Chapter - 1

Introduction of organocatalysis, amine-catalyzed direct Mannich reactions, utilization of succinaldehyde and glutaraldehyde in amine-catalyzed transformations

1.1 Organocatalysis

The word "organocatalysis" is a combination of the words "organic" and "catalyst." It is described as increasing the rate of chemical reactions during the addition of a sub-stoichiometric mass of an organic compound. Organocatalysts, in absence of metals, present an alternative class of catalysts that are cheap, ready availability, non-toxic and environmentally benign processes, reaction conditions which are not sensitive to air and moisture and are easily recovered during work-up. The field has received a great deal of attention in recent years as a result of both the novelty of the concept and, more importantly, the advantages of several organocatalytic reactions meet the standards of well-known organic reactions. Organocatalytic reactions are becoming powerful tools in the construction of complex molecular skeletons and hence being complementary to metal and enzyme catalysis.[1-2] The word organocatalysis has been introduced in the scientific community by MacMillan in 2000, in order to describe the field of organic synthesis that employed low molecular weight simple organic molecule to catalyze given transformations.[3-4] The organocatalysts could be achiral or chiral and are composed of C, H, N, S, and P. During the last decades, organocatalysis has been included among the most important and a successful concept in field of organic chemistry and it has been used for the construction of C-C, C-N, C-O, C-S, C-P, and C-halide bonds.[5-10] Organocatalysis has several advantages due to its synthetic range and for the economic reasons. The absence of metal in organocatalyst brings an undeniable advantage considering both the principles of "green chemistry" and the economic point of view. It is a novel synthetic idea and mostly an alternative to the prevalent transition metal catalysis. Moreover, nature provides us with an array of the enantiopure organic skeleton from which to develop organic catalysts. These are having α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates. Recently the use of small chiral organic molecules as catalysts with the associated advantages to the asymmetric transformation in a metal-free background and under mild and simple reaction conditions has experienced a remarkable growth in the emerging field of chemistry from last one decade.

Indeed, the renewal of proline-catalyzed transformations in early 2000 by Barbas III, List, and MacMillan [3,11] was the initial point of the word 'organocatalysis'. In addition to the initial proline-catalyzed reactions, the word 'organocatalysis' covers nowadays many other well-known reactions such as Mannich, Henry, Baylis-Hilman, Stetter, Knoevenagel reactions, Michael additions, Aldol, phase-transfer catalysis. Further substitution, cycloaddition, rearrangement and elimination

reactions in all types of synthetic processes fall in this category which are having significant contributions in the medicinal, pharmaceutical, agrochemical and various other advanced fields of chemistry and biology.[12] Among all the reactions mentioned in (Figure 1.1), the main emphasis in this part is on organocatalytic direct Mannich reactions.

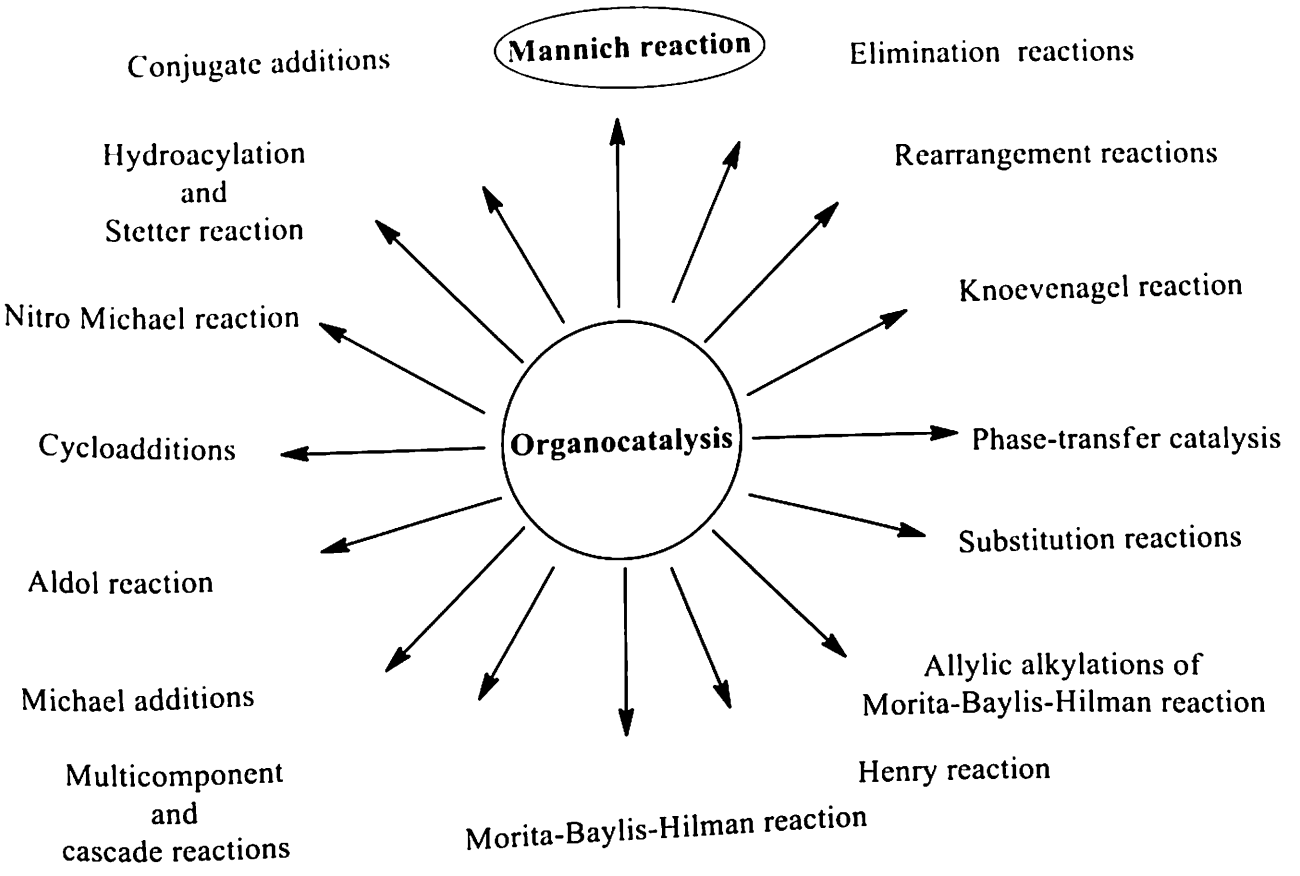


Figure 1.1 Various kinds of organocatalytic reactions

Most of the organocatalysts are air and moisture stable thus more sensible for use in the synthetic laboratory. They are easy to handle even on a large scale and relatively less toxic compared to transition metals. Moreover, commonly the reactions are conducted under mild conditions and high concentrations thus escaping the use of large amounts of solvents and minimizing waste.[13-14] During the last decade, organocatalysis has been one of the most rapidly rising and competitive fields in asymmetric catalysis and developed to 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.

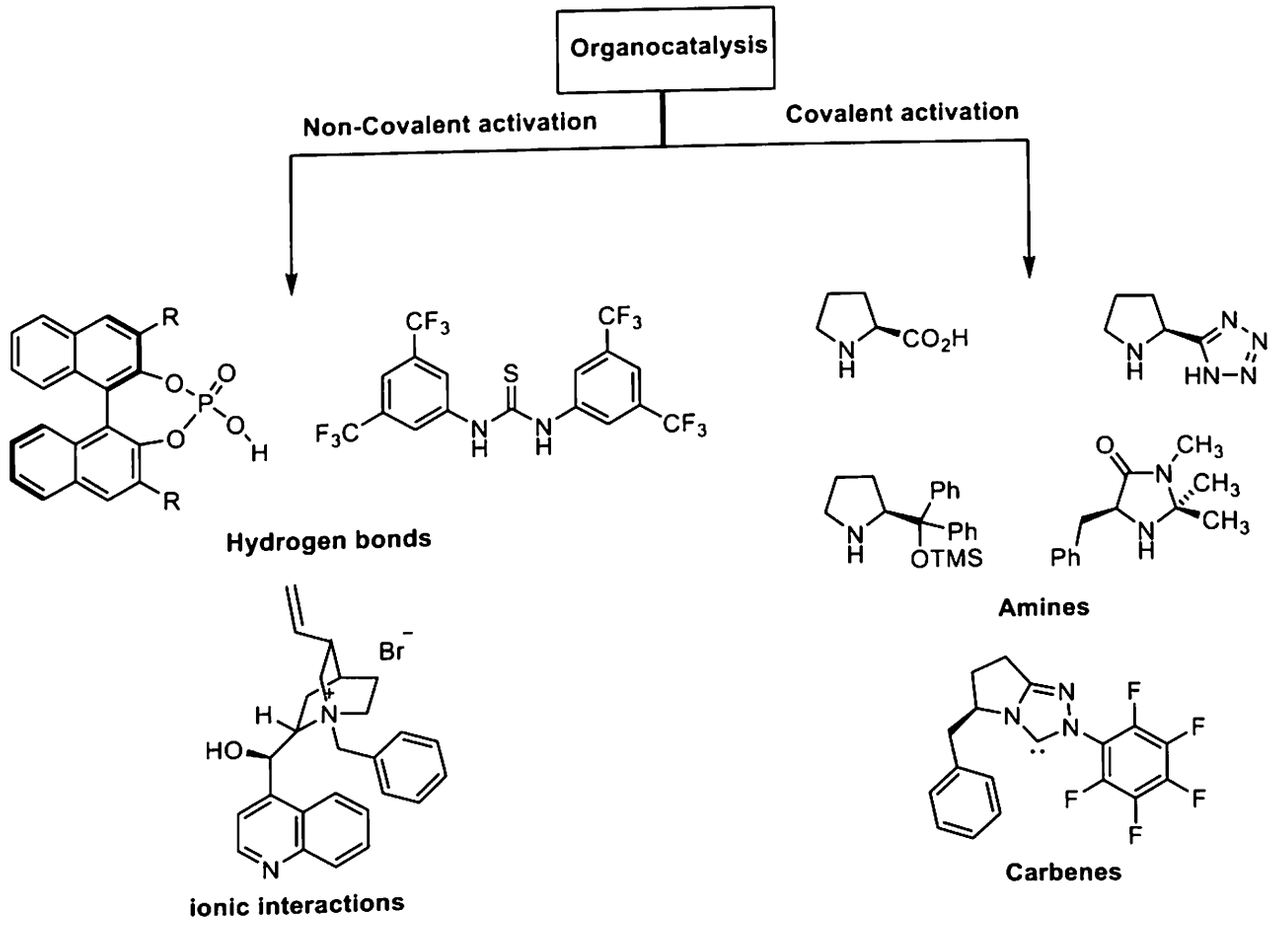


Figure 1.2 General classifications of organocatalysis

Different types of organocatalysts, such as peptides, Cinchona alkaloids, amino acids, chiral thiourea, chiral Bronsted acids etc. express privileged and intriguing characteristics in this emerging field of catalysis. In general, organocatalysis has two main modes 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 covalent catalysis, activation of the substrate takes place through the covalent bond formation between organocatalyst and substrates. In this category, amine catalyst[16] and carbene catalyst[17] are included. Whereas, in non-covalent activations, substrates activation occurs through the non-covalent interactions such as hydrogen bonds[18] (e.g., thioureas[19,20] and phosphoric acids [21-26] or ionic interactions (e.g., chiral phase transfer catalysts derived from cinchona alkaloids)[27] between the substrate and the catalysts.

1.2 Amine catalysis for the organocatalytic reactions

Amines can activate carbonyl compounds toward nucleophilic addition was previously recognized in the late 1800s by Knoevenagel, who studied the aldol condensation of β-ketoesters and malonates with aldehydes and ketones in the presence of amines and even proposed the intermediacy of imine and enamine species.[28-31] This work was further followed by very important discoveries, which include some examples of asymmetric catalysis.[32] The actual investigation of aminocatalysis in asymmetric transformations, occurred in recent years followed by the widespread gratefulness of the generality of this concept. The amine catalytic enamine increasing the HOMO of the substrate, and iminium ion decreases the LUMO of the substrate through the mechanistic patterns (Figure 1.3)[33] have now been expanded to new activation modes, which include extended enamine catalysis (dienamine[34-37] and trienamine[38-41] and SOMO (singly occupied molecular orbital) catalysis characterized by the formation of enamine radical cations.[42-45] Asymmetric organocatalytic activation of the substrate through the covalent mode of activation using small organic molecules has now become the emerging field of organocatalysis. The role of asymmetric covalent aminocatalysis has developed into a scalable, synthetic pattern stimulating the synthetic community towards utilization of these methods for more practical, metal-free syntheses of natural products.

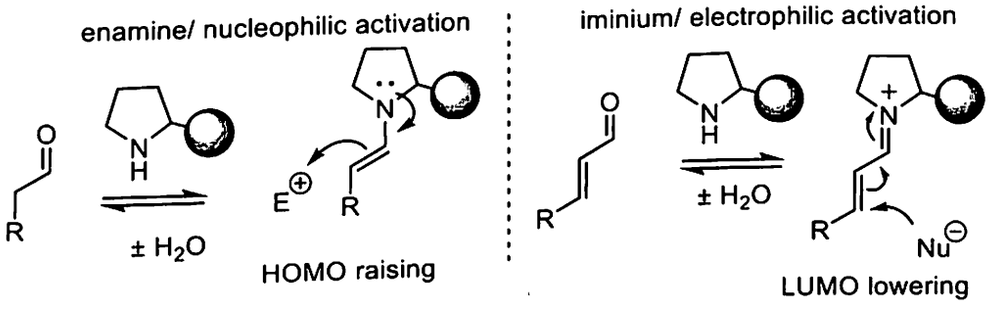


Figure 1.3 Enamine and iminium ion activation modes of aminocatalysis

In particular, amine catalysis through enamine (HOMO) activation appeared as a major contributor in the area of organocatalysis and has been applied in several asymmetric transformations/cascade reactions and to prepare unambiguous products in a simple catalytic one-pot operation.[46-49] Herein, we are particularly interested in the covalent mode of activation of the substrate through amine catalysis and our work deals with the activation of the carbonyl compound through enamine-intermediate (Figure 1.4). Following the turn of the millennium, the role of asymmetric covalent amino catalysis has developed into a scalable, synthetic paradigm to stimulate the synthetic

community toward utilization of these methods for more practical, metal-free synthesis of natural products.

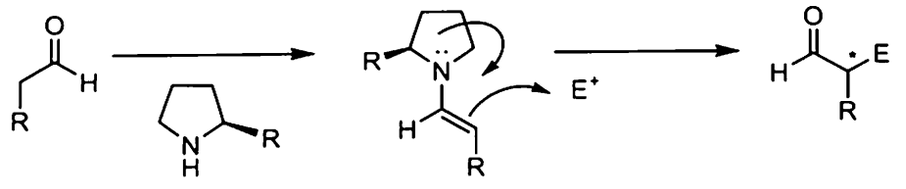
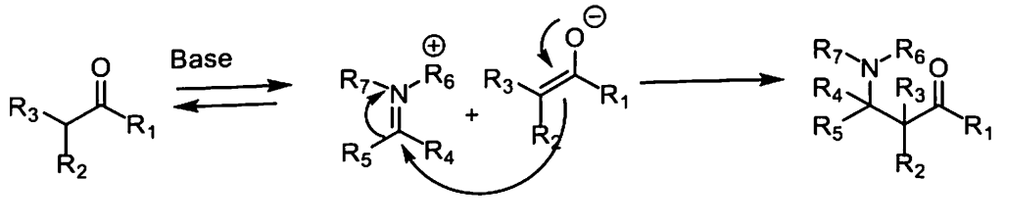


Figure 1.4 Covalent mode of activation of substrates through enamine intermediate catalysis

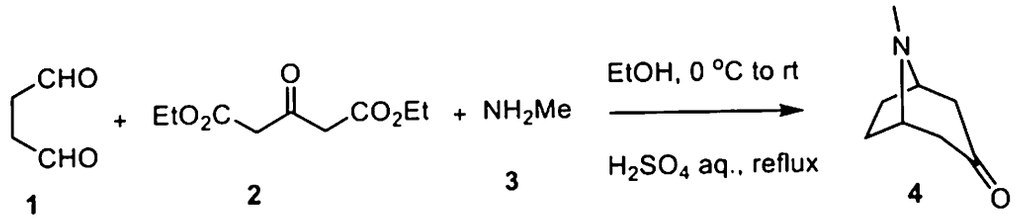
1.3 Mannich Reaction

The Mannich reaction is an efficient route to construct a C-C bond and to direct the synthesis of nitrogen-containing compounds. Across the Mannich reaction, our area of interest is a direct Mannich reaction which involves carbonyl compounds as a Mannich donor, and imines as Mannich acceptor, resulting in the C-C bond formation adjacent to nitrogen in the nitrogen heterocycle as shown in Scheme 1.1. In other words, the Mannich reaction is an organic reaction used to convert a primary or secondary amine and two carbonyl compounds (one non-enolizable aldehyde and one other enolizable carbonyl compound as most important nucleophiles), to *β*-aminocarbonyl compound, also known as a Mannich base. This reaction is also called as amino alkylation. The Mannich reaction was named after a German Chemist Carl Ulrich Franz Mannich in 1912. A general mechanistic aspect is shown in Scheme 1.1.[50]



Scheme 1.1 General Representative Mannich reaction

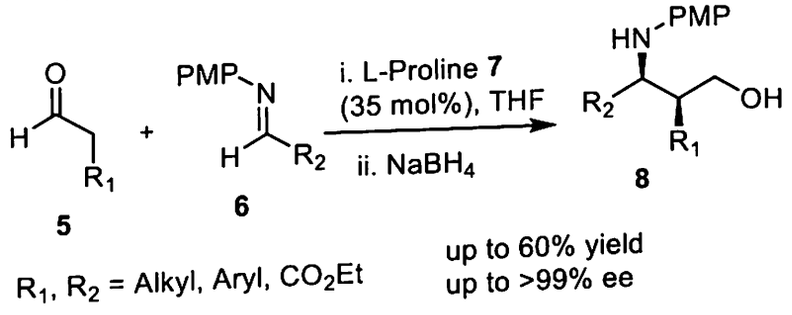
This is an important reaction because of the incorporation of the nitrogen atom into the products, which is often present in natural products and drugs. In fact, the Mannich reaction was already used only five years after its discovery, in 1917, as a key step in Robinson's total synthesis of tropinone **4**.[51] In this reaction succinaldehyde **1**, diethyl acetonedicarboxylate **2**, and methylamine **3** gave the desired product after twofold decarboxylation in a synthesis that is nowadays recognized as a classic in linear synthesis (Scheme 1.2).



Scheme 1.2 Important use of Mannich reaction for the synthesis of tropinone

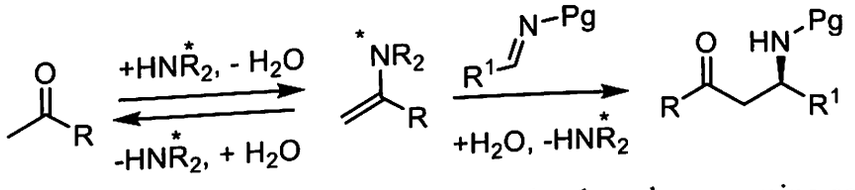
1.4 Development of amino-catalytic direct Mannich reactions

The asymmetric Mannich reaction is one of the most powerful carbon-carbon and carbon-nitrogen bond-forming protocol for the construction of nitrogen-containing compounds.[52-58] The utilization of this reaction allowed for the synthesis of optically active β-amino carbonyl compounds and their derivatives. In some instances, these reactions have proven effective for the generation of biologically significant and synthetically useful β-amino acids that contain a quaternary stereocenter substituted with a nitrogen atom adjacent to the carbonyl group.[59-62] Traditionally, asymmetric Mannich reactions are catalyzed by chiral transition metal complexes.[63-68] But in 2000, List *et al.* first described the use of L-proline 7 as an organocatalyzed Mannich reaction.[69,70] This landmark discovery stimulated the rapid development of many asymmetric organocatalytic Mannich reactions.



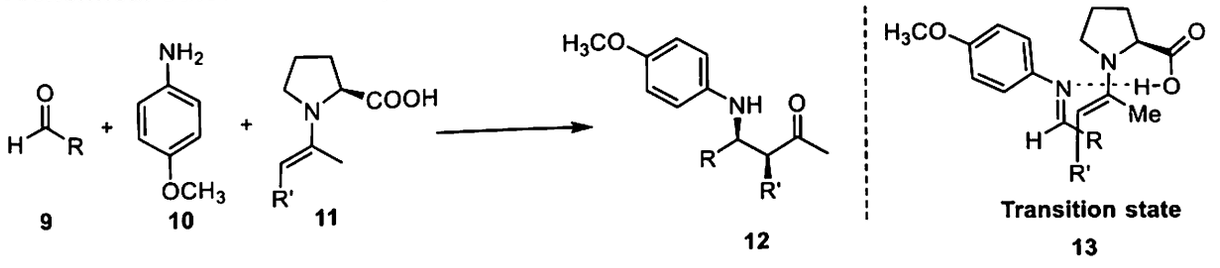
Scheme 1.3 First asymmetric organocatalytic Mannich reaction

Carbonyl groups can often be efficiently activated towards electrophiles by the addition of primary or secondary amines through the iminium-ion formation, which rapidly interconverts to corresponding enamines, behaves as a nucleophilic species. Moreover, if the amine is chiral, asymmetric induction can be transferred to the product as shown in Scheme 1.4.



Scheme 1.4 Direct asymmetric Mannich reaction based on enamine catalysis

The typical organocatalytic approach to the asymmetric Mannich reaction is based on enamine activation of carbonyl compounds using secondary amine organocatalysts.[27] Since its discovery, the Mannich reaction was developed into one of the most versatile C-C and C-N bond forming reactions and allows access to a variety of different building blocks and alkaloids.[71-74] In this chapter, the progress on direct asymmetric Mannich reactions involving chiral aminocatalysis is discussed. Organocatalytic Mannich reactions can be carried out either as three-component one-pot reactions or as reactions of preformed imines with enamine-donors. Chiral amines resulting in chiral enamines can attack a Mannich acceptor, usually a prochiral aldimine, thereby introducing one or two stereocenters in the Mannich product. The catalytic cycle is completed by the regeneration of the amine catalyst through hydrolysis. The products are β-amino-aldehydes or β-aminoketones, which are substituted at the α-position.[75] Among a wide diversity of organocatalysts that have been used in the asymmetric Mannich reaction, the most commonly used catalysts are proline and its derivatives. Mechanistically, the stereochemical outcome of all of the reactions can be explained by involving a transition state **13** as described in Scheme 1.5. The activation of imine through acidic proton of proline takes place through TS **13**, where the nucleophilic attack of *Si*-face of the *anti*-enamine **11** *in situ* formed from ketone and proline, takes place on the *Si*-face of (*E*)-aldimine for the synthesis of *syn*- product **9**.[76] This model explains the stereochemical outcome of many similar reactions that have appeared in the literature.

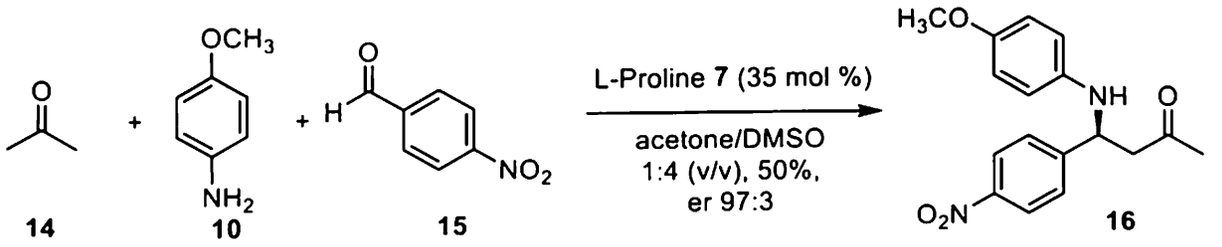


9 10 11 12 13

Scheme 1.5 Proline-catalyzed Mannich reaction involving enamine formation

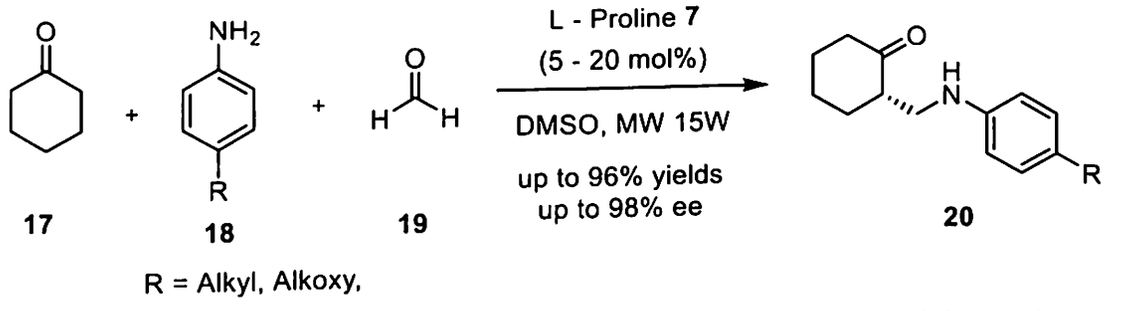
After the initial development of asymmetric Mannich reaction by List, a huge number of protocols were developed by different researchers around the globe which were collectively reviewed by List group.[30] The organocatalytic asymmetric three-component Mannich reaction has significantly expanded the synthetic scope and value of this transformation. List and co-workers reported Mannich reactions of acetone **14**, *p*-anisidine **10**, and aldehydes **15** in the presence of L-proline **7** as a catalyst to the synthesis of aminocarbonyl compounds **16** shown in Scheme 1.6[77].

The main advantage of the three-component procedure is that it does not require any pre-formed imine and enol equivalents.



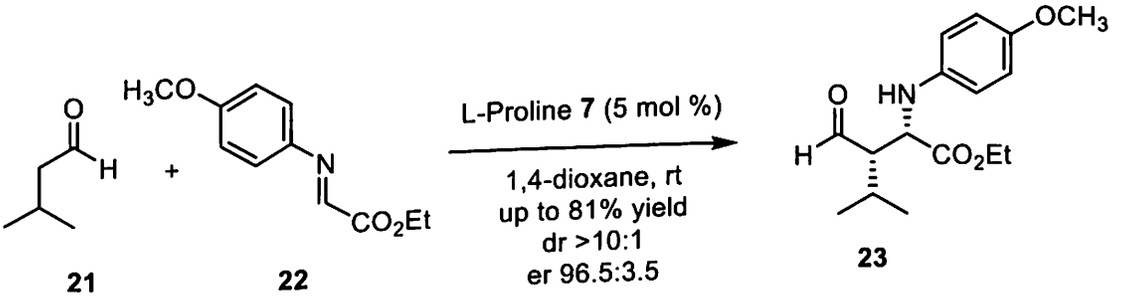
Scheme 1.6 First highly enantioselective Multicomponent direct Mannich reaction

C. Bolm and Rodriguez reported the enantioselective synthesis of *R*-aminomethylation **20** using L-proline **7** catalyzed between ketone **17**, aqueous formaldehyde **19**, and aniline **18** in DMSO under a microwave power of 15W, giving the corresponding product **20** as shown in Scheme 1.7.[78] By using microwave irradiation power heating with simultaneous air-cooling, reaction times and catalyst loadings could be reduced.



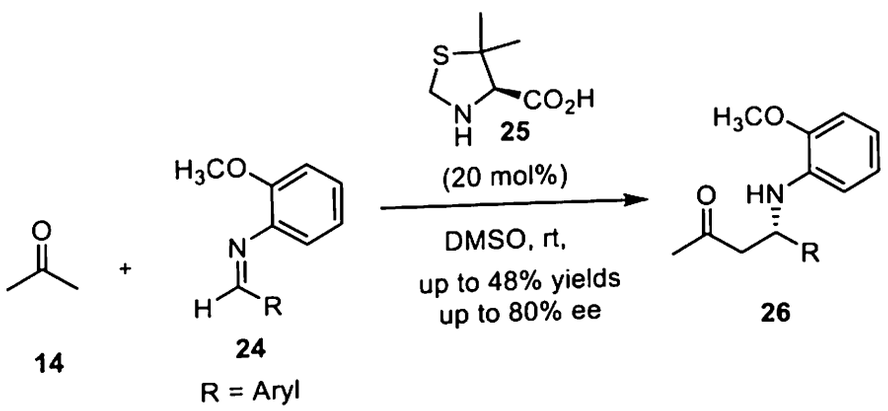
Scheme 1.7 Proline catalyzed Multicomponent asymmetric Mannich reaction

C.F. Barbas III and co-workers reported the proline-catalyzed Mannich reaction with *N*-PMP protected α-imino ester **22** and iso-valeraldehyde **21** to produce protected α-amino acid ester **23** (Scheme 1.8)[79] The diastereomeric ratio was higher with increased steric bulk on the aldehyde. It was found that some products epimerized upon purification by column chromatography. Similar results were reported by the same group with preformed α-imino esters as starting materials,[80-81] these esters are direct precursors of α-amino acids.



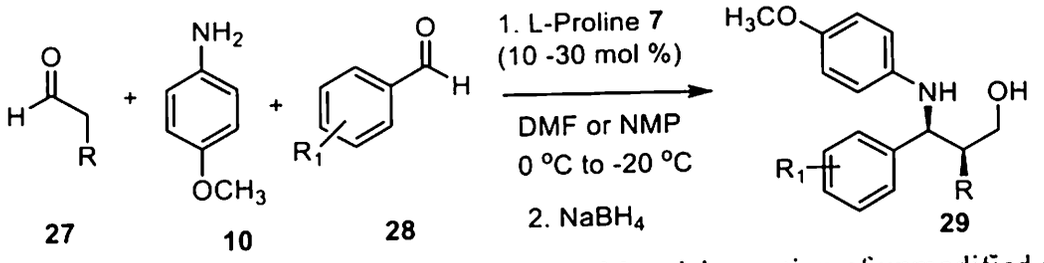
Scheme 1.8 First use of unmodified aldehydes in the proline-catalyzed Mannich reaction

Barbas and co-workers have reported L-5,5-dimethyl thiazolidine- 4-carboxylic acid **25** catalyzed asymmetric Mannich reactions between acetone **14** with a variety of preformed imines **24** or in situ generated aldimines derived from *o*-anisidine for the synthesis of corresponding product **26** (Scheme 1.9).[82]



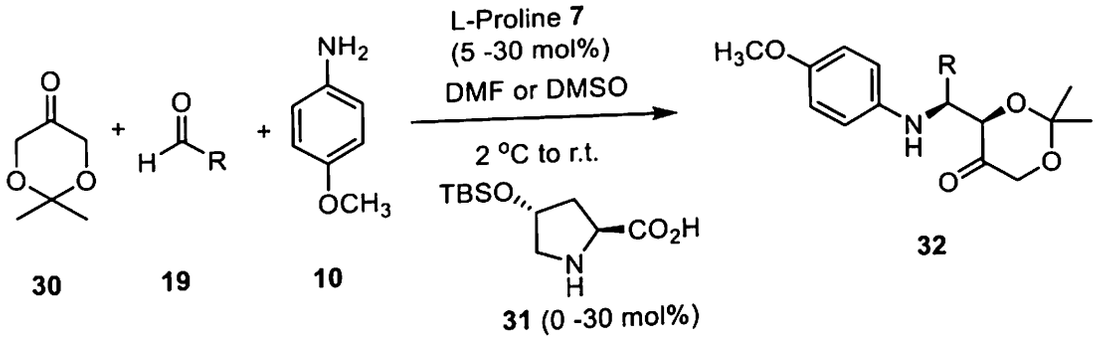
Scheme 1.9 Organocatalytic asymmetric Mannich reaction with preformed imines

The development of a proline-catalyzed cross-Mannich, three-component reaction of two unmodified aldehydes and *p*-methoxyaniline **10** was described independently by the groups of Hayashi,[83] Barbas,[84] and Córdova.[85] While the three methods differ slightly, all used dimethylformamide (DMF) or *N*-methyl pyrrolidinone (NMP) as a solvent and employed a temperature range of 0 °C to –20 °C. In many cases, the products were reduced *in situ* to the corresponding *β*-amino alcohols **29** (Scheme 1.10). A variety of aldehydes **27** could be employed as a donor. The reactions proceeded with good selectivity. Diastereomeric ratios were typical (>95:5), and only very few examples had enantiomeric ratios (<95:5). In addition, the reactions gave high yields (70-90%) in most cases. While aromatic aldehydes **28** were mostly used as acceptors, Barbas also reported the self-Mannich reaction between two aliphatic aldehydes. The products were generally formed with lower selectivities, such as enantiomeric ratios (90.5:9.5 to 93.5:6.5) and diastereomeric ratios (5:1). The product derived from *iso*-valeraldehyde **29** as the bulkiest aldehyde in this screening was formed with (59:41er).



Scheme 1.10 Enantioselective three-component cross-Mannich reaction of unmodified aldehydes

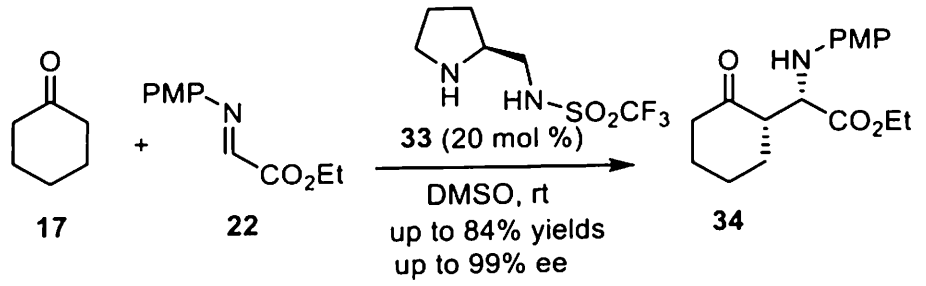
The organocatalytic entry to amino sugars *via* the Mannich reaction has been broadened by the groups of Córdova,[86] Westermann,[87] and Enders[88] with the use of protected dihydroxyacetone **30** (Scheme 1.11). The yields and selectivities of the product **32** were high. The group of Westermann used pre-formed imines from aldehyde **19**, and *p*-methoxy aniline **10** while both Córdova and Enders developed three-component reactions. Moreover, Enders described TBS-protected 4-hydroxyproline **31** to be a better catalyst due to the better solubility.



Scheme 1.11 Synthesis of aminoketones through Mannich reaction

Several researchers have been interested in finding different catalysts, in this context List[89] and Barbas[90] have researched pyrrolidine-derived catalysts for the reaction of ketones and aldehydes in the Mannich reaction. Córdova screened acyclic amino acids such as alanine or serine, which also catalyzed the Mannich reaction with good selectivities,[91] but proline remained the catalyst of choice. This may be because of its high selectivity, easy handling, and the additional advantage of being cheap and available in both enantiomeric forms.

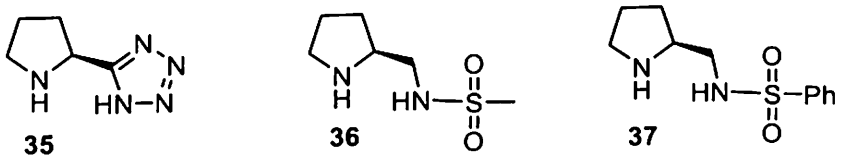
Wanga and co-workers reported the use of pyrrolidine-sulfonamide **33** as a catalyst for the direct Mannich reaction between cyclohexanone **17** and ethyl glyoxylate-imine **22** in protic and aprotic solvents with 76% to 90% yields shown in Scheme 1.12.[92] Hence, the desired Mannich product **34** was obtained with excellent enantioselectivity and diastereoselectivity of the *syn*-product.



17 22 34

Scheme 1.12 Pyrrolidine-sulfonamide as an alternative catalyst to proline

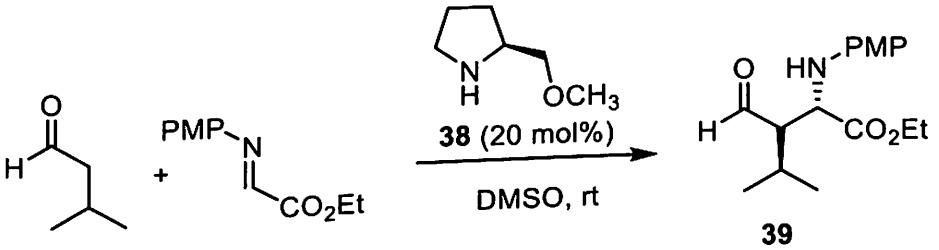
S. Ley and co-workers explored the same reaction to assess catalysts (**35**, **36**, and **37**) (Scheme 1.13) by using mainly less polar solvents. While proline-catalysis is usually conducted in highly polar solvents such as DMSO or DMF due to the low solubility of proline in less polar solvents, the new catalysts were found to be efficient even in DCM or THF, and product **34** (Scheme 1.12) with diastereomeric ratios of (>95:5) and with high enantiomeric ratios (>97.5:2.5). It was inspiring to see that even less catalyst loading of **37** (1 mol %) was enough to catalyze the reaction efficiently and without loss of enantioselectivity.[93]



35 **36** **37**

Scheme 1.13 Improved catalysts for the Mannich reaction

In 2002, Barbas[94] reported the first *anti*-selective organocatalytic Mannich reaction between aldehyde **21** and imine **22** catalyzed through L-2-methoxymethyl pyrrolidine **38** (20 mol%) to give **39** (44-78% yield, er up to 91:9) shown in (Scheme 1.14). Different aldehydes were employed in the initial screening. The diastereoselectivity was typically higher than 90:10, however selectivity dropped to 1:1 when a very small aldehyde like *n*-butanal was employed.

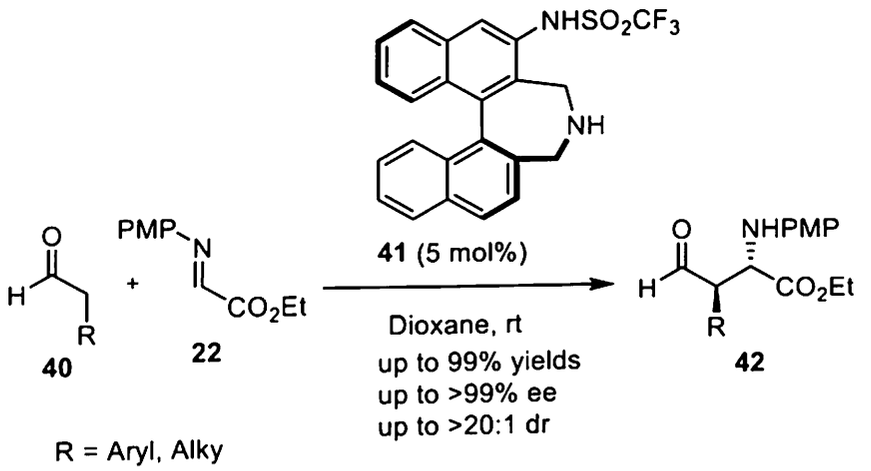


21 **22** **39**

Scheme 1.14 First *anti*-selective organocatalytic Mannich reaction

Maruoka and co-workers reported a highly *anti*-selective asymmetric Mannich reaction between aldehydes **40** and *N*-PMP protected iminoglyoxylates **22** by using a novel axially chiral amino

trifluoromethane sulfonamide **41** as amine catalyst to give α-amino aldehydes **42** with a high *anti/syn*-ratio and enantioselectivity[95] shown in Scheme 1.15. The catalyst **41** is based on a seven-membered ring and the chirality is derived from the BINOL-backbone.



Scheme 1.15 Asymmetric anti-Mannich reaction strategy for *anti*-Mannich base

Barbas' and Jørgensen's also reported C2 symmetric catalyst **43** for the direct *anti*-Mannich reaction with the similar substrates (Scheme 1.15 & Figure 1.5).[97] The excellent enantioselectivity (up to >99) was obtained with **43**, however, it was noted that catalyst **41** was found superior with respect to the catalyst loading (0.2 to 5 mol %) and activity.

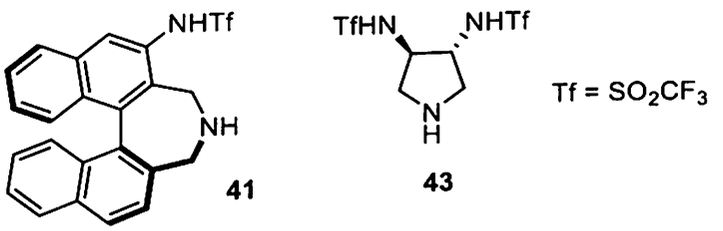
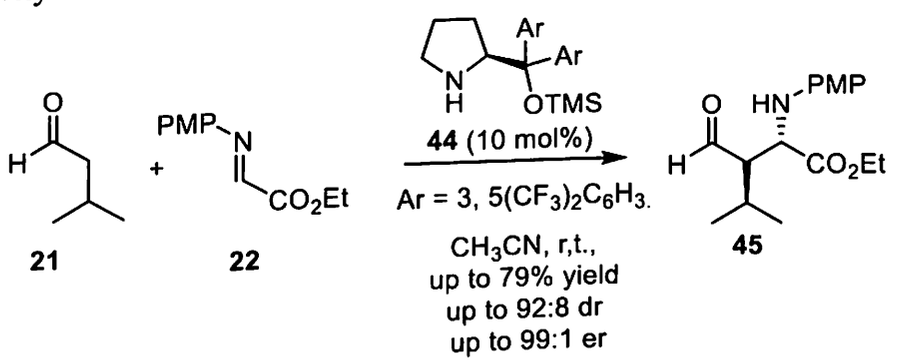


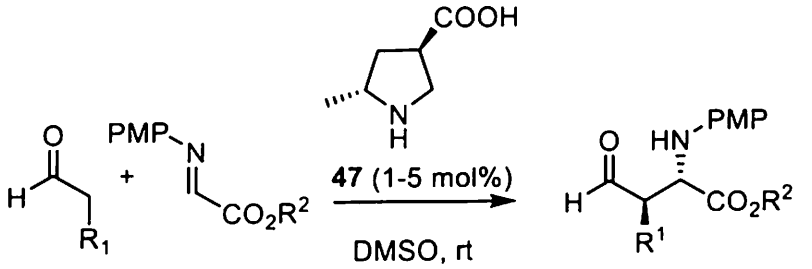
Figure 1.5 Axially chiral BINOL-derived catalyst

Jørgensen's group reported *anti*-Mannich reaction between aldehyde **21** and imine **22** by using α,α-diarylprolinol silyl ether **44** as an efficient catalyst to furnish **45** in high enantio-, and diastereoselectivity shown in Scheme 1.16.[96]



Scheme 1.16 α, α-Diarylprolinol silyl ether **54** for the *anti*-selective Mannich reaction.

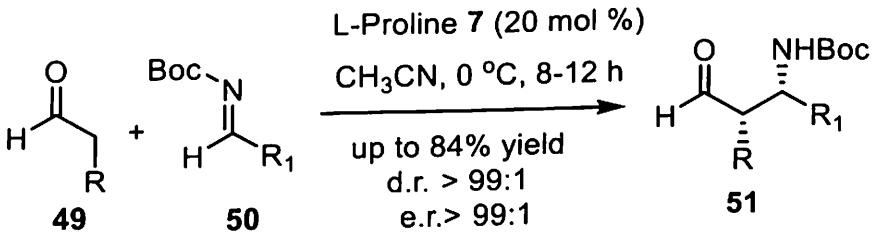
Barbas and Houk reported the Mannich reaction between aldehydes **46** and *N*-PMP-imino-esters **22** using highly selective catalyst (47)[98] to give **48** in good yields (54-92%), and excellent diastereo- (94:6 to 98:2), enantioselectivities (up to >99.5:0.5) shown in Scheme 1.17.



46 **22** **48**

Scheme 1.17 Proline derived amino acid **47** as highly active, *anti*-selective catalyst.

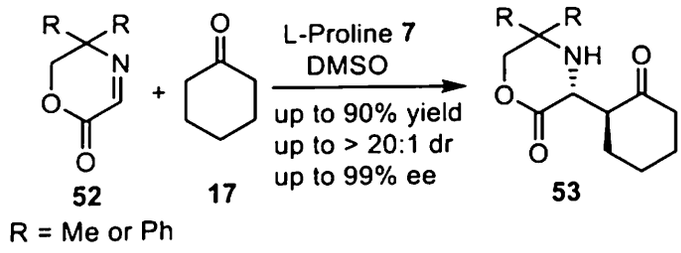
B. List and co-workers reported a Mannich reaction of unmodified aldehydes **49** with *N*-Boc imines **50** using L-proline **7** as a catalyst giving crystalline β-amino aldehydes **51** with high yields and highly diastereo- and enantioselective as shown in Scheme 1.18.[99] The products of this protocol usually precipitated from the reaction mixture and are useful intermediates in the production of *α*-and *β*-substituted *β*-amino acids.



49 **50** **51**

Scheme 1.18 Proline catalyzed Mannich reaction of aldehyde and *N*-Boc-imines.

Glorius and co-workers reported the highly stereoselective synthesis of chiral 3-substituted morpholin-2-ones **53** by using the proline-catalyzed Mannich reaction of unactivated ketones **17** and cyclic imine acceptors **52** shown in Scheme 1.19.[100] These products correspond to *α-D*-amino acids that were protected at the *N*- and *O*-terminus by the diphenylethylene group. This protecting group for *α*-amino acids could be cleaved readily by hydrogenolysis in aqueous ethanol to furnish the free amino acid.

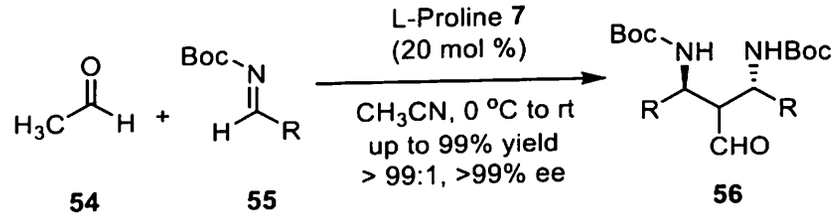


52 17 53

R = Me or Ph

Scheme 1.19 Synthesis of chiral 3-substituted morpholin-2-ones using proline 7

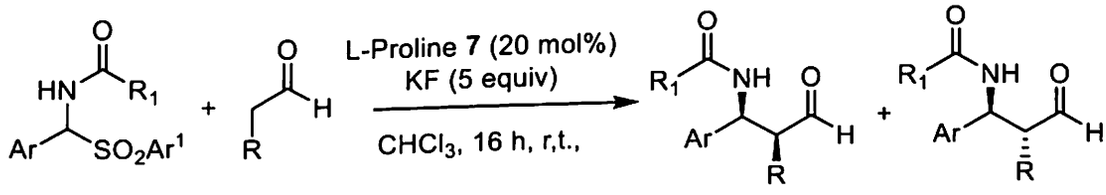
List and co-workers reported a proline-catalyzed highly stereoselective synthesis of pseudo-C2 *β,β'*-symmetric diaminoaldehydes between acetaldehyde **54** and either aromatic or aliphatic *N*-Boc imines **55** with excellent yields and enantioselectivity shown in Scheme 1.20.[101] The method was effectively extended to cross-Mannich reactions, furnishing *β,β'*-diamino aldehydes **56** containing three adjacent stereogenic centers (**Scheme 1.20**).[101]



54 55 56

Scheme 1.20 Double Mannich reaction of acetaldehyde with N-Boc imine

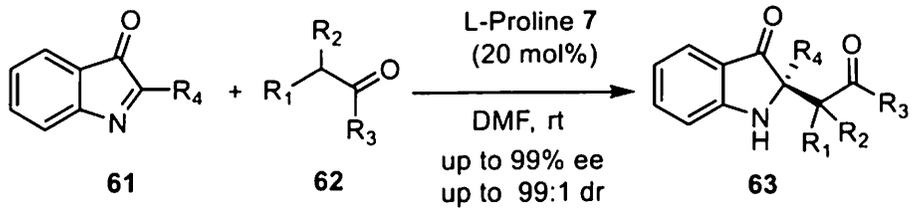
In 2010, Zhao and co-workers reported the one-pot L-proline catalyzed Mannich reactions between α-amidosulfones **57** and aldehydes **58** to give β-amino aldehydes **59** (major product) with good yields and high enantio- (99% ee) and diastereoselectivity (95:5) shown in Scheme 1.21.[102]



57 58 59 60

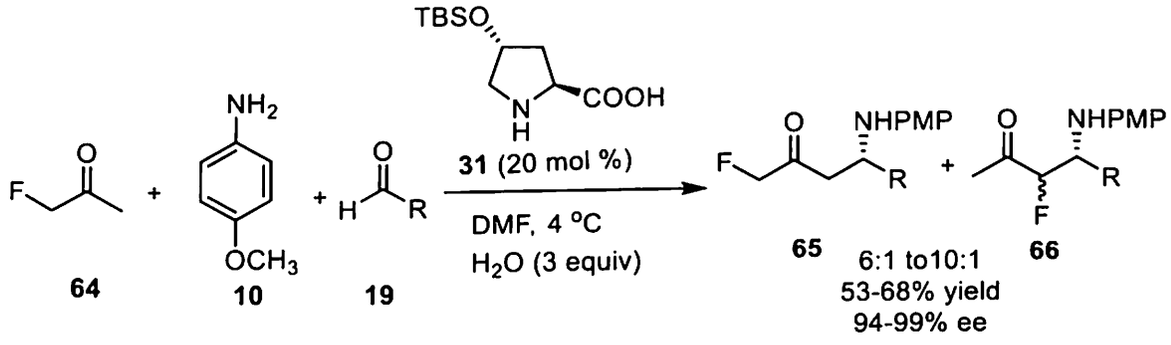
Scheme 1.21 Synthesis of amido sulfones using direct organocatalytic asymmetric Mannich reaction

In the same year, Li and co-workers reported proline-catalyzed direct Mannich reaction of 2-Aryl-3*H*-indol-3-ones **61** with aldehydes or ketones **62** to afford the corresponding aza-quaternary carbon addition product **63** in good yields and excellent enantioselectivity (up to 99 %) (Scheme 1.22).[103]



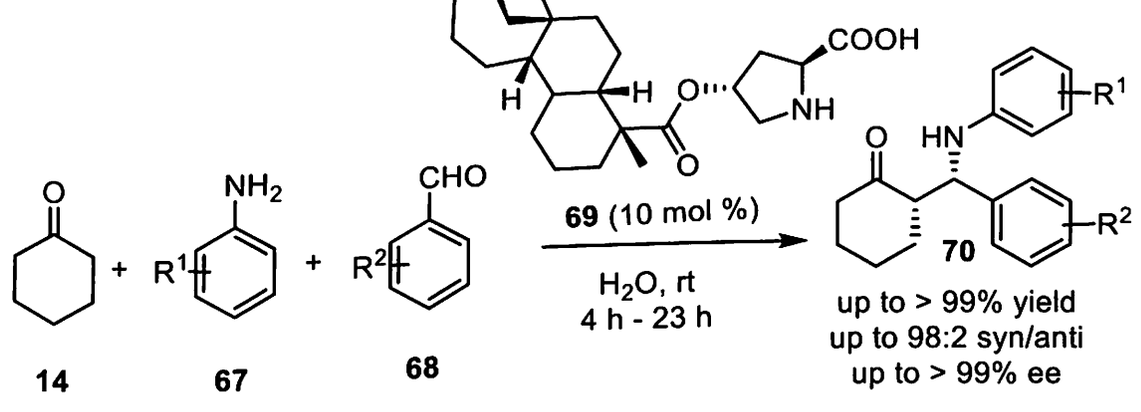
Scheme 1.22 Synthesis of 2-Aryl-3*H*-indol-3-ones with ketones in the presence of Proline **7**

In 2011, Lu and co-workers reported multi-component direct Mannich reaction with fluoroacetate **64**, *p*-anisidine **10**, and aldehydes **19** catalyzed by 4-siloxyproline **31** for pharmaceutically important fluorinated β-amino ketones **65** and **66** with high enantioselectivity shown in Scheme 1.23).[104]



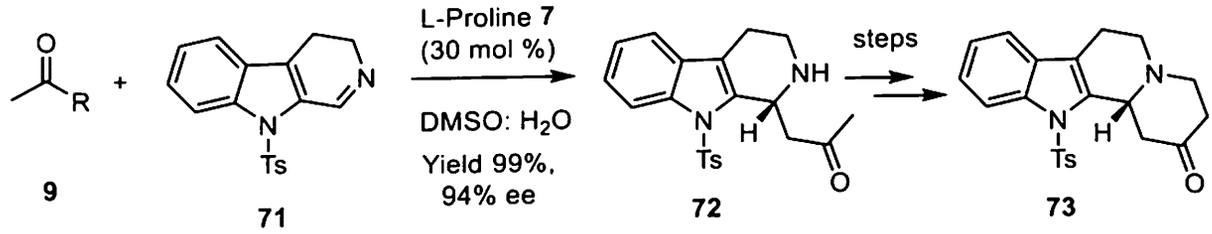
Scheme 1.23 Synthesis of pharmaceutically important fluorinated β-amino ketones

Recently, An and co-workers reported three-component *syn*-Mannich reactions of cyclohexanone **14** and anilines **67** with aromatic aldehydes **68** in H_2O where functionalized proline **69** catalyst afforded product **70** with excellent diastereo- (*syn/anti* up to 98:2) and enantioselectivities (up to >99% ee) (Scheme 1.24).[105]



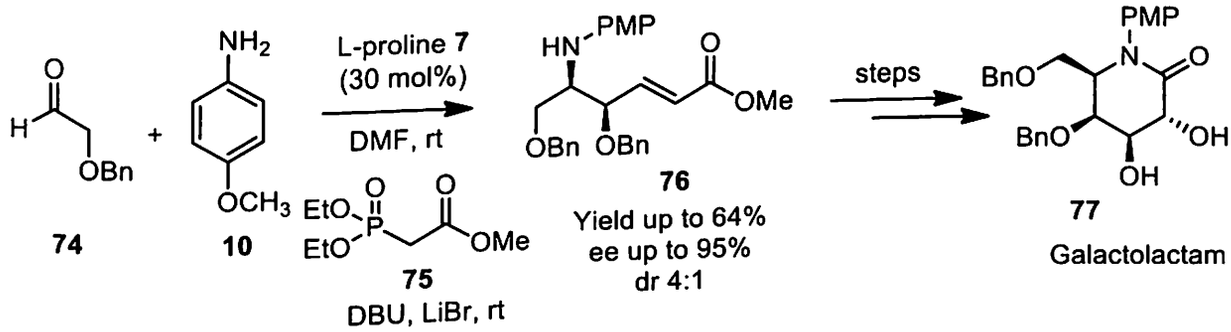
Scheme 1.24 Synthesis of *syn*-Mannich products through amphiphilic organocatalysts

Ohsawa and co-workers reported the asymmetric direct Mannich reaction of 9-tosyl-3,4-dihydro-α-carboline **71** and acetone **9** to give indole-based product **72** with high yields (99 %) and enantioselectivity (94 % ee) as shown in Scheme 1.25.[106] In this process, a small amount of water was found to have an adverse effect on the stereochemical outcome of the reaction. This protocol was further applied for the production of medicinally important indole alkaloids **73**.



Scheme 1.25 Synthesis of 9-Tosyl-3,4-dihydro-*á*-carboline with acetone

Córdova and co-workers reported a stereoselective catalytic one-pot tandem reaction by using Mannich, Horner-Wadsworth-Emmons (HWE), and subsequent Sharpless dihydroxylation sequence to give chiral amino- and iminosugar derivatives77.[107] This protocol involves L-proline **7** as catalyst (30 mol %), α-benzyloxyacetaldehyde **74** reacted with *p*-anisidine **10** to give the corresponding Mannich product, which underwent Wittig reaction to furnish **76** with two stereogenic centers in good yield, enantioselectivity, and diastereoselectivity. Subsequent Sharpless dihydroxylation and further acid-catalyzed cyclization provided the galactolactam **77** in good yield (74%) as shown in Scheme 1.26.



Scheme 1.26 Synthesis of galactolactam using direct Mannich reaction

1.5 Importance of nitrogen heterocycles

Diverse compounds like alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones, and many synthetic drugs and dyes contain heterocyclic rings as core skeletons.[108-110]

Nitrogen heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. They are also widely used in textiles, food and nutrition, leather industry, lubricants and paints, and bio-engineering. Among heterocycles, the five- and six-membered nitrogen-containing heterocycles are probably one of the most common structural motifs spread across natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs constituting the main structure within a huge number of natural products and possess a broad range of biological properties.[111-112] Nitrogen heterocycles especially porphyrins have great pharmacological properties related to the planarity of the system and consequently to its DNA-chain intercalating ability, which makes them suitable for *anti*-neoplastic and mutagenic applications.[113-116] Because of their useful applications in the biological field, synthetic development of nitrogen heterocycles and their related fused scaffolds containing a high degree of diversity has become a leading focus in modern drug design and discovery.[117-121]

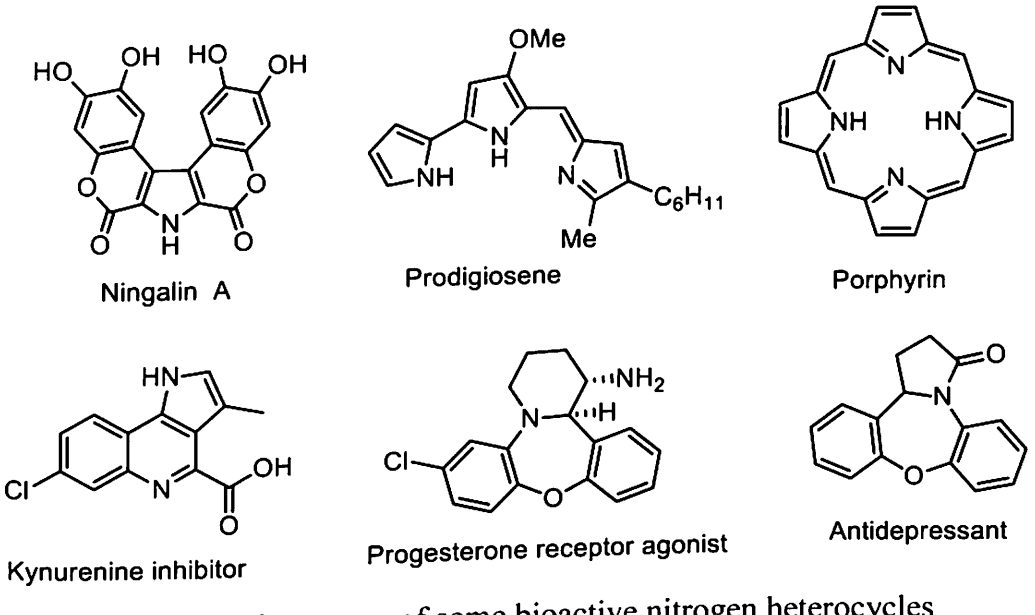


Figure 1.6 Structures of some bioactive nitrogen heterocycles

Among variously sized nitrogen heterocycles, our work in this thesis is mainly focused on the construction of five and six-membered nitrogen heterocycles such as pyrrole-3-methanols, Iodo pyrroles, fused tetracyclic pyrroles, 1,2-dihydropyridines (DHPs) and their related fused natural product based scaffolds having significant importance in the current field of organic synthetic chemistry involving the green concept of amine-catalysis. Some of the biologically important

natural products containing pyrrole ring as the main constituent in their structure are mentioned in the following **Figure 1.6**.[122-126]

1.6 Succinaldehyde in amino-catalytic transformations

Organocatalytic domino reactions involving amine activation of carbonyl compounds have grown to be the latest chemical technology towards the designing and development of useful synthetic methods. In this direction, linear dialdehydes such as succinaldehyde, glutaraldehyde, and other homologous compounds have attracted significant attention as suitable substrates for amine catalyzed transformations. Due to their unique structural features, dialdehydes can be easily engaged in the creation of cascade/tandem transformations for the synthesis of valuable natural products and drug molecules. Linear dialdehydes have been used for various transformations such as aldol/Mannich/Michael/Henry/Baylis-Hillman reactions in an inter-and intramolecular manner. Linear dialdehydes and their derivatives have been documented as important substrates in the area of synthetic organic chemistry.[127] Particularly, the aim of this section is to highlight the importance of succinaldehyde which acts as 1,3-carbon *donor-acceptor* (D-A) precursor for amine catalyzed one-pot transformations to access biologically important complex scaffolds in asymmetric as well as in non-asymmetric fashion with molecular complexity and high selectivity through amine catalysis. Amine catalyzed transformations or Mannich reactions in which linear dialdehydes are organized according to the suitability are shown in Figure 1.7. Amine catalyzed transformations of succinaldehyde and other higher homologated saturated or unsaturated dialdehydes in an intramolecular fashion with various C=C, C=N, C=O bonds.

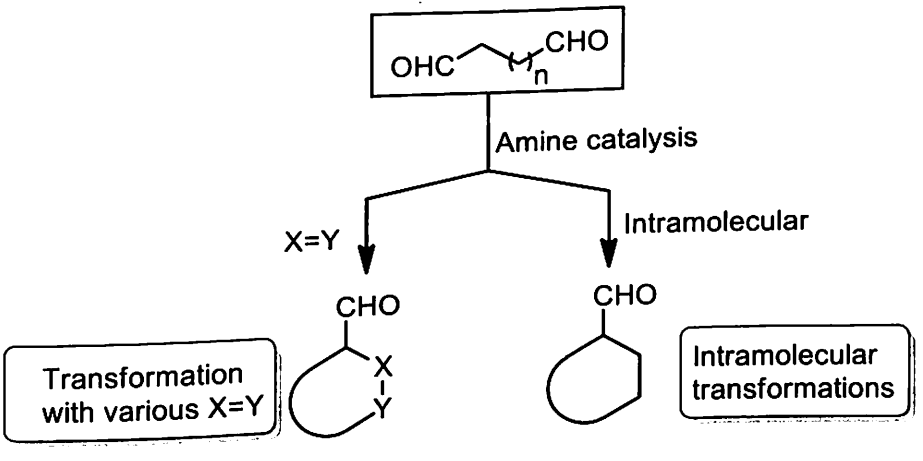
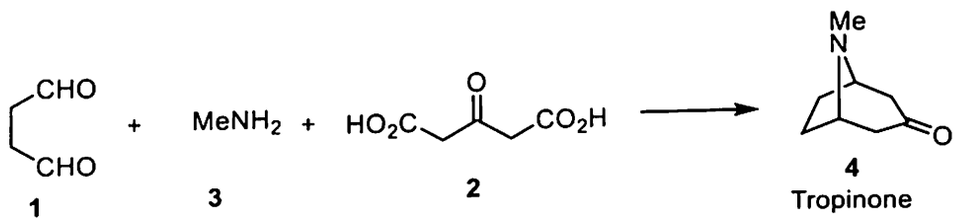


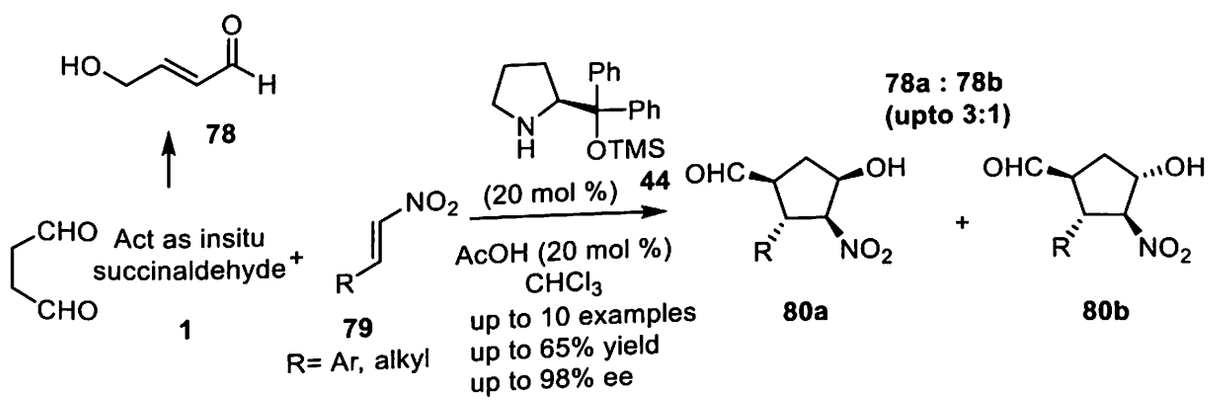
Figure 1.7 Intermolecular transformations of Succinaldehyde in amine catalysis

Succinaldehyde **1** is a 1,4-dicarbonyl compound which undergoes polymerization in neat form, whereas reasonably stable in aqueous solution. The early utilization of succinaldehyde **1** to synthesize tropinone **4**, by Sir Robinson in 1917, within a test tube is still an exciting example of total synthesis that illustrated a new way of synthetic creativity. This conversion showed the original application of dialdehydes in biogenetic-type synthesis because nature uses the identical materials to make similar compounds. This one-pot tandem approach utilized succinaldehyde **1** as a valuable synthetic substrate along with amine **3** and acetone dicarboxylic acid **2** through double Mannich condensation followed by decarboxylation to give the bicyclic tropane skeleton (**4**) (Scheme 1.27).[128] In addition, succinaldehyde **1** has also been applied successfully for the synthesis of various heterocyclic ring systems as well as natural products.[129-131]



Scheme 1.27 synthesis of tropinone from succinaldehyde

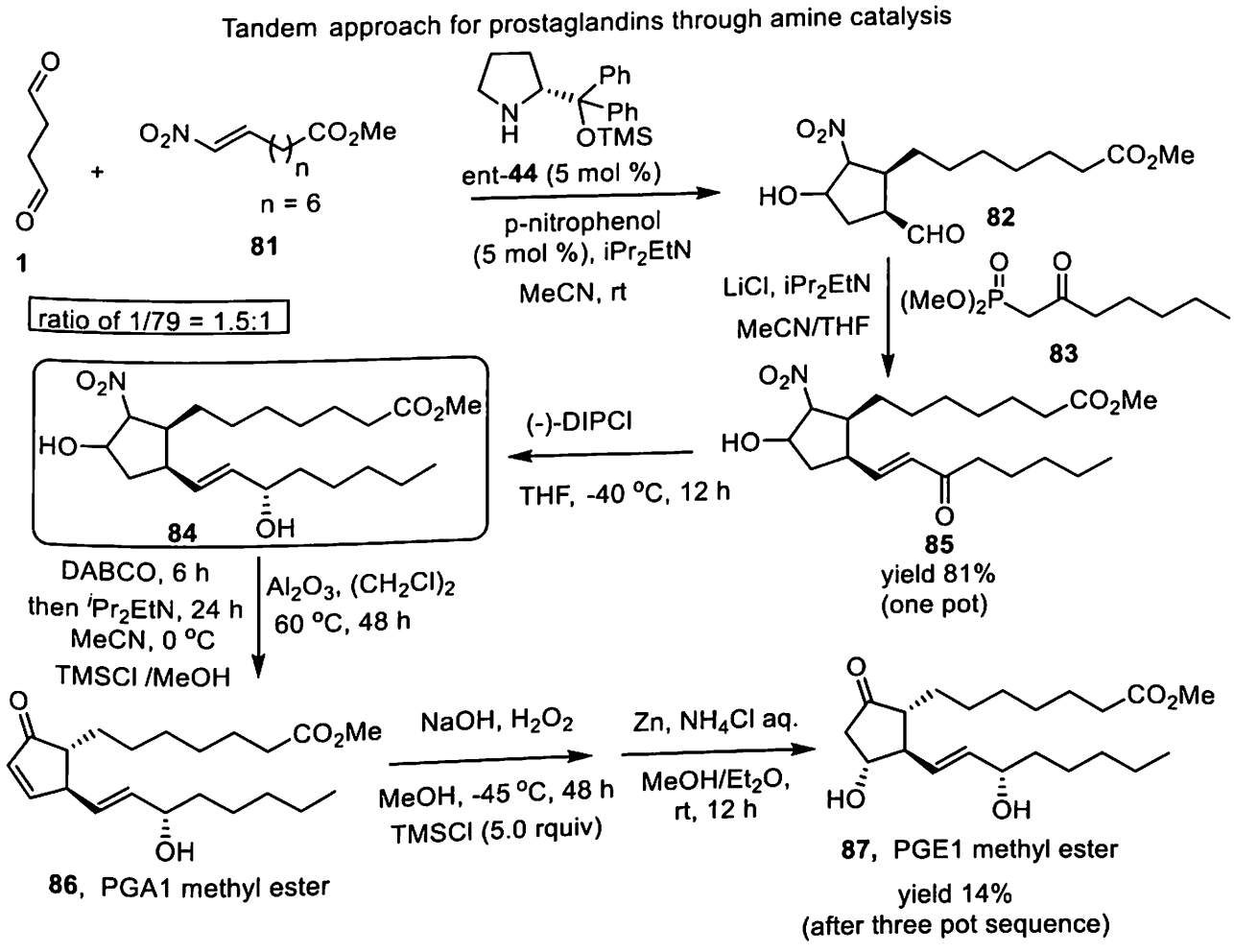
In 2012, Hong and co-workers initially reported the synthesis of cyclopentane carboxaldehyde **80a** and **80b** proceeding through organocatalytic [3+2] Michael-Henry cascade reaction of various nitroalkenes **79** with a masked dialdehyde **78** in good yield with four consecutive stereogenic centers with excellent enantioselectivity (up to 98%) shown in Scheme 1.28.[132]



Scheme 1.28 synthesis of cyclopentane using succinaldehyde *via* amine catalysis

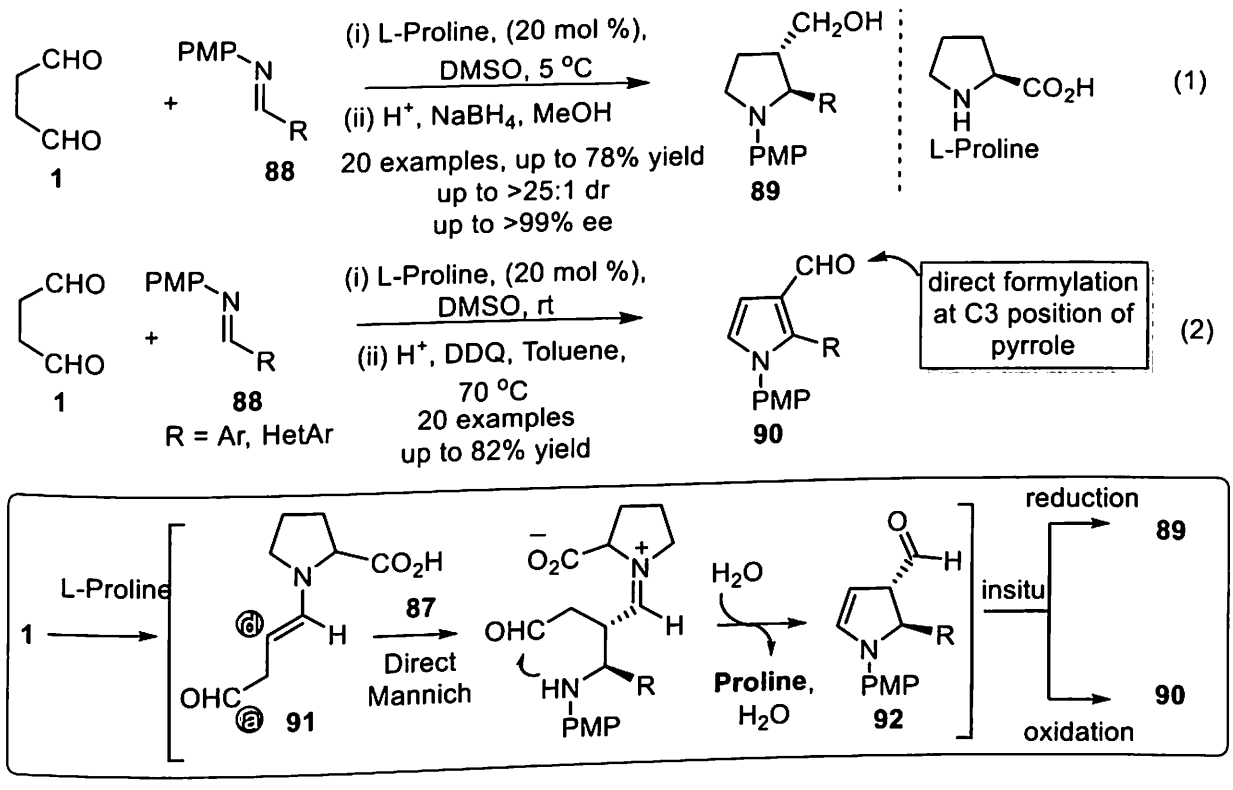
Hayashi and co-workers.[133] developed the direct application of succinaldehyde **1** in amine catalyzed domino reaction through 'pot-economy' for the asymmetric total synthesis of prostaglandins. This practical approach involved direct Michael reaction between succinaldehyde

1 and nitroalkene **81** catalyzed by diphenylprolinol silyl ether *ent*-**44** (5 mol%) followed by intramolecular Henry reaction in presence of $^{i}Pr_2EtN$, as [3+2] cycloaddition and further Horner-Wadsworth-Emmons reaction as one pot transformation to give basic prostaglandin skeleton **84** with high yield and selectivity. Further functional group inter-conversion from the common scaffold **85** with additional two-pot sequence completed the enantioselective synthesis of PGA_1 methyl ester **86** and PGE_1 methyl ester **87** in (25% and 14%) yields respectively (Scheme 1.29). A fascinating part of this short and efficient synthesis was not only the use of inexpensive starting materials but also to complete the synthesis in just three pot sequence with few purification steps, which further reduced the amount of solvent consumption and waste production. Interestingly, one-pot operations were found to be essential due to the unstable nature of intermediates and, therefore, isolation was avoided to enhance the overall yields of the process.



Scheme 1.29 Prostaglandins synthesis using Succinaldehyde

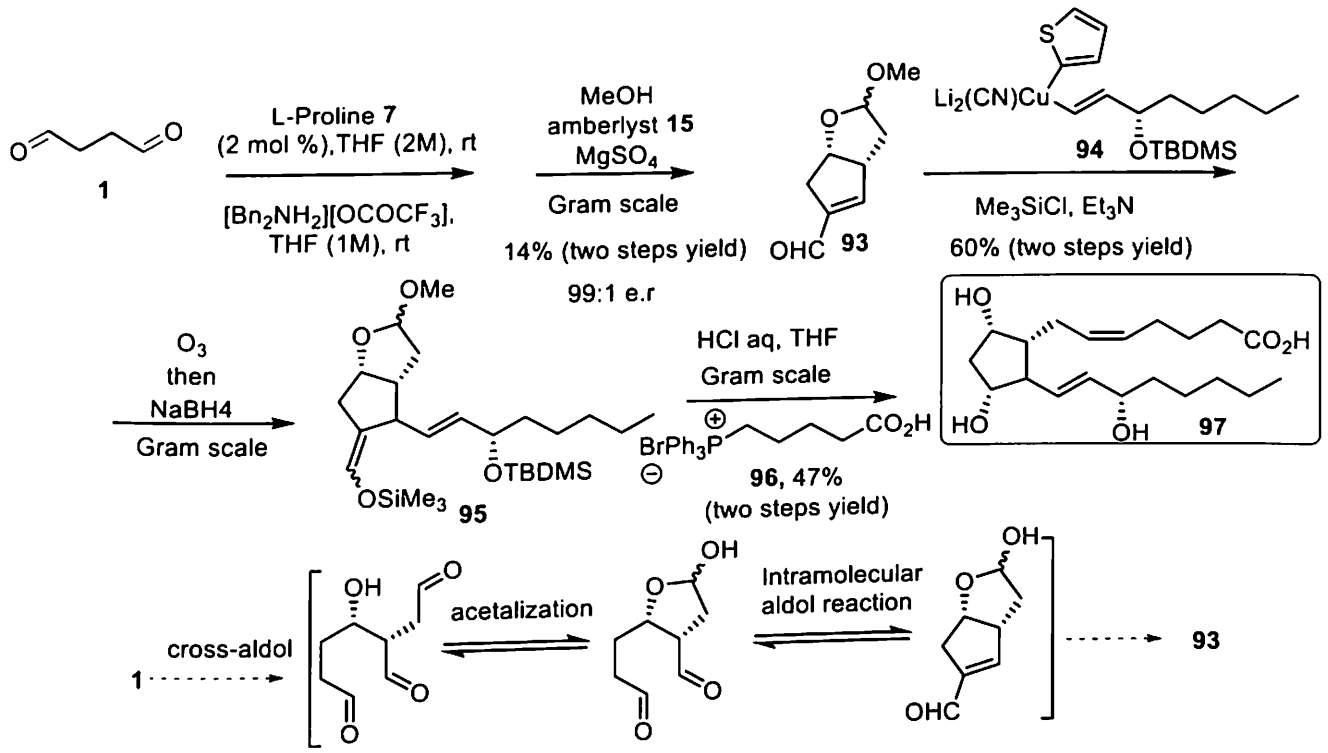
Kumar and co-workers applied succinaldehyde **1** as a biofunctionalized substrate for the quick synthesis of medium-sized nitrogen heterocycles through proline-catalyzed cascade transformations. Initially, they developed a very simple and highly stereoselective one-pot synthesis of pyrrolidines **89** (eq 1, Scheme 1.30)[134] and then the first direct synthesis of substituted pyrrole-3-carboxaldehydes **90** as a two-step protocol was established (eq 2, Scheme 1.30).[135] These two very similar transformations as [3+2] annulation proceed through proline-catalyzed Mannich reaction[136-137] between enamine **91** *in situ* generated from succinaldehyde **1** which serve as readily available 1,3-carbon *donor-acceptor* (D-A) precursor, and imine **88**. The intermediate compound **92** was reduced with $NaBH_4$ in the presence of acid to give *trans*-2,3-substituted pyrrolidine **89** in high yields and excellent enantioselectivities (up to >99% ee), whereas oxidative aromatization of intermediate **92** with DDQ produced substituted pyrrole-3-carboxaldehydes **90** in good to high yields.



Scheme 1.30 Synthesis of pyrrolidines and pyrroles from succinaldehyde

Aggarwal and co-workers reported the application of succinaldehyde in amine catalyzed cascade transformations for stereocontrolled synthesis of prostaglandin $PGF_{2\alpha}$ **97**.[138] This protocol involves the proline-catalyzed direct cross-aldol reaction of succinaldehyde **1** followed by intramolecular aldol condensation to give functionalized bicyclic-enal **93** in one step with excellent

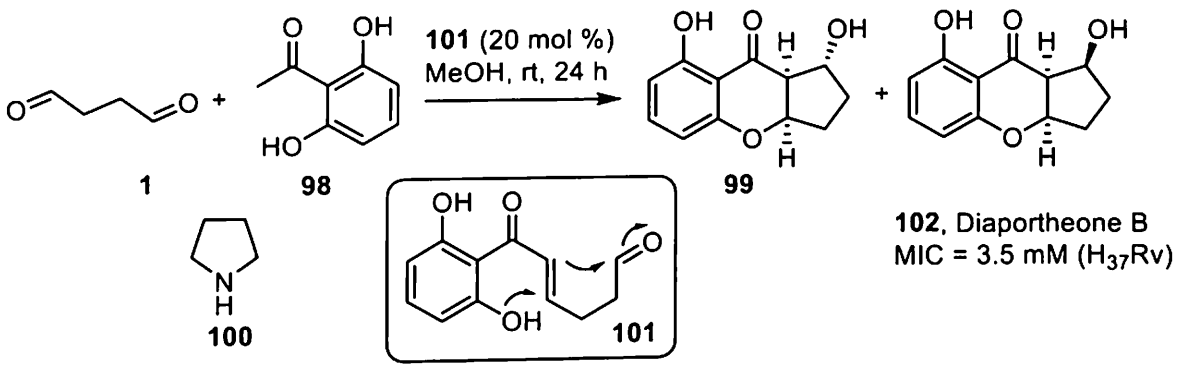
enantioselectivity. Rapid access to the basic five-membered skeleton **93** with well-placed appropriate functionality makes this method quite attractive to synthesize prostaglandin-based drugs through synthetic manipulation by installing remaining groups as shown in Scheme 1.31. This gram scale and economic synthesis of PGF2α **97** was completed in just six linear steps from succinaldehyde **1**, whereas most of the earlier methods were quite lengthy, consuming more time and generating much waste.



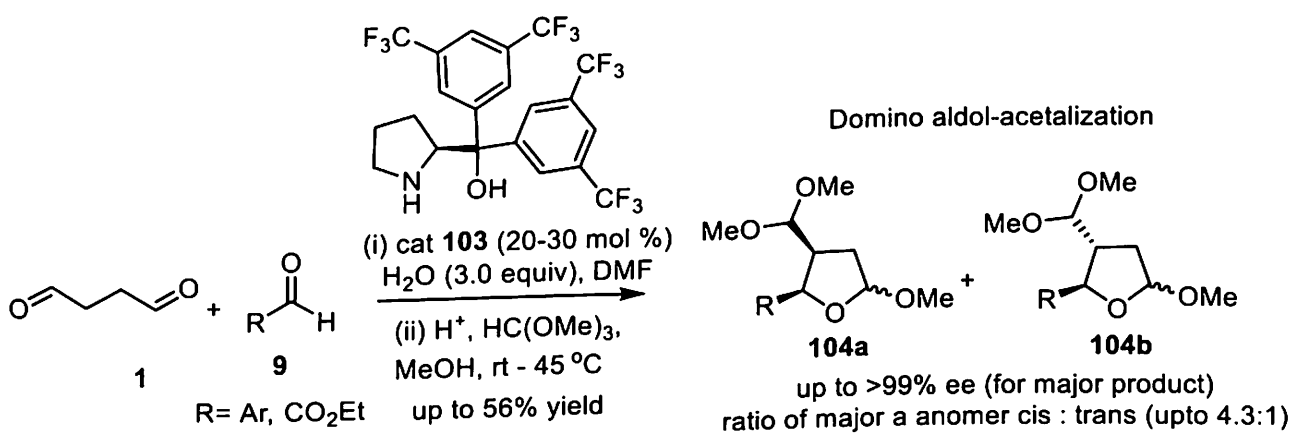
Scheme 1.31 Synthesis of Prostaglandins using succinaldehyde through amine catalysis

Reddy and co-workers have also reported the interesting application of succinaldehyde **1** for the synthesis of Diaportheone B **102** which is an anti-TB agent, through the amine-catalyzed process in a slightly different manner (Scheme 1.32).[139] The overall transformation proceeded through pyrrolidine **100** catalyzed with acetophenone **98** and succinaldehyde **1** to give intermediate **101**, which further cyclized through domino fashion to furnish Diaportheone B **102**. This one-pot process appeared as a quick route to synthesize the skeleton; however, this method suffers from low yields and selectivity issues. The similar application of succinaldehyde **1** under amine catalysis was earlier reported by Mori and co-workers for the efficient synthesis of natural products coniochaetone A and B through domino aldol/cyclization reaction.[140]

Hayashi and co-workers described a diarylprolinol **103** catalyzed domino approach for the asymmetric synthesis of tetrahydrofurans **104a** and **104b** through formal [3+2] cycloaddition between succinaldehyde **1** and other aromatic/activated aldehydes **9** with good yields and high enantioselectivity (up to 99%) as shown in Scheme 1.33.[141]

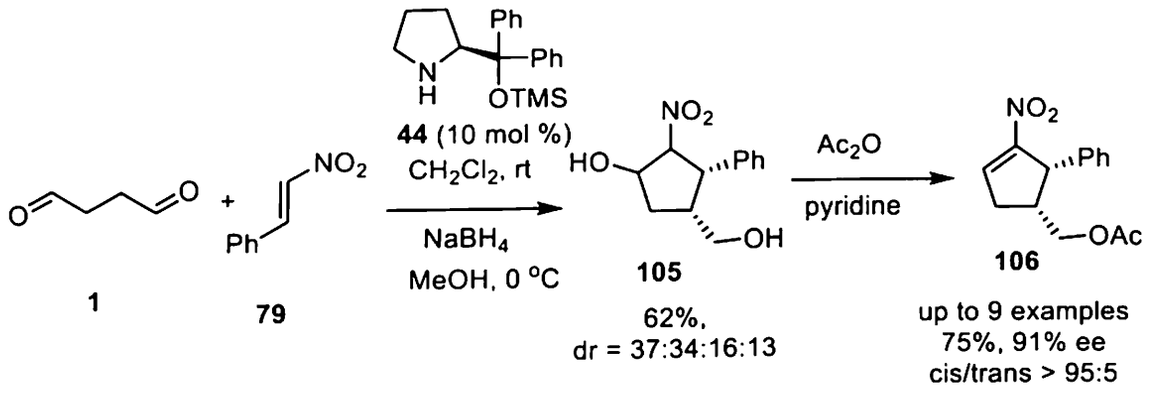


Scheme 1.32 Synthesis of Diaportheone B involving succinaldehyde through amine catalysis



Scheme 1.33 Amine catalyzed transformation for domino aldol/acetalization

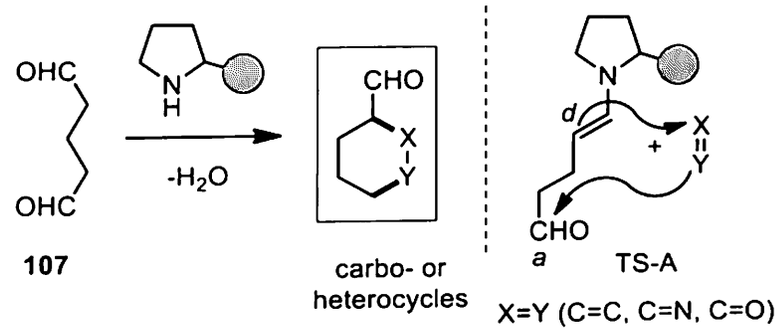
Very recently the same group developed diphenylprolinol silyl ether **44** catalyzed domino Michael/Henry reaction with nitroalkenes **79** and succinaldehyde **1** to furnish *cis*-disubstituted nitropentenes **106** in excellent diastereoselectivities and enantioselectivities after treatment of the Michael product with Ac_2O and pyridine (Scheme 1.34).[142]



Scheme 1.34 Formal [3+2] cycloaddition with succinaldehyde and nitroalkenes

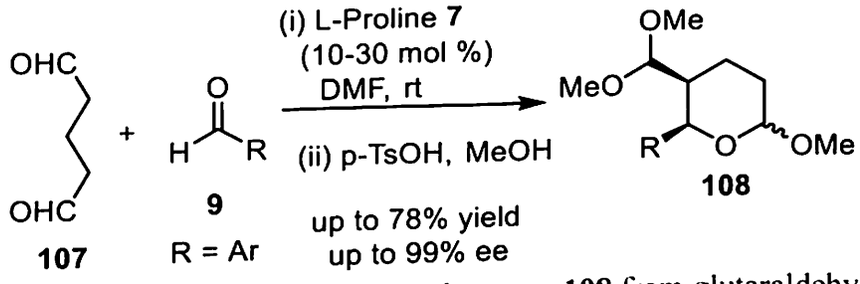
1.7 Glutaraldehyde in amino-catalytic transformations

Linear dialdehydes and their derivatives have been recognized as important substrates in the area of synthetic organic chemistry.[127] In particular, glutaraldehyde, which is a 5-carbon dialdehyde, is a clear, colorless to pale straw-colored, pungent oily liquid that is soluble in all proportions in water and alcohol, as well as in organic solvents. This linear dialdehyde has had great success in synthesis because of its commercial availability and low-cost, in addition to its high reactivity. Glutaraldehyde acts as a suitable cross-linking agent for the enzymes immobilization because it possesses unique chemical behavior in aqueous solution.[143,144] Moreover, glutaraldehyde has also been used successfully for the rapid synthesis of small heterocyclic scaffolds as well as useful alkaloids.[145-149] Since the thesis work was done by using glutaraldehyde as one of the substrates, more attention was devoted to exploring the glutaraldehyde intermolecular transformation in presence of amine catalysts. In general, most of the amine-catalyzed transformations of glutaraldehyde proceed through the enamine formation **TS-A** (Scheme 1.35) from one of the aldehyde group whereas another aldehydic moiety acts as acceptor with various dipolarophile (X=Y), giving carbocyclic/heterocyclic ring systems in one-pot operation without many protection-deprotection steps. The application of glutaraldehyde **107** in amine catalyzed domino transformation is quite obvious as it can give a rapid access to medium-sized carbo-and heterocyclic ring systems depending on counterpart dipolarophile C=C, C=N, C=O used in the reaction, which was collectively reviewed by our group recently.

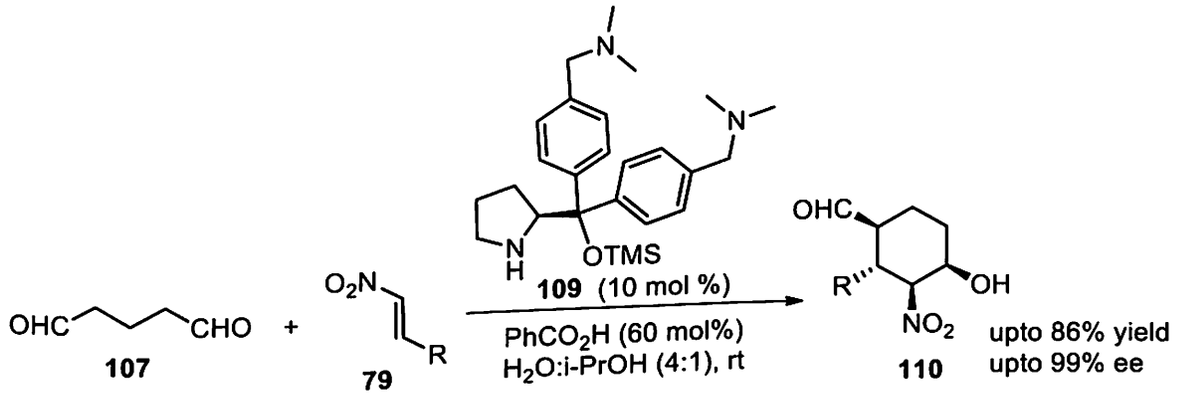


Scheme 1.35 Amine catalyzed transformations of glutaraldehyde with X=Y

Hayashi and co-workers reported the amine-catalyzed chiral synthesis of tetrahydropyrans **108** through domino transformations, in which glutaraldehyde **107** was considered as one of the important synthetic counterparts (Scheme 1.36).[150] This protocol involved proline **7** catalyzed direct aldol reaction between glutaraldehyde **107** and aromatic aldehydes **9**, followed by acid catalyzed acetalization reaction provided *cis*-tetrahydropyrans **108** with excellent enantioselectivity.



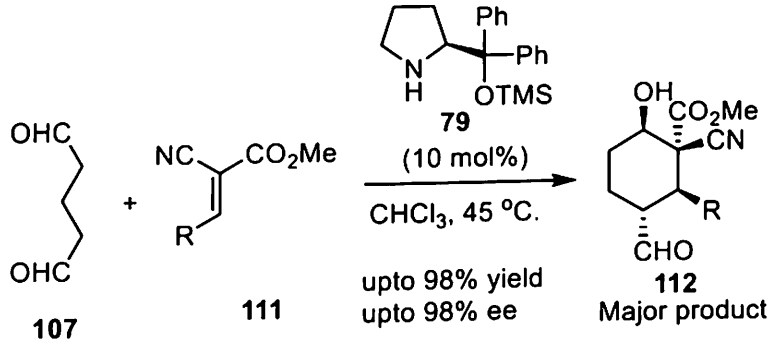
Scheme 1.36 Amine catalyzed synthesis tetrahydropyran **108** from glutaraldehyde and aldehyde



Scheme 1.37 Amine-catalyzed synthesis of functionalized cyclohexane's

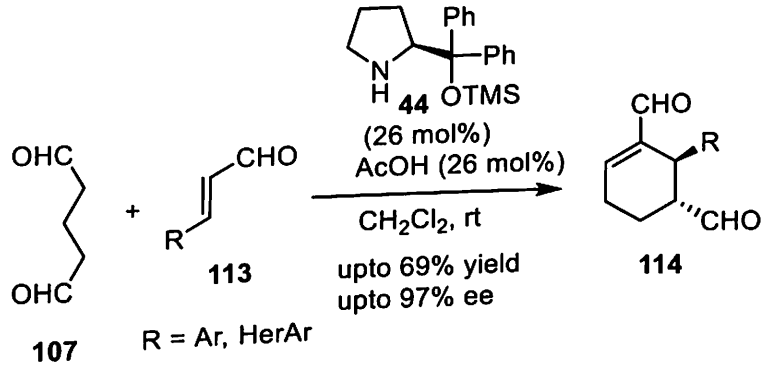
Ni and co-workers reported an organocatalytic approach for functionalized cyclohexanes **110** from glutaraldehyde **107** and activated alkene **79** using the water-soluble and recyclable organocatalysts **109** in high yield and enantioselectivity as shown in Scheme 1.37.[151]

Cordóva and co-workers reported the highly enantioselective synthesis to access functionalized cyclohexanes **112** from alkylidene malonates **111** and glutaraldehyde **107** under amine catalyzed domino Michael/aldol procedure (Scheme 1.38).[152] These functionalized chiral products **112** well decorated with cyano, formyl, hydroxyl, and ester groups, were generated with high yields and enantioselectivities. The resulting products contained four contiguous chiral centers including one quaternary center, could be useful intermediates in synthesis.



Scheme 1.38 Amine catalyzed intermolecular transformation of glutaraldehyde

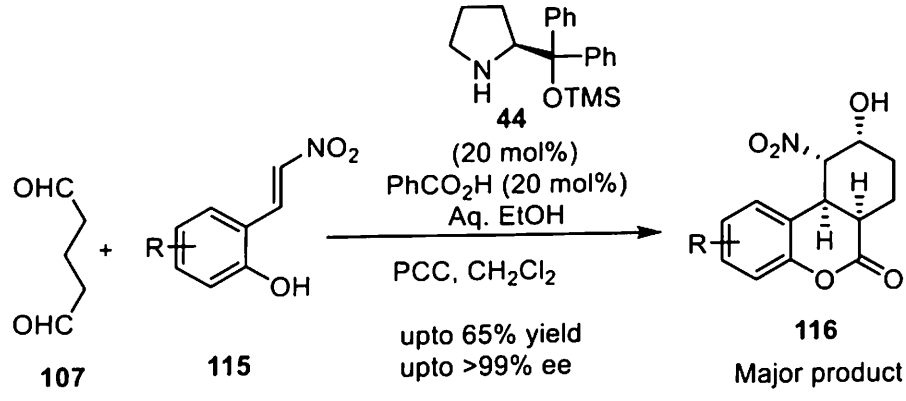
Hong and co-workers reported amine catalyzed asymmetric cascade transformations between glutaraldehyde **74** and 3-arylpropenal **113** to furnish **114** in high yields and excellent enantioselectivity shown in Scheme 1.39.[153] The initial application of glutaraldehyde in the quick synthesis of functionalized cyclohexene derivatives as domino strategy was developed (**Scheme 1.39**).[153] The reaction involved amine catalyzed Michael reaction of glutaraldehyde **74** with 3-arylpropenal **113** followed by intramolecular aldol condensation to access substituted chiral cyclohexene **114**.



Scheme 1.39 Amine catalyzed synthesis of chiral cyclohexenes from glutaraldehyde

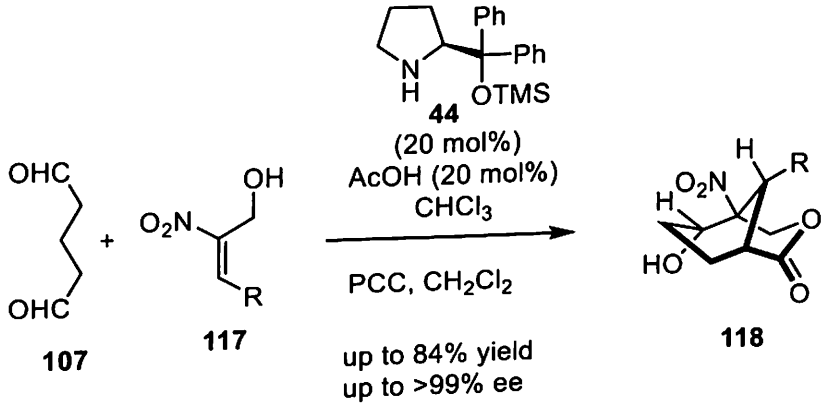
An amine catalyzed domino Michael-acetalization-Henry reaction between easily available glutaraldehyde **107** and *ortho*-hydroxynitrostyrenes **115** to synthesize complex tetrahydro-6*H*-benzo[*c*]chromen-6-ones **116** in asymmetric fashion was reported recently by B. C. Hong group.

(Scheme 1.40).[154] Interestingly, this cascade process performed exceptionally well generated four contiguous chiral centers through three bonds forming steps with excellent stereoselectivity.



Scheme 1.40 Synthesis of domino reaction through amine catalysis using glutaraldehyde

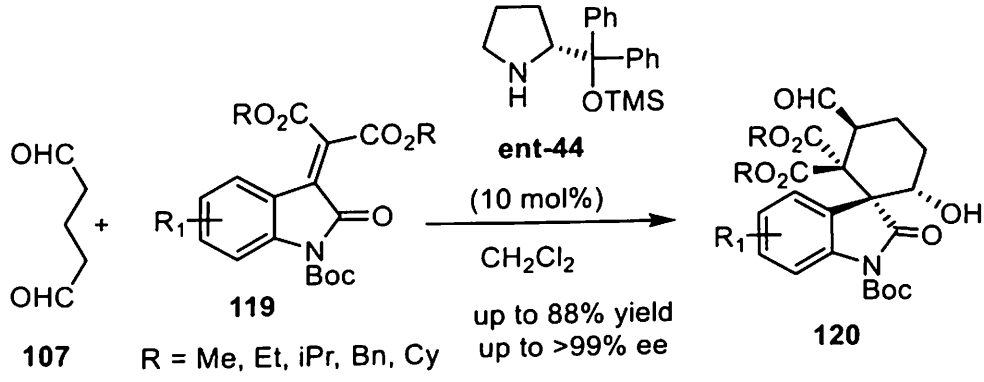
Very recently, Hong *et al.* developed, another interesting application of glutaraldehyde **107** in amine catalyzed transformation to 3-oxabicyclo[3.3.1] nonan-2-ones **118** consisting of four consecutive stereogenic centers (Scheme 1.41).[155] This method involved organocatalytic cascade Michael-Henry acetalization-oxidation reaction of 3-aryl-2-nitroprop-2-enols **117** and furnished bridged bicyclic systems **118** with high yields and excellent selectivity (up to >99% ee). The quick synthesis of highly functionalized bicyclic systems under benign reaction conditions and these products find a wide range of synthetic applications.



Scheme 1.41 Synthesis of oxabicyclic compounds using intermolecular transformation of glutaraldehyde with **117**

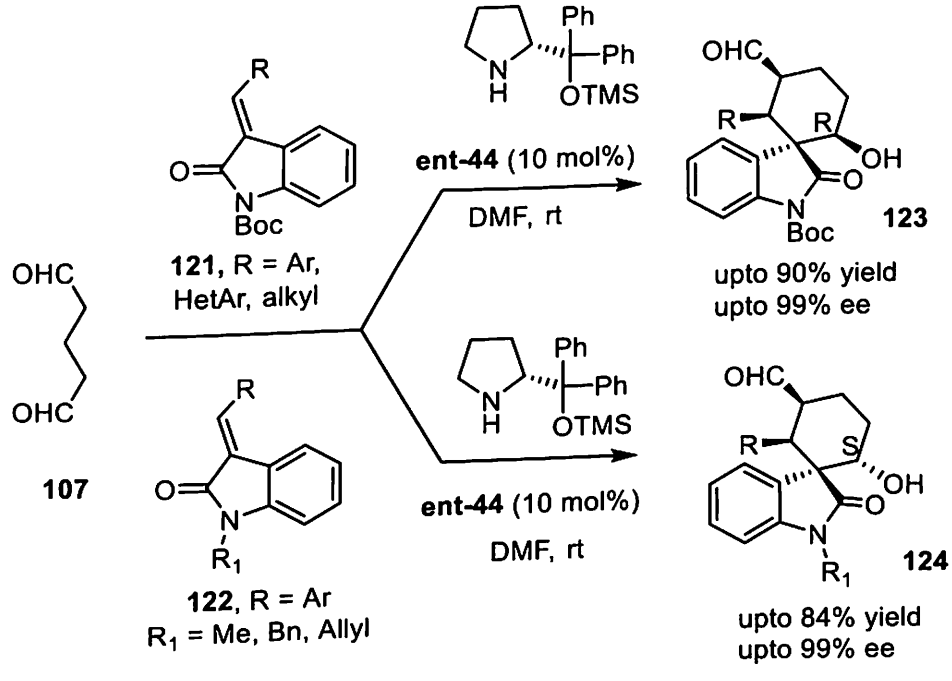
Wang and co-workers exploited the ability of glutaraldehyde **107** in organocatalytic domino Michael/Aldol cyclization using isatin-derived alkenes **119** as Michael acceptors (Scheme 1.42).[156] A series of functionalized spirocyclohexane oxindoles **120** decorated with formyl,

hydroxy, and ester groups were synthesized in asymmetric fashion using amine catalyst **ent-44** (10 mol%) catalysis with high yields and excellent selectivity.



Scheme 1.42 Amine catalyzed synthesis of spiro-compound **120**

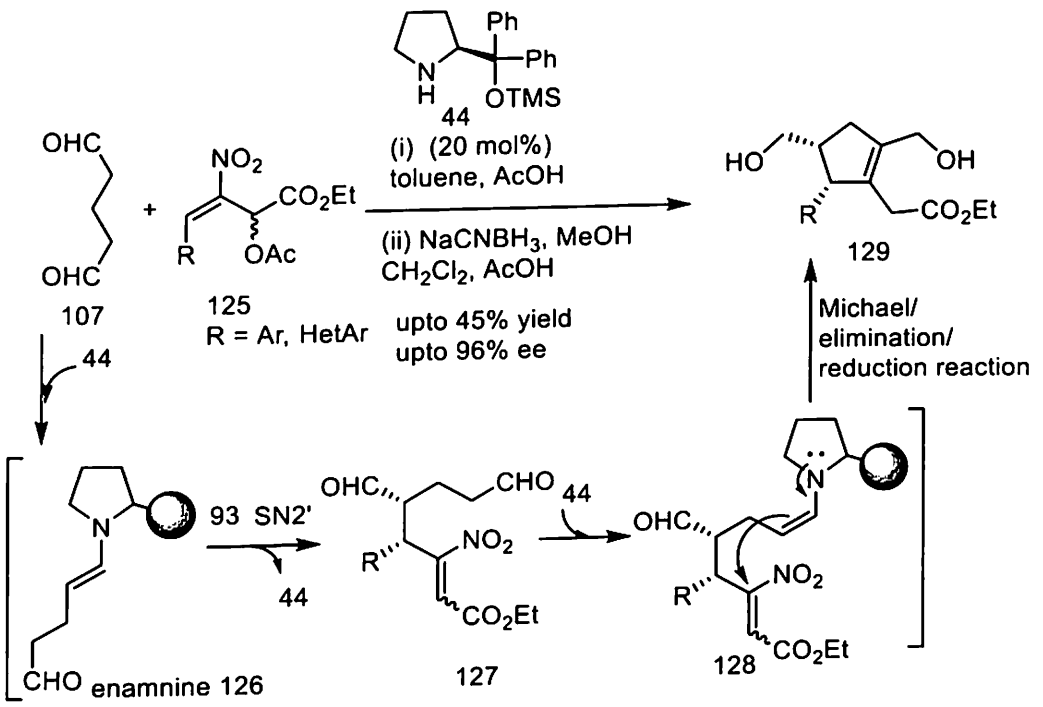
In a very similar protocol, Ghosh *et al.* described the enantioselective synthesis of spirocyclohexane oxindoles **123** and **124** comprising of multiple stereocenters including a spiro-quaternary center from the glutaraldehyde **107** in high yields and excellent enantioselectivities.[157] Interestingly, *N*-protecting groups on the oxindoles moiety played a critical role in aldol ring closure leading to the ultimate stereochemical outcome of the hydroxyl center (Scheme 1.43).



Scheme 1.43 Synthesis of spiro-compounds using Glutaraldehyde

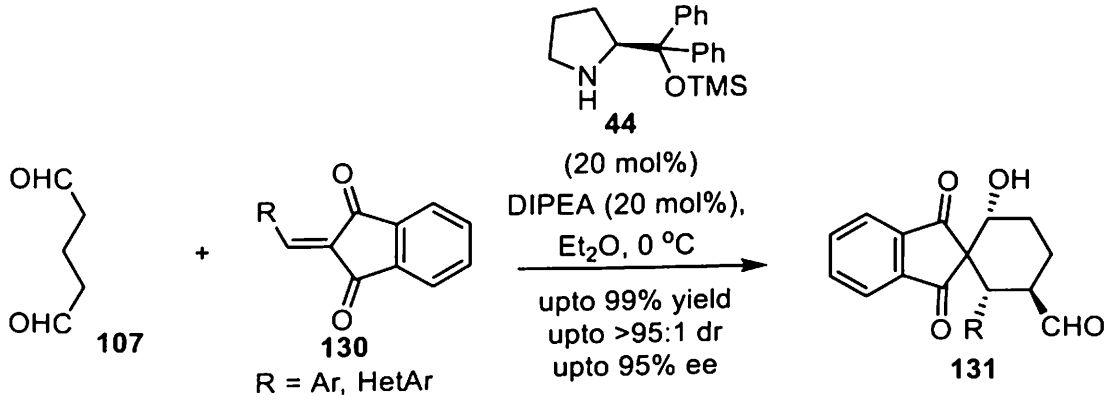
Chen and co-workers developed an amine **44** catalyzed cascade transformation for the synthesis of functionalized cyclopentanes from glutaraldehyde **107** and racemic nitroallylic acetates **93** (Scheme 1.44).[158] In this process, kinetic resolution of racemic **125** was accomplished through

the S$_N$2' reaction followed by intramolecular Michael addition-elimination process in presence of diphenylprolinol silyl ether **44** giving tetra substituted-cyclopentenes **129** with satisfactory yields and high enantioselectivity. The less reactive enantiomeric substrate was generally recovered with good to excellent optical purities. In the mechanism, enamine **126** generated from **107** and **44** gave S$_N$2' reaction with **125**, while another aldehydic moiety underwent intramolecular Michael addition-elimination through intermediate **127** and **128** to give **129** after *in situ* reductions with $NaBH_4$.



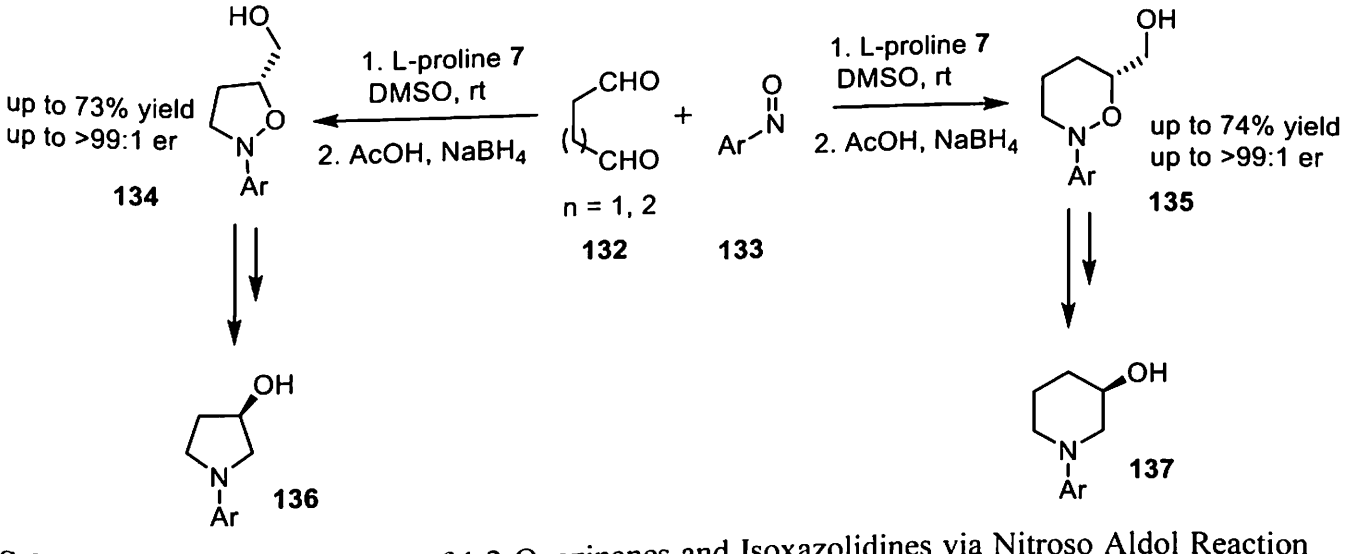
Scheme 1.44 Synthesis of cyclohexenes from glutaraldehyde through amine catalysis

Very recently, another interesting application of glutaraldehyde **107** for the synthesis of spirocyclohexane-carbaldehydes **131** using amine **44** catalyzed was developed by Chen group (Scheme 1.45).[159] The amine **44** catalyzed Michael/Aldol domino sequence between glutaraldehyde **107** and 2-arylideneindane-1,3-diones **130** as [4+2] annulations provided spirocyclohexane-carbaldehydes **131** with high yield and selectivities (up to 95% ee). The overall selectivity of the reaction was found to be additive and temperature dependent, while **130** derived from aryl/heteroaryl groups were employed successfully.



Scheme 1.45 Amine catalyzed synthesis of spirocyclic scaffold **131**

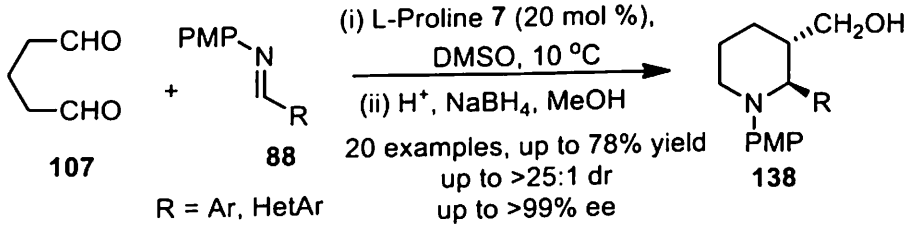
Recently, Ramakrishna and co-workers reported the first asymmetric nitroso aldol reaction with nitrosobenzene **133** and distal dialdehydes **132** in presence of L-proline followed by subsequent reduction to furnish 1,2-oxazinanes **135** and isoxazolidines **134** in high yields and excellent enantioselectivities is shown in Scheme 1.46.[160] The synthetic utility of this protocol has been shown through the production of biologically relevant chiral 3-hydroxypiperidines **137** and pyrrolidine **136** derivatives.



Scheme 1.46 Chiral Synthesis of 1,2-Oxazinanes and Isoxazolidines via Nitroso Aldol Reaction of Distal Dialdehydes

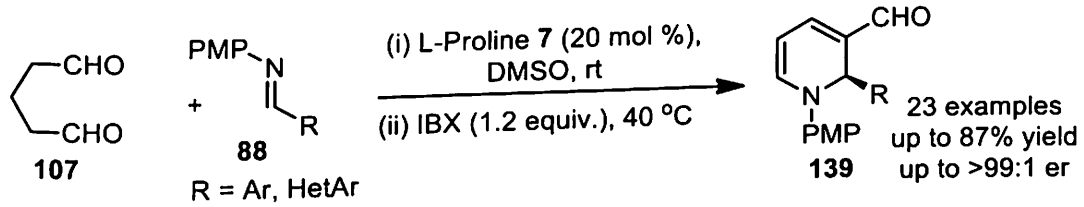
Our group applied glutaraldehyde **107** as a biofunctionalized substrate for the quick synthesis of medium-sized nitrogen heterocycles through proline-catalyzed cascade transformations.[40] In this direction, Kumar and co-workers reported direct Mannich reaction of glutaraldehyde **107** with various *N*-PMP aldimines **88** 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 **138** in high yield and excellent enantioselectivity shown in Scheme 1.47.[161]



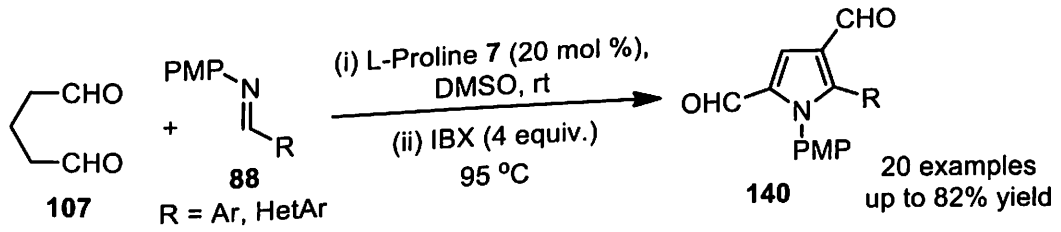
Scheme 1.47 Organocatalytic asymmetric synthesis of functionalized piperidines **138**

Kumar and co-workers developed an operationally simple first metal-free enantioselective synthesis of *N*-PMP-1,2-dihydropyridines **139** via one-pot formal [4+2] cycloaddition between readily available aldimines **88** and aqueous glutaraldehyde **107**. This reaction proceeds through Proline **7** catalyzed direct Mannich/cyclization, followed by IBX mediated site-selective dehydrogenative-oxidation sequence with high yields and selectivity shown in Scheme 1.48.[162]



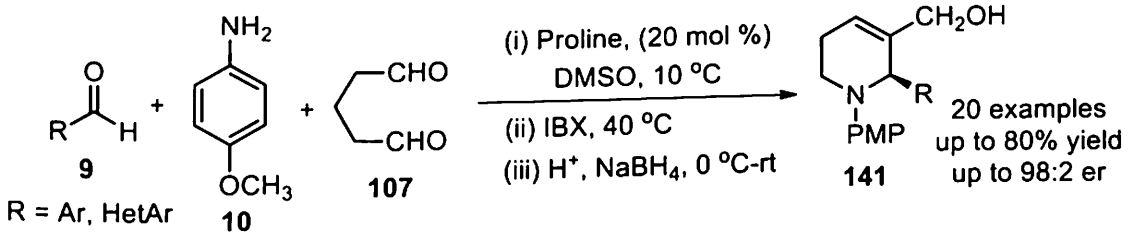
Scheme 1.48 Enantioselective synthesis 1,2 DHPs between glutaraldehyde and imines

Kumar and co-workers developed a new and efficient method for the quick synthesis of 1, 5-disubstituted pyrrole-2,4-dials **140** from commercially available starting materials such as glutaraldehyde **107** and easily accessible imines **88** through organocatalytic [4+2] annulation/IBX oxidation cascade in one pot as an overall *pseudo* [3+2] cycloaddition in high yield shown in Scheme 1.49.[163]



Scheme 1.49 Organocatalytic one pot direct synthesis of *N*-PMP-pyrrole-2,4-dicarbaldehyde

Kumar and co-workers developed an efficient multicomponent-domino sequence in a single flask for the asymmetric synthesis of functionalized 1,2,5,6-tetrahydropyridines (THPs) **141** in good to high yields (up to 80%) and with the excellent enantioselectivity (up to 98:2 er).This method proceeded through amine catalyzed Mannich reaction-cyclization of *in situ* generated imine and glutaraldehyde **107** followed by domino selective IBX-oxidation/$NaBH_4$-reduction under a mild reaction condition, without isolation of intermediate compounds shown in (**scheme 1.50**).[164]



Scheme 1.50 Proline Catalyzed multicomponent Asymmetric Synthesis of N-PMP 1,2,5,6-tetrahydropyridines

1.8 Conclusion and conception

The focus of this Ph.D. work is to expand the scope of amine catalysis towards the synthesis of five-, and six-membered nitrogen heterocycles such as pyrroles and dihyropyridines (DHPs) and related fused heterocycles. This chapter provides an overview in the field of organocatalysis, amine-catalysis and Mannich reactions, reviewing previous work relevant to these studies and involvement of succinaldehyde and glutaraldehyde in amine-catalysis. The recent development showed an augmented interest in the field of organocatalyzed direct Mannich one-pot multicomponent cascade reactions might be due to their utility in various fields, particularly in medicinal chemistry. The recent procedure has the following advantages through organocatalysis: the readily available, inexpensive, bench-stable catalysts, and mild reaction conditions which are very less sensitive to air and moisture. Thus, a remarkable recent development shows an increased attention in the area of organocatalytic cascade reactions. This overview summarized the diverse procedures reported for direct Mannich reactions using the concept of organocatalysis over last more than one decade. Due to the increased interest in nitrogen heterocyclic scaffolds that are present in various medicinally important compounds, the major attention was devoted for the synthesis of these nitrogen heterocycles through environmentally benign amine catalytic Mannich reaction precursors are highly desirable. The general approach for *N*-containing six and five-

membered heterocyclic ring system proceeds through a proline-catalyzed direct Mannich-cyclization reaction between glutaraldehyde and succinaldehyde with cyclic and acyclic imine, followed by reduction and oxidation. Further, the developed methodology was utilized for the synthesis of some biologically active natural products scaffolds from inexpensive and commercially available starting materials *i.e.* linear dialdehydes such as succinaldehyde and glutaraldehyde and various/acyclic cyclic imines. The aim of this thesis is to discuss amino-catalyzed direct Mannich reactions and related annulation reactions for the synthesis of five-membered nitrogen heterocyclic ring system. This chapter provides an overview on the field of organocatalysis, amine-catalysis, Mannich reactions, and the amine-catalyzed intermolecular transformations of glutaraldehyde for the synthesis of important skeletons.

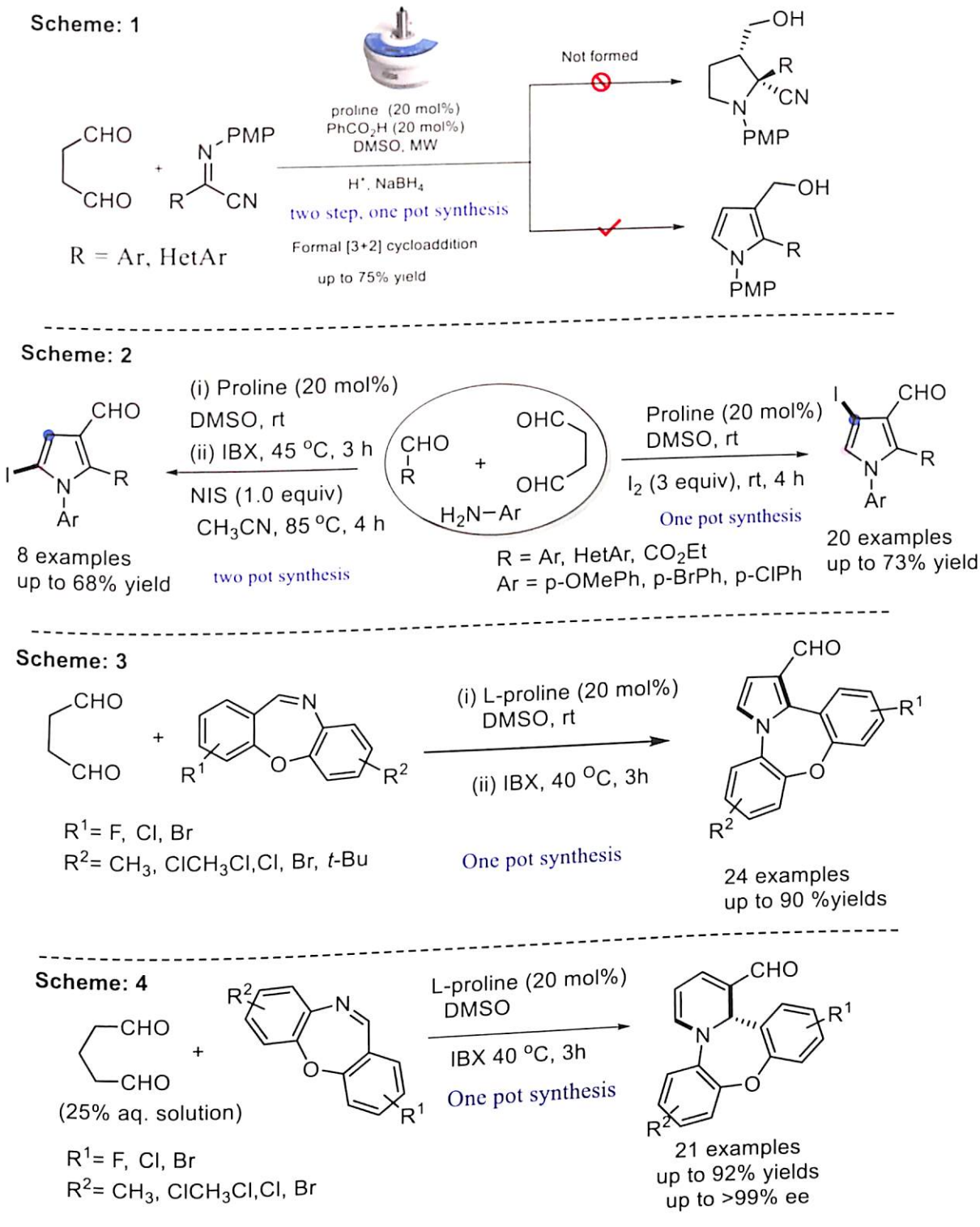


Figure 1.8 General representation of the thesis work

1.9 References

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