Title: The Aryl Cyclopropanation of Para Chloro Styrene

By

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CHM 240 (Research in Chemistry)

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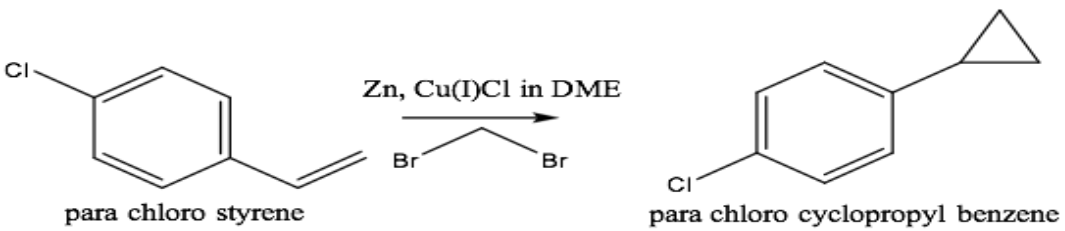
Abstract: I have been exploring the cyclopropanation of chlorinated styrene as a way of extending the metabolism of potential drug candidates. I have been attacking the problem at hand from two directions; both of which being reactions I learned about in Organic Chemistry here at MCC, the Simmons-Smith Reaction, and a Grignard Reaction. In parallel, I have also been working on the integration of electrochemistry into the research lab. We first explored the cyclopropanation of styrene as an indication of the plausibility of the proposed research. Moreover, in the first part of my research, I am employing the principles of the Simmons-Smith Reaction, in which I activate zinc via sonication and reaction with Copper(I)Chloride[1]. The procedure is as followed, a 3-neck 50 mL round bottom flask is charged with Zinc and Copper(I) Chloride, followed by being capped with a septum, reflux condenser and nitrogen inlet tube. The reaction vessel is dried before and after the addition of Zinc and Copper Chloride via vacuum. Before the addition of DME, the reaction vessel is flushed with nitrogen, DME was added via syringe, sonicator is turned on at RT for 45 mins before the addition of Dibromo methane. The reaction vessel is sonicated at RT for 2 hours before para chloro styrene was added via syringe. Sonication continued for 3-4 hours, micro TLC's are done on an hourly basis to monitor the tranversion of starting material to product. Additionally, the second route I am taking to cyclopropanation station is via Grignard reaction. Wherein again I have to reproduce the results from the literature[2] and then test it on simple styrene as an indication of plausibility.

Introduction: Phase 1 metabolism consists of reactions in the liver that convert the parent drug to a more water soluble metabolite via the insertion of a polar functional group. Cytochrome p450 is an enzyme in your liver that is responsible for most drug metabolism. Cyp groups find unusual chemicals and add oxygen to them. Cytochrome p450 is considered to be our first line of defense in the detoxification of harmful chemicals like carcinogens or pollutants. However, cytochrome p450 is an example of an innate catch 22. By sticking oxygen onto unusual chemicals, you're generating reactive oxygen species (ROS). ROS are highly unstable molecules, and they are under extensive research as a means of tumor start-ups. Moreover, the goal of my research is to find a one step synthesis for producing para chloro cyclopropyl benzene.



para chloro styrene

para chloro cyclopropyl benzene

DME= dimethoxy ethane

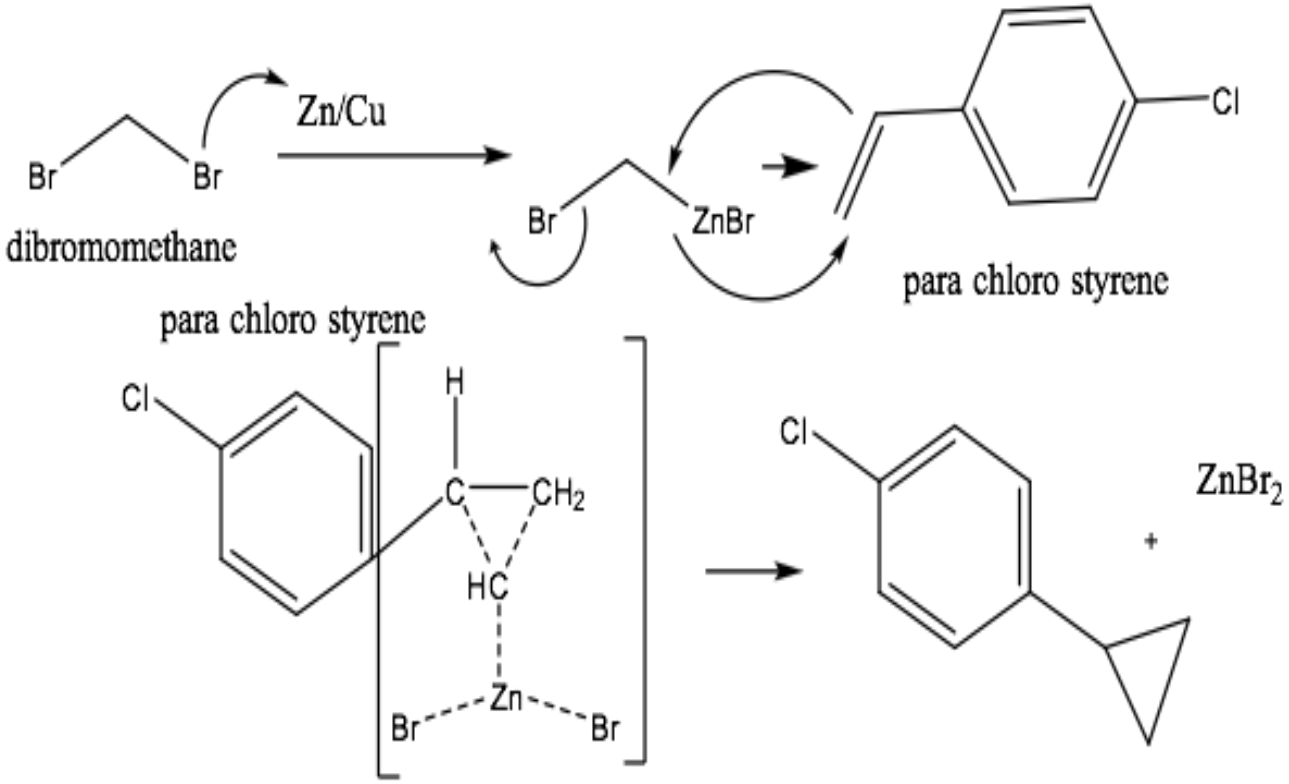
Experimental Section:

Instrumentation: NMR spectra were recorded using NMRReady 60 Analysis Corporation. $CDCL_3$ was used as a reference/blank and also as a solvent for all compounds. Gas Chromatography spectra were recorded using Hewlett Packard Series 2 5890.

Materials: All materials used for preparation were reagent grade and were analyzed for purity with Gas Chromatography and NMR.

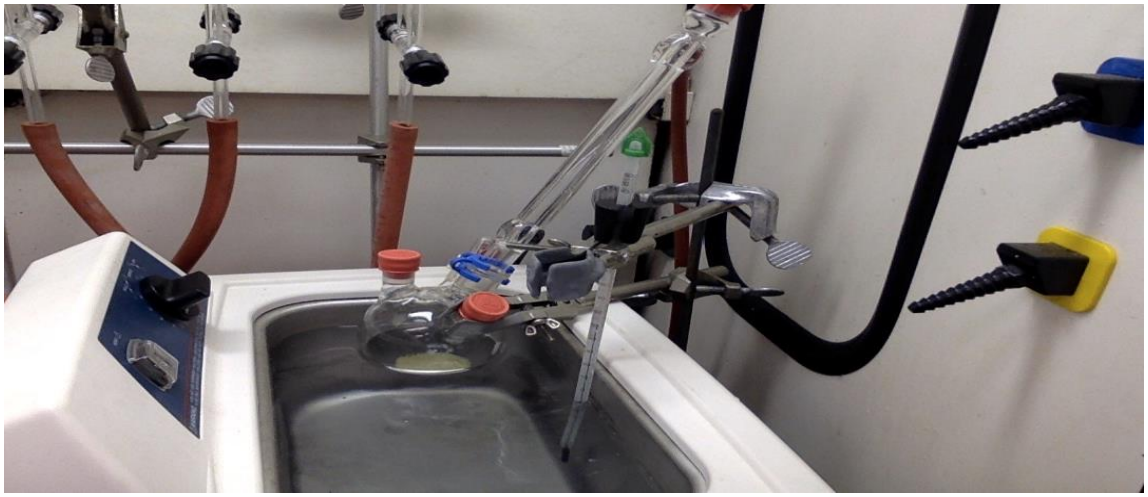
*DME was dried over molecular sieves and tested on GC for purity. Copper(I) Chloride was prepared fresh. T-Butyl Chloride was synthesized, distilled off and tested on GC for purity.

Cyclopropanation via Simmons-Smith Mechanism:



Simmons-Smith Procedure:

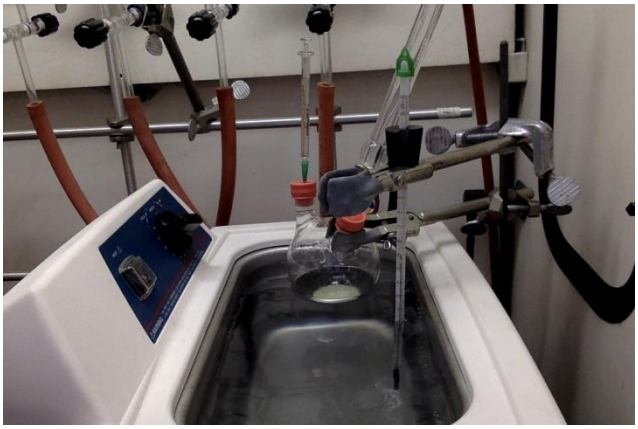
- A clean, oven and vacuum dried 4-neck round bottom flask is charged with Zinc and Cu(I)Cl, equipped with a condenser and a nitrogen inlet tube and then capped with a septum
- Reaction vessel is flushed with nitrogen before the addition of DME via syringe.
- Sonicated at RT for 45 minutes



- Para Chloro Styrene is added via syringe and sonicated at 50*C
- Dibromo methane is added via syringe in four increments every 10 mins at 50*C while sonicating for 2-3 hours.

1st addition of Dibromo Methane

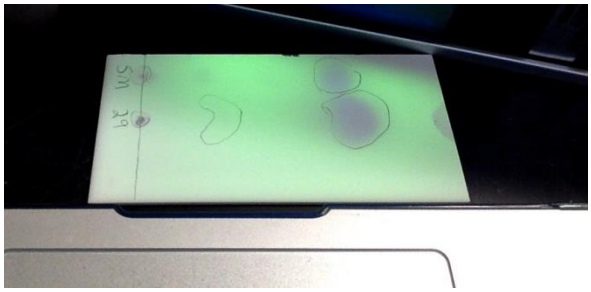
2nd addition of Dibromo Methane



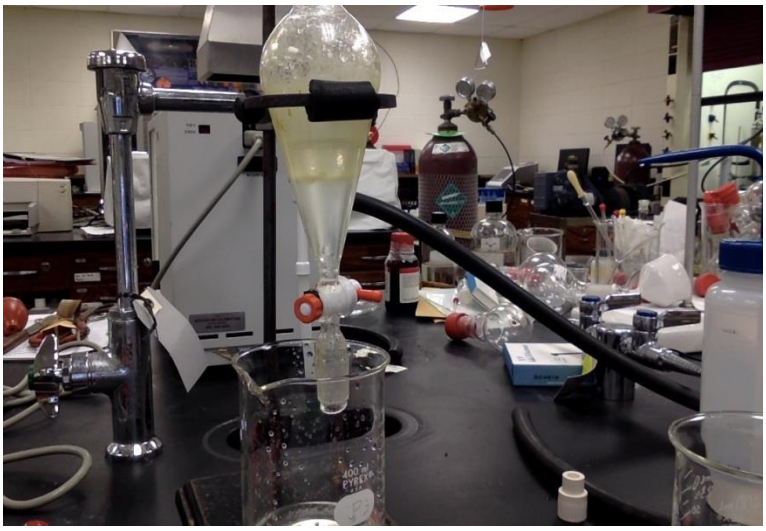
3rd addition of Dibromo Methane

4th addition of Dibromo Methane

- **Dibromo Methane is added in increments in hope of avoiding high concentration of the zinc-carbenoid intermediate.**



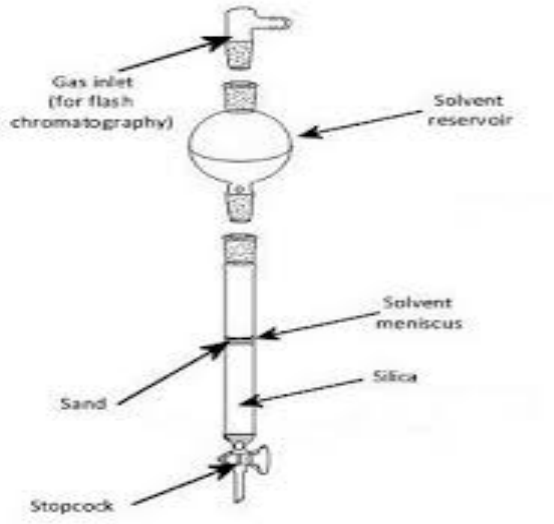
- Micro TLC's are done on an hourly basis to monitor reaction progress
- TLC is done to establish solvent system for Column or Prep TLC



- The reaction is diluted with deionized water and hexane

- Layers were separated via Separatory Funnel
- Aqueous layer was washed with 3x 15mL Hexane
- Combined organic layer was dried over $MgSO_4$

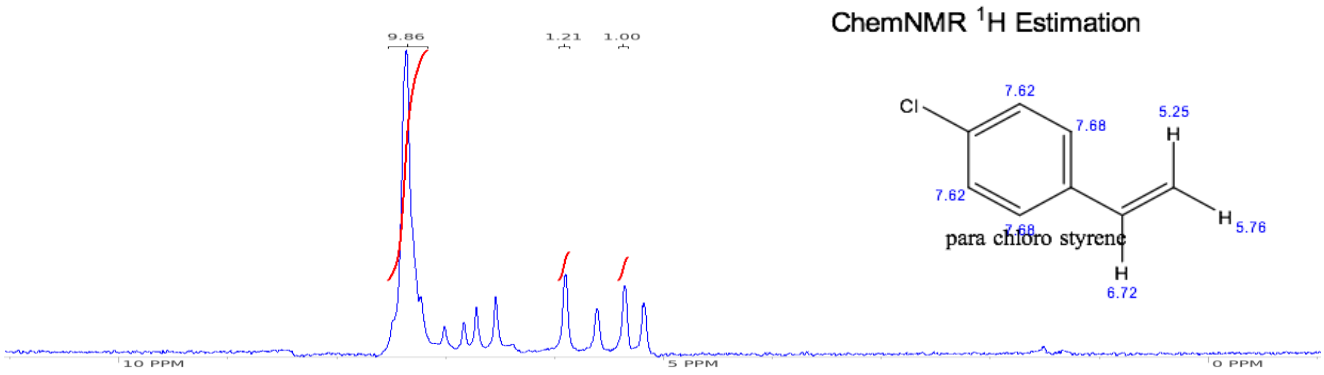
- Solvent was removed via RotoVap
- Round bottom flask is vacuum dried to make sure solvent doesn't interrupt NMR
- Collect NMR
- Depending on results, Column Chromatography or prep TLC are the next step.



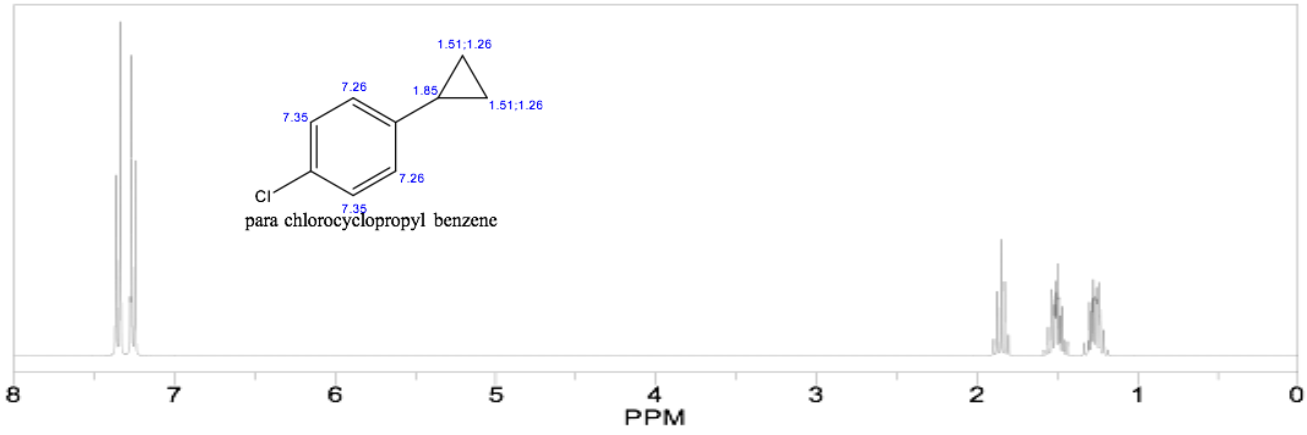
Results and discussion:

- After successful cyclopropanation of simple styrene, cyclopropanation of para chloro styrene under similar conditions were attempted and trial after trial, I am getting peaks where I am supposed to on the NMR from 1-2 ppm, however an unknown multiplet recurrently appears at 3.5 ppm.

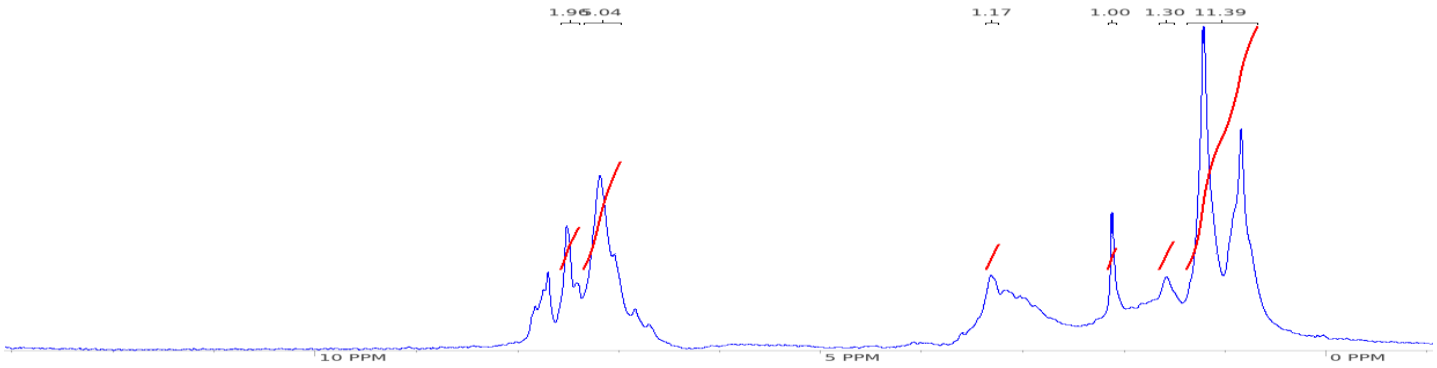
NMR of Starting Material



NMR of DesiredProduct



Trial # 23 Fractions 18-23

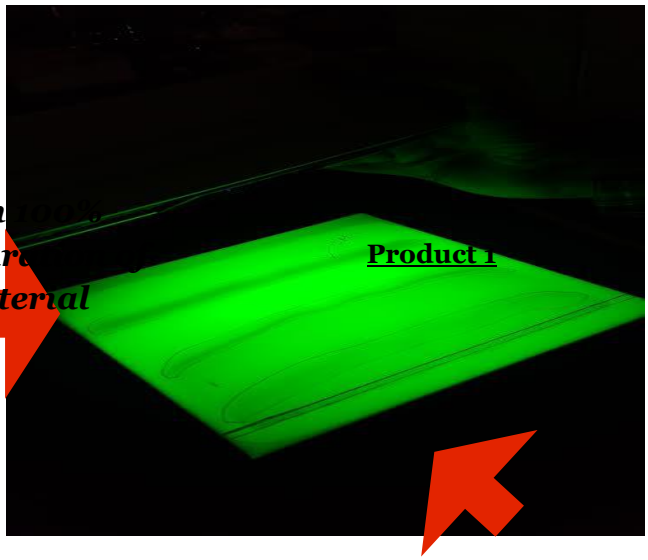


- **Performed Column Chromatography with a 95:5 Hexane to Ethyl Acetate solvent mixture and collected fractions 18-23.**

Trial # 28

TLC after work up with 100%
Heptane shows good separ
product from starting material

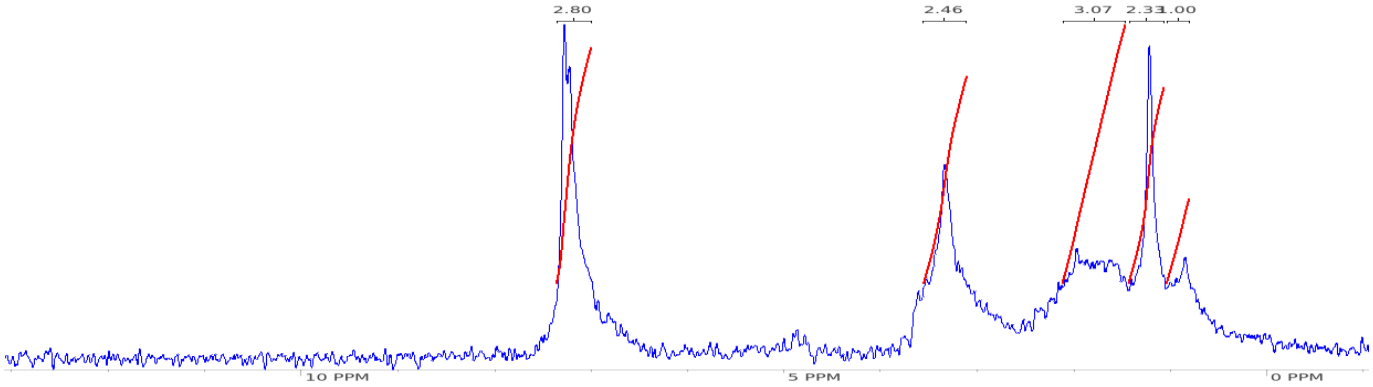
Product 2



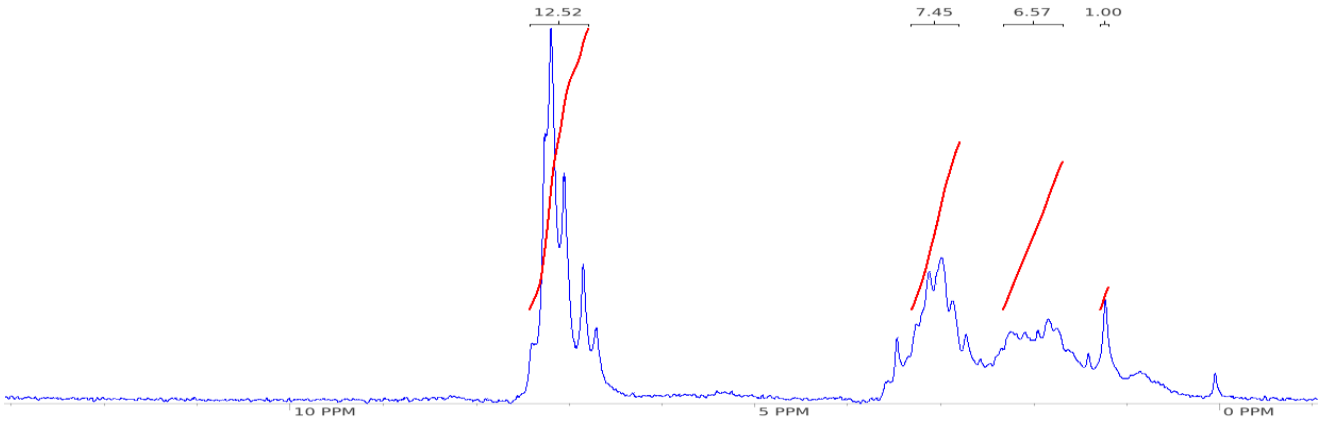
Product 1

- **Performed Prep TLC with 100% heptane then cut out the two products and collected NMR.**

NMR of Product 1



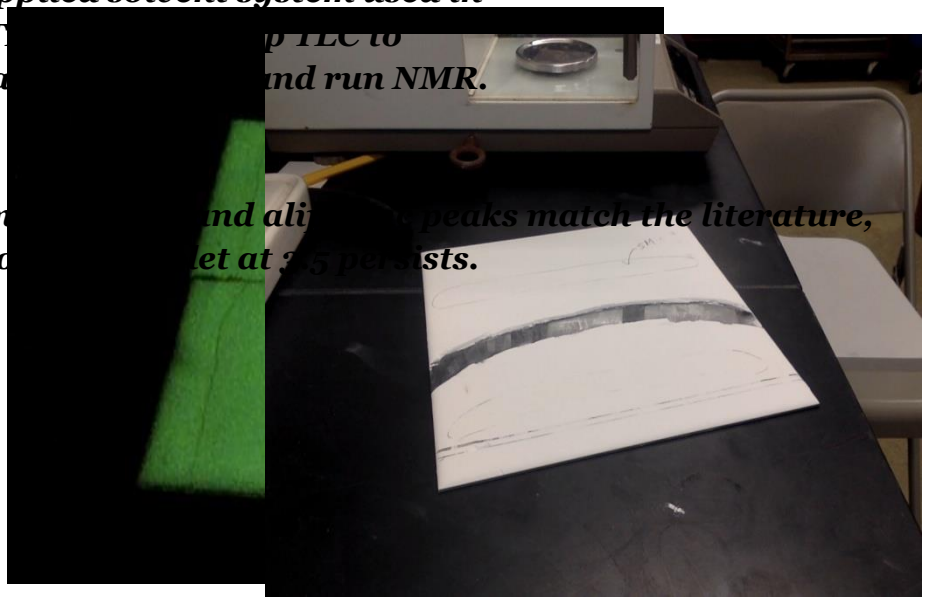
NMR of Product 2



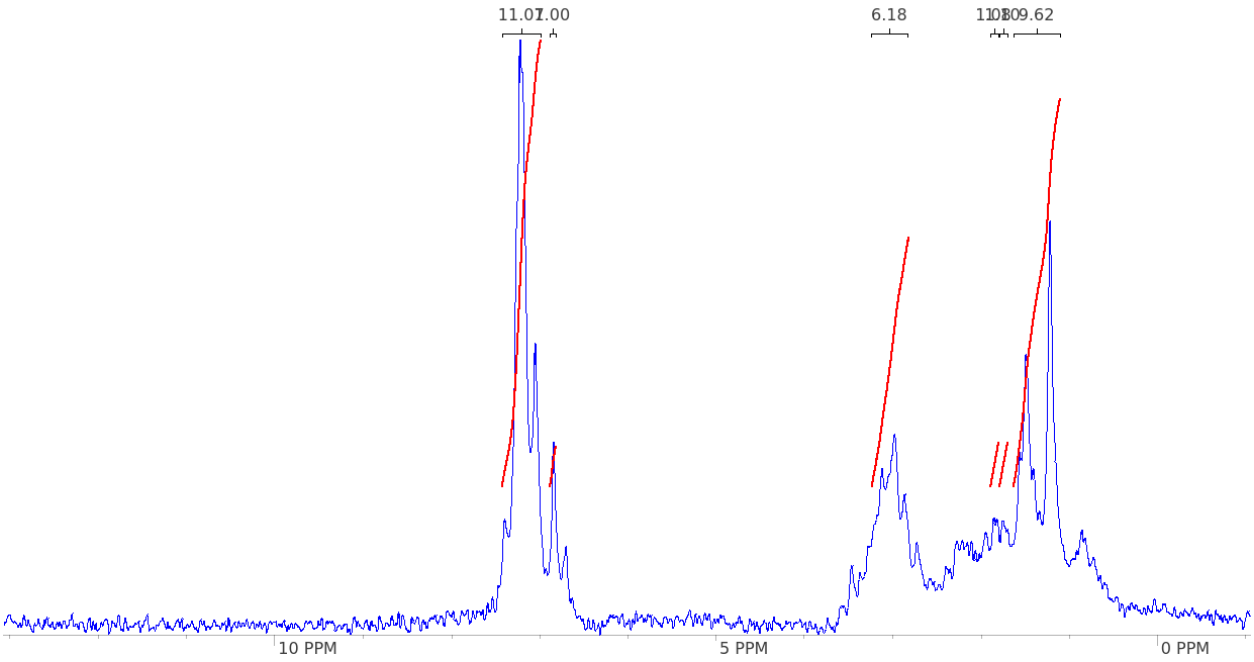
- **Aromatic peaks around 7, and aliphatic proton peaks from 1-2 match literature value, however the unknown multiplet around 3.5 persists.**

Trial # 28 NMR

- ***Applied solvent system used in the T… p TLC to extra… nd run NMR.***



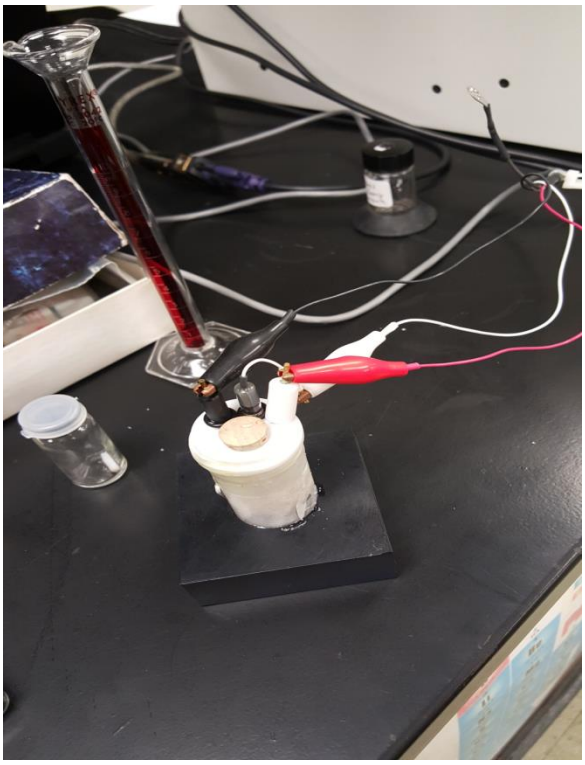
- ***Again, arom… nd ali… peaks match the literature, however unkno… et at … persists.***



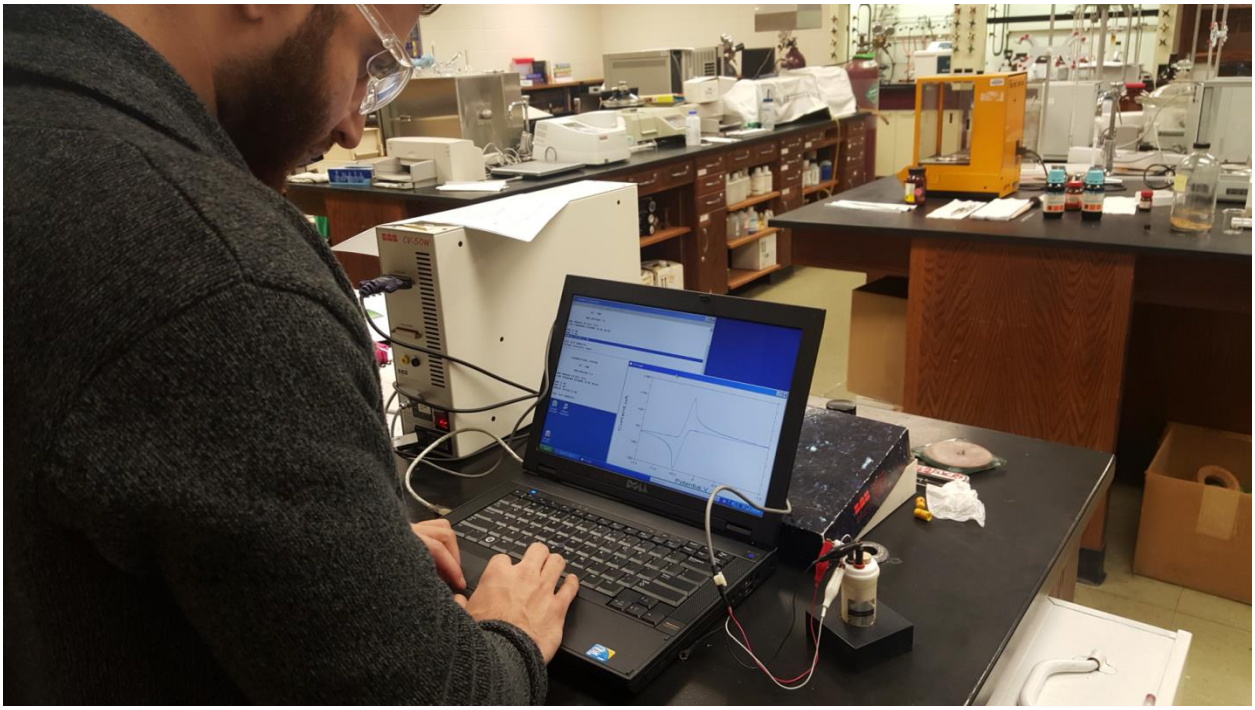
Conclusion:

- **When para chloro styrene was used for zinc cyclopropanation reactions, we repeatedly isolated a pure product, but cannot identify it without a mass spectrometer.**

Electrochemistry:



- **Studying redox property of known organometallic compound, ferrocene.**
- **From this instrument, you can learn 15 techniques, 1 of which is cyclic voltammetry.**
- **Cyclic Voltammetry can tell you whether or not a system is reversible.**



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- Dean David Edwards
- Dr Baraui
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References:

1. A.Charrette *Organic Reactions*, **2001,** *Vol 58*.
2. "Tandem Cyclopropanation with Dibromomethane under Grignard Conditions" (J. Org. Chem., 2008, 73 (19), pp 7543–7554)