Scheme 3.5: Formation of <i>N</i> -phenyl-4-fluoro-2-aminoaniline (6a).....	231
Scheme 3.6: General forward synthesis of 2-aryl-5-bromobenzimidazoles.....	234
Scheme 3.7: Formation of 2-(4-nitrophenyl)-5-bromobenzimidazole (13m).....	237
Scheme 3.8: Boc protection of 13	238
Scheme 3.9: Stannylation of 14	239
Scheme 3.10: Synthesis of diaryliodonium salts 16	240
Scheme 3.11: Miyaura borylation example	241
Scheme 3.12: Boc protection of 2-phenylbenzimidazole	242
Scheme 3.13: Direct iodoarylation of 17	242
Scheme 3.14: Initial steps toward synthesis of 2-aryl-5-iodobenzimidazoles.....	243

Scheme 3.15: Potential route to regioselectively generate compounds 22	249
---	-----

LIST OF TABLES

Table 1.1 Nuclear properties of commonly used positron (β^+) emitters for PET	19
Table 1.2 Radiochemical thermolyses of 16	43
Table 2.1 Phase transfer catalysts added.....	108
Table 2.2 Formation of arylnitroesters.....	110
Table 2.3 Reduction and hydrolysis of arylnitroesters	115

CHAPTER 1

IMPROVED METHODOLOGY FOR FLUORINATION OF ANILINES VIA HYPERVALENT IODINE COMPLEXES: APPLICATION TO THE SYNTHESIS OF [¹⁸F]FLUTEMETAMOL

1.1 Introduction

1.1.1 Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, accounting for 50 to 80 percent of dementia cases.¹ The disease typically presents in elderly individuals. It affects more than 4 million people in the United States alone, presenting in 1% of people aged in their 60s and increasing to nearly 30% of people aged up to 85 years old. As of 2015, 47.5 million people across the world were afflicted with AD. Brookmeyer *et al.*, predicted that by the year 2050 Alzheimer's disease will affect 1 in 85 people.² The disease affects memory, cognitive skills, and behavior. As a degenerative disease, mental function continues to degrade over time, eventually ending in death. There are currently no known treatments to stop or reverse the progression of the disease; however, some treatments may temporarily alleviate symptoms. Some treatments, such as acetylcholinesterase inhibitors and *N*-methyl D-aspartate receptor antagonists are effective for only slightly more than half of the patients taking these drugs, and do not cure AD, but may modestly slow progression of the disease.³ Good methods to diagnose and monitor AD are necessary to treat the disease early (slowing progression before

symptoms appear), and also to further study Alzheimer's disease in order to develop better treatments.

In 1959, Vassar and Culling introduced a cationic benzothiazole dye, thioflavin T (ThT),⁴ which was found to show enhanced fluorescence upon binding to amyloid protein in tissue sections (Figure 1.1). Brain matter from AD afflicted patients could be stained postmortem with ThT to confirm the AD diagnosis, based on dementia symptoms. By 1984, a guideline was established to diagnose patients with dementia from AD. The guideline proposed that the disease pathology and clinical symptoms were synonymous; *i.e.* the patient either fully exhibited AD pathology, was demented, and therefore had developed Alzheimer's disease, or they were completely free from Alzheimer's disease pathology (and were either not demented, or their dementia was caused by other forms of cognitive impairment). Only postmortem could the diagnosis be confirmed by brain tissue staining.

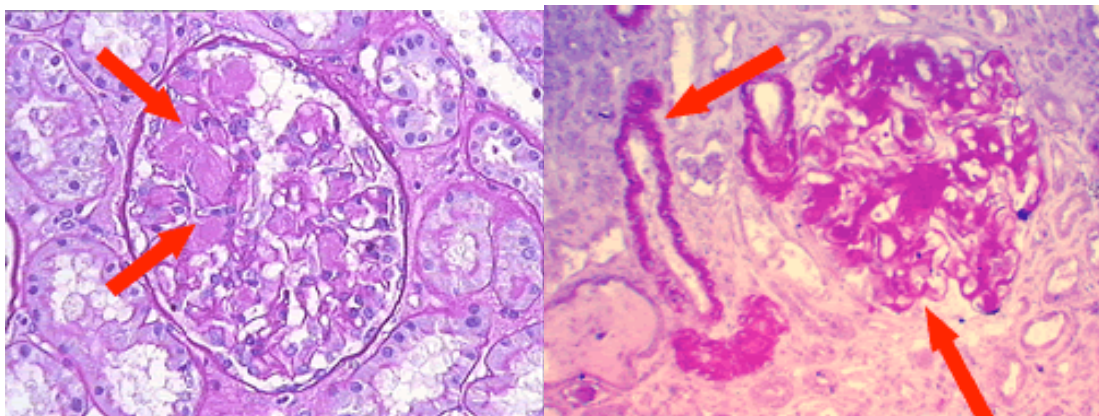
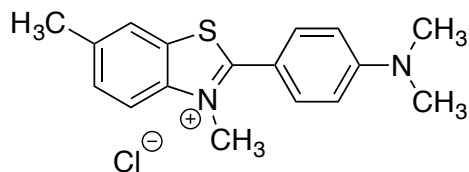


Figure 1.1: Thioflavin T chemical structure and Thioflavin T Congo Red stain of β -amyloid plaques in brain tissue.⁵

In 2001, researchers at the University of Pittsburgh developed a carbon-11 radiolabeled version of ThT, [*N*-methyl-¹¹C]6-Me-BTA-1 (Figure 1.2), that later became known as the Pittsburgh compound B (PiB).⁶ Using positron emission tomography (PET), images of β -amyloid plaques in a patient's brain, before death, are able to be acquired (PET will be discussed further in section 1.1.2 below).

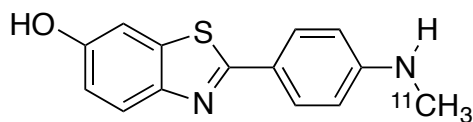


Figure 1.2: Pittsburgh compound B, [*N*-methyl-¹¹C]6-Me-BTA-1

Studies began to test the effectiveness of the recently developed PiB compound as a diagnostic agent, both for cognitive impairment (potentially due to diseases such as AD)

and traumatic brain injury.^{7,8} It was found that generally 30% to 35% of healthy people in their 70s and 80s, exhibiting no cognitive impairment, tested positive in PiB scans. In 2004, a collaborative initiative, the Alzheimer's Disease Neuroimaging Initiative (ADNI), began to seek out new methods to diagnose and monitor AD. More than 800 volunteers underwent testing every 6 to 12 months. Cerebrospinal fluid (CSF) testing, magnetic resonance imaging (MRI), and positron emission tomography (PET) were performed. After five years, some patients who showed no cognitive impairment developed mild cognitive impairment (MCI), some patients who presented with MCI progressed fully to dementia. Nearly 60% of patients who tested positive in PiB scans and had MCI advanced to Alzheimer's disease within a year or two. The results from the ADNI initiative prompted the development of a new set of guidelines for diagnosis of AD.⁹ These guidelines emphasize the importance of the new biomarkers discovered by the ADNI, most notably low CSF levels of the A β ₄₂ protein and elevated CSF tau protein levels, and PET imaging data. This underscores the importance of further research into PET imaging for AD.

1.1.2 Positron Emission Tomography

Positron emission tomography is a non-invasive imaging technique that provides a three-dimensional image of functional processes in biological systems.¹⁰ PET has proven exceptionally useful for early detection and monitoring of disease (a non-invasive clinical diagnosis), for medical research to aid in understanding physiological processes and metabolic pathways, and for drug development and discovery. A PET scan utilizes a

molecule labeled with a positron (β^+) emitting radionuclide, *i.e.* a radiotracer or radiopharmaceutical. The radiotracer is administered to the patient and the metabolite localizes in the body. As the radionuclide decays it ejects a positron, which collides with a nearby electron (Figure 1.3).

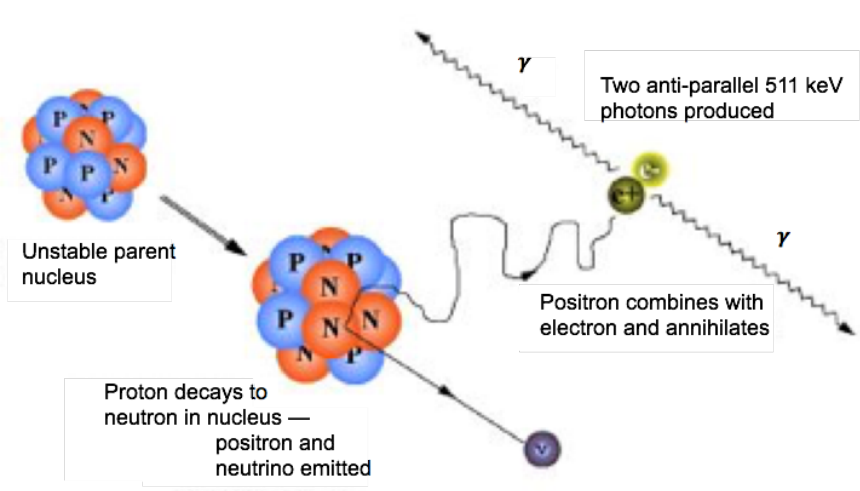


Figure 1.3: Diagram of the annihilation event¹¹

This annihilation event generates two coincident 511 keV γ -rays (corresponding to the masses of the positron and electron). A scintillation detector array monitors these photons, and the detected signals are processed to extrapolate the source of each annihilation event. The distance traveled by the positron before it collides with an electron depends on the kinetic energy (KE) of the ejected positron. Lower KE emitters provide higher resolution images (as they travel less before colliding with an electron). The spatial resolution of a PET scan can show detail as precise as 2–3 mm, depending on the radionuclide used. A PET scan is often acquired along with an X-ray computed tomography scan (X-ray CT, CAT, or simply CT scan) to give anatomical information as

well. An X-ray CT scan acquires a large number of X-ray images, taken from various angles, and computationally combines these images to produce cross-sectional slices. These slices can be used to generate a three-dimensional image of the inside of the region being scanned.

1.1.3 Fluorine-18 as a Radionuclide

Isotope	Half Life	Decay Mode	Avg. Positron KE E_{β^+} avg [keV]	Avg. (Max.) Range in Tissue [mm]
^{11}C	20.39 min	β^+ (99.8%) EC (0.24%)	385	1 (3.8)
^{13}N	9.965 min	β^+ (99.8%) EC (0.2%)	491	1.5 (5)
^{15}O	122.24 s	β^+ (99.9%) EC (0.01%)	735	2.7 (7.6)
^{18}F	109.77 min	β^+ (96.73%) EC (3.3%)	242	0.3 (2.2)
^{124}I	4.18 d	β^+ (22.8%) EC (77.2%)	830	3.3 (9.7)

Table 1.1: Nuclear properties of commonly used positron (β^+) emitters for PET¹²

Table 1.1 lists some commonly used positron emitting radionuclides for PET. Of these radionuclides, [^{18}F], fluorine-18, has the optimal physical properties for certain PET

applications. First, its half-life, about 2 hours, is convenient for relatively complex radiotracer synthesis. It is short enough to collect kinetic data in a reasonable time period, provided the unbound radiopharmaceutical is metabolized quickly, and radioactivity in the patient is short-lived, allowing the PET scan to be an outpatient procedure. Its half-life is long enough to synthesize the radiotracer at a lab with an on-site cyclotron and transport it to nearby satellite PET centers (that lack a full radiochemical lab and cyclotron). Second, the low positron KE of fluorine-18 ensures a short range in tissue; the annihilation event occurs fairly close to the site of radiotracer decay, providing a high resolution PET scan. Third, the decay of fluorine-18 yields innocuous ^{18}O as the product atom. Finally, the nuclear reaction for formation of fluorine-18 from oxygen-18, $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ on ^{18}O -enriched water (H_2^{18}O), can yield several Curie (Ci) amounts of fluorine-18 from a single cyclotron run. As only 5–15 mCi of radiotracer need to be injected for a single human dose, this allows for many PET scans from a single cyclotron run.

Along with the benefits of using fluorine-18 as a radionuclide, fluorine substitution in drugs often leads to improved pharmacological profiles.^{13,14} Despite the relatively high abundance of fluorine in the earth's crust, organofluorine compounds are rare in nature.^{15,16} However, approximately one third of prescribed pharmaceuticals contain a fluorine atom. The high electronegativity and small atomic radius of the fluorine atom, along with the short C–F bond length, cause relatively small structural perturbations compared to other functional group substitutions, but drastically alter the electronic properties, and often improve the bioavailability of the compound.^{17,18}

Fluorine can act as a bioisostere for a variety of functional groups, such as C–H, C=O, and C–OH — pharmaceuticals where these groups have been replaced with fluorine exhibit similar biological properties to the original pharmaceutical. These features make fluorine-18 an attractive radionuclide to use for PET radiotracers; however, introduction of fluoride onto a target drug can be difficult.

1.1.4 Introduction of Fluoride-18 on a Target Molecule

There are several methods for introducing fluoride-18 onto a target molecule. Fluoride-18 is generated in a cyclotron and incorporated into a radiotracer via chemical reaction(s) performed in a lead-shielded, and typically automated system.

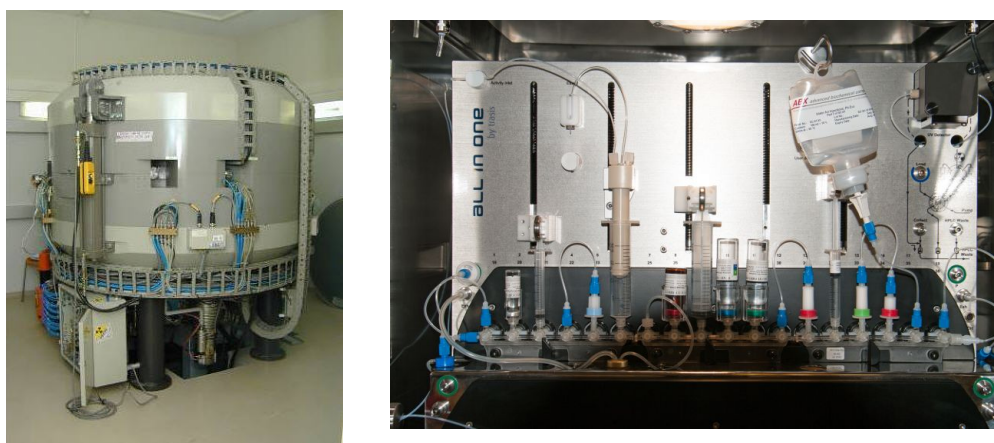


Figure 1.4: A cyclotron (*left*)¹⁹ and an automated synthesis module (*right*)²⁰

A fundamental challenge of introducing fluoride into a target molecule is the difficulty of forming C–F bonds. Fluorine is the most oxidizing and most electronegative element. The fluoride anion, because of its small ionic radius (1.33 Å) and high electronegativity, tends to form strong hydrogen bonds with most hydrogen bond donors (*e.g.* water,

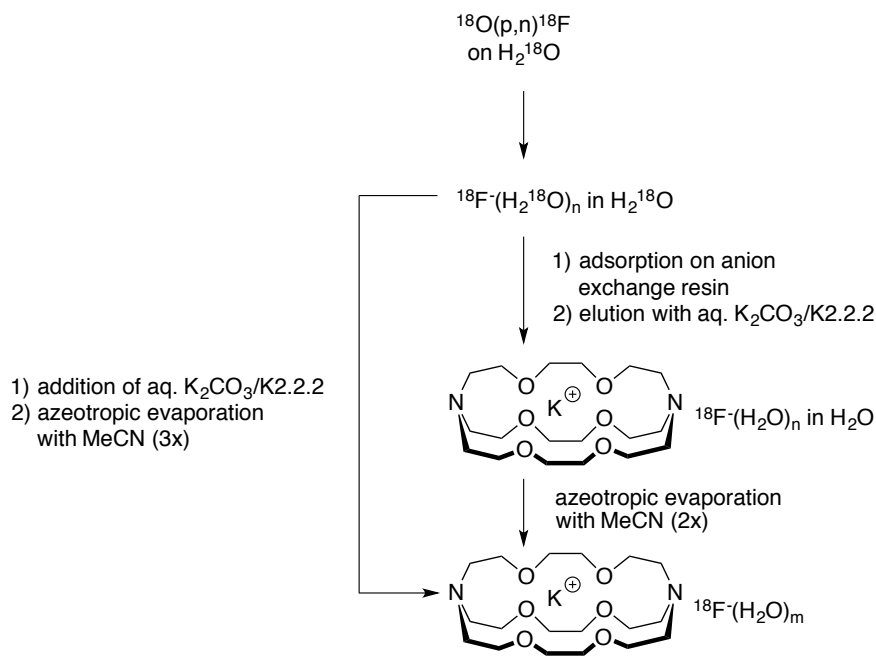
alcohols, amines), which makes reactions with fluoride difficult to control. Fluoride, in the absence of hydrogen bonding, is a potent nucleophile and a strong base, but is rather unreactive when hydrogen bonds are present. A variety of methods have been developed to introduce fluoride-18 onto a target molecule: (a) electrophilic methods (*i.e.* [^{18}F] F_2), (b) nucleophilic methods (*i.e.* [^{18}F] F^-), (c) metal-mediated methods, and (d) thermolysis of hypervalent iodine complexes, typically diaryliodonium triflates or diaryliodonium hexafluorophosphates.

Electrophilic methods, based upon F_2 , tend to be harsh and not selective, so the [^{18}F] F_2 that is generated is often converted into more selective, less reactive ^{18}F -labeled fluorination agents, such as *N*-substituted DABCO derivatives (*e.g.* Selectfluor[®]), *N*-fluorosulfonimides (*e.g.* NFSI), *N*-fluoropyridiniums, acetyl hypofluorite (AcO^{18}F), xenon difluoride (Xe^{18}F_2), and others. The largest drawback to electrophilic methods is that the maximum theoretical radiochemical yield (RCY) can only be 50%.¹⁰ This is because the fluorine-18 produced by the cyclotron must be captured with fluorine-19 gas, forming ^{18}F - ^{19}F , giving rise to a mixture of ^{18}F and ^{19}F being added to the target molecule. In addition, an excess of $^{19}\text{F}_2$ must be added to recover the [^{18}F] F_2 from the reactor/vessel walls, giving low specific activity (the amount of radioactivity per unit mass of radiotracer). Electrophilic labeling routes are only useful where high specific radioactivity tracers are not necessary.

Radiotracers can be generated by nucleophilic methods without adding fluoride-19 in the form of [^{19}F] F_2 . These methods are referred to as “no carrier added” (nca) and offer higher specific activity ($4 \times 10^4 \text{ GBq } \mu\text{mol}^{-1}$) than radiotracers generated

through carrier-added methods.¹⁰ High specific activity is necessary for radiotracers targeting receptors that have high binding affinities (*i.e.* subnanomolar dissociation constants) often radiotracers targeted at imaging the brain. With a low specific activity radiotracer, the excess of ¹⁹F-labeled compound can saturate the target receptor, so little ¹⁸F-labeled compound may bind, leading to low signal for imaging. This can be countered by administering a larger dose, but larger doses often can reach the physiological range of effect, causing side-effects or toxicity. This is especially problematic for PET images on younger children, where larger doses are not safe. Nucleophilic methods, generating high specific activity, can be administered as low doses (typically about 50 pmol), minimizing toxicity and allowing PET scans for children.

From the cyclotron, [¹⁸F]F⁻ is obtained as H¹⁸F in aqueous media.^{21,22} When hydrated, fluoride is very unreactive. To activate it for nucleophilic reactions the fluoride must be dehydrated and stabilized in a polar, aprotic solvent. H¹⁸F can be captured on an ion exchange resin, recovering the unreacted H₂¹⁸O. The [¹⁸F]F⁻ is typically recovered by eluting with aqueous solutions of alkali metal (K⁺, Rb⁺, Cs⁺) salts. Residual water is removed by multiple evaporations using a polar, organic solvent that azeotropes with water, such as acetonitrile. Since most alkali metals bind tightly to fluoride and these salts tend to be nearly insoluble in organic solvents, cryptands (such as Kryptofix 2.2.2) are used to promote ion separation and solubilization of the [¹⁸F]F⁻. Although these solutions are generally free from water, the specific level of hydration is not known and it is very unlikely these solutions are completely anhydrous.¹³

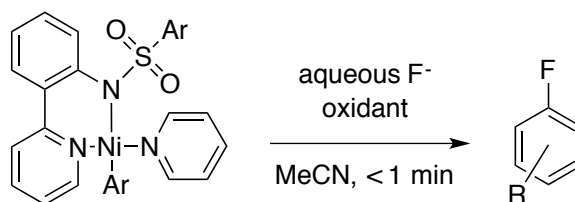


Scheme 1.1: Process to capture $^{18}\text{F}^{-21}$

$[\text{}^{18}\text{F}]\text{F}^-$ can also be recovered by eluting with aqueous solutions of quaternary ammonium (tetramethylammonium, tetrabutylammonium, etc) salts of weakly nucleophilic bases (e.g. bicarbonate, carbonate, hydroxide) and dried in a similar fashion. These salts tend to be more soluble in organic solvents, but again complete dehydration is problematic. For example, dried tetrabutylammonium fluoride (TBAF)²³ is reported to decompose by Hofmann elimination at room temperature. After dehydration the salt is contaminated with large amounts of bifluoride (HF_2^-) and tributylamine. DiMugno and Sun have reported a direct synthesis of highly anhydrous tetrabutylammonium fluoride from ultra-dry starting materials,²⁴ and a “fluoride relay” method, using wet $[\text{}^{19}\text{F}]\text{F}^-$, that can be adapted to an anhydrous $[\text{}^{18}\text{F}]\text{F}^-$ synthesis.²⁵

The drawbacks to the previous methods are mostly due to the reactivity of fluorine sources — electrophilic sources, F_2 , are highly reactive but often unselective and

do not tolerate many functional groups. Nucleophilic sources, in contrast, are only weakly nucleophilic unless rigorously dried, in which case fluoride's basicity often results in unwanted side products. With nucleophilic fluorination harsh conditions are often necessary, in theory a consequence of the kinetic barrier to C–F bond formation. However, as the C–F bond is the strongest of all the C–X single bonds, fluorination of aryl halides is typically a thermodynamically favorable process, and can be approached by catalysis. In the past few years, several methods of metal-mediated fluorination have been reported, successfully converting aryl bromides and/or aryl iodides to the corresponding aryl fluorides.^{26–50} This began with a breakthrough in 2009 by Buchwald and coworkers, using nucleophilic sources of fluoride.²⁶ Later Sanford and coworkers developed a fluorination procedure by oxidizing palladium(II) to palladium(IV) using xenon difluoride.^{26,27} Unfortunately, many of these methods are not compatible with PET methodology, as they require an excess of the fluoride source or an added carrier, provide low yields, or require long reaction times. Recently, Ritter and coworkers have published a series of advances using palladium and nickel complexes.⁵¹



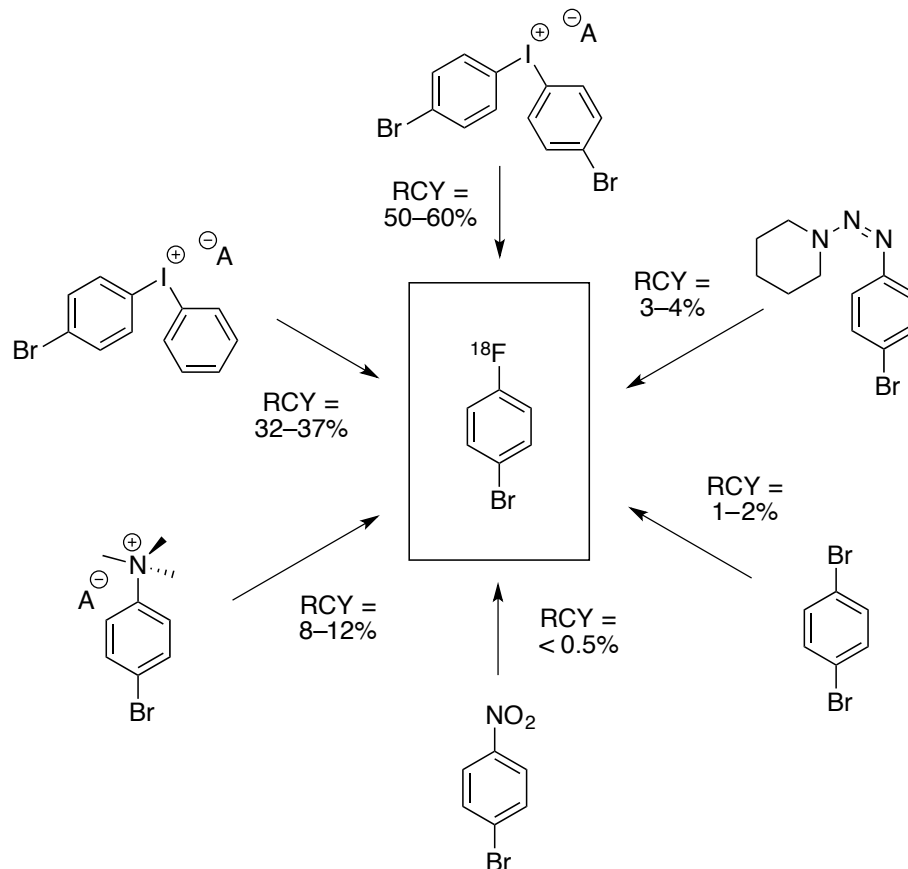
Scheme 1.2: Generation of aryl fluoride from Nickel complex³⁶

A nickel complex is oxidized in the presence of aqueous fluoride. The reductive elimination takes place at room temperature in less than a minute. This method makes

use of extensive drying procedures (used in the previously described nucleophilic methods) unnecessary. The precursor nickel complexes were easily synthesized, and were stable when stored. The authors used this methodology under PET conditions, but on a scale below that of a PET dosage. It is unknown whether this chemistry can produce a sufficient amount of an ^{18}F -labeled radiopharmaceutical to be used for a PET scan.

Another approach that has shown recent advancement is the use of hypervalent iodine(III) complexes to deliver a fluorine atom to an arene. The aryl fluoride is eliminated during thermolysis of diaryliodonium fluoride salts;⁵²⁻⁵⁴ this is the method we use in our lab. Pike and coworkers were the first to use diaryliodonium salts for radiotracer synthesis.⁵⁵ Reactions were carried out in acetonitrile and DMF, polar aprotic solvents, based on the theory that thermolysis of the iodine(III) complex proceeds via an $\text{S}_{\text{N}}\text{Ar}$ -style mechanism. Stang and coworkers have emphasized the similarities between iodonium salt and transition metal chemistries.⁵⁶ Using this knowledge we reasoned that the conceptual framework used to optimize transition metal reactions should be applicable to this chemistry. Removing residual ionic salts and switching to nonpolar solvents dramatically improved yields in our hands.⁵⁷

Emert and coworkers compared various radiosyntheses of symmetrical and unsymmetrical diaryliodonium salts (Scheme 1.3).⁵⁸



Scheme 1.3: Synthesis of 1-bromo-[¹⁸F]fluorobenzene⁵⁶

From their results it is clear that the reaction of the symmetrical bis(4-bromophenyl)iodonium salt provides the best radiochemical yields. The unsymmetrical diaryliodonium salt provides a significantly lower yield, because it could also react through another regiochemical pathway, generating [¹⁸F]fluorobenzene. Although yields of symmetrical precursors are significantly improved, synthesizing symmetrical diaryliodonium salts is challenging when the arenes are more complex. These syntheses can be more time consuming syntheses, and more expensive. Additionally, the thermolysis of unsymmetrical diaryliodonium salts can lead to multiple products that may not be easily separable.

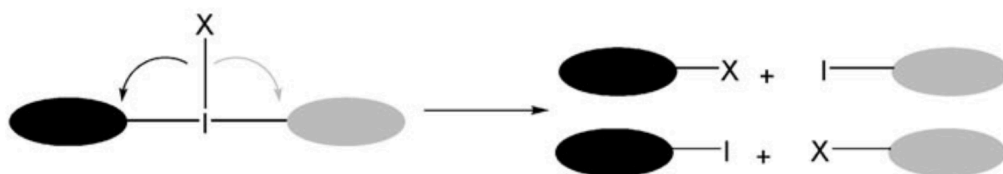


Figure 1.5: Diagram of unsymmetrical diaryliodonium salt thermolysis (reprinted with permission from John Wiley and Sons)⁵⁹

It is believed that in the S_NAr -style nucleophilic attack of fluoride the fluoride preferentially occurs at the *ipso*-carbon of the electron-poor arene.⁶⁰ The electron-poor arene is better able to stabilize the developing negative charge in the transition state. This makes fluorination of electron-rich aromatics challenging. Using 4-methoxyphenyl as a directing group allows for regioselective fluorination of arenes more electron-poor than a para methoxy group. Highly electron-rich arenes, such as arenes with *ortho*- or *para*-alcohols/ethers, or anilines can still be problematic, though we have developed alternative strategies for highly electron-rich arenes such as these.^{57,61,62}

1.1.5 [¹⁸F]Flutemetamol and Its Synthesis

Several other PET radiotracers have been introduced since the development of PiB in 2001 (Figure 1.6).⁶³

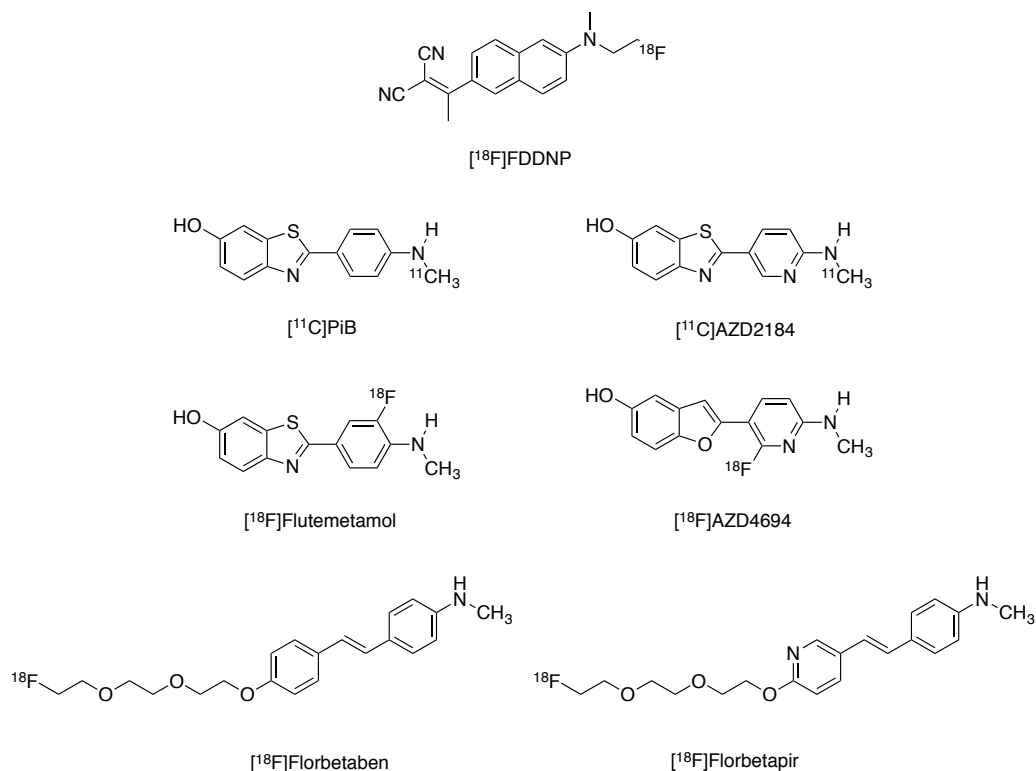
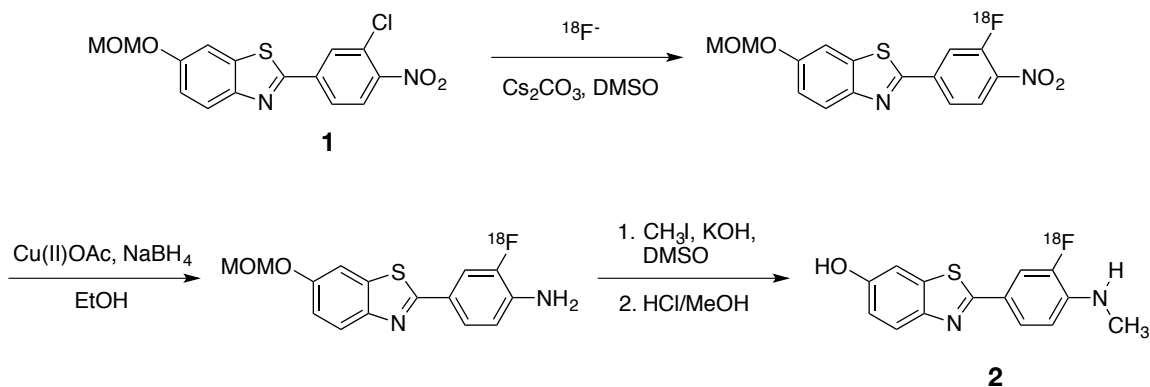


Figure 1.6: Examples of Aβ plaque PET imaging agents

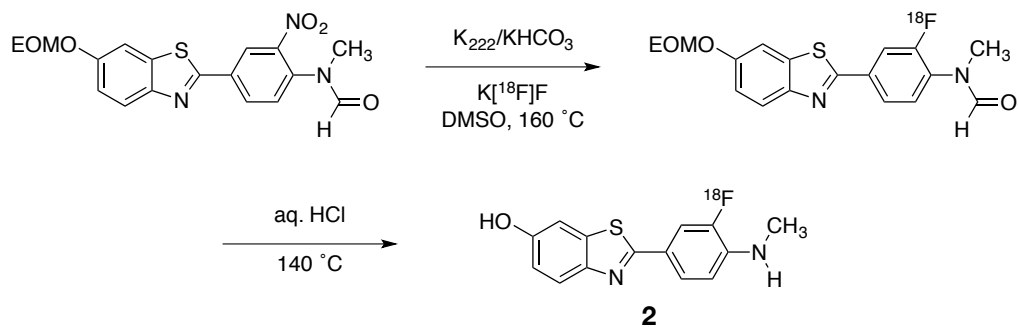
In 2004, Klunk, Mathis, and Wang developed a fluorinated analog of PiB, by introducing a fluoride onto the *ortho*-position of the aniline ring (Scheme 1.4).⁶⁴ The longer half-life of fluorine-18 allows for the production of the radiopharmaceutical at a hospital with a cyclotron and transport to neighboring hospitals for PET scans. The lower kinetic energy of fluorine-18, compared to carbon-11, allows for a higher resolution image (*i.e.* the fluoride-18 nuclide travels a short distance in tissue, so the annihilation event occurs fairly close to the site of radiotracer decay).



Scheme 1.4: Initial patented synthesis of [^{18}F]Flutemetamol

Their approach involved nucleophilic fluorination on an electron-poor nitroarene (**1**), by $\text{S}_{\text{N}}\text{Ar}$. This reaction takes over 60 minutes. After introduction of the radionuclide, three subsequent steps were performed to transform the nitroarene into an *N*-methylaniline for the final product (**2**): (1) reduction of the aryl nitro, (2) methylation of the resulting aniline, and (3) acidic cleavage of the methoxymethyl (MOM) protecting group. The entire process takes 120 minutes, giving a radiochemical yield (not decay corrected) of 0.5%. The large number of steps after generation of the radionuclide in the cyclotron, and the long reaction time, make this synthesis cost-prohibitive.

In 2007, an improved synthesis (Scheme 1.5) was reported.^{63,65} As this synthesis only involves one step after introduction of the radionuclide, acidic cleavage of the ethoxymethyl (EOM) and *N*-formyl protecting groups, radiochemical yields are much higher, 15–25% after optimization for the GE FASTlabTM synthesizer.



Scheme 1.5: Improved synthesis of Flutemetamol

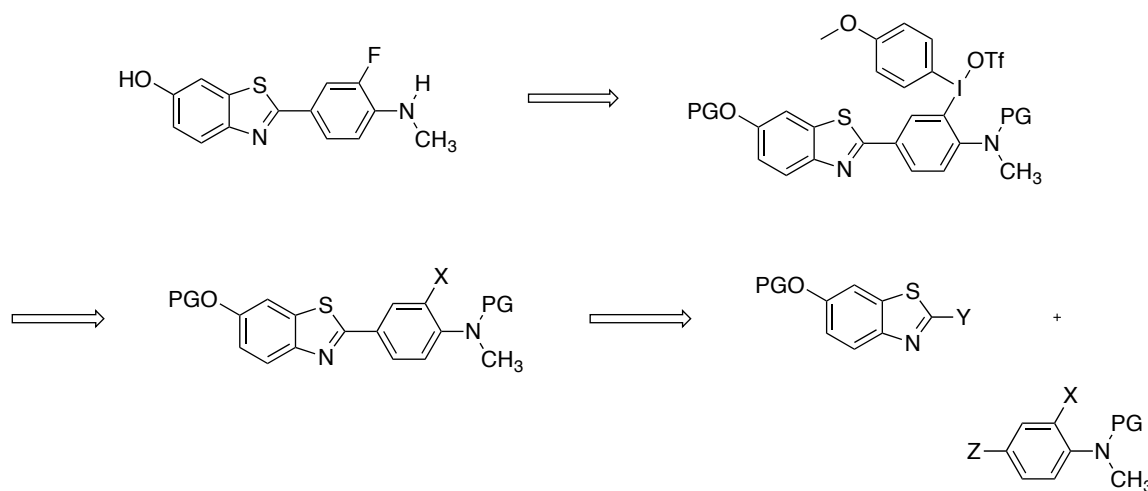
Several studies showed that [^{18}F]flutemetamol performs similarly to [^{11}C]PiB, and provides repeatable results. Flutemetamol was licensed by GE Healthcare and the injected product solution was named VizamyTM. In 2015, VizamyTM entered phase III clinical trials.⁶⁶ VizamyTM received FDA approval and is currently the only PET imaging tracer that is approved for visual interpretation of color images to detect amyloid plaques (rather than black and white images used for other compounds).⁶⁷ These results make flutemetamol an attractive imaging agent for AD diagnosis, monitoring, and research. Although the reduced number of steps after introduction of the radionuclide makes this synthesis more affordable, nucleophilic fluorination by $\text{S}_{\text{N}}\text{Ar}$ reactions still typically involve long reaction times and harsh conditions.

1.2 Results and Discussion

1.2.1 Synthesis of [^{19}F]Flutemetamol via an Iodonium salt

The low radiochemical yield is the most significant drawback to the existing methodologies for the synthesis of Flutemetamol (Scheme 1.4, Scheme 1.5). Given that

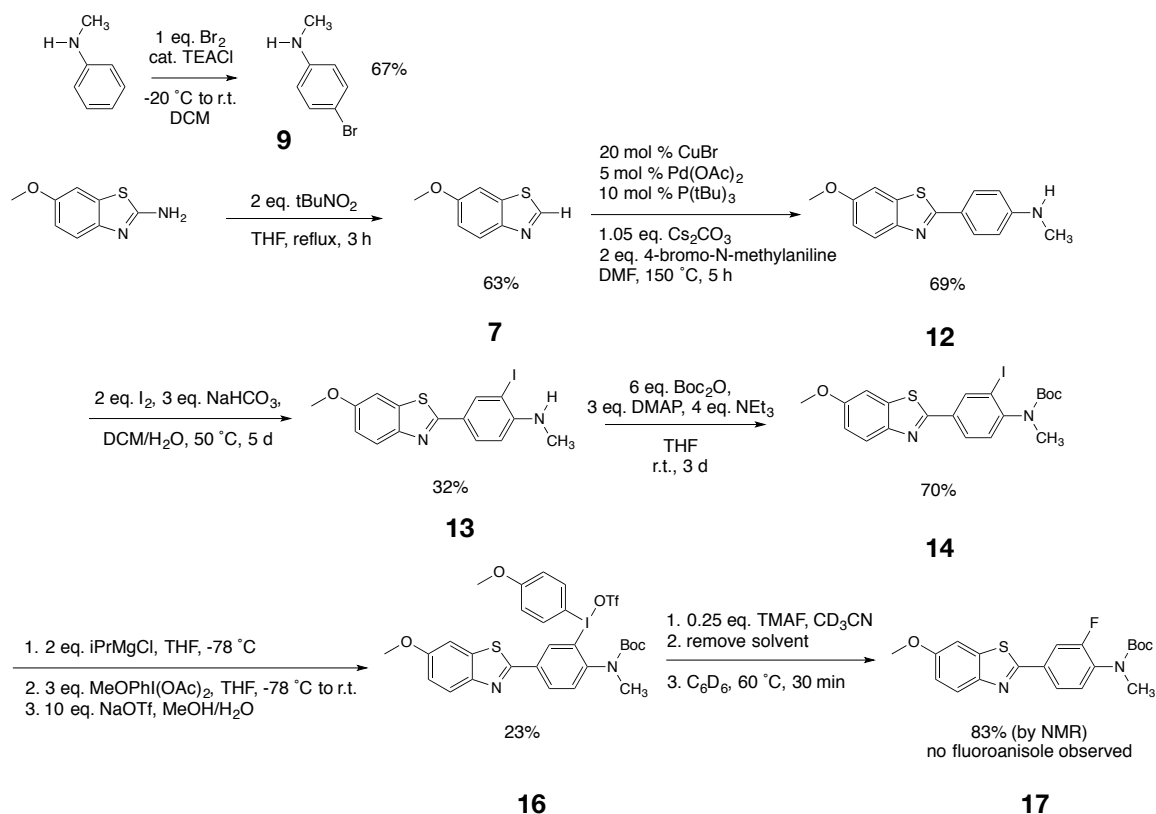
construction and operation of a cyclotron and PET facility is expensive, low radiochemical yields directly translate to high patient costs for each PET scan. Using faster methods, such as thermolysis of diaryliodonium salts, could provide significantly higher yields. A retrosynthesis was designed for flutemetamol using diaryliodonium salt thermolysis. Since the base structure of flutemetamol is a 2-arylbenzothiazole, a convergent synthesis, coupling a benzothiazole synthon with an aniline synthon, was chosen. Protecting groups would be installed either before or after coupling. After coupling, a halogen (nominally iodine or bromine) would be added, or the halogen could potentially be brought in with the aniline moiety. The DiMugno group has shown a number of strategies for synthesizing diaryl iodonium salts from aryl iodides and aryl bromides.^{57,59,61,72,73}



Scheme 1.6: Initial retrosynthesis of [¹⁹F]Flutemetamol

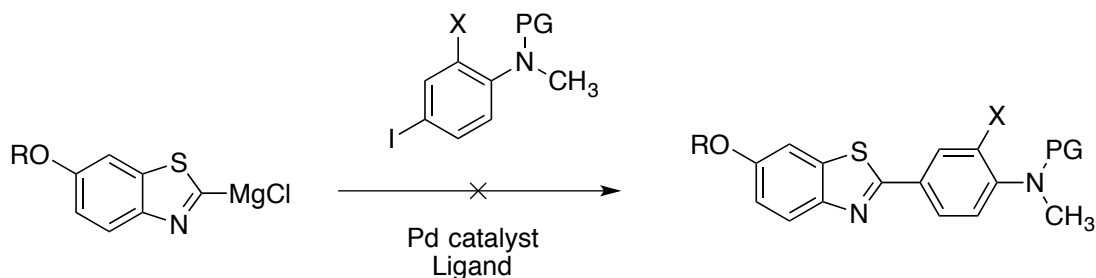
Protecting groups were chosen that could be removed in one step, thus minimizing the number of steps after addition of the radionuclide. Electron-rich aromatics are often

more difficult to fluorinate and very few aniline-containing iodonium salts have been reported in the literature^{68,69} For example, (4-dimethylaminophenyl)iodonium salts have only been isolated as relatively short-lived compounds; inner sphere electron transfer from the arene(s) to the iodine center may be the cause of rapid decomposition. Knowing this, an aniline protecting group was chosen that would remove electron density from the aromatic ring.



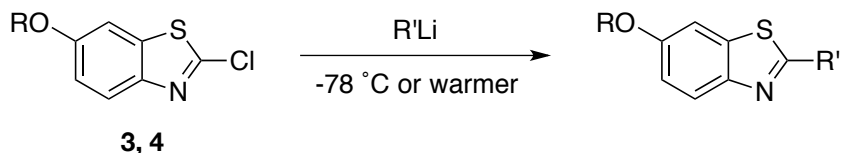
Scheme 1.7: Final synthesis of [¹⁹F]Flutemetamol

A number of synthetic routes were attempted to make the precursor to the iodonium salt. For the initial synthesis a Kumada coupling was attempted, by metalating a 2-chlorobenzothiazole and coupling with a 2,4-diiodoaniline.



Scheme 1.8: Kumada coupling (R=Me, EtOCH₂; X=I, H; PG=OAc, Boc)

It was theorized that coupling would preferentially take place at the less sterically hindered 4-position. This would eliminate the need to later selectively iodinate the aniline in the presence of the methoxybenzothiazole ring. Unfortunately, no methods were successful in metalating the benzothiazole. Preparation of the organozinc analog (to use in a Negishi coupling) was attempted using Rieke zinc, but no metalation occurred. Finally, a variety of butyllithium reagents were reacted with 2-chloro-6-methoxybenzothiazole (**3**) and 2-chloro-6-ethoxymethoxybenzothiazole (**4**), but in every case the butyl group inserted into the C=N bond of the benzothiazole.

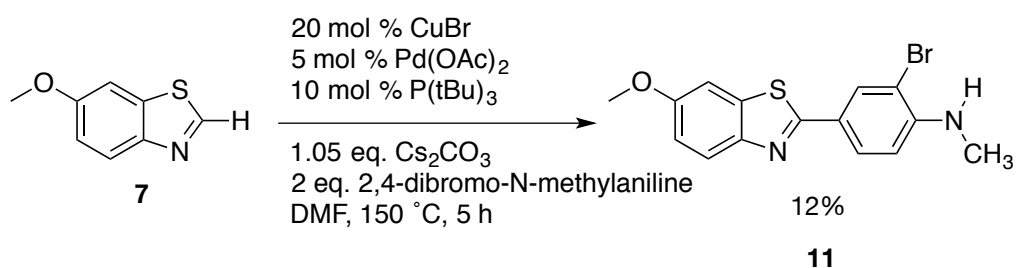


Scheme 1.9: Addition of butyllithium (R=Me, EtOCH₂; R'=n-Bu, s-Bu, t-Bu)

An alternate strategy was adopted, by metalating the aniline and coupling with the 2-chlorobenzothiazole. Similar attempts were tried to metalate the iodo-*N*-methylaniline (both 4-iodo-*N*-methylaniline (**5**) and 2,4-diiodo-*N*-methylaniline (**6**)), but both protecting groups used on the nitrogen (OAc and Boc) caused issues. Either the aniline

was not metalated or, using stronger metalating agents, nucleophilic attack occurred on the protecting group.

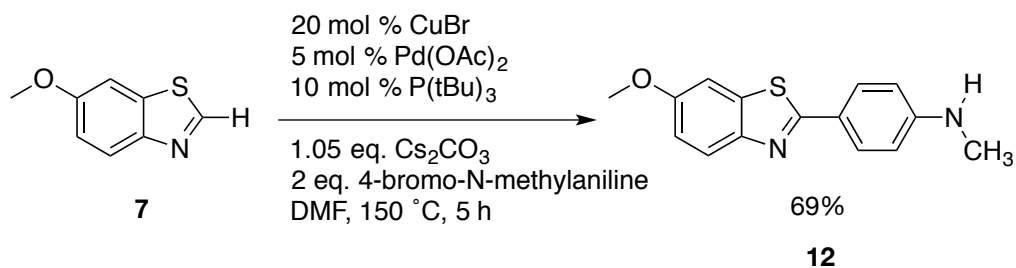
Since the 2-position on the benzothiazole ring is far more acidic than a typical aromatic C-H (In DMSO, the pKa of benzothiazole is 27 vs. ~43 for benzene⁷⁰) 6-methoxybenzothiazole (**7**) could potentially be used in a Sonogoshira-style coupling.



Scheme 1.10: Sonogoshira-style coupling used

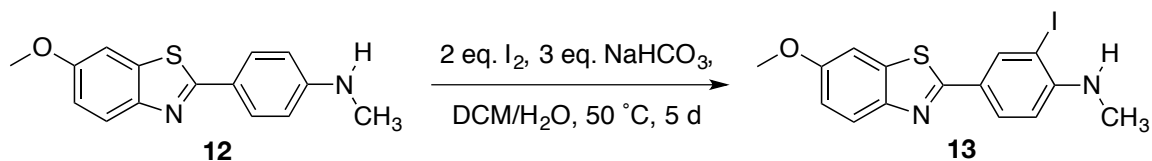
Due to previous difficulties in synthesizing 2,4-diiodoaniline (**8**) (even with ICl addition of the second iodide proceeded slowly, in very low yield), 4-bromo-*N*-methylaniline (**9**) and 2,4-dibromo-*N*-methylaniline (**10**) were synthesized. Coupling with **10** proceeded smoothly, though yields were low due to the *ortho*-coupled side-product and a number of other side-products (the desired product and the *ortho*-coupled product could couple again with **7**). After Boc-protection of the product, no methods were found to form the iodonium salt. Typically, an aryl iodide is oxidized to an arylidonium diacetate, or an aryl halide is converted to a potassium aryltrifluoroborate by formation of a Grignard reagent or by palladium-catalyzed borylation with bis(pinacolato)diboron (Miyaura borylation). The aryl bromide (**11**) was unreactive to form the Grignard reagent at the low temperatures necessary to be compatible with the Boc protecting group. Miyaura

borylation proceeded to remove the Boc protecting group, but the product mixture could not be identified (the borylated product, without the Boc-group, did not appear to be present).



Scheme 1.11: Coupling with 4-bromo-*N*-methylaniline

Coupling with the mono-bromoaniline **5**, to form 4-(6-methoxybenzothiazolyl)-*N*-methylaniline (**12**), proceeds in much higher yields to furnish a more easily purifiable product. The challenge with this route is the difficulty in iodinating the aniline ring. It was presumed that iodination would be facile on both rings, leading to a mixture of multiple mono- and di-iodinated products; unexpectedly iodination was generally slow for both rings. One example from literature showed ICl in acetic acid could selectively iodinate the aniline ring.⁷¹ No experimental conditions were reported in the paper, but all attempts I performed gave no reaction. Strong iodinating agents such as (a) AgOTf/I₂ gave no conversion, and (b) (bis(trifluoroacetoxy)iodo)benzene/I₂, gave less than 10% conversion to the iodinated product (**13**) after all of the oxidant was consumed. It was discovered that iodinating under basic conditions gave the best results.



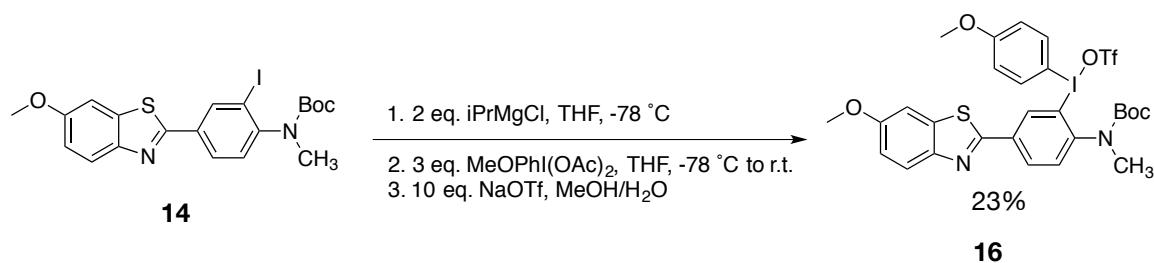
Scheme 1.12: Iodination under basic conditions

This reaction proved quite challenging as stirring the biphasic reaction dramatically decreased yields, by increasing the formation of a black, nearly insoluble tar. Increasing the scale of the reaction also decreased the yield. Using ICl instead of I₂ decreased formation of the tar byproduct and improved conversion, but overall gave similar to worse yields due to other side products, (a) chlorination on the aniline ring, (b) second iodination on the benzothiazole ring, and (c) a product with an unidentified substitution directly on the amine. After an in-depth survey of reaction variables (overall reaction scale, ratios of each reagent, temperature, stirring speed, dimensions of the reaction vessel) it was found that the optimal conditions were to run multiple reactions, each on a 1 g scale, and combine the reaction mixtures before work-up.

Although the aniline ring was initially thought to be fairly electron-rich, after these results it was suspected that the benzothiazole ring is sufficiently withdrawing. This challenge continued with the Boc-protection. A Schotten–Baumann reaction gave low yields, but using a gross excess of all other reagents, (a) di-*tert*-butyl dicarbonate, (b) dimethylaminopyridine, and (c) triethylamine, and running the reaction concentrated in acetonitrile, moderately high yields (60–70%) of **14** were achieved after three days.

We are able to oxidize a variety of aryl iodides with SelectfluorTM, using methodology developed in our group.⁷² However, oxidation of compound **14** proceeded

far more slowly than the oxidant (Selectfluor™) was consumed (presumably the aniline ring was electron-poor and also sterically hindered by the Boc group). Using a Miyaura borylation (as was attempted on the corresponding bromo-compound) also removed the Boc protecting group and did not appear to generate the desired compound (even without the Boc group). Lithiation, followed by generation of the organozinc (as we have used before on less functionalized targets), was not attempted due to the fragile Boc protecting group. However, we theorized that using a milder metalating agent (isopropyl magnesium chloride), under cold conditions, could be successful.

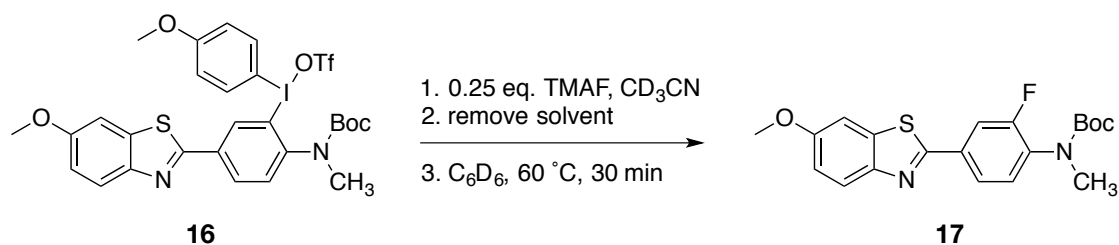


Scheme 1.13: Magnesium-halogen exchange reaction

Halogen-metal exchange using isopropyl magnesium chloride at -78 °C proved workable and proceeded without attack on the Boc protecting group. Though the resulting yields were low (23%), coupling with bis(acetoxy)iodoanisole (**15**) generated the desired product (**16**).

Although many diaryliodonium salts are fairly soluble in ethyl acetate, **16** was nearly insoluble in ethyl acetate, so the crude iodonium salt, **16**, was purified by triturating with hexanes and ethyl acetate to remove the bulk of the impurities. Diaryliodonium salts can be unstable when heated, so recrystallization is usually performed by layering, vapor diffusion, or slow evaporation. These conditions, using a

variety of binary and tertiary solvent sets, produced only impure oils. The crude iodonium salt, **16**, is fully soluble in acetonitrile, but almost completely insoluble in methyl *tert*-butyl ether (MTBE). The crude salt was dissolved in a small portion of acetonitrile and added dropwise to stirring MTBE. Unlike a typical precipitation (*e.g.* DCM into hexanes), the solution remained homogeneous until stirring was stopped and the solution was aged for several minutes. After several minutes the pure diaryliodonium salt gradually crystallized out of solution. We have theorized that MTBE is a weakly coordinating ligand for the iodonium center. Acetonitrile is a strongly coordinating ligand (reducing a solution of **16** under high dynamic vacuum will not liberate all of the acetonitrile). Due to the gross excess of MTBE there is a shift in equilibrium and the bound acetonitrile is replaced by MTBE. The MTBE-salt complex is no longer soluble and crystallizes out. This is observed by residual MTBE in NMR spectra, that does not change despite hours to days of dynamic high vacuum.



Scheme 1.14: Thermolysis reaction

Thermolysis of **16** was performed by dissolving the pure iodonium salt in acetonitrile in an NMR tube fitted with a Teflon screw cap closure. A substoichiometric amount of fluoride, from tetramethylammonium fluoride (TMAF) was added and the TfO⁻ to F⁻ exchange was observed by ¹H and ¹⁹F NMR. The exact amount of fluoride

added was determined by ^1H NMR, based on the integration of TMAF (based on the 12 methyl protons) compared to the integration of the diaryliodonium salt. Polar solvents and stoichiometric or superstoichiometric amounts of fluoride promote aryl swapping. Aryl swapping is a process that can occur with unsymmetrical diaryliodonium salts (Figure 1.7).⁷³ The degree of electronic differentiation between the two arenes determines the ratio of the resulting iodonium complexes. A diaryliodonium salt bearing two similarly electron-rich arenes undergoes aryl exchange to provide a nearly statistical mixture of diaryliodonium salts (1 A_2IF : 2 ABIF : 1 B_2IF). A diaryliodonium salt bearing an electron-rich and an electron-poor arene may undergo aryl exchange, but the unsymmetrical diaryliodonium salt predominates.

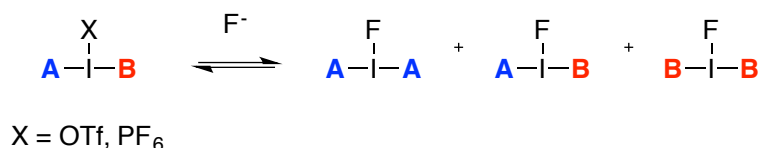


Figure 1.7: Diagram of the aryl swapping process

Aryl swapping was not observed after addition of fluoride to **16**, consistent with how electron-poor the flutemetamol arene appeared (based on previous reactions). Under high dynamic vacuum acetonitrile- d_3 was removed to give an oily solid. The NMR tube was returned to a glove box and dry benzene- d_6 was added. As mentioned previously, nonpolar aprotic solvents allow thermolysis with much less chance of side-products. Ionic salts are much less soluble in benzene, so filtration does not appreciably improve the results.⁵⁷ The NMR tube was sealed and heated at $60\text{ }^\circ\text{C}$, shielded from light. The

reaction was monitored by ^1H and ^{19}F NMR. After 30 minutes, it was found that the reaction was nearly 75% complete (based on integrations of the product (**17**) and the starting iodonium salt (**16**), given that a substoichiometric amount of fluoride was added). After one hour, conversion had slowed significantly. The final conversion was 83%. No fluoroanisole was observed in ^1H or ^{19}F NMR, indicative of high regioselectivity for the reductive elimination pathway that favors fluorination of the aniline ring. This further suggests that the Boc-protected aniline (with an electron withdrawing benzothiazole group) was sufficiently electron-poor (relative to anisole) to favor elimination of 4-iodoanisole, and sufficiently electron-poor to impede aryl swapping during the fluoride exchange. It was also found that heating the reaction using acetonitrile in benzene- d_6 (10% v/v) as the solvent, at 100 °C, for 10 minutes proved successful.

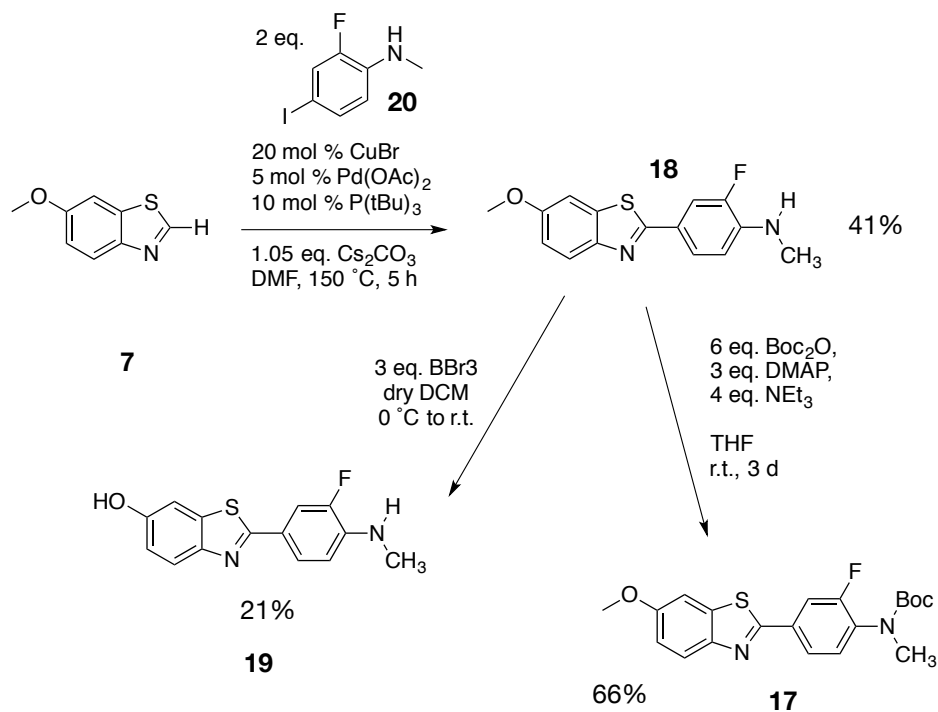
These results suggested that in the radiochemical lab we could see higher radiochemical yields than what is reported for the current VizamylTM preparation of [^{18}F]Flutemetamol (15–25%).

1.2.2 Synthesis of [^{19}F]Flutemetamol HPLC Standards

Since such a small amount of [^{18}F]-labeled radiotracer is produced at a PET facility, purification is performed using a gamma detector, and collecting fractions at high radioactivity. To ensure the desired radiotracer is collected and not free $^{18}\text{F}^-$ or some other by-product, ^{19}F standards are also run on HPLC, using a UV detector, to determine the proper retention time. Given the potential difficulty in removing the methoxy protecting group, I opted to prepare three ^{19}F standards for HPLC: a fully protected

flutemetamol (**17**), a partially deprotected flutemetamol (**18**), after removal of the Boc protecting group, and the fully deprotected [^{19}F]Flutemetamol (**19**).

Using 2-fluoro-4-iodo-*N*-methylaniline (**20**), which we previously prepared in our lab, 6-methoxybenzothiazole (**7**) was coupled with the same Sonogashira-style reaction. Boc-protection of this product yielded the fully protected flutemetamol, **17**. Boron tribromide deprotection of this product yielded the fully deprotected flutemetamol, **19**.



Scheme 1.15: Synthesis of ^{19}F HPLC standards

These compounds were fully characterized by NMR and MS, and using this alternate route the identity of the thermolysis product, described in the previous section, was confirmed.

1.2.3 Synthesis of [¹⁸F]Flutemetamol via a Diaryliodonium Salt

A larger scale synthesis of diaryliodonium salt **16** was performed. The purified salt was passed down an ion-exchange column (using an Amberlite quaternary ammonium resin, previously equilibrated with sodium triflate) to ensure no other anions were present, even as minor impurities. The salt was weighed into vials in 8 mg portions inside a nitrogen-charged glove box. These vials were sealed and kept free from light. The vials were shipped to St. Jude Children's Research Hospital where radiochemistry was performed. Thermolysis was confirmed by radio-TLC (the reaction mixture was spotted on a TLC plate and visualized by UV and gamma detector) and the crude product was purified by HPLC.

Run	Amount of salt	Temp.	Time	Starting Activity	Radio-TLC Product %	HPLC Product %	RCY
1	8 mg	80 °C	10 min	9.37 mCi	64%	–	32.2%
2	8 mg	120 °C	6 min	8.37 mCi	78%	–	38.1%
3	4 mg	60 °C	15 min	13.88 mCi	18%	–	–
4	4 mg	120 °C	20 min	11.59 mCi	95%	95%	53.6%
5	4 mg	120 °C	20 min	5.69 mCi	82%	81%	53.5%
6	4 mg	120 °C	20 min	11.04 mCi	74%	77%	48.0%

Table 1.2: Radiochemical thermolyses of **16**

It was found that only half the amount of diaryliodonium salt (4 mg) was necessary. Heating at 120 °C for 20 minutes gave the best results. By radio-TLC (Figure 1.8), 95% of the total radioactivity was found on the product; only 5% remained at the baseline

(likely unreacted fluoride-18 salts). HPLC of the reaction mixture (Figure 1.8) showed the same results: 95% of the total radioactivity was found at the same retention time as the previously prepared ^{19}F standard; only 5% was found in the void volume peak (the solvent front).

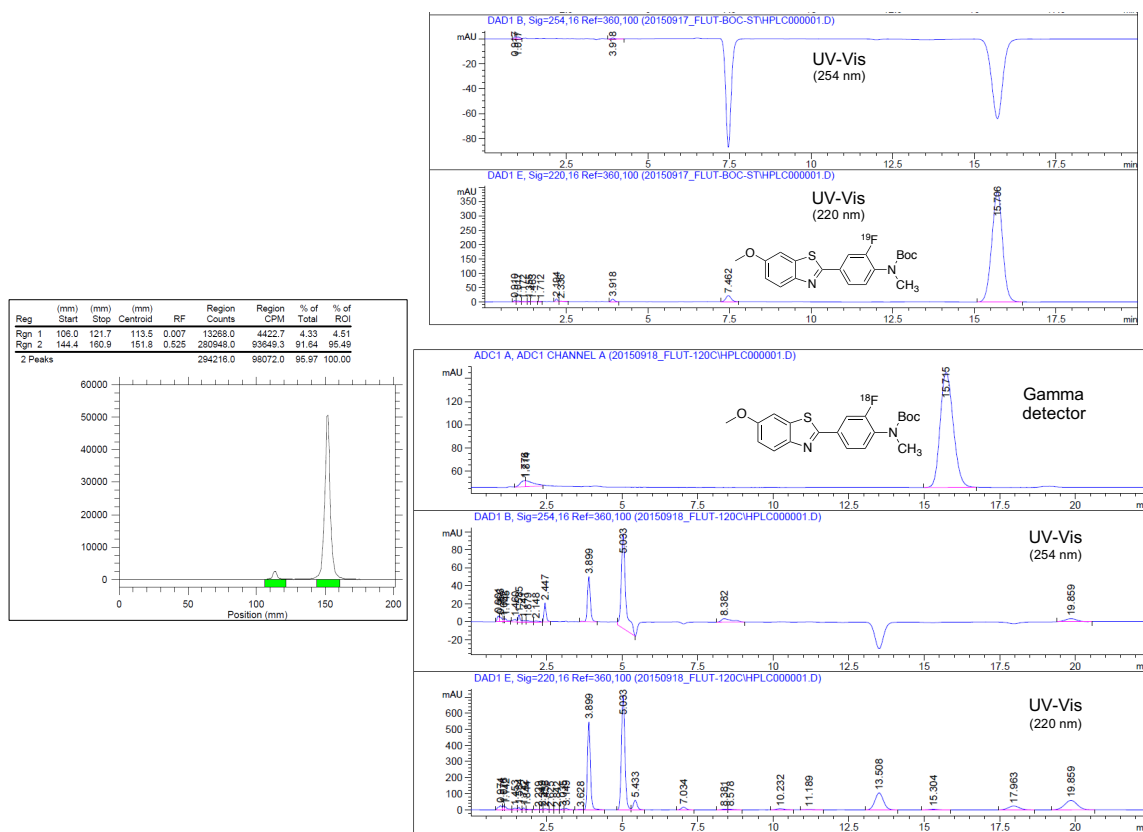


Figure 1.8: Radio-TLC of run 4 (*left*); HPLC trace of ^{19}F standard (*top right*); HPLC trace of run 4 (*bottom right*)

HPLC data are acquired with a gamma detector as well as UV-Vis. As the amount of ^{18}F -radiotracer is small, the compound appears only with gamma detection; a UV-Vis trace is co-acquired to confirm that other impurities (such as the unlabeled ^{19}F analog of the radiotracer) are not present when the radiotracer is collected. After isolation of the

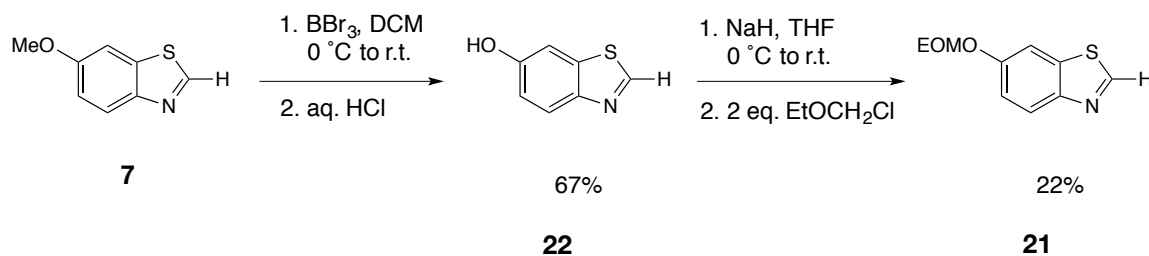
product, correcting for radioactive decay, the radiochemical yield (RCY) was found to be 53.6% (average of 51.7% over three runs). This result is significantly higher than previously reported results (15–25%) for the synthesis of [^{18}F]Flutemetamol. Additional optimization could be performed to potentially raise this yield further. For example, in this run, 15.9% of the starting activity was found remaining in the vial after reaction. Although the composition was not analyzed, this residue may contain some radiofluorinated product; this could potentially be recovered by improving the reaction vessel rinsing step.

Deprotection of the Boc protecting group was performed with the second run, using 4 M aqueous HCl for 10 minutes at 95 °C, and removal was confirmed by comparison on HPLC to the previously prepared ^{19}F standard. Based on reactions run on **14**, deprotection of the methoxy group should also be facile, but requires the use of boron tribromide, or hydroiodic acid and high temperatures (150 °C). Do to the effect of these harsh conditions on the equipment used at St. Jude Children's Research Hospital, and the potential safety risk associated with using such conditions, this deprotection step was not performed.

1.2.4 Future Directions

Although an ethoxymethoxy-protected analog of **16** was not synthesized, the route to the corresponding coupling component, 6-ethoxymethoxybenzothiazole (**21**), was briefly investigated (Scheme 1.16). Deprotection of 6-methoxybenzothiazole (**7**) to produce 6-hydroxybenzothiazole (**22**) proceeded smoothly with boron tribromide. The

lower than expected yield is presumably due to the presence of water in the starting material; more thorough drying of **7** (by vacuum sublimation) may improve this yield. Reacting **22** with aqueous sodium carbonate and chloromethoxyethane did not generate the desired product. Sodium hydride was used, but due to its strong basicity, deprotonation at the 7-position occurred (as evidenced by the formation of 6-ethoxymethoxy-7-ethoxybenzothiazole), significantly lowering the reaction yield. It may be possible to improve the yield by refluxing **22** with sodium carbonate under anhydrous conditions before adding chloromethoxyethane.



Scheme 1.16: Initial synthesis of 6-ethoxymethoxybenzothiazole (**21**)

The rest of the synthesis, using the same or similar conditions, should be possible using **21** in place of **7**, as each of the synthetic routes were chosen to be compatible with acid sensitive groups. Diaryliodonium salts are known to be compatible with ethoxymethoxy (EOM) protecting groups.⁷²

1.3 Conclusion

As research on effective, accessible, and affordable diagnosing, monitoring, and study of Alzheimer's disease continues to intensify, readily available and affordable PET

radiotracers will continue to be sought after. Our demonstration of the ability to prepare [¹⁸F]Flutemetamol using thermolysis of a diaryliodonium triflate, with an initially optimized radiochemical yield of 53.6%, proved quite promising. This yield is substantially higher than the highly optimized 15–25% yields reported by Mason and co-workers.^{63,65} Although deprotection was not performed under our best conditions, it is unlikely this step will hinder the yield significantly. In the future an ethoxymethoxy protecting group could be used, likely with the same or similar synthetic approach outlined here. This type of protecting group has been shown to be compatible with diaryliodonium salt thermolysis using fluorine-19⁷² as well as fluorine-18.⁷⁴ Expanding the approach outlined in this work to develop a diaryliodonium salt using an EOM protecting group, and fully optimizing the radiochemical procedure could offer a very promising alternative to the methodology currently being used for Vizamy1TM.

1.4 References

1. <http://www.who.int/mediacentre/factsheets/fs362/en/> (WHO Factsheet N°362)
2. Brookmeyer, R.; Johnson, E.; Ziegler-Graham, K.; Arrighi, H., “Forecasting the global burden of Alzheimer's disease”, *Alzheimer's & Dementia* **2007**, *3*, 186–191.
3. Kumar, A.; Ekavali, A.S., “A review on Alzheimer’s Disease pathophysiology and its management: An update”, *Pharmacological Reports*, **2015**, *67*, 195–203.
4. Vassar, P. S.; Culling, C. F., “Fluorescent stains, with special reference to amyloid and connective tissues”, *Arch Pathol.* **1959**, *68*, 487–498.
5. <http://www.ndt-educational.org/ferrario4.html> (Renal Amyloidosis)
6. Klunka, W. E.; Wang, Y.; Huang, G.; Debnath, M. L.; Holt, D. P.; Mathis, C. A., “Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain”, *Life Sciences* **2001**, *69*, 1471–1484.
7. Klunk W. E.; Engler H.; Nordberg A.; Wang Y.; Blomqvist G.; Holt D. P.; Bergström M.; Savitcheva I.; Huang GF.; Estrada S.; Ausén B.; Debnath M. L.; Barletta J.; Price J. C.; Sandell J.; Lopresti B. J.; Wall A.; Koivisto P.; Antoni G.; Mathis C. A.; Långström B., “Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B”, *Ann Neurol.* **2004**, *55*, 306–319.
8. Hong, Y. T.; Veenith, T.; Dewar, D.; Outtrim, J. G.; Mani, V.; Williams, C.; Pimlott, S.; Hutchinson, P. J. A.; Tavares, A.; Canales, R.; Mathis, C. A.; Klunk, W. E.; Aigbirhio, F. I.; Coles, J. P.; Baron, J.; Pickard, J. D.; Fryer, T. D.; Stewart, W.;

- Menon, D. K., “Amyloid Imaging with Carbon 11–Labeled Pittsburgh Compound B for Traumatic Brain Injury”, *JAMA Neurology* **2014**, *71*, 23–31.
9. Clifford Jr., R. J.; Albert, M. S.; Knopman, D. S.; McKhann, G. M.; Sperling, R. A.; Carrillo, M. C.; Thies, B.; Phelps, C. H., “The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease”, *Alzheimer’s & Dementia*, **2011**, *7*, 257–262.
10. Amaty, S. M.; Honer, M.; Schubiger, P. A., “Molecular Imaging with PET”, *Chem. Rev.* **2008**, *108*, 1501–1516.
11. http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html
(Introduction to PET Physics)
12. Brown and Firestone **1986**; Brookhaven National Laboratory Internet database, BNL **2003**.
13. Biffinger, J. C.; Kim, H. W.; DiMugno, S. G., “The polar hydrophobicity of fluorinated compounds”, *ChemBioChem* **2004**, *5*, 622–627.
14. DiMugno, S. G.; Sun, H., “The strength of weak interactions: Aromatic fluorine in drug design”, *Curr. Top. Med. Chem.* **2006**, *6*, 1473–1482.
15. Paul, E. A.; Huang, P. M. *Chemical aspects of soil*. In Handbook of Environmental Chemistry, Hutzinger, O., Ed.; Springer-Verlag, Berlin, **1980**, 69–86.

16. O'Hagan, D.; Harper, D. B. "Natural Occurrence of Organofluorine and Other Constituents from *Streptomyces* sp TC1", *J. Fluorine Chem.* **1999**, *100*, 127–133.
17. Schlosser, M., *Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedical Targets*, Ed. Soloshonok, V. A., Wiley, Chichester, **1999**, 613–659.
18. Smart, B. E., "Fluorine substituent effects (on bioactivity)", *J. Fluor. Chem.* **2001**, *109*, 3–11.
19. <https://hadassahsc.wordpress.com/2010/07/23/hadassah-medical-center-installs-new-cyclotron-system—one-of-only-a-handful-worldwide/> (Hadassah Medical Center Installs New Cyclotron System)
20. <http://www.dkfz.de/en/radiochemie/Projects/AutomationOfRadiosyntheses.html> (Automation of Radiosyntheses)
21. Cai, L.; Lu, S.; Pike, V. W., "Chemistry with [¹⁸F]Fluoride Ion", *Eur. J. Org. Chem.* **2008**, *17*, 2853–2873.
22. Alauddin, M. M., "Positron emission tomography (PET) imaging with ¹⁸F-based radiotracers", *Am. J. Nucl. Med. Mol. Imaging.* **2012**, *2*, 55–76.
23. Cox, D. P.; Terpinski, J.; Lawrynowicz, W., "'Anhydrous' tetrabutylammonium fluoride: a mild but highly efficient source of nucleophilic fluoride ion", *J. Org. Chem.* **1984**, *49*, 3216–3219.

24. Sun, H.; DiMugno, S. G., “Anhydrous Tetrabutylammonium Fluoride”, *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.
25. Sun, H.; DiMugno, S. G., “Fluoride relay: a new concept for the rapid preparation of anhydrous nucleophilic fluoride salts from KF”, *Chem. Commun.* **2007**, *5*, 528–529.
26. Watson D.A.; Su M.; Teverovskiy G.; Zhang Y.; Garcia-Fortanet J.; Kinzel T.; Buchwald S.L., “Formation of ArF from LPdAr(F): catalytic conversion of aryl triflates to aryl fluorides”, *Science*, **2009**, *325*, 1661–1664.
27. Ball, N. D.; Sanford, M. S., “Synthesis and reactivity of a mono- σ -aryl palladium(IV) fluoride complex”, *J. Am. Chem. Soc.* **2009**, *131*, 3796–3797.
28. Hollingworth, C.; Gouverneur, V., “Transition metal catalysis and nucleophilic fluorination”, *Chem. Comm.* **2012**, *48*, 2929–2942.
29. Gouverneur, V., “Flipping fluoride’s reactivity”, *Nat. Chem.* **2012**, *4*, 152-154.
30. Furuya, T.; Kamlet, A. S.; Ritter, T., “Catalysis for fluorination and trifluoromethylation”, *Nature* **2011**, *473*, 470–477.
31. Vigalok, A., “Electrophilic fluorination of Group 10 organometallic complexes. Chemistry beyond oxidative addition”, *Organometallics* **2011**, *30*, 4802–4810.
32. Furuya, T.; Klein, J. E. M. N.; Ritter, T., “Carbon-fluorine bond formation for the synthesis of aryl fluorides”, *Synthesis* **2010**, *11*, 1804–1821.
33. Brown, J. M.; Gouverneur, V., “Transition-metal-mediated reactions for Csp²-F bond construction: The state of play”, *Angew. Chem. Int. Ed.* **2009**, *48*, 8610–8614.

34. Gouverneur, V., “A new departure in fluorination chemistry”, *Science* **2009**, *325*, 1630–1631.
35. Furuya, T.; Kutturf, C. A.; Ritter, T., “Carbon-fluorine bond formation”, *Curr. Opin. Drug Disc. Dev.* **2008**, *11*, 803–819.
36. Lee, E.; Hooker, J. H.; Ritter, T., “Nickel-mediated oxidative fluorination for PET with aqueous [18F] fluoride”, *J. Am. Chem. Soc.* **2012**, *134*, 17456–17458.
37. Fier, P. S.; Hartwig, J. F., “Copper-mediated fluorination of aryl iodides”, *J. Am. Chem. Soc.* **2012**, *134*, 10795–10798.
38. Casitas, A.; Canta, M.; Sola, M.; Costas, M.; Ribas, X., “Nucleophilic aryl fluorination and aryl halide exchange mediated by a CuI/CuIII catalytic cycle”, *J. Am. Chem. Soc.* **2011**, *133*, 19386–19392.
39. Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T., “A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging”, *Science* **2011**, *334*, 639–642.
40. Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L., “Evidence for in situ catalyst modification during the Pd-catalyzed conversion of aryl triflates to aryl fluorides”, *J. Am. Chem. Soc.* **2011**, *133*, 18106–18109.
41. Noel, T.; Maimone, T. J.; Buchwald, S. L., “Accelerating palladium-catalyzed C- F bond formation: Use of a microflow packed-bed reactor”, *Angew. Chem. Int. Ed.* **2011**, *50*, 8900–8903.

42. Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L., "Formation of Ar-F from LPdAr(F): Catalytic conversion of aryl triflates to aryl fluorides", *Science* **2009**, *325*, 1661–1664.
43. Tang, P. P.; Wang, W. K.; Ritter, T., "Deoxyfluorination of phenols", *J. Am. Chem. Soc.* **2011**, *133*, 11482–11484.
44. Tang, P. P.; Ritter, T., "Silver-mediated fluorination of aryl silanes", *Tetrahedron* **2011**, *67*, 4449–4454.
45. Tang, P. P.; Furuya, T.; Ritter, T., "Silver-catalyzed late-stage fluorination", *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154.
46. Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P. P.; Goddard III, W. A.; Ritter, T., "Mechanism of C-F reductive elimination from palladium(IV) fluorides", *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807.
47. Furuya, T.; Strom, A. E.; Ritter, T., "Silver-mediated fluorination of functionalized aryl stannanes", *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663.
48. Furuya, T.; Ritter, T., "Fluorination of boronic acids mediated by silver(I)triflate", *Org. Lett.* **2009**, *11*, 2860–2863.
49. Furuya, T.; Kaiser, H. M.; Ritter, T., "Pd-mediated fluorination of arylboronic acids", *Angew. Chem. Int. Ed.* **2008**, *47*, 5993–5996.
50. Furuya, T.; Ritter, T., "Carbon-fluorine reductive elimination from a high-valent palladium fluoride", *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061.

51. Ritter, T.; Campbell, M.G., “Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis”, *Chem. Rev.*, **2015**, *115*, 612–633.
52. Grushin, V. V.; Tolstaya, T. P.; Lisichkina, I. N., “Phenyl-2-p- carboranyliodonium fluoroborate”, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, *9*, 2165–2168.
53. Van der Puy, M., “Conversion of diaryliodonium salts to aryl fluorides”, *J. Fluorine Chem.* **1982**, *21*, 385–392.
54. Grushin, V. V.; Kantor, M. M.; Tolstaya, T. P.; Shcherbina, T. M., “Arylation of anions by diarylhalonium tetrafluoroborates under phase transfer catalysis conditions”, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, *10*, 2332–2338.
55. Pike, V. W.; Aigbirhio, F. I., “Reactions of cyclotron-produced [18F]fluoride with diaryliodonium salts — a novel single-step route to no-carrier-added [18]fluoroarenes”, *J. Chem. Soc., Chem. Commun.* **1995**, *21*, 2215–2216.
56. Stang, P. J., “Polyvalent iodine in organic chemistry”, *J. Org. Chem.* **2003**, *68*, 2997–3008.
57. Wang, B.; Qin, L.; Neumann, K.; Uppaluri, S. H.; Cerny, R.; DiMagno, S. G., “Improved Arene Fluorination Methodology for I(III) Salts”, *Org. Lett.* **2010**, *12*, 3352–3355.
58. Ermert, J.; Hocke, C.; Ludwig, T.; Gail, R.; Coenen, H. H., “Comparison of pathways to the versatile synthon of no-carrier-added 1-bromo-4-[18F]fluorobenzene”, *J. Labelled Compd. Radiopharm.* **2004**, *47*, 429–441.

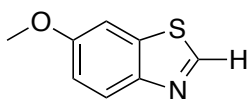
59. Wang, B.; Graskemper, J.; Qin, L.; DiMagno, S. G., “Regiospecific Reductive Elimination from Diaryliodonium Salts”, *Angew. Chemie Int. Ed.* **2010**, *49*, 4079–4083.
60. Yamada, Y.; Kashima, K.; Okawara, M., “Substituent effect in the nucleophilic attack by the bromide ion on the p-tolyl-substituted phenyliodonium ions”, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3179–3180.
61. Wang, B.; Graskemper, J.; Qin, L.; DiMagno, S. G., “Regiospecific Reductive Elimination from Diaryliodonium Salts”, *Angew. Chemie Int. Ed.* **2010**, *49*, 4079–4083.
62. Graskemper, J.; Wang, B.; Qin, L.; Neumann, K.; DiMagno, S. G., “Unprecedented Directing Group Ability of Cyclophanes in Arene Fluorinations with Diaryliodonium Salts”, *Org. Lett.* **2011**, *13*, 3158–3161.
63. Mason, N. S.; Mathis, C. A.; Klunk, W. E., “Positron emission tomography radioligands for in vivo imaging of A β plaques”, *J. Label Compd. Radiopharm* **2013**, *56*, 89–95.
64. Klunk, W. E.; Mathis, C. A.; Wang, Y., “Benzothiazole Derivative Compounds, Compositions and Uses”, WO 2004/083195, September 30, 2004.
65. Mason, N. S.; Klunk W. E.; Debnath, M.; Flatt, N.; Huang, G.; Shao, L.; Mathis, C. A., “Synthesis And Evaluation Of [18F]PiB Analogs As A β Plaque Pet Imaging Agents”, *J. Label. Compd. Radiopharm.* **2007**, *50*, S87.

66. Curtis, C.; Gamez, J. E.; Singh, U.; Sadowsky, C. H.; Villena, T.; Sabbagh, M. N.; Beach, T. G.; Duara, R.; Fleisher, A. S.; Frey, K. A.; Walker, Z.; Hunjan, A.; Holmes, C.; Escovar, Y. M.; Vera, C. X.; Agronin, M. E.; Ross, J.; Bozoki, A.; Akinola, M.; Shi, J.; Vandenberghe, R.; Ikonovic, M. D.; Sherwin, P. F.; Grachev, I. D.; Farrar, G.; Smith, A. P. L.; Buckley, C. J.; McLain, R.; Salloway, S., “Phase 3 trial of flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density”, *JAMA Neurology* **2015**, *72*, 287–294.
67. <http://www.rxlist.com/vizamyl-drug.htm> (Vizamyl)
68. Beringer, F. M.; Lillien, I., “Diaryliodonium Salts. XIII. Salts in which the Cations Bear Carboxyl, Hydroxyl, Alkoxy or Amino Groups”, *J. Am. Chem. Soc.* **1960**, *82*, 725–731.
69. Skulski, L.; Wroczynski, P., “Improved Syntheses of Some Diaryliodonium Salts from Symmetric Diarylmercurials and (Dichloroiodo)arenes (Willgerodt Method)”, *Bull. Pol. Acad. Sci., Chem.* **1999**, *47*, 231–238.
70. Bordwell, F. G., “Equilibrium acidities in dimethyl sulfoxide solution”, *Acc. of Chem. Res.* **1988**, *21*, 456–463.
71. Lu, C.; Jiang, Q.; Wu, C.; Wang, S.; Tang, J.; Liu, C.; Wang, Z., “Synthesis and Radioiodinelabeling of β -Amyloid Plaques Imaging Agent 3'-131I-PIB”, *J. Nuclear and Radiochemistry*, **2008**, *30*, 162–166.

72. Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G., "A Mild and General One-Pot Synthesis of Densely Functionalized Diaryliodonium Salts", *Eur. J. Org. Chem.* **2015**, *2015*, 5919–5924.
73. Wang, B.; Cerny, R.; Uppaluri, S. H.; Kempinger, J. J.; DiMagno, S. G., "Fluoride-promoted ligand exchange in diaryliodonium salts", *J. Fluor. Chem.* **2010**, *131*, 1113–1121.
74. Kuik, W.; Kema, I. P.; Brouwers, A. H.; Zijlma, R.; Neumann, K. D.; Dierckx, R. A.J.O.; DiMagno, S. G.; Elsinga, P. H., "In Vivo Biodistribution of No-Carrier-Added 6-¹⁸F-Fluoro-3,4-Dihydroxy-L-Phenylalanine (¹⁸F-DOPA), Produced by a New Nucleophilic Substitution Approach, Compared with Carrier-Added ¹⁸F-DOPA, Prepared by Conventional Electrophilic Substitution", *J. Nucl. Med.* **2015**, *56*, 106–112.

1.5 Experimental

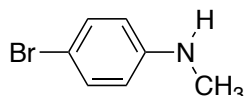
6-Methoxybenzothiazole (7):



tert-Butyl nitrite (18.5 mL, 155.2 mmol) was dissolved in 50 mL THF and heated to reflux under N₂. 2-amino-6-methoxybenzothiazole (14.00 g, 77.6 mmol) was dissolved in 150 mL THF and added dropwise with a pressure-equalizing addition funnel over 1 hour. The solution was refluxed for an additional 3 hours under N₂ and cooled to room temperature. The solution was diluted with ethyl ether and washed three times with sodium thiosulfate in brine (10 g/L). The aqueous layers were extracted once with ethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and the solvent was removed *in vacuo*. The crude oil was precipitated with ether and filtered. The filtrate was concentrated *in vacuo* to yield an oily orange solid, which was chromatographed on silica with ethyl acetate/hexanes (1:1, v/v). The orange solid was sublimed under high dynamic vacuum, at 60 °C. The pale yellow solid was recrystallized from nearly boiling hexanes, cooled slowly to room temperature, and rinsed with cold hexanes, to yield a colorless solid (8.05 g, 62.8%). ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 8.83 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1H), 3.89 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 158.30, 151.65, 147.86, 135.26, 124.15, 116.13, 104.22, 56.02; HRMS: (EI) calcd. for C₈H₇NOS [M]⁺ 165.0248 found 165.0248.

Doyle, M. P.; Dellaria, J. F. Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494–3498.

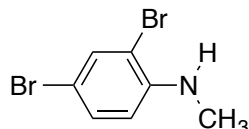
4-Bromo-*N*-methylaniline (9):



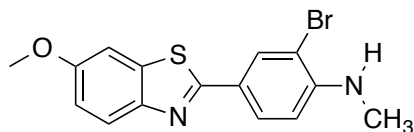
N-Methylaniline (10.8 mL, 0.10 mol) was dissolved in 85 mL dichloromethane in a 500 mL round bottom flask. The solution was cooled to -20 °C with a sodium chloride/ice bath. Tetraethylammonium chloride (1.66 g, 0.01 mol) was dissolved in 2.0 mL methanol and added to the flask. Bromine (5.64 mL, 0.11 mmol) was dissolved in 15 mL dichloromethane and added by syringe pump over 1 hour. The solution was allowed to warm slowly to room temperature overnight, in the dark. The reaction was neutralized with saturated aqueous sodium bicarbonate. The organic layer was washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic layer was dried over sodium sulfate, filtered, and solvent was removed in *vacuo*. The crude liquid was fractionally distilled at 100 mTorr (boiling point 58–61 °C) to yield a yellow liquid (12.53 g, 67.4 %). ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.50 (d, *J* = 8.7 Hz, 2H), 3.74 (br s, NH), 2.83 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 148.35, 132.05, 114.19, 109.07, 30.95; HRMS: (EI) calcd. for C₇H₈BrN [M]⁺ 184.9840, 186.9820 found 184.9840, 186.9827.

Gervat, S.; Léonel, E.; Barraud, J.; Ratovelomanana, V. *Tetrahedron Lett.*, **1993**, *34*, 2115–2118.

2,4-Dibromo-*N*-methylaniline (10):



N-Methylaniline (10.8 mL, 0.10 mol) was dissolved in 100 mL dichloromethane in a 250 mL round bottom flask. Bromine (12.8 mL, 0.25 mol) was added dropwise at a rate sufficient to maintain reflux. The solution was refluxed overnight. The reaction was neutralized with saturated aqueous sodium bicarbonate. The organic layer was washed twice with saturated aqueous sodium bicarbonate and once with brine. The organic layer was dried over sodium sulfate, filtered, and solvent was removed in *vacuo*. The crude oil was chromatographed on silica with ethyl acetate/hexanes (1:99, v/v) to yield a pale yellow solid (14.7 g, 55.3 %). ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.54 (d, $J = 2.2$ Hz, 1H), 7.30 (dd, $J = 8.7$ Hz, $J = 2.2$ Hz, 1H), 6.49 (d, $J = 8.7$ Hz, 1H), 4.40 (br s, NH), 2.88 (s, 3H); ^{13}C NMR (CDCl_3 , 400 MHz, 298 K): δ 145.27, 134.32, 131.44, 111.86, 109.91, 108.01, 30.80; HRMS: (EI) calcd. for $\text{C}_7\text{H}_8\text{Br}_2\text{N}$ $[\text{M}]^+$ 264.8925, 262.8945, 266.8904 found 264.8894, 262.8939, 266.8910.

2-(3-Bromo-4-(methylamino)phenyl)-6-methoxybenzothiazole (11):

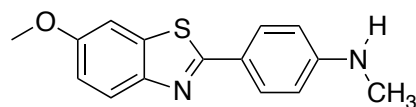
In a nitrogen-charged glove box, 6-methoxybenzothiazole (99.1 mg, 0.60 mmol), 2,4-dibromo-*N*-methylaniline (317.9 mg, 1.2 mmol), palladium(II) acetate (6.7 mg, 0.03 mmol), tri(*tert*-butyl)phosphine (12.1 mg, 0.06 mmol), and copper(I) bromide (17.2 mg, 0.12 mmol) were dissolved in 10 mL dry DMF. The solution was transferred to an airfree storage tube. Solid cesium carbonate (215.1 mg, 0.66 mmol) was added directly to the tube. The reaction was heated at 150 °C for 8 hours. After cooling to room temperature the mixture was diluted with ether, and washed five times with water. The aqueous layers were extracted three times with ether. The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. The solvent was removed in *vacuo* and the crude oil was chromatographed on silica with ethyl acetate/hexanes (10:90 v/v) to yield a pale yellow solid (25.6 mg, 12.2%).

Cole, G. B.; Keum, G.; Liu, J.; Small, G. W.; Satyamurthy, N.; Kepe, V.; Barrio, J. R. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6222–6227.

Alternate method: In a tall Schlenk tube, 2-(4-(methylamino)phenyl)-6-methoxybenzothiazole (1.00 g, 2.5 mmol) was dissolved in 20 mL DCM. The solution was cooled to -78 °C. Bromine (0.14 mL, 2.7 mmol) was diluted with 2 mL DCM and

added dropwise over 15 minutes. The reaction was allowed to warm slowly to room temperature and stirred overnight. The solution was diluted with DCM and washed twice with saturated aqueous sodium bicarbonate, three times with a 10 g/L solution of sodium thiosulfate in brine, and once with brine. The organic layer was dried over sodium sulfate, filtered, and the solvent was removed in *vacuo*. The crude solid was chromatographed on silica with ethyl acetate/hexanes (90:10 v/v) to yield a pale yellow solid (0.6164 g, 70.6%). ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 8.18 (d, $J = 2.0$ Hz, 1H), 7.88 (d, $J = 8.9$ Hz, 1H), 7.86 (dd, $J = 8.6$ Hz, $J = 2.0$ Hz, 1H), 7.33 (d, $J = 2.8$ Hz, 1H), 7.06 (dd, $J = 8.9$ Hz, $J = 2.8$ Hz, 1H), 6.67 (d, $J = 8.6$ Hz, 1H); HRMS: (ESI) calcd. for $\text{C}_{15}\text{H}_{14}\text{BrN}_2\text{OS}$ $[\text{M}+\text{H}]^+$ 349.0010, 350.9990 found 349.0012, 351.0001.

2-(4-(Methylamino)phenyl)-6-methoxybenzothiazole (12):

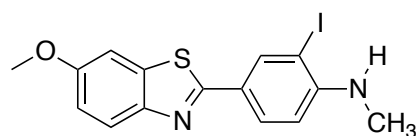


In a nitrogen-charged glove box, 6-methoxybenzothiazole (7.00 g, 42.4 mmol), 4-bromo-*N*-methylaniline (9.46 g, 50.9 mmol), palladium(II) acetate (0.48 g, 2.1 mmol), tri(*tert*-butyl)phosphine (0.86 g, 4.2 mmol), and copper(I) bromide (1.22 g, 8.5 mmol) were dissolved in 200 mL dry DMF. The mixture was transferred to a 500 mL airfree storage flask. Solid cesium carbonate (15.19 g, 46.6 mmol) was added directly to the flask. The reaction was heated at 150 °C, with stirring, for 4 hours. After cooling to room temperature the mixture was diluted with ether, and washed five times with water. The aqueous layers were extracted three times with ether. The combined organic layers were

washed with brine, dried over sodium sulfate, and filtered. The solvent was removed in *vacuo* and the crude oil was chromatographed on silica with ethyl acetate/hexanes/dichloromethane (1:4:5 v/v/v) to yield a pale yellow solid (7.94 g, 69.3%). ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.88 (d, $J = 8.6$ Hz, 1H), 7.87 (d, $J = 9.0$ Hz, 1H), 7.33 (d, $J = 2.5$ Hz, 1H), 7.05 (dd, $J = 9.0$ Hz, $J = 2.5$ Hz, 1H), 6.65 (d, $J = 8.6$ Hz, 1H), 4.10 (br q, $J = 5.0$ Hz, NH), 2.91 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 166.67, 157.35, 151.46, 148.96, 135.93, 128.96, 122.97, 122.89, 115.16, 112.26, 104.56, 77.53, 77.22, 76.90, 56.00, 30.56; HRMS: (ESI) calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{NaOS}$ $[\text{M}+\text{Na}]^+$ 293.0725 found 293.0737.

Cole, G. B.; Keum, G.; Liu, J.; Small, G. W.; Satyamurthy, N.; Kepe, V.; Barrio, J. R. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6222–6227.

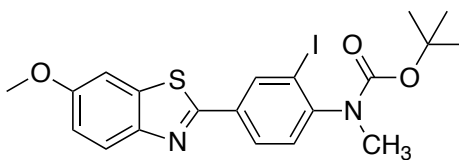
2-(3-Iodo-4-(methylamino)phenyl)-6-methoxybenzothiazole (13):



In a tall Schlenk storage tube, 2-(4-(methylamino)phenyl)-6-methoxybenzothiazole (1.00 g, 2.5 mmol) was dissolved in 20 mL dichloromethane. Iodine (1.28 g, 5.0 mmol) was added with stirring. Saturated aqueous sodium bicarbonate (5 mL) was layered on top. The reaction was heated to 50 °C for 3 days, without stirring. After cooling, more iodine (1.92g, 7.5 mmol) was added, the solution was mixed gently, and the reaction was heated for an additional 2 days at 50 °C, without stirring. The solution was diluted with

dichloromethane and brine, and the layers were separated. The organic layer was washed three times with small portions of sodium thiosulfate in brine (10 g/L), and washed once with brine. The organic layer was dried over sodium sulfate, filtered, and the solvent was removed in *vacuo*. The black solid was triturated three times with boiling MTBE and filtered. MTBE was removed *in vacuo*, and the crude solid was chromatographed on silica with ethyl acetate/hexanes (90:10 v/v) to yield a light orange solid (468.0 mg, 31.9%). ^1H NMR (CD_2Cl_2 , 400 MHz, 298 K): δ 8.38 (d, $J = 2.0$ Hz, 1H), 7.88 (dd, $J = 8.6$ Hz, $J = 2.0$ Hz, 1H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.35 (d, $J = 2.5$ Hz, 1H), 7.04 (dd, $J = 8.9$ Hz, 2.5 Hz, 1H), 6.61 (d, $J = 8.6$ Hz, 1H), 4.64 (q, $J = 5.0$ Hz, NH), 3.87 (s, 3H), 2.96 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (CD_2Cl_2 , 100 MHz, 298 K): δ 164.74, 157.98, 150.58, 149.30, 137.99, 136.51, 129.32, 124.57, 123.39, 115.67, 109.77, 104.85, 84.92, 56.32, 31.22; HRMS: (ESI) calcd. for $\text{C}_{15}\text{H}_{14}\text{IN}_2\text{NaOS}$ $[\text{M}+\text{Na}]^+$ 418.9691 found 418.9680.

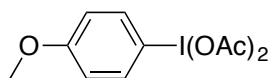
2-(4-(*N*-*tert*-Butyloxycarbonyl-3-iodo-*N*-methyl)phenyl)-6-methoxybenzothiazole (14):



2-(3-Iodo-4-(methylamino)phenyl)-6-methoxybenzothiazole (1.43 g, 3.60 mmol) was dissolved in 25 mL THF. Dimethylamino pyridine (1.32 g, 10.80 mmol) and triethylamine (1.5 mL, 10.80 mmol) were added. Di-*tert*-butyl dicarbonate (4.71 g, 21.60 mmol) was added in portions with stirring. The solution was stirred for 3 days, under N_2 . THF was removed in *vacuo*. The oily solid was dissolved in minimal dichloromethane

and precipitated with 10% diethyl ether in hexanes and filtered. The filtrate was reduced *in vacuo* and chromatographed on silica (deactivated with triethylamine/hexanes (5:95 v/v)) with triethylamine/ethyl acetate/hexanes (0.5:15:84.5 v/v). The crude solid was recrystallized from room temperature ethyl acetate/ether/hexanes, gradually chilling to -20 °C, to yield a white solid (1.25 g, 69.9%). [Note: two rotamers are visible due to restricted rotation of the carbamate bond] ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.50 (d, *J* = 1.9 Hz, 1H), 7.99 (br d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.11 (dd, *J* = 9.0 Hz, *J* = 2.5 Hz, 1H), 3.86 (s, 3H), 3.13 (br s, NCH₃ rotomer), 3.10 (br s, NCH₃ rotomer), 1.52 (br s, *tert*-butyl rotomer), 1.33 (br s, *tert*-butyl rotomer); ¹³C NMR (CD₃CN, 100 MHz, 298 K): δ 163.40, 159.25, 154.49, 149.45, 138.17, 137.81, 134.94, 130.17, 129.07, 124.78, 117.14, 105.47, 100.95, 80.97, 56.62, 36.82, 28.54, 28.17; HRMS: (ESI) calcd. for C₂₀H₂₁IN₂NaO₃S [M+Na]⁺ 519.0215 found 519.0219.

Bis(acetoxy)iodoanisole (15):

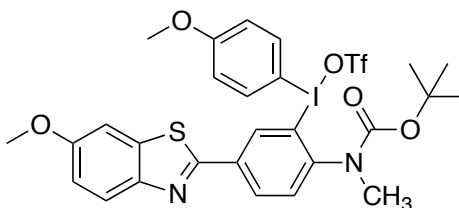


Sodium periodate (11.000g, 51.5 mmol) and sodium acetate (9.000 g, 110.0 mmol) were added to a 100 mL Schlenk storage tube with a stirbar. Acetic acid (50 mL) and acetic anhydride (7.5 mL) were added. 4-iodoanisole (sublimed under vacuum) (11.700 g, 50.0 mmol) was suspended in 25 mL acetic acid and added to the tube with stirring. The tube was sealed and heated to 115 °C for 2.5 hours, stirring vigorously. The mixture was cooled to room temperature and diluted with water (300 mL) and dichloromethane (100

mL). The layers were separated and the aqueous layer was extracted twice with dichloromethane (100 mL). The combined organic layers were dried over sodium sulfate and dichloromethane was removed *in vacuo*. The pale yellow oil was diluted with 200 mL hexanes, triturated, and sonicated until the oil had solidified. The mixture was filtered and the solid was triturated twice with hexanes. The solid was transferred to a 250 mL Schlenk flask along with 100 mL hexanes and 1 mL acetic acid. The mixture was heated to 35 °C under vacuum overnight to yield a colorless solid (16.139 g, 91.7%). ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.05 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 3H), 1.90 (s, 6H); ¹³C NMR (CD₃CN, 100 MHz, 298 K) δ 177.7, 163.7, 138.7, 118.0, 112.0, 56.8, 20.8; HRMS: (HRFAB) calcd. for C₁₄H₁₃NO₄I [M-2OAc+(3-NBA)]⁺ 385.9889 found 385.9885.

K. P. Landge, K. S. Jang, S. Y. Lee, D. Y. Chi, *J. Org. Chem.* **2012**, 77, 5705.

(2-(*N*-*tert*-Butyloxycarbonyl-*N*-methyl)amino-5-(6-methoxybenzothiazolyl))(4-methoxyphenyl)iodonium triflate (16):

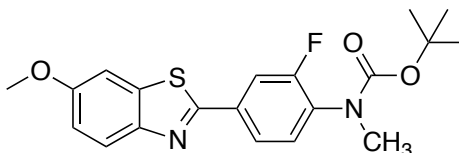


In a nitrogen charged glovebox, 2-(3-iodo-4-(*N*-*tert*-butyloxycarbonyl-*N*-methyl)phenyl)-6-benzothiazole (550.1 mg, 1.11 mmol) was dissolved in 5 mL dry THF in a flame-dried 50 mL Schlenk tube, chilled to -78 °C, and *i*PrMgCl (2.0 M in THF, 1.1 mL, 2.22 mmol)

was added dropwise, with stirring. The solution was stirred for 5 minutes, and transferred by cannula to another 50 mL flame-dried Schlenk tube, containing bis(acetoxy)iodoanisole (1.17 g, 3.33 mmol) in 10 mL dry THF, at -78 °C. The solution was stirred for 15 minutes at -78 °C and allowed to warm slowly to room temperature overnight, in the dark. The solution was concentrated in *vacuo* and diluted with 15 mL methanol. Sodium triflate (1.91 g, 11.1 mmol) was dissolved in 10 mL water/methanol (1:2, v/v) and added dropwise, with vigorous stirring. The solution was stirred vigorously, in the dark, for 30 minutes, concentrated in *vacuo* to remove methanol, and extracted three times with dichloromethane. The organic layers were dried over sodium sulfate and solvent was removed in *vacuo*. The crude oil was triturated, using sonication, with hexanes, and decanted. The solid was sonicated in 15 mL ethyl acetate, chilled to 0 °C, and filtered. The solid was dissolved in acetonitrile, and reduced to an oil *in vacuo*. The oil was dissolved in 8 mL acetonitrile and added to 100 mL methyl *tert*-butyl ether, with stirring. The solution was stirred for 5 minutes and then left undisturbed for 1 hour, as precipitate slowly begins to form. The mixture was cooled gradually to -20 °C, filtered, and washed with cold methyl *tert*-butyl ether. The solid was dissolved in acetonitrile/water (90:10 v/v) and passed through a column of Amberlite-IRA 400 ion exchange resin (previously conditioned with sodium triflate). Acetonitrile was removed *in vacuo*. Water was removed by addition of acetonitrile and removal *in vacuo*, repeated three times. The oil was dissolved in 8 mL acetonitrile and added to 100 mL methyl *tert*-butyl ether, with stirring. The solution was stirred for 5 minutes and then left undisturbed for 1 hour, as precipitate slowly begins to form. The mixture was cooled slowly to -20 °C,

filtered, and washed with cold methyl *tert*-butyl ether. The colorless solid was dried *in vacuo* (0.188 g, 22.5%). ^1H NMR (CD_3CN , 700 MHz, 298 K): δ 8.36 (br s, 1H), 8.22 (dd, $J = 8.5$ Hz, $J = 1.8$ Hz, 1H), 8.08 (d, $J = 9.0$ Hz, 2H), 7.88 (d, $J = 8.9$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 2.5$ Hz, 1H), 7.14 (dd, $J = 8.9$ Hz, $J = 2.5$ Hz, 1H), 7.12 (d, $J = 9.0$ Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.37 (br s, NCH_3), 3.13 (s, 3H from MTBE-complex, 5%), 1.56 (s, 9H), 1.14 (s, 9H from MTBE-complex, 5%); ^{19}F NMR (CD_3CN , 376 MHz, 298 K): δ -79.30; ^{13}C NMR (CD_3CN , 176 MHz, 298 K): δ 164.70, 164.68, 162.39, 159.52, 159.50, 157.92, 149.26, 145.63, 139.57, 137.90, 134.95, 132.55, 127.92, 124.91, 123.06, 121.23, 117.51, 105.50, 103.35, 85.28, 56.83, 56.65, 38.44; HRMS: (ESI) calcd. for $\text{C}_{27}\text{H}_{28}\text{IN}_2\text{O}_4\text{S}$ $[\text{M-OTf}]^+$ 603.0809 found 603.0795.

2-(4-(*N-tert*-Butyloxycarbonyl-3-fluoro-*N*-methyl)phenyl)-6-benzothiazole (17):



In a nitrogen-charged glove box, (2-(*N-tert*-butyloxycarbonyl-*N*-methyl)amino-5-(6-methoxybenzothiazolyl))(4-methoxyphenyl)iodonium triflate (10.0 mg, 0.013 mmol) was dissolved in 0.6 mL acetonitrile- d_3 in an NMR tube fitted with a Teflon screw cap closure. 0.1 mL aliquot (0.0034 mmol, 0.25 eq.) of a stock solution of tetramethyl ammonium fluoride (3.2 mg, 0.034 mmol) in 1.0 mL acetonitrile- d_3 was added. ^1H - and ^{19}F -NMR were acquired and the solvent was removed *in vacuo*. In a nitrogen-charged glove box, dry benzene- d_6 (0.6 mL) was added and the tube was heated to 60 °C for 1 hour in the dark (0.0028 mmol product, 82.8% yield, by internal ^1H -NMR standard).

Solvent was removed *in vacuo*, and the crude oil was chromatographed on silica (deactivated with triethylamine/hexanes (5:95 v/v)) with ethyl acetate/hexanes (20:80 v/v) to yield a pale yellow oil. The product was crystallized from boiling hexanes, cooled to 0 °C, filtered, and washed with cold hexanes to yield a colorless solid (0.7 mg, 54.3%).

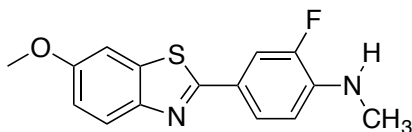
Alternate method: In a nitrogen-charged glove box, (2-(*N*-*tert*-butyloxycarbonyl-*N*-methyl)amino-5-(6-methoxybenzothiazolyl))(4-methoxyphenyl)iodonium triflate (8.0 mg, 0.010 mmol) was dissolved in acetonitrile- d_3 and a 0.1 mL aliquot (0.0025 mmol) of a stock solution of tetramethyl ammonium fluoride (2.6 mg, 0.028 mmol) in 1.0 mL acetonitrile- d_3 was added. The solution was transferred to an NMR tube fitted with a Teflon screw cap closure, ^1H - and ^{19}F -NMR were acquired, and the solvent was removed *in vacuo*. In a nitrogen-charged glove box, a solution of acetonitrile in benzene- d_6 (10% v/v) was added. The NMR tube was heated, in the dark, at 100 °C for 10 minutes. Product formation was confirmed, and found to be quantitative, by ^1H and ^{19}F -NMR.

Alternate method: In a 25 mL round bottom flask 2-(3-fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (9.9 mg, 0.0343 mmol) was dissolved in 1 mL THF. Dimethylamino pyridine (13.4 mg, 0.103 mmol) and triethylamine (15.3 μL , 0.137 mmol) were added. Di-*tert*-butyl dicarbonate (48.0 mg, 0.206 mmol) was added with stirring. The solution was stirred for 2 days, under N_2 . THF was removed *in vacuo*. The crude oil was chromatographed on silica (deactivated with triethylamine/hexanes (5:95

v/v)) with triethylamine/ethyl acetate/hexanes (1:10:89 v/v) to yield a waxy solid (8.8 mg, 66.0%).

^1H NMR (CD_3CN , 400 MHz, 298 K): δ 7.92 (d, $J = 9.0$ Hz, 1H), 7.85 (dd, $J = 8.3$ Hz, $J = 1.9$ Hz, 1H), 7.83 (dd, $J = 8.3$ Hz, $J = 1.9$ Hz, 1H), 7.56 (d, $J = 2.6$ Hz, 1H), 7.45 (dd, $J = 8.5$ Hz, $J = 8.0$ Hz, 1H), 7.14 (dd, $J = 9.0$ Hz, $J = 2.6$ Hz, 1H), 3.88 (s, 3H), 3.27 (br s, NCH_3 rotomer), 3.20 (br s, NCH_3 rotomer), 1.46 (br s, *tert*-butyl rotomer), 1.41 (br s, *tert*-butyl rotomer); ^{19}F NMR (CD_3CN , 376 MHz, 298 K): δ -120.89 (br s, 1F); HRMS: (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{FN}_2\text{NaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 411.1155 found 411.1161.

2-(3-Fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (18):

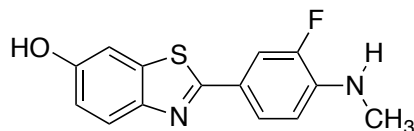


In a nitrogen-charged glove box, 6-methoxybenzothiazole (70.1 mg, 0.425 mmol), 2-fluoro-4-bromo-*N*-methylaniline (as a 50 mol% mixture with 2-fluoro-*N*-methylaniline) (167.7 mg, 1.02 mmol), palladium(II) acetate (4.8 mg, 0.0212 mmol), tri(*tert*-butyl)phosphine (8.6 mg, 0.0425 mmol), and copper(I) bromide (12.2 mg, 0.0849 mmol) were dissolved in 4 mL dry DMF. The mixture was transferred to a small airfree storage tube. Solid cesium carbonate (152.1 mg, 0.467 mmol) was added directly to the tube. The reaction was heated at 150 °C, with stirring, for 4 hours. After cooling to room temperature the mixture was diluted with ether, and washed five times with water. The aqueous layers were extracted three times with ether. The combined organic layers were

washed with brine, dried over sodium sulfate, and filtered. The solvent was removed in *vacuo* and the crude oil was chromatographed on silica with ethyl acetate/hexanes (15:85 v/v). The crude solid was dissolved in boiling hexanes, filtered hot, cooled to 0 °C, and filtered to yield a pale yellow solid (47.1 mg, 41.0%). ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 7.79 (d, *J* = 8.9 Hz, 1H), 7.67 (m, 2H), 7.48 (d, *J* = 2.6 Hz, 1H), 7.07 (dd, *J* = 2.6 Hz, *J* = 8.9 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 9.0 Hz, 1H), 4.95 (br s, NH), 3.85 (s, 3H), 2.88 (d, *J* = 5.2 Hz, 3H); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K): δ -139.57 (ddd, *J* = 11.9 Hz, *J* = 8.2 Hz, *J* = 2.5 Hz, 1F); ¹³C NMR (CD₃CN, 176 MHz, 298 K): δ 165.95, 158.55, 152.77, 151.41, 149.63, 141.54, 141.47, 136.96, 125.52, 123.76, 122.40, 122.36, 116.31, 113.35, 113.23, 111.98, 111.96, 105.63, 56.55, 56.54, 29.95; HRMS: (ESI) calcd. for C₁₅H₁₃FN₂NaOS [M+Na]⁺ 311.0630 found 311.0642.

Cole, G. B.; Keum, G.; Liu, J.; Small, G. W.; Satyamurthy, N.; Kepe, V.; Barrio, J. R. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6222–6227.

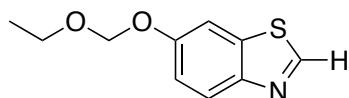
2-(3-Fluoro-4-(methylamino)phenyl)-6-hydroxybenzothiazole (19):



In an oven-baked 25 mL Schlenk flask, 2-(3-fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (25.9 mg, 0.0898 mmol) was dissolved in 1 mL of anhydrous dichloromethane. The solution was chilled in an ice bath and boron tribromide (27.7 μL, 0.269 mmol) was added dropwise. The ice bath was removed and the solution was

stirred, under N₂, in the dark, overnight. Saturate aqueous sodium bicarbonate was carefully added dropwise, until bubbling subsided. 10 mL of methanol/dichloromethane (1:5 v/v) was added. The organic layer was separated and the aqueous layer was extracted twice with 10 mL of methanol/dichloromethane (1:5 v/v). The organic layers were washed twice with saturated aqueous sodium bicarbonate (5 mL). The organic layers were dried over sodium sulfate, and filtered. Solvents were removed *in vacuo*. The crude solid was recrystallized from boiling acetonitrile to yield a pale yellow solid (5.1 mg, 20.7%). ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 7.74 (d, *J* = 8.8 Hz, 1H), 7.66 (m, 2H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.29 (br s, 1H), 6.96 (dd, *J* = 8.7 Hz, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 9.1 Hz, *J* = 8.4 Hz), 4.90 (br s, NH), 2.88 (d, *J* = 5.1 Hz, 3H); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K): δ -139.57 (ddd, *J* = 11.9 Hz, *J* = 8.2 Hz, *J* = 2.5 Hz, 1F); ¹³C NMR (Methanol-d₄ in Acetone-d₆, 176 MHz, 298 K): δ 152.70, 151.34, 141.31, 141.26, 136.91, 125.28, 123.85, 123.78, 122.57, 116.64, 116.28, 113.09, 112.97, 111.78, 111.76, 107.55, 105.37, 56.22, 30.38; HRMS: (ESI) calcd. for C₁₄H₁₁FN₂NaOS [M+Na]⁺ 297.0474 found 297.0488.

Cole, G. B.; Keum, G.; Liu, J.; Small, G. W.; Satyamurthy, N.; Kepe, V.; Barrio, J. R. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6222–6227.

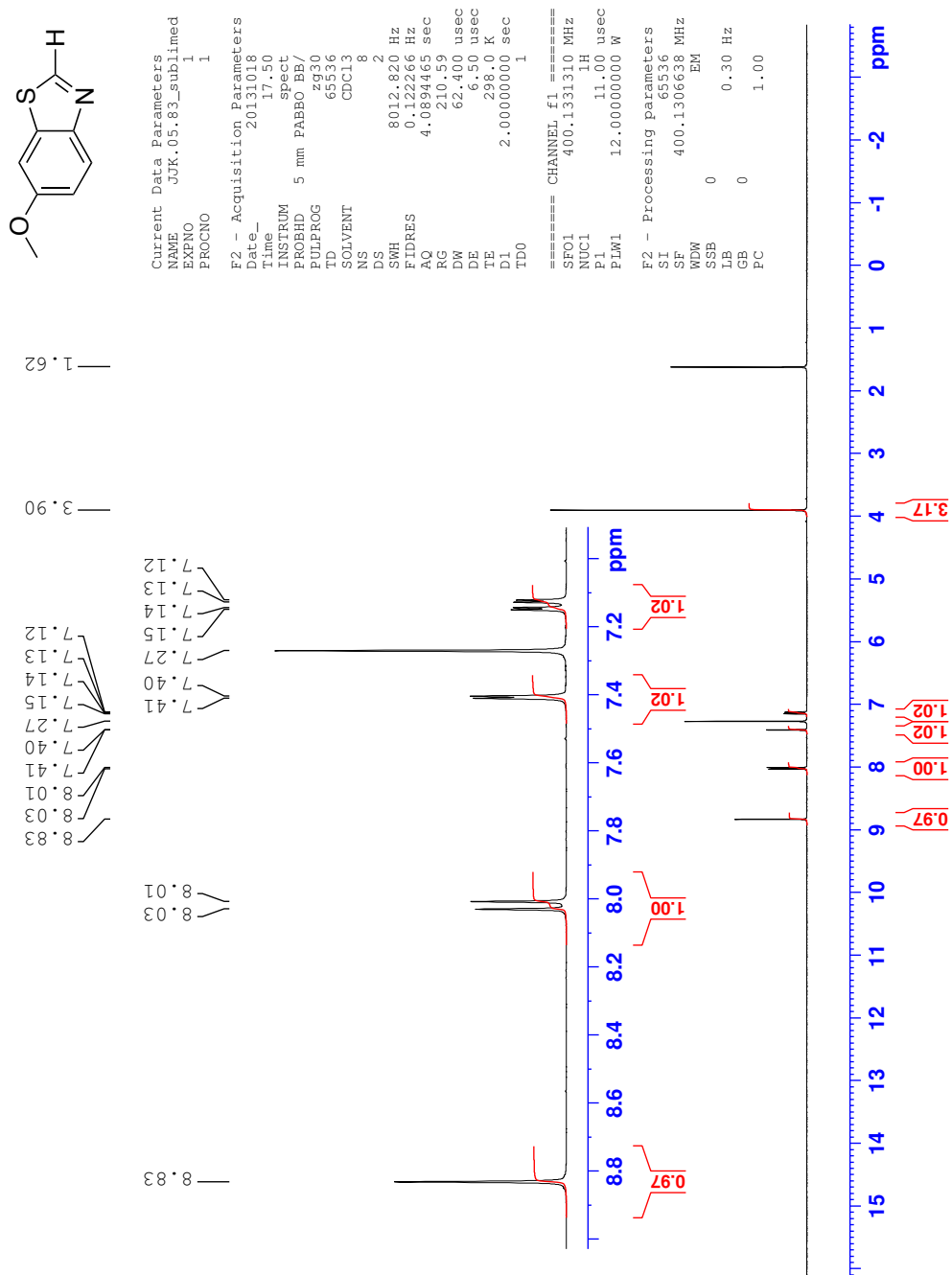
6-(Ethoxymethoxy)benzothiazole (21):

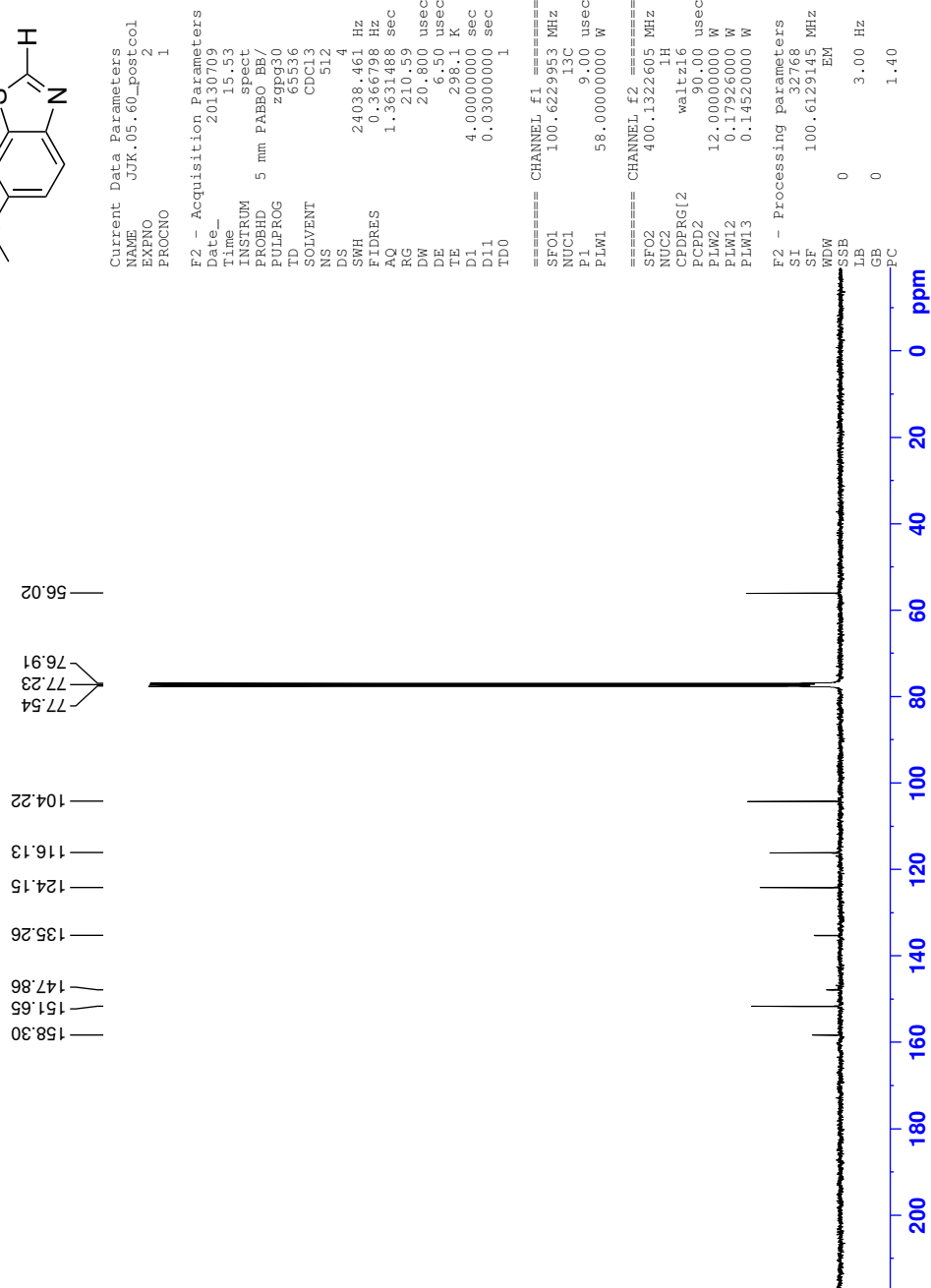
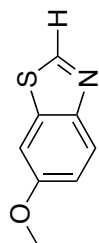
In an oven-baked 100 mL Schlenk flask, under N₂, 6-methoxybenzothiazole (1.00g, 6.053 mmol) was dissolved in dichloromethane (20 mL) with stirring. The solution was cooled to 0 °C ice bath and boron tribromide (1.7 mL, 18.16 mmol) was added by syringe, dropwise. The ice bath was removed and the mixture was stirred, under N₂, overnight. The reaction was quenched, with 0.5 mL deionized water, then carefully neutralized to pH 7 with saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extract twice with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. Dichloromethane was removed *in vacuo* and the solid was dried under high dynamic vacuum. A portion of the solid (500 mg, 3.307 mmol) was dissolved in dry tetrahydrofuran (10 mL), in a 100 mL Schlenk flask, and chilled to 0° C with an ice bath. Under N₂, powdered sodium hydride (83.3 mg, 3.472 mmol) was added in portions. The mixture was stirred for 15 minutes before chloromethyl ethyl ether (0.4 mL, 3.968 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was diluted with ether. The organic layer was separated and washed four times with 2.0 M aqueous sodium hydroxide (to remove any residual starting material) and once with brine. The organic layer was dried over sodium sulfate, filtered, and solvents were removed in *vacuo* to yield a mostly colorless solid (93.5 mg, 13.5%). ¹H NMR (CD₃CN, 300 MHz, 298 K):

δ 8.94 (s, 1H), 7.96 (d, $J = 8.9$ Hz), 7.68 (d, $J = 2.3$ Hz, 1H), 7.20 (dd, $J = 8.9$ Hz, $J = 2.3$ Hz, 1H), 5.28 (s, 2H), 3.71 (q, $J = 7.1$ Hz, 2H), 1.16 (t, $J = 7.1$ Hz, 3H); HRMS: (ESI) calcd. for $C_{10}H_{11}NNaO_2S$ $[M+Na]^+$ 232.0408 found 232.0426.

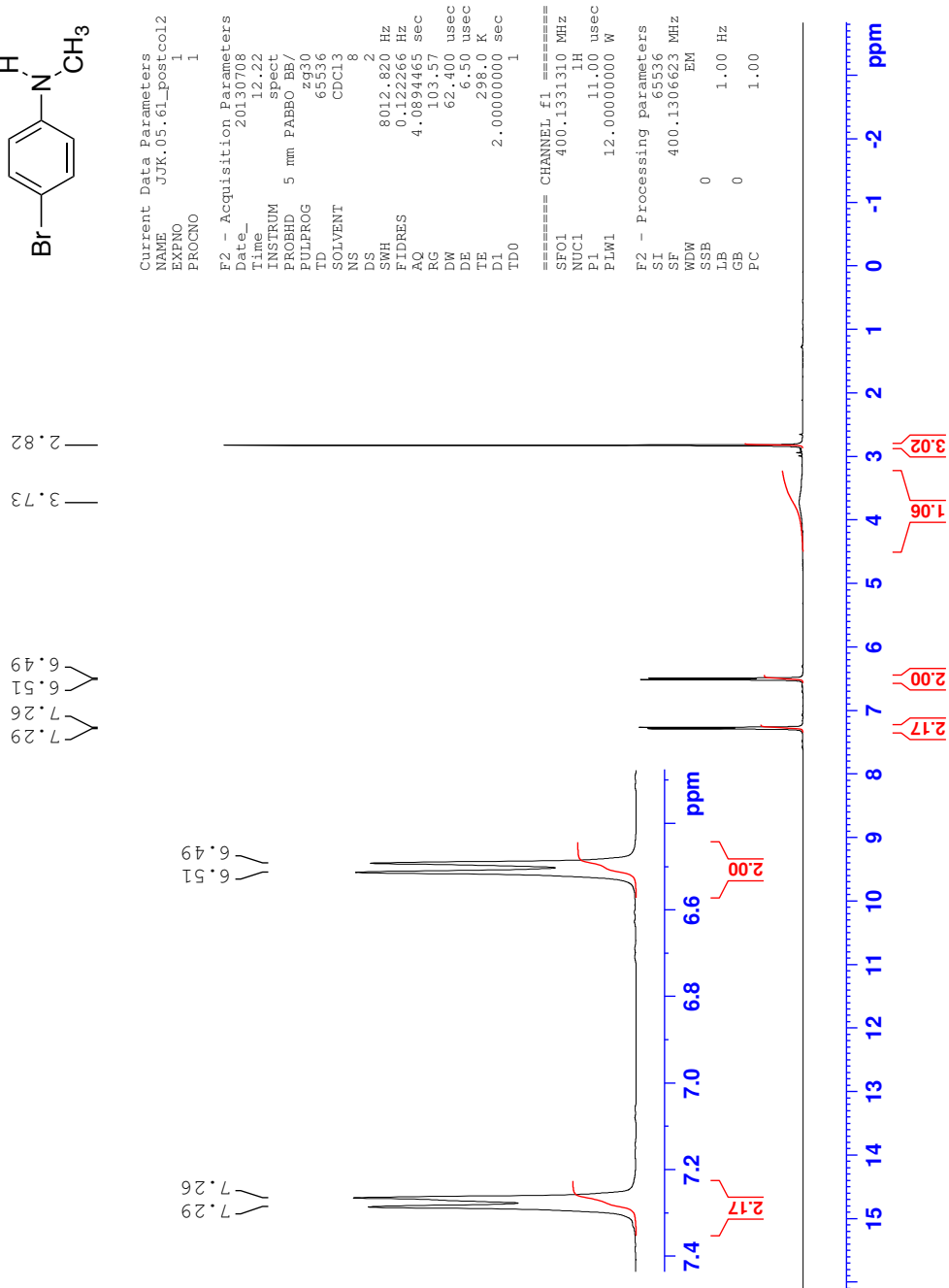
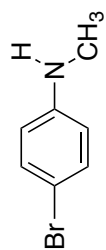
1.6 NMR Spectra

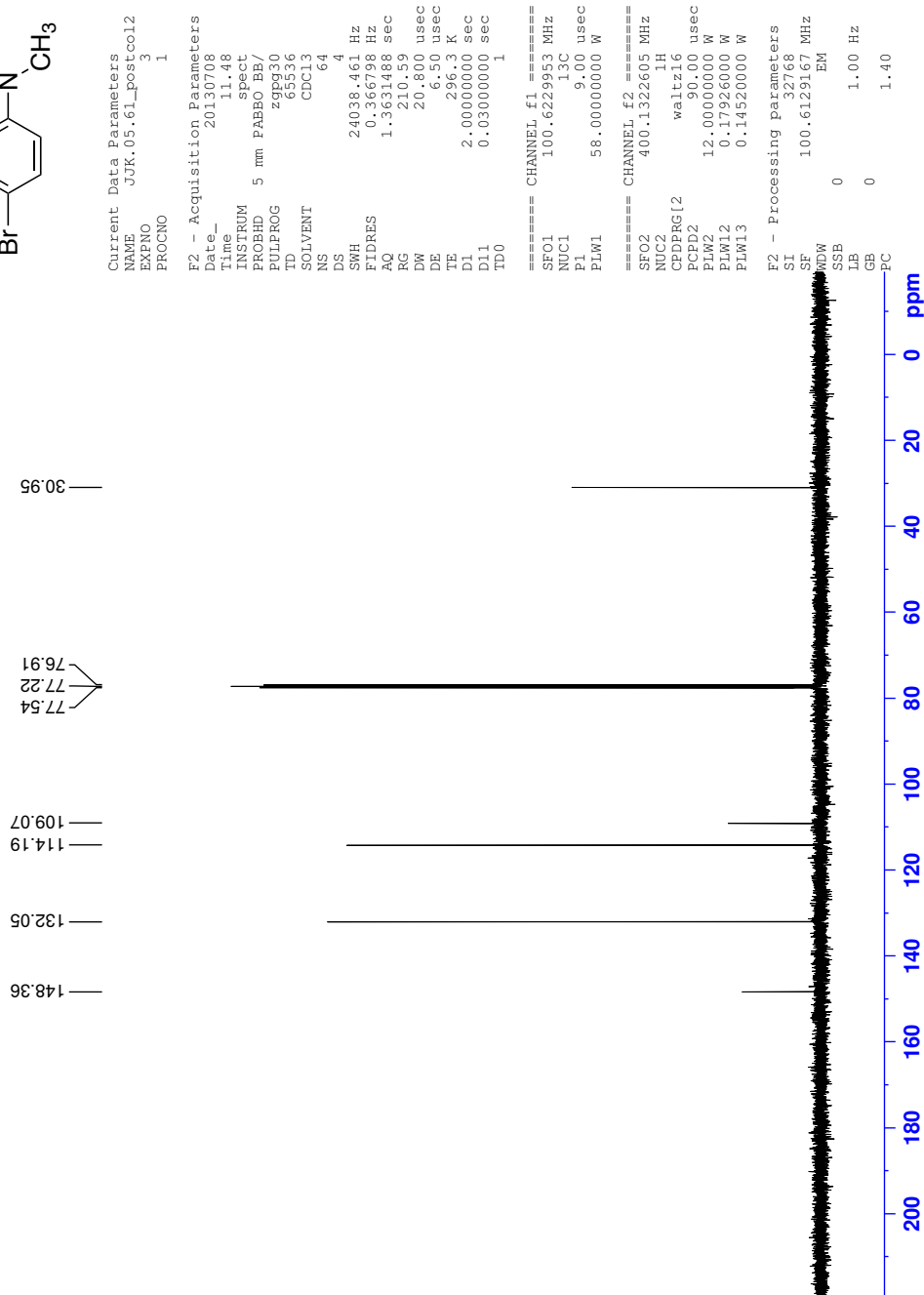
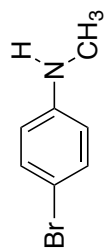
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of 6-methoxybenzothiazole (7)



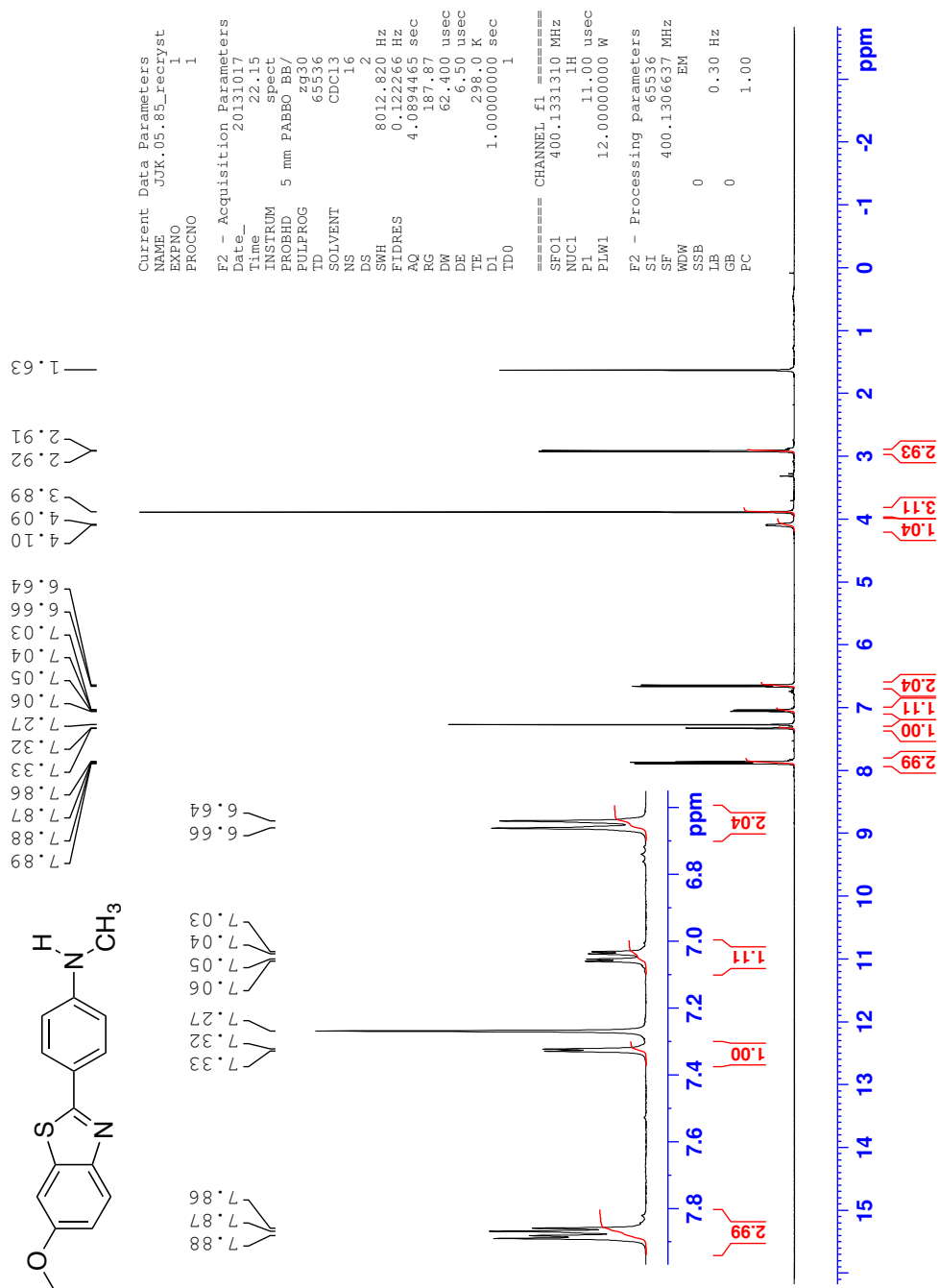
^{13}C NMR (CDCl_3 , 100 MHz, 298 K) spectrum of 6-methoxybenzothiazole (7)

^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of 4-bromo-N-methylaniline (**9**)

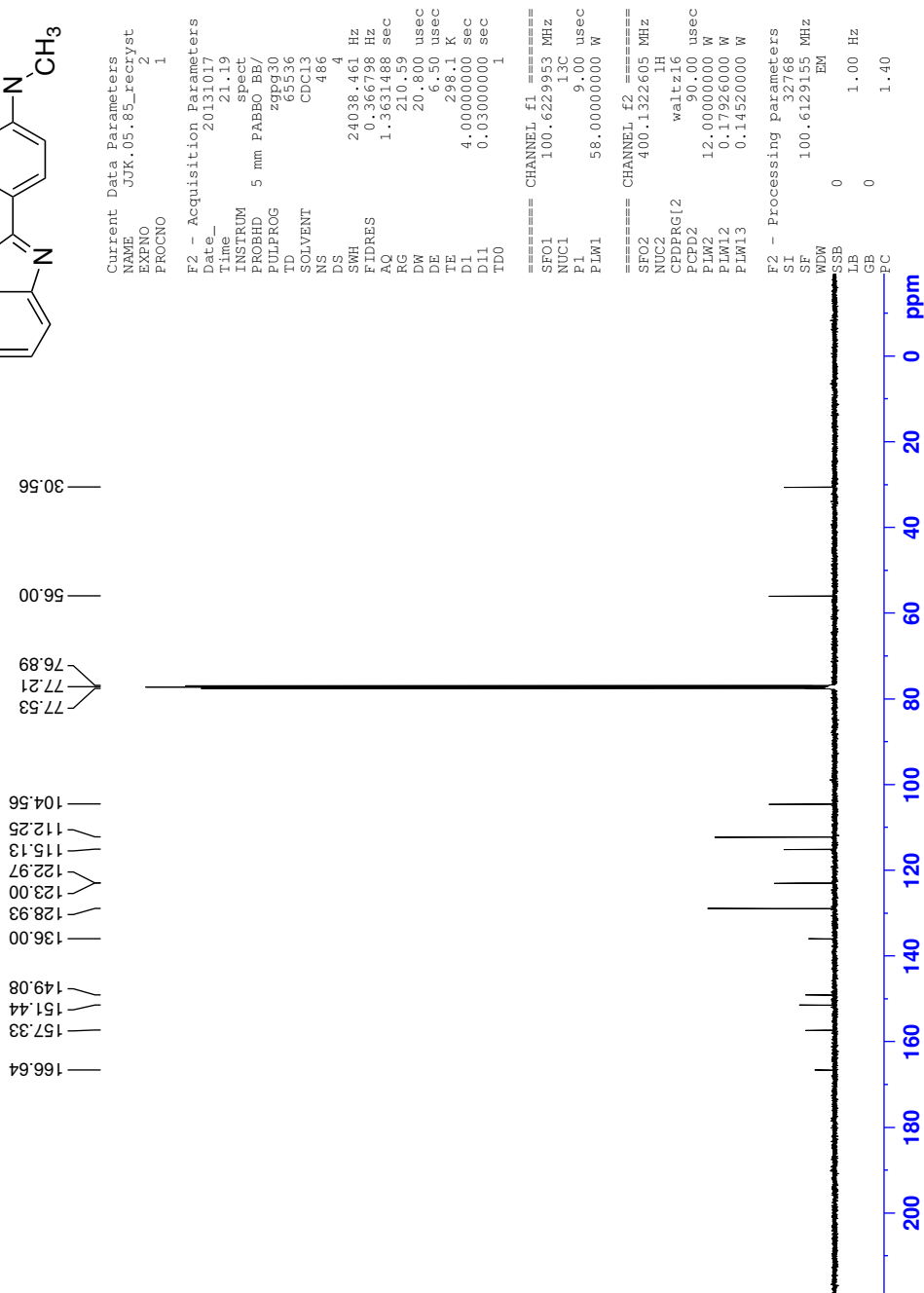
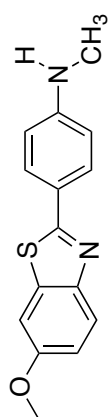


^{13}C NMR (CDCl_3 , 100 MHz, 298 K) spectrum of 4-bromo-N-methylaniline (9)

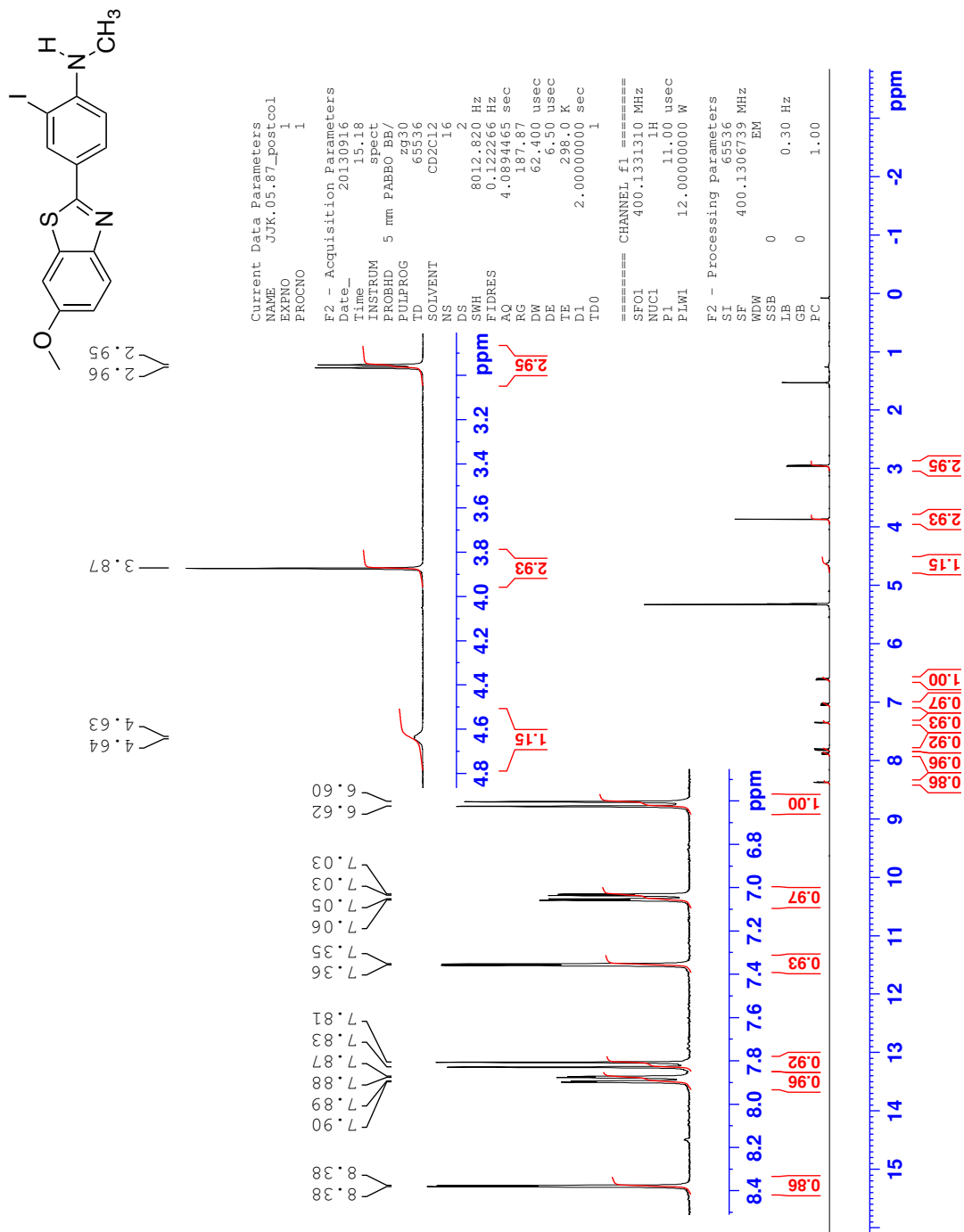
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of 2-(4-(methylamino)phenyl)-6-methoxybenzothiazole (**12**)



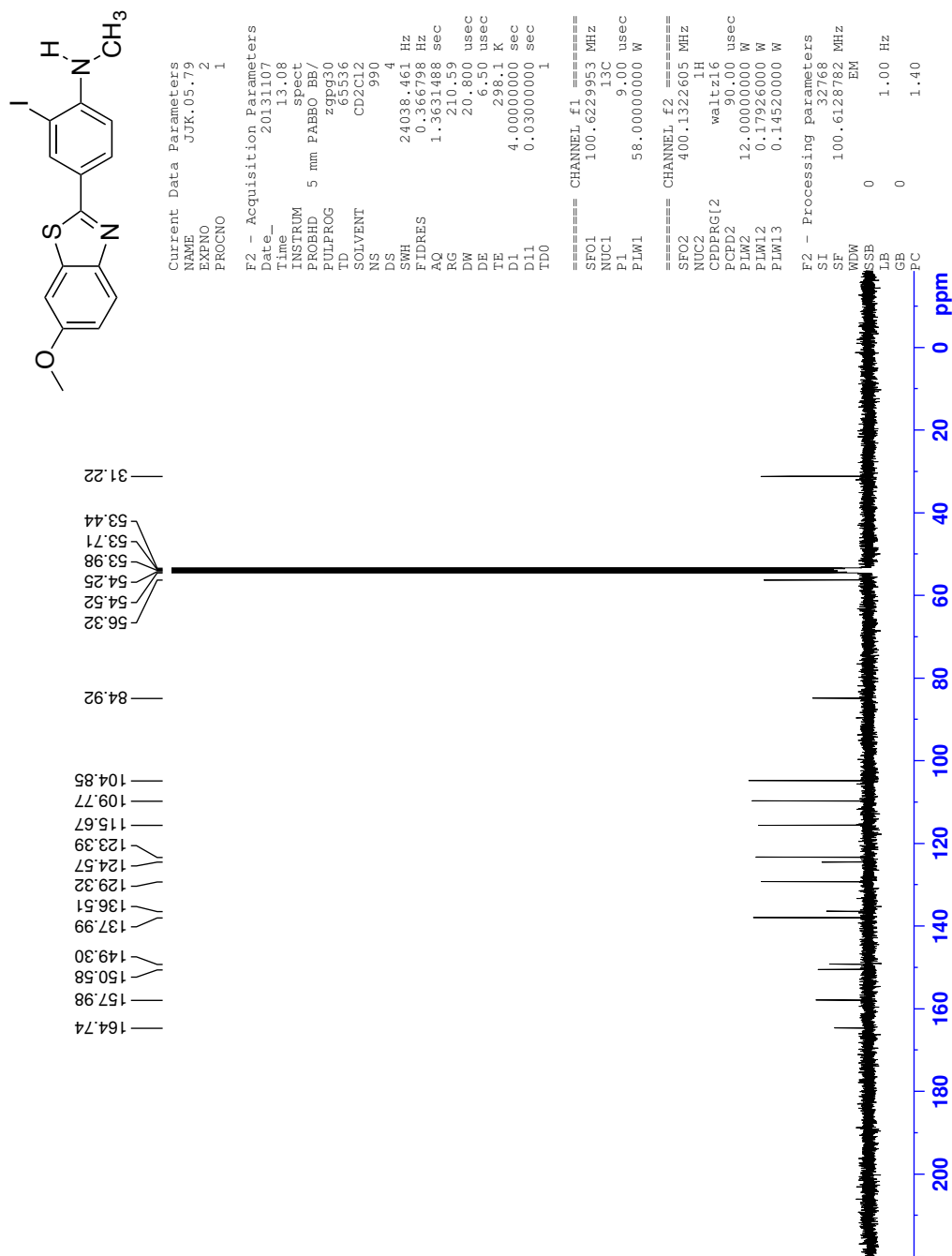
^{13}C NMR (CDCl_3 , 100 MHz, 298 K) spectrum of 2-(4-(methylamino)phenyl)-6-methoxybenzothiazole (**12**)



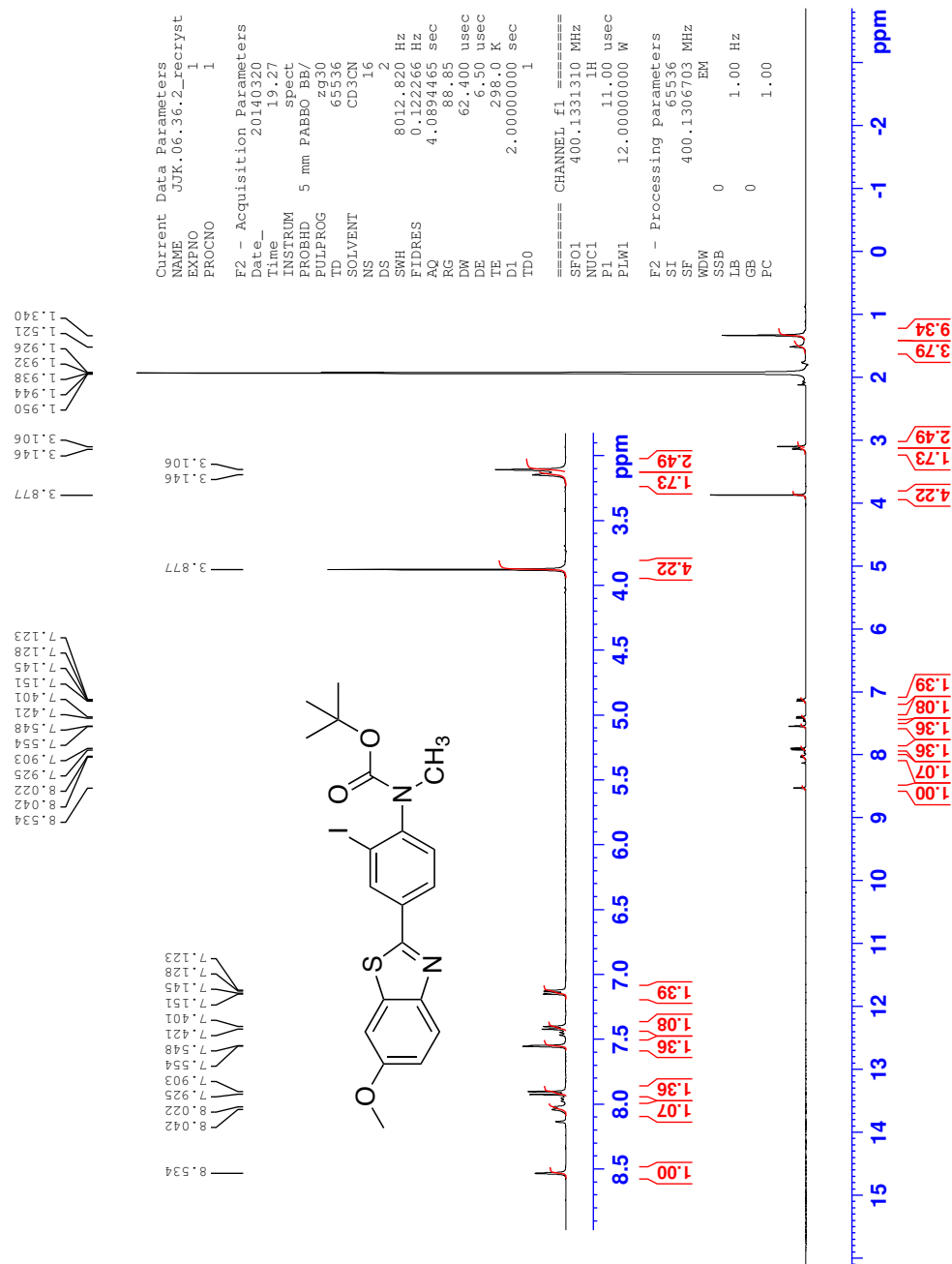
^1H NMR (CD_2Cl_2 , 400 MHz, 298 K) spectrum of 2-(3-iodo-4-(methylamino)phenyl)-6-methoxybenzothiazole (**13**)



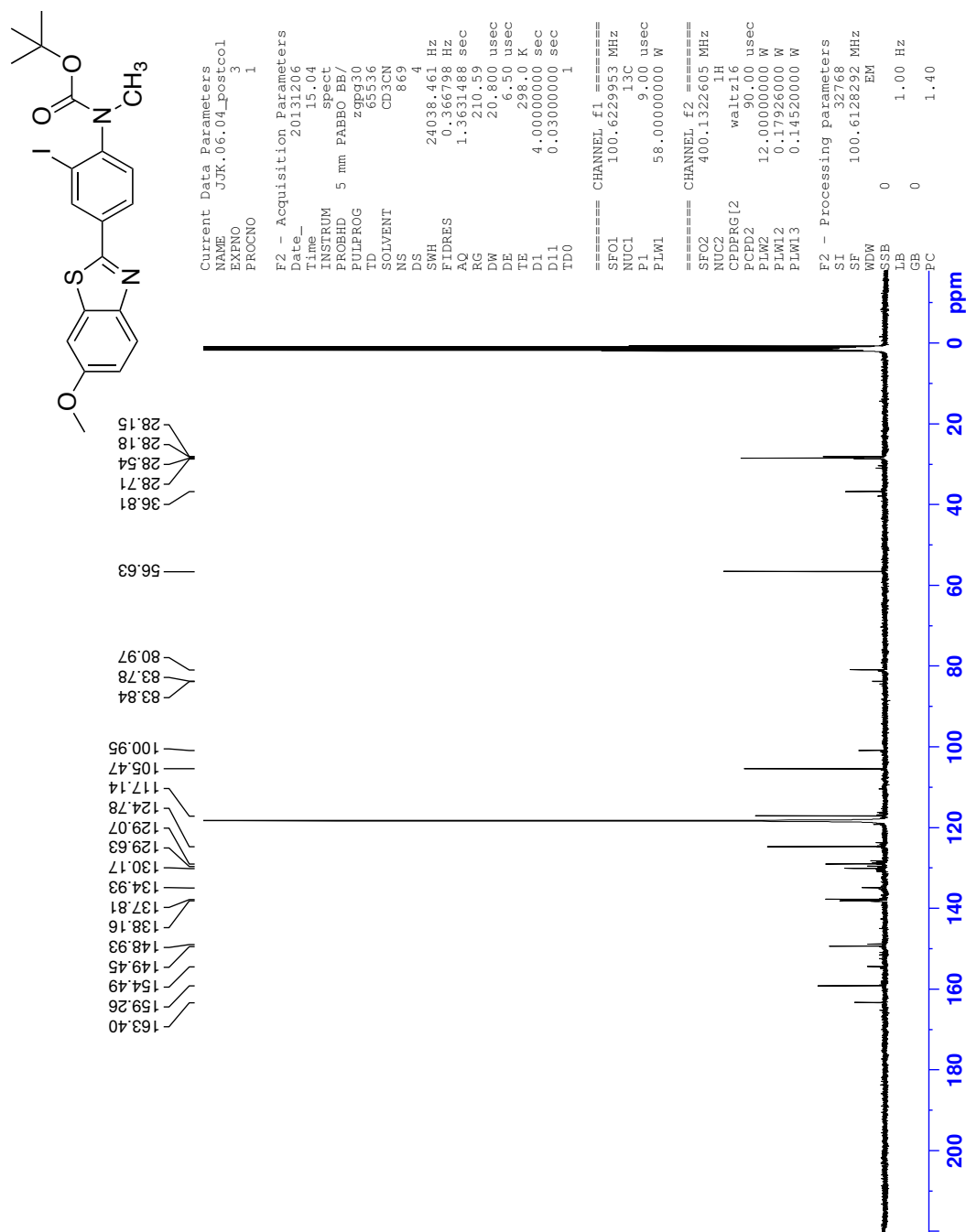
^{13}C NMR (CD_2Cl_2 , 100 MHz, 298 K) spectrum of 2-(3-iodo-4-(methylamino)phenyl)-6-methoxybenzothiazole (**13**)



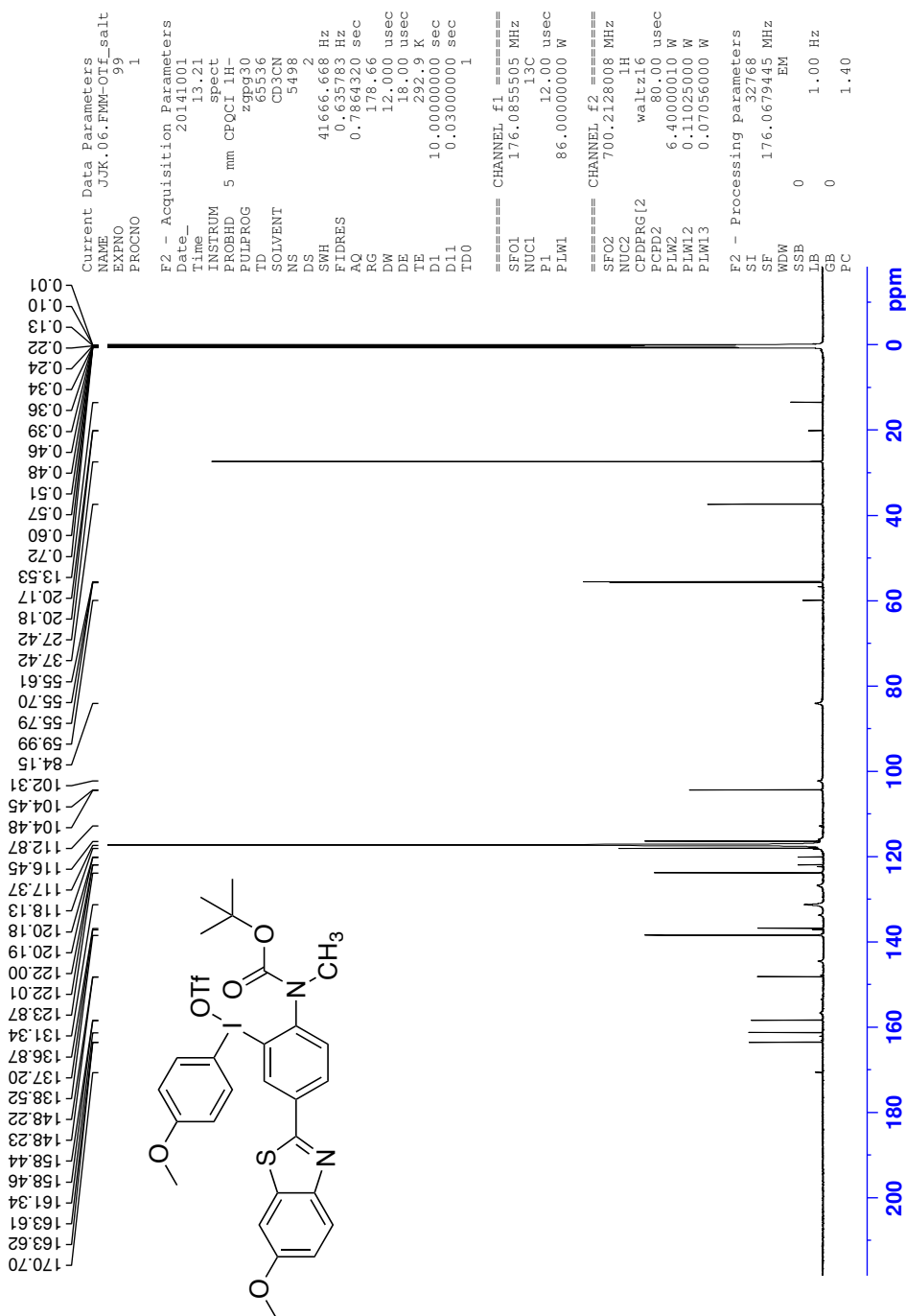
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of 2-(4-(*N*-*tert*-butyloxycarbonyl-3-iodo-*N*-methyl)phenyl)-6-benzothiazole (**14**)



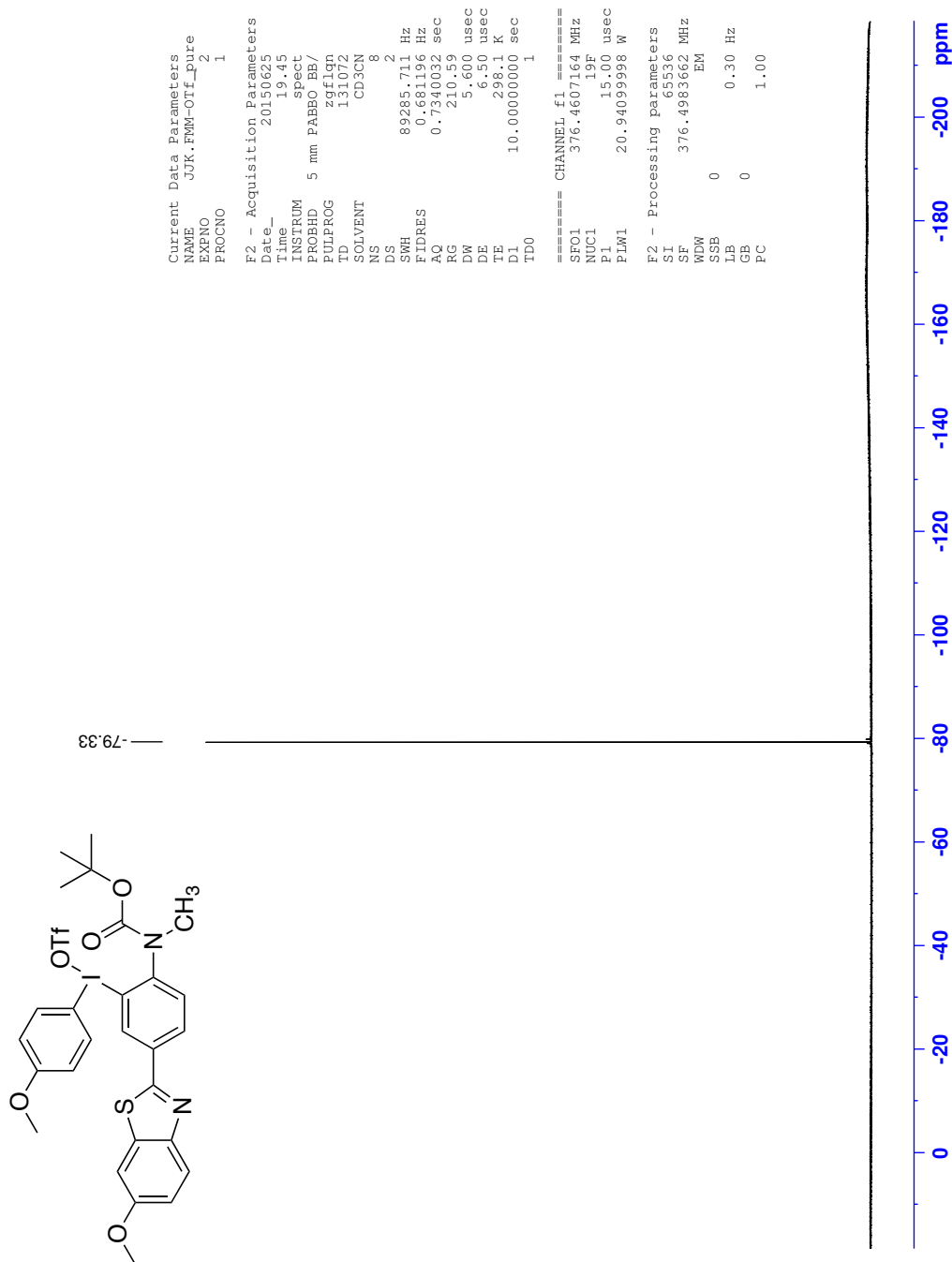
^{13}C NMR (CD_3CN , 100 MHz, 298 K) spectrum of 2-(4-(*N*-*tert*-butyloxycarbonyl-3-iodo-*N*-methyl)phenyl)-6-benzothiazole (**14**)



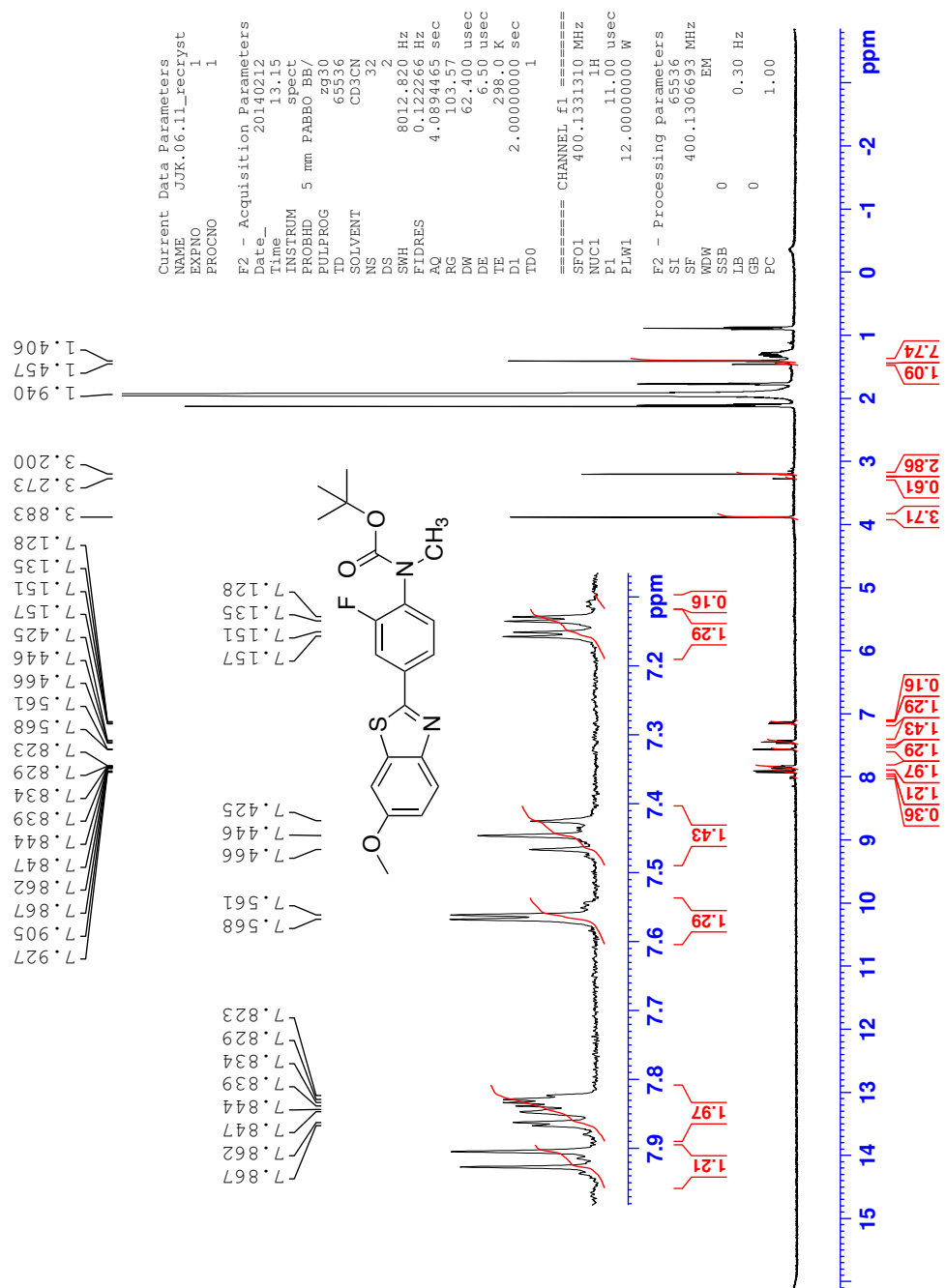
^{13}C NMR (CD_3CN , 176 MHz, 298 K) spectrum of (2-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino-5-(6-methoxybenzothiazolyl))(4-methoxyphenyl)iodonium triflate (**16**)



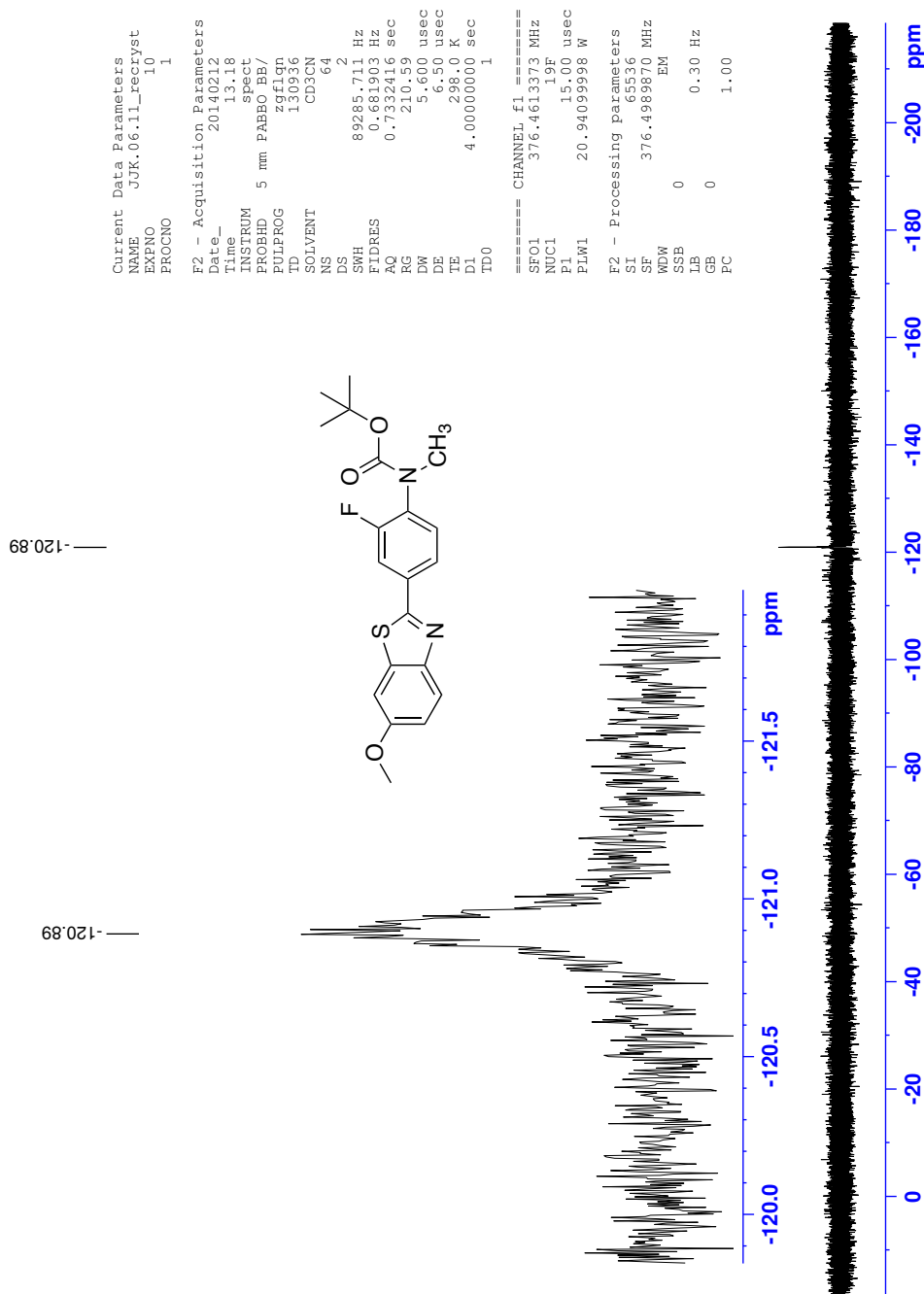
^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of (2-(*N*-*tert*-butyloxycarbonyl-*N*-methylamino-5-(6-methoxybenzothiazolyl))(4-methoxyphenyl)iodonium triflate (**16**)



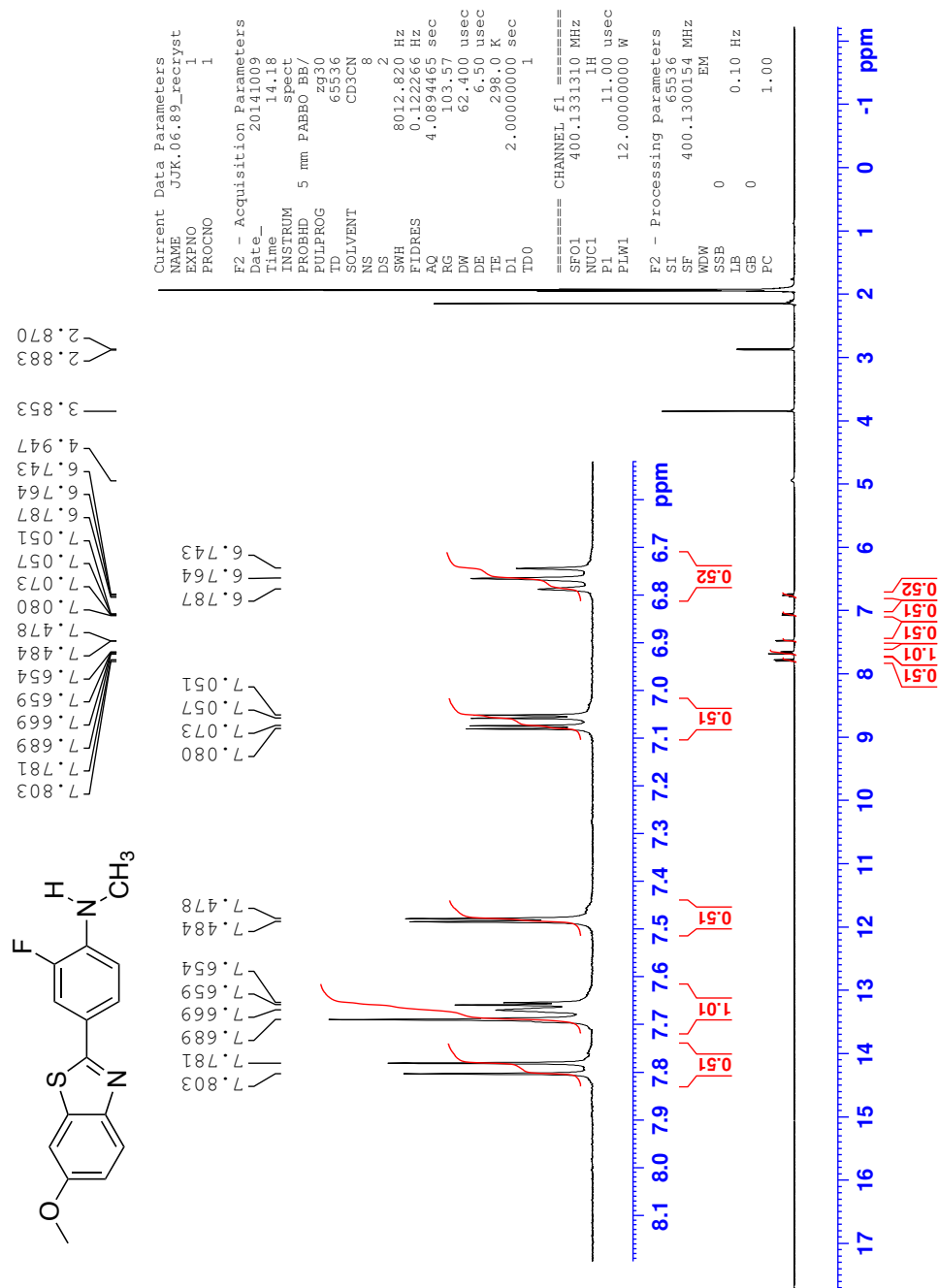
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of 2-(4-(*N*-butyloxycarbonyl-3-fluoro-*N*-methylphenyl)-6-benzothiazole (17)



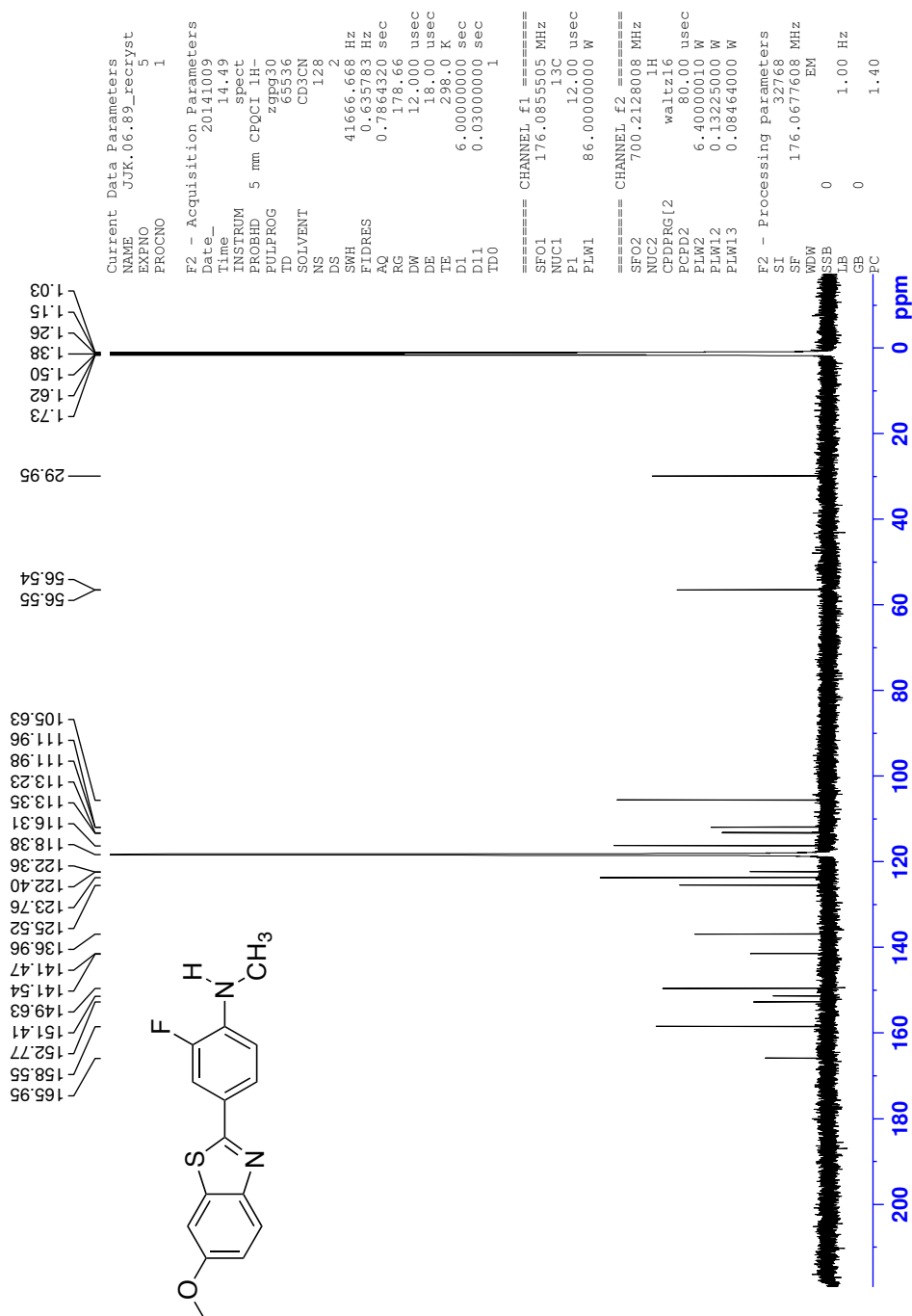
^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of 2-(4-(*N*-butyloxycarbonyl-3-fluoro-*N*-methylphenyl)-6-benzothiazole (17)



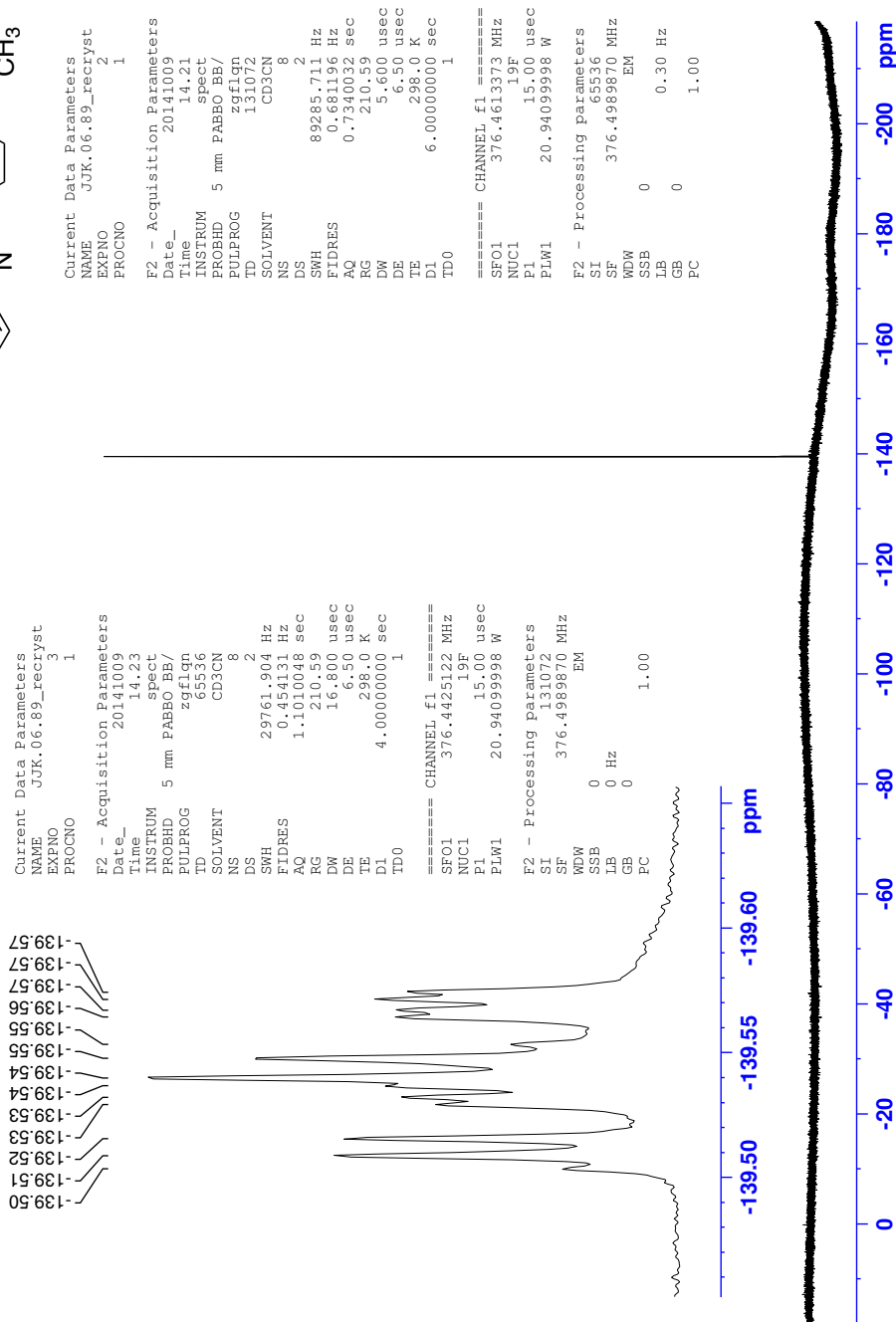
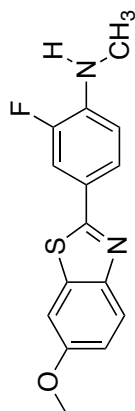
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (**18**)



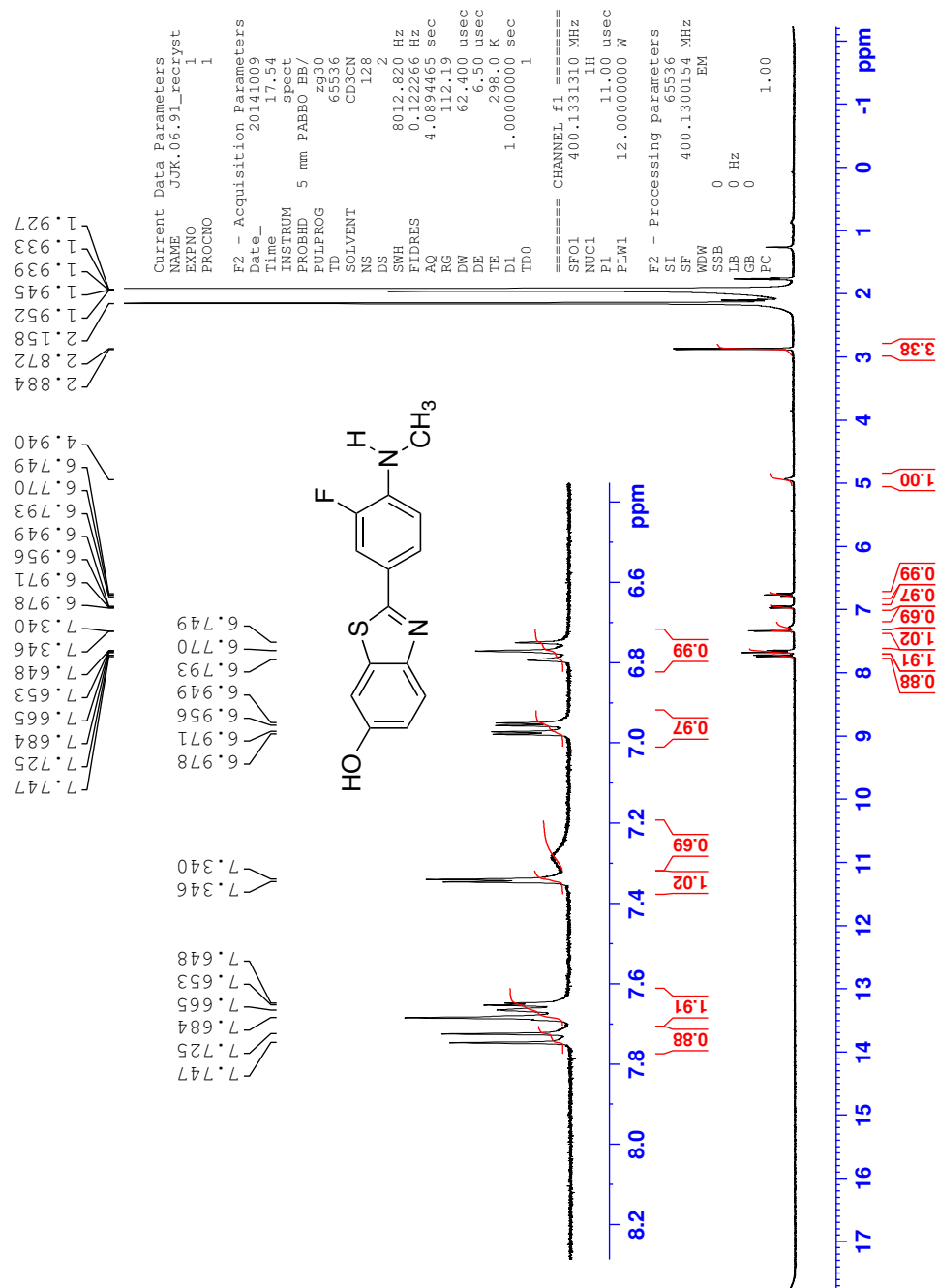
^{13}C NMR (CD_3CN , 176 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (**18**)



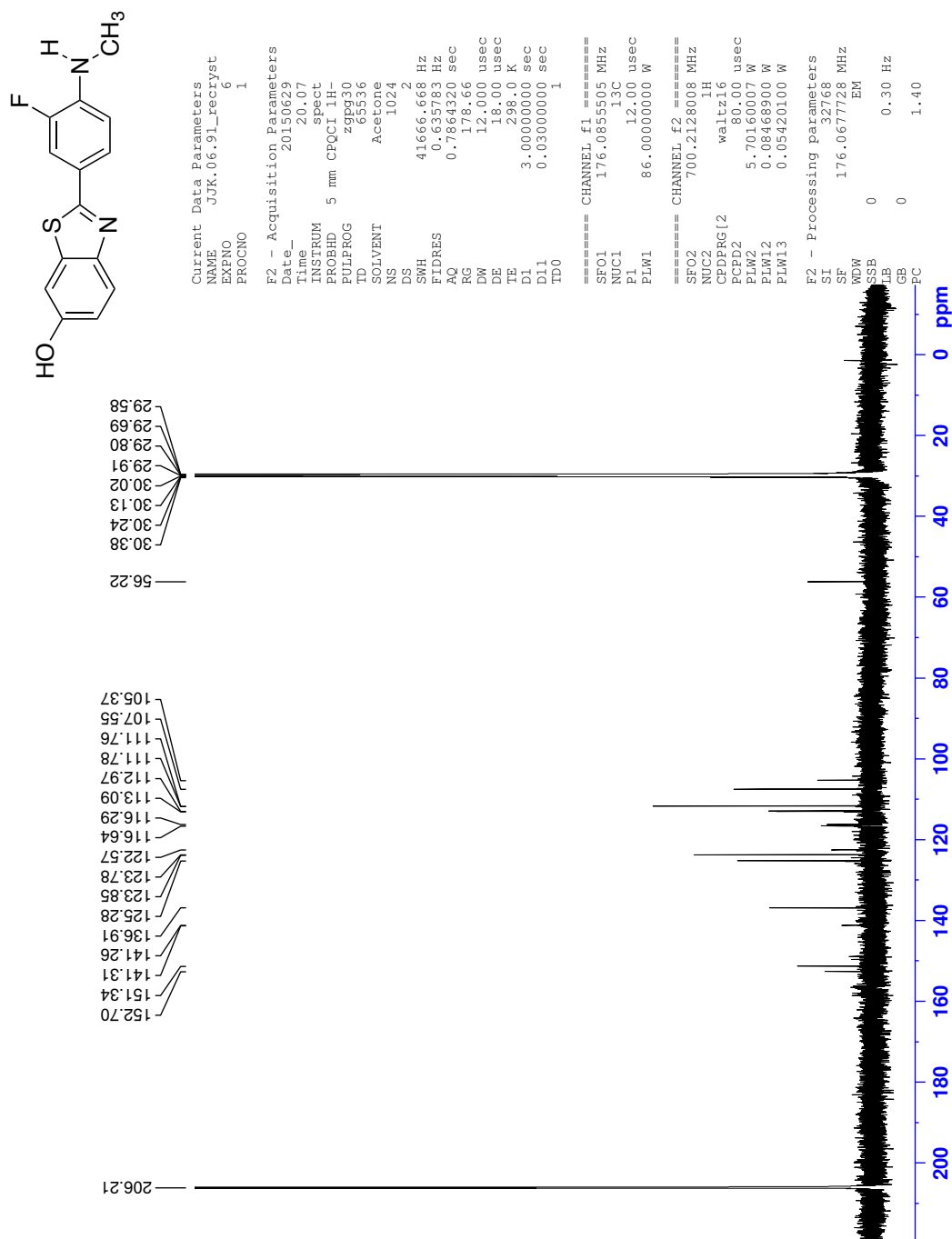
¹⁹F NMR (CD₃CN, 376 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-methoxybenzothiazole (**18**)



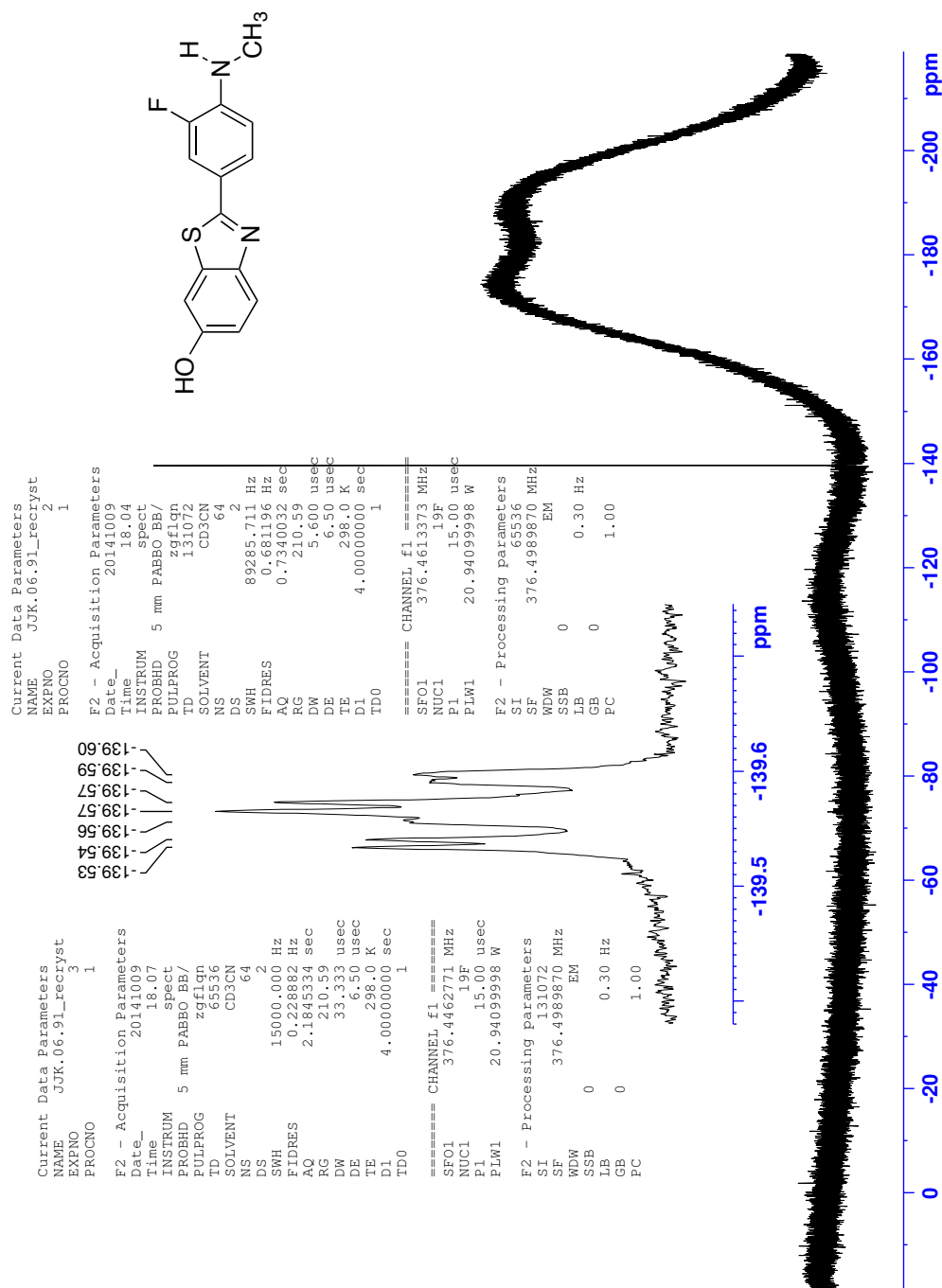
¹H NMR (CD₃CN, 400 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-hydroxybenzothiazole (**19**)



¹³C NMR (Methanol-d₄ in Acetone-d₆, 176 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-hydroxybenzothiazole (**19**)



^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of 2-(3-fluoro-4-(methylamino)phenyl)-6-hydroxybenzothiazole (**19**)

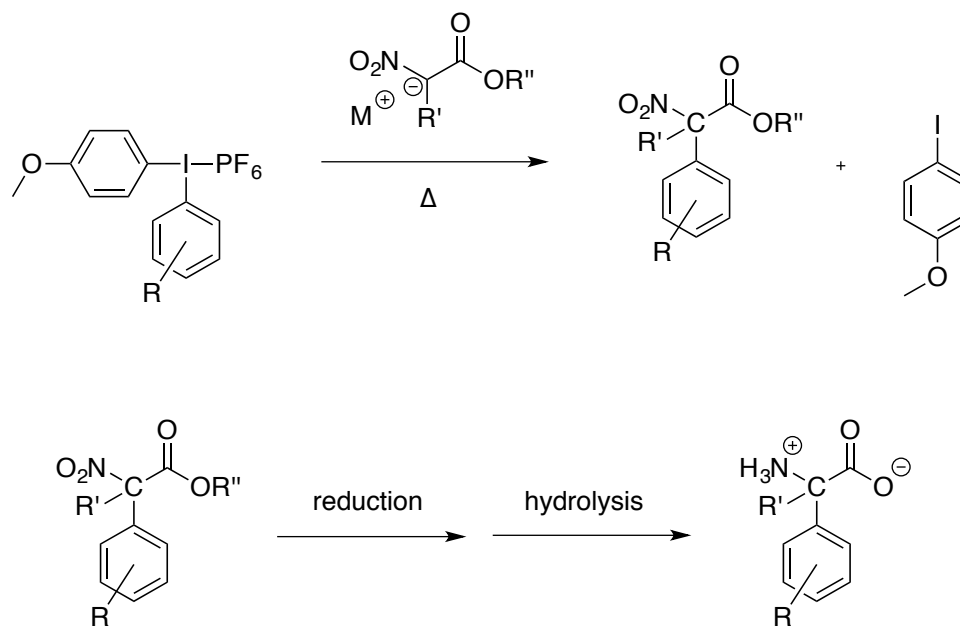


CHAPTER 2

SYNTHESIS OF A VARIETY OF QUATERNARY α -ALKYL α -ARYLAMINO ACIDS

2.1 Introduction

We have utilized hypervalent iodine chemistry to synthesize a variety of fluorinated and iodinated PET radiotracers and radiopharmaceuticals. These compounds can be used to diagnose and monitor diseases such as Parkinson's (L-DOPA), Alzheimer's (Flutemetamol), cancer, and others. Many of the radiotracers we have targeted for cancer diagnostics are amino acids (since tumor cells have a higher uptake and metabolism of amino acids). During this research we have gained an appreciation for the synthesis of amino acids.¹ As we studied the chemistry of hypervalent iodine complexes and continued to develop better methodology we discovered we could use diaryliodonium salts to deliver a variety of functional groups (as anions) to a target arene. Provided the anions were moderately weak soft bases (pKa typically lower than 12),² we could generate a large variety of functionalized arenes. Using stabilized carbon enolates we could generate quaternary α -nitro α -alkyloxycarbonyl arenes that could be reduced and hydrolyzed to the analogous quaternary α -amino acid (Scheme 2.1).



Scheme 2.1: Synthesis of aryl nitro esters and their reduction/hydrolysis

Unlike most naturally-occurring amino acids, which feature a tertiary α -carbon, oxidation pathways that involve abstraction of the proton on the α -carbon are prevented on quaternary non-proteinogenic amino acids.³ They have no enolizable proton, so for enantioenriched amino acids, racemization is not possible. Because of this they show remarkable stability *in vivo*, and can be useful for studying enzyme mechanisms, acting as enzyme inhibitors. They have been studied as metabotropic glutamate antagonists, part of conformationally constrained thrombin inhibitors, selective β_3 adrenergic receptor agonists, sacrificial amine sources for studying dialkylglycine decarboxylase mimics, PLP enzyme inactivators, etc.⁴⁻¹² From a synthetic chemistry perspective these compounds are of interest due to the challenge of constructing functionalized quaternary stereocenters. Finally, in studying the formation of the α -nitro, α -alkyloxycarbonyl

precursors, during thermolysis of diaryliodonium salts, we can gain more insight into the mechanism of hypervalent iodine thermolysis.

2.1.2 Existing Strategies

In general, there is a wide variety of reported routes to quaternary α -amino acids,⁷⁻¹⁹ though synthesis of α -arylated amino acids has historically been challenging.²⁰ The Petasis Reaction, a name reaction to form substituted amines, using an amine, 1,2-diketone, and boronate ester, produces quaternary amino acids (containing substituted amines). Many routes are fairly complex, and involve addition of an aryl or alkyl group as a strong nucleophile (ArMgX, ArLi, etc.) or as an electrophile,¹⁹ often involving heavy metal catalysts (that can be toxic if the products are used *in vivo*) or reactions that can be dangerous, low yielding, or difficult to scale up commercially. Many are of limited scope, some requiring a drastically different synthesis for different amino acids (*i.e.* simultaneously varying the aryl group and the alkyl group requires a new synthesis), or are limited to substituted amines. Demand for quaternary amino acids is high and new methods continue to be developed;¹³⁻¹⁷ for example, a recent development, by Kozłowski and co-workers, involves a tandem α -alkylation (using a Grignard reagent) and α -allylation (using a palladium catalyst), to synthesize α -allyl α -aryl α -amino acids, a previously inaccessible class of quaternary α -amino acids.¹⁸

Our process involves a convergent synthesis, utilizing aryl iodonium salts that are already commercially available (*e.g.* bis(aryl)iodonium hexafluorophosphates) or facile to synthesize.^{1, 21} The alkyl component is also commercially available or facile to

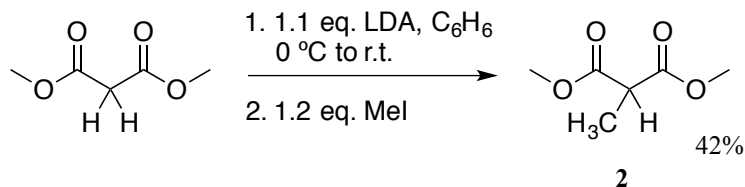
synthesize. Reduction can be done under mild, non-toxic conditions (*e.g.* zinc catalyzed reduction), and ester hydrolysis can be performed under basic or acidic conditions. Over all steps, using commercially available starting materials, our yields average 70%.

Various reactions with diaryliodonium salts and stabilized enolates (*e.g.* diketones, diesters, nitroalkanes) have been reported.^{22,23} Often these routes are plagued with long reaction times, harsh conditions, or small substrate scope. Due to our previous work with diaryliodonium salts²¹ we are able to modify these syntheses and improve reaction times and yields. By switching to less polar solvents and lower temperatures, yields are often improved. Though carbon-carbon bond forming reactions are reported with diesters²² and with nitroalkanes,²³ at the onset of this project no reactions were reporting using nitroesters. Direct arylation of a nitroester would offer a new method for rapidly producing quaternary α -alkyl α -aryl amino acids.

2.2 Results and Discussion

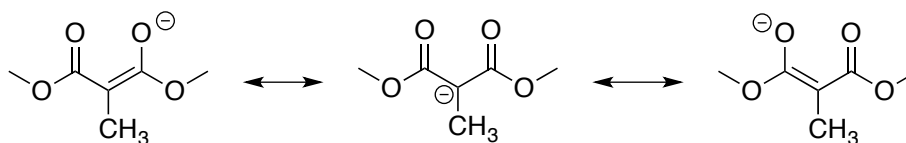
2.2.3 Preparation and Thermolysis of Hypervalent Iodine Complexes

We first began by testing the thermolysis of an symmetrical electron-rich iodonium salt, bis(4-methoxyphenyl)iodonium triflate (**1**). Dimethyl methylmalonate (**2**) was chosen as a synthon for the anion to be delivered. This compound was synthesized by deprotonation of commercially available dimethylmalonate, followed by reaction with iodomethane (Scheme 2.2).



Scheme 2.2: Synthesis of dimethyl methylmalonate

The resulting diester was reacted with sodium methoxide to generate a stable enolate. Using what have become fairly standard conditions in our lab,²¹ the enolate was mixed with the iodonium salt in a non-polar solvent (*e.g.* benzene) and heated, under nitrogen and in the dark. Because the sodium enolate (1,3-dimethoxy-2-methyl-1,3-dioxopropan-2-ide, **3**) is fairly insoluble in non-polar solvents such as benzene, the reaction was run at 140 °C in a sealed NMR tube fitted with a Teflon screw cap closure; however, as will be explained later, phase transfer catalysts were used with the nitroesters, facilitating much lower thermolysis temperatures. Formation of the product was monitored by ¹H-NMR. Due to resonance, three atoms carry a negative charge in the enolate structure (Figure 2.1). We were concerned that arylation could also occur at either of the oxygens.

Figure 2.1: Resonance of the enolate, **3**

Computational methods were employed to investigate the highest occupied molecular orbital (HOMO) of the enolate. A malonic acid anion was used as a simplified structure. The structure was optimized using GAMESS^{24,25} to determine the ground state geometry. A 3D orbital map was plotted (Figure 2.2).

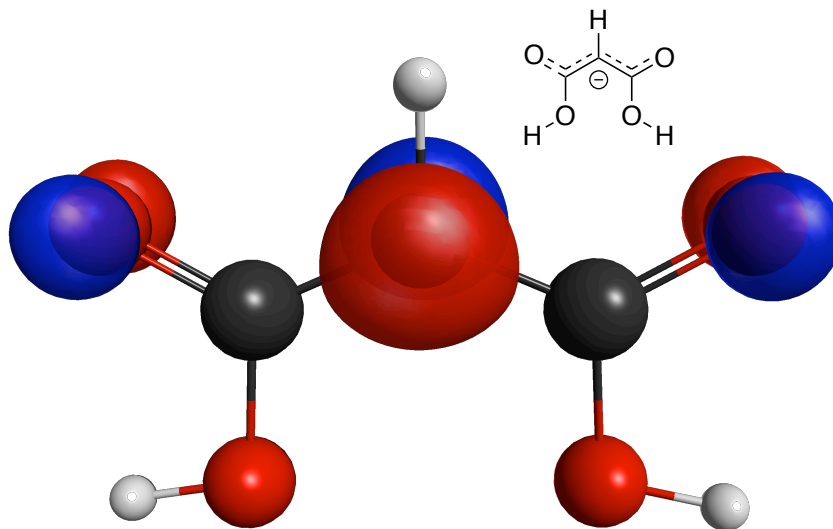
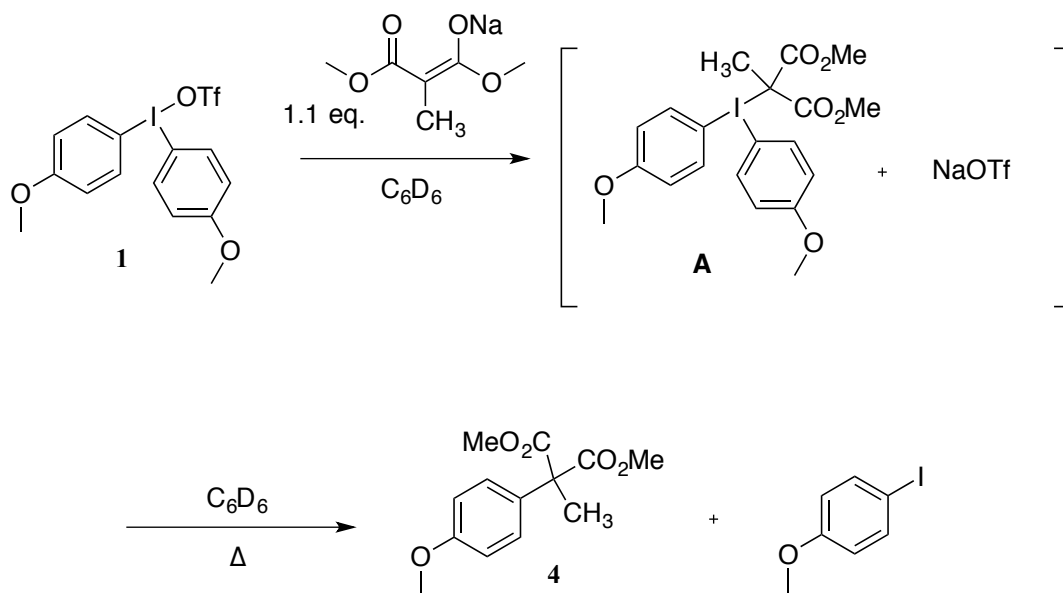


Figure 2.2: 3D orbital map of malonic acid HOMO (B3LYP/6-311G)

Acting as a nucleophile, electrons could be donated from either the carbonyl oxygens or the α -carbon. The P_z orbital coefficient on the α -carbon is slightly larger (0.300) than either of the carbonyl oxygens (0.195), so presumably reaction would prefer carbon bond formation. Also, in theory the the hard-hard interaction of the sodium and the triflate anion would favor exchange, and soft-soft interaction of the iodonium center and the carbanion should be favored over the soft-hard interaction of the iodonium center and the oxygens. As thermolysis of diaryliodonium triflates occurs very slowly,²⁶ so thermolysis will effectively only take place on the intermediate complex, **A** (Scheme 2.3).

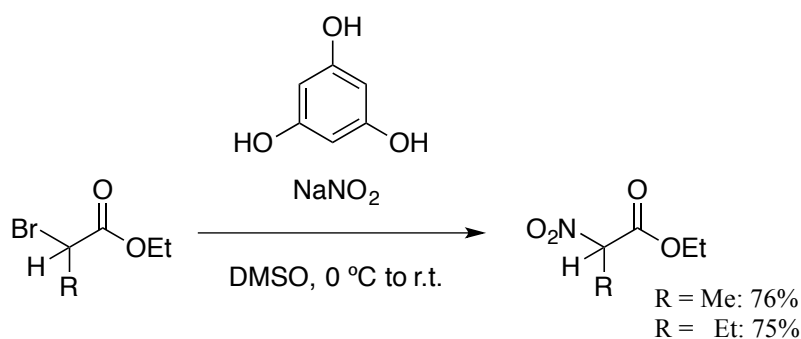


Scheme 2.3: Synthesis of dimethyl 2-(4-methoxyphenyl)-2-methylmalonate (**4**)

Only one ester product was produced (along with 4-iodoanisole). NMR analysis of the product showed that both esters remained equivalent, suggesting that arylation occurred only at the carbon center.

Next, a methodology for synthesizing α -nitroester enolates was developed. Some α -nitroesters are commercially available, but most are expensive. However, most of these compounds can be synthesized from the much less expensive α -bromoesters (Scheme 2.4). Phloroglucinol (1,3,5-trihydroxybenzene) is added to scavenge an undesired nitrite ester by-product. Kornblum and co-workers note that a combination of nitroester, nitrite ester, and sodium nitrite (acting as a base), promotes conversion of nitroester product to an analogous oximinoester.²⁷ Ethyl 2-nitropropionate (**5**) and ethyl 2-nitrobutyrate (**6**) were synthesized in moderate scale (10–20 g).²⁸ Synthesis of ethyl nitroacetate, by this method, proved unsuccessful, so a small amount was purchased.

Kornblum and co-workers,²⁹ report that reaction of ethyl nitroacetate (prepared from ethyl acetoacetate³⁰) with sodium nitrite becomes highly exothermic and produces carbon dioxide, nitrous oxide, and nitrogen.³¹ Reaction of ethyl bromoacetate, with temperature control, does not form ethyl nitroacetate, but rather yields only minor amounts of oxalic acid.



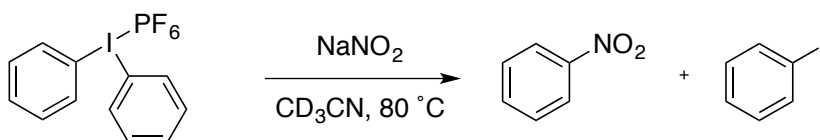
Scheme 2.4: Synthesis of α -nitroesters

Purification was initially performed by fractional vacuum distillation to remove the unreacted α -bromoester (forerun), and separate the product (middle fraction) from the solid phloroglucinol, sodium nitrate, and other impurities (tail).

Due to the strongly electron withdrawing nitro group, these esters are even more acidic (pK_a 9.1 for ethyl nitroacetate in DMSO³²) than diesters (pK_a 18.0 for dimethyl methylmalonate in DMSO³³). A variety of deprotonation conditions were evaluated (LDA, sodium hydride, aqueous carbonate, etc). Deprotonation in dry ethanol using sodium ethoxide generated the pure enolate (sodium 1-ethoxy-2-nitroethenolate (**7**), sodium 1-ethoxy-2-nitropropenolate (**8**) and sodium 1-ethoxy-2-nitrobutenolate (**9**)) under mild conditions, and was chosen for scaling up the synthesis of these enolates.

Commercial sodium ethoxide may be used, but minor impurities imparted a yellow tint to the product, so sodium ethoxide was instead made *in situ* by adding freshly cut sodium metal to cold ethanol.

Thermolysis of diaryliodonium salts using these enolates showed a small (typically less than 10%) formation of nitroarene (*e.g.* nitrobenzene, 4-nitrotoluene, 4-nitroanisole). The identify of this impurity was confirmed by ^1H NMR (by doping each reaction with an aliquot of commercially obtained nitroarene) and GC-MS. No mechanism could be deduced to directly deliver a nitro group from the ester. It was found that thermolysis of bis(phenyl)iodonium hexafluorophosphate in the presence of sodium nitrite at 80 °C slowly formed 4-nitroanisole (Scheme 2.5).

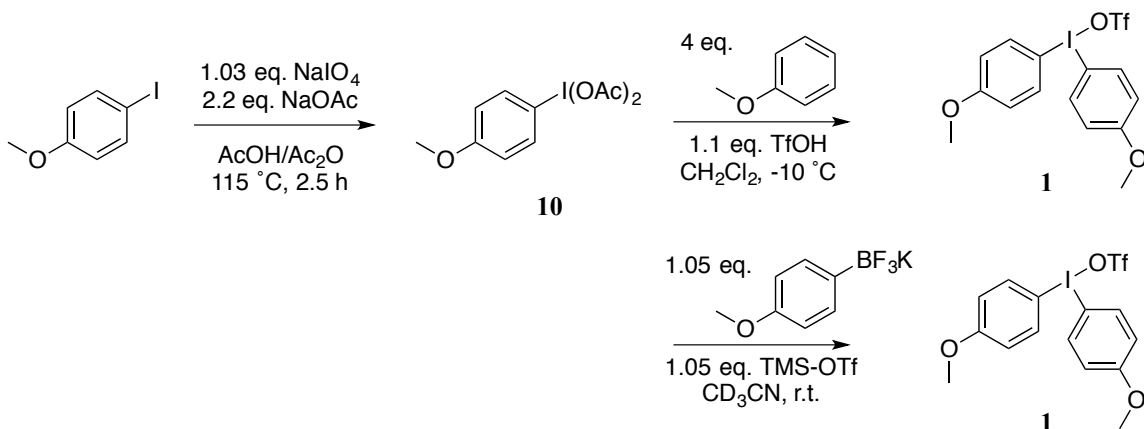


Scheme 2.5: Formation of nitrobenzene

To our knowledge this is the first example of formation of nitroarenes via iodonium salts. Passing the previously purified α -nitroesters through a silica column before deprotonation significantly reduced formation of the nitroarene side-product.

We have developed a variety of methods to generate diaryliodonium salts. The salt used for initial testing, bis(4-methoxyphenyl)iodonium triflate, **1**, can be made by oxidation of 4-iodoanisole to bis(acetoxy)4-iodoanisole (**10**) using sodium periodate,³⁴ followed by an electrophilic aromatic substitution on 4-iodoanisole, activated by triflic

acid.³⁵ It is believed the coupling reaction proceeds by a substitution of one of the acetates by triflate (Scheme 2.6).



Scheme 2.6: Synthesis of bis(4-methoxyphenyl)iodonium triflate (**1**)

The electron-rich anisole ring quickly adds to this highly electrophilic iodonium center. This coupling step must be run carefully (-10 °C, slow addition, excess anisole) or rapid decomposition occurs (observed as a vibrant blue color that quickly deepens to black), presumably due to a second substitution of acetate with triflate to form an extremely reactive electrophile. In an effort to improve this yield, and scale up this and similar salts, milder coupling conditions were developed, by reacting **10** (synthesized as above), commercially available potassium 4-methoxyphenyltrifluoroborate, and a milder activating agent, trimethylsilyl trifluoromethanesulfonate (TMS-OTf).

Other symmetrical diaryliodonium salts can be purchased commercially. For iodonium thermolysis reactions run with [¹⁸F]fluoride (for Positron Emission Tomography), using triflate as a counterion is highly preferred as ¹⁸F-¹⁹F exchange can occur with other anions such as tetrafluoroborate (BF₄⁻) or hexafluorophosphate (PF₆⁻).

For these reactions this is not an issue, so both triflate salts and hexafluorophosphate salts were used interchangeably. Three symmetrical diaryliodonium salts were purchased/synthesized (Figure 2.3), bis(phenyl)iodonium hexafluorophosphate, bis(4-methylphenyl)iodonium hexafluorophosphate, bis(4-methoxyphenyl)iodonium triflate (**1**), providing a range of arene electron density from neutral to electron-rich. In order to test an electron-poor example, the synthesis of bis(4-nitrophenyl)iodonium hexafluorophosphate was attempted. Although this compound is listed in literature, only one successful synthesis is reported.³⁶ This report cites methodology that mentions the difficulty of producing highly electron-deficient symmetrical diaryliodonium salts (due to the system being too unreactive with electron-poor substrates) and does not report synthesis of any diaryliodonium salts as electron-deficient as bis(4-nitrophenyl)iodonium.³⁷ All attempts to synthesize this compound, using 4-iodonitrobenzene and bis(acetoxy)-4-nitrobenzene (**11**) in our hands provided only an impure sample of 4-iodonitrobenzene. Based on NMR spectra taken during reaction, it is suspected that this highly electron-poor iodonium salt may have been generated, but have been too unstable to isolate. Instead, an asymmetrical salt was synthesized, (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**12**). The drastic electronic difference between the withdrawing nitro group and the donating methoxy group would ensure a strong regiochemical preference for elimination of 4-iodoanisole rather than 4-iodonitrobenzene.

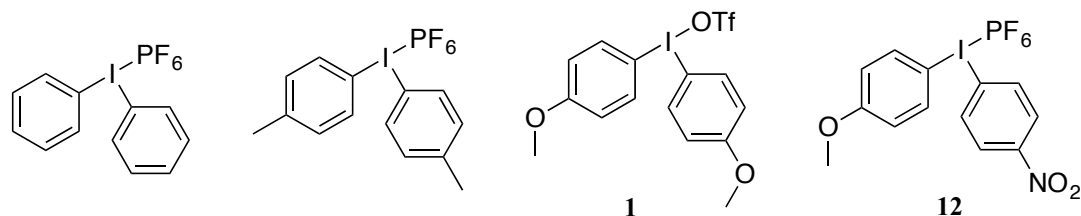
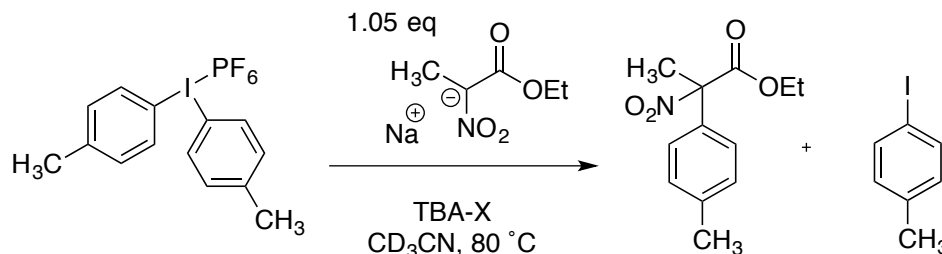


Figure 2.3: List of diaryliodonium salts used

Initially the thermolysis reactions were performed in benzene- d_6 . A non-polar solvent was chosen as with many anions polar solvents tend to promote detrimental side-reactions (presumably disproportionation).²¹ Due to the low solubility of the sodium enolates in non-polar solvents a high thermolysis temperature, 140 °C, was used. This resulted in relatively short reaction times (30 minutes), but also promoted formation of nitroarene. At lower temperature side-reactions are minimized, but solubility of the sodium enolates is significantly worse. Running the thermolysis in a more polar solvent, acetonitrile- d_3 , made little change. The sodium enolates are somewhat more soluble, but not enough to make a significant difference in the necessary temperature.

We therefore turned to the use of a phase transfer catalyst. For fluorination reactions, more soluble fluoride sources (*e.g.* TBAF rather than KF) improve reaction times and yield.³⁸ Following a similar approach, TBA (tetra *n*-butyl ammonium) salts were added (Table 2.1).



Phase Transfer Catalyst	Equivalents	Conversion after 1 h
TBACl	0.25	91%
TBACl	1.05	86%
TBAOTf	0.25	87%
TBAOTf	1.05	89%

Table 2.1: Phase transfer catalysts added

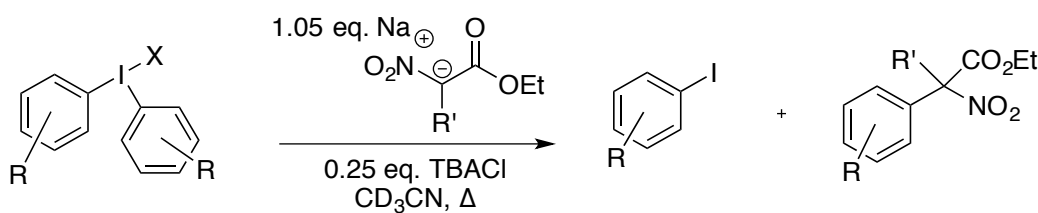
A substoichiometric amount of TBACl was found to increase reaction rate the most. Using a superstoichiometric amount of TBACl actually slowed the reaction. It is possible that a large amount of chloride anions forms a large amount of the corresponding diaryliodonium chloride, which precipitates out of solution. Diaryliodonium chloride salts are highly crystalline, fairly insoluble, and react very slowly. However, some chloride seems to be beneficial as it pairs strongly with sodium. Since sodium chloride is nearly insoluble in organic solvents, its precipitation may drive exchange, forming the more soluble iodonium enolate intermediate (Scheme 2.3, structure A). TBAOTf presumably does not work as well due to the lower affinity for sodium and triflate, and the higher solubility of sodium triflate in organic solvents. With the addition of a phase transfer catalyst, the reaction can be run at lower temperature (80 °C), and although thermolysis is slower, side-products are minimized.

With this methodology established, a variety of reactions were run (Table 2.2) to produce arylnitroesters **13–20**. The methodology was also used by a co-worker, Jordan Veness, toward the synthesis of a quaternary tryptophan analog.³⁹ A slight excess of the sodium enolate was used (as its low solubility makes it easy to remove after reaction) and the reaction was monitored by ¹H NMR, monitoring disappearance of the diaryliodonium salt. After thermolysis was complete, solvent was removed. The two thermolysis products, iodoarene and the arylnitroester, are moderately soluble in non-polar solvents, such as hexanes, while other products (sodium salts, TBA salts, and excess enolate) are insoluble. The polarity difference between the iodoarene and the arylnitroester makes separation possible by silica column chromatography. It was later discovered that the iodoarene makes only a minor impact on the subsequent synthetic steps (nitro reduction and ester hydrolysis); chromatography could be skipped, if desired.

As expected, the more electron-rich diaryliodonium salts reacted more slowly (electron-donating ligands are able to stabilize the iodine(III) center). The most electron-poor diaryliodonium salt, (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**12**), proceeded to react at lower temperatures, so thermolyses with this salt were run at 35 °C. Reactions with longer chain enolates (butyrate esters vs. propionate esters) tended to react slightly faster. Though these enolates have a slightly higher solubility, presumably this is primarily due to the extra steric bulk, which promotes reductive elimination from the iodonium center.

2.2.4 Reaction Kinetics

Isolated yields were found to be somewhat lower than yields based on NMR integrations (Table 2.2). The nitroesters are volatile, and presumably some yield may be lost due to removing solvents and iodoarene under high vacuum. Yields of the aryl nitrobutyrate esters tend to be higher, attributed to a potentially lower volatility of the longer chain ester and slightly higher solubility in the nonpolar solvent used to extract the product from the reaction mixture. As the more electron-rich diaryliodonium salts react more slowly, longer reaction times are required, allowing for the possibility of more side-product formation, contributing to lower yields for the nitroesters formed from bis(4-methoxyphenyl)iodonium triflate (**1**).



Diaryliodonium Salt	Sodium Enolate	Product	Time (h)	% Yield
			4 ^a	73%
			3.5 ^a	93%

			10.5 ^a	78%
			12.5 ^a	92%
			22 ^a	66%
			20 ^a	67%
			7 ^b	95%
			7 ^b	98%

^a Reaction run at 80 °C ^b Reaction run at 35 °C

Table 2.2: Formation of arylnitroesters

Once the arylnitroesters were synthesized, they needed to be reduced (nitro to amine) and hydrolyzed (ester to carboxylic acid). As amino acids are always charged

(anionic carboxylate when basic, cationic ammonium when acidic, or zwitterionic at their pI), purification in the last step could be more challenging. In my experience with the benzimidazole class of radiotracers (Chapter 3), I found the hydrolysis step to run more cleanly than the reduction step. In addition, α -nitro carboxylic acids are prone to decarboxylation.⁴⁰ For these reasons the nitro group reduction was run first, followed by ester hydrolysis.

Nitro groups have a fairly high reduction potential,⁴¹ and therefore are one of the easiest functional groups to reduce.⁴² Mild reductions were investigated. Although Béchamp reductions (Fe^0 , acid)⁴³ worked well for the benzimidazole class of radiotracers (Chapter 3), and there are many references for the reduction of nitroarenes, reduction on nitroalkanes are mentioned rarely in literature.⁴⁴ Attempts to reduce aryl nitroesters using iron in acetic acid or hydrochloric acid showed little to no conversion. Zinc reduction worked quickly and was highly selective to the nitro group. Although it requires the use of concentrated hydrochloric acid, it is a relatively mild reduction method that can be run below room temperature. The reduction is run to completion using an excess of zinc metal, added in portions at 0 °C. Zinc salts can be removed by neutralizing the mixture with aqueous sodium bicarbonate, switching to a less polar organic solvent, *e.g.* dichloromethane, filtering through a membrane filter (PTFE, 0.2 μm), and washing with water. The resulting arylaminoesters can be chromatographed and characterized (*e.g.* ethyl 2-(4-methylphenyl)-2-aminopropanoate, **21**), but it was found that moving forward without chromatography did not impact the next step.

Hydrolysis was performed under basic conditions, to ensure quick and complete hydrolysis of the ester. The arylaminoesters are not very soluble in aqueous media, so a small portion of ethanol was added to facilitate dissolution. The mixture is stirred vigorously and once the arylaminoester (an oil) is fully dissolved the reaction is monitored by ^1H NMR, observing the disappearance of ethyl ester protons. Ethanol was removed *in vacuo*. The resulting amino acid is moderately soluble in aqueous solution, so liquid-liquid extractions proved ineffective to isolate the product. Amino acids are often purified by ion-exchange chromatography, though we chose not to apply that technique here. Since the impurities present were found to be much more soluble in organic solvents than the desired amino acid product, the basic reaction mixture was simply washed several times with diethyl ether or dichloromethane. Isolation of the amino acid was performed by crystallization out of solution at the isoelectronic point, pI. Under basic pH the carboxylic acid is deprotonated, increasing aqueous solubility. Under acidic pH the amine is protonated, also increasing aqueous solubility. At the isoelectronic point, or isoionic point, both the amine is protonated and the carboxylic acid is deprotonated. This net neutral, zwitterionic species is least soluble in aqueous media (Figure 2.4). The pI can be determined by placing the amino acid in an electric field and adjusting pH until the amino acid no longer migrates. Natural amino acids with neutral side chains have isoelectronic points within a narrow range (5.5 to 6.0);⁴⁵ presumably the pI for these unnatural amino acids does not deviate significantly from this range. The solutions were carefully neutralized to about pH 5 with hydrochloric acid, concentrated *in*

vacuo, and chilled to near freezing to allow crystallization of the amino acid. The amino acid products, **22–29**, were isolated by filtration and washed with ice-cold water.

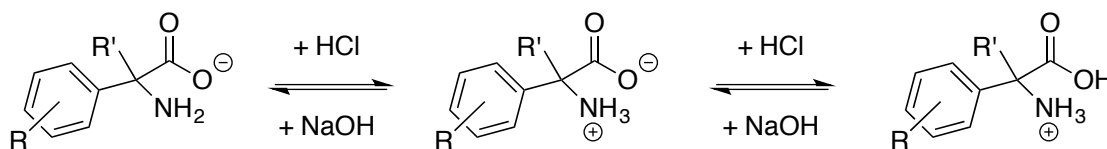


Figure 2.4: Amino acids at varying pH

For the two amino acids generated from (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**28** and **29**), the nitrophenyl is also reduced during the zinc reduction, as expected. As the side chain (aniline) is no longer a neutral side chain, a slightly higher pH of 6 was used.

Zinc reduction and acidic hydrolysis successfully produced the desired quaternary amino acids, **22–29**, in good to excellent yields (Table 2.3). The products were characterized by HR-MS, ¹H, and ¹³C NMR. Although isolation was performed at the predicted pI (due to the solubility being lowest at this point), characterization by NMR was often done at much higher pH. During initial ¹³C-NMR acquisitions of the isolated (pH = 5–6) it was found that the quaternary carbon and even more so the adjacent carbon on the alkyl chain relaxed extremely slowly. Setting relaxation delays of >15 seconds were required, suggesting an approximate *T*₁ of about 3 seconds. Basifying the NMR solutions with sodium hydroxide to pH 11 (p*K*_a of the protonated amine + 2) allowed for significantly shorter relaxation delays (typically 2–3 times shorter).

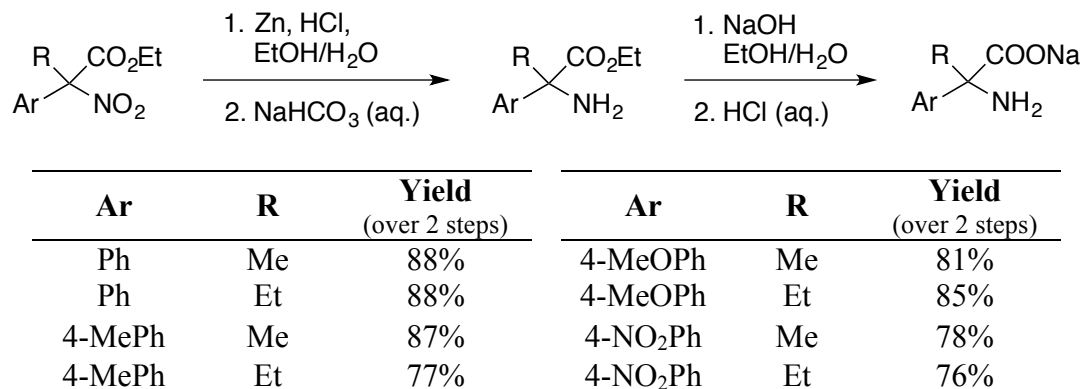


Table 2.3: Reduction and hydrolysis of aryl nitroesters

2.2.5 Chirality

With methodology established for readily synthesizing quaternary α -alkyl α -aryl amino acids, we sought to develop a way to stereoselectively generate a single enantiomer. One approach, utilizing the last step of the synthesis (the hydrolysis) would be to stereospecifically hydrolyze the ester using an esterase. While this approach could work, it would be limited to a maximum yield of 50%. We instead chose to investigate using a chiral directing group on the iodonium salt to selectively deliver the nitroester to one face of the target arene. Based upon research developed by several former members of our group,^{46,47} [2.2]paracyclophane may be used as a regiochemical directing group in diaryliodonium salts. This strategy utilizes out-of-plane steric hindrance, as well as electronic effects, to promote reductive elimination of iodocyclophane in iodonium salt thermolysis (Figure 2.5).

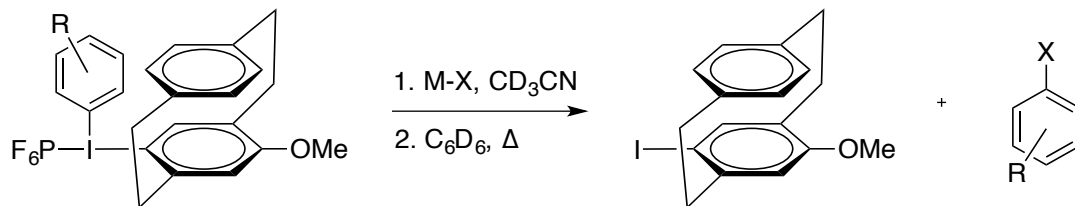


Figure 2.5: Thermolysis of a cyclophane-containing diaryliodonium salt

As cyclophanes exhibit planar chirality, we sought to use this as a chiral directing group. In Figure 2.6, structures **A** and **B** are enantiomers. The iodine and methoxy groups have been moved to the other phenyl ring of the cyclophane. If these structures are simply rotated along the z-axis, **A** (rotated) is analogous to **B**, and **B** (rotated) is analogous to **A**; however, the ethane bridges on the cyclophanes are oriented differently. This difference in the cyclophane orientation implies a difference to each face of the phenyl ring and to each face of the other ligand ($X = \text{OTf}, \text{PF}_6, \text{nitro ester enolate}$).

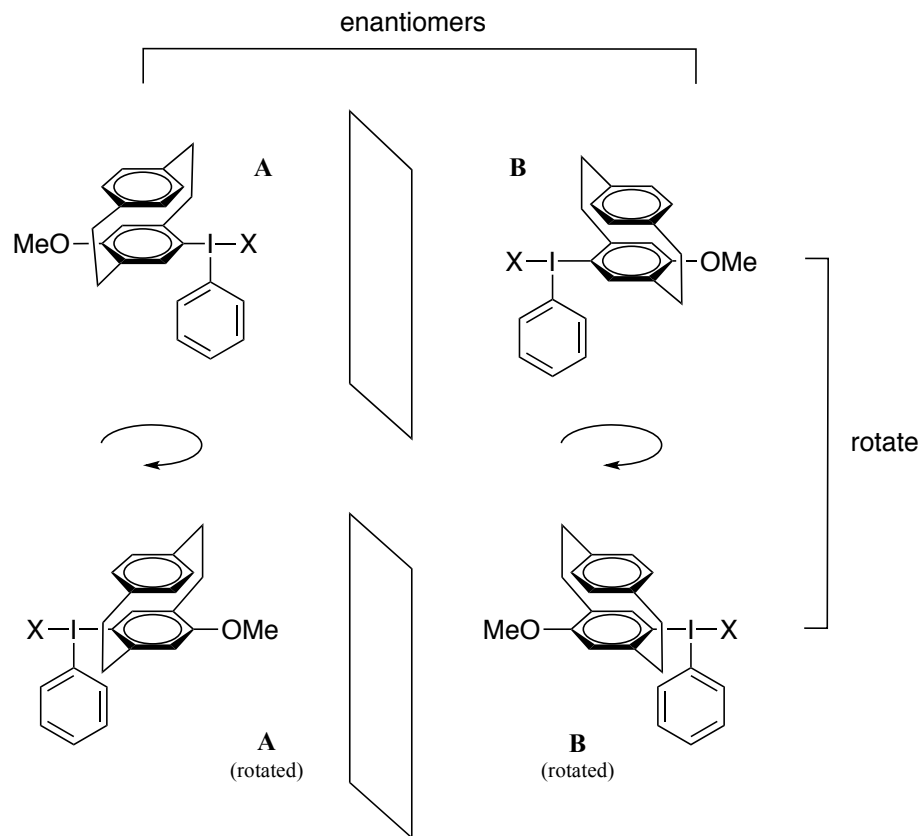
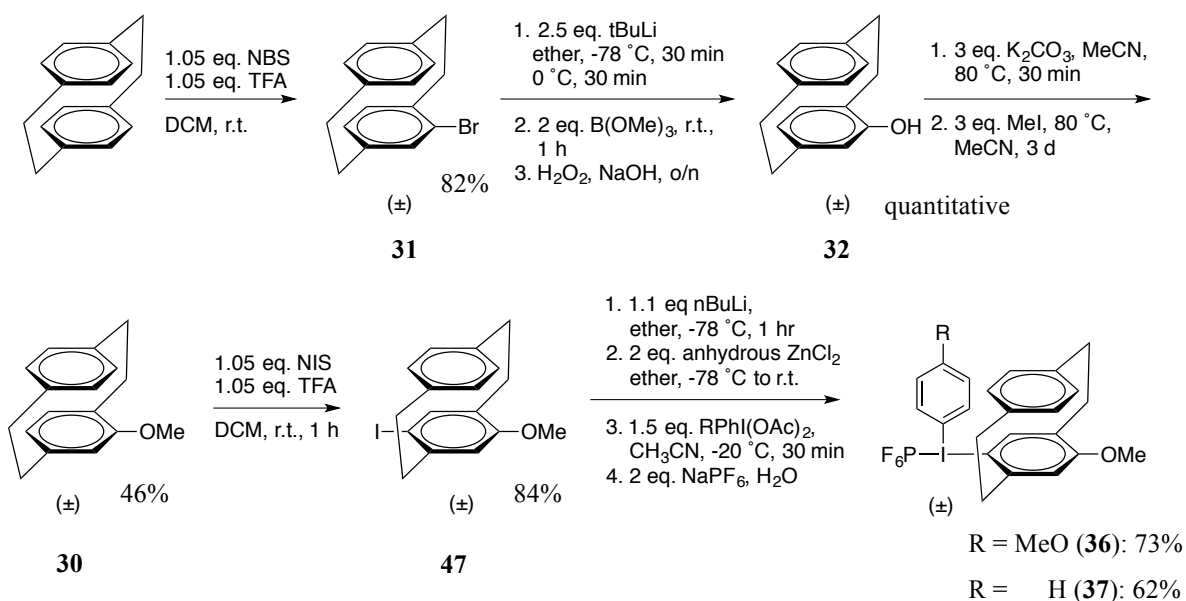


Figure 2.6: Cyclophane phenyl iodonium salt enantiomers

If the energy difference between these faces is sufficiently high during iodonium salt thermolysis, an excess of one of the two product enantiomers will be observed. Isolating a single cyclophane enantiomer and synthesizing an enantiomerically pure diaryliodonium salt could potentially be used to stereoselectively generate quaternary α -alkyl α -aryl nitroesters, and would also be the first example of a diaryliodonium salt being used for enantiocontrol.

In order to ensure thermolysis using a cyclophane and an enolate would be successful, a racemic diaryliodonium salt was first synthesized. Following the approach used previously in our lab,^{47,48} 4-methoxy-[2.2]paracyclophane (**30**) was synthesized

(Scheme 2.7). Commercially available [2.2]paracyclophane was brominated to form **31**. Lithium/halogen exchange, quenching with trimethoxyborane, and oxidation using hydrogen peroxide forms 4-hydroxy-[2.2]paracyclophane (**32**). Methylation with methyl iodide under basic conditions generates 4-methoxy-[2.2]paracyclophane (**30**).

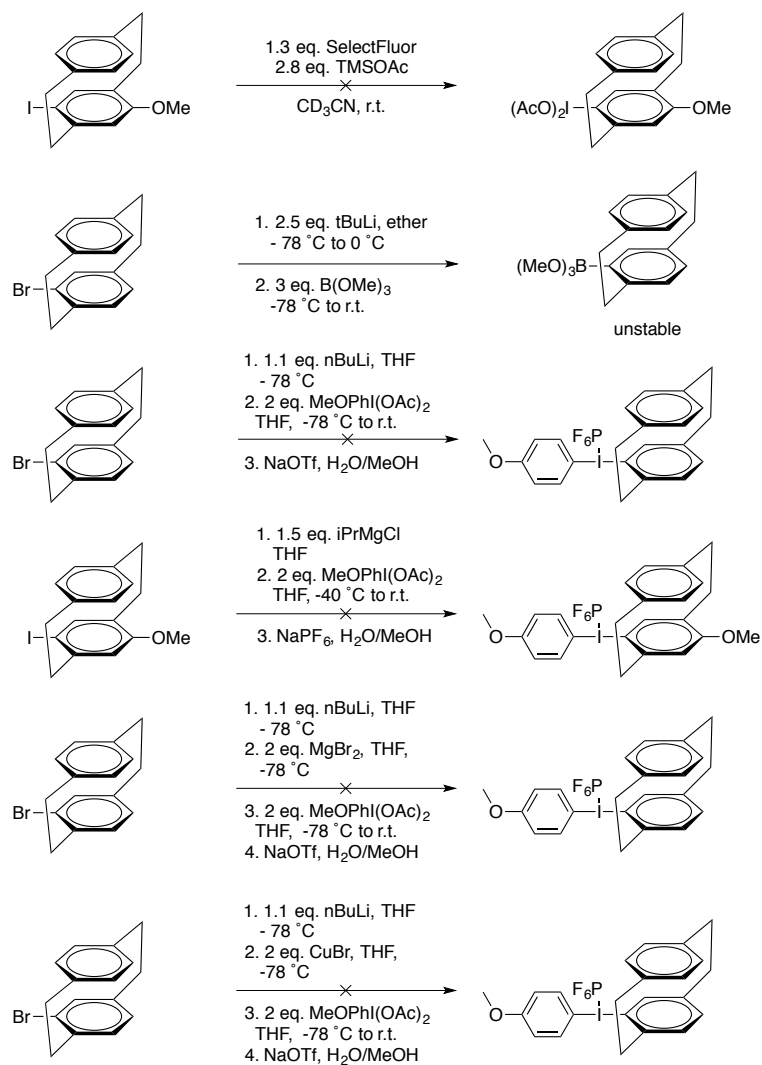


Scheme 2.7: Synthesis of racemic diaryliodonium salts (R=H, OMe)

The previous approach utilized a brominated cyclophane (7-bromo-4-methoxy-[2.2]paracyclophane) to synthesize the diaryliodonium salt (using lithium-halogen exchange). A synthesis of an iodinated cyclophane, 7-iodo-4-methoxy-[2.2]paracyclophane (**33**), was developed in an effort to improve the final synthesis step (generation of the diaryliodonium salt). This could potentially open up the ability to use milder metalation methods (*e.g.* halogen-metal exchange using a Grignard reagent). This route also allows recycling of the cyclophane group after thermolysis — thermolysis

forms the desired product and also eliminates 7-iodo-4-methoxy-[2.2]paracyclophane (47).

Formation of diaryliodonium salts can be challenging. Intermediate salts can be unstable in the presence of strong nucleophiles (such as metalated arenes). Purification is typically done using recrystallization (as normal phase chromatography of highly polar salts is impractical) and highly impure diaryliodonium salts can easily oil out of solution. There are a variety of methods available for synthesizing these salts, but in our experience most of these methods are not conducive for synthesizing cyclophane-containing diaryliodonium salts. A complex approach using an organozinc reagent (generated *in situ*) was previously used for this salt. Unfortunately, this approach gave fairly low yields and due to several potential sources of water/oxygen contamination gave inconsistent results. A variety of approaches were taken (Scheme 2.8). Attempts to form the aryl stannane were previously unsuccessful (presumably due to the steric bulk of the large tin atom and the cyclophane). Oxidation of iodine with Selectfluor[®], using conditions we had previously developed for other iodoarenes,¹ proved unsuccessful; ring-opening and polymerization appeared to occur.



Scheme 2.8: Attempts to form cyclophane salt

Formation of a [2.2]paracyclophane boronate ester (**34**), as a model compound, was successful. As trifluoroborate salts are often more shelf stable, and also more nucleophilic,⁴⁹ the boronate ester was converted to the potassium trifluoroborate salt before isolation. Presumably the salt either was formed and instantly underwent elimination (to form unsubstituted [2.2]paracyclophane), or presence of a proton source caused cleavage of the carbon-boron bond. After thorough investigation, it was found

that simply stirring the boronate ester in methanol or even moderately wet acetonitrile promoted formation of unsubstituted [2.2]paracyclophane. Due to this observation, it was suspected that the boronate ester may be reactive enough to directly couple with an iodonium center (e.g. bis(acetoxy)4-iodoanisole, **10**). Reaction of the crude boronate ester resulted only in reduction of **10** to 4-iodoanisole, presumably due to the presence of methoxide anions (remaining from formation of the boronate ester with trimethoxyborate). However, all attempts to isolate the boronate ester from these methoxide salts were unsuccessful. Washing the boronate ester with any type of aqueous solution (acidic or basic) showed significant formation of unsubstituted cyclophane. Even simply removing the solvent and isolating the desired product by dissolving the crude oil in non-polar solvents and filtering promoted formation of unsubstituted cyclophane.

A lithiated cyclophane proved to be too reactive to couple directly – all bis(acetoxy)4-iodoanisole was reduced to 4-iodoanisole, and all lithiated cyclophane was reduced to unsubstituted [2.2]paracyclophane. Magnesium-halogen exchange with *iso*-propyl magnesium chloride on 7-iodo-4-methoxy-[2.2]paracyclophane (**47**) did not occur at room temperature or below, and when heated formation of 4-methoxy-[2.2]paracyclophane (**30**) occurred nearly as fast as metalation (the aryl Grignard reagent could potentially abstract a proton from *iso*-propyl iodide). A synthesis of 4-iodo-[2.2]paracyclophane was developed. This compound is only known in literature as the product of an iodonium salt thermolysis,⁴⁶ and all attempts to directly iodinate [2.2]paracyclophane proved unsuccessful (presumably to the steric bulk of the

cyclophane and iodine, and the relatively unreactive arene). Lithiation of 4-bromo-[2.2]paracyclophane and substitution on NIS gave the desired iodinated product 7-iodo-[2.2]paracyclophane (**35**), along with inseparable, but unreactive, [2.2]paracyclophane. Further studies (using other Grignard reagents for magnesium-halogen exchange, other solvents, and temperatures) were performed on this model compound, but abstraction of a proton always occurred nearly as fast or faster than metalation. Formation of the aryl Grignard by lithiation followed by transmetalation with magnesium bromide showed the same results as directly coupling with the lithiated cyclophane. Attempts to make an organocuprate and couple also gave the same results.

I sought then to improve the existing organozinc route. Using the original conditions, and monitoring after every step, it was found that lithiation was nearly complete (only a small amount of iodinated arene was left unreacted, presumably due to poor solubility in ether). Formation of reduced iodoarene and protonated cyclophane accounted for nearly all of the lost yield. After a variety of model reactions on 4-bromo-[2.2]paracyclophane (**31**), it was found that several lithiating agents (*n*-butyl lithium, *s*-butyl lithium, and *t*-butyl lithium) reacted well and gave similar results. Using THF as a solvent in *any* step, even after removal of solvent *in vacuo*, gave very poor yields (resulting in nearly total formation of reduced iodoanisole and protonated cyclophane); using ether for the lithiation step and switching to acetonitrile for the coupling step provided the best results. Initially sonicating the cyclophane in ether and warming slightly while stirring before slowly cooling to -78 °C fostered complete conversion in the lithiation step. Using a larger excess of zinc chloride, and flame-drying immediately

before each use, gave the most consistent results. Finally, addition of the organozinc reagent to the bis(acetoxy)iodoarene gave appreciably improved yields of (4-((±)-7-methoxy-[2.2]paracyclophanyl))(4-methoxyphenyl)iodonium hexafluorophosphate (**36**). Due to the low solubility of bis(acetoxy)-4-iodoanisole (**10**) in acetonitrile, higher temperatures (-20 °C) were used for the coupling step. Using a lower temperature (-25 °C or colder), by diluting **10** in a larger volume of acetonitrile did not decrease the formation of reduced iodoanisole, but more protonated cyclophane was observed (likely due to more trace moisture in the larger volume of acetonitrile). The phenyl analog, (4-((±)-7-methoxy-[2.2]paracyclophanyl))(phenyl)iodonium hexafluorophosphate (**37**), was also synthesized using analogous conditions.

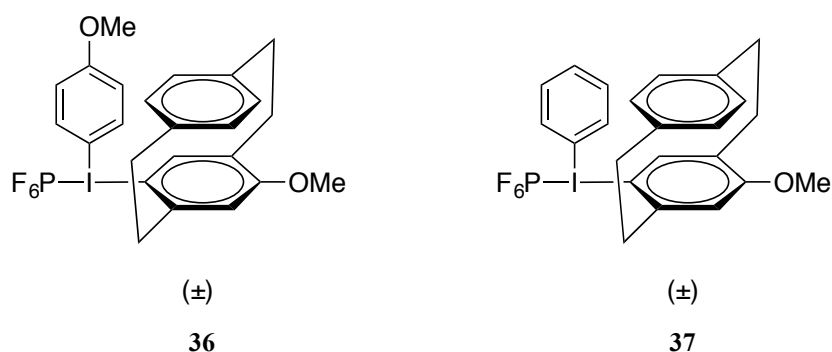


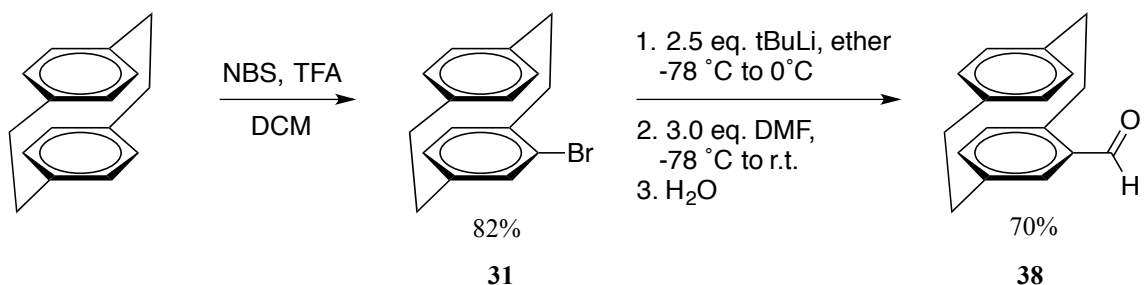
Figure 2.7: Racemic aryl-cyclophanyl iodonium salts synthesized

With two racemic cyclophane iodonium salts synthesized, trial reactions were run to confirm thermolysis occurs similar to the symmetrical iodonium salts. Thermolysis proceeded similarly to the symmetrical salts, though slightly faster. A small amount of iodobenzene and 4-iodoanisole were formed, respectively, but no functionalized cyclophane was observed (the only discernible cyclophane species observed was 7-iodo-

4-methoxy-[2.2]paracyclophane (**47**)). This implies that the regiochemistry of the reaction completely prefers elimination of the iodo-cyclophane and functionalized benzene or anisole; the iodobenzene or 4-iodoanisole impurities must arise from some other mechanism. After thermolysis was complete the products were isolated and characterized. After reduction and hydrolysis, the amino acids were purified and conditions were developed for separation of the two enantiomers on HPLC. Initial separations were performed on a Phenomenex[®] Chirex 3126 chiral column (50 mm length, 4.6 mm diameter, 5 μ m particle size), which specifically separates enantiomers of amino acids. This column utilizes ligand exchange on a copper complex of (D)-penicillamine to separate amino acid enantiomers. Conditions were later established using a Phenomenex[®] Lux Cellulose-1 chiral column (250 mm length, 4.6 mm diameter, 3 μ m particle size), which is able to separate a variety of enantiomers by hydrogen bonding and π - π interactions with the cellulose phenylcarbamate stationary phase. Using this column, the aryl nitroesters formed directly by the thermolysis reactions can be rapidly analyzed without performing the reduction and hydrolysis steps. An Astec[®] CHIROBIOTIC[®] T2 chiral column (250 mm length, 4.6 mm diameter, 5 μ m particle size) was also tried, but no conditions were found that gave any separation.

There are few published approaches based upon isolating single cyclophane enantiomers.^{50, 51} Approaches by fractional crystallization of [2.2]paracyclophanyl naproxen esters attempted by an undergraduate student in our lab, Anh Nguyen, proved unsuccessful. An alternate approach was taken, using diastereomeric imines, based on work by Quici and co-workers.⁵¹ Commercially available [2.2]paracyclophane was

brominated using NBS to form 4-bromo-[2.2]paracyclophane (**31**) as previously described. Conditions were developed to generate the aromatic aldehyde, 4-formyl[2.2]paracyclophane (**38**), by lithiation with *t*BuLi and quenching with DMF (followed by water).



Scheme 2.9: Synthesis of aldehyde **38**

Following formation of **38**, the subsequent approach of Bräse and co-workers⁵² was utilized. Condensation with a stoichiometric amount of enantiopure (*S*)-2-phenylethylamine produced two diastereomeric imines. The reaction was monitored by ¹H NMR. Conversion was observed by a disappearance of the aldehyde proton and appearance of two aldimine protons, slightly farther upfield. It was interesting to note that formation of one diastereomer was slower than the other; this difference in reaction rate, due to planar chirality on the cyclophane, could potentially influence thermolysis later in the synthesis. The crude product was recrystallized from dilute, hot hexanes. The solution was allowed to cool very slowly within an insulated jacket. After an hour or two crystallization began and the flask was left to cool for several hours until crystallization had completed, then moved to the refrigerator for several more hours before filtering and rinsing with cold hexanes. This crude product, crystallizing as nearly colorless beads,

was only slightly enriched in one diastereomer, but contained no other impurities, by ^1H NMR. A second crystallization was performed, in the same manner, but using a different concentration. Crystals formed from this second recrystallization were colorless and formed as sharp, branched needles. In most cases only a single diastereomer was visible in the NMR spectrum. This separation comes at the cost of yield. Only 19% of the total initial molar amount (combination of both the desired and undesired enantiomers) was isolated (which equates to a recovery of 38% of (*S*)-4-formyl-[2.2]paracyclophane (**39**)). If necessary, a third recrystallization could be performed to improve diastereomeric excess, but further sacrifices yield. All mother liquor was combined (and the imines cleaved on silica to recover 4-formyl-[2.2]paracyclophane). As this mother liquor is enriched in the other enantiomer, refluxing with with (*R*)-2-phenylethylamine and recrystallizing in a similar manner should isolate (*R*)-4-formyl-[2.2]paracyclophane. Repeating this process, and alternating the amine used, more of the desired enantiomers could be isolated. The imine, now diastereomerically pure, is easily cleaved on silica (due to non-deactivated silica being acidic), with the enantiopure aldehyde eluting and the amine remaining on silica. Enantiomeric excess was confirmed (94%) using chiral HPLC on a Phenomenex[®] Lux chiral column (250 mm length, 4.6 mm diameter, 3 μm particle size).

Dakin oxidation produces (*S*)-4-hydroxy-[2.2]paracyclophane (**40**). Rather than using carbonate as a base, used previously for the racemic synthesis, sodium hydride was used to deprotonate the phenol. The reaction was run in THF; since 4-hydroxy-[2.2]paracyclophane has a much higher solubility in THF than acetonitrile, the reaction

was run more concentrated, allowing for a faster reaction time. The rest of the synthesis was run under the same conditions as previously explained for the racemic iodonium salt. Though not performed for the racemic synthesis, (*S*)-4-methoxy-[2.2]paracyclophane (**41**) and (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (**42**) were also recrystallized after chromatography. Although a racemic mixture of enantiomers cannot be separated by crystallization (enantiomers of the same compound have the same solubility in achiral solvents), the major enantiomer will preferentially crystallize with like enantiomers, slightly enriching the enantiopurity of the compound.^{53,54,55} This was confirmed by chiral HPLC of (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (**42**), with a further enriched enantiomeric excess of 97% (confirmed on the Lux chiral column).

Using the same improved procedure as described above (4-((*S*)-7-methoxy-[2.2]paracyclophanyl))(phenyl)iodonium hexafluorophosphate (**43**) was synthesized from **42** and bis(acetoxy)iodobenzene. This compound was chosen for initial studies since it thermolyzes relatively quickly (allowing for thermolysis at relatively low temperature in order to maximize any potential enantioselectivity).

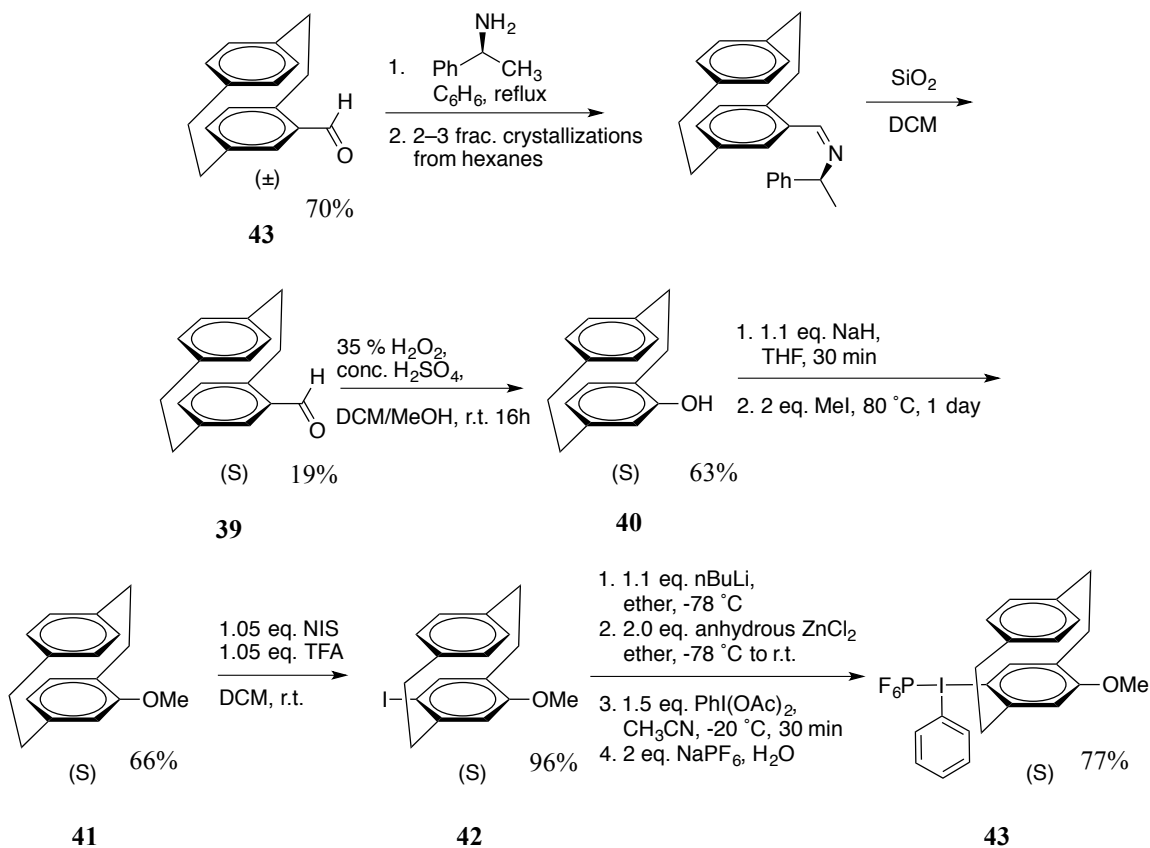


Figure 2.8: Synthesis of enantiopure iodonium salt, **43**

In addition, bis(acetoxy)-4-iodoanisole (**10**) and bis(acetoxy)-4-iodotoluene (**44**) were oxidized from the corresponding 4-iodoarenes using a periodate oxidation, and bis(acetoxy)-4-iodonitrobenzene (**11**) was oxidized from 4-iodonitrobenzene using a SelectfluorTM oxidation.¹ Though not yet performed, these compounds could be coupled with **42**, using the same conditions used to synthesize **43**, to generate the corresponding enantiopure diaryliodonium salts. With these, once conditions are established for thermolysis, all of previously synthesized racemic amino acids (**22–29**) can be synthesized as enantiopure amino acids.

Thermolyses using the sodium salts of ethyl 2-nitropropionate (**8**) and ethyl 2-nitrobutyrate (**9**) were run at 60 °C until completion. The aryl nitroester products were isolated, reduced using the zinc reduction conditions developed previously, and hydrolyzed under basic conditions. The final amino acids were characterized by ¹H-NMR and HR-MS (matching the previous full characterization of the racemic products, **22** and **23**). Unfortunately, after analysis by chiral HPLC no enantioselectivity was found; both sets of amino acids were completely racemic (integrations of the two enantiomers deviated by up to 1%, but repeated injections gave an average ratio of 50.05/49.95).

Ratios of each reagent were altered (substoichiometric, equal, and superstoichiometric amounts of the enolate (**8** and **9**) relative to the iodonium salt (**43**)) and concentration of the reaction mixture was varied, but all reactions gave racemic products. Based on kinetic data, the reaction appears to be pseudo first order. As the solubility of the enolate is low (until the end of the reaction some enolate visibly appears to always stay out of solution, even at reaction temperature), the reaction rate appears to be solely dependent on the concentration of the iodonium salt. No matter if there is a substoichiometric, equal, and superstoichiometric amount of enolate to iodonium salt, the low solubility seems to limit the amount of dissolved enolate to effectively be substoichiometric.

Presumably formation of the iodonium salt occurs quickly (with the enolate that is currently in solution) and the resulting inorganic salt (sodium triflate or sodium hexafluorophosphate) likely precipitates out of solution, making the exchange effectively

irreversible. Collision of the enolate and the iodonium center likely occurs statistically, with little preference, forming an equal, or nearly equal, mixture of both diastereomers: *S* (on the cyclophane), *R* (on the carbon attached to the iodine); and *S* (on the cyclophane), *S* (on the carbon attached to the iodine). If exchange does not readily occur, rather than finding the thermodynamic minimum of the two intermediates, there may always be an equal mixture, which will thermolyze to an equal mixture of both product enantiomers.

We theorized that if an excess of enolate were in solution, exchange may occur more readily, and the thermodynamically favorable intermediate would dominate. Computational methods were employed to investigate the energy differences between these two intermediates. Simplified intermediates were used (removing the methoxy group from the cyclophane, using the propionate-based enolate, and using a methyl ester; Figure 2.9). Three rotamers of each of these simplified intermediates were drawn and optimized using GAMESS.^{24,25}

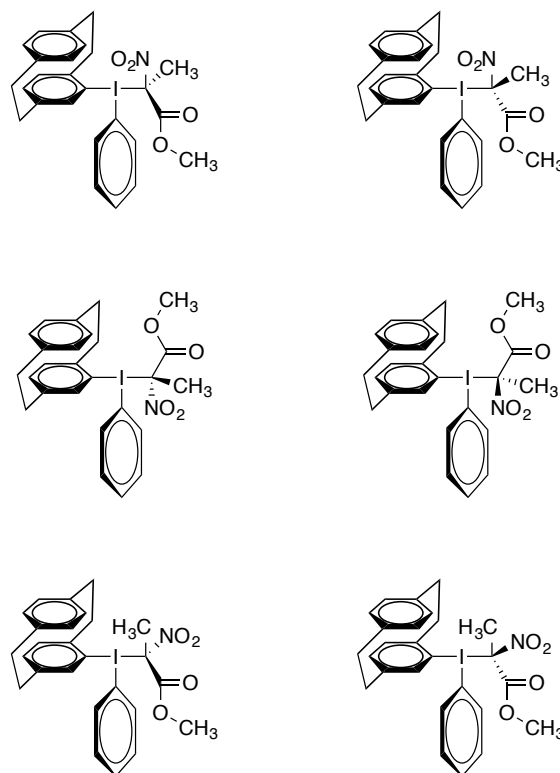


Figure 2.9: Initial structures used for ground state geometry optimizations

In our experience empirical calculations often perform poorly on T-shaped iodonium salts (instead generating nearly tetrahedral structures), so *ab initio* calculations were started directly. Ground state geometry optimizations were performed using B3LYP/3-21G. After Hessian analysis of each structure, to incorporate vibrational energies, a zero-point energy corrected ΔG of 1.517 kcal/mol at 298.15 K was found between the lowest energy rotamer of each intermediate (Figure 2.10).

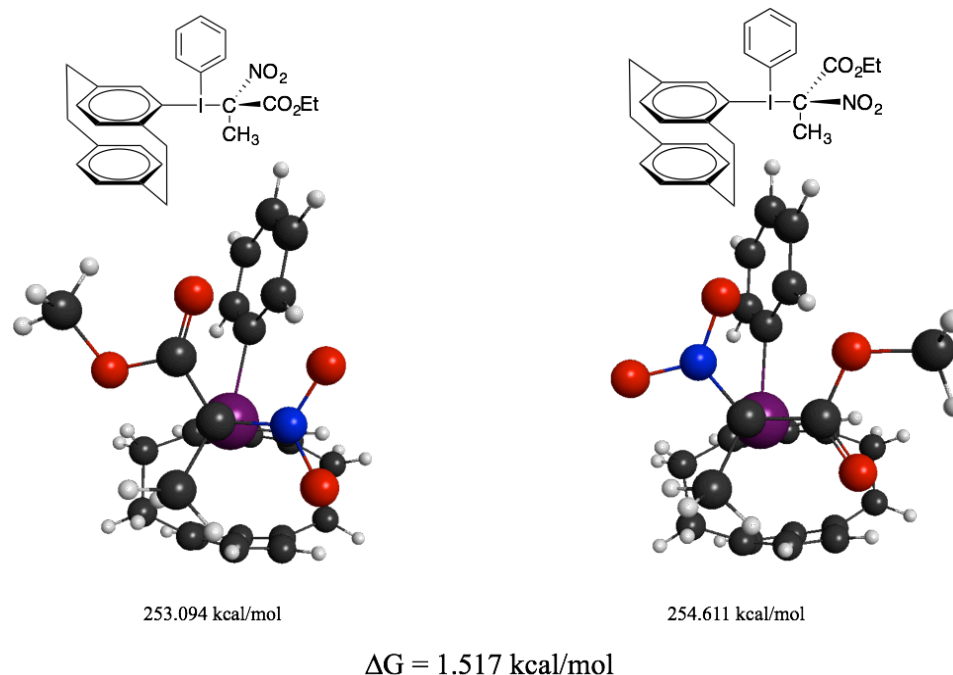


Figure 2.10: Initial ground state energy calculations

Presumably the intermediates could undergo ligand exchange (the two diastereomers are not distinctly visible in ^1H NMR), and at equilibrium there would be an excess of the lower energy compound (13 to 1 at 298.15 K). This distribution may be even higher with the ethyl ester (**9**). Presumably the difference in steric bulk between the alkoxy group and the alkyl group (ethyl ester vs. methyl group in **8**; ethyl ester vs. ethyl group in **9**) dictates the energy difference between the intermediate structures. In the lower energy structure, the sterically smaller group on the enolate aligns with the side closest to cyclophane bridge, so that the sterically larger group may align farther from the cyclophane bridge. Higher level calculations, for each of the lowest energy rotamers, were initiated to obtain a more accurate ground state energy difference. A mixed basis set, B3LYP/DZVP⁵⁶ for the iodine center and B3LYP/6-311G for all other atoms, was

used for the higher level ground state optimizations. Unfortunately, neither calculation would converge, despite multiple attempts using varied input geometries. In all cases the enolate would rearrange to bond to the iodine center at one of the nitro group's oxygens (Figure 2.11). Since the reaction does not progress with oxygen-carbon bond formation these did not seem like reasonable structures along the reaction coordinate.

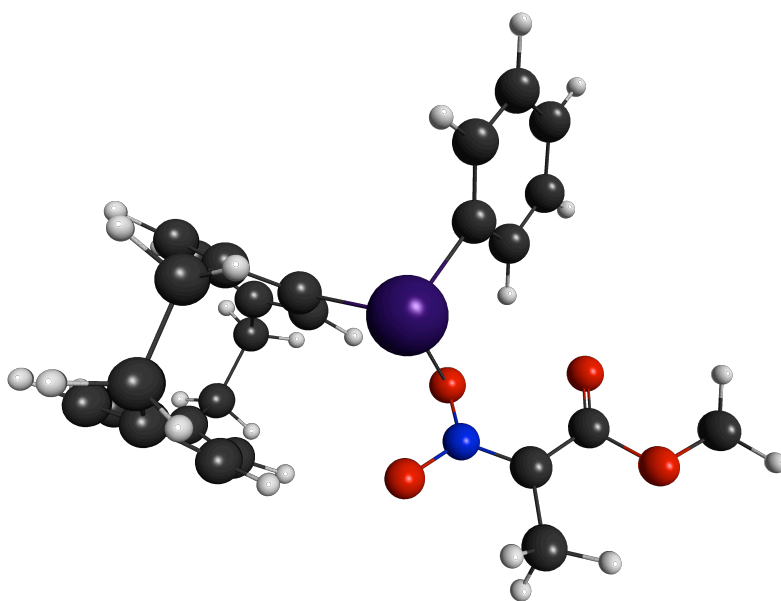


Figure 2.11: Example structure generated from higher level calculation

Despite the lack of higher level energy values, the energy differences in the low-level calculations was promising. Each of these intermediates should undergo reductive elimination to a different aryl nitroester enantiomer. The ratio of these ground state intermediates does not translate directly to an enantiomeric excess; an analysis of the transition state (along the reaction coordinate from each ground state compound above to the appropriate product enantiomer) would be necessary. However, for compounds with this many atoms, especially heavy atoms, the computational time required is often not

practical (each low-level ground state optimization took about two weeks). Based on the difference in ground state energies we were hopeful there would be a similar energy difference between the transition states. We sought to find a way to bring an excess of enolate into solution, in an attempt to promote exchange, and take advantage of the energy difference between the two ground states. Despite historically worse yields found in our lab using more polar solvents for iodonium thermolysis reactions, thermolysis reactions were attempted in DMSO. Using DMSO- d_6 , all reagents dissolved at room temperature. Thermolysis was monitored at room temperature, but no reaction took place. Once the temperature was raised to 40 °C thermolysis began to take place. Though complete thermolysis takes nearly two full days at this temperature, the lower temperature should promote better selectivity. No noticeable side-products were visible in the NMR (compared to reactions in benzene or acetonitrile). Conditions were also established in DMF (with 20% acetonitrile- d_3 to allow for ^1H NMR analysis). Thermolysis also began at 40 °C and no noticeable side-products were visible.

In order to more quickly analyze results, conditions were established for direct separation of enantiomers of the aryl nitroesters by chiral HPLC without performing a two-step reduction/hydrolysis first. Using the Lux chiral column, the two enantiomers were analyzed, after initial aqueous work-up to remove DMSO or DMF (which are not compatible with the Lux column). As a general-purpose chiral column, separation is not as clean as with the Chirex chiral column (Figure 2.12), but the two enantiomers are separable for an initial analysis. An Astec CHIROBIOTIC[®] chiral column was also used, but no separation was found regardless of the conditions used.

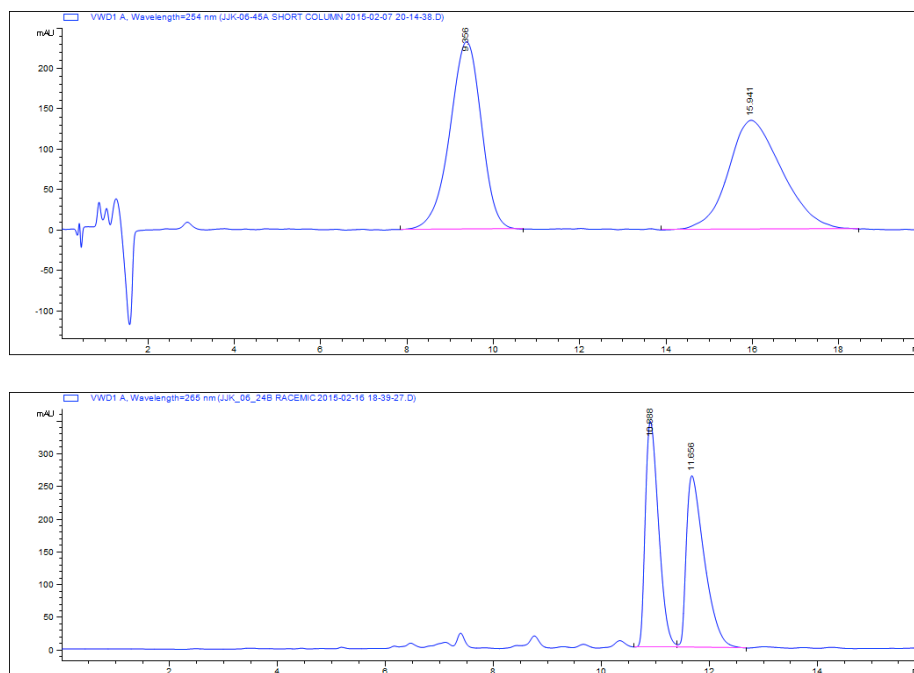


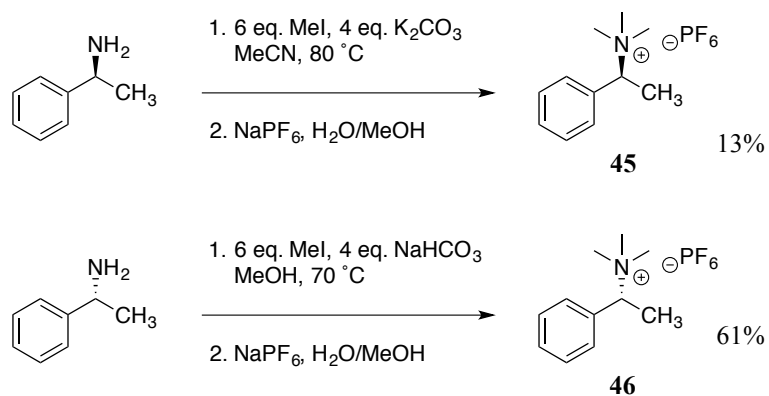
Figure 2.12: Chiral HPLC separations of ethyl 2-nitro-2-phenylpropionate (**13**)
(*top*: Chirex 3126; *bottom*: Lux Cellulose-1)

After initial analysis of the aryl nitroesters on the Lux column, reduction and hydrolysis can still be run, and the product mixture can be analyzed on the Chirex chiral column — this column provides a much larger baseline separation of the amino acid enantiomers than the Lux column provides for the aryl nitroesters. With the Lux column, enantiomeric purity of the aryl nitroester product mixture can be analyzed before the reduction or hydrolysis steps, allowing aliquots, taken from the reaction mixture before and at completion, to be analyzed to investigate potential kinetic resolution. If one enantiomer of the aryl nitroester forms more quickly than the other during thermolysis of **43**, allowing the reaction to run to completion would give an equal mix of enantiomers; halting the reaction before completion would give an enriched mixture of enantiomers.

Thermolysis reactions were performed with superstoichiometric as well as substoichiometric amounts of the enolate to the iodonium salt. Several aliquots were taken throughout the course of the reaction, worked up initially by liquid-liquid extraction to remove DMSO or DMF, and analyzed by chiral HPLC using the Lux column. In DMSO- d_6 , regardless of conditions, all results were racemic (within instrumental error). Even an aliquot taken at 2% conversion showed only 2.4% enantiomeric excess (48.8% to 51.2%), which likely stems from instrumental error (due to the very low amount of product at 2% completion) rather than any actual selectivity. Using DMF (with 30% acetonitrile- d_3 added for NMR), most results showed no selectivity (within instrumental error), but one run, using 80 mol% of the sodium salt of ethyl 2-nitrobutyrate at 40 °C, showed some enantioselectivity. At 66% conversion, after about a day of thermolysis, 26.6% enantiomeric excess was found (63.3% to 36.7%). When taken to completion (at 45 °C), 6.4% enantiomeric excess was found (53.2% to 46.8%). However, due to deviations in the baseline of this HPLC trace, the enantiomeric excess could be attributed to an impurity lying under one of the enantiomer peaks. The partially converted aliquot was concentrated *in vacuo*, dissolved in benzene, and filtered. This should remove any polar contaminants, such as excess enolate and others. The sample was concentrated *in vacuo* again, dissolved in methanol, and filtered. Less polar components, such as (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (**42**) are sparingly soluble in methanol. HPLC analysis of this sample was performed and showed a nearly equal distribution of enantiomers (45.0% to 55.0%). Subsequent runs provided similar results, suggesting either a very small enantiomeric excess, that rapidly decreases with

reaction progress, or simply integration error due to overlapping impurities in the HPLC trace.

We theorized that the intermediate complex (Scheme 2.3, structure A) did not undergo exchange, and initial collision of the enolate and the iodonium center occurs statistically, with little to no preference. A secondary chiral element was introduced. By adding a chiral ammonium salt to the reaction mixture, the sodium enolate, as a soft base, can bind to the soft chiral ammonium salt. This complex, when exchanging with the cyclophane iodonium salt (**43**), should have a higher preference for one face. Commercially available (*R*)- and (*S*)-1-phenylethylamine were methylated with methyl iodide and ion-exchanged with a hexafluorophosphate anion (**45** and **46**). Generation of **45**, using potassium carbonate in acetonitrile, only provided 13% of the desired product, presumably due to Hoffman elimination. For generation of **46**, milder conditions, sodium bicarbonate in methanol, were used and provided 61% of the desired product.

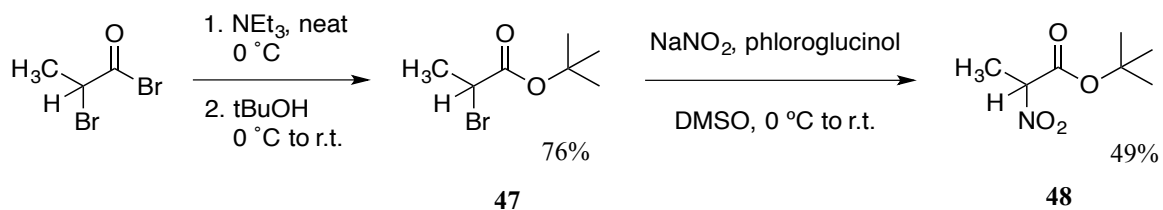


Scheme 2.10: Synthesis of enantiopure *N,N,N*-trimethyl-1-phenylethylammonium hexafluorophosphate salts (**45** and **46**)

Thermolysis reactions in DMF were run under the same conditions as before, but with an excess (3 eq.) of **45** or **46** added; aliquots were taken as the reaction progressed. NMR

analysis showed that thermolysis occurred at the same rate as previous reactions, with no other by-products formed. Unfortunately, HPLC analysis still showed an equal mixture of both enantiomers.

After these results we theorized that at 40 °C, the amount of steric bulk on the cyclophane or the nitro ester did not provide a large enough energy difference to provide stereoselectivity. We sought to design an analogous *tert*-butyl ester to impart more steric bulk on one side of the nitro ester as it approached the iodonium salt. The shorter ester, ethyl 2-nitropropionate (**5**), should provide the most sterically disparate effect. All attempts to hydrolyze ethyl 2-nitropropionate to the corresponding carboxylic acid proved ineffective. Since the α -position is fairly acidic, typical basic methods could not be used. After several attempts, it appeared that under acidic conditions, hydrolysis took place, but decomposition quickly occurred. In the ^1H NMR spectrum, acetic acid, ethanol, and ethyl acetate (presumably an esterification product of the acetic acid and ethanol) were identified along with residual starting material. An alternate route was taken, starting with the more stable α -bromo ester.



Scheme 2.11: Synthesis of *tert*-butyl 2-nitropropionate (**48**)

Commercially available 2-bromopropionyl bromide was carefully esterified with *tert*-butanol to form *tert*-butyl 2-bromopropionate (**47**).⁵⁷ Using the same type of reaction

used to generate the ethyl esters, **5** and **6**, *tert*-butyl 2-bromopropionate was converted to *tert*-butyl 2-nitropropionate (**48**).²⁸ Unlike nitro esters **5** and **6**, the enolate of **48** could not be generated using sodium ethoxide without risk of transesterification. Attempts using potassium *tert*-butoxide in either THF or *tert*-butanol generated the product, but also introduced a sticky yellow impurity that could not be removed. As this ester should be much less soluble in water than the analogous ethyl esters, aqueous sodium carbonate was utilized. Unfortunately, very little product was formed. The neat ester was stirred with a substoichiometric amount of powdered sodium hydride (added slowly in portions) to form the enolate (**49**).

Thermolysis reactions were attempted with the more sterically disparate enolate. Thermolysis began at 40 °C and proceeded in a similar manner, but at a slightly faster rate. A small amount of racemic product was produced using the racemic iodonium salt, **37**, to use for HPLC standards. HPLC conditions were developed and separation was found to be improved with the *tert*-butyl ester product enantiomers. Thermolysis was run with the enantiopure iodonium salt, **43**. Several aliquots were taken over the course of the reaction and analyzed by HPLC. Unfortunately, results were consistent with the ethyl esters; no enantioselectivity was observed.

2.2.6 Future Directions

Increasing the steric hindrance on the ester did not provide enantioselectivity, but it may be worthwhile to rather increase the steric bulk on the cyclophane itself. Rather than using a *p*-methoxy group to make the cyclophane more electron-rich (ensuring full

regioselectivity), an *o*-methoxy group could be used instead. Our group has developed a synthesis for this compound to avoid benzyne formation by abstraction of the *ortho*-cyclophane proton by fluoride.⁴⁷ This compound could be synthesized by utilizing the existing strategy for synthesizing (*S*)-4-hydroxy-[2.2]paracyclophane (**40**), and continuing with the existing strategy for synthesizing (5-(4-methoxy[2.2]paracyclophanyl))(4'-methoxyphenyl)iodonium hexafluorophosphate. Once this compound is synthesized, thermolysis reactions could be run with the existing enolate salts (ethyl and *tert*-butyl) and HPLC analysis could be performed using the same conditions.

2.3 Conclusion

Although a route to stereoselectively produce quaternary α -alkyl α -aryl amino acids was not discovered, a simple procedure for producing quaternary α -alkyl α -aryl amino acids was developed. The convergent nature of the synthesis of these compounds makes this route attractive for screening a variety of unnatural amino acids.

After completion of this work, but before publication of this dissertation, Olofsson and co-workers independently developed a method of delivering nitro esters to arenes using diaryliodonium salts.⁵⁸ The conditions developed are similar to the initial conditions described in this work, but the protic nitro ester is added along with cesium carbonate, to form the enolate salt *in situ*, before thermolysis was performed. No reduction or hydrolysis are performed to make these compounds into amino acids.

We have presented a methodology to rapidly generate quaternary α -alkyl α -aryl amino acids. Using methods such as enzymatic hydrolysis, or separation of enantiomers by chiral HPLC, this approach could be used to synthesize a variety of unnatural amino acids for screening. Stereoselectively generating these compounds, directly from iodonium salt thermolysis, would be ideal, and the methods outlined in this work could be useful for developing a future solution.

2.4 References

1. Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G., "A Mild and General One-Pot Synthesis of Densely Functionalized Diaryliodonium Salts", *Eur. J. Org. Chem.* **2015**, 2015, 5919–5924.
2. Wang, B. "Functionalization of Aromatic Organic Molecules by Anhydrous Fluorides and by Reductive Elimination of Iodine(III)" Ph.D. Dissertation, University of Nebraska, Lincoln, NE, **2010**.
3. Stadtman, E., "Oxidation of Free Amino Acids and Amino Acid Residues in Proteins by Radiolysis and by Metal-Catalyzed Reactions", *Annu. Rev. Biochem.* **1993**, 62, 797–821.
4. Chruma, J. J.; Liu, L.; Zhou, W.; Breslow, R., "Hydrophobic and Electronic Factors in the Design of Dialkylglycine Decarboxylase Mimics", *Bioorg. Med. Chem.* **2005**, 13, 5873–5883.
5. Conway, S. J.; Miller, J. C.; Howson, P. A.; Clark, B. P.; Jane, D. E., "Synthesis of Phenylglycine Derivatives as Potent and Selective Antagonists of Group III Metabotropic Glutamate Receptors", *Bioorg. Med. Chem. Lett.* **2001**, 11, 777–780.
6. Washburn, W. N.; Sun, C.-Q.; Bisacchi, G.; Wu, G.; Cheng, P. T.; Sher, P. M.; Ryono, D.; Gavai, A. V.; Poss, K.; Girotra, R. N.; McCann, P. J.; Mikkilineni, A. B.; Dejneka, T. C.; Wang, T. C.; Merchant, Z.; Morella, M.; Arbeeny, C. M.; Harper, T. W.; Slusarchyk, D. A.; Skwish, S.; Russell, A. D.; Allen, G. T.; Tesfamariam, B.; Frohlich, B. H.; Abboa-Offei, B. E.; Cap, M.; Waldron, T. L.; George, R. J.; Young, D.; Dickinson, K. E.; Seymour, A. A., "BMS-201620: A Selective Beta 3 Agonist",

- Bioorg. Med. Chem. Lett.* **2004**, *14*, 3525–3529.
7. Han, X; Wu, H; Wang, W; Dong, C; Tien, P; Wu, S; Zhou, H-B., “Synthesis and SARs of Indole-Based α -Amino Acids as Potent HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors”, *Org. Biomol. Chem.*, **2014**, *12*, 8308–8317.
 8. Toroeroek, B; Sood, A; Bag, S; Kulkarni, A; Borkin, D; Lawler, E; Dasgupta, S; Landge, S; Abid, M; Zhou, W; Foster, M; LeVine, H; Toeroek, M., “Structure–Activity Relationships of Organofluorine Inhibitors of β -Amyloid Self-Assembly”, *ChemMedChem*, **2012**, *7*, 910–919.
 9. Masaki, Y.; Arasaki, H.; Iwata, M., “Stereospecific Construction of Chiral Quaternary Carbon Compounds from Chiral Secondary Alcohol Derivatives”, *Chem. Lett.* **2003**, *32*, 4–5.
 10. Berkowitz, D. B.; de la Salud-Bea, R.; Jahng, W. J., “Synthesis of Quaternary Amino Acids Bearing a (2'Z)-Fluorovinyl Alpha-branch: Potential PLP Enzyme Inactivators.”, *Org. Lett.* **2004**, *27*, 1821–1824.
 11. Berkowitz, D. B.; Wu, B.; Li, H., “A Formal [3,3]-Sigmatropic Rearrangement Route to Quaternary α -Vinyl Amino Acids: Use of Allylic N-PMP Trifluoroacetimidates”, *Org. Lett.* **2006**, *8*, 971–974.
 12. Karukurichi, K. R.; de la Salud-Bea, R.; Maiti, G.; McFadden, J. M.; Morris, M. L., “Stereoselective Synthesis of Quaternary, α -Vinyl Amino Acids and Their α -(2'Z-Fluoro)Vinyl Congeners: Promising Candidates for PLP Enzyme Inactivation”, ACS Symposium Series 1009; American Chemical Society: Washington, DC, **2009**; 288–

- 303.
13. Chowdari, N. S.; Suri, J. T.; Barbas III, C. F., “Asymmetric Synthesis of Quaternary α - and β -Amino Acids and β -Lactams via Proline-Catalyzed Mannich Reactions with Branched Aldehyde Donors”, *Org. Lett.* **2004**, *6*, 2507–2510.
 14. Cativiela, C.; Díaz-de-Villegas, M. D., “Recent Progress on the Stereoselective Synthesis of Acyclic Quaternary α -Amino Acids”, *Tetrahedron Asymmetry* **2007**, *18*, 569–623.
 15. Cativiela, C.; Ordóñez, M., “Recent Progress on the Stereoselective Synthesis of Cyclic Quaternary α -Amino Acids”, *Tetrahedron Asymmetry* **2009**, *20*, 1–63.
 16. Bera, K.; Namboothiri, I. N. N., “Asymmetric Synthesis of Quaternary α -Amino Acids and Their Phosphonate Analogues”, *Asian J. Org. Chem.* **2014**, *3*, 1234–1260.
 17. Ashfaq, M.; Tabassum, R.; Ahmad, M. M.; Hassan, N. A.; Oku, H.; Rivera, G., “Enantioselective Synthesis of α -Amino Acids: A Review”, *Med. Chem.* **2015**, *5*, 295–309.
 18. Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C., “Asymmetric Synthesis of α -Allyl- α -Aryl α -Amino Acids by Tandem Alkylation/ π -Allylation of α -Iminoesters”, *Org. Lett.* **2014**, *16*, 1948–1951.
 19. Lalonde, J. J.; Bergbreiter, D. E.; Wong, C.-H., “Enzymatic Kinetic Resolution of α -Nitro α -Methyl Carboxylic Acids”, *J. Org. Chem.* **1988**, *53*, 2323–2327.
 20. Gaertzen, O.; Buchwald, S. L., “Palladium-Catalyzed Intramolecular α -Arylation of α -Amino Acid Esters”, *J. Org. Chem.* **2002**, *67*, 465–475.

21. Wang, B.; Qin, L.; Neumann, K.; Uppaluri, S. H.; Cerny, R.; DiMagno, S. G., "Improved Arene Fluorination Methodology for I(III) Salts", *Org. Lett.* **2010**, *12*, 3352–3355.
22. Chen, Z. C.; Jin, Y. Y.; Stang, P. J., "Polyvalent Iodine in Synthesis. 1. An Efficient Route to Isopropylidene Arylmalonates (5-Aryl-Substituted Meldrum's Acid)", *J. Org. Chem.* **1987**, *52*, 4115–4117.
23. Moriarty, R. M.; Vaid, R. K., "Carbon-Carbon Bond Formation Via Hypervalent Iodine Oxidations", *Synthesis* **1990**, *6*, 431–447.
24. Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A., "General Atomic and Molecular Electronic Structure System", *J. Comput. Chem.*, **1993**, *14*, 1347–1363.
25. Gordon, M. S.; Schmidt, M. W., "Advances in electronic structure theory: GAMESS a decade later" in "Theory and Applications of Computational Chemistry: the first forty years"; Dykstra, C.E.; Frenking, G.; Kim, K. S.; Scuseria, G. E., Ed.; Elsevier, Amsterdam, 2005, 1167–1189.
26. Wang, B.; Cerny, R.; Uppaluri, S. H.; Kempinger, J. J.; DiMagno, S. G., "Fluoride-promoted ligand exchange in diaryliodonium salts", *J. Fluor. Chem.* **2010**, *131*, 1113–1121.
27. Kornblum, N.; Blackwood, R. K.; Mooberry, D. D., "The Reaction of Aliphatic Nitro Compounds with Nitrite Esters", *J. Am. Chem. Soc.* **1956**, *78*, 1501–1504.

28. Kornblum, N.; Blackwood, R.; Powers, J., “A New Synthesis of α -Nitroesters”, *J. Am. Chem. Soc.* **1957**, *79*, 2507–2509.
29. Kornblum, N.; Weaver, W. M., “The Reaction of Sodium Nitrite with Ethyl Bromoacetate and with Benzyl Bromide”, *J. Am. Chem. Soc.* **1958**, *80*, 4333–4337.
30. Rodionov, V. M.; Mashinskaya, E. V.; Belikov, V. M. *Zh. Obshch. Khim.* **1948**, *18*, 917.
31. Kornblum, N.; Eicher, J. H., “A New Reaction of α -Nitroesters”, *J. Am. Chem. Soc.* **1956**, *78*, 1494–1497.
32. Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F., “Acidity Inversions of α -NO₂ and α -SO₂CF₃ Activated Carbon Acids as a Result of Contrasting Solvent Effects on Transfer from Water to Dimethyl Sulfoxide Solutions”, *J. Org. Chem.* **2003**, *68*, 6566–6570.
33. Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A., “Ion Pairing and Reactivity of Enolate Anions. 5. Thermodynamics of Ionization of β -Di- and Tricarbonyl Compounds in Dimethyl Sulfoxide Solution and Ion Pairing of Their Alkali Salts”, *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.
34. Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G., “A Mild and General One-Pot Synthesis of Densely Functionalized Diaryliodonium Salts”, *Eur. J. Org. Chem.* **2015**, *2015*, 5919–5924.
35. Wang, B.; Cerny, R.; Uppaluri, S. H.; Kempinger, J. J.; DiMagno, S. G., “Fluoride-promoted ligand exchange in diaryliodonium salts”, *J. Fluor. Chem.* **2010**, *131*,

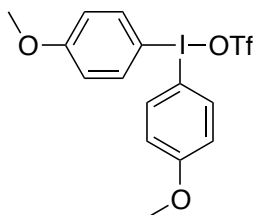
- 1113–1121.
36. Gearba, R. I.; Mueller, K. M.; Veneman, P. A.; Holliday, B. J.; Chan, C. K.; Stevenson, K. J., “Atom-Scale Covalent Electrochemical Modification of Single-Layer Graphene on SiC Substrates by Diaryliodonium Salts”, *J. Electroanal. Chem.* **2015**, *753*, 9–15.
 37. Bielawski, M.; Aili, D.; Olofsson, B., “Regiospecific One-Pot Synthesis of Diaryliodonium Tetrafluoroborates from Arylboronic Acids and Aryl Iodides”, *J. Org. Chem.* **2008**, *73*, 4602–4607.
 38. Sun, H.; DiMugno, S. G., “Anhydrous Tetrabutylammonium Fluoride”, *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051.
 39. Veness, J. “Uses of Diaryliodonium Salts and Methods for Their Synthesis”, Master’s Thesis, University of Nebraska, Lincoln, NE, **2015**.
 40. Finkbeiner, H. L.; Stiles, Martin., “Chelation as a Driving Force in Organic Reactions. IV. Synthesis of α -Nitro Acids by Control of the Carboxylation-Decarboxylation Equilibrium” *J. Am. Chem. Soc.* **1963**, *85*, 616–622.
 41. Meisei, D.; Neta, P., “One-Electron Redox Potentials of Nitro Compounds and Radiosensitizers. Correlation with Spin Densities of Their Radical Anions”, *J. Am. Chem. Soc.* **1975**, *97*, 5198–5203.
 42. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin-Cummings Publishing Co., **1972**.
 43. Béchamp, A., “De L'action des Protosels de fer Sur la Nitronaphtaline et la

- Nitrobenzine. Nouvelle Méthode de Formation des Bases Organiques Artificielles de Zinin”, *Annales de Chimie et de Physique* **1854**, *42*, 186–196.
44. Senkus, M., “Iron Reduction of Some Aliphatic Nitro Compounds”, *Ind. Eng. Chem.* **1948**, *40*, 506–508.
45. CRC Handbook of Chemistry and Physics, 96th ed.; Haynes, W. M., Ed.; CRC Press: Boca Raton, FL, **2015**; Section 7, No. 1–2.
46. Wang, B.; Graskemper, J.; Qin, L.; DiMugno, S. G., “Regiospecific Reductive Elimination from Diaryliodonium Salts”, *Angew. Chemie Int. Ed.* **2010**, *49*, 4079–4083.
47. Graskemper, J.; Wang, B.; Qin, L.; Neumann, K.; DiMugno, S. G., “Unprecedented Directing Group Ability of Cyclophanes in Arene Fluorinations with Diaryliodonium Salts”, *Org. Lett.* **2011**, *13*, 3158–3161.
48. Graskemper, J. “Controlling Reductive Elimination from Novel I(III) Salts Using a SECURE Method”, Master’s Thesis, University of Nebraska, Lincoln, NE, **2010**.
49. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R., “Conversion of Arylboronic Acids into Potassium Aryltrifluoroborates: Convenient Precursors of Arylboron Difluoride Lewis Acids”, *J. Org. Chem.* **1995**, *60*, 3020–3027.
50. Izumi, T.; Hinata, T., “Enzymatic kinetic resolution of [2.2]para-cyclophane derivatives”, *J. Chem. Technol. Biotechnol.* **1992**, *55*, 227–231.
51. Banfi, S.; Manfredi, A.; Montanari, F.; Pozzi, G.; Quici, S., “Synthesis of Chiral Mn(III)-meso-tetrakis-[2.2]-*p*-cyclophanyl-porphyrin: Catalyst for Enantioselective

- Epoxidation”, *J. Mol. Catal. A: Chem.* **1996**, *113*, 77–86.
52. Friedmann, C. J.; Ay, S.; Bräse, S., “Improved Synthesis of Enantiopure 4-Hydroxy[2.2]paracyclophane”, *J. Org. Chem.* **2010**, *75*, 4612–4614.
- 53 Dupray, V. “Recrystallization of Enantiomers from Conglomerates” in “Recrystallization”; Krzysztof Sztwiertnia, Ed., **2012**, 403–424.
- 54 Lorenz, H.; Capla, F.; Polenske, D.; Elsnerand, M. P.; Seidel-Morgenstern, A., “Crystallization Based Separation of Enantiomers”, *J. Univ. Chem. Technol. Metall.*, **2007**, *42*, 5–16.
55. Kostyanovsky, R. G.; Kostyanovsky, V. R.; Kadorkina, G. K.; Torbeev, V. Yu., “Resolution of Racemates with Achiral Reagents”, *Mendeleev Commun.*, **2000**, *10*, 83–84.
56. Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E., “Optimization of Gaussian-Type Basis Sets for Local Spin Density Functional Calculations. Part I. Boron through Neon, Optimization Technique and Validation”, *Can. J. Chem.* **1992**, *70*, 560–571.
57. Linton, B. R.; Reutershan, M. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J., “Asymmetric Michael addition of α -nitro-ketones using catalytic peptides”, *Tetrahedron Lett.* **2007**, *48*, 1993–1997.
58. Dey, C.; Lindstedt, E.; Olofsson, B., “Metal-Free C-Arylation of Nitro Compounds with Diaryliodonium Salts”, *Org. Lett.* **2015**, *17*, 4554–4557.

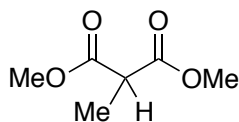
2.5 Experimental

Bis(4-methoxyphenyl)iodonium triflate (1):

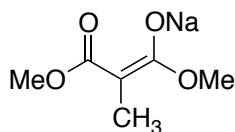


In a flame-dried 25 mL Schlenk flask charged with N₂, bis(acetoxy)iodoanisole (753 mg, 2.13 mmol) was dissolved in 7 mL dry methylene chloride. With stirring, anisole (0.93 mL, 8.52 mmol) was added by syringe. The solution was cooled to -10 °C in a sodium chloride-ice bath. To this solution, triflic acid (0.21 mL, 2.34 mmol) was added dropwise over the course of 10 minutes by syringe. A deep blue color was immediately observed upon addition. After addition, the solution was allowed to warm slowly to room temperature overnight. The solution was reduced to dryness *in vacuo*. The crude solid was recrystallized from methylene chloride by layering with a 10% solution of ether in hexanes to yield a colorless solid (729.6 mg, 69.5%): ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 7.98 (d, *J* = 9.1 Hz, 4H), 7.04 (d, *J* = 9.1 Hz, 4H), 3.83 (s, 6H); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K): δ -79.24 (s, OTf); ¹³C NMR (CD₃CN, 100 MHz, 298 K): δ 164.26, 138.28, 119.07, 103.38, 56.77; HRMS (HRFAB): calcd. for C₁₄H₁₄O₂I [M-OTf]⁺ 341.0038 found 341.0036.

Wang, B.; Cerny, R.L.; Uppaluri, S.; Kempinger, J.J.; DiMagno, S.G. *J. Fluor. Chem.* **2010**, *131*, 1113–1121.

Dimethyl methylmalonate (2):

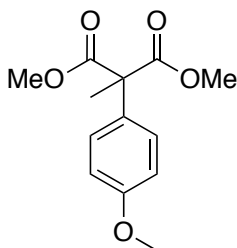
In a flame-dried 100 mL Schlenk flask, dimethyl malonate (3.96 g, 0.030 mmol) was dissolved in dry benzene (20 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and lithium diisopropylamide (16.5 mL, 2.0 M in THF/heptane/ethylbenzene, 0.033 mmol) was added dropwise. The solution was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ and methyl iodide (2.2 mL, 0.036 mmol) was added dropwise. The solution was allowed to warm to r.t. overnight. The sufficiently pure product was isolated under high dynamic vacuum as a colorless oil (1.85 g, 42.3%): ^1H NMR (CD_3CN , 500 MHz, 298 K): δ 3.68 (s, 6H), 3.49 (q, $J = 7.2$ Hz, 1H), 1.33 (d, $J = 7.3$ Hz, 3H).

Sodium 1,3-dimethoxy-2-methyl-3-oxopropenolate (3):

Dry methanol (10 mL) was transferred to a flame-dried 50 mL Schlenk tube by syringe, under nitrogen, and chilled in an ice bath. Freshly cut sodium metal (32.2 mg, 1.1 mmol) was rinsed with dry pentane, and added to the Schlenk tube in portions, slowly. After the sodium had fully reacted, the solution was allowed to warm to room temperature and dimethyl methylmalonate (200.6 μL , 2.3 mmol), dried over 4 \AA molecular sieves, was added dropwise. The solution was stirred for 30 minutes. Methanol was removed in

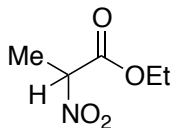
vacuo. The colorless solid was triturated three times, using sonication, with hexanes and dried in *vacuo* (126.8 mg, 52.5%): ^1H NMR (CD_3OD , 400 MHz, 298 K): δ 3.35 (s, 6H), 1.36 (s, 3H); ^{13}C NMR (CD_3OD , 100 MHz, 298 K): δ 172.36, 50.00, 14.01.

Dimethyl 2-(4-methoxyphenyl)-2-methylmalonate (4):



Bis(4-methoxyphenyl)iodonium triflate (0.030 g, 0.030 mmol), sodium 1,3-dimethoxy-2-methyl-3-oxopropenolate (0.011 g, 0.033 mmol) were added to an sealed NMR tube fitted with a Teflon screw cap closure. Benzene- d_6 (0.6 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 140 °C, in the dark. The product was analyzed without isolation: ^1H NMR (C_6D_6 , 400 MHz, 298 K): δ 7.39 (d, $J = 8.9$ Hz, 2H), 6.76 (d, $J = 8.9$ Hz, 2H), 3.32 (s, 6H), 3.26 (s, 3H).

Ethyl 2-nitropropanoate (5):

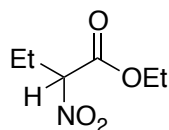


In a 25 mL round bottom flask anhydrous phloroglucinol (267.5 mg, 1.74 mmol) and anhydrous sodium nitrite (207.0 mg, 3.16 mmol) were suspended in DMSO (1.25 mL) with stirring. Ethyl 2-bromobutyrate (210 μL , 1.58 mmol) was added dropwise. The flask

was loosely stoppered, covered in foil, and the suspension was stirred for 1.5 hours. The suspension was poured into ice water (10 mL). The mixture was extracted 5 times with diethyl ether. The organic layers were washed with brine, dried over sodium sulfate, and filtered. Ether was removed *in vacuo* at 100 Torr. The oil was diluted with chloroform (5 mL) and filtered. The solution was chromatographed on silica with ethyl acetate/hexanes (15:85 v/v) to yield a colorless oil (168 mg, 76.1%): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 5.19 (q, $J = 7.2$ Hz, 1H), 4.27 (q, $J = 7.3$ Hz, 2H), 1.77 (d, $J = 7.3$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.30, 83.37, 63.16, 15.81, 13.97; HRMS: (ESI) calcd. for $\text{C}_5\text{H}_8\text{NNa}_2\text{O}_4$ $[\text{M}-\text{H}+2\text{Na}]^+$ 192.0249 found 192.0253.

Kornblum, N.; Blackwood, R. K. *Org. Synth.* **1957**, *37*, 44.

Ethyl 2-nitrobutanoate (6):

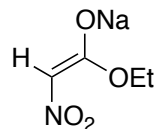


In a 500 mL round bottom flask anhydrous phloroglucinol (20.0 g, 0.16 mol) and anhydrous sodium nitrite (18.0 g, 0.26 mol) were suspended in DMSO (300 mL) with stirring. Ethyl 2-bromobutyrate (20.19 mL, 0.15 mol) was added dropwise. The flask was loosely stoppered, covered in foil, and the suspension was stirred for 2.5 hours. The suspension was poured into ice water (600 mL). Diethyl ether was added (150 mL) and separated. The aqueous layer was extracted 4 times with diethyl ether (50 mL). The organic layers were washed with brine (50 mL), dried over sodium sulfate, and filtered.

Ether was removed *in vacuo* at 100 Torr. The solution was chromatographed on silica with MTBE/hexanes (15:85 v/v) to yield a colorless oil (18.1 g, 74.9%): ^1H NMR (CDCl_3 , 300 MHz, 298 K): δ 5.03 (dd, $J = 9.2$ Hz, $J = 5.6$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.42–2.07 (m, 2H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz, 298 K): δ 164.69, 89.61, 63.11, 24.09, 14.07, 10.35; HRMS: (ESI) calcd. for $\text{C}_6\text{H}_{10}\text{NNa}_2\text{O}_4$ $[\text{M}-\text{H}+2\text{Na}]^+$ 206.0411 found 206.0405; HRMS: (EI^+) calcd. for $\text{C}_6\text{H}_{11}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 184.0586 found 184.0587.

Kornblum, N.; Blackwood, R. K. *Org. Synth.* **1957**, 37, 44.

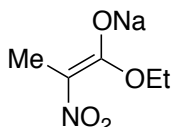
Sodium 1-ethoxy-2-nitroethenolate (7):



Dry ethanol (60 mL) was transferred to a flame-dried 100 mL Schlenk tube by syringe, under nitrogen, and chilled in an ice bath. Freshly cut sodium metal (455.4 mg, 19.8 mmol) was rinsed with dry pentane, and added to the Schlenk tube in portions, slowly. After the sodium had fully reacted, the solution was allowed to warm to room temperature and ethyl nitroacetate (2.3 mL, 20.8 mmol), dried over 4 Å molecular sieves, was added dropwise. A colorless precipitate formed and the mixture was stirred for 30 minutes. Ethanol was removed *in vacuo*. The colorless solid was triturated three times, using sonication, with ether and dried *in vacuo* (2.9463 g, 95.9%): ^1H NMR (CD_3OD ,

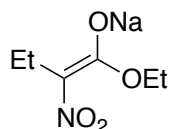
400 MHz, 298 K): δ 4.10 (q, $J = 7.1$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CD₃OD, 100 MHz, 298 K): δ 166.12, 60.17, 14.92.

Sodium 1-ethoxy-2-nitropropenolate (8):



Dry ethanol (60 mL) was transferred to a flame-dried 100 mL Schlenk tube by syringe, under nitrogen, and chilled in an ice bath. Freshly cut sodium metal (551.8 mg, 24.0 mmol) was rinsed with dry pentane, and added to the Schlenk tube in portions, slowly. After the sodium had fully reacted, the solution was allowed to warm to room temperature and ethyl 2-nitropropanoate (3.30 mL, 25.3 mmol), dried over 4 Å molecular sieves, was added dropwise. A colorless precipitate formed and the mixture was stirred for 30 minutes. Ethanol was removed in *vacuo*. The colorless solid was triturated three times, using sonication, with ether and dried in *vacuo* (4.0255 g, 99.2 %): ^1H NMR (CD₃OD, 400 MHz, 298 K): δ 4.15 (q, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CD₃OD, 100 MHz, 298 K): δ 166.38, 113.06, 61.03, 15.20, 14.89.

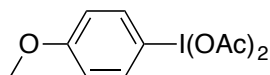
Sodium 1-ethoxy-2-nitrobutenolate (9):



Dry ethanol (60 mL) was transferred to a flame-dried 100 mL Schlenk tube by syringe, under nitrogen, and chilled in an ice bath. Freshly cut sodium metal (551.8 mg, 24.0

mmol) was rinsed with dry pentane, and added to the Schlenk tube in portions, slowly. After the sodium had fully reacted, the solution was allowed to warm to room temperature and ethyl 2-nitrobutyrate (3.7 mL, 25.2 mmol), dried over 4 Å molecular sieves, was added dropwise. A colorless precipitate formed and the mixture was stirred for 30 minutes. Ethanol was removed in *vacuo*. The colorless solid was triturated three times, using sonication, with ether and dried in *vacuo* (4.207 g, 95.7 %): ^1H NMR (CD_3OD , 400 MHz, 298 K): δ 4.16 (q, $J = 7.1$ Hz, 2H), 2.64 (q, $J = 7.3$ Hz, 2H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CD_3OD , 100 MHz, 298 K): δ 166.33, 118.59, 60.86, 23.25, 14.93, 11.65.

Bis(acetoxy)iodoanisole (10):

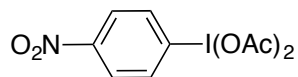


Sodium periodate (11.000g, 51.5 mmol) and sodium acetate (9.000 g, 110.0 mmol) were added to a 100 mL Schlenk storage tube with a stirbar. Acetic acid (50 mL) and acetic anhydride (7.5 mL) were added. 4-iodoanisole (sublimed under vacuum) (11.700 g, 50.0 mmol) was suspended in 25 mL acetic acid and added to the tube with stirring. The tube was sealed and heated to 115 °C for 2.5 hours, stirring vigorously. The mixture was cooled to room temperature and diluted with water (300 mL) and dichloromethane (100 mL). The layers were separated and the aqueous layer was extracted twice with dichloromethane (100 mL). The combined organic layers were dried over sodium sulfate and dichloromethane was removed *in vacuo*. The pale yellow oil was diluted with 200 mL hexanes, triturated, and sonicated until the oil had solidified. The mixture was filtered

and the solid was triturated twice with hexanes. The solid was transferred to a 250 mL Schlenk flask along with 100 mL hexanes and 1 mL acetic acid. The mixture was heated to 35 °C under vacuum overnight to yield a colorless solid (16.139 g, 91.7%). ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.05 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 9.1 Hz, 2H), 3.86 (s, 3H), 1.90 (s, 6H); ¹³C NMR (CD₃CN, 100 MHz, 298 K) δ 177.7, 163.7, 138.7, 118.0, 112.0, 56.8, 20.8; HRMS: (HRFAB) calcd. for C₁₄H₁₃NO₄I [M-2OAc+(3-NBA)]⁺ 385.9889 found 385.9885.

K. P. Landge, K. S. Jang, S. Y. Lee, D. Y. Chi, *J. Org. Chem.* **2012**, *77*, 5705.

Bis(acetoxy)-4-nitrobenzene (11):

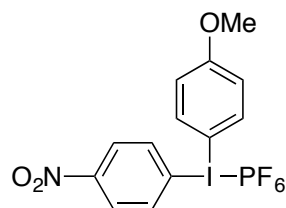


In a nitrogen charged glovebox, 4-iodonitrobenzene (2.34 g, 9.40 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (4.33 g, 12.22 mmol) were suspended in 200 mL acetonitrile in a 500 mL Schlenk storage flask. Trimethylsilyl acetate (3.7 mL, 24.44 mmol) was added with agitation. The flask was sealed and heated to 50 °C for 18 hours in the dark. The reaction was allowed to cool to r.t. and solvent was removed *in vacuo*. The oil was diluted with DCM and washed three times with aqueous acetate buffer (0.5 M sodium acetate, 0.5 M acetic acid) and once with water. The organic layers were dried over sodium sulfate and solvent was removed *in vacuo*. The solid was dissolved in minimal DCM and added to a solution of ether in hexanes (10% v/v). The precipitate was allowed to stand for 30 minutes, and then filtered

through a 0.2 μm PTFE membrane filter. The solid was dried overnight, under high dynamic vacuum (2.93 g, 85.0%). ^1H NMR (400 MHz, CDCl_3 , 298 K) δ 8.32 (d, $J = 8.8$ Hz, 2H), 8.28 (d, $J = 9.2$ Hz, 2H), 2.03 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3 , 298 K) δ 175.0, 147.8, 134.4, 125.1, 124.0, 18.7; HRMS: (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{NO}_6\text{INa}$ $[\text{M}+\text{Na}]^+$ 389.9451 found 389.9455.

Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G. *Eur. J. Org. Chem.* **2015**, 2015, 5919–5924.

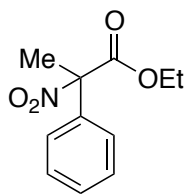
(4-Methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (12):



1-(Diacetoxyiodo)-4-nitrobenzene **1a** (3.00 g, 8.17 mmol) was suspended in 30 mL acetonitrile in a 100 mL Schlenk flask. Potassium 4-methoxyphenyltrifluoroborate (1.83 g, 8.58 mmol) was added. With stirring, a solution of trimethylsilyl trifluoroacetate (1.4 mL, 8.17 mmol) in 3 mL acetonitrile was added dropwise over the course of 15 minutes. The mixture was stirred for 1 hour. Solvent was removed *in vacuo* and the crude oil was dissolved in DCM. The solution was washed three times with aqueous acetate buffer (0.5 M sodium acetate, 0.5 M acetic acid) and once with water. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude oil was triturated three times, using sonication, with 10 mL 10% diethyl ether in hexanes. The

solid was dissolved in acetonitrile and a solution of sodium hexafluorophosphate (13.8 g, 81.7 mmol) was added dropwise with stirring. The mixture was reduced *in vacuo*, and extracted three times with DCM. The organic layers were washed once with water and dried over sodium sulfate. Solvent was removed *in vacuo*, and the solid was suspended, using sonication, in 100 mL distilled benzene, chilled to 10 °C for 30 minutes, and immediately filtered to yield a colorless solid (3.15 g, 76.2%): ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.26 (d, *J* = 9.2 Hz, 2H), 8.20 (d, *J* = 9.2 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 7.10 (d, *J* = 9.2 Hz, 2H), 3.85 (s, OMe); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K): δ -74.14 (d, *J* = 707.2 Hz, PF₆); ¹³C NMR (CD₃CN, 100 MHz, 298 K): δ 164.88, 151.42, 139.39, 136.89, 127.79, 120.18, 119.59, 101.91, 56.91; HRMS: (ESI) calcd. for C₁₃H₁₁INO₃ [M-PF₆]⁺ 355.9784, found: 355.9772.

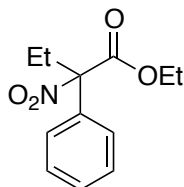
Ethyl 2-nitro-2-phenylpropanoate (13):



Bis(phenyl)iodonium hexafluorophosphate (2.0000 g, 4.69 mmol), sodium 1-ethoxy-2-nitropropenolate (0.8335 g, 4.92 mmol), and tetra n-butylammonium chloride (0.3261 g, 1.17 mmol) were added to a 100 mL Schlenk tube with stirbar. Acetonitrile (50 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky yellow solid was extracted three times with hexanes (3 x 30 mL), using sonication, and hexanes were removed *in vacuo*.

The pale yellow oil was concentrated under high dynamic vacuum to remove iodobenzene. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (5:95 v/v) to yield a colorless oil (0.7637 g, 72.9%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.50–7.39 (m, 5H), 4.35 (q, $J = 7.1$ Hz, 2H), 2.27 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 167.40, 134.29, 130.06, 128.79, 127.68, 95.28, 63.40, 23.32, 14.02; HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{13}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 246.0742 found 246.0750; HRMS (EI^+): calcd. for $\text{C}_{11}\text{H}_{13}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 246.0742 found 246.0737.

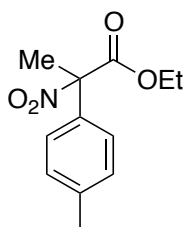
Ethyl 2-nitro-2-phenylbutanoate (14):



Bis(phenyl)iodonium hexafluorophosphate (2.0000 g, 4.69 mmol), sodium 1-ethoxy-2-nitrobutenolate (0.9026 g, 4.92 mmol), and tetra n-butylammonium chloride (0.3261 g, 1.17 mmol) were added to a 100 mL Schlenk tube with stirbar. Acetonitrile (50 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky yellow solid was extracted three times with hexanes (3 x 30 mL), using sonication, and hexanes were removed *in vacuo*. The pale yellow oil was concentrated under high dynamic vacuum to remove iodobenzene. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (5:95 v/v) to yield a colorless oil (1.0365 g, 93.2%): ^1H NMR (CDCl_3 ,

400 MHz, 298 K): δ 7.52–7.45 (m, 2H), 7.45–7.38 (m, 3H), 4.33 (q, $J = 7.1$ Hz, 2H), 2.81–2.63 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.03 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 166.61, 133.51, 129.77, 128.67, 128.15, 99.05, 63.06, 29.41, 14.01, 9.18; HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{15}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 260.0899 found 260.0897.

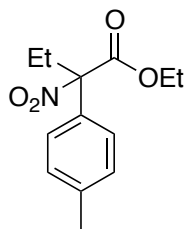
Ethyl 2-(4-methylphenyl)-2-nitropropanoate (15):



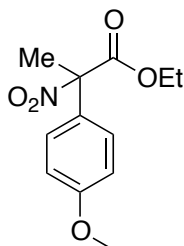
Bis(4-methylphenyl)iodonium hexafluorophosphate (2.1299 g, 4.69 mmol), sodium 1-ethoxy-2-nitropropenolate (0.8335 g, 4.92 mmol), and tetra n-butylammonium chloride (0.3261 g, 1.17 mmol) were added to a 100 mL Schlenk tube with stirbar. Acetonitrile (50 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky yellow solid was extracted three times with hexanes (3 x 30 mL), using sonication, and hexanes were removed *in vacuo*. The pale yellow oil was concentrated under high dynamic vacuum at 30°C to remove 4-iodotoluene. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (7:93 v/v) to yield a colorless oil (0.8713 g, 78.3%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.36 (d, $J = 7.8$ Hz, 2H), 7.24 (d, $J = 7.8$ Hz, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 167.55, 140.25, 131.31, 129.46, 127.63, 95.12, 63.30, 23.19,

21.32, 14.00; HRMS (ESI): calcd. for $C_{12}H_{15}NNaO_4$ $[M+Na]^+$ 260.0899 found 260.0905; HRMS (EI⁺): calcd. for $C_{12}H_{15}NNaO_4$ $[M+Na]^+$ 260.0899 found 260.0894.

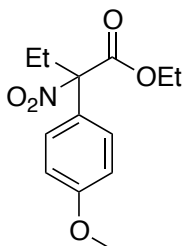
Ethyl 2-(4-methylphenyl)-2-nitrobutanoate (16):



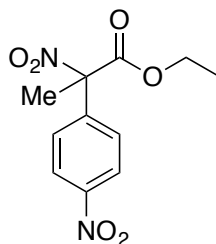
Bis(4-methylphenyl)iodonium hexafluorophosphate (2.1299 g, 4.69 mmol), sodium 1-ethoxy-2-nitrobutenolate (0.9026 g, 4.92 mmol), and tetra n-butylammonium chloride (0.3261 g, 1.17 mmol) were added to a 100 mL Schlenk tube with stirbar. Acetonitrile (50 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky yellow solid was extracted three times with hexanes (3 x 30 mL), using sonication, and hexanes were removed *in vacuo*. The pale yellow oil was concentrated under high dynamic vacuum to remove 4-iodotoluene. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (7:93 v/v) to yield a colorless oil (1.0862 g, 92.2%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.80–2.60 (m, 2H), 2.38 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.3 Hz); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 166.82, 139.97, 130.55, 129.40, 128.15, 98.96, 63.02, 29.29, 21.33, 14.06, 9.23; HRMS (ESI): calcd. for $C_{13}H_{17}NNaO_4$ $[M+Na]^+$ 274.1055 found 274.1053; HRMS (EI⁺): calcd. for $C_{13}H_{17}NNaO_4$ $[M+Na]^+$ 274.1055 found 274.1043.

Ethyl 2-(4-methoxyphenyl)-2-nitropropanoate (17):

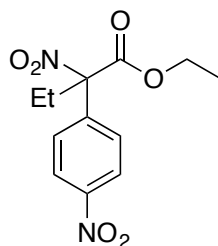
Bis(4-methoxyphenyl)iodonium triflate (1.2746 g, 2.60 mmol), sodium 1-ethoxy-2-nitropropenolate (0.4617 g, 2.73 mmol), and tetra n-butylammonium chloride (0.1807 g, 0.65 mmol) were added to a 50 mL Schlenk tube with stirbar. Acetonitrile (25 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky orange solid was extracted three times with hexanes (3 x 15 mL), using sonication, and hexanes were removed *in vacuo*. The pale orange oil was concentrated under high dynamic vacuum at 60 °C to remove 4-iodoanisole. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (10:90 v/v) to yield a colorless oil (0.6585 g, 65.9%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 7.42 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.25 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 167.70, 160.83, 129.35, 126.08, 114.07, 94.85, 63.30, 55.53, 23.07, 14.03; HRMS (ESI): calcd. for C₁₂H₁₅NNaO₅ [M+Na]⁺ 276.0848 found 276.0855.

Ethyl 2-(4-methoxyphenyl)-2-nitrobutanoate (18):

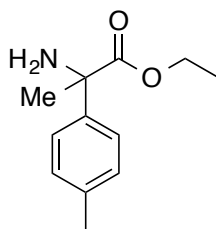
Bis(4-methoxyphenyl)iodonium triflate (1.2746 g, 2.60 mmol), sodium 1-ethoxy-2-nitrobutenolate (0.5000 g, 2.73 mmol), and tetra n-butylammonium chloride (0.1807 g, 0.65 mmol) were added to a 50 mL Schlenk tube with stirbar. Acetonitrile (25 mL) was added to the tube. The tube was sealed, sonicated for 5 minutes, and heated to 80 °C, in the dark. Solvent was removed *in vacuo*. The sticky orange solid was extracted three times with hexanes (3 x 15 mL), using sonication, and hexanes were removed *in vacuo*. The pale orange oil was concentrated under high dynamic vacuum at 60 °C to remove 4-iodoanisole. The oil was chromatographed through a short silica column with ethyl acetate/hexanes (10:90 v/v) to yield a colorless oil (0.4636 g, 66.7%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 7.43 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.7 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.80–2.60 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 166.93, 160.60, 129.84, 125.29, 114.01, 98.68, 62.99, 55.51, 29.06, 14.06, 9.21; HRMS (ESI): calcd. for C₁₃H₁₇NNaO₅ [M+Na]⁺ 290.1004 found 290.1007; HRMS (EI⁺): calcd. for C₁₃H₁₇NNaO₅ [M+Na]⁺ 290.1004 found 290.1017.

Ethyl 2-(4-nitrophenyl)-2-nitropropanoate (19):

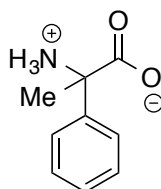
(4-Methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (0.2000 g, 0.2765 mmol), sodium 1-ethoxy-2-nitropropenolate (0.0708 g, 0.2903 mmol), and tetra n-butylammonium chloride (0.0276 g, 0.06913 mmol) were added to a 25 mL Schlenk flask with stirbar. Acetonitrile (3 mL) was added to the flask. The flask was sealed, sonicated for 5 minutes, and heated to 35 °C, in the dark. Solvent was removed *in vacuo* at 35 °C. The sticky yellow solid was chromatographed through a silica column with ethyl acetate/hexanes (10:90 v/v) to yield a pale yellow oil (0.0707 g, 95.3%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 8.29 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 9.0 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 700 MHz, 298 K): δ 166.33, 148.74, 140.61, 129.02, 123.89, 94.47, 64.05, 23.39, 14.00.

Ethyl 2-(4-nitrophenyl)-2-nitrobutanoate (20):

(4-Methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (0.2000 g, 0.2765 mmol), sodium 1-ethoxy-2-nitrobutenolate (0.0767 g, 0.2903 mmol), and tetra n-butylammonium chloride (0.0276 g, 0.06913 mmol) were added to a 25 mL Schlenk flask with stirbar. Acetonitrile (3 mL) was added to the flask. The flask was sealed, sonicated for 5 minutes, and heated to 35 °C, in the dark. Solvent was removed *in vacuo* at 35 °C. The sticky yellow solid was chromatographed through a silica column with ethyl acetate/hexanes (10:90 v/v) to yield a pale yellow oil (0.0765 g, 98.0%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 8.28 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 2H), 4.36 (dq, *J* = 7.1 Hz, *J* = 1.0 Hz, 2H), 2.73 (q, *J* = 7.4 Hz, 2H), 1.32 (t, *J* = 7.1 Hz), 1.03 (t, *J* = 7.4 Hz); ¹³C NMR (CDCl₃, 700 MHz, 298 K): δ 165.62, 148.52, 139.93, 129.47, 123.77, 98.29, 63.75, 29.74, 14.02, 9.02.

Ethyl 2-(4-methylphenyl)-2-aminopropanoate (21):

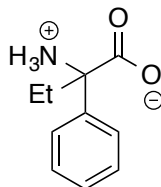
Ethyl 2-(4-methylphenyl)-2-nitropropanoate (0.1482 g, 0.625 mmol) was dissolved in 200 proof ethanol (6.25 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered by syringe through a 0.2 μm PTFE membrane filter, and washed twice with 200 proof ethanol (2 x 2 mL). The solution was extracted three times with dichloromethane. The combined organic layers were washed twice with saturated aqueous sodium bicarbonate and then brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The oil was dissolved in acetonitrile (5 mL) and washed 5 times with hexanes (5 x 2 mL). Acetonitrile was removed *in vacuo* and the crude oil was used without further purification. (0.1049 g, 81.0%): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 7.36 (d, $J = 8.2$ Hz, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 2.31 (s, 3H), 2.05 (br s, NH_2), 1.55 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H).

2-Ammonio-2-phenylpropanoate (22):

Ethyl 2-phenyl-2-nitropropanoate (0.1395 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0903 g, 87.5%): ^1H NMR (10% CD_3OD in $\text{D}_2\text{O}+\text{NaOH}$, pH 12, 500 MHz, 298 K): δ 7.32 (d, $J = 7.3$ Hz, 2H), 7.24 (t, $J = 7.3$ Hz, 2H), 7.16 (t, $J = 7.3$ Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (10% CD_3OD in $\text{D}_2\text{O}+\text{NaOH}$, pH 12, 125 MHz, 298 K):

δ 184.47, 147.09, 129.59, 128.00, 126.28, 62.58, 26.98; HRMS (ESI): calcd. for $C_9H_{10}NNa_2O_2$ $[M-H+2Na]^+$ 210.0512 found 210.0509.

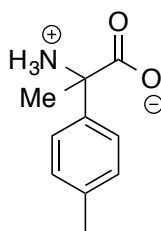
2-Ammonio-2-phenylbutanoate (23):



Ethyl 2-phenyl-2-nitrobutanoate (0.1482 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μ m PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0990 g, 88.4%): 1H NMR ($D_2O+NaOH$, pH 10, 700 MHz, 298

K): δ 7.40 (d, $J = 7.6$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 7.6$ Hz, 1H), 2.12–2.00 (m, 1H), 2.00–1.86 (m, 1H), 0.80 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (10% CD_3OD in $\text{D}_2\text{O} + \text{NaOH}$, pH 10, 176 MHz, 298 K): δ 183.61, 146.36, 129.49, 127.97, 126.72, 66.22, 32.39, 9.25; HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{12}\text{NNa}_2\text{O}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 224.0669 found 224.0656.

2-Ammonio-2-(4-methylphenyl)propanoate (24):

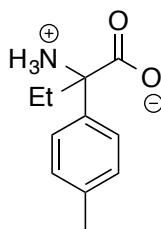


Ethyl 2-(4-methylphenyl)-2-aminopropanoate (0.1049 g, 0.506 mmol) was dissolved in 200 proof ethanol (0.5 mL). 2.0 M aqueous sodium hydroxide (2 mL) was added dropwise with stirring. An oily precipitate formed, but after 2 hours was homogeneous. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0792 g, 87.3%).

Alternate method: ethyl 2-(4-methylphenyl)-2-nitropropanoate (0.1482 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered

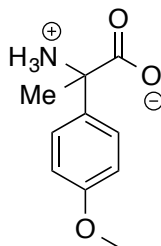
loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0861 g, 76.9%): ^1H NMR ($\text{D}_2\text{O}+\text{NaOH}$, pH 10, 700 MHz, 298 K): δ 7.37 (d, $J = 7.7$ Hz, 2H), 7.25 (d, $J = 7.7$ Hz, 2H), 2.33 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (10% CD_3OD in $\text{D}_2\text{O}+\text{NaOH}$, pH 10, 176 MHz, 298 K): δ 184.49, 144.18, 137.9, 130.05, 126.23, 62.30, 27.00, 21.11; HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{12}\text{NNa}_2\text{O}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 224.0669 found 224.0766.

2-Ammonio-2-(4-methylphenyl)butanoate (25):



Ethyl 2-(4-methylphenyl)-2-nitrobutanoate (0.1571 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with

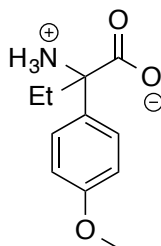
stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0930 g, 77.0%): ^1H NMR (D_2O , pH 5, 500 MHz, 298 K): δ 7.07 (d, $J = 8.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 2.03 (s, 3H), 1.88–1.76 (m, 1H), 1.76–1.64 (m, 1H), 0.58 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (10% CD_3OD in $\text{D}_2\text{O} + \text{NaOH}$, pH 12, 100 MHz, 298 K): δ 184.12, 143.45, 138.17, 130.21, 126.81, 66.03, 32.33, 21.26, 9.34; HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{14}\text{NNa}_2\text{O}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 238.0825 found 238.0811.

2-Ammonio-2-(4-methoxyphenyl)propanoate (26):

Ethyl 2-(4-methoxyphenyl)-2-nitropropanoate (0.1577 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.1580 g, 81.0%): ^1H NMR (D_2O , pH 5, 700 MHz, 298 K): δ 7.40 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 3.76 (s, 3H), 1.89 (s, 3H); ^{13}C NMR

(D₂O, pH 5, 176 MHz, 298 K): δ 174.68, 159.45, 128.48, 127.34, 114.47, 61.73, 55.30, 21.01; HRMS (ESI): calcd. for C₁₀H₁₂NNa₂O₃ [M-H+2Na]⁺ 240.0618 found 240.0609.

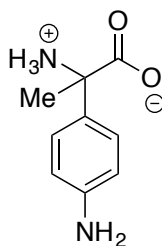
2-Ammonio-2-(4-methoxyphenyl)butanoate (27):



Ethyl 2-(4-methoxyphenyl)-2-nitrobutanoate (0.1671 g, 0.625 mmol) was dissolved in 200 proof ethanol (6 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (1.6345 g, 25 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μ m PTFE membrane filter, and washed twice with dichloromethane (2 x 5 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 5 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 5 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 4 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water, at r.t., and chilled in the refrigerator. The colorless solid was collected by vacuum filtration and washed with cold water (0.0954 g, 85.2%): ¹H NMR (D₂O, pH 4, 700 MHz, 298 K): δ

7.53 (d, $J = 8.2$ Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 2H), 3.96 (s, 3H), 2.25–2.16 (m, 1H), 2.15–2.06 (m, 1H), 0.98 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (10% CD_3OD in D_2O , pH 4, 176 MHz, 298 K): δ 183.24, 157.71, 138.14, 127.26, 114.10, 64.74, 56.16, 55.60, 8.47; HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{17}\text{NNaO}_3$ $[\text{M}-\text{H}+2\text{Na}]^+$ 254.0775 found 254.0763.

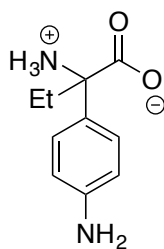
2-Ammonio-2-(4-aminophenyl)propanoate (28):



Ethyl 2-(4-nitrophenyl)-2-nitropropanoate (0.0394 g, 0.1469 mmol) was dissolved in 200 proof ethanol (2 mL). Concentrated aqueous HCl (0.3 mL) was added dropwise with stirring. Zinc dust (0.5450 g, 8.336 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 2 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 2 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 2 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and stirred for 2 hours. The solution was acidified to pH 6 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water and

chromatographed on a reverse phase Waters Sep-Pack (C18 Plus) using 100% water. Solvent was evaporated *in vacuo* to yield a colorless solid (0.0207 g, 78.1%): ^1H NMR ($\text{D}_2\text{O}+\text{NaOH}$, pH 10, 700 MHz, 298 K): δ 6.64 (d, $J = 7.8$ Hz, 2H), 6.19 (d, $J = 7.8$ Hz, 2H), 0.93 (s, 3H); ^{13}C NMR ($\text{D}_2\text{O}+\text{NaOH}$, pH 10, 176 MHz, 298 K): δ 183.49, 168.24, 168.23, 144.64, 135.58, 125.75, 125.71, 115.80, 60.39; HRMS (ESI): calcd. for $\text{C}_9\text{H}_{11}\text{N}_2\text{Na}_2\text{O}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 225.0616 found 225.0613.

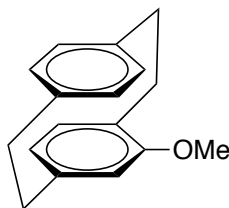
2-Ammonio-2-(4-aminophenyl)butanoate (29):



Ethyl 2-(4-nitrophenyl)-2-nitrobutanoate (0.0406 g, 0.1469 mmol) was dissolved in 200 proof ethanol (2 mL). Concentrated aqueous HCl (1.0 mL) was added dropwise with stirring. Zinc dust (0.5450 g, 8.336 mmol) was added slowly, in portions, with stirring. The suspension was stirred vigorously for 3 hours, covered loosely. The suspension was neutralized with saturated aqueous sodium bicarbonate, filtered through a 0.2 μm PTFE membrane filter, and washed twice with dichloromethane (2 x 2 mL). The layers were separated and the aqueous layer was extracted two times with dichloromethane (2 x 2 mL). The combined organic layers were washed twice with saturated aqueous sodium bicarbonate (2 x 2 mL). Dichloromethane was removed *in vacuo*, the oil was diluted with 200 proof ethanol (2 mL), and concentrated to half the volume to remove trace dichloromethane. The oil was diluted with 2.0 M aqueous sodium hydroxide (2 mL) and

stirred for 2 hours. The solution was acidified to pH 5 with 2.0 M aqueous HCl. Ethanol and water were removed *in vacuo*. The solid was dissolved in minimal water and chromatographed on a reverse phase Waters Sep-Pack (C18 Plus) using 100% water. Solvent was evaporated *in vacuo* to yield a colorless solid (0.0223 g, 76.0%): ^1H NMR (D_2O , pH 5, 400 MHz, 298 K): δ 7.36 (d, $J = 8.3$ Hz, 2H), 6.96 (d, $J = 8.3$ Hz, 2H), 2.47–2.28 (m, 2H), 1.10 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (D_2O , pH 5, 150.9 MHz, 298 K): δ 176.44, 147.19, 129.05 (br), 127.76, 116.77, 67.58, 28.44, 8.27; HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{Na}_2\text{O}_2$ $[\text{M}-\text{H}+2\text{Na}]^+$ 239.0772 found 239.0777.

(±)-4-Methoxy-[2.2]paracyclophane (30):

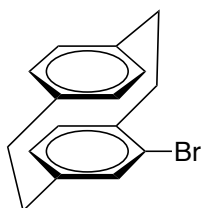


In a 100 mL Schlenk storage tube potassium carbonate (14.15 g, 102.39 mmol) and (±)-4-hydroxy[2.2]paracyclophane (7.420 g, 33.02 mmol) were dissolved in acetonitrile (60 mL) and heated to 80 °C for 30 minutes. Iodomethane (6.35 mL, 102.39 mmol) was added dropwise, the tube was sealed, and the mixture was stirred at 80 °C for 3 days. Solvent was removed *in vacuo*, and the solid was dissolved in ethyl acetate, and water was added. The mixture was neutralized with aqueous hydrochloric acid (0.1 M) and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The solid was chromatographed on silica, loaded using hot hexanes, and eluted as a gradient from 0% ethyl acetate/hexanes (v/v) to 3% to yield

a colorless solid (3.639 g, 46.3%). ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 6.76 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 6.38–6.55 (m, 4H), 6.28 (dd, $J = 7.5$ Hz, $J = 1.4$ Hz, 1H), 5.67 (d, $J = 1.3$ Hz, 1H), 3.71 (s, 3H), 3.42–3.48 (m, 1H), 2.99–3.13 (m, 6H), 2.59–2.66 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 157.6, 142.1, 140.3, 138.8, 135.0, 133.7, 133.1, 131.5, 128.4, 127.5, 124.4, 116.7, 54.3, 35.5, 35.4, 34.1, 31.7; HRMS (EI^+): calcd. for $\text{C}_{17}\text{H}_{18}\text{O}$ $[\text{M}]^+$ 238.1358 found 238.1358.

Cram, D. J.; Day, A. C. *J. Org. Chem.* **1966**, *31*, 1227-32.

(±)-4-Bromo-[2.2]paracyclophane (31):

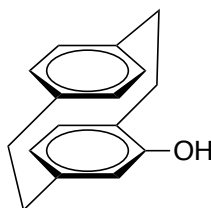


In a 4 L amber bottle, [2.2]paracyclophane (20.00 g, 95.18 mmol) was dissolved in dichloromethane (1.6 L). In a separate beaker, *N*-bromosuccinamide (17.28 g, 97.08 mmol) and trifluoroacetic acid (7.48 mL, 97.08 mmol) were dissolved in dichloromethane (0.8 L) with stirring. Once fully dissolved, this solution was poured into the 4 L amber bottle. The solution was stirred for 2 days, then transferred to a separatory funnel. The solution was washed 3 times with a solution of saturated aqueous sodium bicarbonate in water (1:1 v/v), and once with brine. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo* to yield the crude product (carried forward without further purification) as a nearly colorless powder (29.09 g,

82.2%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.18 (dd, $J = 7.8$ Hz, $J = 1.9$ Hz, 1H), 6.45–6.61 (m, 6H), 3.45–3.52 (m, 1H), 2.80–3.26 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 141.61, 139.33, 139.11, 137.25, 135.05, 133.31, 133.02, 132.91, 132.25, 131.46, 128.69, 126.97, 35.85, 35.48, 34.82, 33.47; HRMS (EI^+): calcd. for $\text{C}_{16}\text{H}_{15}\text{Br}$ $[\text{M}]^+$ 286.0357, 288.0337 found 286.0344, 288.0339.

Cram, D. J.; Day, A. C. *J. Am. Chem. Soc.* **1966**, *31*, 1227–1232.

(\pm)-4-Hydroxy-[2.2]paracyclophane (32):

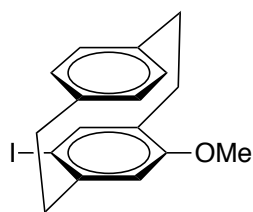


In a flame-dried 1L Schlenk flask with a stirbar, (\pm)-4-bromo-[2.2]paracyclophane (9.500 g, 33.31mmol) was dissolved in dry ether (300 mL). The solution was cooled to -78 °C and *tert*-butyl lithium (1.7 M in pentane, 45 mL, 76.62 mmol) was added dropwise. The suspension was stirred at -78 °C for 20 minutes, warmed to 0 °C, and held at 0 °C for 20 minutes. Trimethylborate (7.36 mL, 66.62 mmol) was added dropwise and the solution was allowed to warm to r.t. over the course of an hour. To this suspension, a solution of hydrogen peroxide (30% v/v in water, 12.4 mL) and sodium hydroxide (0.5 M in water, 16.5 mL) was added dropwise and the mixture was stirred overnight. Additional sodium hydroxide ((0.5 M in water, 33 mL) was added. The mixture was neutralized with saturated aqueous sodium bicarbonate and hydrochloric acid (1 M), and extracted three

times with ether. The organic layers were washed with dilute sodium bisulfite, dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude pale orange solid was used without further purification (7.42 g, quantitative): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.01 (dd, $J = 7.8$ Hz, $J = 1.9$ Hz, 1H), 6.56 (dd, $J = 7.8$ Hz, $J = 1.9$ Hz, 1H), 6.46 (dd, $J = 7.8$ Hz, 1.9 Hz, 1H), 6.38–6.42 (m, 2H), 6.27 (dd, $J = 7.7$ Hz, $J = 1.6$ Hz, 1H), 5.55 (d, $J = 1.6$ Hz, 1H), 4.45 (s, 1H), 3.29–3.39 (m, 1H), 2.87–3.16 (m, 6H), 2.62–2.73 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 153.7, 142.0, 139.6, 138.8, 135.5, 133.0, 132.8, 131.9, 127.9, 125.4, 125.0, 122.6, 35.3, 34.8, 33.8, 31.1; HRMS (EI^+): calcd. for $\text{C}_{16}\text{H}_{16}\text{O}$ $[\text{M}]^+$ 224.1201 found 224.1198.

Krohn, K.; Rieger, H.; Hopf, H.; Barrett, D.; Jones, P. G.; Döring, D. *Chem. Ber.* **1990**, *123* 1729.

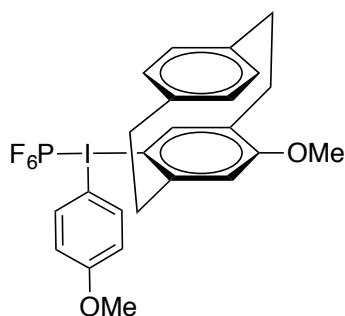
(±)-7-Iodo-4-methoxy-[2.2]paracyclophane (33):



In a 100 mL round bottom flask, (±)-4-methoxy-[2.2]paracyclophane (1.2461 g, 5.27 mmol) was dissolved in dichloromethane (50 mL). In an addition funnel, *N*-iodosuccinimide (1.259g, 5.54 mmol) and trifluoroacetic acid (0.43 mL, 5.54 mmol) were dissolved in dichloromethane (50 mL) with swirling and added to the round bottom flask over 5 minutes. The solution was stirred, in the dark, for 1.5 hours before being

neutralized by saturated aqueous sodium bicarbonate. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed once with saturated aqueous sodium bicarbonate, a solution of sodium metabisulfite in brine (5 g/L), then brine. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was dissolved from minimal boiling hexanes (~60 mL), chilled to -20 °C, filtered, and washed with cold hexanes to yield a pale brown solid (1.605 g, 83.8%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.13 (dd, $J = 7.9$ Hz, $J = 1.8$, 1H), 6.75 (dd, $J = 7.9$ Hz, $J = 1.8$ Hz, 1H), 6.71 (s, 1H), 6.46 (dd, $J = 7.9$ Hz, $J = 1.8$, 1H), 6.40 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 5.69 (s, 1H), 3.68 (s, 3H), 2.82–3.37 (m, 7H), 2.43–2.53 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 157.9, 144.7, 143.9, 139.9, 138.5, 132.9, 131.5, 129.9, 129.6, 128.9, 117.7, 91.9, 54.3, 39.3, 33.6, 33.2, 31.1; HRMS (EI^+): calcd. for $\text{C}_{17}\text{H}_{17}\text{IO}$ $[\text{M}]^+$ 364.0324 found 364.0330.

(4-((±)-7-Methoxy-[2.2]paracyclophanyl))(4-methoxyphenyl)iodonium hexafluorophosphate (36):



In a flame-dried 50 mL Schlenk tube, (±)-7-iodo-4-methoxy-[2.2]paracyclophane (0.1250 g, 0.3432 mmol) was dissolved, with stirring, in warm ether (10 mL), under N_2 . The

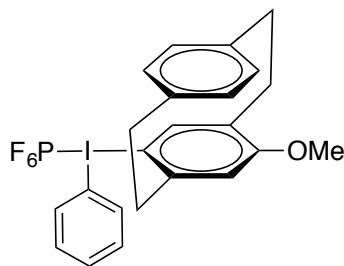
solution was gradually cooled, with vigorous stirring, to $-78\text{ }^{\circ}\text{C}$. To this mixture, *n*-butyl lithium (2.5 M in hexanes, 0.16 mL, 0.3775 mmol) was added, dropwise. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 minutes. In a separate 50 mL Schlenk tube, anhydrous zinc chloride (0.300 g, 2.059 mmol) was gently flame-dried until bubbling subsided. An oven-dried stirbar was added. After cooling to r.t., dry ether (12 mL) was added, under N_2 , and the solid was dissolved using sonication and vigorous stirring. A portion of this solution (4 mL, 0.6864 mmol zinc chloride) was added dropwise to the first Schlenk tube. The suspension was allowed to warm to room temperature and ether was removed under high dynamic vacuum to yield a foam. Dry acetonitrile (3 mL) was added with stirring to dissolve the foam. In a separate flame-dried 50 mL Schlenk tube, bis(acetoxy)-4-iodoanisole (0.1813 g, 0.5148 mmol) was dissolved in dry acetonitrile (10 mL). Both solutions were chilled to $-20\text{ }^{\circ}\text{C}$ and the organozinc chloride solution was added, dropwise, over the course of 5 min to the bis(acetoxy)-4-iodoanisole solution. The resulting solution was held at $-20\text{ }^{\circ}\text{C}$ for 30 minutes before warming to r.t. Deionized water and sodium hexafluorophosphate (0.1441g, 0.8580 mmol) were added, with stirring, and the mixture was concentrated *in vacuo*. The mixture was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was dissolved in minimal dichloromethane and slowly dripped into a stirring solution of ether in hexanes (10% v/v). Stirring was stopped, and after standing for an hour, the mixture was filtered and the solid rinsed three times with hexanes to yield a colorless powder (0.1546 g, 73.2%): $^1\text{H NMR}$ (CD_3CN , 400 MHz, 298 K): δ 8.01 (d, $J = 9.2\text{ Hz}$, 2H), 7.25 (s, 1H),

7.07 (d, $J = 9.2$ Hz, 2H), 6.81 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 6.62 (dd, $J = 7.9$ Hz, $J = 1.9$ Hz, 1H), 6.29 (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H), 6.12 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 6.02 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.31 (ddd, $J = 11.6$ Hz, $J = 9.8$ Hz, $J = 1.7$ Hz, 1H), 3.26 (dd, $J = 8.4$ Hz, $J = 5.7$ Hz, 1H), 3.23 (dd, $J = 13.9$ Hz, $J = 4.3$ Hz, 1H), 3.18 (dd, $J = 12.9$ Hz, $J = 4.1$ Hz, 1H), 3.15 (dd, $J = 8.3$ Hz, $J = 3.0$ Hz, 1H), 3.05 (ddd, $J = 12.8$ Hz, $J = 9.9$ Hz, $J = 6.4$ Hz, 1H), 3.02 (ddd, $J = 12.8$ Hz, $J = 9.9$ Hz, $J = 6.4$ Hz, 1H), 2.68 (ddd, $J = 13.1$ Hz, $J = 10.5$ Hz, $J = 6.4$ Hz, 1H); ^{13}C NMR (CD_3CN , 400 MHz, 298 K): δ 163.3, 161.6, 146.4, 140.5, 139.9, 137.9, 137.4, 133.2, 132.4, 131.4, 131.3, 128.8, 119.8, 118.2, 107.4, 101.1, 55.8, 54.9, 37.2, 34.5, 32.9, 30.7; ^{19}F NMR (CD_3CN , 376 MHz, 298 K): δ -72.7 (d, $J = 706.7$ Hz, 6F); HRMS: (HRFAB) calcd. for $\text{C}_{24}\text{H}_{24}\text{IO}_2$ $[\text{M}]^+$ 471.08210 (100%), 472.08454 (26%) found 471.08221 (100%), 472.08561 (23%).

Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083.

(4-(±)-7-Methoxy-[2.2]paracyclophanyl)(phenyl)iodonium hexafluorophosphate

(37):

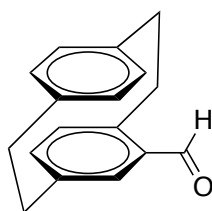


In a flame-dried 50 mL Schlenk tube, (±)-7-iodo-4-methoxy-[2.2]paracyclophane (0.1250

g, 0.3432 mmol) was dissolved, with stirring, in warm ether (10 mL), under N₂. The solution was gradually cooled, with vigorous stirring, to -78 °C. To this mixture, *n*-butyl lithium (2.5 M in hexanes, 0.16 mL, 0.3775 mmol) was added, dropwise. The mixture was stirred at -78 °C for 30 minutes. In a separate 50 mL Schlenk tube, anhydrous zinc chloride (0.300 g, 2.059 mmol) was gently flame-dried until bubbling subsided. An oven-dried stirbar was added. After cooling to r.t., dry ether (9 mL) was added, under N₂, and the solid was dissolved using sonication and vigorous stirring. A portion of this solution (3 mL, 0.6864 mmol zinc chloride) was added dropwise to the first Schlenk tube. The suspension was allowed to warm to room temperature and ether was removed under high dynamic vacuum to yield a foam. Dry acetonitrile (3 mL) was added with stirring to dissolve the foam. In a separate flame-dried 50 mL Schlenk tube, bis(acetoxy)iodobenzene (0.1658 g, 0.5148 mmol) was dissolved in dry acetonitrile (10 mL). Both solutions were chilled to -20 °C and the organozinc chloride solution was added, dropwise, over the course of 5 min to the bis(acetoxy)iodobenzene solution. The resulting solution was held at -20 °C for 30 minutes before warming to r.t. Deionized water and sodium hexafluorophosphate (0.1441g, 0.8580 mmol) were added, with stirring, and the mixture was concentrated *in vacuo*. The mixture was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was dissolved in minimal dichloromethane and slowly dripped into a stirring solution of ether in hexanes (10% v/v). Stirring was stopped, and after standing for an hour, the mixture was filtered and the solid rinsed three times with hexanes to yield a colorless powder (0.1255 g,

62.3%): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.03 (d, $J = 7.9$ Hz, 2H), 7.70 (t, $J = 7.5$ Hz, 1H), 7.54 (t, $J = 7.9$ Hz, 2H), 7.29 (s, 1H), 6.82 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 6.63 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 6.34 (dd, $J = 7.9$ Hz, $J = 1.9$ Hz, 1H), 6.19 (dd, $J = 7.9$ Hz, $J = 1.9$ Hz, 1H), 6.04 (s, 1H), 3.74 (s, 3H), 3.37–2.99 (m, 7H), 2.74–2.64 (m, 1H); ^{19}F NMR (CD_3CN , 400 MHz, 298 K): δ -72.88 (d, $J = 708.0$ Hz, 6F); HRMS (ESI): calcd. for $\text{C}_{23}\text{H}_{22}\text{IO}$ $[\text{M-PF}_6]^+$ 441.0710 found 441.0730.

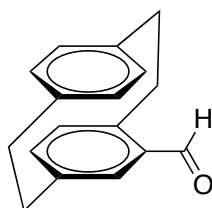
(±)-4-Formyl-[2.2]paracyclophane (38):



In a flame-dried 500 mL Schlenk flask, (±)-4-bromo-[2.2]paracyclophane (4.296 g, 15.07 mmol) was dissolved in warm ether (150 mL), under N_2 , with stirring. The solution was chilled to -78 °C and *tert*-butyl lithium (1.7 M in pentane, 22.2 mL, 37.69 mmol) was added dropwise. The mixture was held at -78 °C for 30 min, warmed to 0 °C, and held at 0 °C for 30 min. The mixture was chilled to -78 °C and *N,N*-dimethylformamide (3.5 mL, 45.22 mmol) was added, dropwise. The mixture was held at -78 °C for 15 minutes, then allowed to warm to r.t. overnight. Solvent was removed *in vacuo* and the solid was dissolved in dichloromethane, washed three times with deionized water. The aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with brine. The organic layers were dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was chromatographed, loaded dry.

[2.2]paracyclophane was removed by flushing the column with hexanes. The product was eluted as a gradient from 5% ethyl acetate/hexanes (v/v) to 10% to yield an off-white solid (2.465 g, 69.8%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 9.95 (s, 1H), 7.02 (s, 1H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.60 (d, $J = 7.8$ Hz, 1H), 6.57 (d, $J = 7.7$ Hz, 1H), 6.50 (d, $J = 7.7$ Hz, 1H), 6.44 (d, $J = 7.9$ Hz, 1H), 6.38 (d, $J = 7.9$ Hz, 1H), 4.11 (t, $J = 11.1$ Hz, 1H), 3.23–2.90 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 192.11, 143.41, 140.84, 139.69, 139.63, 138.26, 136.78, 136.53, 136.30, 133.44, 133.10, 132.55, 132.34, 35.45, 35.33, 35.17, 33.80; HRMS (EI^+): calcd. for $\text{C}_{17}\text{H}_{16}\text{O}$ $[\text{M}]^+$ 236.1201 found 236.1204.

(S)-4-Formyl-[2.2]paracyclophane (39):

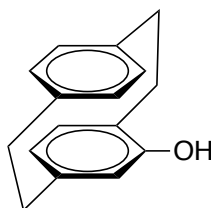


In a 1 L round bottom flask with a stirbar, (\pm)-4-hydroxy-[2.2]paracyclophane (16.111 g, 68.76 mmol) was dissolved in benzene (0.4 L). (*R*)-1-phenethylamine (8.80 mL, 68.76 mmol) was added dropwise and the solution was heated at reflux overnight. Solvent was removed *in vacuo* and the crude oil was placed under high dynamic vacuum. The crude solid was dissolved in gently boiling hexanes (410 mL). The flask was insulated and allowed to cool slowly to room temperature and then chilled to 0 °C. The mixture was filtered and the solid was washed with cold hexanes. The solid was dissolved in gently boiling hexanes (200 mL). The flask was insulated and allowed to cool slowly to room temperature and then chilled to 0 °C. The mixture was filtered and the solid was washed

with cold hexanes. Diastereomeric purity was confirmed by ^1H NMR. The solid was dissolved in dichloromethane and passed down a short silica plug to cleave the imine, yielding the product as a colorless powder (2.988 g, 18.5%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 9.95 (s, 1H), 7.02 (s, 1H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.60 (d, $J = 7.8$ Hz, 1H), 6.57 (d, $J = 7.7$ Hz, 1H), 6.50 (d, $J = 7.7$ Hz, 1H), 6.44 (d, $J = 7.9$ Hz, 1H), 6.38 (d, $J = 7.9$ Hz, 1H), 4.11 (t, $J = 11.1$ Hz, 1H), 3.23–2.90 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 192.11, 143.41, 140.84, 139.69, 139.63, 138.26, 136.78, 136.53, 136.30, 133.44, 133.10, 132.55, 132.34, 35.45, 35.33, 35.17, 33.80; HRMS (EI^+): calcd. for $\text{C}_{17}\text{H}_{16}\text{O}$ $[\text{M}]^+$ 236.1201 found 236.1204; HPLC (Phenomenex® Lux chiral column (250 mm length, 4.6 mm diameter, 3 μm particle size), methanol:water (90:10 v/v), 1.0 mL/min, 254 nm): 19.74 min (*R*); 24.48 min (*S*); ee 94.0%.

Banfi, S.; Manfredi, A.; Montanari, F.; Pozzi, G.; Quici, S. *J. Mol. Catal. A: Chem.* **1996**, *113*, 77–86.

(*S*)-4-Hydroxy-[2.2]paracyclophane (40):

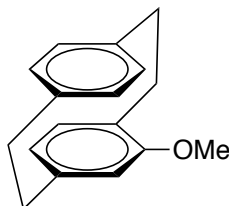


In a 250 mL round bottom flask, (*S*)-4-formyl-[2.2]paracyclophane (2.988 g, 12.72 mmol) was dissolved in dichloromethane (60 mL) and methanol (60 mL). Concentrated sulfuric acid (0.7 mL) was added dropwise. Hydrogen peroxide (35% aqueous, 1.5 mL)

was added dropwise. The solution was stirred, loosely capped, for 16 hours. Solvents were removed *in vacuo*. The crude oily solid was diluted with dichloromethane, and washed two times with deionized water. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was chromatographed on silica, loading in hot dichloromethane, and eluting as a gradient from 100% hexanes to 15% ethyl acetate in hexanes (v/v) to yield a pale orange solid (1.789 g, 63.1%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.01 (dd, $J = 7.8$ Hz, $J = 1.9$ Hz, 1H), 6.56 (dd, $J = 7.8$ Hz, $J = 1.9$ Hz, 1H), 6.46 (dd, $J = 7.8$ Hz, 1.9 Hz, 1H), 6.38–6.42 (m, 2H), 6.27 (dd, $J = 7.7$ Hz, $J = 1.6$ Hz, 1H), 5.55 (d, $J = 1.6$ Hz, 1H), 4.45 (s, 1H), 3.29–3.39 (m, 1H), 2.87–3.16 (m, 6H), 2.62–2.73 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 153.7, 142.0, 139.6, 138.8, 135.5, 133.0, 132.8, 131.9, 127.9, 125.4, 125.0, 122.6, 35.3, 34.8, 33.8, 31.1; HRMS (EI^+): calcd. for $\text{C}_{16}\text{H}_{16}\text{O}$ $[\text{M}]^+$ 224.1201 found 224.1198.

Friedmann, C. J.; Ay, S.; Bräse, S. *J. Org. Chem.*, **2010**, *13*, 4612–4614.

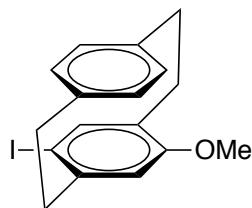
(S)-4-Methoxy-[2.2]paracyclophane (41):



In a nitrogen-charged glove box, (*S*)-4-hydroxy-[2.2]paracyclophane (1.780 g, 7.94 mmol) was dissolved in tetrahydrofuran (20 mL). Sodium hydride (0.210 g, 8.73 mmol)

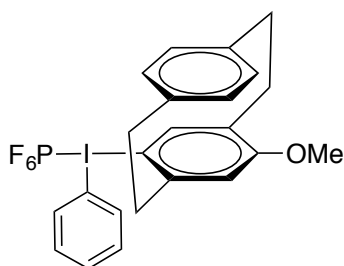
was added in portions, with stirring, waiting for fizzing to subside between additions. The mixture was stirred for an additional 10 minutes, sealed, and removed from the glove box. Under N₂, iodomethane (1.0 mL, 15.88 mmol) was added dropwise. The solution was sealed and heated to 80 °C for 40 hours. Solvent was removed *in vacuo*. The solid was dissolved in ether, washed twice with water, three times with aqueous potassium hydroxide (2.0 M), and once with brine. The organic layers were dried over sodium sulfate and solvent was removed *in vacuo*. The solid was chromatographed on silica, loaded using hot hexanes, and eluted as a gradient from 0% ethyl acetate/hexanes (v/v) to 3% to yield a colorless solid (1.246 g, 66.4%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 6.76 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 6.38–6.55 (m, 4H), 6.28 (dd, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 5.67 (d, *J* = 1.3 Hz, 1H), 3.71 (s, 3H), 3.42–3.48 (m, 1H), 2.99–3.13 (m, 6H), 2.59–2.66 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz, 298 K): δ 157.6, 142.1, 140.3, 138.8, 135.0, 133.7, 133.1, 131.5, 128.4, 127.5, 124.4, 116.7, 54.3, 35.5, 35.4, 34.1, 31.7; HRMS (EI⁺): calcd. for C₁₇H₁₈O [M]⁺ 238.1358 found 238.1358.

(*S*)-7-Iodo-4-methoxy-[2.2]paracyclophane (42):



In a 100 mL round bottom flask, (*S*)-4-methoxy-[2.2]paracyclophane (2.000 g, 8.46 mmol) was dissolved in dichloromethane (25 mL). In a 125 mL Erlenmeyer, *N*-iodosuccinimide (2.000 g, 8.89 mmol) and trifluoroacetic acid (0.69 mL, 8.89 mmol) were

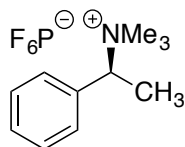
dissolved in dichloromethane (40 mL) with swirling and added to the round bottom flask, in 2 mL portions. The solution was stirred, in the dark, for 1 hour before being neutralized by saturated aqueous sodium bicarbonate. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed once with saturated aqueous sodium bicarbonate, a solution of sodium metabisulfite in brine (5 g/L), then brine. The organic layer was dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was dissolved from minimal boiling hexanes (~100 mL), chilled to $-20\text{ }^{\circ}\text{C}$, filtered, and washed with cold hexanes to yield a pale brown solid (2.964 g, 96.4%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.13 (dd, $J = 7.9$ Hz, $J = 1.8$, 1H), 6.75 (dd, $J = 7.9$ Hz, $J = 1.8$ Hz, 1H), 6.71 (s, 1H), 6.46 (dd, $J = 7.9$ Hz, $J = 1.8$, 1H), 6.40 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H), 5.69 (s, 1H), 3.68 (s, 3H), 2.82–3.37 (m, 7H), 2.43–2.53 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K): δ 157.9, 144.7, 143.9, 139.9, 138.5, 132.9, 131.5, 129.9, 129.6, 128.9, 117.7, 91.9, 54.3, 39.3, 33.6, 33.2, 31.1; HRMS (EI^+): calcd. for $\text{C}_{17}\text{H}_{17}\text{IO}$ $[\text{M}]^+$ 364.0324 found 364.0330; HPLC (Phenomenex® Lux chiral column (250 mm length, 4.6 mm diameter, 3 μm particle size), methanol:water (95:5 v/v), 1.0 mL/min, 254 nm): 20.01 min (*R*); 23.54 min (*S*); ee 96.5%.

(4-((*S*)-7-Methoxy-[2.2]paracyclophanyl))(phenyl)iodonium hexafluorophosphate**(43):**

In a flame-dried 100 mL Schlenk tube, (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (0.5000 g, 1.3728 mmol) was dissolved, with stirring, in warm ether (40 mL), under N₂. The solution was gradually cooled, with vigorous stirring, to -78 °C. To this mixture, *n*-butyl lithium (2.5 M in hexanes, 0.64 mL, 1.510 mmol) was added, dropwise. The mixture was stirred at -78 °C for 30 minutes. In a separate 50 mL Schlenk tube, anhydrous zinc chloride (0.800 g, 5.491 mmol) was gently flame-dried until bubbling subsided. An oven-dried stirbar was added. After cooling to r.t., dry ether (20 mL) was added, under N₂, and the solid was dissolved using sonication and vigorous stirring. A portion of this solution (10 mL, 2.746 mmol zinc chloride) was added dropwise to the first Schlenk tube. The suspension was allowed to warm to room temperature and ether was removed under high dynamic vacuum to yield a foam. Dry acetonitrile (10 mL) was added with stirring to dissolve the foam. In a separate flame-dried 100 mL Schlenk tube, bis(acetoxy)iodobenzene (0.6632 g, 5.491 mmol) was dissolved in dry acetonitrile (40 mL). Both solutions were chilled to -20 °C and the organozinc chloride solution was added, dropwise, over the course of 5 min to the bis(acetoxy)iodobenzene solution. The

resulting solution was held at -20 °C for 30 minutes before warming to r.t. Deionized water and sodium hexafluorophosphate (0.5764 g, 3.432 mmol) were added, with stirring, and the mixture was concentrated *in vacuo*. The mixture was extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and solvent was removed *in vacuo*. The crude solid was dissolved in minimal dichloromethane and slowly dripped into a stirring solution of ether in hexanes (10% v/v). Stirring was stopped, and after standing for an hour, the mixture was filtered and the solid rinsed three times with hexanes to yield a colorless powder (0.6228 g, 77.3%): ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.03 (d, *J* = 7.9 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 2H), 7.29 (s, 1H), 6.82 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 6.63 (dd, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 6.34 (dd, *J* = 7.9 Hz, *J* = 1.9 Hz, 1H), 6.19 (dd, *J* = 7.9 Hz, *J* = 1.9 Hz, 1H), 6.04 (s, 1H), 3.74 (s, 3H), 3.37–2.99 (m, 7H), 2.74–2.64 (m, 1H); ¹⁹F NMR (CD₃CN, 400 MHz, 298 K): δ -72.88 (d, *J* = 708.0 Hz, 6F); HRMS (ESI): calcd. for C₂₃H₂₂IO [M-PF₆]⁺ 441.0710 found 441.0730.

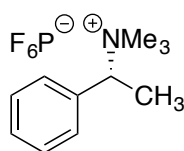
(S)-N,N,N-Trimethyl-1-phenylethanaminium hexafluorophosphate (45):



In a 100 mL Schlenk storage tube, potassium carbonate (31.0 mmol, 4.29g) was suspended in acetonitrile (50 mL) and heated to 80 °C with vigorous stirring. (S)-1-phenylethylamine (7.76 mmol, 1.0 mL) was added dropwise. The mixture was stirred at 80 °C for 15 minutes, cooled to r.t., and iodomethane (46.6 mmol, 2.89 mL) was added.

The tube was sealed and heated to 80 °C overnight. Solvent was removed *in vacuo*, diluted with water (75 mL) and extracted three times with dichloromethane (3 x 25 mL). Solvent was removed *in vacuo*, and the solid was dissolved in minimal methanol and aqueous sodium hexafluorophosphate (1 M, 10 mL) was added with stirring. The mixture was concentrated *in vacuo*, extracted three times with dichloromethane (3 x 25 mL). The organic layers were washed once with deionized water, dried over sodium sulfate, and solvent was removed *in vacuo*. The crude solid was recrystallized from boiling methanol (10 mL), chilled to -20 °C, filtered, and rinsed with cold methanol to yield the product as colorless plates (308 mg, 12.8%): ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 7.51 (m, 5H), 4.57 (q, *J* = 7.0 Hz, 1H), 2.95 (s, 9H), 1.75 (dt, *J* = 1.9 Hz, *J* = 7.0 Hz, 3H); ¹⁹F NMR (CD₃CN, 376 Hz, 298 K): δ -72.74 (d, *J* = 706.5 Hz, 6F); ¹³C NMR (CD₃CN, 100 MHz, 298 K): δ 133.90, 131.69, 131.54, 130.19, 75.29, 52.05 (t, *J* = 8.1 Hz), 15.43; HRMS (ESI): calcd. for C₁₁H₁₈N [M-PF₆]⁺ 164.1439 found 164.1439.

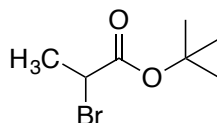
(*R*)-*N,N,N*-Trimethyl-1-phenylethanaminium hexafluorophosphate (46):



In a 100 mL Schlenk storage tube, sodium bicarbonate (31.0 mmol, 2.61 g) was suspended in methanol (40 mL) and (*R*)-1-phenylethylamine (7.76 mmol, 1.0 mL) and iodomethane (46.6 mmol, 2.89 mL) were added. The mixture was stirred for 15 minutes, then sealed and heated to 70 °C overnight. Solvent was removed *in vacuo*, diluted with dichloromethane (50 mL) and washed three times with aqueous sodium

hexafluorophosphate (1 M, 10 mL) and once with deionized water. The organic layers were dried over sodium sulfate, and solvent was removed *in vacuo*. The crude solid was recrystallized from boiling methanol (10 mL), chilled to room temperature, filtered, and rinsed with cold methanol to yield the product as colorless plates (1.460 g, 60.8%): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 7.51 (m, 5H), 4.57 (q, $J = 7.0$ Hz, 1H), 2.95 (s, 9H), 1.75 (dt, $J = 1.9$ Hz, $J = 7.0$ Hz, 3H); ^{19}F NMR (CD_3CN , 376 Hz, 298 K): δ -72.74 (d, $J = 706.5$ Hz, 6F); ^{13}C NMR (CD_3CN , 100 MHz, 298 K): δ 133.90, 131.69, 131.54, 130.19, 75.29, 52.05 (t, $J = 8.1$ Hz), 15.43; HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_{18}\text{N} [\text{M-PF}_6]^+$ 164.1439 found 164.1439.

***tert*-Butyl 2-bromopropionate (47):**

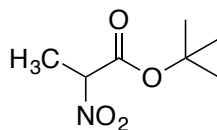


Under nitrogen, 2-bromopropionyl bromide (4.85 mL, 46.30 mmol) was dissolved in 20 mL dry DCM with stirring. The solution was cooled to 0 °C and triethylamine (6.5 mL, 46.30 mmol), dried over KOH, was added by syringe. *tert*-Butanol (5.15 g, 69.48 mmol) was dissolved in 5 mL dry DCM and added dropwise by syringe. A colorless precipitate forms. After addition the solution was allowed to warm to room temperature and stirred for an additional hour. The mixture was transferred to a separatory funnel, washed once with water, once with saturated aqueous sodium bicarbonate, and once with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to a colorless oil *in vacuo*. The crude product was used without further purification (7.378 g, 76.2%): ^1H

NMR (CDCl₃, 400 MHz, 298 K): δ 4.27 (q, J = 6.9 Hz, 1H), 1.78 (d, J = 6.9 Hz, 3H), 1.48 (s, 9H).

Linton, R. B.; Reutershan, H. M.; Aderman, M. C.; Richardson, A. E.; Brownell, R. K.; Ashley, W. C.; Evans, A. C.; Miller, J. S. *Tetrahedron. Lett.* **2007**, 11, 1993–1997.

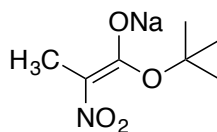
***tert*-Butyl 2-nitropropionate (48):**



In a 250 mL round bottom flask anhydrous phloroglucinol (4.71 g, 38.86 mmol) and anhydrous sodium nitrite (4.23 g, 70.58 mmol) were suspended in DMSO (70 mL) with stirring. *tert*-Butyl 2-bromopropionate (7.38 g, 35.29 mmol) was added dropwise. The flask was loosely stoppered, covered in foil, and the suspension was stirred for 3 hours. The suspension was poured into ice water and extracted 5 times with diethyl ether. The organic layers were washed with brine, dried over sodium sulfate, and filtered. Ether was removed *in vacuo*. The oil was chromatographed on silica with dichloromethane to yield a colorless oil (3.011 g, 48.7%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 5.11 (q, J = 7.1 Hz, 1H), 1.75 (d, J = 7.1 Hz, 3H), 1.50 (s, 9H); ¹³C NMR (CD₃CN, 100 MHz, 298 K): δ 164.25, 84.70, 84.21, 27.89, 15.90; HRMS (ESI): calcd. for C₇H₁₂NNa₂O₄ [M-H+2Na]⁺ 220.0562 found 220.0563; HRMS (EI⁺): calcd. for C₇H₁₃NNaO₄ [M+Na]⁺ 198.0742 found 198.0745.

Kornblum, N.; Blackwood, R. K. *Org. Synth.* **1957**, *37*, 44.

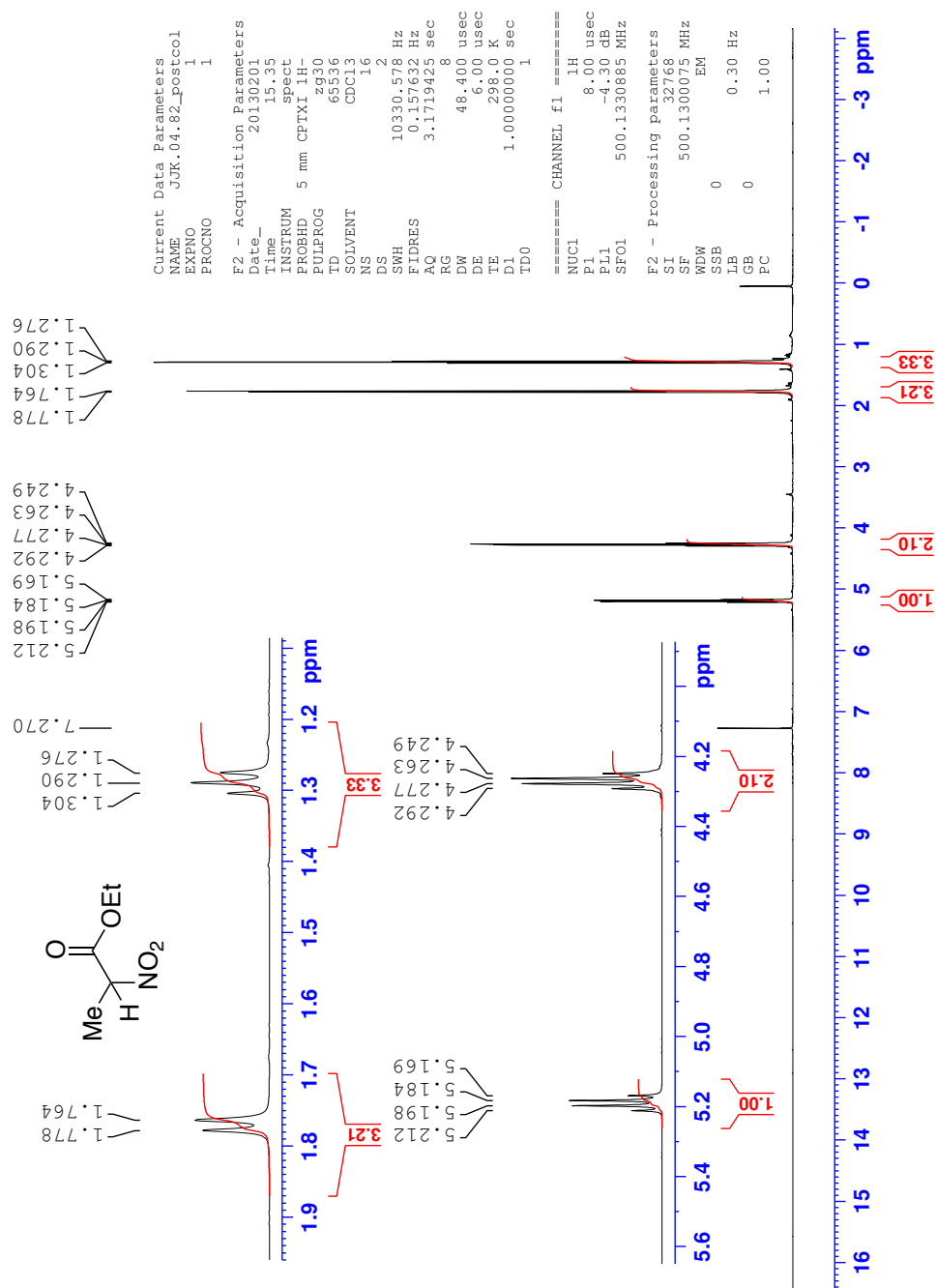
Sodium 1-*tert*-butoxy-2-nitropropionate (49):

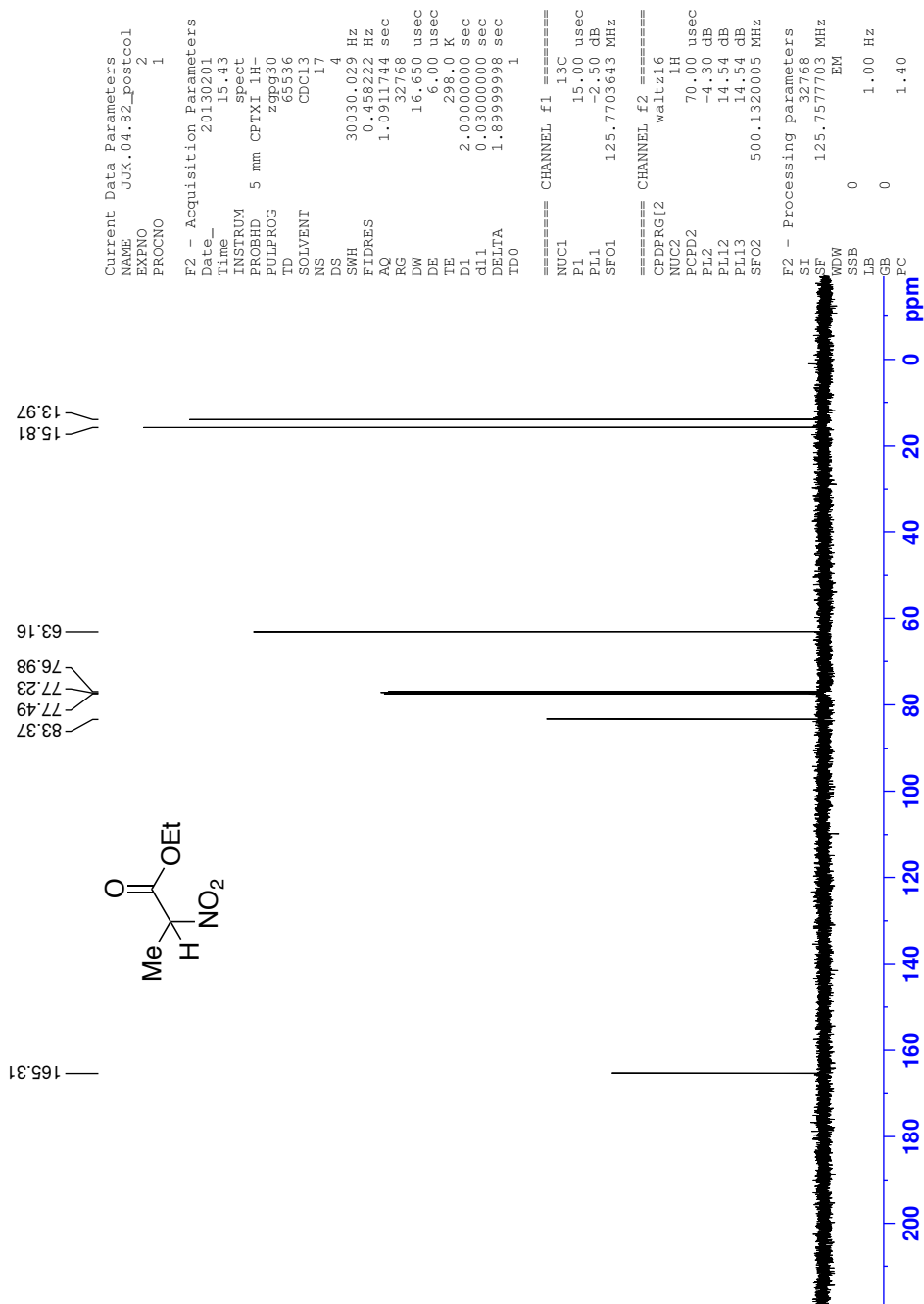


In a flame-dried 50 mL Schlenk tube, *tert*-butyl 2-nitropropionate (0.5000 g, 2.85 mmol) was added under N₂. The tube was chilled to 0 °C. Sodium hydride (0.0650 g, 2.71 mmol) was added in portions under N₂ with vigorous stirring. Once bubbling had subsided, the mixture was diluted with ethyl acetate. The mixture was washed once with minimal deionized water. The organic layer was dried over sodium sulfate and solvent was removed *in vacuo*. The solid was sonicated in ether, filtered, and washed three times with ether to yield a colorless powder (0.4570 g, 81.2%): ¹H NMR (CD₃OD, 400 MHz, 298 K): δ 2.11 (s, 3H), 1.51 (s, 9H); ¹³C NMR (CD₃OD, 100 MHz, 298 K): δ 164.26, 112.81, 79.51, 27.25, 14.14.

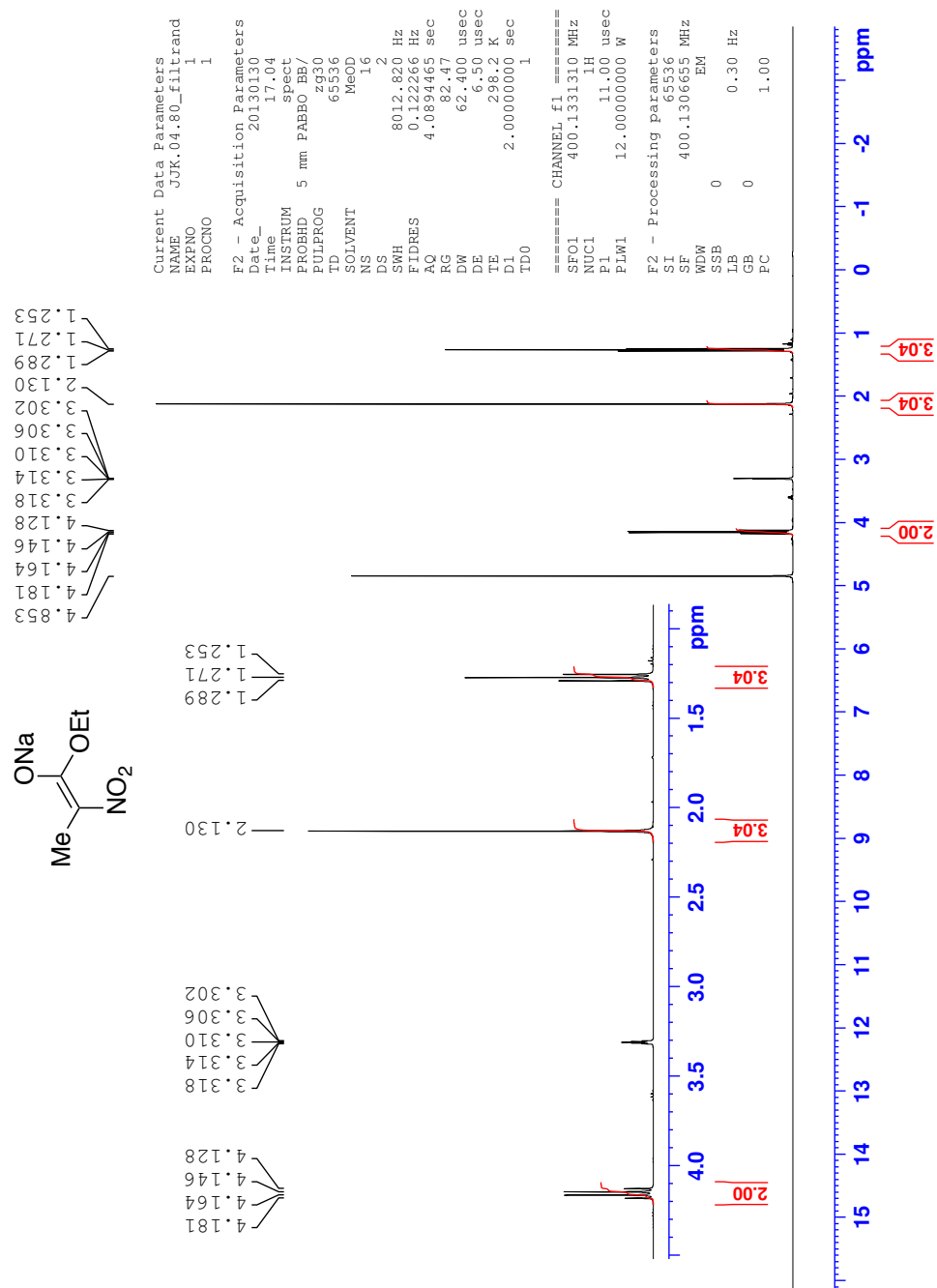
2.6 NMR Spectra

^1H NMR (CDCl_3 , 500 MHz, 298 K) spectrum of ethyl 2-nitropropanoate (**5**)

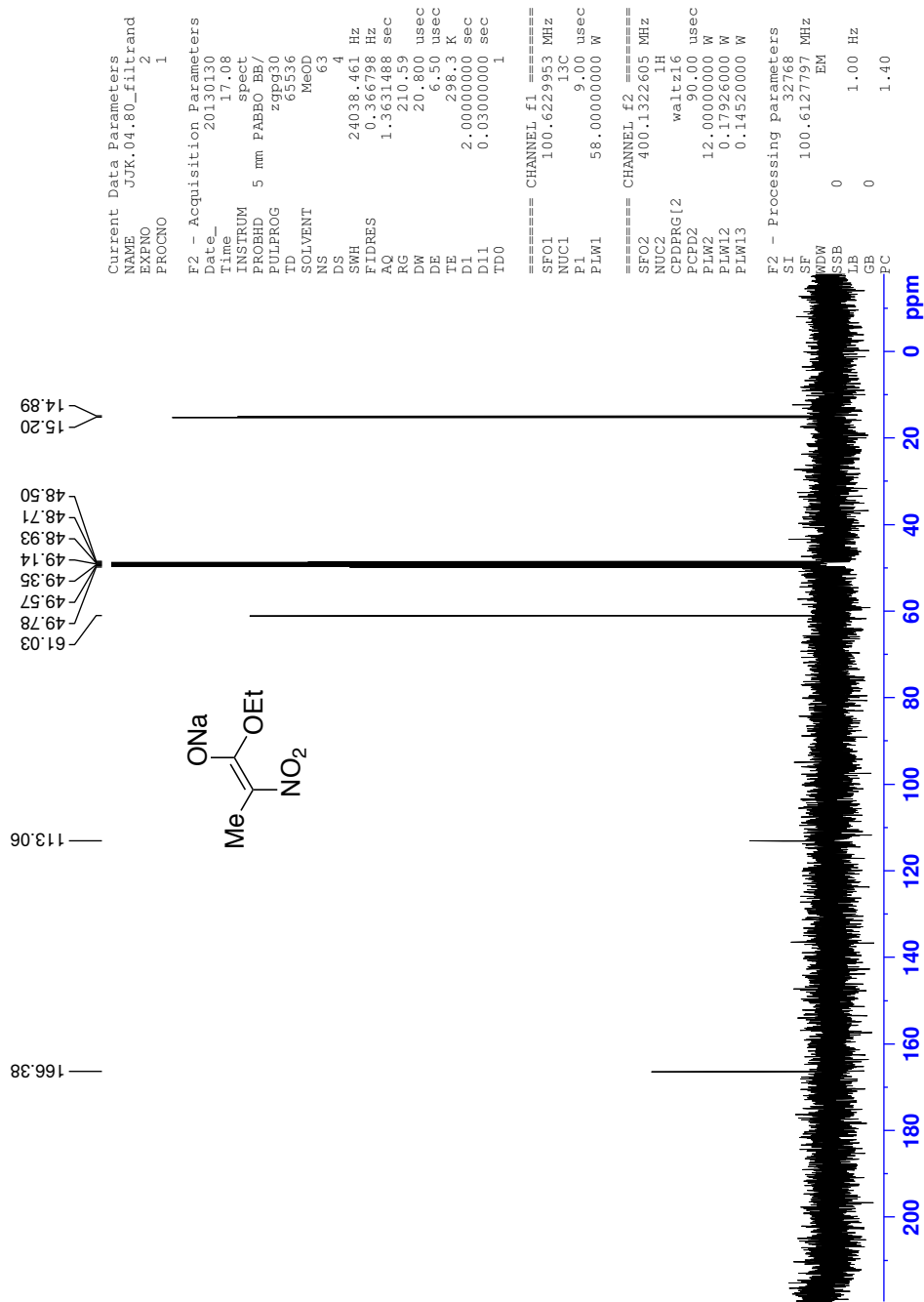


¹³C NMR (CDCl₃, 125 MHz, 298 K) spectrum of ethyl 2-nitropropanoate (5)

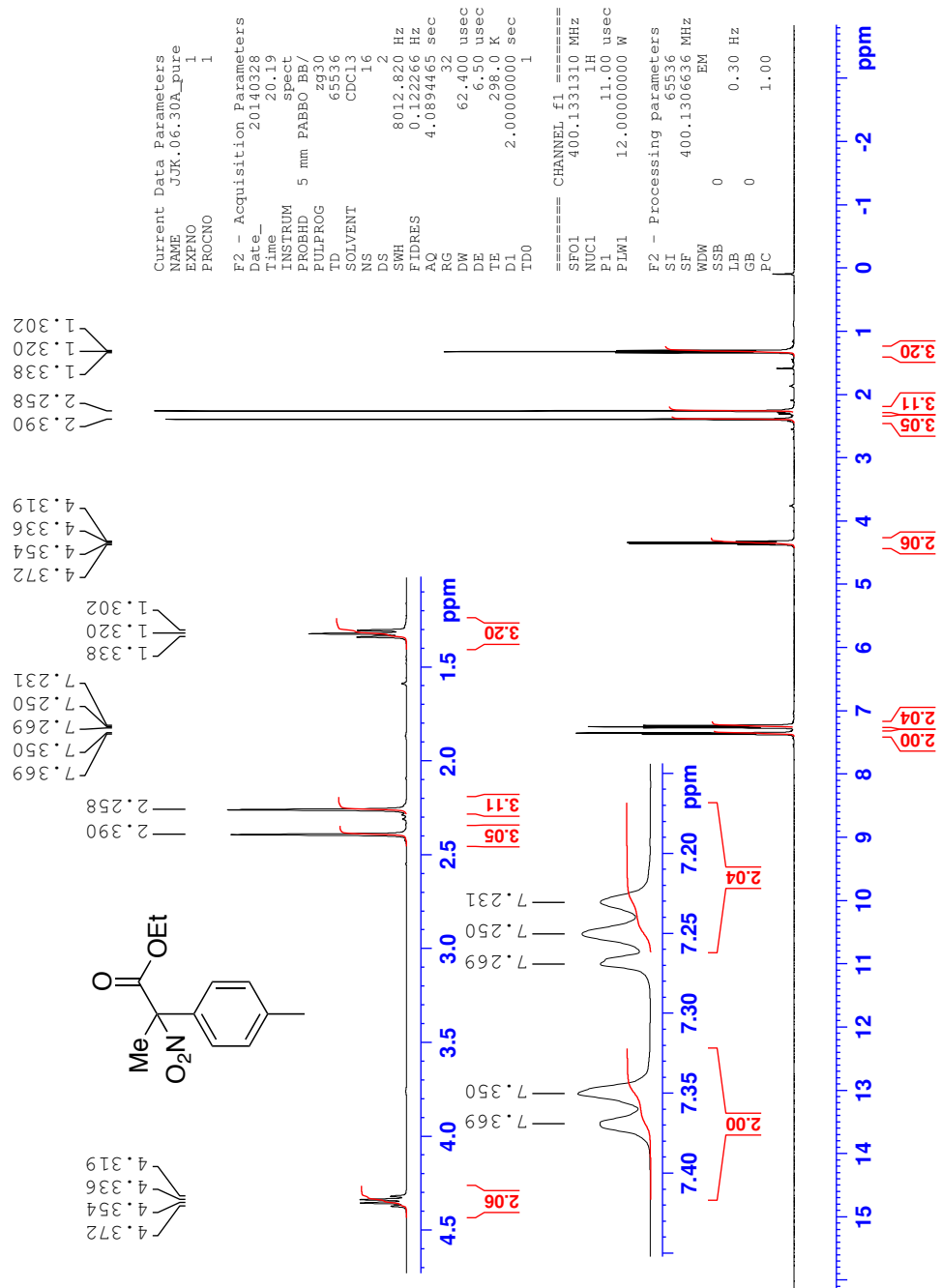
¹H NMR (CD₃OD, 400 MHz, 298 K) spectrum of sodium 1-ethoxy-2-nitroprop-1-enoate
(8)



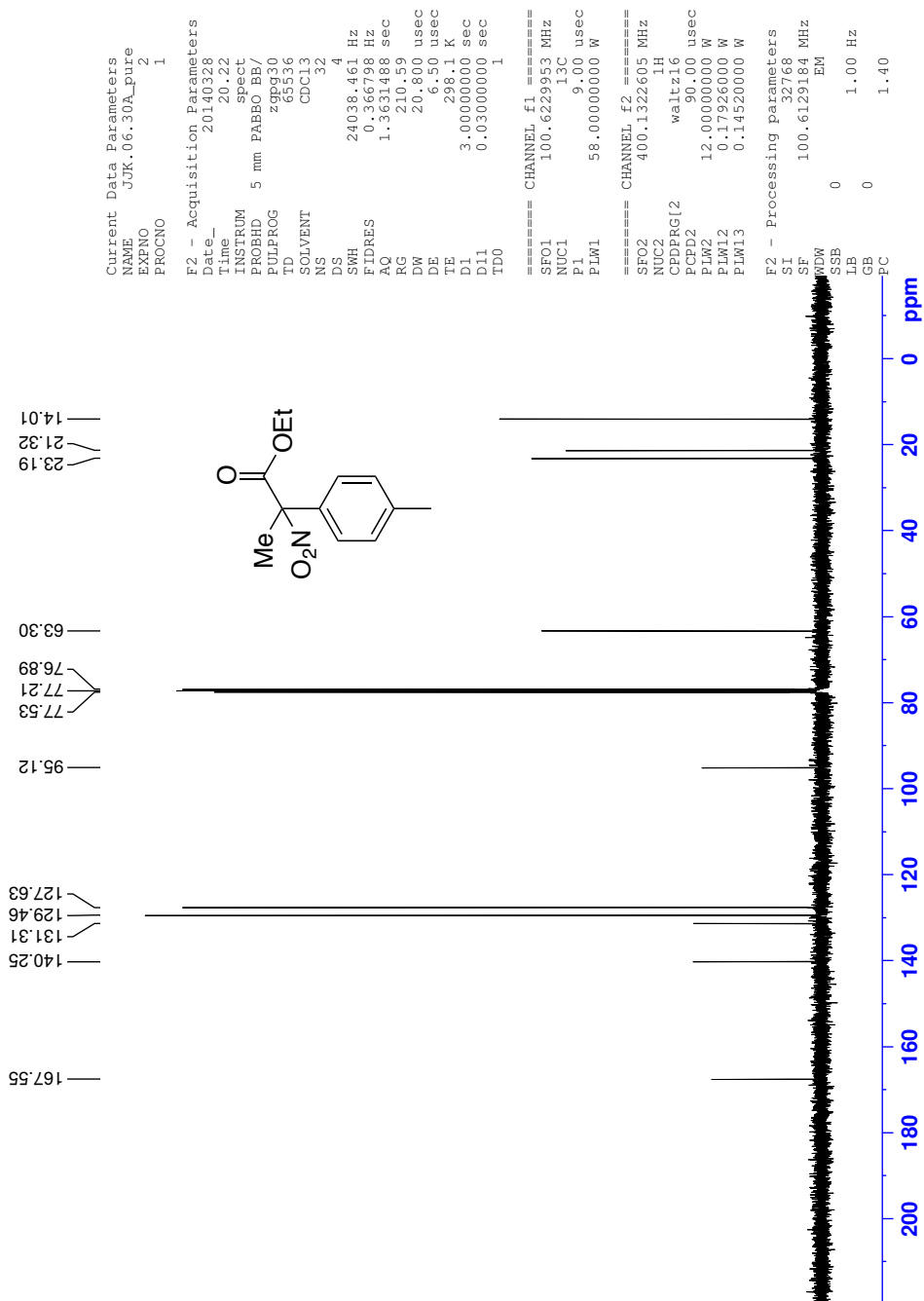
¹³C NMR (CD₃OD, 100 MHz, 298 K) spectrum of sodium 1-ethoxy-2-nitropropenate
(8)



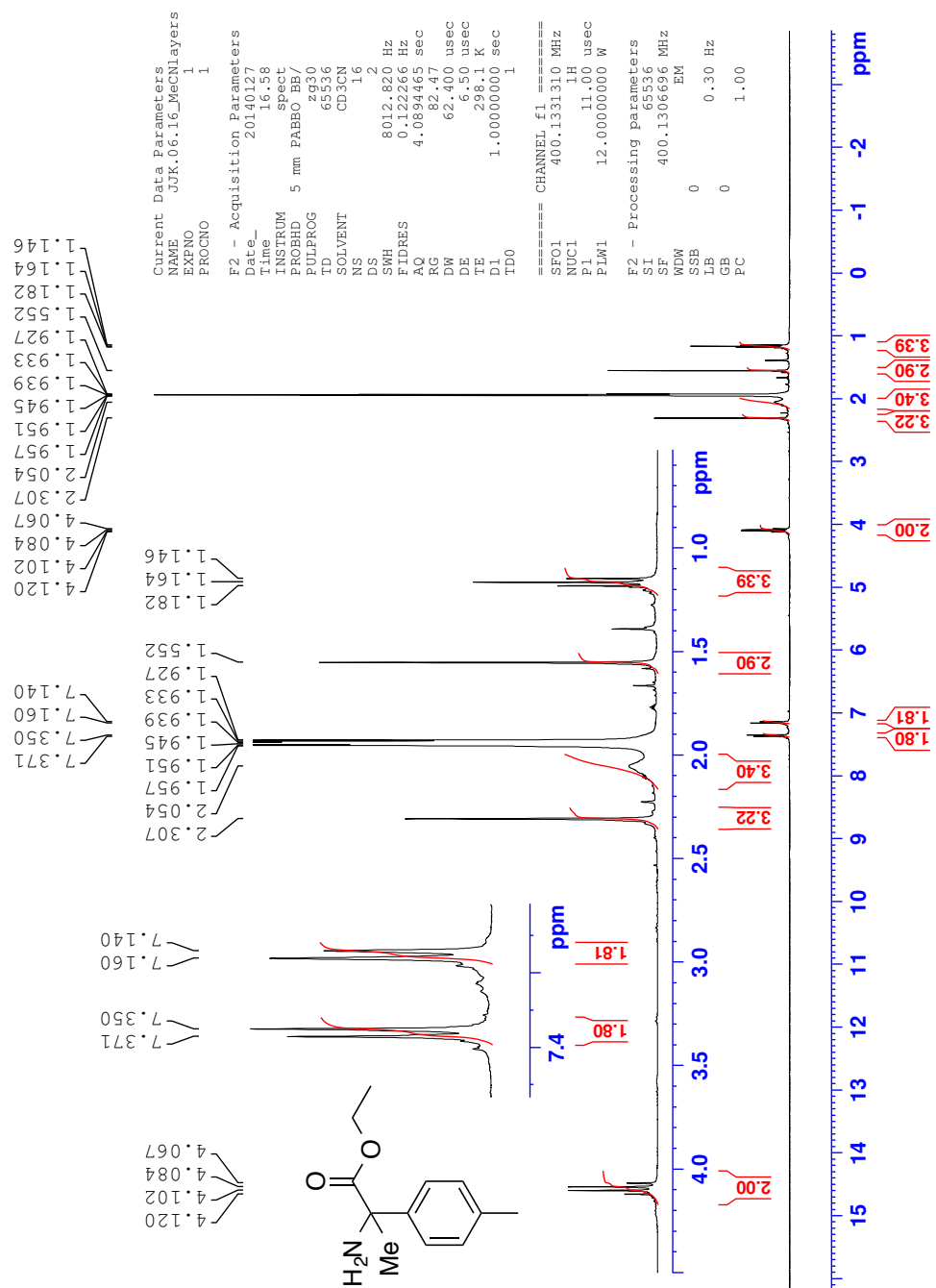
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of ethyl 2-(4-methylphenyl)-2-nitropropanoate (**15**)



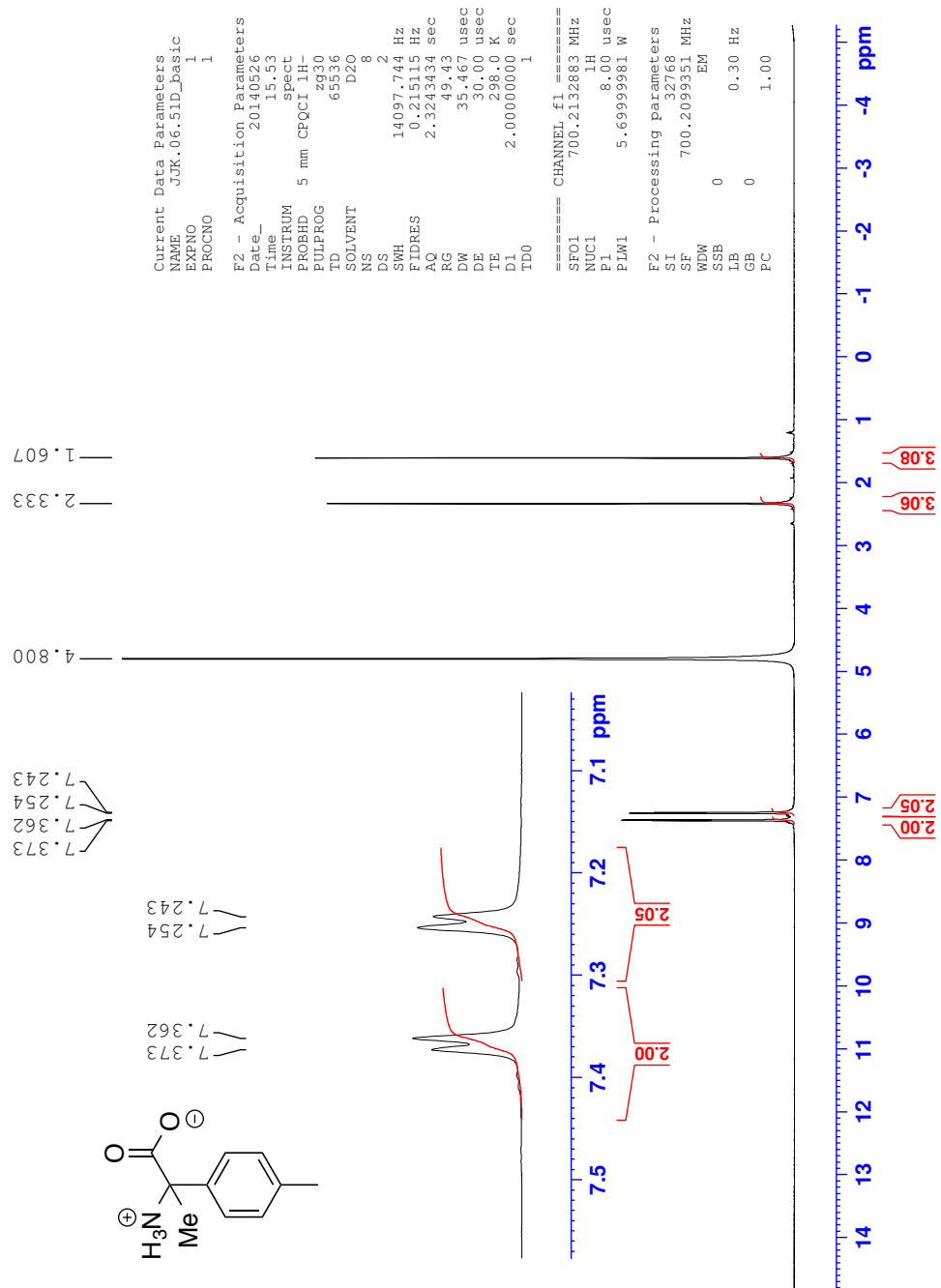
¹³C NMR (CDCl₃, 100 MHz, 298 K) spectrum of ethyl 2-(4-methylphenyl)-2-nitropropanoate (**15**)



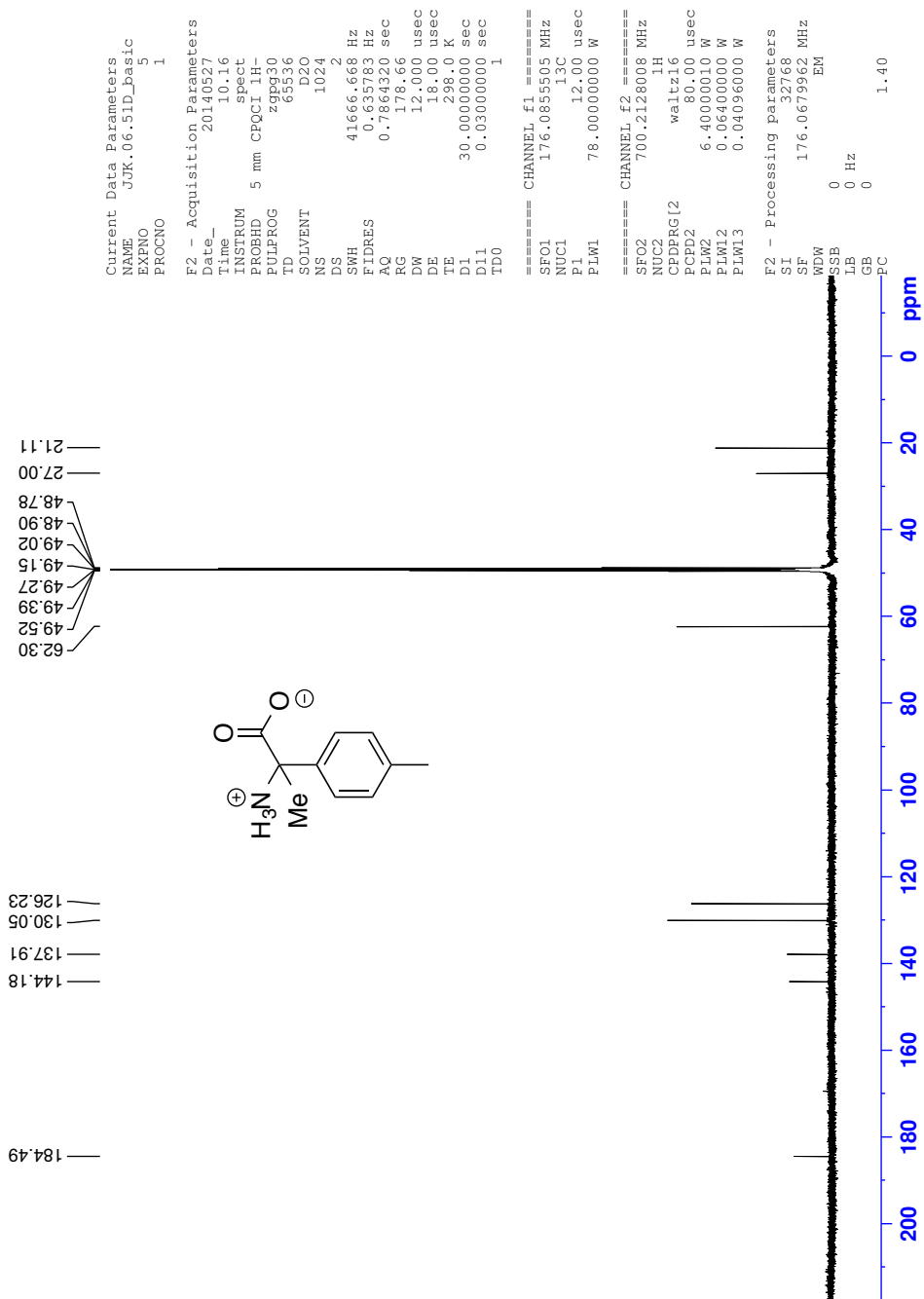
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of ethyl 2-(4-methylphenyl)-2-aminopropanoate (**21**)



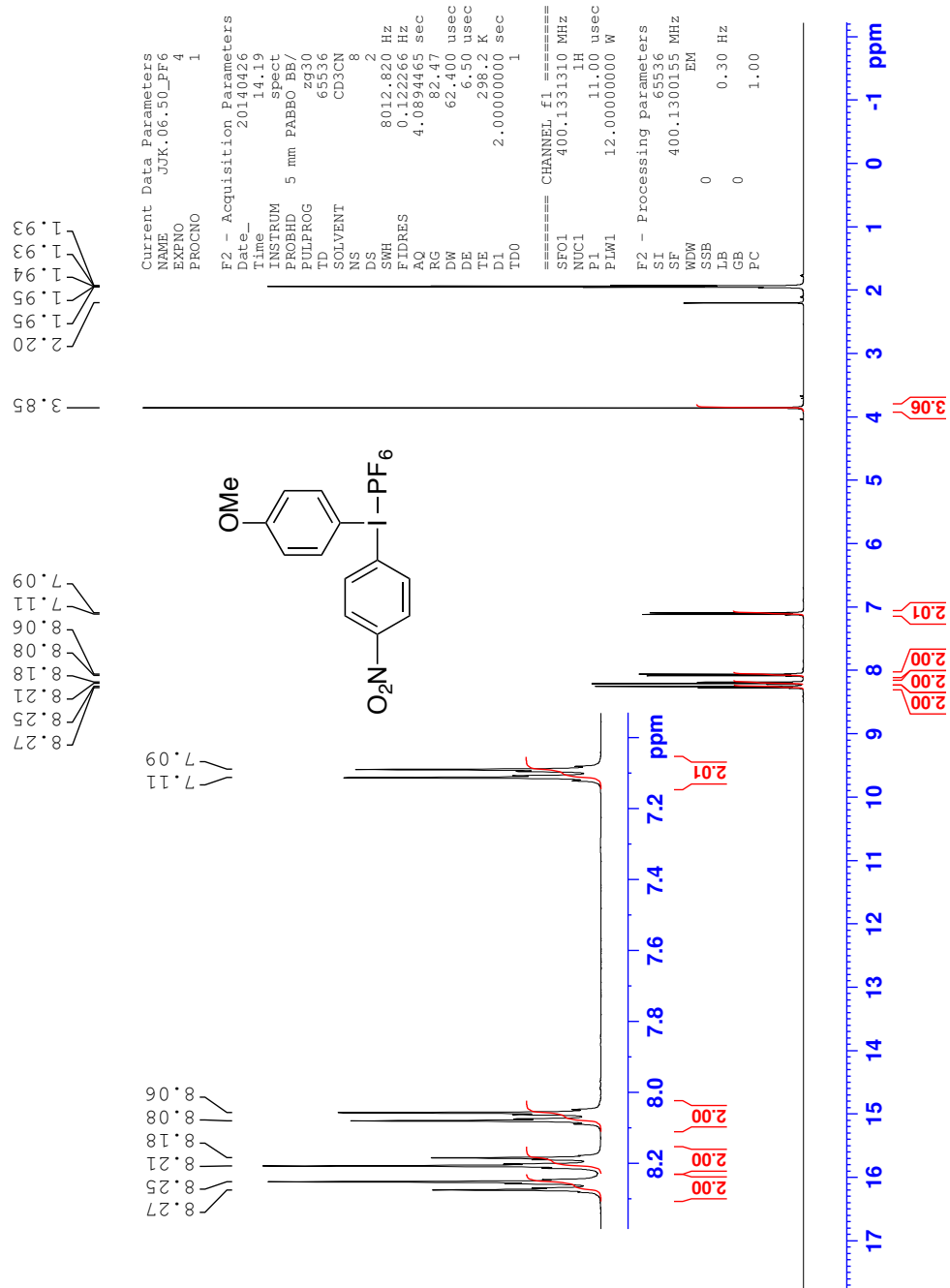
^1H NMR (D_2O , 700 MHz, 298 K) spectrum of 2-ammonio-2-(4-methylphenyl)propanoate (**24**)



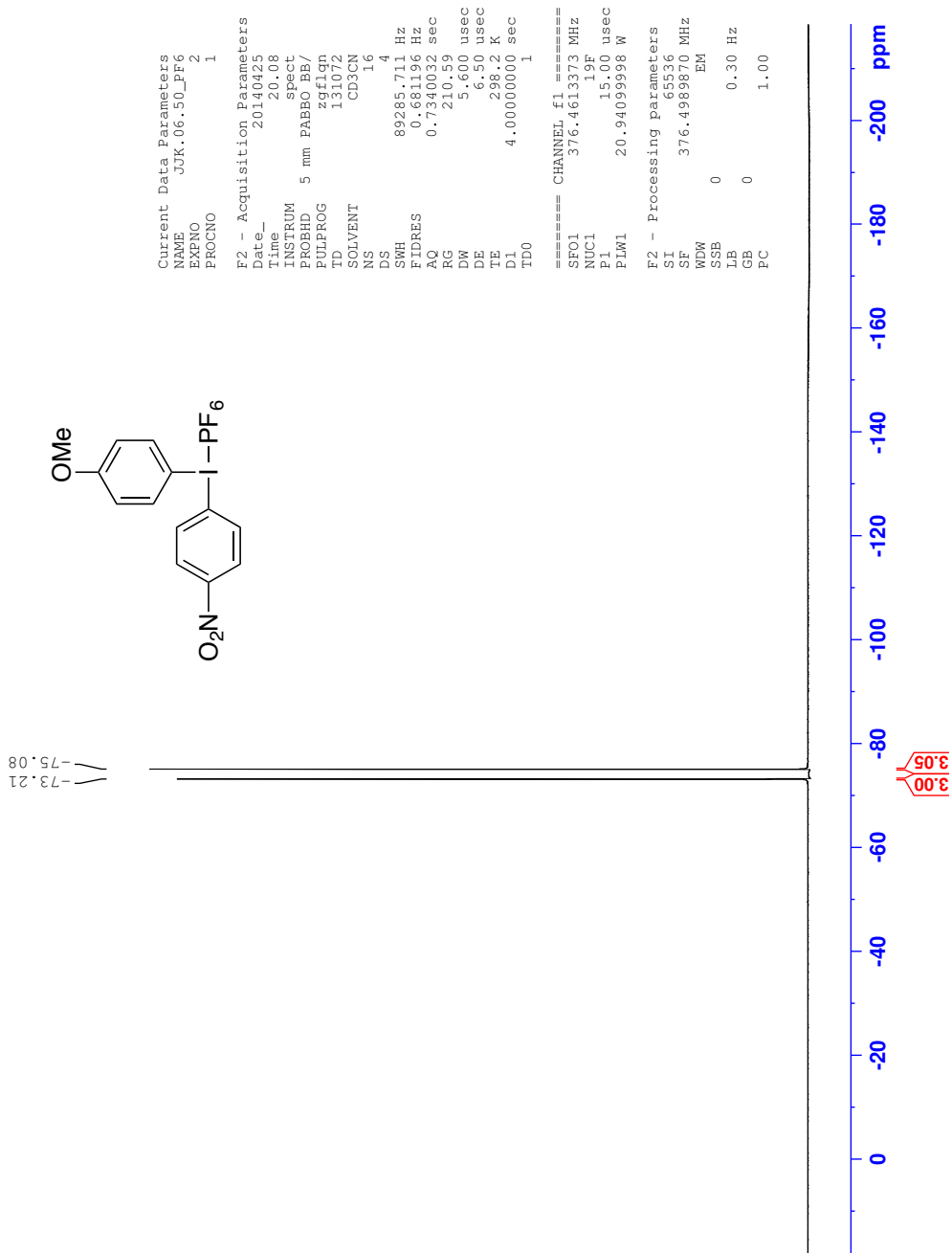
^{13}C NMR (D_2O , 176 MHz, 298 K) spectrum of 2-ammonio-2-(4-methylphenyl)propanoate (**24**)



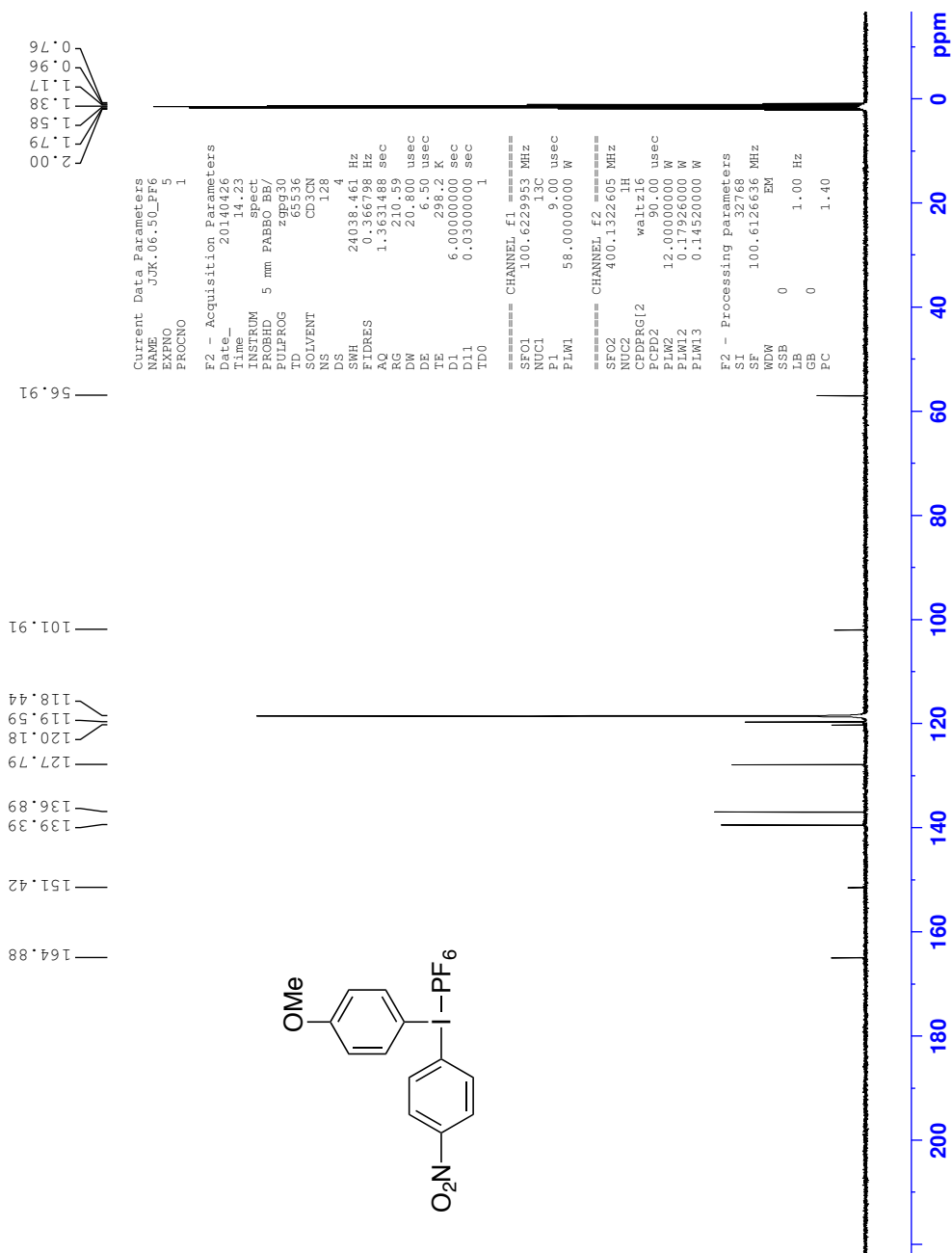
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**12**)

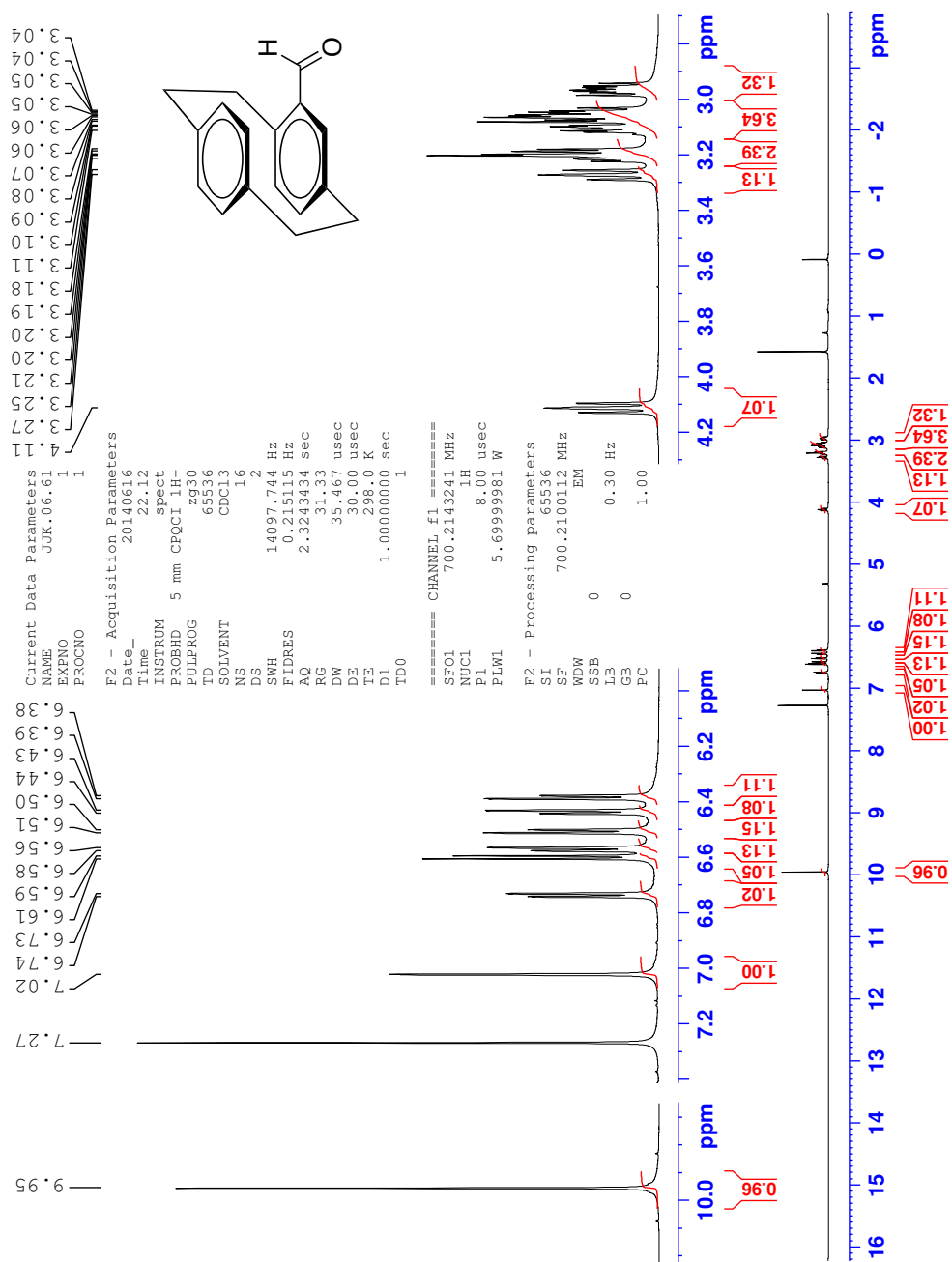


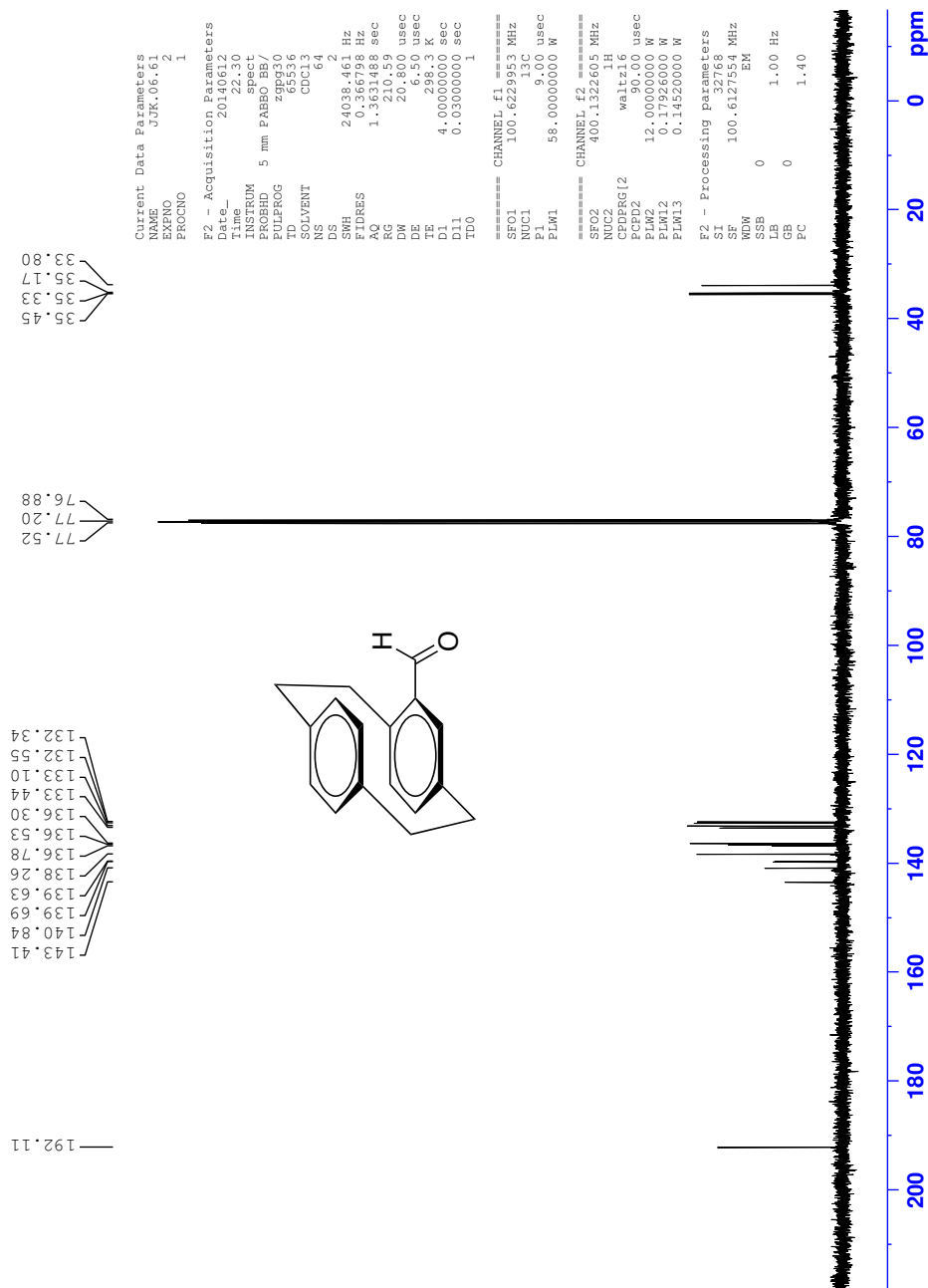
^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**12**)

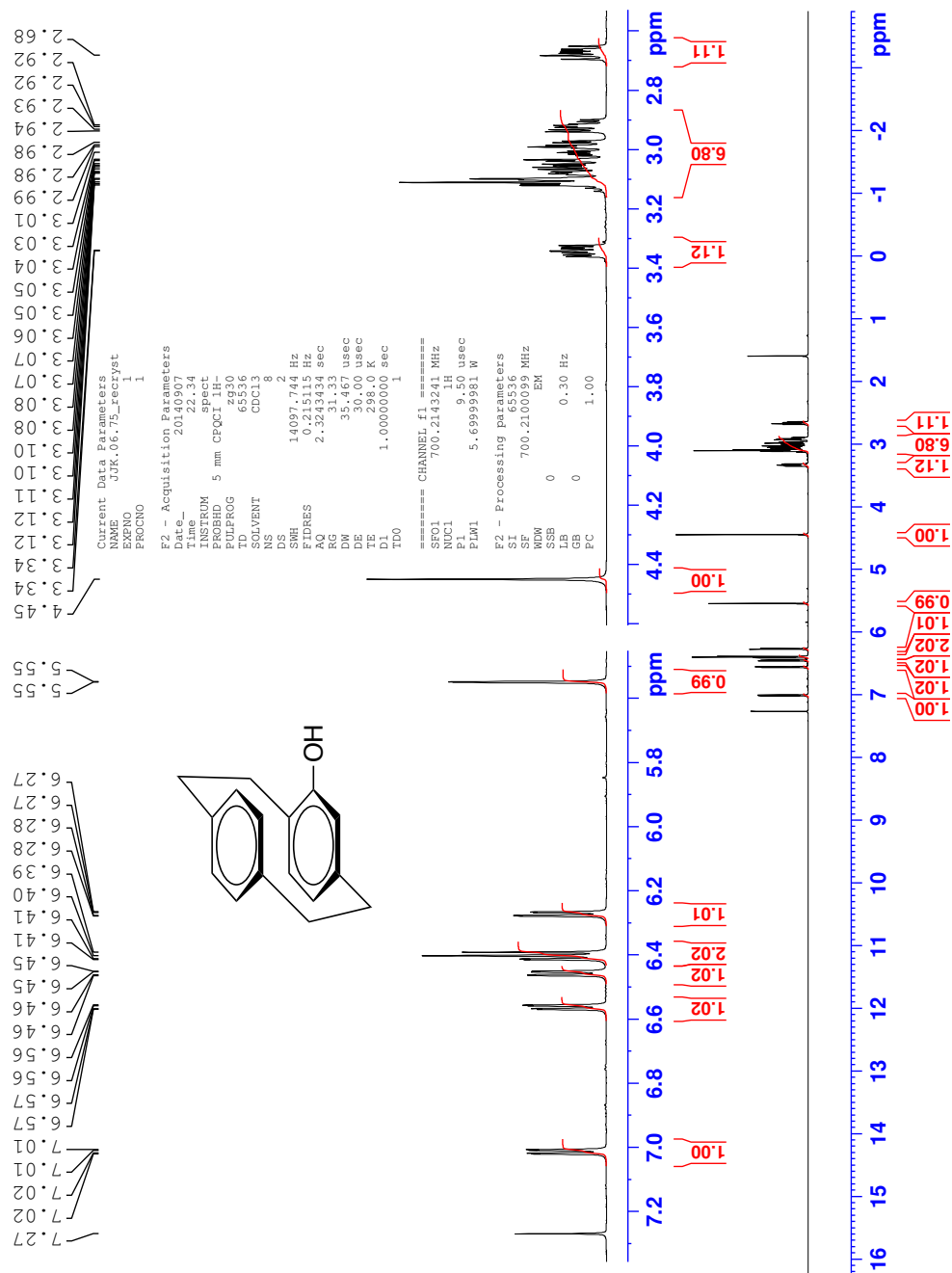


^{13}C NMR (CD_3CN , 100 MHz, 298 K) spectrum of (4-methoxyphenyl)(4-nitrophenyl)iodonium hexafluorophosphate (**12**)

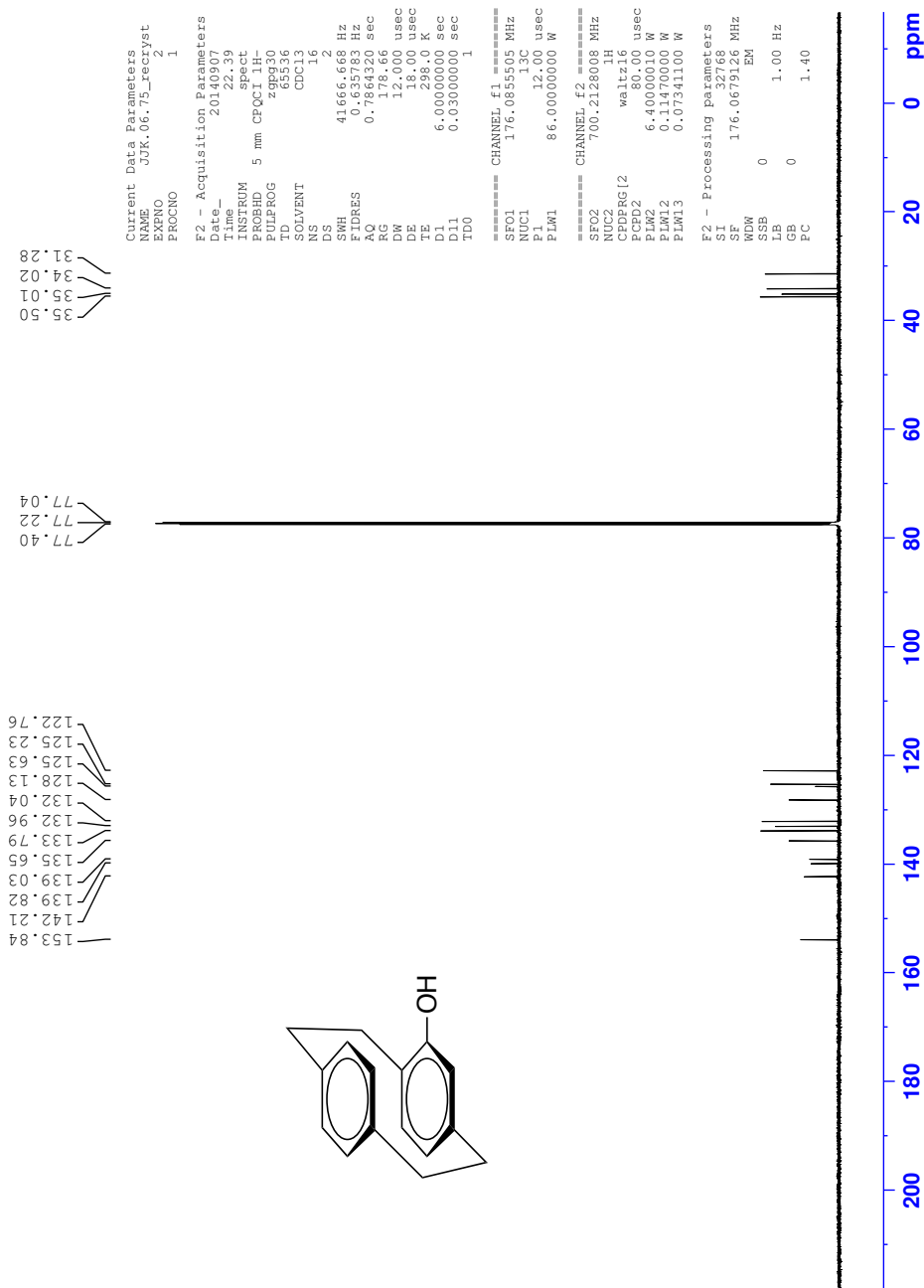


^1H NMR (CDCl_3 , 700 MHz, 298 K) spectrum of (*S*)-4-formyl-[2.2]paracyclophane (**39**)

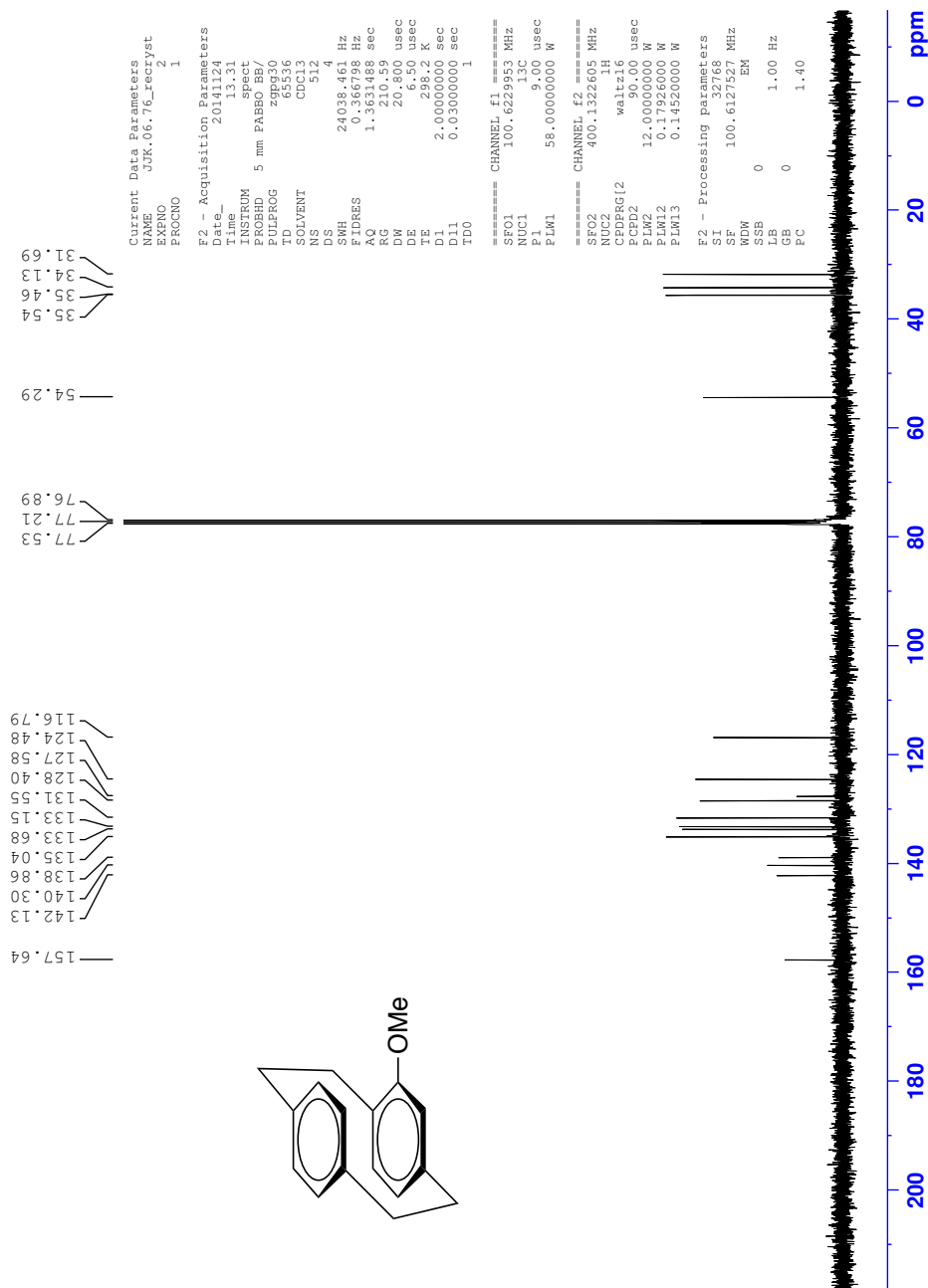
¹³C NMR (CDCl₃, 100 MHz, 298 K) spectrum of (*S*)-4-formyl-[2.2]paracyclophane (**39**)

^1H NMR (CDCl_3 , 700 MHz, 298 K) spectrum of (*S*)-4-hydroxy-[2.2]paracyclophane (**40**)

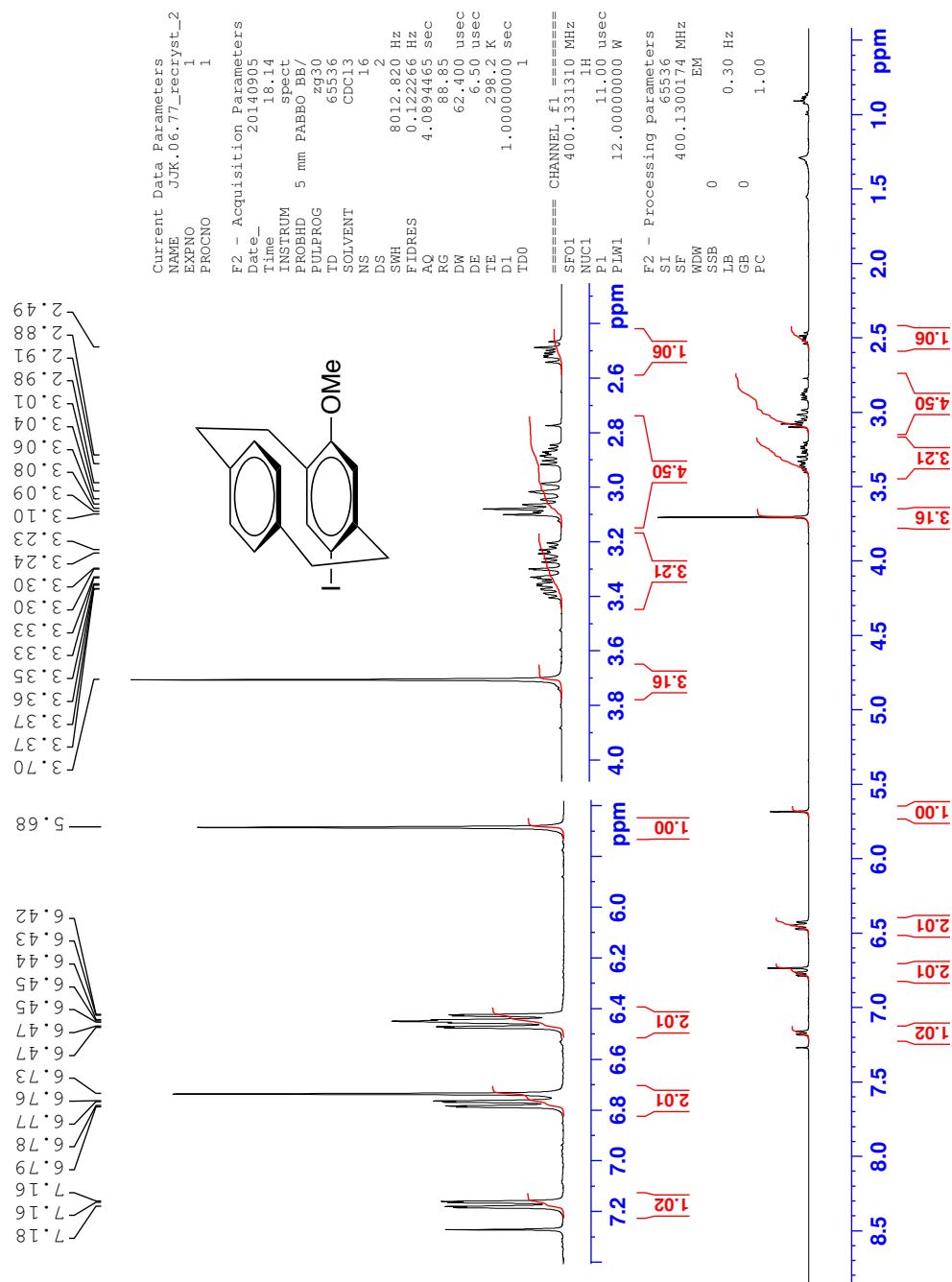
¹³C NMR (CDCl₃, 176 MHz, 298 K) spectrum of (*S*)-4-hydroxy-[2.2]paracyclophane
(40)



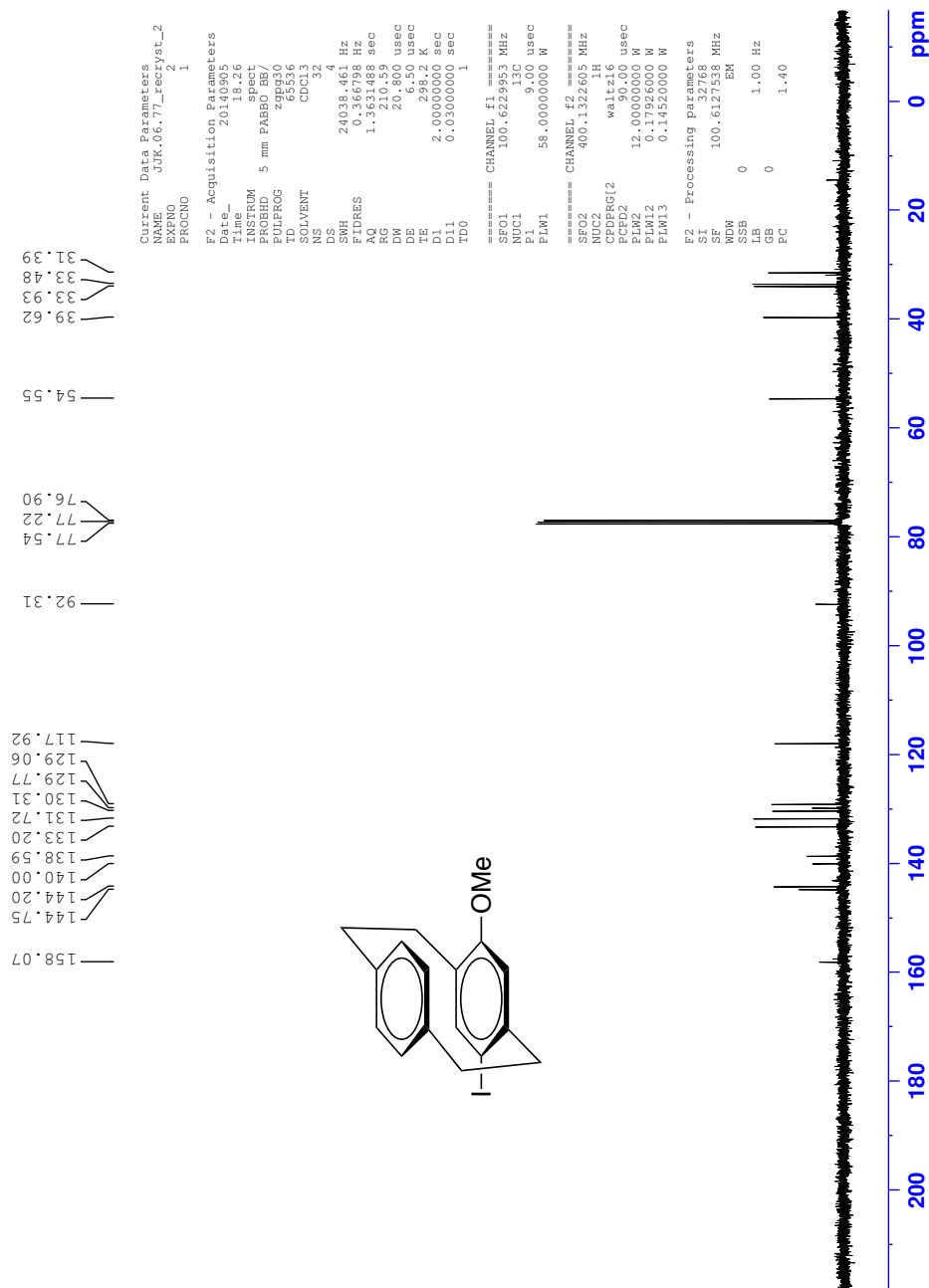
¹³C NMR (CDCl₃, 100 MHz, 298 K) spectrum of (*S*)-4-methoxy-[2.2]paracyclophane (41)



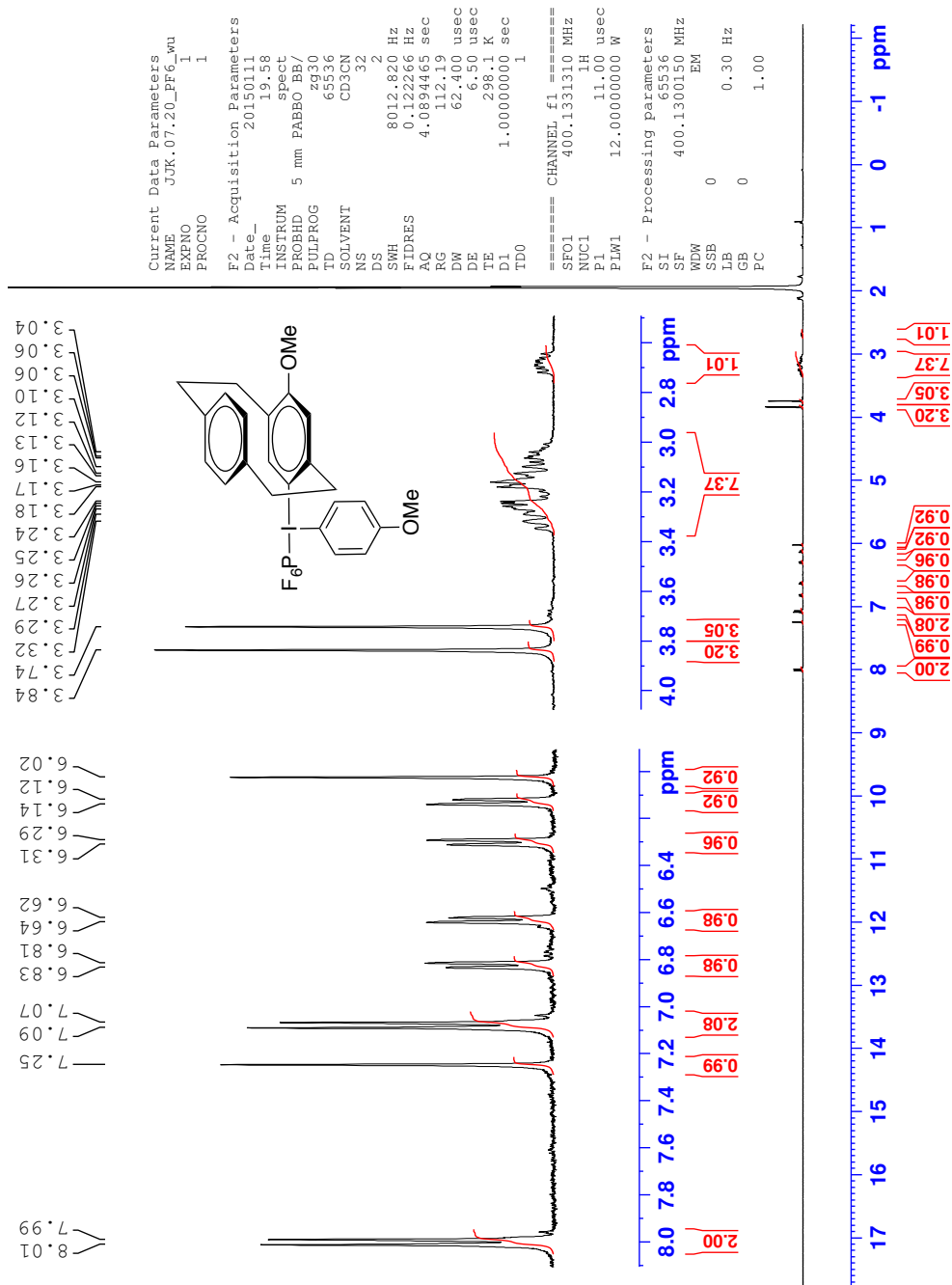
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (**42**)



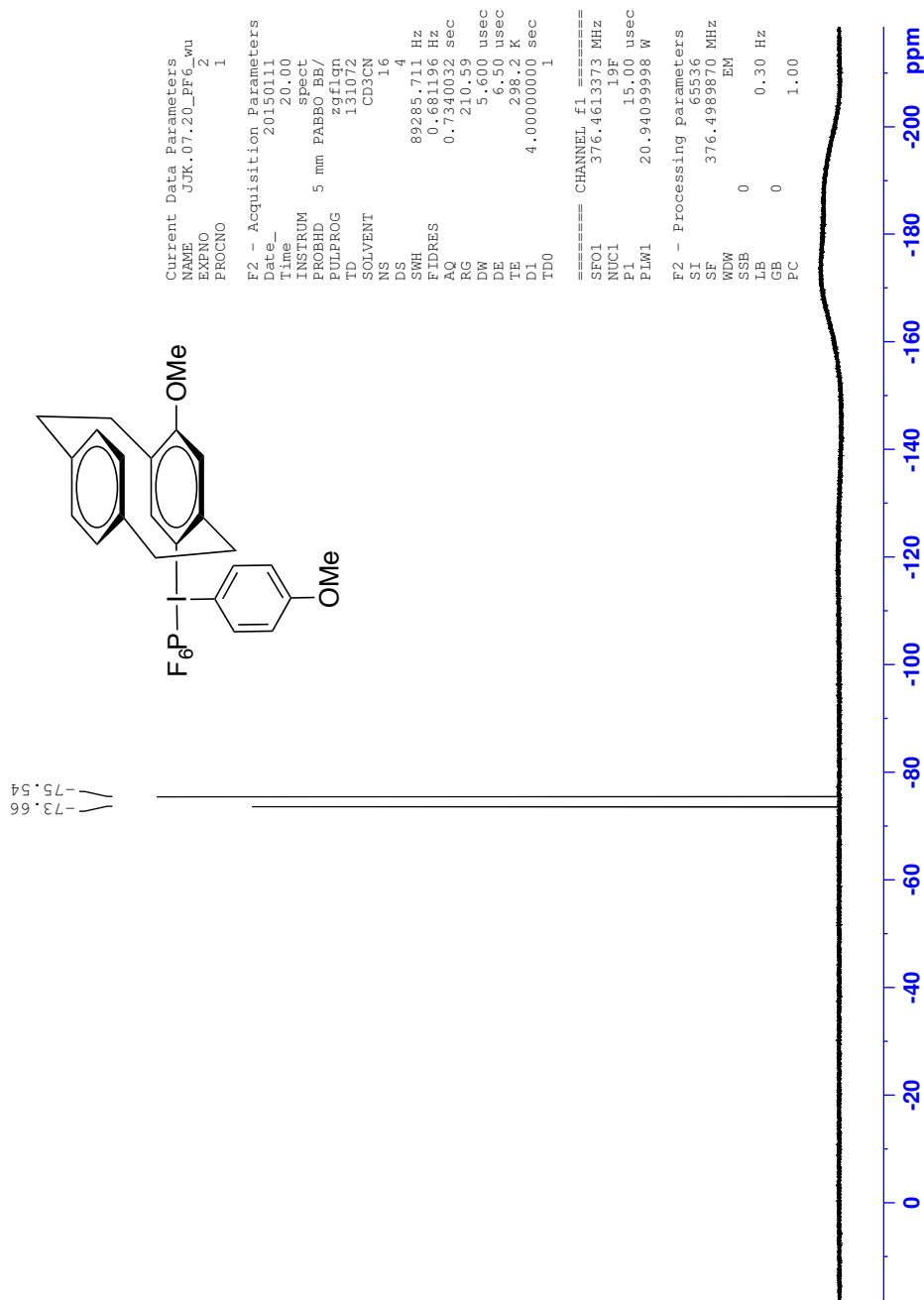
¹³C NMR (CDCl₃, 100 MHz, 298 K) spectrum of (*S*)-7-iodo-4-methoxy-[2.2]paracyclophane (**42**)



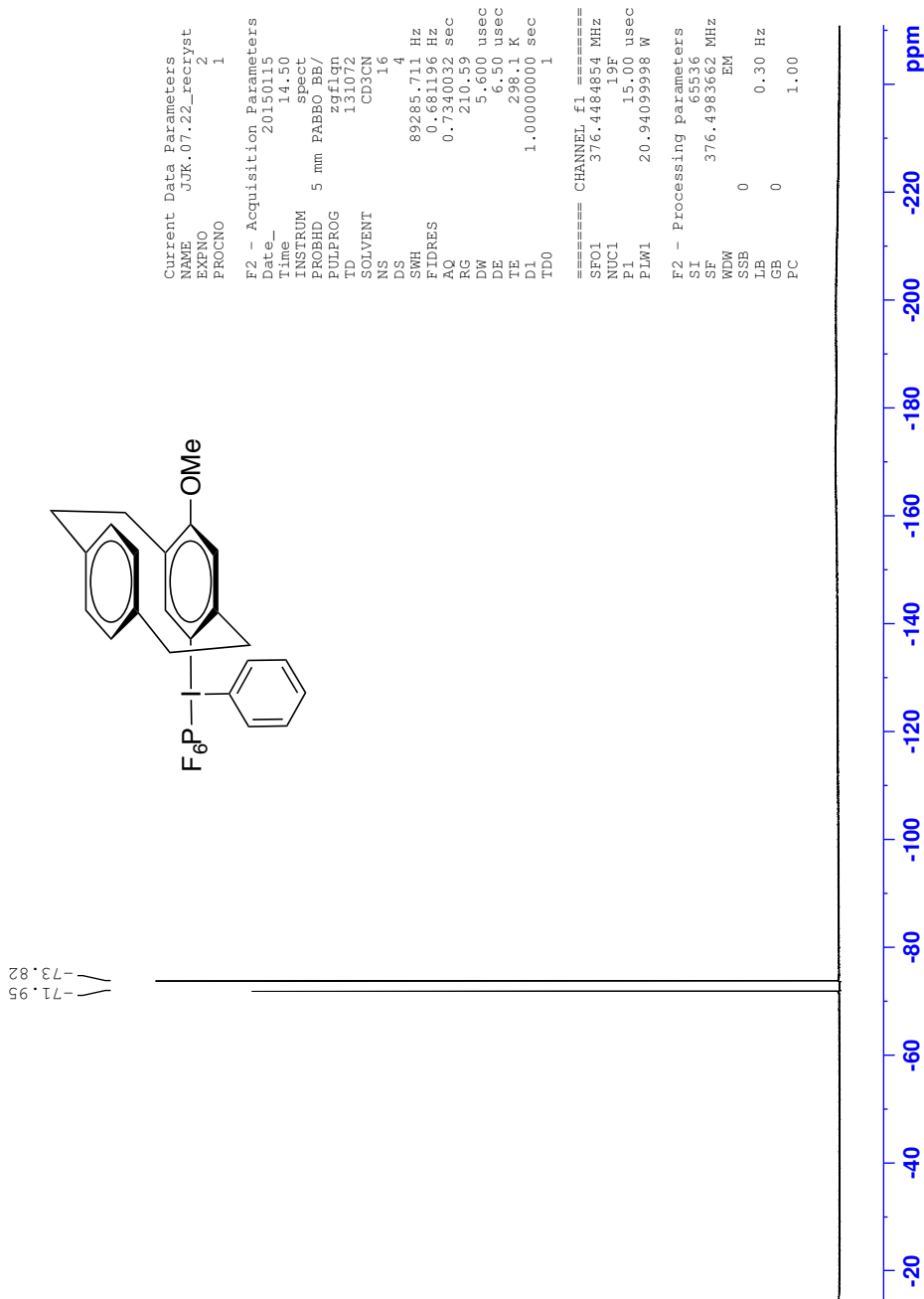
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of (4-((\pm)-7-methoxy-[2.2]paracyclophanyl))(4-methoxyphenyl)iodonium hexafluorophosphate (**36**)

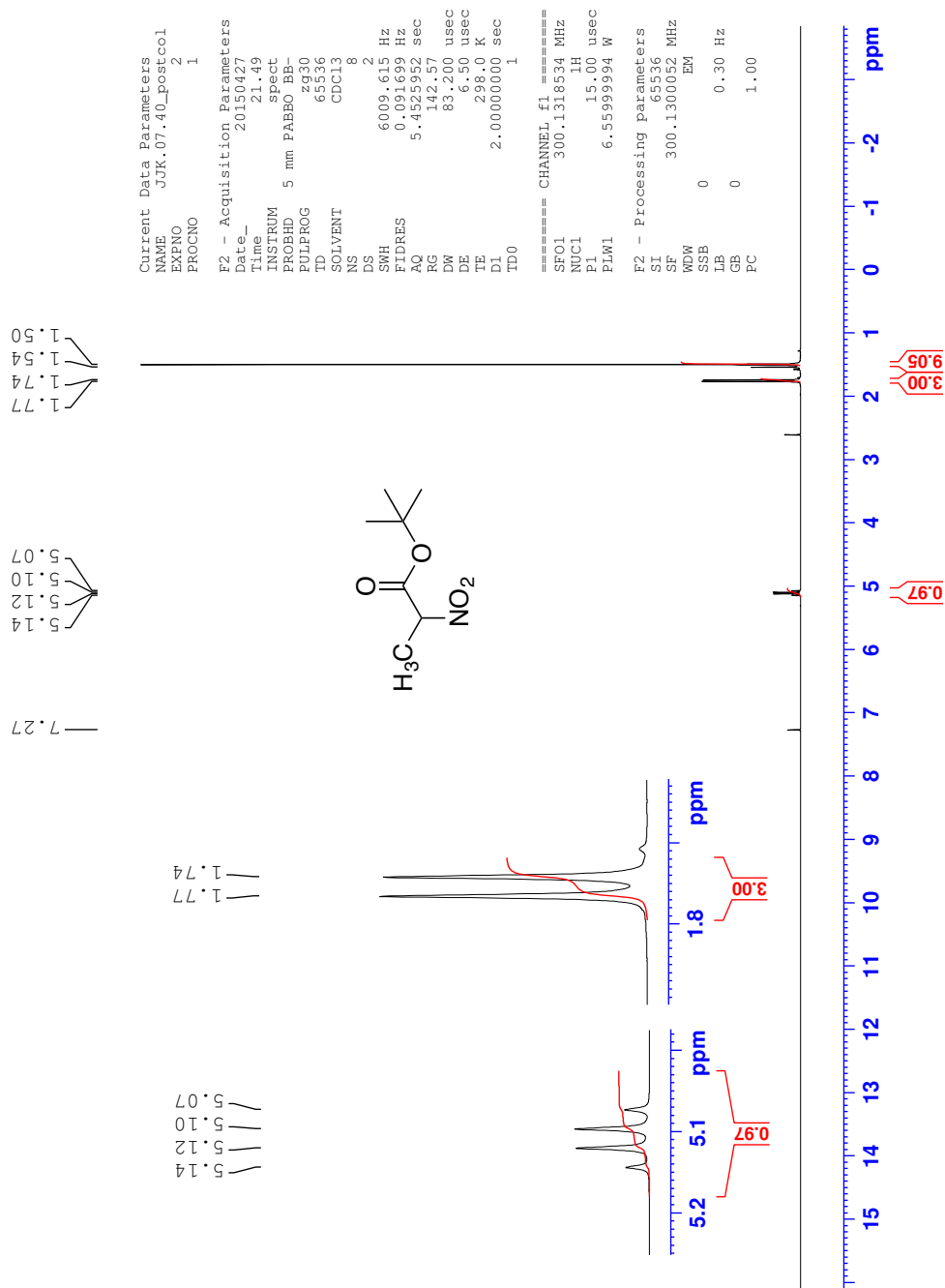


^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of (4-((\pm)-7-methoxy-[2.2]paracyclophanyl))(4-methoxyphenyl)iodonium hexafluorophosphate (**36**)

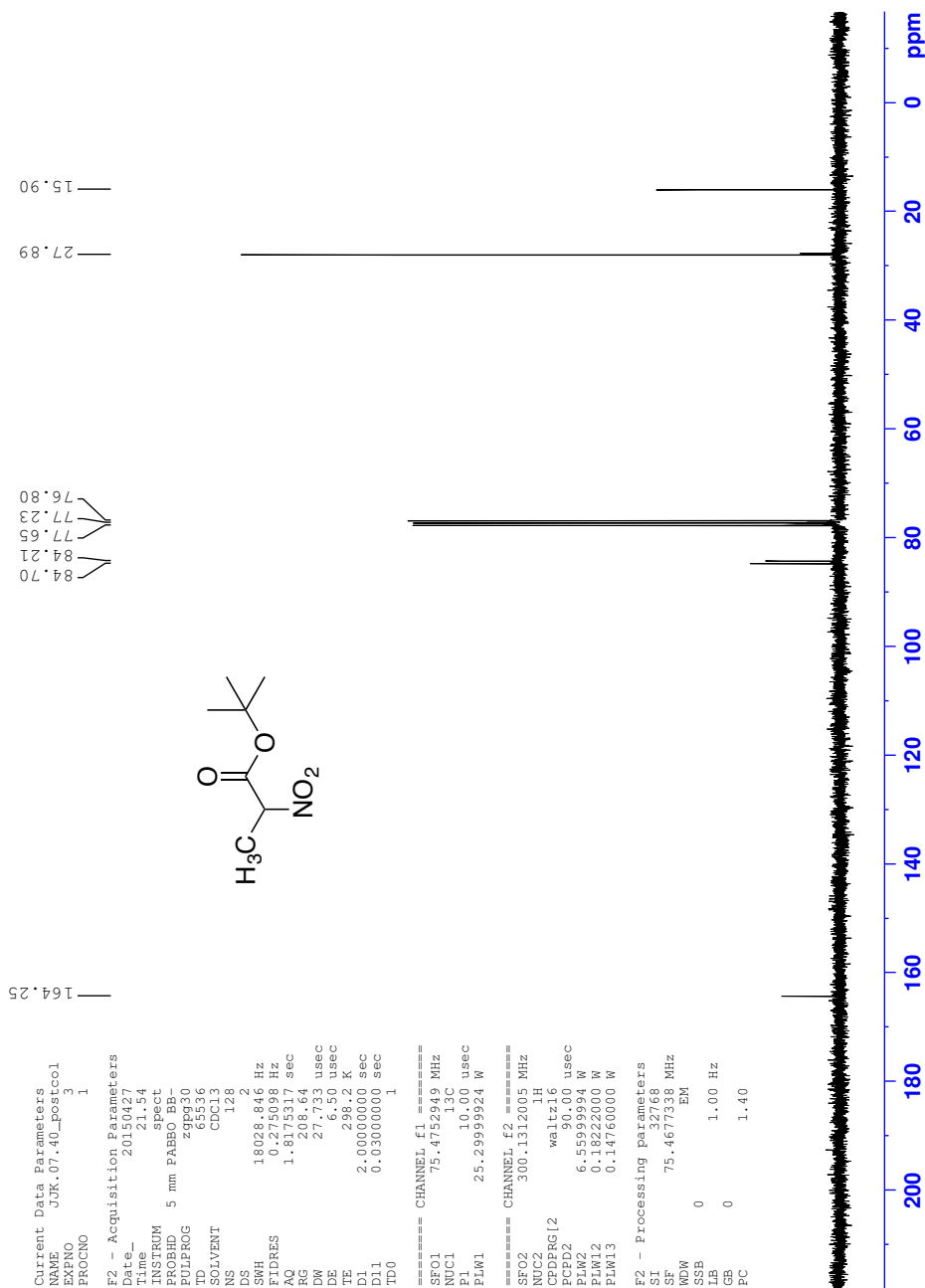


^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of (4-((*S*)-7-methoxy-[2.2]paracyclophanyl))(phenyl)iodonium hexafluorophosphate (**43**)

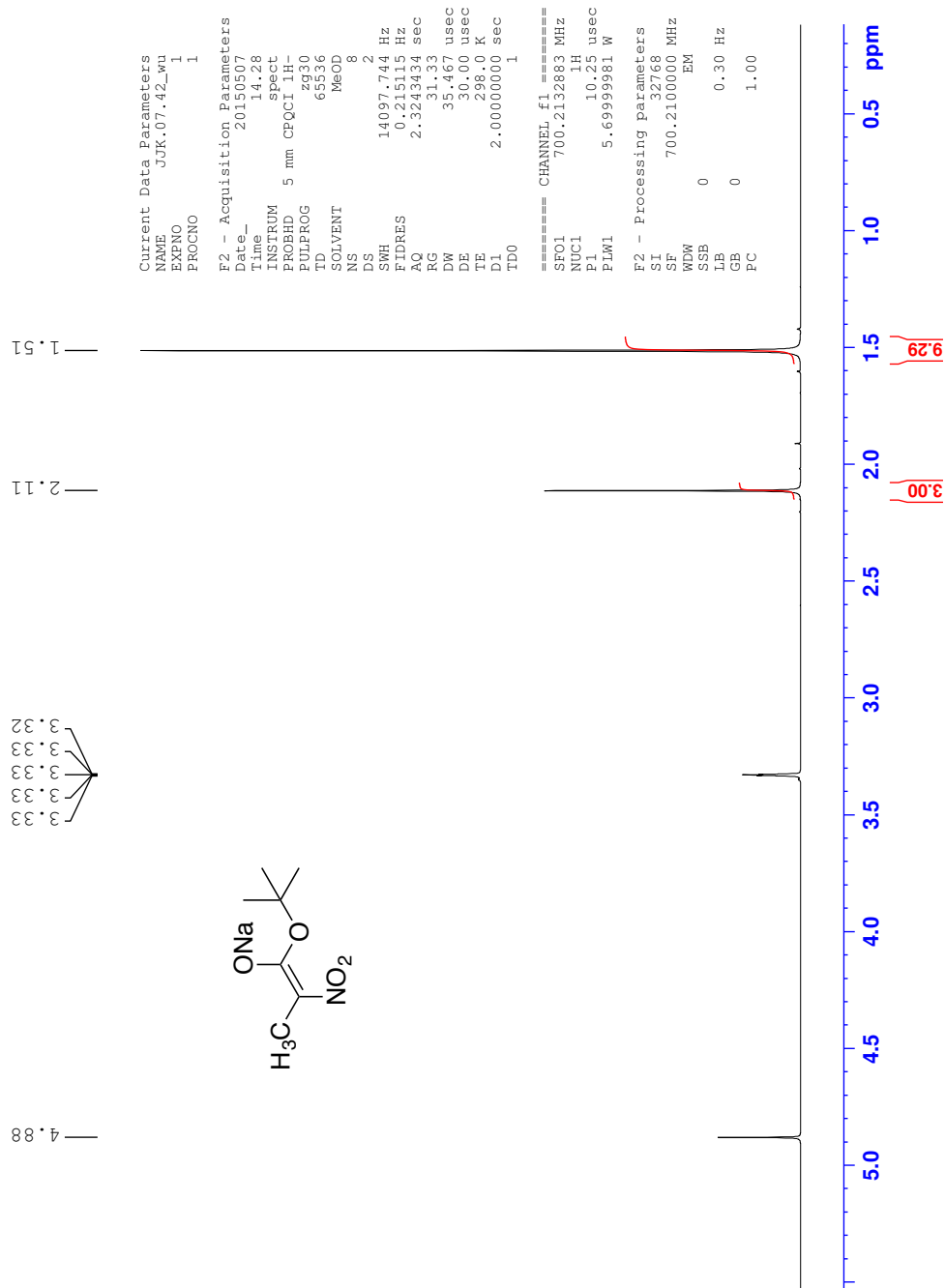


^1H NMR (CDCl_3 , 300 MHz, 298 K) spectrum of *tert*-butyl 2-nitropropionate (**48**)

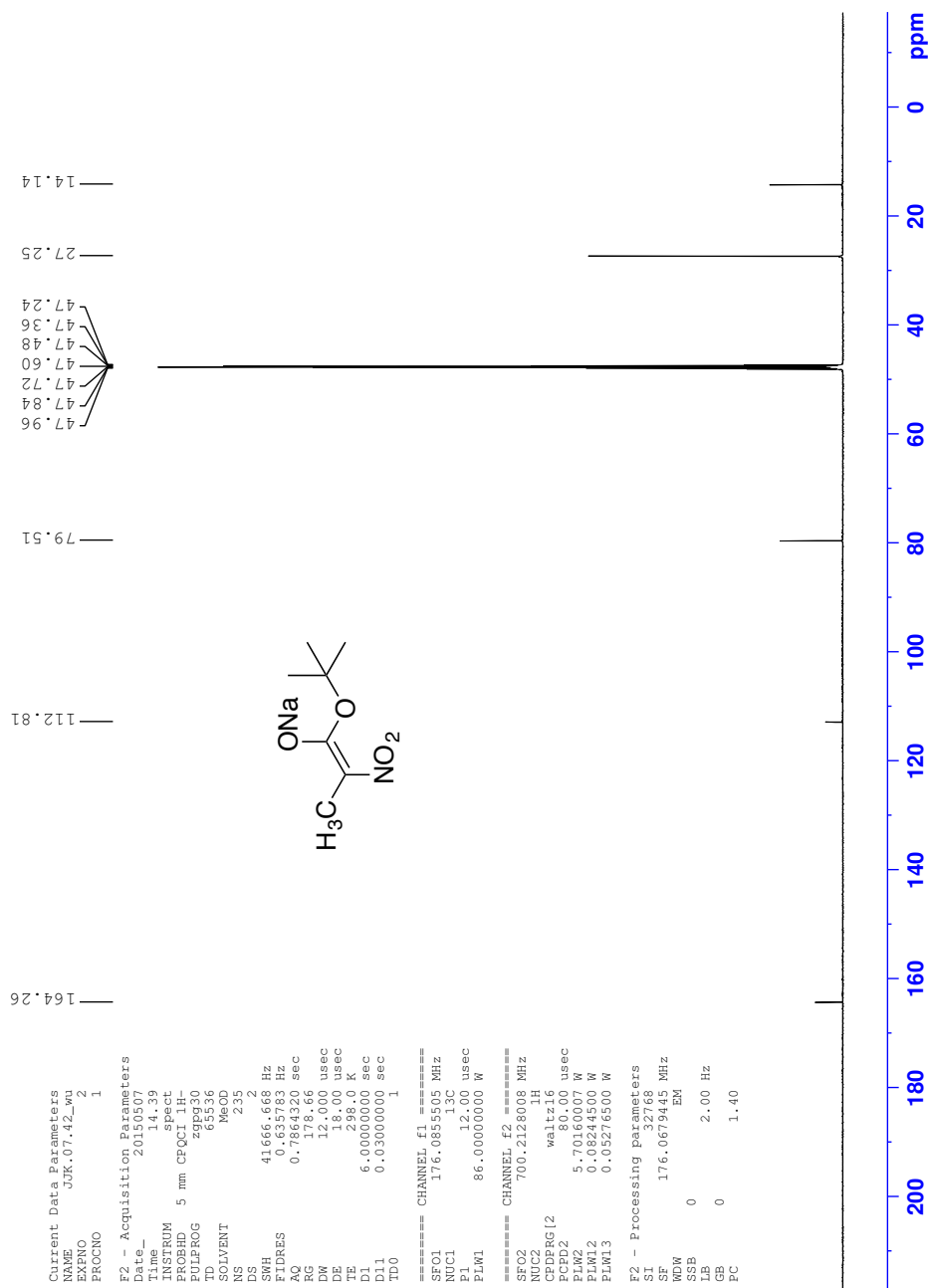
^{13}C NMR (CDCl_3 , 75 MHz, 298 K) spectrum of *tert*-butyl 2-nitropropionate (48)



^1H NMR (CD_3OD , 700 MHz, 298 K) spectrum of sodium 1-*tert*-butoxy-2-nitropropenolate (**49**)



^{13}C NMR (CD_3OD , 700 MHz, 298 K) spectrum of sodium 1-*tert*-butoxy-2-nitropropenolate (**49**)



CHAPTER 3

SYNTHESIS OF A VARIETY OF 2-ARYL-5-FLUOROBENZIMIDAZOLES

3.1 Introduction

In recent years there has been an interest in synthesizing substituted benzimidazoles, particularly 2-arylbenzimidazoles.¹ Benzo-fused imidazoles, oxazoles, and thiazoles have shown a broad range of biological activities.²⁻⁴ This includes anti-tumor,⁵⁻⁸ anti-viral,⁹⁻¹³ anti-microbial,¹⁴⁻¹⁷ anti-fungal,¹ anti-ulcer,¹ anti-histaminic,¹ and anti-inflammatory agents.^{18,19}

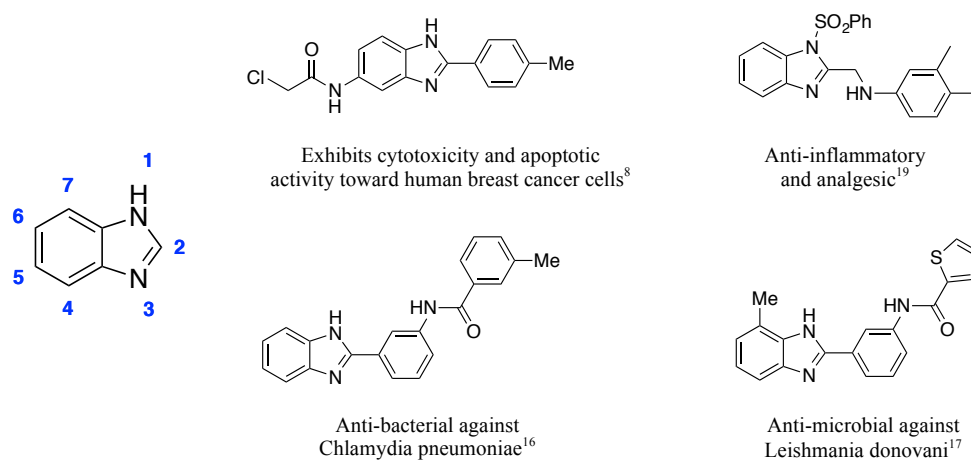


Figure 3.1: Numbering convention for benzimidazole (*left*)²⁰ and some 2-arylbenzimidazoles used as biological agents (*right*)

For material applications, these compounds are useful as nonlinear optics (NLO).²¹⁻²⁴

NLOs can be used for frequency doubling, optical phase conjugation (wavefront

reversal), etc. More recently these compounds have also found application as organic light-emitting diodes (OLED) and liquid crystals.^{25–30}

We are mostly interested in this class of compounds for their biological application. Given their broad range of activity, radio-labeled 2-arylbenzimidazoles could be useful for imaging. These compounds could potentially be used for diagnosing and monitoring cancer patients, studying inflammatory response, and as a diagnostic method for Alzheimer's disease. These compounds are structurally related to benzothiazole and benzoxazole compounds currently used for positron emission tomography (PET) imaging of β -amyloid plaques (Figure 3.2).

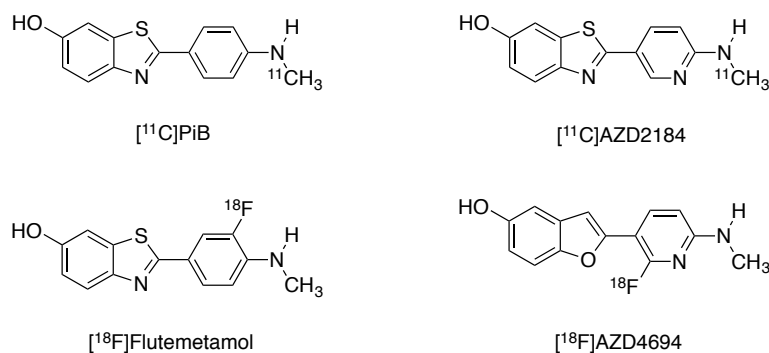


Figure 3.2: Some current PET radiotracers used for imaging β -amyloid plaques

Also, several studies suggest that long-term use of anti-inflammatory drugs may protect patients against the onset of Alzheimer's disease.³¹ The mechanism for this protection is not well understood, and subsequent studies have not found improvement in patients taking standard NSAIDs.³² As these compounds have found use as anti-inflammatory agents, they may be useful as imaging agents as well.

We sought to develop a synthesis of 2-arylbenzimidazoles that could be used as radiotracers for PET. We chose to substitute these compounds with fluoride-18 for the same reasons as discussed previously in relation to the synthesis of Flutemetamol (Chapter 1). Its half-life of about 2 hours is convenient for relatively complex radiotracer synthesis, long enough to synthesize the radiotracer at a lab with an on-site cyclotron and transport it to nearby satellite PET centers (that lack a full radiochemical lab and cyclotron). Its half-life is also short enough to collect kinetic data in a reasonable time period (provided the unbound radiopharmaceutical is metabolized quickly); radioactivity in the patient is short-lived, allowing the PET scan to be an outpatient procedure. The low positron kinetic energy of fluorine-18 ensures a short range in tissue, which provides a high resolution PET scan. The decay of fluorine-18 yields innocuous ^{18}O as the product atom. The nuclear reaction for formation of fluorine-18 from oxygen-18, $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ on ^{18}O -enriched water (H_2^{18}O), can yield several Curie (Ci) amounts of fluorine-18 from a single cyclotron run, allowing for many PET scans from a single cyclotron run. Fluorine substitution of drugs often leads to improved pharmacological profiles.^{33,34} The high electronegativity and small atomic radius of the fluorine atom, along with the short C–F bond length, cause relatively small structural perturbations compared to other functional group substitutions, but drastically alter the electronic properties, and often improve the bioavailability of the compound.^{35,36} These features make fluorine-18 an attractive radionuclide to incorporate into 2-arylbenzimidazoles.

As with the synthesis of Flutemetamol (Chapter 1) we chose to use hypervalent iodine complexes, specifically diaryliodonium triflates and diaryliodonium

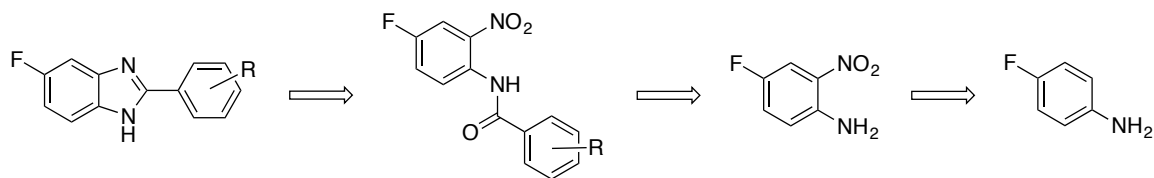
hexafluorophosphates, to introduce fluorine-18 onto the target molecule. A synthesis of diaryliodonium salts, using a variety of substituted benzenes at the 2-position of benzimidazole, was started. We chose to introduce the fluorine atom at the 5-position, as a large variety of 2-arylbenzimidazoles of interest have substitution at the 5-position.²⁻⁴

3.2 Results and Discussion

3.2.1 Direct Synthesis of 2-Aryl-5-[¹⁹F]Fluorobenzimidazoles

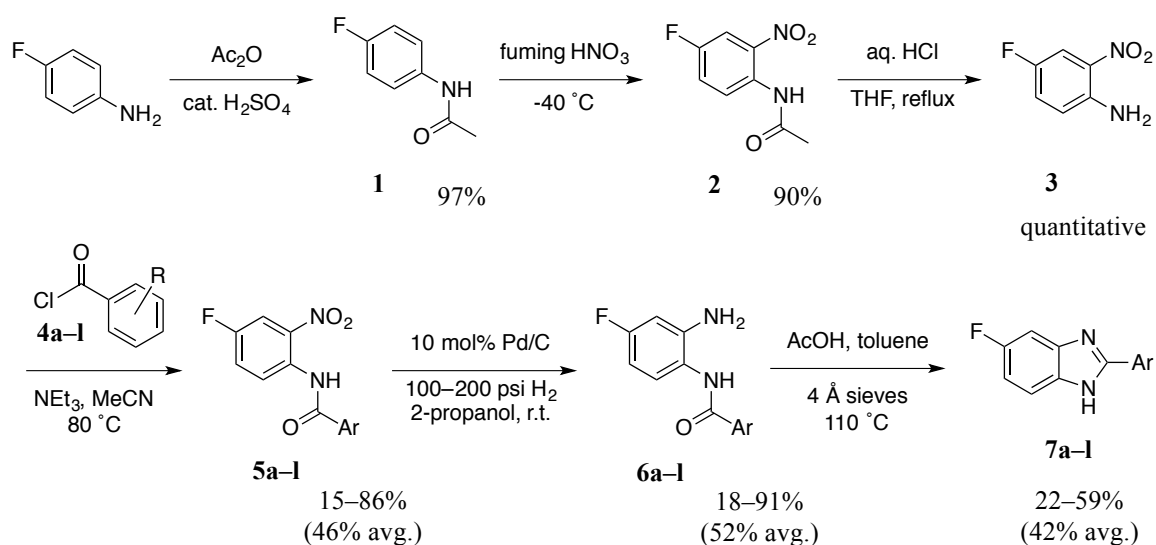
We began by synthesizing [¹⁹F]-fluorinated benzimidazoles directly, without using iodonium salts. A total of 11 2-aryl-5-fluorobenzimidazoles were produced in sufficient purity. These compounds would be useful later in the project as fluorine-19 standards for NMR analysis and HPLC standards for radiochemistry. This shorter synthesis also worked as a model synthesis for the first portion of the subsequent synthesis with iodonium salts. Oakridge National Labs (ORNL) expressed interest in screening these 2-aryl-5-[¹⁹F]fluorobenzimidazoles, so a variety of compounds were synthesized (ORNL subcontract 4000089408).

There is a broad array of methods for synthesizing benzimidazoles.³⁷⁻⁴⁸ A retrosynthesis was designed (Scheme 3.1). We chose a route that built up the benzimidazole by coupling a nitro aniline and substituted benzoyl chloride, followed by reduction and ring closure. This route was chosen as the precursors were inexpensive in large quantities, the synthetic steps generally did not require harsh conditions, and the final step did not require toxic catalysts which could pose issues if used *in vivo*.



Scheme 3.1: Retrosynthesis of 2-aryl-5-fluorobenzimidazoles

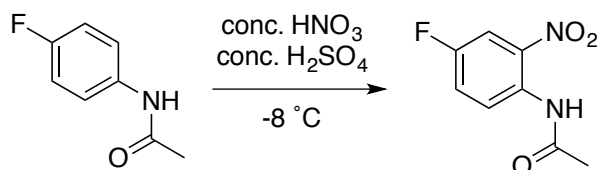
Starting with commercially available 4-bromoaniline, the benzene ring was nitrated. Electrophilic aromatic substitution is not directly possible on anilines due to the extremely activated arene and the easily oxidized amine. Small scale trials rapidly became highly exothermic and turned jet black. The amine was protected using acetic anhydride to form 4-fluoroacetanilide (**1**).^{49, 50} This arene was nitrated using fuming nitric acid to yield 4-fluoro-2-nitroacetanilide (**2**).



Scheme 3.2: General forward synthesis of 2-aryl-5-fluorobenzimidazoles

Conditions were also established for nitration using milder reagents (Scheme 3.3). At $-8\text{ }^\circ\text{C}$, the nitronium cation forms from the combination of concentrated nitric and sulfuric

acids and addition occurs. At lower temperatures the reaction did not progress at a reasonable rate, and higher temperatures promoted a second nitration (to form 4-fluoro-2,6-dinitroacetanilide) and formation of 4-fluoro-3-nitroacetanilide.



Scheme 3.3: Milder nitration conditions

Yields tended to be lower with these reaction conditions, and temperature control proved more difficult. Fuming nitric acid, while more hazardous to use, provided better yields. Due to the stronger conditions, temperatures could be lowered to $-40\text{ }^{\circ}\text{C}$, which greatly minimized formation of side-products. It was found that scaling up the reaction above 2 grams of **1** made temperature control more difficult (presumably due to slower temperature diffusion through the larger solution volume). Since nitration was complete in only 10 minutes, this step was effectively scaled up by repeated nitration on a 2 g scale. Deprotection was performed under acidic conditions to form 4-fluoro-2-nitroaniline (**3**); deprotection with hydroxide also proved effective. Recrystallization was performed after each step for compound characterization; however, it was found that recrystallization after deprotection provided pure product, even if recrystallization was not performed for the acetate protection and nitration steps. Although the route without individual crystallizations gave a poorer yield for the hydrolysis step (to form **3**), the overall yield after three steps was similar.

Amides were generated using acid chlorides (**4a–l**). A variety of acid chlorides could be purchased commercially or readily synthesized; twelve were chosen (Figure 3.3).

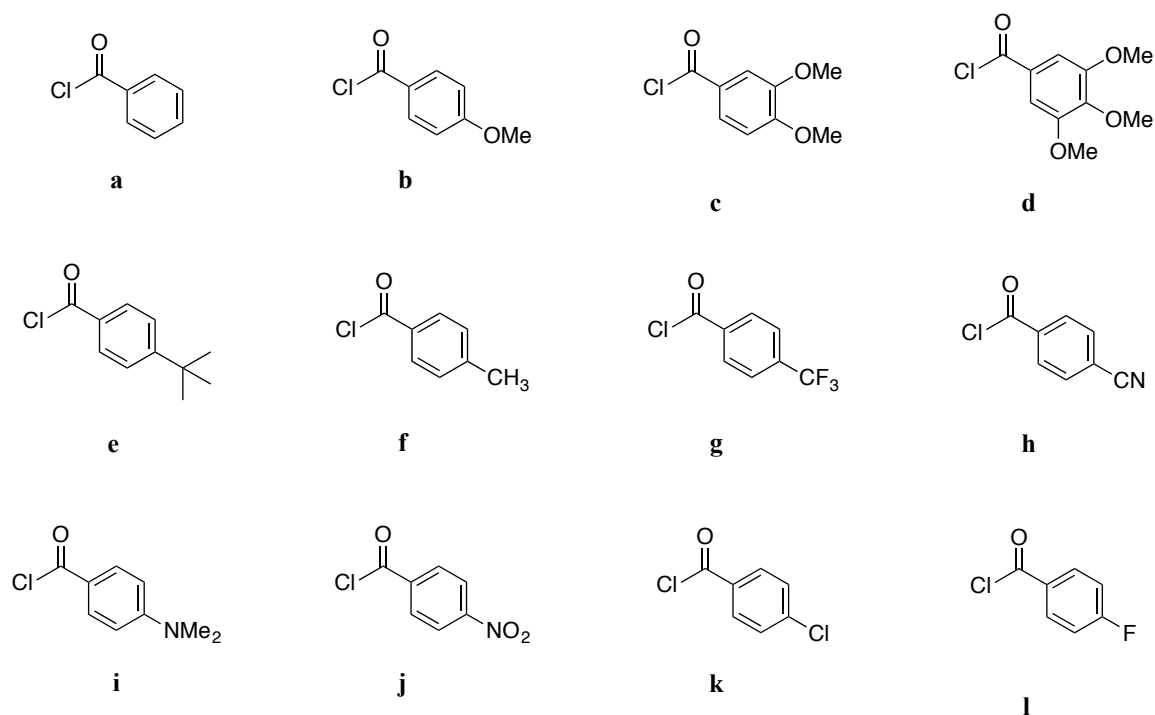
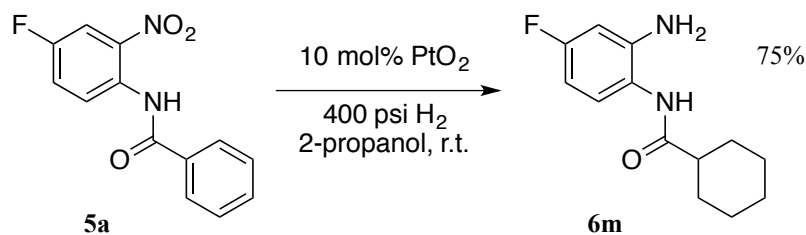


Figure 3.3: Acid chlorides used

Amide formation proved more challenging. Initial reactions, using a 1:1 ratio of aniline (**3**) to acid chloride (**4a–l**) and an excess of triethylamine, went only partially to completion (typically 30–60%). Addition of more acid chloride (1:1.5 **3** to **4a–l**) made little change in the amount of product. Even with the addition of 4-(dimethylamino)pyridine (DMAP), the reaction did not progress further. Changing the solvent from dichloromethane to acetonitrile, a more polar and higher boiling solvent, increased reaction rate, but did not change the amount of product produced. Using

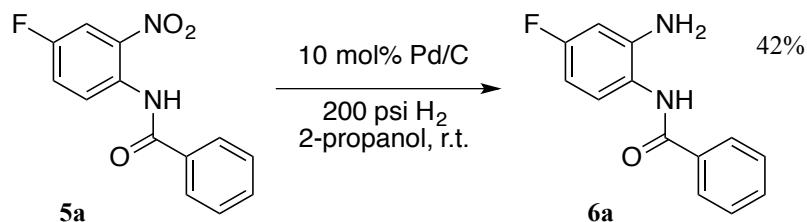
rigorously dry **3**, acetonitrile, and triethylamine made no noticeable change. Fortunately the amide product (**5a-l**) was separable from **3** and the acid chloride (**4a-l**) by recrystallization or column chromatography. Using vacuum sublimation, **3** could be recovered from the impure mother liquor, and further purified using recrystallization.

Reduction of the aryl nitro and ring closure could potentially be performed by a reductive imination. However, we chose to take a two-step approach instead to better study each step. Reduction was performed using hydrogen gas and a metal catalyst.⁵¹ Initially platinum oxide was used with 400 psi H₂ to reduce **5a** to **6a**. Reaction was found to be complete by TLC, but even after purification, NMR showed what seemed to be significant impurities in the aliphatic region. After further analysis we realized that not only was the nitro group reduced to the amine, but the phenyl ring was also reduced to a cyclohexyl ring (Scheme 3.4), exclusively forming *N*-cyclohexyl-4-fluoro-2-aminoaniline (**6m**).



Scheme 3.4: Formation of *N*-cyclohexyl-4-fluoro-2-aminoaniline (**6m**).

Though not the intended outcome, this was fortuitous as it offered a simple route to an additional 2-aryl-5-fluorobenzimidazole. The reaction was run again using lower pressure (200 psi H₂) and palladium over carbon (Pd/C). These conditions (Scheme 3.5) exclusively produced *N*-phenyl-4-fluoro-2-aminoaniline (**6a**).



Scheme 3.5: Formation of *N*-phenyl-4-fluoro-2-aminoaniline (**6a**).

It was found that 100 psi was also sufficient hydrogen pressure to reduce the nitro group. The rest of the amides were reduced using these milder conditions to produce **6b–l**.

Ring closure was performed under acidic conditions.^{52,53} This step presumably occurs in a similar fashion to imine formation (Figure 3.4).

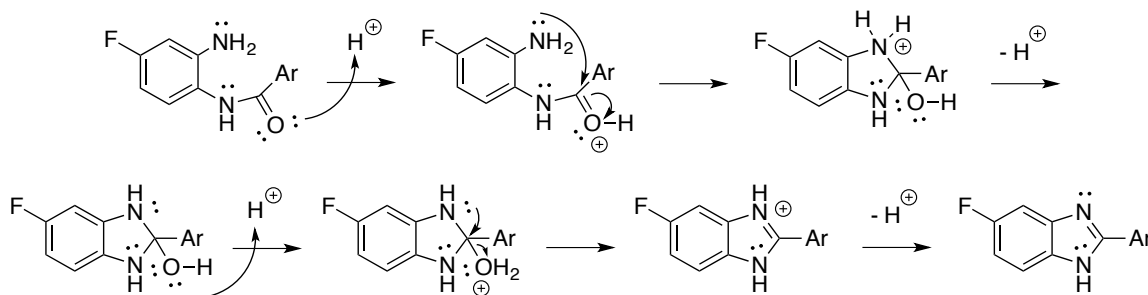


Figure 3.4: Proposed mechanism of ring closure

The added aromatic stability from a 10-electron fused ring system (rather than a single ring 6-electron system) makes this process favorable. The addition of molecular sieves also helps to drive the reaction by removing the water that is eliminated. Neutralization of excess acid and purification by recrystallization or column chromatography provides the 2-aryl-5-fluorobenzimidazoles (**7a–m**). These compounds are fairly insoluble in most organic solvents, and NMR spectra can be complicated due to fast tautomerization

(Figure 3.5); in most cases several of the benzimidazole ring protons are highly broadened or not visible.

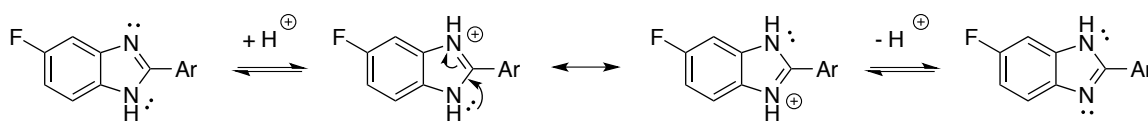


Figure 3.5: Proposed mechanism of tautomerization

We were unable to fully purify compounds **7h** and **7j**, but sent the remaining 11 compounds to ORNL for screening.

3.2.2 Synthesis of 2-Aryl-5-[¹⁸F]Fluorobenzimidazoles Precursors

With fluorine-19 standards completed, synthesis was started toward diaryliodonium salts that could be used as precursors for 2-aryl-5-[¹⁸F]fluorobenzimidazoles. Compounds with tight binding and long half-lives *in vivo* are typically unsuitable for therapeutic use due to their extended duration of effect. However, since the dosage of a radiotracer for PET is typically well below the level of physiological effect, compounds that bind tightly to the target (*e.g.* tumor cells) are often useful as imaging agents. Regardless of the results ORNL might publish, we decided to proceed toward synthesizing the same set of compounds using diaryliodonium salts, which could be used in a radiosynthesis and evaluated as radiotracers for positron emission tomography (PET). Two of these compounds were successfully fluorinated, using conditions suitable for radiofluorination. An additional eight 2-aryl-5-

bromobenzimidazoles were produced and partially carried forward toward production of the analogous PET precursors.

We have developed a wide variety of methods to make diaryliodonium salts,⁵⁴⁻⁵⁶ but at the onset of this project we had only developed a few (Figure 3.6): (1) an aryl iodonium diacetate could be directly coupled with an arene, activated toward electrophilic aromatic substitution (EAS), in the presence of an acid (typically *p*-toluenesulfonic acid^{57,58}) or a Lewis acid (trimethylsilyl *p*-toluenesulfonate (TMS-OTs), trimethylsilyl trifluoromethanesulfonate (TMS-OTf), etc), (2) an aryl iodonium diacetate could be coupled with an aryl trifluoroborate salt in the presence of a Lewis acid, (3) an aryl iodonium diacetate could be coupled with an aryl stannane in the presence of an acid⁵⁹ or a Lewis acid.

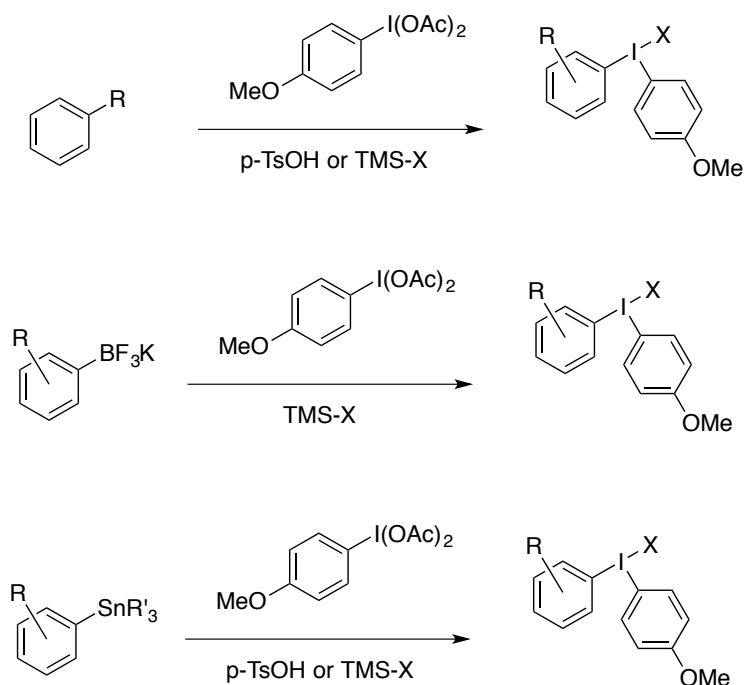
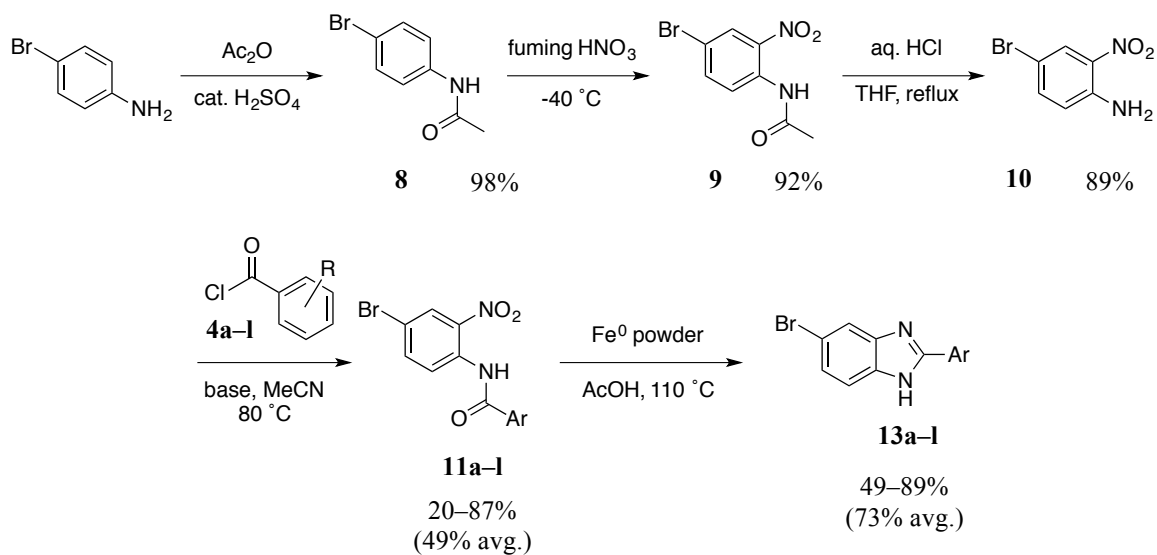


Figure 3.6: Methods for synthesizing diaryliodonium salts

The first route was not practical for synthesizing a broad scope of 2-arylbenzimidazoles, as many of the compounds have electron-rich arenes at the 2-position of the benzimidazole; rather than add to the 5-position of the benzimidazole ring, bis(acetoxy)-4-methoxybenzene could instead add to the other arene. Both the second and third methods could be used with a 2-aryl-5-bromobenzimidazole precursor. A synthesis for 2-aryl-5-bromobenzimidazoles was developed. The same, or similar, synthetic steps from the first synthesis could presumably be used to make brominated (rather than fluorinated) analogs (Scheme 3.6).



Scheme 3.6: General forward synthesis of 2-aryl-5-bromobenzimidazoles

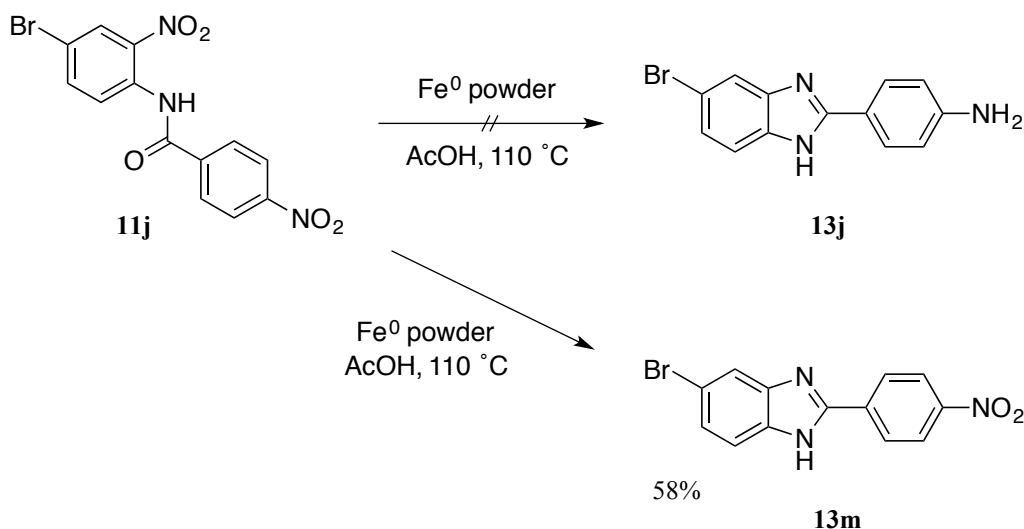
Acetylation proceeded with similar results; 4-bromoacetanilide (**8**) was somewhat less soluble than 4-fluoroacetanilide (**1**), which led to slightly improved yields. Nitration was performed with fuming nitric acid to produce 4-bromo-2-nitroacetanilide (**9**). It was found that this reaction could be scaled to 6 grams of **8** without a significant loss in purity or yield, unlike the synthesis of 4-fluoro-2-nitroacetanilide which provided lower yields

above 2 grams of **1** (due to side-reactions). Presumably this is due to bromine being slightly more deactivating than fluorine,^{60,61} and also that 4-bromoacetanilide (**8**) is slightly less soluble in nitric acid than 4-fluoroacetanilide (**1**), which may slow the reaction slightly. A larger scale batch of **9** was produced by repeated nitration on a 6 g scale. Removal of the acetyl protecting group was performed under the same conditions to produce 4-bromo-2-nitroaniline (**10**).

Once again, amide formation proved challenging. We theorized that a complicated equilibrium existed between the aniline and the amide product (**11a-l**); unreacted aniline could attack the product, cleaving the amide to generate another amide (**11a-l**) and free aniline (**10**). After further investigation it was discovered that in some reactions (*e.g.* formation of **11a, h, k, l**), the imide (caused by a second addition of the acid chloride onto the product amide, **11**) was predominantly formed. Presumably the electron-deficient amide (**11**) was sufficiently acidic to be deprotonated by triethylamine and react with a second equivalent of the acid chloride (**4**). It may be possible for this imide to exist as an intermediate in the equilibrium, even though it was not readily observed in all reactions. Under this assumption, conditions were modified for some compounds, using pyridine instead of triethylamine and a stoichiometric amount of acid chloride. Using this method, yields were significantly improved (in most cases). Some imides (**12a, 12e, 12l**) were isolated by recrystallization and hydrolyzed to the corresponding amide (**11a, 11e, 11l**) by hydrolysis with a suitable amount of sodium hydroxide (determined using several small-scale trial reactions, plotting the amount of remaining imide, and projecting an optimum amount of hydroxide to use).

Rather than take a two-step approach as with the previous synthesis, a mild reduction, run under acidic conditions, was performed to both reduce the nitro group and close the ring to form the 2-aryl-5-bromobenzimidazoles (**13a-l**). Since aromatic nitro groups have a high reduction potential,⁵¹ a variety of conditions could be used.⁶² Tin, zinc, and iron reductions were investigated. It was found that a Béchamp reduction, using iron filings in acetic acid, was able to reduce the nitro group and exact ring-closure.^{63,64} Typically Béchamp reductions are run in hydrochloric acid, but it was found that acetic acid, at 110 °C was sufficient. This reaction is fairly selective to nitro groups (selective even to aromatic nitro groups and tertiary aliphatic nitro groups over other aliphatic nitro groups⁶⁵), so there was little worry of side-reactions on the other aromatic ring. Finally, iron is relatively non-toxic. Due to this mild approach, 5-bromo-2-cyclohexylbenzimidazole (the brominated analog of **7m**) was not synthesized. Slow reaction rate is a drawback to this approach; reaction times varied from overnight to a week. Performing the reaction in a sealed tube removed the concern of evaporation of solvent. Reactions could be easily monitored by color — the initial reaction mixtures are brightly colored due to the vibrantly yellow to orange amides (**11a-l**), and the completed reaction mixtures were a pale rust color, from the oxidized iron. Once the initial yellow color had faded, analysis of the solution by TLC was used to more conclusively gauge reaction progress. Despite long reaction times, there were rarely side-reactions, and the product could be isolated by liquid-liquid extraction and, if necessary, a short silica column. It was later found that the reaction time could be shortened using iron powder rather than iron filings; presumably the larger surface area increases the rate of reduction.

Compound **11j** gave surprising results. In theory the nitro group on both rings would be reduced (Scheme 3.7); however, after purification, the predominant product was 2-(4-nitrophenyl)-5-bromobenzimidazole (**13m**)

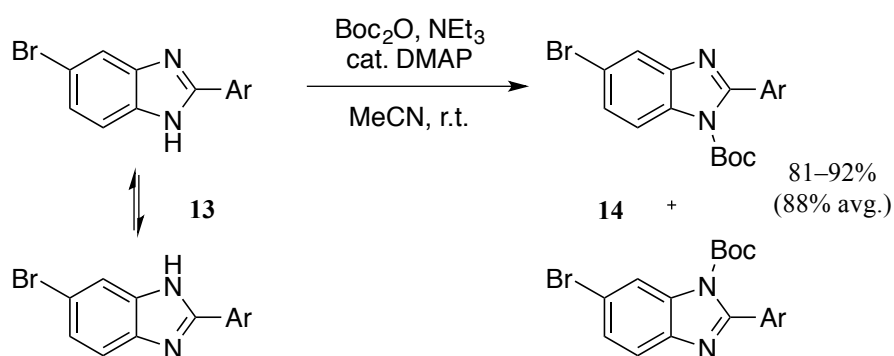


Scheme 3.7: Formation of 2-(4-nitrophenyl)-5-bromobenzimidazole (**13m**)

Compound **13j** was formed (confirmed by EI^+ MS of the crude reaction mixture, showing $[\text{M}]^+$ 287.0047 m/z), but only as a very minor product (not observed by NMR). In the ^1H NMR spectrum of the isolated product, **13m**, protons on the aromatic ring at the 2-position of the benzimidazole (8.9 Hz doublet at 8.40 ppm, 8.9 Hz doublet at 8.23 ppm) were shifted only slightly from those in the ^1H NMR spectrum of **11j** (8.9 Hz doublet at 8.42 ppm, 8.9 Hz doublet at 8.16 ppm).

In total, ten 2-aryl-5-bromobenzimidazoles were produced. We began to carry these compounds forward to produce the analogous diaryliodonium salts. Before formation of the diaryliodonium salt, the acidic NH (pKa of benzimidazole in DMSO is 16.4⁶⁶) needed to be protected. Boc was chosen as the protecting group due to its ease of

introduction and ease of removal (after the fluorination step). Also, the lower polarity of the *tert*-butyl group would hopefully increase solubility of **13** in organic solvents. We have incorporated Boc protecting groups into diaryliodonium salts several times with good success. Boc protection proceeded smoothly with triethylamine in acetonitrile, using DMAP as a catalyst.

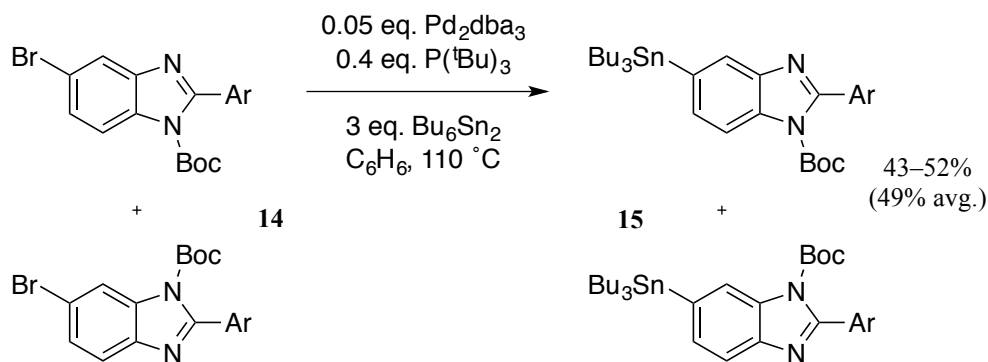


Scheme 3.8: Boc protection of **13**

Due to the rapid equilibrium between the two benzimidazole tautomers, Boc protection gave a nearly equal mixture of two regioisomers of each compound (**14**). Initially, for a few of the set of Boc protections that were run, each regioisomer was isolated separately for characterization. However, these fractions were recombined for the next synthetic steps. For the remainder of the set of compounds **14** produced (eight compounds in all), both regioisomers were isolated as a mixture. Once fluorination is complete and the Boc group is removed, tautomerization will occur again; each regioisomer will yield the same tautomers after deprotection.

Next, **14** were converted to the corresponding aryl tributylstannanes (**15**). This reaction was chosen initially as we had a good deal of experience with these compounds.

Though organotin compounds may be toxic, the amount present after formation and purification of the diaryliodonium salt should be minimal, and the PET dosage is very low. The tributyltin group was chosen as it is far less volatile and less toxic than trimethyltin; the longer chain alkanes should also help to improve compound solubility as did the Boc protecting group. Given the somewhat fragile nature of the Boc protecting group, lithiation or formation of a Grignard reagent could not be used, so a palladium-catalyzed transformation was used (Scheme 3.9).⁶⁷

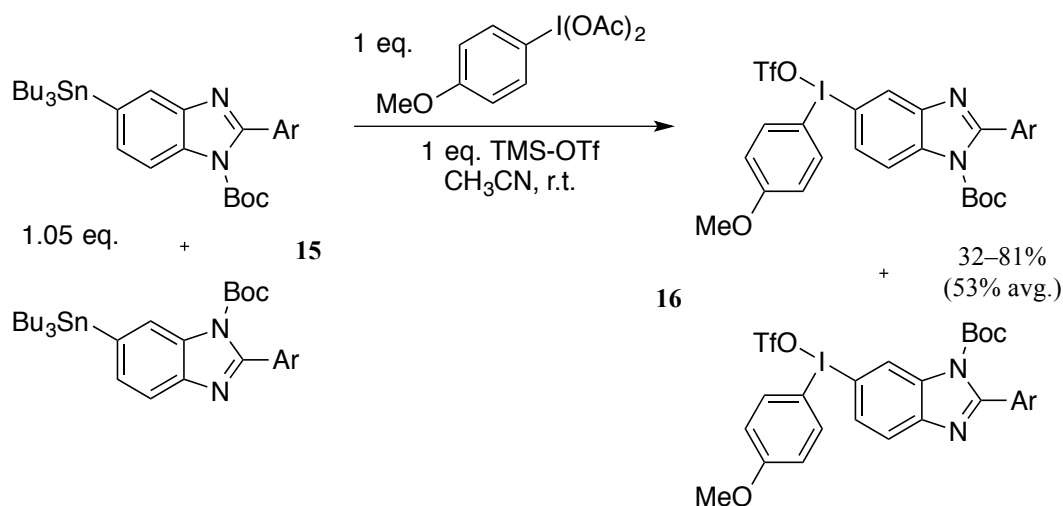


Scheme 3.9: Stannylation of **14**

Reaction progress was monitored by concurrently running a small scale reaction in benzene- d_6 and monitoring by ^1H NMR. Since naturally occurring ^{115}Sn , ^{117}Sn , and ^{119}Sn all have nuclear spin $\frac{1}{2}$, the stannylated products are relatively easy to identify; protons near the tin atom appear with tin satellites. The stannylated products were isolated as a mixture of regioisomers. Once again, for a few of the set of stannylation reactions that were run, each regioisomer was isolated separately for characterization. These fractions were recombined for the next synthetic steps. For the remainder of the set of compounds **15**

produced (four compounds in all were produced in sufficient yield and purity), both regioisomers were isolated as a mixture.

Iodonium salts were synthesized from all of the set of compounds **15** (Scheme 3.10). The diaryliodonium triflates (**16**) formed were isolated as a mixture of regioisomers.

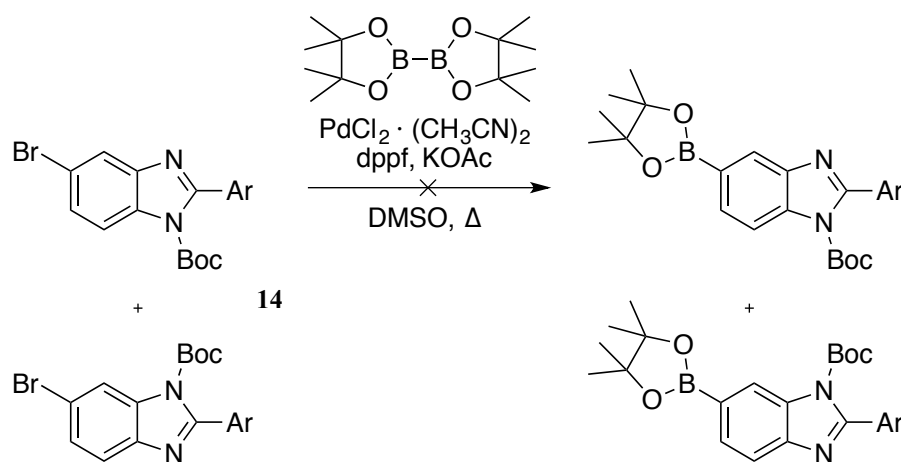


Scheme 3.10: Synthesis of diaryliodonium salts **16**

Purification proved challenging. Even small amounts of residual tin (Bu_3SnOAc is a stoichiometric by-product) caused the salts to oil rather than crystallize. The crude salt could be precipitated from a more polar solvent (THF, ethyl acetate, dichloromethane, etc) with pentane. Repeating this process several times usually yielded a solid. Some compounds were only isolated as a sticky solid, even after repeated precipitations. A number of crystallization methods were attempted: chilling a multiple-solvent solution near the cloud point, layering, vapor diffusion, or slow evaporation. In all cases no crystallization was observed; only an oil was produced. Residual tin compounds are

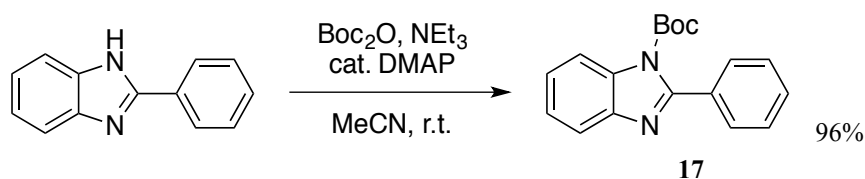
often removed by stirring with a fluoride salt (*e.g.* potassium fluoride in ethanol); unfortunately, this strategy would not be practical as it could leave residual fluoride-19 impurities (even minor amounts could compete with fluoride-18 during radiochemistry). Chromatography can also be used, but no solvent conditions could be established; **16** remained at the baseline on TLC using silica or alumina. Repeated trituration with pentane did remove small amounts of residual tin. Soxhlet extraction using pentane did further purify the salt, but did not remove all of the tin impurity. Performing a liquid-liquid extraction by dissolving compounds **16** in acetonitrile and washing with pentane also removed some, but not all, tin impurity.

We sought to find another strategy to convert **14** to **16** without using tin. Miyaura borylation (Scheme 3.11) was attempted.⁶⁸ Regardless of the conditions used (solvent, base, ligand), the borylation reaction cleaved the Boc protecting group and did not appear to achieve conversion of the carbon-bromine bond to carbon-boron. Boc protection of the crude product mixture recovered **14**, confirming that borylation did not occur.



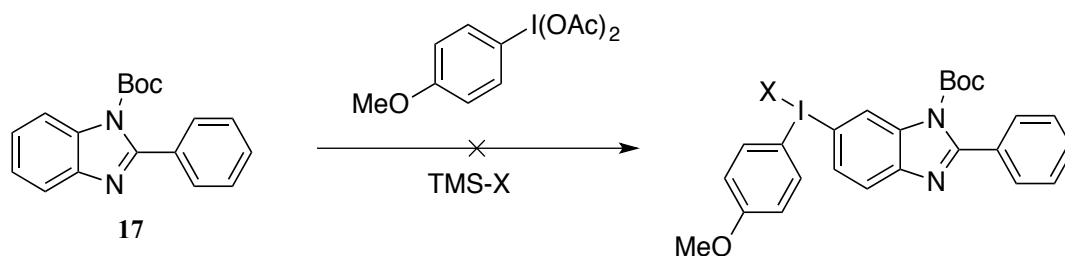
Scheme 3.11: Miyaura borylation example

Despite the potential for undesired iodoarylation of the aromatic ring at the 2-position rather than the benzimidazole aromatic ring, direct addition of *p*-methoxyphenyliodonium diacetate by electrophilic aromatic substitution was tested. Commercially available 2-phenylbenzimidazole was protected with a Boc protecting group to produce **17** (Scheme 3.12).



Scheme 3.12: Boc protection of 2-phenylbenzimidazole

Since there is no substitution on the benzimidazole ring, only one regioisomer is produced. An excess of *p*-methoxyphenyliodonium diacetate (**18**) was combined with **17** in acetonitrile- d_3 (Scheme 3.13). A variety of Lewis acid catalysts were added: TMS-OTs, TMS-OMs, and TMS-OTf.

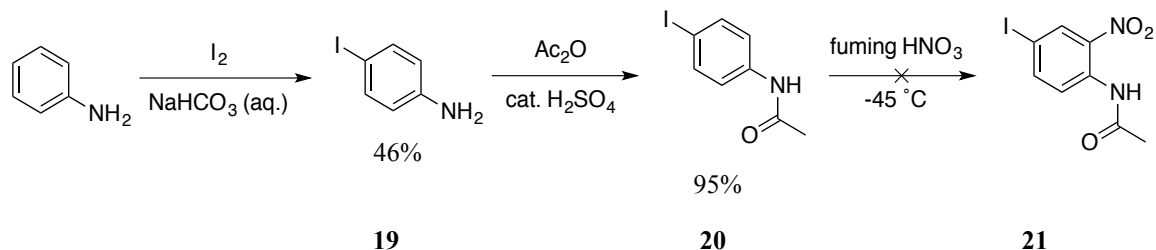


Scheme 3.13: Direct iodoarylation of **17**

Initially 1 equivalent was used; if no reaction occurred, a second equivalent was added. Presumably these Lewis acids undergo exchange with one or both of the acetates on *p*-methoxyphenyliodonium diacetate. The more electron-withdrawing anion(s) decreases

electron density on the iodonium center, increasing the electrophilicity of the compound. With the addition of TMS-OTs, the least electron-withdrawing anion (*i.e.* the weakest), no reaction occurred on **17**. A second equivalent made no change, and neither did heating the reaction mixture. With the addition of TMS-OMs, no reaction occurred on **17**, with one or two equivalents. Once heated, reduction of *p*-methoxyphenyliodonium diacetate to *p*-iodoanisole was observed. Analysis of **17** was inconclusive as many products were formed. With the addition of 1 equivalent of TMS-OTf, at room temperature, reduction of *p*-methoxyphenyliodonium diacetate to *p*-iodoanisole occurred immediately (visible by a vibrant color change and confirmed by ¹H NMR). Analysis of **17** was again inconclusive; other than the sharp peaks for *p*-iodoanisole protons, several very broad peaks were present in the aromatic region.

At this point we had begun to develop another technique for synthesizing diaryliodonium salts, oxidation of aryl iodides to aryl iodonium diacetates using SelectfluorTM and TMS-OAc.⁶⁹ As this reaction only occurs on aryl iodides, a Boc protected 2-aryl-5-iodobenzimidazole needed to be produced. Direct iodination of **17** did not provide the desired aryl iodide. Aniline was iodinated with elemental iodine under basic conditions to selectively give 4-iodoaniline (**19**). Acetyl protection proceeded smoothly using the same conditions as above to produce 4-iodoacetanilide (**20**).



Scheme 3.14: Initial steps toward synthesis of 2-aryl-5-iodobenzimidazoles

Unfortunately, nitration produced less than 10% 4-iodo-2-nitroacetanilide (**21**), instead generating 4-nitroacetanilide as the major product (~90%). Nitration reactions run as cold as possible (fuming nitric acid began to freeze below $-45\text{ }^\circ\text{C}$) still produced primarily 4-nitroacetanilide. Rather than redesigning the synthesis at this point, we decided to continue forward and test fluorination of the diaryliodonium triflates (**16**) produced by the previous route using tin.

Although none of the set of compounds **16** could not be recrystallized after a variety of attempts, for some compounds repeated trituration or Soxhlet extraction was successful at removing the tin impurities below the level of detection by ^1H NMR. Tin impurities may still remain at levels that could be problematic for radiochemistry, but presumably should not cause issues with fluorination on a larger scale (NMR scale) with fluorine-19. Three diaryliodonium triflates (**16d**, **16e**, and **16f**) were produced and purified as a mixture of regioisomers for analysis (Figure 3.7).

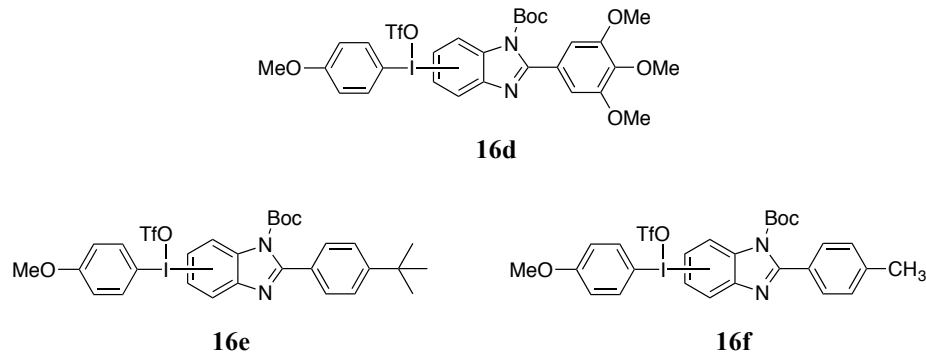


Figure 3.7: Diaryliodonium triflates (**16**) analyzed

Since tin impurities were not observed in the ^1H NMR spectrum, we theorized that issues with recrystallization may be due to the mixture of two regioisomers rather than the presence of a stannane. Compound **16d** was produced as a set of single regioisomers by isolating each regioisomer of **15d** by column chromatography and synthesizing each regioisomer of **16d** in a separate reaction. Unfortunately, neither regioisomer of **16d** could be crystallized, suggesting that residual tin may be preventing crystallization.

Fluorination proceeded smoothly, though regiochemical issues arose. To avoid aryl swapping,⁵⁵ a substoichiometric amount of fluoride, as tetra methylammonium fluoride (TMAF), was added. No aryl swapping was observed in acetonitrile- d_3 . Since thermolysis of diaryliodonium salts in more polar solvents tend to provide lower yield (presumably more polar solvents promote disproportionation), acetonitrile- d_3 was removed and benzene- d_6 was added. In benzene- d_6 , compounds **16** are sparingly soluble, so analysis by ^1H NMR proved difficult. However, after heating at $140\text{ }^\circ\text{C}$ thermolysis proceeded and the fluorinated products could be easily identified by ^{19}F NMR. Two regioisomers were expected as each arises from thermolysis of the respective regioisomer of **16**. The desired Boc protected 2-aryl-5-fluorobenzimidazole products (**22**) were

observed as multiplets around -116 and -117 ppm. For comparison, 2-aryl-5-fluorobenzimidazoles (7), lacking a Boc group, appear around -120 ppm. Unfortunately, in addition to the desired products, a significant portion of 4-fluoroanisole (-124 ppm) was also observed. This was confirmed by doping the NMR sample with commercially available 4-fluoroanisole.

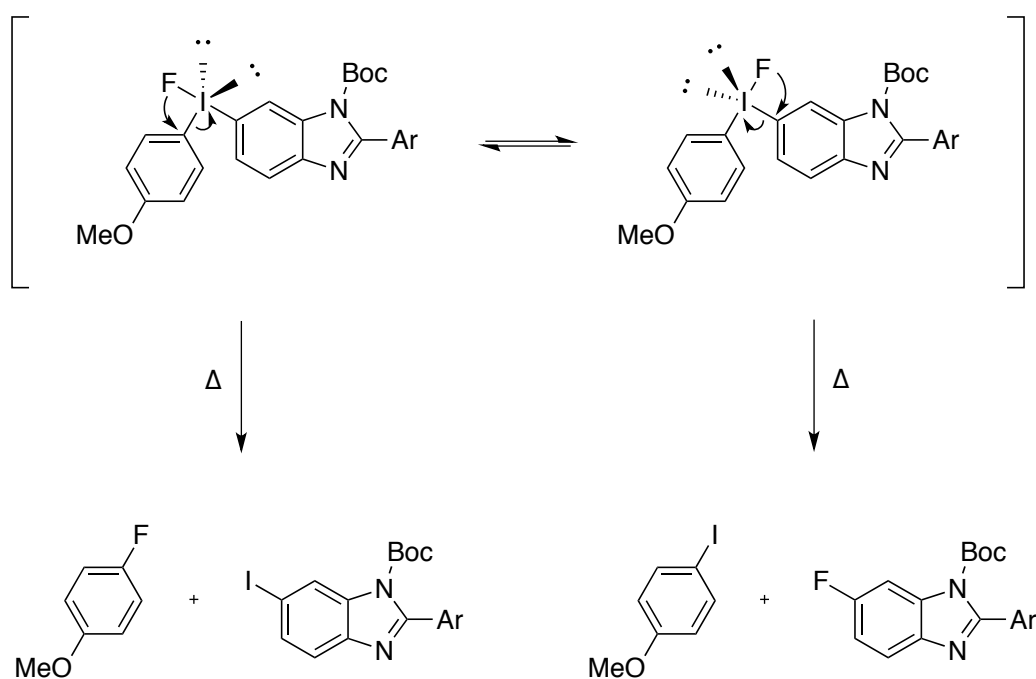


Figure 3.8: Two regiochemical pathways for thermolysis of diaryliodonium salts

This product forms due to a thermolysis pathway which eliminates Boc protected 2-aryl-5-iodobenzimidazoles. The intermediate diaryliodonium fluorides undergo rapid equilibrium between several T-shaped conformations (AX_3E_2 in AXE notation; two shown in Figure 3.8). The anion (fluoride in this case) and arene can only combine when one is axial (A) and one is equatorial (E). Elimination of the most electron-rich arene is typically preferred. Presumably this is due to a build-up of negative charge on the

electron-poor arene in a Meisenheimer-like transition state (Figure 3.9); the more electron-poor arene is better able to stabilize the negative charge.

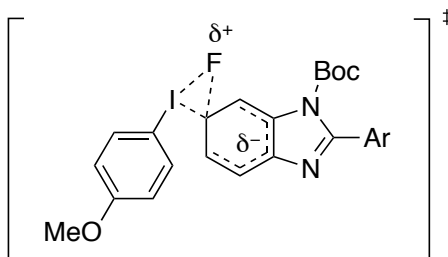


Figure 3.9: Meisenheimer-like transition state

When both arenes (**A** and **B**) are similar in electron density, a mixture of products occurs: **A–F** + **B–I** and **A–I** + **B–F**. In the ^{19}F NMR, both Boc protected 2-aryl-5-fluorobenzimidazole regioisomers (**A–F**) and 4-fluoroanisole (**B–F**) were observed. At 140 °C, thermolysis of compound **16e** provided only 37.3% **A–F** and 62.7% **B–F**. At 80 °C, thermolysis of compound **16f** provided a more favorable 67.7% **A–F** and 32.3% **B–F**. Below 80 °C thermolysis was not observed. For compound **16f**, the products were isolated by Preparative Thin Layer Chromatography (Prep TLC). Both Boc protected 2-(4-methylphenyl)-5-fluorobenzimidazole regioisomers (**22f**) and both Boc protected 2-(4-methylphenyl)-5-iodobenzimidazole regioisomers (**23f**) were isolated in 52% yield. For compound **16e**, the four 2-(4-*tert*-butylphenyl)-5-halobenzimidazole products (**22e** and **23e**) could not be fully separated by Prep TLC. From these results it is likely that both anisole and the corresponding 2-arylbenzimidazole are similar in electron density. Thermolysis at lower temperature utilizes the minor difference in electron density to provide better regioselectivity.

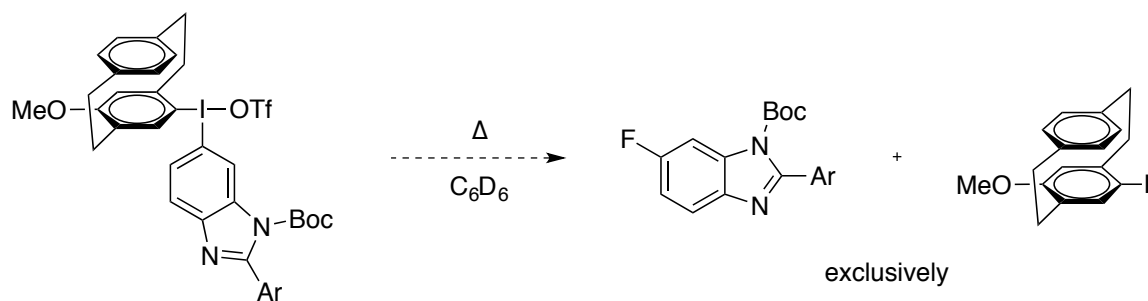
The isolated fluorinated products (**22f**) were deprotected under acidic conditions with trifluoroacetic acid.⁷⁰ The Boc protecting group was removed and the product was characterized. Without the Boc protecting group the two regioisomers were now free to equilibrate by tautomerization. By ¹H NMR, ¹⁹F NMR, and HR-MS, the compound was confirmed to be 2-(4-methylphenyl)-5-fluorobenzimidazole (**7f**), as synthesized previously.

3.2.3 Future Directions

There are other methods that could potentially be used to purify compounds **16**. Though costly, reverse phase chromatography could be used. We have used ion-exchange resins, specifically Amberlite quaternary ammonium resin (previously equilibrated with sodium triflate), to ensure full ion-exchange of diaryliodonium hexafluorophosphates to diaryliodonium triflates (since fluoride-19 atoms in hexafluorophosphate can exchange with fluoride-18). It may be possible to treat compounds **16** with sodium hexafluorophosphate or pass compounds **16** down a dedicated ion-exchange column in an effort to exchange the anion on residual tin salts (such as Bu₃SnOAc) in the hopes that the exchanged salt will bind less tightly and allow crystallization of **16**. Because of the difficulty in removing all traces of residual tin, it may be ideal to redesign the synthesis using an alternate synthetic route. Borylation was not successful, solely removing the Boc protecting group, but it could be worthwhile to attempt a Miyaura borylation on a 2-aryl-5-bromobenzimidazole before Boc protection. As we later discovered with synthesis of cyclophanyl-containing iodonium salts,⁷¹⁻⁷³ an

aryl zinc halide may be coupled with a bis(acetoxy)iodoarene to produce a diaryliodonium salt. Although these compounds are synthesized by lithiation of an aryl halide, which would likely be incompatible with the Boc protecting group, a Negishi coupling could be attempted. More recently we have developed methodology using magnesium-halogen exchange on aryl iodides (see Chapter 1) and in some cases aryl bromides. Designing a synthesis to produce 2-aryl-5-iodobenzimidazoles may be worthwhile. There are many different routes to making benzimidazoles, and since the beginning of this project a number of additional methods have been published.³⁷⁻⁴⁸ Nitration under milder conditions, using a combination of nitric and sulfuric acids (Scheme 3.3), may provide the desired 5-iodo-2-nitroacetanilide. Oxidation of the 2-aryl-5-iodobenzimidazole to iodonium diacetates using SelectfluorTM may be possible.

Poor regioselectivity is an issue we have faced before.^{54,74} For example, due to poor regioselectivity, 2-fluoro-17 β -estradioldimethylether was only able to be produced in 42% yield. This issue could be overcome by using a directing group that employs not only electronic effects, but also steric effects.



Scheme 3.15: Potential route to regioselectively generate compounds **22**

By replacing the 4-iodoanisole synthon with a methoxy-substituted cyclophane (*e.g.* 7-iodo-4-methoxy-[2.2]paracyclophane or 5-iodo-4-methoxy-[2.2]paracyclophane), stereoelectronic control generally affords full regioselectivity, elimination of the corresponding iodocyclophane and fluorination of the desired arene (Scheme 3.15).⁷¹⁻⁷³

3.3 Conclusion

Eleven 2-aryl-5-fluorobenzimidazoles (**7**) were successfully produced. Using these compounds as NMR standards, and using this synthesis as a model synthesis, ten 2-aryl-5-bromobenzimidazoles (**13**) were successfully produced. Although some compounds could only be partially carried forward toward synthesis of **16**, three diaryliodonium triflates (**16**) were generated from these compounds. Poor regioselectivity hindered yields, but fluorination by thermolysis was successful in providing **22**. Deprotection of one compound using trifluoroacetic acid showed this compound was identical to the 2-aryl-5-bromobenzimidazole (**13**) produced without using iodonium salt thermolysis. Given the poor regioselectivity, and potential issues with even trace amounts of residual tin, the methodology outlined in this chapter may not be ideal for testing fluorine-18 analogs of these compounds *in vivo*; however, this methodology would be suitable for initial testing. As 2-aryl-5-[¹⁸F]fluorobenzimidazoles are not reported in the literature, this would be the first example. Given the interest in these compounds in literature,²⁻³⁰ access to radio-fluorinated radiotracers may be useful in cancer diagnosis, monitoring, and treatment, as well as studying inflammatory

pathways, Alzheimer's disease, anti-microbial properties, etc. The work outlined in this chapter provides a methodology for accessing these compounds.

3.4 References

1. Panda, S. S.; Malik, R.; Jain, S. C., "Synthetic Approaches to 2-Arylbenzimidazoles: A Review", *Curr. Org. Chem.* **2012**, *16*, 1905–1919.
2. Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C., "Combinatorial Synthesis of Small Organic Molecules", *Angew. Chem., Int. Ed.* **1996**, *35*, 2288–2337.
3. Nefzi, A.; Ostresh, J. M.; Houghten, R. A., "The Current Status of Heterocyclic Combinatorial Libraries", *Chem. Rev.* **1997**, *97*, 449–472.
4. Loughlin, W. A., "Combinatorial Synthesis: A Heterocyclic Chemist's Perspective", *Aust. J. Chem.* **1998**, *51*, 875–893.
5. Denny, W. A.; Rewcastle, G. W.; Bagley, B. C., "Potential Antitumor Agents, 59: Structure–Activity Relationships for 2-Phenylbenzimidazole-4-Carboxamides, a New Class of 'Minimal' DNA-Intercalating Agents Which May Not Act via Topoisomerase II", *J. Med. Chem.* **1990**, *33*, 814–819.
6. Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P., "Synthesis and SAR of 2-Arylbenzoxazoles, Benzothiazoles and Benzimidazoles as Inhibitors of Lysophosphatidic Acid Acyltransferase- β ", *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455–1459.
7. Suh, J. H.; Yi, K. Y.; Kim, N. J.; Yoo, S. E.; Oh, K.-S.; Cheon, H. G.; Ahn, M.; Lee, B. H.; Jung, W. H.; Rhee, S. D., "Imidazole Derivatives Having Aryl Piperidine Substituent, Method for Preparation Thereof and Pharmaceutical Compositions Containing Same", *PCT Int. Appl.* **2008**, WO2008140239 A1.

8. Chu, B.; Liu, F.; Li, L.; Ding, C.; Chen, K.; Sun, Q.; Shen, Z.; Tan, Y.; Tan, C.; Jiang, Y., "A Benzimidazole Derivative Exhibiting Antitumor Activity Blocks EGFR and HER2 Activity and Upregulates DR5 in Breast Cancer Cells", *Cell Death Dis.* **2015**, *6*, e1686.
9. Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; McKinney, E.; Tang, C. J., "Antirhino/Enteroviral Vinylacetylene Benzimidazoles: A Study of Their Activity and Oral Plasma Levels in Mice", *J. Med. Chem.*, **1997**, *40*, 3937–3946.
10. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B., "Design, Synthesis, and Antiviral Evaluations of 1-(Substituted Benzyl)-2-Substituted-5,6-Dichlorobenzimidazoles as Nonnucleoside Analogues of 2,5,6-Trichloro-1-(α -D-Ribofuranosyl) Benzimidazole", *J. Med. Chem.*, **1998**, *41*, 1252–1262.
11. Roth, M.; Morningstar, M. L.; Boyer, P. L.; Hughes, S. H.; Bukheit, R. W.; Michejda, C. J. "Synthesis and Biological Activity of Novel Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase: 2-Aryl-Substituted Benzimidazoles", *J. Med. Chem.*, **1997**, *40*, 4199–4207.
12. Migawa, M. T.; Giradet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. "Design, Synthesis, and Antiviral Activity of R-Nucleosides: D-And L-Isomers of Lyxofuranosyl- and (5-Deoxylyxofuranosyl) Benzimidazoles", *J. Med. Chem.*, **1998**, *41*, 1242–1251.

13. Tamm, I. "Inhibition of Influenza and Mumps Virus Multiplication by 4,5,6- (or 5,6,7-) Trichloro-1- β -D- Ribofuranosylbenzimidazole", *Science*, **1954**, *126*, 1235–1236.
14. Forseca, T.; Gigante, B.; Gilchrist, T. L., "A Short Synthesis of Phenanthro[2,3-*d*]Imidazoles from Dehydroabiatic Acid: Application of the Methodology as a Convenient Route to Benzimidazoles", *Tetrahedron* **2001**, *57*, 1793–1799.
15. Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach, O.; Meijer, L., "Synthesis, Anti-Inflammatory, Analgesic and Kinase (CDK-1, CDK-5 and GSK-3) Inhibition Activity Evaluation of Benzimidazole/Benzoxazole Derivatives and Some Schiff's Bases", *Bioorg. Med. Chem.* **2006**, *14*, 3758–3765.
16. Keurulainen, L.; Salin, O.; Siiskonen, A.; Kern, J. M.; Alvesalo, J.; Kiuru, P.; Maass, M.; Yli-Kauhaluoma, J.; Vuorela, P., "Design and Synthesis of 2-Arylbenzimidazoles and Evaluation of Their Inhibitory Effect against *Chlamydia Pneumoniae*", *J. Med. Chem.* **2010**, *11*, 7664–7674.
17. Keurulainen, L.; Siiskonen, A.; Nasereddin, A.; Kopelyanskiy, D.; Sacerdoti-Sierra, N.; Leino, T. O.; Tammela, P.; Yli-Kauhaluoma, J.; Jaffe, C. L.; Kiuru, P., "Synthesis and Biological Evaluation of 2-Arylbenzimidazoles Targeting *Leishmania Donovanii*", *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1933–1937.
18. Vinsova, J.; Cermakova, K.; Tomeckova, A.; Ceckova, M.; Jampilek, J.; Cermak, P.; Kunes, J.; Dolezal, M.; Staud, F., "Synthesis and Antimicrobial Evaluation of New 2-

- Substituted 5,7-Di-*tert*-butylbenzoxazoles”, *Bioorg. Med. Chem.* **2006**, *14*, 5850–5865.
19. Gabaa, M.; Gaba, P.; Uppal, D.; Dhingra, N.; Bahia, M. S.; Silakari, O.; Mohan, C., “Benzimidazole Derivatives: Search for GI-friendly Anti-inflammatory Analgesic Agents”, *Acta Pharm Sin B* **2015**, *5*, 337–342.
20. Wright, J. B., “The Chemistry of the Benzimidazoles”, *Chem. Rev.* **1951**, *48*, 397–541.
21. Vijayana, N.; Babua, R. R.; Gopalakrishnana, R.; Ramasamyb, P.; Harrison, W. T. A., “Growth and Characterization of Benzimidazole Single Crystals: A Nonlinear Optical Material”, *J. Cryst. Growth* **2004**, *262*, 490–498.
22. Carella, A.; Centore, R.; Sirigu, A.; Tuzi, A.; Quatela, A.; Schutzmann, S.; Casalboni, M., “Second Order Nonlinear Optical Performances of Polymers Containing Imidazole and Benzimidazole Chromophores”, *Macromol. Chem. Phys.* **2004**, *205*, 1948–1954.
23. Batistaa, R. M. F.; Costaa, S. P. G.; Belsleyb, M.; Raposo, M. M. M., “Synthesis and Second-Order Nonlinear Optical Properties of New Chromophores Containing Benzimidazole, Thiophene, and Pyrrole Heterocycles”, *Tetrahedron* **2007**, *63*, 9842–9849.
24. Kulhánek, J.; Bureš, F., “Imidazole as a Parent π -Conjugated Backbone in Charge-Transfer Chromophores”, *Beilstein J. Org. Chem.* **2012**, *8*, 25–49.

25. Chen, C.; Huang, W.; Lai, M.; Tsao, W.; Lin, J. T.; Wu, Y.; Ke, T.; Chen, L.; Wu, C., “Versatile, Benzimidazole/Amine-Based Ambipolar Compounds for Electroluminescent Applications: Single-Layer, Blue, Fluorescent OLEDs, Hosts for Single-Layer, Phosphorescent OLEDs”, *Adv. Funct. Mater.* **2009**, *19*, 2661–2670.
26. Hung, W.; Chi, L.; Chen, W.; Chen, Y.; Choub, S.; Wong, K., “A New Benzimidazole/Carbazole Hybrid Bipolar Material for Highly Efficient Deep-Blue Electrofluorescence, Yellow–Green Electrophosphorescence, and Two-Color-Based White OLEDs”, *J. Mater. Chem.* **2010**, *20*, 10113–10119.
27. Park, J. H.; Kim, E. K.; El-Deeb, I. M.; Jung, S. J.; Choi, D. H.; Kim, D.; Yoo, K. H.; Kwon, J. H.; Lee, S. H., “New Bipolar Green Host Materials Containing Benzimidazole-Carbazole Moiety in Phosphorescent OLEDs”, *Bull. Korean Chem. Soc.* **2011**, *32*, 841–846.
28. Yang, W.; Ban, X.; Chen, Y.; Xu, H.; Huang, B.; Jiang, W.; Dai, Y.; Sun, Y., “New Host Materials Based on Fluorene and Benzimidazole Units for Efficient Solution-Processed Green Phosphorescent OLEDs”, *Opt. Mater.* **2013**, *35*, 2201–2207.
29. Huang, J.; Leung, M.; Chiu, T.; Chuang, Y.; Chou, P.; Hung, Y., “Novel Benzimidazole Derivatives as Electron-Transporting Type Host to Achieve Highly Efficient Sky-Blue Phosphorescent Organic Light-Emitting Diode (PHOLED) Device”, *Org. Lett.* **2014**, *16*, 5398–5401.
30. Zhao, Y.; Wu, C.; Qiu, P.; Li, X.; Wang, Q.; Chen, J.; Ma, D., “New Benzimidazole-Based Bipolar Hosts: Highly Efficient Phosphorescent and Thermally Activated

- Delayed Fluorescent Organic Light-Emitting Diodes Employing the Same Device Structure”, *ACS Appl. Mater. Interfaces* **2016**, *8*, 2635–2643.
31. Imbimbo, B. P.; Solfrizzi, V.; Panza, F., “Are NSAIDs Useful to Treat Alzheimer's Disease or Mild Cognitive Impairment?”, *Front. Aging Neurosci.* **2010**, *2*, 19.
32. Rogers, J., “The Inflammatory Response in Alzheimer's Disease”, *J. Periodontol.* **2008**, *79*, 1535–1543.
33. Biffinger, J. C.; Kim, H. W.; DiMagno, S. G., “The Polar Hydrophobicity of Fluorinated Compounds”, *ChemBioChem* **2004**, *5*, 622–627.
34. DiMagno, S. G.; Sun, H., “The Strength of Weak Interactions: Aromatic Fluorine in Drug Design”, *Curr. Top. Med. Chem.* **2006**, *6*, 1473–1482.
35. Schlosser, M., “Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedical Targets”, Ed. Soloshonok, V. A., Wiley, Chichester, **1999**, 613–659.
36. Smart, B. E., “Fluorine Substituent Effects (on Bioactivity)”, *J. Fluor. Chem.* **2001**, *109*, 3–11.
37. Grimmett, M. R. “Imidazole and Benzimidazole Synthesis”; Academic Press: San Diego, CA, **1997**.
38. Rosenberg, A. J.; Zhao, J.; Clark, D. A., “Synthesis of Imidazo[4,5-*b*]Pyridines and Imidazo[4,5-*b*]Pyrazines by Palladium Catalyzed Amidation of 2-Chloro-3-Amino-Heterocycles”, *Org. Lett.*, **2012**, *14*, 1764–1767.

39. Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A., "Benzazoles from Aliphatic Amines and *o*-Amino/Mercaptan/Hydroxyanilines: Elemental Sulfur as a Highly Efficient and Traceless Oxidizing Agent", *Org. Lett.*, **2012**, *14*, 5948–5951.
40. Cui, W.; Kargbo, R. B.; Sajjadi-Hashemi, Z.; Ahmed, F.; Gauuan, J. F., "Efficient One-Pot Synthesis of 2-Substituted Benzimidazoles from Triacyloxyborane Intermediates" *Synlett*, **2012**, *23*, 247–250.
41. Siva S. Panda; Ritu Malik; and Subhash C. Jain "Synthetic Approaches to 2-Arylbenzimidazoles: A Review" *Curr. Org. Chem.*, **2012**, *16*, 1905–1919.
42. Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T., "Iodobenzene Catalyzed C–H Amination of N-Substituted Amidines Using *m*-Chloroperbenzoic Acid", *Org. Lett.*, **2013**, *15*, 1334–1337.
43. Nguyen, T. B.; Bescont, J. L.; Ermolenko, L.; Al-Mourabit, A., "Cobalt- and Iron-Catalyzed Redox Condensation of *o*-Substituted Nitrobenzenes with Alkylamines: A Step- and Redox-Economical Synthesis of Diazaheterocycles", *Org. Lett.*, **2013**, *15*, 6218–6221.
44. Baars, H.; Beyer, A.; Kohlhepp, S. V.; Bolm, C., "Transition-Metal-Free Synthesis of Benzimidazoles Mediated by KOH/DMSO", *Org. Lett.*, **2014**, *16*, 536–539.
45. Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M., "Convenient Synthesis of Benzothiazoles and Benzimidazoles through Brønsted Acid Catalyzed Cyclization of 2-Amino Thiophenols/Anilines with β -Diketones", *Org. Lett.*, **2014**, *16*, 764–767.

46. Xue, D.; Long, Y.-Q., “Metal-Free TEMPO-Promoted C(sp³)-H Amination to Afford Multisubstituted Benzimidazoles”, *J. Org. Chem.*, **2014**, *79*, 4727–4734.
47. Gu, Z.-S.; Chen, W.-X.; Shao, L.-X., “*N*-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex-Catalyzed Direct C–H Bond Arylation of (Benz)imidazoles with Aryl Chlorides”, *J. Org. Chem.*, **2014**, *79*, 5806–5811.
48. Mahesh, D.; Sadhu, P.; Punniyamurthy, T., “Copper(I)-Catalyzed Regioselective Amination of *N*-Aryl Imines Using TMSN₃ and TBHP: A Route to Substituted Benzimidazoles”, *J. Org. Chem.*, **2015**, *80*, 1644–1650.
49. Manicke, I. P.; Grigel, P., “Preparation of Acetylsalicylic Acid, Acetanilide and *p*-Acetophenetidide”, *Arch Pharm Ber Dtsch Pharm Ges* **1926**, *264*, 322–324.
50. Mohan, J. “Confirmatory Tests and Derivatization of Common Organic Compounds, Their Derivatization and Classified Tables including Melting and Boiling Points” in “Organic Analytical Chemistry: Theory and Practice”; Alpha Science Int’l Ltd.: Oxford, United Kingdom, **2003**.
51. House, H. O. “Modern Synthetic Reactions”, 3rd ed.; Benjamin/Cummings: Menlo Park, CA, **1972**.
52. Fonseca, T.; Gigante, B.; Gilchrist, T., “A Short Synthesis of Phenanthro[2,3-*d*]imidazoles from Dehydroabiatic Acid. Application of the Methodology as a Convenient Route to Benzimidazoles”, *Tetrahedron* **2001**, *57*, 1793–1799.
53. Patel, P.; Ramalingan, C.; Park, Y., “Synthesis and Antimicrobial Evaluation of Guanylsulfonamides”, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6610–6614.

54. Wang, B.; Qin, L.; Neumann, K.; Uppaluri, S. H.; Cerny, R.; DiMagno, S. G., "Improved Arene Fluorination Methodology for I(III) Salts", *Org. Lett.* **2010**, *12*, 3352–3355.
55. Wang, B.; Cerny, R.; Uppaluri, S. H.; Kempinger, J. J.; DiMagno, S. G., "Fluoride-Promoted Ligand Exchange in Diaryliodonium Salts", *J. Fluor. Chem.* **2010**, *131*, 1113–1121.
56. Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G., "A Mild and General One-Pot Synthesis of Densely Functionalized Diaryliodonium Salts", *Eur. J. Org. Chem.* **2015**, *2015*, 5919–5924.
57. Koser, G. F.; Wettach, R. H.; Smith, C. S., "New Methodology in Iodonium Salt Synthesis. Reactions of [Hydroxy(tosyloxy)iodo]Arenes with Aryltrimethylsilanes", *J. Org. Chem.* **1980**, *45*, 1543–1544.
58. Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H., "One-step α -Tosyloxylation of Ketones with [Hydroxy(tosyloxy)iodo]Benzene", *J. Org. Chem.* **1982**, *47*, 2487–2489.
59. Pike, V. W.; Butt, F.; Shah, A.; Widdowson, D. A., "Facile Synthesis of Substituted Diaryliodonium Tosylates by Treatment of Aryltributylstannanes with Koser's Reagent", *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 245–248.
60. McDaniel, D. H.; Brown, H. C., "An Extended Table of Hammett Substituent Constants Based on the Ionization of Substituted Benzoic Acids", *J. Org. Chem.*, **1958**, *23*, 420–427.

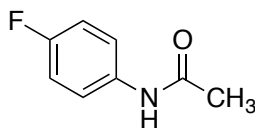
61. Neuman, R. C. Jr. "Substituent Effects" in "Organic Chemistry"; Robert C. Neuman, Jr.: Santa Barbara, CA, **2013**.
62. Booth, G. "Nitro Compounds, Aromatic" in "Ullmann's Encyclopedia of Industrial Chemistry"; John Wiley & Sons: New York, NY, **2007**.
63. Béchamp, A., "De l'action des Protosels de fer sur la Nitronaphtaline et la Nitrobenzine. Nouvelle Méthode de Formation des Bases Organiques Artificielles de Zinin", *Ann. Chim. Phys.* **1854**, *42*, 186–196.
64. Morningstar, M. L.; Roth, T.; Farnsworth, D. W.; Smith, M. K.; Watson, K.; Buckheit, R. W.; Jr., ; Das, K.; Zhang, W.; Arnold, E.; Julias, J. G.; Hughes, S. H.; Michejda, C. J., "Synthesis, Biological Activity, and Crystal Structure of Potent Nonnucleoside Inhibitors of HIV-1 Reverse Transcriptase That Retain Activity against Mutant Forms of the Enzyme", *J. Med. Chem.* **2007**, *50*, 4003–4015.
65. Leonard, M. J.; Lingham, A. R.; Niere, J. O.; Jackson, N. R. C.; McKay, P. G.; Hügel, H. M., "Alternative Synthesis of the Anti-Baldness Compound RU58841", *RSC Adv.* **2014**, *4*, 14143–14148.
66. Bordwell, F. G., "Equilibrium Acidities in Dimethyl Sulfoxide Solution", *Acc. Chem. Res.* **1988**, *21*, 456–463.
67. Farina, V.; Hauck, S. I., "Palladium-Catalyzed Synthesis of Some New Olefinic Stannanes", *J. Org. Chem.*, **1991**, *56*, 4317–4319.

68. Ishiyama, T.; Murata, M.; Miyaura, N., “Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters”, *J. Org. Chem.* **1995**, *60*, 7508–7510.
69. Qin, L.; Hu, B.; Neumann, K.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMugno, S. G., “A Mild and General One-Pot Synthesis of Densely Functionalized Diaryliodonium Salts”, *Eur. J. Org. Chem.* **2015**, *2015*, 5919–5924.
70. Sparks, R.B.; Polam, P.; Zhu, W., Crawleya, M.L.; Takvoriana, A.; McLaughlina, E.; Weib, M.; Alab, P.J.; Gonnevillieb, L.; Taylorc, N.; Lib, Y.L., Wynn, R.; Burnb, T.C.; Liub, P.C.C., Combsa, A.P., “Benzothiazole Benzimidazole (S)-Isothiazolidinone Derivatives as Protein Tyrosine Phosphatase-1B Inhibitors”, *Bioorgan. Med. Chem. Lett.* **2007**, *17*, 736–740.
71. Wang, B.; Graskemper, J.; Qin, L.; DiMugno, S. G., “Regiospecific Reductive Elimination from Diaryliodonium Salts”, *Angew. Chemie Int. Ed.* **2010**, *49*, 4079–4083.
72. Graskemper, J. “Controlling Reductive Elimination from Novel I(III) Salts Using a SECURE Method”, Master’s Thesis, University of Nebraska, Lincoln, NE, **2010**.
73. Graskemper, J.; Wang, B.; Qin, L.; Neumann, K.; DiMugno, S. G., “Unprecedented Directing Group Ability of Cyclophanes in Arene Fluorinations with Diaryliodonium Salts”, *Org. Lett.* **2011**, *13*, 3158–3161.

74. Uppaluri, S. H. “Studies toward Fluorination of Electron Rich Aromatics by Nucleophilic Fluoride”, Ph.D. Dissertation, University of Nebraska, Lincoln, NE, **2013**.

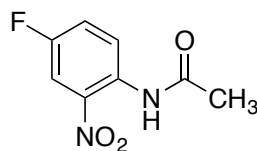
3.5 Experimental

4-Fluoroacetanilide (1):



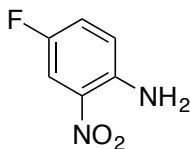
In an oven-dried 100 mL round bottom flask equipped with a stirbar, acetic anhydride (25 mL) was added and cooled to 0 °C. 4-fluoroaniline (5 mL) was added dropwise with stirring. Several drops of concentrated sulfuric acid were added until precipitation began. The mixture was allowed to warm to room temperature over the course of an hour. The mixture was cooled to 0 °C and cautiously neutralized with aqueous sodium bicarbonate. The solid was filtered, washed with cold water, and dried in vacuo. The crude solid was recrystallized from hot 85% aqueous ethanol to yield 4-fluoroacetanilide as a dull colorless solid (7.8 g, 96.8%): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 7.45 (s, NH), 7.34 (dd, 2H, $J = 6.8$ Hz, $J = 2.0$ Hz), 6.89 (t, 2H, $J = 8.8$ Hz), 2.05 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -117.96 (ddd, $J = 13.1$ Hz, $J = 8.3$ Hz, $J = 4.7$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 168.52 (s), 160.60 (s), 158.18 (s), 133.89 (d, $J = 3.0$ Hz), 121.87 (d, $J = 8.0$ Hz), 115.59 (d, $J = 22.1$ Hz), 24.34 (s).

Mohan, J. "Confirmatory Tests and Derivatization of Common Organic Compounds, Their Derivatization and Classified Tables including Melting and Boiling Points" in "Organic Analytical Chemistry: Theory and Practice"; Alpha Science Int'l Ltd.: Oxford, United Kingdom, **2003**.

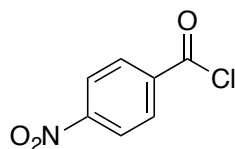
4-Fluoro-2-nitroacetanilide (2):

Fuming nitric acid (25 mL) was dispensed into a 50 mL Erlenmyer flask and cooled to $-40\text{ }^{\circ}\text{C}$ by means of a saturated CaCl_2 /water slurry (cooled by dry ice). 4-Fluoroacetanilide (2.00 g) was added directly (in portions) to the cold acid and the flask was swirled to help dissolve the organic material. After the addition was complete the flask was allowed to stand in the bath (with occasional manual swirling) for 15 min. The mixture was poured onto 100 g of ice and neutralized with saturated aqueous sodium bicarbonate solution. The precipitated solid was filtered, washed with cold water, and dried in vacuo to yield 4-fluoro-2-nitroacetanilide as an essentially pure pale yellow solid (2.34 g, 90.2%): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 10.19 (s, NH), 8.80 (dd, 1H, $J = 4.2\text{ Hz}$, $J = 9.5\text{ Hz}$), 7.93 (dd, 1H, $J = 3.0\text{ Hz}$, $J = 8.5\text{ Hz}$), 7.42 (ddd, 1H, $J = 9.2\text{ Hz}$, $J = 7.0\text{ Hz}$, $J = 4.0\text{ Hz}$), 2.30 (s, 3H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -115.97 (ddd, $J = 8.4\text{ Hz}$, $J = 7.0\text{ Hz}$, $J = 5.2\text{ Hz}$); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 169.17 (s), 158.41 (s), 155.95 (s), 131.59 (s), 124.34 (d, $J = 7.0$), 123.68 (d, $J = 22.1\text{ Hz}$), 112.47 (d, $J = 27.2$), 25.69 (s).

Hay, M. P.; Hicks, K. O.; Pchalek, K.; Lee, H. H.; Blaser, A.; Pruijn, F. B.; Anderson, R. F.; Shinde, S. S.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.*, **2008**, *51*, 6853–6865.

4-Fluoro-2-nitroaniline (3):

In a 250 mL round bottom flask 4-fluoro-2-nitroacetanilide (4.68 g) dissolved in 10 mL THF was treated with 50 mL of aqueous HCl (2 M) and heated at reflux overnight. The solution was neutralized with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and evaporated to yield 4-fluoro-2-nitroaniline compound as an orange solid (3.66 g, 99.7%): ^1H NMR (CDCl_3 , 500 MHz, 298 K) δ 7.81 (dd, 1H, $J = 3.0$ Hz, $J = 9.1$ Hz), 7.18 (ddd, 1H, $J = 3.0$ Hz, $J = 7.1$ Hz, $J = 9.3$ Hz), 6.82 (dd, 1H, $J = 9.2$ Hz, $J = 4.5$ Hz), 6.02 (s, NH₂); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -125.93 (ddd, $J = 4.7$ Hz, $J = 7.2$ Hz, $J = 9.1$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 154.46 (s), 152.56 (s), 141.75 (s), 124.81 (d, $J = 24.0$ Hz), 120.22 (d, $J = 7.3$ Hz), 111.42 (d, $J = 26.1$ Hz).

4-Nitrobenzoyl chloride (4j):

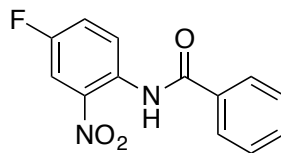
In an oven-baked 250 mL Schlenk flask, dry 4-nitrobenzoic acid (20.0 g, 0.120 mmol) was suspended in thionyl chloride (50 mL), under N₂, at 0 °C. The mixture was brought to reflux until the mixture became homogeneous (6 hours). Unreacted thionyl chloride was removed by distillation under vacuum, with gentle heating as needed. The solid was dried overnight under high dynamic vacuum to yield the product as pale yellow crystals (21.34 g, 96.1%): ¹H NMR (CDCl₃, 500 MHz, 298 K): δ 8.38 (d, *J* = 8.8 Hz, 2H), 8.32 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (CDCl₃, 126 MHz, 298 K): δ 167.26, 138.25, 132.45, 131.57, 124.27.

Mohsin, M. A.; Akhter, Z.; Bolte, M.; Butt, M. S.; Khan, M. S. U.; Siddiqi, H. M. *J Mater Sci*, **2009**, *44*, 4796–4805.

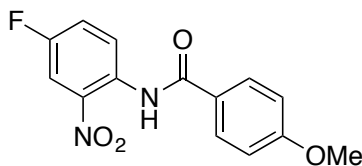
General procedure for the preparation of *N*-arylcarbonyl-5-fluoro-2-nitroanilines (5a–l) with solid acid chlorides: 4-Fluoro-2-nitroaniline (468 mg, 3.00 mmol), the appropriate acid chloride (3.30 mmol), and triethylamine (1 mL) were dissolved in 10 mL of dry acetonitrile. The reaction was heated at 80 °C for 12 hours. The reaction mixture was diluted with 50 mL dichloromethane and washed with 30 mL aqueous sodium bicarbonate diluted in deionized water (1:1 v/v). The aqueous layer was extracted with

15 mL dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the solvent(s) indicated.

General procedure for the preparation of *N*-arylcarbonyl-5-fluoro-2-nitroanilines (5a–l) with liquid acid chlorides: 4-Fluoro-2-nitroaniline (468 mg, 3.00 mmol), and triethylamine (1 mL) were dissolved in 10 mL of dry acetonitrile. The appropriate acid chloride (3.30 mmol) was added dropwise by syringe and the reaction was heated at 80 °C for 12 hours. The reaction mixture was diluted with 50 mL dichloromethane and washed with 30 mL aqueous sodium bicarbonate diluted in deionized water (1:1 v/v). The aqueous layer was extracted with 15 mL dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the solvent(s) indicated.

***N*-Benzoyl-4-fluoro-2-nitroaniline (5a):**

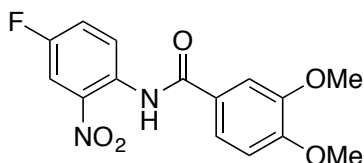
This compound (640 mg, 82%) was obtained as a brilliant yellow solid after recrystallization from hot 95% aqueous ethanol: ^1H NMR (CD_2Cl_2 , 400 MHz, 298 K) δ 11.21 (s, NH), 9.04 (dd, 1H, $J = 5.2$ Hz, $J = 9.3$ Hz), 8.00 (dd, 1H, $J = 2.9$ Hz, $J = 8.1$ Hz), 7.99 (d, 2H, 7.0 Hz), 7.62 (t, 1H, $J = 7.0$ Hz), 7.55 (t, 2H, $J = 8.3$ Hz), 7.47 (ddd, 1H, $J = 3.2$ Hz, $J = 7.0$ Hz, $J = 9.8$ Hz); ^{19}F NMR (CD_2Cl_2 , 376 MHz, 298 K) δ -117.66 (ddd, $J = 5.2$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.68 (s), 158.02 (s), 156.05 (s), 133.78 (s), 132.79 (s), 131.96 (d, $J = 2.6$ Hz), 129.11 (s), 127.35 (s), 124.03 (d, $J = 7.4$ Hz), 123.74 (d, $J = 22.4$ Hz), 112.45 (d, $J = 27.4$ Hz).

***N*-(4-Methoxybenzoyl)-4-fluoro-2-nitroaniline (5b):**

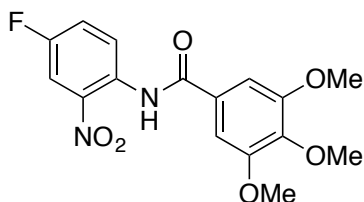
This compound (391 mg, 44.9%) was obtained as yellow needles after recrystallization from 60 mL of hot hexane/ethyl acetate (4:1). Additional crops of crystals could be obtained by concentrating the filtrate: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.13 (s, NH), 9.02 (dd, 1H, $J = 5.3$ Hz, $J = 9.6$ Hz), 7.97 (dd, 1H, $J = 3.1$ Hz, $J = 8.6$ Hz), 7.93 (d, 2H, $J = 8.9$ Hz), 7.44 (ddd, 1H, $J = 3.1$ Hz, $J = 7.1$ Hz, $J = 9.8$ Hz), 7.01 (d, 2H, $J = 8.9$

Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -116.33 (ddd, $J = 5.2$ Hz, $J = 6.9$ Hz, $J = 8.6$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.17 (s), 163.24 (s), 157.82 (s), 155.85 (s), 136.34 (d, $J = 7.8$ Hz), 132.31 (s), 129.31 (s), 123.94 (d, $J = 7.6$ Hz), 123.74 (d, $J = 21.9$ Hz), 114.30 (s), 112.34 (d, $J = 27.2$ Hz), 55.56 (s).

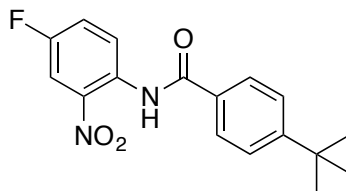
***N*-(3,4-Dimethoxybenzoyl)-4-fluoro-2-nitroaniline (5c):**



This compound (487 mg, 51%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was dichloromethane/hexane (1:1): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.22 (s, NH), 9.05 (dd, 1H, $J = 5.3$ Hz, $J = 9.4$ Hz), 8.00 (dd, 1H, $J = 3.1$ Hz, $J = 8.6$ Hz), 7.56 (br s, 1H), 7.52 (s, 1H), 7.47 (ddd, 1H, $J = 2.9$ Hz, $J = 6.9$ Hz, $J = 9.7$ Hz), 7.00 (s, 1H), 3.99 (s, OCH₃), 3.98 (s, OCH₃); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -116.18 (ddd, $J = 5.2$ Hz, $J = 7.4$ Hz, $J = 8.6$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.20 (s), 157.84 (s), 155.87 (s), 149.33 (s), 136.35 (d, $J = 8.4$ Hz), 132.31 (s), 126.25 (s), 123.89 (d, $J = 10.0$ Hz), 123.76 (d, $J = 4.5$ Hz), 120.30 (s), 112.39 (d, $J = 27.7$ Hz), 110.57 (d, $J = 15.7$ Hz), 56.15 (s), 56.06 (s).

***N*-(3,4,5-Trimethoxybenzoyl)-4-fluoro-2-nitroaniline (5d):**

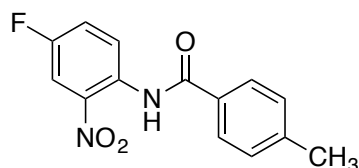
This compound (563 mg, 54%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was dichloromethane: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.23 (s, NH), 9.03 (dd, 1H, $J = 5.3$ Hz, $J = 9.5$ Hz), 8.00 (dd, 1H, $J = 3.1$ Hz, $J = 8.4$ Hz), 7.47 (ddd, 1H, $J = 3.2$ Hz, $J = 7.0$ Hz, $J = 9.8$ Hz), 7.2 (s, 2H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -115.77 (ddd, $J = 5.2$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.44 (s), 158.15 (s), 153.67 (s), 142.15 (s), 136.56 (d, $J = 8.7$ Hz), 132.30 (d, $J = 2.6$ Hz), 129.11 (s), 124.11 (d, $J = 22.0$ Hz), 123.90 (d, $J = 7.3$ Hz), 112.67 (d, $J = 27.0$ Hz), 104.75 (s), 61.20 (s), 56.50 (s).

***N*-(4-*tert*-Butylbenzoyl)-4-fluoro-2-nitroaniline (5e):**

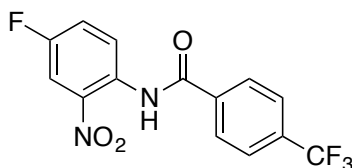
This compound (495 mg, 52%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was hexane/ethyl acetate (93:7): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.20 (s, NH), 9.15 (dd, 1H, $J = 5.2$ Hz, $J = 8.4$ Hz), 7.98 (dd, 1H, $J = 3.0$ Hz, $J = 8.5$ Hz), 7.91 (d, 2H, $J = 5.6$), 7.56 (d, 2H, $J = 5.6$), 7.44 (ddd, 1H, $J = 2.8$ Hz, $J =$

5.4 Hz, $J = 9.4$ Hz), 1.38 (s, 9H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -116.11 (ddd, $J = 4.8$ Hz, $J = 6.2$ Hz, $J = 10.5$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 165.67 (s), 157.92 (s), 156.58 (s), 136.49 (d, $J = 8.1$ Hz), 132.17 (s), 130.91 (s), 127.26 (s), 126.09 (s), 124.02 (d, $J = 7.3$ Hz), 123.74 (d, $J = 22.8$ Hz), 112.42 (d, $J = 29.2$ Hz), 35.14 (s), 31.13 (s).

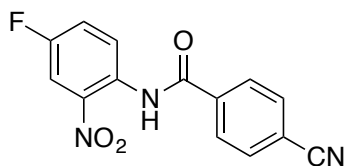
***N*-(4-Methylbenzoyl)-4-fluoro-2-nitroaniline (5f):**



This compound (435 mg, 52.9%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was hexane/ethyl acetate (93:7). Because of the insolubility of the compound it was loaded onto the column using boiling solvent: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.18 (s, NH), 9.05 (dd, 1H, $J = 5.2$ Hz, $J = 9.4$ Hz), 8.00 (dd, 1H, $J = 3.1$ Hz, $J = 8.5$ Hz), 7.88 (d, 2H, $J = 8.2$ Hz), 7.46 (ddd, 1H, $J = 3.1$ Hz, $J = 7.1$ Hz, $J = 9.8$ Hz), 7.34 (d, 2H, $J = 8.0$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -116.06 (ddd, $J = 5.1$ Hz, $J = 6.8$ Hz, $J = 8.2$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.61 (s), 157.90 (s), 155.93 (s), 143.56 (s), 132.15 (d, $J = 2.8$ Hz), 130.94 (s), 129.76 (s), 127.37 (s), 123.98 (d, $J = 7.5$ Hz), 123.71 (d, $J = 23.9$ Hz), 112.39 (d, $J = 26.4$ Hz), 21.59 (s).

***N*-(4-Trifluoromethylbenzoyl)-4-fluoro-2-nitroaniline (5g):**

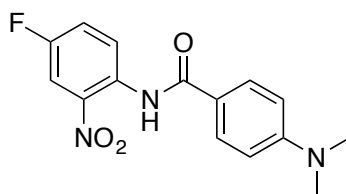
This compound (232 mg, 24%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was hexane/ethyl acetate (93:7): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.24 (s, NH), 9.01 (dd, 1H, $J = 5.1$ Hz, $J = 9.4$ Hz), 8.09 (d, 2H, $J = 8.2$ Hz), 7.99 (dd, 1H, $J = 3.0$ Hz, $J = 8.2$ Hz), 7.80 (d, 2H, $J = 8.3$ Hz), 7.47 (ddd, 1H, $J = 3.0$ Hz, $J = 7.0$ Hz, $J = 10.0$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -114.87 (ddd, $J = 5.2$ Hz, $J = 7.0$ Hz, $J = 10.0$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 164.32 (s), 158.32 (s), 156.34 (s), 137.03 (s), 134.34 (d, $J = 33.0$ Hz), 131.45 (s), 127.82 (s), 126.19 (s), 124.06 (s), 123.96 (d, $J = 11.3$ Hz), 123.74 (s), 112.64 (d, $J = 27.7$ Hz).

***N*-(4-Cyanobenzoyl)-4-fluoro-2-nitroaniline (5h):**

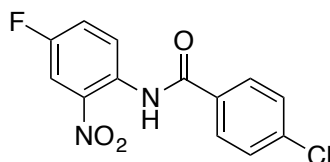
This compound (276 mg, 32.6%) was recrystallized from hot toluene to yield yellow plates: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.17 (s, NH), 8.91 (dd, 1H, $J = 5.2$ Hz, $J = 9.6$ Hz), 7.99 (d, 2H, $J = 8.6$ Hz), 7.92 (dd, 1H, $J = 3.0$ Hz, $J = 8.4$ Hz), 7.76 (d, 2H, $J = 8.7$ Hz), 7.41 (ddd, 1H, $J = 3.1$ Hz, $J = 7.0$ Hz, $J = 9.6$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -114.42 (ddd, $J = 5.2$ Hz, $J = 7.0$ Hz, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz,

298 K) δ 164.04 (s), 137.83 (s), 137.02 (s), 133.17 (s), 131.43 (d, $J = 2.9$ Hz), 128.22 (s), 124.27 (d, $J = 7.4$ Hz), 124.10 (d, $J = 22.1$ Hz), 117.88 (s), 116.57 (s) 113.04 (s), 112.80 (s).

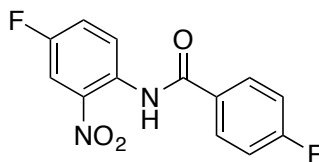
***N*-(4-Dimethylaminobenzoyl)-4-fluoro-2-nitroaniline (5i):**



This compound (378 mg, 41.5%) was obtained as brilliant reddish orange needles from hot ethyl acetate: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.14 (s, NH), 9.08 (dd, 1H, $J = 5.1$ Hz, $J = 9.4$ Hz), 7.98 (dd, 1H, $J = 3.1$ Hz, $J = 8.6$ Hz), 7.89 (d, 2H, $J = 9.0$ Hz), 7.44 (ddd, 1H, $J = 3.1$ Hz, $J = 7.2$ Hz, $J = 9.8$ Hz), 6.77 (d, 2H, $J = 8.9$ Hz), 3.09 (s, 6H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -117.34 (ddd, $J = 5.3$ Hz, $J = 7.1$ Hz, $J = 8.6$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K) δ 165.83 (s), 157.70 (s), 155.73 (s), 153.40 (s), 136.23 (d, $J = 8.1$ Hz), 133.17 (d, $J = 2.8$ Hz), 129.37 (s), 124.10 (d, $J = 7.4$ Hz), 123.95 (d, $J = 22.0$ Hz), 120.18 (s), 112.36 (d, $J = 27.5$ Hz), 111.44 (s), 40.29 (s).

***N*-(4-Chlorobenzoyl)-4-fluoro-2-nitroaniline (5k):**

This compound (132 mg, 15%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was hexane/ethyl acetate (93:7). Because of the insolubility of the compound it was loaded onto the column using boiling solvent: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.18 (s, NH), 9.02 (dd, 1H, $J = 5.1$ Hz, $J = 9.4$ Hz), 8.01 (dd, 1H, $J = 3.0$ Hz, $J = 8.4$ Hz), 7.92 (d, 2H, $J = 8.5$ Hz), 7.52 (d, 2H, $J = 8.5$ Hz), 7.47 (ddd, 1H, $J = 3.0$ Hz, $J = 7.0$ Hz, $J = 9.7$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -115.33 (ddd, $J = 5.2$ Hz, $J = 7.0$ Hz, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz, 298 K) δ 164.80 (s), 158.59 (s), 156.12 (s), 139.46 (s), 132.35 (s), 131.92 (d, $J = 2.9$ Hz), 129.26 (d, $J = 67.6$ Hz), 124.24 (s), 124.14 (d, $J = 5.0$ Hz), 123.90 (s), 112.73 (d, $J = 27.8$ Hz).

***N*-(4-Fluorobenzoyl)-4-fluoro-2-nitroaniline (5l):**

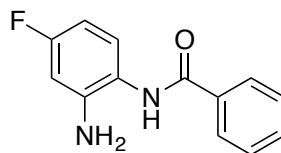
This compound (503 mg, 60.3%) was obtained as a brilliant yellow solid after silica gel chromatography. The eluant was hexane/ethyl acetate (93:7). Because of the insolubility of the compound it was loaded onto the column using boiling solvent: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 11.17 (s, NH), 9.01 (dd, 1H, $J = 5.2$ Hz, $J = 9.4$ Hz), 8.00 (dd, 2H, J

= 5.0 Hz, $J = 9.0$ Hz), 8.00 (dd, 1H, $J = 4.3$ Hz, $J = 10.0$ Hz), 7.48 (ddd, 1H, $J = 3.2$ Hz, $J = 7.1$ Hz, $J = 9.8$ Hz), 7.23 (t, 2H, $J = 8.6$ Hz); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) C_6F_6 internal standard: δ -108.86 (ddd, 1F, $J = 5.0$ Hz, $J = 8.1$ Hz, $J = 13.2$ Hz), -118.75 (ddd, 1F, $J = 5.2$ Hz, $J = 7.0$ Hz, $J = 8.6$ Hz).

General procedure for reduction of *N*-arylcarbonyl-4-fluoro-2-nitroanilines (6a–m):

In a 20 mL vial with a stir bar, the appropriate *N*-arylcarbonyl-4-fluoro-2-nitroaniline (100–500 mg) was suspended in 2-propanol and 10 wt. % palladium on carbon (30–100 mg) was added. The vial was placed in a 375 mL stainless steel Parr pressure reactor and charged with 100–200 psi of H_2 . The pressure reactor was placed on a magnetic stir plate and the solution was stirred under H_2 for 12 h. The reaction rate was generally observed to be governed by the solubility of the particular substrate. The amines obtained from this procedure were generally sufficiently pure to carry on to the subsequent cyclization step.

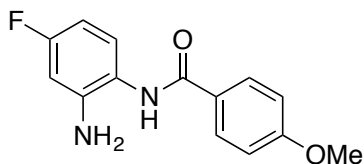
***N*-Benzoyl-4-fluoro-2-aminoaniline (6a):**



This compound (238 mg, 42%) was obtained as a colorless powder: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 8.11 (s, NH), 7.77 (d, 2H, $J = 7.3$ Hz), 7.40 (t, 1H, $J = 7.1$ Hz), 7.32 (t, 2H, $J = 7.7$ Hz), 6.99 (dd, 1H, $J = 6.3$ Hz, $J = 8.4$ Hz), 6.37 (dd, 1H, $J = 2.7$ Hz, $J =$

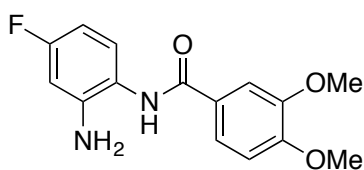
10.5 Hz), 6.27 (ddd, 1H, $J = 2.8$ Hz, $J = 8.4$ Hz, $J = 11.2$ Hz), 4.10 (s, NH₂); ¹⁹F NMR (CDCl₃, 376 MHz, 298 K) δ -117.66 (ddd, $J = 5.2$ Hz, $J = 6.9$ Hz, $J = 8.1$ Hz).

***N*-(4-Methoxybenzoyl)-4-fluoro-2-aminoaniline (6b):**

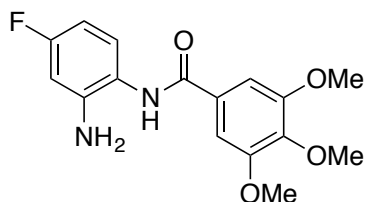


This compound (163 mg, 47%) was obtained as a colorless powder: ¹H NMR (CD₃CN, 400 MHz, 298 K) δ 8.22 (s, NH), 7.91 (d, 2H, $J = 8.9$ Hz), 7.10 (dd, 1H, $J = 6.3$ Hz, $J = 8.7$ Hz), 7.02 (d, 2H, $J = 8.9$ Hz), 6.53 (dd, 1H, $J = 2.9$ Hz, $J = 10.9$ Hz), 6.41 (ddd, 1H, $J = 3.0$ Hz, $J = 8.6$ Hz, $J = 11.5$ Hz), 4.44 (s, NH₂), 3.86 (s, OCH₃); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K) δ -117.34 (ddd, $J = 6.5$ Hz, $J = 8.6$ Hz, $J = 10.7$ Hz).

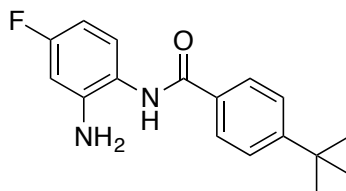
***N*-(3,4-Dimethoxybenzoyl)-4-fluoro-2-aminoaniline (6c):**



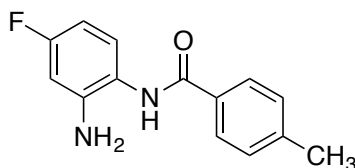
This compound (80 mg, 18%) was obtained as a colorless powder: ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 7.61 (s, NH), 7.50 (s, 1H), 7.43 (dd, 1H, $J = 1.8$ Hz, $J = 8.3$ Hz), 7.16 (dd, 1H, $J = 6.0$ Hz, $J = 8.4$ Hz), 6.9 (d, 1H, $J = 8.3$ Hz), 6.54 (dd, 1H, $J = 2.7$ Hz, $J = 9.7$ Hz), 6.52 (ddd, 1H, $J = 2.5$ Hz, $J = 8.2$ Hz, $J = 11.0$ Hz), 4.02 (s, NH₂), 3.95 (s, 6H); ¹⁹F NMR (CDCl₃, 376 MHz, 298 K) δ -114.92 (ddd, $J = 7.6$ Hz, $J = 9.0$ Hz, $J = 10.5$ Hz).

***N*-(3,4,5-Trimethoxybenzoyl)-4-fluoro-2-aminoaniline (6d):**

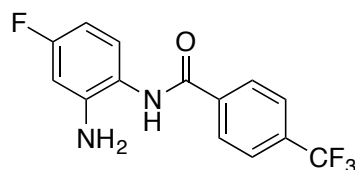
This compound (108 mg, 21%) was obtained as a colorless powder: ^1H NMR (CD_3CN , 400 MHz, 298 K) δ 8.32 (s, NH), 7.22 (s, 2H), 7.11 (dd, 1H, $J = 6.3$ Hz, $J = 8.6$ Hz), 6.54 (dd, 1H, $J = 2.8$ Hz, $J = 10.9$ Hz), 6.43 (ddd, 1H, $J = 2.9$ Hz, $J = 8.4$ Hz, $J = 11.5$ Hz), 3.89 (s, 6H), 3.79 (s, 3H); ^{19}F NMR (CD_3CN , 376 MHz, 298 K) δ -117.13 (ddd, $J = 6.5$ Hz, $J = 8.6$ Hz, $J = 10.6$ Hz).

***N*-(4-*tert*-Butylbenzoyl)-4-fluoro-2-aminoaniline (6e):**

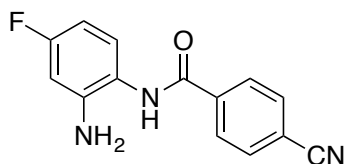
This compound (226 mg, 50%) was obtained as a colorless powder: ^1H NMR (30% CD_3OD in CD_3CN , 400 MHz, 298 K) δ 8.83 (s, NH), 7.86 (d, 2H, $J = 8.5$ Hz), 7.54 (d, 2H, $J = 8.3$ Hz), 7.10 (dd, 1H, $J = 6.2$ Hz, $J = 8.5$ Hz), 6.54 (dd, 1H, $J = 2.8$ Hz, $J = 11.0$ Hz), 6.41 (ddd, 1H, $J = 2.5$ Hz, $J = 8.5$ Hz, $J = 11.3$ Hz), 4.56 (s, NH₂), 1.33 (s, 9H); ^{19}F NMR (30% CD_3OD in CD_3CN , 376 MHz, 298 K) δ -117.20 (ddd, $J = 6.3$ Hz, $J = 8.6$ Hz, $J = 10.8$ Hz).

***N*-(4-Methylbenzoyl)-4-fluoro-2-aminoaniline (6f):**

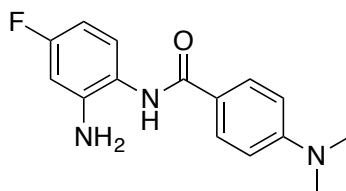
This compound (240 mg, 62%) was obtained as a colorless powder: ^1H NMR (CD_3CN , 400 MHz, 298 K) δ 8.26 (s, NH), 7.83 (d, 2H, $J = 8.0$ Hz), 7.33 (d, 2H, $J = 8.1$ Hz), 7.11 (dd, 1H, $J = 6.3$ Hz, $J = 8.4$ Hz), 6.54 (dd, 1H, $J = 2.9$ Hz, $J = 11.0$ Hz), 6.42 (ddd, 1H, $J = 3.1$ Hz, $J = 8.6$ Hz, $J = 11.5$ Hz), 4.45 (s, NH_2), 2.41 (s, 3H); ^{19}F NMR (CD_3CN , 376 MHz, 298 K) δ -117.22 (ddd, $J = 6.5$ Hz, $J = 8.5$ Hz, $J = 10.9$ Hz).

***N*-(4-Trifluoromethylbenzoyl)-4-fluoro-2-aminoaniline (6g):**

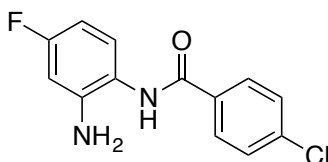
This compound (193 mg, 91%) was obtained as a colorless powder: ^1H NMR (30% CD_3OD in CD_3CN , 400 MHz, 298 K) δ 8.68 (s, NH), 8.09 (d, 2H, $J = 8.2$ Hz), 7.82 (d, 2H, $J = 8.2$ Hz), 7.13 (dd, 1H, $J = 6.4$ Hz, $J = 8.8$ Hz), 6.55 (dd, 1H, $J = 3.0$ Hz, $J = 10.9$ Hz), 6.42 (ddd, 1H, $J = 2.8$ Hz, $J = 8.6$ Hz, $J = 11.3$ Hz), 4.50 (s, NH_2); ^{19}F NMR (30% CD_3OD in CD_3CN , 376 MHz, 298 K) δ -63.47 (s, CF_3), -116.75 (ddd, 1F, $J = 6.1$ Hz, $J = 8.3$ Hz, $J = 10.8$ Hz).

***N*-(4-Cyanobenzoyl)-4-fluoro-2-aminoaniline (6h):**

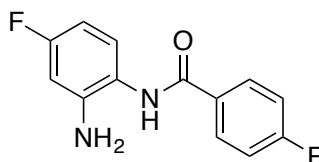
This compound (110 mg, 45%) was obtained as a colorless powder: ^1H NMR (CD_3OD , 400 MHz, 298 K) δ 9.98 (s, NH), 8.37 (d, 2H, $J = 8.0$ Hz), 7.84 (d, 2H, $J = 8.0$ Hz), 7.63 (dd, 1H, $J = 6.0$ Hz, $J = 8.5$ Hz), 7.09 (dd, 1H, $J = 2.7$ Hz, $J = 10.8$ Hz), 6.95 (ddd, 1H, $J = 2.6$ Hz, $J = 8.4$ Hz, $J = 11.0$ Hz), 4.86 (s, NH₂); ^{19}F NMR (CD_3OD , 376 MHz, 298 K) δ -117.31 (m).

***N*-(4-Dimethylaminobenzoyl)-4-fluoro-2-aminoaniline (6i):**

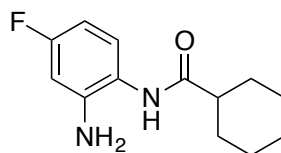
This compound (74 mg, 22%) was obtained as a colorless powder: ^1H NMR (30% CD_3OD in CD_3CN , 300 MHz, 298 K) δ 8.54 (s, NH), 7.80 (d, 2H, $J = 9.0$ Hz), 7.07 (dd, 1H, $J = 6.2$ Hz, $J = 8.7$ Hz), 6.75 (d, 2H, $J = 9.1$ Hz), 6.53 (dd, 1H, $J = 2.9$ Hz, $J = 11.0$ Hz), 6.40 (ddd, 1H, $J = 2.9$ Hz, $J = 8.5$ Hz, $J = 11.4$ Hz), 4.52 (s, NH₂), 3.00 (s, 6H); ^{19}F NMR (30% CD_3OD in CD_3CN , 282 MHz, 298 K) δ -117.64 (ddd, $J = 6.2$ Hz, $J = 8.5$ Hz, $J = 10.9$ Hz).

***N*-(4-Chlorobenzoyl)-4-fluoro-2-aminoaniline (6k):**

This compound (106 mg, 89%) was obtained as a colorless powder: ^1H NMR (30% CD_3OD in CD_3CN , 400 MHz, 298 K) δ 10.12 (s, NH), 8.04 (d, 2H, $J = 7.2$ Hz), 7.62 (t, 1H, $J = 7.4$ Hz), 7.59 (d, 2H, $J = 7.1$ Hz), 7.31 (dd, 1H, $J = 3.1$ Hz, $J = 8.8$ Hz), 7.23 (ddd, 1H, $J = 2.8$ Hz, $J = 7.9$ Hz, $J = 10.9$ Hz), 4.73 (s, NH₂); ^{19}F NMR (30% CD_3OD in CD_3CN , 376 MHz, 298 K) δ -114.77 (ddd, $J = 5.5$ Hz, $J = 8.0$ Hz, $J = 8.9$ Hz).

***N*-(4-Fluorobenzoyl)-4-fluoro-2-aminoaniline (6l):**

This compound (256 mg, 57%) was obtained as a colorless powder: ^1H NMR (30% CD_3OD in CD_3CN , 400 MHz, 298 K) δ 8.88 (s, NH), 7.97 (dd, 2H, $J = 5.5$ Hz, $J = 8.9$ Hz), 7.23 (t, 2H, $J = 8.9$ Hz), 7.09 (dd, 1H, $J = 6.1$ Hz, $J = 8.8$ Hz), 6.53 (dd, 1H, $J = 2.8$ Hz, $J = 10.9$ Hz), 6.41 (ddd, 1H, $J = 2.9$ Hz, $J = 8.6$ Hz, $J = 11.5$ Hz), 4.57 (s, NH₂); ^{19}F NMR (30% CD_3OD in CD_3CN , 376 MHz, 298 K) δ -110.15 (ddd, 1F, $J = 5.5$ Hz, $J = 8.9$ Hz, $J = 14.4$ Hz), -117.00 (ddd, 1F, $J = 6.1$ Hz, $J = 8.4$ Hz, $J = 10.9$ Hz).

***N*-Cyclohexyl-4-fluoro-2-aminoaniline (6m):**

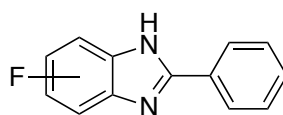
In a 20 mL vial equipped with a magnetic stir bar, *N*-benzoyl-4-fluoro-2-nitroaniline (70 mg) was suspended in 2-propanol and platinum oxide (48.7 mg) was added. The vial was placed in a 375 mL stainless steel Parr pressure reactor and charged with 400 psi of H₂. The pressure reactor was placed on a magnetic stir plate and the solution was stirred under H₂ for 48 h. The crude solid was recrystallized from hot methylene chloride/hexanes to yield colorless crystals (48 mg, 75%) ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 7.35 (s, NH), 6.99 (dd, 1H, *J* = 5.9 Hz, *J* = 8.6 Hz), 6.37 (dd, 1H, *J* = 2.8 Hz, *J* = 10.4 Hz), 6.30 (ddd, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz, *J* = 11.1 Hz), 3.98 (s, NH₂), 2.21 (tt, 1H, *J* = 3.5 Hz, *J* = 11.6 Hz), 1.94–1.79 (m, 2H), 1.78–1.67 (m, 2 H), 1.64–1.53 (m, 1H), 1.45 (ddd, 2H, *J* = 2.9 Hz, *J* = 12.2 Hz, *J* = 15.1 Hz), 1.31–1.08 (m, 3 H); ¹⁹F NMR (CDCl₃, 376 MHz, 298 K) δ -116.38 (ddd, *J* = 6.2 Hz, *J* = 8.5 Hz, *J* = 10.2 Hz).

General procedure for the preparation of 2-aryl-5-fluorobenzimidazoles (7a–m):

In a Schlenk storage tube with a stir bar was placed the appropriate *N*-benzoyl-4-fluoro-2-aminoaniline, 3 Å molecular sieves, and a 13:1 mixture of toluene and acetic acid. The vessel was closed and heated at 110 °C for 12 h. The mixture was allowed to cool and neutralized with aqueous sodium bicarbonate. The mixture was extracted several times with ethyl acetate. The organic layer was dried over sodium sulfate, evaporated, and

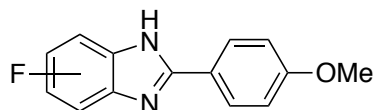
purified as described. NMR spectra generally showed that the two tautomers interconverted on the NMR timescale. More resolved spectra were obtained in CDCl_3 than in CD_3CN , indicating that the rate of tautomer interconversion was slower in the less polar solvent.

2-Phenyl-5-fluorobenzimidazole (7a):

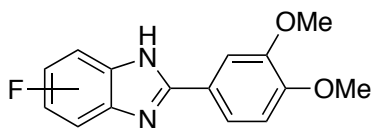


This compound was recrystallized from hot toluene. This compound was obtained as colorless crystals (64.5 mg, 25%): The NMR spectra in CD_3CN showed a nearly equal mixture of the two tautomeric forms: ^1H NMR (CD_3CN , 400 MHz, 298 K) δ 10.96 (s, NH, 2H), 8.08 (d, 4H, $J = 7.0$ Hz), 7.64 (br m, 1H), 7.59–7.46 (m, 7H), 7.39 (br m, 1H), 7.28 (br m, 1H), 7.04 (br m, 1H); ^{19}F NMR (CD_3CN , 376 MHz, 298 K) δ -121.10 (br s, 1F), 123.06 (br s, 1F).

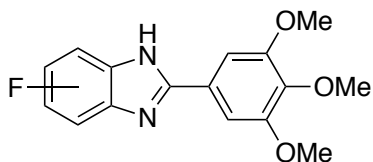
2-(4-Methoxyphenyl)-5-fluorobenzimidazole (7b):



This compound was chromatographed on silica using hexane/ethyl acetate (1:1 v/v). Obtained as a colorless powder (104 mg, 59%): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 7.87 (d, 2H, $J = 8.8$ Hz), 7.46–7.36 (br m, 1H), 7.20–7.13 (br m, 1H), 6.90–6.85 (m), 3.76 (s, OCH_3); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -119.84 (br s).

2-(3,4-Dimethoxyphenyl)-5-fluorobenzimidazole (7c):

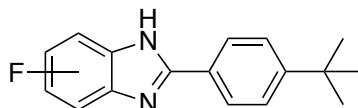
This compound was recrystallized by layering hexane onto a saturated ethyl acetate solution. This compound was obtained as colorless needles (50 mg, 59%): The NMR spectra in CDCl_3 showed a nearly equal mixture of the two tautomeric forms: ^1H NMR (CDCl_3 , 500 MHz, 298 K) δ 9.99 (s, NH), 9.92 (s, NH), 7.71 (dd, 1H, $J = 4.8$ Hz, $J = 8.9$ Hz), 7.67 (dd, 2H, $J = 2.2$ Hz, $J = 3.0$ Hz), 7.50–7.44 (m, 3H), 7.35 (dd, 1H, $J = 4.7$ Hz, $J = 8.9$ Hz), 7.12 (dd, 1H, $J = 2.2$ Hz, $J = 8.4$ Hz), 7.00 (m, 2H), 6.94 (d, 2H, $J = 8.3$ Hz), 3.94 (s, 6H), 3.91 (s, 3H), 3.90 (s, 3H); ^{19}F NMR (CD_3CN , 376 MHz, 298 K) δ -121.69 (br s, 1F), -123.29 (br s, 1F).

2-(3,4,5-Trimethoxyphenyl)-5-fluorobenzimidazole (7d):

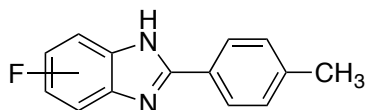
This compound was crystallized from the reaction solution by cooling to 0 °C. The crude solid was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and evaporated. This compound was obtained as a colorless solid (49 mg, 43%): ^1H NMR (CD_3CN , 400 MHz, 298 K) δ 9.77 (s, NH), 7.56 (dd, 1H, $J = 4.9$ Hz, $J = 8.2$ Hz), 7.35 (s, 2 H), 7.34 (dd, 1H,

$J = 2.5$ Hz, $J = 9.5$ Hz), 7.03 (ddd, 1H, $J = 2.5$ Hz, $J = 8.8$ Hz, $J = 10.1$ Hz), 3.92 (s, 6H), 3.79 (s, 3H); ^{19}F NMR (CD_3CN , 376 MHz, 298 K) δ -122.06 (br s).

2-(4-*tert*-Butylphenyl)-5-fluorobenzimidazole (7e):



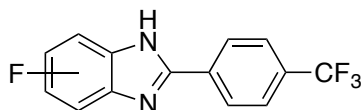
The crude product was treated with 3 mL of ethyl acetate, filtered, and washed with an additional 2 mL of ethyl acetate. The material was transferred to a tared vial and residual solvent was removed under reduced pressure to yield the compound as a colorless powder (104 mg, 43%): The NMR spectra in CDCl_3 showed an equal mixture of the two tautomeric forms: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 9.38 (s, NH, 1H), 9.36 (s, NH, 1H), 7.85 (d, 2H, $J = 8.4$ Hz), 7.84 (d, 2H, $J = 8.4$ Hz), 7.62 (dd, 1H, $J = 4.8$ Hz, $J = 8.8$ Hz), 7.40 (d, 2H, $J = 8.4$ Hz), 7.40 (d, 2H, $J = 8.4$ Hz), 7.38 (dd, 1H, $J = 2.3$ Hz, $J = 8.7$ Hz), 7.28 (dd, 1H, $J = 4.6$ Hz, $J = 8.7$ Hz), 7.05 (dd, 1H, $J = 2.4$ Hz, $J = 8.5$ Hz), 6.92 (ddd, 2H, $J = 2.1$ Hz, $J = 9.0$ Hz, $J = 11.3$ Hz), 1.27 (s, 18H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K) δ -118.66 (ddd, 1F, $J = 4.8$ Hz, $J = 8.6$ Hz, $J = 9.0$ Hz); -120.53 (td, 1F, $J = 4.6$ Hz, $J = 8.6$ Hz).

2-(4-Methylphenyl)-5-fluorobenzimidazole (7f):

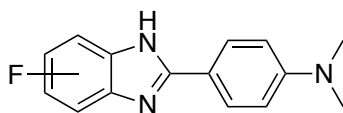
This compound was chromatographed on silica using hexane/ethyl acetate (7:3 v/v). Obtained as a colorless powder (83 mg, 32%).

Alternate method: After thermolysis of the corresponding diaryliodonium salt (**16f**), *N-tert*-butyloxycarbonyl-2-(4-methylphenyl)-5-fluorobenzimidazole and *N-tert*-butyloxycarbonyl-2-(4-methylphenyl)-6-fluorobenzimidazole were isolated by column chromatography on silica. After dissolving in acetonitrile, trifluoroacetic acid (15% by volume) was added dropwise. The solution was stirred until conversion was complete by TLC (~30 minutes). Solvents were removed *in vacuo*. The resulting oil was dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate and solvent was removed *in vacuo*.

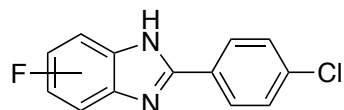
The NMR spectra in CD₃CN showed a nearly equal mixture of the two tautomeric forms: ¹H NMR (CD₃CN, 400 MHz, 298 K) δ 10.93 (s, NH, 2H), 7.96 (d, 4H, *J* = 8.4 Hz), 7.60 (br m, 1H), 7.50 (br m, 1H), 7.35 (d, 4H, *J* = 8.4 Hz), 7.27 (br m, 1H), 7.02 (ddd, 2H, *J* = 2.6 Hz, *J* = 10.1 Hz, *J* = 11.3 Hz); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K) δ -121.38 (br s, 1F), 123.20 (br s, 1F).

2-(4-Trifluoromethylphenyl)-5-fluorobenzimidazole (7g):

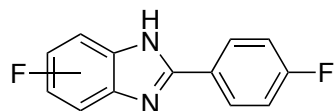
This compound was chromatographed on silica using hexane/ethyl acetate (7:3 v/v). Obtained as a colorless powder (104 mg, 51%): The NMR spectra in CDCl₃ showed a nearly equal mixture of the two tautomeric forms: ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 9.62 (s, NH, 2H), 8.14 (dd, 4H, *J* = 4.9 Hz, *J* = 8.1 Hz), 7.77 (d, 4H, *J* = 6.9 Hz), 7.52 (dd, 1H, *J* = 2.3 Hz, *J* = 9.3 Hz), 7.43 (dd, 1H, *J* = 4.5 Hz, *J* = 8.8 Hz), 7.20 (dd, 1H, *J* = 2.4 Hz, *J* = 8.3 Hz), 7.08 (m, 2H; ¹⁹F NMR (CD₃CN, 376 MHz, 298 K) δ -62.83 (s, 6F), -117.04 (ddd, 1H, *J* = 5.7 Hz, *J* = 9.2 Hz, *J* = 13.8 Hz), -119.48 (ddd, 1H, *J* = 4.7 Hz, *J* = 9.2 Hz, *J* = 13.9 Hz).

2-(4-Dimethylaminophenyl)-5-fluorobenzimidazole (7i):

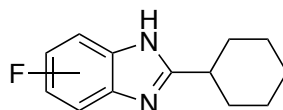
This compound was purified by column chromatography using hexane/ethyl acetate (1:1 v/v). Following evaporation of the solvents the compound was rinsed with CDCl₃ and obtained as a colorless powder (15 mg, 22%): ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 9.90 (br s, NH), 7.93 (d, 2H, *J* = 9.0), 7.46 (br m, 1H), 7.23 (br m, 1H), 6.94 (td, 1H, *J* = 2.4 Hz, *J* = 9.6 Hz), 6.73 (d, 2H, *J* = 9.0 Hz) 3.02 (s, 6H); ¹⁹F NMR (CDCl₃, 376 MHz, 298 K) δ -120.63 (br s).

2-(4-Chlorophenyl)-5-fluorobenzimidazole (7k):

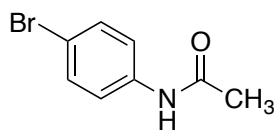
This compound was chromatographed on silica using hexane/ethyl acetate (7:3 v/v). Obtained as a colorless powder (42 mg, 37%): The NMR spectra in CD₃CN showed a nearly equal mixture of the two tautomeric forms: ¹H NMR (CD₃CN, 300 MHz, 298 K) δ 10.35 (s, NH), 8.04 (dd, 2H, *J* = 3.7 Hz, *J* = 7.4 Hz), 7.70–7.38 (br m, 1H), 7.47 (dd, 2H, *J* = 2.5 Hz, *J* = 4.0 Hz), 7.38–7.11 (br m, 1H), 7.01 (dd, 1H, *J* = 2.4 Hz, *J* = 9.5 Hz); ¹⁹F NMR (CD₃CN, 282 MHz, 298 K) δ -118.35 (br s, 1F), 120.21 (br s, 1F).

2-(4-Fluorophenyl)-5-fluorobenzimidazole (7l):

This compound was chromatographed on silica using hexane/ethyl acetate (7:3 v/v). Obtained as a colorless powder which turned yellow upon rotary evaporation (153 mg, 55%): The NMR spectra in CD₃CN showed a nearly equal mixture of the two tautomeric forms: ¹H NMR (CD₃CN, 400 MHz, 298 K) δ 10.99 (s, NH), 8.09 (dd, 2H, *J* = 5.3 Hz, *J* = 8.8 Hz), 7.55 (br m, 1H), 7.32 (br m, 1H), 7.26 (t, 2H, *J* = 9.0 Hz), 7.03 (dd, 1H, *J* = 2.6 Hz, *J* = 9.9 Hz); ¹⁹F NMR (CD₃CN, 376 MHz, 298 K) δ -112.19 (br s, 2F), -121.03 (br s, 1F), 122.92 (br s, 1F).

2-Cyclohexyl-5-fluorobenzimidazole (7m):

This compound was recrystallized from hot hexanes. This compound was obtained as colorless crystals (19 mg, 37%): ^1H NMR ($(\text{CD}_3)_2\text{SO}$, 400 MHz, 298 K) δ 12.21 (s, NH), 7.43 (dd, 1H, $J = 5.0$ Hz, $J = 8.5$ Hz), 7.25 (dd, 1H, $J = 1.9$ Hz, $J = 9.6$ Hz), 6.94 (ddd, 1H, $J = 2.5$ Hz, $J = 8.8$ Hz, $J = 10.0$ Hz), 2.82 (tt, $J = 3.9$ Hz, $J = 11.2$ Hz), 2.00 (dd, 2H, $J = 3.0$ Hz, $J = 13.2$ Hz), 1.69 (dt, 1H, $J = 3.3$ Hz, $J = 11.8$ Hz), 1.58 (ddd, 2H, $J = 3.3$ Hz, $J = 12.4$ Hz, $J = 15.7$ Hz), 1.37 (qt, 2H, $J = 3.5$ Hz, $J = 12.4$ Hz), 1.27 (tt, 1H, $J = 3.0$ Hz, $J = 11.8$ Hz); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$, 376 MHz, 298 K) C_6F_6 internal reference standard δ -124.58 (br s).

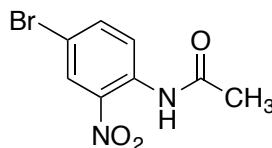
4-Bromoacetanilide (8):

In an oven-dried 2 L round-bottom flask, 4-bromoaniline (50 g, 0.30 mol) was suspended in acetic anhydride (300 mL), and chilled to 0 °C. Concentrated sulfuric acid (15 mL) was slowly added. Once the solution became homogenous, the ice bath was removed and the solution was as allowed to warm to room temperature. After 2 hours, the solution was poured over 400 mL ice-water (~1:1). Once the ice had melted, the mixture was filtered. The solid was dried at 110 °C for several hours to yield the colorless product

(60.82 g, 97.7%): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 7.43 (d, $J = 9.1$ Hz, 2H), 7.40 (d, $J = 9.1$ Hz, 2H), 7.28 (br s, NH), 2.18 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 168.31, 136.93, 131.97, 121.37, 116.88, 24.64; HRMS: (EI^+) calcd. for $\text{C}_8\text{H}_8\text{BrNO}$ $[\text{M}]^+$ 212.9789, 214.9769 found 212.9799, 214.9779.

Mohan, J. "Confirmatory Tests and Derivatization of Common Organic Compounds, Their Derivatization and Classified Tables including Melting and Boiling Points" in "Organic Analytical Chemistry: Theory and Practice"; Alpha Science Int'l Ltd.: Oxford, United Kingdom, **2003**.

4-Bromo-2-nitroacetanilide (9):



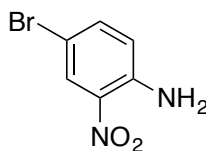
In a 125 mL erlenmeyer flask, fuming nitric acid (75 mL) was cooled to -40 °C in an acetonitrile/dry ice bath. 4-bromoacetanilide (6.00 g, 28.0 mmol) was added, in portions, while swirling the flask. After addition the flask was allowed to stand for 15 minutes. The solution was poured over 200 g of ice. After the ice had melted, the mixture was filtered and the solid was washed with cold water. The solid was recrystallized from ethanol (200 proof) and dried *in vacuo* to yield a pale yellow solid (6.69 g, 92.3%): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 10.27 (br s, NH), 8.73 (d, $J = 9.1$ Hz, 1H), 8.36 (d, $J = 2.3$ Hz, 1H), 7.74 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (CDCl_3 , 126

MHz, 298 K): δ 169.19, 138.97, 136.71, 134.16, 128.42, 123.78, 115.46, 25.84;

HRMS: (EI⁺) calcd. for C₈H₇BrN₂O₃ [M]⁺ 257.9640, 259.9620 found 257.9648, 259.9627.

Hay, M. P.; Hicks, K. O.; Pchalek, K.; Lee, H. H.; Blaser, A.; Pruijn, F. B.; Anderson, R. F.; Shinde, S. S.; Wilson, W. R.; Denny, W. A. *J. Med. Chem.*, **2008**, *51*, 6853–6865.

4-Bromo-2-nitroaniline (10):



In a 250 mL round-bottom flask, 4-bromo-2-nitroacetanilide (1.295 g, 5.00 mmol) was dissolved in 50 mL THF. Aqueous HCl (2 M, 200 mL) was added with vigorous stirring. The mixture was heated to reflux overnight. The solution was neutralized with saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. The organic layers were washed once with brine, dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was sublimed under high dynamic vacuum at 65 °C for 24 hours to yield an orange solid (0.961 g, 88.6%): ¹H NMR (CDCl₃, 500 MHz, 298 K): δ 8.26 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.9 Hz, *J* = 2.2 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 6.14 (br s, NH₂); ¹³C NMR (CDCl₃, 126 MHz, 298 K): δ 143.77, 138.65, 132.60, 128.49, 128.46, 128.42, 120.52, 107.99; HRMS: (EI⁺) calcd. for C₆H₅BrN₂O₂ [M]⁺ 215.9534, 217.9514 found 215.9532, 217.9521.

General procedure for the preparation of *N*-arylcarbonyl-5-bromo-2-nitroanilines (11a–l) by method 1, with liquid benzoyl chlorides: 4-Bromo-2-nitroaniline (3.00 g, 13.8 mmol), and triethylamine (4 mL) were dissolved in 60 mL of dry acetonitrile. The appropriate acid chloride (20.7 mmol) was added dropwise by syringe and the reaction was heated at 80 °C for 20 hours. The reaction mixture was diluted with dichloromethane and transferred to a separatory funnel containing saturated aqueous sodium bicarbonate in deionized water (1:1). The organic layer was separated, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the indicated solvent(s).

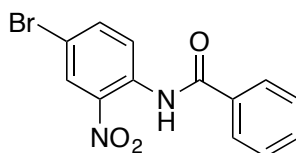
General procedure for the preparation of *N*-arylcarbonyl-5-bromo-2-nitroanilines (11a–l) by method 1, with solid benzoyl chlorides: 4-Bromo-2-nitroaniline (3.00 g, 13.8 mmol), triethylamine (4 mL), and the appropriate acid chloride (20.7 mmol) were dissolved in 60 mL of dry acetonitrile. The reaction was heated at 80 °C for 20 hours. The reaction mixture was diluted with dichloromethane and transferred to a separatory funnel containing saturated aqueous sodium bicarbonate in deionized water (1:1). The organic layer was separated, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the indicated solvent(s).

General procedure for the preparation of *N*-arylcarbonyl-5-bromo-2-nitroanilines (11a–l) by method 2, with liquid benzoyl chlorides: 4-Bromo-2-nitroaniline (4.00 g, 18.4 mmol) and pyridine (3 mL) were dissolved in 25 mL of dry acetonitrile. The appropriate acid chloride (18.4 mmol) was added dropwise by syringe and the reaction was heated at 80 °C for 20 hours. The reaction mixture was diluted with dichloromethane and transferred to a separatory funnel containing saturated aqueous sodium bicarbonate in deionized water (1:1). The organic layer was separated, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the indicated solvent(s).

General procedure for the preparation of *N*-arylcarbonyl-5-bromo-2-nitroanilines (11a–l) by method 2, with solid benzoyl chlorides: 4-Bromo-2-nitroaniline (4.00 g, 18.4 mmol), pyridine (3 mL), and appropriate acid chloride (18.4 mmol) were dissolved in 25 mL of dry acetonitrile. The reaction was heated at 80 °C for 20 hours. The reaction mixture was diluted with dichloromethane and transferred to a separatory funnel containing saturated aqueous sodium bicarbonate in deionized water (1:1). The organic layer was separated, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, evaporated, and purified by column chromatography or recrystallization using the indicated solvent(s).

General procedure for the preparation of *N*-arylcarbonyl-5-bromo-2-nitroanilines (11a–l) by hydrolysis of the corresponding imide: In a 100 mL round-bottom flask, the corresponding imide (6.32 mmol) was dissolved in a solution of methanol (13 mL) in dioxane (22 mL). Sodium hydroxide (34.7 mg, 20 mol%) was crushed and dissolved in methanol (9 mL). This base solution was added, dropwise, with stirring to the flask. The solution darkened in color throughout addition. The solution was stirred for 30 min, diluted with dichloromethane (200 mL), and washed with water (10 mL) in saturated aqueous ammonium chloride (40 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL), dried over sodium sulfate, and solvents were removed *in vacuo*. The crude product was purified by column chromatography or recrystallization using the indicated solvent(s).

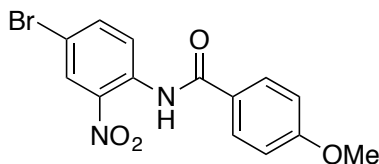
***N*-Benzoyl-4-bromo-2-nitroaniline (11a):**



This compound (method 1: 1.34 g, 30.4%; method 2: 5.16 g, 87.1%) was obtained as dull yellow needles from method 1 after recrystallization from boiling ethanol (200 proof), followed by chromatography on silica with ethyl acetate in hexanes (15%, v/v), or from method 2 after recrystallization from boiling ethanol (200 proof): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.28 (br s, NH), 8.97 (d, $J = 9.1$ Hz, 1H), 8.43 (d, $J = 2.1$ Hz, 1H), 7.99 (d, $J = 7.5$ Hz, 2H), 7.81 (dd, $J = 9.1$ Hz, $J = 2.1$ Hz, 1H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.88, 139.21, 136.89, 134.69,

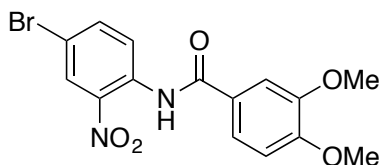
133.87, 133.10, 129.34, 128.63, 127.58, 123.76, 115.59; HRMS: (EI⁺) calcd. for C₁₃H₉BrN₂O₃ [M]⁺ 319.9797, 321.9776 found 319.9803, 321.9783.

***N*-(4-Methoxybenzoyl)-4-bromo-2-nitroaniline (11b):**



This compound was obtained by method 1 (1.64 g, 37.2%) as a dull yellow solid after recrystallization from boiling ethanol in ethyl acetate (2:1 v/v), and by method 2 (2.25 g, 36.6%) after recrystallization from boiling ethyl acetate in hexanes (2:1 v/v): ¹H NMR (CDCl₃, 500 MHz, 298 K): δ 11.22 (br s, NH), 8.95 (d, *J* = 9.1 Hz, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.78 (dd, *J* = 9.1 Hz, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz, 298 K): δ 165.36, 163.52, 139.17, 136.71, 135.03, 129.62, 128.57, 126.03, 123.70, 115.20, 114.53, 55.77; HRMS: (EI⁺) calcd. for C₁₄H₁₁BrN₂O₄ [M]⁺ 349.9902, 351.9882 found 349.9916, 351.9895.

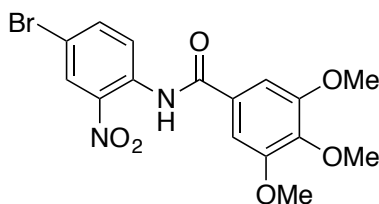
***N*-(3,4-Dimethoxybenzoyl)-4-bromo-2-nitroaniline (11c):**



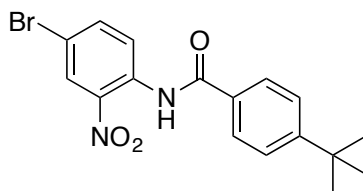
This compound (1.95 g, 37.0%) was obtained by method 1 as a fluffy yellow solid after recrystallization from a dilute solution of boiling ethanol: ¹H NMR (CDCl₃, 500 MHz, 298 K): δ 11.22 (br s, NH), 8.89 (d, *J* = 9.1 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, *J*

= 9.1 Hz, $J = 2.4$ Hz, 1H), 7.50 (dd, $J = 8.1$ Hz, $J = 2.1$ Hz, 1H), 7.48 (d, $J = 2.1$ Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.44, 153.19, 149.57, 139.27, 136.71, 135.02, 128.63, 126.38, 123.61, 120.60, 115.28, 110.86, 110.75, 56.38, 56.28; HRMS: (EI^+) calcd. for $\text{C}_{15}\text{H}_{13}\text{BrN}_2\text{O}_5$ $[\text{M}]^+$ 380.0008, 381.9987 found 380.0023, 382.0006.

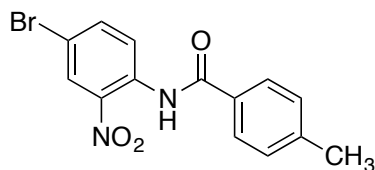
***N*-(3,4,5-Trimethoxybenzoyl)-4-bromo-2-nitroaniline (11d):**



This compound (0.294 g, 19.6%) was obtained by method 1 as a fluffy yellow solid after recrystallization from boiling ethanol in ethyl acetate (3:7, v/v): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.31 (br s, NH), 8.96 (d, $J = 9.1$ Hz, 1H), 8.44 (d, $J = 2.3$ Hz, 1H), 7.82 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 7.22 (s, 2H), 3.97 (s, 6H), 3.94 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.47, 153.71, 142.29, 139.38, 136.73, 134.84, 129.05, 128.69, 123.50, 115.53, 104.83, 61.24, 56.53; HRMS: (EI^+) calcd. for $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_6$ $[\text{M}]^+$ 410.0113, 412.0093 found 410.0103, 412.0072.

***N*-(*tert*-Butylbenzoyl)-4-bromo-2-nitroaniline (11e):**

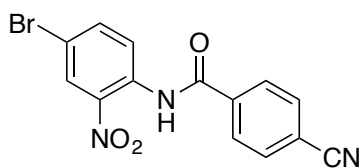
This compound (1.26 g, 24.2%) was obtained by method 1 as dull yellow needles after chromatographing on silica with ethyl acetate in hexanes (7%, v/v). Due to the insolubility of this compound in the elution solvent, it was deposited on silica and dry-loaded onto the column. More material was recovered by hydrolysis of *N,N*-(di-4-*tert*-butylbenzoyl)-4-bromo-2-nitroaniline (0.461 g, 84.5%): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.27 (br s, NH), 8.98 (d, $J = 9.1$ Hz, 1H), 8.43 (d, $J = 2.3$ Hz, 1H), 7.92 (d, $J = 8.5$ Hz, 2H), 7.80 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 7.57 (d, $J = 8.5$ Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.85, 156.90, 139.16, 136.80, 134.87, 130.99, 128.59, 127.48, 126.30, 123.73, 115.36, 35.34, 31.30; HRMS: (EI^+) calcd. for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_3$ [M] $^+$ 376.0423, 378.0402 found 376.0416, 378.0421.

***N*-(4-Methylbenzoyl)-4-bromo-2-nitroaniline (11f):**

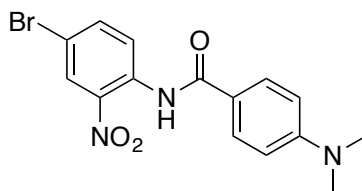
This compound (1.70 g, 36.7%) was obtained by method 1 as dull yellow needles after chromatographing on silica with ethyl acetate in hexanes (7%, v/v). Due to the

insolubility of this compound in the elution solvent, it was deposited on silica and dry-loaded onto the column: ^1H NMR (CDCl_3 , 600 MHz, 298 K): δ 11.25 (s, NH), 8.97 (d, $J = 9.1$ Hz, 1H), 8.42 (d, $J = 2.3$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.80 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 165.87, 143.91, 139.18, 136.87, 134.91, 131.13, 130.02, 128.61, 127.65, 123.79, 115.39, 21.80; HRMS: (EI^+) calcd. for $\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}_3$ $[\text{M}]^+$ 333.9953, 335.9933 found 333.9948, 335.9931.

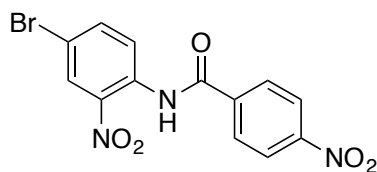
***N*-(4-Cyanobenzoyl)-4-bromo-2-nitroaniline (11h):**



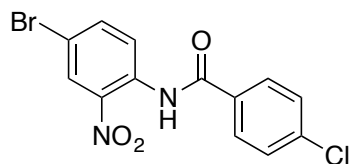
This compound (method 1: 2.74 g, 57.4%; method 2: 1.73 g, 30.2%) was obtained as dull yellow plates after recrystallization from boiling toluene: ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.36 (br s, NH), 8.92 (d, $J = 9.1$ Hz, 1H), 8.46 (d, $J = 1.9$ Hz, 1H), 8.09 (d, $J = 8.2$ Hz, 2H), 7.87 (d, $J = 8.2$ Hz, 2H), 7.85 (dd, $J = 9.1$ Hz, $J = 1.9$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 164.03, 139.43, 137.69, 137.08, 133.96, 133.17, 128.82, 128.23, 123.77, 117.88, 116.64, 116.50; HRMS: (EI^+) calcd. for $\text{C}_{14}\text{H}_8\text{BrN}_3\text{O}_3$ $[\text{M}]^+$ 344.9749, 346.9729 found 344.9762, 346.9743.

***N*-(4-Dimethylaminobenzoyl)-4-bromo-2-nitroaniline (11i):**

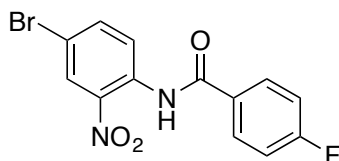
This compound (1.29 g, 25.6%) was obtained by method 1 as a dull red solid after recrystallization from boiling ethyl acetate: ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.20 (br s, NH), 8.99 (d, $J = 9.2$ Hz, 1H), 8.40 (d, $J = 2.4$ Hz, 1H), 7.88 (d, $J = 8.9$ Hz, 2H), 7.76 (dd, $J = 9.2$ Hz, $J = 2.4$ Hz, 1H), 6.67 (d, $J = 8.9$ Hz, 2H), 3.01 (s, 6H).

***N*-(4-Nitrobenzoyl)-4-bromo-2-nitroaniline (11j):**

This compound was obtained by method 1 (8.0 mmol scale) after trituration with hexanes and recrystallization from boiling ethyl acetate in ethanol (2:1 v/v) to yield a yellow solid (2.40 g, 81.9%): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.39 (br s, NH), 8.93 (d, $J = 9.1$ Hz, 1H), 8.47 (d, $J = 2.3$ Hz, 1H), 8.42 (d, $J = 8.9$ Hz, 2H), 8.16 (d, $J = 8.9$ Hz, 2H), 7.87 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 163.79, 150.54, 139.47, 139.29, 137.09, 133.90, 128.85, 128.81, 124.56, 123.76, 116.61; HRMS: (EI^+) calcd. for $\text{C}_{13}\text{H}_8\text{BrN}_3\text{O}_5$ [$\text{M}]^+$ 364.9647, 366.9627 found 364.9663, 366.9627.

***N*-(4-Chlorobenzoyl)-4-bromo-2-nitroaniline (11k):**

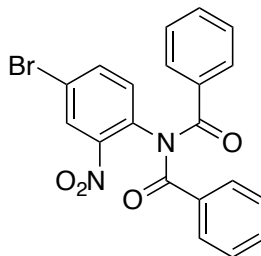
This compound (method 1: 1.35 g, 22.9%; method 2: 4.09 g, 69.4%) was obtained as dull yellow fine needles after recrystallization from ethanol in ethyl acetate (2:1 v/v): ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.26 (br s, NH), 8.93 (d, $J = 9.1$ Hz, 1H), 8.43 (d, $J = 2.3$ Hz, 1H), 7.93 (d, $J = 8.7$ Hz, 2H), 7.82 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 7.53 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 164.81, 139.60, 139.29, 136.93, 134.47, 132.27, 129.66, 128.99, 128.69, 123.74, 115.88.

***N*-(4-Fluorobenzoyl)-4-bromo-2-nitroaniline (11l):**

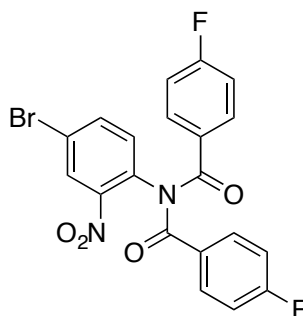
This compound (1.89 g, 88.1%) was obtained as pale yellow needles after hydrolysis of *N,N*-(di-4-fluorobenzoyl)-4-bromo-2-nitroaniline: ^1H NMR (CDCl_3 , 500 MHz, 298 K): δ 11.24 (s, NH), 8.92 (d, $J = 9.1$ Hz, 1H), 8.41 (d, $J = 2.3$ Hz, 1H), 7.99 (dd, $J = 8.7$ Hz, $J = 5.2$ Hz, 2H), 7.80 (dd, $J = 9.1$ Hz, $J = 2.3$ Hz, 1H), 7.22 (t, $J = 8.7$ Hz, 2H); ^{13}C NMR (CDCl_3 , 126 MHz, 298 K): δ 166.75, 164.71, 139.25, 136.87, 134.55, 130.09 (d, $J = 9.4$ Hz), 128.65, 123.69, 116.51 (d, $J = 22.1$ Hz), 115.72; ^{19}F NMR (CDCl_3 , 376 MHz, 298

K): δ -103.87 (m, 1F) ; HRMS: (EI⁺) calcd. for C₁₃H₈BrFN₂O₃ [M]⁺ 337.9702, 339.9682 found 337.9717, 339.9680.

***N,N*-Dibenzoyl-4-bromo-2-nitroaniline (12a):**



This compound (5.01 g, 56.9%) was obtained by method 1 as a faintly yellow solid after recrystallization from boiling ethanol (200 proof), followed by chromatography on silica with ethyl acetate in hexanes as a gradient from 15% (v/v) to 25% (v/v): ¹H NMR (CDCl₃, 500 MHz, 298 K): δ 8.32 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.3 Hz, *J* = 1.2 Hz, 4H), 7.69 (dd, *J* = 8.4 Hz, *J* = 2.3 Hz, 1H), 7.47 (dt, *J* = 8.3 Hz, *J* = 1.2 Hz, 2H), 7.36 (t, *J* = 8.3 Hz, 4H), 7.10 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (CDCl₃, 126 MHz, 298 K): δ 172.19, 144.97, 137.23, 134.19, 132.91, 132.78, 132.27, 129.30, 129.19, 128.76, 128.73, 128.70, 128.68, 128.67, 128.65, 121.98; HRMS (EI⁺): calcd. for C₂₀H₁₃BrN₂O₄ [M]⁺ 424.0059, 426.0038 found 424.0047, 426.0035.

***N,N*-(Di-4-fluorobenzoyl)-4-bromo-2-nitroaniline (12l):**

This compound (2.92 g, 67.6%) was obtained by method 1 as a pale yellow solid after recrystallization from hexanes in ethyl acetate (4:1 v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 8.31 (d, $J = 2.3$ Hz, 1H), 7.78 (dd, $J = 8.8$ Hz, $J = 5.2$ Hz, 4H), 7.70 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 1H), 7.04 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 4H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K): δ -103.88 (m, 2F); HRMS (EI^+): calcd. for $\text{C}_{20}\text{H}_{11}\text{BrF}_2\text{N}_2\text{O}_4$ $[\text{M}]^+$ 459.9870, 461.9850 found 459.9886, 461.9853.

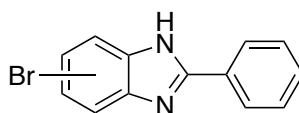
General procedure for reduction/cyclization of *N*-arylcarbonyl-4-bromo-2-nitroanilines (13a–m): In a 50 mL Schlenk storage tube with a stirbar, *N*-aryl-4-bromo-2-nitroaniline was combined with iron powder or iron filings (400 mol%). Hot acetic acid (15–30 mL) was added until the mixture could be stirred smoothly. The tube was sealed and heated to 110 °C for 24 hours to a week, monitoring reaction progress by TLC. The reaction mixture was transferred to a 250 mL round-bottom flask and benzene (20 mL) was added to facilitate azeotropic removal of acetic acid. Volume was reduced to an oil *in vacuo* with heating. The oil was dissolved in ethyl acetate and carefully washed three times with a mixture of saturated aqueous sodium bicarbonate and brine (1:1 v/v).

The organic layer was dried over sodium sulfate and solvent was removed *in vacuo*.

The crude product was purified by column chromatography or recrystallization using the indicated solvent(s).

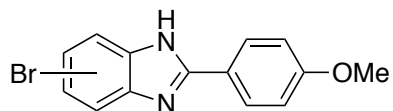
Morningstar, M. L.; Roth, T.; Farnsworth, D. W.; Smith, M. K.; Watson, K.; Buckheit, R. W.; Jr., ; Das, K.; Zhang, W.; Arnold, E.; Julias, J. G.; Hughes, S. H.; Michejda, C. J. *J. Med. Chem.* **2007**, *50*, 4003–4015.

2-Phenyl-5-bromobenzimidazole (13a):



This compound (16.1 mmol scale, 3.90 g, 89.0%) was obtained as a sufficiently pure colorless powder after liquid-liquid extraction: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 9.65 (br s, NH), 8.04 (d, $J = 7.9$ Hz, 2H), 7.80 (br s, 2H), 7.52 (m, 3H), 7.39 (dd, $J = 8.5$ Hz, $J = 1.8$ Hz, 1H).

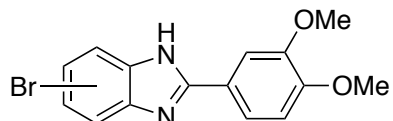
2-(4-Methoxyphenyl)-5-bromobenzimidazole (13b):



This compound (6.4 mmol scale, 1.59 g, 82.0%) was obtained as a sufficiently pure colorless powder after liquid-liquid extraction: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ

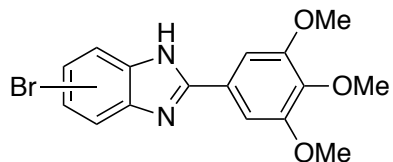
9.32 (br s, NH), 7.97 (d, $J = 8.9$ Hz, 2H), 7.76 (br s, 1H), 7.51 (br s, 1H), 7.37 (dd, $J = 8.5$ Hz, $J = 1.7$ Hz, 1H), 7.04 (d, $J = 8.9$ Hz, 2H), 3.90 (s, 3H).

2-(3,4-Dimethoxyphenyl)-5-bromobenzimidazole (13c):



This compound (2.4 mmol scale, 0.672 g, 85.7%) was obtained as a colorless powder after chromatographing with methanol in dichloromethane (7% v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 10.03 (br s, NH), 7.75 (br s, 1H), 7.68 (br s, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.48 (br s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

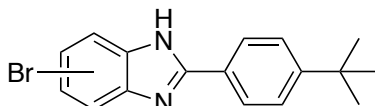
2-(3,4,5-Trimethoxyphenyl)-5-bromobenzimidazole (13d):



This compound (3.6 mmol scale, 1.23 g, 94.4%) was obtained as a colorless powder after chromatographing on silica using methanol in dichloromethane (3% v/v). The NMR spectra in CD_2Cl_2 showed a nearly equal mixture of the two tautomeric forms: ^1H NMR (CD_2Cl_2 , 400 MHz, 298 K) δ 10.65 (br s, 0.5H), 10.56 (br s, 0.5H), 7.92 (br s, 0.5H), 7.69 (br s, 1H), 7.42 (br s, 0.5H), 7.41 (dd, $J = 8.4$ Hz, $J = 1.7$ Hz, 1H), 7.32 (s, 2H), 3.86 (s, 3H), 3.84 (s, 6H); HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 385.0164,

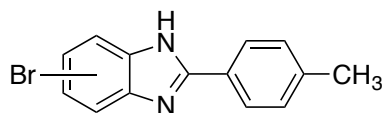
387.0143 found 385.0153, 387.0143; HRMS: (EI⁺) calcd. for C₁₆H₁₅BrN₂O₃ [M]⁺ 362.0266, 364.0246 found 362.0262, 364.0243.

2-(4-*tert*-Butylphenyl)-5-bromobenzimidazole (13e):

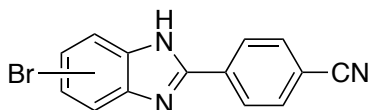


This compound (3.2 mmol scale, 0.763 g, 69.2%) was obtained as a colorless powder after chromatographing on silica using methanol in dichloromethane (3% v/v): ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.73 (br s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.46 (br s, 1H), 7.34 (dd, *J* = 8.7 Hz, *J* = 1.2 Hz, 1H), 1.35 (s, 9H); HRMS: (EI⁺) calcd. for C₁₇H₁₇BrN₂ [M]⁺ 328.0575, 330.0555 found 328.0579, 330.0554.

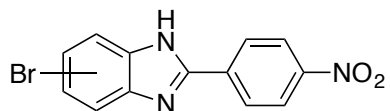
2-(4-Methylphenyl)-5-bromobenzimidazole (13f):



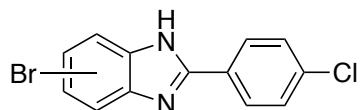
This compound (7.8 mmol scale, 1.43 g, 64.1%) was obtained as a colorless powder after chromatographing with methanol in dichloromethane (3% v/v). The NMR spectra in CDCl₃ showed a nearly equal mixture of the two tautomeric forms: ¹H NMR (CDCl₃, 400 MHz, 298 K) δ 9.49 (br s, NH), 7.95 (br s, 0.5H), 7.92 (d, *J* = 7.9 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 0.5H), 7.61 (br s, 0.5H), 7.38 (dd, *J* = 10.4 Hz, *J* = 1.8 Hz, 1H), 7.36 (br s, 0.5H), 7.33 (d, *J* = 7.9 Hz, 2H); HRMS (ESI): calcd. for C₁₄H₁₂BrN₂ [M+Na]⁺ 287.0184, 289.0163 found 287.0180, 289.0176.

2-(4-Cyanophenyl)-5-bromobenzimidazole (13h):

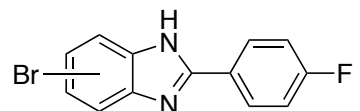
This compound (4.4 mmol scale, 0.841 g, 61.4%) was obtained as a colorless powder after dry column vacuum chromatography on silica using three respective fractions of dichloromethane, ethyl acetate, and acetone: ^1H NMR (CD_2Cl_2 , 400 MHz, 298 K) δ 10.48 (br s, NH), 8.02 (d, $J = 7.9$ Hz, 2H), 7.64 (m, 3H), 7.41 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 8.5$ Hz, 1H); HRMS: (EI^+) calcd. for $\text{C}_{14}\text{H}_8\text{BrN}_3$ $[\text{M}]^+$ 296.9902, 298.9881 found 296.9904, 298.9893.

2-(4-Nitrophenyl)-5-bromobenzimidazole (13m):

This compound (4.1 mmol scale, 0.760 g, 58.4%) was obtained as a colorless powder after chromatographing with methanol in dichloromethane (5% v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 9.64 (br s, NH), 8.40 (d, $J = 8.9$ Hz, 2H), 8.23 (d, $J = 8.9$ Hz, 2H), 7.84 (br s, 1H), 7.60 (br s, 1H), 7.46 (dd, $J = 8.5$ Hz, $J = 1.6$ Hz, 1H).

2-(4-Chlorophenyl)-5-bromobenzimidazole (13k):

This compound (11.5 mmol scale, 1.74 g, 49.2%) was obtained as a sufficiently pure colorless powder after liquid-liquid extraction: ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 10.35 (br s, NH), 7.97 (d, $J = 8.4$ Hz, 2H), 7.75 (br s, 1H), 7.49 (br s, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 7.9$ Hz, 1H).

2-(4-Fluorophenyl)-5-bromobenzimidazole (13l):

This compound (4.2 mmol scale, 0.873 g, 71.4%) was obtained as a colorless powder after chromatographing with methanol in dichloromethane (3% v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K) δ 9.47 (br s, NH), 8.02 (dd, $J = 8.8$ Hz, $J = 5.2$ Hz, 2H), 7.79 (br s, 1H), 7.51 (br s, 1H), 7.40 (dd, $J = 8.5$ Hz, $J = 1.8$ Hz, 1H), 7.22 (t, $J = 8.8$ Hz, 2H); ^{19}F NMR (CDCl_3 , 376 MHz, 298 K): δ -109.06 (br m, 1F); HRMS: (EI^+) calcd. for $\text{C}_{13}\text{H}_8\text{BrFN}_2$ [$\text{M}]^+$ 289.9855, 291.9834 found 289.9856, 291.9831.

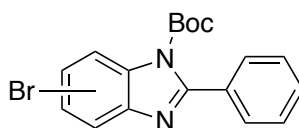
General procedure for Boc-protection of 2-aryl-5-bromobenzimidazoles (14a–k): In

a 100 mL round-bottom flask with a stirbar, 2-aryl-5-bromobenzimidazole was suspended in acetonitrile (10–30 mL; dried over 3\AA molecular sieves) with triethylamine

(400 mol%; dried over potassium hydroxide). *N,N*-dimethylaminopyridine (30 mol%) was added in portions. Di-*tert*-butyl dicarbonate (200 mol%) was added slowly, in portions. The mixture was stirred, under N_2 , for 12–24 hours. Solvent was removed *in vacuo* and the resulting oil was diluted with dichloromethane. The mixture was washed twice with a mixture of saturated aqueous ammonium chloride and brine (1:1 v/v). The organic layer was dried over sodium sulfate and solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica, deactivated with triethylamine in hexanes (5% v/v), using the indicated solvent(s).

Sue, M. D.; Delgado, M. M. M.; Joseph, S. J.; J, A. R.; G, L. B.; Iii, H. R. L.; Isabel, S. G.; Dehua, H.; Lyn, S. K.; K, P. G.; Simon, P. J.; William, P. P.; Radnia, T. L.; Sophie, P. *PCT Int. Appl.* **2008**, WO2008051493 A3.

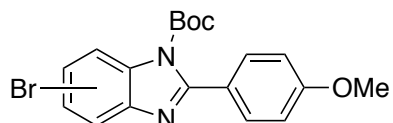
***N-tert*-Butyloxycarbonyl-2-phenyl-5-bromobenzimidazole (14a):**



A nearly equal mixture of two regioisomers (14.3 mmol scale, 4.54 g, 85.1%) was obtained as a colorless waxy solid after chromatography, on deactivated silica, with ethyl acetate in hexanes (15% v/v): 1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.19 (d, $J = 2.0$ Hz, 1H), 7.94 (d, $J = 8.8$ Hz, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 7.62 (m, 5H), 7.50 (m, 8H), 1.38 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (CD_3CN , 126 MHz, 298 K): δ 155.82, 155.27, 149.08,

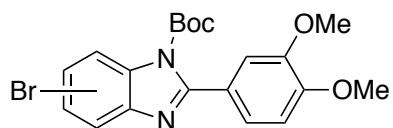
149.02, 144.94, 142.70, 135.89, 134.03, 133.28, 130.52, 130.28, 128.82, 128.43, 128.19, 123.39, 122.11, 118.65, 117.51, 117.24, 86.68, 86.61, 27.76.

***N*-tert-Butyloxycarbonyl-2-(4-methoxyphenyl)-5-bromobenzimidazole (14b):**



A nearly equal mixture of two regioisomers (5.3 mmol scale, 1.53 g, 89.5%) was obtained as a pale yellow foam after chromatography, on deactivated silica, with ethyl acetate in hexanes (15% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.16 (d, $J = 1.8$ Hz, 1H), 7.91 (d, $J = 8.7$ Hz, 1H), 7.86 (d, $J = 1.8$ Hz, 1H), 7.59 (m, 5H), 7.47 (m, 2H), 7.03 (d, $J = 8.7$ Hz, 4H), 3.87 (s, 6H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (CD_3CN , 126 MHz, 298 K): δ 161.96, 161.92, 156.02, 155.48, 149.36, 149.30, 145.09, 142.84, 136.08, 134.22, 131.99, 131.96, 128.21, 128.18, 125.31, 125.25, 123.23, 121.99, 118.70, 118.11, 117.47, 117.31, 114.25, 86.74, 86.67, 56.17, 27.87, 27.84.

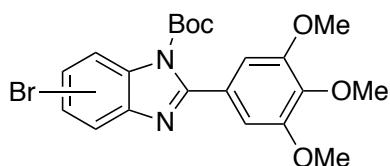
***N*-tert-Butyloxycarbonyl-2-(3,4-dimethoxyphenyl)-5-bromobenzimidazole (14c):**



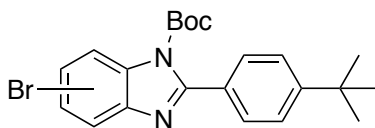
A nearly equal mixture of two regioisomers (2.0 mmol scale, 0.746 g, 88.0%) was obtained as a colorless waxy solid after chromatography, on deactivated silica, with ethyl acetate in hexanes (30% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.16 (d, $J = 1.7$ Hz, 1H), 7.91 (d, $J = 8.6$ Hz, 1H), 7.87 (d, $J = 1.7$ Hz, 1H), 7.60 (d, $J = 8.5$ Hz, 1H), 7.49 (m,

2H), 7.22 (d, $J = 1.7$ Hz, 2H), 7.19 (m, 2H), 7.02 (d, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 1.43 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (CD_3CN , 150 MHz, 298 K): δ 156.10, 155.56, 151.70, 151.66, 149.54, 149.36, 149.29, 145.02, 142.79, 136.06, 134.19, 128.31, 128.24, 125.50, 125.44, 123.42, 123.39, 123.26, 122.03, 118.68, 117.49, 117.29, 114.00, 111.94, 86.66, 86.59, 56.60, 56.53, 27.86, 27.83; HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 455.0582, 457.0562 found 455.0598, 457.0614.

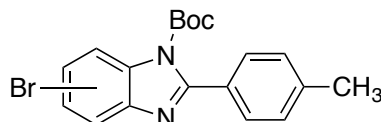
***N*-tert-Butyloxycarbonyl-2-(3,4,5-trimethoxyphenyl)-5-bromobenzimidazole (14d):**



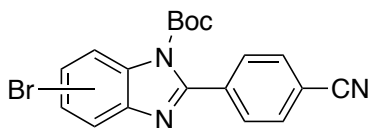
A nearly equal mixture of two regioisomers (0.95 mmol scale, 0.399 g, 90.3%) was obtained as a colorless waxy solid after chromatography, on deactivated silica, with ethyl acetate in hexanes (30% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.21 (d, $J = 1.7$ Hz, 1H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 1.7$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.53 (dd, $J = 8.5$ Hz, $J = 1.9$ Hz, 1H), 7.53 (dd, $J = 8.5$ Hz, $J = 1.9$ Hz, 1H), 6.90 (s, 4H), 3.83 (s, 12H), 3.78 (s, 6H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (CD_3CN , 150 MHz, 298 K): δ 155.91, 155.40, 154.05, 154.03, 149.23, 149.21, 144.93, 142.74, 140.45, 136.03, 134.13, 128.88, 128.79, 128.63, 128.44, 123.46, 122.28, 118.79, 117.62, 117.39, 108.08, 108.07, 86.65, 86.56, 61.12, 61.10, 57.06, 57.04, 27.87, 27.87; HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{23}\text{BrN}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 485.0688, 487.0668 found 485.0690, 487.0647.

***N*-tert-Butyloxycarbonyl-2-(4-*tert*-butylphenyl)-5-bromobenzimidazole (14e):**

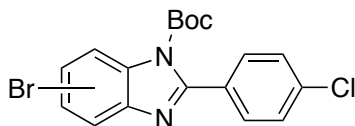
A nearly equal mixture of two regioisomers (1.7 mmol scale, 0.472 g, 81.1%) was obtained as a colorless waxy solid after chromatography, on deactivated silica, with ethyl acetate in hexanes (2% v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 8.25 (d, $J = 1.9$ Hz, 1H), 7.93 (d, $J = 8.9$ Hz, 1H), 7.91 (d, $J = 1.9$ Hz, 1H), 7.63 (d, $J = 8.9$ Hz, 1H), 7.55 (d, $J = 8.3$ Hz, 4H), 7.49 (d, $J = 8.3$ Hz, 4H), 7.49 (m, 2H), 1.39 (s, 9H), 1.37 (s, 9H).

***N*-tert-Butyloxycarbonyl-2-(4-methylphenyl)-5-bromobenzimidazole (14f):**

A nearly equal mixture of two regioisomers (4.8 mmol scale, 1.71 g, 92.0%) was obtained as a colorless foam after chromatography, on deactivated silica, with ethyl acetate in hexanes (10% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.16 (d, $J = 1.7$ Hz, 1H), 7.91 (d, $J = 8.7$ Hz, 1H), 7.87 (d, $J = 1.7$ Hz, 1H), 7.60 (d, $J = 8.7$ Hz, 6H), 7.50 (m, 4H), 7.30 (d, $J = 8.0$ Hz, 1H), 2.41 (s, 6H), 1.40 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (CD_3CN , 75 MHz, 298 K): δ 156.30, 155.76, 149.35, 149.29, 145.13, 142.90, 141.10, 141.05, 136.10, 134.23, 130.39, 130.33, 130.31, 129.51, 128.45, 128.31, 123.41, 122.18, 118.78, 117.55, 117.39, 86.87, 86.79, 27.84, 27.81, 21.54; HRMS (EI^+): calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_2$ $[\text{M}-\text{Br} + \text{Na}]^+$ 331.1422 found 331.1421.

***N*-tert-Butyloxycarbonyl-2-(4-cyanophenyl)-5-bromobenzimidazole (14h):**

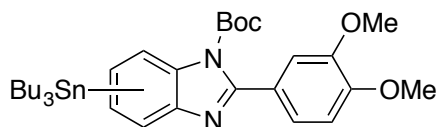
A nearly equal mixture of two regioisomers (1.6 mmol scale, 0.435 g, 86.2%) was obtained as a colorless waxy solid after chromatography, on deactivated silica, with ethyl acetate in hexanes (2% v/v): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 8.25 (d, $J = 1.9$ Hz, 1H), 7.95 (d, $J = 1.9$ Hz, 1H), 7.93 (d, $J = 8.7$ Hz, 1H), 7.79 (d, $J = 8.7$ Hz, 4H), 7.77 (d, $J = 8.7$ Hz, 4H), 7.55 (dd, $J = 8.7$ Hz, $J = 1.9$ Hz, 1H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.54 (dd, $J = 8.5$ Hz, $J = 1.9$ Hz, 1H), 1.47 (s, 9H), 1.47 (s, 9H).

***N*-tert-Butyloxycarbonyl-2-(4-chlorophenyl)-5-bromobenzimidazole (14k):**

A nearly equal mixture of two regioisomers (5.7 mmol scale, 2.13 g, 92.3%) was obtained as a colorless oily solid after chromatography, on deactivated silica, with dichloromethane: ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.20 (d, $J = 2.0$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 2.0$ Hz, 1H), 7.62 (m, 5H), 7.52 (m, 6H), 1.41 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (CD_3CN , 126 MHz, 298 K): δ 154.87, 154.33, 149.07, 149.01, 144.97, 142.76, 136.25, 136.20, 136.01, 134.14, 132.15, 132.12, 132.08, 132.07, 129.03, 128.77, 128.44, 123.55, 122.31, 118.92, 118.67, 117.67, 117.56, 87.12, 87.04, 27.81, 27.78.

General procedure for stannylation of *N*-*tert*-butyloxycarbonyl-2-aryl-5-bromobenzimidazoles (15a–f): *N*-*tert*-Butyloxycarbonyl-2-aryl-5-bromobenzimidazole was transferred to a 50 mL Schlenk storage tube. In a glovebox, charged with N₂, bis(dibenzylideneacetone)palladium(0) (5 mol%) and tris(*tert*-butyl)phosphine (40 mol%) were suspended in a small portion of dry benzene (~1–5 mL). This mixture was added to the storage tube by pipet. By syringe, bis(tributyltin) (300 mol%), distilled under vacuum, was added to the storage tube. The mixture was diluted with more benzene to approximately 0.1 M. The tube was sealed, and heated to 110 °C for 24–48 hours (to monitor reaction progress, a 16 μmol reaction, using 0.6 mL benzene-d₆, was set up in an NMR tube fitted with a Teflon screw cap closure). Benzene was removed *in vacuo* and the crude oil was purified by column chromatography on silica, deactivated with triethylamine in hexanes (5% v/v), using the indicated solvents.

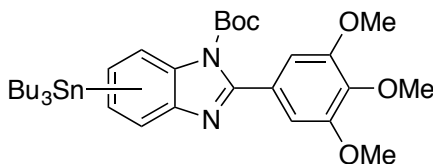
***N*-*tert*-Butyloxycarbonyl-2-(3,4-dimethoxyphenyl)-5-(tributylstannyl)-benzimidazole (15c):**



A mixture of two regioisomers (1.4 mmol scale, 0.400 g, 43.4%) was obtained as a pale yellow viscous oil after chromatography, on deactivated silica, with a gradient from hexanes (100%) to ethyl acetate in hexanes (20% v/v), run twice successively: ¹H NMR (CD₃CN, 400 MHz, 298 K): δ 8.11 (s, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.80 (s, 1H), 7.67

(d, $J = 7.4$ Hz, 1H), 7.46 (m, 2H), 7.23 (m, 3H), 7.19 (dd, $J = 4.5$ Hz, $J = 2.0$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 3.87 (s, 6H), 3.83 (s, 6H), 1.59 (m, 12H), 1.49 (s, 9H), 1.44 (s, 9H), 1.34 (m, 12H), 1.13 (m, 12H), 0.88 (m, 18H); ^{13}C NMR (CD_3CN , 100 MHz, 298 K): δ 154.43, 151.47, 151.43, 149.86, 149.77, 149.48, 143.94, 143.86, 138.80, 137.64, 135.09, 133.29, 132.77, 128.46, 126.14, 125.97, 123.37, 123.33, 122.96, 120.25, 115.44, 114.06, 111.87, 86.03, 85.97, 56.58, 56.52, 29.94, 28.11, 28.09, 28.06, 27.94, 14.03, 10.48, 10.35.

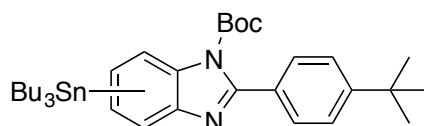
***N*-tert-Butyloxycarbonyl-2-(3,4,5-trimethoxyphenyl)-5-(tributylstannyl)-benzimidazole (15d):**



A mixture of two regioisomers (1.5 mmol scale, 0.501 g, 50.0%) was obtained as a pale yellow sticky solid after chromatography, on deactivated silica, with a gradient from hexanes (100%) to ethyl acetate in hexanes (10% v/v), run twice successively: ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.14 (s, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.82 (s, 1H), 7.68 (d, $J = 7.9$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 6.92 (s, 2H), 6.91 (s, 2H), 3.83 (s, 12H), 3.79 (s, 6H), 1.58 (m, 12H), 1.47 (s, 9H), 1.42 (s, 9H), 1.35 (m, 12H), 1.14 (m, 12H), 0.88 (m, 18H); ^{13}C NMR (CD_3CN , 150 MHz, 298 K): δ 154.13, 153.90, 149.64, 143.76, 140.19, 139.12, 137.79, 134.95, 133.45, 132.79, 129.38, 129.19, 128.52, 122.90, 120.30, 115.39, 108.07, 85.96, 61.02, 56.95, 29.88, 28.05, 28.02, 27.97,

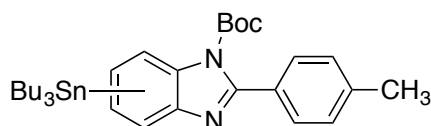
27.87, 13.96, 10.46, 10.32; HRMS (ESI): calcd. for $C_{33}H_{50}N_2NaO_5Sn$ $[M+Na]^+$ 697.2639 found 697.2625.

***N*-tert-Butyloxycarbonyl-2-(4-*tert*-butylphenyl)-5-(tributylstannyl)-benzimidazole (15e):**



A mixture of two regioisomers (0.27 mmol scale, 0.0914 g, 52.3%) was obtained as a pale yellow viscous oil after chromatography, on deactivated silica, with a gradient from hexanes (100%) to ethyl acetate in hexanes (15% v/v): 1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.13 (s, 1H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.81 (s, 1H), 7.67 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 4H), 7.51 (d, $J = 8.4$ Hz, 4H), 7.46 (m, 2H), 1.58 (m, 12H), 1.44 (s, 9H), 1.35 (s, 18H), 1.33 (m, 12H), 1.13 (m, 12H), 0.88 (m, 18H).

***N*-tert-Butyloxycarbonyl-2-(4-methylphenyl)-5-(tributylstannyl)-benzimidazole (15f):**

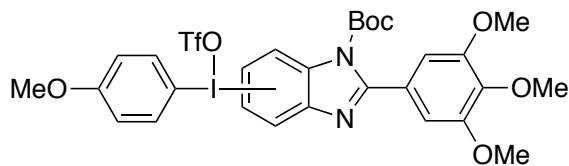


A mixture of two regioisomers (4.4 mmol scale, 1.37 g, 51.7%) was obtained as a pale yellow viscous oil after chromatography, on deactivated silica, with a gradient from hexanes (100%) to ethyl acetate in hexanes (10% v/v): 1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.12 (s, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.81 (s, 1H), 7.67 (d, $J = 7.1$ Hz, 1H), 7.52

(m, 4H), 7.46 (dd, $J = 11.0$ Hz, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 4H), 2.41 (s, 6H),
1.57 (m, 12H), 1.47 (s, 9H), 1.42 (s, 9H), 1.34 (m, 12H), 1.13 (m, 12H), 0.88 (m, 18H);
 ^{13}C NMR (CD_3CN , 100 MHz, 298 K): δ 154.59, 154.56, 149.80, 149.72, 144.02, 143.94,
140.72, 140.67, 138.92, 137.66, 135.06, 133.37, 132.77, 130.96, 130.84, 130.35, 130.33,
129.42, 128.55, 123.04, 120.33, 115.49, 86.15, 86.11, 29.95, 28.13, 28.10, 28.00, 27.88,
21.51, 14.05, 10.49, 10.36.

General procedure for diaryl iodonium salt formation from *N*-*tert*-butyloxycarbonyl-2-aryl-5-tributylstannylbenzimidazoles (16d–f): In a nitrogen-charged glove box, the appropriate aryl tin compound (1.05 eq.) and bis(acetoxy)-4-methoxybenzene (1 eq.) were dissolved in minimal dry acetonitrile in a glass vial. In another glass vial, trimethylsilyl trifluoromethanesulfonate (1 eq.) was dissolved in approximately 0.4x the previous volume of acetonitrile. The trimethylsilyl trifluoromethanesulfonate solution was added, dropwise, over the course of 5 minutes to the first vial, with stirring. The solution was removed from the glove box, and solvent was removed *in vacuo*. The crude oil was dissolved in minimal dichloromethane and added to 30x the volume of a solution of ether in pentane (10% v/v). A sticky yellow solid immediately precipitated. The mixture was allowed to stand for 15 minutes before being vacuum filtered through a 0.2 μm PTFE membrane filter. The product was further purified, using the indicated method.

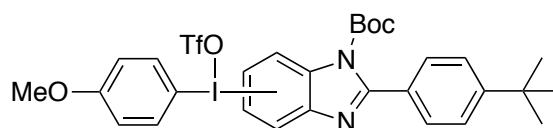
(*N*-*tert*-Butyloxycarbonyl-2-(3,4,5-trimethoxyphenyl)-5-benzimidazolyl)(4-methoxyphenyl)iodonium triflate (16d):



A mixture of two regioisomers (0.445 mmol scale, 0.282 g, 81.0%) was obtained as yellow powder after dissolving in minimal dichloromethane, diluting with pentane to the cloud point, adding more dichloromethane to bring back into solution, and pouring into a stirring solution of ether in pentane (10% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ

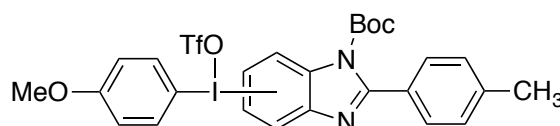
8.76 (d, $J = 1.8$ Hz, 1H), 8.48 (d, $J = 1.8$ Hz, 1H), 8.17 (d, $J = 8.7$ Hz, 1H), 8.06 (d, $J = 9.2$ Hz, 4H), 8.02 (dd, $J = 8.7$ Hz, $J = 1.8$ Hz, 2H), 7.85 (d, $J = 8.7$ Hz, 1H), 7.43 (s, 2H), 7.07 (d, $J = 9.2$ Hz, 4H), 6.90 (s, 2H), 3.84 (s, 6H), 3.82 (s, 12H), 3.78 (s, 6H), 1.40 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CD_3CN , 400 MHz, 298 K): δ -79.30 (s, OTf); HRMS (ESI): calcd. for $\text{C}_{28}\text{H}_{30}\text{IN}_2\text{O}_6$ $[\text{M-OTf}]^+$ 617.1149 found 617.1178.

(*N*-*tert*-Butyloxycarbonyl-2-(4-*tert*-butylphenyl)-5-benzimidazolyl)(4-methoxyphenyl)iodonium triflate (16e):



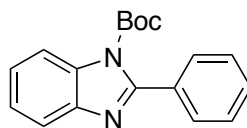
A mixture of two regioisomers (0.252 mmol scale, 0.060 g, 32.3%) was obtained as an off-white solid after dissolving in minimal dichloromethane, diluting with pentane to the cloud point, adding more dichloromethane to bring back into solution, and pouring into a stirring solution of ether in pentane (10% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.75 (s, 1H), 8.47 (s, 1H), 8.16 (d, $J = 8.6$ Hz, 2H), 8.12–7.93 (m, 6H), 7.82 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 9.1$ Hz, 4H), 7.50 (d, $J = 9.1$ Hz, 4H), 6.95 (d, $J = 9.0$ Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 1.39 (s, 36H); ^{19}F NMR (CD_3CN , 400 MHz, 298 K): δ -79.30 (s, OTf).

(*N*-*tert*-Butyloxycarbonyl-2-(4-methylphenyl)-5-benzimidazolyl)(4-methoxyphenyl)iodonium triflate (16f):



A mixture of two regioisomers (0.427 mmol scale, 0.149 g, 46.1%) was obtained as an off-white solid after recrystallization by layering pentane onto a solution of dichloromethane/ethyl acetate (1:1 v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): 8.72 (d, $J = 1.9$ Hz, 1H), 8.47 (d, $J = 1.9$ Hz, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 8.05 (d, $J = 9.0$ Hz, 4H), 8.01 (dd, $J = 8.7$ Hz, $J = 1.9$ Hz, 2H), 7.83 (d, $J = 8.7$ Hz, 1H), 7.53 (d, $J = 9.2$ Hz, 2H), 7.52 (d, $J = 9.2$ Hz, 2H), 7.33 (d, $J = 9.0$ Hz, 4H), 7.06 (d, $J = 9.2$ Hz, 2H), 7.05 (d, $J = 9.2$ Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 1.39 (s, 9H), 1.38 (s, 9H); ^{19}F NMR (CD_3CN , 400 MHz, 298 K): δ -79.30 (s, OTf); HRMS (ESI): calcd. for $\text{C}_{26}\text{H}_{26}\text{IN}_2\text{O}_3$ [M-OTf] $^+$ 541.0988 found 541.1009.

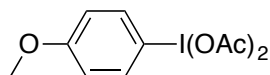
***N*-*tert*-Butyloxycarbonyl-2-phenylbenzimidazole (17):**



In a 100 mL round-bottom flask with a stirbar, 2-phenylbenzimidazole (0.500 g, 2.57 mmol) was suspended in acetonitrile (20 mL; dried over 3Å molecular sieves) with triethylamine (1.4 mL, 10.28 mmol; dried over potassium hydroxide). *N,N*-dimethylaminopyridine (0.063 g, 0.771 mmol) was added in portions. Di-*tert*-butyl

dicarbonate (1.124 g, 5.14 mmol) was added slowly, in portions. The mixture was stirred, under N₂, for 12–24 hours. Solvent was removed *in vacuo* and the resulting oil was diluted with dichloromethane. The mixture was washed twice with a mixture of saturated aqueous ammonium chloride and brine (1:1 v/v). The organic layer was dried over sodium sulfate and solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica, deactivated with triethylamine in hexanes (5% v/v), using ethyl acetate in dichloromethane (1% v/v), to yield a waxy colorless solid (0.728 g, 96.2%): ¹H NMR (CD₃CN, 400 MHz, 298 K): 8.05 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.68–7.56 (m, 2H), 7.56–7.45 (m, 3H), 7.45–7.32 (m, 2H), 1.38 (s, 9H).

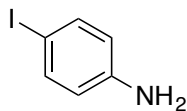
Bis(acetoxy)iodoanisole (18):



4-Iodoanisole (2.34 g, 10.0 mmol) was dissolved in 90 mL of glacial acetic acid and heated to 40 °C with stirring. Sodium perborate tetrahydrate (13.6 g, 110.0 mmol) was added in portions over the course of one hour. After addition, the reaction mixture was heated at 40 °C for 8 h. Once cooled to r.t., the mixture was reduced to approximately half the volume by vacuum distillation. The remaining mixture was mixed with 100 mL deionized water and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate. Solvent was removed *in vacuo*, and the crude oil was triturated with hexanes, using sonication, and filtered. The crude solid was dissolved in a minimal amount of dichloromethane, and dropped into a solution of diethyl ether in pentane (10% v/v). The precipitate was aged for 1 h before being

filtered to yield a colorless powder (2.43 g, 69.2%): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.05 (d, $J = 9.1$ Hz, 2H), 7.05 (d, $J = 9.1$ Hz, 2H), 3.86 (s, 3H), 1.90 (s, 6H); ^{13}C NMR (CD_3CN , 100 MHz, 298 K) δ 177.7, 163.7, 138.7, 118.0, 112.0, 56.8, 20.8; HRMS: (HRFAB) calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_4\text{I}$ $[\text{M}-2\text{OAc}+(3\text{-NBA})]^+$ 385.9889 found 385.9885.

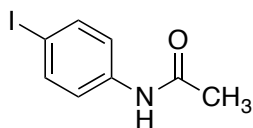
4-Iodoaniline (19):



In a 100 mL round-bottom flask, aniline (2.75 g, 0.030 mol) and sodium bicarbonate (3.75 g, 0.045 mol) were dissolved in water (25 mL). The mixture was cooled to 12–15 °C by the addition of ice. While stirring, iodine (6.35 g, 0.025 mol) was added in several (10–15) portions over the course of 30 min. The mixture was stirred for an additional 30 min until the iodine color had faded significantly. Crude 4-iodoaniline is collected by vacuum filtration and dried *in vacuo*. The crude product was mixed with pet ether (25 mL) in a 100 mL round-bottom flask and brought to reflux while stirring. After 15 minutes the solution was cooled to just below reflux and the liquid was decanted into a beaker. The beaker was cooled to -10 °C in an ice-salt bath and the solution stirred until crystallization was complete. The product was isolated by filtration as colorless needles (0.460 g, 45.8%): ^1H NMR (CDCl_3 , 400 MHz, 298 K): δ 7.41 (d, $J = 8.8$ Hz, 2H), 6.47 (d, $J = 8.8$ Hz, 2H); HRMS (EI^+): calcd. for $\text{C}_6\text{H}_6\text{IN}$ $[\text{M}]^+$ 218.9545 found 218.9546.

Brewster, R. Q. *Org. Synth.* **1931**, *11*, 62.

4-Iodoacetanilide (20):

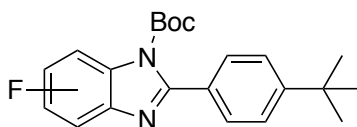


In an oven-dried 100 mL round-bottom flask, 4-iodoaniline (1.00 g, 4.47 mmol) was suspended in acetic anhydride (10 mL), and chilled to 0 °C. Concentrated sulfuric acid (~0.5 mL) was added dropwise. Once the solution became homogenous, the ice bath was removed and the solution was as allowed to warm to room temperature. After 3 hours, the solution was poured over 10 mL ice-water (~1:1). Once the ice had melted, the mixture was filtered. The solid was dried at 110 °C for several hours to yield the product as a nearly colorless solid (1.12 g, 95.0%): ¹H NMR (CDCl₃, 400 MHz, 298 K): δ 7.61 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.24 (br s, NH), 2.16 (s, 3H); HRMS (EI⁺): calcd. for C₈H₈INO [M]⁺ 260.9651 found 260.9649.

General fluorination procedure (22e and 23f): In a nitrogen-charged glove box, the appropriate diaryliodonium triflate (2.0 eq.) was dissolved in 0.5 mL acetonitrile-d₃. In a separate vial a stock solution of tetramethylammonium fluoride (2.5 eq.) was dissolved in 1.0 mL acetonitrile-d₃. A portion of this stock solution (1.0 eq., 0.1 mL) was added to the diaryliodonium salt solution. The mixture was transferred into an NMR tube fitted with a Teflon screw cap closure, sealed, and analyzed by ¹H and ¹⁹F NMR. Solvent was removed *in vacuo* and the tube was returned to the glove box. Benzene-d₆ (0.6 mL) was

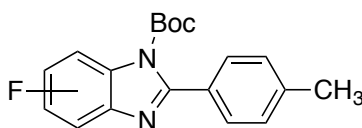
added. The tube was sealed, and heated in the dark until thermolysis was complete by ^1H and ^{19}F NMR. Solvent was removed *in vacuo* and the crude oil was purified by column chromatography on silica, deactivated with triethylamine in hexanes (5% v/v), using the indicated solvents.

***N*-tert-Butyloxycarbonyl-2-(4-*tert*-butylphenyl)-5-fluorobenzimidazole (22e):**



After thermolysis at 140 °C for 30 min, a mixture of two regioisomers (0.005 mmol scale, 37.3% by NMR) was identified by ^1H and ^{19}F NMR, but not isolated: ^1H NMR (C_6D_6 , 400 MHz, 298 K): δ 8.03–7.94 (m, 2H), 7.87 (dd, $J = 9.9$ Hz, $J = 2.2$ Hz, 1H), 7.78 (dd, $J = 9.1$ Hz, $J = 5.3$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 4H), 7.49 (d, $J = 8.0$ Hz, 4H), 7.32 (m, 2H), 1.20 (s, 18H), 1.18 (s, 18H); ^{19}F NMR (C_6D_6 , 400 MHz, 298 K): δ -116.01 (s, 1F), -117.82 (s, 1F).

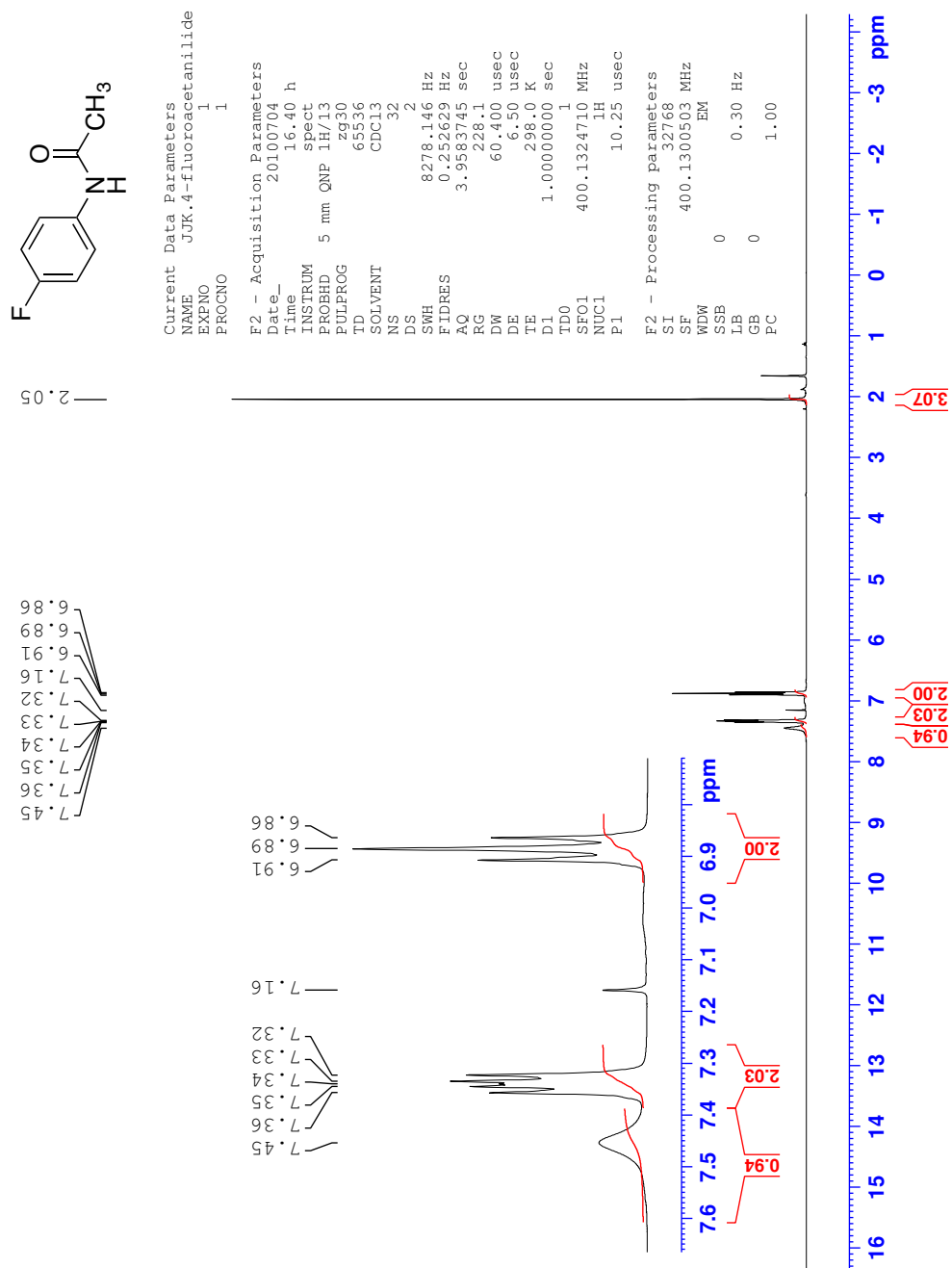
***N*-tert-Butyloxycarbonyl-2-(4-methylphenyl)-5-fluorobenzimidazole (22f):**

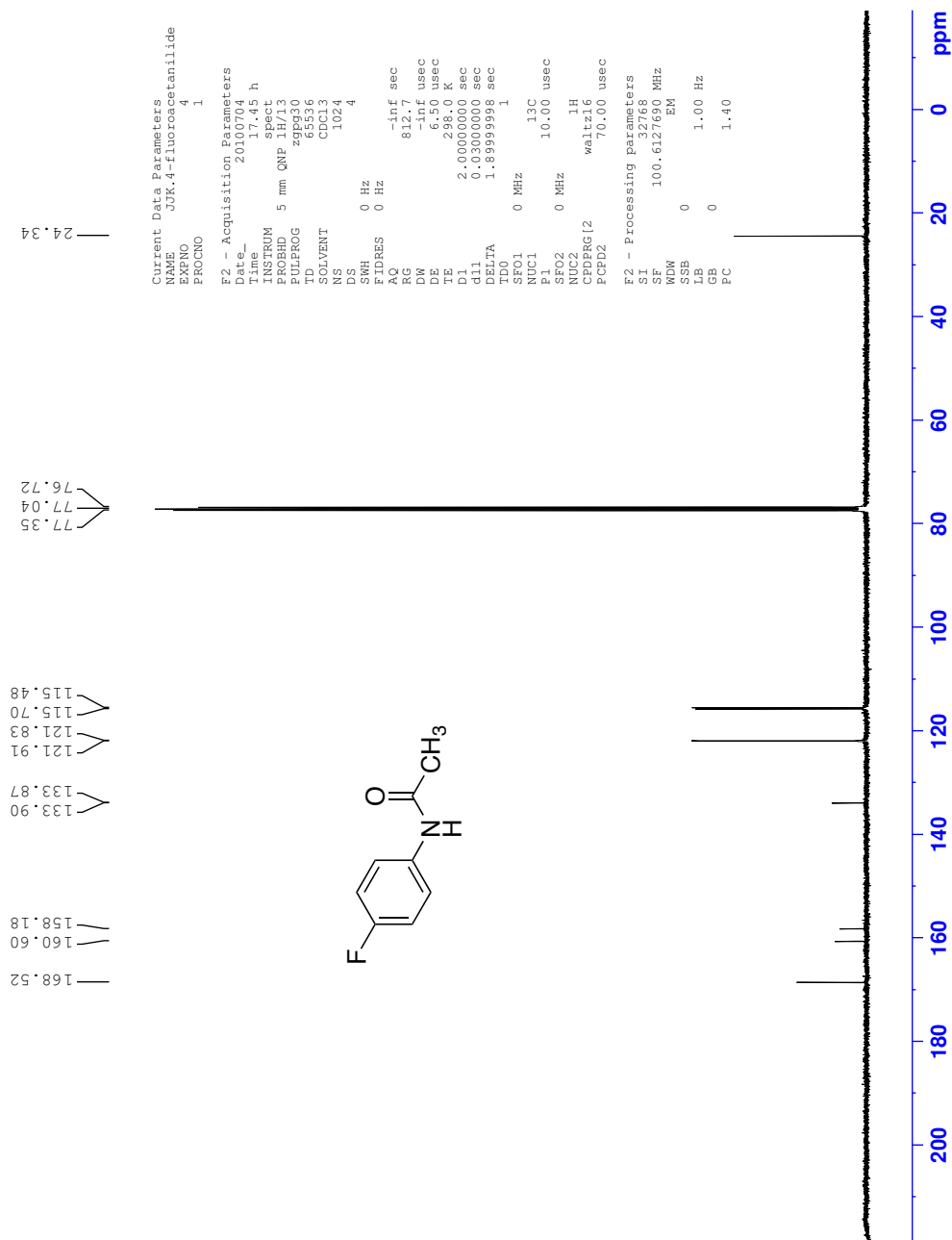


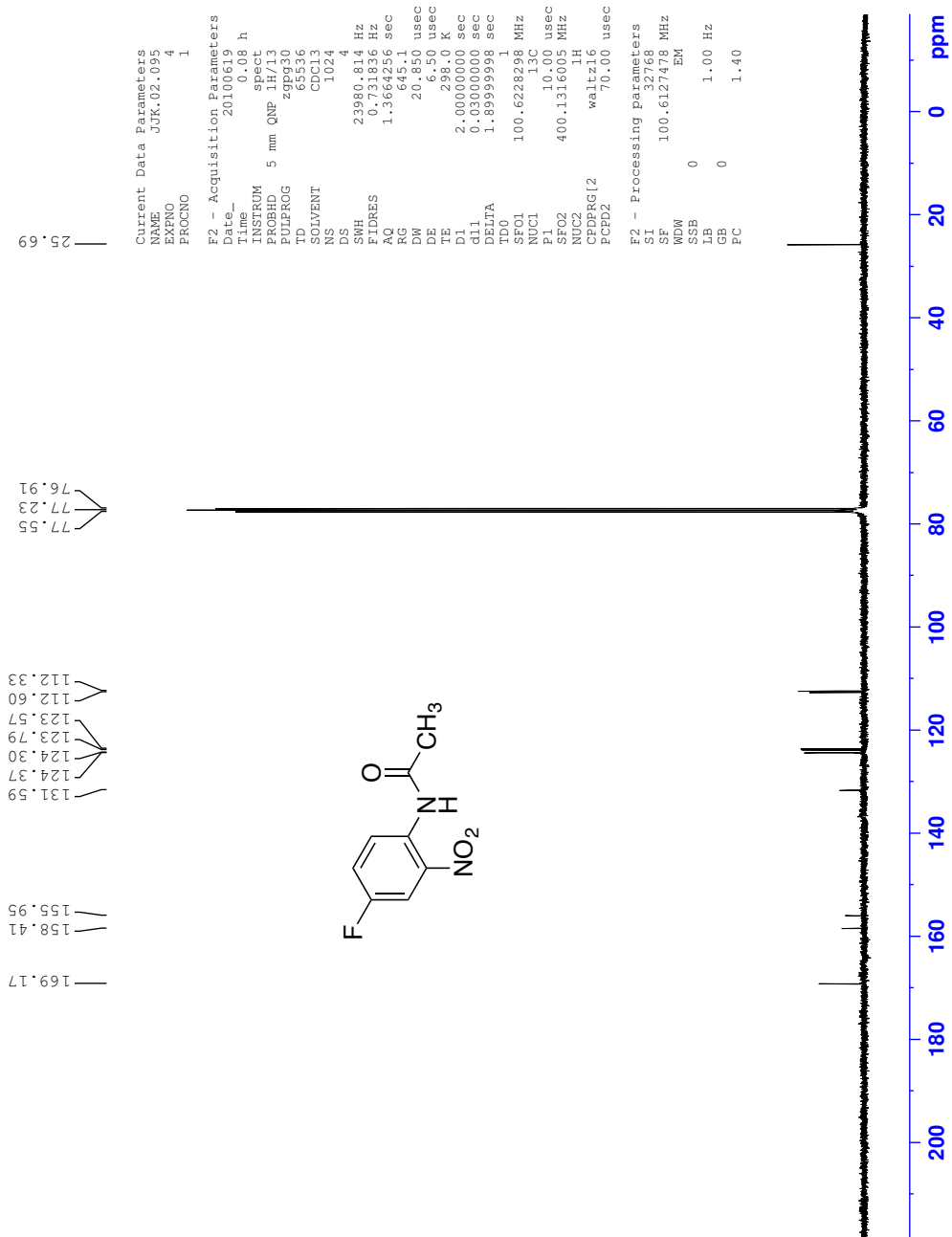
After thermolysis at 80 °C for 2 h, a mixture of two regioisomers (0.025 mmol scale, 4.3 mg, 51.8% isolated) was obtained as a waxy solid after preparative thin-layer chromatography, on deactivated silica, with ethyl acetate in hexanes (12% v/v): ^1H NMR (CD_3CN , 400 MHz, 298 K): δ 8.00 (dd, $J = 8.9$ Hz, $J = 5.1$ Hz, 1H), 7.75 (dd, $J = 9.7$ Hz,

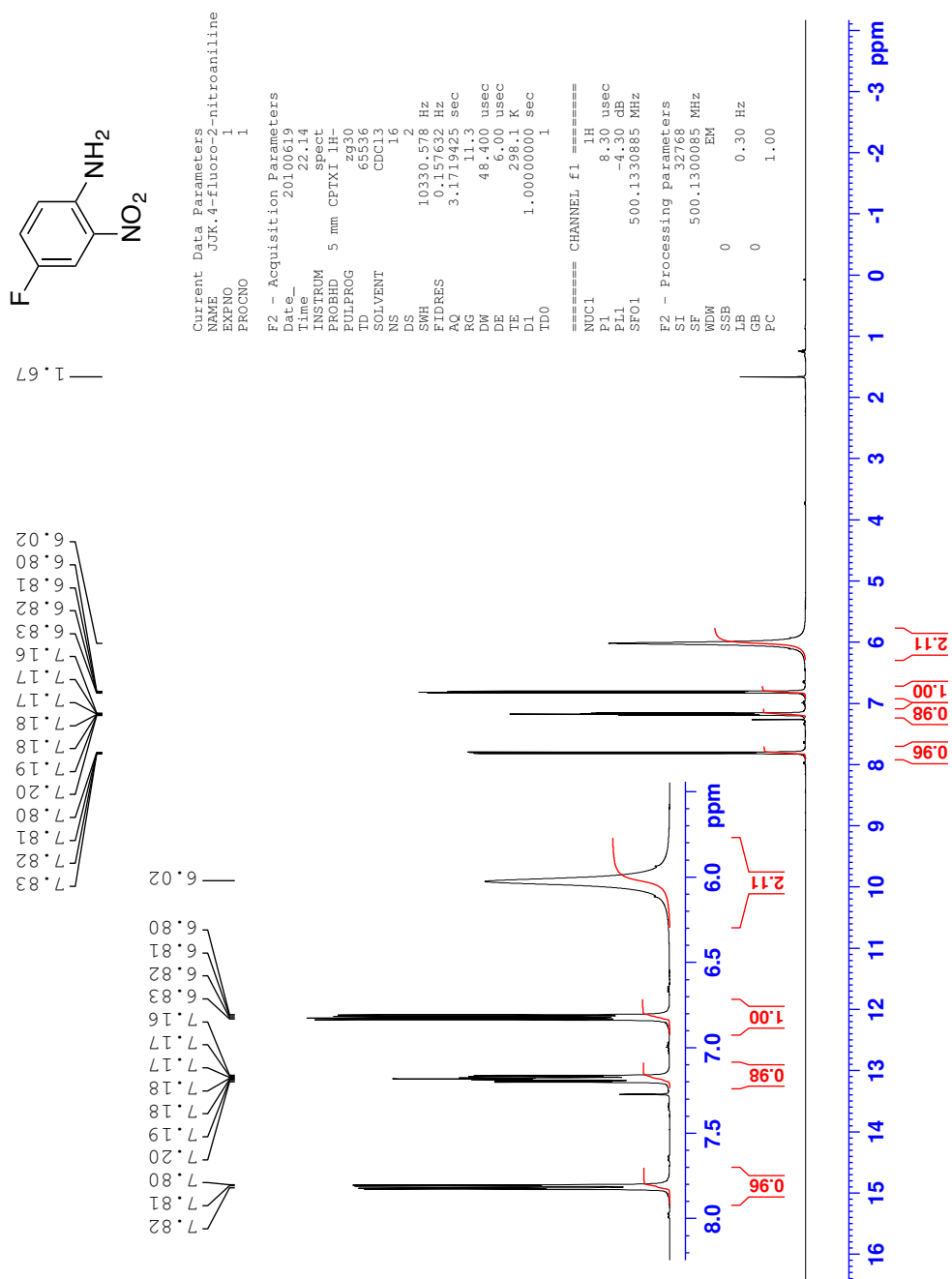
$J = 2.7$ Hz, 1H), 7.68 (dd, $J = 8.9$ Hz, $J = 5.1$ Hz, 1H), 7.51 (d, $J = 7.9$ Hz, 4H), 7.44 (dd, $J = 9.7$ Hz, $J = 2.7$ Hz, 1H), 7.31 (d, $J = 7.9$ Hz, 4H), 7.17 (ddd, $J = 18.6$ Hz, $J = 9.7$ Hz, $J = 2.7$ Hz, 2H), 2.42 (s, 6H), 1.41 (s, 18H); ^{19}F NMR (CD_3CN , 400 MHz, 298 K): δ -116.10 (s, 1F), -117.13 (s, 1F); HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{12}\text{FN}_2$ $[\text{M-Boc}+2\text{H}]^+$ 227.0985 found 227.1100.

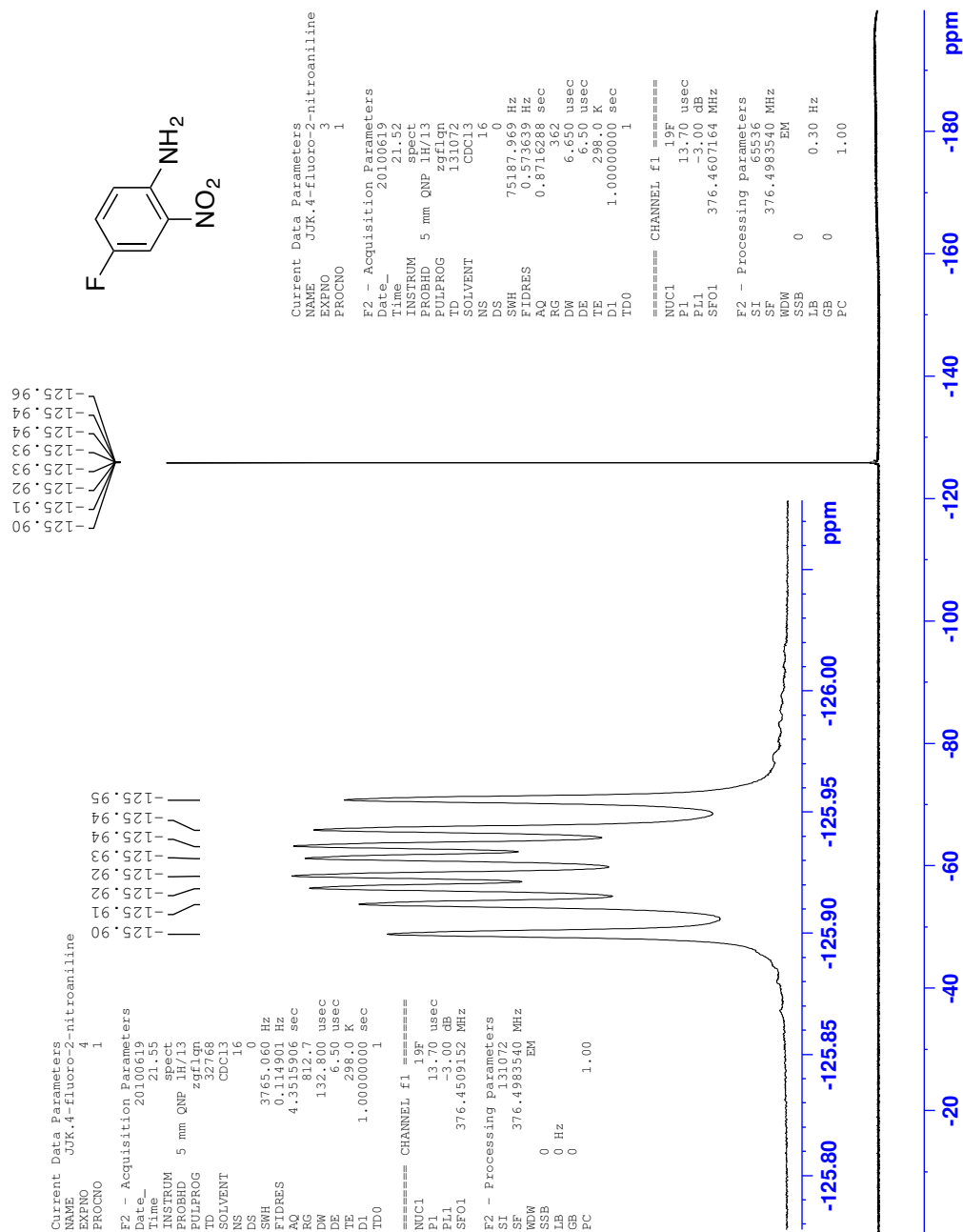
3.6 NMR Spectra

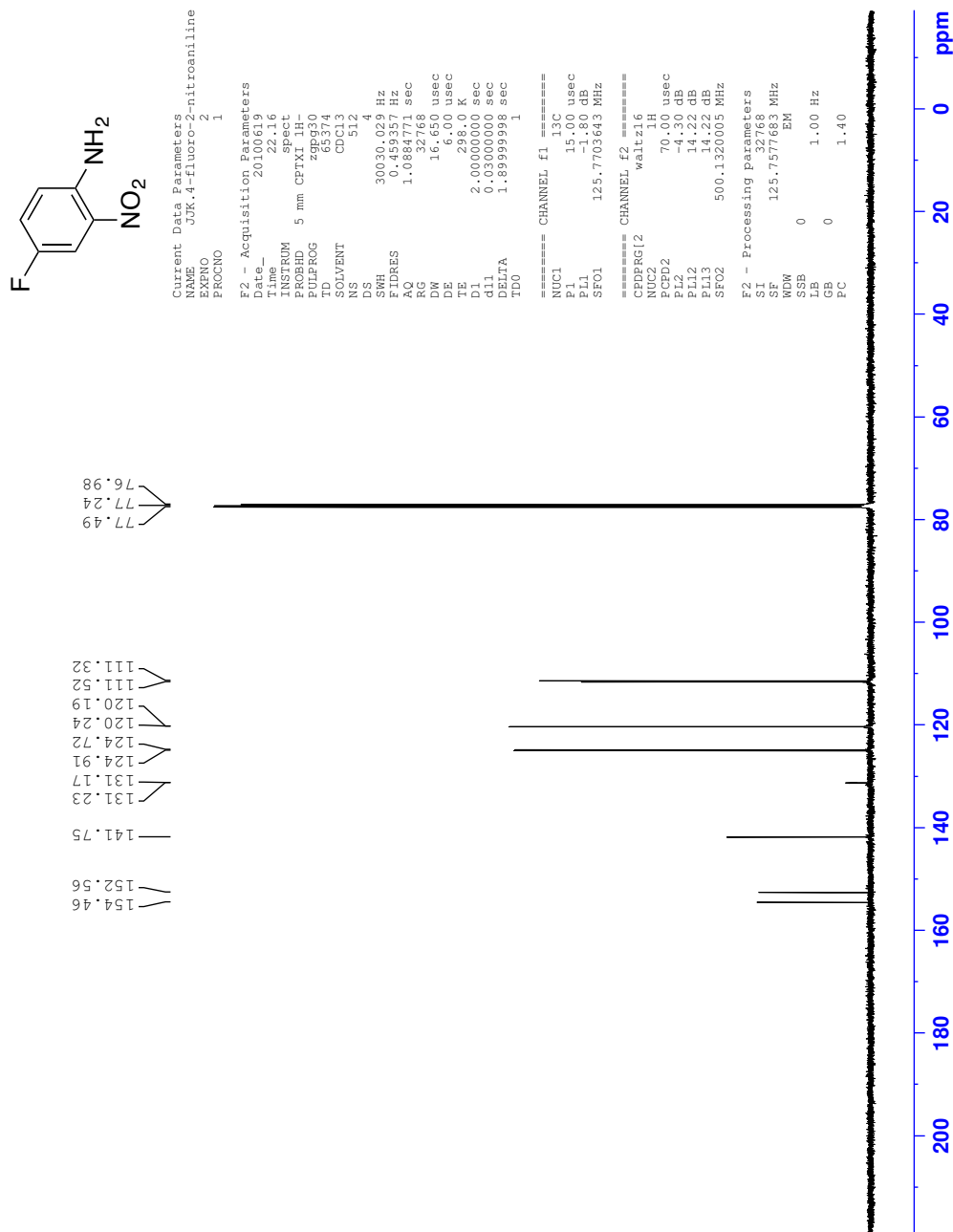
 ^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of 4-fluoroacetanilide (**1**)

^{13}C NMR (CDCl_3 , 100 MHz, 298 K) spectrum of 4-fluoroacetanilide (1)

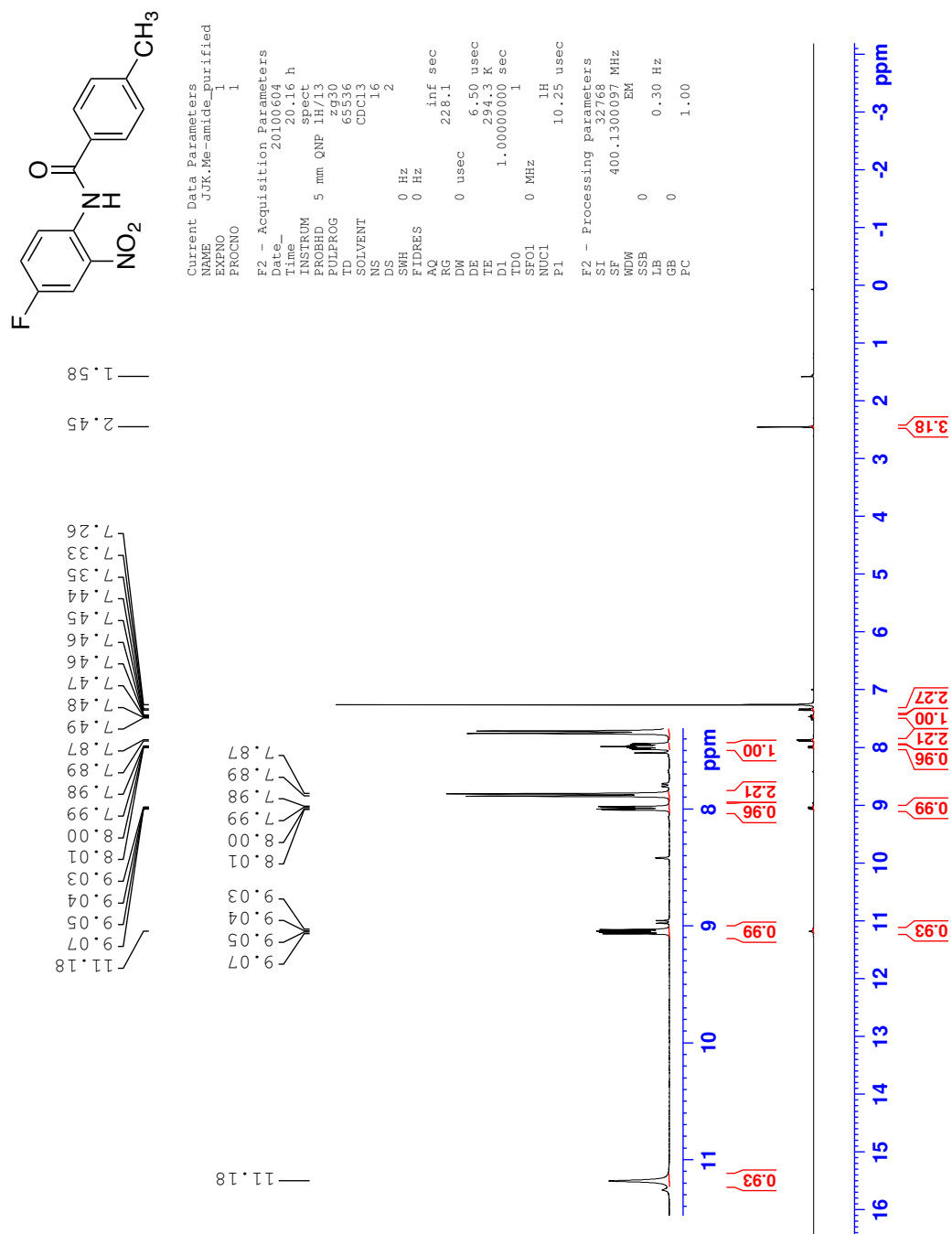
^{13}C NMR (CDCl_3 , 100 MHz, 298 K) spectrum of 4-fluoro-2-nitroacetanilide (2)

^1H NMR (CDCl_3 , 500 MHz, 298 K) spectrum of 4-fluoro-2-nitroaniline (3)

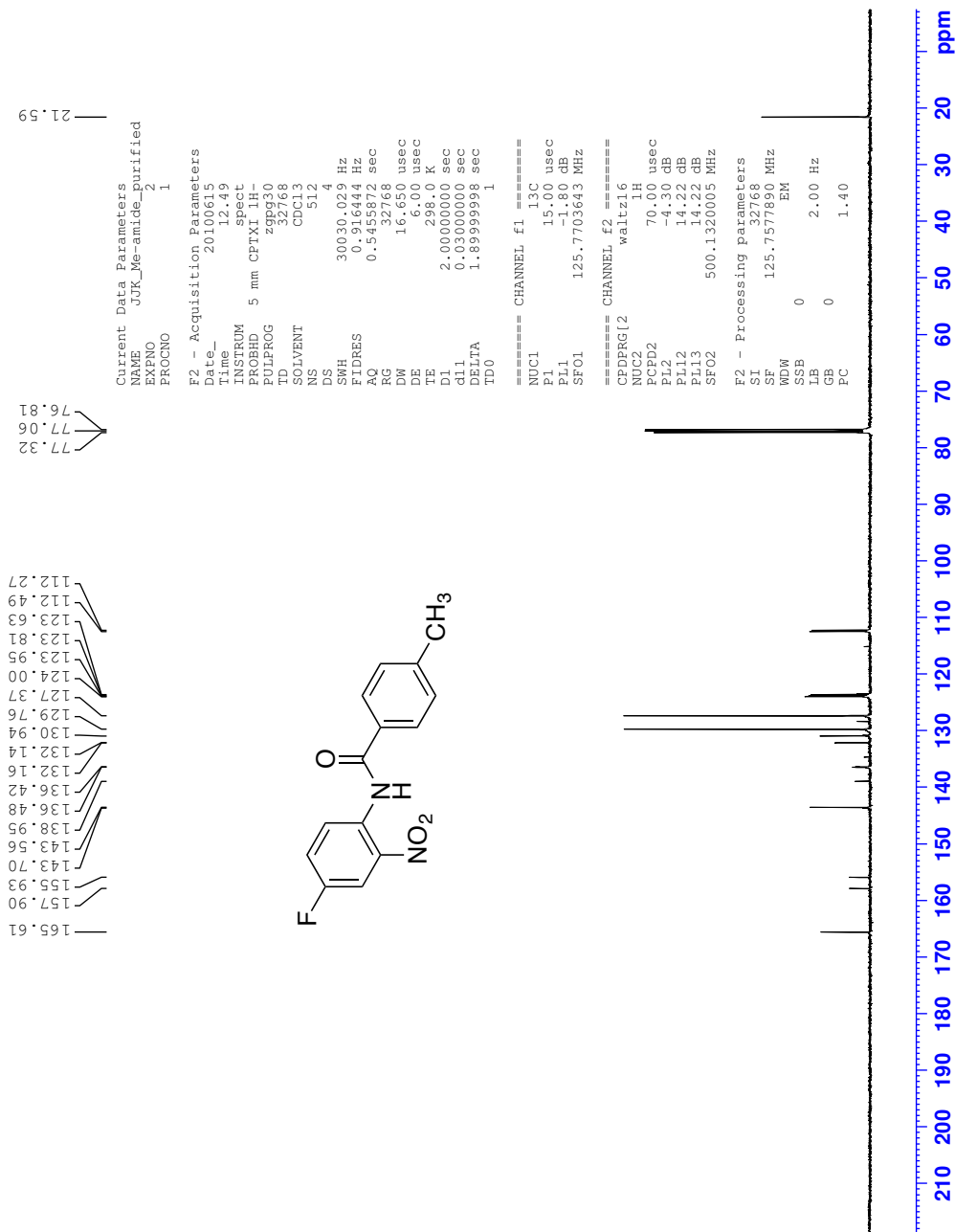
¹⁹F NMR (CDCl₃, 376 MHz, 298 K) spectrum of 4-fluoro-2-nitroaniline (**3**)

¹³C NMR (CDCl₃, 126 MHz, 298 K) spectrum of 4-fluoro-2-nitroaniline (3)

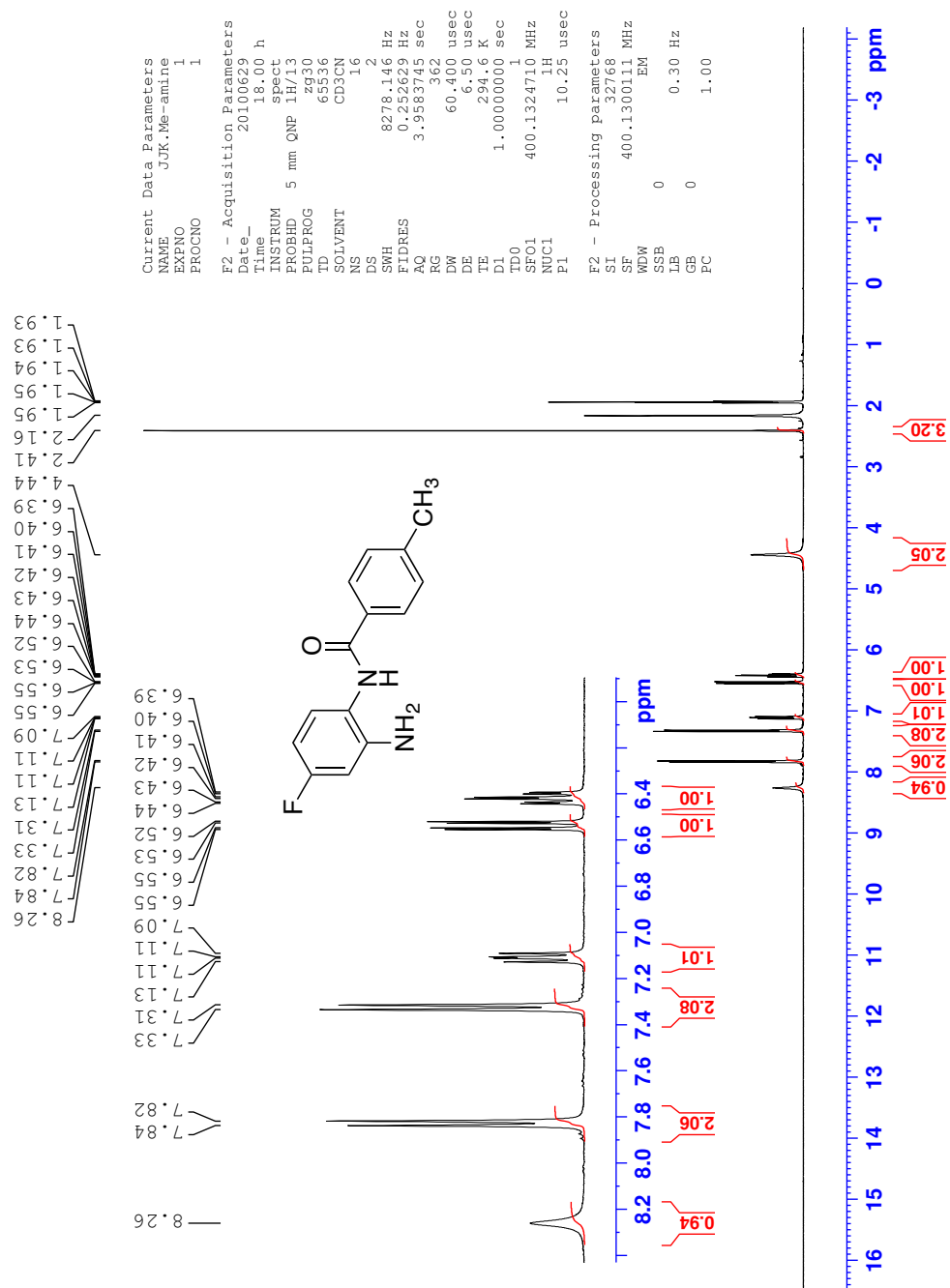
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of *N*-(4-methylbenzoyl)-4-fluoro-2-nitroaniline (**5f**)



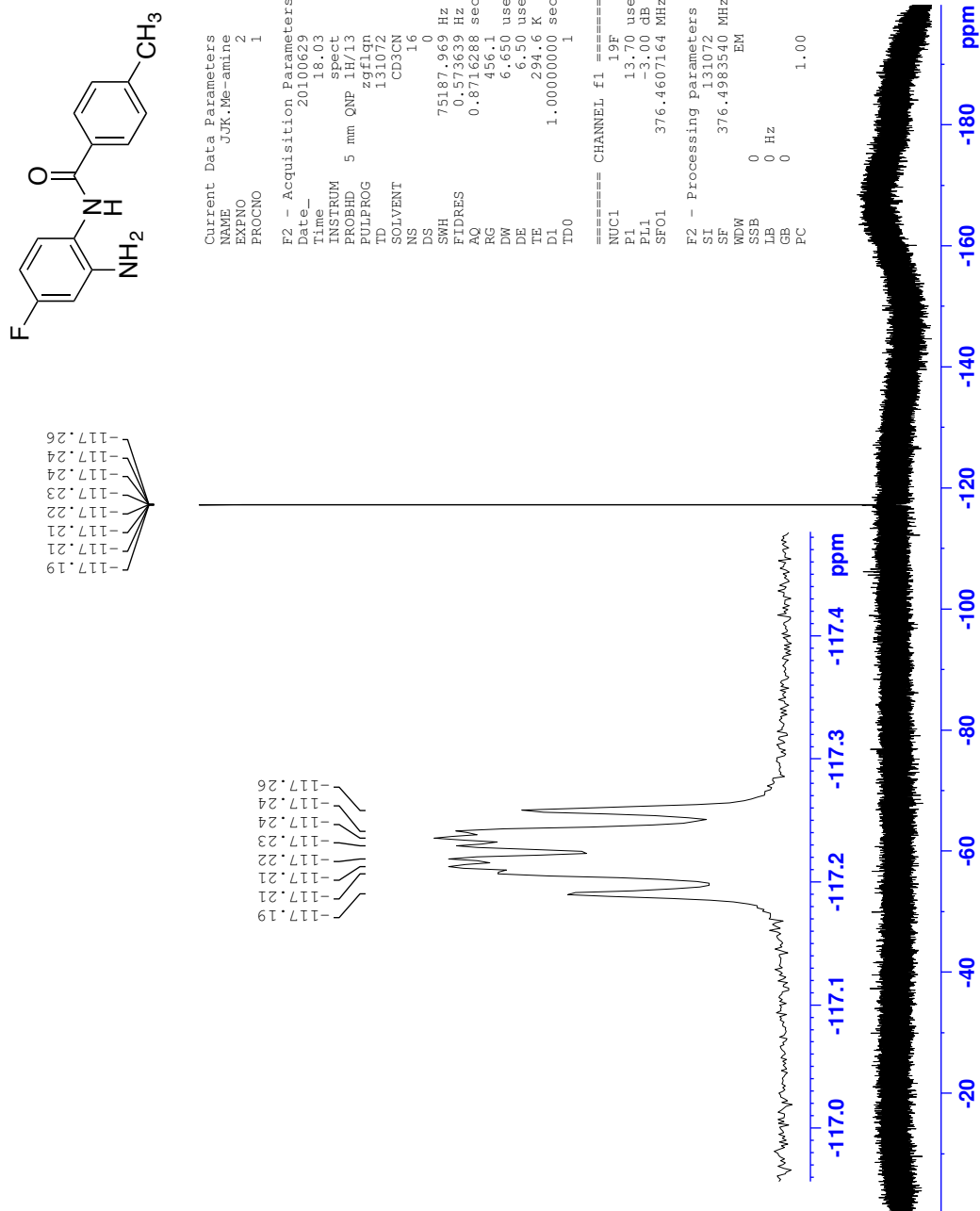
^{13}C NMR (CDCl_3 , 126 MHz, 298 K) spectrum of *N*-(4-methylbenzoyl)-4-fluoro-2-nitroaniline (**5f**)



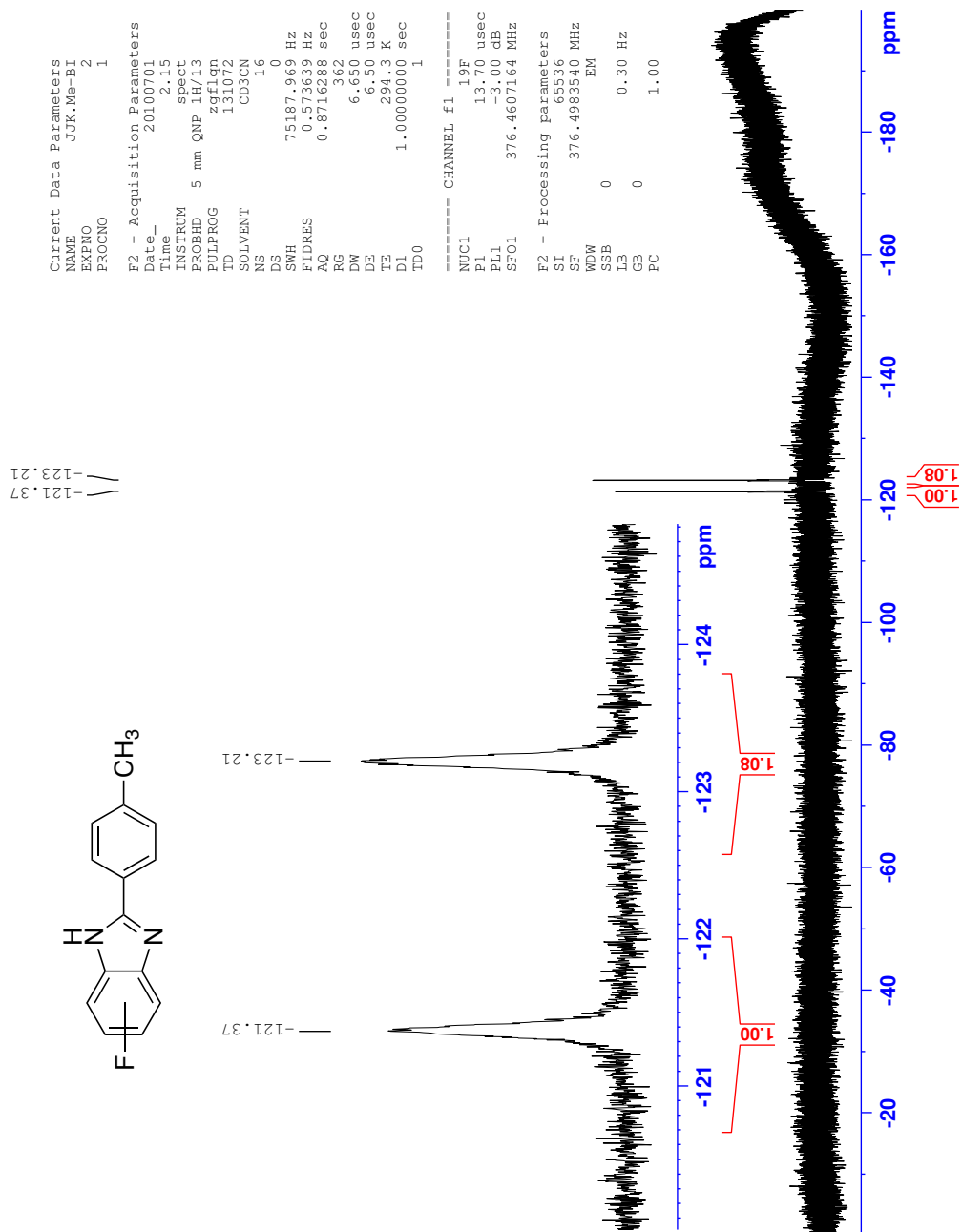
^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of *N*-(4-methylbenzoyl)-4-fluoro-2-aminoaniline (**6f**)

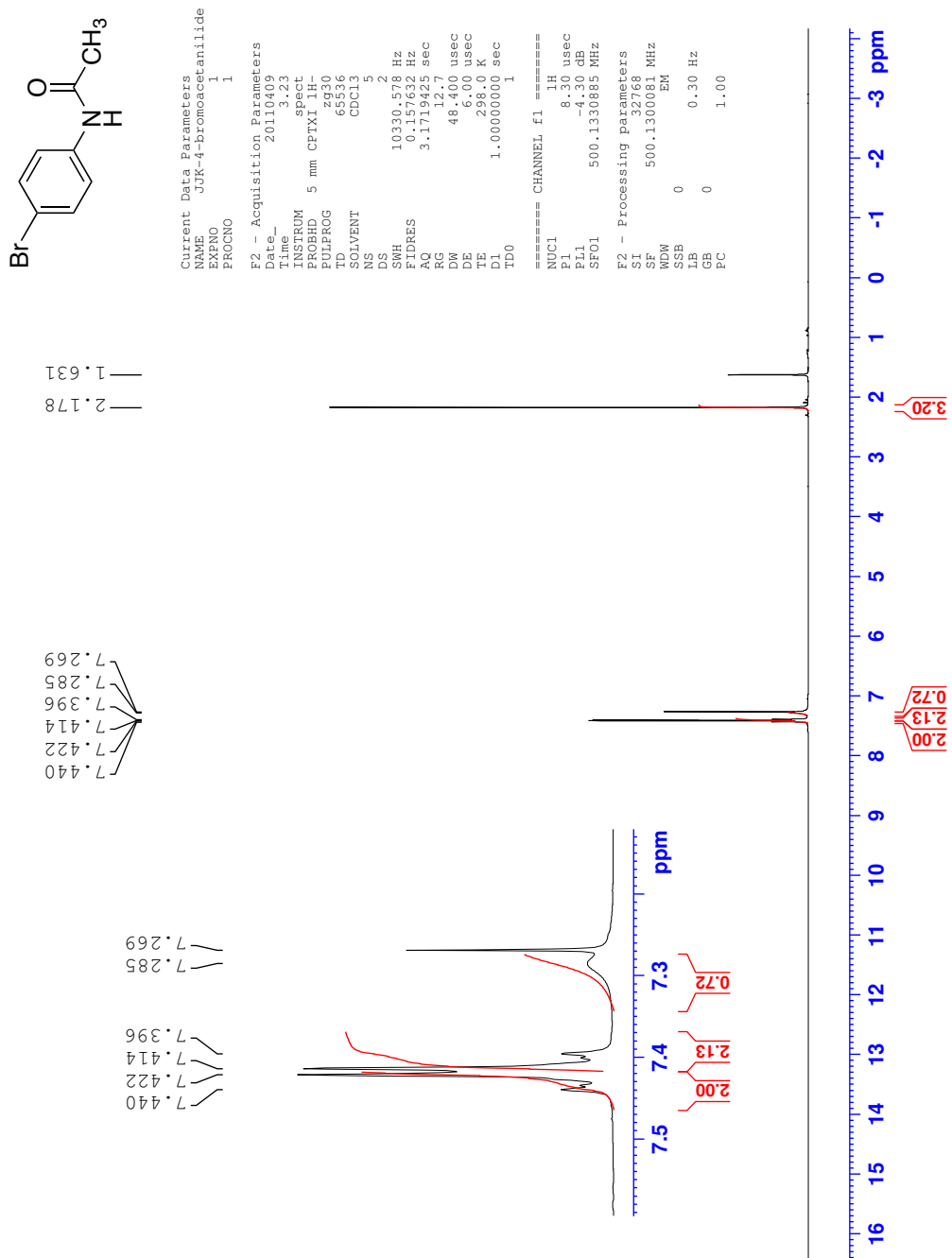


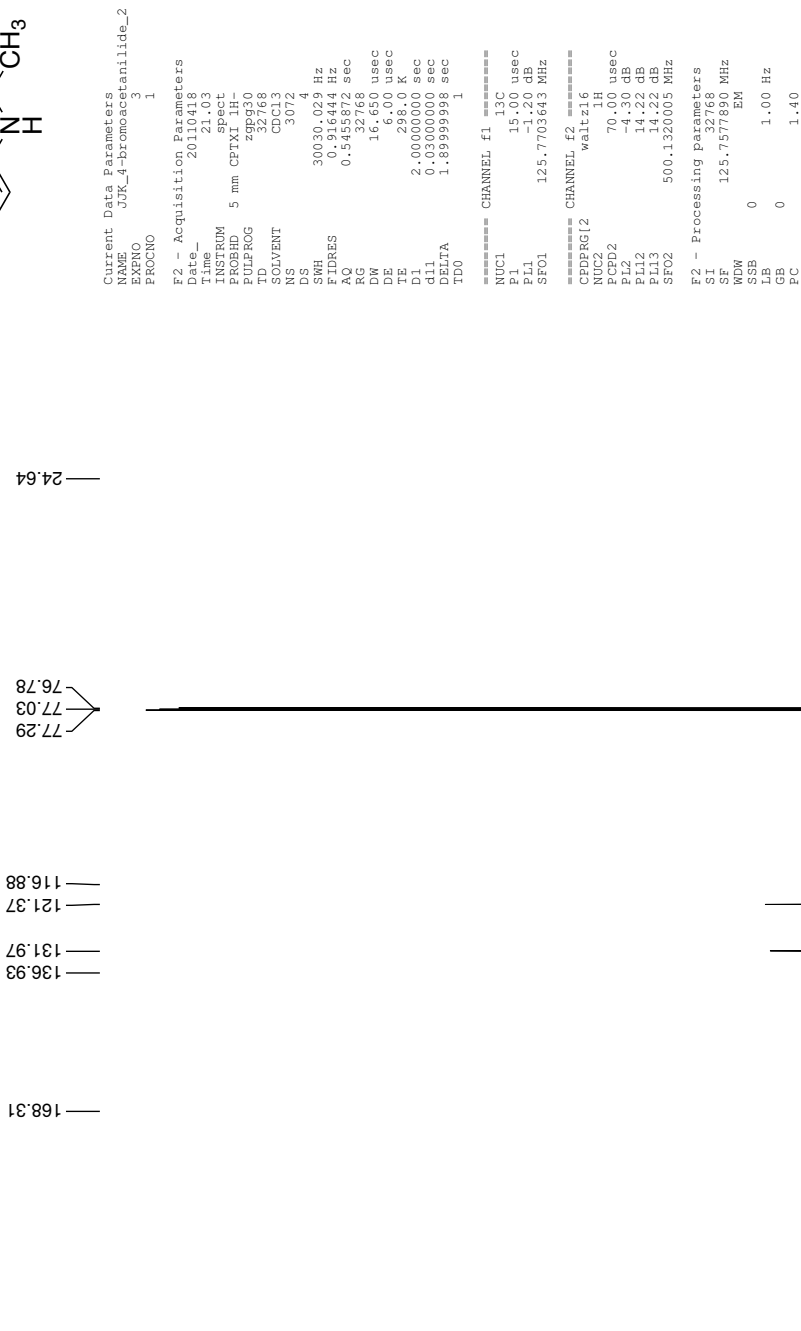
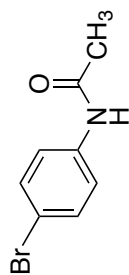
^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of *N*-(4-methylbenzoyl)-4-fluoro-2-aminoaniline (**6f**)



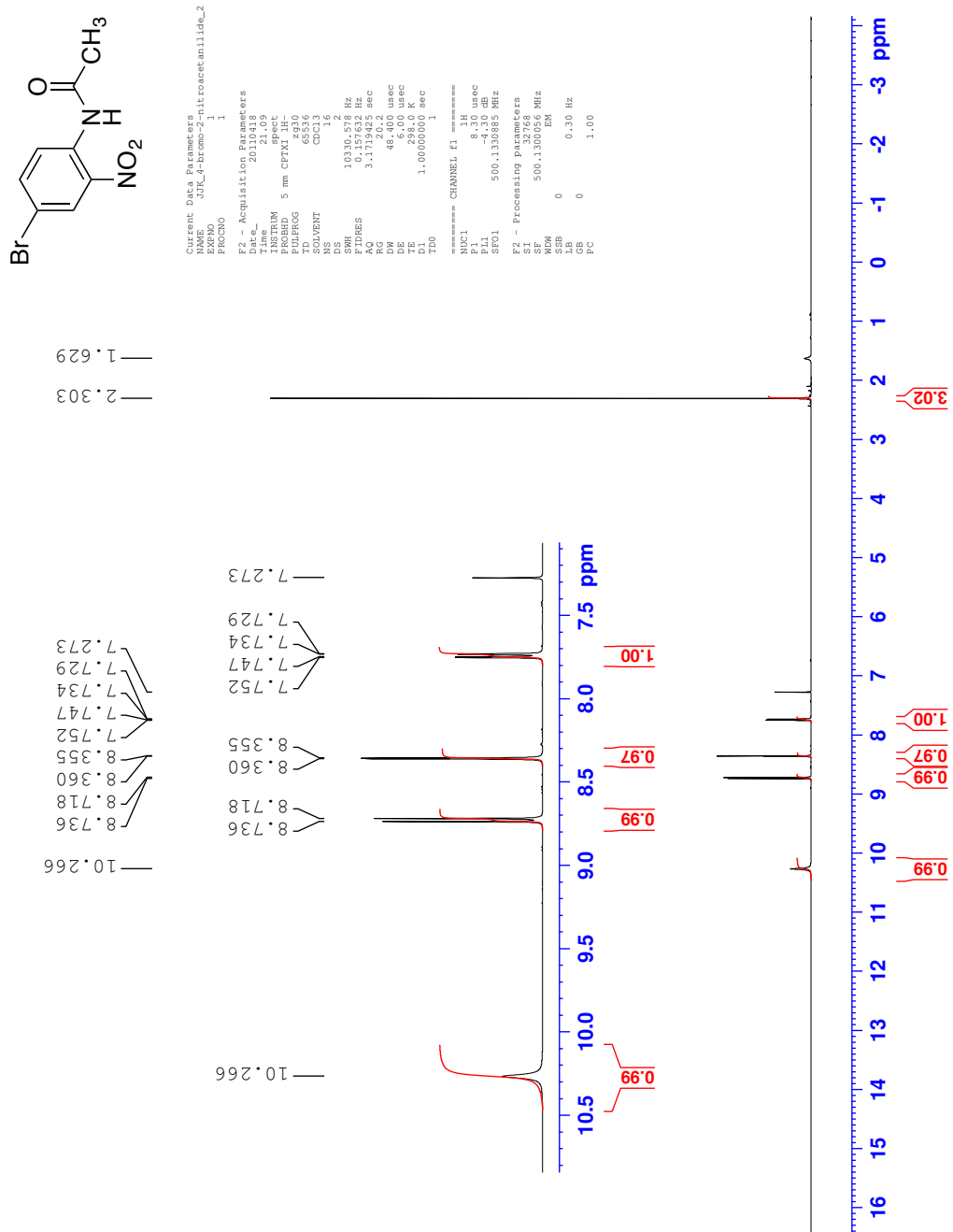
^1H NMR (CD_3CN , 376 MHz, 298 K) spectrum of 2-(4-methylphenyl)-5-fluorobenzimidazole (**7f**)

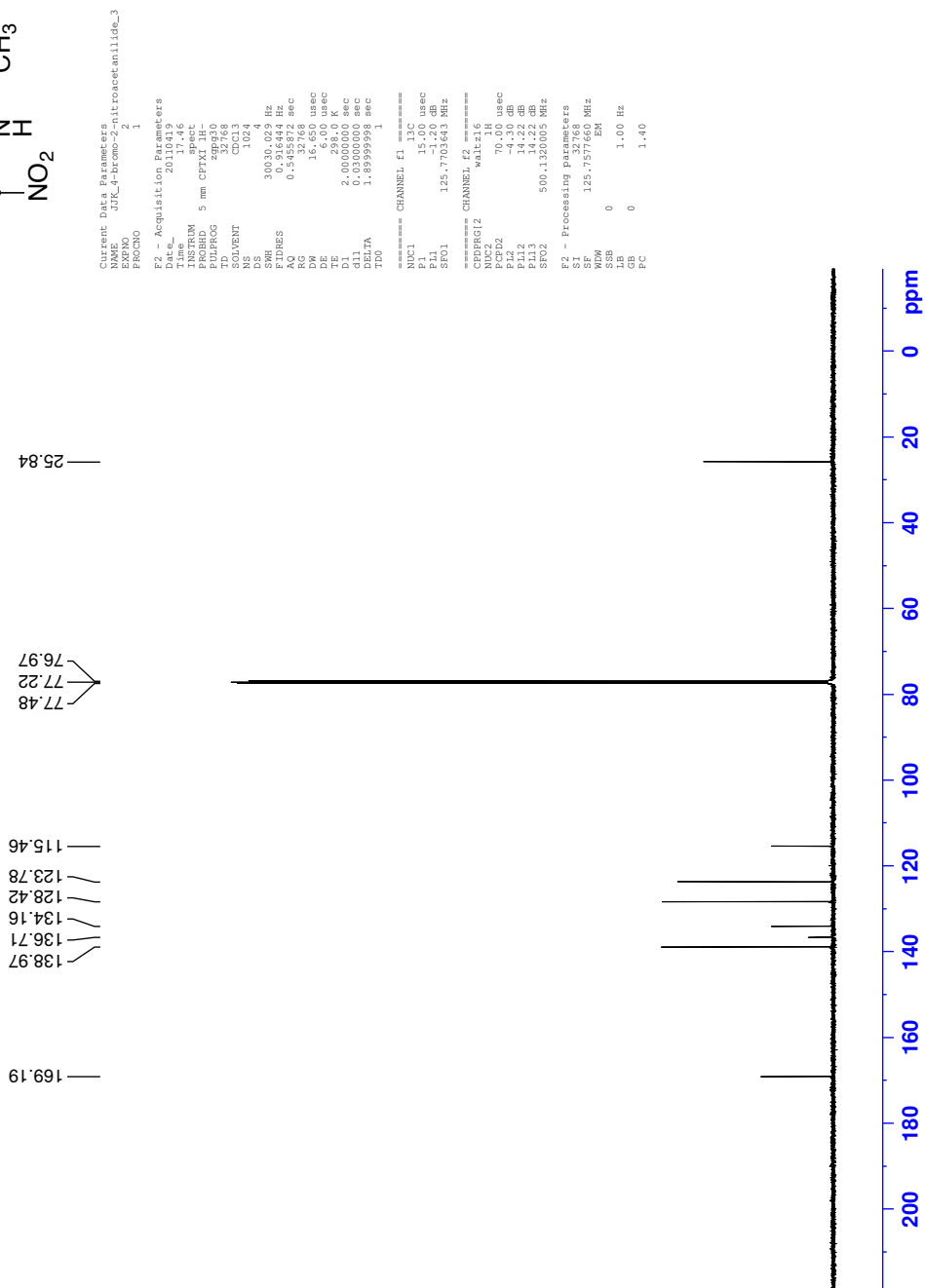
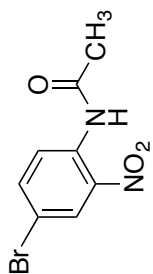


^1H NMR (CDCl_3 , 500 MHz, 298 K) spectrum of 4-bromoacetanilide (**8**)

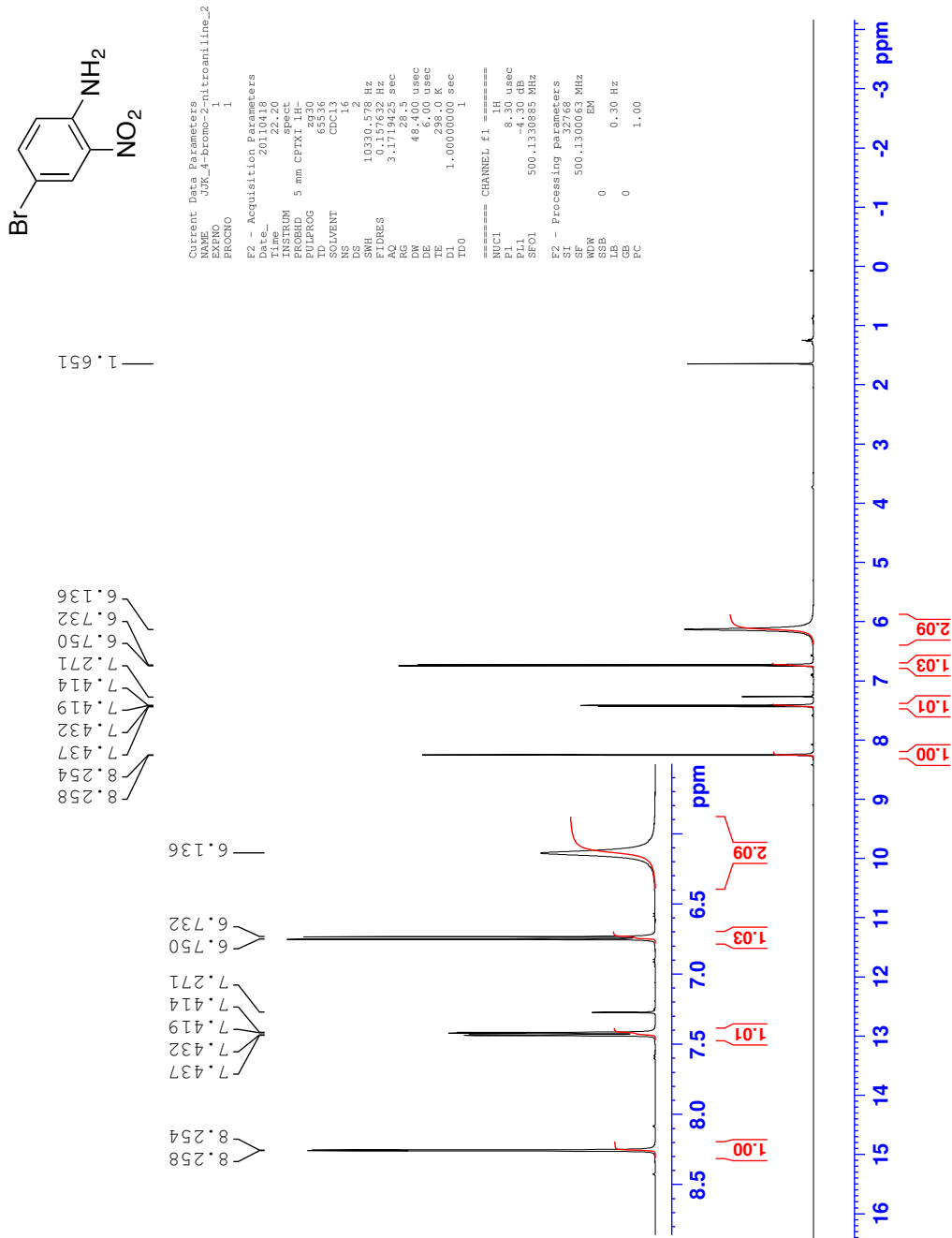
^{13}C NMR (CDCl_3 , 126 MHz, 298 K) spectrum of 4-bromoacetanilide (**8**)

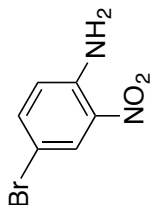
^1H NMR (CDCl_3 , 500 MHz, 298 K) spectrum of 4-bromo-2-nitroacetanilide (**9**)



¹³C NMR (CDCl₃, 126 MHz, 298 K) spectrum of 4-bromo-2-nitroacetanilide (9)

^1H NMR (CDCl_3 , 500 MHz, 298 K) spectrum of 4-bromo-2-nitroaniline (**10**)



^{13}C NMR (CDCl_3 , 126 MHz, 298 K) spectrum of 4-bromo-2-nitroaniline (**10**)

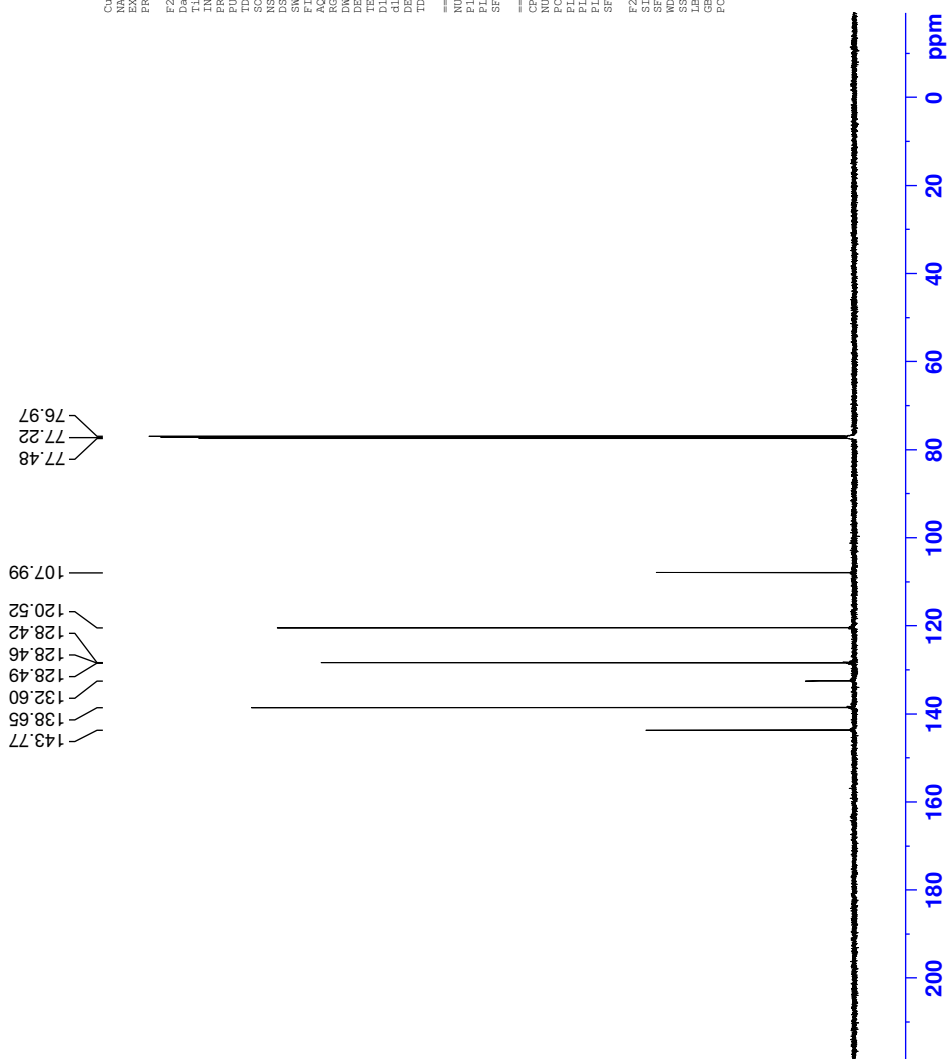
Current Data Parameters
 NAME JXR_4-bromo-2-nitroaniline_3
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20110814
 Time 18:54
 INSTRUM spect
 PROBRD 5 mm CPXI 1H-
 PULPROG zgpg30
 SOLVENT CDCl3
 NS 1024
 DS 4
 SWH 3000.044 Hz
 FWHM 0.91644 Hz
 AQ 0.5455872 sec
 RG 32768
 DN 16.650 usec
 DE 288.0 usec
 TE 298.0 K
 D1 2.0000000 sec
 d11 0.0300000 sec
 DELTA 1.8999999 sec
 TD 120

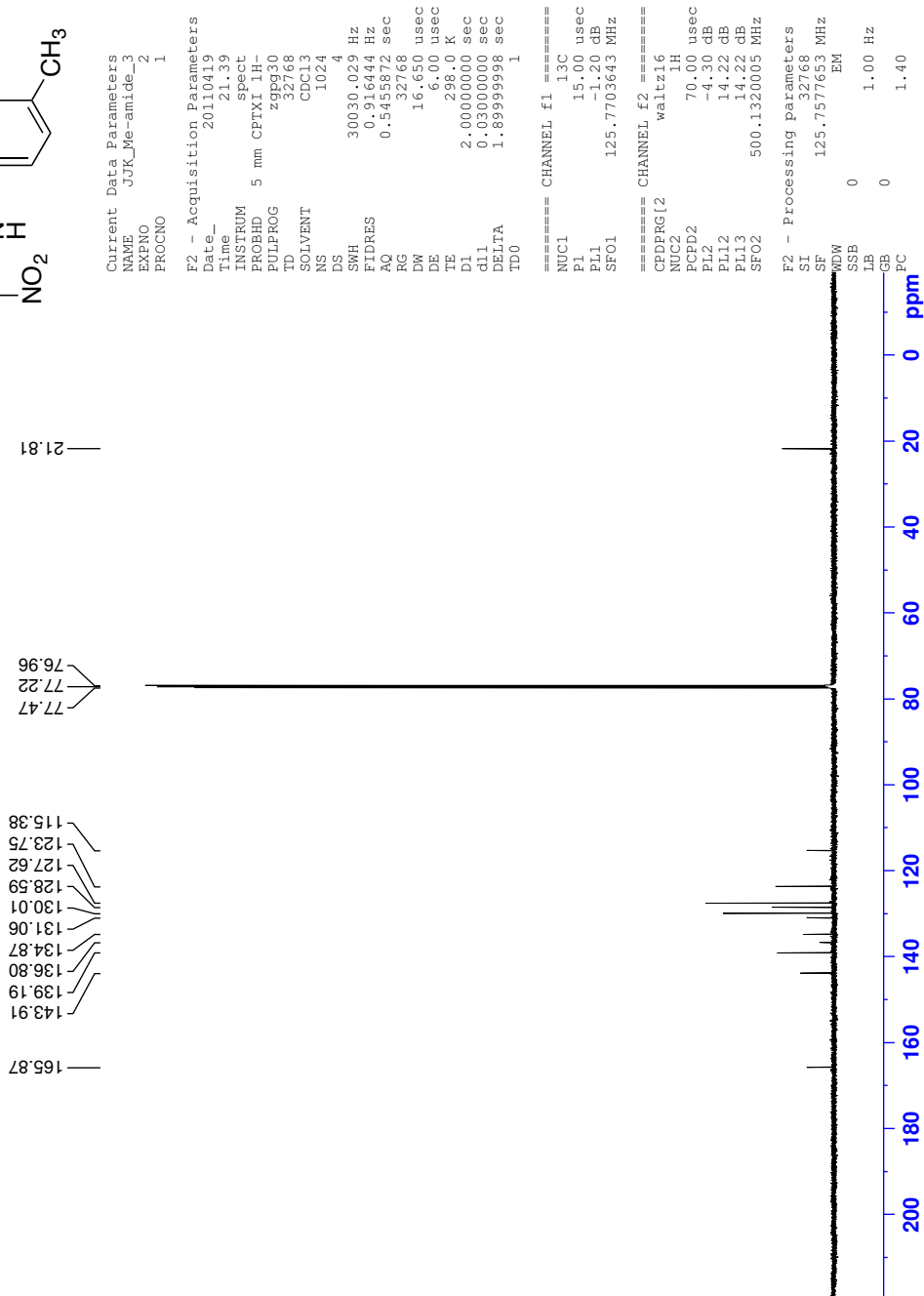
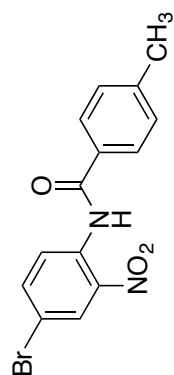
===== CHANNEL f1 =====
 NUC1 ^{13}C
 P1 13.00 usec
 PL1 -1.20 dB
 SFO1 125.7703643 MHz

===== CHANNEL f2 =====
 CDPRCT2 waltz16
 NUC2 ^1H
 PCPD2 70.00 usec
 PL2 -4.30 dB
 PL12 14.22 dB
 PL13 14.22 dB
 SFO2 500.1320005 MHz

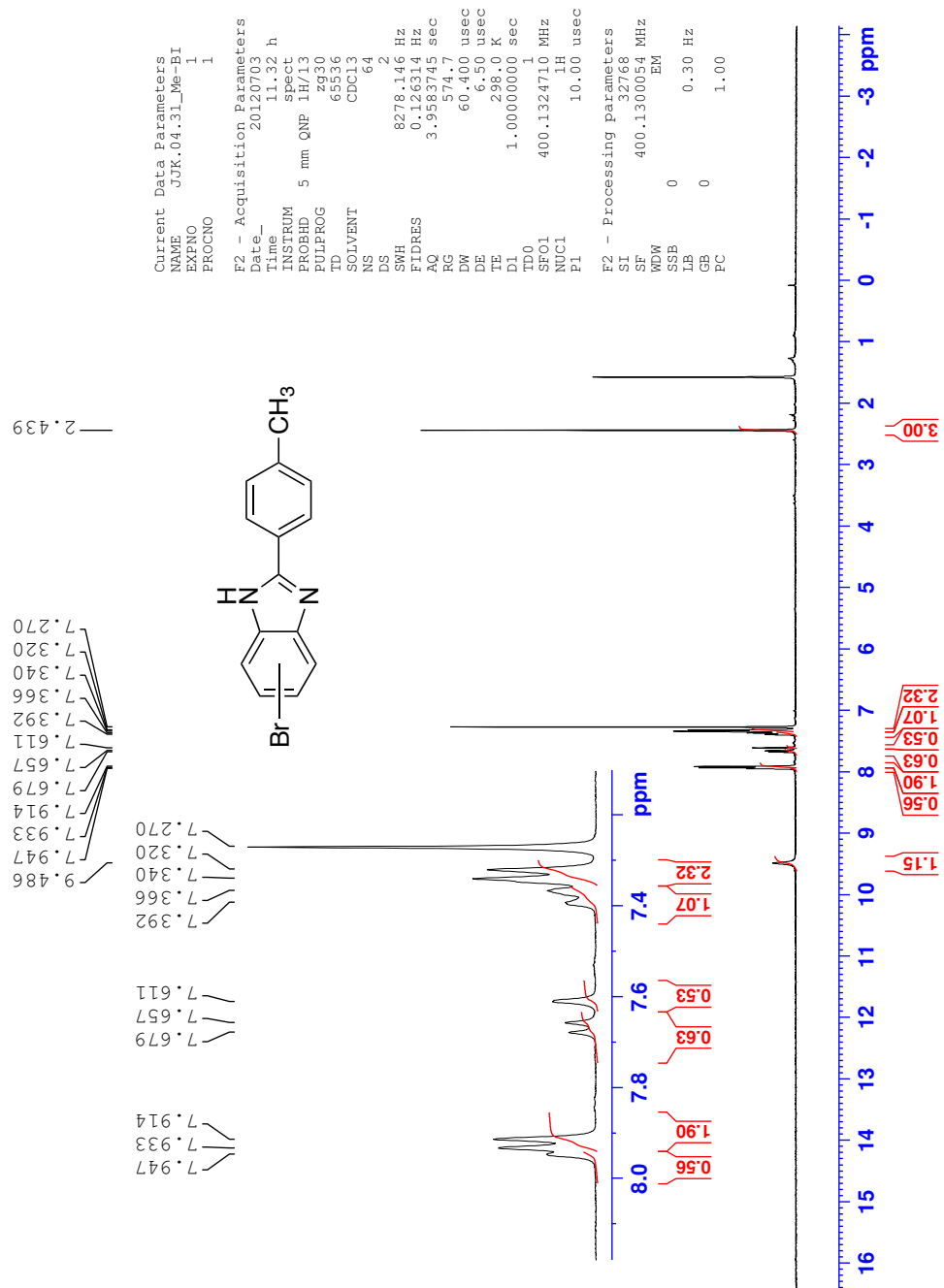
F2 - Processing parameters
 SF 125.767697 MHz
 WDW EM
 SSB 0
 GB 0
 PC 1.40



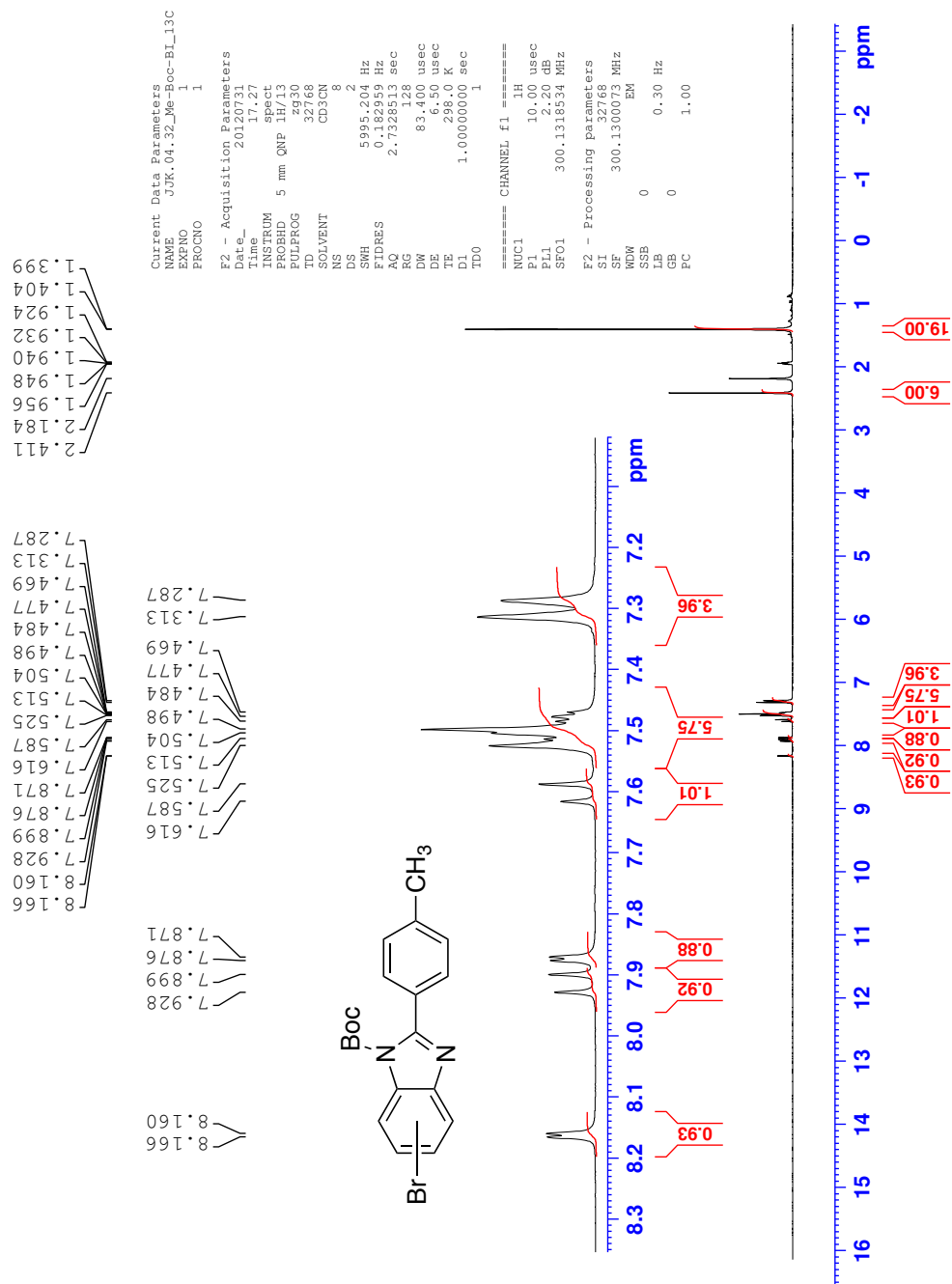
^{13}C NMR (CDCl_3 , 126 MHz, 298 K) spectrum of *N*-(4-methylbenzoyl)-4-bromo-2-nitroaniline (**11f**)



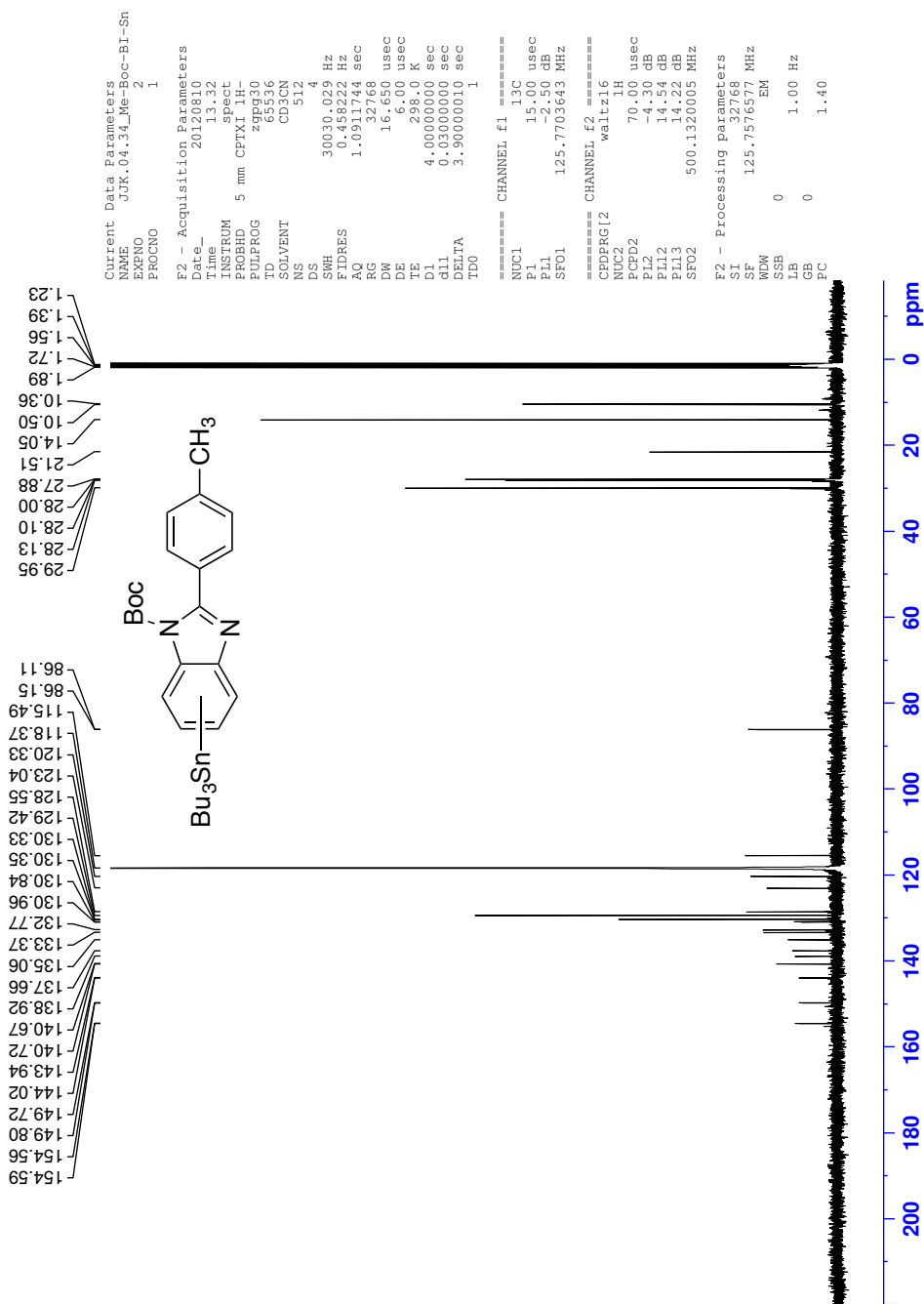
^1H NMR (CDCl_3 , 400 MHz, 298 K) spectrum of 2-(4-methylphenyl)-5-bromobenzimidazole (**13f**)



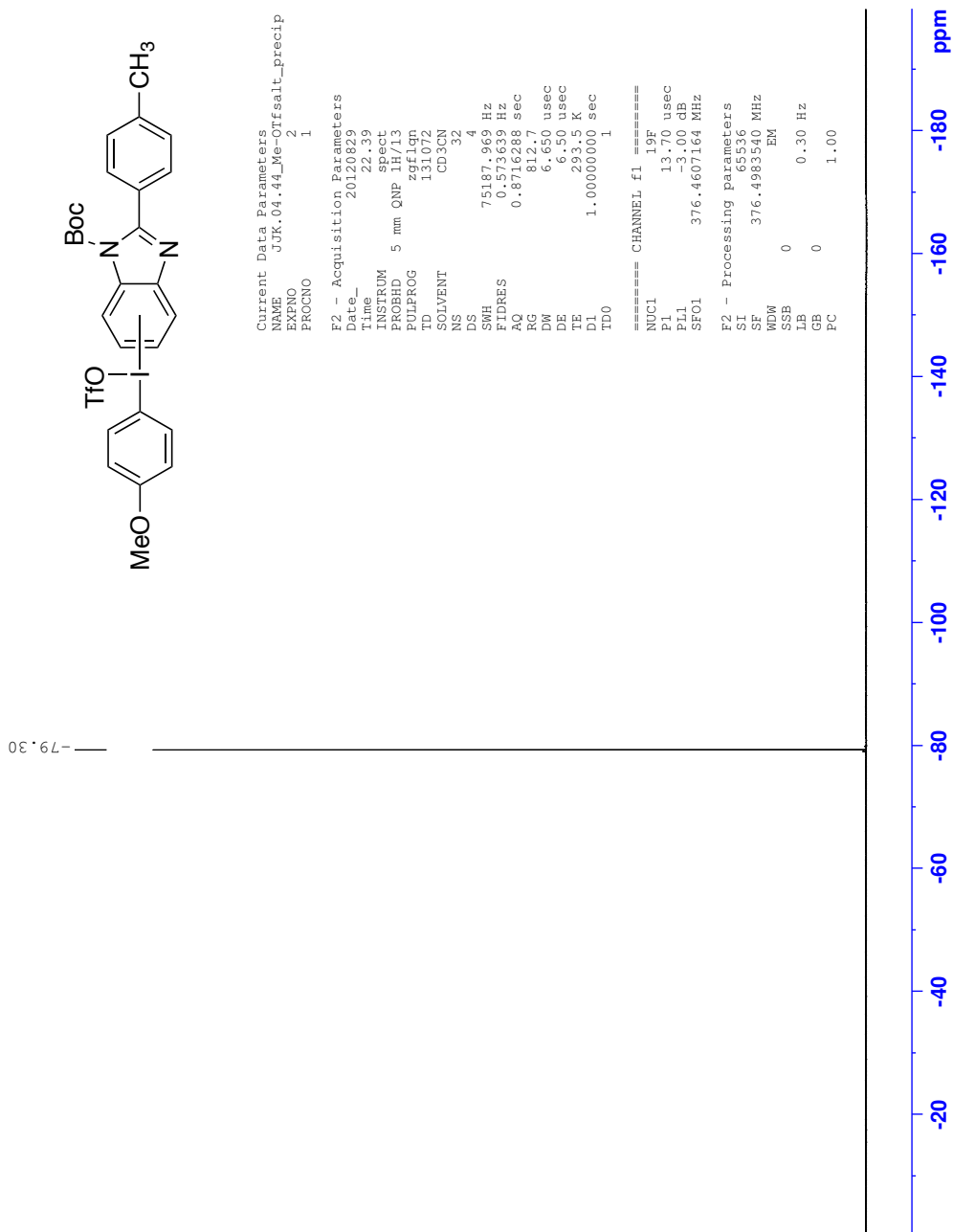
^1H NMR (CD_3CN , 300 MHz, 298 K) spectrum of *N*-*tert*-butyloxycarbonyl-2-(4-methylphenyl)-5-bromobenzimidazole (**14f**)



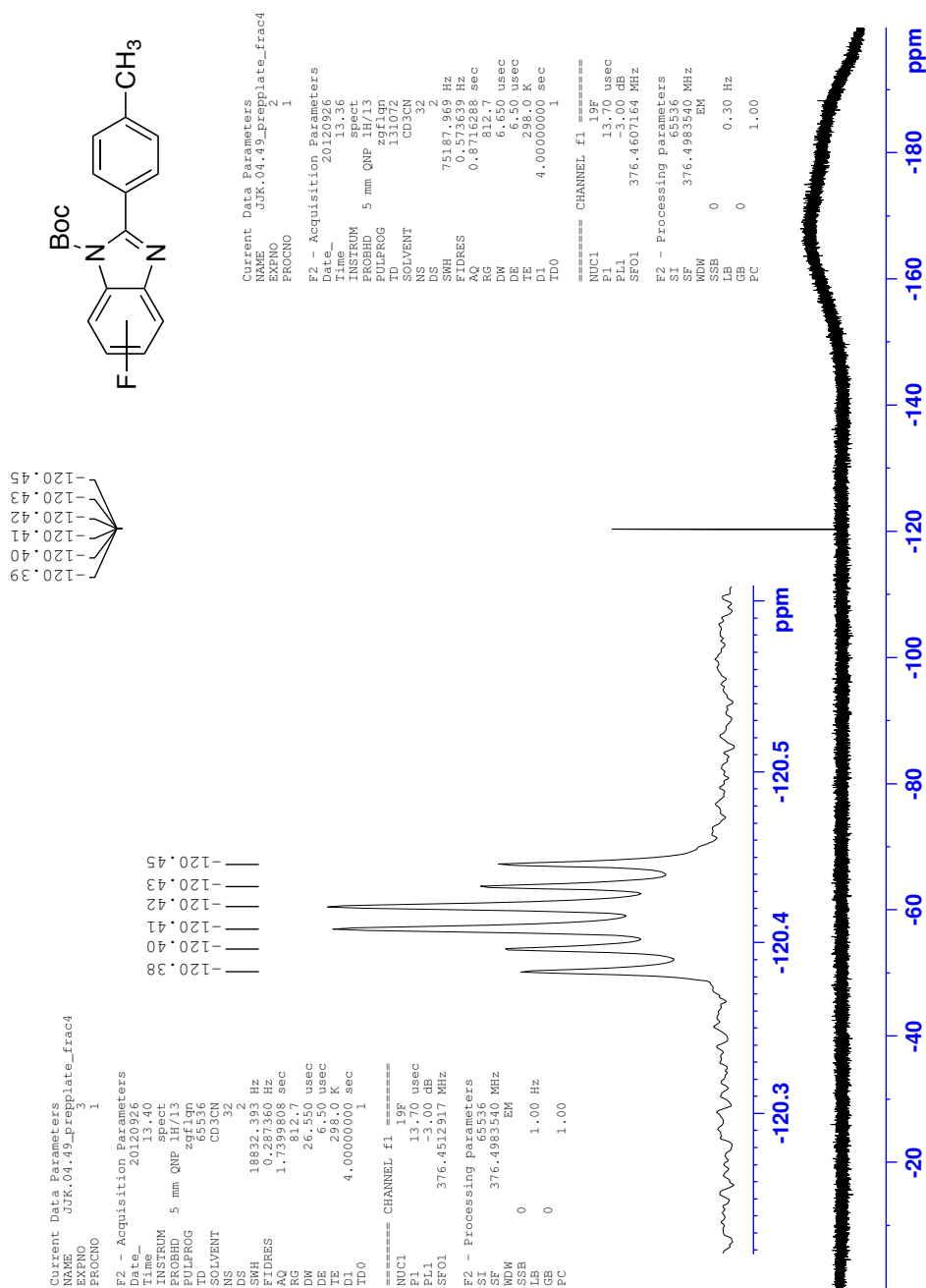
^{13}C NMR (CD_3CN , 126 MHz, 298 K) spectrum of *N*-*tert*-butyloxycarbonyl-2-(4-methylphenyl)-5-(tributylstannyl)-benzimidazole (**15f**)



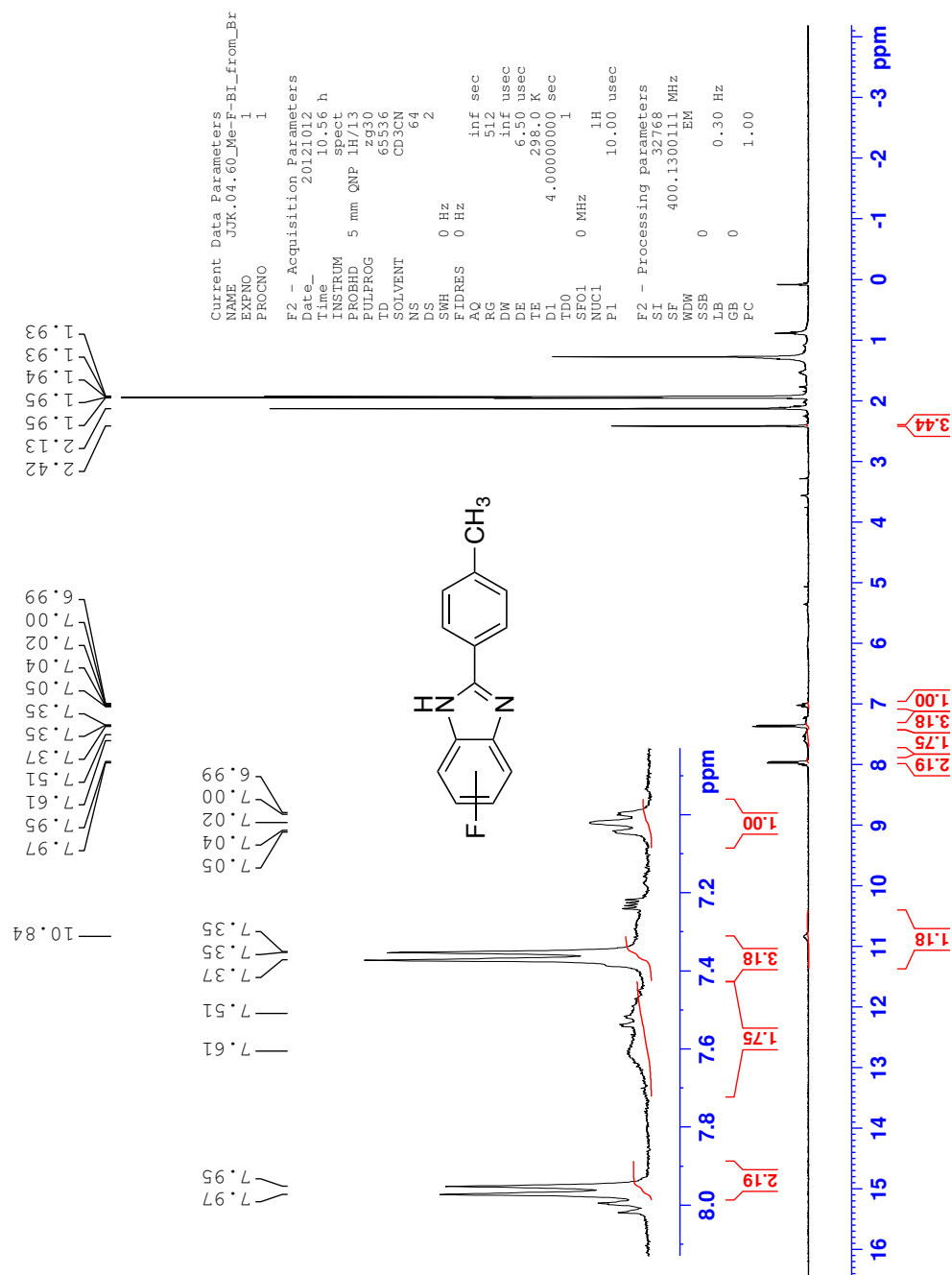
^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of (*N*-*tert*-butyloxycarbonyl)-2-(4-methylphenyl)-5-benzimidazolyl)(4-methoxyphenyl)iodonium triflate (**16f**)



^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of *N*-*tert*-butyloxycarbonyl-2-(4-methylphenyl)-5-fluorobenzimidazole (**22f**)



^1H NMR (CD_3CN , 400 MHz, 298 K) spectrum of 2-(4-methylphenyl)-5-fluorobenzimidazole (**7f**) by deprotection of **22f** with trifluoroacetic acid



^{19}F NMR (CD_3CN , 376 MHz, 298 K) spectrum of 2-(4-methylphenyl)-5-fluorobenzimidazole (**7f**) by deprotection of **22f** with trifluoroacetic acid

