

Synthesis and Characterization of Dibenzofuran-based Pincer Ligands

Hannah Chapin
Mentored by Dr. Elliott Hulley

Chemistry and Art

Art and science seem to have very disparate ways of processing information. One views the expanse and gestalts, the other begins with the minute and ascends to larger understanding by assembling structural blocks. But they share in the practices of observation, disciplined and inciteful to the particulars, focusing on the essential, the elegant, the excessive, demanding a capacity to operate or challenge the constraints that the discipline dictates. Through organic chemistry the two worlds of art and science converged for me for the first time. The synthetic process had visual representations creating a space where drawings helped to explain the chemistry behind the reaction. Through research I discovered that the discipline of chemistry was not linear-but structured chaos. Like art, research is as much about being lost and guessing as exploring known territory; it allows one to profit from cognitive labors, to draw out the implications of findings, to integrate them in practice. The process is intricate, but out of the compounds a grander representation can be created. Research also offers a softer, more engaging process to assist in managing the rigidity and difficulty of chemistry. It adapts the chemical theories taught in class, adding utility and fluidity to a resolute process, and effectively acts as a vehicle for exploration and discovery. I am appreciative of the value research added to my education at the University of Wyoming.

Background

Wyoming, a key energy state in our nation, is one of the top ten natural gas (e.g. methane) and petroleum producing states. Oil shale and tar sands contain the lucrative product of petroleum, however, the byproduct of the extraction, methane, is less profitable for the state. Due to the low market value of methane, the current existing capture and transport technologies are not economically feasible. This results in a substantial amount of flaring to eliminate methane, where it is ignited at the point of extraction, resulting in a substantial amount of CO₂ waste dispersed into the atmosphere. Flaring is an unfortunate practice, since the energy released is not captured and utilized. Over time, the issues connected to petroleum production and the associated methane flaring are likely to get worse - prices for petroleum products continue to follow an ascending trend while prices for the inevitable byproduct of methane follow a descending trend. Transforming methane into more practical products (e.g. propane) is an essential process that needs to be addressed.

Introduction

In modern synthesis, the modification of organic substrates (i.e. the chemical species of interest) is one of the most desired reactions by organometallic chemists. Advancements in this field are still required to deliberately access a particular carbon-hydrogen (C-H) bond. The benefits of such a bond activation include massive, energy-scale applications (e.g. methane transformation) to pharmaceutical and laboratory-scale applications. As explained in the background, petroleum is an important resource for Wyoming, but it does create an expendable byproduct. C-H bond heterolytic activation and functionalization could potentially play a key role in influencing the issues surrounding methane and its conversion into a more lucrative product.

The work I assisted with in the Hulley group was based on designing pincer ligand platforms for use in modular C–H activation systems. Pincer ligands utilize two or more strong coordinate bond donors to force coordination of a weak donor. The inflexibility of the pincer-metal interaction confers high thermal stability to the resulting complexes. To provide a scope of how important chelation is: it is used to provide nutritional supplements, in chelation therapy to remove toxic metals from the body, as contrast agents in MRI scanning, in chemical water treatment to assist in the removal of metals, and in fertilizers. Pincer ligands are widely used in fundamental studies and used in our lab to investigate the control of electrophilicity in transition metal frustrated Lewis pairs.

It is anticipated that these ligand platforms will allow for control of proton generation and movement as it pertains to C-H activation through group transfer reactions. Furthermore, it is expected that a systematic means will be developed to control heterolytic activation, where the electrons are unequally shared by atoms, and functionalization, where the hydrocarbon is chemically converted into more useful products, of C–H bonds. For part of this research, bifunctional systems of novel dibenzofuran-based pincer ligands, (for cleaving the C–H bond across two functional groups) were employed. Eventually these systems will aid in the study of C–H activation by using intramolecular forces, where the atoms are held together within a molecule and/or intermolecular forces that exist between molecules.

One major goal of this research is to understand the polarizing effects that transition metals impart upon the C–H bonds of hydrocarbon substrates. The pK_a values of hydrocarbon bonds are ordinarily extremely high, but when a transition metal is coordinated (such as rhodium) the acidity of the C-H bond increases substantially. This induced polarization of a coordinated C-H bond is

fundamentally important to understand how to design the next-generation of electrophilic activation systems.

The second goal of this research corresponds with the first goal. In order to understand the polarizing effects C-H bonds coordinated to transitional metals, the molecular systems were specifically designed to activate heterolytic aryl and alkyl C-H bonds via the coupling of Bronsted bases with electrophilic metal centers (metals with vacant orbitals). For intramolecular systems, a Bronsted base will be positioned in the secondary coordination sphere of an electrophilic transition metal. For intermolecular systems, combinations of electrophilic complexes and sterically encumbered bases will be utilized.

The third goal of the research is to study the profound flexibility that can be provided to the molecular system design by splitting the role of C-H bond cleavage across two orthogonal moieties. For example, by positioning a pendant, in which a side group is attached to a backbone chain, relative to the bound substrate the pendant can assist in targeted kinetic deprotonation. This strategical positioning of different pendant bases will allow for probing of many aspects of heterolytic activation in molecular systems.

Results/Discussion

With research, much of an undergraduate's experience begins with getting accustomed to the lab and learning new techniques. My first couple of months of research included practicing the synthesis of 4,6-dilithiodibenzofuran-1.5(TMEDA), honing new skills and gaining confidence working in the glovebox. Dibenzofuran was used as the backbone because of the accessibility of the dilithiated complex, a known compound that is readily obtained from deprotonation of dibenzofuran.¹

The reaction of dibenzofuran with 3 equivalents of *sec*-BuLi and TMEDA in hexane followed by storage at room temperature for 24 hours resulted in the desired precipitation. However, isolation of the light brown crystals proved difficult and eventually further reactions with this compound were carried out in solution. This compound is extremely air sensitive, thus the reaction was carried out in a glovebox. The ^1H NMR spectra of 4,6-dilithiodibenzofuran was in agreement with the dilithiation of the dibenzofuran backbone. Treatment of the dilithiated compound with bis(*N,N*-diisopropylamino)chlorophosphine resulted in the formation of the target dibenzofuran derivative (Figure 1, where $\text{R} = \text{N}^i\text{Pr}_2$). The yield of the salt was quite low and in order for crystals to form, it had to be stored for a couple of days in the freezer in solution. Once crystals formed, the X-ray diffractometer was used to determine the structure of the compound (Figure 2).

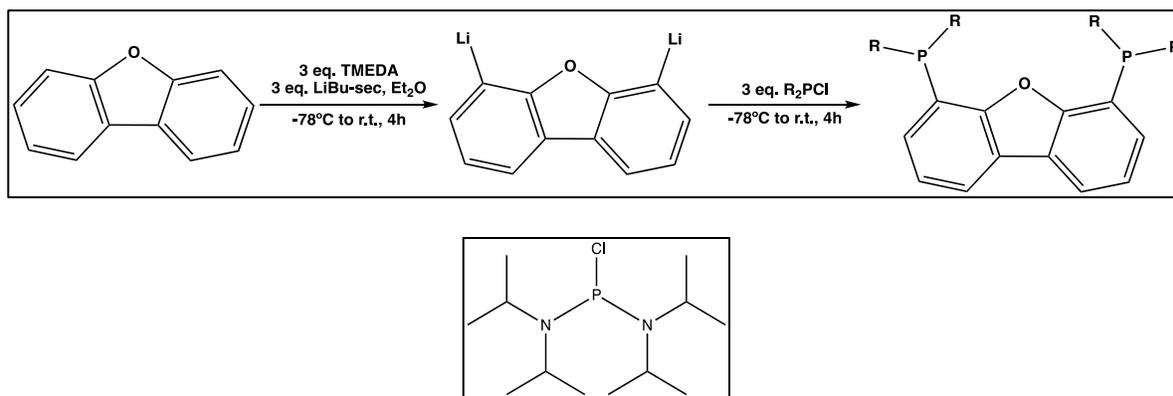


Figure 1: (Top) Synthesis of a POP-pincer ligand family using a dibenzofuran framework and (bottom) the bis(*N,N*-diisopropylamino)chlorophosphine used in the current work

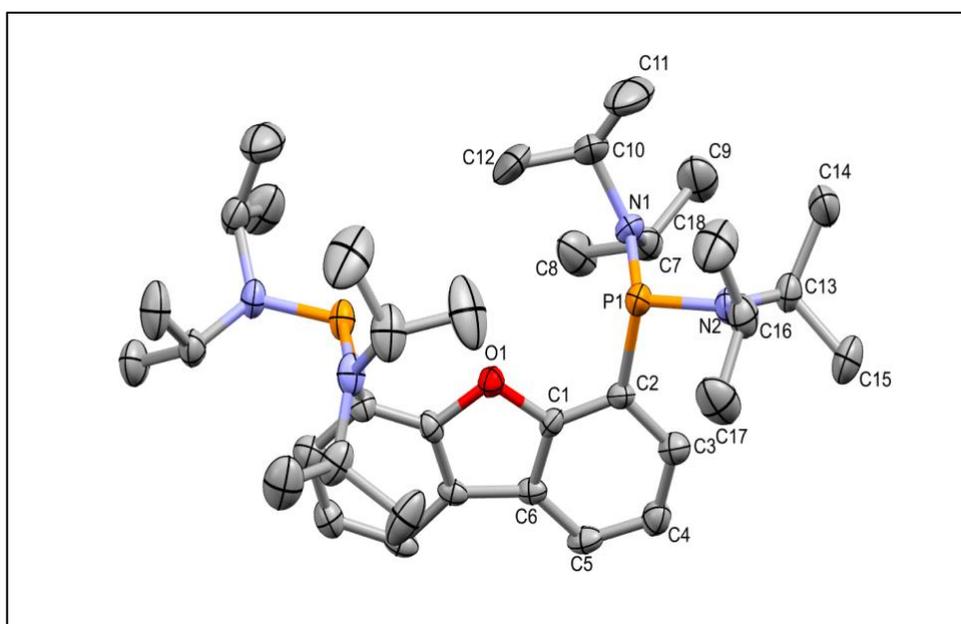


Figure 2: (Top) Crystals of of $\text{dbf}(\text{P}(\text{N}^i\text{Pr})_2)_2$ and (bottom) its solid-state structure from X-ray Crystallography

A compound containing a rhodium transition metal was added to the amino-phosphine ligand. This coordination of rhodium to the polydentate ligand was too slow to react due to the steric encumbrances resulting from the size of the amino-phosphine groups. The phosphine-carbon

bond is also highly reactive, so other unintended reactions occurred. After heating this compound in an oil bath for a couple of days, the reaction was abandoned.

Following the isolation of $\text{dbf}(\text{P}(\text{N}^i\text{Pr})_2)_2$, hydrochloric acid (in diethyl ether solution) was added to protonate off the amido groups (Figure 3). The resulting tetrachloride ($\text{dbf}(\text{PCl}_2)_2$) was stripped of solvent and then washed with pentane. The ^1H and ^{31}P NMR spectra were in consistent with that expected for the target compound.

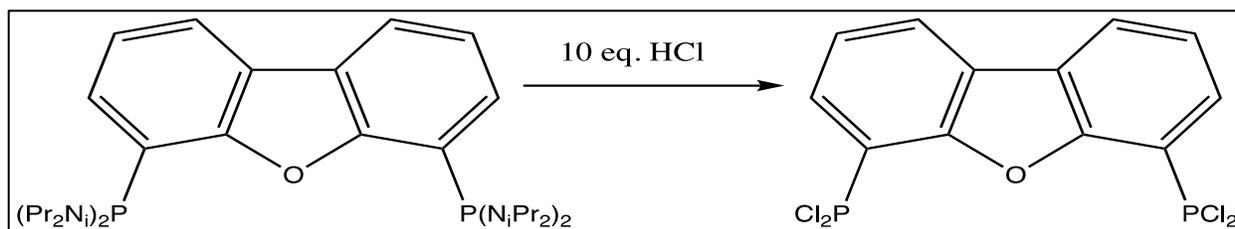


Figure 3: Synthesis of the $\text{dbf}(\text{PCl}_2)_2$ ligand precursor.

Future Work

Short term work for this lab includes the production of more 4,6-Bis(dichlorophosphine)dibenzofuran for further complexation and increasing the yield of this product. One such future complexation includes utilizing arylphosphite-based systems (Figure 4) which are particularly attractive, due to their weak donor properties.

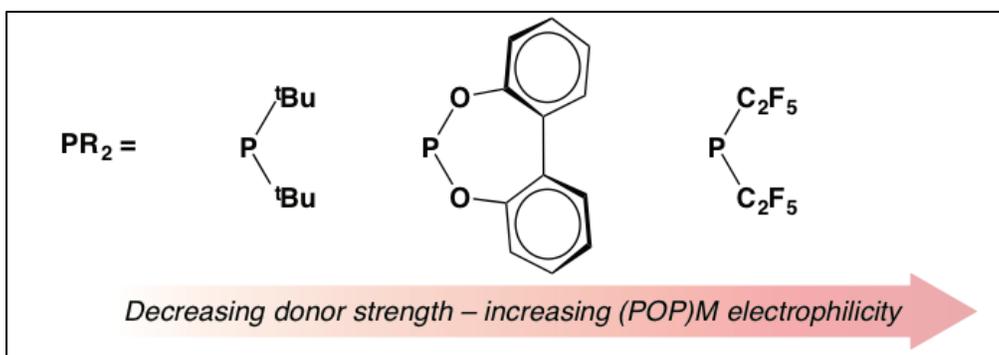


Figure 4: Arylphosphite-based systems of a wide variety of P-donor strengths and steric encumbrances.

Long term goals are to develop a systematic means to control heterolytic activation and functionalization of C–H bonds. To that end, these ligand precursors will be employed to develop a family of complexes that vary in their ability to facilitate C–H bond activation.

Conclusion

Energy waste associated with flaring of methane is a problem worth addressing. By developing a systematic means to control heterolytic activation and functionalization of carbon-hydrogen (C-H) bonds, methane could be converted into a more lucrative byproduct. This substantial energy-scale application could benefit Wyoming's and the nation's economy to capture and retain methane. Using heterolytic C-H cleavage, selective hydrocarbon functionalization (where the hydrocarbon is chemically converted into more useful products) will be readily tunable. Future work will include complexation and characterization of the activated carbon-hydrogen bond.

Experimental

All operations were performed at an altitude of 7220 ft (ambient pressure 0.77 atm) under air-free conditions (e.g. vacuum-line or glovebox). Unless otherwise noted, solvents used in syntheses were purified by passing through the neutral alumina columns of an Innovative Technology, Inc., Pure Solv™ purification system, followed by degassing and storage in a glovebox over activated 3Å molecular sieves. Syntheses reported to occur at 'ambient temperature' should be taken as 22±3 °C. All starting materials were purchased from Strem or Sigma-Aldrich and used as received.

NMR Spectroscopy. All operations utilized re-sealable NMR tubes (J-Young). Temperatures quoted for NMR experiments are based on calibrations and have an uncertainty of ± 0.5 °C. NMR spectra were obtained on a BRUKER 400 spectrometer. NMR chemical shifts are reported relative to deuterated solvent signals (for ^{13}C NMR) or residual protio solvent signals (for ^1H NMR). Deuterated NMR solvents were purchased from Cambridge Isotopes Laboratories, dried over 3Å molecular sieves under N_2 and then vacuum distilled.

Synthesis of 4,6-Dilithiodibenzofuran-1.5(tmeda)

Since air-sensitive compounds were used, the reaction was carried out under N_2 atmosphere using standard glovebox and Schlenk techniques. Our synthetic approach followed a procedure reported by an organometallics group at Texas A&M University. First, 500 mg of dibenzofuran was completely dissolved in a solution containing three equivalents of TMEDA (1.35 mL) and 2 mL of hexane. Three equivalents of sec-Butyllithium (6.4 mL) was added drop-wise to the suspension at room temperature. After the solution was allowed to stir for 24 hours at room temperature, it was cooled to -30°C for 3 hours. A light brown compound precipitated out of the dark brown solution; this suspension was used for further reactions. The ^1H NMR spectra were consistent with the previously reported syntheses.

Synthesis of Bis(N,N-diisopropylamino)chlorophosphine

Under N_2 conditions, a 5 L three neck round-bottom flask was equipped with a Friedrich's condenser, a ground glass stirrer bearing, and a silicon rubber septum. Roughly 2 L of anhydrous diisopropylamine was added to the flask and diluted by the addition of 2 L of anhydrous acetonitrile. An ice bath was placed under the flask and the solution was mixed vigorously using

a mechanical stirrer for 30 minutes. In a dry 2L flask, 313 g of phosphorus trichloride and 1 L of anhydrous acetonitrile was added. This solution was then added slowly by cannulation to the solution of diisopropylamine solution being stirred. The ice bath was removed after the addition was complete and the reaction mixture was left to stir overnight. In order to remove diisopropylamine hydrochloride, the reaction was filtered and washed with anhydrous ether. The ether portions were combined, concentrated in vacuo, and the residue was recrystallized from hexane. The NMR spectra were consistent with previously published syntheses.

Synthesis of (iPr₂NP)₂dbf

Under N₂ conditions, 1.6 g of bis(N,N-diisopropylamino)chlorophosphine was dissolved in a mixture of 10 mL of ether and 5 mL of tetrahydrofuran (THF). Once dissolved this solution was transferred into the Schlenk flask containing 4,6-Dilithiodibenzofuran-1.5(tmeda). After the solution was allowed to stir for 24 hours at room temperature, it was cooled to -30° for another 24 hours. ¹H and ³¹P NMR spectra were recorded using the Bruker Avance III 400 MHz NMR (Figure 5).

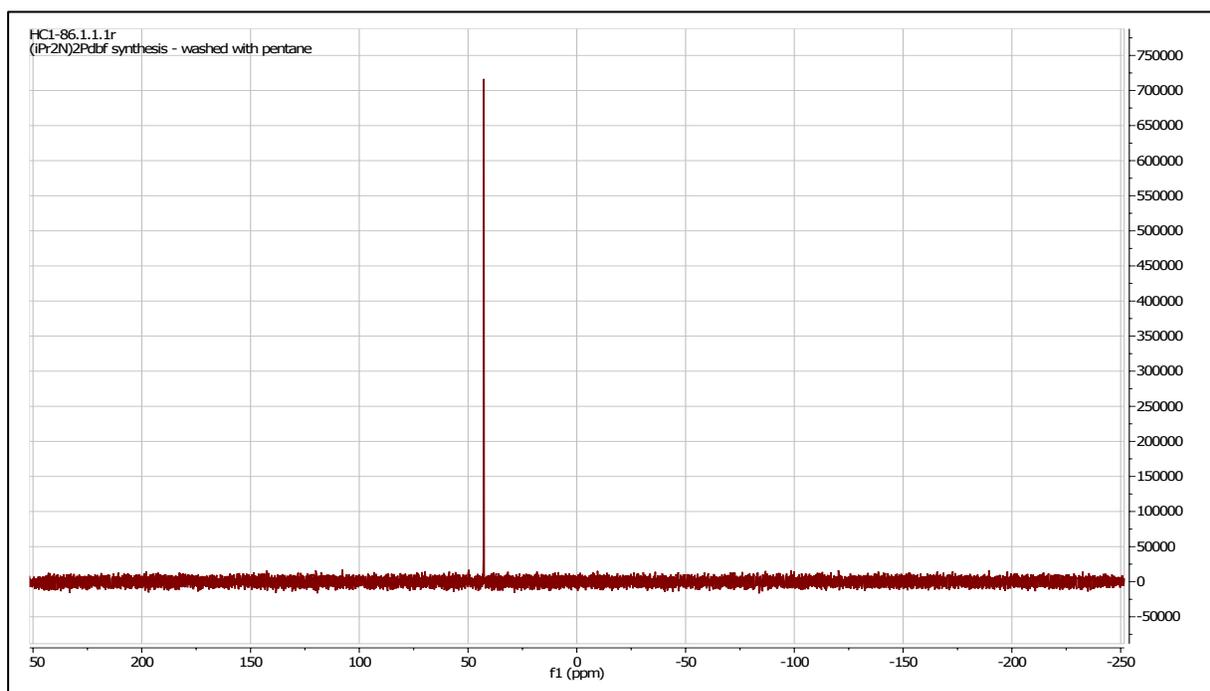
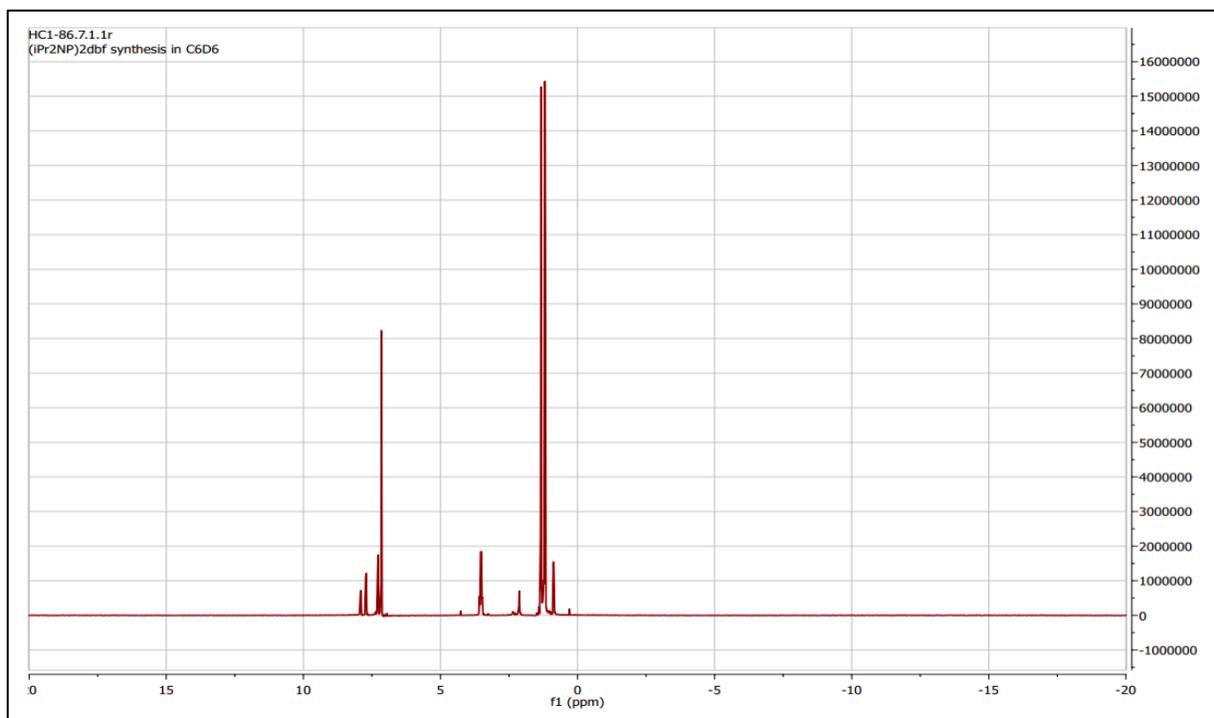


Figure 5: (Top) ¹H NMR spectrum and (bottom) singlet peak of ³¹P NMR spectrum for the amino-phosphine ligand.

Attempted Synthesis of dbf-(P(NⁱPr₂)₂)₂RhCl

Since air-sensitive compounds were used, the reaction was carried out under N₂ atmosphere using standard glovebox techniques. In two separate vials, 19.9 mg of [(COE)₂RhCl]₂ and two equivalents (22mg) of (iPr₂NP)₂dbf was distributed. Approximately 10 mL of fluorobenzene (PhF) was added between the two vials. Using a pipette, the [(COE)₂RhCl]₂ was moved into the solution of (iPr₂NP)₂dbf and mixed. A ³¹P NMR spectrum was recorded using the Bruker Avance III 400 MHz NMR. The data was not congruent with what was expected, so more PhF was added to the NMR tube. The tube was left in a 60°C oil-bath overnight and a black precipitate formed. Another NMR spectrum was acquired and once again the NMR tube was left to sit overnight in an oil bath. NMR spectra revealed a mixture of products and this reaction was not pursued further.

Synthesis of 4,6-Bis(dichlorophosphine)dibenzofuran

Under N₂ conditions, 500 mg of (iPr₂NP)₂dbf was measured into a Schlenk flask and 30 mL of ether was added. The solution was removed from the glovebox and moved to the line to sit in an ice bath. Ten equivalents (~ 4 g) of hydrochloric acid (HCl) was slowly added to the solution. The reaction was allowed to stir for 30 minutes and was then stripped. The salt was washed with 20 mL of toluene and the precipitate was filtered off. The filtrate was concentrated in vacuo yielding a white powder. ¹H and ³¹P NMR spectra are shown in Figure 6.

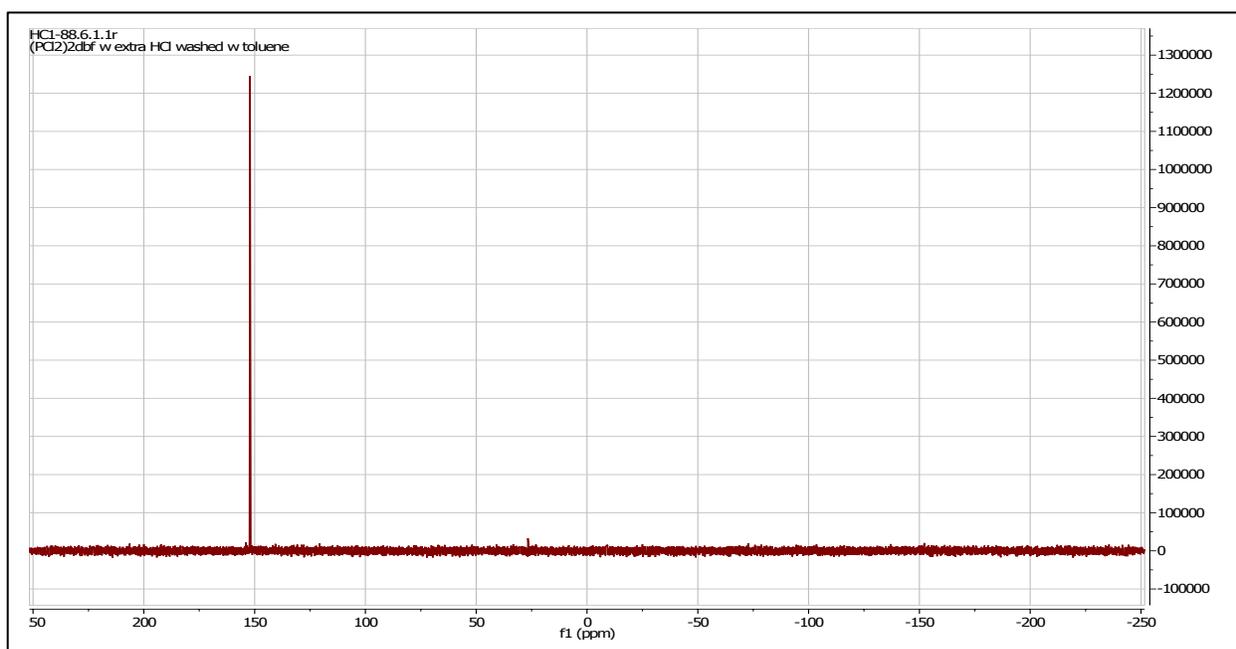
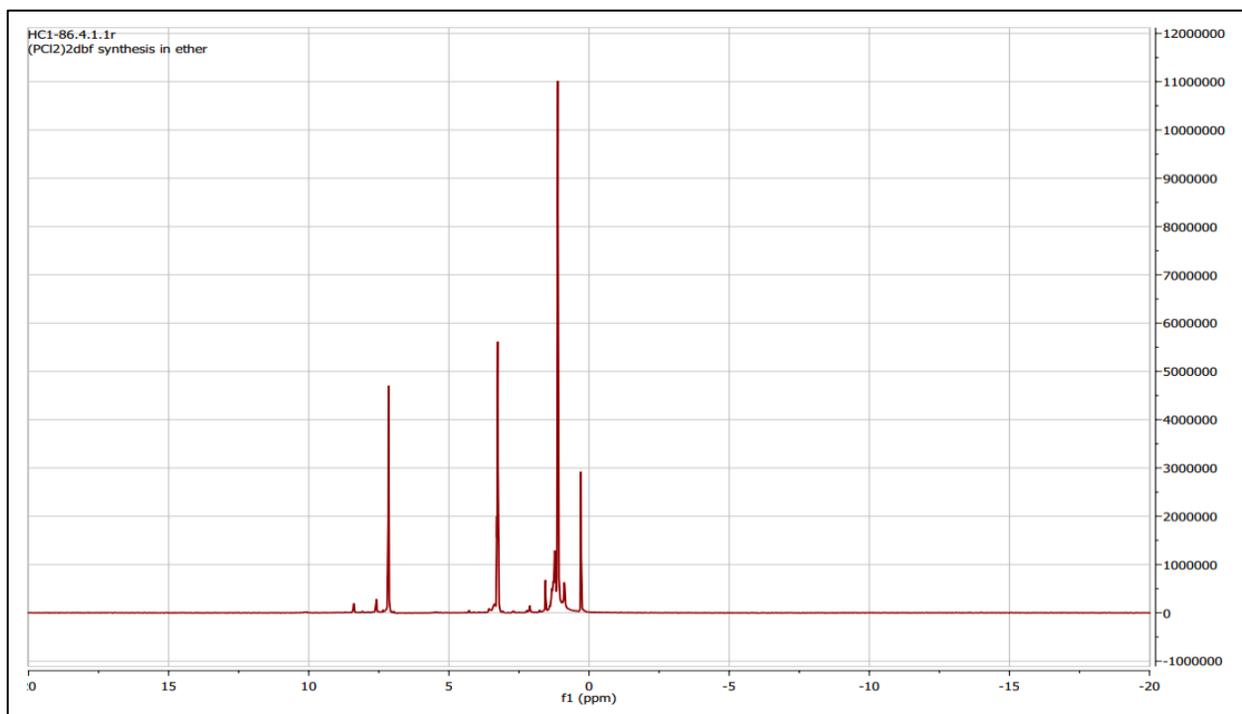


Figure 6: (Top) ¹H NMR spectrum and (bottom) Downfield shift of singlet peak of ³¹P NMR spectrum for 4,6-Bis(dichlorophosphine)dibenzofuran (dbf(PCl₂)₂).

Works Cited

1. Wang, Huadong, and François P. Gabbaï. "Synthesis, Structure, and Cyclic Voltammetry of 4,6-Bis(Dimesitylboryl)Dibenzofuran: Isolation of 4,6-Dilithiobenzofuran and 4,5-Dilithio-9,9-Dimethylxanthene as Tmeda Adducts." *Organometallics*, vol. 24, no. 12, 26 Apr. 2005, pp. 2898–2902., doi:10.1021/om050165m.
2. Dellinger, D. J., Sheehan, D. M., Christensen, N. K., Lindberg, J. G., & Caruthers, M. H. (2003). Solid-Phase Chemical Synthesis of Phosphonoacetate and Thiophosphonoacetate Oligodeoxynucleotides. *Journal of the American Chemical Society*, 125(4), 940–950. <https://doi.org/10.1021/ja027983f>
3. Noyori, R. & Hashiguchi, S. Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes. *Acc. Chem. Res.* 30, 97–102 (1997).
4. Dub, P. A. & Gordon, J. C. The mechanism of enantioselective ketone reduction with Noyori and Noyori–Ikariya bifunctional catalysts. *Dalt. Trans.* 45, 6756–6781 (2016).
5. Goldberg, J. M. *et al.* Detection of an Iridium-Dihydrogen Complex: A Proposed Intermediate in Ionic Hydrogenation. *J. Am. Chem. Soc.* 139, (2017).
6. Dubois, D. L. Development of Molecular Electrocatalysts for Energy Storage. *Inorg. Chem.* 53, 3935–3960 (2014).
7. Rakowski DuBois, M. & DuBois, D. L. Development of Molecular Electrocatalysts for CO₂ Reduction and H₂ Production/Oxidation. *Acc. Chem. Res.* 42, 1974–1982 (2009).
8. Liu, T. *et al.* Synthesis, characterization, and reactivity of Fe complexes containing cyclic diazadiphosphine ligands: The role of the pendant base in heterolytic cleavage of H₂. *J. Am. Chem. Soc.* 134, 6257–6272 (2012).
9. Raugei, S. *et al.* The Role of Pendant Amines in the Breaking and Forming of Molecular Hydrogen Catalyzed by Nickel Complexes. *Chem. - A Eur. J.* 18, 6493–6506 (2012).
10. Liu, T., DuBois, D. L. & Bullock, R. M. An iron complex with pendent amines as a molecular electrocatalyst for oxidation of hydrogen. *Nat. Chem.* 5, 228–233 (2013).
11. Hulley, E. B., Welch, K. D., Appel, A. M., DuBois, D. L. & Bullock, R. M. Rapid, Reversible Heterolytic Cleavage of Bound H₂. *J. Am. Chem. Soc.* 135, 11736–11739 (2013).
12. Bullock, R. M., Appel, A. M. & Helm, M. L. Production of hydrogen by electrocatalysis: making the H–H bond by combining protons and hydrides. *Chem. Commun.* 50, 3125–3143 (2014).
13. Jeletic, M. S. *et al.* A cobalt hydride catalyst for the hydrogenation of CO₂: Pathways for catalysis and deactivation. *ACS Catal.* 4, (2014).
14. Jeletic, M. S. *et al.* Understanding the Relationship between Kinetics and Thermodynamics in CO₂ Hydrogenation Catalysis. *ACS Catal.* 7, (2017).