LOVELY PROFESSIONAL UNIVERSITY,

Punjab

DISSERTATION-II

(Dec-2017)

Topic:

"Novel L-Prolinamide derivatives as a potential organocatalyst for asymmetyric Aldol reactions"

SCHOOL OF PHYSICAL SCIENCES AND CHEMICAL ENGINEERING

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DISSERTATION TOPIC: Novel L-Prolinamide derivatives as a potential organocatalyst for asymmetyric Aldol reactions

SUPERVISOR NAME: Dr. Nitin Tandon

DESIGNATION: Assistant Professor

CERTIFICATE

This is to certify that Jutika Saikia is working on her dissertation project entitled "Novel L-Prolinamide derivatives as a potential organocatalyst for asymmetyric Aldol reactions" under my guidance. The current work is her original investigational study. The dissertation proposal is apt for the submission and the partial fulfillment of the conditions for obtaining the dergree of M.Sc. in Chemistry.

Date: 29 Feb, 2017

NAME OF THE SUPERVISOR: DR. NITIN TANDON

SIGNATURE:

SUBMITTED BY:

JUTIKA SAIKIA

REG NO. 11611669

M.Sc. CHEMISTRY (Honors)

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Firstly, I would like to acknowledge my supervisor, Dr. Nitin Tandon for helping me throughout this work. He properly guided me in the entire study. He never failed to clear my doubts at any time of the day.

I am grateful to everyone in my department and to Dr. Ramesh Chand Thakur, Head of the department, for giving me a wonderful environment and opportunity to do this project. A special thanks goes to Dr. Harminder Singh for his help in the report.

Last but not the least, my gratitude towards my parents for being there for me and supporting me in every step of my life. My appreciation also goes to my friends who have willingly helped me throughout the time.

CONTENTS

INTRODUCTION

During the research based on catalytic asymmetric organic synthetic methods, researchers have focused mainly on metal-mediated catalysis. Metal complexes have catalysed a wide variety of transformations stereoselectively. But with its positive part, there comes the drawbacks. Many catalytic metal complexes are difficult to remove from the products, they are highly toxic, and expensive **[16]**. Thus with the growing interest in the asymmetric synthesis of chiral molecules, there are still opportunities for the development of alternative approaches. Therefore lot of efforts are being made by different research groups to develop metal free ligands as potential catalyst for carrying out different synthetic transformations. This has opened up a new area of design and synthesis of organic molecules known as organocatalysts which can catalyse different chemical reactions by overcoming the limitations associated with the metal ligands. The field of organocatalysts has witnessed a substantial growth in the recent past **[17, 18, 19]**. Various organic molecules have been reported in literature for their activity as organocatalyst like proline and its derivatives **[20, 21]**, pyrrolidine and its derivatives **[22, 23]**, natural products **[24]**, etc. Out of these, proline and its derivatives have proved to be most favorable in catalyzing various reactions like Aldol **[25, 26]**, Mannich **[27, 28]**, Micheal **[29, 30]** and Robinson Annealation reactions **[31]** with better stereochemical control. L-proline and its derivative showed 99% ee. Also proline is inexpensive, it exists in both enantiomeric forms and its reactions can normally be done at ambient temperature. Literature survey has revealed that Aldol reaction can lead to the synthesis of intermediates which can act as starting material for various types of molecules of biological and medicinal use **[32]**. Therefore the main focus of the present work is to develop prolinamide derivatives to explore their use on rate of reaction as well as on the stereochemical output in case of Aldol reaction and check their utility for carrying out Aldol reaction and to study their effect on rate of reaction and stereoselectivity.

LITERATURE REVIEW

In early 1970's L-proline catalysed intramolecular aldol cyclization was explored by Hajos and Parrish, called the Hajos-Parrish-EderSauer-Wiechert reaction. They isolated hydrindane dione (Compound-1, Fig-1). The experiment was done using 3 mole percent of L-proline in DMF. After 20 hours the reaction lead to 96.5:3.5 enantiomeric ratio of aldol product (Compound-2, Fig-1). But the field did not expand even after getting such encouraging results. **[1]**

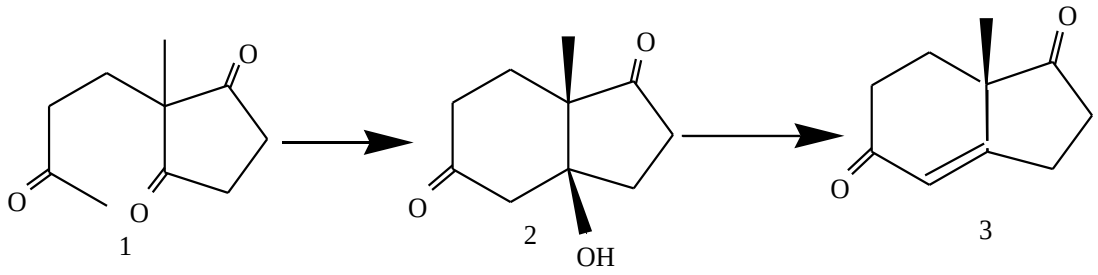


Fig-1

The interest on proline and its derivatives as a catalyst rekindled in 1990's. Barbas performed the first Aldol reaction with acetone and 4-nitrobenzaldehyde in presence of 30 mole percent of L-proline. In this conditions the Aldol product gave 68% yield with 88:12 enantiomeric ratio (Fig-2).

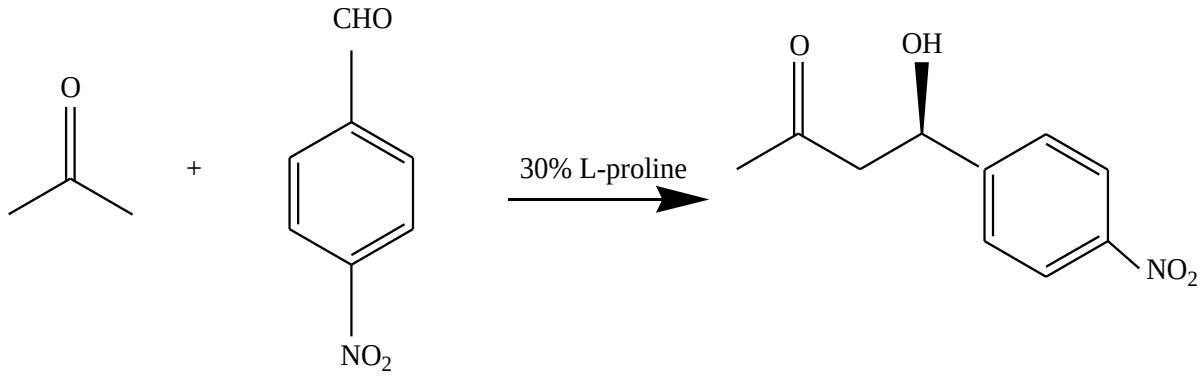


Fig-2

The conclusion drawn by Barbas and his co-workers was that the branched aliphatic aldehydes gave highest yield and enantioselectivity. The alpha unbranched aldehydes turned out to give less yield and medium enantioselectivity. Simple benzaldehyde showed enantioselectivity of 57%. The

presence of an electron withdrawing group in the benzene ring showed more enantioselectivity than the presence of an electron donating group. For example- p-nitrobenzaldehyde showed 71% enantioselectivity whereas methoxy benzaldehyde showed 48% enantioselectivity. **[2]**

Benzamin List and his co-workers performed proline catalysed intermolecular Aldol reaction (Fig-3). Various conclusions that alpha unbranched aldehydes turned out to be difficult substrate and it did not provide the corresponding Aldol products under standardised conditions. Branched aldehydes gave upto 96% enatioselectivity whereas alpha unbranched aldehydes gave enantioselectivity as low as 67%. The attachment of a cyclic chain to an aldehydic group gave enatioselectivity upto 84%. **[3]**

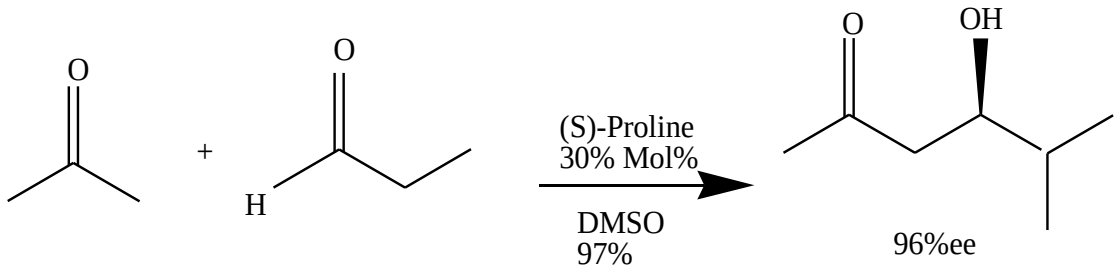


Fig-3

Barry M. Trost and Cheyenne S. Brindle compared many proline catalysed based reactions and concluded that the facts and findings of Barbas and his co-workers were right. Even after modifying the reactions with different temperature, pressure, substituting the groups etc., the end results were almost similar (Fig-4). **[4]**

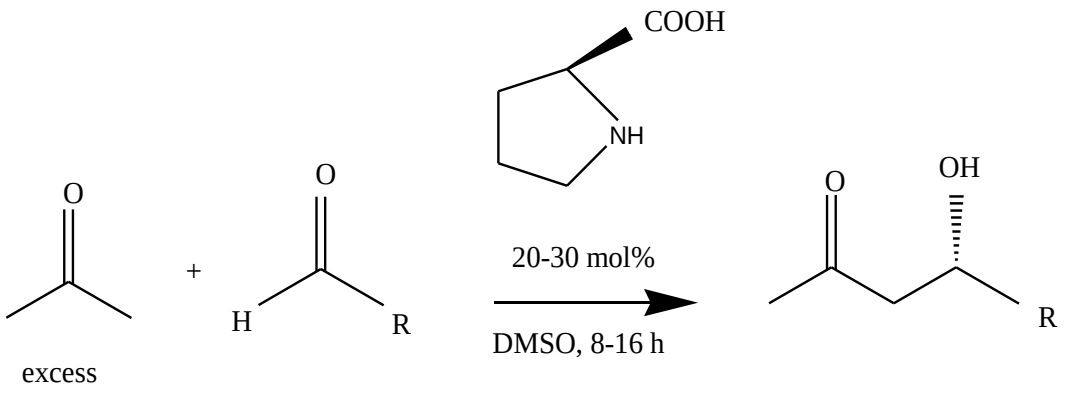


Fig-4

Alberto Martinez and his co-workers set up two reactions to compare the effect of branched aldehydes and unbranched aldehydes. (Fig-5)

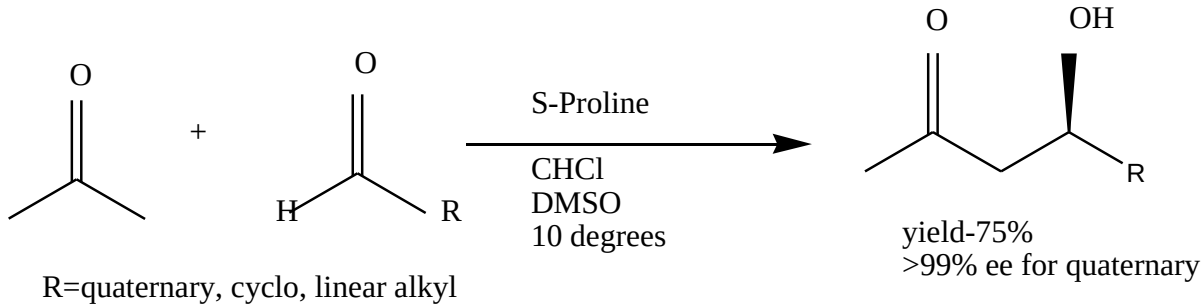


Fig-5

The enantioselectivity for branched aldehydes was found to be above 90%. In the case of alpha unbranched aldehydes, the enatioselectivity went upto 70%. As the chain increased, the enantioselectivity decreased. Also when there was branching in the beta position, it decreased enatioselectivity further to 47% in comparision to 51% of the unsubstituted benzaldehyde. **[5]**

Kazumasa Funabiki and his co-workers prepared a trifluoromethylated molecules using trifluoroacetaldehyde (CF_3CHO). However, it was found that this method with CF_3CHO had drawbacks as there was use of excessive amount of concentrated sulphuric acid under high reaction temperature. The generated aldehyde could not be stored as-at room temperature it was gaseous, it had high hygroscopicity and it was so highly reactive that it lead to self-polymerization.

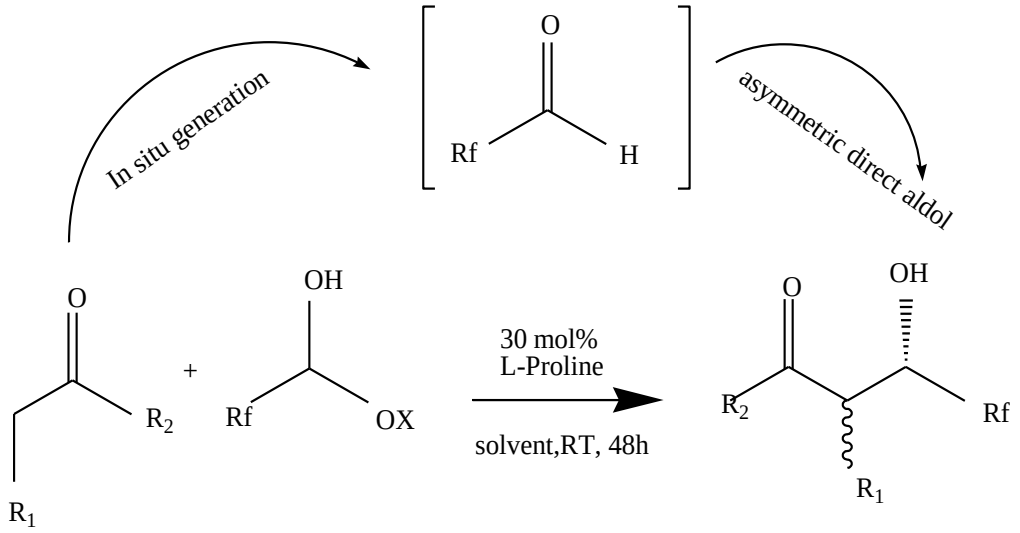


Fig-6

So to overcome their problem they used L-proline for catalysing direct asymmetric Aldol reaction of trifluroacetaldehyde ethyl hemiacetal with ketones which were not modified (Fig-6). This produced beta-hydroxy-beta-trifluoromethylated ketones with good diastereoselectivity (nearly 96% de) and enantioselectivity (nearly 91% ee). **[6]**

S. Chandrasekhar, Ch. Narsihmulu, N. Ramakrishna Reddy and S. Shameem Sultana did Aldol reaction catalyzed by L-proline. They used di-acetone as one of the reactants. (Fig-7).

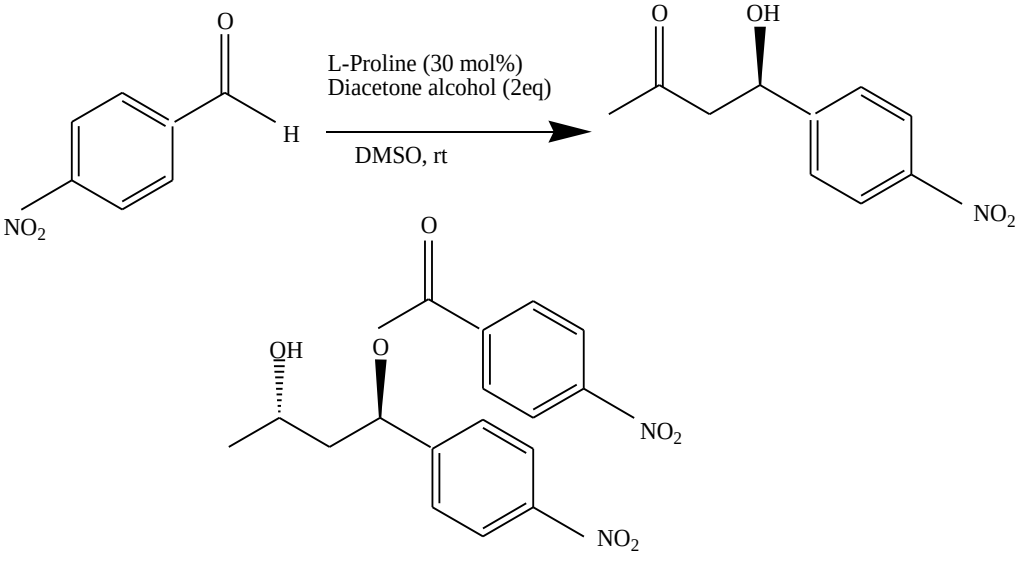
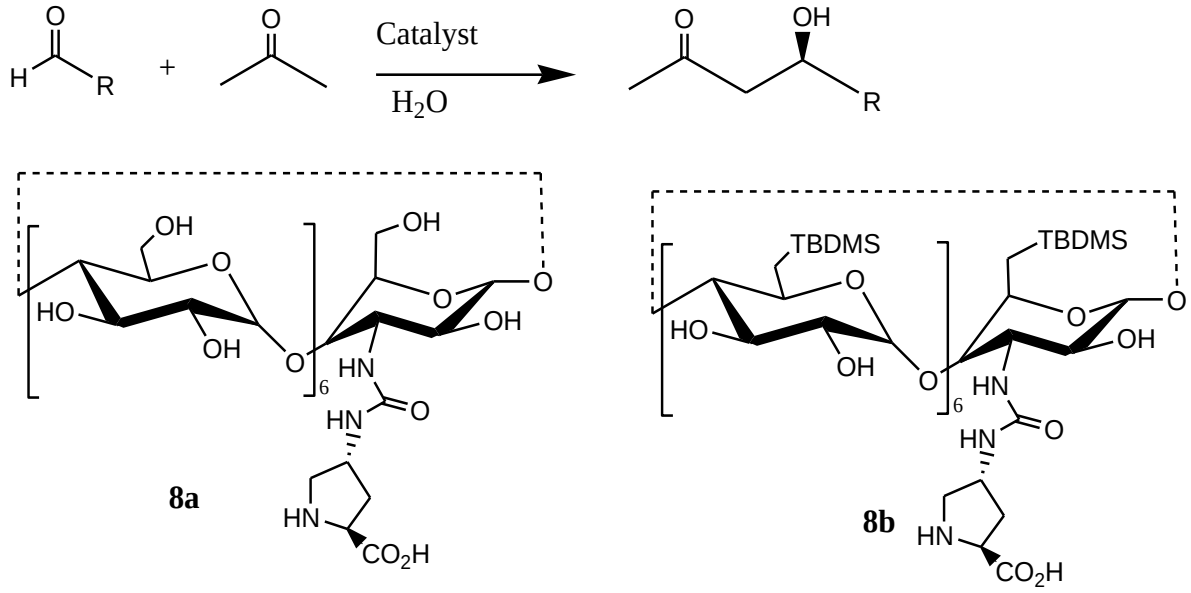


Fig-7

Various aromatic aldehydes and aliphatic aldehydes were studied for the above reaction and the aldol adducts were isolated having good yields (nearly 40–91%) and good enantiomeric excess (nearly 48–86% ee). **[7]**

Kegang Liu and his co-workers worked on proline derivatives as a catalyst during Aldol reaction. They used proline derived beta-cyclo dextrin conjugate covalently linked by a urea spacer. It was used as a water-soluble, effective catalyst for highly enantioselective aldol reactions between aldehydes and acetone in aqueous media. He compared the catalyst by changing the 'R' groups (Fig-8). Studies found that when R=H was tested with different solvents, it gave more enantioselectivity.



Beta-cyclodextrin-proline catalyst linked through urea

Fig-8

The results showed that the electron withdrawing group in the para position of benzaldehydes furnished the corresponding Aldol adducts in high yields. Even if the halogenated 4-fluorobenzaldehye and 4-chlorobenzaldehyde resulted in low yields but the eantiomeric excess varied from 77% to 82%.The stereoselectivities of electron rich derivatives of benzaldehyde was high because of their higher binding ability. High yield and enantioselectivity was also found in unbranched aliphatic aldehydes but the branched and bulky aldehydes were least reactive substrate for the given reaction. **[8]**

Tumma Naresh and his co-workers worked on two new pyrrolidine derivatives azidothymidine (AZT)-prolinamide 9a and 9b (Fig-12). The reaction had very slight variation in reaction time , yield and selectivity when there was change in slovent system. The reactions with catalyst 9a were found to be better than those catalyzed by 9b (Fig-9).

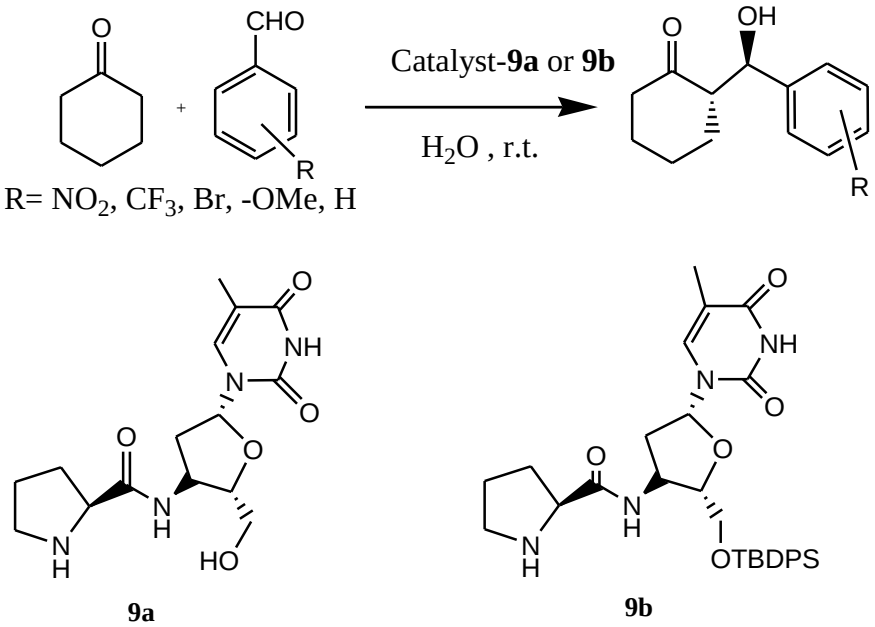


Fig-9

The presence of electron withdrawing group in the ring gave better results than electron donating groups attached to the ring. Like nitro group attached to the ring gave 81% yield and 91% ee with catalyst-9a whereas attachment of methoxy group to the ring gave 77% yield and 75% ee with catalyst-1. **[9]**

Togapur Pavan Kumar and his co-workers did further research on prolinamides. They did direct Aldol reaction between cyclohexanone and p-nitrobenzaldehyde which proceeded well in all solvents giving products having high yields and selectivities (Fig-10).

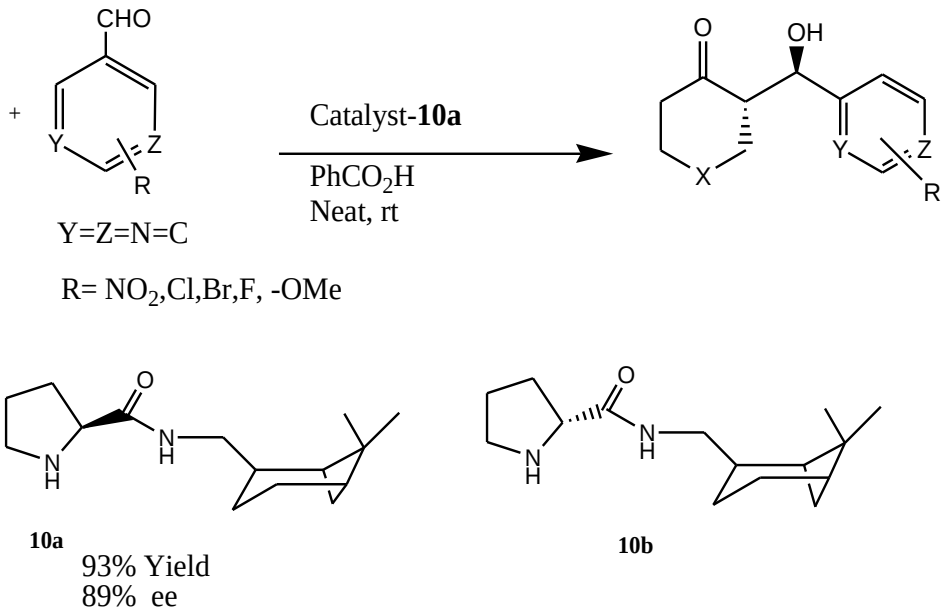


Fig-10

Their results showed that the reaction proceeded at room temperature with 20 mol % of catalyst 10a and 5 mol % of benzoic acid in a solvent free medium leading to the product having 94% yield (95:5 anti/syn) and 93% enantiomeric excess. **[10]**

Pascuala Vizcaíno-Milla and his co-scientist used recoverable Pyrimidine-derived Prolinamides as a bifunctional organocatalysts for enantioselective Aldol reactions having no slovent. They studied the two catalyst 11a and 11b (Fig-11). It was found that catalyst 11b was more productive than 11a. The recovery of catalyst 11b was done by carrying out 1g scale reaction between cyclohexanone of 4-nitrobenzaldehyde. The reaction took place in 36 h with 51:1diastereotopic ratio; 83% yield of pure anti-aldol was obtained after recrystallization and anti-product was obtained with 95 % enantiomeric excess. After workup, the yield of the recovered catalyst 87 %. While the reaction was completed there were different observations. Cyclohexanone reacted with aromatic aldehydes forming corresponding anti aldols in good yields (up to 56–94 %), good diastereoselectivities (90:10 to 96:4) and good enantioselectivities (99 %). Whereas cyclopentanone reacted with p-nitrobenzaldehyde to give mainly syn-aldol under prolinamide. Catalysis gave 91% and 30% ee for anti and syn product respectively. **[11]**

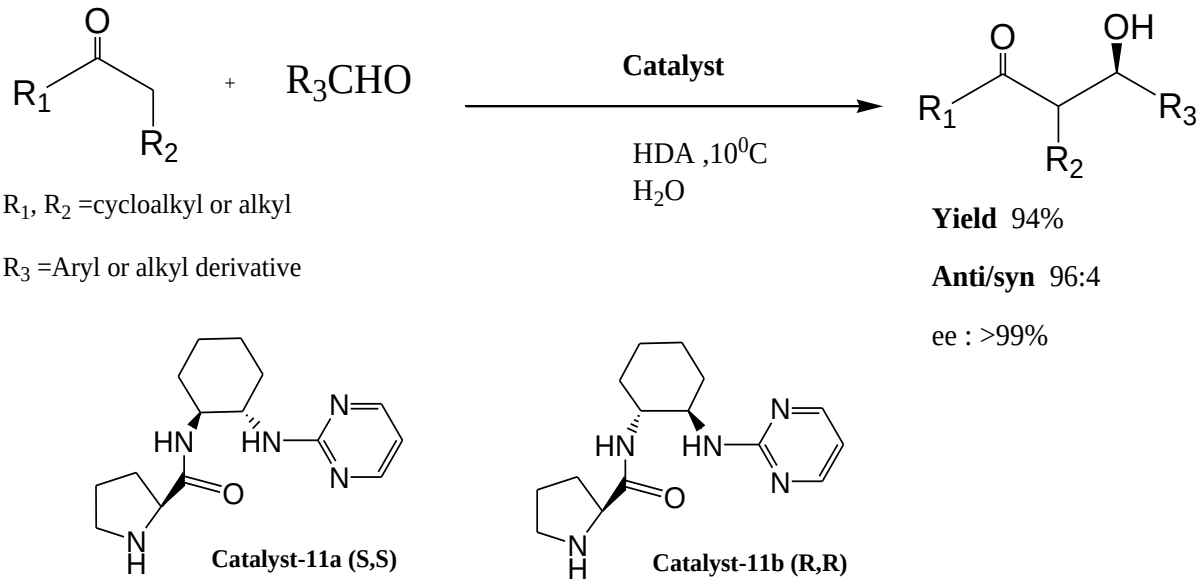


Fig-11

Liu Hua and his co-workers did extensive work on asymmetric Aldol reactions. They worked basically on 2, 2, 2-trifluoro-1-phenylethanone. The trifluoromethyl group, due to its electron-withdrawing nature, increased the positive charge density on the carbonyl carbon thereby increasing the reactivity in proline catalyzed intermolecular aldol reaction (Fig-12).

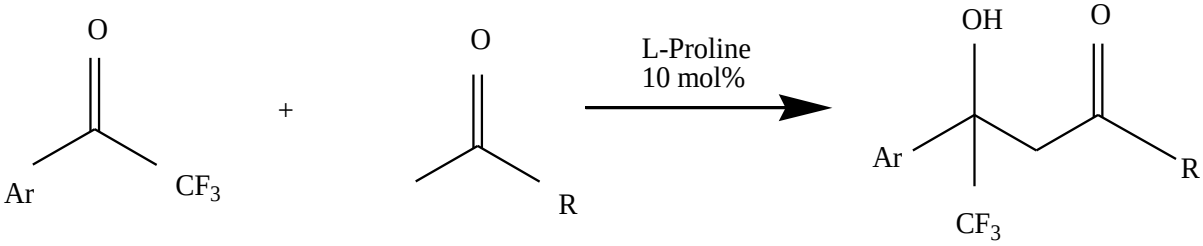


Fig-12

The reaction proceeded with acetone and 2,2,2-trifluoro-1-phenylethanone at room temperature. After 4 hours the aldol product was formed and giving quantitative yield with 49% ee. When the same reaction proceeded in -20 degrees with increase of ee% to 64%. Also when R was replaced by $–CH_3CH_2$ group and

Ar was replaced by p-ClC_6H_4 then the ee% decreased to 3.4% at room temperature. **[12]**

Demetrios D. Chronopoulos and few other scientsts did aldol reaction based on Fullerene–proline hybrids. There was study of three different $C_{60\ proline}$ catalyst giving its various characterizations. It was observed that using C_{60}–proline organocatalyst 13b during the Aldol reaction gave aldol product with higher enantioselectivity than reference organocatalyst 13c (Fig-13). When C_{60}–proline 13a was used as the organocatalyst there was moderate enantioselectivity.

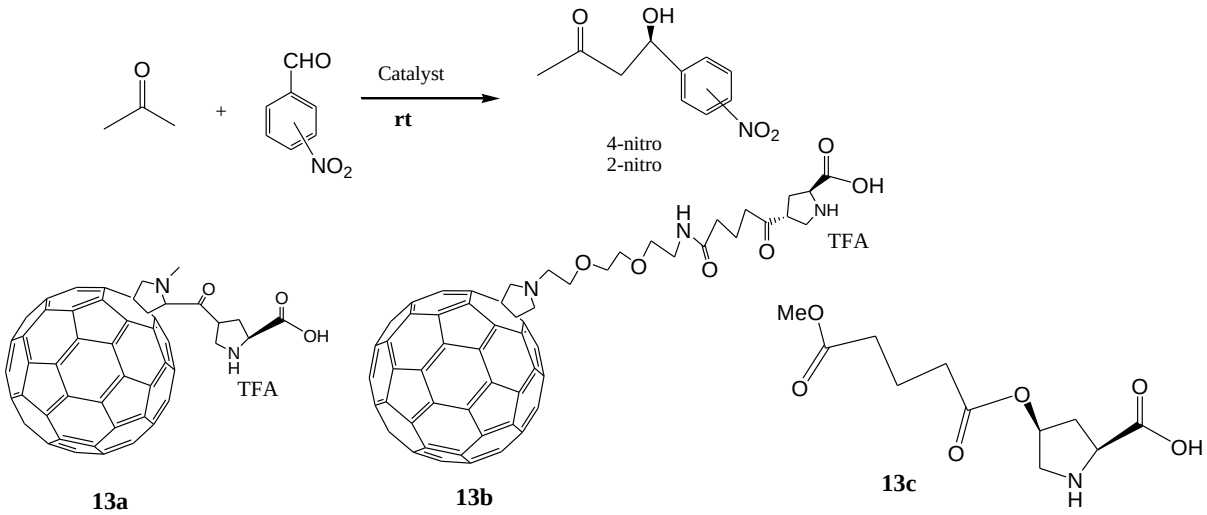


Fig-13

This was because the latter had steric hindrance by the proline unit which was in closer to the fullerene sphere, thus, preventing to catalyze the reaction with high enantioselectivity. Moreover, there was significant rate acceleration (2 h instead of 42 h) of the Aldol reaction in aqueous medium. Their main focus was to increase the yield of Aldol product in presence of DMSO and enhancing the enantioselectivity in water. **[13]**

Haydee Rojas Cabrera and co-workers reported a homochiral L-prolinamido-sulfonamides as organocatalysts which was used in aldol reactions. Organocatalysts 1–7(Fig-14) were prepared from enantiomerically pure (R, R)-11, 12-diamino-9, 10-dihydro-9, 10-ethanoanthracene. They evaluate based on the optimization process of organocatalysts 14a-14i (10 mol %) in a solution of

dichloromethane, acetic acid (20 mol %) and H_2O (1.0 equivalent) (Fig-14). The Aldol reaction resulted in high yields (92-97%) and good enantioselectivities (84–90%). They made an observation that different substituents did not have much effect on the organocatalysts. Organocatalyst-14d gave highest catalytic effect where maximum yield of 97% along with enantioselectivity of 90%ee were observed. The minimum ee of 84% with maximum yield 97% were recorded in case of catalyst-14e, which bearing bulkier and electron rich group, (tri (iso) propyl) phenyl. **[14]**

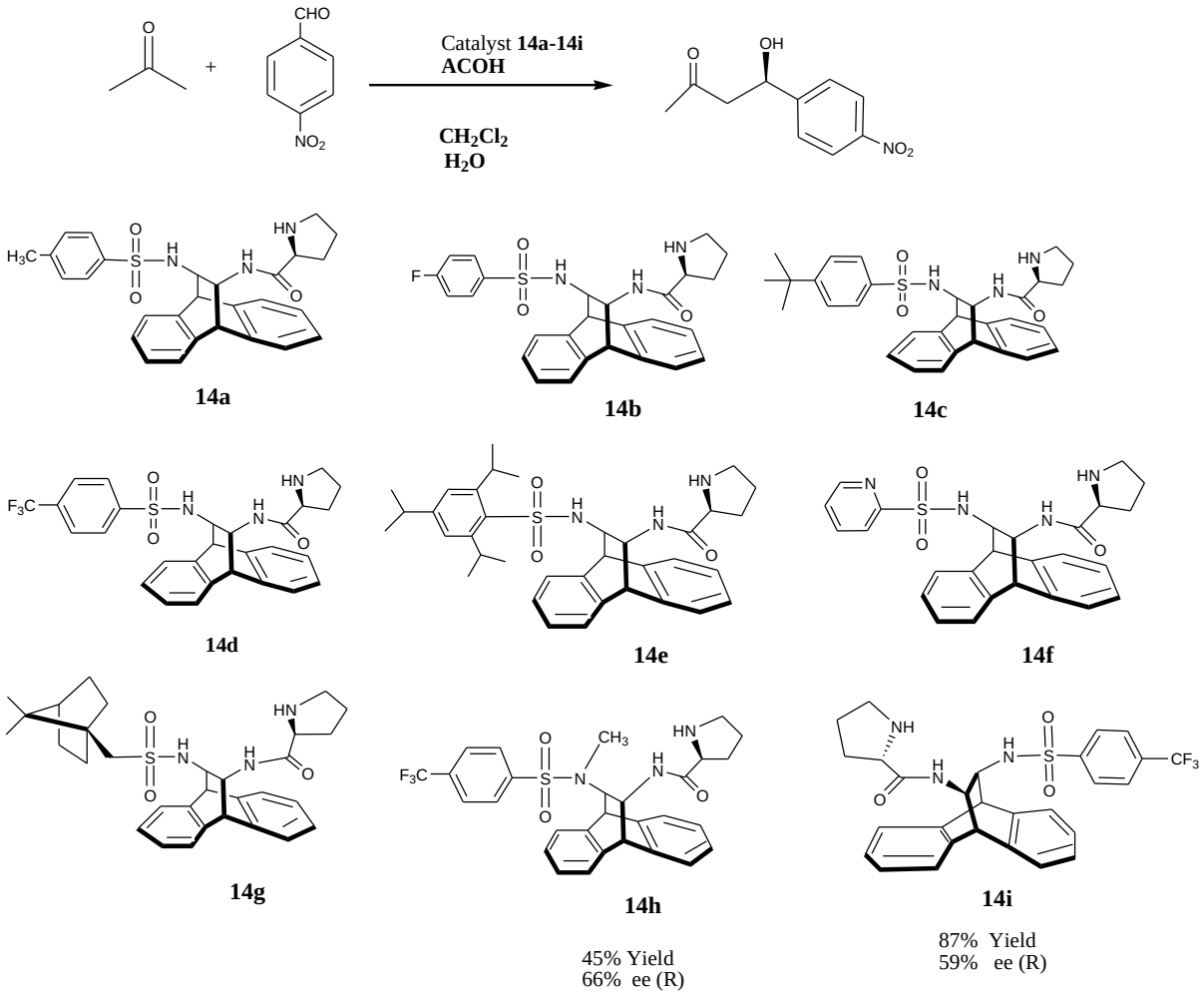


Fig-14

LIU Ling and his co-workers worked on L-Proline catalyzed Aldol reactions between acetone and aldehydes using supercritical fluids (Fig-15).

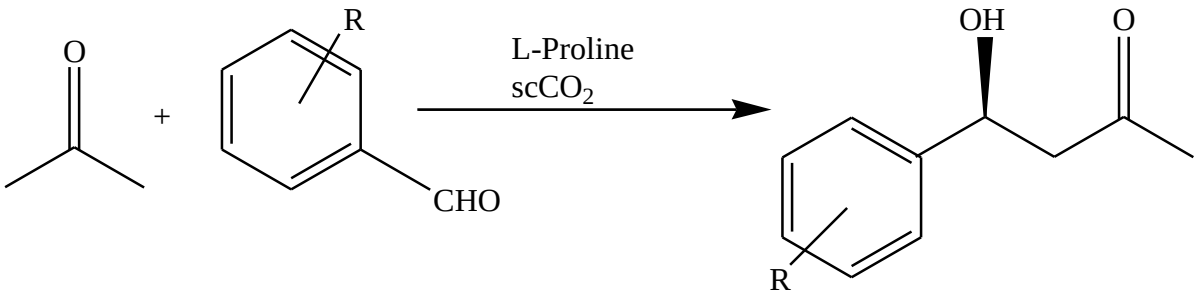


Fig: 15

Their experiment resulted with aldol product having 84% enantioselectivity. Also the process did not use the high-boiling-point polar solvents like DMSO. Even the reaction showed efficiency with 15 mol% catalyst. Their results illustrated tha the high- pressure technique was an effective way to promote the above type of asymmetric catalysis. **[15]**

OBJECTIVE

The literature survey has revealed that the proline and its derivatives proved to be the potent organocatalysts for carrying out various synthetic transformation. But derivatives which imparts better yield suffer with fair control on the stereoselectivity and the catalysts having better control on the stereochemical output suffer with the lesser yield. Therefore, there is still a need to develop new prolinamide derivatives which can give greater stereochemical control over the reaction with desired yield.

The objectives of the present work are as follows.

1. To synthesize L-proline derivatives from commercially available L-Proline and amine via multiple step synthesis, by varying the amide moiety.
2. Characterization of synthesized L-prolinamide derivatives by using various spectroscopic techniques like IR, NMR etc.
3. To study the effect of L-Prolinamide derivatives on rate of reaction of aldol reaction between acetone and P-nitrobenzaldehyde.
4. To study the effect of L-prolinamide derivatives on stereochemical output of Aldol reaction.

PLAN OF WORK

Stage-1: Synthesis of Prolinamide derivatives

In the first stage, commercially available L-proline will be protected as L-Boc – proline under basic conditions at nitrogen end to make carboxylic end available for its participation for amide coupling by using different amines via DCC coupling. Once the desired amide formation takes place, the final stage will be the deprotection of the BOC under acidic conditions to get the desired prolinamide derivatives as potential organocatalysts (Fig-16).

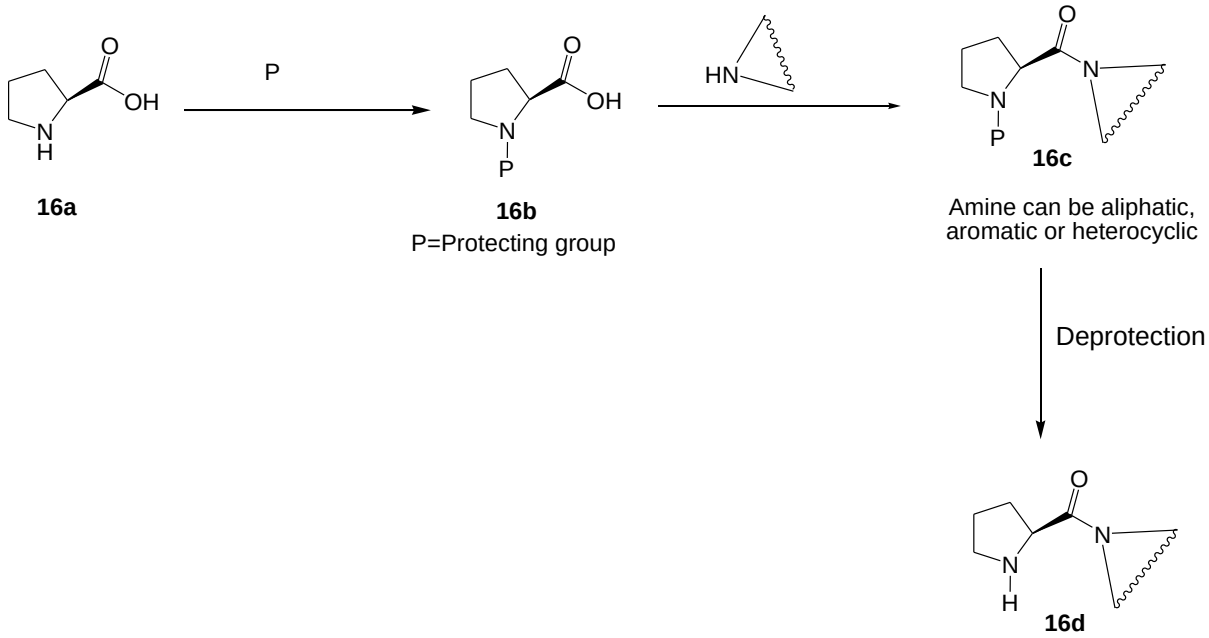


Fig-16

Stage-2: Characterization of the synthesized prolinamide derivatives

The prolinamide derivatives synthesized in stage-1 will be subjected to different spectroscopic tecgniques like 1H-NMR, IR etc for their structure elucidation.

Stage-3: Study of Aldol reaction of acetone and p-nitrobenzaldehyde in the presence of synthesized prolinamide derivative

The synthesized prolinamide derivatives will be studied for their effect on of Aldol reaction between p-nitrobenzaldehyde and acetone in terms of rate of reaction and stereochemical output (Fig-17).

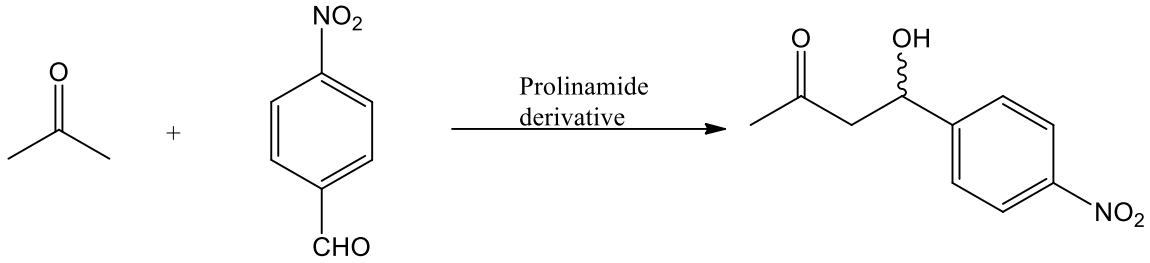


Fig-17

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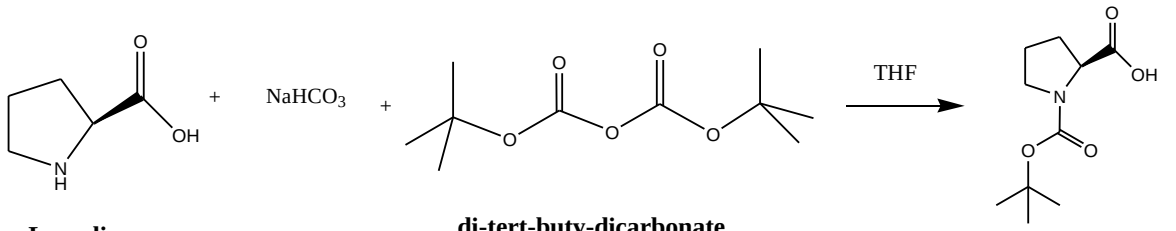
Stage-1: Synthesis of prolinamide derivatives

Step-1: Protection of L-Proline



L-proline **di-tert-buty-dicarbonate** **BOC-L-proline**

Fig- 18

Procedure-

1 g (0.008mol) of L-proline was dissolved in the mixture of 10 ml of water and 40 ml of THF at 30^{o}C. 0.803g of sodium bicarbonate (1.1 mol) was added to reaction mass after 5 minutes and the reaction mass was stirred for 10 minutes. 2.08g (1.1mol) of BOC anhydride was added to reaction mass and the solution was stirred for 8 hours. The progress of the reaction was monitored by TLC in 9:1 DCM:MeOH mixture. After the reaction was complete, pH of the reaction mass was maintained at 5-6 with the help of 10% citric acid solution. Added 100ml of ethyl acetate and stirred the reaction mass for 10 minutes. The ethyl

acetate layer was separated and distilled under reduced pressure at 55-60^{o}C to isolate crude L-BOC-Proline as white solid.

Results:

TLC-

TLC-1: For BOC-Proline

Distance travelled by solvent= 5.8 cm

Distance travelled by reactant= 2.4cm

Distance travelled by reaction mass= 4.6cm

Rf for reactant= 0.428

Rf for product= 0.793

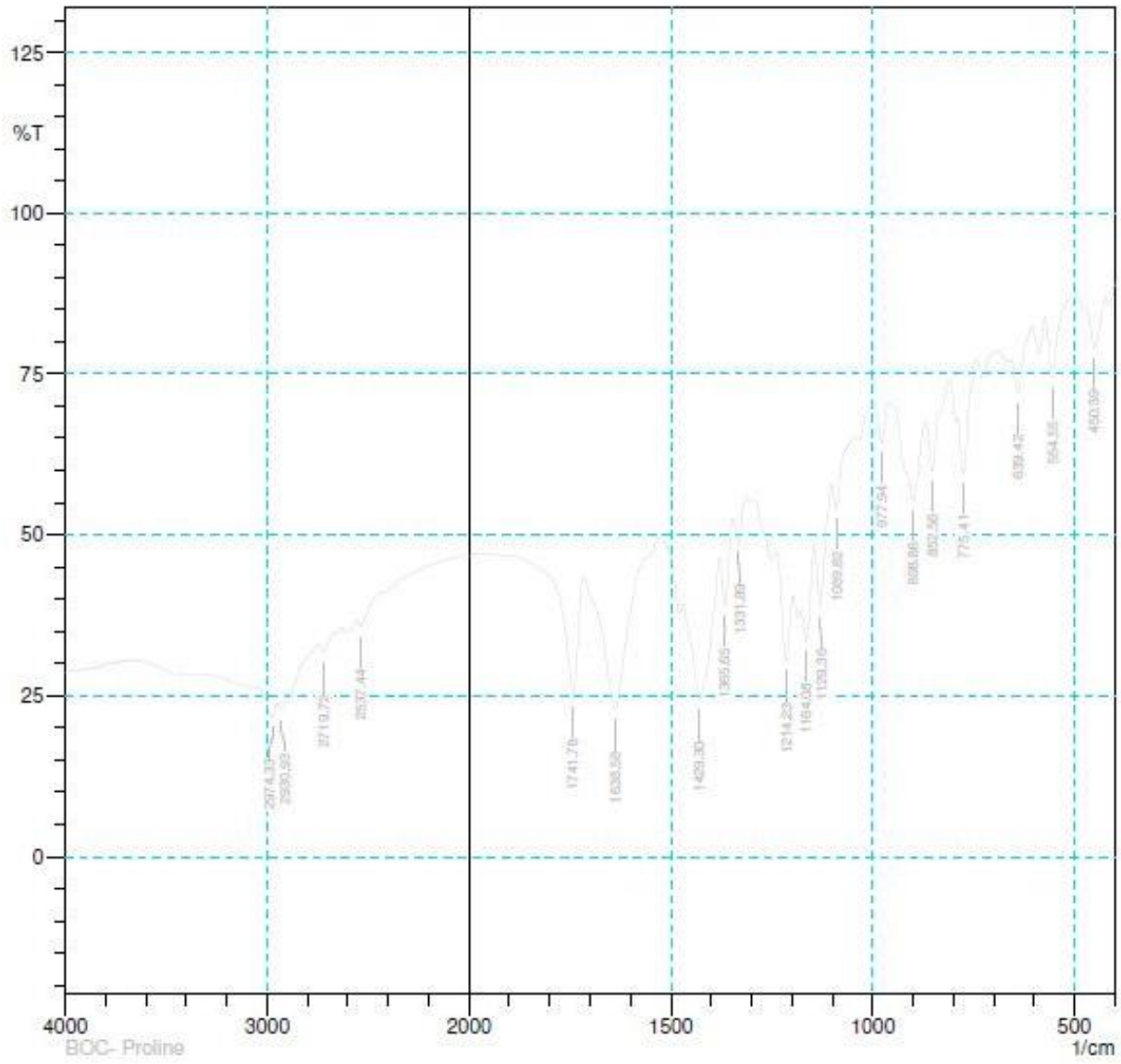
Experimental Yield = 1.56g

Theoretical Yield = 1.86g

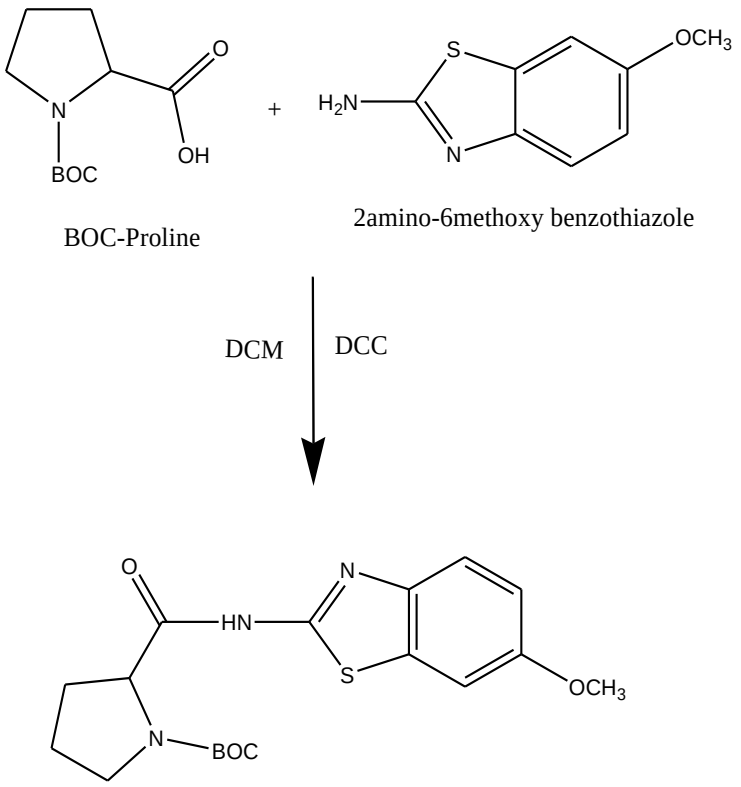
Percentage Yield =75%

Melting point= 137^{0}C

Characteristic IR peaks (cm^{-1}, KBr): ν(C=O acid) 1741, ν(C=O amide) 1638, ν (C-O-) 1164, 1129



Step-2: Synthesis of BOC-proline derivative



BOC-Proline

2amino-6methoxy benzothiazole

Fig-18

Procedure:

A mixture of 0.500g BOC L-Proline and 0.376g (0.9mol equivalent) 2-amino-6methoxy benzothiazole in0.479mL (1.2mol equivalent) DiPEA was dissolved in 10mL DCM. The reaction was stirred for 5minutes. Simultaneously a solution of 0.527g (1.1mol equivalent) DCC and 10mL of DCM was prepared. This solution was added to the first solution dropwise (in 30-40minutes). The reaction was stirred for 4-5hours. The progress of the reaction was monitored by TLC in 5:5 Hexane: ethylacetate mixture. When the reaction was complete, workup was done.20mL DCM and 10mL H_2O was added to the reaction mixture and stirred for 10minutes.Lower layer of DCM was taken and 10% $NaHCO_3$ was added. Again it was stirred and the lower layer of DCM was taken and treated with 5% acetic acid. The lower layer was separated and given a wash with 10mL H_2O. Then the solvent was removed by rotavapor and brownish solid of the required product was left behind.

Results:

TLC-

TLC-2: For BOC-L-Proline derivative

Distance travelled by solvent= 5.6 cm

Distance travelled by reactant= 3.4cm

Distance travelled by reaction mass=0.9 cm

Rf for reactant= 0.642

Rf for product= 0.16

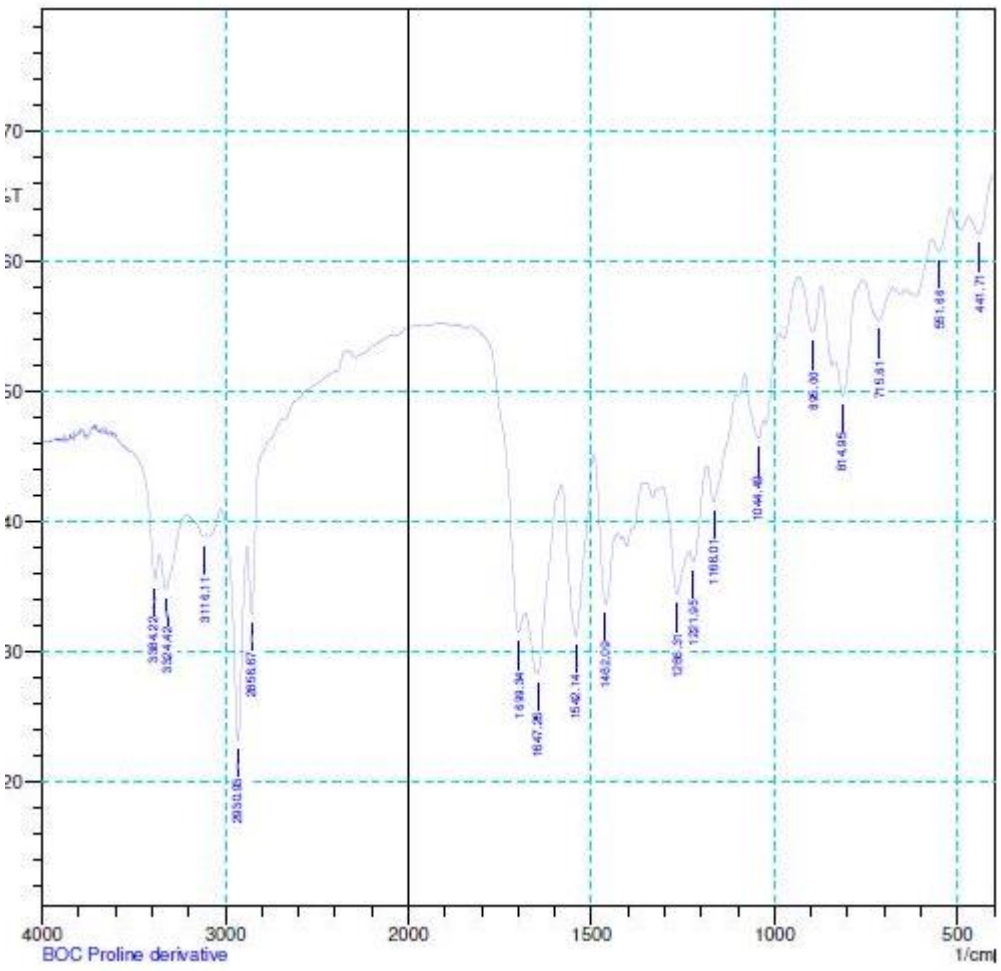
Experimental Yield = 0.35g

Theoretical Yield = 0.787g

Percentage Yield =44%

Characteristic IR peaks (cm^{-1}, KBr): ν (O-H stretching) 3364, ν(C=O amide) 1699, ν(C=O acid) 1647, ν (C-O-) 1166, ν (C=C stretching) 1647

From the characteristic peak of C=O of amide and acid we can conclude that the required product was obtained.



Stage-2: Optimization of reaction condition for Aldol reaction

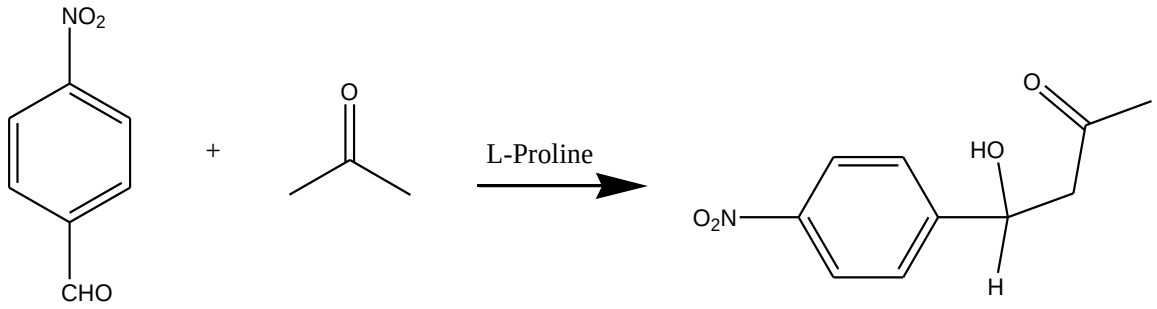


Fig-19

Procedure:

Prepare two mixtures containing 10mL acetone, 500mg 4-nitrobenzaldehyde and 10mg L-Proline. Stir the mixture. In one of the reaction mass add 1mL H_2O and in other mixture add 2ml H_2O. It was observed that the mixture having 1mL took nearly 10hrs for completion whereas the 2mL took 6hrs for completion.

Therefore, the reaction mass having 2mL of water was considered to be optimized reaction.

TLC-

TLC-3: For addition of 1mL in Aldol reaction

Distance travelled by solvent= 2.8 cm

Distance travelled by reactant= 2.4cm

Distance travelled by reaction mass= 1.6cm

Rf for reactant= 0.92

Rf for product= 0.57

TLC 4: For addition of 2mL in Aldol reaction

Distance travelled by solvent= 5.2cm

Distance travelled by reactant= 4.5cm

Distance travelled by reaction mass= 2.4cm

Rf for reactant= 0.865

Rf for product= 0.461

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