# Modern Synthetic Tool L-Proline as an Organocatalyst

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**ABSTRACT**

*Organocatalysis is going to be an art in Synthetic Green Chemistry and Synthesis manly stated to be used for accelerating the rate of chemical reaction with a substoichiometric amount of an organic compounds which does not contain a metal atom [1,2]. It has developed into a practical synthetic paradigm. The area of as a L-Proline organocatalysis has been one of the most dynamic and rapidly growing fields in organic synthesis over the last decade, largely due to its great potential for realizing highly complex, effective , selective asymmetric transformations and amine derivatives also used for various reactions such as asymmetric Aldol condensation , asymmetric Michael reaction, organocatalytic H activation, asymmetric anti 1,2 diol, epoxide formation, transamination, Mannich reactions, asymmetric α- hydroxyamination, polymerization, One pot Multi-component reactions and in synthesis of some class of flavanoid molecules. This review article provides update information on recent reports and explains usefulness of L-Proline organocatalysis and its efficiency for this approach and scope. The data on the methods of synthesis, chemical reactions, and work on this in various publications over the last decade are reviewed here.*

**Keywords:** Organocatalysis, Heterogenous catalysis; Asymmetric aldol condensation, Transamination, L-Proline.

## INTRODUCTION

In organic synthesis when small organic molecules are used as catalyst then the reaction is said to be organocatalysis. It is a relatively modern field within the province of chiral catalyst for synthesis. Organocatalysts have been documented at irregular intervals over the past 20 years, which was seen from the early age of synthetic chemistry. Indeed, the credits the discovery of first organocatalytic reaction goes to J. Von Liebig, who found accidently the transformation of dicyan onto oxamide in the presence of aqueous solution of acetaldehyde [3]**.** In the resent ten years it was widely accepted that Organocatalysis to be a modern synthetic tool in their catalysis toolbox. It was Bredig and Fiske who first reported examples of an asymmetric Organocatalysis by almost 100 years ago using yeast shown in **scheme-1**[4]. In the observation their used catalytic amount of the enantiopure cinchona alkaloids, quinidines or quinines, which facilitated the addition of HCN to benzaldehyde and finally gave an enantio selective enriched reaction product.



**Scheme-1: Yeast catalyzed**
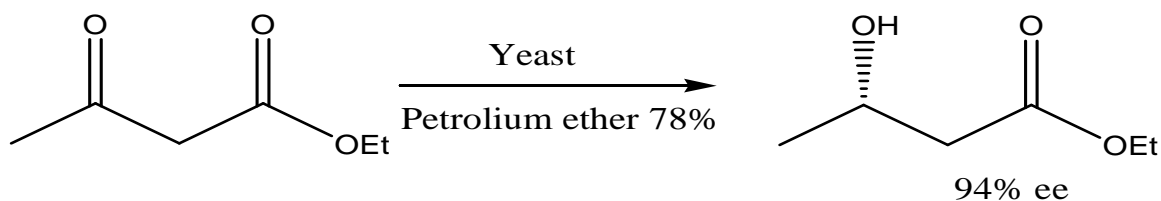
In last ten years, the organocatalytic mediated asymmetric Michael type reaction have emerged as one of the important C-C bond forming reactions in organic synthesis.[5] This synthetic chemistry covers the nitro and keto grous[6-7]development of efficient amine-based catalysts of thioureas, primary,[8] and secondary,[9] which improve the selectivity[10] and also the importance of multifunctional chiral organocatalysts [11-12].

The advent of Organocatalysis brought the prospect of a complementary mode of catalysis with the potential for saving in cost, time and energy, an easier experimental procedures, and reduction in chemical waste [12].

**Advantages**
The advantage of organocatalysis over metal catalysis is that organocatalysts easily form Lewis acids thus, organic catalysts are more prominent to form heteroatom-cantered Lewis bases and the most studied catalysts based on Nitrogen and Phosphorus forms, with amine catalysts being more easily available than their phosphorus-containing counterparts, mainly due to the natural abundance. P-containing chiral is not available in nature but the substrate is being used for catalytic, and consequently all of these catalysts are synthesized in laboratory[13].Organocatalysis is an important area of research in recent decade because it provides a strong tool for catalyzing reactions in the absence of transition metals and a way to mimic nature in the enzyme catalysis. Many organocatalysts are simple small and large organic molecules that is important for excellent selectivity in asymmetric reactions, give good yield and easy to work up. Organocatalysts have several advantages. They are usually reused, recycled in mechanism, inexpensive, readily available and non-toxic for nature [14-17] Many organocatalysts are inert towards moisture and oxygen, this advantage gives its importance for such demanding reaction conditions over inert atmosphere, low temperature, absolute solvents etc. are in many instances, not required and it can be used in pharmaceuticals [18-19]also. These catalysts activate both the donor and acceptor because of their bifunctional nature to have commonly a Lewis base and Bronsted acid center [20-21].

**Asymmetric Catalysis**
The current wave of interest in organocatalysis however, is centered on asymmetric catalysis. Even that development is older than most of us recognize as exemplified by Hajos-Parrish reaction using L-Proline for asymmetric aldol condensations that was first reported in 1970′s. In the past decade there is appraisable growth which has been seen regarding these types of research [22].

**Scope and Importance**
The organocatalyst chemistry is popular due to its versatility for synthetic importance. This Chemistry includes different types of catalysts. Some of them are chiral( L-Proline )showing Symmetric and Asymmetric synthesis and contains NHC catalyst[23], Thiamine Hydrochloride[24] , Guanidine Hydrochloride[25]Urea, Thio(urea)[26]and its derivatives and some  other organic Molecules which are involved in this type of synthesis.

**Applications of Organcatalysts**
In era of green chemistry were dimension of everything is going to be environment friendly with their improved property. The catalysts as organic molecule with basic nature are also used in several chemical processes and valuable for society. In this paper we have collected all literature information on application of organocatalysts reported in the last decade.

**L-Proline**
B. List and coworkers have reported the first example of the asymmetric Mannich reaction using L-proline in year 2000 and its function as an organocatalyst.[27] eg. When  acetone (excess), *p*-nitrobenzaldehyde, and *p*-anisidine are treated with  L-proline (35 mol%) gave the targeted adduct in 50% yield with 94% ee nature of product as shown in scheme 1. The B. List and W. Notz have developed the simple *anti* 1,2 diol reaction[28] as shown in reaction scheme 2.
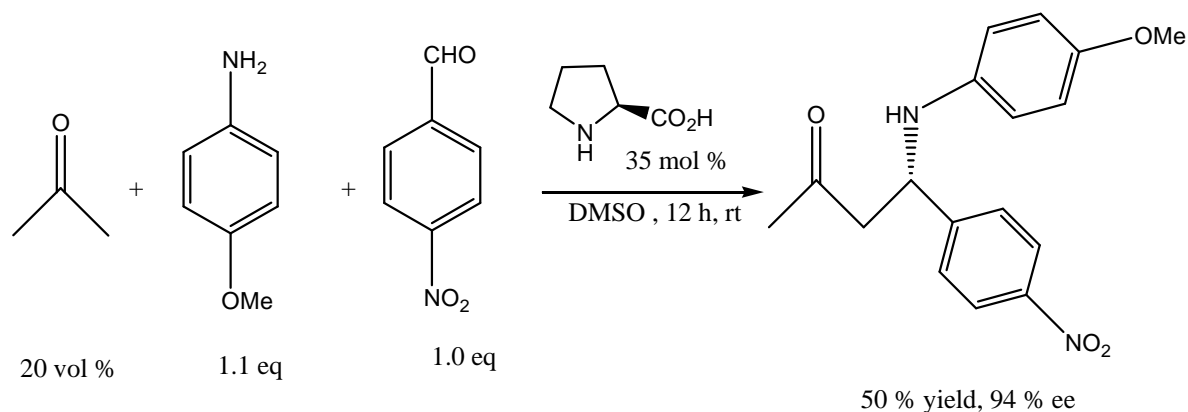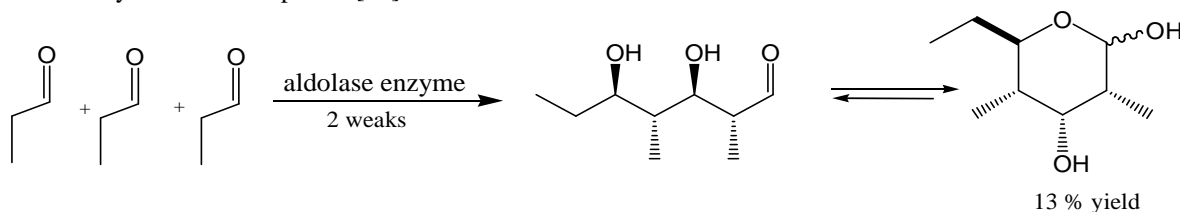
**Scheme 2: Asymmetric Mannich reactions catalyzed by L-Proline**
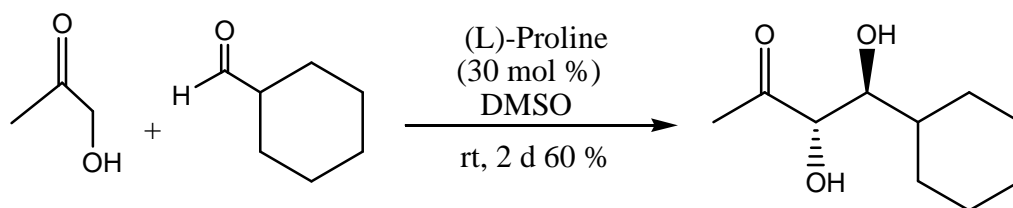


**Scheme 3 : Asymmetric Diol Formation**

The L-Proline is very versatile reagent for Asymmetric Synthesis in Organic Chemistry and using such type of nature of L-proline we can perform self aldol condensation reactions.
Increase in yields is also reported [29].



**Scheme 4. Aldolase-catalyzed self-aldolization of propionaldehyde**

The reaction shown in scheme 3 is an simple enzymatic reaction but when it is performed with L-Proline then it goes fast with moderate yield[30].
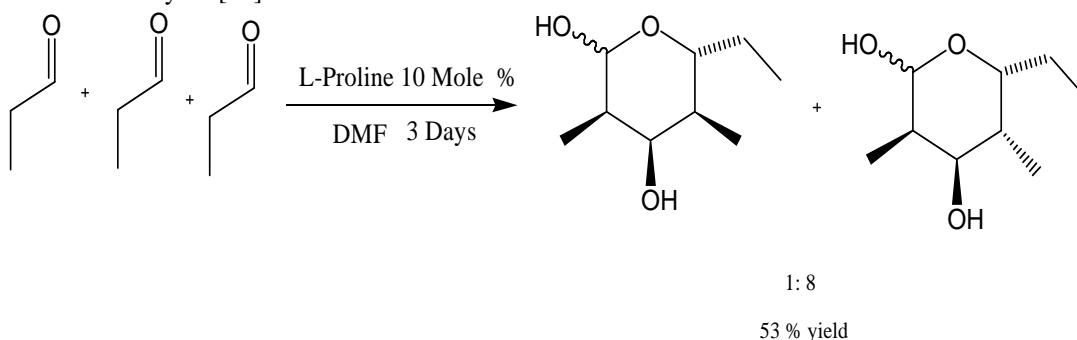


**Scheme 5:. Proline-catalyzed self-aldolization reaction of propionaldehyde**

The product of scheme-5 showed Pyranoses four asymmetric centers when catalyzed under proline catalysis which is excellent diastereoselectivity catalyst and enantioselectivity (47% ee) from three aldehyde molecules. The identity of each aldehyde component can potentially be freely varied providing access to a wide range of molecules. Above method is a simple one-pot procedure giving direct access to carbohydrates and polyketides that are traditionally prepared by using multi-step reaction procedures.

Scheme-6a showed α- hydroxyaldehydes are optically active and very important in intermediates for organic synthesis. Thus, many methods are recently developed for this utility and their preparation[31, 32] for fast,

transformation from chiral natural sources. eg. amino acids, sugars, and chiral α- hydroxy acids. Such a need arises for development of direct catalytic enantioselective α- aminooxylation of aldehydes using nitrosobenzene and L-proline as catalyst[33].
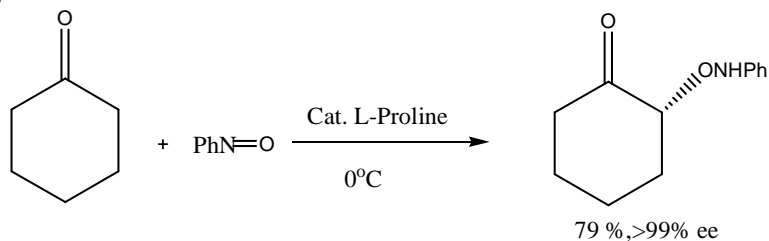


**Scheme 6 a. Direct asymmetric α-aminooxylation of cyclohexanone**

Due to L-proline as catalyst and nitroso benzene as oxidant the above reaction was carried at low temperature. In this reaction the side reaction and dimer formation of nitroso benzene as well as aldol reactions is suppressed [34].

The small organic molecule can perform a better organocatalytic reactions thus, L-proline also plays important role in aldol intramolecular condensation and also asymmetric α-hydroxyamination of α-branched Aldehydes[35].The reaction is aqueous aldol condensation in which acetone reacts with 4-nitrobenzaldehyde in absence of surface active agent. The reaction is carried by mixing acetone (20 mmol), 4-nitrobenzaldehyde (4 mmol) and L-proline (0.16 mmol, 40 mol%) in pure water (15 ml). The reaction was kept for five days at 40°C, the anticipated aldol product was obtained with yield up to 15%. Hence need raised to increase the yield of product.
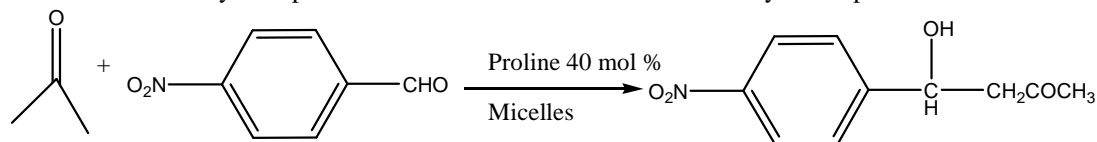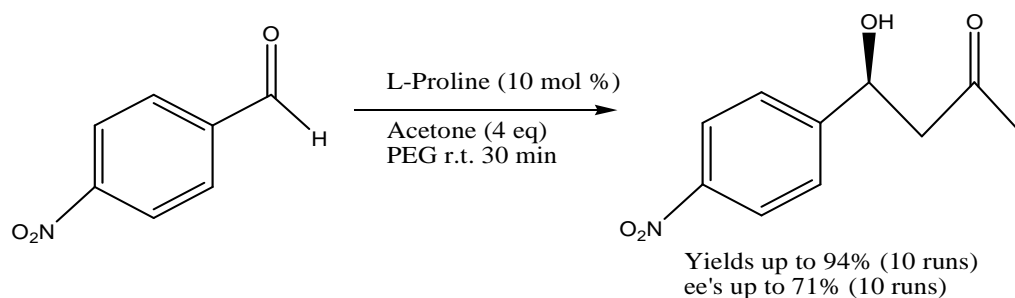


**Scheme 6b**

In this modification anionic surface active agent sodium dodecyl sulfate (20 mol% SDS), was added in the reaction, which gave 87% yield of aldol condensation product, only in 24 hr this yield is comparatively higher than that of the corresponding reaction which was performed in organic solvents (68 %) scheme :6c**.**
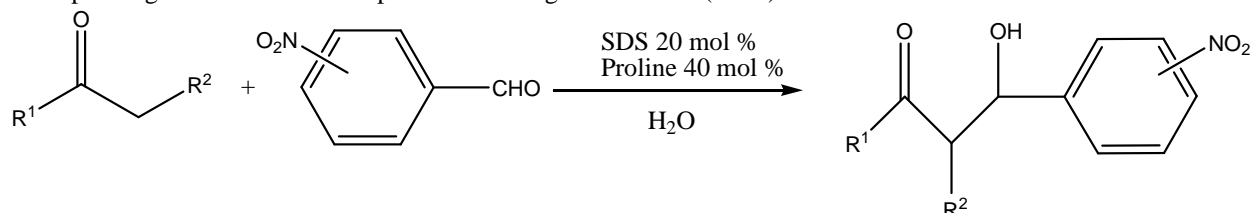


**Scheme 6c: Aldol reactions of ketones with nitrobenzaldehydes in SDS micelle**

In the above reaction it was found that only the pyrrolidine ring (in L-proline) was useful in micelles and the carboxylic acid group (in L-proline) did not take part in reaction mechanism. The L-proline methyl ester and L-hydroxyproline can catalyze the same aldol reaction micelles, giving the aldol product with yields 82 and 70%, respectively when acetone reacts with P-Nitro benzaldehyde in above mentioned conditions. The L-amino and some D-amino acids are also used as catalyst but product was obtained in trace amount. The above results show that the reaction mechanism in micelle may be different from that in organic solvents. On this basis, an amine catalyzed mechanism is proposed for the aldol reaction in micelles [35].

The S. Chandrasekhar *et al* performed the Asymmetric aldol reaction in poly(ethylene glycol) L-proline as catalyst. It is a rapid and direct aldol reaction. L-proline catalyzed the PEG as solvent with comparable enantioselectivitie product. It was achieved by reacting various aldehydes and acetone. One can include most powerful C-C bond formation by the asymmetric aldol reaction of an aldehyde and a modified or unmodified ketones[36]. Since some amide derivatives of L-Proline can also be used for aldol condensation [37, 38] (scheme :7).

**Scheme 7 : L-Proline catalyzed asymmetric aldol reactions in PEG**

The efficiency of the conversion of product was examined by subjecting various aldehydes to an aldol reaction in poly(ethylene glycol). All the examples studied gave similar results to those reported using conventional solvents and other methods (The 2- and 3-nitrobenzaldehydes). In   L-proline catalyzed asymmetric aldol reactions by using poly(ethylene glycol) as recyclable solvent,  it runs 10  time faster without loss of activity of either the catalyst or solvent[39].

The another type of enantioselective direct intermolecular aldol reactions [39] by using L-proline catalyzed reactions of tetrahydro-4*H*-thiopyran-4-one with  different types of aldehydes. The reaction which is directed aldol reaction [40] has performed enol(ate) derivatives with various aldehydes is among the most powerful and useful methods for stereochemically controlled C-C bond formation[41-42].

The tetrahydro-4H-thiopyranone under goes aldol reactions with different types of Aldehydes which are catalyzed by proline effectively.  The wet DMF or DMSO gave the anti adducts in excellent enantioselectivity good yield as well. By performing desulfurization of these adducts they converted to products having applications in polypropionate synthesis [43].

**C-C bond Forming Reactions**
The higher reactivity and diastereoselectivity were found by sequential investigation of two-directional aldol reactions of tetrahydro-4H-thiopyranone in the context of a thiopyran-based
synthetic path way to polypropionates[44, 45].
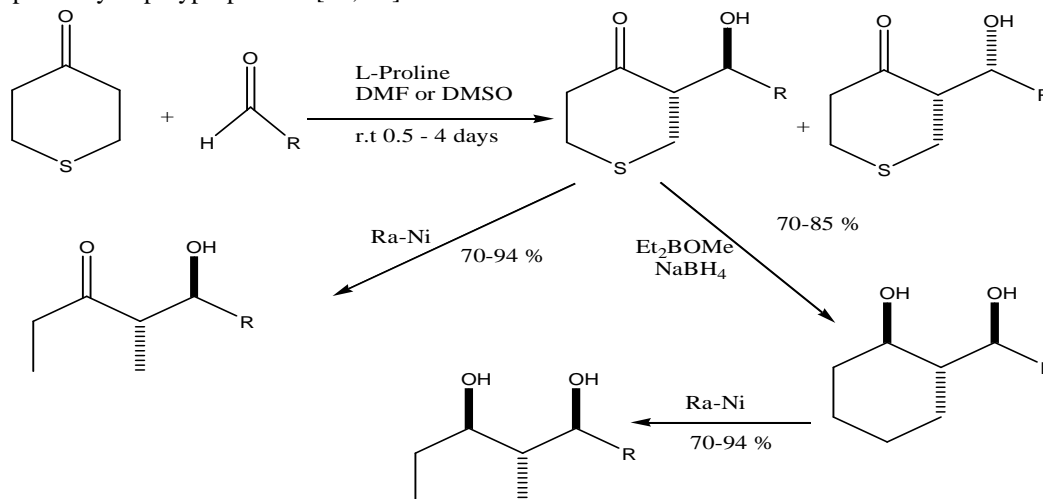


**Scheme 8: Proline-catalyzed aldol reactions**

The desulfurization of enantioenriched aldol products was achieved by using Raney Ni and the relation of syn–anti isomerization were studied. The aldols and their derivatives are useful in polypropionate synthesis and are of commercial importance.

**Flavanoid Class**
The research activity in the flavanoid[46] class of molecules is important due to their excellent biological activities. The new synthetic method development for the synthesis of substituted flavanones[47] and chalcones[48] was catalyzed by L-proline.[ 49].
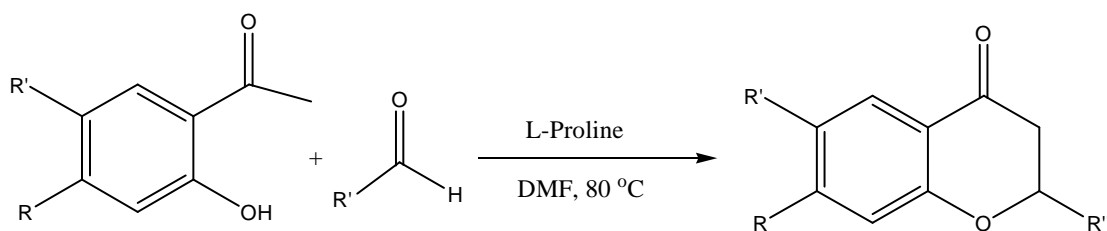
**Scheme 9: L-Proline catalyzed synthesis of flavanones**

**Spiroflavanone**

Another type of flavanones is spiroflavanones. They were synthesized from ketones and substituted 2-hydroxyacetophenones using L-proline (30 mol %) as catalyst in solvent DMF. The isolation is done in case of aldehydes, mixtures of flavanones and chalcones with ease. The exclusive products are ketones spirocyclic flavanones.
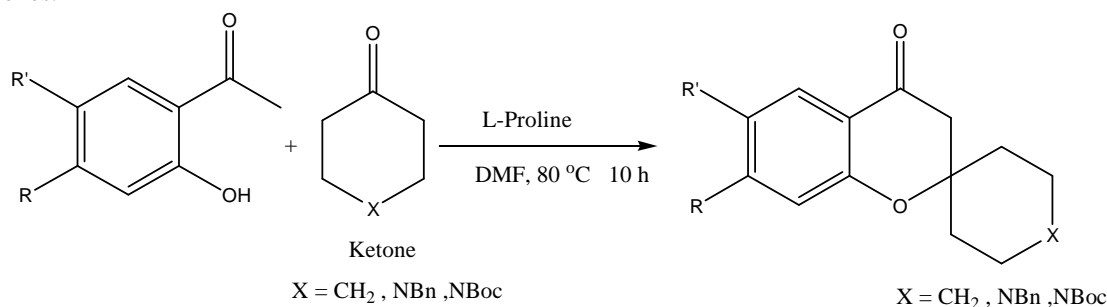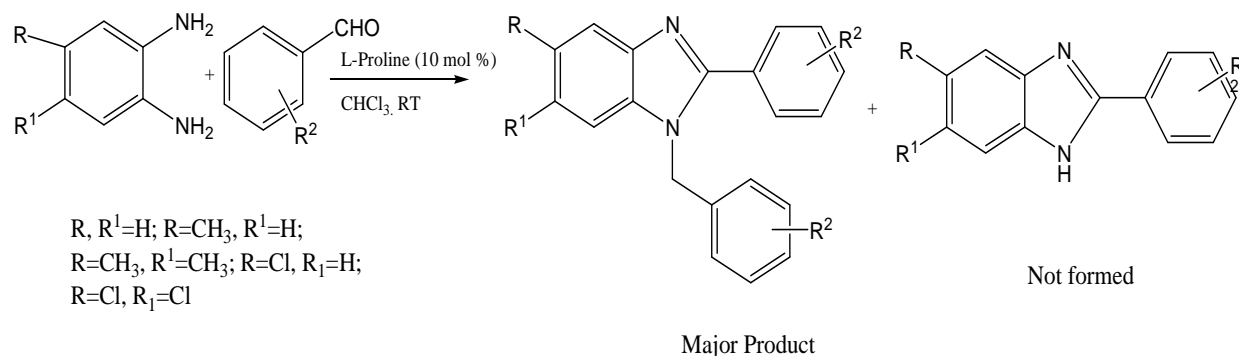


**Scheme 10: L-Proline catalyzed synthesis of spiroflavanones**

Spirocyclization study was done on nature of reactivity in flavanone synthesis by using unsubstituted cyclohexanone and disubstituted pyridine-4-one. The results showed that the disubsitituted cylcohexanones (pyridine-4-one) under go very easy spirocyclization as compared to unsubstiutied and the yield was also very high. Finally, the various substituted flavanones and chalcones were synthesized by using an L-proline as efficient Organocatalyst in the synthesis. [50]. It is shown in scheme-10.

**Use of ionic liquids**

The ionic liquids also play an important role in synthesis. Asymmetric reactions catalyzed by small organic molecules have become very attractive in recent years.[51] Asymmetric aldol synthesis was successfully done on N-terminal prolyl-dipeptide derivatives as chiral Organocatalyst[52] and it was also used in asymmetric stereoselective tetrahydroxanthenones synthesis[53]. The applications of L-proline as organocatalyst in Mannich and direct aldol[54-56] and it could efficiently synthesize various derivatives of benzimidazoles. The synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles was studied with proline efficacy (20 mol %) after model reactions set up on o-phenylenediamine with benzaldehyde[57].



**Scheme 11: L-Proline catalyzed selective synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles**

The above (Scheme-11) selectivity will be useful in synthesizing derivatives of 2-aryl-1-arylmethyl-1H benzimidazoles with good yields. The above method explained by Ravi Varala, Aayesha Nasreen was not reported earlier carried out by using L-proline catalyzed as organocatalyst for the preparation of benzimidazoles[58].

The L-Proline and L-Serine[59-60] can also be used for reductive purposes of γ-*N*-benzylamino-β-ketophosphonates[61]. In this initial synthetic study of (*S*)-*N*-benzyl-*O*-benzylpyrrolidine-2-carboxylate was carried out by treating of L-proline with benzyl bromide and $K_2CO_3$ and refluxed with ethanol[62], but poor yield was obtained in this method. Hence for improving yield this yield method was modified and developed by Overman and co-workers. It was more efficient for synthesis of Compound **A (Scheme 12).** Thus, Benzyl bromide and $NaHCO_3$ in *N,N*-dimethylformamide (DMF) on treatment with L-proline at 100 ºC provided the corresponding *N*-benzyl *O*-benzyl proline **A** in 83% yield. Nevertheless, with the *O*-benzyl ester **A** as synthesized and goes for transformation to β-ketophosphonate **B (scheme:12)** [75]**.** The reaction of **A** with the lithium salt of dimethyl methylphosphonate in three equivalents at -78 ºC in THF gave corresponding *N*-benzylamino-β- ketophosphonate **B** in yield up to 80%
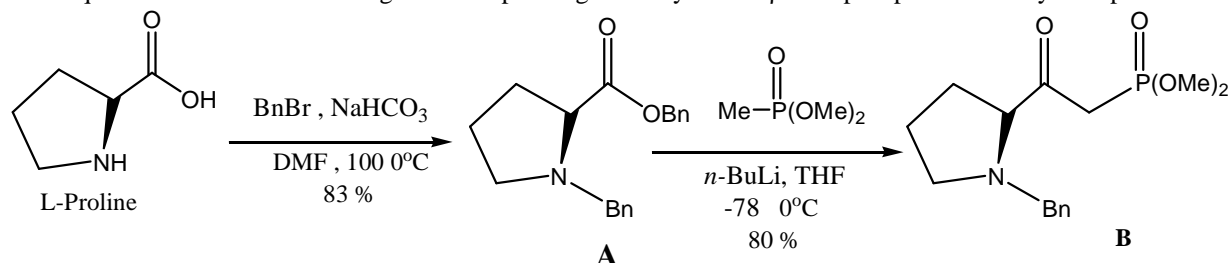


**Scheme 12: Preparation of â-ketophosphonate(i)**

β-ketophosphonate **B** under goes reduction with $NaBH_4$ in methanol to form a mixture of the γ-amino-β-hydroxyphosphonates in *syn*-**A** and *anti*-**A** in a 69:31 ratio. The good yield was reported in favor of *syn*-**A**(**scheme:13**).
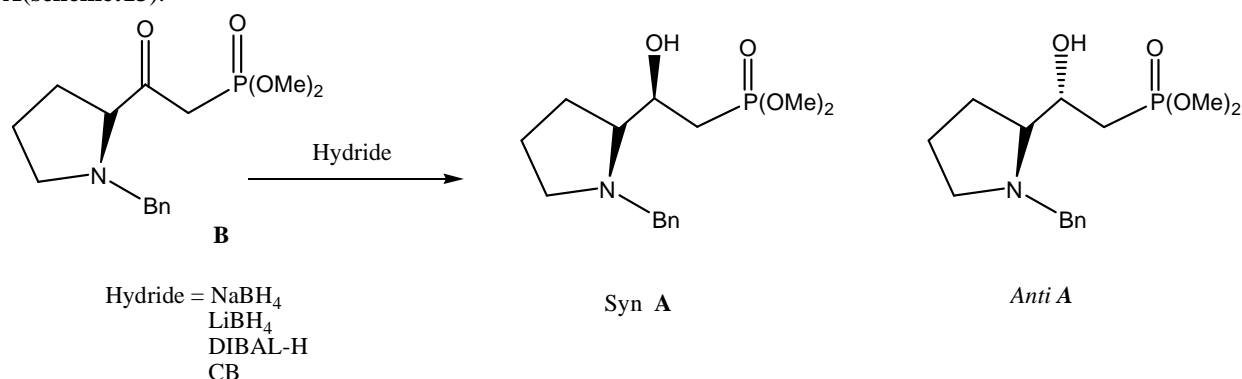


**Scheme 13: Diastereoselective reduction of B-ketophosphonate(ii)**

The following are key advantages of this methodology (i) it smoothly proceeds at room temperature and therefore is able to sustain various functional groups (ii). It has mild reaction conditions, can perform easy work-up, and clean reaction (ii). The reaction time is short and wide range of substrate applicability.

**Silica-supported L-proline Organocatalyst:**
Alexandra Zamboulis et al [63] studied silica-based Organocatalyst which are prepared via sol-gel process from silylated derivatives of L-proline, features either a carbamate or an ether linker. Co-gelification with variable amounts of TEOS was performed with and without porogen to yield high surface area solids. Hybride organic /inorganic silicas with combined properties of the organic compounds and the solid structure of the silica network,[64-65] obtained from organosilanes are very promising material for applications . Over the past two decades, several orgaosilyl with specific organic motifs have been designed and used to confer sought-after properties such as solid phase extraction.[66-69] Photolumininescence [70] or catalysis[71-72] to the resulting hybride silica. In the latter field the sol-gel process has been used to produce covalently bonded catalytic species. Alexandra Zamboulis and others [73] have developed such solid catalysts for different kinds of reactions including metathesis, coupling and asymmetric reactions.

**One Pot L-Proline Catalyzed Synthesis**
S. Chandrasekhar *et al* [74] used L-proline as Organocatalyst in one-pot synthesis and they worked on synthesis of substituted 2-aryl-2,3-dihydroquinolin-4(1H)-ones, with good yields. 2-hydroxyacetophenones and aryl aldehydes undergo a smooth one-pot condensation cyclization in the presence of L-proline as organocatalyst to furnish flavanones in high yields. They have described a general strategy for the synthesis of aza-analogs of flavanones starting from o-aminoacetophenone(**Scheme-14**).
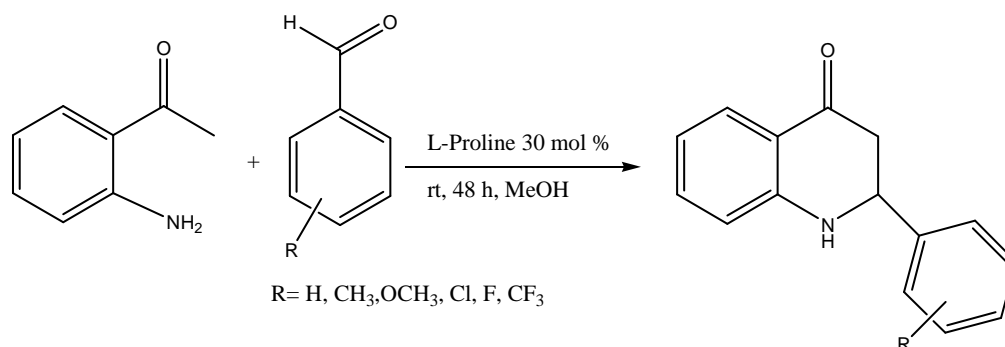
**Scheme -14: Synthesis of aza-analogs of flavanones starting from o-aminoacetophenone**

S. Chandrasekhar *et al* have reported that the equal molar quantities of o-aminoacetophenone and benzaldehyde on stirring together in the presence of L-proline (30 mol %) and methanol (5 ml) and work-up furnished 2-phenyl 2, 3-dihydroquinolin- 4(1H)-one in 85% yield. They claim that in this mechanism the catalyst can be recovered at the end of reaction [74]. Asymmetric synthesis using L-proline was also reviewed by Hiyoshizo Kotsuki considering various reactions such as Mannich reactions, Michael addition reactions, α-oxidation, α-amination and some C-C bond forming reactions [75].

**Multicomponent Reactions:**
Due to synthetic efficiency of multicomponent reactions [76] in intrinsic atom-economy and high reactivity, and procedural simplicity (MCRs)[77-79], Chhanda Mukhopadhyay and his co-workers have worked on synthesis of various highly substituted pyridines at room temperature. This is reported for the first time. This mild and simple expeditious synthesis was catalyzed by L-proline (15 mol%) and it gave highly substituted products with excellent yields of pyridines at ambient temperature.
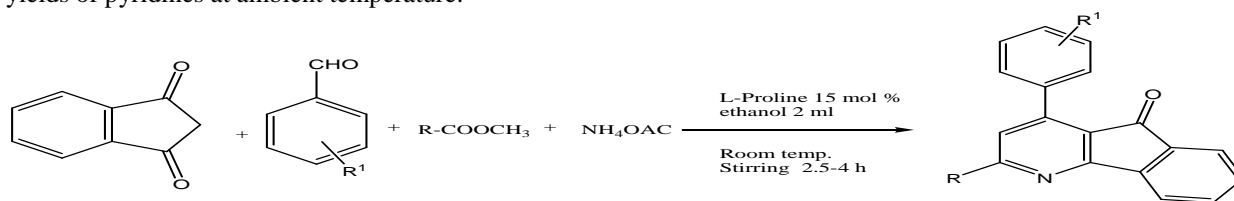


**Scheme 15: Synthesis of highly substituted pyridines**

The authors finally conclude that, this facile and novel one-pot multicomponent methodology catalyzed by L-Proline 15 mol% gave the substituted pyridines [80] as products.

E. Rajanarendar *et al* [80] have proposed as the L-Proline catalyst in one pot synthesis Hantzsch condensation of isoxazolyl polyhydroquinolines. (**Scheme:16**)
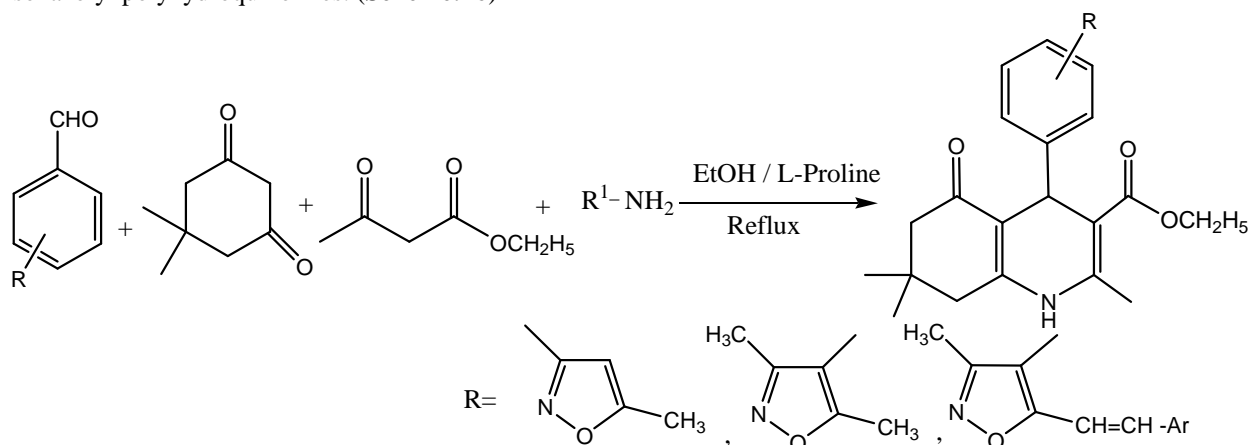


**Scheme 16: Synthesis isoxazolyl polyhydroquinolines**

In above synthesis the product is obtained by inexpensive organocatalyst L-Proline. It shows the alternative and efficient catalyst for one pot synthesis [81-82].

**L-Proline Catalyzed Three-Component reactions**

Ali Reza Karimi and coworkers have developed synthetic rout to excellent diastereoselectivities. cis-isoquinolonic acids[156] which is catalyzed by L-Proline in one pot three-component which gave excellent yields. This method consists of the reaction between aromatic aldehydes, anilines, and homophthalic anhydride catalyzed by L-Proline (10 mol %) as organocatalyst.
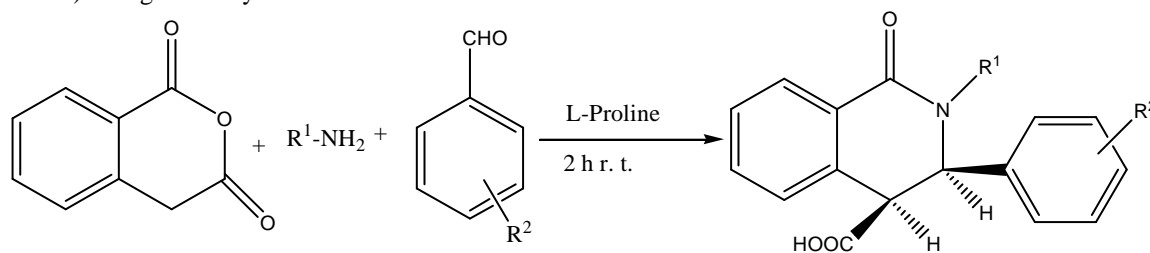


**Scheme 17: Synthesis of cis-isoquinolonic acids**

They have reported a simple and convenient method for the multicomponent synthesis of cis-isoquinolonic acids. L-Proline as the organocatalyst and proline has potential to catalyze efficiently. This reaction product is diastereoselective and yield is high thus, chemotherapeutics potential may be shown in the new developed products[82].

The another one pot synthesis was done by Songlei Zhu [85]using L-Proline as organocatalyst for the synthesis of Pyrano[3,2-*c*]quinolin-2,5-dione derivatives. They have worked on synthesis of derivatives of series of 4-aryl-6-methyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-2,5(6*H*)-diones. This is three component reactions in which aromatic aldehydes, 4-hydroxy-1-methylquinolin-2(1*H*)-one, and Meldrum's acid and L-proline in catalytic amount formed the desired product[83]. The reaction is as shown in **Scheme 18.**
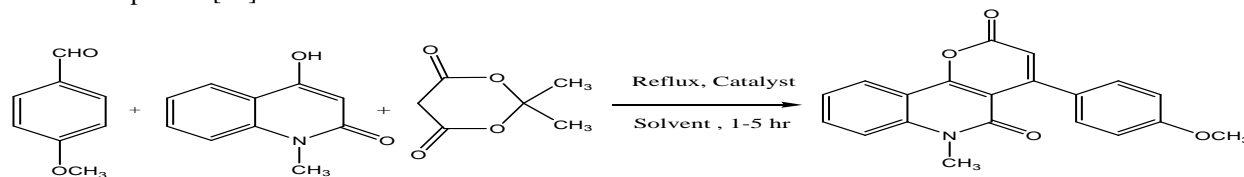


**Scheme 18 : The typical reaction**

When the reaction was conducted in the presence of L-proline (10 mol%) in ethanol, the target compound was obtained in 91% yield and when other solvents were used for this reaction then the results showed that ethanol gave much better results compared to acetonitrile, chloroform, acetic acid, *N,N*-dimethylformamide (DMF), and water. The optimized condition was then used for the synthesis of different derivatives of estimated product.

E. Rajanarendar *et al* have used L-Proline[81] in 2012 and PTSA in year 2015[85] in one-pot three-component aza-Diels–Alder reaction. They applied the role of organocatalyst for the synthesis of aryl or isoxazole imines in situ using aromatic or isoxazoleamines and aromatic aldehydes with nitrostyrylisoxazoles to afford the isoxazolyl tetrahydroquinolines or isoxazolo[2,3- a]pyrimidines as end products.

The reaction was first started by stirring an equi. molar mixture of aniline, benzaldehyde, and nitrostyrylisoxazole with of L-Proline(10 mol %) at ambient temperature in acetonitrile as solvent by stirring up to 3 h(**scheme:19**).



Trans Isomer          Cis Isomer
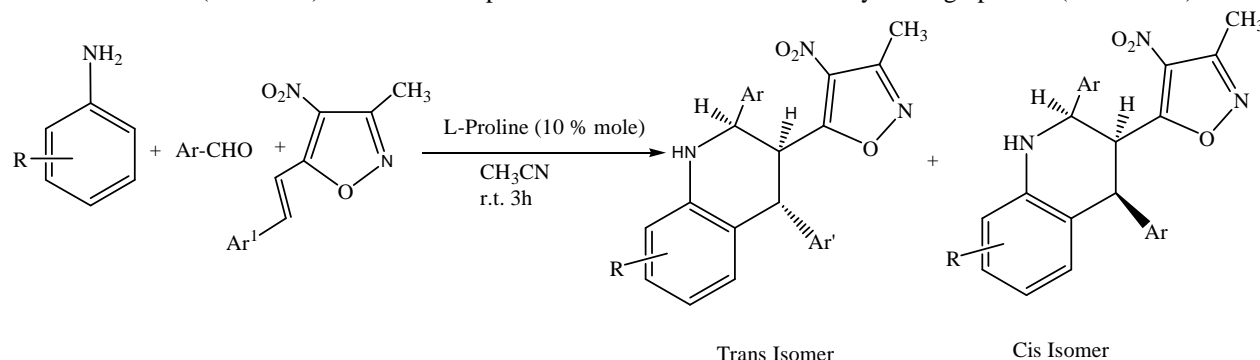
**Scheme 19: One-pot synthesis of isoxazolyl tetrahydroquinolines**
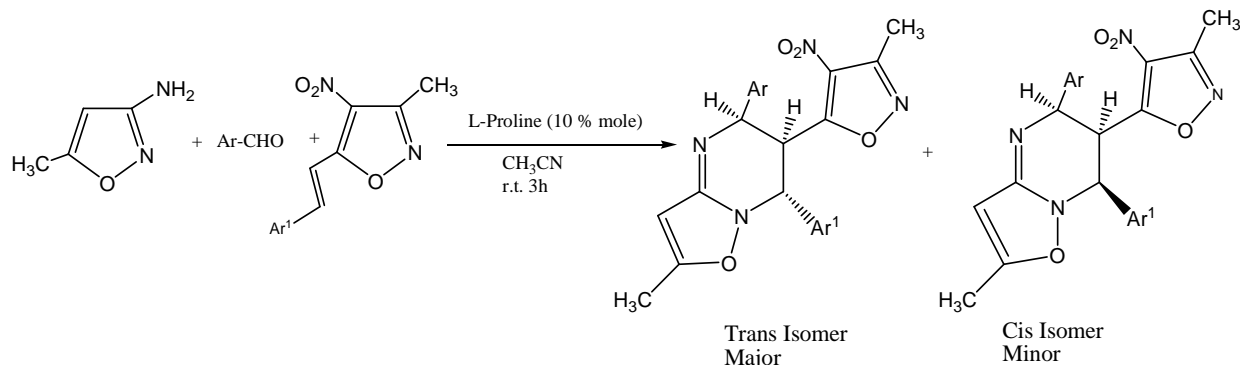
**Scheme 20:One-pot synthesis of isoxazolyl tetrahydroquinolines**

The aza-Diels–Alder reaction can be also employed for diaza butadienes, They investigated the three-component reaction of 3-aminoisoxazole and benzaldehyde with nitrostyrylisoxazole in acetonitrile with of L-proline(10 mol %) at room temperature. The reaction afforded isoxazolo[2,3-a]pyrimidines[90] as major and minor in excellent yields as shown in **scheme: 20**.

Noha M. Hilmy Elnagdi *et al* have done work on multicomponent reaction (MCR) of aromatic aldehydes and malononitrile with various active methylenes in the presence of L-proline which produced pyran and thiopyran derivatives stereospecifically and afforded good yields.



81 % yield
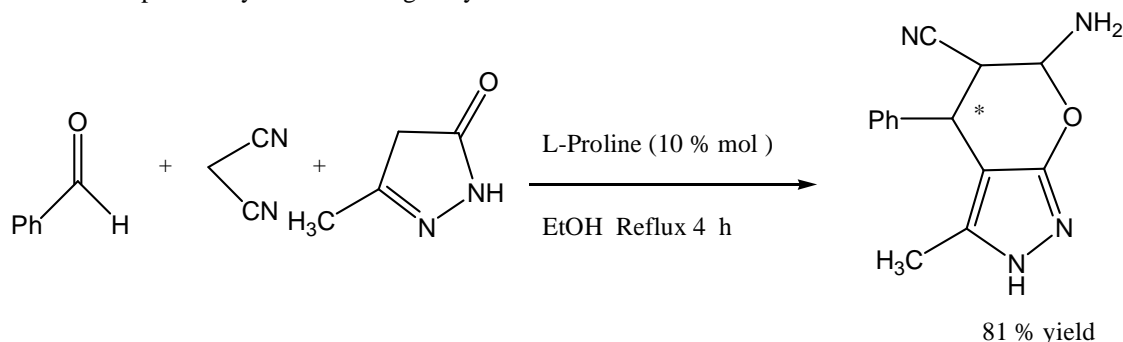
**Scheme 21: Synthesis of 6-amino-3,4-dimethyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile**

Benzaldehyde malononitrile and 3-oxo-3-phenylpropanenitrile were reacted with of L-proline(10% mol) as a catalyst, to form  2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile as final product with  83% yield and 70% ee [84]. It is shown in **scheme 22**.



ee = 70 %
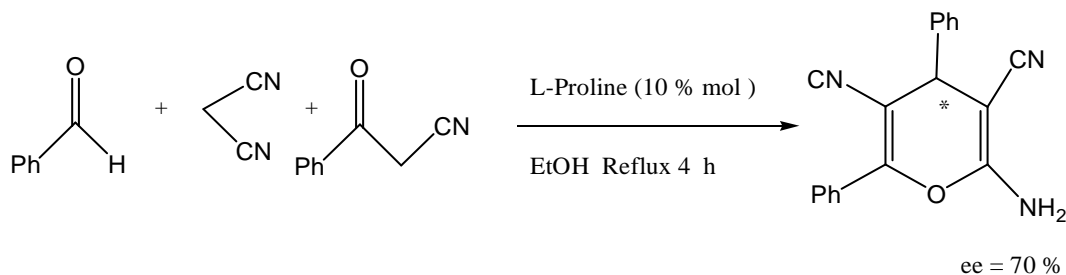
**Scheme 22: Synthesis of 2-amino-4, 6-diphenyl-4H-pyran-3,5-dicarbonitrile**

The usefulness of proline is well known fact and its versatile nature too. In some cases the use of L-Poline is done by making its different useful derivatives or proline based organocatalyst which may function as enantioselective in aldol reaction and it is recognized as one of the most powerful C-C bond making reaction in organic recent synthesis [84].  Prashant B. Thorat *et al* has synthesized the new organocatalyst using hydrogen bond based concept and efficiently catalyzed asymmetric aldol reaction and gave high yield with excellent diastereoselectivity and enantioselectivity[85] (**Scheme-23**).
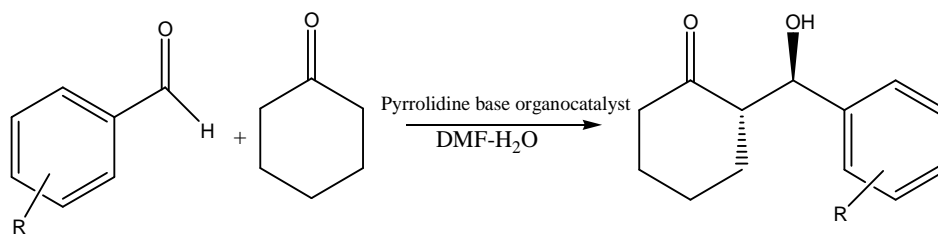
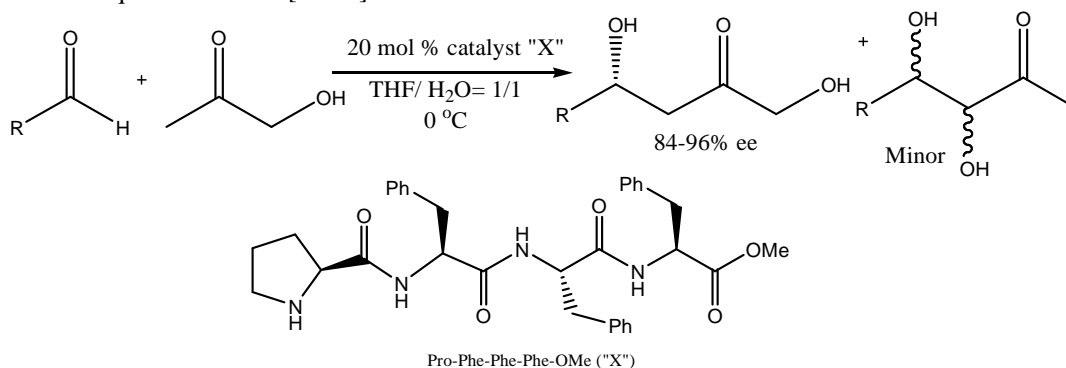**Scheme 23 A: Reaction of cyclohexanone and aromatic aldehydese**
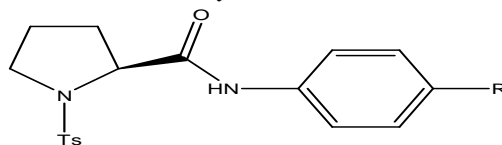


**R= H, CH₃, Cl ,F**
**Pyrrolidine based organocatalysts.**

Pyrrolidine based molecule is a new type of (neutral) organocatalyst. The aldol product can be achieved by catalyzing it as organocatalyst.**(Scheme:23 A).**

**Prolinamide Organocatalyst:**
Liu-Zhu Gong and coworkers have developed approach of L-proline based catalyst in peptide for direct aldol reaction[86] and water in silica-supported[87] prolinamide organocatalysts. They have explained significance in reaction solvent which is catalyzed by organocatalyst by the use of water[88-90] as well as organic solvent[91].Water is easily available solvent in nature and makes the reaction safer to hold. They have developed an efficient water-compatible reactions of great significance in green chemistry, From the literature they found that L-proline amides resultant **(Scheme: 23 B)** from chiral amino alcohols which acted as proficient catalysts for some aldol reaction in aqueous medium [92-93].



Pro-Phe-Phe-Phe-OMe ("X")

**Scheme: 23 B The arrangement and direction of functional groups, within the Catalyst plays main role in selectivity**
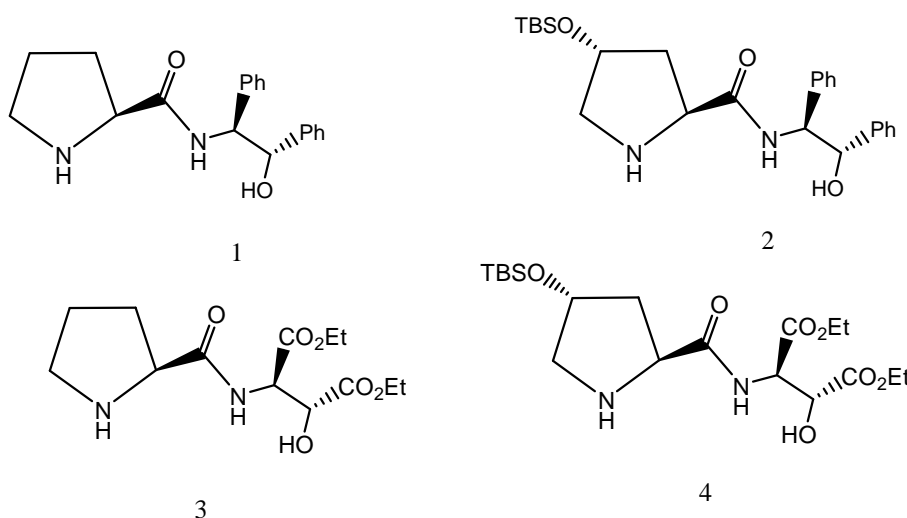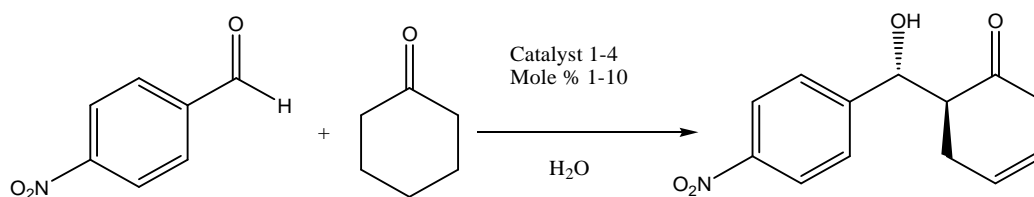
**Scheme 24 :Various L-Proline amide derivative catalyzed direct aldol reaction  of cyclohexanone with 4- nitrobenzaldehyde**

The reaction show trans-4-Hydroxy-prolinamide catalyzed direct asymmetric aldol reactions of cyclohexanone with various aldehydes using water as solvent. It gave aldol products.
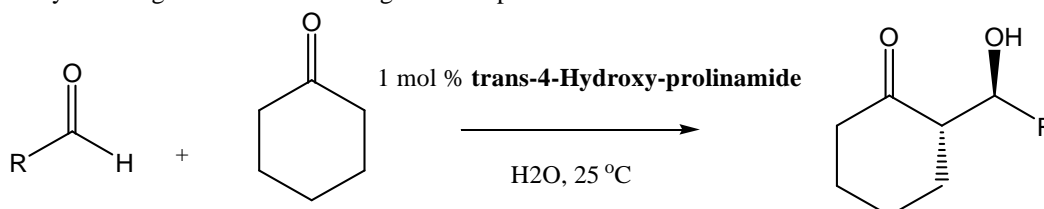
**Scheme 25 : Adol Reaction Catalyzed by trans-4-Hydroxy-prolinamide**

Jun-Feng Zhao *et al* have revealed and developed a highly efficient organocatalyzed direct aldol reactions of acyclic ketones and cyclic ketones substrate and then reacted it with various aromatic aldehydes in water. At the end of reaction the yield of product was high and tremendous with diastereo and also enantioselective[94].

**Symmetric Epoxidation**
The application of L-Proline based catalyst is to synthesizes asymmetric epoxidation and it is well known fundamental reaction in organic synthesis [95-96]. When α,β-unsaturated aldehydes react with peroxides or sodium percarbonate in existence of Chiral pyrrolidine derivatives, proline and amino acid resulting imidazolidinone which acts as a organocatalyst and is called as  asymmetric epoxidation.
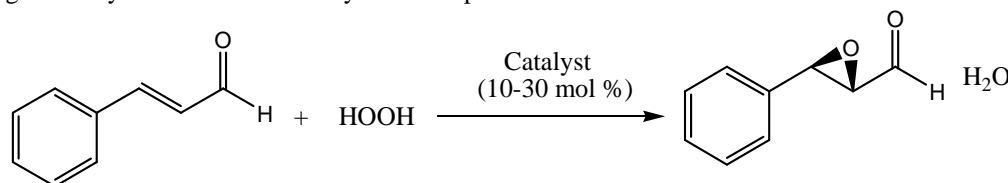
**Scheme 26: Direct catalytic asymmetric epoxidation**
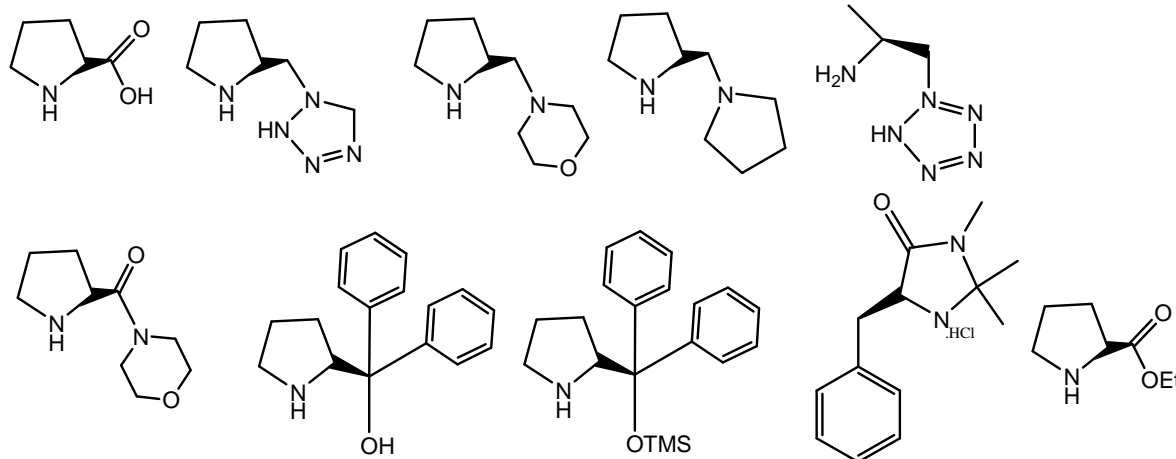
**Fig-Various L-Proline based Organocatalysst for reaction optimization**

Armando Cordova et al have explained the probable mechanism of direct organocatalytical asymmetric epoxidation. a variety of α,β-unsaturated aldehydes which start activity with minimum by the chiral pyrrolidine derivative it is then followed by stereoselective nucleophilic attack conjugatively on the β-carbon which resulted in the formation of chiral enamine derivative. Thus, it is in aqueous media, hydrogen peroxide and non –toxic metal-free proline based organocatalyst makes this process environmentally safe and friendly[97].

Casimir J R, *et al* reported that β-Acetamide ketone and ester has important function as inter-mediates in organic synthesis due to several bioactivity and polyfuntional nature of compounds using modified Dakin-West Reaction.[98] and Neeta Sing *et al* have also reported synthesis of β-acetomindo ketones and esters (Scheme: 27) by using one pot four-component reaction pathway catalyzed by L-Proline[99].
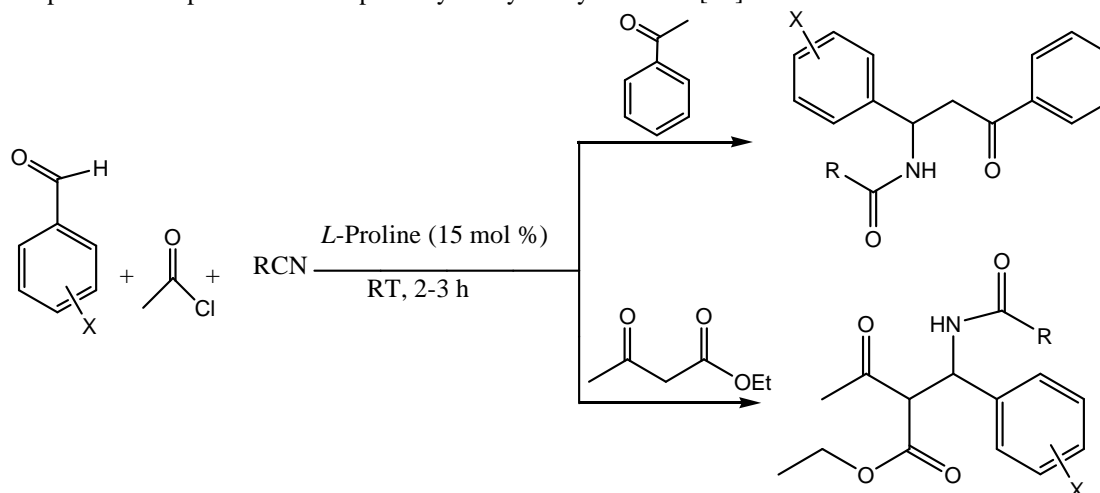


**Scheme 27 : Synthesis of B-amino carbonyl compounds**

In this reaction authors performed reaction with the new advantages methodology with easy work up, a simple process and give efficient synthesis of β -acetoamido carbonyl compounds by using L-Proline as organocatalyst.

**Spirocyclic:**
The Alireza Hasaninejadb and co workers have developed a novel method for the synthesis of spiro compounds by multi component reaction and L-Proline as bifunctional organocatalyst. Spirocyclic structures showed that one sp3 carbon atom is common between two rings hence, it could show biological properties. Due to this chemists are interested in such compounds in organic chemistry[100-101].
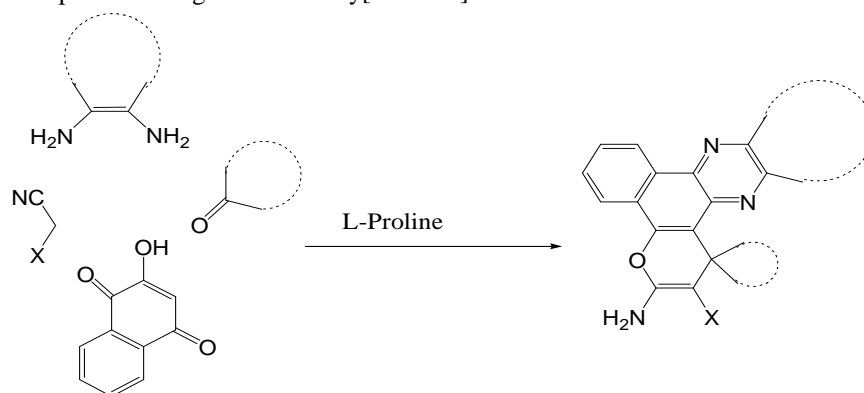


**Scheme 28 : One-pot, four-component synthesis of novel spiro**

By using this scheme the various derivatives of spirobenzo[c]pyr-ano[3,2-a]phenazine were synthesized in the presence of L-proline and highly efficient  with economically inexpensive organocatalyst and product with high yields[102]. In the nature system amide bond is one of the most important linkages. It is present in most peptides and proteins [103-104].

The transamonation is also of importance in forming amide linkages and it was efficiently catalyzed by L-Proline as shown in **Scheme 29.**
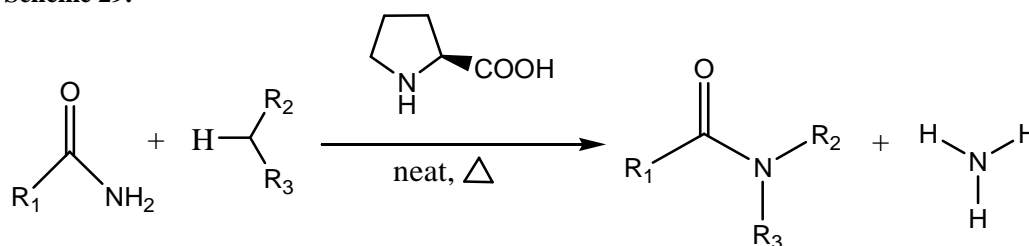


**Scheme 29: L-Proline Catalyzed Transamidation**

Sadu Nageswara Rao *et al* have reported the development of a novel L-proline catalyzed selective transamidation reaction by comparing with previously known transamidation catalysts. They have claimed that it can be applied effectively to wide range of benzylic, aromatic, aliphatic, propargylic, and heteroaromatic amine transamidation products with good to excellent yields [105].

**Bronsted Acid-Type Organocatalysis:**
According to Torsten Weil *et al* the synthesis of poly (vinyl alcohol)- and poly(vinyl alcohol-co-ethylene)- can be cooperatively catalyzed by organocatalysts and Bronsted acids[106]. This is a direct aldol polymerization of acetaldehyde in new approach. Acetaldehyde, the keto form of vinyl alcohol [107]   polymerization by C-O bond formation forms polyacetals[108] poly- (vinyl alcohol) by consecutive C-C bond formation.
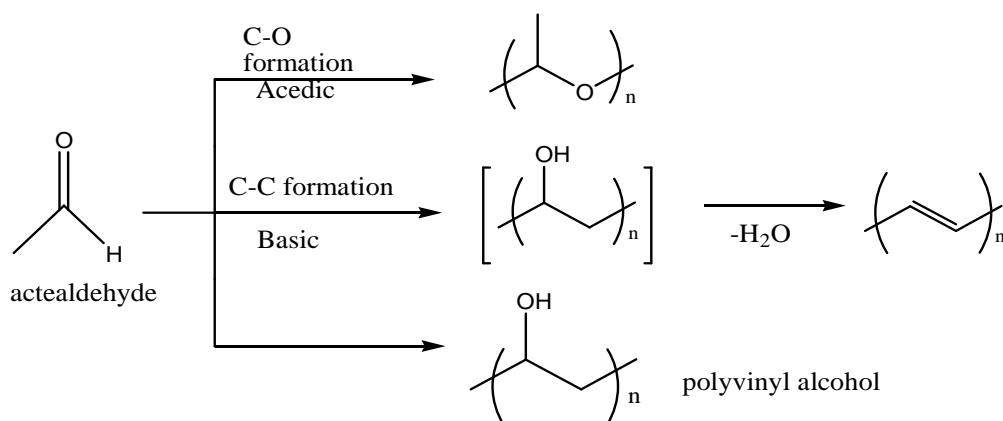


**Scheme 30 : Synthesis of poly(vinyl alcohol)- and poly(vinyl alcohol-co-ethylene**

**Aldol polymerization:**
Shuhei Kusumoto and its co-workers [109] explain the direct aldol polymerization[110] of acetaldehyde catalyzed by organocatalysis and it gives poly(vinyl alcohol) [103c]and poly(vinyl alcohol-coethylene)[ 111 ] oligomers. It contains a substantial amount of main-chain 1,3-hydroxy groups.
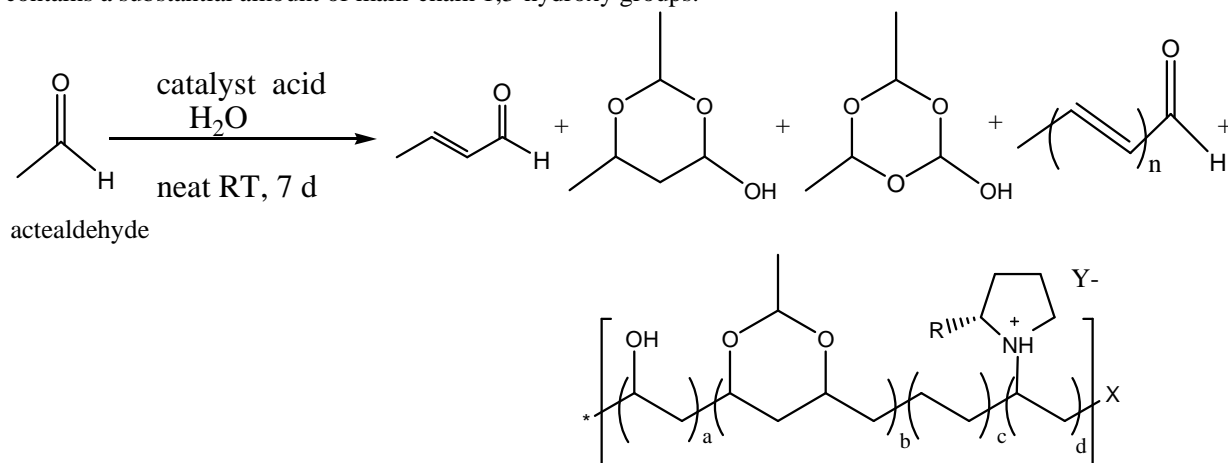


**Scheme 26 : Synthesis of Oligomers**
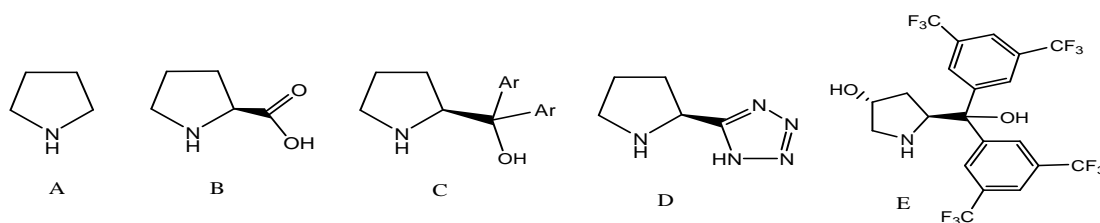


These are different types of organocatalyst made from L-proline which is useful for various synthetic purpose and multi-step enzyme-organocatalysis (**E**) [112]. From this 1,3-hydroxy groups oligomers were prepared in  substantial amount and present in  main-chain of oligomers. According to Yun Xu and co-workers showed catalytic efficiency

is influenced not only by the anion-mediated affinity between the catalyst and the substrate, but also by the anion tunable stability of the transition state [114].

Haritz Sardon et al also gave the tool for polymer synthesis, they drew interest to new trends in isocynate-free polyurethane synthesis and the key role that organocatalysis is playing in these novel polymerization processes, guanidine[115] amidines, N-heterocyclic carbenes[116-117] and organic strong Bronsted acid to catalyze the synthesis of metal free polyurethanes [118-119] .
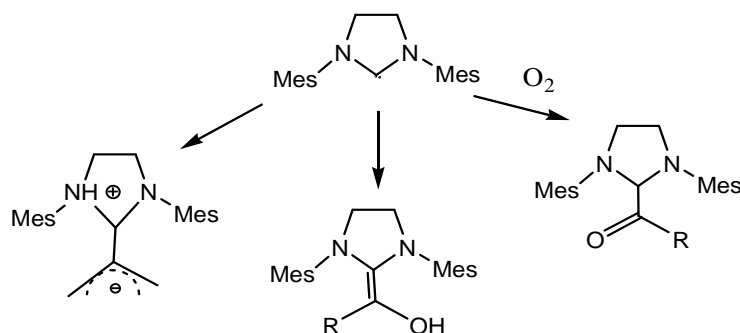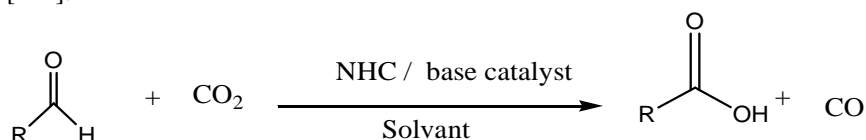
**Decarboxylation**
Recently Shuichi Nakamura have reported that the rate of decarboxylation of β-ketoacids goes via Mannich reaction with ketimines by using saccharide based thiourea catalysts [120].
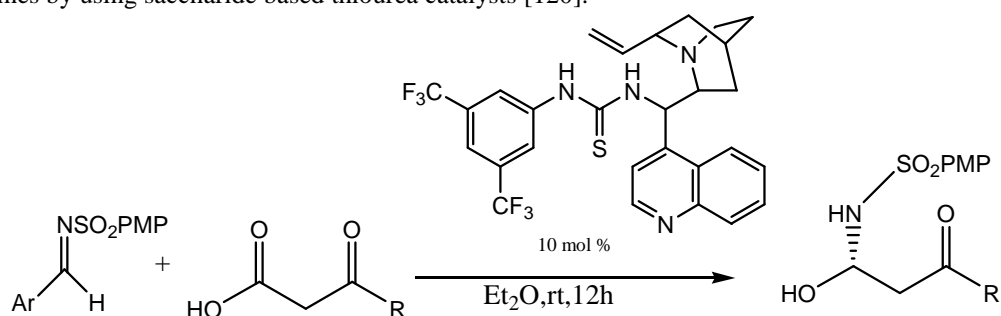
**Carboxylation:**
Zhang and coworkers achieved the NHC [121] catalysts mediated $CO_2$ reduction of the aromatic aldehydes as oxygen acceptors [121].

**L-Proline supported on Magnetic Nanostructures**
As resent study progresses we came to know that catalyst play main role in resent scientific development as they promise to improve product yields, reduce reaction temperature and produce required selectivity in asymmetric synthesis related to name reactions for eg. Friedel–Crafts[123-124], Olefin isomerisation [125], Mannich/aldol[126-127, Henry[128-130], Diels–Alder[131], cycloaddition [132-133], transamination [134-135] and Michael addition,[136-137] Morita–Baylis–Hillman,[138-139] There were two types of Homogenious catalysis and Heterogeneous catalysis that should be in same phase.

Organocatalysts , a metal free organic compounds of relatively low molecular weight and simple structure capable of promoting a reaction in a substoichimetric amount, have received paramount interest in the last year. According to Radoslaw Mrowczynki *et al* there is a considerable interest in the immobilization of organic catalyst molecules onto heterogeneous substrate. Another way recycling the catalyst is a valuable concept in green chemistry for this several methods have been applied to solve the issue. There after the concept of magnetism was used for separation of Organocatalyst (L-proline) supported on metal (**Scheme 27**) [140]. In this case nanopartical(MNP'S)[141-144] showed many advantages for recycling and recovering[145]. These catalysts are having great promising function to aldol condensation [146],
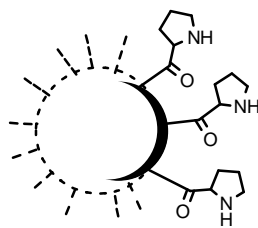
**Scheme 27 : L-Proline supported on Fe₂O₃ Nanoparticals**

Nasseri and co-workers have bound methylene dipyridine to silica shell on the surface of $Fe_2O_3$ nanoparticals[147] with the help of triethoxysilane[148] derivatives as a linker as shown is **Scheme 28.**
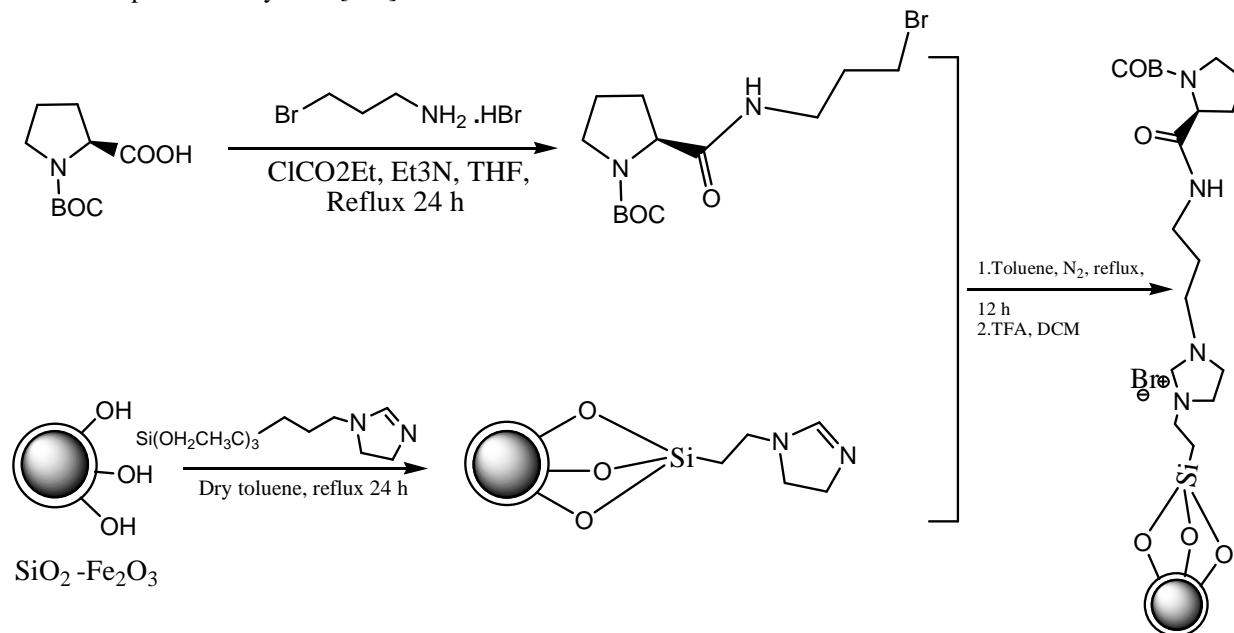


**Scheme 28: MDP to silica shell on the surface of Fe₂O₃ Nanoparticals**

Ciarn Dlaigh et al developed MNP's supported on DMAP analogue[149] and most of reaction are one pot synthesis of a target compounds in a same reaction pot[150]. Aldol is a carbon-carbon bond forming reaction [151-152] or it may be metal free catalytic condition [153] and especially the applicationof the organocatalytic reaction to constant the alkaloid scaffolds[154]. Alexandra Zamboulis and others have made efforts to synthesized a series of related new hybrid silicas immobilized the L-proline motif have been prepared using the sol–gel process starting from two kinds of silylated L-proline derivatives A and B[155].
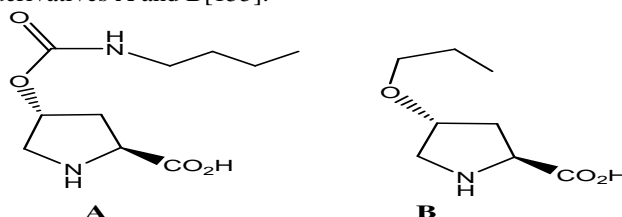


**CONCLUSION**

In summery, the development and use of L-Proline has become most popular catalyst among all the organocalatysts. In last five year's literature and publications showed its fast growing importance towards organic synthesis due to its ability to perform a variety of transformations. It is also complimented by their readily availability, nature friendly, stability, tolerance to moisture and water, easy handling. Various derivatives of organocatalysts can also show versatile application in sol–gel process, polyurethanes, L-Proline immobilized nanoparticals, NHC catalysts and Homogenious as well as heterogeneous in asymmetric catalysis.

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