Worcester Polytechnic Institute
Department of Chemistry and Biochemistry

Palladium-Catalyzed Non-Directed C-H Amination of Arenes

A Major Qualifying Project submitted for review to the faculty of
WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the
Degree of Bachelor of Science

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Abstract

Aromatic C-N bonds can be found in the chemical structures of many pharmaceuticals on the market today. Devising more direct synthetic routes to these functionalities could be highly beneficial to the pharmaceutical industry by making some syntheses more efficient than when approached from a classical organic standpoint. Most biologically active molecules are larger and more functionally diverse than common laboratory reagents, so formation of aromatic C-N bonds can become difficult in the later stages, especially when harsh chemical methods are used. Though there exist synthetic routes that do not utilize harsh conditions, most examples require the prefunctionalization of a substrate or the conversion of the installed functional group after the fact; both cases are not desirable in late-stage functionalization applications. This project focuses on the development of a catalytic system for the direct conversion of aromatic C-H bonds to aromatic C-N bonds that does not require the prefunctionalization of the substrate and also avoids conditions too harsh for large molecules. Additionally, this project seeks to install functional groups useful in biologically active molecules to eliminate the need for further conversion. Finally, this project aims at demonstrating the versatility of this system, investigating reactions done on a variety of substrates and installing a variety of functional groups.

Acknowledgements

I would like to thank Dr. Marion Emmert for guiding me through this project and pushing me to become a better researcher. I would also like to thank Dr. H.M. Dhammika Bandara, without whose help I surely would not have made it through the first term, and his current absence is quite noticeable. Additionally, I would like to thank Mark Mantell who has been helping me invaluably this past semester. Finally, I would like to thank the entirety of the Emmert lab for being excellent help and company in the lab.

1. Introduction

1.1 Motivation

Many of the top selling pharmaceuticals on the market today contain aromatic C-N bonds (
Figure 1)[1]. One challenge in the synthesis of complex molecules such as these is modifying the molecule during the late stages of its development. Some reaction conditions, such as high heat or the presence of a strong oxidant, are not compatible with many functional groups, which makes them largely unsuitable for applications in the synthesis of complex molecules[2]. One promising route for the late-stage functionalization of molecules is C-H bond functionalization[3]. This method allows for the direct conversion of a C-H bond to a C-FG bond, in this case, a C-N bond[3]. This project focuses on the development of a one-step process with a high functional group tolerance for the non-directed C-H amination of aromatic arenes.

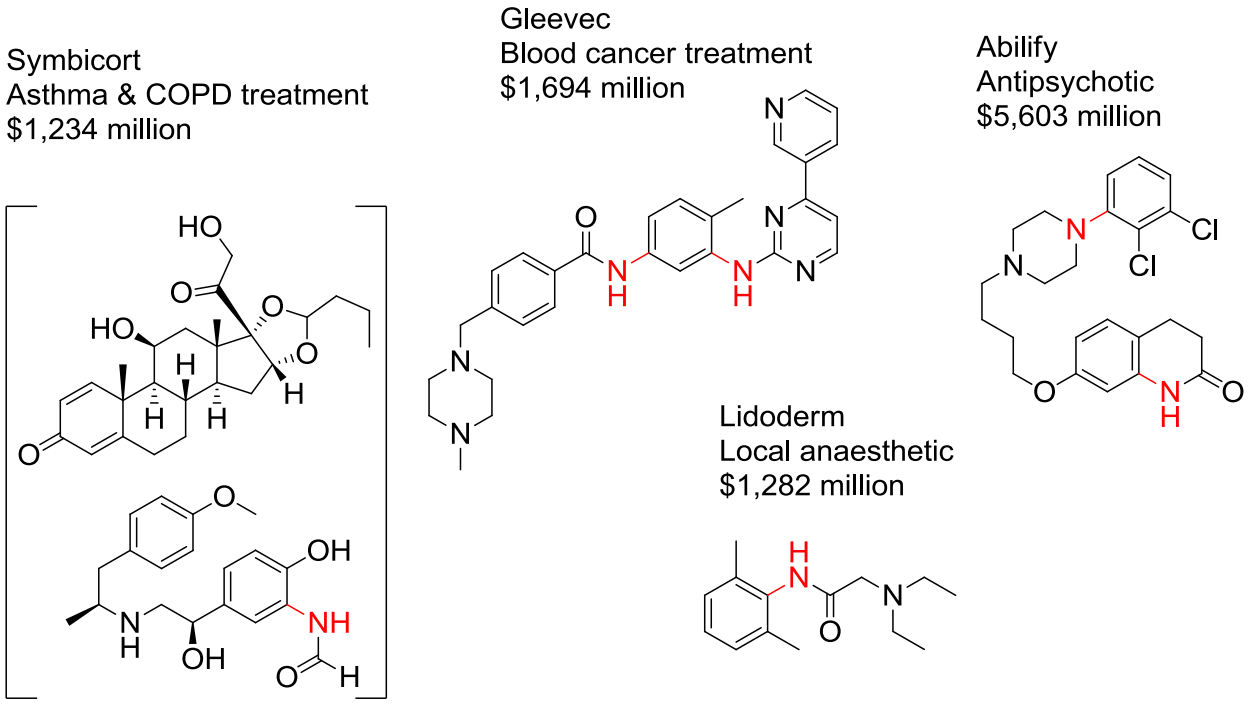
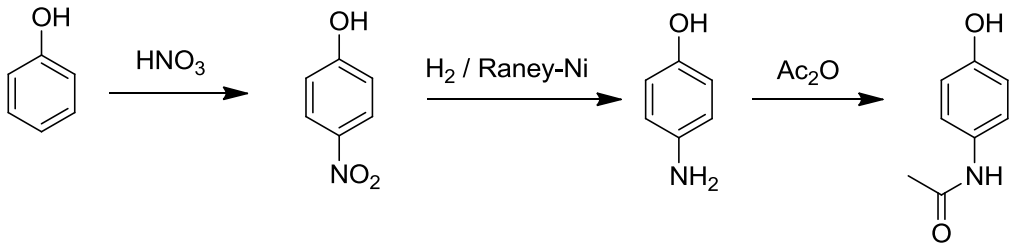


Figure 1. Examples of top selling pharmaceuticals in 2012 containing aromatic C-N bonds[1]

1.2 Classical Approaches

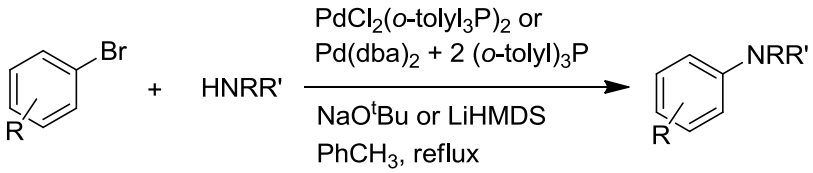
The formation of aromatic C-N bonds has been a tool of the organic chemist for quite some time. A classical organic approach to the formation of these bonds is through the process of nitration. Pictured in the first two steps of Scheme 1, the arene is first nitrated using a strong acid, and then it is reduced to the aromatic amine[4]. Though effective, there are issues with this synthesis when trying to form aromatic C-N bonds in large molecules. Nitric acid, a strong acid, would be expected protonate receptive sources, making it much too harsh for use in late-stage functionalization[3]. This nitro-group that is added to the arene in the first step is virtually useless for pharmaceutical molecules; there is not a single nitro- group on any of the top one hundred selling pharmaceuticals of 2012, so this group would have to be converted to something more useful[1]. The second step in this reaction, the reduction of the nitro- group to an amine, takes place at high temperatures[4], reinforcing the point that this process is not suitable for use in late-stage functionalization.



Scheme 1. Synthesis of acetaminophen from phenol[4]

Another classical approach to the formation of aromatic C-N bonds is through Buchwald-Hartwig amination, a process that uses a palladium catalyst and a strong base to achieve the amination of an aromatic ring[5]. This approach usually occurs in very high yield, generally above 65%; however, it is not a feasible option for late-stage functionalization[5]. This is because the Buchwald-Hartwig amination requires the prefunctionalization of the aromatic ring, converting it into an aryl halide, before the C-N

bond can be formed (Scheme 2)[5]. In the late stages of drug development, this kind of prefunctionalization is rarely possible[3]. On top of the issue of prefunctionalization, there is the issue of the strongly basic conditions presented by sodium *tert*-butoxide, for these conditions do not bode well for large, functionally diverse molecules[3].

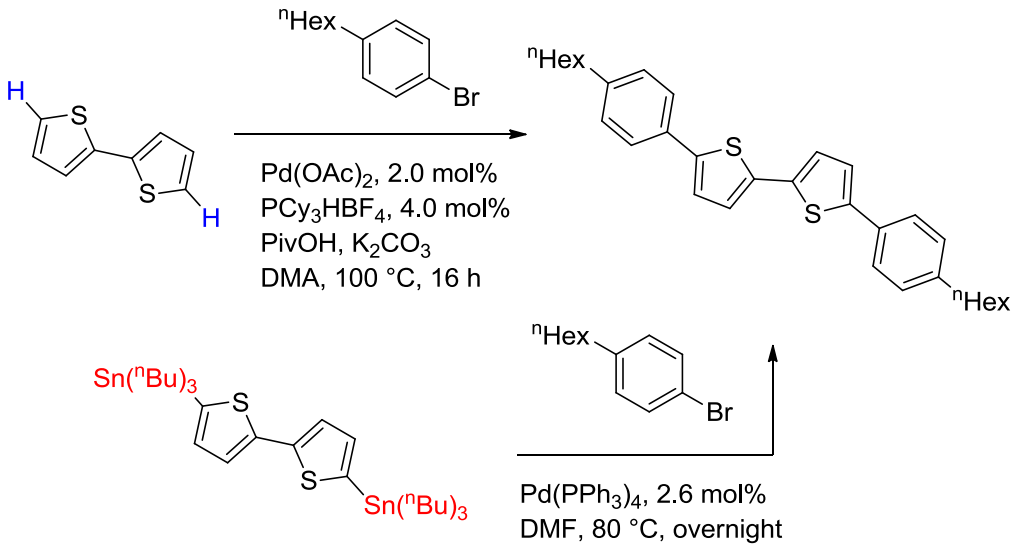


Scheme 2. Example of Buchwald-Hartwig amination[5]

1.3 C-H Bond Functionalization

It should be noted that the previously discussed methods for the amination of aromatic rings would require either the alteration of the ring before the formation of the C-N bond, or the conversion of the newly introduced functional group to something more useful. One good way to avoid these problems is to functionalize the C-H bond, which would be equivalent to converting the H atom directly into a useful functional group[3]. This feat in the past was quite difficult because the C-H bond is omnipresent in organic molecules, and there is nothing particularly remarkable about it that makes it a widely targeted reaction site[3]. Advances in the field of C-H bond activation, however, have made this direct conversion possible, providing shortcuts to products that were previously more difficult to synthesize[3]. As a general example, pictured in Scheme 3 are two synthetic pathways for the same molecule, 5,5'-bis(4-hexylphenyl)-2,2'-bithiophene; the bottom pathway uses more classical catalytic methods by converting the bulky tributylstannyl groups to the desired functional groups[6], but the top pathway utilizes C-H functionalization to convert the much simpler, unsubstituted 2,2'-bithiophene directly into the desired product[7]. Not only is the atom economy better without the use of said bulky,

toxic tin groups, but the yield is also improved from 68% in the classical method to 80% in the C-H activation method[6,7].



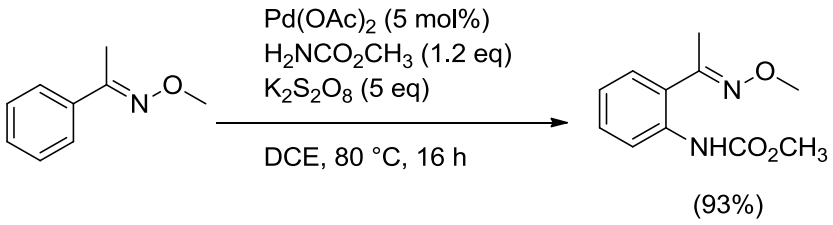
Scheme 3. Different synthetic pathways for forming a compound, the bottom reaction is a classical organic approach[6] and the top reaction is a C-H activation approach[7]

The concept of C-H activation has indeed been applied to the formation of aromatic C-N bonds and has been thoroughly demonstrated by Sanford[8] and many others*. Collectively, these researchers have shown that the formation of C-X or C-C bonds is possible in both an intermolecular fashion and an intramolecular fashion by using palladium catalysts. Currently, the most broadly used approach to C-H functionalization falls under the category of ligand-directed transformations with C-H amination being no exception[8].

1.3.1 Directed C-H bond amination

In ligand-directed C-H bond functionalization, the reaction occurs by way of a directing group, which coordinates to the palladium center in the catalyst and allows said metal center to become additionally coordinated to the carbon in the activated C-H bond[8]. An example of this is shown in Scheme 4, and a proposed mechanism for this reaction is

shown in Figure 2, where the chelation of the palladium metal center can be seen. Although many of Sanford's product yields for this method of aromatic amination are greater than 75%[8], ligand-directed C-H bond functionalization is not as widely applicable to the synthesis of pharmaceuticals as it might appear. The process is only useful for adding products proximal to a previously functionalized carbon atom, and it requires the presence of a directing group[8]; in many pharmaceuticals, neither of these drawbacks are acceptable[1].



Scheme 4. An example of ligand-directed C-H bond amination[9]

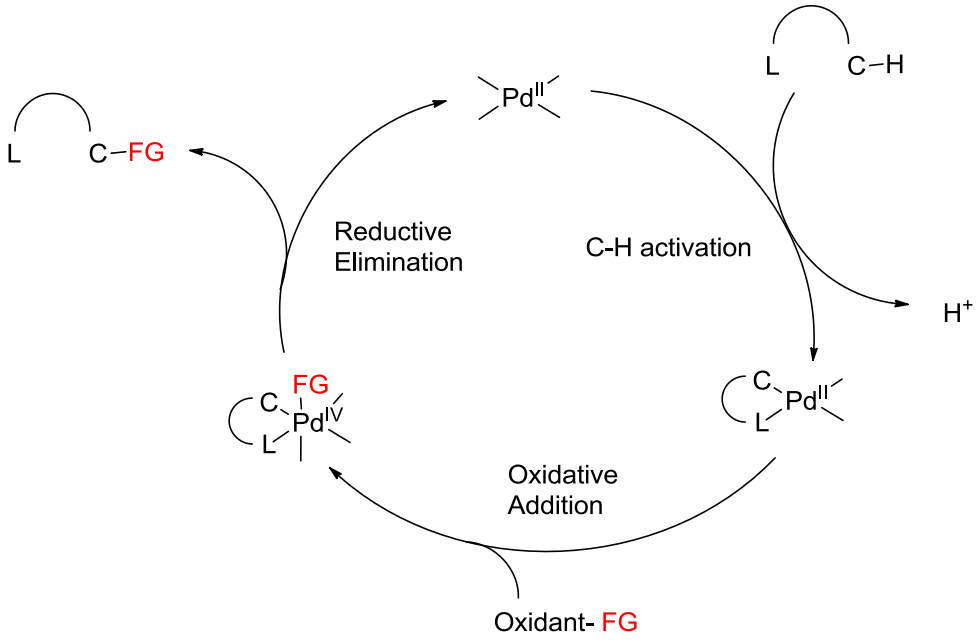
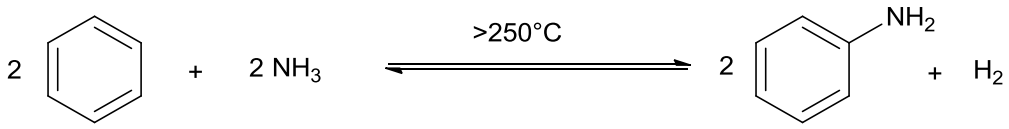


Figure 2. A proposed general catalytic cycle for ligand-directed C-H bond functionalization[8]

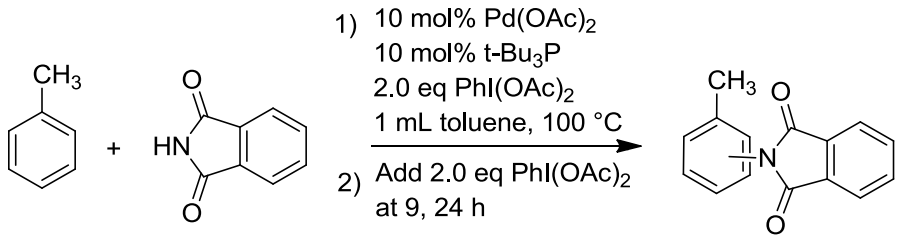
1.3.2 Non-directed C-H bond amination

Similar to the process of ligand-directed C-H bond functionalization is that of non-directed C-H bond functionalization; this approach still utilizes the activation of the C-H bond, but it does not require the use of a directing group. Therefore, it is potentially useful for the installation of functional groups at positions other than on the carbon proximal to a directing group[9]. The simplest example of this is an industrial approach that achieves the non-directed C-H amination of benzene using ammonia and a Group VIII metal catalyst, shown in Scheme 5; however, this reaction proceeds best at high temperatures[11]. The yield of aminated product increases from 2% at 300 °C to 14% at 600 °C[11], which is extremely poor, and this excessive temperature is not compatible with the delicacy of large, complex molecules[3].



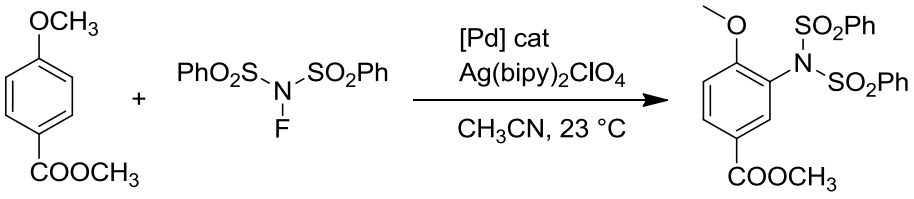
Scheme 5. Industrial amination of benzene using ammonia and a Group VIII metal catalyst[11]

Advances in catalysis and C-H bond functionalization have brought about more effective methods of non-directed aromatic C-H bond amination, as demonstrated by John F. Hartwig in Scheme 6[10]. The reaction pictured below produced a product yield of 70%, with a selectivity favoring the formation of meta- and para-substituted arenes[10]. One drawback to this method of amination is the necessity of the sequential addition of $PhI(OAc)_2$, for this can be a major timing issue for the chemist in charge of performing this reaction[10]. The yield drops to 56% when 8 equivalents are added instantaneously because this reagent is needed over time to regenerate the palladium catalyst, so there is not really a way to escape sequential addition of $PhI(OAc)_2$[10]. Another drawback to this method of amination is the functional group that is introduced; the phthalimide group is not useful in pharmaceutical molecules[1], so it would require further alteration, which truly diminishes the novelty of C-H functionalization itself[3].



Scheme 6. Non-directed aromatic C-H bond amination[10]

An alternate route for non-directed aromatic C-H bond amination was developed by Tobias Ritter and his group, and it is detailed below in Scheme 7[12]. The major drawback to this approach is identical to the approach devised by Hartwig; the functional group that is introduced on to the arene is not useful for pharmaceutical applications[1] and would require further alteration, which is a vast underutilization of the tool of direct C-H functionalization[3].



Scheme 7. Alternate version of non-directed aromatic C-H bond amination[12]

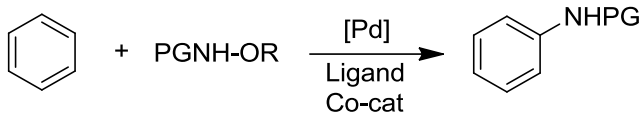
1.4 Project goal

This project seeks to develop and optimize a method for the palladium catalyzed formation of aromatic C-N bonds that has a large functional group tolerance, a wide array of functional group addition possibilities, and reaction conditions that will allow for use in late-stage molecular development.

1.4.1 Significance

The features that distinguish the process proposed by this project from those proposed previously are the versatility and the simplicity. Versatility in this case means that the process will be applicable to a wide array of substrates, particularly substituted benzenes, but versatility also refers to the plethora of functional groups that can be installed on a substrate. Simplicity in this case means that the reaction does not require careful observation or inconvenient incremental addition of a reagent to produce a significant yield, and it also occurs at the moderate temperature of 100 °C, not too harsh for application to large molecules[3].

1.4.2 Project approach



Scheme 8. General scheme for project-developed non-directed aromatic C-H bond amination[12]

The approach to late-stage amination that is taken by this project makes use of a palladium catalyst, acridine-type ligands, and a co-catalyst additive that manage to install a nitrogen functionality onto an arene[13]. The palladium catalyst used is palladium (II) acetate, which has been shown to be effective in aromatic C-H bond aminations by Sanford[8] and also by Hartwig[10]. The ligands studied are electron rich and are thought to facilitate the ligand exchange in the reductive elimination step of the reaction (Figure 3)[13]. In order to show that this developed process has a large functional group tolerance, a substrate scope investigation was performed, exchanging the benzene substrate, pictured above in Scheme 8, for various substituted benzene derivatives. To ensure that a wide array of functional groups could be installed, various sources of nitrogen were tested, denoted as “PGNH-OR” in Scheme 8. Since the PGNH- part of this reagent remains attached to the arene at the end of the reaction, the protecting group, PG was varied to demonstrate versatility. These sources of nitrogen are

intended to allow for the direct installation of a variety functional groups useful in molecules intended for biological activity.

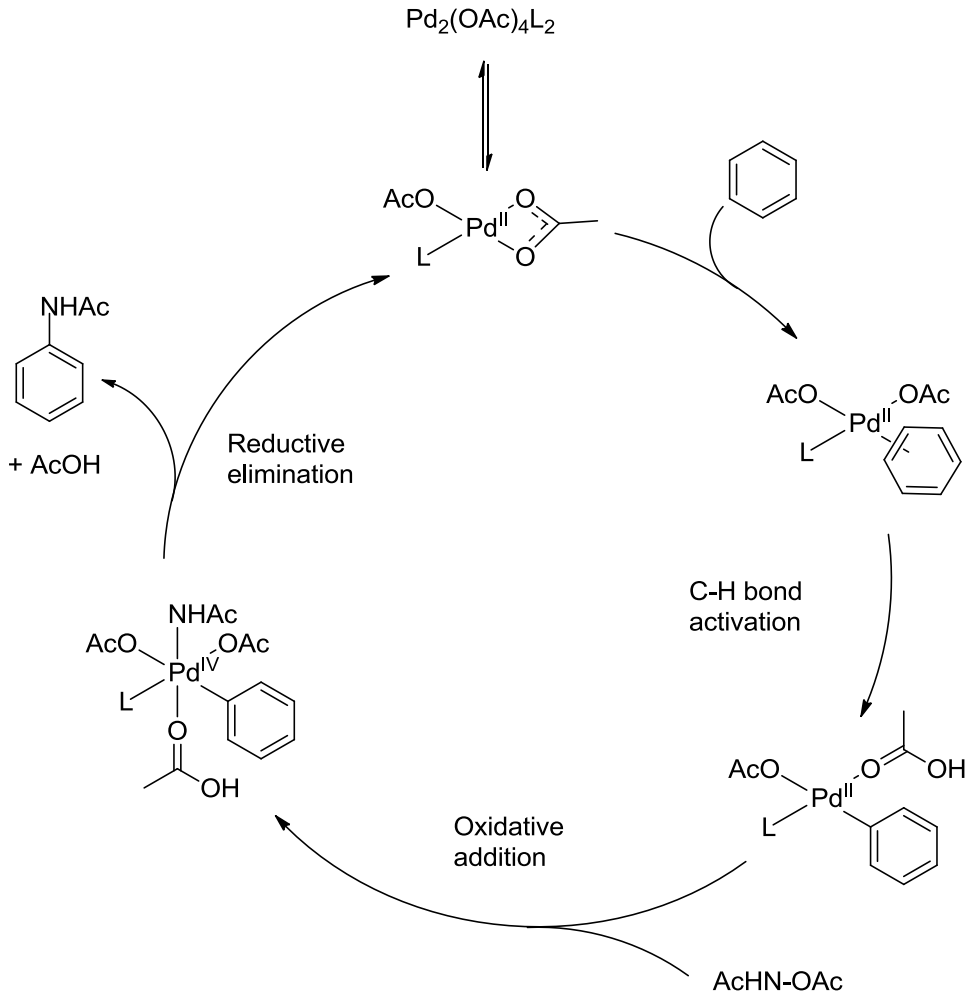


Figure 3. Proposed catalytic cycle for project developed amination[13]

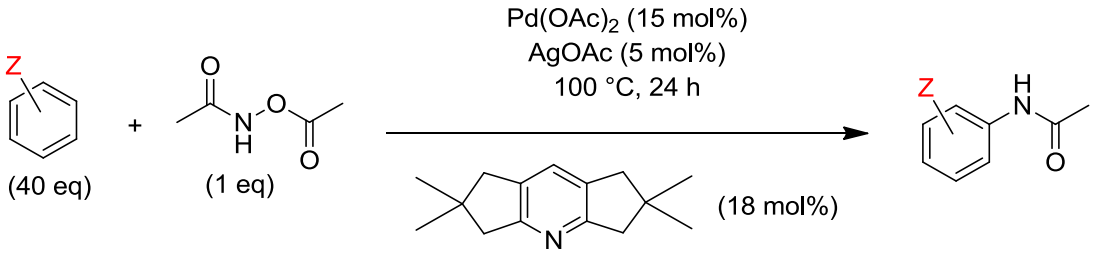
2. Results and Discussion

2.1 Catalytic Reactions with Benzene as the Solvent

In order to investigate the applicability and versatility of the devised C-H amination system, certain aspects of the optimized catalytic system were altered.

2.1.1 Scope of Substrates

The purpose of the substrate scope was to demonstrate that the devised C-H amination system would be applicable to a variety of arene substrates. This is an important feature of this system because it was designed with the concept of late stage development in mind. A desirable reaction system, with respect to late stage development, will be widely applicable and will have a large tolerance of functional groups. This is because of the innate functional group diversity of large molecules in the later stages of their development; a reaction system that can only form aromatic C-N bonds on a unique substrate is not very useful to chemists who must deal with a wide array of substrates. The substrates tested in this scope were all benzene rings substituted with one or more electron withdrawing or weakly electron donating groups, making the arene ring more electron deficient than the original benzene substrate. The proposed mechanism suggests that this may not favor the coordination of the aromatic ring with the Pd (II) center, but the results presented below are not sufficient to prove this hypothesis. The yields for this scope of arenes were poor (
Figure 4), suggesting that this reaction system, under the optimized conditions for benzene, is not effective when applied to similar arenes substituted with electron withdrawing or weakly electron donating groups.



Scheme 9. General scheme for simple arene substrate scope

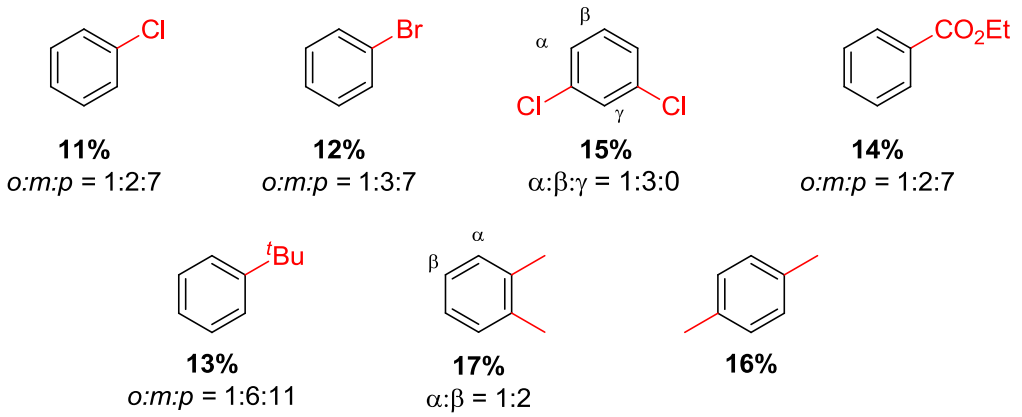


Figure 4. Above are pictured the results of the arene substrate scope with isomeric preference included

Though the results of this substrate scope are not definitive enough to draw conclusions about the effect that electron withdrawing and donating groups may have on the reaction mechanism, the isomeric distribution of the products is definitive enough to draw a simple conclusion. This reaction system favors the formation of the product that is least hindered by steric effects; this can be seen in every example above, so in this case, at least, the product formation is governed by steric effects rather than electronic effects. Further exploration of substrates and manipulation of reaction conditions are necessary to draw any additional conclusions.

2.1.2 Scope of Amination Reagents

In order to further demonstrate the versatility and applicability of this reaction system, amination reagents with varied protecting groups were tested. These protecting groups are what remain attached to the nitrogen atom on the other side of the arene after the reaction occurs, so being able to work with various sources of nitrogen would mean that various functional groups can be installed, making this reaction system desirably versatile. Shown below (Figure 5) are several nitrogen sources that were tested under the optimized reaction conditions, which yield 52% with *N*-acetoxyacetamide as the source of nitrogen[12].

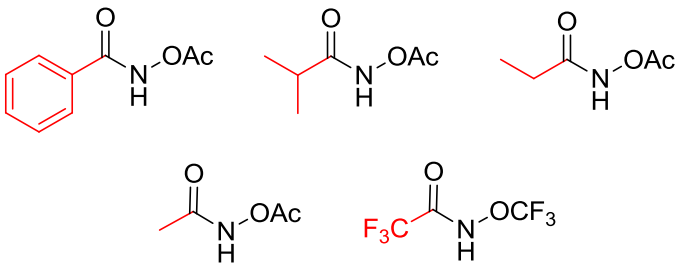


Figure 5. Pictured are the amination reagents involved in this scope in listed order (left to right)

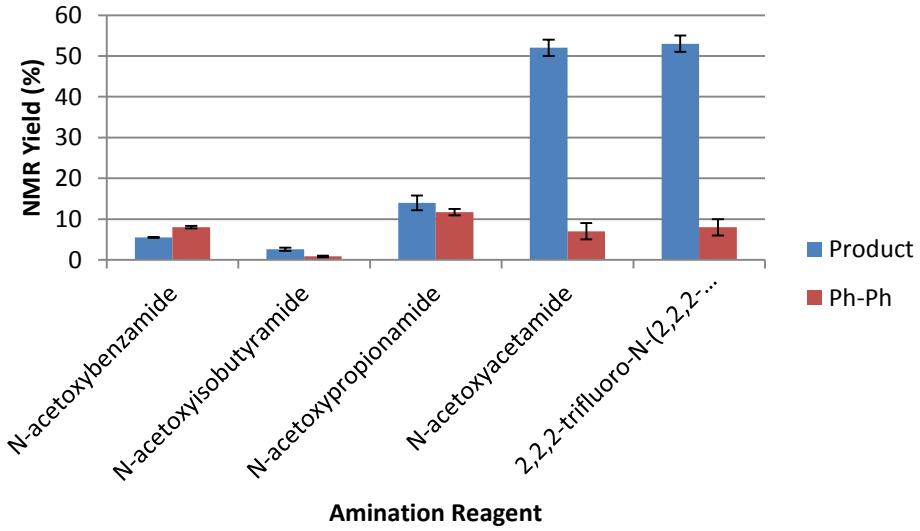


Figure 6. Results of the amination reagent scope with byproduct formation.

As can be seen in Figure 6, the amination reagents that vary from *N*-acetoxyacetamide do not yield much product, the highest average only reaching 14%. The reasons for this low yield, roughly 40% below the initial amination reagent, are yet unclear, but it can be reasoned that since the reaction system was optimized with a certain amination reagent, it may work uniquely well for this reagent, regardless of its similarities to other reagents. This again shows issues with the reaction system's versatility, which makes it rather impractical when it comes to late-stage functionalization applications.

2.2 Catalytic Reactions with Mesitylene as the Solvent

Reactions were done with mesitylene as the solvent in place of benzene so that benzene could be added in a more stoichiometric manner and so that the system could grow in applicability overall.

2.2.1 Ligand Screen

A series of ligands were studied in this system to determine the optimal one(s) for the new solvent system. Yields for these reactions are given below, and the optimal ligands were shown to be acridine and quinoline, which both produced more product than the ligand optimal for the system with benzene as the solvent, though it is not yet clear why mesitylene seems to favor these ligands. Both of these ligands were studied in the further optimization of the mesitylene system along with 1,2,3,4,5,6,7,8-octahydroacridine, which is a ligand with similar characteristics.

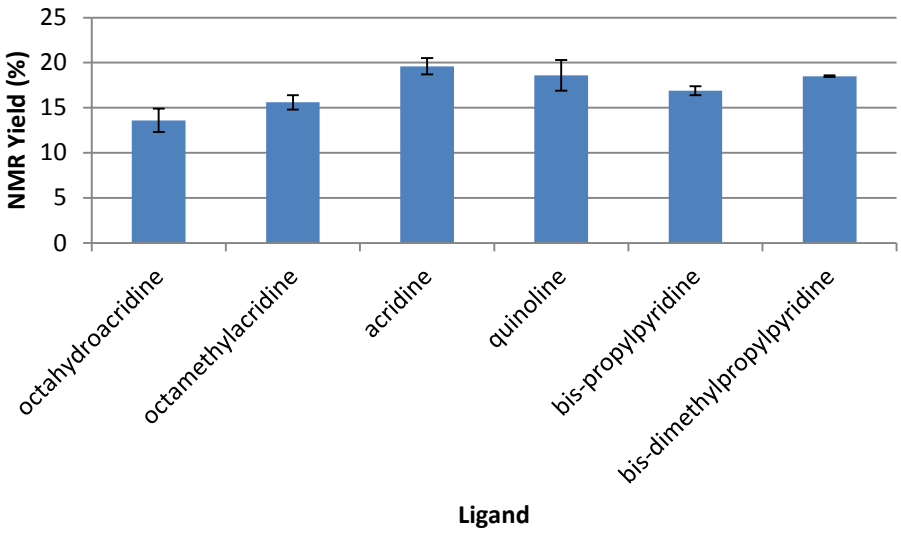


Figure 7. Calculated NMR yields of ligand screen for mesitylene system

2.2.2 Mesitylene Loading Screen

To further optimize the catalytic system in mesitylene and examine the effect of reagent concentration on the product yield, different volumes of this solvent were added to the reaction vials. As can be seen in the results presented below, the differing concentrations had little effect on the product yield, although yields seemed to peak at the 1.5 mL mark, so this is the volume that was selected for the optimal mesitylene system. Due to its poor performance, 1,2,3,4,5,6,7,8-octahydroacridine was removed from the group of ligands being studied in this system.

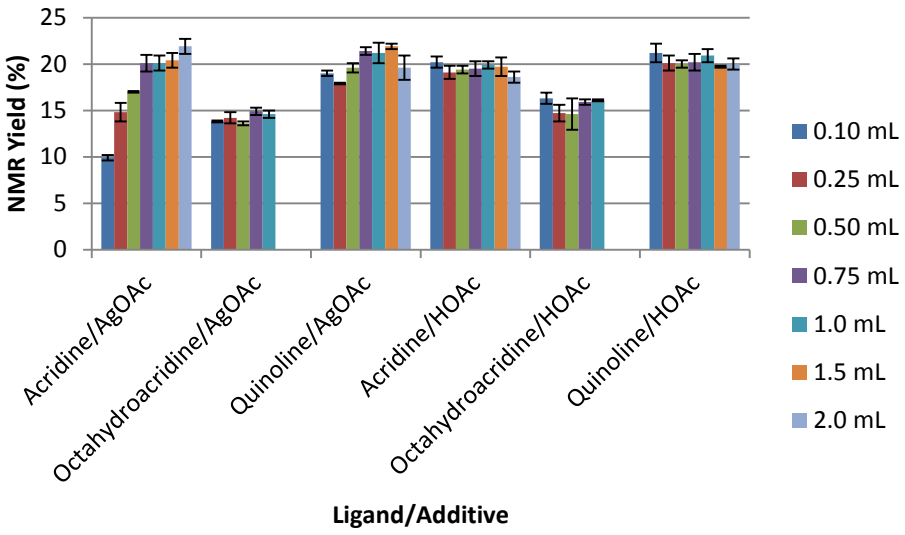


Figure 8. Calculated NMR yields for mesitylene loading study

2.2.3 Amination Reagent Loading Screen

With the optimal conditions being established, the loading of amination reagent was investigated next, and it resulted in the highest yields of any catalytic system seen under this project title. By increasing the amount of amination reagent twofold, the yield jumped nearly 10% from that with only 1 equivalent of amination reagent, and similar jumps are seen upon every increase of reagent loading, but the top yields were seen at the highest amount of amination reagent tested: 8 equivalents. Though these give the best numbers, it would be interesting to see if there is some loading between 4 and 8 equivalents that gives a maximum yield, or if the yield simply increases upon the addition of more amination reagent. This screening, however, has taken this project in a fantastic direction and it is hopeful that even higher yields will be seen with the further development of this solvent system.

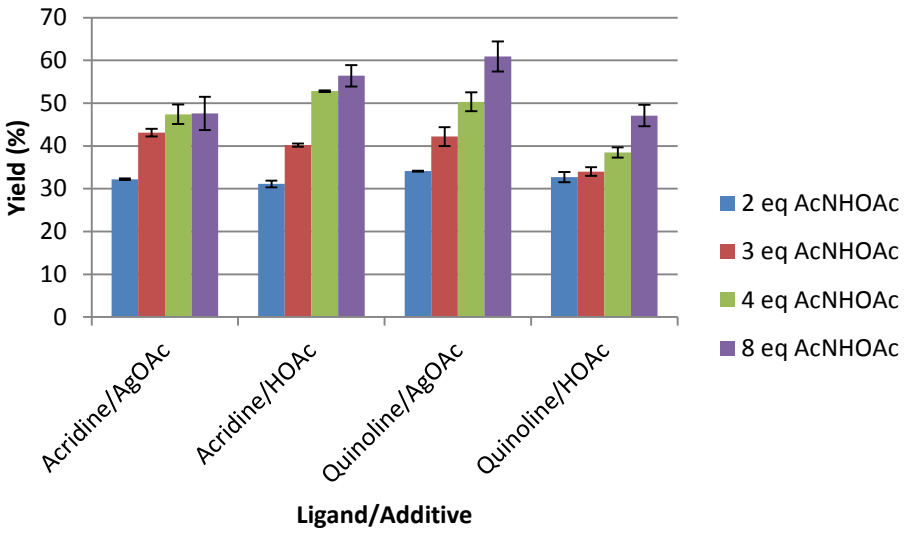


Figure 9. Calculated NMR yields of amination reagent loading study

3. Experimental

3.1 General Information

All reactions were performed in air unless stated otherwise. All reagents were obtained from reputable chemical suppliers and were used as purchased without further alteration or purification unless noted as such. Solvents were obtained from Pharmco-Aaper and were ACS/USP reagent grade, except for n-heptane, which was HPGC/HPLC grade.

3.2 Analysis

3.2.1 NMR spectroscopy

^{1}H-NMR spectra were recorded on a Bruker BioSpin 500MHz Avance III Digital NMR spectrometer (^{1}H: 500 MHz) in $CDCl_3$. These ^{1}H-NMR spectra were largely used to determine product purity, so no internal standard was used.

3.2.2 GC-MS

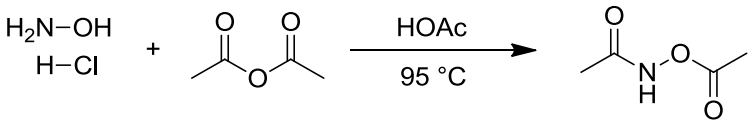
In order to determine the presence of products and byproducts in catalytic reactions, GC-MS analysis was used. GC-MS analysis was performed on a GC-MS System 5975 Series Quadrupole.

3.3 Synthesis of amination reagents

The amination reagent primarily used in the following catalytic studies was synthesized easily from hydroxylamine hydrochloride and acetic anhydride.

3.3.1 Synthesis of *N*-acetoxyacetamide

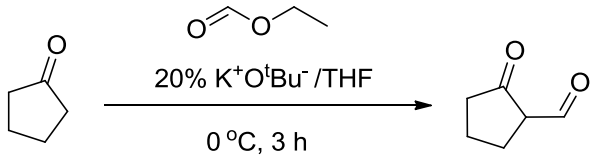
Hydroxylamine hydrochloride (1.50 g, 21.6 mmol, 1.00 eq) was added to 30 mL of glacial acetic acid in a 100 mL round bottom flask. Additionally, acetic anhydride (4.08 mL, 43.2 mmol, 2.00 eq) was added to this flask. The flask was then attached to a reflux condenser and refluxed at 95 °C for 24 h. The solvent was removed via rotary evaporation, and the product was recrystallized from hot EtOAc, affording 1.85 g (73%) of very small, white, needle-like crystals.



Scheme 10. Synthesis of *N*-acetoxyacetamide

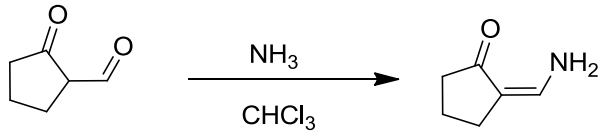
3.4 Synthesis of ligands

3.4.1 Synthesis of 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine



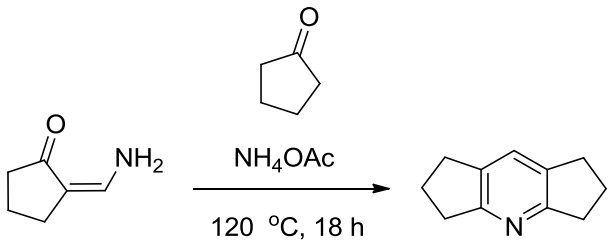
Scheme 11. Conversion of cyclopentanone to 2-oxocyclopentanecarbaldehyde

To a 100 mL round bottom flask was added a 20% solution of potassium *tert*-butoxide in THF (14.0 mL). The flask was cooled to 0 °C using an ice water bath, and ethyl formate was added (6.30 mL). Cyclopentanone (1.75 mL) was added to ethyl formate (15.2 mL) to create a solution that was then slowly added to the cool reaction flask; the flask was sealed and stirred at 0 °C for 3 hours. After this time, HCl (1.00 M) was added to the reaction flask until the precipitated material disappeared, the phases were separated in a separatory funnel, and the organic layer was dried under vacuum to give the aldehyde product (2.11 g). A small amount of this was used to take a ^{1}H-NMR spectrum that verified the identity of the product.



Scheme 12. Conversion of 2-oxocyclopentanecarbaldehyde to 2-(aminomethylene)cyclopentanone

After being dissolved in chloroform (3.00 mL), all of the 2-oxocyclopentanecarbaldehyde was transferred to a 20 mL glass scintillation vial with a septum cap. Using 2 needles, Teflon tubing, and electrical tape, a system was devised to allow ammonia to be bubbled through the solution. The ammonia gas was produced by the heating of equimolar amounts of calcium hydroxide and ammonium chloride in a round bottom flask in the solid state. For 30 minutes, ammonia was bubbled through the reaction solution, then the vial was disconnected from the bubbling system, and the reaction was allowed to sit at room temperature overnight. The brown semi solid was dissolved in a 1:1 solution of chloroform and petroleum ether (1.50 mL), and the resulting solution was left in the freezer for 3 hours. After this time, the supernatant was decanted, and the remaining brown solid was dried under vacuum to produce a deep red-brown crust (0.466 g).



Scheme 13. Conversion of 2-(aminomethylene)cyclopentanone to 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine

2-(aminomethylene)cyclopentanone (0.360 g) was transferred to a 20 mL glass scintillation vial, and cyclopentanone (0.300 mL) and ammonium acetate (7.2 mg) were added to the vial. This vial was sealed with a Teflon lined cap and was heated and

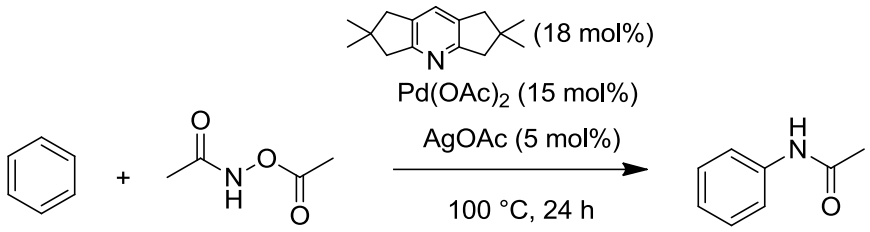
stirred at 120 °C for 18 hours, the mixture liquefying with heat. After this time, the vial was removed from heat and allowed to cool to room temperature, then it was washed with diethyl ether (3 x 10 mL), which then was dried over magnesium sulfate. This solution was then subject to purification by column chromatography (10% hexanes/ ethyl acetate). The solvent was removed from the collected liquid fractions, and the product was dried under vacuum to give an orange-brown solid (96.0 mg, 14%). The product identity and purity was verified by ^{1}H-NMR.

3.5 Catalytic studies: substrate scope

The following studies were performed to investigate the scope of substrates to which this method of amination is applicable and to demonstrate its versatility. Already knowing that this reaction proceeds in moderate yield when benzene is used as the substrate, derivatives of benzene were studied. Substrates investigated include both electron rich and electron poor arenes.

3.5.1 Catalytic study of benzene as the substrate – General procedure

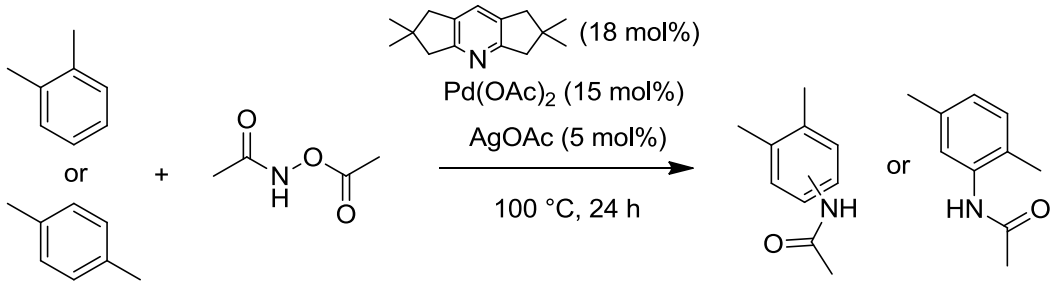
To a 4 mL glass scintillation vial were added $Pd(OAc)_2$ (4.72 mg, 0.210 mmol, 0.15 eq), *N*-acetoxyacetamide (16.4 mg, 1.40 mmol, 1.00 eq), 2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (0.541 mg, 0.252 mmol, 0.180 eq), and AgOAc (1.20 mg, 0.0700 mmol, .0.050 eq). Benzene (0.50 mL, 5.6 mmol, 40. eq) was added, and a magnetic stirring bar was inserted. The vial was sealed with a plastic, Teflon-lined cap and was placed on a hot plate at 100 ^{O}C and for 24 h while stirring. Once complete, the reaction was cooled to RT and prepared for analysis by GC-MS; to the reaction vial was added approximately 1.5 mL of $NaHCO_3$ and approximately 1.5 mL of EtOAc. The vial was capped and shaken to extract and separate aqueous and organic layers. The organic layer was then removed and filtered through a plug of celite rinsed with EtOAc and was followed by analysis by GC-MS to confirm the presence of the desired product.



Scheme 14. Amination of benzene

3.5.2 Study of xylenes as the substrate

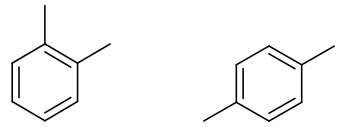
As in the general procedure (3.3.1), $Pd(OAc)_2$ (4.72 mg, 0.210 mmol, 0.15 eq), the amination reagent N-acetoxyacetamide (16.4 mg, 1.40 mmol, 1.00 eq), 2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (0.541 mg, 0.252 mmol, 0.180 eq), and the co-catalyst AgOAc (1.2 mg, 0.070 mmol, 0.050 eq) were added to a vial and were reacted in xylene (5.6 mmol, 40. eq) at 100 °C for 24 h. After 24 h, the reaction was removed from heat, allowed to cool to RT, and was worked up for analysis by GC-MS as previously stated.



Scheme 15. General amination of xylenes

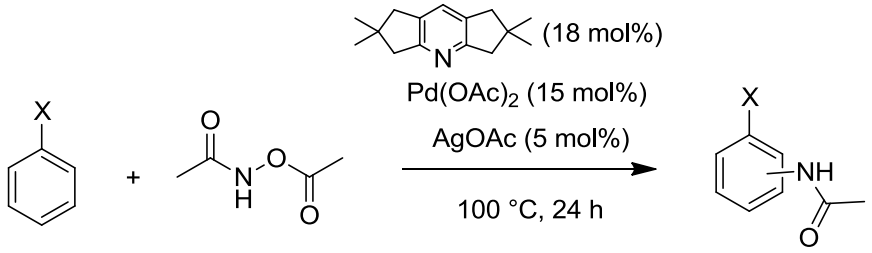
Table 1. Below are listed the amounts of each xylene used and the results of the GC-MS analysis

Entry	Substrate	Amount (mL)	Product observed
1TDN18-5	*ortho*-xylene	0.68	Yes
1TDN18-8	*para*-xylene	0.69	Yes



3.5.3 Study of halogenated benzene derivatives as the substrate

As in the general procedure (3.3.1), $Pd(OAc)_2$ (4.72 mg, 0.210 mmol, 0.15 eq), the amination reagent *N*-acetoxyacetamide (16.4 mg, 1.40 mmol, 1.00 eq), 2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (0.541 mg, 0.252 mmol, 0.180 eq), and the co-catalyst AgOAc (1.2 mg, 0.070 mmol, 0.050 eq) were added to a vial and were reacted in a halogenated benzene derivative (5.6 mmol, 40. eq) at 100 ^{O}C for 24 h. After 24 h, the reaction was removed from heat, allowed to cool to RT, and was worked up for analysis by GC-MS as previously stated.

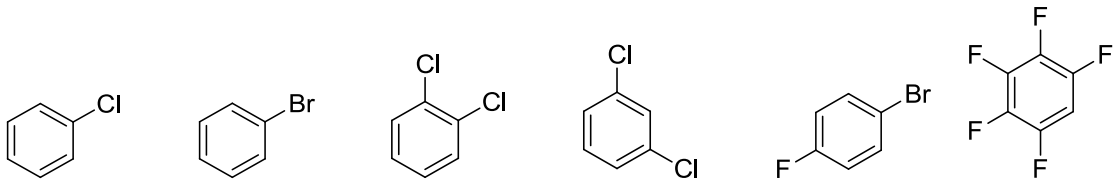


Scheme 16. General amination of halogenated benzene derivatives

Table 2. Below are listed the amounts used of each halogenated benzene derivative and the results of their GC-MS analysis

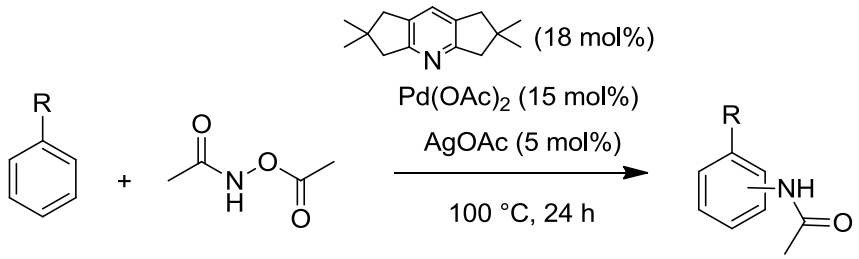
Entry	Substrate	Amount (mL)	Product observed
1TDN20-1	chlorobenzene	0.57	Yes
1TDN20-3	bromobenzene	0.59	Yes
1TDN20-5	1,2-dichlorobenzene	0.63	Yes
1TDN22-1	1,3-dichlorobenzene	0.64	Yes
1TDN22-7	1-bromo-4-	0.87	No

	fluorobenzene		
1TDN22-8	pentafluorobenzene	0.62	No



3.5.4 Study of additional benzene derivatives as the substrate

As in the general procedure (3.3.1), $Pd(OAc)_2$ (4.72 mg, 0.210 mmol, 0.15 eq), the amination reagent *N*-acetoxyacetamide (16.4 mg, 1.40 mmol, 1.00 eq), 2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (0.541 mg, 0.252 mmol, 0.180 eq), and the co-catalyst AgOAc (1.2 mg, 0.070 mmol, 0.050 eq) were added to a vial and were reacted in a benzene derivative (5.6 mmol, 40. eq) at 100 °C for 24 h. After 24 h, the reaction was removed from heat, allowed to cool to RT, and was worked up for analysis by GC-MS as previously stated.



Scheme 17. General amination of additional benzene derivatives

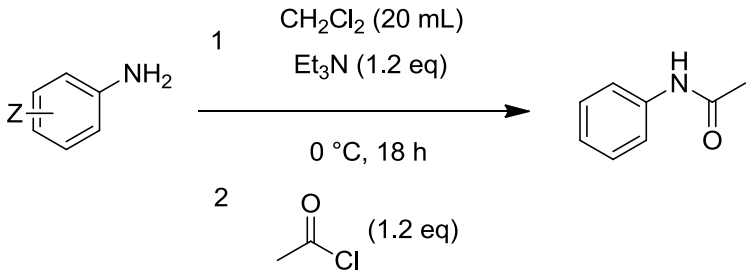
Table 3. Below are listed the amounts used of each additional benzene derivative and the results of their analysis by GC-MS

Entry	Substrate	Amount (mL)	Product observed
1TDN21-1	ethyl benzoate	0.80	Yes
1TDN21-6	phenyl acetate	0.71	No

1TDN22-2	1,3-methyl-2-nitrobenzene	0.76	Yes
1TDN22-3	*tert*-butylbenzene	0.87	Yes

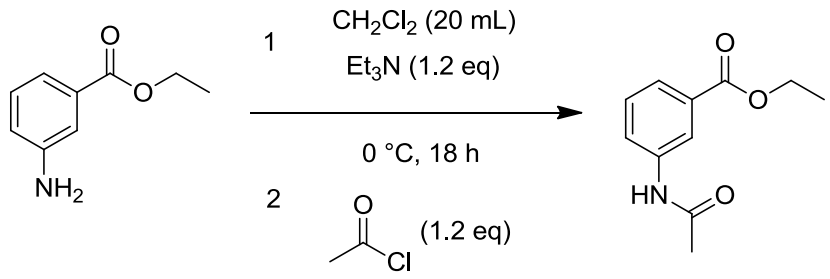
3.6 Synthesis of products for GC calibration

In order to properly determine yields and isomeric preference (ortho-/meta-/para-substitutions), the GC needed to be calibrated for the specific desired products. To do this, the desired acetamide products were synthesized from their corresponding anilines according to the scheme below. All anilines were obtained from Alfa Aesar through VWR.



Scheme 18. General conversion of anilines to acetamides

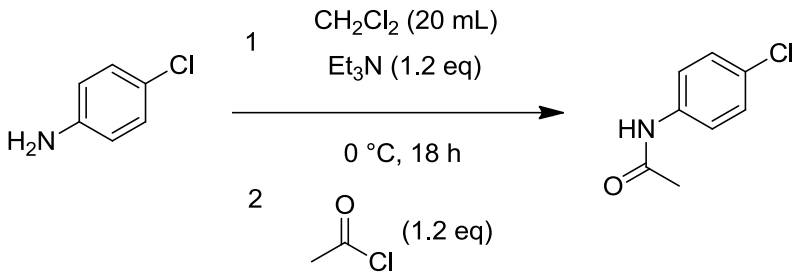
3.6.1 Conversion of ethyl 3-aminobenzoate to ethyl 3-acetamidobenzoate



Scheme 19. Conversion of ethyl 3-aminobenzoate to ethyl 3-acetamidobenzoate

Ethyl 3-aminobenzoate (1.00 g, 6.05 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.01 mL, 7.26 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.51 mL, 7.26 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts. To the reaction was added 15 mL of saturated $NaHCO_3$ in water, and the entire mixture was transferred to a separatory funnel, which was capped and shaken to achieve better extraction. The organic layer was isolated, the aqueous layer discarded, and the funnel was cleaned. Then the organic layer was washed twice with HCl (1 M, 15 mL), each time the funnel was cleaned, the organic layer was isolated, and the aqueous layer was discarded. The resulting organic solution was dried over $MgSO_4$, filtered, and the solvent was removed via rotary evaporation. The resulting material was then dried under vacuum overnight. This afforded a crude product and was then analyzed via ^{1}H-NMR spectroscopy by dissolving 10 mg of the product in 0.6 mL of $CDCl_3$. Though mostly clean, this spectrum still showed impurities, so the product was subject to recrystallization in a 1:1 mixture of EtOAc and hexanes**.** This afforded 0.893 g (71%) of a purified product.

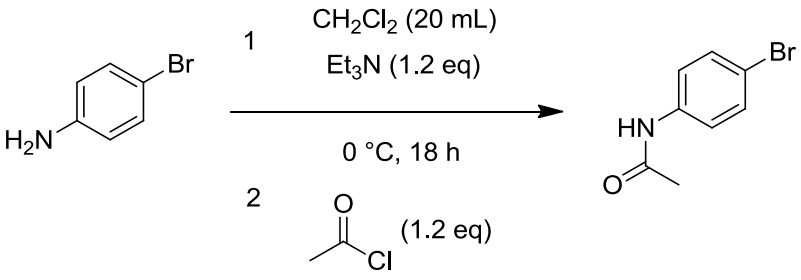
3.6.2 Conversion of 4-chloroaniline to *N*-(4-chlorophenyl)acetamide



Scheme 20. Conversion of 4-chloroaniline to *N*-(4-chlorophenyl)acetamide

4-chloroaniline (1.00 g, 7.84 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.32 mL, 9.41 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.67 mL, 9.41 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of CH_2Cl_2 and hexanes**.** This afforded 0.424 g (32%) of a purified product.

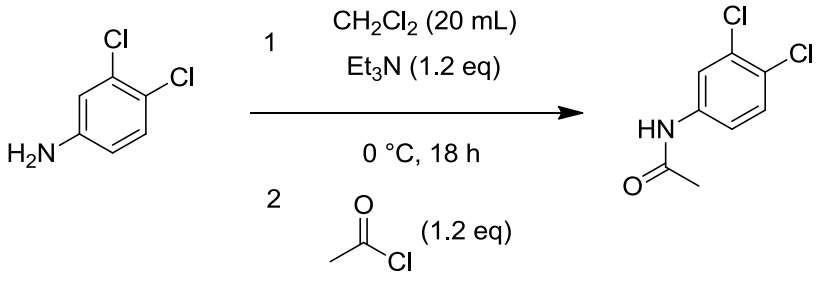
3.6.3 Conversion of 4-bromoaniline to *N*-(4-bromophenyl)acetamide



Scheme 21. Conversion of 4-bromoaniline to *N*-(4-bromophenyl)acetamide

4-bromoaniline (1.00 g, 5.81 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (0.97 mL, 6.97 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.50 mL, 6.97 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of CH_2Cl_2 and hexanes. This afforded 0.311 g (25%) of a purified product.

3.6.4 Conversion of 3,4-dichloroaniline to *N*-(3,4-dichlorophenyl)acetamide

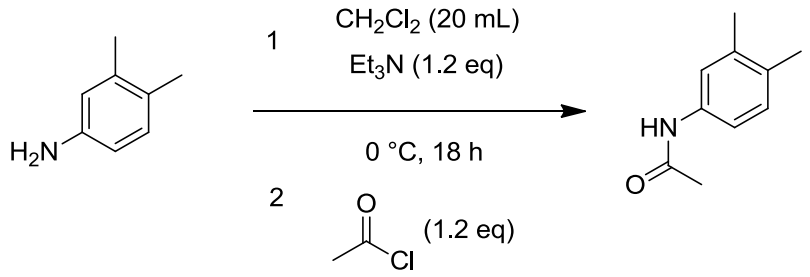


Scheme 22. Conversion of 3,4-dichloroaniline to *N*-(3,4-dichlorophenyl)acetamide

3,4-dichloroaniline (1.00 g, 6.17 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.03 mL, 7.40 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.53 mL, 7.40 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants

and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of CH_2Cl_2 and hexanes. This afforded 0.689 g (55%) of purified product.

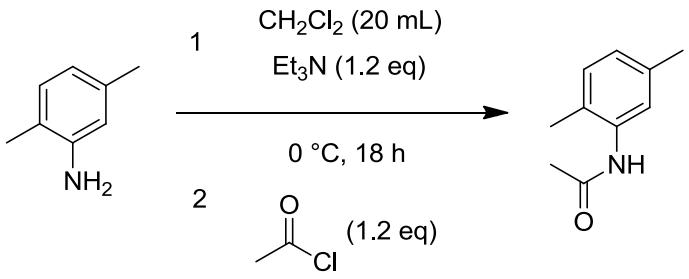
3.6.5 Conversion of 3,4-dimethylaniline to *N*-(3,4-dimethylphenyl)acetamide



Scheme 23. Conversion of 3,4-dimethylaniline to *N*-(3,4-dimethylphenyl)acetamide

3,4-dimethylaniline (1.00 g, 8.25 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.38 mL, 9.90 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.71 mL, 9.90 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of EtOAc and hexanes**.** This afforded 0.951 g (71%) of a purified product.

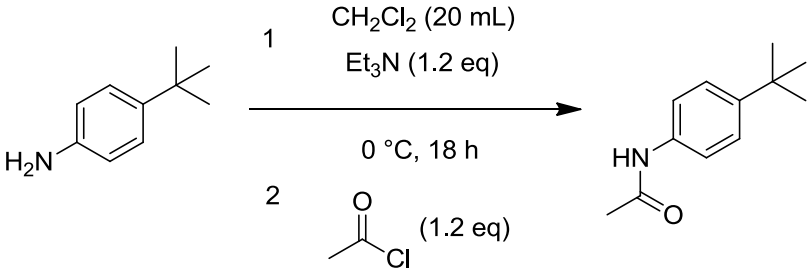
3.6.6 Conversion of 2,5-dimethylaniline to *N*-(2,5-dimethylphenyl)acetamide



Scheme 24. Conversion of 2,5-dimethylaniline to N-(2,5-dimethylphenyl)acetamide

2,5-dimethylaniline (1.00 g, 8.25 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.38 mL, 9.90 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.71 mL, 9.90 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of EtOAc and hexanes**.** This afforded 0.978 g (73%) of a purified product.

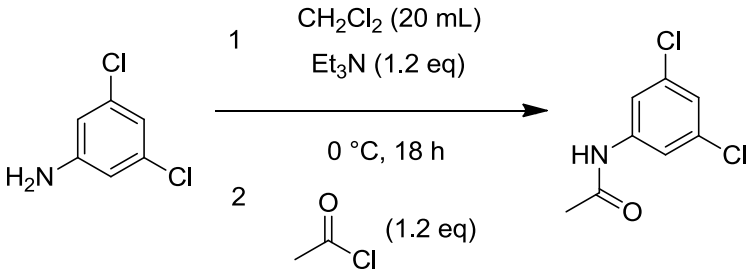
3.6.7 Conversion of 4-(*tert*-butyl)aniline to *N*-(4-(*tert*-butyl)phenyl)acetamide



Scheme 25. Conversion of 4-(*tert*-butyl)aniline to *N*-(4-(*tert*-butyl)phenyl)acetamide

4-(*tert*-butyl)aniline (1.00 g, 6.70 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.12 mL, 8.04 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.57 mL, 8.04 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of EtOAc and hexanes**.** This afforded 0.808 g (63%) of a purified product.

3.6.8 Conversion of 2,4-dichloroaniline to *N*-(2,4-dichlorophenyl)acetamide



Scheme 26. Conversion of 2,4-dichloroaniline to *N*-(2,4-dichlorophenyl)acetamide

2,4-dichloroaniline (1.00 g, 6.17 mmol, 1.00 eq) was added to a 100 mL round bottom flask containing 20 mL of CH_2Cl_2. To this flask was also added Et_3N (1.03 mL, 7.40 mmol, 1.20 eq) and a magnetic stir bar. This flask was then capped and submerged in an ice bath to cool the reaction mixture to 0 °C; once it had reached said temperature, the flask was uncapped, and acetyl chloride (0.53 mL, 7.40 mmol, 1.20 eq) was added, causing the formation of a white vapor over the liquid in the flask. The flask was recapped and allowed to stir in the ice bath for 18 h. At the end of this time, the reaction underwent an acid/ base workup to extract the desired product from remaining reactants

and byproducts as stated above (3.6.1). This afforded a crude product. After workup, it was analyzed in the same manner as above (3.6.1) by ^{1}H-NMR, and similarly, the spectrum showed impurities, so the product was subject to recrystallization in a 1:1 mixture of CH_2Cl_2 and hexanes. This afforded 0.714 g (57%) of a purified product.

3.7 Determination of aryl–acetamide product GC stability

To ensure that the product calibration of the GC was accurate, meaning that the products would not degrade in the apparatus and give false yields, their stability was tested. This was done by making a serial dilution of the products with an internal standard that is known not to degrade in the apparatus. A stable product is expected to have the same relative concentration difference between dilutions as the internal standard. The series was a one half dilution of every vial for seven vials, making the final vial 2^{-7} times the concentration of the initial vial. This was achieved by removing half of the initial solution and diluting this half with EtOAc in a separate vial. The initial vial of ethyl 3-acetamidobenzoate was prepared by dissolving 10 mg of said product in 4 mL of EtOAc and then adding 10 µL of PhCl. The vial was agitated to promote proper mixing of components, and approximately 2 mL were transferred to a separate vial. To this separate vial, 2 mL of EtOAc were added, returning the solution to its initial volume but at half the concentration. This was repeated until there were 7 diluted vials, and this procedure was performed identically for each of the products listed below, unless otherwise noted.

Table 4. Conditions of the initial vial in the serial dilution used to determine product stability in the GC instrument

	Product	Amount (mg)	Standard (10 µL)	GC Stable
1	ethyl 3-acetamidobenzoate	10	PhCl	Yes
2	*N*-(4-chlorophenyl)acetamide	4	PhBr	Yes
3	*N*-(4-bromophenyl)acetamide	10	PhCl	Yes
4	*N*-(3,4-dichlorophenyl)acetamide	10	PhCl	Yes

5	*N*-(3,4-dimethylphenyl)acetamide	10	PhCl	Yes
6	*N*-(2,5-dimethylphenyl)acetamide	10	PhCl	Yes
7	*N*-(4-(*tert*-butyl)phenyl)acetamide	10	PhCl	Yes
8	*N*-(2,4-dichlorophenyl)acetamide	10	PhCl	Yes

3.8 Determination of aryl-acetamide product yield

The purified aryl-acetamide products were used to calibrate the GC instrument. Once this was done, the catalytic reactions in question were reanalyzed, and the yield of acetamide product was determined by comparison to an internal standard of PhCl and by comparison to the calibration spectra. Calculated yields are displayed below in Table 5 along with isomeric selectivity.

Table 5. Calculated GC yields of the arene substrate scope

Entry	Substrate	GC Yield (%)	Selectivity
1TDN21-1	ethyl benzoate	14 ± 2	1:2:7 (o:m:p)
1TDN20-1	chlorobenzene	11 ± 2	1:2:7 (o:m:p)
1TDN20-3	bromobenzene	12 ± 2	1:3:7 (o:m:p)
1TDN22-1	1,3-dichlorobenzene	15 ± 2	1:3:0 (α:β:γ)
1TDN18-5	*ortho*-xylene	17 ± 2	1:2 (α:β)
1TDN18-8	*para*-xylene	16 ± 2	n/a
1TDN22-3	*tert*-butylbenzene	13 ± 3	1:6:11 (o:m:p)

3.9 Catalytic studies: amination reagent scope

The following studies were performed to investigate the scope of installable groups to which this method of amination is applicable and to demonstrate its versatility. Already knowing that this reaction proceeds in moderate yield when *N*-acetoxyacetamide is used as the source of nitrogen, analogs of this were studied.

3.9.1 Study of varied acetamide substituents

In analogy to the optimized conditions described above (3.5.1), catalytic reactions were prepared to examine the efficacy of three alternate sources of nitrogen, which are displayed below (Figure 10). To a 4 mL glass scintillation vial were added $Pd(OAc)_2$ (4.72 mg, 0.210 mmol, 0.15 eq), an amination reagent (1.40 mmol, 1.00 eq), 2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine (0.541 mg, 0.252 mmol, 0.180 eq), and AgOAc (1.20 mg, 0.0700 mmol, 0.050 eq). Benzene (0.50 mL, 5.6 mmol, 40. eq) was added, and a magnetic stirring bar was inserted. The vial was sealed with a plastic, Teflon-lined cap and was placed on a hot plate at 100 ^{O}C and for 24 h while stirring. After 24 h, the vials were removed from heat and allowed to cool to room temperature, and the solvent was removed under vacuum. To each evacuated vial was added 0.70 mL of a standard solution of 1,3-dinitrobenzene in $CDCl_3$ (10 mg/ mL), the vial was shaken, and the resulting mixture was filtered through a plug of celite into an NMR tube for analysis. Calculated NMR yields are given in Table 6.

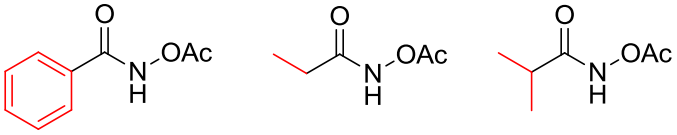


Figure 10. Tested amination reagents with varied protecting groups

Table 6. Calculated NMR yields of amination reagent scope

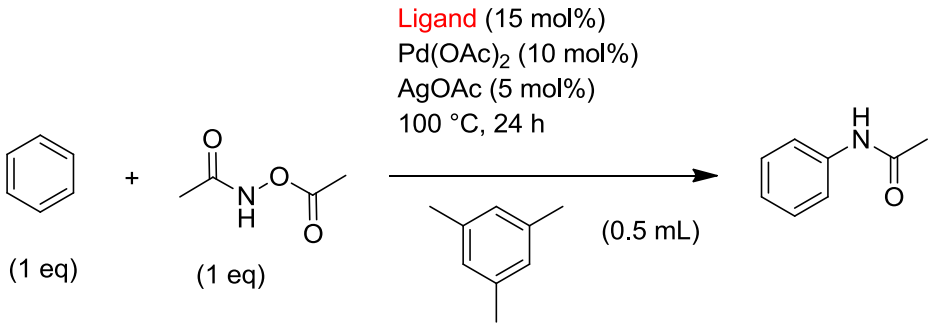
Entry	Reagent	Added amount (mg)	NMR Yield (%)
1TDN31-1	*N*-acetoxybenzamide	25.1	5.5 ± 0.1
1TDN31-2	*N*-acetoxyisobutyramide	20.3	2.6 ± 0.3
1TDN31-3	*N*-acetoxypropionamide	18.4	14 ± 2

3.10 Catalytic studies: mesitylene solvent system

The following studies were performed to investigate the efficacy of mesitylene as the solvent for this catalytic system with benzene no longer in excess. Mesitylene was chosen for this role because of its performance in previous studies in this lab.

3.10.1 Study of ligands

In analogy to the previously established conditions for C-H amination in mesitylene, various acridine-type ligands were investigated to determine their effectiveness in this modified solvent system. To a 4 mL glass scintillation vial were added $Pd(OAc)_2$ (3.10 mg, 0.0140 mmol, 0.10 eq), *N*-acetoxyacetamide (32.4 mg, 0.140 mmol, 1.00 eq), a ligand (0.0210 mmol, 0.150 eq), AgOAc (1.20 mg, 0.00700 mmol, 0.050 eq), and mesitylene (0.50 mL, 3.59 mmol, 26 eq). Benzene (12.5 µL, 0.140 mmol, 1.00 eq) was added, and a magnetic stirring bar was inserted. The vial was sealed with a plastic, Teflon-lined cap and was placed on a hot plate at 100 ^{O}C and for 24 h while stirring. After 24 h, the vials were removed from heat and allowed to cool to room temperature. To each vial was added 0.50 mL of a standard solution of 1,3-dinitrobenzene in $CDCl_3$ (10 mg/ mL), the vial was shaken, and the resulting mixture was filtered through a plug of celite into an NMR tube for analysis. Calculated NMR yields for the amination product are given in Table 7.



Scheme 27. Ligand screen for mesitylene systeme

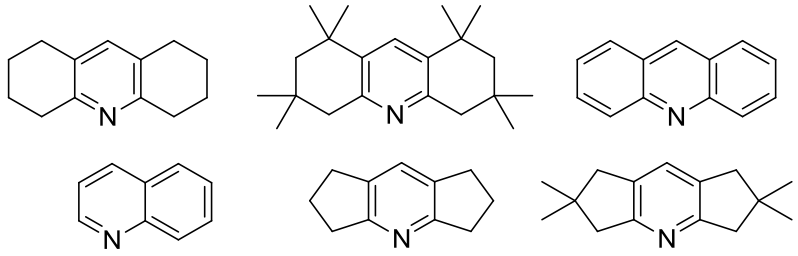


Figure 11. Ligands in listed order (left to right)

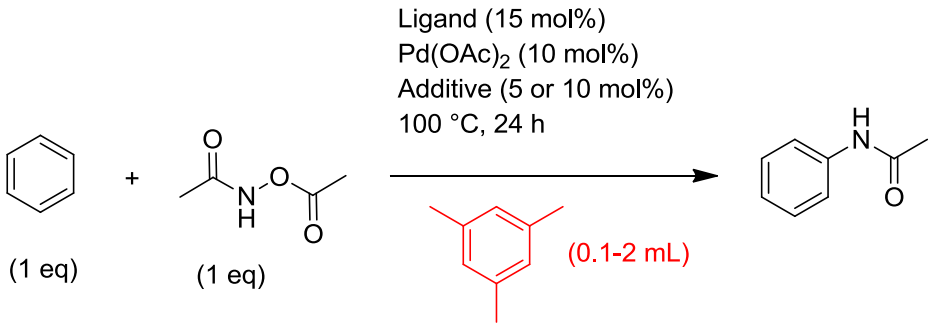
Table 7. Calculated NMR yields of mesitylene ligand screen

Entry	Ligand	Amount (mg)	Yield (%)
1TDN32-1	1,2,3,4,5,6,7,8-octahydroacridine	3.9	13.6 ± 1.3
1TDN32-2	1,1,3,3,6,6,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroacridine	6.3	15.6 ± 0.8
1TDN32-4	acridine	3.8	19.6 ± 0.9
1TDN32-10	quinoline	2.7	18.6 ± 1.7
1TDN32-12	1,2,3,5,6,7-hexahydrodicyclopenta[*b,e*]pyridine	x	16.9 ± 0.5
1TDN32-13	2,2,6,6-tetramethyl-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine	x	18.5 ± 0.1

3.10.2 Study of effects of mesitylene loading

In analogy to the previously established conditions for C-H amination in mesitylene, various volumes of said solvent were investigated to determine the optimal reaction volume for this system. To a 4 mL glass scintillation vial were added $Pd(OAc)_2$ (3.10 mg, 0.0140 mmol, 0.10 eq), *N*-acetoxyacetamide (32.4 mg, 0.140 mmol, 1.00 eq), a ligand (0.0210 mmol, 0.150 eq), AgOAc (1.20 mg, 0.00700 mmol, 0.050 eq) or HOAc (8.4 µL, 0.0140 mmol, 0.100 eq), and mesitylene (0.100-2.00 mL). Benzene (12.5 µL, 0.140 mmol, 1.00 eq) was added, and a magnetic stirring bar was inserted. The vial

was sealed with a plastic, Teflon-lined cap and was placed on a hot plate at 100 ^{O}C and for 24 h while stirring. After 24 h, the vials were removed from heat and allowed to cool to room temperature. To each vial was added 0.50 mL of a standard solution of 1,3-dinitrobenzene in $CDCl_3$ (10 mg/ mL), the vial was shaken, and the resulting mixture was filtered through a plug of celite into an NMR tube for analysis. Calculated NMR yields for the amination product are given in Table 8.



Scheme 28. Solvent loading screen for mesitylene system

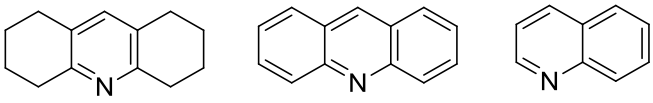


Figure 12. Tested ligands in listed order (left to right)

Table 8. Calculated NMR yields of mesitylene loading screen

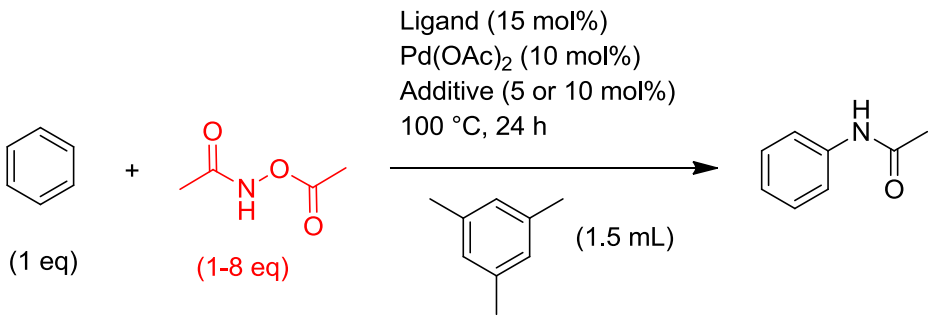
Entry	Ligand	Additive	Volume mesitylene (mL)	Yield (%)
1TDN36-1	1,2,3,4,5,6,7,8-octahydroacridine	HOAc	0.10	16.3 ± 0.6
1TDN36-2	"	"	0.25	14.7 ± 0.9
1TDN36-3	"	"	0.50	14.6 ± 1.7
1TDN36-4	"	"	0.75	15.9 ± 0.3

1TDN36-5	“	“	1.0	16.1 ± 0.1
1TDN36-6	acridine	HOAc	0.10	20.2 ± 0.6
1TDN36-7	“	“	0.25	19.1 ± 0.7
1TDN36-8	“	“	0.50	19.4 ± 0.4
1TDN36-9	“	“	0.75	19.5 ± 0.8
1TDN36-10	“	“	1.0	19.9 ± 0.4
1TDN36-11	quinoline	HOAc	0.10	21.2 ± 1.0
1TDN36-12	“	“	0.25	20.1 ± 0.8
1TDN36-13	“	“	0.50	20.0 ± 0.4
1TDN36-14	“	“	0.75	20.2 ± 0.9
1TDN36-15	“	“	1.0	20.9 ± 0.7
MM88A/B	acridine	AgOAc	0.10	9.9 ± 0.3
MM88C/D	“	“	0.25	14.8 ± 1.0
MM88E/F	“	“	0.50	17.0 ± 0.1
MM88G/H	“	“	0.75	20.1 ± 0.9
MM88I/J	“	“	1.0	20.1 ± 0.8
MM89A/B	1,2,3,4,5,6,7,8-octahydroacridine	AgOAc	0.10	13.8 ± 0.1
MM89C/D	“	“	0.25	14.2 ± 0.6
MM89E/F	“	“	0.50	13.6 ± 0.2
MM89G/H	“	“	0.75	14.9 ± 0.4
MM89I/J	“	“	1.0	14.6 ± 0.4
MM90A/B	quinoline	AgOAc	0.10	19.0 ± 0.3
MM90C/D	“	“	0.25	17.9 ± 0.1
MM90E/F	“	“	0.50	19.6 ± 0.5
MM90G/H	“	“	0.75	21.4 ± 0.4
MM90I/J	“	“	1.0	21.2 ± 1.1
1TDN36-16	acridine	HOAc	1.5	19.7 ± 1.0
1TDN36-17	“	“	2.0	18.6 ± 0.6
1TDN36-18	quinoline	HOAc	1.5	19.7 ± 0.1
1TDN36-19	“	“	2.0	20.0 ± 0.6

MM88K/L	acridine	AgOAc	1.5	20.4 ± 0.8
MM88M/N	“	“	2.0	21.9 ± 0.8
MM90K/L	quinoline	AgOAc	1.5	21.9 ± 0.3
MM90M/N	“	“	2.0	19.6 ± 1.3

3.10.3 Study of effects of amination reagent loading

In analogy to the previously established conditions for C-H amination in mesitylene, various volumes of said solvent were investigated to determine the optimal amination reagent loading for this system. To a 4 mL glass scintillation vial were added $Pd(OAc)_2$ (3.10 mg, 0.0140 mmol, 0.10 eq), *N*-acetoxyacetamide (1.00-8.00 eq), a ligand (0.0210 mmol, 0.150 eq), AgOAc (1.20 mg, 0.00700 mmol, 0.050 eq) or HOAc (8.4 µL, 0.0140 mmol, 0.100 eq), and mesitylene (1.5 mL, 10.8 mmol, 78 eq). Benzene (12.5 µL, 0.140 mmol, 1.00 eq) was added, and a magnetic stirring bar was inserted. The vial was sealed with a plastic, Teflon-lined cap and was placed on a hot plate at 100 ^{O}C and for 24 h while stirring. After 24 h, the vials were removed from heat and allowed to cool to room temperature. To each vial was added 0.50 mL of a standard solution of 1,3-dinitrobenzene in $CDCl_3$ (10 mg/ mL), the vial was shaken, and the resulting mixture was filtered through a plug of celite into an NMR tube for analysis. Calculated NMR yields for the amination product are given in Table 9.



Scheme 29. Amination reagent loading screen for mesitylene system

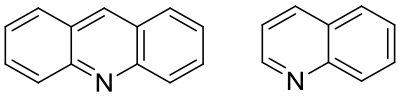


Figure 13. Tested ligands in listed order (left to right)

Table 9. Calculated NMR yields of amination reagent loading screen

Entry	Ligand	Additive	Amination reagent (eq)	Yield (%)
1TDN37-1	acridine	HOAc	2.00	31.1 ± 0.8
1TDN37-2	"	"	3.00	40.2 ± 0.4
1TDN37-3	"	"	4.00	**52.8 ± 0.2**
1TDN37-4	"	"	8.00	**56.4 ± 2.5**
1TDN37-5	quinoline	HOAc	2.00	32.7 ± 1.2
1TDN37-6	"	"	3.00	34.0 ± 1.0
1TDN37-7	"	"	4.00	38.5 ± 1.2
1TDN37-8	"	"	8.00	47.1 ± 2.5
MM92A/B	acridine	AgOAc	2.00	32.2 ± 0.2
MM92C/D	"	"	3.00	43.1 ± 0.9
MM92E/F	"	"	4.00	47.4 ± 2.3
MM92G/H	"	"	8.00	47.6 ± 3.9
MM93A/B	quinoline	AgOAc	2.00	34.1 ± 0.1
MM93C/D	"	"	3.00	42.2 ± 2.2
MM93E/F	"	"	4.00	50.3 ± 2.2
MM93G/H	"	"	8.00	**60.9 ± 3.5**

4. Future Directions

In the future, surely more substrates will be investigated, be they electron rich or poor, benzene analog or not. Some such substrates are naphthalene and *N*-methylimidazole, which have been touched upon in past research, but they have not been explored intensely enough to be discounted. Another potential direction is that of a more thorough amination reagent scope, and this is for the same reason as the substrate scope: applicability. In order for this reaction system to be seen as useful, it needs to be versatile, a characteristic it has just begun to show.

The ligand involved in this system will also be investigated, but in place of electron rich ligands, which have been used so far in the catalytic studies, electron deficient ligands will be explored. Mechanistically speaking, electron deficient ligands should favor the formation of desired product, but this claim certainly requires more evidence.

5. Attachments

5.1 GC-MS Spectra

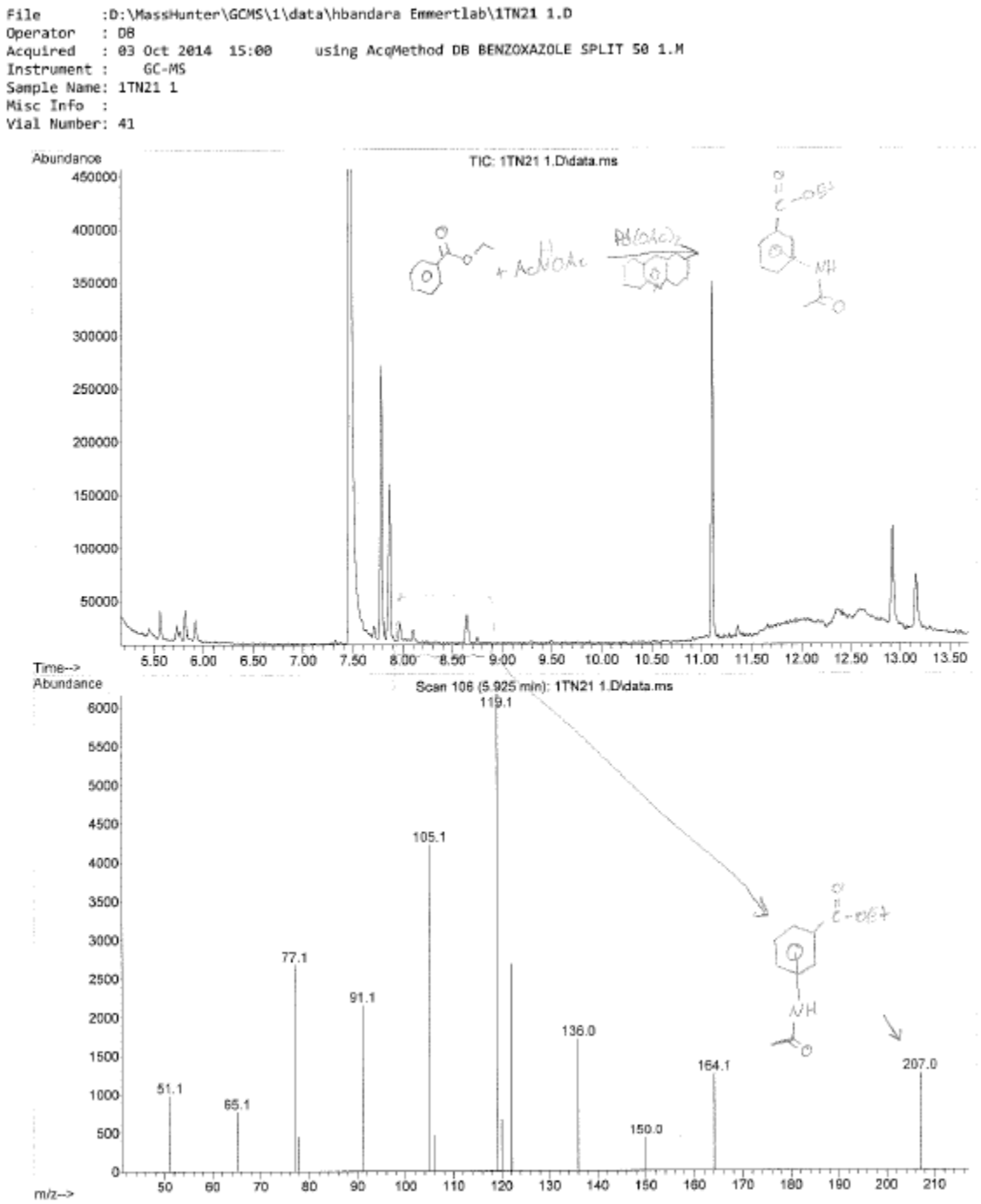


Figure 14. GC-MS spectrum from 1TDN21-1

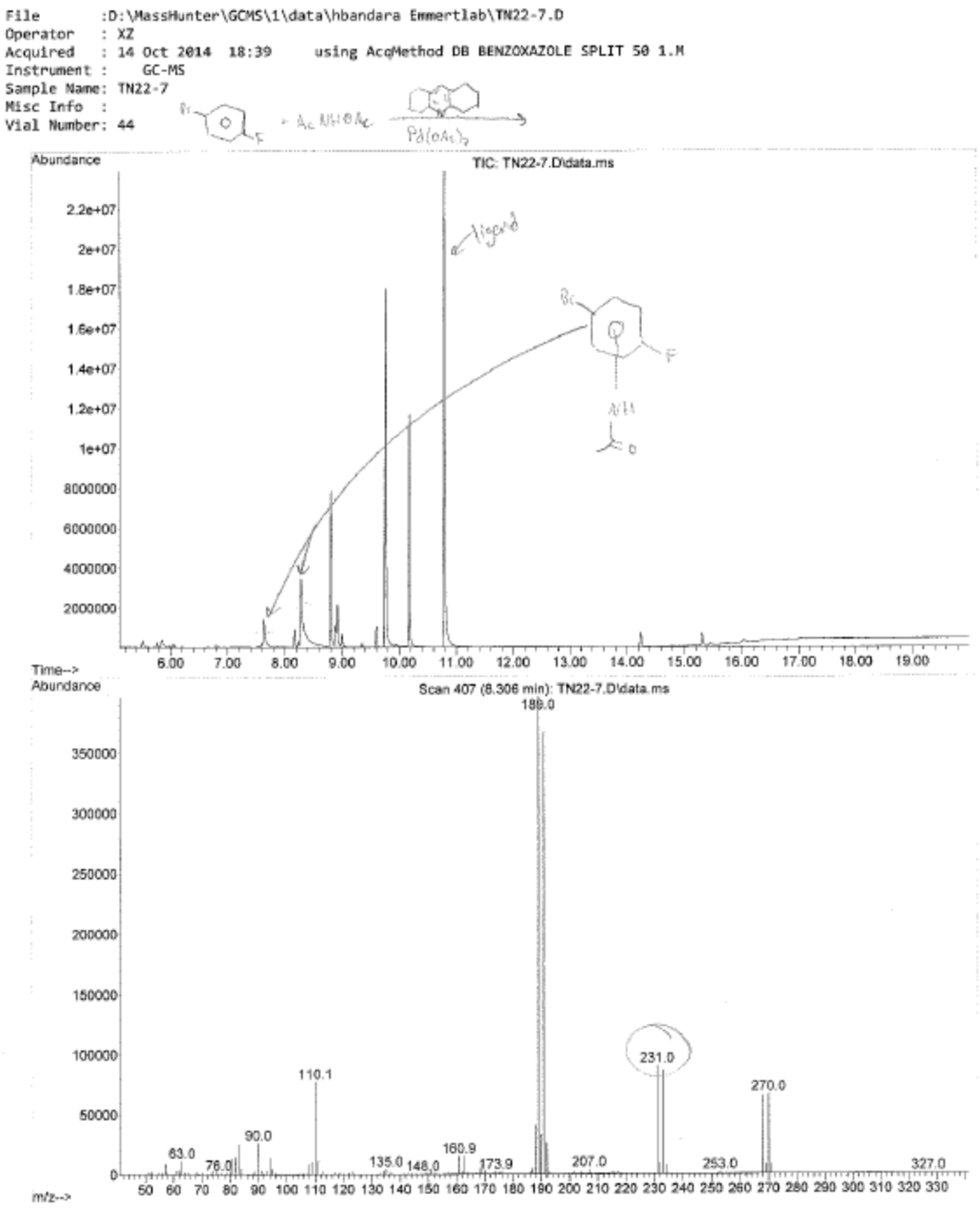


Figure 15. GC-MS spectrum for 1TDN22-7

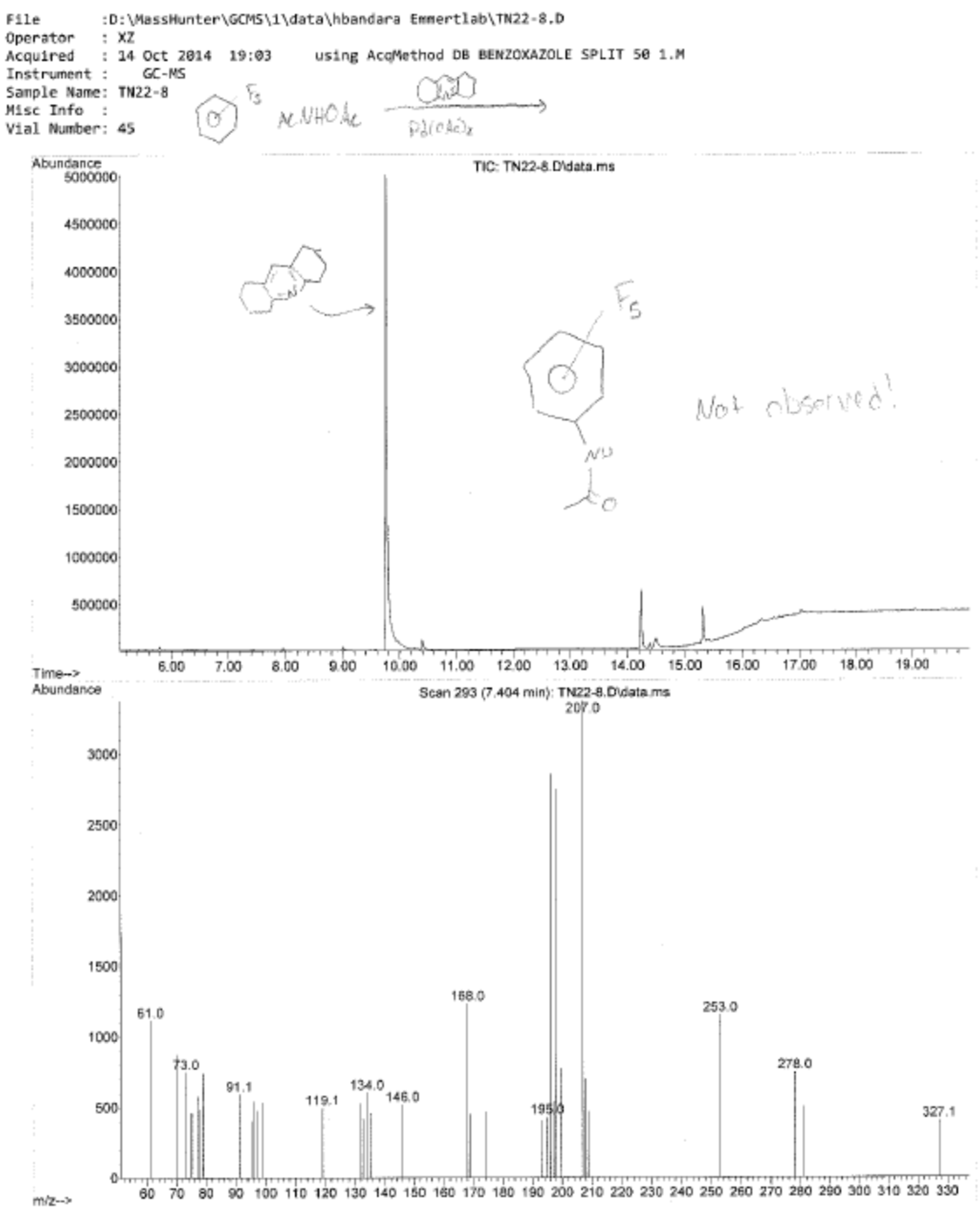


Figure 16. GC-MS spectrum for 1TDN22-8

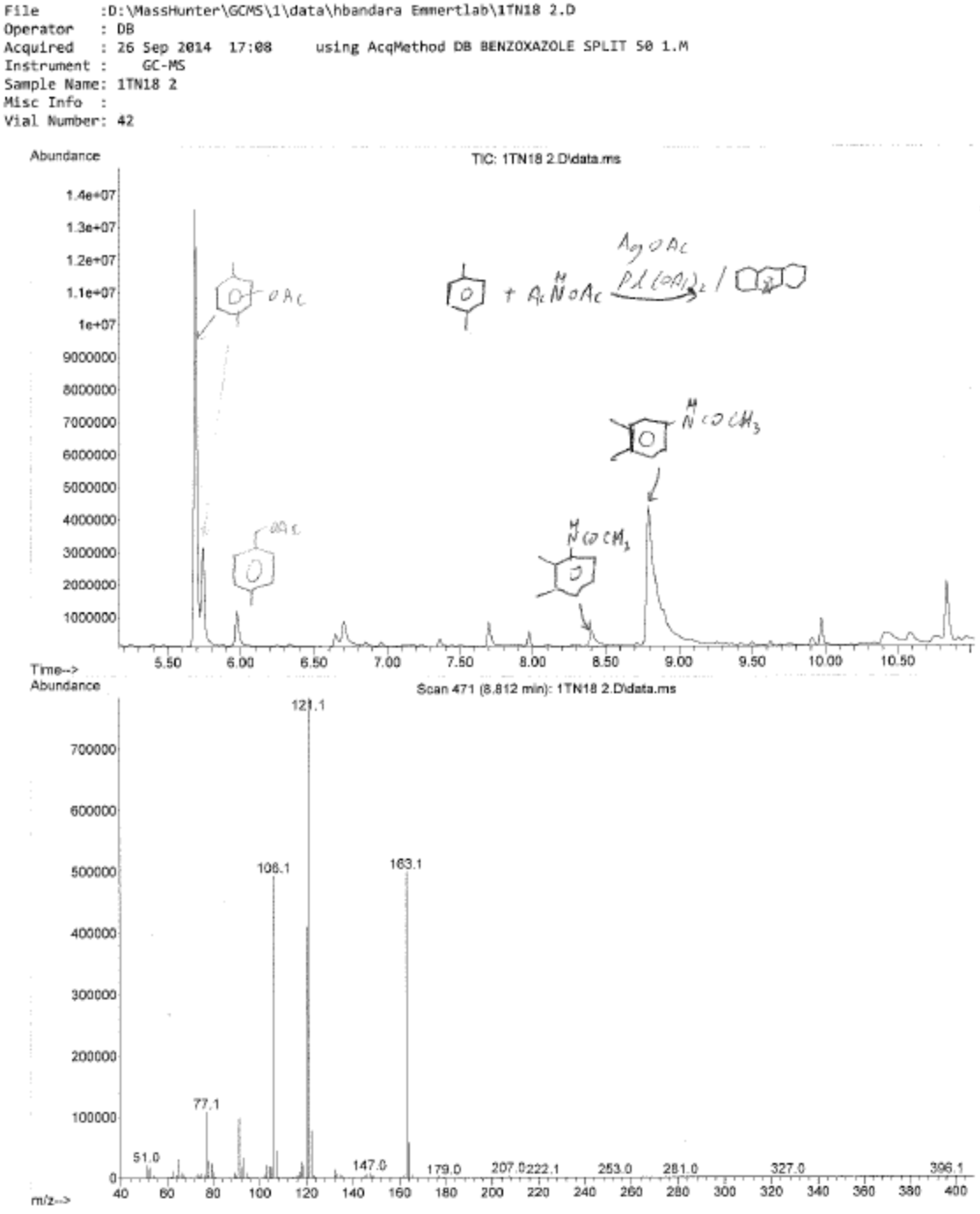


Figure 17. GC-MS spectrum for 1TDN18-8

File :D:\MassHunter\GCMS\1\data\mamantell Emmertlab\9-19-2014\TN18
... .D
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Instrument : GC-MS
Acquired : 19 Sep 2014 19:23 using AcqMethod DB BENZOXAZOLE SPLIT 50 1.M
Sample Name: TN18.1
Misc Info :

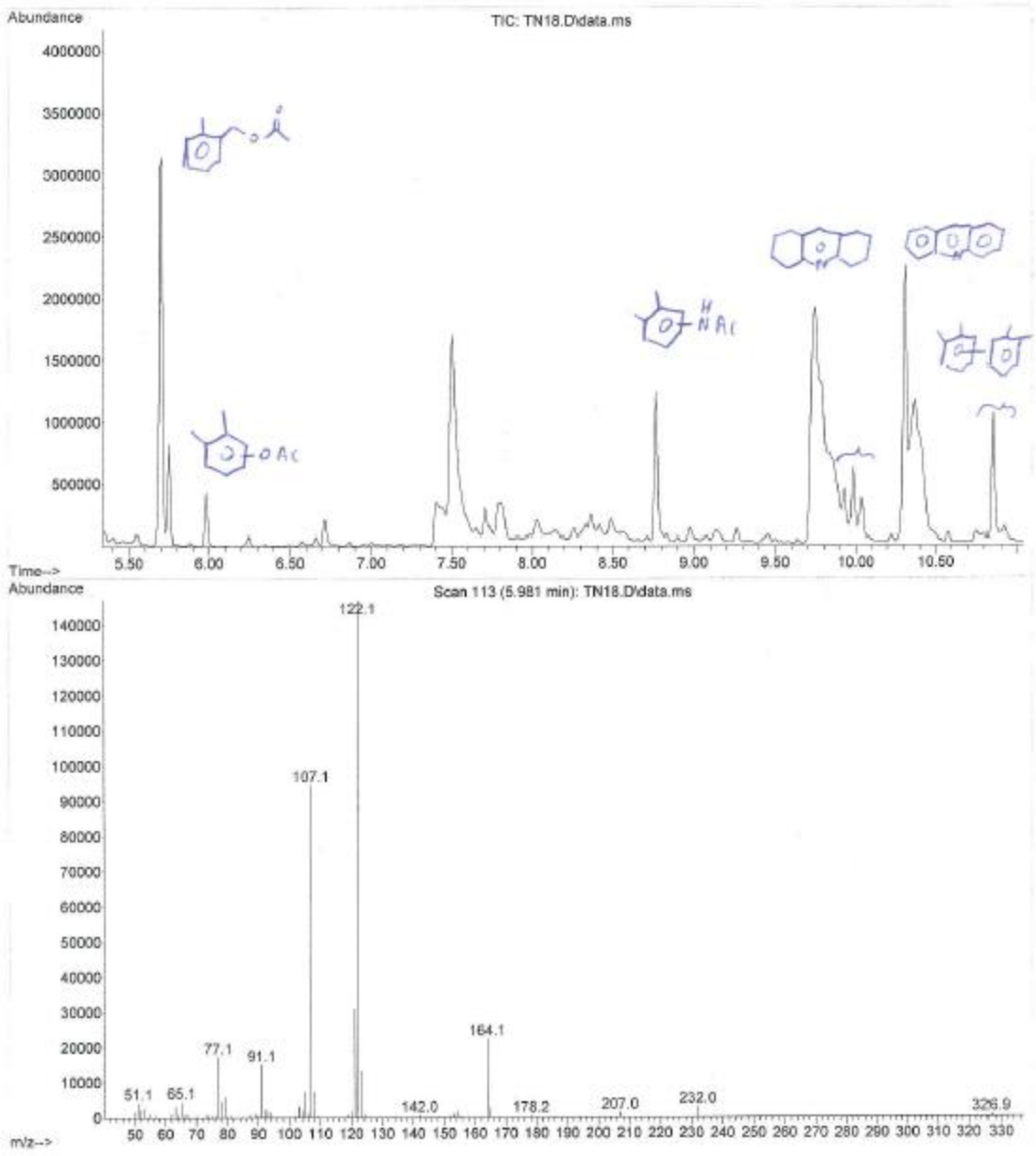

Figure 18. GC-MS spectrum of 1TDN18-5

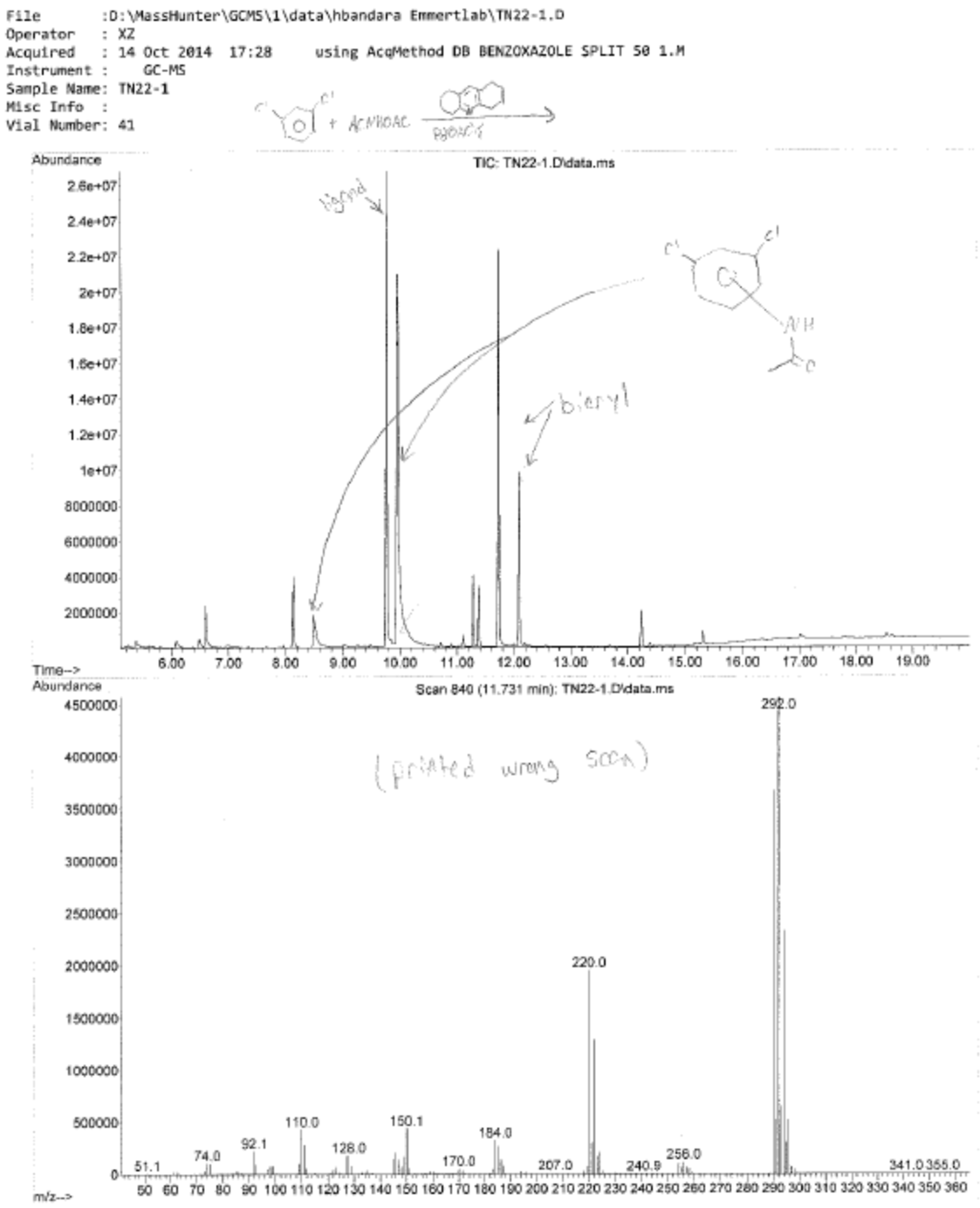

Figure 19. GC-MS spectrum for 1TDN22-1

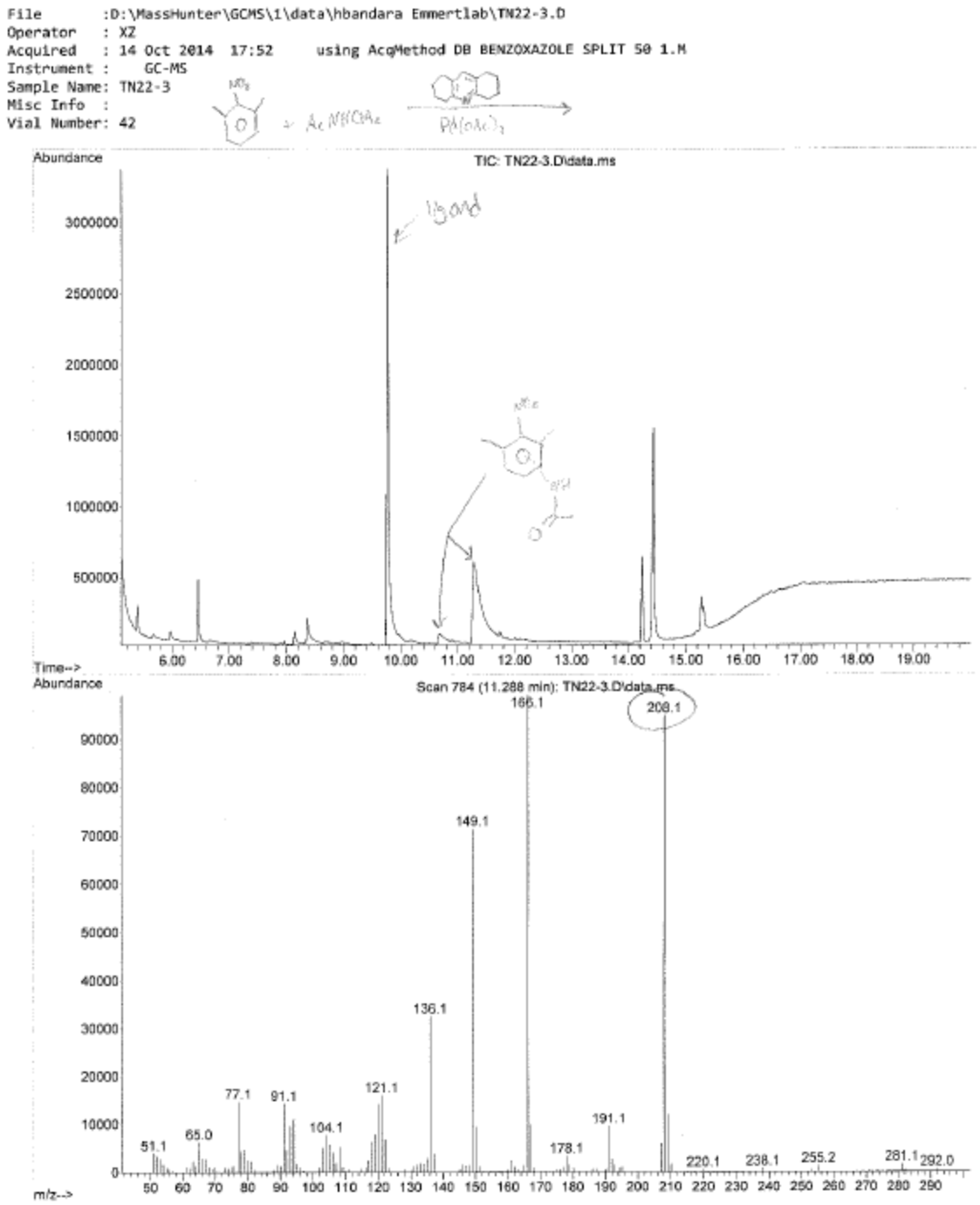

Figure 20. GC-MS spectrum for 1TDN22-2

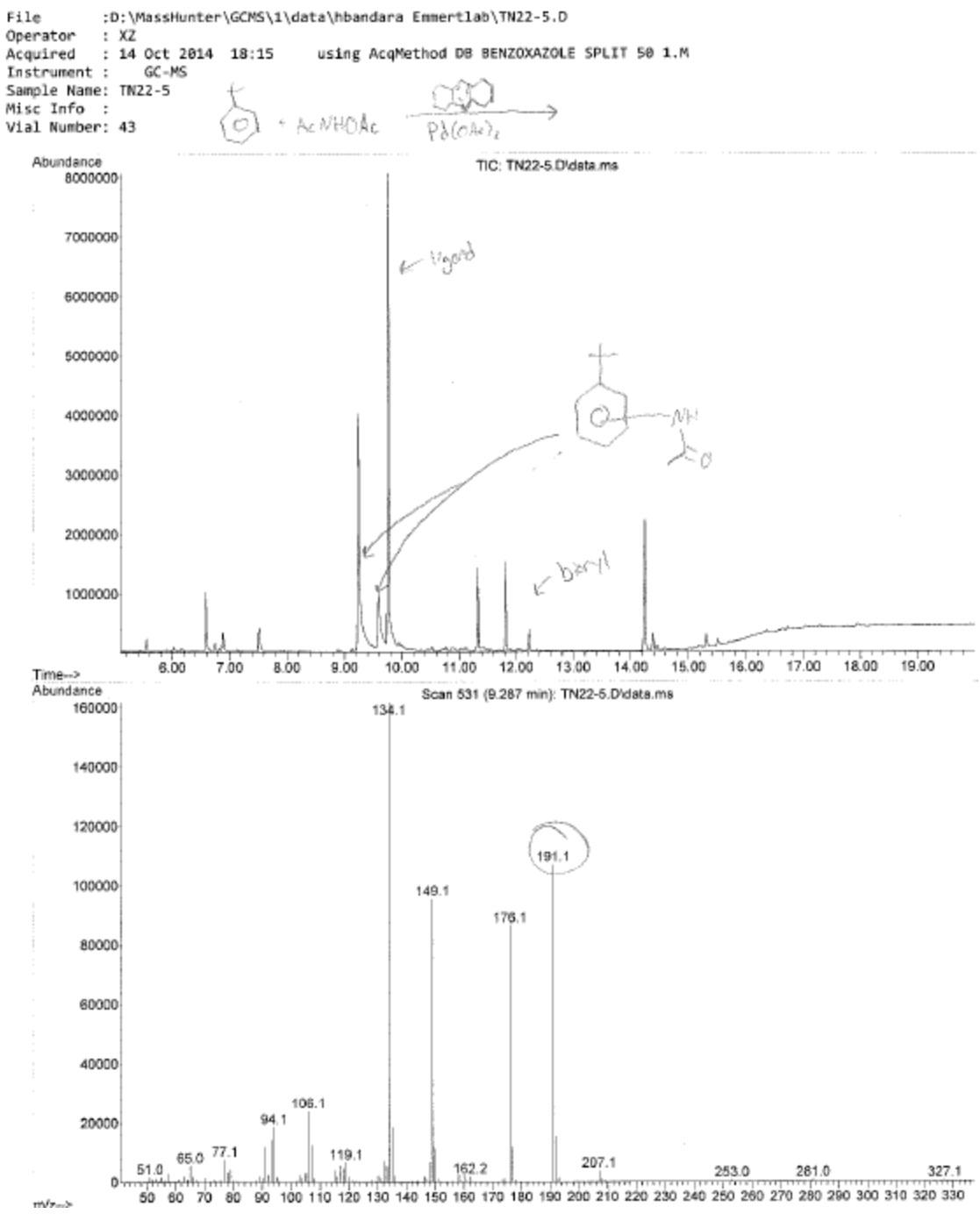

Figure 21. GC-MS spectrum for 1TDN22-3

5.2 ^{1}H-NMR Spectra

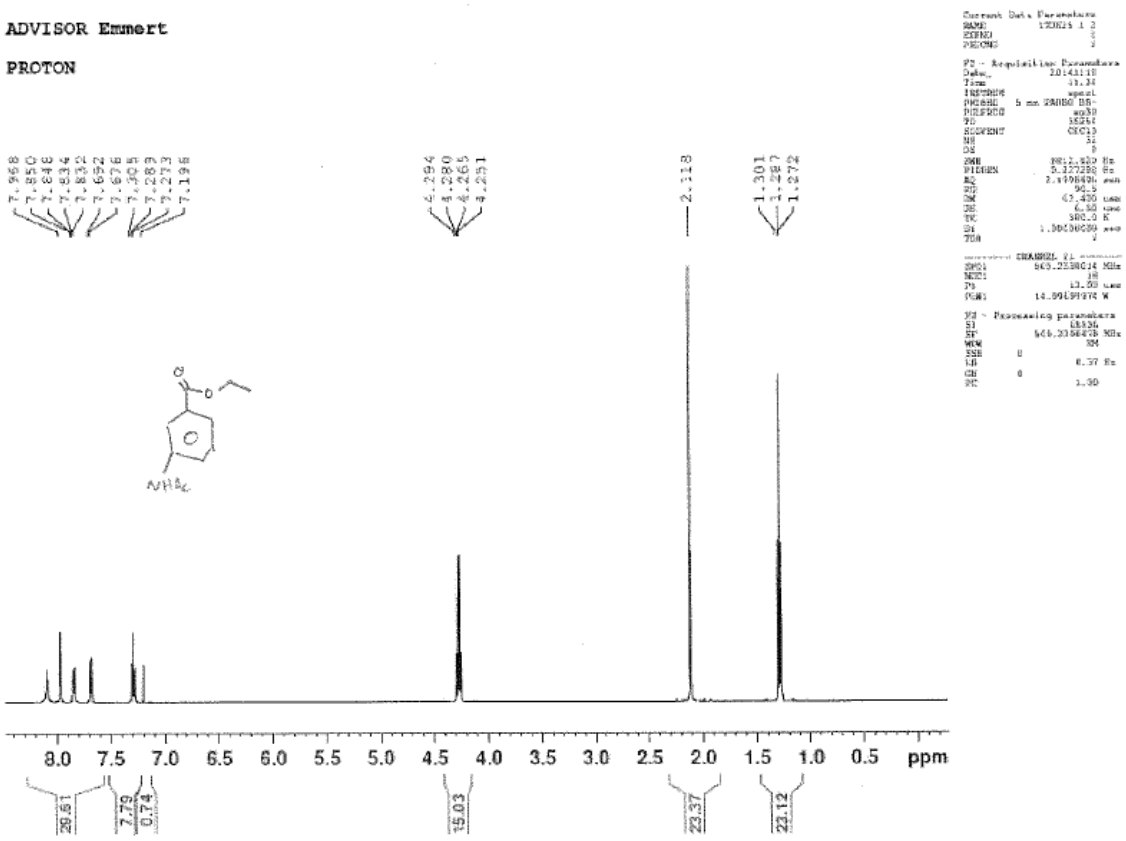

Figure 22. NMR spectrum corresponding to product 3.6.1

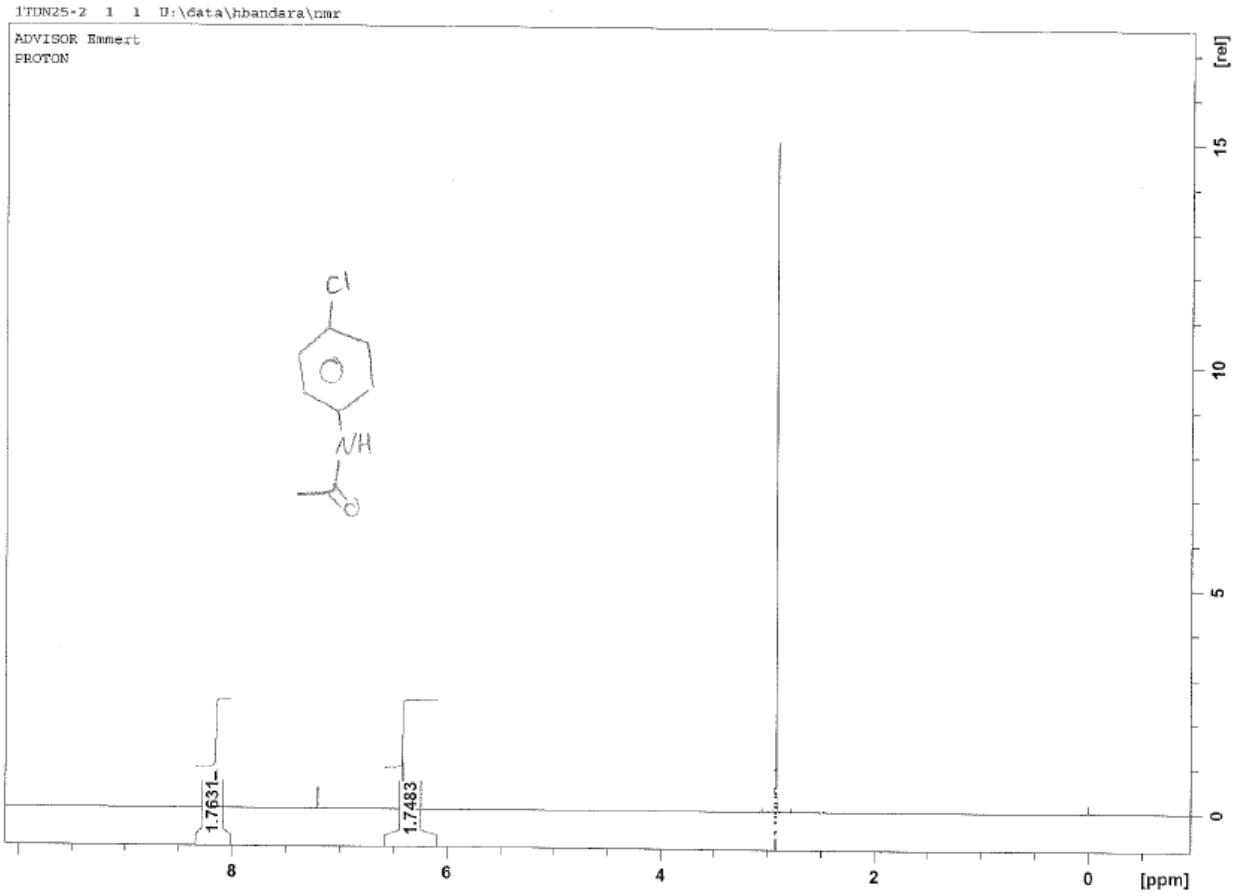

Figure 23. NMR spectrum corresponding to product 3.6.2

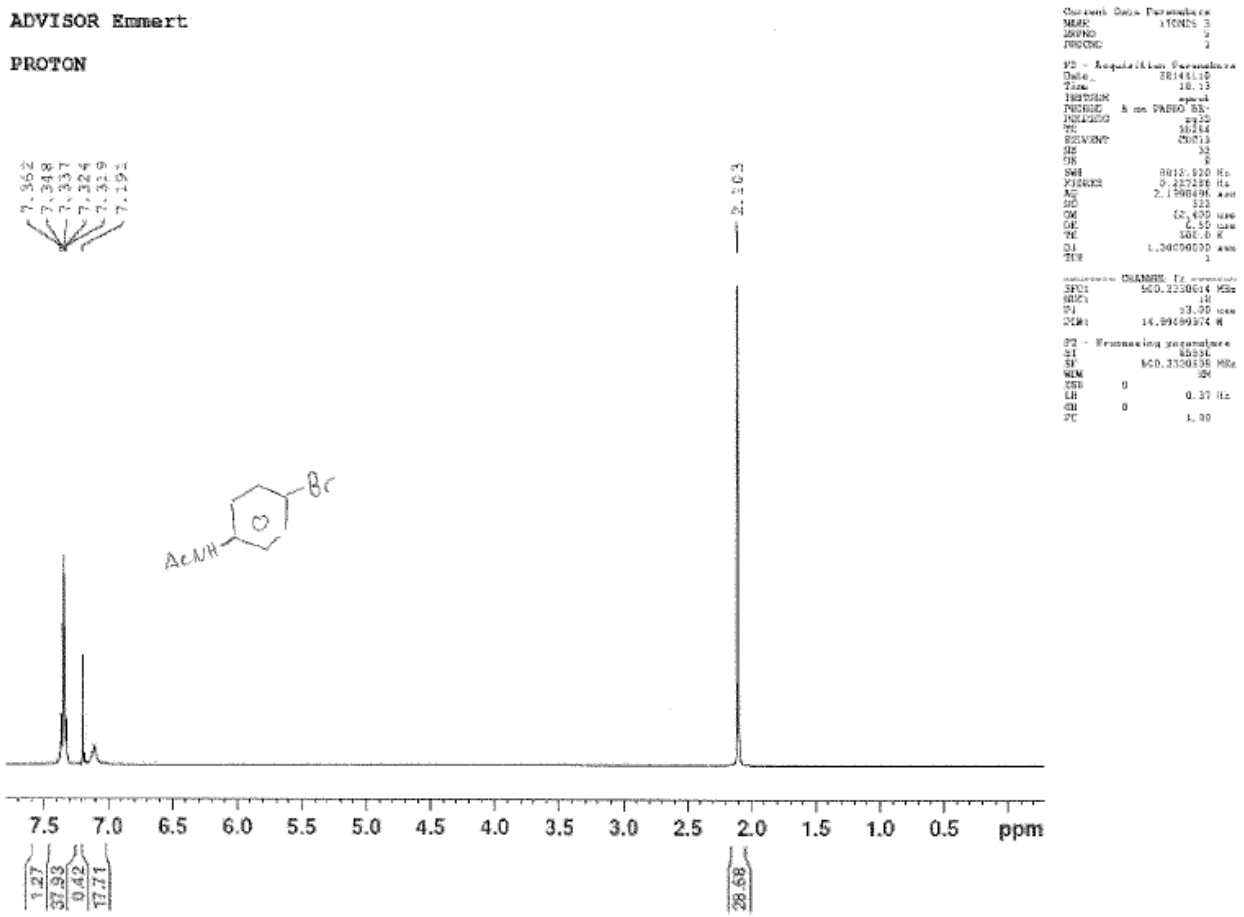

Figure 24. NMR spectrum corresponding to product 3.6.3

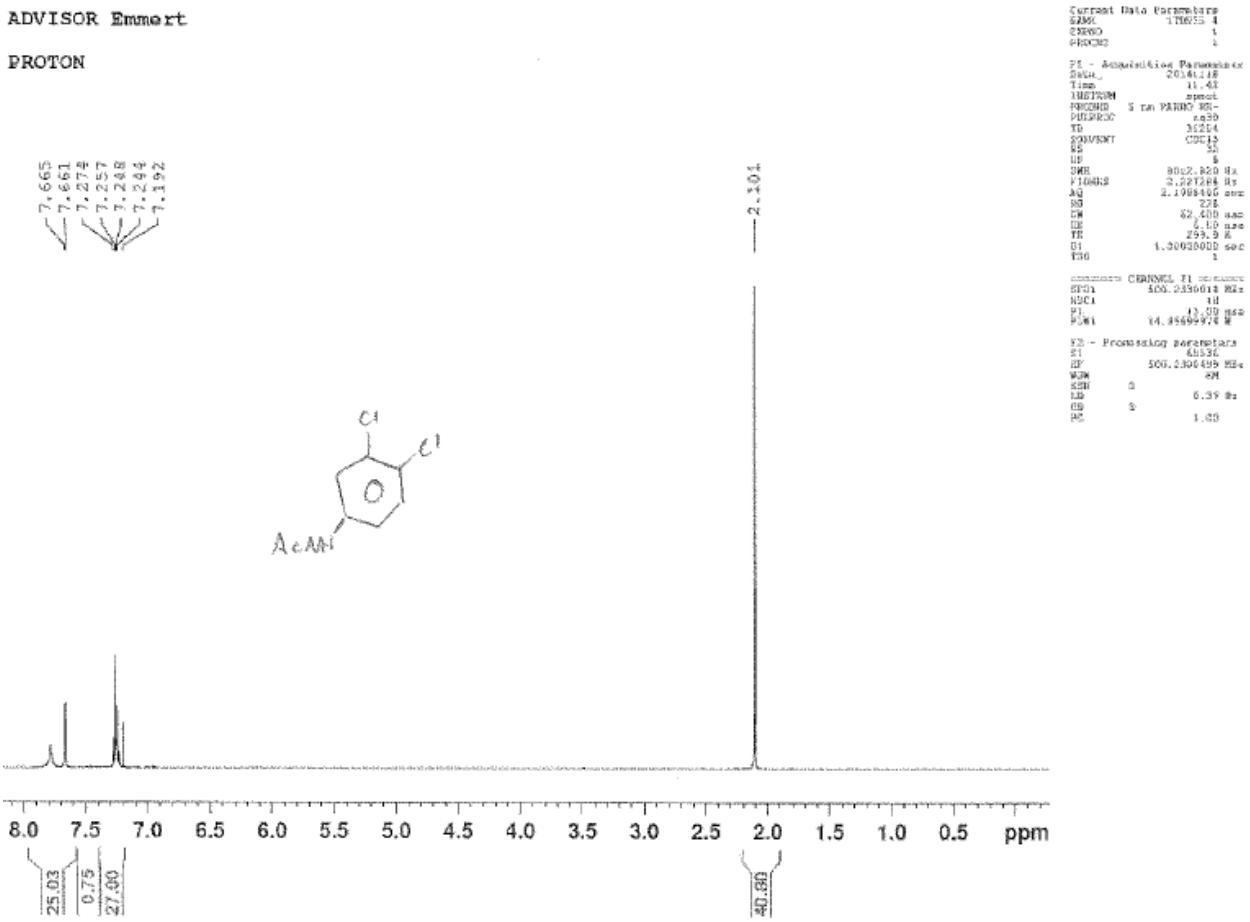

Figure 25. NMR spectrum corresponding to product 3.6.4

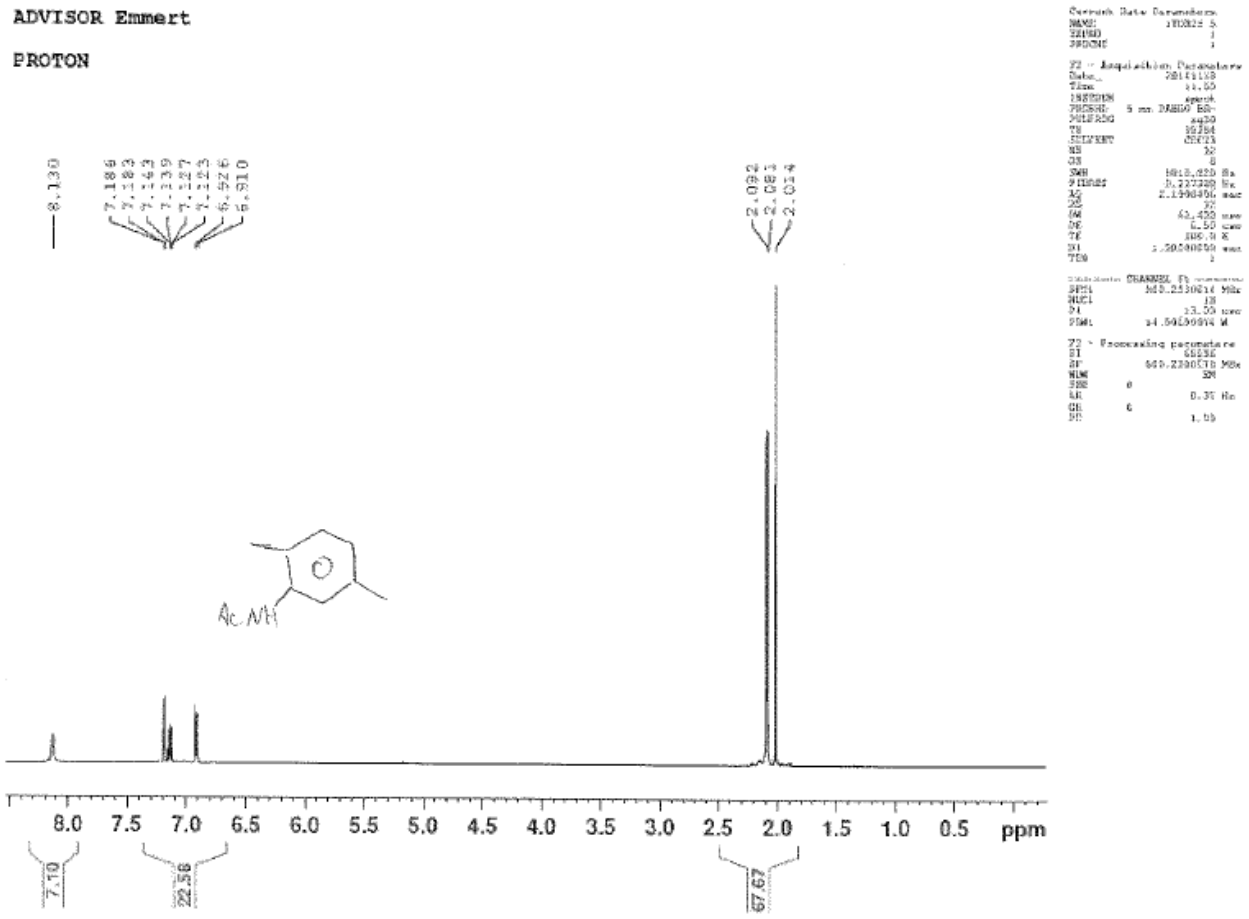

Figure 26. NMR spectrum corresponding to product 3.6.6

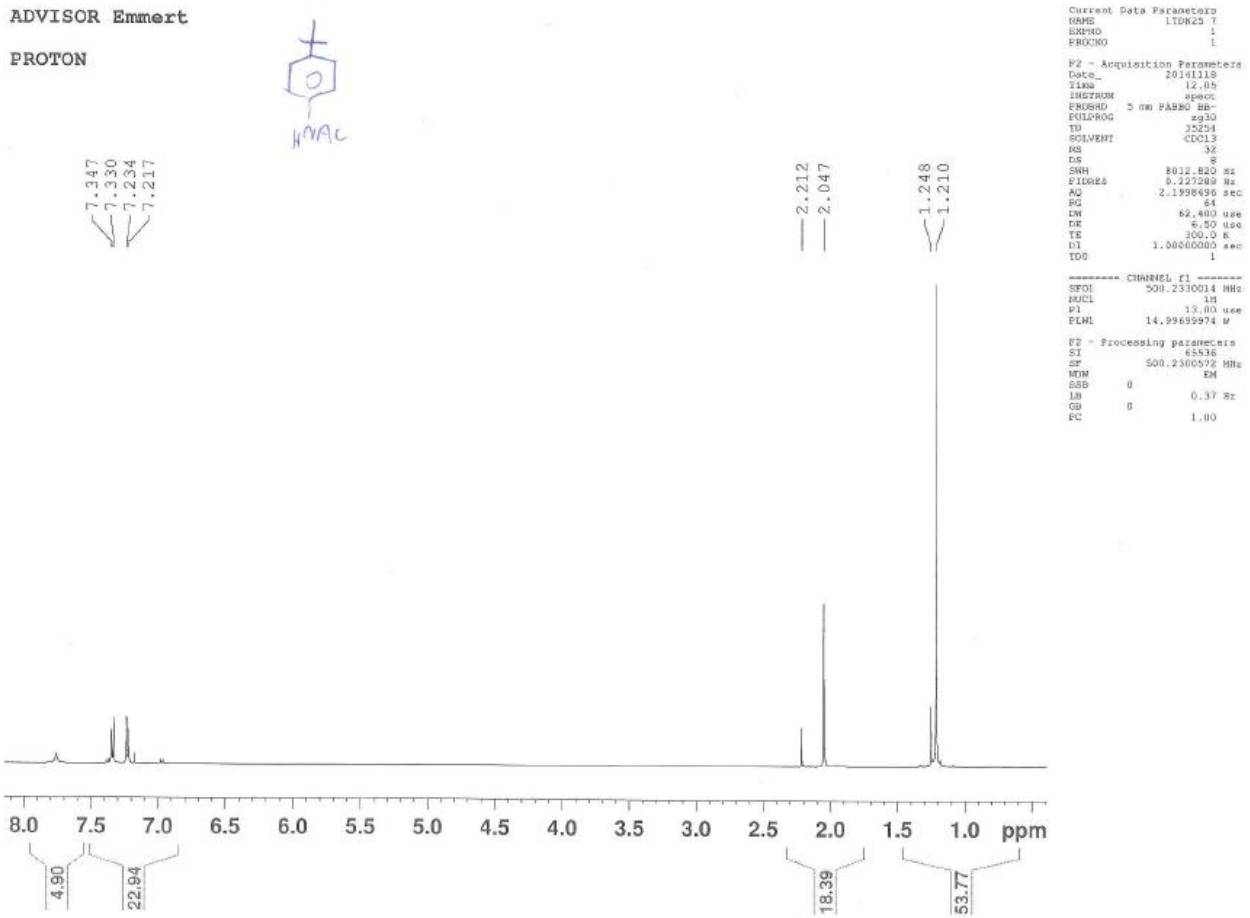

Figure 27. NMR spectrum corresponding to product 3.6.7

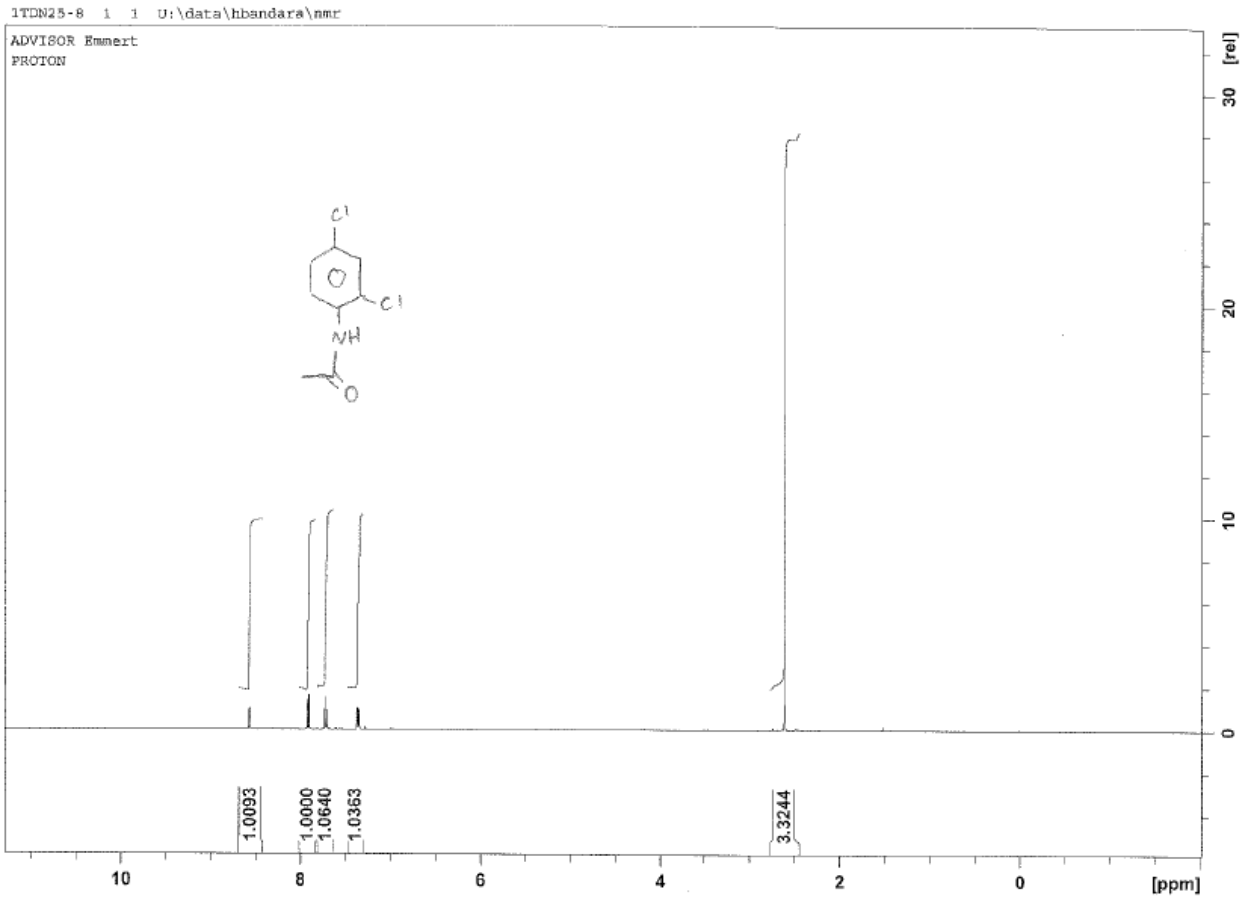

Figure 28. NMR spectrum corresponding to product 3.6.8

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