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Silver-Catalyzed Synthesis of Disubstituted Fluorinated Isoxazoles

by
Micah Dean Stewart

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

Oxford
2019

Approved by

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Reader: Professor Susan Pedigo, Ph.D.

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First, I would like to thank Dr. Roy. Her guidance throughout this entire process has helped me get here, and I have learned so much thanks to her. I also want to thank the other members of my committee, Dr. Rowland and Dr. Pedigo.

I am also thankful for the other members of the Roy lab. They have all taught me something and have made my time in the lab such an enjoyable experience. I am especially grateful for Sweta. She's been an amazing mentor and has always been there to answer my many questions, and I could not have made it without her.

Lastly, I want to thank my friends and family, who have supported me throughout this entire process and helped motivate me on my worst days. Your support means more than you all can ever know.

ABSTRACT

The presence of fluorine can provide organic compounds with useful biological properties, such as increased metabolic stability and drug uptake. Because of these advantages, fluorinated compounds make up about 30% of the drug industry. However, fluorination of complex molecules is difficult due to fluorine's high electronegativity.

Fluorinated isoxazoles are of particular interest in the pharmaceutical industry. Isoxazoles are five-membered heterocycles with oxygen and nitrogen in the 1, 2 positions that are able to engage in interactions unavailable to other ring structures, conferring advantageous biological properties upon compounds containing them. However, there are limited synthetic routes for fluorinated isoxazoles, and those that have been reported in the past have poor yields and require harsh conditions.

In 2014, a gold-catalyzed cyclization-fluorination of O-methyl oximes to produce fluorinated isoxazole was reported. The goal of this project was to test synthetic routes of fluorinated isoxazoles that require less expensive materials, focusing on the synthesis of 4-fluoro-3,5-disubstituted isoxazole via a silver-catalyzed cyclization.

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LIST OF ABBREVIATIONS

AgBF ₄	tetrafluoroborate
CuI	copper(I) iodide
EtOH	ethanol
equiv.	equivalent
h	hour
H ₂ SO ₄	sulfuric acid
L	ligand
MeCN	acetonitrile
NH ₂ OH HCl	hydroxylamine hydrochloride
n.o.	not observed
Nu	nucleophile
Pd	palladium
Pd(Ph ₃) ₂ Cl ₂	bis(triphenylphosphine)palladium(II) chloride
Py.Cl ₂ .F	2,6-dichloro-1-fluoropyridiniumtetrafluoroborate
rt	room temperature
TEA	triethylamine
THF	tetrahydrofuran

Chapter 1: Introduction & Background

Section 1.1 – Fluorine in Medicinal Chemistry

Characteristics of Fluorine

Fluorine is becoming increasingly important in medicinal chemistry. Today, around 25% of pharmaceutical drugs in the United States contain fluorine, due to the number of unique properties fluorine possesses¹.

The Van der Waals radius of fluorine is 1.47 Å, similar to hydrogen's, which is 1.20 Å². This allows fluorine to act as a substitute for hydrogen while causing minimal steric hindrance, making it a bioisostere of hydrogen². Because the size and conformation of the molecule is preserved, the biological activity of the compound is retained². This makes fluorine an important substitute in pharmaceuticals, due to the number of hydrocarbons available in organic drug compounds².

Fluorine is the most electronegative atom, with a value of 3.98 on the Pauling Electronegativity Scale, compared to 2.20 for hydrogen, 2.55 for carbon, and 3.44 for oxygen². This causes fluorine to change the pK_a of nearby functional groups, which can alter the bioavailability, kinetics, and binding affinity of fluorinated compounds². These alterations can then lead to changes in the toxicity, potency, and selectivity of the compound². For example, adding fluorine to compounds containing basic polar amines can reduce the effects of the amine's lone pairs due to its strong electron withdrawing properties². Because overly basic and polar amines can decrease a drug's ability to permeate cell membranes, adding fluorine can increase bioavailability, making the drug more effective².

Fluorine's high electronegativity also affects its bonding capabilities with carbon. Bonds between carbon and fluorine are short in length and very stable with a bond energy of 116 kcal/mol³. For comparison, carbon-hydrogen bond energy is 99 kcal/mol³. Because carbon-

fluorine bonds have an increased oxidative and thermal stability, they cannot be metabolized as quickly as carbon-hydrogen bonds³. This decreased metabolism allows more time for drug uptake³.

Bond	Bond Length (Å)	Bond Dissociation Energy (kcal/mol)
C-H	1.09	99
C-F	1.39	116
C-OH	1.43	85

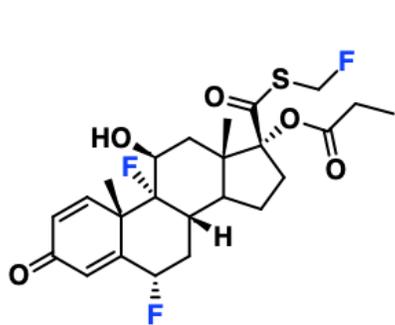
Table 1. Physicochemical properties of the carbon-fluorine bond compared to other C-X bonds³

Addition of fluorinated functional groups can either increase or decrease lipophilicity depending on the structure, and therefore affect the partitioning of a drug into membranes as well as hydrophobic interactions with specific binding sites³. For example, when fluorine replaces a hydrogen atom in a benzene molecule, lipophilicity is increased moderately, and when replaced with a trifluoromethyl group, it increases significantly³. Increased lipophilicity leads to increased receptor activity in the lipid bilayer of the cell membrane, allowing for increased drug uptake³. If a drug is too hydrophilic, the drug will be readily absorbed at the small intestine but cannot be delivered to the cell³. If a drug is too lipophilic, it will not be absorbed well and therefore be unable to reach the cell³. This characteristic is known as bioavailability and must be balanced to properly administer a drug to a target cell³. Adding fluorine to a structure can help achieve the desired level. An important class of fluorine-containing drugs that have gained prominence is the selective serotonin reuptake inhibitors (SSRIs). Of the most widely used drugs in this class, only one, sertraline, does not contain a fluorine atom, and it has the shortest half-life of the SSRIs and is absorbed the most slowly³. These properties may all be attributed to the lack

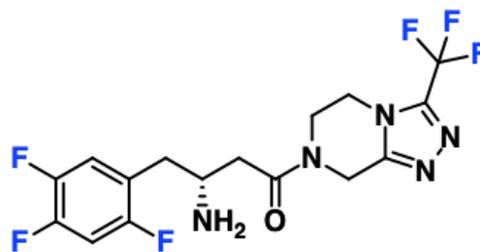
of fluorine, demonstrating just how useful the addition of fluorine is in controlling drug metabolism³.

Integrating fluorine into compounds also provides improved metabolic stability against oxidation enzymes in the liver³. Drugs administered orally are transported immediately from the small intestine to the liver where they are oxidized, but substitution of hydrogen for fluorine in compounds prevents the degradation of the drug via oxidative attack³. This is due to the strength of the carbon-fluorine bond, which allows for resistance against enzyme degradation³. Thus, the drug's structure is preserved, increasing its half-life. The incorporation of fluorine into a compound can also prevent toxic or "non-productive" metabolism, making the drug safer³.

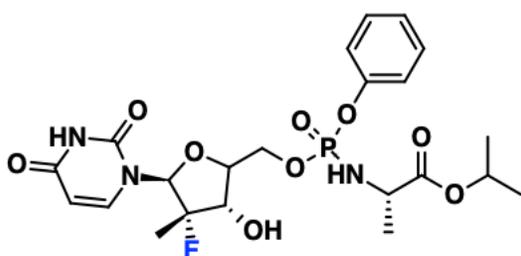
Due to these characteristics, fluorine is playing an increasingly important role in drug discovery. According to a 2015 survey, several drugs containing fluorine were among the most-prescribed and/or profitable in the pharmaceutical market⁴. In fact, four of the top ten best-selling name brand drugs in 2015, (Crestor, Sovaldi, Advair, Januvia) contained at least one fluorine atom⁵. These drugs, which made \$19.6 billion in 2015, contain a wide array of functions⁵. Crestor is a member of the statin family, used in the treatment of high cholesterol⁵. Sovaldi is used to treat hepatitis C⁵. Advair is an oral inhaler used to treat asthma and pulmonary disease, and Januvia is an antidiabetic drug that makes more insulin available for the body to use⁵. This wide range of uses shows the diversity of fluorine in pharmaceuticals.



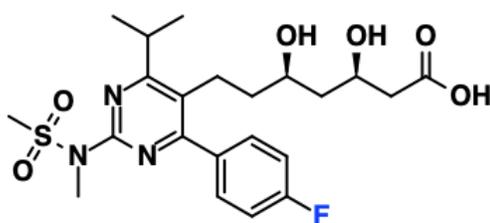
Advair



Januvia



Sovaldi



Crestor

Figure 1: Examples of fluorine-containing pharmaceuticals⁴

Limitations in Drug Design

Even though fluorine plays such an important role in the pharmaceutical industry, there are several restrictions in the synthesis of fluorinated drugs. Many of the conventional fluorination reactions developed in the early twentieth century are limited only to simple molecules, so fluorination of complex molecules at certain locations is challenging⁶. Additionally, only a few fluorinating enzymes have been found, making it very rare in nature⁶. Because of this, chemists are working to develop synthetic routes to integrate fluorine into organic compounds⁶. However, synthetic methods for fluorinating compounds also present challenges, one being that the reactivity of fluorine is limited by its electronegativity⁶. The electrons around fluorine are strongly attracted to its nucleus, making it unlikely for them to form

a bond with another atom⁶. Fluorine is also able to form strong hydrogen bonds, making it a weak nucleophile in the presence of hydrogen donors⁶. This makes it difficult to perform nucleophilic substitution reactions that replace hydrogen atoms with fluorine⁶. Fluoride is a better nucleophile when hydrogen-bond donors are excluded, but it is also basic, which can lead to undesired side reactions⁶.

Section 1.2 – Isoxazoles in Medicinal Chemistry

Isoxazoles are five-membered aromatic heterocycles with oxygen and nitrogen in the 1, 2 positions⁷. They exhibit a large range of biological properties, including anti-cancer, anti-convulsant, anti-Alzheimer, anti-diabetic, anti-viral, immune-modulatory, and analgesic (Figure 2)⁸. These beneficial properties have led to isoxazoles becoming the focus of many medicinal chemistry studies in recent years⁷. Isoxazole rings are present in a large number of pharmaceuticals, contributing to their biological activity due to the presence of its two electronegative atoms in a 1,2-relationship⁹. These atoms are able to engage in hydrogen bond donor/acceptor interactions with a variety of compounds unavailable to other ring structures, allowing the compound to display useful properties it would otherwise not possess⁹.

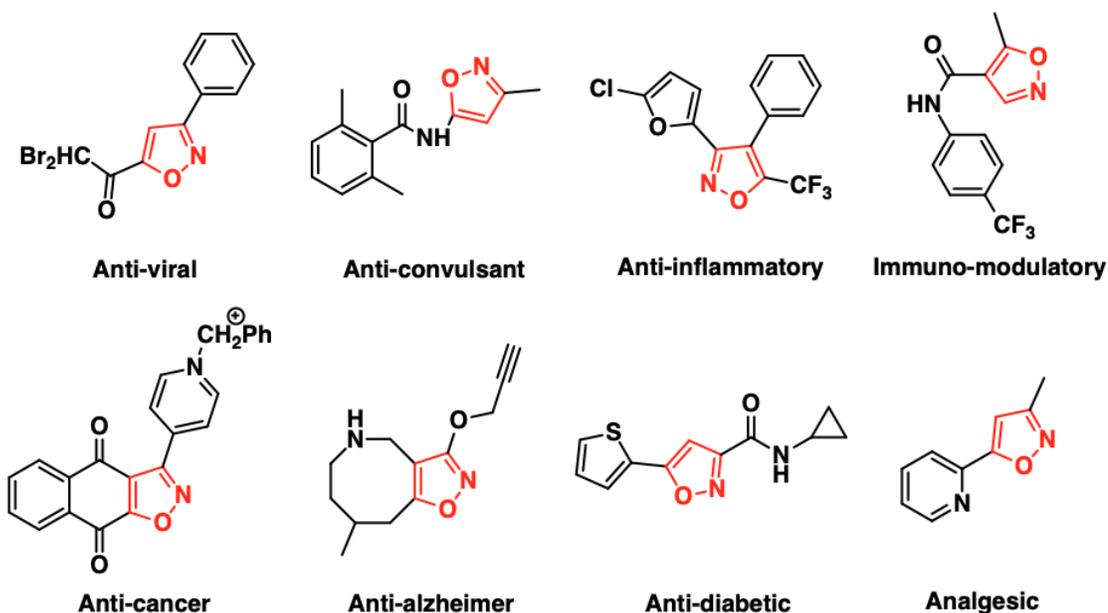


Figure 2: Examples of drugs containing isoxazole rings⁸

Isoxazole Synthesis Methods

Several synthetic routes have been developed to construct isoxazole core structures. Examples include the [3 + 2] cycloaddition of alkynes/alkenes and nitrile oxides, intermolecular cyclization of α,β -unsaturated oximes, intermolecular cyclization of oximes with C-C double/triple bonds, and palladium-catalyzed reactions⁹. However, synthetic routes for fluorinated isoxazoles in particular are limited due to the difficulty caused by direct fluorination⁹. Reported synthetic routes often have poor yields and require harsh conditions¹⁰. The past representative route for the synthesis of fluoroisoxazoles involves the condensation of 2-fluoro-1,2-diketone and hydroxylamine·HCl in EtOH/ H_2SO_4 ¹⁰. This route suffers from a poor yield and needs strongly acidic conditions¹⁰. Another route involves electrophilic fluorinating reagents, but the reaction is sluggish and requires ever harsher reaction conditions such as reflux in sulfolane¹⁰. This also results in low yields (28-39%) and trifluorinated byproducts¹⁰. These

pathways are shown in Figure 3. Due to the importance of fluorine and isoxazoles in pharmaceuticals, the need for a practical synthetic route of fluorinated isoxazoles is crucial.

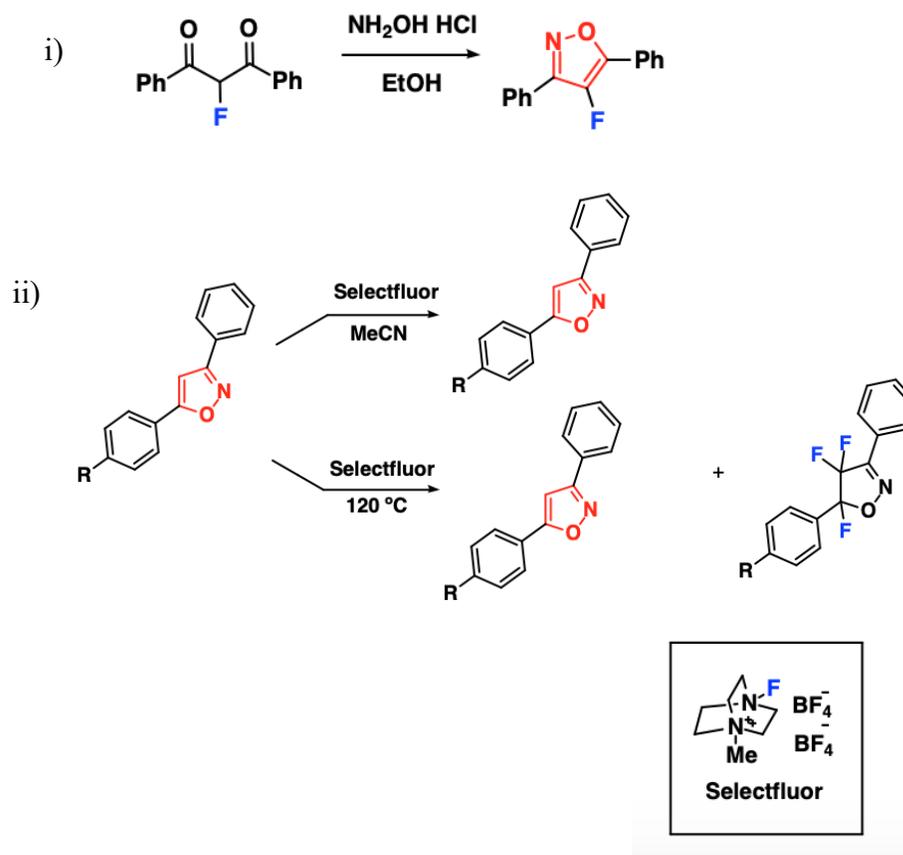


Figure 3: Reaction schemes for the synthesis of fluorinated isoxazoles¹⁰

Chapter 2: Results and Discussion

Section 2.1 – Hypothesis

A gold-catalyzed cyclization-fluorination of O-methyl oximes to form fluorinated isoxazoles was reported in 2014 (Figure 4)¹⁰. Our lab hoped to discover an alternative route to produce fluorinated isoxazoles using a less expensive catalyst.

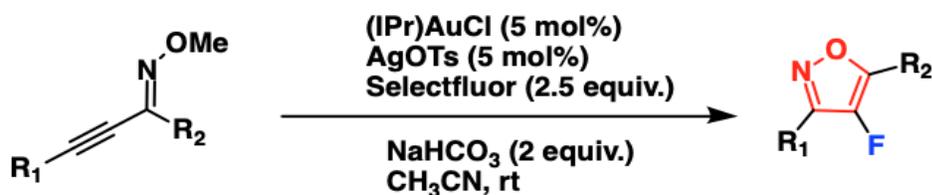


Figure 4: Synthesis of 4-fluoroisoxazole via gold catalysis¹⁰

A silver-catalyzed synthesis of disubstituted isoxazoles via cyclization of alkynyl oxime ethers was recently reported¹¹. Using this report, our lab previously hypothesized that silver(I) is able to activate the carbon-carbon triple bond found in oxime and cyclize to form an oxonium intermediate. When an electrophilic fluorinating source is added, the silver is eliminated, and fluorinated isoxazole is produced, as shown in Figure 4. For preliminary investigation, our lab chose (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime as a model substrate to carry out the cyclization reaction with. Preliminary results showed that carrying out the reaction in the presence of AgBF₄ and Py.Cl₂.F, stirring in MeCN in an inert atmosphere at 80 °C for 48 hours led to decent yields of fluorinated isoxazole and a protonated isoxazole byproduct. We decided to use this preliminary data to optimize the reaction.

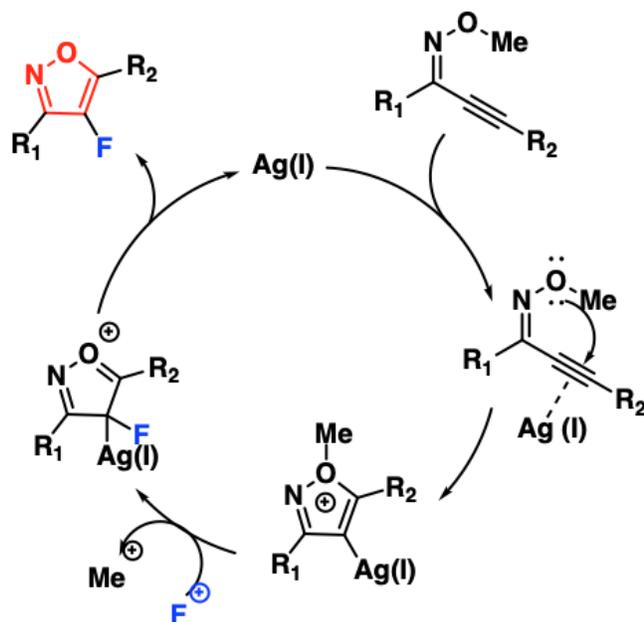


Figure 5: Silver-catalyzed synthesis of 4-fluoro disubstituted isoxazole

Section 2.2 – Ynone Synthesis

The Roy lab previously found that the cyclization reaction of the model substrate (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime could produce a fluorinated isoxazole. However, a protonated isoxazole was also formed as a by-product. The goal of this experiment was to produce the oxime substrate previously used and then further optimize the cyclization reaction previously reported. However, an ynone starting material had to first be prepared, from which the oxime substrate could be formed.

The first reaction involved the preparation of an ynone via palladium/copper catalyzed Sonogashira coupling of a terminal acetylene and acid chloride. The palladium-catalyzed Sonogashira reaction is a very useful method for creating new bonds starting from alkynyl halides and terminal alkynes and is widely used for synthesizing acetylenic ketones, such as

ynones, that act as building blocks for the synthesis of pharmaceuticals and other organic materials¹². Because acyl chlorides oxidatively add to Pd(0) species, forming a Pd(II) intermediate, it is possible to intercept this species with a nucleophile, as shown in Figure 4¹³.

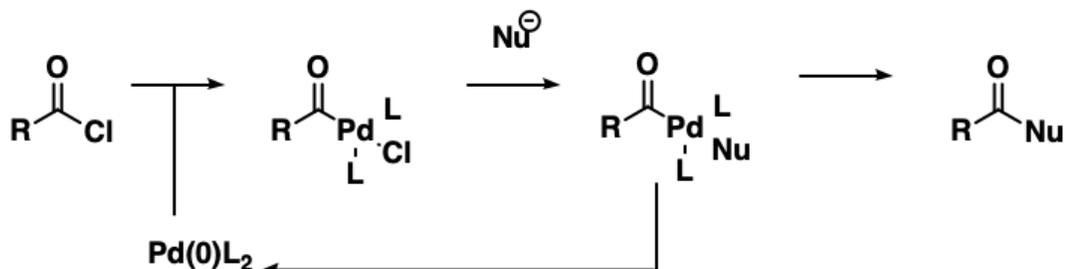


Figure 6: Sonogashira coupling reaction

In Sonogashira reactions terminal alkynes are activated as nucleophiles using a CuI catalyst under basic conditions¹². A large range of functional groups on the acetylene are compatible with this reaction¹². Alkyl, ester, and protected amino groups in particular give isolated products in high yields¹².

Three separate reactions were run at room temperature for 24 hours. The resulting product was 1-phenyl-3-(p-tolyl)prop-2-yn-1-one, and the obtained product was a dark brown solid. The results are shown in Table 2.

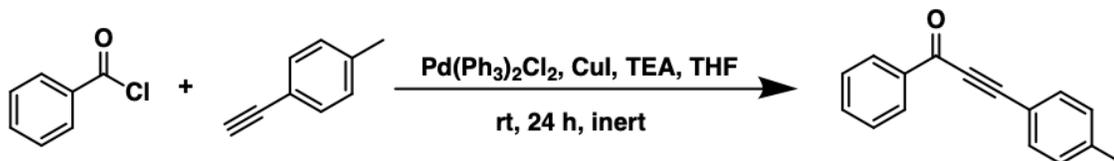


Figure 7: Ynone Synthesis Scheme

Table 2: Ynone synthesis results

Entry	Temperature	Time (h)	Yield (%)
1	rt	24	77.3
2	rt	24	36.72
3	rt	24	37.10

Section 2.3 – Oxime Synthesis

The second step of the project involved preparation of the *O*-methyl oxime substrate by stirring the prepared ynone in the presence of methoxylamine hydrochloride, pyridine, and Na₂SO₄ at room temperature, with methanol acting as the solvent.

Three separate reactions were run at room temperature for 26 hours. The resulting product was (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime, and the obtained product was a yellow oil. The results are shown in Table 3.

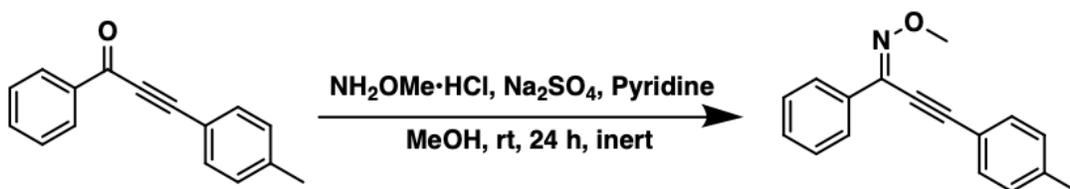


Figure 8: Oxime Synthesis Scheme

Table 3: Oxime synthesis results

Entry	Temperature	Time (h)	Yield (%)
1	rt	26	16.9
2	rt	26	15.7
3	rt	26	39.31

Section 2.3 – Optimization

The cyclization reaction with oxime was previously carried out in the presence of 1 equivalent of AgBF_4 and $\text{Py}\cdot\text{Cl}_2\cdot\text{F}$, while stirring in MeCN at 80 °C for 48 hours. Results showed that this produced a mixture of fluorinated isoxazole and protonated isoxazole in 45% and 32% respectively. The goal of this experiment was to repeat these conditions and then further optimize the synthesis reaction with other catalysts.

In this experiment, the standard reaction conditions included 1 equivalent of oxime, 2 equivalents of $\text{Py}\cdot\text{Cl}_2\cdot\text{F}$. The silver catalyst equivalence varied however. The results are shown in Table 4.

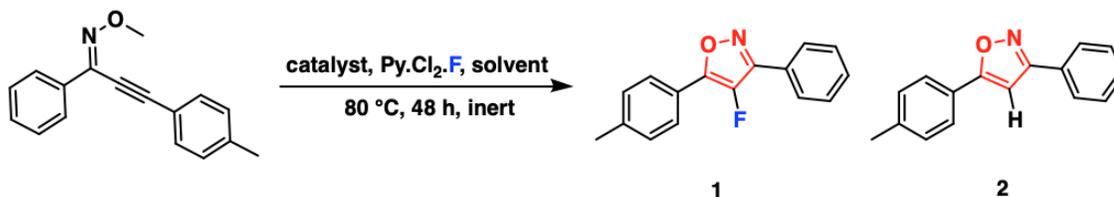


Figure 9: Synthesis of 4-fluoro disubstituted isoxazole

Table 4: Optimization for silver catalyzed synthesis of 4-fluoro isoxazole

Entry	Temperature (°C)	Ag Catalyst, equiv.	Solvent	Yield, 1 (%) ^[a]	Yield, 2 (%)
1	80	AgBF ₄ , 1	MeCN	n.o.	n.o.
1	80	AgBF ₄ , 2	MeCN	n.o.	n.o.

[a] isolated yield n.o.: not observed

Section 2.5 – Conclusion

Neither our desired product nor its protonated by-product were observed in either of the optimization reactions. In previous reactions done in our lab, these reactions were performed in an inert atmosphere. However, we were not able to replicate these conditions due to broken equipment, which may have affected the results.

We were in the process of determining the cause of these results when our work was cut short due to the COVID-19 pandemic. However, the optimization of this reaction will be continued in our laboratory using previous results from the silver-catalyzed cyclization-fluorination of (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime to yield fluorinated isoxazole.

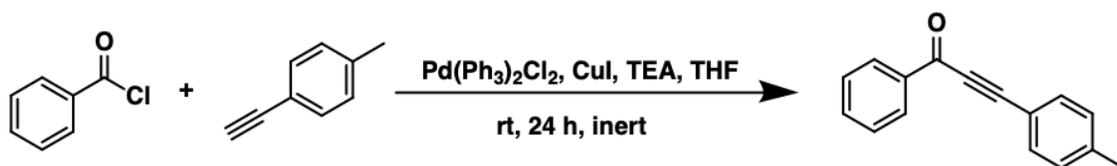
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Supplemental Information

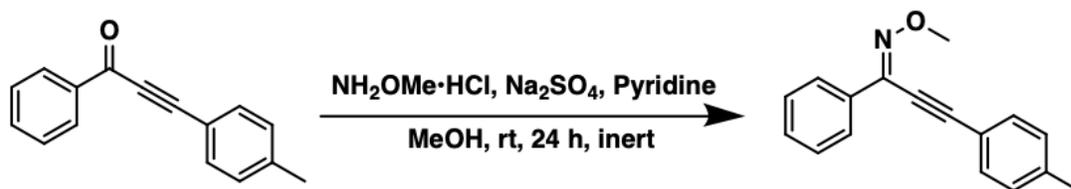


- (1) A reaction tube with a magnetic stir bar containing 24.6 mg copper(I) iodide (0.10 equiv.) and 45.4 mg bis(triphenylphosphine)palladium(II) chloride (0.05 equiv.) was degassed and back filled with argon three times. 363 mg benzoyl chloride (2 equiv.) was dissolved in 2 mL THF and added to the mixture. Then 150 mg 1-ethynyl-4-methylbenzene (1 equiv.) was dissolved in 0.54 mL Et₃N (3 equiv.), added dropwise. 1.5 mL THF was then added to the reaction vial. The vial was then stirred at 25 °C for 24 hours. After completion of reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate in a separatory funnel. After the layers were separated, the organic phase was dried over anhydrous Na₂SO₄ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The product was a dark brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.23 (m, *J* = 7.7 Hz, 2H), 7.61 (dd, *J* = 15.2 Hz, 3H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H).

- (2) A reaction tube with a magnetic stir bar containing 164 mg copper(I) iodide (0.10 equiv.) and 302.1 mg bis(triphenylphosphine)palladium(II) chloride (0.05 equiv.) was degassed and back filled with argon three times. 2.420 g benzoyl chloride (2 equiv.) was dissolved in 12 mL THF and added to the mixture. Then 1000 mg 1-ethynyl-4-

methylbenzene (1 equiv.) was dissolved in 3.6 mL Et₃N (3 equiv.), added dropwise. 11 mL THF was then added to the reaction vial. The vial was then stirred at 25 °C for 24 hours. After completion of reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate in a separatory funnel. After the layers were separated, the organic phase was dried over anhydrous Na₂SO₄ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The product was a dark brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.26-8.23 (m, 2H), 7.63 (dd, *J* = 11.6 Hz, 3H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H).

- (3) A reaction tube with a magnetic stir bar containing 327.9 mg copper(I) iodide (0.10 equiv.) and 604.3 mg bis(triphenylphosphine)palladium(II) chloride (0.05 equiv.) was degassed and back filled with argon three times. 4.841 g benzoyl chloride (2 equiv.) was dissolved in 12 mL THF and added to the mixture. Then 2.0 g 1-ethynyl-4-methylbenzene (1 equiv.) was dissolved in 7.2 mL Et₃N (3 equiv.), added dropwise. 11 mL THF was then added to the reaction vial. The vial was then stirred at 25 °C for 24 hours. After completion of reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate in a separatory funnel. After the layers were separated, the organic phase was dried over anhydrous Na₂SO₄ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The product was a dark brown solid. ¹H NMR (400 MHz, CDCl₃) δ 8.28-8.23 (m, 2H), 7.68-7.6 (dd, 3H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H).

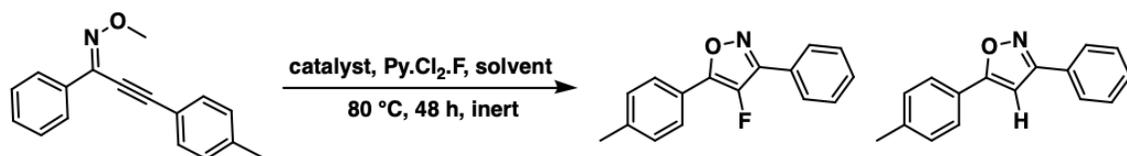


(4) In a reaction vial with a magnetic stir bar, 100 mg 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (1 equiv.), 75.8 mg *O*-methylhydroxylamine hydrochloride (2 equiv.), and 129 mg sodium sulfate (2 equiv.) were dissolved in .5 mL MeOH. 0.073 mL pyridine (2 equiv.) was then added via syringe dropwise over 20 minutes, and the mixture was stirred at room temp for 26 hours. After completion of the reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate in a separatory funnel. The organic layer was then dried over anhydrous Na₂SO₄ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The obtained product was a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (m, *J* = 6.7, 3.0 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.43-7.38 (dd, 3H), 7.20 (d, *J* = 7.8 Hz, 2H), 4.15 (s, 3H), 2.39 (s, 3H).

(5) In a reaction vial with a magnetic stir bar, 500 mg 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (1 equiv.), 379 mg *O*-methylhydroxylamine hydrochloride (2 equiv.), and 645 mg sodium sulfate (2 equiv.) were dissolved in .5 mL MeOH. 0.731 mL pyridine (4 equiv.) was then added via syringe dropwise over 20 minutes, and the mixture was stirred at room temp for 26 hours. After completion of the reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate

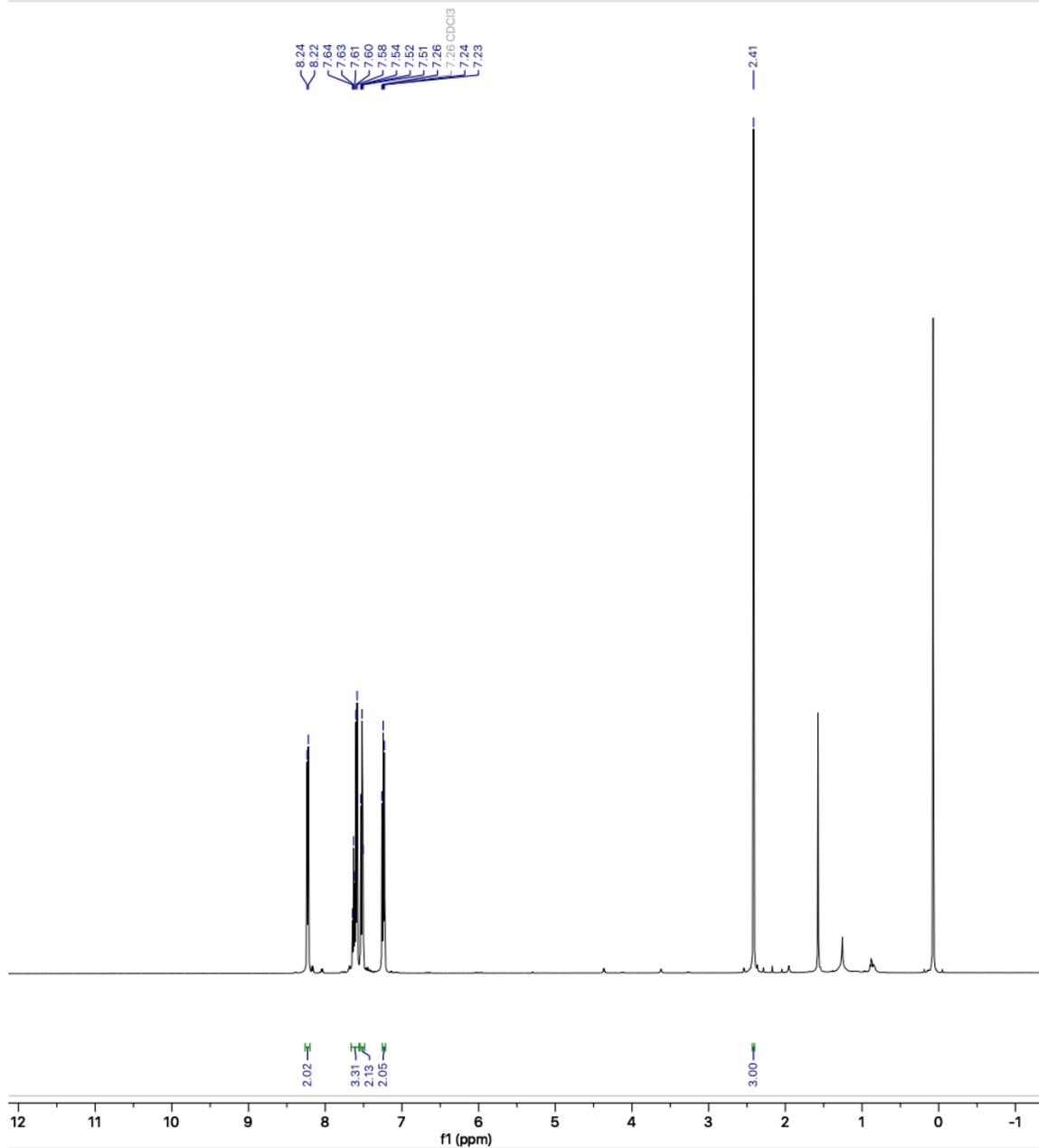
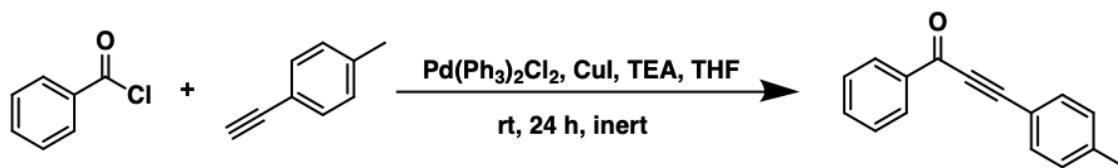
in a separatory funnel. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The obtained product was a yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92 (m, $J = 6.6, 3.0$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 7.42-7.39 (dd, 3H), 7.19 (d, $J = 7.9$ Hz, 2H), 4.14 (s, 3H), 2.39 (s, 3H).

(6) In a reaction vial with a magnetic stir bar, 1000 mg 1-phenyl-3-(p-tolyl)prop-2-yn-1-one (1 equiv.), 758.3 mg *O*-methylhydroxylamine hydrochloride (2 equiv.), and 1.290 g sodium sulfate (2 equiv.) were dissolved in 10 mL MeOH. 1.46 mL pyridine (4 equiv.) was then added via syringe dropwise over 20 minutes, and the mixture was stirred at room temp for 26 hours. After completion of the reaction and confirmation by TLC chromatography, the mixture was quenched with water and extracted with ethyl acetate in a separatory funnel. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent. The obtained product was a yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.95-7.91 (m, 2H), 7.54 (d, $J = 8.1$ Hz, 2H), 7.42 (dd, $J = 6.7, 2.8$ Hz, 3H), 7.21 (d, $J = 7.9$ Hz, 2H), 4.16 (s, 3H), 2.41 (s, 3H).

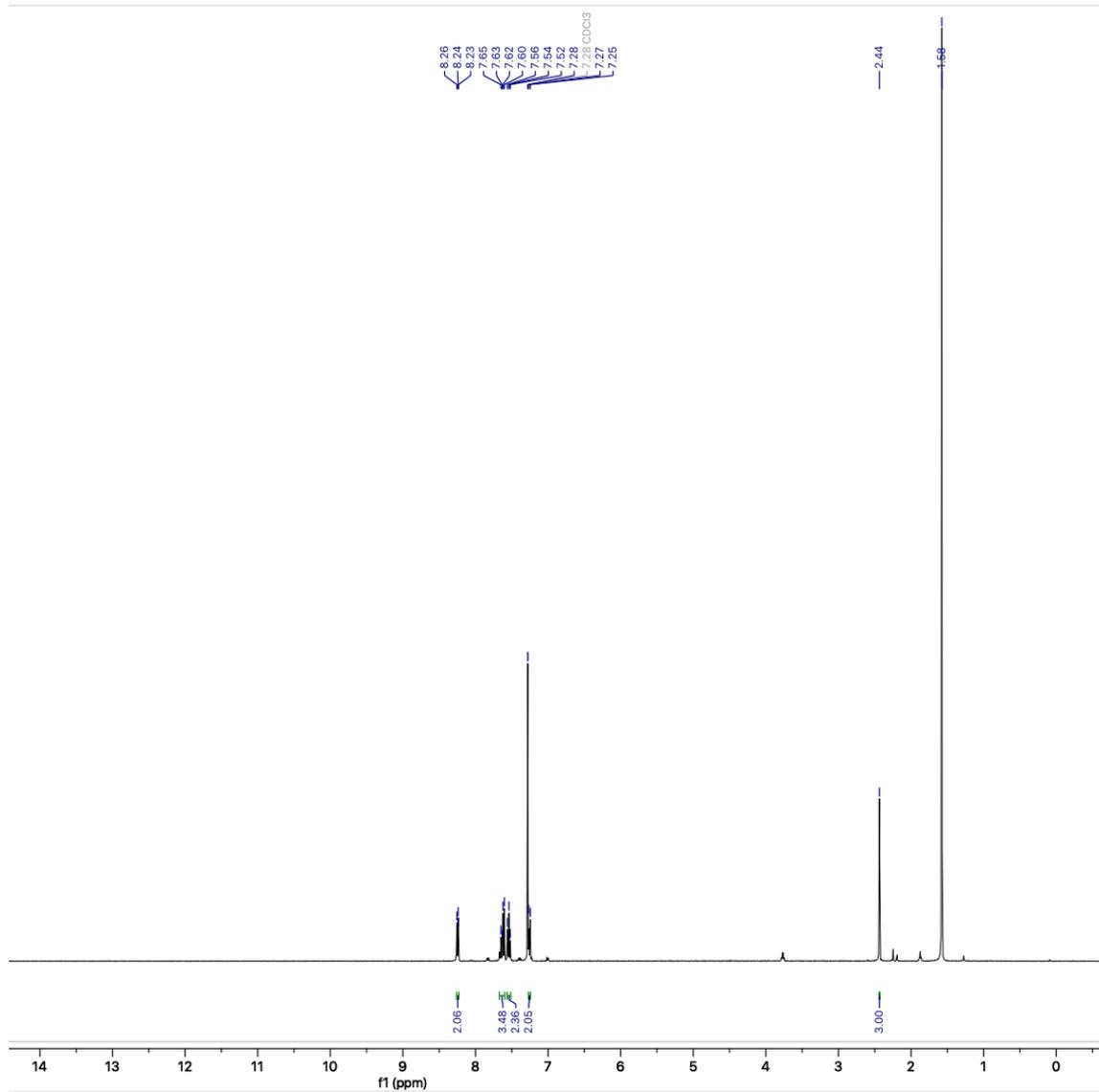
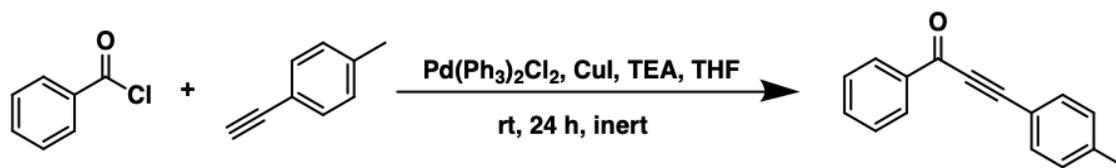


- (7) A reaction vial with a magnetic stirring rod was charged with 30 mg (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime (1 equiv.) and 61 mg 2,6-dichloro-1-fluoropyridin-1-ium tetrafluoroborate (2 equiv.). The reaction vial was then degassed and back-filled with argon three times. 23 mg (Tetrafluoro-15-boranyl)silver (1 equiv.) was then added. After that, 0.3 mL MeCN was added via syringe. The reaction vial was then stirred at 80 °C for 48 hours. ^{19}F NMR (377 MHz, CDCl_3) δ -113.09- -113.18 (m).
- (8) A reaction vial with a magnetic stirring rod was charged with 20 mg (*Z*)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one *O*-methyl oxime (1 equiv.) and 41 mg 2,6-dichloro-1-fluoropyridin-1-ium tetrafluoroborate (2 equiv.). The reaction vial was then degassed and back-filled with argon three times. 31 mg (Tetrafluoro-15-boranyl)silver (2 equiv.) was then added. After that, 0.3 mL MeCN was added via syringe. The reaction vial was then stirred at 80 °C for 48 hours. ^{19}F NMR (377 MHz, CDCl_3) δ -113.06 (d, $J = 8.8$ Hz), -148.94, -149.31 (d, $J = 23.0$ Hz), -149.51, -151.95, -178.34.

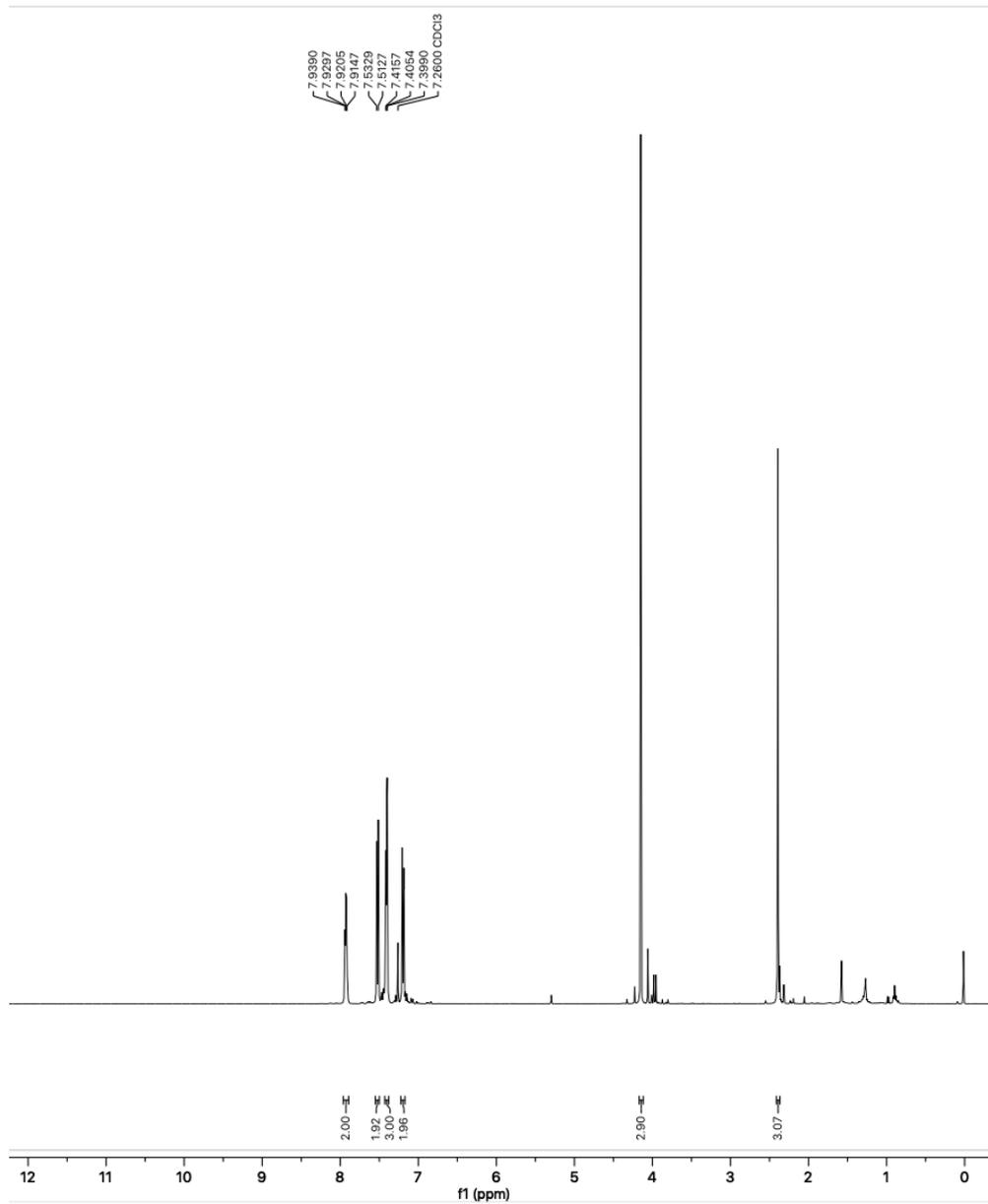
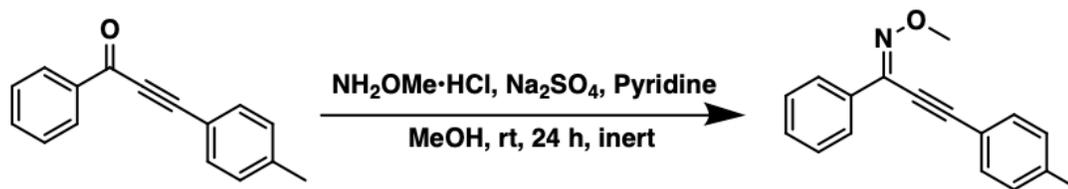
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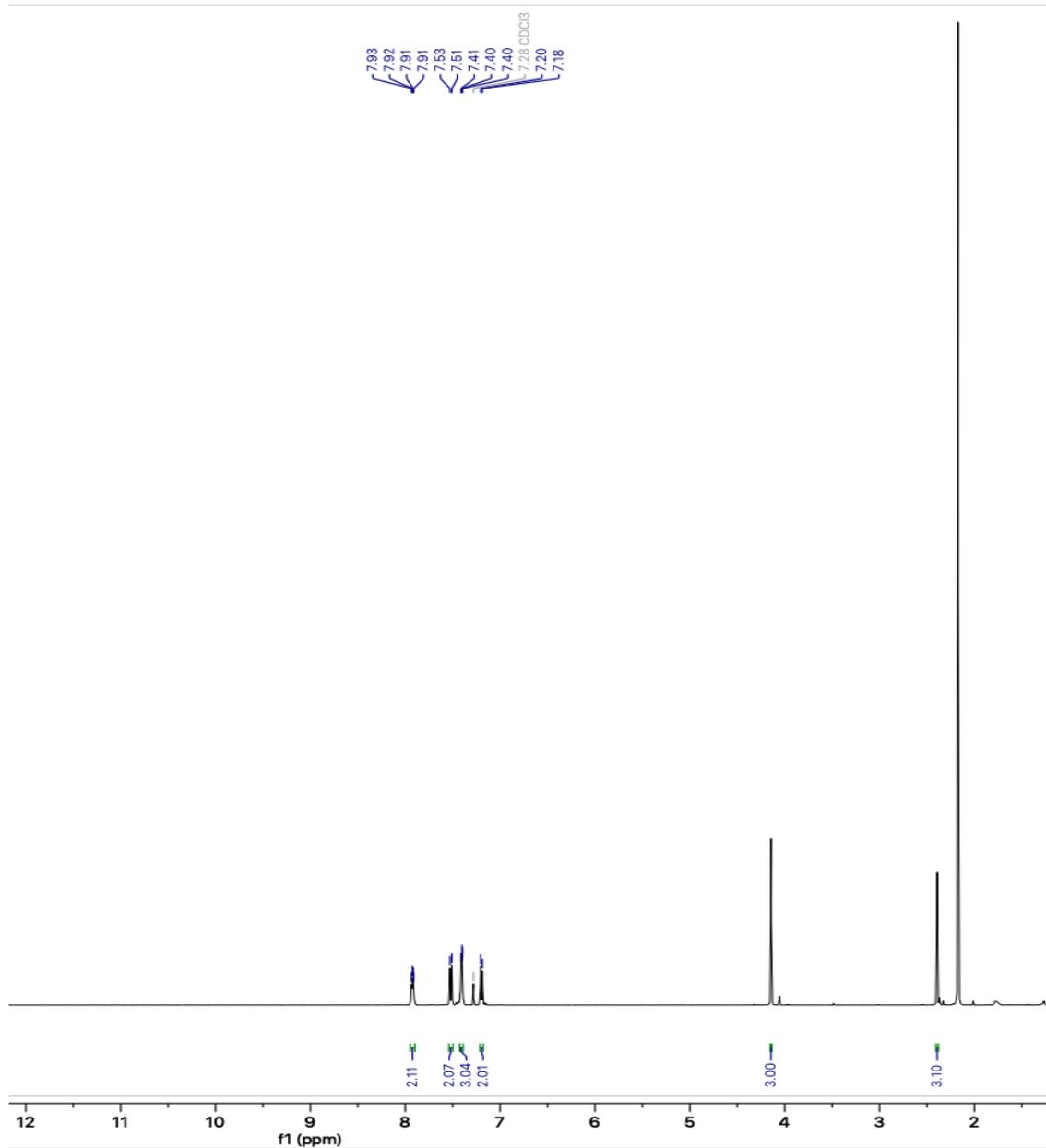
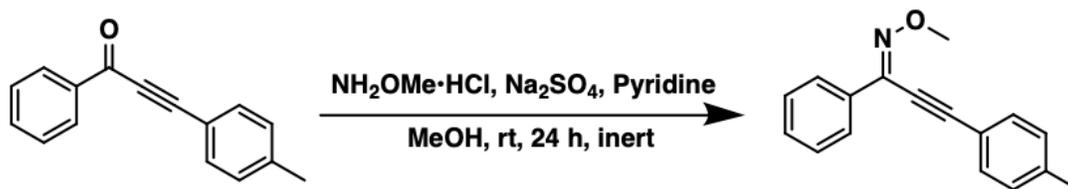
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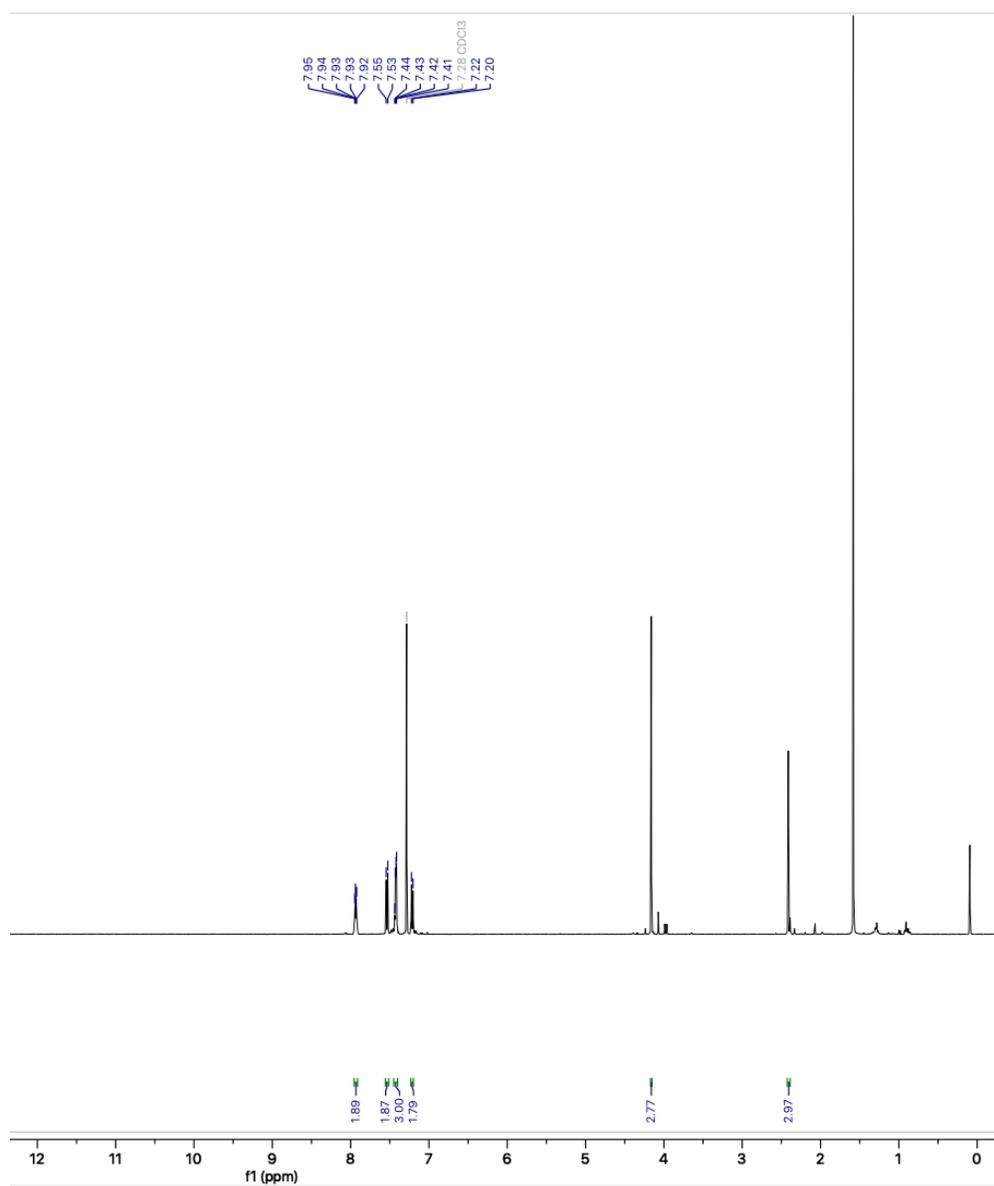
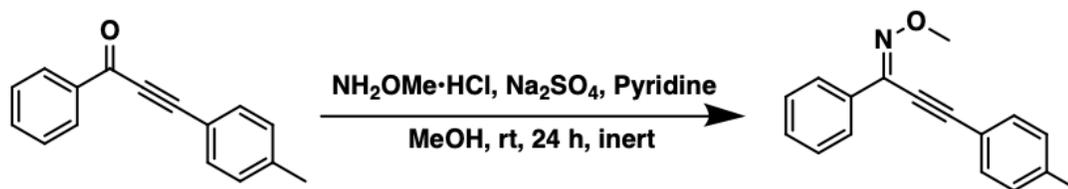
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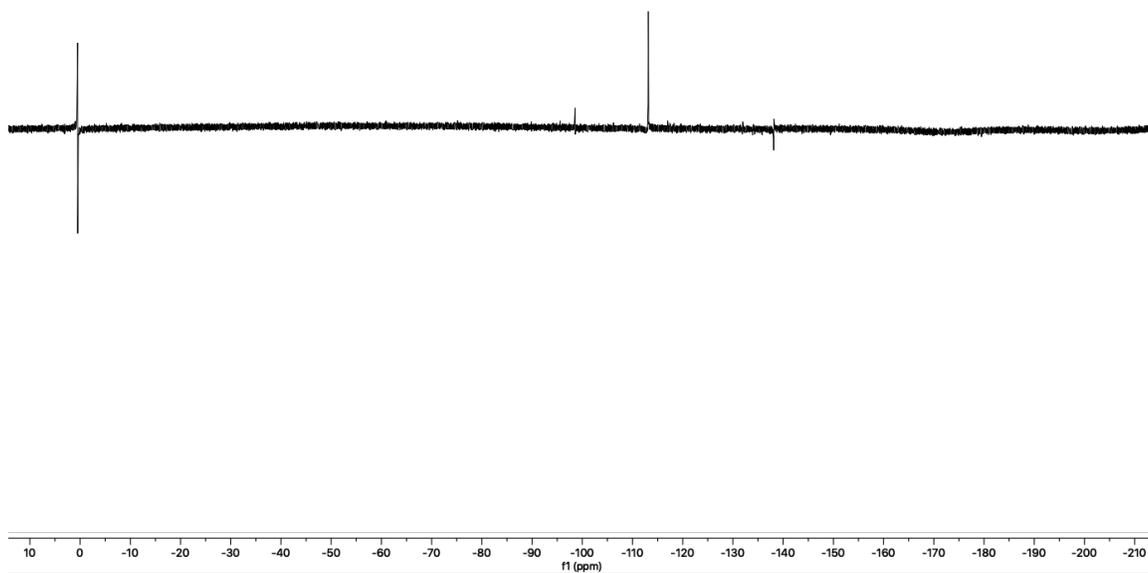
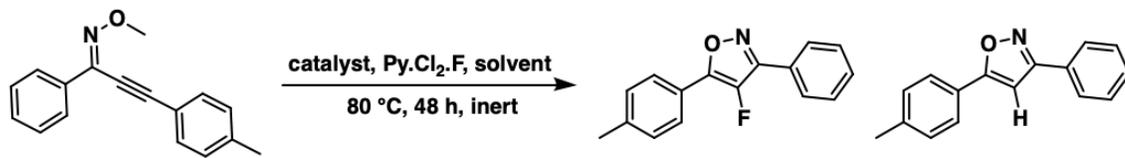
(5)



(6)



(7)



(8)

