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Organocatalysis: An Asymmetric Approach

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Abstract : Chirality has significant importance in chemistry and it is classified as sub-disciplines of chemistry. Many organic compounds which are found naturally such as, amino acids and vitamins are chiral. The concept of chirality was first introduced in 1815 by French chemist Jean Baptiste Biot when he discovered optical activity in nature. Since then, Chirality has become of tremendous importance in our daily life. Enantiomeric compounds have diverse chemical properties, these molecules have different tastes and odours. Hence, it is obvious that the two enantiomers of a molecule will interact differently with a living organism, as in some cases, only one enantiomer of a drug provides the desired effect while the other could be lethal. The broad utility of synthetic chiral molecules in pharmaceuticals, electronic and optical devices, as components in polymers with novel properties and as probes of biological function, has made to search for single enantiomer molecules. In this chapter focuses various asymmetric transformations using organic catalysts.

Index Terms **- Organocatalysis, Asymmetric synthesis, L-proline derivatives, Applications, enantioselectivity.**

Introduction

The term ‘organocatalysis’ is the metal free chemical transformations by using low molecular weight organic molecules as catalysts. Although field of organocatlysis is few decades old, reactions using organic molecule as catalysts has been used from a century back. An addition reaction of HCN to aldehydes using organocatalyst has been reported in 1912 by Bredig and Fiske. In 1960 Pracejus demonstrated carbon – carbon bond forming reactions by using cinchona alkaloids although in low enantioselectivity. [1-3] However, organocatalysis gained popularity in the years of 2000 when List and Barbas et al carried out asymmetric aldol reaction by using proline as organocatalyst. [4] In last two decades many researchers across world have published enamours documents of successful transformation using organocatalysis.

At present, organocatalysis stands independently as important key to bring out chemical transformations with good sterocontrolled products. It has advantages such as, avoiding hazardous conditions and chemicals, metal free, low costing catalysts and can be used as chiral activator. Moreover, owing to its structural diversity of these catalysts show both Brønsted acid or base nature to act as a bifunctional catalyst. For instance, *L*-proline, the nitrogen in cyclic framework offers basicity and nucleophilicity whereas hydrogen from carboxyl structure shows acidic nature. [5] Thus, felicitate reaction by forming iminium or enamine with carbonyl group of ketone or aldehyde substrates while acidic hydrogen forms hydrogen bonding which stabilizes and controls transition state resulting stereoselective reactions. [4-5] Literature revels that these small organic molecules have great ability to catalyses carbon- carbon (C-C), [6-15] carbon – nitrogen (C-N), [16-23] carbon – oxygen (C-O) [24-28] and carbon – sulphur (C-S) [29-31] bond forming reactions.

The organocatalytic process are powerful tool to drive asymmetric synthetic process. Specially in pharmaceutical and food industries where demand for single enantiomer is more. Organocatalytic asymmetric processes are excellent solution to these industries, it benefits by eliminating resolution of racemic mixture thus avoiding the waste. Further, organocatalysts is an alternative catalytic process to industries for preparation of pharmaceutical products preventing metal contamination. In this chapter, the trends and developments of organoctalysis and its application in asymmetric synthetic will be discussed.

Discussion

The first asymmetric synthesis using *L*- proline was demonstrated by Eder, Sauer, and Weichert in the year 1971. [32] Although catalytic loading was high, reaction was able to produce enriched optical active products (**2**) in good yields. Similar reaction was performed by Hajos and Parrish using optimised reaction conditions which was able to reduce catalytic loading to 3 mole % with excellent enantiomeric excess but yield was moderate 52% yield (**2**) (**Figure 1**). [33]

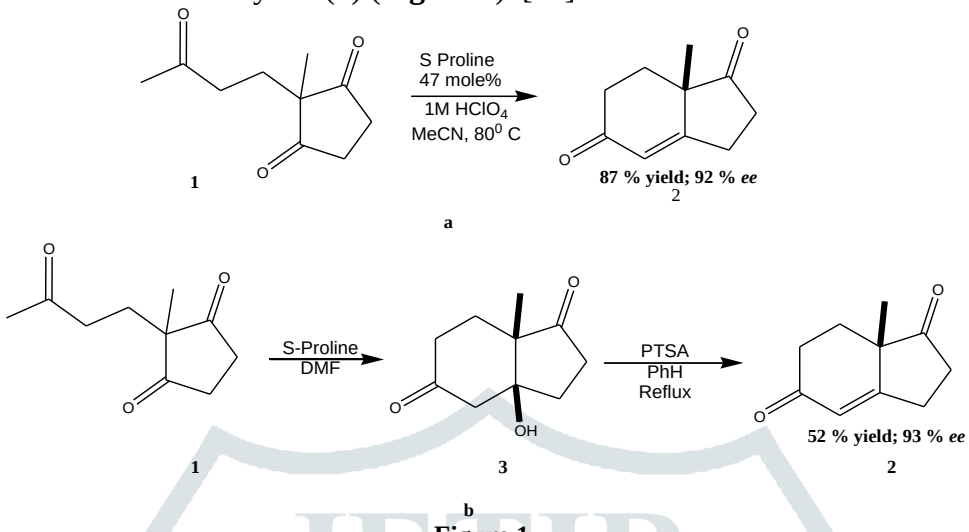


Figure 1.

Although up to late 1990s very few articles were published on organocatalysis, this field was rooted in these years. [34-37] The results of organocatalytic studies started to be highlighted after 2000, when List and Barbas reinvestigated direct asymmetric aldol condensation reaction using 30 % *L*- proline as catalyst (**Figure 2**). [4] Even though yield of product was not so high (68 %) it opened route for metal free version for transition state (**7**).

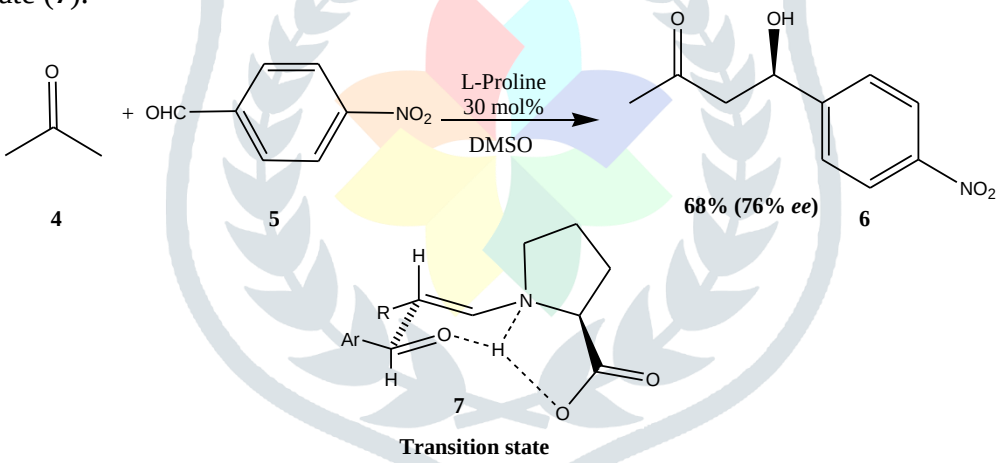


Figure 2.

At the same time, successful Diel-Alder reaction using imidazolidinone catalyst was shown by McMillan group. The cycloaddition reaction of (*E*)-cinnamaldehyde (**8**) and cyclopentadiene (**9**) was reacted in presence of organocatalyst **10** to offer excellent yield and optical purity (**Figure 3**). The reaction was proceeded by formation of reversible iminium ions thus lowering LUMO activation energy (**12**). [38] He published series of papers and shown potential of small organic molecule in catalysing reactions through LUMO activation of molecules. [38-41]

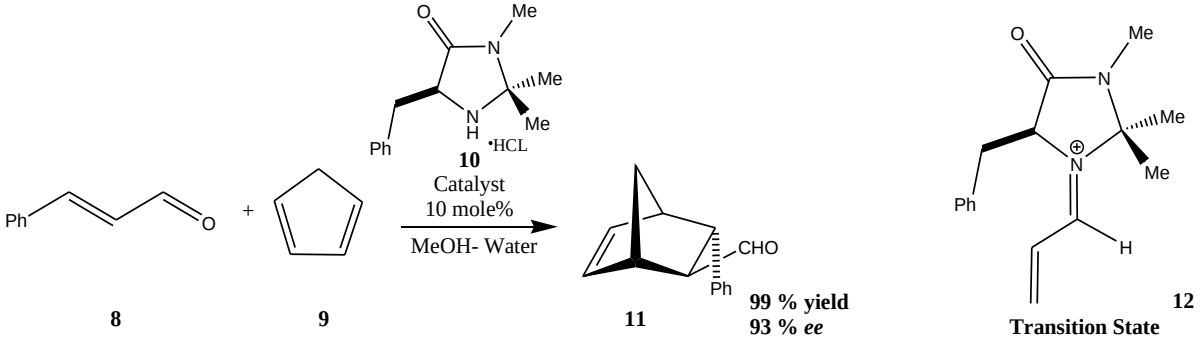
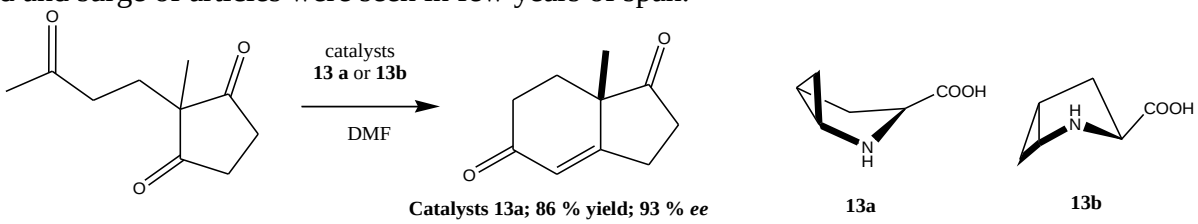


Figure 3.

These two remarkable findings on organocatalysts helped organocatalysis to establish as independent stream of catalysis. After these publications the scope of organocatalytic field was further explored and surge of articles were seen in few years of span.



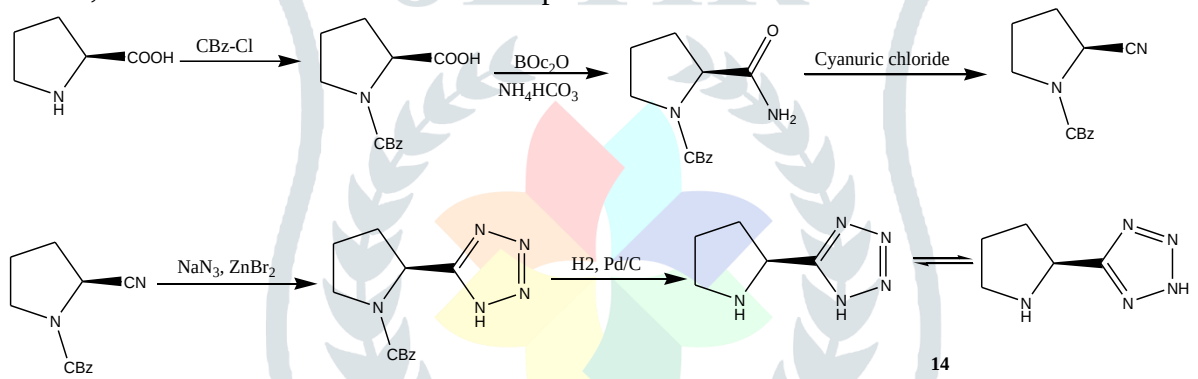
Catalysts 13a; 86 % yield; 93 % *ee*
Catalysts 13b; 67 % yield; 83 % *ee*

13a **13b**

Figure 4.

Hajos-Parrish-Eder-Sauer-Wiechert reaction was restudied by Hanessian *et al* by using *cis*- and *trans*-4,5-Methanoprolines (**Figure 4**). The reaction was studied with hybrid density functional theory (B3LYP). From studies it was found, iminium transition state formed from planar *cis*-4,5-methanoproline organocatalyst (**13a**) forms more stable conformation than that of *trans*-4,5-Methanoproline (**13b**). Thus, catalysts *cis*-4,5-methanoproline (1**3a**) was better choice for catalysis and able to draw high yield and enantioselectivity (86% yield, 93% ee), whereas the *trans*-4,5-methanoproline (**13b**) was not very efficient (67% yield, 83% ee) and showed very slow rate of reaction [42].

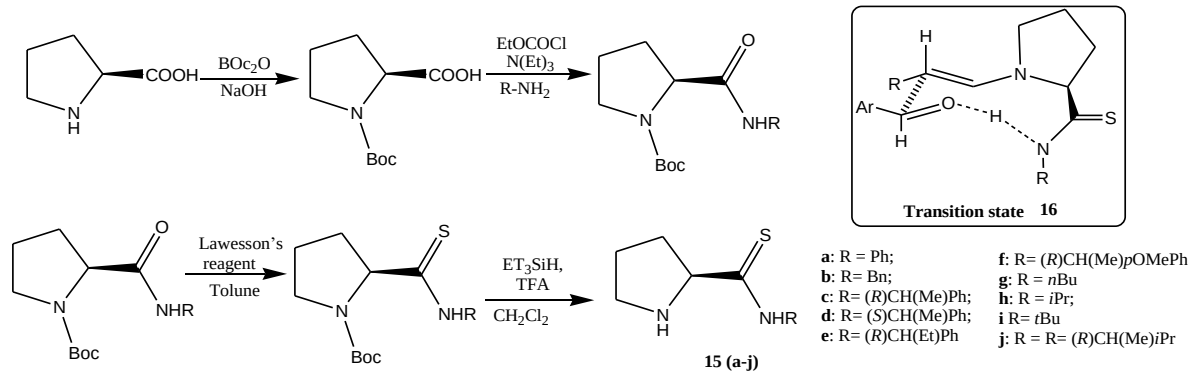
A, Hartikka and P. Arvidsson synthesized novel organocatalysts 5-pyrrolidine-2-yltetrazole (**14**) by modifying carboxylic acid of proline with the tetrazole (**Figure 5**). The catalyst **14** was used in aldol condensation which showed increased reactivity over proline in DMSO and DMF solvents with 20 % catalytic loading.[43] The catalyst **14** was able to bring down activation energy through more stable transition state, which increased conversion rate up to more than 90%with 76% *ee* in 4 hours.



14

Figure 5.

In 2006, D. Gryko with Lipinski, prepared various *L*-proline-derived thioamides **15(a-j)** by reacting *L*-proline and chiral and achiral amines. (**Figure 6**) These catalysts were screened for aldol reaction. [44] The studies confirmed mechanistic approach and necessity of chiral centre in catalyst to form Houk and List type transition state. [45] The catalyst Pyrrolidine-2-carbothioic acid (1-phenyl-ethyl)-amide (**15c**) catalysed reaction offering good yield with better *ee* for products. When catalyst **15c** was reacted with ketone in absence of aldehyde, it formed imidazolidinethiones which was stable and could be isolated. when it was further reacted with aldehyde it gave low yield and unacceptable optical purity. Similar study was done using benzaldehyde in absence of acetone it gave oxazolidinone but failed to obtain fruitful result when reacted with ketone. This concluded that reaction followed imine–enamine mechanism and the transition state (**16**) which was stabilised by more acidic N-H protons of catalyst to provide enhanced stereo control on reaction.



Transition state 16

a: R = Ph;
b: R= Bn;
c: R= (*R*)CH(Me)Ph;
d: R= (*S*)CH(Me)Ph;
e: R= (*R*)CH(Et)Ph
f: R= (*R*)CH(Me)*p*OMePh
g: R = *n*Bu
h: R = *i*Pr;
i R= *t*Bu
j: R = R= (*R*)CH(Me)*i*Pr

15 (a-j)

Figure 6.

Janda and co-workers researched asymmetric aldol reaction in water using proline-nicotine based catalyst **17** in the aqueous medium. In search of alternate route to base catalysed aldol reaction, a new system was developed in buffer solution and nornicotine organocatalysts (**Figure 7**). [46] In series of publications Janda recognized role of water in the reaction between acetone and aromatic benzaldehyde in alkaline medium (pH 8) by adding phosphate buffer in presence of nornicotine organocatalyst (**17**). The role of water in transition state (**18**) was studied by combined deuterium isotopic kinetic effects and computational studies to propose intermediate. [47] Although reaction claimed to be aqueous, small amount of polar solvent DMSO was added to dissolve water in soluble substrates. The reaction offered high yields and considerable enantioselectivity. It was found that aldehydes with negative inductive effect reacted faster and produced good results. The nornicotine system helped to establish Hammett correlation on reaction rates. [48-49].

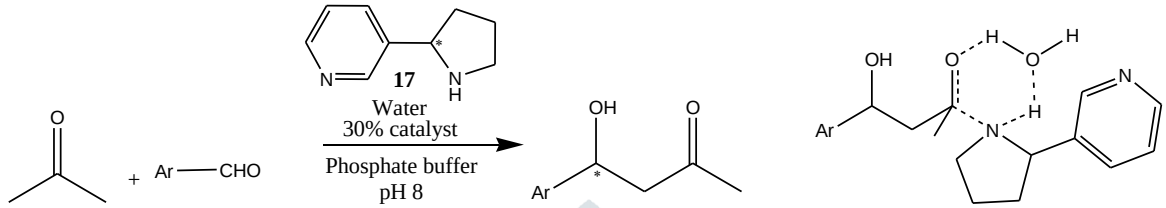


Figure 7.

In an interesting report by Gong *et al.*, which illustrated that the addition of water changed regiochemistry of reaction by reacting same substrates under different reaction conditions two different compounds were obtained. The presence water alters the regioselectivity of enamine intermediate and hence the reaction (**Figure 8**). Similar results were seen in the reaction between hydroxyacetone and 4-nitrobenzaldehyde. The reaction in a THF:water solvent system offered 1,4-Dihydroxy-4-(4-nitro-phenyl)-butan-2-one in good yield and optical purity (92 % and 90 % *ee*), whereas the reaction performed in only THF solvent produced chiral 3,4-Dihydroxy-4-(4-nitro-phenyl)-butan-2-one although with less selectivity (36 % yield, 97 % *ee*). Then similar protocol was applied to Fluoroacetone with aldehyde in THF solvent it produced 94 % 3-Fluoro-4-hydroxy-4-(4-nitro-phenyl)-butan-2-one with 95% *ee*. Whereas when THF - water system offered 62% yield and 80 % *ee* for the product 1-Fluoro-4-hydroxy-4-(4-nitro-phenyl)-butan-2-one. From theoretical calculations it was depicted that the role of a hydrogen bonding network is crucial to stabilize the enamine transition state. [50]

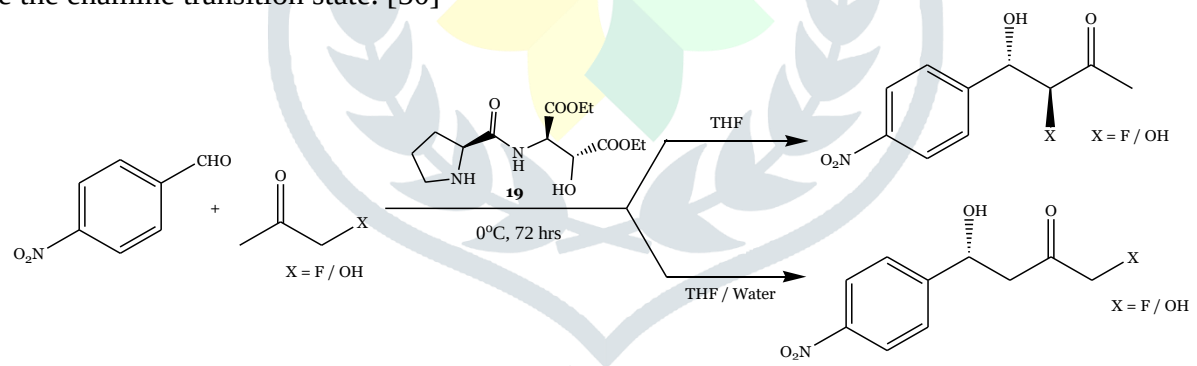


Figure 8.

R. S. Schwab *et al.* prepared a series of chiral cysteine-derived prolinamides and tested their application in the organocatalytic asymmetric aldol reaction (**Figure 9**). In addition, a selenium-containing chiral organocatalyst was also synthesized and studied. The organocatalysts **20**(**a-h**) and **21** were synthesized by reaction of *S*-alkyl-*L*-cysteine methyl ester and *N*-Boc-*L*-proline. The obtained amide was subjected to double Grignard addition reaction to the ester group or reduction with sodium borohydride. The final product **20** was obtained by removing the Boc group of reduced hydroxy *N*-Boc prolinamide (**Figure 9**). Organocatalysts **21** was synthesized using same protocol starting with selenium alkyl-*L*-cysteine methyl ester. The reaction was optimized by sulphur containing organocatalyst **20a** and similar conditions were used for selenium containing organocatalyst (**21**).

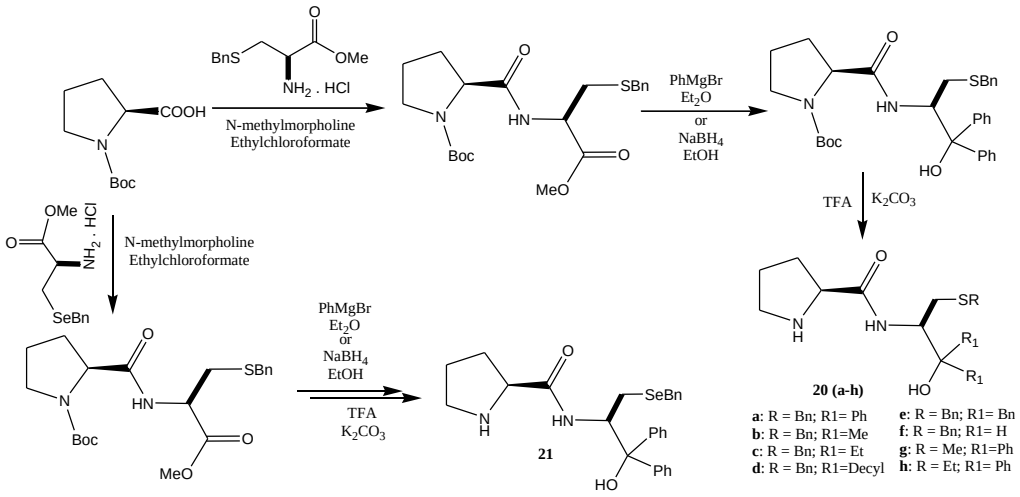


Figure 9.

The reactants were allowed to react for 24 hrs at low temperature in acetone as solvent with 10 mole % catalytic loading. Although catalytic loading was not so high reaction could furnish satisfactory yield up to 83% for aldol products with excellent optical purity up to 94*ee*. Selenium derived prolinamide **21** proved to be inefficient catalyst producing 50 % of desired product and 85 %*ee* under optimized conditions. [51]

Hayashi *et al.* demonstrated modification of proline at 4 position to form 4-*tert*-butyldimethylsiloxyproline **22**. The organocatalyst was derived from commercially available *trans*-4-hydroxyproline. The catalyst **22** showed superior catalytic activity than *L*-proline for a-aminoxylation of carbonyl, the O-nitroso aldol/ Michael, and Mannich reaction (**Figure 10**). The catalyst (**22**) displayed greater yields (up to 66% for a-aminoxylation; 76 % for O-nitroso aldol reaction; 63% for Mannich reaction) and better enantioselectivities (up to 99% for a-aminoxylation; 99 % for O-nitroso aldol reaction; 96% for Mannich reaction).[52]

Further, in his subsequent publication, application of siloxyproline (**23**) was studied in the asymmetric aldol reaction. The catalyst siloxyproline **23** worked well in solvent water to afford aldol products in excellent yield (up to 89%) and enantioselectivity (up to 97%) for *anti*-isomer. [53]

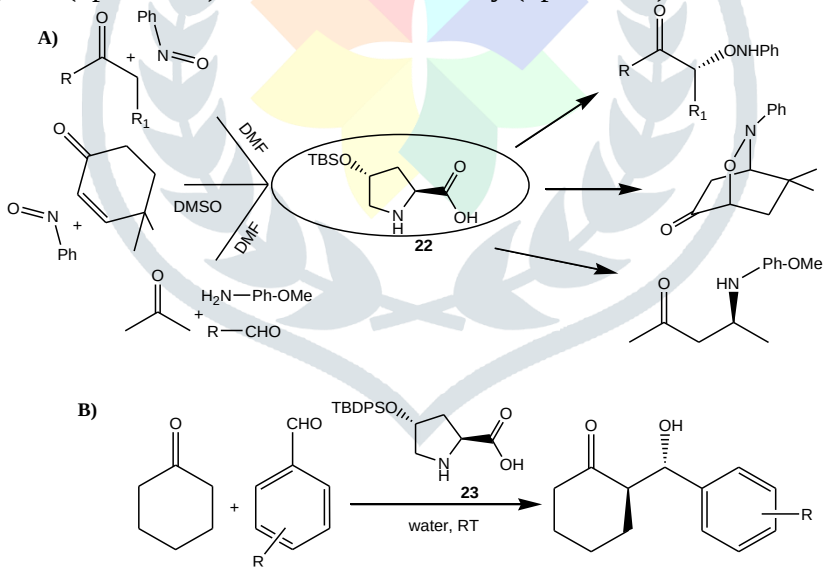


Figure 10.

Xu and co-researcher studied rational electronic tuning of catalysts to improve enantioselectivity also the correlation between the enantiomeric ratio of product and the Hammett constant of the catalyst substituent in the asymmetric Aldol reaction system (**Figure 11**). To understand the electronic tuning, the catalysts **24 a-d** were designed with very similar structural features and tested in direct Aldol the reaction. When all catalysts were screened in aldol reaction, catalyst **24d** was found to be better choice in DMSO solvent yielding 74% product with 68% *ee* for *anti*-isomer. [54]

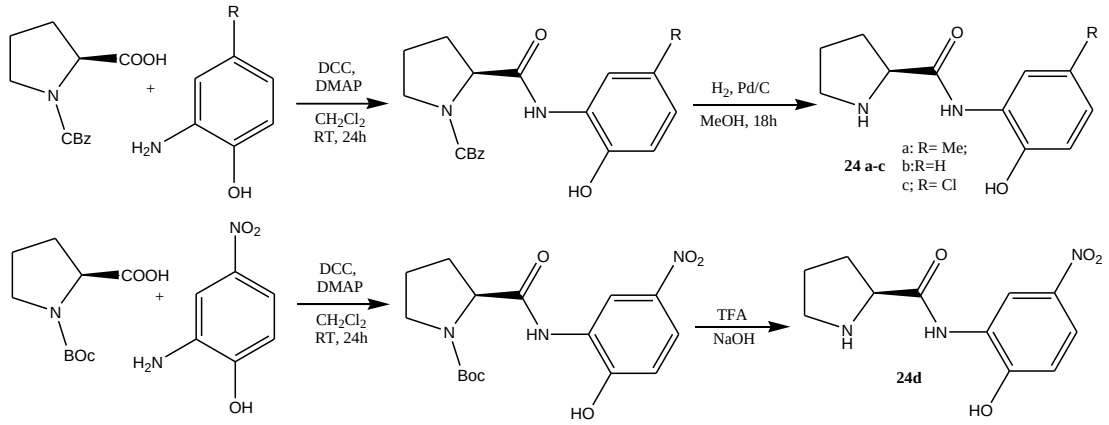


Figure 11.

It can be concluded that for all catalysts, substrate with electron-withdrawing groups offered good diastereoselectivity and enantioselectivity than those with electron-donating groups. The Hammett constants for *meta* and *para* substrate were well in agreement with the enantiomeric ratios. Thus, effect of improved enantiomeric excess was explained by rationally tuning catalyst structure.

A series of thiazolidine amides derived catalysts (**25 a-d**)) were synthesized from different β-amino alcohols (**Figure 12**) by duo scientists Rambo and Schneider. [55] The synthesized catalysts were studied in aldol reaction and asymmetric Michael addition. The influence of electronic and steric characteristics of synthesized organocatalyst was studied in aldol reaction. For aldol reaction, catalyst **25a** was very efficient when used both brine solution and water solvents, in both cases it gave more than 90% yield however in brine solution *ee* was greater. Replacement of phenyl group of catalyst **25a** by hydrogen proved to be disastrous for desired product in terms of yield. Although performance was improved with catalysts **25b** and **25c** but less efficient than catalyst **25d**. Scope of reaction was extended further in Michael addition reaction between cyclohexanone and trans-β-nitrostyrene, reaction furnished moderate yield 60% with 99 % *ee* for *syn* isomer.

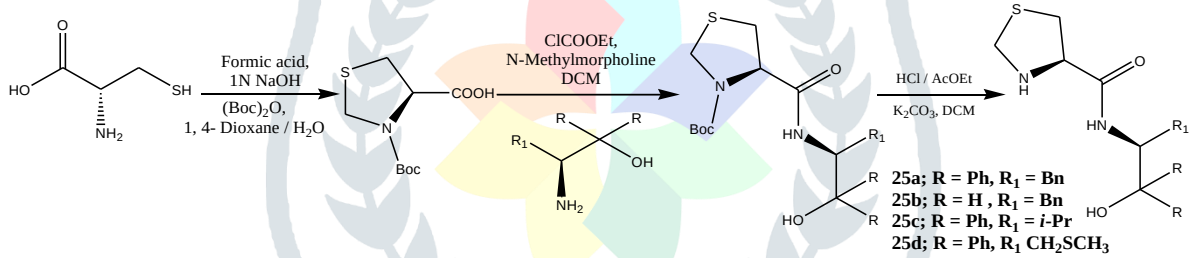


Figure 12.

Wennemers and his group provided mechanistic approach for improving organocatalytic reactions (**Figure 13**). They studied kinetic aspect of organocatalytic reactions to reduce catalytic loadings. [56] The conjugate addition reactions between aldehyde and nitroolefin was chosen as model reaction using 1 mole % peptide catalyst **26** to understand the kinetic influence of the reaction. They discovered that enamine formation occurs fast in absence of water even at lower concentrations of aldehydes. However, with addition of nitroalkene imine formation take place which depends on water. Thus, studies showed that rate determining step does not depends on enamine formation but also hydrolysis of the resulting imine complex.

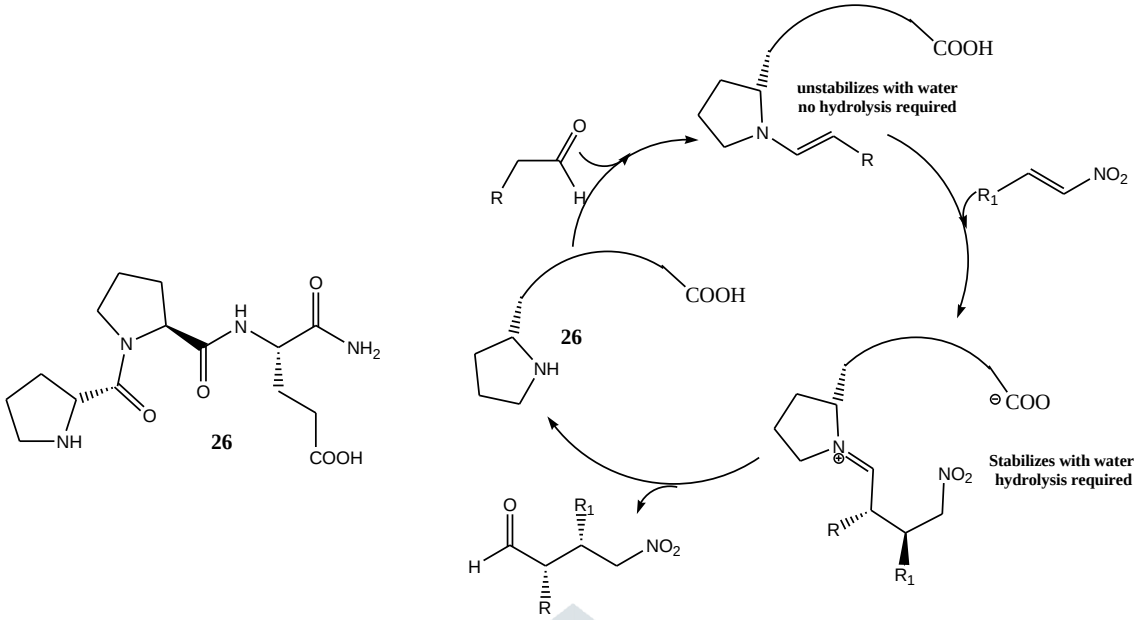


Figure 13. Mechanistic study of aldol reaction using catalysts 26.

Asymmetric hydrogenation reaction of unsaturated β-aminoacids was attempted by Wu *et al*. using various analogues of chiral pyrrolidine sulfoxide organocatalyst (**27 a-f**) at very low temperature. The reaction was optimized by using varying reaction parameter such as catalysts and solvents. Best condition for the reduction of (Z)-ethyl 3-phenyl-3-(benzylamino) acrylate was achieved at -40° C by reacting with reducing agent trichlorosilane in presence of catalyst **27d** and water as Brønsted acidic additive (**Figure 14**). The reaction performed well in presence of 1.0 equivalent water as additive in toluene to produce yield up to 98% and 96% *ee* for desired products. It was believed that reduction proceeds through enamine - imine tautomerization β-enamino ester due to protonation of the nitrogen atom, which also increase the electrophilicity of the imine followed by attach $HSiCl_3$. Resultant transition state was controlled by non-bonding interactions with organocatalyst leading to conversion of product. [57]

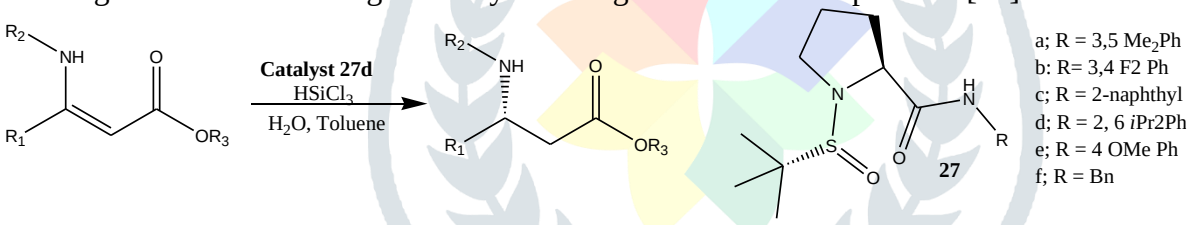


Figure 14.

From literature it is evident that, pyrrolidine-based catalysts prominently work through enamine or iminium mode of action using primary or secondary amine group of organocatalysts. For the first time, Thorat *et al*, in series of publications demonstrated exclusive use of hydrogen bonding with N-H moiety and non-bonding interactions for catalysing various asymmetric reactions using *N*-protected pyrrolidine-based catalysts. The catalysts **28 (a-d)** and **29 (a-c)** were developed by introducing *N*- tosyl /acyl group on reactive amine of proline and substituted carboxylic part by amide group (**Figure 15**). [58--64]

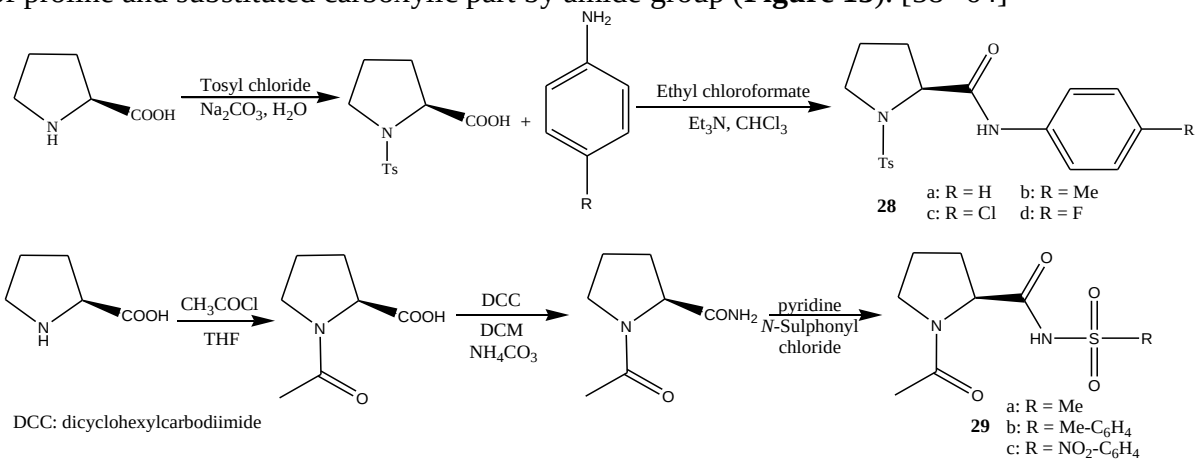


Figure 15.

The catalysts **28** (**a-d**) were screened in aldol and Henry reaction. In both type of reaction catalyst **28b** worked efficiently in to give excellent results. The Catalyst **28b** catalysed direct asymmetric aldol reaction to afford yield up to 92% with *anti:syn* ratio up to 100 % and up to 95 % enantioselectivity for *anti*-

stereoisomer. [58] Whereas, it also proved to be exceptional for production of asymmetric β-nitroalcohols along with assistance of water molecule to form product up to 87% and up to 94 % optical enrichment. [59]

The catalyst **29** (**a-c**) were tested in carbon phosphorous bond forming reactions. *viz*, synthesis of α-aminophosphates and β-malanophosphate. The catalyst **29b** was productive for asymmetric synthesis of α-aminophosphates and achieved good yields up to 90 % with enantioselectivity up to 92 %. [60] It was also fruitful to drive formation of asymmetric β-malanophosphate which gave moderate to high yield (85–64%) and good enantiomeric excess (78–53%). [61]

The catalyst **29b** along with base triethylamine catalysed Baylis-Hillman reaction offering good to high yields (73–90%) and with excellent enantiomeric excesses (up to 96%). [62] When catalyst **29 (a-c)** and base triethylamine were employed in direct aldol reaction between of chloroacetone with *p*-nitrobenzaldehyde it could fetch up to 90 % yield and 92%*ee* under optimized conditions. These optimized conditions were explored for the Knoevenagel condensation reaction where it gave traditional product as α, β unsaturated ketones at room temperature (up to 89% yield) (**Figure 16)**. However, when temperature of reaction was dropped down to -78° C, it yielded novel chiral α-cyno-β-hydroxy ketones in excellent yield with high anti selectivity and enantioselectivity. Nevertheless, rise in temperature dehydrates product destroying chiral centre and forms α, β unsaturated ketones. [63]

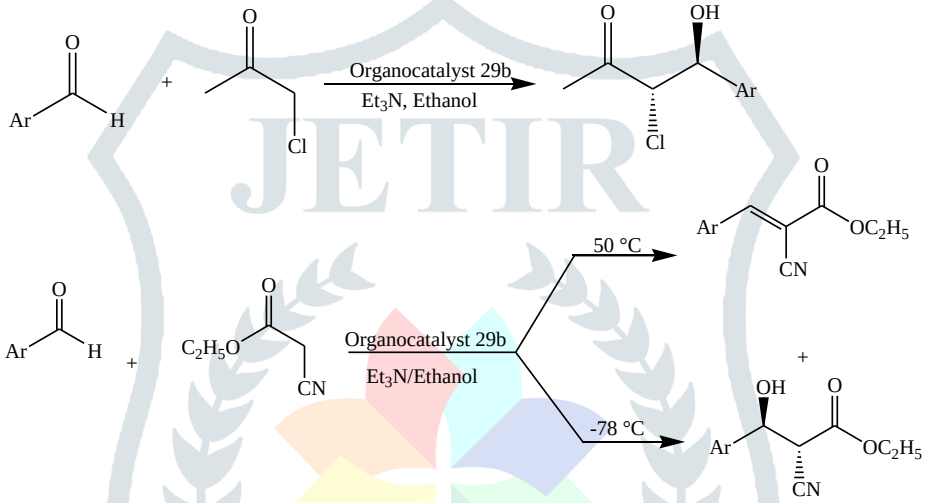


Figure 16.

Further catalyst **29** was modified and used in the asymmetric synthesis of highly dense piperidine derivatives (**Figure 17**). The organocatalyst **29e** successfully produced desired compound up to 92% yield for pure *anti* at 80°C. When reaction was performed at lower temperature at 5°C, although in moderate yields (up to 48%), dominant *syn* distereomer was obtained up to 100 % *dr* for some selected products. Albeit, yields for the reaction were improved (up to 76%) when it was raised to room temperature but stereocontrol was lost. [64]

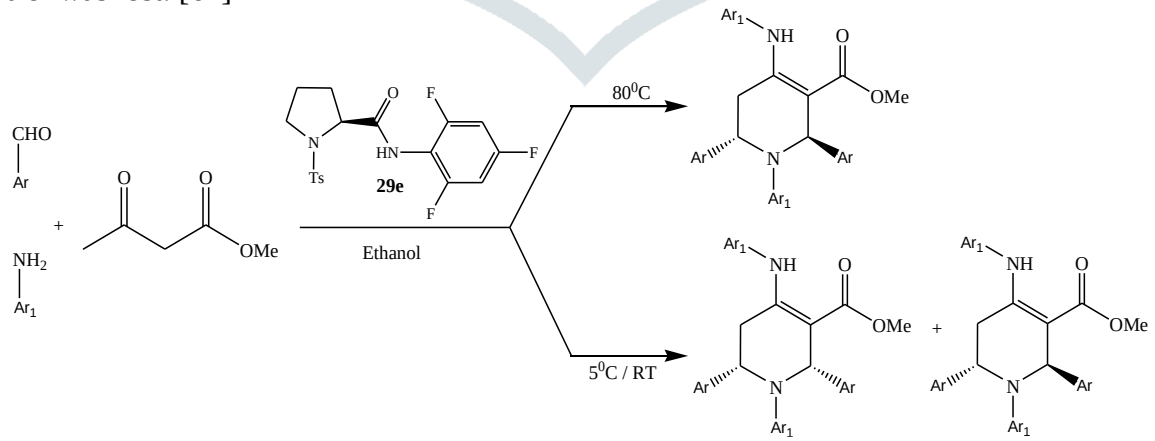
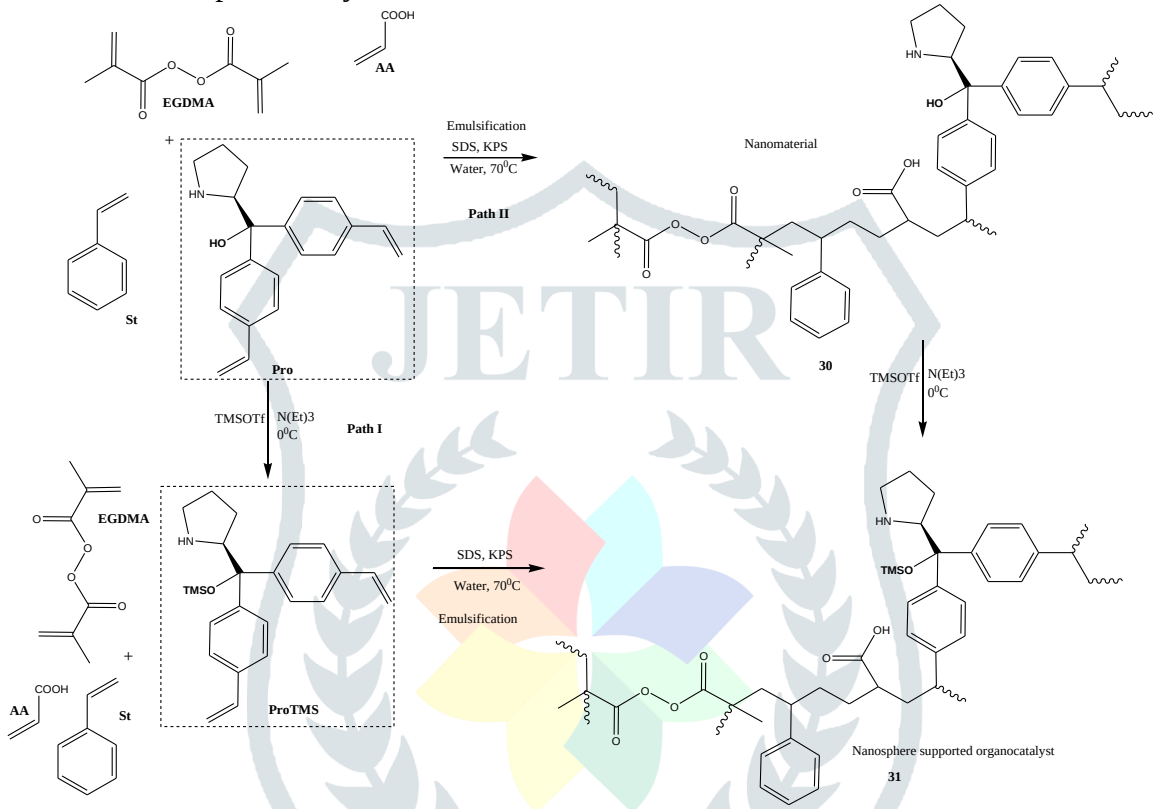


Figure 17.

Ma and others prepared nanosphere based Heterogeneous organocatalysts (**31**) for asymmetric reactions. Theses catalysts were obtained by the two different paths (**Figure 18**). In path I, emulsion polymerization of (*S*)-α, α- *bis*(4-vinyl) phenylprolinoltrimethylsilyl ether (ProTMS) with ethylene glycol methacrylate (EGDMA), styrene (St) and acrylic acid (AA) was achieved using Sodium dodecyl sulphate (SSD) as emulsifying agent in aqueous solution. Whereas Path II, a mixture of (*S*)-α, α- *bis* (4-vinylphenyl) prolinol (Pro), with EGDMA, styrene (St) and acrylic acid (AA) was emulsified to obtain nanosphere

material **30** followed by treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to get desired catalyst **31**. The various catalysts were prepared by taking differing amount of all reacting substrates, specially(*S*)-α, α- *bis* (4-vinylphenyl) prolinol (Pro). Heterogeneous organocatalysts were utilized in different C-C bond forming reactions. The catalytic activity of catalysts was found to be dependent on route by which catalysts were prepared. Catalysts (**31**) prepared by route II was more reactive than catalysts prepared by route I. The catalyst which was prepared by reacting 178.2 mg of nanosphere organomaterial **30** with TMSOTf in basic medium followed by quenching with 40ml water, proved to be the best catalyst amongst all. The Heterogeneous asymmetric three-component/triple Michael/Michael/aldol organocascade reaction *via* above said catalyst helped to obtain up to 78% yield, >19:1 *dr* and upto 99%*ee*). In addition, [4 + 2]-type cycloaddition of cyclohexenylidenemalononitrile with α, β-unsaturated aromatic aldehydes was also achieved in high yield (up to 86%, > 19:1 *dr* and up to 99% *ee*). Furthermore, the polymeric nanospheres was reused up to few cycles. [65]



EGDA-ethylene glycol dimethacrylate; AA-Acrylic acid, SDS-sodium dodecyl sulfate; St- styrene; TMSOTf-trimethylsilyl trifluoromethanesulfonate KPS- potassium peroxydisulfate; ProTMS - (S)-α, α -bis(4-vinyl)phenylprolinoltrimethylsilyl ether, Pro- (S)-α, α - bis (4-vinylphenyl)prolinol

Figure 18.

Kokotos and his research group derived a series of fluorine substituted prolinamide derivaties **33 (a-e)** as organocatalysts (**Figure 19)**. These catalysts were used in aldol reaction for their performance. Catalyst **33a** and other *o*-floro-substituted prolinamide derivatives performed well in water-organic solvent system. Almost similar yield and sterocontrol was observed for *o*-floro-substituted prolinamide catalysts. Moreover, catalyst **33d** was most efficient. It was demonstrated that the catalysts have powerful hydrogen bonding interactions with reacting substrates leading to stabilized transition state (**34**). Thus, provide great control over steroselectivity of products. Scope of catalyst was studied for various aromatic and aliphatic aldehydes with cyclohexane to obtain aldol products. Aromatic aldehydes were more suitable with catalyst **33d** giving products in high yields (up to 100%) with greater diastereo- (up to 95:5) and enantioselectivities (up to 97%), however the aliphatic aldehydes could not give good yields, but optical purity was maintained. [66]

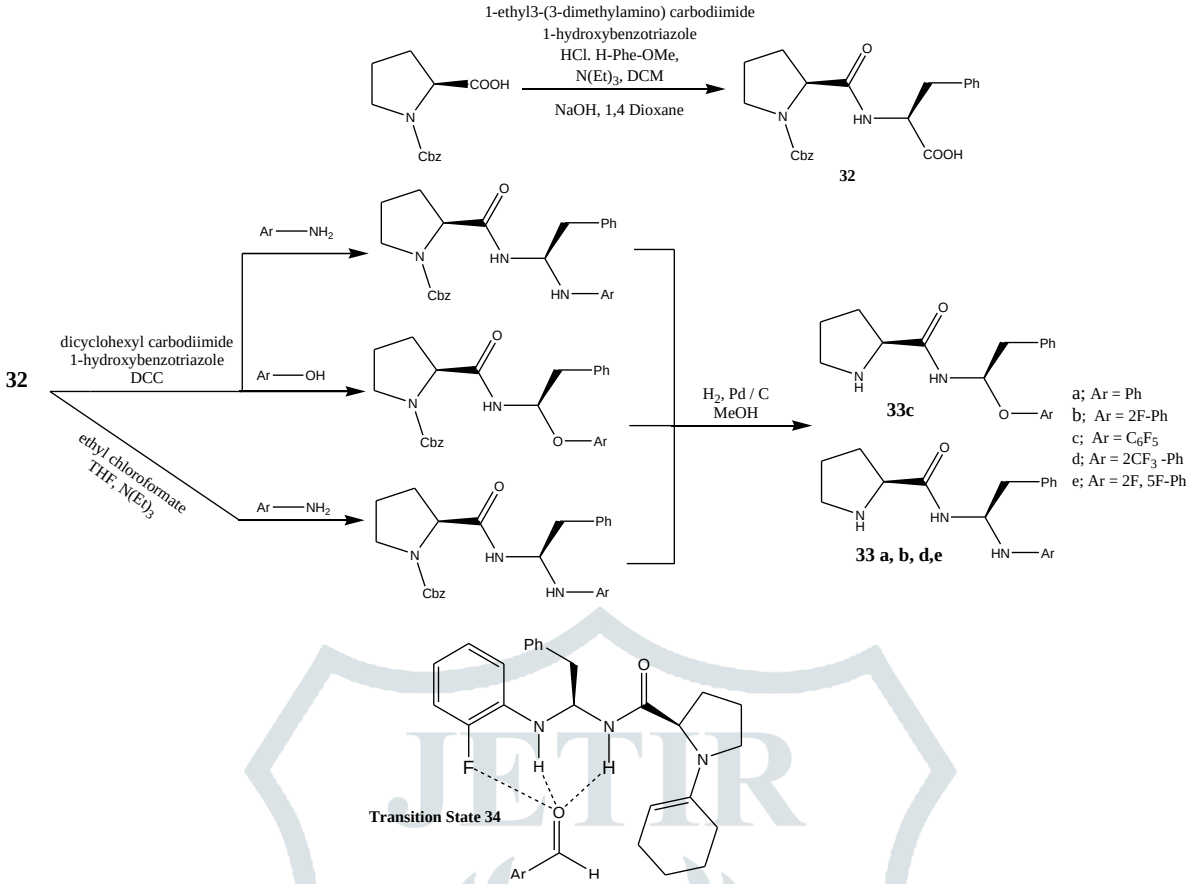


Figure 19.

A. Pich and his co-scientists demonstrated use of microgel covalently bonded proline polymer catalysts for the synthesis of asymmetric aldol reaction. Various microgel catalysts were prepared based on different proportions of L-proline and method of preparation ie., batch process **35a** and semi batch process **35b**. In batch process L-proline was incorporated in core of microgel, and in semi batch process it was in periphery of microgel (**Figure 20**). Application of these microgel catalysts was studied in both heterogeneous (water as solvent) and homogeneous (methanol as solvent) reaction conditions. Thus, catalytic mode could be tune by choosing nature of solvent and distribution of L-proline in microgel network. In homogeneous condition reaction executed well in presence of microgel catalyst in which L-proline was present in periphery of microgel (**35b**). In contrast, heterogeneous condition worked well with catalyst in which L-proline was integrated in core of microgel (**35a**). The aldol reaction in methanol and water offered up to 98 % and up to 88 %yield respectively and up to 93% *and* 90% *ee* respectively. [67]

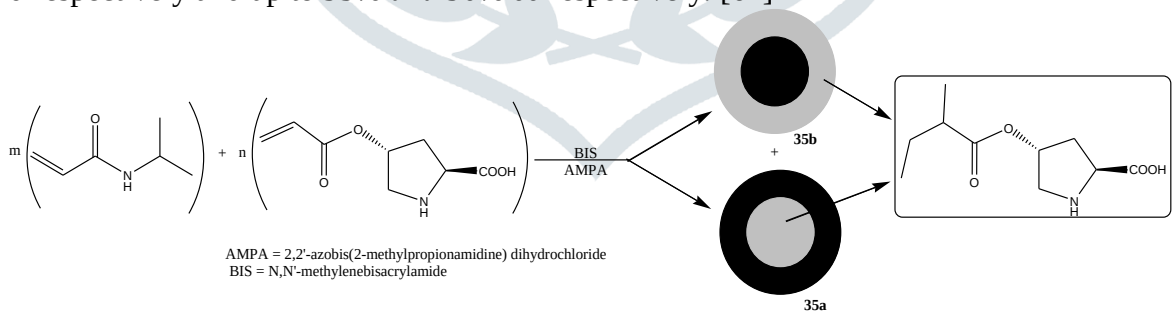


Figure 20.

Various enantiomeric transformations of O,O-dimenthyl α-iminotrifluoroethylphosphonates (NH-iminophosphonates) (**36**) was shown using organocatalytic pathways by Y.V. Rassukana *et al* (**Figure 21**). When opticaly pure dimenthyl phosphites was reacted with trifluoroacetonitrile under mild basic conditions, the reaction afforded two disteromers of dimenthyl iminophosphonates (**36**).

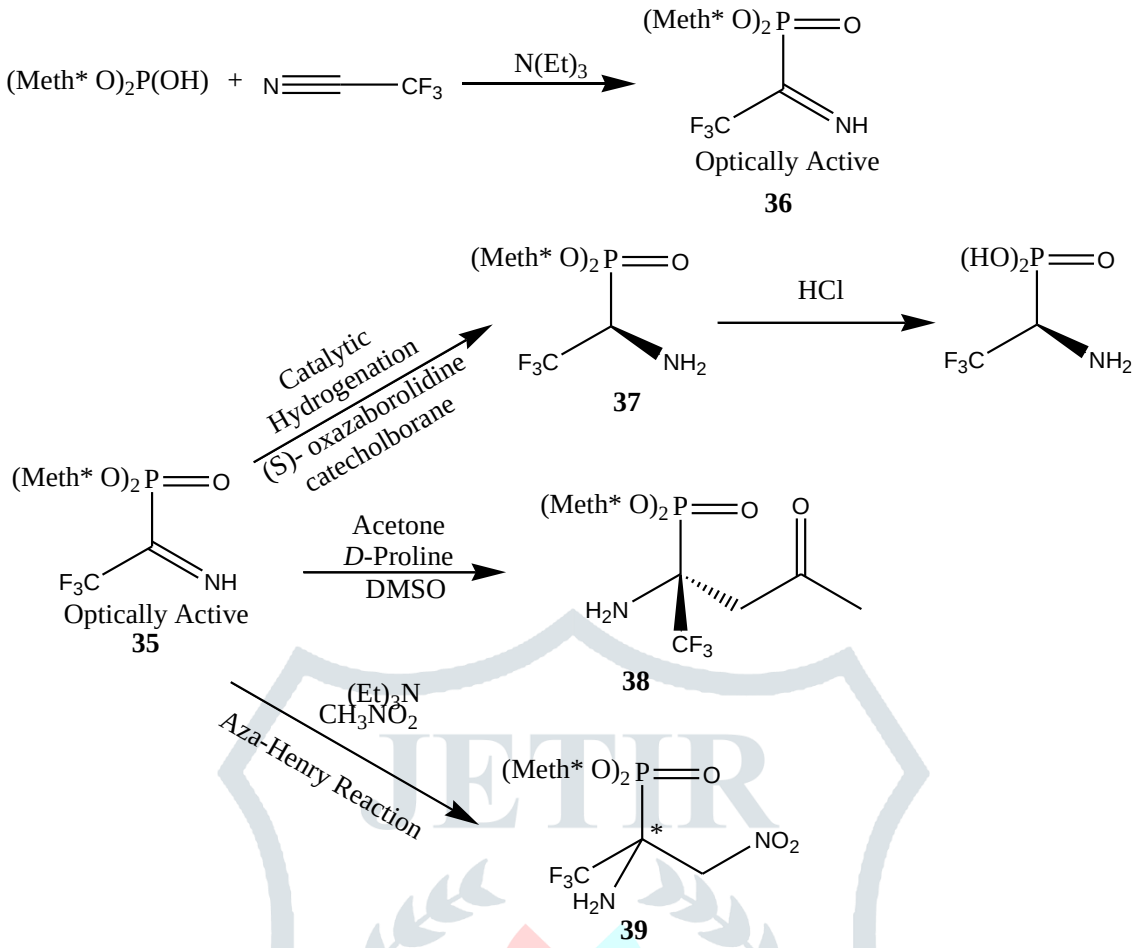
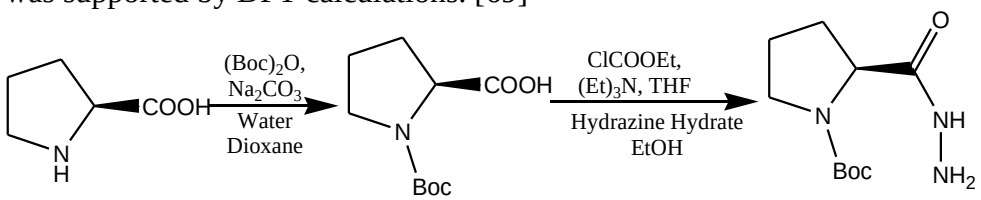


Figure 21.

This product was reduced in presence of catalyst chiral (*S*) oxazaborolidine and catecholborane as an additive, which resulted in optically active amino phosphonates (**37**) up to 84% yield and 86% *dr*. Non chiral catalysts although forced reaction to occur but failed in terms of stereo selectivity. Further, NH-iminophosphonates was treated with acetone to undergo Mannich reaction in presence of proline enantiomers to receive product (**38**) up to 86% yield and highest 87 % *de* in case of *D*-Proline catalyst. Furthermore, disteroselective Aza-Henry reaction was shown under mild basic conditions by reacting (+)-1 with nitromethane to obtain 94 % α-amino-β-nitro-phosphonates (**39**) with (2:1 *dr*). The reaction revealed good stereo control, which was supposed because of negative inductive effect of CF3 group and easily accessible N-unprotected C-N bond. [68]

Antonio and Juaristi synthesized new series of chiral derivative pyrrolidine thio tetrazole derivatives **40 (a-c)**. The derivatives were prepared under microwave irradiation in basic conditions resulting in high yielding protocol (**Figure 22**). Further these chiral compounds were tested in aldol reaction. Among all catalysts, excellent results were obtained with catalysts **40a** under solvent free condition in absence of additive. The reaction gave up to 96 % yield and up to 90% ee for anti-isomer. Although reaction was performed under solvent free conditions, enamine formation between catalysts and ketone produced water molecules, which activate aldehyde molecule to form transition state (**41**) leading to formation of product. The mechanism was supported by DFT calculations. [69]



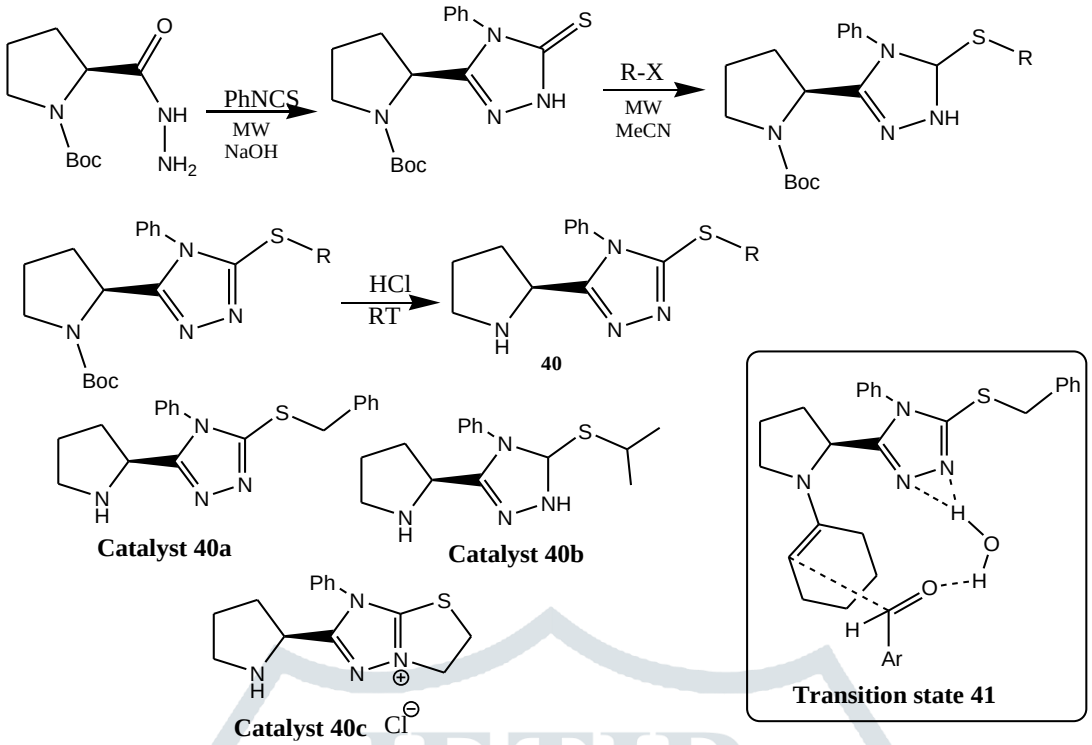


Figure 22. Synthesis of catalysts **40 (a-c)** and transition state **41**.

T. Satoh and his research team prepared three one-handed helical poly(phenylacetylene)s with proline and its analogue as attachments PPA-Pro, (**43a**) PPA-Pro-Pro (**43b**) and PPA-Pro-Hyp (**43c**) (**Figure 23**). All three catalysts were employed in the synthesis of aldol reaction for its catalytic evaluation. Catalytic activity was compared with its monomer catalysts (**42 a-c**). The catalysts, PPA-Pro-Pro (**43b**) and PPA-Pro-Hyp (**43c**) bearing dipeptide moiety resulted the greater catalytic activity and stero control than its monomer catalysts. The enlightening catalytic activity of polymer catalysts was due to the synergistic effect of the dipeptide structure with the one-handed helical mainchain of the polymer catalyst. Moreover, Catalytic performance could be increased to some extent by adding imidazole as an additive to aldol process along with dipeptide polymer catalyst. The catalysts in presence of additive yielded aldol product 64% for catalysts PPA-Pro and PPA-Pro-Pro, 69% in case of PPA-Pro-Hyp, whereas, *ee* value was highest 34% in case of PPA-Pro-Hyp. Moreover, catalysts were also reused without loss of significant activity up to few cycles. [70]

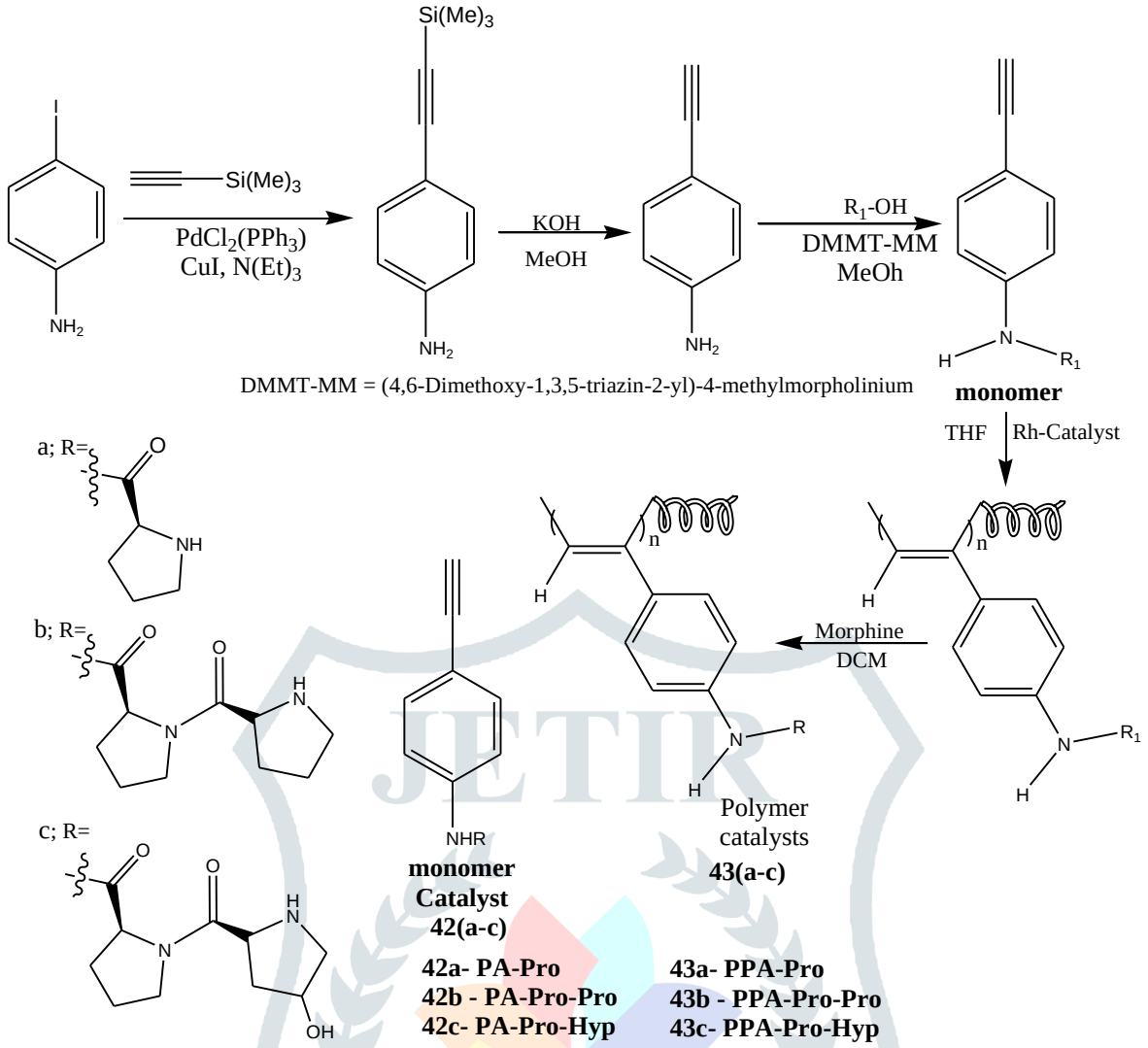


Figure 23. Synthesis of monomer **42 (a-c)** and Polymer catalysts **43(a-c)**

Hayashi in another report, demonstrated use of commercially available flurosubstituted prolinol based catalysts **44**for cross aldol reaction. The direct cross-aldol reaction was investigated between α, β - unsaturated aldehyde and propane aldehyde derivatives. The reaction was progressed in presence of organocatalyst **44** and acid additives to offer high yields for *anti*-isomer rich γ, δ-unsaturated β-hydroxy aldehydes (**45)** with enhanced enantioselectivity, which was treated further with Wittig reagent ($Ph_3P=CHCO_2Et$) in situ to obtain α, β-unsaturated ester (**46**) up to 90% yield and up to 98% *ee* for *anti*-products (**Figure 24)**. The reaction was claimed to be the first example of using acid as an additive. The role of acid was to lower the LUMO level of reactant aldehyde and help in stabilising transition state to felicitate reaction. [71]

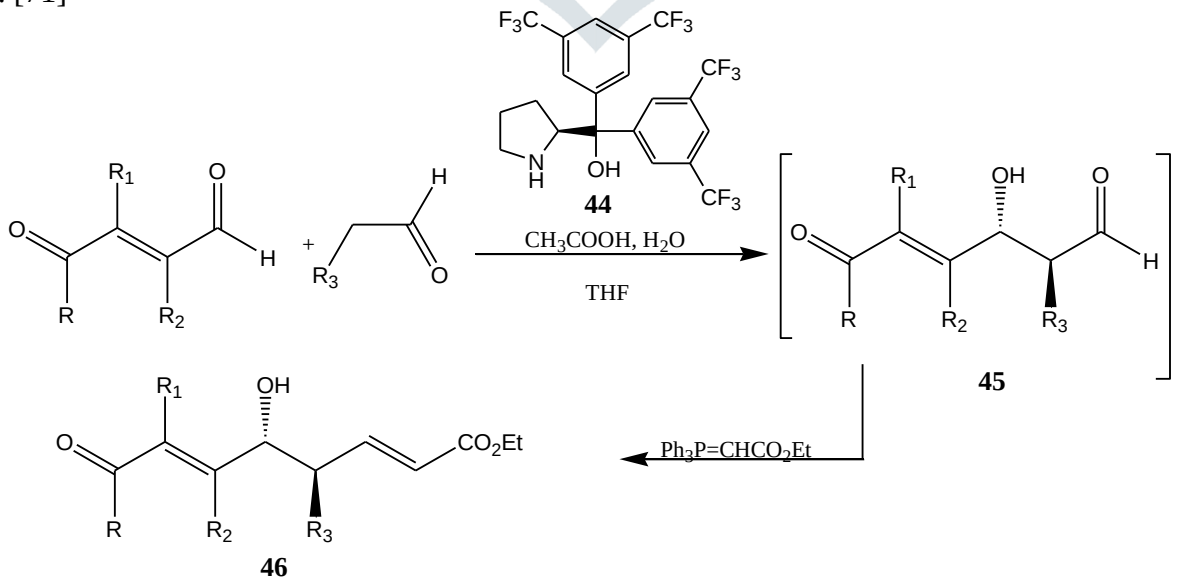


Figure 25.

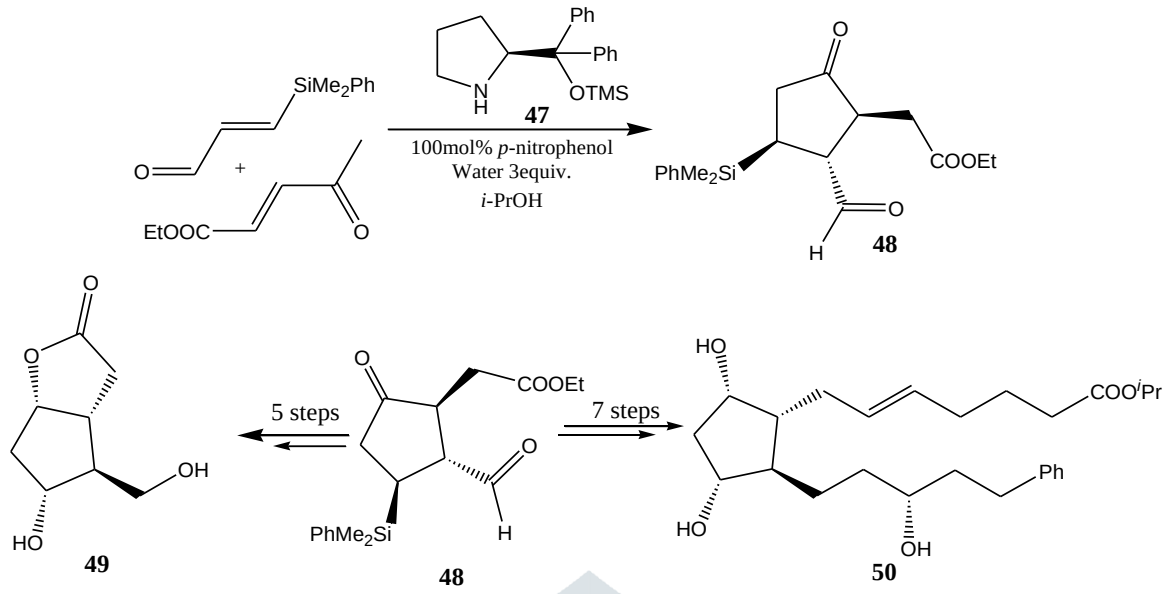


Figure 25.

Hayashi in his subsequent publications, revelled protocols for total synthesis of Corey lactone (**49**) and Latanoprost (**50**) drugs via multistep processes (**Figure 25**). The common key step of total synthesis was the production of main precursor [3-(Dimethyl-phenyl-silanyl)-2-formyl-5-oxo-cyclopentyl]-acetic acid ethyl ester (**48**), which was achieved by organoctalytic pathway efficiently and in pure optical form. The compound **48** was obtained by reacting 3-(dimethylphenylsilyl) propenal and ethyl 4-oxo-2-pentenoate in presence of commercially available prolinol based organocalalyst **47**. The reaction proceeded via [3+2] cycloaddition reaction and afforded single isomer with 99% optical purity and 90% yield. Duo scientists have proposed this method to be pot economical and time economical total synthesis.[72]

Recently, Mohanta and Bez have set protocol for the effective asymmetric synthesis of oxa-Michael addition reaction of *β*-nitroalkene and salicylaldehyde. Series of proline derivatives analogues **51 (a-j)** were designed and prepared to test the hypothesis in evaluation of asymmetric synthesis of chromenes (**Figure 26**). All catalysts supported propositions made and helped to understand mechanism well. Reaction proceeded *via* known reversible iminium ion formation with free NH of pyrrolidine catalyst. Moreover, iminium ion formation assisted to lower the nucleophilicity of the hydroxy group in salicylaldehyde. Further, *Si*-face attach of *β*-nitroalkene to this activated complex formed transition state (**52**), thus producing desired product with upto 96% yield and upto 99% *ee*. [73]

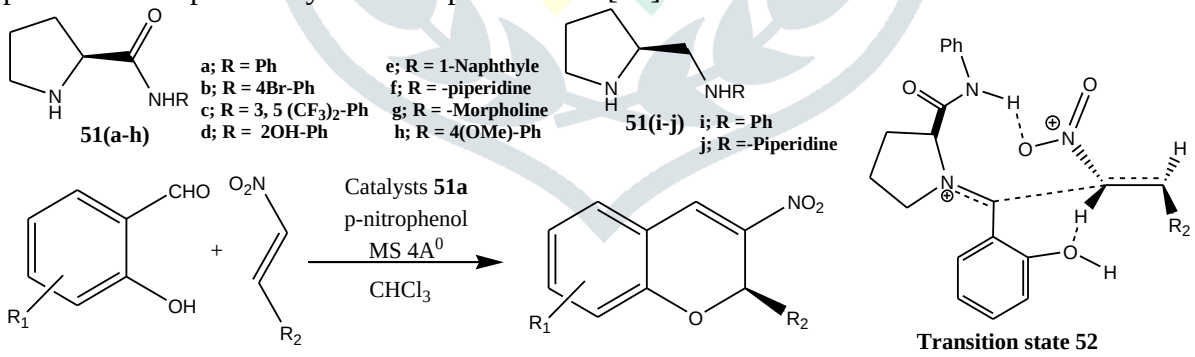


Figure 26.

Summary:

Above section evidently revels the efficiency and potency of small organic chiral molecules like, proline and its derivatives in synthetic chemistry. From last two decades it has been emerging as one of the most powerful weapons to obtain optically pure isomers, thus, avoiding tedious job of resolution of racemic mixtures. One of the most important advantages of organocatalysis is to evade non-hazardous reagents and reaction conditions and ability to control stereoselectivity of reaction by tunning catalytic structures. However, the main restriction of organocatalytic transformation is due to its high catalytic loadings (10 mol% or higher). Nevertheless, there are quite few reports where catalytic loadings very low, [74] organocatalytic field needs interrogation and development in this part as to stand with the catalytic requirements of enzymes or metal catalysts mediated reactions.

From few years, organocatalysis has been explored successfully in medicinal chemistry [75-76] and industries [77]. Organocatalysis is primary key for the expectation of atom efficiency, energy efficiency, and environmental issues and need for sustainable chemistry. [78-79] Organocatalysis are progressing its path in industries such as pharmaceutical and food industry, where metal free methods are utmost in demands and metals are not expected even in trace amount. Consequently, Asymmetric organocatalytic field is one of the most popular and significant field. Still, organocatalysis has to meet various challenges but surely will keep unlocking useful routes for synthetic organic chemistry and industry.

Acknowledgment

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