An Asymmetrical Ferrocene-Bridged Ligand to Hold Dissimilar Metal Ions

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Bachelor of Sciences

Submitted in partial fulfilment of the requirements for

College Honors

Departmental Distinction in Chemistry

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Title: An Asymmetrical Ferrocene-Bridged Ligand to Hold Dissimilar Metal Ions

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Abstract

Nature is the most successful chemist for activating and interconverting small molecules into more useful ones. A key feature of many enzymes that carry out these transformations is their use of asymmetric, bimetallic active sites. This means that the enzyme is able to hold two different metals each in a unique coordination environment. This work describes our efforts towards applying these lessons and developing ligands that can hold two dissimilar metal ions in unique coordination environments. We have explored different approaches to develop a ligand that is able of holding two different metal ions. We sought to attach two different arms of the ligand with different metal binding sites to a central bridging moiety which will act as the backbone for the entire complex. We began our work using a pyrazole as the backbone. After many difficulties related to the synthesis of a pure pyrazole, we took a new approach toward the synthesis. In particular, we will describe the synthesis of a ferrocene derivative wherein one cyclopentadienyl ring supports a bis(pyridyl)amine ligand and the other cyclopentadienyl ring supports a phosphine ligand. This synthesis has been successful so far and we are three steps away from a completed ligand with the capability of holding two dissimilar metal ions.

Introduction

Many small molecules commonly encountered are kinetically inert, meaning their reactions to form new products suffer from high energy barriers. These properties will hinder the transformation of abundant small molecules into more useful products. Nature is able to overcome these hurdles quite easily. Enzymes are able to perform these transformations at ambient temperatures and pressures. Many enzymes that perform these transformations, share a common characteristic. The enzymes have bimetallic active sites. These sites are asymmetric in either the identity of the metal or the coordination sphere around the metal. For example, two different carbon monoxide dehydrogenase (CODH) enzymes are able to interconvert CO_2 and CO.[1] Each uses two different metals in order to carry out the reaction. One of these CODH enzyme uses a molybdenum metal ion in one portion of the active site and a copper metal ion in the other, Figure 1.[1] The other CODH enzyme uses both an iron ion and nickel ion in its active site.[1] Another example of a heterobimetallic enzyme is the diiron nitric oxide reductase for the production of N_2O from NO using a heme and a non-heme iron, again this requires two different types of binding sites for the different types of irons (Figure 1).[1-3]

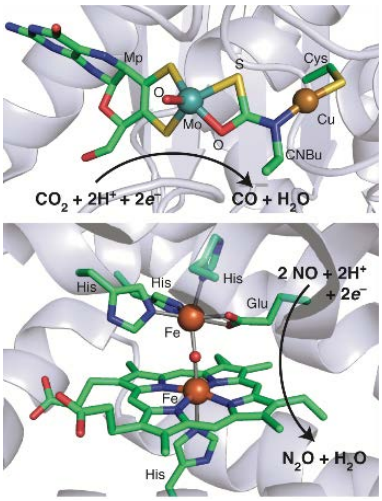


Figure 1: Mo/Cu CODH (top) and diiron nitric oxide reductase (bottom) use two metals in different environments for the cleavage of CO_2 and production of N_2O, respectively.

Each of the metal combinations of the enzyme examples require different binding environments for each metal and, therefore, require different ligand types. This is due to a phenomenon known as hard-soft acid-base theory (HSAB).[15] Metals are considered acids because they are electron acceptors. They can qualify as

either hard or soft. Hard metals have high charge density, are weakly polarizable, and have a small atomic radius.[19] A comparison can be drawn between a hard metal and a cue ball. Soft metals have low charge density, are strongly polarizable, and have a large atomic radius.[19] Soft metals can be compared to a beach ball. The binding site is the ligand and is referred to as the base because it acts as the electron pair donor. The same hard or soft categorization applies to the bases. When it comes time to binding, hard acids prefer hard bases and soft acids prefer soft base. Hence, the need for two different types of binding sites in ligands where two different metals are used in the complex. For example, the carbon monoxide dehydrogenase enzyme described above uses a molybdenum ion as the hard metal and the copper ion as the soft metal. Molybdenum requires a hard-binding site and the copper requires a soft binding site.

Designing molecules that mimic the enzymes with asymmetric bimetallic active sites would allow for many potential opportunities for small molecule transformations. The two metals would cooperatively activate an incoming small molecule, resulting in increased reactivity. Bimetallic molecules have been created a variety of ways including through metal-metal bonded species and non-interacting metals far apart in the molecule. For example, a titanium/cobalt complex with metal-metal multiple bonds was creative for the use of N-N cleavage in the process of ammonia production.[16] Another example is a zirconium/cobalt complex that reacts with organic azides.[17] For the purpose of bond-forming and bond-breaking reactions, a co-facial arrangement of open coordination sites with moderate and flexible metal distances is ideal, because it allows site to maintain changes to the ligand that will occur during catalysis.[5]

The goal of this thesis project performed under Dr. Nicholas Piro, was to create a ligand using a ferrocene derivative as the bridge between the two different binding sites. The two binding sites are a nitrogen-rich arm and a phosphine arm. The nitrogen arm will act as the hard base and allow for the binding of hard metals. The phosphine arm will act as the soft base allowing for the binding of soft metals. Based on these characteristics of the arms of the ligand, we will then be able to attach a different metal to the binding site in each arm. This will allow for the testing of the effects of the two environments on the reactivity of the ligand. We will then be able to attach two different metals to each arm to test the effects of the two environments on the reactivity of the ligand. Future work should also include control ligands where only one arm and metal are present. The control ligands will allow for clearer delineation of how the bimetallic nature of the ligand affects its reactivity.

Early Work: A Pyrazole-Based Approach

This project began with the goal of using a pyrazole as the bridging ligand between the two arms (Figure 2). Many symmetrical bimetallic molecules have used pyrazolates as bridging ligands.[18] The use of pyrazoles in asymmetric complexes is fairly limited. An example is the synthesis of an asymmetric pyrazolate ligand using nickel (II) ions as the binding metals which was one of the first of its kind.[18] We opted for an approach using an asymmetric pyrazole with two different binding sites to bind in the plane of the substrate. This attempt was ultimately

unsuccessful due to the inability to purify the pyrazole and the requirement of a pure pyrazole in order to proceed through the synthesis.

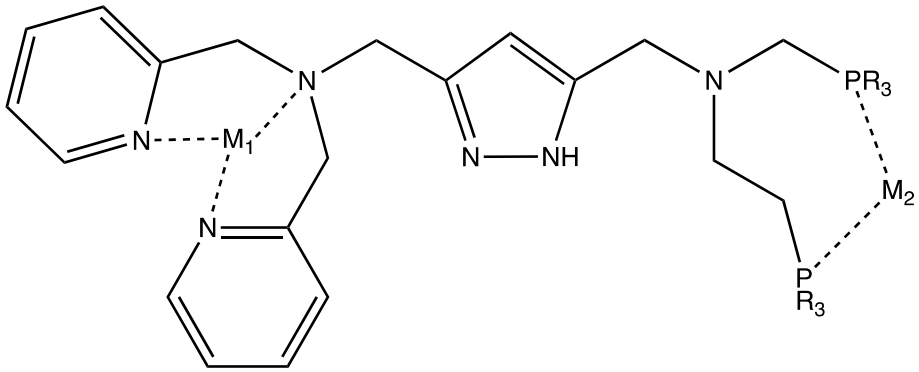
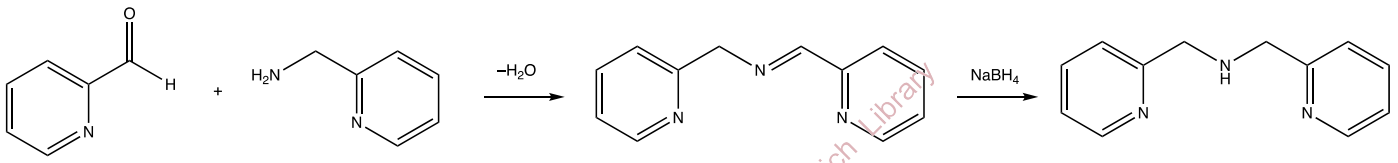


Figure 2: The pyrazole attached to both the nitrogen and phosphine donor arms is depicted with a metal bound to each arm is depicted.

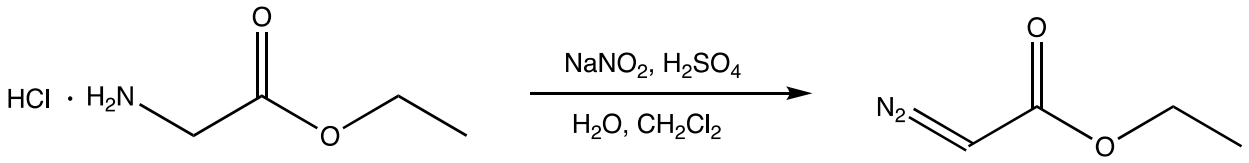
Results and Discussion

For this project, the compound to be used as the nitrogen arm was the first thing to be synthesized. This resulted in the successful synthesis of the N,N-Bis(2-pyridylmethyl)amine (Scheme 1).



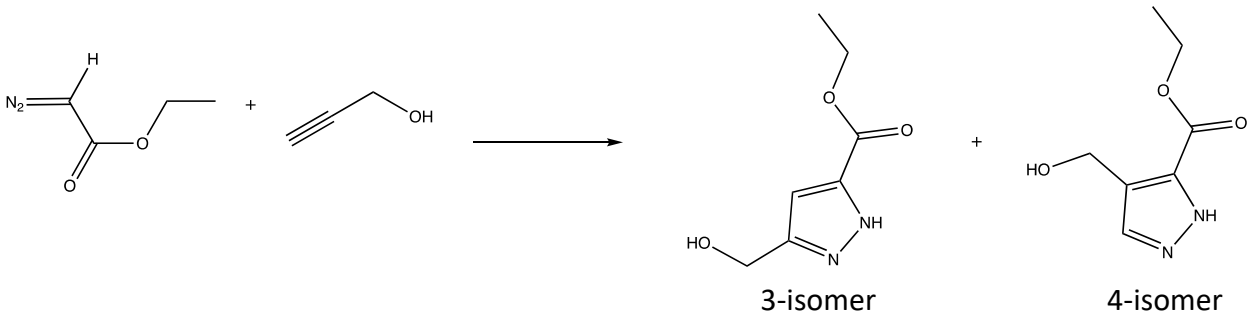
Scheme 1: Molecular structure of the N,N-Bis(2-pyridylmethyl)amine. This compound is used as the nitrogen donor on one arm of the ligand. This nitrogen donor was used for both the pyrazole bridged ligand as well as the ferrocene bridged ligand.

Following the synthesis of the amine, one of the proposes ligand arms, we sought to prepare the pyrazole backbone from a cycloaddition of ethyl diazoacetate (EDA). The EDA we used was originally purchased commercially but later synthesized when the stock of the compound ran out. The EDA was synthesized by reaction of ethyl glycinate hydrochloride with sodium nitrite (Scheme 2).



Scheme 2: Synthesis of ethyl diazoacetate (EDA) for use as the starting material in synthesizing the pyrazole.

The pyrazole was then synthesized via a cycloaddition of EDA and propargyl alcohol (Scheme 3). This reaction was originally run in toluene based on a reaction found in the literature.[12] This resulted in a very slow reaction and, as a result, poor yield when the reaction was stopped. Due to this, we then decided to run the cycloaddition in benzene as the solvent in order to encourage the production of the pyrazole and hopefully decrease the reaction time resulting in a higher yield.



Scheme 3: Synthesis of both the desired 3-isomer and the undesired 4-isomer of the pyrazole from ethyl diazoacetate (EDA) and propargyl alcohol.

This reaction resulted in the production of two different isomers of the pyrazole as products. Our unsuccessful attempts to purify the pyrazole will be discussed below. Due to our inability to separate these diastereomers, the synthesis of the pyrazole bridged ligand stopped here.

Throughout the synthesis of the pyrazole bridged ligand, changes were made to adapt to problems with different steps of the synthesis. The first problem that was encountered was the low yield and slow reaction time during the synthesis of the pyrazole using toluene as the solvent. We made the decision to change the solvent from toluene to benzene. Toluene, also known as methylbenzene, has a methyl group coming off of the six-member aromatic ring which benzene lacks. The reaction with toluene gave a very impure product and with many impurities present via inspection of the hydrogen NMR. Before changing the solvent to benzene, we tested the theory by running a scaled down version using much less material in a sealed NMR tube. Benzene is considered more toxic than toluene and is a carcinogen according to the safety data sheet.[9, 10]

For this reason, we wanted to test the idea of changing solvents before scaling up. The reaction was heated in the sealed reaction NMR tube placed in an oil bath. Deuterated benzene was used as the solvent. Deuterated solvents have deuterium atoms in place of hydrogen atoms on the molecule. Deuterium– ^{2}H, ^{2}D, or just D– has a spin of I=1 and is, therefore, not detected in a ^{1}H NMR spectrum where the I=1/2 proton nucleus is detected.[11] Approximately every hour and then after being allowed to run overnight, the reaction tube containing the EDA, and propargyl alcohol in benzene-d_6 was removed from the oil bath and an NMR spectrum of the reaction was obtained. The reaction seemed to be occurring smoothly as confirmed via hydrogen NMR, so the decision was made to run the reaction on a normal scale using benzene as the solvent. The reaction was run in a pressure flask while heating in the oil bath in order to avoid the release of benzene vapors into the atmosphere. After the reaction was complete, a ^{1}HNMR spectrum of the product mixture was obtained. While the yield of pyrazoles in the mixture was good, there were two isomers present in the NMR spectrum (Figure 4).

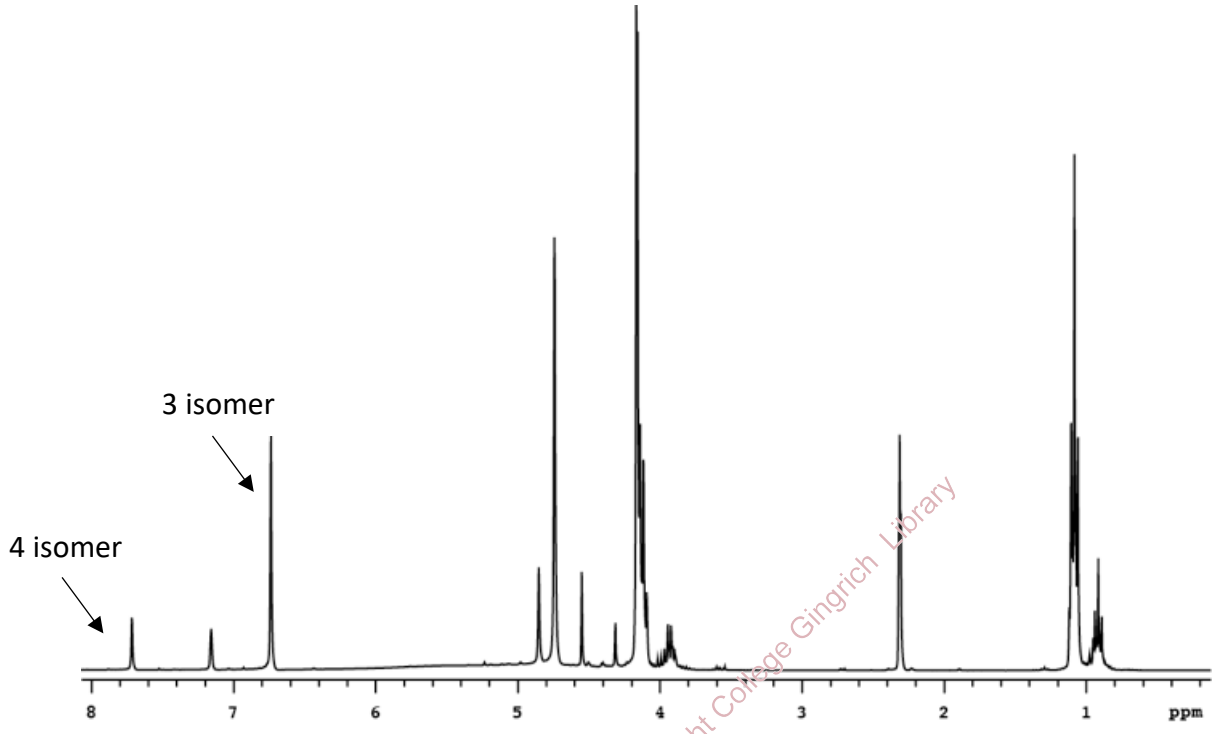


Figure 4: ^{1}H NMR spectrum of the pyrazole product from the cycloaddition of EDA and propargyl alcohol. The distinct peak corresponding to the 3-isomer occurs at 6.75 ppm and the one corresponding to the 4-isomer at 7.70 ppm.

While many of the hydrogen peaks of the different isomers of the pyrazole occur at about the same chemical shift, they each also exhibit a distinct aromatic signal which allowed for us to distinguish between the two isomers. The aromatic peak for the 4 isomer is more deshielded than that of the 3 isomer.[12] Deshielded means the chemical shift is higher for this hydrogen of

the 4 isomer than for that of the 3 isomer. This is likely due to the position of the C-H bond on the ring relative to that of the nitrogens on the ring. The C-H of the 4-isomer is in much closer proximity to the nitrogens on the ring compared to that of the 3-isomer. Nitrogens are electron withdrawing groups so the C-H closer to the nitrogen has less electron density. This results in a higher chemical shift. This is due to the fact that the ester group and the alcohol group are in closer proximity to each other in the 4 isomer than the 3 isomer. This results in the aromatic peak of the 4 isomer appearing at about 7.70 ppm and the aromatic peak of the 3 isomer appearing around 6.75 ppm. Integrating the two peaks gives the ratio of hydrogen atoms contributing to each position. From the integration, the ratio of 3 isomer to 4 isomer was determined to be 6 to 1. The 3 isomer was the desired isomer and was present in only a slightly higher quantity.

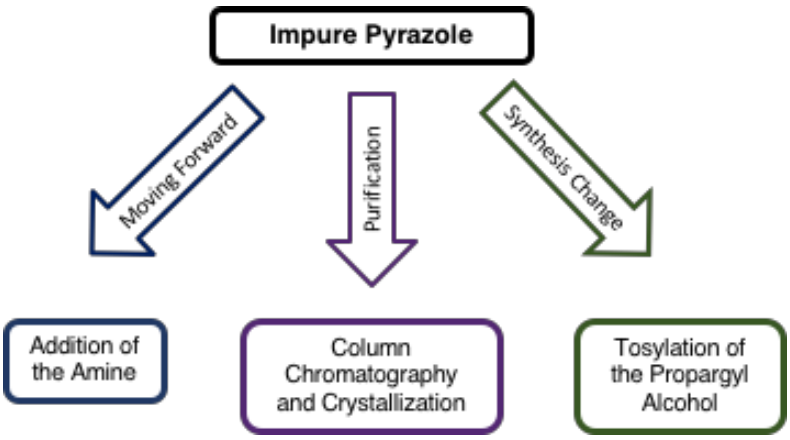
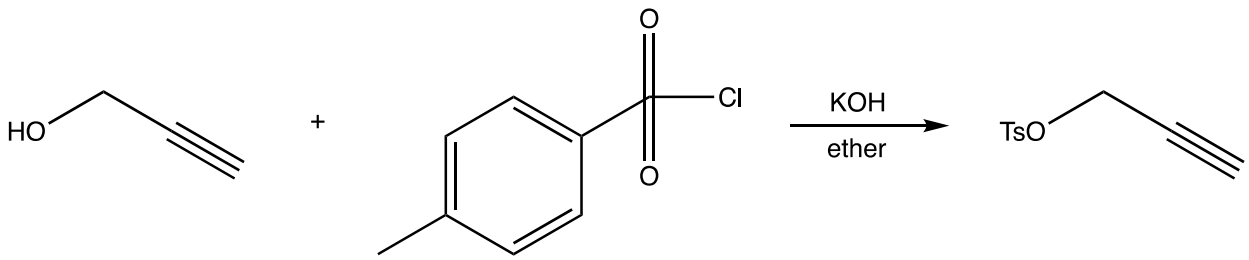


Figure 5: Flow chart of the pathways followed in the attempt to synthesize the complete pyrazole bridged ligand.

Throughout the synthesis, many different paths were taken in the attempt to produce the ligand (Figure 5). We attempted to move forward through the synthesis using the impure product. Unfortunately, addition of the amine to the impure pyrazole product resulted in the production of a dark brown, tar-like substance. This contrasted significantly with the white powder which should have been produced had the desired pyrazole been isolated alone through separation and purification. The ^{1}H NMR spectrum was obtained but the appearance of the spectrum led us to believe the desired product was not synthesized.

The two isomers of the pyrazole were also attempted to be separated using column chromatography on silica gel. The eluent was chosen after investigating the use of different solvents and combinations of solvents through the analysis of thin layer chromatography (TLC). With the polarity of the isomers being very similar, they were eluting off the column at very similar rates, therefore, eluting into the same fractions and not separating. Multiple attempts were made using different solvents for the column chromatography with no success.

We then took a different approach. Instead of attempting to purify the already impure pyrazole, we attempted to synthesize a purer pyrazole from the cycloaddition. In this reaction, the propargyl alcohol was first tosylated by addition of a *p*-toluenesulfonyl group to the oxygen, Scheme 3. For the synthesis of the propargyl tosylate, the propargyl alcohol and p-toluenesulfonyl chloride were dissolved in diethyl ether. Powdered potassium hydroxide was added at -5˚C. The solution was allowed to warm to room temperature then heated. The solution was extracted and rotary evaporated to yield the product as an oil.



Scheme 4: Synthesis of propargyl tosylate from propargyl alcohol and p-toluenesulfonyl.

Tosylating the propargyl alcohol creates propargyl tosylate where the hydroxyl group of the alcohol is replaced with the much bulkier tosylate group. The propargyl tosylate was used in place of propargyl alcohol during the cycloaddition with ethyl diazoacetate. The goal here was to promote the formation of the less hindered 3-isomer by including the bulky tosylate group. In forming the 4 isomer, the tosylate group was expected to clash with the ester already present in ethyl diazoacetate due to the close proximity to each other in the final molecule. However, upon running the reaction and examination of the NMR spectrum, it was found that the tosylation strategy resulted in the production of many of other byproducts as is evident from the broad peaks in the spectrum. These observations led us to conclude that the tosylation of propargyl alcohol would be unhelpful, Figure 6.

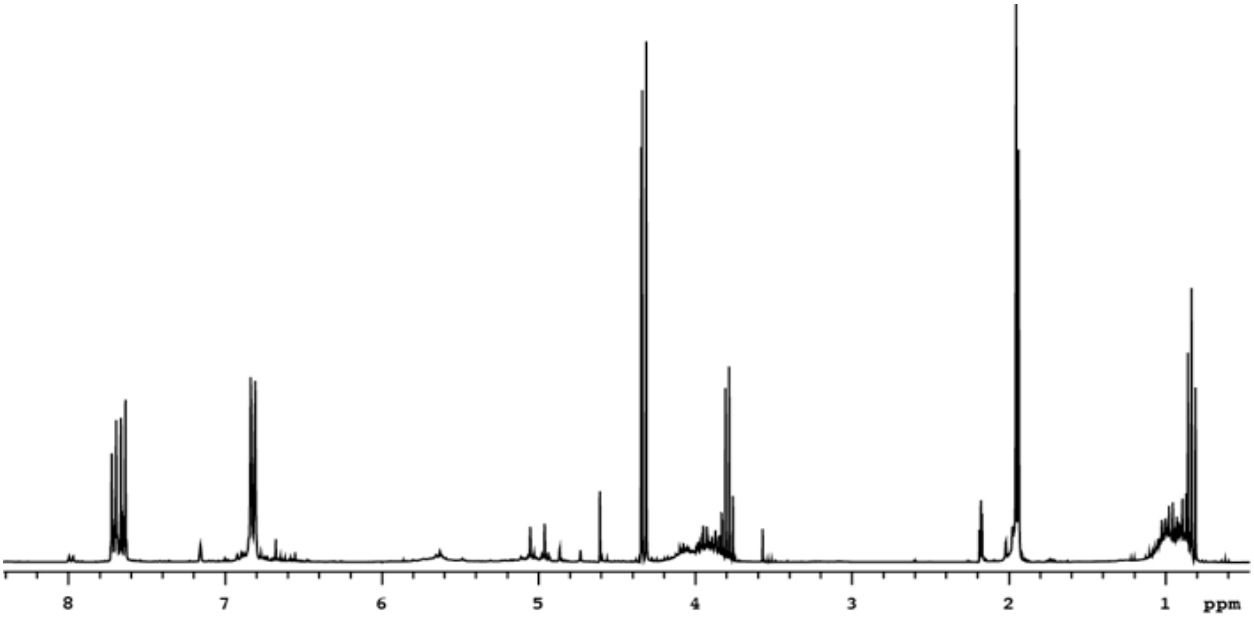


Figure 6: ^{1}H NMR spectrum of the product of the propargyl tosylate with EDA reaction.

There were also some experimental attempts made to try to separate the isomers through selective recrystallization of the pyrazole isomers from different solvents. Many different solvents were screened, including methanol, methylene chloride, acetone, and chloroform. Most of these attempts proved to be unsuccessful. One attempt was met with minor success: the pyrazole was dissolved in acetone, placed in the freezer, and the solvent was allowed to slowly evaporate. The resulting solid was then partially dissolved in deuterated chloroform, $CDCl_3$. Upon attempting to dissolve the solid, some dissolved while part of it remained solid. An NMR was taken of the dissolved portion of the pyrazole and integration revelaed that the 3-isomer was now present in a ratio of about 25:1 over the 4-isomer. Unfortunately, this was unable to be replicated on a larger scale.

Conclusion

We came to the conclusion that there was no efficient and inexpensive way to separate the 3 isomer from the 4 isomer of the pyrazole. After some attempts to continue the synthesis with the impure pyrazole, we concluded that without purifying the pyrazole, the project could not advance. Addition of the amine in order to create the nitrogen arm of the ligand was impossible without the pure 3 isomer of the pyrazole. This led us to reevaluate the structure of the ligand and pursue a new strategy utilizing a ferrocene backbone ligand instead of a pyrazole-linked template.

A New Approach: Ferrocene-linked Ligands for Holding Dissimilar Metals

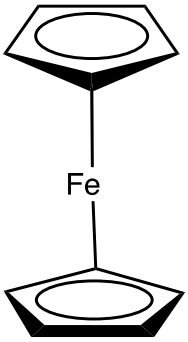


Figure 7: Structure of ferrocene.

The current approach to our goal of synthesizing a ligand with the potential to hold two different metals utilizes a ferrocene derivative as the bridge between each of the asymmetric arms of the ligand. The choice to use ferrocene as the bridging ligand in place of the pyrazole is due to many advantageous features of the ferrocene molecule. Ferrocene contains an iron atom sandwiched between two cyclopentadienyl rings (Figure 7). The strong bonding of the iron atom in the ferrocene helps to cause stability of the molecule. Another factor of its unusual stability is that the planar cyclopentadienyl rings are best described as aromatic anions with 6π electrons.[8] The ability to selectively perform chemistry on the cyclopentadienyl rings also makes the ferrocene a good choice as the bridging ligand. The ferrocene bridge will also allow for the nitrogen and phosphine groups to be kept in close proximity thanks to the torsion of the Cp-Fe-Cp axis. We hope this will enable cooperative reactivity between the two metal sites.[1] The ligand will again feature both a phosphine donor and a nitrogen donor set. The nitrogen donor set is *N,N*-bis(2-pyridylmethyl)amine and the phosphine donor is the diphenylphosphine (Figure 8).

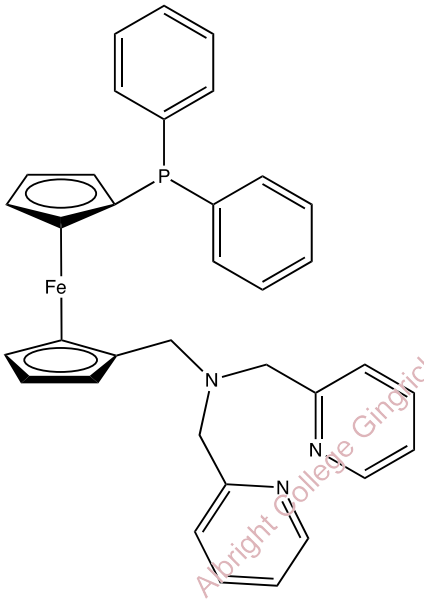
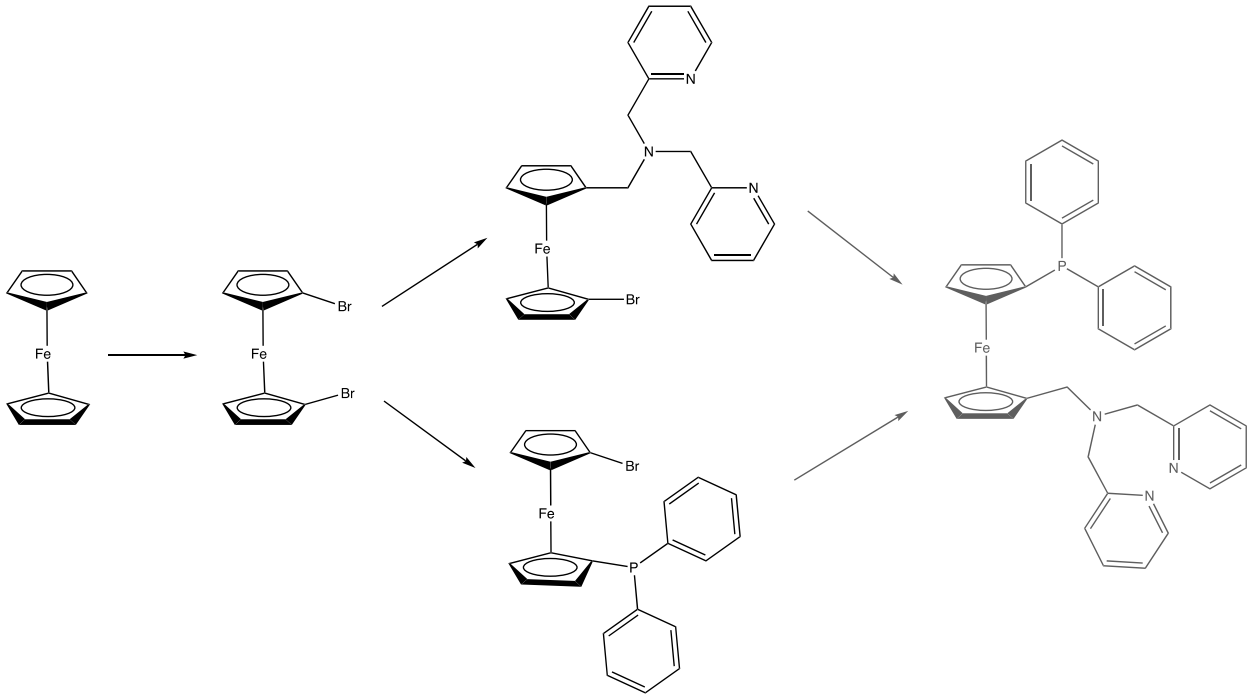


Figure 8: 1-N,N-Bis(pyridylmethyl)amino-1'-diphenylphosphino ferrocene ligand. This is the target ligand for our synthesis.

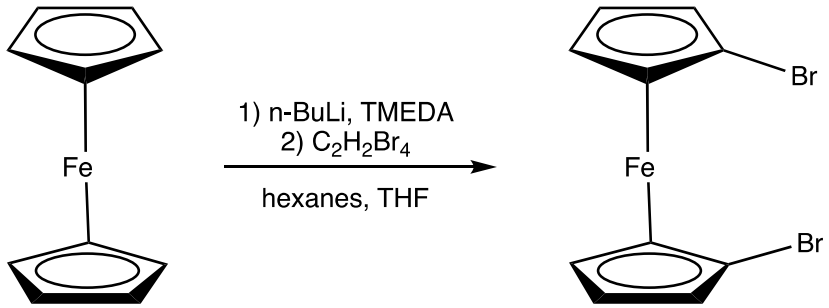
Experimental

Two synthetic routes to the ferrocene derived ligand are shown in Scheme 5. Our first approach to the ferrocene bridged ligand began with the synthesis from ferrocene to 1,1'-dibromoferrocene, the nitrogen donor arm was added followed by the phosphine arm.



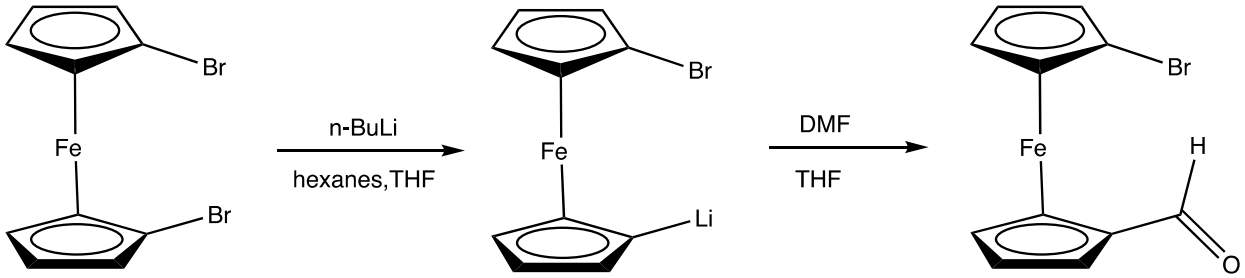
Scheme 5: Both routes taken to attempt to achieve the final ligand.

The 1,1'-dibromoferrocene is synthesized through the addition of tetrabromoethane to ferrocene in THF and hexanes (Scheme 6).[13] In the glovebox, ferrocene is dissolved in tetrahydrofuran (THF) in a dried Schlenk flask with a stir bar. The n-butyllithium is added and the resulting solution is allowed to stir overnight. The solution is washed and the tetrabromoethane is added. A Nuclear Magnetic Resonance (NMR) spectrum was obtained of the crude 1,1'-dibromoferrocene. This spectrum is obtained to ensure the product was made. Thin layer chromatography (TLC) was performed to decide the proper eluent for use for column chromatography. The crude product was purified with flash column chromatography using hexanes as the eluent. The NMR spectra of the purified product was then obtained.



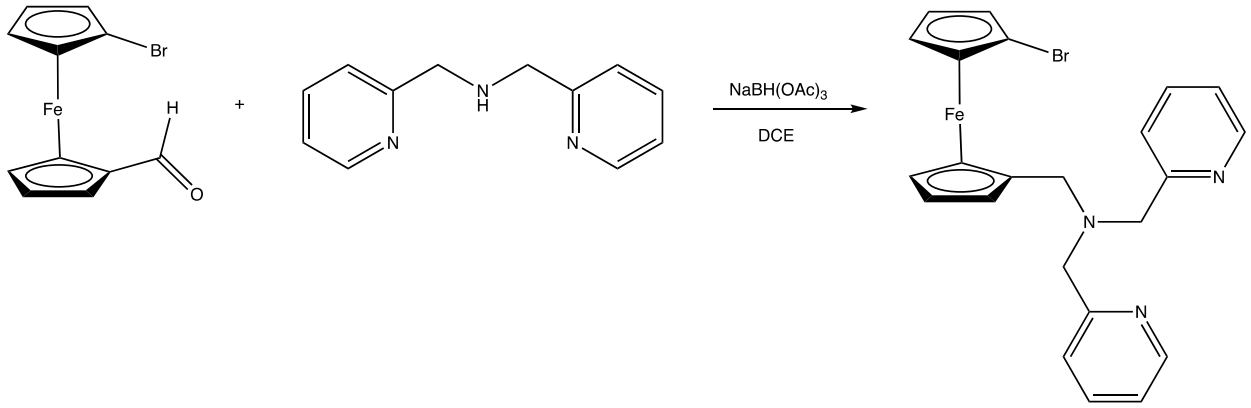
Scheme 6: Synthesis of 1,1'-dibromoferrocene from ferrocene.

The 1-bromo-1'-formylferrocene was synthesized from the 1,1'-dibromoferrocene. The 1,1'-dibromoferrocene was placed in a Schlenk flask with dry THF, n-butyllithium in hexanes was added to the solution to lithiate at one of the bromine positions. The solution was then treated with dimethylformamide (DMF) to replace the lithium with a formyl group (Scheme 7).



Scheme 7: Synthesis of 1-bromo-1'-formylferrocene via lithiation.

The nitrogen arm was then added in place of the formyl group. The 1-bromo-1'-formylferrocene was dissolved in dichloroethane (DCE) and the dipycolylamine (DPA) was added followed by $NaBH(OAc)_3$ (Scheme 8) .

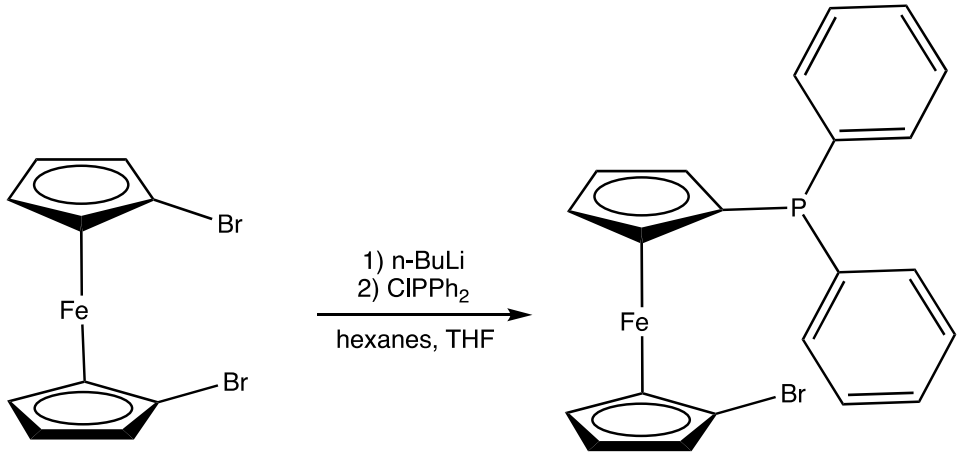


Scheme 8: Addition of the nitrogen arm to the ferrocene through reductive amination.

After addition of the nitrogen arm of the ligand, we performed the final step to add the phosphine arm. The 1-bromo-1'-formylferrocene was dissolved in dry THF and treated with n—butyllithium to replace the bromine with a lithium. The solution was then treated with diphenylphosphine chloride to add the phosphine arm. After working up the product and obtaining an NMR spectrum, we found the reaction to be unsuccessful. The NMR showed mostly starting material. We believe there were complications with the nitrogen arm of the ligand and the n-butyllithium reagent.

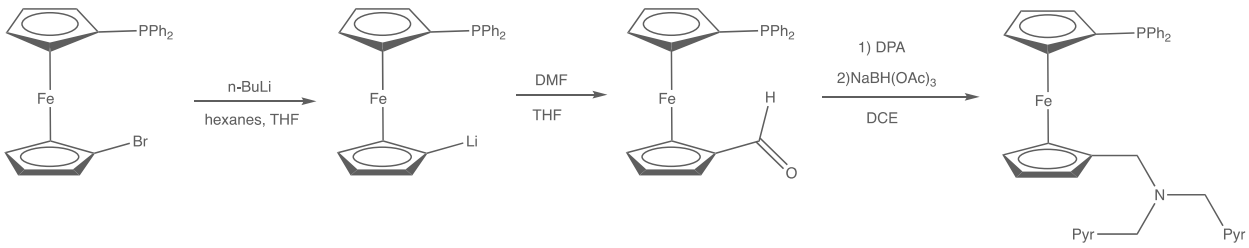
After the attempt to perform the synthesis starting with the addition of the nitrogen arm was unsuccessful we decided to try a second route as shown in Scheme 2. This route begins the same way through the synthesis of 1,1'-dibromoferrocene from ferrocene. The phosphine and nitrogen donor arms are then added respectively.

The purified 1,1'-dibromoferrocene was dissolved in THF in the glovebox in a Schlenk flask with a stir bar. Tetramethylethylenediamine (TMEDA) was added followed by n-butyllithium. After 30 minutes of stirring in a bath of dry ice and isopropanol, chlorodiphenylphosphine was added, and the reaction went from orange to red. The reaction was allowed to stir overnight as it warmed to room temperature. An NMR spectrum of the crude 1-bromo-1'-diphenylphosphinoferrocene was obtained. TLC was performed to determine the proper eluent for column chromatography. The product is purified using column chromatography with 3 to 1 hexanes to dichloromethane followed by pure dichloromethane as the eluent. The solvent was removed using rotary evaporation to yield a crystalline solid which was then ground down and further dried on the vacuum line (Scheme 9).[14]



Scheme 9: Synthesis of 1-bromo-1'-diphenylphosphinoferrocene for 1,1'-dibromoferrocene.

We are now three steps away from the final ligand. We will lithiate at the position of the bromine and treat with dimethylformamide replace with a formyl group. The dipycolylamine (DPA) will then be added via reductive amination in place of the formyl group (Scheme 10).



Scheme 10: Synthesis showing the final three steps to achieve the final ligand.

Results and Discussion

The synthesis of the N,N-Bis(2-pyridylmethyl)amine has consistently been performed successfully and efficiently resulting in a pure product. After the synthesis and purification of the amine, the hydrogen NMR spectrum of the oil is obtained in deuterated chloroform (Figure 9).

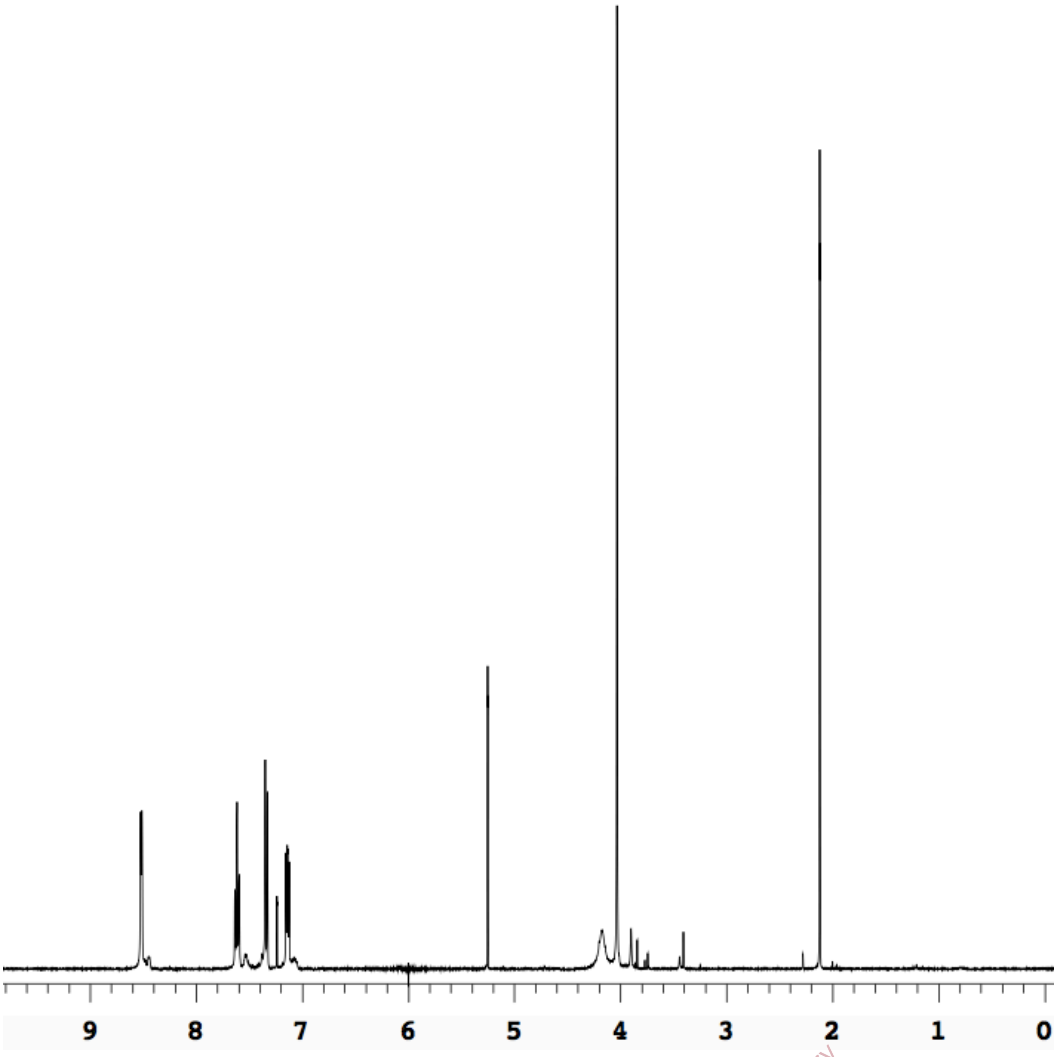


Figure 9: NMR spectrum of N,N-Bis(2-pyridylmethyl)amine.

The 1,1'-dibromoferrcoene is synthesized from the starting material of ferrocene. The ^{1}H NMR of the product was analyzed to determine the purity of the compound (Figure 10). The two peaks around 4.40 ppm and 4.50 ppm correspond to the 2 different hydrogen environments of the cyclopentadienyl rings. The top and bottom rings are equivalent in chemical environment since they each have one bromine attached.

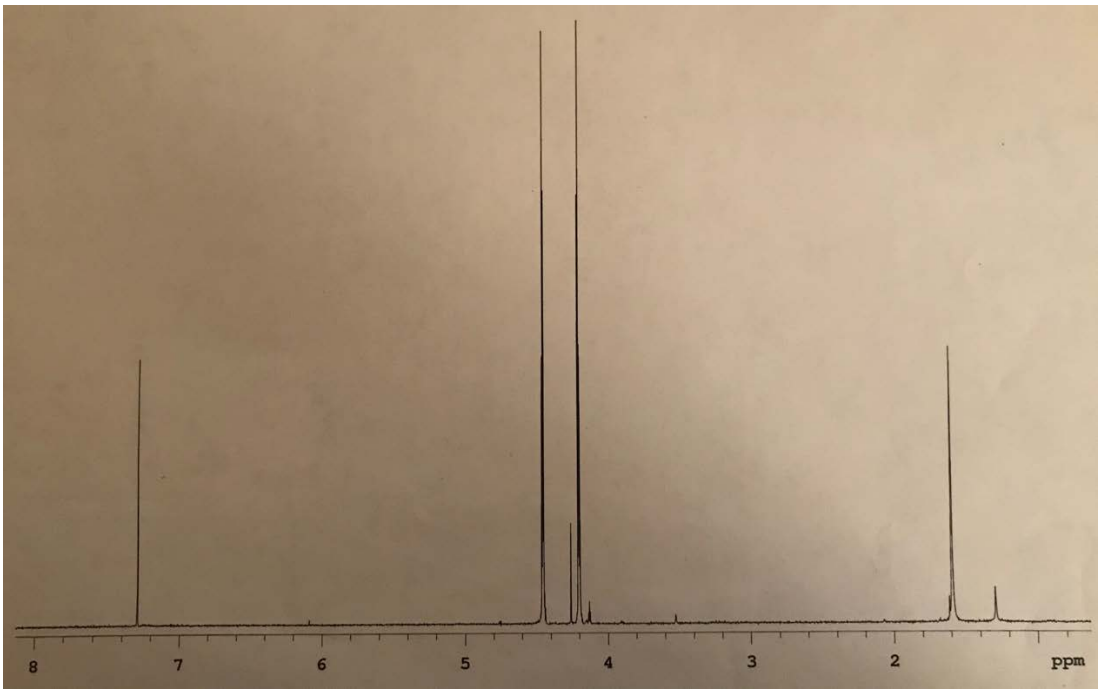


Figure 10: ^{1}H NMR spectrum of 1,1'-dibromoferrocene.

During the first attempt to synthesize the ferrocene bridged ligand, the nitrogen donor was added to the 1,1'-dibromoferrocene. The ^{1}H NMR spectrum of the purified product was obtained in deuterated chloroform (Figure 11).

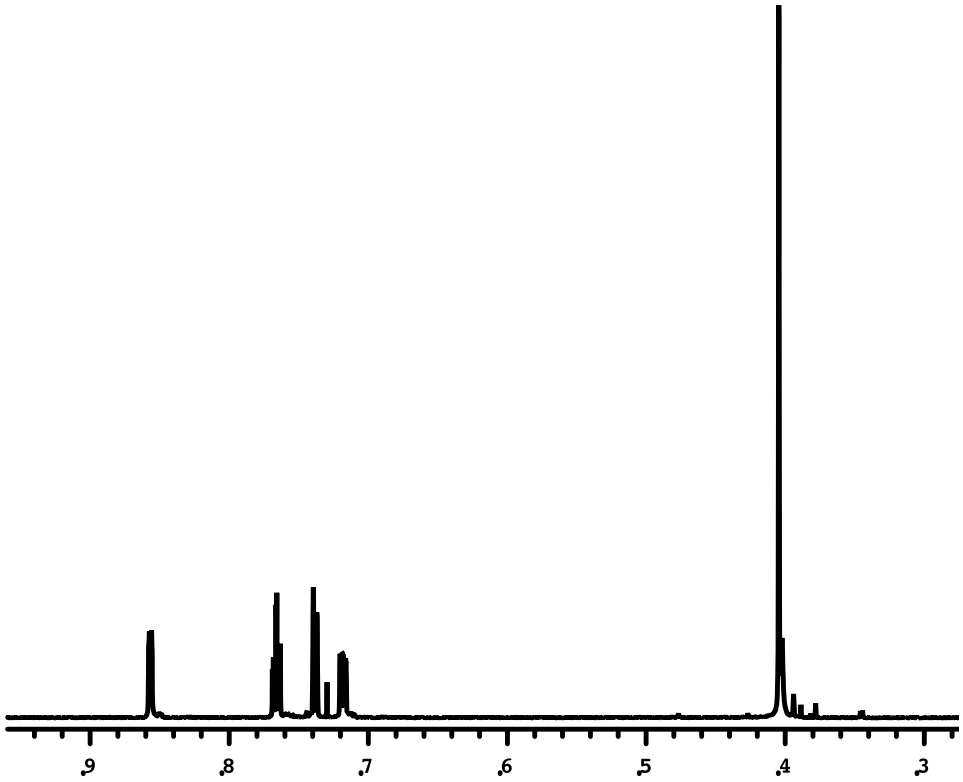


Figure 11: ^{1}H NMR spectrum of 1-bromo-1'-dipicolylamineferrocene.

The most recent attempt at synthesizing the ligand switched the order of the addition of the phosphine and the amine. This time, the phosphine is added first through synthesis using the 1,1'-dibromoferrocene and diphenylphosphine chloride. A ^{1}H NMR spectrum of the resulting dried product was then obtained in deuterated chloroform (Figure 12). The region of chemical shift from about 4.0 to 4.5 ppm shows the peaks corresponding to hydrogens on the cyclopentadienyl rings. The chemical shift from about 7.25 ppm to 7.40 ppm shows the peaks corresponding to the hydrogens on the phenyl rings. These phenyl rings are present on the diphenylphosphine arm of the ligand. This region should show a multiplet since each hydrogen on the rings should exhibit a slightly different chemical shift. Analysis of this region of the NMR shows the phenyl rings do not exhibit many impurities. Full analysis of each region of the hydrogen NMR spectrum for 1-bromo-1'-diphenylphosphinoferrocene indicates the impurity present in the product is most likely due to grease which was unable to be removed from the final product. This indicated that the reaction should proceed smoothly and yield a pure product if we are careful to avoid contamination with other substances.

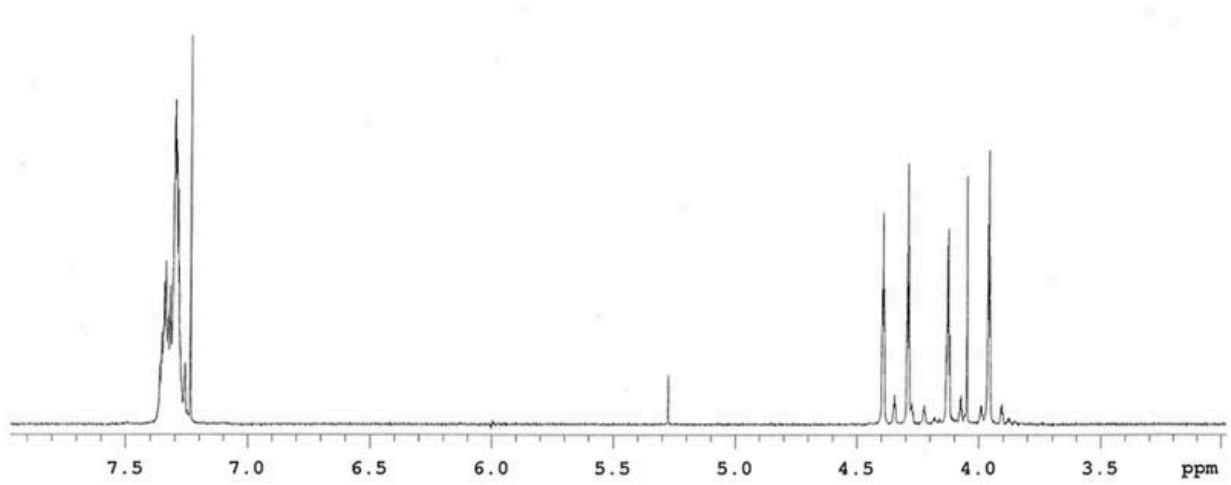


Figure 12: ^{1}H NMR spectrum of 1-bromo-1'-diphenylphosphinoferrocene.

Conclusions and Future Directions

The synthesis of the ligand using a ferrocene derivative as the backbone for the complex has been significantly more successful than the attempt to synthesize the complex using a pyrazole as the bridge. We have, however, still had some difficulties in the ligand synthesis. Our original attempt to attach the amine followed by the phosphine donor resulted in low yields and difficulties in synthesizing the final step. This resulted in changing our approach to the synthesis by attaching the phosphine donor first followed by the amine.

While this attempt resulted in some difficulties, we have successfully synthesized the ligand up to 1-bromo-1'-diphenylphosphinoferrocene. We began with ferrocene and were able to add tetrabromoethylene to create 1,1'-dibromoferrocene. From here the diphenylphosphine chloride was added to create the 1-bromo-1'-diphenylphosphinoferrocene. We are three steps away from the final ligand. We will lithiate the final bromine and replace with a formyl, then we will add the dipycolylamine as the nitrogen donor.

After this synthesis is complete, we will begin binding metals beginning with copper in both positions. The symmetric homobimetallic ligands will also be synthesized to act as the control ligands. The reactivity will then be assessed by probing the reactivity of inert substrates such as carbon dioxide. The reactivity of the heterobimetallic ligand will then be compared to that of the homobimetallic ligands.

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