Title: Amine-Catalyzed Direct Asymmetric Mannich Reaction[1]

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Abstract:

We explored the natural amino acid L- proline to be catalysts for the direct asymmetric Mannich-type reaction of acetone with a variety of preformed aldimines derived from o-anisidine. In the first part of this project, we explored the direct asymmetric Mannich-type reaction between acetone and N-(p-nitrobenzylidene)Aniline, in the presence of 30 mol % of L-proline. N-(p-nitrobenzylidene)Aniline was the intermediate compound which made between Aniline and 4-nitrobenzaldehyde. The reaction was set under normal condition and room temperature. We got 2 conformation products. Detail characterization of two products was determined by TLC, Column Chromatography, NMR, and HPLC. The percent yield of main product was 67.5%, and the published value was 52%. In the second part of this project, we explored the same asymmetric Mannich-type reaction using p-Anisaldehyde instead of 4-nitrobenzaldehyde. We got an unknown compound, and we could not identify the structure of this compound until we get mass spectrum. In the third part of this project, we explored one-pot three-component reaction between acetone, Aniline, and p-Anisaldehyde in the presence of 30 mol % of L-proline. We got 2 conformation products too, but the ratio of major and minor conformers is switched.

Introduction:

Asymmetric Mannich-type reactions are employed in the organic synthesis of natural compound and medicinal compound. Asymmetric Mannich- type reactions have typically involved addition of enolates to chiral aldimines[2] or hydrazons[3] wherein the chiral controller of the reaction of the reaction is used in stoichiometric amounts. Base on the amine- catalyzed direct asymmetric aldol reactions[4], the researcher developed the chiral amine-based catalysis of direct asymmetric Mannich-type reactions. The goal of the this project was to replicate the amine-catalyzed direct asymmetric Mannich reaction, published by Tetrahedron Letter, with the different electron with-drawing group and electron donating group.

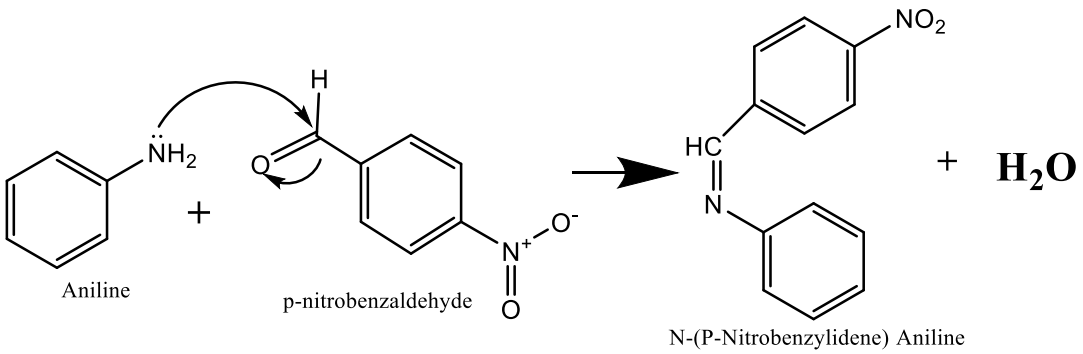
Experimental Section:

Instrumentation: NMR spectra were recorded using NMRReady^{TM} 60 Nanalysis Corporation. $CDCL_3$ was used as a reference/ blank and also as solvent for all compounds. D_2O was used for identify –NH proton group.

Materials: All materials used for preparation were reagent graded and used without further purification except for p-Anisaldehyde. p-Anisaldehyde was purified using Column Chromatography with silica gel as stationary phase and pentane/ ethyl acetate(3:1) as mobile phase.

First Experiment:

Step 1: The Reaction of P- nitrobenzaldehyde and Aniline



- In a 100 ml round-bottomed flask fitted with a reflux condenser, place p-nitrobenzaldehyde (0.01mol), aniline (0.01mol), and 4ml rectified spirit.

- Heat the solution under reflux, using a water bath, for 30 minutes. Set solution on one side to cool.

- Collect the solid deposit by filtration and wash well with cold aqueous ethanol.

- Recrystallize a small portion from methanol.

- The melting point is 91ºC – 92º C.

Characterization of N-(p-nitrobenzylidene)Aniline through NMR

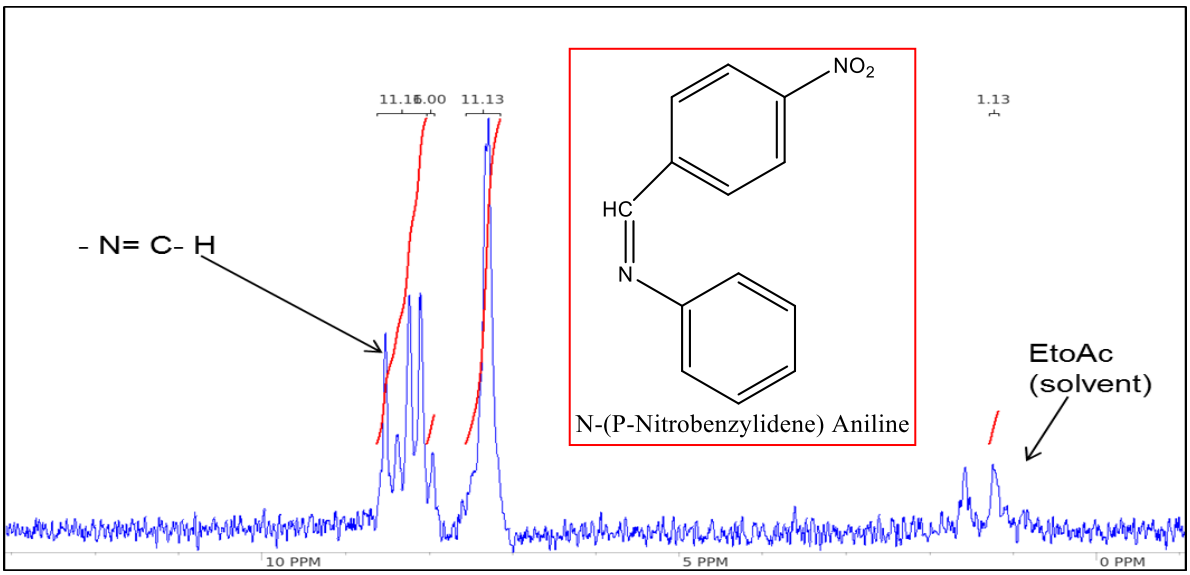
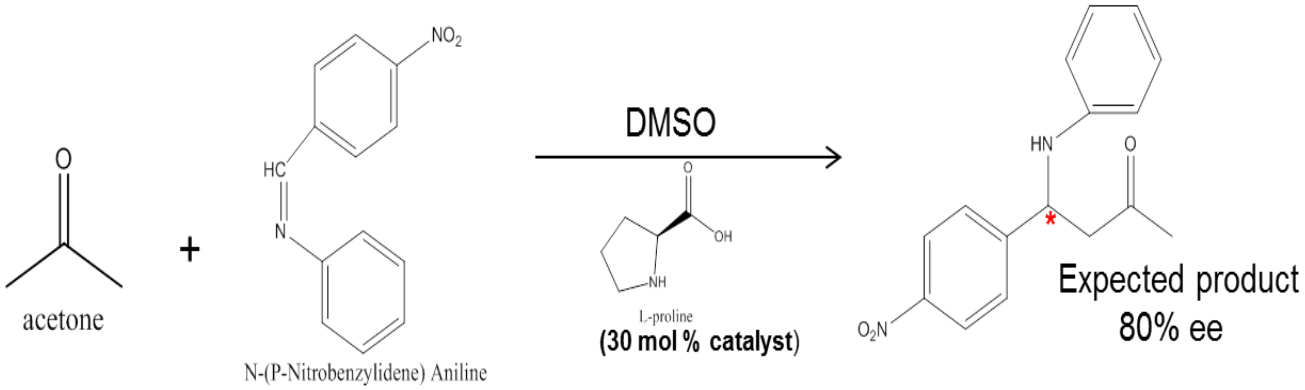


Figure 1: NMR spectrum of N-(p-nitrobenzylidene)Aniline .

Step 2: L- Proline catalyzed Enantioselective Mannich reaction



- L- Proline (0.16mmol) was stirred in 4ml DMSO/acetone (4:1) for 15 minutes.

- N-(p-nitrobenzylidene) aniline (0.4mmol) was added and the mixture was stirred for 24 hours.

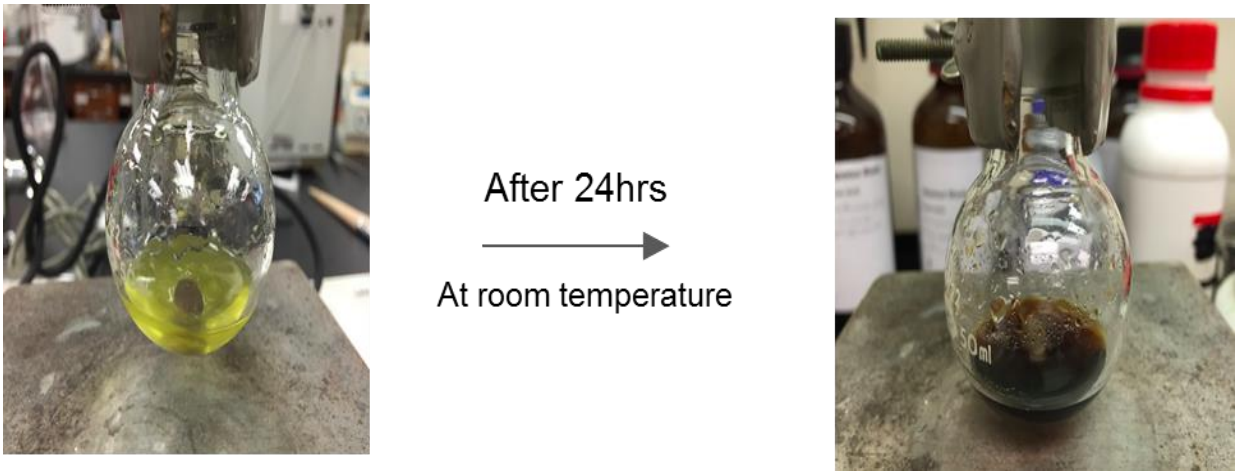


Figure 2. Left: The mixture of Amino acid L-proline, DMSO, acetone and N-(p-nitrobenzylidene) aniline at the beginning stage of the reaction. Right: The mixture after 24 hours of stirring under room temperature.

- The crude solution was washed with 4ml aqueous NH_4Cl, and the aqueous layer was extracted with 3times of 20ml Ethyl Acetate.

Figure 3: Crude product was extracted with EtoAc

- The organic layer was dried with Na_2SO_4.

- Evaporation of the solvent gave crude product.

- Purified by flash chromatography: Hexane: EtoAc (1:1), and checked the results with TLC.

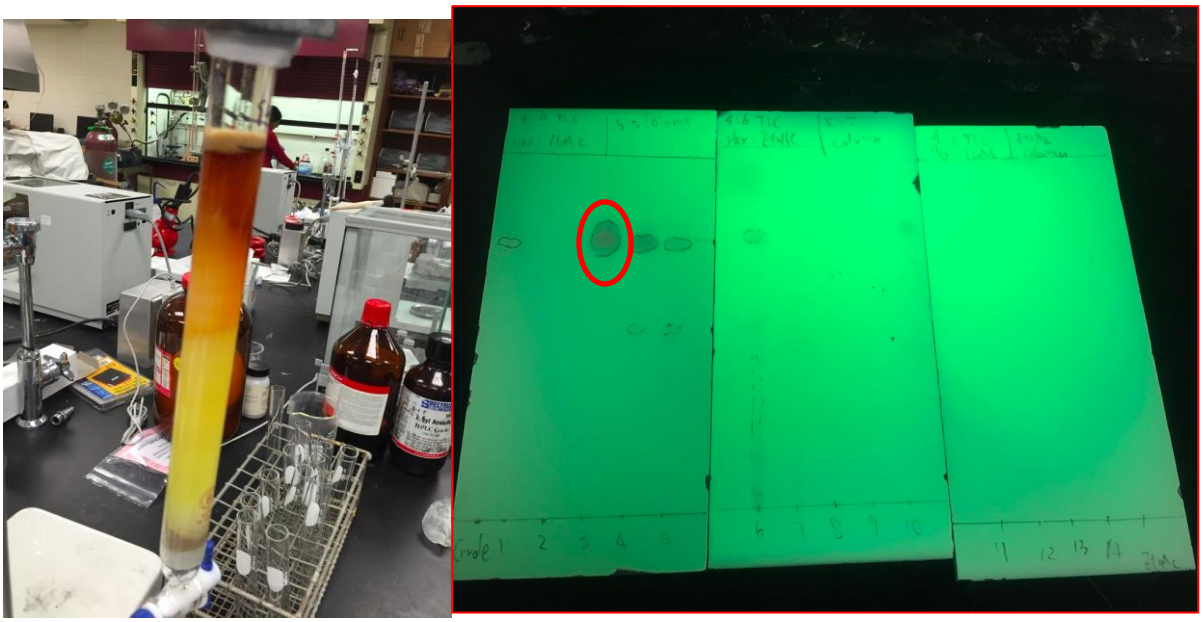


Figure 4: Left: purified the crude product by flash chromatography. Right: TLC plate result of the product after extraction. Solvent: 4:6(hexane : EtoAc)

- Only collect tube 3.

Result and discussion:

After purified the crude product using flask chromatography, the TLC plates show only test tube 3 have pure product. The percent yield of this product id 67.5%. This product was dried out by Rotavap and characterized using NMR and HPLC.

Characterization of main product through NMR

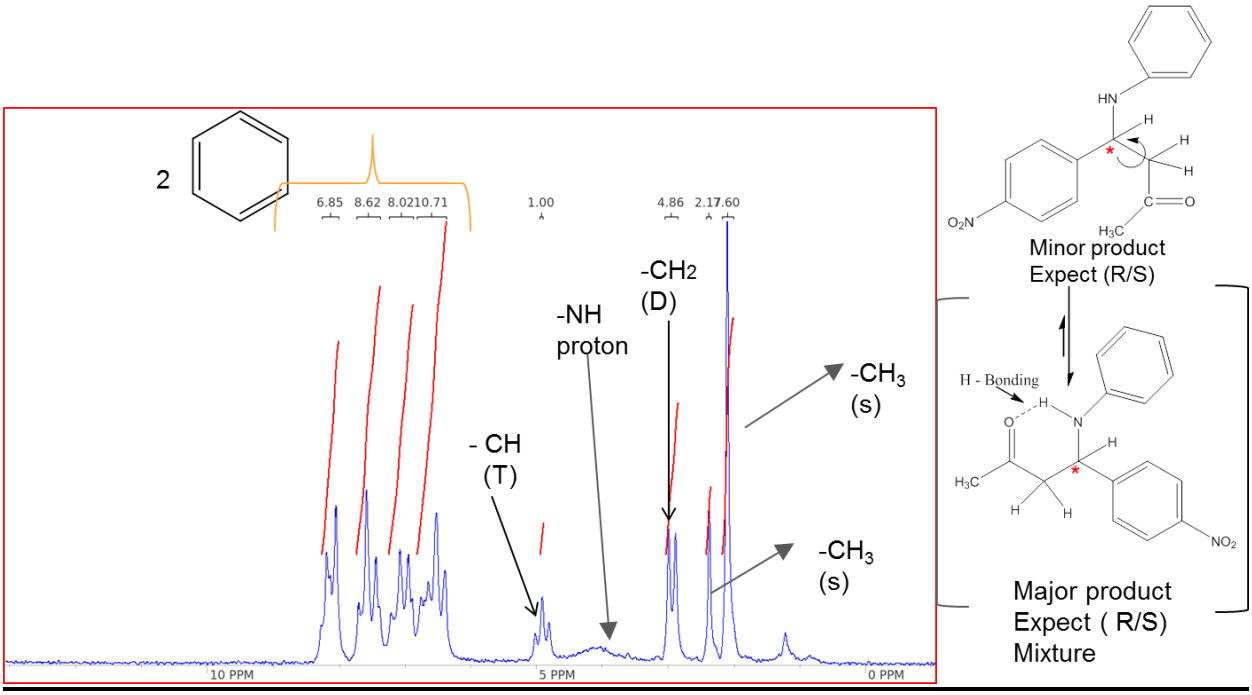


Figure 5: Experimental NMR spectrum of first reaction product.

- Most the characteristic peaks match the structure of estimated compound. As expected, we see the 2 AB pattern around 6 to 8 ppm. A triplet is show –CH proton and a doublet is show–CH_2 proton. There are two singlet peaks show that in this product, we got two conformation compounds. One is opening structure, and the other has H-Bonding. Most the characteristic peaks are there, but we also need –NH proton peak. The –NH peak can go through anywhere in NMR spectrum. We can see that all peaks are nice and sharp, only around 4 ppm has a small shoulder. We expected that small shoulder is –NH proton peak, so we added a drop of D_2 O to NMR tube.

- Do D_2O Exchange Reaction

NMR Result of D_2O Exchange Reaction

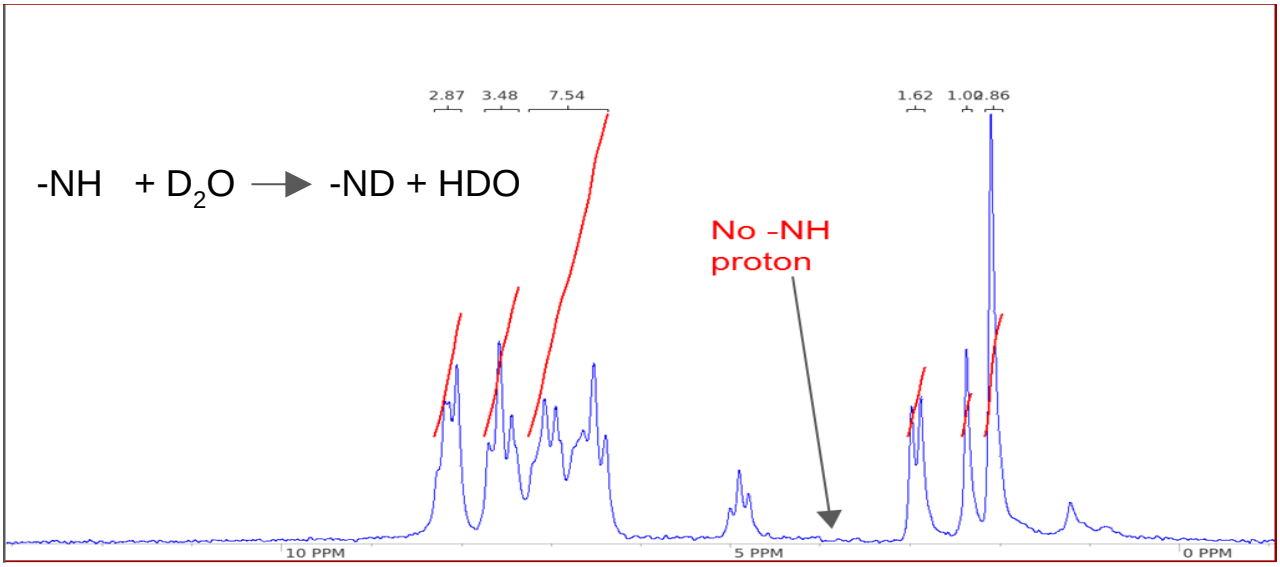
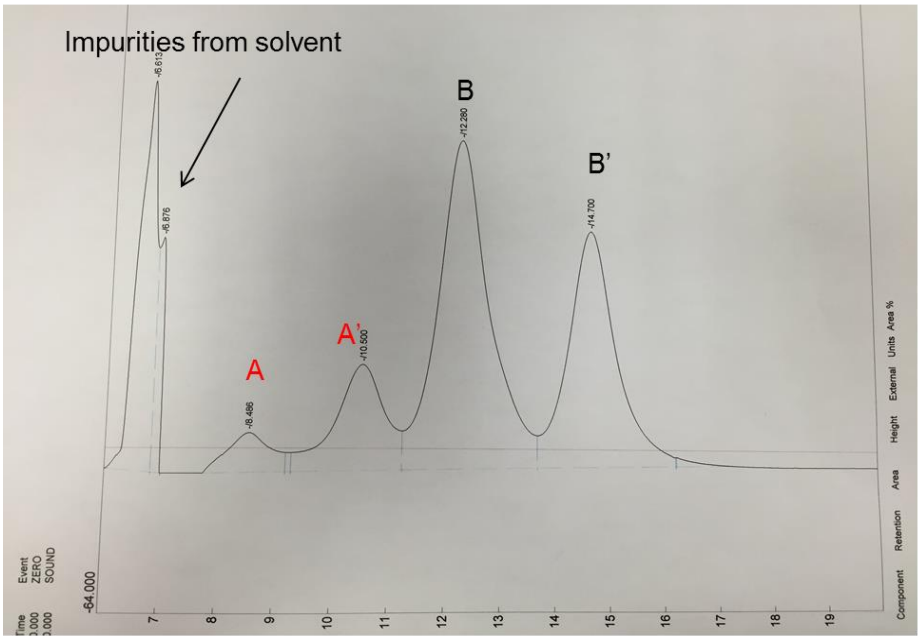


Figure 6: NMR spectrum of after added one drop D_2O

- After the D_2O exchange reaction, we could not see any shoulder around 4 ppm. And this spectrum provides that small shoulder was the –NH proton peak. Two small peaks around 1 ppm is the solvent system (EtoAc and Hexane)

- Do HPLC using chiral column (supplied by Dr. Feng Liang). Iamda max: 323nm.



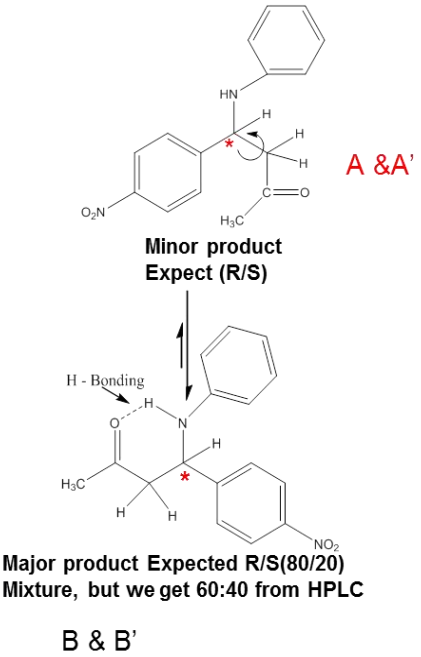
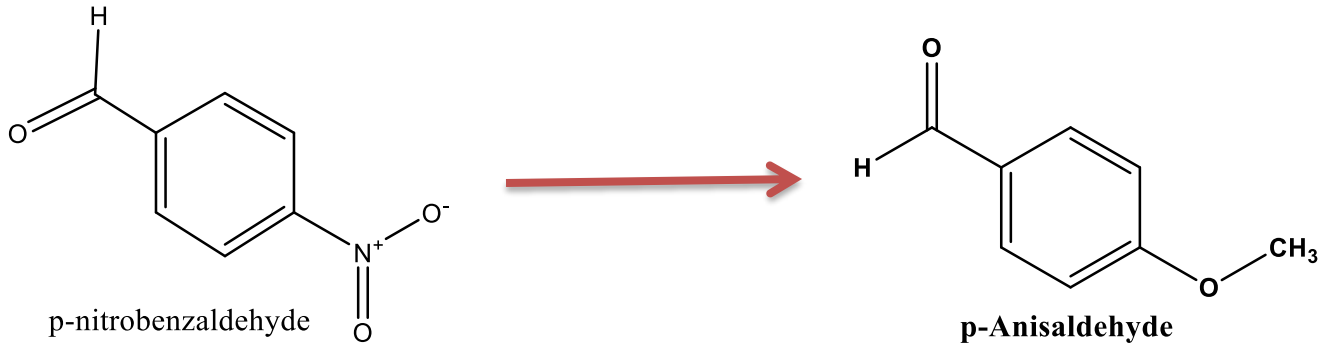


Figure 7: HPLC spectrum with chiral column.

- In the HPLC spectrum, the first two peaks are impurities from the solvent. The solvent is 80/20(Hexane/ ethanol). Then, there were four peaks show on spectrum. Two small peaks, and two lager peaks. We expected that two small peaks are minor product(R/S), as shown A&A'. Two lager peaks are major product(R/S), as shown B&B'. Base on this result we knew that there were four conformers. Also, the major product expected get 80/20 (R/S) mixture, but we get 60/40(R/S) mixture.

Second Experiment:

- So far we have successfully did the Mannich reaction with p-Nitrobenzaldehyde which has an electron withdrawing group (-NO_2). In the next phase of my research, I carried the same reaction using p- Anisaldehyde instead of p-Nitrobenzaldehyde. The p- Anisaldehyde has an electron donating group. We would see that effect of reaction.



- The bottle of p- Anisaldehyde was old, so we check the compound using TLC. The TLC result below show that some impure compound in that bottle.

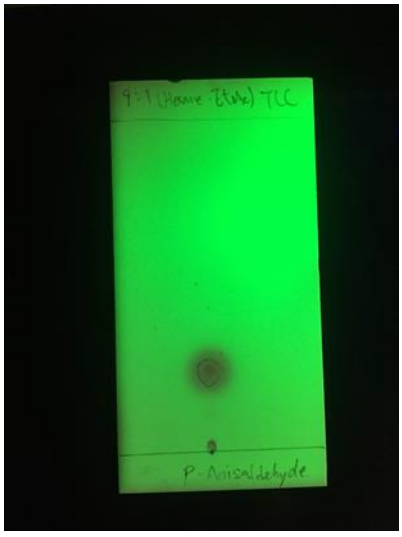
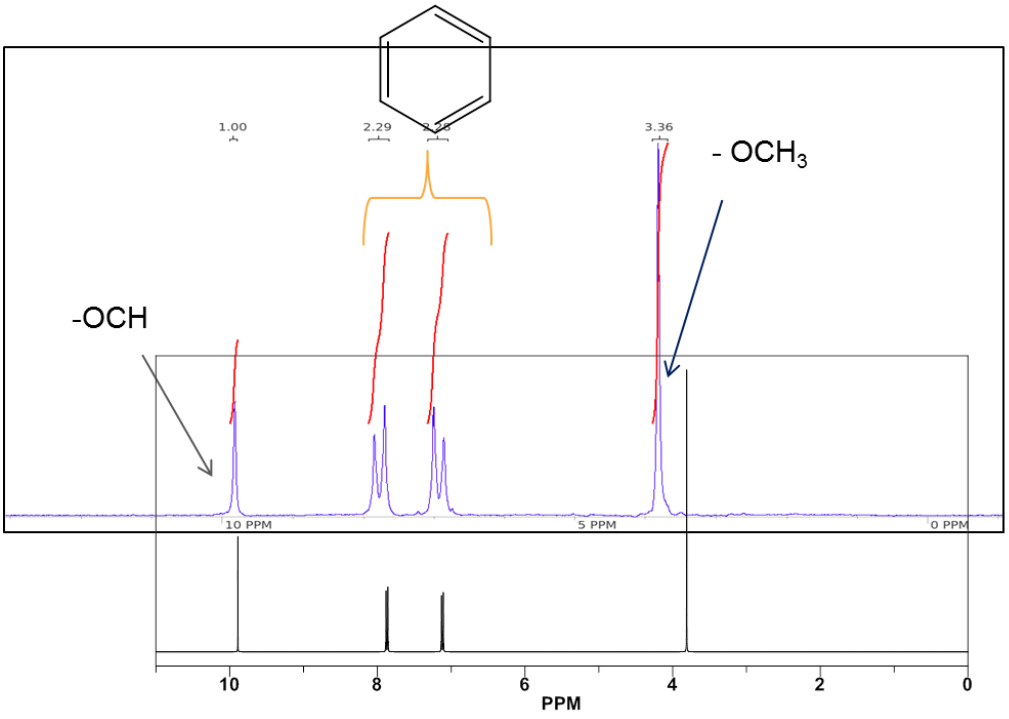
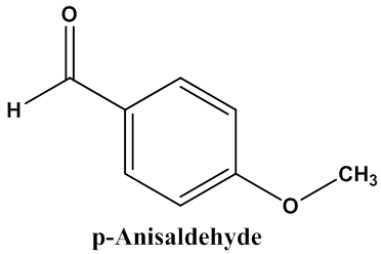


Figure 8: TLC plate of contaminated p- Anisaldehyde. Solvent: 90/10(Hexane : EtoAc)

- The contaminated p- Anisaldehyde was purified by Flash Chromatography. The NMR spectrum of the purified p- Anisaldehyde was match the computer generated spectrum.

NMR Result of P-Anisaldehyde after Column Chromatography

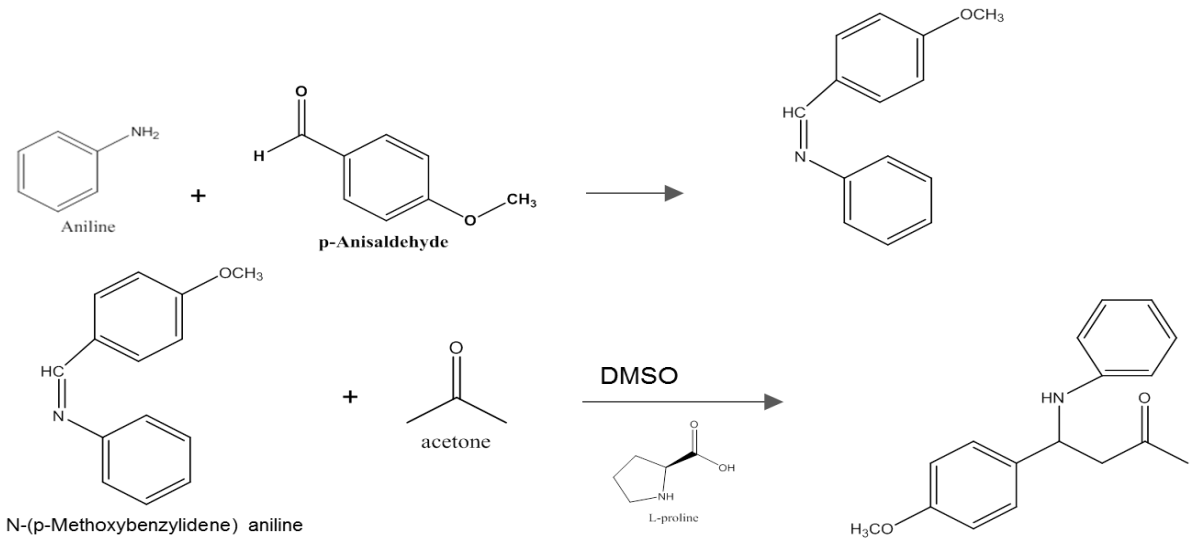




p-Anisaldehyde

Figure 9: NMR spectrum of purified p- Anisaldehyde overlaid with the theoretical NMR spectrum generated by computer software.

Second Reaction: L- Proline catalyzed Enantioselective Mannich reaction with p- OMe-Benzaldehyde



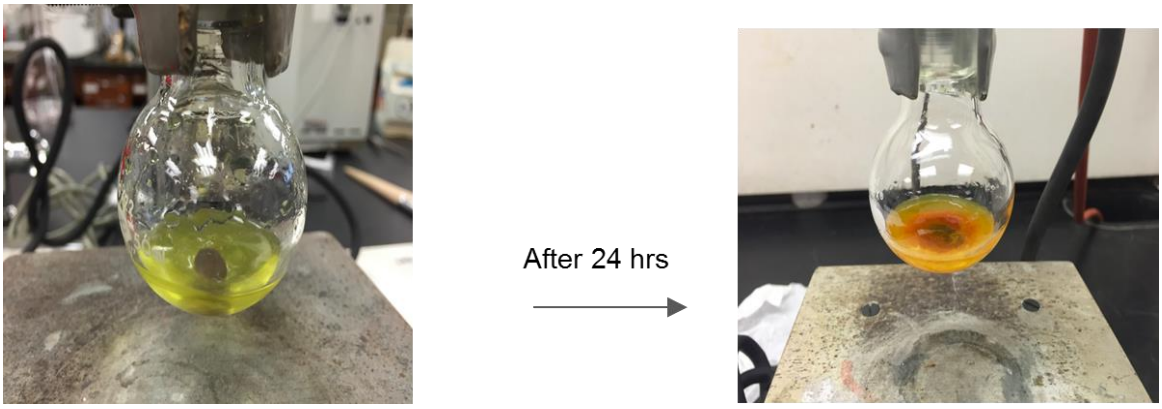


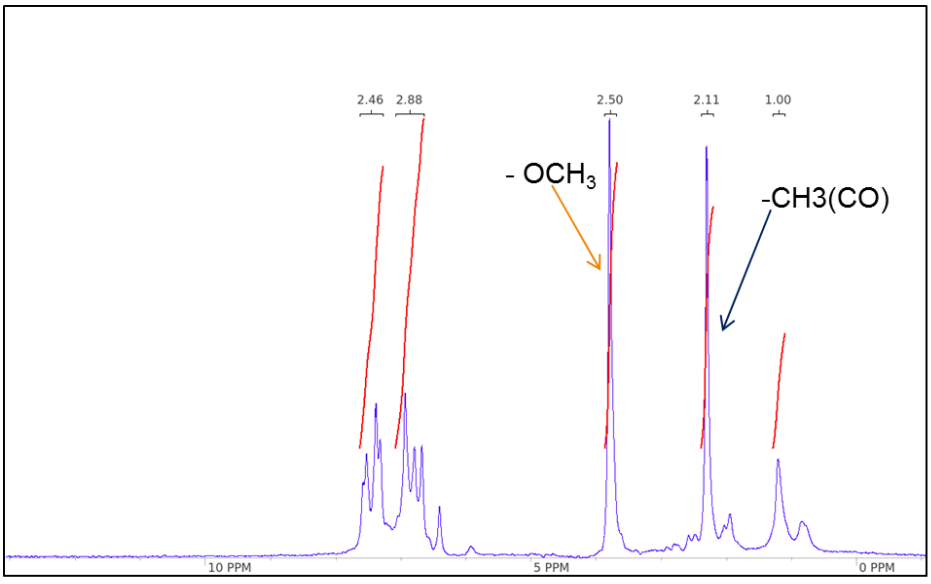
Figure 10: Left: The mixture of Amino acid L-proline, DMSO, acetone and N-(p-Methoxybenzylidene) aniline at the beginning stage of the reaction. Right: The mixture after 24 hours of stirring under room temperature.

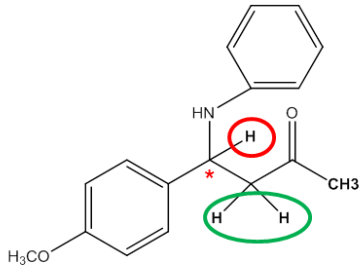
- L- Proline was stirred in DMSO/acetone (4:1) for 15 minutes.

- N-(p-Methoxybenzylidene) aniline was added and the mixture was stirred for 24 hours.

- The reaction with p- Anisaldehyde was also run under the similar condition with the first reaction. Reaction work up also same as first reaction.

The NMR spectrum of second reaction product





Expected product

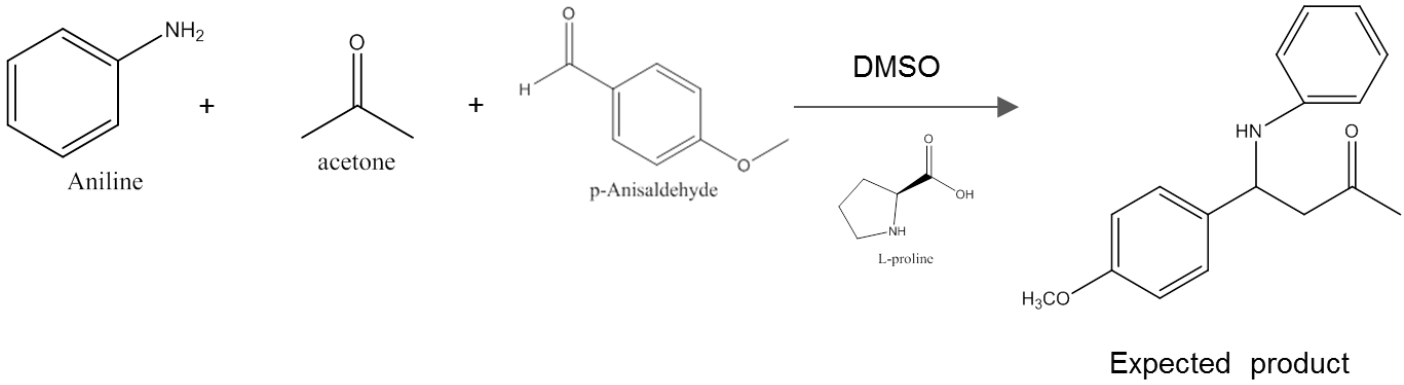
In this spectrum, we do not see the triplet of –CH proton and doublet of –CH2 proton

We don't know the structure of this compound!

Figure 11: The NMR spectrum of second reaction product with $CDCl_3$

- We could not identify the structure of this compound until we get mass spectrum.

Three Experiment: Attempted the same reaction without isolating the intermediate imine compound.



- Combine all reagents at once.

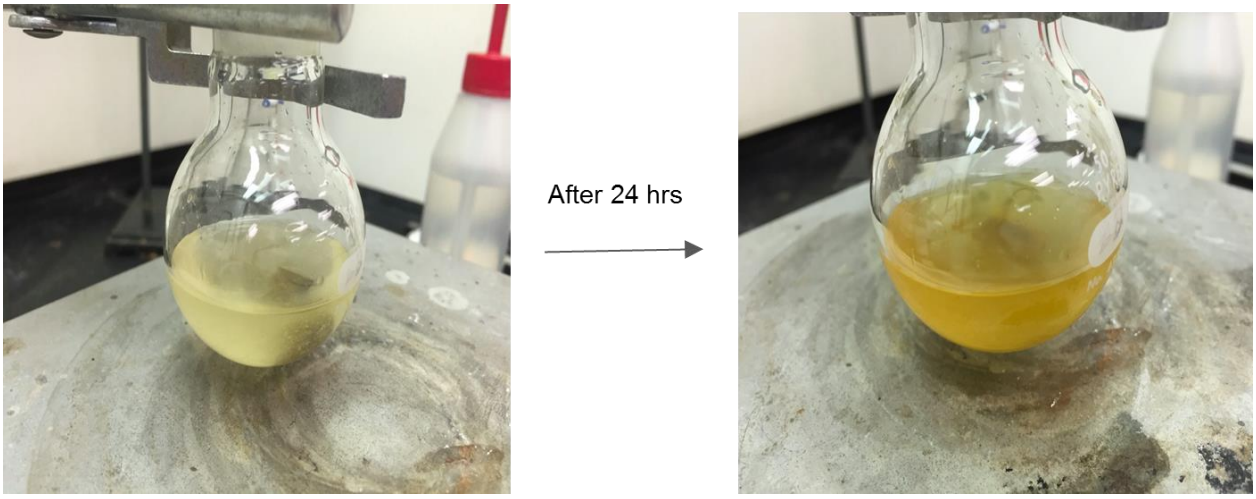


Figure 12: Left: The mixture of Amino acid L-proline, DMSO, acetone, aniline, and p-Anisaldehyde at the beginning stage of the reaction. Right: The mixture after 24 hours of stirring under room temperature.

- L- Proline was stirred in DMSO/acetone (4:1) for 15 minutes.

- Aniline and p - Anisaldehyde were added and the mixture was stirred for 24 hours.

-The reaction with p- Anisaldehyde was also run under the similar condition with the first reaction. Reaction work up also same as first reaction. Check the result with NMR.

The NMR spectrum of third reaction product

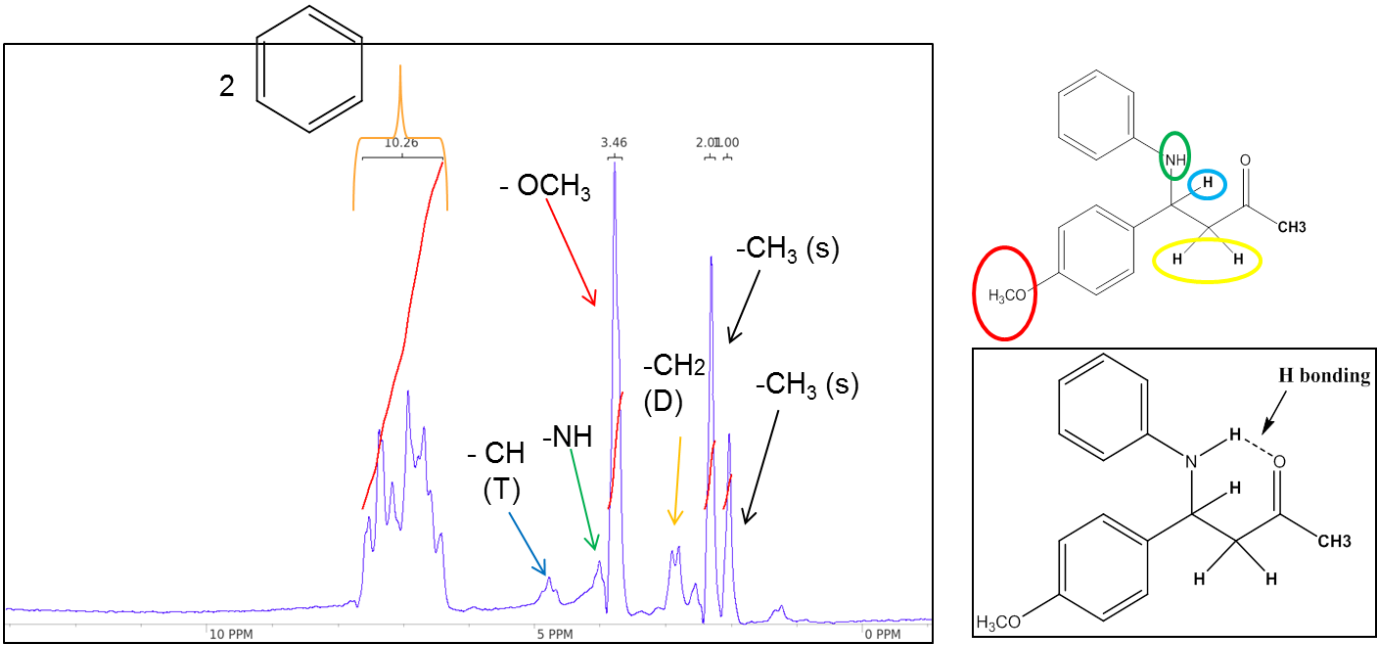


Figure 12: The NMR spectrum of third reaction product with $CDCl_3$

- We could see this product is much closer to expected product. We can see the triplet of –CH proton, and the doublet of $–CH_2$ proton. Also, in this spectrum, we found two singlets $–CH_3$ proton, it's mean that we got two conformation compounds. However, the ratio of major and minor conformers is switched.

- We also did the D_2O exchange reaction to find that which peak is –NH proton.

NMR Result of D_2O Exchange Reaction

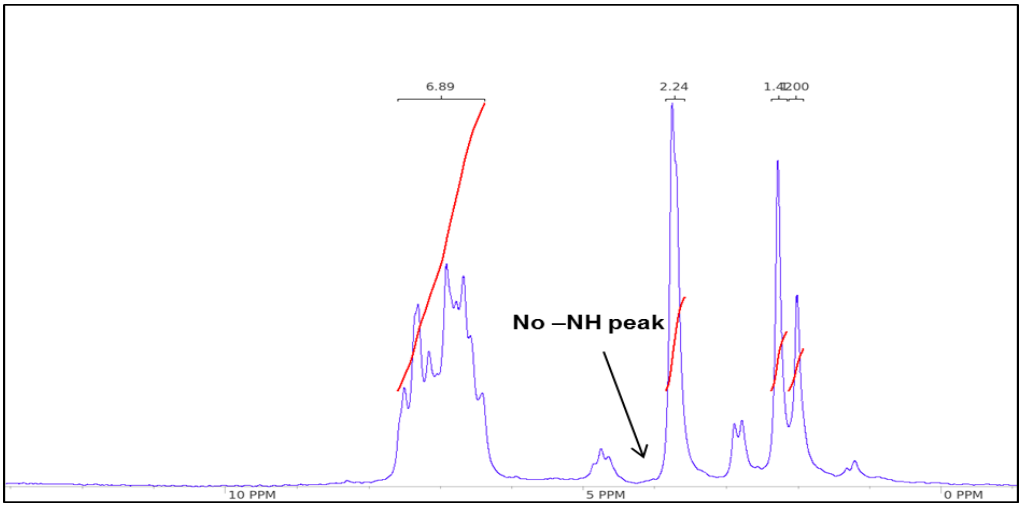


Figure 13: NMR spectrum of after added one drop D_2O

Conclusion:

In summary, we have replicate successful the amino-catalyzed direct asymmetric Mannich-type reaction. From my research work, we got the Mannich type catalytic reaction with L-Proline. We selected L-Proline because it is water soluble and can be easily removed by aqueous solution. It is also inexpensive therefore it could be run in big scale. We also identified conformers in our reactions. From HPLC result, we found two enantiomers(R/S) of major products and enantiomers(R/S) of minor products. This part was not match from the published paper. We are in a process of identifying the unknown product from my second reaction. When we compared the NMR results between first reaction and third reaction, we found that when electron withdrawing group [-NO2] is present, our major conformer is hydrogen bonded compound but when electron donating group [-OCH3] is present, we found the ratio of major and minor conformers is switched. We are currently investigating the results.

Acknowledgments:

I would like to thank all of the people listed below. This project could not been done without your support.

- Dr. Phalguni Ghosh
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- Dr. Steven Rowley
- Dr. Parag Muley, Chair Person , Natural Sciences
- Dr. David Edwards, Dean, Natural Sciences
- Peer Students
- Bristol-Myers Squibb for financial support
- Chemistry Lab Staff : Douglas Reardon, David Rossen

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