UNIVERSITY OF CALIFORNIA

Santa Barbara

Trace Metal Catalysis in Water: Enabling Technologies for Environmentally Friendly Organic Synthesis

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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March 2020

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March 2020

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I would like to thank Bruce H. Lipshutz for his excellent guidance as my graduate advisor. I thank my committee members for serving on this committee. I specifically want to thank Dr. Chris Gabriel, Dr. Daniel Lippincott, Dr. Alex Moreland, and Dr. Roscoe Linstadt for their advice, training, and comradery during graduate school.

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- Designed and synthesized a novel class of phosphine ligands for ppm level Pd-catalyzed cross-couplings in aqueous media. The ligand EvanPhos is now commercially available from Aldrich (catalog: 902292).
- Optimized and broadened the substrate scope of Pd-catalyzed aminations of protected hydrazines as precursors for indole derivatives.
- Optimized the synthesis of Fe/ppm Pd nanoparticle catalysts for scale-up and commercialization by Aldrich (catalog: 799661).
- Developed a novel Fe/ppm Cu nanoparticle system. This catalyst was applied to azide-alkyne click reactions in water.
- Trained chemists from Novartis, AbbVie, and Eli Lilly on the use of designer surfactants for the synthesis of active pharmaceutical ingredients.
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- Revised synthetic pathways for greater yield, cost, and time efficiency.

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- Compiled and analyzed data for HIV/Methamphetamine addiction research studies
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Patents

Lipshutz, B.H.; Landstrom, E.B.; Handa, S. "Biaryl ligands for transition metal catalyzed reactions". Patent no. US20180117574A1

Publications

Lippincott, D.J.; Landstrom, E.B.; Cortes-Clerget, M.; Lipshutz, B.H.; Buescher, K.; Schreiber, R.; Durano, C.; Parmentier, M.; Ye, N.; Wu, B.; Yang, H.; Andersson, M.;

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Presentations and Posters

Landstrom, E.B. *A Novel Monophosphine Ligand Scaffold for Sustainable Pd-Catalyzed Cross-Couplings.* Connecticut College. September **2018**.

Landstrom, E.B.; Lipshutz, B.H. *New Phosphine Ligand Scaffold for Greener Palladium-Catalyzed Cross Couplings*. Presented at the American Chemical Society 21st Annual Green Chemistry and Engineering Conference. June **2017**.

Adenot, A.; Landstrom, E.B.; Cahiez, G.; Lipshutz, B. H. *Environmentally Responsible Azide-Alkyne Cycloadditions Enabled by ppm Cu/Fe Nanomaterials and Micellar Catalysis*. Presented at the French American Chemical Society Meeting, Santa Barbara, California, June **2016**.

Landstrom E.B. *Still paying for Pd in your Pd-catalyzed reactions? Why? Use Fe nanoparticles containing naturally occurring ppm Pd, and get it for free!* Presented at the

American Chemical Society Western Regional Meeting. San Marcos, California, November **2015**.

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ABSTRACT

Trace Metal Catalysis in Water: Enabling Technologies

for Environmentally Friendly Organic Synthesis

by

Evan Barrett Gam Landstrom

Organic synthesis is the cornerstone of small molecule pharmaceutical development and manufacturing. Unfortunately, making these medications still relies on the use of toxic organic solvents as the reaction medium. These solvents represent ~80% of the organic waste stream generated by the pharmaceutical industry. Additionally, key catalytic reactions involve unsustainably high levels of endangered precious metals.

Throughout the course of this research new reaction conditions were developed to address these concerns. With respect to solvents, the designer surfactant TPGS-750-M in water was chosen as the reaction medium. This commercially available surfactant has significant literature track record of enabling organic transformations in aqueous media, often with mild reaction conditions.

There are a plethora of catalysts in the literature that enable critical organic transformations, such as the Suzuki-Miyaura coupling, that can be effective at low catalyst loadings. Unfortunately, they often require harsh reaction conditions involving high heat and organic solvents to achieve optimal yields of the desired product. In light of this, new, more effective catalysts and shrewd implementation of available catalysts was investigated.

By combining aqueous micellar media with judicious catalyst design and implementation, new reaction conditions were developed in good-to-excellent product yields

of critical bond-forming reactions that are used extensively in pharmaceutical synthesis, namely C-C, C-N, and “click” reactions. All of these are conducted in an environmentally friendly manner in an aqueous medium with no more than 0.05-0.5 mol % (500-5000 ppm) of metal catalyst.

Table of Contents and Figures

I. Introduction and General Experimental

A. Green Chemistry

In 1998 Anastas and Warner published the 12 Principles of Green Chemistry in "Green Chemistry: Theory and Practice."[1] This list serves to highlight an essential problem with the field of chemistry: it is an inherently dangerous and wasteful field. The 12 Principles serve as a roadmap to highlight these issues and offers suggestions on how to mitigate them. While seemingly aspirational initially, the chemistry community has risen to the challenge with a multitude of researchers across academia, industry, and government pouring significant effort into the development of processes that will enable chemistry, especially synthetic chemistry, to reach a point where the practice can be truly called both green and sustainable. The importance of this pursuit is highlighted by the existence of the Presidential Green Chemistry Challenge Awards, and chemistry journals dedicated to publications on green and sustainable chemistry. In the remainder of this introductory passage the reasoning and motivation behind the research discussed in subsequent chapters will be covered.

B. Solvents

Synthetic organic chemistry is a field that has been conducted largely in organic solvents, invoking the adage "like dissolves like." The drawbacks to the use of these solvents are myriad. The vast majority of organic solvents are toxic to people and the environment at large, posing an immediate safety hazard to any who may be exposed to them. Exposure can lead to a multitude of medical issues including cancer, injury, and birth defects. Due to their harmful nature they must be stringently disposed of as hazardous waste which is a costly and problematic process in its own right. A majority of organic solvents is flammable and pose a significant safety risk due to fire and explosion. Almost all of the

flammable solvents have flash points that can be easily reached at temperatures often encountered during synthetic processes. Extensive engineering controls must be employed for their safe use. Even with those engineering controls, accidents and injuries can still occur.

But how much of a problem is this, especially when looking at organic synthesis in the service of the pharmaceutical industry? A big one. According to the American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable organic solvents alone account for 56% of the entire waste stream generated by the pharmaceutical industry.[2] While that figure alone should give any reasonable chemist pause, it must also be viewed through a different lens. What that statistic really means is that 56% of the waste generated has no hope of even being incorporated as part of the desired product, an active pharmaceutical ingredient (API). It is simply the medium for conducting a reaction. It is appalling that this is considered the norm; this is an issue that needs to be addressed. Additionally, a variety of solvents that used to be considered standard are increasingly under legal scrutiny (DMF, DCM, etc.; Figure 1). Their use is outright banned or soon to be banned under the European Union R.E.A.C.H. agreement due to their particularly egregious safety and pollution hazards.[3] The rest of the world will eventually follow suit. Clearly an alternative is needed.

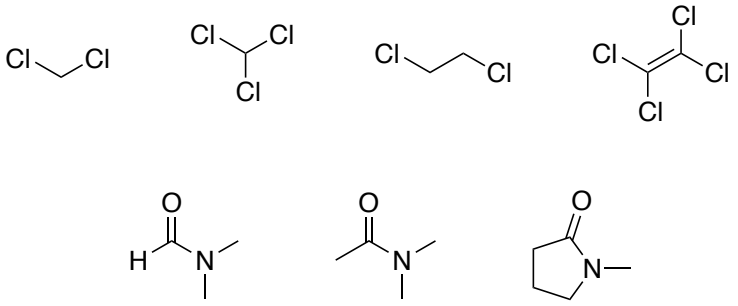

Figure 1: Structures of problematic solvents.

C. Precious Metals

One tenet of the 12 Principles of Green Chemistry is the utilization of catalytic (enzymatic, organo-, or metallic) methods, as opposed to stoichiometric reagents, for the synthesis of chemical matter. While this is, in theory, ideal, the nature of the catalysts requires some scrutiny. Some of the most useful catalytic metals reside within the platinum group or coinage group of elements in the d-block of the Periodic Table. These metals are critical for the synthesis of APIs. Key treatments for a variety of disease would not exist if these metals and the chemistries associated with them had not been developed. Supply issues will soon become of grave importance for these metals according to the ACS Green Chemistry Institute.[4] Their current rates of usage in the range of 1-5 mol % or higher is simply an unsustainable practice. Once again, an alternative or significant improvement must be found wherein catalysts are designed and implemented in such a manner that significantly lower catalyst loadings are competent for the desired transformation.

D. Is There Hope?

All is not lost. Nature has been using trace quantities of metals in the active sites of enzymes since the dawn of life to create both simple and complex organic molecules. Modern organic chemistry has only been conducted in organic solvents by humans using their own hands over the past, at most, 200 years. Throughout evolution, however, organic chemistry has been conducted by nature in an aqueous medium. Can modern organic chemists learn an obvious lesson and follow nature's lead?

Yes. But how? The interior of enzymatic cores are typically nonpolar regions that exist in polar aqueous environments due to the (oftentimes complex) folding of protein structures. Luckily, organic chemists can replicate this type of nonpolar environment with the use of appropriately and newly engineered surfactants. Surfactants, above their critical micellar

concentration (CMC), spontaneously form micellar aggregates with greasy, hydrophobic cores that exclude water and mimic the environment of anhydrous organic solvents. Partitioning of reagents from the polar aqueous medium to the interior of micelles yields reactant concentrations around two molar.[5] This allows reaction partners and catalysts to reach locally high reactant and catalyst concentrations that cannot be typically achieved in traditional organic solvents. Consequently, catalyst loadings and reaction temperatures can drop significantly. But not any old the shelf surfactant will do.

Over the years designer surfactants have been created to address the specific needs of synthetic chemists. These commercially available surfactants can facilitate a variety of organic transformations that would typically require toxic, flammable, or environmentally egregious organic solvents.[6-9] Vitamin E-based TPGS-750-M (Figure 2), which is benign by design, has proven to be a workhorse surfactant and its use is the focus of the research discussed in later chapters. TPGS-750-M is particularly effective due to its unique micellar structure. A solution of TPGS-750-M forms 50-60 nm super-micelle aggregates of micelles, instead of the typical 5-15 nm free floating micelles characteristic of other surfactants which allows more facile exchange of reaction partners between micelles (Figure 3).[10]

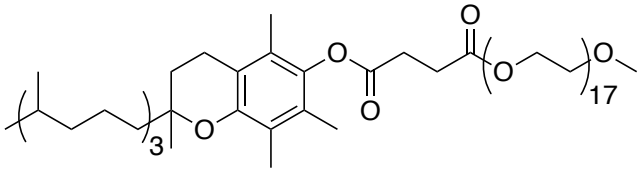

Figure 2: Structure of TPGS-750-M

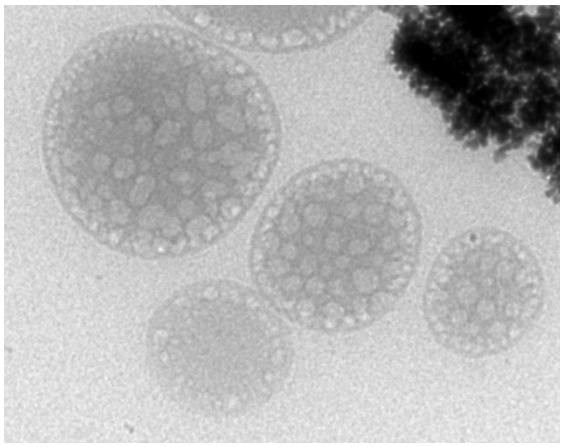

Figure 3: TPGS-750-M micellar aggregates

The relative greenness of any organic transformation can be quantified by Sheldon's E factor. The E factor is a simple metric that is reached by dividing the total mass of waste (in this case solvent) by the mass of product obtained. Typical E factors for the pharmaceutical industry are between 25-100 or greater.[10] Switching to designer surfactant-enabled reactions puts E factors in the range of 1-5, which is more typical of the fine chemicals industry.[6-9] Calculation of the E factors obtained during these studies will be a common thread in the coming chapters.

The following chapters will describe three novel approaches to catalyst design and/or implementation that yield relevant bond-forming methodologies, namely C-C, C-N, and "click" reactions, in environmentally responsible aqueous conditions with low catalyst loadings.

E. General Experimental

Unless otherwise noted, all reactions were performed under an atmosphere of argon. All commercially available reagents were used without further purification. Organoazides used for click reactions were prepared using known procedures.[12] A 2 wt % TPGS-750-M/H_2O solution was prepared by dissolving 20 mg TPGS-750-M per mL water (degassed with

argon prior to mixing, HPLC grade). TPGS-750-M was made as previously described or was donated by PHT International.[7] Tetrahydrofuran (THF) and toluene, obtained from Fisher Scientific, were degassed by sparging with argon and dried by pushing through a column of activated aluminum oxide. HPLC grade ethyl acetate (EtOAc), obtained from Fisher Scientific, was degassed by sparging with argon for a minimum of 2 h while stirring. All glassware and stir bars were cleaned with aqua regia prior to use to avoid trace metal contamination. Palladium catalysts were purchased from Spectrum Chemicals or were graciously donated by Johnson Matthey. The source of palladium acetate can have a dramatic effect on success of the reaction as noted by Colacot and co-workers.[13] Spectrum and Johnson Matthey branded palladium was found to be competent. Strem and Sigma-Aldrich palladium acetate were found to be inferior. Reagents were purchased from Sigma-Aldrich, Combi-Blocks, Alfa Aeser, or Acros Orgnaics, *n*-Butyllithium (nominally 2.5 M) was purchased from Sigma-Aldrich and titrated with diphenylacetic acid prior to each use. Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 glass backed plates (Merck, 0.25 mm thick) or Aluminum Oxide 60 F254 polyester backed plates (Sigma-Aldrich, 0.2 mm thick). The developed chromatogram was analyzed by UV lamp (254 nm). UV inactive compounds were visualized using aqueous potassium permanganate ($KMnO_4$), aqueous dinitrophenylhydrazine, aqueous ceric ammoniumnitrate/phospho-molybdic acid, or butanolic vanillin and developed with a heat gun. Flash chromatography was performed using Silicycle Siliaflash® P60 Unbonded Grade Silica: Particle size: 40-60 μm, Pore size: 60 Å. ^{1}H and ^{13}C NMR data were recorded at 297.8 K on an Agilent® Technologies 400 MHz or Varian Unity Inova® 500 MHz. ^{19}F and ^{31}P NMR were recorded at 297.8 K on an Agilent® Technologies 400 MHz. The FID was processed using MestReNova (release: 10.0). Chemical shifts in ^{1}H NMR spectra are reported in parts per

million (ppm) on the δ scale with the residual ^{1}H resonance from deuterated chloroform set at 7.26 ppm, deuterated acetone set at 2.05 ppm, and deuterated dimethyl sulfoxide set at 2.50 ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sep = septet, m = multiplet, br = broad, dt = doublet of triplets, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets), coupling constant in Hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra were referenced through the chloroform ^{13}C resonance reported at 77.16 ppm from the central peak on the δ scale according to IUPAC recommended secondary referencing method and the manufacturer's protocols. Reactions were deemed complete by TLC or via GCMS analyses. GCMS data were recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies). A capillary column HP-5MS cross-linked 5% phenylmethylpolysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min.

F. References

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II. EvanPhos: A Novel Biaryl Scaffold for Monophosphine Ligands and their Application to Suzuki-Miyaura Couplings.

A. Introduction

Seminal work disclosed by Akira Suzuki and Norio Miyaura in 1979 focused on a method for the construction of C(sp^2)-C(sp^2) aryl-alkenyl bonds employing a palladium catalyst leading to cross coupling of aryl halides and alkenyl catecholboranes (Figure 1), later coined as the Suzuki-Miyaura coupling (SMC).[1]

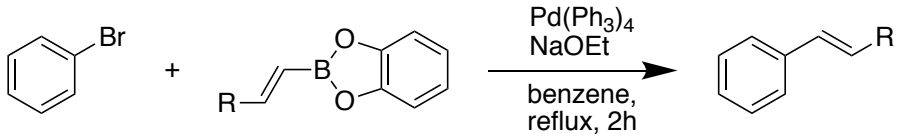


Figure 4: First reported SMC

This work would eventually lead Suzuki to share the 2010 Nobel Prize in Chemistry with Ei-Ichi Negishi and Richard Heck for the development of palladium-catalyzed cross couplings in organic synthesis. The decision to award the prize was likely informed by rapid rise to prominence of the SMC within the pharmaceutical, agrochemical, and materials sectors. In 2014 it was the second most commonly utilized reaction methodology in process chemistry and the fifth most utilized in medicinal chemistry.[2] It's widespread use can be attributed to its robust nature, functional group tolerance, and facile scalability. However, the transformation of an initial disclosure to robust methodology did not occur instantaneously. Early reports noted that the substrate scope was limited by known reactivity trends of aryl halides in oxidative addition to Pd^0, especially since catalyst choice in earlier times was limited to mainly tetrakis(triphenylphosphine)palladium derivatives or their analogous Pd^{II} salts.[1] Extensive effort was, therefore, poured into the still highly active research field of ligand design for transition metal-catalyzed reactions.

B. Background of Ligand Design

Triphenylphosphine is a ubiquitous phosphine ligand owing to its inexpensive nature and long bench life. However, it is among the least reactivity-inducing ligands available for Pd-catalyzed cross coupling reactions. To understand why, the mechanism of the SMC must be discussed (Figure 2). The first step before initiation of the catalytic cycle is activation of the palladium catalyst when utilizing Pd^{II} salts followed by ligand dissociation as needed to achieve a coordinatively unsaturated complex, typically a 12-electron LPd species but in some cases such as with triphenylphosphine a 14-electron L_2Pd complex can suffice. Mechanisms and methods for Pd activation will be discussed in depth later on. Once an appropriate Pd^0 species is present it undergoes oxidative addition to the aryl halide (step 1)

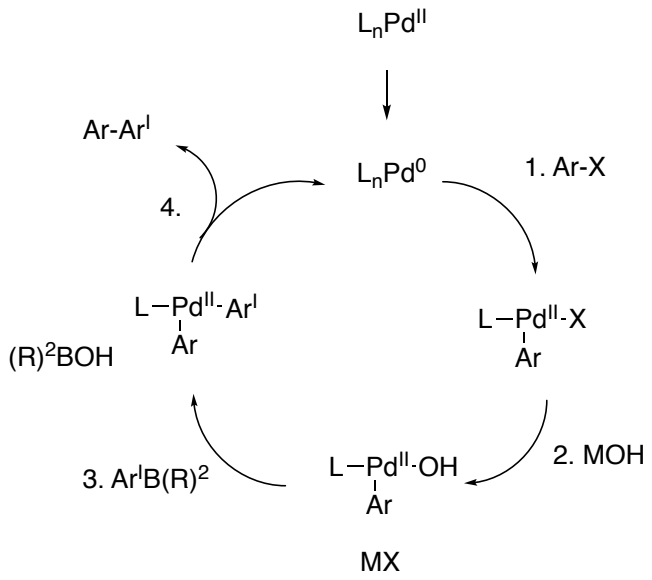


Figure 5: SMC catalytic cycle

to generate an organo-palladium-halide complex. Halide coupling partners typically follow the reactivity trend of I > Br = OTf > Cl. This is followed by a metathesis (step 2) with hydroxide to form and an organo-oxopalladium(II) species. This is crucial because despite early beliefs that transmetallation occurs through a tetracoordinate organoboronate, Hartwig

showed that this is not energetically favorable.[4] Rather, transmetallation (step 3) occurs through a neutral organoboron and an oxo-palladium. This is followed by a reductive elimination (step 4) to yield the cross-coupled product while regenerating the active Pd^0 catalyst.

The stereoelectronic properties of a ligand can significantly impact multiple steps of this reaction. In 1989, Osborn concluded that for optimal activity of a Pd complex towards chloroarene activation the ligand on Pd must feature both significant basicity ($pK_a > 6.5$) and large steric volume ($\theta > 160°$).[5] After studying various effects of ligand stereoelectronic properties Buchwald reached several key conclusions relating to dialkyl biaryl monophosphine ligands.[6-8] Sterically encumbered ligands tend to favor the 12 electron LPd^0 complex which, being coordinatively unsaturated complex, accelerates the oxidative addition step. Strongly electron-donating alkyl groups (Cy, *t*-Bu, Ad) increase the basicity and steric volume around phosphorus similarly enhancing oxidative addition. These same attributes can increase the rate of transmetallation by again ensuring a coordinatively unsaturated monoligated Pd(II) species (compared to PPh_3 which allows for two ligands on the metal center throughout the cycle). The large alkyl groups facilitate reductive elimination by pushing the coupling substituents on Pd into close proximity.

These insights in ligand design have been developed over two decades of active research. It is widely appreciated that there is no one ligand that can accomplish all couplings. A multitude of ligands must be screened to identify one that works for a particular substrate combination *en route* to a molecule of biological interest. A variety of groups have synthesized monophosphine ligands that, when complexed with an appropriate Pd pre-catalyst, exhibit high activity towards cross-coupling reactions using low catalyst loadings (Figure 3).[7-14] While these can be powerful in their own right they are not without

faults. While Buchwald ligands are bench stable they suffer from oxidation/deactivation on their own in solution and over the course of reactions. CataCXium only shows high activity with simple, unfunctionalized coupling partners.[10] BI-DIME and Handphos require lengthy, inefficient, environmentally questionable, and often frustrating syntheses. Several of these

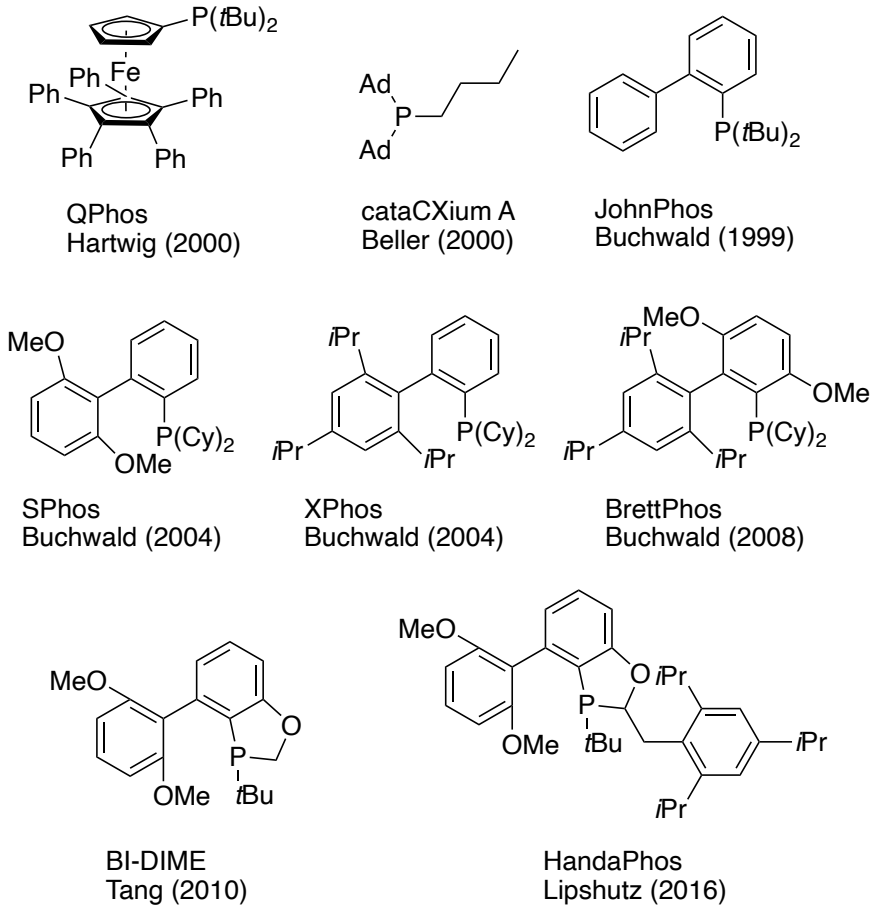


Figure 6: Modern era highly-active ligands for SMC

ligands on Pd as catalysts require harsh coupling conditions at elevated temperatures in organic solvent. Often less appreciated is the need to rethink how cross-coupling reactions are conducted with regard to catalyst loading. Literature catalyst loadings are typically in the range of 1-5 mol % (10,000-50,000 ppm). Due to palladium's endangered nature, new catalyst systems requiring only low catalyst loadings (< 0.5 mol%) should help to make these processes sustainable.[15]

Key to many of these ligands is the presence of an *ortho* biaryl scaffold. While this has proven to be a powerful platform, there was a lingering question. Would an alternative biaryl substitution pattern also provide a ligand with powerful and diverse reactivity? To that end we endeavored to develop a novel ligand scaffold that is cheap, simple to craft, modular in nature, and capable of facilitating the SMC of densely functionalized heterocyclic coupling partners under traditional solvent or aqueous micellar conditions at low catalyst loadings and mild temperatures.

C. Results and Discussion

Drawing inspiration from a variety of other ligands, we developed a rationale for key parameters in the structure and synthesis of the biaryl scaffold. A 2,6-disubstituted upper ring bearing electron-donating groups could further increase the basicity and nucleophilicity at phosphorus. These substituents could also have coordination potential to form a pseudo-bidentate ligand similar to Buchwald ligands. A bulky lower ring could provide additional steric crowding. Critical to realizing these goals was an appreciation for the cost and availability of the starting materials and the manner in which the biaryl framework would be assembled. Given the abundance of aryl halides, boronic acids, and their generally attractive price points we chose to use a SMC to construct the biaryl system (Figure 4). We also aimed to avoid cryogenic (< 20 ºC) conditions if possible. Commercially available 1-bromo-2,4-dimethoxybenzene was coupled with (2-methoxynaphthalen-1-yl)boronic acid. While this coupling can proceed with a variety of catalysts in toluene it was ultimately optimized to proceed with the newly devised ligand in TPGS-750-M/H_2O in 88% yield. Subsequent lithiation of the biaryl in THF at 0° C followed by nucleophilic addition to commercially available chlorodicyclohexylphosphine afforded the new ligand EvanPhos in 77% yield

(69% overall).[16] Utilizing EvanPhos to construct the challenging tri-*ortho* substituted biaryl framework hinted at the high activity of this catalyst system (Figure 4).

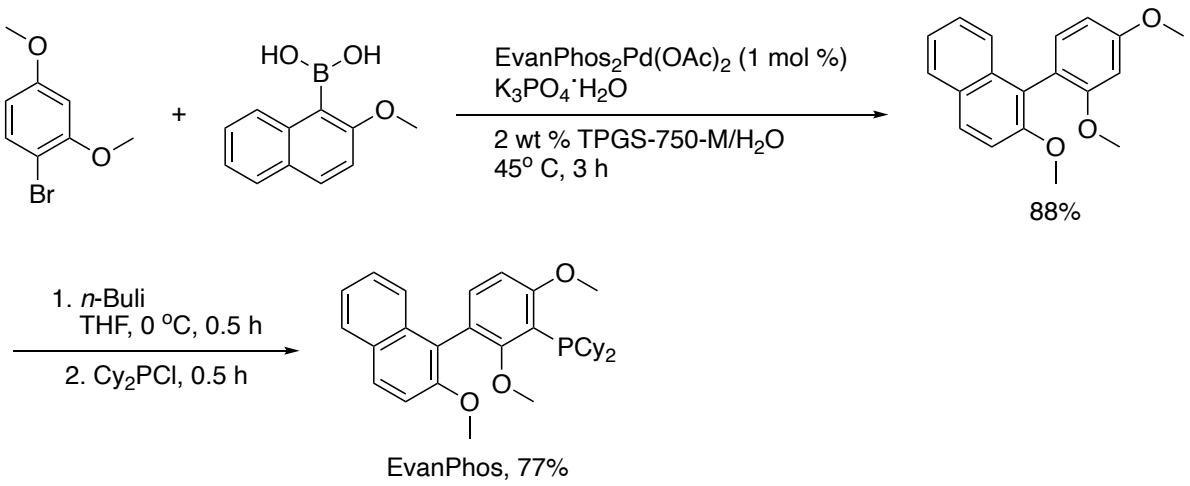


Figure 7: Two-step sequence to EvanPhos

While the main focus in the Lipshutz is to avoid the using bulk organic solvents for reaction,s we nonetheless desired to test the performance of EvanPhos in both aqueous and traditional solvent conditions. While performing reactions in organic solvenst is less ideal from an environmental standpoint than solely aqueous media, this drawback can be mitigated by choosing a solvent that is both low in toxicity and derived from renewable feedstocks such as EtOAc. Initial testing of EvanPhos utilizing 0.5 mol % $Pd(OAc)_2$ to form nitrogen-rich biaryl **1** led to 70% conversion in 24 hours in toluene, a common literature solvent for the SMC, while the same coupling performed in EtOAc led to complete conversion and a 90% isolated yield in 16 hours, later improving to 92% in 2 hours under optimized conditions (pre-reduction with DIBAL). Given the stark reactivity difference between EtOAc and toluene we sought to interrogate the substrate scope of coupling partners in EtOAc utilizing 0.1-0.5 mol % Pd (Figure 5). A wide variety of aryl bromides and boronic acids bearing diverse electronics could be smoothly coupled in EtOAc (Figure 5). Notably, this catalyst system was widely applicable to the synthesis of a multitude of

functionalized heterocycles in good-to-excellent isolated yields. Examples that can typically pose significant issues in cross-coupling chemistry due the coordinative ability of the nitrogen or sulfur interfering with the catalytic cycle posed no apparent issues.

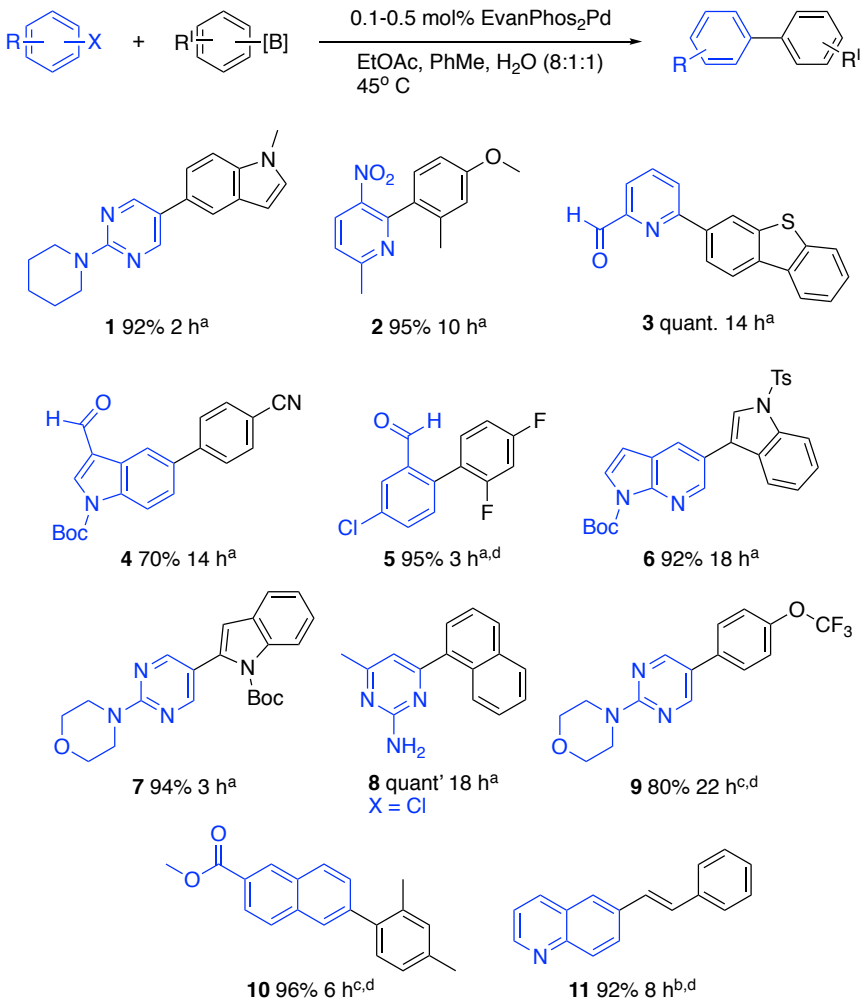


Figure 8: Cross-couplings in EtOAc using [$Pd(OAc)_2$ + 2EvanPhos]. Conditions: a.) $Pd(OAc)_2$ (0.5 mol%). EvanPhos (0.9–1.0 mol%) reduced with DIBAL/PhMe, halide (0.5 mmol), organoboron (0.75 mmol), $K_3PO_4 \cdot H_2O$ (0.75 mmol), EtOAc (0.8 mL), PhMe (0.1 mL from catalyst solution), DI H_2O (0.1 mL). 45 °C. Reaction times not optimized at 0.1 mol% Pd. b.) $Pd(OAc)_2$ (0.25 mol%) EvanPhos (0.45–0.5 mol%). c.) $Pd(OAc)_2$, (0.1 mol%), EvanPhos (0.18–0.2 mol%). d.) No DIBAL preactivation.

Within our group it has been observed that stock solutions of ligand/pre-catalyst complexes which are necessary to achieve low catalyst loadings at the 0.5 mmol scale can result in irreversible catalyst decomposition over time even when stored under inert conditions. Notably, SPhos undergoes a dramatic color change over the course of 22 hours

resulting in significant loss of catalytic activity (Figure 6). This is likely due to known intramolecular phosphine oxidation pathways when ligated to $Pd(OAc)_2$.[17] EvanPhos exhibits no such color change over the same time period and maintains identical catalytic activity, indicative of this ligand's resistance to these intramolecular deactivation processes (Figure 7).

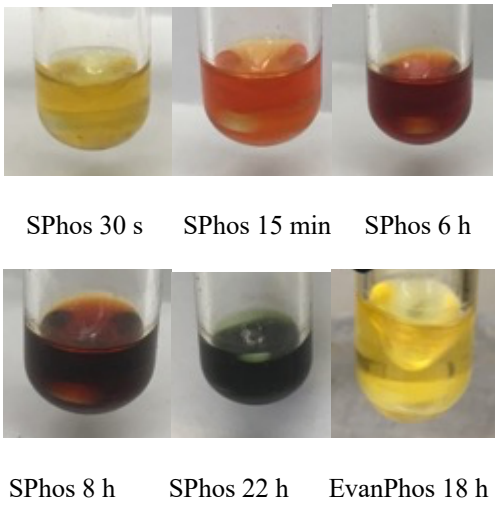


Figure 6: Color changes for ligands ligated to $Pd(OAc)_2$

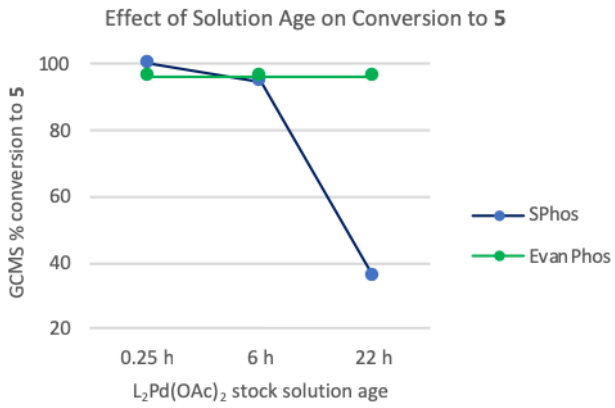


Figure 7: Effect of stock solution age on catalytic activity

While good reactivity was observed in EtOAc we view this solvent as a stepping stone towards ultimately conducting reactions in aqueous micellar media. To that end a variety of,

once again, functionalized "drug-like" (hetero)aryl bromides and boronic acids were synthesized in good-to-excellent yields utilizing 0.1-0.5 mol% EvanPhos$_2$Pd (Figure 8).

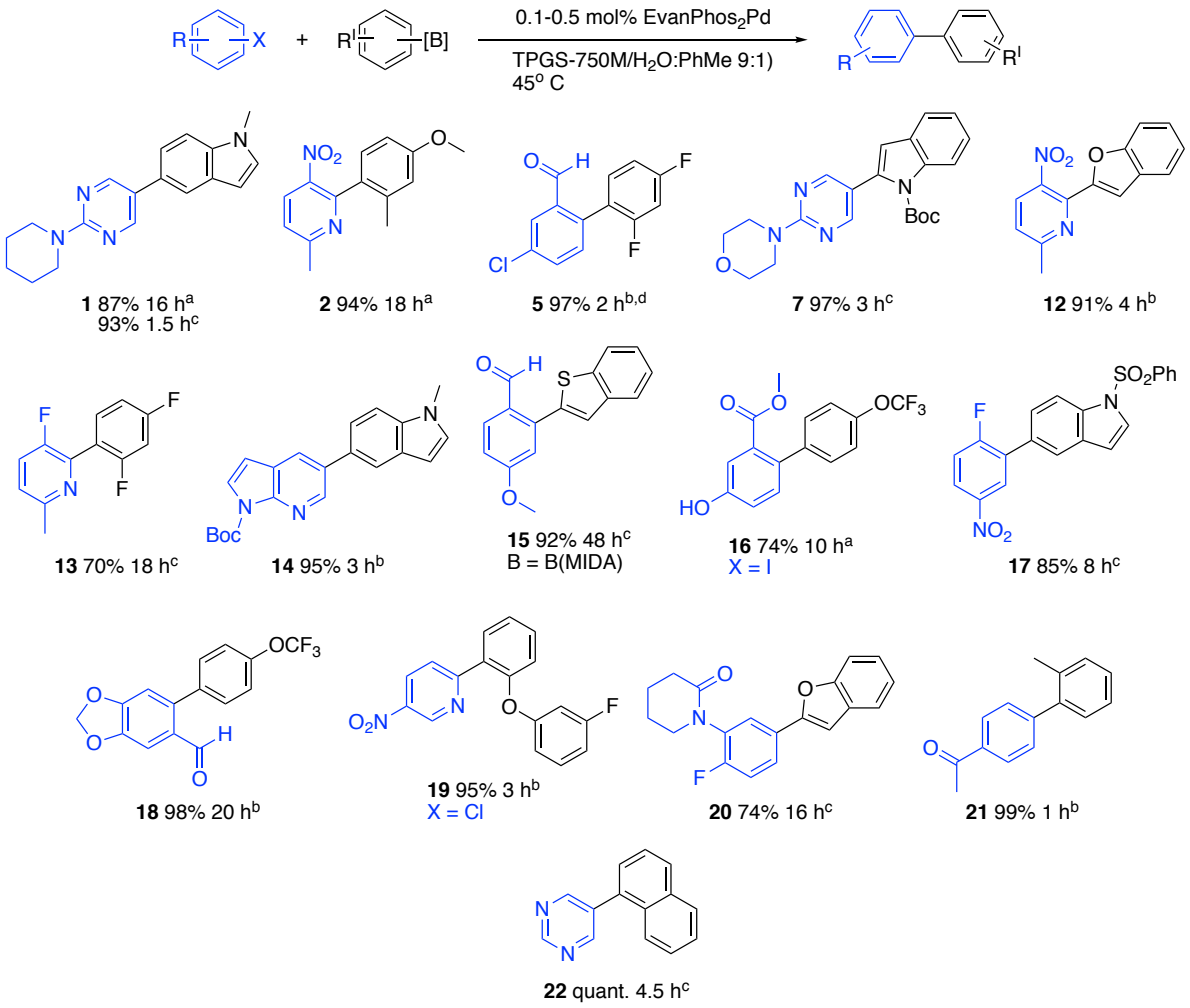


Figure 8: SMC couplings in TPGS-750-M utilizing EvanPhos$_2$Pd. Conditions: Conditions: a.) Pd(OAc)$_2$ (0.1 mol%), EvanPhos (0.18–0.2 mol%) reduced with DIBAL/PhMe, halide (0.5 mmol), organoboron (0.75 mmol), K$_3$PO$_4$·H$_2$O (0.75 mmol). 2 wt% TPGS-750-M/H$_2$O (0.9 mL), PhMe (0.1 mL from catalyst solution) 45 °C. Reaction times not optimized at 0.1 mol% Pd. b.) Pd(OAc)$_2$ (0.25 mol%), EvanPhos (0.45–0.5 mol%). c.) Pd(OAc)$_2$ (0.5 mol%), EvanPhos (0.9–1.0 mol%). d.) No DIBAL

Several of these synthesized examples were compared to literature methods previously used for their synthesis (Figure 9). In all three cases EvanPhos compares favorably with regard to solvent, temperature, and/or catalyst loading.

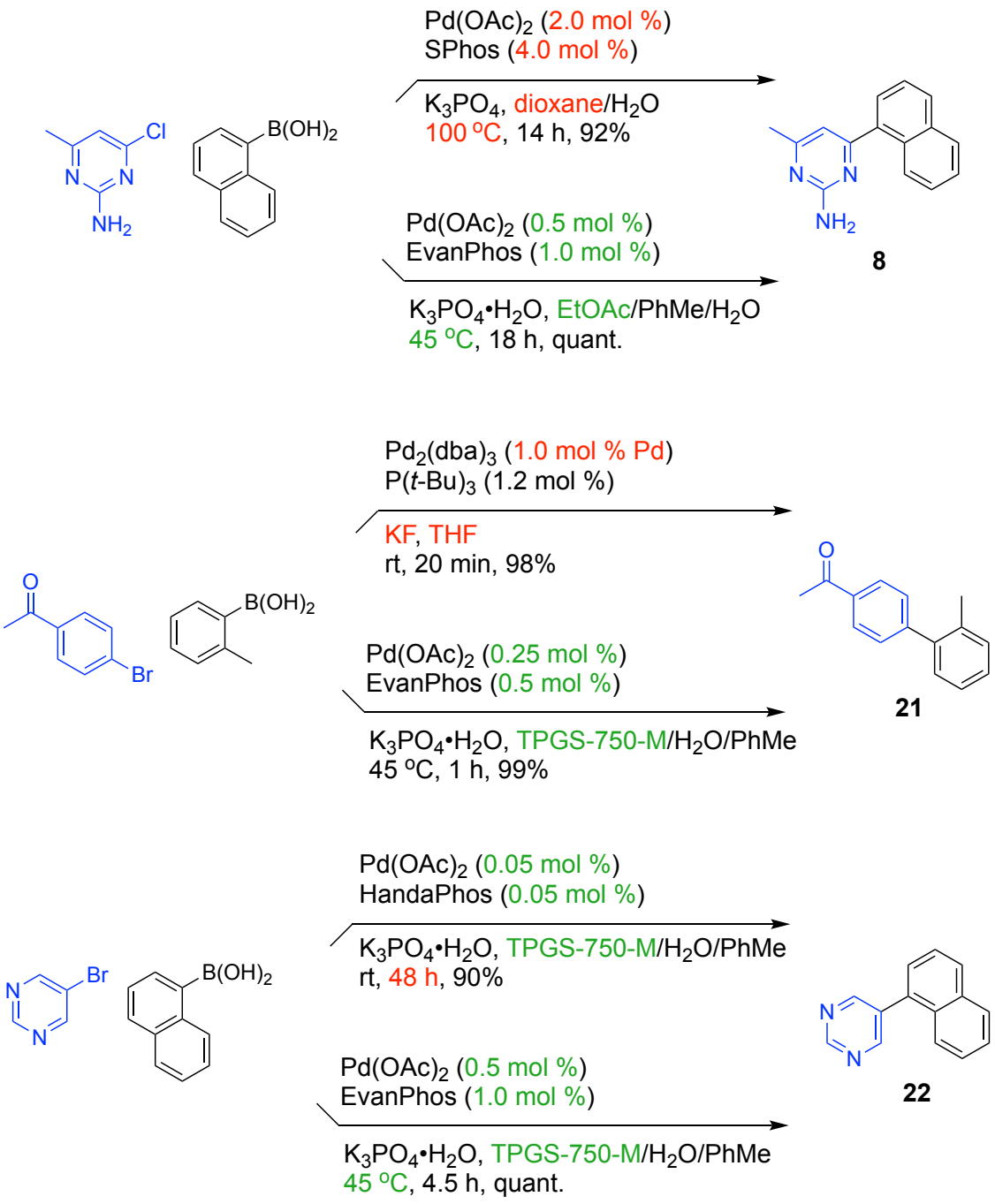


Figure 9: Comparisons of EvanPhos with literature methods

As a featured case the coupling to form biaryl **23** (Figure 10), an intermediate en route to CETP inhibitor anacetrapib, was conducted under micellar catalysis conditions using only

500 ppm Pd (0.05 mol%). Even using such a low catalyst loading, **21** could be isolated cleanly in 91% yield.

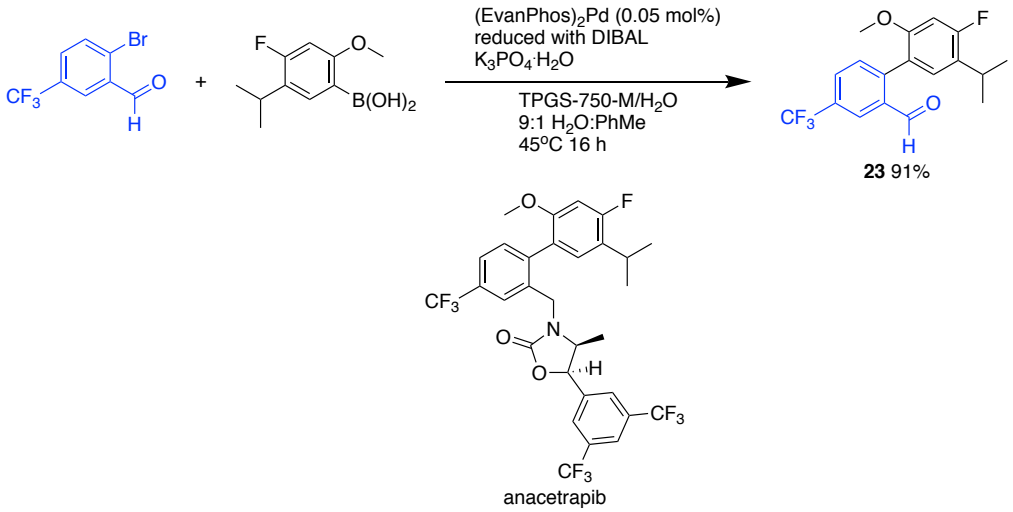


Figure 10: Synthesis of Anacetrapib intermediate

Utilizing $(EvanPhos)_2Pd$ at the 1000-2500 ppm level results in low levels of residual palladium contamination in the products (Figure 11). This is an important benefit as all of the products analyzed for residual palladium contained between 1-10 ppm palladium, well within the FDA mandated limit of 10 ppm (10 μg/g drug/day).[18] As such, use of EvanPhos complexed palladium at these low loadings is an option for the ultimate step of an API synthesis without fear of exceeding the FDA mandated 10 ppm limit.

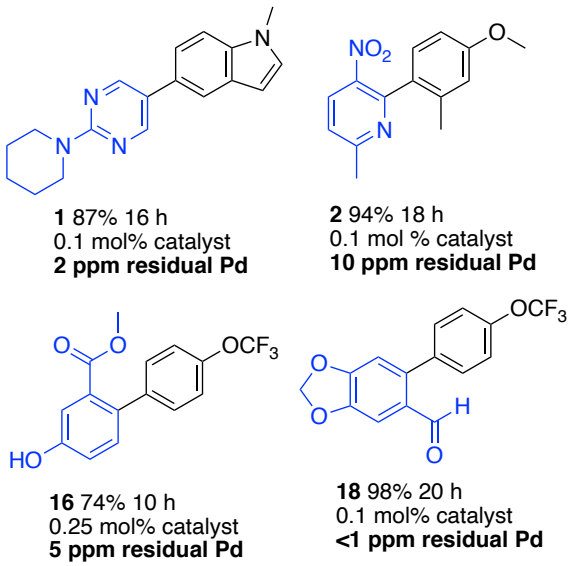


Figure 11: Residual Pd levels

To gain better insight into the nature of the catalyst two compounds were synthesized and isolated as bis-EvanPhos ligated $Pd(OAc)_2$ and $PdCl_2$ which were both bench stable and catalytically active vs. a toluene based mixture of ligand and $Pd(OAc)_2$. Attempts to obtain crystals suitable for single crystal X-ray crystallographic analysis proved futile for the $Pd(OAc)_2$ complex but gratifyingly, crystals could be obtained for the $PdCl_2$ complex (Figure 12). Two interesting features are noted in this crystal structure that bears C_i symmetry. First, there is a weak 3.076 Å coordination between the resorcinol methoxy closest to the naphthyl system and the metal center. This would later prove to be a salient feature throughout the catalytic cycle based on DFT calculations. Second, counter-intuitively the biaryl bond is rotated such that the bulkier ring of the napthyl system is facing the metal center rather than the less congested methoxy group. MN15 based calculations place the crystallographically observed rotation 4.36 kcal/mol lower in energy than the initially predicted rotation predicted rotation.

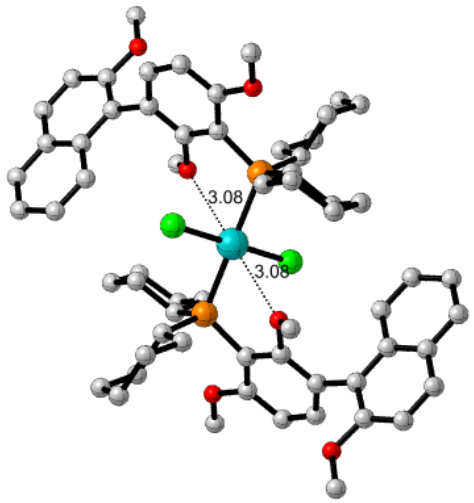


Figure 12: X-ray crystal structure of EvanPhos$_2$PdCl$_2$. Hydrogens omitted for clarity

An analogue of EvanPhos wherein the cyclohexyls are replaced with *t*-butyl groups was synthesized. When the Pd(OAc)$_2$ complex of *t*-buEvanPhos was synthesized an unexpected reaction occurred leading to the formation of an anionic bidentate P,O-desmethyl (*t*-BuEvanPhos)PdOAc complex (Figure 13). Due to the presence of mEtOAc in the crude product, we conclude that this complex arises from an intramolecular nucelophillic displacement of the methyl group by the acetate ion (Figure 14) . Attempts to obtain single crystals of this compound yielded another unexpected result. Rather than the single atomic Pd complex, a Pd dimer crystallized from solution (Figure 13). This complex was only visible by ESI-MS at exceedingly high concentrations while the majority of observed species in the MS was identified as the single atomic Pd complex. This leads us to conclude the single Pd atom complex is the dominant species in the mixture. This isolated powder was tested in several SMC reactions and proved to have essentially identical reactivity to EvanPhos. At the time of publication this was the first literature example of an anionic P,O bidentate ligand showing catalytic activity in a SMC (Figure 15).

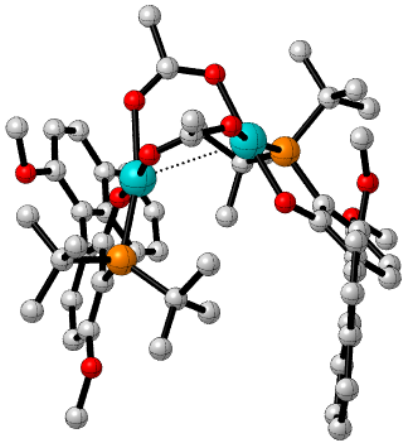


Figure 13: X-ray crystal structure of desmethyl (t-BuEvanPhos)$_2$Pd$_2$(OAc)$_2$. Hydrogens omitted for clarity.

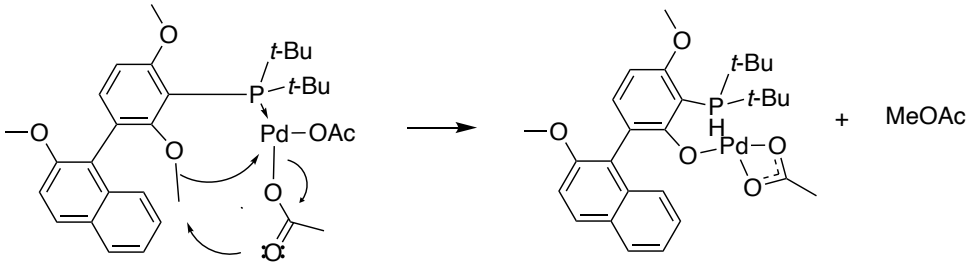
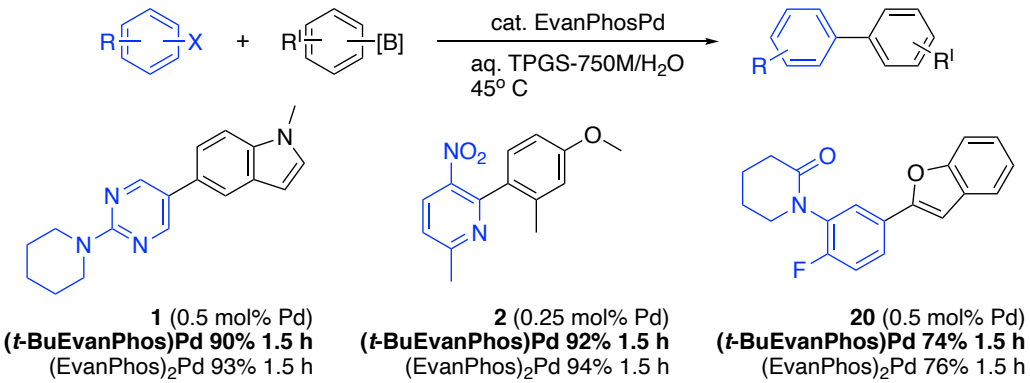


Figure 14: Formation of desmethyl *t*-BuEvanPhosPdOAc



1 (0.5 mol% Pd)
(*t*-BuEvanPhos)Pd 90% 1.5 h
(EvanPhos)$_2$Pd 93% 1.5 h

2 (0.25 mol% Pd)
(*t*-BuEvanPhos)Pd 92% 1.5 h
(EvanPhos)$_2$Pd 94% 1.5 h

20 (0.5 mol% Pd)
(*t*-BuEvanPhos)Pd 74% 1.5 h
(EvanPhos)$_2$Pd 76% 1.5 h

Figure 15: Comparisons betweent EvanPhos and t-BuEvanPhos

Given the modular nature of the EvanPhos synthesis other ligands have been prepared in search of enhanced reactivity. This effort has led to discovery of N_2Phos (Figure 16) which shows greater reactivity upon complexation with Pd at both lower catalyst loadings and with aryl chlorides that could not be usefully coupled with EvanPhos.[19] Additionally, EvanPhos has been incorporated into a novel substituted palladacycle for enhanced catalytic activity (Figure 16).[20]

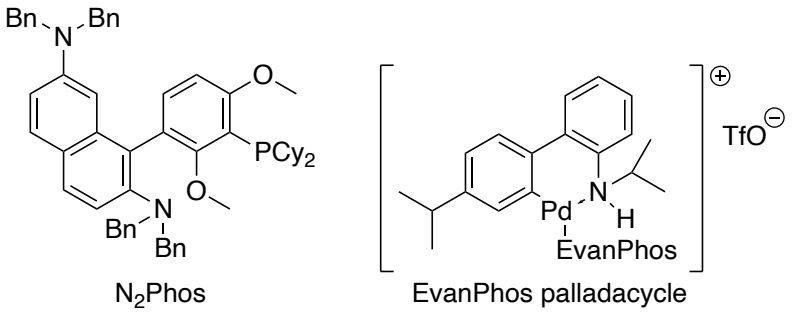
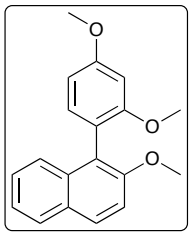


Figure 19: Structure of N_2Phos and EvanPhos palladacycle

D. Conclusion

In summary, a newly designed ligand, EvanPhos, is described which when combined with palladium as a ca. 2 : 1 complex serves as a pre-catalyst for SM couplings in either EtOAc or under micellar conditions in water with equal efficiency. It can be prepared in two simple steps from either $(CH_3CN)PdCl_2$ or $Pd(OAc)_2$, and is readily converted to a highly active Pd(0) species. This catalyst is even more reactive in the atypical organic medium EtOAc, rather than in commonly used toluene or ethereal solvents, and functions with loadings in the 0.05–0.5 mol% range of Pd. EvanPhos is also resistant to common intermolecular redox processes that lead to catalyst deactivation of other biaryl ligands.

E. Experimental Procedures and Analytical Data for the Synthesis of EvanPhos (2) and its Pd Complexes.



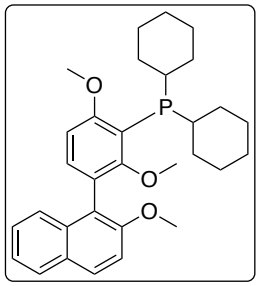
1-(2,4-Dimethoxyphenyl)-2-methoxynaphthalene. An oven-dried 5 mL conical microwave vial containing an oblong stir bar was charged with $Pd(OAc)_2$ (7.0 mg) and EvanPhos (29 mg) and sealed with a septum. The vial was evacuated and refilled 3x with argon. Toluene (0.64 mL) was added via syringe and the mixture was stirred for a minimum of 30 min under an inert atmosphere. A 4 mL dram vial containing an oblong stir bar was charged with 1-bromo-2-methoxynaphthalene (119 mg, 0.5 mmol), 2,4-dimethoxyphenylboronic acid (173 mg, 0.95 mmol) and tribasic potassium phosphate monohydrate (173 mg, 0.75 mmol). The vial was fitted with a rubber septum and then evacuated and refilled 3x with argon. A 2 wt % solution of TPGS-750-M/H_2O (0.9 mL) was added via syringe followed by the previously prepared catalyst solution (0.1 mL). The septum was removed and quickly replaced with a PTFE-lined threaded cap. The dram vial was placed in an aluminum reactor block containing a magnetic stir plate with a thermocouple set to 49 ^oC (NOTE: this yields a temperature of 45 ^oC within the reaction vial). The reaction was stirred rapidly for 3 h. The vial was removed from the reactor block and allowed to cool to rt. The reaction was extracted with EtOAc (3 x 1 mL) in flask and the combined organic layers were flushed through a Pasteur pipette plugged with cotton and 4 cm of silica gel into a 50 mL round-bottomed flask. Volatiles were removed *in vacuo*. The product was purified *via* flash chromatography on silica gel eluting with 1:4 diethyl

ether/hexanes R_f = 0.20 in 1:4 diethyl ether:hexanes. The column was flushed with 100% diethyl ether. The pure product was collected. The impure fractions were collected along with the ether flush, concentrated *in vacuo*, and the resulting crude sample was chromatographed over silica gel eluting with 1:4 diethyl ether/hexanes. The pure fractions were combined and volatiles removed *in vacuo* to yield the title compound as an off-white powder (combined 130 mg, 88%).

Gram scale synthesis of 1-(2,4-dimethoxyphenyl)-2-methoxynaphthalene. A 100 mL Schlenk flask containing a an oblong football shaped magnetic stir bar was consecutively charged with $(EvanPhos)_2Pd(OAc)_2$ (60.3 mg, 0.05 mmol), 1-bromo-2-methoxynaphthalene (1.186 g, 5.0 mmol), 2,4-dimethoxyphenylboronic acid (1.592 g, 8.75 mmol), and tribasic potassium phosphate monohydrate (2.02 g, 8.75 mmol). The flask was sealed with a septum then subjected to 3 evacuation/argon refill cycles. The flask was charged with toluene (1.5 mL), and an aqueous solution of 2 wt % TPGS-750-M (8.5 mL). The flask was submerged in a heated oil bath (bath temperature 48 ^oC) and stirred vigorously for 5 h. After cooling to rt the mixture was diluted with EtOAc (40 mL) and stirred vigorously until all solids had dissolved. The mixture was transferred to a separatory funnel, washing with EtOAc to ensure complete transfer, and the phases were separated. The organic phase was dried over anhydrous Na_2SO_4 followed by solvent removal *in vacuo*. The crude material was chromatographed as before to yield the title compound as an off-white powder (1.251 g, 85%)

^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.44 – 7.40 (m, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.67 – 6.63 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.38, 158.63,

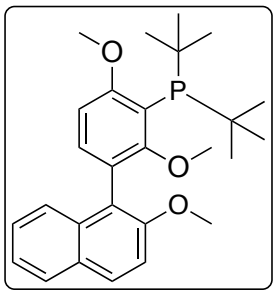
154.47, 133.97, 132.63, 129.04, 128.90, 127.80, 126.03, 125.31, 123.33, 121.77, 117.67, 114.10, 104.40, 99.03, 56.93, 55.66, 55.34.



EvanPhos: dicyclohexyl(2,6-dimethoxy-3-(2-methoxynaphthalen-1-yl)phenyl)phosphane. A flame dried 250 mL 3-neck round bottomed flask containing a football shaped magnetic stir bar was charged with 1-(2,4-dimethoxyphenyl)-2-methoxynaphthalene (4.573 g, 15.53 mmol) under a flow of argon. The vessel was evacuated and back-filled with argon three times. The vessel was charged with anhydrous THF (75 mL) and stirred until dissolution of the biaryl was visually complete. The vessel was submerged in an ice bath and stirred for 20 min. *n*-Butyllithium (2.23 [M] in hexanes, 6.9 mL, 15.38 mmol) was added to the stirring solution dropwise via syringe over 20 min. Upon complete addition of *n*-butyllithium, the solution was allowed to stir in the ice bath for 30 min. Neat chlorodicyclohexylphosphine (3.35 mL, 15.16 mmol) was added dropwise via syringe over the course of 15 min. The solution was allowed to stir in the ice bath for 30 min. at which point the vessel was removed from the ice bath. Stirring was continued at rt for 1 h. The solution was quenched with water (25 mL) and diluted with diethyl ether (100 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with a solution of 10% sulfuric acid/water (5 x 20 mL) and the acidic layers were collected into a 1 L beaker. Diethyl ether (150 mL) was added to the beaker that was then cooled in an ice bath. Solid sodium carbonate was slowly added while gently swirling until gas evolution had ceased [CAUTION: extremely

exothermic. Add carbonate slowly and add more diethyl ether as needed to maintain approximately 100-150 mL of diethyl ether in the beaker]. The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The ether was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The mixture was chromatographed over basic aluminum oxide eluting with 30% diethyl ether/hexanes (R_f = 0.26 30% diethyl ether/hexanes) which yielded a flocculent white solid (5.73 g, 77%). **IMPORTANT NOTES CONCERNING ISOLATION**: this chromatographic purification must be run in 20 min or less. Extended time in contact with the aluminum oxide will result in oxidation of the ligand to the phosphine oxide. The less time spent during chromatography directly translates to a lower percentage of phosphine oxide in the final product. Silica gel is extremely useful for analytically determining purity of the fractions by TLC but results in rapid oxidation of the phosphine to the phosphine oxide during column chromatography. **DO NOT USE SILICA GEL FOR PURIFICATION AND RUN THE ALUMINUM OXIDE CHROMATOGRAPHIC PURIFICATION RAPIDLY**. Additionally, fractions should be collected and concentrated rapidly. Allowing the phosphine to sit in the chromatographic eluent exposed to atmosphere will result in oxidation of the phosphine to the phosphine oxide as well. Finally, once the last traces of solvent are removed *in vacuo* the product will foam vigorously and expand to consume the full headspace of the vessel and will likely end up in the rotary evaporator and/or hi-vac lines. To avoid this use a significantly larger vessel than one would normally pick for this scale of reaction. A batch synthesized on the scale presented here should use a 1 L round-bottomed flask or other appropriate vessel for concentration/solvent evaporation. ^{1}H NMR with ^{31}P decoupling (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.0 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.48 – 7.43 (m, 1H), 7.39 – 7.29 (m, 3H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H),

3.22 (s, 3H), 2.46 – 2.30 (m, 2H), 2.01 – 1.88 (m, 2H), 1.81 – 1.54 (m, 8H), 1.37 – 1.06 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.78, 164.65, 163.30, 154.43, 134.41, 133.87, 129.17, 129.14, 127.95, 126.42, 125.39, 123.56, 122.56, 121.98, 113.93, 106.20, 61.05, 56.90, 55.58, 34.76 (d, *J* = 11.5 Hz), 34.32 (d, *J* = 11.7 Hz), 32.71 (d, *J* = 24.5 Hz), 32.34 (d, *J* = 22.2 Hz), 30.70 (dd, *J* = 8.8, 6.4 Hz), 27.64 – 27.15 (m), 26.67. ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.81, 164.71, 163.35, 154.49, 134.44, 133.93, 129.21, 129.18, 127.96, 126.42, 125.44, 123.58, 122.68, 122.04, 114.02, 106.24, 61.06, 61.03, 56.93, 55.59, 34.86, 34.76, 34.44, 34.35, 32.82, 32.63, 32.48, 32.30, 30.81, 30.74, 30.68, 27.64, 27.59, 27.57, 27.53, 27.42, 27.34, 27.31, 27.22, 26.71 (complexity due to phosphorus coupling). ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.24 (phosphine oxide appears at 50.80). Chemical Formula: $C_{31}H_{39}O_3P$. EI-MS [M*$^+$] calcd: 490.2637; found: 490.2630.

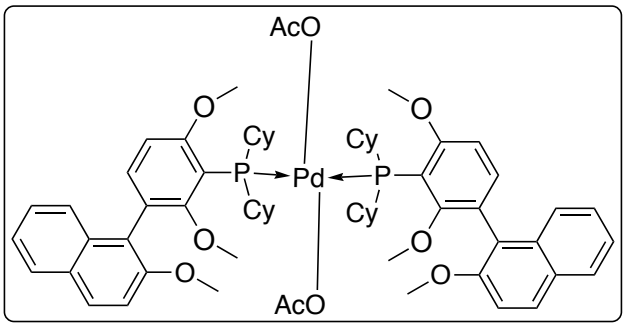


***t*-BuEvanPhos.Di-*t*-butyl(2,6-dimethoxy-3-(2-methoxynaphthalen-1-yl)phenyl)phosphane.** A flame dried 400 mL cylindrical pressure vessel with 24/40 jointed side arm and threaded screw cap (see page 6 for picture of the reaction apparatus) containing a football shaped magnetic stir bar was charged with 1-(2',4'-dimethoxyphenyl)-2-methoxynaphthalene (1.30 g, 4.42 mmol) under a flow of argon. The vessel was charged with anhydrous THF (25 mL) and sealed with a rubber septum. The mixture was stirred until dissolution of the biaryl was visually complete. The vessel was submerged in an ice bath and stirred for 20 min. *n*-Butyllithium (2.39 [M] in hexanes, 1.77 mL, 4.22 mmol) was added to the stirring solution dropwise via syringe over 20 min. Upon complete addition of *n*-

butyllithium, the solution was allowed to stir in the ice bath for 30 min. Neat di-*t*-butylchlorophosphane (0.76 mL, 4.22 mmol) was added dropwise via syringe over the course of 15 min. The solution was allowed to stir in the ice bath for 30 min. at which point the vessel was removed from the ice bath. Stirring was continued at rt for 1 h. The rubber septum was removed and neat Cu(I)Cl (0.605 g, 4.22) was added to the vessel. Residual Cu(I)Cl was rinsed into the vessel with anhydrous THF (5 mL). The vessel was sealed with a threaded screw cap, placed in an oil bath set to 90 °C, and stirred for 18 h. The vessel was cooled to rt. The solution was quenched with water (25 mL) and diluted with diethyl ether (100 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with a solution of 10% sulfuric acid/water (5 x 20 mL) and the acidic layers were collected into a 1 L beaker. Diethyl ether (150 mL) was added to the beaker that was then cooled in an ice bath. Solid sodium carbonate was slowly added while gently swirling until gas evolution had ceased [CAUTION: extremely exothermic. Add carbonate slowly and add more diethyl ether as needed to maintain approximately 100-150 mL of diethyl ether in the beaker]. The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The ether was removed *in vacuo* and the resulting viscous oil was flushed through a plug of basic alumina with 30% ether/hexanes. The solvent was removed *in vacuo* yielding a white powder (0.833 g, 45%).

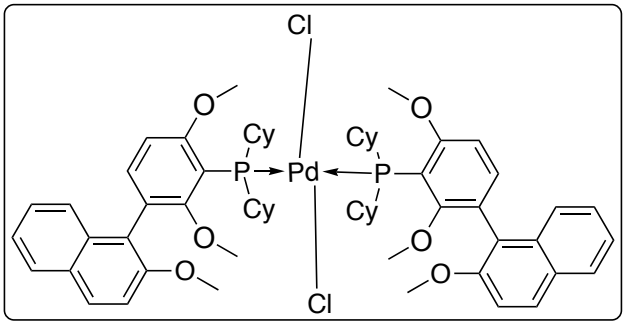
^{1}H NMR with ^{31}P decoupling (400 MHz, $CDCl_3$) δ 7.91 – 7.77 (m, 2H), 7.52 – 7.45 (m, 1H), 7.40 – 7.27 (m, 3H), 7.21 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 3.84 (s, 6H), 3.27 (s, 3H), 1.27 (d, J = 11.3 Hz, 18H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 61.89, 24.75. Molecular formula: $C_{27}H_{35}O_3P$ ESI-MS $[M+H]^+$ calcd: 439.2402; found: 439.2389.

General procedure for the synthesis of (EvanPhos)$_2$Pd and related complexes. A dry 25 mL round-bottom flask containing a magnetic stir bar was charged with an appropriate palladium(II) salt under an argon atmosphere. Sufficient dry toluene was added to achieve 0.4 [M] relative to the palladium(II) salt and the mixture was stirred until dissolution of the palladium was complete. A separate dry 25 mL round-bottom flask was charged the appropriate ligand (2.05:1 L:Pd) and dissolved in dry toluene to achieve 0.4 [M]. The ligand solution was transferred to the palladium solution via syringe in a dropwise fashion over the course of 30 min. Upon complete addition the flask containing the ligand was rinsed with a small portion of dry toluene and this was subsequently transferred to the palladium-containing flask. The mixture was allowed to stir for 1-2 h (EvanPhos) 24 h (*t*-BuEvanPhos) under an argon atmosphere. A yellow powdery precipitate was observed in all cases. A 22 gauge vent needle was placed into the septum to halve the volume of toluene in the flask. The mixture was vacuum filtered and the resulting yellow powder was rinsed liberally with hexanes. The material was transferred to a vial and volatiles were removed *in vacuo*.

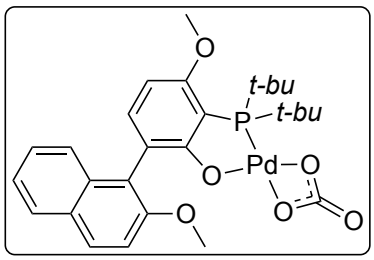


EvanPhos$_2$[Pd(OAc)$_2$]. Synthesized according to the general procedure utilizing Pd(OAc)$_2$ (86 mg, 0.38 mmol) and EvanPhos (383 mg, 0.781 mmol). Material was isolated as a yellow

powder (366 mg, 85%). Chemical Formula: $C_{66}H_{84}O_{10}P_2Pd$. ESI-MS $[M+H-2(OAc)]^+$ calcd: 1087.4408; found: 1087.4413.



EvanPhos)$_2$PdCl$_2$. Synthesized according to the general procedure utilizing $(MeCN)_2PdCl_2$ (52 mg, 0.2 mmol) and EvanPhos (202 mg, 0.411 mmol). Material was isolated as a yellow powder (154 mg, 67%). Chemical Formula: $C_{62}H_{78}Cl_2O_6P_2Pd$. ESI-MS $[M+H-2(Cl)]^+$ calcd: 1087.4408; found: 1087.4404.



(*t*-BuEvanPhos)Pd(OAc). Synthesized according to the general procedure utilizing $Pd(OAc)_2$ (60 mg, 0.27 mmol) and EvanPhos (234 mg, 0.53 mmol). Material was isolated as a yellow powder. Chemical Formula: $C_{58}H_{76}O_{10}P_2Pd$. ESI-MS $[M+2CH_3CN-(OAc)]^+$ calcd: 611.1167; found: 611.1642.

General procedure for catalyst solution preparation and optional pre-reduction. $Pd(OAc)_2$ (3.0-11.0 mg) and EvanPhos (1.75-2.0 equiv EvanPhos : Pd) were added to a dry

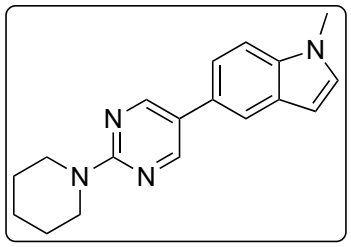
5 mL microwave vial containing an oblong stir bar. The vial was sealed with a rubber septum and the vial was evactuated and refilled with argon 3x. Dry toluene was added to the vial to achieve a concentration of 0.56 mg $Pd(OAc)_2$/0.1 mL toluene for a 0.5 mmol scale reaction (0.56 mg $Pd(OAc)_2$ in 0.1 mL toluene yields 0.5 mol % catalyst loading). To achieve lower catalyst loadings, e.g., 0.1-0.25 mol % Pd, dilute this mixture accordingly). The mixture was stirred at a moderate speed for a minimum of 30 min under an argon atmosphere. OPTIONAL: For reactions that may be slow to initiate pre-reduction of the catalyst with DIBAL may be beneficial. After 30 min, DIBAL (1.0 [M] in toluene or DCM, 2.0-2.1 equiv relative to Pd) was added dropwise. Complete reduction is accompanied by the mixture turning brown/black. At this point the catalyst is ready and may be added to the reaction mixture. This procedure is exactly the same for the use of isolated $EvanPhos_2PdX_2$ catalysts in place of $Pd(OAc)_2$ + 2EvanPhos.

General procedure A for Suzuki-Miyaura reactions in EtOAc. A 4 mL dram vial containing an oblong magnetic stir bar was charged with solid halide (0.5 mmol), organoboron (0.75 mmol, though many reactions can be conducted effectively with 0.625 mmol) and potassium phosphate monohydrate (0.75 mmol). The vial was fitted with a rubber septum, and then evacuated and refilled with argon 3x. At this point liquid halides could be added via syringe. Degassed EtOAc (0.8 mL), DI water (0.1 mL), and the catalyst solution (0.1 mL = 0.1-0.5 mol % Pd) were added sequentially to the vial via syringe. Unless otherwise noted the catalyst was pre-reduced with DIBAL. The septum was removed and quickly replaced with a PTFE lined threaded cap. The vial was placed in an aluminum heating block over a stir plate with stir rate set to 1100 rpm and a thermocouple probe in the aluminum block set to 49 ºC (NOTE: this yields a temperature of 45 ºC within the reaction vial). Reactions were followed by TLC and/or GC/MS monitoring. When the reactions were

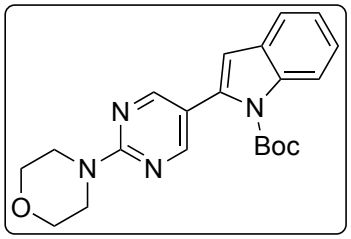
judged complete (or continued progress was not observed for incomplete reactions) the vial was cooled to rt. The mixture was flushed through a Pasteur pipette containing a cottton plug and silica gel. If needed the vial was rinsed with additional EtOAc to remove any material remaining. Volatiles were removed *in vacuo* and the crude mixture purified via flash chromatography.

General procedure B for Suzuki-Miyaura reactions in aqueous TPGS-750-M. A 4 mL dram vial containing an oblong magnetic stir bar was charged with solid halide (0.5 mmol), organoboron (0.75 mmol, though many reactions can be conducted effectively with 0.625 mmol) and potassium phosphate monohydrate (0.75 mmol). The vial was fitted with a rubber septum and then evacuated and refilled with argon 3x. At this point liquid halides could be added via syringe. A solution of 2 wt % aq. TPGS-750-M (0.9 mL) and the catalyst solution (0.1 mL = 0.05-0.5 mol % Pd) were added sequentially to the vial. Unless otherwise noted the catalyst was pre-reduced with DIBAL. The septum was removed and quickly replaced with a PTFE lined threaded cap. The vial was placed in an aluminum heating block over a stir plate with stir rate set to 1100 rpm with a thermocouple probe in the aluminum block set to 49 ^{o}C (NOTE: this yields a temperature of 45 ^{o}C within the reaction vial). Reactions were followed by TLC and/or GC/MS monitoring. When the reactions were judged complete (or continued progress was not observed for incomplete reactions) the vial was cooled to rt. The mixture was extracted with EtOAc (3 x 1 mL) and the organic phase was flushed through a Pasteur pipette containing a cotton plug and silica gel. Volatiles were removed *in vacuo* and the crude mixture was purified via flash chromatography.

F. Substrates

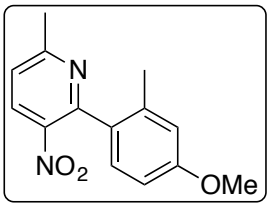


1-Methyl-5-(2-(piperidin-1-yl)pyrimidin-5-yl)-1*H*-indole. Synthesized utilizing 5-bromo-2-(piperidin-1-yl)pyrimidine and (1-methyl-1*H*-indol-5-yl)boronic acid according to general procedure A (3.5 h, 134 mg, 92% yield. 0.5 mol % Pd) and general procedure B (16 h, 127 mg, 87%. 0.1 mol % Pd) (1.5 h, 136 mg, 93%. 0.5 mol % Pd) (1.5 h, 132 mg, 90%. 0.5 mol % of isolated *t*-BuEvanPhosPd[OAc]). White solid, turns red over time when exposed to the atmosphere. R_f = 0.31 in 3:20 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 2H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 3.83 (d, *J* = 5.8 Hz, 7H), 1.76 – 1.61 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.92, 156.15, 136.23, 129.79, 129.26, 127.41, 123.83, 120.31, 118.24, 109.96, 101.32, 45.20, 33.08, 25.93, 25.07. Chemical Formula: $C_{18}H_{20}N_4$ ESI-MS $[M+H]^+$ calcd: 293.1766; found: 293.1767.

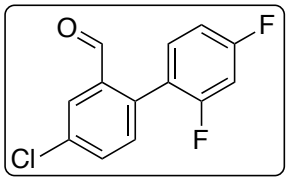


***t*-Butyl 2-(2-morpholinopyrimidin-5-yl)-1*H*-indole-1-carboxylate**: Synthesized utilizing 4-(5-bromopyrimidin-2-yl)morpholine and (1-(*t*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid according to general procedure A (3 h, 179 mg, 94% yield. 0.5 mol % Pd) and general procedure B (3 h, 185 mg, 97%, 0.5 mol % Pd). White solid. R_f = 0.23 in 3:17

EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.21 (m, 2H), 6.55 (s, 1H), 3.90 – 3.82 (m, 4H), 3.83 – 3.75 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.84, 157.27, 150.23, 137.27, 135.08, 129.25, 124.67, 123.27, 120.56, 117.87, 115.85, 110.63, 84.28, 66.96, 44.49, 28.11. Chemical Formula: $C_{21}H_{24}N_4O_3$. ESI-MS $[M+Na]^+$ calcd: 403.1746; found: 403.1748.

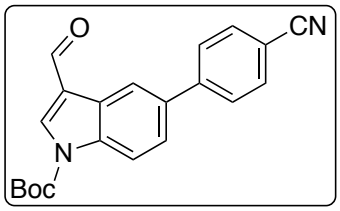


2-(4-Methoxy-2-methylphenyl)-6-methyl-3-nitropyridine. Synthesized utilizing 2-bromo-6-methyl-3-nitropyridine and (4-methoxy-2-methylphenyl)boronic acid according to general procedure A (10 h, 123 mg, 95% yield. 0.5 mol % Pd) and general procedure B (1.5 h, 121 mg, 94%. 0.1 mol % Pd) (1.5 h, 118 mg, 92%, 0.25 mol % of isolated *t*-BuEvanPhosPd[OAc]). Viscous yellow oil that slowly solidifies. R_f = 0.19 in 3:17 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.85 – 6.75 (m, 2H), 3.82 (s, 3H), 2.69 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.74, 160.10, 153.75, 144.58, 137.47, 132.55, 129.65, 129.46, 122.16, 116.08, 111.44, 55.38, 24.97, 19.90. Chemical Formula: $C_{14}H_{14}N_2O_3$ ESI-MS $[M+Na]^+$ calcd: 281.0902; found: 281.0902.

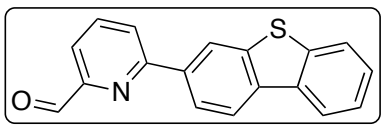


4-Chloro-2',4'-difluoro-[1,1'-biphenyl]-2-carbaldehyde. Synthesized utilizing 2-bromo-5-chloro-benzaldehyde and (2,4-difluorophenyl)boronic acid without DIBAL pre-reduction of the catalyst according to general procedure A (3 h, 120 mg, 95% yield, 0.5 mol % Pd) and

general procedure B (2 h, 122 mg, 97 %, 0.5 mol % Pd). R_f = 0.53 in 3:17 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (d, *J* = 3.0 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 7.64 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.00 (dtd, *J* = 27.7, 9.1, 8.6, 2.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.01 (d, *J* = 2.3 Hz), 163.46 (dd, *J* = 251.5, 11.6 Hz), 159.80 (dd, *J* = 249.7, 12.2 Hz), 136.17, 135.43, 135.15, 133.87, 132.96, 132.68 (dd, *J* = 9.6, 4.1 Hz), 128.08, 120.84, 112.13 (dd, *J* = 21.4, 4.0 Hz), 104.50 (d, *J* = 25.8 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -108.24 (p, *J* = 7.7 Hz, J^1 C-F= 251.5 Hz), -110.84 (q, *J* = 8.4 Hz, J^1 C-F= 249.7). Chemical Formula: $C_{13}H_7ClF_2O$ CI-MS [M^+] calcd: 252.0154; found: 252.0154.

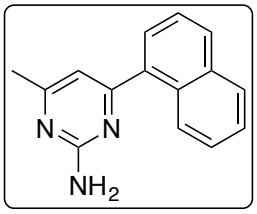


***t*-Butyl 5-(4-cyanophenyl)-3-formyl-1*H*-indole-1-carboxylate.** Synthesized utilizing *t*-butyl 5-bromo-3-formyl-1*H*-indole-1-carboxylate and (4-cyanophenyl)boronic acid according to general procedure A (14 h, 121 mg, 70% yield, 0.5 mol % Pd) R_f = 0.16 in 3:17 EtOAc/ hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.53 (s, 1H), 8.31 – 8.21 (m, 2H), 7.75 (q, *J* = 8.1 Hz, 4H), 7.64 (d, *J* = 8.7 Hz, 1H), 1.73 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.81, 148.67, 145.60, 137.44, 136.16, 135.97, 132.71, 128.15, 126.97, 125.48, 121.70, 121.04, 119.10, 115.91, 110.92, 86.27, 77.48, 77.16, 76.84, 28.22. Chemical Formula: $C_{21}H_{18}N_2O_3$ ESI-MS [M+Na]$^+$ calcd: 369.1215; found: 369.1208.

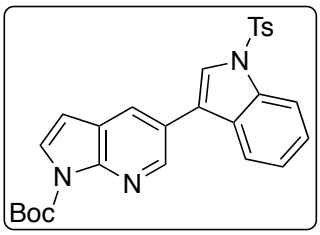


6-(Dibenzo[*b*,*d*]thiophen-3-yl)picolinaldehyde. Synthesized utilizing 6-bromopicolinaldehyde and dibenzo[*b*,*d*]thiophen-3-ylboronic acid according to general procedure A (14 h, 144 mg, quantitative) R_f = 0.24 in 9 EtOAc:hexanes. ^{1}H NMR (400

MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.84 (d, *J* = 1.7 Hz, 1H), 8.31 – 8.22 (m, 1H), 8.14 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.01 (dd, *J* = 6.6, 2.3 Hz, 1H), 7.97 – 7.82 (m, 4H), 7.55 – 7.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.01, 157.74, 152.87, 141.07, 139.97, 137.92, 136.30, 135.53, 134.68, 127.21, 125.44, 124.71, 124.42, 123.24, 123.02, 121.96, 120.13, 119.79. Chemical Formula: $C_{18}H_{11}NOS$ ESI-MS $[M+Na]^+$ calcd: 312.0459; found: 312.0458.

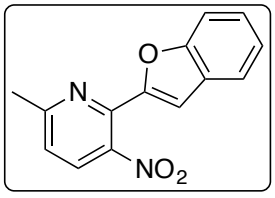


4-Methyl-6-(naphthalen-1-yl)pyrimidin-2-amine : Synthesized utilizing 4-chloro-6-methyl-pyrimidin-2-amine and naphthalene-1-boronic acid according to general procedure A (18 h, 118 mg, quantitative. 0.5 mol % Pd) R_f = 0.17 in 3:17 EtOAc:hexanes. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.10 (m, 1H), 7.95 – 7.85 (m, 2H), 7.58 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.57 – 7.45 (m, 3H), 6.79 (s, 1H), 5.24 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.56, 167.80, 163.03, 136.86, 134.01, 130.72, 129.77, 128.55, 127.05, 126.77, 126.20, 125.54, 125.32, 112.23, 24.30. Chemical Formula: $C_{15}H_{13}N_3$ ESI-MS $[M+Na]^+$ calcd: 258.1007; found: 258.1011.

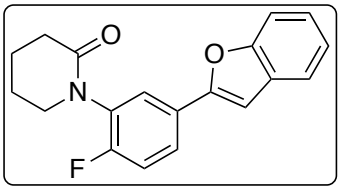


***t*-Butyl 5-(1-tosyl-1*H*-indol-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate** : Synthesized utilizing *tert*-butyl 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate and (1-tosyl-1*H*-indol-

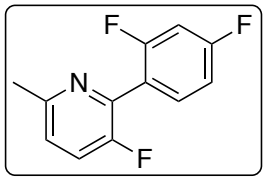
3-yl)boronic acid according to general procedure A (18 h, 224 mg, 92%, 0.5 mol % Pd) R_f = 0.35 in 3:17 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.1 Hz, 1H), 8.10 – 8.02 (m, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.77 – 7.66 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.55 (d, *J* = 4.0 Hz, 1H), 2.33 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.92, 147.73, 145.27, 144.57, 135.45, 135.11, 130.08, 129.38, 128.29, 127.49, 126.99, 125.19, 124.09, 123.83, 123.23, 123.18, 121.28, 120.15, 113.96, 104.58, 84.37, 28.19, 21.68. Chemical Formula: $C_{27}H_{25}N_3O_4S$ ESI-MS $[M+Na]^+$ calcd: 510.1463; found: 510.1476.



2-(Benzofuran-2-yl)-6-methyl-3-nitropyridine. Synthesized utilizing 2-bromo-6-methyl-3-nitro-pyridine and benzofuran-2-ylboronic acid according to general procedure B (4 h, 116 mg, 91%, 0.25 mol % Pd) R_f = 0.25 in 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 9.8 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.21 (m, 2H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.14, 155.82, 151.21, 141.12, 132.30, 128.02, 126.30, 123.61, 122.75, 122.17, 112.04, 109.38, 24.87. Chemical Formula: $C_{14}H_{10}N_2O_3$ CI-MS $[M]^+$ calcd: 254.0591; found: 254.0694.

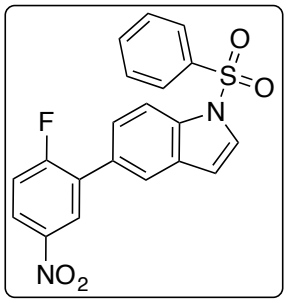


1-(5-(Benzofuran-2-yl)-2-fluorophenyl)piperidin-2-one. Synthesized utilizing 1-(5-bromo-2-fluorophenyl)piperidin-2-one and benzofuran-2-ylboronic acid according to general procedure B (16 h, 114 mg, 74%, 0.5 mol % Pd) (16 h, 118 mg, 76%, 0.5 mol % of isolated *t*-BuEvanPhosPd[OAc]) R_f = 0.22 in 40% EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.17 (m, 3H), 6.96 (s, 1H), 3.65 (t, *J* = 5.3 Hz, 2H), 2.65 – 2.57 (m, 2H), 1.99 (p, *J* = 3.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 157.90 (d, *J* = 252.8 Hz), 154.95, 154.43 (d, *J* = 1.5 Hz), 131.27 (d, *J* = 13.9 Hz), 129.18, 127.74, 125.95 (d, *J* = 1.9 Hz), 125.58 (d, *J* = 8.1 Hz), 124.55 (d, *J* = 8.0 Hz), 123.16, 121.10, 117.32 (d, *J* = 21.3 Hz), 111.23 (d, *J* = 21.3 Hz), 101.63, 51.46 (d, *J* = 1.8 Hz), 32.71, 23.52, 21.52. ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.24 – -120.31 (m, J^1 C-F= 252.8 Hz). Chemical Formula: $C_{19}H_{16}FNO_2$ ESI-MS $[M+Na]^+$ calcd: 332.1063; found: 332.1067.

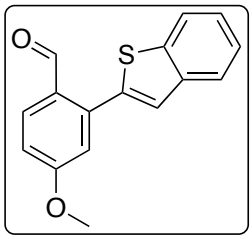


2-(2,4-Difluorophenyl)-3-fluoro-6-methylpyridine. Synthesized utilizing 2-bromo-3-fluoro-6-methylpyridine and (2,4-difluorophenyl)boronic acid according to general procedure B (20 h, 78 mg, 70%, 0.5 mol % Pd) R_f = 0.43 in 3:17 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (td, *J* = 8.4, 6.4 Hz, 1H), 7.38 (t, *J* = 8.8 Hz, 1H), 7.18 (dd, *J* = 8.4, 3.6 Hz, 1H), 7.01 (td, *J* = 8.3, 2.4 Hz, 1H), 6.96 – 6.87 (m, 1H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.72 (dd, *J* = 250.6, 11.8 Hz), 160.51 (dd, *J* = 253.2, 12.0 Hz), 155.86 (d, *J* = 256.8 Hz), 154.50 (d, *J* = 4.8 Hz), 140.94 (d, *J* = 15.4 Hz), 132.62 (ddd, *J* = 9.9, 5.0, 1.3 Hz), 124.13 – 124.05 (m), 123.88, 120.34 – 120.00 (m), 111.86 (dd, *J* = 21.4, 3.8 Hz), 104.25 (t, *J* = 25.7 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -108.81 – -108.91 (m, J^1 C-F

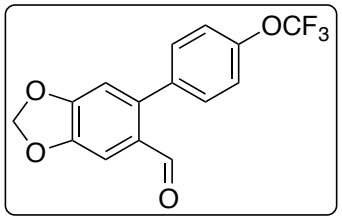
= 250.6 Hz), -109.95 (dq, J = 30.6, 8.9 Hz, J^1 C-F= 253.7 Hz), -126.82 (ddd, J = 30.5, 9.3, 3.6 Hz, J^1 C-F= 256.8 Hz). Chemical Formula: $C_{12}H_8F_3N$ CI-MS $[M]^+$ calcd: 223.0609; found: 223.0609.



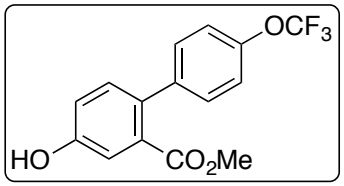
5-(2-Fluoro-5-nitrophenyl)-1-(phenylsulfonyl)-1*H*-indole. Synthesized utilizing 2-bromo-1-fluoro-4-nitrobenzene and (1-(phenylsulfonyl)-1*H*-indol-5-yl)boronic acid according to general procedure B (8 h, 168 mg, 85%, 0.5 mol % Pd) R_f = 0.28 in 1:4 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, J = 6.6, 2.9 Hz, 1H), 8.25 – 8.18 (m, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.92 (dd, J = 7.5, 1.7 Hz, 2H), 7.74 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 3.7 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.30 (t, J = 9.2 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.31 (d, J = 258.8 Hz), 144.62, 138.30, 134.97, 134.21, 131.25, 130.67, 130.55, 129.56, 128.80, 127.51, 126.96, 126.90 (d, J = 5.6 Hz), 125.59 (d, J = 3.0 Hz), 124.53 (d, J = 10.1 Hz), 122.23 (d, J = 3.2 Hz), 117.34 (d, J = 25.8 Hz), 113.99, 109.37.. ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.04 (dt, J = 9.6, 4.7 Hz). Chemical Formula: $C_{20}H_{13}FN_2O_4S$ ESI-MS $[2M+Na]^+$ calcd: 815.1058; found: 815.1064.



2-(Benzo[*b*]thiophen-2-yl)-4-methoxybenzaldehyde. Synthesized utilizing 2-bromo-4-methoxy-benzaldehyde and benzo[*b*]thiophen-2-ylboronic acid MIDA ester according to general procedure B (48 h, 92%) R_f = 0.38 in 3:17 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.86 (ddd, *J* = 18.0, 7.0, 2.1 Hz, 2H), 7.41 (tt, *J* = 7.3, 5.7 Hz, 2H), 7.31 (s, 1H), 7.10 – 7.00 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.61, 163.59, 140.62, 140.56, 139.90, 138.82, 130.42, 128.12, 126.33, 125.14, 125.06, 124.08, 122.28, 115.97, 115.06, 77.48, 77.16, 76.84, 55.88. Chemical Formula: $C_{16}H_{12}O_2S$ ESI-MS $[M+Na]^+$ calcd: 291.0456; found: 291.0462.

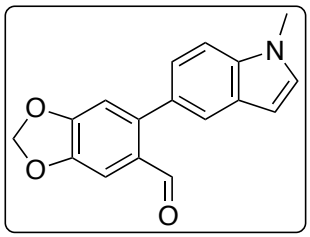


6-(4-(Trifluoromethoxy)phenyl)benzo[*d*][1,3]dioxole-5-carbaldehyde. Synthesized utilizing 6-bromopiperonal and 4-(trifluormethoxy)benzeneboronic acid according to general procedure B (20 h, 152 mg, 98%. 0.25 mol % Pd); R_f = 0.44 in 1:4 EtOAc:hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.47 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.82 (s, 1H), 6.11 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.15, 152.35, 149.36, 148.28, 142.05, 136.37, 131.62, 129.05, 120.96, 110.33, 106.65, 102.40. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.85 (J^1C-F= 287.7 Hz). Chemical Formula: $C_{15}H_9F_3O_4$ ESI-MS $[M-Na]^-$ calcd: 333.0351; found: 333.0355.

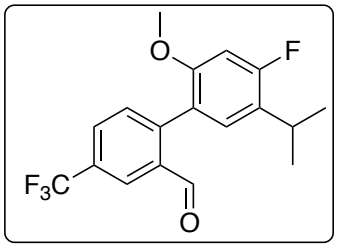


Methyl 4-hydroxy-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-carboxylate. Synthesized utilizing methyl 5-hydroxy-2-iodobenzoate and 4-(trifluoromethoxy)benzeneboronic acid

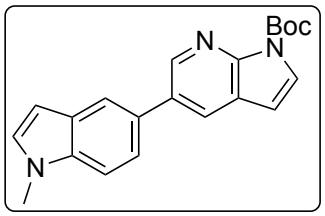
according to general procedure B (10 h, 116 mg, 74%. 0.1 mol % Pd) R_f = 0.45 in 40% EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 9.2 Hz, 2H), 7.58 (s, 1H), 7.56 (s, 1H), 7.33 (dd, *J* = 8.1, 4.3 Hz, 3H), 5.50 (s, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.87, 152.63, 135.28, 131.68, 131.16, 130.75, 130.66, 122.36, 121.54, 117.42, 52.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.79 (J^1 C-F= 257.6 Hz). Chemical Formula: $C_{15}H_{11}F_3O_4$ ESI-MS $[M-H]^-$ calcd: 311.0531; found: 311.0537.



6-(1-Methyl-1*H*-indol-5-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde. Synthesized utilizing 5-bromo-piperonal and (1-methyl-1*H*-indol-5-yl)boronic acid according to general procedure A (20 h, 113 mg, 81%. 0.1 mol % Pd) without pre-reduction of the palladium acetate and utilizing toluene:water 9:1 as the reaction medium. R_f = 0.40 in 1:4 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.48 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 6.93 (s, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.09 (s, 2H), 3.85 (s, 3H). **^{13}**C NMR (126 MHz, $CDCl_3$) δ 191.61, 152.00, 147.44, 145.39, 136.53, 130.19, 129.14, 128.84, 128.52, 124.07, 122.89, 110.88, 109.20, 106.26, 102.08, 101.46, 33.17. Chemical Formula: $C_{17}H_{13}NO_3$ ESI-MS $[M+Na]^+$ calcd: 302.0793; found: 302.0790.

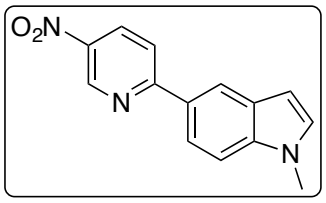


4'-Fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde. Synthesized utilizing 2-bromo-5-(trifluoromethyl)benzaldehyde and (4-fluoro-5-isopropyl-2-methoxy-phenyl)boronic acid according to general procedure B (20 h, 155, 91%, 0.05 mol % Pd). R_f = 0.60 in 1:4 Et_2O/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.25 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 11.9 Hz, 1H), 3.72 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.2 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.16, 161.78 (d, *J* = 248.3 Hz), 155.46 (d, *J* = 10.2 Hz), 144.54, 134.49, 132.21, 130.17, 129.96 (q, *J* = 3.4 Hz), 129.76 (d, *J* = 7.4 Hz), 127.94 (d, *J* = 15.6 Hz), 124.08 (q, *J* = 3.8 Hz), 121.12 (d, *J* = 3.5 Hz), 99.42 (d, *J* = 27.8 Hz), 55.92, 26.88, 22.91.^{19}F NMR (376 MHz, $CDCl_3$) δ -62.84 (J^1 C-F= 272.4 Hz), -114.25 (dd, *J* = 11.8, 8.4 Hz, J^1 C-F = 248.3 Hz). Chemical Formula: $C_{18}H_{16}F_4O_2$ ESI-MS $[M+Na+MeOH]^+$ calcd: 395.1246; found: 395.1236.

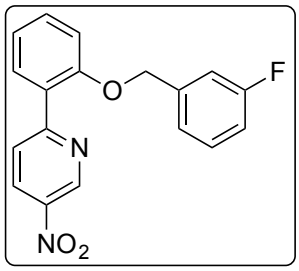


***t*-Butyl 5-(1-methyl-1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate**. Synthesized utilizing *t*-butyl 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate and (1-methyl-1*H*-indol-5-yl)boronic acid according to general procedure B (3 h, 165 mg, 95%, 0.005 mol % Pd). R_f = 0.21 in 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.08 (s, 1H), 7.85 (s, 1H), 7.66 (d, *J* = 3.9 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.11 (d, *J* = 3.0

Hz, 1H), 6.55 (m, 2H), 3.83 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.13, 147.41, 144.79, 136.40, 133.64, 130.28, 129.84, 129.19, 127.66, 127.03, 123.13, 121.64, 119.86, 109.84, 104.80, 101.44, 84.07, 33.10, 28.27. Chemical Formula: $C_{21}H_{21}N_3O_2$ ESI-MS $[M+Na]^+$ calcd: 370.1531; found: 370.1527.

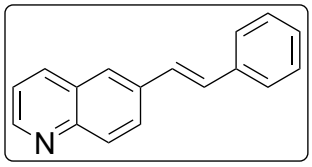


1-Methyl-5-(5-nitropyridin-2-yl)-1*H*-indole. Synthesized utilizing 2-bromo-5-nitropyridine and (1-methyl-1*H*-indol-5-yl)boronic acid according to general procedure A (20 h, 106 mg, 84%. 0.1 mol % Pd) without pre-reduction of the palladium acetate and utilizing toluene:water 9:1 as the reaction medium. R_f = 0.32 in 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, *J* = 2.7 Hz, 1H), 8.49 (dd, *J* = 8.9, 2.7 Hz, 1H), 8.41 (d, *J* = 1.7 Hz, 1H), 8.02 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 3.1 Hz, 1H), 6.62 (d, *J* = 3.1 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.51, 144.87, 142.00, 138.30, 132.00, 130.45, 128.96, 128.00, 121.44, 121.39, 119.64, 109.96, 102.54, 33.07. Chemical Formula: $C_{14}H_{11}N_3O_2$ ESI-MS $[M+H]^+$ calcd: 254.0930; found: 254.0923.

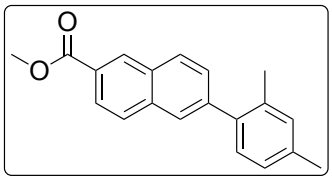


2-(2-((3-Fluorobenzyl)oxy)phenyl)-5-nitropyridine. Synthesized utilizing 2-chloro-5-nitropyridine and (2-((3-fluorobenzyl)oxy)phenyl)boronic acid according to general procedure B (3 h, 154 mg, 95%, 0.25 mol % Pd). R_f = 0.24 in 1:4 EtOAc:hexanes. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 2.6 Hz, 1H), 8.43 (dd, *J* = 8.8, 2.7 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.34 (td, *J* = 7.9, 5.7 Hz, 1H), 7.21 – 6.98 (m, 6H), 5.17 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.08 (d, *J* = 246.8 Hz), 161.38, 156.41, 144.97, 142.52, 138.99 (d, *J* = 7.4 Hz), 131.98 (d, *J* = 2.9 Hz), 130.85, 130.50, 130.41, 127.41, 125.07, 122.71 (d, *J* = 2.9 Hz), 122.05, 115.23 (d, *J* = 21.2 Hz), 114.23 (d, *J* = 22.1 Hz), 113.19, 70.14. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.35 (td, *J* = 9.0, 5.7 Hz, J^1 C-F= 246.8 Hz). Chemical Formula: $C_{18}H_{13}FN_2O_3$ ESI-MS $[M+H]^+$ calcd: 325.0988; found: 325.0977.

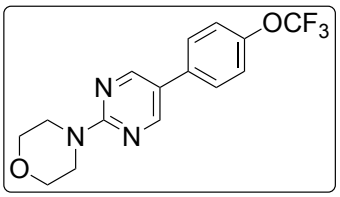


(*E*)-6-Styrylquinoline. Synthesized utilizing 5-bromoquinoline and (*E*)-phenethylboronic acid acid according to general procedure A with no DIBAL pre-reduction (8 h, 106 mg, 92%, 0.25 mol% Pd). R_f = 0.15 in 1:4 EtOAc:hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.56 (dd, *J* = 8.6, 1.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.69 (m, 3H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.46, 148.70, 137.32, 135.52, 133.00, 132.30, 129.41, 129.39, 128.96, 128.27, 126.89, 126.60, 124.36, 124.03, 121.08. Chemical Formula: $C_{17}H_{13}N$ EI-MS $[M^{\cdot}]^+$ calcd: 231.1048; found: 231.1048

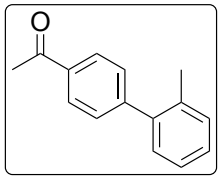


Methyl 6-(2,4-dimethylphenyl)-2-naphthoate. Synthesized utilizing methyl 6-bromo-2-naphthoateand (E)-phenethylboronic acid acid according to general procedure A with no

DIBAL pre-reduction (6 h, 140 mg, 96%, 0.1 mol% Pd). R_f = 0.58 in 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.08 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.80 (s, 1H), 7.53 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.17 – 7.09 (m, 2H), 4.00 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.44, 142.18, 138.58, 137.56, 135.58, 135.39, 131.40, 131.36, 130.99, 129.99, 129.05, 128.89, 128.32, 127.80, 127.35, 126.78, 125.65, 52.41, 21.26, 20.59. Chemical Formula $C_{20}H_{18}O_2$. EI-MS $[M^{\cdot}]^+$ calcd: 290.1307 found: 290.1314

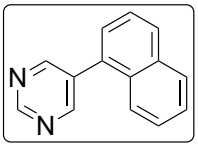


4-(5-(4-(Trifluoromethoxy)phenyl)pyrimidin-2-yl)morpholine. Synthesized utilizing 4-(5-bromopyrimidin-2-yl)morpholine and 4-(trifluoromethoxy)phenylboronic acid acid according to general procedure A with no DIBAL pre-reduction (22 h, 130 mg, 80%, 0.1 mol% Pd). R_f = 0.58 in 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 2H), 7.51 – 7.46 (m, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.89 – 3.77 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.30, 156.00, 148.76, 134.54, 127.36, 122.23, 121.86, 119.61, 66.96, 44.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.91 (J^1 C-F= 257.4 Hz). Chemical Formula $C_{15}H_{14}F_3N_3O_2$. EI-MS $[M^{\cdot}]^+$ calcd: 325.1038 found: 325.1049



1-(2'-Methyl-[1,1'-biphenyl]-4-yl)ethan-1-one. Synthesized according to a modified general procedure B. EvanPhos$_2$Pd(OAc)$_2$ (1.5 mg, 0.0013 mmol), 4-bromoacetophenone (100 mg, 0.5 mmol), 2-methylphenylboronic acid (102 mg, 0.75 mmol), and potassium

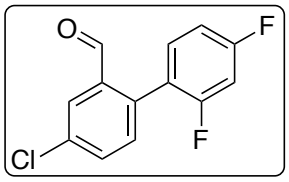
phosphate monohydrate (173 mg, 0.75 mmol) were added to a 4 mL vial with an oblong stir bar. The vial was fitted with a septum and purged under a strong flow of argon for 5 min. Toluene (0.1 mL) then TPGS-750-M solution (0.9 mL) were added to the vial. The septum was removed and the vial was quickly sealed with a threaded screw-cap. The vial was placed in an alumnimum heating block and stirred for 1 h. The reaction was cooled to rt and extracted 3 x 1 mL EtOAc. The crude was purified by silica gel flash chromatography (104 mg, 99%, 0.25 mol% Pd). R_f= 0.43 in 1:4 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 2H), 7.45 – 7.42 (m, 2H), 7.31 – 7.21 (m, 4H), 2.65 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.01, 147.09, 140.86, 135.70, 135.29, 130.66, 129.63, 129.59, 128.35, 128.03, 126.07, 26.83, 20.55. Chemical Formula $C_{15}H_{14}O$. EI-MS $[M^{\cdot}]^+$ calcd: 210.1045 found: 210.1046.



5-(Naphthalen-1-yl)pyrimidine. Synthesized according to a modified general procedure B. $EvanPhos_2Pd(OAc)_2$ (3.0 mg, 0.0025 mmol), 5-bromopyrimidine (79 mg, 0.5 mmol), naphthalene-1-boronic acid (129 mg, 0.75 mmol), and potassium phosphate monohydrate (173 mg, 0.75 mmol) were added to a 4 mL vial with an oblong stir bar. The vial was fitted with a septum and purged under a strong flow of argon for 5 min. Toluene (0.1 mL) then TPGS-750-M solution (0.9 mL) were added to the vial. The septum was removed and the vial was quickly sealed with a threaded screw-cap. The vial was placed in an alumnimum heating block and stirred for 4.5 h. The reaction was cooled to rt and extracted 3 x 1 mL EtOAc. The crude was purified by silica gel flash chromatography (103 mg, quantitative, 0.5 mol % Pd). R_f= 0.14 in 1:4 1:4 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.90 (s, 2H), 7.96 (dd, J = 8.3, 3.8 Hz, 2H), 7.76 (d, J = 8.2 Hz, 1H), 7.62 – 7.49 (m,

3H), 7.43 (d, J = 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.78, 157.45, 134.48, 133.91, 132.54, 131.30, 129.57, 128.82, 127.89, 127.22, 126.58, 125.57, 124.69. Chemical Formula $C_{14}H_{10}N_2$. EI-MS $[M\cdot]^+$ calcd: 206.0844 found: 206.0849.

G. Catalyst Stability Study EvanPhos vs. SPhos.



Following the general procedure for catalyst stock solution preparation (no DIBAL pre-reduction) and general procedure A (0.5 mol % $Pd(OAc)_2$), three reactions for each ligand (SPhos and EvanPhos) based on stock solution age were set up utilizing 2-bromo-5-chloro-benzaldehyde and (2,4-difluorophenyl)boronic acid (1.1 equiv). Conversions were determined by GCMS at 1 h (SPhos) or 2 h (EvanPhos) based on the relative ratio of starting bromide to product. SPhos catalyst age: 0.25 min 100%, 6 h 95%, 22 h 36%. EvanPhos catalyst age: 15 min 96%, 6 h 96%, 22 h 96%.

H. E Factor and Recycling Study

The initial reaction was set up according to the general procedure B. After 2 h, the aqueous solution was extracted three times with MTBE (0.75 mL total), placed in a 10 mL round bottom flask, and the solvent was removed via rotary evaporation. The crude product was purified by flash column chromatography as described previously using EtOAc/hexane to provide the desired compound.

E Factor calculation:

Note: density of MTBE = 0.74 g/mL, toluene = (0.867 g/mL)

$$\textbf{E Factor} = \frac{\textbf{Waste (mg)}}{\textbf{Product (mg)}}$$

$$\frac{(0.75\ \text{mL MTBE})\left(0.74\ \frac{\text{g}}{\text{mL}}\right) + (0.10\ \text{mL toluene})(0.867\ \frac{\text{g}}{\text{mL}})}{0.136\ \text{g}} = 4.7$$

Re-use of surfactant solution. The vial was sparged with argon and then sequentially charged with bromide (0.5 mmol), boronic acid (0.625 mmol), and tribasic potassium phosphate monohydrate (0.5 mmol), and catalyst solution (0.1 mL). The headspace of the vial was flushed with argon then capped, sealed, and stirred at 45 °C according to the general procedure.

First run: 93% yield

Second run: 95% yield

Third run: 90% yield

I. Residual Palladium Analysis

Robertson Microlit Laboratories
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Min-Kyu Cho
Novartis Institute for Biomedical Research
250 Mass. Ave.
Cambridge, Massachusetts 02139

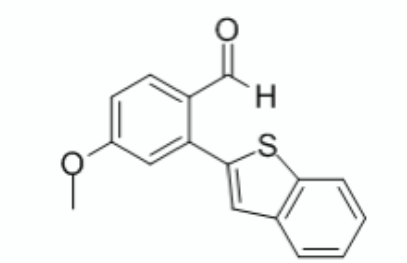
CIB001

Sample #: REILJO3-001-EXP088 **Test #:** 1 **Received:** 05/30/2017 **Completed:** 06/01/2017

ICP-OES: Palladium = 178 ppm

Services
ICP-OES

Synthesized with 0.5 mol% Pd (5000 ppm)



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CIB001

Min-Kyu Cho
Novartis Institute for Biomedical Research
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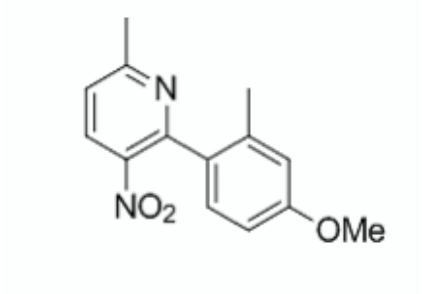
Sample #: REILLJO3-001-EXP093 **Test #:** 1 **Received:** 08/04/2017 **Completed:** 08/08/2017

ICP-OES: Palladium = 10 ppm

Services
ICP-OES

Synthesized with 0.1 mol % Pd (1000 ppm)



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CIB001

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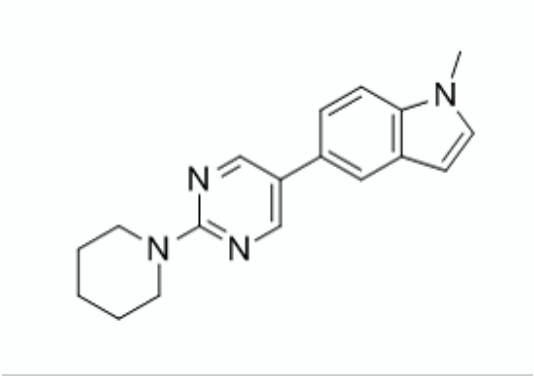
Sample #: REILLJO3-001-EXP094 **Test #:** 1 **Received:** 08/04/2017 **Completed:** 08/08/2017

ICP-OES: Palladium = 2 ppm

Services
ICP-OES Synthesized with 0.1 mol% Palladium (1000 ppm)



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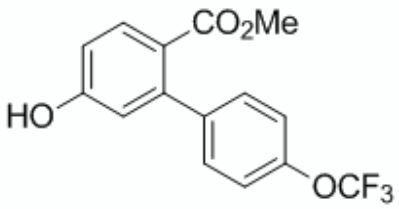
Cambridge, Massachusetts 02139

Sample #: REILLJO3-001-EXP095 **Test #:** 1 **Received:** 08/04/2017 **Completed:** 08/08/2017

ICP-OES: Palladium = < 1 ppm

Services
ICP-OES

Synthesized with 0.1 mol% Palladium (1000 ppm)



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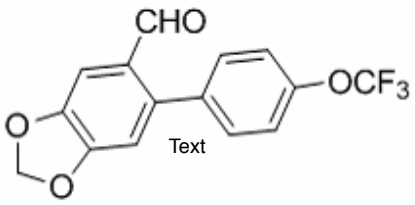
Cambridge, Massachusetts 02139

Sample #: REILLJO3-001-EXP096 **Test #:** 1 **Received:** 08/04/2017 **Completed:** 08/08/2017

ICP-OES: Palladium = 5 ppm

Services
ICP-OES

Synthesized with 0.25 mol% Palladium (2500 ppm)



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CIB001

Min-Kyu Cho
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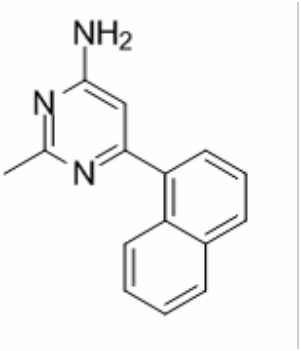
Cambridge, Massachusetts 02139

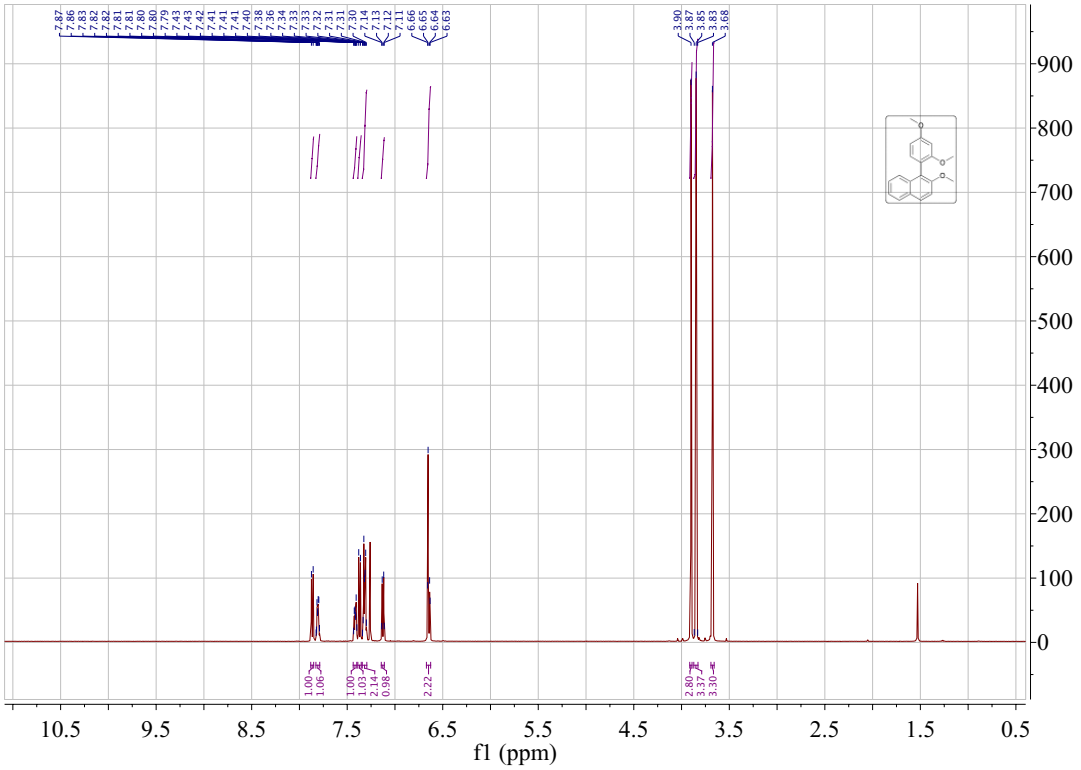
Sample #: REILJO3-001-EXP084 **Test #:** 1 **Received:** 05/30/2017 **Completed:** 06/01/2017

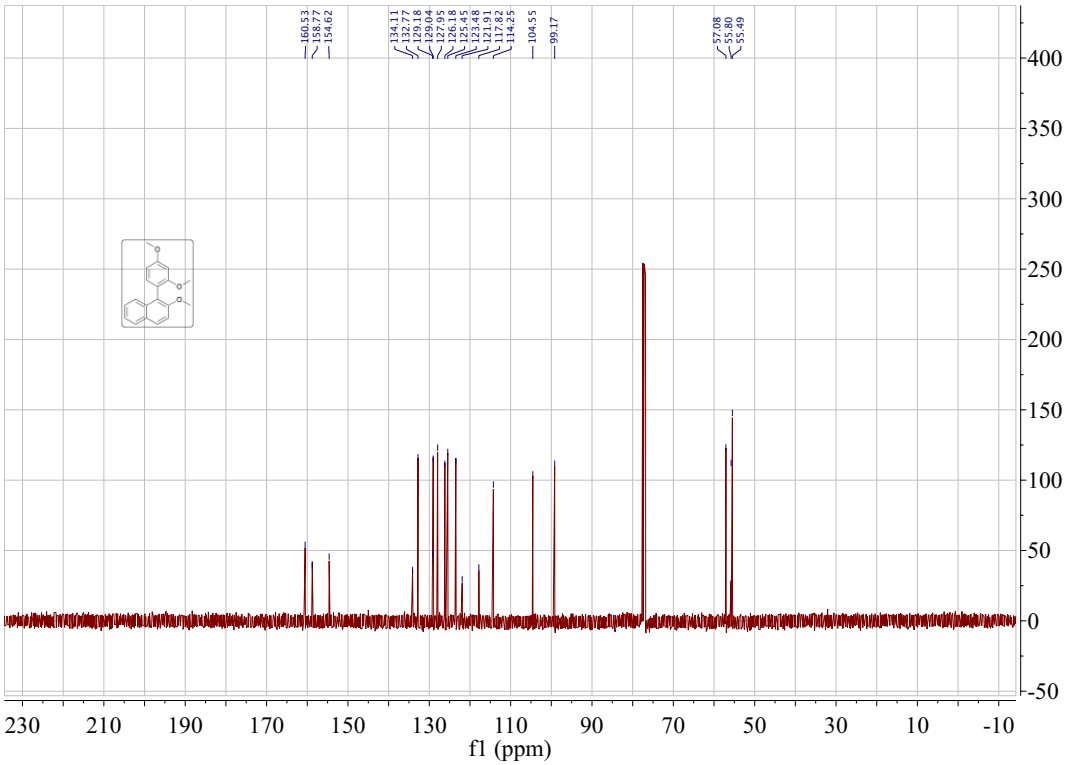
ICP-OES: Palladium = 211 ppm

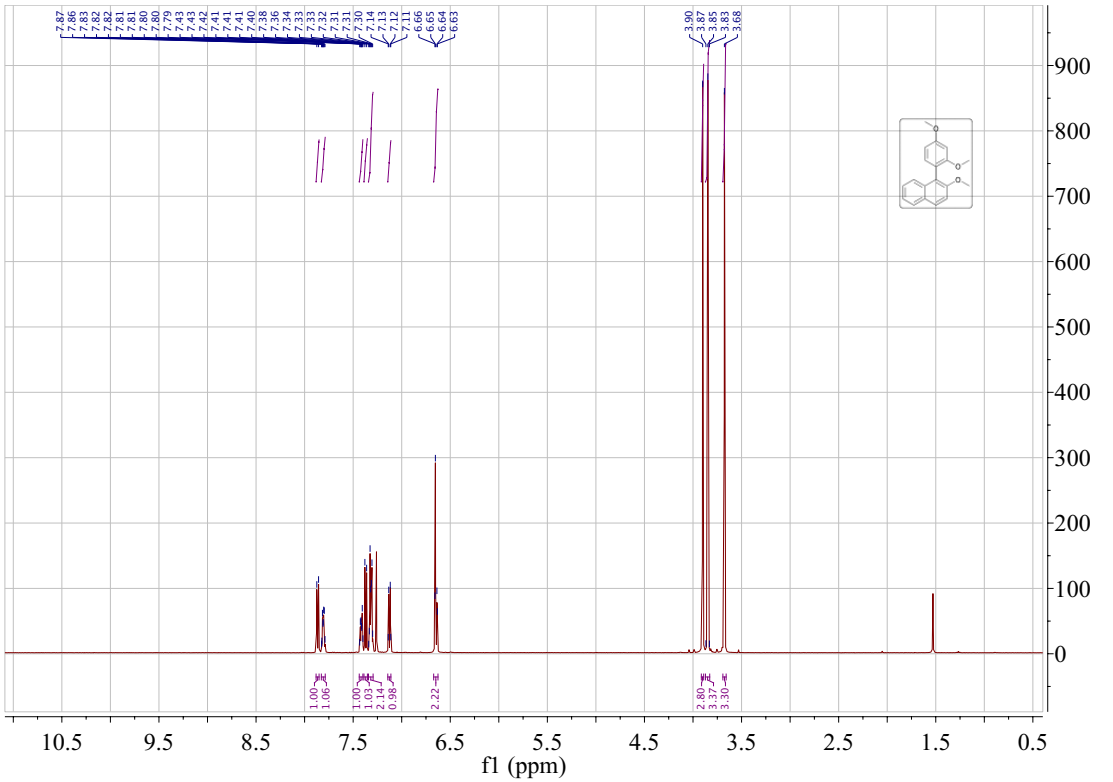
Services ICP-OES Synthesized with 0.5 mol% Palladium (5000 ppm)



J. NMR Spectra



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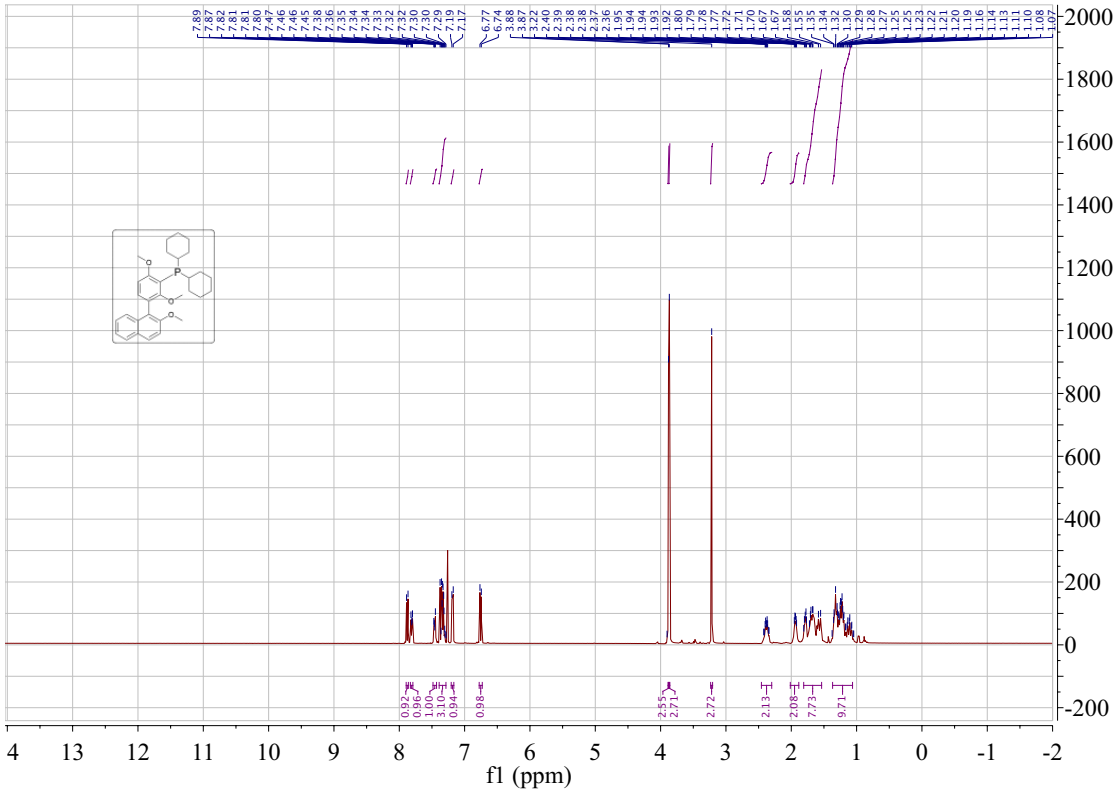
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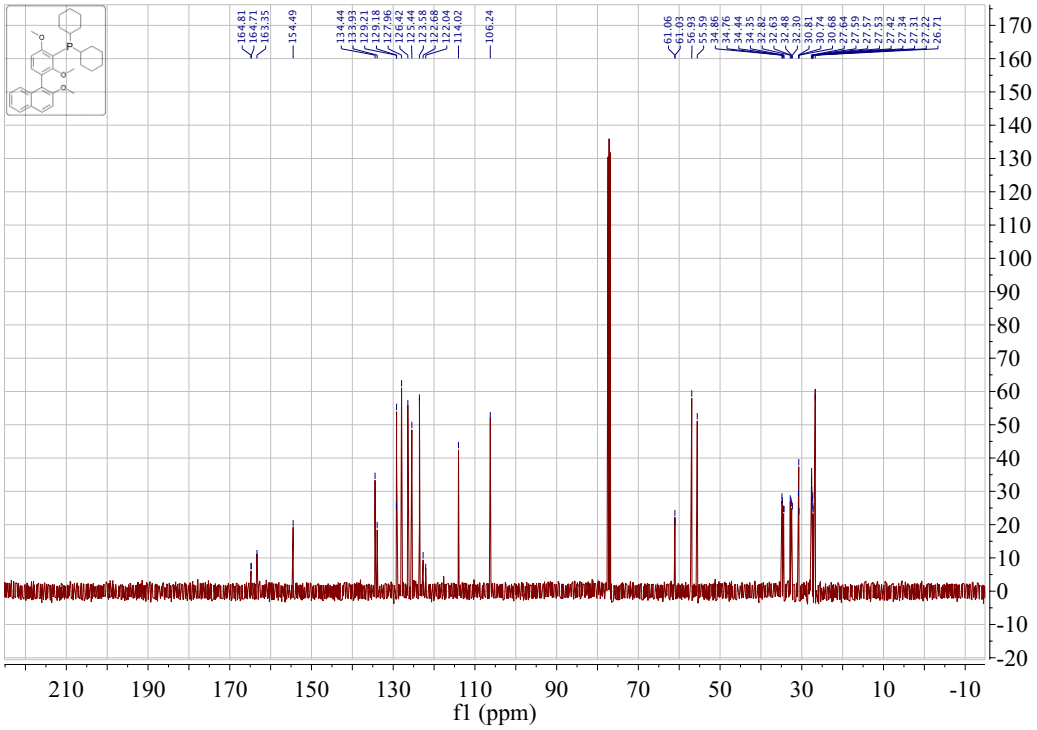
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154.49
134.44
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126.42
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122.68
122.04
114.02
106.24
61.06
61.03
56.93
55.59
34.86
34.76
34.44
34.35
32.82
32.63
32.48
32.30
30.81
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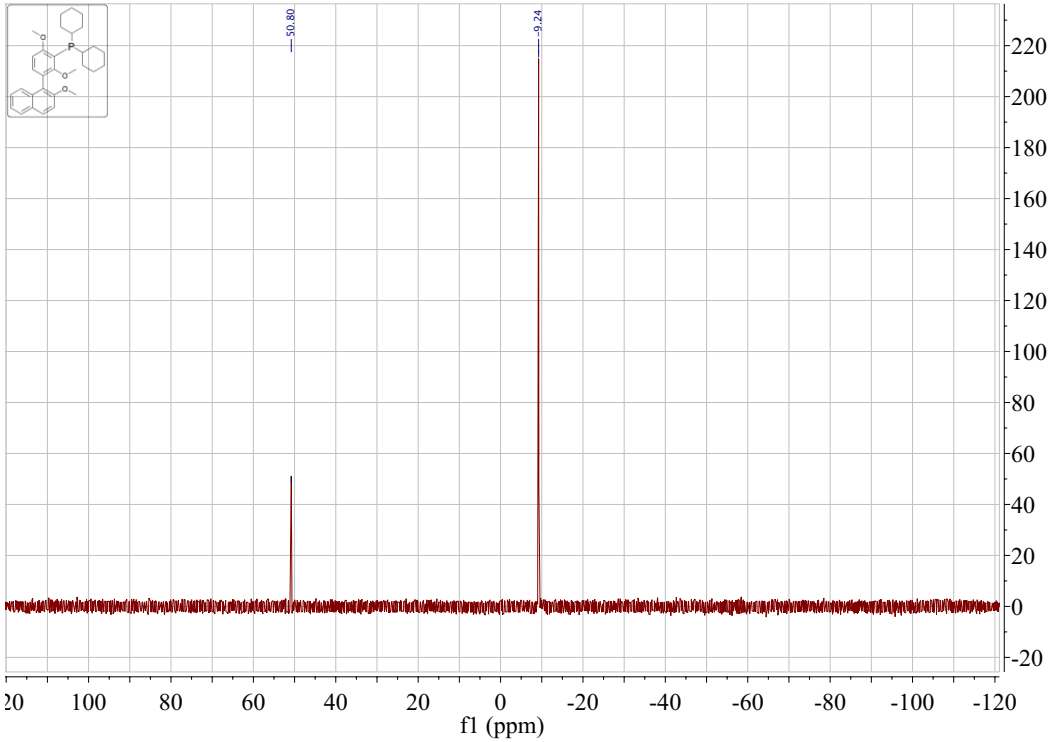
f1 (ppm)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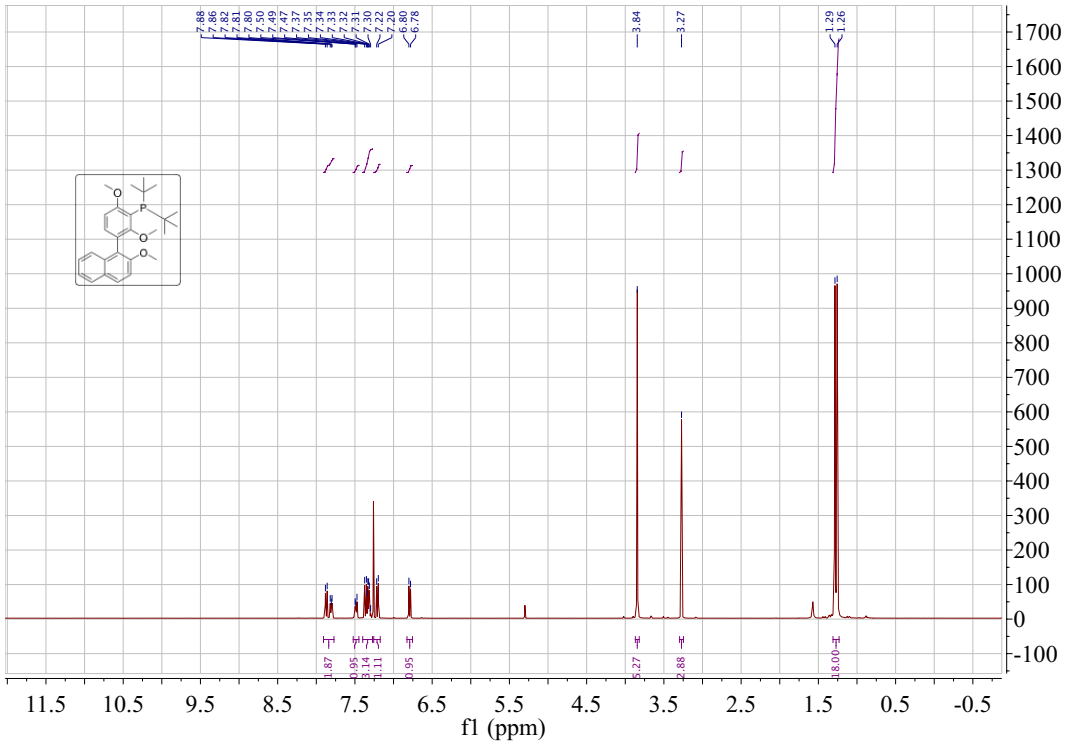
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7.82
7.81
7.80
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7.49
7.47
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7.35
7.34
7.33
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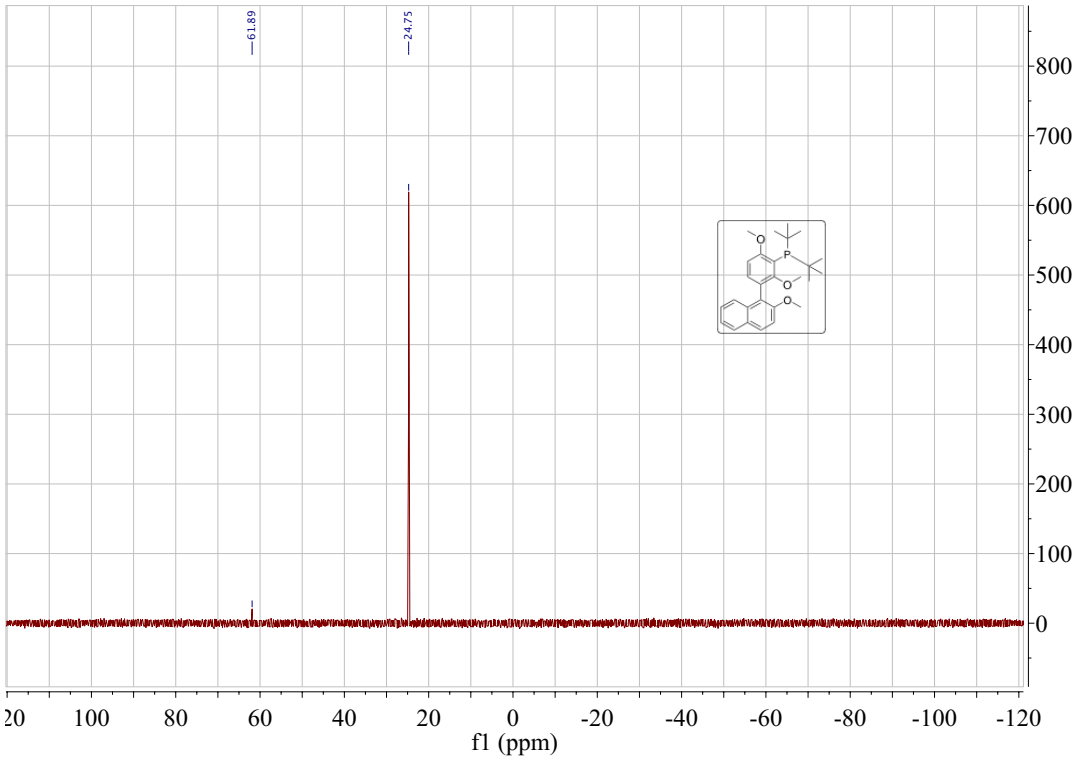
7.30
7.22
7.20
6.80
6.78
3.84
3.27
1.29
1.26
1.87
0.95
3.14
1.11
0.95
5.27
2.88
18.00
f1 (ppm)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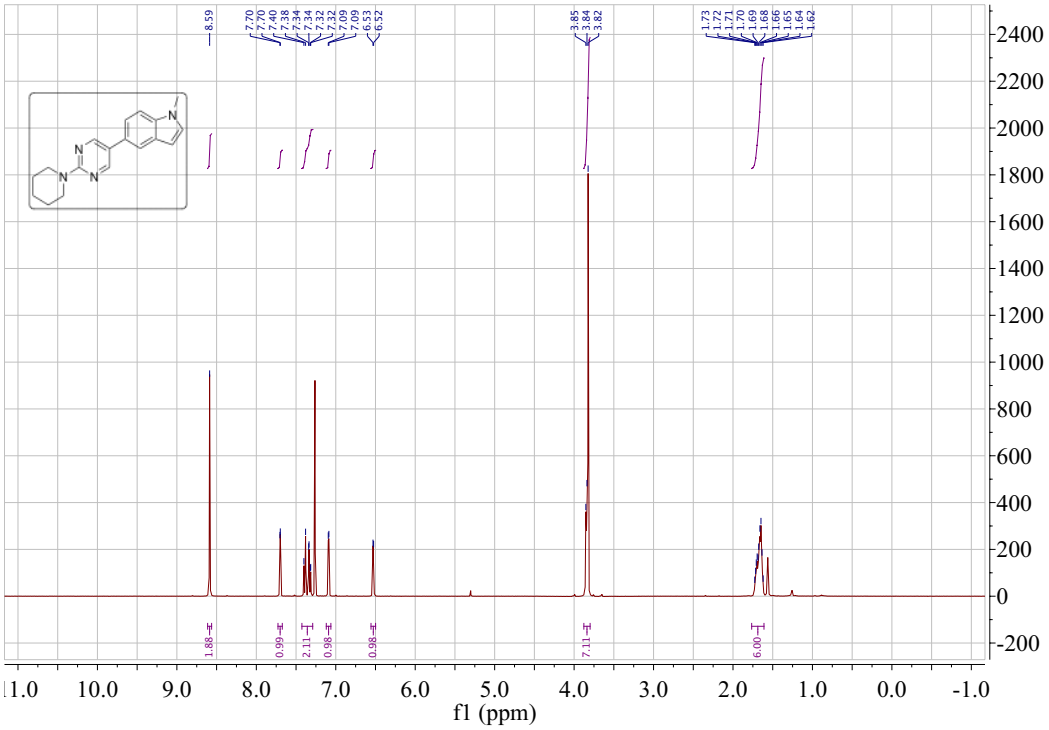
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7.34
7.32
7.32
7.09
7.09
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6.52
3.85
3.84
3.82
1.73
1.72
1.71
1.70
1.69
1.68
1.66
1.65
1.64
1.62
1.88
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2.11
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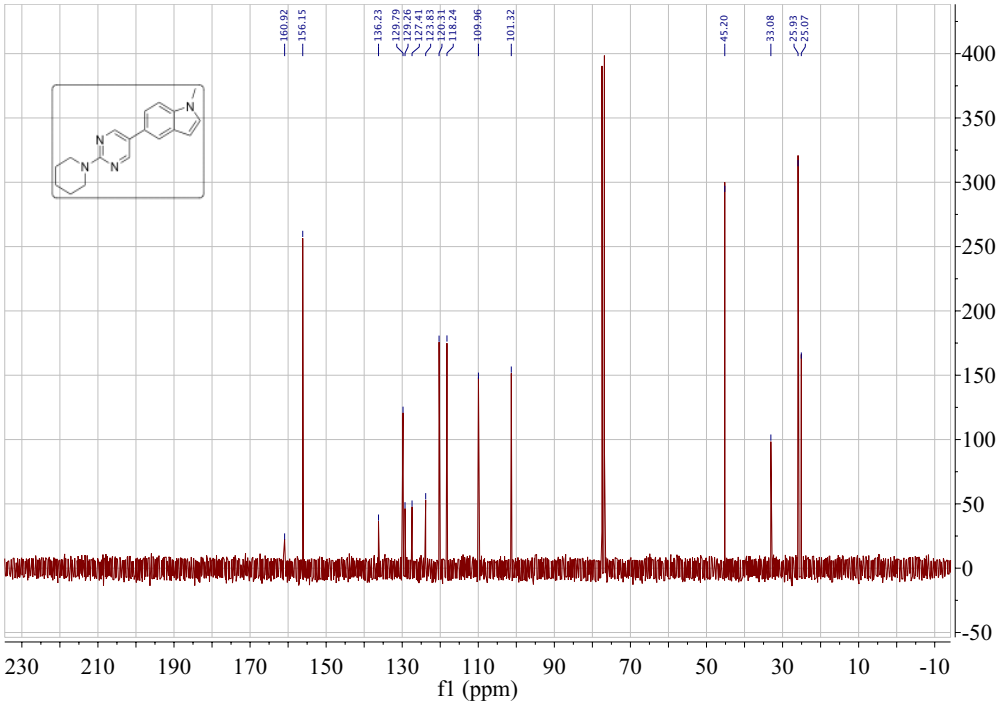
0.98
7.11
6.00
f1 (ppm)


160.92
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136.23
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129.26
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120.31
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109.96
101.32
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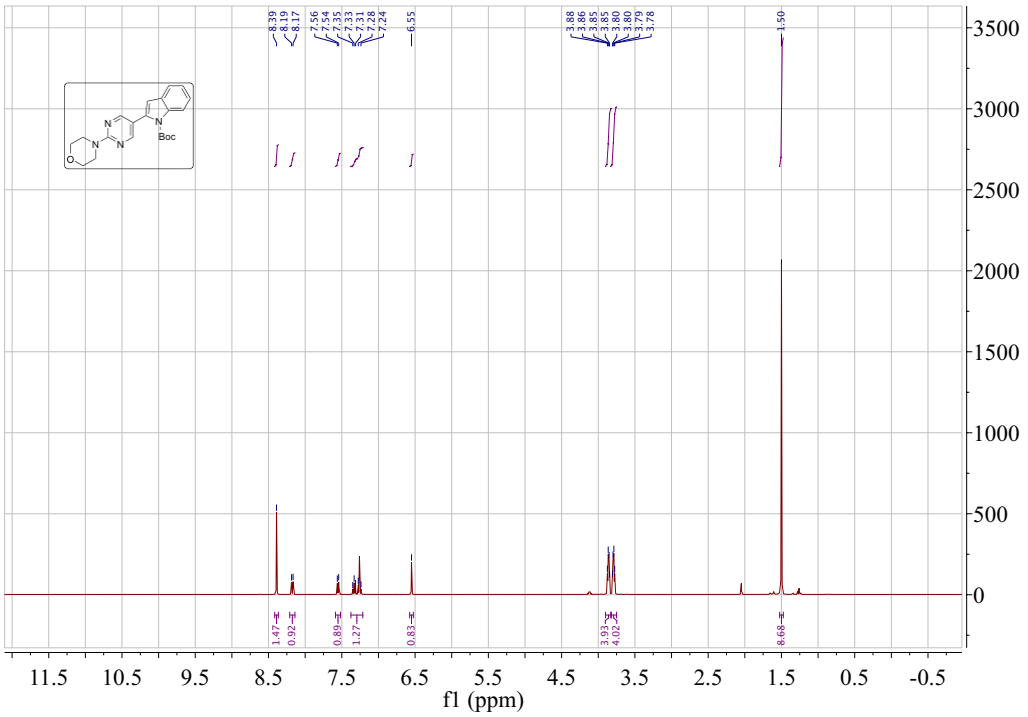
33.08
25.93
25.07
f1 (ppm)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8.17
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7.54
7.35
7.33
7.31
7.28
7.24
6.55
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3.86
3.85
3.85
3.80
3.80
3.79
3.78
1.50
Boc
1.47
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0.89
1.27
0.83
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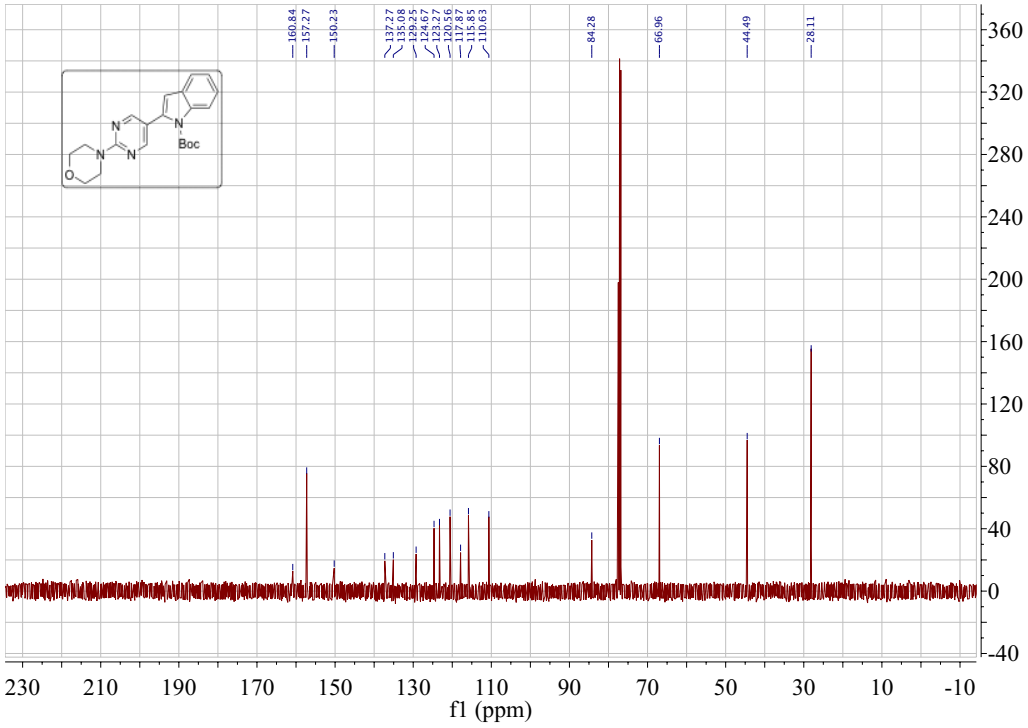
f1 (ppm)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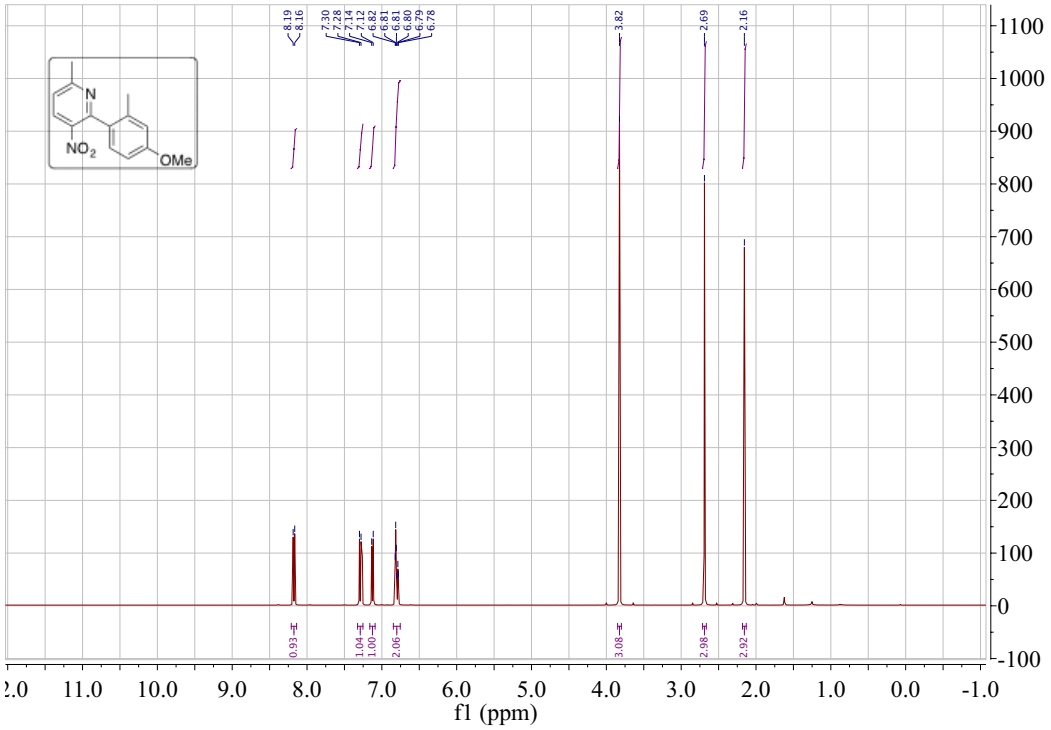
28.11
Boc
f1 (ppm)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7.14
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6.81
6.80
6.79
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1.00
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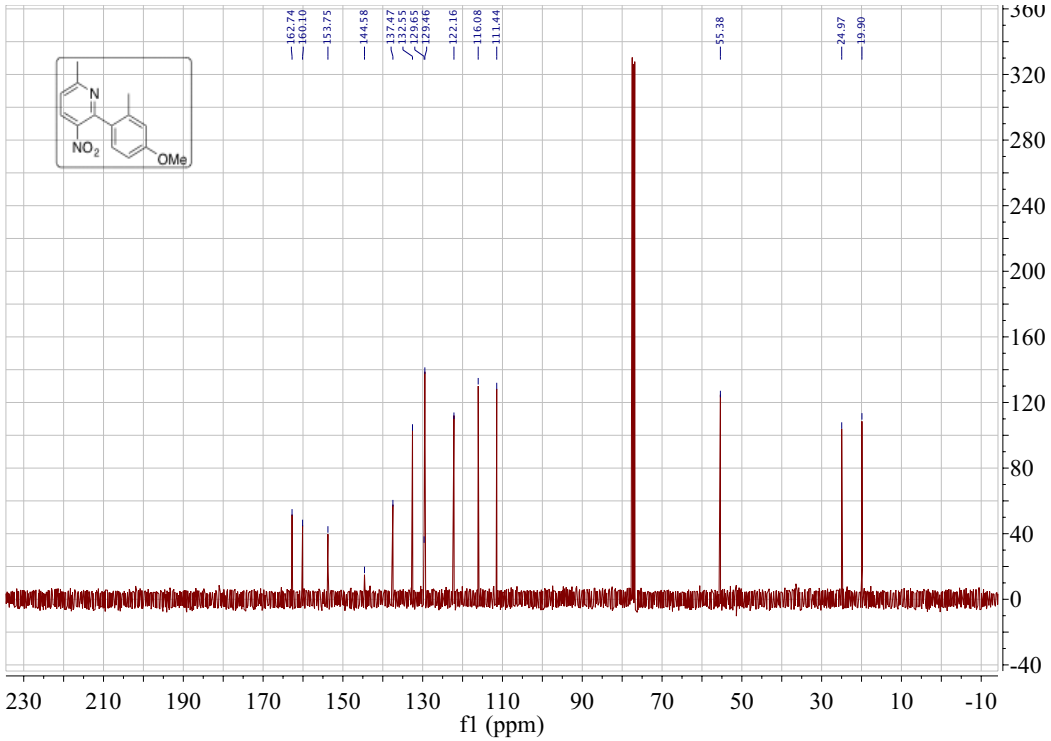
2.92
f1 (ppm)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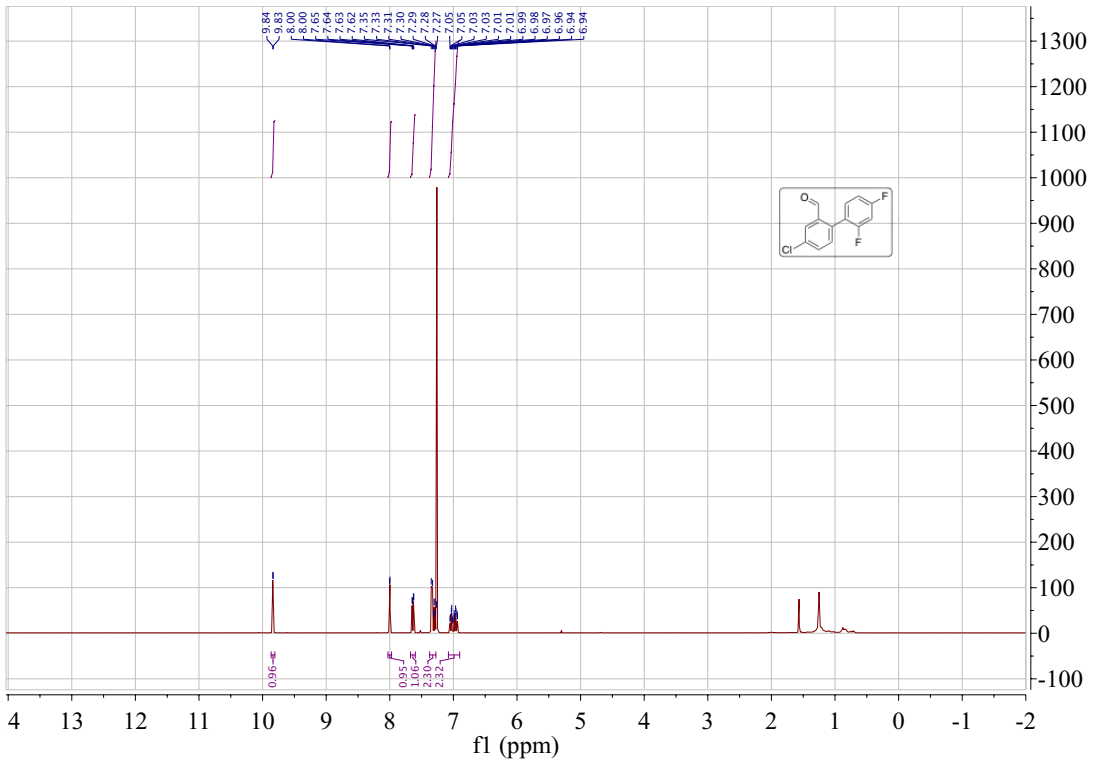
24.97
19.90
f1 (ppm)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7.35
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7.31
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7.29
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7.27
7.05
7.03
7.01
6.99
6.98
6.97
6.96
6.94
6.94
O
F
Cl
F
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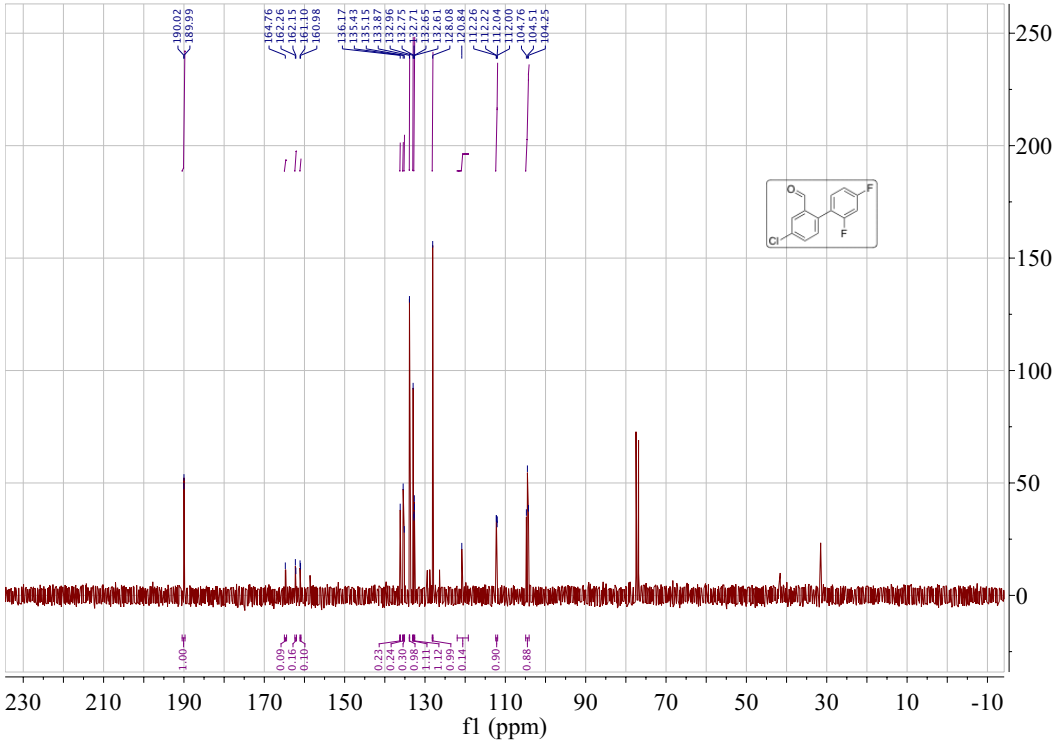
2.30
2.32
f1 (ppm)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132.95
132.71
132.65
132.61
128.08
120.84
112.26
112.22
112.04
112.00
104.76
104.51
104.25
O
F
Cl
F
1.00
0.09
0.16
0.10
0.23
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1.11
1.12
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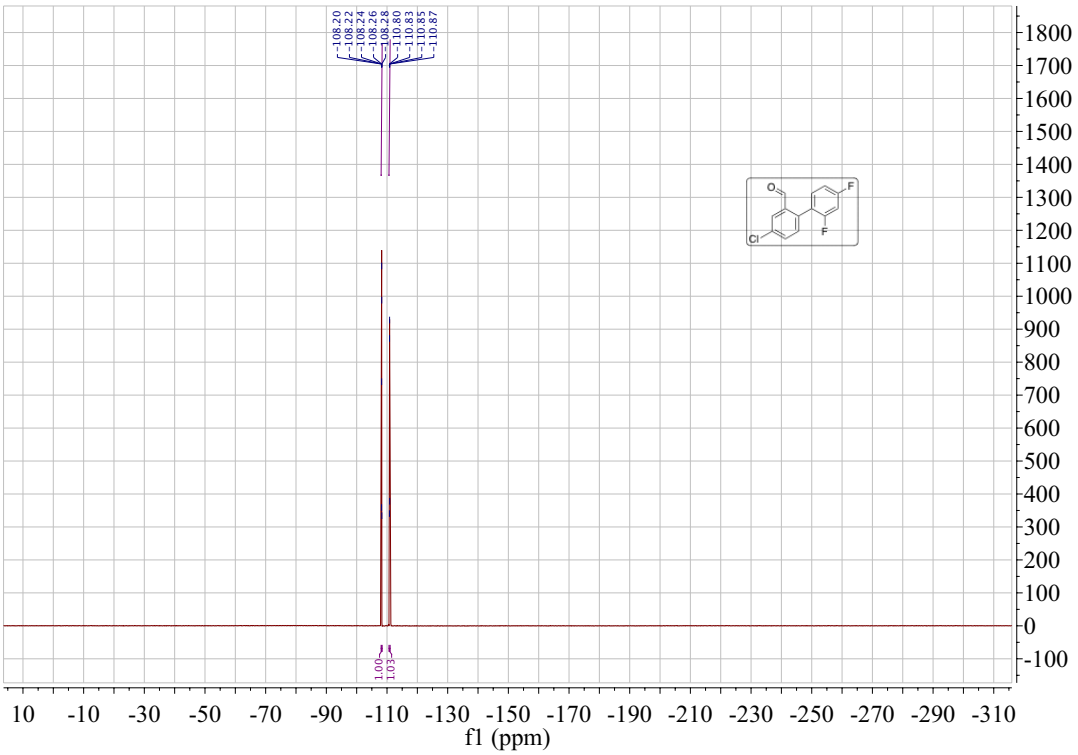
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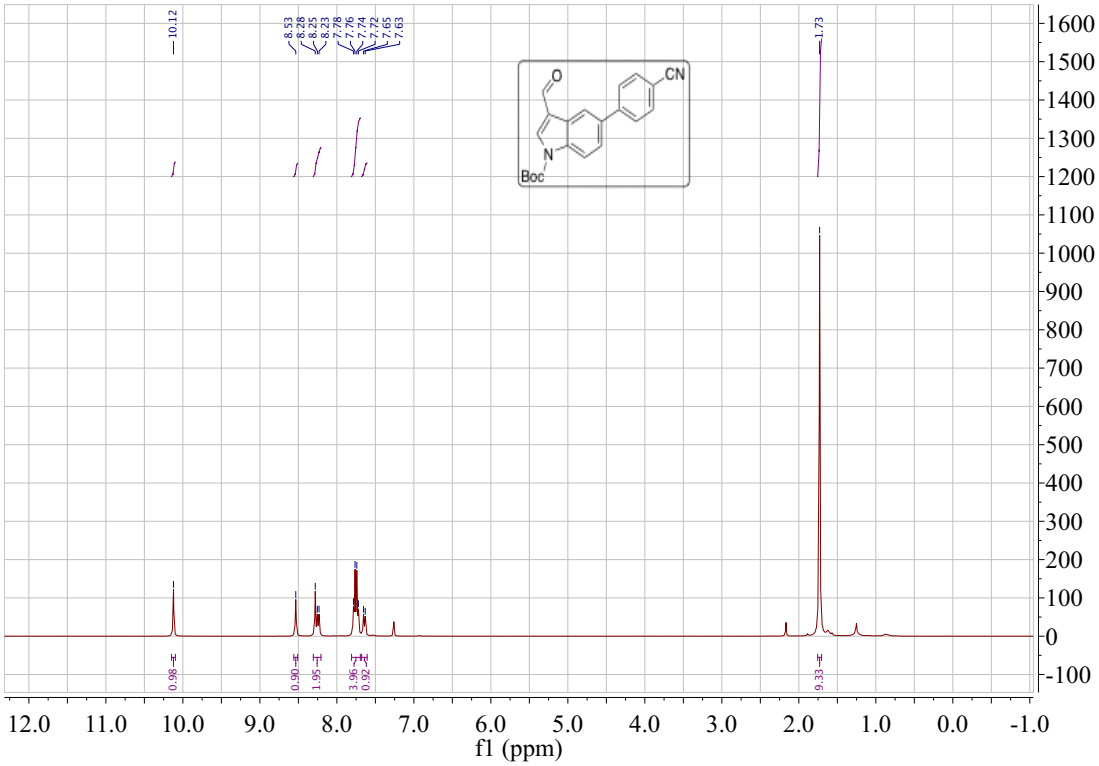
Cl
F
1.00
1.03
f1 (ppm)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CN
N
Boc
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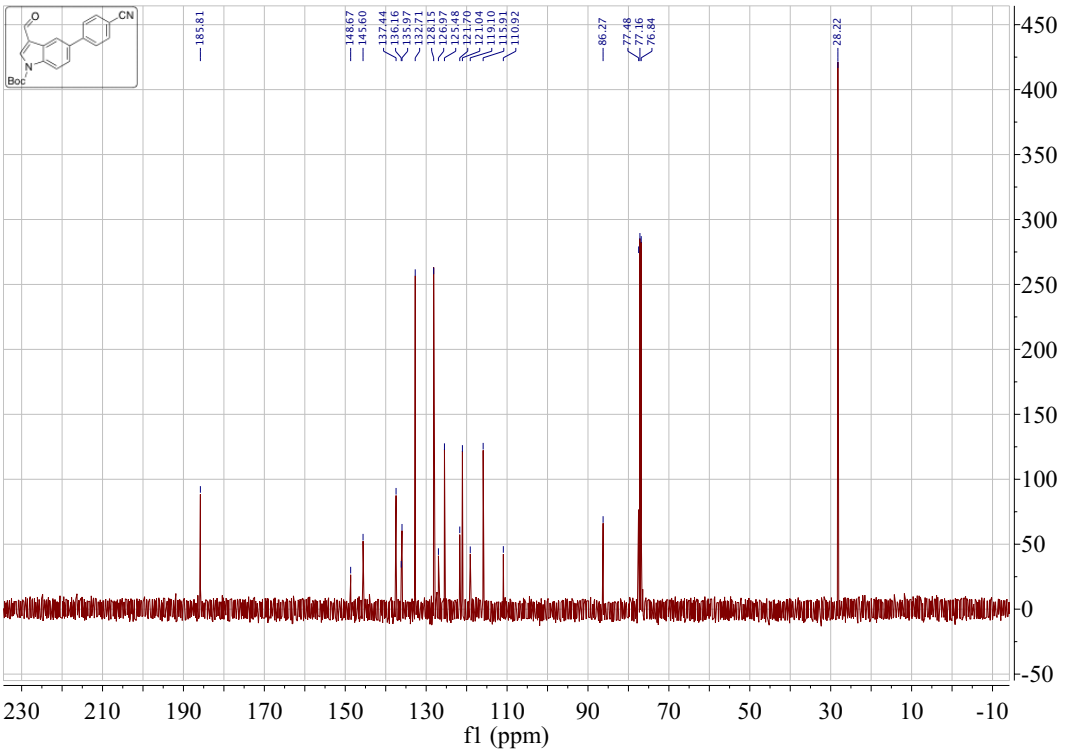
0.90
1.95
3.96
0.92
9.33
f1 (ppm)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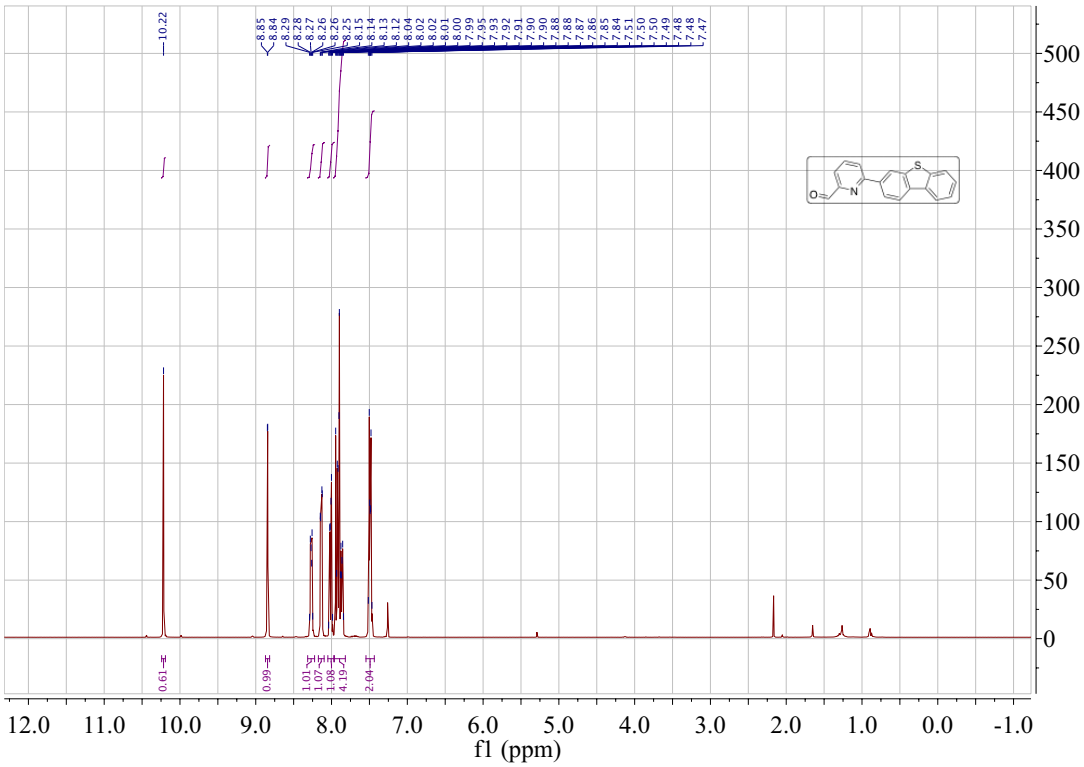
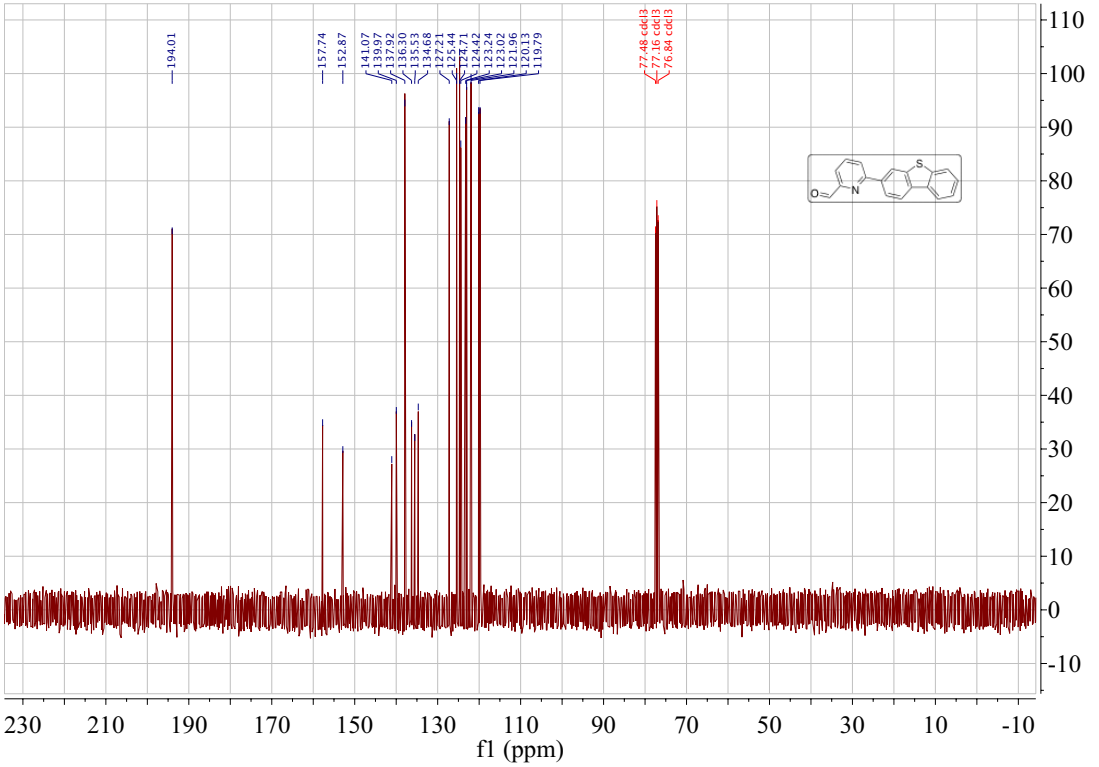
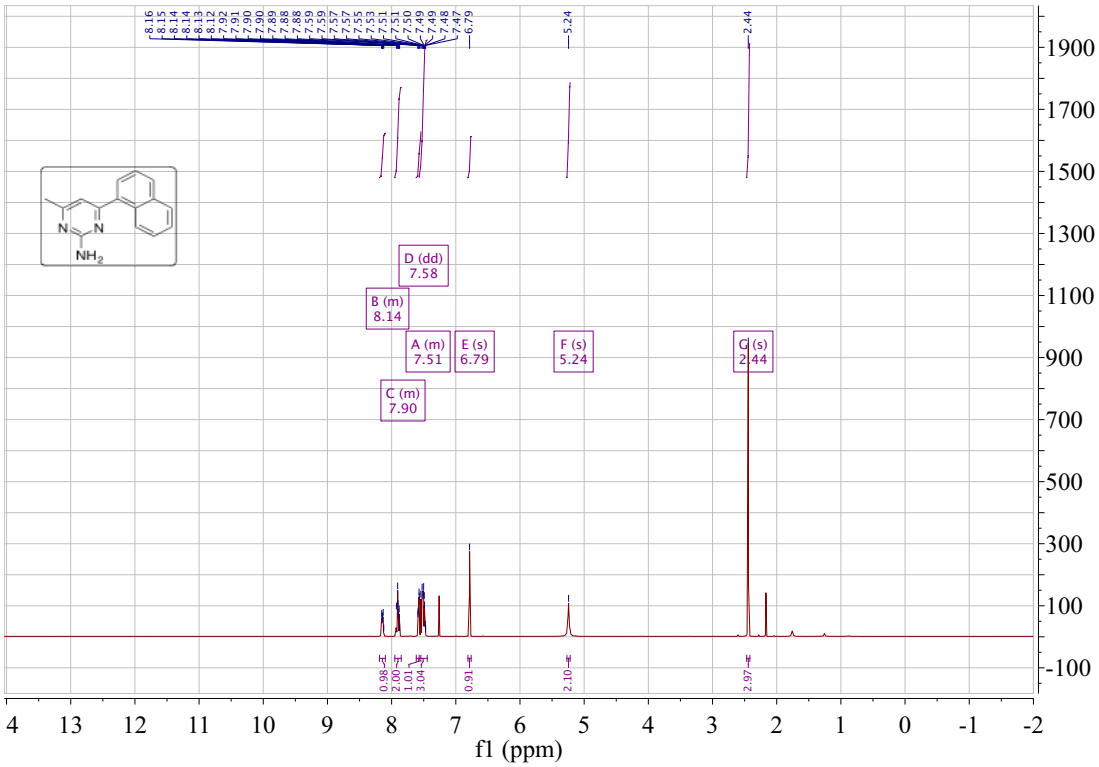
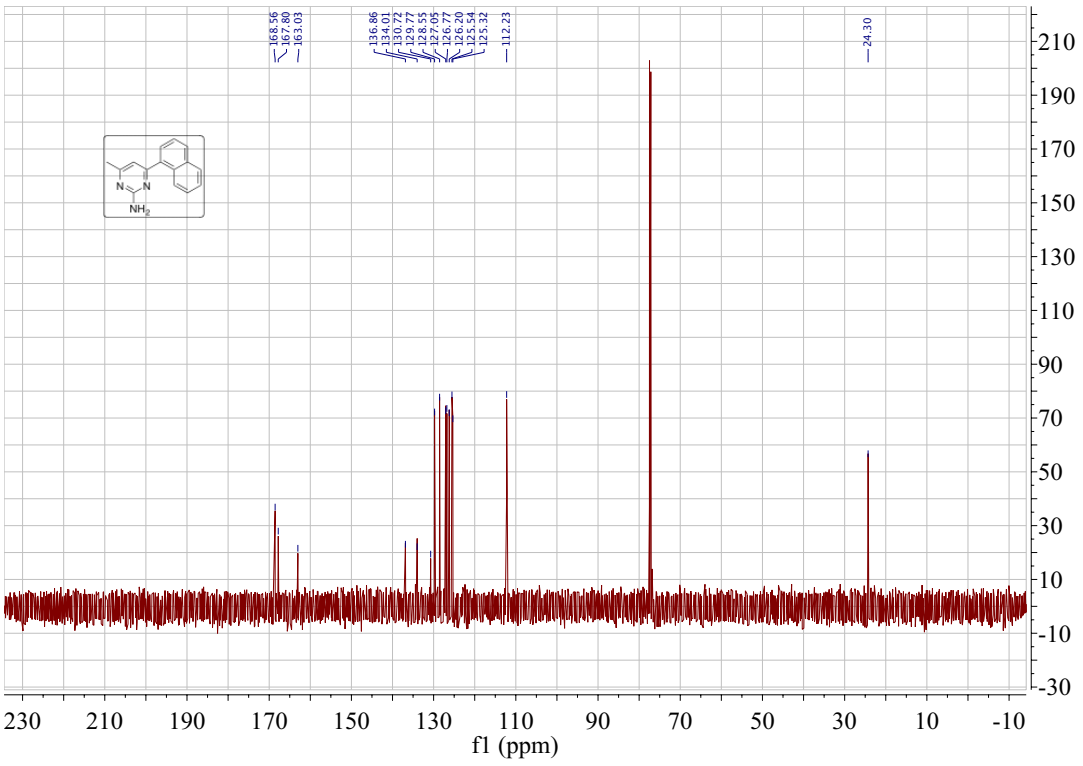
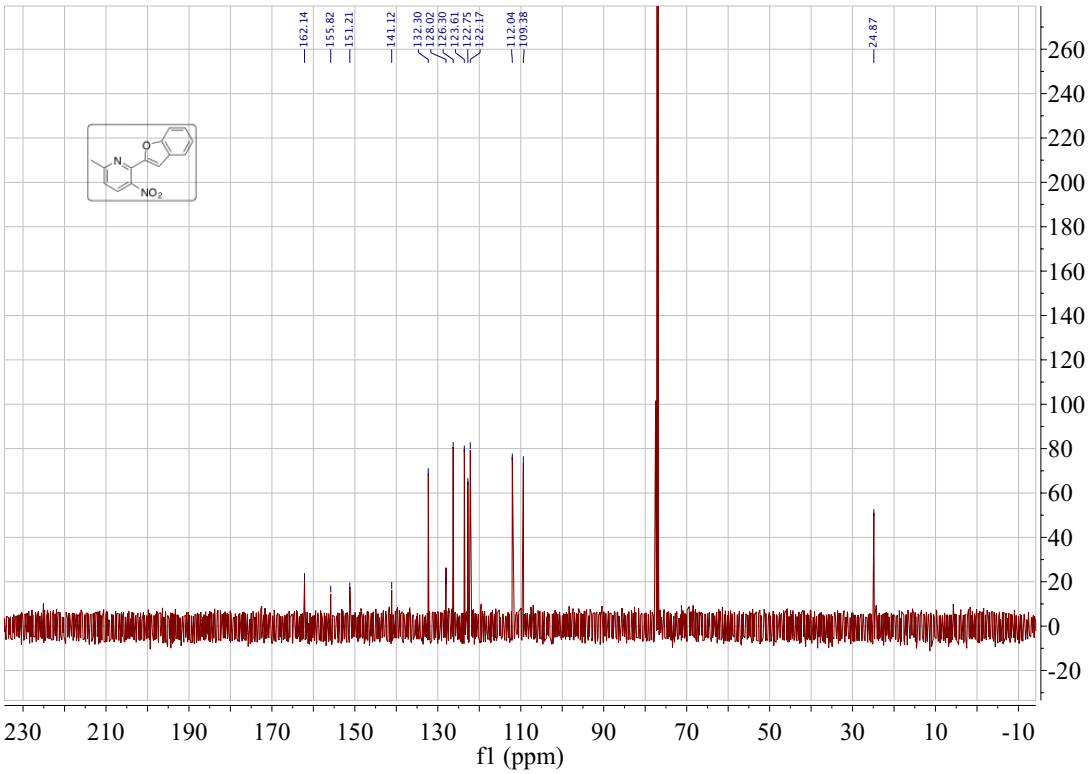
121.04
119.10
115.91
110.92
86.27
77.48
77.16
76.84
28.22
Boc
f1 (ppm)

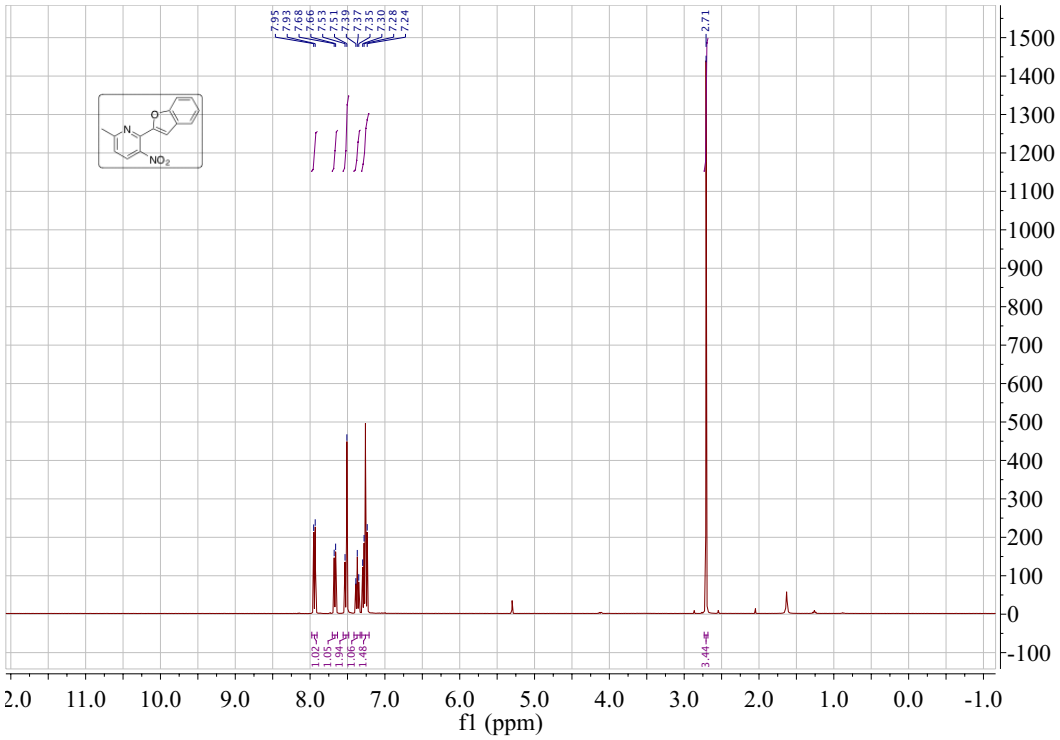

10.22
8.85
8.84
8.29
8.28
8.27
8.26
8.25
8.15
8.14
8.13
8.12
8.04
8.02
8.02
8.01
8.00
7.99
7.95
7.93
7.92
7.91
7.90
7.90
7.88
7.88
7.87
7.86
7.85
7.84
7.51
7.50
7.50
7.49
7.48
7.48
7.47
0.61
0.99
1.01
1.07
1.08
4.19
2.04
f1 (ppm)

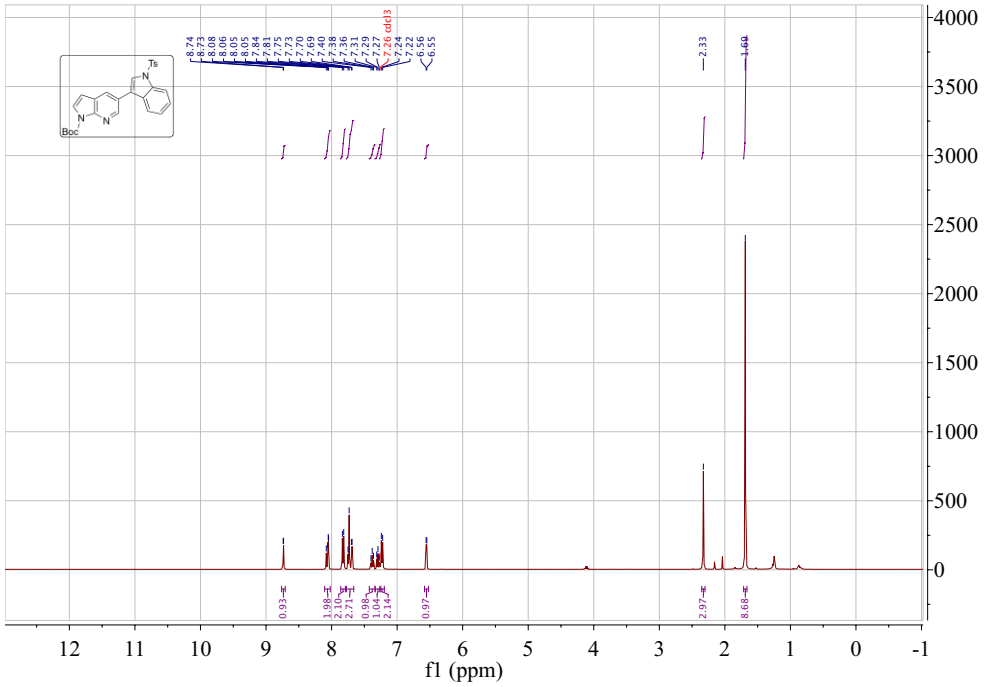

194.01
157.74
152.87
141.07
139.97
137.92
136.30
135.53
134.68
127.21
125.44
124.71
124.42
123.24
123.02
121.96
120.13
119.79
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
O
N
S
f1 (ppm)

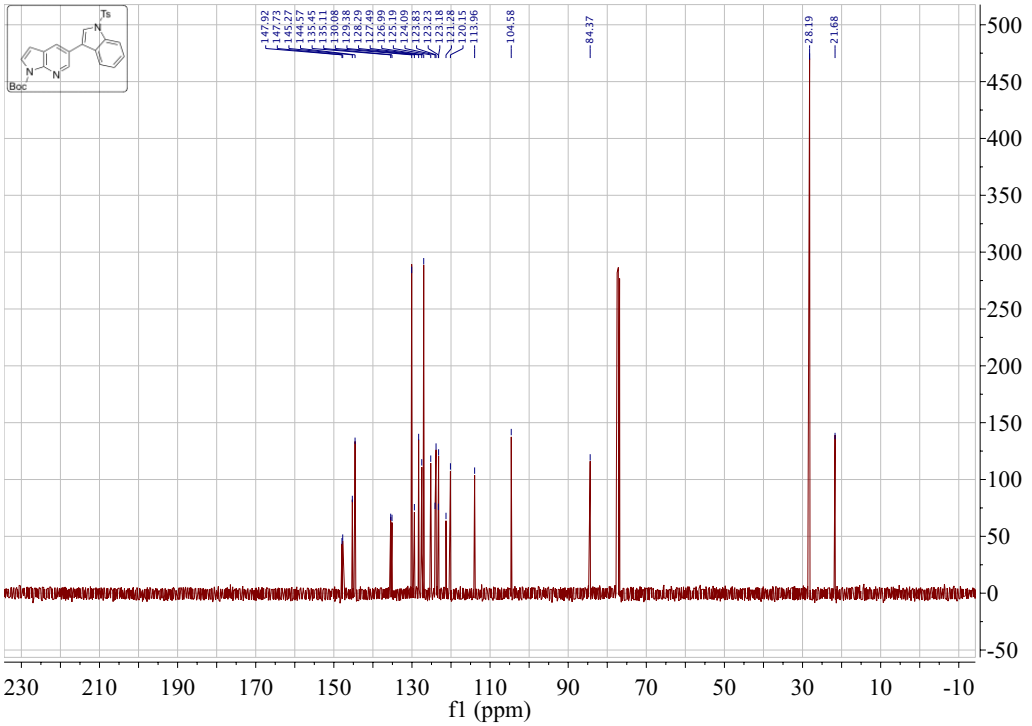

8.16
8.15
8.14
8.14
8.13
8.12
7.92
7.91
7.90
7.90
7.89
7.88
7.88
7.59
7.57
7.57
7.55
7.53
7.51
7.51
7.50
7.49
7.49
7.48
7.47
6.79
5.24
2.44
N
N
NH2
D (dd)
7.58
B (m)
8.14
A (m)
7.51
E (s)
6.79
F (s)
5.24
G (s)
2.44
C (m)
7.90
0.98
2.00
1.01
3.04
0.91
2.10
2.97
f1 (ppm)

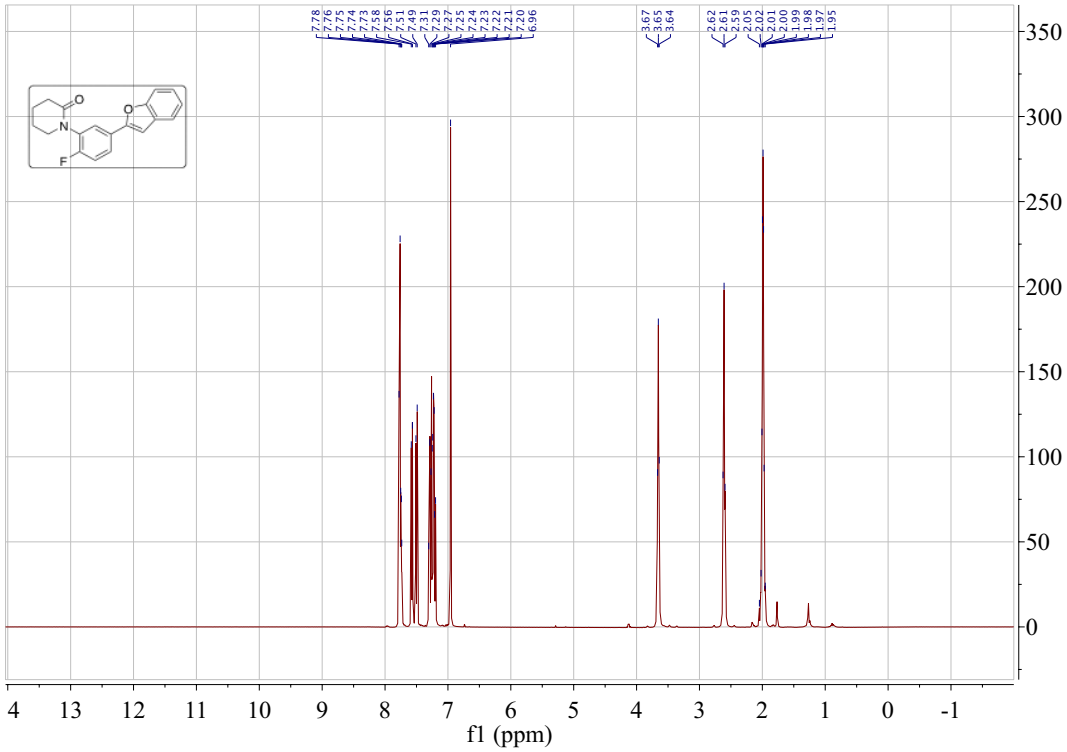

168.56
167.80
163.03
136.86
134.01
130.72
129.77
128.55
127.05
126.20
125.54
125.32
112.23
24.30
NH2
f1 (ppm)

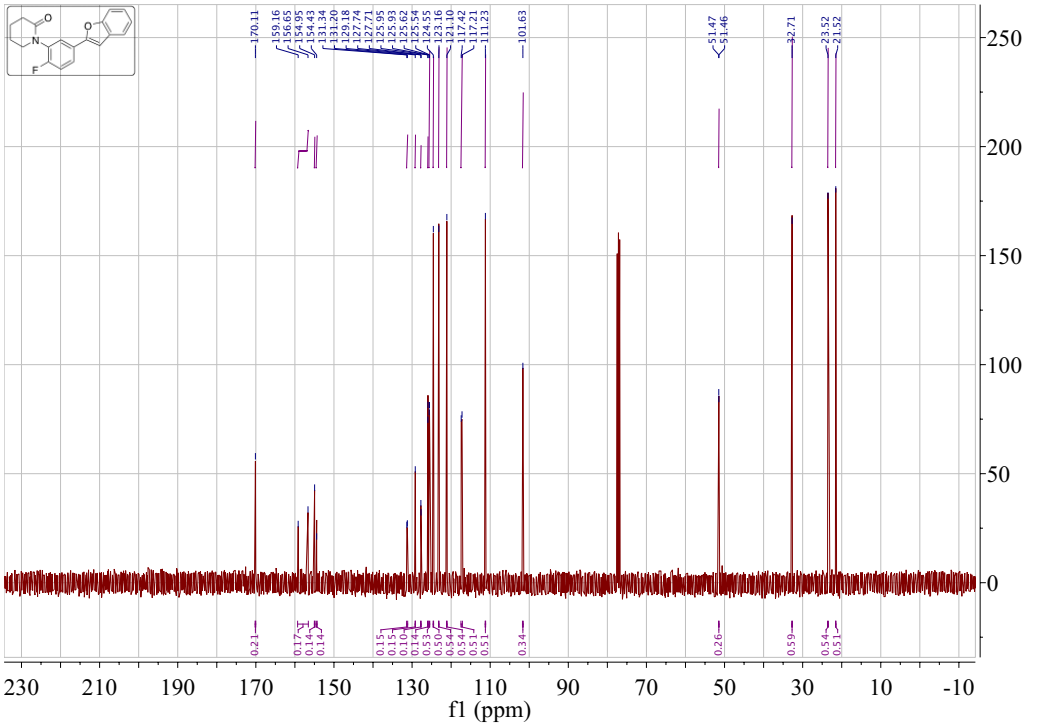

162.14
155.82
151.21
141.12
132.30
128.02
126.50
123.61
122.75
122.17
112.04
109.38
24.87
NO2
f1 (ppm)

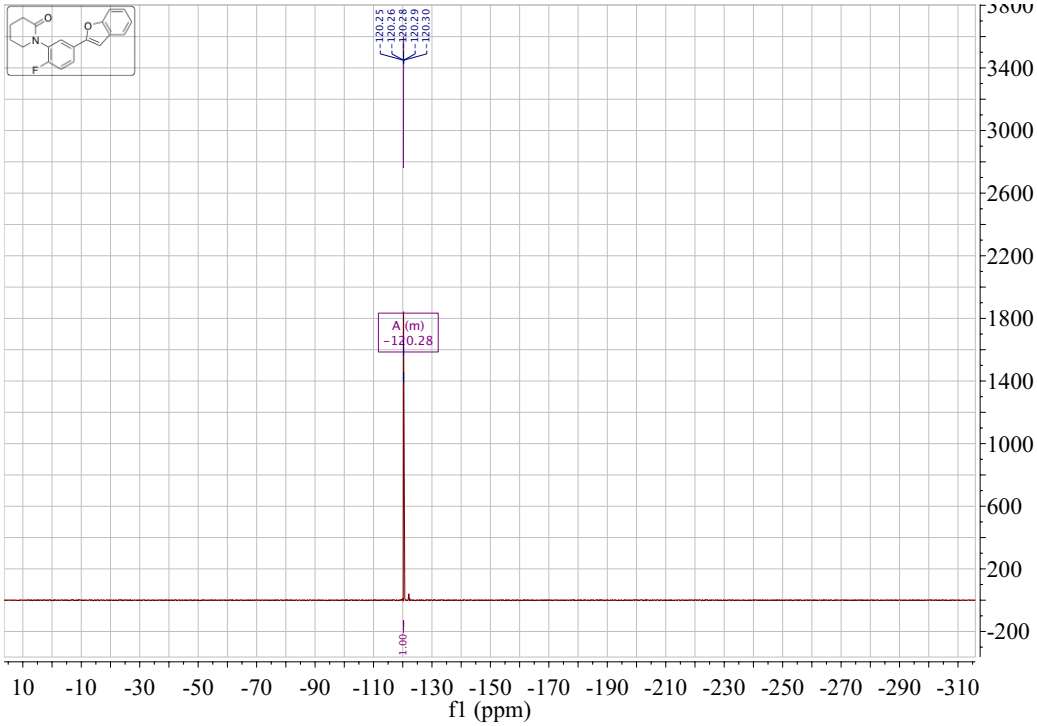

7.95
7.93
7.68
7.66
7.53
7.51
7.39
7.37
7.35
7.30
7.28
7.24
2.71
O
N
NO2
1.02
1.05
1.94
1.06
1.48
3.44
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
2.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
f1 (ppm)

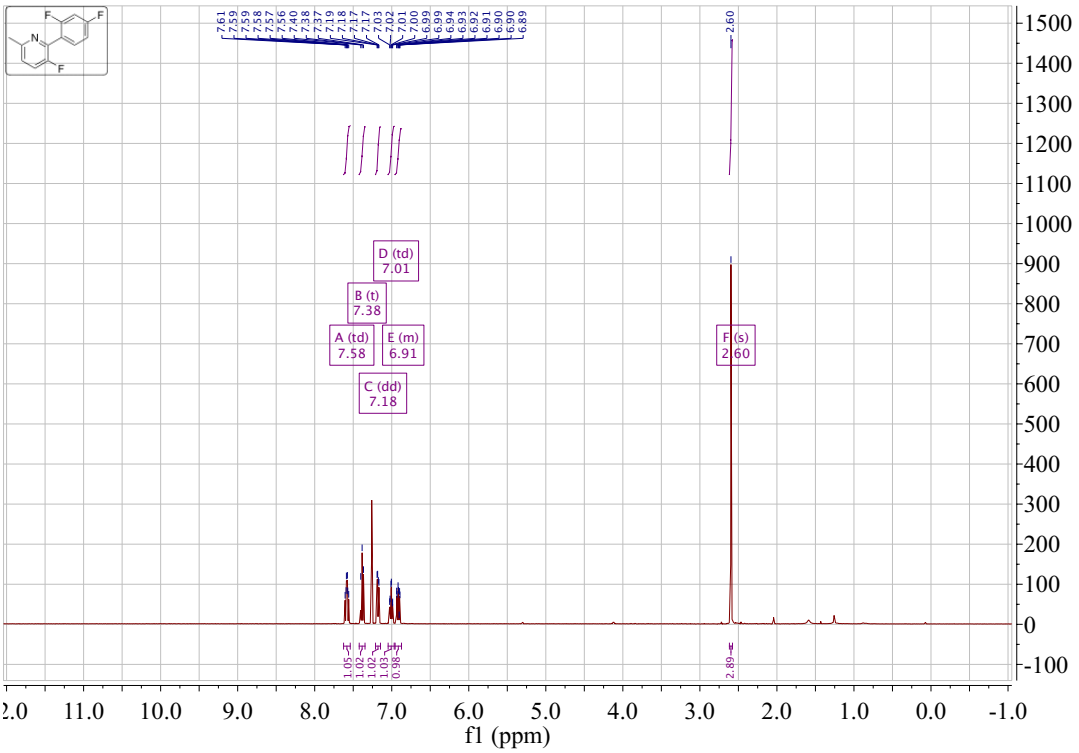

8.74
8.73
8.08
8.06
8.05
8.05
7.84
7.81
7.75
7.73
7.70
7.69
7.40
7.38
7.36
7.31
7.29
7.27
7.26 cdcl3
7.24
7.22
6.56
6.55
2.33
1.60
Ts
N
N
N
Boc
0.93
1.98
2.10
2.71
0.98
1.04
2.14
0.97
2.97
8.68
4000
3500
3000
2500
2000
1500
1000
500
0
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

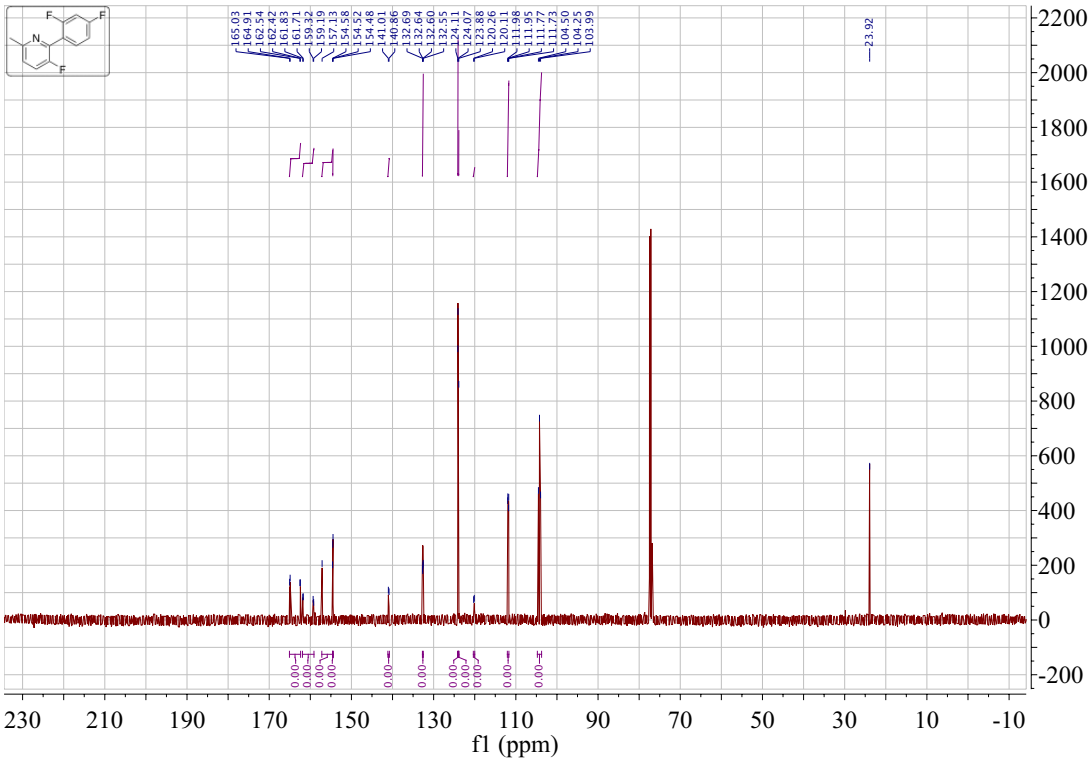

Ts
Boc
147.92
147.73
145.27
144.57
135.45
135.11
130.08
129.38
128.29
127.49
126.99
125.19
124.09
123.83
123.23
123.18
121.28
120.15
113.96
104.58
84.37
28.19
21.68
500
450
400
350
300
250
200
150
100
50
0
-50
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

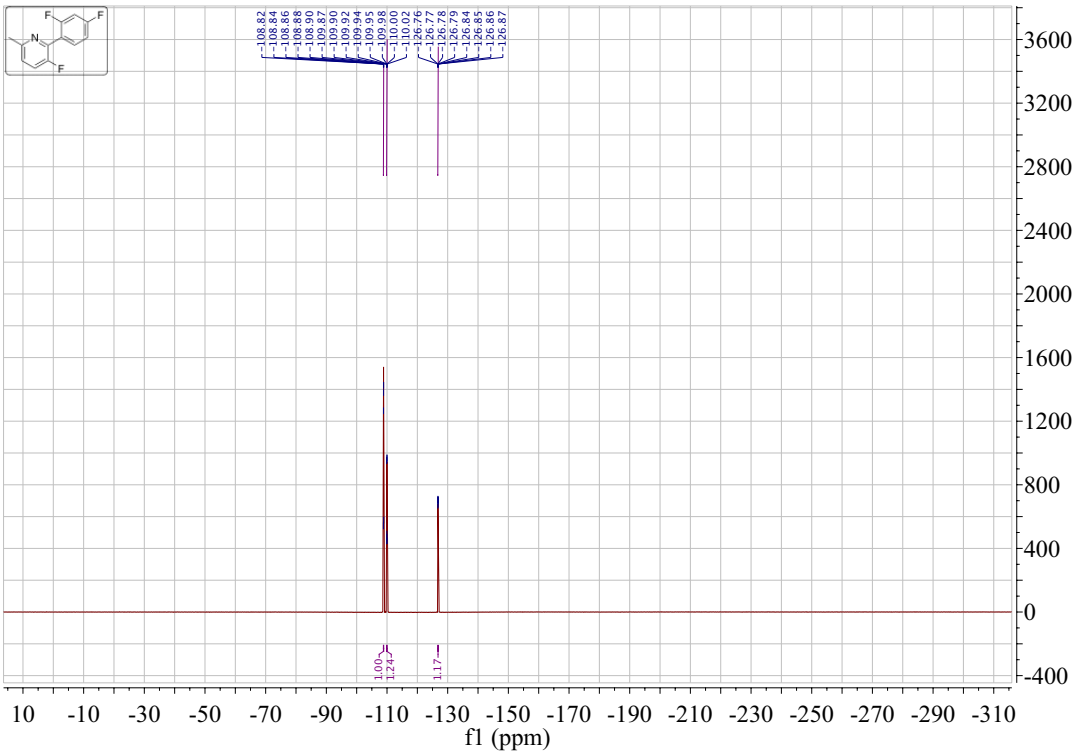

O
N
O
F
7.78
7.76
7.75
7.74
7.73
7.58
7.55
7.51
7.49
7.31
7.29
7.27
7.25
7.24
7.23
7.22
7.21
7.20
6.96
3.67
3.65
3.64
2.62
2.61
2.59
2.05
2.02
2.01
2.00
1.99
1.98
1.97
1.95
350
300
250
200
150
100
50
0
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

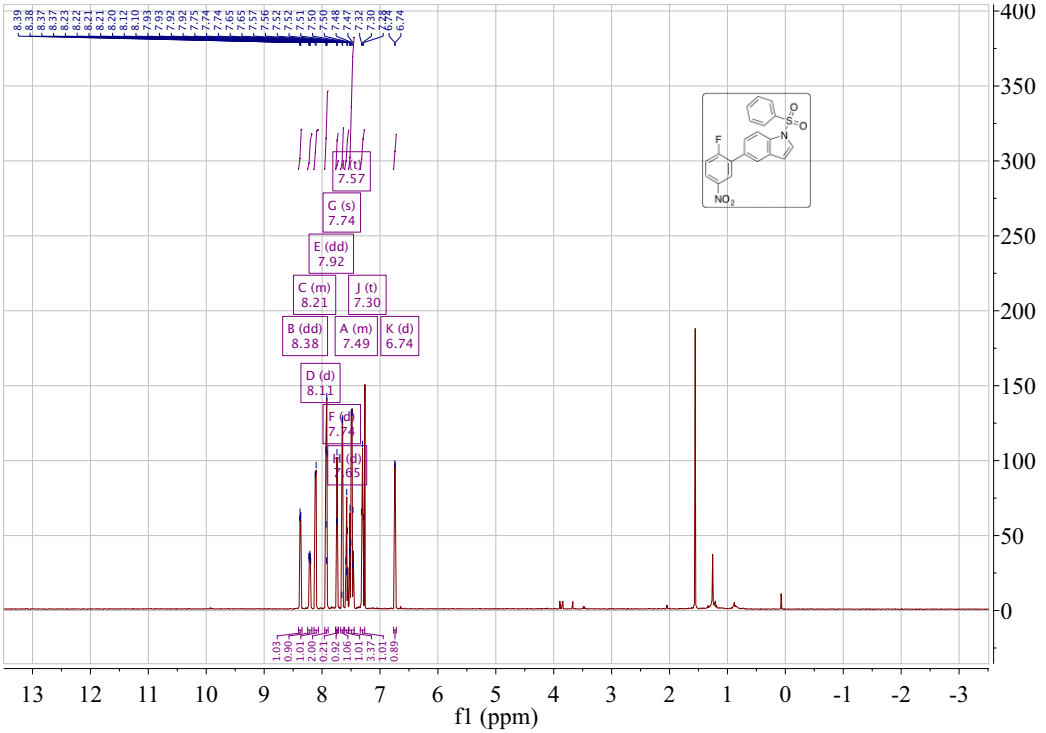

170.11
159.16
156.65
154.95
154.43
131.34
131.20
130.18
127.74
127.71
125.95
125.93
125.62
125.54
124.55
123.16
121.10
117.42
117.21
111.23
101.63
51.47
51.46
32.71
23.52
21.32
250
200
150
100
50
0
230
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

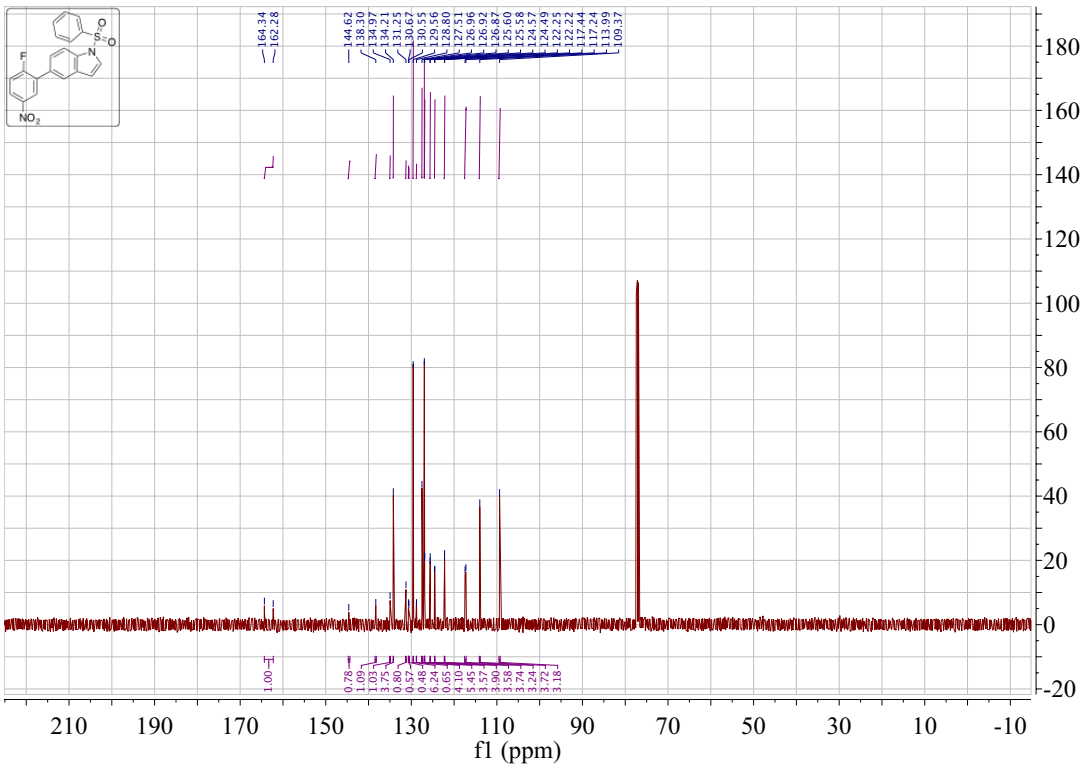

120.25
120.26
120.28
120.29
120.30
A (m)
-120.28
1.00
3800
3400
3000
2600
2200
1800
1400
1000
600
200
-200
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290
-310
f1 (ppm)

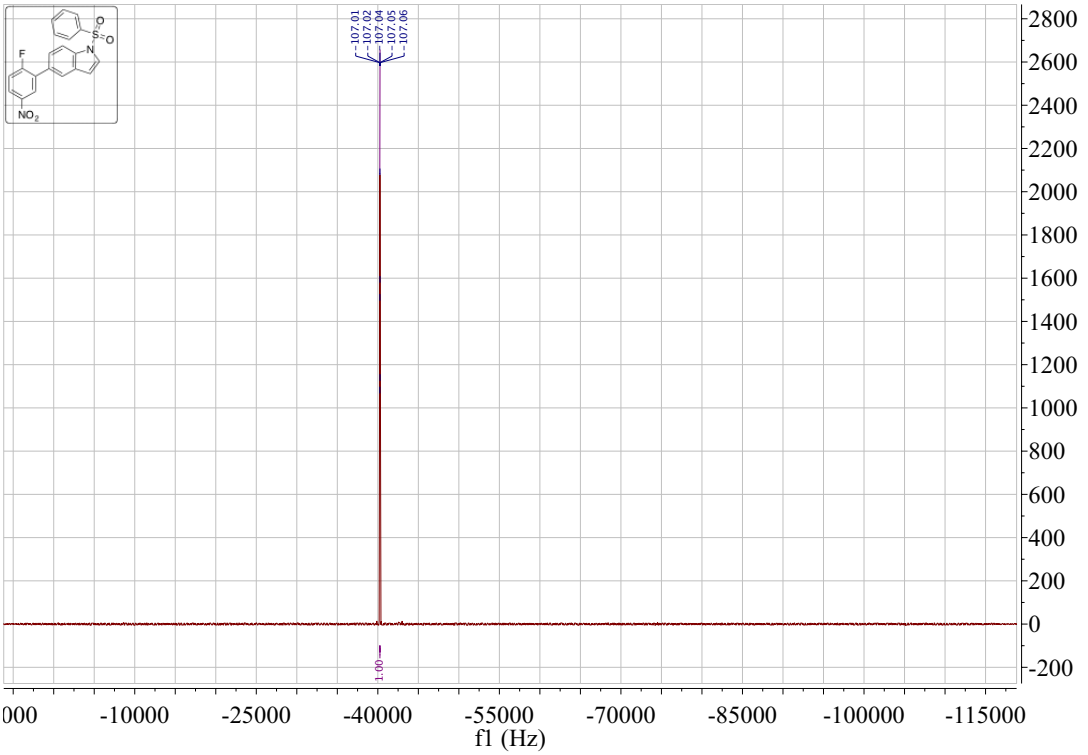

D (td)
7.01
B (t)
7.38
A (td)
7.58
E (m)
6.91
C (dd)
7.18
F (s)
2.60
f1 (ppm)

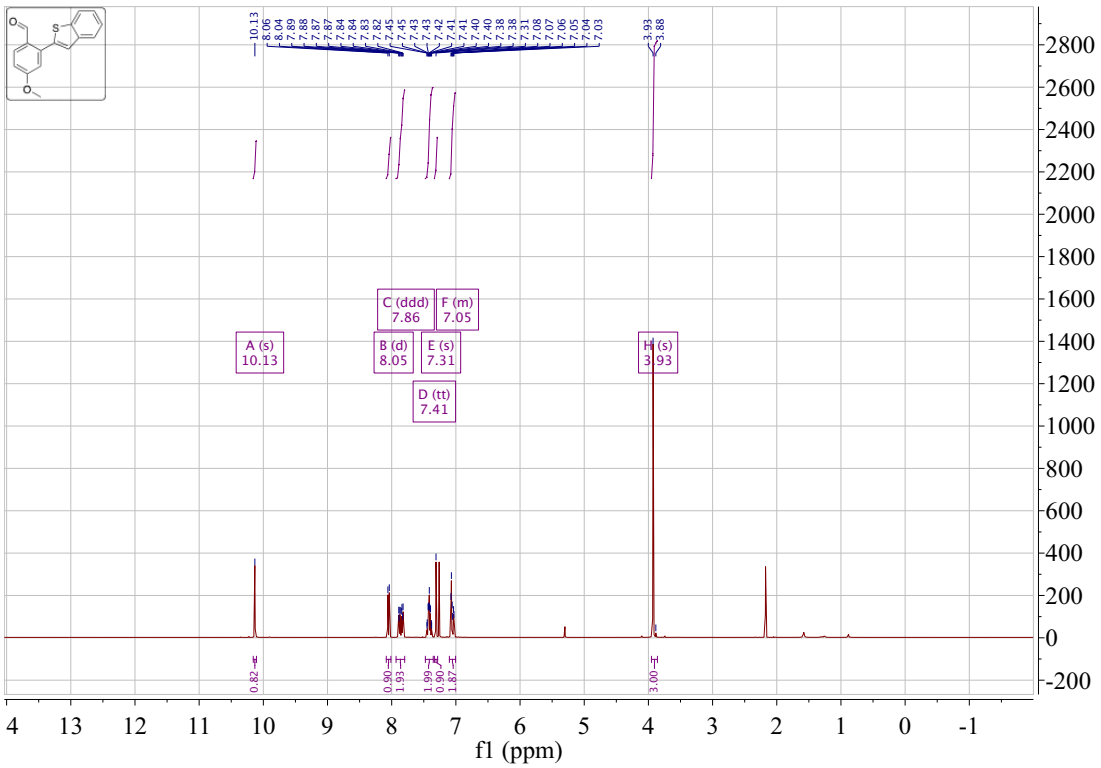

f1 (ppm)

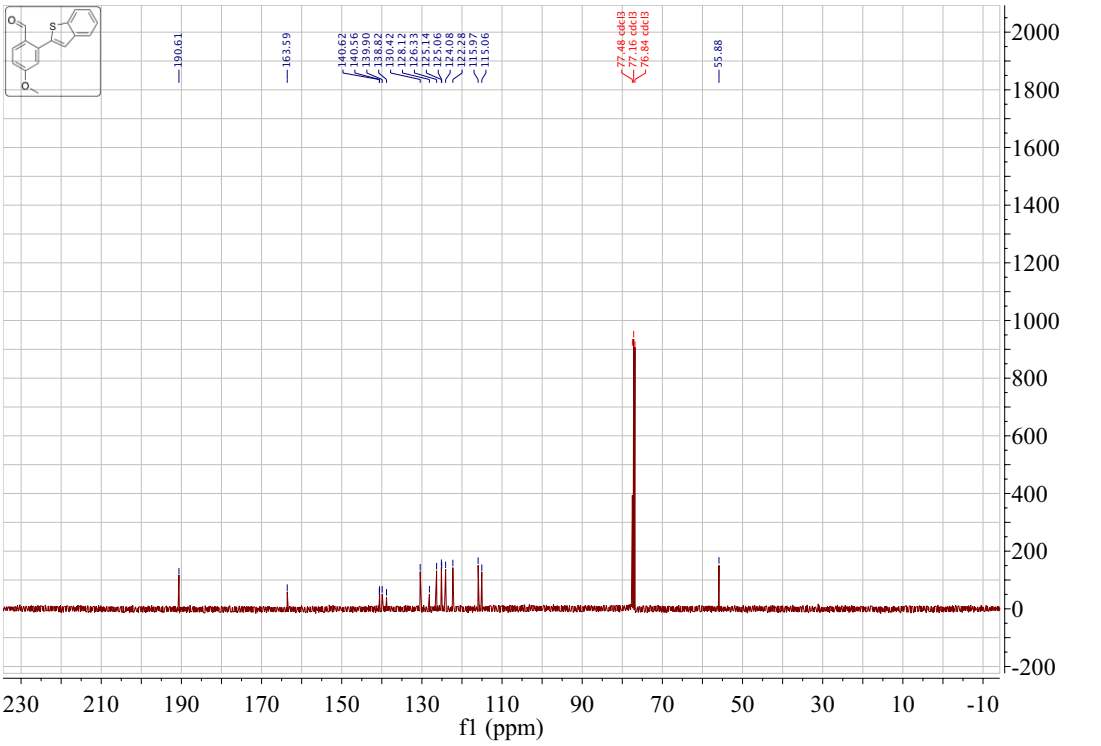

f1 (ppm)

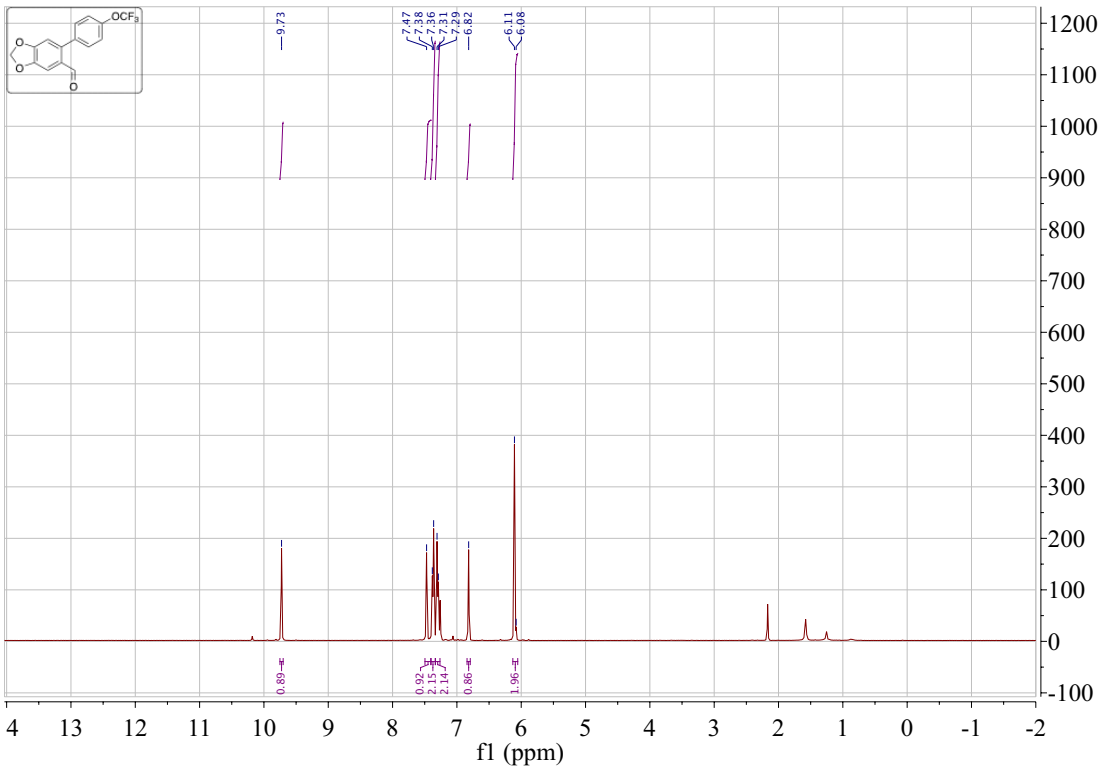

TM (t)
7.57
G (s)
7.74
E (dd)
7.92
C (m)
8.21
J (t)
7.30
B (dd)
8.38
A (m)
7.49
K (d)
6.74
D (d)
8.11
F (d)
7.74
H (d)
7.65
f1 (ppm)

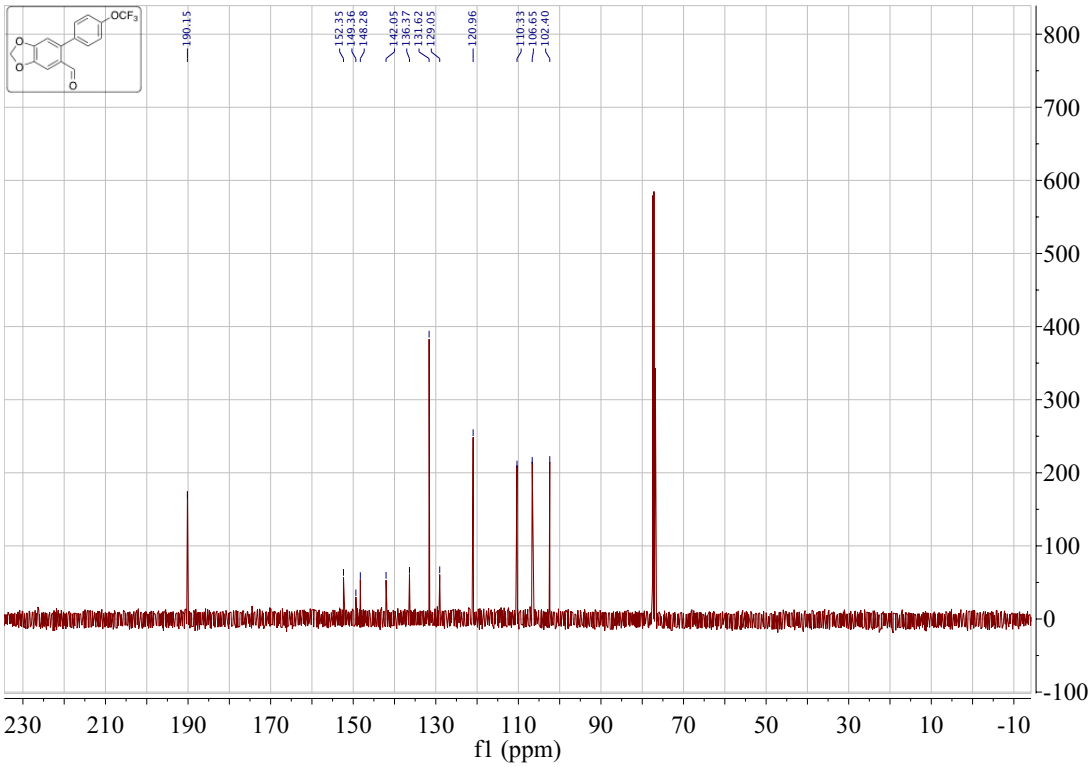

164.34
162.28
144.62
138.30
134.97
134.21
131.25
130.67
130.55
129.56
128.80
127.51
126.96
126.92
126.87
125.60
125.58
124.57
124.49
122.25
122.22
117.44
117.24
113.99
109.37
1.00
0.78
1.09
1.03
3.75
0.80
0.57
0.48
6.24
0.65
4.10
5.45
5.57
3.90
3.58
3.74
3.24
3.72
3.18
F
NO2
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

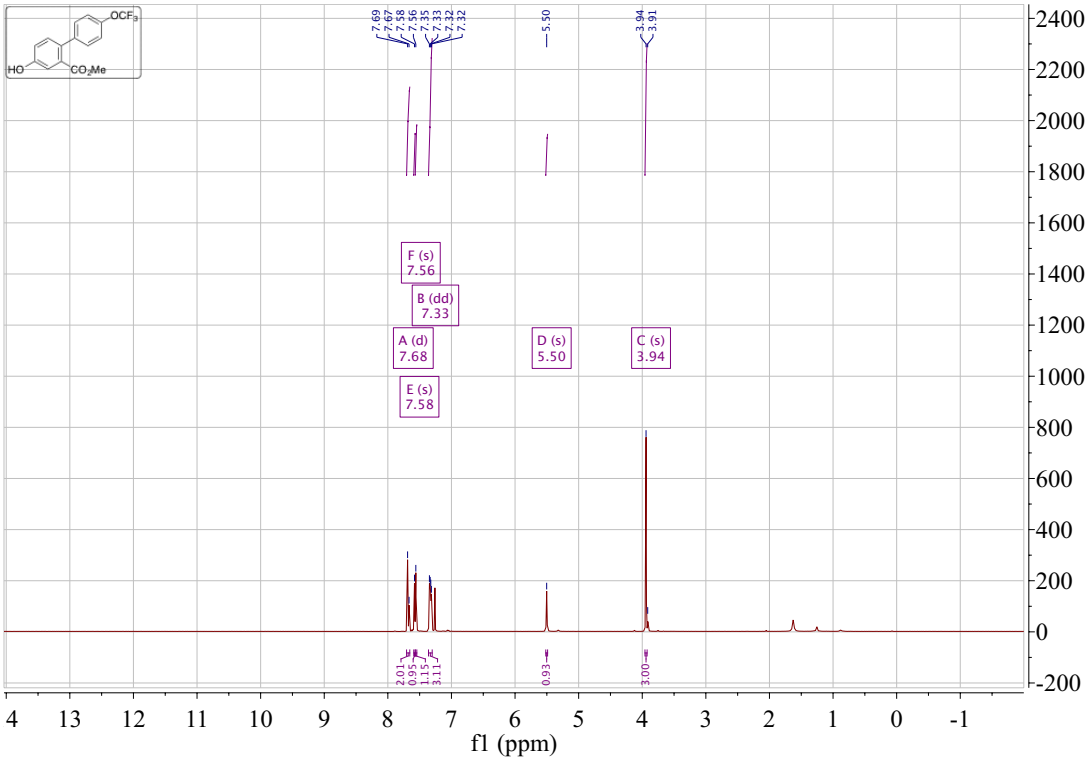

-107.01
-107.02
-107.04
-107.05
-107.06
1.00
F
NO2
000
-10000
-25000
-40000
-55000
-70000
-85000
-100000
-115000
f1 (Hz)

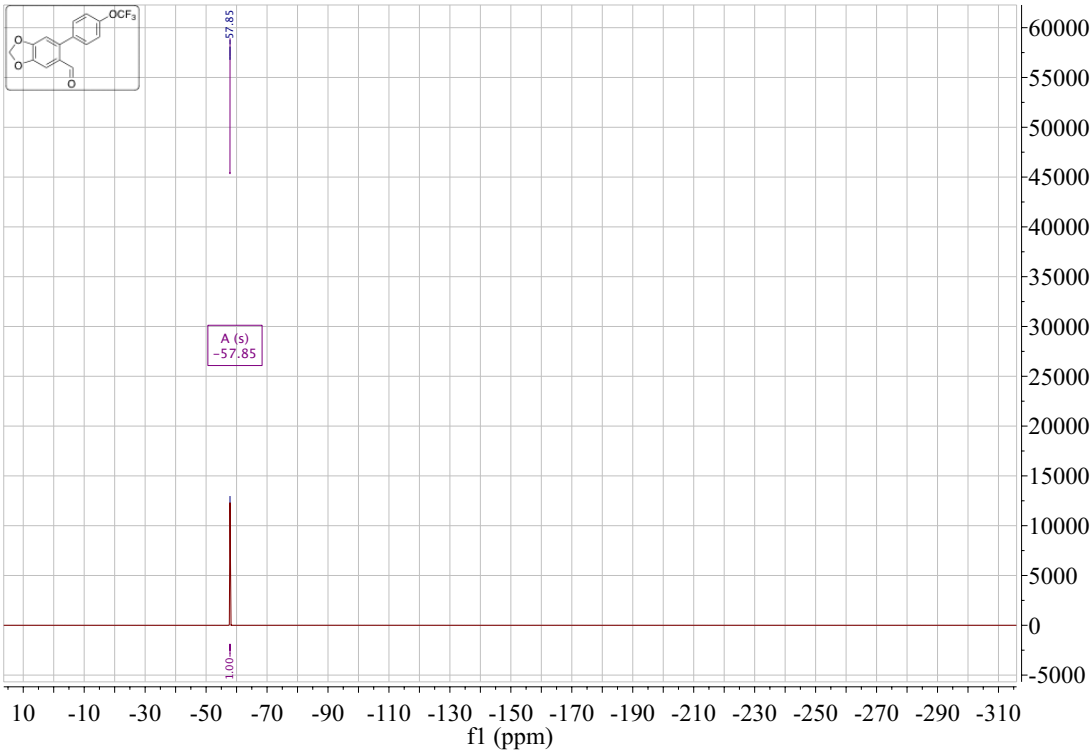

A (s)
10.13
B (d)
8.05
C (ddd)
7.86
D (tt)
7.41
E (s)
7.31
F (m)
7.05
H (s)
3.93
f1 (ppm)

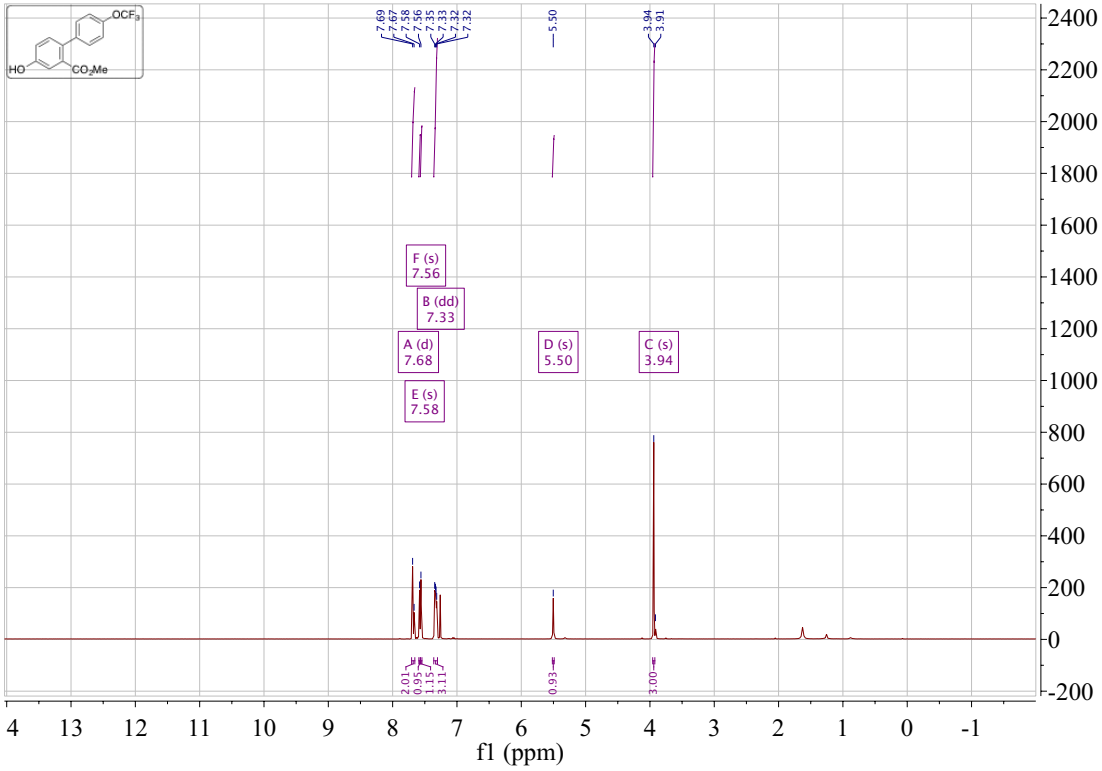

190.61
163.59
140.62
140.56
139.90
138.82
130.42
128.12
126.33
125.14
125.06
124.08
122.28
115.97
115.06
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
55.88
f1 (ppm)

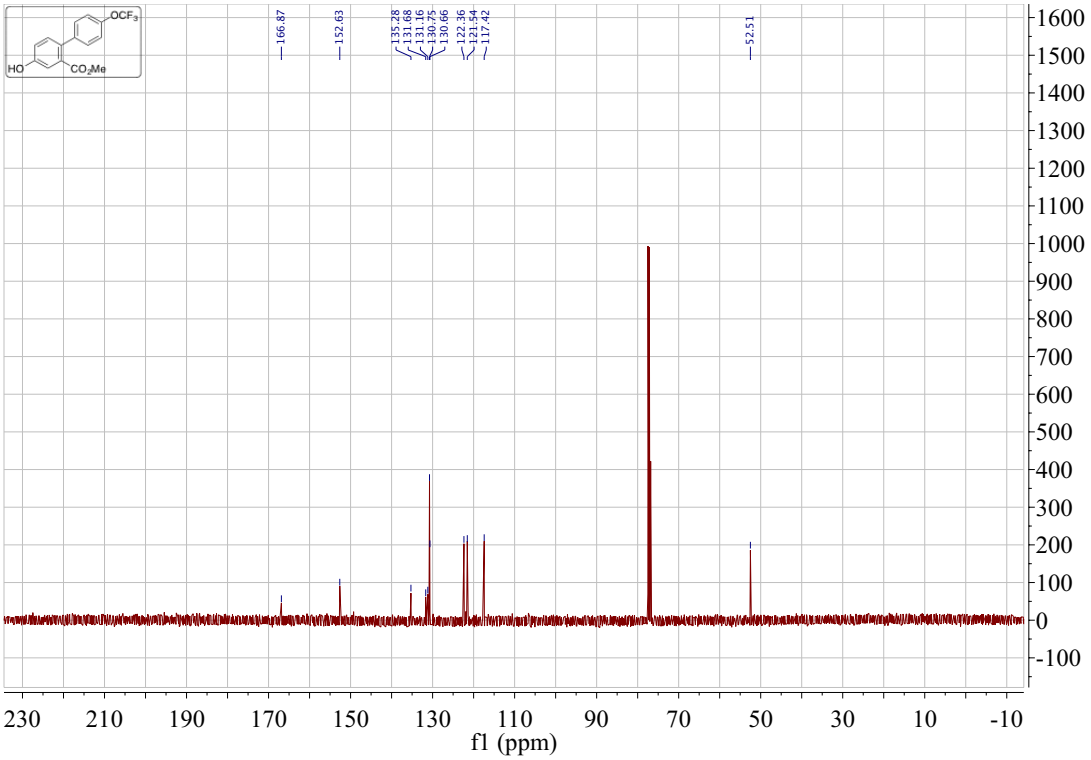

OCF3
O
O
O
9.73
7.47
7.38
7.36
7.31
7.29
6.82
6.11
6.08
0.89
0.92
2.15
2.14
0.86
1.96
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)

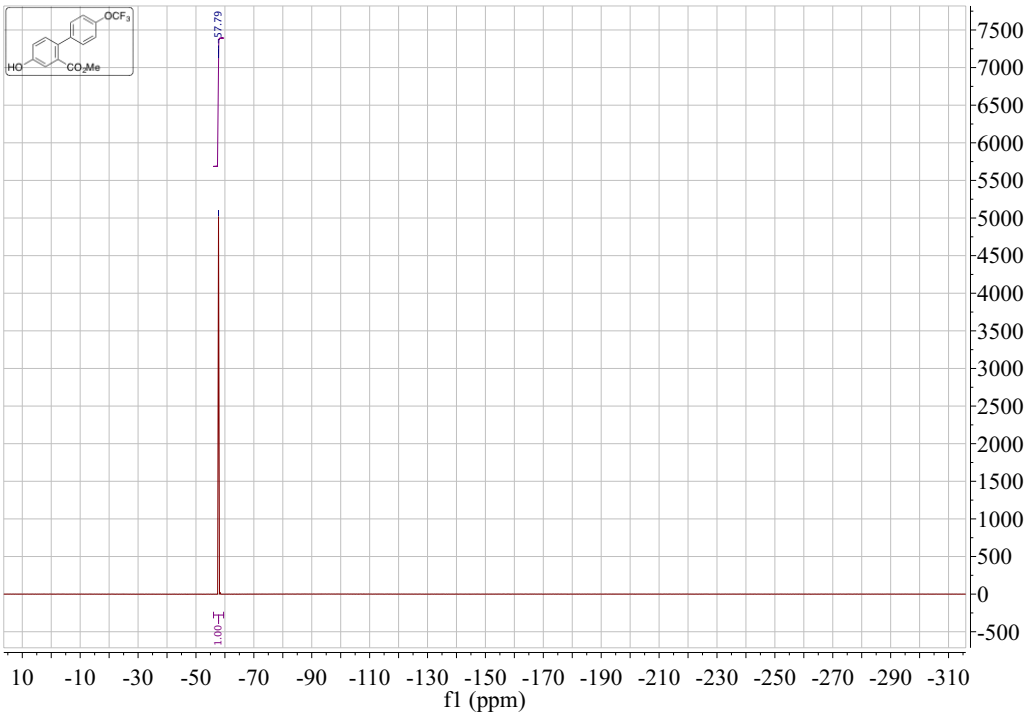

OCF3
O
O
O
190.15
152.35
149.36
148.28
142.05
136.37
131.62
129.05
120.96
110.33
106.65
102.40
800
700
600
500
400
300
200
100
0
-100
230 210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

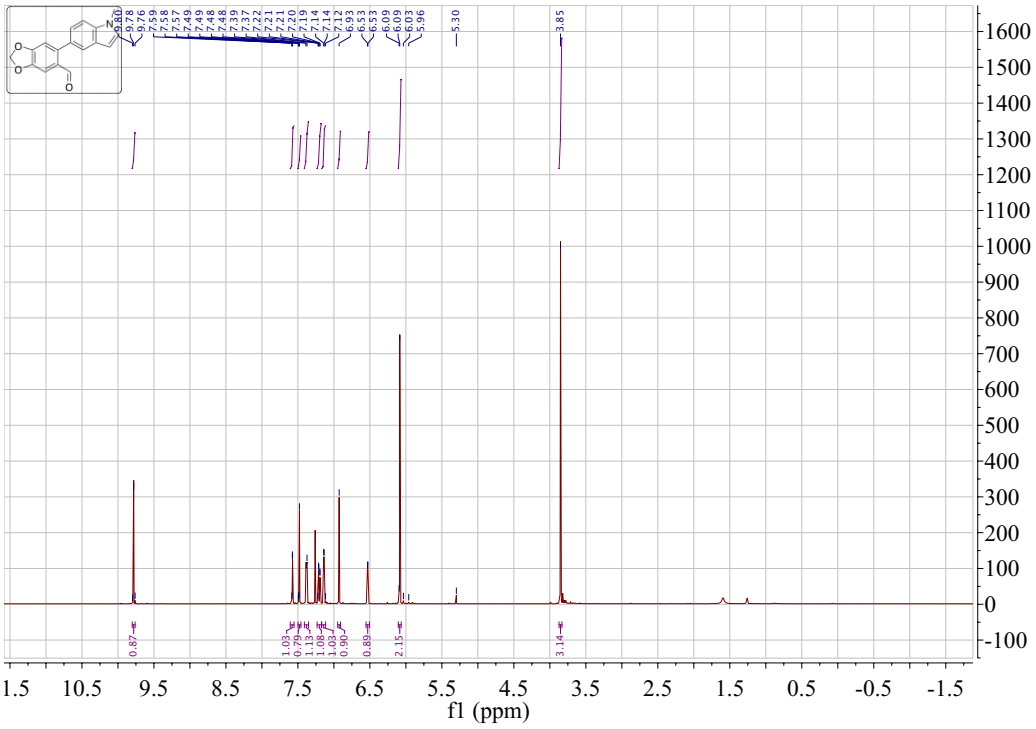

OCF3
HO
CO2Me
7.69
7.67
7.58
7.56
7.35
7.33
7.32
7.32
5.50
3.94
3.91
F (s)
7.56
B (dd)
7.33
A (d)
7.68
D (s)
5.50
C (s)
3.94
E (s)
7.58
2.01
0.95
1.15
3.11
0.93
3.00
f1 (ppm)

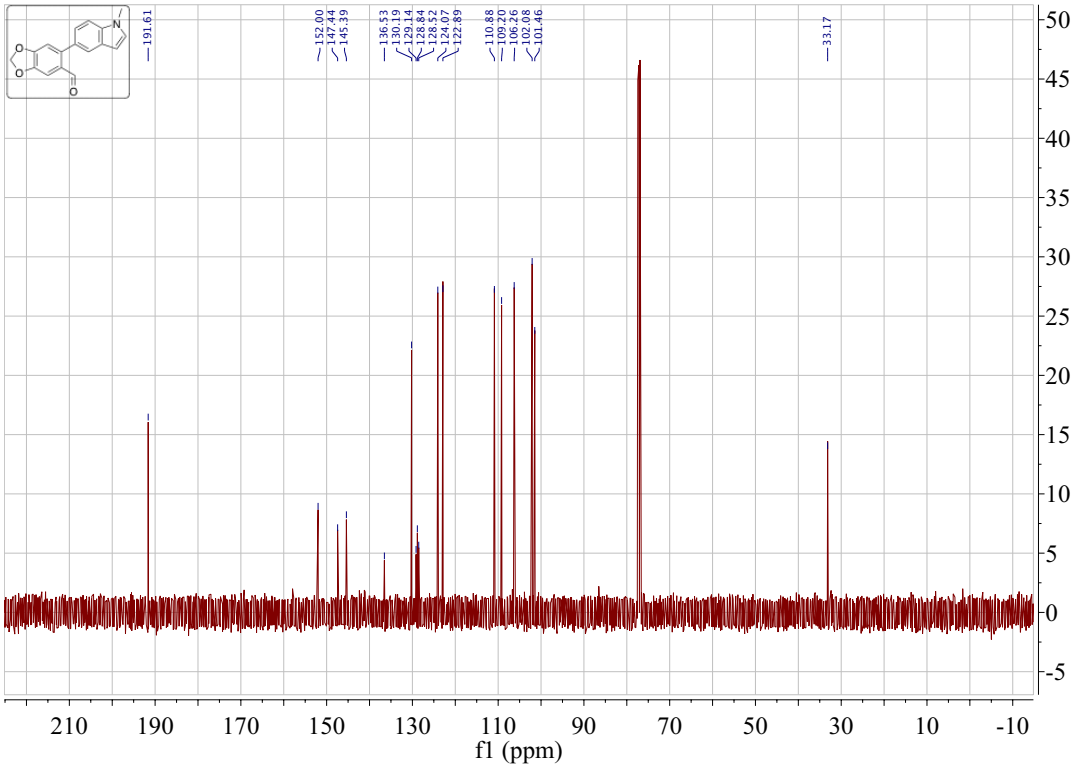

OCF3
O
O
O
57.85
A (s)
-57.85
1.00
f1 (ppm)

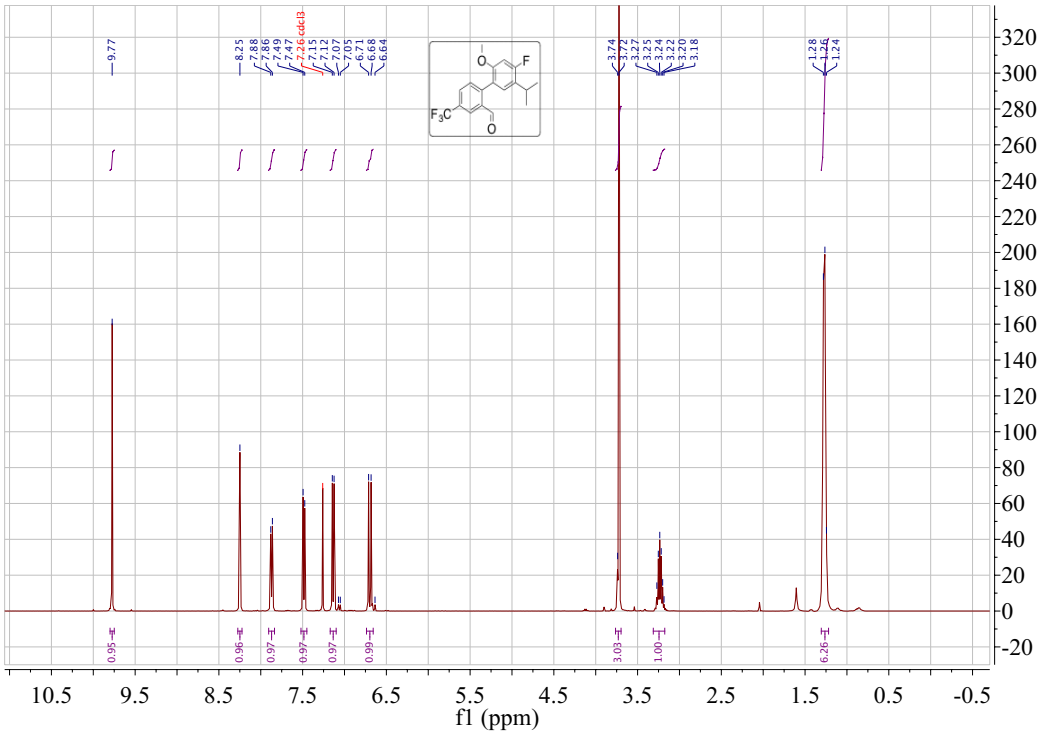

OCF3
HO
CO2Me
7.69
7.67
7.58
7.56
7.35
7.33
7.32
5.50
3.94
3.91
F (s)
7.56
B (dd)
7.33
A (d)
7.68
D (s)
5.50
C (s)
3.94
E (s)
7.58
2.01
0.95
1.15
3.11
0.93
3.00
f1 (ppm)

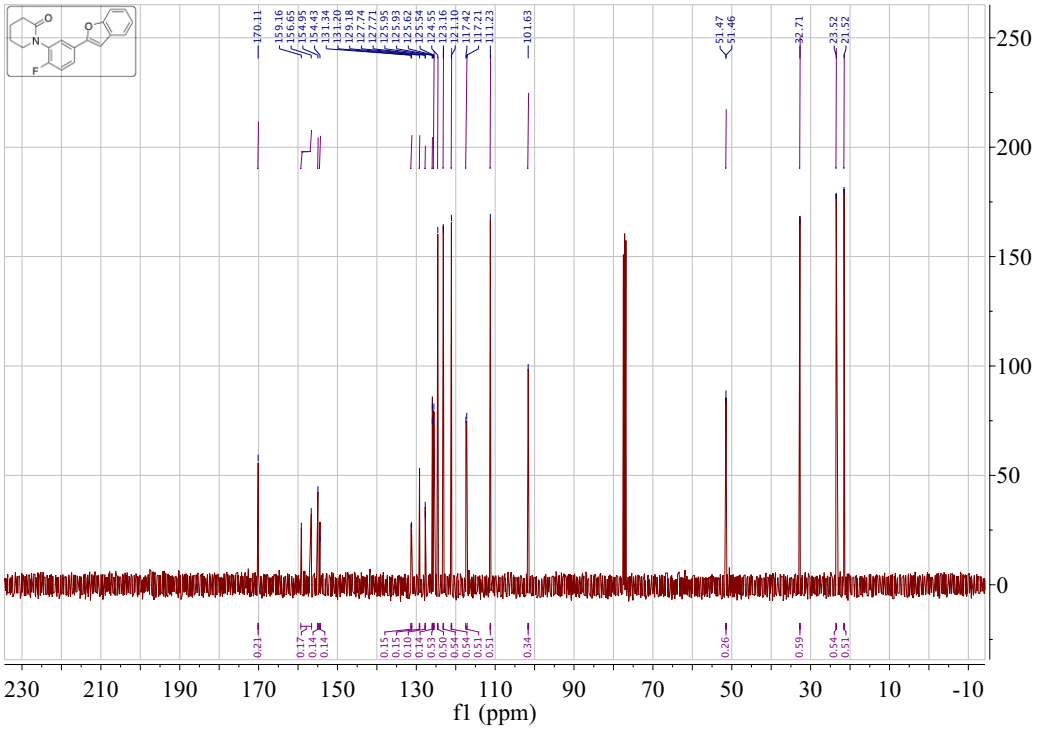

OCF3
HO
CO2Me
166.87
152.63
135.28
131.68
131.16
130.75
130.66
122.36
121.54
117.42
52.51
f1 (ppm)


OCF3
HO
CO2Me
7.79
1.00
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290 -310
f1 (ppm)


9.80
9.78
9.76
7.59
7.58
7.57
7.49
7.49
7.48
7.48
7.39
7.37
7.22
7.21
7.21
7.20
7.19
7.14
7.12
6.93
6.53
6.09
6.09
6.03
5.96
5.30
3.85
0.87
1.03
0.79
1.13
1.08
1.00
0.90
0.89
2.15
3.14
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
1.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
f1 (ppm)


191.61
152.00
147.44
145.39
136.53
130.19
129.14
128.84
128.52
124.07
122.89
110.88
109.20
106.26
102.68
101.46
33.17
f1 (ppm)


9.77
8.25
7.88
7.86
7.49
7.47
2.26 cdcl3
7.15
7.12
7.07
7.05
6.71
6.68
6.64
3.74
3.72
3.27
3.25
3.24
3.22
3.20
3.18
1.28
1.26
1.24
0.95
0.96
0.97
0.97
0.97
0.99
3.03
1.00
6.26
f1 (ppm)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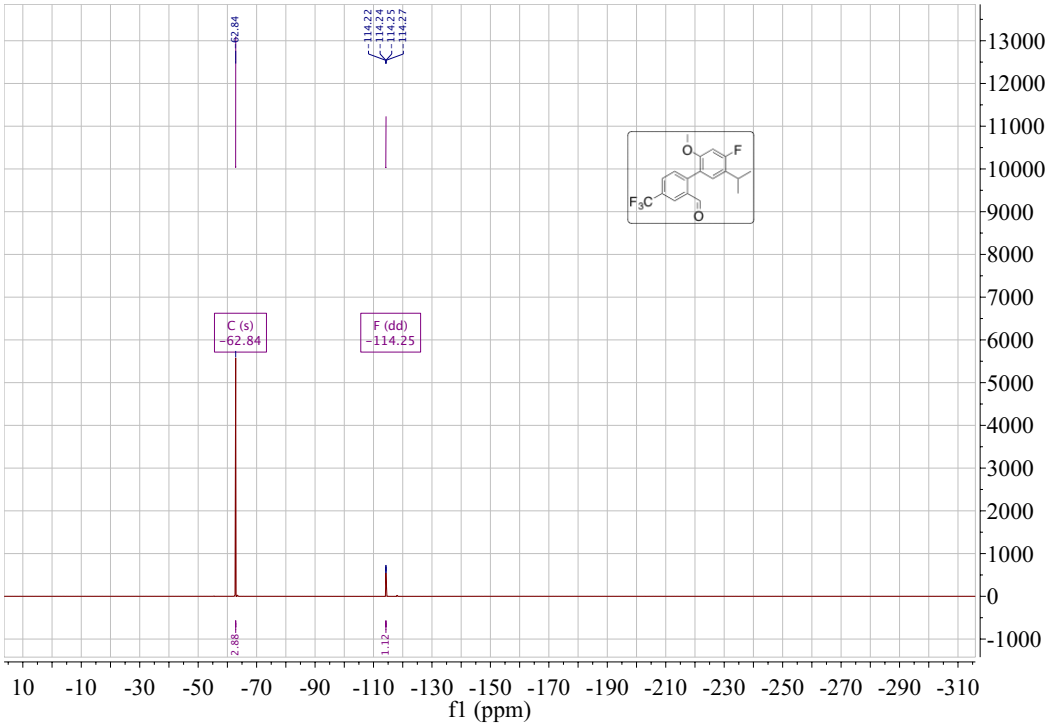
f1 (ppm)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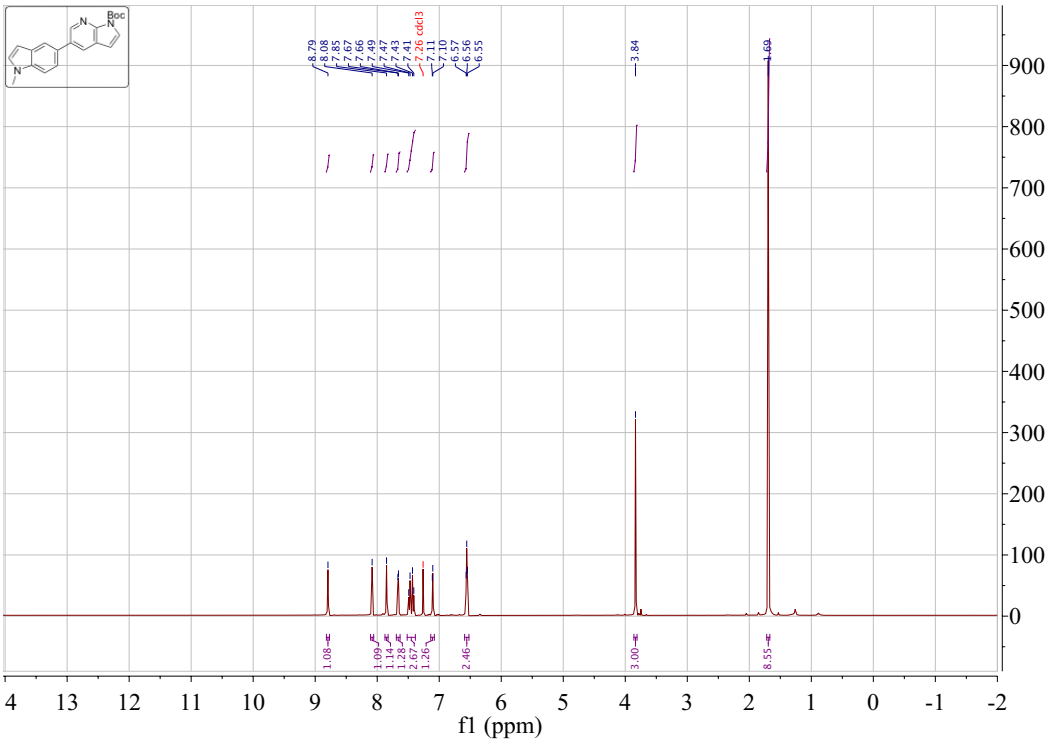
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6.57
6.56
6.55
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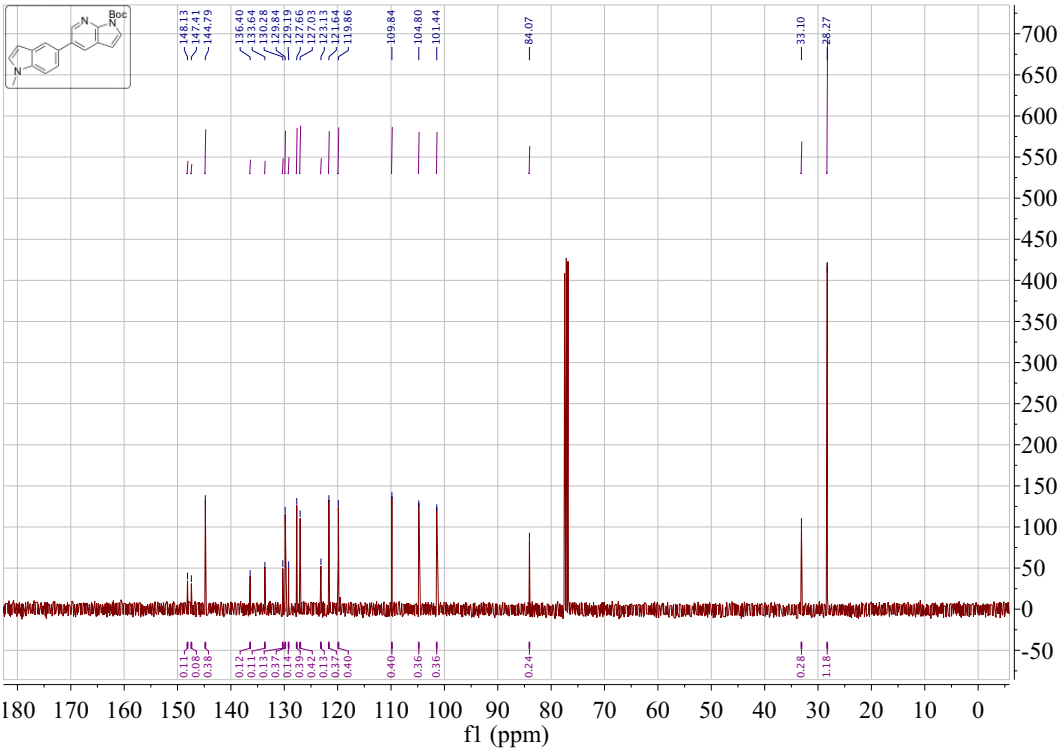
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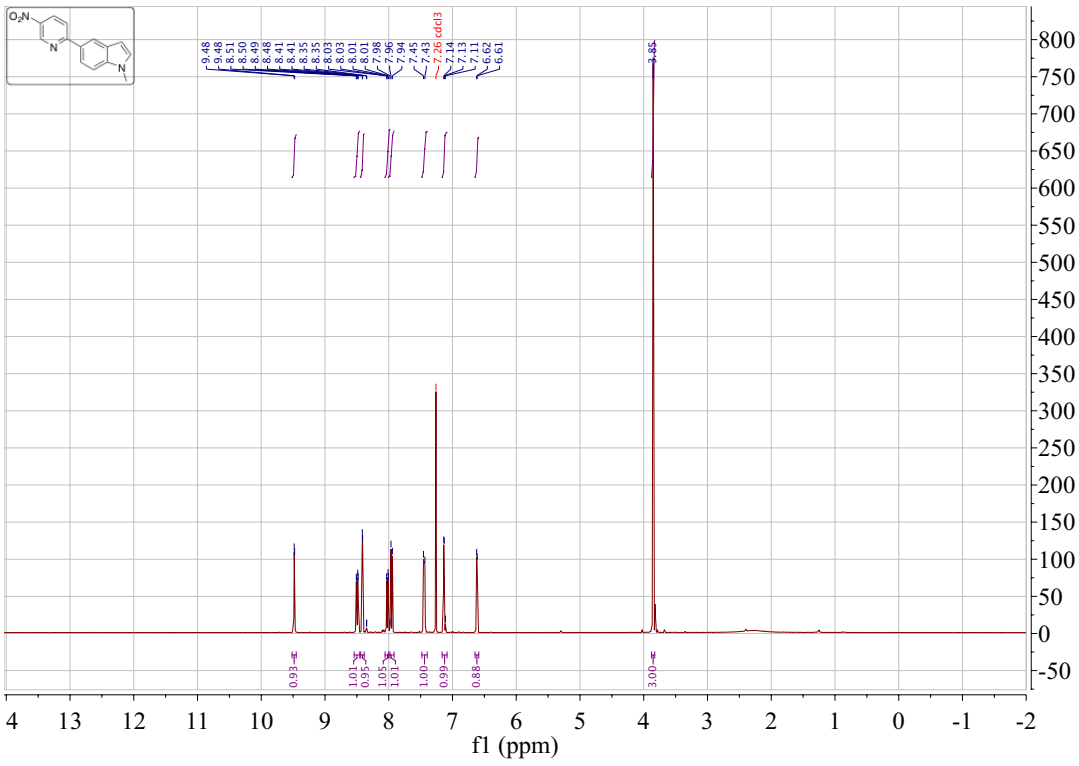
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7.11
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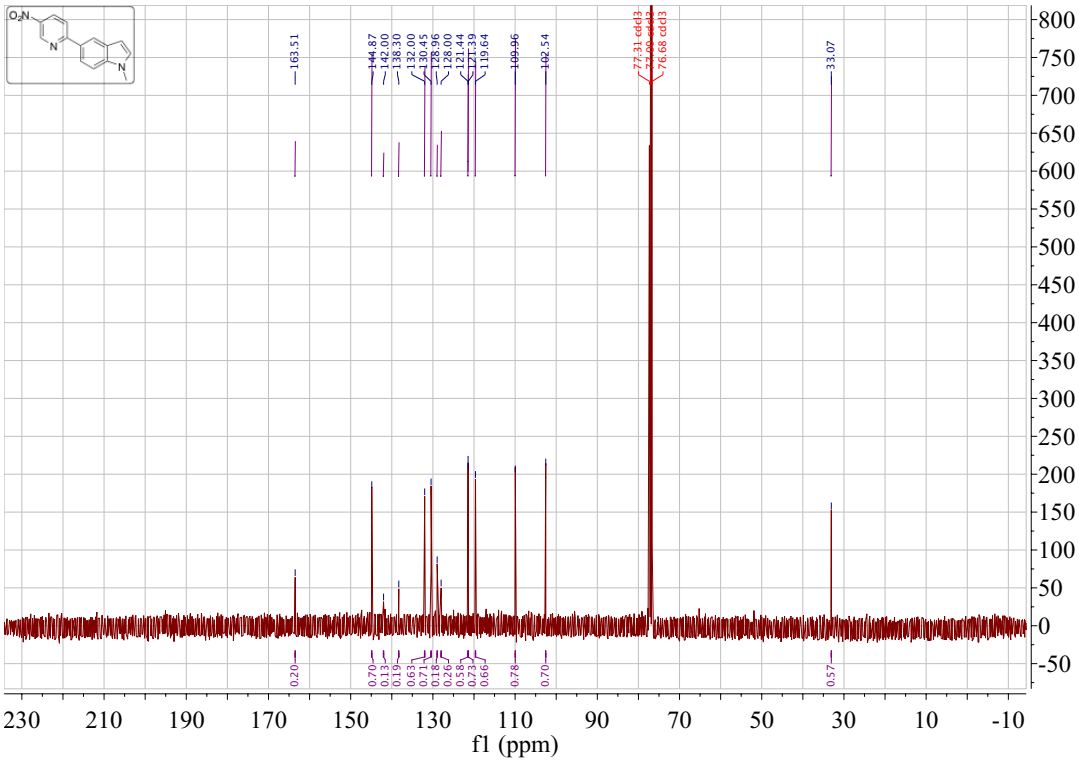
f1 (ppm)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77.00 cdcl3
76.68 cdcl3
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0.20
0.70
0.13
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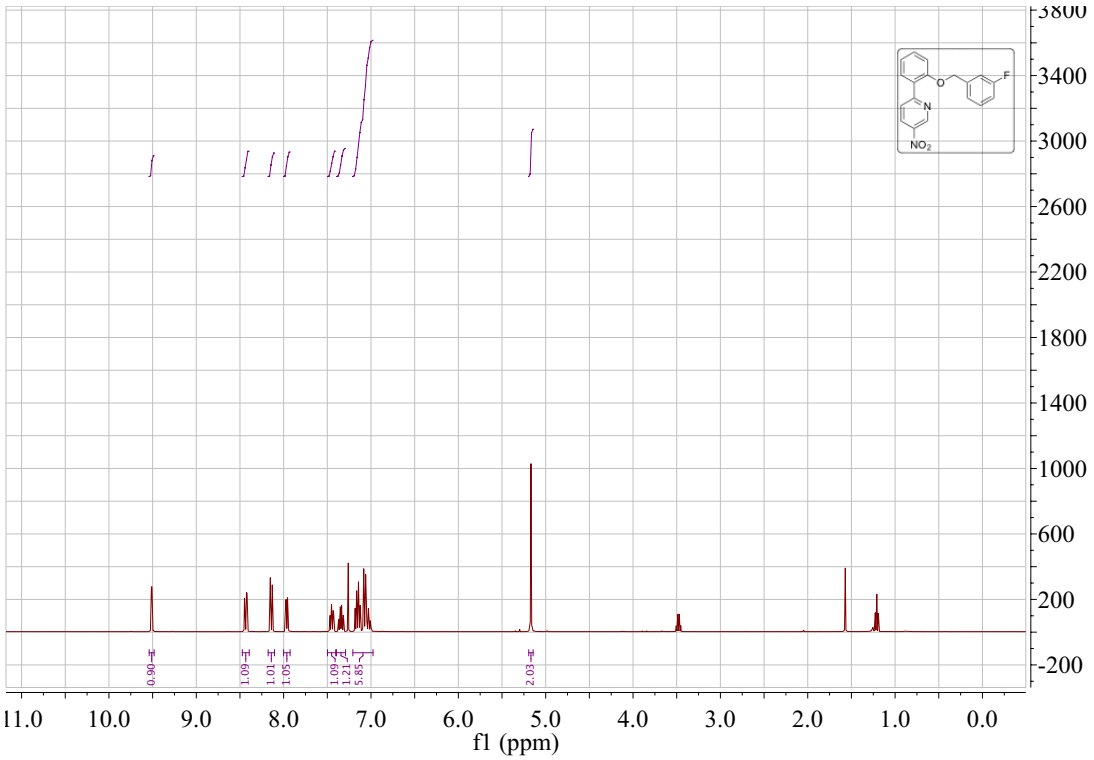
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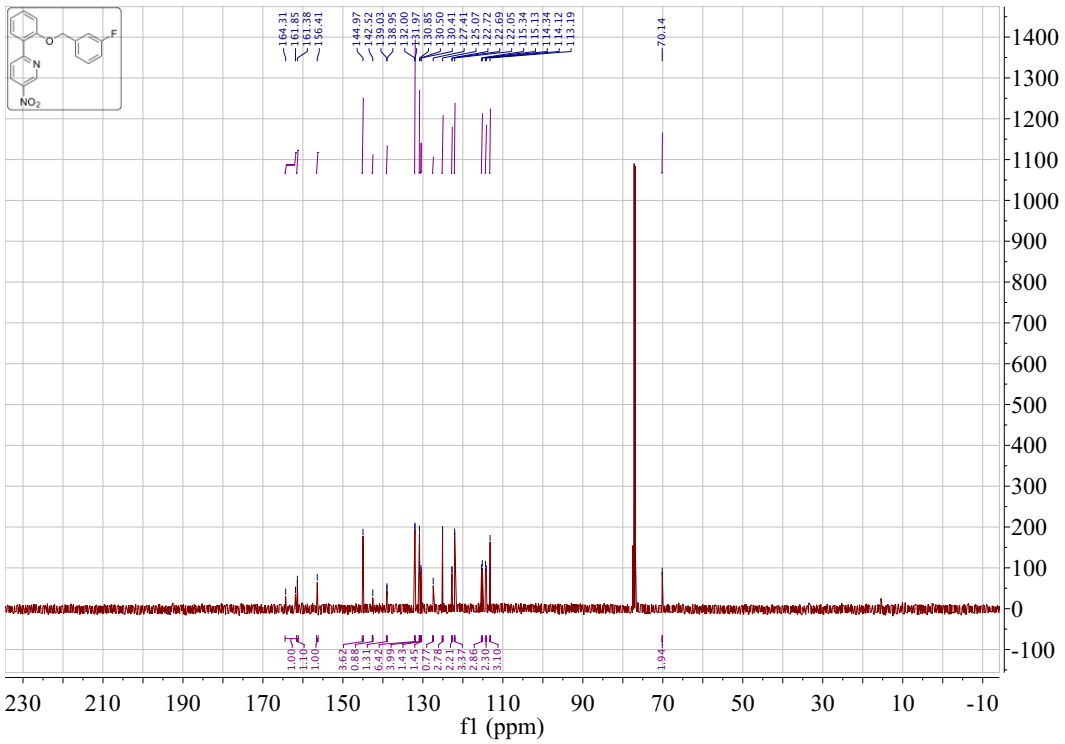
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2.86
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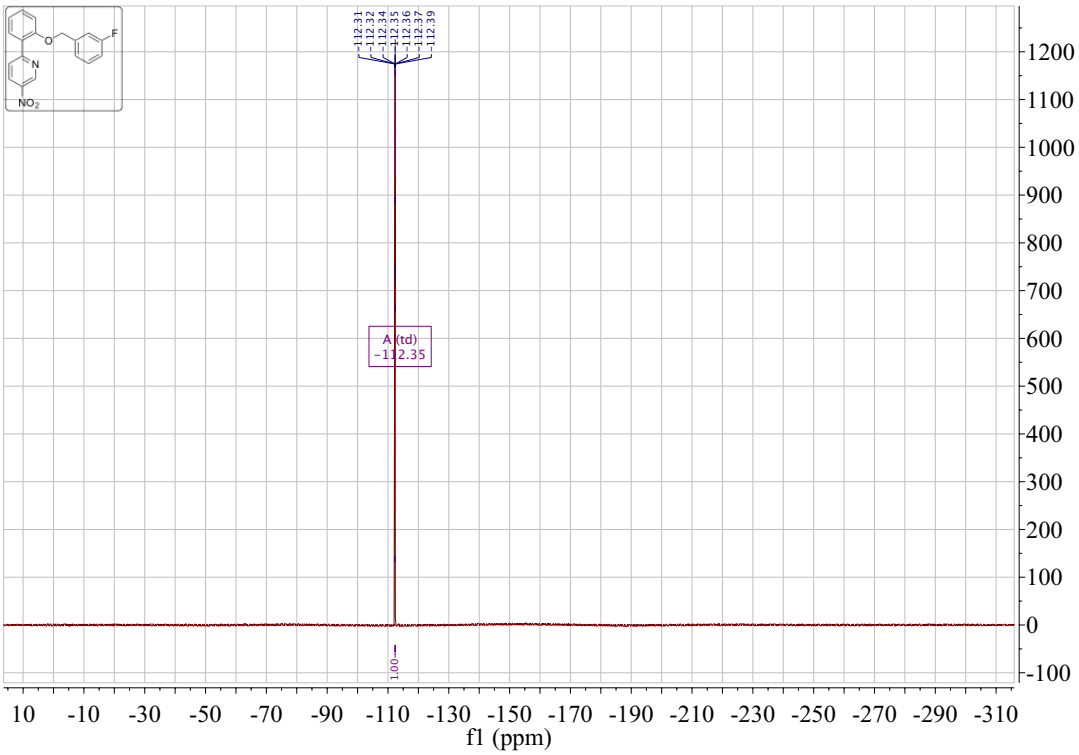
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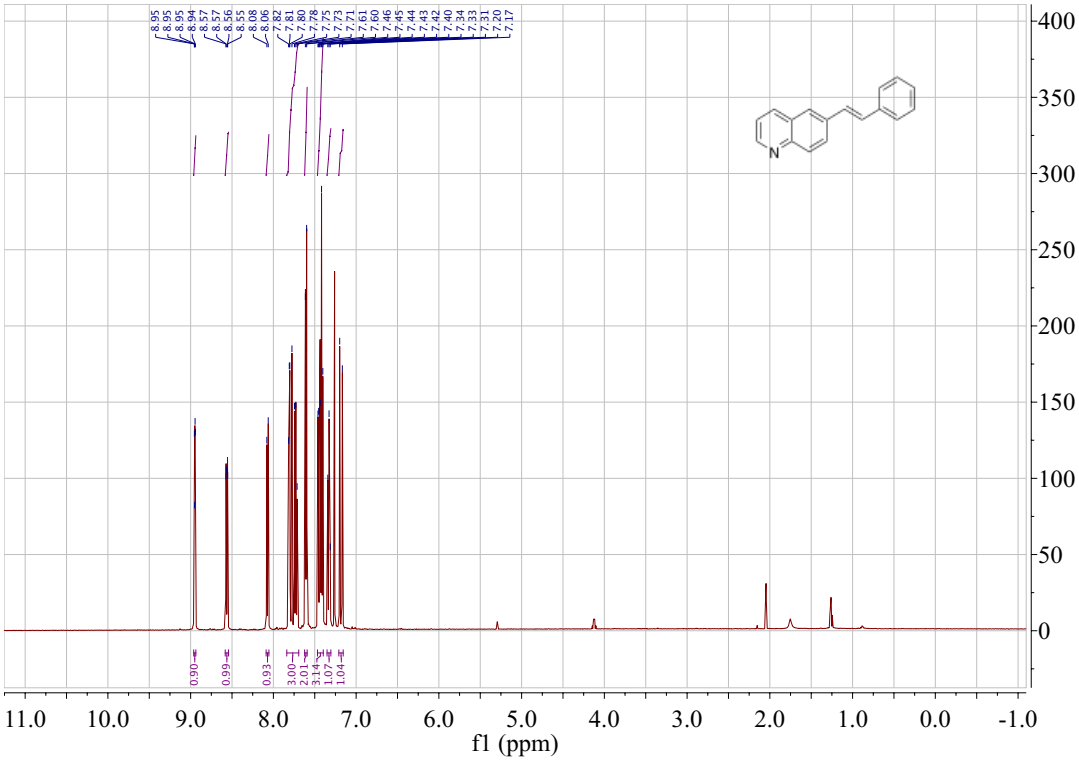
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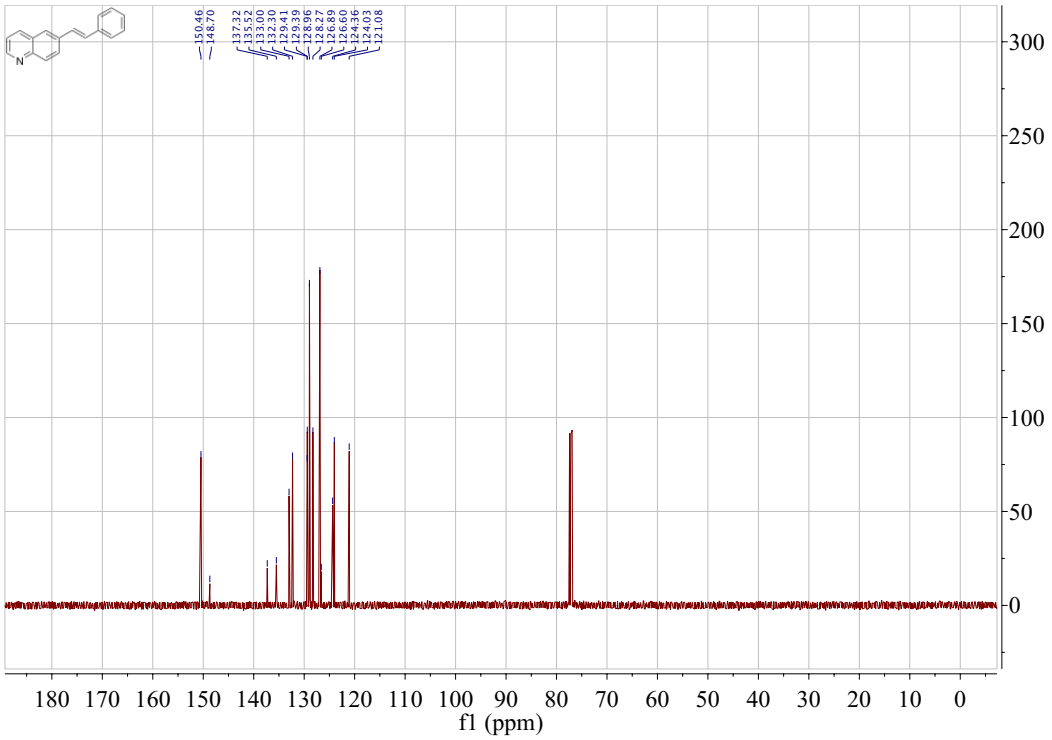
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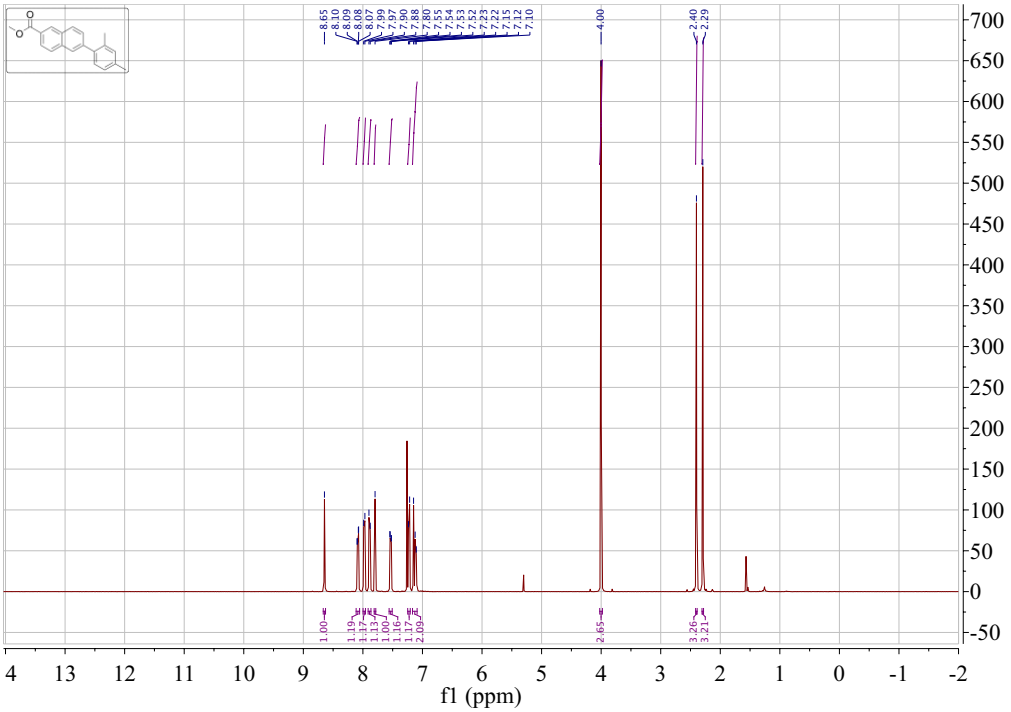
f1 (ppm)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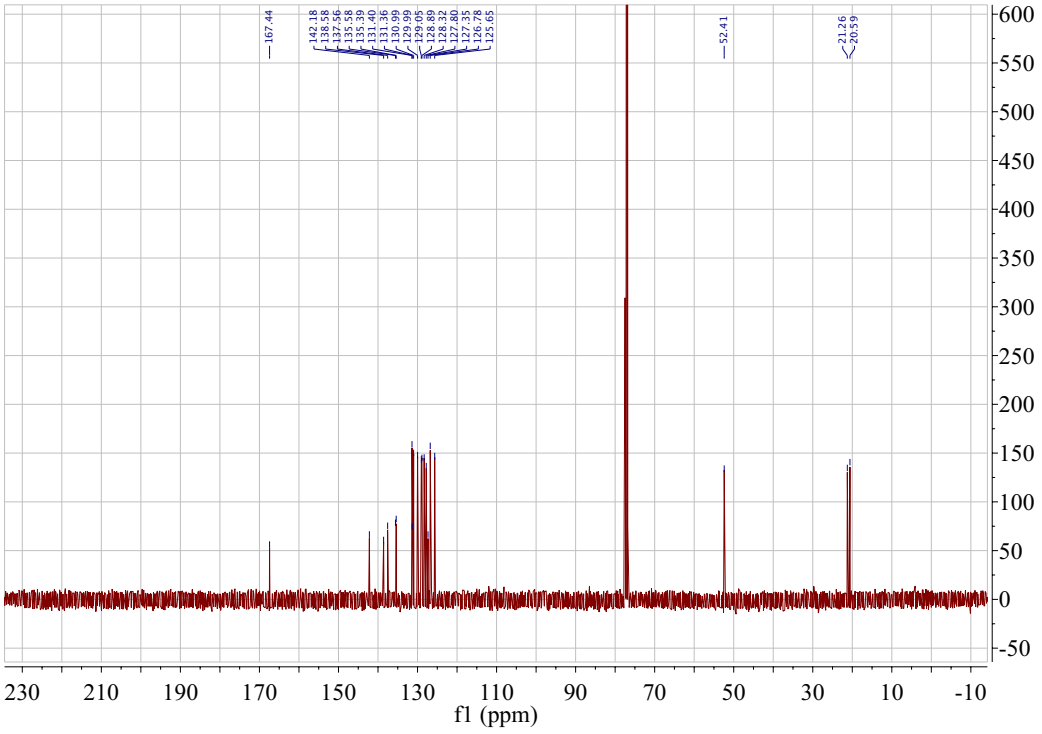
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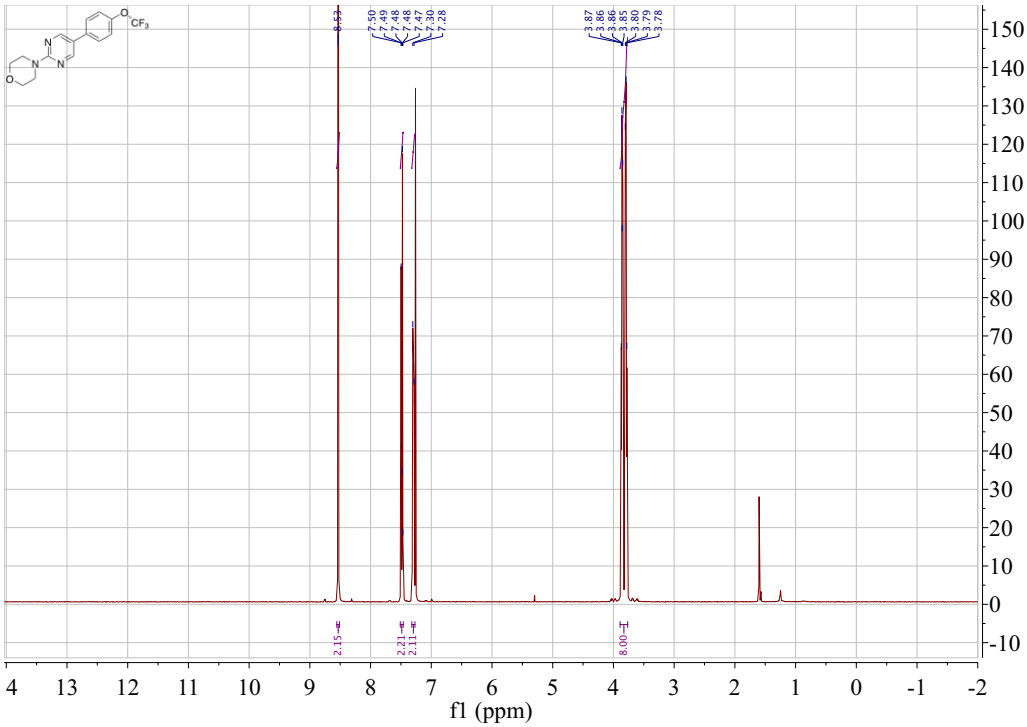
20.59
f1 (ppm)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2.21
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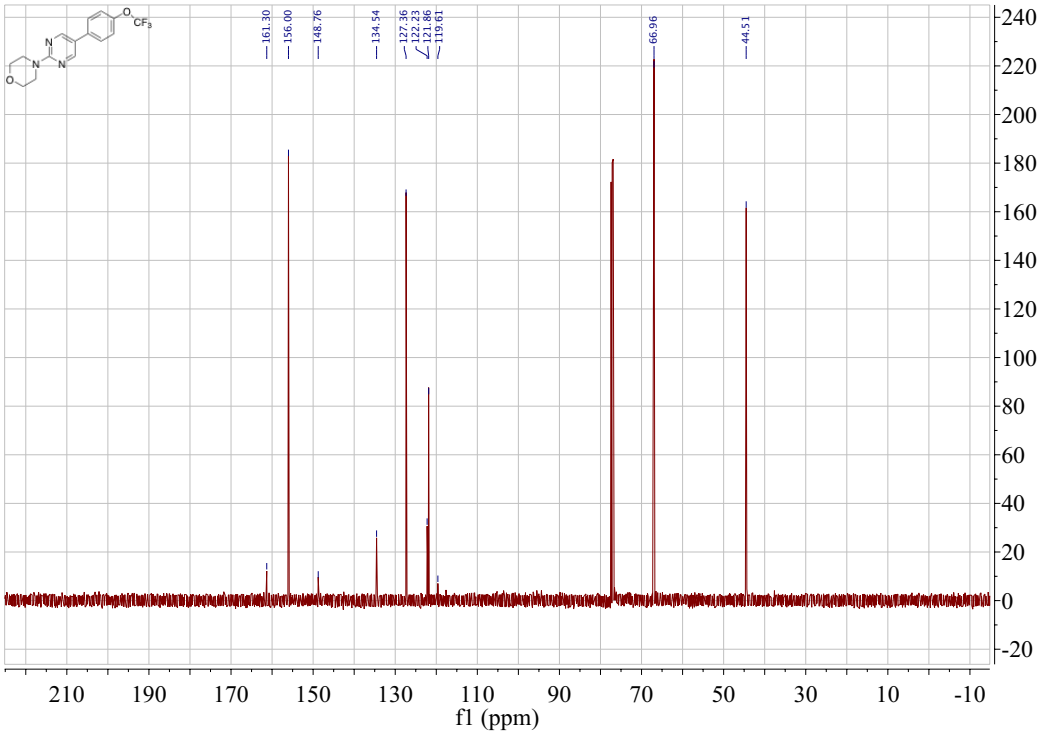
8.00
f1 (ppm)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160
140
120
100
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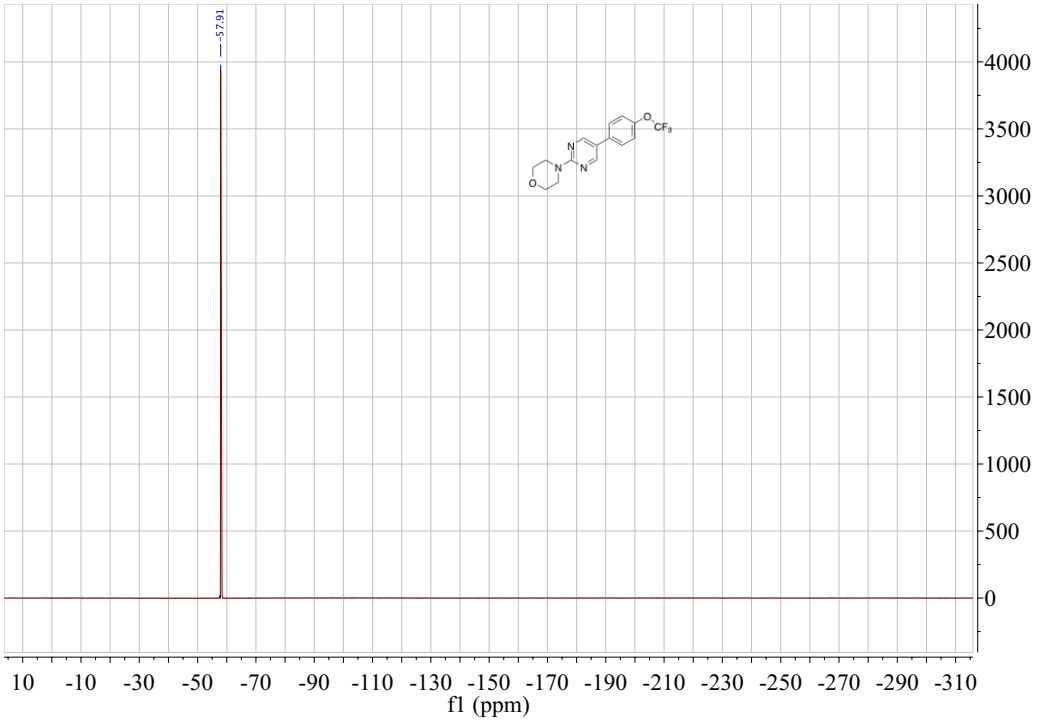
f1 (ppm)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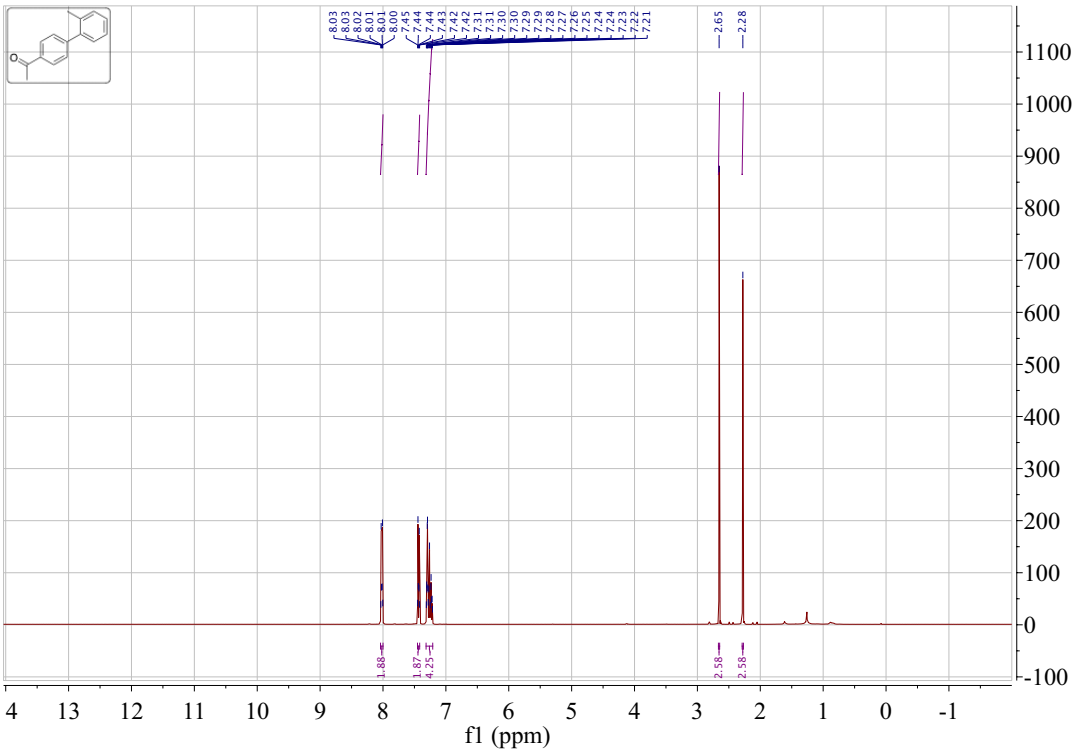
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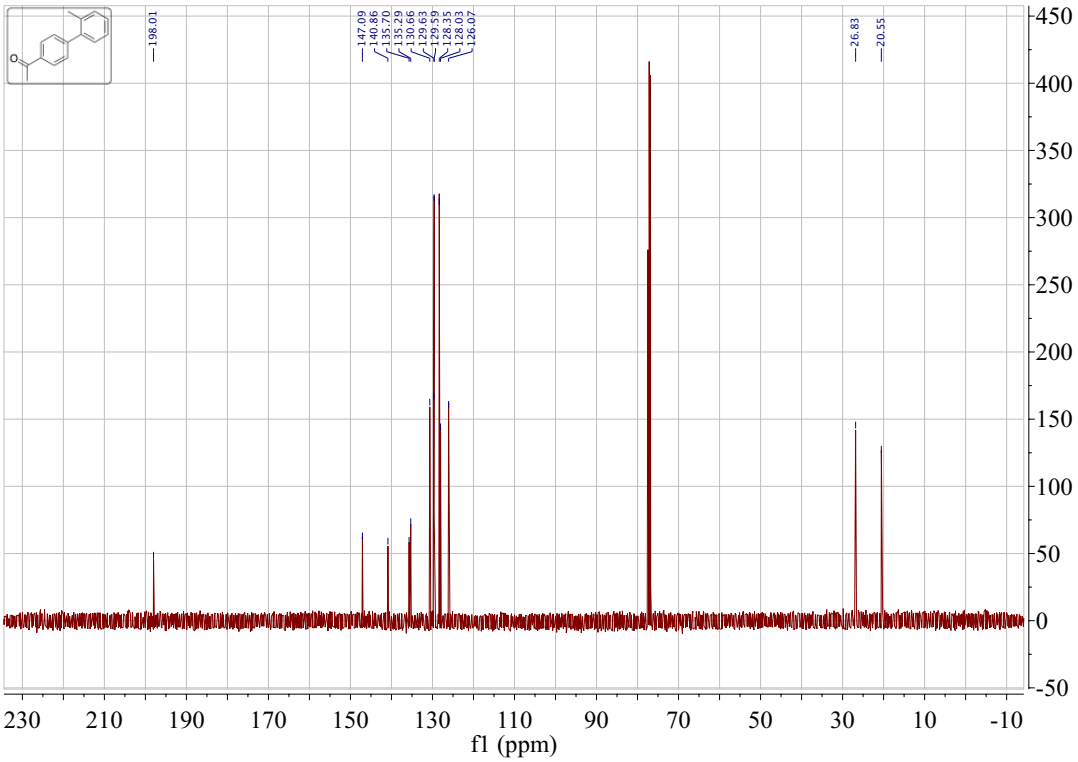
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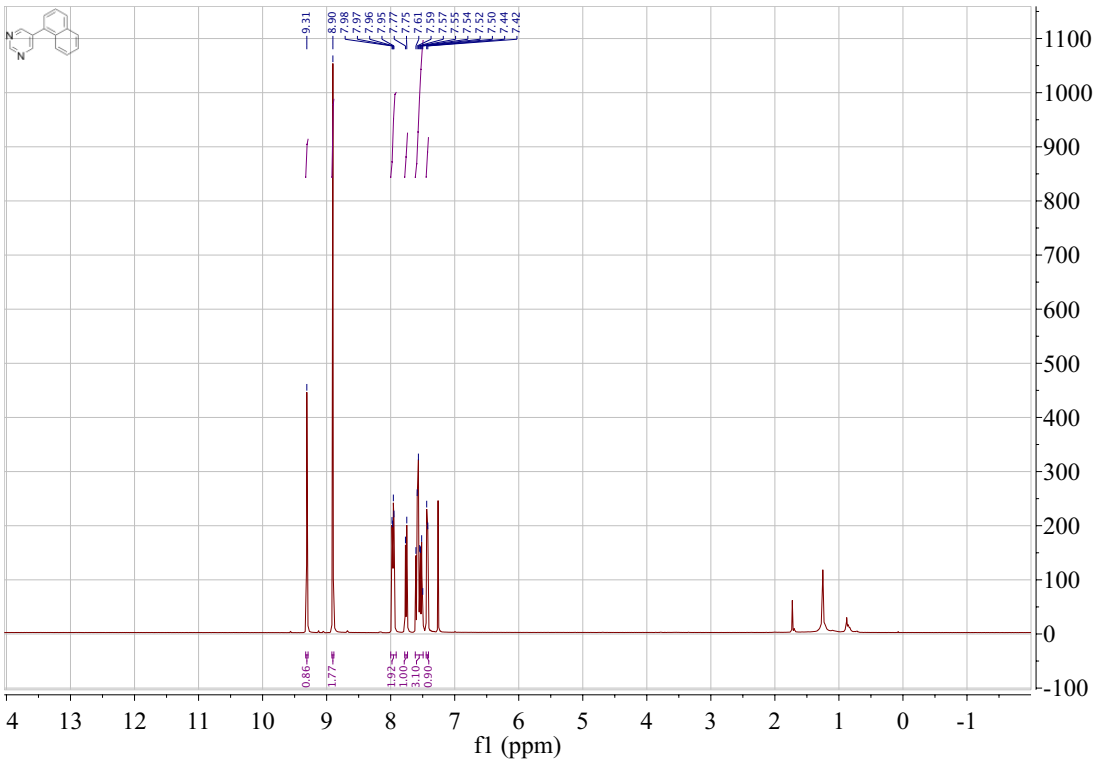
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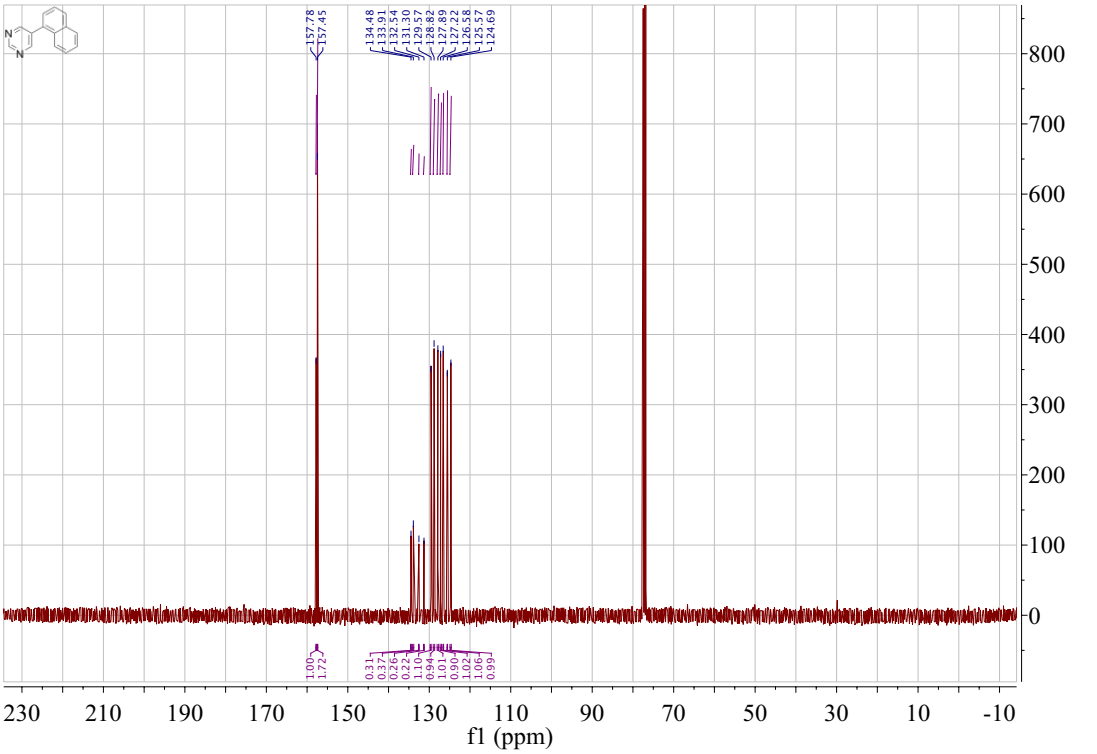
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0.26
0.22
1.10
0.94
0.17
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1.02
1.06
0.99
f1 (ppm)

K. References

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III. Development of An Aqueous Palladium-Catalyzed C-N Coupling with *t*-Butyl Carabazate En Route to Indoles and Pyrazoles

A. Introduction

The indole nucleus is a ubiquitous privileged structure found in a variety of biological molecules, natural products, medicines, and illicit substances (Figure 1).[1] Due to the ubiquity of indoles in such important molecules the pursuit of methods to synthesize indoles has been an active area of research since Bayer first produced indole from the decomposition of Indigo dye, reported in 1866.[1]

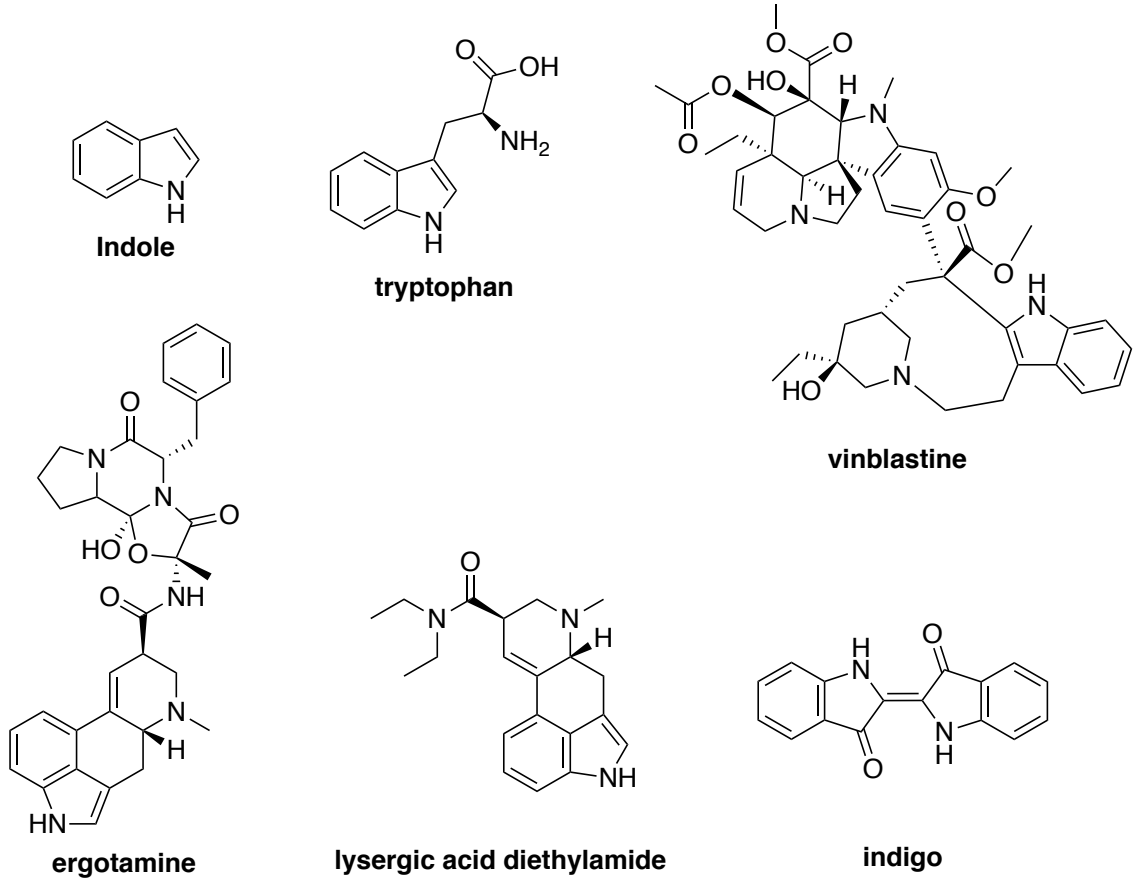


Figure 10: Representative examples of indole containing molecules

While various methods have been reported for the synthesis of indole derivatives, the most widely used method is the Fisher indole synthesis disclosed by Emil Fisher in 1883.[1,2]

The Fisher indole synthesis consists of condensing an enolizable ketone onto an aryl hydrazine under acidic conditions followed by enolization, then a [3,3] sigmatropic reagent and ultimate expulsion of ammonia (Figure 2).

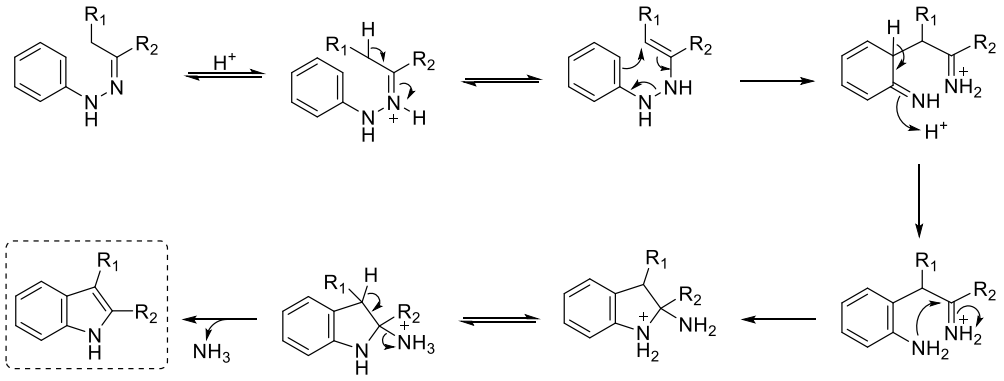


Figure 11: Mechanism of the Fisher indole cyclization

The aryl hydrazines necessary for this method are typically prepared via diazotation of aniline derivatives utilizing sodium nitrite and aqueous acid followed by reduction of the diazonium salt to the aryl hydrazine. Unfortunately, these diazonium salts and their corresponding aryl hydrazines are unstable and typically need to be used immediately. To overcome this shortfall the Buchwald modification to the Fisher indole synthesis was disclosed in 1999.[3] With this modification the hydrazine moiety is introduced via a palldium-catalyzed C-N coupling between aryl halides and benzophenone hydrazone (BPH) (figure 3). The protected aryl benzophenone hydrazone can be isolated and stored prior to being subjected to the indolization, affording greater flexibility to the sequence of reactions involved. Another facet to this modification is that the aryl benzophenone hydrazone or deprotected aryl hydrazine need not be isolated and can instead be readily telescoped into a "one-pot" coupling, deprotection, condensation, cyclization sequence. While there are many attractive features to this modification it does have several drawbacks. The "one-pot" protocol, while lacking any intermediate purification, involves an initial coupling in toluene

at 80 °C followed by evaporation of toluene to allow for a solvent switch to ethanol. This wasteful solvent switch in tandem with high temperatures for the initial coupling, palladium loadings of up to 5 mol% leading significant residual palladium contamination, and the use of two equivalents of *p*-toluenesulfonic acid (PTSA) leaves much to be desired. The equilibrium protection/deprotection of the benzophenone moiety can interfere with the desired condensation on the enolizable ketone. Additionally, the presence of benzophenone waste complicates the purity profile of the final product and can be challenging to separate from the desired indole product since it is formed in stoichiometric quantities.

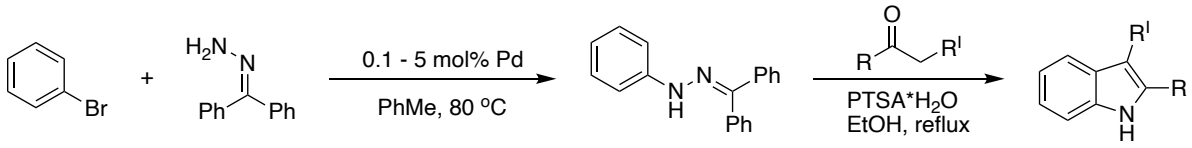


Figure 12: Buchwald modification to the Fisher indole synthesis

While previous efforts in the group had been focused on the coupling of BPH and Michler's ketone hydrazone (MKH) (Figure 3) for this method, the aforementioned purification issues led us to search for an alternative protected hydrazine surrogate for use in this method.[4] Previous work in the group on the palladium-catalyzed coupling of protected ammonia equivalents hinted at the possibility of using *t*-butyl carbazate (a.k.a. Boc-hydrazine) as the source of hydrazine. A quick literature search buoyed our hopes as there have been several reports of palladium-catalyzed and copper-catalyzed couplings of *t*-butyl carbazate in the past.[5-7]

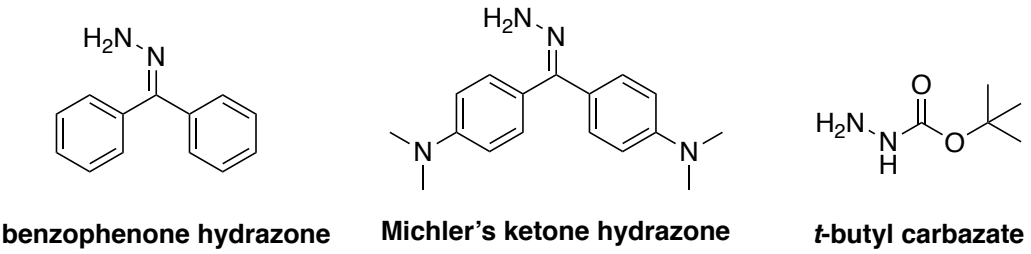


Figure 13: Structures of several hydrazine surrogates

To that end, we endeavored to develop a mild aqueous coupling of *t*-butylcarbazate that could be easily telescoped into a net 4-step, 1-pot coupling, deprotection, condensation, cyclization sequence.

B. Results and Discussion

Prior optimization screenings utilizing MKH had indicated that 0.5 mol% of [*t*BuBrettPhosPd(allyl)]OTf was the best catalyst system.[4] When applied to a coupling between 4-bromobiphenyl and *t*-butyl carbazate (1.1 equiv) in 2 wt% TPGS-750-M/H_2O at 45 ^oC with triethylamine (1.5 equiv.) as the base led to complete consumption of the halide in 18 h by TLC. Increasing the equivalents of both base and nucleophile to two led to complete consumption of the halide in 90 minutes by TLC. While triethylamine was effective it had to be freeze-pump-thawed on a consistent basis to remove oxygen. Sodium *t*-butoxide, a base widely used in C-N coupling reactions, showed identical activity to triethylamine by another group member for the coupling of BPH.[4]

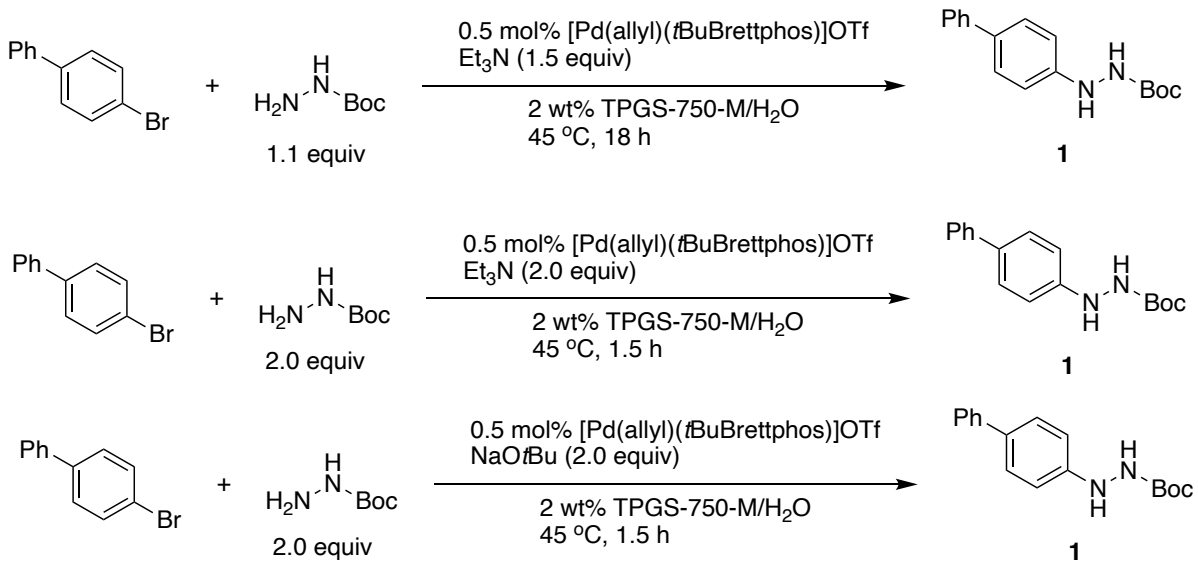


Figure 14: Evolution of coupling conditions with 4-bromobiphenyl

When these conditions were applied to a coupling with 4-bromoanisole a maximum of 90% conversion was observed after five hours with noticeable Pd-black formation. Increasing the temperature to 55 °C led to rapid Pd-black formation and only minor conversion by TLC. Based on previously published work pointing to conversion enhancements when the ligand to Pd ratio is greater than 1:1, a ligand ratio of 2:1 was tested and complete conversion of 4-bromoanisole was achieved in six hours.[8]

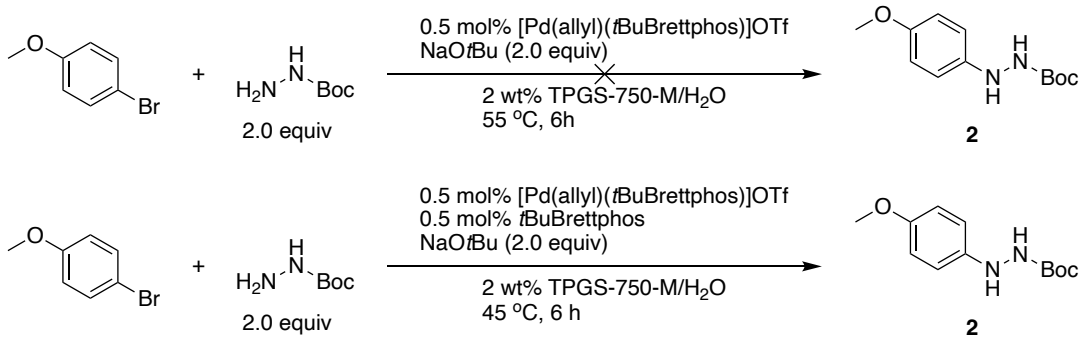


Figure 15: Optimization of ligand ratio

A previous report on the coupling of *t*-butyl carbazate showed that the ratio of branched to linear products was dependent on both ligand and substrate, with *ortho*-substituted

substrates providing exclusively the linear coupling product.[7] While for the scope of this study the exact ratio does not make a difference because the Boc deprotected intermediates would be identical, we still chose to determine the ratio of the products and to ascertain an isolated yield of the coupled product as a measure of the efficacy of the bond-forming method. 1-Bromo-4-*t*-butylbenzene was treated under optimized conditions leading to complete consumption of the starting material after 90 minutes by TLC. The products were only partially separable chromatographically. However, sufficient amounts of both *t*-butyl 1-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate (**3**) and *t*-butyl 2-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate (**4**) could be isolated independently to measure the NMR spectrum of each product. Combining all the material led to an isolated yield of 92% and a 2:1 ratio of **3** to **4** based on ^{1}H NMR analysis.

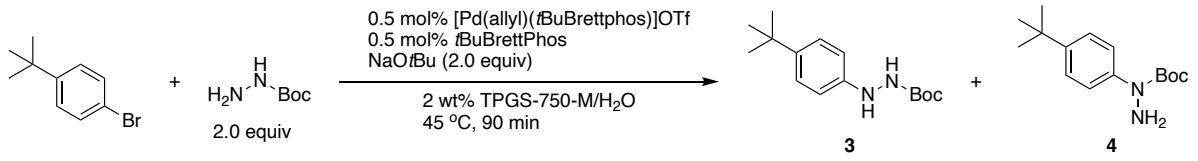


Figure 16: Determination of product distribution

While the coupling of 4-*t*-butyl-1-bromobezene was clearly efficient, we also wanted to address the issues of a complete solvent switch for the cyclization and for the use of two equivalents of PTSA which leads to excess organic waste for the sole purpose of supplying a proton.[3] Since the coupling was already occurring in water, simple dilution with ethanol seemed to be a logical and straightforward choice. Sulfuric acid has long been known to be an effective acid for the Fisher indole synthesis.[1] Thus, final conditions were realized by conducting the initial coupling in TPGS then utilizing an enolizable ketone (2 equiv), concentrated sulfuric acid (3 equiv), diluting the reaction mixture with ethanol to a global

concentration of 0.2 [M] relative to the starting halide and refluxing in a sealed vial overnight.

Using these conditions a broad range of electron-rich and electron-neutral substrates could be successfully coupled and directly telescoped into the Fisher cyclization (Figure 8).

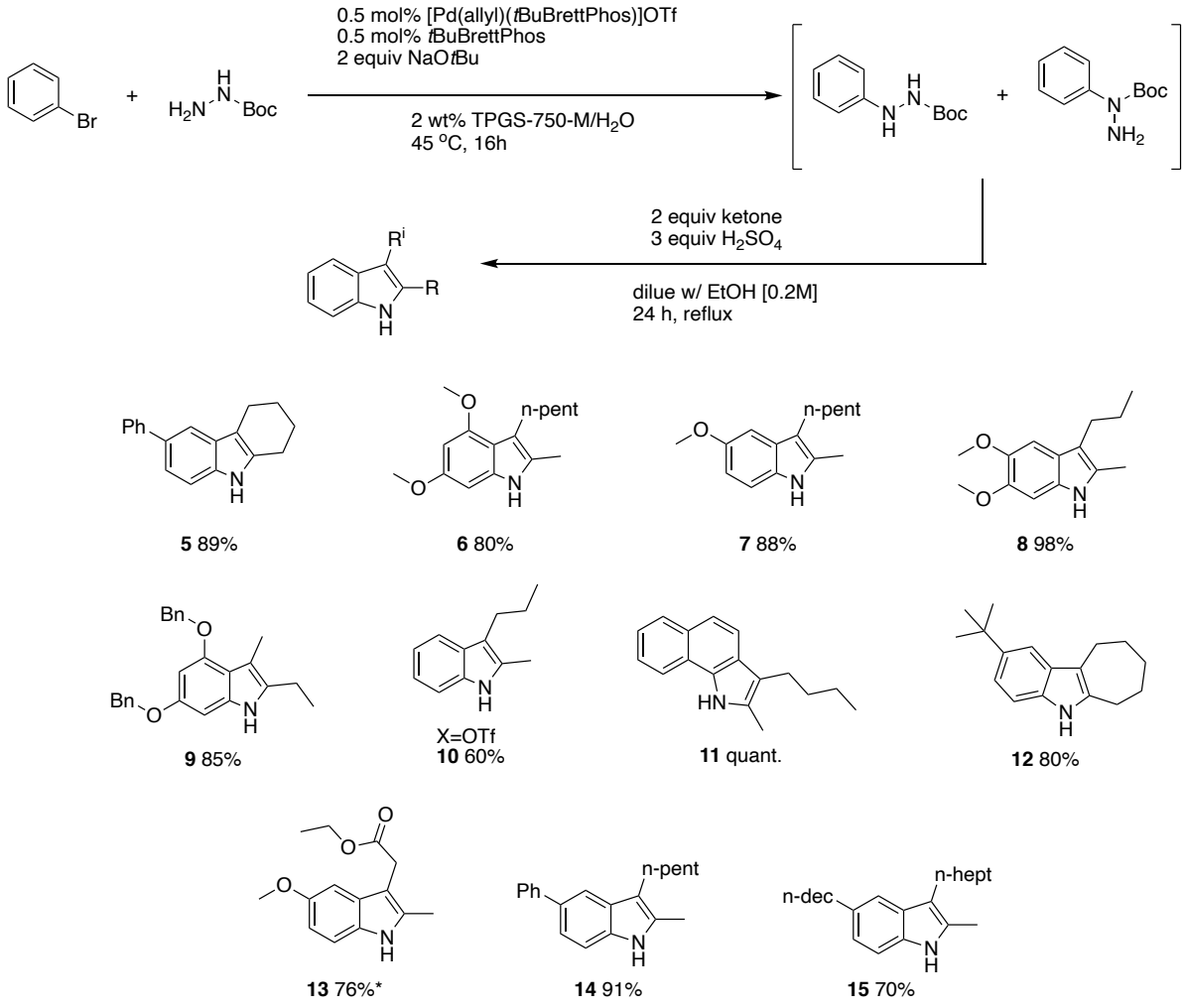


Figure 17: Substrate scope of telescoped indole synthesis

Based on the established efficiency of the coupling we were delighted to see that the deprotection, condensation, cyclization sequence was successful even though excess water (40% v/v) was present which might have inhibited condensation of the desired ketone (with the exception of **13** where the latter portions were conducted in absolute ethanol). These

results compared favorably with Buchwald's method wherein we were able to isolate **5**, **8**, and **14** in 89%, 98%, and 91% vs. 92%, 54%, and 81% respectively. While **13** did require the use of absolute ethanol for the cyclization this allowed for the synthesis of this key intermediate en route to the painkiller indomethacin from 4-bromoanisole and levulinic acid in a 5-step coupling, deprotection, condensation, cyclization, ester-formation sequence.

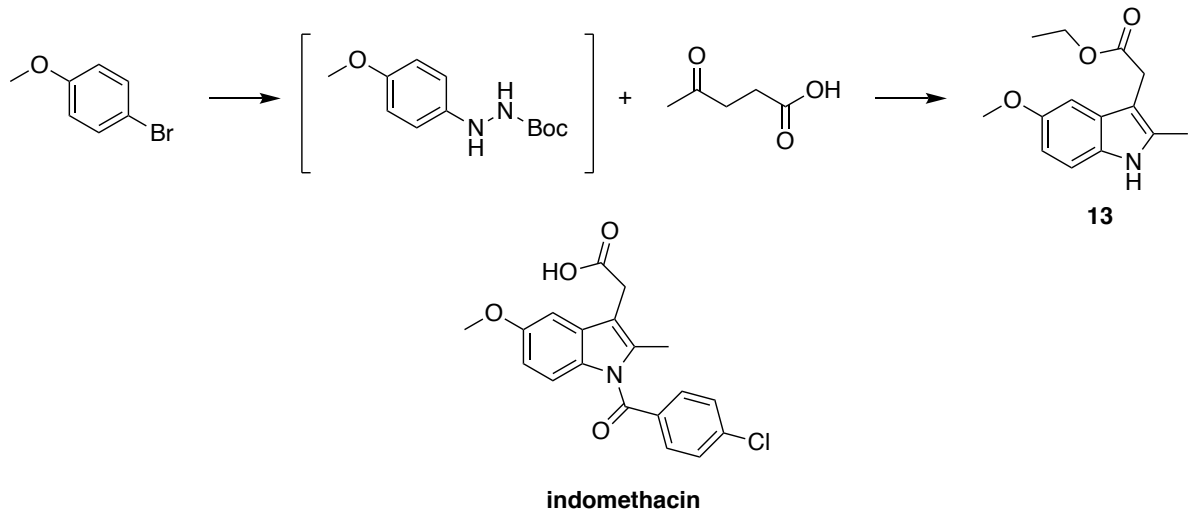


Figure 18: Synthesis of indomethacin intermediate

The Fisher indole synthesis is limited in its applications. Only electron-neutral or electron-rich substrates are able to undergo the [3,3]-sigmatropic rearrangement. This leaves electron-deficient substrates as useless for this methodology despite being more efficient partners towards initial palladium catalysis. However, these substrates are suitable for the Knorr pyrazole synthesis as evidenced by the generation of **16** (Figure 10).[9] Additionally, substrates bearing an *ortho*-nitrile can be easily cyclized to form 3-aminoindazole such as **17** which could be isolated quantitatively with no purification needed.

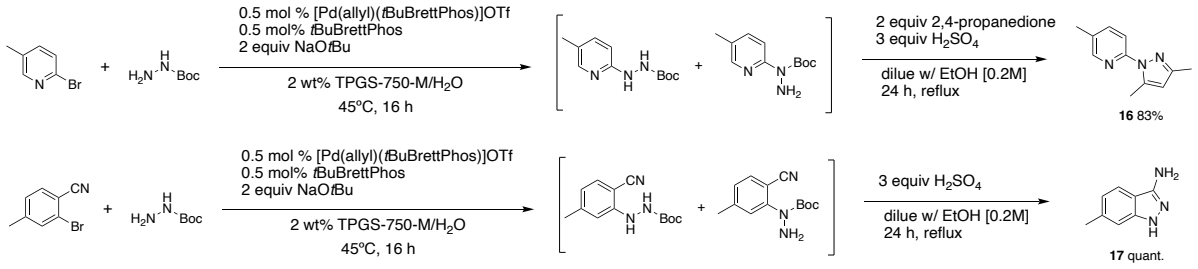


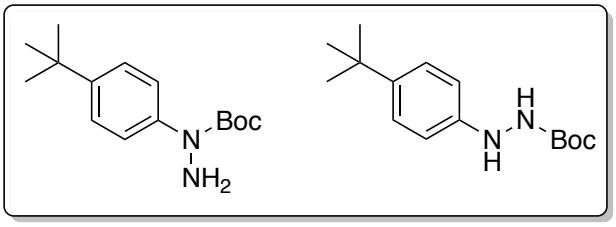
Figure 19: Synthesis of a pyrazole and 3-aminoindazole

C. Conclusion

In summary, an efficient and mild method was developed for the C-N coupling of *t*-butyl carbazate to yield protected aryl hydrazines which can be readily telescoped into several named reactions for the synthesis of nitrogen heterocycles. This method address several issues associated with previous methods particularly with respect to catalyst loading and generation of stoichiometric organic waste.

D. Experimental

Synthesis of mixture of *t*-butyl 2-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate and *t*-butyl 1-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate.



To a 1 dram screw-cap vial equipped with an oblong stir bar was added in order [*t*BuBrettPhos Pd(allyl)]OTf (3.9 mg, 0.005 mmol), *t*BuBrettPhos (2.4 mg, 0.005 mmol), sodium *t*-butoxide (192 mg, 2 mmol), and *t*-butyl carbazate (264 mg, 2 mmol). The vial was fitted with a septum and was evacuated/back-filled with argon 3 times. 1-Bromo-4-(*t*-butyl)benzene (173 μL, 213 mg, 1 mmol) was added via microliter syringe followed by 2

mL of a 2 wt% TPGS-750-M/H_2O solution (Caution: a mild exotherm is noticed upon addition of water). Under a stream of argon the septum was quickly removed and replaced with a PTFE lined screw-cap. The vial was placed in an aluminum reactor well plate set to 45 °C with a thermocouple probe and the reaction was stirred at 1000 rpm. TLC analysis at 90 minutes showed complete consumption of starting material. The reaction was cooled to rt and extracted with *t*-butyl methyl ether 3 x 500 μL. The organic phase was passed through a short Pasteur pipette plug of silica gel. The crude was purified by flash chromatography to yield a mixture of *t*-butyl 1-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate and *t*-butyl 2-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate in a 67:33 ratio as determined by ^{1}HNMR analysis. R_f = 0.1 in 1:19 EtOAc:hexanes 244 mg. 92%. *t*-butyl 1-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 8.6, 1.9 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.39 (s, 1H), 5.70 (s, 1H), 1.48 (s, 8H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.73, 126.12, 112.87, 81.26, 34.18, 31.64, 28.42. *t*-butyl 2-(4-(*t*-butyl)phenyl)hydrazine-1-carboxylate NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.4 Hz, 1H), 7.36 (s, 1H), 7.32 (dt, *J* = 8.8, 2.3 Hz, 2H), 4.43 (s, 2H), 1.51 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.60, 140.60, 125.23, 123.09, 81.78, 34.49, 31.51, 28.51.

E. E Factor Calculation

MTBE density: 740 mg/mL

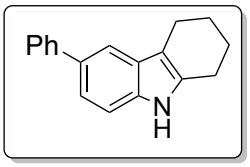
$$\textbf{E Factor} = \frac{\textbf{Waste (mg)}}{\textbf{Product (mg)}}$$

$$(1.5\ \text{mL MTBE})\left(740\frac{\text{mg}}{\text{mL}}\right) \div 244\ \text{mg} = 4.55$$

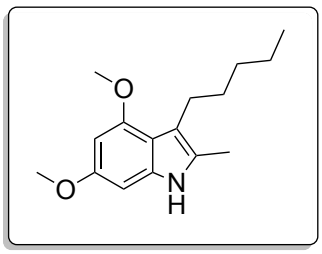
F. Experimental Procedures and Analytical Data

To a 1 dram screw-cap vial equipped with an oblong magnetic stir bar was added in order [*t*BuBrettPhos Pd(allyl)]OTf (3.9 mg, 0.005 mmol), *t*BuBrettPhos (2.4 mg, 0.005 mmol), sodium *t*-butoxide (192 mg, 2 mmol), halide or pseudo-halide coupling partner if solid (1 mmol) and *t*-butyl carbazate (264 mg, 2 mmol). The vial was fitted with a septum and was evacuated/back-filled with argon 3 times. Liquid halide or pseudo-halide (1 mmol) was added via microliter syringe followed by 2 mL of a 2 wt% TPGS-750-M/H_2O solution (Caution: a mild exotherm is noticed upon addition of water). Under a stream of argon the septum was quickly removed and replaced with a PTFE lined screw-cap. The vial was placed in an aluminum well plate set to 45 ^oC with a thermocouple probe and the reaction was stirred at 1000 rpm. After 16 h the reaction was cooled to rt (reaction times were not optimized). The mixture was transferred to a 2 dram screw-cap vial equipped with the aid of 3 mL of absolute ethanol followed by the previously used magnetic stir bar. The mixture was placed in an aluminum well plate set to 90-95 ^oC and a stirring rate of 1000 rpm. To the stirring mixture was added concentrated sulfuric acid slowly (0.16 mL, 3 mmol) and the mixture was allowed to stir open to air while the ketone was being measured out (CAUTION: A large exotherm is observed upon addition of sulfuric acid. Additionally, this portion of the sequence will produce hydrazine. Appropriate safety measures should be observed). The ketone (2 mmol) was added. The vial was sealed with a PTFE screw-cap and stirred. During the first hour of the reaction it was removed from the well plate several times, allowed to cool for 10 minutes, and then opened to vent CO_2 and butene gas. After 24 hours stirring with heat the vial was cooled to room temperature (reaction times were not optimized). The mixture was transferred to a 60 mL separatory funnel with the aid of a saturated aqueous sodium bicarbonate solution. Additional saturated bicarbonate solution

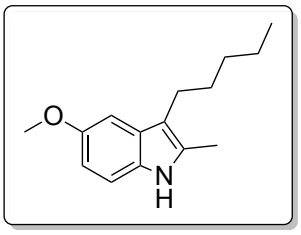
was added until a pH >7 was achieved. The aqueous mixture was extracted with ethyl acetate or diethyl ether 3 X 6 mL. Volatiles were removed *in vacuo*. The crude was purified by flash chromatography. If the ketone and heterocycle product have identical R_fs and ketone is still present in the crude mixture then the crude was dissolved in 5 mL methanol in a 25 mL round bottom flask with a magnetic stir bar. Excess sodium borohydride was added and the mixture was stirred at room temperature for 5 hours. Saturated aqueous ammonium chloride (10 mL) was added slowly. The mixture was transferred to a 60 mL separatory funnel and extracted with 3 X 6 mL ethyl acetate. Volatiles were removed *in vacuo*. The crude was then purified by flash chromatography.



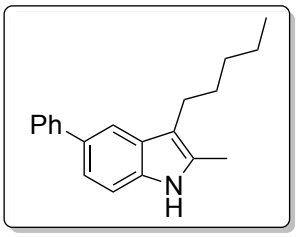
6-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole: Following the general procedure starting with 4-bromobiphenyl (233 mg, 1 mmol) and subsequently cyclohexanone (0.21 mL, 2 mmol), 220 mg of product was isolated as an off-white solid (89% yield). R_f = 0.23 in 1:9 Et_2O:hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.59 (m, 4H), 7.50 – 7.30 (m, 4H), 2.76 (dt, *J* = 16.6, 6.1 Hz, 4H), 1.94 (dddd, *J* = 18.6, 12.1, 5.8, 3.0 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.95, 135.21, 134.94, 132.72, 128.61, 128.38, 127.39, 126.15, 120.78, 116.39, 110.55, 23.31, 23.23, 20.96. Molecular formula: $C_{18}H_{17}N$. EI-MS $[M^{\cdot}]^+$ calcd: 247.1361 found: 247.1355



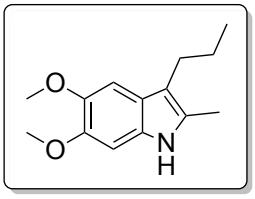
4,6-Dimethoxy-2-methyl-3-pentyl-1*H*-indole: Following the general procedure starting with 1-bromo-3,5-dimethoxybenzene (217 mg, 1 mmol) and subsequently 2-octanone (0.31 mL, 2 mmol), 209 mg of product was isolated as an pale oil (80% yield) following sodium borohydride reduction of the crude product. R_f = 0.15 in 2:8 EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.35 (s, 1H), 6.18 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.27 (s, 3H), 1.60 (p, *J* = 7.3 Hz, 2H), 1.35 (h, *J* = 6.3 Hz, 4H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 156.46, 154.38, 136.61, 127.27, 112.83, 112.69, 91.00, 86.56, 77.22, 55.63, 55.05, 31.71, 31.59, 25.29, 22.60, 14.17, 11.23. Molecular formula: $C_{16}H_{23}NO_2$ EI-MS $[M^{\cdot}]^+$ calcd: 261.1729 found: 261.1726.



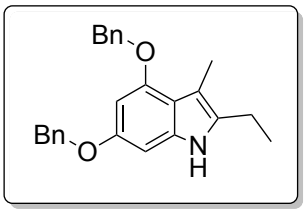
5-Methoxy-2-methyl-3-pentyl-1*H*-indole: Following the general procedure starting with 4-bromoanisole (0.126 mL, 1 mmol) and subsequently 2-octanone (0.31 mL, 2 mmol), 209 mg of product was isolated as a brown oil (80% yield). R_f = 0.24 in 2:8 Et_2O:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.97 (s, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 3.87 (s, 3H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.35 (d, *J* = 7.0 Hz, 5H), 0.94 – 0.85 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.88, 131.75, 130.54, 129.45, 112.55, 110.78, 110.29, 101.05, 56.18, 31.95, 30.46, 24.25, 22.79, 14.27, 11.93. Molecular formular: $C_{15}H_{21}NO$. EI-MS $[M^{\cdot}]^+$ calcd: 231.1623 found: 231.1621.



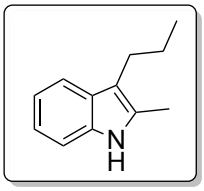
2-Methyl-3-pentyl-5-phenyl-1*H*-indole: Following the general procedure starting with 4-bromobiphenyl (233 mg, 1 mmol) and subsequently 2-octanone (0.31 mL, 2 mmol), 253 mg of product was isolated as a pale solid (91% yield). R_f = 0.33 in 2:8 Et_2O:hexanes. ^1H NMR (500 MHz, cdcl$_3$) δ 7.71 (s, 1H), 7.68 (d, *J* = 7.3 Hz, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.29 (m, 3H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.67 (p, *J* = 7.4 Hz, 2H), 1.37 (h, *J* = 3.6 Hz, 4H), 0.94 – 0.89 (m, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 143.13, 134.93, 132.72, 131.48, 129.47, 128.72, 127.54, 126.25, 120.72, 116.93, 113.06, 110.40, 31.98, 30.66, 24.25, 22.80, 14.28, 11.88. Molecular formula: $C_{20}H_{23}N$. EI-MS $[M\cdot]^+$ calcd: 277.1830 found: 277.1818.



5,6-Dimethoxy-2-methyl-3-propyl-1*H*-indole: Following the general procedure starting with 4-bromoveratrole (0.144 mL, 1 mmol) and subsequently 2-hexanone (0.25 mL, 2 mmol), 228 mg of product was isolated as a pale solid (98% yield). R_f = 0.1 in 2:8 EtOAc:hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 6.94 (s, 1H), 6.81 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.33 (s, 3H), 1.64 (h, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.22, 144.67, 129.47, 129.38, 121.80, 112.14, 100.93, 94.57, 56.71, 56.50, 26.41, 23.98, 14.25, 11.85. Molecular formula: $C_{14}H_{19}NO_2$ EI $[M\cdot]^+$ calcd: 233.1416 found: 233.1412.

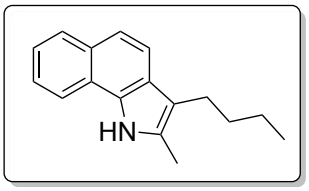


4,6-bis(Benzyloxy)-2-ethyl-3-methyl-1*H*-indole: **5,6-dimethoxy-2-methyl-3-propyl-1*H*-indole**: Following the general procedure starting on a reduced scale with (((5-bromo-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (341 mg, 0.92 mmol), [*t*BuBrettPhos Pd(allyl)]OTf (3.6 mg, 0.0046 mmol), *t*BuBrettPhos (2.2 mg, 0.0046 mmol), sodium *t*-butoxide (178 mg, 1.85 mmol), *t*-butyl carbazate (244 mg, 1.85 mmol) and subsequently 3-pentanone (0.20 mL, 1.85 mmol) and sulfuric acid (0.15 mL 0.185 mmol) 293 mg of product was isolated as a pale solid (85% yield). R_f = 0.21 in 2:8 Et_2O:hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.32 (m, 10H), 6.47 (s, 1H), 6.38 (s, 1H), 5.16 (s, 2H), 5.07 (s, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.71, 153.88, 137.70, 137.67, 136.63, 133.74, 128.63, 128.54, 127.90, 127.67, 127.64, 127.26, 113.95, 106.30, 93.11, 88.61, 70.75, 69.91, 19.11, 14.34, 10.82. Molecular formula: $C_{25}H_{25}NO_2$ ESI-MS $[M+Na]^+$ calcd: 394.1783 found: 394.1780.

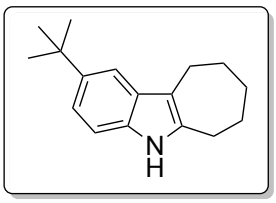


2-Methyl-3-propyl-1*H*-indole: Following the general procedure starting with phenyl trifluoromethanesulfonate (0.162 mL, 1 mmol) and subsequently 2-hexanone (0.25 mL, 2 mmol), 104 mg of product was isolated as a brown oil (60% yield). R_f = 0.3 in 1:9 Et_2O:hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.11 (dt, *J* = 15.4, 7.1 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.38 (s, 3H), 1.68

(h, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.25, 130.73, 128.90, 120.74, 118.93, 118.19, 112.25, 110.09, 29.74, 26.18, 23.89, 14.11, 11.68. Molecular formula: $C_{12}H_{15}N$ ESI-MS $[M + C_2H_5]^+$ calcd: 202.1596 found: 202.1598.

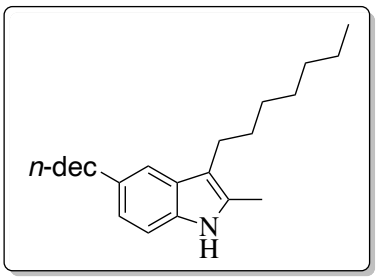


3-Butyl-2-methyl-1*H*-benzo[*g*]indole: Following the general procedure starting with 2-bromonapthalene (0.140 mL, 1 mmol) and subsequently 2-heptanone (0.28 mL, 2 mmol), 237 mg of product was isolated as a red solid (quantitative yield). R_f = 0.22 in 2:8 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.92 (t, J = 7.5 Hz, 2H), 7.66 (d, J = 8.6 Hz, 1H), 7.49 (t, J = 8.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 2.77 (t, J = 7.5 Hz, 2H), 2.48 (s, 3H), 1.66 (p, J = 7.6 Hz, 2H), 1.42 (h, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.89, 129.21, 128.87, 128.73, 125.13, 124.44, 123.11, 121.34, 119.68, 119.06, 118.88, 114.39, 38.79, 33.40, 26.27, 23.95, 22.65, 14.10, 11.79. Molecular formula: $C_{17}H_{19}N$ ESI-MS $[M + H]^+$ calcd: 238.1596 found: 238.1590.

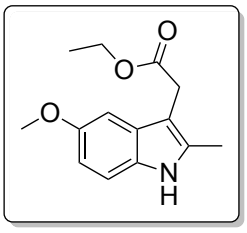


2-(*t*-Butyl)-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole: Following the general procedure starting with 4-*t*-butylbromonezene (0.173 mL, 1 mmol) and subsequently cycloheptanone (0.24 mL, 2 mmol), 193 mg of product was isolated as a yellow oil (80% yield). R_f = 0.18 in 1:19 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.49 (s, 1H), 7.21 (d, J = 1.4 Hz, 2H), 2.88 – 2.79 (m, 3H), 1.96 – 1.88 (m, 2H), 1.85 – 1.75 (m, 5H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.94, 137.66, 132.36, 128.92, 118.84, 113.72, 113.44,

109.71, 34.63, 32.06, 31.92, 29.65, 28.76, 27.62, 24.66. Molecular formula: $C_{17}H_{23}N$ EI-MS $[M^{\cdot}]^{+}$ calcd: 241.1830 found: 241.1831.

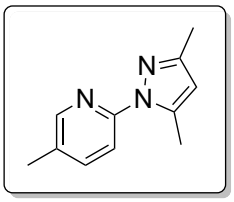


5-Decyl-3-heptyl-2-methyl-1*H*-indole: Following the general procedure starting with 1-bromo-4-*n*-decylbenzene (0.270 mL, 1 mmol) and subsequently 2-decanone (0.38 mL, 2 mmol), 255 mg of product was isolated as a pale solid (70% yield) after reduction of the crude mixture with sodium borohydride. R_f = 0.25 in hexanes. H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.28 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 2.74 – 2.62 (m, 4H), 2.35 (s, 3H), 1.64 (dp, *J* = 21.9, 7.3 Hz, 4H), 1.42 – 1.21 (m, 23H), 0.89 (t, *J* = 6.8 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.83, 133.63, 130.76, 129.11, 121.79, 117.52, 112.33, 109.84, 36.41, 32.65, 32.13, 32.08, 30.96, 29.83, 29.78, 29.61, 29.52, 29.45, 24.28, 22.87, 22.85, 14.29, 11.85. Molecular formula: $C_{26}H_{43}N$ ESI-MS $[M + H]^{+}$ calcd: 370.3474 found: 370.3482.

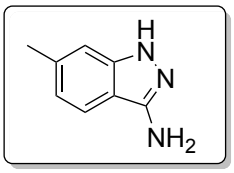


Ethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate: Following a modified general procedure starting with 4-bromoanisole (0.126 mL, 1 mmol), after stirring for 16 hours the aqueous coupling mixture was extracted with 3 x 1 mL EtOAc and collected in a 2 dram vial. Volatiles were removed *in vacuo*. The deprotection/cyclization was then conducted as

described in 5 mL of absolute ethanol utilizing levulinic acid(0.20 mL, 2 mmol), 188 mg of product was isolated as a brown oil (76% yield). R_f = 0.17 in 2:8 EtOAc:hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.65 (s, 2H), 2.36 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.10, 154.10, 133.52, 130.17, 128.96, 110.93, 104.50, 100.48, 60.68, 55.91, 30.60, 28.29, 14.28, 11.80. Molecular formula: $C_{14}H_{17}NO_3$ ESI-MS $[M + Na]^+$ calcd: 270.1106 found: 270.1115.



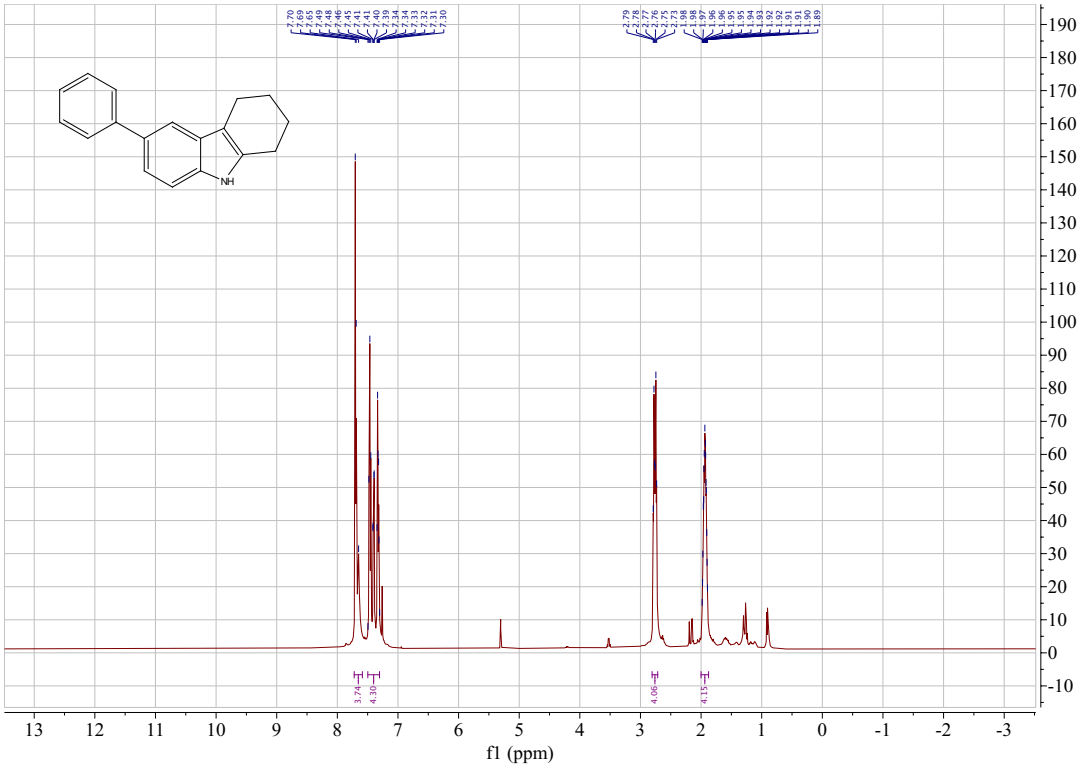
2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-methylpyridine: Following the general procedure starting with 2-bromo-5-methylpyridine (172 mg, 1 mmol) and subsequently acetylacetone (0.21 mL, 2 mmol), 155 mg of product was isolated as a yellow solid (83% yield). R_f = 0.26 in 1:9 EtOAc:hexanes. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 – 8.21 (m, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.55 (m, 1H), 5.97 (s, 1H), 2.58 (d, *J* = 0.9 Hz, 3H), 2.34 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.42, 149.43, 147.51, 141.06, 138.77, 130.28, 115.63, 108.47, 17.83, 14.07, 13.58. Molecular formula: $C_{11}H_{13}N_3$ ESI-MS $[M + H]^+$ calcd: 188.1188 found: 188.1185.

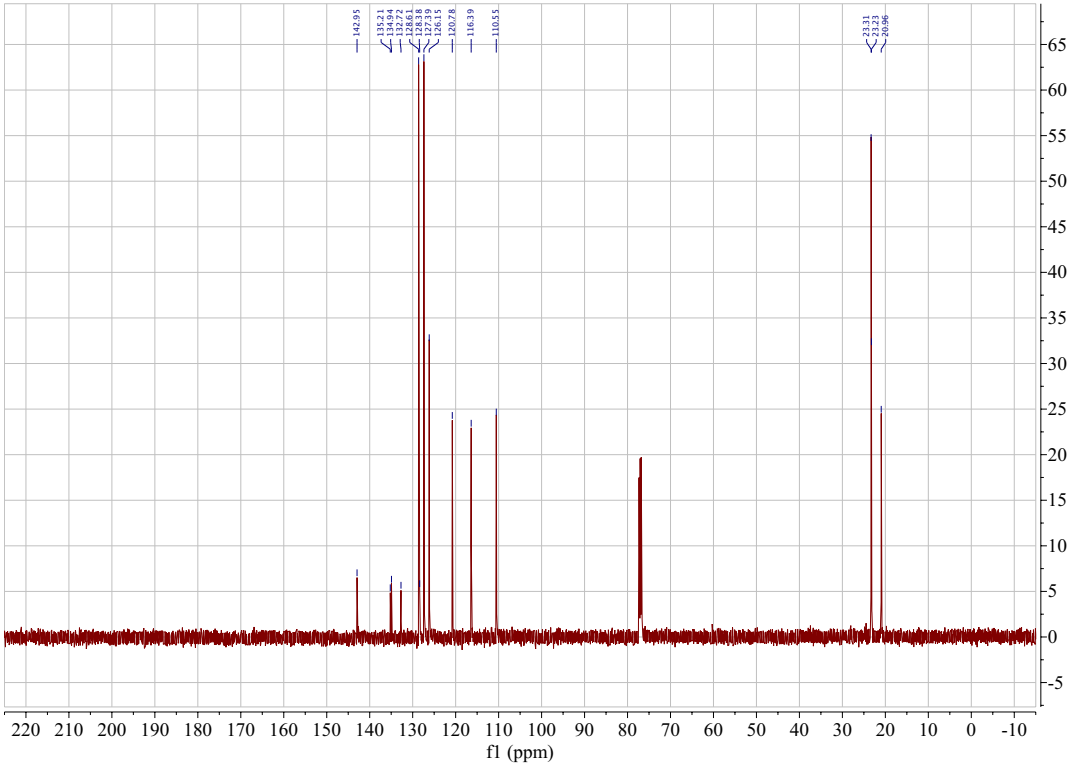


6-Methyl-1*H*-indazol-3-amine: Following the general procedure starting with 2-bromo-4-methylbenzonitrile (196 mg, 1 mmol)147 mg of product was isolated as a brown solid with no purification required after extraction and evaporation of volatiles (quantitative yield). R_f

0.30 in 1:4:4 EtOH:EtOAc:hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.09 (s, 1H), 6.90 (d, J = 8.2 Hz, 1H), 4.31 – 3.87 (m, 2H), 2.46 (s, 3H). Molecular formula: $C_8H_9N_3$ ESI-MS $[M + H]^+$ calcd: 148.0875 found: 148.0877.

G. NMR Spectra

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134.94
132.22
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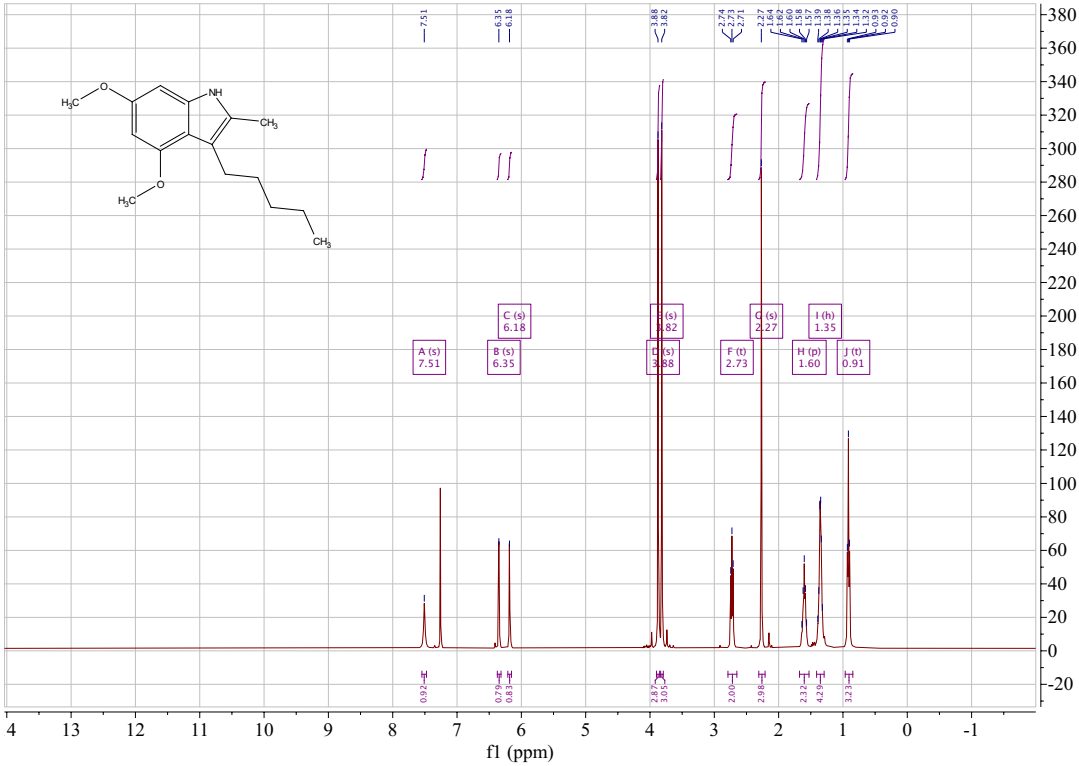
126.15
120.78
116.39
110.51
23.31
23.23
20.96
f1 (ppm)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6.35
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3.82
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2.71
2.27
1.64
1.60
1.58
1.37
1.36
1.35
1.34
1.32
0.93
0.92
0.90
A (s) 7.51
B (s) 6.35
C (s) 6.18
D (s) 3.88
E (s) 3.82
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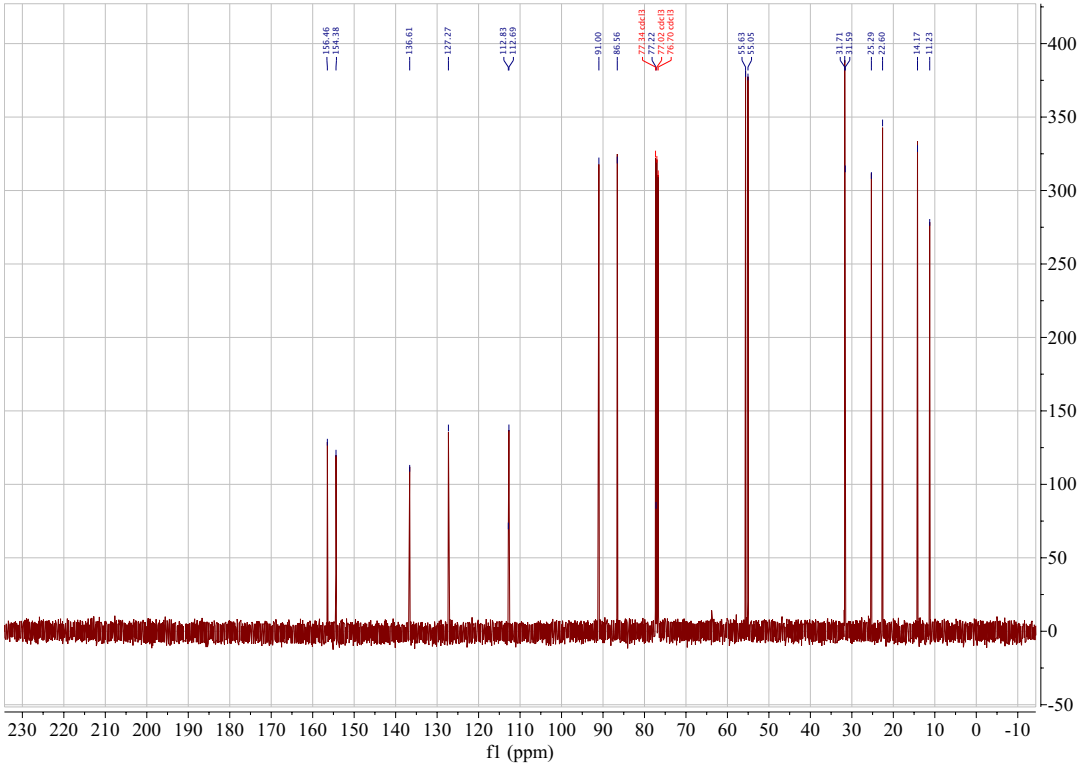
G (s) 2.27
H (p) 1.60
I (h) 1.35
J (t) 0.91
f1 (ppm)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86.56
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22.60
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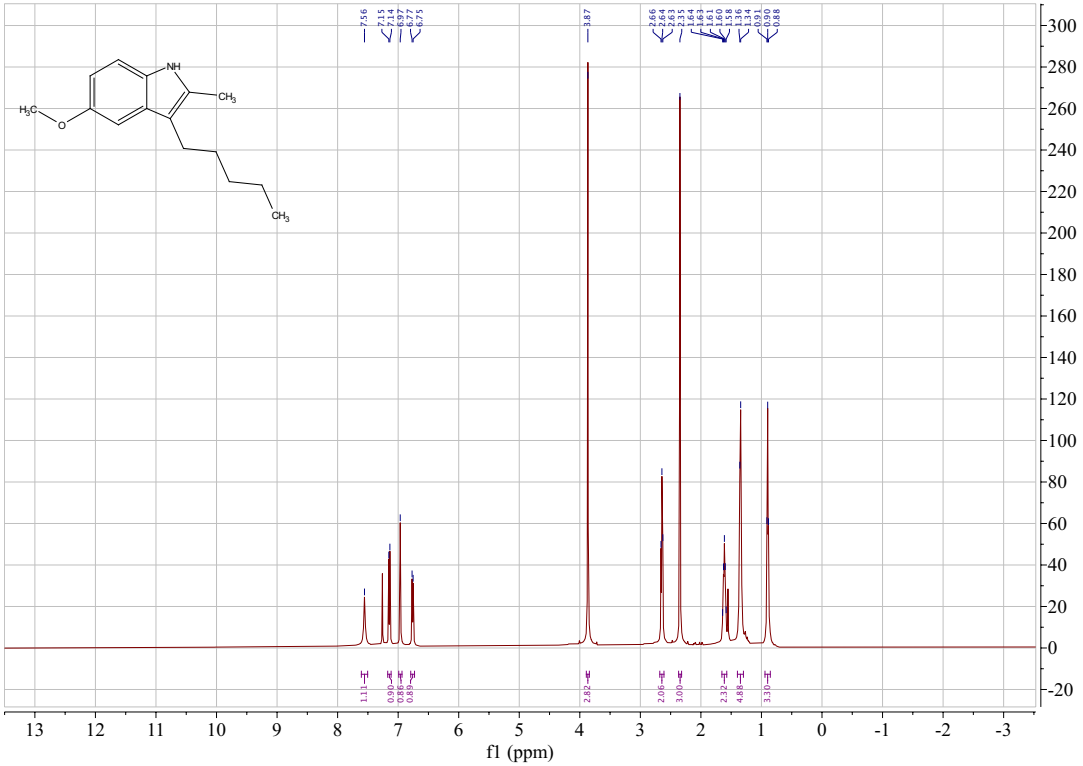
11.23
f1 (ppm)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2.63
2.53
1.64
1.63
1.61
1.60
1.58
1.36
1.34
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0.90
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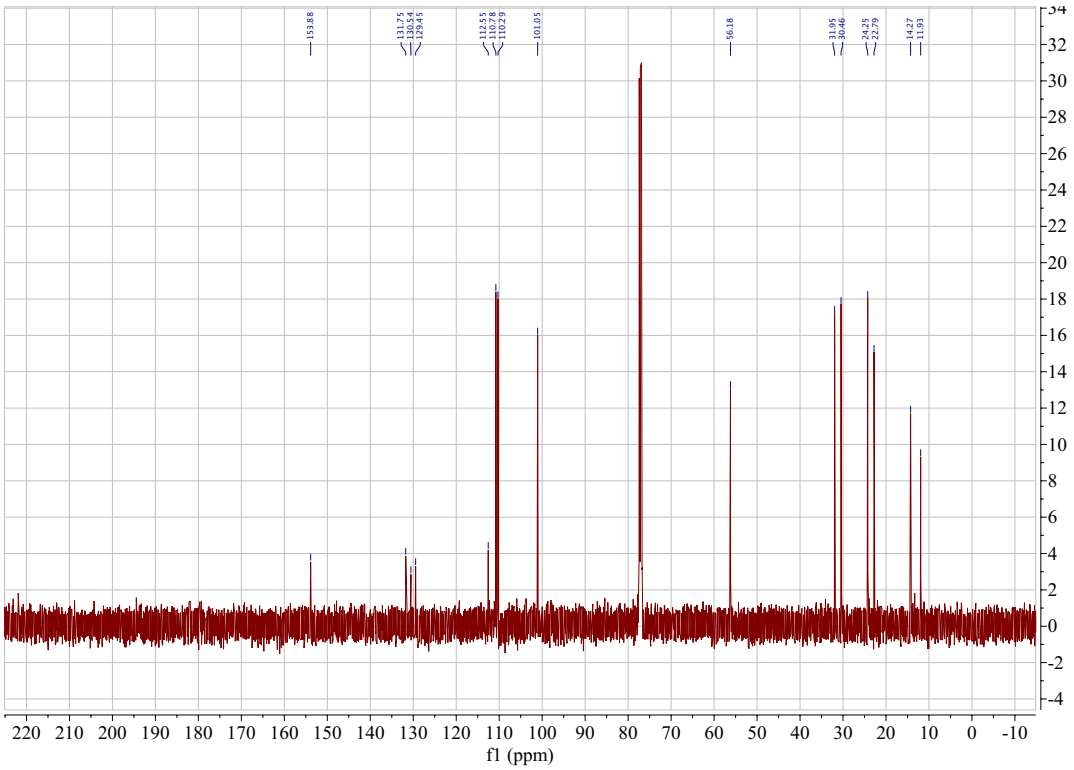
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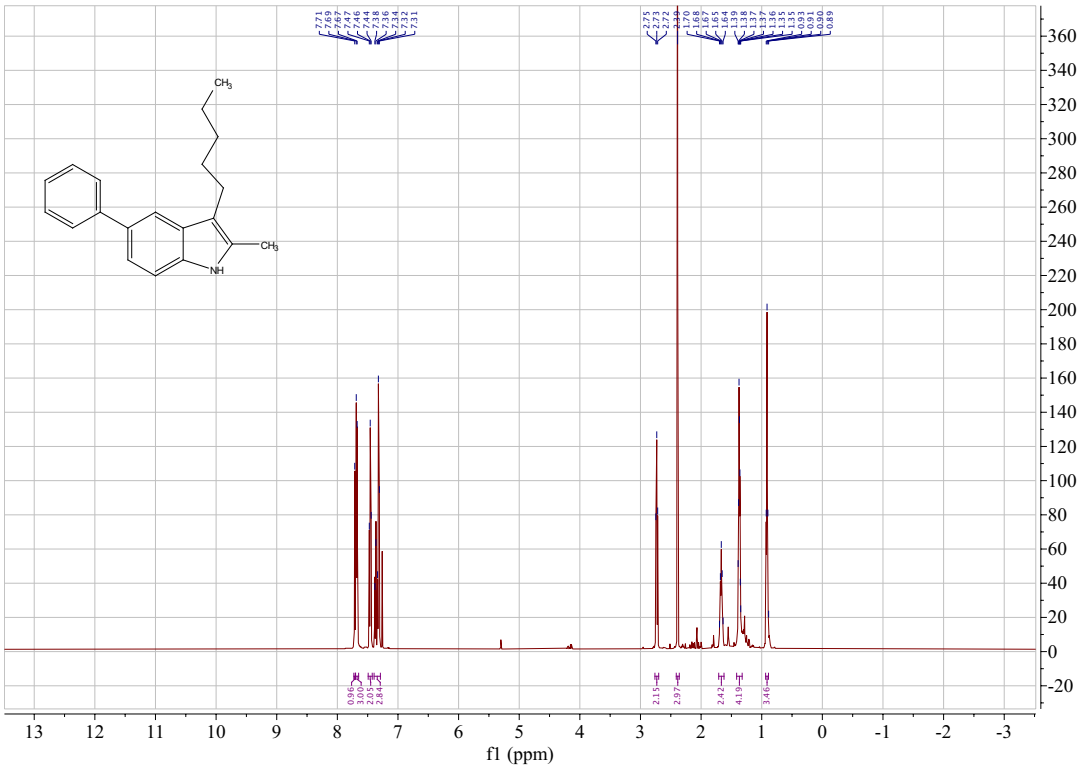
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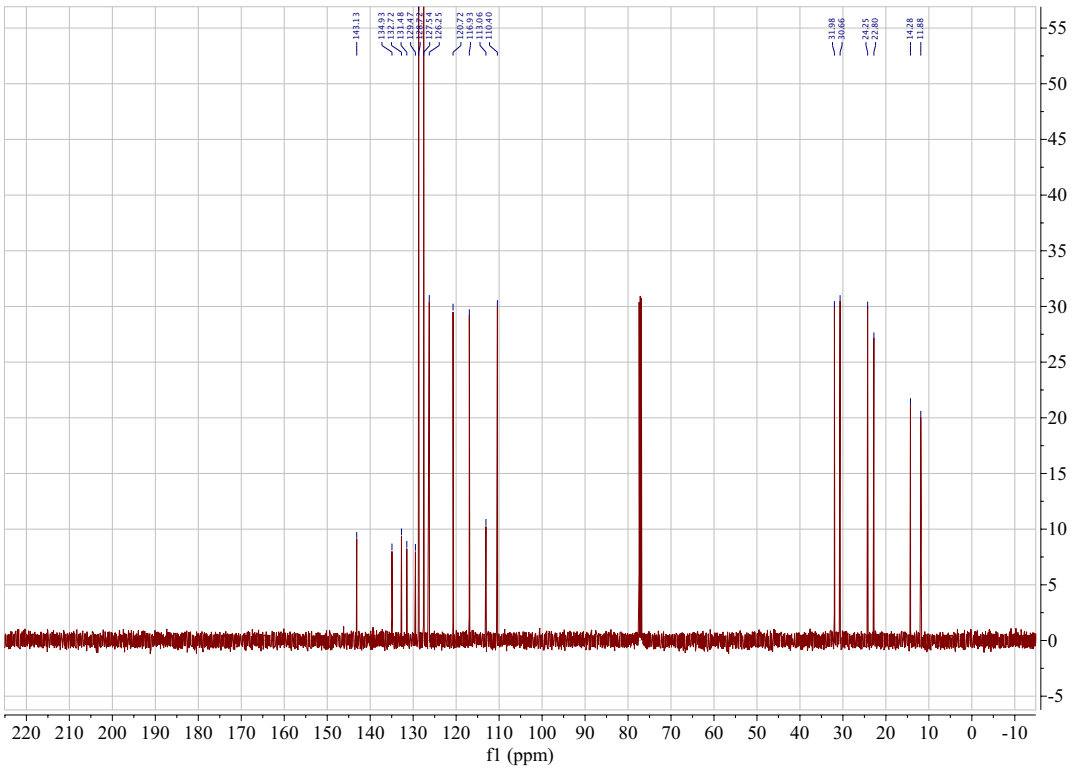
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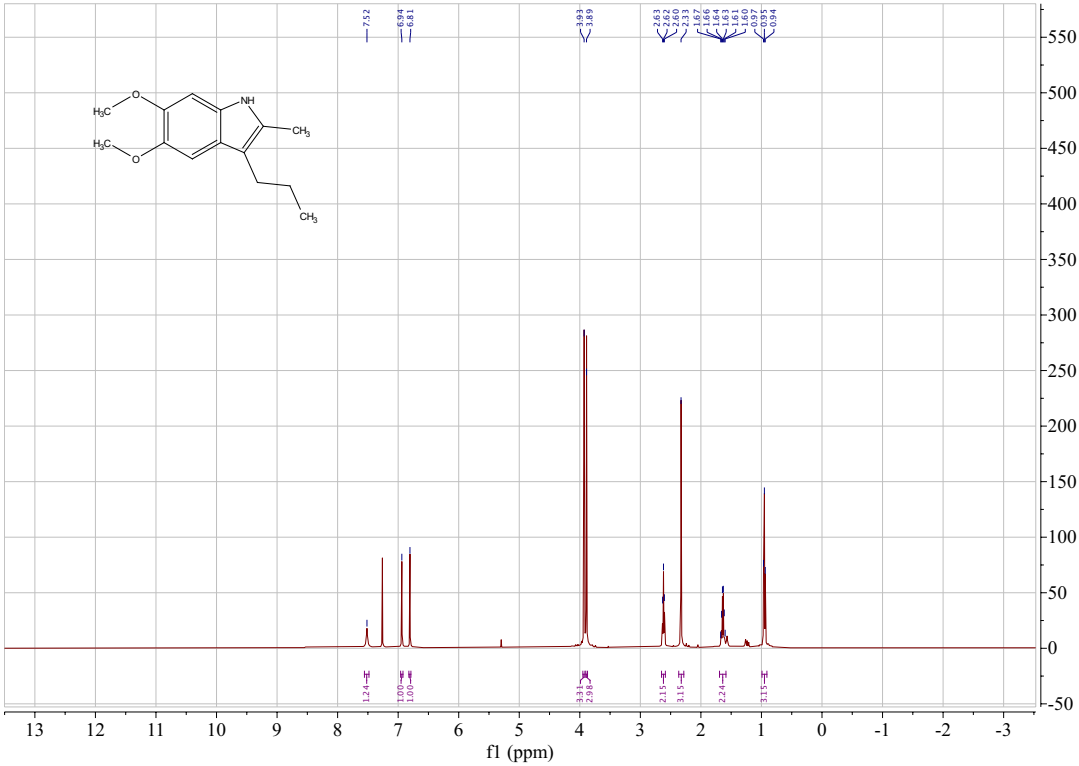
11.88
f1 (ppm)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1.66
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1.63
1.61
1.60
0.97
0.96
0.94
O
H3C
O
H3C
NH
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CH3
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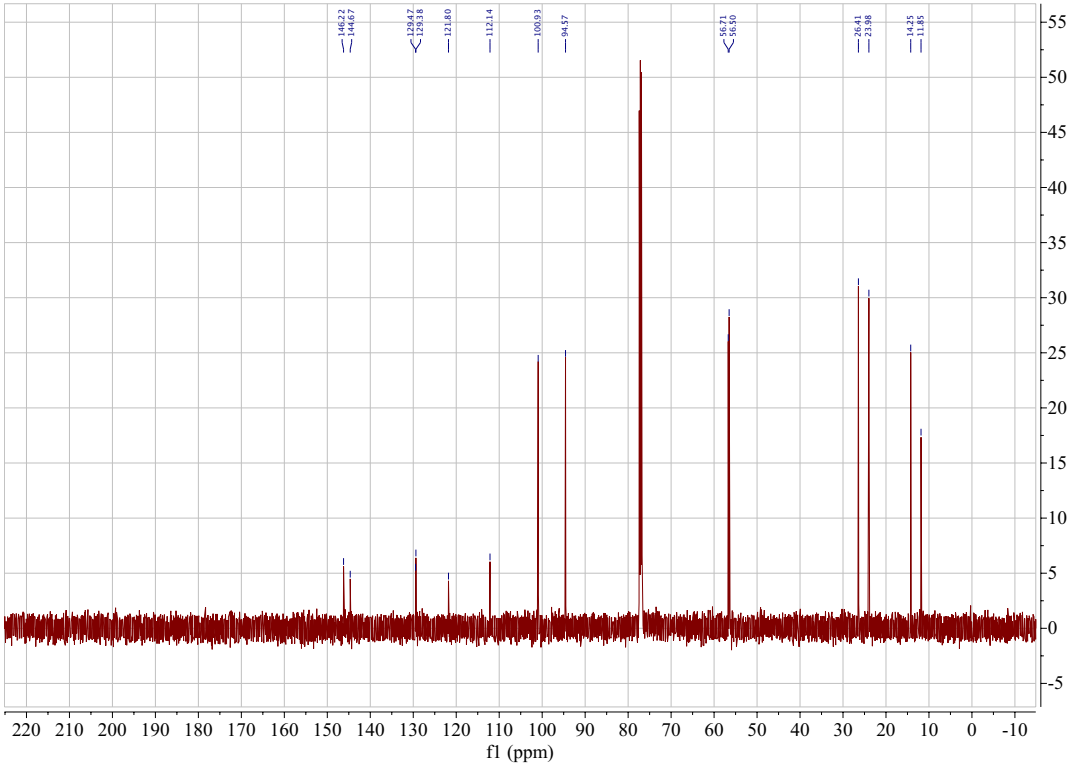
3.15
2.24
3.15
f1 (ppm)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56.50
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23.98
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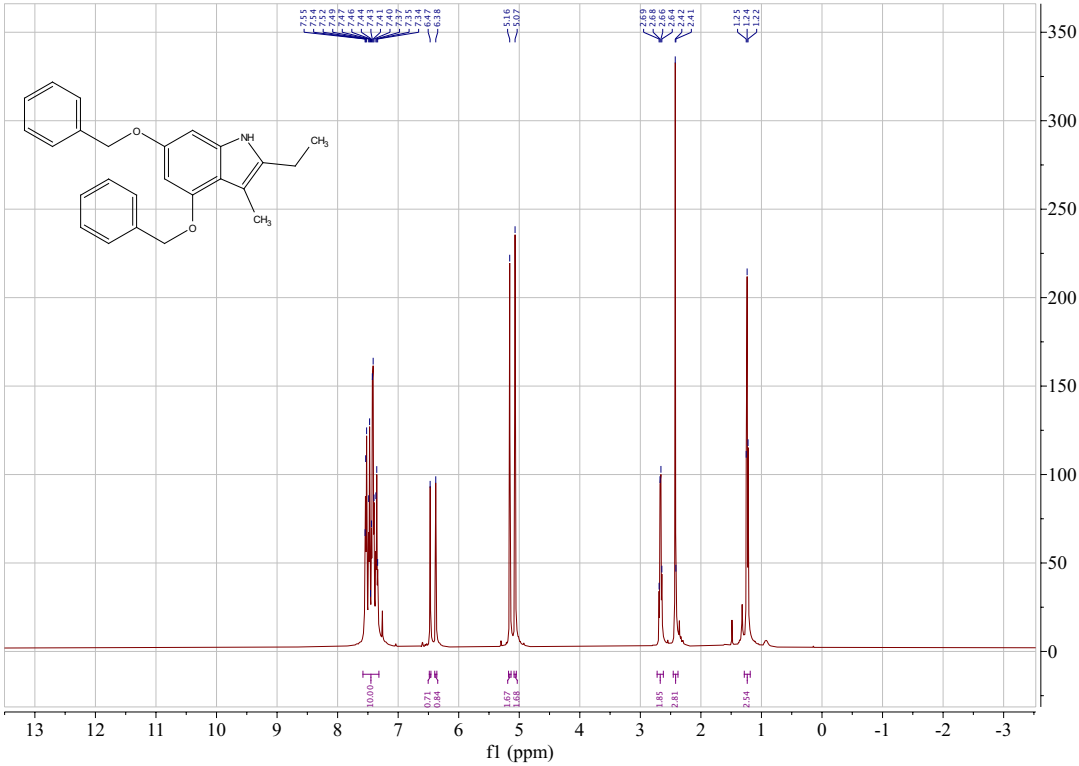
11.85
f1 (ppm)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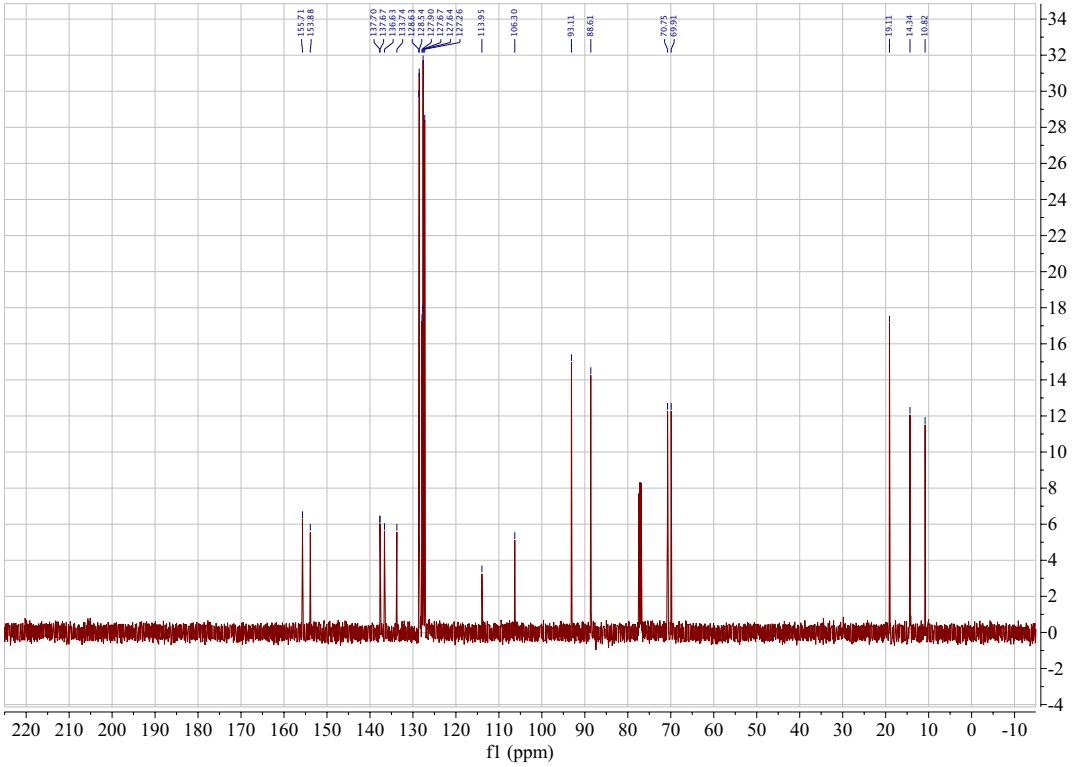
CH3
O
O
f1 (ppm)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127.72
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19.11
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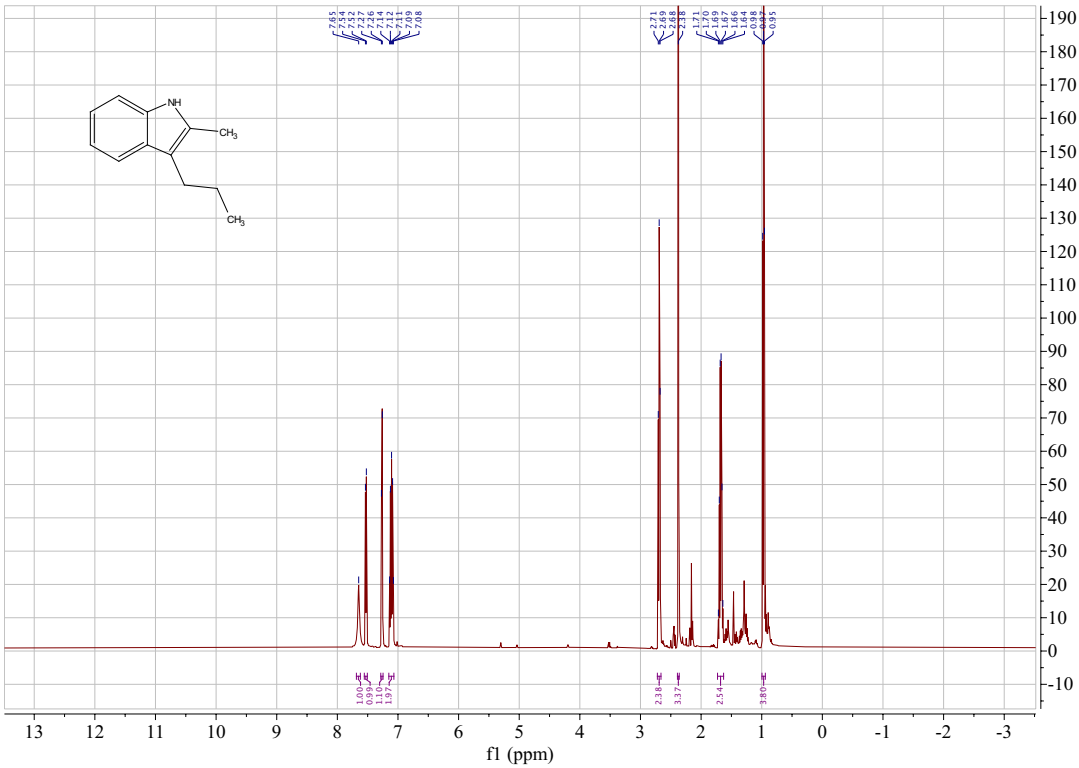
10.82
f1 (ppm)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7.09
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2.71
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2.68
2.38
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1.70
1.69
1.67
1.66
1.64
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1.02
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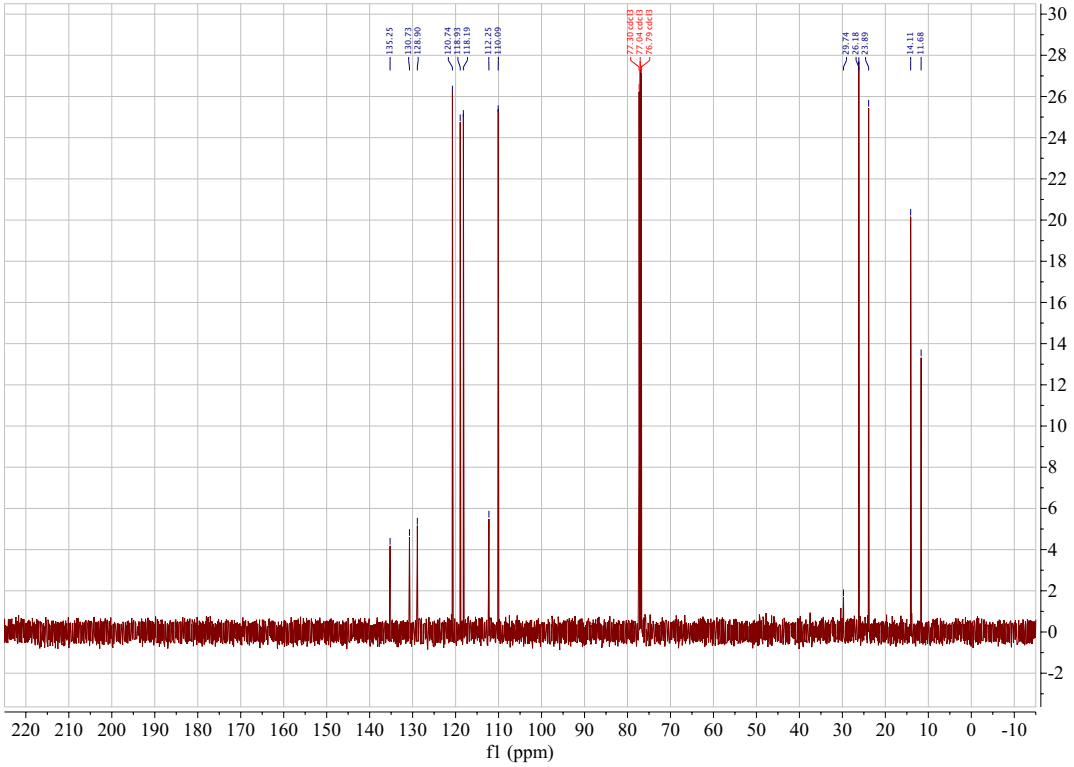
3.80
f1 (ppm)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118.19
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110.09
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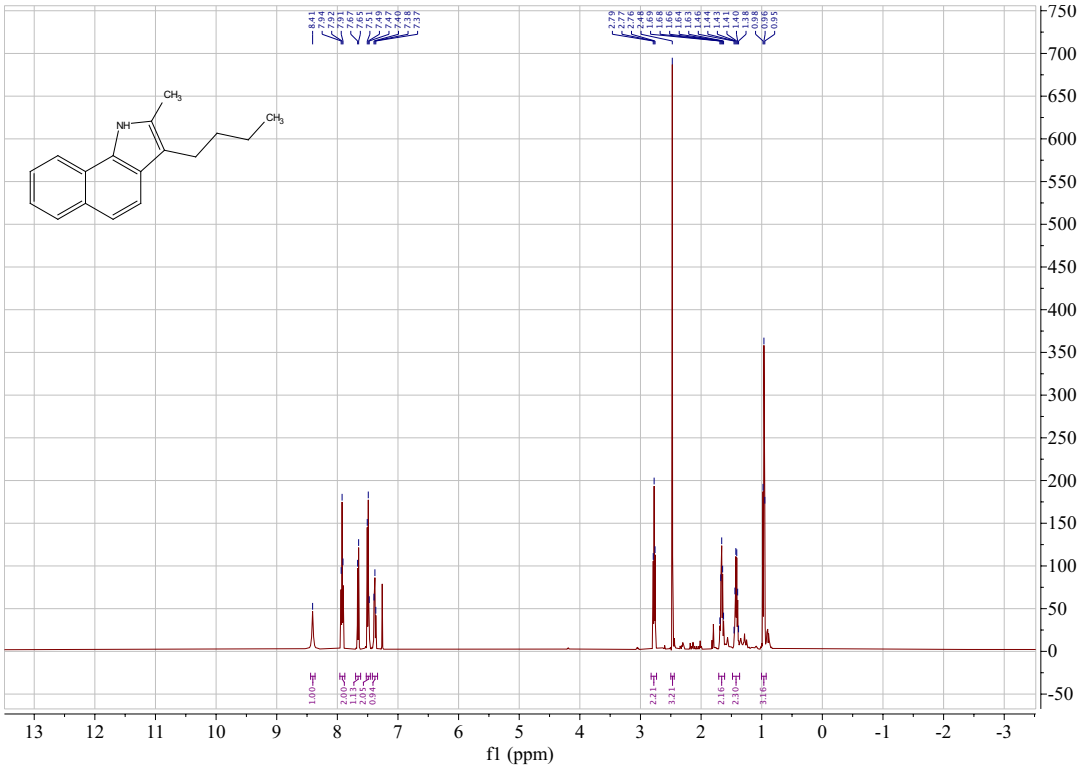
23.89
14.11
11.68
f1 (ppm)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1.68
1.66
1.64
1.63
1.46
1.44
1.43
1.41
1.40
1.38
0.98
0.96
0.95
NH
CH3
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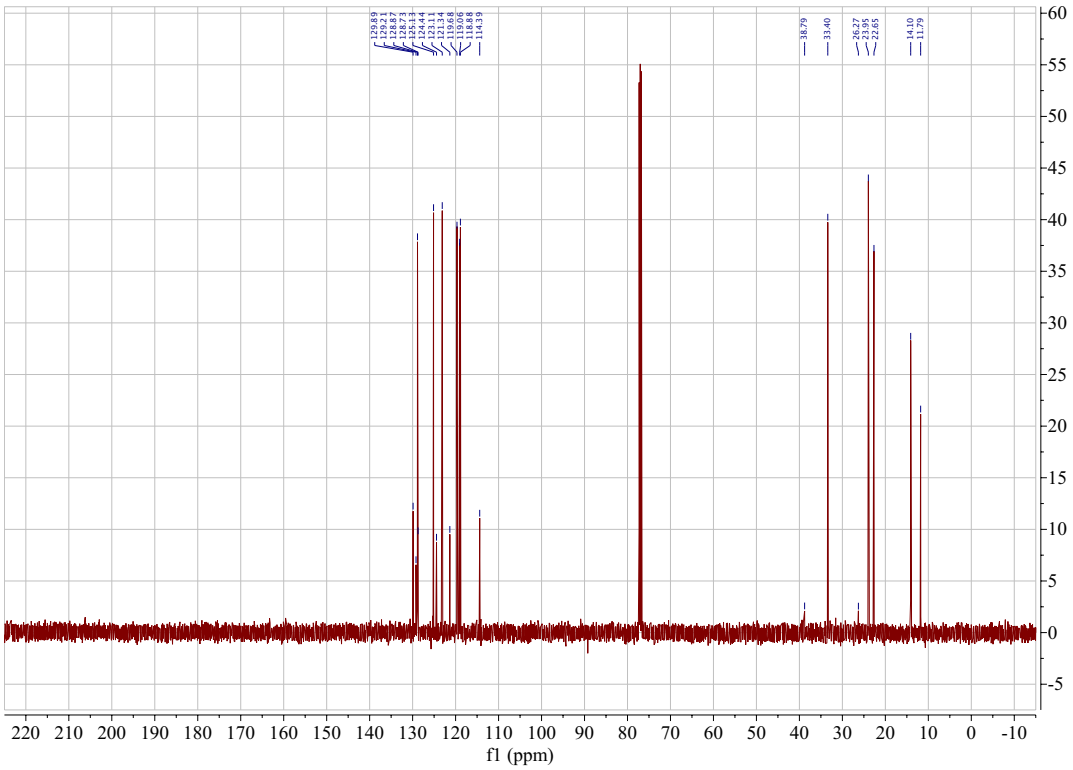
3.16
f1 (ppm)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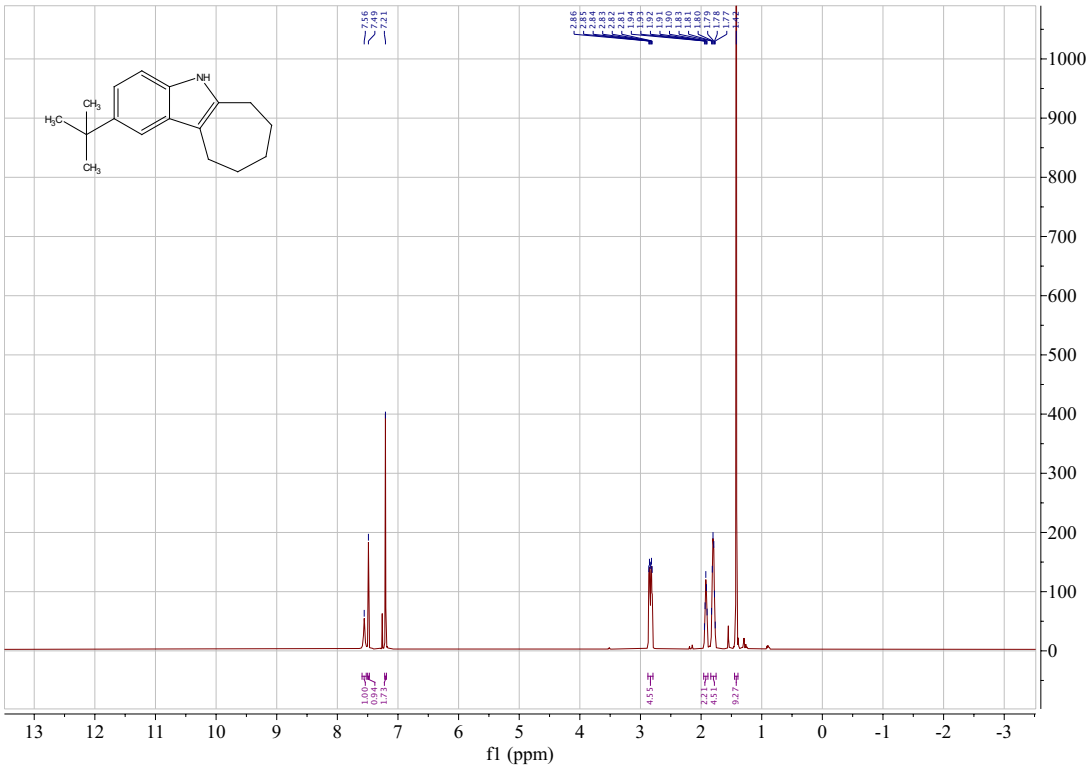
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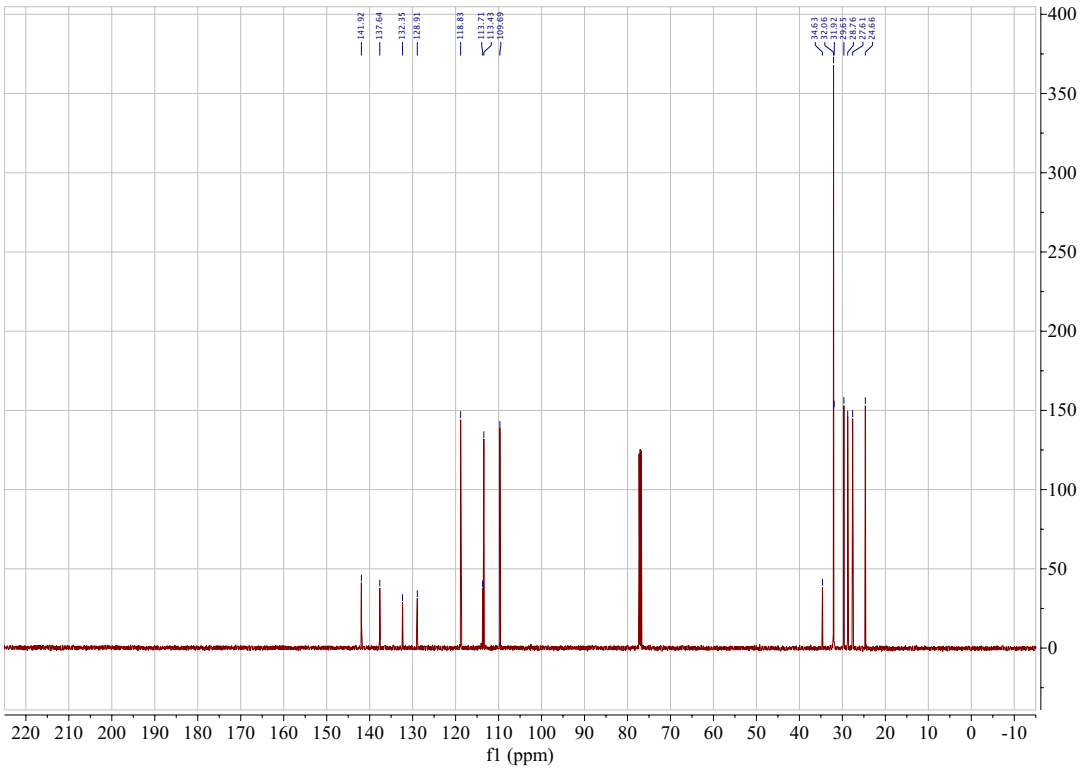
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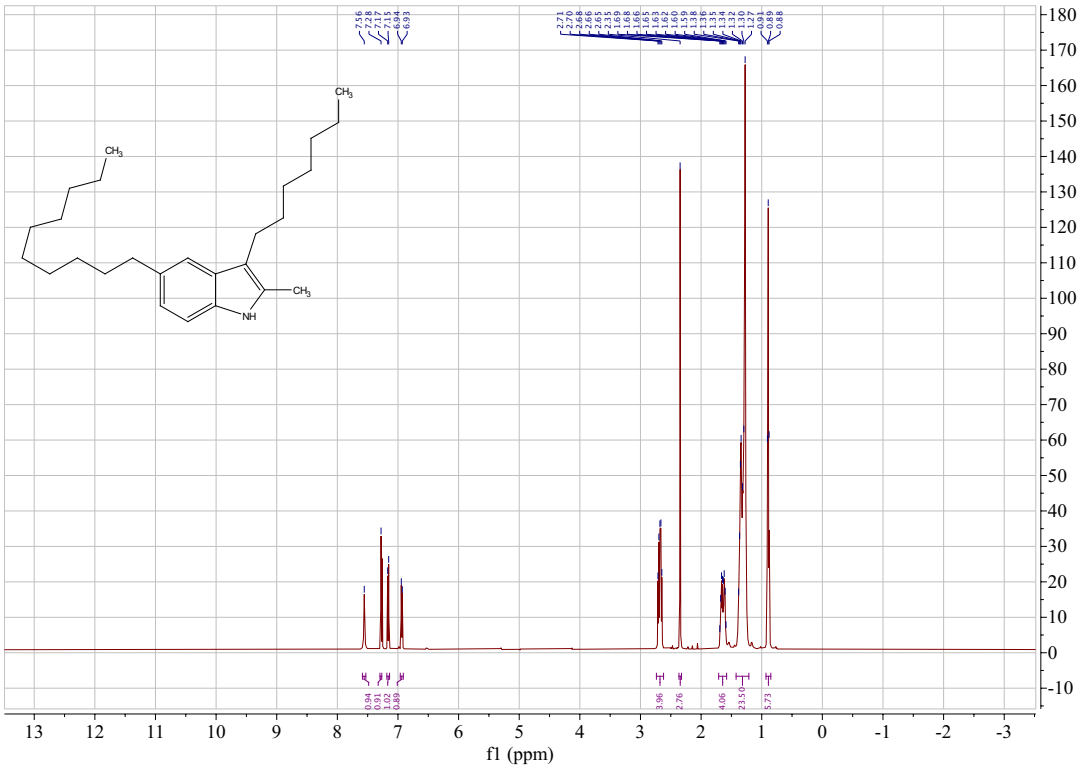
f1 (ppm)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CH3
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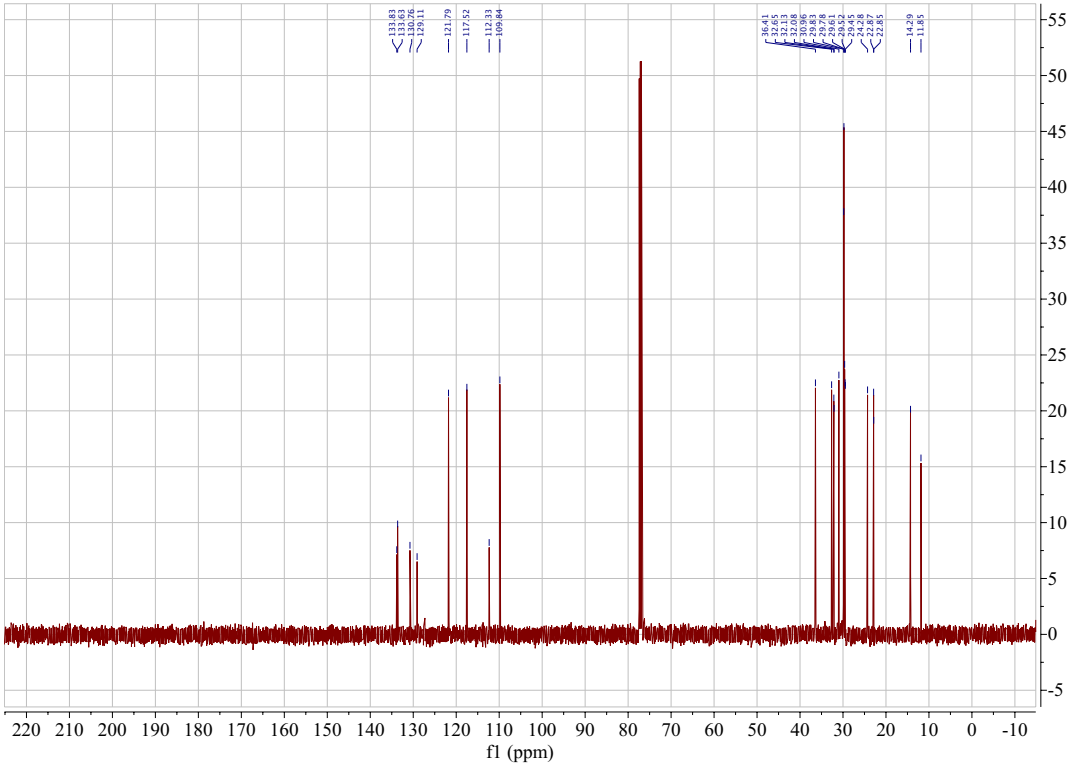
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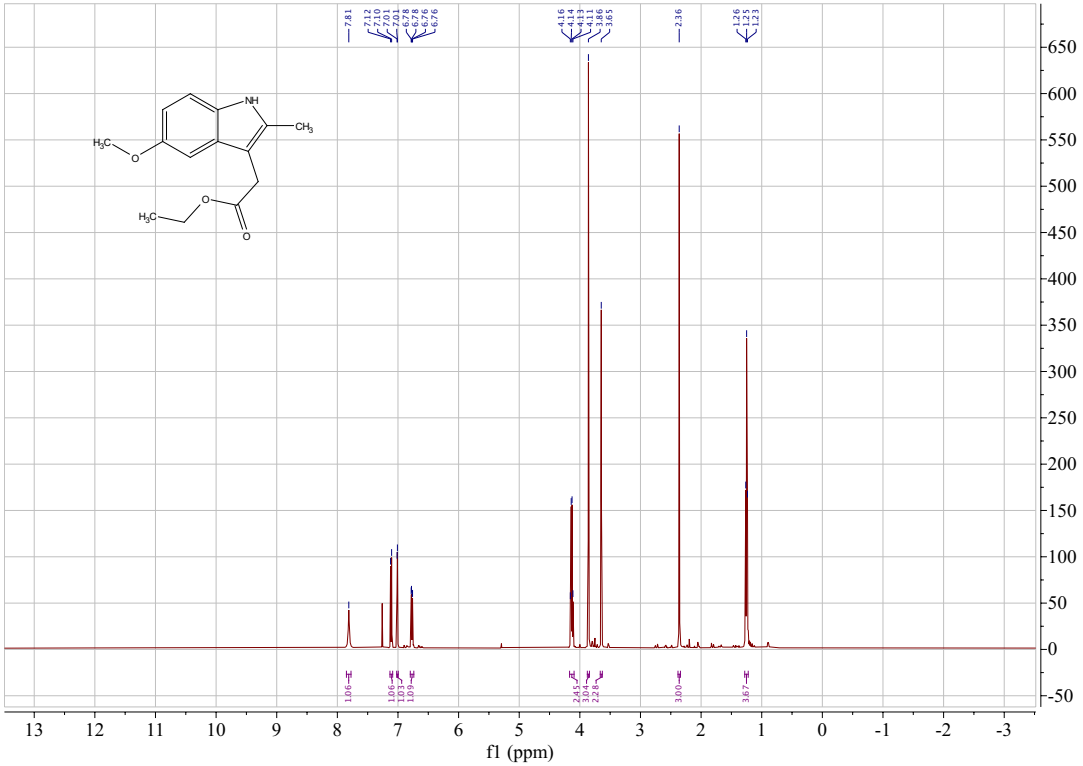
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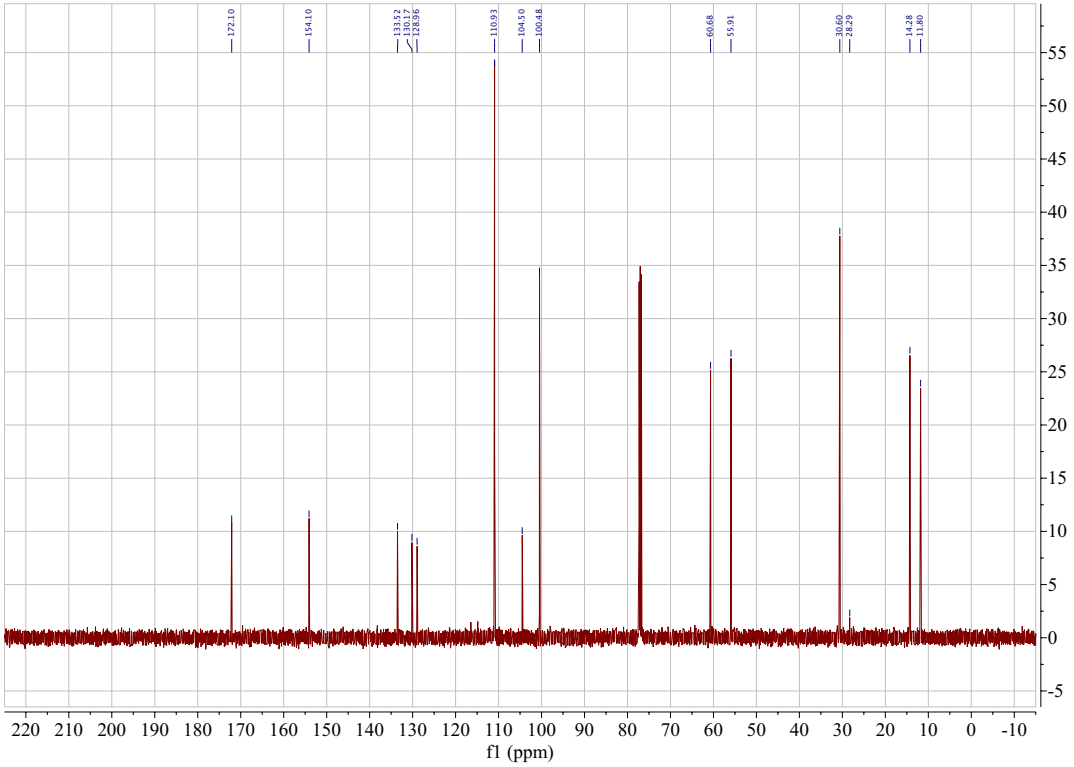
H3C
O
O
H3C
O
f1 (ppm)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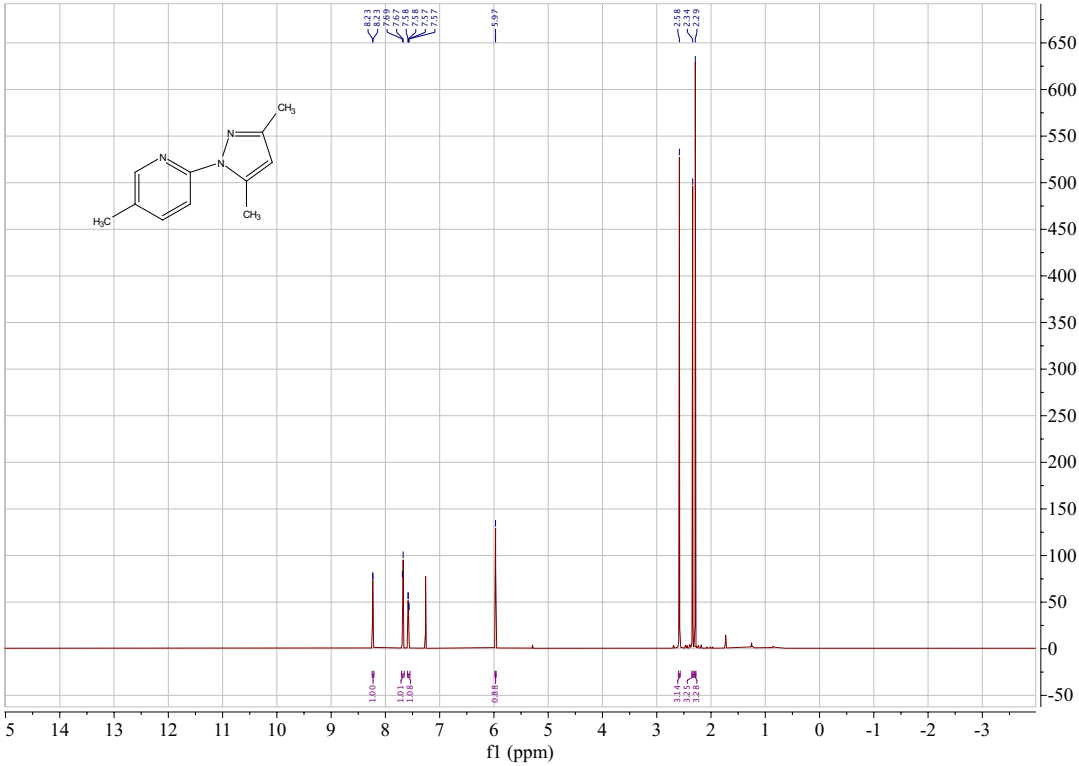
28.29
14.28
11.80
f1 (ppm)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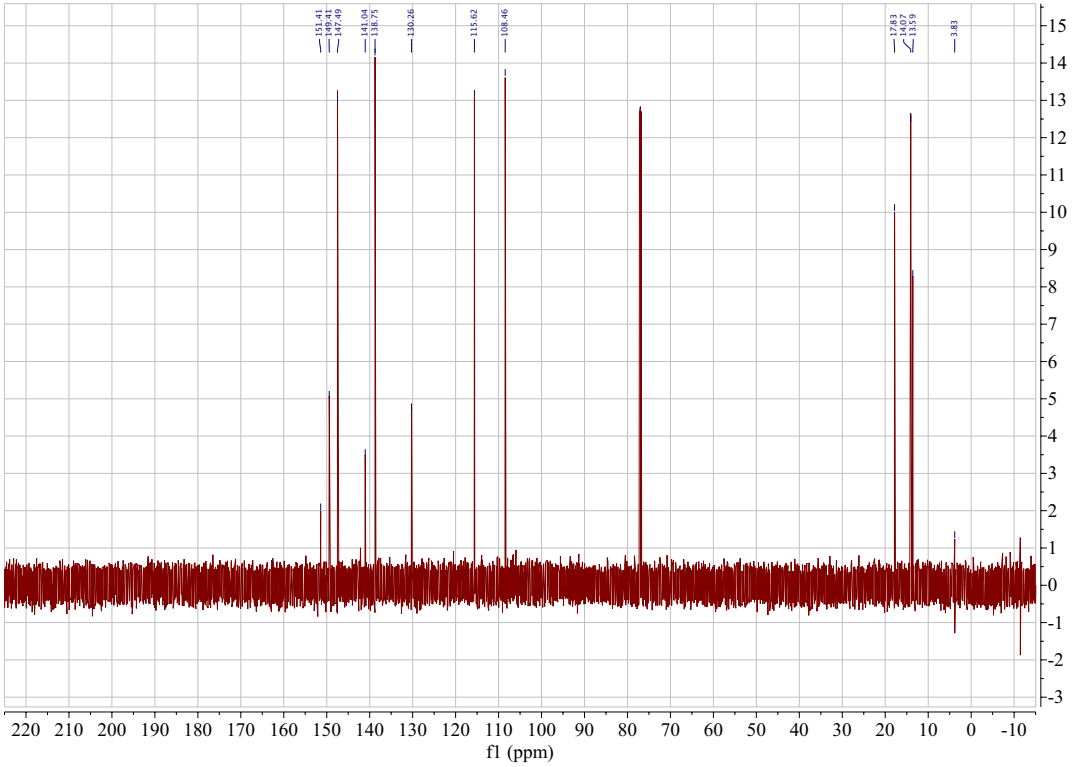
f1 (ppm)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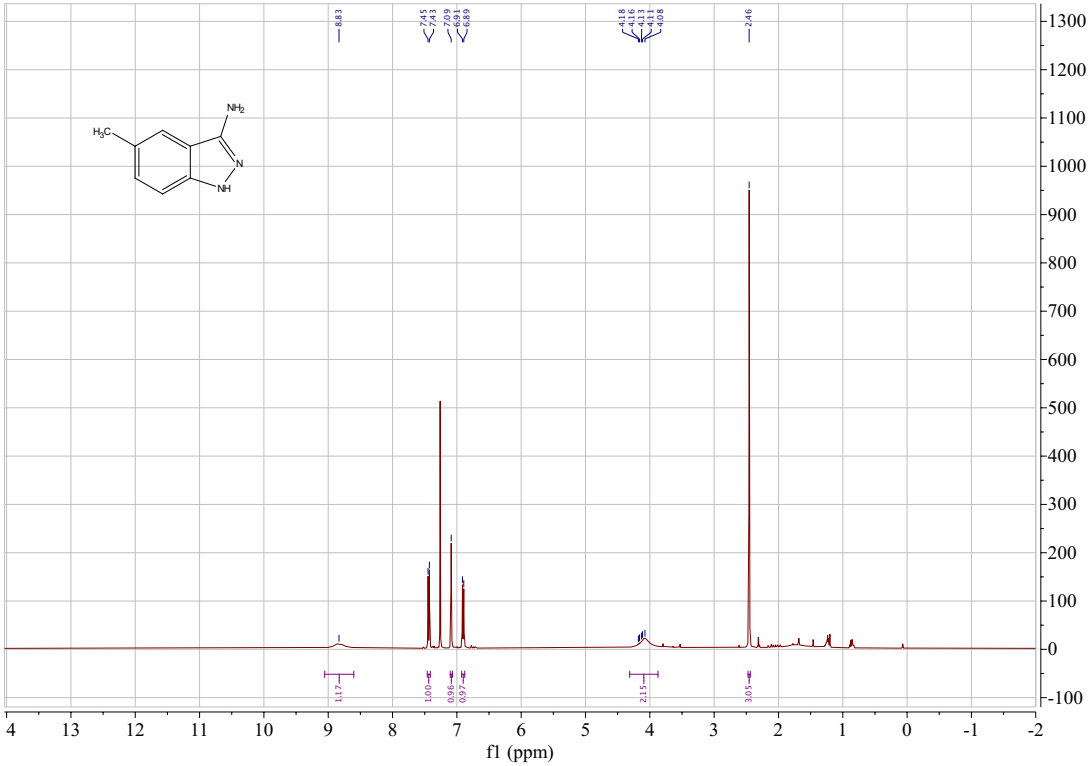
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4.08
2.46
NH2
H3C
N
NH
1.17
1.00
0.96
0.97
2.15
3.05
f1 (ppm)

H. References

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IV. Development of an Fe/ppm Cu Nanoparticle Catalyst for the Cu-Catalyzed Azide-Alkyne Cycloaddition in Water

A. Introduction

The Huisgen cycloaddition, originally discovered 1893 and later popularized by Huisgen in the mid-20th century, is a thermally induced formal [3+2] 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne (Figure 1).[1] While efficient, this thermally induced reaction leads to the possibility of two regioisomeric products with limited selectivity. In the early 2000s Fokin/Sharpless and Meldal independently disclosed a Cu(I)- catalyzed variant of this reaction with terminal alkynes that leads exclusively to a 1,4- rather than 1,5- substitution pattern (Figure 1). This Cu-catalyzed azide/alkyne cycloaddtion (CuAAC) would later join a group of reactions called "click" chemistry, so named due their predictability, robustness, and mild conditions thanks to their rapid, energetically favorable nature.

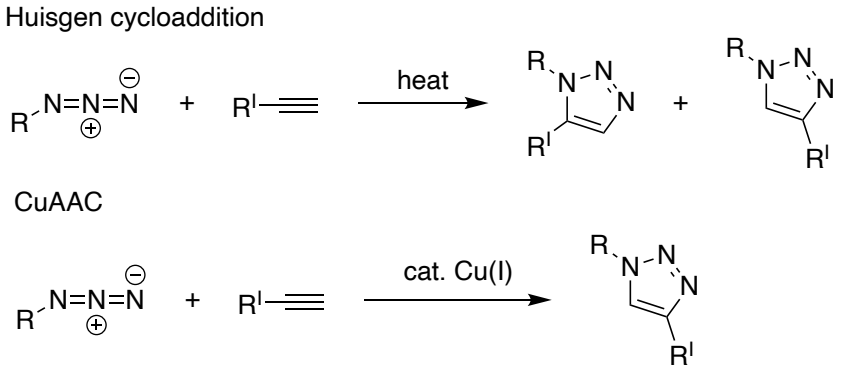


Figure 20: Huisgen cycloaddtion vs. CuAAC

This click reaction has a multitude of applications to chemical biology, drug discovery, combinatorial chemistry, and materials science.[2-5] A variety of Cu(I) species can function as effective catalysts for this reaction, including any copper halide or carboxylate in the

presence of a base, typically an amine.[1] Cu(II) sources such as $CuSO_4$ can work as well when in the presence of a reducing agent such as sodium ascorbate.

The Lipshutz group has developed a class of nanoparticles wherein ppm levels of catalytic metals are embedded in an Fe-based framework that enables a variety of reactions to be performed in water.[6-9] These nanoparticles are uniquely effective in micellar media due to the coordinative ability of the PEG chains which leads to aggregation of the micelles in high concentrations in the region of the catalyst. This phenomenon has been named the "nano-to-nano" effect. Due to this high local concentration, very low global loadings of the catalytically active metal are needed to successfully perform these reactions. Based on this we endeavored to develop a Fe/ppm Cu nanoparticle catalyst for mild CuAAC reactions in aqueous micellar media.

B. Results and Discussion

The preparation of the nanoparticles followed a preparation analogous to those previously utilized for making Suzuki-Miyaura nanoparticles.[6,10] For a single reaction 97% $FeCl_3$ and CuOAc (1000 ppm) were stirred together in THF under an inert atmosphere for ten minutes followed by the slow addition of a THF solution of MeMgCl (1.5 equivalents relative to iron) until a dark brown precipitate formed (Figure 2). The THF was removed *in vacuo* and the resulting material directly used in the cycloaddition. Alternatively, the material could be prepared on >0.5 g scale. After removal of THF in *vacuo* the material was triturated with pentane followed by removal of volatiles *in vacuo*. These nanoparticles could be used directly in a CuAAC reaction, stored under argon for use 2-3 days later, or stored in a solution of 2 wt% TPGS-750-M with ascorbic acid for future use.

Figure 21: Nanoparticle synthesis.

EDX analysis of the nanoparticles revealed that the bulk of the material is Mg, Cl, C, and O with a minor amount of Fe. Cu levels were below the detection limit (Figure 3). Cryo-TEM analysis of the nanoparticles in a 2 wt % solution of TPGS-750-M/H_2O reveals, as was expected, aggregation of the nanoparticles around micelles (Figure 4). The same analysis performed on a post-reaction solution showed even greater aggregation of the nanoparticles

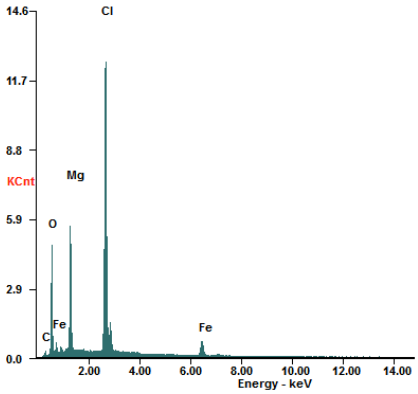


Figure 22: EDX analysis of nanoparticles

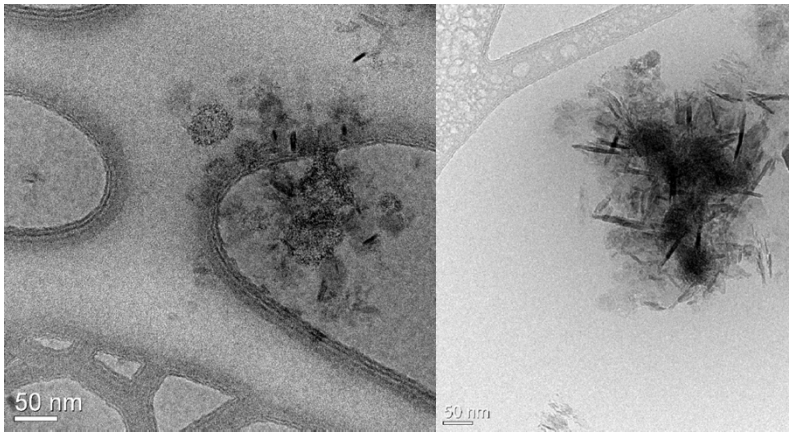


Figure 23: Cryo-TEM images of fresh (left) nanoparticle solution and used (right) nanoparticle solution

With these nanoparticles we synthesized a variety of substrates bearing divergent functional groups (Figure 5). With respect to the alkyne, alkyl chains, halides, unprotected alcohols, protected alcohols, and variously substituted aromatic groups were well tolerated. A plethora of different benzylic azides were successfully used bearing a mix of various electron-donating and electron-withdrawing groups, although a methyl ester substituted aromatic azide and a purely alkyl azide proved to be poor reactants for this transformation leading to substrates **12** and **13,** respectively.

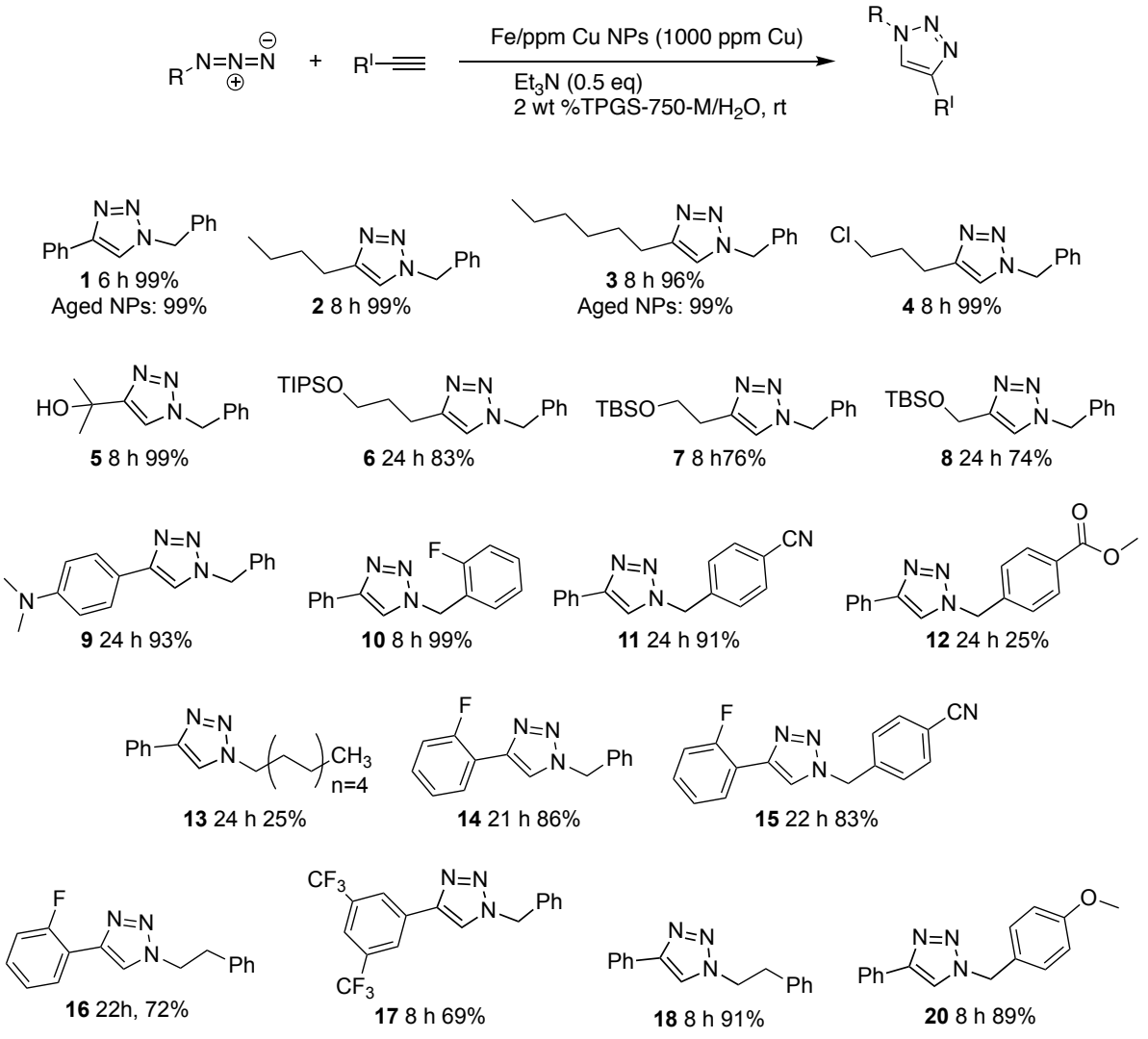


Figure 24: Substrate scope of CuAAC reactions

Recycle and E Factor studies were conducted to assess the "greenness" of this catalyst and methodology. An initial coupling leading to product **1** was isolated in quantitative yield. After extraction of the crude the same catalyst and solution was reused *in situ* to sequentially generate products **4**, **3**, and **10** in excellent yields. An E Factor, based on organic solvent usage of 4.1 was achieved for the combined four uses of this recycled surfactant solution and catalyst, which is an order of magnitude below what is typical for the pharmaceutical industry.[11]

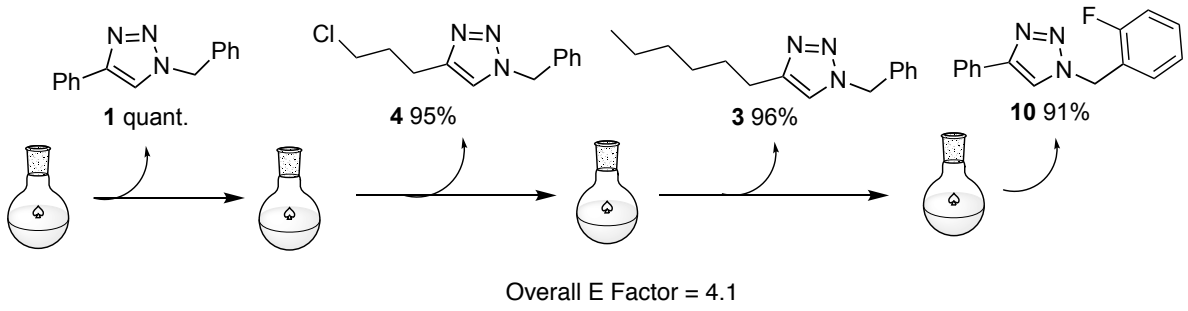


Figure 25: E Factor and recycling

C. Conclusion

A new nanoparticle catalyst of iron doped with ppm levels of copper was successfully proposed and applied to copper-catalyzed azide-alkyne cycloadditions in aqueous TPGS-750-M at room temperature. A variety of diversely substituted aryl and alkyl azides and alkynes could be coupled under these conditions. Both the aqueous medium and catalyst were recyclable *in situ* leading to a low E Factor. The result is an attractive method for running green CuAAC reactions.

D. General Experimental

General procedure A for CuAAC reactions: In a flame dried 10 mL microwave reaction vial, $FeCl_3$ (4.1 mg, 5 mol %) was added under anhydrous conditions. The reaction vial was closed with a rubber septum and the mixture was evacuated and backfilled with

argon three times. Dry THF (0.7 mL) and CuOAc in THF (0.061 mL, 1000 ppm; 1 g/L) were added to the vial and the mixture was stirred for 10 min at rt, after which MeMgCl in THF (0.75 mL, 7.5 mol %; 0.5 M) was added to the reaction mixture. While maintaining an inert atmosphere, THF was evaporated under reduced pressure. An aqueous solution of 2 wt % TPGS-750-M (1.0 mL) was then added to the vial followed by sequential addition of alkyne (0.5 mmol), azide (0.6 mmol, 1.2 equiv), and triethylamine (0.0349 mL, 0.25 mmol, 0.5 equiv). The mixture was stirred vigorously at rt. After complete consumption of starting material, as monitored by TLC or GC-MS, EtOAc (1 mL) was added to the reaction mixture, which was then stirred *gently* for 5 min (NOTE : vigorous stirring or shaking in the reaction flask or in a separatory funnel during the extraction process resulted in the formation of an intractable emulsion with consequent reductions in isolated yields). Stirring was stopped and the organic layer was separated with the aid of a centrifuge. The organic layer was removed and the extraction process was repeated two additional times. The combined organic layers were dried over anhydrous magnesium or sodium sulfate, or flushed through a plug of dried silica gel. The solvent was then evacuated under reduced pressure to obtain crude material which was purified by flash chromatography over silica gel using EtOAc/hexanes as eluent.

Preparation of Fe/ppm Cu nanoparticles: In a tared flame dried two-neck round-bottomed flask, anhydrous pure $FeCl_3$ (121.7 mg, 0.75 mmol) and CuOAc (1.839 mg, 0.015 mmol) were placed under an atmosphere of dry argon. The flask was closed with a septum, and dry THF (10 mL) was added. The reaction mixture was stirred for 10 min at rt. While maintaining a dry atmosphere at rt, MeMgCl (2.25 mL, 1.125 mmol; 0.5 M solution) in THF was very slowly (1 drop/two sec) added to the reaction mixture. After complete addition of the Grignard reagent, the reaction mixture was stirred for an additional 30 min at rt. An

appearance of a dark-brown coloration was indicative of generation of nanomaterial. The stir bar was removed and THF was evaporated under reduced pressure at rt followed by washing the mixture with dry pentane to provide a light brown-colored nanopowder. The nanomaterial was dried under reduced pressure at rt for 10 min (603 mg) and could then be used directly for CuAAC reactions under micellar conditions. Dividing the starting mass of CuOAc by the final weight in the flask yields CuOAc concentration in the isolated catalyst

Determination of Cu concentration in isolated catalyst.

$$[\mathbf{CuOAc}] = \frac{\mathbf{1.839\ mg\ CuOAc}}{\mathbf{603\ mg\ NPs}} = \frac{\mathbf{0.305\ mg\ CuOAc}}{\mathbf{100\ mg\ NPs}}$$

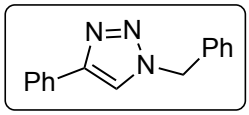
$$\mathbf{0.5 mmol\ substrate \times 0.001\ equiv\ CuOAc\ \{1000\ ppm\ Cu\} \times 122.59\ FW\ CuOAc = 0.061\ mg\ CuOAc\ for\ 0.5\ mmol\ scale\ reaction}$$

$$\frac{\mathbf{100\ mg\ NPs}}{\mathbf{0.305\ mg\ CuOAc}} \times \mathbf{0.061\ mg\ CuOAc} = \mathbf{20\ mg\ NPs}$$

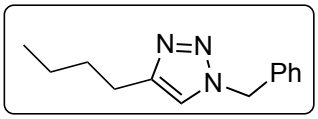
General procedure B for CuAAC reaction with aged catalyst. In a flame dried 10 mL microwave reaction vial, aged nanomaterial (20 mg) and vitamin C (8.8 mg, 0.05 mmol) were added. The reaction vial was closed with a rubber septum and the mixture was evacuated and backfilled with argon three times. An aqueous solution of 2 wt % TPGS-750-M (1.0 mL) was added to the vial. After 24 h stirring at rt, while maintaining the inert atmosphere, alkyne (0.5 mmol), azide (0.6 mmol, 1.2 equiv), and triethylamine (0.0349 mL, 0.25 mmol, 0.5 equiv) were added. The mixture was stirred vigorously at rt. After complete consumption of starting material, as monitored by TLC or GC-MS, EtOAc (1 mL) was added to the reaction mixture, which was stirred gently for 5 min (NOTE : vigorous stirring or shaking in the reaction flask or in a separatory funnel during the exctraction process resulted in the formation of an intractable emulsion with consequent reductions in isolated yields). Stirring was stopped and the organic layer was separated with the aid of a centrifuge. The organic layer was removed and the extraction process was repeated two

additional times. The combined organic layers were dried over anhydrous magnesium sulfate or sodium sulfate, or flushed through a plug of dried silica gel. The solvent was then evacuated under reduced pressure to obtain crude material which was purified by flash chromatography over silica gel using EtOAc/hexanes as eluent.

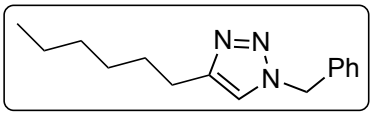
E. Analytical Data for Triazole Products



1-Benzyl-4-phenyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A or B using phenylacetylene (51 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 118 mg was isolated as a white powdery crystal (99%). R_f = 0.33 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.81 (m, 2H), 7.66 (s, 1H), 7.37-7.42 (m, 5H), 7.30-7.33 (m, 3H), 5.59 (s, 2H). Spectrum matched literature.[12]

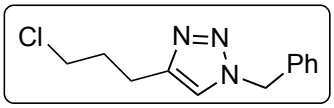


1-Benzyl-4-butyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using 1-hexyne (41 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 107 mg was isolated as a clumpy white solid (99%). R_f = 0.28 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.38 (m, 3H), 7.23-7.25 (m, 2H), 7.17 (s, 1H), 5.48 (s, 2H), 2.68 (t, *J* = 8 Hz, 2H), 1.61 (p, *J* = 7.5 Hz, 2H), 1.35 (sext, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). Spectrum matched literature.[13]

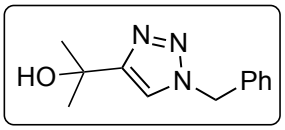


1-Benzyl-4-hexyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using 1-octyne (55 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 117 mg was solated as a

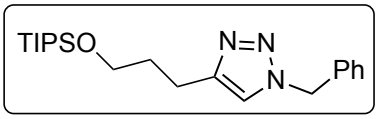
fluffy white crystalline solid (96%) or 120 mg from procedure B (99%). R_f = 0.32 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.37 (m, 3H), 7.23-7.24 (m, 2H), 7.17 (s, 1H), 5.47 (s, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.62 (p, *J* = 7.5 Hz, 2H), 1.25-1.33 (m, 6H), 0.85 (t, *J* = 6.5 Hz, 3H). Spectrum matched literature.[14]



1-Benzyl-4-(3-chloropropyl)-1*H*-1,2,3-triazole: Synthesized according to general procedure A using 6-chloro-1-pentyne (51 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 116 mg was isolated as a flaky off-white solid (99%). R_f = 0.21 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.40 (m, 3H), 7.25-7.27 (m, 2H), 7.24 (s, 1H), 5.50 (s, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.15 (p, *J* = 7 Hz, 2H). Spectrum matched literature.[15]

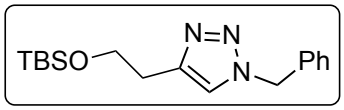


2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol. Synthesized according to general procedure A using 2-methylbut-3-yn-2-ol (42 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 107 mg was isolated as a white powdery solid (99%). R_f = 0.31 (2:25 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.39 (m, 3H), 7.34 (s, 1H), 7.27 (dd, *J* = 8, 2.5 Hz, 2H), 5.49 (s, 2H), 2.54 (s, 1H), 1.60 (s, 6H). Spectrum matched literature.[16]

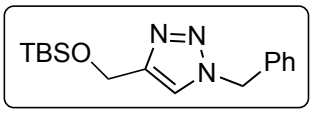


1-Benzyl-4-(3-((triisopropylsilyl)oxy)propyl)-1*H*-1,2,3-triazole. Synthesized according to general procedure A using triisopropyl(pent-4-yn-1-yloxy)silane (120 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 155 mg was isolated as a colorless, viscous oil (83%). R_f

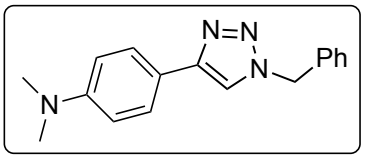
= 0.37 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.38 (m, 3H), 7.24-7.26 (m, 2H), 7.19 (s, 1H), 3.70 (t, *J* = 6.5 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 1.89 (p, *J* = 7.5 Hz, 2H), 1.03 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.60, 135.08, 129.18, 128.74, 128.11, 120.81, 62.53, 54.13, 32.52, 22.22, 18.15, 12.06. ESI-MS $[M + Na]^+$ calcd: 396.2447 found: 396.2462



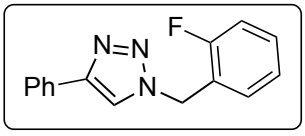
1-Benzyl-4-(2-((*t*-butyldimethylsilyl)oxy)ethyl)-1*H*-1,2,3-triazole: Synthesized according to general procedure A using triisopropyl(but-3-yn-1-yloxy)silane (113 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 120 mg was isolated as a colorless, viscous oil (76%). R_f = 0.26 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.43 (m, 3H), 7.31-7.32 (m, 3H), 5.54 (s, 2H), 3.88 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6.5 Hz, 2H), 0.86 (t, 9H), 0.00 (t, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.97, 134.95, 129.19, 128.77, 128.24, 121.92, 62.34, 54.16, 29.62, 25.98, 18.32, -5.32. ESI-MS $[M + Na]^+$ calcd: 340.1821 found: 340.1817.



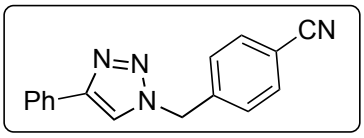
1-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-1,2,3-triazole: Synthesized according to general procedure A using triisopropyl(prop-2-yn-1-yloxy)silane (106 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 112 mg was isolated as a colorless, viscous oil (74%). R_f = 0.34 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.27-7.30 (m, 3H), 7.19 (dd, J = 7.5, 2 Hz, 2H), 5.44 (s, 2H), 4.76 (s, 2H), 0.81 (s, 9H), 0.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.93, 129.19, 128.79, 128.09, 121.62, 114.62, 58.11, 54.23, 26.01, 18.47, -5.14. ESI-MS $[M + Na]^+$ calcd: 326.1665 found: 326.1673



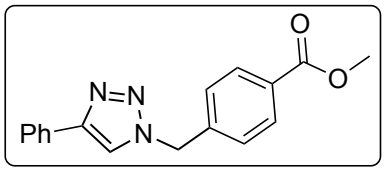
4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*,*N*-dimethylaniline. Synthesized according to general procedure A using 4-ethynyl-*N,N*-dimethylaniline (73 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 129 mg was isolated as a maroon crystalline solid (93%). R_f = 0.40 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 9 Hz, 2H), 7.52 (s, 1H), 7.35-7.40 (m, 3H), 7.30 (d, *J* = 8 Hz, 2H), 6.74 (d, *J* = 9 Hz, 2H), 5.55 (s, 2H), 2.97 (s, 6H). Spectra matched literature.[17]



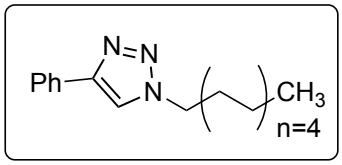
1-(2-Fluorobenzyl)-4-phenyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using phenylacetylene (51 mg, 0.5 mmol) and 1-(azidomethyl)-2-fluorobenzene (83 mg, 0.55 mmol). 125 mg was isolated as a white powdery crystal (99%). R_f = 0.29 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.76 (s, 1H), 7.30-7.42 (m, 5H), 7.15 (q, *J* = 10 Hz, 2H), 5.64 (s, 2H). Spectrum matched literature.[18]



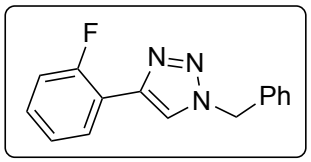
4-((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzonitrile. Synthesized according to general procedure A using phenylacetylene (51 mg, 0.5 mmol) and 4-(azidomethyl)benzonitrile (87 mg, 0.55 mmol). 118 mg was isolated as a white powder (91%). R_f = 0.30 (1:1 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.72 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.32-7.43 (m, 5H), 5.65 (s, 2H). Spectrum matched literature.[19]



Methyl 4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzoate. Synthesized according to general procedure A using phenylacetylene (51 mg, 0.5 mmol) and methyl 4-(azidomethyl)benzoate (105 mg, 0.55 mmol). 37 mg was isolated as an off-white crystalline solid (25%). R_f = 0.39 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.81 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.69 (s, 1H), 7.31-7.42 (m, 5H), 5.64 (s, 2H), 3.92 (s, 3H). Spectrum matched literature.[20]

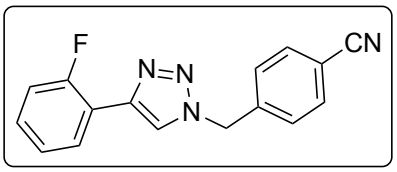


1-Decyl-4-phenyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using phenylacetylene (51 mg, 0.5 mmol) and methyl 1-azidodecane (101 mg, 0.55 mmol). 25 mg was isolated as a flaky white powder (25%). R_f = 0.38 (1:3 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.74 (s, 1H), 7.42 (t, *J* = 8 Hz, 2H), 7.32 (t, *J* = 6.5 Hz, 1H), 4.39 (t, *J* = 7 Hz, 2H), 1.94 (p, *J* = 7 Hz 2H), 1.26-1.35 (m, 14H), 0.87 (t, *J* = 7 Hz, 3H). Spectrum matched literature.[21]

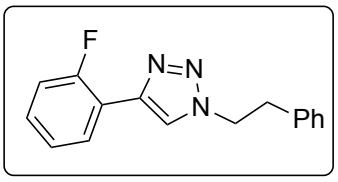


1-Benzyl-4-(2-fluorophenyl)-1*H*-1,2,3-triazole. Synthesized according to general procedure A using 1-ethynyl-2-fluorobenzene (60 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 109 mg was isolated isolated as a white crystalline solid (86%). R_f = 0.32 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (td, *J* = 7.6, 2.0 Hz, 1H), 7.86 (d, *J* =

3.7 Hz, 1H), 7.42 – 7.22 (m, 7H), 7.13 – 7.08 (m, 1H), 5.60 (s, 2H). Spectrum matched literature.[22]

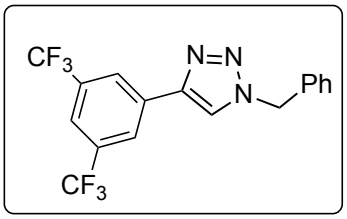


4-((4-(2-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)methyl)benzonitrile. Synthesized according to general procedure A using 1-ethynyl-2-fluorobenzene (60 mg, 0.5 mmol) and 4-(azidomethyl)benzonitrile (87 mg, 0.55 mmol). 115 mg was isolated Isolated as a white crystalline solid (83%). R_f = 0.43 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (td, *J* = 7.6, 1.9 Hz, 1H), 7.92 (d, *J* = 3.6 Hz, 1H), 7.68 – 7.66 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.26 (td, *J* = 8.0, 1.4 Hz, 1H), 7.12 (ddd, *J* = 11.1, 8.2, 1.2 Hz, 1H), 5.66 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.34, 158.37, 142.17, 139.99, 133.03, 129.77, 129.71, 128.45, 127.92, 127.89, 124.83, 124.80, 123.02, 122.91, 118.36, 118.25, 115.89, 115.72, 112.94, 105.13, 53.55. ESI-MS $[M+Na]^+$ calcd: 301.0865 found: 301.0869.

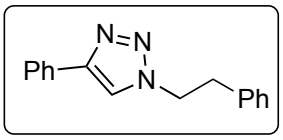


4-(2-Fluorophenyl)-1-phenethyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using 1-ethynyl-2-fluorobenzene (60 mg, 0.5 mmol) and (2-azidoethyl)benzene (81 mg, 0.55 mmol). 96 mg was isolated as an off-white flaky powder (72%). R_f = 0.31 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (td, *J* = 7.6, 2.0 Hz, 1H), 7.70 (d, *J* = 3.7 Hz, 1H), 7.35 – 7.21 (m, 4H), 7.17 – 7.14 (m, 2H), 7.13 – 7.09 (m, 1H), 4.66 (t, *J* = 7.3 Hz, 2H), 3.27 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 137.11, 129.37, 129.30,

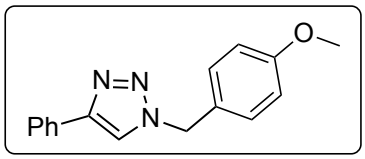
129.00, 128.85, 127.98, 127.95, 127.28, 124.73, 124.70, 123.18, 123.07, 115.84, 115.67, 51.86, 36.94. ESI-MS $[M+Na]^+$ calcd: 290.1069 found: 290.1066.



1-Benzyl-4-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole. Synthesized according to general procedure A using 1-ethynyl-3,5-bis(trifluoromethyl)benzene (119 mg, 0.5 mmol) and benzyl azide (73 mg, 0.55 mmol). 128 mg was isolated as a white powder (69%). R_f = 0.38 (1:3 EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 2H), 7.81 (s, 1H), 7.80 (s, 1H), 7.39-7.44 (m, 3H), 7.3 (dd, *J* = 7.5, 2 Hz, 2H), 5.62 (s, 2H). Spectrum matched literature.[23]

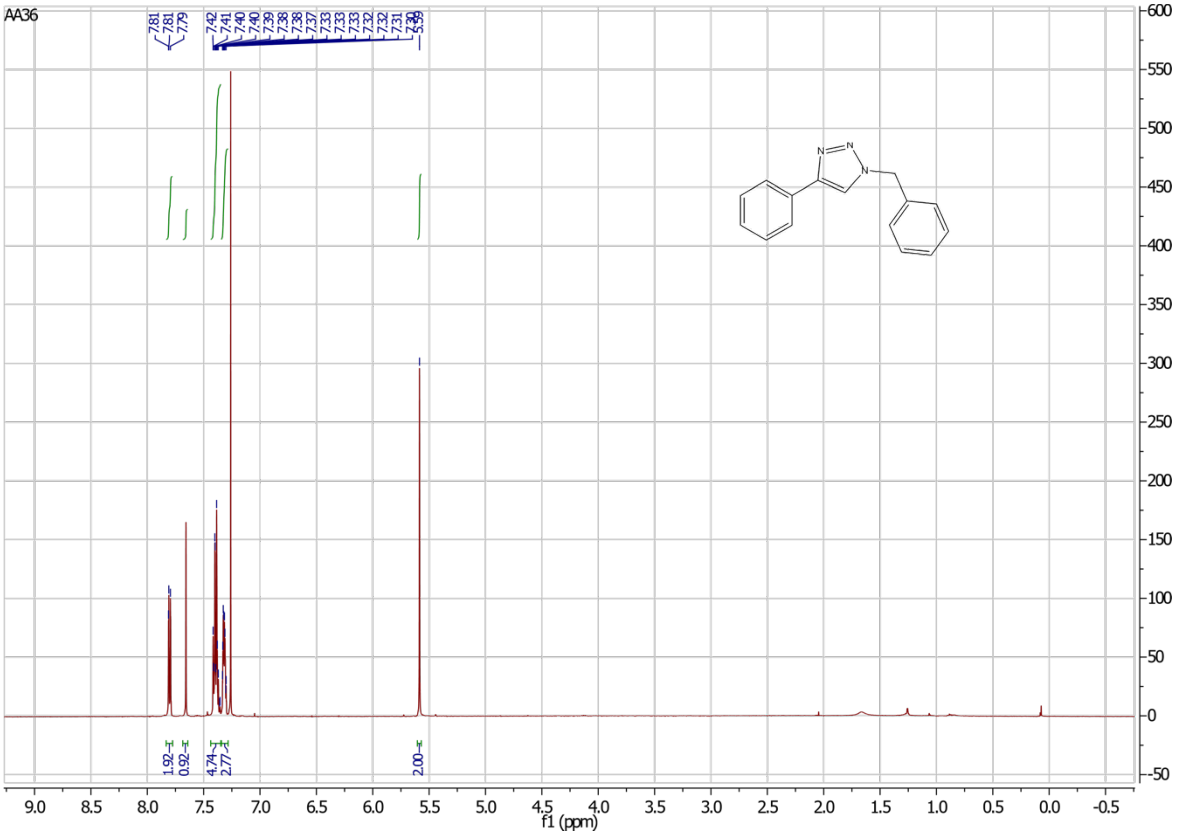


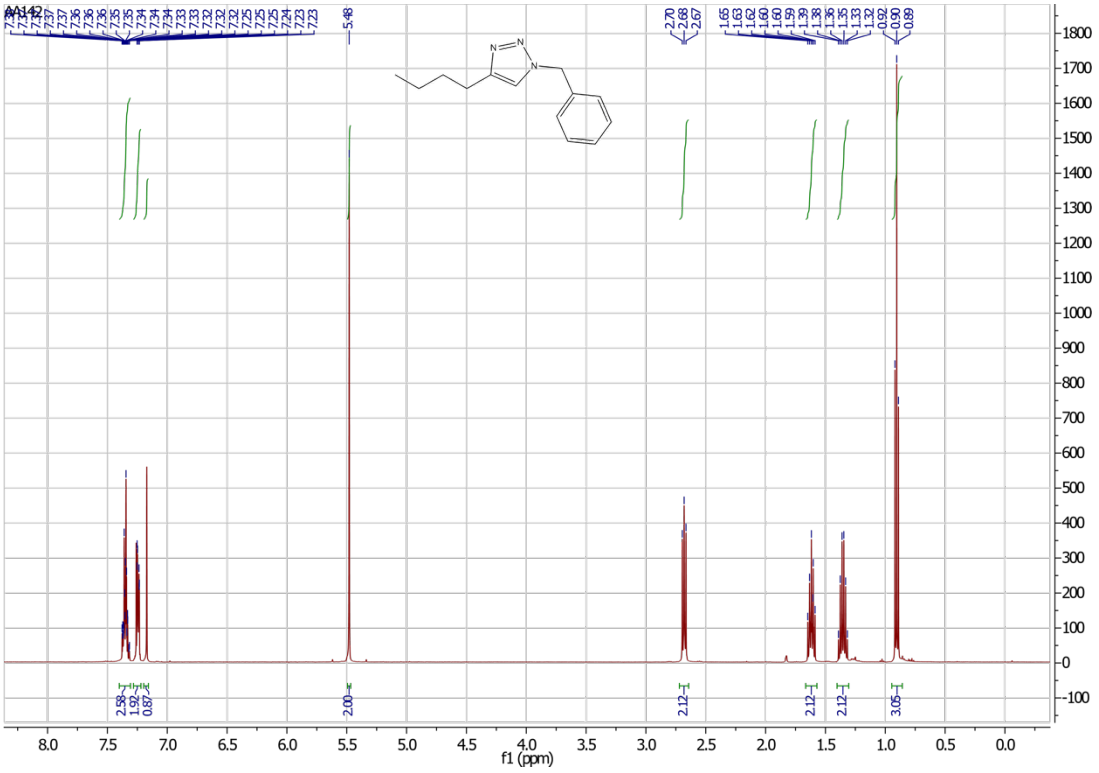
1-Phenethyl-4-phenyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using phenyl acetylene (51 mg, 0.5 mmol) and (2-azidoethyl)benzene (81 mg, 0.55 mmol). 113 mg was isolated as a white crystal (91%). R_f = 0.49 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.46 (s, 1H), 7.41 (t, *J* = 8 Hz, 2H), 7.25-7.34 (m, 4H), 7.14 (d, *J* = 8 Hz, 2H), 4.64 (t, *J* = 7 Hz, 2H), 3.26 (t, *J* = 7 Hz, 2H). Spectrum matched literature.[24]

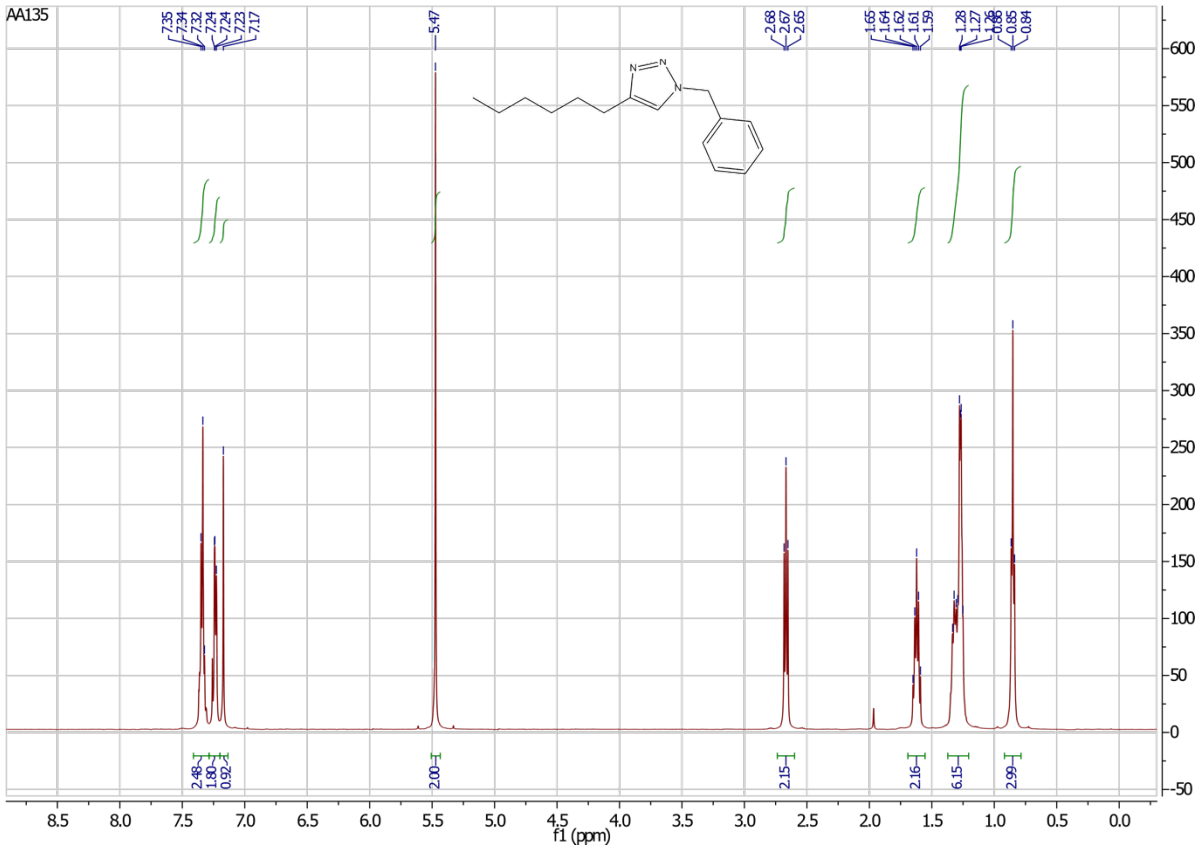


1-(4-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole. Synthesized according to general procedure A using phenyl acetylene (51 mg, 0.5 mmol) and 4-(azidomethyl)anisole (90 mg, 0.55 mmol). 118 mg was isolated isolated as a brownish white shiny crystalline solid (89%). R_f = 0.47 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): 7.79 (dd, *J* = 8, 1 Hz, 2H), 7.62 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.25-7.32 (m, 3H), 6.91 (dt, *J* = 9, 2 Hz, 2H), 5.50 (s, 2H), 3.81 (s, 3H). ESI-MS $[M+Na]^+$ calcd: 288.1113 found: 288.1116

E. NMR Spectra



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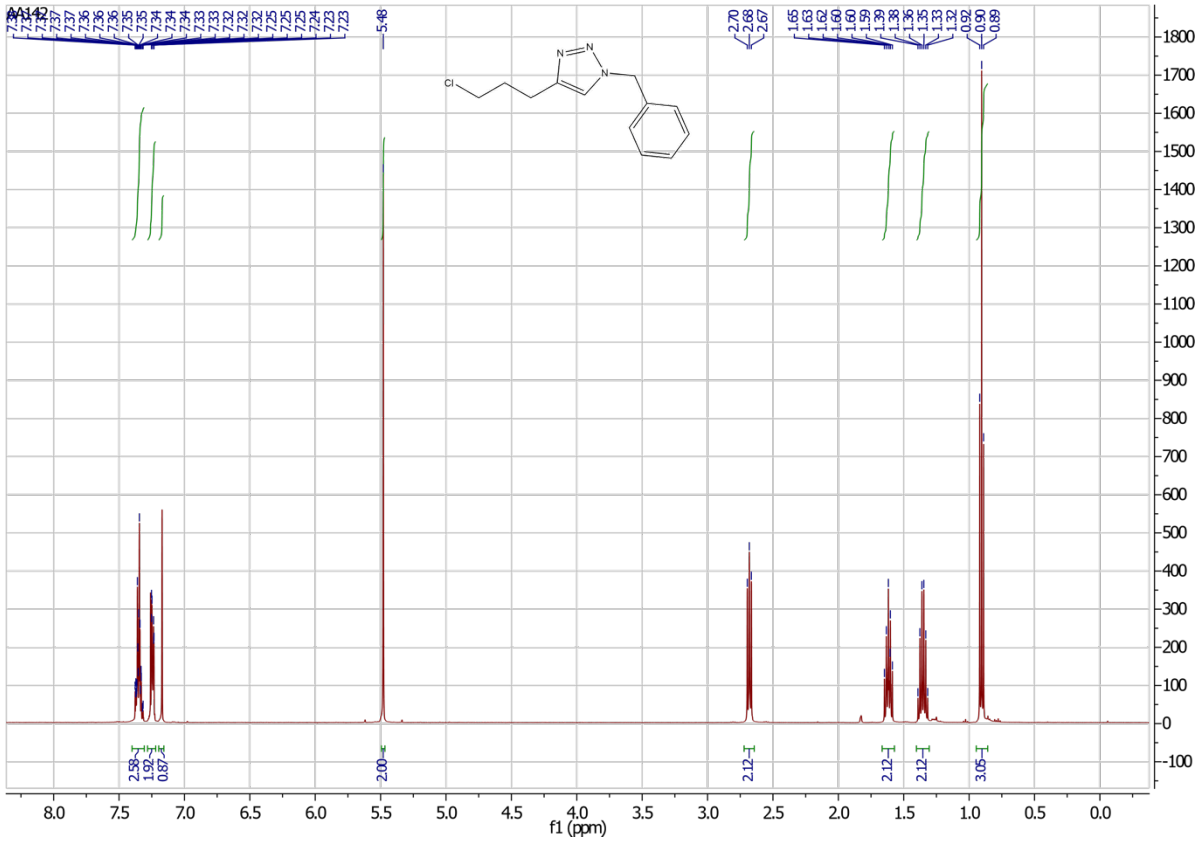
f1 (ppm)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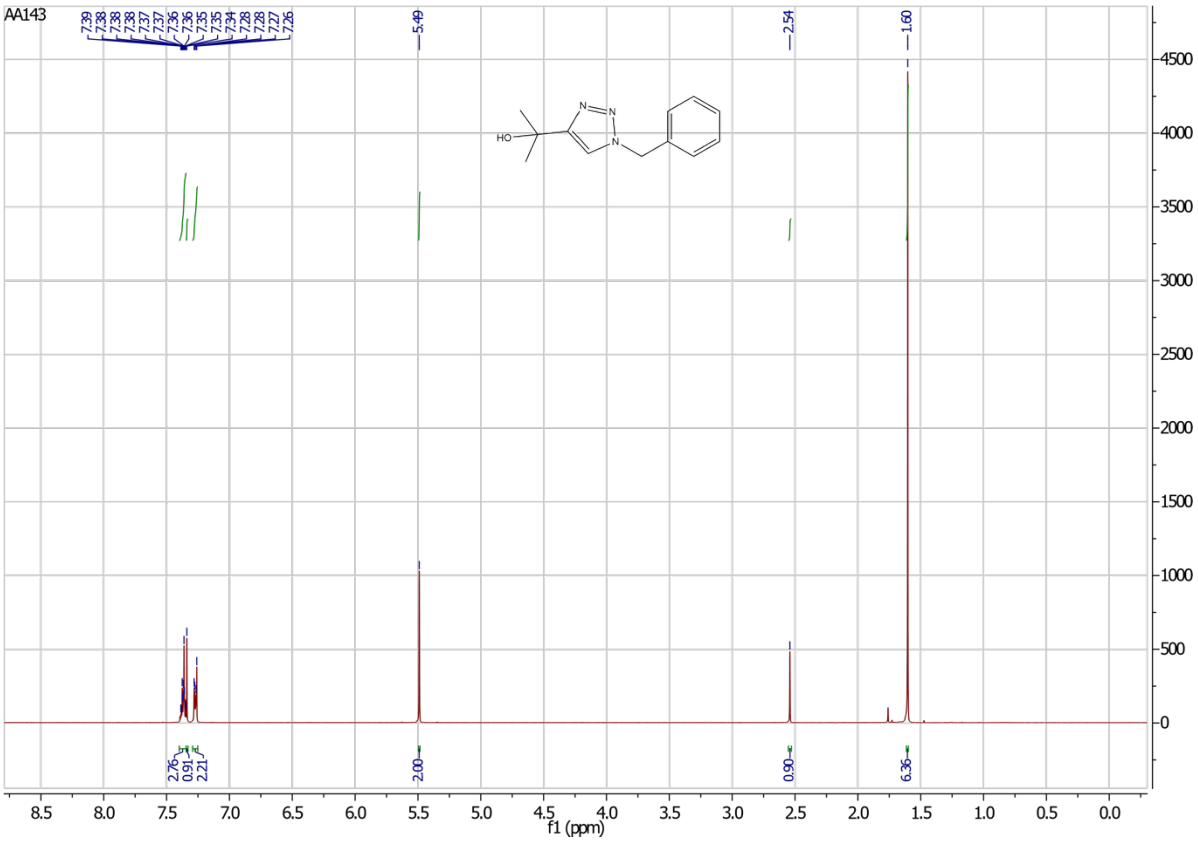
f1 (ppm)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7.35
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7.28
7.27
7.26
5.49
2.54
1.60
HO
N
N
N
2.76
0.91
2.21
2.00
0.90
6.36
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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0.5
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3500
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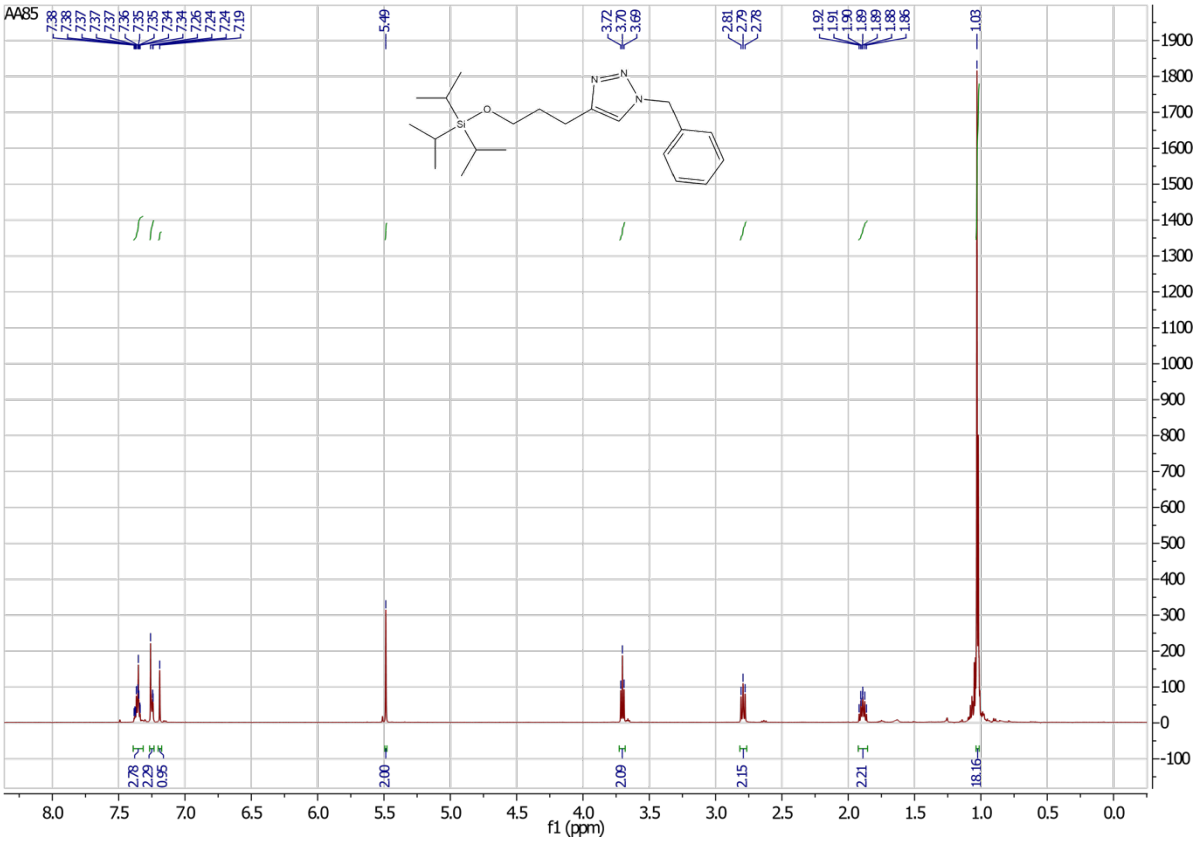
1500
1000
500
0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7.34
7.26
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7.19
5.49
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3.69
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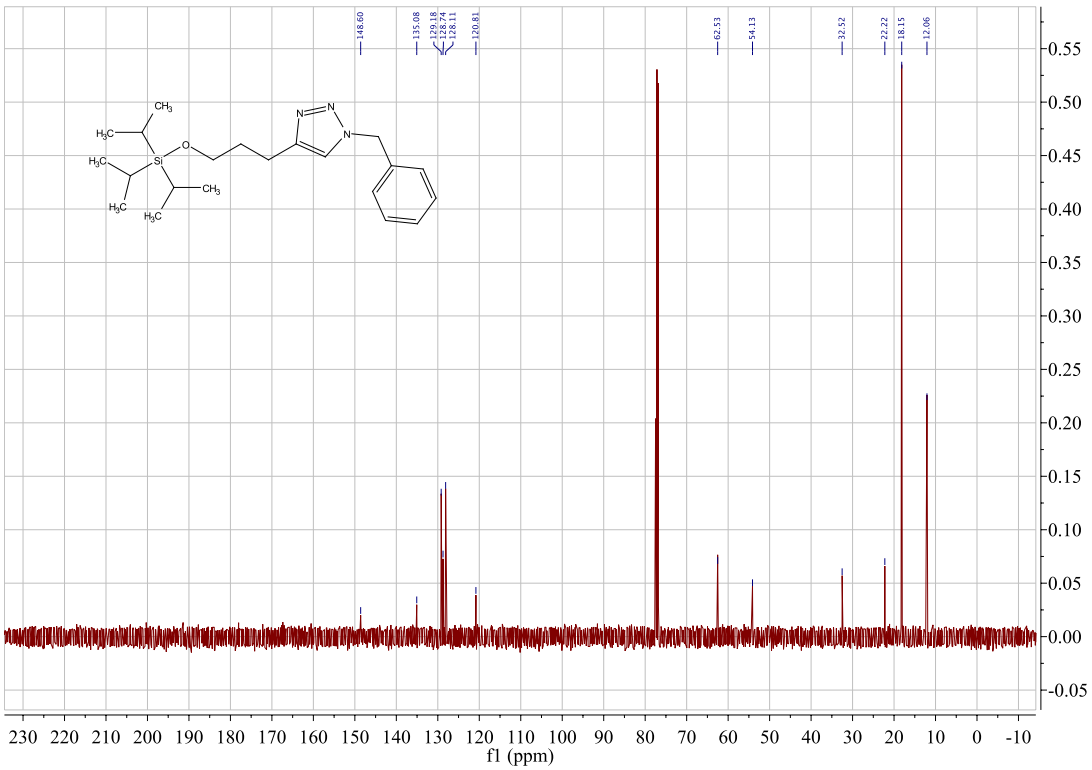
1.91
1.90
1.89
1.89
1.88
1.86
1.03
Si
O
N
N
N
2.78
2.29
0.95
2.00
2.09
2.15
2.21
18.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100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128.11
120.81
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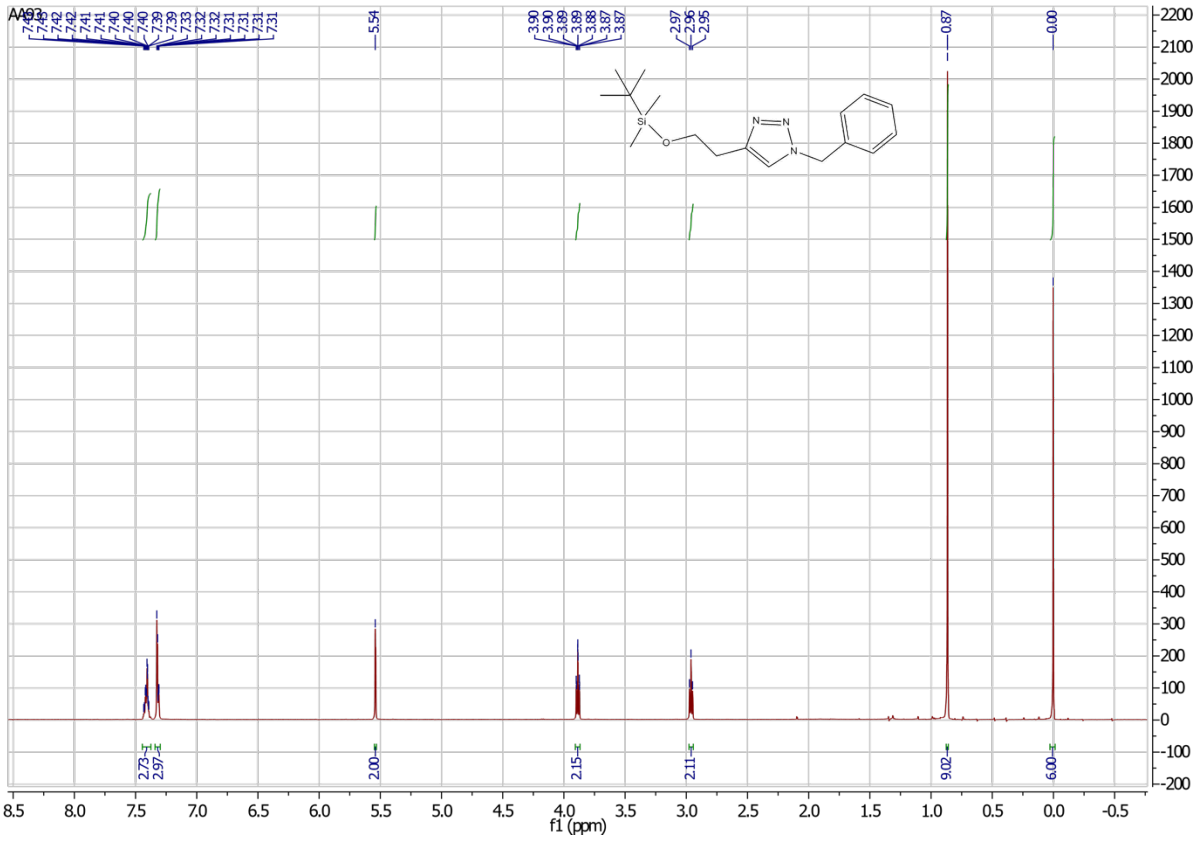
54.13
32.52
22.22
18.15
12.06
f1 (ppm)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3.87
2.97
2.96
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0.00
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2.97
2.00
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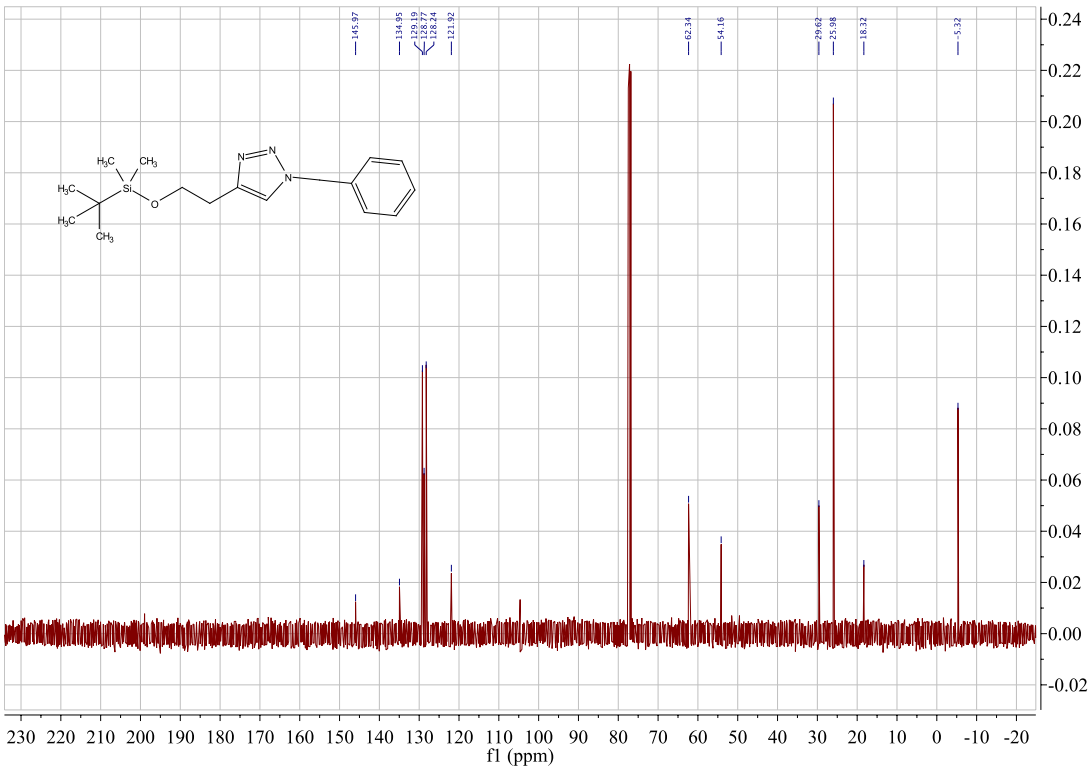
2.11
9.02
6.00
f1 (ppm)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128.24
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54.16
29.62
25.98
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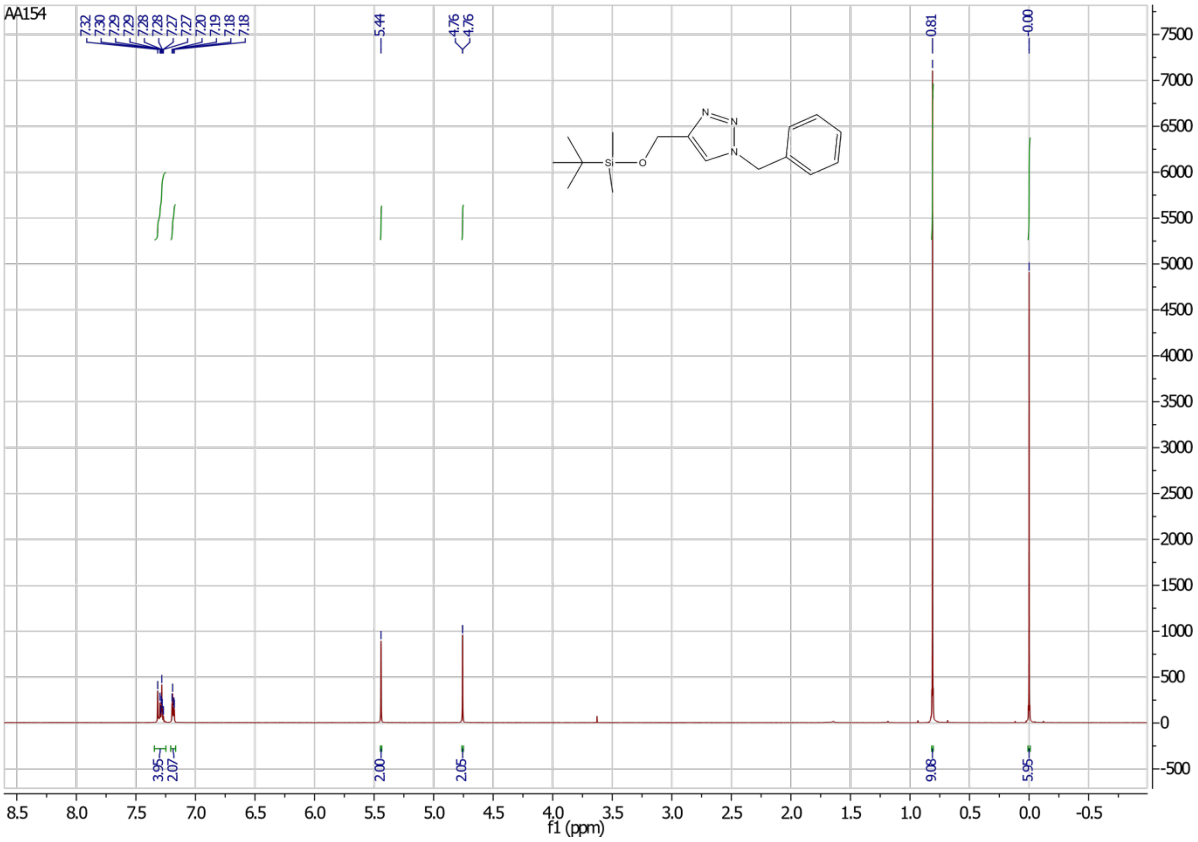
-5.32
f1 (ppm)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7.29
7.28
7.28
7.27
7.27
7.20
7.19
7.18
7.18
5.44
4.76
4.76
0.81
0.00
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2.07
2.00
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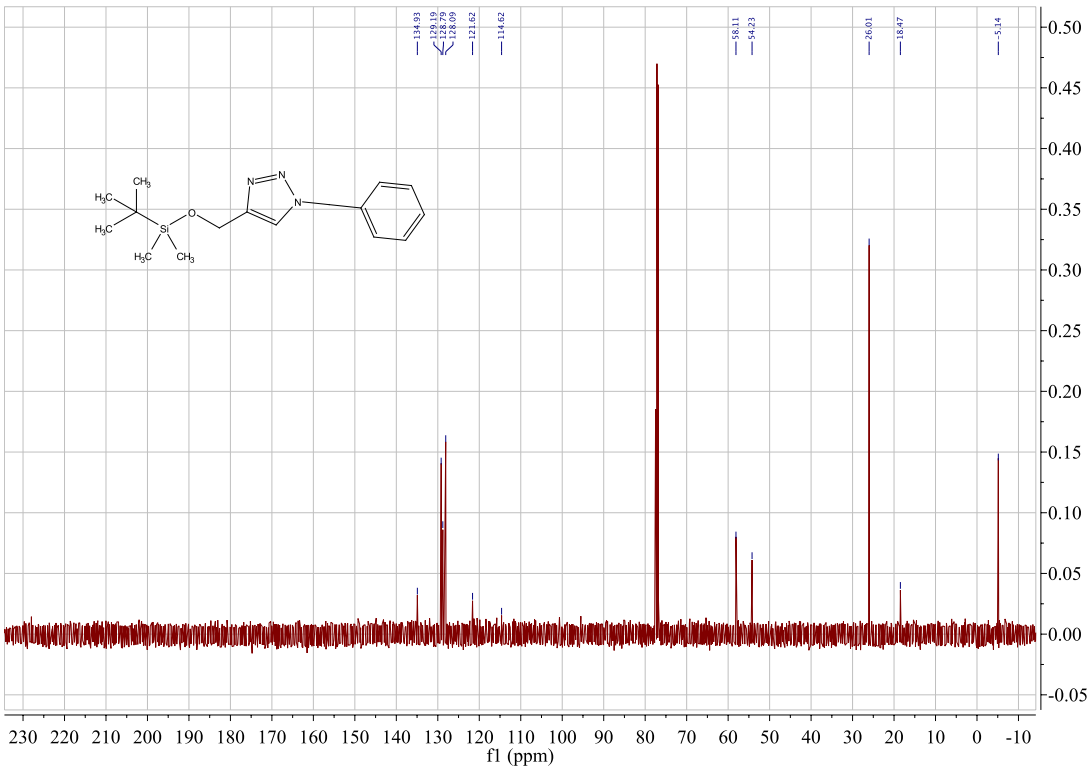
9.08
5.05
f1 (ppm)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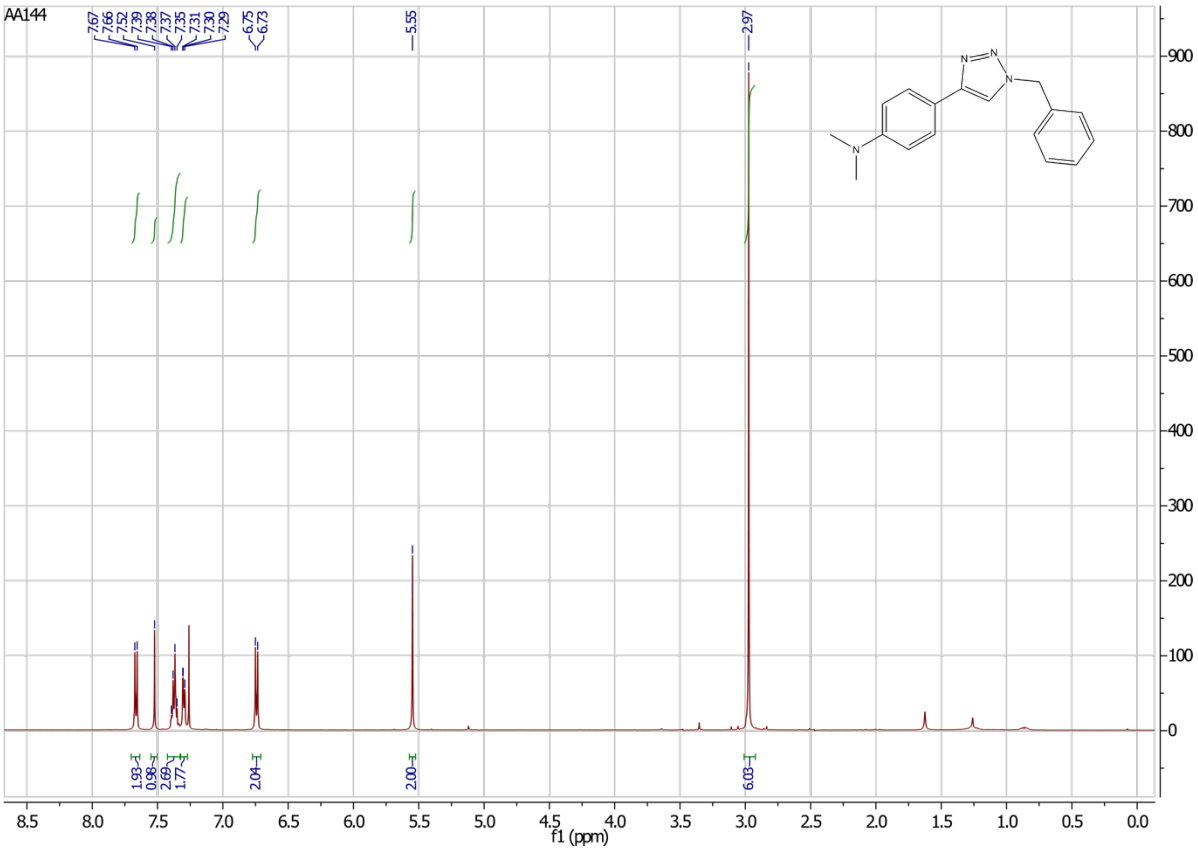
f1 (ppm)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7.38
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7.30
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1.77
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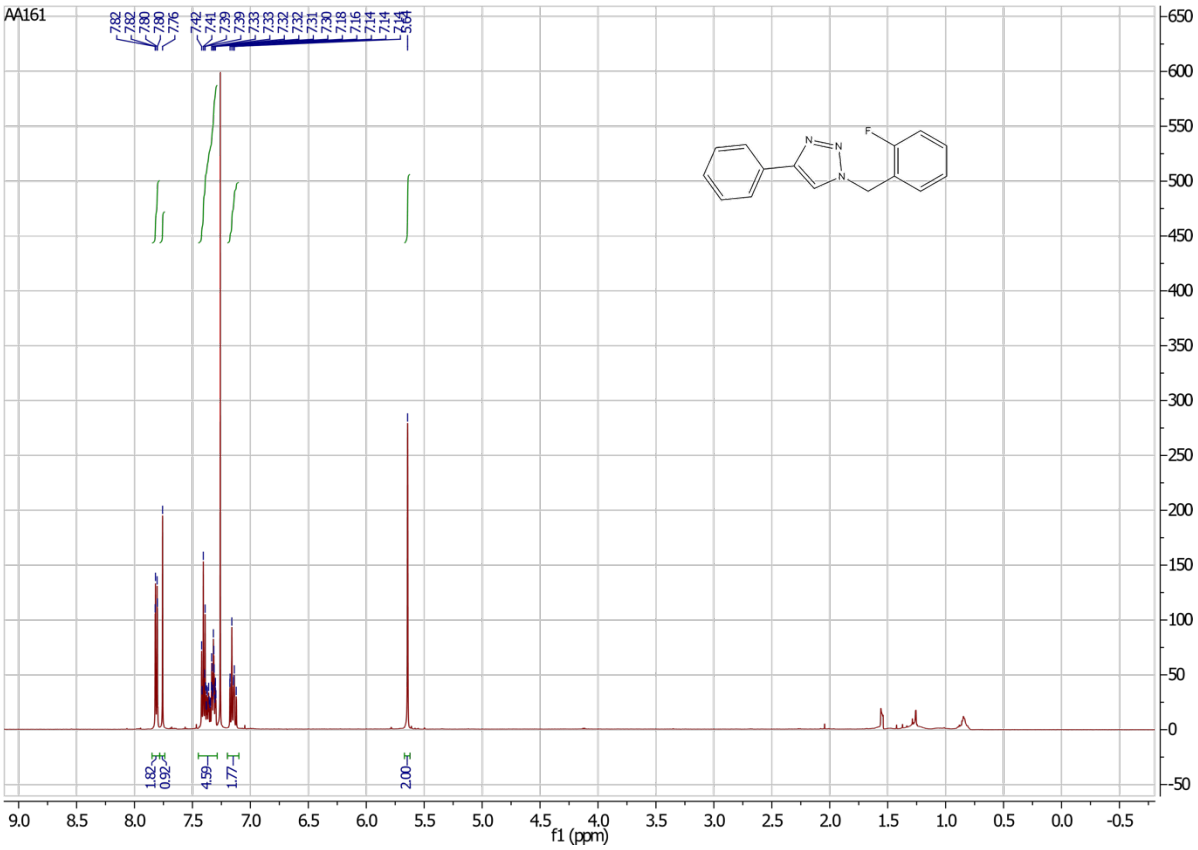
6.03
f1 (ppm)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7.39
7.33
7.33
7.32
7.32
7.31
7.30
7.18
7.16
7.14
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2.00
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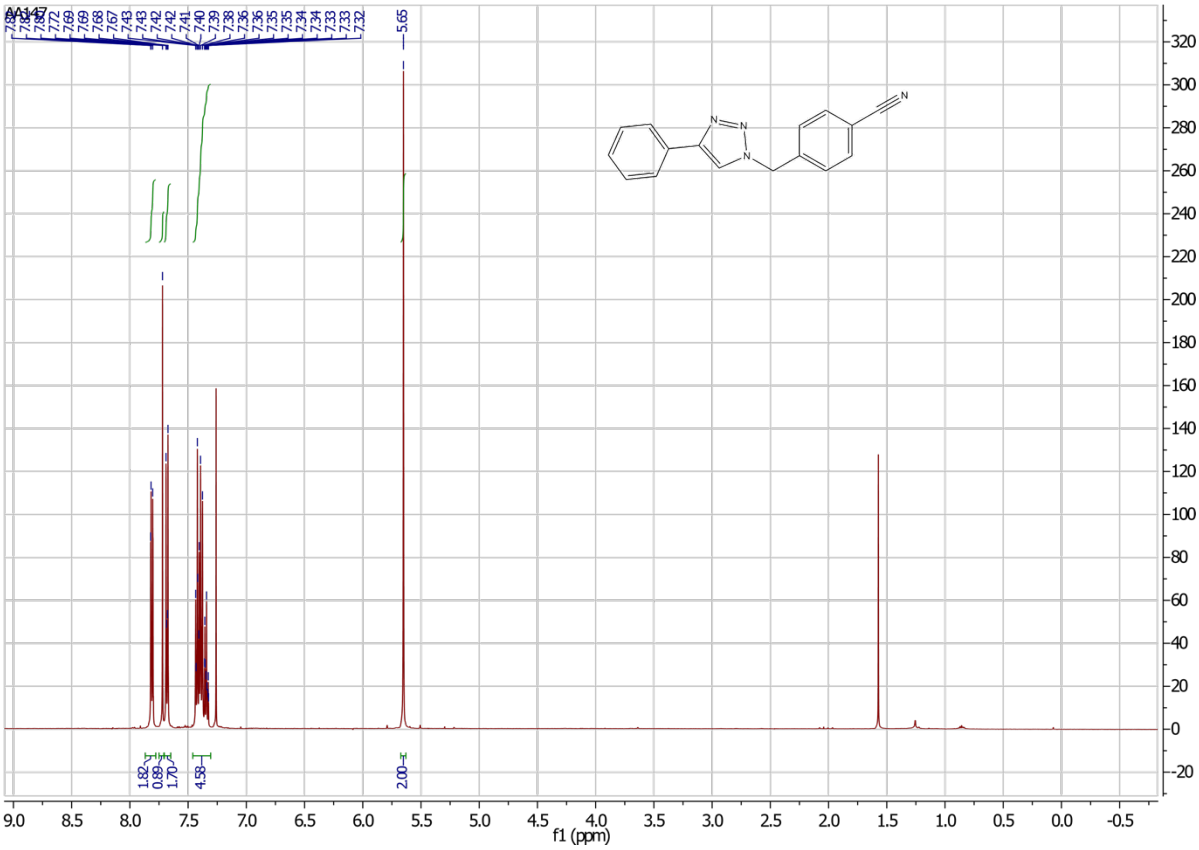
N
N
f1 (ppm)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7.38
7.36
7.36
7.35
7.35
7.34
7.34
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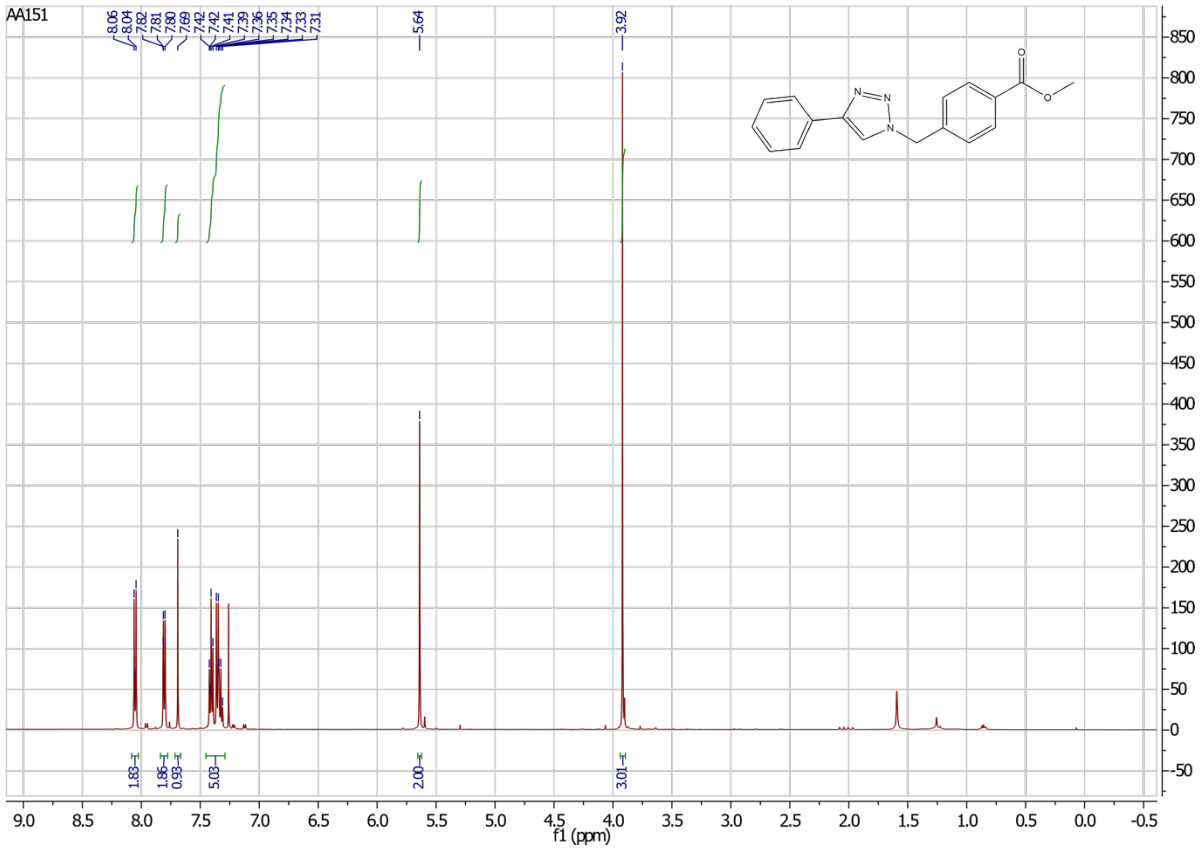
N
N
f1 (ppm)


AA151
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7.35
7.34
7.33
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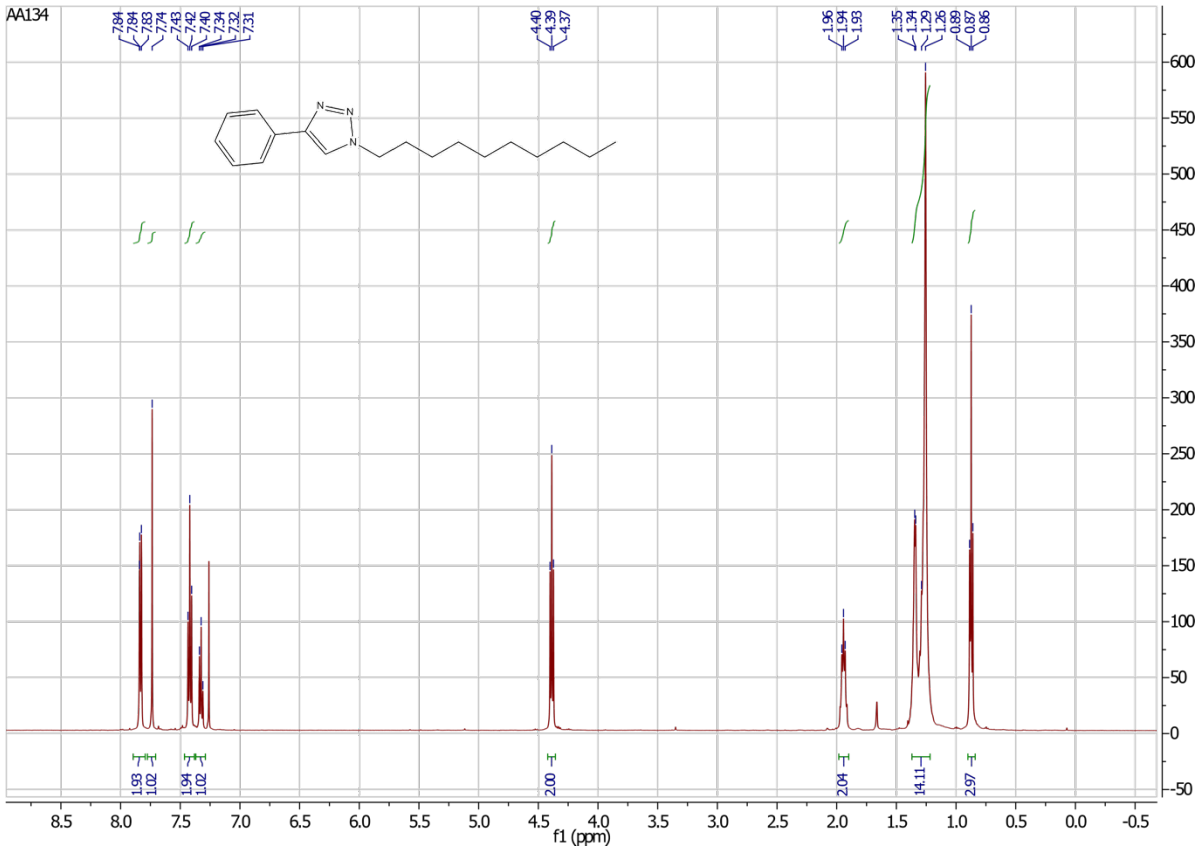
0.93
5.03
2.00
3.01
f1 (ppm)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7.32
7.31
4.40
4.39
4.37
1.96
1.94
1.93
1.35
1.34
1.29
1.26
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1.94
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2.04
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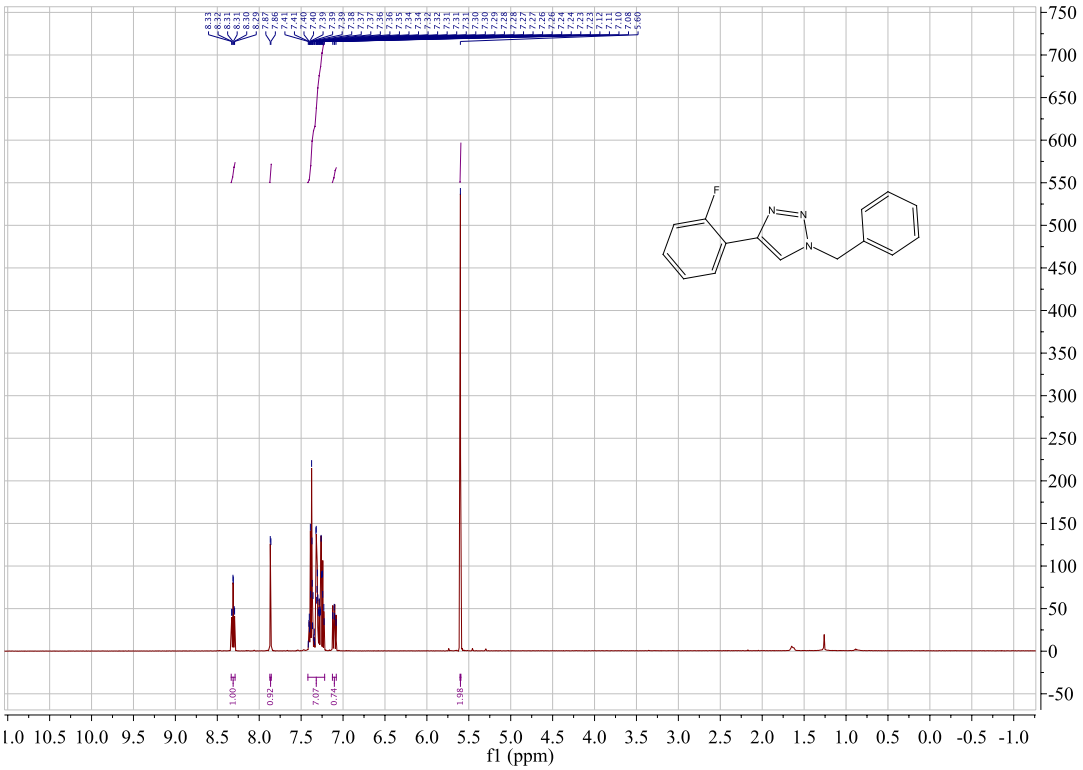
f1 (ppm)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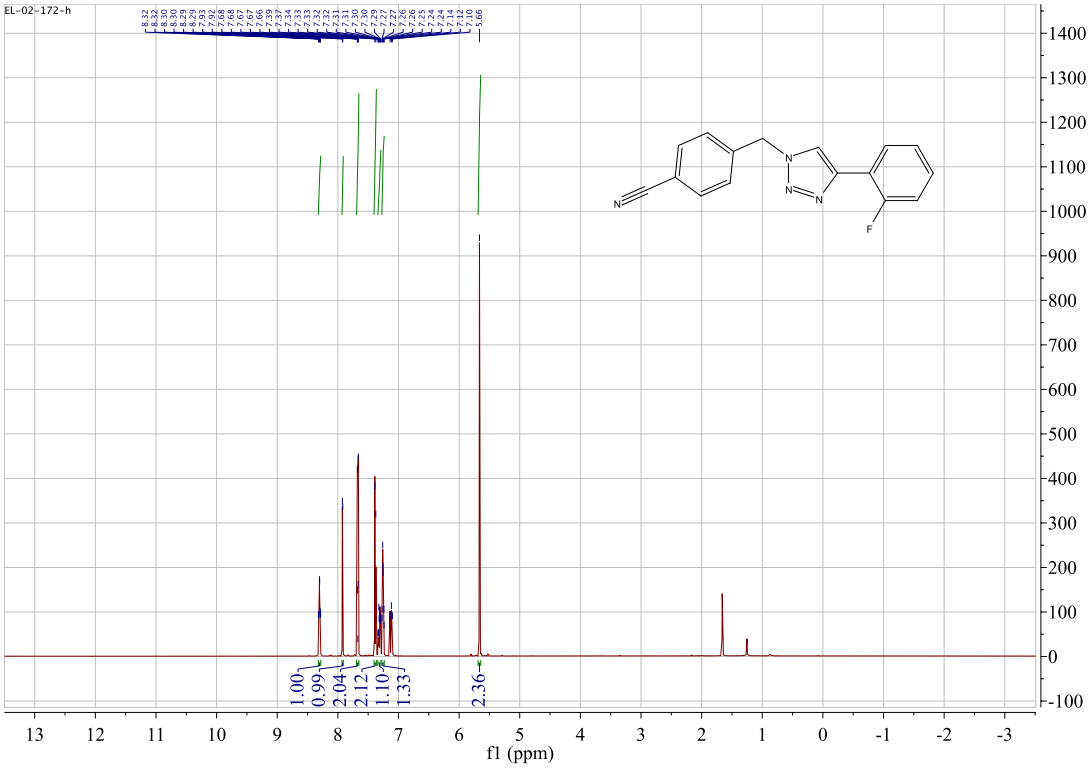
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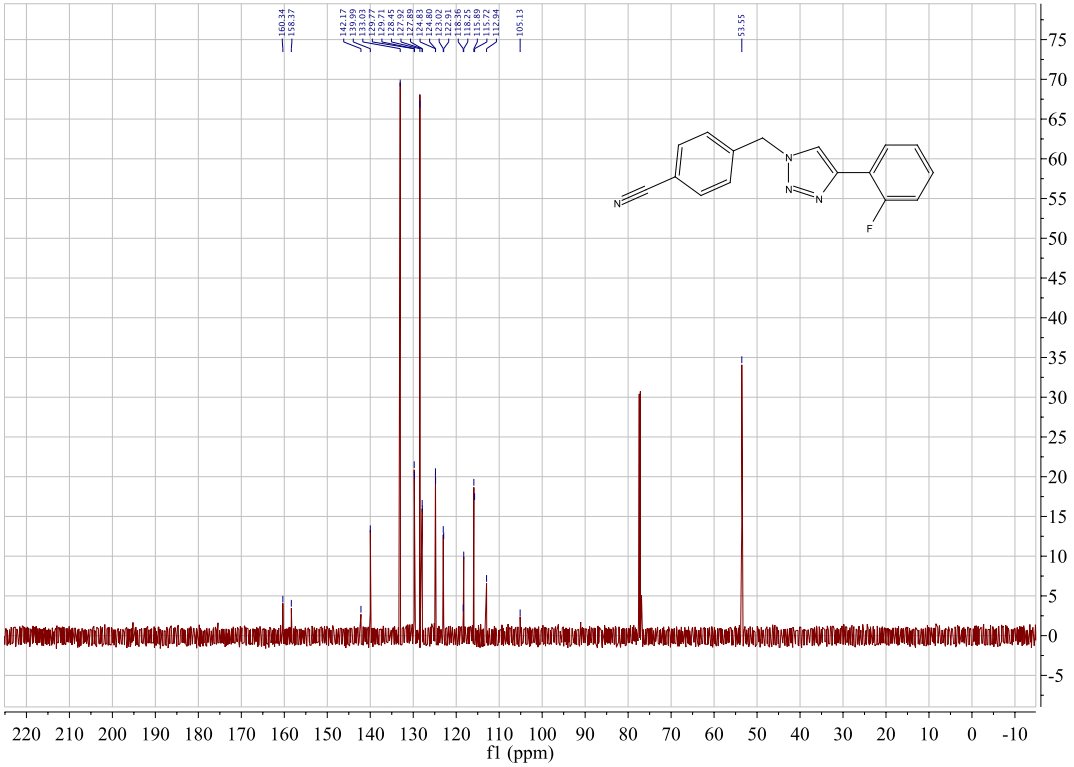
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124.60
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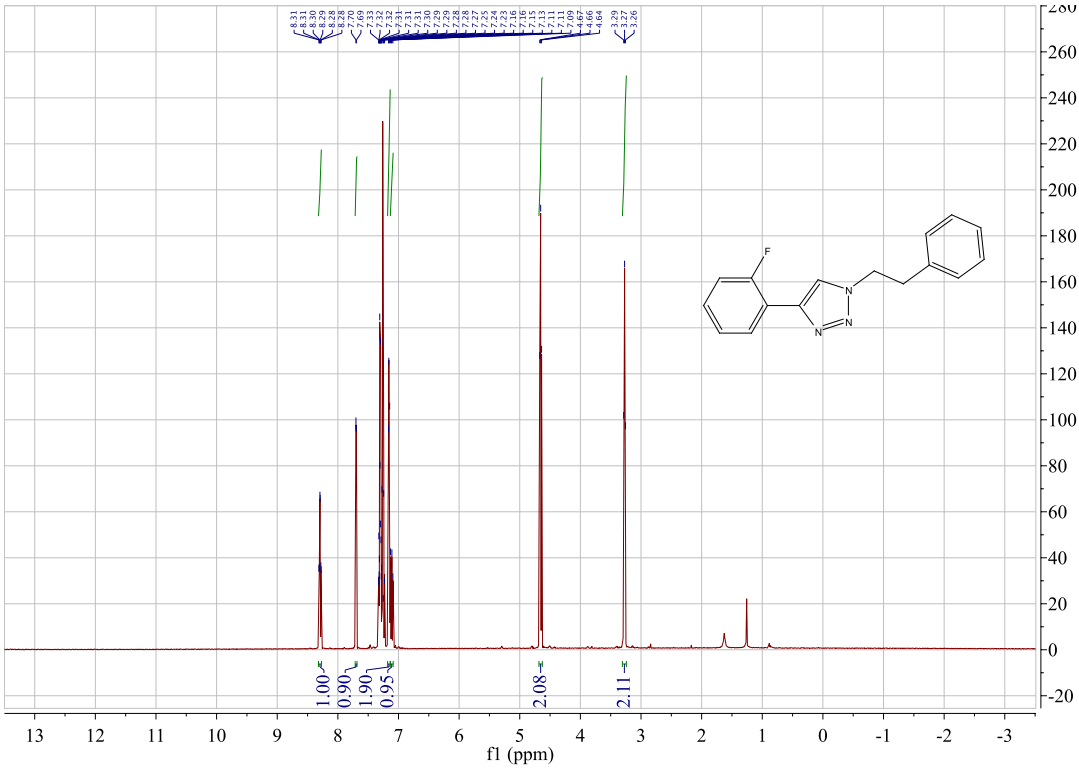
105.13
53.55
N
N
N
F
fl (ppm)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4.67
4.66
4.64
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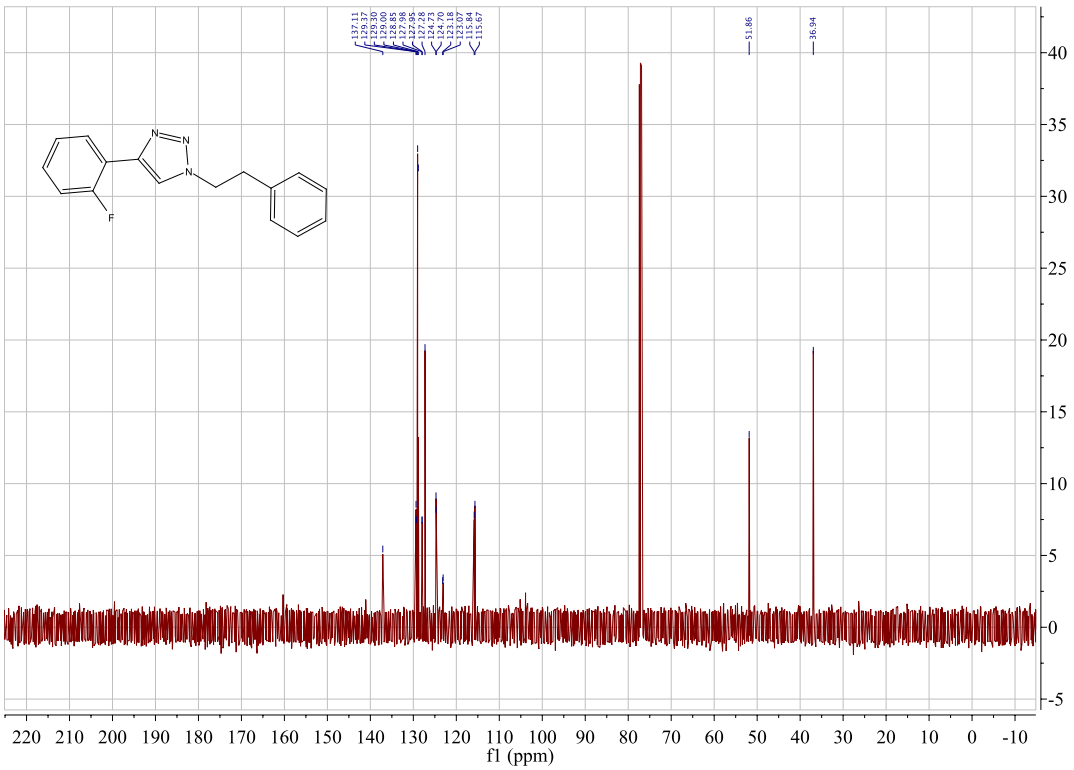
2.11
fl (ppm)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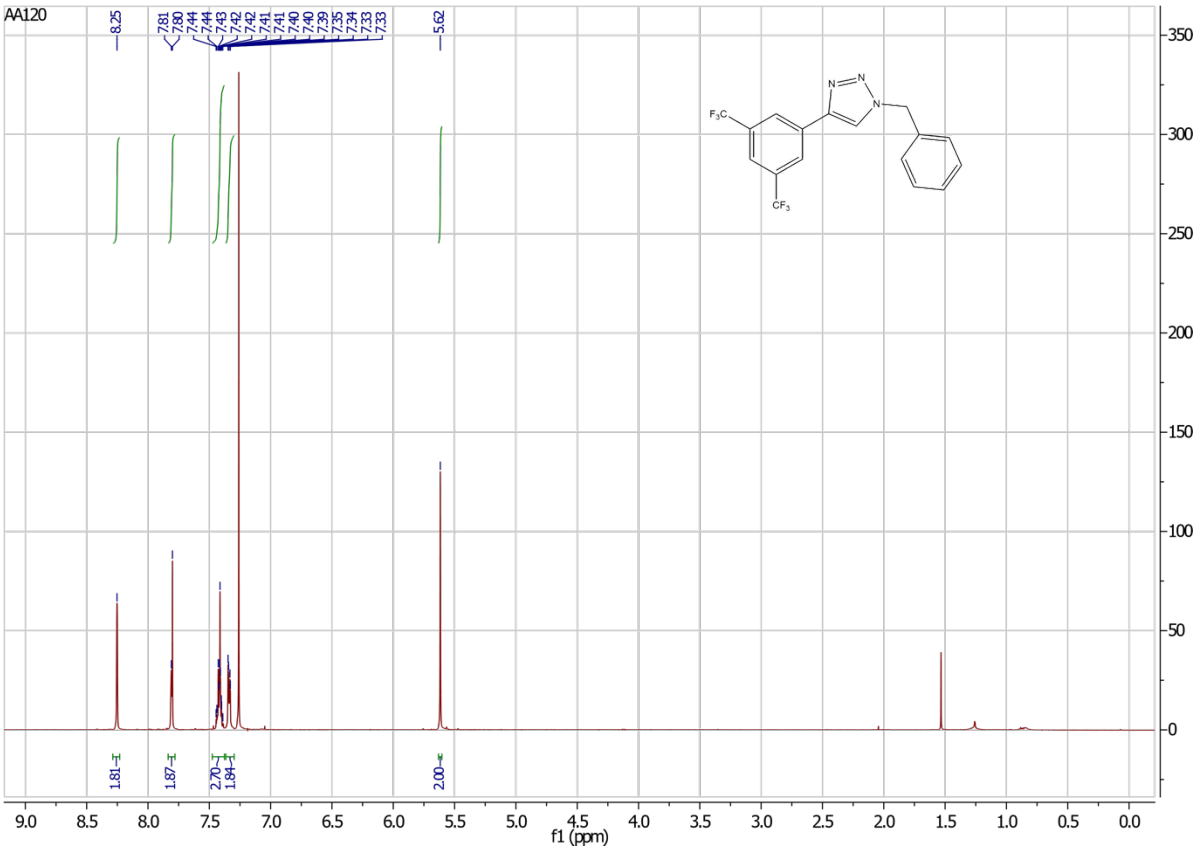
F
f1 (ppm)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CF3
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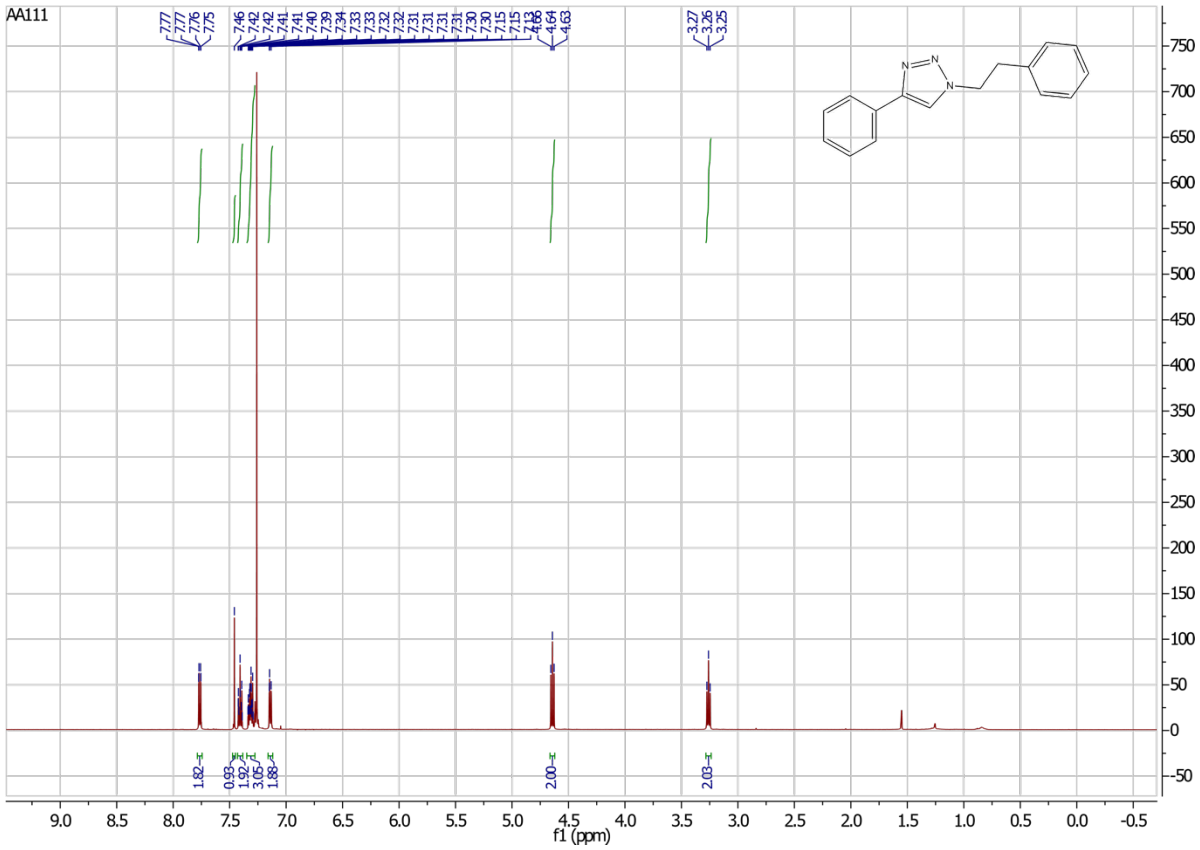
f1 (ppm)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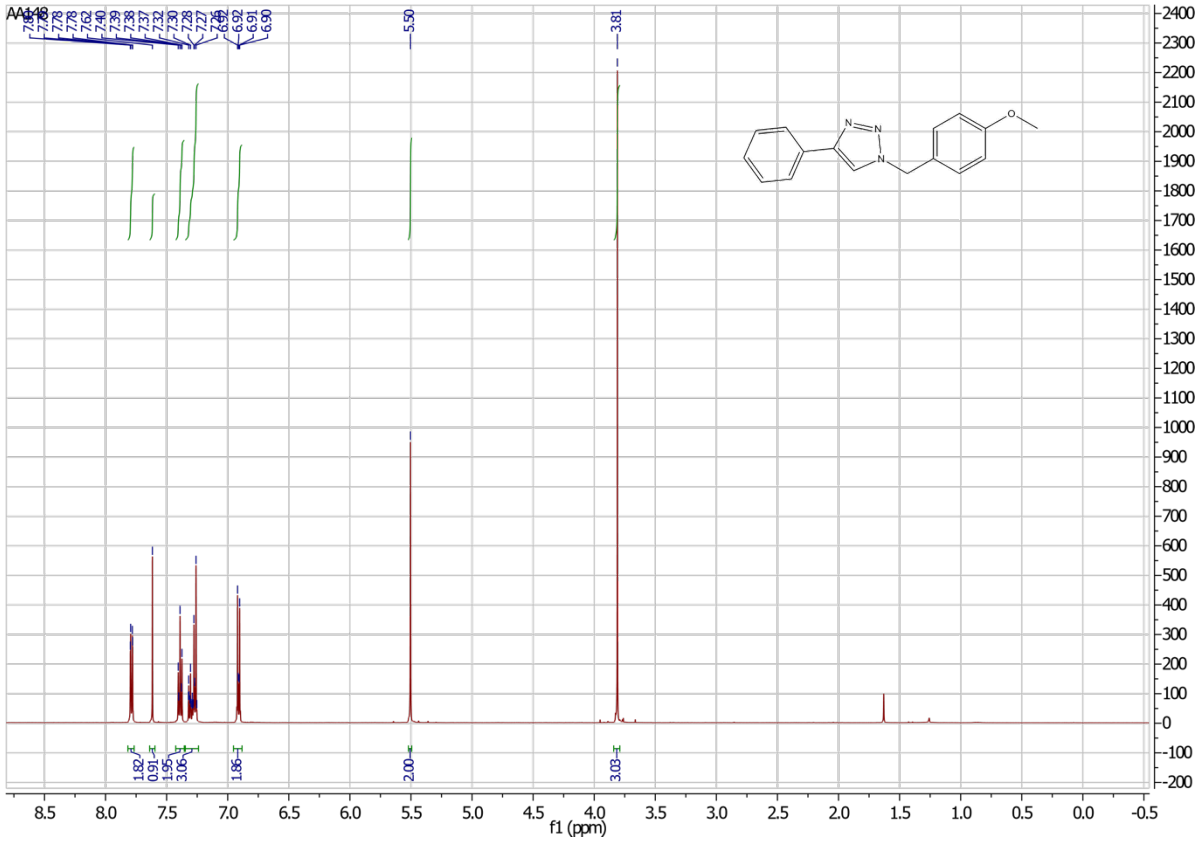
f1 (ppm)


AA148
f1 (ppm)

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