SYNTHESIS OF A COBALT PORPHYRIN COMPLEX TO BE USED AS A CATALYST IN REACTIONS INVOLVING ORGANIC RADICAL INTERMEDIATES

By

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University Honors
University of California, Riverside

APPROVED

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Abstract

Radical intermediates appear frequently in organic synthesis due to the fact that they are highly reactive and can be used to generate a variety of useful products. However, the traditional synthesis of radicals involves hazardous reagents and carcinogens, and generates a large amount of waste. Therefore, it would be desirable to use safer, inexpensive, and abundant starting materials, such as alcohols, which are relatively simple to synthesize. The approach that will be studied in this research is the activation of alcohols using a cobalt metal catalyst and visible light energy to generate radical intermediates that can be used in a variety of reactions. Once a radical intermediate is obtained from the starting alcohol, it can undergo a few transformations, including the loss of carbon dioxide to effect deoxygenation or cross-coupling, or alternatively formation of various ester products. The goal of the project is to identify an efficient cobalt catalyst that gives high yields across a variety of substrates. The objective is achieved by synthesizing several cobalt complexes, testing their photochemical properties and evaluating their performance in several reactions.

Acknowledgements

I would like to first acknowledge my faculty mentor, Dr. Dave Martin, and thank him for his guidance and constant support. I would also like to thank my graduate student mentor, Dana Chambers, for guiding me through every step of this project and teaching me skills and knowledge well beyond. I would also like to thank Abigail Feceu for giving me my initial training over the summer and all her help throughout the year. I like to thank the rest of the Martin laboratory research group, for always being welcoming and kind. Special thanks to Dr. Jack Eichler for his support at a time I believe I was out of options, and for helping me get this amazing opportunity. Finally, I would like to thank my honors counselor, Latoya Ambrose, and the rest of the university honors staff.

Introduction

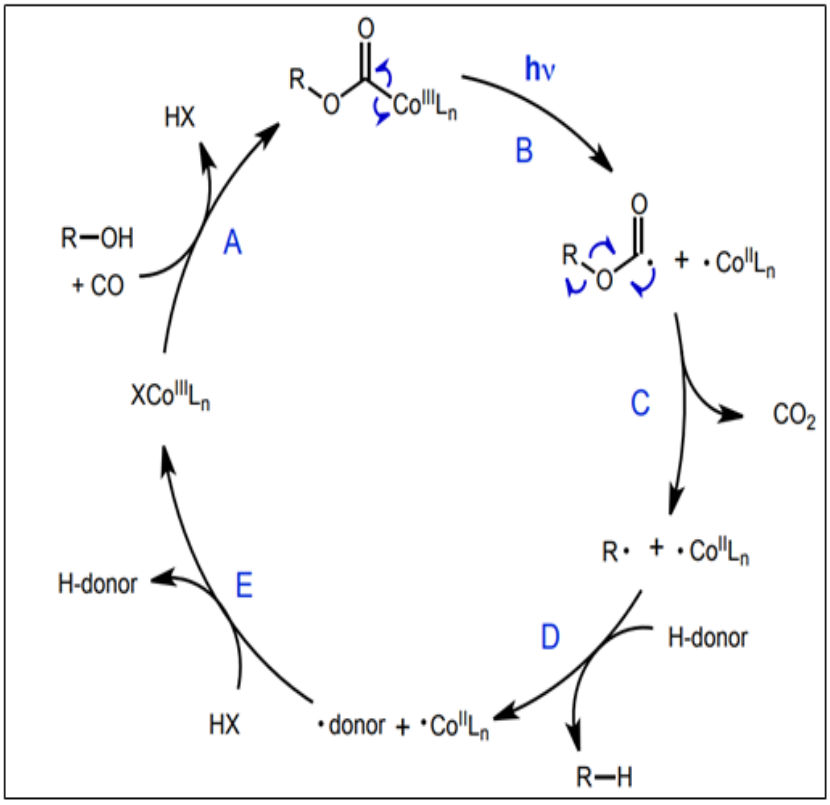
In the past, radical intermediates were synthesized in a multistep synthesis. One example is the Barton-McCombie deoxygenation, a method that was developed in order to deoxygenate secondary alcohols. Such methods generally involve a few steps to ultimately replace the hydroxyl group with hydrogen (Gimisis). Generally, the alcohol (HO-R) is first pre-activated by being converted into a xanthate ester (ROC(S)SR'). Then, a radical initiator is used to produce tributyltin radical which then reacts with the xanthate to produce a radical intermediate. The R-O bond is them homolytically cleavaged to produce a carbon radical, which would then be used in further reactions to achieve the desired product (Figure 1). This synthesis involves the production of toxic, stoichiometric by-products such as tributyltin xanthate and other tributyltin compounds (Bu_3SnX), and requires the use of toxic tributyltin reagent. Therefore, it is desirable to find a new method to synthesize these radicals without generating toxic waste and using toxic reagents.

Metal catalysts are often used in order to minimize the amount of waste generated in chemical processes. The approach tested in this study uses a catalyst that is inspired by a radical metal complex found in nature, Cobalamin (Vitamin B_{12}). The structure of Cobalamin consists of cobalt metal in the center, which is surrounded by four nitrogens that make up a Corrin ring. The cobalt is also bounded to an R group by a relatively weak Co-C bond. The weak bond enables an equilibrium state between the formation of a cobalt-based and carbon radicals and the undissociated form (Figure 2). Drawing inspiration from the structure of cobalamin, a few model complexes were created for the radical catalyst: cobaloxime, cobalt-salen, cobalt-salophen, and porphyrin (Figure 3). All these model complexes have a cobalt center that is surrounded by a similar ring and can bond with a ligand through a weak Co-C bond (20-35 kcal/mol). In the

synthesis process, the catalyst forms a bond with a compound that contains the alcohol starting material, which is then broken to ultimately create the radical intermediate.

The use of a cobalt catalyst to create a radical intermediate can be illustrated by a proposed catalytic cycle in which the radical intermediate is formed, and then undergoes further reactions to achieve overall deoxygenation of the alcohol.

Figure 4:



A The first step of the cycle is the generation of the cobalt complex. A cobalt complex that has one of the model structure described above ($XCo^{III}Ln$) is carbonylated, by being reacted with carbon monoxide and the desired alcohol starting material (R-OH).

B The next step is the activation of the cobalt complex. Using visible light, the weak Co-C bond is broken, generating a cobalt complex radical ($\cdot Co^{II}Ln$) and a carbon radical.

C Then the carbon radical generated in the previous step further reacts to result in the formation of carbon dioxide and the desired radical intermediate.

D A hydrogen donor is used to obtain the final product of the overall deoxygenation reaction(R-H).

E The radical metal complex and a radical formed from the hydrogen donor are reacted with an acid (HX) to regenerate the initial cobalt complex and hydrogen donor.

Some of the work that has already been done in Dr. Dave Martin's research laboratory focuses on the synthesis and use of the cobalt complexes. The research was published in a journal article titled "Synthesis and Characterization of Alkoxycarbonyl Cobalt Complexes via Direct Carbonylation Methods." In that study, alkoxycarbonyl cobalt (III) complexes were synthesized. The article showed the synthesis of the complexes from Co(III) precursors, using 1 atm of CO and a weak base. The substrate scope of the carbonylation with various alcohols was examined, using Co(salen)OTs, Co(salen)I or Co(salen)Br as the starting material. Additionally, the alkoxycarbonyl cobalt (III) complexes were synthesized from Co(II) salen and Co(II) salophen precursors, using 1 atm of CO and an oxidant, and a few different substrates were tested.

As part of my work in the research group, I have focused on synthesizing one of the cobalt catalysts. The majority of the model complexes mentioned above have already been used in synthesizing cobalt catalysts and have been tested in a few reactions. The one model complex that has only recently been looked at is porphyrin. The complex is different than the other model structures as it corresponds more closely to the original Cobalamin structure. Some of the work and analysis that has already been done with that structure had shown promising results.

Therefore, the next step would be to synthesize a variety of porphyrin complexes, using different starting complexes and substituents. Then, the catalysts will be used in a variety of reactions and will be characterized using different methods to see how effectively it can generate the desired radical intermediate. The cobalt catalyst that I was synthesizing is 5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine cobalt(II) (Figure 4). This cobalt catalyst is composed of porphyrin with a methoxyphenyl on its meso positions (5,10,15,20). In this experiment, cobalt porphyrin **(1)** is synthesized in a three-step synthesis starting from 4-methoxy-benzaldehyde and pyrrole. Then, the performance of the cobalt porphyrin in the proposed catalytic cycle is tested by first carbonylating the complex and then capturing the resulting carbon radical by reacting it with a stable free radical, 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO).

Introduction figures:

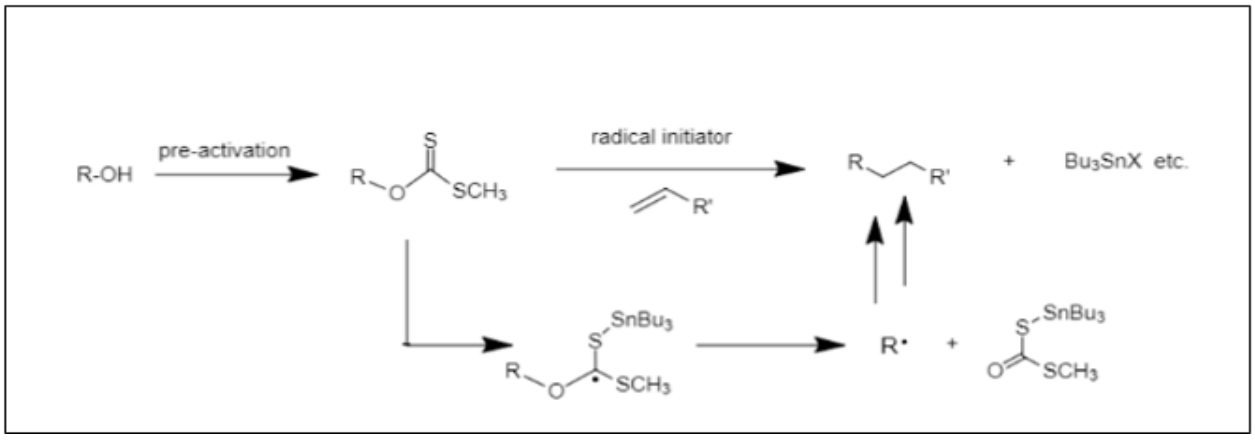


Figure 1: Deoxygenation of alcohol using a radical intermediate.

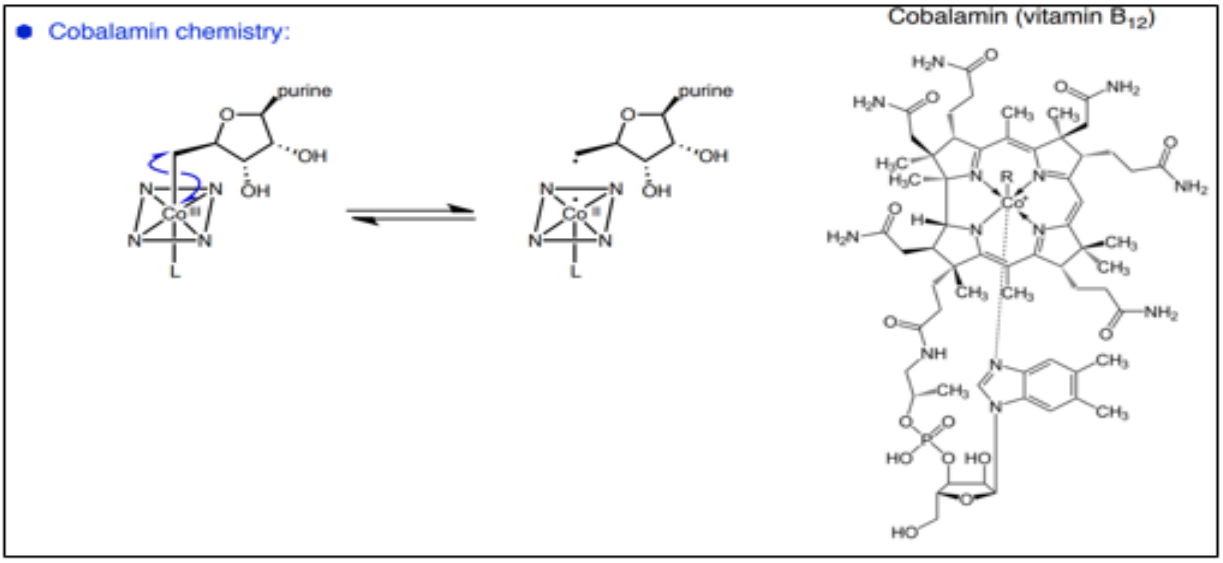


Figure 2: Cobalamin chemistry

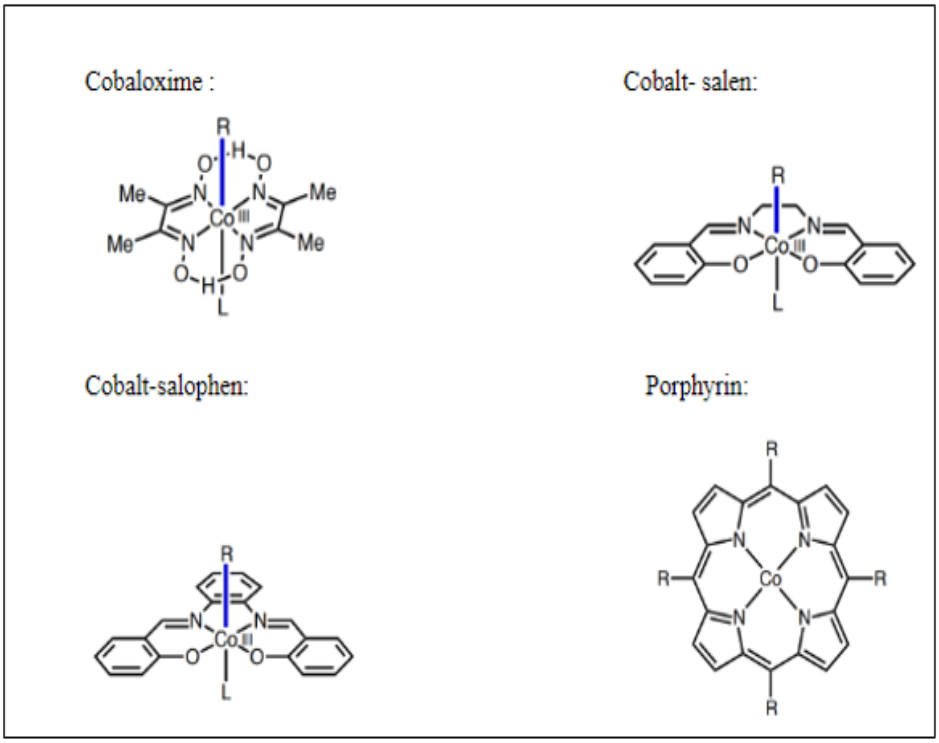


Figure 3: Model complexes of the cobalamin radical.

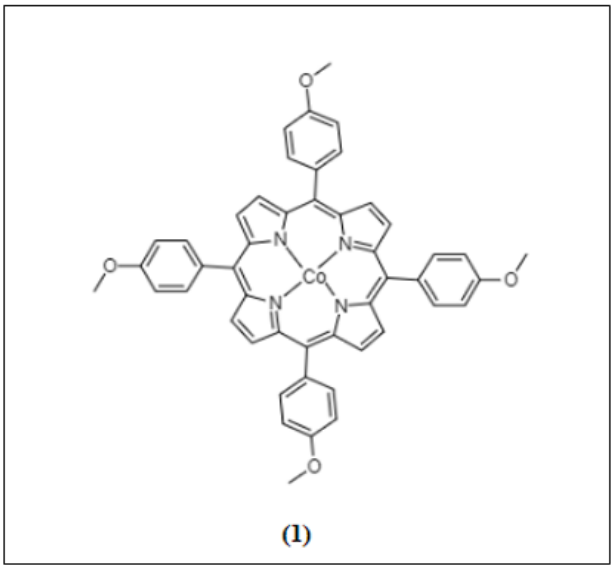


Figure 5: 5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphine cobalt(II)

Results and Conclusion

Synthesis:

The first goal of the project was to synthesize the cobalt-porphyrin **(1)** from commercially available starting materials. The complex was synthesized in three steps. Initially, a dipyrromethane containing the desired R group is synthesized. Then, the porphyrin is constructed by reacting the dipyrromethane with an aldehyde. Finally, the cobalt is added using a cobalt (II) complex to achieve the desired cobalt-porphyrin.

Step 1: First, dipyrromethane **(2)** was synthesized. The commercially available 4-methoxy-benzaldehyde was added to 25 equivalent of pyrrole and purged under N_2. The starting materials were reacted with 0.1 equivalent of Trifluoroacetic acid, and then 0.6 equivalents of a base, triethylamine (figure 6). The reaction was protected from light and carried out air-free. The product was then purified and yields around 20-40 % were obtained (table 1). NMR analysis was performed to identify the product.

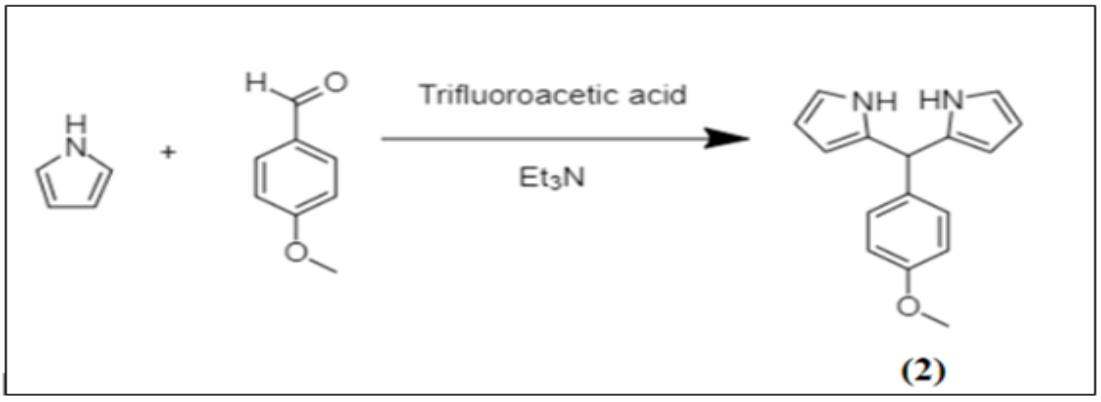


Figure 6: Step 1, synthesis of dipyrromethane **(2)**.

Table 1

Run	Yield
1	8.00 mg (32%)
2	225.5 mg (20 %)
3	896.1 mg (44 %)

Step 2: In the next step, it was attempted to synthesize the desired porphyrin by reacting dipyrromethane **(2)** with more of the initial aldehyde. 1 equivalent of 4-methoxy-benzaldehyde was added to 1 equivalent of dipyrromethane **(2)** in chloroform. The starting materials were reacted with 0.8 equivalents of boron trifluoride-diethyl ether. The reaction was heated to 60 ℃ and left to stir overnight under N_2. Then, chloranil was added and the reaction was allowed to stir for an additional hour, protected from light (figure 7).

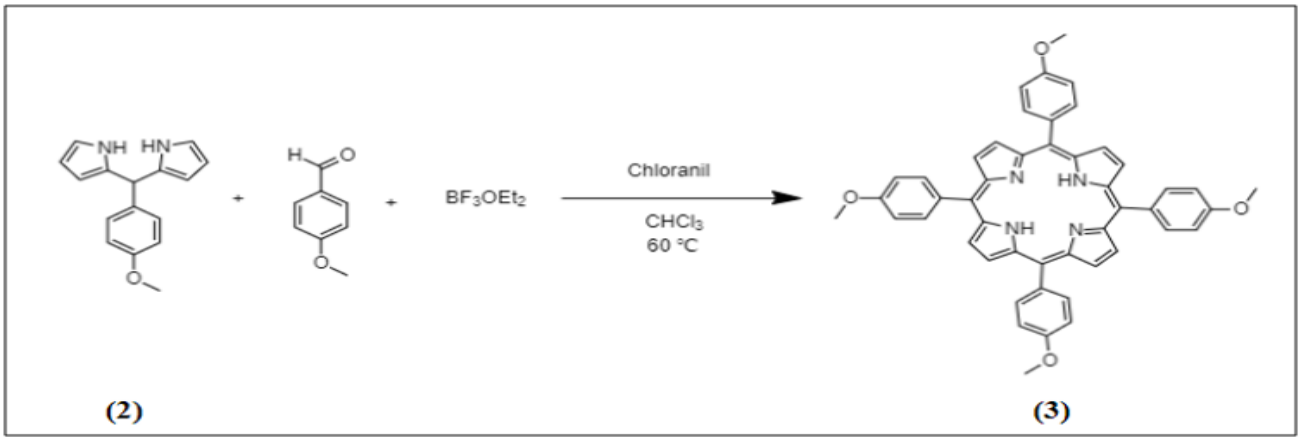


Figure 7: First trial of the synthesis of porphyrin **(3)**.

However, the synthesis was not successful. A TLC of the product was taken to determine if the reaction was completed. It appeared that no product was obtained. Then the crude material was compared to the pure product that was previously made and it was confirmed that no product was obtained (figure 6).

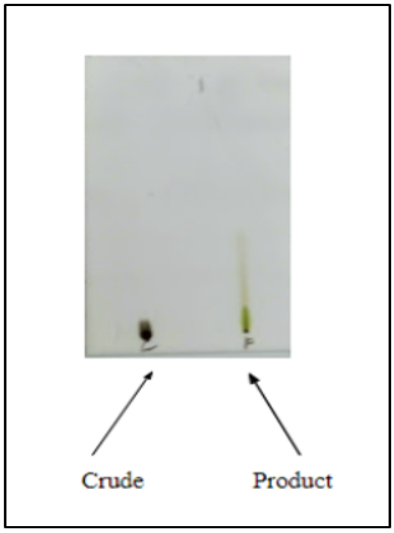


Figure 8: A TLC analysis of the product of the first trial of the synthesis of porphyrin **(3)**. A comparison of the crude product (left) to the purified desired product (right) indicates that the reaction failed.

It was suspected that performing the reaction under high temperature did not allow it to go to completion, and an alternative method was used to synthesize the porphyrin complex. Similarly to the previous procedure, a mixture of dipyrromethane **(2)** and 1 equivalent of 4-methoxy-benzaldehyde in chloroform was degassed. Then, only 0.6 equivalent of boron trifluoride-diethyl ether was added, and the reaction was stirred at room temperature overnight, protected from light. 1.5 equivalent of 2,3-Dichloro-5,6-Dicyanobenzoquinone (DDQ) was added , followed by addition of triethylamine (figure 9). After the triethylamine was added, the solution was allowed to stir for a short period of time and then the mixture was directly purified

using a silica column. NMR analysis of the obtained product was performed, and it was confirmed that the desired product was made. However, porphyrin **(3)** was synthesized in low yields (table 2).

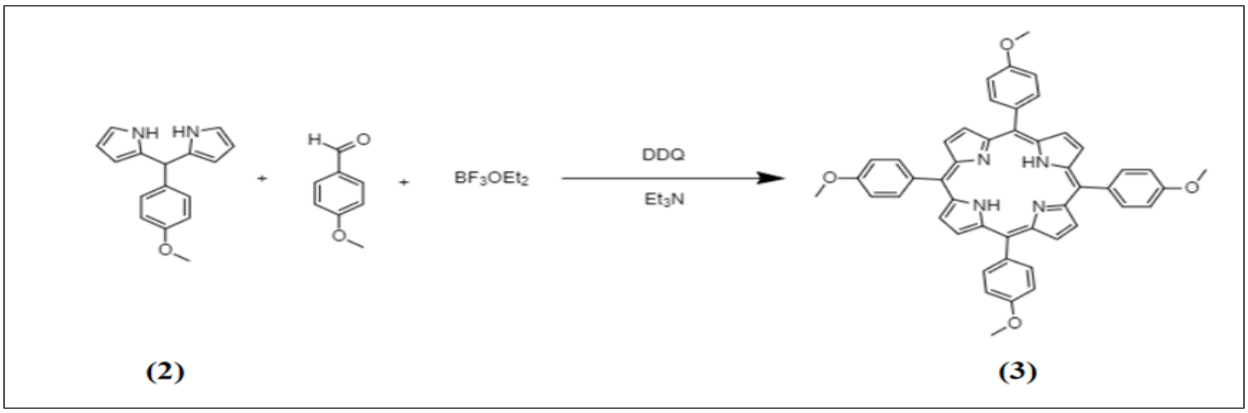


Figure 9: second trial of the synthesis of porphyrin **(3)**.

Table 2

Run	Yield
1	32.1 mg (8.74%)
2	54.6 mg (14.86 %)
3	31.7 mg (8.63%)
4	48.6 mg (13.22%)

Although relatively low yields of the product were obtained, it is determined that the reaction was able to go to completion using the second procedure. The major difference between the first and the second procedure is that during the first procedure the reaction was heated and in

the second procedure the reaction was carried out in room temperature. Therefore, it is suggested that the reaction is heat sensitive.

Step 3: Lastly, the cobalt was added to porphyrin **(3)** to obtain the final catalyst, cobalt porphyrin **(1).** 2 equivalents of cobalt (II) acetate tetrahydrate were added to 1 equivalent of porphyrin **(3)**. Dimethylformamide was used as the solvent. The reaction was refluxed overnight. Then, an aqueous workup was performed using dichloromethane to separate the product from the starting materials (Figure 10). The product was obtained in a relatively high yield of 60.51 %. Due to the fact that cobalt cannot be detected by NMR, mass spectrometry analysis was performed to identify the product.

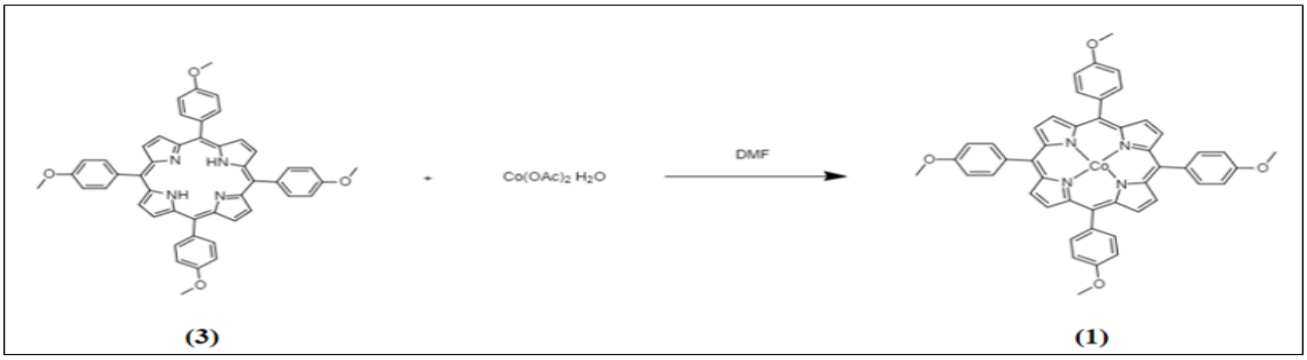


Figure 10: synthesis of cobalt porphyrin **(1).**

Yield: 29.7 mg (60.51 %).

Another run of the reaction was done on a larger scale, requiring 162 mL of solvent. Therefore, the solvent was not injected using a syringe and the reaction was exposed to air in order to add the solvent. That resulted in a very low yield of 2.98 %. In addition, the product could not be characterized using mass spectrometry. The fact that the reaction had very little to no success in that run indicating that the process is highly air sensitive.

Performance of the catalyst:

After the catalyst was successfully synthesized, its performance in the proposed catalytic cycle was tested. The goal was to determine whether the catalyst can be used to generate a carbon radical. The alcohol that was chosen to test the catalyst was 1-Phenylethanol.

Carbonylation of the cobalt-porphyrin: First, the cobalt porphyrin was carbonylated, as was illustrated in step A of the suggested catalytic cycle (figure 3). One equivalent of cobalt porphyrin (1) was reacted with one equivalent 2, 3-Dichloro-5, 6-Dicyanobenzoquinone (DDQ) and five equivalents of the alcohol. The solvent that was used is toluene. The solution was put in a pressure vessel and 2 atm of carbon monoxide were applied (figure 11). NMR analysis was done to characterize the product.

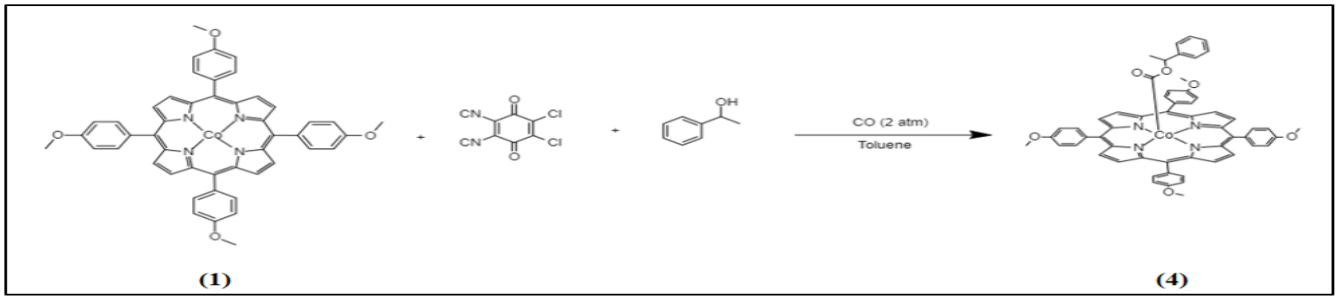


Figure 11: carbonylation of cobalt porphyrin **(1)**.

Yield: 0.1214 g.

The yield obtained is higher than the theoretical yield. In the NMR analysis, it was apparent that the product was not dry and water was present in the NMR sample. This can explain the high yield that was obtained. However, the NMR can confirm that the product was made.

Irradiation of the cobalt- porphyrin: After the desired alcohol is used to carbonylate the cobalt porphyrin complex, a carbon radical can be generated using light, as described in steps B and C of the proposed catalytic cycle (figure 3). In order to determine whether a carbon radical was formed, a stable free radical is added to the reaction. The free radical will react with any other radical that is present in the mixture. Therefore, it can be determined that a carbon radical is formed if the product of reacting the carbon radical with the added radical is obtained. In this experiment, 2, 2, 6, 6-Tetramethyl-1-piperidinyloxy (TEMPO) was used to trap the radical.
1 equivalent of product **(4)** was reacted with two equivalents of TEMPO. The solvent used was chloroform. The solution was degassed and the radical was activated using visible light (figure 12). NMR analysis was done to characterize the product. The desired product was obtained in a yield of 34.56 %.

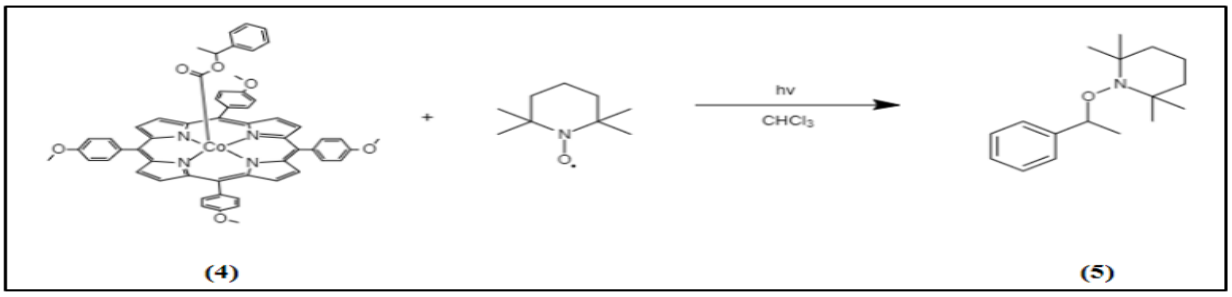


Figure 12: irradiation of the porphyrin.

Yield: 0.0018 g (34.56 %).

Compound (5) is a product of a reaction between the desired radical (6) and TEMPO (figure 13). Therefore, by obtaining product (5) it can be determined that a radical was formed.

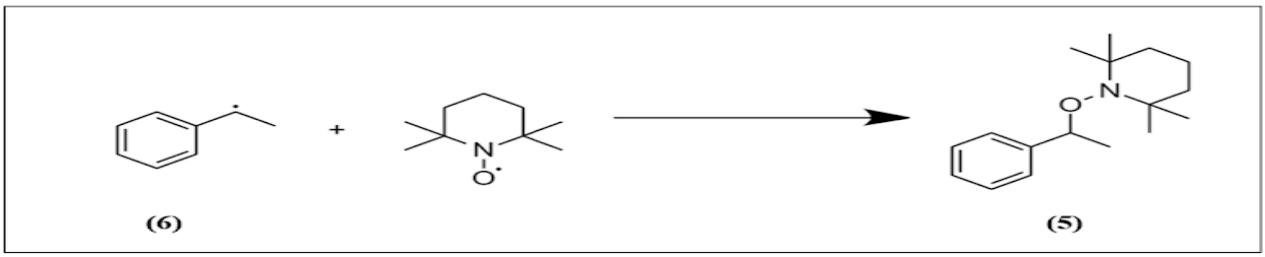


Figure 13: trapping the desired radical using TEMPO.

Conclusion:

The study demonstrated a method of synthesizing a cobalt-porphyrin complex from commercially available starting materials and under mild conditions. A cobalt porphyrin complex was synthesized from pyrrole and an aldehyde in a three step synthesis, using mild bases and oxidants with little or no heat added. The formation of the porphyrin and its precursors was confirmed by NMR. The cobalt-porphyrin product was characterized using mass spectrometry. In addition, it was demonstrated that the cobalt-porphyrin complex can be used to generate a carbon radical, by first carbonylating the complex and then using visible light energy for activation. The reaction was carried out using a relatively low pressure of carbon monoxide, and generated benign waste. The formation of the carbonylated cobalt-porphyrin was confirmed by NMR. The formation of the carbon radical was confirmed by trapping the radical formed using TEMPO and characterizing the product using NMR. It was observed that the synthesis of the porphyrin complex was heat sensitive, but the reaction was able to go to completion in room temperature. However, low yield were obtained, and additional study can be done to optimize the synthesis. It was also observed that the addition of cobalt to the porphyrin complex is air sensitive, but the product was obtained in good yield.

Experimental

Synthesis:

Step 1:

Synthesis of 5-(4-methoxyphenyl) dipyrromethane

Aldehyde (1 eq.) in pyrrole (25 eq.) is added to a round-bottom flask and purged under N_2 for 10 minutes at room temperature. TFA (0.1 eq.) is added dropwise and the reaction is stirred under N_2 for 30 minutes. Then, Et_3N (0.6 eq.) is added dropwise and the reaction is stirred for additional hour and the flask is covered with foil to protect the reaction from light. The pyrrole is removed in vacuo, with toluene added to help remove all the solvent. A yellow oil is obtained (the product can be put under high vacuum to remove the solvent entirely). The product is purified using a silica column and a solution of 5 % ethyl acetate in hexanes is used as the eluent. The product can be further purified by dissolving in a little bit of DCM and recrystallizing in hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 2H, pyrrole N-H), 7.14 (d, 2H, Ar-H), 6.85 (d, 2H, Ar-H), 6.71 (d, 2H, α-*H*), 6.17 (d, 2H, β-*H*), 5.93 (s, 2H, β-*H*), 5.45 (s, 1H, C-H), 3.81 (s, 3H, CH_3). Consistent with the NMR results obtained by Kesavan et al. (Kesavan).

Step 2:

Second trial

Synthesis of 5, 10, 15, 20-Tetrakis (4-methoxyphenyl)-21*H*, 2 3*H*-porphine

A mixture of dipyrromethane (1 eq.) and aldehyde (1 eq.) in chloroform (103.6 mL per 1 mmol of dipyrromethane) is purged under N_2 for 10 minutes. BF_3OEt_2 (0.6 eq.) is added dropwise. The flask is covered with foil to protect the reaction from light and the reaction is stirred under

N_2 at room temperature overnight. DDQ (1.5 eq.) is then added and the reaction is stirred for another hour. Et_3N (2.1 mL per 1 mmol of dipyrromethane) is added. The crude mixture is then directly poured into a silica column and DCM is used as the eluent.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.87 (s, 8H, β-H), 8.13 (d, 8H, Ph-H *ortho*), 7.29 (d, 8H, Ph-H *meta*), 4.11 (s, 12H, Ph-OMe-H). Consistent with the NMR results obtained by Momo et al. (Momo).

Step 3:

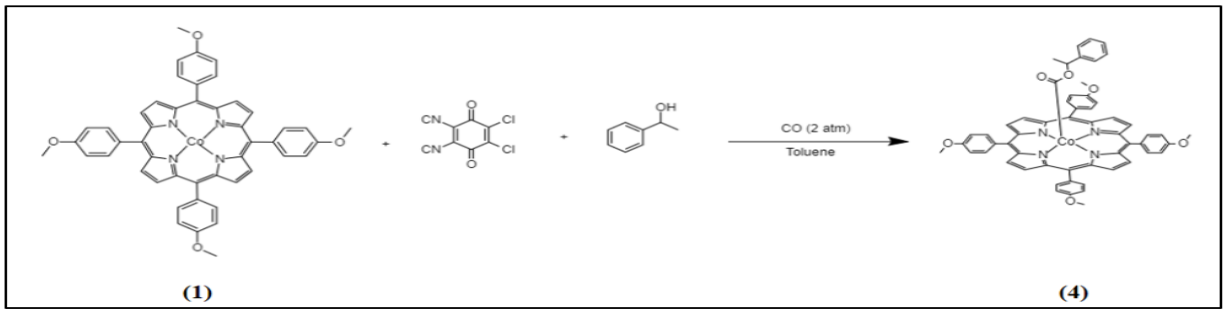
Synthesis of 5, 10, 15, 20-Tetrakis (4-methoxyphenyl)-21*H*,23*H*-porphine cobalt(II)

Porphyrin (1 eq.) and $Co(OAc)_2H_2O$ (2 eq.) are added to a round bottom flask. The flask is evacuated and filled with N_2 three times to clear the air out. DMF (20 mL per 0.062 mmol of porphyrin) is added. The reaction is refluxed overnight. The solvent is removed in vacuo and the product is processed with an aqueous workup with DCM. A silica column is used to purify the product with DCM as the eluent.

Mass spectrometry: HRMS (QTOF) m/z calcd for C48H36CoN4O4 791.2069, found 791.1886.

Performance of the catalyst:

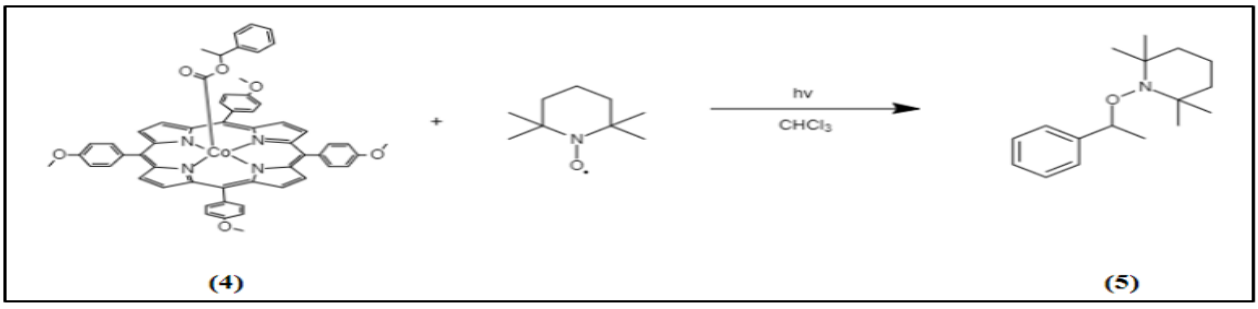
Carbonylation of the cobalt-porphyrin:



Cobalt porphyrin (1 eq.) and DDQ (1 eq.) are weighed into a 20 mL vial. Then toluene (83.33 mL/mmol of cobalt porphyrin), and the alcohol (5 eq.) are added. The reaction is degassed in the pressure vessel, and left to stir overnight under CO. The solvent is removed in vacuo and put under high vacuum for an hour. Then, the product is dissolved in a minimum amount of DCM and recrystallized from pentane. The product is left in the fridge to recrystallize for approx. 5 minutes. The product is then put into vacuum filtration using celite and washed with pentane. Finally, the remaining material is washed with 2:1 hexanes: DCM mixture to obtain the product in solution.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.89 (s, 8H), 7.23, 6.87 (t, 1H), 6.73 (t, 2H), 5.07 (d, 2H), 4.08 (d, 12H), 3.26 (q, 1H), -0.59 (d, 3H).

Irradiation of the cobalt-porphyrin:



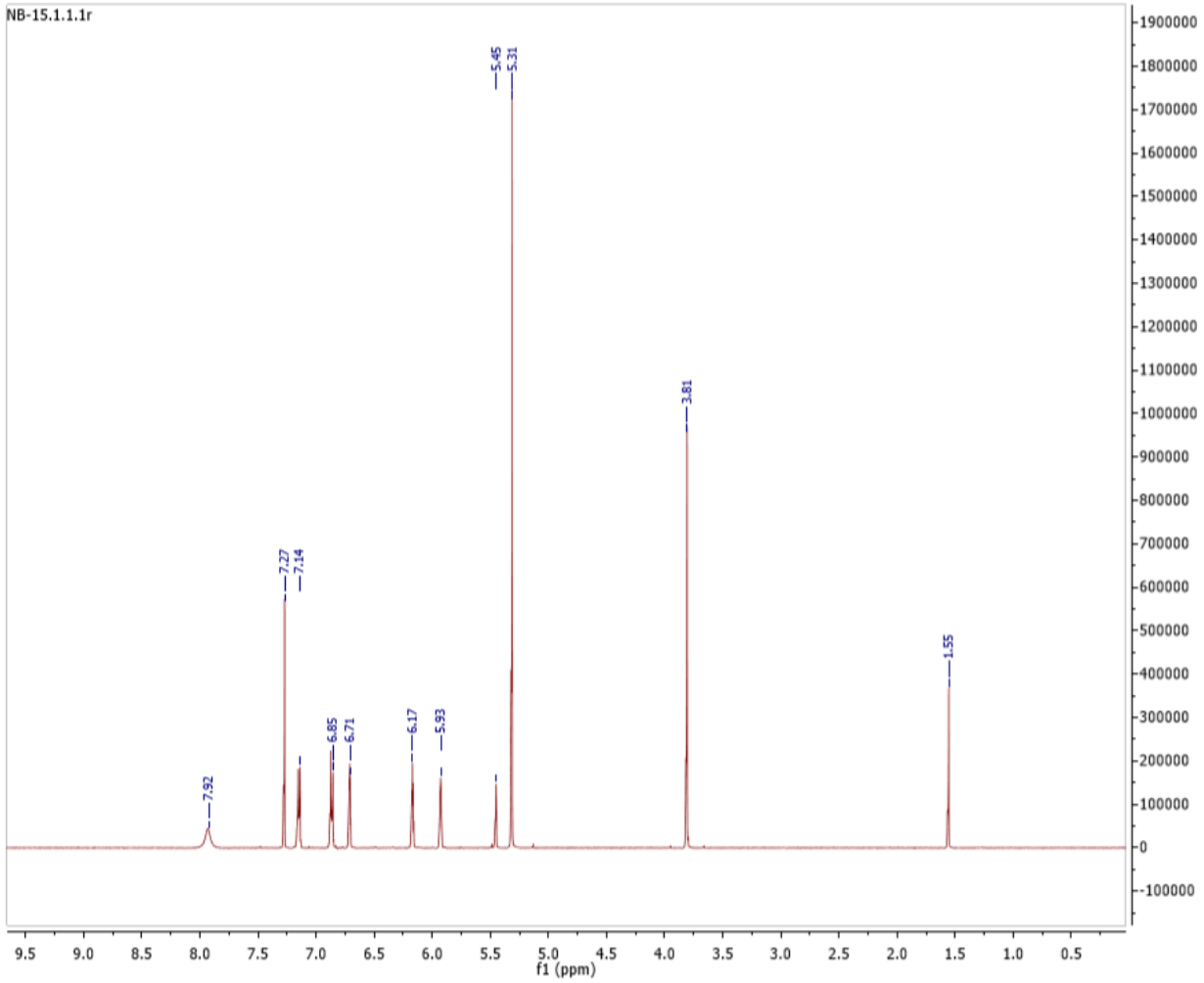
The carbonylated cobalt porphyrin (1 eq.) and TEMPO (2 eq.) are added to a Shlenk tube, and the tube is filled with N_2 and evacuated three times. Then, chloroform (75 mL/ mmol of cobalt porphyrin) is added. The solution is degassed using the freeze-pump-thaw cycle three times. The reaction is then stirred in light overnight. The solvent is removed in vacuo and filtered through celite and washed with hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20 (m, ~5H), 4.73 (q, 1H), 1.51 (d, 3H), 1.2 (s, ~12H), 1.1 (t, 4H), 0.91 (t, 2H).

Supporting Information

NMR spectra:

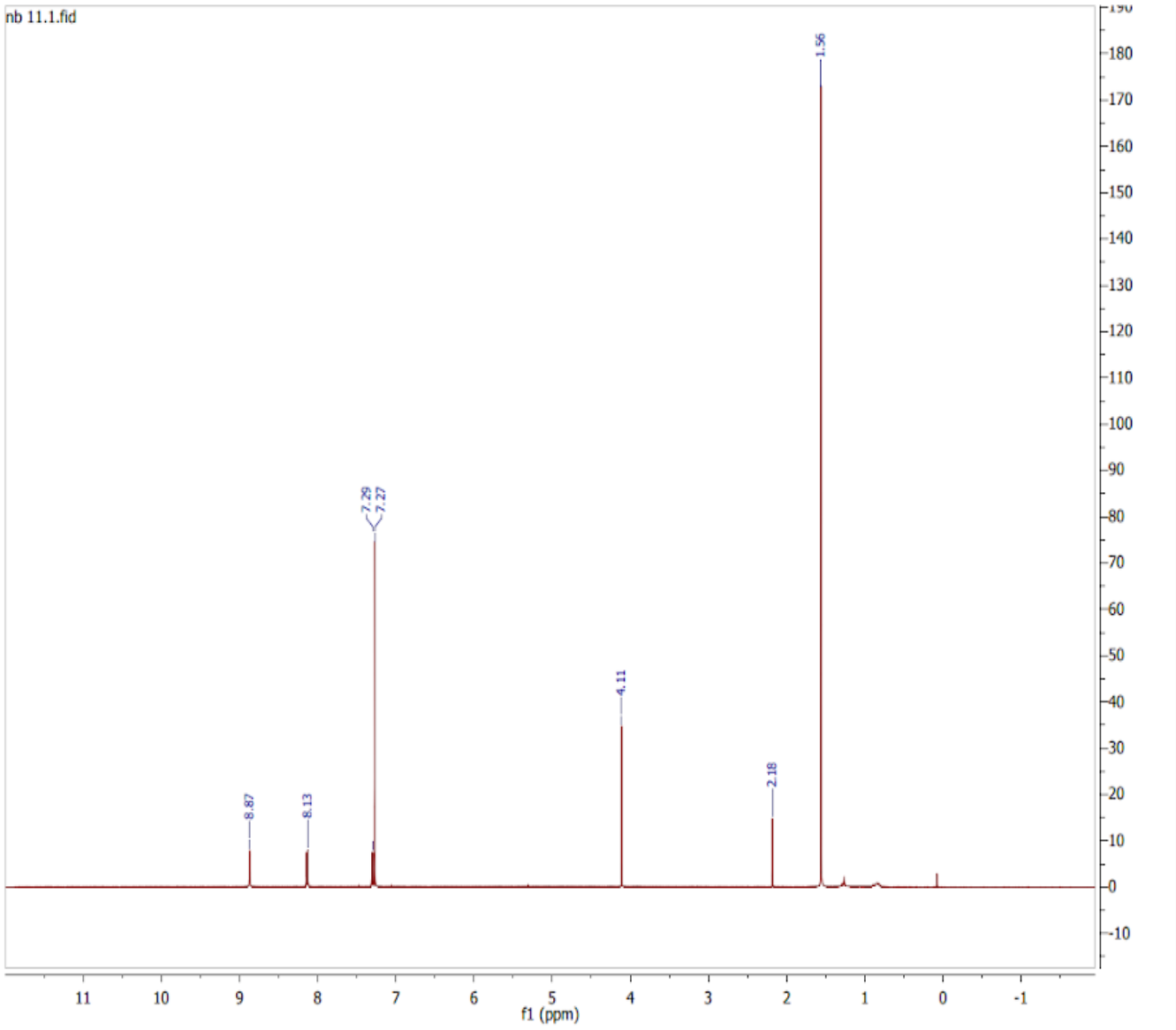
5-(4-methoxyphenyl) dipyrromethane(2)



Diagnostic peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 2H, pyrrole N-H), 7.14 (d, 2H, Ar-H), 6.85 (d, 2H, Ar-H), 6.71 (d, 2H, α-*H*), 6.17 (d, 2H, β-*H*), 5.93 (s, 2H, β-*H*), 5.45 (s, 1H, C-H), 3.81 (s, 3H, CH_3).

Contaminants: 1.55 ppm(water), 5.31 (DCM).

5, 10, 15, 20-Tetrakis (4-methoxyphenyl)-21*H*,23*H*-porphine



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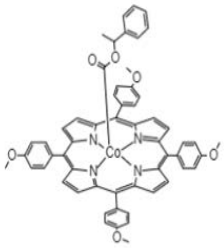
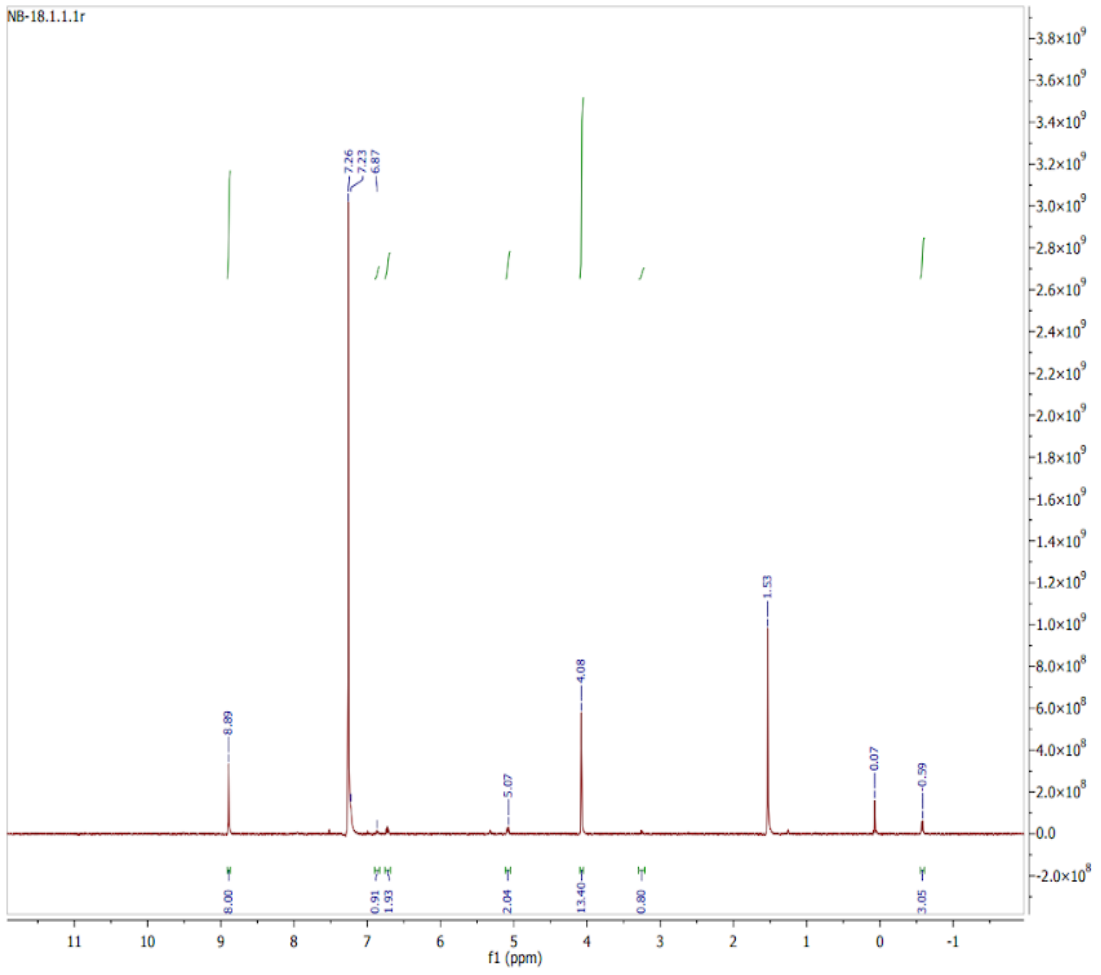
Contaminants: 1.56 ppm (water), 2.18 ppm (acetone).

Compound (4)



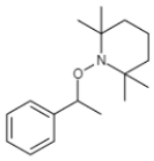
(4)



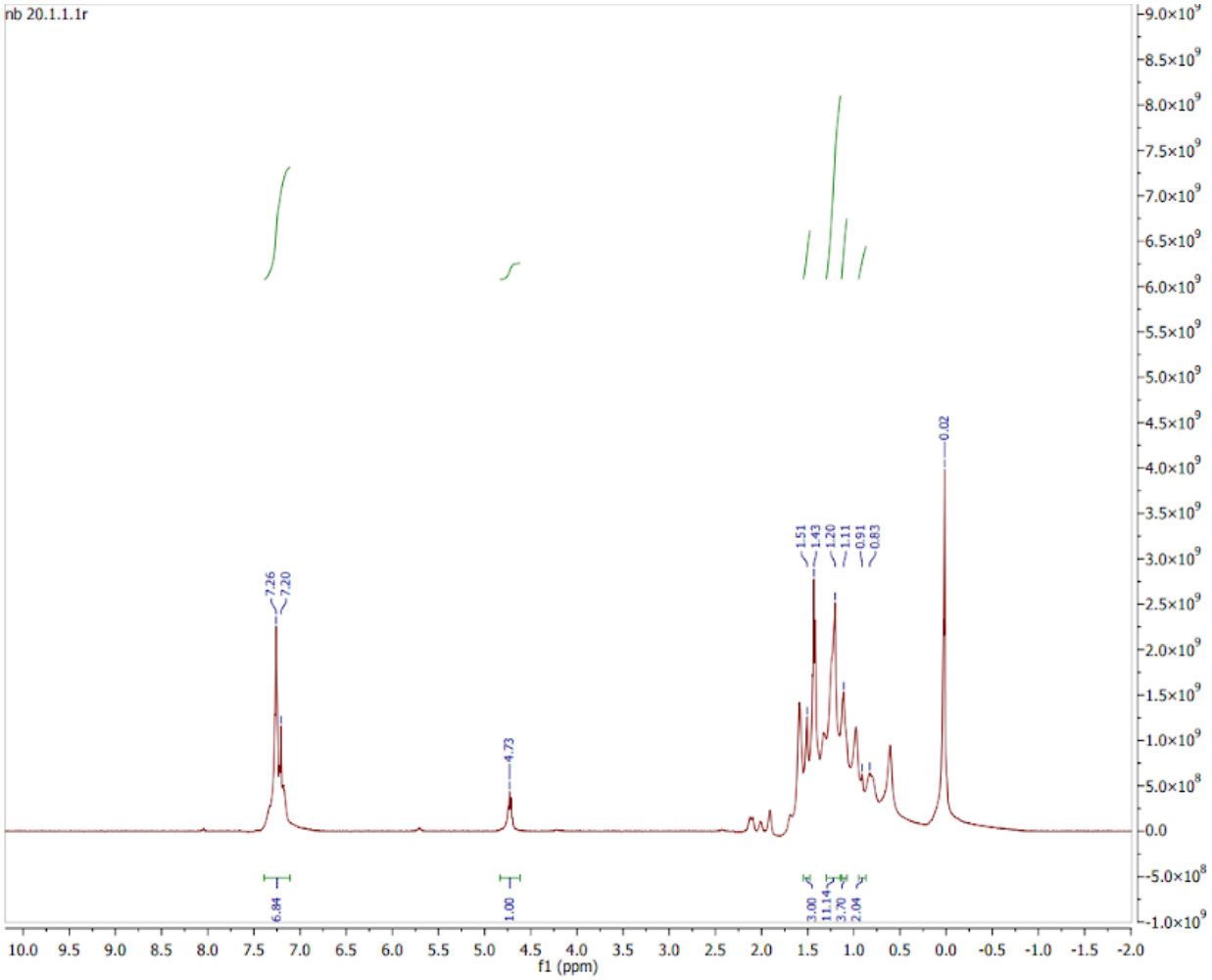
Diagnostic peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.89 (s, 8H), 7.23, 6.87 (t, 1H), 6.73 (t, 2H), 5.07 (d, 2H), 4.08 (d, 12H), 3.26 (q, 1H), -0.59 (d, 3H).

Contaminants: 1.53 ppm (water), 0.07 ppm (HMDSO).

Compound (5)



(5)



Diagnostic peaks: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20 (m, ~5H), 4.73 (q, 1H), 1.51 (d, 3H), 1.2 (s, ~12H), 1.1 (t, 4H), 0.91 (t, 2H).

Contaminants: 1.43 ppm (water), 0.83 ppm (hexanes), 0.02 ppm (HMDSO).

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