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Producing Dihydrofurans Using Palladium (II) Catalyst and Optimized Base

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Producing Dihydrofurans Using Palladium (II) Catalyst and Optimized Base

A Thesis

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Chandler Scott Mitchell

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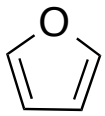
Abstract

Dihydrofurans serve as building blocks for other compounds in organic synthesis. The main goal of this project was to discover an efficient and relatively inexpensive pathway for producing monosubstituted dihydrofurans in high yield from cyclic boronic half acids. Aldehydes were converted to homoallylic alcohols by the addition of allylmagnesium bromide. The alcohols were then transformed into cyclic boronic half acids using ring-closing metathesis with Grubbs 1st Generation Catalyst and alkenyl boronic esters. Finally, monosubstituted dihydrofurans were produced using a palladium (II) catalyst with a base. Palladium (II) catalysts that were tested include [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, palladium (II) acetate with and without triphenylphosphine, palladium (II) chloride with and without triphenylphosphine, and bis(triphenylphosphine)palladium(II) dichloride. The effect of an alkyl halide on dihydrofuran yield due to Suzuki-Miyaura coupling side product formation was also observed using 1-bromo-3-phenylpropane. Due to time constraints potassium carbonate was the only base that was tested. The results indicate that dihydrofuran production is possible with various palladium (II) catalysts using potassium carbonate as a base. Palladium (II) acetate with the addition of triphenylphosphine appears to form dihydrofuran in the highest yield.

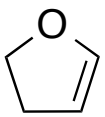
Background

Furans are of value in the world of chemistry because of their wide variety of applications. These compounds contain a five-membered aromatic ring with one oxygen and four carbon atoms. Numerous furan derivatives are widely used industrially because of their structure and properties. Derivatives of this heterocyclic set of compounds in particular, known as dihydrofurans, play both biological and chemical roles. Dihydrofurans differ from furans in that they contain the same five-membered ring, except two of the four carbons have been saturated with hydrogen atoms.



furan

3,4-dihydrofuran



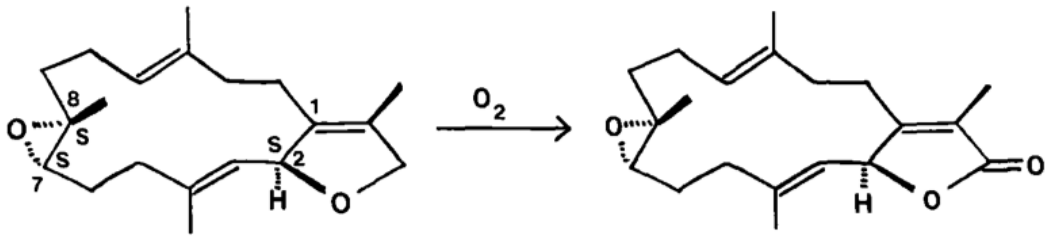
2,3-dihydrofuran

Utility of Dihydrofurans

Dihydrofurans often find their use in the pharmaceutical industry. In a general sense, they are commonly used in the synthesis of other compounds that might be valuable themselves. Some dihydrofuran derivatives also possess a wide variety of bioactivities, including antibacterial effects in biological systems (Cui). Ranitidine is an example of a dihydrofuran-containing compound. This drug treats and prevents a multitude of problems seen in the process of digestion, including heartburn, gastroesophageal reflux disease, and ulcers along the lining of the stomach and intestines (Buchta).

The synthesis of dihydrofurans has proven to be quite difficult. The natural products sarcophytoxide and sarcophine contain substituted dihydrofurans. These natural products are

isolated from a couple species of soft coral, but the extraction tends to be an arduous procedure with limited recovery.



1 (+)-sarcophytoxide **2** (+)-sarcophine

In the laboratory, production of dihydrofurans is a challenging process. The traditional means of production are considered unsatisfactory because of the high costs of the catalysts utilized within the reaction, the difficulty of starting material acquisition, the time that goes into the process, and the harsh reaction conditions (Cui).

Cyclic Boronic Half Acid Formation

The use of cyclic boronic half acids to make dihydrofurans will prove to be a much better alternative to the traditional synthetic routes. For one, boron compounds for the most part are stable and easy to obtain through chemical procedures that do not produce measurable levels of toxins (Batory). Secondly, there are experimental works published with chemical procedures similar to the production of CBHAs, so some knowledge related to the subject has already been laid out (Casey). Lastly, this procedure will require the use of a compound known as Robert H. Grubb's catalyst. The use of this compound is advantageous because of its high efficiency, availability, stability, and ability to perform reactions with multiple functional groups (Greco). The reaction for CBHA production with the Grubb's catalyst is shown below (Figure 3).

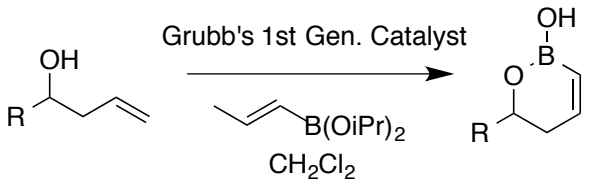


Figure 3. General ring closing metathesis reaction scheme used for step two of the synthesis pathway.

Grignard Reaction

A Grignard reaction is a relatively simple method of forming carbon-carbon bonds where addition takes place on the carbon of a ketone or aldehyde (Smith). Given that the starting compounds for this experiment are aldehydes without any other reactive functional groups, a Grignard reaction fits perfectly into the design of this synthetic step, as it requires the addition of three additional carbons. The general reaction scheme is shown below (Figure 2) where formation of homoallylic alcohol takes place, which can then be used to create cyclic boronic half acids.

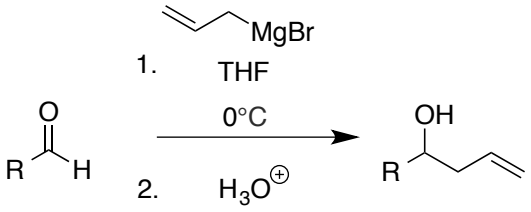


Figure 2. General Grignard reaction scheme used for step one of the synthesis pathway.

Palladium Catalyst

Palladium-based catalysts were selected for this final reaction because palladium is widely recognized for its ability to foster carbon-carbon bond formation ("Palladium-Catalyzed Cross Couplings in Organic Synthesis: Scientific Background on the Nobel Prize

in Chemistry 2010"). Palladium (II) has a d^8 electron configuration and often forms organometallic compounds with square planar geometries. This specific geometry allows for two open axial coordination sites, which make it a great catalyst. Additionally, palladium has two characteristics that make it unique from other transition metals. For one, its ground-state electronic structure is $4d^{10}5s^0$, and as a result is the only transition metal with a filled *d* orbital coupled with an empty *s* orbital. Secondly, the lowest *d* to *p* transition for palladium is larger in energy than the same transition for similar metals. Consequently, palladium's catalytic activity is presumed to arise from its 4*d* electrons. This likely plays a large role in making palladium such a great catalyst for these types of reactions (Hartings). The general reaction scheme is shown below (Figure 4).

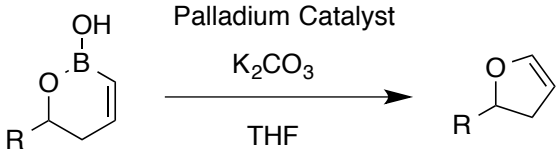


Figure 4. General palladium (II) catalyst-based reaction scheme used for step three of the synthesis pathway.

Suzuki-Miyaura Coupling

It is well documented that palladium catalysts are often used to perform what is called Suzuki-Miyaura coupling. Reported in 1979 by Akira Suzuki, this reaction involves the coupling of aryl halides with organoboronic acids. It is one of the most efficient methods of carbon-carbon bond formation known today. This coupling reaction is commonly used to synthesize poly-olefins, syrenes, and substituted biphenyls, and has even integrated alkyl bromides (Kovala-Demertzi). Palladium is a terrific catalyst for this coupling reaction because is has just the right orbital energy to associate with a carbon-carbon double bond

(Hartings). The following general reaction scheme depicts the outcome of a Suzuki-Miyaura coupling reaction using cyclic boronic half acids and an alkyl halide as starting materials (Figure 5).

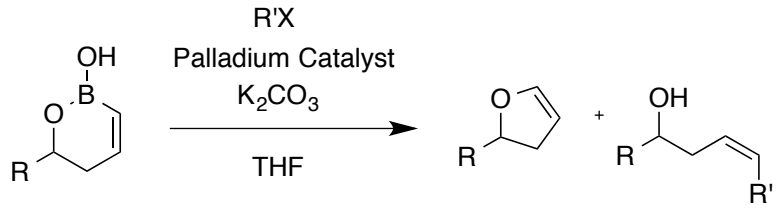


Figure 5. Proposed reaction scheme for palladium-based reaction with alkyl halide introduced. The two products from this reaction are a Suzuki-Miyaura coupling product and a monosubstituted dihydrofuran byproduct. R=aryl. R'= aryl, vinyl.

This reaction is extremely useful in organic synthesis because the geometry of the double bond is preserved due to the stereospecificity of the Suzuki-Miyaura coupling reaction. When used with cyclic boronic half acids, the result is a *cis*-double bond. (McNulty).

As the reaction scheme shows, this coupling reaction under certain conditions produces a dihydrofuran side-product. Because dihydrofurans have value of their own, it is the goal of this project to tweak the conditions used in the above Suzuki-Miyaura coupling reaction to optimize dihydrofuran side-product formation. To do this, different palladium (II) catalysts will be used in the final step of the synthetic pathway. Recent experiments have shown that this palladium catalyst based reaction also necessitates the use of a base. In 2011, Amatore and coworkers discovered that the base actually plays three roles that favor the reaction: 1) Formation of the activated palladium complex, 2) promotion of a reductive elimination from an intermediate palladium complex in the reaction, and 3) formation a trialkyl borate intermediate (Amatore et al.). It will be interesting to see if certain palladium

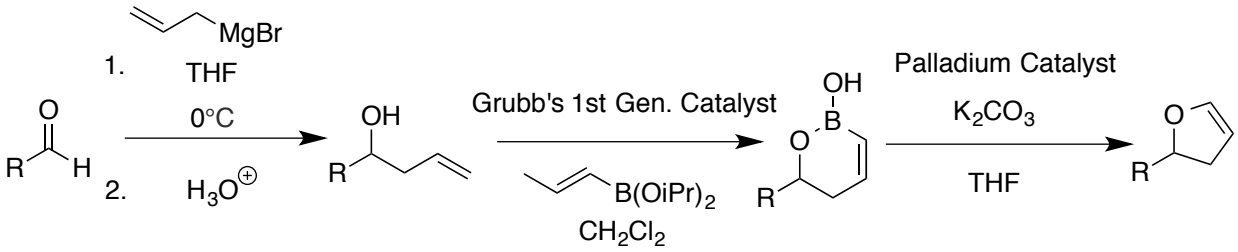
catalysts and bases favor the dihydrofuran or coupling product when an alkyl halide is introduced to the reaction.

Project Design

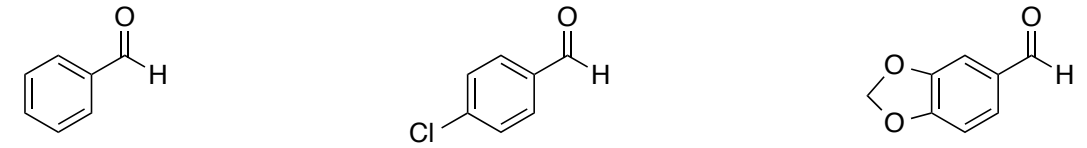
The first step of the synthesis of dihydrofurans is to form homoallylic alcohols, which will then undergo ring-closing metathesis to form cyclic boronic half acids. That entails that this Grignard reaction involve the introduction of an allyl group onto the aldehyde carbon. Once the homoallylic alcohols are successfully created and isolated, they are now ready for the next step of the synthesis pathway: cyclic boronic half acid formation. Once this is complete, the final reaction involves the formation of dihydrofurans from the cyclic boronic half acids created in the previous step using a palladium-based catalyst. Palladium catalysts that were used for this reaction step include [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, palladium (II) acetate, palladium (II) chloride, and bis(triphenylphosphine)palladium(II) dichloride. Additionally, triphenylphosphine was used in combination with palladium (II) acetate and palladium (II) chloride. This is because phosphines are labile, sometimes requiring additional ligand ("Palladium-Catalyzed Cross Couplings in Organic Synthesis: Scientific Background on the Nobel Prize in Chemistry 2010"). Supplementation with PPh_3 helps keep the palladium coordinated despite loss of the labile phosphine ligands. While it is confirmed that other bases can be used for this reaction, potassium carbonate is well documented and is therefore a good starting point for base selection when testing different palladium (II) catalysts (Lipshutz et al.).

Results

Reaction Scheme:



Three aldehydes were selected as starting material for this synthetic procedure. These three aldehydes were benzaldehyde, 4-chlorobenzaldehyde, and piperonal shown below (Figure 6).



Benzaldehyde 4-Chlorobenzaldehyde Piperonal

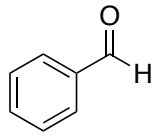
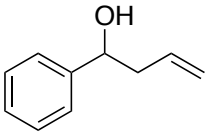
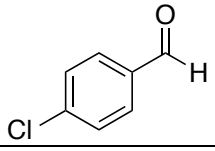
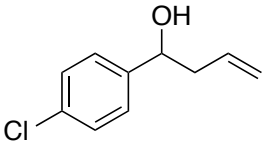
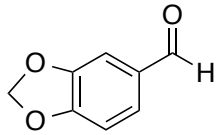
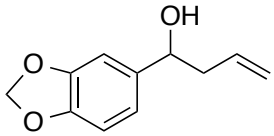
Figure 6: Three aldehyde starting compounds to produce homoallylic alcohols.

All three aldehydes derivatives were specifically selected because of their relatively large molecular weight. A higher molecular weight allows for easier separation of products. This is specifically useful for CBHA separation later on, which can be isolated by recrystallization, a process that takes less time with higher molecular weights.

Conversion of the three aldehydes to homoallylic alcohols using the step one Grignard reaction shown in Figure 2 resulted in comparable yields (Table 1). These yields, however, were rather low. The reason for such minimal yields likely has to do with the fact that these starting aldehydes and the Grignard reagent were not recently purchased. As a

result, air exposure over time has likely increased decomposition. There is also the possibility of contamination. Had these aldehydes been extensively purified before use and the Grignard reagent recently purchased, the resulting homoallylic alcohols would likely have higher yields. Despite low yields, all three homoallylic alcohols were successfully made.

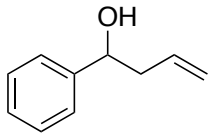
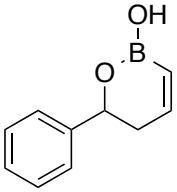
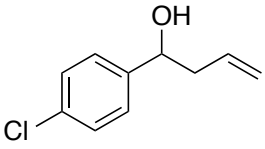
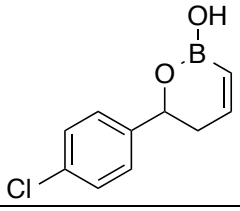
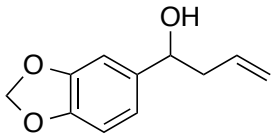
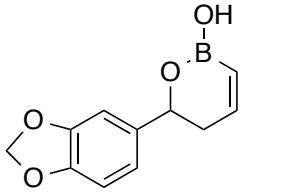
Table 1: Aldehyde reactants and homoallylic alcohol products from the step one Grignard reaction and their respective yields.

Aldehyde	Homoallylic Alcohol	% Yield
		36.1%
		34.2%
		32.5%

H^1 NMR data of these alcohol products was collected before and after purification. Their spectra after purification are shown in the appendix.

Upon completion of step one of the synthetic pathway, the alcohols shown in Figure 2 were purified enough for cyclic boronic half acid production. This was done by microwaving each alcohol with 1.5 equivalents of the trans-1-propen-1-ylboronic acid diisopropyl ester under nitrogen in methylene chloride. The solution was then washed with water and brine solution. The organic extracted was dried, filtered, and concentrated before collecting ^1H NMR data. Finally, the product was purified with column chromatography and ^1H NMR data was collected again. The yields for each CBHA product are shown below (Table 2).

Table 2: Homoallylic alcohol reactants and cyclic boronic half acid products from the step two ring-closing metathesis reaction and their respective yields.

Homoallylic Alcohol	Cyclic Boronic Half Acid	% Yield
		85.7%
		79.4%
		82.4%

H^1 NMR data for these CBHA products was collected before and after purification. Their spectra after purification are shown in the appendix.

With the purification of three unique cyclic boronic half acid derivatives, the next phase of the study was to experiment with different palladium (II) catalysts and bases. Due to time constraints, the only base that was tested was K_2CO_3. Palladium (II) catalysts that were tested include [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, palladium (II) acetate, palladium (II) acetate with the addition of triphenylphosphine, palladium (II) chloride, palladium (II) chloride with the addition of triphenylphosphine, and bis(triphenylphosphine)palladium(II) dichloride. All experimentation with these catalysts included the use of potassium carbonate as a base and tetrahydrofuran as a solvent. To keep the effects of the CBHA's substitution on each palladium (II) catalyst's efficiency controlled, only the 4-chlorobenzaldehyde CBHA derivative was used in this part of the study. Each of

these palladium-catalyzed reactions began with 0.05 mL of 4-chlorobenzaldehyde CBHA starting material. The theoretical yield for these reactions was calculated to be 0.043 grams of dihydrofuran product. The final masses of each product mixture for all palladium-catalyzed reactions are recorded in Table 3 and the resulting CBHA derivative is shown below (Figure 7).

Table 3: Final mass of each product mixture for 4-chlorobenzaldehyde dihydrofuran reactions with percent yields. Masses were not collected if ^{1}H NMR did not show dihydrofuran production.

Catalyst	(dppf)$PdCl_2$	$Pd(OAc)_2$	$PdCl_2(PPh_3)_2$	$Pd(OAc)_2$+ PPh_3	$PdCl_2$	$PdCl_2$+PPh_3
RX	0.038g (88.4%)	N/A	0.035g (81.4%)	0.038g (88.4%)	N/A	N/A
No RX	0.035g (81.4%)	N/A	0.037g (86.0%)	0.040g (93.0%)	N/A	0.033g (76.7%)

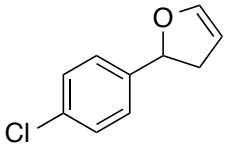


Figure 7. 4-Chlorobenzaldehyde Dihydrofuran derivative.

Once these reactions were completed, ^{1}H NMR data was collected. Their spectra are shown in Appendix Figure 1a-f.

The presence of an alkyl halide was also tested with these reactions to see if Suzuki-Miyaura coupling would take place. The alkyl halide selected was 1-bromo-3-phenylpropane.

The same palladium (II) catalysts were used for this part of the experiment except for palladium (II) chloride with and without the addition of triphenylphosphine due to time constraints. ^{1}H NMR data for these reactions was collected and their spectra are shown in Appendix Figure 2a-d.

Discussion

Observing the ^{1}H NMR spectra in Figure 8a-c., it is clear that all three homoallylic alcohol derivatives were successfully formed and collected after purification. The three key signals that infer homoallylic alcohol product formation appear around 4.7 ppm, 5.1 ppm, and 5.8 ppm. The terminal alkene within the allyl group is responsible for these three signals, with each corresponding to the hydrogens shown below (Figure 8).

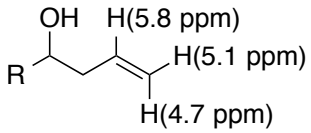


Figure 8. ^{1}H NMR signal values of the three hydrogens located on each homoallylic alcohol's vinyl group.

While there appears to be some initial aldehyde (appearing just below 10 ppm) remaining in all three product mixtures, these aldehyde peaks are miniscule relative to the other signals. There also appears to be some remaining solvent in each spectra. Given more time, this solvent would be removed to give cleaner spectra. All in all, the data suggests that these three homoallylic alcohols are ready for cyclic boronic half acid production.

The main signals that points to CBHA formation can be found at about 6.9 ppm and 5.8 ppm. These peaks correspond to the hydrogens on the alkene located within the boronic ring shown below (Figure 9).

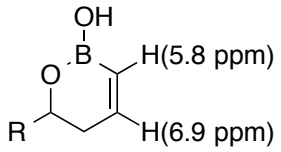


Figure 9. ^{1}H NMR signal values of the two hydrogens located on each CBHA's boronic ring alkene group.

Product formation of the benzaldehyde and 4-chlorobenzaldehyde CBHA derivatives is easy to detect within their respective spectra because of the similar lone signal right at 6.9. In the case of the piperonal CBHA, however, this signal is covered up by other signals from its aromatic ring and is not as easily detected. Its spectrum also does not appear as clean as the other two, but it contains a signal right at 5.8, indicating that the piperonal CBHA derivative is likely within this isolate product mixture. Moving forward, the benzaldehyde and 4-chlorobenzaldehyde CBHA derivatives are clearly ready for dihydrofuran production, but the piperonal derivative remains in question.

Two of the three CBHA's have successfully been made, and palladium catalyst and base testing can now take place. 4-Chlorobenzaldehyde CBHA was selected out of these two at random and potassium carbonate was selected as the controlled base to first observed differences amongst only the palladium catalysts. The various catalysts, excluding palladium (II) chloride with and without the addition of triphenylphosphine (which was solely tested without), were tested with and without an alkyl halide present. When viewing the resulting ^{1}H NMR data, there were three outcomes to watch for: dihydrofuran formation, starting

material, and finally oxidation. The dihydrofuran product displays signature peaks at values of about 4.7 ppm, 5.4 ppm and 6.3 ppm. These corresponding hydrogens are shown below (Figure 10). Presence of starting material and oxidation would display respective signals at 6.9 ppm and just less than 10 ppm.

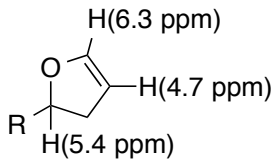


Figure 10: ^{1}H NMR signal values of the three hydrogens used to detect dihydrofuran production with spectra.

The following two tables, differing only by presence or absence of an alkyl halide, display the results of all the different palladium (II) catalysts.

Table 4: Results of various Palladium (II) catalysts in reaction with 4-chlorobenzaldehyde CBHA derivative and potassium carbonate. No alkyl halide was included.

Catalyst	Dihydrofuran	Starting Material	Oxidation
$(dppf)PdCl_2$	+	+	+
$Pd(OAc)_2$	-	–	+
$PdCl_2(PPh_3)_2$	+	+	+
$Pd(OAc)_2$+ PPh_3	+	-	-

$PdCl_2$	-	+	+
$PdCl_2$+PPh_3	+	+	+

Table 5: Results of various Palladium (II) catalysts in reaction with 4-chlorobenzaldehyde CBHA derivative and potassium carbonate. 1-Bromo-3-phenylpropane was included in the reaction mixture.

Catalyst	Dihydrofuran	Starting Material	Oxidation
(dppf)$PdCl_2$	+	+	+
$Pd(OAc)_2$	-	-	+
$PdCl_2(PPh_3)_2$	+	+	+
$Pd(OAc)_2$+ PPh_3	+	-	-

Conclusion

Based off the yields and the resulting ^{1}H NMR data collected for the first two steps, cyclic boronic half acid production from aldehydes and homoallylic alcohols is a relatively inexpensive, efficient, and easy endeavor. With CBHA formed, it is then possible to form monosubstituted dihydrofuran derivatives using several different palladium (II) catalysts and potassium carbonate as a base. Dihydrofuran production is also possible with and without an alkyl halide based on the results using 1-bromo-3-phenylpropane. From the results shown in Tables 4 and 5, it is clear that some palladium catalysts performed better than others. It appears that four of the six used

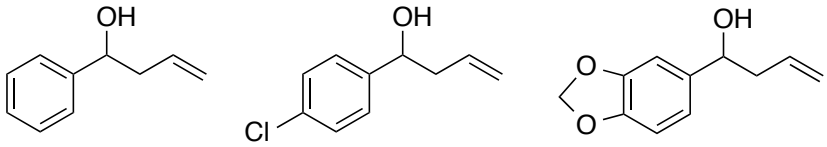
produced dihydrofuran with and without an alkyl halide present (assuming $PdCl_2$+PPh_3 with RX would have if reaction took place). It seems that out of the six catalysts studied, palladium (II) acetate with the addition of triphenylphosphine was the most efficient. It is interesting that without triphenylphosphine, palladium (II) acetate instead favored oxidation. It may be that the triphenylphosphine stabilized the palladium catalyst, keeping it coordinated during the reaction to favor dihydrofuran production. All in all, this study was a success in that an efficient means of dihydrofuran production was found using palladium (II) acetate with the addition of triphenylphosphine as a catalyst and potassium carbonate as a base.

There are plenty of obvious future ventures for this study. For one, there are still more palladium (II) catalysts to experiment with. But, it will also be interesting to study the effects of other metal-based catalysts on dihydrofuran production. Secondly, there was not enough time to research other alkyl halides and bases on both dihydrofuran production and coupling. It is also possible that changing up the alkyl halide and/or the base may have effect on yield or dihydrofuran vs. Suzuki-Miyaura coupling product favoritism. These are all future works that would be worth researching.

Experimental

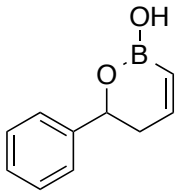
General Details. All manipulations for the Grignard reaction were carried out using standard Schlenk techniques under an atmosphere of ultra high purity nitrogen. All solvents were collected from MBRAUN solvent system. Benzaldehyde, 4-chlorobenzaldehyde, piperonal, 1-bromo-3-phenylpropane, potassium carbonate, and all palladium (II) catalysts were obtained from Sigma Aldrich and were used without further purification. Grubbs 1st

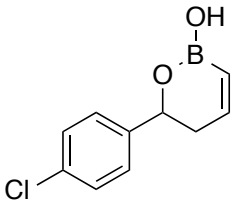
Generation Catalyst, allyl magnesium bromide, and trans-1-propen-1-ylboronic acid diisopropyl ester were stored under nitrogen at 0°C. ^{1}H NMR spectra were recorded at 298 K on a Bruker BioSpin Avance III HD 400 Nanobay System Spectrometer, with an operating frequency at 400 MHz. Chemical shifts are quoted in parts per million and are relative to external $SiMe_4$. Ring closing metathesis reactions and all palladium catalyzed reactions were heated using a CEM Discover SP Microwave System w/ActiVent Technology, 12V. All product mixtures were purified using a HP1050 series HPLC system.

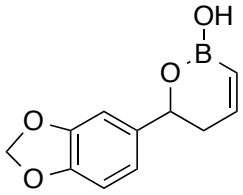


Synthesis of 1-phenyl-3-buten-1-ol, 1-(4-chlorophenyl)-3-buten-1-ol, and 1-(3,4-methylene dioxiphenyl)-3-buten-1-ol. To a stirred solution of 2.5 g of aldehyde (benzaldhehyde, 4-chlorobenzaldehyde, and piperonal, respectively) in THF at 0°C was added 1.1 molar equivalent of allyl magnesium bromide. The solution was stirred for 1 hour before 50 mL of 10% aqueous HCl was added in the span of 20 minutes. To the solution was added diethyl ether (20 mL). The organic layer was washed with 10% HCl (3x) and brine solution (1x) sequentially and the organic extract was isolated, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified using flash chromatography to yield 1.26 g of 1-phenyl-3-buten-1-ol (36.1%), 1.11 g of 1-(4-chlorophenyl)-3-buten-1-ol (34.2%), and 1.04 g of 1-(3,4-methylene dioxiphenyl)-3-buten-1-ol (32.5%). **1-phenyl-3-buten-1-ol** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): $\boldsymbol{\delta}_H$ 7.26-7.44 (m, 5H), 5.78 (m, 1H), 5.08-5.15 (m, 2H), 4.66 (m, 1H), 2.42 (m, 1H), 2.41 (s, 1H), 1.79 (m, 1H) ppm. **1-(4-chlorophenyl)-3-buten-1-ol** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): $\boldsymbol{\delta}_H$ 7.20-

7.28 (m, 4H), 5.76 (m, 1H), 5.10-5.16 (m, 2H), 4.66 (m, 1H), 2.58 (s, 1H), 2.44 (m, 1H), 1.81 (m, 1H) ppm. **1-(3,4-methylene dioxiphenyl)-3-buten-1-ol** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): δ_H 6.82 (s, 1H), 6.74-6.77 (m, 2H), 5.92 (s, 2H), 5.77 (m, 1H) 5.08-5.14 (m, 2H), 4.60 (m, 1H), 2.68 (s, 1H), 2.42 (m, 1H), 1.83 (m, 1H) ppm.

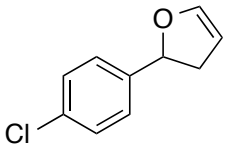






Synthesis of CBHA's. To a 10 mL microwave vial containing 4 mL of methylene chloride and a stir bar was added 0.05 equivalents of Grubbs 1st Generation Catalyst. The solution was placed under nitrogen before adding 1.5 equivalents of trans-1-propen-1-ylboronic acid diisopropyl ester and 0.3 mL of 1-phenyl-3-buten-1-ol, 1-(4-chlorophenyl)-3-buten-1-ol, or 1-(3,4-methylene dioxiphenyl)-3-buten-1-ol. The reaction mixture was heated in the CEM Discover SP Microwave System for 4 hours (90°C, 17.2 bar, high stirring, 150 W), and then 20 mL of diethyl ether was added. The organic components were consecutively washed with 3 portions of water (15 mL each), then 15 mL of brine solution. The organic extract was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified using flash chromatography to afford 0.30 g of benzaldehyde CBHA (85.7%), 0.27 g of 4-chlorobenzaldehyde CBHA (79.4%), and 0.28 g of piperonal CBHA (82.4%). **Benzaldehyde CBHA** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): δ_H 7.24-7.38 (m, 5H), 6.96 (m, 1H), 5.83 (m, 1H), 5.14 (m, 1H), 2.44 (s, 1H), 1.28 (m, 1H), 0.88 (m, 1H) ppm. **4-Chlorobenzaldehyde CBHA** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): δ_H 7.28-7.33 (m, 4H), 6.91 (m, 1H), 5.80 (m, 1H), 5.10 (m, 1H), 2.13 (s, 1H), 1.24 (m, 1H), 0.87 (m,

1H) ppm. **Piperonal CBHA** ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): δ_H 6.72-6.97 (m, 3H), 6.72 (m, 1H), 5.90 (m, 1H), 5.52 (s, 2H) 5.09 (m, 1H), 2.41 (s, 1H), 1.26 (m, 1H, 1.83), 0.91 (m, 1H) ppm.



Synthesis of chloro-dihydrofuran. To a 10 mL microwave vial containing 1 mL of THF and a stir bar was added 0.05 equivalents desired palladium catalyst and 2.0 equivalents of potassium carbonate. The solution was placed under nitrogen before adding 1.0 equivalents of 1-bromo-3-phenylpropane and 0.05 mL of chloro CBHA. The reaction mixture was heated in the CEM Discover SP Microwave System for 4 hours (90°C, 17.2 bar, high stirring, 150 W), and then 20 mL of diethyl ether was added. The organic components were consecutively washed with 3 portions of water (15 mL each), then 15 mL of brine solution. The organic extract was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified using flash chromatography to afford the yields listed in the results section.

Chlorodihydrofuran ^{1}H NMR ($CDCl_3$ with 0.05% v/v TMS, 400 MHz): δ_H 7.22-7.40 (m, 4H), 6.30 (m, 1H), 5.42 (m, 1H), 4.61 (m, 1H), 2.49 (m, 1H), 1.76 (m, 1H) ppm.

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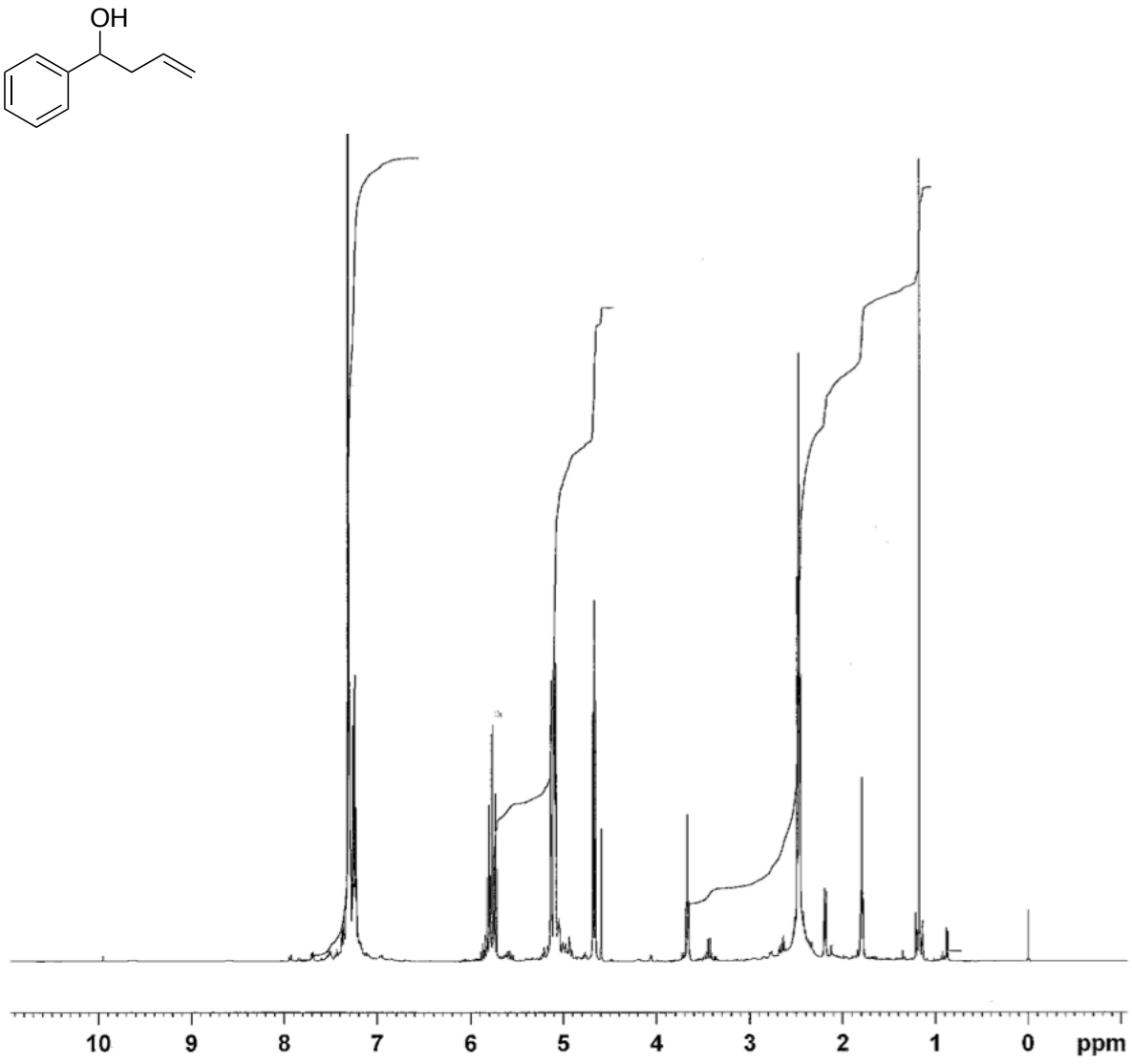
Appendix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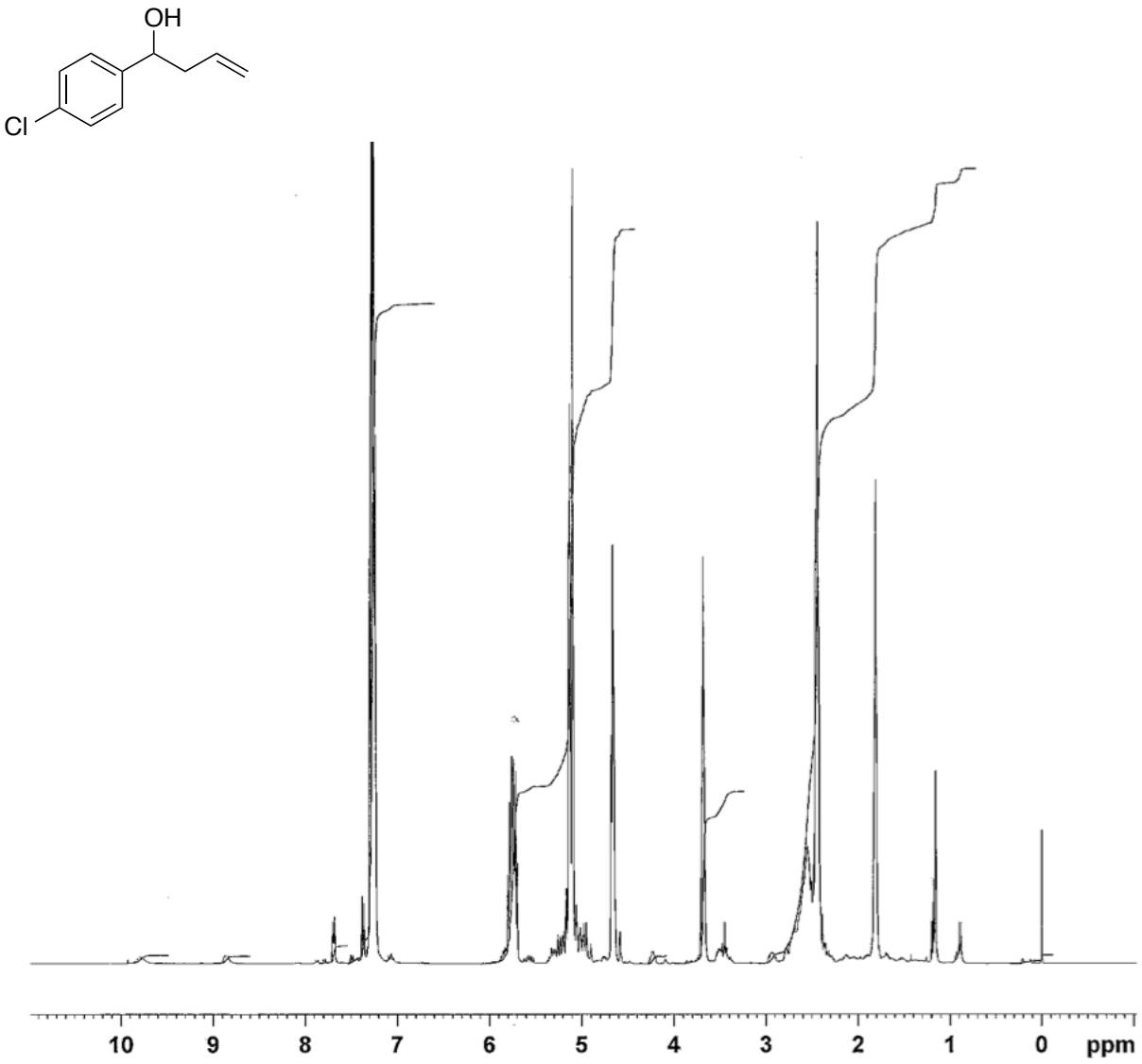
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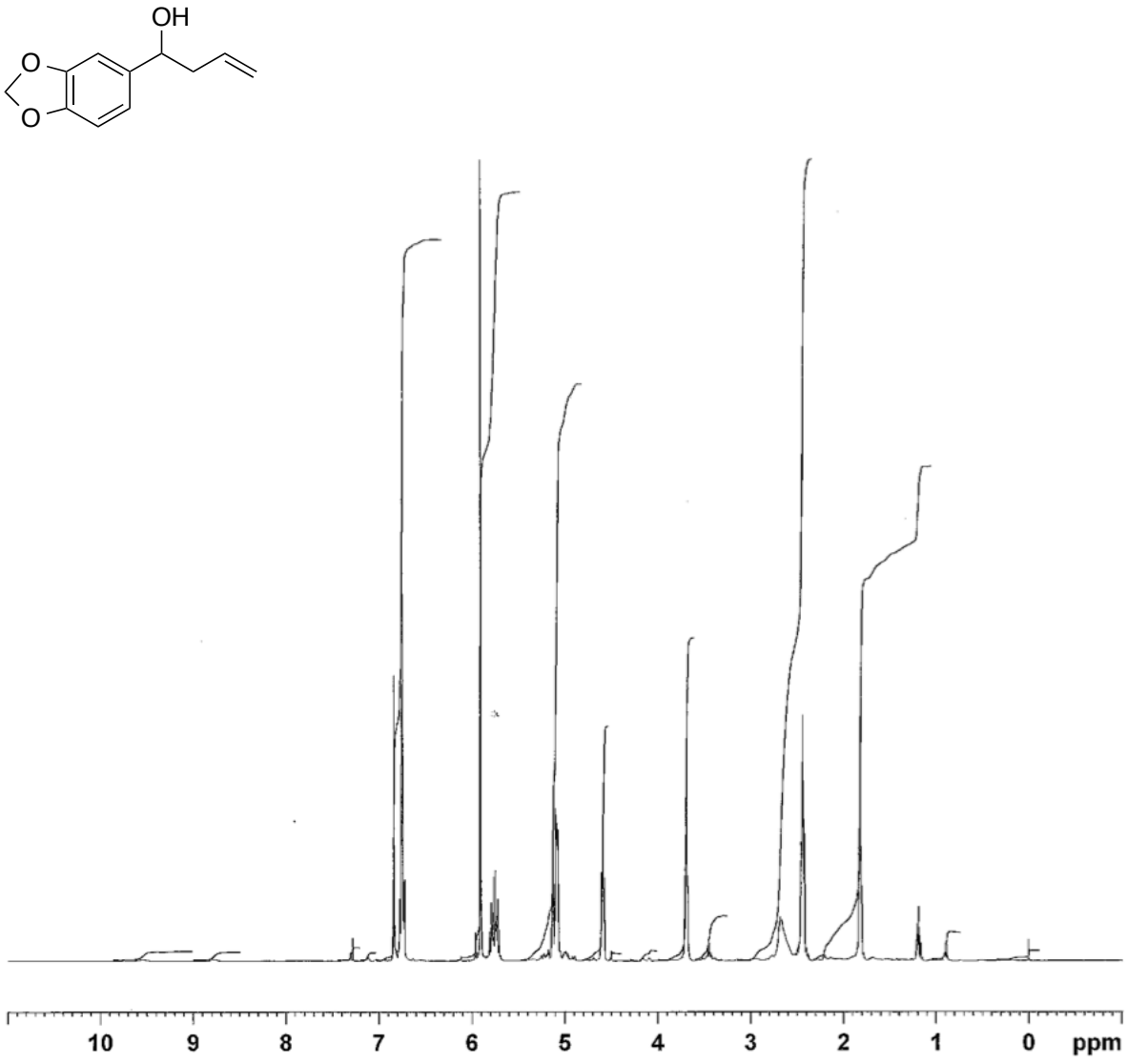
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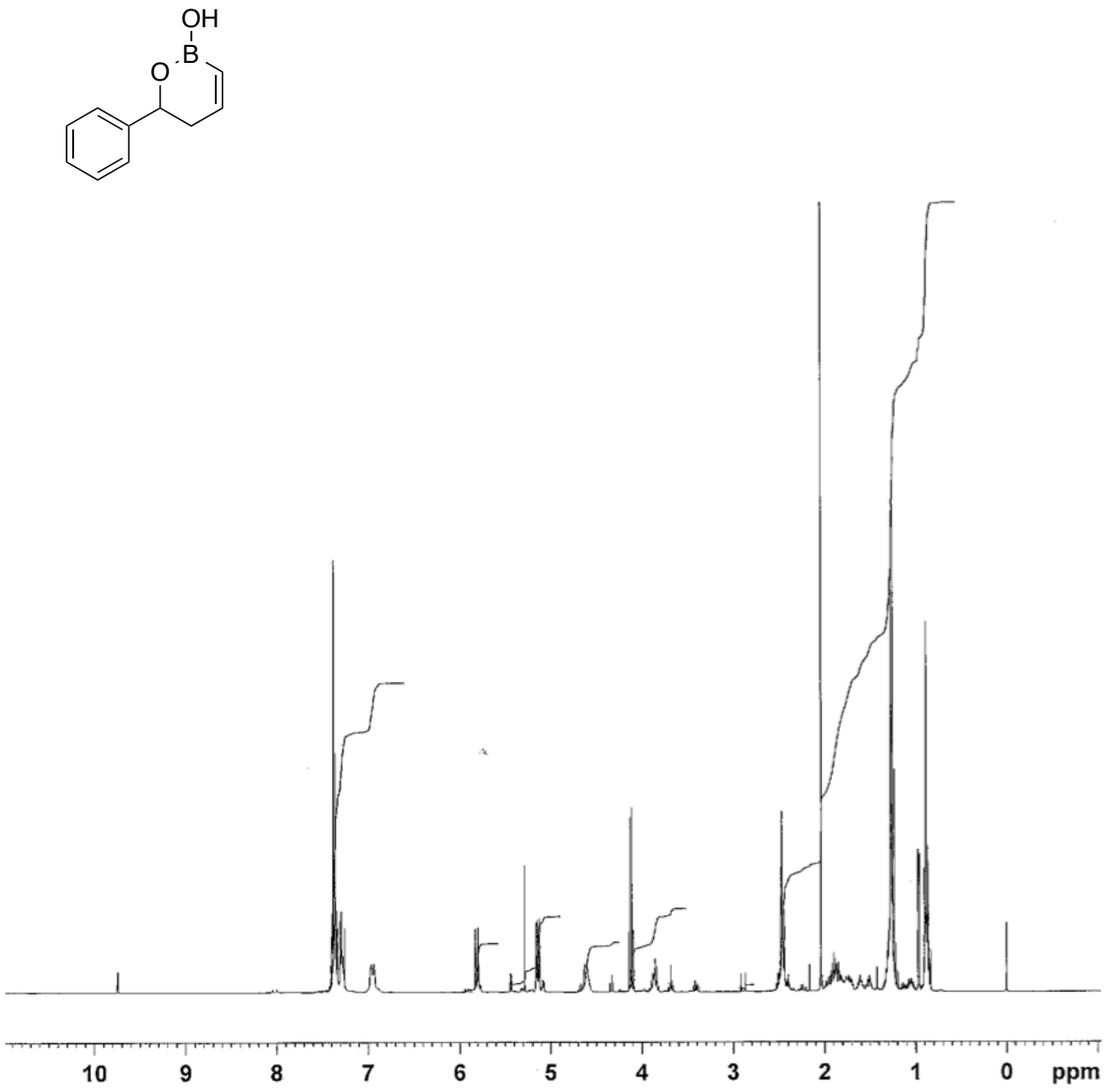
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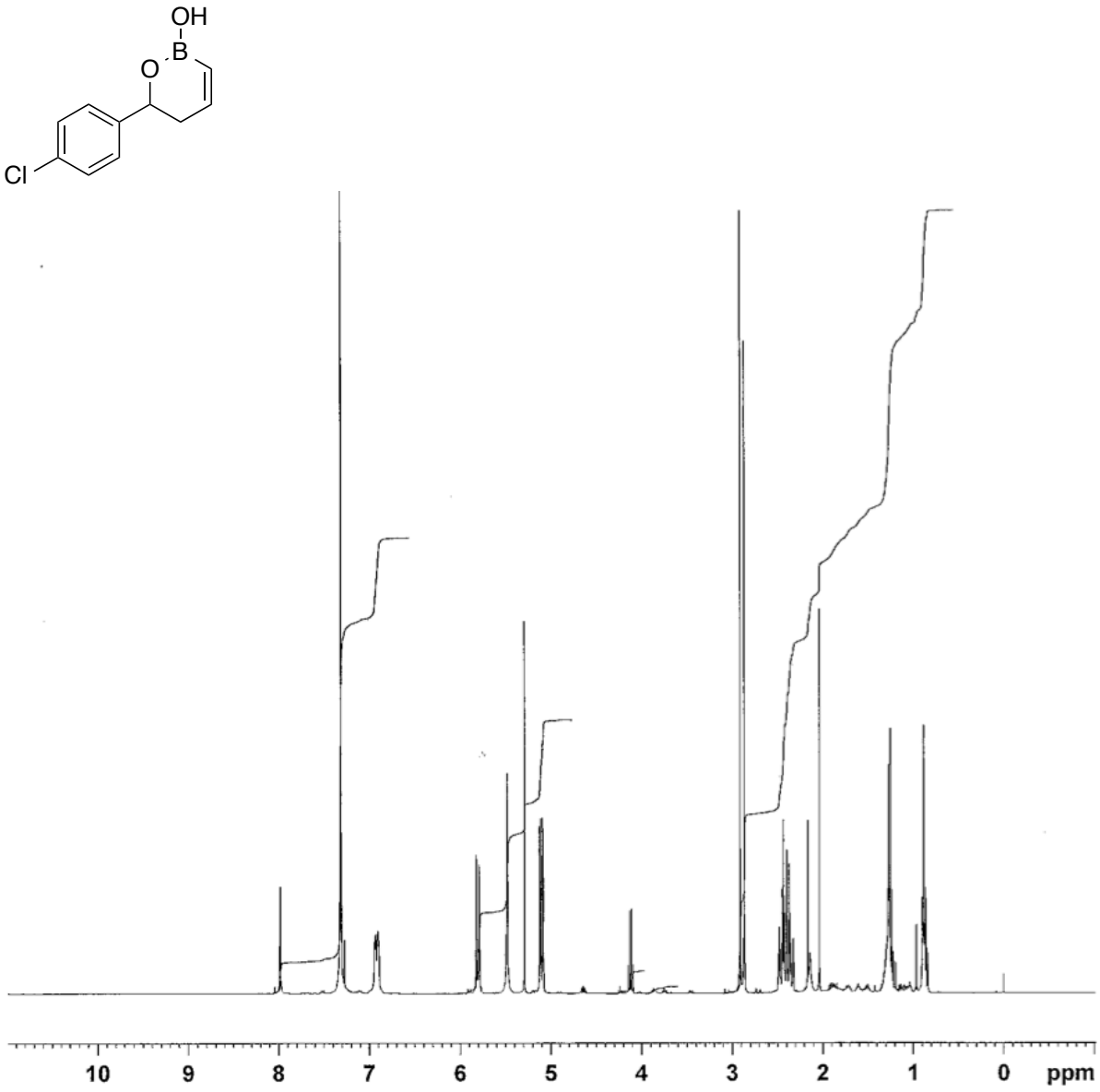
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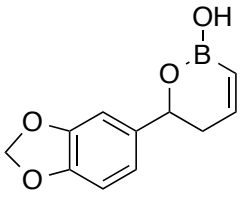
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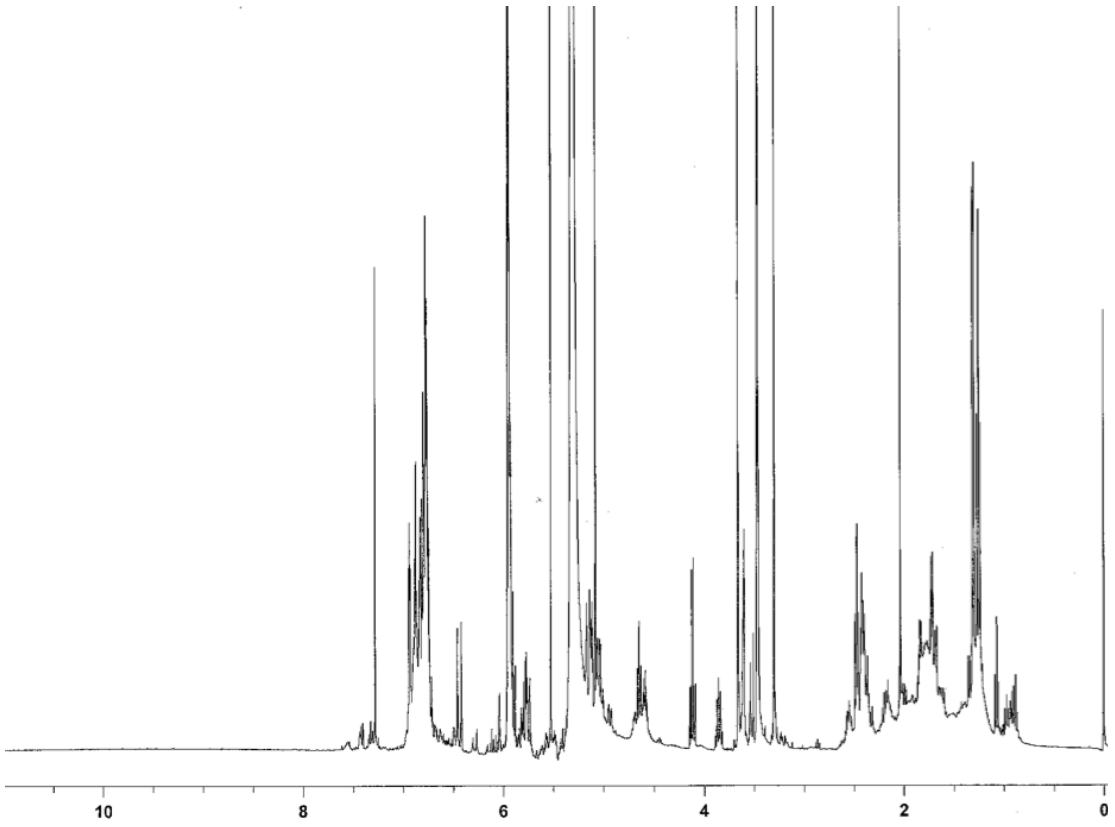
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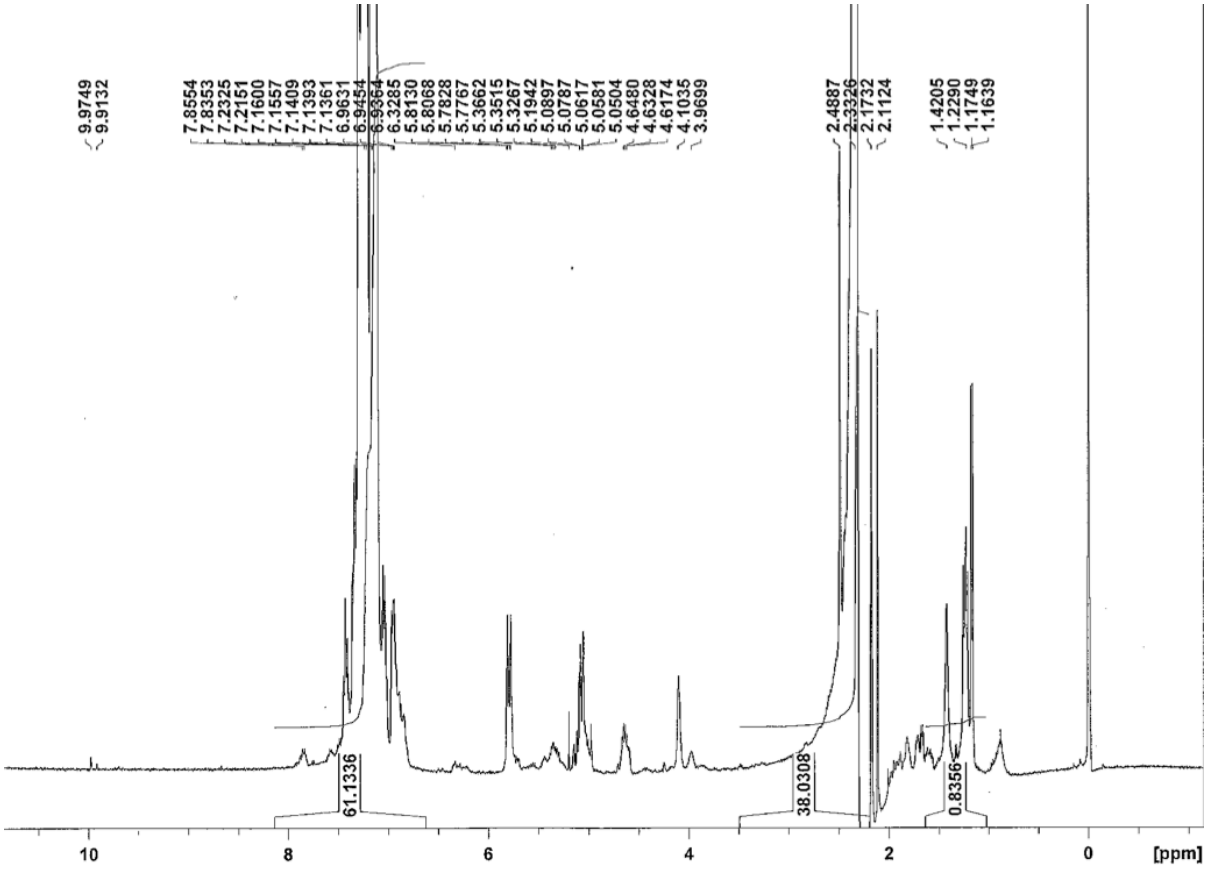
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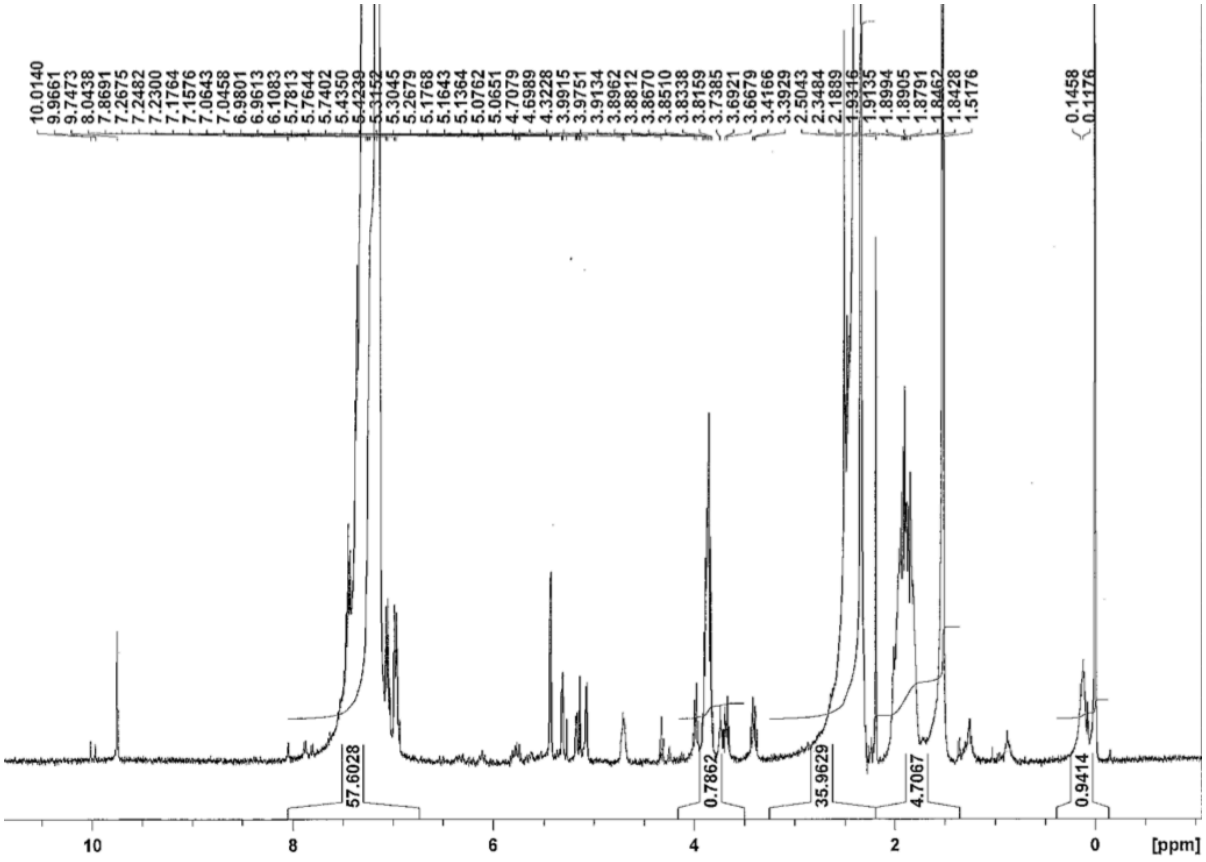
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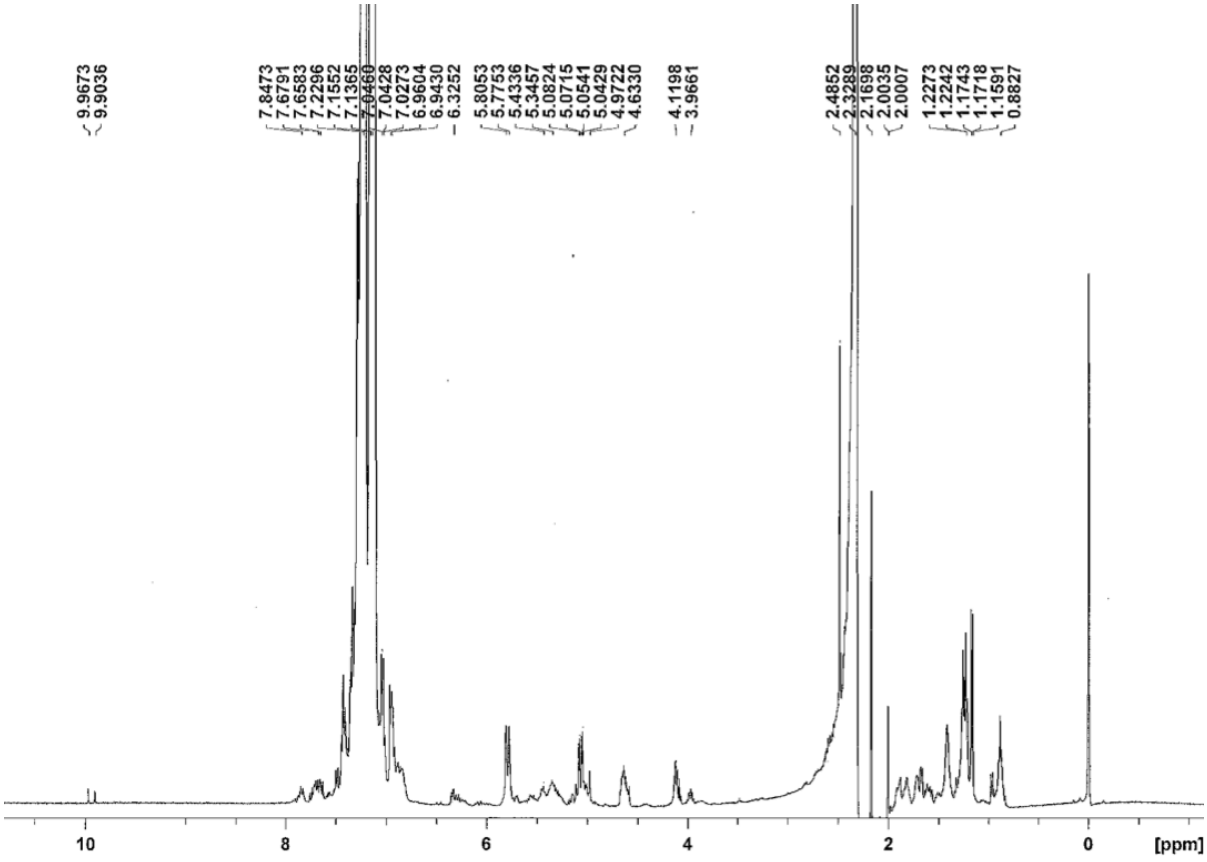
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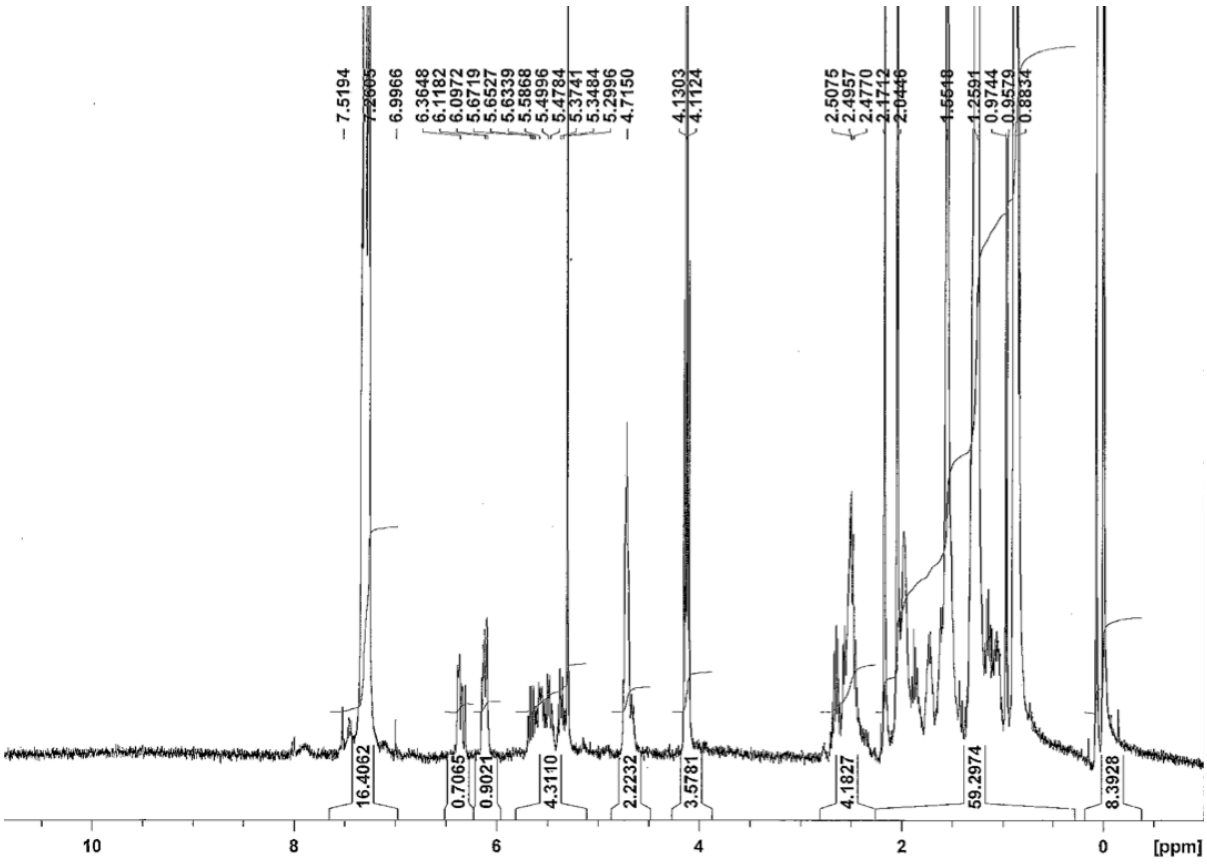
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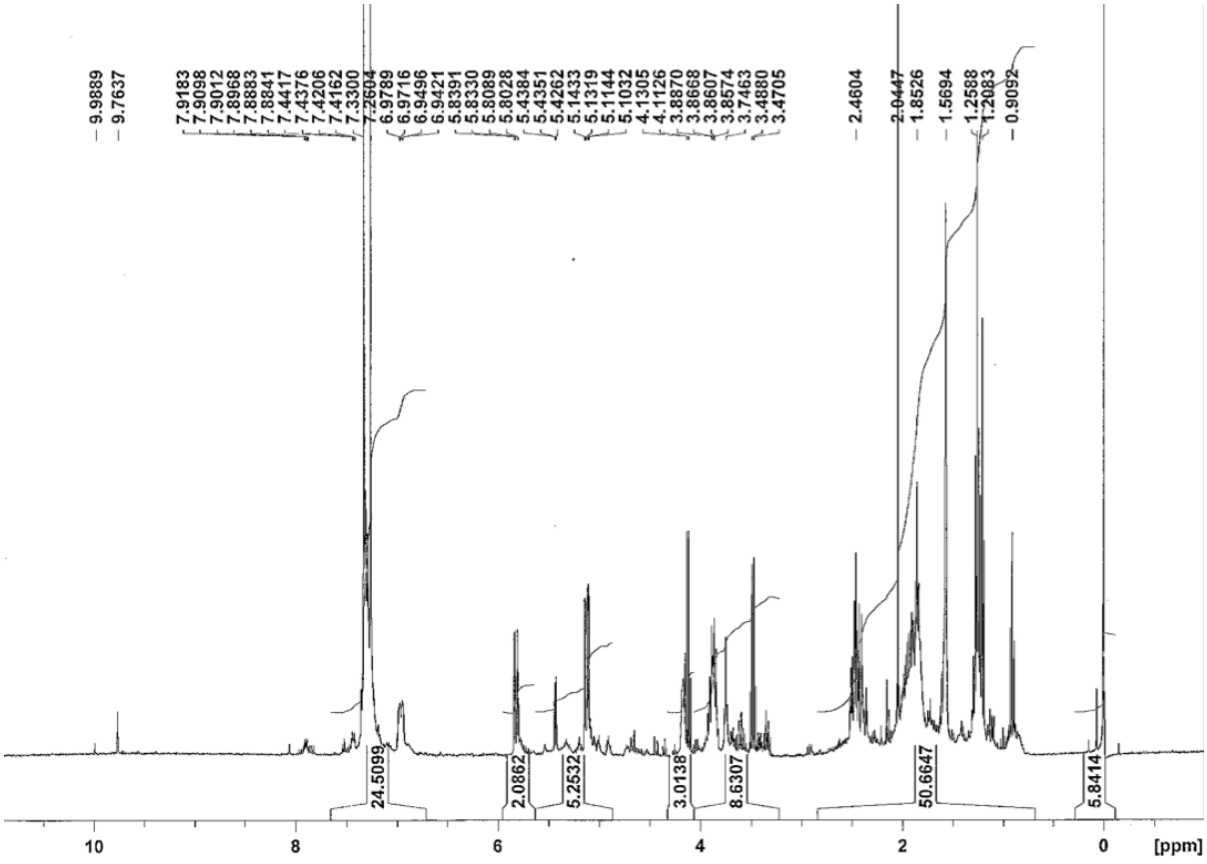
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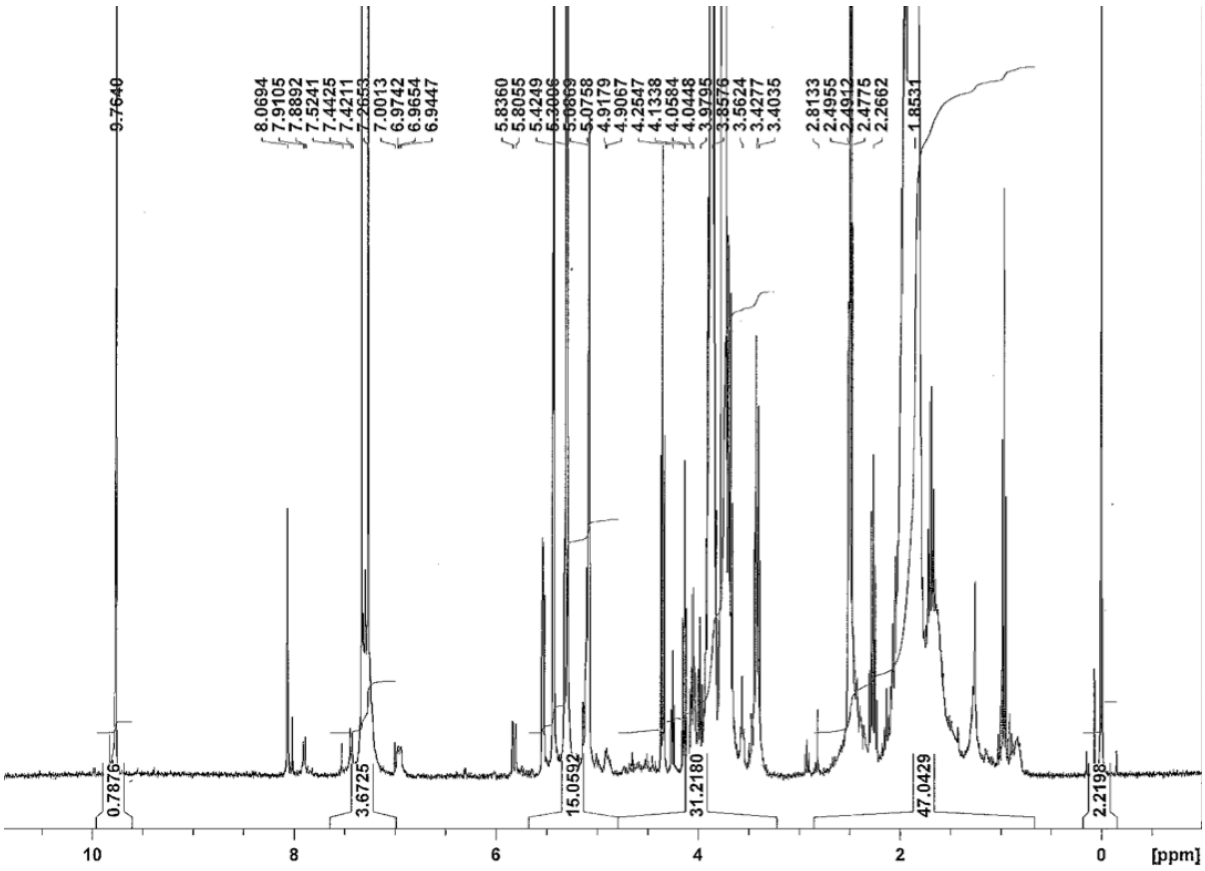

Appendix Figure 1a-f. ^{1}H NMR data of products resulting from the various palladium catalyzed reactions listed above using 4-chlorobenzaldehyde CBHA without the addition of an alkyl halide. Spectra are depicted in the following order: Reaction catalyzed by a. [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, b. palladium (II) acetate, c. bis(triphenylphosphine)palladium(II) dichloride, d. palladium (II) acetate with the addition of triphenylphosphine, e. palladium (II) chloride, and f. palladium (II) chloride with the addition of triphenylphosphine.

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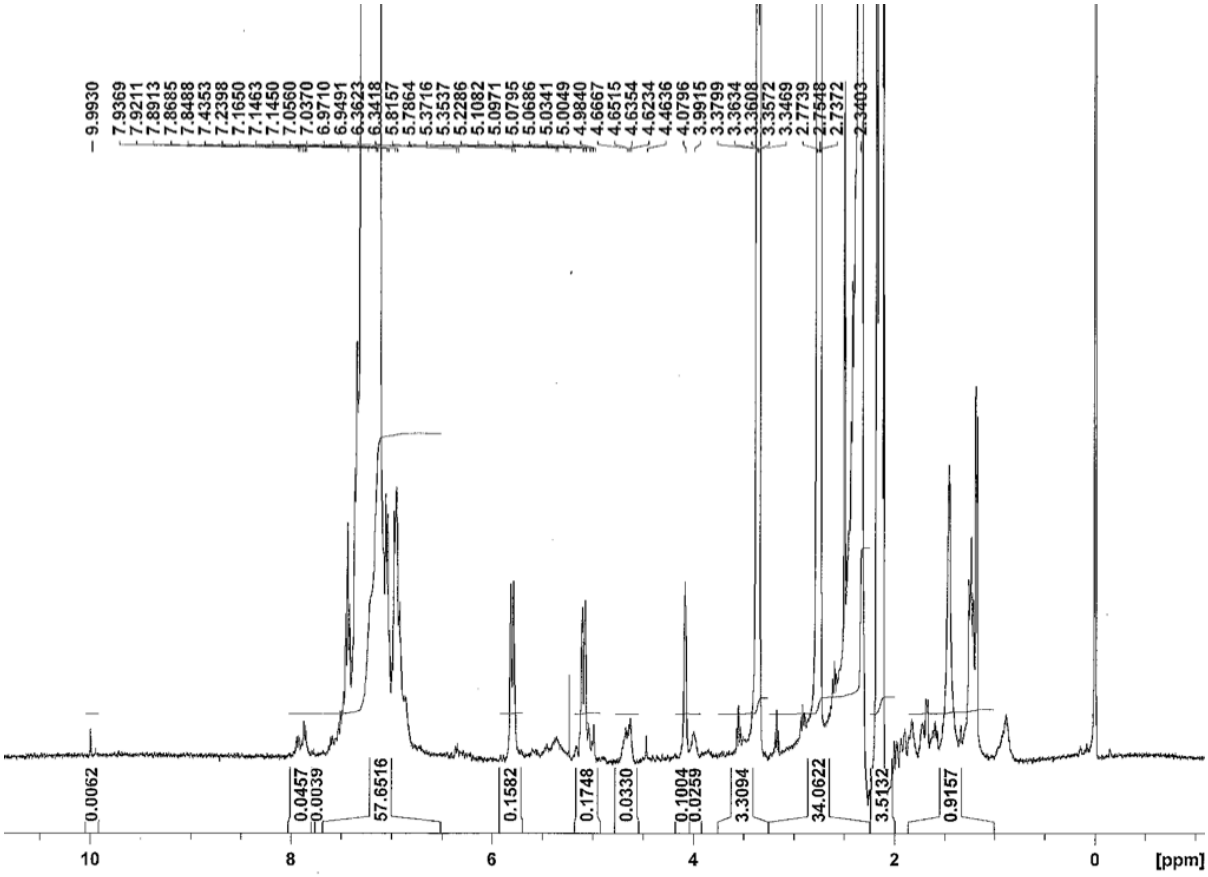
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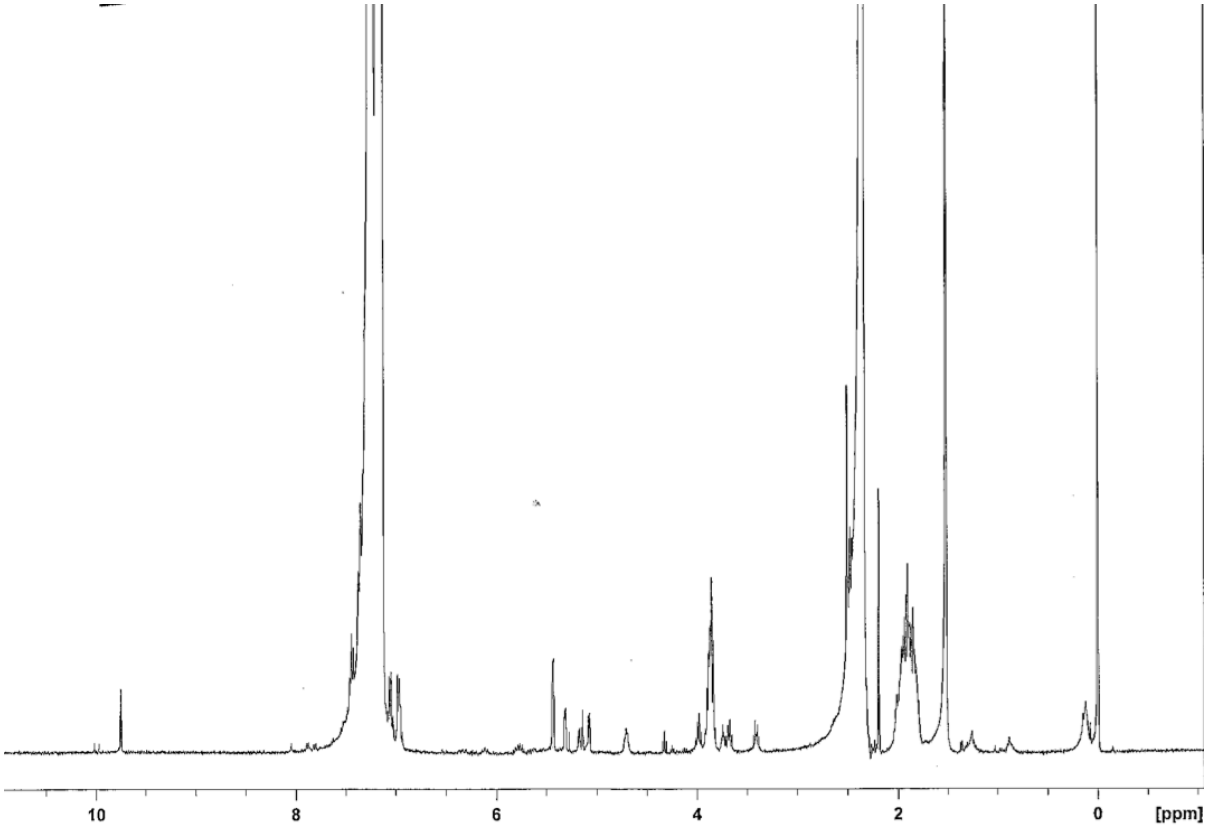
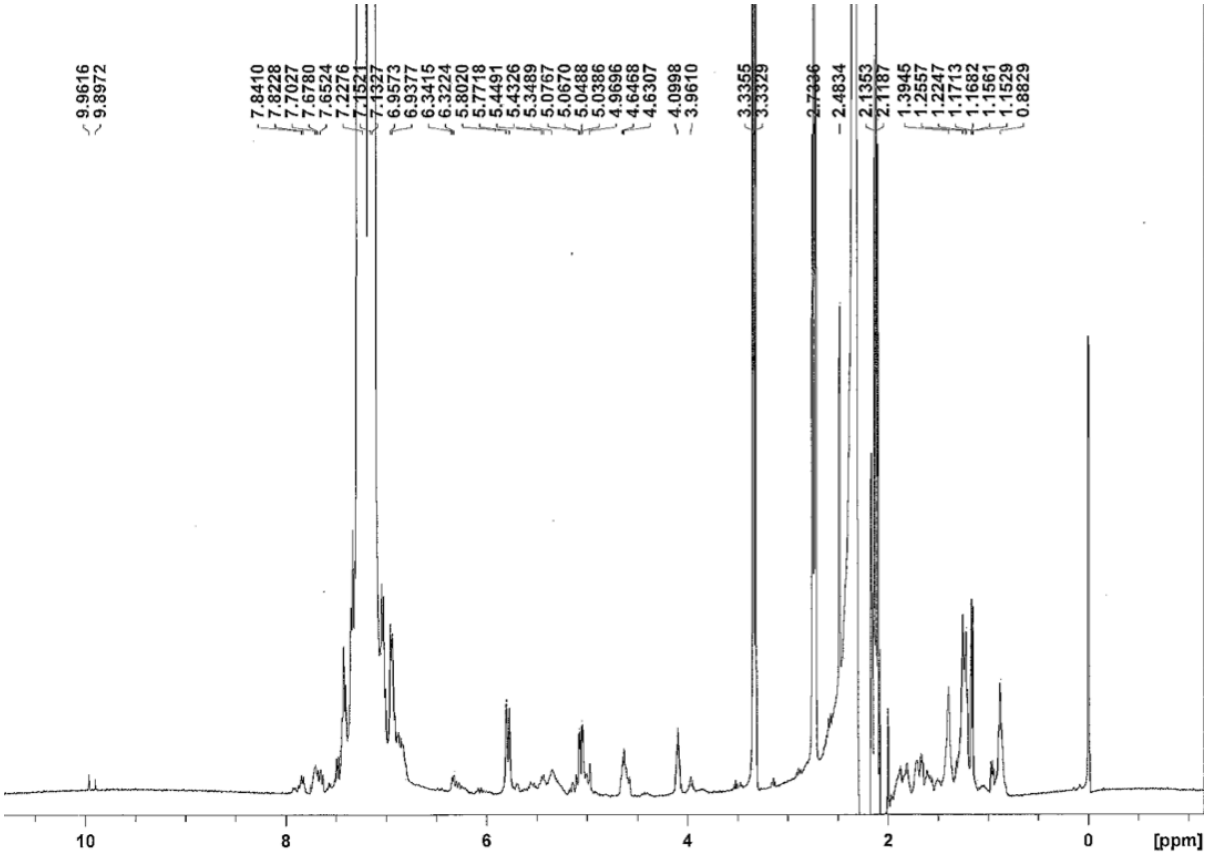
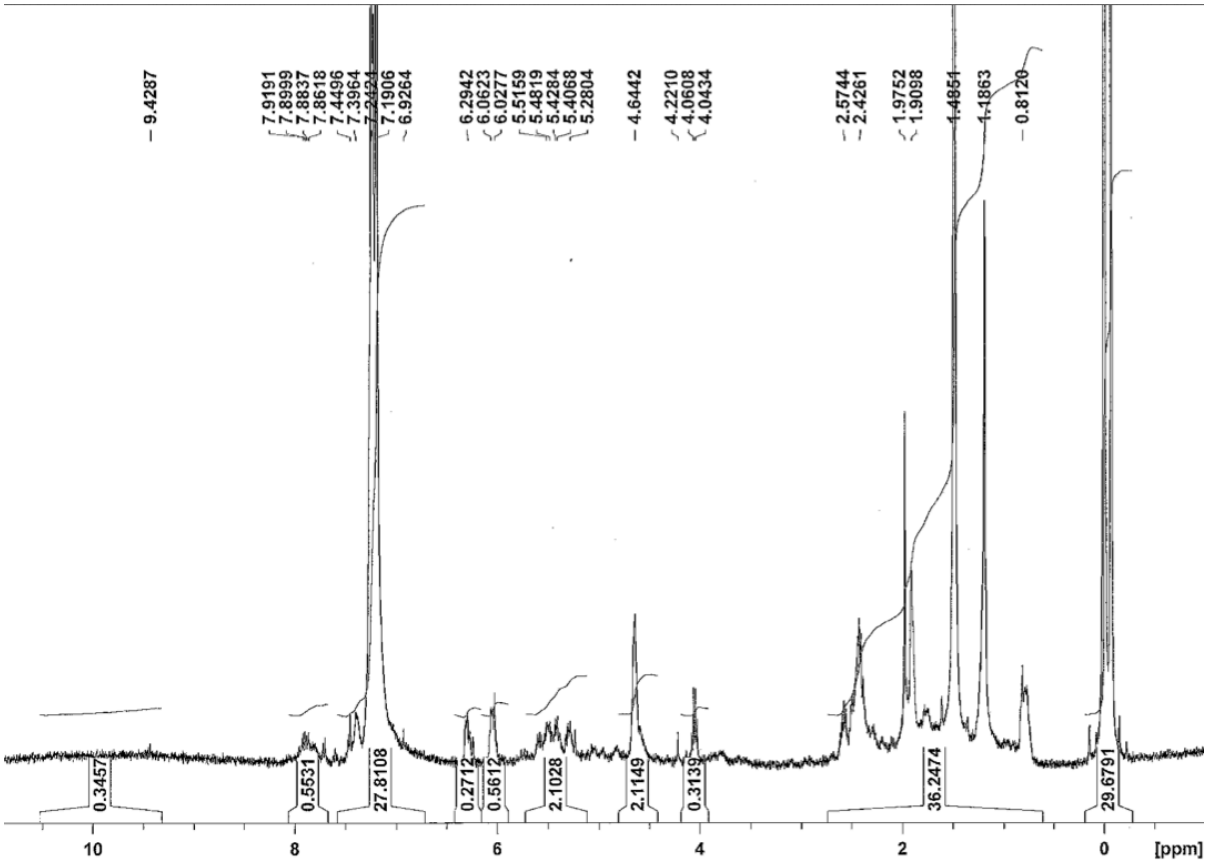


C.


9.9616
9.8972
7.8410
7.8228
7.7027
7.6780
7.6524
7.2276
7.1521
7.1327
6.9573
6.9377
6.3415
6.3224
5.8020
5.7718
5.4491
5.4326
5.3489
5.0767
5.0670
5.0488
5.0386
4.9696
4.6468
4.6307
4.0998
3.9610
3.3355
3.3329
2.7336
2.4834
2.1353
2.1187
1.3945
1.2557
1.2247
1.1713
1.1682
1.1561
1.1529
0.8829
10
8
6
4
2
0
[ppm]

D.



Appendix Figure 2a-d. ^{1}H NMR data of products resulting from the various palladium catalyzed reactions listed above using 4-chlorobenzaldehyde CBHA with the addition of the alkyl halide 1-bromo-3-phenylpropane. Spectra are depicted in the following order: Reaction catalyzed by a. [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, b. palladium (II) acetate, c. bis(triphenylphosphine)palladium(II) dichloride, and d. palladium (II) acetate with the addition of triphenylphosphine.