Title: Asymmetric Michael Addition Catalyzed by a Chiral Polystyrene-Immobilized Pyrrolidine

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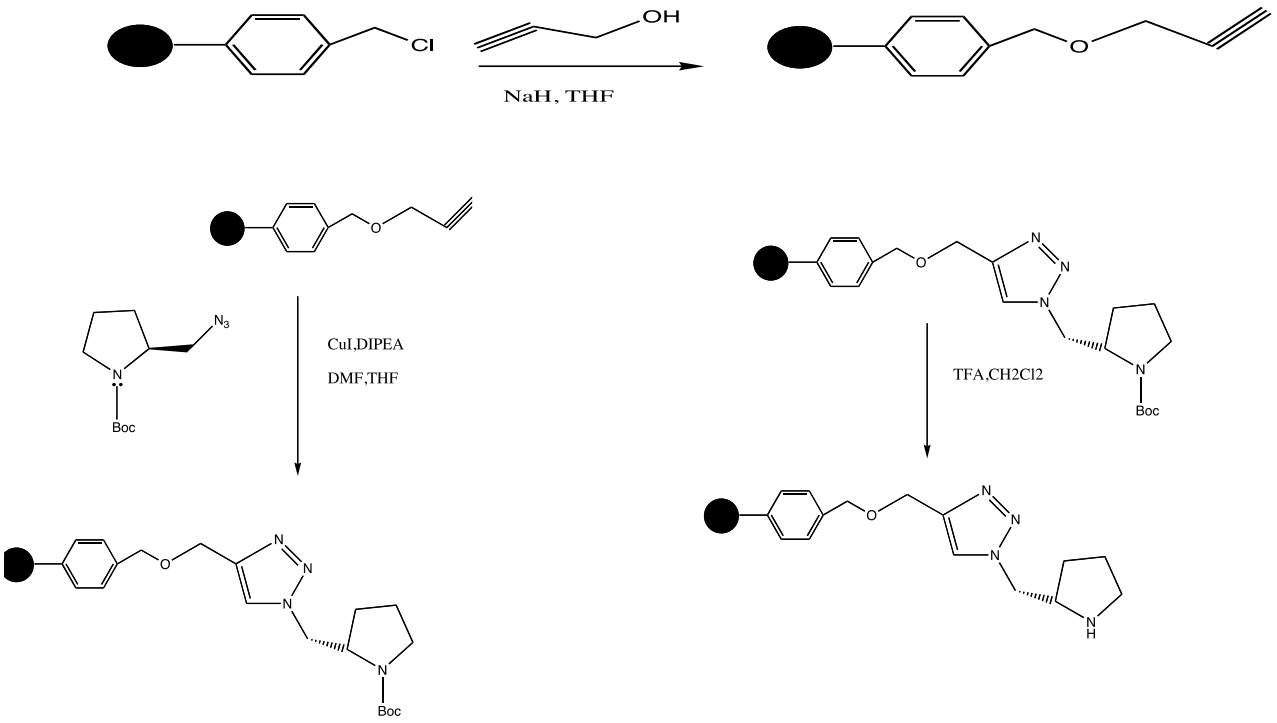
Abstract:

Polystyrene-immobilized pyrrolidine has been synthesized using Merrifield resin to attach propargyl alcohol via a S_{N2} mechanism. The Terminal alkyne then reacts with an organic azide through a click 1,3-cycloaddtion to produce a chiral organocatalyst. The organocatalyst is synthesized to give high yield (up to 99%), and stereoselectivity (up to 99% ee) of a Michael addition reaction between cyclohexanone and nitrostyrene.

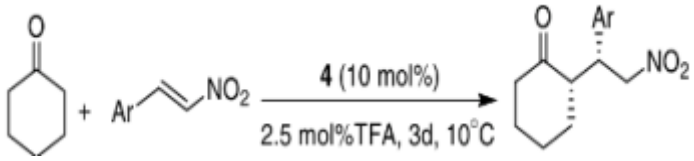
Introduction:

Asymmetric Michael addition reaction is carbon-carbon classic reaction that produces a racemic mixture. Previous works have focused on synthesizing chiral catalyst to produce enantiomer excess (ee). For example, Ishii, Sekiguchi, and kotsuki have created a chiral pyrrolidine from cyclic sulfamate.[5] Also, Alza, Cambeiro, Jmeno and Pericas have used 4-ethynylbenzyl alcohol to attach to Merrifield resin that is more stereoselective then propargyl alcohol.[1] These pyrrolidine catalysts work by forming an enamine intermediate to shield the si-face of the enamine double bond giving the syn-addition of the reaction.[5] Stereoselectivity is important in pharmaceutical fields because many drugs have to have certain configurations on their chiral centers otherwise the drug may be ineffective or dangerous to your body. For example, naproxen also known as Aleve has one chiral center in its structure. If this chiral center has an R configuration, then the drug will cause liver damage, In Contrast, if its chiral center has an S configuration then it will act as an anti-inflammatory.

Synthesis of the Catalyst:



Michael Addition Reaction:



Experimental:

Before the experiment could be performed, propargyl alcohol has to be distillated because the reagent was old and it was polymerizing with itself. A simple distillation was setup and the propargyl alcohol was collected around it boiling point of 115 degrees Celsius.

A 100mL round bottom flask containing 1.00 gram of Merrifield (1.6mmol loading per gram) resin is swelled with 10 mL of THF. Then 0.3ml of propargyl alcohol is added to the flask. A septum is attached to the round bottom flask and the mixture is purged with helium gas. Another 10 mL of THF is added to through the septum and mixture is purged again with helium gas. Lastly, Sodium hydride that is dispersed in 60% mineral oil is added to the flask. The reaction takes place under an inert atmospheric reflux conditions. The mixture is reflux for 24 hours. The crude mixture is then filtered by vacuum setup. The resin is then washed with plenty of THF, 5mL of water and then 5ml of THF. The resin is then stored in a desiccator over night to dry.

Next, 0.1026g of resin from the previous step is added to a 50 mL round bottom flask. After the resin is added to the round bottom flask 1.0 mL of THF and DMF is added with a syringe. The solution is purged with helium gas. After the mixture is purged, 56 μL of DIPEA is added with a micropipette. Finally, 50 μL of the organic azide is added to the flask followed by the addition of 0.030 grams of copper (I) Iodine to attach the azide to the terminal alkyne to form the 1,2,3-triazole cyclic ring by click 1,3-cycloaddition. A control reaction was prepared at the same time when performing this step. The control reaction consisted of all reagents in step two
of constructing the catalyst beside the resin. Both flasks were stirred for 24 hours.

The reaction mixture is collected and placed in a test tube. The resin was separated from the mixture using a centrifuge. The resin is then washed with THF and methylene chloride. The resin is centrifuged in between washes to separate the resin from the solvent. The resin was then transferred to a small beaker where it was combined with methylene chloride and 12 μL of TFA to hydrolysis the blocking group. The mixture is

stirred for one hour. Finally, the resin is washed again with methylene chloride under vacuum filtration and stored in the desiccator for 24 hours to give the desired catalyst.

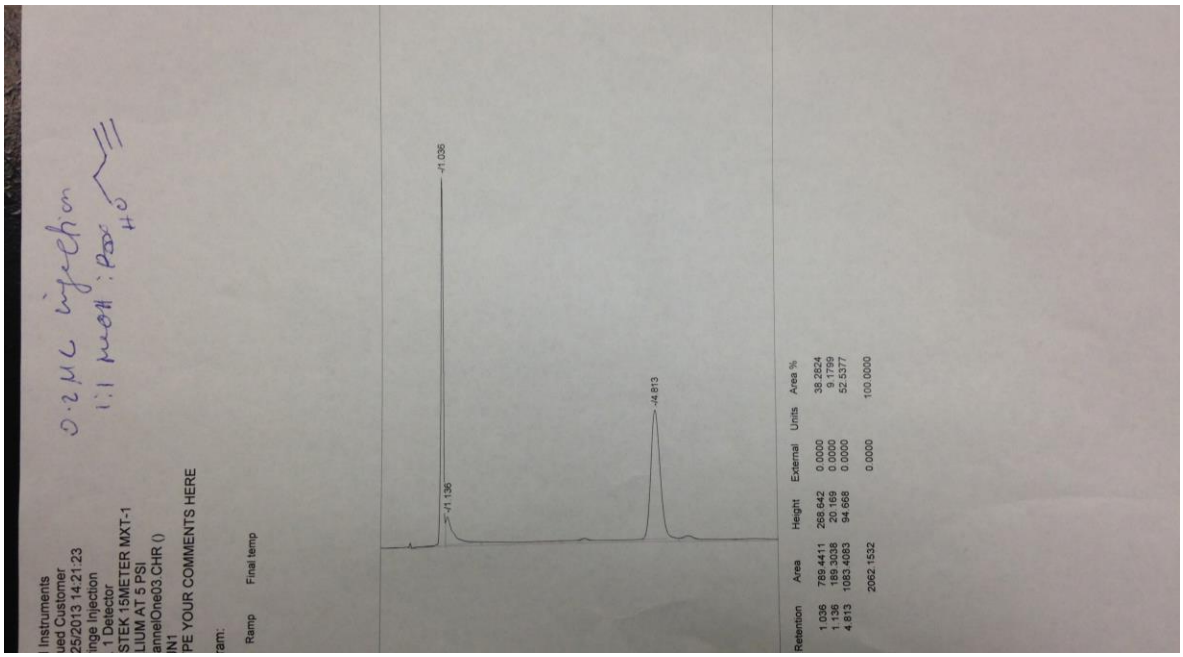
The Michael addition reaction was set up by adding 75mg of the organocatalyst to a 25 mL round bottom flask. A bulk solution of 21 μL of TFA in 46 mL of cyclohexanone is prepared. From this solution 2.5 mL is added to the flask and then followed by 75 mg of nitrostyrene. The flask is stirred for 72 hours at 10 degrees Celsius. The combined reaction mixture is then purified by column chromatography to get the Michael addition product. A second trial was performed to test the recyclability of the catalyst.

Results and Discussion:

The propargyl alcohol was characterized by gas and IR chromatography. The gas chromatography was setup by injecting the machine with a one to one ratio of methanol and the alcohol. The gas chromatography was injected with .2μL. The oven temp was 120 degrees Celsius and the detector and injection temperature was set at 180 degrees Celsius. Propargyl alcohol had a retention time of 4.8 minutes and methanol and a retention time of about 1.0 minute. The data also showed a third peak around the retention time of water. As a result another injection was performed where the concentration of water was increased. There is now a long sharp peak at the same retention time indicating it was water. Figure one shows the characteristic peaks of propargyl alcohol in the gas chromatography.

A.

Figure 1.A



B.

Figure 1 B.

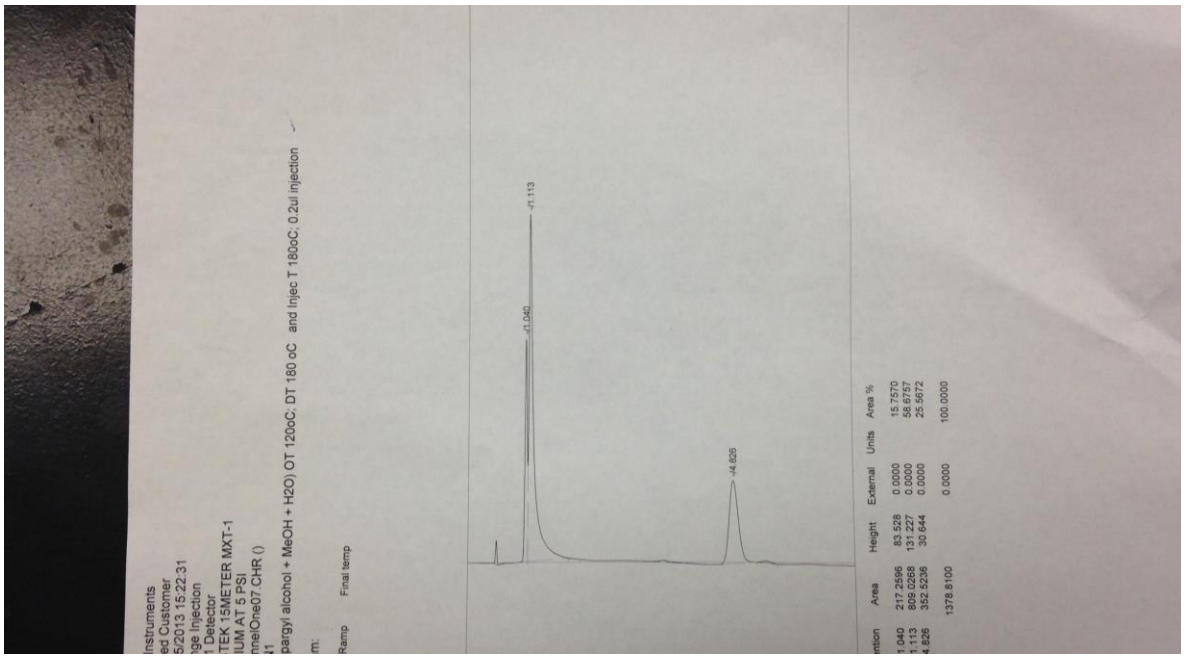
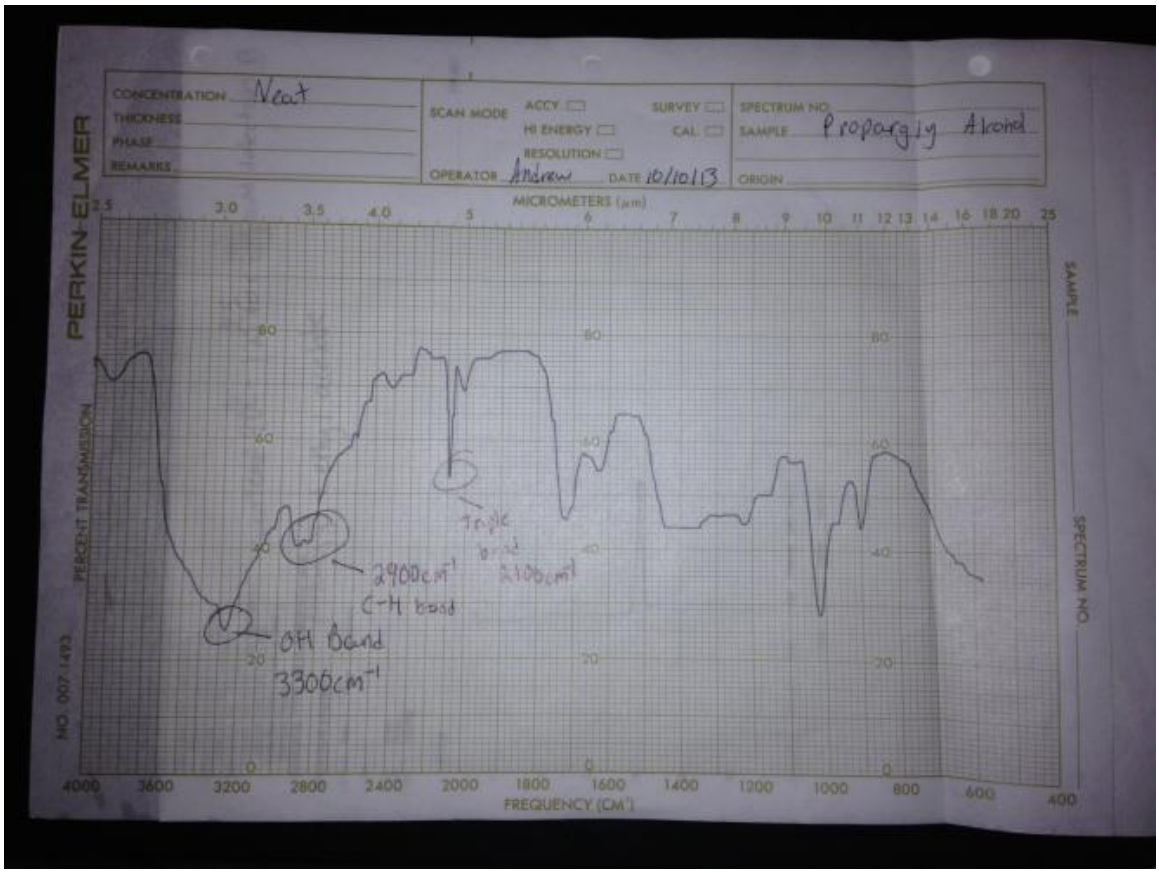


Figure1. Characteristic peak of propargyl alcohol (Retention time=4.8min.) in a gas chromatography. **A** is the one to one ratio of methanol Ret. T=1.04 min. and the propargyl alcohol. **B** is the GC profile of **A** with increased concentration of water (Ret. 1.131 min).

The IR spectrometer also confirmed it was propargyl alcohol. The data showed a broad OH peak at 3300cm^{-1} and a small sharp peak at 2100 cm$^{-1.}$ These bands indicate it has an alcohol and alkyne functional group. Figure 2 shows characteristic peaks data for the IR.

Figure 2. IR of Propargyl Alcohol



The research was mainly focused on trial two because of experimental error that occurred in trial one. A sample of the crude reaction mixture on a TLC plate showed there were two spots on the plate. The solvent system was a ratio of 95 percent hexane and 5 percent ethyl acetate. One of the spots was hook shape and the over spot did not move with the solvent front and stayed on the bottom of the TLC. The Michael addition

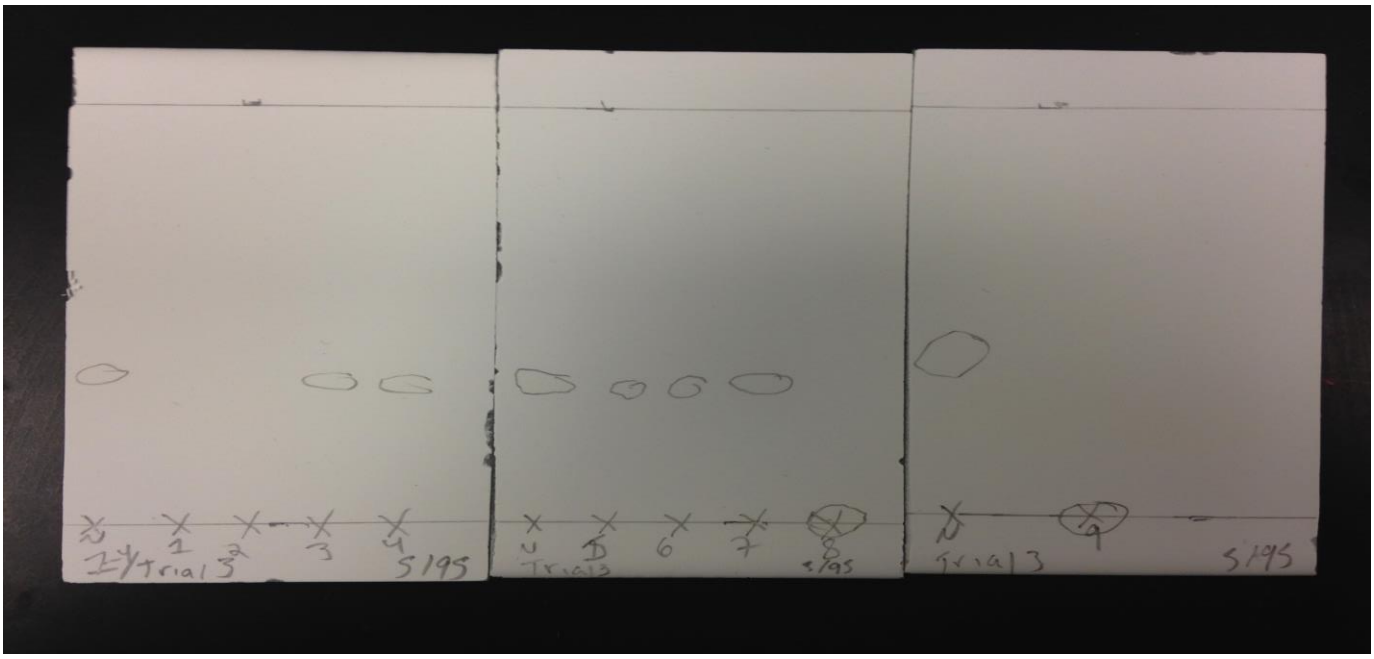
product was purified by column chromatography to obtain the Michael addition product. The results are listed in table 1. Fraction 2-6 only had one spot, which was the hook spot when performing the TLC. Fractions 7-12 were collected by increasing he polarity of the solvent system to 100 percent ethanol to flush out the polar product. The TLC of fraction 11-12 showed that there was a second product. Fractions 2-6 were combined and fraction 7-12 were also combined. Another TLC was performed after the solvent evaporated from both combined fractions. The TLC revealed that the hook shape spot was nitrostyrene. The hook shape spot lost its characteristic of its usual hook shape and had the same rf value of nitrostyrene. The hook shape spot was most likely caused by TFA sticking to the silica gel and increasing the rf value. When the fractions were let to evaporate the TFA must have evaporated out with the solvent. Furthermore, the TLC also showed the other spot that did not move with the solvent front.

Column chromatography was used again to isolate the second spot that was not moving with the solvent front. The column chromatography was loaded with fractions 7-12 from the previous column chromatography. The results are in table 2. Only fractions 8 and 9 contain the bottom product that was originally in trial 2. Fractions 1-5 were collected by a solvent system of 95 percent hexane and 5 percent ethyl acetate. Fractions 5-9 were collected by a solvent system of 90 percent ethyl acetate and 10 percent methanol.

	Table 1	
Trial 2		
Fraction	Nitrostyrene	Desired Product
1	N	N
2	Y	N
3	Y	N
4	Y	N
5	Y	N
6	Y	N
7	Y	N
8	Y	N
9	Y	N
10	Y	N
11	Y	Y
12	Y	Y

	Table 2	
Trial 3		
Fraction	Nitrostyrene	Desired Product
1	N	N
2	N	N
3	Y	N
4	Y	N
5	Y	N
6	Y	N
7	Y	N
8	N	Y
9	N	Y

TLC data for trial 2 and 3
N=No
Y=Yes



TLC plates for Trial 3.
See supplementary section for complete TLC plates

Polystyrene-immobilized pyrrolidine has been created to catalyze the reaction between the nitrostyrene and cyclohexanone to give high yields, up to 99%. However, only little product was obtained. This means that the catalyst was not effectively synthesized. One on the limitation was characterizing the resin to verify if the propargyl alcohol and the organic azide attached to the resin at the loading sites. The laboratory facility lacks the equipment to press a KBr pellet, which would be used for solid-state infrared spectroscopy. The resin needs to be pressed by 8 tons of pressure to get an opaque enough disk to use in the machine.[2] Although, the resin cannot be characterized by infrared spectroscopy, a visual color change occurred when performing the click chemistry. A green color change occurred in the experimental reaction but not in the control reaction. Copper (II) is a green color and is a by-product of click chemistry.[3] The control reaction suggests that the propargyl alcohol did attach to the loading sites in step one when synthesizing the catalyst. This illustrates that there was reaction between an alkyne and a azide to oxidize the Cu(I) to Cu(II). The challenge is proving how much in each step of synthesizing the catalyst did the alcohol and the organic azide attached to the loading sites. Figure 3 illustrates the change in color for my control reaction.

Figure 3

A few minutes after starting control reaction experiment

24 hour of stirring

Conclusion:

In conclusion, more research is needed to see if the asymmetric Michael addition was successful. Without proper equipment the results cannot be effectively analyzed. However, research is this field is promising because it gives organic chemist and pharmaceutical fields an effective method to produce a stereoselective reaction when normally the reaction produces a racemic mixture.

Acknowledgment:

I would like to thank Professor Ghosh and Professor Rowley for dedicating their time by helping me. Finally, I would like to give gratitude towards our Dean, David Edward and our Chairperson, Dr. Parag Muley of the natural science department to give use the opportunity to execute the research projects. Lastly, this research would not have been possible without the finical support of **Bristol-Myers Squibb.**

Reference

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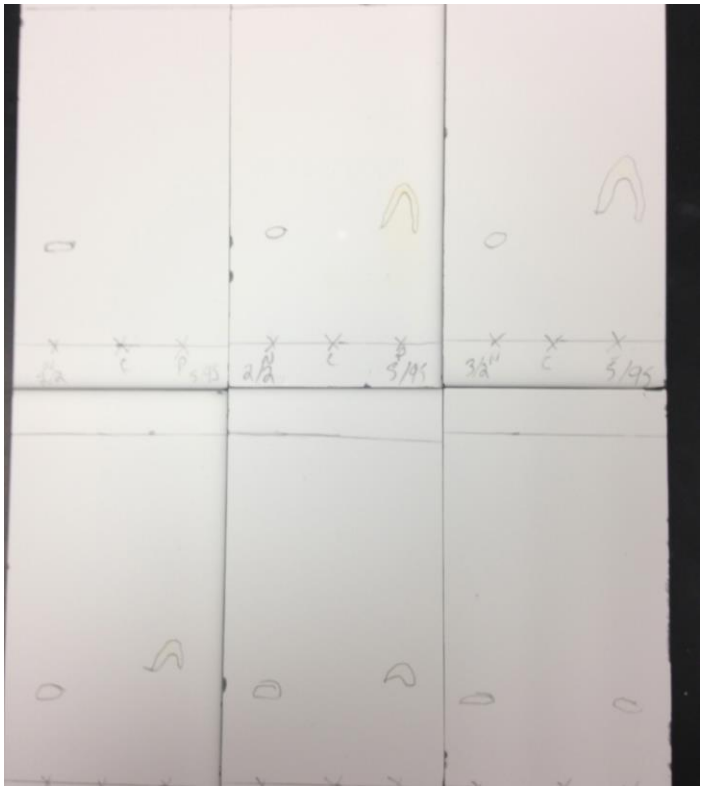
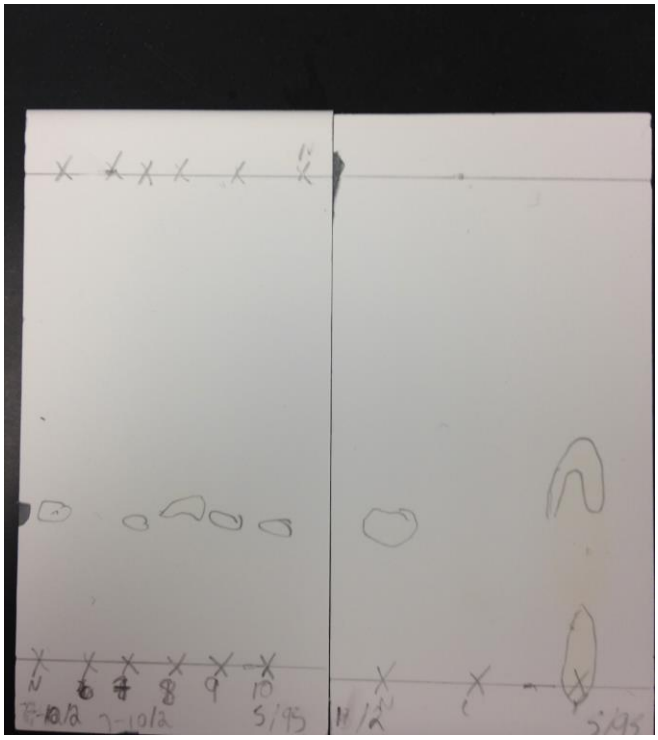
Supplementary:



Trial 2. Fraction 1-6



Trial 2 Fractions 7-12

Fraction 2-6 and Fraction 7-12 combined

After evaporation

60 % hexane and 40% ethyl acetate