Chapter I

Introduction to amine catalysis, Mannich reaction and linear dialdehydes

1.1 Organocatalysis

In general, the term organocatalyst refers to "organic" and "catalyst" meaning the utilization of organic molecules as catalysts in synthetic transformations. Wolfgang Langenbeck gave the name organocatalyst for the first time in 1928.[1] Organocatalysts can be consist of carbon, hydrogen, nitrogen, halogens, and other non-metal atoms, and its mode of action should be non-metallic. In 2000, MacMillan and others recoined the term of organocatalysis before the scientific community to explain the utilization of small, simple, and low molecular weight organic molecules in organic synthetic transformation.[2-3] This area of research area has already gained a lot of interest among synthetic chemists and emerged as a fascinating area in the last one and half decade, because of its conceptual novelty and handy way to construct the complex molecules in a cost-economic manner.[4] Organocatalytic C-C, C-N, C-O, C-S, and C-X bond formation in asymmetric and non-asymmetric fashion have set a benchmark in the area of catalysis.[5-10] Organocatalysts offer several advantages, e.g., inexpensive, metal-free, non-toxic, easy accessibility, low moisture/air sensitivity, and cost-effective over the earlier modes of catalysis. Nature has provided us many enantiomerically pure organic molecules from where we can pick the desired unit, e.g., carbohydrates, nucleic acids, and amino acids, which can be used as such in the original form or can be further modified as per the requirement used as a catalyst for the synthetic transformations. With the various modes of activations of substrates, organocatalysis has already been applied to multiple synthetic transformations, such as Mannich, Henry, Michael additions, Aldol, Baylis-Hilman, Knoevenagel reactions, Stetter reaction and in cycloaddition, elimination, rearrangements, substitution reactions and many more type of organic conversion (**Figure 1.1**). These reactions having already been applied for the many carbo-, and heterocyclic compounds that show enormous applications in chemistry, biology, and pharmaceuticals. [12] During our study, we are particularly interested in the amine-catalyzed Mannich reaction and its use in the synthesis of medium-sized nitrogen heterocycles (MNHs) in asymmetric and non-asymmetric fashion. Usually, organocatalysts are comparatively less virulent than transition metals; therefore, very easy to handle even at the multi-gram level. The availability of organocatalysts is excellent and can withstand air and moisture, usually requires low amounts, and often transformations are carried out under soft reaction conditions and moderate concentration.[13]

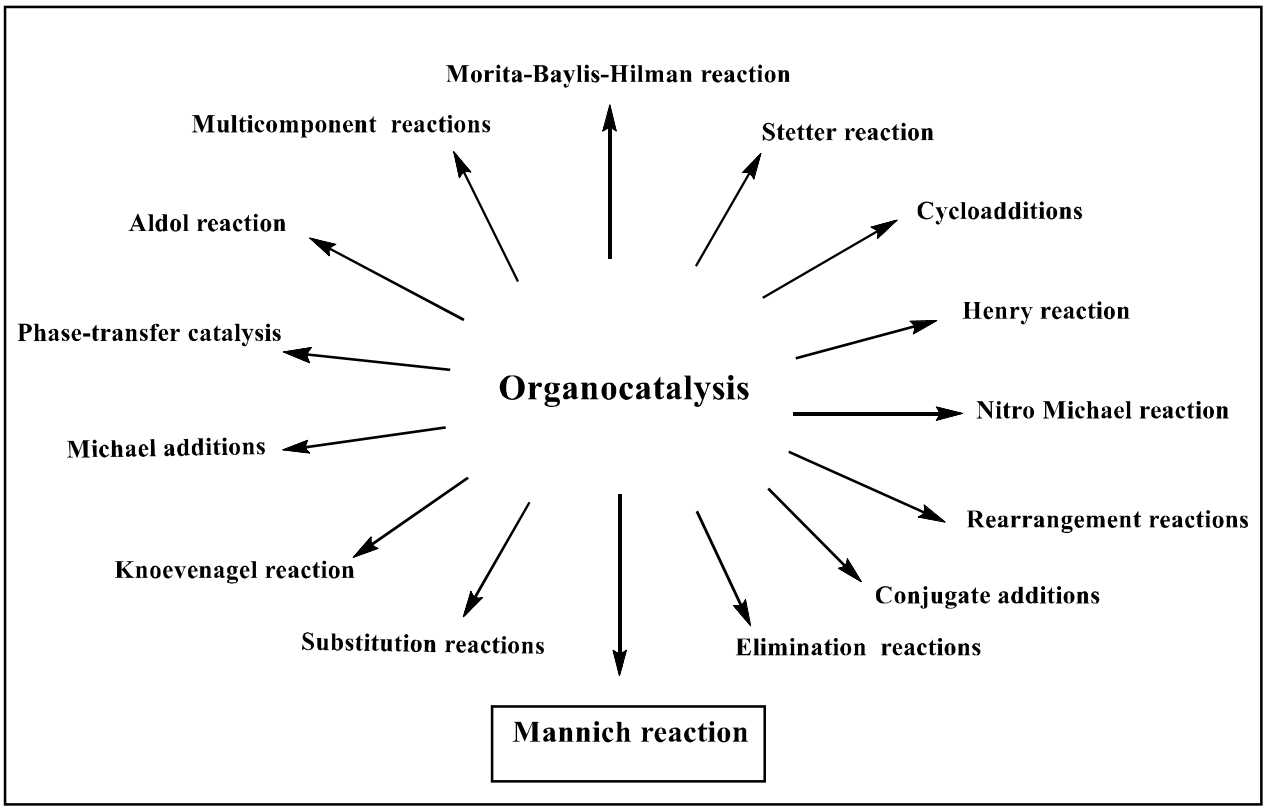


Figure 1.1 Scope of organocatalysis for several type reactions

During the last decade, organocatalysis has been one of the most rapidly growing and competitive fields in asymmetric catalysis and developed as a third pillar next to metal and biocatalysis.[15] In addition to this uniqueness, organocatalysts are tolerant of several functional groups, seeks to reduce energy use, and avoid time-consuming and protecting group manipulations for carrying out such type of chemical transformations.[14, 15] Organocatalysts, particular, involves peptides, amino, chiral thiourea, cinchona alkaloids, squiramide, chiral brønsted acid, and chiral brønsted base, and quinine, work through various modes of activation. In general, organocatalysis has two main patterns of activation through which they activate the substrates (both nucleophile and the electrophile), in addition to generating a chiral environment responsible for setting the chirality in the product. Organocatalysts can be classified into two main categories, such as non-covalent and covalent catalysis depends on their modes of interaction with the substrate. A structurally diverse range of organocatalysts are available, a selection of which is shown in (**Figure 1.2**).

In non-covalent activation, the catalyst activates the substrate *via* non-covalent interaction such as ionic interaction, e.g., cinchona alkaloids derived chiral phase transfer catalyst or hydrogen bonding catalyst,[16] e.g. phosphoric acid[17-22] squiramide and thiourea.[23,24] Whereas, in covalent

catalysis, activation of the substrate takes place through the covalent bond formation between organocatalyst and substrates.[15] Amine catalysis and carbene catalysis are included In this category.[25]

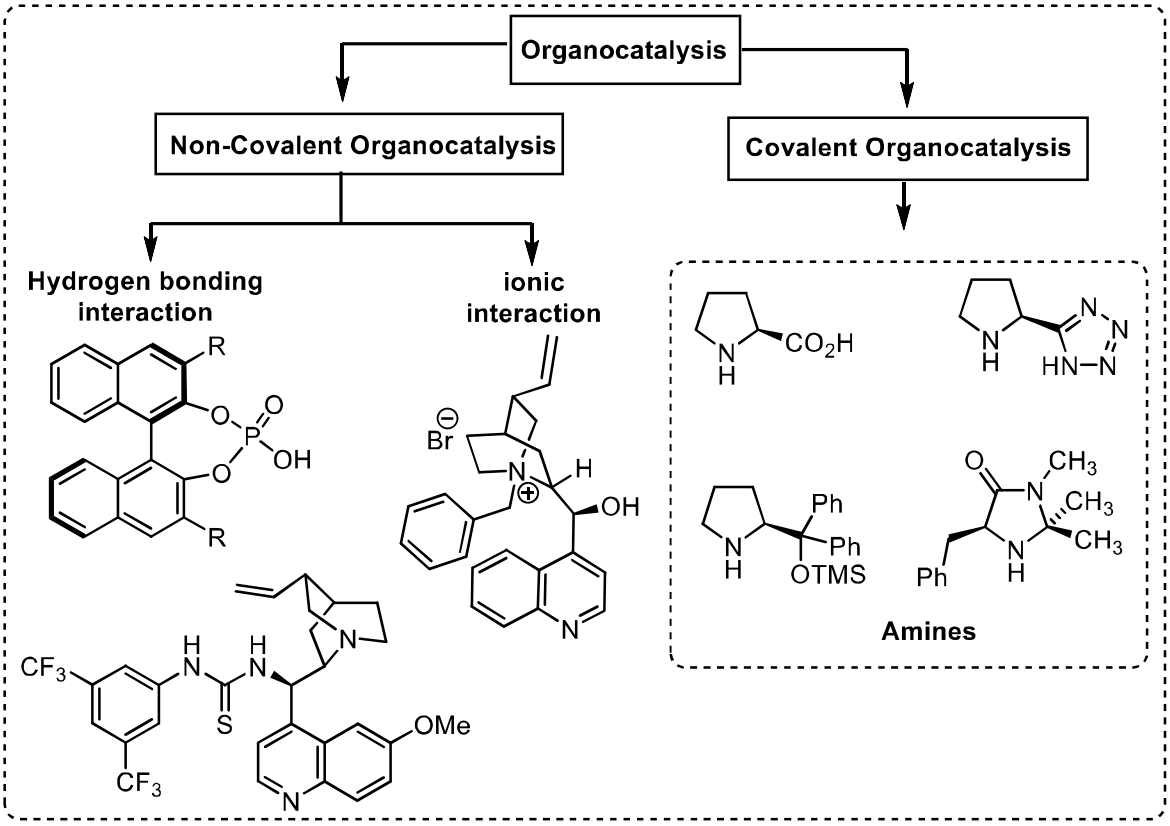


Figure 1.2 Activation of the substrate through different activation strategies

1.2 Amine catalysis

In the 19th century, Knoevenagel investigated that carbonyl functionality can be activated for nucleophilic addition, in the presence of amine, carbonyl compounds (aldehydes and ketones) with malonates and β-ketoesters and proposed the mechanism of intermediates, i.e., enamine and iminium ion intermediates.[27-30] After Knoevenagel, due to the novelty of the concept, several scientists explored this concept and made various essential discoveries, including many asymmetric catalytic examples.[31] Due to the originality and simplicity of the idea, it has been widely and became the most promising area of research for chemists. Amine catalysis is flanked between enamine and iminium-ion intermediates. In enamine-activation, HOMO (highest occupied molecular orbital) energy level of enamine-intermediate increases, i.e., electron density increases due to lone pair of nitrogen, is in conjugation with substrate double bond. While, in the case of

iminium-ion activation, LUMO (lowest unoccupied molecular orbital), the electron density of substrate withdraws by positive charge nitrogen ion; as a result, lowered the energy level of LUMO (**Figure 1.3)**. This concept put forth its elaboration and extended up to SOMO (singly occupied molecular orbital), diamine,[32-35] and triamine.[36-39] Substrate activation by covalent mode carried out by small and simple organic molecules now became a stable and versatile field in organocatalysis. Asymmetric amine-catalysis methodology has now been transformed for large scale synthesis, which provokes the scientific community to apply this concept for their metal-free asymmetric and more useful combination of natural moieties.

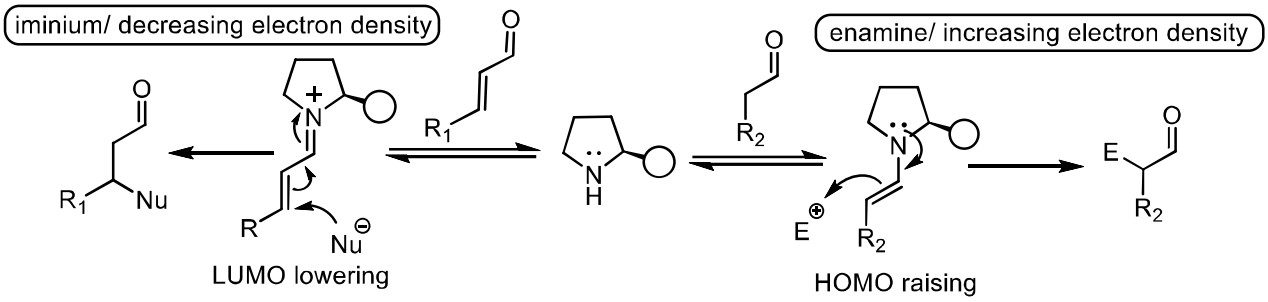


Figure1.3 Amine catalysis involving iminium-ion and enamine activation modes

Mainly, in amine catalysis, enamine intermediate has made significant contributions in the growing area of organocatalysis through various asymmetric transformation/cascade/domino reaction in one-pot operations. Considering our research interest in the covalent mode of substrate activation, we focused on amine catalysis, which deals with the activation of carbonyl compounds through enamine intermediate (**Figure 1.4)**.

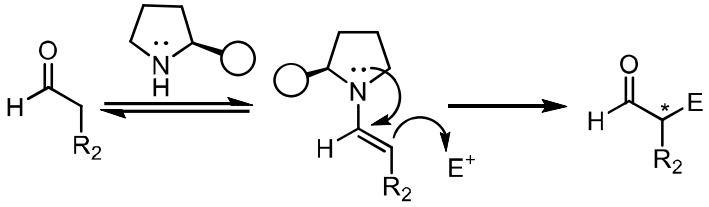
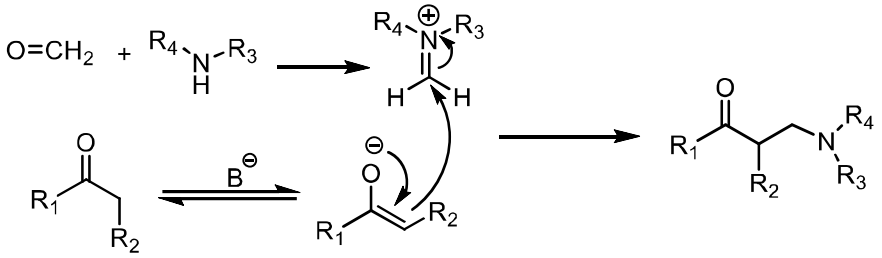


Figure 1.4 Covalent mode of activation of substrates *via* enamine intermediate

1.3 Mannich Reaction

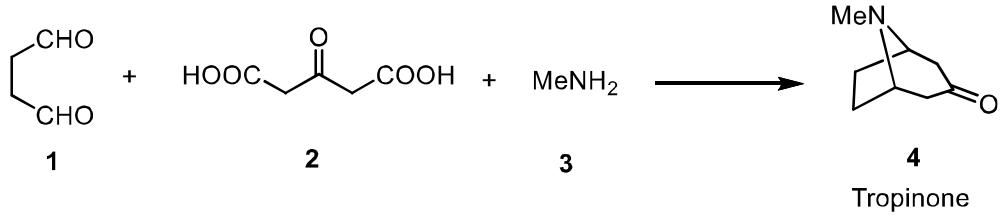
The Mannich reaction was named after scientist Carl Ulrich France Mannich in 1912. This reaction has been explored extensively for metal-free amine catalyzed asymmetric as well as non-asymmetric transformation. This nucleophilic addition is known as amino alkylation, which involves non-enolizable carbonyl compounds (having no α-hydrogen) and enolizable carbonyl compounds (having α-hydrogen). The whole transformation underwent condensation in the

presence of secondary and primary amine, which activated non-enolizable carbonyl compounds (**Scheme 1.1).** [40]



Scheme 1.1 Formal representation of Mannich reaction

This reaction mentioned in the above methodology is perfect, because it easily incorporates nitrogen atom in the products, in several pharmaceutical compounds and natural products. Only after five years of discovery of Mannich reaction, in 1917, Robinson did the total synthesis of tropinone **4**[41] by using Mannich reaction. As described above, succinaldehyde **1,** diethyl 3-oxopentanedioate **2,** and methylamine **3** have reacted and transformed into resulting product tropinone **4**. The systematic presentation of the reaction shown below (**Scheme 1.2**).



Scheme 1.2 Important application of Mannich reaction for tropinone synthesis

1.4 Development of amino-catalytic direct Mannich reaction

The asymmetric Mannich reaction has great potential to construct carbon-carbon bonds handily; therefore, it is very efficient to direct the synthesis of nitrogen-containing heterocyclic compounds.[42-48] The Mannich reaction involves carbonyl compounds as Mannich donor and pro1c0hiral imines as Mannich acceptor, resulting in the C-C bond formation adjacent to nitrogen in the nitrogen heterocycles. Mannich reaction has been classified as a direct and indirect Mannich reaction based on the reacting partner; if preformed imine and enolate equivalent are used, then it's called indirect Mannich reaction and if imine as well as enolate generated *in situ* in a reaction it is called direct Mannich reaction (**Figure 1.5)**.[49]

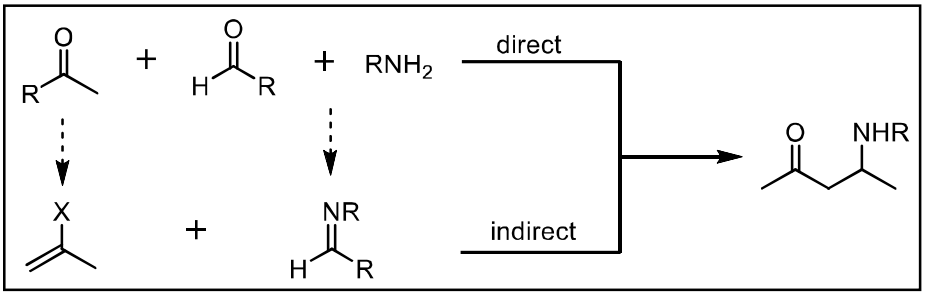
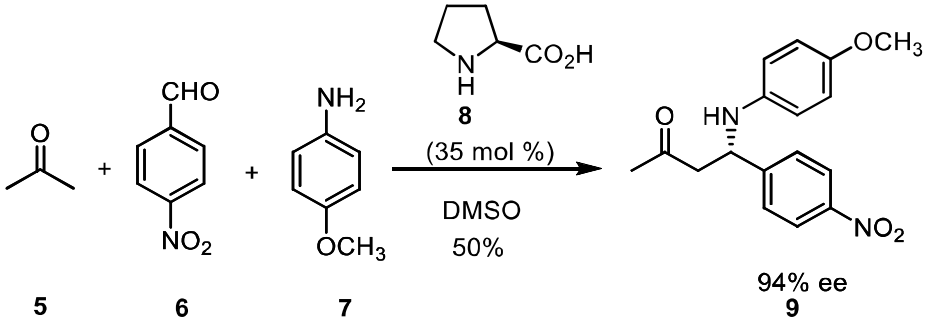


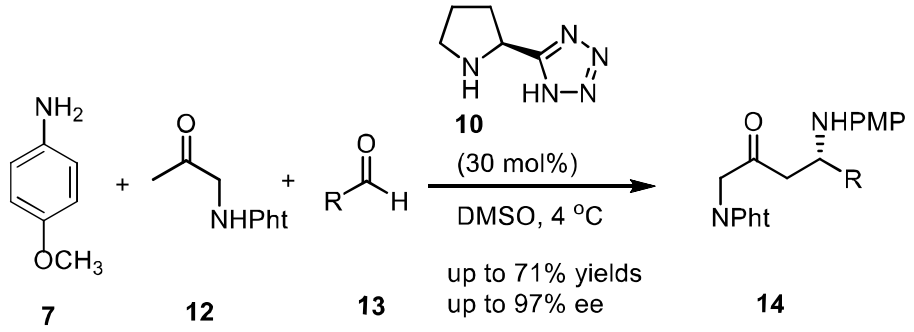
Figure 1.5 Representation of direct and indirect Mannich reaction

Chiral amine catalyst generates chiral enamine intermediates in the course of the reaction, which attack Mannich accepter, usually prochiral aldimines as a result of the formation of *β*-aminocarbonyl (*β*- aminoketones, *β*- amino aldehyde)[50] as the Mannich product with one and more stereocenters. The great quality of a catalyst is to generate chirality in molecules smoothly; at the end of the reaction, the catalyst gets regenerate for further reaction. A wide range of organocatalysts have been developed for asymmetric Mannich reactions, among them, proline and its derivatives have emerged as most applied organocatalyst to access *β*-amino carbonyl compounds asymmetrically. In some examples, these strategies have proved to be efficient for the synthesis of biologically useful *β*-amino acids having quaternary stereocenters, which are substituted by nitrogen atom next to a carbonyl group.[51-54] In the initial stage of exploration of the Mannich reaction, metal catalysis was explored for this reaction; however, List and co-workers used L-proline as amine-catalysts for the direct Mannich reaction.[55,56] They developed the first efficient proline-catalyzed asymmetric three-component direct Mannich reaction of different ketones **5**, *p*-anisidine **7,** and aldehydes **6.** The grateful quality of the proline catalyst is to provide the desired Mannich product in the enantiopure form **(Scheme 1.3).** This milestone discovery attracts the scientific community to work in the area of the organocatalytic Mannich reaction.



Scheme 1.3 First organocatalytic asymmetric Mannich reaction

Barbas III and co-workers[57] have also initially explored the Mannich reaction in the presence of pyrrolidine based tetrazole catalyst **10**, involving protected amino ketones **12**, aldehydes **13** and *p*-anisidine **7** with high regio-, and enantioselectivity, that proven to be a good method to synthesize 1,4-diamines **14** asymmetrically from phthalimido ketones as shown in **(Scheme 1.4)**.



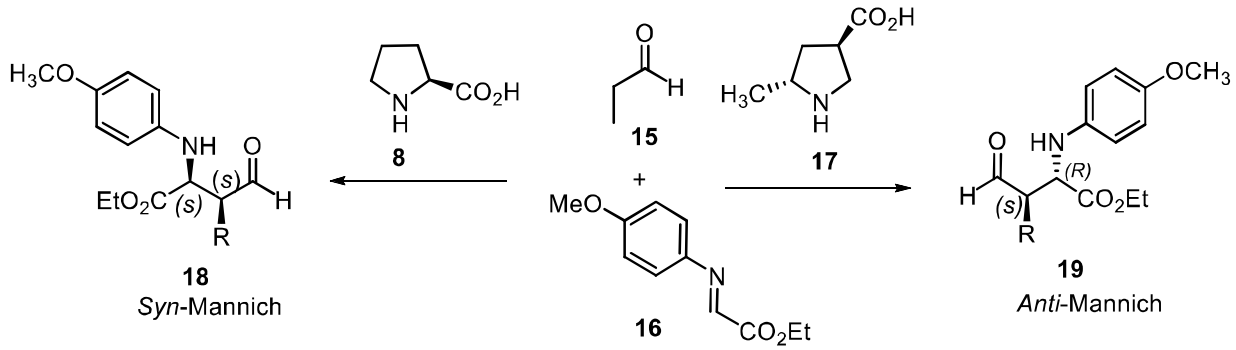
Scheme 1.4 Synthesis of Protected 1,4-Diamine through asymmetric Mannich

Apart from direct and indirect Mannich reaction, Mannich reaction also classified based on the stereochemical outcome of the product.

(1) *Syn*-Mannich reaction: Mannich products receive the *cis*-stereochemistry

(2) *Anti*-Mannich reaction: Mannich products have *trans*-stereocenters

In Mannich reaction relative configuration of the product, i.e., *syn*- and *anti*-conformation can be explained through the transition state. The following transformation explains below gives a clear idea concerning these two complementary mechanisms.



Scheme 1.5 Organocatalytic asymmetric Mannich reactions in *syn*/*anti*-fashion

1.4.1 *Syn*-Mannich reaction, mechanism and utility

Based on the catalytic approach using L-proline as organocatalysts, Mannich reactions exclusively provide *Syn*-Mannich products that have been disclosed in literature so far. The reason behind *Syn*-product is the stereochemical repulsion of PMP (*p*-$OMeC_6H_4$) and proline moiety. Besides,

hydrogen bond activation of imines by acid functionality of proline is responsible for *Si*-face attack at aldimines by the *Si*-face of *(E)*-enamine.

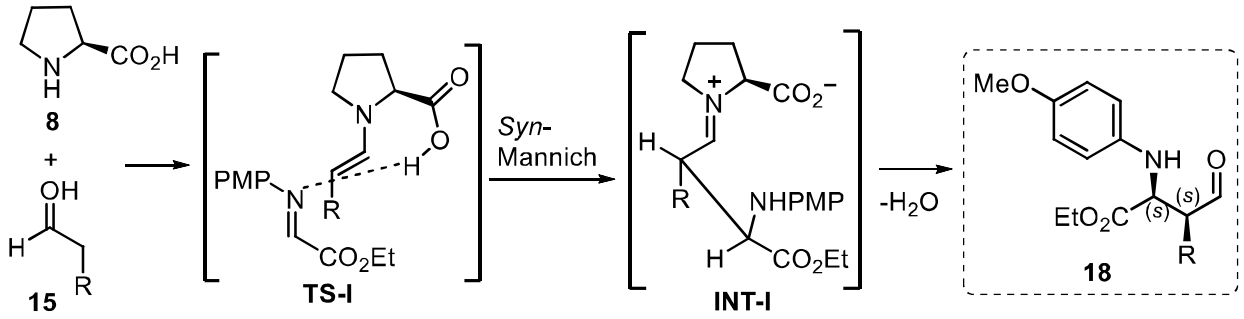
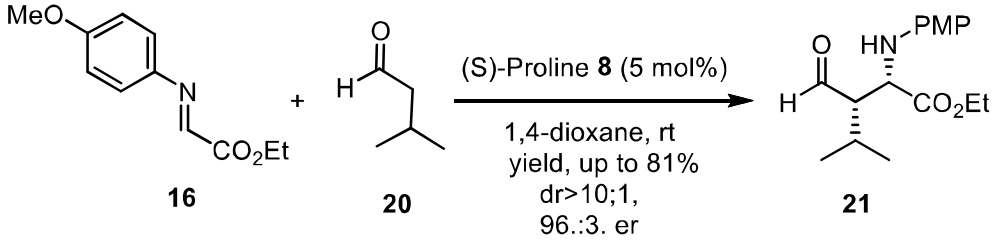


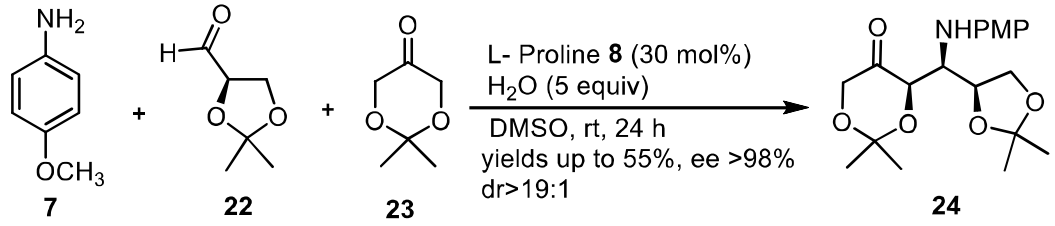
Figure 1.6 Mechanistic representation of the organocatalytic asymmetric *syn*-Mannich reaction

Barbas and co-workers contributed to developed the proline catalyzed Mannich reaction by incorporated aldehydes as donors.[58] Moreover, *N*-PMP protected α-amino-ester **21** was synthesized by treated corresponding starting materials *N*-PMP protected α-imino ester **16** with an excess of iso-valeraldehyde **20 (Scheme 1.6).**



Scheme 1.6 Proline-catalyzed Mannich reaction using unmodified aldehydes in the first time

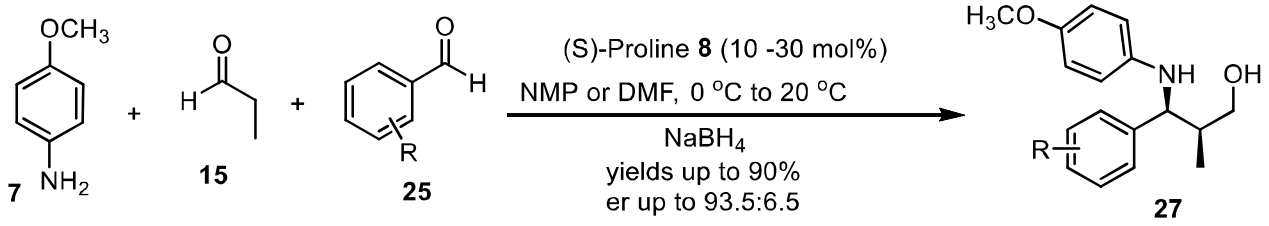
Diastereomeric ratio enhanced as the steric hindrance increases on aldehydes. Again, similar results were published by the same group when treated preformed α-imino-esters as starting substrate.[59] Córdova group promoted a three-component asymmetric *syn*-Mannich hypothesis by treating protected *p*-anisidine **7**, aldehydes **22,** and dihydroxyacetone **23** with L-proline **8** to afford protected 4-amino-4-deoxy-D-fructose **24** shown in **(Scheme 1.7)**.



Scheme 1.7 Asymmetric Mannich reaction for the synthesis of amino sugar derivative

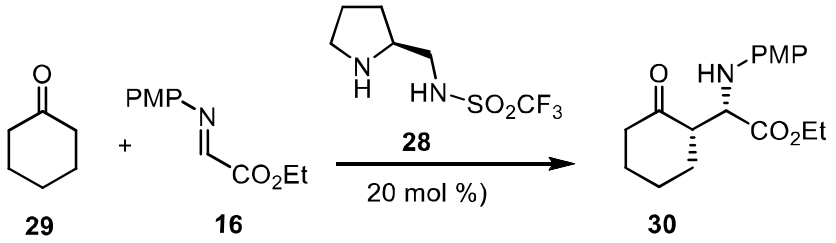
Hayashi**,**[60] Córdova[61], and co-workers independently developed proline-catalyzed three-

component, the cross-Mannich reaction of *p*-anisidine 7 and aldehydes. However, both methods were slightly different from each other, but they used the common solvent system,i.e., *N*-methyl pyrrolidinone (NMP)and Dimethylformamide (DMF), even the operating temperature was also similar, range of 0 °C to –20 °C. In most cases, the final product was N-protected *β*-amino alcohols **27**, which was obtained by *in situ* reductions of corresponding N-protected *β*-amino-aldehydes by $NaBH_4$ (**Scheme 1.8**).



Scheme 1.8 Representation of three-component enantioselective cross-Mannich reaction

Aldehydes **15** could be varied, serve as a donor; however, the aromatic aldehydes **25** mostly behaved as acceptors. The reactions showed excellent selectivity and enantiomeric ratios (around 95:5) in most of the cases. The diastereomeric ratios were also high up to >95:5 with good to excellent yields (70-90%) in most of the cases. Barbas and coworkers also reported the self-Mannich reaction between two aliphatic aldehydes,[62] however, the selectivities of products generally formed were neither enantiomerically, nor diastereomerically sound. The product **27** was derived with poor *er* (59:41) even sterically bulky aldehydes; *iso*-valeraldehyde **20** was used in the screening process. Thus, proline has been widely used as a catalyst in Mannich reaction because of its high selectivity, easy handling, and nontoxic nature. Apart from this, both the enantiomeric form of proline are cheap and easily accessible. Although, other catalysts derived from pyrrolidine to perform Mannich reaction between ketones and aldehydes have been developed by List[55], and Barbas[63] but proline remain as the best choice of catalyst. Córdova also screened alanine or serine (acyclic amino acids) catalyst to catalyzed Mannich reaction, which also exhibited good selectivities.[64] Wang and co-workers developed proline's modified pyrrolidine-sulfonamide **28** catalyst as an alternative of proline to catalyzed the Mannich reaction of ethyl glyoxylate imine **16** and cyclohexanone **29** in aprotic and protic solvents. The resulting *syn*-Mannich products **30** formed was obtained with high enantiomeric ratios (>98.5:1.5), as well as diastereomeric ratios (>95:5) with yields vary from moderates to good (76% to 90%) (**Scheme 1.9**).[65]



Scheme 1.9 Pyrrolidine-sulfonamide as an alternative form of proline catalyst

As the solubility of proline is low in less polar solvents, the proline-catalyzed reaction is usually conducted in highly polar solvents such as DMSO or DMF. Moreover, S. Ley and co-workers evaluated catalysts **31**, **32,** and **33** (**Figure 1.7**) in less polar solvents for similar sets of reactions. He found a new catalyst that was efficient in DCM or THF, obtained product **30 (Scheme 1.9**) with diastereomeric ratios (>95:5), and with high enantiomeric ratios (>97.5:2.5). Even low catalyst **33 (**1.0 mol%) loading was capable enough of catalyzing the reaction efficiently with maintaining enantioselectivity.[66]

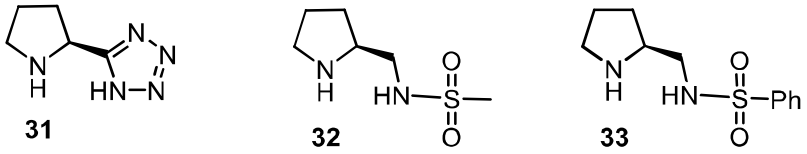
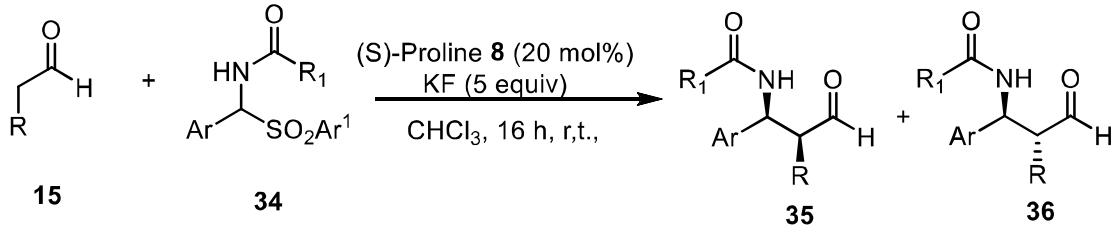


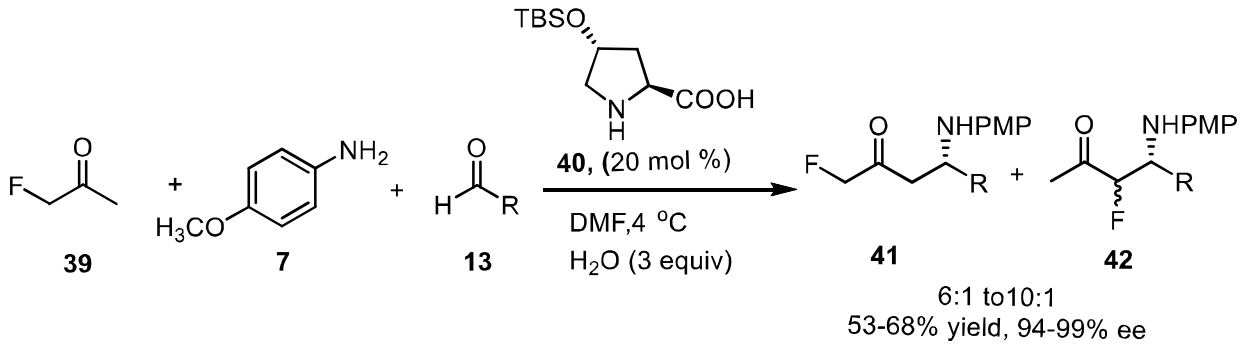
Figure 1.7 The improved forms of amine-catalysts for the Mannich reaction

Zhao and co-workers, in 2010, reported the organocatalytic Mannich reactions involving aldehydes **15** and *α*-amidosulfones **34** afforded *β*-amino aldehydes **35** (major product) in one pot with good yields and high enantioselectivity up to (99% ee) and diastereoselectivity (95:5) (**Scheme 1.10**).[67]



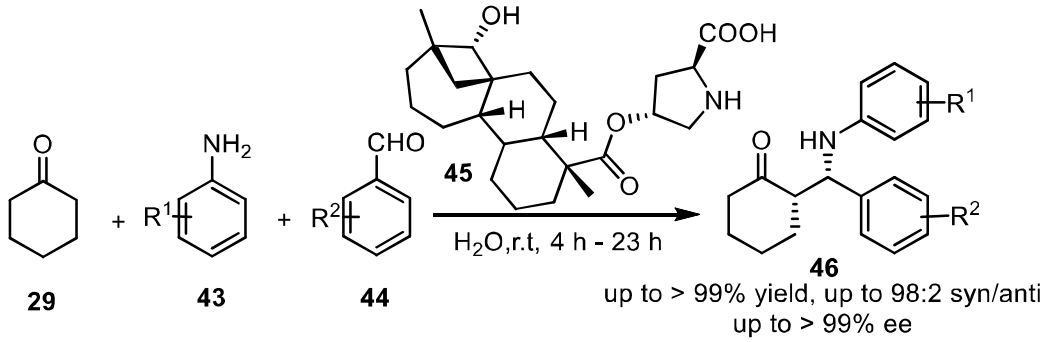
Scheme 1.10 Direct organocatalytic asymmetric Mannich reaction of aldehydes and amidosulfones

In 2011, Lu *et al.* reported a high enantioselective multi-component direct Mannich reaction, employing fluoroacetate **39**, *p*-anisidine**7**, and aldehydes **13** catalyzed by 4-siloxyproline **40** furnished efficient, important fluorinated *β*-amino ketones **41, 42** having pharmaceutical importance **(Scheme 1.11).**[68]



Scheme 1.11 Organocatalytic synthesis off fluorinated *β*-amino ketones

Y. J. An *et al.*[69] recently developed functionalized proline **45** that catalyzed three-component asymmetric *syn*-Mannich reactions of aromatic aldehydes **44** with cyclohexanone **29** and anilines **43** in the presence of water furnished product **46** with excellent enantioselectivities (up to >99%) and diastereoisomeric ratio (*anti*/*syn* up to 98:2) (**Scheme 1.12**).



Scheme 1.12 Representing *syn*-Mannich reaction using amphiphilic organocatalysts

The two proline-derived catalysts (**17** and **47**), catalyzing the asymmetric *anti*-Mannich reaction if the reaction proceeds through any one of the given transition states, as shown in **(Figure 1.8).** In transition state, **TS-**IIa imine approaches from the back phase because top-phase is blocked by the large group and in transition state IIb due to steric hindrance within catalyst due to below the plane methyl group, enamine double bond move away from methyl and towards acid functionality. In 2002, Barbas and co-workers reported the first organocatalytic Mannich product with *anti*-stereoselective outcome in which imine **16** and aldehydes **49** were reacted in the presence of (*S*)-2-methoxymethylpyrrolidine **38** (20 mol%) as catalyst to furnished *β*-formyl-functionalized leucine derivative **50** (R_1= *i*Pr) with 44-78% yields, with high enantiomeric ratio (up to 91:9) (**Scheme 1.13**). Employing first designed chiral amino trifluoromethanesulfonamide **51** (5 mol%) as an amine catalyst[71] by Maruoka and co-workers enhanced the *anti*-selectivity of Mannich product. This reaction involved *N*-PMP protected imino-glyoxylates **16** and aldehydes **13,** underwent

smooth transformation affording α-amino-aldehydes **48** with excellent enantiomeric access and great *anti*/*syn*-ratio. Trifluoromethanesulfonamide catalyst **51** based on a seven-member BINAP ring, and its backbone is responsible for generating chirality in the product**(Scheme 1.14)**.

1.4.2 Direct *anti*-Mannich reaction, and mechanism

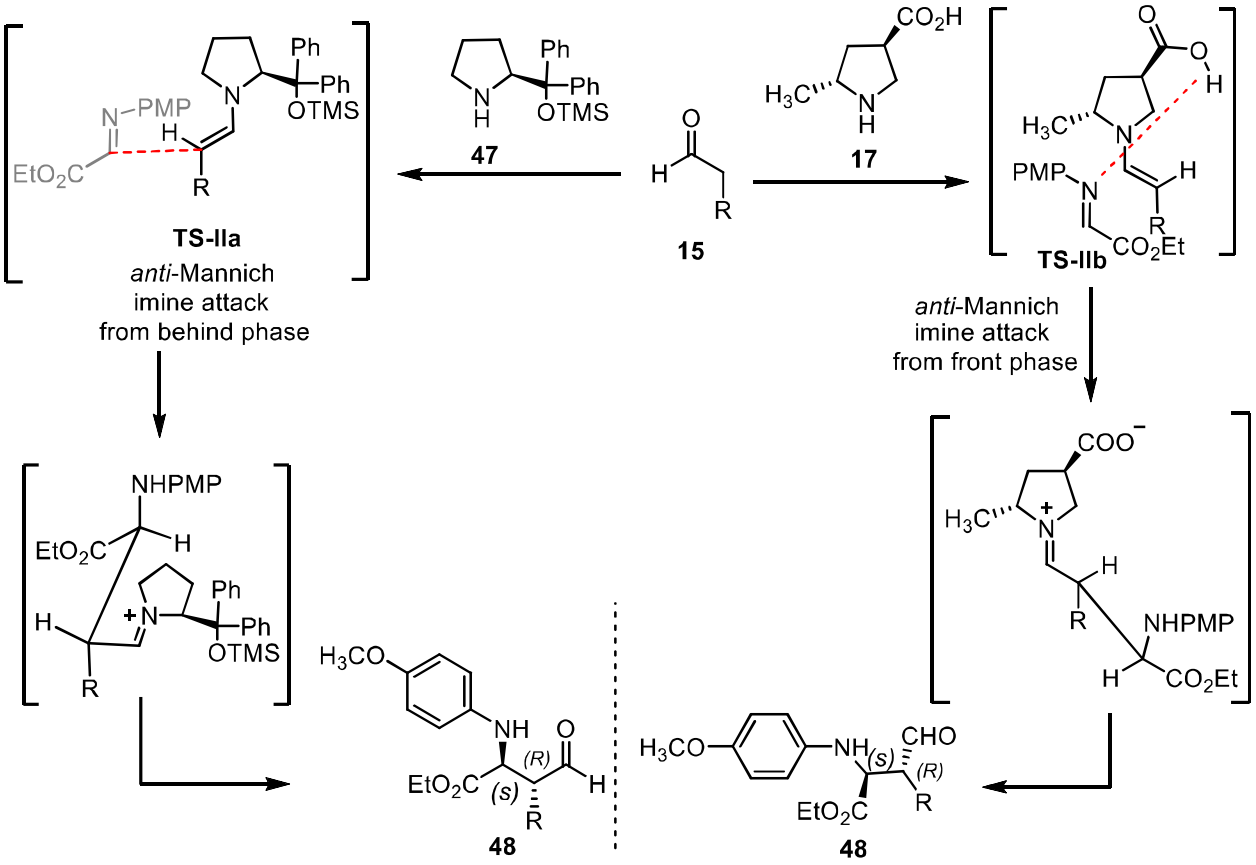
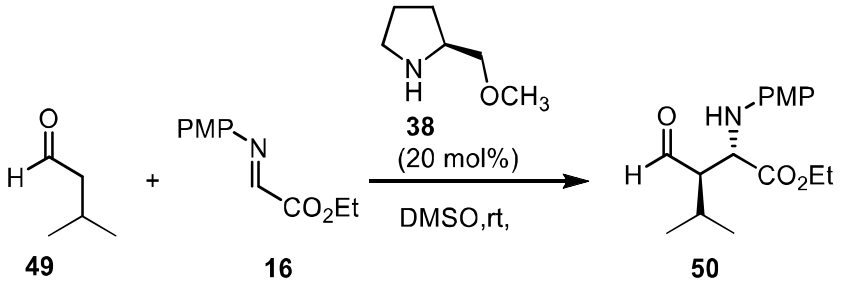


Figure 1.8 Mechanistic aspect of the organocatalytic asymmetric *anti*-Mannich reaction



Scheme 1.13 First *anti*-selective organocatalytic Mannich reaction

Similarly, Barbas-III and Jorgensen invented modified proline catalyst **52** having a substitution at 3rd and 4th carbon with C_2 symmetric (**Figure 1.9)** to examine the direct *anti*-Mannich reaction with the same substrates represented in **Scheme 11.4**.[72] They got excellent enantiomeric access

(up to >99%) which is parallel to catalyst **51** in this aspect, but in another aspect catalyst **52** was superior to catalyst **51** concerning catalyst loading (0.2 to 5 mol %) and activity **(Figure 1.9)**

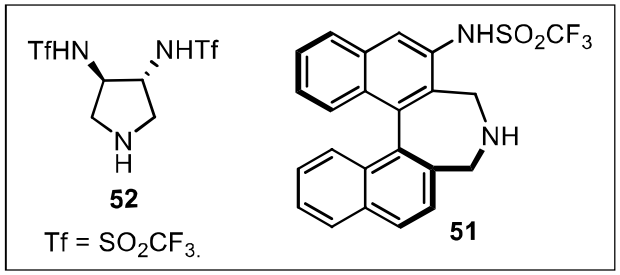
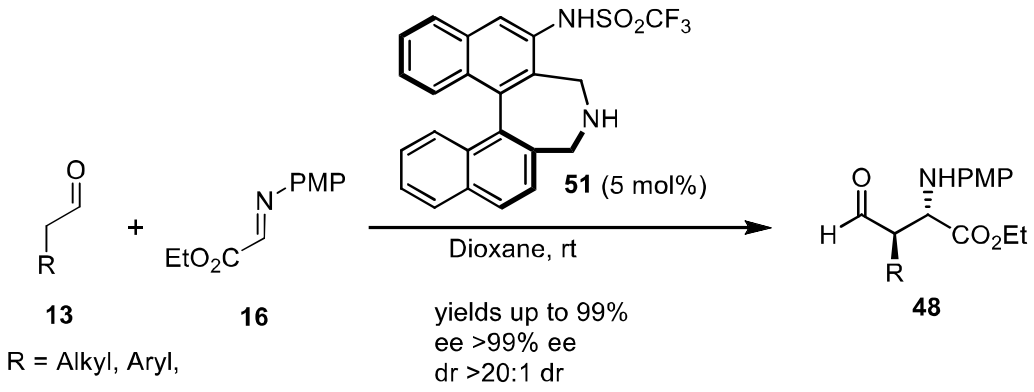
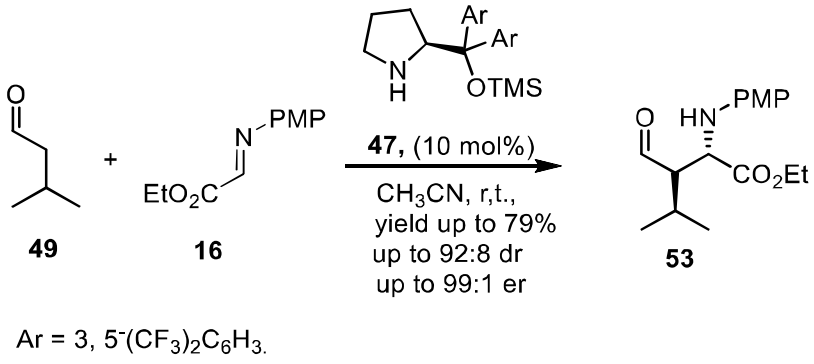


Figure 1.9 Maruoka's developed chiral BINOL-derived catalyst



Scheme 1.14 Trifluoromethanesulfonamide catalyzed asymmetric anti-Mannich reaction

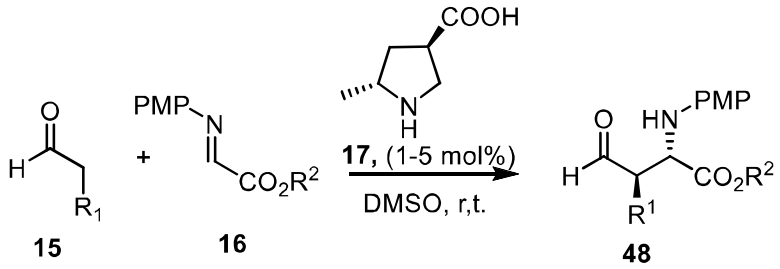
Later, Jørgensen and co-workers developed *α,α*-diaryl prolinolsilyl ether **47** to catalyze the *anti*-Mannich reaction to further enhanced the diastereo- and enantioselectivities, used imine **16** and aldehydes **49** to afford **53** (**Scheme 1.15**).[73]



Scheme 1.15 *Anti*-selective Mannich reaction catalyzed by *α, α*-Diarylprolinol silylether**54**

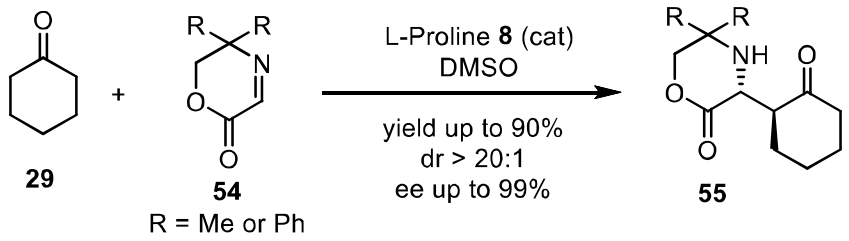
The collective synthetic efforts made by Barbas and Houk groups, developed pyrrolidine derived efficient catalyst **17**[74] for the highly selective *anti*-Mannich reaction between *N*-PMP-imino-esters **16** and aldehydes **15** through *syn*-enamine transition state-provided product **48** with excellent

diastereo- (94:6 to 98:2) and enantioselectivities (>98.5:1.5) (**Scheme 1.16**).



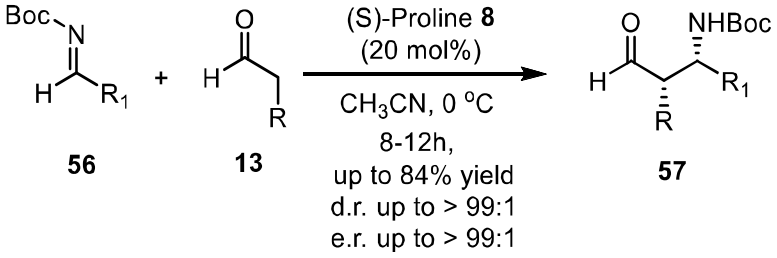
Scheme 1.16 Pyrrolidine derived efficient catalyst**26**as highly active, *anti*-selective catalyst

Glorius *et al*. developed another synthetic route for direct *anti*-Mannich reaction, catalyzed by proline in the same year. The respective reaction involved cyclic imine **54** served as acceptor and unactivated ketones**29,** transform into products**55**in an *anti*-Mannich fashion corresponding to the protected α-*D*-amino acid. (**Scheme 1.17**).[75]In aqueous ethanol, the protecting group of α-amino acids, could be cleaved readily to the furnished free amino acid on hydrogenolysis.



Scheme 1.17 Proline catalyzed the synthesis of chiral 3-substituted morpholine-2-ones

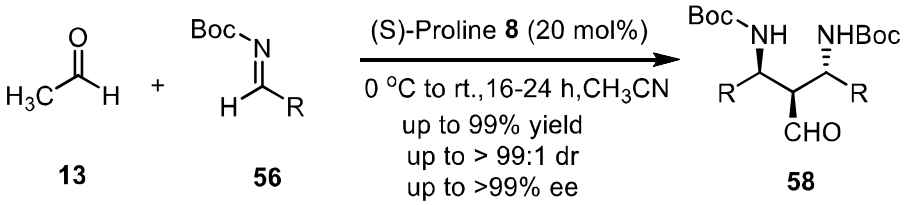
List and co-workers have also used (*S*)-proline as a catalyst for the *anti*-Mannich reaction of *N*-Boc imines **56** with unmodified aldehydes **13** provided crystalline β-amino aldehydes **57** which precipitated from the reaction mixture, with high yields and excellent diastereo- and enantioselective as shown in (**Scheme 1.18**).[76] For the synthesis of α-and β-substituted β-amino acids, product **57** serves as useful intermediates.



Scheme1.18 Asymmetric Mannich reaction of aldehyde and *N*-Boc-imines catalyzed by Proline

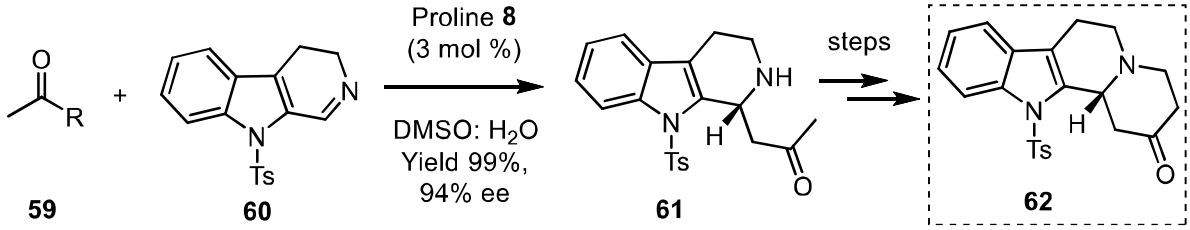
List and his co-workers introduced the asymmetric catalytic synthesis of β,β'-symmetric diamino-aldehydes **58** in one-pot with excellent stereoselectivities using acetaldehyde **13** and either

aromatic or aliphatic *N*-Boc imines **56** as starting materials. This method was efficient elaborated to cross-Mannich reactions and prepared *β,β'*-diamino aldehydes **60** having three adjacent chiral centers (**Scheme 1.19**).[56]



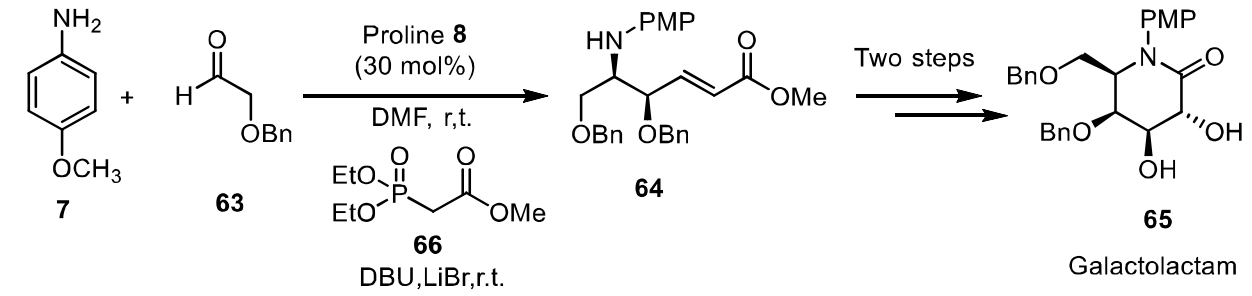
Scheme 1.19 Double Mannich reaction of acetaldehyde and N-Boc imine

Ohsawa *et al.* developed the direct Mannich reaction of acetone **59** and 9-tosyl-3,4-dihydro-*α*-carboline **60** catalyzed by (*S*)-proline **8** afforded indole-based product **61** with excellent yield (99 %) and enantioselectivity up to (94% ee)(**Scheme 1.20**).[77] It was found that aqueous conditions exhibit contrary effects of the stereochemical outcome of the product. This methodology was further utilized for the synthesis of medicinally useful indole alkaloids **62**.



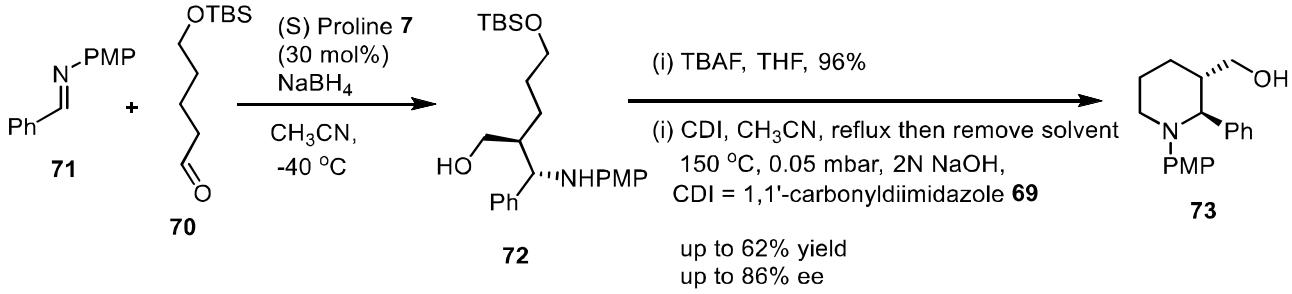
Scheme 1.20 Synthesis of medicinally important Chiral indole alkaloid **62**

Córdova *et al*. developed a stereoselective (*S*)-proline **8** (30 mol%) catalyzed the one-pot tandem reaction that involved a Mannich, Horner-Wadsworth-Emmons, followed by Sharpless dihydroxylation to produce optically active amino- and iminosugar derivatives **65**.[78] This transformation used (*S*)-proline **8** (30 mol%) as a catalyst, *p*-anisidine **7,** and *α*-benzyloxy-acetaldehyde **63** to furnished corresponding Mannich product, which produced corresponding Wittig product **67** with two stereocenters in good yield (64%), diastereoselectivity (4:1 dr) and enantioselectivity (95%), followed by the Sharpless dihydroxylation and acid-catalyzed cyclization given galactolactam **65** in good yield (74%) (**Scheme 1.21**).



Scheme 1.21 Direct Mannich reaction furnished Galactolactam

Christmann and Xu's groups employed the amine catalytic approach to synthesize the functionalized piperidines **73** in chiral fashion. This *syn*-Mannich reaction involved linear aldehyde **70**, imines **71,** and reducing agent $NaBH_4$ followed by subsequent intramolecular cyclization of amine moiety with alcohol. The product was formed in yield (up to 62%) and enantiomeric access (up to 86%) **(Scheme 1.22).**[79,80]

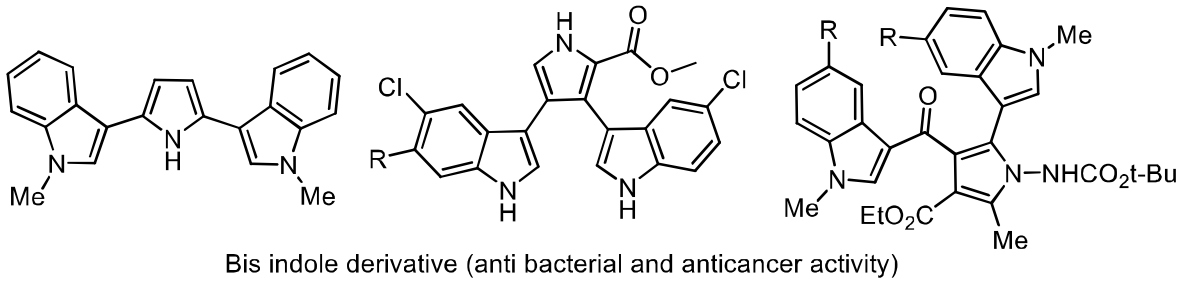


Scheme 1.22 Amine catalytic asymmetric synthesis of functionalized piperidines

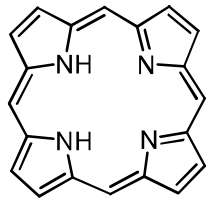
1.5 Importance of nitrogen heterocycles

Heterocyclic rings are present as core skeleton in most of the diverse compounds like alkaloids, vitamins, hormones, antibiotics, hemoglobin, essential amino acids, dyes, and many synthetic drugs.[81-83]Biomimetics and reactive pharmacophores are one of the extraordinary properties of heterocyclic nuclei, which largely contributed as key elements in various drugs and a wide spectrum of biologically important compounds.[84,85] Nitrogen heterocycles, such as porphyrins, show great pharmacological properties; as a result, its DNA-chain intercalating ability, which makes it appropriate for *anti*-neoplastic and mutagenic applications**.** The high degree of varieties, advantageous biological applications, and synthetic application of nitrogen-containing heterocycles and its derivatives have gained a lot of focus in modern drug design and discovery.[86-90] As we know, amine catalyzed an organocatalytic Mannich reaction is a capable tool for designing nitrogen-containing heterocycles with various ring sizes. The main focus of the thesis is on the construction of five-, and six-membered heterocycles and their medical importance. The utility of

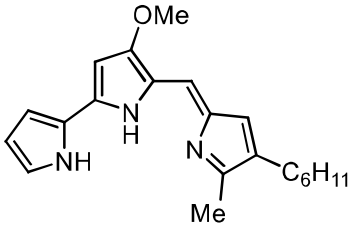
five and six-membered nitrogen-containing heterocycles in synthetic and natural products chemistry is well documented in the literature. Few naturally occurring and biological important structure units containing five and six-membered *N*-heterocyclic ring as basic core structures are depicted in the following (**Figure 1.10)**.[118-136]



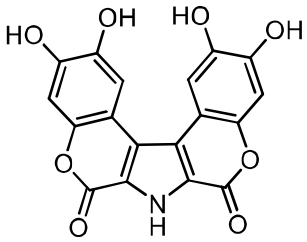
Bis indole derivative (anti bacterial and anticancer activity)



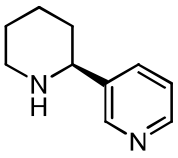
Porphyrin



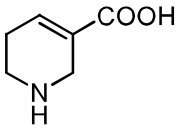
Prodigiosene



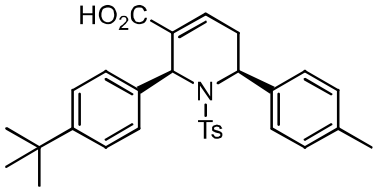
Ningalin



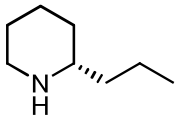
Anabasine
insecticide



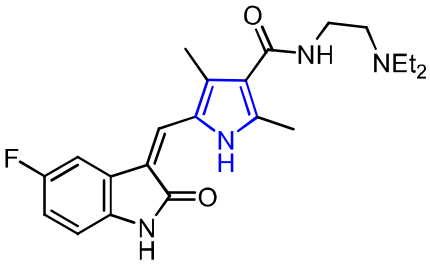
(VI)
Guvacine



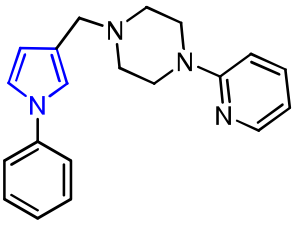
Anticancer agent



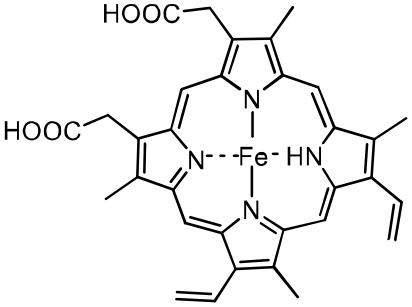
(S)-coniine
alkaloid



sunitinib



antipsychotic agent



Heme

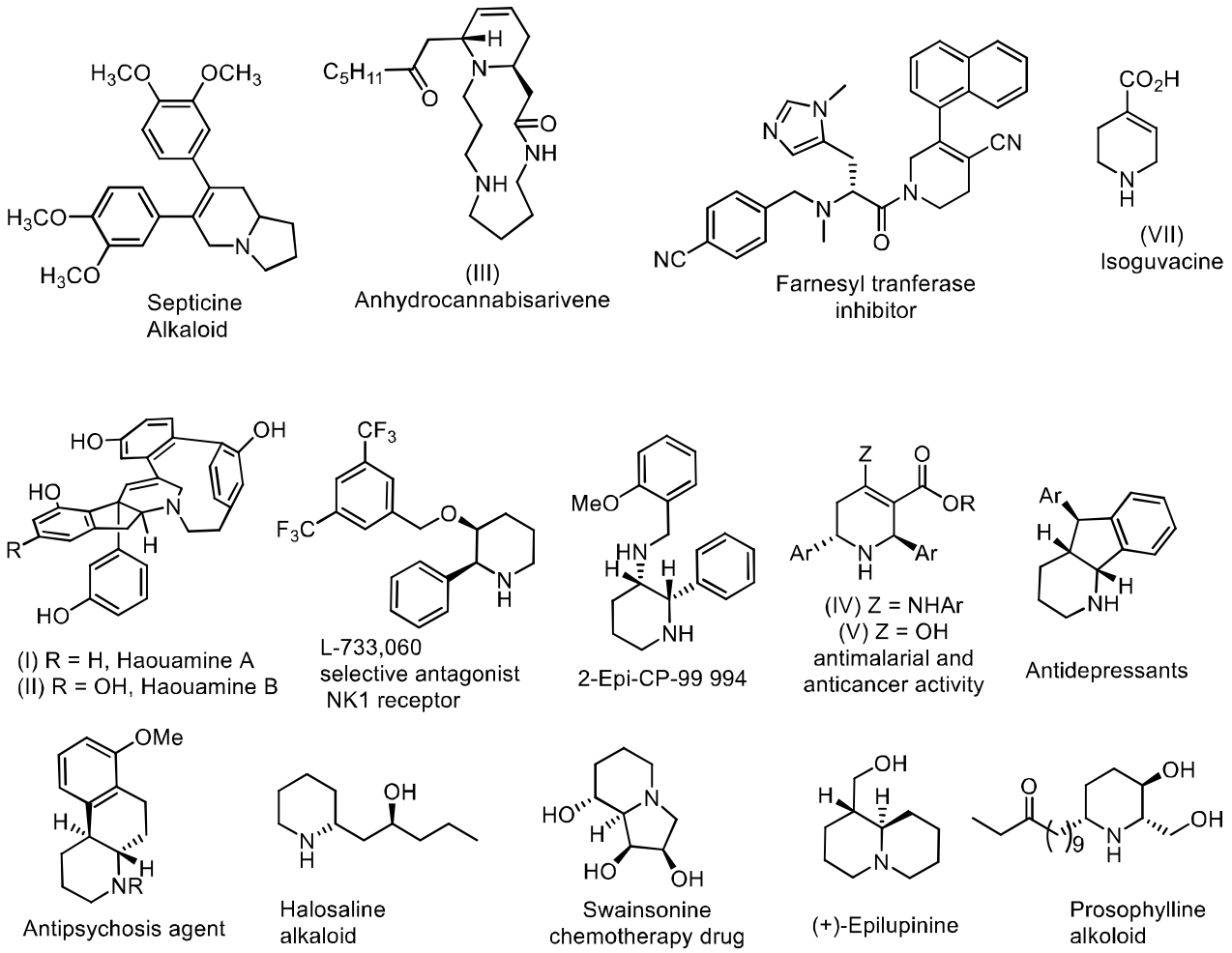


Figure 1.10 Few bioactive five and six-membered heterocyclic derivative

1.6.1 Linear dialdehydes in amino-catalytic transformations

Organocatalytic domino/cascade reactions through amine activation of carbonyl compounds have become the ultra-modern transformations to the design and synthesis of cyclic ring systems. In this direction, linear dialdehydes such as succinaldehyde, glutaraldehyde, and other similar moieties have received ample attention as appropriate substrates for transformations catalyzed by amine. Apart from highly commercial availability with low cost and high reactivity, its unique structural features have the competency to easily perform the domino/cascade/tandem transformations for the synthesis of valuable drug molecules and natural products. There are several transformations, such as aldol/Mannich/Michael/Henry/Baylis-Hillman reaction, where linear dialdehydes have been utilized. In the area of synthetic organic chemistry, linear dialdehydes have been recognized as important substrates.[91]Amine catalyzed transformations containing linear dialdehydes transform according to the suitability as presented in **(Figure 1.11).** Linear dialdehydes and other higher

homologated unsaturated or saturated dialdehydes undergo intramolecular and intermolecular transformation with various X=Y (C=C, C=N, C=O).

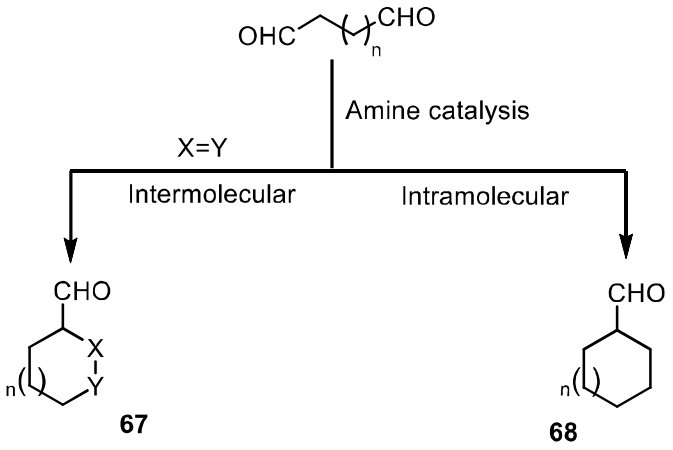
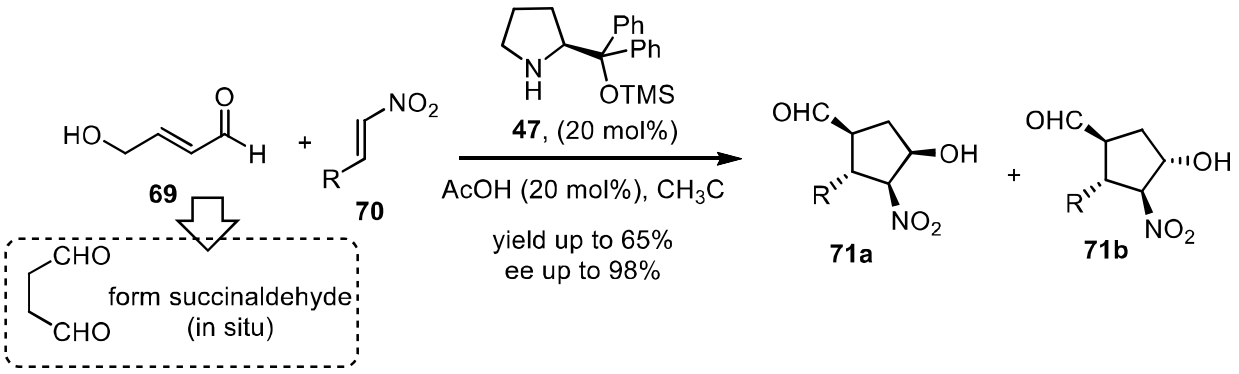


Figure1.11: Possible transformation of linear aldehydes

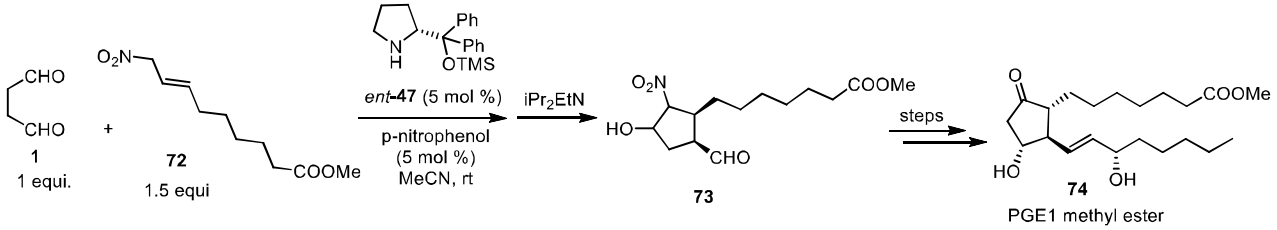
1.6.2 Succinaldehyde for amino-catalytic transformations

Succinaldehyde is a simple 1, 4-dicarbonyl compound that can act like 1, 3-carbon donor-acceptor (D-A) precursor in amine catalyzed transformations to synthesized biologically useful sophisticated scaffolds in non-asymmetric as well as in asymmetric fashion with high selectivity through amine catalysis. Succinaldehyde **(1)** is reasonably stable in aqueous solution, a very bitter smell. In 1917, Sir Robinson utilized succinaldehyde **(1)** to synthesized tropinone **(4)**. This one-pot tandem reaction used succinaldehyde **(1)** as a precious synthetic substrate along, acetone dicarboxylic acid **(2),** and amine **(3)** *via* twofold Mannich condensation followed by decarboxylation to produce the bicyclic tropane skeleton **(4) (Scheme 1)**.[41] Besides this, a wide number of natural products, as well as heterocyclic ring systems, have also been synthesized successfully by succinaldehyde.[92-94] An initial organocatalytic [3+2] Michael-Henry cascade transformation developed by Hong *et al.* in 2012 using cascade reaction of numerous nitroalkenes **(70)** and masked dialdehyde **(69)** to furnished cyclopentane-carboxaldehyde **(71a and 71b)**with four successive stereocenters with impressive enantioselectivity (up to 98%) **(Scheme 1.23).**[95]



Scheme 1.23 Cyclopentane synthesis by amine catalyzed using *in-situ* succinaldehyde

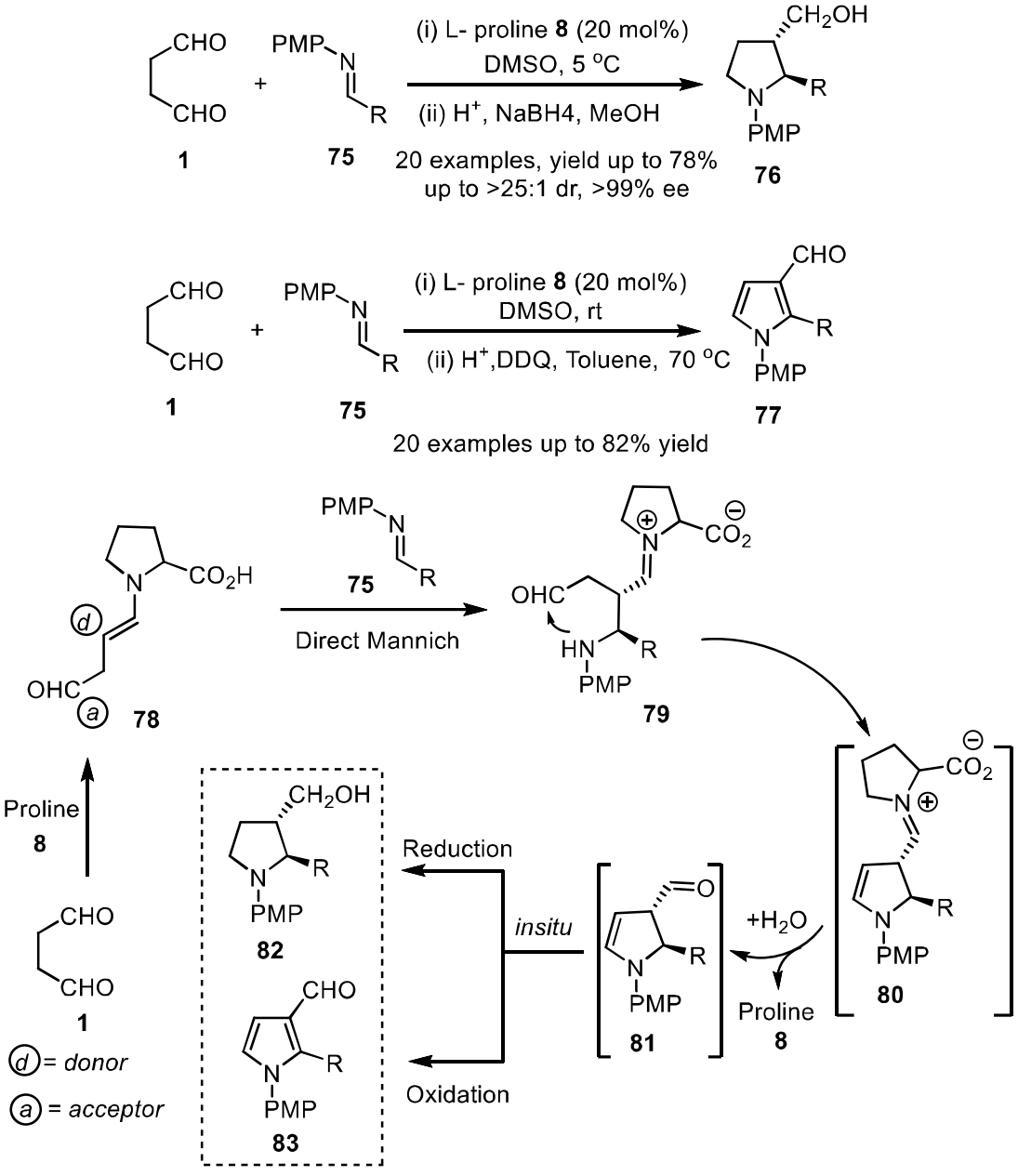
Hayashi and co-workers further explored the tremendous application of succinaldehyde through an amine-catalyzed domino reaction for the total asymmetric synthesis of prostaglandins.[96] This innovative approach proceeded through following steps, i.e., succinaldehyde **(1)** and nitroalkene **(72)** underwent direct Michael reaction catalyzed by diphenyl prolinolsilyl ether **ent-47** (5 mol%) followed by intramolecular Henry reaction in the presence of *i*-Pr_2EtN to furnish compound **73** which was subsequently converted to **PGA1** methyl ester **(74)** (**Scheme 1.24**). The glory of this transformation was not only using inexpensive starting materials but also completed in just three pots with some purification steps that resulted in a reduction in waste production and less-solvent consumption.



Scheme 1.24 Succinaldehyde as an appropriate substrate for the synthesis of Prostaglandins

Kumar *et al*. utilized succinaldehyde **(1)** as a substrate in proline-catalyzed organocatalytic one-pot cascade Mannich transformations to design the synthesis of nitrogen heterocycles. Initially, they developed a five-membered heterocycle; pyrrolidines **(76)** with exceptionally good stereoselectivities and good yield **(Eqn. 1, Scheme 1.25)**.[97] Followed by the first direct synthesis of substituted pyrrole-3-carboxaldehydes **(77)** in a two-step strategy was disclosed **(Eqn. 2, Scheme 1.25).**[98] These two [3+2] annulation transformations were identical up to intermediates **80,** and **81**. In case, intermediate **81** was reduced with $NaBH_4$ in, the presence of acid afforded *trans*-2,3-substituted pyrrolidine **(76)** with excellent enantioselectivities (up to >99% ee) and high yields. Whereas, intermediate underwent oxidative-aromatization by DDQ furnished substituted

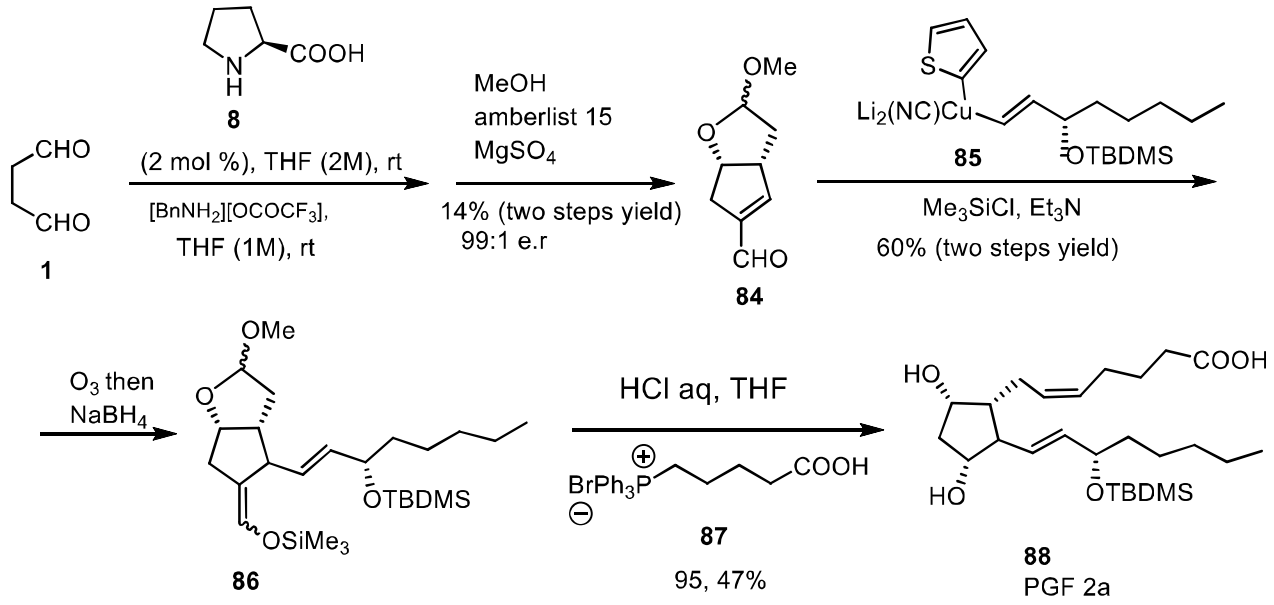
pyrrole-3-carboxaldehydes **(77)** in good to high yields. Both [3+2] annulation transformation proceeded through the Mannich reaction[99,100] catalyzed by proline between enamine **(78)** and imine **(75).** Enamine was *in situ* generated from succinaldehyde **(1)**, serve as easily available 1,3-carbon donor-acceptor (D-A) precursor, and proline **8**.



Scheme 1.25 Application of succinaldehyde for the synthesis of pyrrolidines/pyrroles

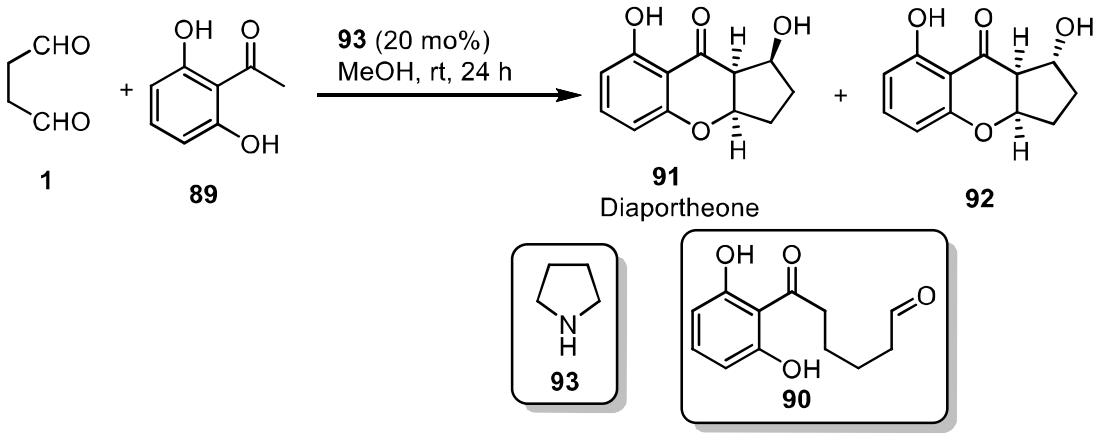
In the stereocontrolled synthesis of prostaglandin PGF2α **88,**[101] first use of succinaldehyde in amine catalyzed cascade reaction was explored by Agarwal and co-workers. The first step was the one-step synthesis of functionalized bicyclic-enal **84** with an excellent enantiomeric excess (98%),

produced by the direct cross-aldol reaction of succinaldehyde **(1)** followed by intramolecular aldol condensation proline catalyzed. Most of the earlier methods for the synthesis of PGF2α **(88)** were lengthy, absolutely time-consuming and produce plenty of waste whereas this method was very economical for the synthesis of PGF2α **88** and completed in just six steps from succinaldehyde **(1)** and can synthesize in gram scale **(Scheme 1.26).**



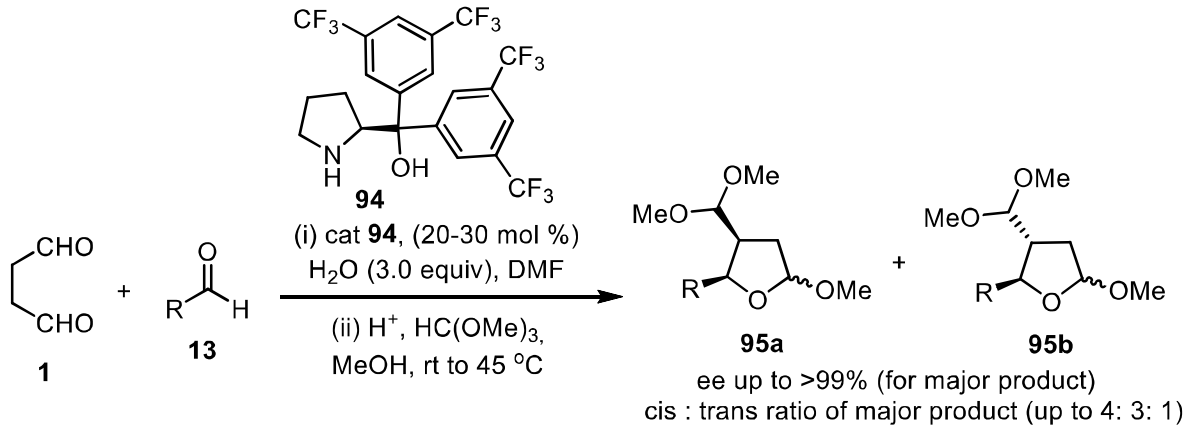
Scheme1.26 Organocatalytic cascade strategy using succinaldehyde for Prostaglandins synthesis

Reddy and co-workers have also discovered the captivating utility of succinaldehyde **1** for the amine catalyzed the synthesis of anti-TB agent Diaportheone B **91 (Scheme 1.27)**.[102] The overall transformation was catalyzed by amine **101**, involving condensation of 2, 6-dihydroxy acetophenone **89** with succinaldehyde **1** to generated very reactive intermediate **90**, which subsequently underwent cyclization through domino fashion furnished Diaportheone B **(92)**. Although this method suffers from low yields and selectivity, this synthesis appeared as a quick path to synthesize the skeleton in one-pot. Earlier, Mori and co-workers reported a similar application for the efficient synthesis of natural products coniochaetone A and B through domino aldol/cyclization reaction involving succinaldehyde **1** under amine catalysis.[103]

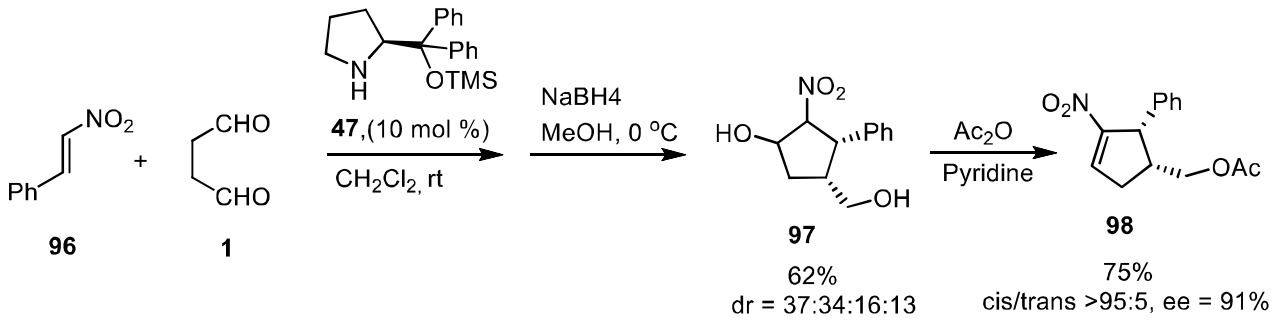


Scheme 1.27 Amine catalyzed cascade strategy for Diaportheone B using succinaldehyde

Hayashi and co-workers reported a formal [3+2] cycloaddition domino approach of succinaldehyde **1** and other aromatic/activated aldehydes **13** for the asymmetric synthesis of tetrahydrofurans **95a** and **95b (Scheme 1.28)**.[104] This transformation proceeds with direct aldol reaction of succinaldehyde **1** with several aldehydes catalyzed by **94**, and intramolecular cyclization to afford **95a** and **95b** with good yields and high enantioselectivity (up to 99%). The same group later published the enantioselective domino Michael/Henry reaction introducing reacting partner succinaldehyde **1** nitroalkenes **96** in the presence of diphenyl prolinolsilyl ether **47**as an organocatalyst the resulting *cis*-disubstituted nitroalkenes **98** produced with excellent diastereoselectivity and enantioselectivity **(Scheme 1.29)**.[105]



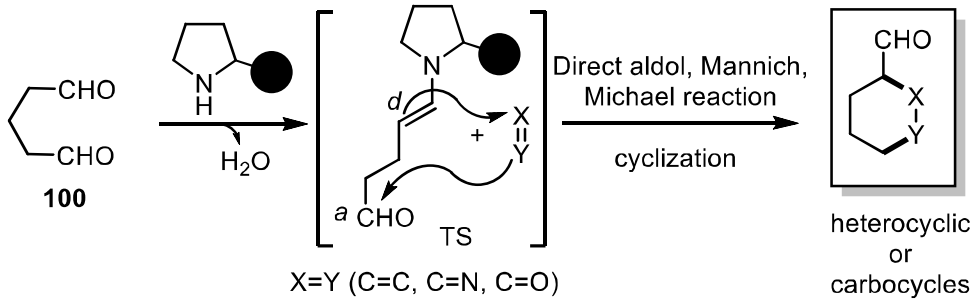
Scheme 1.28 Domino aldol/acetalization as [3+2] annulation catalyzed by Amine



Scheme 1.29 [3+2] annulation involving succinaldehyde with nitroalkenes reacting partner

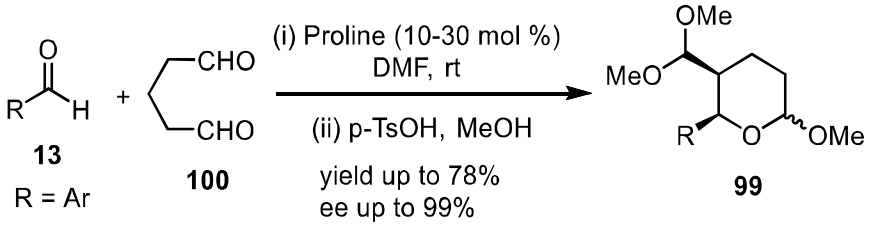
1.6.3 Glutaraldehyde in amine catalytic intermolecular transformations

Glutaraldehyde, 1,5-dicarbonyl compound, act as 1, 4-carbon donor-acceptor (D-A) precursor is a clear, pungent oily liquid, colorless to pale straw-colored, completely soluble in water and organic solvents. Apart from the successful and convenient synthesis of numerous small heterocyclic as well as useful alkaloids by glutaraldehyde,[106-110] in aqueous solution, it also shows exclusive chemical behavior, therefore, acts as appropriate cross-linking agent for the immobilization of the enzymes.[111,112] The amine catalyzed reaction of glutaraldehyde involves the formation of enamine-**TS** in which one of the carbonyl act as a donor through enamine-intermediate bind, and another aldehyde-moiety act as acceptor, reacts with dipolarophile (X=Y) consequently produced carbocyclic/heterocyclic ring systems in the one-pot operation. Amine catalyzed cascade transformations of glutaraldehyde **100** react with various dipolarophile X=Y (C=C, C=N, C=O) and furnished a series of hetero- and carbocyclic framework, this topic was recently reviewed by our group (**Scheme 1.30).**[113]



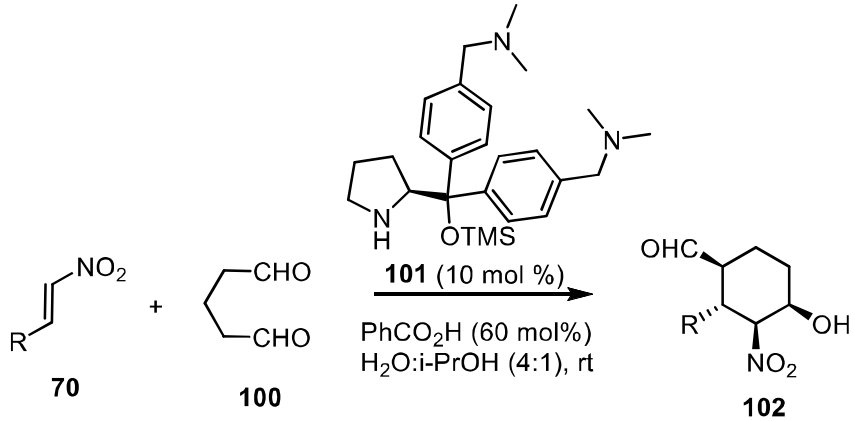
Scheme 1.30 Amine catalyzed intermolecular transformations through glutaraldehyde

Hayashi and co-workers used glutaraldehyde as one of the significant synthetic counterparts developed proline **8** catalyzed direct aldol reaction of glutaraldehyde **100** with several aromatic aldehydes followed by acid-mediated acetalization reaction for the synthesis of *cis*-tetrahydropyrans **99** in good yields and excellent selectivity (up to 99 % ee) (**Scheme 1.31**).[114]

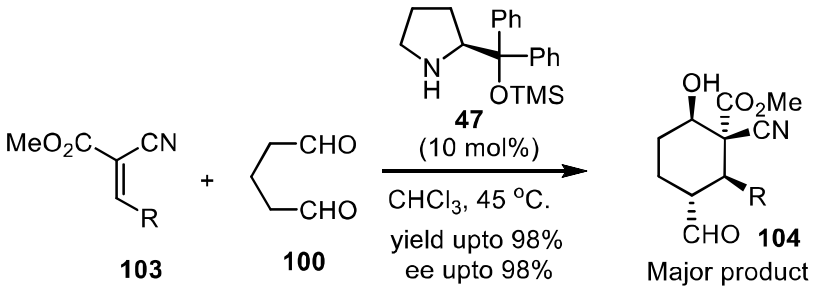


Scheme 1.31 Amine catalyzed glutaraldehyde derived synthesis of tetrahydropyran

A water-soluble organocatalytic approach developed by Ni and co-workers to synthesized functionalized cyclohexanes**102** by glutaraldehyde **100** and activated alkene **70**as starting reacting partners in the presence of recyclable and aqueous soluble organocatalysts**101.**[115] The drawback of the catalyst was its expensiveness, but this problem was overcome and made this strategy more practical by water used as a nontoxic solvent along with recycling of catalysts from four to seven times with low variation in product yields and selectivity's **(Scheme 1.32)**.



Scheme 1.32 Intermolecular transformation of glutaraldehyde for chiral cyclohexanes

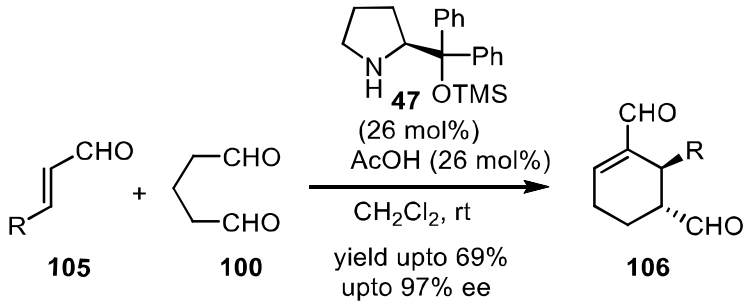


Scheme 1.33 Amine catalyzed intermolecular change for functionalized cyclohexanes

Cordóva *et al.* found the highly enantioselective approach to produced functionalized cyclohexanes **104** through domino Michael/aldol catalyzed by amine involved numerous alkylidene malonates as suitable dipolarophiles **103** and glutaraldehyde **100**.[116] This functionalized chiral products **104** decorated with several functional groups such as hydroxyl,

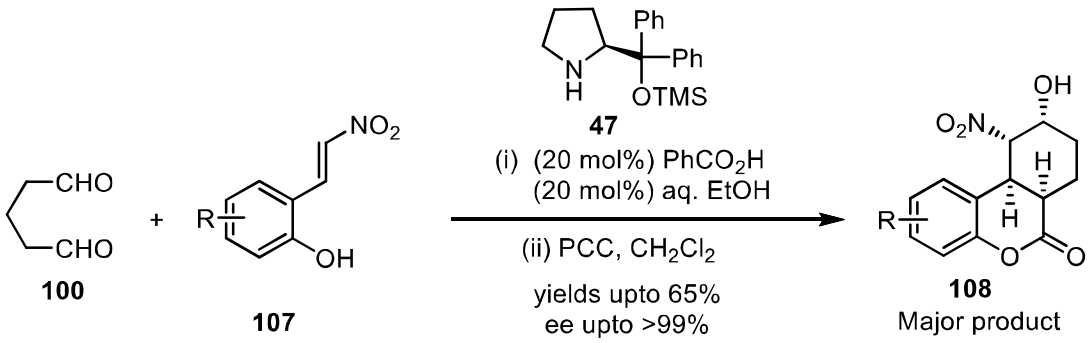
formyl, ester, and cyanogroups. The resulting products functionalized cyclohexanes **104** contained four consecutive chiral centers and one quaternary center generated with high yields and enantioselectivity **(Scheme 1.33)**.

Hong and co-workers have made their considerable contribution by developing amine catalyzed asymmetric cascade transformations using glutaraldehyde for the synthesis of multifunctional cyclohexene derivatives *via* cascade strategy (**Scheme 1.34**).[117] The reaction proceeded by Michael-reaction of glutaraldehyde **100** with 3-arylpropenal **105** catalyzed by amine followed by intramolecular aldol condensation to furnished **106** in excellent enantioselectivity and high yields.



Scheme 1.34 Amine catalyzed transformation for chiral cyclohexenes

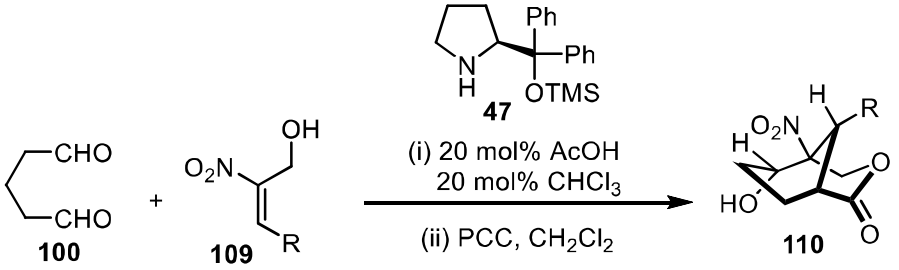
B. C. Hong *et al.* reported the asymmetric synthesize interesting, complex tetrahydro-6*H*-benzo[*c*]chromen-6-ones **108** involving a reaction between cheap and readily available glutaraldehyde **100** and *ortho*-hydroxynitrostyrenes **107** *via* amine catalyzed domino Michael-acetalization-Henry reaction (**Scheme 1.35**).[118] Interestingly, execution of this cascade transformation was exceptionally well, because it generated four consecutive chiral centers through three bonds formation with excellent stereoselectivities.



Scheme 1.35 Domino reaction of glutaraldehyde catalyzed by amine catalyzed

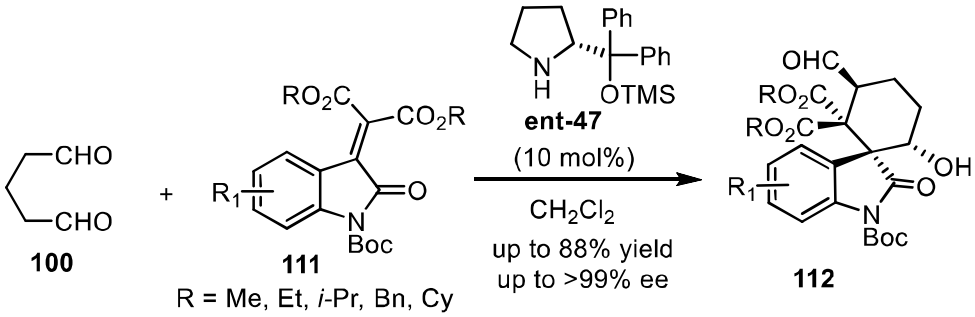
The Hong group has developed another exciting application of glutaraldehyde **100** through amine catalyzed cascade synthesis of bicyclic systems 3-oxabicyclo[3.3.1]nonan-2-ones **110** contains four successive stereocenters. This method precedes through the organocatalytic cascade Michael-

Henry acetalization-oxidation reaction of 3-aryl-2-nitroprop-2-enols **109.** The synthesis of multi-functionalized bicyclic systems **86** formed under benign reaction conditions shown high yields, excellent enantioselectivity (>99%), and found several synthetic applications (**Scheme 1.36)**.

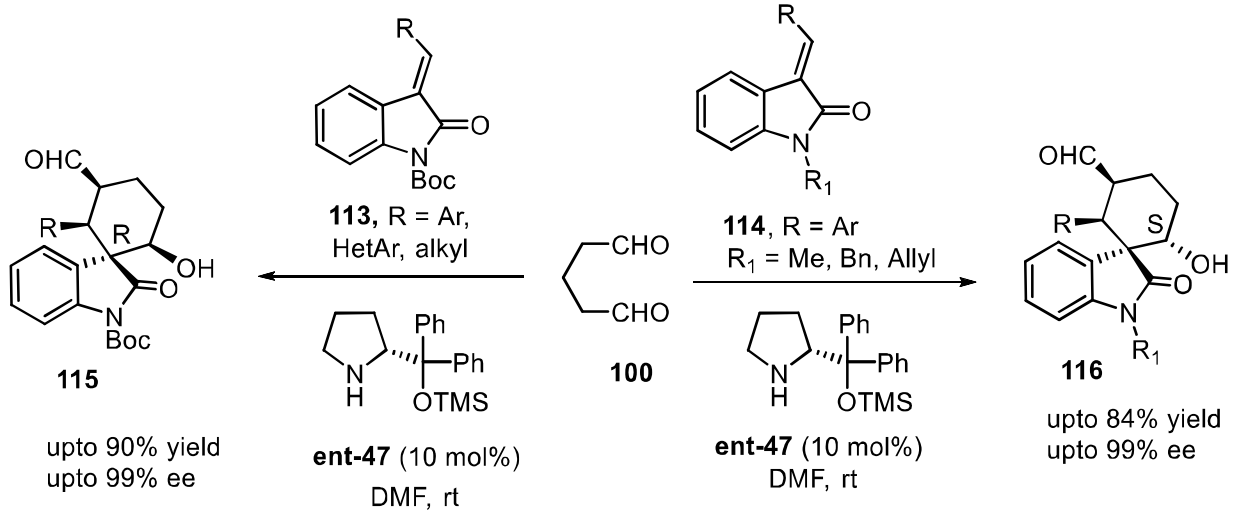


Scheme 1.36 Oxa-bicyclic system synthesis from Intermolecular transformation of glutaraldehyde

Wang and co-workers explored glutaraldehyde **100,** for organocatalytic domino, Michael/Aldol cyclization with isatin-derived alkenes**111**and corresponding poly-cyclic products were obtained **(Scheme 1.37)**.[119] Using amine **ent-47** catalyzed synthesis of functionalized asymmetric spirocyclohexane oxindoles **112** containing several hydroxy, ester, and formyl groups and with high yields and excellent selectivity.



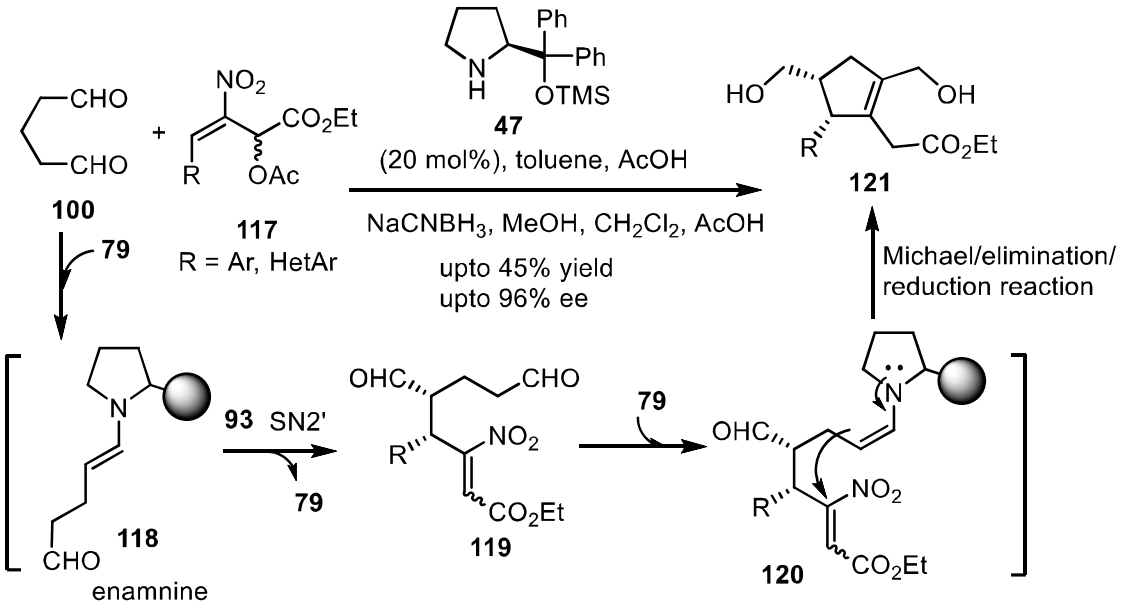
Scheme 1.37 The synthesis of spiro-compounds using glutaraldehyde for annulation reactions



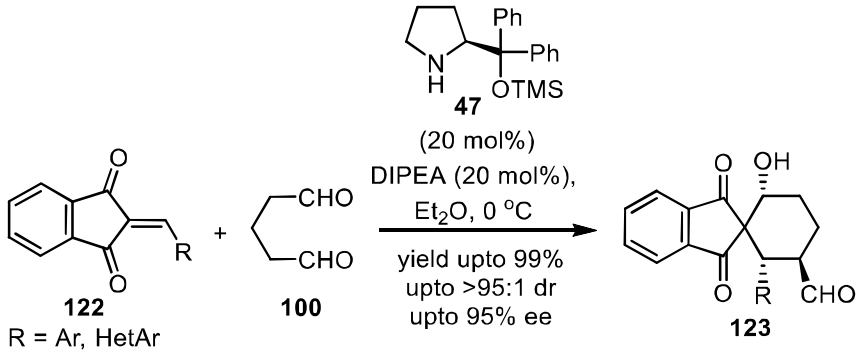
Scheme 1.38 Amine catalyzed Spiro-oxindole synthesis from glutaraldehyde

In a very similar strategy, Ghosh *et al*. also described the spirocyclohexane oxindoles **115**, **116** integrations in enantioselective fashion decorated with multiple stereocenters and an additional one spiro-quaternary center in high yields and excellent enantioselectivities **(Scheme 1.38)**.[120]

Chen and co-workers developed the synthesis of functionalized cyclopentane through amine **47** catalyzed cascade transformation of glutaraldehyde **100** with racemic nitroallylic acetates **117** (**Scheme 1.39**).[121] The enamine **118** was generated from glutaraldehyde **100** and catalyst **47**, underwent S_N2 reaction with nitroallylic acetates **117** produce S_N2 product **119** while another aldehyde functional group of product **119** binds with **47** to perform intramolecular Michael addition-elimination produced **121** after $NaBH_4$ reduction perform *in-situ*.



Scheme 1.39 Synthesis of functionalized cyclopentenes from glutaraldehyde *via* amine catalysis

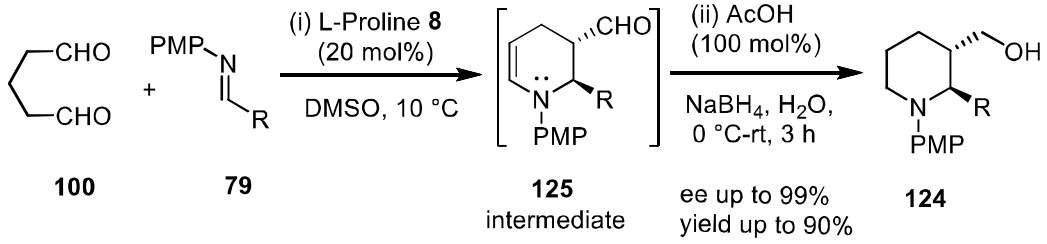


Scheme 1.40 Amine catalyzed transformation to synthesize spirocyclic scaffolds

The same group provided another exciting application of glutaraldehyde **100** for the synthesis of spirocyclohexane-carbaldehydes **123** using amine catalysis (**Scheme 1.40**).[122] Glutaraldehyde **100**

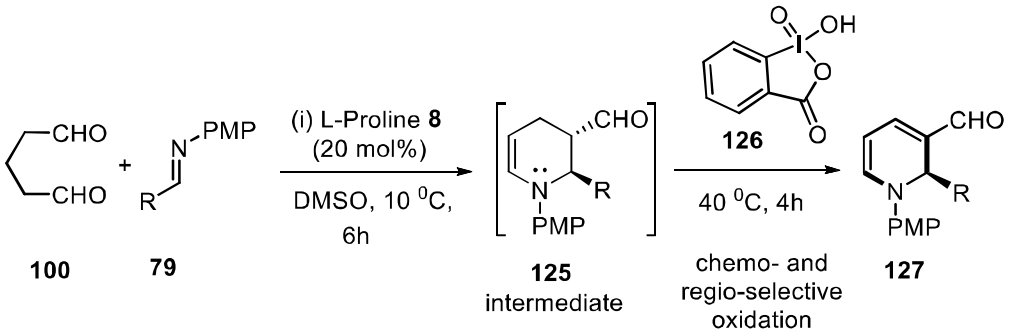
and 2-arylideneindane-1,3-diones **122** underwent amine **47** catalyzed Michael/Aldol domino sequence as [4+2] annulations furnished spirocyclohexane-carbaldehydes **123** with high yield and selectivity's (up to 95% ee).

Our group applied glutaraldehyde **100** as a biofunctionalized substrate for the quick synthesis of medium-sized nitrogen heterocycles through proline-catalyzed cascade transformations.[40] In this direction, Kumar and co-workers reported direct Mannich reaction of glutaraldehyde **107** with various *N*-PMP aldimines **79** followed by acid-catalyzed reductive cyclization, through 1,4-carbon *donor-acceptor* strategy as formal [4+2] cycloaddition under very mild conditions to the synthesis of piperidine **124** in high yield and excellent enantioselectivity shown in **Scheme 1.41**. [123]



Scheme1.41 Proline catalyzed organocatalytic asymmetric synthesis of piperidine

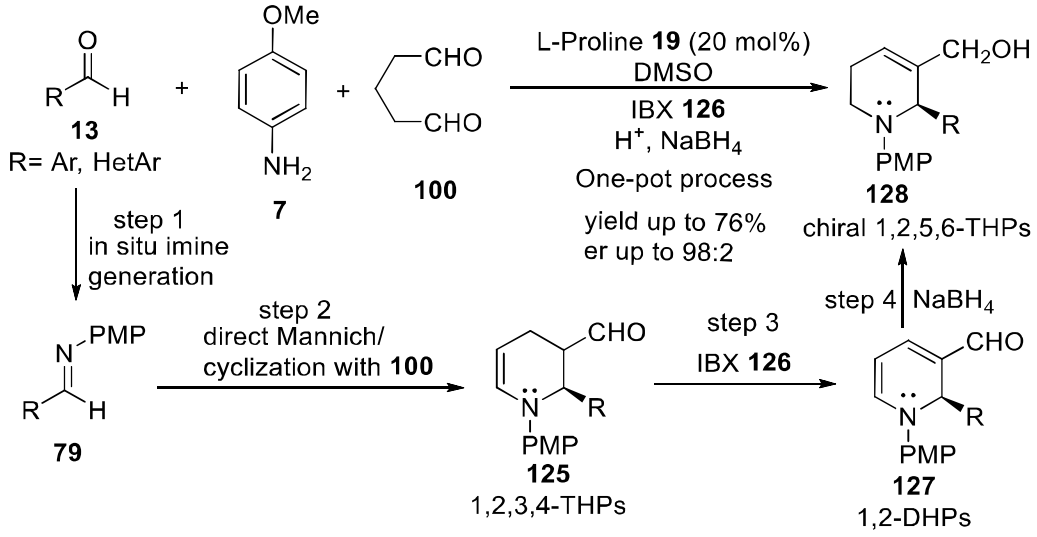
Kumar and co-workers developed an operationally simple first metal-free enantioselective synthesis of *N*-PMP-1,2-dihydropyridines **127** via one-pot formal [4+2] cycloaddition between readily available aldimines **79** and aqueous glutaraldehyde **100**. This reaction proceeds through Proline **8** catalyzed direct Mannich/cyclization, followed by IBX mediated site-selective dehydrogenative-oxidation sequence with high yields and selectivity shown in **Scheme 1.42).** [124]



Scheme1.42 Proline catalyzed asymmetric synthesis of dihydropyridine

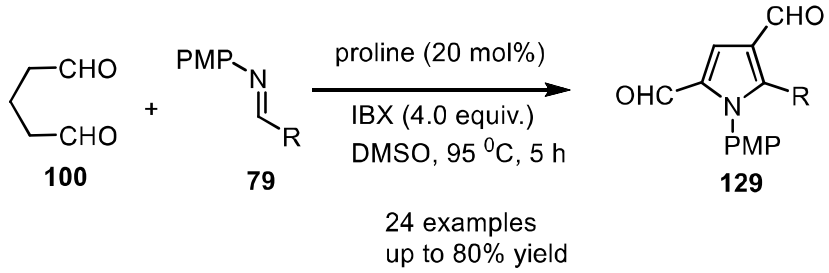
In continuation, we further explore the glutaraldehyde to synthesized tetrahydropyridine, which is found in the significant number of essential alkaloids as a basic skeleton and also exhibits anticancer activities**.** This multi-step one-pot synthesis has been carried out by aromatic and heteroaromatic aldehydes, *p*-anisidine, and glutaraldehyde in the presence of L-proline as a

catalyst. The final product asymmetric 1,2,5,6-THP was synthesized in good yield (up to 76%) and good enantiomeric ratio (up to 98:2) with following successive sequence, in the first step *in situ* imine generation, underwent direct Mannich reaction with glutaraldehyde then cyclization afforded 1,2,3,4-THPs followed by consecutive oxidation with IBX and reduction by $NaBH_4$ respective 3rd and 4th steps **(Scheme1.43)**.[125]



Scheme 1.43 Multi-component synthesis of tetrahydropyridine in one pot

Recently our group also developed a new *pseudo*-[3+2] annulation method for the synthesis of substituted pyrrole-2,4-dialdehydes **129** in good yield (up to 80%). This direct Mannich reaction/cyclization transformation involves again glutaraldehyde **100,** and imine **79** and proline as catalyst followed 2-iodoxybenzoic (IBX)-mediated oxidative rearrangement of intermediate 1,2-DHPs to pyrrole-2,4-dialdehydes **129 (Scheme 1.43).**[126]



Scheme 1.43 Synthesis of substituted pyrrole-2,4-dialdehydes *via* pseudo**-**[3+2]**-**annulation

1.7 Conclusion and conception

This Ph.D. thesis work aims to enhance the scope of amine catalysis Organocatalytic asymmetric/non-asymmetric Mannich reaction towards the synthesis of five and six-membered nitrogen heterocycles and reveals their biological importance and their presence in a vast number

of natural products. The involvement of the organocatalytic direct Mannich reaction as a one-pot domino/cascade reaction could be a dominant route for the syntheses of nitrogen-heterocyclic compounds in both asymmetrically as well as in non-asymmetrically. This chapter provides a brief introduction about the history of organocatalysis, amine-catalysis, Mannich reactions reviewing previous literature reports, particularly involving succinaldehyde (1, 4-dicarbonyl compound) as 1,3-carbon donor-acceptor (D.A) precursor and glutaraldehyde (1, 5-dicarbonyl compound) as 1, 4-carbon donor-acceptor (D.A) precursor. The literature review on the importance and application of nitrogen-containing heterocycles in diverse disciplines of science has been discussed. Therefore, the syntheses of fused heterocyclic libraries consisting of extremely precious five and six-membered scaffolds are highly demanding. In this direction, the strategy was developed and preceded *via* proline catalyzed direct Mannich reaction of commercially available inexpensive starting substrates such as succinaldehyde, glutaraldehyde with several *N*-protected protected indole-imines followed by oxidative aromatization and supporting site-selective reduction to furnished indole tagged pyrrole and indole tethered piperidine motifs respectively and exhibited their biological activities. Besides this, metal-catalyzed self-dimerization and cross addition of indole to 2-phenyl indole is also an innovative part of the thesis, which eliminates the use of hazardous and costly reagents employed in previous methods. It could be noticeable that organocatalysis is the answer to long-standing challenges, were associated with metal-mediated and other approaches. The present organocatalytic protocol has several advantages such as cheap, readily available, mild reaction conditions, bench-stable catalysts, stable against air and moisture. Therefore, this recent glorious organocatalytic development shows an increased interest among the organic chemists. This thesis work extensively utilized succinaldehyde as well as glutaraldehyde *via* organocatalytic direct Mannich reaction followed by oxidation or reduction based on product requirement produce five and six-member *N*-heterocycles and well discussed in the thesis (**Figure 1.12).**

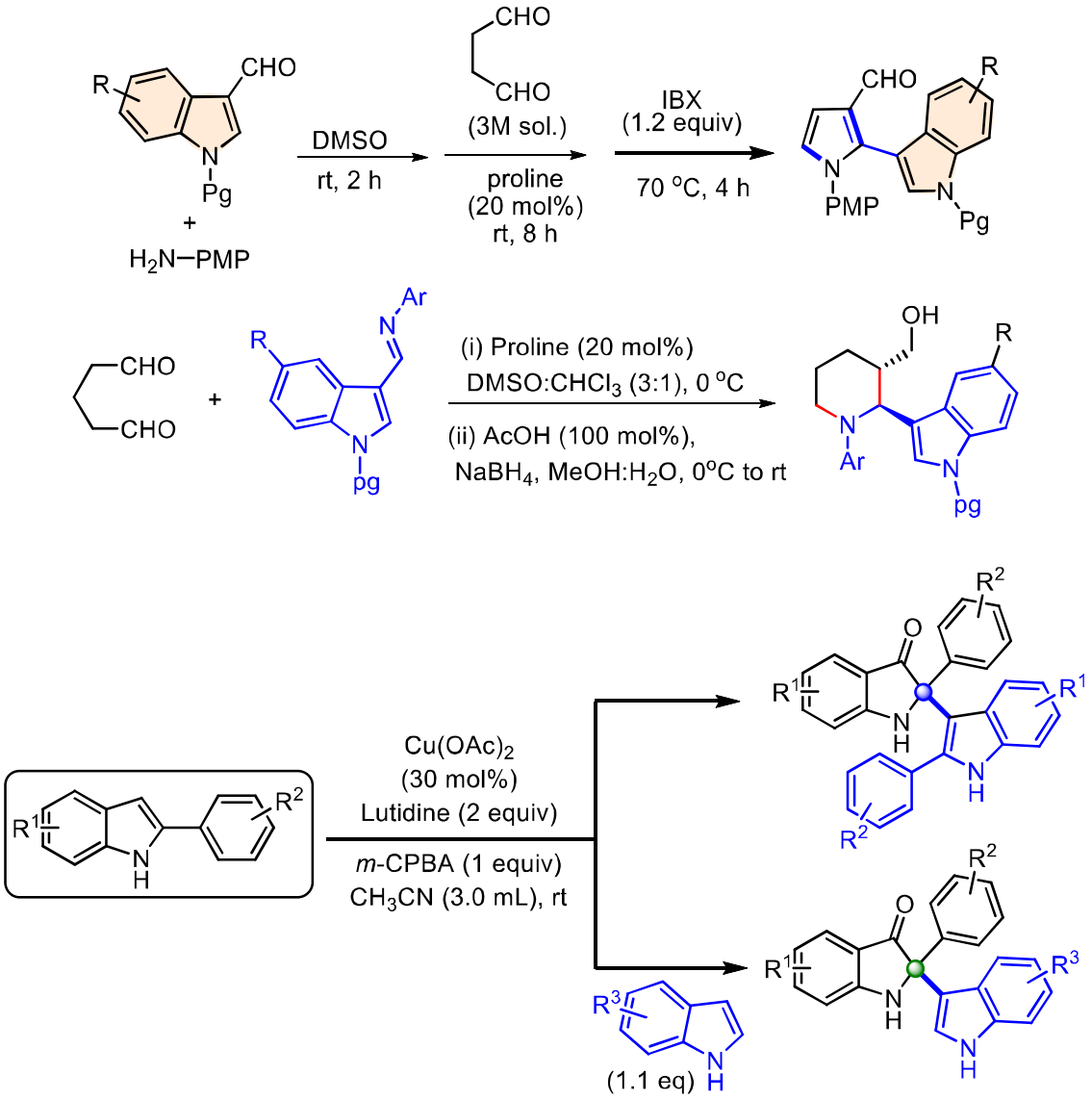


Figure 1.12 Representation of overall thesis work affording indole based heterocycles through Amine-catalyzed transformations and also the Cu-catalyzed transformations

1.8 Notes and references

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